CLINICAL PROTOCOL	
Title:	**A Prospective Phase II Trial of NovoTTF-100A with Bevacizumab (Avastin) in Patients with Recurrent Glioblastoma**
Protocol Number:	CASE3313 Protocol EF-
Principal Investigator:	Manmeet Ahluwalia, MD.
Study Sponsor:	Cleveland Clinic, 9500 Euclid Ave, Cleveland, Ohio 44195 NovoCure Ltd. POB 15022 MATAM Center Haifa, 31905, Israel
Signature & Date:	Signed: _____ Dated: _____
Version Date:	~~11/03/2015~~05/09/2016

SYNOPSIS:

Name of Sponsor/Company: Cleveland Clinic NovoCure Ltd.	
Therapies under investigation: Bevacizumab NovoTTF-100A	
Title of Study: A Prospective Phase II Trial of NovoTTF-100A with Bevacizumab in Patients with Recurrent Glioblastoma	
Study Centers: Cleveland Clinic, University of Cincinnati, Boca Raton Regional Hospital	
Principal Investigator: Manmeet Ahluwalia, MD.	
Studied period (years): 3 years Date first patient enrolled: April 2013 Estimated date endpoint obtained: December 2017 Estimated date last patient completed: December 2017	**Phase of development:** 2

Rationale:

Despite advances in surgery, radiation therapy and chemotherapy, including establishment of concurrent radiation and temozolomide followed by temozolomide as standard of care, glioblastoma (GBM) remains an incurable disease with a dismal median overall survival of 15-18 months[1]. Bevacizumab (Avastin; Genentech, South San Francisco, CA) is a humanized monoclonal antibody that inhibits VEGF and is the first antiangiogenic therapy to be approved for use in patients with cancer. The BRAIN study, a phase II randomized trial evaluated the role of bevacizumab (alone or in combination with irinotecan) in 167 patients with recurrent GBM[2]. The progression free survival (PFS) at 6 months (PFS-6) was 42.6% and 50.3%, objective response rate (ORR) was 28.2% and 37.8% and median overall survival (OS) was 9.2 months and 8.7 months in the monotherapy and combination arms respectively. In a study done at the National Cancer Institute (NCI), 48 patients with recurrent GBM were treated with bevacizumab producing a response rate (RR) of 35%, PFS-6 of 29% and a median OS of 31 weeks[3]. Clinical benefit was evident with decreasing cerebral edema, tapering steroid doses and improvement in neurological function in nearly half of the patients. Addition of irinotecan to patients who progressed following bevacizumab did not provide any additional benefit.

The results of these two studies compared favorably to historic controls of PFS-6 of 15% for GBM[4] and the Food and Drug Administration (FDA) approved bevacizumab for patients with recurrent GBM in May 2009 as a monotherapy. However, the duration of effect of bevacizumab appears to be limited and there are growing concerns about the long-term efficacy of bevacizumab. To date, clinical trials with bevacizumab with recurrent glioblastoma have shown an improvement of PFS without

substantial improvement in OS.

Emerging patterns of tumor progression distant from the primary site and recurrence after bevacizumab therapy suggest that VEGF inhibition alone is insufficient for long-term tumor control and may change the natural history of glioma progression. Hence strategies that target invasion may be needed to prevent this pattern of resistance.

Bevacizumab has been associated with prolonged OS in phase III trials of metastatic colorectal and non-small-cell lung cancers and with prolonged PFS in metastatic breast and renal cancers in combination with chemotherapy or biologics. Except GBM, all the approved indications for bevacizumab have been in combination with chemotherapy. However based on the results of the BRAIN study, bevacizumab was approved as a monotherapy. One hypothesis for the lack of survival benefit in GBM with the addition of chemotherapy to bevacizumab is that treatment with bevacizumab leads to normalization of the blood brain barrier (BBB) and this may decrease peritumoral edema, producing short-term benefit.

