NRG ONCOLOGY
Radiation Therapy Oncology Group

RTOG 1205

(ClinicalTrials.gov NCT #:* 01730950*)

Randomized Phase II Trial of Concurrent Bevacizumab and Re-Irradiation Versus Bevacizumab Alone as Treatment for Recurrent Glioblastoma

Amendment 8: October 3, 2016

Sample consent form version: October 3, 2016
To be attached to protocol version: October 3, 2016

Informed Consent Template for Cancer Treatment Trials (English Language)

RTOG 1205

Randomized Phase II Trial of Concurrent Bevacizumab and Re-Irradiation Versus Bevacizumab Alone as Treatment for 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 people who choose to take part. Please take your time to make your decision about taking part. You may discuss 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, called a glioblastoma or gliosarcoma, which has become worse after previous treatment.

Why is this study being done?

Bevacizumab is a commercially available drug that is FDA approved for the treatment of glioblastoma that has returned after treatment (recurrent glioblastoma). However, treatment with bevacizumab alone has only modestly improved survival in patients with this type of brain tumor. For this reason, researchers are evaluating other treatments, including bevacizumab combined with radiation. The purpose of this study is to determine whether adding radiation to bevacizumab is more effective than using bevacizumab alone to treat recurrent glioblastomas..

In this trial patients will be randomly assigned to receive either bevacizumab alone or bevacizumab and radiation therapy.

How many people will take part in the study?

About 178 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 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.

- Magnetic resonance imaging (MRI) or computed tomography (CT) scan of the brain
    - An MRI is imaging using a strong magnetic field to look at one part of your body

    - A CT scan is a study using x-rays to look at one part of your body
- Laboratory tests for
    - Blood counts
    - Kidney function
    - Liver function
    - A sample of your urine will be tested
- History/physical examination
- Neurologic examination
- Evaluation of your ability to carry out daily activities
- Pregnancy test (if you are a woman of child-bearing potential)

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 tests and procedures. They are part of regular cancer care.

- Physical examination
- Neurologic examination
- Evaluation of your ability to carry out daily activities
- Laboratory tests for blood count and evaluation of urine
- MRI/CT scan
- Blood pressure monitoring

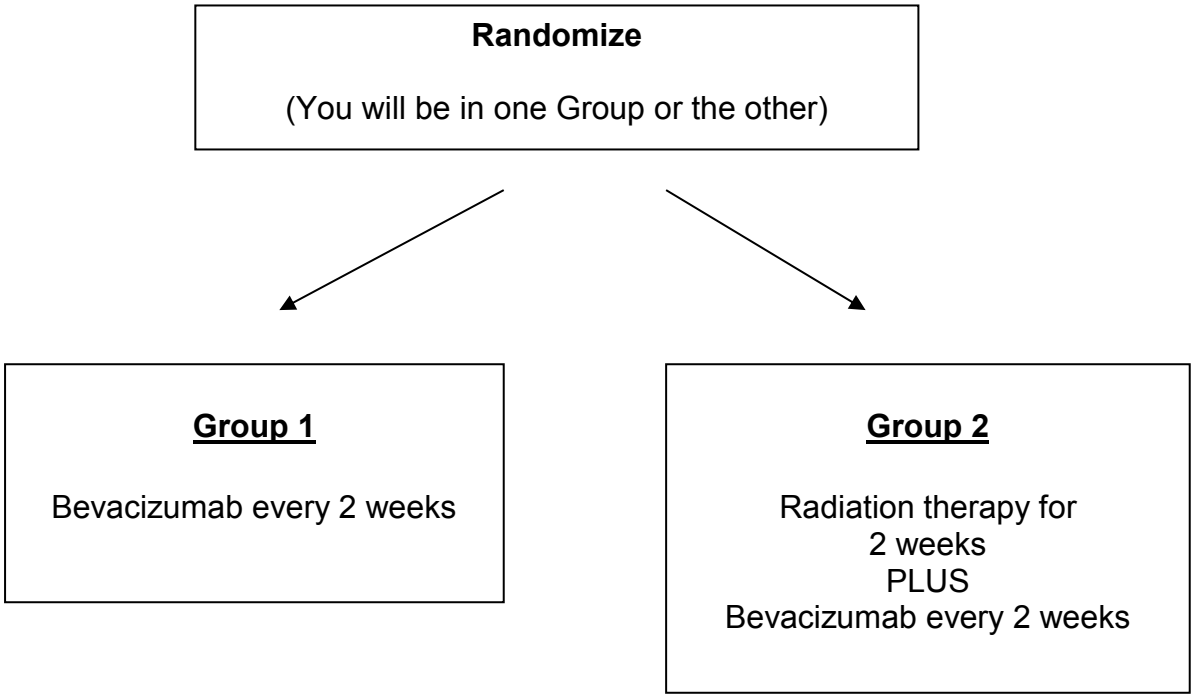
You will be "randomized" into one of the study groups described below. Randomization means that you are put into a group by chance. A computer program will place you in one of the study groups. Neither you nor your doctor can choose the group you will be in. You will have an equal chance of being placed in either group.

