PRINCIPAL INVESTIGATOR: Jason M. Redman, MD

STUDY TITLE: A Sequential Window of Opportunity Trial of Anti-PD-L1/TGF-β trap (M7824) Alone and in Combination with TriAd Vaccine and N-803 for Resectable Head and Neck Squamous Cell Carcinoma not Associated with Human Papillomavirus Infection

STUDY SITE: NIH Clinical Center

Cohort: Affected Patients

Consent Version: 11/19/2021

WHO DO YOU CONTACT ABOUT THIS STUDY?

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KEY INFORMATION ABOUT THIS RESEARCH

This consent form describes a research study and is designed to help you decide if you would like to be a part of the research study.

You are being asked to take part in a research study at the National Institutes of Health (NIH). This section provides the information we believe is most helpful and important to you to in making your decision about participating in this study. Additional information that may help you make a decision can be found in other sections of the document. Taking part in research at the NIH is your choice.

You are being asked to join this study because you have a kind of head and neck cancer which has not been treated before, and your tumor requires surgical removal.

The purpose of this study is to learn if giving therapy aimed at your immune system (immunotherapy) could help shrink your tumor before surgery. The time-period between your cancer diagnosis and surgery gives us an opportunity to test immunotherapy drugs. We also want to find out whether it is safe to give the drugs together to determine if giving you immunotherapy before surgery helps prevent your tumor from coming back in the future.

The immunotherapy drugs you may receive include:

- M7824 -a drug that blocks pathways that cancer cells use to prevent your immune system from fighting your cancer.
- Tri-Ad vaccine - combination of three cancer vaccines (ETBX-011, ETBX-061, and ETBX-051) that are designed to teach your immune system how to target and then kill cancer cells.

- N-803 - a drug that can supercharge and increase the number of different types of immune cells called T cells and NK cells that may be able to kill your tumor cells.

M7824, N-803 and Tri-Ad vaccine are all investigational which means that they have not been approved by the U.S. Food and Drug Administration (FDA) to treat head and neck cancer. However, the FDA has given us permission to use M7824, N-803 and TriAd in this study.

For people with your type of cancer, treatments are not typically given before you receive your head and neck cancer treatment from your regular cancer doctors. If you choose to not take part in this study, your head and neck cancer treatment given by your regular cancer doctors will not change. This study adds these immunotherapy drugs before the treatment you would receive anyway. Side effects can occur with immunotherapy drugs as explained later in consent. By participating in this study, you will be at risk of experiencing these side effects.

If you decide to join this study, here are some of the most important things you should know:

Depending on when you enter the study, you will have treatment with M7824 alone (group A), M7824 + TriAd vaccine (group B) or M7824 + TriAd vaccine + N-803 (group C). The first few participants enrolled with be in group A. If we find that it is safe, the next set of participants will be enrolled in group B. If that combination is well tolerated, the final set of participants will be enrolled in group C.

The treatment is given as follows:

- M7824 is given as an IV (intravenous) infusion. A small plastic tube is put into a vein in your arm and the medication is given once on day 1 and day 15 of treatment.
- TriAd vaccine and N-803 are given as an injection under the skin. This is similar to receiving a vaccine shot. If you receive these treatments, N803 and TriAd vaccines are given on day 1 of treatment.

We will collect samples (biopsies) of your tumor, normal mucosa (lining of your food pipe) and skin before you begin any study therapy. We will try to collect these samples in clinic, but if it is not safe to do so, we will collect them in the operating room under anesthesia. Before treatment begins you will have new CT scans performed.

You will be seen in the NIH Clinical Center by your study team 1-2 times weekly while you are receiving treatment. Each of these clinic visits will take 2-4 hours. The treatments will be given in the Oncology Outpatient Center. Three to four weeks after your study therapy started, you will have new CT scans and possibly more biopsies. These visits are important for your safety and they are required. You will then be sent back to your regular cancer doctors for surgery and any required treatment such as radiation after your surgery. The standard treatment is not part of the study. Starting about two weeks after and going through three months after your last dose of study therapy, we will check in with you by phone or email every two weeks. During this period we will also need to see you once at the Clinical Center approximately 4- 5 weeks after your last dose. At three months after your last dose, you will visit the NIH Clinical Center for follow-up tests. You will have tests done (physical exams, blood work and scans) to see how you are doing and to see how you are healing from your treatments. We will also collect blood

samples from you for research purposes. Starting after three -month visit, you will receive a phone/email check-in every 3 months till you are 2 years out from surgery.

You may experience side effects from taking part in this study. Some can be mild or very serious, temporary, long-lasting, or permanent, any may include death. For example: M7824 may cause skin problems (such as rash), inflammation to organs inside the body, low red blood cell count (anemia) and bleeding. It is possible that the anemia and/or bleeding may be so severe that you require a blood transfusion. You cannot join this study if you are not willing to have a blood transfusion. It is possible that one or more side effects from these drugs could cause a delay in your planned surgery. It is also possible that M7824 could increase your risk of bleeding during or after surgery. Some common side effects due to TriAd vaccine are pain, tenderness, swelling or redness at the injection site. Some common risks due to N803 include fatigue, nausea, vomiting, fever, chills, sweats, decreased appetite and joint pains. Risks have been explained in detail later in the consent. If you are in group C, you may also have to temporarily stop taking some of your current medications (like beta blockers) for two weeks because it interacts with N-803.