Novocure (Haifa, Israel) has developed a novel therapy (NovoTTF-100A) utilizing alternating electric fields and has shown that when properly tuned, very low intensity, intermediate frequency electric fields (TTFields) inhibit the growth of tumor cells (including glioma). Given its mechanism of action, TTFields are explained in detail with both preclinical and clinical data provided below and in the attached appendix, NovoTTF not dependent on the BBB for its efficacy. The inhibitory effect with TTFields has been demonstrated in all proliferating cancer cell types tested, whereas, non-proliferating cells and normal tissues were unaffected. Promising clinical results have been demonstrated in pilot studies of both newly diagnosed GBM in combination with temozolomide as well as recurrent GBM when treated with NovoTTF-100A. In a phase III trial NovoTTF monotherapy demonstrated comparable efficacy to chemotherapy with a more favorable safety profile and quality of life benefit in the recurrent GBM setting resulting in FDA approval of NovoTTF given the single agent activity of NovoTTF and bevacizumab in GBM and the mechanism of action of NovoTTF not being limited by normalization of the blood brain barrier by use of bevacizumab, this is a rational and promising combination to evaluate further in a clinical trial.

Objectives:

Primary:

- To determine the efficacy of the combination of bevacizumab and NovoTTF-100A in bevacizumab-naïve patients with recurrent GBM as measured by 6-month progression-free survival (PFS6)

Secondary:

- To assess safety and tolerability of the combination of bevacizumab and NovoTTF-100A in this population
- To evaluate overall survival in this population
- To determine objective response rate (ORR) by modified RANO criteria in this population
- To assess time-to-progression in this population
- To assess neurocognitive outcome and quality of life in this population

Methodology:

This is an open label single arm phase 2 trial evaluating the efficacy and safety of the combination of bevacizumab and NovoTTF-100A in bevacizumab-naïve patients with recurrent GBM.

Number of Patients:

Approximately 40 patients with recurrent GBM will be enrolled 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.

Eligibility Criteria:

Inclusion criteria:

1. Patients with histologically confirmed glioblastoma or other grade IV malignant glioma (i.e. gliosarcoma, small cell glioblastoma, etc.), recurrent after prior external-beam fractionated radiotherapy and temozolomide chemotherapy.
2. Patients with upto two prior recurrences are allowed.
3. Karnofsky performance status ≥ 70.
4. Age ≥ 22 years old.
5. Patients must have the following laboratory values:
   - Absolute neutrophil count (ANC) $\geq 1.5 \times 10^9$/L
   - Platelets $\geq 100 \times 10^9$/L
   - Hemoglobin (Hgb) > 9 g/dL
   - Serum total bilirubin: ≤ 1.5 x ULN
   - ALT and AST ≤ 3.0 x ULN
   - Serum creatinine ≤ 1.5 x ULN
   - Blood coagulation parameters: INR ≤ 1.5
6. Minimum interval since completion of radiation treatment is 12 weeks
7. Minimum interval since last drug therapy:
   - 3 weeks since last non-cytotoxic therapy
   - 3 weeks must have elapsed since the completion of a non-nitrosourea-containing chemotherapy regimen
   - 6 weeks since the completion of a nitrosourea-containing chemotherapy regimen.
8. Patients must have signed an approved informed consent and authorization permitting release of personal health information.

9. Patients with the potential for pregnancy or impregnating their partner must agree to follow acceptable birth control methods to avoid conception. The effects of bevacizumab on developing fetus or nursing infant are not known. Female patients of child-bearing potential must have a negative pregnancy test.
10. Patients must have no concurrent malignancy except curatively treated basal or squamous cell carcinoma of the skin or carcinoma in situ of the cervix and breast, adequately treated stage I or II cancer from which the patient is in complete remission. Patients with other prior malignancies must be disease-free for ≥ three years.
11. Patients must be maintained on a stable corticosteroid regimen from the time of their baseline scan until the start of treatment and/or for at least 5 days before starting treatment.

