INSTITUTE: National Cancer Institute

STUDY NUMBER: 14-C-0150 PRINCIPAL INVESTIGATOR: A.P. Chen, M.D.

STUDY TITLE: Phase I Study of Ganetespib and Ziv-Aflibercept in Patients with Advanced Gastrointestinal Carcinomas, Non-Squamous Non-Small Cell Lung Carcinomas, Urothelial Carcinomas, and Sarcomas

Continuing Review Approved by the IRB on 05/18/15
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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?

The purpose of this study is to test the safety of the combination of ganetespib and ziv-aflibercept, and to 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. 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 research study because you have advanced cancer that has progressed after receiving standard treatment, or for which no effective therapy exists. We hope that this combination of study drugs will slow down the growth of your cancer.

How many people will take part in this Study?

Up to 26 patients will take part in this study.

Description of Research Study

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

If you are accepted and you choose to take part, you will begin receiving **ganetespib** and z**iv-aflibercept**. Both drugs are given as an infusion through a vein. Ganetespib is given once a week on the same day for three weeks in a row, followed by a one week rest period. Ziv-aflibercept is given once a week every other week. The drugs are given in cycles; each cycle is 28 days (4 weeks) long. Each patient may receive a different dose based on when he or she entered the study. Your dose of study drugs may be decreased by the study doctor if you are not tolerating it well. Study doctors have already seen some serious side effects on this study that are related to the agents and so new patients will be receiving a lower dose of the combination.

Most of the exams, tests, and procedures you will have are part of your regular care such as a complete medical history, blood tests, and scans to measure your tumors. We would also do a pregnancy test in women who are able to become pregnant. The team will also give you a chart describing the tests and procedures that will be done each day during the study.

While you are at the Clinical Center we will perform study tests and procedures to see how the study drugs are affecting your body. If you develop any side effects, you may be asked to visit more often.

How long will I be in this study?
You will stay in the study as long as you are tolerating the drugs and your tumors are either stable or getting better, but you can choose to leave the study at any time.

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

- Eye exam by a qualified eye doctor that involves adding eye drops to dilate, or widen, your eyes so that we can tell during the study if your eyes or vision have been affected by the

study drugs. We may do another eye exam during the study to find out if your eyes or vision have changed.

- **Blood cells for research:** We will also be collecting blood samples from some patients to find out the effects of the drugs on any tumor cells in your blood. Giving these samples is optional. Each blood collection is about 2 teaspoons (8 mL).

- **Tumor Biopsy:** You may be asked to undergo imaging-directed biopsy of your tumor (removal of a small bit of tissue for microscopic examination) once in the first cycle and a second time in the second cycle. We are collecting biopsy samples to study the effects of study drugs on your tumor. Biopsies are an important part of this trial and are done for research purposes. Biopsies are optional in the early part of this study (called the dose escalation phase).

  If you decide not to have biopsies collected, you will still receive study drugs and other tests that are part of the study and detailed above. **However, at a certain point in the study called the expansion phase, willingness to undergo tumor biopsies will be required for taking part in this study.** We will tell you if biopsies are required before you decide to take part in the study. No more than two biopsy procedures will be performed during the study. After the first 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. You will be asked to sign a separate consent form for each biopsy procedure.

  Tumor biopsies are only collected by trained personnel. Biopsies are collected using a small 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.

  Typical risks of biopsy collection include, but are not limited to, bleeding, infection, pain, and scarring. If you experience any complications from the biopsy, medical care will be offered to you. You will be counseled in more detail about biopsies, and you will be asked to sign a separate consent form that will describe the procedures and risks at that time. Your safety is the most important thing at all times. If upon attempting the first biopsy, no tissue can be obtained or it has caused you harm, further biopsies will not be done. After you are enrolled in this study, if for any reason the biopsies cannot be done safely, you may still receive the study drugs but the biopsies will not be done.

  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 the initial 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_____

- **^{89}Zr-Panitumumab PET/CT:** You may be asked to participate in a whole-body imaging study with ^{89}Zr-panitumumab. PET/CT is a type of scan that uses low dose x-rays to detect small amounts of radioactive chemicals (tracer), which allow us to see where the body tracer is going. We are doing this to learn whether the study drugs ganetespib and ziv-aflibercept reduce how much of a protein called EGFR is made by your cancer cells without needing to collect a biopsy sample to measure EGFR directly in your tumor. The amount you will be given for imaging is much lower than the dose given to treat cancer, and this dose is not expected to help treat your cancer. For the PET scan, a small amount of a radioactive chemical will be injected through an intravenous (IV) catheter into your arm. ^{89}Zr-panitumumab imaging will take place before you start treatment and again during the third week of the first cycle of treatment. This imaging is optional for patients on the dose escalation phase but required in the expansion phase. We will tell you if ^{89}Zr-panitumumab imaging is required before you decide to take part in the study.

