CINJ 081603: “Randomized Three-Arm Trial to Evaluate the Effect of Neoadjuvant Apalutamide Alone or in Combination with Abiraterone Acetate and GnRH Agonist, and Prednisone on Enhancing Surgical Outcome of Nerve-Sparing Radical Prostatectomy in men with High-Risk Prostate Cancer

NCT02949284

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cinj.org
p. 732-235-2465

CONSENT TO TAKE PART IN A RESEARCH STUDY

Title of Study: Randomized Three-Arm Trial to Evaluate the Effect of Neoadjuvant Apalutamide Alone or in Combination with Abiraterone Acetate and GnRH Agonist on Enhancing Surgical Outcome of Nerve-Sparing Radical Prostatectomy in men with High-Risk Prostate Cancer

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This consent form is part of an informed consent process for a research study and it will provide information that will help you to decide whether you wish to volunteer for this research study. It will help you to understand what the study is about and what will happen in the course of the study.

If you have questions at any time during the research study, you should feel free to ask them and should expect to be given answers that you completely understand.

After all of your questions have been answered, if you still wish to take part in the study, you will be asked to sign this informed consent form.

The study doctor (the principal investigator) or another member of the study team (an investigator) will also be asked to sign this informed consent form. You will be given a copy of the signed consent form to keep.

You are not giving up any of your legal rights by volunteering for this research study or by signing this consent form.

Sponsor of the study:
The Rutgers Cancer Institute of New Jersey is the sponsor of this research study with funding and medication support from Janssen Scientific Affairs, LLC.

Why is this study being done?
This study is being done to see the effects (good and/or bad) of adding androgen deprivation therapy prior to surgery for advanced prostate cancer (the cancer that has grown outside your prostate and may have grown into the seminal vesicles, but has not spread to other parts of the body). Androgen deprivation therapy (ADT) lowers levels of androgens (male sex hormones, such as testosterone) that prostate cancer cells need to grow. This is known as chemical castration.

The current treatment for advanced prostate cancer is surgery (also known as radical prostatectomy) or radiation therapy. It is up to the treating physicians to determine which option is best for you.

Radical prostatectomy is an operation to remove the prostate gland and some of the tissue around it. Although radical prostatectomy has been considered an effective surgical management for patients with high-risk prostate cancer, many patients suffer from erectile dysfunction (inability to maintain an erection) and urinary incontinence (inability to control urination) as a result of nerve damage that occurs during surgery. It is known that giving chemotherapy and/or hormone therapy before surgery results in better cancer control in certain types of cancers. Researchers want to know if treating patients with ADT prior to radical prostatectomy will reduce nerve damage that may occur during surgery.

The purpose of this study is to see if treatment with ADT prior to surgery reduces nerve damage that may occur during surgery.

Subjects will be randomized into one of the groups below:

Group 1: Treatment with apalutamide prior to surgery. Apalutamide is a type of androgen receptor antagonist, which means that it blocks activity of the male hormone testosterone. Apalutamide is approved by the Food and Drug Administration for the treatment of non-metastatic castration resistant prostate cancer (cancer that is resistant to hormone treatment but has not yet spread) and metastatic castration sensitive prostate cancer (cancer that has spread but is treatable with hormone treatment).

Group 2: Treatment with apalutamide, abiraterone acetate and GnRH prior to surgery. GnRH agonists are drugs that lower androgen levels. Abiraterone acetate is a drug that helps stop cells from making androgen. This is given with prednisone. Abiraterone acetate is not approved for patients with high-risk prostate cancer. It is approved for patients with metastatic castration-resistant prostate cancer and patients with metastatic high risk castration sensitive prostate cancer (cancer that has spread and is aggressive but it is treatable with hormone treatment).

Group 3: Surgery alone, no treatment with ADT before the surgery.

Why have you been asked to take part in this study?
You have been asked to participate in this study because you have advanced prostate cancer that will be removed by surgery.

Who may take part in this study?
You may take part in this study if you are 18 years of age or greater with advanced prostate cancer. Additionally, you may take part in this study if:

- Your cancer can be removed by surgery
- You are able to swallow pills
- You are able to keep your doctor's appointments
- You have read and signed this consent form

Who may not participate in this study?

You may not be included in this study if:

- Your cancer has spread to other parts of the body
- You have previously been treated with androgen deprivation therapy
- You are not a candidate for surgery

The study doctor and/or research team will also ask you other questions about your medical history in order to make sure that you qualify to be in this study.

How long will the study take and how many subjects will participate?

If you are randomized to receive ADT treatment prior to surgery, you will receive ADT for three months prior to surgery. After surgery you will continue to have follow-up for up to two years.

Approximately 90 patients will take part in this study.

What will you be asked to do if you take part in this research study?

Before you begin study treatment:

You will have some exams, tests and procedures to find out if you can take part in this study. Most of the exams, tests, and procedures you will have are part of the usual approach for your cancer. However, your doctor will do some extra testing as part of the study. Procedures not part of regular medical care are marked with an asterisk (*). Additional study specific procedures are discussed below under the section titled "Study Specific Exams." The testing that you will need to have if you take part in this study is discussed below. If some of these have been done recently they may not need to be repeated, this will be up to the study doctor.

