CONSENT FOR CANCER RESEARCH

Project Title: A PHASE II STUDY OF THE EFFICACY AND SAFETY OF AXITINIB GIVEN ON AN INDIVIDUALIZED SCHEDULE FOR METASTATIC RENAL CELL CANCER AFTER TREATMENT WITH ANTI-PD-1 OR ANTI-PD-L1 INHIBITORS

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Research Nurse: Laura Wood, RN

Sponsor: Pfizer, Inc.

Cancer research studies are coordinated by physicians and scientists from Cleveland Clinic, University Hospitals and Case Western Reserve University (CWRU) through the NIH National Cancer Institute (NCI) designated Case Comprehensive Cancer Center (CaseCCC). The goal of this collaboration is to enhance cancer treatment and research in Northeast Ohio. This study is being offered at Cleveland Clinic (CC).

The purpose of this document is to provide you with information to consider in deciding whether to participate in this research study. Consent must be based on an understanding of the nature and risks of the treatment, device or procedure. Please ask questions if there is anything you do not understand.

Introduction

We are asking you to participate in a research study. The purpose of this document is to summarize your discussion with the research team and provide you with written information to help you decide whether you want to participate in research. Your decision is completely voluntary.

Your treating doctor may also be an investigator on this research study. If so, your doctor will have an interest in both your welfare and in the research study. You are not required to take part in this research study offered by your doctor. You may ask for a second opinion from another doctor who is not linked to this study. If you choose not to be in this study, the quality of your regular medical care will not be affected.

Please ask any questions you may have about the study or this consent form before signing it. Please take your time to make your decision. You will be given a copy of this form to keep.

One or more of the Investigators conducting this study serve as consultants for the company that makes products used in this study. These financial interests are within permissible limits established by the local institutional Conflict of Interest Policy. If you have any questions regarding conflicts of interest, please ask you study doctor or call the Cleveland Clinic Institutional Review Board at (216) 444-2924.

Purpose

You are being asked to participate in a research study of axitinib in patients with advanced kidney cancer who have already received therapy for treatment of kidney cancer.

Axitinib is a drug which is approved by the FDA for patients with advanced kidney cancer who have already received some treatment. It works by reducing blood flow to a tumor. Axitinib is normally give at 5mg twice per day and sometimes this dose is increased if patients tolerate it. The purpose of this study is to figure out a different way to decide which dose of axitinib each patient should receive based on the side effects they experience.

About 40 people will take part in this research study at 4 different hospitals and approximately 27 people will take part at the Cleveland Clinic.

Study Procedures

As a participant in this study, you will be asked to return to the Cleveland Clinic 2 weeks after starting the study and then every 4 weeks. If you need to reach us sooner, we will always be available to talk to you by phone or schedule you for an appointment. Your participation in this study will last for as long as you are taking axitinib. These visits will always take place at the Taussig Cancer Institute at the Cleveland Clinic.

The following chart outlines what will happen at these your office visits. The same information is listed in greater detail following the table.

Visit/ Phone call	**What will be done at this visit? What is the purpose of the phone call?**	**What will need to be brought and/or done at this visit?**
Screening (prior to starting the trial)	1. Performance Status (a measure of your ability to perform certain everyday tasks) 2. Physical Examination (including height, weight, temperature, blood pressure and pulse) 3. Blood collection for organ function (chemistry), blood (hematology), thyroid, and pregnancy (if applicable) (10 mL / ~ 2 teaspoons) 4. Full body CT scan	Please bring a list of all your medications.

