RESEARCH CONSENT
Date Approved: September 11, 2017
Inova IRB: C.F. Bonds-Beeken, IRB Coordinator
IRB File # 16-2200

Informed Consent for a Research Study

Study Title: A Phase II Study of Oral Calcitriol in Combination with Ketoconazole in Androgen Independent Prostate Cancer

Sponsor: Inova Schar Cancer Institute

Principal Investigator: Donald Trump, MD

Site of Investigation:

IMG Hematology and Oncology
8505 Arlington Blvd, Suite 100
Fairfax, VA 22031

IMG Hematology and Oncology
8501 Arlington Blvd, Suite 340
Fairfax, VA 22031

Study Related Contact Information: 24-hour number: 703-970-6430

Introduction
You may be eligible to take part in a research study. This research consent form gives you important information about the study. It explains why this research study is being done, what is involved in participating in the research study, the possible risk and benefits of participation, choices for participation and your rights as a research participant.

Please take your time to review this information carefully. You may also wish to talk to others (for example, your family, friends, or other doctors) about your participation. The decision to participate is yours. You may leave the study at any time without losing any benefits you would have normally received. If you decide to take part in the study, you will be asked to initial each page and sign and date at the end of this form. We will give you a copy of the form so that you can refer to it while you are involved in this research study. We encourage you to ask questions now and at any time in the future.

What if I am already participating in another study?
Are you already participating in any other research studies? Yes ☐ No ☐
If yes, please state which study (ies) _____

While participating in this study, you may not take part in any other research study without approval from the principal investigator.

Why is this study being done?
This study is being done to determine how therapy with calcitriol in combination with the drug ketoconazole and the drug hydrocortisone will affect PSA levels in men with prostate cancer who have progressed while receiving abiraterone (Zytiga).

Calcitriol is the most active form of vitamin D and is naturally produced in our bodies. In this study calcitriol will be given by mouth. Ketoconazole is a drug that is available in pill form. Ketoconazole is approved by the Food and Drug Administration (FDA) for the treatment of infections caused by fungus. The side effects of ketoconazole, when used alone, are well known. We also know that ketoconazole changes how the body breaks down other drugs. Ketoconazole blocks several chemicals in the human body that are important in breaking down drugs like calcitriol. This could result in higher and more prolonged amounts of calcitriol in the blood and in tumor or other tissues. This may improve the antitumor effects of calcitriol, but may also result in more unknown toxicities. Hydrocortisone is a steroid that is often used to decrease inflammation and treat conditions such as allergic reactions or over activity of the immune system such as asthma.

This study is being done because laboratory and limited clinical studies suggest that calcitriol has the ability to slow or stop cancer growth. These studies were done on cancer tissue grown either artificially or in mice. Clinical studies have been done in humans which also indicate that calcitriol has anticancer effects. Work in the laboratory has shown that the addition of ketoconazole to calcitriol enhances its effects against the growth of tumors; the administration of these agents together may result in stronger inhibition of tumor growth. This study will attempt to determine if this drug combination will affect your prostate cancer.

How many people will take part in this study?

This study will include a sufficient number of patients to assure that 12 patients are completely evaluable for response and side effects. This is estimated to require enrollment of 15-18 patients in total.

If your cancer seems to respond to the treatments received in this study, then you may continue on the same treatment and you will be followed every 1-3 months by one of the doctors on the study. If you decide to withdraw from the study or the doctor decides to take you off the study, then you may need to be followed by the doctor(s) for a short time (up to 30 days) to watch for ongoing or potential side effects.

What other choices do I have if I do not take part in this study?
If you decide not to take part in this study, you have other choices. For example:

- You may choose to have the usual approach to treating your cancer, which you may discuss with your doctor. Ketoconazole + hydrocortisone would be one standard approach.
- You may choose to take part in a different study, if one is available;
- or you could decide not to be treated

How long will I be in this study?
If you decide to participate, you will be in this study for up to one year or until disease progression (if sooner than one year) and you may be in long term follow up for up to five years. If the treatment is still working at one year your doctor may discuss whether continuing calcitriol treatment is recommended but you will no longer receive calcitriol as part of this study.

What will happen if I take part in this research study?
Starting on day 1 and continuing throughout the study you will receive the following drugs:

1.) Calcitriol will be taken by mouth, three days, each week (Monday, Tuesday, and Wednesday). The daily dose will be 10mcg (20 tablets).

