Informed Consent Form

Quantitative MRSI to Predict Early Response to Standard RT/Temozolomide ± Belinostat Therapy in Newly-Diagnosed Glioblastomas

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Emory University
Consent to be a Research Subject

COHORT 2 CONSENT

Title: Winship2434-13: Quantitative MRSI to Predict Early Response to Standard RT/Temozolomide ± Belinostat Therapy in Newly-Diagnosed Glioblastomas

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Study Support: National Cancer Institute (NCI)

Introduction

You are being asked to be in a medical research study. This form is designed to tell you everything you need to think about before you decide to consent (agree) to be in the study or not to be in the study. **It is entirely your choice. If you decide to take part, you can change your mind later on and withdraw from the research study.** The decision to join or not join the research study will not cause you to lose any medical benefits. If you decide not to take part in this study, your doctor will continue to treat you.

Before making your decision:

- Please carefully read this form or have it read to you
- Please listen to the study doctor or study staff explain the study to you
- Please ask questions about anything that is not clear

You can take a copy of this consent form, to keep. Feel free to take your time thinking about whether you would like to participate. You may wish to discuss your decision with family or friends. Do not sign this consent form unless you have had a chance to ask questions and get answers that make sense to you. By signing this form you will not give up any legal rights.

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 may search this Web site at any time.

Study Overview

Glioblastoma (GBM) is a very aggressive brain tumor that is almost never cured by standard therapy. Standard therapy includes surgery, radiation therapy (RT) and chemotherapy. In this study, we are testing whether a new imaging study called high resolution 3D magnetic resonance spectroscopic imaging (MRSI) can identify

early response to a drug called belinostat. This imaging study can be done in regular MRI scanner without any injection of contrast agent.

Belinostat has been approved by the FDA for use in another type of cancer. We do not know if this drug is useful in the treatment of GBMs. Belinostat is in a class of drugs called histone deacetylase inhibitors (HDACi) that changes the structure of tumor DNA. This leads to changes in the type of proteins made by tumor cells. It appears to reprogram tumor genes to carry out normal brain activity. This is called "re-differentiation". At the same time, it appears to increase sensitivity of tumor cells to chemotherapy and RT.

Previous studies suggest that glioblastoma tumors that respond to HDACi therapy show changes in their biochemical content. The studies suggest these changes can be seen on magnetic resonance spectroscopic imaging (MRSI). MRSI is performed on a standard MRI scanner and provides information about the chemical contents in the brain/tumor. These changes on MRSI seem to signify response to the HDACi. However, we do not know whether these changes will predict better outcomes in patients with GBM treated with HDACi. In addition, we still need to establish the range of changes on MRSI we would see in patients treated with just standard RT and temozolomide (TMZ) chemotherapy.

In this study, newly-diagnosed GBM patients will be assigned to one of two cohorts. In cohort 1, patients will be treated with standard RT and TMZ only. MRSI will be performed prior to and two weeks after starting RT/TMZ. These MRSI scans after starting therapy will allow us to define the range of changes we will see with patients treated with standard RT/TMZ alone. In cohort 2, patients will be treated with standard RT and TMZ with belinostat. These patients on cohort 2 will be treated with a five day course of belinostat alone starting one week before initiation RT/TMZ and then will start standard RT and TMZ chemotherapy with two additional five day courses of belinostat (initiated every three weeks). MRSI will be done before and after the initial five day course of belinostat only treatment window as well as after two weeks of standard RT/TMZ chemotherapy with belinostat. These MRSI scans after starting therapy will classify "responders" and "non-responders."

Subjects will continue with standard therapy (RT with concurrent and adjuvant TMZ) alone (cohort 1) or with belinostat (cohort 2, given as a 5 day courses at start of the third and sixth week RT/TMZ). Cohort 1 is a pilot study that will allow us to establish the baseline for the range of changes we expect to see on MRSI after standard RT and TMZ. The main measurement for cohort 2 on the study is how long participants remain alive without evidence of progression (progression free survival). We will compare progression free survival in the MRSI responders and non-responders. In this way, we can find out if MRSI is useful for identifying patients that will have a good response to belinostat therapy. Another goal of this study is determining whether MRSI can predict how long patients remain alive after therapy (overall survival).

Finally, patients with GBM often have clinical depression. This may be due, in part, to changes in brain chemistry from tumors. Belinostat may reverse some of the biochemical changes seen in the brain of GBM patients, so we think that this therapy may have anti-depressive effects. We will also test mood, neurocognitive function and quality-of-life. We will correlate with results on MRSI.

