INFORMED CONSENT FORM

Sponsor / Study Title:	**MANA RBM / ESCALATE, A Phase III Randomized Study Comparing Xtandi or Nubeqa with Radium-223 vs Xtandi or Nubeqa with Placebo and the Effect upon Symptomatic Skeletal Event-Free Survival for mCRPC Patients**
Protocol Number:	**PC18-1005**
Principal Investigator: (Study Doctor)	«PiFullName»
Telephone:	«IcfPhoneNumber»
Additional Contact(s): (Study Staff)	«AdditionalStaffMemberContacts»
Address:	«PiLocations»

KEY INFORMATION

You are invited to take part in a research study. This research study is studying Xtandi (enzalutamide) or Nubeqa (darolutamide) followed by Xofigo (radium-223) or Placebo (saltwater) as a possible treatment for metastatic castration-resistant prostate cancer (mCRPC). MANA RBM is sponsoring this research study. This Informed Consent provides a summary of this research. It describes the important information that we believe most people need in order to decide whether to take part in this research.

Please read this form carefully. Take your time to ask the study doctor or study staff as many questions about the study as you would like. The study doctor or study staff can explain words or information that you do not understand. Reading this form and talking to the study doctor or study staff may help you decide whether to take part or not. If you decide to take part in this study, you must sign your name at the end of this form and date it.

What should you know about this research?

- The study doctor is being paid by a grant from Bayer Pharmaceutical for carrying out this study.
- Someone will explain this research to you.
- Taking part in this research is voluntary. Whether you take part is up to you. If you don't take part, it won't be held against you.
- You can take part now and later drop out, and it won't be held against you.
- If you don't understand, ask questions.
- Ask all the questions you want before you decide.

Answering the research question will help doctors learn more about best time to add Xofigo after Xtandi or Nubeqa for future patients.

There are risks to taking study drugs and the study procedures that are described later in this document. Some risks could be serious and not all of the side effects/risks are known. You will be monitored closely for any health changes during this study.

What is the research question the study is trying to answer?

The research is designed to answer whether adding monthly Xofigo injection following 12-16 weeks of oral Xtandi or Nubeqa improves your prostate cancer outcome. The best time to add monthly injections of Xofigo after 12-16 weeks of Xtandi or Nubeqa has not been established. This study will add Xofigo after you have taken Xtandi or Nubeqa for 12-16 weeks, rather than giving Xofigo at the same time as Xtandi or Nubeqa. This will allow researchers to evaluate if this dosing schedule will prevent or delay the negative consequences of cancer which has spread to bone such as bone pain, fractures, and spinal cord compression (an area of cancer that presses on the spinal cord). More information on all drugs used in this study are explained later in this document.

About 599 subjects will take part in this research.

How long will you be in this research?

It may take up to 42 days to be accepted into the study during the screening process. Upon entry into the study, there are three (3) phases:

Phase 1 will be 12-16 weeks of an oral (by mouth) therapy. In this phase you will take only Xtandi or Nubeqa with your androgen deprivation therapy (ADT) and a bone health agent.

Phase 2 will take up to 6 months and will include the addition of 1-6 monthly injections with Xofigo (a form of radiation therapy) or placebo along with Xtandi or Nubeqa.

Phase 3 will be follow-up which can last about 3-4 years on average. In total you can expect to be in the study for up to 4 years.

What happens to the information collected for this research?

Efforts will be made to keep your records private to the degree allowed by law. Research records are stored and kept according to legal requirements. You will not be identified in any reports or publications about this study. No one can promise complete secrecy.

Your records may be reviewed by the following groups:

- The IRB (Institutional Review Board) committee that oversees the research;
- The sponsor of the study, their agents or study monitors;
- U.S. Food and Drug Administration;
- Your insurance company;
- Members of the study staff;
- Additional groups explained in the HIPAA Authorization for Research.

If you consent to the additional blood draw for future prostate cancer research those samples will be de-identified (no name or medical record number) and may be used by others without seeking additional consent from you.

