PRINCIPAL INVESTIGATOR: James Gulley, MD, PhD.

STUDY TITLE: Phase I/II Trial Investigating the Safety, Tolerability, Pharmacokinetics, Immune and Clinical Activity of **S**X-682 in Combination with Bin**T**rafusp **A**lfa (M7824 or TGF-β "Trap"/PD-L1) with CV301 **T**RICOM in Advanced Solid Tumors (STAT).

STUDY SITE: NIH Clinical Center

Cohort: Affected patients

Consent Version: 03/18/2022

WHO DO YOU CONTACT ABOUT THIS STUDY?

James Gulley, MD, PhD, [redacted]

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 in making your decision about participating in this study. Additional information that may help you decide can be found in other sections of the document. Taking part in research at the NIH is your choice.

You are being asked to take part in this study because you have been diagnosed with a metastatic cancer, which may be Triple Negative Breast Cancer (TNBC) or p16 negative Head and Neck Squamous Cell Cancer (HNSCC) and your doctor has found that you are not a candidate for curative surgery. You may also be asked to participate in the first part of the study only (see description below),if you have a solid tumor.

The purpose of this study is to find a safe dose of SX-682 in combined treatment with M7824 and CV301 vaccines and to see if this combined treatment will cause your tumors to shrink.

The use of SX-682, M7824 and CV301 vaccines in this study is considered investigational which means these drugs have not been approved by the U.S. Food and Drug Administration (FDA) to treat cancer. However, the FDA has given us permission to use these drugs in this study.

SX-682 and M7824 are drugs that block the pathways that cancer cells use to prevent your immune system from fighting your cancer. 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.

CV301 vaccines (MVA-BN-CV301 and FPV-CV301) are designed to create immune cells that can recognize and kill certain types of cancer.

There are other standard of care drugs and/or procedures that may be used to treat your disease, and these can be given to you by your regular cancer doctor if you are not in this study. For example: there is chemotherapy and radiation therapy. The treatment given in this study and the known possible side effects may or may not be significantly different than if you were to receive standard care or participate in another clinical trial.

SX-682 and M7824 have been found to decrease blood counts (anemia), cause bleeding, problems with heart, kidney, the immune system and other organs. 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. The CV301 vaccines may cause fever, flu-like symptoms, chills and nausea.

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

- First, we will perform tests to find out if you fit the study requirements. We will do standard blood tests and scans to test your health and see the status of your disease.
- The study is divided into 3 parts. In part 1 we will try to find the safe dose of SX-682 by itself and then followed by treatment with M7824 and CV301 vaccines. In part 2, we will try to find the safe dose of SX-682 combined with M7824 and CV301 vaccines. In part 3, we will try to find out if the safe dose of SX-682 in combined treatment with M7824 and CV301 vaccines from part 1 or 2 is effective in shrinking your tumor.
- Depending on when you enter the study, you will have treatment with the following drugs for up to 2 years.
    - SX-682 alone for 2 weeks followed by treatment with M7824 and CV301 vaccines (group 1),
    - SX-682 alone for 2 weeks followed by combination treatment with SX-682, M7824 and CV301 vaccines (group 2),
    - SX-682, M7824 and CV301 vaccines in combination (group 3)

  You cannot choose which part of the study to enroll in; enrollment will occur in sequential fashion, meaning that participants will enroll as they are screened and determined to be eligible.
- If you fit the study requirements and decide to take part, you will start your treatment with SX-682 tablets that are taken by mouth twice a day. We will then send you home with a supply of SX-682 that you will need to take.
- 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 every two weeks. It could also be given through a central catheter (known as a port or mediport) if you already have one installed.