Procedures

Before the research starts (screening):

After signing this consent form, you will be asked to have some screening tests or procedures to find out if you can be in the research study. 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 (questions about your health, current medications, and any allergies) will be taken.
- A physical examination including height and weight will be performed.
- Your performance status, or how your disease affects your daily activities will be assessed.
- An assessment of your tumor will be made by MRI (magnetic resonance imaging).
- Blood tests, including chemistry, hematology, and other routine tests, will be done to make sure that there are no problems with your organs that would make it unsafe for you to enroll in this study. This will require 1 tablespoon of blood.
- A pregnancy test for women of childbearing potential will be obtained. An additional 1 teaspoon of blood will be drawn for this test.
- Slides made from your tumor tissue will be evaluated by a study neuropathologist at your study site to confirm the diagnosis.

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:
If you take part in this research study, you will be assigned to cohort 1 (standard therapy only) or cohort 2 (standard therapy + belinostat). Assignment to a cohort will be done sequentially with completion of accrual to cohort 1 before starting accrual to cohort 2. **What follows will now apply for patients assigned to cohort 2.**

After assignment to **cohort 2**, you will have the following tests and procedures:

Medications before radiation therapy (cycle 0):

Belinostat

You will be given belinostat for a five day course consecutive days as an intravenous medication starting one week before the start of radiation therapy.

Radiation therapy (Cycle 1):

You will have radiation therapy (RT) about 5 days/week for about 6 weeks.

Medications during radiation therapy:

Temozolomide (TMZ)

TMZ chemotherapy will be given as a pill by mouth. It is started on the first day of radiation. It will be given daily (7 days/week) for the duration of RT (about 6 weeks). The dose of TMZ that is used in this phase of treatment will be based on your height and weight. TMZ must be taken at least one hour before or two hours after eating. Prior to receiving TMZ, you will be given a medicine to prevent nausea.

Belinostat

After the initial five day course (see above), belinostat will continue to be given as two additional five day courses of belinostat given at the start of the third and sixth week of RT/TMZ. You will be given belinostat as an intravenous medication. The belinostat dose patients are expected to be able to tolerate based on previous studies is 1000mg/m^2/day given as a daily intravenous dose over a five day course every three weeks. However, the final dose of belinostat that is used will be determined in the first 6-18 patients enrolled to cohort 2. You will be informed by your physician what dose of belinostat you will be receiving.

Rest period:
Following RT, there will be a four-week break in which you will not take any study medications.

Adjuvant Phase (Cycles 2-7, every 28 days, may extend up to cycle 13 at physician's discretion):
After the 4-week rest period, you will re-start TMZ. Each cycle will last 28 days. If you do not have any bad side effects, you will continue on to the next cycle of treatment with no break in between cycles.

Medications after radiation therapy:

Temozolomide

TMZ will be given by mouth for the first 5 days of every 28-day cycle. The dose of TMZ that is used in this phase of treatment will be based on your height and weight. TMZ must be taken at least one hour before or two hours after eating. Before taking TMZ, you will be given a medicine to prevent nausea. Treatment with TMZ will continue for 6-12 cycles (cycles 2-7, may extend up to cycle 13 at physician's discretion) as long as there are no bad side effects or tumor growth.

Blood tests:

Up to 2 teaspoons of blood will be taken weekly for the first 6 weeks. After that, you will have blood tests before each cycle for the remainder of the study. These tests are needed to monitor for damage to your organs or bone marrow.

MRI scans:

A diagnostic MRI scan with and without intravenous contrast will be done one week before the start of therapy if the immediate post-operative MRI scan was done > 28 days from registration. This is for RT treatment planning and establishment of a pre-treatment baseline.

About 11 weeks after the start of therapy (after the 5 day course of belinostat one week prior to start of RT/ TMZ, 6 weeks RT/TMZ/belinostat, and 4 weeks break), you will have another diagnostic MRI scan with and without intravenous contrast. This is to look at the status of your tumor. If there is no change, or if your tumor shrinks, you will continue treatment for two 28-day cycles (Cycles 2 and 3). Near the end of Cycle 3, you will have another diagnostic scan. These scans will be repeated every 8 weeks for the duration of treatment and every 12 weeks thereafter.

MRSI scans:

MRSI scans will be performed on a normal MRI machine and will not require intravenous contrast. These studies will take approximately 1 hour and may be done with or separate from normal diagnostic MRIs.

The timing for MRSIs are as follows:

1) Within 7 days before starting therapy (belinostat alone, may receive scan anytime on first day of therapy),
2) 1 week after starting belinostat alone (at start of RT/TMZ),
3) 2 weeks after start of RT/TMZ, and
4) 11 weeks after starting therapy (4 weeks after completion of RT/TMZ/belinostat).

MRSI scans are for research purposes only and results will not be used to plan your care.

Physical exams:

Physical exams will be performed every other week during cycle 1 and then before every cycle.

