INSTITUTE: National Cancer Institute

STUDY NUMBER: 12-C-0009 PRINCIPAL INVESTIGATOR: A. P. Chen, M.D.

STUDY TITLE: Phase Ib Study of the Combination of Pazopanib, an Oral VEGFR Inhibitor, and ARQ 197 (Tivantinib), an Oral MET Inhibitor, in Patients with Refractory Advanced Solid Tumors

Continuing Review Approved by the IRB on 02/23/2015
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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.

Why is this study being done?

We are studying two drugs in this trial, **pazopanib** and **ARQ 197**. The use of pazopanib and ARQ 197 together is experimental. Pazopanib works by blocking the formation of new blood vessels in tumors, a process called angiogenesis. New blood vessels provide oxygen and nutrients to growing cancers, and blocking this process can cause cancer cells or the supporting blood vessels to stop growing. Pazopanib is approved by the United States Food and Drug

Administration (FDA) for treating patients with renal cell carcinoma. ARQ 197 (tivantinib) is an experimental drug that has shown some effects against tumor cells in the laboratory and in experimental animals. This drug works by blocking a protein called c-MET needed for cancer cells to grow and survive. In laboratory studies, some drugs that block angiogenesis increase the production of c-MET in tumors, which helps cancer cells adapt to not having enough oxygen, so the tumor can keep growing. Blocking both angiogenesis and c-MET with pazopanib and ARQ 197 together may limit cancer cells' ability to survive.

The purpose of this study is to test the safety of the combination of pazopanib and ARQ 197, and find out the doses of these drugs that can be safely given to humans. We are trying to understand how these drugs work in humans. For that, this study will look at how pazopanib and ARQ 197 may affect the levels of certain proteins in your tumor. To do this, we will look at cells from a small piece of tumor in some of the patients on this study before and after giving study drugs. Discuss with your study doctor whether you need to undergo tumor biopsies as part of this study.

Although we hope this experimental therapy will decrease the size of your tumor, we cannot promise or predict the benefits of the treatment at this time. The drugs used in this study have known side effects that will be reviewed with you by your medical team before you sign the consent form.

Why are you being asked to take part in this study?

You are being asked to take part in this study because there are no standard treatments that are very effective for the cancer you have. We hope that this combination of study drugs will slow down the growth of your cancer.

Have these drugs been given to other people?

Pazopanib is already approved by the FDA to treat patients with renal cell cancer. So far, more than 2000 patients have received pazopanib in clinical trials for different types of cancer.

ARQ 197 is an experimental agent. More than 580 patients with different types of cancer have taken part in clinical trials of ARQ 197. Patients have been given ARQ 197 in different doses and schedules. Overall, ARQ 197 was well tolerated, but the study team will tell you about side effects that may happen if you take part in this study

How many people will take part in this study?

Up to 56 patients will take part in this study.

Description of Research Study

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

Before you begin the study
You will need to have the following examinations, tests, or procedures to find out if you can be in the study. These tests are part of your regular cancer care and should be done by your health care team even if you do not join the study. If you have had them recently, they may not need to be repeated. This will be up to your study doctor.

If you decide that you would like to participate in this study, you will be asked to sign this consent form. You will then have the examinations, tests, and procedures listed below done to see if you can take part in the study (this is called the screening/baseline evaluation).

- **Complete medical history.**
- **Physical examination,** including height, weight, blood pressure, pulse, and temperature.
- **Standard blood** tests (requiring about 1 tablespoon of blood in total), which include measurement of your white blood cells, red blood cells, platelets, blood sugar and electrolytes, how your liver and kidneys work, and how well your **blood** clots.
- **Pregnancy test** in women who are able to become pregnant.
- **Urine tests:** A urine test will be done to check the level of protein excreted by your kidneys. Depending on the results of blood tests, you may be asked to collect your urine for 24 hours for further testing.
- EKG and echocardiogram or MUGA scan to check your heart.
- **CT scans** of your chest, abdomen, and pelvis to measure your tumor(s). Other imaging tests may be done as needed.

During the study

After you are accepted for this study and you choose to take part, you will begin taking the study drugs pazopanib and ARQ 197. Pazopanib and ARQ 197 are taken by mouth. The study drugs will be given in cycles. All cycles are 4 weeks (28 days) long. **This study has two parts, a dose escalation phase and an expansion phase.** In the dose escalation phase, the doses of pazopanib and ARQ 197 will be escalated (increased) until the highest doses that can be safely given to humans are determined. These are the doses of study drugs will be given to patients in

the expansion phase. Patients enrolled in the expansion phase will be given pazopanib alone for 1 week and then both drugs together.