  Your study team will explain ^{89}Zr-panitumumab injections and PET/CT scans to you in more detail, and you will be asked to sign a separate consent.

  The PET scanner is shaped like a doughnut. You will lie on your back on a bed that slides in and out of the scanner. Each scan is expected to last approximately 70 minutes. After the scan, you will receive instructions about drinking fluids and urinating to limit your exposure to radioactivity. The amount of radioactivity in your blood will be measured from a small amount of blood (about 2 teaspoons) drawn before ^{89}Zr-panitumumab injection and before each image is collected.

  This scan is for research purposes only. The results of this scan will not affect or benefit you, but it will help researchers learn whether the ^{89}Zr-panitumumab imaging is useful

for patients who have tumors that make too much EGFR. If you choose to not undergo ^{89}Zr-panitumumab PET/CT imaging, this will not affect your care. You may still take part in the study and receive the study drugs and other tests that are part of the study.

I agree to undergo ^{89}Zr-panitumumab PET/CT scans for research purposes:

Yes ____ No _____ Initials_____

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**:**

- you may choose to have the usual approaches described above
- you may choose to take part in a different study, if one is available
- you may continue your standard care as usual (see table below), and not take part in this study
- or you may choose not to be treated, but you may want to receive comfort care to relieve symptoms

Examples of treatments which are indicated for your particular cancer include:

Colorectal cancer	oxaliplatin- and irinotecan- based chemotherapy
Non-squamous non-small cell lung cancer	erlotinib for patients who have an EGFR mutation, crizotinib for patients who have ALK rearrangement, pemetrexed, paclitaxel, or platinum-based chemotherapy
Urothelial cancer	platinum-based chemotherapy

Please talk to your doctor about these and other options. You should have received at least one of the treatments above (or both treatments in the case of colorectal cancer) before you may be eligible for this study. Your doctor may decide that it is not safe for you to receive a particular treatment or you have the right to refuse a treatment, but before you decide to take part in this study you should discuss all available treatment options with your local doctor.

Risks or Discomforts of Participation

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 agents 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 study doctor will provide you with information about other drugs you may need to avoid while receiving the study drug.

The table below shows 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.

High blood pressure is one common side effect of ziv-aflibercept. Your blood pressure will be closely watched while you are receiving ziv-aflibercept. This will include having your blood pressure checked at each clinic visit prior to your treatment for that week. You will also be asked to check your blood pressure at home at least once a day for the entire length of the study. If you have high blood pressure while receiving ziv-aflibercept, your study doctor may recommend follow-up with your primary care physician and/or start or increase medications to lower your blood pressure. Eye problems, including blurred vision, have also been reported in patients taking the study drugs. Please tell us if you have any problems with your vision or eyes.

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

COMMON, SOME MAY BE SERIOUS

In 100 people receiving ganetespib, more than 20 may have:

- Diarrhea
- Nausea
- Tiredness

OCCASIONAL, SOME MAY BE SERIOUS

In 100 people receiving ganetespib, from 4 to 20 may have:

- Anemia (low red blood cell count) which may require blood transfusion
- Pain in belly, constipation, vomiting
- Weight loss, loss of appetite
- Dehydration
- Dizziness, headache
- Difficulty sleeping
- Shortness of breath
- Acne

RARE, AND SERIOUS

In 100 people receiving ganetespib, 3 or fewer may have:

- Abnormal heart beat
- Heart stops beating
- Liver damage which may cause yellowing of the eyes and skin, swelling
- Severe blood infection
- Kidney damage which may require dialysis

Risks and side effects related to **ziv-aflibercept** may include:

COMMON, SOME MAY BE SERIOUS

In 100 people receiving ziv-aflibercept, more than 20 and up to 100 may have:

- Anemia which may require blood transfusion
- Pain
- Nausea
- Tiredness
- Loss of appetite
- Headache
- Changes in voice
- High blood pressure which may cause blurred vision

OCCASIONAL, SOME MAY BE SERIOUS

In 100 people receiving ziv-aflibercept, from 4 to 20 may have:

- Constipation, diarrhea, vomiting
- Sores in mouth which may cause difficulty swallowing
- Swelling of arms, legs
- Fever