- A medical history including questions about your health, current medications, and any allergies
- A physical exam, including blood pressure, pulse, rate of breathing, temperature, height, weight, and evaluation of your ability to carry out daily activities.
- Blood tests
    - Approximately 2 teaspoons (10 mL) for routine testing, such as, a complete blood count, kidney and liver function tests to ensure that it is safe to administer any of the drugs included in this study
    - Approximately 2 teaspoons (10 mL) for prostate function and thyroid function tests
- Urine test
- Electrocardiogram (ECG) to measure the electrical activity of your heart
- Digital rectal exam, an exam of the lower rectum to check the prostate gland
- An assessment of your tumor by scan. Scans may include:
    - Chest x-ray
    - Computed tomography (CT): a scan that uses x-rays to look at one part of your body. It may be done with or without contrast. Contrast means that dye is injected into your vein to increase the differences between normal and abnormal tissue.

- Magnetic Resonance Imaging (MRI) of the prostate: an imaging that uses a strong magnetic field to look at one part of your body and providing more detailed information about your disease.
- Bone scan: an imaging test that helps detect cancer in the bones

STUDY TREATMENT

If the tests, exams, procedures show that you can be in the study and you are agreeable to continue then you will be randomized to the study. "Randomization" means that you will be assigned to a treatment group by chance neither the study doctor nor you get to choose. You have an equal chance of being randomized into one of the three treatment arms.

Arm 1: You will be randomized to receive apalutamide for three months prior to surgery. Apalutamide is a 60 mg tablet. You will take 4 tablets of apalutamide for a total dose of 240 mg with or without food every day.

Arm 2: You will be randomized to receive apalutamide plus abiraterone acetate and GnRH agonist for three months prior to surgery. Apalutamide and abiraterone acetate are tablets. You will take 4 – 60 mg tablets of apalutamide for a total dose of 240 mg with or without food daily. You will take 4 – 250 mg tablets of abiraterone acetate for a total dose of 1000 mg with 2 - 5 mg prednisone tablets for a total dose of 10mg without food daily. GnRH, either Lupron or Zoladex, will be given as an injection once at the beginning of treatment; (it will be up to the study doctor to decide which is best for you). Treatment with apalutamide will begin one week before starting abiraterone acetate and GnRH.

Arm 3: You will be randomized to receive surgery alone.

If you are randomized to Arm 1 or Arm 2:

- The medications (apalutamide and abiraterone acetate) should be swallowed whole with water. Do not crush or chew the tablets.
- You will need the following examinations, tests, and procedures described below. Some of these exams, tests, and procedures are part of your regular medical care. Procedures not part of regular medical care are marked with an asterisk (*).

Day 1:

- You will be asked about any medications you are currently taking, both prescription and over the counter
- Study medication will be given to you*
- If you are randomized to Arm 2, you will also receive an injection with the GnRH agonist*

Weeks 5, 9 and 13:

- A physical exam. The research doctor or another research healthcare professional will complete a physical assessment, including blood pressure, pulse, rate of breathing, temperature, and weight, and an evaluation of your ability to carry out daily activities.

- You will be asked to report any symptoms and health problems you have and any new medications you have started.
- Blood tests
    - Approximately 2 teaspoons (10 mL) for routine testing, such as, a complete blood count, kidney and liver function tests to ensure that it is safe to administer any of the drugs included in this study. This will be done every 2 weeks for the first 3 months, then monthly, if you are randomized to Arm 2.
    - Approximately 2 teaspoons (10 mL) for prostate function and thyroid function tests.
- Urine test

Week 13:

- Multiparametric MRI*

Week 14-17:

- You will be scheduled to have surgery to remove the prostate by robotic assisted radical prostatectomy (RARP).

If you are randomized to Arm 3: you will need the following examinations, tests, and procedures described below. Some of these exams, tests, and procedures are part of your regular medical care.

Week 1-6 (at surgeon's discretion):

- You will undergo surgery with robotic assisted radical prostatectomy (RARP).

Follow up (all arms):
After the surgery, you will return for follow up visits. The first visit will be 1 week after surgery, then monthly for the first 3 months, then every 3 months for two years. The following assessments will be done at these visits:

- A physical exam. The research doctor or another research healthcare professional will complete a physical assessment, including blood pressure, pulse, rate of breathing, temperature, weight, and an evaluation of your ability to carry out daily activities.
- You will be asked to report any symptoms and health problems you have and any new medications you have started.
- Blood tests
    - Approximately 2 teaspoons (10 mL) for routine testing, such as, a complete blood count, kidney and liver function tests to ensure that it is safe to administer any of the drugs included in this study
    - Approximately 2 teaspoons (10 mL) for prostate function and thyroid function tests
    - PSA will be done at all visits, including months 1 and 2
- Urine test

Study Specific Exams:
The following exams, tests and procedures are not part of regular cancer care. These are being done because you are on study.

Questionnaires:
You will be asked to complete three questionnaires. These are being done to help doctors determine how the treatment is affecting your urinary and sexual functioning. The questionnaires should take about 15 minutes to complete. If any of the questions make you feel uncomfortable, you do not have to answer them. You will be asked to complete the questionnaires:

- After you sign consent (during screening)
- If you are on Arms 1 or 2:
    - Day 1 of treatment
    - Week 5, 9 and 13 of treatment
- All follow up visits

Specimens for Study:
You will have surgery to remove your cancer. Researchers would like to keep some of the tissue that is left over for future research studies for up to 10 years. In addition, we would like to collect blood and urine samples for future research. The blood, urine and tissue samples will be kept and may be used to learn more about prostate cancer. These samples will be used in research to see if proteins in the blood and/or tissue can predict how the cancer will respond to therapy. The research that may be done with your tissue and blood is not designed specifically to help you. It might help people who have cancer and other diseases in the future. Your specimens will be used for genetic research (about diseases that are passed on in families). Reports about research done with your blood, urine and tissue will not be given to you or your doctor. These reports will not be put in your health record and will not have an effect on your care.

