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A Phase II Study of Enzalutamide Plus Dutasteride/Finasteride as First Line Treatment for Vulnerable Patients ≥ 65 Years with Systemic Prostate Cancer

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This consent form describes the research study, what you may expect if you decide to take part and important information to help you make your decision. Please read this form carefully.

The study staff will explain this study to you. Please ask questions about anything that is not clear before you agree to participate. You may take this consent form home to think about and discuss with family or friends.

- Being in this study is voluntary – it is your choice.
- If you join this study, you can change your mind and stop at any time.
- If you choose not to take part, your routine medical care will not be changed in any way.
- There are risks from participating and you should understand what these mean to you.

Introduction

You are being asked to take part in this study because you are age 65 or older and will require treatment for prostate cancer.

This study is being conducted at the University of Rochester's James P. Wilmot Cancer Institute and the Clinical Cancer Center at the Medical College of Wisconsin. At the University of Rochester this study is being conducted by Dr. Chunkit Fung and Dr. Supriya Mohile.

Purpose of Study

The purpose of this study is to see how long treatment with enzalutamide and dutasteride or enzalutamide and finasteride will keep the Prostate Specific Antigen (PSA) from rising, and may control cancer growth in patients aged 65 or older receiving this combination as first time treatment

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for systemic prostate cancer. PSA is a protein produced by the prostate tissue, which is used as a marker to determine prostate cancer growth. The study will also monitor the impact of this drug combination on quality of life and other issues relevant to the elderly.

The standard treatment for systemic prostate cancer usually includes Androgen Deprivation Therapy (ADT), which lower a man's testosterone level. ADT can have side effects that are more difficult to tolerate for older patients with cancer. Some treatments that are available for patients are better tolerated, but do not keep the PSA from rising for very long.

Treatment with enzalutamide has been well-tolerated in research studies involving the elderly and has been shown to decrease PSA, increasing the amount of time it takes for the cancer to progress. Studies with dutasteride and finasteride also suggest good tolerability and PSA outcomes compared to standard of care for the elderly. This study is being done to see if the combination of the two drugs (enzalutamide and dutasteride or enzalutamide and finasteride) will still be tolerable in the elderly population and to measure how well the drugs affect the PSA. Both the combinations of enzalutamide and dutasteride, as well as enzalutamide and finasteride are not currently approved as first time treatment for prostate cancer. Dutasteride will be the agent of choice. However, if for any reason dutasteride cannot be obtained, finasteride would be administered.

Description of Study Procedures

If you decide to take part in this study, you will be asked to undergo some initial tests to ensure that you meet all the criteria necessary to take part in the study. Once you have completed your initial testing and meet the eligibility criteria, you will be offered the chance to undergo breast radiation to prevent breast tenderness, a potential side effect of treatment. Your doctor will discuss this possibility with you based on your current health status.

You will then be asked to take a combination of 2 oral (taken by mouth) drugs daily. The drugs used on this study are either 160mg of enzalutamide (4 tablets) and 0.5mg of dutasteride (1 tablet), or a combination of 160mg of enzalutamide (4 tablets) and 5 mg of finasteride (1 tablet), which will be taken each day for a 28-day cycle. Treatment will continue as long as you are tolerating treatment and your prostate cancer is either responding to treatment or remains stable.

During the study you will have the following assessments:

- You will be asked about your medical history and current medications you are taking.
- You will have physical exams (including vital signs, blood pressure, weight, temperature)
- You will have periodic Comprehensive Geriatric Assessments, which would include assessment of health areas specific to the elderly (i.e. quality of life, ability to perform basic daily activities, memory, physical performance, mood, and social support)
- You will have routine blood work such as Complete Blood Count with differential, Comprehensive Metabolic Panel, Prostate Specific Antigen (PSA) and Testosterone levels. Routine blood samples are usually 3 to 5 mL (approximately 1 teaspoon or less).
- You will have a research blood draw for serum dihydrotestosterone (a hormone) at four time points: pre-study, at Cycle 4, Cycle 9, and at 30 days after your last treatment dose. Some of the study drugs, dutasteride or finasteride, can inhibit this hormone so we will measure your blood level to see if these agents lower the dihydrotestosterone levels.
- You will have routine scans and imagine tests to monitor the status of your cancer.