1 week and 2 weeks after starting trial	A phone call will be made to check on how you are doing with the current medication dose.	
Every four weeks	1. Performance Status (a measure of your ability to perform certain everyday tasks) 2. Physical Examination (including height, weight, temperature, blood pressure and pulse) 3. Blood collection for organ function (chemistry) and blood (hematology), (10 mL / ~ 2 teaspoons)	Please bring the diary sheet we provided and your axitinib medication bottle.
Every eight weeks	1. Performance Status (a measure of your ability to perform certain everyday tasks) 2. Physical Examination (including height, weight, temperature, blood pressure and pulse) 3. Blood collection for organ function (chemistry), blood (hematology) ,and thyroid 2. Full body CT scan. After 1 year of treatment, CT scans will be done every 12 weeks if your physician feels this is appropriate for you.	Please bring the diary sheet we provided and your axitinib medication bottle.
One week and two weeks after each dose change	A phone call will be made or a clinic visit if needed to check how you are doing on the new medication dose.	Please bring the diary sheet we provided and your axitinib medication bottle.

Screening visit:

This visit takes place within the four weeks before you start the medication. During this visit, your team will perform a physical exam on you and order some blood work listed in the table above to determine whether you qualify for the study. You will also have a full-

body CT scan done if you have not had one within 28 days of when you are scheduled to start on this clinical trial.

First 14 days / 2 weeks on the clinical trial

Every 28 days on this clinical trial is called a "cycle."
The starting dose of axitinib is 5mg taken twice a day.

1 week and 2 weeks after starting axitinib we will contact you by phone to ask about any side effects you are experiencing on axitinib. Although there are many possible side effects listed in section 4, the most bothersome are mouth pain, diarrhea, pain in hands and/or feet, and fatigue. Depending of how severe the side effects are we may ask you to stop taking the axitinib for a few days or take a lower dose. If needed, we will arrange for you to see us in clinic.

Every 2 week / 14 days

Every time we change the dose of your medication we reach out to you by phone within seven days later to see how you are tolerating the new dose.

a. If you are having serious toxicities **within the first week**, the dose of axitinib you are taking will be lowered.
b. If you are having serious toxicities **within the second week** you will receive a break from the axitinib for a few days and then resume at the same dose.
c. If you are still doing well on that dose **after 2 weeks**, your dose of axitinib will be increased.

It is exceedingly important that you follow your medical team's instructions with regard to taking your axitinib at the prescribed dose, holding axitinib when advised, and not restarting axitinib until advised. This is for your safety

Every 4 weeks / 28 days

Every 28 days, a new "cycle" begins. At the start of the cycle, we will see you in clinic for a physical examination and to assess the toxicities you are experiencing while on your current dose of axitinib. We will perform blood collection as mentioned in the table above.

After 1 year on treatment, doctor visits and study assessements may be done every 12 weeks if your physician feels this is appropriate for you.

Every 8 weeks

In addition to the tests that are done every 4 weeks, at every 8 week mark we will do a full body CT scan. After 1 year on treatment, your CT scans will be done every 12 weeks if your physician feels this is appropriate for you.

If you withdraw from the study prior to its completion, you will be asked to return all study medication and, for your safety, come in for a final clinical visit in order to see how you are feeling and assess any side effects.

Risks

The risks in this study are the risks of the medication axitinib. The following are the side effects of axitinib whether it is taken on this study or not.

Very Common (occurs in greater than or equal to 10% of patients):

- diarrhea
- high blood pressure
- fatigue
- decrease appetite
- nausea
- hoarseness
- redness and/or pain in hands and feet
- weight decreased
- vomiting
- weakness
- constipation
- decreased thyroid function
- cough
- mucosal inflammation
- pain in joints
- soreness or swelling of the mouth
- shortness of breath
- abdominal pain
- bleeding events (including nose bleeding, blood in urine, rectal bleeding, bleeding from lung/blood in sputum, brain bleeding, gastrointestinal bleeding)
- headache
- rash
- pain in extremity
- protein in urine
- disturbance of taste
- dry skin

- upset stomach

Common (occurs in 1% to 10% of patients):

