PRINCIPAL INVESTIGATOR: Ravi Madan, M.D.

STUDY TITLE: Phase II Trial of Combination Immunotherapy in Biochemically Recurrent Prostate Cancer

STUDY SITE: NIH Clinical Center

Cohort: *Patients with advanced castration resistant prostate cancer and patients with biochemically recurrent prostate cancer*

Consent Version: *04/26/2023*

WHO DO YOU CONTACT ABOUT THIS STUDY?

Principal Investigator: Ravi Madan, M.D. [redacted]

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). 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. Taking part in research at the NIH is your choice.

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?

Androgen deprivation therapy (ADT) and close clinical monitoring are one standard therapy option for prostate cancer patients who have biochemical progression (rise in PSA) after local radiation or surgery therapy. This group of patients are also referred to as biochemical recurrent (BCR) prostate cancer patients. Another approach is monitoring of patients and their PSA values over time. This study was initially done to determine if combination treatment of immunotherapy drugs called PROSTVAC, CV301, and MSB0011359C (M7824) can induce an anti-tumor attack. These drugs are investigational drugs that have not yet been approved by the

U.S. Food and Drug Administration (FDA). However, as M7824 had more unwanted side effects than we expected, we will no longer give it on this study. We will still continue to assess persons who have received at least one dose of M7824 for changes in PSA.

This study comprises two parts: the first part of the study, called the lead-in portion of the study, is designed to test the safety of the dose being given for participants with castration-resistant prostate cancer. This is done because this drug is in the early stages of being tested in humans. Six participants will be included in this part of the study.

The second part of the study will test if the drugs can decrease PSA values for participants with biochemical recurrent prostate cancer and continue to test the safety of the drugs.

WHY ARE YOU BEING ASKED TO TAKE PART IN THIS STUDY?

You are being asked to take part in this study because:

For the first part (lead-in) part of the study: You have castration-resistant prostate cancer.

For the second part of the study: You have been diagnosed with biochemical recurrent prostate cancer.

HOW MANY PEOPLE WILL TAKE PART IN THIS STUDY?

We plan to enroll up to 40 participants in the study.

DESCRIPTION OF RESEARCH STUDY

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

Before you begin the study:

You will need to have a physical exam, blood tests and scans to find out if you can be in the study. The exams and tests are part of regular cancer care and may be done even if you do not join the study. However, there are some extra exams, tests and procedures that you will need to have if you take part in this study. If you had some of the tests recently, they may not need to be repeated.

These tests include:

- Medical history and physical exam
- Blood tests including a complete blood count, chemistry panel, testosterone and prostate-specific antigen (PSA) levels
- Urine tests
- CT scan of chest/abdomen/pelvis
- Bone scan
- Human immunodeficiency virus (HIV) test.

As part of this study, we will test you for infection with HIV, the virus that causes AIDS. If you are infected with HIV, you will not be able to take part in this study. We will tell you what the results mean, how to find care, how to avoid infecting others, how we report HIV

infections, and the importance of informing your partners at possible risk because of your HIV infection

- Hepatitis B and C. If these tests are positive, you will not be eligible to participate in the study because there is a possibility the vaccine may harm you.
- A sample of tissue from any previous surgery or biopsy, if available, will be tested at NCI to confirm your diagnosis, stage, and status of your disease.

We will collect approximately 2 ½ tablespoons for routine laboratory tests during screening.

During the study:

Once you agree to participate in this study and you are fit to join, the following will occur:

- If you are participating in the biochemical recurrence portion of the study, you will undergo surveillance (close monitoring) with four consecutive monthly PSA checks followed by PROSTVAC and CV301 for 4 months (cycles 1-4) then PROSTVAC, CV301. You may have received MSB0011359C for up to 3 months, though it may have been fewer if you had not completed three months at the time it was discontinued from this study.
- If you are participating in the lead-in portion of this study, you will not undergo the surveillance period. You will go directly to cycle 1 of the study, and you will receive study drugs at the dose that is equal to the doses received by the participants in the biochemical recurrence cohort (BCR cohort), and you will receive PROSTVAC and CV301 monthly until you meet any of the conditions in the stopping therapy section.

