**PRINCIPAL INVESTIGATOR:** James L. Gulley, M.D., PhD.

**STUDY TITLE:** Phase I/II Study of PROSTVAC in Combination with Nivolumab in Men with Prostate Cancer

**STUDY SITE:** NIH Clinical Center (CC)

Cohort: Affected patient

Consent Version: August 23, 2022

## WHO DO YOU CONTACT ABOUT THIS STUDY?

James L. Gulley, MD, PhD

[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?

The aim of this study is to see if this PROSTVAC vaccine in combination with nivolumab is safe for castration resistant prostate cancer (CRPC) patients and once it's safely been determined to evaluate immune response in the tumor after treatment in all other prostate cancer patients who are candidates for surgical removal of their prostate.

Clinical work with PROSTVAC is based on the idea that the immune system (group of cells and organs in the body that recognize and fight infection) can be taught to find and kill certain cancer cells, in this case prostate cancer cells. This is an investigational vaccine treatment, which means that it is not approved for use on the general public and can only be used in a research study.

Nivolumab is a drug that has been approved by the FDA to treat melanoma. However, this drug has not been approved to treat prostate cancer either alone or in combination and its use in this trial is experimental.

If you have castration-resistant prostate cancer (CRPC), you will be included in the lead in cohort evaluating the safety and tolerability of the combination of PROSTVAC and nivolumab in the castration resistant setting.

If you have localized prostate cancer, you will be assigned to one of two groups or cohorts that will be enrolled sequentially (one after the other). Both cohorts will receive the combination of PROSTVAC and nivolumab given at around the same time.

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

You have been asked to take part in this research study because you have prostate cancer.

**HOW MANY PEOPLE WILL TAKE PART IN THIS STUDY?**

We plan to enroll up to 29 patients 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 testing will be performed on a separate protocol. 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. The following is a list of what we need to make sure you can do this study:

- Provide a sample of your tumor from previous surgery or biopsy so that we may confirm your disease. If a sample is not available and you do not have castration resistant prostate cancer, we ask you to undergo a biopsy to obtain fresh tissue (required)
- Medical history and physical exam.
- Routine blood and urine tests
- Electrocardiogram (ECG)
- Scans or other imaging studies, if you have CRPC
- 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 experimental treatment may harm you.
- As part of this study, we will test you for infection with HIV, the virus that causes AIDS.

**During the study**

Once you agree to participate in this study and you are fit to join, you will be assigned to one of the following groups/arms:

**Lead in CRPC Cohort for safety:**

If you have castration-resistant prostate cancer, you will be given the first vaccine injection called vaccinia-PROSTVAC (PROSTVAC-V) (week 0). Prior to this dose, we may need to repeat the CT scan if the one done at screening was too long ago. Two, four, and eight weeks after the first vaccine injection you will be given a booster injection called fowl pox-PROSTVAC (PROSTVAC-F). The nivolumab will be administered every two weeks. Alternately, if you have remained on protocol beyond 1 year, you will be given higher dose of nivolumab every 4 weeks. Six weeks after the first vaccine injection you will be given nivolumab only. Restaging CT and Bone scan will be performed on week 12 and if your disease does not get worse, you will have the option to continue treatment every 4weeks with Nivolumab until your disease gets worse (This will be evaluated with scans every 12 weeks).

The nivolumab and vaccine injections are given in the infusion center in the day hospital.

**Neoadjuvant Cohorts:**

**PROSTVAC + nivolumab**

You will be given the first vaccine injection called PROSTVAC-V (week 0). Two, four, and eight weeks after the first vaccine injection you will be given a booster injection called PROSTVAC-F. Six weeks after the first vaccine injection you will be given nivolumab only. When given on the same day, PROSTVAC-F will be administered first, followed by nivolumab.

Your doctor may decide that your standard of care surgery can be performed as early as five weeks or as long as 12 weeks after your first vaccine injection. If your surgery is done before you are scheduled to receive nivolumab on week six or PROSTVAC-F on week eight, you will not receive these doses and will not need to come in for study visits on those days.

The nivolumab and vaccine injections are given in the day hospital.

For more information about the two types of vaccine and an explanation of why there are two kinds, please see below under Vaccinia Virus and Fowl pox Virus.

Once you join the study, we will provide you with a schedule. You can expect blood tests, vital signs and a physical exam with each clinic visit.