Exclusion criteria:

1. Patients who have had previous treatment either with bevacizumab, and or NovoTTF 100A system
2. Patients who have undergone major surgery (e.g. intra-thoracic, intra-abdominal or intra-pelvic), open biopsy or significant traumatic injury ≤ 4 weeks prior to starting study drug, or patients who have had minor procedures, percutaneous biopsies or placement of vascular access device ≤ 1 week prior to starting study drug, or who have not recovered from side effects of such procedure or injury
3. Patients with impaired cardiac function or clinically significant cardiac diseases, including any of the following:
    - History or presence of serious uncontrolled ventricular arrhythmias
    - Any of the following within 6 months prior to starting study drug: myocardial infarction (MI), severe/unstable angina, Coronary Artery Bypass Graft (CABG), Congestive Heart Failure (CHF), Cerebrovascular Accident (CVA), Transient Ischemic Attack (TIA), Pulmonary Embolism (PE)
    - Uncontrolled hypertension (defined by a SBP ≥ 160 mm Hg or DBP ≥ 100 mm Hg while on anti-hypertensive medications)
4. Patients with cirrhosis, or active viral or nonviral hepatitis.
5. Implanted pacemaker, shunts, defibrillator or deep brain stimulator, other implanted electronic devices in the brain or documented clinically significant arrhythmias.
6. Infra-tentorial tumor
7. Evidence of increased intracranial pressure (clinically significant papilledema, vomiting and nausea or reduced level of consciousness)
8. Known sensitivity to conductive hydrogels
9. Known diagnosis of human immunodeficiency virus (HIV) infection (HIV testing is not mandatory)
10. Other concurrent severe and/or uncontrolled concomitant medical conditions (e.g. active or uncontrolled infection, uncontrolled diabetes) that could cause unacceptable safety risks or

compromise compliance with the protocol

11. Pregnant or breast-feeding women
12. Patients unwilling or unable to comply with the protocol
13. Patients with leptomeningeal disease

Duration of Treatment:

Bevacizumab will be given at a dose of 10mg/Kg IV every 2 weeks and NovoTTF-100A will be worn continuously. Previously studies have shown that patient who wear NovoTTF-100A system > 18 hours/ day derive more benefit from the device.

Patients are eligible for treatment with the combination of bevacizumab and NovoTTF-100A until disease progression or unacceptable toxicity.

A patient should be withdrawn from study treatment if, in the opinion of the Investigator, it is medically necessary, or if it is the wish of the patient. In addition, patients will be withdrawn from treatment in the case of:

1. Modified RANO criteria defined disease progression. In cases where modified RANO criteria cannot be applied, progression should be based on unequivocal evidence of progressive disease sufficient to require a change in therapy.
2. A need for surgery, radiation, or for other anticancer therapy not specified in the protocol.
3. Lost to follow-up or noncompliant.
4. Pregnancy. Pregnant patients should be followed for the duration of the pregnancy and the outcome of the pregnancy should be documented.

Parameters to be Assessed:

Safety:

Safety assessments will include physical exams, performance status, laboratory results (complete blood counts and serum chemistry) and 12-lead ECG's (in patients who develop arrhythmia), and additional studies as clinically indicated. Data Safety Toxicity Committee will review safety data. See Section 10 for data safety monitoring. In addition, recurring teleconferences will be held with the principal investigator or other investigators.

Efficacy:

Modified RANO criteria will be applied to assess response and progression.

Survival will be calculated using the KM methodology (time from enrollment to date of death or date of last follow-up)

Statistical methods:

This trial will enroll enough participants to discriminate between a 36% and 56% PFS6 rate. The trial will accrue 40 participants. The trial will be declared successful if at least 20 achieve PFS6. This design assumes an exact 5% type I error (one-sided) and a maximum 20% type II error.

Primary Endpoint:

- Efficacy of the combination of bevacizumab and NovoTTF-100A in bevacizumab-naïve patients with recurrent GBM as measured by 6-month progression-free survival (PFS6) by KM methodology.

Secondary Endpoints:

- Safety and tolerability of combination of bevacizumab and NovoTTF-100A in this population by CTCAE version 4.0.
- Median overall survival (OS) by KM methodology.
- Objective response rate (ORR) using modified RANO criteria.
- Time-to-progression in this population by KM methodology.
- Time to reliable change (decline) in neurocognitive function by KM methodology

Funding, Regulatory, and Feasibility Issues:

Up to 48 patients will be enrolled for a total of 40 evaluable patients in the trial. Every year 125-150 patients with recurrent GBM are seen at Cleveland Clinic. Approximately 2-3 patients per month will be entered onto the study and accrual will be completed in 6-12 months. All patients will be followed until progression.