Just as we do not know what side effects you might have, we cannot know if you will benefit from taking part in this study. However, your taking part in this study can help us learn about cancer treatment and may help others in the future.

M7824 has been tried in other types cancers. Recently, the manufacturer of the drug closed 3 large studies because the drug was not shown to help those patients more than standard therapies. In addition, in some cases it seemed like the drug might make the cancer grow faster. However, the type of cancer treated in those studies was not the same as your cancer.

You are free to stop participating in the trial at any time. If you decide to stop, the study doctor may ask you to agree to certain tests to make sure it is safe for you to stop.

The remaining document will now describe more about the research study. This information should be considered before you make your choice. Members of the study team will talk with you about the information described in this document. 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). Take the time needed to ask any questions and discuss this study with NIH staff, and with your family, friends, and personal health care providers.

If the individual being asked to participate in this research study is not able to give consent to be in this study, you are being asked to give permission for this person as their decision-maker. The term “you” refers to you as the decision-maker and/or the individual being asked to participate in this research, throughout the remainder of this document.

IT IS YOUR CHOICE TO TAKE PART IN THE STUDY

You may choose not to take part in this study for any reason. If you join this study, you may change your mind and stop participating in the study at any time and for any reason. In either case, you will not lose any benefits to which you are otherwise entitled. However, to be seen at the NIH, you

must be taking part in a study or are being considered for a study. If you do choose to leave the study, please inform your study team to ensure a safe withdrawal from the research.

WHY IS THIS STUDY BEING DONE?

This is a research study. The main purpose of this study is to learn if giving M7824 alone or in combination with TriAd vaccine and N-803 can shrink your previously untreated head and neck tumor prior to your planned surgery or help prevent your tumor from coming back after all of your treatment. Prior clinical studies with these investigational agents have helped researchers learn about the recommended doses that are safe when each study drug is given alone, but we do not have information about whether they are safe when given together. As part of this study, we will also test the safety of the combination.

WHAT WILL HAPPEN DURING THE STUDY?

Before signing this consent, you will have been screened on another protocol to find out if you met the criteria to join the study. Once you have met criteria and decide to enroll, you will undergo treatments on day 1 and 15.

You will need to visit the NIH Clinical Center 1-2 times weekly for testing during the treatment period. It is important that you come to all of these scheduled visits.

Depending on when you enter the study, you will receive M7824 alone (group A), M7824 + TriAd vaccine (group B) or M7824 + TriAd vaccine + N-803 (group C).

- If you are enrolled in group A, you will receive M7824 alone on days 1 and 15
- If you are enrolled in group B, you will receive M7824 on days 1 and 15 plus TriAd vaccine on day 1.
- If you are enrolled in group C, you will receive M7824 on days 1 and 15 plus TriAd vaccine with N-803 on day 1.

The day before receiving your first treatments on day 1, you will have biopsies performed in either the ENT clinic or in the operating room under anesthesia.

The following standard tests are done to assess your health and tumor status:

Within 14 days before starting the treatment

- Your vital signs (e.g. pulse, blood pressure, breathing rate) will be measured as part of medical exam.
- Medical history and physical exam
- CT or MRI scan (if not done within 28 days before you start treatment)
- Routine laboratory tests
- EKG (electrocardiogram) to monitor your heart
- Pregnancy test for women (if not done within 3 days before you start treatment).
- As a part of clinical testing, we will use a flexible tube inserted through your nose to see your upper airway (endoscopy) and will do a test to check your immune markers

- **During the study:**

Day 1 (usually a Friday when treatment starts):

- Your vital signs (e.g. pulse, blood pressure, breathing rate) will be measured before and after M7824 infusion.
- All participants (groups A, B and C) will receive M7824 through an IV
- For the prevention of possible allergic reactions, you may receive an antihistamine such as Benadryl and acetaminophen (Tylenol) before the M7824 infusion.
- If you are enrolled in **group B**, TriAd vaccine (injection under the skin on your arms or legs) will be given with M7824.
- If you are enrolled in **group C**, N-803 (injection under the skin on your stomach) and TriAd vaccine (as said above) will be given with M7824.

Day 15 (usually a Friday):

- Physical examination and check-up to see how you are doing
- Medical history and vital signs
- Routine blood and urine tests
- Endoscopy
- You will receive M7824 alone (group A, B or C)

Day 21-28:

- Endoscopy
- CT scans/MRI
- Routine blood tests

Additional research testing

In addition to the tests that we will conduct to determine whether you are having side effects or if you are responding to the study therapy, we will also use blood and tumor biopsy samples from you for purpose of research only. Tests on these samples will look at the effects of therapy on your immune system and tumor activity. Unless noted otherwise below, the blood samples will be collected at baseline (before you receive any study intervention), at every visit on day 8, 15, 21-28, 105 (± 3 days) and at surgery. We will collect tissue samples at baseline (required) and during day 21-28 (optional) or at surgery. Providing tissue samples is optional and it will not impact your participation for this study. A separate consent form will be provided to you at the time of the biopsy for you to grant permission to that procedure if you agree to this biopsy.

