

KANSAS CITY CLINICAL ONCOLOGY PROGRAM**RANDOMIZED PHASE III TRIAL COMPARING EVEROLIMUS PLUS PLACEBO VERSUS EVEROLIMUS PLUS BEVACIZUMAB FOR ADVANCED RENAL CELL CARCINOMA PROGRESSING AFTER TREATMENT WITH TYROSINE KINASE INHIBITORS**

This is a clinical trial, a type of research study. Your study doctor will explain the clinical trial to you. Clinical trials include only people who choose to take part. Please take your time to make your decision about taking part. You may discuss your decision with your friends and family. You can also discuss it with your health care team. If you have any questions, you can ask your study doctor for more explanation.

You are being asked to take part in this study because you have a form of advanced kidney cancer which has not responded to at least one previous treatment with oral medications targeting a special protein substance on the surface of the kidney cancer cell. This protein normally receives signals from other molecules that promote the growth of the blood supply to kidney cancer cells.

Why is this study being done?

The purpose of this study is to compare the effects of a drug called everolimus alone with those of the combination of everolimus and a drug called bevacizumab for advanced kidney cancer to find out which is better. In this study, you will get either the combination of everolimus and a placebo or the combination of everolimus and bevacizumab.

Bevacizumab is an antibody that can block a protein called 'vascular endothelial growth factor' (VEGF), and can slow the growth of new blood vessels in the tumor. Bevacizumab (also called Avastin®) has been approved by the Food and Drug Administration for the treatment of advanced colon, lung, and breast cancer, and glioblastoma (a type of brain cancer). Bevacizumab is also approved for the treatment of advanced kidney cancer in combination with interferon. Bevacizumab use in combination with everolimus in this study of advanced kidney cancer should be considered experimental.

Everolimus (also called Afinitor®) is a drug that has been shown to stop the growth of cancer cells in some patients. Everolimus has been approved by the FDA for the treatment of advanced kidney cancer that has not responded to at least one prior treatment.

How many people will take part in the study?

About 700 people will take part in this study.

What will happen if I take part in this research study?

Before you begin the study ...

You will need to have the following exams, tests or procedures to find out if you can be in the study. These exams, tests or procedures are part of regular cancer care and may be done even if you do not join the study. If you have had some of these tests recently, they may not need to be repeated. This will be up to your study doctor.

- Medical history and physical examination
- Blood and urine tests
- Hepatitis B and C tests (you may receive hepatitis B therapy to prevent reactivation from a "sleeping" state if you have evidence of prior hepatitis B infection)
- Pregnancy test if you are a woman of child bearing age
- CT or MRI scans of the chest, abdomen and brain.

If the exams, tests and procedures show that you can be in the study, and you choose to take part, you will be "randomized" into one of the study groups described below. Randomization means that you are put into a group by chance. A computer program will place you in one of the study groups. Neither you nor your doctor can choose the group you will be in. You will have an equal chance of being placed in either group.

Group 1 (often called "Arm A"): everolimus and placebo (salt water)

Group 2 (often called "Arm B"): everolimus and bevacizumab (the experimental drug).

The placebo is given in Arm A so that patients in both groups receive similar-looking treatments. That means all patients take everolimus every day and receive an infusion every two weeks that will contain either bevacizumab or placebo. This way, neither you nor your doctor can tell which group or arm you are in, and that makes the study more objective. In case of an emergency or if your cancer worsens, your doctor may be able to find out whether you are getting the bevacizumab or the placebo.

During the study ...