- CV301 vaccines will be given as injections under the skin in the upper arms or thighs. This is similar to receiving a vaccine shot and will be done on day 1 and 15 of the first 28-day cycle and on day 1 of each cycle for the following 4 cycles, then day 1 of every 3 cycles.
- You will not need to stay in the hospital for this study, though your doctor might decide to admit you for safety purposes. You have to come to the Clinical Center every 2 weeks while you are receiving treatment. Each visit should last no more than 8 hours. Combined treatment with three drugs will continue for one year, after that you will have treatment with M7824 and SX-682 only for another year. If you have unacceptable side effects (both drugs) or you are no longer benefiting from the study therapy, it can be stopped earlier. If you are tolerating and benefiting from the study drugs, treatment may continue after 2 years.
- At your visits, will have clinical, laboratory, and imaging tests to see how you are doing and to assess your disease. We will also collect required samples from you (such as: blood and tissue) for both clinical and research purposes.
- As described above and later in more detail in this consent form, you may have side effects if you take part in this study. Some can be mild or very serious, temporary, long-lasting, or permanent, and may include death. You will be seen regularly during the study. You will have clinical, laboratory, and imaging tests to see how you are doing and see how your disease is responding. We will also collect samples from you (such as blood and tumor tissues) for both clinical and research purposes. Some of the samples are required and some are optional.
- After the study treatment has ended, we would like to see you in the Clinical Center once or twice for first month. If you stop treatment for reasons other than worsening of your disease, we will continue to invite you for imaging studies approximately every 3 months until your disease gets worse. You can also have these studies done locally and send us the results. If your disease gets worse, we will contact you by phone or e-mail every year for 2 years to check on your health.
- You will need to practice an effective form of birth control during the study treatment and for 6 months after you finish study treatment (the restricted period).
- Some drugs and vaccines are not allowed during this study. Please let you doctor know about all medicines you are taking or planning to take.

This study may benefit you by shrinking of your tumor or lessening of your symptoms, such as pain, that are caused by the cancer. Even if you do not benefit from this study, the results from our research will help others in the future.

You are free to stop taking part in the trial at any time. If you decide to stop, the study doctor may ask you to agree to certain tests or have you follow up with your own doctor to make sure you are safe.

The remaining document will now describe the research study in more detail. This information should be considered before you make your choice. Members of the study team will talk with you

about the information in this document. Some people have personal, religious, or ethical beliefs that may limit the kinds of medical or research interventions in which they would want to participate. Take the time you need 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 for themselves, you, as the Legally Authorized Representative, will be their decision-maker and, you are being asked to give permission for this person to be in this study. For the remainder of this document. the term "you" refers to you as the decision-maker and/or the individual being asked to participate in this research

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?

The purpose of this study is to find a safe dose of SX-682 in combined treatment with M7824 and CV301 vaccines and to see if this combined treatment will cause your tumors to shrink.

We are asking you to join this research study because you have been diagnosed with a metastatic cancer, which may be Triple Negative Breast Cancer (TNBC) or p16 negative Head and Neck Squamous Cell Cancer (HNSCC) and your doctor has found that you are not a candidate for curative surgery. You may also be asked to participate in the first part of the study only if you have a solid tumor.

The use of SX-682, M7824 and CV301 vaccines in this study is considered investigational which means this combination has not been approved by the U.S. Food and Drug Administration (FDA) to treat cancer. However, the FDA has given us permission to use these drugs in this study.

SX-682 and M7824 are drugs that blocks pathways that cancer cells use to prevent your immune system from fighting your cancer.

CV301 vaccines (MVA-BN-CV301 and FPV-CV301) are designed to create immune cells that can recognize and kill certain types of cancer.

The study is broken into 3 parts. In part 1 we will try to find the safe dose of SX-682 by itself and then followed by treatment with M7824 and CV301 vaccines. In part 2, we will try to find the safe dose of SX-682 combined with M7824 and CV301 vaccines. In part 3, we will try to find out if the safe dose of SX-682 in combined treatment with M7824 and CV301 vaccines from part 2 is effective in shrinking your tumor.

WHAT WILL HAPPEN DURING THE STUDY?

