COMbination of Bipolar Androgen Therapy and Nivolumab in Patients with Metastatic Castration-Resistant Prostate Cancer

Principal Investigator: Mark C. Markowski, M.D., PhD

NCT03554317

Consent form approval date: October 6, 2020

If you are using Epic for this study, fax a copy of the signed consent form to 410-367-7382.

Patient I.D. plate

RESEARCH PARTICIPANT INFORMED CONSENT AND PRIVACY AUTHORIZATION FORM

Protocol Title: **COMbination of Bipolar Androgen Therapy and Nivolumab in Patients with Metastatic Castration-Resistant Prostate Cancer [COMBAT-CRPC]**

Application No.: **IRB00164973**

Sponsor: **Johns Hopkins University**
United States Army Medical Research and Materiel Command

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1. What you should know about this study:

- You are being asked to join a research study. This consent form explains the research study and your part in it. Please read it carefully and take as much time as you need. Ask your study doctor or the study team to explain any words or information that you do not understand.
- You are a volunteer. If you join the study, you can change your mind later. There will be no penalty or loss of benefits if you decide to quit the study.
- During the study, we will tell you if we learn any new information that might affect whether you wish to continue to participate.
- If we think your participation in this study may affect your clinical care, information about your study participation will be included in your medical record, which is used throughout Johns Hopkins. Doctors outside of Johns Hopkins may not have access to this information. You can ask the research team to send this information to any of your doctors.
- When Johns Hopkins is used in this consent form, it includes The Johns Hopkins University, The Johns Hopkins Hospital, Johns Hopkins Bayview Medical Center, Howard County General Hospital, Johns Hopkins Community Physicians, Suburban Hospital, Sibley Memorial Hospital and All Children's Hospital.
- Biospecimens will be collected in this study. Biospecimens may include any of the following: blood, tissue, saliva, urine, bone marrow, cells, etc. Most biospecimens contain DNA, which is the genetic code for each person.

- 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.
- If you would like to review the information for this study, or a summary of the results, ask the study team doctor for the ClinicalTrials.gov study registration number.

2. Why is this research being done?

This aim of this research is to find out if rapid cyclical treatment with testosterone in combination with nivolumab leads to lowering of PSA levels in men with metastatic prostate cancer that is resistant to androgen deprivation therapy (also referred to as metastatic castration resistant prostate cancer). We also want to determine if treating first with testosterone may cause nivolumab to work more effectively against your cancer.

This study is based on our prior and current studies using high dose testosterone in men with metastatic castration resistant prostate cancer, in which we observed decreases in PSA levels in a subset of patients. Further laboratory and animal studies found that high dose testosterone can damage the DNA (i.e. genes) of cancer cells resulting in cell death. This increase in DNA damage may result in changes in the tumor DNA making it recognizable to the immune system with the addition of nivolumab.

Nivolumab (BMS-936558) is a human monoclonal antibody made in a laboratory. Antibodies exist normally in your body. An antibody is a type of protein normally made by immune cells that helps protect the body against foreign matter, such as bacteria and viruses. These antibodies attach, or bind to, foreign matter in a very specific way, and this binding helps the body clear the infection. Nivolumab works by attaching to and blocking a protein called PD-1. PD-1 is present on different types of cells in the immune system and can shut down the immune cells so that they do not effectively fight disease. Antibodies that block the PD-1 protein on these immune cells can potentially stop PD-1 from shutting down the immune cells, thus allowing the cells to recognize and help the body destroy the cancer cells.

Nivolumab is approved by the Food and Drug Administration (FDA) for the treatment of patients with advanced skin, kidney and lung cancers. Nivolumab is not approved by the FDA for the treatment of metastatic prostate cancer and its use in this study is considered investigational. Nivolumab is currently being studied in prostate cancer, but no clinical benefit has been shown at the time of study initiation.

The testosterone used in this study will be administered as an intramuscular (IM) injection. Testosterone is approved by the FDA for the treatment of hypogonadism (low testosterone in the blood). It is not approved for use in prostate cancer and therefore its use in this study is investigational. The testosterone is given at the standard dose that is used to treat men with low testosterone levels in their blood. However, the purpose is to increase your testosterone levels above normal briefly, before they return to low levels.

Men with prostate cancer who have been on continuous castrating therapy and who have received prior treatment with Zytiga or Xtandi and have signs of worsening prostate cancer that include either new tumor growth on bone or CT scan or increasing PSA levels in the blood may join. Prior treatment with other kinds of hormonal therapy or one chemotherapy is allowed.

How many people will be in this study?

Up to 44 participants are expected to enroll in this study. About 34 of these participants are expected to be enrolled at Johns Hopkins.

