Phase I Dose Finding, Arm 1

Phase I Study of MK-1775 with Radiation and Temozolomide in Patients with Newly Diagnosed Glioblastoma and Evaluation of Intratumoral Drug Distribution in Patients with Recurrent Glioblastoma

This is a clinical trial (a type of research study). Your study doctor will explain the clinical trial to you. Clinical trials include only subjects who choose to take part. Please take your time to make your decision about taking part. Discuss it with your family and friends. You can also discuss it with your health care team. If you have any questions, you can ask your study doctor for more explanation.

You are being asked to take part in this study because you have a newly diagnosed brain tumor that is a glioblastoma. This research is a study evaluating a drug called MK-1775 given in combination with standard radiation therapy and temozolomide as a possible treatment for newly diagnosed glioblastoma.

WHY IS THIS STUDY BEING DONE?

This research study is a Phase I clinical trial which tests the safety of an investigational drug and also tries to define the appropriate dose of investigational drug to use for further studies. "Investigational" means that the drug is being studied. It also means that the FDA (U.S. Food and Drug Administration) has not approved the drug for use in patients, including people with your type of cancer. This research is being done because this type of tumor is almost never cured with surgery, radiation, or chemotherapy. For this reason, we are trying to find new drugs to improve treatment for this tumor. The study you are being asked to join uses an investigational drug called MK-1775.

This part of the study is a dose-finding study. This means that we want to find the best dose of MK-1775 to give with temozolomide. Temozolomide (TMZ) is a type of chemotherapy and is considered part of "standard" therapy for this disease. TMZ is an FDA-approved drug that has been found to increase the survival of patients with brain tumors. MK-1775 may increase the effect of temozolomide (TMZ).

The combination of TMZ and radiation therapy is now considered the "standard of care" for treatment of glioblastoma. When TMZ is given as part of standard of care it is given first with radiation therapy as a daily treatment for 6 weeks. After radiation therapy is complete it is given 5 out of every 28 days for several months.

In order to find the best dose of MK-1775 to give with TMZ, the first part of this study will be divided into 2 groups, Arm 1 and Arm 2. In Arm 1 we will test the best dose of MK-1775 to give when taking TMZ every day during the 6 weeks of radiation therapy. In Arm 2 we will test

the best dose of MK-1775 to give when taking standard TMZ for 5 out of every 28 days following the completion of radiation therapy.

You are being asked to participate in Arm 1.

You will be assigned a dose of MK-1775 when you enter the study. You will be told what your dose is and it will not be increased. You will be given the same or a lower dose throughout your treatment. You will be given a lower dose if you experience side effects that require reduced dosing. We will also be looking at the side effects of MK-1775 and temozolomide.

HOW MANY PEOPLE WILL TAKE PART IN THIS STUDY?

A minimum of 6 and a maximum of 36 people will take part in the study.

WHAT IS INVOLVED IN THE STUDY?

This study will take place in an outpatient setting.

Before you begin the study, you will need to have the following exams, tests or procedures to find out if you can be in the study. These exams, tests or procedures are part of regular cancer care and may be done even if you do not join the study. If you have had some of them recently, they may not need to be repeated. This will be up to your study doctor.

- You will have a complete physical exam and blood tests. Your physical examination will include:
  - a medical history
  - measurement of your height, weight, blood pressure, temperature, respiratory rate, heart rate
  - performance status, which measures the degree of your ability to complete daily activities (e.g., dressing and eating)

- You will have a complete neurological exam to test your ability to think, your muscle strength, balance, and other functions of the brain.

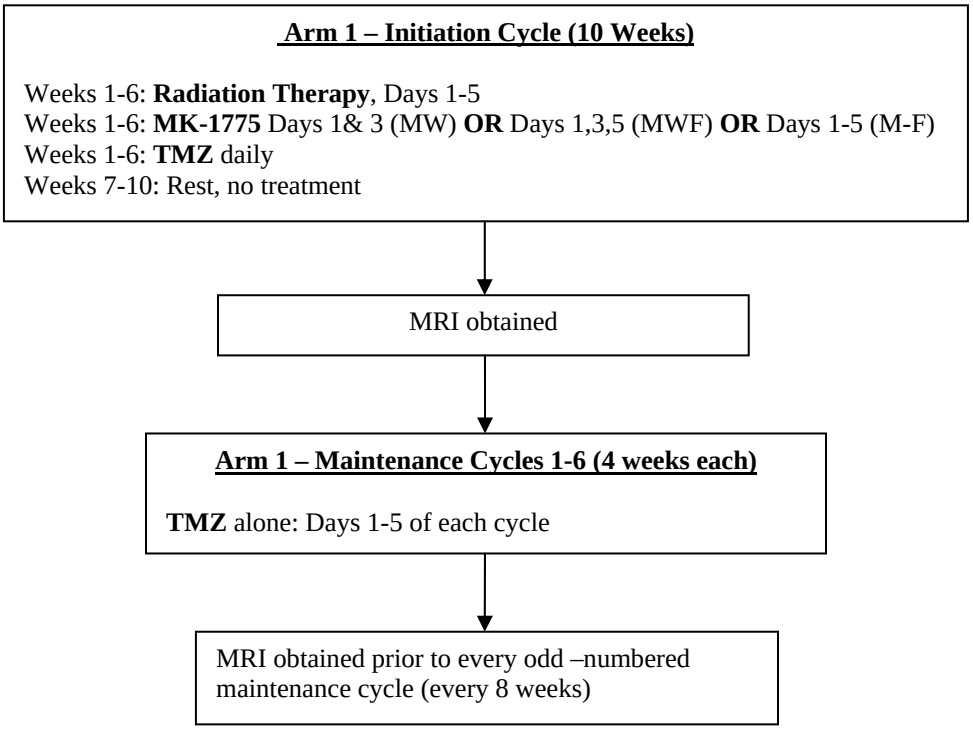
- To measure the extent of your brain tumor, you will have an MRI (magnetic resonance imaging) scan, which is a method of obtaining pictures of internal soft bodily tissue through the use of powerful magnets and radio waves.

- As part of your screening tests, about 3 tablespoons of blood will be drawn from one of your veins to conduct laboratory tests (e.g., standard blood count including a count of your platelets, and blood chemistries). You will also be asked to have a pregnancy test if you are a woman that is able to have children. If you are pregnant you will not be permitted to participate in this study.

- You will need to supply a complete list of your current medications to the study doctor. This includes over-the-counter medications and herbal supplements.

- **As a part of this study** we will collect samples of your tumor tissue for research purposes. Some of the tumor tissue that was taken during your surgery or biopsy, if sufficient tissue is available, will be sent to a lab for analysis. The tissue samples will be used to characterize the immunochemistry and molecular biology of your tumor. Glioblastoma can be very different in each patient. We hope to learn about the characteristics of your tumor. We will use the information we collect about this kind of tumor to help us better treat patients with glioblastoma in the future.

Study Plan



INITIATION CYCLE

During the initial cycle of treatment, MK-1775 will be taken in the form of a pill either on a Monday/Wednesday, Monday/Wednesday/ Friday, or a Monday thru Friday schedule (2 days, 3 days, or 5 days, depending on your assigned dose) each week during radiation therapy. The number of pills you take will depend on your assigned dose. Your study doctor or nurse will provide specific dosing instructions. Radiation will be given daily on weekdays (Monday thru Friday), in an outpatient setting for about 6 weeks. There is nothing investigational about the radiation that will be given.

During radiation therapy you will also take temozolomide (TMZ) daily. Temozolomide is given in the form of a pill that you will take every day (7 days a week) for 6 weeks while you are receiving radiation. The number of pills you take every day will depend on your body size. Swallow capsules whole with a glass of water. Do not open or chew the capsules. If capsules are accidentally opened or damaged, be careful not to breathe in (inhale) the powder from the capsules or get the powder on your skin or mucous membranes (for example, in your nose or mouth). If contact with any of these areas happens, flush the area with water.

You will begin taking MK-1775 and temozolomide together on the first day of radiation. You will take your pills about one hour before you receive radiation.

TMZ and MK-1775 must be taken on an empty stomach. You cannot eat or drink anything except water for two hours before taking your pills and for one hour after taking your pills. Medication to prevent nausea and vomiting may be prescribed by your doctor while taking temozolomide.

If you miss a dose or vomit after taking your dose do not replace it; missed or vomited doses should not be made up.

You will be asked to record the date, time, and the number of pills you take each day of the study in a pill diary for each medication, as you take your dose. You will need to bring the diaries and any extra pills and medication containers with you to your monthly visit to the study doctor.

You should avoid consuming grapefruit and grapefruit juice while taking the study medication due to possible interactions. You should not take any herbal remedies while you are on this study.

Medication to prevent infection is required for all patients receiving daily temozolomide during radiation therapy, and sometimes while taking temozolomide after radiation treatment. Your doctor will recommend and prescribe appropriate medication. This is part of standard care for treatment with temozolomide and radiation.

During the 4 weeks directly after radiation therapy ends you will not take any temozolomide or MK-1775. These first ten weeks of treatment (6 weeks of radiation+TMZ+MK-1775 and 4 weeks of “rest” or no treatment) are called the Initiation Cycle. An MRI of your brain will be obtained after you complete the Initiation Cycle. This MRI is part of your standard radiation therapy follow-up care.

MAINTENANCE CYCLES

After your Initiation Cycle you will begin four-week (28-day) cycles of treatment called *maintenance* cycles. In these maintenance cycles you will no longer take MK-1775. You will take temozolomide alone, during the first 5 days of each cycle. The number of pills you take each day will depend on your body size. This is part of standard therapy for treatment of glioblastoma.

TMZ must be taken on an empty stomach. You cannot eat or drink anything except water for one hour before and for one hour after taking your pills. Medication to prevent nausea and vomiting will be prescribed by your doctor while taking temozolomide in the maintenance cycles. This is part of standard care for 5-day temozolomide treatment.

If you miss a dose or vomit after taking your dose do not replace it; missed or vomited doses should not be made up.

You will be asked to record the date, time, and the number of pills you take each day of the study in a pill diary for each medication, as you take your dose. You will need to bring the diaries and any extra pills and medication containers with you to your monthly visit to the study doctor.

You should avoid consuming grapefruit and grapefruit juice while taking the study medication due to possible interactions. You should not take any herbal remedies while you are on this study.

After the second maintenance cycle another MRI will be obtained. If this MRI shows that the tumor size is the same or smaller, you will begin another four-week cycle of treatment, up to 6 maintenance cycles. An MRI will be obtained before every other cycle (every 8 weeks) to see if your tumor is growing. These brain scans (MRI) are part of routine cancer care.

During the study, physical and neurologic exams will be repeated and your vital signs will be measured (including temperature, heart rate, blood pressure, respiratory rate). Routine blood tests will be done. If at any point your blood counts are low, these blood tests will be repeated more often. Your blood counts will be checked at least once every week during study treatment.

Research Blood Samples:
As part of this study, we will be collecting extra blood samples in order to check the amount and activity of MK-1775 in your blood. Approximately 1 teaspoon of blood will be drawn for each sample. These extra blood tests are for research purposes only and would not be part of your standard care. The costs associated with collecting and processing these blood samples will not be charged to you or your insurance company.

<u>If you are on a Monday/Wednesday or Monday/Wednesday/Friday (2 or 3 days per week) dosing schedule</u> of MK-1775, a total of 16 extra blood samples will be drawn: 7 samples each day on Days 1 and 22, and 1 sample each on Days 2 and 23.

These blood samples will be drawn on the following days during the Initiation Cycle:

- Day 1: 5 minutes pre-dose and then 30 minutes, 1 hour, 2 hours, 4 hours, 6 hours and 8 hours post-dose.
- Day 2: 24 hours after MK-1775 was administered on Day 1
- Day 22: 5 minutes pre-dose and then 30 minutes, 1 hour, 2 hours, 4 hours, 6 hours and 8 hours post-dose.
- Day 23: 24 hours after MK-1775 was administered on Day 22

If you are on a Monday thru Friday (5 days per week) dosing schedule of MK-1775a total of 24 extra blood samples will be drawn: 7 samples each day on Days 1, 4, and 22, and 1 sample each on Days 2, 5, and 23.

These blood samples will be drawn on the following days during the Initiation Cycle:

- Day 1: 5 minutes pre-dose and then 30 minutes, 1 hour, 2 hours, 4 hours, 6 hours and 8 hours post-dose.
- Day 2: 24 hours after MK-1775 was administered on Day 1
- Day 4: 5 minutes pre-dose and then 30 minutes, 1 hour, 2 hours, 4 hours, 6 hours and 8 hours post-dose.
- Day 5: 24 hours after MK-1775 was administered on Day 4
- Day 22: 5 minutes pre-dose and then 30 minutes, 1 hour, 2 hours, 4 hours, 6 hours and 8 hours post-dose.
- Day 23: 24 hours after MK-1775 was administered on Day 22

HOW LONG WILL I BE IN THE STUDY?

You will likely be on study treatment for at least 18 weeks. Treatment will continue unless your tumor grows or you have side effects that require discontinuation, or you want to stop treatment. If the MRI taken after the second maintenance cycle shows that the tumor size is the same or smaller, you will begin a third 4-week cycle of treatment. As long as your tumor does not grow and as long as you do not experience any bad side effects you may continue to receive additional 4-week cycles, up to six cycles. If the MRI shows that your tumor is growing you will stop study treatment and you and your doctor will discuss other treatment options.

Every two (2) months for the first two years after your treatment on the study has ended, someone from the study will contact you or your medical records will be reviewed to follow your disease. After two years, this will occur every 6 months for the remainder of your life.

CAN I STOP BEING IN THE STUDY?

Your participation in your clinical trial is completely voluntary. You can stop participating at any time. If you decide not to participate it will not affect your medical care at this institution. If you join this study you may withdraw from it at any time. However, if you decide to withdraw from the study, we encourage you to talk to the study doctor first.

Your study doctor may end your participation in the study if it is judged to be in your best interest or if you are unable to follow the rules of the study.

When you withdraw from the study for any reason, all medication and study drug bottles must be returned to the study site. You will also be asked to return to the site so that the study doctor may perform a proper, final safety evaluation. Every 2 months for the first two years after your treatment on the study has ended, someone from the study will contact you or your medical

records will be reviewed to follow your disease; after two years, this will occur every 6 months for the remainder of your life.

WHAT ARE THE RISKS OR SIDE EFFECTS OF THE STUDY?

While on the study, you are at risk for the following side effects. You should discuss these with the study doctor and/or your regular doctor. There also may be other side effects that we cannot predict. You should also discuss any other side effects that you may experience. Other drugs will be given to make the side effects less serious and uncomfortable.

Many side effects go away shortly after the MK-1775 is stopped, but in some cases side effects can be serious or long-lasting or permanent or fatal. Like chemotherapy drugs, MK-1775 has the potential to damage DNA; MK-1775 should only be taken by cancer patients.

Risks Associated with MK-1775

COMMON, SOME MAY BE SERIOUS In 100 people receiving MK-1775, more than 20 may have:
• Anemia which may require blood transfusion • Bruising, bleeding

OCCASIONAL, SOME MAY BE SERIOUS In 100 people receiving MK-1775, from 4 to 20 may have:
• Ringing in the ear • Belly pain • Diarrhea, nausea, vomiting • Tiredness, fever • Infection, especially when white blood cell count is low

Risks Associated with Temozolomide (TMZ)

TMZ is a chemotherapy drug that is considered part of standard treatment. TMZ may cause the following:

Likely (more than a 20% chance this will happen):

- Nausea, upset stomach and vomiting with temozolomide occur often and can be severe in some people.
- Fatigue
- Constipation
- Loss of appetite
- Headache
- Weakness
- Weight loss
- Shortness of breath

- Hair loss
- Chills
- Abnormal sensations, such as numbness, burning, and/or tingling
- A drop in the red blood count may result in anemia, which could lead to shortness of breath, dizziness, weakness and/or fatigue. As a result you may need a blood transfusion.

Frequent (between 10-20% chance this will happen):

- Dizziness
- Rash
- Generalized pain
- Swelling in the legs and feet caused by excess fluid in the body tissues
- Diarrhea
- A drop in blood counts, in particular, a decrease in the number of neutrophils in the blood (a type of white blood cell that helps fight infection), may result in severe infection such as pneumonia that may require IV antibiotics and medication to increase your white blood cells. This could potentially lead to a hospital stay. This can be serious or life threatening.
- A drop in the number of platelets in the blood that may result in easy bruising and bleeding in mucous membranes, wounds, or other tissues. If this happens, you might require a transfusion.

Occasional (chance of less than 10% that this will happen):

- Itchy skin
- Difficulty walking/unsteady gait
- Increased risk of infection which may be serious or life threatening
- Pain while swallowing
- Abdominal pain
- Elevated blood sugar, which may lead to infection, increased thirst and increased urination
- Sleepiness
- Difficulty falling asleep
- Redness of the skin
- Fever
- Allergic reactions that may include a rash, hives, fever, difficulty breathing, and low blood pressure. Although usually reversible with treatment, it can be severe and life threatening.
- Anxiety
- Depression
- Opportunistic infections (may occur when temozolomide is used in combination with radiation treatment and steroids)—An infection caused by an organism that usually does not cause illness, but causes disease when a person’s immune response (resistance) to infection is

impaired.
- Abnormal liver function tests—which means that your liver is not functioning properly and can cause malaise (a vague feeling of bodily discomfort), fatigue, and jaundice (yellowing of the skin). Although this is usually mild and reversible, this can be serious or life threatening and result in liver failure.
- Abnormal kidney function tests, which means the kidneys aren't working properly. When the kidneys do not work properly, wastes can build up in your blood, leading to swelling in the arms and legs, tiredness and weakness. This could become severe, requiring hospitalization and dialysis to clean the wastes out of your blood. If the wastes are not removed from your blood, this could cause seizures and be life threatening.
- Prolonged treatment with temozolomide may also increase the risk of developing a rare lung infection called pneumocystis pneumonia (PCP), which may result in the following symptoms: fever, cough and difficulty breathing.