If you take part in parts 1 or 2 of the study, you will take SX-682 alone by mouth during first 2 weeks.

After that you will get combined treatment in cycles (1 Cycle = 28 days).

Depending on the time you enter the study, you will continue treatment with M7824 + CV301 vaccines (group 1), or continue treatment with M7824 + CV301 vaccines + SX-682 (group 2).

If you are enrolled during part 3 of the study, you will receive a combination of SX-682, M7824 and CV301 from the begining of study.

M7824 will be given to you through an IV (intravenous catheter, a small plastic tube that is put into a vein, usually in your arm) once every 2 weeks (on days 1 and 15 of every cycle).

CV301 vaccines will be given as injections under the skin in the upper arms or thighs. This is similar to receiving a vaccine shot and will be done on day 1 and 15 of cycle 1, on day 1 of each cycle for the following 4 cycles and then on day 1 of every 3 cycles.

SX-682 should be taken by mouth 2 times a day. Try to space your doses out evenly throughout the day, so ideally, take a dose between 6-9 am and between 6-9 pm with approximately 1 cup (240 mL) of water. You should take tablets at least two hours after a solid meal and at least one hour before the next solid meal. If you need to take your SX-682 earlier than scheduled or you missed a dose, you can take it up to 2 hours before or after the scheduled time. If you vomit after taking SX-682, please, do not immediately take another tablet unless the tablet is visible. You should simply proceed with next dose as scheduled.

You will be given a Medication Diary to complete for each cycle. In the diary, you will be asked to record the date and time of each dose of SX-682. You will also be asked to record missed doses. Please bring the diary with you to every study visit.

At each visit, please also bring all empty bottles and any unused medication you may have.

If your doctor is convinced that you have unacceptable side effects caused by one of the treatment drugs, this drug will be stopped, and you may continue treatment with the other drug(s) if your study doctor finds that it is in your interest.

Combined treatment with all three (M7824, SX-682 and CV 301) drugs/vaccine will continue for one year, after that you will have treatment with M7824 and SX-682 only for another year. If you have unacceptable side effects (both drugs) or you are no longer benefiting from the study therapy, it can be stopped earlier. If you are tolerating and benefiting from the study drugs, treatment may continue after 2 years.

Before you begin the study

Before you begin this study, you will need to have standard clinical exams and tests to make sure you are eligible for this study. The exams and tests are part of regular cancer care. These tests will be done under a separate protocol.

You will also be asked to provide documentation to confirm your diagnosis. If documentation is not available, we will perform a biopsy (collect a sample of your tumor) to confirm your diagnosis.

If treatment does not start within 28 days before initiation of study therapy, some tests may need to be repeated.

During the study

Ongoing procedures before treatment, and on days 1 and 15 of every cycle:

- Physical examination, including weight and vital signs.
- Electrocardiogram (EKG – a record of your heartbeat) to evaluate your heart (up until cycle 6).
- Discussion of any symptoms you might be having and review of your medications.
- Routine blood tests to find out if you are anemic, have low blood counts, and if your liver, kidneys, thyroid, clotting system and other organs are working well
- Pregnancy test if you are a woman who can have children before taking the drug on days 1 only.

Ongoing procedures before and during treatment:

- Imaging assessments/scans – either a CT (a series of x-ray images taken of parts of your body) or if you cannot have a CT scan, MRI (magnetic testing, which does not involve any radiation) of chest, abdomen and pelvis at 6 weeks after starting treatment then every 8 weeks after that (groups 1 and 2), or every 8 weeks (group 3).
  - A computer tomography (CT) scan produces a series of x ray images taken of parts of your body.
  - Magnetic resonance imaging (MRI) uses a strong magnetic field and radio waves to take pictures of your body. The MRI scanner is a metal cylinder surrounded by a strong magnetic field. During the MRI, you will lie on a table that can slide in and out of the cylinder. We will place soft padding or a coil around your head. You will be in the scanner about 30 minutes. You may be asked to lie still for up to 30 minutes at a time. While in the scanner you will hear loud knocking noises, and you will be fitted with earplugs or earmuffs to muffle the sound. You will be able to communicate with the MRI staff at all times during your scan, and you may ask to be moved out of the machine at any time.
- Flexible pharyngolaryngoscopy – procedure to look into your throat and larynx, or voice box using laryngoscope, a small plastic tube with tiny video camera, that put into your nose (before treatment and during treatment if you have head or neck cancer and your doctor thinks it is necessary).
- Each visit should last no more than 8 hours.