There is a risk of potential loss of confidentiality. Every effort will be made to keep your information confidential; however, this cannot be guaranteed. You may stop your participation in this study at any time. A non-medical risk is the disclosure of your protected health information (PHI). PHI is any health information that is collected about you, including your history and new information collected during this study. If your study involves the use of your medical records, you will have an opportunity to review the ways in which your PHI may be used and disclosed in the HIPAA Authorization for Research part of this consent.

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 decide to take part in this research study, you will have tests, exams and procedures that are part of your usual care and you will have additional ones for study purposes. There are 3 drugs that are being studied in this research. Xtandi, Nubeqa and Xofigo. You will take by mouth either Xtandi or Nubeqa for 12-16 weeks. Then you will have either Xofigo or placebo (saline) injected into your veins monthly for 6 months while you continue taking either Xtandi or Nubeqa. Whether you take Xtandi or Nubeqa or receive Xofigo or placebo will be decided by randomizations (flip of a coin) performed by a computer.

What impact will participating in this research have on you? Will your participation reduce your options for standard treatments?
It is not yet known exactly how your participation in this study will impact your future treatment options.

How will your experience in this study differ from treatment outside of the study
There will be a few tests that may not normally done such as:

- Questions about how often you take Xtandi or Nubeqa
- A few tests, similar to games, using an iPAD to measure your cognitive function (brain function)
- A walking test
- ECG (to measure the electrical activity of your heart)
- Two questionnaires answered on an iPAD: one to see how you feel and another to see how well your brain is working

Your doctor visits will take extra time due to these extra tests.

In what ways is this research new?
In this study, if you are on the study drug (Xofigo), you will receive it earlier than you would typically receive it if you were not on this study. It is more common to receive Xofigo only after further prostate cancer progression has occurred. If you are on the placebo (saltwater), your study treatment will be closer to what occurs in most clinical practices.

BACKGROUND AND PURPOSE
You are being asked to participate in this research study because you have ***metastatic castration-resistant prostate cancer (mCRPC.***

Despite your current treatment, your prostate cancer has progressed, and your physician would like to add a drug that will attempt to slow or stop your cancer from growing. For your prostate cancer cells to grow, something called an androgen has to attach to a protein in the prostate cancer cell. The drug your physician would like to add to your current treatment works by blocking the attachment of androgen to prostate cancer cell proteins to slow or stop the cancer from growing. Xtandi and Nubeqa are two such drugs that will be used during the first 12 weeks of this research study, and will continue during and possibly after Xofigo (radium-223) or placebo (saltwater) is added and completed.

If prostate cancer spreads to other parts of the body, it nearly always goes to the bones first. Bone metastasis (spread) can be painful and can cause other problems, such as fractures (breaks), spinal cord compression (an area of cancer that presses on the spinal cord), or high blood calcium levels, which can be dangerous or even life threatening. To treat cancer that has spread to bone, medications called radiopharmaceuticals which that contain radioactive elements are injected into a vein and travel to areas of damaged bones (like those containing cancer spread). Once there, they give off radiation that kills cancer cells. These drugs can be used

to treat prostate cancer that has spread to many bones. Xofigo is such a drug and will be used in this research study.

The purpose of this research study is to:

- Test the safety and effectiveness of the study drugs, Nubeqa or Xtandi followed by radium-223 or placebo (saltwater).
- Determine if adding radium-223 earlier after mCRPC diagnosis will result in fewer fractures and bone-related problems.

Xtandi and Xofigo are routine drugs used for your type of cancer; cancer that has metastasized (spread). Nubeqa is routinely given for cancers that have not metastasized (spread).

The use of ***Nubeqa*** in this study is investigational. An investigational use is one that is not approved by the United States Food and Drug Administration (FDA) for a particular disease status (indication). Nubeqa has been approved by the FDA for patients whose prostate cancer has **not** spread to other parts of the body; it has **not** been approved by the FDA for patients whose prostate cancer **has** spread to other parts of the body. Nubeqa will be supplied to you by the study at no cost to you or your insurance company. You have a 50% chance of getting Nubeqa.

Xtandi is FDA approved for patients that have demonstrated that their prostate cancer has spread to other parts of the body. Therefore, Xtandi is billable to your insurance company and you will be responsible for any co-pay payments. A prescription will be written for you to fill. You have a 50% chance of getting Xtandi.