Your samples will be stored for up to 10 years in the Rutgers Cancer Institute of New Jersey Biorepository Service (BRS), which is owned and operated by Rutgers Cancer Institute of New Jersey. The repository is located at 195 Little Albany Street, New Brunswick, NJ, 08903. Only personnel authorized to handle and store your samples will have access to your samples.

You will be asked to provide the following samples at the following time points:

If you are in Arm 1 or 2:

- Before beginning treatment: blood (approximately 10 teaspoons [50 ml]) and urine
- Week 5, 9 and 13: blood (approximately 6 teaspoons [30 ml]) and urine
- At the time of surgery: blood (approximately 10 teaspoons [50 ml]), urine and tissue left over from the surgery

If you are in Arm 3:

- Before beginning treatment: blood (approximately 10 teaspoons [50 ml]) and urine
- At the time of surgery: tissue left over from the surgery

During Follow up for all arms:

- First follow up: blood (approximately 10 teaspoons [50 ml]) and urine
- Monthly for the first 3 months, then every 3 months for two years: blood (approximately 6

teaspoons [30 ml]) and urine
- At the 2-year study visit: blood (approximately 10 teaspoons [50 ml]) and urine

You are the owner of the samples. This gives you the right to have the specimen materials destroyed at any time by withdrawal of your consent. If you choose to have your samples destroyed, you must do so by writing to the study doctor.

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If you decide to have your samples destroyed, any information which was generated prior to your request will not be withdrawn, but no further studies will be done.

Can you stop being in the study?
Yes. You can decide to stop at any time. Tell the doctor if you are thinking about stopping or decide to stop. He or she will tell you how to stop safely.

It is important to tell the doctor if you are thinking about stopping so any risks from the study drugs can be evaluated by your doctor. Another reason to tell your doctor that you are thinking about stopping is to discuss what follow-up care and testing could be most helpful for you.
The doctor may stop you from taking part in this study at any time if he/she believes it is in your best interest, if you do not follow the study rules, or if the study is stopped.

What are the risks and/or discomforts you might experience if you take part in this study?
You may have side effects while on the study. Everyone taking part in the study will be watched carefully for any side effects. However, study doctors do not know all the side effects that may happen and there is always the risk of unknown side effects occurring. Sometimes during a study, the Sponsor may learn new facts about the study medications/treatments. It is possible that this information might make you change your mind about being in the study. If new information is discovered, your study doctor will tell you about it right away.

Side effects may range from mild to very serious. It is not possible to tell which side effect will affect you or how mild or severe the side effect might become. We can only tell you what other people have experienced. Please talk with your study doctor about these side effects.

All medicines have the potential to cause an allergic reaction. Some allergic reactions and side-effects may potentially be life threatening. If you do experience any side effects, your doctor may need to give you medicines to help lessen the side effect.

Your study doctor may give you drugs to help lessen any side effects. Side effects may stop or appear to lessen soon after you stop taking the study drugs. In some cases, side effects can be serious, long lasting, or may never go away. You should talk to your study doctor about any side effects that you

have while taking study drug.

Risks and side effects related to apalutamide (JNJ-56021927)
Doctors don't yet know all of the side effects that could happen when taking apalutamide. You will be watched carefully during this study for any side effects.

Likely (very common, ≥10%), out of 100 people who receive apalutamide, 10 or more may have the following:
Fatigue
Skin rash
Joint pain and Muscle spasms (Arthralgia)
Weight Loss
Fall
Fracture
Increased blood pressure (hypertension)
Hot flush
Diarrhea
**Decreased appetite

Less likely (common, ≥1-<10%), out of 100 people who receive apalutamide, 1- 10 may have the following:
Itching
Changes in thyroid function (hypothyroidism)
Increase in triglycerides
Increase in cholesterol
Change in experience of taste (dysgeusia)
Reduced or blocked blood flow to the heart, including heart attack (Ischemic Heart Disease, including Myocardial Infarction)
Reduced or blocked blood flow to the brain, including stroke (Ischemic Cerebrovascular Disorders)
Alopecia (hair loss)

Uncommon (≥0.1%-<1%) but serious, out of 100 people who receive apalutamide, less than 1 may have the following:
Seizure
*Inflammation within the lungs that may lead to permanent damage (Interstitial lung disease)
*An uncontrollable urge to move your legs due to an uncomfortable sensation (Restless leg syndrome)

Rare (≥0.01%-<0.1%) but serious, out of 1000 people who receive apalutamide, less than 1 may have the following:
***Life-threatening rash with blisters and peeling over much of the body (Stevens-Johnson syndrome/Toxic epidermal necrolysis)
***Skin rash with fever, and blood cell abnormalities including increase in white blood cells

(lymphocytes and eosinophils), a decrease in platelets and potential life threatening inflammation of internal organs (Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS))

*this is information provided voluntarily by Doctors using apalutamide in routine clinical practice where frequency cannot be estimated; however frequency of this event can be estimated from clinical trials and is assessed as uncommon.

**this is information provided voluntarily by doctors using apalutamide in routine clinical practice where frequency cannot be estimated; however, frequency of this event can be estimated from clinical trials and is assessed as very common.

***this is information provided voluntarily by doctors using apalutamide in routine clinical practice where frequency cannot be estimated; however, frequency of this event can be estimated from clinical trials and is assessed as rare.

