RTOG FOUNDATION

RTOG 3503

(ClinicalTrials.gov NCT #: **02743078***)*

PHASE II TRIAL OF OPTUNE® PLUS BEVACIZUMAB IN BEVACIZUMAB-REFRACTORY RECURRENT GLIOBLASTOMA

Amendment 5: December 12, 2017

Sample consent form version: December 12, 2017
To be attached to protocol version: December 12, 2017

Consent Form

Study Title for Study Participants: Testing the benefit of tumor treating fields Optune® therapy in glioblastoma that has progressed after treatment with bevacizumab

<<PI_FIRST_NAME>> <<PI_LAST_NAME>>
<<PHONE_NUMBER>>

Official Study Title for Internet Search on http://www.ClinicalTrials.gov:

RTOG Foundation Study 3503, Phase II Trial of Optune® Plus Bevacizumab in Bevacizumab-Refractory Recurrent Glioblastoma

What is the usual approach to my brain tumor*?*

You are being asked to take part in this study because you have a glioblastoma (a type of brain tumor) that has grown back (recurred) or not gotten better after being treated with bevacizumab. People who are not in a study are usually treated with a combination of chemotherapy or some form of radiation if their tumors recur after treatment with bevacizumab. For patients who receive the usual approach for this cancer, between 2 and 15 out of 100 are free of further cancer growth at 6 months and on average 0 out of 100 are free of further cancer growth at 2 years.

What are my other choices if I do not take part in this study?

If you decide not to take part in this study, you have other choices. For example:

- you may choose to have the usual approach described above
- you may choose to take part in a different study, if one is available
- or you may choose not to be treated for cancer but you may want to receive comfort care to relieve symptoms.

Why is this study being done?

Bevacizumab is a commercially available drug that is FDA (U.S. Food and Drug Administration) approved for the treatment of glioblastoma that has returned after treatment (recurrent glioblastoma). However, treatment with bevacizumab alone has not improved survival in patients with this type of brain tumor by a lot. For this reason, researchers are evaluating other treatments, including bevacizumab combined with other therapies.

The purpose of this study is to test any good and bad effects of adding bevacizumab to a type of therapy for brain tumors called Optune. Optune is a portable device that produces electrical signals, called Tumor Treating Fields ("TTFields"). The use of the Optune device in this study is considered investigational. Although Optune is FDA approved for use in treating newly diagnosed and recurrent glioblastoma, it is intended for use alone for patients with recurrent tumors after failing standard therapies and with temozolomide in newly diagnosed patients. Optune is not approved by the FDA for use with bevacizumab.

Optune uses very low intensity, "wave-like" electric signals to slow or stop cancer cell growth. The Optune device administers therapy through electrodes applied to the head of the patient. Because cancer cells are dividing, Optune affects cancer cells and generally does not harm healthy cells.

The addition of Optune to bevacizumab could shrink your tumor or prevent it from growing, but it could also cause side effects. This study will allow the researchers to know whether this different approach is better, the same, or worse than the usual approach. To be better, the addition of Optune to bevacizumab would increase life by 2 months or more compared to the usual approach of using chemotherapy.

For some patients, it may be possible to receive this combination treatment of Optune and bevacizumab together without participating in a study. This is called "off label" use because it is not an FDA approved combination treatment and it has not been formally studied to determine if it is better than the usual treatment.

There will be about 85 people taking part in this study.

What are the study groups?

Before any study-related tests and procedures are performed, you will be asked to read and sign this consent document. All study participants will receive bevacizumab (10 mg/kg) intravenously (by inserting a needle into a vein in your arm) once every 2 weeks over 30 minutes on a 4 – week cycle, along with Optune. Bevacizumab is a usual treatment for patients with recurrent glioblastoma. Optune is experimental for patients with recurrent glioblastoma when used in combination with bevacizumab.

Optune is a portable device worn on your head that includes special adhesive electrodes called "transducer arrays" that send wave-like electric signals directly into your tumor. The layout of the electrodes will be mapped to the location of your tumor. The electrodes are placed directly on your scalp as part of an adhesive bandage that covers your head. You will be required to shave your head in order to place the arrays. Optune also includes a portable battery, a carrying case, a battery charger, power cords, and a connection cable. You will receive training and support to learn how to use the device from both your study team and the Optune support team. You will wear Optune continuously throughout the day for at least 18 hours a day with breaks allowed for personal needs. The transducer arrays will be replaced 2 to 3 times per week with help of a caregiver. The device records your time on therapy to help you meet the treatment goal.