When you are finished taking the drugs (treatment)

Within 30 days after you have finished taking the study drug, you will be asked to return to the Clinical Center once or twice for end of treatment and/or safety follow up visits. At these visits, you will be asked questions about your health, get a physical exam and undergo blood tests.

If you have been taken off treatment for reasons other than worsening of your disease, you will continue to have imaging studies approximately every 3 months until your disease worsens. You can have these studies at home institution and send us results.

If you are unable to return for these visits, we will obtain the information from you by telephone or e-mail.

Once you stop coming to Clinical Center for safety visits and your scans, we will call or e-mail you every year for 2 years to check on your health.

Each visit should last no more than 8 hours.

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 collect samples from you and perform tests for purposes of research only. Tumor and blood samples may be used to look at the effects of therapy on your immune system, markers of tumor activity, how well tumor genes are working, to check drug level in the blood and free tumor DNA and tumor cells circulating in the blood.

Blood samples

Blood samples around 0.5 cup (~130 ml) total will be collected including all days as indicated below. This amount of blood is within the blood collection total limit (550 ml) that could be drawn from adult participants within any 8-week period.

- on first day of treatment before taking drug (groups 1 and 2)
- on first day of treatment every few hours after taking drug for up to 6 hours (group 1 only)
- on day 7 of treatment before and approximately 30 minutes after taking drug (group 1 only)
- on day 1 of cycle 1 before treatment
- on day 1 of cycle 1 at the end of M7824 infusion (group 1 and 2 only)
- on day 15 of cycle 1
- on day 1 of cycles 2 and 3 before treatment

Tumor samples

We will ask you to provide samples of your tumors from previous surgeries or biopsies if available. We also may perform three optional tumor biopsies: before therapy, at the time of first imaging study and at the time of worsening of the disease. Please see Risks from Biopsy for the risks of biopsy. You can participate in this study even if you decide not to undergo the biopsy procedures. You will be asked to sign a separate consent each time you agree to have an optional biopsy.

Tumor and blood samples collected for research purposes on this study may be used to look for specific changes in the DNA in tumors that could be used to develop new ways of diagnosing and treating cancer. DNA (also called deoxyribonucleic acid) in the 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 change in the DNA is what causes tumors to form and to grow. RNA (also called ribonucleic acid) carries the instructions from the DNA to the parts of your cells that make proteins.

To look at your RNA, we may use do what is called "RNA sequencing." This is where we will do special tests in the lab to look at the sequence, or order, of how your RNA are put together.

To determine which parts of the RNA have mutated, we will compare the RNA in your tumor cells to RNA from normal cells. We will then analyze the results from similar tumors to see if there are any changes in the RNA that are common to a particular type of tumor.

HOW LONG WILL THE STUDY TAKE?

You will come to the NIH Clinical Center to get treatment and check status of your health every two weeks for 2 years or until your disease gets worse or you have unacceptable side effects at which time, we will stop treatment. If you are tolerating and benefiting from the study drugs, treatment may continue after 2 years.

Visits will range from 4-8 hours in length.

Some of these visits may be done with your local provider if you are unable to return to the NIH.

After stopping treatment, we would like to see you regularly in the NIH Clinical until your disease worsens. If your disease gets worse, we will contact you during the following 2 years to check on your health.

