CONSENT FOR CANCER RESEARCH

Project Title: A Prospective Phase II Trial of NovoTTF-100A with Bevacizumab (Avastin) in Patients with Recurrent Glioblastoma

Cleveland Clinic
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Sponsor: NovoCure Inc.

Cancer research studies are coordinated by physicians and scientists from Cleveland Clinic, University Hospitals and Case Western Reserve University (CWRU) through the NIH National Cancer Institute (NCI) designated Case Comprehensive Cancer Center (Case CCC). The goal of this collaboration is to enhance cancer treatment and research in Northeast Ohio. This study is being offered at Cleveland Clinic (CC)

The purpose of this document is to provide you with information to consider in deciding whether to participate in this research study. Consent must be based on an understanding of the nature and risks of the treatment, device or procedure. Please ask questions if there is anything you do not understand. Your participation is voluntary and will have no effect on the quality of your medical care if you choose not to Participate.

Conflict of Interest Disclosure
One or more of the Investigators conducting this study serve as consultants for the company that makes products used in this study. These financial interests are within permissible limits established by the local institutional Conflict of Interest Policy. If you have any questions regarding conflicts of interest, please ask your study doctor or call the Cleveland Clinic Institutional Review Board at (216) 444-2924.

Introduction/Purpose

You are being asked to take part in this study because you have been diagnosed with a brain tumor called glioblastoma or other grade IV malignant glioma (i.e. Gliosarcoma, small cell glioblastoma, etc). This research is being done because this type of tumor is almost never cured with surgery, radiation, or chemotherapy. Since your disease has a high chance of recurring or progressing despite the maximal possible standard therapy, your doctor has recommended participating in a controlled clinical trial to test treatment using the device, the NovoTTF-100A, and Bevacizumab.

NovoTTF-100A is a device and Bevacizumab is a study drug that have both been approved by the FDA (Food and Drug Administration) for use as monotherapy in treating glioblastoma multiforme.

The purpose of this study is to determine the efficacy of the combination of Bevacizumab and NovoTTF-100A in Bevacizumab naïve (meaning you have never received bevacizumab before) patients with recurrent GBM as measured by 6-month progression free survival. We also want to find out what effects (good and bad) NovoTTF-100A and Bevacizumab have on you and your brain tumor.

The treatment with NovoTTF100A was well tolerated in previous trials, with no treatment related serious

adverse events seen in any of the patients. Mild to moderate contact dermatitis (an inflammation of the skin) appeared beneath the electrode gel in all patients during treatment. The skin reaction improved with use of steroid and/or antibiotic creams.

In a pivotal trial, 237 recurrent GBM patients were randomized to receive either the NovoTTF-100A alone (120 patients), or a standard chemotherapy (117 patients) selected by the treating physician. All patients had at least one previous progression of their tumor. The majority of NovoTTF-100A patients tolerated the treatment well and mild to moderate skin contact dermatitis was the only significant side effects associated with the device treatment. Topical treatments easily improved skin condition.

The 120 recurrent GBM patients treated with the NovoTTF-100A device alone had comparable overall survival and progression free period to patients receiving chemotherapy. In addition, these patients experienced significantly fewer side effects, and had a much higher quality of life compared to the group that received standard chemotherapy. In the US, the FDA has approved the treatment of Novo TTF-100A for recurrent GBM patients based on the findings in this clinical trial.

This trial that you are being asked to participate in will be a single arm multi-center phase II and will accrue 40 people with recurrent glioblastoma multiforme. The trial will be conducted at the sites of the Case Comprehensive Cancer Center and the enrollment will be up to 40 patients, the University of Cincinnati and Boca Raton Regional Hospital will also participate in this Phase II trial. An additional 8 patients may be enrolled to replace ineligible patients or patients who withdraw consent prior to receiving study treatment.

Study Procedures

Once your doctor has determined that you have met all of the requirements for participation in the study, you will start Bevacizumab and it will be administered intravenously on days 1 and 15 of each 28 day cycle. Each cycle is 28 days in duration. And the NovoTTF-100A is recommended to be worn at least 18 hours / day until the tumor progresses or you are not able to tolerate the treatment. Previously studies have shown that patients who wear NovoTTF-100A system greater than18 hours a day derive more benefit from the device. Bevacizumab is approved for patients with recurrent GBM and will be from the commercial supply and not provided in the study. The dose of bevacizumab will be 10mg/kg of actual body weight. The dose will be determined using body weight determined at the beginning of each treatment cycle.

