INSTITUTE: National Cancer Institute

STUDY NUMBER: 08-C-0020 PRINCIPAL INVESTIGATOR: Marston Linehan, M.D.

STUDY TITLE: A Phase 2 Study of ZD6474 (Vandetanib) in Patients with Von Hippel Lindau Disease and Renal Tumors

Continuing Review Approved by the IRB on 06/27/11
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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.

BACKGROUND INFORMATION

What is a Research Study?

A research study is a carefully supervised study that is done in humans to answer specific questions about a study drug or a new way of using an approved drug. Research studies are used to determine whether study drugs or treatments are safe and effective in humans.

You are being asked to take part in this study, also known as a clinical trial, because you have kidney cancer related to von Hippel-Lindau (VHL) disease. You are invited to join this phase II study of an investigational (research) drug called ZD6474 (also known as vandetanib or ZACTIMA).

What is this document?

This document is an informed consent form that will provide you with information about this research study. Before you can make a decision about whether or not to participate, you should understand what this study involves and the possible risks and benefits associated with this study. If you have any questions after reading this document, please ask the study doctor or study nurse to explain any words or information that you do not understand. If you agree to participate in this research study, you should be sure that all your questions are answered and that you understand your rights as a study subject. After you sign this form you will be given a copy to keep.

Why is this study being done?

The purpose of this research study is to determine if the study drug ZD6474 can be used as a treatment for kidney tumors in people who have VHL and whether it can safely be given to patients with VHL. ZD6474 is an experimental drug that is being tested as a new medication for a variety of cancers, including clear cell renal carcinoma which is the type of kidney cancer seen in VHL patients. ZD6474 is given once daily by mouth as a pill or liquid.

Why might ZD6474 work in cancer patients?

One way tumors are able to grow is by growth and development of new blood vessels which bring nutrients and oxygen to the tumor. This process happens because proteins (called receptors) on the surface of cells lining blood vessels and cancer cells receive chemical signals that encourage the growth of new blood vessels. Cancer cells also have other receptors on their surface that promote growth of cancer cells directly in response to proteins called 'growth factors'. In laboratory experiments, ZD6474 works by blocking both these kinds of receptors on the surface of cancer cells or on the lining of blood vessels within cancers. Blocking these receptors may cause cancer cells or the blood vessels to stop growing.

ZD6474 has been tested in adults who have a variety of different cancers in clinical trials, but the drug has not been approved by the US Food and Drug Administration (FDA) as a cancer treatment. We do not know whether ZD6474 will slow or stop the growth of renal cancer or whether this drug will be effective in your cancer.

One of the goals of this study is to try and understand better how ZD6474 may work in humans with kidney cancer. At specific times throughout this study, your blood will be collected and analyzed. These samples will be studied to look for special markers that may help researchers understand how ZD6474 is affecting you and/or your tumor and to develop tests that may be helpful in the study of kidney cancer.

How many people will participate in this study?

The study will initially involve 12 patients enrolled at the NIH. If one or more people in this group have tumors that shrink following treatment with ZD6474, another 25 patients can enter the study. The plan is to enter up to 37 patients with VHL on to this study.

WHAT WILL HAPPEN IF I TAKE PART IN THIS RESEARCH STUDY?

What are the chances that I will get the study drug?

All eligible subjects enrolled in this study will receive the study drug ZD6474. This study is an open label study, which means that both you and your doctor will know what amount of ZD6474 you are taking.

How often will I need to visit the hospital, clinic, or doctor's office?

You will visit the NIH clinical center to help your doctors determine whether you are a suitable candidate for this study. This visit will involve meetings with doctors, nurses and other staff conducting this study as well as blood and urine tests and x-rays. Once you decide to participate in the study, you will need to come to the NIH every 2 weeks during the first four weeks of treatment to meet with your doctors and research nurse and also have several tests done. After the first four weeks, you will need to return for a visit once every four weeks. The length of each visit will depend upon the number of tests that are being done. Some visits will be longer than other visits.

What will I be responsible for if I participate in this study?

During this study you will not be able to receive any other cancer treatments other than ZD6474. You will be asked not to participate in any other clinical trials involving another experimental treatment while you are being treated in this study.