Tissue Slides:

Tumor tissue is required for this study. Special studies will be performed to try to identify markers that may predict response to belinostat. In addition, if you have a biopsy and/or surgery for tumor progression after study treatment, this tissue will also be sent to the investigators. This additional tissue will also be assessed for factors that may predict failure to therapy. These special studies on your tumor tissue are for research purposes only and results will not be used to plan your care.

Neurocognitive and quality-of-life studies:

We want to know how your life has been affected by your brain tumor and its treatment. This study looks at how you are doing during your brain tumor treatment. Your memory and thinking ability (neurocognitive function) and general sense of well-being (quality-of-life) will be evaluated by a tests and questionnaires. These will be done in your doctor's office. It takes about 20 minutes to complete these tests and questionnaires.

The timing of these tests is as follows:

1) Within 7 days before to the day of starting therapy (belinostat alone, may be performed anytime on first day of therapy),
2) 11 weeks after starting therapy (4 weeks after completion of RT/TMZ/belinostat), and
3) every 6 months thereafter. Tests are repeated until either tumor progression or 2 years without progression after completion of radiation therapy.

This information may help doctors better understand what effects this treatment has on patients and may eventually help patients and doctors decide which medicines to use to treat these brain tumors. As always, we will do our best to make sure that your personal information will be kept private.

Assessment of mood:

Because many patients with GBMs develop depression, we are interested in assessing your mood during the course of treatment. You will be asked to complete a questionnaire in your doctor's office. It should take 10-15 minutes to complete this questionnaire. The timing of this questionnaire will be at the time of each MRSI scan. This information will allow us to determine whether belinostat may benefit depressive symptoms in patients with GBM brain tumors. We will again do our best to make sure that your personal information will be kept private.

Other requirements:

Since the effect of standard RT/TMZ and the study drugs taken with other medications may not be known, it is important that you tell the research doctor about all drugs, prescription and non-

prescription drugs, herbal preparations and nutritional supplements that you are taking or planning to take.

Study Diagram:

Registration

Confirm patient eligibility. About 30 patients will enroll to **cohort 1** (standard RT/TMZ) and up to 51 patients will enroll to **cohort 2** (standard RT/TMZ + belinostat). May start enrollment to **cohort 2** after 14 **cohort 1** patients have been accrued at all sites.

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Baseline imaging

MRSI in 7 day window (days -6 to 0) prior to start of belinostat only for the belinostat cohort (**cohort 2**)

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Initial one week drug window (cycle 0, vorinostat cohort (cohort 2))

Belinostat alone (1000mg/m2/day IV*), days 1 through 5 (the latest time to begin therapy at the start of the 6^{th} week, or 36^{th} day from surgery)

MRSI on day 8 (from start of belinostat), or day 1 of cycle 1

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Concurrent chemoradiation phase of therapy (cycle 1)

RT to 60 Gy over six weeks (5x/week, Mon-Fri, 30 total treatments) with concomitant daily temozolomide (75mg/m^2/day, 7x/week, Mon-Sun, 42 total doses) for the standard therapy cohort (cohort 1) and belinostat (1000mg/m^2/day* IV for two five day courses) starting on the third and sixth week of RT/TMZ for the belinostat cohort (**cohort 2**)

MRSI after 2 weeks of RT/TMZ + belinostat (belinostat cohort will receive belinostat alone starting one week prior to starting RT/TMZ)

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Rest period (4 weeks)

Standard MRI (with gadolinium) and MRSI in one week window prior to starting adjuvant temozolomide (in 4th week after completion of radiation)

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Adjuvant phase of therapy (cycles 2-7, every 28 days, up to cycle 13 at physician's discretion)

Adjuvant temozolomide (150-200mg/m^2/day, days 1-5 of each cycle)

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Followup schedule

Initially at 4 weeks post-radiation then prior to every even-numbered cycle (every 2 months x 1 year) then every 3 months x 2 years. Subsequent followup schedule will be determined by patient's physician.

Standard MRI (with gadolinium) will be obtained with each followup visit

* Belinostat dosing may vary if this dose is not tolerated based on initial enrollment to **cohort 2**.

Enrollment:

Up to 81 people (30 in **cohort 1** and up to 51 in **cohort 2**) will take part in this study, with 60 expected to take part here at the Emory Winship Cancer Institute. Enrollment in **cohort 2** will initiate after 14 patients have accrued to **cohort 1**. When eligible, patients will be offered enrollment in **cohort 2** but may still be enrolled to **cohort 1** if the patient refuses **cohort 2** entry due to belinostat drug therapy but still agrees to undergo MRSI scans with standard RT/TMZ.

Risks and Discomforts

There are risks to taking part in any research study. One risk is that you may get a drug or dose of a drug that does not help treat your disease or that makes your condition or disease worse. Another risk is that there may be side effects.