The expansion phase will start only after the dose escalation phase has been completed. Your study doctor will tell you which phase of the study you will be in.

If you are in the dose escalation phase, you will take pazopanib once a day and ARQ 197 twice a day about 12 hours apart, every day. You will receive a different dose based on when you entered the study. If you are in the expansion phase, you will take pazopanib only for the first week, and then both drugs together for the rest of the study.

The study doctor may decrease your dose of study drug if you are not tolerating it well. Food may change the way your body handles pazopanib, so pazopanib should be taken with water at least 1 hour before or 2 hours after a meal. ARQ 197 should be taken with a meal. For example, on days when both drugs are taken, you should take pazopanib with only water when you wake up, then take the morning dose of ARQ 197 1 hour later with breakfast. Each day that you take study drugs, you will be asked to fill in a diary to show when you took the study drugs, how many pills you took, and report any side effects you may have had.

For some study procedures we will need you to come to the Clinical Center. You will also have tests performed because you are in the study to see how the study drugs are affecting your body and to find out how your body handles the study drugs. This will include imaging studies (for example, CT scans) every 2 cycles (every 8 weeks) to find out if your cancer has responded.

Clinical Center Visits: We will ask that you come to the Clinical Center for at least 3 days during the first cycle, and then at the beginning of each cycle. If you are enrolled in the dose escalation phase and choose to have a tumor biopsy, you will need to come to the Clinical Center for one more day during Cycle 1. During the first cycle only, you will be admitted to the Clinical Center for the first 2 days of drug administration to make it easier to collect research blood samples. For patients who have been on study for six or more cycles and are tolerating treatment well, clinic visits may be performed once every 2 cycles (every 2 months). Please see the study chart for more details.

Standard procedures being done because you are in this study; these may be done more often because you are in the study:

- **Clinic visit** to ask how you are feeling and to evaluate you with a physical examination on multiple days during the first cycle and on the first day of each cycle from then on (cycles are 4 weeks long). For patients who have been on study for six or more cycles and are tolerating treatment well, clinic visits may be performed once every 2 cycles (every 2 months). Please see the study chart for more details.

- **Vital signs:** You will need to have your vital signs measured each time you are seen in the outpatient clinic.

We will ask that you buy a blood pressure monitor (the cost of may be reimbursed to you; discuss with your study team) and measure your own blood pressure at home at least once a day (preferably twice a day) throughout the study. You will record the readings in a diary. If your systolic blood pressure (top number) is ever more than 150 or your diastolic blood pressure (bottom number) more than 90, you should re-measure your blood pressure 1 to 4 hours later. If your systolic pressure is still greater than 150 or your diastolic blood pressure is still greater than 90, please contact your study team for instructions. You should also call the research team if you experience any symptoms of high blood pressure, such as chest pain, shortness of breath, headache, blood in the urine, or double vision.

- **Blood tests:** Measurement of your white blood cells, red blood cells and platelets, and measurements of your blood sugar and electrolytes and of how your liver and kidneys work will be done each time you are seen in the outpatient clinic. You may need blood tests more often if the study doctor thinks they are needed to check for signs of possible damage to your liver. All of these blood tests combined will require 1-2 tablespoons (20-30 mL) of blood each time.
- **Urine test** to check urine protein will be done during the first cycle and then before you start each new cycle. For patients who have been on study for six or more cycles and are tolerating treatment well, urine tests may be performed once every 2 cycles (every 2 months). Please see the study chart for more details. You may need it more frequently if the study doctor thinks it is needed to check for signs of possible damage to your kidneys. Depending on the results of urine tests, you may be asked to collect your urine for 24 hours for further testing.
- **EKG** to check your heart will be done on multiple days during the first cycle. Some patients will have EKG on day 1 of Cycle 2. Please see the study chart for more details. You may need it more frequently if the study doctor thinks it is needed to check for signs of possible damage to your heart.
- **CT scans** or other imaging tests such as ultrasound (an examination using sound waves) or MRI (an examination using magnetic field and radio waves) that detect your tumor will be done every 2 cycles (about every 8 weeks) while you are receiving treatment. This is done so that any benefit of the treatment can be determined, and so that if your cancer is not responding to the treatment, the study team can tell you and help you move to a different treatment program (discussed further below).

