INFORMED CONSENT/AUTHORIZATION FOR PARTICIPATION IN RESEARCH

A Phase II Study of Dose-Dense Temozolomide and Lapatinib for Recurrent Low-Grade and Anaplastic Supratentorial, Infratentorial and Spinal Cord Ependymoma

Study Chair: ***(insert name of local PI)***

Participant's Name Medical Record Number

You are being asked to take part in this clinical research study at (***insert site name)***. This consent form explains why this research study is being done and what your role will be if you choose to take part. This form also describes the possible risks connected with being in this study. After reviewing this information with the person responsible for your enrollment, you should know enough to be able to make an informed decision on whether you want to take part in the study.

You are being asked to take part in this study because you have a brain or spinal cord tumor (ependymoma) that has returned after treatment.

PURPOSE OF STUDY

The goal of this clinical research study is to learn if lapatinib when given in combination with temozolomide can help to control ependymoma that has come back after treatment. The safety of this combination will also be studied.

DESCRIPTION OF STUDY

The Study Drugs

Temozolomide is designed to kill cancer cells by damaging DNA (the genetic material of cells). This could cause the tumor cells to die.

Lapatinib is designed to prevent or slow down the growth of cancer cells by blocking proteins inside the cancer cell, called the Her2/neu receptor and the epidermal growth factor receptor (EGFR).

Screening Tests

Signing this consent form does not mean that you will be able to take part in this study. You will have "screening tests" to help the doctor decide if you are eligible to take part in this study. If you have had some of them within the past 14 days, they may not need to be repeated. The following tests and procedures will be performed:

- You will be asked about any drugs you may be taking.
- Your complete medical history will be recorded.
- You will have a complete physical exam, including measurement of your vital signs (heart rate, temperature, breathing rate, and blood pressure), height, and weight.
- You will be asked how well you are able to perform the normal activities of daily living (performance status).

- You will have a neurological exam (a test to check your level of brain and nerve function).
- Blood (about 2-3 tablespoons) will be drawn for routine tests. This routine blood draw will also include a pregnancy test for women who are able to have children. If you are a woman who is able to have children, the pregnancy test must be negative in order for you to take part in this study.
- Blood (about 1 teaspoon) will be drawn for tests to check your blood's ability to clot.
- If you are taking anti-seizure drugs, blood (about 1 teaspoon) will be drawn to check the level of anti-seizure drug in your blood.
- You will have an magnetic resonance imaging (MRI) scan to measure the tumor.
- You will have an electrocardiogram (ECG--a test to measure the electrical activity of the heart).
- You will have either a multigated acquisition (MUGA) scan (if the doctor thinks it is needed) or an echocardiogram to check your heart function.
- You will be asked to complete a questionnaire about your quality of life. The questionnaire will take about 5 minutes to complete.
- Samples of tumor tissue (such as disease diagnosis slides or tumor tissue leftover from a previous biopsy) is needed to verify your diagnosis. If there is extra tumor tissue available, this will be used to test the biomarkers. Biomarkers are chemical "markers" in the blood/tissue that may be related to your reaction to the study drug.

The study doctor will discuss the screening test results with you. If the screening tests show that you are not eligible to take part in the study, you will not be enrolled. Other treatment options will be discussed with you.

Study Drug Administration

If you are found to be eligible to take part in this study, **every day**, you will take lapatinib by mouth once a day in the morning. You should take lapatinib 1 hour before or 1 hour after eating, with at least 1 cup (about 8 oz.) of water.

On **Days 1-7 and 15-21 of each cycle**, you will take temozolomide by mouth 1 time each day. You will start to take a lower dose of temozolomide for the first 2 cycles, then take a higher dose for Cycles 3 and beyond if you tolerate the treatment. It should be taken at least 2 hours before and 2 hours after eating with 1 cup (about 8 oz.) of water.

You should swallow temozolomide and/or lapatinib whole, one right after the other, without chewing either of the study drugs. If you vomit while taking temozolomide and lapatinib, you cannot take more capsules before the next scheduled dose. You should report any missed pills or trouble you have with taking the pills to your study doctor. Your study doctor will give you a form (patient diary) to fill out to keep track of your treatment. You will be asked to return your completed diary and pill bottles at each visit with your doctor.

Each study "cycle" is 28 days.

