INSTITUTE: National Cancer Institute

STUDY NUMBER: 07-C-0058 PRINCIPAL INVESTIGATOR: Christina M. Annunziata, MD, PhD

STUDY TITLE: A Phase II Study of Sorafenib and Bevacizumab in Epithelial Ovarian, Fallopian, and Peritoneal Cancer

Continuing Review Approved by the IRB on 02/10/14
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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.

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 cancer that has not responded to standard treatments or for which no standard treatments have been identified.

Why is this study being done?
The purpose of this study is to determine the effectiveness of the combination of two anti-cancer drugs, sorafenib and bevacizumab, and to find out what effects, good and/or bad, these drugs may have on you and your cancer. This study will also look at how the drugs may affect the cancer by measuring amounts of different proteins in small biopsy samples of your tumor taken before you start treatment and after different times of treatment. Optional biopsies will be performed 6 weeks after treatment begins and at the completion of therapy.

Using these drugs together is experimental. These drugs work by targeting the blood vessels that allow tumors to grow. Our theory is that by combining two drugs that target blood vessels, we can more effectively block the formation of blood vessels that feed tumors. On the phase 1 trial of this combination that is also being performed by our group, 6 of 14 ovarian cancer patients have had documented tumor shrinkage. Both of these drugs have been approved by the FDA for use in other cancers but have not been approved for ovarian cancer. However, we have been studying the combination and believe it to be of potential value in ovarian cancer.

How many people will take part in the study?
Between 74-78 people will take part in this study. The study will be divided into 2 groups. One group will enroll patients who have received bevacizumab in the past and the other group will enroll patients who have not had treatment with bevacizumab. Patients in both groups will receive the same treatment. There will be no difference in dose or scheduling of the drugs between groups.

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 them recently, they may not need to be repeated. This will be up to your study doctor.

Blood tests: measurements of how your liver, kidneys and blood clotting work, measurement of your white blood cells, red blood cells and platelets, your blood sugar and blood electrolytes. Since ovarian, fallopian, and peritoneal cancer may make the protein CA-125, we ask that you have your CA-125 level checked as well. These will be done during your first visit to NIH as an outpatient.

- Urinalysis.
- CT Scan (or similar imaging test) to assess where your cancer may be
- Tissue block (pathology slides from biopsy or surgery) of the cancer to submit to the study doctor or a member of the research team

If the initial exams, tests, and procedures show that you are eligible to be in the study, you will have the following tests and procedures performed during your participation. They are part of regular cancer care.

- Clinic visit to ask how you are feeling and to evaluate you with a physical examination every 4 weeks while you remain on the study.
- Blood tests: measurements of how your liver, kidneys and blood clotting work, measurement of your white blood cells, red blood cells and platelets, your blood sugar and blood electrolytes will be done every 2 weeks for one month then every 4 weeks. A CA-125 measurement will also be done every 4 weeks.
- Urinalysis. This will be done every 2 weeks prior to receiving the bevacizumab infusion.

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

- Computed tomography (CT) or other imaging test such as ultrasound or MRI that can detect your tumor will be done every 8 weeks while you are on the study. This is done so that any benefit of the study can be determined and if your cancer is not responding to the study drugs, the study team can advise you of this and help you to move to a different treatment program (discussed further below).
- Twice weekly blood pressure measurements (for the first 8 weeks). You will be given a blood pressure cuff to use at home and we will ask you to record your blood pressure measurements and report them to us.

You will need these exams and procedures that are either being tested in this study or being done to see how the study is affecting your body.