All chemotherapy drugs 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 drugs and between individuals. For investigational drugs, not all of the risks are known at this time. You need to tell your doctor or a member of the study team immediately if you experience any side effects. There may be side effects from the study drug or procedures that are not known at this time.

Since many drugs used to treat cancer are designed to cause the rapidly dividing cancer cells in your body to slow down or die, these drugs can also cause other rapidly dividing normal cells in your body to slow down or die. These include the blood cells that help to fight infection (white blood cells), the blood cells that help the blood clot (platelets), and the blood cells that carry oxygen in your body (red blood cells). When anticancer drugs cause a decrease in these blood cells, it is called bone marrow suppression. While you are participating in this research study, your blood cell levels will be monitored closely.

Please notify your doctor if any of the following occur:

- A fever of 100.5 F or above.
  This could be a sign of an infection. If you have a low white blood cell count, this can be serious, life-threatening or fatal. You may have to take antibiotics or be admitted to the hospital.
- Low energy or shortness of breath.
  This could be a sign of anemia (not enough red blood cells). If this becomes severe, you may need to come into the clinic or hospital to have a transfusion of red blood cells.
- You bruise easily, or, when injured, you do not stop bleeding.
  This could be a sign that your platelets (blood cells that help with clotting) are low. This can be serious or life-threatening. You may need to come into the clinic or hospital for a transfusion of platelets.

Many cancers are associated with an increased risk of blood clots forming that could lead to swelling in the legs and arms. These clots may travel to the lungs causing shortness of breath or to the brain causing a stroke. This may become serious and life threatening. Some chemotherapeutic drugs can increase this risk. It is important to let your doctor know if you have increased shortness of breath or difficulty breathing.

Other common side effects include nausea, vomiting, and loss of appetite. You may also experience constipation, loose stools or diarrhea. It is important to increase your fluid intake if diarrhea occurs. If this becomes severe, you may have to be hospitalized and receive intravenous fluids.

Everyone taking part in the research study will be watched carefully for side effects. You will be monitored during your chemotherapy to keep track of your blood counts and organ function, particularly your kidney and liver function. Doctors don't know all the side effects that may happen. Side effects may be mild or very serious. Your health care team may give you medicines to help lessen side effects. If you experience side effects, they may go away after you stop taking the study drug. Some side effects can be mild; but others can be long lasting and may never go away. There is also a risk of death. You should talk to your doctor about any side effects you have while taking part in the study.

Since the effect of standard RT/TMZ and the study drug taken with other medications may not be known, it is important that you tell the research doctor about all prescription and non-prescription drugs, herbal preparations and nutritional supplements that you are taking or planning to take.

Risks associated with Belinostat

Likely risks of belinostat (events occurring more than 10% of the time):

- Feeling sick to your stomach (nausea), which is temporary and may require additional medication.
- Fatigue, which is temporary and should get better when treatment is stopped.
- Throwing up (vomiting), which is temporary and may require additional medication.
- Low red blood cell count (anemia), which may make you feel tired and short of breath. If this happens, you may be started on a drug to increase your red blood cell count. Severe anemia may require a transfusion of red blood cells.
- Loss of appetite, which is temporary and should get better when treatment is stopped.
- Difficulty in passing stools (constipation).
- Loose stools (diarrhea), which is temporary and may require additional medication and/or a delay in your treatment.
- Change in the sense of taste (dysgeusia)
- Hair loss (alopecia)
- Flushing

Less likely risks of belinostat (events occurring less than or equal to 1-10% of the time):

- Decreased platelet count, which increases the risk of easy bleeding and/or bruising. This could result in the need for a platelet transfusion.
- Decreased number of white blood cells (lymphocyte, neutrophil/granulocyte) or total number of white blood cells (leukocytes).
- Sensation of fluttering in the chest (palpitations)
- Blurred vision
- Stomach bloating or pain
- Dry mouth
- Flatulence
- Sores in the mouth (stomatitis)