Study Visits

Every 2 weeks, blood (about 2-3 teaspoons) will be drawn for routine tests and to check your blood's ability to clot.

Every 8 weeks, the following tests and procedures will be performed:

- You will have a physical exam, including measurement of your vital signs.
- You will have a neurological exam.
- Your performance status will be recorded.
- You will be asked about any drugs you may be taking and if you have experienced any side effects.
- You will complete the quality of life questionnaire.
- You will have an MRI scan to check the status of the disease.
- You will have either a MUGA scan (if the doctor thinks it is needed) or an echocardiogram.

Length of Study

You will be on study treatment for up to 2 years. You will be taken off study treatment early if the disease gets worse or you experience intolerable side effects.

After you are off study, you may be able to continue taking lapatinib for as long as the doctor thinks it is in your best interest. Your doctor will discuss this with you.

End-of-Study Visit

After you go off study treatment, you will have an end-of-study visit. At this visit, the following tests and procedures will be performed:

- You will have a physical exam.
- Your performance status will be recorded.
- You will be asked about any drugs you may be taking and if you have experienced any side effects.
- You will have a neurological exam.
- Blood (about 3 teaspoons) will be drawn for routine tests and to check your blood's ability to clot.
- You will complete the questionnaire.
- You will have an MRI scan to check the status of the disease.
- You will have either a MUGA scan (if the doctor thinks it is needed) or an echocardiogram.

Long-Term Follow-up Visit

If you go off treatment (having completed the maximum 24 months on study drug treatment) and have stable disease or response, you will have an MRI scan to check the status of the disease every 2 months for first year after you are off study, then every 3 months for the second year, then every 4 months for the third year, and then every 6 months from then on.

If you continue taking lapatinib after you have completed up to 24 months on study treatment, you will have a clinic visit and an MRI scan to check the status of the disease every 2 months for as long as the doctor thinks it is needed. At the clinic visits, you will be asked how you are doing.

If you went off study treatment because the disease got worse or you experienced intolerable side effects, after the end-of-study visit, the study staff will call you every 3 months from then on to check how you are doing. Each phone call will take about 5 minutes.

This is an investigational study. Temozolomide is FDA approved or commercially available for the treatment of tumors of the nervous system. Lapatinib is FDA approved and commercially available for the treatment of breast cancer. However, lapatinib is not FDA approved for the treatment of brain tumors. The use of lapatinib with temozolomide in the treatment of brain tumors and spinal tumors is investigational.

While you are on study, lapatinib will be provided at no cost to you. If lapatinib becomes FDA approved for the treatment of ependymoma while you are on study, you may have to pay for the remaining doses. You and/or your insurance provider will be responsible for the cost of temozolomide.

Up to 58 patients will take part in this multicenter study. Up to **(*insert local accrual ceiling*)** will be enrolled at **(*insert site name*)**.

RISKS, SIDE EFFECTS, AND DISCOMFORTS TO PARTICIPANTS

While on this study, you are at risk for side effects. These side effects will vary from person to person. The more commonly occurring side effects are listed in this form, as are rare but serious side effects that the drugs are known to cause. You should discuss these with the study doctor. You may also want to ask about uncommon side effects that have been observed in small numbers of patients but are not listed in this form. Many side effects go away shortly after treatment is stopped, but in some cases side effects may be serious, long-lasting or permanent, and may even result in hospitalization and/or death.

Temozolomide Side Effects

Likely (occurring in more than 20% of patients)

• fatigue • headache • seizures	• hair loss • nausea • vomiting	• constipation • loss of appetite

Temozolomide may likely cause low white blood counts. This means that while you take the drug, there is more of a chance of getting an infection, including pneumonia.

Common (occurring in 3-20% of patients)

• arm and/or leg swelling • weakness (such as weakness on one side of the body) • confusion • dizziness • fever • memory problems and/or loss • difficulty sleeping • drowsiness • anxiety • depression • abnormal muscle movements	• itching • dry skin • excess steroid in the body (possible bruising and/or increase in size of the face and/or neck) • diarrhea • taste changes • sores in the mouth • difficulty swallowing • abdominal pain • weight gain	• tickling/tingling sensation • unusual manner of walking • joint, muscle, and/or back pain • abnormal vision (such as blurry and/or double vision) • head cold • cough • sore throat

/coordination • partial paralysis • skin rash	• female breast pain • loss of urinary control • urinary tract infection • frequent urination	• inflammation of the sinuses • difficulty breathing • allergic reaction • viral infection

Temozolomide may commonly cause low blood cell counts (red blood cells, and platelets). You may have problems with bleeding and /or bruising. You may become anemic, fatigued, and/or shortness of breath. You may need a blood transfusion.