Xofigo is FDA approved for patients that have demonstrated that their prostate cancer has spread to other parts of the body. Xofigo will be provided through the study for 50% of subjects and 50% will get a placebo (inactive substance) instead.

Why is this study using a placebo (saltwater) and why is it double blinded at this phase?

The best and most reliable form of research is a double-blinded (you and the research team don't know which medication is being given), placebo-(saltwater) controlled study. In this research 50% of subjects receives the active drug Xofigo. The other 50% receives a placebo (saltwater) that will look like the real drug but has no clinical effect. Again, subjects in both groups do not know whether they are getting the real drug or placebo thus they are blinded. Furthermore, the direct research team managing this study is also not told about which group is receiving which study treatment (making it a "double-blind" experiment). The purpose of this kind of study is to eliminate the power of suggestion. If the people in the group that receives real drug (Xofigo) do significantly better than those in the placebo (saltwater) group, it is a strong indication that the real drug (Xofigo) works and perhaps could be used earlier after mCRPC diagnosis.

About 599 subjects will be screened in this study, of which about 499 will receive Nubeqa or Xtandi (Phase 1), and about 414 will receive Xofigo monthly injections Radium-223 or Placebo (Phase 2).

WHAT WILL HAPPEN DURING THE STUDY

Your voluntary participation in this study will last approximately ***4 years*** and will include as many as ***35*** study visits to the study center.

Screening:

Before any study-related tests and procedures are performed, you will be asked to read and sign this consent document. If you have had some of these tests or procedures within 42 days of starting the study drug, they may or may not have to be repeated. The screening tests and procedures listed below are performed to

determine if you qualify to take part in this study. If the review of your medical history and/or medications show you do not qualify for the study, you might not need to do all the screening tests.:

- Lab work to make sure you can take either Xtandi or Nubeqa (about 2 tablespoons)
- ECG: a test that measures the electrical activity of the heartbeat.
- MRI or CT and bone scans images to see bone and tissue structures inside your body.
- Review of your medical history including your risk for future bone fractures.
- Review of your use of bone health agents and your past prostate cancer treatments.
- Collection of information about you including race, ethnicity, and highest level of education.
- Review of medications you are currently taking and recently stopped medications.
- A physical examination including measurement of your height, weight, vital signs, and current health status
- Using an iPAD, you will do practice tests to get you familiar with the real tests that will be done later in the study
- Collect a blood sample (about 2 teaspoons) for future prostate cancer research (this is optional) and you can decline to participate on the signature page of this document
- Obtain a prescription for enzalutamide and start the process for insurance coverage.

Screening can be completed in multiple visits, if needed. The total time should take about 2 hours.

After screening, but before your first dose of Xtandi or Nubeqa:

- Using an iPad you will complete two (2) questionnaires to measure your cognitive (brain) status and the way you are feeling (well-being). An iPAD will also be used to take a series of four (4) tests to further measure your cognitive (brain) function
- You will have a walking test to see how fast you can safely get up from a chair and walk 10 feet, turn around and return to your chair

If you are eligible (fit all entry criteria) you will be randomized (flip of a coin) by a computer to one of the two androgen blocking drugs Xtandi or Nubeqa.

This visit should take about one hour to complete.

This study will use competitive enrollment. This means that when a target number of subjects begins the study, all further enrollment will be closed. Therefore, it is possible that you could be in the screening phase, ready to begin the study, and be discontinued without your consent if the target number of subjects has already begun the study.

If you qualify to take part in this study and go on to receive the study treatment, then the following will happen:

Study Treatment – Phase 1

For your first study treatment phase, you will be randomly assigned by chance (like the flip of a coin) to receive either Xtandi or Nubeqa. You will have a 50% (1 in 2) chance of receiving Xtandi and a 50% (1 in 2) chance of receiving Nubeqa. This part of the study is open-label. This means that you, the Investigator, study staff and the Sponsor will know the study drugs and the doses that you are given.

- If you are assigned to Xtandi, you will need to get your prescription filled, start taking the study medication according to the Investigator's instruction, and notify your Investigator when you have started the drug.