Rare: many of the following rare side effects may be life-threatening or lead to life-threatening events:
- Altered consciousness (diminished sense of awareness of self and/or environment).
- Pulmonary blood clot which can lead to a respiratory arrest.
- Blood clot formed in the veins of the leg (deep venous thrombosis) which may manifest as a dull ache or heaviness in the limb. If the clot moves to other organs, it can be serious or life threatening.
- Permanent bone marrow damage may result in a drop in the number of platelets, white blood cell counts, and red blood cell counts.
- Stomach bleeding
- Idiopathic Thrombocytopenia Purpura (ITP) may occur. ITP may cause bleeding and bruising. Bleeding may be serious or life threatening and may require a blood transfusion. This condition can resolve with treatment.
- Stroke (cerebrovascular accident) has been reported; the relationship of this event to temozolomide is unclear.
- Secondary cancer, such as leukemia
- Bleeding from the lungs may occur accompanied by respiratory failure.
- Atrial fibrillation (an irregular quickening of the heart beat) and cardiac failure.
- Air or gas in the abdomen causing pain and discomfort
- Inflammation and/or infection of the intestines, which may cause pain and discomfort

Risks Associated with Radiation Therapy:

You will receive standard radiation therapy in the Initiation Cycle. Risks and side effects related to the radiation therapy include:

Likely risks:

- Scalp redness or soreness
- Hair loss, which may be temporary or permanent
- Ear/ear canal reactions, such as dryness of ear canal, hardening of the wax in the ear canal, or redness of the external ear, possibly causing temporary hearing loss
- Fatigue, lethargy
- Temporary worsening of brain tumor symptoms such as headaches, seizures, or weakness

Less likely risks:

- Problems with mental functioning (neurocognitive problems), including memory deficits, which may be permanent
- Permanent hearing loss
- Condition in which the lens of the eye becomes cloudy (cataracts). This may require surgery to repair.
- Behavioral change, which can be due to physical effects of radiation therapy such as fatigue or headaches
- Nausea, vomiting

- Temporary worsening of existing neurological problems, such as decreased vision, drowsiness, and weakness of your arms and legs
- Endocrine problems related to changes to the pituitary gland, a gland that produces hormones that control other glands. Symptoms can include problems with your thyroid gland, sugar metabolism, fertility, or decrease in ability to regulate water, which may lead to excessive urination.
- Dry mouth or altered taste

Rare but serious risks:

- Severe local damage to normal brain tissue, a condition called necrosis (tissue deterioration). Radiation necrosis can mimic recurrent brain tumor and may require surgery for diagnosis and treatment.
- Injury to the eyes with the possibility of blindness
- Development of other tumors (either benign or malignant)

Side effects due to blood drawing may include: pain, bruising, bleeding or other discomfort at the blood drawing site. Anemia (low red blood cells), fainting or infection at the blood drawing site may occur (very unlikely).

Reproductive Risks

Because there may be a risk of birth defects if a fetus is exposed to MK-1775 or temozolomide, you should not use this drug if you and your partner are planning to have a baby during this study or two months following the end of the study. A barrier method of birth control (e.g.

condom, diaphragm) plus a spermicide must be used during the study and for eight (8) weeks after your last dose of study drug. You should not nurse a baby while on this study.

Risks of MRI

The effects of magnetic fields in an MRI scanner have been extensively studied, and there are no known significant risks with an MRI exam. You may, however, be bothered by feelings of confinement (claustrophobia), and by the noise made by the magnet during the procedure. You will be asked to wear earplugs or earphones while in the magnet. You may not participate in this study if you have a pacemaker, an implanted defibrillator or certain other implanted electronic or metallic devices. It is important for you to advise the MRI staff if you have had brain surgery for a cerebral aneurysm, or if you have implanted medical or metallic devices, shrapnel, or other metal, such as metal in your eye.

Gadolinium Risk

The contrast agent you will receive is FDA-approved and used routinely for MRI exams. It contains a material called gadolinium. The injection of contrast may cause discomfort, tingling or warmth in the lips, metallic taste in the mouth, tingling in the arm, nausea, or headache. These symptoms occur in less than 1% (less than 1 in 100) of people and go away quickly.

There is a small risk of an allergic reaction to gadolinium; however, a severe allergic reaction occurs in less than one in 300,000 people. Insertion of the needle (small plastic tube) to give you gadolinium may cause minor pain, bruising and/or infection at the injection site.

People with severe kidney failure who receive gadolinium are at risk of developing Nephrogenic Systemic Fibrosis/Nephrogenic Fibrosing Dermopathy (NSF/NFD). This disease causes fibrosis, which is the formation of too much connective tissue in the skin and internal organs throughout the body. People develop skin thickening that may prevent bending and extending joints, resulting in decreased movement of the joints. The skin changes can cause feelings of burning, itching and pain that can be severe. In addition, people may experience fibrosis that spreads to other parts of the body such as the diaphragm, muscles in the thigh and lower abdomen, and the lining of blood vessels in the lung.

NSF/NFD is a serious progressive disease and can result in death. If you have severe kidney failure and receive gadolinium, the risk of developing NSF/NFD is 1-5 % (up to 1 to 5 per 100 people). We may require a blood sample (about 1 tablespoon) to check your kidney function before you receive gadolinium contrast for your MRI.

Please notify a doctor, nurse or technologist if you are allergic to gadolinium, if you have any kidney problems, or if you experience any of these or other side effects. If you do not know if you have kidney problems or if you do not know if your kidney problems fall in the severe category, you can ask the principal investigator of your study to give you this information.

A physician will be available during the procedure to administer any necessary care if side effects do occur, and to determine when or if the injection of the gadolinium should be stopped.

Financial risks: There may be extra costs with this treatment. Some of the costs may not be covered by the hospital or the insurance company. We encourage you to work closely with your insurance company to find out exactly what is covered for this research study.

This study may also have risks to you that cannot be determined at this time. You will be told of any potential risks that may be discovered while you are participating in this study.

For more information about risks and side effects, ask the study doctor or contact:

ARE THERE BENEFITS TO TAKING PART IN THE STUDY?

If you agree to take part in this study, there may or may not be direct medical benefit to you. We hope the information learned from this study will benefit other patients with brain tumors in the future.

WHAT OTHER CHOICES DO I HAVE IF I DO NOT TAKE PART IN THIS STUDY?

Your other choices may include:

- Getting treatment or care for your cancer without being in a study
- Taking part in another study
- Getting no treatment
- Getting comfort care, also called palliative care. This type of care helps reduce pain, tiredness, appetite problems and other problems caused by the cancer. It does not treat the cancer directly, but instead tries to improve how you feel. Comfort care tries to keep you as active and comfortable as possible.

Talk to your doctor about your choices before you decide if you will take part in this study.

WILL MY MEDICAL INFORMATION BE KEPT PRIVATE?

This section tells you what information about you may be used and given out in this study and who may give and receive the information. By signing this consent form, you agree that health information that identifies you may be used and/or given out as needed in this study. _____ has a policy to protect health information that may identify you. Federal and state laws also protect your privacy. _____ has procedures in place to support these policies and laws.

a. What information about you may be used or given out in this study?
Information that identifies you and relates to your health or medical condition may be used or given out in this study. Information that identifies you can include your name, address, telephone number, date of birth, Social Security number and other details about you. Information that relates to your health or medical condition includes:

Information obtained from the activities and procedures outlined in this consent form, which may include:

i) things done to see if you can join this study, such as physical examinations, blood and urine tests and any other information that you share with us, including information about your health history and your family health history; and

ii) information obtained during the study, such as how you respond to the study activities or procedures, information we learn in study visits, phone calls, surveys, physical examinations, blood and urine tests, x-rays and other tests and any other medical information we learn from you as a participant in this study.

b. Who may use and give out information about you?
Some people may see your health information and may give out your health information during this study. These include the research study doctor and the research staff, the institutional review boards and their staff, legal counsel, audit and compliance staff, officers of the organization and other people who need to see the information to help this study or make sure it is being done as it should.

c. Who may see your health information?
Other organizations may see your health information during this study. These include:

- Governmental entities that have the right to see or review your health information, such as the Office of Human Research Protections and the Food and Drug Administration
- Doctors and staff at other places that are participating in this study
- The Pharmaceutical Collaborator (includes the National Cancer Institute's pharmaceutical collaborators who provide investigational drug to the NCI)
- The sponsors of this study and people that the sponsor may contract with for this study. The name of the sponsor is DCTD/NCI (Division of Cancer Treatment and Diagnosis/National Cancer Institute)
- The Data Safety Monitoring Board
- An outside institutional review board
- The Adult Brain Tumor Consortium (ABTC)

d. Why will this information be used and given out?
Your information will be used and given out to carry out this study and to evaluate the results of this study.

e. What if you decide not to give your permission to use and give out your health information?
You do not have to give your permission to use or give out your health information. However, if you do not give permission, you may not participate in this study.

f. May you withdraw or cancel your permission?

You may cancel your agreement to allow your health information to be used or given out at any time by sending a written notice to the Institutional Review Board Office, _____. If you do this, you are leaving this study. If you leave this study, no new health information about you will be gathered after that date. However, information gathered before that date may be used or given out if it is needed for this study or any follow-up for this study.

g. Is your health information protected after it has been given to others?

If your health information is given to someone not covered by these policies and laws, that information may no longer be protected, and may be used or given out without your permission.

h. Does this consent form have an end date?

This authorization to use and give out health information continues until the end of this study and any necessary data analysis follow-up activities for this study.

i. What is the role of the IRB?

Research studies involving human volunteers are reviewed by an Institutional Review Board (IRB). The IRB is made up of doctors, nurses, scientists, non-scientists and people from the community. The IRB is responsible for protecting participant's 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 can search this Web site at any time.

WHAT ARE THE COSTS?

Taking part in this study may lead to added costs to you or your insurance company. Some of the costs of the blood tests and brain scans may not be covered by your insurance company. We encourage you to work closely with your insurance company to find out exactly what is covered for this research study.

The NCI (National Cancer Institute) will provide you with the investigational agent MK-1775 free of charge while you take part in this study. The NCI does not cover the cost of getting MK-1775 ready and giving it to you, so you or your insurance company may have to pay for this.

Even though it probably won't happen, it is possible that the manufacturer may not continue to provide MK-1775 to the NCI for some reason. If this would occur, other possible options are:

- You might be able to get MK-1775 from the manufacturer but you or your insurance company may have to pay for it.

- If there is no MK-1775 available at all, no one will be able to get more and the study would close.

If a problem with getting MK-1775 occurs, your study doctor will talk to you about these options.

Should this agent become commercially available or approved for this indication 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 the company no longer provides the drug.

Temozolomide is commercially available for brain tumor treatment.

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

For more information on clinical trials and insurance coverage, you can visit the National Cancer Institute's Web site at http://cancer.gov/clinicaltrials/understanding/insurance-coverage. You can print a copy of the "Clinical Trials and Insurance Coverage" information from this Web site.

Another way to get the information is to call 1-800-4-CANCER (1-800-422-6237) and ask them to send you a free copy.

WHAT HAPPENS IF I AM INJURED BECAUSE I TOOK PART IN THIS STUDY?

It is important that you tell your study doctor, _____ *[investigator's name(s)],* if you feel that you have been injured because of taking part in this study. You can tell the doctor in person or call him/her at _____ *[telephone number]*.

In the case of injury or illness resulting from this study, emergency medical treatment is available but will be provided at the usual charge. No funds have been set aside to compensate you in the event of injury. You or your insurance company will be charged for continuing medical care and/or hospitalization.

WHAT ARE MY RIGHTS IF I TAKE PART IN THIS STUDY?

Taking part in this study is voluntary. You may choose not to take part or may leave the study at any time. Leaving the study will not result in any penalty or loss of benefits to which you are entitled.

We will talk to you about new information that may affect your health, welfare, or willingness to stay in this study.

WHOM DO I CALL IF I HAVE QUESTIONS OR PROBLEMS?

For questions about the study or a research-related injury, contact your study doctor _____ (*name{s}*) at _____ (*telephone number*).

For questions about your rights as a research participant, contact the_____ (*name of center*) Institutional Review Board (a group of people who review the research to protect your rights) at _____ (*telephone number*).

WHERE CAN I GET MORE INFORMATION?

You may call the National Cancer Institute's Cancer Information Service at:

1-800-4-CANCER (1-800-422-6237)

You may also visit the NCI Web site at http://cancer.gov/

- For NCI's clinical trials information, go to: http://cancer.gov/clinicaltrials/
- For NCI's general information about cancer, go to http://cancer.gov/cancerinfo/

You will get a copy of this form. If you want more information about this study, ask your study doctor.

SIGNATURE

I have been given a copy of this form. I have read it or it has been read to me. I understand the information and have had my questions answered. I agree to take part in this study.

Participant _____

Date _____

Investigator _____

Date _____

Phase I Dose Finding, Arm 2

Phase I Study of MK-1775 with Radiation and Temozolomide in Patients with Newly Diagnosed Glioblastoma and Evaluation of Intratumoral Drug Distribution in Patients with Recurrent Glioblastoma

This is a clinical trial (a type of research study). Your study doctor will explain the clinical trial to you. Clinical trials include only subjects who choose to take part. Please take your time to make your decision about taking part. Discuss it with your family and friends. You can also discuss it with your health care team. If you have any questions, you can ask your study doctor for more explanation.

You are being asked to take part in this study because you have a newly diagnosed brain tumor that is a glioblastoma. This research is a study evaluating a drug called MK-1775 given in combination with temozolomide as a possible treatment for newly diagnosed glioblastoma.

WHY IS THIS STUDY BEING DONE?

This research study is a Phase I clinical trial which tests the safety of an investigational drug and also tries to define the appropriate dose of investigational drug to use for further studies. "Investigational" means that the drug is being studied. It also means that the FDA (U.S. Food and Drug Administration) has not approved the drug for use in patients, including people with your type of cancer. This research is being done because this type of tumor is almost never cured with surgery, radiation, or chemotherapy. For this reason, we are trying to find new drugs to improve treatment for this tumor. The study you are being asked to join uses an investigational drug called MK-1775.

This part of the study is a dose-finding study. This means that we want to find the best dose of MK-1775 to give with temozolomide. Temozolomide (TMZ) is a type of chemotherapy and is considered part of "standard" therapy for this disease. TMZ is an FDA-approved drug that has been found to increase the survival of patients with brain tumors. MK-1775 may increase the effect of temozolomide (TMZ).

The combination of TMZ and radiation therapy is now considered the "standard of care" for treatment of glioblastoma. When TMZ is given as part of standard of care it is given first with radiation therapy as a daily treatment for 6 weeks. After radiation therapy is complete it is given 5 out of every 28 days for several months.

In order to find the best dose of MK-1775 to give with TMZ, the first part of this study will be divided into 2 groups, Arm 1 and Arm 2. In Arm 1 we will test the best dose of MK-1775 to give when taking TMZ every day during the 6 weeks of radiation therapy. In Arm 2 we will test the best dose of MK-1775 to give when taking standard TMZ for 5 out of every 28 days following the completion of radiation therapy.

You are being asked to participate in Arm 2. Arm 2 includes only patients who have completed radiation therapy combined with TMZ.

You will be assigned a dose of MK-1775 when you enter the study. You will be told what your dose is and it will not be increased. You will be given the same or a lower dose throughout your treatment. You will be given a lower dose if you experience side effects that require reduced dosing. We will also be looking at the side effects of MK-1775 and temozolomide.

HOW MANY PEOPLE WILL TAKE PART IN THIS STUDY?

A minimum of 6 and a maximum of 48 people will take part in the study.

WHAT IS INVOLVED IN THE STUDY?

This study will take place in an outpatient setting.

Before you begin the study, you will need to have the following exams, tests or procedures to find out if you can be in the study. These exams, tests or procedures are part of regular cancer care and may be done even if you do not join the study. If you have had some of them recently, they may not need to be repeated. This will be up to your study doctor.

- You will have a complete physical exam and blood tests. Your physical examination will include:
  - a medical history
  - measurement of your height, weight, blood pressure, temperature, respiratory rate, heart rate
  - performance status, which measures the degree of your ability to complete daily activities (e.g., dressing and eating).

- You will have a complete neurological exam to test your ability to think, your muscle strength, balance, and other functions of the brain.

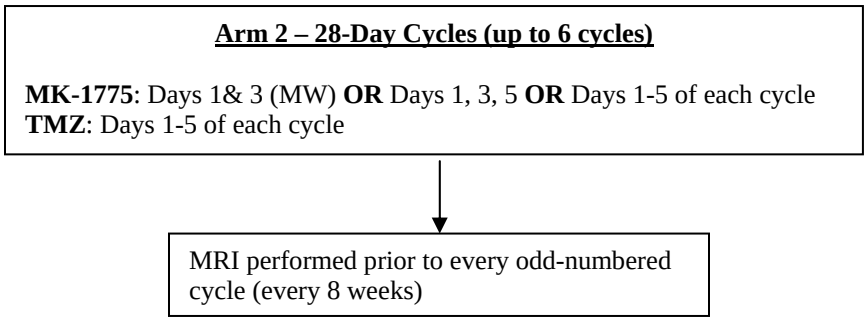
- To measure the extent of your brain tumor, you will have an MRI (magnetic resonance imaging) scan, which is a method of obtaining pictures of internal soft bodily tissue through the use of powerful magnets and radio waves.

- As part of your screening tests, about 3 tablespoons of blood will be drawn from one of your veins to conduct laboratory tests (e.g., standard blood count including a count of your platelets, and blood chemistries). You will also be asked to have a pregnancy test if you are a woman that is able to have children. If you are pregnant you will not be permitted to participate in this study.

- You will need to supply a complete list of your current medications to the study doctor. This includes over-the-counter medications and herbal supplements.

- As a part of this study we will collect samples of your tumor tissue for research purposes. Some of the tumor tissue that was taken during your surgery or biopsy, if sufficient tissue is available, will be sent to a lab for analysis. The tissue samples will be used to characterize the immunochemistry and molecular biology of your tumor. Glioblastoma can be very different in each patient. We hope to learn about the characteristics of your tumor. We will use the information we collect about this kind of tumor to help us better treat patients with glioblastoma in the future.

Study Plan



Treatment cycles are 28 days (4 weeks). You will begin taking MK-1775 and temozolomide together on the same day at the beginning of each cycle (Day 1).

MK-1775 will be taken in the form of a pill during the first 5 days of each cycle, either on Days 1 and 3; or on Days 1, 3, and 5; or on Days 1-5, depending on your assigned dose. The number of pills you take will also depend on your assigned dose. Your study doctor or nurse will provide specific dosing instructions.

You will take temozolomide on the first 5 days of each cycle. The number of pills you take each day will depend on your body size. Swallow capsules whole with a glass of water. Do not open or chew the capsules. If capsules are accidentally opened or damaged, be careful not to breathe in (inhale) the powder from the capsules or get the powder on your skin or mucous membranes (for example, in your nose or mouth). If contact with any of these areas happens, flush the area with water.