Tests and procedures that are either being tested in this study or being done to see how the study is affecting your body:

- **Measurement of pazopanib and ARQ 197 in your blood:** You will be admitted to the Clinical Center for the first 2 days of drug administration to make it easier to collect research blood samples. This will help us find out how your body handles the drugs. Blood will be collected during Cycle 1 at multiple time points. Please see the study chart for more details. The total blood for these tests will be about 4-5 tablespoons (about 50-66 mL). These research blood tests are mandatory and will be required for every patient.
- **Measurements of the drugs' effects in your blood:** We will collect blood samples to examine the effects of the study drugs on targets in your blood at multiple time points during Cycle 1 and once before Cycle 2. Please see the study chart for more details. The total blood for all research tests will be less than 2 tablespoons (about 20 mL). These research blood tests are mandatory and will be required for every patient.
- **Other research blood samples:** We will also collect a small amount of blood (10 mL) to test whether you have a variation in a certain gene and see if this has an effect on how your body handles the drugs. This research blood test is mandatory and will be required for every patient.
- **Tumor biopsies:** During the dose escalation phase, tumor biopsies will be optional; however, **in the expansion phase, patients will be required to undergo research tumor biopsies to take part in the study. Your study doctor will discuss this with you. Only if you have disease that in the opinion of your study doctor can be safely biopsied, will you be eligible to take part in the expansion phase.** We will tell you if biopsies are required before you decide to take part in the study.

After you are accepted to take part in the study, you will be asked to undergo imaging-directed biopsy of your tumor (removal of a small bit of tissue for microscopic examination) once before you receive the study drug and a second time after you receive the study drug on day 7 or 8 of Cycle 1. Biopsies are a very important part of this trial and are done for research purposes. Evaluating the tumor biopsies will help your study doctors understand how the drug works on tumor cells. Tumor biopsies are optional during the dose escalation phase. In the expansion phase, after the initial biopsy, if you decide not to have further biopsies, you will still receive study drugs and have other tests that are part of the study.

Trained personnel will perform these biopsies. If any complication occurs, we will offer medical care. If upon attempting the first biopsy procedure, no tissue can be obtained or it has caused you harm, the second biopsy procedure will not be done. After you are enrolled in this study, if for any reason the biopsies cannot be done safely, you can still receive the study drugs but the biopsies will not be performed.

Biopsies will be done using a small bore needle under imaging guidance (CT, MRI, or ultrasound as deemed appropriate by the interventional radiologist performing the biopsy). Imaging helps the specialized radiologist know that the needle has been placed into the tumor mass. You will be given an anesthetic to numb the area around where the needle is placed. Typical risks of such 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 form that will describe the procedure and its risks at that time. Your safety is the most important thing at all times.

The biopsies are for research purposes and will not benefit you. They might help other people in the future. Even if you sign "yes" to have biopsies, you can change your mind at any time. Please read the sentence below and think about your choice. After reading the sentence, circle and initial the answer that is right for you.

1) Have you been informed that you will be in the dose escalation phase in this study?

Yes No Initials_____

I agree to have the tumor biopsies for the escalation phase of the research study (optional).

Yes No Initials_____

2) Have you been informed that you will be in the expansion phase in this study?

Yes No Initials_____

I agree to have the tumor biopsies for the expansion phase of the research study (mandatory).

Yes No Initials_____

Study Chart

The treatment is given over periods called cycles. All cycles are 4 weeks long. Treatment cycles will be repeated as long as you are tolerating the drugs and your cancer is either stable or getting better. Each cycle is numbered in consecutive order. The chart below shows what will happen during Cycle 1 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 shows what will happen to you after you sign the consent and start the study. There are separate charts for the dose escalation phase and the expansion phase. Your study doctor will tell you which phase of the study you will be in.

Pazopanib and ARQ 197 should be taken with water at least 1 hour before or 2 hours after a meal. ARQ 197 should be taken with a meal. The drug tablets should be swallowed whole with water and may not be crushed or broken.

For patients who have been on study for six or more cycles and are tolerating treatment well, clinic visits may be performed once every 2 cycles (every 2 months).