Rare but serious (occurring in fewer than 3% of patients)

- hallucinations
- nervous system disease (possible pain and/or weakness)
- nerve damage (possible numbness, tingling, and pain)
- damage from radiation (such as skin damage)
- severe skin damage with loss of a large portion of skin
- severe skin damage with inflammation of the bowel
- allergic skin reaction
- high blood sugar (possible diabetes)
- low blood levels of potassium (possible weakness)
- bone marrow disease where not enough blood cells are made
- weight loss
- fever due to low white blood cell counts
- bruising
- bleeding
- lung inflammation
- flu-like symptoms
- injection site reactions (skin redness, irritation, pain, itching, swelling, and/or warmth)
- opportunistic infection
- herpes infection causing painful skin rash (shingles)
- new occurrence of cancer (including myeloid leukemia)
- severe allergic reaction

The following side effects have been reported in research studies with temozolomide. It is unclear if these side effects were caused by temozolomide, but they may be:

- hole in the stomach and/or intestines, which may cause the contents to leak
- inflammation of the gallbladder
- death
- dehydration
- inflammation of the pancreas
- abnormal kidney test (possible decreased kidney function)
- nosebleeds
- deficient oxygen in the blood and tissues
- presence of bacteria or their toxins in blood or tissues (sepsis)

<u>Lapatinib Side Effects</u>

Likely (occurring in more than 20% of patients)

- pain, swelling, blistering, and/or redness of the hands/feet
- skin rash
- diarrhea
- nausea
- vomiting
- abnormal liver test (possible liver damage)
- jaundice (yellowing and/or darkening of skin)

Lapatinib may likely cause low blood cell counts (red blood cells and white blood cells). This means that while you take the drug, there is more of a chance of getting an infection,

including pneumonia. You may become anemic and/or have problems with bleeding, bruising, fatigue, and/or shortness of breath. You may need a blood transfusion.

Common (occurring in 3-20% of patients)

- fatigue
- difficulty sleeping
- flushing
- dry skin
- acne
- itchy skin
- abdominal pain
- abdominal bloating
- early satiety (feeling full)
- inflammation of the mucus membrane
- mouth sores
- upset stomach
- poor appetite
- weight loss
- gas
- heartburn
- taste change
- arm and/or leg pain
- general weakness
- back pain
- difficulty breathing
- headache
- flu-like symptoms

Lapatinib may commonly cause low platelet counts. You may have problems with bleeding and/or bruising. You may need a blood transfusion if a problem with bleeding occurs.

Rare but serious (occurring in fewer than 3% of patients)

- decreased heart function
- chest pain caused by a heart spasm
- irregular heartbeat
- liver damage
- lung disease
- lung inflammation

The following side effects have been reported in research studies with lapatinib. It is unclear if these side effects were caused by lapatinib, but they may be:

- heart failure
- low blood pressure
- enlarged heart
- high blood pressure
- tumor growth in the heart
- inflammation of the membrane surrounding the heart
- heart attack
- blockage of a blood vessel that supplies blood to the heart
- irregular heartbeat
- infection of the heart
- inflammation of the muscle of the heart
- coma
- bleeding in the brain
- fever
- dizziness
- shock
- abnormal behavior
- confusion
- low blood sugar
- low blood levels of potassium (possible weakness)
- high blood sugar (possible diabetes)
- low blood level of sodium (possible headache, confusion, seizures, and/or coma)
- low blood levels of phosphate (possible bone damage)
- decreased thyroid hormones
- inflammation of the thyroid gland
- constipation
- inflammation of the stomach lining
- blockage of intestine
- low volume of blood
- inflammation of the blood vessels
- liver failure
- abnormal liver test (possible liver damage)
- chronic inflammation of the liver
- arm and/or leg swelling
- general pain, joints and muscles
- facial swelling
- blurred vision
- kidney failure
- kidney impairment
- increased creatinine blood level (possible kidney problems)
- pulmonary embolism (blood clot to lung)
- cough