TMZ and MK-1775 must be taken on an empty stomach. You cannot eat or drink anything except water for two hours before taking your pills and for one hour after taking your pills. Medication to prevent nausea and vomiting will be prescribed by your doctor while taking temozolomide. This is part of standard care for 5-day temozolomide treatment.

If you miss a dose or vomit after taking your dose do not replace it; missed or vomited doses should not be made up.

You will be asked to record the date, time, and the number of pills you take for each medication in a pill diary, as you take your dose. You will need to bring the diary and any extra pills and medication containers with you to your monthly visit to the study doctor.

You should avoid consuming grapefruit and grapefruit juice while taking the study medication due to possible interactions. You should not take any herbal remedies while you are on this study.

After the second cycle an MRI will be obtained. If this MRI shows that the tumor size is the same or smaller, you will begin another four-week cycle of treatment, up to 6 cycles. An MRI will be obtained before every other cycle (every 8 weeks) to see if your tumor is growing. These brain scans (MRI) are part of routine cancer care.

During the study, physical and neurologic exams will be repeated and your vital signs will be measured (including temperature, heart rate, blood pressure, respiratory rate). Routine blood tests will be done. If at any point your blood counts are low, these blood tests will be repeated more often. Your blood counts will be checked at least once every week during study treatment.

Research Blood Samples:
As part of this study, we will be collecting extra blood samples in order to check the amount and activity of MK-1775 in your blood. Approximately 1 teaspoon of blood will be drawn for each sample. These extra blood tests are for research purposes only and would not be part of your standard care. The costs associated with collecting and processing these blood samples will not be charged to you or your insurance company.

<u>If you are on a Monday/Wednesday or Monday/Wednesday/Friday (2 or 3 days per week) dosing schedule</u> of MK-1775, a total of 8 extra blood samples will be drawn: 7 samples on Day 1, and 1 sample on Day 2.

These blood samples will be drawn on the following days during the first cycle:

- Day 1: 5 minutes pre-dose and then 30 minutes, 1 hour, 2 hours, 4 hours, 6 hours and 8 hours post-dose.
- Day 2: 24 hours after MK-1775 was administered on Day 1

<u>If you are on a Monday thru Friday (5 days per week) dosing schedule</u> of MK-1775, a total of 16 extra blood samples will be drawn: 7 samples each day on Days 1 and 4, and 1 sample each day on Days 2 and 5.

These blood samples will be drawn on the following days during Cycle 1.

- Day 1: 5 minutes pre-dose and then 30 minutes, 1 hour, 2 hours, 4 hours, 6 hours and 8 hours post-dose.
- Day 2: 24 hours after MK-1775 was administered on Day 1
- Day 4: 5 minutes pre-dose and then 30 minutes, 1 hour, 2 hours, 4 hours, 6 hours and 8 hours post-dose.
- Day 5: 24 hours after MK-1775 was administered on Day 4

HOW LONG WILL I BE IN THE STUDY?

You will likely be on study treatment for at least 8 weeks. Treatment with MK-1775 and temozolomide will be continued on the same schedule unless your tumor grows or you have side effects that require discontinuation, or you want to stop treatment. If the MRI taken after the second cycle shows that the tumor size is the same or smaller, you will begin a third 4-week cycle of treatment. As long as your tumor does not grow and as long as you do not experience any bad side effects you may continue to receive additional 4-week cycles, up to six cycles. If the MRI shows that your tumor is growing you will stop MK-1775 treatment and you and your doctor will discuss other treatment options.

Every two (2) months for the first two years after your treatment on the study has ended, someone from the study will contact you or your medical records will be reviewed to follow your disease. After two years, this will occur every 6 months for the remainder of your life.

CAN I STOP BEING IN THE STUDY?

Your participation in your clinical trial is completely voluntary. You can stop participating at any time. If you decide not to participate it will not affect your medical care at this institution. If you join this study you may withdraw from it at any time. However, if you decide to withdraw from the study, we encourage you to talk to the study doctor first.

Your study doctor may end your participation in the study if it is judged to be in your best interest or if you are unable to follow the rules of the study.

When you withdraw from the study for any reason, all medication and study drug bottles must be returned to the study site. You will also be asked to return to the site so that the study doctor may perform a proper, final safety evaluation. Every 2 months after your treatment on the study has ended, someone from the study will contact you or your medical records will be reviewed to follow your disease; after two years, this will occur every 6 months for the remainder of your life.

WHAT ARE THE RISKS OR SIDE EFFECTS OF THE STUDY?

While on the study, you are at risk for the following side effects. You should discuss these with the study doctor and/or your regular doctor. There also may be other side effects that we cannot predict. You should also discuss any other side effects that you may experience. Other drugs will be given to make the side effects less serious and uncomfortable.

Many side effects go away shortly after the MK-1775 is stopped, but in some cases side effects can be serious or long-lasting or permanent or fatal. Like chemotherapy drugs, MK-1775 has the potential to damage DNA; MK-1775 should only be taken by cancer patients.

Risks Associated with MK-1775

COMMON, SOME MAY BE SERIOUS In 100 people receiving MK-1775, more than 20 may have:
• Anemia which may require blood transfusion • Bruising, bleeding

OCCASIONAL, SOME MAY BE SERIOUS In 100 people receiving MK-1775, from 4 to 20 may have:
• Ringing in the ear • Belly pain • Diarrhea, nausea, vomiting • Tiredness, fever • Infection, especially when white blood cell count is low

Risks Associated with Temozolomide (TMZ)

TMZ is a chemotherapy drug that is considered part of standard treatment. TMZ may cause the following:

Likely (more than a 20% chance this will happen):

- Nausea, upset stomach and vomiting with temozolomide occur often and can be severe in some people.
- Fatigue
- Constipation
- Loss of appetite
- Headache
- Weakness
- Weight loss
- Shortness of breath
- Hair loss
- Chills
- Abnormal sensations, such as numbness, burning, and/or tingling
- A drop in the red blood count may result in anemia, which could lead to shortness of breath, dizziness, weakness and/or fatigue. As a result you may need a blood transfusion.

Frequent (between 10-20% chance this will happen):

- Dizziness
- Rash
- Generalized pain
- Swelling in the legs and feet caused by excess fluid in the body tissues
- Diarrhea

- A drop in blood counts, in particular, a decrease in the number of neutrophils in the blood (a type of white blood cell that helps fight infection), may result in severe infection such as pneumonia that may require IV antibiotics and medication to increase your white blood cells. This could potentially lead to a hospital stay. This can be serious or life threatening.
- A drop in the number of platelets in the blood that may result in easy bruising and bleeding in mucous membranes, wounds, or other tissues. If this happens, you might require a transfusion.

Occasional (chance of less than 10% that this will happen):

- Itchy skin
- Difficulty walking/unsteady gait
- Increased risk of infection which may be serious or life threatening
- Pain while swallowing
- Abdominal pain
- Elevated blood sugar, which may lead to infection, increased thirst and increased urination
- Sleepiness
- Difficulty falling asleep
- Redness of the skin
- Fever
- Allergic reactions that may include a rash, hives, fever, difficulty breathing, and low blood pressure. Although usually reversible with treatment, it can be severe and life threatening.
- Anxiety
- Depression
- Opportunistic infections (may occur when temozolomide is used in combination with radiation treatment and steroids)—An infection caused by an organism that usually does not cause illness, but causes disease when a person's immune response (resistance) to infection is impaired.
- Abnormal liver function tests—which means that your liver is not functioning properly and can cause malaise (a vague feeling of bodily discomfort), fatigue, and jaundice (yellowing of the skin). Although this is usually mild and reversible, this can be serious or life threatening and result in liver failure.
- Abnormal kidney function tests, which means the kidneys aren't working properly. When the kidneys do not work properly, wastes can build up in your blood, leading to swelling in the arms and legs, tiredness and weakness. This could become severe, requiring hospitalization and dialysis to clean the wastes out of your blood. If the wastes are not removed from your blood, this could cause seizures and be life threatening.
- Prolonged treatment with temozolomide may also increase the risk of developing a rare lung infection called pneumocystis pneumonia

(PCP), which may result in the following symptoms: fever, cough and difficulty breathing.

Rare: many of the following rare side effects may be life-threatening or lead to life-threatening events:

- Altered consciousness (diminished sense of awareness of self and/or environment).
- Pulmonary blood clot which can lead to a respiratory arrest.
- Blood clot formed in the veins of the leg (deep venous thrombosis) which may manifest as a dull ache or heaviness in the limb. If the clot moves to other organs, it can be serious or life threatening.
- Permanent bone marrow damage may result in a drop in the number of platelets, white blood cell counts, and red blood cell counts.
- Stomach bleeding
- Idiopathic Thrombocytopenia Purpura (ITP) may occur. ITP may cause bleeding and bruising. Bleeding may be serious or life threatening and may require a blood transfusion. This condition can resolve with treatment.
- Stroke (cerebrovascular accident) has been reported; the relationship of this event to temozolomide is unclear.
- Secondary cancer, such as leukemia
- Bleeding from the lungs may occur accompanied by respiratory failure.
- Atrial fibrillation (an irregular quickening of the heart beat) and cardiac failure.
- Air or gas in the abdomen causing pain and discomfort
- Inflammation and/or infection of the intestines, which may cause pain and discomfort

Side effects due to blood drawing may include: pain, bruising, bleeding or other discomfort at the blood drawing site. Anemia (low red blood cells), fainting or infection at the blood drawing site may occur (very unlikely).

Reproductive Risks

Because there may be a risk of birth defects if a fetus is exposed to MK-1775, you should not use this drug if you and your partner are planning to have a baby during this study or two months following the end of the study. A barrier method of birth control (e.g. condom, diaphragm) plus a spermicide must be used during the study and for eight (8) weeks after your last dose of study drug. You should not nurse a baby while on this study.

Risks of MRI

The effects of magnetic fields in an MRI scanner have been extensively studied, and there are no known significant risks with an MRI exam. You may, however, be bothered by feelings of confinement (claustrophobia), and by the noise made by the magnet during the procedure. You will be asked to wear earplugs or earphones while in the magnet. You may not participate in this study if you have a pacemaker, an implanted defibrillator or certain other implanted electronic or

metallic devices. It is important for you to advise the MRI staff if you have had brain surgery for a cerebral aneurysm, or if you have implanted medical or metallic devices, shrapnel, or other metal, such as metal in your eye.

Gadolinium Risk

The contrast agent you will receive is FDA-approved and used routinely for MRI exams. It contains a material called gadolinium. The injection of contrast may cause discomfort, tingling or warmth in the lips, metallic taste in the mouth, tingling in the arm, nausea, or headache. These symptoms occur in less than 1% (less than 1 in 100) of people and go away quickly.

There is a small risk of an allergic reaction to gadolinium; however, a severe allergic reaction occurs in less than one in 300,000 people. Insertion of the needle (small plastic tube) to give you gadolinium may cause minor pain, bruising and/or infection at the injection site.

People with severe kidney failure who receive gadolinium are at risk of developing Nephrogenic Systemic Fibrosis/Nephrogenic Fibrosing Dermopathy (NSF/NFD). This disease causes fibrosis, which is the formation of too much connective tissue in the skin and internal organs throughout the body. People develop skin thickening that may prevent bending and extending joints, resulting in decreased movement of the joints. The skin changes can cause feelings of burning, itching and pain that can be severe. In addition, people may experience fibrosis that spreads to other parts of the body such as the diaphragm, muscles in the thigh and lower abdomen, and the lining of blood vessels in the lung.

NSF/NFD is a serious progressive disease and can result in death. If you have severe kidney failure and receive gadolinium, the risk of developing NSF/NFD is 1-5 % (up to 1 to 5 per 100 people). We may require a blood sample (about 1 tablespoon) to check your kidney function before you receive gadolinium contrast for your MRI.

Please notify a doctor, nurse or technologist if you are allergic to gadolinium, if you have any kidney problems, or if you experience any of these or other side effects. If you do not know if you have kidney problems or if you do not know if your kidney problems fall in the severe category, you can ask the principal investigator of your study to give you this information.

A physician will be available during the procedure to administer any necessary care if side effects do occur, and to determine when or if the injection of the gadolinium should be stopped.

Financial risks: There may be extra costs with this treatment. Some of the costs may not be covered by the hospital or the insurance company. We encourage you to work closely with your insurance company to find out exactly what is covered for this research study.

This study may also have risks to you that cannot be determined at this time. You will be told of any potential risks that may be discovered while you are participating in this study.

For more information about risks and side effects, ask the study doctor or contact:

ARE THERE BENEFITS TO TAKING PART IN THE STUDY?

If you agree to take part in this study, there may or may not be direct medical benefit to you. We hope the information learned from this study will benefit other patients with brain tumors in the future.

WHAT OTHER CHOICES DO I HAVE IF I DO NOT TAKE PART IN THIS STUDY?

Your other choices may include:

- Getting treatment or care for your cancer without being in a study
- Taking part in another study
- Getting no treatment
- Getting comfort care, also called palliative care. This type of care helps reduce pain, tiredness, appetite problems and other problems caused by the cancer. It does not treat the cancer directly, but instead tries to improve how you feel. Comfort care tries to keep you as active and comfortable as possible.

Talk to your doctor about your choices before you decide if you will take part in this study.

WILL MY MEDICAL INFORMATION BE KEPT PRIVATE?

This section tells you what information about you may be used and given out in this study and who may give and receive the information. By signing this consent form, you agree that health information that identifies you may be used and/or given out as needed in this study. _____ (*name of center*) has a policy to protect health information that may identify you. Federal and state laws also protect your privacy. _____ (*name of center*) has procedures in place to support these policies and laws.

a. What information about you may be used or given out in this study?
Information that identifies you and relates to your health or medical condition may be used or given out in this study. Information that identifies you can include your name, address, telephone number, date of birth, Social Security number and other details about you. Information that relates to your health or medical condition includes:

Information obtained from the activities and procedures outlined in this consent form, which may include:

i) things done to see if you can join this study, such as physical examinations, blood and urine tests and any other information that you share with us, including information about your health history and your family health history; and

ii) information obtained during the study, such as how you respond to the study activities or procedures, information we learn in study visits, phone calls, surveys, physical examinations,

blood and urine tests, x-rays and other tests and any other medical information we learn from you as a participant in this study.

b. Who may use and give out information about you?

Some people may see your health information and may give out your health information during this study. These include the research study doctor and the research staff, the institutional review boards and their staff, legal counsel, audit and compliance staff, officers of the organization and other people who need to see the information to help this study or make sure it is being done as it should.

c. Who may see your health information?

Other organizations may see your health information during this study. These include:

- Governmental entities that have the right to see or review your health information, such as the Office of Human Research Protections and the Food and Drug Administration
- Doctors and staff at other places that are participating in this study
- The Pharmaceutical Collaborator (includes the National Cancer Institute's pharmaceutical collaborators who provide investigational drug to the NCI)
- The sponsors of this study and people that the sponsor may contract with for this study. The name of the sponsor is DCTD/NCI (Division of Cancer Treatment and Diagnosis/National Cancer Institute)
- The Data Safety Monitoring Board
- An outside institutional review board
- The Adult Brain Tumor Consortium (ABTC)

d. Why will this information be used and given out?

Your information will be used and given out to carry out this study and to evaluate the results of this study.

e. What if you decide not to give your permission to use and give out your health information?

You do not have to give your permission to use or give out your health information. However, if you do not give permission, you may not participate in this study.

f. May you withdraw or cancel your permission?

You may cancel your agreement to allow your health information to be used or given out at any time by sending a written notice to the Institutional Review Board Office, _____. If you do this, you are leaving this study. If you leave this study, no new health information about you will be gathered after that date. However, information gathered before that date may be used or given out if it is needed for this study or any follow-up for this study.

g. Is your health information protected after it has been given to others?

If your health information is given to someone not covered by these policies and laws, that information may no longer be protected, and may be used or given out without your permission.

h. Does this consent form have an end date?
This authorization to use and give out health information continues until the end of this study and any necessary data analysis follow-up activities for this study.

i. What is the role of the IRB?
Research studies involving human volunteers are reviewed by an Institutional Review Board (IRB). The IRB is made up of doctors, nurses, scientists, non-scientists and people from the community. The IRB is responsible for protecting participant's 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 can search this Web site at any time.

WHAT ARE THE COSTS?

Taking part in this study may lead to added costs to you or your insurance company. Some of the costs of the blood tests and brain scans may not be covered by your insurance company. We encourage you to work closely with your insurance company to find out exactly what is covered for this research study.

The NCI (National Cancer Institute) will provide you with the investigational agent MK-1775 free of charge while you take part in this study. The NCI does not cover the cost of getting MK-1775 ready and giving it to you, so you or your insurance company may have to pay for this.

Even though it probably won't happen, it is possible that the manufacturer may not continue to provide MK-1775 to the NCI for some reason. If this would occur, other possible options are:

- You might be able to get MK-1775 from the manufacturer but you or your insurance company may have to pay for it.

- If there is no MK-1775 available at all, no one will be able to get more and the study would close.

If a problem with getting MK-1775 occurs, your study doctor will talk to you about these options.

Should this agent become commercially available or approved for this indication 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 the company no longer provides the drug.

Temozolomide is commercially available for brain tumor treatment.

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

For more information on clinical trials and insurance coverage, you can visit the National Cancer Institute's Web site at http://cancer.gov/clinicaltrials/understanding/insurance-coverage. You can print a copy of the "Clinical Trials and Insurance Coverage" information from this Web site.

Another way to get the information is to call 1-800-4-CANCER (1-800-422-6237) and ask them to send you a free copy.

WHAT HAPPENS IF I AM INJURED BECAUSE I TOOK PART IN THIS STUDY?

It is important that you tell your study doctor, _____ *[investigator's name(s)]*, if you feel that you have been injured because of taking part in this study. You can tell the doctor in person or call him/her at _____ *[telephone number]*.

In the case of injury or illness resulting from this study, emergency medical treatment is available but will be provided at the usual charge. No funds have been set aside to compensate you in the event of injury. You or your insurance company will be charged for continuing medical care and/or hospitalization.

WHAT ARE MY RIGHTS IF I TAKE PART IN THIS STUDY?

Taking part in this study is voluntary. You may choose not to take part or may leave the study at any time. Leaving the study will not result in any penalty or loss of benefits to which you are entitled.

We will talk to you about new information that may affect your health, welfare, or willingness to stay in this study.

WHOM DO I CALL IF I HAVE QUESTIONS OR PROBLEMS?

For questions about the study or a research-related injury, contact your study doctor _____ (*name{s}*) at _____ (*telephone number*).