Several medications (both prescription and non-prescription), 'alternative/complementary' or herbal preparations, dietary supplements, and foods such as grapefruit juice, can have undesirable interactions with ZD6474. You will not be allowed to take certain medications, supplements, and grapefruit juice during your participation in this study. Your doctor or the study staff will review the list of drugs that you are currently taking, as well as those that you took prior to participating in this study. Once you are on study, **please talk to your NIH doctors prior to starting any new drugs, dietary supplements or herbal or complementary medications**.

Drugs that affect the normal growth of blood vessels can delay or complicate wound healing following injury or surgical procedures. You should not schedule any elective surgeries while you are being treated in this study. **If you have an unplanned surgery, inform you doctor immediately, as you may not be able to continue study drug treatment.**

You need to keep your scheduled NIH visits and follow the instructions of your physicians and study nurse. If you cannot keep one of your planned visits, call your research nurse and reschedule the visit.

You will also be asked to keep a diary of when you take the medication and any side effects that you experience. You will also need to bring your ZD6474 pill bottles with you to every visit for the team to count your remaining ZD6474 pills. You will be given a blood pressure cuff and be taught how to take your own blood pressure. You will be asked to take your blood pressure at home periodically and keep a diary of the readings. **If you experience any worrisome side effects or if your systolic blood pressure (upper or higher number) is above 150, or if your diastolic (lower number) is above 100 or above, you should call your doctors at the NIH or seek medical attention from your local doctors as soon as possible.**

Agents such as ZD6474, which interfere with blood vessel formation or growth may cause developmental problems in fetuses and breast-feeding or young children. Therefore, if you are pregnant or breast-feeding you may not participate in this study. If you are female and old enough to get pregnant, you will be given a pregnancy test before you are given ZD6474. An appropriate and effective method of birth control (which may include abstinence) must be used by any person who is able to become pregnant or father a child and is receiving ZD6474. Birth control must be continued and breast feeding avoided for three months after the last dose of ZD6474 is given to ensure that most of the drug is out of your body. If you become or are found to be pregnant while receiving ZD6474, you must notify one of the doctors listed

on this form right away. If you become pregnant while you are taking ZD6474 you must stop taking ZD6474, and you will not be able to continue treatment with ZD6474. If you are a male, you should not attempt to father a child while you are on this drug and for at least three months after stopping the drug. You must use an appropriate and effective method of birth control during this period. The effect of this drug on your ability to bear or father children after you discontinue treatment is unknown.

WOMEN OF CHILD-BEARING POTENTIAL

There might be unknown risks to the unborn child if you are or if you become pregnant during the study. Due to these risks, you must not participate in this study if you are pregnant, or plan to become pregnant during the research study period, or are breast-feeding a child.
If you are a woman of child-bearing potential:

- By signing this consent form, you confirm to the best of your knowledge that you are not pregnant now and you do not intend to become pregnant during this study
- A pregnancy test will be done to confirm that you are not pregnant before you take part in this study
- You must avoid becoming pregnant and use an acceptable method of birth control during this study.

If at any time during this study you think you might be pregnant, or later learn that you were pregnant during the study, you must contact the study doctor immediately for further instructions about your participation in this study and follow-up.

MALE Patients

The study drug used in this study could affect your sperm and could potentially harm a child that you may father while in this study. You must avoid unprotected sex with a pregnant partner (or woman of child-bearing potential not using birth control) or donating sperm during the study and for three months following the last dose, since the potential for problems with the fetus has not yet been thoroughly investigated. Men should use a condom during the trial and for three months following the last dose.

If your partner becomes pregnant, you must notify the study doctor of any outcomes of the pregnancy from the date of the first dose until *three months* after last dose of ZD6474.

TYPES OF TESTS OR PROCEDURES INVOLVED WITH THIS STUDY

Once you meet with your doctors and research team at the NIH and undergo the necessary tests to determine if you are a suitable candidate for this study, you can decide whether you want to participate. If you choose to take part, then you will be started on ZD6474. This drug is given by mouth once every day (treatment periods are divided arbitrarily into cycles-a cycle of ZD6474 is 28 days). You will be instructed about how to take ZD6474.

During the 1st cycle, you will need to return to the NIH every 2 weeks on the same day of the week as of your first dose of ZD6474. If you stay on the drug after the 1st cycle, you will return to the NIH every four weeks.

