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# FOcal Radiation for Oligometastatic Castration-rEsistant Prostate Cancer (FORCE)

NCT03556904

# UNIVERSITY OF MICHIGAN
# CONSENT TO BE PART OF A RESEARCH STUDY

## 1. KEY INFORMATION ABOUT THE RESEARCHERS AND THIS STUDY

**Study title:** Focal Radiation for Oligometastatic Castration-Resistant Prostate Cancer (FORCE): A Phase II Randomized Trial

**Company or agency sponsoring the study:**

- The University of Michigan is the sponsor of this trial and Dr. Zachery Reichert is the lead investigator (sponsor-investigator).
- Prostate Cancer Foundation

**Names, degrees, and affiliations of the principal investigator:**

**Principal Investigator**

Zachery Reichert, MD, PhD Internal Medicine, Hematology/Oncology, University of Michigan

### 1.1 Key Study Information

You may be eligible to take part in a research study. This form contains information that will help you decide whether to join the study. All information in this form is important. Take time to carefully review this information. After you finish, you should talk to the researchers about the study and ask them any questions you have. You may also wish to talk to others such as your friends, family, or other doctors about your possible participation in this study. If you decide to take part in the study, you will be asked to sign this form. Before you do, be sure you understand what the study is about.

## 2. PURPOSE OF THIS STUDY

### 2.1 Study purpose:

This study is looking at a type of cancer called metastatic castration-resistant prostate cancer (CRPC). Systemic therapy alone, such as chemotherapy, is not curative for subjects with this type of cancer. The main purpose of this study is to assess whether the addition of radiotherapy to standard of care systemic treatment for men with oligometastatic castration–resistant prostate cancer improves over systemic therapy alone.

You are being asked to take part in this study because you have oligometastatic castration-resistant prostate cancer.

## 3. INFORMATION ABOUT STUDY PARTICIPANTS (SUBJECTS)

Taking part in this study is completely **voluntary**. You do not have to participate if you don't want to. You may also leave the study at any time. If you leave the study before it is finished, there will be no penalty to you, and you will not lose any benefits to which you are otherwise entitled.

### 3.1 Who can take part in this study?

You are being asked to take part in this study because you have oligometastatic castration-resistant prostate cancer.

Every study has strict guidelines for determining which people may participate. These are called eligibility criteria. You will need to meet all of these criteria before you can participate in this study. If you agree to consider participating in this study, you will undergo evaluations to see if you meet the eligibility criteria for this study. Even though you may meet all the criteria for participation, it is possible that you may not be enrolled in this study for other reasons. These reasons will be explained to you should this occur.

**3.2 How many people (subjects) are expected to take part in this study?**
A total of approximately 72 subjects at several institutions will take part in this study, including approximately 57 from the University of Michigan.

## 4. INFORMATION ABOUT STUDY PARTICIPATION

**4.1 What will happen to me in this study?**
The study team will explain the research study and answer any questions you have about the study. If you still want to participate in the study the study team will request you sign the consent form prior to any activities occurring that pertain to the study. Once your consent is obtained, the study team will look through your medical chart, ask you questions, and begin scheduling tests and procedures to determine if you are eligible for the study. The study team will inform you of the types of tests and procedures required before the study begins.

Many of the procedures that will be performed during the study, including routine blood tests, disease evaluations, physical examinations, vital signs (blood pressure, heart rate, breathing rate, and temperature) and measurement of height and weight, would normally be done as part of your standard of care regardless of study participation. However, some of these may be done more frequently as a result of your participation in this study. Tests and procedures that are done more often than your regular medical care because of your study participation and that are solely for research purposes will be identified below. The study staff will inform you of the types of tests and procedures you have to undergo during the study.

Refer to the study calendar at the end of this section for information about what to expect during each study visit.

<u>Subject Responsibilities</u>
As a subject in this study, you are responsible (among others) to:

- Follow the instructions the Investigator and study staff give you;
- Attend all study visits as scheduled;
- Not be part of any other research study while participating in this study, including medical devices;
- Report any changes to your health, side effects or injury to the Investigator, whether you think they are related to the study drug or not;
- Complete study questionnaires

**Before starting the study:** Some exams, tests, and procedures will be required to find out if you can be in this study. If you have had some of the tests recently, they may not need to be repeated. The screening tests and procedures do not have to be completed in one day and you are allowed to take breaks if you have multiple procedures in one day.

The following tests and procedures will be performed during screening and/or at one or more study visits. Refer to the study calendar in Attachment 1 for information about which procedures will be performed at certain study visits.

- **Medical History:** A complete medical history will be taken, including any medications you have used or are currently using and any prior cancer therapies you have had. History of infections, bowel/bladder problems and seizures will also be taken.
- **Physical Exam** & **Vital Signs:** Your blood pressure, temperature, heart rate/pulse, height, and weight will be measured. Your study doctor will ask your date of birth, race, and ethnicity. Additionally, your study doctor will examine you physically, and also assess your body condition from the status of limitation to daily life (Called ECOG performance status).
- **Blood Samples:** We will use a needle to take blood samples from your vein. Some of the blood samples will be used up during analysis and others will be kept for longer periods of time.
    - **Hematology and Chemistry:** These blood samples (about 2-3 teaspoons per each sample) will be used to evaluate your blood counts and blood chemistry.
    - **Correlative Studies (Circulating Analytes):** Blood samples will be collected to look for any tumor cells or DNA that may circulate in the blood. Each blood draw will be a total collection of (2-3 teaspoons). *These samples will be taken for research purposes.*