2.) Ketoconazole will be taken by mouth, three times, every day. Each dose will be 400mg (2 tablets) for a total daily dose of 1200mg (6 tablets).

3.) Beginning the day before the first dose of calcitriol, hydrocortisone will be taken by mouth every day throughout the study, 2 times a day. The dose will be 20mg (2 tablets) in the morning and 10mg (1 tablet) in the evening. The total daily dose is 30mg. Hydrocortisone is given to protect your adrenal glands from the effects of the ketoconazole (ketoconazole may reduce the amount of hormone released by your adrenal glands).

A prior study determined that 10 mcg of calcitriol is the maximum safe dose that can be given with standard doses of ketoconazole + hydrocortisone. Ketoconazole and hydrocortisone are standardly used in the treatment of men with prostate cancer such as yours; calcitriol is used in routine practice to treat vitamin D deficiency, vitamin D deficiency associated with chronic renal failure and has been used to treat cancer in prior studies at doses up to 38 micrograms per day for 3 days every week has been given without any toxicity. However, only limited clinical experience is available on the use of these 3 drugs together.

The following is a schedule of the treatments you will take and the procedures in which you will participate if you enroll in this study:

Schedule

Calcitriol 10mcg 3days a week;
Ketoconazole 400mg 3 times a day;
Hydrocortisone 2 times a day 20mg AM, 10mg PM

Day	-1	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	1
Calcitriol		C	C	C					C	C	C					C	C	C					C	C	C					C
Keto conazole		K	K	K	K	K	K	K	K	K	K	K	K	K	K	K	K	K	K	K	K	K	K	K	K	K	K	K	K	K
Hydro cortisone	H	H	H	H	H	H	H	H	H	H	H	H	H	H	H	H	H	H	H	H	H	H	H	H	H	H	H	H	H	H

Top row in table reflects days of treatment, starting Day 1 of therapy.
K = ketoconazole 400 mg TID (1200mg/day).
C = Calcitriol 10 mcg three days a week (e.g. Monday, Tuesday, and Wednesday)
H =Hydrocortisone 20mg AM, 10mg PM (starting in the evening before the first dose of calcitriol)

If you take part in the study, you will have the following tests and procedures:
Procedures that are part of regular cancer care and may be done even if you do not join the study: These are procedures that would be done as part of the standard of care of patients with cancer that are being treated with a chemotherapeutic regimen outside a study setting. This includes procedures such as:

- CAT scans (computerized pictures of your body with or without a dye injected into your vein) to determine the amount of cancer in your body.
- Other types of x-rays or MRI (pictures of your body that depend on magnetic fields) may be done in special situations to determine the amount or size of tumor in your body. These pictures can be taken between 6-12 weeks and will help determine if your tumor is growing, shrinking, or maintaining its previous size. All such studies are part of the regular and routine assessment of the status of the cancer in your body and are not done solely for research purposes.
- A full physical and history will be done before treatment and then every 4 weeks.
- Blood tests including a complete blood count (to determine your ability to fight infections, presence and severity of anemia, and risk for bleeding) and liver and kidney will be done on a monthly basis. Blood will be drawn using a needle and a syringe from a vein in your arm or a port or central line if you have one (a catheter that has been previously inserted through a large vein to facilitate blood draws and medication administration). The equivalent of 1 tablespoon will be drawn on a weekly basis.

Other than taking the study drug combination there are no special procedures being done because you are enrolled in this study. You will be asked to complete a daily diary that tracks the medications you are taking in this study.

What risks can I expect from taking part in this study?
If you choose to take part in this study, there is a risk that you may:

- Lose time at work or home and spend more time in the hospital or doctor's office than usual
- Be asked sensitive or private questions which you normally do not discuss
- The most important non-medical risk is the disclosure of your protected health information (PHI). PHI is any health information that is collected about you, including your history and new information collected during this study. You will have an opportunity to review the ways in which your PHI may be used and disclosed in the authorization section of this form that begins on page 7.

There is also a risk that you could have side effects.

Here are important points about side effects:

- The study doctors do not know who will or will not have side effects.
- Some side effects may go away soon, some may last a long time, or some may never go away.
- Some side effects may interfere with your ability to have children.
- Some side effects may be serious and may even result in death.