At clinic visits during your participation in this study you will have the following tests and procedures. They are part of regular cancer care.

- Vital signs (pulse rate, respiration rate, oral temperature, and blood pressure), weight, and performance status will be taken at each study visit.
- Blood will be collected for chemistry, hematology, and other labs to determine if the study drug is causing any ill effects on your body. These samples will be taken at each study visit. About 3-5 teaspoons will be taken each time you visit the doctor for this study.
- If you are a female and able to get pregnant, a pregnancy test will be done within the week before starting the study and once every four weeks during treatment before your continue with each new cycle.

The following tests and procedures will also be done. Even though they are part of regular cancer care, it is possible they are being done more often because you are in this study.

- You will have imaging scans (CT or MRI) done approximately every 12 weeks to assess the size of your tumors (or sooner if your doctor feels it is necessary)
- You will have urine collected during the 1st week of every cycle.
- You will have an electrocardiogram (EKG) and routine blood work done every week during the 1st two cycles. If you stay on the drug longer, then EKGs will be performed every four weeks. This means that some of the EKGs and blood work will need to be performed locally near your home and the results sent to the NIH.

The following research studies will be done to see how ZD6474 is affecting your body.

- Your blood will be taken before and after the ZD6474 dose at weeks 1 and 3 of the 1st cycle, and every four weeks after that, as well as the end of treatment to look for special markers affecting you and/or your tumor that may be helpful in the study of kidney cancer. About 8 tablespoons will be collected for this portion of the research tests.

STUDY CHART

The chart below shows what will happen to you during the course of your treatment.

DAY	WHAT TO DO AND WHAT WILL HAPPEN TO YOU
Day 1, Week 1 of each cycle	• ZD6474 tablets will be given to you along with a pill diary, blood pressure monitor, side effect diary, and blood pressure diary.
Day 1 of Weeks 1 and 3 of the 1st cycle, and Day 1 of every cycle (4 weeks) after 1st cycle (Week 5, 9, 13, etc.)	• NIH visit • Have a history taken of how you feel, have a physical examination, and vital signs by a Health Care Provider in the Urology (OP3) Clinic • Review your blood pressure, side effects and pill diaries • Blood draw for research and routine lab tests before ZD6474 dose, and blood draw for research tests after ZD6474 dose • Urine tests • EKG will be done
Day 1, every week for Weeks 2, 4, 6, 7 & 8,	• EKG and routine blood tests will be done by your local doctor with results sent to NIH.
Every 12 weeks (starting with week 13)	• A CT scan or MRI will determine how your tumor is being affected by the therapy.

Can I stop being in the study?

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

It is important to tell the study doctor if you are thinking about stopping so any risks from ZD6474 can be evaluated by your doctor. Another reason to tell your doctor that you are thinking about stopping is to discuss what follow up care and testing could be most helpful for you.

The study doctor may stop you from taking part in this study at any time if he/she believes it is in your best interest; if you do not follow the study rules; or if the study is stopped.

When am I finished with the Study?

You may continue to receive ZD6474 treatment in this study until:

- your tumors get larger, or
- your doctor feels you are not benefiting from ZD6474, or
- you experience intolerable side effects or side effects which make it unsafe for you to continue, or
- the doctors taking care of you feel it is not in your best interest to continue, or
- you choose to withdraw from this study, or
- you are unable to keep scheduled medical appointments or take the study medication as instructed, or
- a better therapy becomes available, or
- you are a female and become pregnant, or
- the drug is no longer available or the study closes

Safety Follow-up Visit/End of study visit:

If you come off of the treatment for any of the reasons listed above, we would like to continue to check up on you periodically through phone calls to you, your family or your home doctor's office.

If you experience a side effect or abnormal laboratory results, your study doctor may ask that you come back for additional visits until the side effect resolves

SIDE EFFECTS OR RISKS FROM BEING IN THE STUDY

More than 5000 patients with different types of tumors have been treated with ZD6474. A variety of side effects have been seen in patients receiving ZD6474 and are described below. In addition to the possible side effects listed below, there is always the risk of uncommon or unexpected side effects that you may experience when taking ZD6474. Your doctor will closely monitor you throughout this study and discuss with you any questions regarding risks, discomforts and side effects.