If you are in group 1 (often called "Arm 1"), you will receive bevacizumab alone. The bevacizumab will be given by vein (intravenously) every 2 weeks for as long as it is working and there are no intolerable side effects..

If you are in group 2 (often called "Arm 2"), you will receive bevacizumab and radiation therapy. The bevacizumab will be given by vein (intravenously) every 2 weeks for as long as it is working and there are no intolerable side effects. You will receive 10 treatments of radiation, which will be delivered daily (typically 5 treatments per week), for 2 weeks.

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.



How long will I be in the study?
If you are in Group 1, you will be asked to take bevacizumab alone every two weeks as long as it is working and there are no intolerable side effects. If you are in Group 2, you will take bevacizumab 2 weeks before radiation therapy, during radiation therapy, and then every 2 weeks after radiation therapy as long as it is working and there are no intolerable side effects. The radiation will be given to you over 2 weeks.

You will be followed every 8 weeks while on treatment and then also if you are removed from protocol treatment. Follow-up will continue every 8 weeks for 1 year, then every 6 months for 1 year, then annually. If you are unable to be seen in clinic by your study doctor, you may be contacted by the study doctor or the clinic staff.

Can I stop being in the study?

Yes. You can decide to stop at any time. Tell the 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 the study doctor if you are thinking about stopping so any risks from the bevacizumab or radiation plus bevacizumab can be evaluated by your doctor.

Another reason to tell your doctor that you are thinking about stopping is to discuss what follow-up care and testing could be most helpful for you.

The 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.

What side effects or risks can I expect from being in the study? (10/3/16)

If you choose to take part in this study, there is a risk that:

- You may lose time at work or home and spend more time in the hospital or doctor's office than usual
- You may be asked sensitive or private questions which you normally do not discuss

The radiation and bevacizumab used in this study may affect how different parts of your body work such as your liver, kidneys, heart, and blood. The study doctor will be testing your blood and will let you know if changes occur that may affect your health.

There is also a risk that you could have side effects from the study drug(s)/study approach.

Here are important points about side effects:

- The study doctors do not know who will or will not have side effects.
- Some side effects may go away soon, some may last a long time, or some may never go away.
- Some side effects may interfere with your ability to have children.
- Some side effects may be serious and may even result in death.

Here are important points about how you and the study doctor can make side effects less of a problem:

- Tell the study doctor if you notice or feel anything different so they can see if you are having a side effect.
- The study doctor may be able to treat some side effects.
- The study doctor may adjust the study drugs to try to reduce side effects.

The tables below show the most common and the most serious side effects that researchers know about. There might be other side effects that researchers do not yet know about. If important new side effects are found, the study doctor will discuss these with you.