- Research blood samples (5 tubes or about 8 teaspoons) also will be taken at every 4 week clinic visit. Note: Research blood samples will no longer be collected each cycle after 04/11/14.
- PET (Positron Emission Tomography). This will be done before you start study drugs, on the third day after you start taking the medications, and 6 weeks into treatment. A PET scan is used by doctors to look at how different parts of the body utilize a sugar-nutrient called glucose. The test works by injecting into your body a small amount of sugar labeled with a tiny amount of radioactivity that the PET imaging machine can detect. You are put in a chamber that looks like a tube while the machine performs the test. Cancer cells tend to consume sugar nutrients faster than normal cells and may pick up more signal than the normal cells. This test is being done to determine if there is any change in your tumor's activity level with the addition of these two drugs.

- Dynamic contrast-enhanced MRI or DCE-MRI. This will be done before you start study drugs, on the third day after you start taking the medications, and 6 weeks into treatment. This is a test that does not use any radiation. Instead, it uses magnetic energy to examining the inside of your body with a special non-radioactive dye, so that doctors can measure blood flow into the tumor. You are put in a chamber that looks like a tube while the machine performs the test. This test is being done to determine if there is any change in your tumor's blood flow with the addition of these two drugs.
- Biopsy of your tumor: This will be done before you start a study drug. In addition, there are 2 optional tumor biopsies 1) at 6 weeks into treatment and 2) if you are taken off this study because your tumor progresses or because of side effects of the treatment, These biopsies are not required but may help us understand these drugs work on cancer cells. The biopsy will be performed by an experienced, highly skilled interventional radiologist. The procedure is performed with a small needle directed by either ultrasound or CT scan This biopsy will be used for research purposes, not for diagnostic purposes. You will not be allowed to undergo such a procedure if there is significant risk of harm from this procedure.
- Quality of Life questionnaire: As part of this study, you will answer a questionnaire that asks you questions about your symptoms and how you are feeling about the study and your life. The questionnaire will be given to you just before you start the treatment and then every 8 weeks and when you come off study.

The tumor biopsy, capture of a small piece of your cancer, is a necessary part of this trial and is done for research purposes. No formal pathology review of these biopsy specimens will be done routinely. Trained personnel will perform the biopsy keeping your safety in mind. All efforts will be made to minimize risks and discomfort involved with these biopsies. If any complication occurs, we will provide the medical care as appropriate. If, upon attempting the first biopsy, no tissue can be obtained or it has caused you harm, subsequent biopsies will not be done. If for any reason the biopsies cannot be done safely, you may still receive the study drugs.

Biopsies will be done either using a small bore needle under CT guidance (looking at the needle location by CT scan). The CT scan helps the specialized radiologist know that the needle has been placed into the tumor mass. The needle biopsy is done by inserting a needle through the skin into the tumor mass. Typical risks of both procedures include, but are not limited to bleeding, infection, pain, and scarring. You will be counseled in more detail about the procedure and you will be asked to sign a separate consent that will describe the procedure and its associated risks at that time. Your safety is the most important thing at all times.

When I am finished taking sorafenib and bevacizumab?
Your participation in this study will continue until either you or your study doctor decides that this medication is not beneficial to you or you wish you stop. Your participation is voluntary; so you may stop taking sorafenib and bevacizumab at any time. We ask that you speak to your study doctor if you are thinking about this and before you stop taking the medications. Your study doctor will be monitoring you and your cancer while you are taking sorafenib and bevacizumab. If your cancer is worsening, then the study doctor will suggest that you stop the experimental therapy and s/he will discuss other options with you. Also, if you are experiencing effects from the therapy which are dangerous to your health or too difficult for you to tolerate, you and the study team may decide that you should stop the study drugs. At the end of the study, no additional testing will be required unless you experience side effects from the study medications that we need to follow. We will ask you to consider an optional biopsy that would be performed the same way as the previous biopsies, again performed for only research purposes. This biopsy is not a required procedure and you are free to choose not to have it performed.

If you are taken off of sorafenib for any reason including toxicity of the drug, you may continue on study with treatment with bevacizumab alone, if there is not evidence to suggest that your tumor is resistant to bevacizumab. You, your home physician, and your study doctor will discuss the option of continuing on bevacizumab alone versus other treatment options.

