ID: UMCC 2017.055

NCT03300505

ARRx in Combination With Enzalutamide in Metastatic Castration Resistant Prostate Cancer

MODEL CONSENT TO BE PART OF A RESEARCH STUDY

1. KEY INFORMATION ABOUT THE RESEARCHERS AND THIS STUDY

Study title: ARRO-CITO: Phase Ib/II Single-Arm Multi-Center Study of IONIS AR-2.5$_{Rx}$, a Next Generation Androgen Receptor Antisense Oligonucleotide in combination with Enzalutamide in Metastatic Castration Resistant Prostate Cancer

Company or agency sponsoring the study: The University of Michigan along with support by Ionis Pharmaceuticals/Suzhou Ribo Life Science Co. Ltd.

Names, degrees, and affiliations of the principal investigator and study coordinator (if applicable):

Principal Investigator:
Ajjai Alva, MD Department of 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 join the study, you will be asked to sign this form before you can start study-related activities. Before you do, be sure you understand what the study is about.

A research study is different from the regular medical care you receive from your doctor. Research studies hope to make discoveries and learn new information about diseases and how to treat them. You should consider the reasons why you might want to join a research study or why it is not the best decision for you at this time.

Research studies do not always offer the possibility of treating your disease or condition. Research studies also have different kinds of risks and risk levels, depending on the type of the study. You may also need to think about other requirements for being in the study. For example, some studies require you to travel to scheduled visits at the study site in Ann Arbor or elsewhere. This may require you to arrange travel, change work schedules, find child care, or make other plans. In your decision to participate in this study, consider all of these matters carefully.

This research is studying the use of a new drug in small numbers of people to learn about its safety and its effect on your body at certain doses as a treatment for metastatic castration resistant prostate cancer. Researchers want to understand how the drug works in your body and how your body will react to it. This study will be using the drugs IONIS-AR-2.5$_{RX}$ and enzalutamide. IONIS-AR-2.5$_{Rx}$ will be given through a vein in your arm. You will take enzalutamide by mouth. Others procedures that will take place throughout the course of the study include physical exams, blood draws, scans of your cancer, urine collection, tests to measure your hearts health along with other items listed later in this document. Your health-related information and biospecimens (blood and tissue) will be collected for this research study.

There can be risks associated with joining any research study. The type of risk may impact whether you decide to join the study. For this study, a brief list of some of most commonly seen risks may include Flu-like symptoms, weakness, diarrhea, nausea, vomiting, loss of appetite and abnormal liver lab tests. More detailed information will be provided later in this document.

This study may not offer any benefit to you now but may benefit others in the future by helping people to live longer or improve the quality of life.

We expect the amount of time you will participate in the study to vary depending on how your disease responds to the study intervention and if you have any major side effects.

You can decide not to be in this study. Alternatives to joining this study include receiving standard of care treatment for this disease, taking part in a different study, receiving palliative care, or having no treatment.

Even if you decide to join the study now, you are free to leave at any time if you change your mind.

More information about this study continues in Section 2 of this document.

2. PURPOSE OF THIS STUDY

2.1 Study purpose:

This is a Phase Ib/II study which means that the goals are to see if the combination of IONIS AR-2.5$_{Rx}$ and enzalutamide is safe as well as whether is it effective in improving outcomes. The first part of the study will try to find out what effects, good and/or bad, this drug combination has on you and your cancer, and to find a dose to use in the second part of the trial.

Prostate cancer is the second leading cause of cancer deaths in men and treatment options for patients with castrate resistance prostate cancer (CRPC) are limited. Currently enzalutamide and abiraterone acetate have become standard of care first line therapy for men with CRPC; however, the cancer is known to develop resistance to these therapies.

The purpose of this study is to test the effectiveness (how well the drug works), safety, and tolerability of the investigational drug combination of IONIS-AR-2.5$_{Rx}$ plus enzalutamide in patients with metastatic castration resistant prostate cancer.

IONIS-AR-2.5$_{Rx}$ has not been approved by the FDA for the treatment of prostate cancer and so it is considered to be investigational for this study.

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?

Adult men who have metastatic castrate resistant prostate cancer that have progressive disease despite ongoing treatment with androgen deprivation therapy (ADT).

There are many other inclusion and exclusion criteria which the doctors will use to determine if you can participate in this study. It is important that you discuss your full medical history and all of your medications with your doctor.

3.2 How many people (subjects) are expected to take part in this study?
A total of approximately 35 subjects at several institutions will take part in this study, including approximately (INSERT NUMBER) from (INSERT INSTITION NAME).