Each treatment group will receive treatment over 4-week periods. A 4-week period is called "a cycle" and will involve two office visits. Regardless of which treatment group you are in, you will receive treatment on the following schedule:

	Week 1	Week 2	Week 3	Week 4
Everolimus	1 or 2 pills every day	1 or 2 pills every day	1 or 2 pills every day	1 or 2 pills every day
Bevacizumab/placebo	IV infusion	Rest	IV infusion	Rest

You will be asked to take 1 or 2 pills of everolimus by mouth every day on an empty stomach or with a light, fat-free meal. You will be asked to record the day, number of pills taken and time of each dose of everolimus on a medication calendar. You will be asked to bring the calendar with you to clinic visits every two weeks. Bevacizumab or placebo will be given intravenously (through a vein in your arm) every 2 weeks at the time of the office visit. The first intravenous infusion will be over 90 minutes but subsequent infusions may be shortened to 60 or 30 minutes if you tolerate them well.

Tests and Procedures:

During the time that you are receiving the study treatment, you will need the following tests and procedures. They are part of regular cancer care.

- CT or MRI scans every 8 weeks to monitor your disease

You will need these tests and procedures that are part of regular cancer care. They are being done more often because you are in this study.

- Medical history, physical examinations, blood and urine tests every 2 weeks for 6 months and then every 4 weeks

When I am finished taking the treatment...

After you have finished receiving the study treatment, you will be asked to have physical examinations and scans to monitor your disease for up to 5 ½ years after you started the study.

How long will I be in the study?

You will be asked to take the study treatment for as long as your kidney cancer is responding to, or is stabilized by the drugs and you do not have any severe side effects from the drugs. If your cancer worsens, you will stop study treatment. If your cancer is not growing but you develop severe side effects from the drugs, your doctor may ask you to stop taking one or both study drugs. After you are finished taking both study drugs, the study doctor will ask you to visit the office for periodic checkups for at least 5½ years after you started the study.

Approval Date: 11/7/12 to 10/1/12
 Assurance #: FWA00003582

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 the study drugs 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.

What side effects or risks can I expect from being in the study?

You may have side effects while on the study. 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 happen. Side effects may be mild or very serious. Your health care team may give you medicines to help lessen side effects. Many side effects go away soon after you stop taking the drugs. In some cases, side effects can be serious, long lasting, or may never go away. There also is a very small risk of death.

You should talk to your study doctor about any side effects that you have while taking part in the study.

Risks and side effects related to the drugs include:

Group 1 (Everolimus and placebo)

Likely:

- Soreness in the mouth or throat
- High blood cholesterol or triglyceride levels
- Skin rash
- Tiredness (fatigue)
- Headache
- Cough
- Nausea or vomiting
- Infection
- Dry skin
- Diarrhea

Less Likely:

- Decreased appetite
- Low blood levels of phosphate, magnesium, sodium or calcium. If severe, these low levels can lead to abnormal function of nerves, muscles or brain
- Small decrease in platelets that could lead to bleeding

- High blood sugar levels or the development of diabetes, which may require treatment
- Severe hepatitis (liver infection) in patients who are carriers of the hepatitis virus. If you are a carrier of hepatitis, you will be given an antibiotic medicine to prevent the virus from becoming active.

Rare but serious:

- Inflammation of the lungs, which may result in shortness of breath. If you develop new lung problems, including cough, difficulty breathing, or fever, you should stop taking everolimus and contact your doctor immediately.
- Sudden death

Group 2 (Everolimus and bevacizumab)

Likely:

- Soreness in the mouth or throat
- Skin rash
- Headache
- Nausea or vomiting
- Dry skin
- High blood pressure
- Diarrhea
- High blood cholesterol or triglyceride levels
- Tiredness (fatigue)
- Cough
- Infection

Less Likely:

- Decreased appetite
- Small decrease in platelets that could lead to bleeding
- High blood sugar levels or the development of diabetes, which may require treatment
- Severe hepatitis (liver infection) in patients who are carriers of the hepatitis virus. If you are a carrier of hepatitis, you will be given an antibiotic medicine to prevent the virus from becoming active.
- Heartburn
- Weight loss
- Aches in various body parts including the abdomen, chest, joints, or muscles
- Shortness of breath
- Hoarseness
- Stuffy or runny nose
- Itching
- Hives
- Dizziness or fainting