How long will I be in this study?

You will receive the study treatment for as long as it is working and there are no intolerable side effects. After you finish the study treatment, your doctor will continue to watch you for side effects and follow your condition indefinitely.

What possible risks can I expect from taking part in this study? **(9/13/16)**

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
- The study approach may not be better, and could possibly be worse, than the usual approach for your cancer.

The treatment 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 drug 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 bevacizumab, which is a usual approach for this type of cancer:

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 • Dry mouth, low appetite, constipation, diarrhea, heartburn, nausea, vomiting, or dehydration • Changes in taste • Internal bleeding which may cause black tarry stool, blood in vomit, coughing up of 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 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 bones which may cause loss of teeth or loss of motion • Headache • Numbness, tingling, or pain in the fingers or toes • Hoarseness, voice changes, stuffy or runny nose, or cough • Dry skin • Swelling and redness of the skin • Blood clot in limbs or lungs which may cause swelling, pain, or 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, or 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.

Possible side effects of Optune therapy, which is an experimental approach for this type of cancer when used in combination with bevacizumab

COMMON, SOME MAY BE SERIOUS In 100 people receiving Optune Therapy, more than 20 and up to 100 may have:
• Skin irritation, swelling, itching, and redness in the area of the transducers

OCCASIONAL, SOME MAY BE SERIOUS In 100 people receiving Optune Therapy, from 4 to 20 may have:
• Malaise (feeling of discomfort or uneasiness) • Muscle twitching • Fall • Skin ulcer • Rash • Headache • Seizures • Tiredness • Infection • Allergic reaction to the adhesive

RARE, AND SERIOUS In 100 people receiving Optune Therapy, 3 or fewer may have:
• Blood clot which may cause swelling, pain, shortness of breath • Pain, burn at the site of the transducers

Do not use Optune if you are known to be sensitive to conductive gels like the gel used on EKG stickers. In this case, skin contact with the gel used with Optune may cause increased redness and itching, and rarely may lead to severe allergic reactions such as shock and breathing problems.

Falls have been reported by patients using the Optune system. Patients wearing the portable device should be cautious of the wires and be sure the portable equipment is secure and comfortable prior to walking to prevent tripping and falls.

Let your study doctor know of any questions you have about possible side effects. You can ask the study doctor questions about side effects at any time.

Reproductive risks: You should not get pregnant, breastfeed, or father a baby while in this study. The treatments used in this study could be very damaging to an unborn baby. Check with the study doctor about what types of birth control, or pregnancy prevention, to use while in this study. Women of childbearing potential must use an adequate method to avoid pregnancy while receiving bevacizumab and for 180 days after the last dose of bevacizumab. Men must use an adequate method to avoid pregnancy while receiving bevacizumab and for 90 days after the last dose of bevacizumab.

What possible benefits can I expect from taking part in this study?

It is not possible to know at this time if the study approach is better than the usual approach so this study may or may not help you. This study will help researchers learn things that will help people in the future.

Can I stop taking part in this study?

Yes. You can decide to stop at any time. If you decide to stop for any reason, it is important to let the study doctor know as soon as possible so you can stop safely. If you stop, you can decide whether or not to let the study doctor continue to provide your medical information to the organization running the study.

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

The study doctor may take you out of the study:

- If your health changes and the study is no longer in your best interest
- If new information becomes available
- If you do not follow the study rules
- If the study is stopped by the sponsor, IRB or FDA.

What are my rights in this study?

Taking part in this study is your choice. No matter what decision you make, and even if your decision changes, there will be no penalty to you. You will not lose medical care or any legal rights.