Patient Acceptability/Ethics and Consent Issues:

There are no effective therapies for patients with recurrent GBM that have increased survival and the combination of bevacizumab and NovoTTF-100A is promising as bevacizumab has improved progression free survival however without improvement in overall survival and addition of NovoTTF-100A may help prevent invasion that is one of the mechanisms of resistance in GBM patients that progress on bevacizumab. Both NovoTTF and bevacizumab are approved by the FDA as single agents in the treatment of recurrent GBM. The efficacy of the combination is not known and may offer additional benefits to this patient population.

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1. OBJECTIVE

1.1. Study Design

This will be an open label Phase II trial in adult (age ≥ 22 years) with recurrent glioblastoma (GBM).

1.1.1. Primary:

To determine the efficacy of the combination of bevacizumab and NovoTTF-100A in bevacizumab-naïve patients with recurrent GBM as measured by 6-month progression-free survival (PFS6)

1.1.2. Secondary:

- To assess safety and tolerability of the combination of bevacizumab and NovoTTF-100A in this population,
- To evaluate overall survival in this population,
- To determine objective response rate (ORR) by modified RANO criteria in this population,
- To assess time-to-progression in this population
- To assess neurocognitive function (NCF) and quality of life (QOL) in this population.

2. BACKGROUND AND RATIONALE:

2.1. Glioblastoma and Angiogenesis

Although the recent addition of temozolomide to radiation therapy for the treatment of glioblastoma (GBM) has resulted in improved outcomes, the estimated 2-year survival with maximal therapy remains only 27%[1]. Despite treatment of patients with GBM with maximal possible surgical resection, radiation and temozolomide almost all patients recur. The prognosis is especially grim for patients who have recurrent GBM. The median survival for these patients remains only 3-9 months. Hence, new therapies for GBM are urgently needed. One promising area of therapeutic approach has been targeting the angiogenesis. Angiogenesis, the formation of new capillaries and blood vessels, is a tightly controlled, multi-step process that is a component of normal physiology. It is also a key development in the formation and proliferation of cancers particularly for them to grow beyond 2-3 mm in size[5-6]. GBM is one of the most vascular of all solid tumors with increased vascular density and expression of multiple proangiogenic growth factors and their receptors both on the tumor vasculature and on tumor cells themselves[7]. These include members of the vascular endothelial growth factor (VEGF) family, basic fibroblast growth factor (bFGF), transforming growth factor beta (TGF), tumor necrosis factor alpha (TNF), platelet-derived growth factor (PDGF), transforming growth factor alpha (TGF), hepatocyte growth factor (HGF), angiogenin, interleukin-8 and placental growth factor (PlGF) [8-9]. The VEGF pathway is believed to be the main pathway involved in the angiogenesis in GBM, and VEGF-A and its receptor VEGFR-2, in particular, appear to be the key in stimulating angiogenesis in GBM[7].

2.2. Vascular Endothelial Growth Factor and GBM

VEGF-A (hereafter referred to as VEGF) is one of several related cytokines in the VEGF family, but is distinct in that it acts as an endothelial cell-specific mitogen and is the most commonly expressed of its class[10]. The biological activity of VEGF is mediated principally by two tyrosine kinase receptors, VEGFR-1 and VEGFR-2[9-10]. VEGF is overexpressed in GBM both on tumor cells and on the cells in the surrounding stroma[11]. Increased expression of VEGF is associated with increased tumor aggressiveness and decreased survival in GBM. VEGFR-2 is the main receptor for VEGF and therefore, the primary mediator of VEGF activity on endothelial and tumor cells[12]. Like VEGF, VEGFR-2 expression is strongly upregulated in tumor endothelium[10]. VEGFR-2 expression has been associated with increased tumor microvessel density, advanced disease, increased risk of metastasis and recurrence, and lower relapse-free survival in patients with a variety of cancers[5]. Based on these observations, anti-VEGF approaches have been increasingly studied in GBM in clinical trials.