- Low white blood cell count (neutrophils) that may lead to serious or fatal infections
- Fever with low levels of white blood cells that may indicate infection
- Low blood levels of phosphate, magnesium, sodium or calcium. If severe, these low levels can lead to abnormal function of nerves, muscles or brain
- Lowered red blood cell count that may cause tiredness or shortness of breath (if the counts get too low, you may need a transfusion)
- Leakage of protein in the urine, which may be a sign of kidney damage and can lead to kidney failure
- Blood in the urine
- Bleeding the stomach or intestine
- Abnormal liver function as seen on a blood test: ALT, AST, Alkaline phosphatase, bilirubin
- Abnormal blood test of bone health: alkaline phosphatase
- Mild to moderate bleeding in the tumor, stomach, intestines or other parts of the body
- Vaginal bleeding
- Minor nosebleed
- 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.
- Infection in soft tissues around the rectum. In rare cases, the infections can be serious or life-threatening.
- Irritation of the bowels
- Constipation
- Blockage of the stomach or intestine
- Blockage of the intestine and severe constipation
- Abnormal heart rhythm, which may be serious
- Delayed or poor wound healing after surgery
- Allergic reactions
- Reactions associated with infusion of the bevacizumab such as chills, fever or nausea, that can be severe
- Damage to the jawbone that may be painful and might require surgery to remove the damaged area. Rarely, the damage could be permanent. This might be more likely to occur if you also take a medicine in the group called "bisphosphonates."

Rare but serious:

- Heart attack, decreased heart function, or heart failure
- Chest pain (angina)
- Stroke
- Transient ischemic attack (mini-stroke)
- Severe or life-threatening internal or external uncontrolled bleeding
- Serious or fatal bleeding from the tumor, brain, gut or the lungs
- Severe allergic reaction that can result in difficulty breathing or drop in blood pressure

- 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.
- Perforations in other places in the body, including the nose
- Fistula: An abnormal connection between organs in the body
- Stomach or other gastrointestinal ulcers
- Kidney damage or kidney failure
- Clots in small blood vessels in the kidney that can cause complications, some of which are serious. These include abnormal destruction of red blood cells or cells that help to clot blood, and kidney failure.
- Reversible Posterior Leukoencephalopathy Syndrome (RPLS) or similar leukoencephalopathy syndrome: RPLS is a medical condition related to leakiness of blood vessels in the brain and can cause confusion, blindness or vision changes, seizure, and other symptoms, as well as changes in brain scans. This condition is usually reversible, but in rare cases, it is potentially life-threatening or fatal and may have long-term effects on brain function.
- Inflammation of the lungs, which may result in shortness of breath. If you develop new lung problems, including cough, difficulty breathing, or fever, you should stop taking everolimus and contact your doctor immediately.
- Sudden death

Reproductive risks: Bevacizumab may cause loss of function of the ovaries that can lead to menopause. The effect of this on fertility is unknown.

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 and for 6 months after you complete study treatment. 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.

For more information about risks and side effects, ask your study doctor.

Are there benefits to taking part in the study?

Taking part in this study may or may not make your health better. While doctors hope the combination of everolimus and bevacizumab will be more useful against kidney cancer compared to the usual treatment, there is no proof of this yet. We do know that the information from this study will help doctors learn more about the study drugs as a treatment for kidney cancer. This information could help future cancer patients.

What other choices do I have if I do not take part in this study?

Your other choices may include:

- Getting treatment or care for your cancer without being in a study. This may include other commercially available drugs for the treatment of kidney cancer.
- Taking part in another study
- Getting no treatment except comfort care, also called palliative care. 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.

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

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.