- If you are assigned to Nubeqa, you will get your first bottle of study medication at this visit and can start taking the medication according to the Investigator's instruction.
- You will continue to take your current hormone therapy as well as a bone protective drug which your study doctor has already ordered for you as routine therapy.

You will have the following study visits and undergo the following procedures:

Phase 1 PSA Visits, 3 visits:
You will need to take the study medication assigned to you by the first randomization. Xtandi is usually given (4 capsules) once daily and Nubeqa is usually given (2 tablets) twice daily.

During the visits, the following will be done:
- PSA blood levels checked
- Review how you are feeling, doctor visits or hospitalizations that have occurred
- Review and dispense study medications, when needed

The PSA test is routinely done for all patients regardless of whether they are or are not participating in a study while receiving these drugs. These monthly visits should take about ½ hour to complete. Your scans will be scheduled every 12-weeks, which is also routine while taking these drugs. This visit may take approximately one hour to complete

Evaluation for Second Study Treatment Phase of the Study:
After taking either Xtandi or Nubeqa for at least 12 weeks you and your study doctor will decide if you can go onto the second study treatment phase. In order to make the decision your study doctor will need to:
- Repeat the same scans you had when you entered the study (CT or MRI and bone scan)
- Repeat lab work (about 2 tablespoons) will be used to help determine if it is safe for you to move to the second study treatment phase.
- Repeat ECG
- A short physical examination, vital signs, and determination of your current health status.
- Review all medications you are taking
- Using an iPad you will complete two (2) questionnaires to measure your cognitive (brain) status and the way you are feeling (well-being). An iPAD will also be used to take a series of four (4) tests to further measure your cognitive (brain) function
- Walking test
- Collect a blood sample (about 2 teaspoons) for future prostate cancer research if you consented to this
- Review how you are feeling, doctor visits or hospitalizations that have occurred
- Review of your study medications and dispensing more study medication, if needed

If you are eligible (fit all entry criteria) for the second study treatment phase, you will be randomized (flip of a coin) by a computer to either Xofigo or placebo. If the decision is made not to proceed to the second randomization, your study doctor will discuss other treatment options with you and your participation in the study will end after collection of End of Study information.

Study Treatment – Phase 2
For your second study treatment phase, you will be randomly assigned by chance (like the flip of a coin) to receive either Xofigo (radium-223) or placebo (inactive substance). You will have a 50% (1 in 2) chance of Xofigo (radium-223) and a 50% (1 in 2) chance of receiving placebo. This second random assignment is a double-blind, which means neither you nor the Investigator will know to which of these study drug groups you are assigned. In case of an emergency, however, the Investigator can get this information.

Xofigo is FDA approved for men whose cancer has spread to bones. Xofigo will be supplied to you by the study at no cost to you or your insurance company.

Xofigo or Placebo Injection Visits:
For this second phase of the research you will be taking all the same medications you have been taking for the past 12-16 weeks and you will have monthly injections of Xofigo or placebo until 6 doses have been given. Xofigo or placebo will be administered in a radiation therapy clinic. The research staff will schedule your injections for you and will tell you where the clinic is located. It should take less than a ½ hour for these visits.

Clinic visits before 2nd- 6th injection visits:
You will return to the clinic every month after your first Xofigo or placebo dose to have routine blood work done to monitor you for safety and review your medications in order to make sure it is still safe for you to receive the next month's injection. These visits should take about ½ hour.

The clinic visits between injection visits will include:
- Vital signs and determination of your current health status
- Review how you are feeling, doctor visits or hospitalizations that have occurred
- Review all medications you are taking
- Review of your study medications and dispensing more study medication, if needed

Imaging visits while taking Xofigo:
Every 3 months starting from the date of your first injection of Xofigo or placebo you will have the same imaging tests (CT/MRI/bone scan) you had before, an abbreviated physical exam, and the site staff will ask you questions about how you are feeling and about any doctor visits or hospitalizations that have occurred since your last visit.

These are routine for patients with prostate cancer undergoing these therapies. The scans should take approximately one hour.

Follow-up– Phase 3
After you have completed or stopped the Xofigo/placebo injections and your study doctor has determined that your disease has or has not progressed based on your imaging results and your clinical findings, your study doctor will make a decision about your next treatment option. This may include continuing Xtandi or Nubeqa or possibly starting you on a new treatment. If you continue Nubeqa, it will be supplied to you by the study.