You will be followed 4 weeks after stopping treatment with a phone call. If additional lab tests need to be done, you may be asked to return to the clinic for a follow-up visit.

Study Chart
The treatment is given over 28-day periods of time called cycles. The 28 day treatment cycle will be repeated as long as you are tolerating the medication and your cancer is either steady or getting better. Each cycle is numbered in consecutive order. The chart below shows what will happen to you during Cycles 1 and 2 and future cycles. The left-hand column shows the day in the cycle and the right-hand column tells you what will happen on that day. This schedule indicates what will happen to you after you sign consent and start the study. You will be asked to record your usage of the study medication in a study diary. This must be done each day for each dose. You will be provided with a new diary every month.

Sorafenib is a pill that is taken by mouth twice daily for 5 days out of every week; we will tell you which five days to take the pills. Sorafenib should be taken on an empty stomach with 250 cc of water (large glass). Bevacizumab is injected into your veins once every two weeks. Initially it will be given to you over 90 minutes, and if you have no side effects from the infusion, we will gradually shorten the administration time to 30 minutes.

Cycle 1 and 2

Day	What to do and what will happen to you
Before starting study	Sign informed consent. Fill out Quality of Life questionnaire Get routine blood tests. Check-in to the outpatient clinic. Have a history of how you feel taken and undergo a physical examination by a Health Care Provider PET, DCE-MRI, and tumor biopsy will be done after signing informed consent but before starting the study drugs.
Cycle 1 Day 1	1)Begin taking sorafenib by mouth twice a day for 5 out of 7 days a week (Monday-Friday). You will continue to take sorafenib for 5 out of 7 days for the next 4 weeks, which will complete cycle 1 2)Blood draws for research will be obtained on days 1 and 3 3)Receive bevacizumab by vein on the same day sorafenib starts. This will occur every 2 weeks. 4) Begin recording pill consumption daily and twice weekly blood pressure. Record this is in your study diary.
Cycle 1 Day 3/4	PET and DCE-MRI will be done. Take your sorafenib on these tests days.
Cycle 1 Day 15	Routine blood work and urine testing (for protein) at the day hospital. If your blood and urine tests indicate everything is safe, you will receive your dose of bevacizumab by vein.
Cycle 2 Day 1	Return to the outpatient clinic to see your Health Care Provider. Have a history of how you feel taken and undergo a physical examination. Routine blood work and urine testing for protein. Research bloods will be collected. If your exam and blood and urine tests indicate everything is safe within limits, you will receive your dose of bevacizumab by vein. Continue sorafenib twice daily 5 out of 7 days for the next 4 weeks.
Cycle 2 Day 15/16	Routine blood work and urine testing for protein Research bloods will be collected. PET, DCE-MRI, and tumor biopsy (optional) will be done. Take your sorafenib on these days. If your exam and blood and urine tests indicate everything is safe within limits, you will receive your dose of bevacizumab by vein
All other Cycles Day 1	Return to the outpatient clinic to see your Health Care Provider. Have a history of how you feel taken and undergo a physical examination. Routine blood work and urine testing for protein. Start next cycle of sorafenib by mouth twice a day days 1-5 of 7.

	If your exam and blood and urine tests indicate everything is safe within limits, you will receive your next dose of bevacizumab by vein in the day hospital.
All cycles Day 15	Provide a urine sample for testing and have your blood pressure checked. Receive bevacizumab by vein in the day hospital.
Every other cycle	You will have CT scan or other imaging every other cycle (every 8 weeks) to determine how your tumor is being affected by the therapy. This result will be used to guide continuation of therapy. Fill out Quality of Life questionnaire

Can I stop being in the study?

Yes. You can decide to stop at any time. Tell the study team if you are thinking about stopping or decide to stop. They will help you to stop safely and determine if a final follow-up visit is needed.

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 Bayer Health Care Corporation and Onyx Pharmaceuticals 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 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.

