Research Consent Form
Dana-Farber/ Harvard Cancer Center
BIDMC/BWH/CH/DFCI/MGH/Partners Network Affiliates OHRS 04.15.13

Protocol Title:
A study to evaluate vascular normalization in patients with recurrent glioblastoma treated with bevacizumab using FMISO PET and Vascular MRI.

DF/HCC Principal Research Doctor / Institution:
Elizabeth Gerstner, MD/ Massachusetts General Hospital

A. INTRODUCTION

You are invited to take part in a clinical trial, a type of research study because you have a type of brain cancer called glioblastoma that has returned after previous treatment. For purposes of this research, you will be referred to as a "participant". This research study is exploring the flow of blood and oxygen in your tumor changes from treatment with bevacizumab or bevacizumab and lomustine using FMISO-PET and MRI scans.

It is expected that about 40 people will take part in this research study.

The National Cancer Institute is supporting this research study by providing funding for the study.

This research consent form explains why this research study is being done, what is involved in participating in the research study, the possible risks and benefits of participation, alternatives to participation, and your rights as a research participant. The decision to participate is yours. If you decide to participate, please sign and date at the end of this form. We will give you a copy so that you can refer to it while you are involved in this research study. If you choose not to participate in this research study, the research doctors will discuss other treatment options with you and/or refer you back to your primary doctor.

We encourage you to take some time to think this over, to discuss it with other people and your primary doctor, and to ask questions now and at any time in the future.

B. WHY IS THIS RESEARCH STUDY BEING DONE?

This research study is a Pilot Study. The purpose of a pilot study is to obtain the preliminary data needed to justify performing a la0072ger clinical trial on the effectiveness of an investigational intervention. In this research study, we are using FMISO-PET and MRI scans to explore the delivery of bevacizumab or

bevacizumab and lomustine as a combination to the blood vessels in your tumor before and after treatment.

Bevacizumab is approved by the U.S. Food and Drug Administration for use in people with your type of cancer. It works by targeting a specific protein called VEGF, which plays a role in promoting the growth or spreading of tumor blood vessels. Since anti-VEGF agents also affect normal blood vessels in the brain, they can inhibit the way other drugs used in combination with bevacizumab are delivered to the tumor.

Lomustine may also be used during this study in combination with bevacizumab under the discretion of your oncologist. Lomustine is approved by the U.S. Food and Drug Administration for use in people with your type of cancer. It works by stopping fast-growing cancer cells from dividing by binding to and damaging the DNA within these cancer cells.

In PET scans, a radioactive substance is injected into the body. The scanning machine finds the radioactive substance, which tends to go to cancer cells. For the PET scans in this research study, we are using an investigational radioactive substance called FMISO. “Investigational” means that the role of FMISO-PET scans is still being studied and that research doctors are trying to find out more about it. FMISO goes to areas with low oxygenation so parts of the tumor that do not have enough oxygen can be seen.

In addition, a vascular MRI will be used to evaluate the changes in tumor blood flow, blood volume, and how receptive blood vessels are. This scan will occur at baseline and on Day 1 of each 28 day Cycle for the first six Cycles and then every month thereafter. This scan will be performed at the same time of the FMISO-PET scans prior to therapy, Day 14 and Day 28.

C. WHAT OTHER OPTIONS ARE THERE?

Taking part in this research study is voluntary. Instead of being in this research study, you have other options which may include the following:

- Receive standard treatment including bevacizumab or bevacizumab and lomustine without FMISO -PET scans.
- Take part in another research study.
- Receive no therapy specific to your cancer.
- Comfort care, also called palliative care. This type of care may help to reduce pain, tiredness, appetite problems and other problems caused

by the cancer. It does not treat the cancer directly, but instead tries to treat the symptoms.

Please talk to the research doctor about your options before you decide whether you will take part in this research study.

D. WHAT IS INVOLVED IN THE RESEARCH STUDY?

Before the research starts (screening): After signing this consent form, you will be asked to undergo some screening tests or procedures to find out if you can be in the research study. Many of these tests and procedures are likely to be part of regular cancer care and may be done even if it turns out that you do not take part in the research study. If you have had some of these tests or procedures recently, they may or may not have to be repeated.

