PRINCIPAL INVESTIGATOR: Ramaprasad Srinivasan, M.D., Ph.D.

STUDY TITLE: A Phase II Study of Bevacizumab and Erlotinib in Subjects with Advanced Hereditary Leiomyomatosis and Renal Cell Cancer (HLRCC) or Sporadic Papillary Renal Cell Cancer

STUDY SITE: NIH Clinical Center

Cohort: Standard

Consent Version: September 1, 2021

WHO DO YOU CONTACT ABOUT THIS STUDY?

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This consent form describes a research study and is designed to help you decide if you would like to be a part of the research study.

The remaining document will now describe the research study in more detail. This information should be considered before you make your choice. Members of the study team will talk with you about the information in this document. Some people have personal, religious, or ethical beliefs that may limit the kinds of medical or research interventions in which they would want to participate. Take the time you need to ask any questions and discuss this study with NIH staff, and with your family, friends, and personal health care providers.

If the individual being asked to participate in this research study is not able to give consent for themselves, you, as the Legally Authorized Representative, will be their decision-maker and you are being asked to give permission for this person to be in this study. For the remainder of this document, the term "you" refers to you as the decision-maker and/or the individual being asked to participate in this research.

IT IS YOUR CHOICE TO TAKE PART IN THE STUDY

You may choose not to take part in this study for any reason. If you join this study, you may change your mind and stop participating in the study at any time and for any reason. In either case, you will not lose any benefits to which you are otherwise entitled. However, to be seen at the NIH, you must be taking part in a study or are being considered for a study. If you do choose to leave the study, please inform your study team to ensure a safe withdrawal from the research.

WHY IS THIS STUDY BEING DONE?

There are currently no drugs that are known to be effective in patients with papillary kidney cancer that have spread beyond the kidneys. The purpose of this research study is to determine if a combination of two drugs, (1) bevacizumab (also known by the trade name Avastin) and (2) erlotinib (also known by the trade name Tarceva) can be used as a treatment for certain forms of kidney tumors and whether this combination can effectively be given to patients with kidney cancer.

Why might the combination of bevacizumab and erlotinib work in cancer patients?

Both bevacizumab and erlotinib have been approved for use by the US Food and Drug Administration (FDA) in various cancers including lung cancer and kidney cancer. Typically, bevacizumab and erlotinib are given either alone or in combination with other forms of chemotherapy or other anti-tumor drugs. The combination of bevacizumab and erlotinib has been studied in patients with kidney cancer and appears to be safe in the doses you will receive in this study. The combination of bevacizumab and erlotinib is experimental and has not yet been approved for use by the US Food and Drug Administration. Bevacizumab is given intravenously every two weeks while erlotinib is a pill that you will be asked to take daily.

We do not know whether this combination will slow or stop the growth of your kidney cancer.

HOW MANY PEOPLE WILL PARTICIPATE IN THIS STUDY?

Up to 85 participants will be enrolled on the study.

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

If you decide to participate in this study, you will undergo a series of tests to determine if you are eligible to participate in the study and if it is safe for you to receive bevacizumab and erlotinib.

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

All eligible participants enrolled in this study will receive bevacizumab and erlotinib. This study is an open label study, which means that both you and your doctor will know what drugs you are taking and what amount of bevacizumab and erlotinib you are taking.

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

Initially, 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 be evaluated at least every 2 weeks by a physician/nurse and have blood and urine studies performed prior to receiving your next dose of bevacizumab. You will need to come to the NIH at least every 4 weeks during the first eight weeks of treatment to meet with your doctors and research nurse and also have several tests done. After the first eight weeks, you will need to return for a visit at least once every eight weeks (more frequently if studies such as CT scans are required). 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 cancer treatments other than bevacizumab and erlotinib. 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 erlotinib and/or bevacizumab. 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, **you must talk to your NIH doctors prior to starting any new drugs (including prescribed or over-the-counter medications), 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 or for 2-3 months following your last dose of bevacizumab. **If you have an unplanned surgery, inform your doctor at the NIH immediately, as it may not be safe for you 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 erlotinib and any side effects that you experience. You will also need to bring your erlotinib pill bottles with you to every visit for the team to count your remaining 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 140, or if your diastolic (lower number) is above 90, you should call your doctors at the NIH and/or seek medical attention from your local doctors as soon as possible.**

