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Sponsored and Funded by the National Cancer Institute

CONSENT FORM

CIRB R0825: Phase III Double-Blind Placebo-Controlled Trial of Conventional Concurrent Chemoradiation and Adjuvant Temozolomide Plus Bevacizumab Versus Conventional Concurrent Chemoradiation and Adjuvant Temozolomide in Patients with Newly Diagnosed Glioblastoma.

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CIRB R0825: Phase III Double-Blind Placebo-Controlled Trial of Conventional Concurrent Chemoradiation and Adjuvant Temozolomide Plus Bevacizumab Versus Conventional Concurrent Chemoradiation and Adjuvant Temozolomide in Patients with Newly Diagnosed 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 people who choose to take part. We recognize that this study is very complex; please take your time to make your decision with your friends and family. 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 that is a glioblastoma.

Why is this study being done?

A recent study demonstrated that combining a drug called temozolomide with radiation treatment and following this treatment with temozolomide treatment improved tumor control compared with radiation alone. Therefore, the combination of temozolomide with radiation followed by temozolomide alone has become the standard of care for patients with glioblastoma. Bevacizumab is an antiangiogenic agent, which means that it can interrupt the body's ability to grow new blood vessels, causing tumors to shrink. There is also information that demonstrates that bevacizumab may eliminate poorly formed blood vessels in tumors, resulting in improved blood flow. This improved blood flow may result in better delivery of chemotherapy agents. There are preliminary studies that suggest that combining chemotherapy drugs with bevacizumab may be better than either the chemotherapy agent alone or bevacizumab alone for treating some types of tumors. The study doctors want to see whether this will be true for glioblastoma.

The purpose of this study is to determine whether the addition of bevacizumab to the standard chemoradiation will further improve the outcome. This study will find out what effects, good and/or bad, this change in treatment has on you and on your tumor compared with standard treatment. Bevacizumab has not been approved by the US Food and Drug Administration for the treatment of glioblastoma.

In addition, this study will try to determine whether the response to the bevacizumab and the overall outcome depend on a genetic pattern (molecular profile) in the tumor. After you register for the study, a sample of your tumor tissue will be submitted to a central laboratory to confirm that your tumor is a glioblastoma and to determine the molecular profile (genetic analysis) of the tumor tissue. The molecular profile will look at whether your tumor has certain combinations of the following genes that have been found to be important in determining response to glioblastoma treatment: MGMT, AQP1, CHI3L1, EMP3, GPNMB, IGFBP2, LGALS3, OLIG2, PDPN, RTN1. This information will be used to place you in one of the study arms in a way that makes sure that the number of patients with these gene combinations is balanced in each group (stratification). The molecular profile results will be used for research purposes only and will not be given to you or your study doctor.

How many people will take part in the study?

About 942 people will take part in this study.

What will happen if I take part in this research study?

Before you begin the study...

You will need to have the following exams, tests, and procedures to find out if you can be in the study. These exams, tests, and 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.

- Blood work for blood counts and biochemistry
- MRI scan of your brain (an image of your brain produced by magnetic rays) [NOTE: If unavailable, a CT scan, which takes computerized images of your brain, may be done instead]
- Pregnancy test if indicated

During the study...

If the exams, tests, and procedures show that you can be in the study, and you choose to take part, then you will need the following exams, tests, and procedures. They are part of regular cancer care.

- MRI (or CT) scan of your brain
- Blood work for blood counts as well as kidney and liver function
- Documentation of any side effects you are experiencing from treatment

MRI/CT scans, blood work, and documentation of side effects will be repeated throughout the study so that your study doctor can monitor you. Your study doctor will send your MRI/CT scans to a central agency. Radiologists may look at those scans to evaluate your response to the treatment. Your name and other information that may identify you by name will be removed from the scans.

You will also be asked to complete a medication diary while you are receiving treatment; this will help document when you take your medication and any side effects you experience.

When you enter the study, your study doctor will need to send the block of tumor tissue obtained at the time of your brain tumor surgery to a central pathology site. There, a pathologist will confirm that the tumor is a glioblastoma and will also determine whether there is adequate tumor tissue to perform the analysis for genetic (molecular) profile. If the tumor is not a glioblastoma and/or if the tissue is not adequate for performing the molecular analyses, you will not be able to continue on the study.

You will begin the study treatment by taking temozolomide at the same time that you receive radiation therapy. You will take temozolomide capsules orally every morning (7 days a week) for a maximum of 7 weeks. You may need to take several temozolomide capsules for each dose, since the exact dose you receive depends on your body weight. You will take each dose with an 8-ounce glass of water on an empty stomach at least 1 hour before eating. You should not open or split the capsules, and you should swallow them whole and never chew them. You should store the temozolomide at room temperature, away from excessive heat, moisture and light and away from children and pets.

You will receive radiation therapy Monday through Friday for a total of 30 radiation treatments.

