INSTITUTE: National Cancer Institute

STUDY NUMBER: 16-C-0034 PRINCIPAL INVESTIGATOR: Mark Gilbert, M.D.

STUDY TITLE: A Phase II Trial of Oral Pazopanib plus Oral Topotecan Metronomic Antiangiogenic Therapy for Recurrent Glioblastoma Multiforme (A) without Prior Bevacizumab Exposure and (B) after Failing Prior Bevacizumab

Continuing Review Approved by the IRB on 11/07/16
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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 goal of this clinical research study is to learn if pazopanib when given in combination with topotecan can help to control glioblastoma. The safety of this drug combination will also be studied.

This is an investigational study. Pazopanib is FDA approved and commercially available for the treatment of renal cell cancer. Topotecan is FDA approved and commercially available for the treatment of lung cancer. In this study, the combination of pazopanib and topotecan being used to treat brain tumors is investigational. At this time, this combination is only being used in research.

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

You are being asked to take part in this study because you have glioblastoma (brain tumor) that is recurrent (has returned after treatment).

How many people will take part in this study?

Up to 66 participants will be enrolled in this multicenter study. Up to 6 will take part at NCI.

Description of Research Study

Before you begin the study

You will have screening tests to help the doctor decide if you are eligible to take part in this study. If some of these tests have been performed within the past 14 days, they may not need to be repeated. These tests include medical history, physical exam, routine blood and urine tests, CT scan or MRI of your brain, CT scan or x-ray of your chest, an EKG and you will also complete a questionnaire about your quality of life.

During the study

If you are found to be eligible to take part in this study, you will be assigned to a study group based on if you have received a drug called bevacizumab in the past.

You will be in Group A if you have not received bevacizumab in the past.

You will be in Group B if you have received bevacizumab in the past.

Both groups will receive pazopanib and topotecan at the same dose level and on the same schedule. Up to 34 participants will be enrolled in Group 1 and up to 32 participants will be enrolled in Group 2.

Study Drug Administration

Each cycle is 28 days.

You will take capsules of topotecan by mouth 1 time every day at about the same time each day. You should swallow the capsules whole with at least 1 cup (8 ounces) of water, with or without food.

You will take tablets of pazopanib by mouth 1 time every day at about the same time each day. They should be taken on an empty stomach (at least 1 hour before and 2 hour after eating) with about 1 cup (8 ounces) of water.

Pazopanib should be taken whole with water and must not be broken or crushed.

If a dose of pazopanib is missed, it should not be taken if it is less than 12 hours until the next dose.

If you vomit after taking the study drugs, you should not take a replacement dose on that day. You should resume taking the study drugs at the next scheduled dose on the following day. If vomiting continues, you should tell your doctor.

You will be given a study drug diary to record the times that you take the study drugs and if you vomit. You should bring the diary to each study visit.

Study Visits

At Week 1, your blood pressure will be measured.

At Week 2, your blood pressure will be measured and blood (about 1 teaspoon) will be drawn for routine tests.

At Week 4, you will have an EKG.

Every 4 weeks:

- You will have a physical exam.
- Blood (about 2 teaspoons) will be drawn for routine and biomarker testing.
- Urine will be collected to check your kidney function.

Every 8 weeks:

- You will have a neurological exam.
- Blood (about 1 teaspoon) will be drawn to check thyroid function.
- You will have an EKG.
- If you are in Group A, you will have a brain MRI or CT scan at Week 4 of Cycle 2, and then every other cycle after that (Cycles 4, 6, 8 and so on) to check the status of the disease. You will also complete the symptom questionnaire at these visits.

- If you are in Group B, you will have a brain MRI or CT scan at Week 4 of Cycles 1, 2, 3, and then every other cycle after that (Cycles 5, 7, 9 and so on) to check the status of the disease. You will also complete the symptom questionnaire at these visits.

At any time during the study, extra tests may be performed if the doctor thinks they are needed for your safety. The study doctor will tell you more about any extra tests.

End-of-Treatment Visit

Within 14 days after your last dose of the study drugs, you will have an end-of-treatment visit. The following tests and procedures will be performed:

- You will have a physical exam.
- Blood (about 2 teaspoons) will be drawn for routine and biomarker testing. This blood draw will also include a pregnancy test if you can become pregnant.

Length of Treatment

You may take the study drugs for up to 1 year. You will no longer be able to take the study drugs if the disease gets worse, if intolerable side effects occur, or if you are unable to follow study directions.

Your participation on the study will be over after the long-term follow-up phone calls.

Long-Term Follow-Up Calls

After you have stopped taking the study drugs and completed your end-of-treatment visit, the study staff will call you 1 time every 3 months from then on to check on how you are doing. Each phone call should last about 5 minutes.

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 6 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
- condoms with spermicide
- diaphragm with spermicide

Alternative Approaches or Treatments

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

While on this study, you are at risk for side effects. These side effects will vary from person to person. The more commonly occurring side effects are listed in this form, as are rare but serious side effects. You should discuss these with the study doctor. You may also want to ask about uncommon side effects that have been observed in small numbers of patients but are not listed in this form. Many side effects go away shortly after treatment is stopped, but in some cases, side effects may be serious, long-lasting or permanent, and may even cause death.

Tell the study staff about any side effects you may have, even if you do not think they are related to the study drugs.