Bevacizumab (Avastin; Genentech, South San Francisco, CA) is a humanized monoclonal antibody that inhibits VEGF and is the first antiangiogenic therapy to be approved for use in patients with cancer. In combination with chemotherapy or biologics, bevacuzimab was associated with prolonged overall survival (OS) in phase III trials of metastatic colorectal[13] and non–small-cell lung[14] cancers and with prolonged PFS in metastatic breast[15] and renal[16] cancers compared with placebo or chemotherapy alone. In a single-institute, phase II trial of patients with recurrent glioblastoma, bevacuzimab in combination with irinotecan demonstrated 46% 6-month PFS and 57% overall response (OR) rates[17]. This represented substantial improvement over prior trials for recurrent malignant glioma that, in aggregate, have resulted in response rates less of than 15% and median PFS of 9 weeks[4]. Following this a phase II randomized clinical trial was performed to evaluate the benefit of the addition of irinotecan to bevacizumab. In this clinical trial 167 patients with recurrent GBM received either bevacizumab alone or bevacizumab in combination with irinotecan; there was no statistically significant difference in the median overall survival (OS) for bevacizumab therapy alone (9.2 months) when compared to the combination bevacizumab and irinotecan therapy (8.7 months)[2]. Another phase II study evaluated the approach of bevacizumab monotherapy in patients with recurrent GBM followed by irinotecan combined with bevacizumab[3]. In this study, 17/48 patients (35%) achieved an initial radiographic response and the PFS-6 was reported to be 29%. Based on the results of these two Phase II trials, FDA approved bevacizumab for patients with recurrent GBM[2-3].
However, the duration of effect of bevacizumab appears to be limited and there are growing concerns about the long-term efficacy of bevacizumab. Emerging patterns of tumor progression distant from the primary site and recurrence after bevacizumab therapy suggest that VEGF inhibition alone is insufficient for long-term tumor control and may change the natural history of glioma progression[18]. Hence strategies that target invasion may be needed to prevent this pattern of resistance.

2.3. Angiogenesis and invasion in glioblastoma

The two processes, angiogenesis and tumor cell invasion, are closely associated. In gliomas, VEGF promotes both angiogenesis and invasion of tumor cells[19]. "Invasion" of endothelial cells into the tumor is an important component of the angiogenic process. In most studies, bevacizumab was used in combination with traditional cytotoxic agents. In other tumors bevacuzimab has been associated with prolonged overall survival (OS) in phase III trials of metastatic colorectal[13] and non–small-cell lung[14] cancers and with prolonged PFS in metastatic

breast[15] and renal[16] cancers combination with chemotherapy or biologics. However this has not been the case in GBM as treatment with bevacizumab leads to normalization of the blood brain barrier and this decreases the amount of chemotherapy or targeted therapy reaching the tumor.

2.4. Introduction to electric fields

In the laboratory setting and in clinical practice, alternating electric fields show a wide range of effects on living tissues. At very low frequencies (under 1 kHz), alternating electric fields stimulate excitable tissues through membrane depolarisation[20-21]. The transmission of such fields by radiation is insignificant and therefore they are usually applied directly by contact electrodes (transducer arrays), though some applications have also used insulated electrodes (transducer arrays). Some well known examples of such effects include nerve, muscle and heart stimulation by alternating electric fields[20-21]. In addition, low frequency pulsed electric fields have been claimed to stimulate bone growth and accelerate fracture healing. However, as the frequency of the alternating electric field increases above 1 kHz, the stimulatory effect diminishes. Under these conditions although a greater fraction of the fields penetrates the cells, due to the parallel resistor-capacitor nature of all biological membranes, the stimulatory power greatly diminishes as the alternating cell membrane hyper–depolarization cycles are integrated such that the net effect is nulled.

At very high frequencies (i.e., above many MHz), while the integration becomes even more effective, a completely different biological effect is observed. At these frequencies tissue heating becomes dominant due to dielectric losses. This effect becomes more intense as field intensity or tissue dissipation factor increase[22]. This phenomenon serves as the basis for some commonly used medical treatment modalities including diathermy and radio frequency tumor ablation, which can be applied through insulated electrodes (transducer arrays)[23].