HOW MANY PEOPLE WILL PARTICIPATE IN THIS STUDY?

We plan to have up to 105 people take part in this study.

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

The drug used in this study may affect how different parts of your body work such as your liver, kidneys, heart, and blood. The study doctor will be testing your blood and will let you know if changes occur that may affect your health.

Here are important points about side effects:

- The study doctors do not know who will or will not have side effects.
- Some side effects may go away soon, some may last longer.
- Some side effects may be serious and may even result in death.

Here are important points about how you and the study doctor can make side effects less of a problem:

- Tell the study doctor if you notice or feel anything different so they can see if you are having a side effect.
- The study doctor may be able to treat some side effects.
- The study doctor may adjust the study drugs to try to reduce side effects.

SX-682

- Low blood cell counts, which may lead to anemia, bleeding, or infection.
- Problems with your heart noted on electrocardiogram (EKG – a record of your heartbeat)

- Widespread immune activation known as "cytokine storm", which may include fever, muscle aches, confusion, drop in blood pressure, difficulty breathing, or kidney failure.
- Tumor lysis syndrome (TLS) is caused by the sudden, rapid death of cancer cells in response to treatment. When cancer cells die, they may spill their inner (intracellular) contents, which accumulate faster than they can be eliminated. This debris from the cancer cells can change the balance of the chemistry of the body, which can be dangerous. Symptoms of tumor lysis syndrome include severe nausea and vomiting, shortness of breath, an irregular heartbeat, kidney failure, urine abnormalities, severe fatigue and/or joint pain.
- Immune suppression, which may lead to infection.
- Increase in frequency and/or severity of immune-related adverse events of M7824 and/or CV301, which may make worse the side effects of the other drugs you will take (see under M7824 and CV301).

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)
- Skin growths called keratoacanthomas that resemble skin cancer. These usually go away after treatment and can leave a scar.
- Rash, blisters, skin discoloration and other skin abnormalities
- Bleeding has been frequently observed in patients receiving M7824. Patients may experience bleeding in different sites such as gums, nose, ears, eyes, vagina, breast); have blood in the urine or stool; cough up or vomit blood; or have bleeding in internal organs, including within the lungs and gastrointestinal tract, the brain or head. . Occasionally, this bleeding can be serious and potentially life threatening or fatal. If the bleeding is severe you may require 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, or if you take aspirin or prescription medication to thin your blood.

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

Occasional (occurring in less than 5% of patients)

- Chills (feeling cold)
- Shortness of breath
- 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
- Stroke
- Slow wound healing. If you are having surgery please discuss with your doctor.
- Thickening of the skin, nails

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.

Allergic reactions or reactions related to the infusions might occur during treatment.

Although M7824 is a fully human protein the risk cannot be completely excluded. Usually, these reactions are mild to moderate and can be treated with drugs, but in very rare cases they can also be severe, life-threatening which require advanced cardiac life support, or fatal.

For the prevention of infusion-related side effects and possible allergic reactions you may receive a premedication of an antihistamine drug (Benadryl® or similar) and acetaminophen (Tylenol®) 30 to 60 minutes before the infusion.

There is a risk for keratoacanthomas, a type of skin lesion. These appear as small bumps and have the potential to turn into squamous cell carcinoma skin cancer gradually over time. We work with a dermatologist at the NIH. If you develop a keratoacanthoma while on this study, we will make every attempt to prevent progression to skin cancer. The dermatologist will monitor you regularly and can remove these lesions if indicated.