The administration of any drug involves a general risk of allergic drug reactions. The symptoms that may occur include headache, rashes/hives, flushing, swollen skin, breathlessness, dizziness, nausea, and sometimes vomiting. In rare cases, life-threatening reactions may develop, including choking attacks, dangerously low blood pressure and loss of consciousness, which will require immediate treatment.

To our knowledge, patients with VHL have not received this drug outside this trial and hence it is not known whether these patients may develop additional or more severe side effects than non-VHL patients.

If at any time you have any questions about side effects or if you think you have a side effect or a change in your health condition, it is important that you speak to your study physician.

Known side effects in patients receiving ZD6474

All drugs have potential side effects. One of the purposes of this study is to learn about the possible side effects of ZD6474. Many drug-related side effects will go away shortly after stopping the drug, but in some cases side effects may be serious, long, lasting, or permanent. During your study treatment and for at least 30 days after your last dose of ZD6474, it will be very important for you to report any possible side effects or symptoms that you develop to your study doctor.

Everyone taking part in the study will be watched carefully for any side effects. However, doctors don't know all the side effects that may occur. Side effects may be mild or very serious. Your health care team may give you medicines to help lessen some side effects. It may become necessary to temporarily or permanently discontinue ZD6474 or alter the dose of the drugs due to side effects you experience.

Patients in clinical studies using ZD6474 have reported the following symptoms and side effects related to ZD6474:

<u>Likely / Common (> 10%):</u>
- skin rashes
- nausea
- loss of appetite
- weight loss
- diarrhea
- constipation
- high blood pressure
- changes on the EKG without any symptoms
- feeling tired
- headache
- dizziness
- depression and anxiety
- sleeplessness

<u>Less Likely (1% to 11%)</u>
- blood in the urine
- protein in the urine
- changes in lab values of electrolytes and liver function tests
- low platelet count, anemia, and low white blood count
- bruises
- gum bleeding, mouth sores or yeast infections
- fever
- lack of energy and weakness
- dehydration

- vomiting or heartburn
- shortness of breath
- cough
- pain, including pain associated with tumor
- itching
- pain, redness, or peeling of the hands and feet
- increased blood levels of calcium, a mineral normally found in blood
- changes in levels of parathormone, a substance made in your body that regulates the levels of calcium and phosphorus
- Inflammation of the pancreas
- Inflammation/infection of the intestines
- Abnormal accumulation of fluid in the brain
- Decrease in thyroid function
- Stroke
- Mild nose bleeding
- Abnormal taste in mouth
- Dry or irritated eyes
- Kidney stones

Rare but Serious

- Life-threatening high blood pressure
- Symptomatic and / or life threatening heart rhythm changes
- Formation of clots, such as in the lung or in the legs
- Bleeding, from tumors or non tumor sites
- Bleeding in or around the brain
- Lack of blood flow to heart (heart attack), brain (stroke), eye (blindness),legs, or bowel
- Serious or life threatening complications from rashes
- Lung inflammation and stiffening, infections or fluid accumulation around the lungs
- Blockage or penetration of the bowel or gall bladder duct
- Kidney failure
- Problems with wound healing and spreading bacterial infection of the deeper layers of skin and soft tissu
- Heart Failure, which is the weakening of the heart's ability to pump blood has also been reported and may be related to vandetanib. We will be monitoring your heart function with an ekg. If significant changes occur, we may need to stop therapy.
- Seizures, some patients have had seizures while taking vandetanib, and in one case a patient with seizures also had swelling in the brain that was found on an MRI scan, which got better after vandetanib was stopped. If you develop seizures, dizziness, headache, changes in your vision, or confusion, you should let your study doctor know as soon as possible. **These may be symptoms of reversible posterior leukoencephalopathy syndrome (RPLS).**

In addition, a number of other side effects have been reported in clinical trials using ZD6474 alone, in combination with other chemotherapy agents or radiation. It is unclear whether these side effects are related to ZD6474, or are caused by other factors (such as chemotherapy or radiation). These side effects include:

- Infections, including life-threatening bacterial infections
- Facial nerve palsies or reversible confusion, seizures and swelling in the brain
- Brief loss of consciousness

- Weakening of the heart muscle or inability of the heart to pump efficiently
- Severe breathing problems or lung failure
- Development of an abnormal pathway between the esophagus (tube connecting the throat to the stomach) and trachea (windpipe) or surrounding structures
- Development of an abnormal communication between the intestines and surrounding structures, including the urinary bladder

AstraZeneca is monitoring patients receiving vandetanib. You and your study doctor will be told if we have further information about vandetanib that might be relevant to your willingness to continue to take part in the study.