Screening

Before joining this study you will need to have some tests and examinations. Your doctor will perform:

- Medical history including history of prior treatments.
- Physical examination (Including height, weight, and vital signs).
- Neurological exam which evaluates the function of your brain (may include tests of your vision, eye movement, how your eyes respond to light, hearing, reflexes, speech, balance, and a sense of touch, and ability to recognize and remember things).
- Blood work (approximately 1-2 tablespoons).
- KPS (Karnofsky performance scale)
- Neurocognitive function

- You will have a MRI (Magnetic Resonance Imaging) scan of your brain.
- You will also have laboratory tests (urine, complete metabolic panel, and a complete blood count) to make sure you are not at increased risk for side effects.
- If you are a woman of childbearing potential a pregnancy test will be obtained. If the results of this test are positive you cannot take part in this study. Some of these tests would be done if you do not take part in this study. This is done to assess your overall medical condition.
- Quality of life questionnaire

Treatment

The NovoTTF-100A treatment and Bevacizumab will be administered on an outpatient basis; NovoTTF-100A treatment will be initiated in the outpatient clinic. During this visit you will be instructed on how to operate the device, replace depleted batteries, recharge them and connect to an external battery pack overnight. Treatment will consist of wearing four (4) electrically insulated caps/sheets with numerous electrodes on your head for the duration of the treatment. Placement of caps/sheets that contain electrode will require shaving of your scalp before treatment. The electrodes will continuously emit low level energy that is believed to disrupt tumor growth. After this visit you will continue treatment at home where you can maintain your regular daily routine. You will need to visit a technical support clinic twice a week during treatment in order to replace the electrodes and re-shave your scalp. It is also possible to train a family member to replace electrodes which will cut down on the number of trips necessary to the technical support clinic to as few as twice per month. Each treatment course will consist of continuous NovoTTF-100A treatment for 18 hours/ continuously together with Bevacizumab given days 1 and 15 for a 28 day cycle. The treatment will continue as long as you are benefitting from treatment (tumor is stable or shrinking) or your physician feels you are deriving benefit from the treatment.

This device, NovoTTF-100A system is constructed of plastic and weighs 3 kg (6.6l pounds) and 220 x220x50mm in size. This device (battery pack) will be placed inside a cloth bag and should be worn as a shoulder bag across the body. The electrodes should be worn continuously. You will not be able to wash your head while the electrodes are in place. You can wash your head at the time of the electrodes replacement (twice a week). Other times you can take shower/bath with a shower cap on your head to protect the electrodes from getting wet.

Other Therapy
All supportive therapy for optimal medical care will be given during the study period at the discretion of the attending physician(s) within the parameters of the protocol and documented on each site's source documents as concomitant medication.

- Anticonvulsants: Anticonvulsants may be used as clinically indicated. Doses at study entry and at specific time points of the treatment must be recorded.

- Corticosteroids: Corticosteroids may be administered at the treating physician's discretion. Doses at study entry and at specific time points of the treatment must be recorded.

All treatment and follow-up procedures continue per protocol during the trial. You will need to return once a month to the hospital outpatient clinics where you will be examined by a physician who will perform a physical exam. Blood test (about 1-2 Tablespoons) will be taken to perform tests as outlined in

the study. Additionally, you will be asked to complete questionnaires that test quality of life and neurological function. A routine MRI of the head will be performed at the beginning of the study (baseline) and every 8 weeks of treatment. An MRI will also be performed at the end of the study or within a week if your tumor grows. These routine visits will continue for as long as you remain on treatment. After stopping treatment, you will need to return once per month for two more months to the outpatient clinic for similar follow up examinations except for the MRIs and Quality of Life questionnaires. The NovoTTF-100 device can be returned to the study team at this time. During the visits to the clinic you will be examined physically and neurologically. Additionally, blood tests will be performed. After this follow up plan, you will be contacted once per month by telephone to answer basic questions about your health status but will not need to return to the clinic for visits, except as directed by your doctor for your routine care.

Risks

While in this study, you may develop side effects. In addition, there may be side effects that are currently unknown, or that we cannot predict. You will be monitored for side effects throughout this study.

While participating in the study, you may suffer from other complications traditionally associated with the GBM disease process, including seizures, neurological and functional decline, headaches, nausea, vomiting and death. While it may be difficult to determine whether these events are related to treatment with the NovoTTF-100A, it is unlikely but unknown if such treatment will increase these risks. You should discuss these with the researcher and/or your regular doctor.