- **OPTIONAL Radiographic Correlative Research Study:** If you are randomized to Arm 2, you may decide to undergo an additional PET/CT scan before starting radiation therapy. PET is an established scanning technique that uses small amounts of radioactive material, in this study 68Ga-PSMA. This radioactive (tracer) material is injected in one of your veins and then spreads throughout the body. Using such PET scanners, one can see where the radioactive material is located in the body. CT utilizes x-rays that travel through your body from the outside. CT images provide an exact outline of your body organs. This scan is needed to produce high-quality PET images. PET/CT merges PET and the CT scanners into a single device. It is a clinically accepted and FDA approved cancer-imaging device. This will be performed before the start of radiation. You can make your choice in section 12 of this consent. *This scan will be performed for research.*

  **<u>What is 68Ga-PSMA PET/CT?</u>**
  PSMA is a naturally occurring substance (receptor) which is found in the normal prostate, but much more so in prostate cancer. Gallium-PSMA is a substance that binds to this PSMA receptor. When radiolabeled with Gallium-68 (68Ga-PSMA), it can be used to image prostate cancer in the human body. By participating, you may receive 68Ga-PSMA PET/CT imaging as part of this study. Please note that the <u>radioactive</u> material (68Ga-PSMA) is <u>not approved by the U.S. Food and Drug Administration (FDA) and its use is investigational</u>.

- **Subject Questionnaire:** You will need to complete one questionnaire to assess your quality of life. *This is for research purposes.*

- **Tumor Assessment:** Radiologic evaluations and measurements will be performed via computed tomography (CT) scan, magnetic resonance imaging (MRI), or bone scan. Scans which look at the status of your disease and evaluate your response to your investigational study treatment. An MRI scan uses magnets to create images of the inside of your body. A CT scan uses X-rays to create image of the inside of your body. If you have cancer in your bones, a bone scan may be used in addition.
- **Simulation Visit**
- **Treatment Planning**

**Study Intervention (for Research):**
This study will be conducted under two arms:

- Arm 1: Systemic standard of care treatment
- Arm 2: Systemic standard of care treatment plus radiotherapy

For this study a cycle is defined as 42 days.

Subjects will be randomized to an arm of the trial, like a flip of a coin.

Current systemic standard of care treatment is most commonly enzalutamide or abiraterone in combination with prednisone, both of which options are FDA approved in this setting of prostate cancer. Abiraterone is taken orally once daily at 1,000 mg (two 500 mg tablets or four 250 mg tablets) with prednisone 5 mg daily or 5 mg twice a day. Enzalutamide is taken orally once daily at 160 mg (four 40 mg capsules). Abiraterone must be taken on an empty stomach (no food 2 hours prior and 1 hour after) while enzalutamide can be taken with or without food. All drugs must be swallowed whole without crushing, chewing, dissolving or breaking. Either oral systemic standard of care treatment options will be given daily (no breaks), indefinitely until treatment failure.

Docetaxel chemotherapy is also an option (although less common then the above oral medications) that your medical oncologist may consider. This is given by injection every 3 weeks.

Radiation exposure:
Radiotherapy will be delivered to a dose between conventional 30 Gy in 10 fractions, to SBRT with 50 Gy in 5 fractions. Multiple techniques (such as timing treatment with your breathing, using pads to position subjects consistently and giving lower dose radiation from multiple different angles) will minimize radiation to normal tissues will be done.

Subjects on Arm 2 may participate in an optional imaging procedures to be carried out for research reasons. Subjects which agree will be exposed to radiation in the form of beta and gamma rays. The biological effect of radiation is measured in terms of Sieverts (Sv) or mSv (1/1000 Sv). The PET/CT scanner has two components: both the CT portion of the scan and the PET portion of the scan expose you to a small amount of radiation.

- **30 (± 7) days after radiation termination**

- Physical exam, vital signs
- Blood samples will be collected to evaluate your blood counts and blood chemistry
- Blood samples will be collected to look for any tumor cells or DNA that may circulate in the blood
- Discussion with provider regarding any side effects
- Subject Questionnaire

**End of Treatment:**
If you stop the study intervention for any reason , you will be asked to return for an End of Treatment visit 30 days after your last treatment dose .

**Follow-up:**
If you stop the study intervention for reasons other than disease progression, you will be followed for disease status every 6 months (± 31 days) via telephone or office visit for up to 2.5 years from treatment stop or until disease progression or you start another prostate cancer directed therapy (excluding bisphosphonates or RANKL inhibitors), whichever comes first.

If you stop the study intervention for progression, patients you will be followed for survival and start of any other prostate cancer directed therapy (excluding bisphosphonates or RANKL inhibitors) every 6 months (± 31 days) via telephone or office visit documentation for up to 2.5 years from treatment discontinuation.

OPTIONAL Research Samples Stored for Unspecified Future Research:
Besides the information about the main study, the following information is specific to unspecified future use of identifiable data and/or biospecimens. We would also like your permission to keep some of your blood and medical information collected in the main study, so that we may study it in future research. The future research may be similar to this study or may be completely different.

You can take part in the main study even if you decide not to let us keep your blood and medical information for future research.

If you give us permission, we will use your blood and medical information for future research. Even if you give us permission now to keep some of your blood and medical information, you can change your mind later and ask us to destroy it. Keep in mind, however, that once we have analyzed your blood we may not be able to take the information out of our research.