- dizziness
- upper abdominal pain
- muscle pain
- pruritus (itch)
- dehydration
- nose bleed
- hemorrhoids
- hair loss
- decrease in red blood cell count (the oxygen carrying cells)
- ringing in ear
- pain or burning feeling of the tongue
- elevation in blood calcium and/or potassium
- elevation of blood lipase and amylase (may be a sign of altered pancreatic function)
- elevation of blood creatinine (may be a sign of altered kidney function)
- erythema (redness of skin)
- elevation of liver function blood test (such as ALT, AST, and alkaline phosphatase)
- sudden blocking of vein or artery by a clot of blood cell (blood clot in body and leg, or in lung, in eye causing visual disturbance/change in vision, transient ischemic attack (stroke), myocardial infarction (heart attack), cerebrovascular accident (stroke)),increased thyroid function
- wound healing complication, heart problems (heart failure/congestive heart failure, ventricular dysfunction/failure (meaning your heart does not pump normally and could lead to symptoms such as fatigue, breathing problems and swelling), both heart and lung failure, heart attack, decrease of heart pump efficiency

Uncommon (occurs in less than 1% of patients):

- increase of red blood cell or hemoglobin
- elevation of bilirubin blood test
- hypertensive crisis (severe, sudden increase in blood pressure)
- transient ischemic attack
- visual disturbance/change in vision
- blood clot in body
- reversible posterior leukoencephalopathy syndrome which has possible symptoms of headache, confusion, drowsiness, difficulty seeing, and seizures
- tumor destruction leading to hole in the intestine (perforation)
- fistula (abnormal tube-like passage from one normal body cavity to another body cavity or the skin)

Risks of CT scans

If you take part in this research, you will have one or more medical imaging studies which use radiation. The imaging studies will include a CT scan. To give you an idea about how much radiation you will get, we will make a comparison with an every-day situation. Everyone receives a small amount of unavoidable radiation each year. Some of this radiation comes from space and some from naturally-occurring radioactive forms of water and minerals. This research gives your body the equivalent of about 2 extra years' worth of this natural radiation. The radiation dose we have discussed is what you will receive from this study only, and does not include any exposure you may have received or will receive from other tests.

The insertion of the needle to draw blood is painful; however, the discomfort is brief. For most people, needle punctures to get blood samples do not cause any serious problems; however, they may cause bleeding, bruising, discomfort, infections, dizziness, or fainting.

Reproductive Health/Sexual Activity

There is the potential for effects on male and female reproductive organs that could affect fertility, and the potential for developmental effects to an unborn child.

Women

There is a risk of effects on female reproductive organs in this study that may impair fertility.

The effects of axitinib on a pregnancy or a nursing child are not known. If you are currently pregnant, planning to become pregnant or breastfeeding a child, you should not join this study. If you are of childbearing potential (physically able to have children) and you are sexually active, you must use birth control consistently and correctly during the study and for at least 3 months after you have stopped taking the study drug. The study doctor will discuss with you the permitted methods of birth control for this study and will help you select birth control that is appropriate for you. The study doctor will instruct you in correct use of your selected birth control method and review with you at each visit your responsibility to use your selected birth control method consistently and correctly.

Birth control methods, even when used consistently and correctly, are not perfect. If you become pregnant during the study, or you want to stop your required birth control during the study, you should tell the study doctor immediately. You will be withdrawn from the study if you discontinue birth control or you become pregnant.

Before the study, a pregnancy test is done for all women. This test might not detect an early pregnancy. Pregnancy tests may be repeated during the study. If you think you are pregnant, tell the study doctor immediately.

Men

There is a risk of effects on male reproductive organs and for reduced sperm count in this study that may impair fertility.

The effects of axitinib on sperm are not known. If you are planning to father a child, you should not join this study. If your partner is of childbearing potential (physically able to have children) and you are sexually active, you must use birth control consistently and correctly during the study and for at least 3 months after you have stopped taking the study drug. The study doctor will discuss with you the permitted methods of birth control for this study and will help you select birth control that is appropriate for you. The study doctor will instruct you in correct use of your selected birth control method and review with you at each visit your responsibility to use your selected birth control method consistently and correctly.

