

INSTITUTE: National Cancer Institute

STUDY NUMBER: 15-C-0124 PRINCIPAL INVESTIGATOR: William Dahut, M.D.

STUDY TITLE: Neoadjuvant Androgen Deprivation and Enzalutamide: Using Multiparametric MRI to Evaluate Intraprostatic Tumor Responses and Androgen Resistance Patterns in Newly Diagnosed Prostate Cancer

Continuing Review Approved by the IRB on 01/15/20

Amendment Approved by the IRB on 08/06/19 (J)

Date posted to web: 01/18/20

Standard

INTRODUCTION

We invite you to take part in a research study at the National Institutes of Health (NIH).

First, we want you to know that:

Taking part in NIH research is entirely voluntary.

You may choose not to take part, or you may withdraw from the study at any time. In either case, you will not lose any benefits to which you are otherwise entitled. However, to receive care at the NIH, you must be taking part in a study or be under evaluation for study participation.

You may receive no benefit from taking part. The research may give us knowledge that may help people in the future.

Second, some people have personal, religious or ethical beliefs that may limit the kinds of medical or research treatments they would want to receive (such as blood transfusions). If you have such beliefs, please discuss them with your NIH doctors or research team before you agree to the study.

Now we will describe this research study. Before you decide to take part, please take as much time as you need to ask any questions and discuss this study with anyone at NIH, or with family, friends or your personal physician or other health professional.

Why is this study being done?

This study is being done to develop improved techniques for the detection of prostate cancer both before and after pre-operative treatment. In this study we will be testing whether we can use a technique called multi parametric magnetic resonance imaging (mpMRI) for localizing and

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detecting prostate cancer. We also want to determine if two drugs used in combination prior to surgery will provide any benefit to people who have non metastatic prostate cancer (cancer that has not spread to other parts of the body). There are several therapies available to treat prostate cancer. This study will utilize a combination of androgen deprivation therapy (example goserelin or leuprolide) and enzalutamide followed by surgery. Goserelin and enzalutamide are both approved by the Food and Drug Administration (FDA) to treat prostate cancer. However, less is known about the effect of using these drugs in combination before surgery.

Why are you being asked to take part in this study?

You are being asked to take part in this study because you have been recently diagnosed with prostate cancer that is non-metastatic and you are a candidate for a radical prostatectomy following treatment. After considering all treatment options discussed with you, including possible radiation therapy options, you have decided to undergo a radical prostatectomy as part of the standard care for your cancer.

How many people will take part in this study?

About 55 people at NIH will take part in this study.

Description of Research Study

What will happen if you take part in this research study?

Before you begin the study

Certain standards (criteria) have been established to ensure that you are a medically appropriate candidate for this trial. These criteria also make sure that the results of this study can be used to help make decisions about treating other patients. We will record your medical history and give you a physical examination. You will undergo standard blood tests including a complete blood count, chemistry panel, and prostate-specific antigen (PSA) levels, and scans and x-rays as part of the NCI Screening Protocol.

During the study

If you are found to be eligible for this trial, you will be asked to complete the following tests and procedures:

- Physical Exam and vital signs monthly
- Provide samples of blood, urine or saliva for standard and research testing. The total amount of blood we will draw for research in this study is about 75ml (5 tablespoons).
- ECG before treatment and surgery
- 3T mpMRI after 6 months of treatment

You will be offered the opportunity to fill in your wishes for research and care, and assign a substitute decision maker on the “NIH Advance Directive for Health Care and Medical Research Participation” form so that another person can make decisions about your medical care in the event that you lose the ability to provide on-going consent during the course of the study.

3T mpMRI

During the procedure, you will be asked to lie down on the MRI platform and turn on your side with your back to the nurse or technician. A brief digital exam will be performed to assess the anus for safe probe insertion and then an endorectal probe will be inserted. Then, you will need to turn on your back so that you can be positioned within the bore of the scanner. You will also be given earphones or earplugs to help block out noise from the MRI scanner.

While inside the MRI bore and during the course of the scan, you, doctors, and technologists may communicate via a microphone and room loudspeaker system. In order for us to obtain the best images and data, you will need to remain motionless and relaxed during the entire exam, which lasts about 60 minutes.

Upon completion of the exam, you will be moved outside of the MRI bore and the endorectal probe will be removed.

Following these tests and procedures you will take the two study medications for 6 months. Enzalutamide is given by mouth. You will take 4 pills one time per day. Goserelin is given by injection once every 3 months for 6 months (2 doses in 6 months). If Goserelin is not available another form of androgen deprivation therapy may be prescribed. The doses and how you take these alternate medications may be different. If an alternate medication is prescribed, the study staff will let you know how much medication and how often you will need to take it.