3. What will happen if you join this study?

If you agree to be in this study, we will ask you to do the following things:

Screening Period:

There will be a screening period to see if you can participate in the study. During the screening period the following procedures will be performed:

- The study team will ask you questions about your medical history and current health and review your medical record.
- A physical examination and vital signs (body temperature, blood pressure, pulse, respiratory rate, weight).
- Eastern Cooperative Oncology Group (ECOG) performance status score. This is a scale used to assess how your cancer is progressing and how your cancer affects your daily living abilities.
- Review of other medications you are currently taking.
- Collection of a blood sample (about 3 tablespoons of blood) for laboratory tests which measure your blood chemistry, including kidney, pancreas, and liver function, count your red and white blood cells and platelets, measure your thyroid function, and measure how long it takes your blood to clot.
- Blood test to monitor levels of Prostate Specific Antigen (PSA).
- Blood test to determine your level of testosterone.
- Blood samples will be obtained for Hepatitis B and C testing. The law requires us to report positive tests to the health department. This reporting will include information that identifies you (for example, name, date of birth, home address, phone number, etc.) as required by Maryland law. The health department may use this information to contact you for further follow up and/or to help conduct health surveillance activities aimed at preventing or controlling diseases.
- Collection of a urine sample for routine analysis.
- Electrocardiogram (ECG): This is a test that gives a picture of the electrical action of your heart.
- CT or MRI scan and bone scan (if these have not been performed in the past 4 weeks). Computed tomography (CT) scan or magnetic resonance imaging (MRI) of the known areas of disease will be done. These pictures will allow your doctor to monitor your disease before, during, and after you receive the study drugs. In addition, bone scans will be completed to measure your disease.
- If you are eligible for the study and choose to participate, you will be scheduled for an image-guided biopsy of your tumor tissue, which is required prior to the start of the testosterone and the nivolumab regimen.

If, based on the results of the screening visit tests and procedures, you qualify to continue to participate in the study, you will be scheduled for a clinic visit after which you will start on the testosterone regimen. Testosterone is given for 3 months prior to the addition of nivolumab.

All participants who enroll in the study will have the same procedures and receive the same study drug (testosterone alone for the first 12 weeks (3 months) then nivolumab will be added at week 16).

Study Drug Administration Period:

If you are found to be eligible to continue to participate in the study, you will return to the clinic to begin the study drugs. Testosterone is given as an injection into the muscle of the buttock. Nivolumab is given as an intravenous (IV) infusion.

You will visit the study doctor as instructed. Each study drug cycle is about 4 weeks. The study doctor or staff will discuss with you when and on which days to report to the clinic.

During Cycles 1-3 (Every 4 weeks, total of 12 weeks): TESTOSTERONE ONLY PERIOD

You will return to the clinic every 4 weeks. At each visit, the following tests and procedures will be performed:

- Review of any changes in your health and medications since your last visit.
- You will be asked about the symptoms you are having from your disease and any side effects you may be experiencing.
- Measurement of your weight and vital signs.
- An evaluation of your ability to carry out daily activities will be performed.
- A physical examination.
- Collection of a blood sample (about 2 tablespoons of blood) for laboratory tests which measure your blood chemistry, including kidney and liver function, count your red and white blood cells and platelets.
- Blood test to monitor levels of Prostate Specific Antigen (PSA).
- Blood test to determine your level of testosterone.
- Rectal swab: A cotton swab is placed into the rectum. The swab is rotated gently, and removed. You will have a rectal swab before you start receiving testosterone, at the end of the testosterone only period, and after 3 cycles of starting the testosterone and nivolumab period. Rectal swabs will be done for research purposes.
- Administration of testosterone into the muscle of the buttock.

During Cycles 4 and beyond (every 4 weeks): TESTOSTERONE AND NIVOLUMAB PERIOD

You will return to the clinic every 4 weeks. At each visit, the following tests and procedures will be performed:

- Review of any changes in your health and medications since your last visit.
- You will be asked about the symptoms you are having from your disease and any side effects you may be experiencing.
- Measurement of your weight and vital signs.
- An evaluation of your ability to carry out daily activities will be performed.
- A physical examination.
- Collection of a blood sample (about 2 tablespoons of blood) for laboratory tests which measure your blood chemistry, including kidney, pancreas, and liver function, count your red and white blood cells and platelets, measure your thyroid function, and monitor for autoimmune conditions.
- Blood test to monitor levels of Prostate Specific Antigen (PSA).
- Blood test to determine your level of testosterone.
- Administration of testosterone into the muscle of the buttock.
- Nivolumab will be given intravenously (IV) through a vein in the arm.

Every 3 months:

You will have a CT scan and bone scan every 3 months while you are enrolled in the study, as well as a CT and bone scan at the end of the study (if it has been at least 1 month since your last CT and bone scan).

The following tests will be done for research:

- Collection of a blood sample (about 8 tablespoons) for research at the time of your first treatment, 12 weeks after your first treatment, and at the time of disease worsening (progression).
- In addition to the biopsy performed during the screening period, a SECOND image-guided tumor biopsy will be performed after 12 weeks of testosterone. This procedure is considered mandatory and part of this study.

Optional Tumor Biopsies:

We would like your permission to perform a third optional image-guided tumor biopsy at the time of disease worsening (progression) while receiving both testosterone and nivolumab. This procedure is considered optional. If you refuse to have this biopsy, it will not affect your participation on this study nor will it affect your future care.

Will you give permission to take part in this optional tumor biopsy at the time of disease worsening or progression while receiving both testosterone and nivolumab?