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

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

Types of immune-related side effects:

- joint pain
- arthritis (inflammatory disease of the joint)
- 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)
- hyperthyroidism (increased function of thyroid gland)
- thyroiditis (inflammatory disease of the thyroid gland)
- autoimmune hepatitis (inflammatory disease of the liver caused by the body's immune system): 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)
- dry eyes
- inflammatory eye disease
- diabetes mellitus (high blood sugar levels)
- Problems with your adrenal glands (Adrenal Insufficiency): 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

- 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
- Autoimmune encephalitis is a type of brain inflammation where the body's immune system attacks healthy cells and tissues in the brain or spinal cord
- psoriasis
- autoimmune disorder (body's immune system attacks its own cells) potentially affecting any area of the body and can result in swelling, pain, and/or organ dysfunction
- myocarditis (inflammation of the heart muscle)
- skin rash with blisters that can be itchy
- 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
- Pancreatitis (inflammation of the pancreas)
- 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.

CV301 vaccines

Likely

- Injection-site reaction (pain or discomfort, itching, redness, firmness, swelling, skin thickening, or bumps)
- Flu-like symptoms (fatigue, soreness, general body pain, abdominal pain, cough, fever, headache)

Less Likely

- Acute fever
- Chills
- Chest tightness
- Shortness of breath
- Arm or leg pain and/or swelling
- Headache
- Loss of appetite
- Weight loss
- Diarrhea
- Constipation
- Rash
- Nausea
- Dizziness
- Mild inflammation of tissue lining the lungs
- Chronic inflammation of the skin
- Difficulty sleeping
- Open sores (ulcers) at the injection site
- Bruising at the injection site
- Warmth at the injection site
- Enlarged lymph nodes
- Low blood levels of sodium
- Inflammation of the testicles
- Inflammation of thyroid tissue
- Joint pain

Rare but Serious

- Difficulty breathing
- Low blood pressure
- Wheezing
- Clots in the lung
- Clots in the leg

- Kidney damage
- Decreased blood oxygen levels
- Fluid around the lining of the lungs
- Fluid around the lining of the heart

Risks from Biopsy

This procedure usually causes only brief discomfort at the site from which the biopsy is taken. Rarely, infection or bleeding may occur at the needle site.

Risks from Blood Collection

Side effects of blood draws include pain and bruising in the area where the needle was placed, lightheadedness, and rarely, fainting and infection. When large amounts of blood are collected, low red blood cell count (anemia) can develop.

Risks from Contrast dye used in CT scans

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, you should notify it to the Study team. If you have had kidney problems/failure in the past, please notify it to 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 6 months after you finish study treatment (the restricted period). 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, please contact the study team as soon as possible. If you think or know you have become pregnant during the restricted period, please contact the research team member identified at the top of this document 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 during 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 period, please contact the study team as soon as possible. If you and your partner plan for your partner to become pregnant after the restricted period, 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 9 CT scans (chest/abdomen/pelvis) and up to 3 CT-guided biopsies (optional). The amount of radiation exposure you will receive from these procedures is equal to approximately 12.3 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." This study will expose you to more radiation than you get from everyday background radiation. No one knows for sure whether exposure to these low amounts of radiation is harmful to your body.

The CT scans that you get in this study will expose you to the roughly the same amount of radiation as 41 years of background radiation. Being exposed to too much radiation can cause harmful side effects such as an increase in the risk of cancer. The risk depends on how much radiation you are exposed to. Please be aware that about 40 out of 100 people (40%) will get cancer during their lifetime, and 20 out of 100 (20%) will die from cancer. The risk of getting cancer from the radiation exposure in this study is 1.2 out of 100 (1.2%) and of getting a fatal cancer is 0.6 out of 100 (0.6 %).

Risks of MRI

People are at risk for injury from the MRI magnet if they have some kinds of metal in their body. It may be unsafe for you to have an MRI scan if you have pacemakers or other implanted electrical devices, brain stimulators, some types of dental implants, aneurysm clips (metal clips on the wall of a large artery), metal prostheses (including metal pins and rods, heart valves, and cochlear implants), permanent eyeliner, tattoos, an implanted delivery pump, or shrapnel fragments. Welders and metal workers may have small metal fragments in the eye. You will be screened for these conditions before having any MRI scan. If you have a question about metal in your body, you should inform the staff. You will be asked to complete an MRI screening form before each MRI scan you have.