Dose Escalation Phase

Day	What to do and what will happen to you
Before starting study drugs	• Check in at Outpatient Clinic • Get routine blood and urine tests • Pregnancy test for women who are able to become pregnant • Have a history taken of how you feel and undergo a physical examination including vital signs by a Health Care Provider • CT or MRI scan will be done • Research blood samples will be taken • Research tumor biopsy may be taken (optional) • EKG and echocardiogram or MUGA scan will be done to check your heart
Cycle 1, Day 1	• Admitted to Clinical Center • Begin taking pazopanib and ARQ 197 by mouth each day • Blood samples for measurement of pazopanib and ARQ 197 will be taken at multiple time points over a 12-hour period (pre-dose, and 1, 2, 4, 6, and 12 hours after the start of study drug administration) • Blood samples for measurements of the drugs' effects will be taken at multiple time points (pre-dose, and 2, 4, and 6 hours after study drug)
Cycle 1, Day 2-7	• Continue taking pazopanib and ARQ 197 by mouth each day

Day	What to do and what will happen to you
Cycle 1, Day 8	• Continue taking pazopanib and ARQ 197 by mouth: take the morning dose of ARQ 197 with food early in the morning, then fast until tumor biopsy. Take pazopanib at least 1 hour before food. • Get routine blood tests Only for patients who undergo research tumor biopsies (optional): • Check in at Outpatient Clinic • Have a history taken of how you feel and undergo a physical examination including vital signs by a Health Care Provider • Research tumor biopsy will be taken 8-12 hours after the morning dose of ARQ 197
Cycle 1, Day 9-14	• Continue taking pazopanib and ARQ 197 by mouth each day
Cycle 1, Day 15	• Check in at Outpatient Clinic • Have a history taken of how you feel and undergo a physical examination including vital signs by a Health Care Provider • Get routine blood and urine tests • Continue taking pazopanib and ARQ 197 by mouth each day • Blood samples for measurement of pazopanib and ARQ 197 will be taken at multiple time points over a 6-hour period (pre-dose, and 1, 2, 4, and 6 hours after the start of study drug administration) • Blood samples for measurements of the drugs' effects will be taken (once before the dose of study drug) • EKG will be done 3-6 hours after the morning dose of ARQ 197
Cycle 1, Day 16-21	• Continue taking pazopanib and ARQ 197 by mouth each day
Cycle 1, Day 22	• Get routine blood tests • Continue taking pazopanib and ARQ 197 by mouth each day
Cycle 1, Day 23-28	• Continue taking pazopanib and ARQ 197 by mouth each day • Get routine blood tests every 2 weeks
Cycle 2 onwards, Day 1	• Check in at Outpatient Clinic • Have a history taken of how you feel and undergo a physical examination including vital signs by a Health Care Provider • Get routine blood and urine tests • Blood samples for measurement of the drugs' effects will be taken before

Day	What to do and what will happen to you
	study drugs are given (cycle 2 only) • Continue taking pazopanib and ARQ 197 by mouth each day
Cycle 2, Day 2-28	• Continue taking pazopanib and ARQ 197 by mouth each day • Have blood pressure checked by a health care provider every 2 weeks • Get routine blood tests every 2 weeks
Cycle 3 and onwards	• Continue taking pazopanib and ARQ 197 by mouth each day • CT scans to determine how your tumor is responding to the treatment will be done every 2 cycles (every 8 weeks) • Get routine blood tests at months 3 and 4 and afterwards if the study doctor thinks they are needed to check for signs of possible damage to your liver

Expansion Phase

Day	What to do and what will happen to you
Before starting study drugs	• Check in at Outpatient Clinic • Get routine blood and urine tests • Pregnancy test for women who are able to become pregnant • Have a history taken of how you feel and undergo a physical examination by a Health Care Provider • CT or MRI scan will be done • Research blood samples will be taken • Research tumor biopsy will be taken • EKG and echocardiogram or MUGA scan will be done to check your heart
Cycle 1, Day 1	• Admitted to Clinical Center • Have a history taken of how you feel and undergo a physical examination including vital signs by a Health Care Provider • Begin taking pazopanib by mouth each day • EKG will be done 3-6 hours after taking the study drug • Blood samples for measurement of pazopanib will be taken at multiple time points over a 12-hour period: pre-dose, and 1, 2, 4, 6, and 12 hours after the start of study drug administration Blood samples for measurements of the drug's effects will be taken at multiple time points: pre-dose, and 2, 4, and 6 hours after study drug