YES ☐ _____
Signature of Participant

NO ☐ _____
Signature of Participant

End of Study Drug Regimen Visit / 28-Day Follow-up Visit:

If you complete all of the study drug regimen/intervention cycles or if you are withdrawn from the study at any time, you will come in for an end of study drug regimen visit 28 days after your last dose of study drug to have the following procedures done:

- Review of any changes in your health and medications since your last visit.
- Measurement of your weight and vital signs.
- An evaluation of your ability to carry out daily activities will be performed.
- A physical examination.
- Collection of a blood sample (about 2 tablespoons of blood) for laboratory tests which measure your blood chemistry, including kidney and liver function, count your red and white blood cells and platelets, and monitor for autoimmune conditions.
- Imaging tests: CT or MRI of the abdomen and pelvis, CT or MRI of the chest (or chest X-ray), and bone scan, as determined by the study doctor.
- Collection of blood (8 tablespoons) for research purposes.
- Optional tumor biopsy as discussed above

Off Study Follow-up (100-Day Follow-up / Every 28-Days Follow-up):

If you complete all of the study drug regimen/intervention cycles, you will be contacted 100 days after your last dose of study drug for assessment of any adverse side effects.

If you are withdrawn from the study at any time due to adverse side effects, you will be contacted monthly following your end of study drug regimen visit/28-day follow-up visit to reassess any active adverse events until the event has resolved or stabilized.

Following completion of the 100-day follow-up/Adverse event resolution or stabilization date, you will be contacted every 6 months for up to 1 year following your last dose of study drug.

The procedures and visits in this clinical trial are different from the standard treatments. If you choose to join the study, there are more frequent clinic visits (every month instead of every 3 months), more frequent blood tests (monthly instead of every 3-6 months), and receiving testosterone +/- nivolumab instead of standard treatments. You will not be receiving an FDA approved medication that has been shown in clinical studies to make patients with your type of cancer live longer.

The results from all study tests (blood tests, CT, and bone scans) will be available to you and your physicians.

It is important that you tell the study staff about any other medicines, vitamins, nutritional or herbal supplements you are taking before and during the study. It is possible that your study drug could affect your other medication and there are certain medications that you will not be allowed to take with the study drug during the study, including other anti-cancer therapies and certain vaccines. Your study doctor will provide you with a list of medications that you must avoid while you are taking your study drug, so it is important to consult your study doctor before taking anything new.

Color Genomics Saliva Test:
You will be asked to provide an optional saliva sample to be analyzed (via Color Genomics) for the most relevant genes for mutations associated with prostate cancer per standard of care practice. You and/or your insurer will be financially responsible for the cost of this test. If you do not wish to provide an optional saliva sample to be analyzed, it will not affect your ability to participate in this trial.

In the hereditary cancer genetic test, Color Genomics uses a sequencing platform to analyze the risk of developing hereditary cancer due to inheritance of a pathogenic mutation in 30 cancer predisposition genes. Thus, inherited prostate cancer genomic data provided by Color Genomics can further allow us to personalize screening and target specified effective therapies for each patient disease.

You will be asked to provide an optional saliva sample (tube collection) at home, via a Color Genomics kit. This optional collection will be performed prior to the second study treatment visit to consenting participants. Color Genomics will analyze the genes from the patient salvia sample. You will have access to the results and will be allowed to make an appointment with one of the Color Genomics' genetic counselors at no cost. Further, Color Genomics will also keep the patient updated if any information related to their results changes.

Color Saliva Test Procedure:
- A study team member will create a Color Genomics Account, and submit an order. Information provided in the order form will include your first and last name, sex, date of birth, mailing address, mobile or home number, and your email.
- You will then receive an email to sign the Color Genomics consent; this can be done during one of the time point visits or from your personal computer.
- Once you have agreed and signed the Color Genomics consent, your kit will be activated and shipped to your home.
- In order to not delay results or ruin sample, you must wait 30 minutes if you have: had any food or drink, brushed your teeth, used mouthwash, smoked, or chewed gum.
- You will be required to spit into the provided funnel until the amount of saliva reaches the "fill to" line. This might take a few minutes (thinking of candy or rubbing your cheeks can speed up the process). Remembering that saliva bubbles do not count.
- Once your kit is complete, ship the sample back to Color Genomics in the postage-paid package provided.

Once the results are available, you will receive an email from Color Genomics providing you with access to the results, tools to the website to share the information with family and primary care physicians, as well as the contact information to communicate with Color Genomics genetic counselors (free of charge).

Will you give permission to take part in this optional gene sequencing analysis via Color Genomics? If you refuse to participate in this analysis, this will not affect your participation on this study nor will it affect your future care.

YES ☐ _____
Signature of Participant

NO ☐ _____
Signature of Participant

Optional additional blood sample collection

We would like to collect an additional blood sample to characterize the effect of testosterone on the production of inflammatory chemokines and cytokines. Chemokines are a family of small cytokines, or signaling proteins secreted by cells. Inflammatory chemokines function mainly as chemo-attractants for leukocytes, recruiting monocytes, neutrophils, and other effector cells from the blood to sites of infection or tissue damage. Certain inflammatory chemokines activate cells to initiate an immune response or promote wound healing. The results of the testing will only be used for research and not to guide your medical care. The results will not be added to your medical record and you will not know the results. You will not be billed for this additional blood sample collection.

