RESEARCH SUBJECT INFORMATION AND CONSENT FORM

TITLE: Phase 2 Study of Sorafenib, Valproic Acid, and Sildenafil in the Treatment of Recurrent High-Grade Glioma

PROTOCOL NO.: MCC-14816
VCU IRB# HM14816

SPONSOR: VCU Massey Cancer Center
Richmond, VA 23298

PRINCIPAL INVESTIGATOR: Mark Malkin, M.D.
Virginia Commonwealth University (VCU)
[redacted]

INTRODUCTION

This informed consent form will tell you about this research study, which is also called a clinical trial. Your study doctor or study team will explain the research study to you. Research studies only include people who choose to take part. You have the option to not participate. You may take home an unsigned copy of this consent form so that you can discuss the study with your family or friends before making your decision. You may also discuss it with your health care team. If you have any questions, ask your study doctor or study team for more explanation. Please take your time to make your decision about taking part in this study.

OVERVIEW AND KEY INFORMATION

Taking part in this study is your choice

You can choose to take part or you can choose not to take part in this study. You also can change your mind at any time. Whatever choice you make, you will not lose access to your medical care or give up any legal rights or benefits.

If you decide not to enter this study, there are other treatments available. You should talk with your doctor about other possible treatments. You do not have to participate in this study to be treated for high-grade glioma.

Why is this study being done?

The purpose of this research study is to test the safety, tolerability, and effectiveness of the combination of three drugs, sorafenib (Nexavar®), valproic acid (Depakote®), and sildenafil (Viagra®), when used to treat high-grade glioma, a type of brain tumor. Sorafenib is an anti-cancer drug approved by the FDA in other types of cancer, but not brain tumors. Valproic acid, available in generic form or a variety of trade names/forms, is used as a standard approach to treating or preventing seizures in patients with high-grade glioma and may enhance the effectiveness of sorafenib in treating cancer. Sildenafil is a medication used for the treatment of erectile dysfunction, and may help with getting sorafenib into the brain tumor. You are being asked to participate in this study because you have been diagnosed with recurrent high-grade

glioma, and may meet the study entry requirements. Approximately 44 individuals will participate in this study.

What will happen if I take part in this study?

If you decide to take part in this research study, you will be asked to sign this consent form after you have had all your questions answered.

Most of the exams, tests, and procedures you will have are part of the usual approach when treating advanced cancer, if you plan to have cancer treatment. Your study doctor or study team will tell you about these. The results of the usual exams, tests, and procedures may also be used for the research purposes of this study. We give you more information in the "Procedures" section.

All three drugs (sorafenib, valproic acid, and sildenafil) are taken by mouth twice a day, every day. There is no IV chemotherapy during this study. There may be times where your doctor will have you not take one or more of the three drugs, depending on side effects. Should any changes in drug doses become necessary, this will be communicated to you.

You will receive study treatment for as long as the possible benefits outweigh the risks and the study remains open. This is likely to be a period of time measured in months. If there are significant findings that might affect your interest in participation, they will be shared with you. Upon completing the study treatment, you will be followed for late side effects.

What are the risks of taking part in this study?

We want to make sure you know about a few key risks right now. We give you more information in the "Risks and Discomforts" section.

The combination of sorafenib, valproic acid, and sildenafil is investigational, which means that its safety and effectiveness is not known. The study is being conducted because test tube studies suggest that the combination may be effective for the treatment of high-grade glioma. It is not clear whether the combination of these drugs will lead to more side effects.

Some of the most common side effects that the study doctors know about are:

- Fatigue
- Hair thinning or patchy hair loss
- Diarrhea
- Nausea
- Loss of appetite
- Weight loss
- High blood pressure
- Rash, including a red, blistering, painful rash of the hands and feet
- Pain (including headache, abdomen, mouth, bone, and tumor pain)
- Tremor

What are the benefits of taking part in this study?

There is no guarantee that you will receive any medical benefits from being in this study. The study drugs may or may not be helpful for your type of cancer. Patients in the future may benefit from the knowledge gained through your participation in the study.

PROCEDURES

Before you begin the study:

You will need to have the following exams, tests or procedures to determine whether you can be in the study:

- An MRI or contrast-enhanced CT scan of your brain
- History and physical examination by your doctor
- An ECG to evaluate the electrical activity of your heart
- Blood tests to assess your blood, kidney function, and liver function
- Pregnancy test, if applicable

These exams, tests or procedures are part of regular cancer care and may be done even if you do not join the study. If you have had some of them recently, they may not need to be repeated. This will be up to your study doctor.

During the study:

You will take sorafenib, valproic acid, and sildenafil tablets by mouth twice daily, on an empty stomach. You will keep a daily drug diary.

At each visit, you should bring all of your remaining study drug supply to the research clinic.