Here are important points about how you and the study doctor can make side effects less of a problem:

- Tell the study doctor if you notice or feel anything different so they can see if you are having a side effect.
- The study doctor may be able to treat some side effects.

Ketoconazole:

Likely Side Effects: those that occur in approximately 10% - 30% of persons who receive this drug. The most common side effects of ketoconazole are nausea and drowsiness. Less often, vomiting and loss of appetite can occur.

Unlikely Side Effects: those that occur in approximately 5% to 9% of persons who receive this drug. Irritation of the liver, recognizable by changes in blood tests that are signs of liver function, is uncommon but very rarely can be extremely dangerous (less than 1 in 100 people).

Rare but Serious Side Effects: Those that occur in less than 1% of persons who receive this drug. Dry skin and dry eyes may also occur in some people.

Potentially serious effects of ketoconazole may result if ketoconazole changes the manner in which your body metabolizes ("handles") certain drugs. There are many drugs that can be changed by ketoconazole. Your doctor and the research nurse will have gone over your list of medications to be sure it would be safe for you to take ketoconazole. Be sure to notify your doctor of all medications, vitamins, tonics, herbs, or other substances you are taking so it can be clear that it would be safe for you to take ketoconazole.

All of these side effects will probably stop when the drug is stopped, but also may get better on their own even while the drug is continued.
Some medications are not permitted in patients on ketoconazole therapy; among the prohibited medications are phenytoin, carbamazepine, barbiturates, rifampin, and St. John's Wort. These medicines may increase or decrease the liver metabolism (breakdown) of ketoconazole, thus possibly changing blood levels of ketoconazole. There are other medications which may have these effects. Please be sure your doctor is aware of ALL the medications you are taking. Your doctor may adjust these medicines as medically indicated.
The drug used in this program may involve other risks - including possible life threatening reactions - that are not known at present.

International Normalized Ratio (INR) elevations are blood tests which measure ability or time for blood to clot and/or bleeding events, and have been reported in some patients taking warfarin or Coumadin® while on ketoconazole therapy. Patients taking warfarin or Coumadin® should be monitored regularly for changes in prothrombin time or INR (blood tests of blood clotting time), and monitored more frequently at the time ketoconazole is started.

Calcitriol: Most of the side effects described with calcitriol are related to elevations in calcium levels. These have been noted when calcitriol was given on a daily or every other day basis. Oral calcitriol given three times per week or once a week has not been associated with hypercalcemia (high blood calcium levels) or any other significant side effects even when given at very high doses. The prior work on this trial demonstrated that this dose and schedule of ketoconazole + calcitriol is safe and well-tolerated. This has involved only 37 patients so we cannot be certain that some serious side effects will not occur. The anticipated side effects of this combination are those related to an increase in blood calcium related to calcitriol. Side effects that could be related to high calcitriol levels inducing high calcium and phosphate levels in the blood may occur. High calcium levels can cause kidney dysfunction and stones, bladder stones, weakness, dehydration, constipation, muscle aches, and nausea, vomiting and dysphagia (difficulty in swallowing).
If the calcium levels become too high (rarely), then confusion, kidney failure, irregular heartbeats, inflammation of the pancreas, and coma may occur.

Hydrocortisone: In this study, hydrocortisone will be administered at low doses and is designed to replace any suppression of normal body steroid production by ketoconazole. Hydrocortisone at the dose prescribed on this study rarely may be associated with fluid retention, weight gain, and increase in blood sugars. In addition, restlessness may occur, but is less likely. Confusion is unlikely to happen at the dose that will be given on this study.

Low phosphorous levels: If the phosphorous level (a mineral in blood) in your blood work shows that it is low; your doctor may need to replace it.

Are there reproductive risks while on this study?
This study may involve risks to you or your unborn child that are not known at this time therefore you should not father a baby while on this study.

Male patients must use an effective method of birth control, such as condoms with spermicide, abstinence or have had a vasectomy, when participating in this study and should continue use of birth control for three months after receiving the last dose of the drug to be sure that the drug has cleared from the body. Males who are receiving treatment should not donate sperm for at least three months after the study is completed. Discuss birth control measures with your doctor.

Are there benefits to taking part in this study?
Taking part in this study may or may not make your health better. We hope the information learned from this study will benefit others in the future.