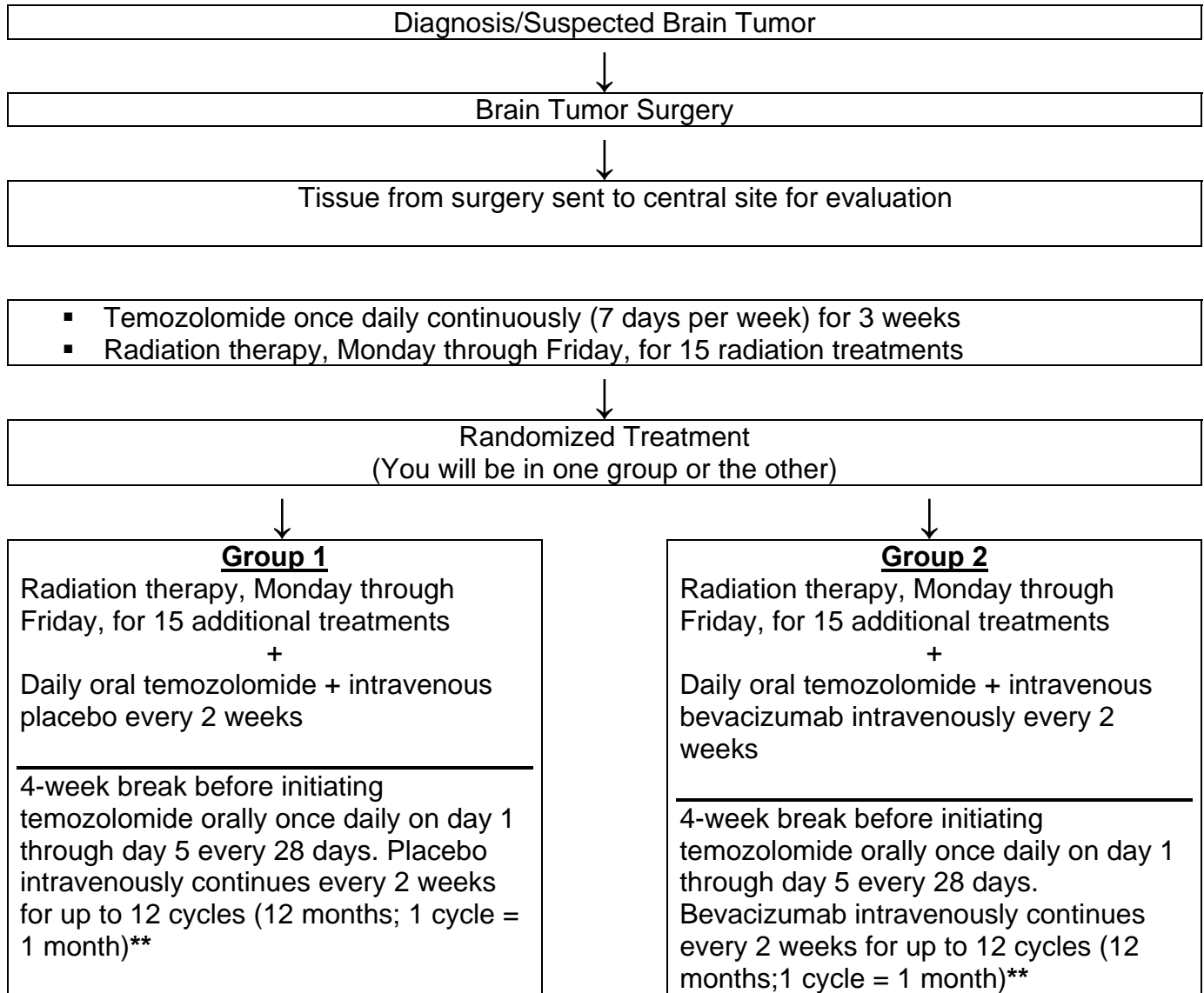
By day 3 of week 2 during your radiation treatment, you will be “randomized” into one of the study groups described below. Randomization means that you are put into a group by chance. A computer program will place you in one of the study groups. During initial accrual to the study (for the first 60 patients randomized), you will have a 2 in 3 (67%) chance of being placed in the group that includes bevacizumab and a 1 in 3 (33%) chance of being placed in the group that includes placebo. Subsequently (after 60 patients have been randomized), you will have a 1 in 3 (33%) chance of being placed in the group that includes bevacizumab and a 2 in 3 (67%) chance of being placed in the group that includes placebo. After enrollment between the two treatment arms is balanced (after 120 patients have been randomized to either the bevacizumab or placebo group), you will have an equal chance of being placed in either group. You will begin the randomized part of your treatment with the 4th week of radiation therapy.

You will receive an intravenous treatment of either bevacizumab or placebo every 2 weeks beginning during week 4 of radiation and continuing until the end of the temozolomide treatment. This includes during radiation treatment, for the 4 week rest between radiation and the restart of temozolomide until the completion of the adjuvant (after radiation) temozolomide treatment. You will take temozolomide every evening on day 1 through day 5 every 28 days for up to 12 cycles (48 weeks; 1 cycle = 4 weeks).

See next page for Study Plan chart.

Study Plan

Another way to find out what will happen to you during the study is to read the chart below. Start reading at the top and read down the list, following the lines and arrows.



**If your disease gets worse while you are receiving protocol treatment or afterwards, you will be offered the possibility of receiving bevacizumab, either alone or in combination with temozolomide or irinotecan. Your study doctor will discuss these options with you.*

When I am finished taking the study treatment...

You will be followed at regular check-ups, including MRI or CT scans, every 3 months after completing treatment for the first year, then every 4 months for the second year, and then every 6 months for the rest of your life.

How long will I be in the study?

You will receive radiation plus temozolomide for a maximum of 7 weeks. The intravenous treatment will start at the beginning of the fourth week of radiation. You will then be asked to take temozolomide and the intravenous treatment for up to 12 months following completion of radiation. The exact amount of time you take the post-radiation temozolomide and intravenous treatment will depend on your response to the drug.

After you are finished taking the temozolomide, the study doctor will ask you to visit the office or clinic for follow-up exams every 3 months after completing treatment for the first year, then every 4 months for the second year, and then every 6 months for the rest of your life.

Can I stop being in the study?

Yes. You can decide to stop at any time. Tell your study doctor if you are thinking about stopping or decide to stop. He or she will tell you how to stop safely.