You will be asked to return to the clinic once each month for safety tests which will include a physical exam, having your vital signs taken and standard blood tests.

If your PSA rises during the study, other treatment options may be available to you including new imaging studies, re-biopsy and possibly earlier surgery. The study doctor will discuss all these options with you and you will have the opportunity to decide which is best for your care.

Research Studies

Tumor samples that have been collected during surgery will be analyzed by the pathologist and the results will be discussed with you.

All of your samples collected for research purposes on this study (such as your tumor, saliva, urine and blood) may be used to look for specific changes in the DNA of genes that may cause prostate cancer or other types of cancer. DNA (also called deoxyribonucleic acid) in the cells carries genetic information and passes it from one generation of cells to the next – like an instruction manual. Normal tissue contains the DNA (instructions) that you were born with,

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DNA in tumor cells has changed – or mutated – and we think that change in the DNA is what causes tumors to form and to grow.

To look at your DNA, we may use do what is called “whole genome sequencing.” This is where we will do special tests in the lab to look at the entire sequence, or order, of how your DNA is put together. This is what makes you unique.

To determine which parts of the DNA have mutated, we will compare the DNA in your tumor cells to DNA from your normal cells. We will then analyze the results from similar tumors to see if there are any changes in the DNA that are common to a particular type of tumor. To examine your tissue we may use several different techniques depending on the type of tissue we collect. These could include growing cell lines (cells which keep dividing and growing in the laboratory, sometimes for years allowing us to continually study those cells), xenograft studies (placing or growing cells in another animal, such as mice), and looking in detail at the parts of the genes that produce specific proteins.

However, you should know that the analyses that we perform in our laboratory are for research purposes only; they are not nearly as sensitive as the tests that are performed in a laboratory that is certified to perform genetic testing or testing for routine clinical care. For these reasons, we will not give you the results of the research tests done on your research samples in most cases. There may be exceptions to what we share with you and this is described in the next section, “Return of research results.”

Return of research results

When we are examining your DNA, it is possible that we could identify possible changes in other parts of your DNA that are not related to this research. These are known as “incidental medical findings”.

These include:

- Changes in genes that are related to diseases other than cancer
- Changes in genes that are not known to cause any disease. These are known as normal variations.
- Changes in genes that are new and of uncertain clinical importance. This means that we do not know if they could cause or contribute to a disease or if they are normal variations.

Since the analyses that we perform in our laboratory are not nearly as sensitive as the tests that are performed in a laboratory that is certified to perform genetic testing, the genetic changes that we find may or may not be valid. Therefore, we do not plan to inform you of all of the genetic results of testing on your tissue and blood that is performed in our research lab. However, in the unlikely event that we discover a finding believed to be clinically important based on medical

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standards at the time we first analyze your results, we will contact you. This could be many years in the future. We will ask you to have an additional tube of blood drawn to verify the findings we have seen in our lab. If the results are verified, you will be re-contacted and offered a referral to a genetic healthcare provider to discuss the results.

Note: In order for us to contact you about genetic variants as described above, we must maintain your up to date contact information. This will allow us to contact you at the time findings are discovered.

When you are finished taking the drugs

After you have completed the study medications, you will be asked to undergo another 3T mpMRI, blood tests and then you will have surgery to remove your prostate. This surgery may be performed at either the Clinical Center or Walter Reed Bethesda. After the surgery you will return for a follow up visit about 6-10 weeks after your prostate is removed and then we will call you yearly for the next five years to check your PSA level.

Standard of Care Treatment

Treatments covered under this study include a combination of medications and surgery to treat your cancer. These treatments will not be experimental. Your doctors will describe your treatment plan to you in detail before asking you to sign this consent form. You may be asked to sign a separate consent form for any treatment procedures not outlined in this consent.

Birth Control

If you are the partner of a woman who can become pregnant, you and your partner will need to practice an effective form of birth control before starting study treatment, during study treatment, and for 3 months after you finish study treatment. If you think that your partner is pregnant, you should tell your study doctor or nurse at once.

Effective forms of birth control include:

- abstinence
- intrauterine device (IUD)
- hormonal [birth control pills, injections, or implants]
- tubal ligation
- vasectomy

Risks or Discomforts of Participation

What side effects or risks can I expect from being in this study?