Possible Side Effects of Radiation to the Brain (6/23/14)

COMMON, SOME MAY BE SERIOUS In 100 people receiving radiation to the brain, more than 20 and up to 100 may have:
• 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

OCCASIONAL, SOME MAY BE SERIOUS In 100 people receiving radiation to the brain, from 4 to 20 may have:
• 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, AND SERIOUS In 100 people receiving radiation to the brain, 3 or fewer may have:
• 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)

Possible Side Effects of Bevacizumab (10/3/16)

Table Version Date: May 23, 2016

COMMON, SOME MAY BE SERIOUS In 100 people receiving bevacizumab, more than 20 and up to 100 may have:
• High blood pressure which may cause headache or blurred vision

OCCASIONAL, SOME MAY BE SERIOUS In 100 people receiving bevacizumab, from 4 to 20 may have:

- Anemia which may require blood transfusion
- Low white cell count that may increase the risk of infection
- Infection, including collection of pus in the belly or rectum
- Abnormal heartbeat which may cause palpitations or fainting
- Pain in the belly, rectum, chest, joints, muscles, or tumor
- Low appetite, constipation, diarrhea, heartburn, nausea, vomiting, or dehydration
- Internal bleeding which may cause black tarry stool, blood in vomit, coughing up blood, or blood in urine
- Bleeding from other sites, including the vagina or nose
- Blockage of internal organs which may cause vomiting or inability to pass stool
- Sores in the mouth
- Allergic reaction during or after infusion of bevacizumab which may cause fever, chills, rash, itching, hives, low blood pressure, wheezing, shortness of breath, swelling of the face or throat
- Delay in healing of wounds or spontaneous opening of wounds
- Weight loss, tiredness, or dizziness
- Muscle weakness
- Damage to organs which may cause loss of teeth or loss of motion
- Headache
- Numbness, tingling or pain in the fingers or toes
- Hoarseness, stuffy nose, or cough
- Dry skin
- Swelling and redness of the skin
- Blood clot in limbs or lungs which may cause swelling, pain, shortness of breath
- Leakage of protein in the urine, which can rarely lead to damage to the kidney

RARE, AND SERIOUS

In 100 people receiving bevacizumab, 3 or fewer may have:

- Clots in the arteries, causing stroke (which may cause paralysis or weakness) or heart attack (which may cause chest pain or shortness of breath). This risk is significantly increased in patients who are elderly or with history of diabetes
- Heart failure which may cause shortness of breath, swelling of ankles, and tiredness
- Bowel perforation (a tear in the bowel) that can cause pain or bleeding and require surgery to repair
- A tear or hole (fistula) in internal organs such as the nose, throat, lungs, esophagus, rectum, or vagina. These conditions may cause serious infections or bleeding and require surgery to repair
- Sores in the throat
- Flesh-eating bacteria syndrome, an infection in the deep layers of skin
- Bleeding in the tumor, brain, belly or lungs which may cause confusion, blood in stool or coughing up blood
- Brain damage which may cause headache, seizure, blindness (also known as Reversible Posterior Leukoencephalopathy Syndrome)
- Kidney damage which may require dialysis
- Redness, pain or peeling of palms and soles

Additional Notes on Possible Side Effects for Bevacizumab:

- Risk in children or adolescents: abnormal bone changes which may interfere with growth.
- Risk in pre-menopausal women: more likely to develop menopause when taking bevacizumab.

Reproductive risks: You should not become pregnant or father a baby while on this study and for at least 6 months after because the drugs in this study can affect an unborn baby. 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. Women should not breastfeed a baby while on this study. It is important you understand that you need to use birth control while on this study.

Check with your study doctor about what kind of birth control methods to use and how long to use them. Some methods might not be approved for use in this study. If you would like to have children in the future, you should talk to your physician about this. **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 doctors hope that adding radiation to bevacizumab will be more useful against cancer compared to bevacizumab alone, there is no proof of this yet. We do know that the information from this study will help doctors learn more about combining bevacizumab and radiation as a treatment for cancer. 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 cancer without being in a study
- Taking part in another study
- Getting no treatment
- Other chemotherapies your physician can discuss with you.

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? (4/15/14)
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.

Organizations that may look at and/or copy your medical records for research, quality assurance, and data analysis include:

- NRG Oncology
- The National Cancer Institute (NCI) and other government agencies, like the Food and Drug Administration (FDA), involved in keeping research safe for people

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.

[Note to Informed Consent Authors: the above paragraph complies with the new FDA regulation found at 21 CFR 50.25(c) and must be included verbatim in all informed consent documents. The text in this paragraph cannot be revised.]

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.

Bevacizumab is FDA-approved for recurrent glioblastoma and will be billed to your insurance company. Radiation therapy will be billed to your insurance company. All study related procedures are part of standard monitoring for patients and will be billed to your insurance company.