Organizations that may look at and/or copy your medical records for research, quality assurance, and data analysis include:

- Cancer and Leukemia Group B (CALGB)
- The National Cancer Institute (NCI) and other government agencies, like the Food and Drug Administration (FDA), involved in keeping research safe for people
- Genentech, Inc. (the makers of bevacizumab/placebo.)
- Novartis (the makers of everolimus; Novartis is providing financial support for some components of this study.)

If your doctor is participating in this study through the Cancer Trials Support Unit (the CTSU is a clinical trials mechanism sponsored by the NCI to provide greater access to phase III trials), a record of your progress will also be kept by the CTSU. If your record is used or disseminated for such purposes, it will be done under conditions that will protect your privacy to the fullest extent possible consistent with laws relating to public disclosure of information and the law-enforcement responsibilities of the agency.

The CALGB has received a Certificate of Confidentiality from the federal government, which will help us to protect your privacy. The Certificate protects against the involuntary release of information about you collected during the course of the study. The researchers involved in this project may not be forced to identify you in any legal proceedings (criminal, civil, administrative, or legislative) at the federal, state, or local level. However, some information may be required by the Federal Food, Drug, and Cosmetic Act, the U.S. Department of Health and Human Services, or for purposes of program review or audit. Also, you may choose to voluntarily disclose the protected information under certain circumstances. For example, if you or your guardian requests the release of information about you in writing (through, for example,

a written request to release medical records to an insurance company), the Certificate does not protect against that voluntary disclosure.

What are the costs of taking part in this study?

You and/or your health plan/ insurance company will need to pay for some or all of the costs of treating your cancer in this study. Some health plans will not pay these costs for people taking part in studies. Check with your health plan or insurance company to find out what they will pay for. Taking part in this study may or may not cost your insurance company more than the cost of getting regular cancer treatment.

There will be no charge to you for the study drug, bevacizumab/placebo. However, you or your health plan may need to pay for costs of the supplies and personnel who give you the drug. You or your health plan will be billed for the cost of the everolimus.

The National Cancer Institute (NCI) will supply the study drug, bevacizumab/placebo at no charge while you take part in this study. The NCI does not cover the cost of getting bevacizumab/placebo the ready (making the IV) and giving it to you, so you or your insurance company may have to pay for this.

Even though it probably won't happen, it is possible that the manufacturer may not continue to provide the bevacizumab/placebo to the NCI for some reason. If this would occur, other possible options are:

- You might be able to get the bevacizumab/placebo from the manufacturer or your pharmacy but you or your insurance company may have to pay for it.
- If there is no bevacizumab/placebo available at all, no one will be able to get more and the study would close.

If a problem with getting bevacizumab/placebo occurs, your study doctor will talk to you about these options.

You will not be paid for taking part in this study.

For more information on clinical trials and insurance coverage, you can visit the National Cancer Institute's Web site at <http://cancer.gov/clinicaltrials/understanding/insurance-coverage>. You can print a copy of the "Clinical Trials and Insurance Coverage" information from this Web site.

Another way to get the information is to call 1-800-4-CANCER (1-800-422-6237) and ask them to send you a free copy.

What happens if I am injured because I took part in this study?

It is important that you tell your study doctor, _____ [investigator's name(s)], if you feel that you have been injured because of taking part in this study. You can tell the doctor in person or call him/her at _____ [telephone number].

You will get medical treatment if you are injured as a result of taking part in this study. You and/or your health plan will be charged for this treatment. The study will not pay for medical treatment.

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. You can still get your medical care from our institution.

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.

A Data Safety Monitoring Board will be regularly meeting to monitor safety and other data related to this study. The Board members may receive confidential patient information, but they will not receive your name or other information that would allow them to identify you by name.

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.

Who can answer my questions about the study?

You can talk to your study doctor about any questions or concerns you have about this study. Contact your study doctor _____ [name(s)] at _____ [telephone number].

For questions about your rights while taking part in this study, call the Kansas City Clinical Oncology Program Institutional Review Board (a group of people who review the research to protect your rights) at 913-948-5588.