For both portions of the study, the following drugs will be given:

- PROSTVAC vaccine regimen consists of PROSTVAC-V (priming vaccine) and PROSTVAC -F (booster vaccine). PROSTVAC will be administered as a shot under the skin as follows
  - Vaccinia version of the vaccine/ priming vaccine: on Cycle1 Day1
  - Fowlpox version of the vaccine/ booster vaccine: on Cycle1 Day15, Cycle2 Day1, Cycle3 Day1, Cycle4 Day1, Cycle5 Day1, Cycle6 Day1, Cycle7 Day1.
- The CV301 vaccine regimen consists of MVA-BN-CV301 (priming vaccine) and FPV-CV301 (booster vaccine). CV301 will be administered as a shot under the skin as follows
  - MVA-BN-CV301 version of the vaccine/ priming vaccine: on Cycle1 Day1, Cycle1 Day15
  - FPV-CV301 version of the vaccine/ booster vaccine: on Cycle2 Day1, Cycle3 Day1, Cycle4 Day1, Cycle5 Day1, Cycle6 Day1, Cycle7 Day1.
- MSB0011359C will be administered as an IV infusion starting after 4 months of concurrent PROSTVAC and CV301: on Cycle5 Day1, Cycle5 Day15, Cycle6 Day1, Cycle6 Day15, Cycle7 Day1, Cycle7 Day15.

You will be monitored with vital signs (blood pressure, heart rate, respiratory rate, temperature) prior to drug administration and for 30 minutes or 1 hour after drug administration.

While you are on study therapy, we will perform tests and exams for safety. This may include a physical exam (at each visit), routine urine tests, routine blood tests (at each visit), and

scans/imaging (Tc 99 scintigraphy or CT scan). For the biochemical recurrence part of the study, you will have imaging on day 1 of cycle 1. For the lead-in part of the study, you will have imaging on day 1 of cycles 3, 6 and 9, and every 3 months after cycle 9 until your safety visit, at which point you will be removed from study.

If you are in the lead in portion of the study, we will collect approximately the following amount of blood for routine lab tests: 3 tablespoons at the start of each cycle, day 15 of cycles 1 – 3, end of treatment and safety visit.

If you are in the biochemical recurrence portion, we will collect approximately the following amounts of blood for routine lab tests during the study: 3 tablespoons during baseline, day 1 of each cycle, on day 15 of cycles 1, 5, 6, and 7, end of treatment and during follow up.

Additional studies for research

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 perform the following for purposes of research only. The research studies include:

Research blood samples

Research tests will be done on blood taken at various times during your participation in this study: at baseline and before drug administration on Cycle1 Day1, Cycle2 Day1, and Cycle5 Day15. Each of these blood draws will take about 5 tablespoons of blood, which is within the limit that the NIH has set for the amount of blood that can be taken for research.

NaF PET Scans

For participants in the BCR cohort, you will be required to have two NaF PET scans done at any point when possible during the 4-month surveillance period and at your post treatment follow up visit. The scans will help us learn more about how PET images change over time compared to how PSA levels change. More information about the PET scans is given further into the consent.

Quality of Life (QOL) Surveys for participants in the BCR cohort

We are trying to learn about how the changes in your PSA levels affect your quality of life. To help us understand how these changes affect you, we will ask you (*if you are in the BCR cohort*) to complete 2 optional prostate cancer specific QOL surveys. If you agree to complete the surveys, it will take about 10 minutes of your time. We will ask you to take the surveys at baseline, start of treatment, month 4 and month 7 after starting treatment and approximately every 3 months thereafter until you are off study.

Stool Collection

We are also interested in learning more about the bacteria in your gut and how it can affect treatment, your PSA and your immune system. Because of this, you will be asked if you are willing to provide stool samples before you begin study treatment (during the surveillance period), after 3-4 months on treatment and after completion of 7 months of treatment. Additionally, you may be asked to ship the samples back to the research team. If that is the case, you will be provided instructions and shipping materials. The samples will be stored for future studies in an unrestricted database.

When we store your specimens and data, we take precautions to protect your information from others that should not have access to it.

The stool samples are optional. You may choose not to provide them and still participate in the study.

Yes, I wish to provide stool samples.

No, I do NOT wish to provide stool samples.

All of your samples collected for research purposes on this study (such as the tumor and normal tissue) 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.

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**."

When you are finished taking the drugs (treatment)

We would like to see you again for a safety visit within approximately 4 weeks after you have stopped taking the study drugs in order to perform the following tests:

- History and physical exam
- Blood tests including a complete blood count, chemistry panel, and prostate-specific antigen (PSA) levels
- Research blood

After the safety visit, we would still like to follow you on this study for any late side effects and to see how you do on other treatments. Follow-up visits will occur monthly for the first five

months, and after that we may contact you or your local physician every 4-8 weeks. We may request copies of tests (blood tests and imaging/scans) from your local physician.

