

RESEARCH SUBJECT INFORMATION AND CONSENT FORM

TITLE: A PHASE II STUDY OF GLIADEL, CONCOMITANT TEMOZOLOMIDE AND RADIATION, FOLLOWED BY DOSE DENSE THERAPY WITH TEMOZOLOMIDE PLUS BEVACIZUMAB FOR NEWLY DIAGNOSED MALIGNANT HIGH GRADE GLIOMA

PROTOCOL NO.: KARE 004
WIRB® Protocol #20080121

SPONSOR: Kentucky Astrocytoma Research Endeavor (KARE)
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STUDY-RELATED

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Richard A. Rovin, M.D.
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This consent form may contain words that you do not understand. Please ask the study doctor or the study staff to explain any words or information that you do not clearly understand. You may take home an unsigned copy of this consent form to think about or discuss with family or friends before making your decision.

You are being invited to participate in this research study under the direction of Renato V. LaRocca, M.D. or Dr. Richard A. Rovin. Approximately 40 subjects will be enrolled in this study. This study will involve research treatment in the outpatient (clinic) setting.

SOURCE OF FUNDING

Funding for this research study will be provided by MGI Pharma, Inc., the manufacturer of the Gliadel® Wafer.

PURPOSE OF THE STUDY

This study is designed to evaluate the safety and effectiveness of a combination of radiation and temozolomide therapy followed by dose dense temozolomide therapy plus bevacizumab following the standard of care implantation of Gliadel® wafers. Gliadel® wafers are FDA approved for the treatment of patients with newly diagnosed, moderate to high-grade malignant glioma (brain tumors). Gliadel® wafers (BCNU, carmustine), are designed to deliver chemotherapy directly into the surgical cavity created when as much as possible of the brain tumor is surgically removed. After surgery and placement of these wafers during your standard of care surgery, you will then receive research treatment with radiation therapy to the brain along with a daily dose of a chemotherapy drug called temozolomide (Temodar®). Approximately 1 month following completion of radiation treatments you will begin therapy with temozolomide at a higher dose and bevacizumab (Avastin®). This study will also evaluate the duration of your response to treatment and how long you survive your disease overall.

DESCRIPTION OF PROCEDURES

As part of your standard of care, you will have a physical and neurological examination, a preoperative brain MRI and laboratory evaluations that will include a complete blood count, chemistries (to check your kidney and liver functions), and routine urine tests. A urine pregnancy test will be required if you are a woman who is able to have children. These tests are

very important and are a necessary part of your care since they will provide information that will enable your study doctor to determine your response to this treatment study. These tests, which may take a few hours to complete, are standard of care and are covered by most insurance companies.

You will have had surgery to remove a primary brain tumor known as a glioma. At the time of surgery, your neurosurgeon will have attempted to remove as much of the glioma as was possible and then will have placed Gliadel® wafers containing the chemotherapy drug BCNU into the cavity that was left. Within 48 hours after surgery, you will have had another MRI to determine if any tumor remains.

Before beginning treatment on this research study, your brain tumor tissue that was removed during your surgery will be evaluated by a pathologist (doctor who examines tissue) to find out if your brain tumor is a moderate to high-grade glioma. Your tumor tissue will also be tested to see if a specific DNA is in your tumor tissue. If your brain tumor is not moderate to high-grade glioma, you will not be allowed to continue in the study.

Within 14 to 28 days after your surgery, you will begin radiation therapy to the brain tumor which will consist of approximately six weeks of treatments, one treatment per day, five days a week. At the same time as the radiation treatments you will begin taking a chemotherapy pill called temozolomide by mouth every day (7 days per week). Your actual dose will be calculated based on your current height and weight.

Within approximately 45 days of completing the combination radiation and chemotherapy, you will then be evaluated for additional temozolomide treatment at a higher dose that is again based on your height and weight and bevacizumab. Temozolomide at the higher dose will be given daily for days 1-7 and again on days 15-21 out of a 28 day cycle for up to 12 cycles. Bevacizumab will be given at a dose based on your weight through an IV every other week.

You will be evaluated approximately every three months through your clinical examination with a physician during your routine standard of care visits and through routine standard of care MRIs of your brain. Your routine exams will include current medical history review, medication review, performance status assessments (evaluations), and neurological exams that are considered standard of care following your surgery. Any adverse (bad or harmful) events during this time will be documented. These visits should take approximately one half hour. After the first year you will then be evaluated approximately every six months for one more year (total of two years after your surgery). You will be followed after that approximately one time per year to see how you are doing.

RISKS, INCONVENIENCES, AND DISCOMFORTS

The research treatment you will receive during this study is concomitant (both together) radiation to the brain with daily temozolomide followed by higher dose temozolomide and bevacizumab.