Many side effects, including skin rashes, diarrhea, high blood pressure and EKG changes are often reversible and can usually be improved by reducing the dose of ZD6474. If you develop a skin rash, creams and oral medications can be given. If you develop diarrhea related to the ZD6474, medications to stop the diarrhea can be used.

Your skin will be more sensitive to the sun, and you should minimize your exposure to the sun. This may be done by reducing the time you are out in the sun, using a hat and clothing to cover most of your body and applying sunscreens with an SPF 45 or higher any time you are outdoors. It is recommended that you take preventative action to prevent the rash from occurring while receiving study medication and for 3 to 4 weeks after stopping treatment by using the afore mentioned guidelines.

Also, you must notify the study team when the first sign of a rash occurs so that the appropriate steps can be taken in an attempt to prevent the rash from becoming severe.

Your eyes may be more dry and changes to your corneas may occur. In order to prevent corneal ulcers and other eye problems, do not wear contact lenses while taking ZD6474.

Your blood pressure will be monitored carefully on the study and, if found to be elevated, medications to lower your blood pressure can be used. If you have uncontrolled high blood pressure, this elevated pressure can cause damage to other organs including the heart, kidneys, or brain. Having uncontrolled blood pressure increases the risk of heart attack and stroke in adults. High blood pressure may be associated with no symptoms; however, dizziness, headache or nose bleed can occur in patients with high blood pressure. You will be asked to record your blood pressure at least once a day. **If your systolic blood pressure (upper or higher number) is above 150, or if your diastolic (lower number) is above 100 or above, please call your doctors at the NIH or seek medical attention from your local doctors as soon as possible.**

We will monitor your heart function closely by performing ECG/EKGs periodically to look at your heart rate and rhythm. This procedure is associated with minimal discomfort. Abnormalities on the EKG have been reported in patients taking ZD6474 on other trials. Some of these abnormalities can have serious or life-threatening consequences if appropriate action is not taken (usually stopping or reducing the dose of ZD6474 and/or ensuring that blood electrolyte levels are normal). However, as a result of close monitoring and timely intervention, no serious problems or symptoms related to these EKG abnormalities have been reported so far.

AstraZeneca has observed changes in ECGs in some patients being treated with vandetanib. These changes in the ECG may be drug-related and usually occur without symptoms; accordingly, frequent safety follow-up visits have been built into all studies. Similar changes in the ECGs of patients receiving other medications have led to heart rhythm changes, some of which have been life threatening. **However, it is estimated that between 0.1 to**

1% of patients receiving vandetanib 300 mg have developed heart rhythm changes linked to life-threatening arrhythmia called Torsades de Pointes. Torsades de Pointes has been associated with sudden death. If any such changes are noted on your ECGs, you may need to attend additional visits for further safety assessments.

The risk of developing changes in the ECG and serious heart rhythm changes will be greater if you have diarrhea, vomiting, high fever, faintness or dizzy spells, or are unable to maintain a normal diet. **You should report any of these symptoms to your doctor immediately.** You should review your medications and diet with your doctor at each visit while you are continuing to receive study medication.

These changes in the ECG usually occur without you being able to sense it happening, so frequent follow-up has been built into the study. You may be able to sense some changes in the heart rhythm such as rapid or irregular heart beating, dizziness, light-headedness, chest discomfort, shortness of breath, and losing consciousness. **These or other new symptoms or possible side effects should be reported immediately to your doctor.**

A rare side effect of anti-blood vessel agents such as ZD6474 is a risk of bleeding, which can sometimes occur at the site of or from tumors. Although patients taking ZD6474 on other trials have experienced bleeding (including one case of bleeding into the brain) it is not clear how frequently bleeding occurs or whether these are related to ZD6474. Other drugs (including some drugs that are approved by the FDA for treating kidney cancer) have been associated with bleeding, which, in some cases have been life-threatening or fatal. Since patients with VHL have tumors at multiple locations within the body, bleeding from tumors can have serious or life-threatening consequences, especially if it involves hemangioblastomas in areas such as the brain, the spinal cord or angiomas in the eye.