Day	What to do and what will happen to you
Cycle 1, Day 2-6	• Continue taking pazopanib by mouth each day • Admitted to Clinical Center
Cycle 1, Day 7	• Continue taking pazopanib by mouth • Blood samples for measurement of pazopanib will be taken at multiple time points over a 6-hour period: pre-dose, and 1, 2, 4, and 6 hours after the start of study drug administration
Cycle 1, Day 8	• Check in at Outpatient Clinic • Have a history taken of how you feel and undergo a physical examination including vital signs by a Health Care Provider • Get routine blood and urine tests • Blood samples for measurements of the drugs' effects will be taken once before the dose of study drug • Continue taking pazopanib by mouth, then fast until tumor biopsy. • Research tumor biopsy will be taken • EKG will be done 3-6 hours after study drug administration • Start taking pazopanib and ARQ 197 by mouth each day
Cycle 1, Day 9-28	• Continue taking pazopanib and ARQ 197 by mouth each day • Get routine blood tests every 2 weeks starting from week 3
Cycle 2 onwards, Day 1	• Check in at Outpatient Clinic • Have a history taken of how you feel and undergo a physical examination including vital signs by a Health Care Provider • Get routine blood and urine tests • Blood samples for measurements of the drugs' effects will be taken (once before the dose of study drug) (cycle 2 only) • Continue taking pazopanib and ARQ 197 by mouth each day
Cycle 2, Day 2-28	• Continue taking pazopanib and ARQ 197 by mouth each day
Cycle 3 and onwards	• Continue taking pazopanib and ARQ 197 by mouth each day • CT scans to determine how your tumor is responding to the treatment will be done every 2 cycles (every 8 weeks) • Get routine blood tests at months 3 and 4 and afterwards if the study doctor thinks they are needed to check for signs of possible damage to your liver

Alternative Approaches or Treatments

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

Instead of being in this study, you have these options

- Getting treatment or care for your cancer without being in a study
- Taking part in another study
- Getting 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. Instead, it tries to improve how you feel. Comfort care tries to keep you as active and comfortable as possible.

Please talk to your doctor about these and other options.

Risks or Discomforts of Participation

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

You may have side effects while on the study. Everyone taking part in the study will be watched carefully for any side effects. But, doctors do not know all the side effects that may happen when taking pazopanib and ARQ 197 together. There may be other side effects that we cannot predict.

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 with those medicines, and others can go away soon after you stop taking the study drugs. In some cases, side effects can be serious, long lasting, may never go away, or may result in death. You should talk to your study team about all side effects that you have while taking part in the study.

High blood pressure is one common side effect of pazopanib. Your blood pressure will be closely watched while you are taking pazopanib. This will include having your blood pressure measured every 2 weeks by a health care provider for the first 2 cycles in the dose escalation phase, or on day 1 and day 8 of cycle 1 in the expansion phase, then at least every cycle for the duration of treatment. You will also be checking your blood pressure at home at least once a day (preferable twice a day) for the entire study. If you have high blood pressure while taking pazopanib, your study doctor may recommend follow-up with your primary care physician and/or starting or increasing medication to lower blood pressure.

Grapefruit juice has been shown to affect how the body handles some drugs by blocking the activity of the body's cytochrome P450 (CYP450) system. CYP450 is important in breaking

down substances in the body, including pazopanib and many other drugs. Therefore, please avoid grapefruit juice or grapefruit while taking pazopanib. Acetaminophen and the herbal supplement St. John's wort can also affect blood levels of drugs such as pazopanib, so these should be avoided. Taking pazopanib can increase blood levels of drugs used to lower blood sugar. If you are taking medicine to lower your blood sugar, discuss with this your study doctor. You should check your blood sugar regularly during the study and contact the study team if your blood sugar is too low or if you have symptoms of low blood sugar. We do not know if taking pazopanib will cause other drugs you may be taking to work differently. **It is very important that you talk to a member of the research team before beginning any new drugs, over-the-counter medications, vitamins, or alternative therapies.**

Risks and side effects related to **pazopanib** may include:

