Appendix A

Phase I Treatment of Adults with Recurrent Supratentorial High-Grade Glioma with Gliadel Wafers Plus Temodar®

CONSENT FOR RESEARCH FOR ADULTS
Phase I Treatment of Adults with Recurrent Supratentorial High-Grade Glioma with Gliadel Wafers Plus Temodar®
IRB #: _________________

You are being asked to take part in a research study entitled “Phase I Treatment of Adults with Recurrent Supratentorial High-Grade Glioma with Gliadel Wafers Plus Temodar®.” Your physicians at [the medical institution] study the nature of disease and try to develop better methods of diagnosis and treatment. This is called clinical research. In order for you to decide whether you should agree to be part of this study, you should understand enough about its risks and benefits to make an informed decision. This process is known as informed consent.

This consent form contains detailed information about the clinical study that the person doing the research will discuss with you. Once you understand the study, you will be asked to sign this form if you agree to take part in the study. You will be given a copy of the signed form to keep as a record.

By signing this document you give your consent to the medical procedures to be performed and to take part in the research study. Please read this consent form carefully. Do not hesitate to ask questions about any of the information in it.

This study has been designed to evaluate the drug Temodar® in combination with Gliadel wafers (containing BCNU chemotherapy). The purpose of this study is to define the maximum dose of Temodar® that can be safely administered in combination with Gliadel wafers (approved by the U.S. Food and Drug Administration [FDA]). Response to treatment and side effects will be evaluated.

You are being asked to consent to participate because you have a recurrent high-grade glioma brain tumor (glioblastoma multiforme, anaplastic astrocytoma, or gliosarcoma).

Your physician has told you that standard therapies are no longer controlling your tumor. For this reason, your physician is asking you to participate in this investigational study with Gliadel wafers plus Temodar®. This study will attempt to make clear what dose of Temodar® is likely to be the best dose to use in future studies when the drug is used with Gliadel wafers. Therefore, you may get a dose that is later shown to be too low, and therefore not helpful. Or you may get a dose that is too high, and therefore very toxic. Or the treatment that you are considering may be helpful to control your disease temporarily. However, the treatment is investigational, and therefore it is not possible to predict the likelihood of benefit to you at this time.

Treatment with Gliadel wafers (containing BCNU chemotherapy) is based upon the implantation (placement) of the wafers in the cavity created during surgery. You will have as many Gliadel wafers as possible (maximum of 8) placed at the time of surgery.

Treatment with Temodar® is based upon a 28-day cycle that will begin two weeks after the implantation of the Gliadel wafers. You will receive the drug on days 1 through 5 of the 28-day cycle. The treatment will be repeated every 28 days. Temodar® is an oral capsule; the actual number of capsules you receive will vary depending upon your weight and any side effects that you may experience throughout

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the study. It is recommended that you not eat for a minimum of one hour prior to each dose and for two
hours after each dose.

The actual duration of therapy will depend upon your response to the treatment and the
development of side effects. No more than 12 cycles (12 months) of therapy will be given.

Various routine tests are required in this study. These include urinalysis, laboratory blood tests, and
a physical and neurological examination. These are considered routine evaluations and would most likely
have been ordered by your physician to evaluate your health status whether or not you were considered
for participation in this study. Other tests that will be done as a part of this study are MRI brain scans,
chest x-rays, and ECGs (heart tracings). Pretreatment evaluations particular to this study include, if
applicable, a pregnancy test within 24 hours prior to starting study drug therapy. In addition, a breast
exam will be done on males and females. (Rats given Temodar® in toxicity studies have developed
cancerous tumors of the breast. The significance of this finding for humans is not known presently.)

Approximately every month, you will be seen in the clinic for a physical and neurological
examination and blood laboratory tests. An MRI scan of your brain will be done after every cycle. Blood
laboratory tests (about 1 teaspoon each) will be required on days 1 and 21 of every 28-day cycle.
Additional tests may be done at the discretion of your physician as part of your regular care throughout
the study.

Your participation in this study may or may not result in any direct benefit to you. The treatment you
receive may decrease the size of your tumor and extend your life. However, it is not possible to predict or
guarantee a favorable response to this treatment.

You have been told that should the disease become worse, should side effects become very severe,
should new scientific developments occur that indicate that the treatment is not in your best interest, or
should the doctor feel that this treatment is no longer proper, the Temodar® treatment would be stopped
and a different type of treatment would be discussed. The Gliadel wafers will not be removed once they
are placed at the time of surgery.

Both the disease and the treatment are associated with potentially life-threatening complications and
side effects. Those side effects are uncomfortable, and some are potentially dangerous or even life-
threatening, but will usually clear up once the treatments have ended. There is also the risk of very
uncommon or previously unknown side effects occurring. The most common side effects of the
treatment to be used in this study are listed below:

Gliadel wafers: seizures, brain edema (swelling), healing abnormalities, wound infection, and body
pain.