- Physical weakness (asthenia)
- Chest pain
- Injection site reaction or phlebitis (inflammation of the vein where the drug is infused).
- Peripheral edema (swelling in the arms or legs)
- Fever (pyrexia)
- Allergic reaction to drug
- Yeast infection in mouth/throat (oral candidiasis)
- Upper respiratory infection
- Infusion reaction
- Increased blood level of a liver enzyme (ALT/SGPT or AST/SGOT).
- Increased blood levels of alkaline phosphatase
- Increased blood level of creatinine indicative of worse kidney function
- Prolonged QTc (changes in the conduction of electricity through the heart which may increase risk of an arrhythmia)
- Weight loss
- Dehydration, which is temporary and may require additional fluids, either by mouth or by IV (intravenous, through a small tube inserted into your vein) infusion.
- High blood sugar
- Low calcium, magnesium and sodium levels which may require correction
- Low potassium, which is temporary, seen on blood tests and may require potassium supplements.
- Joint or muscle pain/discomfort (arthralgia and myalgia)
- Dizziness (or a sensation of lightheadedness, unsteadiness, spinning).
- Headaches
- Lethargy
- Weakness, numbness or pain of extremities (peripheral neuropathy)
- Difficulty sleeping (insomnia)
- Cough
- Shortness of breath (dyspnea)
- Nosebleed (epistaxis)
- Hiccups
- Runny nose (allergic rhinitis)
- Dry skin
- Increased sweating (hyperhidrosis)
- Rash
- Itchiness
- Decreased or increased blood pressure
- Inflammation of veins (phlebitis)

Rare but serious risks of belinostat (events occurring less than 2-3% of the time):

- Signs of liver damage that may progress to liver failure.
- Signs of kidney damage that may progress to kidney failure.
- Tumor lysis syndrome only reported in patients with myelodysplastic syndrome (including leukemias, lymphomas and myelomas) where rapid tumor destruction leads to increased blood levels of electrolytes and uric acid which may cause acute kidney failure.

Risks associated with Temozolomide (TMZ)

Likely risks of TMZ (events occurring more than 20% of the time):

- Feeling sick to your stomach (nausea).
- Throwing up (vomiting).
- Decreased appetite (anorexia).
- Difficulty in passing stools (constipation).
- Headache.
- Fatigue.
- Fever (pyrexia).

Less likely risks of TMZ (events occurring less than or equal to 20% of the time):

- Fall in the white blood cell counts that leads to a higher risk of infection (neutropenia).
- Fall in the platelet count leading to a higher risk of bleeding (thrombocytopenia).
- Fall in the red blood cell count leading to anemia (feeling tired and low energy) (anemia).
- A low number of a particular white blood cell, which is important to the immune system (lymphopenia).
- Sores in the mouth (stomatitis).
- Loose stools (diarrhea).
- Pain in the belly (abdomen).
- Change in liver function tests (tests that show how the liver is working).
- Rash (psoriasis).
- Itchiness (pruritis).
- Lack of interest in or ability to carry out daily activities.
- Weakness (asthenia).
- Dizziness.
- Anxiety.
- Depression.
- Memory loss.
- Muscle pain (myalgia).
- Joint pain (arthralgia).
- Tingling or burning in your arms or legs.
- Shortness of breath (dyspnea).
- Cough.
- Swelling in your arms or legs (edema).
- Increased need to pass urine.

Rare but serious risks of TMZ (events occurring less than 2-3% of the time):

- Problem with the bone marrow that causes decreased production of red cells, white cells, or platelets that can sometimes turn into blood cancer called Myelodysplastic syndrome.
- Convulsions.
- Weakness on one side of your body (hemiparesis).

- Abnormal coordination.
- Inability to move an arm or leg (paralysis).
- Severe skin reaction.
- Fever, chills, swelling of body, shortness of breath (allergic reaction).
- Re-activation of hepatitis infection (if you have previously been diagnosed with Hepatitis-A type of infection in the liver).
- A blood disorder in which the body's bone marrow does not make enough new blood cells (Aplastic Anemia).
- Inflammation in the lungs (pneumonitis).
- Change in kidney function tests (tests that show the kidneys are working).
- Later development of secondary leukemia, lymphoma or other cancers.
- Liver damage which may cause yellowing of eyes and skin, swelling and may result in liver failure.

Risks and side effects related to the radiation therapy

Likely (events occurring greater than 20% of the time):

- Short-term reddening and drying of the skin, fatigue, and hair loss within treated area.

Less Likely (events occurring less than or equal to 20% of the time):

- Feeling sick to your stomach (nausea).
- Throwing up (vomiting).
- Headache.

Rare but serious (events occurring less than 2-3% of the time):

- Seizures.
- Coma.
- Lower white blood cell and platelet counts raising the risk of infection and bleeding.
- Radiation therapy at these dose levels also may cause damage to normal brain, but this is rare.
- Specific effects depend upon the location of the area(s) of damage but may be a decrease in judgment, memory, emotions, vision, hearing, sensation, or ability to control movement.

MRI and MRSI

Rarely, allergic reactions to the contrast (dye) material injected into the vein for your scan can happen, causing rash, itching, or in severe cases, trouble breathing or a lowering of your blood pressure. If you have had an allergy to contrast material used for MRI in the past you should tell your doctor. Some people who are claustrophobic (have a fear of enclosed places) might feel anxiety or nervousness during an MRI or MRSI.