Drugs that affect the normal growth of blood vessels can delay or complicate wound healing following injury or surgical procedures. You should not schedule any elective surgeries while you are being treated in this study. If you have an unplanned surgery, inform you doctor immediately, as you may not be able to continue study drug treatment.

The long-term side effects of ZD6474 are not known. It is possible that there may be temporary or permanent side effects of ZD6474 that have not yet been identified.

The effects of ZD6474 on the human fetus or nursing infant are not known. ZD6474 is harmful to fetal development in animals.

Known side effects of the procedures that will be done in this research study

Blood Collection

The risks associated with blood collection include discomfort, pain, bleeding, bruising, redness, swelling and/or bruising where the blood is drawn from your arm. Fainting and infection are rare, but can happen with blood collection. By signing this consent form, you are authorizing NIH investigators to use your blood samples for those procedures identified in the study protocol.

ECG

A recording of the normal electrical activity of your heart is taken by placing electrodes (pieces of metal attached to wires) on the skin of your chest, arms, and legs. There is minimal discomfort and there are no risks.

Echo

An echocardiogram is an ultrasound of your heart. An ultrasound is an image made from sound waves. There is no discomfort and there are no risks.

Imaging studies

You will have a CT scan or MRI to measure the size of your cancer(s) before starting the treatment and some or all of these scans will be used to periodically monitor the change in the size of your cancer(s) on ZD6474. These scans are common standard imaging tests used in the diagnosis and monitoring of many diseases. Although these tests have been in use for many years, their potential long term effects on the body are still being learned.

MRI Scan

There are no known harmful effects from the strong magnetic field used for MRI. However, the magnet is so powerful that it may affect pacemakers, artificial limbs, and other medical devices that contain iron. You should tell the study staff about any metal devices that you may have in your body.

Iron pigments in tattooed eyeliner can cause eye irritation.
There is slight risk of developing an allergic reaction if contrast material is used during the MRI scan. However, most reactions are mild and can be controlled using medication.

The MRI scan is performed in a long narrow tube. You may experience discomfort related to lying still in an enclosed space for a prolonged period of time. The study staff prior to performing the procedure will provide additional instructions to you. If this occurs, cool air can be blown over you by a fan if desired or your doctor can order a medicine to help you relax during this scan. Keeping the room well lit can also reduce this claustrophobic feeling.

CT Scan

If a contrast agent (the special dye) is given with the scan there is a small risk of having a reaction to the contrast. These reactions can include nausea, pain in the vein where the contrast was given, headache, a metallic or bitter taste in the mouth, and a warm or flushing feeling that lasts from 1-3 minutes. Rarely, these symptoms may require treatment. In very rare cases, people have had more severe allergic reactions that result in shortness of breath, wheezing, or lowering of the blood pressure. If you have had a reaction in the past, be sure to tell your doctor or nurse about it.

You will be exposed to a limited and medically acceptable dose of radiation during the procedure. There is always a slight risk from being exposed to any radiation, including the low levels of X-rays used for a CT scan.

The radiation dose you receive, if your scans include the use of X-rays or radioactive chemicals, is within the safe limits defined by the NIH Radiation Safety Guidelines, and is considered essential for your medical care.

Delay in surgical resection of kidney tumor(s)

Von Hippel-Lindau patients with kidney tumors that have reached a certain size (usually around 3cm) would normally be advised to undergo surgery to remove them. Surgical removal of tumors is done to lessen the risk of spread to other

organs. Removing your kidney tumors does not mean that your cancer has been 'cured'. Even if you have surgery to remove your kidney tumor(s), it is possible that you will develop new tumors and may need surgery again in the future.

Your tumors may or may not be large enough to require surgical resection in the near future. If they are large enough to require surgery, a delay in surgery may result if you choose to participate in this study and your tumors do not decrease in size with ZD6474. We feel that delaying surgery for approximately 12 weeks is unlikely to greatly increase the risk of tumor spread from your kidneys. After 12 weeks, depending on the effect of ZD6474 on your tumors, a decision will be made about whether it is safe to delay surgery any further. If any of your kidney tumors should be very large, we will advise surgery at the earliest possible time and will exclude you from the current study.