COMMON, SOME MAY BE SERIOUS In 100 people receiving pazopanib, more than 20 may have:
• Diarrhea, nausea, vomiting • Tiredness • Bruising, bleeding • Infection, especially when white blood cell count is low • Loss of appetite • Change in hair color • High blood pressure which may cause blurred vision
OCCASIONAL, SOME MAY BE SERIOUS In 100 people receiving pazopanib, from 4 to 20 may have:
• Anemia which may require blood transfusion • Abnormal heartbeat • Pain • Constipation, heartburn • Sores in mouth which may cause difficulty swallowing • Swelling of arms, legs • Fever • Weight loss • Dehydration • Dizziness, headache • Changes in taste • Cough, shortness of breath • Internal bleeding which may cause coughing up blood, black tarry stool, or blood in vomit • Bleeding from multiple sites including the nose • Hair loss, rash, skin changes • Redness, pain or peeling of palms and soles

RARE, AND SERIOUS In 100 people receiving pazopanib, 3 or fewer may have:
• Anemia, kidney problems which may require dialysis • Blood clot which may cause confusion, paralysis, swelling, pain, or shortness of breath • Heart failure, heart attack which may cause shortness of breath, swelling of ankles, and tiredness • A tear or hole in internal organs that may require surgery • Liver damage which may cause yellowing of eyes and skin • Change in the heart rhythm • Brain damage which may cause headache, seizure, blindness (also known as Reversible Posterior Leukoencephalopathy Syndrome) • Kidney damage which may require dialysis • Swelling or scarring of the lungs which may cause shortness of breath

Risks and side effects related to **ARQ-197** so far include:

OCCASIONAL, SOME MAY BE SERIOUS In 100 people receiving ARQ 197, from 4 to 20 may have
• Anemia which may require blood transfusion • Abnormal heartbeat • Diarrhea, nausea, vomiting • Tiredness • Infection, especially when white blood cell count is low • Loss of appetite • Rash
RARE, AND SERIOUS In 100 people receiving ARQ 197, 3 or fewer may have
• Redness, pain or peeling of palms and soles

Reproductive Risks:
If you are a woman who is breast feeding or pregnant, you may not take part in the study because we don't know how the combination of these medicines would affect your baby or your unborn child. If you are a woman who can become pregnant, or are the partner of a woman who can become pregnant, you will need to practice an effective form of birth control before starting study treatment, during study treatment, and for 2 months after you finish study treatment. If you think that you or your partner is pregnant, you should tell your study doctor or nurse at once.

Effective forms of birth control include:

- Abstinence
- tubal ligation
- hormonal [injections, or implants]: estrogen containing pills are not allowed due to the risk of blood clotting
- intrauterine device (IUD)
- vasectomy

Side Effects of Blood Draw:
Infrequent (occurs in 1 to 10 out of 100 people): persistent pain and discomfort at the injection or needle insertion site as well as possible infection, bleeding, bruising, and soreness.

Potential Risks Related to Research-Related Imaging Studies:
This research study involves exposure to radiation from up to 2 CT scans (used in biopsy collections). This radiation exposure is not required for your medical care and is for research purposes only. The amount of radiation you will receive in this study is 0.29 rem, which is below the guideline of 5 rem (or 0.5 rem in children) per year allowed for research subjects by the NIH Radiation Safety Committee. The average person in the United States receives a radiation exposure of 0.3 rem per year from natural sources, such as the sun, outer space, and the earth's air and soil. If you would like more information about radiation, please ask the investigator for a copy of the pamphlet, An Introduction to Radiation for NIH Research Subjects.

While there is no direct evidence that the amount of exposure received from participating in this study is harmful, there is indirect evidence it may not be completely safe. There may be a very slight increase in the risk of cancer.

Please tell your doctor if you have had any radiation exposure in the past year, either from other research studies or from medical tests or care, so we can make sure that you will not receive too much radiation. Radiation exposure includes 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 you will not be permitted to participate in this research study. It is best to avoid radiation exposure to unborn infants since they are more sensitive to radiation than adults.

Potential Benefits of Participation

Are there benefits to taking part in this study?

Taking part in this study may or may not make your health better. We hope that you will get personal medical benefit from taking part in this study, but there is no proof of this yet. These potential benefits could include shrinking of your tumor or lessening of your symptoms, such as pain, that are caused by the cancer. You should discuss other treatment options with the study team and your home doctor before deciding to take part in this study. We do know that information from this study will help doctors learn more about these study drugs. This information will also help future cancer patients.