If you continue taking Xtandi or Nubeqa you will visit the clinic every 12 weeks for:
- Repeat the same scans you had when you entered the study (CT or MRI and bone scan)
- Repeat of your blood work
- Vital signs
- Review all medications you are taking
- Review how you are feeling, doctor visits or hospitalizations that have occurred
- Review of your study medications and dispensing more study medication, if needed
- Once every 48 weeks: Repeat ECG, determination of your current health status, and walking test

Follow up visits will be done until either your disease progresses, or your study doctor decides to start a therapy that is not allowed on this research study. These visits should take about an hour.

End of Follow-up:
If you or your study doctor decides to stop your Xtandi or Nubeqa due to progression of your mCRPC or in order to start a new therapy that is not allowed on the study, you will be asked to return to the clinic for:

- Return of study medication(s), if applicable
- Review how you are feeling, doctor visits or hospitalizations that have occurred
- Review all medications you are taking
- Review of your study medications
- Collect a blood sample (about 2 teaspoons) for future prostate cancer research if you consented to and if your disease has progressed

This visit will take about 1 hour.

After Study Treatment:
Because this is a research study, the study drug will be given to you only during this study and not after the study is over. We will contact you every 6 months to see how you are doing. This can be done with a phone call or a review of your medical record. In the event we cannot reach you, we will perform a public records search until the study ends for all subjects.

EXPECTATIONS
If you participate in this study, you will be expected to:

- Attend study visits to complete the visit expectations
- Complete iPAD tests and questionnaires
- Take study medications per Investigator's instruction.
- Bring partial and full medication bottles to visits for verification you are taking medications.

Could being in this research hurt you?
While on the study, you are at risk for the following side effects. Most of them are listed below but they will vary from person to person

RISKS, SIDE EFFECTS, AND/OR DISCOMFORTS

Risks of Xtandi

Xtandi likely side effects (seen in greater than 50% of patients):

- Increased blood sugar
- Feeling tired or weak

Xtandi frequent side effects (seen in 1-50% of patients):

- Back pain
- Hot flush
- Constipation
- Diarrhea
- Joint pain
- Blood counts decreased
- Decreased appetite
- Muscle pain
- Upper/lower respiratory infection
- Changes in blood chemistry

- Swelling of the face, arms, hands, lower legs, or feet
- Increase in blood pressure
- Nausea
- Falls
- Headache
- Dizziness
- Weight loss or lack or hunger
- Troubled breathing with exertion
- Muscle weakness
- Fractures
- Not able to sleep
- Blood in the urine
- Changes in taste
- Spinal cord compression
- Tingling of the hands or feet
- Anxiety
- Confusion or memory problems
- Frequent urination
- Decreased sensation (skin)
- Itching
- Dry skin
- Enlarged breast tissue (males)
- Nosebleed
- Muscle stiffness
- Restless legs

Xtandi rare side effects (seen in less than 1% of patients):

- Seizures

Risks of Nubeqa

Nubeqa frequent side effects (seen in 1-50% of patients):

- Feeling tired or weak
- Back pain
- Joint pain
- Arm, leg, hand, or foot pain
- Nausea
- Constipation
- Diarrhea
- Decreased appetite
- Muscle pain
- Vomiting
- Anemia (decreased red blood cells)
- Headache
- Difficulty with sleep
- Weight decreased
- Swelling in hands, arms, legs and feet

- Blood in urine
- Bone pain
- Hot flashes
- High blood pressure
- Troubled breathing with exertion
- Fall
- Common cold
- Prostate cancer
- Rash
- Changes in blood (lab) results
- General health decline
- Acute kidney injury
- Gas
- Enlarged breasts in males
- Abdominal bloating
- Changes in taste
- Slow elimination
- Infection
- Frequent urination
- Kidney infection
- Difficulty with urination
- Urinary tract infection

Nubeqa rare side effects (seen in less than 1% of patients):

- Pneumonia

Risks of Xofigo

Xofigo likely side effects (seen in greater than 50% of patients):