It is important to tell your study doctor if you are thinking about stopping, so he or she can evaluate any risks from the temozolomide and radiation. Another reason to tell your study doctor that you are thinking about stopping is to discuss what follow-up care and testing could be most helpful for you.

Your study doctor may stop you from taking part in this study at any time if he/she believes it is in your best interest; if you do not follow the study rules; or if the study is stopped.

Will I find out which treatment I received?

If your disease gets worse either while you are receiving protocol treatment or afterwards, you and your study doctor will be able to find out whether you were assigned to the placebo or bevacizumab arm. You will then be offered the possibility of receiving unblinded bevacizumab, regardless of the arm you were assigned to. Your study doctor will discuss with the possible treatments you can receive with unblinded bevacizumab. They are:

- Bevacizumab alone
- Bevacizumab with temozolomide
- Bevacizumab with irinotecan

What side effects or risks can I expect from being in the study?

You may have side effects while on the study. Everyone taking part in the study will be watched carefully for any side effects. However, doctors don't know all the side effects that may happen. Side effects may be mild or very serious. Your health care team may give you medicines to help lessen side effects. Many side effects go away soon after you stop taking the drugs. In some cases, side effects can be serious, long lasting, or may never go away. A severe side effect rarely may be life threatening. Although the risk of death is low, you should tell your study doctor immediately if you experience any of these side effects.

All side effects will be treated in the best way possible and this may involve anti-nausea medications, hospitalization for antibiotics, platelet transfusions, stool softeners or laxatives, and steroids or antihistamines for allergic reactions. There are guidelines for reducing the doses of chemotherapy drugs or eliminating them altogether should you experience serious or intolerable side effects. To avoid potential drug interactions, you should consult your physician or pharmacist before taking any new medications, including over the counter (non-prescription) medications.

You should talk to your study doctor about any side effects that you have while taking part in the study.

Risks and side effects related to the radiation include those that are:

Likely

- Scalp redness or soreness
- Hair loss, which may be temporary or permanent
- Ear/ear canal reactions, possibly resulting in a short-term hearing loss
- Fatigue
- Lethargy
- Temporary aggravation of brain tumor symptoms such as headaches, seizures, or weakness

Less Likely

- Mental slowing
- Permanent hearing loss
- Cataracts
- Behavioral change
- Nausea
- Vomiting
- Temporary worsening of existing neurological deficits, such as decreased vision, drowsiness, and weakness of your arms and legs
- Endocrine problems causing abnormalities in the level of some hormones related to changes to the pituitary gland
- Dry mouth or altered taste

Rare but Serious

- 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)

Risks and side effects related to temozolomide include those that are: (7/20/09)

Likely

- Nausea and/or vomiting
- Decreased appetite
- Headache
- Constipation
- Drowsiness/Fatigue
- Inability to sleep
- Hair loss

Less Likely

- Decrease in blood counts that may cause infection, bleeding, and bruising
- Diarrhea
- Fever
- Sores in your mouth
- Rash
- Elevated liver enzymes (reversible)
- Swelling in your arms and legs
- Memory loss
- Confusion
- Itchiness
- Increased need to urinate
- Weakness
- Back pain
- Dizziness
- Tingling/burning in your arms and legs
- Anxiety
- Depression
- Stomach pain
- Blurred vision

Rare but Serious

- Decreased ability to carry out daily activities
- Convulsions
- Weakness on one side of your body
- Abnormal coordination
- Paralysis
- Myelodysplastic syndrome (problem with the bone marrow that causes decreased production of red cells, white cells, or platelets that can sometimes turn into blood cancer)

Risks and side effects related to bevacizumab include those that are (8/2/10):

Likely

- Diarrhea
- Nausea or the urge to vomit
- Vomiting
- Fatigue or tiredness
- Headache or head pain
- High blood pressure

Less Likely

- Lack of enough red blood cells (anemia)
- Fast heartbeat usually originating in an area located above the ventricles
- Feeling of spinning or whirling
- Belly pain
- Inflammation (swelling and redness) of the large bowel (colon)
- Constipation
- Heartburn
- Bleeding in some organ(s) of the digestive tract

- Partial or complete blockage of the small and/or large bowel. Ileus is a functional rather than actual blockage of the bowel.
- Irritation or sores in the lining of the mouth
- Reaction that can occur during or following infusion of the drug. The reaction may include fever, chills, rash, low blood pressure, and difficulty breathing.
- Chest pain not heart-related
- Pain
- Allergic reaction by your body to the drug product that can occur immediately or may be delayed. The reaction may include hives, low blood pressure, wheezing, swelling of the throat, and difficulty breathing.
- Infection
- Infection (collection of pus) around the rectum
- Premature opening of a wound along surgical stitches after surgery
- Increased blood level of a liver enzyme (ALT/SGPT)
- Increased blood level of a liver or bone enzyme (alkaline phosphatase)
- Increased blood level of a liver enzyme (AST/SGOT)
- Increased blood level of a liver pigment (bilirubin) often a sign of liver problems
- Increased blood level of a heart muscle protein (troponin I) indicating damage to the heart muscle
- Decreased number of a type of white blood cell (neutrophil/granulocyte)
- Weight loss
- Decrease in the total number of white blood cells (leukocytes)
- Loss of appetite
- Joint pain
- Abnormal changes in the growth plate that may affect the growth of long bones in very young children. This side effect appeared to be reversible after the treatment was stopped but has not been assessed with long-term use of the bevacizumab drug.
- Muscle pain
- Dizziness (or sensation of lightheadedness, unsteadiness, or giddiness)
- Fainting
- Sudden decrease of kidney function
- Blood in the urine
- More protein leaking into the urine than usual, often a sign of kidney disease
- Bleeding in the vagina
- Cough
- Shortness of breath
- Nose bleed
- Hoarseness
- Stuffy nose
- Itching
- Skin rash
- Hives
- Formation of a blood clot that plugs the blood vessel; blood clots may break loose and travel to another place, such as the lung