The study team may stop you from taking part in this study at any time if they believe 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?

If you choose to take part in this study, there is a risk that:

- You may lose time at work or home and spend more time in the hospital or doctor's office than usual
- You may be asked sensitive or private questions which you normally do not discuss

The bevacizumab and sorafenib used in this study may affect how different parts of your body work such as your liver, kidneys, heart, and blood. The study doctor will be testing your blood and will let you know if changes occur that may affect your health.

There is also a risk that you could have side effects from the study drugs/study approach.

Here are important points about side effects:

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

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

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

The tables below show the most common and the most serious side effects that researchers know about. There might be other side effects that researchers do not yet know about. If important new side effects are found, the study doctor will discuss these with you.

Risks and side effects related to sorafenib include those which are:

Likely:

- Belly pain
- Diarrhea
- Nausea or the urge to vomit
- Fatigue or tiredness
- Increased blood level of a liver enzyme (ALT/SGPT)
- Increased blood level of a liver or bone enzyme (alkaline phosphatase)
- Increased blood level of a liver enzyme (AST/SGOT)
- Increased blood level of a liver pigment (bilirubin) often a sign of liver problems
- Increased blood level of creatinine (a substance normally eliminated by the kidneys into the urine)
- Increased INR (measure of the ability of the blood to clot properly) which increases the risk of bleeding
- Increased blood level of fat-digesting enzyme (lipase)
- Decreased number of a type of white blood cell (lymphocyte)

- Decreased number of a type of blood cell that helps to clot blood (platelet)
- Increased blood level of a digestive enzyme (amylase)
- Weight loss
- Decrease in the total number of white blood cells (leukocytes)
- Loss of appetite
- Increased blood sugar level
- Decreased levels of a blood protein called albumin
- Decreased blood level of calcium
- Decreased blood level of sodium
- Decreased blood level of phosphate
- Hair loss
- Swelling and redness of the skin on the palms of the hands and soles of the feet
- Skin rash with the presence of macules (flat discolored area) and papules (raised bump)

Less Likely:

- Lack of enough red blood cells (anemia)
- Fever associated with dangerously low levels of a type of white blood cell (neutrophils)
- Irritation or sores in the lining of the anus
- Fluid collection in the abdomen
- Constipation
- Bleeding in some organ(s) of the digestive tract
- Irritation or sores in the lining of the mouth
- Irritation or sores in the lining of the rectum
- Irritation or sores in the lining of the small bowel
- Vomiting
- Swelling of the arms and/or legs
- Fever
- Chest pain not heart-related
- Infection
- Test that shows a problem in blood clotting
- Increased blood level of cholesterol
- Increased blood level of a liver enzyme (GGT)
- Decreased blood level of carbon dioxide
- Decreased number of a type of white blood cell (neutrophil/granulocyte)
- Increased blood level of calcium
- Increased blood level of potassium
- Increased blood level of sodium

- Increased blood level of uric acid, a waste material from food digestion
- Decreased blood sugar level
- Decreased blood level of potassium
- Joint pain
- Back pain
- Bone pain
- Muscle spasms
- Muscle pain
- Leg and/or arm pain
- Dizziness (or sensation of lightheadedness, unsteadiness, or giddiness)
- Headache or head pain
- Inflammation (swelling and redness) or degeneration of the peripheral nerves (those nerves outside of brain and spinal cord) causing numbness, tingling, burning
- Difficulty sleeping or falling asleep
- Sudden decrease of kidney function
- Blood in the urine
- Bleeding in the kidney
- Presence of blood in a fallopian tube (tube between ovary to uterus [womb])
- Bleeding in the ovary
- Bleeding in the prostate
- Bleeding in the spermatic cord (a structure resembling a cord that suspends the testis within the scrotum and contains the vas deferens [the tube that carries sperm] and other vessels and nerves)
- Bleeding in the testis
- Bleeding in the uterus (womb)
- Bleeding in the vagina
- Bleeding from the lungs
- Cough
- Shortness of breath
- Nose bleed
- Irritation or sores in the lining of the voice box
- Irritation or sores in the lining of the throat
- Irritation or sores in the lining of the windpipe
- Voice change
- Dry skin
- Itching
- High blood pressure