As with all treatments, there are several side effects or risks from the treatments provided in this study. However, doctors don't know all the side effects that may happen with this combination

of drugs, so it is important to report any changes that you notice, even if your study team does not ask specifically about them. Side effects may be mild or severe. Your study team will give you medicines to help lessen side effects. Many side effects go away with those medicines and others may go away soon after you stop treatment. In some cases, side effects can be serious, long-lasting, or may never go away. In very rare instances, they could cause death.

Possible side effects of enzalutamide:

Likely	Less Likely	Rare but Serious
<ul style="list-style-type: none"> • Ankle swelling • Fatigue • Headache • Hot flashes • Diarrhea • Low blood counts • Back pain • Upper respiratory tract infection • Nipple tenderness 	<ul style="list-style-type: none"> • High blood pressure • Dizziness, anxiety • Dry skin • Blood in urine • Jaundice • Weakness of muscles 	<ul style="list-style-type: none"> • Seizures

Possible Side effects of goserelin:

Likely (greater than 5%)	Less Likely (1%–5%)	Rare but Serious
<ul style="list-style-type: none"> • Hot flashes • Generalized pain or pain in the pelvis or bone • Enlarged breasts • Weakness 	<ul style="list-style-type: none"> • Pain in abdomen and/or back • Flu-like symptoms • Headache • Cardiac problems (chest pain, clots, varicose veins) • Diarrhea • Vomiting blood • Sugar in blood • Low red cells (anemia) • Swelling in hands or feet • Dizziness • Numbness or tingling • Frequent urination, unable to void, unable to hold urine, urinary infection, 	<ul style="list-style-type: none"> • Infection in blood • Heart failure • Stroke • Clot that may travel to lungs or brain

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	blood in urine • Impotence • Itchy skin • Herpesvirus of the skin	
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Other Risks

Risks from X-rays and / or Scans

Radiological testing, such as CT scans, MRIs, X-rays and/or radioactive drugs may be used to assess the treatment of your disease at various times during therapy. The cumulative radiation exposure from these tests is considered very small and is unlikely to adversely affect you or your disease. Because some of these tests require administration of contrast you could experience pain, bruising, and/or infection at the site of injection, or an allergic reaction to the contrast agent. Please notify the investigator if you know or suspect you are allergic to contrast dye.

ECG

There are no significant risks or discomforts associated with an ECG. Some patches will be adhered to your skin that may cause some reddening or slight itching.

Blood draws

There may be some side effects associated with the procedures for drawing blood in this study, but the person drawing your blood will attempt to minimize this discomfort. Side effects include pain and bruising in the area where the needle is inserted, lightheadedness, and rarely, fainting. When large amounts of blood are collected, low red blood cell count (anemia) is a risk.

Risks of mpMRI

The mpMRI examination poses almost no risk to the average patient when appropriate safety guidelines are followed. Although the strong magnetic field is not harmful in itself, implanted medical devices that contain metal may malfunction or cause problems during an MRI exam. You will be asked if you have any such devices implanted prior to the exam. It is possible to experience some mild discomfort during placement of the endorectal probe.

Risks of Biopsy

A hollow needle is used to withdraw small cylinders (or cores) of tissue from your tumor using a MRI scan or ultrasound for guidance. The needle is put in 3 to 6 times to get the samples, or cores. This procedure usually causes only brief discomfort at the site from which the biopsy is taken and you will be offered medication to help numb the pain. Biopsy collection may cause bruising and bleeding, but usually does not leave scars. Rarely infection may occur at the needle site.

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Psychological or Social Risks Associated with Loss of Privacy

The following general points are indirectly related to your participation in the research study:

1. **Unanticipated medical information:** During the course of this investigation, it is possible (although not likely) that we will obtain unanticipated information about your health or genetic background.
2. **Release of genetic information:**
 - Your privacy is very important to us and we will use many safety measures to protect your privacy. However, in spite of all of the safety measures that we will use, we cannot guarantee that your identity will never become known. 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 help identify you. Similarly, it may be possible that genetic information from you could be used to help identify them.
 - Patterns of genetic variation also can be used by law enforcement agencies to identify a person or his/her blood relatives. Therefore, your genetic information potentially could be used in ways that could cause you or your family distress, such as by revealing that you (or a blood relative) carry a genetic disease.
 - It is possible also that someone could get unauthorized access or break into the system that stores information about you. Every precaution will be taken to minimize this risk.
 - There also may be other privacy risks that we have not foreseen.