Rare But Serious

- Damage of or clots in small blood vessels in the kidney that can cause complications, some of which are serious including abnormal destruction of red blood cells (hemolysis) or platelets (that help to clot blood) and kidney failure
- Collection of signs and symptoms that indicate sudden heart disease in which the heart does not get enough oxygen. Sudden symptoms such as chest pain, shortness of breath, or fainting could indicate heart disease and should be reported right away. Signs such as abnormal EKG and blood tests can confirm damage to the heart.
- Heart failure: inability of the heart to adequately pump blood to supply oxygen to the body
- Decrease in heart's ability to pump blood during the "active" phase of the heartbeat (systole)
- Heart attack caused by a blockage or decreased blood supply to the heart
- Irregular heartbeat resulting from an abnormality in the one of the lower chambers of the heart (ventricle)
- Ventricular fibrillation: irregular heartbeat that involves the lower chambers of the heart (ventricles) that results in uncoordinated contraction of the heart; life threatening and potentially fatal, needing immediate attention
- Gastrointestinal fistula: Abnormal hole between an organ of the digestive tract and another organ or tissue
- Gastrointestinal perforation : A tear or hole in the stomach or gut that can lead to serious complications and may require surgery to repair
- Sore (ulcer) somewhere in the digestive tract
- Serious, life-threatening allergic reaction requiring immediate medical treatment by your doctor. The reaction may include extremely low blood pressure, swelling of the throat, difficulty breathing, and loss of consciousness.
- Leakage from stomach due to breakdown of an anastomosis (surgical connection of two separate body structures)
- Bleeding in the brain
- Stroke caused by decreased blood flow to the brain
- Abnormal changes in the brain that can cause a collection of symptoms including headache, confusion, seizures, and vision loss associated with MRI imaging findings (RPLS)
- A condition in which the kidneys leak a large amount of protein into the urine that can cause complications including swelling and kidney failure
- Kidney failure
- Abnormal hole between part of the urinary system and another organ or tissue
- Abnormal hole between the vagina and another organ or tissue
- Abnormal hole between the lower breathing tube and the body cavity that surrounds the lungs
- Bleeding from the lungs
- Hole in the wall that separates the nostrils of the nose
- Abnormal hole between the breathing tube (windpipe) and the tube that goes from mouth to stomach through which food passes (esophagus). This is life-threatening and potentially fatal.
- Blockage or narrowing of a blood vessel (artery) that can cause damage or loss of function including a heart attack or stroke

(NOTE: For patients with worsening disease after initial protocol treatment who opt to receive bevacizumab in combination with irinotecan)

Risks and side effects related to irinotecan include those that are:

Likely

- Delayed diarrhea (occurring within hours of receiving study drug and lasting up to 5-7 days)
- Abdominal cramping, including delayed abdominal cramping (stomach pain that can last for 5-7 days)
- Nausea and vomiting
- Lack of appetite
- Sweating
- Flushing
- Runny nose
- Teary eyes
- Hair loss
- Weakness
- Decrease in blood cells (due to the drug preventing your body from making and keeping new blood cells)
- Sudden urge to have a bowel movement occurring shortly after the irinotecan infusion. *Note:* Dehydration has occurred as a consequence of diarrhea, particularly when associated with severe vomiting. Diarrhea that occurs at a time when the white blood cell count is low can be especially dangerous, which can make you more susceptible to severe infections that could be life-threatening. Should you experience a fever or other sign of infection when your white blood cell count is very low, you may need to be admitted to the hospital for precautionary measures and receive intravenous antibiotics until your blood cell counts rise to safe levels.

Diarrhea has been the most frequent severe side effect associated with receiving irinotecan. When severe diarrhea has occurred, some patients have had to be admitted to the hospital to receive intravenous fluids until the diarrhea resolved (usually in 5-7 days). With early recognition and proper treatment, the likelihood of severe diarrhea may be decreased. In order to minimize the severity of the diarrhea, you are advised to follow these directions:

1. Be aware of your bowel movements. If they become softer than usual or if you have any increase in the number of bowel movements over what is normal for you, begin taking loperamide tablets right away.
2. Take two loperamide (Imodium) tablets immediately after the onset of diarrhea or increased frequency of bowel movements, and then take one tablet every two hours until you have been without a bowel movement for 12 hours straight. At night, you may take two tablets every four hours so that you won't have to wake up so often. Make sure that you drink plenty of fluids (soups, juices, etc.) to replace the fluids lost in the bowel movements. If your soft bowel movements or diarrhea do not stop within 36 hours, call your study doctor. Should you become weak, lightheaded, or feel faint, call your study doctor immediately. Don't take loperamide tablets unless you have loose or frequent stools or diarrhea.

Less Likely

- Mouth sores
- Frequent bowel movements (sometimes with blood noted in your bowel movements)
- Redness or irritation of your skin at infusion sites

Rare but Serious

- Lung problems with symptoms shortness of breath, nonproductive (dry) cough, and abnormal chest x-ray
- Abnormal blood, kidney and liver lab results, which could indicate serious blood, kidney, or liver problems

Note: If you are on a blood thinner (warfarin), you will need to be monitored for any interaction between irinotecan and warfarin. If you have any bleeding or bruising, you should let your physician know.