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 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, tumor evaluations (radiology scans), 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. Administration of the study drug combination, tissue and some blood sample collection and analysis are solely for research purposes. 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.

During the study you must:
- Follow the instructions you are given.
- Come to the study center for your visits with the study doctor.
- Tell the study doctor or study staff about any changes in your health and/or medications you are taking.
- Tell the study doctor or study staff if you want to stop being in the study at any time.

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 them 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 below for information about which procedures will be performed at certain study visits.
- **Medical history**: including any past treatments, surgeries, infection and autoimmune diseases.
- **Medication review**: It is important that you tell your doctor about all of the medications that you have been taking, including over the counter medicines, vitamins or herbal treatments.
- **Physical exam**: including measurement of your height, weight, blood pressure, heart rate, respiratory rate and temperature.
- **Performance status**: Your ability to perform day to day activities and care for yourself
- **Routine blood tests**: will be drawn to measure your:
  - General health (hematology, chemistry and coagulation)
  - prostate specific antigen (PSA)
  - testosterone levels
  - thyroid function

- **Scans of your cancer**: these could include Computed tomography (CT) of the chest, CT or magnetic resonance imaging (MRI) of the upper and lower belly or chest x-rays or a bone scan. *These will only be collected every 12 weeks or as often as your physician thinks is necessary.*
    - A CT scan uses special x-ray equipment to make detailed pictures of body tissues and organs. For the CT scan, you may be given a "contrast material" (a special dye that makes it easier for doctors to see different tissues in your body). You will be asked to lie still and may be asked to hold your breath for a few seconds. The CT scan is done in the Radiology Department and takes about half an hour.
    - A MRI scan takes an image of your head or body to observe the location and size of your tumor. For the MRI scan, you may be given a "contrast material" (a special dye that makes it easier for doctors to see different tissues in your body). You will be asked to lie down on a narrow bed which will slide into a tunnel that is 6 feet long by 22 inches across and is open at each end. You will be asked to lie quietly for about one hour, during which time you will hear a loud machine-like noise. A MRI scan takes about an hour and a half to complete.
    - Bone scan. 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 before, during, and after you receive the study treatment
- **Toxicity evaluation:** You will be asked about any side effects or illnesses you experience.
- **Tumor tissue:** Your doctor will check to see if you have enough stored tissue sample of your tumor that was collected previously. If you do not have enough stored tissue, you will be asked to undergo a fresh tissue biopsy prior to starting treatment. Your decision to have or not have the biopsy will not affect your medical care and you will not lose any benefits to which you are entitled; however, you can only participate in this study if your biopsy has tumor and can be analyzed.
    - Optional biopsies may be collected after 2 cycles of study intervention and end of treatment. You can make your choice in Section 12 for the optional biopsies. *This is for research purposes.*
- **Quality of life questionnaire:** You will be asked to complete a quality of life questionnaire asking about your symptoms and how your disease and symptoms make you feel. You may find some of the questions uncomfortable to answer. You do not have to answer any question you do not want to answer. This is for research purposes. *This is for research purposes*
- **Blood for Research (approximately 3-5 tablespoons):** Will be drawn for testing for biomarkers (testing of substances such as proteins that tell us how the drug is working in your body). *This is for research purposes.*
- **Blood for pharmacokinetic (PK) analysis:** A total of about 2 tsps of blood will be drawn for PK testing prior to and within 2 minutes before you stop **EACH** dose of IONIS-AR-2.5$_{Rx}$. This analysis is being done to determine plasma IONIS-AR-2.5$_{Rx}$ concentrations from these samples. PK analysis measures the amount of study drug in the body at different time points. These blood samples may also be used for other analyses related to the study drug. *This is for research purposes.*

Study Intervention:
If you qualify to participate in the study based on the results of the screening tests and procedures, you will return to the study doctor's clinic.

For this study a cycle is defined as 21 days.

You may receive medications before each infusion to help prevent side effects of the study drug infusions.

Also starting Cycle 1 day 1 you will begin taking 81 mg aspirin until your doctor tells you otherwise.

IONIS-AR-2.5$_{Rx}$ will be given through a vein in your arm over 60 minutes on days 1, 4, 8, 11 and 15 of Cycle 1. Starting with Cycle 2 and for all other cycles, IONIS-AR-2.5$_{Rx}$ will be given through a vein in your arm over 60 minutes on days 1, 8, and 15.

You will also take enzalutamide by mouth every day in 21 day cycles starting Day 1 of each cycle.