Seizures have been observed very rarely in subjects taking part in apalutamide studies. Your doctor will confirm that you have no history of seizures and will check throughout the study that you are not taking other medications that can increase your risk of seizures. Please inform your doctor of all medications you are taking and any changes in medications. If you think you might have had a seizure, or convulsion, or have lost consciousness (passed out), let your doctor know right away.

More than 1 in 10 patients have developed a rash. Some rashes may need medical attention. The rash may be confined to one area of your body or may spread across your body. Contact your doctor at the first sign of rash or any symptoms of rash (like itching) during the study. Rashes that are painful, blisters on or near the lips, eyes or genitals; peeling of areas of skin surface, may need immediate evaluation by your doctor. If you develop rash with fever at the same time; contact your doctor immediately for evaluation. You may be given medicines to apply to your skin or take by mouth to help the signs and symptoms of rash. Also the study medication may be temporarily held.

Scarring of the inner lining of the lung (Interstitial lung disease) has been observed in patients taking apalutamide. Inform your doctor if you have any history of lung problems. Contact your doctor right away if you experience symptoms such as shortness of breath, breathing difficulty, cough or fever. Life-threatening rash with blisters and peeling over much of the body (Toxic epidermal necrolysis) has been observed in patients taking apalutamide. Inform your doctor if you have any history of severe skin allergic reactions.

Medication interaction with apalutamide

Some medication can affect the level of study drug in your blood. You need to tell your study doctor of all the medications and supplements (e.g., herbs, vitamins) you are taking, as well as any changes in medications. Your study doctor can determine if these medications or supplements interact with the study drug.

For patients who have difficulty swallowing tablets whole

The recommended dose of apalutamide tablets may be mixed with 4 ounces (120 mL) of applesauce, for patients who have difficulty swallowing tablets whole. Do not crush the tablets. Stir applesauce upon introduction of whole tablets as well as at 15 minutes and 30 minutes afterwards until tablets are dispersed (well mixed with no chunks remaining). Using a spoon, swallow the mixture right away. Rinse the mixture container with 2 ounces of water and immediately drink the contents. Repeat the rinse with 2 ounces of water one more time to ensure the whole dose is taken. The mixture should be consumed within one hour of preparation.

Risks and side effects related to the abiraterone acetate
You may ask your doctor for printed information about abiraterone acetate and the potential side effects (this is called a package insert).

Frequent, out of 100 people who receive abiraterone acetate, more than 20 may have the following:
- hypokalaemia (low blood potassium, a mineral that helps regulate heart rate/function, fluid balance in the body and is needed for adequate body function)
- hypertension (high blood pressure)

Very common, out of 100 people who receive abiraterone acetate, between 10-19 may have the following:
- edema peripheral (swelling of the legs as a result of the body keeping too much fluid)

Common, out of 100 people who receive abiraterone acetate, between 5 to 9 may have the following:
- dyspepsia (uncomfortable feeling in upper belly, indigestion)
- hematuria (presence of blood in the urine)
- Alanine aminotransferase increased and/or aspartate aminotransferase increased (enzymes in the blood that measure the function of the liver)
- urinary tract infection
- fractures (a break in the bone)

Less Common, out of 100 people who receive abiraterone acetate, less than 5 may have the following:
- hypertriglyceridemia (high levels of fats (triglycerides) in the blood)
- angina pectoris (chest pain)
- atrial fibrillation (a fast and irregular heartbeat)
- tachycardia (rapid heartbeats)

Uncommon, out of 1000 people who receive abiraterone acetate, 1 to 9 may have the following:
- adrenal insufficiency (decreased function of adrenal glands that normally help maintain blood pressure, balance minerals and fluid in your body)

- cardiac failure (heart failure, the heart is unable to supply enough blood flow to meet the body's needs.)
- arrhythmia (changes in the rhythm of the heart)
- abnormal ECG with QT prolongation (an abnormal finding on the ECG)
- bone density decreased (loss of strength of bones)
- myopathy (muscle weakness and/or muscle pain)

Unknown (frequency isn't determined since data was derived from post-marketing experience and there was no report from clinical studies)

- allergic alveolitis (swelling and irritation of the lung)
- failure of the liver to function (called acute liver failure)
- Rhabdomyolysis (breakdown of muscle tissue)
- Torsades de Pointes (rapid or irregular heart rate associated with feeling faint or lightheaded)
- Anaphylactic reaction (severe allergic reaction that may include symptoms such as difficulty swallowing or breathing, swollen face, lips, mouth, tongue or throat, or an itchy rash)

There is a small chance of severe allergic reaction to the drug which may be life-threatening.

Abiraterone acetate may cause harm to the liver. Approximately 13% of patients taking abiraterone acetate have had abnormal blood levels of liver enzymes. Rarely, failure of the liver to function may occur, which can lead to death. Interruption or discontinuation of the treatment with abiraterone acetate was sufficient to normalize the liver enzymes in majority of these cases. Your liver function will be monitored closely by blood tests every two weeks for the first 3 months of the study and monthly thereafter. If elevations in your liver function enzymes are observed, the dose of your study medication will be adjusted or discontinued.

Abiraterone acetate should be used with caution in patients with a history of heart disease. Before treatment with abiraterone acetate, high blood pressure must be controlled and low potassium must be corrected. Potassium is needed for proper function of your heart, and other essential body systems.

It is important that you contact your study doctor right away if you cannot come to your regularly scheduled visit or get your blood tests. This is because some patients have no symptoms when their blood potassium is low. Contact your study doctor immediately if:

- You feel weak, have constipation, muscle pain, or cramps. These symptoms may be caused by low blood potassium.
- Your appetite decreases, or if you develop diarrhea. Potassium may become low if you are not eating well, or is lost through diarrhea.