- **A medical history,** which includes questions about your health, current medications, and any allergies.
- **Physical Exam** including measuring your height, weight and vital signs
- **Performance status**, which evaluates how you are able to carry on with your usual activities.
- **Routine Blood tests**
- **Blood pregnancy test** for women of childbearing potential.
- **Urine test** to test your kidney function.

If these tests show that you are eligible to participate in the research study, you will begin the study treatment. If you do not meet the eligibility criteria, you will not be able to participate in this research study.

After the screening procedures confirm that you are eligible to participate in the research study:

Please note that this study does not add any additional treatment to participants with your type of cancer. There will be no change in your treatment with bevacizumab or bevacizumab and lomustine based on the results of any procedures or tests carried out as a part of the study.

If you take part in this research study each treatment cycle will last 28 days.

Prior to Therapy
You will have the following procedures done before you receive bevacizumab or bevacizumab and lomustine**:**

- **An assessment of your tumor** by Vascular MRI (Magnetic Resonance Imaging) and FMISO-PET scans at Baseline (7-14 days prior to start of bevacizumab or bevacizumab and lomustine).
- **Blood pregnancy test** for women of childbearing potential.

Day 1
You will have the following procedures done after you receive bevacizumab or bevacizumab and lomustine**:**

- **An assessment of your tumor** by Vascular MRI (Magnetic Resonance Imaging) after you have received bevacizumab or bevacizumab and lomustine

Day 14
You will have the following procedures done before you receive bevacizumab**:**

- **An assessment of your tumor** by Vascular MRI (Magnetic Resonance Imaging) and FMISO-PET scans before you have received bevacizumab.
- **Blood pregnancy test** for women of childbearing potential.

Day 28
You will have the following procedures done before you receive bevacizumab**:**

- **An assessment of your tumor** by Vascular MRI (Magnetic Resonance Imaging) and FMISO-PET scans before you have received bevacizumab.

FMISO-PET Scans:

You will have your scans performed in Charlestown, MA at the Martinos Center. You will be injected with two separate intravenous (IV) injections (listed below). Intravenous means a short catheter will be placed into a vein in your arm.

- FMISO for PET scan and a contrast dye for the MRI scan
- Drawing blood to assess the radioactivity of FMISO

The PET scan will take approximately 60-75 minutes. You will receive one injection of FMISO. Following the injection of the radiotracer, blood samples will be taken from the second IV line. The tracer is given through a vein (IV) and travels through your blood and collects in organs and tissues. You will need to wait nearby as the tracer is absorbed by your body. This takes about 90 minutes.

Then, you will lie on a narrow table that slides into a large tunnel-shaped scanner. The PET will pick up signals from the tracer and a computer will change

the signals into 3D pictures that will be displayed on a monitor for your study doctor to read.

MRI Scan:

MRI scans will last about 60-75 minutes. This will occur at the same time as the PET scan. You will be injected with contrast dye twice during the MRI scan. You will have 3 MRI scans (prior to starting treatment, day 1 of treatment and day 14 of treatment) that would not have routinely been performed if you were not participating in this study.

Blood samples will be collected during the PET scans in order to measure how your blood vessels are processing the radiotracer FMISO and how well it is being delivered to the tumor tissue.

You will be assessed for side effects via clinic visit or phone call about 24 hours after each of the visits above.

Planned Follow-up: We would like to call you every 3 months for three years after your day 28 visit to see how you are doing and if you are experiencing any side effects. If you were removed from the study due to an unacceptable side effect, you will be followed until it has been resolved.

E. HOW LONG WILL I BE IN THIS RESEARCH STUDY?

You will be in this research study for about 1 year, and followed for three years after completion of day 28.

The research doctor may decide to take you off the research study for many reasons including if:

- It is considered to be in your best interest
- The study treatment or procedures are found to be unsafe or ineffective
- There is any problem with following study treatments and procedures
- Your condition worsens
- Or for other unforeseen reasons that make it necessary to stop your participation in the research study

If you are removed from the research study, the research doctor will explain to you why you were removed.

In addition, you can stop participating in the research study at any time, however, the FDA requires that any information collected up to the point of your withdrawal cannot be removed from the study. If you decide to stop participating in this research study, we encourage you to talk to the research doctor and your primary doctor first.