Risks of Brain Tumor Surgery:

The risks from surgery to remove the tumor vary, depending on the size and location of the tumor. Your study surgeon will explain the specific risks from this procedure to you before surgery. Risks may include:

- Injury to brain tissue, which may lead to
- Nerve or muscle weakness or paralysis, and
- Loss of mental functions such as memory, speech and understanding;
- Injury to blood vessels, which could result in bleeding; and
- Infection.

You will receive a separate consent for the surgery that will include greater detail about that procedure and its risks.

Gliadel® Wafer:

The most commonly reported adverse events are:

- Brain swelling and inflammation, which may cause loss of brain function;
- Abnormal or delayed wound healing and possible leakage of cerebrospinal fluid;
- Infection in the brain;
- Seizures.

The chemotherapeutic drug temozolomide (Temodar®) is FDA approved for recurrent gliomas, and some forms of skin cancer, but not for the treatment of newly diagnosed brain tumors. The most common side effects associated with temozolomide that have been reported are:

- nausea
- vomiting
- convulsions
- headache
- constipation
- fever
- back pain

Also, a decrease in the amount of white blood cells in your blood stream can occur which can increase your susceptibility to infection. Temozolomide can also lower your red blood cell count resulting in anemia and making you tired and short of breath. Your platelets, which help your blood clot, may also decrease as a result of treatment. This can result in easy bruising and possible bleeding. These effects are usually temporary. Transfusions, antibiotics, as well as injections of agents called “growth factors” are available to try to aid in your recovery from some of these side effects. Some patients may experience an allergic reaction, which in rare cases can be life-threatening. You will receive a standard drug to try to prevent a type of pneumonia called PCP, while you receive temozolomide.

The chemotherapeutic drug bevacizumab (Avastin®) is FDA approved for metastatic (spreading) colon or rectal cancer, but not for the treatment of newly diagnosed brain tumors. The most common side effects associated with bevacizumab that have been reported are:

- generalized weakness
- pain
- abdominal pain
- nausea and vomiting
- poor appetite
- constipation
- upper respiratory infection
- low white blood cell count that can put you at increased risk for infection
- proteinuria - leaking of protein into the urine
- nose bleed
- diarrhea
- hair loss
- mouth sores
- and headache

Other less common side effects that have been reported are:

- shortness of breath
- dizziness
- high blood pressure
- weight loss
- muscle aches and pains

Rare but serious complications of bevacizumab are:

- gastrointestinal (referring to the stomach or intestine) perforation
- wound healing complications
- hemorrhage (severe bleeding)
- hypertensive crisis (severe high blood pressure)
- nephrotic syndrome -a condition marked by very high levels of protein in the urine
- swelling, especially around the eyes, feet and hands. This syndrome is caused by damage to the glomeruli (tiny blood vessels in the kidney that filter waste and excess water from the blood and send them to the bladder as urine)
- RPLS is a medical problem in which blood vessels in the brain leak. It can cause confusion, blindness or vision changes, seizure and other symptoms. It can usually be reversed, but in rare cases, it can be life threatening and may have a long-term effect on brain function.

Limited field radiotherapy (radiation therapy) has been associated with:

- skin reactions
- raised intracranial pressure (swelling of the brain tissue)

- brain necrosis (damage to normal brain tissue)
- fatigue
- a temporary decrease in white blood cells, platelets and red blood cell
- hair loss
- impairment of intellectual functions

Your participation in this study could result in risks and side effects that are currently unknown. In order to monitor side effects, it will be necessary to have blood samples (1-2 teaspoons) taken at the start of chemotherapy before receiving treatment and at each routine office visit throughout your treatment period. The risk of simple blood draws include: discomfort and/or bruising at the site of puncture, and less commonly, the formation of a swelling of the vein and surrounding tissue, bleeding from the puncture site.

Ten percent (1 out of 10) or more of subjects with malignant gliomas may develop a serious condition of thrombosis (blood clot) in their legs. Such blood clots may break off and travel to the lungs (pulmonary embolism) where severe damage could occur potentially leading to death. You will be monitored for evidence of any blood clots. If you do develop a blood clot, you will receive routine standard of care treatment with medications in pill form or as an injection, or both, to thin the blood.

PREGNANCY/CONTRACEPTION

It is unknown if this therapy may have an effect on an embryo or fetus by causing changes to the genetic material which could be associated with birth defects or mental retardation. There may be risk to an embryo or fetus (unborn child), which are currently unknown. If you are a pregnant woman, or breast-feeding, you cannot take part in this study.

It is important that during the course of this study you avoid pregnancy.

If you and your partner are capable of having children, contraceptive methods must be used. Your study doctor will discuss effective contraceptive methods and options with you. If your birth control methods are interrupted, or if there is any suspicion or confirmation of pregnancy, you must notify Dr. Renato V. LaRocca immediately at 502-561-8200. If you are a woman and become pregnant, you may have to consider ending the pregnancy. You may become sterile (unable to have children) from your chemotherapy.