These tests may include (as recommended by your doctor):

- Routine CT scans of the chest, abdomen and pelvis.
- Routine bone scans to look for bone metastases
- Routine bone density scans (DEXA)
- Routine chest X-rays

If you stop study treatment for reasons other than progressive disease (your cancer has gotten worse) you will have physical exams and PSA for disease assessment performed every 6 months for the first year and as clinically indicated thereafter. If you stop study treatment because your disease has gotten worse, we would like to follow up with physical exams every 6 months for the first year after disease progression and as clinically indicated thereafter.

Number of Subjects

Approximately 40 subjects from 2 study centers (University of Rochester and the Medical College of Wisconsin) will take part in this research. Locally, about 20 subjects will participate.

Duration of the Study

Your participation in the study is expected to last until the study medications do not work for the prostate cancer or your decision to withdraw from the study. After you no longer use the study medications, we will continue to follow up with you long-term survival and safety data.

Risks of Participation

Androgen deprivation therapy (ADT) is the standard treatment for systemic prostate cancer. However, older patients may not tolerate the side effects of ADT. This study examines a new combination treatment (enzalutamide and dutasteride or enzalutamide and finasteride) that may or may not benefit you. In addition, you may have side effects while on the study. Everyone taking part in the study will be watched carefully for any side effects. Side effects may be mild or very serious. Many side effects go away soon after discontinuing treatment, some could have lasting effects.

Risks and side effects of Enzalutamide

Common side effects associated with the use of enzalutamide are:

- Constipation
- Weight loss
- Decreased appetite
- Diarrhea
- Falls
- Feeling tired (fatigue)
- Swelling of the limbs
- Pain in joints
- Weakness in the muscles
- Pain in muscles and bones

• Back pain
• Headache
• Anxiety
• Trouble falling or staying asleep
• Blood in urine
• Hot flush (hot flash)
• High blood pressure (hypertension)
• Altered taste in mouth

Rare side effects associated with the use of enzalutamide are:

• Low white blood cell count (needed to fight infection)
• Hallucination (seeing or feeling things that are not there)
• Dry skin
• Itching
• Restless leg syndrome (an uncontrollable urge to move a part of the body, usually the leg)
• Gynecomastia (enlarged male breast)

Serious but infrequently reported side effects in enzalutamide-treated patients are:

• Seizures: Some people have had seizures during treatment with enzalutamide. If you take enzalutamide you may be at risk of having a seizure. You should avoid activities where a sudden loss of consciousness could cause serious harm to yourself or others. Tell your healthcare provider right away if you have had an episode of loss of consciousness or seizure
•Posterior reversible encephalopathy syndrome (PRES): There have been rare reports of PRES, a rare, reversible condition involving the brain, in patients treated with enzalutamide. If you have a seizure, worsening headache, confusion, blindness or other vision problems, please contact your doctor right away. Your doctor will stop enzalutamide if you develop PRES.

Risks and side effects of Dutasteride

The most common side effects of dutasteride include:
- trouble getting or keeping an erection (impotence)*
- a decrease in sex drive (libido)*
- ejaculation problems*
- enlarged or painful breasts.

Serious but infrequently reported side effects of dutasteride include:
- swelling of your face, tongue, or throat
- skin reactions, such as skin peeling

If you notice breast lumps or nipple discharge, you should talk to your healthcare provider.

Some of these events may continue after you stop taking dutasteride.

Men who have taken this drug should not donate blood for at least six months after discontinuation of the drug.

Risks and side effects of Finasteride
The most common side effects of finasteride include:

- a decrease in sex drive (libido)*
- ejaculation problems*
- enlarged or painful breasts.
- dizziness

Serious but infrequently reported side effects of dutasteride include:

- swelling of your face, tongue, or throat
- skin reactions, such as skin peeling

Some of these events may continue after you stop taking finasteride.

Risks of Combined Treatment with Enzaludamide and Dutasteride/Finasteride
There is limited past experience in the use of combined therapy with enzalutamide and dutasteride or enzalutamide and finasteride in the treatment of prostate cancer. Therefore, there may be unknown risks associated with this combined treatment regimen. The risks of the known side effects listed above may be more or less severe when the two drugs are used in combination. There may be other new side effects that may be discovered when using this combined treatment.

You will be informed immediately of any new risks or changes in risks that are discovered during the study.