Do you agree to have 10mL of additional blood collected before you start study drug administration ("Cycle 1 Day 1"), 3 hours after the first testosterone injection, 3 days after the first testosterone injection, Cycle 2 Day 1, and Cycle 7 Day 1? If you refuse to participate in this analysis, it will not affect your participation on this study nor will it affect your future care.

YES ☐ _____
Signature of Participant

NO ☐ _____
Signature of Participant

The Genetic Information Nondiscrimination Act (GINA) may help protect you from health insurance or health-related employment discrimination based on genetic information.

The law provides that health insurance companies and group health plans:

- may not ask for genetic information from this research and,
- may not use genetic information when making decision about eligibility or premiums.

The law will not stop health insurance companies from using genetic information to decide whether to pay claims. The law does not apply to other types of insurance (such as life, disability or long-term care).

Despite the GINA protections and the best efforts of the research team to protect your information, you may still be at risk if information about you were to become known to people outside of this study.

Request to collect and store biospecimens for future research

As part of this research study, we would like to ask you to let us store your biospecimens and health information for future research. This research could involve other diseases and involve research tools such as gene sequencing or creation of cell lines. These samples may also be distributed to other

researchers, but they will not contain any information that could be used to identify you. You may limit the future use of any banked samples by contacting the study doctor.

The research may involve research tools such as gene sequencing or the creation of cell lines.

- Gene sequencing of your DNA provides researchers with the code to your genetic material.
- Cell lines are living tissue samples that can be grown in a laboratory. A cell line can provide an unlimited supply of cells in the future without requiring more samples from you. Each cell contains your complete DNA.

The study doctor can provide you with additional information if you have questions. Also, further information about our use of your biospecimens can be found in this consent document under the heading *What happens to Data and Biospecimens that are collected in the study?*

Will you allow us to store the biospecimens we collect for this study for use in future research?

YES ☐ _____
Signature of Participant

NO ☐ _____
Signature of Participant

Incidental Findings

The CT scans you are having as part of this research study will be reviewed by a qualified person just as it would be if you were having the CT scans as part of your routine medical care.

There is a possibility that while reviewing your CT scans we may see an abnormality that we did not expect to see in this study. This is what is called an "incidental finding."

We will let you know if we see such an incidental finding. Depending on the type of incidental finding, we may contact you by mail or by phone. In the case of a potential serious emergency, someone may go to your home.

A qualified person (usually a member of the research team) will talk to you if there is an incidental finding. You do not have an option to decline information about an incidental finding.

If you want, we will give information about this incidental finding to your primary doctor or we will refer you to an appropriate doctor for further evaluation.

- An incidental finding may cause you to feel anxious.
- Since an incidental finding will be part of your medical record, it may affect your current or future life or health insurance coverage. This risk will vary depending on the type of insurance plan involved.

The costs for any care that will be needed to diagnose or treat an incidental finding would not be paid for by this research study. These costs would be your responsibility.

How long will you be in the study?

We anticipate that most participants will be on the study for about 18 months. Some participants may be a part of the study for a shorter time period and some may be for a longer time period.

4. What are the risks or discomforts of the study?

Side effects can be mild, moderate or severe (these are explained below).

- Mild: You are aware of the side effect but it doesn't really bother you.
- Moderate: You need to take some sort of action (like painkillers for a headache).
- Severe: The side effect stops you from doing what you normally would be doing.

Treatment with testosterone or nivolumab has been associated with the following laboratory findings and/or clinical symptoms, generally of mild or moderate severity and generally not requiring treatment to be stopped.

You may experience none, some or all of the side effects listed below.

Risks of Testosterone Injection

Very common side effects (occur in 10% or more of patients):

- Inflammation and pain at the site of intramuscular injection
- Fluid retention
- Increased or decreased libido

Common side effects (occur in 1 to less than 10% of patients):

- Enlargement of breast tissue (gynecomastia)
- Excessive frequency of erection
- Prolonged erection (priapism)
- Worsening urinary symptoms due to benign prostatic hyperplasia (BPH)
- Acne
- Nausea
- Headache
- Anxiety, Depression
- Increased cholesterol level
- Decreased blood glucose
- Increased risk of a blood clot in your legs or lungs
- Increased red blood cell count

Uncommon side effects (occur in up to 1% of patients):

- Alterations in liver function tests
- Jaundice
- Cardiac events such as heart attack or stroke

Rare but serious side effects:

- Allergic reaction to testosterone

The Study Doctor may decide to interrupt and/or reduce your testosterone dose if you experience certain side effects.

In this study, you will be given testosterone, a hormone that can cause your prostate cancer to acutely worsen. During this study, you will be allowed to continue on treatment with testosterone with a PSA value that is rising. This may lead to delay in changing treatment, disease progression, and/or the development of new symptoms (i.e. pain). It is important that you share with your doctor, any new or concerning symptoms that you may experience on this trial.

There may be risks involved in taking this drug that have not yet been discovered. There is always a risk involved in taking an experimental drug but every precaution will be taken. If you suffer any side effects or injuries, or your condition gets worse, tell your study doctor immediately so you can receive appropriate care.