For questions about your rights as a research participant, contact the_____ (*name of center*) Institutional Review Board (a group of people who review the research to protect your rights) at _____ (*telephone number*).

WHERE CAN I GET MORE INFORMATION?

You may call the National Cancer Institute's Cancer Information Service at:

1-800-4-CANCER (1-800-422-6237)

You may also visit the NCI Web site at http://cancer.gov/

- For NCI's clinical trials information, go to: http://cancer.gov/clinicaltrials/
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You will get a copy of this form. If you want more information about this study, ask your study doctor.

SIGNATURE

I have been given a copy of this form. I have read it or it has been read to me. I understand the information and have had my questions answered. I agree to take part in this study.

Participant _____

Date _____

Investigator _____

Date _____

Phase I Combination Dose

Phase I Study of MK-1775 with Radiation and Temozolomide in Patients with Newly Diagnosed Glioblastoma and Evaluation of Intratumoral Drug Distribution in Patients with Recurrent Glioblastoma

This is a clinical trial (a type of research study). Your study doctor will explain the clinical trial to you. Clinical trials include only subjects who choose to take part. Please take your time to make your decision about taking part. Discuss it with your family and friends. You can also discuss it with your health care team. If you have any questions, you can ask your study doctor for more explanation.

You are being asked to take part in this study because you have a newly diagnosed brain tumor that is a glioblastoma. This research is a study evaluating a drug called MK-1775 given in combination with standard radiation therapy and temozolomide as a possible treatment for newly diagnosed glioblastoma.

WHY IS THIS STUDY BEING DONE?

This research study is a Phase I clinical trial which tests the safety of an investigational drug and also tries to define the appropriate dose of investigational drug to use for further studies. "Investigational" means that the drug is being studied. It also means that the FDA (U.S. Food and Drug Administration) has not approved the drug for use in patients, including people with your type of cancer. This research is being done because this type of tumor is almost never cured with surgery, radiation, or chemotherapy. For this reason, we are trying to find new drugs to improve treatment for this tumor. The study you are being asked to join uses an investigational drug called MK-1775.

The purpose of this study is to test the safety of MK-1775 when it is added to the "standard" treatment for glioblastoma, which is radiation combined with temozolomide (TMZ). Temozolomide (TMZ) is an FDA-approved chemotherapy that has been found to increase the survival of patients with brain tumors. MK-1775 may increase the effect of temozolomide (TMZ).

The combination of TMZ and radiation therapy is considered the "standard of care" for treatment of glioblastoma. When TMZ is given as part of standard of care it is given first with radiation therapy as a daily treatment for 6 weeks. After radiation therapy is complete TMZ is given 5 out of every 28 days for several months. You will be given both radiation therapy and TMZ while you also receive MK-1775.

HOW MANY PEOPLE WILL TAKE PART IN THIS STUDY?

Twelve people will take part in this portion of the study.

WHAT IS INVOLVED IN THE STUDY?

This study will take place in an outpatient setting.

Before you begin the study, you will need to have the following exams, tests or procedures to find out if you can be in the study. These exams, tests or procedures are part of regular cancer care and may be done even if you do not join the study. If you have had some of them recently, they may not need to be repeated. This will be up to your study doctor.

- You will have a complete physical exam and blood tests. Your physical examination will include:
  - a medical history
  - measurement of your height, weight, blood pressure, temperature, respiratory rate, heart rate
  - performance status, which measures the degree of your ability to complete daily activities (e.g., dressing and eating)

- You will have a complete neurological exam to test your ability to think, your muscle strength, balance, and other functions of the brain.

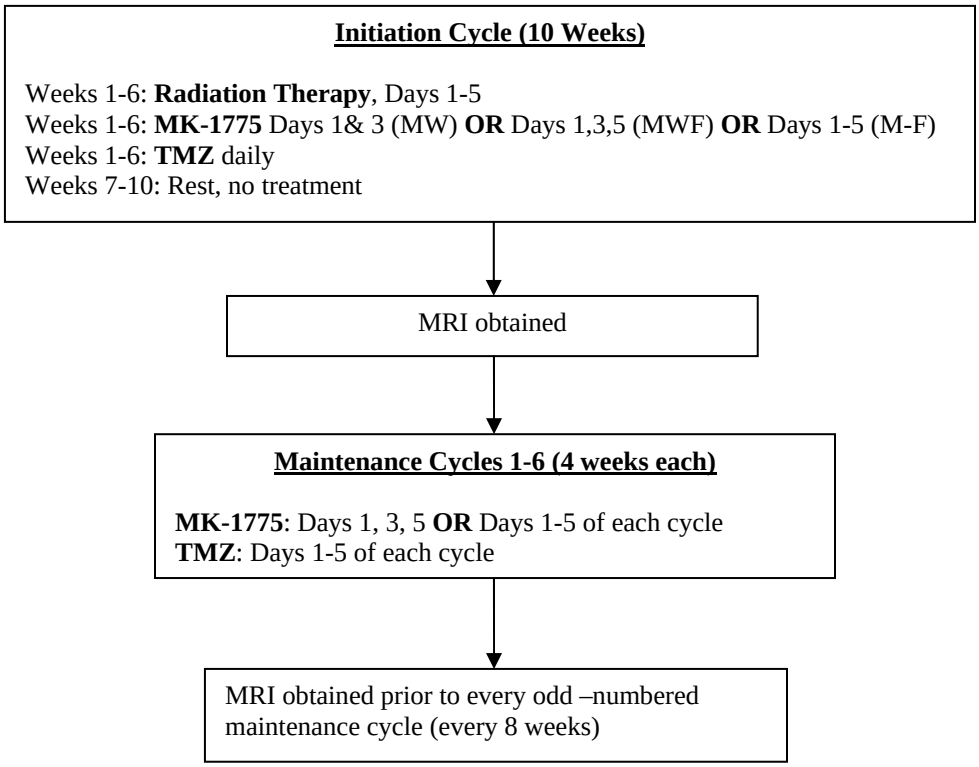
- To measure the extent of your brain tumor, you will have an MRI (magnetic resonance imaging) scan, which is a method of obtaining pictures of internal soft bodily tissue through the use of powerful magnets and radio waves.

- About 3 tablespoons of blood will be drawn from one of your veins to conduct laboratory tests (e.g., standard blood count including a count of your platelets, and blood chemistries). You will also be asked to have a pregnancy test if you are a woman that is able to have children. If you are pregnant you will not be permitted to participate in this study.

- You will need to supply a complete list of your current medications to the study doctor. This includes over-the-counter medications and herbal supplements.

- As a part of this study we will collect samples of your tumor tissue for research purposes. Some of the tumor tissue that was taken during your surgery or biopsy, if sufficient tissue is available, will be sent to a lab for analysis. The tissue samples will be used to characterize the immunochemistry and molecular biology of your tumor. Glioblastoma can be very different in each patient. We hope to learn about the characteristics of your tumor. We will use the information we collect about this kind of tumor to help us better treat patients with glioblastoma in the future.

Study Plan



INITIATION CYCLE

During the initial cycle of treatment, MK-1775 will be taken in the form of a pill either on a Monday/Wednesday, Monday/Wednesday/ Friday or a Monday thru Friday schedule (2 days, 3 days, or 5 days depending on the dose and schedule established in the Phase I-Arm 1 portion of this study *[dose to be determined]*) each week during radiation therapy. The number of pills you take will depend on your assigned dose. Your study doctor or nurse will provide specific dosing instructions. Radiation will be given daily on weekdays (Monday thru Friday), in an outpatient setting for about 6 weeks. There is nothing investigational about the radiation that will be given.

During radiation therapy you will also take temozolomide (TMZ) daily. Temozolomide is given in the form of a pill that you will take every day (7 days a week) for 6 weeks while you are receiving radiation. The number of pills you take every day will depend on your body size. Swallow capsules whole with a glass of water. Do not open or chew the capsules. If capsules are accidentally opened or damaged, be careful not to breathe in (inhale) the powder from the capsules or get the powder on your skin or mucous membranes (for example, in your nose or mouth). If contact with any of these areas happens, flush the area with water.

TMZ and MK-1775 must be taken on an empty stomach. You cannot eat or drink anything except water for two hours before taking your pills and for one hour after taking your pills.

Medication to prevent nausea and vomiting may be prescribed by your doctor while taking temozolomide.

If you miss a dose or vomit after taking your dose do not replace it; missed or vomited doses should not be made up.

You will be asked to record the date, time, and the number of pills you take each day of the study in a pill diary for each medication, as you take your dose. You will need to bring the diaries and any extra pills and medication containers with you to each visit to the study doctor.

You should avoid consuming grapefruit and grapefruit juice while taking the study medication due to possible interactions. You should not take any herbal remedies while you are on this study.

Medication to prevent infection is required for all patients receiving daily temozolomide during radiation therapy, and sometimes while taking temozolomide after radiation treatment. Your doctor will recommend and prescribe appropriate medication. This is part of standard care for treatment with temozolomide and radiation.

You will begin taking MK-1775 and temozolomide together on the first day of radiation. You will take your pills about one hour before you receive radiation.

During the 4 weeks directly after radiation therapy ends you will not take any temozolomide or MK-1775. These first ten weeks of treatment (6 weeks of radiation+TMZ+MK-1775 and 4 weeks of "rest" or no treatment) are called the Initiation Cycle. An MRI of your brain will be obtained after you complete the Initiation Cycle. This MRI is part of your standard radiation therapy follow-up care.

MAINTENANCE CYCLES

After your Initiation Cycle you will begin four-week (28-day) cycles of treatment called *maintenance* cycles. You will begin taking MK-1775 and temozolomide together on the same day at the beginning of each cycle (Day 1).

MK-1775 will be taken in the form of a pill during the first 5 days of each cycle, either on Days 1, 3, and 5 or on Days 1-5, depending on the dose and schedule established in the Phase I-Arm 2 portion of this study *(dose to be determined)*. The number of pills you take will also depend on your assigned dose. Your doctor or nurse will provide specific dosing instructions.

You will take temozolomide on the first 5 days of each cycle. The number of pills you take each day will depend on your body size.

TMZ and MK-1775 must be taken on an empty stomach. You cannot eat or drink anything except water for two hours before taking your pills and for one hour after taking your pills. Medication to prevent nausea and vomiting will be prescribed by your doctor while taking

temozolomide in the maintenance cycles. This is part of standard care for 5-day temozolomide treatment.

If you miss a dose or vomit after taking your dose do not replace it; missed or vomited doses should not be made up.

You will be asked to record the date, time, and the number of pills you take for each medication in a pill diary, as you take your dose. You will need to bring the diary and any extra pills and medication containers with you to your monthly visit to the study doctor.

You should avoid consuming grapefruit and grapefruit juice while taking the study medication due to possible interactions. You should not take any herbal remedies while you are on this study.

After the second maintenance cycle an MRI will be obtained. If this MRI shows that the tumor size is the same or smaller, you will begin another four-week cycle of treatment, up to 6 maintenance cycles. An MRI will be obtained before every other cycle (every 8 weeks) to see if your tumor is growing. These brain scans (MRI) are part of routine cancer care.

During the study, physical and neurologic exams will be repeated and your vital signs will be measured (including temperature, heart rate, blood pressure, respiratory rate). Routine blood tests will be done. If at any point your blood counts are low, these blood tests will be repeated more often. Your blood counts will be checked at least once every week during study treatment.

Research Blood Samples:
As part of this study, we will be collecting extra blood samples in order to check the amount and activity of MK-1775 in your blood. Approximately 1 teaspoon of blood will be drawn for each sample. These extra blood tests are for research purposes only and would not be part of your standard care. The costs associated with collecting and processing these blood samples will not be charged to you or your insurance company.

<u>If you are on a Monday/Wednesday or Monday/Wednesday/Friday (2 or 3 days per week) dosing schedule</u> of MK-1775, a total of 16 extra blood samples will be drawn: 7 samples each day on Days 1 and 22, and 1 sample each on Days 2 and 23.

These blood samples will be drawn on the following days during the Initiation Cycle:

- Day 1: 5 minutes pre-dose and then 30 minutes, 1 hour, 2 hours, 4 hours, 6 hours and 8 hours post-dose.
- Day 2: 24 hours after MK-1775 was administered on Day 1
- Day 22: 5 minutes pre-dose and then 30 minutes, 1 hour, 2 hours, 4 hours, 6 hours and 8 hours post-dose.
- Day 23: 24 hours after MK-1775 was administered on Day 22

If you are on a Monday thru Friday (5 days per week) dosing schedule of MK-1775, A total of 24 extra blood samples will be drawn: 7 samples each day on Days 1, 4, and 22, and 1 sample each on Days 2, 5, and 23.

These blood samples will be drawn on the following days during the Initiation Cycle:

- Day 1: 5 minutes pre-dose and then 30 minutes, 1 hour, 2 hours, 4 hours, 6 hours and 8 hours post-dose.
- Day2: 24 hours after MK-1775 was administered on Day 1
- Day 3: 5 minutes pre-dose and then 30 minutes, 1 hour, 2 hours, 4 hours, 6 hours and 8 hours post-dose.
- Day 4: 24 hours after MK-1775 was administered on Day 4
- Day 22: 5 minutes pre-dose and then 30 minutes, 1 hour, 2 hours, 4 hours, 6 hours and 8 hours post-dose.
- Day 23: 24 hours after MK-1775 was administered on Day 22

HOW LONG WILL I BE IN THE STUDY?

You will likely be on study treatment for at least 18 weeks. Treatment with MK-1775 and temozolomide will be continued on the same schedule unless your tumor grows or you have side effects that require discontinuation, or you want to stop treatment. If the MRI taken after the second maintenance cycle shows that the tumor size is the same or smaller, you will begin a third 4-week cycle of treatment. As long as your tumor does not grow and as long as you do not experience any bad side effects you may continue to receive additional 4-week cycles, up to six cycles. If the MRI shows that your tumor is growing you will stop MK-1775 treatment and you and your doctor will discuss other treatment options.

Every two (2) months for the first two years after your treatment on the study has ended, someone from the study will contact you or your medical records will be reviewed to follow your disease. After two years, this will occur every 6 months for the remainder of your life.

CAN I STOP BEING IN THE STUDY?

Your participation in your clinical trial is completely voluntary. You can stop participating at any time. If you decide not to participate it will not affect your medical care at this institution. If you join this study you may withdraw from it at any time. However, if you decide to withdraw from the study, we encourage you to talk to the study doctor first.

Your study doctor may end your participation in the study if it is judged to be in your best interest or if you are unable to follow the rules of the study.

When you withdraw from the study for any reason, all medication and study drug bottles must be returned to the study site. You will also be asked to return to the site so that the study doctor may perform a proper, final safety evaluation. Every 2 months after your treatment on the study has ended, someone from the study will contact you or your medical records will be reviewed to

follow your disease; after two years, this will occur every 6 months for the remainder of your life.

WHAT ARE THE RISKS OR SIDE EFFECTS OF THE STUDY?

While on the study, you are at risk for the following side effects. You should discuss these with the study doctor and/or your regular doctor. There also may be other side effects that we cannot predict. You should also discuss any other side effects that you may experience. Other drugs will be given to make the side effects less serious and uncomfortable.

Many side effects go away shortly after the MK-1775 is stopped, but in some cases side effects can be serious or long-lasting or permanent or fatal. Like chemotherapy drugs, MK-1775 has the potential to damage DNA; MK-1775 should only be taken by cancer patients.

Risks Associated with MK-1775

COMMON, SOME MAY BE SERIOUS In 100 people receiving MK-1775, more than 20 may have:
• Anemia which may require blood transfusion • Bruising, bleeding

OCCASIONAL, SOME MAY BE SERIOUS In 100 people receiving MK-1775, from 4 to 20 may have:
• Ringing in the ear • Belly pain • Diarrhea, nausea, vomiting • Tiredness, fever • Infection, especially when white blood cell count is low

Risks Associated with Temozolomide (TMZ)

TMZ is a chemotherapy drug that is considered part of standard treatment. TMZ may cause the following:

Likely (more than a 20% chance this will happen):

- Nausea, upset stomach and vomiting with temozolomide occurs often and can be severe in some people.
- Fatigue
- Constipation
- Loss of appetite
- Headache
- Weakness
- Weight loss
- Shortness of breath

- Hair loss
- Chills
- Abnormal sensations, such as numbness, burning, and/or tingling
- A drop in the red blood count may result in anemia, which could lead to shortness of breath, dizziness, weakness and/or fatigue. As a result you may need a blood transfusion.

Frequent (between 10-20% chance this will happen):

- Dizziness
- Rash
- Generalized pain
- Swelling in the legs and feet caused by excess fluid in the body tissues
- Diarrhea
- A drop in blood counts, in particular, a decrease in the number of neutrophils in the blood (a type of white blood cell that helps fight infection), may result in severe infection such as pneumonia that may require IV antibiotics and medication to increase your white blood cells. This could potentially lead to a hospital stay. This can be serious or life threatening.
- A drop in the number of platelets in the blood that may result in easy bruising and bleeding in mucous membranes, wounds, or other tissues. If this happens, you might require a transfusion.

Occasional (chance of less than 10% that this will happen):

- Itchy skin
- Difficulty walking/unsteady gait
- Increased risk of infection which may be serious or life threatening
- Pain while swallowing
- Abdominal pain
- Elevated blood sugar, which may lead to infection, increased thirst and increased urination
- Sleepiness
- Difficulty falling asleep
- Redness of the skin
- Fever
- Allergic reactions that may include a rash, hives, fever, difficulty breathing, and low blood pressure. Although usually reversible with treatment, it can be severe and life threatening.
- Anxiety
- Depression
- Opportunistic infections (may occur when temozolomide is used in combination with radiation treatment and steroids)—An infection caused by an organism that usually does not cause illness, but causes disease when a person’s immune response (resistance) to infection is

impaired.
- Abnormal liver function tests—which means that your liver is not functioning properly and can cause malaise (a vague feeling of bodily discomfort), fatigue, and jaundice (yellowing of the skin). Although this is usually mild and reversible, this can be serious or life threatening and result in liver failure.
- Abnormal kidney function tests, which means the kidneys aren't working properly. When the kidneys do not work properly, wastes can build up in your blood, leading to swelling in the arms and legs, tiredness and weakness. This could become severe, requiring hospitalization and dialysis to clean the wastes out of your blood. If the wastes are not removed from your blood, this could cause seizures and be life threatening.
- Prolonged treatment with temozolomide may also increase the risk of developing a rare lung infection called pneumocystis pneumonia (PCP), which may result in the following symptoms: fever, cough and difficulty breathing.