We will also request at the safety visit that you enroll onto our Long-Term Follow-up Study 04-C-0274 which the study team can go over with you.

RISKS OR DISCOMFORTS OF PARTICIPATION

Because the drugs used in this study are investigational drugs, all possible side effects cannot be predicted. If you suffer from any of these side effects described below (or any others not listed) or you think you are experiencing a side effect during this study, please tell your study doctor immediately. Any side effects or other health issues occurring during the study will be followed up by the study doctor.

PROSTVAC

The risks, discomforts, and side effects of using both the PROSTVAC prime (Vaccinia) and PROSTVAC boost (Fowlpox) vaccines are described below.

Vaccinia Virus (Prime Vaccine)

The first vaccine injection you will receive is PROSTVAC-Vaccinia. It is made from the vaccinia virus. Vaccinia virus has been given to hundreds of millions of people worldwide to prevent the disease smallpox.

A potential problem that can occur with vaccinia vaccination is the accidental spread of the virus to another part of your body. This happens rarely (incidence 1 in 4000 in some reports), however, it is very important to protect against it. You can transfer the virus to your eye and mucous membranes (inner lining) of the nose, mouth or genitals by scratching the vaccination site and then rubbing the eye or an open skin area. If you participate in this study, you will have to take special care of your vaccination site and wash your hands often to prevent spreading the virus.

You may "shed" live virus from the vaccination site until the vaccination site heals completely. Until the site has healed completely, you could spread the virus to others. You must avoid close contact with the following people for approximately 3 weeks after the vaccinia vaccination only:

- persons with weak immune systems such as persons with leukemia or lymphoma, people with AIDS, or those receiving treatment to lower their immune system (for example, after organ transplantation).
- persons with eczema or other skin disorders that leave the skin open like surgical wounds, burns, chicken pox, or skin injuries like deep cuts.
- pregnant or breast-feeding women
- or, children under 3 years of age

"Close contact" means that these people share your house with you, are in physical contact with you, come in contact with your bed linens or clothes, and/or you take care of them and touch them.

How is the vaccine given?

In clinical studies of PROSTVAC, the vaccine is given by injection under the skin (subcutaneous). A dressing will be placed over the vaccination site to reduce the risk of accidental spreading. It is

very important that you keep the vaccination site covered. Hand washing is also necessary. A dressing is placed over the vaccination site and you will be given instructions on how to take care of it.

What other risks or side effects can I expect from the vaccinia vaccine?

Most people may get some redness and swelling in the surrounding area, approximately 1-4 inches (2-10 centimeters) in size. This lasts for about 7-14 days and may be come with itching and soreness. There is typically full healing and no leftover scarring from the subcutaneous injection. On average, vaccinia stays active in your body for about 10-14 days. Before you receive your next vaccine, you will be evaluated for any signs of bacterial infection, blisters, vesicles, (lesions seen on your skin at or around your vaccine site) or signs of vaccinia infection.

Possible side effects can also be related to allergic responses the vaccine itself. An allergic reaction to the study vaccine may be development of a rash or hives within 7 to 10 days after vaccination, which usually gets better within 2 to 4 days. Rarely, a serious allergic reaction requiring hospitalization may occur.

Serious side effects from the vaccinia vaccine are most common in young children, subjects with disorders of the immune system, and individuals with skin disorders. That is why precautions are taken to exclude such individuals from exposure.

Serious reactions such as post-vaccinia encephalomyelitis ("brain inflammation") can lead to coma and death. Growth of a large non-healing sore and death are the most severe complications after vaccination. They occur mostly in very young children who are exposed to vaccinia for the first time, or in people with weak immune system; these people are not eligible for this study and must be avoided after vaccination. The death rate for people receiving revaccination with vaccinia for smallpox is about 1 in 10 million.

These serious reactions have not been seen in any subjects treated with PROSTVAC-V to date.

If symptoms for any of the vaccinia complications listed above appear, or if close contact occurs between a vaccinia-vaccinated participants and another at risk person should happen, contact the protocol investigator or study coordinator right away. You will be given the contact information.

There are ways to treat the exposure if caught early.