Patients undergoing treatment with radiation and temozolomide are at increased risk of developing a specific type of pneumonia (lung infection) called Pneumocystis. There are specific antibiotic treatments that are given during the radiation and temozolomide treatments to reduce the chance of developing this pneumonia. Risks and side effects related to each antibiotic treatment (either trimethoprim-sulfamethoxazole or pentamidine or dapsone) to prevent Pneumocystis pneumonia include the following:

Trimethoprim-sulfamethoxazole

Likely

- Itching
- Rash

Less Likely

- Decreased hemoglobin level (anemia)
- Feeling of general discomfort or uneasiness
- Fever
- Nausea
- Vomiting

Rare but Serious

- Low white blood cell count, which may cause problems with infection
- Low blood platelet count, which may cause problems with bruising, bleeding, and blood clotting
- Temporary abnormalities in liver function tests, which may cause fatigue and skin discoloration
- Aplastic anemia (a form of anemia in which the bone marrow dramatically decreases or stops blood cell production)
- Other abnormalities in blood tests
- Liver irritation resembling hepatitis

- Problems with kidney function, which may lead to increased urination and kidney failure
- Pseudomembranous colitis (a diarrheal disease that can occur in patients taking antibiotics and can cause watery diarrhea, fever, and abdominal cramping)
- Stevens-Johnson syndrome (a severe skin reaction similar to a bad burn that can involve the lining of the mouth and eye)

Pentamidine

Likely

- Bronchospasm (difficulty breathing due to the squeezing of breathing passages in the lungs)
- Cough
- Shortness of breath
- Chills
- Rash
- Chest pain
- Headache
- Increased potassium levels in your blood

Less Likely

- Metallic taste, which may lead to decreased appetite

Rare but Serious

- Dizziness
- Abnormal heart rhythms
- Low blood pressure
- Low white blood cell count, which may cause problems with infection
- Low blood platelet count, which may cause problems with bruising, bleeding, and blood clotting
- Low red blood cell count, which may cause fatigue
- Low blood sugar
- High blood sugar
- Pancreatitis (inflammation of the pancreas that is severe enough to cause symptoms like belly pain, vomiting, nausea)
- Kidney damage
- Liver irritation resembling hepatitis
- Vomiting
- Fever
- Fatigue
- Severe allergic reactions
- Collapsed lung

Dapsone

Less Likely

- Abdominal pain
- Nausea
- Vomiting
- Kidney injury
- Vertigo (spinning sensation)
- Blurred vision
- Tinnitus (noises or buzzing in the ears)
- Fever
- Headache
- Lupus-like syndrome (might include joint pain, aching, rashes, fever, sores in the mouth, kidney injury), which usually resolves when drug is stopped
- Numbness, pins and needles, and loss of strength and coordination in the hands and feet due to injury to nerves in the arms and legs. Usually this improves if the dapsone is stopped.
- Low red blood cell count, caused by speeding up the break down of red cells. If you develop this problem dapsone will be stopped.

Rare but Serious

- Retinal and optic nerve damage, which may cause permanent visual loss or blindness
- Pancreatitis (inflammation of the pancreas that is severe enough to cause symptoms like belly pain, vomiting, nausea)

Reproductive risks:

You should not become pregnant or father a baby while on this study because the drugs in this study can affect an unborn baby. Women should not breast feed a baby while on this study. Also, because bevacizumab remains in your body for weeks to months, you should continue to use adequate contraceptive measures and avoid nursing a baby for at least 6 months after your last dose of bevacizumab or placebo, although the optimal or the maximal time required for drug clearance cannot be precisely predicted. It is important you understand that you need to use birth regulation (regulation highly effective: abstinence, IUD, birth control pills, tubal ligation or partner's vasectomy and less effective: condom, diaphragm or cervical cap) while on this study. Check with your study doctor about what kind of birth regulation (regulation highly effective: abstinence, IUD, birth control pills, tubal ligation or partner's vasectomy and less effective: condom, diaphragm or cervical cap) methods to use and how long to use them. Some methods might not be approved for use in this study. If you are a woman of childbearing age, and have not been surgically sterilized (tubal ligation or hysterectomy), you must have a pregnancy test before enrolling in this study.

Temozolomide may make it harder for a woman to become pregnant or for a man to cause a woman to become pregnant even after the chemotherapy has been completed. There is not enough information about temozolomide in men and women of childbearing age who subsequently try to have children to know how likely problems will be.

For more information about risks and side effects, ask your study doctor.

Are there benefits to taking part in the study?

Taking part in this study may or may not make your health better. While researchers hope the addition of bevacizumab to the established treatment will be more useful against your brain tumor compared to the usual treatment, there is no proof of this yet. We do know that the information from this study will help researchers learn more about bevacizumab as a treatment for brain tumors. This information could help future cancer patients.

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 brain tumor without being in a study; this could include the standard therapy arm of this trial (radiation plus temozolomide followed by temozolomide)
- Taking part in another study
- Getting no treatment other than close observation and follow-up
- Surgery alone or surgery in combination with radiation treatment and/or other chemotherapy drugs

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

Will my medical information be kept private?

Data will be housed at the Radiation Therapy Oncology Group (RTOG) Headquarters in a password-protected database. If your study doctor is a member of the North Central Cancer Treatment Group (NCCTG), your data will also be kept in a confidential file at NCCTG as applicable. We will do our best to make sure that the personal information in your medical records will be kept private. However, we cannot guarantee total privacy. Your personal information may be given out if required by law. If information from this study is published or presented at scientific meetings, your name and other personal information will not be used. Organizations that may look at and/or copy your medical records for research, quality assurance, and data analysis include:

- RTOG
- Qualified representatives of Genentech, the company that makes bevacizumab
- Local institutional research boards
- The National Cancer Institute (NCI) and other government agencies, like the Food and Drug Administration (FDA), involved in keeping research safe for people
- The American College of Radiology Imaging Network (ACRIN) [the central agency that is storing your MRI/CT scans so that radiologists can evaluate your response to the treatment]
- The central institutional review board (CIRB)

What are the costs of taking part in this study?