BIRTH CONTROL

Agents such as bevacizumab and erlotinib, 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 enrolled in the study. An appropriate and effective method of birth control (which may include but not limited to abstinence, hormonal contraceptives (birth control pills, injections, or implants), intrauterine device (IUD), tubal ligation, or vasectomy) must be used by any person who is able to become pregnant or father a child and is receiving bevacizumab or erlotinib. Birth control must be continued and breast feeding avoided for six months after the last dose of bevacizumab and erlotinib is given to ensure that most of the drug is out of your body. If you become or are found to be pregnant while participating in the study, you must notify one of the doctors listed on this

form right away. If you become pregnant while you are taking bevacizumab or erlotinib you must stop taking the drug(s), and you will not be able to continue treatment on study. If you are a male, you should not attempt to father a child while you are on the study drugs and for at least six (6) months after stopping the drugs. You must use an appropriate and effective method of birth control during this period in discussion with your NIH study team. The effect of this drug on your ability to bear or father children after you discontinue treatment is unknown.

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 bevacizumab and erlotinib. Bevacizumab is given intravenously every two weeks in a hospital/doctor's office, while erlotinib is a pill that you will be asked to take daily. Treatment periods are divided arbitrarily into cycles- a cycle of treatment is 28 days.

You will need to be seen in an oncologist's office at least once every two weeks, before your next dose of bevacizumab. During these visits, you will have the following performed:

- Vital signs (pulse rate, respiration rate, oral temperature, and blood pressure) and weight
- A urine sample checked to determine if it is safe for you to receive bevacizumab.

You will need to return to the NIH at least every 4 weeks, usually on the same day of the week as your first dose of bevacizumab and erlotinib. If you stay on the drugs after the 2nd cycle, you will return to the NIH at least every eight weeks.

At clinic visits every 4 weeks 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.
- 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 approximately every 4 weeks. 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 8-12 weeks to assess the size of your tumors (or sooner if your doctor feels it is necessary). You will also have a PET scan if clinically required.

- You will have urine collected before every dose of bevacizumab (i.e, approximately every 2 weeks).
- If you have HLRCC and skin tumors associated with this disease (leiomyomas), you will be seen by a dermatologist and have photographs and measurements of your skin tumors to determine how they are responding to treatment

The following research studies will be done to see how bevacizumab and erlotinib are affecting your body.

- Your blood will be taken before the first dose of bevacizumab/erlotinib and after cycles 1, 2, 4, 6, and 8 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.
- Tumor Biopsy (Optional): We may request that you undergo a biopsy of one of your tumors at two time points during the study (before you begin treatment and approximately one month following start of treatment). The tumor samples we obtain will be used to look for special markers affecting you and/or your tumor that may be helpful in the study of kidney cancer and in understanding the effect of the study drugs on the tumor. The biopsy will be performed by physicians specially trained in the necessary procedures. We will only ask you to undergo the biopsies if we feel that the tumor can be easily accessed (such as tumors on the skin, in the kidney, liver, uterus or lymph nodes in the abdomen) and there are no major risks associated with the procedure. Kidney or liver biopsies will not be performed solely for research purposes while you are receiving bevacizumab. The procedure and the risks involved will be explained to you before the procedure and you will be asked to sign a separate consent form if you wish to undergo the biopsy. You may decline the biopsies without affecting you participation in the trial in any way.

STUDY CHART

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

Cycle 1

Day	**What you do**
One to seven days before starting study	• Undergo screening for this trial (blood tests, urine tests, EKG, echocardiogram, CT, MRI, PET scan, bone scan).
Day before starting study	• Be seen in NIH clinic the day before starting study.
Day 1	• Begin receiving bevacizumab intravenously once every 14 days. • Begin taking erlotinib by mouth once a day. Keep taking daily until the end of study, unless told to stop by your health care team.

Day	What you do
Day 15	• Get blood and urine tests. • Be seen in NIH clinic • Receive bevacizumab • Continue erlotinib
Day 28	• End of cycle 1

Future cycles

Day	What you do
Day 1	• Return to NIH clinic for your next exam and to begin the next cycle. • Have a history taken of how you feel, have a physical examination, and vital signs by a Health Care Provider • Review your blood pressure, side effects and pill diaries with the NIH team • Blood and urine studies
Days 1-28	• Receive bevacizumab intravenously on days 1 and 15 of each cycle if you have no bad side effects and your cancer is not getting worse. Call the doctor at **240-760-6251** if you do not know what to do. • Keep taking erlotinib once a day if you have no bad side effects and your cancer is not getting worse. Call the doctor at **240-760-6251** if you do not know what to do. • Get routine blood and urine tests every 2-4 weeks as instructed (more if your doctor tells you to). • Get restaging CT and MRI scans every 8-12 weeks (more if your doctor tells you to).
Day 29	• Return to clinic on OP-3 for your next exam and to begin the next cycle.