If you have diabetes, your blood sugar may drop if you take abiraterone acetate plus prednisone/prednisolone with some medicines for diabetes such as pioglitazone or repaglinide. Tell

your healthcare provider if you monitor your blood sugar while taking a medicine for diabetes and notice a drop in your blood sugar.

There are also risks associated with handling abiraterone acetate. This medicine may cause harm to the unborn child if taken by women who are pregnant. Women who are pregnant or who may be pregnant should wear gloves if they need to touch abiraterone acetate tablets**.** You should notify any caregivers of this information, to ensure the appropriate precautions are taken.

Certain drugs may interact with abiraterone acetate. You need to tell your study doctor of all medications and supplements (e.g., herbs, vitamins) you take. The study treatment must be taken only by you. It must also be kept out of the reach of children or persons of limited capacity to understand.

Abiraterone acetate is provided as 250 mg tablets. You will take 4 tablets by mouth once daily on an empty stomach. Abiraterone acetate must be taken on an empty stomach with water at least one hour before or two hours after a meal. The tablets should be swallowed whole with water. It is important to stay on this schedule. How abiraterone acetate enters your body can be quite different depending on when you eat. This is why abiraterone acetate should not be taken with food.

Abiraterone acetate must be stored at room temperature (between 15ºC to 30ºC, or 59°F to 86°F) with the cap on tightly, and should not be refrigerated. If you miss a dose of study drug, do not try to make it up. It should be omitted.

Risks and side effects related to prednisone

Prednisone is given with abiraterone acetate to reduce or stop some of the side effects of abiraterone acetate, such as high blood pressure, low blood potassium, and swelling of the legs.

You should tell the study doctor if you have ever had a reaction to prednisone. You may ask your doctor for printed information about prednisone and the potential side effects (this is called a package insert).

Prednisone should never be stopped suddenly. If you need to stop your doctor will advise on how to slowly cut down the dose and stop the drug. If you were to stop taking prednisone suddenly you could have:

- Weakness and tiredness
- Very low blood pressure
- Very low blood sugar
- Abnormal blood minerals

Prednisone is a type of drug called a corticosteroid. Corticosteroids can weaken your body's ability to fight off infection, and can make infections hard to diagnose or treat. If you develop fever, or suspect you have an infection, you should alert your study doctor right away.

Other side effects caused by corticosteroids

- Fluid retention
- Stomach bleeding
- Indigestion
- Seizures
- Swelling of the brain
- Emotional changes
- Mood swings or severe depression
- Eye problems such as cataracts or glaucoma
- Insomnia (sleeplessness, wakefulness)
- Elevated blood sugar (*for diabetics, this can make your glucose level more difficult to control)*
- Increased blood calcium (*extra calcium is stored in your bones or passed out of your body in urine and stool).*

Risks and side effects associated with long term use of corticosteroids

Cushing's syndrome: Taking corticosteroids over a long period of time can cause a condition called Cushing's syndrome. Symptoms include:

- Weight gain
- Muscle weakness
- A moon faced appearance
- Thin, fragile skin
- Brittle bones
- Purplish stripe marks on the skin

Adrenal insufficiency: May occur due to long term use of steroid medicines taken orally. It can be life threatening at times of major illness and extreme physical stress. Symptoms of adrenal insufficiency include:

- Weakness and fatigue
- Low blood pressure
- Nausea
- Vomiting
- Diarrhea
- Irritability and/or restlessness

While these reactions are usually not severe, they are potentially fatal if not treated.

Risks and side effects related to GnRH

Likely, out of 100 people who receive GnRH, more than 10 may have the following:

- Excessive sweating
- Temporary growth in tumor or worsening of tumor related problems.
- Decrease in bone mineral density
- Headache or head pain
- Hot flashes
- Decrease in sexual desire
- Sexual dysfunction
- Decrease in breast tissue
- Acne
- Swelling of the arms and/or legs

Less likely, out of 100 people who receive GnRH, 1- 10 may have the following:

- Lack of enough red blood cells (anemia)
- Heart attack or heart failure
- High blood pressure
- Feeling the heart racing; 'skipping a beat'; pounding
- Widening of blood vessels (vasodilation)
- Fast heart beat
- Lazy eye
- Dry eyes
- Loss of appetite
- Increased appetite
- Nausea, or the urge to vomit
- Belly pain
- Constipation
- Diarrhea
- Heartburn
- Excess gas
- Ulcer
- Vomiting
- Dry mouth
- Reaction at the site of the injection
- Voice changes
- Fever
- Infection
- Flu-like symptoms
- Weight gain or weight loss
- High blood sugar level
- Weakness
- Joint pain

- Bone pain
- Abnormal increase in muscle tension and a reduced ability of a muscle to stretch
- Leg cramps
- Muscle pain
- Condition of the nervous system that causes numbness, tingling, burning.
- Dizziness (or sensation of lightheadedness, unsteadiness, or giddiness)
- Anxiety
- Depression
- Difficulty sleeping or falling asleep
- Changes in mood
- Urinary frequency
- Blockage in the urinary tract
- Infection of the urinary tract
- Pelvic symptoms
- Increase in breast tissue
- Decrease in ability to have an erection
- Increase in sexual desire
- Pain or swelling of the breasts
- Sore throat
- Infection of the respiratory tract
- Chronic obstructive pulmonary disease (COPD), a disorder that makes it hard to breath and may cause you to cough up mucus
- Cough
- Swelling of the airways
- Swelling of the sinuses
- Nose bleed
- Swelling of the mucus membranes inside the nose
- Hair disorders
- Itching
- Rash; flaking or sloughing of skin
- Change in skin color or bruising
- Bleeding