Reproductive Risks

The treatments used in this research study may affect a fetus. While taking part in this research study, you should not become pregnant or father a baby. Also, you should not nurse a baby while on treatment. We can provide counseling about preventing pregnancy for either male or female study participants.

Women who are pregnant or nursing a child may NOT participate in this trial. If you are a female of childbearing potential, your doctor must confirm that you are not pregnant by drawing a sample of blood at the screening

visit. You must confirm that you do not intend to become pregnant during the trial. If you are of childbearing potential your doctor will discuss appropriate birth control measures with you. For the pregnancy test, blood will be taken from a vein in your arm with a needle within 7 days before you enter the study. You will be told if you are pregnant or not. If you are pregnant, you will not be able to take part in the study. If you become pregnant while on the study you will be taken off the study.

If you are sexually active you should use birth control pills or a barrier method of contraception (such as condoms or diaphragm) with a spermicidal agent during the trial. For women, this should continue for approximately 12 weeks after the last dose of the drug to ensure that the drug has cleared from the body.

For men, contraception should also continue for 12 weeks after the last dose of the drug, to ensure that all sperm present in the body during the clinical trial have been replaced.

If you will be taking the study drug home, keep it out of the reach of children or anyone else who may not be able to read or understand the label. Do not let anyone else take the study drug besides you.

Blood Tests
The collecting of blood samples (about 1 tablespoon each time) throughout this study may cause mild discomfort or pain from the needle puncture and possible bruising or mild bleeding. The risk of infection is slight and will be further reduced by keeping the puncture site clean and dry.

There is also risk of dizziness and fainting that is associated with blood draws.

For more information about risks and side effects please contact your physician.

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

New Information

It is possible that the researchers will learn something new during the study about the risks of being in it. If this happens, they will tell you about it. Then you can decide if you want to continue to be in this study or not. You may be asked to sign a new consent form that includes the new information if you decide to stay in the study.

Benefits
Your brain tumor may improve while you are in this study but it may not, and it may even get worse. This study is designed to learn more about whether MRSI can provide clinicians with additional diagnostic information and whether adding belinostat to standard therapy (including radiation therapy and TMZ chemotherapy) is beneficial for patients with your type of brain tumor. The study results may be used to help others in the future.

Compensation
You will not be offered payment for being in this study.

Other Treatment Outside this Study

If you decide not to enter this study, there is care available to you outside of this research. You do not have to be in this study to be treated for your brain tumor.

Your other choices may include:

- The current standard treatment, radiation therapy + TMZ followed by TMZ alone, is available and you do not have to enter the study to receive it.
- Taking part in another research study.
- Getting no treatment.
- Get comfort care, also called palliative care. This type of care may help to reduce pain, tiredness, appetite problems and other problems caused by the brain tumor. It does not treat the tumor directly, but instead tries to improve how you feel. Comfort care tries to keep you as active and comfortable as possible.

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

Confidentiality

Certain offices and people other than the researchers may look at your medical charts and study records. Government agencies and Emory employees overseeing proper study conduct may look at your study records. These offices include the Food and Drug Administration, the Office for Human Research Protections, the Emory Institutional Review Board, the Emory Office of Research Compliance, the Office for Clinical Research, the Clinical Trials Audit & Compliance Office, the Radiation Safety Committee, and the Emory Winship Cancer Center Data Safety Monitoring Board. Spectrum, the drug manufacturer may also look at your study records. Emory will keep any research records we create private to the extent we are required to do so by law. A study number rather than your name will be used on study records wherever possible. Your name and other facts that might point to you will not appear when we present this study or publish its results.

There is a Certificate of Confidentiality for this Study:

We will do everything we can to keep others from learning about your participation in the research. To further help protect your privacy, the investigators have obtained a Confidentiality Certificate.

What the Certificate of Confidentiality protects:

The National Institutes of Health has given this study a Certificate of Confidentiality. Emory would rely on it to not give out study information that identifies you. For example, if Emory received a subpoena for study records that identify you, we would say no. The Certificate gives Emory legal backup to say no. It covers information about you that could harm your image or finances. It also covers information about you that could harm your chances at a job or getting insurance.

What the Certificate of Confidentiality does not protect:

The Certificate does not prevent you or someone other than you from making disclosing your information. The Certificate also does not prevent Emory from releasing information about you:

- Information to state public health offices about certain infectious diseases
- Information to law officials if child abuse has taken place

- Information Emory gives to prevent immediate harm to you or others
- Information Emory gives to the study sponsor as part of the research

Research Information Will Go Into the Medical Record:
If you are or have been an Emory Healthcare patient, you have an Emory Healthcare medical record. If you are not and have never been an Emory Healthcare patient, you do not have one. Please note that an Emory Healthcare medical record **will** be created if you have any services or procedures done by an Emory provider or facility for this study.