Potential Benefits of Participation

You are being offered this experimental drug (ZD6474) because it may be of benefit to you in treating your VHL disease. One potential benefit may be shrinkage of your tumors that would enable you to delay or avoid surgery. Another possible benefit might be changes to the tumor environment (such as decreased blood supply) that may make surgical removal of your tumor(s) easier. However, there is no guarantee that this drug is of benefit to humans or that you will benefit from taking part in the study. The drug you receive may even be harmful to you.

Individual patients will not have a benefit from taking part in the investigational procedures such as research done on your blood samples or tumor tissue. However, future patients may benefit from what is learned.
Your participation in this study is voluntary.

Potential Benefits to Society

The knowledge gained from this study may benefit others. Your participation may help to determine if ZD6474 treatment can be safely and effectively given to other patients with VHL.

Alternative to Participation/ Alternative Approaches or Treatments

You may choose not to participate in this study. Other treatment options may be available to you. Your doctor is very willing to discuss the benefits and side effects of other ways to treat your tumors including the option of surgical resection of your tumor(s), treatment of your symptoms only, and other investigational protocols that may be available for your condition.

Your other choices may include:

- Getting care for your cancer without being in a study
- Taking part in another study
- Surgical removal of your tumor(s)
- Getting no treatment

If you agree to participate in this study then you and your doctor have determined that there are no other standard therapies available that have been shown to improve your chance of survival or cure, or you have refused other treatment options available to you.

CONFIDENTIALITY OF MEDICAL INFORMATION

Will my 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. Your personal information may be given out if required by law. If information from this study is published or presented at scientific meetings, your name and other personal information will not be used.

All patients will be given a number upon signing this informed consent form. The number will be used throughout the study as your main identifier on study documents that will be sent to AstraZeneca (the drug company that provides the drug used in this trial). Every effort will be made to ensure that documents that contain your personal information will be crossed out and replaced with your subject identification number if sent to AstraZeneca.

All research samples will be labeled with a unique bar code number. Only the investigator and designated study site staff (i.e. staff at the NIH) will have the key to link the bar-coded samples to the subject to which they correspond.

Neither your results nor your samples will be identified with your name in communications with AstraZeneca. A number will be used in all regulatory documentation related to this study. It is a requirement that your involvement in this study be noted in your medical records.

Since research studies on samples you provide are not expected to benefit you directly or to change your treatment course, these results will not be placed in your medical record and will not be made available to you, members of your family, your personal physician, or other third parties.

The confidentiality of your medical records will be maintained to the extent permitted by the applicable laws. If results of the trial are published, your identity will remain confidential. Using your subject number only, the results and other information from the study may be submitted to regulatory agencies in countries where the study drug may be submitted for approval.

WHAT WILL BE DONE WITH MY BLOOD AND TUMOR SAMPLES?

Consent for Tissue/ Blood (specimen) Banking

During the course of the study, several research studies will be performed on your blood and tissue samples. These studies will be done to try to better understand:

- how the drug is handled by your body (i.e, how it is absorbed and broken down)
- what effects the drug has on your body
- whether the drug affects any components of the mechanism that is responsible for formation of new blood vessels in or growth of tumors

Your research blood samples obtained during your participation in the study will be stored in freezers in research laboratories at the NIH and used to test for information required for this study. All samples used for research will be coded and no personal information will be included in order to protect your privacy.

Optional Studies

Please read each sentence below and think about your choice. After reading each sentence, circle and initial the answer that is right for you. No matter what you decide to do, it will not affect your care.

1. My tissue, blood, and urine specimens may be kept for use in research to learn about, prevent, or treat cancer.

Yes No Initials_____

2. My specimens may be kept for use in research to learn about, prevent or treat other health problems (for example: diabetes, Alzheimer's disease, or heart disease).

Yes No Initials_____

3. Someone may contact me in the future to ask permission to use my specimen(s) in new research not included in this consent. If the risks of the new research are not covered by this consent, you may be asked to sign consent.

Yes No Initials_____

4. I want to be contacted in the future if any information is learned that may direct impact my health or the health of my relatives. I understand that for you to contact me in the future, I need to notify you of any changes in my address.
Yes No Initials _____

Will I be compensated for participating in this study?