Temodar® can cause decreases in blood counts. This can lead to: decreased white cells, which may
make you more vulnerable to infection; a lower number of red cells, which may result in anemia and give
you symptoms of shortness of breath, weakness, and fatigue; a lower number of platelets, which may
result in easy bruising or bleeding for a longer time. The medication’s effect on the blood counts is
usually temporary, and some of the decreases in cell counts can be helped with transfusions of blood or
blood products until your blood counts recover.

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Nausea and vomiting occur occasionally and can be severe in some people. Medications may be given either to prevent these symptoms or to treat them. If nausea and/or vomiting occur, you will be given medications to treat them. Other side effects include headache, rash, kidney problems, elevated liver function tests (which may cause your skin to be yellow), hair loss, diarrhea, constipation, high blood sugar (which may make you dizzy), and loss of appetite. Additional rare side effects include itching and burning, decreased energy, and sleepiness.

The collecting of blood samples 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.

Side effects not yet known to researchers may occur. Every effort will be made to minimize side effects and ease your discomfort. Your doctor will examine you regularly and order tests necessary to monitor side effects and determine response.

Treatment with chemotherapy may involve unforeseeable risks to an unborn child, and it is not known whether taking these drugs now can have effects on any future children that you may have. If you are a woman and are pregnant or breast feeding, you cannot take part in this study. You will be given a blood pregnancy test before you begin the study to make sure that you are not pregnant. If there is a chance you could become pregnant during this study, you should not participate in the study, or you must use a highly effective means of birth control while you are taking part. For women of childbearing potential, medically acceptable contraceptives include (1) surgical sterilization, (2) approved hormonal contraceptives (such as birth control pills, Depo-Provera, or Depolupron), (3) barrier methods (such as a condom or diaphragm) used with a spermicide, or (4) an intrauterine device (IUD). If you become or are found to be pregnant while you are taking part in this study, you must notify us immediately so that management of the pregnancy and the possibility of stopping treatment can be discussed.

If you are a man, you should also use a means of birth control while you are taking part in this study, because we do not know what effect the study drug may have on your sperm and what effect this would have upon the development of an unborn child.

Alternatives to this therapy that could be considered include the use of drugs or other therapies that have been previously tried in the treatment of this disease, including starting radiation therapy now, or investigational drugs. An additional alternative is to take no further therapy, which would almost certainly result in the continued progression of the disease. The physician can provide detailed information about the disease and the benefits of the various treatments available. You have been told that you should feel free to discuss the disease and outlook for the future with the physician.

During this research project, new information regarding the risks and benefits of the study may become known to the investigator. If this occurs, they will tell you about this new information. New information may show that you should no longer participate in the research. If this occurs, the person supervising the research will stop your participation in it. In either case, you will be offered all available care that suits your needs and medical conditions.

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Your privacy and research records will be kept confidential. However, authorized research investigators and agents of the FDA have the right to inspect the records involving you. Health care providers involved with your care will have access to research-related information contained in your medical records. Privacy and confidentiality of the records will be protected to the extent provided by law. The results of this research may be published. Published reports will not include your name or any other information that would identify you.

By signing this form, you consent to this review and also to the release of medical records, imaging studies, and laboratory and pathology specimens, as necessary, for evaluation of your disease and therapy.

Participation in this study is voluntary.

No compensation for participation will be given. You are free to withdraw your consent for participation in this treatment program at any time without prejudice to subsequent care. Refusal to participate will involve no penalty. If you do not take part in or withdraw from the study, you will continue to receive care.

Temodar® is commercially available. You or your third-party insurance carrier will be responsible for the costs of hospitalization, the Gliadel wafers, clinic visits, x-rays, laboratory or other tests. How much you will have to pay depends on whether or not you have insurance and what costs your insurance will cover. Insurance coverage cannot be guaranteed for all tests and treatments related to this study. However, you may discuss this issue with the [medical institution admission staff (telephone number)] and/or your insurance company before you agree to participate. Treatment to help control side effects may also result in added costs.

Immediate, necessary care is available if an individual is injured because of participation in a research project. However, there is no provision for free medical care or for monetary compensation provided by [the medical institution]. Further information concerning this and also your rights as a subject in a research study can be obtained from [the hospital risk management staff (telephone number)]. Further information on this study can be obtained by contacting [the study physician] in [the clinical department at (telephone number)].

"I have read all of the above, had the opportunity to ask questions, and willingly give my consent for participation in this study. Upon signing this form, I will receive a copy."

__________________________  ________________________
Patient Signature              Date

__________________________  ________________________
Person Obtaining Consent      Date