We may share your blood and medical information with other researchers, so that they can use it in their research. Their research may be similar to this study or may be completely different. Once we have shared your blood and medical information with other researchers, we will not be able to get it back. Future use of your identifiable data and/or specimens will be conducted in compliance with applicable regulatory requirements.

You will not find out the results of future research on your blood a samples. Allowing us to do future research on your blood and medical information will not benefit you directly.

With appropriate permissions, your samples and collected information may also be shared with other researchers here, around the world, and with companies.

Your identifiable private information or identifiable biospecimens may be stripped of identifiers and used for future research studies or distributed to another researcher for future research studies without additional informed consent.

Research can lead to new discoveries, such as new tests, drugs, or devices. Researchers, their organizations, and other entities, including companies, may potentially benefit from the future research on your blood and medical information. You will not have rights to these discoveries or any proceeds from them.

You can make your choice about whether to participate in the Optional substudy (storage of research samples for future use) in Section 12 of the consent.

**4.2 How much of my time will be needed to take part in this study?**
Participating in a research study can be an inconvenience to your daily life. Please consider study time commitments and responsibilities as a research subject when you are deciding to participate.

The length of your study visits will vary depending on which procedures need to be done. The screening visit may take approximately 4 hours.

Radiotherapy will be administered per radiation oncologist recommendation. It will complete within 8 weeks, but may be daily (Monday-Friday) for several weeks. Each session takes approximately 30 minutes.

On clinic days when you are not receiving radiation, each visit will take approximately 1 hour (unless you are receiving docetaxel, then it is 4 hours). On days when you see the oncologist and receive radiotherapy, these visits may take approximately 3 hours. If you need to have a CT, MRI or bone scan, these visits will take longer.

**4.3 When will my participation in the study be over?**
The average time of study treatment is expected to be under 2 years, but some may respond longer. You will also be followed every 6 months (± 31 days) via telephone or office visit for up to 2.5 years from treatment discontinuation.

**4.4 What will happen with my information and/or biospecimens used in this study?**
Your collected information and biospecimens may also be shared with other researchers, both here or around the world, or with companies.

Additionally:

• With appropriate permissions, your identifiable collected information and biospecimens may be shared, and/or,

• Without your additional consent, your identifiable private information and identifiable biospecimens may be stripped of identifiers and used for future research studies or distributed to another researcher for future research studies.

## 5. INFORMATION ABOUT RISKS AND BENEFITS

**5.1 What risks will I face by taking part in the study? What will the researchers do to protect me against these risks?**

Your study doctor and study staff will monitor you closely for side effects. Even with frequent blood tests and other examinations, taking the study drug involves risks, and some side effects cannot be predicted. Side effects can range from mild to severe and life-threatening. Many side effects will get better when you stop taking the study drug, but some may be long lasting or may never go away. Side effects may even cause death. You should tell your study doctor immediately about any side effects that you have or any change in how you feel while on this study. If you have side effects, your dose may have to be reduced, or you may have to stop taking the drugs and wait until you feel better before you start again. Your study team may give you medicines or lower your dose of drugs to help lessen side effects. If any side effect is intolerable, you may have to permanently stop taking the drugs.

These risks will be minimized by monitoring you carefully. We will provide the usual supportive care that would be routinely given to someone with your condition. If you have side effects from the investigational study treatment, we will make appropriate adjustments as defined by the study protocol. You may need to discontinue the investigational study treatment if the side effects are too serious.

• If you have signs of infection, you will receive appropriate antibiotics.
• If you have signs of bleeding you may need to receive transfusions of platelets, plasma, or red cells.
• If you are at risk of having blood clots, you will receive an anticoagulant (blood thinner).
• If your hemoglobin level is too low, you may receive a red cell transfusion.
• If you start feeling sick to your stomach, you will be given medications to help reduce nausea.
• If you have vomiting, you may be given fluids through an IV.

The known or expected risks are:

**Risks of Abiraterone:**

The following side effects are common (occurring in greater than 30%) for subjects taking abiraterone:

- Fluid Retention
- Increased triglycerides
- Increased liver enzymes (AST)

These side effects are less common (occurring in 10-29%) side effects for subjects receiving abiraterone:

- Joint swelling / discomfort
- Decreased levels of potassium in your blood (hypokalemia)
- Swelling of the hands/feet (Peripheral Edema)

- Muscle aches / discomfort
- Decreased levels of phosphorus in your blood (hypophosphatemia)
- Hot flashes
- Diarrhea
- Urinary tract infections
- Cough
- Increased ALT (liver enzyme)

**Risks of Enzalutamide:**

The following side effects are common (occurring in greater than 30%) for subjects taking enzalutamide:

- Fatigue

These are less common (occurring in 10-29%) side effects for subjects receiving enzalutamide:

- Back pain, joint aches, musculoskeletal pain
- Diarrhea
- Hot flashes
- Peripheral edema (swelling in your hand, arms, legs, or feet)
- Low white blood cell count
- Headache
- Upper respiratory tract infection
- Dizziness
- Muscle weakness

Among the uncommon side effects, subjects taking enzalutamide should be aware that there is a risk for seizures in subjects taking this medication. Although it occurs in less than 1% of subjects, they should be aware of the risk when engaging in any activity where sudden loss of consciousness could cause serious harm to themselves or others.