The samples included for these studies include:

- blood (around 1 cup total volume over time)
- tissue

All of your blood and tissue samples collected for research purposes on this study may be used to look for specific changes in the DNA that could be used to develop new ways of diagnosing and treating cancer. DNA (also called deoxyribonucleic acid) in cells carries genetic information and passes it from one generation of cells to the next – like an instruction manual. Normal tissue

contains the DNA (instructions) that you were born with, DNA in tumor cells has changed – or mutated – and we think that these changes in the DNA is what causes tumors to form and to grow.

To look at your DNA, we may use do what is called "whole genome sequencing." This where we will do special tests in the lab to look at the entire sequence, or order, of how your DNA is put together. This is what makes you unique.

To determine which parts of the DNA have mutated, we will compare the DNA in your tumor cells to DNA from your normal cells. We will then analyze the results from similar tumors to see if there are any changes in the DNA that are common to a particular type of tumor. To examine the tumor and normal tissue we may use several different techniques depending on the type of tissue we collect. These could include growing cell lines (cells which keep dividing and growing in the laboratory, sometimes for years allowing us to continually study those cells), xenograft studies (placing or growing cells in another animal, such as mice), and looking in detail at the parts of the genes that produce specific proteins.

However, you should know that the analyses that we perform in our laboratory are for research purposes only; they are not nearly as sensitive as the tests that are performed in a laboratory that is certified to perform genetic testing or testing for routine clinical care. For these reasons, we will not give you the results of the research tests done on your research samples in most cases. There may be exceptions to what we share with you and this is described later in this consent form in the section for "Return of research results."

HOW LONG WILL THE STUDY TAKE?

After you have completed study therapy

You will return the care of your surgeon to have your scheduled surgery.

Starting about two weeks after your last dose of study therapy (~ day 28) and going through three months after your last dose of study therapy (~day 105), we will check in with you by phone or email every two weeks.

In addition, we will need to see you at the Clinical Center four to five weeks after you have completed study therapy (~ day 49) so we can do blood tests. Day 49 visit can be scheduled up to eight weeks after you have completed therapy as it depends upon how long you stay in the hospital for surgery and may be skipped if your study doctor decides it is safe to do so. Three months after your last dose (~day 105) we will see you again at the Clinical Center for additional blood tests, medical history, physical examination and an endoscopy.

Long-term follow-up visit

We will contact you every 3 months by telephone/email to ask questions about your state of health until you are 2 years out from surgery.

If you agree to take part in this study, your involvement is expected to last for 2 years.

HOW MANY PEOPLE WILL PARTICIPATE IN THIS STUDY?

We plan to have approximately 40 people participate in this study at the NIH.

WHAT ARE THE RISKS AND DISCOMFORTS OF BEING IN THE STUDY?

There are risks, discomforts, and inconveniences associated with any research study. These deserve careful thought. You should talk with the study doctors if you have any questions.

It is probable that you will experience some of the side effects listed, but it is unlikely that you will experience all of them. You will be watched closely, and we will give you medicines to try and prevent or reverse the side effects. However, doctors don't know all the side effects that may happen. Side effects may be mild or very serious. In some cases, side effects can be serious, long lasting, or may never go away. We will tell you if we learn any new information that may affect your health, welfare, or decision to stay in this study. You should talk to your study doctor about any side effects that you have while taking part in the study.

It is possible that one or more side effects from these immunotherapy drugs could delay your surgery. Your regular cancer doctors need to be aware that you are participating in this study.

Risks of M7824

Common (occurring in more than 5% of patients)

- Tiredness
- Nausea
- Diarrhea
- Constipation
- Vomiting
- Swelling of your lower legs or hands
- Fever
- Decreased appetite
- Loss of body fluids (dehydration)
- Wart-like growths on the skin called keratoacanthomas that can turn into skin cancer. These usually go away after treatment but we can remove them if they do not.
- Rash, blisters, skin discoloration and other skin abnormalities
- Bleeding has been frequently observed in people receiving M7824. Participants may experience bleeding in different organs such as gums, nose, ears, eyes, vagina, breast, blood in the urine, stool, or bleeding in the internal organs or skull, coughing up or vomiting blood. Occasionally, this bleeding can be serious and potentially life threatening and require you to have a blood transfusion. If you experience any bleeding on this trial, please tell the study team

immediately. Tell your doctor if you've had a life-long problem of frequent or excessive bleeding or bruising.

  - It is possible that M7824 could increase the risk of bleeding during or after your surgery.
  - Unfortunately, we cannot tell you for sure how likely it is that you may experience bleeding as this is a new event that we have seen in patients in other studies at NCI. However, if we learn more information that may be helpful, we will update you.