Other potential risks of the NovoTTF-100A include risk of electrical or mechanical failure, electrical shock, and electromagnetic interference. The electrical or mechanical failure leading to electrical shock is a very rare (<1%) risk with use of the NovoTTF-100A. The seriousness of these risks may be mild or very serious. There may also be a rare risk of death.

Treatment with the NovoTTF-100A is not expected to cause any serious side effects. If they occur each Will be evaluated and treated by the physician and should heal completely after treatment is stopped. It is possible that investigational treatment will cause any of the following:

- Local warmth and tingling sensation beneath the electrodes
- Allergic reaction to the plaster or to the gel
- Skin breakdown
- Infection at the sites of electrode contact with the skin
- Electrode overheating leading to pain and/or local skin burns
- Headache
- Fatigue
- Irritation

Bevacizumab: A monoclonal antibody

Bevacizumab is a monoclonal antibody approved by the FDA for the treatment of patients with colorectal cancer, lung cancer, glioblastoma, and kidney cancer. Subjects with other types of cancer have also received treatment with bevacizumab and their cancer has responded to bevacizumab treatment. Side effects associated with the use of bevacizumab include the following: holes in the intestinal tract, high blood pressure, impaired wound healing, an increased incidence of blood clotting in blood vessels that

have resulted in stroke or heart attack, blood clotting in the blood vessels of the lung, bleeding, increased protein in the urine, rare reports of very high blood pressure that affects the brain and eyes, inability of the heart to supply sufficient blood flow to meet the body's needs, tear between the membranes separating different organs in the body, and reactions to the bevacizumab infusion.

Reproductive Risks

Because there may be a risk of birth defects if a fetus is exposed to NovoTTF-100A device and Bevacizumab, you should not use this device or drug if you and your partner are planning to have a baby during this study or two months following the end of the study. A barrier method of birth control (condom or diaphragm) used with a spermicide, surgical sterilization, approved hormonal contraceptives such as birth control pills, or an intrauterine device (IUD) must be used during the study and for eight (8) weeks after your last dose of study drug. You should not nurse a baby while on this study. Ask about counseling and more information about preventing pregnancy.

Risk of the MRI

The MRI (Magnetic Resonance Imaging) itself is a painless procedure that has few known side effects. Some patients experience claustrophobia or anxiety while in the MRI, which is a tunnel-shaped machine. The MRI is a powerful magnet. You must not have any metal objects on or in your body, for example, brain aneurysm clips or a pacemaker, to be able to have a MRI scan. Some tattoo dye may have been combined with metal particles. Prior to having your MRI done you must be checked for renal function. The MRI creates a series of repetitive knocking sounds when the magnetic field gradients are turned on and off. Because of the volume of these sounds, you will be given ear protection in the form of foam earplugs by the technician at Cleveland Clinic. One or possibly two injections of a liquid contrast medium which contains
Gadolinium will be used during the treatment planning and procedure to improve the MRI images. Gadolinium can cause a condition called nephrogenic systemic fibrosis (NSF) in patients with kidney disease or dysfunction. This is a debilitating disease which causes thickening of the skin, muscles and internal organs throughout the body. It is a potentially fatal disease for which there is no known cure.

Blood Draw

Blood test requires placing a needle in a vein to get blood. It may cause mild and temporary discomfort including mild soreness, lightheadedness, slight bruising, swelling and/or bleeding, infection, fainting and irritation or perforation of the vein. Infection where the needle is inserted is very rare.

Benefits

There may be no direct benefit to you from participating in this study. There is no guarantee that NovoTTF-100A and Bevacizumab can relieve your symptoms or stop progression of your cancer, and your symptoms could remain unchanged. There will be no other direct benefit to you because of your participation in the study above and beyond the potential benefit of the NovoTTF-100A treatment, Bevacizumab drug and frequent visits to your physician. Data collected in this study may help doctors to provide better treatment for glioblastoma multiforme in the future.

Alternatives

You may choose not to take part in this study. You may decide that you prefer to be treated by some other method. There may be alternative treatments available for your cancer, including:

- Other investigational therapies.
- Local radiation therapy (e.g. gamma knife)
- Second line chemotherapy
- Combination of the above.
- Palliative Care or hospice

Costs

The NovoTTF-100A Device. And Bevacizumab will not be provided because it is commercially approved. You or your insurance company will need to pay for the cost of NovoTTF-100A Device and Bevacizumab. You or your insurance company will be responsible for payment of all other medical care that would normally be part of the treatment cost of standard of care. We encourage you to work closely with your insurance company to find out exactly what is covered for this research study.

There will be no payment for your participation.