In addition, all magnetic objects (like watches, coins, jewelry, and credit cards) must be removed before entering the MRI scan room.

People with fear of confined spaces may become anxious during an MRI. Those with back problems may have back pain or discomfort from lying in the scanner. The noise from the scanner is loud enough to damage hearing, especially in people who already have hearing loss. Everyone having a research MRI scan will be fitted with hearing protection. If the hearing protection comes loose during the scan, you should let us know right away.

There are no known long-term risks of MRI scans

Risks of gadolinium enhanced MRI

The risks of an IV catheter include bleeding, infection, or inflammation of the skin and vein with pain and swelling.

Mild symptoms from gadolinium infusion occur in fewer than 1% of those who receive it and usually go away quickly. Mild symptoms may include coldness in the arm during the injection, a metallic taste, headache, and nausea. In an extremely small number, fewer than one in 300,000 people, more severe symptoms have been reported including shortness of breath, wheezing, hives, and lowering of blood pressure. You should not receive gadolinium if you previously had an allergic reaction to it. You will be asked about such allergic reactions before gadolinium is given.

People with kidney disease are at risk for a serious reaction to gadolinium contrast called "nephrogenic systemic fibrosis (NSF)". This condition always involves the skin and can also involve the muscles, joints and internal organs. NSF has resulted in a very small number of deaths.

A blood test of your kidney function may be done within the month before an MRI scan with gadolinium contrast. You will not receive gadolinium for a research MRI scan if your kidney function is below the safe level.

Most of the gadolinium contrast leaves the body in the urine. However, the FDA has issued a safety alert that indicates small amounts of gadolinium may remain in the body for months to years. The long-term effects of the retained gadolinium are unknown. Some types of gadolinium contrast drugs are less likely to remain in the body than others. In this study, we will use the gadolinium contrast drugs that are less likely to remain in the body.

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 include shrinking of your tumor or lessening of your symptoms, such as pain, that are caused by the cancer.

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, 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.

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

Results of research studies performed on this study will not be shared with you.

EARLY WITHDRAWAL FROM THE STUDY

Your doctor may decide to stop your therapy for the following reasons:

- if your disease worsens or comes back during treatment
- if you become pregnant
- if you have side effects from the treatment that your doctor thinks are too severe
- if you need treatment that is not allowed on this study

- if study drugs become unavailable
- if new information shows that another treatment would be better for you
- 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 30 days after 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, Bavarian Nordic, Syntrix 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 colorectal 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 that are similar to this study 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.

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. The amount and form of these payments are determined by the NCI Travel and Lodging Reimbursement Policy. You will be given a summary of the policy which provides 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 National Institutes of Health and the research team for this study have developed CV301 being used in this study. This means it is possible that the results of this study could lead to payments to NIH. By law, the government is required to share such payments with the employee inventors. You will not receive any money from the development of CV301.

The NIH and the research team for this study are using SX-682, M7824 and CV301 vaccines developed by Syntrix, EMD Serono and Bavarian Nordic through a joint study with your study team and the company. These 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 NIH 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 of National Cancer Institute.
- Qualified representatives from Syntrix, EMD Serono or Bavarian Nordic, the pharmaceutical companies who provides SX-682, M7824 and CV301 vaccines.

The researchers conducting this study and the NIH follow applicable laws and policies to keep your identifying information private to the extent possible. However, there is always a chance that, despite our best efforts, your identity and/or information about your participation in this research may be inadvertently released or improperly accessed by unauthorized persons.

In most cases, the NIH will not release any identifiable information collected about you without your written permission. However, your information may be shared as described in the section of this document on sharing of specimens and data, and as further outlined in the following sections.

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 information that 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 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, James Gulley, MD, PhD [redacted] You may also call the NIH [redacted] 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: _____.