INSTITUTE: National Cancer Institute

STUDY NUMBER: 14-C-0001 PRINCIPAL INVESTIGATOR: Andrea Apolo, M. D.

STUDY TITLE: Phase II Study of Axitinib (AG-013736) with Evaluation of the VEGF-pathway in Metastatic, Recurrent or Primary Unresectable Pheochromocytoma/Paraganglioma

Continuing Review Approved by the IRB on 03/25/19
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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?

Axitinib (AG-013736) is an investigational (experimental) drug that is being studied in patients with metastatic pheochromocytoma/paraganglioma. This drug was approved by the FDA in 2012 for the treatment of kidney cancer. Although it is FDA-approved, it is still considered experimental in this study because it has never been studied in people with pheochromocytoma/paraganglioma. The main goal of this study is to find out if axitinib is able to stop tumors from growing, or shrink tumors in patients with this type of cancer.

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

You are being asked to be a part of this study because you have a diagnosis of metastatic pheochromocytoma/paraganglioma and have tried at least one treatment for the disease that either did not work or is no longer working. Taking part in this study may or may not make your health better. While doctors hope axitinib 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 axitinib as a treatment for cancer and could help future cancer patients.

How many people will take part in this study?

Twelve patients will be enrolled at first. If at least one of the first 12 patients has a good response (shrinkage or disappearance of their tumors) a total of 37 patients will be enrolled.

Description of Research Study

You will receive the study drug, axitinib, orally twice a day, every day, in 28-day cycles. You will start at a dose of 5mg twice a day. After 4 weeks, your dose may be increased to 7mg twice a day and later on to 10mg twice a day after you are carefully checked by your study team and are feeling good without any significant side effects. You may take axitinib with or without food.

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

Evaluation Tests before the Study Begins

Prior to starting (or "enrolling") on the study, an evaluation will be done at the NIH Oncology Clinic to determine if this study is appropriate for you. This is called "screening" and a different consent form explains the tests required for screening.

All cancer diagnoses must be confirmed by a pathologist at the NIH, who will look at the specimen slides from your prior biopsy or surgery. If a pathology specimen is not available from previous surgery, a pathology report from a prior biopsy or surgery confirming your diagnosis will be accepted. Results from an imaging study that would only be positive in an adult patient with your diagnosis may also be accepted.

What does this study involve?

During the study

If you enroll in the study you will need the following tests and procedures as part of the study. Many of these are part of regular cancer care. They are being done more often because you are in this study.

- Blood and urine tests will be done once every 4 weeks during the first 3 months, and then once every 12 weeks after the first 3 months
- Blood tests for research-only purposes will be done at the beginning of the first cycle and then at 8, 16 and 24 weeks.
- You will check your blood pressure twice a day during the first 4 weeks, then once a

week after the first 4 weeks. You will have a diary to write down your blood pressure readings.

• You will have a CT and/or MRI scan every 12 weeks as part of this study. The scan compares the baseline scan (before you begin axitinib) to the scan after receiving axitinib, in order to figure out if the tumor(s) are the same size, smaller, or larger. You will need to have the scans in order to participate in the study.

When you are finished taking the drugs

You will be invited to clinical center approximately 4 weeks following the last dose of study drug. The following assessments will be performed at this visit:

- Medical history and physical exam
- Routine blood and urine tests
- 24-hour urine test
- Review of your side effects

If you are unable to travel to the NIH, we will contact you by telephone and ask you about any side effects you might have and any new treatments you may have started.

Birth Control

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 this medicine 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 3 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
- intrauterine device (IUD)
- hormonal [birth control pills, injections, or implants]
- tubal ligation
- vasectomy

Drug Interactions

You should not drink grapefruit juice or smoke cigarettes while participating in this study. Grapefruit juice and cigarette smoking are both known to interfere with the body's ability to process the study medication. You should contact the research team before taking any

medication or supplement. Other medications and supplements may interact with axitinib and might affect the activity and/or side effects of axitinib.

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. Side effects can be mild or 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 drug. In some cases, side effects can be serious, long lasting, or may never go away, and can even result in death.

You should talk to your study doctor about any side effects that you have while taking part in the study. Likely side effects are those seen in up to one third of patients who received single agent axitinib in earlier trials.