RELATED STUDIES

Please note: The following section of the informed consent form is about additional research studies that are being done with people who are taking part in the main study. You may take part in these additional studies if you want to. You can still be a part of the main study even if you say "no" to taking part in any of these additional studies.

The results of these research studies will not be provided to you or your doctor, nor will the results have any effect on your treatment. It is unlikely that what we learn from these studies will have a direct benefit to you. However, the information learned from these studies may benefit other patients in the future.

The results from these studies may be published, but individual patients will not be identified in these publications.

There will be no charge to you for participating in these research studies. Your sample and information will only be used for research and will not be sold. The research done with your sample may help to develop new products in the future.

The greatest risk to you is the release of information from your health records. We will do our best to make sure that your personal information will be kept private. The chance that this information will be given to someone inappropriate is very small.

In the future, people who do research may need to know more about your health. While the Cancer and Leukemia Group B may give them reports about your health, it will not give them your name, address, phone number, or any other information that will let the researchers know who you are.

If you decide now to participate and then change your mind at any time about participating in these studies for any reason, you should contact your institution and let them know that you do not want the researchers to use your sample. The sample will then no longer be used for research. It will either be destroyed or returned to your institution for storage. The sample will also be returned to your institution upon request if needed for any other medical or legal reasons.

You can say "yes" or "no" to each of the following studies. Please mark your choice for each study. No matter what you decide to do, it will not affect your care.

Studies on tissue, blood, and urine:

As part of this research study, we would like to request your permission to study cells from your tumor. The tumor samples were previously obtained when your disease was first diagnosed or when you had surgery. No additional biopsy will be required. These tumor samples will be used in a laboratory to investigate kidney cancer. This will include looking at the cells in your tumor tissue to detect changes in genetic material that may have occurred. These types of changes are not usually passed down from generation to generation and are not considered to be inherited.

The researchers would like to keep some of the tissue that was left over for future research. If you agree, this tissue will be kept and may be used in research to learn more about cancer and other diseases. Please read the information sheet called "How is Tissue Used for Research" to learn more about tissue research. [This NCI information sheet is available at <http://www.cancerdiagnosis.nci.nih.gov/specimens/patient.html>]

In addition, the researchers would also like to collect additional samples of your blood and urine. The researchers would like to investigate whether substances in your blood (sometimes called tumor markers) are related to the way that your body responds or doesn't respond to the chemotherapy you receive in this trial. Approximately 4 teaspoons of additional blood and 1 teaspoon of urine would be collected at the beginning of the study and then about 2 teaspoons of blood and 1 teaspoon of urine would be collected every 8 weeks while you are receiving study treatment.

1) I agree that my specimens may be used for the research described above.

_____ Yes _____ No Initials _____

Genetic studies on blood cells:

Researchers at special CALGB laboratories wish to determine whether there is a relationship between genes and response to treatment and treatment outcomes, and side effects. No research studies will be performed that can knowingly reveal genetic information that might be of risk to you or to your family.

In order to study genes, the DNA must be removed from your blood sample. DNA is the substance that makes up your genes. Genes are the units of inheritance that are passed down from generation to generation. They are responsible for eye color, hair color, blood type, and hundreds of other traits.

New scientific tools will now allow researchers to look at your whole DNA, not just one part or one gene. This kind of research can provide information to researchers about the development of cancer and response to treatment. It can also provide information about a variety of other conditions and diseases, including heart disease, diabetes and Alzheimer's disease.

Because the information gained in these genetic studies can be very useful to the research community, the National Institutes of Health (NIH) has requested that these data be placed in a central database housed at the NIH. The goal is to speed up the process for discovery of new treatments, prevention and diagnosis of disease. Researchers must get approval from the NIH before they can access the research results and health-related information from your specimen. All information will be coded with a unique number. Researchers will not have access to your identity; they will only see coded information.