You and/or your health plan/insurance company will need to pay for some or all of the costs of treating your cancer in this study. Some health plans will not pay these costs for people taking part in studies. Check with your health plan or insurance company to find out what they will pay for. Taking part in this study may or may not cost your insurance company more than the cost of getting regular cancer treatment. The study agent, bevacizumab or placebo, will be

provided free of charge while you are participating in this study. However, if you should need to take the study agent much longer than is usual, it is possible that the supply of free study agent that has been supplied to the NCI could run out. If this happens, your study doctor will discuss with you how to obtain additional drug from the manufacturer and you may be asked to pay for it. Your health plan may need to pay for costs of the supplies and personnel who give you the bevacizumab or placebo.

You will not receive 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 if you feel that you have been injured because of taking part in this study. You can tell your study doctor in person or call him/her at the number on the cover page.

You will get medical treatment if you are injured as a result of taking part in this study. You and/or your health plan will be charged for this treatment. The study will not pay for medical treatment.

What are my rights if I take part in this study?

Taking part in this study is your choice. You may choose either to take part or not to take part in the study. If you decide to take part in this study, you may leave the study at any time. No matter what decision you make, there will be no penalty to you and you will not lose any of your regular benefits. Leaving the study will not affect your medical care. You can still get your medical care from our institution.

We will tell you about new information or changes in the study that may affect your health or your willingness to continue in the study.

In case of injury resulting from this study, you do not lose any of your legal rights to seek payment by signing this form.

A Data Safety Monitoring Board will be regularly meeting to monitor safety and other data related to this study. The Board members may receive confidential patient information, but they will not receive your name or other information that would allow them to identify you by name.

Who can answer my questions about the study?

You can talk to your study doctor about any questions or concerns you have about this study. Contact your study doctor at the number on the cover page.

For questions about your rights while taking part in this study, call the MultiCare Health System Institutional Review Board (a group of people who review the research to protect your rights) at 253-403-3877.

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) or TTY: 1-800-332-8615

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/>

Please note: This section of the informed consent form is about additional research that is being done with people who are taking part in the main study. You may take part in this additional research if you want to. You can still be a part of the main study even if you say “no” to taking part in this additional research. You can say “yes” or “no” to each of the following studies.

Quality of Life/Neurocognitive Function Study

We want to know your view of how your life has been affected by cancer and its treatment. This “quality of life/neurocognitive function” sub-study looks at how you are feeling physically and emotionally during your cancer treatment. It also looks at how you are able to carry out your day-to-day activities. Patients participating in the main part of the study will be asked to participate by having their symptoms, quality of life, and neurocognitive function evaluated.

This information will help doctors better understand how patients feel during treatments and what effects the medicines are having. In the future, this information may help patients and doctors as they decide which medicines to use to treat cancer.

If you agree to participate in this part of the study, you will be asked to complete a neurocognitive assessment and two quality of life questionnaires at the following times throughout the main part of the study:

- When you register for the study;
- At weeks 6, 10, 22, 34, 46, and 62 of your study treatment; and
- Thereafter, at the same time that you receive your follow-up MRI (or CT) scan (every 3 months after completing treatment for the first year, then every 4 months the second year, and then every 6 months).

The quality of life questionnaires and the symptom assessment will take approximately 30 minutes to complete. If any questions make you feel uncomfortable, you may skip those questions and not give an answer.

If you decide to take part in this sub-study, the only thing you will be asked to do is fill out the questionnaires and undergo the assessment. You may change your mind about completing the questionnaires and undergoing the assessment at any time. You may stop participating in this part of the study at any time without affecting your care or your participation in the main part of the study.

Just like in the main study, we will do our best to make sure that your personal information will be kept private.

Please circle your answer.

I choose to take part in the Quality of Life/Neurocognitive Function Study. I agree to fill out the Quality of Life/Neurocognitive Function Questionnaires.

YES

NO

Consent Form for Use of Tissue, Blood, and Urine for Research

About Using Tissue, Blood, and Urine for Research

You have had surgery to see if you have cancer. Your doctor has removed some tissue to do some tests. The results of these tests will be given to you by your doctor and will be used to plan your care. We plan to examine the block of tumor tissue to confirm that the tumor is a glioblastoma and to use the tissue to evaluate the genetic (molecular) profile. These studies are essential components of the clinical trial and therefore permission to use the tissue block for this purpose is mandatory.

We would like to keep some of the tissue that is left over for future research. If you agree, this tissue will be kept and may be used in research to learn more about brain tumors. Please read the information sheet called "How is Tissue Used for Research" to learn more about tissue research. This information sheet is available to all at the following web site:

http://www.rtog.org/tissue%20for%20research_patient.pdf

As a result of your participation in the trial, you also will have blood tests performed before you start treatment. We would like to keep for future research about three tablespoons of the blood taken at that time. If you agree, this blood will be kept and may be used in research to learn more about cancer and other diseases.

In addition, we would like to keep some of your urine for future research. We would collect your urine at the following times: before you start treatment, 1 month after you start treatment with radiation and temozolomide, and 1 month after you start the randomized part of the trial. We would keep about five tablespoons of urine at each of these times. If you agree, the urine will be kept and may be used in research to learn more about cancer and other diseases.

The research that may be done with your tissue, blood, and urine is not designed specifically to help you. It might help people who have brain tumors and other diseases in the future. Reports about research done with your tissue, blood, and urine will not be given to you or your doctor. These reports will not be put in your health record. This research will not have an effect on your care.

Things to Think About

The choice to let us keep the left over tissue, blood, and urine for future research is up to you. No matter what you decide to do, it will not affect your care.