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 study treatment 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.

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

WHEN AM I FINISHED WITH THE STUDY?

You may continue to receive treatment in this study until:

- your tumors get larger, or
- your doctor feels you are not benefiting from study treatment, 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. You may also be asked to get CT scans or MRIs to assess your tumors periodically.

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

Both bevacizumab and erlotinib have been approved for use by the US Food and Drug Administration in many different kinds of cancers. These drugs are typically given either alone, or in combination with a variety of chemotherapy or other antitumor agents. In addition, the combination of bevacizumab and erlotinib has been studied in some cancers (but not approved yet by the US Food and Drug Administration), including patients with a type of kidney cancer (clear cell kidney cancer). Known side effects associated with these drugs are listed 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 bevacizumab and/or erlotinib. 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 and may result in death.

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 bevacizumab and/or erlotinib

All drugs have potential side effects. 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 bevacizumab and erlotinib, it will be very important for you to report any possible side effects or symptoms that you develop to your study doctor. Recent changes by the US Food and Drug Administration to the bevacizumab package insert about the risks of this drug are also described below.

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 either bevacizumab or erlotinib or both or alter the dose of the drugs due to side effects you experience.

The following side effects thought to be related to treatment have been reported in patients treated with bevacizumab and/or erlotinib:

Risks and side effects related to the use of bevacizumab include:

Very Likely (>20%):

- Nose bleeds
- High blood pressure
- Fatigue
- Skin rash, which may some time be severe
- Headache
- Soreness in mouth or throat

Less Likely (5-20%)

- Mild to moderate bleeding in the tumor, stomach, intestines, or other parts of the body.
- Blood clots in the veins: blood clots can occur in the veins of the leg and the lungs or other organs. These events can be life-threatening.
- Clots in the arteries, including stroke or heart attack. These conditions can be life-threatening or fatal.
- Leakage of protein in the urine, which can rarely lead to damage to the kidney
- Reactions associated with infusion of the bevacizumab: rash, chills, fever, rigor

- Infection: in various organs and tissues including skin, abdomen, soft tissues around the rectum. In rare incidents, the infections can be serious and life-threatening.
- Blockage or inflammation of the bowels
- Nonspecific stomach and intestinal symptoms: low appetite, heart burn, constipation, diarrhea, nausea, vomiting.
- Aches in various body parts, including abdomen, back, chest, joints and tumor sites
- Shortness of breath, cough
- Other: Hoarseness, watery eyes, stuff nose, weight loss, altered taste, dizziness; decrease in red cells that may be associated with fatigue
- Changes in blood chemistries (electrolytes and proteins) such as low levels of phosphate or albumin
- Changes in thyroid hormone levels (hypothyroidism)

Rare but serious (<5%)

- Serious or fatal bleeding from the tumor, brain, intestines, or the lungs
- Bowel perforation and bowel anastomotic dehiscence (a tear or hole in the gastrointestinal tract) that can lead to life-threatening complications and require surgery to repair.
- Fistula formation: defect in the walls of luminal organs such as the nose, upper airways, lungs, esophagus, rectum, or vagina. Fistula formation may lead to life-threatening complications including serious infections, bleeding or dysfunction of the organs.
- Heart problems (including irregular heartbeats, fluid collections surrounding the heart, heart attack or heat failure)
- Stroke
- Delayed or poor wound healing after surgery
- Reversible Posterior Leukoencephalopathy Syndrome (RPLS) (<1%): A medical condition related to leakiness of blood vessels in the brain and can cause confusion, blindness or vision changes, or seizure, as well as abnormal brain scans. This condition is usually reversible, but in rare cases, it is potentially life-threatening and may cause long-term brain damage.
- Reversible changes in the liver functions
- Severe allergic reactions that result in difficulty breathing or drop in blood pressure
- Low white cell counts when combined with chemotherapies, which may lead to increased incidence of serious and fatal infections.
- Low red blood cell count (anemia) that can be caused by bleeding or the destruction of red blood cells in the body, including microangiopathic hemolytic anemia (MAHA), which is a condition where abnormal clot formation in small blood vessels can lead to kidney failure, reduction in red blood cell and platelet count and other manifestations. Severe forms of MAHA may be life-threatening.
- Abnormal changes in the lungs that may cause difficulty breathing or respiratory failure
- Osteonecrosis of the jaw (destruction of part of the jaw bone)