For questions about your rights while in this study, call the _____ *(insert name of center)* Institutional Review Board at _____ *(insert telephone number). (Note to Local Investigator: Contact information for patient representatives or other individuals at a local institution who are not on the IRB or research team but take calls regarding clinical trial questions can also be listed here.)*

What are the costs of taking part in this study?(12-DEC-2017)

As the participant in this study, you will not have any out of pocket costs related to the rental of the Optune System if you have Medicare or Medicaid, insurance that covers such costs, or you qualify for financial assistance provided by Novocure, the manufacturer of Optune. If you have insurance, you may have coverage for Optune while participating in this clinical trial and Novocure will attempt to seek reimbursement from your insurance company for use in this clinical trial. If your insurance company does not provide coverage for Optune or your financial cost share would be unaffordable, you may be eligible for need-based financial assistance. It is recommended that you contact Novocure prior to signing this consent at 855-282-9301 in order to understand your potential financial responsibility prior to signing this consent. If your insurance company or Novocure do not provide coverage for Optune, then you will be responsible for the costs of the Optune rental.

You and/or your health plan/insurance company will need to pay for all of the other costs of your cancer while in this study, including the cost of tests, procedures, chemotherapy, or medicines to manage any side effects, unless you are told that certain tests are supplied at no charge. Before you decide to be in the study, you should check with your health plan or insurance company to find out exactly what they will pay for.

You will not be paid for taking part in this study.

What happens if I am injured or hurt because I took part in this study? (12-DEC-2017)

If you get physically ill or injured as the direct result of being in this study, then, depending on what insurance you may have, the company providing the device, Novocure, will pay for the reasonable and necessary costs for your immediate medical treatment of the illness or injury if it:

(a) is not a medical condition that you had before you started the study;
(b) is not the result of the natural progress of your disease or condition;
(c) is not caused by your failure to follow the study plan; and
(d) is not proven to be directly caused by the negligence of a [*site*] employee. "Negligence" is the failure to follow a standard duty of care.

If your case meets all four of these requirements and you are uninsured or have Medicare or Medicaid, then Novocure will pay all of the costs of your medical treatment for the illness or injury. If you have Medicare or Medicaid, Novocure may need information about your identity and your treatment. They will give this information to the government agencies that run these programs.

If your case meets all four of these requirements and you have private insurance, your insurer may be told that you are in a research study and given information about your treatment. You will have to pay for any costs that Novocure or your insurer does not pay. Novocure will not pay for costs such as co-payments that your insurer says you have to pay.

If you feel this injury was a result of medical error, you will not lose any of your legal rights or release the Sponsor, the study doctor, the study staff, or study site from liability for mistakes or intentional misconduct by signing this consent document.

Who will see my medical information?

Your privacy is very important to us and the researchers will make every effort to protect it. Your information may be given out if required by law. For example, certain states require doctors to report to health boards if they find a disease like tuberculosis. However, the researchers will do their best to make sure that any information that is released will not identify you. Some of your health information, and/or information about your specimen, from this study will be kept in a central database for research. Your name or contact information will not be put in the database.

There are organizations that may inspect your records. These organizations are required to make sure your information is kept private, unless required by law to provide information. Some of these organizations are:

- The study sponsor (RTOG Foundation Inc.)
- Novocure, the manufacture of Optune, which is supporting the study
- The Institutional Review Board, IRB, which is a group of people who review the research with the goal of protecting the people who take part in the study.
- The Food and Drug Administration, (FDA), the federal agency that regulates use of drugs and devices in the United States.

If a study staff witnesses or believes that you have been a victim of abuse, neglect, domestic violence, or exploitation in the home environment a protective services agency or government authorities will be notified as required by law.

Where can I get more information?

You may visit the NCI Web site at http://cancer.gov/ for more information about studies or general information about cancer. You may also call the NCI Cancer Information Service to get the same information at: 1-800-4-CANCER (1-800-422-6237).

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.

Who can answer my questions about this study?

You can talk to the study doctor about any questions or concerns you have about this study or to report side effects or injuries. Contact the study doctor at the phone number listed on page 1 of this document.

My Signature Agreeing to Take Part in the Study

I have read this consent form or had it read to me. I have discussed it with the study doctor and my questions have been answered. I will be given a signed copy of this form. I agree to take part in the study.

Participant's signature _____

Participant's printed name _____

Date of signature _____

Signature of person(s) conducting the informed consent discussion _____

Printed name of person conducting the informed consent discussion _____

Date of signature _____