If you agree to be in this study, a copy of the consent form and HIPAA patient form that you sign **will** be placed in your Emory Healthcare medical record. Emory Healthcare may create study information about you that can help Emory Healthcare take care of you. For example, the results of study tests or procedures. These useful study results **will** be placed in your Emory Healthcare medical record. Anyone who has access to your medical record will be able to have access to all the study information placed there. The confidentiality of the study information in your medical record will be protected by laws like the HIPAA Privacy Rule. On the other hand, some state and federal laws and rules may not protect the research information from disclosure.

Emory does not control results from tests and procedures done at other places, so these results would not be placed in your Emory Healthcare medical record. They will not likely be available to Emory Healthcare to help take care of you. Emory also does not have control over any other medical records that you may have with other healthcare providers. Emory will not send any test or procedure results from the study to these providers. If you decide to be in this study, it is up to you to let them know.

The researchers will review the results of certain study tests and procedures only for the research. The researchers **will not** be looking at the results of these tests and procedures to make decisions about your personal health or treatment. For this study, those things include:

1) the MRSI scans,
2) special studies performed on the tumor tissue,
3) results of the neurocognitive tests, quality-of-life assessments and assessments of mood (depression survey).

In Case of Injury

If you get ill or injured from being in the study, Emory would help you to get medical treatment. Emory and the sponsor have not, however, set aside any money to pay you or to pay for this medical treatment. The only exception is if it is proved that your injury or illness is directly caused by the negligence of an Emory or sponsor employee. "Negligence" is the failure to follow a standard duty of care.

If you become ill or injured from being in this trial, your insurer will be billed for your treatment costs. If you do not have insurance, or if your insurer does not pay, then you will have to pay these costs.

If you believe you have become ill or injured from this research, you should contact Dr. Hui-Kuo Shu at telephone number [redacted] or Dr. Jeffrey Olson at telephone number [redacted]. You should also let any health care provider who treats you know that you are in a research study.

Costs

The study sponsor will pay for certain items and services that you may receive if you take part in this study. These study-related costs provided by the study sponsor will include but are not limited to the following:

1) the study drug belinostat will be provided free of charge for this study,
2) all MRSI scans,
3) special studies on the tumor tissue, and
4) administration of neurocognitive/quality-of-life/mood tests and assessments.

While belinostat will be provided to you free of charge for this study, it is a commercially available drug. Should this agent become FDA approved for glioblastoma during the course of this study, you may be asked to purchase subsequent doses of the drug needed to complete the study in the event that Spectrum no longer provides the drug. If there is no belinostat available at all, no one will be able to get more and the study would close. If a problem with getting belinostat occurs, your study doctor will talk to you about these options.

As indicated above, MRSI scans will be provided to you free of charge for this study. However, diagnostic MRI studies are part of the standard-of-care assessment and followup for patients with your brain tumor. Therefore, the cost of these diagnostic MRIs will be billed as part of the normal management of your brain tumor.

You will have to pay for the items or services for which the study sponsor does not pay. The sponsor will not pay for your regular medical care. If you have insurance, Emory will submit claims to your insurance for items and services that the sponsor does not cover. Emory will send in only those claims for items and services that it reasonably believes your insurance will pay and that the sponsor has not paid.

The actual amount that you have to pay depends on whether or not you have health insurance and whether or not that insurance will pay for any research study costs. Generally, insurance companies will not pay for items and services that are required just for a research study. Some insurance companies will not pay for regular medical treatment or treatment for complications if you are in a study. How much you will have to pay for any co-payments, deductibles or co-insurance depends on your plan. Emory and the sponsor will not pay for these costs.

It is a good idea to contact your insurance provider and tell them you want to be in this research study. Ask them what they will pay for and what they will not pay for. You can also ask the study team for help in figuring out what you will have to pay.

If you do not have insurance, Emory will review your case as part of its program for low-income patient care. The standard policies of that program will apply. The program will figure out if you have to pay any costs for taking part in the study and what those costs will be.

Withdrawal from the Study

You have the right to leave a study at any time without penalty. For your safety, however, you should consider the study doctor's advice about how to go off the study treatment. If you leave the study before the final planned study visit, the researchers may ask you to have some of the final steps done.

The researchers and sponsor also have the right to stop your participation in this study without your consent if:

- They believe it is in your best interest;
- You were to object to any future changes that may be made in the study plan;
- or for any other reason.

Authorization to Use and Disclose Protected Health Information

The privacy of your health information is important to us. We call your health information that identifies you, your "protected health information" or "PHI." To protect your PHI, we will follow federal and state privacy laws, including the Health Insurance Portability and Accountability Act and regulations (HIPAA). We refer to all of these laws as the "Privacy Rules." Here we let you know how we will use and disclose your PHI for the study.