Fertility and Pregnancy Risks
Enzalutamide blocks the action of the male sex hormone, so it can cause infertility and impotence and may contribute to loss of muscle and bone mass, hot flashes or breast growth. Although the risk of getting your partner pregnant while taking enzalutamide is low, there is a risk of harm to the fetus. Therefore, you must agree to utilize effective birth control methods to ensure that your partner does not become pregnant in order to participate in this trial.

Dutasteride and finasteride have been shown to reduce sperm count, semen volume, and sperm movement. However, the effect of these agents on male fertility is not known. Given the risk of harm to the fetus, you must agree to utilize effective birth control methods to ensure that your partner does not become pregnant in order to participate in this trial. Women of childbearing potential should not handle this medication, as it can be absorbed through the skin and could cause birth defects.

You and/or your partner (if still of child bearing age) must agree to use a highly effective birth control method while you are participating in this trial. Examples of highly effective birth control are double- barrier (condom or diaphragm, with spermicidal jelly). Women can use an intrauterine device; injectable, or implanted hormonal contraceptives, which are considered highly effective. *Oral hormonal contraceptives should only be used in combination with another method.* Please discuss with your study doctor if the contraception method(s) you are using are acceptable.

Benefits of Participation

You might not benefit from being in this research study. The potential benefit to you from being in this study might be that your cancer would be controlled longer.

New Study Findings

If we discover anything that might make you change your mind about continuing in the study, we will let you know.

Alternatives to Participation

Your other choices may include:

- Getting treatment or care for your cancer without being in a research study.
- Taking part in another research study
- Getting no treatment.

If you decide that you don't want any more treatment, one of your options is called "comfort care." Comfort care includes pain medication and other support. It aims to maintain your comfort and dignity rather than cure disease. Usually this care can be provided at home.

If you think you might prefer comfort care, please discuss this with your family, friends and your doctor.

Talk to your study doctor about your choices before you decide to take part in this study.

Sponsor Support

The University of Rochester is receiving payment from Astellas and Medivation, the companies supplying the study drug enzalutamide, for conducting this research study.

Costs

You and/or your health insurance company will be billed for parts of the study that are standard care for your disease. Standard of care tests, procedures, and medications are those that you would undergo or receive as part of treatment for your condition whether you were participating in a research study or not. Your health insurance company may or may not pay for these charges. You will be responsible for all of the costs linked with this study that are related to standard care and are not covered by other payers (HMO, health insurance company, etc.), such as co-pays, deductibles, and other out-of-pocket expenses that you would normally be required to pay for the treatment of your cancer.

The study drug enzalutamide will be provided by the study sponsors at no cost to you. The drugs dutasteride and finasteride used in the study are commercially available and will be billed to you or your insurance company. The type of agent used for each patient will depend on insurance approval. Dutasteride will be the agent of choice. However, if for any reason dutasteride cannot be obtained, finasteride would be administered. Procedures that are done only for the study, such as the blood draw for serum dihydrotestosterone and the Comprehensive Geriatric Assessments will

be paid for by the study and will not be billed to you or your insurance company.

You might have unexpected expenses from being in this study. Ask your study doctor to discuss the costs that will or will not be covered by the sponsor. This discussion should include who will pay the costs of treating possible side effects.

Payments
You will not be paid for participating in this study.

Circumstances for Dismissal
There are some cases where you could be removed from the study without your consent. You may be withdrawn from the study if your disease becomes worse or if your doctor feels that staying in the study is harmful to your health. You may be withdrawn from the study if you do not keep appointments for study visits, if you experience a treatment delay of more 30 days, or if you cannot complete study activities. You will also be withdrawn from the study if you will need to start a new treatment for prostate cancer.

You also may decide that you no longer wish to participate in this research study. If you decide you would like to stop being in this study, we ask that you notify your study doctor or study coordinator of your decision to stop participation. You will be asked to complete one additional end-of-study visit for safety follow-up.

Early Termination
To ensure your safety after you have stopped the study drug, you will be asked to return approximately 30 days after your last dose to complete an end-of-study visit which will include physical exam, review of medical history and current medications, and end-of study blood work.

If you come off treatment due to the progression of you cancer, information about any other cancer therapies you may receive and how they work for you will be monitored until the study closes.

If you come off treatment early for any other reason other than the progression of your cancer, information about your physical exams and PSA test results will be collected to monitor the status of your cancer until the study closes.