SAFEGUARDS

There may be risks that are unknown, and you will have regular doctor visits to monitor for any problems that may arise during your participation in this study. You must disclose to the study doctor all past and present diseases and allergies of which you are aware and all drugs and medications which you are presently using. You must keep him updated with any changes in your medication that may eventually be made by other physicians not involved in this study. Your participation in this study may be stopped at any time if your study doctor feels it is in your best interest.

Your condition may not get better or may become worse during this study.

Only the study subject should take the study drug. It must be kept out of the reach of children and people who may not be able to read or understand the label.

BENEFITS

The spread of your brain cancer may be stopped or slowed by participating in this study, but there is no guarantee of this. It is also hoped that other subjects will benefit from an increased understanding of this particular approach to therapy.

COST

The cost of all procedures will be billed to you or your insurance, because they are considered standard care. Temozolomide (Temodar®) is approved for treatment of some types of brain tumors and not others. Therefore, depending on the type of brain tumor you have, it is possible that your insurance company may not cover the cost of this chemotherapy treatment.

The approximate cost of the temozolomide taken during the course of radiation therapy, once a day for 6 weeks, could be over \$4,000.00 and then you may be continuing on a higher dose of Temozolomide taken a few weeks out of the month for up to 12 months longer. Your actual dose and therefore cost is directly related to your height and weight at the time.

If your insurance company will not cover temozolomide use for your tumor type, based on financial need, you may be able to receive free drug or drug assistance from a program called "Commitment to Care" (1-800-521-7157) sponsored by Schering Pharmaceuticals, the maker of temozolomide. If you do not qualify for this assistance you may have to cover the cost of the drug yourself, or you and your study doctor may opt to discontinue your participation in the study.

Gliadel wafers will be billed to you or your insurance company, because they have been approved for some brain tumors.

Bevacizumab (Avastin®) is approved for some types of cancers and not others. Therefore, depending on the type of brain tumor you have, it is possible that your insurance company may not cover the cost of this chemotherapy treatment.

The cost of bevacizumab taken during the study could be very expensive. If your insurance were not to cover bevacizumab you may have to cover the cost of the drug yourself, or you and your study doctor may opt to discontinue your participation in this study, or to consider participation in another study.

Ask your study doctor to discuss the costs that will or will not be covered by the sponsor. This discussion should include the costs of treating possible side effects. Otherwise, you might have unexpected expenses from being in this study.

PAYMENT FOR PARTICIPATION

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

ALTERNATIVES

You do not have to participate in this study to receive treatment for your cancer.

Your study doctor will discuss the benefits and potential side effects of other forms of treatment for your brain tumor. Such alternative therapies include surgery alone, surgery followed by radiation, surgery followed by radiation and other chemotherapy drugs, or supportive care measures alone.

If you decide that you don't want any more active treatment, one of your options is called "comfort care." Comfort care includes pain medication and other support. It aims to maintain your comfort and dignity rather than cure disease. Usually this care can be provided at home.

If you think you might prefer comfort care, please discuss this with your family, friends and your doctor.

You should feel free to ask any questions about your disease or this research study now or in the future. You can refuse to participate in this study and still receive standard therapy for your brain tumor. You can receive all treatments under this study with the exception of bevacizumab, without being in the study. You can also participate in another study called KARE 003 and receive all treatments under this study, with the exception of bevacizumab.

RESEARCH-RELATED INJURY

If you are injured as a direct result of your participation in this study, treatment for the injury will be provided at a facility of your choosing. You or your insurance company will be billed for the costs of such medical treatment in the usual manner. Your health insurance company may or may not pay for treatment of injuries as a result of your participation in this study.

The sponsor has no plans to pay for things such as lost wages, inconvenience or discomfort. This does not waive your rights in the event of negligence.

AUTHORIZATION TO USE AND DISCLOSE INFORMATION FOR RESEARCH PURPOSES

Federal regulations give you certain rights related to your health information. These include the right to know who will be able to get the information and why they may be able to get it. The study doctor must get your authorization (permission) to use or give out any health information that might identify you.

What information may be used and given to others?

If you choose to be in this study, the study doctor will get personal information about you. This may include information that might identify you. The study doctor may also get information about your health including:

- Past and present medical records
- Research records
- Records about phone calls made as part of this research
- Records about your study visits
- Information obtained during this research about
 - Physical exams
 - Laboratory, x-ray, and other test results
 - Questionnaires
- Records about any study drug you received

Who may use and give out information about you?

Information about your health may be used and given to others by the study doctor and staff. They might see the research information during and after the study.

Who might get this information?