It is not known if this treatment will help you or not. Possible help may include shrinkage or disappearance of your cancer. This would result in a decrease in your symptoms and improvement in your quality of life. It is also possible that the investigational treatments may prove to be less useful or even harmful to you. You understand that no guarantee of help can be made to you for taking part in this research study. Future patients may be helped from the results and information gained from this study.

Can I stop being in the study?
Yes. You can decide to stop at any time. It is important to tell the study doctor if you are thinking about stopping so any risks from the calcitriol, ketoconazole and/or hydrocortizone 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.

Tell the study doctor if you are thinking about stopping or decide to stop. He or she will tell you how to stop safely and will work with you to obtain a written confirmation of your decision to revoke your authorization.

Your participation can also be stopped without your approval by any of the following:

- the study doctor
- the Institutional Review Board (IRB – hospital committee that reviews and approves research)

Your doctor may decide to take you off this study if 1) your cancer progresses despite study treatment; 2) you develop an illness that prevents further administration of treatment; 3) you develop unacceptable side effects; 4) you decide to withdraw from the study; or 5) the doctor believes that your condition is unacceptable for further treatment.

What are my rights if I take part in this study?
Taking part in this study is your choice. No matter what decision you make, and even if your decision changes, there will be no penalty to you. You will not lose medical care or any legal rights. A member of your research team will tell you about new information or changes in the study that may affect your health or your willingness to continue in the study.

If you would like more information about your rights as a participant in a research study, contact: Inova Health System Institutional Review Board (IRB) at (703) 776-3167. The Inova Health System IRB may contact you by mail or telephone to find out if you were satisfied with your study participation.

What are the costs of taking part in this study?
Examinations, scans, laboratory tests, and other medical procedures and treatments that would routinely be needed to monitor and treat your illness are known as "standard of care" services. Charges for these services will be billed to you and/or your insurance carrier in the usual manner. You will be responsible for all co-payments, deductibles, and/or account balances as determined by your individual health insurance contract.

You and/or your health plan/ insurance company will need to pay for some or all of the costs of treating your prostate cancer in this study. Some health plans will not pay these costs for people taking part in studies. Check with your health plan or insurance company to find out what they will pay for. You may be responsible for any co-payments and deductibles that are standard for your insurance charges

Calcitriol will be provided to you free of charge. Hydrocortisone and ketoconazole are commercially available and will be billed directly to you and/or your insurance company. The use of medications to help with side effects could result in added costs to you. Either you and/or your insurance company will be responsible for the costs of these drugs. In some cases, third party carriers (insurance companies, health care plans, Medicare, Medicaid) may not cover these costs. Since the policy of each carrier is different, there is no way to predict which costs are covered until after the claims are submitted.

Will I be paid for taking part in this study?
You will receive no payment for taking part in this study.

It is possible that this research project will result in developing treatments, devices, new drugs, or procedures. If this happens, you understand that you will not receive any financial payment from the resulting use of information gained and developed through your participation in the research study.

What if I am injured because I took part in this study?
In the event that you believe you have been injured because of taking part in this study, it is important that you call your study doctor. You can call Dr. Donald Trump principal investigator, at **703-970-6430** and he/she will review the matter with you. Inova Health System and the study doctor do not provide funds or free medical treatment for injuries that result from taking part in this study. However, in the event of injury resulting from this research, medical treatment is available.

You should not expect anyone to pay you for pain, worry, lost income, or non-medical care costs that occur from taking part in this research study. No funds have been set aside by Inova Health System or Inova Medical Group to repay you in case of injury.

You are not waiving any legal rights because of your participation in this study.

Will my medical information be kept private?
We will keep your records private to the amount allowed by law. Research are stored and kept according to legal requirements. You will not be identified in any reports or publications about this study. However, certain people and groups will have access to your research and medical records. The sponsor of the study will look at your research and medical records. The Inova Health System Institutional Review Board (IRB) and federal and state agencies that have authority over the study may look at your research records. Members of the study staff will also have access to your research records. Additional groups, which are explained in the authorization section beginning on page 7, may also have access to these records.

Who can answer my questions about the study?
You can talk to your study doctor about any questions or concerns you have about this study. Contact your study doctor, Donald Trump, MD at **703-970-6430**

Where can I get more information?
A description of this clinical trial will be available on 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.