- Ovarian failure in premenopausal women when combined with chemotherapies, which may lead to temporary or permanent loss of ovarian function (infertility or decreased levels of the female hormone estrogen)
- Sudden death

Risks and side effects related to the use of erlotinib include:

Likely (>20%):

- Skin rash- This can vary from mild to moderate skin rash to severe, life-threatening forms (relatively rare) associated with blistering and peeling of large areas of skin
- Diarrhea
- Loss of appetite
- Fatigue

Less Likely (5-20%):

- Eye problems, including abnormal growth of eyelashes, dry eyes, ulceration or perforation of the cornea. To minimize some of these side effects, you **must not use contact lenses** while on study
- Nausea and vomiting
- Dehydration
- Malaise
- Generalized weakness
- Abnormalities in blood tests used to measure blood thinning (INR)
- Abnormal blood tests indicating liver inflammation or failure. Severe, life-threatening liver failure reported rarely
- Shortness of breath, cough
- Infection, which can sometimes be life threatening
- Fever
- Chills
- Mouth sore
- Dry skin, itching
- Nail changes
- Abdominal pain
- Weight loss
- Muscle aches
- Hair loss
- Heartburn
- Dizziness
- Headache
- Anxiety, depression
- Neuropathy-Pain related to nerve damage, often affecting the tips of fingers and toes
- Constipation

- Changes in blood chemistries (electrolytes and proteins) such as low levels of phosphate or albumin

Rare but serious (<5%):

- Lung problems (interstitial lung disease)-Inflammation of the lung that can lead to cough, fever, difficulty in breathing. These changes may be permanent and life-threatening
- Kidney failure
- Bowel perforation and bowel anastomotic dehiscence (a tear or hole in the gastrointestinal tract) that can lead to life-threatening complications, and require surgery to repair.
- Clots in the arteries, including stroke or heart attack. These conditions can be life-threatening or fatal.
- Stroke as a result of or complicated by bleeding into the brain
- Hemolytic Uremic Syndrome- A condition where abnormal clot formation in small blood vessels can lead to kidney failure, reduction in red blood cell and platelet count and other manifestations. Severe forms may be life-threatening.
- Mild to moderate bleeding in the tumor, stomach, intestines, or other parts of the body.

Taking bevacizumab and erlotinib together has not been shown to increase the risks or side effects seen with each drug when taken alone.

Many side effects, including skin rashes, diarrhea, high blood pressure, spilling protein in the urine etc. are often reversible and can usually be improved by temporarily or permanently stopping the study drugs. If you develop a skin rash, creams and oral medications can be given. If you develop diarrhea related to the study drugs, medications to stop the diarrhea can be used.

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

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 140, or if your diastolic (lower number) is above 90, please call your doctors at the NIH and/or seek medical attention from your local doctors as soon as possible.**

One side effect of anti-blood vessel agents such as bevacizumab is a risk of bleeding, which can sometimes occur at the site of or from tumors. The bleeding is often mild and stops with little or no intervention, but may some times be life-threatening.

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 bevacizumab and erlotinib are not fully known. It is possible that there may be temporary or permanent side effects of these drugs that have not yet been identified.

You should not become pregnant or father a baby while on this study because the drugs in this study can affect an unborn baby. Women should not breastfeed a baby while on this study. It is important you understand that you need to use birth control while on this study. Check with your study doctor about what kind of birth control methods to use and how long to use them. Some methods might not be approved for use in this study. Bevacizumab and erlotinib may lead to you being unable to have children in the future.

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 major discomfort and there are no known risks of significance.

Imaging studies

You will have a CT scan, MRI, ultrasound scans and/or PET scans 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 treatment. 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.

PET Scan

PET, also called Positron emission tomography, lets the doctor see the activity of cells in specific tissues of the body. It requires that you be given an intravenous (IV) fluid, similar to a sugar fluid, on which we have attached a radioactive particle that allows the fluid to be seen with a special camera. The sugar fluid goes to cells that are most active, like cancer cells, and allows the doctors to see if you have a tumor. This procedure exposes you to a small and medically acceptable dose of radiation.