- Formation of a blood clot that plugs the blood vessel; blood clots may break loose and travel to another place, such as the lung

Rare but Serious:

- Collection of signs and symptoms that indicate sudden heart disease in which the heart does not get enough oxygen. Sudden symptoms such as chest pain, shortness of breath, or fainting could indicate heart disease and should be reported right away. Signs such as abnormal EKG and blood tests can confirm damage to the heart.
- Decrease in heart's ability to pump blood during the "active" phase of the heartbeat (systole)
- Heart attack caused by a blockage or decreased blood supply to the heart
- Gastrointestinal perforation : A tear or hole in the stomach or gut that can lead to serious complications and may require surgery to repair
- Serious, life-threatening allergic reaction requiring immediate medical treatment by your doctor. The reaction may include extremely low blood pressure, swelling of the throat, difficulty breathing, and loss of consciousness.
- Bleeding in the brain
- Abnormal changes in the brain that can cause a collection of symptoms including headache, confusion, seizures, and vision loss associated with MRI imaging findings (RPLS)
- Severe reaction of the skin and gut lining that may include rash and shedding or death of tissue
- Potentially life-threatening condition affecting less than 10% of the skin in which cell death causes the epidermis (outer layer) to separate from the dermis (middle layer)

Risks and side effects related to bevacizumab include those which are:

COMMON, SOME MAY BE SERIOUS In 100 people receiving bevacizumab, more than 20 and up to 100 may have:
• High blood pressure which may cause headache or blurred vision

OCCASIONAL, SOME MAY BE SERIOUS In 100 people receiving bevacizumab, from 4 to 20 may have:
• Anemia which may require blood transfusion • Low white cell count that may increase the risk of infection • Infection, including collection of pus in the belly or rectum • Abnormal heartbeat which may cause palpitations or fainting • Pain in the belly, rectum, chest, joints, muscles, or tumor • Low appetite, constipation, diarrhea, heartburn, nausea, vomiting, or dehydration

OCCASIONAL, SOME MAY BE SERIOUS In 100 people receiving bevacizumab, from 4 to 20 may have:
• Internal bleeding which may cause black tarry stool, blood in vomit, coughing up of blood, or blood in urine • Bleeding from other sites, including the vagina or nose • Blockage of internal organs which may cause vomiting or inability to pass stool • Sores in mouth • Allergic reaction during or after infusion of bevacizumab which may cause fever, chills, rash, itching, hives, low blood pressure, wheezing, shortness of breath, swelling of the face or throat • Delay in healing of wounds or spontaneous opening of wounds • Weight loss, tiredness, or dizziness • Damage to the jawbone which may cause loss of teeth • Headache • Numbness, tingling, or pain in the fingers or toes • Hoarseness, stuffy nose, or cough • Blood clot in limbs or lungs which may cause swelling, pain, or shortness of breath • Leakage of protein in the urine, which can rarely lead to damage to the kidney

RARE, AND SERIOUS In 100 people receiving bevacizumab, 3 or fewer may have:
• Clots in the arteries, causing stroke (which may cause paralysis or weakness) or heart attack (which may cause chest pain or shortness of breath). This risk is significantly increased in patients who are elderly or with history of diabetes • Heart failure which may cause shortness of breath, swelling of ankles, or tiredness • Bowel perforation (a tear in the bowel) that can cause pain or bleeding and require surgery to repair • A tear or hole (fistula) in internal organs such as the nose, throat, lungs, esophagus, rectum, or vagina. These conditions may cause serious infections or bleeding and require surgery to repair • Flesh-eating bacteria syndrome, an infection in the deep layers of skin • Bleeding in the tumor, brain, belly, or lungs which may cause confusion, blood in stool or coughing up blood • Brain damage which may cause headache, seizure, blindness (also known as Reversible Posterior Leukoencephalopathy Syndrome) • Kidney damage which may require dialysis

Additional Notes on Possible Side Effects for Bevacizumab:

- Risk in children or adolescents: abnormal bone changes which may interfere with growth.
- Risk in pre-menopausal women: more likely to develop menopause when taking bevacizumab.