Risks of Nivolumab

Very common side effects (occur in 10% or more of patients):

- Diarrhea
- Fatigue
- Itching
- Rash

Common side effects (occur in 1 to less than 10% of patients):

- Abdominal pain
- Alkaline phosphatase increased (lab test result associated with liver or bone abnormalities)
- ALT increased (lab test result associated with abnormal liver function)
- Amylase increased (lab test result associated with pancreas inflammation)
- AST increased (lab test result associated with abnormal liver function)
- Chills
- Constipation
- Cough
- Creatinine increased (lab test result associated with decreased kidney function)
- Decreased appetite
- Dizziness
- Dry mouth
- Dry skin
- Fever
- Headache
- Increased blood sugar
- Inflammation of the colon
- Inflammation of the mouth
- Infusion-related reaction
- Lipase increased (lab test result associated with pancreas inflammation)
- Joint pain or stiffness
- Loss of color (pigment) from areas of skin
- Lung inflammation (pneumonitis - see details below)
- Musculoskeletal pain
- Nausea
- Redness
- Shortness of breath
- Sodium levels in the blood low
- Swelling, including face, arms, and legs
- Thyroid gland function decreased
- Thyroid gland function increased
- Thyroid stimulating hormone increased (lab test result associated with abnormal thyroid function)

- Tingling, burning, numbness or weakness, possibly in arms, legs, hands, and feet
- Vomiting

Uncommon side effects (occur in up to 1% of patients):

- Adrenal gland function decreased
- Allergic reaction/hypersensitivity
- Bilirubin (liver function blood test) increased
- Bronchitis
- Cranial nerve disorder
- Diabetes
- Dry eye
- Hair loss
- Heart rate increased
- Heart rhythm abnormal
- High blood pressure
- Hives
- Inflammation of the eye
- Inflammation of the heart
- Inflammation of the kidney
- Inflammation of the pancreas
- Inflammation of the pituitary gland
- Inflammation of the stomach
- Inflammation of the thyroid gland
- Liver inflammation
- Low blood pressure
- Pituitary gland function decreased
- Psoriasis: characterized by patches of abnormal, scaly skin
- Renal (kidney) failure or kidney injury
- Respiratory failure
- Sodium levels in blood low
- Upper respiratory tract infection
- Vertigo (feeling off balance which can lead to dizziness)
- Vision blurred

Rare but serious side effects:

- Anaphylactic reaction (severe allergic reaction)
- Damage to the protective covering of the nerves in the brain and spinal cord
- Diabetes complications resulting in excess blood acids and diabetic coma
- Erythema multiforme, a skin inflammatory reaction
- Guillain-Barre syndrome, an autoimmune disorder associated with progressive muscle weakness or paralysis
- Inflammation of blood vessels
- Inflammation of the brain, potentially life-threatening or fatal
- Inflammation of the heart
- Muscle inflammation
- Myasthenic syndrome (neurologic syndrome characterized by muscle weakness) including myasthenia gravis, a nerve disease that may cause weakness of eye, face, breathing, and swallowing muscles

- Polymyalgia rheumatica, an inflammatory disorder causing muscle pain and stiffness
- Rhabdomyolysis, muscle fiber released into the blood stream which could damage your kidneys
- Rosacea, acne-like skin condition resulting in redness of face
- Sarcoidosis, a disease involving abnormal collections of inflammatory cells (granulomas) in organs such as lungs, skin, and lymph nodes
- Stevens-Johnson syndrome, inflammatory disorder of skin and mucous membranes, resulting in blistering and shedding of skin
- Toxic epidermal necrolysis, a potentially fatal disease characterized by blistering and peeling of the top layer of skin resembling a severe burn
- Histiocytic necrotizing lymphadenitis or Kikuchi lymphadenitis, disorder of the lymph nodes which causes the lymph nodes to become enlarged, inflamed and painful, commonly affecting lymph nodes of the neck and possibly associated with fever or muscle and joint pains
- Vogt-Koyanagi-Harada syndrome, a disease that affects the pigmented tissue; this may affect the eye leading to swelling, pain and/or blurred vision; the ear leading to hearing loss, ringing in the ears and/or the skin leading to loss of skin color

Lung Inflammation (pneumonitis):
It is possible that nivolumab may cause inflammation of the tissues of the lung. This adverse effect has been reported infrequently in patients treated with nivolumab. While many patients with X-ray or CT abnormalities have not developed any symptoms, some patients have developed mild to severe symptoms and in rare cases, death has occurred as a result of their lung inflammation. Signs and symptoms of lung inflammation may include difficulty breathing, pain or discomfort while breathing, chest pain, cough, shortness of breath, increased rate of breathing, fever, low blood oxygen levels or fatigue.

Your study doctor and nurse will watch you closely for changes in your ability to breathe and for other signs or symptoms that might show you are developing this type of lung inflammation and will perform regular tests including physical exams, measurement of oxygen levels through non-invasive testing (i.e. pulse oximeter), blood tests, chest x-rays and/or CT scans.

Please inform your study doctor or nurse AT ONCE if you experience any of the following:

- Any new or increased shortness of breath.
- Any new or increased chest pain.
- Any new or increased pain/difficulty while breathing.
- Any new or increased cough or any significant change in your type of cough; for example, any new or increased mucous or blood in your cough.
- Any change in the amount of oxygen you require.
- Any fever, fatigue or other symptoms that occur at the same time as any changes to your breathing or other lung symptoms.