- Shortness of breath
- Cough
- Anemia - low number of red blood cells that can cause tiredness and shortness of breath. May require a transfusion.
- Abdominal pain
- Headache
- Itching

Occasional (occurring in less than 5% of patients)

- Chills (feeling cold)
- Blood clots that form throughout the body, blocking small blood vessels. Symptoms may include chest pain, shortness of breath, leg pain, problems speaking, or problems moving parts of the body
- Easy bruising
- Reaction to other drugs such as rash, anaphylaxis, and changes in blood
- Infusion-related reaction, including dizziness or fainting (low blood pressure), flushing, rash, fever, shortness of breath or sick to your stomach, or pain at the site of infusion. Although usually reversible with treatment, it can be severe or life threatening.
- Back pain
- Cancerous growth on the skin that can be removed r
- Stroke
- Slow wound healing. If you are having surgery, please discuss with your doctor.
- Thickening of the skin, nails
- Allergic reactions or reactions related to the infusions might occur during treatment. Usually, these reactions are mild to moderate and can be treated with drugs but could also be severe to life-threatening which could require advanced cardiac life support and even fatal reactions might occur.

For the prevention of infusion-related side effects and possible allergic reactions you may receive a premedication of an antihistamine drug and acetaminophen 60 to 120 minutes before the 1st and 2nd infusion.

In addition, immune-related side effects are possible. These adverse events are caused by over activity of your body's immune-system caused by M7824. The immune system normally protects you from infections and foreign substances, such as cancer. If the immune system is overactive, it may think that parts of the body, including vital organs, are foreign substances and attack them.

Examples of these side effects are listed below. In rare cases, immune-related side effects can be life threatening or fatal.

Types of immune-related side effects:

- pneumonitis (inflammatory disease of the lung): symptoms may include but are not limited to a new or worsening cough, shortness of breath possibly with fever. Preliminary data suggested that there may be the tendency of higher frequency and severity in Japanese patients compared with non-Japanese patients: tell your study doctor right away if you have any of these symptoms as it may need to be treated urgently
- hypothyroidism (decreased function of the thyroid gland seen on labs that your doctors will check)
- hyperthyroidism (increased function of thyroid gland seen on labs that your doctors will check)
- thyroiditis (inflammatory disease of the thyroid gland seen on labs that your doctors will check)
- autoimmune hepatitis (inflammatory disease of the liver caused by the body's immune system seen on labs that your doctors will check): Signs and symptoms of this include yellowing of the skin or whites of the eyes, dark urine, severe nausea and vomiting, pain in the upper right side of your abdomen, skin itchiness, not feeling hungry and bleeding or bruising more easily than normal
- thrombocytopenia (decrease of the blood platelets that can cause bleeding in extreme cases. Your doctor will use blood work to check your platelets
- inflammatory eye disease
- diabetes mellitus (high blood sugar levels)
- decreased function of the adrenal glands or other glands that produce important hormones. This may cause stomach pains, vomiting, muscle weakness and fatigue, depression, low blood pressure, weight loss, kidney problems, and changes in mood and personality. These complications may be permanent and may require hormone replacement
    - On a different clinical trial, people who received M7824 in combination N-803 and a vaccine similar to the Tri-Ad vaccine used in this study had an increased risk of developing decreased adrenal function, requiring daily medication for life. People who developed this condition received treatment for at least 2 months or more, before developing this condition. This is more treatment than you will receive on this trial. Whether or not receiving Tri-Ad vaccine in combination with M7824 and N-803 on this study will increase your risk of this condition is unknown. Since this condition could occur months after receiving immunotherapy, it is important that

you tell your outside doctor that you were on an immunotherapy if you experience decreased energy, headaches, persistent nausea/vomiting, or dizziness after you are done with your NIH follow up period.

- inflammatory disease of muscles characterized by pain and tenderness
- colitis (inflammatory disease of the large intestine): It may cause abdominal pain and diarrhea with or without blood. Fever may be present. It may require you to receive additional fluids. If left untreated, in rare occasions this may lead to a tear in the wall of the intestine which can be serious and life threatening
- impairment of the brain function
- myocarditis (heart inflammation)
- inflammation of the pancreas
- Skin rash with blisters
- Kidney problems: you may have an increase of creatinine levels in a blood test (creatinine is a protein marker that measures kidney function) but not have any symptoms or feel unwell. Uncommonly a patient may experience nephritis which is an inflammation of the kidneys that stops the kidneys from working properly
- Problems with the pituitary gland (hypopituitarism): Hypopituitarism refers to decreased output of hormones from the pituitary gland in the brain and may be caused by inflammation of the pituitary gland (hypophysitis). Symptoms may include headaches, thirstiness, and trouble seeing or double vision, leakage of breast milk or irregular periods in women. These complications may be permanent and may require hormone replacement
- Liver problems: Increases in the blood level of substances called enzymes found within your liver cells. The enzyme changes are unlikely to make you feel unwell, however, if these blood enzyme levels become very high, your study doctor may need to stop the study medication
- Nervous system problems: symptoms can include unusual weakness of legs, arms, or face, numbness, or tingling in hands or feet. In rare situations, there is the potential for the inflammation of the nervous system to be severe.

In addition to the above, we have seen a few cases of nodular regenerative hyperplasia. This is when small growths, or nodules, occur in the liver. These usually do not cause symptoms, but can occasionally be associated with high blood pressure in the vein to the liver which could over time lead to liver damage.