Intermediate frequency electric fields (i.e., tens of kHz to MHz), alternate too fast to cause nerve-muscle stimulation and involve only minute dielectric losses (heating). Such fields, of low to moderate intensities, are commonly considered to have no biological effect[22]. However, a number of non-thermal effects, of minor biological consequence, have been reported even at low field intensities. These include microscopic particle alignment (i.e., the pearl chain effect[24]) and cell rotation[25]. With pulsed relatively strong electric fields, $> 10^3$ V/cm and 100 ms pulse length, reversible pore formation appears in the cell membrane, a phenomenon usually called electroporation[26].

2.5. NovoCure's Tumor treating electric fields (TTFields)

Preclinical studies have shown that when properly tuned, very low intensity, intermediate frequency electric fields (TTFields) stunt the growth of tumor cells[27]. This inhibitory effect was demonstrated in all proliferating cancer cell types tested, whereas, non-proliferating cells and normal tissues were unaffected. Interestingly, different cell types showed specific intensity and frequency dependencies of TTField inhibition. It has been shown that two main processes occur at the cellular level during exposure to TTFields: arrest of proliferation and dividing cell destruction. The damage caused by TTFields to these replicating cells was dependent on the orientation of the division process in relation to the field vectors, indicating that this effect is non-thermal. Indeed, temperature measurements made within culture dishes during treatment and on the skin above treated tumors in-vivo, showed no significant elevation in temperature compared to control cultures/mice. Also, TTFields caused the dividing cells to orient in the direction of the applied field in a manner similar to that described in cultured human corneal epithelial cells exposed to constant electric fields[28]. At the sub-cellular level it was found that

TTFields disrupt the normal polymerization-depolymerization process of microtubules during mitosis. Indeed, the described abnormal mitotic configurations seen after exposure to TTFields are similar to the morphological abnormalities seen in cells treated with agents that interfere directly[29-30] or indirectly[31-33] with microtubule polymerization (e.g., paclitaxel).

2.6. Mechanisms of action of TTFields

In order to explain how TTFields cause orientation dependent damage to dividing cells and disrupt the proper formation of the mitotic spindle Novocure modeled the forces exerted by TTFields on intracellular charges and polar particles using finite element simulations. Two main mechanisms by means of which the electric fields may affect dividing cells were recognized. The first relates to the field effect on polar macromolecule orientation. Within this framework, during the early phases of mitosis, i.e., in pre-telophase, when tubulin polymerization-depolymerization drives the proliferation process, the electric field forces any tubulin dimers, positioned further than 14nm away from the growing end of a microtubule, to orient in the direction of the field. This force moment, (10^{-5} pN) acting on the dimers, is sufficient to interfere with the proper process of assembly and disassembly of microtubules that is essential for chromosome alignment and separation[34]. This effect can explain the mitotic arrest of TTField treated cells[35].

The second mechanism, which interferes with cell division, and is most likely to play an important role in cell destruction, becomes dominant during cleavage. As seen in simulations, the electric field within quiescent cells is homogenous, whereas the field inside mitotic cells, during cytokinesis, is not homogenous. An increased field line concentration (indicating increased field intensity) is seen at the furrow, a phenomenon that highly resembles the focusing of a light beam by a lens. This in-homogeneity in field intensity exerts a unidirectional electric force, on all intracellular charged and polar entities (including induced dipoles), pulling them towards the furrow (regardless of field polarity). For example, for a cleavage furrow that reached a diameter of 1μm in an external field of only 1 V/cm, the force exerted on the microtubules is in the order of 5pN. This magnitude is compatible with the reported forces necessary to stall microtubule polymerization which is 4.3 pN[36]. With regards to other particles, such as cytoplasmic organelles, they are polarized by the field within dividing cells. Once polarized, the forces acting on such particles may reach values up to an order of 60 pN resulting in their movement towards the furrow at velocities that may approach 0.03 m/sec. At such velocity, cytoplasmic organelles would pile up at the cleavage furrow within a few minutes, interfering with cytokinesis and possibly leading to cell destruction. It has also been found that the electric forces acting on intracellular particles are maximal when the axis of division is aligned with the external field. This is consistent with the dependence of the destructive effect of TTFields on the angle between division axis and the field, as demonstrated experimentally. In addition, the calculated dependence of the magnitude of this force on frequency is consistent with the experimentally determined frequency dependence of the inhibitory effect of TTFields on melanoma and glioma cell proliferation (120 kHz vs. 200 kHz, respectively).