You will be seen by a research nurse and/or doctor every 2 weeks for the first 8 weeks—after which you will be seen every month.

Doctors are trying to learn which types of brain tumors will respond to this treatment the best. Doctors will analyze your tissue from a prior biopsy to look for the presence of certain proteins that may predict who will respond to treatment. A new research-only biopsy will not be needed; all tests can be performed on tissue that has already been collected.

MRI or contrast-enhanced CT scans will be performed at regular intervals, to follow the status of the cancer. This helps doctors determine whether the treatment is working or not. MRI or contrast-enhanced CT scans will be performed every 1-2 months, depending on whether or not the tumor appears to be shrinking.

Blood tests—testing your blood, kidney, and liver function—will be done every other week for the first 8 weeks and then at the beginning of each cycle.

EKGs will be repeated after about two weeks and eight weeks of treatment.

If you develop side effects from the treatment, please talk with your study team or doctor about them. Your doctor may investigate with additional tests, such as x-rays, CTs, EKGs or blood tests. You may need additional medications, such as electrolytes by mouth or intravenously to manage side effects. Additional specialists (such as a cardiologist) could be asked to consult on your situation. Sometimes hospitalization is required to manage side effects or perform additional monitoring. Occasionally, certain side effects may make it impossible to continue study treatment. Your doctor or nurse will discuss with you the nature of those tests, treatments, and decisions at the time they are determined to be necessary.

After you are finished with the study treatment we would like to stay in touch with you and your family to see how you are doing. We would like to keep track of your medical condition for the rest of your life. We would like to do this by calling you on the telephone once a month to see how you are doing. Keeping in touch with you and checking on your condition helps us to look at the long-term effects of the study treatment.

Study Plan

This study plan outlines all tests and exams in addition to the actual treatment. The timing of some routine assessments may vary from that shown, depending on your situation. For instance, some participants will continue with response evaluation after treatment stops, while others may not, depending on the status of their cancer when treatment ends.

Test	Before you start study treatment	Cycle 1				Cycle 2				Monthly after week 8*	Off study treatment follow-up	
		First 8 weeks									Initial 30-day period	Extended period
		1	2	3	4	5	6	7	8			
History and physical exam	X	X		X		X		X		X		
Vital signs, weight	X	X		X		X		X		X	X	
Side effects review	X	X		X		X		X		X		
Drug diary and pill count		X		X		X		X		X		
Review of all other medications	X	X		X		X		X		X		
Pregnancy test, counseling	X											
Heart test (EKG)	X		X							8th week of treatment		
Response evaluation	X	Every 2 months or more frequently if needed										
Analysis of prior biopsy sample	X											
Routine blood tests	X	X		X		X		X		X		
Valproic acid level	X		X		X		X			As needed		
Measurement of how long it takes for your blood to clot (for participants taking warfarin)	X	As needed										

* Note: Timing may be extended for participants who remain on study for longer than 36 months

RISKS AND DISCOMFORTS

Your condition may not get better or may become worse while you are in this study.

Only the study participants can take the study drugs. They must be kept out of the reach of children and persons who may not be able to read or understand the label.

You may have some side effects while on the study. Side effects may be mild or serious, even possibly fatal. You may be asked to take additional medicines to prevent or control side effects. Some side effects are predictable from past experience with sorafenib, valproic acid, or sildenafil alone, but other, new side effects may appear. Many side effects go away soon after stopping study treatment, but in some cases side effects may never go away. You should talk to your study doctor about any side effects that you have while taking part in the study.

Possible side effects associated with the use of sorafenib include:

Occurring in 10% or more of patients:

- Rash, including a red, blistering, painful rash of the hands and feet
- Redness, dryness, itching, or peeling of your skin
- Pain (including headache, abdomen, mouth, bone and joints, and tumor pain)
- Fatigue
- Weakness
- Weight loss
- Hair thinning or patchy hair loss
- Nausea
- Vomiting
- Diarrhea
- Constipation
- Bleeding, including internal bleeding
- Condition of the nervous system that causes numbness, tingling, burning
- Low white blood cells, which may lead to infection
- Chemical abnormalities of the blood (low phosphate, increased lipase, increased amylase)
- Loss of appetite
- Voice changes
- Cough
- Infection
- Shortness of breath
- Fever
- High blood pressure

Occurring in 1% to 10% of patients:

- Acne
- Flushing
- Folliculitis
- Thickening of the skin, nails
- Skin cancer (squamous cell)
- Inflammation and sores of the membrane lining the digestive tract
- Dry or irritated mouth and tongue
- Indigestion