Risks of Tri-Ad Vaccine

The combination of the ETBX-011, ETBX-061, and ETBX-051 vaccines with other agents on this study has not been previously given to humans before, so risks and discomforts may occur that we cannot predict. While in the study, you may have side effects. They may be mild or very serious. Please tell your nurse or doctor about any side effects you experience. Your study doctor

may give you medications to try to help lessen some of the side effects. All subjects in the study will be monitored for side effects.

The side effects listed below have occurred in people receiving ETBX-011. ETBX-061 and ETBX-051.

Likely (Occurring in more than 50% of patients)

- Pain, tenderness, swelling or redness at the injection site
- Fever
- Flu-like symptoms
- Myalgia (muscle pain)
- Chills

Less Likely (Occurring in less than 5% of patients)

- Anorexia
- Nausea
- Headache

Risks of N-803

Common (Occurring in more than 50% of patients) side effects of N-803 are listed below. One or more of these side effects may begin 1-2 days after receiving N-803 and go away a few days later.

- Fatigue
- Large red rash and/or swelling at the site of injection that fades over 1-2 weeks
- Fever
- Chills
- Sweats

Other potential side effects of N-803 (Occurring in less than 15% of patients)

- Fast heart rate
- Dry eyes
- Abnormal liver enzymes
- Flushing
- Itching rash
- Stomach pain
- Decreased appetite
- Nausea
- Vomiting
- Diarrhea
- Joint pain
- Headache
- Blood in the urine

- Muscle pains
- Altered taste
- Redness, soreness, or swelling at the injection site 2 to 3 days after injection
- Shortness of breath
- Constipation
- Leg swelling
- Low blood pressure
- Cough
- Muscle twitching
- Dehydration
- Anemia (low red blood cell counts)
- Low white blood cell counts
- Atrial fibrillation, a quivering or irregular heartbeat (arrhythmia), that can lead to blood clots, stroke, heart failure and other heart-related complication and may require the addition of a blood thinner.

More than one of these side effects may happen at the same time. If you experience any of these symptoms, follow the instructions provided by your study doctor.

Risks of study procedures

Blood draws

Risks include temporary discomfort, pain, redness, bleeding, bruising, and swelling at the site where the needle is inserted, and/or very rarely inflammation/infection of the vein, which could require antibiotics. You may also experience dizziness, nausea, or rarely, fainting during blood taking. Please tell the study doctor if you do not feel well after having your blood drawn.

Tumor, normal mucosa and skin biopsies

There may be some temporary pain or discomfort during the procedure and afterwards in the area where the tissue was removed. You may also experience some bruising around the biopsy site over the following days. In rare cases an infection or bleeding may occur. If your tumors are not accessible in the clinic or a biopsy in the clinic is deemed unsafe by the study doctor, biopsies may be performed in the operating room under general anesthesia. Side effects of general anesthesia may include temporary confusion, difficulty passing urine, bruising or soreness from the IV drip, nausea and vomiting, shivering and feeling cold, and sore throat.

Nasopharyngo-laryngoscopy (Endoscopy)

In this procedure, a physician gently places a small, thin, flexible endoscope with a camera down through your nose to view your upper airway anatomy above the vocal cords. This procedure takes only a few minutes, is painless and does not require any sedation. It is a normal part of an ENT exam.

CT scans due to contrast dye

If contrast dye is used, there is a risk for allergic reaction to the dye. If you are allergic to or sensitive to medications, contrast dye, iodine, or shellfish, please notify your study doctor. If you have had kidney failure or other kidney problems in the past, please notify your study doctor.

What are the risks related to pregnancy?

If you are able to become pregnant, we will ask you to have a pregnancy test before starting this study. You will need to practice an effective form of birth control before starting study treatment, during study treatment, and for 2 months after you finish study treatment (the restricted period). For a portion of the study, you will need to use effective birth control methods and try not to become pregnant. Your study team will provide additional details on how long this will be required and what methods may be used. If you become pregnant, there may be unknown risks to the fetus or unborn child, or risks that we did not anticipate. There may be long-term effects of the treatment being studied that could increase the risk of harm to a fetus. You must tell the study doctor if your birth control method fails during the restricted period. If you think or know you have become pregnant during the restricted period please contact the study team as soon as possible.

If you are a sexually active person with a partner able to become pregnant, it is important that your partner not become pregnant the restricted period. There may be unknown risks to a fetus or risks we did not anticipate. You and your partner must agree to use birth control if you want to take part in this study. If you think your partner has become pregnant during the restricted time, please contact the study team as soon as possible. If you and your partner plan for your partner to become pregnant after the restricted time, please discuss this with the study team.

What are the risks of radiation from being in the study?

During your participation in this research study, you will be exposed to radiation from up to 3 CT scans of the neck and chest area in a year. The amount of radiation exposure you will receive from these procedures is equal to approximately 0.99 rem. A rem is a unit of absorbed radiation.

Every day, people are exposed to low levels of radiation that come from the sun and the environment around them. The average person in the United States receives a radiation exposure of 0.3 rem per year from these sources. This type of radiation is called “background radiation.” No one knows for sure whether exposure to these low amounts of radiation is harmful to your body.