- low blood supply to the brain tissue
- fainting
- degenerative nerve disease
- painful fingers and feet/toes
- skin changes including nail changes and/or hives
- hand-foot syndrome (pain, swelling, blistering, and/or redness of the hands and/or feet)
- shingles (painful skin rash)
- inflammation of the tissue underneath the skin (cellulitis)
- infection in stomach and/or intestines
- inflammation of the large bowels
- bloody stools
- bloody vomit
- break/slit of the tissue of the anus
- mouth bleeding
- dehydration
- bleeding in the digestive system
- painful urination
- urinary tract infection
- (DVT) a blood clot within a large vein (in the legs or pelvis)
- (DIC) excessive clotting or bleeding throughout the body
- nose bleeds
- respiratory failure (inability to breathe)
- pus-filled areas in the lung
- coughing up blood
- swelling of the throat or voice box
- difficulty and/or painful swallowing
- respiratory tract infection
- allergic reaction
- sudden death
- viral infection
- incomplete or faulty development of a body organ (aplasia)

There is a chemical that is present in lapatinib in small quantities. This chemical by itself may cause changes to genes (DNA--the genetic material of cells) that may lead to an increased chance of developing new cancer or tumors.

Using the **study drugs together** may cause side effects that are not seen when each is given alone.

Because certain other drugs can interact with temozolomide, review all drugs that you are taking with your healthcare provider, including those that you take without a prescription.

Blood draws may cause pain, bleeding, and/or bruising. You may faint and/or develop an infection with redness and irritation of the vein at the site where blood is drawn. Frequent blood collection may cause anemia (low red blood cell count), which may create a need for blood transfusions.

Questionnaires may contain questions that are sensitive in nature. You may refuse to answer any question that makes you feel uncomfortable. If you have concerns after completing the questionnaire, you are encouraged to contact your doctor or the study chair.

Certificate of Confidentiality

To help us protect your privacy, we have obtained a a Certificate of Confidentiality from the National Institutes of Health. The Certificate protects against the involuntary release of information about subjects collected during the course of our covered studies. The researchers involved in the studies cannot be forced to disclose the identity or any information collected in the study in any legal proceedings at the federal, state, or local level, regardless of whether they are criminal, administrative, or legislative proceedings. However, the subject or the researcher may choose to voluntarily disclose the protected information under certain circumstances. For example, if the subject or his/her guardian requests the

release of information in writing, the Certificate does not protect against that voluntary disclosure. Furthermore, federal agencies may review our records under limited circumstances, such as a DHHS request for information for an audit or program evaluation or an FDA request under the Food, Drug and Cosmetics Act. The Certificate of Confidentiality will not protect against the required reporting by hospital staff of information on suspected child abuse, reportable communicable diseases, and/or possible threat of harm to self or others.

This study may involve unpredictable risks to the participants.

Pregnancy Related Risks

Because taking part in this study can result in risks to an unborn or breastfeeding baby, you should not become pregnant, breastfeed a baby, or father a child while on this study. You must use birth control during the study if you are sexually active.

Birth Control Specifications: Women who are able to become pregnant and men who are able to father a child must use birth control while on study and for 6 months after the last dose of study drugs. Acceptable forms of birth control include birth control pills and/or condoms.

Males: Tell the doctor right away if your partner becomes pregnant or suspects pregnancy.

Females: If you are pregnant, you will not be enrolled on this study. If you become pregnant or suspect that you are pregnant, you must tell your doctor right away.

Getting pregnant may result in your removal from this study.

POTENTIAL BENEFITS

Treatment with lapatinib and temozolomide may help to control the disease. Future patients may benefit from what is learned. There may be no benefits for you in this study.

ALTERNATE PROCEDURES OR TREATMENTS

You may choose not to take part in this study. You may choose to receive other treatments for ependymoma that has come back (such as chemotherapy, radiation therapy, or a combination of both). You may choose to receive other investigational therapy, if available. You may choose not to have treatment for cancer at all. In all cases, you will receive appropriate medical care, including treatment for pain and other symptoms of cancer.

Additional Information

You may ask the study chair any questions you have about this study. You may contact the study chair, ***insert local PI name*****, at** ***insert local PI contact information***. You may also contact the Chair of ***insert local IRB name*** (IRB - a committee that reviews research studies) at ***insert local IRB contact information*** with any questions that have to do with this study or your rights as a study participant.