**Risks of Prednisone:**

The following side effects are common (occurring in greater than 30%) for subjects taking prednisone:

- Increased appetite
- Irritability
- Difficulty sleeping (insomnia)
- Swelling in your ankles and feet (fluid retention)
- Nausea, take with food
- Heartburn
- Muscle weakness
- Impaired wound healing
- Increased blood sugar levels. (Persons with Diabetes may need to have blood sugar levels monitored more closely and possible adjustments to diabetes medications)

The following are less common side effects (occurring in 10 to 29%) for subjects receiving prednisone:

- Headaches
- Dizziness
- Mood swings
- Cataracts and bone thinning (with long-term use)

**Risks of Docetaxel:**

The following side effects are common (occurring in greater than 30%) for subjects taking docetaxel:

- Hair loss
- Nail changes
- Diarrhea
- Nausea
- Vomiting
- Low blood counts
- Numbness
- Fevers

The following are less common side effects (occurring in 10 to 29%) for subjects receiving docetaxel:

- Swelling
- Mouth sores
- Nerve pain
- Infections

Among an uncommon side effects, subjects taking docetaxel should be aware that there is a risk of severe skin rashes or blood clots requiring hospitalization. These occur in less than 1% of subjects.

**Risks of Radiation:**

This treatment is associated with both short term side effects and long term risks. Radiation is delivered to a specific site and the side effects are related to which structures are within the treatment field. Most subjects will experience redness or erythema at the treated site which typically resolves within 1-2 weeks. Rarely, the treated site may become infected and require antibiotics. The treated tumor may initially become irritated during radiation therapy leading to increased pain and discomfort. Additionally, temporary hair loss in the treated region is expected. Subject may also experience feeling tired and nausea during radiation. The long term risks of radiation include hardening or fibrosis of the treated skin, changes in skin pigmentation, and the formation of small superficial blood vessels on the skin known as spider veins or telangiectasia. If the treated site is close to the eye, cataracts are also a long term risk of radiation. Radiation therapy to or near the testes or ovaries may lead to infertility. Radiation therapy can also affect vital organs in the body including the liver, lungs, and kidneys. Additionally, radiation therapy can cause a secondary cancer at the treated site.

Likely (occurring in over 20% of people):

- Nausea
- Feeling tired
- Temporary hair loss

- Cataracts (only if treated lesion is close to the eye)
- Skin redness
- Changes in skin pigmentation

Less Likely (occurring in less than 20% of people):

- Infection
- Permanent hair loss
- Skin hardening or fibrosis
- Swelling or edema

Rare, but Serious (occurring in less than 2% of people):

- New (secondary) cancers
- Damage to vital organs including lung, liver, kidneys, and bowel
- Fracture

**Blood Draws Risks:** Collection of blood samples may cause pain, bleeding, bruising, or infection. It is also possible that you may feel lightheaded or faint. Please tell your study doctor or the study nurse if you do not feel well after having your blood drawn at any time during your study participation.

**68Ga-PSMA PET/CT Scan Risks:**

The known or expected risks are related to the injection of the radioactive substance $^{68}$Ga-PSMA as well as the radiation associated with PET/CT imaging. If you are claustrophobic you may feel some anxiety while positioned in the PET/CT scanner. Also, some individuals find it uncomfortable to stay in one position for the duration of this scan. The researchers have taken steps to minimize the risks of this study. Even so, you may still have problems or side effects related to your participation, even when the researchers are careful to avoid them.

For the intravenous IV line placement and blood draws, the risks are:

- bleeding, discomfort, bruising at the site, and the rare risk of infection
- dizziness, lightheadedness or even fainting when the needle is put in or taken out.

Steps to minimize the risks:

- only qualified personnel will place the IV
- we will use sterile technique to decrease the chance of infection
- the IV will be removed once the imaging is completed.

**For $^{68}$Ga-PSMA the risks are:**

$^{68}$Ga-PSMA was also tested in animal safety and toxicology studies, according to international guidelines. $^{68}$Ga-PSMA has been used widely and successfully in prostate cancer patient outside of the U.S. without any reported side effects. However - as mentioned - the radioactive drug $^{68}$Ga-PSMA is not approved by the Food and Drug Administration (FDA).

**Radiation exposure:**

During the course of this study, as a result of the imaging procedures to be carried out for research reasons, you will be exposed to radiation in the form of beta and gamma rays. The biological effect of radiation is measured in

terms of Sieverts (Sv) or mSv (1/1000 Sv). The PET/CT scanner has two components: both the CT portion of the scan and the PET portion of the scan expose you to a small amount of radiation.

The radiation exposure you will be exposed to in this study will be 16.61 mSv or less. The effects on the body of this radiation exposure will be added to your overall lifetime radiation risk. Your life-time radiation risk includes the background radiation you are exposed to naturally like everyone else living on this planet, which is on the average 3 mSv per year; the maximum radiation you will be exposed to in this study is about 5 years of average background radiation. In terms of radiation a person may get exposed to during medical care, the maximum amount you could receive in this study (thus both PET/CT studies) is similar to the radiation received in one (1) routine X-ray CT scans (CAT scan) of the abdomen and pelvis. The US Federal Government requires that the annual amount of radiation exposure of radiation workers does not exceed 50 mSv per year; the radiation you will be exposed to in this study is about one-third this amount.

Please tell us if you have had any major radiation exposure in the past, particularly in the past two years, such as treatment with x-rays or radioactivity, or diagnostic x-rays, CT-scans or nuclear medicine scans. You must understand also that it is important that you inform the investigators of your participation in any other research studies during the past year.