Rare but serious, out of 100 people who receive GnRH, less than 1 may have the following:

- Stroke
- Heart attack
- Formation or presence of a blood clot inside a blood vessel

Risks and side effects related to leuprolide acetate

Likely, out of 100 people who receive leuprolide acetate, more than 10 may have the following:

- Nausea or the urge to vomit

- Vomiting
- Burning or stinging at the site of the injection
- Headache or head pain
- Pain
- Difficulty sleeping or falling asleep
- Depression
- Hot flashes or excess sweating
- Shrinking of the testicles

Less likely, out of 100 people who receive leuprolide acetate, 1- 10 may have the following:

- Swelling
- High or low blood pressure
- Fast heart beat
- Slow heart beat
- Low levels of oxygen in the heart causing chest pain
- Feeling the heart racing; 'skipping a beat'; pounding
- Abnormal bowel function
- Ulcer
- Blockage somewhere in the intestines
- Constipation
- Diarrhea
- Irritation and/or swelling of the stomach, intestines and/or colon
- Skin reaction at the site of the injection
- Flu-like symptoms
- Infection of the urinary tract
- Infection
- Increased blood levels of blood urea nitrogen (BUN), a substance normally eliminated by the kidneys into the urine
- Increased blood level of creatinine, a substance normally eliminated by the kidneys into the urine
- Abnormal blood chemistry
- Increased blood phosphate level
- Increased blood uric acid level
- Low levels of a blood protein called albumin
- Low levels of blood protein
- Dehydration
- Increased levels of fats (lipids) in the blood
- Weight gain or weight loss
- Weakness
- Bone pain
- Problems with the joints
- Muscle pain

- Condition of the nervous system that causes numbness, tingling, burning
- Nervous feeling
- Anxiety
- Confusion
- Fatigue or tiredness
- Dizziness (or sensation of lightheadedness, unsteadiness, or giddiness)
- Urinary disorders
- Sudden constricting of the bladder
- Difficulty emptying the bladder
- Enlarged breasts in males
- Breast tenderness
- Pain in the testicles
- Inability to have an erection of the penis adequate for sexual intercourse. Also called impotence.
- Decrease in sexual desire
- Excessive urinating at night
- Emphysema: a condition where the air sacs of the lungs are damaged and enlarged, causing breathlessness
- Nose bleed
- Collection of fluid between the thin layers of tissue (pleura) lining the lung and the wall of the chest cavity
- Collection of fluid in the lungs
- Shortness of breath
- Cough
- Acne
- Hair loss
- Bruising
- Infection of the skin that occurs when the white blood cell count is low
- Itching
- Rash; flaking or sloughing of skin
- Varicose vein: A vein that has enlarged and twisted, often appearing as a bulging, blue blood vessel that is clearly visible through the skin
- Formation or presence of a blood clot inside a blood vessel

Rare but serious, out of 100 people who receive leuprolide acetate, less than 1 may have the following:

- Irregular heart beat
- Heart attack or heart failure
- Fainting
- Bleeding in the digestive tract
- Allergic reaction
- Seizure

Risks and side effects related to Radical Prostatectomy (Surgery)
Your doctor will talk to you about the risks of surgery. Listed below are the likely side effects that happen in more than 5% of the men and the unlikely side effects that will happen in 5% or less of the men that have radical prostatectomy.

Likely, out of 100 people who undergo Radical Prostatectomy (Surgery), more than 10 may have the following:

- Time away from work
- Pain
- Permanent scarring or bending of the skin in the area of the incision
- Frequency or urgency to urinate that may last for several months after the surgery
- Impotence (inability to achieve erections satisfactory for intercourse)
- Inability to ejaculate

Less Likely, out of 100 people who undergo Radical Prostatectomy (Surgery), 1- 10 may have the following:

- Wound infection
- Urinary tract infection
- Blood loss
- Edema (swelling) in the pelvis/scrotal area or leg
- Urinary incontinence (leaking of urine), possibly permanent, that is frequent and may require the use of a pad
- Urinary retention (not able to pass urine) that may need to have catheter placed in the bladder for several weeks
- Injury to adjacent organs (rectum, nerve tissue, blood vessels, ureter [tube draining the kidney to the bladder])
- Lymphocele (collection of lymph fluid in the pelvis)
- Ileus (blockage of the intestines)
- Blood clot in the leg (deep venous thrombosis or pulmonary embolism (blood clot in the lung)

Rare but serious, out of 100 people who undergo Radical Prostatectomy (Surgery), less than 1 may have the following:

- Heart attack
- Stroke
- Death

Though it is unlikely, there is a chance your disease worsens with treatment with apalutamide alone or in combination with GnRH agonist.

You will be asked to sign a separate consent for surgery.

Reproductive risks:
You should not father a baby while on this study because the drugs in this study can affect an unborn baby. It is important you understand that you need to use birth control while on this study. Check with your study doctor about what kind of birth control methods to use and how long to use them. Some methods might not be approved for use in this study. Based on your condition, it is unlikely that you could father a child. However, should your partner become pregnant, you should notify your study doctor.

For more information about risks and side effects, ask your study doctor.

Risks associated with using your specimens for future research:
Your privacy is very important to us and we will use many safety measures to protect your privacy. However, in spite of all the safety measures that we will use, we cannot guarantee that your identity will never been known.