The researchers will ask you to complete a drug diary to track what days you take enzalutamide. Please bring your drug diary and medication bottles (with extra capsules) with you when you return for each appointment.

Below are general rules for taking enzalutamide:

- Take either with food or without food
- Swallow whole (do NOT chew, crush or cut the capsule)
- The medication SHOULD NOT be ingested if broken, cracked or otherwise not intact.
- If you miss a dose DO NOT "make it up". Skip the missed dose and start taking enzalutamide with the next scheduled dose.

You will continue to receive the study intervention as long as you are tolerating the treatment and your disease hasn't progressed.

Follow Up

If you stop the study intervention for any reason you will be asked to return for an end of treatment visit within 60 days of your last dose of the study intervention.

After you complete the end of treatment visit you will have an office visit or be contacted by a member of the study team every 12 weeks for up to 36 months.

Study Procedures Table:

Procedures	Screening	Treatment								End of Treatment	Follow-up
		Cycle 1					Cycle 2+				
		D 1	D 4	D 8	D 11	D 15	D 1	D 8	D 15		
Medical history	X	X	X	X	X	X	X	X	X		
Medication review	X	X	X	X	X	X	X	X	X		
Physical exam	X	X		X		X	X				
Performance status	X	X					X			X	
Routine blood tests	X	X	X	X	X	X	X	X	X	X	
Scans of your cancer	X	*Every 12 weeks or per your physician*								X	X
Toxicity evaluation	X	X	X	X	X	X	X	X	X	X	
Tumor Tissue from previous biopsy	X										
Tumor Tissue Biopsy	X (required only if tumor tissue from prior biopsy not available)								X (optional)	X (optional)	
Quality of life questionnaire		X					X			X	
Blood for research	X										
Blood for pharmacokinetic analysis		X	X	X	X	X	X	X	X		
Follow-up (every 12 weeks)											X

OPTIONAL Research Samples Stored for Unspecified Future Use:

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, tumor tissue 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, tumor tissue and medical information for future research.

If you give us permission, we will use your blood, tissue and medical information for future research. Even if you give us permission now to keep some of your blood, tissue 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 and tissue, we may not be able to take the information out of our research.

We may share your blood, tissue 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, tissue 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 and tissue samples. Allowing us to do future research on your blood, tissue and medical information will not benefit you directly.

The University of Michigan, the investigators or a collaborating researcher may benefit financially from future research on your blood, tissue and medical information.

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.

4.2 How much of my time will be needed to take part in this study?
The study drugs are given in cycles. One cycle is 21 days.

The initial screening visit will take approximately 3-5 hours. Each study visit is expected to take approximately 4-6 hours.

Once you have been removed from treatment you will need to have an end of treatment visit. Then you will have follow-up visits every 12 weeks for up to 36 months. Each visit will take between 1-2 hours.

4.3 When will my participation in the study be over?
The maximum time you will be in the study will depend on how your disease responds to the study intervention and how well you tolerate the study intervention. After you stop taking the study intervention you will be asked to come back for an end of treatment visit and then we will follow you either by phone or a clinic visit every 12 weeks for up to 36 months.

4.4 What will happen with my information and/or biospecimens used in this study?
Your collected information and may be shared with Ionis Pharmaceuticals/Suzhou Ribo Life Science Co. Ltd. Your collected information and biospecimens may also be shared with other researchers, both here or around the world, or with companies. Any sharing is subject to contractual obligations with Ionis Pharmaceuticals/Suzhou Ribo Life Science Co. Ltd.

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?
The drugs used in the study may cause certain side effects and discomforts. You may have all, some, or none of the known side effects. There is also a risk that other rare or unknown side effects may occur. Your doctors and nurses will check you closely for side effects, and may give you medicines or other treatments to stop or reduce some of these effects. Some side effects may go away soon after the study medication is stopped, but in some cases, side effects may be serious, long lasting, and/or permanent. There is even a chance that a side effect may cause death. If you have any side effects, it is important that you report them to your study doctor or research staff.

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.