**Steps to minimize reproductive risks:**

All subjects will be asked to empty their bladder within two hours to minimize bladder exposure. This radiation dose is not expected to produce any harmful effects. The use of these PET tracers is considered to be generally safe and effective as approved by the University of Michigan Radioactive Drug Research Committee in accordance with Food and Drug Administration regulations (21 CFR 361.1). Adverse reactions to tracers used in this study have not been reported. However, the possibility exists for a rare reaction to any of the drugs or procedures to which the participant will be exposed. ACLS-certified staff will be in attendance at all times during the study and an emergency cart will be in close proximity.

Other physical risks involve possible muscle aches from lying still. Medical intervention will be furnished by UMHS if serious adverse effects would occur.

**CT Scan Risks:** CT imaging uses ionizing radiation, which increases your risk of cancer. Everyone is exposed to naturally occurring ionizing radiation every day. The amount of radiation exposure from 1 CT scan is approximately comparable to 1-3 years of natural background radiation. The contrast substance injected during the CT scan may cause pain, burning feeling, sweating, and rarely an allergic reaction that can be serious. If you know you're allergic to iodine, you must inform your doctor immediately. The contrast agent used in the CT scan may cause kidney damage, especially if you're diabetic, dehydrated, and if you're older. In addition, your thyroid function may be affected.

**MRI Risks:**

MRIs done for research that use IV contrast have risks similar to MRIs done for clinical care. Contrast is used to improve the pictures of the inside of the body made by the MRI. Common risks of MRI include: feeling fearful of being in a small enclosed space (claustrophobia) when you are lying inside the MRI scanner, feeling uncomfortable because of the loud noises made by the machines, and feeling uncomfortable with the physical sensations you may feel during the process. You are also exposed to some risk because of the injected contrast, gadolinium-DTPA, which may cause headache, nausea, and local burning sensation.

The contrast agent, gadolinium has been linked to development of Nephrogenic Fibrosing Dermopathy (NFD), also known as Nephrogenic Systemic Fibrosis (NSF). NFD is a thickening of the skin, organs and other tissues and is a rare complication in subjects with kidney disease who undergo an MRI with contrast material. To help prevent this, we will check how well your kidneys work before you have any MRIs. Because of the use of contrast, all female subjects who are able to have children will be required to use adequate birth control. If you have implanted metal objects such as a pacemaker, artificial limbs, or metal joints, you will not be able to have an MRI done, and may not be able to take part in this research.

**Bone Scan Risks:**

A bone scan is a procedure in which a very small amount of radioactive material is injected into a vein in your arm. The radioactive material is then transported by your blood into your bones. This will allow the doctor to monitor the cancer in your bones.

This test uses a small amount of radiation; however, the effects of radiation add up over a lifetime. It is possible that having several of these tests may add to your risk of injury or disease.
When deciding to enter this study, think about your past and future contact with radiation. Examples of contact with radiation include x-rays taken for any reason or radiation therapy for cancer treatment.

**Questionnaire Risks:**

As part of the study, you will be asked to complete questionnaires. Some of the questions may seem very personal or embarrassing. They may make you uncomfortable. You may refuse to answer any of the questions that you do not wish to answer. If the questions make you uncomfortable, we can help you to find a counselor.

**Privacy and Confidentiality Risks:**

There are also non-physical risks associated with taking part in this study, such as the risks associated with the loss of privacy or confidentiality. For example, if your identity as a participant in this research or your identifiable genetic or health information were disclosed to unauthorized persons, there is the possible risk of discrimination by employers or insurance providers. The researchers believe that the risks of such improper disclosure are very small because strict privacy and confidentiality procedures for this research have been adopted.

**Reproductive Risks:**

Men must agree to either abstain from sexual activities that could result in pregnancy or use an acceptable form of birth control while taking part in this study from the time of enrollment, all during investigational study treatment (including during temporary breaks from therapy), and for at least 90 days after the last dose of study drug. Acceptable forms of birth control are male latex condom (with or without spermicide) or vasectomy (with confirmed azoospermia). In addition, men should not donate sperm or semen while taking part in the study and for at least 90 days after the last dose of study drug.

As with any research study, there may be additional risks that are unknown or unexpected.

**5.2 What happens if I get hurt, become sick, or have other problems as a result of this research?**
The researchers have taken steps to minimize the risks of this study. Even so, you may still have problems or side effects, even when the researchers are careful to avoid them. Please tell the researchers listed in Section 10 "Contact Information" (below) about any injuries, side effects, or other problems that you have during this study. You should also tell your regular doctors.

**5.3 If I take part in this study, can I also participate in other studies?**
*Being in more than one research study at the same time, or even at different times, may increase the risks to you. It may also affect the results of the studies*. You should not take part in more than one study without approval from the researchers involved in each study.

**5.4 How could I benefit if I take part in this study? How could others benefit?**
You may not receive any personal benefits from being in this study. There is a chance that the study intervention may improve your quality of life or increase the length of disease-free survival. The researchers hope that the information learned from this study will help other subjects with this type of cancer in the future.

**5.5 Will the researchers tell me if they learn of new information that could change my willingness to stay in this study?**
Yes, the researchers will tell you if they learn of important new information that may change your willingness to stay in this study. If new information is provided to you after you have joined the study, it is possible that you may be asked to sign a new consent form that includes the new information.