- Difficulty swallowing
- Taste changes
- Heart burn
- Flu-like illness
- Low red blood cells, which may cause tiredness or shortness of breath
- Low platelets, which may cause bleeding and bruising
- Chemical abnormalities of the liver without liver dysfunction
- Low blood levels of potassium (possible weakness)
- Low blood levels of calcium (possible weakness and/or cramping).
- Low blood levels of sodium
- Excess protein in the urine. This may cause fluid retention
- Muscle pain, spasms
- Depression
- Erectile dysfunction
- Runny nose
- Nosebleed
- Underactive thyroid gland (possible weight gain, heart failure, constipation)
- Heart failure
- Decreased blood flow to the heart or heart attack (less than 3% of patients)
- Kidney failure

Rare but serious (occurring in less than 1% of patients):

- Severe increase in blood pressure that can lead to a stroke
- Inflammation of the pancreas or gall bladder
- Intestinal damage, including formation of a leak
- Infection of the bile duct
- Liver failure

Possible side effects associated with the use of valproic acid include:

Occurring in 10% or more of patients:

- Headache
- Weakness
- Nausea
- Diarrhea
- Vomiting
- Abdominal pain
- Loss of appetite
- Tremor
- Dizziness
- Drowsiness
- Double vision
- Lazy eye
- Blurred vision
- Difficulty sleeping
- Nervousness
- Respiratory infection
- Infection

- Loss of platelets, which may cause bleeding and bruising. Bleeding may be serious or life-threatening and may require a blood transfusion
- Hair loss

Occurring in 5% to 10% of patients:

- Fever
- Constipation
- Indigestion
- Difficulty walking
- Mood swings
- Thinking abnormal
- Bruising
- Weight gain
- Weight loss
- Hair loss
- Rash
- Swelling of the arms, legs
- Memory changes
- Involuntary eye movement
- Depression
- Sore throat
- Shortness of breath
- Ringing in the ears
- Back pain
- Accidental injury

Rare but serious (occurring in less than 1% of patients):

- Inflammation of the pancreas (possibly with abdominal pain, bleeding)
- Liver injury/liver failure

Possible side effects associated with the use of sildenafil include:

- Erection
- Headache
- Facial flushing
- Abnormal vision, such as changes in color vision (such as having a blue color tinge) and blurred vision.
- Changes in blood pressure (can lower blood pressure in some people)
- Indigestion
- Stuffy nose
- Back pain
- Muscle pain
- Nausea
- Dizziness
- Rash
- Upset stomach

Rarely reported side effects associated with sildenafil include:

- An erection that will not go away (priapism). If you have an erection that lasts more than 4 hours, get medical help right away. If it is not treated right away, priapism can permanently damage your penis.
- Sudden vision loss in one or both eyes. Sudden vision loss in one or both eyes can be a sign of a serious eye problem called non-arteritic anterior ischemic optic neuropathy (NAION). Stop taking sildenafil and call your study doctor right away if you have sudden vision loss in one or both eyes.
- Sudden hearing decrease or hearing loss. Some people may also have ringing in their ears (tinnitus) or dizziness. If you have these symptoms, stop sildenafil and contact your study doctor right away.
- Heart attack, stroke, irregular heartbeats and death have happened rarely in individuals taking sildenafil. Most, but not all, of these individuals had heart problems before taking sildenafil. It is not known if sildenafil caused these problems.

Allergic reaction to sorafenib, valproic acid, or sildenafil is possible. Severe allergic reactions can be life-threatening.

Other, less frequent side effects also have been reported for these drugs. One of these includes some changes to your heart tracing (ECG) that can signal a serious problem. If you notice any "fluttering" of your heart or heart palpitations; if you feel dizzy or close to fainting or "passing out", or if you do faint or pass out: seek emergency medical assistance, and also talk to your study doctor about this. Talk to your study doctor if you want more information about these or other less frequent side effects.

Another less frequent problem is irritation or inflammation of the pancreas (called pancreatitis). If you have pain in your abdomen, nausea, vomiting, or decreased appetite, talk to your study doctor. While these symptoms can occur for other reasons, they can also signal pancreatitis and might require prompt medical evaluation.

Interactions with other medications: There are numerous medications that can interact with the study drugs. Your study team will review your current medications to be sure that there are no concerns before you start the study medications. You should not start taking any new medications (over-the-counter or prescription) without first checking with your study team about possible interactions. Drug interactions are a problem because they may cause you to have more side effects. They may also lead to decreased effectiveness of medications. Certain medications may even make it impossible to continue with the study treatment due to the increased risks.

We ask that you not start any non-urgent new medications without first checking with your study team about possible interactions with the study drug. You will also be given a pocket card by your study team that identifies your participation in a clinical trial. Carry this with you at all times. You can show it to any provider you see outside of the study team so that they can check with a study team member or doctor about any possible interactions that may occur with new medications added while you are in this trial.

A study team member is available during regular business hours (Monday – Friday, 8am to 5pm) at [redacted].