Fowlpox Virus (Boost Vaccine)

PROSTVAC-F (the second and later doses of PROSTVAC) is based on fowlpox virus. Fowlpox virus naturally infects birds, not mammals, and has been researched and used in other vaccines for at least twenty years. The virus does not grow (replicate) in human cells and is not known to cause human disease. Previous studies have shown that using the fowlpox-based vaccine after the vaccinia-based vaccine causes a better clinical response compared to using the virus alone or using fowlpox before vaccinia. The vaccines including fowlpox virus have been given in research studies to both animals and humans for HIV, malaria and cancer.

What risks or side effects can I expect from the fowlpox vaccine?

Side effects from fowlpox are mild and could include injection site reactions, fever, fatigue (feeling very tired), anemia (low red blood cell count) and leucopenia (low white blood cell count). With

any experimental treatment, there is the risk of unexpected and serious or deadly complications even if they have not been seen previously.

Additional risks and side effects related to the vaccine therapy with PROSTVAC-V and PROSVTAC-F:

Likely:

- Injection site reaction (pain, swelling, itching, induration, and redness)
- Tiredness (fatigue or lethargy), general or leg weakness
- Fever
- Shaking chills (feeling cold)
- Nausea
- Swollen glands that may become bigger and tender

Less likely:

- Headache
- Allergic reaction
- Sweating
- Wound problems
- Vomiting
- Confusion and disorientation (not knowing where you are)
- Loss of appetite
- Yeast infection
- Constipation
- Cough
- Diarrhea
- Indigestion
- Facial tingling or numbness
- Muscle ache
- Itching

Rare but serious:

An uncommon blood condition called thrombotic thrombocytopenic purpura (TTP). One person treated with this vaccine developed TTP. It is not known if this was related to the vaccine or from something else. TTP is a serious disease that is associated with low blood counts (both red blood cells that carry oxygen and platelets that help your blood clot), bleeding, fever, neurologic symptoms (such as changes in level of alertness including coma, headache, difficulty speaking, confusion or paralysis) and kidney problems. The symptoms are caused by clots that form or spread

to other organs. This can usually be treated with a therapy. Should you go on this trial, we will follow you closely for any signs or symptoms of this disease.

Other Potential Side Effects

Additional side effects could be related to the immune response to the PSA and/or TRICOM proteins that are part of the vaccines. Some normal human cells (such as normal prostate cells) have these proteins on their surface. If the vaccine causes an immune reaction against these normal cells, you could develop swelling or inflammation of these tissues. While unlikely, it is also possible that if you develop a very active antibody (immune) reaction after the vaccination, you could develop something called serum sickness which can cause fevers, rashes, joint pains, and less commonly, kidney failure and swelling of the blood vessels (vasculitis) or any part of your body. None of these symptoms have been observed to date in subjects receiving the Bavarian Nordic vaccines, but the possibility of their occurrence exists.

CV301

The risks, discomforts, and side effects of using both the CV301 prime (MVA-BN-CV301) and boost (FPV-CV301) vaccines are described below.

MVA-BN-CV301 (Prime Vaccine)

The MVA-BN-CV301 priming vaccine has not been tested in humans. However, the MVA-BN portion of the vaccine, as well as other MVA-BN-derived vaccines, have been tested in over 7,700 people and have been shown to be well-tolerated with low occurrence of serious side effects. As of 31-July-2016, a total of 7 out of 7,758 vaccinated subjects reported serious adverse drug reactions to MVA-BN in completed and ongoing trials.

The most common side effects associated with MVA-BN and other MVA-BN-derived vaccines that you may experience include mild to moderate flu-like symptoms such as:

- Fever
- Chills
- Muscle or joint ache
- Tiredness (Fatigue)

In addition, you may experience some localized reactions at the site where the vaccine is injected under your skin (subcutaneously). These injection site reactions may include any or all of the following:

- Swelling
- Localized pain
- Hardness of a small area of skin around the injection site (Induration)
- Redness

As with any experimental compound, there is always a risk of unexpected and serious or deadly complications that may not have been previously observed.

FPV-CV301 (Boost Vaccine)

The FPV-CV301 vaccine has not been tested in humans. However, the FPV-CV301 boosting vaccine uses a fowlpox virus that naturally occurs in birds (not mammals /humans) and has been tested and used in other vaccines for at least twenty years. The virus does not grow (replicate) in human cells and does not cause human disease. Vaccines using fowlpox virus have been given to both animals and humans to treat HIV, malaria, and cancer.