Rare: many of the following rare side effects may be life-threatening or lead to life-threatening events:
- Altered consciousness (diminished sense of awareness of self and/or environment).
- Pulmonary blood clot which can lead to a respiratory arrest.
- Blood clot formed in the veins of the leg (deep venous thrombosis) which may manifest as a dull ache or heaviness in the limb. If the clot moves to other organs, it can be serious or life threatening.
- Permanent bone marrow damage may result in a drop in the number of platelets, white blood cell counts, and red blood cell counts.
- Stomach bleeding
- Idiopathic Thrombocytopenia Purpura (ITP) may occur. ITP may cause bleeding and bruising. Bleeding may be serious or life threatening and may require a blood transfusion. This condition can resolve with treatment.
- Stroke (cerebrovascular accident) has been reported; the relationship of this event to temozolomide is unclear.
- Secondary cancer, such as leukemia
- Bleeding from the lungs may occur accompanied by respiratory failure.
- Atrial fibrillation (an irregular quickening of the heart beat) and cardiac failure.
- Air or gas in the abdomen causing pain and discomfort
- Inflammation and/or infection of the intestines, which may cause pain and discomfort

Risks Associated with Radiation Therapy:

You will receive standard radiation therapy in the Initiation Cycle. Risks and side effects related to the radiation therapy include:

Likely risks:

- Scalp redness or soreness
- Hair loss, which may be temporary or permanent
- Ear/ear canal reactions, such as dryness of ear canal, hardening of the wax in the ear canal, or redness of the external ear, possibly causing temporary hearing loss
- Fatigue, lethargy
- Temporary worsening of brain tumor symptoms such as headaches, seizures, or weakness

Less likely risks:

- Problems with mental functioning (neurocognitive problems), including memory deficits, which may be permanent
- Permanent hearing loss
- Condition in which the lens of the eye becomes cloudy (cataracts). This may require surgery to repair.
- Behavioral change, which can be due to physical effects of radiation therapy such as fatigue or headaches
- Nausea, vomiting

- Temporary worsening of existing neurological problems, such as decreased vision, drowsiness, and weakness of your arms and legs
- Endocrine problems related to changes to the pituitary gland, a gland that produces hormones that control other glands. Symptoms can include problems with your thyroid gland, sugar metabolism, fertility, or decrease in ability to regulate water, which may lead to excessive urination.
- Dry mouth or altered taste

Rare but serious risks:

- Severe local damage to normal brain tissue, a condition called necrosis (tissue deterioration). Radiation necrosis can mimic recurrent brain tumor and may require surgery for diagnosis and treatment.
- Injury to the eyes with the possibility of blindness
- Development of other tumors (either benign or malignant)

Side effects due to blood drawing may include: pain, bruising, bleeding or other discomfort at the blood drawing site. Anemia (low red blood cells), fainting or infection at the blood drawing site may occur (very unlikely).

Reproductive Risks

Because there may be a risk of birth defects if a fetus is exposed to MK-1775 or temozolomide, you should not use this drug if you and your partner are planning to have a baby during this study or two months following the end of the study. A barrier method of birth control (e.g. condom, diaphragm) plus a spermicide must be used during the study and for eight (8) weeks after your last dose of study drug. You should not nurse a baby while on this study.

Risks of MRI

The effects of magnetic fields in an MRI scanner have been extensively studied, and there are no known significant risks with an MRI exam. You may, however, be bothered by feelings of confinement (claustrophobia), and by the noise made by the magnet during the procedure. You will be asked to wear earplugs or earphones while in the magnet. You may not participate in this study if you have a pacemaker, an implanted defibrillator or certain other implanted electronic or metallic devices. It is important for you to advise the MRI staff if you have had brain surgery for a cerebral aneurysm, or if you have implanted medical or metallic devices, shrapnel, or other metal, such as metal in your eye.

Gadolinium Risk

The contrast agent you will receive is FDA-approved and used routinely for MRI exams. It contains a material called gadolinium. The injection of contrast may cause discomfort, tingling or warmth in the lips, metallic taste in the mouth, tingling in the arm, nausea, or headache. These symptoms occur in less than 1% (less than 1 in 100) of people and go away quickly.

There is a small risk of an allergic reaction to gadolinium; however, a severe allergic reaction occurs in less than one in 300,000 people. Insertion of the needle (small plastic tube) to give you gadolinium may cause minor pain, bruising and/or infection at the injection site.

People with severe kidney failure who receive gadolinium are at risk of developing Nephrogenic Systemic Fibrosis/Nephrogenic Fibrosing Dermopathy (NSF/NFD). This disease causes fibrosis, which is the formation of too much connective tissue in the skin and internal organs throughout the body. People develop skin thickening that may prevent bending and extending joints, resulting in decreased movement of the joints. The skin changes can cause feelings of burning, itching and pain that can be severe. In addition, people may experience fibrosis that spreads to other parts of the body such as the diaphragm, muscles in the thigh and lower abdomen, and the lining of blood vessels in the lung.

NSF/NFD is a serious progressive disease and can result in death. If you have severe kidney failure and receive gadolinium, the risk of developing NSF/NFD is 1-5 % (up to 1 to 5 per 100 people). We may require a blood sample (about 1 tablespoon) to check your kidney function before you receive gadolinium contrast for your MRI.

Please notify a doctor, nurse or technologist if you are allergic to gadolinium, if you have any kidney problems, or if you experience any of these or other side effects. If you do not know if you have kidney problems or if you do not know if your kidney problems fall in the severe category, you can ask the principal investigator of your study to give you this information.

A physician will be available during the procedure to administer any necessary care if side effects do occur, and to determine when or if the injection of the gadolinium should be stopped.

Financial risks: There may be extra costs with this treatment. Some of the costs may not be covered by the hospital or the insurance company. We encourage you to work closely with your insurance company to find out exactly what is covered for this research study.

This study may also have risks to you that cannot be determined at this time. You will be told of any potential risks that may be discovered while you are participating in this study.

For more information about risks and side effects, ask the study doctor or contact:

ARE THERE BENEFITS TO TAKING PART IN THE STUDY?

If you agree to take part in this study, there may or may not be direct medical benefit to you. We hope the information learned from this study will benefit other patients with brain tumors in the future.

WHAT OTHER CHOICES DO I HAVE IF I DO NOT TAKE PART IN THIS STUDY?

Your other choices may include:

- Getting treatment or care for your cancer without being in a study
- Taking part in another study
- Getting no treatment
- Getting comfort care, also called palliative care. This type of care helps reduce pain, tiredness, appetite problems and other problems caused by the cancer. It does not treat the cancer directly, but instead tries to improve how you feel. Comfort care tries to keep you as active and comfortable as possible.

Talk to your doctor about your choices before you decide if you will take part in this study.

WILL MY MEDICAL INFORMATION BE KEPT PRIVATE?

This section tells you what information about you may be used and given out in this study and who may give and receive the information. By signing this consent form, you agree that health information that identifies you may be used and/or given out as needed in this study. _____ (*name of center*) has a policy to protect health information that may identify you. Federal and state laws also protect your privacy. _____ (*name of center*) has procedures in place to support these policies and laws.

a. What information about you may be used or given out in this study?
Information that identifies you and relates to your health or medical condition may be used or given out in this study. Information that identifies you can include your name, address, telephone number, date of birth, Social Security number and other details about you. Information that relates to your health or medical condition includes:

Information obtained from the activities and procedures outlined in this consent form, which may include:

i) things done to see if you can join this study, such as physical examinations, blood and urine tests and any other information that you share with us, including information about your health history and your family health history; and

ii) information obtained during the study, such as how you respond to the study activities or procedures, information we learn in study visits, phone calls, surveys, physical examinations, blood and urine tests, x-rays and other tests and any other medical information we learn from you as a participant in this study.

b. Who may use and give out information about you?

Some people may see your health information and may give out your health information during this study. These include the research study doctor and the research staff, the institutional review boards and their staff, legal counsel, audit and compliance staff, officers of the organization and other people who need to see the information to help this study or make sure it is being done as it should.

c. Who may see your health information?

Other organizations may see your health information during this study. These include:

- Governmental entities that have the right to see or review your health information, such as the Office of Human Research Protections and the Food and Drug Administration
- Doctors and staff at other places that are participating in this study
- The Pharmaceutical Collaborator (includes the National Cancer Institute's pharmaceutical collaborators who provide investigational drug to the NCI)
- The sponsors of this study and people that the sponsor may contract with for this study. The name of the sponsor is DCTD/NCI (Division of Cancer Treatment and Diagnosis/National Cancer Institute)
- The Data Safety Monitoring Board
- An outside institutional review board
- The Adult Brain Tumor Consortium (ABTC)

d. Why will this information be used and given out?

Your information will be used and given out to carry out this study and to evaluate the results of this study.

e. What if you decide not to give your permission to use and give out your health information?

You do not have to give your permission to use or give out your health information. However, if you do not give permission, you may not participate in this study.

f. May you withdraw or cancel your permission?

You may cancel your agreement to allow your health information to be used or given out at any time by sending a written notice to the Institutional Review Board Office, _____. If you do this, you are leaving this study. If you leave this study, no new health information about you will be gathered after that date. However, information gathered before that date may be used or given out if it is needed for this study or any follow-up for this study.

g. Is your health information protected after it has been given to others?

If your health information is given to someone not covered by these policies and laws, that information may no longer be protected, and may be used or given out without your permission.

h. Does this consent form have an end date?

This authorization to use and give out health information continues until the end of this study and any necessary data analysis follow-up activities for this study.

i. What is the role of the IRB?

Research studies involving human volunteers are reviewed by an Institutional Review Board (IRB). The IRB is made up of doctors, nurses, scientists, non-scientists and people from the community. The IRB is responsible for protecting participant's 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 can search this Web site at any time.

WHAT ARE THE COSTS?

Taking part in this study may lead to added costs to you or your insurance company. Some of the costs of the blood tests and brain scans may not be covered by your insurance company. We encourage you to work closely with your insurance company to find out exactly what is covered for this research study.

The NCI (National Cancer Institute) will provide you with the investigational agent MK-1775 free of charge while you take part in this study. The NCI does not cover the cost of getting MK-1775 ready and giving it to you, so you or your insurance company may have to pay for this.

Even though it probably won't happen, it is possible that the manufacturer may not continue to provide MK-1775 to the NCI for some reason. If this would occur, other possible options are:

- You might be able to get MK-1775 from the manufacturer but you or your insurance company may have to pay for it.

- If there is no MK-1775 available at all, no one will be able to get more and the study would close.

If a problem with getting MK-1775 occurs, your study doctor will talk to you about these options.

Should this agent become commercially available or approved for this indication 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 the company no longer provides the drug.

Temozolomide is commercially available for brain tumor.

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

For more information on clinical trials and insurance coverage, you can visit the National Cancer Institute's Web site at http://cancer.gov/clinicaltrials/understanding/insurance-coverage. You can print a copy of the "Clinical Trials and Insurance Coverage" information from this Web site.

Another way to get the information is to call 1-800-4-CANCER (1-800-422-6237) and ask them to send you a free copy.

WHAT HAPPENS IF I AM INJURED BECAUSE I TOOK PART IN THIS STUDY?

It is important that you tell your study doctor, _____ *[investigator's name(s)],* if you feel that you have been injured because of taking part in this study. You can tell the doctor in person or call him/her at _____ *[telephone number]*.

In the case of injury or illness resulting from this study, emergency medical treatment is available but will be provided at the usual charge. No funds have been set aside to compensate you in the event of injury. You or your insurance company will be charged for continuing medical care and/or hospitalization.

WHAT ARE MY RIGHTS IF I TAKE PART IN THIS STUDY?

Taking part in this study is voluntary. You may choose not to take part or may leave the study at any time. Leaving the study will not result in any penalty or loss of benefits to which you are entitled.

We will talk to you about new information that may affect your health, welfare, or willingness to stay in this study.

WHOM DO I CALL IF I HAVE QUESTIONS OR PROBLEMS?

For questions about the study or a research-related injury, contact your study doctor _____ (*name{s}*) at _____ (*telephone number*).

For questions about your rights as a research participant, contact the_____ (*name of center*) Institutional Review Board (a group of people who review the research to protect your rights) at _____ (*telephone number*).

WHERE CAN I GET MORE INFORMATION?

You may call the National Cancer Institute's Cancer Information Service at:

1-800-4-CANCER (1-800-422-6237)

You may also visit the NCI Web site at http://cancer.gov/

- For NCI's clinical trials information, go to: http://cancer.gov/clinicaltrials/
- For NCI's general information about cancer, go to http://cancer.gov/cancerinfo/

You will get a copy of this form. If you want more information about this study, ask your study doctor.

SIGNATURE

I have been given a copy of this form. I have read it or it has been read to me. I understand the information and have had my questions answered. I agree to take part in this study.

Participant _____

Date _____

Investigator _____

Date _____

Intratumoral Drug Distribution Stage 1: Tissue Sampling

Phase I Study of MK-1775 with Radiation and Temozolomide in Patients with Newly Diagnosed Glioblastoma and Intratumoral Drug Distribution in Patients with Recurrent Glioblastoma

This is a clinical trial (a type of research study). Your study doctor will explain the clinical trial to you. Clinical trials include only subjects who choose to take part. Please take your time to make your decision about taking part. Discuss it with your family and friends. You can also discuss it with your health care team. If you have any questions, you can ask your study doctor for more explanation.

You are being asked to take part in this study because you have a brain tumor (glioblastoma multiforme), which has grown or has recurred and requires surgery.

WHY IS THIS STUDY BEING DONE?

This research study is a clinical trial evaluating an investigational drug called MK-1775. "Investigational" means that the drug is being studied. It also means that the FDA (U.S. Food and Drug Administration) has not approved the drug for use in patients, including people with your type of cancer. This research is being done because this type of tumor is almost never cured with surgery, radiation, or chemotherapy. For this reason, we are trying to find new drugs to improve treatment for this tumor.

The purpose of this study is to find out how much MK-1775 reaches your brain tumor. People with glioblastoma multiforme that has grown or recurred, and require brain surgery to remove the tumor, may participate in this study. We will take some extra tumor samples during your surgery. The way the surgery is performed will not be affected by the study. However, once the pathologists have confirmed your diagnosis, some of the tumor that the surgeons remove will be sent to a laboratory to study certain features of the tissue. These studies will not affect your care or treatment in any way.

HOW MANY PEOPLE WILL TAKE PART IN THIS STUDY?

Twelve people will take part in this portion of the study.

WHAT IS INVOLVED IN THE STUDY?

This study will take place in both an inpatient setting (surgery) and outpatient setting (pre- and post-surgical treatment).

Before you begin the study, you will need to have the following exams, tests or procedures to find out if you can be in the study. These exams, tests or procedures are part of regular cancer care and may be done even if you do not join the study. If you have had some of them recently, they may not need to be repeated. This will be up to your study doctor.

- You will have a complete physical exam and blood tests. Your physical examination will include:
  - a medical history
  - measurement of your height, weight, blood pressure, temperature, respiratory rate, heart rate
  - performance status, which measures the degree of your ability to complete daily activities (e.g., dressing and eating).

- You will have a complete neurological exam to test your ability to think, your muscle strength, balance, and other functions of the brain.

- To measure the extent of your brain tumor, you will have an MRI (magnetic resonance imaging) scan, which is a method of obtaining pictures of internal soft bodily tissue through the use of powerful magnets and radio waves.

- As part of your screening tests, about 3 tablespoons of blood will be drawn from one of your veins to conduct laboratory tests (e.g., standard blood count including a count of your platelets, and blood chemistries). You will also be asked to have a pregnancy test if you are a woman that is able to have children. If you are pregnant you will not be permitted to participate in this study.

- You will need to supply a complete list of your current medications to the study doctor. This includes over-the-counter medications and herbal supplements.

- **A research blood sample** (about 1 teaspoon) will be drawn before you start treatment to compare with blood samples that will be taken after you start taking MK-1775. This extra blood test is for research purposes only and would not be part of your standard care. The costs associated with collecting and processing this blood sample will not be charged to you or your insurance company.

- As a part of this study we will collect samples of the tumor tissue from your initial diagnosis of glioblastoma. Some of the tumor tissue that was taken during your initial brain tumor surgery/biopsy, if sufficient tissue is available, will be sent to a lab for analysis. The tissue samples will be used to characterize the immunochemistry and molecular biology of your tumor. Glioblastoma can be very different in each patient. We hope to learn about the characteristics of your tumor. We will use the information we collect about this kind of tumor to help us better treat patients with glioblastoma in the future.

You will be sequentially assigned to a treatment group, Group 1 or Group 2:

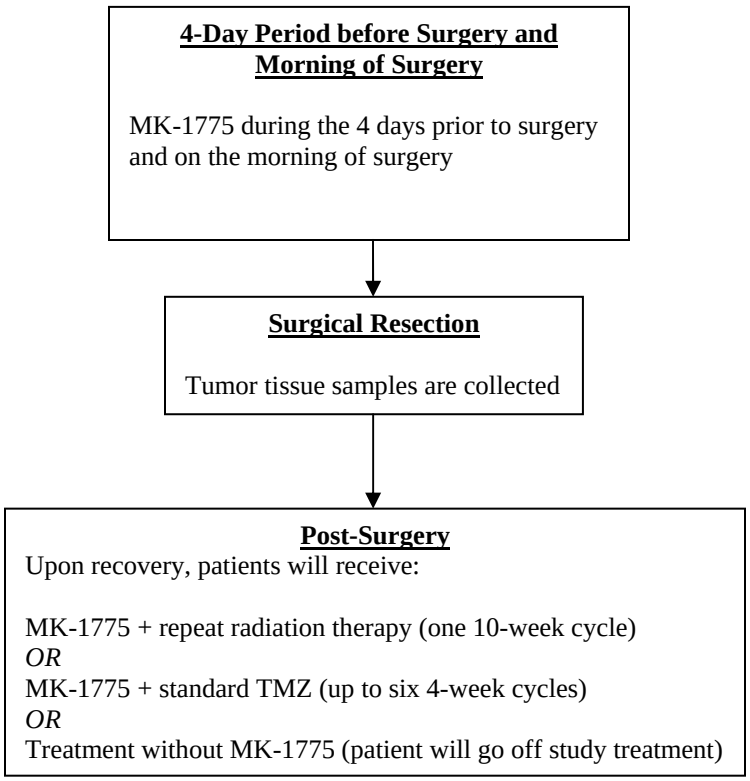
You will be told what your dose and schedule of MK-1775 is and it will not be increased.