Topotecan and pazopanib each may cause low blood cell counts (red blood cells, platelets, and/or white blood cells):

- A low red blood cell count (anemia) may cause difficulty breathing and/or fatigue. You may need a blood transfusion.
- A low platelet count increases your risk of bleeding (such as nosebleeds, bruising, stroke, and/or digestive system bleeding). You may need a platelet transfusion.
- A low white blood cell count increases your risk of infection (such as pneumonia and/or severe blood infection). Infections may occur anywhere and become life-threatening. Symptoms of infection may include fever, pain, redness, and difficulty breathing.

Topotecan Side Effects

Common (occurring in more than 20% of patients)

• fatigue • weakness • fever • hair loss (partial or total)	• nausea • vomiting • diarrhea • constipation	• pain • severe life-threatening infection (possible low blood pressure, kidney

• abdominal pain	• low blood cell counts (red, platelets, white) • difficulty breathing	failure, and/or heart failure)

Occasional (occurring in 3-20% of patients)

• headache • skin rash • abnormal sensation (such as pins and needles) • intestinal blockage	• loss of appetite • mouth blisters/sores (possible difficulty swallowing)	• abnormal liver tests (possible liver damage or yellowing of the skin and/or eyes) • cough

Rare but serious (occurring in fewer than 3% of patients)

• tissue swelling	• lung inflammation (possible difficulty breathing)	• allergic reaction (possibly life-threatening, such as difficulty breathing, low blood pressure, and/or organ failure)

Pazopanib Side Effects

Common (occurring in more than 20% of patients)

• high blood pressure • fatigue • headache • change in hair color • abnormal salts, minerals, and/or acids in the blood (possible weakness, swelling, fatigue, low blood pressure, organ failure, heart problems, changes in mental status, and/or seizure)	• high blood sugar (possible diabetes) • overactive thyroid gland (possible weight loss, heart rate changes, and/or sweating) • diarrhea • nausea • abnormal digestive blood test (possible inflammation of the pancreas)	• weight loss • loss of appetite • vomiting • abnormal taste • abdominal pain • low blood cell counts (white/platelets) • abnormal liver tests (possible liver damage and yellowing of the skin and/or eyes) • pain (muscle/bone/tumor)

Occasional (occurring in 3-20% of patients)

• swelling (arm/leg) • chest pain • severe heart problems • blood clots in a vein (possible pain, swelling, and/or redness) • dizziness • difficulty sleeping • voice changes • chills • hand-foot syndrome (palms of hands/soles of feet having pain, swelling, and blistering)	• skin rash • hair loss (partial or total) • lightening of skin • dry skin • nail changes • low blood sugar • underactive thyroid gland (possible weight gain, heart failure, and/or constipation) • upset stomach • bleeding in the mouth	• mouth blisters/sores (possible difficulty swallowing) • weakness • blurry vision • blood in the urine • abnormal kidney test (possible kidney damage) • difficulty breathing • cough • collapsed lung (possibly difficulty breathing) • nosebleed

Rare but serious (occurring in fewer than 3% of patients)

• irregular heartbeat • heart attack/failure • decreased blood supply to the heart • severe increase in blood pressure (possible stroke) • swelling (face) • temporary stroke symptoms • brain damage that may be reversible (possible	• uncontrolled movements • stroke • bleeding in/around the brain • multiple blood clots (possible organ dysfunction and/or failure) • inflammation of the pancreas (possible abdominal pain)	• bleeding or blood in the stool • abnormal connections or passageways between different parts of the digestive system • liver damage • decreased kidney function (possible kidney failure) • coughing up blood

headache, confusion, seizures, and/or vision loss)	• hole in the intestines (possibly leaking contents into the abdomen)	• blood clots in the lung (possible failure to breathe) • bleeding in or from the tumor

Frequency Unknown

Pazopanib may cause fatal liver damage.

Other Risks

Blood draws may cause pain, bleeding, and/or bruising. You may faint and/or develop an infection with redness and irritation of the vein at the site where blood is drawn. Frequent blood collection may cause anemia (low red blood cell count), which may create a need for blood transfusions.

Questionnaires may contain questions that are sensitive in nature. You may refuse to answer any question that makes you feel uncomfortable. Collection of this information is authorized under 42 USC 285. If you have concerns about completing the questionnaire, you are encouraged to contact your doctor or the Principal Investigator.

This study may involve unpredictable risks to the participants**.**

Potential Benefits of Participation

Are there benefits to taking part in this study?

The aim of this study is to determine a safe dose and 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.

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, Brain Tumor Trials Collaborative (BTTC) or their agent(s)
- Qualified representatives from Novartis, the pharmaceutical company who produces pazopanib.

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 your disease comes back during treatment
- if you become pregnant while on study therapy
- if you have side effects from the treatment that your doctor thinks are too severe

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 Brain Tumor Trials Collaborative (BTTC), Novartis 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.

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.

The National Institutes of Health and the research team for this study are using drugs developed by Novartis through a joint study with your researchers and the company. The company also provides financial support for this study.

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, Mark Gilbert, M.D., Building 82, Room 235A, Telephone: 301-402.638**3**. 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 NOVEMBER 07, 2016 THROUGH NOVEMBER 6, 2017.

Signature of Investigator — Date

Print Name

Signature of Witness — Date

Print Name