The CT and bone scans that you get in this study will expose you to the roughly the same amount of radiation as 3.3 years of background radiation. Most of the time, this amount of extra radiation is not harmful to you. However, scientists believe that being exposed to too much radiation can cause harmful side effects. This could include getting a new cancer. We estimate that this could happen in about 1 out of every 1000 people who get a very large amount of extra radiation.

You may not participate in this study if you are pregnant. If you are able to become pregnant, we will perform a pregnancy test before exposing you to radiation. You must tell us if you may have

become pregnant within the previous 14 days because the pregnancy test is unreliable during that time.

Psychological or Social Risks Associated with Return of Incidental or Secondary Findings

As part of the research study, it is possible that you could learn that you have genetic risks for another disease or disability. This may be upsetting and, depending on what you learn, might create a need to make challenging decisions about how to respond.

Although your genomic information is unique to you, you share some genomic similarities with your children, parents, brothers, sisters, and other blood relatives. Therefore, learning your research results could mean something about your family members and might cause you or your family distress. Before joining the study, it may be beneficial to talk with your family members about whether and how they want you to share your results with them.

Privacy Risks Associated with Return of Incidental or Secondary Findings

Although your genetic information is unique to you, you do share some genetic information with your children, parents, brothers, sisters, and other blood relatives. Consequently, it may be possible that genetic information from them could be used to help identify you. Similarly, it may be possible that genetic information from you could be used to help identify them. Patterns of genetic variation also can be used by law enforcement agencies to identify a person or his/her blood relatives.

Protections against misuse of genetic information

This study involves genetic testing on samples. Some genetic information can help predict future health problems of you and your family and this information might be of interest to your employers or insurers. The Genetic Information Nondiscrimination Act (GINA) is a federal law that prohibits plans and health insurers from requesting genetic information or using genetic information. It also prohibits employment discrimination based on your health information. However, GINA does not address discrimination by companies that sell life insurance, disability insurance, or long-term care insurance. GINA also does not protect you against discrimination based on an already-diagnosed condition or disease that has a genetic component.

WHAT ARE THE BENEFITS OF BEING IN THE STUDY?

You might not benefit from being in this study. However, the potential benefit to you might be shrinking of your tumor or decrease in yoursymptoms, 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.

Are there any potential benefits to others that might result from the study?

In the future, other people might benefit from this study because what we learn in this study may eventually be used to treat others with your disease.

WHAT OTHER OPTIONS ARE THERE FOR YOU?

Before you decide whether or not to be in this study, we will discuss other options that are available to you. Instead of being in this study, you could:

- choose to be treated with surgery alone and not have additional study therapy treatment, radiation or with drugs already approved by the FDA for your disease
- choose to take part in a different study, if one is available
- choose not to be treated for cancer but you may want to receive comfort care to relieve symptoms.

You should discuss with your doctor your other choices and their risks and benefits.

DISCUSSION OF FINDINGS

New information about the study

If we find out any new information that may affect your choice to participate in this study, we will get in touch with you to explain what we have learned. This may be information we have learned while doing this study here at the NIH or information we have learned from other scientists doing similar research in other places.

Return of research results

When we are examining your DNA, it is possible that we could identify possible changes in other parts of your DNA that are not related to this research. These are known as "incidental medical findings".

These include:

- Changes in genes that are related to diseases other than cancer
- Changes in genes that are not known to cause any disease. These are known as normal variations.
- Changes in genes that are new and of uncertain clinical importance. This means that we do not know if they could cause or contribute to a disease or if they are normal variations.

Since the analyses that we perform in our laboratory are not nearly as sensitive as the tests that are performed in a laboratory that is certified to perform genetic testing, the genetic changes that we find may or may not be valid. Therefore, we do not plan to inform you of all of the genetic results of testing on your tissue and blood that is performed in our research lab. However, in the unlikely event that we discover a finding believed to be clinically important based on medical standards at the time we first analyze your results, we will contact you. This could be many years in the future. We will ask you to have an additional tube of blood drawn to verify the findings we have seen in our lab. If the results are verified, you will be re-contacted and offered a referral to a genetic healthcare provider to discuss the results.

EARLY WITHDRAWAL FROM THE STUDY

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 worsens or comes back during treatment
- if you have side effects from the treatment that your doctor thinks are too severe
- if you become pregnant
- if the M7824 and/or TriAd vaccine and/or N-803 may become unavailable
- if new information shows that another treatment would be better for you
- if you do not follow the study rules
- if the study is stopped for any reason

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

After therapy is stopped, we would like to see you for a safety visit after around one month of your last dose.

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 EMD Serono and Immunity bio (previously NantCell) or designated representatives.

STORAGE, SHARING AND FUTURE RESEARCH USING YOUR SPECIMENS AND DATA

Will Your Specimens or Data Be Saved for Use in Other Research Studies?