If you decide now that your tissue, blood, and urine can be kept for research, you can change your mind at any time. Just contact us and let us know that you do not want us to use your tissue, blood, and urine. Then any tissue that remains will be returned to the institution that submitted it.

In the future, people who do research may need to know more about your health. While the Radiation Therapy Oncology Group may give them reports about your health, it will not give them your name, address, phone number, or any other information that will let the researchers know who you are.

Sometimes tissue, blood, and urine are used for genetic research. Even if your tissue, blood, and urine are used for this kind of research, the results will not be put in your health records.

Your tissue, blood, and urine will be used only for research and will not be sold. The research done with your tissue, blood, and urine may help to develop new products in the future.

Benefits

The benefits of research using tissue, blood, and urine include learning more about what causes brain tumors and other diseases, how to prevent them and how to treat them.

Risks

The greatest risk to you is the release of information from your health record. We will do our best to make sure that your personal information will be kept private. The chance that this information will be given to someone else is very small.

Making Your Choice

Please read each sentence below and think about your choice. After reading each sentence circle "Yes" or "No". If you have any questions, please talk to your study doctor or nurse, or call our research review board at 253-403-3877.

No matter what you decide to do, it will not affect your care. If you agree that your tissue, blood, and urine may be used for research, you can change your mind at any time if you give a written request to your study doctor.

1. My tissue, blood, and urine may be kept for use in research to learn about, prevent, or treat brain tumors.

Yes No

2. My tissue, blood, and urine may be kept for use in research to learn about, prevent or treat other health problems (for example: diabetes, Alzheimer's disease, or heart disease).

Yes No

3. Someone may contact me in the future to ask me to take part in more research.

Yes No

Consent Form for ACRIN 6686: Advanced Imaging Sub-Study

[LIMITED INSTITUTIONS: Potential participants at advanced imaging-qualified institutions must be asked to consider the Advanced MR component and, if amenable, consent to the advanced imaging sequence]

About Advanced Imaging in the Study

In addition to the standard imaging you are being asked to undergo in the RTOG 0825 study, you are being asked to participate in an advanced MRI study. A total of 264 patients will be included in the advanced imaging portion of the study.

Researchers hope that the advanced MRI will help them learn more about how blood is supplied to the cancer and the tumor's response to the investigational treatment. The advanced MRI will take more time to complete (each examination takes between 45 and 60 minutes) than the regular MRI examinations.

Advanced imaging will take place at four (4) time points:

Within 5 days of starting chemoradiation



Within a couple of days of receiving either placebo or bevacizumab



The day of or the day after you receive the placebo or bevacizumab



*Seven weeks later, after you have received several cycles of the study treatment
(after you are done with chemoradiation)*

MRI examinations require that you lie flat in the MR scanner while imaging is performed. During this time, you will receive an intravenous (through a tube placed in a vein in your arm) medication, called gadolinium that helps doctors see areas of blood flow to tumors.

Risks

MRI. For most patients, there are no specific risks associated with MRI scanning, but some may experience anxiety, stress, claustrophobia, or discomfort. You will not be allowed to have an MRI scan if you have certain types of metallic or electrical devices (such as a pacemaker or certain aneurysm clips) placed in your body. If you had previous surgery to your heart or brain, doctors will determine whether the MRI is safe for you. You will not be allowed to have an MRI if you have any metal pieces in your brain, spinal cord, or eyes. If your job has ever placed you at risk for exposure to metallic fragments (such as metal working or welding), doctors will perform an x-ray of your eyes prior to the study to determine that MRI is safe for you.

Gadolinium Contrast Agent. The gadolinium used during the MRI is an FDA-approved MRI contrast agent with very few side effects. The dose used in the advanced MRI tests is "double dose," which is injected rapidly. Some but not all MRI contrast agents have been FDA-approved for double dose, but double dose of all of these agents has been used in many hospitals around the world without evidence of negative effects from the increased dose. Approximately 2 percent of participants experience some side effects with the use of

gadolinium; however, they are mostly mild (nausea, headache, hives, temporary low blood pressure).

Serious side effects are very rare. In very rare cases a condition called nephrogenic systemic fibrosis (NSF)/nephrogenic fibrosing dermopathy (NFD) has been reported. NSF and NFD are conditions associated with the gadolinium contrast agent that affects people who have severe kidney disease. Symptoms include tightening or scarring of the skin and organ failure. In some cases, NSF and NFD can be deadly. These conditions have not been seen in patients with normal working kidneys or mild problems in kidney function. Prior to study entry and throughout the study and your treatment, we will determine if your kidneys are working properly in order to make sure the gadolinium contrast agent is safe for you. You will receive prompt medical attention for any reactions to the contrast agent.

Benefits

You will not directly benefit from the results of the advanced imaging study, but we hope that the results will help other people with brain cancer in the future. The results of the advanced MRI central reviews will not be sent to you or your doctor and will not be used to determine your treatment. You or your insurance company will not be charged for these MRI scans.

Making Your Choice

If you decide to participate in the study, these advanced images will be part of the study. We will do our best to make sure that the personal information in your medical record will be kept private. However, we cannot guarantee total privacy. Your personal information may be given out if required by law. If information from this study is published or presented at scientific meetings, your name and other personal information will not be used.

Records of your progress while on the study will be kept in a confidential form at this institution and in a computer file at the headquarters of the American College of Radiology Imaging Network (ACRIN) in Philadelphia, PA. Copies of your MR images will be permanently kept on file at ACRIN. This information will be used for research purposes only. All identifying information will be taken off of the films to maintain confidentiality. Future research studies may be conducted on other aspects of the data collected during the study. At this time it is not known what type of studies may be conducted. Some possibilities may be issues affecting patient care or future studies of a medical or non-medical nature.