The most common side effects that you may experience from the use of fowlpox vaccines are mild and may include the following:

- Fever
- Tiredness (Fatigue)
- Low red blood cell count (Anemia)
- Low white blood cell count (Leucopenia)

In addition, you may experience some localized reactions at the site where the boosting vaccine is injected under your skin (subcutaneously). These injection site reactions may include any or all of the following:

- Swelling
- Localized pain
- Hardness of a small area of skin around the injection site (Induration)
- Redness

As with any experimental compound, there is always a risk of unexpected and serious or deadly complications that may not have been previously observed.

MSB0011359C (M7824)Treatment with MSB0011359C (M7824) on this study has been discontinued based on an assessment of the risks and benefits of this agent in this people with your type of cancer. In the first 6 participants who received MSB0011359C (M7824) in the biochemical recurrent group (second part of the study), one participant experienced inflammation of the colon and one participant experienced inflammation in the muscle tissue of the heart, which required high doses of steroids to treat. Based on this information and no clear clinical benefit for the participants who had been treated, MSB0011359C (M7824) has been removed from the study treatment regimen.

Common side effects (occurring in more than 5% of patients):

- Fatigue (tiredness and lack of energy)
- 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 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. 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. May require a transfusion.
- Abdominal pain
- Headache
- Itching

Occasional side effects (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

- Stroke
- Slow wound healing. Tell your study doctor aware if you plan to undergo any kind of surgery while you are participating in this study.
- Thickening of the skin, nails

Infusion-related reactions including hypersensitivity (allergic reactions to the drug infusion)

Allergic reactions or reactions in the context with the infusions might occur during treatment. Although M7824 is a fully human protein the risk cannot be completely excluded. In general, these reactions are mild to moderate and can be handled with appropriate drugs, but in very rare cases severe to life-threatening (anaphylactic reaction) and even fatal reactions might occur, which require advanced cardiac life support.

For the prevention of infusion-related adverse 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 every infusion. In addition, as a preventive measure, you will undergo an overnight stay at the hospital for observation after the first two infusions of the study drug. For other doses, you will be asked to remain in the study center for at least 2 hours after the end of the infusion.

Immune-related Adverse Events (irAEs)/Autoimmune Disorders

In addition, Immune-related adverse events (irAEs)/autoimmune disorders (illnesses caused by an over activity of your body's immune-system that normally protects you from infections) are possible. The immune system normally works to protect you from things that are harmful such as infections, foreign substances, and sometimes from cancer. If the immune system is overactive, it can attack normal parts of the body because it mistakenly recognizes them as foreign/harmful.

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 (inflammation in the lungs): 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)
- You may develop inflammation of the liver called hepatitis. 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)
- Uveitis (inflammation in the eyes)

- 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
- Myositis (inflammation of a muscles characterized by pain and tenderness)
- Inflammation of the intestines (colitis). 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
- Myocarditis (inflammation of muscle of the heart)
- Pemphigoid (fluid-filled blisters that can be itchy)
- Kidney problems: you may have an increase in 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 (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 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.

Rash with hyperkeratosis/keratoacanthoma/skin cancer

There is a risk for keratoacanthoma, a certain type of skin lesion. These appear as small bumps and have the potential to turn into squamous cell carcinoma skin cancer gradually over time. Your study doctor will carefully monitor your skin for any of these changes. If a suspicious skin rash or lesion is detected, your study doctor may take a skin biopsy (small piece of tissue) for analysis in a laboratory. You may also be asked to see a skin specialist (dermatologist) for further assessment and testing. The skin lesion may need to be surgically removed.

Embryofetal toxicity

Based on how the study drug works, there is also a risk of embryofetal toxicity (risks to your unborn baby). Please read the below section ***For women*** and ***For men*** carefully.

Birth Control

Your study doctor will discuss the risks to unborn children for drugs used in this study. The effects of the study drugs, if any, on unborn children are unknown. If your partner is capable of becoming

pregnant and you wish to participate in this study, and you have not had your prostate or testicles removed, or you are not receiving continuous hormone therapy, then you must use a medically acceptable method of birth control and refrain from donating sperm while you are receiving study drugs and for a period of at least 4 months after your last dose of the study drugs.

If your partner becomes pregnant during the course of treatment, you must inform your doctor immediately. Your doctor will ensure that you and your partner receive information about options available to you in relation to pregnancy and that you and your partner are fully supported in whichever option you chose. Acceptable birth control options for you and your partner include:

- surgical sterilization (you and/or your partner)
- approved hormonal contraceptives or therapies (such as birth control pills, Depo-Provera, or Lupron Depot)
- barrier methods (such as a condom or diaphragm) used with a spermicide
- an intrauterine device (IUD)

Other Risks

The study treatment may involve risks to you that are currently unknown. Your cancer may not get better or may become worse while you are in this study.