Risks and side effects of axitinib may include:

Likely	Less Likely	Rare but Serious
• Fatigue • Diarrhea • Hypertension • Nausea • Anorexia	• Hoarseness of voice • Shortness of breath • Weight loss • Constipation • Headache • Vomiting • Cough • Leg pain • Gastroesophageal reflux disease • Mouth soars • Abdominal pain • Back pain • Insomnia • Leg swelling • Rash • Dizziness	• Decrease in the white blood cells (the cells that fight infection) and can result in infection that may or may not require treatment with antibiotics • Decrease in red blood cells (the cells that carry oxygen to your body), which can cause tiredness and shortness of breath and may required a transfusion of red blood cells) • Decrease in platelets (the cells that help with blood clotting) which can increase the risk of bleeding or bruising • Loss of protein in urine • Intestinal perforations • Stroke • Thrombosis (Blood clots) • Myocardial Infarction (heart

	• Muscle pains • Thyroid abnormalities • Increased blood glucose • Electrolyte abnormalities • Low blood pressures • Skin peeling from hands and feet also known as the hand and foot syndrome	attacks) • Arrhythmias (Heart rate or rhythm abnormalities) • Abnormal kidney function or failure • Liver function abnormality or failure • Reversible posterior leukoencephalopathy, a disorder associated with findings on MRI. The symptoms include headache, high blood pressure, decreased alertness, change in mental functioning, seizures, and vision loss, including blindness. These symptoms are usually reversible. • Elevated levels of triglycerides.

Since the drug is still being studied there may be other side effects that have not been described before.

If you are pregnant you will not be permitted to participate in this research study. If you are breast feeding and the protocol involves injection of radioactive material you will not be permitted to participate. It is best to avoid radiation exposure to unborn or nursing infants since they are more sensitive to radiation than adults.

Potential Benefits of Participation

Are there benefits to taking part in this study?

The aim of this study is to see if this experimental treatment will cause your tumors to shrink. We do not know if you will receive personal, medical benefit from taking part in this study. These potential benefits could include shrinking of your tumor or lessening of your symptoms, such as pain, that are caused by the cancer. Because there is not much information about the drug's effect on your cancer, we do not know if you will benefit from taking part in this study, although the knowledge gained from this study may help others in the future who have cancer.

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 on a study
- Taking part in another study
- Getting no treatment at all
- 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.

Research Subject's Rights

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.

Will your medical information be kept private?

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

- The National Cancer Institute (NCI) and other government agencies, like the Food and Drug Administration (FDA), which are involved in keeping research safe for people.
- National Cancer Institute Institutional Review Board
- The study Sponsor, Dr. Tito Fojo or his representatives

- Qualified representatives from Pfizer, the pharmaceutical company who produces axitinib.

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.

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 the cancer grows or becomes worse 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

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 Pfizer 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.

Certificate of Confidentiality

To help us protect your privacy, we have obtained a Certificate of Confidentiality. The researchers can use this Certificate to legally refuse to disclose information that may identify you in any federal, state, or local civil, criminal, administrative, legislative, or other proceedings, for example, if there is a court subpoena. The researchers will use the Certificate to resist any demands for information that would identify you, except as explained below.

You should also know that there are several circumstances in which the Certificate does not provide coverage. These include when information:

- will be used for auditing or program evaluation internally by the NIH; or
- must be disclosed to meet the legal requirements of the federal Food and Drug Administration (FDA).
- is necessary for your medical treatment and you have consented to this disclosure;
- is for other research.

In addition, identifiable, sensitive information protected by this Certificate cannot be admissible as evidence or used for any purpose in any action, suit, or proceeding without your consent.

You should understand that a Certificate of Confidentiality does not prevent you or a member of your family from voluntarily releasing information about yourself or your involvement in this research. If an insurer, employer, or other person obtains your written consent to receive research information, then the researchers will not use the Certificate to withhold that information. The Certificate of Confidentiality will not protect against the required reporting by hospital staff of information on suspected child abuse, reportable communicable diseases, and/or possible threat of harm to self or others.

Conflict of Interest

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

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

Pfizer Pharmaceuticals, Inc. is providing Axitinib for this study to NIH without charge. No NIH employee involved in this study receives any payment or other benefits from Pfizer Pharmaceuticals, Inc.

Use of Specimens and Data for Future Research

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

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

If you do not want your stored specimens and data used for future research, please contact us in writing and let us know that you do not want us to use your specimens and/or data. Then any

specimens that have not already been used or shared will be destroyed and your data will not be used for future research. However, it may not be possible to withdraw or delete materials or data once they have been shared with other researchers.

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, Andrea Apolo, M.D., Building 10, Room 13N240, Telephone: 301-480-0536. You may also call the Clinical Center Patient Representative at 301-496-2626. If you have any questions about the use of your specimens or data for future research studies, you may also contact the Office of the Clinical Director, Telephone: 240-760-6070.

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 MARCH 25, 2019 THROUGH APRIL 22, 2020.

_____ _____ _____ _____
Signature of Investigator Date Signature of Witness Date

_____ _____
Print Name Print Name