As part of this study, we will look for any signs that your cancer is getting worse.

Your PSA level will be checked at each visit when blood is taken.

<u>Research blood samples</u>

An important part of this study is testing the effects of this treatment on your tumor and immune system. Research tests will be done on blood taken at different times during the study. The NIH has set a limit on the maximum amount of blood that can be taken for research. This limit is based on your age. For adults, no more than 37 tablespoons can be taken over an 8-week period.

We may at various time points during the study, collect blood samples to study your immune system (group of cells and organs in the body that recognize and fight infection). Blood samples will also be used for gene expression evaluation. The samples we collect will help us better understand how the vaccine works inside the human body. The samples are for research purposes only.

**When you are finished taking the drugs (treatment)**

When you stop treatment, we will ask you to return to our clinic for a safety visit about 4-5 weeks after your last treatment. During the safety visit we will collect blood samples, do vital signs and physical exam. We may ask you to do other tests and procedures that are part of regular cancer care, or have a CT scan of the chest, abdomen, and pelvis or MRI and bone scan if needed to evaluate your cancer.

When the cancer requires treatment again (disease progression) we will take you off this study and ask you to enroll on a long term follow up study for patients who receive vaccine injections. On the long term follow up study we will contact you once a year until death or until you refuse further follow up. We will ask you about your PSA and prostate cancer treatment.

**STANDARD OF CARE TREATMENT**

For patients with castration resistant prostate cancer, standard of care hormonal treatment known as Androgen Deprivation Therapy (ADT) is given in this trial. For patients with local prostate cancer, standard of care treatment with radical prostatectomy may be given on this trial. These treatments will not be experimental and may be performed by your study doctor or your regular doctor. Your doctors will describe your treatment plan to you in detail before asking you to sign this consent form. You may be asked to sign a separate consent form for any treatment procedures not outlined in this consent.

**Incidental Findings**

We may conduct genetic studies of your samples to look for DNA changes. DNA (also called deoxyribonucleic acid) are the molecules inside cells that carry genetic information and pass it from one generation of cells to the next – like an instruction manual. When we are examining your DNA, it is possible that we could identify possible changes in 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.

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. Changes that we observe unrelated to our research may or may not be valid. Therefore, we do not plan to inform you of the 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 that is believed to be clinically important based on medical standards at the time we first analyze your results, we will contact you. This could be many years in the future. We will ask you to have an additional tube of blood drawn to verify the findings we have seen in our lab. If the results are verified, you will be re-contacted and offered a referral to a genetic healthcare provider to discuss the results.

**RISKS OR DISCOMFORTS OF PARTICIPATION**

Vaccinia Virus

The first vaccine injection you will receive is PROSTVAC-V. 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 patients 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 patient 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.

Fowl pox Virus

PROSTVAC-F (the second and later doses of PROSTVAC) is based on fowl pox virus. Fowl pox 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 fowl pox-based vaccine after the vaccinia-based vaccine causes a better clinical response compared to using the virus alone or using fowl pox before vaccinia. The vaccines including fowl pox 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 fowl pox vaccine?**

Side effects from fowl pox 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 (Occurring in greater than 1 in 10 patients):*

- 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 (Occurring in less than 1 in 10 patients):*

- 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 (Occurring in less than 1 in 1,000 patients):*

- An uncommon blood condition called thrombotic thrombocytopenic purpura (TTP). One patient 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.

Possible Side Effects of Nivolumab

**Special precautions**

Side effects of Nivolumab may happen anytime during treatment or even after your treatment has ended. Some of the common and less common side effects can be serious. **Call or see your healthcare provider right away if you develop any problems listed below or if the symptoms get worse.**

| **VERY COMMON SIDE EFFECTS (Occurring in greater than 1 in 10 patients)** |
|---|
| • Fatigue<br>• Diarrhea<br>• Rash, itching |

| **Common Side Effects (Occurring in up to 1 in 10 patients)** |
|---|
| • Nausea<br>• Vomiting<br>• Constipation<br>• Mouth ulcers and sores<br>• Dry mouth<br>• Decreased appetite<br>• Fever<br>• Chills (feeling cold)<br>• Muscle pain, weakness, stiffness, spasms<br>• Joint pain or stiffness<br>• Headache<br>• Dizziness, fainting<br>• Abdominal pain<br>• Difficulty breathing<br>• Cough<br>• Dry skin<br>• Skin color changes<br>• Allergic reactions during/after infusion: Fever, chills, flushing, change in blood pressure, swelling of the face/lips/throat, difficulty breathing which may be serious<br>• Infusion related reactions<br>• Anemia, may require blood transfusion<br>• Low platelet counts<br>• Pain or swelling in your arms, legs, ankles or body<br>• Tingling, burning, or numbness in hands and feet<br>• Inflammation of the colon (colitis) – Can be fatal |