Where Can I Get More Information?

For more information about MRI scans you can go to ACRIN's Web site at http://www.acrin.org/files/mri_description.doc. You or your doctor can print a description of MRI scans from this Web site.

You may call the National Cancer Institute's Cancer Information Service at:
1-800-4-CANCER (1-800-422-6237) or TTY: 1-800-332-8615

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/>

Please circle your answer.

If I qualify, I choose to take part in the ACRIN 6686 advanced MRI study that is being done for research as a part of the RTOG 0825 treatment study.	
Yes	No

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

I have been given a copy of all pages 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.

_____	_____	_____
Patient's name (printed or typed)	Patient's Signature	Date
_____	_____	_____
Physician name (printed or typed)	Physician Signature	Date
_____	_____	_____
Signature of person conducting the Informed consent discussion	Date	

Authorization to Use or Disclose (Release) Identifiable Health Information For Research

Participant's Name: _____

Birthdate: _____

1. What is the purpose of this form?

The Cancer Trials Support Unit (CTSU) is an organization that does research to learn about the causes of cancer, and how to prevent and treat cancer. Researchers would like to use your health information for research. This information may include data that identifies you. Please carefully review the information below. If you agree that researchers can use your identifiable health information, you must sign and date this form to give them your permission.

2. What health information do the researchers want to use?

The researchers want to abstract and use the portions of your medical record that they will need for their research. If you enter a CTSU research study, information that will be used and/or released may include your complete medical record, and in particular, the following:

- the history and diagnosis of your disease
- specific information about treatments you received
- information about other medical conditions that may affect your treatment
- medical data, including laboratory test results, tumor measurements, CT scans, MRIs, X-rays, photographs of radiation therapy target areas, and pathology results
- information on side effects (adverse events) you may experience, and how these were treated
- long-term information about your general health status and the status of your disease
- tissue and/or blood samples, associated data related to the analysis of the samples

You may request a blank copy of the CTSU data forms from the Northwest CCOP to learn what information will be shared.

3. Why do the researchers want my health information?

The Northwest CCOP will collect your health information and share it with the CTSU if you enter a Cooperative Group research study, or to evaluate your eligibility for a study. The CTSU researchers will use your information for the following cancer research study. You are being asked to take part in a study known as **CIRB R0825: PHASE III DOUBLE-BLIND PLACEBO-CONTROLLED TRIAL OF CONVENTIONAL CONCURRENT CHEMORADIATION AND ADJUVANT TEMOZOLOMIDE PLUS BEVACIZUMAB VERSUS CONVENTIONAL CONCURRENT CHEMORADIATION AND ADJUVANT TEMOZOLOMIDE IN PATIENTS WITH NEWLY DIAGNOSED GLIOBLASTOMA.**

4. Who will be able to use my health information?

The Northwest CCOP will use your health information for research. As part of this research, they may give your information to the following Groups taking part in the research. The Northwest CCOP may also permit staff from these Groups to review your original records as required by law for audit purposes.

the Cancer Trials Support Unit (CTSU), a research group sponsored by the National Cancer Institute (NCI) to provide greater access to cancer trials
Radiation Therapy Oncology Group (RTOG)
public health agencies and other government agencies (including non-U.S.) as authorized or required by law
other people or organizations assisting with CTSU research efforts and the Food and Drug Administration
central laboratories, central review centers, and central reviewers. The central laboratories and review agencies may also give your health information to those groups listed above.

5. *How will information about me be kept private?*

The CTSU will keep all identifiable health information confidential to the extent possible, even though they and other federal research groups are not subject to the same federal privacy laws governing clinical centers. The CTSU will not release identifiable health information about you to others except as authorized by this form, or required by law. If your identifiable health information must be shared with other organizations, the privacy laws that govern those organizations would apply.

6. *What happens if I do not sign this authorization form?*

If you do not sign this authorization form, you will not be able to take part in a research study for which you are being considered.

7. *If I sign this form, will I automatically be entered into the research study?*

No, you cannot be entered into any research study without further discussion and separate consent. After discussion, you may decide to take part in the research study. At that time, you will be asked to sign a separate research consent form.

8. *What happens if I want to withdraw my authorization?*

You can change your mind at any time and withdraw this authorization. This request for withdrawal must be made in writing. Beginning on the date you withdraw your authorization, no new identifiable health information will be used for research. However, researchers may continue to use the health information that was provided before you withdrew your permission.

If you sign this form and enter the research study, but later change your mind and withdraw your authorization, you will be removed from the research study at that time.

To withdraw your authorization, please contact the person below. She will make sure your written request to withdraw your authorization is processed correctly.

Karyn Hart, RHIT, CCRP
Clinical Research Associate Supervisor
Northwest CCOP
315 Martin Luther King Jr., Way
Tacoma, WA 98405
(253) 403-1461

9. How long will this authorization last?

If you agree by signing this form that researchers can use your identifiable health information, this authorization has no expiration date. However, as stated above, you can change your mind and withdraw your permission at any time.

10. What are my rights regarding my identifiable health information?

You have the right to refuse to sign this authorization form. You have the right to review and/or copy records of your health information kept by the Northwest CCOP. You do not have the right to review and/or copy records kept by the CTSU or other researchers associated with the research study.

Signatures

I agree that my identifiable health information may be used and disclosed for research purposes described in this form.

Signature of Patient or
Patient's Legal Representative: _____ Date: _____

Printed Name of Legal Representative (if any): _____

Representative's Authority to Act for Patient: _____

Signature of Person Obtaining Authorization: _____

Printed Name of Person Obtaining Authorization: _____