Research Subject's Rights

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 this study. If you decide to take part, 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.

What are the costs of taking part in this study?

If you choose to take part in the study, the following will apply, in keeping with the NIH policy:

- You will receive study treatment at no charge to you. This may include surgery, medicines, laboratory testing, x-rays, or scans done at the Clinical Center, National Institutes of Health (NIH), or arranged for you by the research team to be done outside the Clinical Center, NIH if the study related treatment is not available at the NIH.
- There are limited funds available to cover the cost of some tests and procedures performed outside the Clinical Center, NIH. 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 Clinical Center, NIH.
    - Once you have completed taking part in the study, medical care will no longer be provided by the Clinical Center, NIH.
    - The NCI will supply pazopanib and ARQ 197 at no charge while you take part in this study.
- Even though it probably won't happen, it is possible that the manufacturer may not continue to provide the pazopanib and ARQ 197 to the NCI for some reason. If this would occur, other possible options are:
- You might be able to get the pazopanib and ARQ 197 from the manufacturer or your pharmacy but you or your insurance company may have to pay for it.
- If there is no pazopanib and ARQ 197 available at all, no one will be able to get more and the study would close.
- If a problem with getting pazopanib and ARQ 197 occurs, your study doctor will talk to you about these options. Medicines that are not part of the study treatment will not be provided or paid for by the Clinical Center, NIH.

Stopping Therapy

Your doctor may decide to stop your therapy for the following reasons:

- if he/she believes that it is in your best interest
- if your disease comes back during treatment
- if you have side effects from the treatment that your doctor thinks are too severe
- if new information shows that another treatment would be better for you
- if too many patients in the study experience severe side effects
- if you become pregnant

In this case, you will be informed of the reason therapy is being stopped.

You can stop taking part in the study at any time. However, if you decide to stop taking part in the study, we would like you to talk to the study doctor and your regular doctor first. 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 the Cancer Therapy Evaluation Program (CTEP) at the National Cancer Institute (NCI) 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 cannot be recalled and destroyed.

Follow-up

You will be followed for 30 days after taking the last dose of study drug. We will call you after about 30 days to ask about any side effects that were ongoing when you stopped therapy, or any new side effects that might be related to the study therapy. If you have side effects that might be related to the study drugs that have not gotten better after 30 days, we will call you every 2 weeks until the side effects have become stable or gotten better. The follow-up period will end if you enroll on another protocol or start receiving standard therapy.

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.

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, including research 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 the pharmaceutical collaborator may also review the medical records.

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.

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). 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.

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 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 data. Then any tissue or blood that remains will be destroyed and your data will not be used for future research.

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_____

OTHER PERTINENT INFORMATION

1. Confidentiality. When results of an NIH research study are reported in medical journals or at scientific meetings, the people who take part are not named and identified. In most cases, the NIH will not release any information about your research involvement without your written permission. However, if you sign a release of information form, for example, for an insurance company, the NIH will give the insurance company information from your medical record. This information might affect (either favorably or unfavorably) the willingness of the insurance company to sell you insurance.

The Federal Privacy Act protects the confidentiality of your NIH medical records. However, you should know that the Act allows release of some information from your medical record without your permission, for example, if it is required by the Food and Drug Administration (FDA), members of Congress, law enforcement officials, or authorized hospital accreditation organizations.

2. Policy Regarding Research-Related Injuries. The Clinical Center will provide short-term medical care for any injury resulting from your participation in research here. In general, no long-term medical care or financial compensation for research-related injuries will be provided by the National Institutes of Health, the Clinical Center, or the Federal Government. However, you have the right to pursue legal remedy if you believe that your injury justifies such action.

3. Payments. The amount of payment to research volunteers is guided by the National Institutes of Health policies. In general, patients are not paid for taking part in research studies at the National Institutes of Health. Reimbursement of travel and subsistence will be offered consistent with NIH guidelines.

4. Problems or Questions. If you have any problems or questions about this study, or about your rights as a research participant, or about any research-related injury, contact the Principal Investigator, Dr. Alice Chen, Building 31 Room 3A44, Telephone: (301) 496-4291. If you have any questions about the use of your tissue for future research studies, you may also 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 23, 2015 THROUGH FEBRUARY 22, 2016. _____ _____ _____ _____ Signature of Investigator Date Signature of Witness Date _____ _____ Print Name Print Name	