| Common Side Effects (Occurring in up to 1 in 10 patients) |
|---|
| • Inflammation of the lung (pneumonitis) – Can be fatal<br>• Abnormal blood chemistry, including abnormal liver, kidney, and pancreas function tests<br>• High blood sugar (hyperglycemia)<br>• Hypothyroidism, a condition where the thyroid gland doesn't produce enough hormones. Symptoms include fatigue, cold sensitivity, constipation, dry skin and weight gain.<br>• Hyperthyroidism, a condition where the thyroid gland produces too much thyroid hormone. Symptoms include weight loss, rapid or irregular heartbeat, sweating and irritability.<br>• Hyponatremia, when there is not enough sodium in the blood |

| UNCOMMON SIDE EFFECTS (Occurring in up to 1 in 100 patients) |
|---|
| • Hair loss<br>• Adrenal insufficiency, a disorder in which the adrenal glands do not produce enough hormones<br>• High or low blood pressure<br>• Fast heart rate<br>• Irregular heart rhythm<br>• Blurry vision, dry eyes, eye inflammation<br>• Pain, swelling and redness of the eyelid and area around the eye and restricted eye movement (orbital myositis)<br>• Inflammation of the liver (hepatitis) – Can be fatal<br>• Hives<br>• Erythema multiforme, a skin disorder that presents as red, raised patches that often look like a "target"<br>• Psoriasis, a skin condition that results in a buildup of skin cells that form dry, scaly patches<br>• Pemphigoid, a malfunction of the immune system which results in skin rashes and blistering<br>• Can't sleep<br>• Decreased white blood cell counts<br>• Inflammation of the kidney, kidney failure requiring dialysis<br>• Dehydration<br>• Upper respiratory infections<br>• Inflammation of the pancreas<br>• Inflammation of the pituitary gland<br>• Condition in which the pituitary gland does not produce enough hormones |

**UNCOMMON SIDE EFFECTS (Occurring in up to 1 in 100 patients)**

- Sarcoidosis, a condition where growths made of inflammatory cells develop on the organs of the body
- Bronchitis
- Inflammation of the mouth and lining of digestive tract
- Inflammation of the muscles
- Low blood oxygen level, or respiratory failure
- Diabetes mellitus (high blood sugar, can result in coma)

**RARE (SERIOUS) SIDE EFFECTS (Occurring in up to 1 in 1000 patients)**

- Increased blood acid levels caused by diabetes
- Increased blood sugar for too long caused by diabetes. This may cause dehydration or confusion.
- Rosacea
- Fluid around lungs
- Inflammation of the brain (encephalitis) – Can be fatal
- Inflammation of the blood vessels which could cut off blood supply to tissues and organs
- Cranial nerve disorder which may affect smell, taste, vision, sensation in the face, facial expression, hearing, balance, speech, swallowing and muscles of the neck
- Guillain-Barre Syndrome: Is associated with progressive muscle weakness or paralysis
- Autoimmune disorders
- Anaphylaxis: An allergic reaction that causes your immune system to release a flood of chemicals that can cause you to go in shock.
- Rhabdomyolysis (muscle fiber released into the blood stream which could damage your kidney) and polymyositis (chronic muscle inflammation with muscle weakness) has been reported in one patient.
- Toxic epidermal necrolysis: A potentially fatal disease characterized by blistering and peeling of the top layer of skin resembling a severe burn, has occurred in patients who received nivolumab treatment.
- Stevens-Johnson syndrome: a disorder that affects the skin, mucous membrane, genitals and eyes. This can cause flu like symptoms followed by a red or purple rash that forms blisters and peeling skin.
- Myasthenia gravis: A nerve disease that may cause weakness of eye, face, breathing, and swallowing muscles. One death in a patient who received nivolumab combined with ipilimumab was considered due to myasthenia gravis and severe infection (sepsis).
- Polymyalgia rheumatica: an inflammatory disorder that causes muscle pain and stiffness