Bevacizumab is the common name for the commercial drug Avastin. The bevacizumab used in this trial, however, is for use in research studies only and may be made at locations different from those where Avastin is made. Although some differences may exist, bevacizumab for research use and the commercial drug, Avastin, are manufactured by a similar process, meet similar standards for final product testing, and are expected to be very similar in safety and effectiveness.

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

Other risks associated with this study include risks related to radiation exposure associated with the tests you will receive. This research study involves exposure to radiation from PET scans and potentially from CT scans used to guide biopsies for your safety. Please note that this radiation exposure is not necessary for your medical care and is for research purposes only. The total amount of radiation you will receive in this study is from 3 injections (scans or repetitions) of 15 mCi of F-18 FDG (a radioactively labeled form of sugar) in the PET scans and from CT directed biopsies (when needed). The NIH Radiation Safety Committee has reviewed the use of radiation in this research study and has approved this use as involving slightly more than minimal risk and necessary to obtain the research information desired.

Using the standard way of describing radiation dose, from participating in this study, you will receive a total of 14.6 rem to your bladder wall, 10.1 rem to your heart wall, and 7.4 rem to your spleen. All other organs will receive smaller amounts of radiation.

Although each organ will receive a different dose, the amount of radiation exposure you will receive from these procedures is equal to a uniform whole-body exposure of 3.7 rem. This calculated value is known as the "effective dose" and is used to relate the dose received by each organ to a single value. The amount of radiation received in this study is within the dose guideline established by the NIH Radiation Safety Committee for research subjects. The guideline is an effective dose of 5 rem (or 5,000 mrem) received per year[2].

For comparison, the average person in the United States receives a radiation exposure of 0.3 rem (or 300 mrem) per year from natural background sources, such as from the sun, outer space, and from radioactive materials that are found naturally in the earth's air and soil. The dose that you will receive from this research study is about the same amount you would normally receive in

12.3 years from these natural sources. If you would like more information about radiation and examples of exposure levels from other sources, please ask the investigator for a copy of the pamphlet called, *An Introduction to Radiation for NIH Research Subjects*.

The effects of radiation exposure on humans have been studied for over 60 years. In fact, these studies are the most extensive ever done of any potentially harmful agent that could affect humans. In all these studies, no harmful effect to humans has been observed from the levels of radiation you will receive by taking part in this research study. However, scientists disagree on whether radiation doses at these levels are harmful. Even though no effects have been observed, some scientists believe that radiation can be harmful at any dose - even low doses such as those received during this research.

One possible effect that could occur at these doses is a slight increase in the risk of cancer. Please be aware that the natural chance of a person getting a fatal cancer during his/her lifetime is about 1 out of 4 (or 25 percent). The increase in the chance of getting a fatal cancer, as a result of the radiation exposure received from this research study, is 0.15%. Therefore, the total risk of fatal cancer may be estimated to increase from 25 percent to 25.15%. This change in risk is small and cannot be measured directly. Compared with other everyday risks, such as flying in an airplane or driving a car, this increase is considered slight.
Please tell your doctor if you have taken part in other research studies or received any medical care at the NIH or other places/hospitals that used radiation. This way we can make sure that you will not receive too much radiation. Consider x-rays taken in radiology departments, cardiac catheterization, and fluoroscopy as well as nuclear medicine scans in which radioactive materials were injected into your body.