## 6. OTHER OPTIONS

**6.1 If I decide not to take part in this study, what other options do I have?**
You do not have to participate in this trial to receive care for your cancer. There may be other ways of treating your metastatic castration-resistant prostate cancer.
These include, but are not limited to:

- You may receive other standard treatments for your cancer outside the trial such as abiraterone/prednisone, enzalutamide, docetaxel, sipuleucel-T, Radium-223 or other experimental treatments.
- You may be eligible for other cancer research studies
- You may receive treatment for pain or other symptoms only
- You may choose to receive no treatment at all

Your doctor can tell you more about these other treatments, their risks and their possible benefits. You should have this discussion about the risks and benefits or other alternatives prior to making your decision about whether or not you wish to take part in this research study.

## 7. ENDING THE STUDY

**7.1 If I want to stop participating in the study, what should I do?**

You are free to leave the study at any time. If you leave the study before it is finished, there will be no penalty to you. You will not lose any benefits to which you may otherwise be entitled. If you choose to tell the researchers why you are leaving the study, your reasons for leaving may be kept as part of the study record. If you decide to leave the study before it is finished, please tell one of the persons listed in Section 10 "Contact Information" (below).

**7.2 Could there be any harm to me if I decide to leave the study before it is finished?**

If you decide to leave the study early, please notify someone on the study team. They will instruct you on how to stop the study safely and you will be advised whether any additional test may need to be done for your safety.

**7.3 Could the researchers take me out of the study even if I want to continue to participate?**

Yes. There are many reasons why the researchers may need to end your participation in the study. Some examples are:

- ✓ The researcher believes that it is not in your best interest to stay in the study.
- ✓ You become ineligible to participate.
- ✓ Your condition changes and you need treatment that is not allowed while you are taking part in the study.
- ✓ You do not follow instructions from the researchers.
- ✓ The study is suspended or canceled.

## 8. FINANCIAL INFORMATION

**8.1 Who will pay for the costs of the study? Will I or my health plan be billed for any costs of the study?**

The study will pay for research-related items or services that are provided only because you are in the study. If you are not sure what these are, see Section 4.1 above or ask the researchers for a list. If you get a bill you think is wrong, call the researchers' number listed in section 10.1.

The drugs abiraterone, prednisone, enzalutamide or docetaxel are standard of care, and will be paid for by your insurance company.

You or your health plan will pay for all the things you would have paid for even if you were not in the study, like:

- Health care given during the study as part of your regular care
- Items or services needed to give you study drugs or devices
- Monitoring for side effects or other problems
- Deductibles or co-pays for these items or services.

If you do not have a health plan, or if you think your health plan may not cover these costs during the study, please talk to the researchers listed in Section 10 below or call your health plan's medical reviewer.

The study team has given you instructions about this research study. It is important that you follow these instructions carefully. If you get sick, have a medical complication, or are injured as a result of your being in the study, call Dr. Reichert, at (734) 764-3066 or (734) 936-4000 (Hospital Operator – 24-hour paging). The doctor will either treat you or send you to another doctor for treatment.

By signing this form, you do not give up your right to seek payment if you are harmed as a result of being in this study.

**8.2 Will I be paid or given anything for taking part in this study?**
No. You will not be paid for taking part in this study.

**8.3 Who could profit or financially benefit from the study results?**
The University of Michigan and the researchers conducting the study have no financial interest in the outcome of the study.

Research can lead to new discoveries, such as new tests, drugs, or devices. Researchers, their organizations, and other entities, including companies, may potentially benefit from the use of the data or discoveries. You will not have rights to these discoveries or any proceeds from them.

## 9. CONFIDENTIALITY OF SUBJECT RECORDS AND AUTHORIZATION TO RELEASE YOUR PROTECTED HEALTH INFORMATION

The information below describes how your privacy and the confidentiality of your research records will be protected in this study.

**9.1 How will the researchers protect my privacy?**
The University of Michigan has rules to protect information about you. Federal and state laws also protect your privacy. Upon enrolling in this study, you will be assigned a unique identification number. All records related to the study will use this identification number instead of your name or other personally identifying information whenever possible. We will take measures to protect the privacy and security of all your personal information, but we cannot guarantee complete confidentiality of study data.

Medical information created by this research study may become part of your hospital medical record and may be forwarded to your primary doctor. Information that does not become part of your medical record will be stored in your study file.

You have the right to request access to your protected health information that is used or shared during this research and that is related to your study treatment for your disease, but you may access this information only after the study is completed. To request this information, please contact the researchers listed in Section 10 “Contact Information” (below).

**Genetic Risks:**

The federal Genetic Information Nondiscrimination Act (GINA) generally makes it illegal for health insurance companies, group health plans, and most employers to discriminate against you based on your genetic information. This law does not protect you against genetic discrimination by companies that sell life insurance, disability insurance, or long-term care insurance. Under this law:

- Health insurance companies and group health plans may not request your genetic information that we obtain from this research
- Health insurance companies and group health plans may not use your genetic information when making decisions regarding your eligibility or premiums
- Employers with 15 or more employees may not use your genetic information that we obtain from this research when making a decision to hire, promote, or fire you or when setting the terms of your employment

GINA does not apply to the following groups, however these groups have policies in place that provide similar protections against discrimination:

- Members of the US Military receiving care through Tricare
- Veterans receiving care through the Veteran's Administration (VA)
- The Indian Health Service
- Federal employees receiving care through the Federal Employees Health Benefits Plans

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.