You will not be paid 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].*

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

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 _____ *[name(s)]* at _____ *[telephone number].*

For questions about your rights while taking part in this study, call the _____ *[name of center]* Institutional Review Board (a group of

people who review the research to protect your rights) at _____ *(telephone number). [Note to Local Investigator: Contact information for patient representatives or other individuals in a local institution who are not on the IRB or research team but take calls regarding clinical trial questions can be listed here.]*

*You may also call the Operations Office of the NCI Central Institutional Review Board (CIRB) at 888-657-3711 (from the continental US only). *[*Only applies to sites using the CIRB.]*

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

You can say "yes" or "no" to each of the following studies. Please mark your choice for each study.

Consent Form for Use of Tissue for Research

About Using Tissue for Research (8/20/15)

You have had a biopsy (or surgery) to see if you have cancer. Your doctor removed some body tissue to do some tests. The results of these tests were given to you by your doctor and will be used to plan your care.

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 cancer and other diseases.

In addition to the tumor tissue, if you agree, you will have blood drawn before you start treatment and at 8 weeks after you begin treatment. We would like to keep about 2 tablespoons of blood at each of these times. Urine will be collected before you start treatment and at 8 weeks after you begin treatment also. This blood and urine will be kept to be used in research to learn more about cancer and other diseases.

Your tissue/blood/urine may be helpful for research whether you do or do not have cancer. The research that may be done with your tissue/blood/urine is not designed specifically to help you. It might help people who have cancer and other diseases in the future.

Reports about research done with your tissue will not be given to you or your doctor. These reports will not be put in your health record. The research will not have an effect on your care.

Things to Think About

The choice to let us keep the left over tissue/blood/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/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/urine. Then any tissue/blood/urine that remains will no longer be used for research; any remaining tissue will be returned and any remaining blood and urine will be destroyed.

In the future, people who do research may need to know more about your health. While the doctor/institution 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/urine is (are) used for genetic research (about diseases that are passed on in families). Even if your tissue/blood/urine is (are) used for this kind of research, the results will not be put in your health records.

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

Benefits

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

Risks (11/20/13)
The greatest risk to you is the release of information from your health records. 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.

Some of your genetic and health information may be placed in central databases that may be public, along with information from many other people. Information that could directly identify you will not be included. The samples are given a code to protect your privacy before they are used. Any related information given to researchers will also be coded. Researchers will receive the code instead of any information that might directly identify you.

There can be a risk in knowing genetic information. New health information about inherited traits that might affect you or your blood relatives could be found during a research study. Even though your genes are unique, you share some of the same genes with your blood relatives.

Although we are not able to know all of the risks from taking part in research on inherited traits, we believe that the risks to you and your family are very low, because your samples will be coded. Research results will not be returned to you or your doctor.

Very rarely health or genetic information could be misused by employers, insurance companies, and others. For example, life insurance companies may charge a higher rate based on this information.

Many states have laws to protect against genetic discrimination *[list appropriate state information if your state or locality has such laws]*. Additionally, a federal law called the Genetic Information Non-Discrimination Act, or GINA, is in effect. This law prohibits health insurer or employer discrimination. The law does not include other types of misuse by life insurance, disability, or long term care insurance. To learn more about the GINA Law, please ask *[Note to local investigator: Contact information for patient representatives or other individuals in a local institution who are not on the IRB or research team but take calls regarding clinical trial questions can be listed here.]*

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 doctor or nurse, or call our research review board at IRB's phone number.

No matter what you decide to do, it will not affect your care.

1. My specimens may be kept for use in research to learn about, prevent, or treat cancer, as follows:
   - Tissue ☐Yes ☐ No
   - Blood ☐Yes ☐ No
   - Urine ☐Yes ☐ No

2. My specimens 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), as follows:
   - Tissue ☐Yes ☐ No
   - Blood ☐Yes ☐ No
   - Urine ☐Yes ☐ No

3. Someone may contact me in the future to ask me to take part in more research.
   ☐Yes ☐ No

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 all _____ *[insert total of number of pages]* 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.

Participant _____

Date _____