Bone Scan

This test allows us to determine if there has been spread of cancer to your bones. Prior to the scan, a radioisotope (a small amount of radioactive material) is given into an intravenous catheter. The scan is then done with a sensitive camera. This procedure exposes you to a small and medically acceptable dose of radiation.

Tumor Biopsy Risks

The biopsy procedure usually causes only brief discomfort at the site from which the biopsy is taken. Rarely, infection or bleeding may occur at the needle site.

Research Radiation Risks

During your participation in this research study, you may be exposed to radiation from CT, PET and bone scans and biopsies under CT guidance each year. The amount of radiation exposure from these procedures is equal to approximately 13.68. A rem is a unit of absorbed radiation.

Every day, people are exposed to low levels of radiation that come from the sun and the environment around them. The average person in the United States receives a radiation exposure of 0.3 rem per year from these sources. This type of radiation is called "background radiation." This study will expose you to more radiation than you get from everyday background radiation. No one knows for sure whether exposure to these low amounts of radiation is harmful to your body.

The CT, PET and bone scans and biopsies under CT guidance that you get in this study will expose you to the roughly the same amount of radiation as 45.6 years' worth of background radiation. Being exposed to too much radiation can cause harmful side effects such as an increase in the risk of cancer. The risk depends on how much radiation you are exposed to. Please be aware that about 40 out of 100 people (40%) will get cancer during their lifetime, and 20 out of 100 (20%) will die from cancer. The risk of getting cancer from the radiation exposure in this study is 1.4 out of 100 (1.4%) and of getting a fatal cancer is 0.7 out of 100 (0.7%).

POTENTIAL BENEFITS OF PARTICIPATION

You are being offered this experimental drug regimen because it may be of benefit to you in treating your kidney cancer. One potential benefit may be shrinkage of your tumors that may or may not lead to other benefits such as improved quality of life, prolongation of life or delay in growth of your tumors. However, there is no guarantee that this drug combination is of benefit in kidney cancer or that you will benefit from taking part in the study. The drugs you receive may even be harmful to you.

Individual patients will not have a direct 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 the combination of bevacizumab and erlotinib is safe and/or effective in patients with papillary kidney cancer.

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
- Getting comfort care only. This type of care helps reduce pain, tiredness, appetite problems and other problems caused by the cancer. It does not treat the cancer directly,

but instead tries to improve how you feel. Comfort care tries to keep you as active and comfortable as possible.
- 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.

WHAT WILL BE DONE WITH MY BLOOD AND TUMOR SAMPLES?

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 or other aspects of tumor growth
- Whether specific types of genetic abnormalities are associated with your tumors

Your research blood and tumor 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.

DRUG MANUFACTURER

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

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

The National Institutes of Health and the research team for this study are using a drug developed by Genentech through a joint study with your researchers and the company. The company also

provides financial support for this study.

WHAT ARE MY RIGHTS IF I TAKE PART IN THIS STUDY?

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.

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.

USE OF SPECIMENS AND DATA FOR FUTURE RESEARCH

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

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

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

COMPENSATION, REIMBURSEMENT, AND PAYMENT

Will you receive compensation for participation in the study?

Some NIH Clinical Center studies offer compensation for participation in research. The amount of compensation, if any, is guided by NIH policies and guidelines.

You will not receive compensation for participation in this study.

Will you receive reimbursement or direct payment by NIH as part of your participation?

Some NIH Clinical Center studies offer reimbursement or payment for travel, lodging or meals while participating in the research. The amount, if any, is guided by NIH policies and guidelines.

On this study, the NCI will cover the cost for some of your expenses. Some of these costs may be paid directly by the NIH and some may be reimbursed after you have paid. The amount and form of these payments are determined by the NCI Travel and Lodging Reimbursement Policy. You will be given a summary of the policy which provides more information.

Will taking part in this research study cost you anything?

NIH does not bill health insurance companies or participants for any research or related clinical care that you receive at the NIH Clinical Center.

- If some tests and procedures are performed outside the NIH Clinical Center, you may have to pay for these costs if they are not covered by your insurance company.
- Medicines that are not part of the study treatment will not be provided or paid for by the NIH Clinical Center.
- Once you have completed taking part in the study, medical care will no longer be provided by the NIH Clinical Center.