If you are pregnant or breast feeding, you may not participate in this research study. It is best to avoid radiation exposure to unborn or nursing children since they are more sensitive to radiation than adults.

Are there benefits to taking part in the study?
Taking part in this study may or may not make your health better. Bevacizumab by itself has been shown to be useful in the treatment of certain cancers such as colorectal cancer. Sorafenib by itself has been shown to be useful in the treatment of certain cancers such as kidney cancer. While doctors hope sorafenib and bevacizumab will be useful against your cancer, there is no proof of this yet. We do know that the information from this study will help doctors learn more about sorafenib and bevacizumab as a treatment for cancer. This information will 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 standard treatment or care for your cancer in the community
- Taking part in another study
- Both drugs are commercially available, although not approved for your condition, and you can obtain them if your doctor agrees to prescribe them
- Getting no treatment
- Getting comfort care, also called palliative care. This type of care helps reduce pain, tiredness, appetite problems, and other problems caused by 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:

- The National Cancer Institute (NCI) and other government agencies, like the Food and Drug Administration (FDA), involved in keeping research safe for people.

- Qualified representatives from Bayer Health Care Corporation and Onyx Pharmaceuticals who produce sorafenib and are the pharmaceutical sponsors of this trial. Genentech Pharmaceuticals who produce bevacizumab.

A description of this clinical trial will be available on http://www.ClinicalTrials.gov. 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.

What are the costs of taking part in this study?
While you are on study at the National Cancer Institute, we will pay for the medications and treatments associated with the study. We cannot, however, assume the cost of your overall

medical care. Any studies done outside of the NCI may require you or your insurance company to cover the cost of the service.
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 team Nicole Houston, RN (301) 443-6431, and/or Principal Investigator Dr. Christina Annunziata (301) 402-7189 if you feel that you have been injured because of taking part in this study.

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 if you are eligible and choose to participate in another trial.

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.

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 team, Nicole Houston, RN (301) 443-6431, and/or Principal Investigator Dr. Christina Annunziata (301) 402-7189.

For questions about your rights while taking part in this study, call the Clinical Center Patient Representative at (301) 496-2626.

Please note: This 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.

You can say "yes" or "no" to each of the following studies. Please mark your choice for each study.

Optional Studies

We would like to keep some of the specimens and data that are collected for future research. These specimens and data will be identified by a number and not your name. The use of your specimens and data will be 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 decide now that your specimens and data can be kept for research, you can change your mind at any time. Just contact us and let us know that you do not want us to use your specimens and/or data. Then any specimens that remain will be destroyed and your data will not be used for future research.

Benefits

The benefits of research using tissue include learning more about what causes cancer and other diseases, how to prevent them, and how to treat them.

Risks

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 else is very small.

Making Your Choice

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 specimens and data may be kept for use in research to learn about, prevent, or treat cancer.

Yes No Initials _____

2. My specimens and data 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) and/or data in new research not included in this consent.

Yes No Initials _____

4. I agree to have the two optional tumor biopsies for research test at week 6 and at the end of the study as specified in this study. I may decide at any time to change my mind about the biopsies even if I agree to them at this time.

Yes No Initials _____

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.

Conflict of Interest

The National Institutes of Health (NIH) reviews NIH staff researchers at least yearly for conflicts of interest. The following link contains details on this process *http://ethics.od.nih.gov/procedures/COI-Protocol-Review-Guide.pdf*. 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

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 for 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 your study team, Nicole Houston, RN (301) 443-6431 and/or Principal Investigator, Dr. Christina Annunziata (301) 402-7189. If you have any questions about the use of your specimens or data for future research studies, please contact the Office of the Clinical Director, Telephone: (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 FEBRUARY 10, 2014 THROUGH FEBRUARY 9, 2015.

Signature of Investigator _____ Date _____

Print Name _____

Signature of Witness _____ Date _____

Print Name _____