A study doctor is available 24 hours a day, 7 days a week. To contact the Study Doctor On-Call, call the VCU Health System Hospital Operator at [redacted] and ask for the physician carrying pager number [redacted]

Reproductive risks: You should not become pregnant or father a baby while on this study because the study treatment could harm an unborn baby. Women should not breastfeed a baby while on this study. Males should not father a child for at least 2 months after stopping study treatment. It is important to use a medically accepted form of birth control. Accepted methods of birth control include total abstinence, birth control pills, an IUD, diaphragm, progesterone injections or implants, or condoms plus a spermicide. Methods of birth control other than total abstinence are not 100% effective, and should pregnancy occur there is a risk of injury to an unborn baby.

If you or your partner becomes pregnant during the study you should notify the researcher right away.

BENEFITS TO YOU AND OTHERS

There is no guarantee that you will receive any medical benefits from being in this study. The information from this research study may lead to a better treatment in the future for people with high-grade glioma.

COSTS

Sildenafil and sorafenib will be provided without charge. You and/or your insurance will be billed for the standard costs of care of your type of cancer.

CONFIDENTIALITY

Research information about you will be kept confidential through the use of password protected electronic files, locked research areas, and the use of ID numbers. All personal identifying information will be kept in password protected files. Access to all data will be limited to study personnel. Samples used for research purposes (the biopsy) will be stored with the same confidentiality safeguards as the research information. A data and safety monitoring plan is established.

Your doctor will need to evaluate an old biopsy on you to test for the presence of certain proteins that may help determine which patients are best treated with this drug combination. No new research-related tests are required. The information will be kept confidential.

This study does not plan to use your biopsy samples to sequence all or part of your DNA. In the future, the identifiers could be removed from the information and samples you provide for this study. After that removal, your information and samples could be used for new studies without asking for your consent again. Those possible new studies could be done by this study team or other researchers and might involve sequencing all or part of your DNA. If any inventions or discoveries result from the use of your samples, there are no plans to share any money or profits with you. In general, we will not give you any individual results for this study.

You should know that research information about you may be reviewed or copied by the sponsor of the research or by Virginia Commonwealth University. Personal information about you might be shared with or copied by authorized officials of the Federal Food and Drug Administration, or the Department of Health and Human Services, or other official agencies.

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.

Although results of this research may be presented at meetings or in publications, identifiable personal information pertaining to participants will not be disclosed.

COMPENSATION FOR INJURY or ILLNESS

If you are injured by, or become ill, from participating in this study, please contact your study doctor immediately. Medical treatment is available at the Virginia Commonwealth University Health System (VCU Health System). Your study doctor will arrange for short-term emergency care at the VCU Health System or for a referral if it is needed.

Fees for such treatment may be billed to you or to appropriate third party insurance. Your health insurance company may or may not pay for treatment of injuries or illness as a result of your participation in this study.

To help avoid research-related injury or illness it is very important to follow all study directions.

VOLUNTARY PARTICIPATION AND WITHDRAWAL

Your participation in this study is voluntary. You may decide to not participate in this study. Your decision not to take part will involve no penalty or loss of benefits to which you are otherwise entitled. If you do participate, you may freely withdraw from the study at any time. Your decision to withdraw will involve no penalty or loss of benefits to which you are otherwise entitled.

Your participation in this study may be stopped at any time by the study doctor or the sponsor without your consent. The reasons might include:

- the study doctor thinks it necessary for your health or safety;
- you have not followed study instructions;
- the sponsor has stopped the study; or
- administrative reasons require your withdrawal.

If you stop the study treatment, you should follow up with the study team to be checked for side effects.

QUESTIONS

In the future, you may have questions about your study participation. You may also have questions about a possible side effect, reaction to study medication, or a possible research-related injury. If you have any questions, complaints, or concerns about the research, contact:

Mark Malkin, M.D.
Virginia Commonwealth University (VCU)
[redacted]

If you have questions about your rights as a research participant or concerns/complaints about the research, you may contact:

Office of Research
Virginia Commonwealth University
800 East Leigh Street, Suite 3000
Box 980568
Richmond, VA 23298
(804) 827-2157

Do not sign this consent form unless you have had a chance to ask questions and have received satisfactory answers to all of your questions. Additional information about participation in research studies can be found at http://www.research.vcu.edu/irb/volunteers.htm.

CONSENT

I have been provided with an opportunity to read this consent form carefully. All of the questions that I wish to raise concerning this study have been answered.

By signing this consent form, I have not waived any of the legal rights or benefits, to which I otherwise would be entitled. My signature indicates that I freely consent to participate in this research study. I will receive a copy of the consent form once I have agreed to participate.

_____
Participant Name, printed

_____ _____
Participant Signature Date

_____ _____
Signature of Person Conducting Informed Consent Date

_____
Printed Name of Person Obtaining Consent

_____ _____
Investigator Signature (if different from above) Date

_____
Printed Name of Investigator