- While your specimens will be coded and will not contain information used to identify you, such as your name, address, telephone number, or medical record number, people may develop ways in the future that would allow someone to link your medical information in our protected database back to you. It is also possible that there could be violations to the security of the computer systems used to store the codes linking your medical information to you.
- Genetic testing will be performed on the tissues samples. Although your genetic information is unique to you, you do share some genetic information with your children, parents, brothers, sisters, and other blood relatives. Consequently, it may be possible that genetic information from them could be used to identify you. Similarly, it may be possible that genetic information from you could be used to help identify them. Further, patterns of genetic variation also can be used by agencies to identify a person or his/her blood relatives (for example, to establish relationships between parents and their children).
- There also may be other privacy risks that we have not foreseen.

<u>Economic Risks of Harm</u>:

- Since some genetic variations can help to predict the future health problems of you and your relatives, this information might be of interest to health providers, life insurance companies, and others. Therefore, your genetic information potentially could be used in ways that could cause you or your family economic distress.

There is a federal law call the Genetic Information Nondiscrimination Act (GINA). In general, this law makes it illegal for health insurance companies, group health plans, and most employers to discriminate against you based on your genetic information. This law generally will protect you in the following ways:

1) health insurance companies and group health plans may not request your genetic information

that we get from this research;

2) health insurance companies and group health plans may not use your genetic information when making decisions regarding your eligibility or premiums; and
3) Employers with 15 or more employees may not use your genetic information that we get from this research when making a decision to hire, promote, or fire you or when setting the terms of your employment. However, it does not protect you against discrimination by companies that sell life insurance, disability insurance, or long-term care insurance.

Are there any benefits for you if you choose to take part in this research study?
Taking part in this study may or may not make your health better. While some doctors and researchers hope that having hormone therapy before surgery will reduce nerve damage, there is no proof of this yet. We do know that the information from this study will help doctors learn more about the combination of hormonal therapy and surgery for prostate cancer. This information could help future cancer patients in choosing optimal combination of therapies.

What are your alternatives if you don't want to take part in this study?
You do not have to take part in this research study. If you decide not to take part in this study, you have other choices. Instead of being in this study, you can:

- Choose to have the usual approach to treatment described above without being in a study
- Take part in another study

Please talk to the study doctor about your choices before you decide if you will take part in this study.

How will you know if new information is learned that may affect whether you are willing to stay in this research study?
During the course of the study, you will be updated about any new information that may affect whether you are willing to go on taking part in the study. If new information is learned that may affect you after the study or your follow-up is completed, you will be contacted.

Will there be any cost to you to take part in this study?
You and/or your insurance company will be billed for the costs of your treatment that are considered standard of care (for example, doctor/ Advanced Practice Nurse (APN) visits, nursing care to administer the treatments, routine lab tests, restaging scans, etc.) as you would have received these services even if you were not participating in this study. You will be responsible for any co-payments due for office visits, co-insurances and deductibles due on any tests and/or procedures that are required and considered standard care.

The apalutamide and abiraterone acetate will be provided at no charge while you take part in this study.

The multiparametric MRI done on this study will be billed to the study.

Taking part in this study may cost your or your insurance company additional costs. If you have any questions about insurance coverage, including any out of pocket expenses you might incur, or which laboratory or facilities you are allowed to have tests at, a financial counselor will be made available to you upon request.

For more information on clinical trials and insurance coverage, you can visit the National Cancer Institute's Web site at: http://www.cancer.gov/clinicaltrials/learningabout/payingfor

You can print a copy of the "Clinical Trials and Insurance Coverage" information from this Web site. Another way to get the information is to call 1-800-4-CANCER (1-800-422-6237) and ask them to send you a free copy.

Will you be paid to take part in this study?
You will not be paid for your participation in this research study.

How will information about you be kept private or confidential?
All efforts will be made to keep your personal information in your research record confidential, but total confidentiality cannot be guaranteed.

Your personal health information, identifiers and research data are stored and kept in a secure area in the Cancer Institute of New Jersey. Computer screens containing personal health identifiers are inaccessible to public view. Only the study doctor and research team will have direct access.

A description of this clinical trial will be available on 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 website at any time.

What will happen if you are injured during this study?
Subjects in this study will be exposed to certain risks of personal injury in addition to those associated with standard forms of treatment, which were discussed in the Risk and Discomforts section of this consent form. In addition, it is possible that during the course of this study, new adverse effects of apalutamide, abiraterone acetate, prednisone, GnRH and surgery that result in personal injury may be discovered. The University will make appropriate referrals for medical and/or dental treatment for subjects who sustain personal injuries or illnesses as a direct consequence of participation in the research. The subject's health insurance carrier or other third-party payer will be billed for the cost of this treatment; provided that the University shall not submit to federally funded programs, e.g., Medicare, Medicaid or CHAMPUS, for reimbursement first if submission to such programs is prohibited by law. No financial compensation will be provided by the University and no other type of assistance is available from the University.

You are not giving up any of your legal rights by signing this informed consent form or by taking part in this research study.

What will happen if you do not wish to take part in the study or if you later decide not to stay

in the study?
Participation in this study is voluntary. You may choose not to participate or you may change your mind at any time.

If you do not want to enter the study or decide to stop participating, your relationship with the study staff will not change, and you may do so without penalty and without loss of benefits to which you are otherwise entitled.