- Inflammation of the spinal cord
- Inflammation of the heart (myocarditis): May cause your heart to have difficulty pumping blood throughout your body, which can cause chest pain, difficulty breathing, swelling in your legs. You may also experience a fast or irregular heartbeat that can cause dizziness or fainting. Sometimes this condition can lead to death.
- Liver injury
- Double vision
- Demyelination or loss of protective coating around your nerve fibers
- Meningitis or swelling of the brain or spinal cord membranes
- A hole developing in your intestinal tract
- Haemophagocytic lymphohistiocytosis, when the immune system is overactive and attacks the organs in the body.
- Kikuchi- Fujimoto disease: Inflammation or enlargement of lymph nodes

Complications associated with stem cell transplant using donor stem cells (allogeneic stem cell transplant): These complications are caused by attack of donor cells on the host organs (inducing liver, skin and gut), and can lead to death. If you are considering an allogeneic stem transplant after participating in this study, please tell your doctor that you have received nivolumab therapy, since the risk and severity of transplant-associated complications may be increased.

These symptoms might or might not be caused by problems with your lungs, colon, liver, thyroid, pituitary or adrenal glands, pancreas, kidneys, heart, brain, nervous system, or skin affected by nivolumab.

A new drug may show an increase in side effects or unexpected effects as more studies are conducted. For your safety, you will be followed closely by your Study Doctor and the study staff for any undesirable or unexpected side effects during your participation in this study and each time you receive nivolumab.

There may be other side effects of nivolumab that are unknown. You will be told about any new findings that develop during the course of this study that may affect your decision to stay in the study.

***Risks to an Unborn Child and Sexual Partner***

**Birth Control**

Your study doctor will discuss the risks to unborn children for drugs other than PROSTVAC that may be used in this study. The effects of PROSTVAC, 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 while you are receiving study vaccine and for a period of up to 7 months after your last dose of study vaccine.

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 biopsy:* The biopsy 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 X-rays and / or Scans:* Radiological testing, such as CT scans, , X-rays and/or radioactive drugs may 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:* 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.

MRI: There are no known risks of physical harm associated with MRI. MRI machines produce loud banging noises which cause some people to become stressed or upset. You may also feel uncomfortable inside the machine if you do not like being inside small places or have difficulty lying still.

*Contrast agents (for CT and/or MRI):* You may receive a contrast agent such as Gadolinium as part of your CT scan or MRI. Contrast agents can cause allergic reactions and kidney damage. Allergic reactions can include mild itching associated with hives but can also result in a serious life-threatening emergency from difficulty breathing. If this occurs, it is treatable.

Gadolinium is an FDA-approved medication used to improve MRI images. About 98% of patients receiving gadolinium have no symptoms related to the injection of this medication. Mild symptoms

that may occur include: coldness in the arm at injection, a metallic taste, headache, and nausea. In an extremely small number of patients, more severe symptoms have been reported including: shortness of breath, wheezing, and lowering of blood pressure.

MRI contrast agents containing gadolinium can cause a rare disease known as Nephrogenic Systemic Fibrosis (NSF) mostly in patients with severe kidney disease. NSF has been nearly eliminated by screening kidney function prior to MRI. To try and avoid NSF, we do not give gadolinium to patients with severe kidney disease in this research study. NSF can cause tight rigid skin, trouble bending joints, pain, weakness, and can scar body organs. NSF is debilitating and may cause death. We will check your kidney function before giving you any gadolinium contrast.

Recent reports indicate that some gadolinium may be retained in the brain, bone, and skin. In May 2018, the FDA stated that no harmful effects have been identified related to gadolinium in the brain, but it is continuing to study the issue. You will receive additional information called a "medication guide" about the contrast medication you will receive.

Gadolinium will be administered for research purposes and as clinically indicated. We will check your kidney functions before giving you any gadolinium contrast.

**What are the risks of radiation from being in the study if you have CRPC?**

During your participation in this research study, you will be exposed to radiation from up to 5 CT scans (chest/abdomen/pelvis) and up to 5 Tc99 scans annually not including the scans already performed at screening. You may also have up to one CT guided biopsy. The amount of radiation exposure you will receive from these procedures is equal to approximately 8.25 rem. A rem is a unit of absorbed radiation.