If you start to develop symptoms, your study doctor will ask you to return to the clinic for additional tests, which could include a physical exam, measurement of oxygen levels, blood tests, chest X-rays, and/or CT scans. You will be monitored very closely for changes in your overall lung symptoms, monitoring may require hospitalization. You may require specific treatment in order to control pneumonitis. You may also be seen by a special doctor called a pulmonologist, who has special training to be an expert in how your lungs work.

Prolonged treatment with medicines that suppress inflammation, sometimes needed to manage the side effects of nivolumab treatment, may lower your body's ability to fight off certain infections (i.e.

opportunistic infections). These infections may require treatment with antibiotic or antifungal medications and may be fatal.

Risks of Blood Draw:
You may feel some discomfort when the needle is placed in your vein to draw blood for testing. Sometimes a bruise may develop where the blood was drawn or the needle was placed, and occasionally infection or bleeding may develop at the puncture site. Light-headedness and/or fainting may occur during blood collection.

Risks Related to Imaging
This research study includes exposure to radiation from x-rays or gamma-rays if you have CT-guided biopsies. This radiation exposure is for research purposes only and is not part of your medical care. X-rays and gamma rays can damage the genetic material (DNA) in cells. At low doses, cells usually can repair this damage. There is some possibility that an incorrect repair may increase the risk of cancer in your lifetime. The normal lifetime risk of cancer is 25%. A radiation dose of 15 rems (a rem is a unit of radiation dose) would increase your lifetime risk to 25.6%.

The radiation exposure that you may get in this research study is 5.0 rems (The radiation exposure that you will get from the three CT guided biopsies is 2.4 rem. You will also receive 0.8 rems for one extra bone scan and 1.8 rems for one extra CT scan if you have the scans repeated at the time of disease worsening) (a rem is a unit of absorbed radiation). To put that in context, the average person in the United States gets a radiation exposure of 0.3 rems per year from natural sources, like the sun, outer space, air, food, and soil. People who work with radiation (for example, X-ray technologists) are allowed a maximum exposure of 5.0 rems each year. Although these levels of radiation are thought to cause an increased risk of cancer, studies in people who work with radiation have rarely shown a measurable increase in cancer risk.

The radiation exposure described here is what you will get from this research study only. It does not include any exposure you may have received or will receive from other tests outside of this study that are a part of your medical care. Radiation risk builds up with each exposure. You should think about your own history of radiation exposure from tests (like X-rays or CT scans) in deciding about the radiation in this study. If you have questions about the total amount of radiation you will be receiving, you should ask your doctor.

Other Risks in the Study:
Your cancer may continue to grow if you elect to participate in this study. You may develop symptoms from cancer or the cancer may spread during this clinical trial.

Genetic information is unique to you and your family, even without your name or other identifiers. Johns Hopkins follows procedures to prevent people who work with your DNA information from being able to discover it belongs to you. However, new techniques are constantly being developed that may in the future make it easier to re-identify genetic data, so we cannot promise that your genetic information will never be linked to you.

There may be side effects and discomforts that are not yet known.

5. Are there risks related to pregnancy?

You must agree not to cause pregnancy during the study and for a period of 7 months after you receive the last dose of study drug. Pregnancy could possibly result in birth defects or death to the embryo or

fetus that is conceived while you are receiving the study drug or after you receive the last dose of study drug. It is, therefore, very important that you do not cause a pregnancy.

If you are a man who is still able to get a woman pregnant (in other words, not surgically sterilized), you must agree for you or your partner to use 2 acceptable methods of contraception (for example, a barrier method such as a diaphragm, condom with spermicide, cervical cap, or sponge) for up to 7 months after the last dose of study drug.

If you do cause a pregnancy while in this research study, you must agree to inform your study doctor immediately. The study doctor will ask to follow the outcome of your partner's pregnancy.

In case of a pregnancy, your partner's pregnancy and its outcome will be reported to Bristol-Myers Squibb, the manufacturer of the study drug. Your pregnant partner will be asked to read and sign a separate consent form to allow this information to be sent to Bristol-Myers Squibb.

This research may hurt an embryo or fetus in ways we do not currently know.

6. Are there benefits to being in the study?

You may or may not directly benefit from being in this study. If you take part in this study, you may help others in the future.

7. What are your options if you do not want to be in the study?

If you decide not to join this study, other options are available. You do not have to join this study to get treatment. Other treatments include additional androgen deprivation therapy or chemotherapy along with blood work, CT scans, and bone scans.

You do not have to join this study. If you do not join, your care at Johns Hopkins will not be affected.

8. Will it cost you anything to be in this study?

You will receive a separate Insurance and Research Participant Financial Responsibility Information Sheet (Sheet).

This Sheet will give you the following information:

- The procedures, tests, drugs or devices that are part of this research and that will be paid for by the study (no cost to you).
- The procedures, tests, drugs or devices that will be billed to you and/or your health insurer. If you have health insurance, you will be responsible for any co-pays or deductibles not covered by your insurance.

9. Will you be paid if you join this study?

You will not be paid to join this study.