F. WHAT ARE THE RISKS OR DISCOMFORTS OF THE RESEARCH STUDY?

There are risks to taking part in any research study. One risk is that there may be side effects from the procedures performed in the research study.
All cancer treatments can have side effects, which can range from mild and reversible to severe, long lasting and possibly life-threatening. There is a great deal of variability among side effects of different cancer treatments and between individuals. In a research study, all of the risks or side effects may not be known before you start the study. **You need to tell your doctor or a member of the study team immediately if you experience any side effects.**

During the research study, you will be notified of newly discovered side effects or significant findings, which may affect your health or willingness to participate. You may be asked to sign a new consent form that shows that you have been informed of new information relating to this research study.

Risks Associated with FMISO

If you receive Ativan or another sedative, there is a small risk of a reaction to the sedative medication. A sedative would be administered if you will have trouble lying still during the PET scan or are claustrophobic.

We will not administer this drug if you have had a bad reaction to similar medications in the past or if your medical history suggests that you are at risk for a reaction. If you receive a sedative, you will not be allowed to drive yourself home.

After the FMISO PET scan, relaxation is advised. As a result of your participation in this study, you will be exposed to radiation for the injection of FMISO. Please note that this radiation is not necessary for your medical care and is for research purposes only.

The total amount of radiation exposure you will get from taking part in this study is equal to a whole body exposure of about 4.8 milliSieverts (mSv). A mSv is a unit of radiation dose. This amount of radiation is about the same as you would

normally get in about 16 months from natural background sources from the earth and the sky.

A possible effect that could occur at doses used in this study is a slight increase in the risk of developing cancer later in life.

Since the effects of radiation can be cumulative, it is important to know of your past research related radiation exposure. If you have participated in other research studies in the past 12 months that have involved radiation exposure please inform the investigators or study staff. If it is determined that your prior radiation exposure exceeds our current guidelines, it is possible that you will not be allowed to participate in this study.

Radiation Risks Associated with Scans and X-Rays:
While you are in this research study, PET scans, and/or other scans utilizing radioactivity will be used to evaluate your disease. The PET scans could have the following risks:

- Discomfort or a general feeling of unease from lying still on your back for a total of about 60-75 minutes for each scan.
- Fear of being in an enclosed space (claustrophobia)

The frequency of these exams is greater than what you would receive as standard care. In the long term, over many years, there is a very low risk of developing a new cancer as a result of the radiological evaluation and treatment for your cancer.

Risks Associated with MRI Scans:
When having an MRI (Magnetic Resonance Imaging) scan, you will lie still on a table that slides into a tunnel slightly wider than your body. People who feel uncomfortable in confined spaces (claustrophobia) may feel uncomfortable in the narrow cylinder. If you feel uncomfortable in confined spaces, please tell your research doctor. Your doctor may give you a medication to make you feel more comfortable. As images are taken, a loud banging noise will be produced. Earplugs or headphones will be available if needed. The MRI can be stopped at any time at your request, but the scan may not be complete.

Risks Associated with Contrast Agents Used During Scans:
There is a small risk with using a contrast agent that is injected into a vein during the MRI scan. The contrast agent is a special dye that highlights organs, blood vessels or tissue to make them more visible. Depending on the type of contrast agent that is used, it may cause decreased kidney function or worsen kidney function in people who already have decreased kidney function. Therefore, we

will monitor your kidney function closely while you participate in this study. If there is any change in your kidney function, we may have to remove you from the study.

Uncommonly, some people have allergic reactions (such as hives and itching) to the contrast agent. Serious reactions (for example, drop in blood pressure, difficulty breathing or severe allergic reaction and death) are rare.

Reproductive Risks:
The FMISO used in the PET scans for this research study may affect a fetus. While participating in this research study, you should not become pregnant or father a baby, and should not nurse a baby. Let your doctor know immediately if you become pregnant or find out that you are going to be the father of a child. We can provide counseling about preventing pregnancy for either male or female study participants.

Non-Physical Risks:
Because of side effects or the time required for tests and clinic visits while you are on this research study, you may be unable to keep up with your normal daily activities.

G. WHAT ARE THE BENEFITS OF THE RESEARCH STUDY?

You will not receive any direct benefit from participating in this study. We hope the information learned from this research study will help doctors learn more about using PET scans to tailor treatment plans for patients with your type of cancer in the future.