Termination of Participation

Taking part in this study is voluntary. You may choose not to take part or may leave the study at any time. Leaving the study will not result in any penalty or loss of benefits to which you are entitled. We will tell you about new information that may affect your health, welfare or willingness to stay in this study.

Research Related Injuries

If you experience physical injury or illness as a result of participating in this research study, medical care is available at the Cleveland Clinic s or elsewhere. There will be no additional costs to you for research-related physical injury or illness as a result of being in this study. However, routine medical care for your condition (care you would have received whether or not you were in this study) will be charged to you or your insurance company. You may wish to contact your insurance company to discuss this further.

Further information about research-related injuries is available by contacting the Cleveland Clinic Institutional Review Board at (216) 444-2924 .

Confidentiality

The results of your examination will be collected in a centralized computer or data registry at Cleveland Clinic, 9500 Euclid, Cleveland, Ohio 44195. Data will be stored in a password-protected database. Only approved research personnel will have access to this information.

Tests and procedures done solely for this research may be placed in your medical records to indicate your participation in this study. Upon completion of the study, you may have access to the research information if contained in the medical record.

Authorization to Use or Disclose (Release) Health Information that Identifies You for a Research Study.

If you sign this document, you give permission to Manmeet Ahluwalia, M.D. and his research staff at Cleveland Clinic to use or disclose (release) your protected health information, or PHI, that identifies you for the purposes of the research and to Case Western Reserve University for administration.

The Personal Health Information (PHI) that we may use or disclose (release) for this research may include your name, address, telephone number, date of birth, Social Security number and information from your medical chart, lab tests, or certain health information relating to your health or condition.

Some of the tests and procedures done solely for this research study may also be placed in your medical record so other doctors know you are in this study. Upon completion of the study, you may have access to the research information that is contained in your medical record.

In addition to the investigators and research staff listed above, your PHI may be looked at by other groups involved with the study such as the Cleveland Clinic Institutional Review Board and the Case Comprehensive Cancer Center Protocol Review and Monitoring Committee. Your PHI may also be used by and/or disclosed (released) to:

- Data coordinating centers
- NovoCure (Sponsor) and its representatives
- Other Institutional Review Boards or Data Safety and Monitoring Boards
- Your insurance company
- The Food and Drug Administration and Governmental agencies in other countries
- The Department of Health and Human Services
- The National Committee for Quality Assurance; and
- Cleveland Clinic

Once your personal health information is released it may be re-disclosed and no longer protected by privacy laws. Your research information may be used and disclosed indefinitely, but you may stop these uses and disclosures at any time by writing to Dr. Manmeet Ahluwalia at Cleveland clinic, 9500 Euclid Avenue, Cleveland, Ohio 44195 at 216-444-6145. Your participation in the research will stop, but any information previously recorded about you cannot be removed from the records and will continue to be used as part of this research. Also, information already disclosed outside the Cleveland Clinic cannot be retrieved. This will not affect your rights to treatment or benefits outside the research study.

The Cleveland Clinic will not use your information collected in this study for another research purpose without your written permission; unless the Cleveland Clinic Institutional Review Board (IRB) assures your privacy and confidentiality is protected.

The IRB is a committee whose job it is to protect the safety and welfare of research subjects.

By signing this informed consent form, you are authorizing such access to your research and medical record information. If you choose not to sign this consent form, you will not be able to participate in this research study. This Authorization does not have an expiration date.

Contact information

Dr. Manmeet Ahluwalia has described to you what is going to be done; the risk, hazards, and benefits

involved, and can be contacted at 216/444-6145 (office). During non-business hours you should contact Cleveland Clinic page operator at 216/444-2200 and ask for the Neurological attending physican that is on call.

Further information with respect to illness or injury resulting from a research procedure as well as a research subjects' rights is available from the Cleveland Clinic Institutional Review Office at (216) 444-2924.

Where Can I Obtain Additional Information on Clinical Trials?

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.

Signature

Signing below indicates that you have been informed about the research study in which you voluntarily agree to participate; that you have asked any questions about the study that you may have; and that the information given to you has permitted you to make a fully informed and free decision about your participation in the study. By signing this consent form, you do not waive any legal rights, and the investigator(s) or sponsor(s) are not relieved of any liability they may have. A copy of this consent form will be provided to you.

_____ _____ _____

Signature of Participant ***Date*** ***Printed Name of Participant***

I have discussed the information contained in this document with the participant and it is my opinion that the participant understands the risks, benefits, alternatives and procedures involved with this research study.

_____ _____

Signature of Person Obtaining Consent ***Date***

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Printed Name of Person Obtaining Consent