As part of this study, we are obtaining specimens and data from you. We will remove all the identifiers, such as your name, date of birth, address, or medical record number and label your specimens and data with a code so that you cannot easily be identified. However, the code will be linked through a key to information that can identify you. We plan to store and use these specimens and data for studies other than the ones described in this consent form that are going on right now, as well as studies that may be conducted in the future. These studies may provide additional information that will be helpful in understanding head and neck cancer, or other diseases or conditions. This could include studies to develop other research tests, treatments, drugs, or devices, that may lead to the development of a commercial product by the NIH and/or its research or commercial partners. There are no plans to provide financial compensation to you if this happens. Also, it is unlikely that we will learn anything from these studies that may directly benefit you.

I give permission for my coded specimens and data to be stored and used for future research as described above.

_____ Yes _____ No

Initials Initials

Will Your Specimens or Data Be Shared for Use in Other Research Studies?

We may share your coded specimens and data with other researchers. If we do, while we will maintain the code key, we will not share it, so the other researchers will not be able to identify you. They may be doing research in areas similar to this research or in other unrelated areas. These researchers may be at NIH, other research centers and institutions, or commercial entities.

I give permission for my coded specimens and data to be shared with other researchers and used by these researchers for future research as described above.

_____ Yes _____ No

Initials Initials

If you change your mind and do not want us to store and use your specimens and data for future research, you should contact the research team member identified at the top of this document. We will do our best to comply with your request but cannot guarantee that we will always be able to destroy your specimens and data. For example, if some research with your specimens and data has already been completed, the information from that research may still be used. Also, for example, if the specimens and data have been shared already with other researchers, it might not be possible to withdraw them.

In addition to the planned use and sharing described above, we might remove all identifiers and codes from your specimens and data and use or share them with other researchers for future research at the NIH or other places. When we or the other researchers access your anonymized data, there will be no way to link the specimens or data back to you. We will not contact you to ask your permission or otherwise inform you before we do this. We might do this even if you answered "no" to the above questions. If we do this, we would not be able to remove your specimens or data to prevent their use in future research studies, even if you asked, because we will not be able to tell which are your specimens or data.

NIH policies require that your clinical and other study data be placed in an internal NIH database that is accessible to other NIH researchers for future research. These researchers will not have access to any of your identifiers, such as your name, date of birth, address, or medical record number; and your data will be labeled with only a code. We cannot offer you a choice of whether your data to be placed in this database or not. If you do not wish to have your data placed in this database, you should not enroll in this study.

Will Your Genomic Data Be Shared Outside of This Study?

As part of this research study, we will put your genomic data in a large database for broad sharing with the research community. These databases are commonly called data repositories. The information in this database will include but is not limited to genetic information, race and ethnicity, and sex. If your individual data are placed in one of these repositories, they will be labeled with a code and not with your name or other information that could be used to easily identify you, and only qualified researchers will be able to access them. These researchers must

receive prior approval from individuals or committees with authority to determine whether these researchers can access the data.

Summary information about all of the participants included in this study (including you*)* is being placed in a database and will be available through open access. That means that researchers and non-researchers will be able to access summary information about all the participants included in the study, or summary information combined from multiple studies, without applying for permission. The risk of anyone identifying you with this information is very low.

As part of this study, we will put your genomic data in a large database which will be freely available to the public. These databases are commonly called data repositories. These data are intended for other researchers to use and learn from but anyone can gain access to them, including law enforcement. The information in this database will include but is not limited to genetic information, race, ethnicity and sex. If your individual data are placed in one of these repositories, they will be labeled with a code and not with your name or other information that could be used to easily identify you. This information when combined with information from other public sources could be used to identify you, though we believe it is unlikely that this will happen.

NIH policies require that genomic data be placed in a repository for sharing. Therefore, we cannot offer you a choice of whether your data will be shared. If you do not wish to have your data placed in a repository, you should not enroll in this study.

How Long Will Your Specimens and Data be Stored by the NIH?

Your specimens and data may be stored by the NIH indefinitely.

Risks of Storage and Sharing of Specimens and Data

When we store your specimens and data*,* we take precautions to protect your information from others that should not have access to it. When we share your specimens and data, we will do everything we can to protect your identity, for example, when appropriate, we remove information that can identify you. Even with the safeguards we put in place, we cannot guarantee that your identity will never become known or someone may gain unauthorized access to your information. New methods may be created in the future that could make it possible to re-identify your specimens and data.

COMPENSATION, REIMBURSEMENT, AND PAYMENT

Will you receive compensation for participation in the study?

Some NIH Clinical Center studies offer compensation for participation in research. The amount of compensation, if any, is guided by NIH policies and guidelines.

You will not receive compensation for participation in this study.

Will you receive reimbursement or direct payment by NIH as part of your participation?

Some NIH Clinical Center studies offer reimbursement or payment for travel, lodging or meals while participating in the research. The amount, if any, is guided by NIH policies and guidelines.

On this study, the NCI will cover the cost for some of your expenses. Some of these costs may be paid directly by the NIH and some may be reimbursed after you have paid. Someone will work with you to provide more information.

Will taking part in this research study cost you anything?

NIH does not bill health insurance companies or participants for any research or related clinical care that you receive at the NIH Clinical Center.

- If some tests and procedures are performed outside the NIH Clinical Center, 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 NIH Clinical Center.
- Once you have completed taking part in the study, medical care will no longer be provided by the NIH Clinical Center.