10. Can you leave the study early?

- You can agree to be in the study now and change your mind later.
- If you wish to stop, please tell us right away.
- Leaving this study early will not stop you from getting regular medical care.

If you leave the study early, Johns Hopkins may use or give out your health information that it has already collected if the information is needed for this study or any follow-up activities.

11. Why might we take you out of the study early?

You may be taken out of the study if:

- Staying in the study would be harmful.
- You need treatment not allowed in the study.
- You fail to follow instructions.
- The study is cancelled.
- There may be other reasons to take you out of the study that we do not know at this time.

If you are taken out of the study or stop taking the study drug, we will ask you to come in for a final visit about 1 month after your last dose of study drug. You will have a physical exam, blood tests, review of your medications, CT scan, and bone scan. We will also contact you by telephone and/or email 100 days after your last dose of study drug to review and assess any adverse side effects you may experience and once every 6 months for up to 1 year following. We will also contact you monthly for reassessment if you discontinue the study because of adverse side effects, continuing until the event(s) resolve or stabilize.

12. How will your privacy be protected?

We have rules to protect information about you. Federal and state laws and the federal medical Privacy Rule also protect your privacy. By signing this form, you provide your permission, called your "authorization" for the use and disclosure of information protected by the Privacy Rule.

The research team working on the study will collect information about you. This includes things learned from the procedures described in this consent form. They may also collect other information including your name, address, date of birth, and information from your medical records (which may include information about HIV status, drug, alcohol or STD treatment, genetic test results or mental health treatment).

The research team will know your identity and that you are in the research study. Other people at Johns Hopkins, particularly your doctors, may also see or give out your information. We make this information available to your doctors for your safety.

People outside of Johns Hopkins may need to see or receive your information for this study. Examples include government agencies (such as the Food and Drug Administration), safety monitors, other sites in the study, and companies that sponsor the study.

The Department of Defense (DoD) and the U.S. Army Medical Research and Materiel Command (USAMRMC) will have access to study records for audit purposes.

If you are in a cancer study that receives federal funding, the National Cancer Institute (NCI) now requires that we report identifiable information (such as, zip code) about your participation. You may contact the NCI if you have questions about how this information is used.

We cannot do this study without your authorization to use and give out your information. You do not have to give us this authorization. If you do not, then you may not join this study.

We will use and disclose your information only as described in this form and in our Notice of Privacy Practices; however, people outside Johns Hopkins who receive your information may not be covered by this promise or by the federal Privacy Rule. We try to make sure that everyone who needs to see your information keeps it confidential – but we cannot guarantee that your information will not be re-disclosed.

The use and disclosure of your information has no time limit. You may revoke (cancel) your permission to use and disclose your information at any time by notifying the Principal Investigator of this study by phone or in writing. If you contact the Principal Investigator by phone, you must follow-up with a written request that includes the study number and your contact information. The Principal Investigator's name, address, phone, and fax information are on page one of this consent form.

If you do cancel your authorization to use and disclose your information, your part in this study will end and no further information about you will be collected. Your revocation (cancellation) would not affect information already collected in the study, or information we disclosed before you wrote to the Principal Investigator to cancel your authorization.

Study Sponsor:
A sponsor of this study is the Department of Defense Prostate Cancer Research Program (DoD PCRP). Representatives of the DoD may need to review your research records as part of the study and are authorized to do so.

13. Will the study require any of your other health care providers to share your health information with the researchers of this study?

14. As a part of this study, the researchers may ask to see your health care records from your other health care providers. **What does a conflict of interest mean to you as a participant in this study?**
A researcher has a financial or other interest in this study.

In some situations, the results of this study may lead to a financial gain for the researcher and/or Johns Hopkins. This financial interest has been reviewed in keeping with Johns Hopkins' policies. It has been approved with certain conditions, which are intended to guard against bias and to protect participants.

If you have any questions about this financial interest, please talk to Dr. Mark Markowski at 410-955-0567. This person is a member of the study team, but does not have a financial interest related to the study. You may also call the Office of Policy Coordination (410-361-8667) for more information. The Office of Policy Coordination reviews financial interests of researchers and/or Johns Hopkins.

15. What treatment costs will be paid if you are injured in this study?

Neither Johns Hopkins nor the DoD PCRP, a study sponsor, have a program to pay you if you are hurt or have other bad results from being in the study. However, medical care at Johns Hopkins is open to you as it is to all sick or injured people.

The costs for any treatment or hospital care you receive as the result of a study-related injury that are not covered by a health insurer will be billed to you.

By signing this form you will not give up any rights you have to seek compensation for injury.

16. What other things should you know about this research study?

a. What is the Institutional Review Board (IRB) and how does it protect you?
The Johns Hopkins Medicine IRB is made up of:

- Doctors
- Nurses
- Ethicists

- Non-scientists
- and people from the local community.

The IRB reviews human research studies. It protects the rights and welfare of the people taking part in those studies. You may contact the IRB if you have questions about your rights as a participant or if you think you have not been treated fairly. The IRB office number is 410-955-3008. You may also call this number for other questions, concerns or complaints about the research.