Risks from Scans

Radiological testing, such as CT scans, Tc-99 scans and PET scans will be used to assess the treatment of your disease at various times during therapy. The cumulative radiation exposure from these tests is considered very small and is unlikely to adversely affect you or your disease. Because some of these tests require administration of contrast you could experience pain, bruising, and/or infection at the site of injection, or an allergic reaction to the contrast agent. Please notify the investigator if you know or suspect you are allergic to contrast dye.

ECG

There are no significant risks or discomforts associated with an ECG. Some patches will be adhered to your skin that may cause some reddening or slight itching.

Blood draws

Over a two-week period, approximately 6 ½ tablespoons of blood will be collected in the lead in portion and approximately 9 tablespoons of blood will be collected in the biochemical recurrence portion. There may be some side effects associated with the procedures for drawing blood in this study, but the person drawing your blood will attempt to minimize this discomfort. Side effects include pain and bruising in the area where the needle is inserted, lightheadedness, and rarely, fainting. When large amounts of blood are collected, low red blood cell count (anemia) is a risk.

Radiation Exposure from Imaging

During your participation in this research study, you will be exposed to radiation from three CT scans of the chest, abdomen and pelvis, three Tc-99 whole-body scans and two 18F NaF PET scans. The amount of radiation exposure you will receive from these procedures is equal to approximately 6.0 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, Tc-99 and 18F NaF PET scans that you get in this study will expose you to the roughly the same amount of radiation as 20 years' worth 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 0.6 out of 100 (0.6%) and of getting a fatal cancer is 0.3 out of 100 (0.3%).

Psychological or Social Risks Associated with Loss of Privacy

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.

POTENTIAL BENEFITS OF PARTICIPATION

Are there benefits to taking part in this study?

The aim of this study is to see if this combination treatment of PROSTVAC, CV301, and MSB0011359C will cause a reduction in your PSA levels. We do not know if you will receive personal medical benefit from taking part in this study. These potential benefits could include shrinking of your tumor or lessening of your symptoms, such as pain, that are caused by the cancer. Because there is not much information about the drug's effect on your cancer, we do not know if you will benefit from taking part in this study, although the knowledge gained from this study may help others in the future who have cancer.

ALTERNATIVE APPROACHES OR TREATMENTS

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

Instead of being in this study, you have these options:

- Taking part in another study
- Getting treatment with standard therapy outside this study (ADT alone or ADT with chemotherapy)
- Observation only, where your doctor, depending on his clinical judgment and your opinion, follows your PSA and watches you for cancer recurrence.

Please talk to your doctor about these and other options.

STOPPING THERAPY

You will continue to receive therapy and medical follow-up until:

- The study is completed;
- You decide that you no longer wish to participate in the study;
- You experience unacceptable side effects;
- Your cancer gets worse;
- The doctor feels that it is unsafe for you to continue;
- New information becomes available that suggests another treatment would be better for you; or
- The study is stopped.

You can stop taking part in the study at any time. However, if you are thinking about dropping out of the study, please tell your research team so they can tell you how to end your participation safely.

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 Bavarian Nordic, EMD Serono, or designated representatives. If you withdraw your consent and leave the trial, any samples of yours that have been obtained for the study and stored at the NCI can be destroyed

upon request. However, any samples and data generated from the samples that have already been distributed to other researchers or placed in the research databases cannot be recalled and destroyed.

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

Your specimens and data will be used for research purposes only and will not benefit you. It is also possible that the stored specimens and data may never be used. Results of research done on your specimens and data will not be available to you or your doctor.

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 provide another sample 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.

RESEARCH SUBJECT'S RIGHTS

Conflict of Interest

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

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

The National Institutes of Health and the research team for this study are using drugs developed by Bavarian Nordic and EMD Serono through a joint study with your researchers and the companies. The companies also provide financial support for this study.

Use of Specimens and Data for Future Research

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

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

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

Genomic Data Sharing

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. 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.

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

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 or their agent(s)
- Qualified representatives from Bavarian Nordic, the pharmaceutical company who produces PROSTVAC CV301 vaccine
- Qualified representatives from EMD Serono, the pharmaceutical company who produces MSB0011359C (M7824)

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 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, Ravi Madan, [redacted]. You may also call the NIH Clinical Center Patient Representative [redacted], or the NIH Office of IRB Operations [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: _____.