Since some genetic variations can help to predict future health problems for you and your relatives, this information might be of interest to health care providers, life insurance companies, and others. However, Federal and State laws provide some protections against discrimination based on genetic information. For example, the Genetic Information Nondiscrimination Act (GINA) makes it illegal for health insurance companies, group health plans, and most employers to discriminate against you based on your genetic information. However, GINA does not prevent companies that sell life insurance, disability insurance, or long-term care insurance from using genetic information as a reason to deny coverage or set premiums. GINA also does not apply to members of the United States military, veterans obtaining health care through the Veteran's Administration, individuals covered by the Indian Health Service or Federal Employees Health Benefits. Lastly, GINA does not forbid insurance medical underwriting based on your current health status though the Affordable Care Act limits consideration of pre-existing conditions by insurers.

Potential Benefits of Participation

Are there benefits to taking part in this study?

The primary aim of this study is to see if mpMRI imaging is a good method to localize and detect prostate cancer. During the study we will also administer 2 drugs in combination. Although these drugs are already approved for treating prostate cancer, less is known about how they work together and what effect they have when given before surgery. It is possible that you will receive some additional personal medical benefit from participating in this trial, but we cannot be certain. These potential benefits could include shrinking of your tumor or lessening of your symptoms, such as pain, that are caused by the cancer. We hope that the knowledge gained from this study may help to detect prostate cancer. We also hope that that you will receive direct benefit to your cancer but because we do not have enough information about how these drugs work together, it is also possible that you may receive no benefit. However, the information gained during this trial may help others with cancer in the future.

Alternative Approaches or Treatments

What other choices do I have if I do not take part in this study?

Instead of being in this study, you have these options:

- Getting treatment or care for your cancer without being in a study
- Taking part in another study
- Getting comfort care, also called palliative care. This type of care helps reduce pain, tiredness, appetite problems and other problems caused by the cancer. It does not treat the cancer directly. Instead, it tries to improve how you feel. Comfort care tries to keep you as active and comfortable as possible.

Please talk to your doctor about these and other options.

Stopping Therapy

Your doctor may decide to stop your therapy for the following reasons:

- if he/she believes that it is in your best interest
- if you have side effects from the treatment that your doctor thinks are too severe
- if new information shows that another treatment would be better for you

In this case, you will be informed of the reason therapy is being stopped.

You can stop taking part in the study at any time. However, if you decide to stop taking part in the study, we would like you to talk to the study doctor and your regular doctor first.

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If you decide at any time to withdraw your consent to participate in the trial, we will not collect any additional medical information about you. However, according to FDA guidelines, information collected on you up to that point may still be provided to Astellas Pharma US Inc or designated representatives. If you withdraw your consent and leave the trial, any samples of yours that have been obtained for the study and stored at the NCI can be destroyed upon request. However, any samples and data generated from the samples that have already been distributed to other researchers or placed in the research databases **cannot** be recalled and destroyed.

Research Subject's Rights

What are the costs of taking part in this study?

If you choose to take part in the study, the following will apply, in keeping with the NIH policy:

- You will receive study treatment at no charge to you. This may include surgery, medicines, laboratory testing, x-rays or scans done at the Clinical Center, National Institutes of Health (NIH), or arranged for you by the research team to be done outside the Clinical Center, NIH if the study related treatment is not available at the NIH.
- There are limited funds available to cover the cost of some tests and procedures performed outside the Clinical Center, NIH. You may have to pay for these costs if they are not covered by your insurance company.
- Medicines that are not part of the study treatment will not be provided or paid for by the Clinical Center, NIH.
- Once you have completed taking part in the study, medical care will no longer be provided by the Clinical Center, NIH.

Will your medical information be kept private?

We will do our best to make sure that the personal information in your medical record will be kept private. However, we cannot guarantee total privacy. Organizations that may look at and/or copy your medical records for research, quality assurance, and data analysis include:

- The National Cancer Institute (NCI), Walter Reed Bethesda, and other government agencies, like the Food and Drug Administration (FDA), which are involved in keeping research safe for people.
- National Institutes of Health Intramural Institutional Review Board
- Qualified representatives from Astellas Pharma US, Inc, the pharmaceutical company who produces enzalutamide.

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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.

Certificate of Confidentiality

To help us protect your privacy, we have obtained a Certificate of Confidentiality. The researchers can use this Certificate to legally refuse to disclose information that may identify you in any federal, state, or local civil, criminal, administrative, legislative, or other proceedings, for example, if there is a court subpoena. The researchers will use the Certificate to resist any demands for information that would identify you, except as explained below.

You should also know that there are several circumstances in which the Certificate does not provide coverage. These include when information:

- will be used for auditing or program evaluation internally by the NIH; or
- must be disclosed to meet the legal requirements of the federal Food and Drug Administration (FDA).
- is necessary for your medical treatment and you have consented to this disclosure;
- is for other research.