When the Johns Hopkins School of Medicine Institutional Review Board (IRB) reviews a study at another site, that site (institution) is solely responsible for the safe conduct of the study and for following the protocol approved by the Johns Hopkins IRB.

b. What do you do if you have questions about the study?
Call the principal investigator, Dr. Mark C. Markowski at 410-614-0567. If you wish, you may contact the principal investigator by letter or by fax. The address and fax number are on page one of this consent form. If you cannot reach the principal investigator or wish to talk to someone else, call the IRB office at 410-955-3008.

c. What should you do if you are injured or ill as a result of being in this study?
If you think you are injured or ill because of this study, call Dr. Mark C. Markowski at 410-955-0567 during regular office hours.

If you have an urgent medical problem related to your taking part in this study, call the medical oncology clinic at 410-955-8893 during regular office hours and at 410-955-4331 after hours and on weekends.

d. What happens to Data and Biospecimens that are collected in the study?
Johns Hopkins, our research partners, and the DoD PCRP, a sponsor of this research, work to understand and cure diseases. The biospecimens and/or data you provide are important to this effort.

Both Johns Hopkins and the DoD PCRP, a sponsor of this research, may study your data and the tissue, blood or other specimens collected from you.

If you join this study, you should understand that you will not own your biospecimens or data, and should researchers use them to create a new product or idea, you will not benefit financially.

With appropriate protections for privacy, Johns Hopkins may share your biospecimens and information with our research sponsors and partners.

17. What does your signature on this consent form mean?

Your signature on this form means that: You understand the information given to you in this form, you accept the provisions in the form, and you agree to join the study. You will not give up any legal rights by signing this consent form.

WE WILL GIVE YOU A COPY OF THIS SIGNED AND DATED CONSENT FORM

Signature of Participant	(Print Name)	Date/Time
Signature of Person Obtaining Consent	(Print Name)	Date/Time
Signature of Witness to Consent Procedures (optional unless IRB or Sponsor required)	(Print Name)	Date/Time

I have received the separate Insurance and Research Participant Financial Responsibility Information Sheet.

Signature of Participant, LAR or Parent/Guardian	(Print Name)	Date/Time

NOTE: A COPY OF THE SIGNED, DATED CONSENT FORM MUST BE KEPT BY THE PRINCIPAL INVESTIGATOR; A COPY MUST BE GIVEN TO THE PARTICIPANT; IF YOU ARE USING EPIC FOR THIS STUDY A COPY MUST BE FAXED TO 410-367-7382; IF YOU ARE NOT USING EPIC A COPY MUST BE PLACED IN THE PARTICIPANT'S MEDICAL RECORD (UNLESS NO MEDICAL RECORD EXISTS OR WILL BE CREATED).

ONLY CONSENT FORMS THAT INCLUDE THE JOHNS HOPKINS MEDICINE LOGO CAN BE USED TO OBTAIN THE CONSENT OF RESEARCH PARTICIPANTS.

DOCUMENTATION OF PHYSICIAN/MID-LEVEL PROVIDER CONSENT

My signature below indicates that I have discussed the risks, benefits, and alternatives, answered any questions, and believe the participant is able to make an informed choice to join the study.

Signature of Physician/Mid-Level Provider	(Print Name)	Date/Time
Signature of Participant	(Print Name)	Date/Time
Signature of Witness to Consent Procedures (optional unless IRB or Sponsor required)	(Print Name)	Date/Time

NOTE: A COPY OF THE SIGNED, DATED CONSENT FORM MUST BE KEPT BY THE PRINCIPAL INVESTIGATOR; A COPY MUST BE GIVEN TO THE PARTICIPANT; IF YOU ARE USING EPIC FOR THIS STUDY A COPY MUST BE FAXED TO 410-367-7382; IF YOU ARE NOT USING EPIC A COPY MUST BE PLACED IN THE PARTICIPANT'S MEDICAL RECORD (UNLESS NO MEDICAL RECORD EXISTS OR WILL BE CREATED).

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MEDICINE

Insurance and Research Participant Financial Responsibility Information Sheet

Clinical Research Study Title: COMbination of Bipolar Androgen Therapy and Nivolumab in Patients with Metastatic Castration-Resistant Prostate Cancer [COMBAT-CRPC]

Principal Investigator: Mark Markowski

eIRB #: IRB00164973

Date: 07/21/2020 – CIR00059512

The following procedures, tests, drugs or devices are part of this research and will be supplied free of charge by the study:

- Testosterone Cypioinate IM
- Rectal Swab
- Germline DNA Testing
- Hepatitis B/C
- RECIST Read
- Core Tumor Biopsy
- Plasma for MANAs/TAAs
- Plasma for Chemokines
- 18F-DCFPyL PET imaging Scan #1 & #2 [including radiotracer]
- Nivolumab IV

You and/or your health insurer will be responsible for all other procedures, tests, drugs or devices that are part of this study such as the following:

- EKG
- Drug Administration [for both drugs]
- Physical Exam
- CBC, Diff
- CMP
- PSA
- Serum Testosterone
- Serum Amylase, Lipase, CK, TSH [with reflex T3,T4]
- Coagulation
- Urinalysis
- Radiologic Tests

If you have health insurance, you will be responsible for any co-pays or deductibles not covered by your insurance.

For questions about your bill, including payment plans, financial assistance or information changes, please call:

1-855-662-3017