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

The CT and bone scans that you get in this study will expose you to the roughly the same amount of radiation as 27.5 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 0.8 out of 100 (0.8%) and of getting a fatal cancer is 0.4 out of 100 (0.4%).

**Risks Associated with Genetic Testing**

*Privacy Risks*

Your privacy is very important to us and we will use many safety measures to protect your privacy. However, in spite of all of the safety measures that we will use, we cannot guarantee that your identity will never become known. While neither the public nor the controlled-access databases developed for this project will have information such as your name, address, telephone number, or

social security number, it may be possible to identify you based on the information in these databases and other public information (including information you tell people or post about yourself). The risk of this happening is currently very low.

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.

It is possible also that someone could get unauthorized access or break into the system that stores information about you. Every precaution will be taken to minimize this risk. There also may be other privacy risks that we have not foreseen.

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

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

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

*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 PROSTVAC vaccine in combination with nivolumab is safe for castration resistant prostate cancer (CRPC) patients and to evaluate changes in the immune cells in the tumor after treatment in all other cancer patients.

We do not know if you will receive personal medical benefit from taking part in this study.

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
- For patients with castration resistant prostate cancer, you have the option to get treatment with standard therapy outside this study therapy targeting male hormones (androgens) or chemotherapy or both.
- For patients with local prostate cancer, you have the option to get treatment with standard therapy outside this study with prostatectomy or radiation therapy or receive 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 experience unacceptable side effects;
- Your cancer gets worse (castration resistant cohort only);
- You have been unable to comply with the protocol requirements
- 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, Inc., Bristol-Myers Squibb or their 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.

## 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 vaccine developed in collaboration with the National Cancer Institute under a Cooperative Research and Development Agreement with Bavarian Nordic, Inc. The company also provides financial support for this study.

Bristol-Myers Squibb is providing the nivolumab for this study to NIH without charge. No NIH employee involved in this study receives any payment or other benefits from Bristol-Myers Squibb.

**OPTIONAL BIOPSY**

In the unlikely event that a biopsy was not available, we would like to collect tumor samples by doing a biopsy before you begin treatment. The risks of this procedure as listed under "Other risks". The biopsies to be performed are exclusively for research purposes and will not benefit you. It might help other people in the future. You will be given the opportunity to decide if you would like to participate at the time of the procedures.

**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 it 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.

## 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.
- Qualified representatives from Bavarian Nordic, Inc., the pharmaceutical company who produces PROSTVAC vaccine.
- Qualified representatives from Bristol-Myers Squibb, the pharmaceutical company who produces nivolumab.

When results of an NIH research study are reported in medical journals or at scientific meetings, the people who take part are not named and identified. In most cases, the NIH will not release any information about your research involvement without your written permission. However, if you sign a release of information form, for example, for an insurance company, the NIH will give the insurance company information from your medical record. This information might affect (either favorably or unfavorably) the willingness of the insurance company to sell you insurance.

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

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

**Certificate of Confidentiality**

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

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

The Certificate does not protect your information when it:

1. is disclosed to people connected with the research, for example, information may be used for auditing or program evaluation internally by the NIH; or

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

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

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

**Privacy Act**

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

## POLICY REGARDING RESEARCH-RELATED INJURIES

The NIH Clinical Center will provide short-term medical care for any injury resulting from your participation in research here. In general, no long-term medical care or financial compensation for research-related injuries will be provided by the NIH, the NIH Clinical Center, or the Federal Government. However, you have the right to pursue legal remedy if you believe that your injury justifies such action.

## PROBLEMS OR QUESTIONS

If you have any problems or questions about this study, or about your rights as a research participant, or about any research-related injury, contact the Principal Investigator, James L. Gulley, MD, PhD, Phone: 301-480-7164, Email: gulleyj@mail.nih.gov. You may also call the NIH Clinical Center Patient Representative at 301-496-2626, or the NIH Office of IRB Operations at 301-402-3713, if you have a research-related complaint or concern.

## CONSENT DOCUMENT

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

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

| Signature of Research Participant | Print Name of Research Participant | Date |
|---|---|---|

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

| Signature of LAR | Print Name of LAR | Date |
|---|---|---|

**Investigator:**

| Signature of Investigator | Print Name of Investigator | Date |
|---|---|---|

**Witness should sign below if either:**

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

| Signature of Witness | Print Name of Witness | Date |
|---|---|---|

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

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

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