There will be no financial compensation for participating in this study.

What are the costs of taking part in this study?

The study drug, ZD6474, will be provided to you free of charge by AstraZeneca, Inc. through the NIH. There is no cost to you for the drug itself or for any test or procedure performed solely for research purposes. NIH will pay for the cost of the blood tests, x-rays, scans, drug preparation and pharmacy fees, and other laboratory tests associated with your research-related care at NIH while you are enrolled in this study. You or your insurance company will have to pay for all care outside of NIH, which includes non-research related costs that are associated with your routine care for your underlying disease.

Drug Sponsor/Manufacturer

The study drug is provided by AstraZeneca, Inc. It is possible that the information obtained from your participation on this study may become valuable for commercial research and development purposes (including patentable inventions), which may be of significant benefit to society, the sponsor of this study, individual researchers, or other third parties. You will not receive direct financial benefit from such research and development.

Conflict of Interest

The National Institutes of Health and the research team for this study are using ZD6474 developed by Astra Zeneca through a joint study with your researchers and the company. This means it is possible that the results of this study could lead to payments to NIH scientists and to the NIH. By law, government scientists are required to receive such payments for their inventions. You will not receive any money from the development of ZD6474.

What are my rights if I take part in this study?

Taking part in this study is your choice. You may choose either to take part or not to take part in the study. If you decide to take part in this study, you may leave the study at any time. No matter what decision you make, there will be no penalty to you and you will not lose any of your regular benefits. Leaving the study will not affect your medical care.

We will tell you about new information or changes in the study that may affect your health or your willingness to continue in the study.

In the case of injury resulting from this study, you do not lose any of your legal rights to seek payment by signing this form.

Participation in this research trial may make you ineligible to participate in other experimental drug trials. This is because researchers may not understand the effect of one research drug on another. The Principal Investigator or an Associate Investigator may end your participation in this study if they feel that termination is medically indicated due to side effects, progression of disease or compliance. Upon completing this study, you may be given the choice of taking part in other research protocols that may be appropriate for you or you will be referred to the care of your primary physician.

A copy of the informed consent is on file at the Center for Cancer Research, National Cancer Institute and a copy will be made available to you. Your signature on this form indicates that you agree to participate in this medical research study under the direction of the principal investigator as listed above. 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 other authorized people including representatives of the NCI or drug manufacturer (AstraZeneca Pharmaceuticals, LP), and the staff of the National Cancer Institute who may inspect and study your medical records. Your participation in this study does not constitute a promise of long-term care at the NIH Clinical Center.

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, W. Marston Linehan, M.D.; National Institutes of Health, National Cancer Institute, CRC,1W-5942, 9000 Rockville Pike, Bethesda MD 20892 Telephone: 301-496-6353. Other researchers you may call are: Sally Fowler, R.N. at (301) 435-6255, Dr. Ramaprasad Srinivasan, the lead Associate Investigator (301) 496-6353, or the Urologic Oncology Fellow on call at pager (301) 496-1211 (24-hour phone number). If you have any questions about the use of your tissue in future research studies, you may also contact the Office of the Clinical Director at (301) 496-4251.

You may also call the Clinical Center Patient Representative at (301) 496-2626.

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

COMPLETE APPROPRIATE ITEM(S) BELOW:

A. Adult Patient's Consent

I have read the explanation about this study and have been given the opportunity to discuss it and to ask questions. I hereby consent to take part in this study.

Signature of Adult Patient/Legal Representative _____ Date _____

Print Name _____

B. Parent's Permission for Minor Patient.

I have read the explanation about this study and have been given the opportunity to discuss it and to ask questions. I hereby give permission for my child to take part in this study.
(Attach NIH 2514-2, Minor's Assent, if applicable.)

Signature of Parent(s)/Guardian _____ Date _____

Print Name _____

C. Child's Verbal Assent (If Applicable)

The information in the above consent was described to my child and my child agrees to participate in the study.

Signature of Parent(s)/Guardian _____ Date _____ Print Name _____

THIS CONSENT DOCUMENT HAS BEEN APPROVED FOR USE FROM JUNE 27, 2011 THROUGH JUNE 26, 2012.

Signature of Investigator _____ Date _____

Print Name _____

Signature of Witness _____ Date _____

Print Name _____