Your participation in this research study is strictly voluntary. You may choose not to take part in this study without any penalty or loss of benefits to which you are otherwise entitled. You may also withdraw from participation in this study at any time without any penalty or loss of benefits. If you decide at any time to withdraw your consent to participate in the trial, we will not collect any additional medical information about you. However, according to FDA guidelines, information collected on you up to that point may still be provided to the National Cancer Institute IRB or designated representatives. If you withdraw your consent and leave the trial, any samples of yours that have been obtained for the study and stored at the NCI can be destroyed upon request. However, any samples and data generated from the samples that have already been distributed to other researchers or placed in the research databases can**not** be recalled and destroyed.

If you decide you want to stop taking part in the study, it is recommended for your safety that you first talk to your doctor.

This study or your participation in it may be changed or stopped at any time by the study chair, the U.S. Food and Drug Administration (FDA), the Office for Human Research Protections (OHRP - a regulatory agency that oversees research in humans), or the IRB of ***insert local IRB name***..

You will be informed of any new findings that might affect your willingness to continue taking part in the study.

This study is coordinated by The National Cancer Institute, Center for Cancer Research

Dr. Mark R. Gilbert (Study Chair) has received compensation from GlaxoSmithKline as a Scientific Advisor. The financial interests are within the limits of the conflict of interest policy.

STUDY COSTS AND COMPENSATION

(Tailor per local institution policy)

If you suffer injury as a direct result of taking part in this study, ***insert site name*** health providers will provide medical care. However, this medical care will be billed to your insurance provider or you in the ordinary manner. You will not be reimbursed for expenses or compensated financially by ***insert site name*** or the National Cancer Institute for this injury. You may also contact the Chair ***insert local IRB name and contact information*** with questions about study-related injuries. By signing this consent form, you are not giving up any of your legal rights.

Certain tests, procedures, and/or drugs that you may receive as part of this study may be without cost to you because they are for research purposes only. However, your insurance provider and/or you may be financially responsible for the cost of care and treatment of any complications resulting from the research tests, procedures, and/or drugs, including hospitalization, nausea, vomiting, low blood cell counts, and dehydration. Standard medical care that you receive under this research study will be billed to your insurance provider and/or you in the ordinary manner. Before taking part in this study, you may ask about which parts of the research-related care may be provided without charge, which costs your insurance provider may pay for, and which costs may be your responsibility. You may ask that a financial counselor be made available to you to talk about the costs of this study.

There are no plans to compensate you for any patents or discoveries that may result from your participation in this research.

You will receive no compensation for taking part in this study.

WILL YOUR MEDICAL INFORMATION BE KEPT PRIVATE?

We will do our best to make sure that the personal information in your medical record will be kept private. However, we cannot guarantee total privacy. Organizations that may look at and/or copy your medical records for research, quality assurance, and data analysis include:

- The National Cancer Institute (NCI) and other government agencies, like the Food and Drug Administration (FDA), which are involved in keeping research safe for people, or their agent(s)
- ***Insert local IRB name***
- National Cancer Institute Institutional Review Board
- Qualified representatives from GlaxoSmithKline, the pharmaceutical company who produces lapatinib.
- All investigators participating in this protocol.

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.

Notes to consent form authors:
The NCI has recommended that HIPAA regulations be addressed by the local institution. Language pertaining to HIPAA compliance may or may not be included in the local consent form, depending on local institutional policy.

CONSENT/AUTHORIZATION

I understand the information in this consent form. I have had a chance to read the consent form for this study, or have had it read to me. I have had a chance to think about it, ask questions, and talk about it with others as needed. I give the study chair permission to enroll me on this study. By signing this consent form, I am not giving up any of my legal rights. I will be given a signed copy of this consent document.

_____ _____

SIGNATURE OF PARTICIPANT DATE

PERSON OBTAINING CONSENT

I have discussed this clinical research study with the participant, using language that is understandable and appropriate. I believe that I have fully informed this participant of the nature of this study and its possible benefits and risks and that the participant understood this explanation.

_____ _____

SIGNATURE OF STUDY CHAIR OR PERSON AUTHORIZED TO OBTAIN CONSENT DATE