The known or expected risks are:

Side Effects ASSOCIATED WITH IONIS-AR-2.5$_{Rx}$

Likely (occurring in more than 20% of people):

- Flu-like syndrome (may include fever, chills, tiredness, headache, muscle and joint pain)
- Abnormal blood tests which suggest that the drug is affecting the liver or kidneys
- Nausea and vomiting
- Rash or dry itchy skin (pruritus)
- Diarrhea
- Loss of appetite
- Feeling weak or tired
- Abnormal taste
- Low platelet count (thrombocytopenia)
- Abdominal pain and cramping
- Constipation
- Weight loss
- Trouble sleeping
- Mouth pain
- Trouble with your blood clotting

Less likely and possibly serious (occurring in less than or equal to 20% of people):

- Pulmonary embolism - A blood clot that causes a sudden blockage in a lung blood vessel, usually due to a blood clot that traveled to the lung from the leg. A pulmonary embolism is a serious condition that can cause: Permanent damage to part of your lung from lack of blood flow to lung tissue; Low oxygen levels in your blood; Damage to other organs in your body from not getting enough oxygen; If a clot is large, or if there are many clots, a pulmonary embolism can cause death.
- Deep vein thrombosis - Blood clot formed in the veins of the leg which may manifest as a dull ache or heaviness in the limb. If the clot moves to other organs, it can be serious or life threatening.

Side Effects ASSOCIATED WITH ENZALUTAMIDE

Likely (occurring in more than 20% of people):

- Weakness or feeling more tired than usual
- Back pain
- Decreased appetite
- Constipation
- Diarrhea
- Pain in your joints
- Hot flashes
- Swelling in your hands, arms, legs or feet
- Shortness of breath
- Muscle or bone pain

- Weight loss
- Low white blood cell count
- Headache
- Cold like symptoms

Less Likely (occurring in 4-20% of people):

- Muscle weakness
- Dizziness or a feeling that you or things around you are moving or spinning (vertigo)
- Trouble falling or staying asleep (insomnia)
- Trouble breathing (pneumonia)
- Back pain with nerve problems in the lower body, including leg numbness or weakness
- Pink or red urine (hematuria)
- Sensation of tingling, burning, pricking, or numbness of skin (paresthesia)
- Anxiety
- High blood pressure (hypertension)
- Falls (loss of balance) which may lead to injuries such as broken bones
- Itching
- Dry skin
- Difficulty remembering, reduced concentration, forgetfulness, or trouble thinking clearly

Rare, but Serious (occurring in less than 3% of people):

- Seizures (convulsions)
- Hallucinations

Aspirin

You will be required to take low-dose aspirin to help with prevention of blood clots during the study. Some of the most common side effects of aspirin are stomach pain, heart burn, nausea and vomiting.

Blood tests

Blood samples will be taken from a vein in your arm during the study. The taking of a blood sample may cause some discomfort and bruising, and there is a potential for infection. Other risks, although rare, include dizziness and fainting.

Questionnaires

Filling out the questionnaires could lead you to feel uncomfortable or upset. Please tell the study doctor or study staff if you feel uncomfortable or upset while filling out a questionnaire. You have the right to refuse to answer any questions.

Tumor Biopsy

A piece of a tumor will be removed for testing. Potential risks and discomforts that you may experience as a result of the procedure depend upon the location of the tumor. The more common risks/discomforts include pain, bleeding, infection, damage to tissues, and healing complications. Your doctor will further explain any specific risks that may apply based on the procedure, and you will sign a separate consent for the procedure which will provide risk information in more detail. In order to make the procedure more comfortable, you will get a local anesthetic to numb the area. A mild sedative may also be given to you.

- It is possible that a mutation found in the tumor DNA is also a mutation in your normal tissue (inheritable, or passed down in families). Since we are not testing normal tissue, we cannot tell if an abnormal gene in

the tumor could also be in your normal (non-tumor) cells. Your study doctor will discuss this result with you. If your test results show that you have gene mutations that are possibly inherited, your doctor may recommend that you meet with a genetic counselor and, if warranted, undergo further genetic testing on non-tumor tissue to determine if the mutation is inherited. This type of testing is considered standard care and is not part of this study.

- As with all medical screening tests, there is a chance of a false positive or a false negative result. A "false positive" refers to the identification of a genetic change that is not present. A "false negative" is the failure to find a genetic change that indeed exists. The tests have been designed to ensure that the possibility of incorrect results is low.

Research samples/Loss of Confidentiality

Your samples will be coded however there is a risk of loss of confidentiality of your information. If your samples are provided to research collaborators the following information may be made available: your diagnosis and treatments, the time the samples were collected in relation to your study regimen, your disease status, and demographic data (for example gender, race, age, etc.).

Reproductive risks

The study drugs can affect your reproductive system, resulting in sperm production becoming irregular or stopping permanently. In addition, you may experience erectile dysfunction or a decreased desire for sex during treatment. Talk to your study doctor about options for treating erectile dysfunction.