If you are assigned to Group 1, you will start taking MK-1775 starting 4 days prior to your surgery at the dose and schedule established in the Phase I-Arm 1 portion of this study *(dose to be determined)*.

If you are assigned to Group 2, you will start taking MK-1775 4 days prior to your surgery at the dose and schedule established in the Phase I-Arm 2 portion of this study *(dose to be determined)*.

Taking MK-1775 prior to surgery in this way is for research purposes only and is not intended as a treatment for your glioblastoma.

Study Plan



During the study, you will undergo inpatient surgery for your brain tumor as part of your regular cancer care.

Four days before your surgery is scheduled, you will begin taking MK-1775 at your assigned dose (Group 1 or Group 2 dose). MK-1775 is taken in the form of a pill. The number of pills you take will depend on your assigned dose. Your study doctor or nurse will provide specific dosing instructions.

MK-1775 should be taken on an empty stomach. You cannot eat or drink anything except water for two hours before taking your pills and for one hour after taking your pills.

If you miss a dose or vomit after taking your dose do not replace it; missed or vomited doses should not be made up.

You will be asked to record the date, time, and the number of pills you take each day in a pill diary which you will bring to your clinic visits.

You should avoid consuming grapefruit and grapefruit juice while taking the study medication due to possible interactions. You should not take any herbal remedies while you are on this study.

Research Blood Samples: At the beginning of your surgery a blood sample will be drawn. Another blood sample will be drawn at the end of your surgery. About 1 teaspoon of blood will be drawn for each sample. These blood samples will be used to determine how much MK-1775 is in your blood. These extra blood tests are for research purposes only and would not be part of your standard care. The costs associated with collecting and processing these blood samples will not be charged to you or your insurance company.

During your surgery a portion of your tumor will be taken to determine the concentration of MK-1775 in your tumor and to study certain features of the tissue. The way the surgery is performed will not be affected by the study. These tumor samples are for research purposes only and you will not be charged for the cost of collecting and processing these samples.

After surgery you will have a post-surgical MRI scan.

After you have recovered from surgery (within 30 days), for both Group 1 and Group 2, you may continue treatment with MK-1775 combined with either repeat radiation treatment OR repeat standard temozolomide. You may also elect NOT to receive further treatment with MK-1775. You should discuss these options with your study doctor.

Prior to post-surgical treatment, a physical and neurologic exam will be repeated as well as routine blood tests. If more that 21 days since your last MRI have passed before re-starting treatment, you will need another MRI performed.

<u>If you elect MK-1775 + repeat radiation therapy:</u>

There is one 10-week treatment cycle. MK-1775 will be taken in the form of a pill either on a Monday/Wednesday, Monday/Wednesday/ Friday or a Monday thru Friday schedule (2 days, 3 days, or 5 days depending on the dose and schedule established in the Phase I-Arm 1 portion of this study [*dose to be determined*]) each week during radiation therapy. The number of pills you take will depend on your assigned dose. Your study doctor or nurse will provide specific dosing instructions. Radiation will be given daily on weekdays (Monday thru Friday), in an outpatient setting for 6 weeks. There is nothing investigational about the radiation that will be given.

You will begin taking MK-1775 on the first day of radiation. You will take your pills about one hour before you receive radiation.

MK-1775 must be taken on an empty stomach. You cannot eat or drink anything except water for two hours before taking your pills and for one hour after taking your pills.

If you miss a dose or vomit after taking your dose do not replace it; missed or vomited doses should not be made up.

You will be asked to record the date, time, and the number of pills you take each day of the study in a pill diary, as you take your dose. You will need to bring the diary and any extra pills and medication containers with you to your visits to the study doctor.

You should avoid consuming grapefruit and grapefruit juice while taking the study medication due to possible interactions. You should not take any herbal remedies while you are on this study.

During the study, physical and neurologic exams will be repeated and your vital signs will be measured (including temperature, heart rate, blood pressure, respiratory rate). Routine blood tests will be done. If at any point your blood counts are low, these blood tests will be repeated more often. Your blood counts will be checked at least once every week during study treatment.

Following 6 weeks of radiation therapy + MK-1775 you will have 4 weeks of "rest" or no treatment. An MRI of your brain will be obtained after you complete this 10-week cycle. This MRI is part of your standard radiation therapy follow-up care. Your study treatment will then be completed.

<u>If you elect MK-1775 + repeat TMZ treatment:</u>

Treatment cycles are 28 days (4 weeks). You will begin taking MK-1775 and temozolomide together on the same day at the beginning of each cycle (Day 1).

MK-1775 will be taken in the form of a pill during the first 5 days of each cycle, either on Days 1 and 3; or on Days 1, 3, and 5; or on Days 1-5, depending on the dose and schedule established in the Phase I-Arm 2 portion of the study (*dose to be determined*). The number of pills you take will depend on your assigned dose. Your study doctor or nurse will provide specific dosing instructions.

You will take temozolomide on the first 5 days of each cycle (Days 1-5). The number of pills you take each day will depend on your body size. Swallow capsules whole with a glass of water. Do not open or chew the capsules. If capsules are accidentally opened or damaged, be careful not to breathe in (inhale) the powder from the capsules or get the powder on your skin or mucous membranes (for example, in your nose or mouth). If contact with any of these areas happens, flush the area with water.

TMZ and MK-1775 must be taken on an empty stomach. You cannot eat or drink anything except water for two hours before taking your pills and for one hour after taking your pills.

Medication to prevent nausea and vomiting will be prescribed by your doctor while taking temozolomide. This is part of standard care for 5-day temozolomide treatment.

If you miss a dose or vomit after taking your dose do not replace it; missed or vomited doses should not be made up.

You will be asked to record the date, time, and the number of pills you take for each medication in a pill diary, as you take your dose. You will need to bring the diary and any extra pills and medication containers with you to your monthly visit to the study doctor.

You should avoid consuming grapefruit and grapefruit juice while taking the study medication due to possible interactions. You should not take any herbal remedies while you are on this study.

After the second cycle an MRI will be obtained. If this MRI shows that the tumor size is the same or smaller, you will begin another four-week cycle of treatment, up to 6 cycles. An MRI will be obtained before every other cycle (every 8 weeks) to see if your tumor is growing. These brain scans (MRI) are part of routine cancer care.

During the study, physical and neurologic exams will be repeated and your vital signs will be measured (including temperature, heart rate, blood pressure, respiratory rate). Routine blood tests will be done. If at any point your blood counts are low, these blood tests will be repeated more often. Your blood counts will be checked at least once every week during treatment with TMZ.

HOW LONG WILL I BE IN THE STUDY?

If you receive post-surgical MK-1775 + repeat radiation therapy, you will likely be on treatment for about 14 weeks, including your pre-surgical treatment and surgery.

If you receive post-surgical MK-1775 + repeat TMZ, you may continue on the same schedule unless your tumor grows or you have side effects that require discontinuation, or you want to stop treatment. If the MRI taken after the second cycle shows that the tumor size is the same or smaller, you will begin a third 4-week cycle of treatment. As long as your tumor does not grow and as long as you do not experience any bad side effects you may continue to receive additional 4-week cycles, up to six cycles. If the MRI shows that your tumor is growing you will stop MK-1775 treatment and you and your doctor will discuss other treatment options.

If you elect not to receive post-surgical treatment with MK-1775, you will go off treatment following recovery from surgery and your post-surgery follow-up visit.

Every two (2) months for the first two years after your treatment on the study has ended, someone from the study will contact you or your medical records will be reviewed to follow your disease. After two years, this will occur every 6 months for the remainder of your life.

CAN I STOP BEING IN THE STUDY?

Your participation in your clinical trial is completely voluntary. You can stop participating at any time. If you decide not to participate it will not affect your medical care at this institution. If you join this study you may withdraw from it at any time. However, if you decide to withdraw from the study, we encourage you to talk to the study doctor first.

Your study doctor may end your participation in the study if it is judged to be in your best interest or if you are unable to follow the rules of the study.

When you withdraw from the study for any reason, all medication and study drug bottles must be returned to the study site. You will also be asked to return to the site so that the study doctor may perform a proper, final safety evaluation. Every two (2) months after your treatment on the study has ended, someone from the study will contact you or your medical records will be reviewed to follow your disease; after two years, this will occur every 6 months for the remainder of your life.

WHAT ARE THE RISKS OR SIDE EFFECTS OF THE STUDY?

While on the study, you are at risk for the following side effects. You should discuss these with the study doctor and/or your regular doctor. There also may be other side effects that we cannot predict. You should also discuss any other side effects that you may experience. Other drugs will be given to make the side effects less serious and uncomfortable.

Many side effects go away shortly after the MK-1775 is stopped, but in some cases side effects can be serious or long-lasting or permanent or fatal. Like chemotherapy drugs, MK-1775 has the potential to damage DNA; MK-1775 should only be taken by cancer patients.

Risks Associated with MK-1775

COMMON, SOME MAY BE SERIOUS In 100 people receiving MK-1775, more than 20 may have:
• Anemia which may require blood transfusion • Bruising, bleeding

OCCASIONAL, SOME MAY BE SERIOUS In 100 people receiving MK-1775, from 4 to 20 may have:
• Ringing in the ear • Belly pain • Diarrhea, nausea, vomiting • Tiredness, fever • Infection, especially when white blood cell count is low

Risks Associated with Temozolomide (TMZ)

TMZ is a chemotherapy drug that is considered part of standard treatment. TMZ may cause the following:

Likely (more than a 20% chance this will happen):

- Nausea, upset stomach and vomiting with temozolomide occurs often and can be severe in some people.
- Fatigue
- Constipation
- Loss of appetite
- Headache
- Weakness
- Weight loss
- Shortness of breath
- Hair loss
- Chills
- Abnormal sensations, such as numbness, burning, and/or tingling
- A drop in the red blood count may result in anemia, which could lead to shortness of breath, dizziness, weakness and/or fatigue. As a result you may need a blood transfusion.

Frequent (between 10-20% chance this will happen):

- Dizziness
- Rash
- Generalized pain
- Swelling in the legs and feet caused by excess fluid in the body tissues
- Diarrhea
- A drop in blood counts, in particular, a decrease in the number of neutrophils in the blood (a type of white blood cell that helps fight infection), may result in severe infection such as pneumonia that may require IV antibiotics and medication to increase your white blood cells. This could potentially lead to a hospital stay. This can be serious or life threatening.
- A drop in the number of platelets in the blood that may result in easy bruising and bleeding in mucous membranes, wounds, or other tissues. If this happens, you might require a transfusion.

Occasional (chance of less than 10% that this will happen):

- Itchy skin
- Difficulty walking/unsteady gait
- Increased risk of infection which may be serious or life threatening
- Pain while swallowing
- Abdominal pain
- Elevated blood sugar, which may lead to infection, increased thirst and increased urination
- Sleepiness
- Difficulty falling asleep

- Redness of the skin
- Fever
- Allergic reactions that may include a rash, hives, fever, difficulty breathing, and low blood pressure. Although usually reversible with treatment, it can be severe and life threatening.
- Anxiety
- Depression
- Opportunistic infections (may occur when temozolomide is used in combination with radiation treatment and steroids)—An infection caused by an organism that usually does not cause illness, but causes disease when a person's immune response (resistance) to infection is impaired.
- Abnormal liver function tests—which means that your liver is not functioning properly and can cause malaise (a vague feeling of bodily discomfort), fatigue, and jaundice (yellowing of the skin). Although this is usually mild and reversible, this can be serious or life threatening and result in liver failure.
- Abnormal kidney function tests, which means the kidneys aren't working properly. When the kidneys do not work properly, wastes can build up in your blood, leading to swelling in the arms and legs, tiredness and weakness. This could become severe, requiring hospitalization and dialysis to clean the wastes out of your blood. If the wastes are not removed from your blood, this could cause seizures and be life threatening.
- Prolonged treatment with temozolomide may also increase the risk of developing a rare lung infection called pneumocystis pneumonia (PCP), which may result in the following symptoms: fever, cough and difficulty breathing.

Rare: many of the following rare side effects may be life-threatening or lead to life-threatening events:

- Altered consciousness (diminished sense of awareness of self and/or environment).
- Pulmonary blood clot which can lead to a respiratory arrest.
- Blood clot formed in the veins of the leg (deep venous thrombosis) which may manifest as a dull ache or heaviness in the limb. If the clot moves to other organs, it can be serious or life threatening.
- Permanent bone marrow damage may result in a drop in the number of platelets, white blood cell counts, and red blood cell counts.
- Stomach bleeding
- Idiopathic Thrombocytopenia Purpura (ITP) may occur. ITP may cause bleeding and bruising. Bleeding may be serious or life threatening and may require a blood transfusion. This condition can resolve with treatment.
- Stroke (cerebrovascular accident) has been reported; the relationship of this event to temozolomide is unclear.
- Secondary cancer, such as leukemia

- Bleeding from the lungs may occur accompanied by respiratory failure.
- Atrial fibrillation (an irregular quickening of the heart beat) and cardiac failure.
- Air or gas in the abdomen causing pain and discomfort
- Inflammation and/or infection of the intestines, which may cause pain and discomfort

Risks Associated with Radiation Therapy:

You will receive standard radiation therapy if you elect post-surgical treatment with MK-1775 + repeat radiation therapy. Risks and side effects related to the radiation therapy include:

Likely risks:

- Scalp redness or soreness
- Hair loss, which may be temporary or permanent
- Ear/ear canal reactions, such as dryness of ear canal, hardening of the wax in the ear canal, or redness of the external ear, possibly causing temporary hearing loss
- Fatigue, lethargy
- Temporary worsening of brain tumor symptoms such as headaches, seizures, or weakness

Less likely risks:

- Problems with mental functioning (neurocognitive problems), including memory deficits, which may be permanent
- Permanent hearing loss
- Condition in which the lens of the eye becomes cloudy (cataracts). This may require surgery to repair.
- Behavioral change, which can be due to physical effects of radiation therapy such as fatigue or headaches
- Nausea, vomiting
- Temporary worsening of existing neurological problems, such as decreased vision, drowsiness, and weakness of your arms and legs
- Endocrine problems related to changes to the pituitary gland, a gland that produces hormones that control other glands. Symptoms can include problems with your thyroid gland, sugar metabolism, fertility, or decrease in ability to regulate water, which may lead to excessive urination.
- Dry mouth or altered taste

Rare but serious risks:

- Severe local damage to normal brain tissue, a condition called necrosis (tissue deterioration). Radiation necrosis can mimic recurrent brain tumor and may require surgery for diagnosis and treatment.
- Injury to the eyes with the possibility of blindness
- Development of other tumors (either benign or malignant)

Side effects due to blood drawing may include: pain, bruising, bleeding or other discomfort at the blood drawing site. Anemia (low red blood cells), fainting or infection at the blood drawing site may occur (very unlikely).

Reproductive Risks
Because there may be a risk of birth defects if a fetus is exposed to MK-1775 or temozolomide, you should not use this drug if you and your partner are planning to have a baby during this study or two months following the end of the study. A barrier method of birth control (e.g. condom, diaphragm) plus a spermicide must be used during the study and for eight (8) weeks after your last dose of study drug. You should not nurse a baby while on this study.

Risks of MRI
The effects of magnetic fields in an MRI scanner have been extensively studied, and there are no known significant risks with an MRI exam. You may, however, be bothered by feelings of confinement (claustrophobia), and by the noise made by the magnet during the procedure. You will be asked to wear earplugs or earphones while in the magnet. You may not participate in this study if you have a pacemaker, an implanted defibrillator or certain other implanted electronic or metallic devices. It is important for you to advise the MRI staff if you have had brain surgery for a cerebral aneurysm, or if you have implanted medical or metallic devices, shrapnel, or other metal, such as metal in your eye.

Gadolinium Risk
The contrast agent you will receive is FDA-approved and used routinely for MRI exams. It contains a material called gadolinium. The injection of contrast may cause discomfort, tingling or warmth in the lips, metallic taste in the mouth, tingling in the arm, nausea, or headache. These symptoms occur in less than 1% (less than 1 in 100) of people and go away quickly.

There is a small risk of an allergic reaction to gadolinium; however, a severe allergic reaction occurs in less than one in 300,000 people. Insertion of the needle (small plastic tube) to give you gadolinium may cause minor pain, bruising and/or infection at the injection site.

People with severe kidney failure who receive gadolinium are at risk of developing Nephrogenic Systemic Fibrosis/Nephrogenic Fibrosing Dermopathy (NSF/NFD). This disease causes fibrosis, which is the formation of too much connective tissue in the skin and internal organs throughout the body. People develop skin thickening that may prevent bending and extending joints, resulting in decreased movement of the joints. The skin changes can cause feelings of burning, itching and pain that can be severe. In addition, people may experience fibrosis that spreads to other parts of the body such as the diaphragm, muscles in the thigh and lower abdomen, and the lining of blood vessels in the lung.

NSF/NFD is a serious progressive disease and can result in death. If you have severe kidney failure and receive gadolinium, the risk of developing NSF/NFD is 1-5 % (up to 1 to 5 per 100 people). We may require a blood sample (about 1 tablespoon) to check your kidney function before you receive gadolinium contrast for your MRI.

Please notify a doctor, nurse or technologist if you are allergic to gadolinium, if you have any kidney problems, or if you experience any of these or other side effects. If you do not know if you have kidney problems or if you do not know if your kidney problems fall in the severe category, you can ask the principal investigator of your study to give you this information.

A physician will be available during the procedure to administer any necessary care if side effects do occur, and to determine when or if the injection of the gadolinium should be stopped.

Financial risks: There may be extra costs with this treatment. Some of the costs may not be covered by the hospital or the insurance company. We encourage you to work closely with your insurance company to find out exactly what is covered for this research study.

This study may also have risks to you that cannot be determined at this time. You will be told of any potential risks that may be discovered while you are participating in this study.

For more information about risks and side effects, ask the study doctor or contact:

ARE THERE BENEFITS TO TAKING PART IN THE STUDY?

If you agree to take part in this study, there may or may not be direct medical benefit to you. We hope the information learned from this study will benefit other patients with brain tumors in the future.

WHAT OTHER CHOICES DO I HAVE IF I DO NOT TAKE PART IN THIS STUDY?

Your other choices may include:

- Getting treatment or care for your cancer without being in a study
- Taking part in another study
- Getting no treatment
- Getting comfort care, also called palliative care. This type of care helps reduce pain, tiredness, appetite problems and other problems caused by the cancer. It does not treat the cancer directly, but instead tries to improve how you feel. Comfort care tries to keep you as active and comfortable as possible.