CLINICAL TRIAL REGISTRATION AND RESULTS REPORTING

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.

CONFIDENTIALITY PROTECTIONS PROVIDED IN THIS STUDY

Will your medical information be kept private?

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

- The NIH and other government agencies, like the Food and Drug Administration (FDA), which are involved in keeping research safe for people.
- National Institutes of Health Intramural Institutional Review Board.
  Qualified representatives from Genentech Inc, the pharmaceutical company who produces bevacizumab and erlotinib.

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.

If we share your specimens or data with other researchers, in most circumstances we will remove your identifiers before sharing your specimens or data. You should be aware that there is a slight possibility that someone could figure out the information is about you.

Further, the information collected for this study is protected by NIH under a Certificate of Confidentiality and the Privacy Act.

Certificate of Confidentiality

To help us protect your privacy, the NIH Intramural Program has received a Certificate of Confidentiality (Certificate). With this certificate, researchers may not release or use data or information about you except in certain circumstances.

NIH researchers must not share information that may identify you in any federal, state, or local civil, criminal, administrative, legislative, or other proceedings, for example, if requested by a court.

The Certificate does not protect your information when it:

1. is disclosed to people connected with the research, for example, information may be used for auditing or program evaluation internally by the NIH; or
2. is required to be disclosed by Federal, State, or local laws, for example, when information must be disclosed to meet the legal requirements of the federal Food and Drug Administration (FDA);
3. is for other research;
4. is disclosed with your consent.

The Certificate does not prevent you from voluntarily releasing information about yourself or your involvement in this research.

The Certificate will not be used to prevent disclosure to state or local authorities of harm to self or others including, for example, child abuse and neglect, and by signing below you consent to those disclosures. Other permissions for release may be made by signing NIH forms, such as the Notice and Acknowledgement of Information Practices consent.

Privacy Act

The Federal Privacy Act generally protects the confidentiality of your NIH medical records we collect under the authority of the Public Health Service Act. In some cases, the Privacy Act protections differ from the Certificate of Confidentiality. For example, sometimes the Privacy Act allows release of information from your medical record without your permission, for example, if it is requested by Congress. Information may also be released for certain research purposes with due consideration and protection, to those engaged by the agency for research purposes, to certain federal and state agencies, for HIV partner notification, for infectious disease or abuse or neglect reporting, to tumor registries, for quality assessment and medical audits, or when the NIH is involved in a lawsuit. However, NIH will only release information from your medical record if it is permitted by both the Certificate of Confidentiality and the Privacy Act.

POLICY REGARDING RESEARCH-RELATED INJURIES

The NIH 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 NIH, the NIH Clinical Center, or the Federal

Government. However, you have the right to pursue legal remedy if you believe that your injury justifies such action.

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, Ramaprasad Srinivasan, ramasrin@nih.gov, 240-760-6251. You may also call the NIH Clinical Center Patient Representative at 301-496-2626, or the NIH Office of IRB Operations at 301-402-3713, if you have a research-related complaint or concern.

CONSENT DOCUMENT

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

Adult Research Participant: I have read the explanation about this study and have been given the opportunity to discuss it and to ask questions. I consent to participate in this study.

Signature of Research Participant	Print Name of Research Participant	Date

Legally Authorized Representative (LAR) for an Adult Unable to Consent: I have read the explanation about this study and have been given the opportunity to discuss it and to ask questions. I am legally authorized to make research decisions on behalf of the adult participant unable to consent and have the authority to provide consent to this study. As applicable, the information in the above consent was described to the adult participant unable to consent who agrees to participate in the study.

Signature of LAR	Print Name of LAR	Date

Investigator:

Signature of Investigator	Print Name of Investigator	Date

Witness to the oral short-form consent process only: This section is only required if you are doing the oral short-consent process and this English consent form has been approved by the IRB for use as the basis of translation.

Signature of Witness*	Print Name of Witness	Date

***NIH ADMINISTRATIVE SECTION TO BE COMPLETED REGARDING THE USE OF AN INTERPRETER:**

____ An interpreter, or other individual, who speaks English and the participant's preferred language facilitated the administration of informed consent and served as a witness. The investigator obtaining consent may not also serve as the witness.

____ An interpreter, or other individual, who speaks English and the participant's preferred language facilitated the administration of informed consent but did not serve as a witness. The name or ID code of the person providing interpretive support is: _____.