In addition, identifiable, sensitive information protected by this Certificate cannot be admissible as evidence or used for any purpose in any action, suit, or proceeding without your consent.

You should understand that a Certificate of Confidentiality does not prevent you or a member of your family from voluntarily releasing information about yourself or your involvement in this research. If an insurer, employer, or other person obtains your written consent to receive research information, then the researchers will not use the Certificate to withhold that information.

The Certificate of Confidentiality will not protect against the required reporting by hospital staff of information on suspected child abuse, reportable communicable diseases, and/or possible threat of harm to self or others.

Conflict of Interest

The National Institutes of Health (NIH) reviews NIH staff researchers at least yearly for conflicts of interest. This process is detailed in a Protocol Review Guide. You may ask your research team for a copy of the Protocol Review Guide or for more information. Members of the research team who do not work for NIH are expected to follow these guidelines but they do not need to report their personal finances to the NIH.

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Members of the research team working on this study may have up to \$15,000 of stock in the companies that make products used in this study. This is allowed under federal rules and is not a conflict of interest.

The National Institutes of Health and the research team for this study are using a drug developed by Astellas Pharma US, Inc. through a joint study with your researchers and the company. The company also provides financial support for this study.

Use of Specimens and Data for Future Research

To advance science, it is helpful for researchers to share information they get from studying human samples. They do this by putting it into one or more scientific databases, where it is stored along with information from other studies. A researcher who wants to study the information must apply to the database and be approved. Researchers use specimens and data stored in scientific databases to advance science and learn about health and disease.

We plan to keep some of your specimens and data that we collect and use them for future research and share them with other researchers. We will not contact you to ask about each of these future uses. These specimens and data will be stripped of identifiers such as name, address or account number, so that they may be used for future research on any topic and shared broadly for research purposes. Your specimens and data will be used for research purposes only and will not benefit you. It is also possible that the stored specimens and data may never be used. Results of research done on your specimens and data will not be available to you or your doctor. It might help people who have cancer and other diseases in the future.

If you do not want your stored specimens and data used for future research, please contact us in writing and let us know that you do not want us to use your specimens and/or data. Then any specimens that have not already been used or shared will be destroyed and your data will not be used for future research. However, it may not be possible to withdraw or delete materials or data once they have been shared with other researchers.

We may put your research data in a large database for broad sharing with the research community. These databases are commonly called data repositories. These data repositories might or might not be located at the NIH. The information in this database could include but is not limited to genetic information, ethnicity and sex. If your individual research data is placed in one of these repositories, it will not be labeled with your name or other information that could be used to easily identify you, and only qualified researchers will be able to look at your data. These researchers must receive prior approval from individuals or committees to access the data.

Your summary genomic data is being placed in an unrestricted database, so researchers will be able to access summary information about all the participants included in the study (including you), or summary information combined from multiple studies, without applying for permission. The risk of anyone identifying you with this information is very low.

OTHER PERTINENT INFORMATION

1. Confidentiality. When results of an NIH research study are reported in medical journals or at scientific meetings, the people who take part are not named and identified. In most cases, the NIH will not release any information about your research involvement without your written permission. However, if you sign a release of information form, for example, for an insurance company, the NIH will give the insurance company information from your medical record. This information might affect (either favorably or unfavorably) the willingness of the insurance company to sell you insurance.

The Federal Privacy Act protects the confidentiality of your NIH medical records. However, you should know that the Act allows release of some information from your medical record without your permission, for example, if it is required by the Food and Drug Administration (FDA), members of Congress, law enforcement officials, or authorized hospital accreditation organizations.

2. Policy Regarding Research-Related Injuries. The Clinical Center will provide short-term medical care for any injury resulting from your participation in research here. In general, no long-term medical care or financial compensation for research-related injuries will be provided by the National Institutes of Health, the Clinical Center, or the Federal Government. However, you have the right to pursue legal remedy if you believe that your injury justifies such action.

3. Payments. The amount of payment to research volunteers is guided by the National Institutes of Health policies. In general, patients are not paid for taking part in research studies at the National Institutes of Health. Reimbursement of travel and subsistence will be offered consistent with NIH guidelines.

4. Problems or Questions. If you have any problems or questions about this study, or about your rights as a research participant, or about any research-related injury, contact the Principal Investigator, William Dahut, M.D., Building 10, Room 3-2571, Telephone: 240-760-6187. You may also call the Clinical Center Patient Representative at 301-496-2626. If you have any questions about the use of your specimens or data for future research studies, you may also contact the Office of the Clinical Director, Telephone: 240-760-6070.

5. Consent Document. Please keep a copy of this document in case you want to read it again.