Talk to your doctor about your choices before you decide if you will take part in this study.

WILL MY MEDICAL INFORMATION BE KEPT PRIVATE?

This section tells you what information about you may be used and given out in this study and who may give and receive the information. By signing this consent form, you agree that health information that identifies you may be used and/or given out as needed in this study.
_____ (*name of center*) has a policy to protect health information that may

identify you. Federal and state laws also protect your privacy. _____ (*name of center*) has procedures in place to support these policies and laws.

a. What information about you may be used or given out in this study?
Information that identifies you and relates to your health or medical condition may be used or given out in this study. Information that identifies you can include your name, address, telephone number, date of birth, Social Security number and other details about you. Information that relates to your health or medical condition includes:

Information obtained from the activities and procedures outlined in this consent form, which may include:

i) things done to see if you can join this study, such as physical examinations, blood and urine tests and any other information that you share with us, including information about your health history and your family health history; and

ii) information obtained during the study, such as how you respond to the study activities or procedures, information we learn in study visits, phone calls, surveys, physical examinations, blood and urine tests, x-rays and other tests and any other medical information we learn from you as a participant in this study.

b. Who may use and give out information about you?
Some people may see your health information and may give out your health information during this study. These include the research study doctor and the research staff, the institutional review boards and their staff, legal counsel, audit and compliance staff, officers of the organization and other people who need to see the information to help this study or make sure it is being done as it should.

c. Who may see your health information?
Other organizations may see your health information during this study. These include:

- Governmental entities that have the right to see or review your health information, such as the Office of Human Research Protections and the Food and Drug Administration
- Doctors and staff at other places that are participating in this study
- The Pharmaceutical Collaborator (includes the National Cancer Institute's pharmaceutical collaborators who provide investigational drug to the NCI)
- The sponsors of this study and people that the sponsor may contract with for this study. The name of the sponsor is DCTD/NCI (Division of Cancer Treatment and Diagnosis/National Cancer Institute)
- The Data Safety Monitoring Board
- An outside institutional review board
- The Adult Brain Tumor Consortium (ABTC)

d. Why will this information be used and given out?

Your information will be used and given out to carry out this study and to evaluate the results of this study.

e. What if you decide not to give your permission to use and give out your health information?
You do not have to give your permission to use or give out your health information. However, if you do not give permission, you may not participate in this study.

f. May you withdraw or cancel your permission?
You may cancel your agreement to allow your health information to be used or given out at any time by sending a written notice to the Institutional Review Board Office, _____. If you do this, you are leaving this study. If you leave this study, no new health information about you will be gathered after that date. However, information gathered before that date may be used or given out if it is needed for this study or any follow-up for this study.

g. Is your health information protected after it has been given to others?
If your health information is given to someone not covered by these policies and laws, that information may no longer be protected, and may be used or given out without your permission.

h. Does this consent form have an end date?
This authorization to use and give out health information continues until the end of this study and any necessary data analysis follow-up activities for this study.

i. What is the role of the IRB?
Research studies involving human volunteers are reviewed by an Institutional Review Board (IRB). The IRB is made up of doctors, nurses, scientists, non-scientists and people from the community. The IRB is responsible for protecting participant's 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 can search this Web site at any time.

WHAT ARE THE COSTS?

Taking part in this study may lead to added costs to you or your insurance company. Some of the costs of the blood tests and brain scans may not be covered by your insurance company. We encourage you to work closely with your insurance company to find out exactly what is covered for this research study.

The NCI (National Cancer Institute) will provide you with the investigational agent MK-1775 free of charge while you take part in this study. The NCI does not cover the cost of getting MK-1775 ready and giving it to you, so you or your insurance company may have to pay for this.

Even though it probably won't happen, it is possible that the manufacturer may not continue to provide MK-1775 to the NCI for some reason. If this would occur, other possible options are:

- You might be able to get MK-1775 from the manufacturer but you or your insurance company may have to pay for it.

- If there is no MK-1775 available at all, no one will be able to get more and the study would close.

If a problem with getting MK-1775 occurs, your study doctor will talk to you about these options.

Should this agent become commercially available or approved for this indication 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 the company no longer provides the drug.

Temozolomide is commercially available for brain tumor treatment.

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

For more information on clinical trials and insurance coverage, you can visit the National Cancer Institute's Web site at http://cancer.gov/clinicaltrials/understanding/insurance-coverage. You can print a copy of the "Clinical Trials and Insurance Coverage" information from this Web site.

Another way to get the information is to call 1-800-4-CANCER (1-800-422-6237) and ask them to send you a free copy.

WHAT HAPPENS IF I AM INJURED BECAUSE I TOOK PART IN THIS STUDY?

It is important that you tell your study doctor, _____ *[investigator's name(s)]*, if you feel that you have been injured because of taking part in this study. You can tell the doctor in person or call him/her at _____ *[telephone number]*.

In the case of injury or illness resulting from this study, emergency medical treatment is available but will be provided at the usual charge. No funds have been set aside to compensate you in the event of injury. You or your insurance company will be charged for continuing medical care and/or hospitalization.

WHAT ARE MY RIGHTS IF I TAKE PART IN THIS STUDY?

Taking part in this study is voluntary. You may choose not to take part or may leave the study at any time. Leaving the study will not result in any penalty or loss of benefits to which you are entitled.

We will talk to you about new information that may affect your health, welfare, or willingness to stay in this study.

WHOM DO I CALL IF I HAVE QUESTIONS OR PROBLEMS?

For questions about the study or a research-related injury, contact your study doctor _____ (*name{s}*) at _____ (*telephone number*).

For questions about your rights as a research participant, contact the_____ (*name of center*) Institutional Review Board (a group of people who review the research to protect your rights) at _____ (*telephone number*).

WHERE CAN I GET MORE INFORMATION?

You may call the National Cancer Institute's Cancer Information Service at:

1-800-4-CANCER (1-800-422-6237)

You may also visit the NCI Web site at http://cancer.gov/

- For NCI's clinical trials information, go to: http://cancer.gov/clinicaltrials/
- For NCI's general information about cancer, go to http://cancer.gov/cancerinfo/

You will get a copy of this form. If you want more information about this study, ask your study doctor.

SIGNATURE

I have been given a copy of this form. I have read it or it has been read to me. I understand the information and have had my questions answered. I agree to take part in this study.

Participant _____

Date _____

Investigator _____

Date _____

Intratumoral Drug Distribution Stage 2: Microdialysis

Phase I Study of MK-1775 with Radiation and Temozolomide in Patients with Newly Diagnosed Glioblastoma and Intratumoral Drug Distribution in Patients with Recurrent Glioblastoma

This is a clinical trial (a type of research study). Your study doctor will explain the clinical trial to you. Clinical trials include only subjects who choose to take part. Please take your time to make your decision about taking part. Discuss it with your family and friends. You can also discuss it with your health care team. If you have any questions, you can ask your study doctor for more explanation.

You are being asked to take part in this study because you have a brain tumor (glioblastoma multiforme), which has grown or has recurred and requires surgery.

WHY IS THIS STUDY BEING DONE?

This research study is a clinical trial evaluating an investigational drug called MK-1775 as a possible treatment for glioblastoma. "Investigational" means that the drug is being studied. It also means that the FDA (U.S. Food and Drug Administration) has not approved the drug for use in patients, including people with your type of cancer. This research is being done because this type of tumor is almost never cured with surgery, radiation, or chemotherapy. For this reason, we are trying to find new drugs to improve treatment for this tumor.

The purpose of this study is to find out how much MK-1775 reaches your brain tumor. People with glioblastoma multiforme that has grown or recurred, and require brain surgery to remove the tumor, may participate in this study.

After taking one dose of MK-1775, samples of fluid from your brain tumor and surrounding tissue will be collected using very thin tubes called microdialysis catheters. We will use these samples to measure how much MK-1775 reaches the brain tumor. The use of microdialysis catheters to collect brain fluid is an FDA-approved method. These catheters are already being used in patients who have sustained severe brain trauma from head injuries. The catheters are smaller in size than the standard needle that will be used to take tumor samples in your surgery.

The way the surgery is performed will not be affected by the study.

HOW MANY PEOPLE WILL TAKE PART IN THIS STUDY?

Six people will take part in the microdialysis portion of the study.

WHAT IS INVOLVED IN THE STUDY?

This study will take place in both an inpatient setting (surgery and microdialysis sample collection) and outpatient setting (post-surgical treatment).

Before you begin the study, you will need to have the following exams, tests or procedures to find out if you can be in the study. These exams, tests or procedures are part of regular cancer care and may be done even if you do not join the study. If you have had some of them recently, they may not need to be repeated. This will be up to your study doctor.

- You will have a complete physical exam and blood tests. Your physical examination will include:
  - a medical history
  - measurement of your height, weight, blood pressure, temperature, respiratory rate, heart rate
  - performance status, which measures the degree of your ability to complete daily activities (e.g., dressing and eating)

- You will have a complete neurological exam to test your ability to think, your muscle strength, balance, and other functions of the brain.

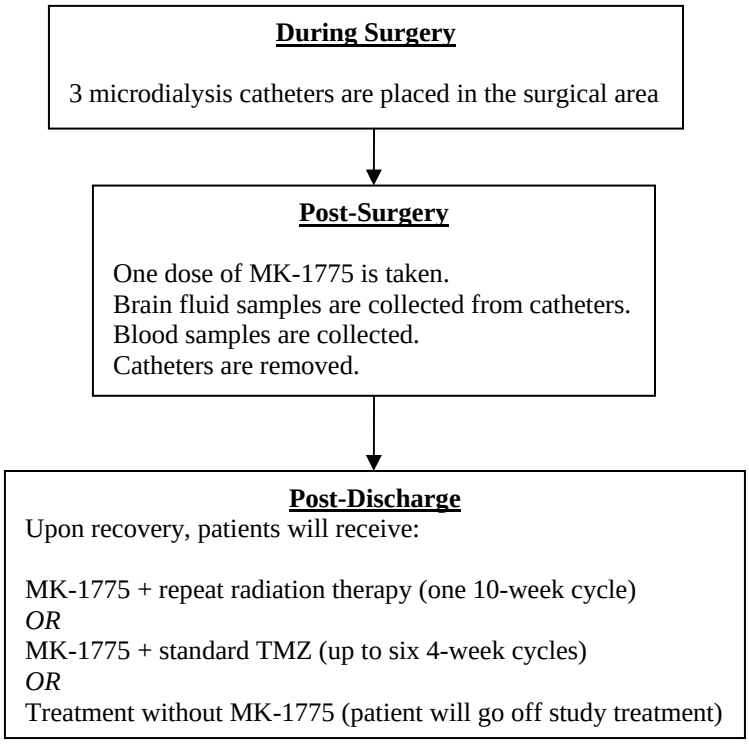
- To measure the extent of your brain tumor, you will have an MRI (magnetic resonance imaging) scan, which is a method of obtaining pictures of internal soft bodily tissue through the use of powerful magnets and radio waves.

- About 3 tablespoons of blood will be drawn from one of your veins to conduct laboratory tests (e.g., standard blood count including a count of your platelets, and blood chemistries). You will also be asked to have a pregnancy test if you are a woman that is able to have children. If you are pregnant you will not be permitted to participate in this study.

- You will need to supply a complete list of your current medications to the study doctor. This includes over-the-counter medications and herbal supplements.

- As a part of this study we will collect samples of the tumor tissue from your initial diagnosis of glioblastoma. Some of the tumor tissue that was taken during your initial brain tumor surgery/biopsy, if sufficient tissue is available, will be sent to a lab for analysis. The tissue samples will be used to characterize the immunochemistry and molecular biology of your tumor. Glioblastoma can be very different in each patient. We hope to learn about the characteristics of your tumor. We will use the information we collect about this kind of tumor to help us better treat patients with glioblastoma in the future.

Study Plan



During the study, you will undergo inpatient surgery for your brain tumor as part of your regular cancer care. During the surgery a biopsy of your tumor will be performed to confirm if the tumor is active at this time. If tissue sampling confirms active tumor cells, **3 microdialysis catheters will be placed into the tumor and surrounding tissue at the time of surgery**. These catheters are very small devices (about the size of a thin piece of spaghetti) that will be used to collect fluid directly from your brain tumor and surrounding tissue. The microdialysis catheters are not part of regular cancer care.

After you recover from surgery, a CT scan will be obtained to ensure correct positioning of the catheters. If all three catheters were successfully placed you will continue with the study; if the catheters were not able to be placed appropriately, you will go off the study and will not receive MK-1775.

Tubing on the catheters will be attached to small pumps and a neutral solution will begin to flow through the microdialysis catheters in your brain. During the time the catheters are in use your movement will be restricted. You should be able to get up to a chair or bedside commode but will not be able to leave your room.

When you have recovered from surgery for 12-24 hours, while you are still an inpatient in the hospital, **you will receive one dose of MK-1775** *(dose to be determined).* MK-1775 is given in the form of a pill. The number of pills you take will depend on your assigned dose. Taking one

dose of MK-1775 in this way is for research purposes only and is not intended as a treatment for your glioblastoma.

Starting 30 minutes before you take MK-1775, **small samples of the fluid from your brain will be collected from the microdialysis catheters every 30 minutes until 24 hours following your dose**. The catheters will be stopped after this time and a local anesthesia will be given prior to removing the catheters and the entry site of each catheter will be closed with a suture.

During the time that samples of brain fluid are being collected, we will be collecting extra **research blood samples** in order to look at the levels of MK-1775 in your blood. 18 extra blood samples will be drawn. About a teaspoon of blood will be taken for each sample.

- 1 sample will be drawn 30 to 5 minutes before taking MK-1775
- 17 additional samples will be drawn over the 24 hours following your dose at the following times: 15 min, 30 min, 1hour, 2 hours, 3 hours, 4 hours, 5 hours, 6 hours, 7 hours, 8 hours, 10 hours, 12 hours, 14 hours, 16 hours, 18 hours, 20 hours and 24 hours

The brain fluid sample collection and the extra blood samples are for research purposes only and would not be part of your standard care. The costs associated with collecting and processing these samples will not be charged to you or your insurance company.

After surgery you will have a post-surgical MRI scan.

You will be discharged from the hospital when your surgeon has determined that you have recovered sufficiently from your surgical procedure.

After you have recovered from surgery (within 30 days) you may continue treatment with MK-1775 combined with either repeat radiation treatment OR repeat standard temozolomide. You may also elect NOT to receive further treatment with MK-1775. You should discuss these options with your study doctor.

Prior to post-surgical treatment, a physical and neurologic exam will be repeated as well as routine blood tests. If more that 21 days since your last MRI have passed before re-starting treatment, you will need another MRI performed.

<u>If you elect MK-1775 + repeat radiation therapy:</u>

There is one 10-week treatment cycle. MK-1775 will be taken in the form of a pill either on a Monday/Wednesday, Monday/Wednesday/ Friday or a Monday thru Friday schedule (2 days, 3 days, or 5 days depending on the dose and schedule established in the Phase I-Arm 1 portion of this study [*dose to be determined]*) each week during radiation therapy. The number of pills you take will depend on your assigned dose. Your study doctor or nurse will provide specific dosing instructions. Radiation will be given daily on weekdays (Monday thru Friday), in an outpatient setting for 6 weeks. There is nothing investigational about the radiation that will be given.

You will begin taking MK-1775 on the first day of radiation. You will take your pills about one hour before you receive radiation.

MK-1775 should be taken on an empty stomach. You cannot eat or drink anything except water for two hours before taking your pills and for one hour after taking your pills.

If you miss a dose or vomit after taking your dose do not replace it; missed or vomited doses should not be made up.

You will be asked to record the date, time, and the number of pills you take each day of the study in a pill diary, as you take your dose. You will need to bring the diary and any extra pills and medication containers with you to your visits to the study doctor.

You should avoid consuming grapefruit and grapefruit juice while taking the study medication due to possible interactions. You should not take any herbal remedies while you are on this study.

During the study, physical and neurologic exams will be repeated and your vital signs will be measured (including temperature, heart rate, blood pressure, respiratory rate). Routine blood tests will be done. If at any point your blood counts are low, these blood tests will be repeated more often. Your blood counts will be checked at least once every week during study treatment.

Following 6 weeks of radiation therapy + MK-1775 you will have 4 weeks of "rest" or no treatment. An MRI of your brain will be obtained after you complete this 10-week cycle. This MRI is part of your standard radiation therapy follow-up care. Your study treatment will then be completed.

<u>If you elect MK-1775 + repeat TMZ treatment:</u>

Treatment cycles are 28 days (4 weeks). You will begin taking MK-1775 and temozolomide together on the same day at the beginning of each cycle (Day 1).

MK-1775 will be taken in the form of a pill during the first 5 days of each cycle, either on Days 1 and 3; or on Days 1, 3, and 5; or on Days 1-5, depending on the dose and schedule established in the Phase I-Arm 2 portion of the study (*dose to be determined*). The number of pills you take will depend on your assigned dose. Your study doctor or nurse will provide specific dosing instructions.

You will take temozolomide on the first 5 days of each cycle (Days 1-5). The number of pills you take each day will depend on your body size. Swallow capsules whole with a glass of water. Do not open or chew the capsules. If capsules are accidentally opened or damaged, be careful not to breathe in (inhale) the powder from the capsules or get the powder on your skin or mucous membranes (for example, in your nose or mouth). If contact with any of these areas happens, flush the area with water.

TMZ and MK-1775 must be taken on an empty stomach. You cannot eat or drink anything except water for two hours before taking your pills and for one hour after taking your pills. Medication to prevent nausea and vomiting will be prescribed by your doctor while taking temozolomide. This is part of standard care for 5-day temozolomide treatment.

If you miss a dose or vomit after taking your dose do not replace it; missed or vomited doses should not be made up.

You will be asked to record the date, time, and the number of pills you take for each medication in a pill diary, as you take your dose. You will need to bring the diary and any extra pills and medication containers with you to your monthly visit to the study doctor.

You should avoid consuming grapefruit and grapefruit juice while taking the study medication due to possible interactions. You should not take any herbal remedies while you are on this study.

After the second cycle an MRI will be obtained. If this MRI shows that the tumor size is the same or smaller, you will begin another four-week cycle of treatment, up to 6 cycles. An MRI will be obtained before every other cycle (every 8 weeks) to see if your tumor is growing. These brain scans (MRI) are part of routine cancer care.