You may want to consider sperm banking if you may wish to have a child in the future. Discuss these options with your study doctor. You should not donate sperm or semen while taking the study drugs.

Exposure of an unborn child to these medications could cause birth defects; therefore, you should not father a child while on these medications. It is important that you understand that you need to use birth control from the time you sign this consent and continuing throughout the course of treatment and for at least 120 days after IONIS-AR-2.5$_{Rx}$ or 120 days after enzalutamide, whichever is later, is discontinued. If you are sexually active, you must be surgically sterile (vasectomy or surgical castration), or you must agree to use a barrier method of birth control, such as male condom (with or without spermicide) and your partner should also use acceptable birth control. Using condoms and a second method of birth control for couples is recommended. Be aware that pregnancy may occur even if you use an acceptable birth control method. Some birth control methods might not be approved for use in this study. Discuss these options with your study doctor and how long you should continue using birth control after stopping the medications. Talk to your study doctor about birth control methods for this trial. The following methods are considered acceptable birth control methods:

Primary forms

- tubal sterilization (tubes tied)
- vasectomy
- intrauterine device
- hormonal oral contraceptive (transdermal patch, injectables, Implantables)

Secondary forms

- male latex condom with or without spermicide
- diaphragm with spermicide
- cervical cap with spermicide
- vaginal sponge (contains spermicide)

Any birth control method can fail. Using two forms of birth control at the same time greatly reduces the chances of pregnancy.

If you think your partner becomes pregnant during the study, you must tell the study doctor immediately. The study doctor may ask for information about the pregnancy and the birth of the baby. We will ask for your partner's permission to collect information about the pregnancy and health of the baby.

Let your study doctor know of any questions you have about possible side effects. You can ask the study doctor questions about side effects at any time.

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 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 direct benefits from being in this study. However, information gained in this study may help future patients who are diagnosed with prostate cancer.

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 be in this study to get treatment for your cancer. Other possible options include:

- Additional treatment with standard of care drugs such as
  - Docetaxel chemotherapy
  - Cabazitaxel chemotherapy
- You could participate in other research trials using drugs not already approved for prostate cancer patients
- You could receive palliative care
- You could choose not to receive any treatment.

You should talk to your study doctor and your regular physician about each of your options and their risks and benefits before you decide if you want to take part in this 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 study drug IONIS-AR-2.5$_{Rx}$ will be provided by Ionis Pharmaceuticals free of charge.

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
- Enzalutamide
- 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
- Treatment of complications

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 (INSERT PI), at (INSERT PHONE NUMBER). 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?
You will not be paid to take part in this study.

8.3 Who could profit or financially benefit from the study results?
Information obtained from this study may help the supporter Ionis Pharmaceuticals/Suzhou Ribo Life Science Co. Ltd. and/or the University of Michigan learn more about the causes, risks, treatments, or how to prevent this and other health problems. Ionis Pharmaceuticals/Suzhou Ribo Life Science Co. Ltd., the University of Michigan, or physicians at the university could profit financially from this information.

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?
(INSERT INSTITUTION NAME) 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 or payment for your study treatment, 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 information

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, (INSERT INSTITUTION), 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.
- Ionis Pharmaceuticals/Suzhou Ribo Life Science Co. Ltd., 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 (INSERT INSTITUTION) medical record.
- 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 (INSERT INSTITUTION) and government officials make sure that the study was conducted properly

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

(INSERT INFORMATION BELOW)

Principal Investigator:
Mailing Address:
Telephone:

Study Coordinator:
Mailing Address:
Telephone:

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

(INSERT INSTITUTIONAL IRB INFORMATION)

11. RECORD OF INFORMATION PROVIDED

11.1 What documents will be given to me?

You will receive a copy of the signed and dated informed consent

Your signature in the next section means that you have received copies of all of the following documents:

- 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 Optional Research Biopsies
This project involves optional biopsies for research purposes. I understand that it is my choice whether or not to take part in these optional research biopsies. 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.

Post Cycle 2:

_____ Yes, I agree to take part in the optional post Cycle 2 research biopsy.

_____ No, I do not agree to take part in the optional post Cycle 2 research biopsy.

End of treatment

_____ Yes, I agree to take part in the optional end of treatment research biopsy.

_____ No, I do not agree to take part in the optional end of treatment research biopsy.

Print Legal Name: _____

Signature: _____

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

Consent/Assent to Collect and Store 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 take part in this optional research. 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 blood and tissue samples for future research.

_____ No, I do not agree to let the study team keep and store my blood and tissue samples 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): _____