PHI that will be Used/Disclosed:

The PHI that we will use and/or disclose (share) for the research study includes

- Medical information about you including your medical history and present/past medications.
- Results of exams, procedures and tests you have before and during the study.
- Laboratory test results.

Purposes for which your PHI will be Used/Disclosed:

We will use and disclose your PHI for the conduct and oversight of the research study. We will use and share your PHI to provide you with study related treatment and for payment for such treatment. We will also use and share your PHI to conduct normal business operations. We may share your PHI with other people and places that help us conduct or carry out the study, such as laboratories, data management centers, data monitors, contract research organizations, Institutional Review Boards (IRBs) and other study sites. If you leave the study, we may use your PHI to determine your health, vital status or contact information.

Authorization to Use PHI is Required to Participate:

By signing this form, you give us permission to use and share your PHI as described in this document. You do not have to sign this form to authorize the use and disclosure of your PHI. If you do not authorize the use and disclosure of your PHI for the study, then you may not participate in the research study or receive research-related treatment. You may still receive non-research related treatment.

People that will Use and/or Disclose Your PHI:

The following people and groups will use and disclose your PHI in connection with the research study:

- The Principal Investigator and the research staff will use and disclose your PHI to conduct the study and give you study related treatment.

- Emory may use and disclose your PHI to get payment for study related treatment and to run normal business operations.
- The Principal Investigator and research staff will share your PHI with other people and groups to help conduct the study or to provide oversight for the study.
- Dr.Hui-Kuo Shu is the Sponsor of the study. The Sponsor may use and disclose your PHI to make sure the research is done correctly and to collect and analyze the results of the research. The Sponsor may disclose your PHI to other people and groups like study monitors to help conduct the study or to provide oversight for the study.
- The following people and groups will use your PHI to make sure the research is done correctly and safely:
    - Emory offices that are part of the Human Research Participant Protection Program and those that involved in study administration and billing. These include the Emory IRB, the Emory Research and Healthcare Compliance Offices, and the Emory Office for Clinical Research.
    - Government agencies that regulate the research including: Office for Human Research Protections; Food and Drug Administration
    - Public health agencies.
    - Research monitors and reviewer.
    - Accreditation agencies.

Expiration of Your Authorization
This authorization will not expire because it is a research study.

Revoking Your Authorization
If you sign this form, at any time later you may revoke (take back) your permission to use your information. If you want to do this, you must write to:

Dr. Hui-Kuo Shu
1365-C Clifton Road NE
Atlanta, GA 30322

At that point, the researchers would not collect any more of your PHI. But they may use or disclose the information you already gave them so they can follow the law, protect your safety, or make sure that the study was done properly and the data is correct. If you revoke your authorization you will not be able to stay in the study.

Other Items You Should Know
Not all people and entities are covered by the Privacy Rules. HIPAA only applies to health care providers, health care payers or health care clearinghouses. If we disclose your information to people who are not covered by the Privacy Rules, including HIPAA, then your information won't be protected by the Privacy Rules. People who do not have to follow the Privacy rules can use or disclose your information with others without your permission if they are allowed to do so by the laws that cover them.

To maintain the integrity of this research study, you generally will not have access to your PHI related to this research until the study is complete. When the study ends, and at your request, you generally will have access to your PHI that we maintain in a designated record set. A designated record set is data that includes medical

information or billing records that your health care providers use to make decisions about you. If it is necessary for your health care, your health information will be provided to your doctor.

We may remove identifying information from your PHI. Once we do this, the remaining information will not be subject to the Privacy Rules. Information without identifiers may be used or disclosed with other people or organizations and/or for other purposes besides this study.

Contact Information

Contact Dr. Jeffrey Olson at [redacted] or Dr. Hui-Kuo Shu at [redacted]

- if you have any questions about this study or your part in it,
- if you feel you have had a research-related injury or a bad reaction to the study drug, or
- if you have questions, concerns or complaints about the research

Contact the Emory Institutional Review Board at [redacted]:

- if you have questions about your rights as a research participant.
- if you have questions, concerns or complaints about the research.
- You may also let the IRB know about your experience as a research participant through our Research Participant Survey at http://www.surveymonkey.com/s/6ZDMW75.

Consent

Please, print your name and sign below if you agree to be in this study. By signing this consent form, you will not give up any of your legal rights. We will give you a copy of the signed consent, to keep.

_____
Printed Name of Subject

_____ _____ ____:____ am / pm
Signature of Subject Date Time (please circle)

_____
Printed Name of Person Obtaining Consent

_____ _____ ____:____ am / pm
Signature of Person Obtaining Consent Date Time (please circle)