Participation in this additional research study would require an additional sample of blood (about 2 teaspoons).

The greatest risk to you is the release of information from your health records. We will do our best to make sure that your personal information will be kept private. The chance that this information will be given to someone is very small. Below are some of the steps we have taken to protect your privacy and confidentiality:

- Blood samples will be stored at a CALGB laboratory. The CALGB Statistical Center will perform all analyses of data and store all study results. Your blood sample will not be stored with your name on it. Instead, it will be labeled with a special CALGB identification number. The only location where your name and special identification number will be stored together is at the CALGB Statistical Center. The greatest effort will be made to see that all personal information that can identify you is kept under conditions that protect your privacy.
- Information about your participation in this study and results of any tests performed on your sample will be kept only at the CALGB Statistical Center. This information will not be made available to your doctors or to individual researchers at CALGB. Test results from this study will not be put in your medical records. All study information, including

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test results, is stored under conditions that limit access in order to protect the privacy of the people participating in the study.

- The Cancer and Leukemia Group B has received a Certificate of Confidentiality from the federal government, which will help us to protect your privacy. More information about the Certificate can be found in the paragraph "Will my medical information be kept private?"
- A federal law (Genetic Information Non-Discrimination Act, GINA) will help lower the risk from health insurance or employment discrimination on the basis of genetic information. The federal law does not include other types of misuse by life insurance, long-term care or disability insurance. If you want to learn more about the GINA Law, which went into effect in 2009, you can find information about it on the internet or ask the study staff. In addition to the federal law, some states have laws that also help protect against genetic discrimination.

While we believe that the risks to you and your family are very low, we cannot tell you exactly what all of the risks are from taking part in genetic research studies. Your privacy and confidentiality will be protected to the fullest extent possible.

You have the right to receive the planned therapy on this study without participating in the proposed research study on your blood sample. Please read the sentence below and think about your choice. After reading the sentence, please mark your choice, sign your name, and provide the current date. **No matter what you decide to do, it will not affect your care.**

2) I agree that my blood may be used for the genetic research studies described above.

_____ Yes _____ No Initials _____

Storage of your specimens:

The researchers would also like to store any portion of the tissue, blood and urine that is not used up by the related studies described above. These samples may be stored indefinitely. You can still take part in the treatment study, and the research study described above without giving your consent for your samples to be stored.

It is not possible for you or the CALGB to know what studies of cancer may be appropriate in the future. We ask that you give permission in advance for other studies to be performed using the blood without being re-contacted to give permission for each test.

3) My specimens may be kept for future unknown use in research to learn about, prevent, treat, or cure cancer.

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_____ Yes _____ No Participant _____ Date _____

4) My specimens may be kept for research about other health problems (for example: causes of diabetes, Alzheimer's disease and heart disease.

_____ Yes _____ No Participant _____ Date _____

5) My doctor or someone from CALGB may contact me in the future to ask me to take part in more research.

_____ Yes _____ No Participant _____ Date _____

Where can I get more information?

You may call the National Cancer Institute's Cancer Information Service at:

1-800-4-CANCER (1-800-422-6237) or TTY: 1-800-332-8615

You may also visit the NCI Web site at <http://cancer.gov/>

- For NCI's clinical trials information, go to: <http://cancer.gov/clinicaltrials/>
- For NCI's general information about cancer, go to <http://cancer.gov/cancerinfo/>

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

Release

By signing this form you authorize KCCOP to access and obtain information that is required for the study. This may include your medical records, labs, radiologic films and reports and pathology specimens. This authorization to disclose your medical records shall not expire, even upon death, unless specifically revoked in writing by you.

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

Signature

I have been given a copy of all 15 pages of this form. I have read it or it has been read to me. I understand the information and have had my questions answered. I agree to take part in this study.

Participant _____

Date _____

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Signature of Person Obtaining Consent _____

Date _____

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