Authorization to Use and Disclose Information for Research Purposes

This authorization form will explain how health information about you will be used, protected, and disclosed (shared). In addition, you will receive a summary of Inova Health System's "Notice of Privacy Practices". If the study requires you to have follow-up visits in the investigators' private practice office, you should ask for a copy of his/her "Notice of Privacy Practices" at the time of your visit. If you agree to participate in the research, and authorize the use and disclosure of your medical information for research purposes, please sign this form. If you choose not to authorize the use and disclosure of your health information you may not participate in the research study.

What protected health information about me will be used or disclosed as part of this research?
You will be asked about your health information that is relevant to the study. In addition, your non-research medical records will be reviewed and researchers may need to discuss your health information with your treating doctor(s), if applicable. Researchers will also collect new information about you as a result of the research tests, procedures, visits and/or questionnaires/interviews. This collected information constitutes and is called your "Research Record".

The following health information will be obtained from your medical record:
- clinic visits notes
- lab reports, imaging reports, pathology reports

Who will be authorized to use or disclose my protected health information?
If you agree to participate in the study, you authorize the investigators and research study staff to use and disclose your protected health information contained in your Research Record.

To whom will the protected health information be disclosed?
Your protected health information will be disclosed only to research staff participating in this study.

Your information <u>may</u> be given to:
- Doctors and healthcare professionals at other sites taking part in the study
- Doctors and healthcare professionals at Inova Health System
- US Food and Drug Administration (FDA)
- US Department of Health and Human Services (DHHS)
- National Cancer Institute (NCI)
- National Institute of Health (NIH)
- Institutional Review Board at Inova and/or their affiliates
- Data safety monitoring board, an independent group that reviews the side effects of the research.

All reasonable efforts will be used to protect the confidentiality of your protected health information which may be disclosed with others in support of this research. Once your health

information is shared with the sponsor, federal agencies and others as described above, there is no guarantee that these recipients will not further disclose your protected health information to other persons who may not be bound by this authorization, or who otherwise may be permitted to use or disclose your protected health information in ways that you do not intend.

Why is it necessary to share my protected health information with others?
The reason is to conduct the research as described in the consent form for the research study.

How long does my authorization remain in effect?
This authorization expires upon the completion of the study.

How can I take back my authorization?
You may take back your authorization at any time by sending a written request to Donald Trump, MD, 8505 Arlington Blvd, Suite 100, Fairfax, VA 22031. If you take back your authorization, your participation in the study will end and no further private health information will be acquired. The study staff may keep or disclose information obtained before you took back your authorization in order to preserve the scientific integrity of the study.

If you choose not to authorize the use and disclosure of your health information or withdraw from the study, you will continue to have access to medical care at Inova Health System and IMG Hematology and Oncology.

Will I have access to the information in my Research Record?
While the study is in progress, your access to your Research Record will be temporarily limited to ensure proper evaluation of the research study results. You will continue to have access to your non-research medical record during the study. You will be able to see your Research Record when the research is completed. You have the right to see and copy the medical information that is collected from you during the study and kept by the Inova Health System. You will have that right for so long as that information is maintained by the study staff and the other entities that are subject to federal privacy regulations. This does not include information about the study itself, such as protocols, which may otherwise be confidential, and which does not relate to an individual subject.

Signature Page

As a member of the research team, I have explained the purpose, the procedures, the benefits and risks that are involved in this research study. Any questions that have been raised have been answered to the individual's satisfaction.

Signature of Person Obtaining Consent*	Printed Name	Date

You, the undersigned have been informed about this study's purpose, procedures, possible benefits and risks, and you have read this consent and received a copy of this consent, including the section regarding authorization to use and disclose protected health information. You have been given the opportunity to ask questions before you sign, and you have been told that you can ask other questions at any time. You voluntarily agree to give your consent to participate in this research study.

You are free to withdraw from the study at any time and you do not have to say why you no longer wish to participate. You will notify Dr. Donald Trump if you are leaving the study because of any side effects you might experience. This withdrawal will not in any way affect your future treatment or medical management. You agree to cooperate with Dr. Donald Trump and the research staff and to inform them immediately if you experience any unexpected or unusual symptoms.

Signature of Subject	Date

Printed Name of Subject

Signature of Legally Authorized Representative (When applicable)	Date

Printed Name of Legally Authorized Representatives and Relationship to Participant

**The person conducting the informed consent discussion has signed above as witness. The following witness lines may be left blank, unless an impartial witness is required.*

Signature of Witness	Printed Name of Witness	Date