H. CAN I STOP BEING IN THE RESEARCH STUDY AND WHAT ARE MY RIGHTS?

You have the right to choose not to sign this form. If you decide not to sign this form, you cannot participate in this research study.

You can stop being in the research study at any time. Tell the research doctor if you are thinking about stopping or decide to stop. He or she will tell you how to stop. Leaving the research study will not affect your medical care outside of the research study.

If you choose not to participate, are not eligible to participate, or withdraw from this research study, this will not affect your present or future care and will not cause any penalty or loss of benefits to which you are otherwise entitled.

It is important to tell the research doctor if you are thinking about stopping so your research doctor can evaluate the risks from stopping the study drug. Another reason to tell your research doctor that you are thinking about stopping is to discuss what follow-up care and testing could be most helpful for you.

I. WILL I BE PAID TO TAKE PART IN THIS RESEARCH STUDY?

You will not be paid for your participation in this research study.

We may use your samples and information to develop a new product or medical test to be sold. The sponsor, hospital, and researchers may benefit if this happens. There are no plans to pay you if your samples are used for this purpose.

J. WHAT ARE THE COSTS?

Taking part in this research study might lead to added costs to you or your insurance company.

You will not be charged for FMISO.

You or your insurance company will be charged for portions of your care during this research study that are considered standard care. You may be responsible for co-payments and deductibles that are typical for your insurance coverage.

Bevacizumab and lomustine are commercially available which means that the FDA has approved them for use in patients with your type of cancer. Because there is evidence that supports using this drug in patients with your type of cancer, you or your insurance company will be billed for the cost of bevacizumab or bevacizumab and lomustine if receiving both treatments.

If you have questions about your insurance coverage, or the items you might be required to pay for, please call financial services for information. The contact information for financial services are:

- Massachusetts General Hospital: (617) 726-2191

The National Cancer Institute provides an online resource to help people participating in cancer clinical trials understand which services their insurance company is required by law to pay. This can be found at the website below or can be provided by the study team:

www.cancer.gov or 1-800-4-CANCER (1-800-422-6237)

K. WHAT HAPPENS IF I AM INJURED OR SICK BECAUSE I TOOK PART IN THIS RESEARCH STUDY?

If you think you have been injured as a result of taking part in this research study, tell the person in charge of this research study as soon as possible. The research doctor's name and phone number are listed in this consent form.

We will offer you the care needed to treat injuries directly resulting from taking part in this research. We may bill your insurance company or other third parties, if appropriate, for the costs of the care you get for the injury, but you may also be responsible for some of them.

There are no plans for Massachusetts General Hospital to pay you or give you other compensation for the injury. You do not give up your legal rights by signing this form.

L. WHAT ABOUT CONFIDENTIALITY?

We will take measures to protect the privacy and security of all your personal information, but we cannot guarantee complete confidentiality of study data.

Medical information created by this research study may become part of your hospital medical record and may be forwarded to your primary doctor. Information that does not become part of your medical record will be stored in your study file. It may also become part of a DF/HCC research database.

The results of this research study may be published. You will not be identified in publications without your permission.

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.

M. WHOM DO I CONTACT IF I HAVE QUESTIONS ABOUT THE RESEARCH STUDY?

If you have questions about the study, please contact the research doctor or study staff as listed below:

Massachusetts General Hospital

- Elizabeth Gerstner, MD: 617-724-8770

24-hour contact: MGH: Elizabeth Gerstner, MD at (617) 724-8770 or page at (617) 726-2000, ask for beeper 13385.

For questions about your rights as a research participant, please contact a representative of the Office for Human Research Studies at DFCI (617) 632-3029. This can include questions about your participation in the study, concerns about the study, a research related injury, or if you feel/felt under pressure to enroll in this research study or to continue to participate in this research study.

N. PRIVACY OF PROTECTED HEALTH INFORMATION

Federal law requires Dana-Farber/Harvard Cancer Center (DF/HCC) and its affiliated research doctors, health care providers, and physician network to protect the privacy of information that identifies you and relates to your past, present, and future physical and mental health conditions ("protected health information"). If you enroll in this research study, your "protected health information" will be used and shared with others as explained below.