**9.2 What information about me could be seen by the researchers or by other people? Why? Who might see it?**

Signing this form gives the researchers your permission to obtain, use, and share information about you for this study, and is required in order for you to take part in the study. Information about you may be obtained from any hospital, doctor, and other health care provider involved in your care, including:

- Hospital/doctor's office records, including test results (X-rays, blood tests, urine tests, etc.)
- Mental health care records (except psychotherapy notes not kept with your medical records)
- Alcohol/substance abuse treatment records
- HIV/AIDS status
- Sexually transmitted disease or other communicable disease status
- Health plan/health insurance records
- All records relating to your condition, the treatment you have received, and your response to the treatment
- Billing information
- Demographic information
- Personal identifiers

There are many reasons why information about you may be used or seen by the researchers or others during or after this study. Examples include:

- The researchers may need the information to make sure you can take part in the study.
- The researchers may need the information to check your test results or look for side effects.
- University of Michigan, Food and Drug Administration (FDA), and/or other government officials, auditors, and/or the IRB may need the information to make sure that the study is done in a safe and proper manner.
- Study sponsors or funders, or safety monitors or committees, may need the information to:
    - Make sure the study is done safely and properly
    - Learn more about side effects
    - Analyze the results of the study
- Insurance companies or other organizations may need the information in order to pay your medical bills or other costs of your participation in the study.
- The researchers may need to use the information to create a databank of information about your condition or its treatment.
- Information about your study participation may be included in your regular UMHS medical record.
- If you receive any payments for taking part in this study, the University of Michigan accounting department may need your name, address, social security number, payment amount, and related information for tax reporting purposes.
- Federal or State law may require the study team to give information to government agencies. For example, to prevent harm to you or others, or for public health reasons.

The results of this study could be published in an article, but would not include any information that would let others know who you are.

**9.3 What happens to information about me after the study is over or if I cancel my permission?**
As a rule, the researchers will not continue to use or disclose information about you, but will keep it secure until it is destroyed. Sometimes, it may be necessary for information about you to continue to be used or disclosed, even after you have canceled your permission or the study is over.

Examples of reasons for this include:

- To avoid losing study results that have already included your information
- To provide limited information for research, education, or other activities (This information would not include your name, social security number, or anything else that could let others know who you are.)
- To help the University of Michigan and government officials make sure that the study was conducted properly

As long as your information is kept within the University of Michigan Health System, it is protected by the Health System's privacy policies. For more information about these policies, ask for a copy of the University of Michigan "Notice of Privacy Practices". This information is also available on the web at http://www.uofmhealth.org/patient+and+visitor+guide/hipaa.

**9.4 When does my permission expire?**

Your permission expires at the end of the study, unless you cancel it sooner. You may cancel your permission at any time by writing to the researchers listed in Section 10 "Contact Information" (below). If you withdraw your permission, you may no longer be eligible to participate in this study.

## 10. CONTACT INFORMATION

**10.1 Who can I contact about this study?**

Please contact the researchers listed below to:

- Obtain more information about the study
- Ask a question about the study procedures or treatments
- Talk about study-related costs to you or your health plan
- Report an illness, injury, or other problem (you may also need to tell your regular doctors)
- Leave the study before it is finished
- Express a concern about the study

| | |
|---|---|
| Principal Investigator: | Zachery Reichert, MD, PhD |
| Mailing Address: | 1500 East Medical Center Drive<br>Ann Arbor, MI 48109 |
| Telephone: | (734) 764-3066 |
| Emergency Contact: | (734) 936-4000 (Hospital Operator – 24-hour paging) |

You may also express a concern about a study by contacting the Institutional Review Board listed below.

University of Michigan Medical School Institutional Review Board (IRBMED)
2800 Plymouth Road
Building 520, Room 3214
Ann Arbor, MI 48109-2800
Telephone: (734) 763-4768 (For International Studies: US Country Code: 001)
Fax: (734) 763-1234
Email: irbmed@umich.edu

## 11. RECORD OF INFORMATION PROVIDED

**11.1 What documents will be given to me?**

Your signature in the next section means that you have received signed and dated copies of all of the following documents *(Note: In addition to the copy you receive, copies of this document will be stored in a separate confidential research file and may be entered into your regular University of Michigan medical record.)*:

- This "Consent to be Part of a Research Study" document.
- Other (specify):_____

## 12. SIGNATURES

**Consent/Assent to Participate in the Research Study**

I understand the information printed on this form. I have discussed this study, its risks and potential benefits, and my other choices with_____. My questions so far have been answered. I understand that if I have more questions or concerns about the study or my participation as a research subject, I may contact one of the people listed in Section 10 (above). I understand that I will receive a copy of this form at the time I sign it and later upon request. I understand that if my ability to consent or assent for myself changes, either I or my legal representative may be asked to re-consent prior to my continued participation in this study.

Print Legal Name: _____

Signature: _____

Date of Signature (mm/dd/yy): _____

**Consent/Assent for Participating in an Optional 68Ga- PSMA PET/CT Scan**

This project involves an OPTIONAL 68 Ga-PSMA PET/CT scan for those subjects in Arm 2. I understand that it is my choice whether or not to take part in an OPTIONAL 68Ga-PSMA PET/CT Scan.

I understand that if my ability to consent or assent for myself changes, either I or my legal representative may be asked to re-consent prior to my continued participation in this study.