Birth control methods, even when used consistently and correctly, are not perfect. If you want to stop your required birth control during the study, you should tell the study doctor immediately. You will be withdrawn from the study if you discontinue birth control.

Pregnancy

If you, or your partner, becomes pregnant during the study or within at least 3 months after you have stopped taking the study drug, please tell the study doctor immediately. Please also tell the doctor who will be taking care of you/your partner during the pregnancy that you took part in this study. The study doctor will ask if you/your partner or your pregnancy doctor is willing to provide updates on the progress of the pregnancy and its outcome. If you/your partner agree, this information will be provided to the study sponsor for safety monitoring follow-up.

Benefits

This study may or may not have potential benefits to you as a participant in this study.

Study Restrictions / Patient Responsibilities / Alternatives to Participation

Regardless of dose level, all doses of axitinib should be taken with food. Axitinib doses should be taken as close to 12 hours apart as possible. If you miss a dose, you may take a “make-up” dose up to 3 hours prior to the next dose. If it is less than 3 hours to your next scheduled dose, please skip the missed dose. If you happen to vomit and lose a dose, please do not make up that dose. It is extremely important to take the specified number of tablet(s) from EACH bottle as instructed, twice daily. If you are given more than one bottle of pills, do not mix the tablets from the different bottles.

There are certain medications that may not be good to take while you are taking axitinib. In order to protect your safety while on the study, please let your doctor know of all medications you are taking while you are on study. Your doctor will let you know if your medications can be taken with axitinib. Certain drugs may reduce the amount of axitinib in your blood and their use will not be permitted while on study. In addition it is recommended that you not drink grapefruit juice, eat grapefruit, or take the herbal product St. John's Wort.

If you do not wish to participate in this study, you can still be treated with axitinib the way it is usually prescribed. We can also look for a different clinical trial if you would like to consider that.

Costs and Compensation

Pfizer will provide the study drug axitinib.

Routine medical care for your condition (care you would have received whether or not you were in this study) will be charged to you or your insurance company. You may wish to contact your insurance company to discuss this further. Treatments to help control side effects could result in added costs.

Cleveland Clinic will not pay for the costs of procedures, tests, visits and hospitalizations in connection with this research. We can assist you in determining if your insurance will cover the costs of tests and procedures done for this research study.

Research-Related Injury

If you experience physical injury or illness as a result of participating in this research study, medical care is available at Cleveland Clinic or elsewhere; however, Cleveland Clinic will not provide free care or compensation for lost wages.

Further information about research-related injuries is available by contacting the Cleveland Clinic Institutional Review Board at (216) 444-2924

For more information on clinical trial and insurance coverage, you can visit the National Cancer Institute's (NCI) website at:

http://cancer.gov/clinicaltrials/understanding/insurance-coverage

You can print a copy of the 'Clinical Trials and Insurance Coverage' information from this website. Another way to get information is to call 1-800-4-CANCER (1-800-422-6237) and ask NCI for a free copy.

Privacy and Confidentiality

If you volunteer to participate in this research, your protected health information (PHI) that identifies you will be used or disclosed to Moshe Ornstein, MD and the research staff at Cleveland Clinic for the purposes of this research and to Case Western Reserve University for administration.

The PHI that we may use or disclose (release) for this research may include your name, address, phone number, date of birth, Social Security number, information from your medical record, lab tests, or certain information relating to your health or condition.

Some of the tests and procedures done solely for this research study may also be placed in your medical record so other doctors know you are in this study. Upon completion of the study, you may have access to the research information that is contained in your medical record. In addition to the investigators and research staff listed above, your PHI may be looked at by other groups involved with the study such as the Cleveland Clinic Institutional Review Board and the Case Comprehensive Cancer Center Protocol Review and Monitoring Committee. Your PHI may also be used by and/or disclosed (released) to:

- Pfizer, the study sponsor;
- The Food and Drug Administration;
- The Department of Health and Human Services;
- The National Cancer Institute (NCI);
- Other Institutional Review Boards;
- Data Safety and Monitoring Boards;

Once your personal health information is released it may be re-disclosed and no longer protected by privacy laws.