- Allergic reaction which may cause rash, low blood pressure, wheezing, shortness of breath, swelling of the face or throat
- Infection, especially when white blood cell count is low
- Non-healing surgical site
- Bruising, bleeding
- Weight loss
- Dehydration
- Dizziness
- A tear or hole in internal organs that may require surgery
- Cough, shortness of breath
- Runny nose
- Hair loss, rash, skin changes
- Redness, pain or peeling of palms and soles
- Blood clot which may cause swelling, pain, shortness of breath, confusion, paralysis

RARE, AND SERIOUS

In 100 people receiving ziv-aflibercept, 3 or fewer may have:

- Anemia, kidney problems which may require dialysis
- Chest pain
- Heart attack, Heart failure which may cause shortness of breath, swelling of ankles, cough or tiredness
- A blood clot in the heart
- Stroke which may cause weakness
- Brain damage which may cause headache, seizure, blindness (also known as Reversible Posterior Leukoencephalopathy Syndrome)
- Mini stroke
- Kidney damage which may require dialysis

No side effects are expected from the ^{89}Zr-panitumumab imaging study because the dose of drug is so low. You will be monitored closely during this study for any new signs and symptoms. The side effects most likely during the ^{89}Zr-panitumumab infusion are discomfort at the injection site, pain, respiratory difficulties, flushing, dizziness, itching/rash, and any other symptoms that could be secondary to an allergic reaction. You will need to keep very still under the PET scanner for a period of 70 minutes, which you may find slightly uncomfortable. You may need to keep your arms over your head for some of the imaging procedures, which may make your shoulders sore. There is also the possibility that there may be unforeseen risks associated with this agent, about which nothing is yet known. Any new findings that may affect your decision to remain in the study will be provided to you and your doctor.

Potential Risks Related to Blood Samples

Possible side effects from drawing the blood sample include mild pain, bleeding, bruising, and infection at the site of the needle insertion. Fainting or light-headedness can sometimes occur, but usually last only a few minutes.

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) as well as from participation in ^{89}Zr-panitumumab PET/CT imaging. This radiation exposure is not required for your medical care and is for research purposes only.

The total amount of radiation you may receive in this study is 7.2 rem, which exceeds the radiation dose permitted to research subjects at NIH, but the NIH Radiation Safety Committee has approved the higher dose in view of the value of the scientific information to be obtained. The radioactivity of each injected dose of ^{89}Zr-panitumumab is less than 1 mCi (2 mCi in total).

The radiation dose from CT scans used for biopsy collection only 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.

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 and your partner 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 using at least two of the following:

- abstinence
- tubal ligation
- barrier methods (condoms)
- hormonal (birth control pills, injections, or implants)
- intrauterine device (IUD)
- vasectomy

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 drugs' 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.

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.
- The study agents ganetespib and ziv-aflibercept, will be provided free of charge while you are participating in this study. Even though it is unlikely, there is a possibility that at some point the supply of study agents may run out, necessitating taking you off-study.

Will your medical information be kept private?
Your privacy is very important to us and the researchers will make every effort to protect it. Your information may be given out if required by law. For example, certain states require doctors to report to health boards if they find a disease like tuberculosis. However, the

researchers will do their best to make sure that any information that is released will not identify you. Some of your health information, and/or information about your specimen, from this study will be kept in a central database for research.

There are organizations that may inspect your records. These organizations are required to make sure your information is kept private, unless required by law to provide information. Some of these organizations are:

- The National Cancer Institute (NCI), which is sponsoring this study
- NCI's pharmaceutical partners
- The Institutional Review Board (IRB), a group of people who review the research with the goal of protecting the people who take part in the study
- The Food and Drug Administration (FDA), which regulates the testing of experimental drugs

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

You can decide to stop at any time. If you decide to stop for any reason, it is important to let your study doctor know as soon as possible so you can stop safely. If you stop, you can decide whether or not to let the study doctor continue to include your medical information in the study. Your study doctor will tell you about new information or changes in the study that may affect your health or your willingness to continue in the study.

Your study doctor may take you out of the study:

- If your health changes and the study is no longer in your best interest
- If new information becomes available
- If you do not follow the study rules
- If the study is stopped by the sponsor, IRB, or FDA

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.

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 data. Then any specimens that remain 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 or other health problems.
Yes No Initials_____

2. Someone may contact me in the future to ask permission to use my specimen(s) and 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, 31 Center Drive, Building 31, Room 3A44, Telephone: 301-496-4291. 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 MAY 18, 2015 THROUGH MAY 17, 2016.

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

Print Name _____ Print Name _____