- Bone pain

Xofigo frequent side effects (seen in 1-50% of patients):

- Nausea
- Weight decreased
- Feeling tired or weak
- Diarrhea
- Dehydration
- Redness, pain or swelling at injection site
- Low blood cell counts
- Vomiting
- Constipation
- Progression of cancer
- Swelling in arms or legs (extremities)
- Urinary tract infection
- Troubled breathing with exertion
- Dizziness
- Fever

- Decreased appetite
- General health decline
- Difficulty with sleeping
- Difficulty with urination
- Blood in urine
- Headache
- Fracture
- Spinal cord compression
- Pneumonia
- Tingling sensation in skin
- Common cold
- Frequent urination
- Confusion
- Rectal bleeding
- Kidney failure and impairment

Xofigo rare side effects (seen in less than1% of patients):

- Joint swelling

There also may be other side effects or discomforts that we cannot predict, especially to a fetus or embryo. Because the drugs in this study may affect an unborn baby, you should not father a baby while on this study. Your study doctor will discuss this with you.

RISKS OF STUDY PROCEDURES

- Blood samples: Possible side effects from blood drawing include faintness, inflammation of the vein, pain, bruising, or bleeding at the site of puncture. There is also a slight possibility of infection.
- Electrocardiogram (ECG): Skin irritation is rare but could occur during an ECG from the electrodes or gel that is used.
- Questionnaires: The questionnaires used in this study may be upsetting. You do not need to answer any questions that you are not comfortable with.

Despite getting study treatments, your symptoms of mCRPC may not improve or may get worse.

ALLERGIC REACTION RISKS

As with taking any drug, there is a risk of allergic reaction. If you have a very serious allergic reaction, you may be at risk of death. Some symptoms of allergic reactions are:

- Rash
- Wheezing and difficulty breathing
- Dizziness and fainting
- Swelling around the mouth, throat or eyes
- A fast pulse
- Sweating

Please seek treatment immediately and tell the study doctor and study staff if you have any of these symptoms.

UNFORESEEN RISKS

Since the use of the Nubeqa for mCRPC is investigational, there may be other risks that are unknown. Additionally, there may be unknown risks to a pregnancy, embryo, or fetus if your female partner become pregnant.

BIRTH CONTROL RESTRICTIONS

In order to reduce the risk of pregnancy, you should use an effective method of birth control while you are participating in this study and for 6 months after your last dose of the study drug. Acceptable methods of birth control for use in this study are condoms plus spermicidal agent. The Investigator or study staff will discuss this with you.

If your female partner becomes pregnant while you are participating in this study or within 6 months after you have stopped taking the study drug, tell your Investigator or study staff immediately.

ALTERNATIVES TO PARTICIPATION

You do not have to be in this study to receive treatment for your mCRPC. Your options may include:

- Your physician may order Xtandi as well as Xofigo which are routine drugs to give for patients whose cancer has spread. There might be other drugs that your physician can discuss with you, including the risks and benefits of their use.

- If you decide that you don't want any more active treatment, one of your options is called "comfort care", also called palliative care. This type of care helps reduce pain, tiredness, appetite problems and other problems caused by the cancer. It does not treat the cancer directly, but instead tries to improve how you feel. Comfort care tries to keep you as active and comfortable as possible. If you think you might prefer comfort care, please discuss this with your family, friends and your doctor.

Your participation in this study is voluntary. Please talk to the study doctor about your options before you decide whether or not you will take part in this study.

NEW FINDINGS

Any new important information that is discovered during the study and which may influence your willingness to continue participation in the study will be provided to you.

BENEFITS

You may benefit as a result of your participation in this study. There is, however, no guarantee that you will benefit from your participation in this study. Information learned from the study may help other people in the future.

COMPENSATION FOR PARTICIPATION

(This language will be modified by each site for visit payments, travel, or for patient assistance for obtaining prescription Xtandi. If no compensation is planned, this section will be removed or will state no compensation will be given for visits).

You will be paid up to a total of $xx.xx if you complete this study. You will be paid for the visits you complete according to the following schedule:

- $xx.xx for Visits xxx.
- $xx.xx for Visits xxx.
- $xx.xx for Visits xxx.