CONFLICT OF INTEREST(COI)

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

The NIH and the research team for this study are using drugs and vaccine developed by EMD Serono and Immunity Bio (previously NantCell) through a joint study with your study team and the companies. The companies also provide financial support for this study.

CLINICAL TRIAL REGISTRATION AND RESULTS REPORTING

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.

CONFIDENTIALITY PROTECTIONS PROVIDED IN THIS STUDY

Some of your health information, and/or information about your specimen, from this study will be kept in a central database for research. Your name or contact information will not be put in the database. Your test results will be identified by a unique code and the list that links the code to your name will be kept separate from your sample and health information. Your information may be given out if required by law. For example, certain states require doctors to report to health boards if they find a disease like tuberculosis. However, the researchers will do their best to make sure that any information that is released will not identify you.

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 and other government agencies, like the Food and Drug Administration (FDA), which are involved in keeping research safe for people.
- National Institutes of Health Intramural Institutional Review Board
- The study Sponsor Center for Cancer Research or their agent(s)
- Qualified representatives from EMD Serono, the pharmaceutical company who produces M7824 and Immunity Bio (previously NantCell), the pharmaceutical company who produces N-803 and TriAd vaccine.

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.

If we share your specimens or data with other researchers, in most circumstances we will remove your identifiers before sharing your specimens and data. You should be aware that there is a slight possibility that someone could figure out the information is about you.

Further, the information collected for this study is protected by NIH under a Certificate of Confidentiality and the Privacy Act.

Certificate of Confidentiality

To help us protect your privacy, the NIH Intramural Program has received a Certificate of Confidentiality (Certificate). With this certificate, researchers may not release or use data or information about you except in certain circumstances.

NIH researchers must not share information that may identify you in any federal, state, or local civil, criminal, administrative, legislative, or other proceedings, for example, if requested by a court.

The Certificate does not protect your information when it:

1. is disclosed to people connected with the research, for example, information may be used for auditing or program evaluation internally by the NIH; or
2. is required to be disclosed by Federal, State, or local laws, for example, when information must be disclosed to meet the legal requirements of the federal Food and Drug Administration (FDA);
3. is for other research;
4. is disclosed with your consent

The Certificate does not prevent you from voluntarily releasing information about yourself or your involvement in this research.

The Certificate will not be used to prevent disclosure to state or local authorities of harm to self or others including, for example, child abuse and neglect, and by signing below you consent to those disclosures. Other permissions for release may be made by signing NIH forms, such as the Notice and Acknowledgement of Information Practices consent.

Privacy Act

The Federal Privacy Act generally protects the confidentiality of your NIH medical records we collect under the authority of the Public Health Service Act. In some cases, the Privacy Act protections differ from the Certificate of Confidentiality. For example, sometimes the Privacy Act allows release of information from your medical record without your permission, for example, if it is requested by Congress. Information may also be released for certain research purposes with due consideration and protection, to those engaged by the agency for research purposes, to certain federal and state agencies, for HIV partner notification, for infectious disease or abuse or neglect reporting, to tumor registries, for quality assessment and medical audits, or when the NIH is involved in a lawsuit. However, NIH will only release information from your medical record if it is permitted by both the Certificate of Confidentiality and the Privacy Act.

POLICY REGARDING RESEARCH-RELATED INJURIES

The NIH 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 NIH, the NIH Clinical Center, or the Federal Government. However, you have the right to pursue legal remedy if you believe that your injury justifies such action.

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, Jason M. Redman at jason.redman@nih.gov or 240-858-3305. You may also call the NIH Clinical Center Patient Representative at 301-496-2626, or the NIH Office of IRB Operations at 301-402-3713, if you have a research-related complaint or concern.

CONSENT DOCUMENT

Please keep a copy of this document in case you want to read it again.

Adult Research Participant: I have read the explanation about this study and have been given the opportunity to discuss it and to ask questions. I consent to participate in this study.

Signature of Research Participant	Print Name of Research Participant	Date

Legally Authorized Representative (LAR) for an Adult Unable to Consent: I have read the explanation about this study and have been given the opportunity to discuss it and to ask questions. I am legally authorized to make research decisions on behalf of the adult participant unable to consent and have the authority to provide consent to this study. As applicable, the information in the above consent was described to the adult participant unable to consent who agrees to participate in the study.

Signature of LAR	Print Name of LAR	Date

Investigator:

Signature of Investigator	Print Name of Investigator	Date

Witness should sign below if either:

1. **A short form consent process has been used to enroll a non-English speaking subject or**
2. **An oral presentation of the full consent has been used to enroll a blind or illiterate subject**

Signature of Witness*	Print Name of Witness	Date

***NIH ADMINISTRATIVE SECTION TO BE COMPLETED REGARDING THE USE OF AN INTERPRETER:**

____ An interpreter, or other individual, who speaks English and the participant's preferred language facilitated the administration of informed consent and served as a witness. The investigator obtaining consent may not also serve as the witness.

____ An interpreter, or other individual, who speaks English and the participant's preferred language facilitated the administration of informed consent but did not serve as a witness. The name or ID code of the person providing interpretive support is: _____.