Your research information may be used and disclosed indefinitely, but you may stop these uses and disclosures at any time by writing to:

Moshe Ornstein, M.D.
Cleveland Clinic Taussig Cancer Center
9500 Euclid Avenue/Desk CA-60
Cleveland, Ohio 44195
Phone: 216-445-6592

Your participation in the research will stop, but any information previously recorded about you cannot be removed from the records and will continue to be used as part of this research. Also, information already disclosed outside the Cleveland Clinic cannot be retrieved. This will not affect your rights to treatment or benefits outside the research study.

The Cleveland Clinic will not use your information collected in this study for another research purpose without your written permission; unless the Cleveland Clinic Institutional Review Board (IRB) assures your privacy and confidentiality is protected. The IRB is a committee whose job it is to protect the safety and welfare of research subjects.

By signing this informed consent form, you are authorizing such access to your research and medical record information. If you choose not to sign this consent form, you will not be able to participate in this research study. This Authorization does not have an expiration date.

Voluntary Participation

Your participation in this research study is voluntary. Choosing not to participate will not alter your usual health care or involve any penalty or loss of benefits to which you are otherwise entitled. If you decide to join the study, you may withdraw at any time and for any reason without penalty or loss of benefits. If information generated from this study is published or presented, your identity will not be revealed.

In the event new information becomes available that may affect the risks or benefits associated with this study or your willingness to participate in it, you will be notified so that you can decide whether or not to continue participating.

Removal from the Study

The study doctor or Pfizer may decide to take you out of the study if:

a. You do not follow the directions of the study doctor
b. You develop a serious illness that is not related to taking part in the study
c. The study doctor decides that the study is not in your best interest
d. Pfizer, the responsible regulatory authority, or Institutional Review Board/Independent Ethics Committee (IRB/IEC) decides to stop the study
e. You become pregnant, intend to become pregnant or are nursing a child during this study.

Questions about the Research

If you have any questions, you can ask the Principal Investigator and/or research staff.

Moshe Ornstein, M.D.

Cleveland Clinic Taussig Cancer Center
9500 Euclid Avenue/Desk CA-60
Cleveland, Ohio 44195
Phone: 216-445-6592

Emergency and After-hours Contact Information

If you are a Cleveland Clinic patient, you should contact the page operator at (216) 444-2200 or toll free at (800) 223-2273, and ask for the oncologist (cancer doctor) that is on call.

If the researchers cannot be reached, or if you would like to talk to someone other than the researcher(s) about: concerns regarding the study, research participant's rights; research-related injury; or other human subjects issues, you may contact the Institutional Review Board (IRB) at Cleveland Clinic IRB 216-444-292.

Where Can I Get More Information?

You may call the National Cancer Institute's Cancer Information Services at:
1-800-4-CANCER (1-800-422-6237)

You may also visit the NCI website 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

You will get a copy of this form. If you want more information about this study, ask your study doctor.

US National Institutes of Health (NIH) Clinical Trial Database

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.

Signature

Signing below indicates that you have been informed about the research study in which you voluntarily agree to participate; that you have asked any questions about the study that you may have; and that the information given to you has permitted you to make a fully informed and free decision about your participation in the study. By signing this consent form, you do not waive any legal rights, and the investigator(s) or sponsor(s) are not relieved of any liability they may have. A copy of this consent form will be provided to you.

_____ _____
Signature of Participant ***Date***

_____
Printed Name of Participant

I have discussed the information contained in this document with the participant and it is my opinion that the participant understands the risks, benefits, alternatives and procedures involved with this research study.

_____ _____
Signature of Person Obtaining Consent ***Date***

_____
Printed Name of Person Obtaining Consent