During the study, physical and neurologic exams will be repeated and your vital signs will be measured (including temperature, heart rate, blood pressure, respiratory rate). Routine blood tests will be done. If at any point your blood counts are low, these blood tests will be repeated more often. Your blood counts will be checked at least once every week during radiation therapy or treatment with TMZ.

HOW LONG WILL I BE IN THE STUDY?

If you receive post-surgical MK-1775 + repeat radiation therapy, you will likely be on treatment for about 14 weeks, including your pre-surgical treatment and surgery.

If you receive post-surgical MK-1775 + repeat TMZ, you may continue on the same schedule unless your tumor grows or you have side effects that require discontinuation, or you want to stop treatment. If the MRI taken after the second cycle shows that the tumor size is the same or smaller, you will begin a third 4-week cycle of treatment. As long as your tumor does not grow and as long as you do not experience any bad side effects you may continue to receive additional 4-week cycles, up to six cycles. If the MRI shows that your tumor is growing you will stop MK-1775 treatment and you and your doctor will discuss other treatment options.

If you elect not to receive post-surgical treatment with MK-1775, you will go off treatment following recovery from surgery and a post-surgery follow-up visit.

Every two (2) months for the first two years after your treatment on the study has ended, someone from the study will contact you or your medical records will be reviewed to follow your disease. After two years, this will occur every 6 months for the remainder of your life.

CAN I STOP BEING IN THE STUDY?

Your participation in your clinical trial is completely voluntary. You can stop participating at any time. If you decide not to participate it will not affect your medical care at this institution. If you join this study you may withdraw from it at any time. However, if you decide to withdraw from the study, we encourage you to talk to the study doctor first.

Your study doctor may end your participation in the study if it is judged to be in your best interest or if you are unable to follow the rules of the study.

When you withdraw from the study for any reason, all medication and study drug bottles must be returned to the study site. You will also be asked to return to the site so that the study doctor may perform a proper, final safety evaluation. Every 2 months after your treatment on the study has ended, someone from the study will contact you or your medical records will be reviewed to follow your disease; after two years, this will occur every 6 months for the remainder of your life.

WHAT ARE THE RISKS OR SIDE EFFECTS OF THE STUDY?

While on the study, you are at risk for the following side effects. You should discuss these with the study doctor and/or your regular doctor. There also may be other side effects that we cannot predict. You should also discuss any other side effects that you may experience. Other drugs will be given to make the side effects less serious and uncomfortable.

Many side effects go away shortly after the MK-1775 is stopped, but in some cases side effects can be serious or long-lasting or permanent or fatal. Like chemotherapy drugs, MK-1775 has the potential to damage DNA; MK-1775 should only be taken by cancer patients.

Risks Associated with MK-1775

COMMON, SOME MAY BE SERIOUS In 100 people receiving MK-1775, more than 20 may have:
• Anemia which may require blood transfusion • Bruising, bleeding

OCCASIONAL, SOME MAY BE SERIOUS In 100 people receiving MK-1775, from 4 to 20 may have:
• Ringing in the ear • Belly pain • Diarrhea, nausea, vomiting • Tiredness, fever • Infection, especially when white blood cell count is low

Risks Associated with Temozolomide (TMZ)

TMZ is a chemotherapy drug that is considered part of standard treatment. TMZ may cause the following:

Likely (more than a 20% chance this will happen):

- Nausea, upset stomach and vomiting with temozolomide occurs often and can be severe in some people.
- Fatigue
- Constipation
- Loss of appetite
- Headache
- Weakness
- Weight loss
- Shortness of breath
- Hair loss
- Chills
- Abnormal sensations, such as numbness, burning, and/or tingling
- A drop in the red blood count may result in anemia, which could lead to shortness of breath, dizziness, weakness and/or fatigue. As a result you may need a blood transfusion.

Frequent (between 10-20% chance this will happen):

- Dizziness
- Rash
- Generalized pain
- Swelling in the legs and feet caused by excess fluid in the body tissues
- Diarrhea
- A drop in blood counts, in particular, a decrease in the number of neutrophils in the blood (a type of white blood cell that helps fight infection), may result in severe infection such as pneumonia that may require IV antibiotics and medication to increase your white blood cells. This could potentially lead to a hospital stay. This can be serious or life threatening.
- A drop in the number of platelets in the blood that may result in easy bruising and bleeding in mucous membranes, wounds, or other tissues. If this happens, you might require a transfusion.

Occasional (chance of less than 10% that this will happen):

- Itchy skin
- Difficulty walking/unsteady gait
- Increased risk of infection which may be serious or life threatening
- Pain while swallowing
- Abdominal pain

- Elevated blood sugar, which may lead to infection, increased thirst and increased urination
- Sleepiness
- Difficulty falling asleep
- Redness of the skin
- Fever
- Allergic reactions that may include a rash, hives, fever, difficulty breathing, and low blood pressure. Although usually reversible with treatment, it can be severe and life threatening.
- Anxiety
- Depression
- Opportunistic infections (may occur when temozolomide is used in combination with radiation treatment and steroids)—An infection caused by an organism that usually does not cause illness, but causes disease when a person's immune response (resistance) to infection is impaired.
- Abnormal liver function tests—which means that your liver is not functioning properly and can cause malaise (a vague feeling of bodily discomfort), fatigue, and jaundice (yellowing of the skin). Although this is usually mild and reversible, this can be serious or life threatening and result in liver failure.
- Abnormal kidney function tests, which means the kidneys aren't working properly. When the kidneys do not work properly, wastes can build up in your blood, leading to swelling in the arms and legs, tiredness and weakness. This could become severe, requiring hospitalization and dialysis to clean the wastes out of your blood. If the wastes are not removed from your blood, this could cause seizures and be life threatening.
- Prolonged treatment with temozolomide may also increase the risk of developing a rare lung infection called pneumocystis pneumonia (PCP), which may result in the following symptoms: fever, cough and difficulty breathing.

Rare: many of the following rare side effects may be life-threatening or lead to life-threatening events:

- Altered consciousness (diminished sense of awareness of self and/or environment).
- Pulmonary blood clot which can lead to a respiratory arrest.
- Blood clot formed in the veins of the leg (deep venous thrombosis) which may manifest as a dull ache or heaviness in the limb. If the clot moves to other organs, it can be serious or life threatening.
- Permanent bone marrow damage may result in a drop in the number of platelets, white blood cell counts, and red blood cell counts.
- Stomach bleeding

- Idiopathic Thrombocytopenia Purpura (ITP) may occur. ITP may cause bleeding and bruising. Bleeding may be serious or life threatening and may require a blood transfusion. This condition can resolve with treatment.
- Stroke (cerebrovascular accident) has been reported; the relationship of this event to temozolomide is unclear.
- Secondary cancer, such as leukemia
- Bleeding from the lungs may occur accompanied by respiratory failure.
- Atrial fibrillation (an irregular quickening of the heart beat) and cardiac failure.
- Air or gas in the abdomen causing pain and discomfort
- Inflammation and/or infection of the intestines, which may cause pain and discomfort

Risks Associated with Radiation Therapy:

You will receive standard radiation therapy if you elect post-surgical treatment with MK-1775 + repeat radiation therapy. Risks and side effects related to the radiation therapy include:

Likely risks:

- Scalp redness or soreness
- Hair loss, which may be temporary or permanent
- Ear/ear canal reactions, such as dryness of ear canal, hardening of the wax in the ear canal, or redness of the external ear, possibly causing temporary hearing loss
- Fatigue, lethargy
- Temporary worsening of brain tumor symptoms such as headaches, seizures, or weakness

Less likely risks:

- Problems with mental functioning (neurocognitive problems), including memory deficits, which may be permanent
- Permanent hearing loss
- Condition in which the lens of the eye becomes cloudy (cataracts). This may require surgery to repair.
- Behavioral change, which can be due to physical effects of radiation therapy such as fatigue or headaches
- Nausea, vomiting
- Temporary worsening of existing neurological problems, such as decreased vision, drowsiness, and weakness of your arms and legs
- Endocrine problems related to changes to the pituitary gland, a gland that produces hormones that control other glands. Symptoms can include problems with your thyroid gland, sugar metabolism, fertility, or decrease in ability to regulate water, which may lead to excessive urination.
- Dry mouth or altered taste

Rare but serious risks:

- Severe local damage to normal brain tissue, a condition called necrosis (tissue deterioration). Radiation necrosis can mimic recurrent brain tumor and may require surgery for diagnosis and treatment.
- Injury to the eyes with the possibility of blindness
- Development of other tumors (either benign or malignant)

Side effects due to blood drawing may include: pain, bruising, bleeding or other discomfort at the blood drawing site. Anemia (low red blood cells), fainting or infection at the blood drawing site may occur (very unlikely).

Reproductive Risks
Because there may be a risk of birth defects if a fetus is exposed to MK-1775 or temozolomide, you should not use this drug if you and your partner are planning to have a baby during this study or two months following the end of the study. A barrier method of birth control (e.g. condom, diaphragm) plus a spermicide must be used during the study and for eight (8) weeks after your last dose of study drug. You should not nurse a baby while on this study.

Risks of MRI
The effects of magnetic fields in an MRI scanner have been extensively studied, and there are no known significant risks with an MRI exam. You may, however, be bothered by feelings of confinement (claustrophobia), and by the noise made by the magnet during the procedure. You will be asked to wear earplugs or earphones while in the magnet. You may not participate in this study if you have a pacemaker, an implanted defibrillator or certain other implanted electronic or metallic devices. It is important for you to advise the MRI staff if you have had brain surgery for a cerebral aneurysm, or if you have implanted medical or metallic devices, shrapnel, or other metal, such as metal in your eye.

Gadolinium Risk
The contrast agent you will receive is FDA-approved and used routinely for MRI exams. It contains a material called gadolinium. The injection of contrast may cause discomfort, tingling or warmth in the lips, metallic taste in the mouth, tingling in the arm, nausea, or headache. These symptoms occur in less than 1% (less than 1 in 100) of people and go away quickly.

There is a small risk of an allergic reaction to gadolinium; however, a severe allergic reaction occurs in less than one in 300,000 people. Insertion of the needle (small plastic tube) to give you gadolinium may cause minor pain, bruising and/or infection at the injection site.

People with severe kidney failure who receive gadolinium are at risk of developing Nephrogenic Systemic Fibrosis/Nephrogenic Fibrosing Dermopathy (NSF/NFD). This disease causes fibrosis, which is the formation of too much connective tissue in the skin and internal organs throughout the body. People develop skin thickening that may prevent bending and extending joints, resulting in decreased movement of the joints. The skin changes can cause feelings of burning, itching and pain that can be severe. In addition, people may experience fibrosis that spreads to

other parts of the body such as the diaphragm, muscles in the thigh and lower abdomen, and the lining of blood vessels in the lung.

NSF/NFD is a serious progressive disease and can result in death. If you have severe kidney failure and receive gadolinium, the risk of developing NSF/NFD is 1-5 % (up to 1 to 5 per 100 people). We may require a blood sample (about 1 tablespoon) to check your kidney function before you receive gadolinium contrast for your MRI.

Please notify a doctor, nurse or technologist if you are allergic to gadolinium, if you have any kidney problems, or if you experience any of these or other side effects. If you do not know if you have kidney problems or if you do not know if your kidney problems fall in the severe category, you can ask the principal investigator of your study to give you this information.

A physician will be available during the procedure to administer any necessary care if side effects do occur, and to determine when or if the injection of the gadolinium should be stopped.

Financial risks: There may be extra costs with this treatment. Some of the costs may not be covered by the hospital or the insurance company. We encourage you to work closely with your insurance company to find out exactly what is covered for this research study.

This study may also have risks to you that cannot be determined at this time. You will be told of any potential risks that may be discovered while you are participating in this study.

For more information about risks and side effects, ask the study doctor or contact:

ARE THERE BENEFITS TO TAKING PART IN THE STUDY?

If you agree to take part in this study, there may or may not be direct medical benefit to you. We hope the information learned from this study will benefit other patients with brain tumors in the future.

WHAT OTHER CHOICES DO I HAVE IF I DO NOT TAKE PART IN THIS STUDY?

Your other choices may include:

- Getting treatment or care for your cancer without being in a study
- Taking part in another study
- Getting no treatment
- Getting comfort care, also called palliative care. This type of care helps reduce pain, tiredness, appetite problems and other problems caused by the cancer. It does not treat the cancer directly, but instead tries to improve how you feel. Comfort care tries to keep you as active and comfortable as possible.

Talk to your doctor about your choices before you decide if you will take part in this study.

WILL MY MEDICAL INFORMATION BE KEPT PRIVATE?

This section tells you what information about you may be used and given out in this study and who may give and receive the information. By signing this consent form, you agree that health information that identifies you may be used and/or given out as needed in this study. _____ (*name of center*) has a policy to protect health information that may identify you. Federal and state laws also protect your privacy. _____ (*name of center*) has procedures in place to support these policies and laws.

a. What information about you may be used or given out in this study?
Information that identifies you and relates to your health or medical condition may be used or given out in this study. Information that identifies you can include your name, address, telephone number, date of birth, Social Security number and other details about you. Information that relates to your health or medical condition includes:

Information obtained from the activities and procedures outlined in this consent form, which may include:

i) things done to see if you can join this study, such as physical examinations, blood and urine tests and any other information that you share with us, including information about your health history and your family health history; and

ii) information obtained during the study, such as how you respond to the study activities or procedures, information we learn in study visits, phone calls, surveys, physical examinations, blood and urine tests, x-rays and other tests and any other medical information we learn from you as a participant in this study.

b. Who may use and give out information about you?
Some people may see your health information and may give out your health information during this study. These include the research study doctor and the research staff, the institutional review boards and their staff, legal counsel, audit and compliance staff, officers of the organization and other people who need to see the information to help this study or make sure it is being done as it should.

c. Who may see your health information?
Other organizations may see your health information during this study. These include:

- Governmental entities that have the right to see or review your health information, such as the Office of Human Research Protections and the Food and Drug Administration
- Doctors and staff at other places that are participating in this study
- The Pharmaceutical Collaborator (includes the National Cancer Institute's pharmaceutical collaborators who provide investigational drug to the NCI)

- The sponsors of this study and people that the sponsor may contract with for this study. The name of the sponsor is DCTD/NCI (Division of Cancer Treatment and Diagnosis/National Cancer Institute)
- The Data Safety Monitoring Board
- An outside institutional review board
- The Adult Brain Tumor Consortium (ABTC)

d. Why will this information be used and given out?
Your information will be used and given out to carry out this study and to evaluate the results of this study.

e. What if you decide not to give your permission to use and give out your health information?
You do not have to give your permission to use or give out your health information. However, if you do not give permission, you may not participate in this study.

f. May you withdraw or cancel your permission?
You may cancel your agreement to allow your health information to be used or given out at any time by sending a written notice to the Institutional Review Board Office, _____. If you do this, you are leaving this study. If you leave this study, no new health information about you will be gathered after that date. However, information gathered before that date may be used or given out if it is needed for this study or any follow-up for this study.

g. Is your health information protected after it has been given to others?
If your health information is given to someone not covered by these policies and laws, that information may no longer be protected, and may be used or given out without your permission.

h. Does this consent form have an end date?
This authorization to use and give out health information continues until the end of this study and any necessary data analysis follow-up activities for this study.

i. What is the role of the IRB?
Research studies involving human volunteers are reviewed by an Institutional Review Board (IRB). The IRB is made up of doctors, nurses, scientists, non-scientists and people from the community. The IRB is responsible for protecting participant's 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 can search this Web site at any time.

WHAT ARE THE COSTS?

Taking part in this study may lead to added costs to you or your insurance company. Some of the costs of the blood tests and brain scans may not be covered by your insurance company. We

encourage you to work closely with your insurance company to find out exactly what is covered for this research study.

The NCI (National Cancer Institute) will provide you with the investigational agent MK-1775 free of charge while you take part in this study. The NCI does not cover the cost of getting MK-1775 ready and giving it to you, so you or your insurance company may have to pay for this.

Even though it probably won't happen, it is possible that the manufacturer may not continue to provide MK-1775 to the NCI for some reason. If this would occur, other possible options are:

- You might be able to get MK-1775 from the manufacturer but you or your insurance company may have to pay for it.

- If there is no MK-1775 available at all, no one will be able to get more and the study would close.

If a problem with getting MK-1775 occurs, your study doctor will talk to you about these options.

Should this agent become commercially available or approved for this indication 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 the company no longer provides the drug.

Temozolomide is commercially available for brain tumor treatment.

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

For more information on clinical trials and insurance coverage, you can visit the National Cancer Institute's Web site at http://cancer.gov/clinicaltrials/understanding/insurance-coverage. You can print a copy of the "Clinical Trials and Insurance Coverage" information from this Web site.

Another way to get the information is to call 1-800-4-CANCER (1-800-422-6237) and ask them to send you a free copy.

WHAT HAPPENS IF I AM INJURED BECAUSE I TOOK PART IN THIS STUDY?

It is important that you tell your study doctor, _____ *[investigator's name(s)]*, if you feel that you have been injured because of taking part in this study. You can tell the doctor in person or call him/her at _____ *[telephone number]*.

In the case of injury or illness resulting from this study, emergency medical treatment is available but will be provided at the usual charge. No funds have been set aside to compensate you in the event of injury. You or your insurance company will be charged for continuing medical care and/or hospitalization.

WHAT ARE MY RIGHTS IF I TAKE PART IN THIS STUDY?

Taking part in this study is voluntary. You may choose not to take part or may leave the study at any time. Leaving the study will not result in any penalty or loss of benefits to which you are entitled.

We will talk to you about new information that may affect your health, welfare, or willingness to stay in this study.

WHOM DO I CALL IF I HAVE QUESTIONS OR PROBLEMS?

For questions about the study or a research-related injury, contact your study doctor _____ (*name{s}*) at _____ (*telephone number*).

For questions about your rights as a research participant, contact the_____ (*name of center*) Institutional Review Board (a group of people who review the research to protect your rights) at _____ (*telephone number*).

WHERE CAN I GET MORE INFORMATION?

You may call the National Cancer Institute's Cancer Information Service at:

1-800-4-CANCER (1-800-422-6237)

You may also visit the NCI Web site at http://cancer.gov/

- For NCI's clinical trials information, go to: http://cancer.gov/clinicaltrials/
- For NCI's general information about cancer, go to http://cancer.gov/cancerinfo/

You will get a copy of this form. If you want more information about this study, ask your study doctor.

SIGNATURE

I have been given a copy of this form. I have read it or it has been read to me. I understand the information and have had my questions answered. I agree to take part in this study.

Participant _____

Date _____

Investigator _____

Date _____