If you do not complete the study, for any reason, you will be paid for each study visit you do complete.

You will be paid _____ ["after each visit," "annually," "bi-weekly," etc.]

If you have any questions regarding your compensation for participation, please contact the study staff.
[OR]
You will not receive any monetary compensation for your participation in this study.

[If applicable:] We will reimburse you for the cost of [describe: e.g., traveling to your study visits]. You will be reimbursed approximately [e.g., 2 weeks, 1 month, etc.] after you submit your travel receipts to the study staff.

CONFIDENTIALITY
Records of your participation in this study will be held confidential except when sharing the information is required by law or as described in this informed consent. The Investigator, the sponsor or persons working on behalf of the sponsor, and under certain circumstances, the United States Food and Drug Administration (FDA) and the Institutional Review Board (IRB) will be able to inspect and copy confidential study-related records which identify you by name. This means that absolute confidentiality cannot be guaranteed. If the results of this study are published or presented at meetings, you will not be identified.

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.

COMPENSATION FOR INJURY
If you become ill or are injured while you are in the study, get the medical care that you need right away. You should inform the healthcare professional treating you that you are participating in this study. If you tell the study staff that you think you have been injured, then they will direct you to get the care you need.

(NOTE: The remaining language will be negotiated between sites and Bayer, the funding source for this study, and inserted into this section for consistency. If no compensation for injury is negotiated, this will be stated.)

By signing this document, you will not lose any of your legal rights or release anyone involved in the research from responsibility for mistakes.

COSTS
There will be no charge to you for your participation in this study. Two study drugs (Nubeqa and Radium-223 or placebo), study-related procedures, and study visits will be provided at no charge to you or your insurance company. The only cost to you will be your usual (non-study) treatments for prostate cancer including imaging, non-study medications, and insurance costs associated with obtaining the study medication Xtandi, if you are assigned to the Xtandi study treatment.

WHOM TO CONTACT ABOUT THIS STUDY
During the study, if you experience any medical problems, suffer a research-related injury, or have questions, concerns or complaints about the study, please contact the Investigator at the telephone number listed on the first page of this consent document. If you seek emergency care, or hospitalization is required, alert the treating physician that you are participating in this research study.

An institutional review board (IRB) is an independent committee established to help protect the rights of research subjects. If you have any questions about your rights as a research subject, and/or concerns or complaints regarding this research study, contact:

- By mail:
  Study Subject Adviser
  Advarra IRB
  6940 Columbia Gateway Drive, Suite 110
  Columbia, MD 21046
- or call toll free: 877-992-4724
- or by email: adviser@advarra.com

Please reference the following number when contacting the Study Subject Adviser: Pro00042616.

VOLUNTARY PARTICIPATION / WITHDRAWAL

Your decision to participate in this study is voluntary. You may choose to not participate or you may withdraw from the study for any reason without penalty or loss of benefits to which you are otherwise entitled and without any effect on your future medical care. However, please note that the FDA requires that any information collected up to the point of your withdrawal cannot be removed from the study.

If you or your study doctor decides to stop your participation, you will be asked to return to the clinic for:

- Return of study medication(s), if applicable
- Review how you are feeling, doctor visits or hospitalizations that have occurred
- Review all medications you are taking
- Review of your study medications

This visit should take about an hour.

The Investigator or the sponsor can stop your participation at any time without your consent for the following reasons:

- If it appears to be medically harmful to you;
- If you fail to follow directions for participating in the study;
- If it is discovered that you do not meet the study requirements;
- If the study is canceled; or
- For administrative reasons.

If you leave the study for any reason, the Investigator may ask you to have some end-of-study tests for your safety.

CONSENT STATEMENT

I have read and understand the information in this informed consent document. I have had an opportunity to ask questions and all of my questions have been answered to my satisfaction. I voluntarily agree to participate in this study until I decide otherwise. I do not give up any of my legal rights by signing this consent document. I will receive a copy of this signed and dated consent document.

_____
Subject's Printed Name

_____ _____
Subject's Signature Date

_____
Printed Name of the Person Conducting the Consent Discussion

_____ _____
Signature of the Person Conducting the Consent Discussion Date