1. What protected health information about me will be used or shared with others during this research?

- Existing medical records, including mental health records.
- New health information created from study-related tests, procedures, visits, and/or questionnaires

2. Why will protected information about me be used or shared with others?

The main reasons include the following:

- To conduct and oversee the research described earlier in this form;
- To ensure the research meets legal, institutional, and accreditation requirements;
- To conduct public health activities (including reporting of adverse events or situations where you or others may be at risk of harm); and
- To provide the study sponsor with information arising from an adverse event or other event that relates to the safety or toxicity of the drug for the purpose of this or other research relating the study drug and its use in cancer; and,

- Other reasons may include for treatment, payment, or health care operations. For example, some medical information produced by this research study may become part of your hospital medical record because the information may be necessary for your medical care. (You will also be given a notice for use and sharing of protected health information.)

3. Who will use or share protected health information about me?

- DF/HCC and its affiliated research doctors and entities participating in the research will use and share your protected health information. In addition, other DF/HCC offices that deal with research oversight, billing or quality assurance will be able to use and share your protected health information.

4. With whom outside of DF/HCC may my protected health information be shared?

While all reasonable efforts will be made to protect the confidentiality of your protected health information, it may also be shared with the following entities:

- Outside individuals or entities that have a need to access this information to perform functions relating to the conduct of this research such as analysis by outside laboratories on behalf of DF/HCC and its affiliates (for example, data storage companies, insurers, or legal advisors).
- Other research doctors and medical centers participating in this research, if applicable
- Federal and state agencies (for example, the Department of Health and Human Services, the Food and Drug Administration, the National Institutes of Health, and/or the Office for Human Research Protections), or other domestic or foreign government bodies if required by law and/or necessary for oversight purposes. A qualified representative of the FDA and the National Cancer Institute may review your medical records.
- Hospital accrediting agencies
- A data safety monitoring board organized to oversee this research, if applicable

Some who may receive your protected health information may not have to satisfy the privacy rules and requirements. They, in fact, may share your information with others without your permission.

5. For how long will protected health information about me be used or shared with others?

- There is no scheduled date at which your protected health information that is being used or shared for this research will be destroyed, because research is an ongoing process.

6. Statement of privacy rights:

- You have the right to withdraw your permission for the research doctors and participating DF/HCC entities to use or share your protected health information. We will not be able to withdraw all the information that already has been used or shared with others to carry out related activities such as oversight, or that is needed to ensure quality of the study. To withdraw your permission, you must do so in writing by contacting the researcher listed above in the section: “Whom do I contact if I have questions about the research study?”
- You have the right to request access to your protected health information that is used or shared during this research and that is related to your treatment or payment for your treatment, but you may access this information only after the study is completed. To request this information, please contact the researcher listed above in the section: “Whom do I contact if I have questions about the research study?”

O. DOCUMENTATION OF CONSENT

My signature below indicates:

- I have had enough time to read the consent and think about participating in this study;
- I have had all of my questions answered to my satisfaction;
- I am willing to participate in this study;
- I have been told that my participation is voluntary and I can withdraw at any time

Signature of Participant or Legally Authorized Representative

Date

Relationship of Legally Authorized Representative to Participant

DFCI Protocol Number: 13-482	Approved Date (DFCI IRB Approval): 03/28/2019
Date Posted for Use: 05/23/2019	

Adult Participants

To be completed by person obtaining consent:

The consent discussion was initiated on _____ (date).

Signature of individual obtaining consent: _____

Printed name of above: _____

Date: _____

☐ A copy of this signed consent form will be given to the participant or legally authorized representative, or, where the participant is a minor, the participant's parent or legal guardian.

For Adult Participants

☐ 1) The participant is an adult and provided consent to participate.

☐ 1a) Participant (or legally authorized representative) is a non-English speaker and signed the translated Short Form in lieu of English consent document:

As someone who understands both English and the language spoken by the participant, I interpreted and/or witnessed, in the participant's language, the researcher's presentation of the English consent form. The participant was given the opportunity to ask questions.

Signature of Interpreter/Witness: _____

Printed Name of Interpreter/Witness: _____

Date: _____

☐ 1b) Participant is illiterate

The consent form was read to the participant who was given the opportunity to ask questions.

Signature of Witness: _____

Printed Name of Witness: _____

Date: _____

☐ 2) The participant is an adult who lacks capacity to provide consent and his/her legally authorized representative:

☐ 2a) gave permission for the adult participant to participate

☐ 2b) did not give permission for the adult participant to participate

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