You may also withdraw your consent for the use of your data, but you must do this in writing to
Saum B. Ghodoussipour, MD
Rutgers Cancer Institute of New Jersey
195 Little Albany Street
New Brunswick, NJ 08903

Any data that has already been collected cannot be withdrawn because there may not be any identifiers to link the data with you. We are required by the Food and Drug Administration, however, to continue to report anything that relates to the safety of these drugs.

At any time, the study doctor can take you out of this study because it would not be in your best interest to stay in it. Your study doctor can stop treatment even if you are willing to stay in the study.

If you decide to withdraw from the study for any reason, you may be asked to return for at least one additional visit for safety reasons.

Who can you call if you have any questions?
If you have any questions about taking part in this study or if you feel you may have suffered a research related injury, you can call the study doctor:

Saum B. Ghodoussipour, MD
Rutgers Cancer Institute of New Jersey
(732) 235-2465

If you have any questions about your rights as a research subject, you can call:

IRB Director
(732)-235-9806

What are your rights if you decide to take part in this research study?
You have the right to ask questions about any part of the study at any time. You should not sign this form unless you have had a chance to ask questions and have been given answers to all of your questions.

PERMISSION (Authorization) TO USE OR SHARE HEALTH INFORMATION THAT

IDENTIFIES YOU FOR A RESEARCH STUDY

Information about you and your health is personal and private, so this information generally cannot be used in research without your written permission. The next few paragraphs tell you about how researchers want to use and share your health information in this research study. Your information will only be used as described here or as allowed or required by law. Ask questions if you do not understand any part of the research or the use of your health information. If you sign this consent form, you agree to let the researchers use your information in the research and share it with others as described below.

What is the purpose of the research and how will my information be used?
You are being invited to take part in this research study which is described at the beginning of this form. The purpose of collecting and using your health information for this study is to help researchers answer the questions that are being asked in the research.

What information about me will be used?

- All information in your medical record
- Hospital discharge summaries
- Radiology records or images (MRI, CT, PET scans)
- Medical history or treatment
- Medications
- Consultations
- Laboratory/diagnostic tests or imaging
- EKG and/or EEG reports
- Psychological testing, surveys or questionnaires
- Pathology reports, specimen(s) or slide(s)
- Operative reports (about a surgery)
- Emergency Medicine reports

Who may use, share or receive my information?
The research team may use or share your information collected or created for this study with the following people and institutions:

- Rutgers University researchers involved in the study;
- The Rutgers University Institutional Review Board and Compliance Boards
- Robert Wood Johnson University Hospital (RWJUH)
- Rutgers Cancer Institute of New Jersey (CINJ)
- Janssen Scientific Affairs, LLC
- The Office for Human Research Protections in the U.S. Dept. of Health and Human Services
- Representatives of the National Cancer Institute (NCI), Food and Drug Administration (FDA), and other U.S. and international governmental regulatory agencies involved in overseeing research

Those persons or organizations that receive your information may not be required by Federal privacy

laws to protect it and may share your information with others without your permission, if permitted by the laws governing them.

Will I be able to review my research record while the research is ongoing?
No. We are not able to share information in the research records with you until the study is over. To ask for this information, please contact the Principal Investigator, the person in charge of this research study.

Do I have to give my permission?
No. You do not have to permit use of your information. But, if you do not give permission, you cannot take part in this research study. (Saying no does not stop you from getting medical care or other benefits you are eligible for outside of this study.)

If I say yes now, can I change my mind and take away my permission later?
Yes. You may change your mind and not allow the continued use of your information (and to stop taking part in the study) at any time. If you take away permission, your information will no longer be used or shared in the study, but we will not be able to take back information that has already been used or shared with others. If you say yes now but change your mind later for use of your information in the research, you must write to the researcher and tell him or her of your decision:

Saum B. Ghodoussipour, MD
Rutgers Cancer Institute of New Jersey
195 Little Albany Street
New Brunswick, NJ 08903.

How long will my permission last?
There is no set date when your permission will end. Your health information may be studied for many years.

Where can you get more information?
You may call the National Cancer Institute's Cancer Information Service at:
Voice: 1-800-4-CANCER (1-800-422-6237)

You may also visit the NCI Web site at http://cancer.gov/
For NCI's clinical trials information, go to: http://cancer.gov/clinicaltrials/
For NCI's general information about cancer, go to http://cancer.gov/cancerinfo/

If you do not have access to a personal computer, you may access these websites and other information at a computer in the Resource and Learning Center on the second floor of the Cancer Institute of New Jersey at no cost to you.

Thank you for considering participation in this research.

AGREEMENT TO PARTICIPATE

You have read this entire form, or it has been read to you, and you believe that you understand what has been discussed.

All of your questions about this form or this study have been answered.

I agree to take part in this study.

Subject Name:_____

Subject Signature:_____ Date:_____

FOR NON-ENGLISH SPEAKING SUBJECTS:

Signature of Reader/Translator If the Subject Does Not Read English Well:

The person who has signed the short form, _____, does not read English well. You read English well and are fluent in _____ (*name of the language)*, a language that the subject (his/her parent(s)/legal guardian) understands well. You understand the content of this consent form and you have translated for the subject (his/her parent(s)/legal guardian) the entire content of this form. To the best of your knowledge, the subject (his/her parent(s)/legal guardian) understands the content of this form and has had an opportunity to ask questions regarding the consent form and the study, and these questions have been answered (his/her parent(s)/legal guardian).

Reader/Translator Name:_____

Reader/Translator Signature:_____ Date:_____

Witness Name:_____

Witness Signature:_____ Date:_____

Signature of Investigator/Individual Obtaining Consent:

Investigator/Person Obtaining Consent:_____

Signature:_____ Date: _____