Compensation for Injury
If you are directly injured by the drug that is being studied, or by the clinical procedures solely required to participate in the study, you may need to pay for treatment of your injuries, but you will not be required to pay for emergency medical treatment provided at Strong Memorial Hospital or Highland Hospital. The University may seek payment for this care from your health insurer or third parties. Decisions regarding care and compensation for any other research related injury will be made on a case-by-case basis.

Confidentiality of Records and Authorization to Use and Disclose Information for Research Purposes

For subjects enrolled at the University of Rochester/Strong Memorial Hospital, the results from laboratory tests, exams and other tests conducted for this study will be in the Strong Memorial Hospital electronic medical record, along with documentation of your study visit.

The University of Rochester makes every effort to keep the information collected from you private. In order to do so, we will limit access of research information collected on this study to include only trained research personnel assigned to this study. Sometimes, however, researchers need to share information that may identify you with people that work for the University, regulators or the study sponsor.

If you have never received a copy of the University of Rochester Medical Center (URMC) and Affiliates Notice of Privacy Practices, please ask the investigator for one.

What information may be used and given to others?

The study doctor will get your personal and medical information. For example:

- Research records
- Records about phone calls made as part of this research
- Records about your study visits
- Past and present medical records related to the study
- Results of medical tests

Who may use and give out information about you?

- The study doctor and the study staff
- URMC and Affiliates

Your information may be given to:

- The Department of Health and Human Services
- The University of Rochester
- Astellas/Medivation
- The U.S. Food and Drug Administration (FDA) may also need to inspect study records at some point during the study or even after it has been completed. In the event that this should occur, every effort will be made to keep identifying information about you private.

Why will this information be used and/or given to others?

- To do the research
- To study the results
- To see if the research was done right

If the results of this study are made public, information that identifies you will not be used.

What if I decide not to give permission to use and give out my health information?

Then you will not be able to be in this research study.

May I review or copy my information?

Yes, but only after the research is over.

How long will this be permission be valid?
This permission will last indefinitely.

May I cancel my permission to use and disclose information?
Yes. You may cancel your permission to use and disclose your health information at any time. You do this by sending written notice to the study doctor. Upon receiving the written notice, the study team will no longer use or disclose your health information and you will not be able to stay in this study. Information that has already been gathered may need to be used and given to others for the validity of the study.

May I withdraw from the study?
Yes. If you withdraw your permission to be in the study, no new health information identifying you will be gathered after that date. Information that has already been gathered may still be used and given to others.

Is my health information protected after it has been given to others?
No. There is a risk that your information will be given to others without your permission.

A description of this clinical trial will be available on the internet at: http://www.Clinical Trials.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.

Contact Persons
For more information concerning this research or if you feel that your participation has resulted in any research related injury, emotional or physical discomfort, please contact:

Dr. Chunkit Fung at **585-275-5863 (24-hours)**.

Please contact the University of Rochester Research Subjects Review Board at 265 Crittenden Blvd., CU 420315, Rochester, NY 14642, Telephone (585) 276-0005 or (877) 449-4441 for the following reasons:

- You wish to talk to someone other than the research staff about your rights as a research subject;
- To voice concerns about the research;
- To provide input concerning the research process;
- In the event the study staff could not be reached.

Voluntary Participation
Taking part in this study is voluntary. You are free not to take part or to withdraw at any time, for whatever reason. No matter what decision you make, there will be no penalty or loss of benefit

to which you are entitled. In the event that you do withdraw from this study, the information you have already provided will be kept in a confidential manner.

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SIGNATURE/DATES

After reading and discussing the information in this consent form you should understand:

- Why this study is being done;
- What will happen during the study;
- Any possible risks and benefits to you;
- Other options you may have instead of being in the study;
- How your personal information will be protected;
- What to do if you have problems or questions about this study.

Subject Consent

I have read (or have had read to me) the contents of this consent form and have been encouraged to ask questions. I have received answers to my questions. I agree to participate in this study. I have received (or will receive) a **signed** copy of this form for my records and future reference.

_____
Subject Name (Printed by Subject)

_____ _____
Signature of Subject Date

Person Obtaining Consent

I have read this form to the subject and/or the subject has read this form. I will provide the subject with a **signed** copy of this consent form. An explanation of the research was given and questions from the subject were solicited and answered to the subject's satisfaction. In my judgment, the subject has demonstrated comprehension of the information. I have given the subject adequate opportunity to read the consent before signing.

_____
Name and Title (Print)

_____ _____
Signature of Person Obtaining Consent Date