Your information may be given to the sponsor of this research. “Sponsor” includes any persons or companies that are working for or with the sponsor, or are owned by the sponsor.

Information about you and your health which might identify you may be given to:

- The U.S. Food and Drug Administration (FDA)
- Department of Health and Human Services (DHHS) agencies
- Governmental agencies in other countries
- Jewish Hospital & St. Mary’s HealthCare, Inc.
- The Western Institutional Review Board® (WIRB®)
- MGI Pharma, Inc. (Eisai Corporation of North America)

Because of the need to share your protected health information with personnel and staff needed to conduct this research, absolute confidentiality cannot be guaranteed.

Why will this information be used and/or given to others?

Information about you and your health that might identify you may be given to others to carry out the research study. The sponsor will analyze and evaluate the results of the study. In addition, people from the sponsor and its consultants will be visiting the research site. They will follow how the study is done, and they will be reviewing your information for this purpose.

The information may be given to the FDA. It may also be given to governmental agencies in other countries. This is done so the sponsor can receive marketing approval for new products resulting from this research. The information may also be used to meet the reporting requirements of governmental agencies.

The results of this research may be published in scientific journals or presented at medical meetings, but your identity will not be disclosed.

The information may be reviewed by WIRB®. WIRB is a group of people who perform independent review of research as required by regulations.

What if I decide not to give permission to use and give out my health information?

By signing this consent form, you are giving permission to use and give out the health information listed above for the purposes described above. If you refuse to give permission, you will not be able to be in this research.

May I review or copy the information obtained from me or created about me?

You have the right to review and copy your health information. However, if you decide to be in this study and sign this permission form, you will not be allowed to look at or copy your information until after the research is completed.

May I withdraw or revoke (cancel) my permission?

Yes, but this permission will not stop automatically.

For Indiana Site:

This permission will be good until December 31, 2050.

You may withdraw or take away your permission to use and disclose your health information at any time. You do this by sending written notice to the study doctor. If you withdraw your permission, you will not be able to continue being in this study.

When you withdraw your permission, no new health information which might identify you will be gathered after that date. Information that has already been gathered may still be used and given to others. This would be done if it were necessary for the research to be reliable.

Is my health information protected after it has been given to others?

If you give permission to give your identifiable health information to a person or business, the information may no longer be protected. There is a risk that your information will be released to others without your permission.

QUESTIONS

For additional information, questions, concerns or complaints about this research, your participation in this study and your rights as a research subject, or if at any time you feel you have experienced a research-related injury, contact Dr. Richard Rovin at Marquette General Hospital at 1-906-228-9440 or Marquette General Neurosurgery at 1-906-225-4575 or 1-888-886-4644.

If you have any questions about your rights as a research subject, or if you have questions, concerns or complaints about the research, you may contact:

The Patient Advocate at Marquette General Health System at (906) 228-9440.

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.

PARTICIPATION/STUDY WITHDRAWAL

Your participation in this study is voluntary. You may decide not to participate or you may leave the study at any time. Your decision will not result in any penalty or loss of benefits to which you are entitled.

Your participation in this study may be stopped at any time by the study doctor or the sponsor without your consent for any of the following reasons:

- if it is in your best interest;
- you do not later consent to any future changes that may be made in the study plan;
- or for any other reason.

NEW INFORMATION

You will be told if any new information is learned which may change your decision to be in this study. You may be asked to sign a revised consent form if this occurs. At any time, your study doctor will go over questions you may have regarding your disease and treatment choices. If you have any questions, you can reach a study coordinator at 906-225-6995.

If you agree to be in this study, you will be given a copy of this signed and dated informed consent for your personal records.

ACKNOWLEDGMENT OF CONSENT AND SIGNATURES

I have read this consent form (or it has been read to me).

I have been given the opportunity to ask questions and all of them have been answered to my satisfaction.

I voluntarily consent to participate in this study.

I authorize the use and disclosure of my health information to the parties listed in the authorization section of this consent for the purposes described above.

I authorize my brain tumor tissue to be released to Kentuckiana Cancer Institute for further pathology review.

By signing this consent form, I have not given up any of my legal rights.

Name of Subject

Signature of Subject

Date Signed

Printed Name of Person Conducting Informed Consent Discussion

Signature of Person Conducting Informed
Signed Consent Discussion

Date Signed

Signature of Investigator (if different from above)

Date Signed

----- **Use the following only if applicable** -----

If this consent form is read to the subject because the subject is unable to read the form, an impartial witness not affiliated with the research or investigator must be present for the consent and sign the following statement:

I confirm that the information in the consent form and any other written information was accurately explained to, and apparently understood by, the subject. The subject freely consented to be in the research study.

Signature of Impartial Witness

Date Signed

Note: This signature block cannot be used for translations into another language. A translated consent form is necessary for enrolling subjects who do not speak English.