_____ Yes, I would like to participate in an optional 68Ga-PSMA PET/CT scan
_____ No, I do NOT want to participate in an optional 68Ga-PSMA PET/CT scan

Print Legal Name: _____

Signature: _____

Date of Signature (mm/dd/yy): _____

For Blood for unspecified future research

**Consent/Assent to collect and store for OPTIONAL Research Samples for unspecified future research**
This project involves the option to allow the study team to keep your identifiable specimens/data for use in future research. I understand that it is my choice whether or not to allow future use of my specimens. I understand that if my ability to consent or assent for myself changes, either I or my legal representative may be asked to re-consent prior to my continued participation in this study.

_____ Yes, I agree to let the study team keep and store my specimens for future research.

_____ No, I do not agree to let the study team keep and store my specimens for future research.

Print Legal Name: _____

Signature: _____

Date of Signature (mm/dd/yy): _____

**Principal Investigator or Designee**

I have provided this participant and/or his/her legally authorized representative(s) with information about this study that I believe to be accurate and complete. The participant and/or his/her legally authorized representative(s) indicated that he or she understands the nature of the study, including risks and benefits of participating.

Legal Name: _____

Title: _____

Signature: _____

Date of Signature (mm/dd/yy): _____

Attachment 1: Study Calendar (Cycle is 42 Days)

| Visit Window | Screening (Day -28 to registration) | Day 1 of Cycle 1 and 2 | Day 1 of Cycle 3 and 4 | Day 1s of Cycle 5+[a] | End of Treatment | Follow Up |
|---|---|---|---|---|---|---|
| Informed Consent | X | | | | | |
| Medical/Surgical History, Demographics, Histologic Confirmation | X | | | | | |
| Randomization | X | | | | | |
| PE, Vitals, Weight, Height | X | X | X | X | X | |
| Performance Status | X | X | X | X | X | |
| Adverse Event, Toxicity Evaluations | | X | X | X | X | |
| Medication Review including First Line Systemic Therapy | X | X | X | X | X | |
| Radiotherapy Administration | | X[c] | | | | |
| First Line Systemic Therapy | | X | X | X | | |
| Radiologic evaluations and measurements[b] | X | Radiologic tests are performed every 8 weeks (± 7 days) for the first 2 years. Radiologic tests then are performed every 6 months (± 2 weeks) while in the treatment phase of the study. | | | X | |
| Serum Chemistry, LDH | X | X | X | X | X | |
| CBC with Differential | X | X | X | X | X | |
| PSA | X | X | X | X | X | |
| Testosterone | X | | | | | |
| Questionnaires | X | Within 30 days (±7 days) after radiation completion and every 3 months (± 4 weeks) from randomization for the first 24 months. | | | X | |
| Circulating Correlatives[d] | X | X | X | | X | |
| Radiologic Correlatives | X[f] | | | | | |
| Follow-up | | | | | | X[e] |

a. Subjects will have a clinical and laboratory evaluation every 28 days (±14 days) for 24 weeks.
b. Radiographic evaluation will include radionuclide bone scan, CT or MRI of abdomen and pelvis, and CT, CXR or MRI of the chest as appropriate.
c. Radiotherapy must be delivered during Cycles 1 and 2
d. Circulating correlatives are collected at screening, Cycle 1 Day 1 (±14 days), Cycle 3 Day 1 (±14 days), Cycle 4 Day 1 (±14 days) and EOT (±14 days).
e. Follow-up: every 6 months via telephone or office visit for up to 2.5 years from last study intervention
f. For Subjects on Arm 2 this should be completed before radiologic evaluations begin.

# PERSONAL CENSUS FORM

UMCC # 2017.163

Name _____ Date _____

The National Cancer Institute requires that The University of Michigan Comprehensive Cancer Center report race and ethnicity information about people who participate in clinical research to ensure that all populations are offered the opportunity to participate.

☐ Check here if you do not wish to provide some or all of the information below.

1. What race do you consider yourself to be? (Please select *one or more*)
   - ☐ American Indian/Alaska Native[a]
   - ☐ Asian[b]
   - ☐ Black or African American[c]
   - ☐ Native Hawaiian or Other Pacific Islander[d]
   - ☐ White[e]
   - ☐ More than one race[f]
2. Do you consider yourself to be Hispanic[g]? ☐ Yes ☐ No

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[a] American Indian or Alaska Native- A person having origins in any of the original peoples of North, Central, or South America, and who maintains tribal affiliation or community attachment.

[b] Asian- A person having origins in any of the original peoples of the Far East, Southeast Asia, or the Indian subcontinent, including, for example, Cambodia, China, India, Japan, Korea, Malaysia, Pakistan, the Philippine Islands, Thailand and Vietnam.

[c] Black or African American- A person having origins in any of the black racial groups of Africa. (Terms such as “Haitian” or “Negro” are sometimes used in addition to “Black” or “African American.”)

[d] Native Hawaiian or Other Pacific Islander- A person having origins in any of the original peoples of Hawaii, Guam, Samoa, or other Pacific Islands.

[e] White- A person having origins in any of the original peoples of Europe, the Middle East, or North Africa.

[f] More than one race- (It is preferred that this be selected in addition to the selection of the specific races listed above, but this may also be solely selected.)

[g] Hispanic or Latino- A person of Mexican, Puerto Rican, Cuban, Central or South American, or other Spanish culture or origin, regardless of race. The term “Spanish origin” is sometimes used in addition to “Hispanic” or “Latino.”