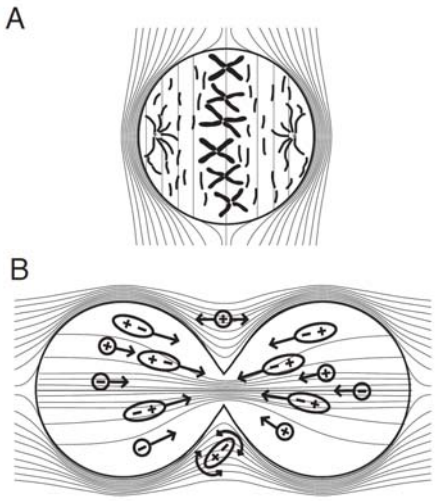


Figure 1 Tumor Treating Fields Mechanism of Action: (A) Disruption of the formation of the mitotic spindle in metaphase and (B) Positive dielectrophoresis during anaphase.

2.7. In Vivo effects of TTFields

Novocure has shown that TTFields can be applied effectively to animals through electrodes (transducer arrays) placed on the surface of the body[27, 37]. Using a special type of electrically insulated electrodes (transducer arrays), significant inhibition of the growth of both intradermal melanoma (B16F1) in mice and intracranial glioma (F-98) in rats was seen after less then one week of treatment. This growth inhibition was accompanied by a decrease in angiogenesis within the tumor, due to inhibition of endothelial cell proliferation.

Extensive safety studies in healthy rabbits and rats exposed to TTFields for protracted periods of time have shown no treatment related side effects. The reasons for the surprisingly low toxicity of TTField treatment can be explained in the light of the known passive electric properties of normal tissues within the body and the effects of electric fields applied via insulated electrodes (transducer arrays). More specifically, two types of toxicities may be expected in an electric field based treatment modality. First, the fields could interfere with the normal function of excitable tissues within the body causing, in extreme cases, cardiac arrhythmias and seizures. However, this is not truly a concern with TTFields since, as frequencies increase above 1 kHz, excitation by sinusoidal electric fields decreases dramatically due to the parallel resistor-capacitor nature of the cell membrane (with a time constant of about 1ms). Thus, as expected, in both acute and chronic application of TTFields to healthy animals, no evidence of abnormal cardiac rhythms or pathologic neurological activity was seen.

Secondly, the anti-mitotic effect of TTFields might be expected to damage the replication of rapidly dividing normal cells within the body (bone marrow, small intestine mucosa). Surprisingly, no treatment related toxicities were found in any of the animal safety trials performed by Novocure, even when field intensities 3 fold higher than the effective anti-tumoral dose were used. The lack of damage to intestinal mucosa in TTField-treated animals is probably a reflection of the fact that the small intestine mucosal cells have a slower replication cycle than neoplastic cells and that the intestine itself most likely changes its orientation in relation to the applied field quite often, lowering the efficacy of TTField mediated mitotic disruption. Bone

marrow, on the other hand, is naturally protected from TTFields by the high electric resistance of both bone and bone marrow compared to most other tissues in the body. To test the later assumption, the TTField intensity within the bone marrow of a long bone was modeled using the finite element mesh (FEM) method. It was found that the intensity of TTFields was 100-fold lower within the bone marrow compared to the surrounding tissues (including within solid tumors). Thus, hematopoietic cell replication should not be affected even when TTField intensities 10-fold higher than necessary to inhibit tumor growth are applied.

2.8. The NovoTTF-100A Device

The NovoTTF-100A is a portable battery operated device which produces TTFields within the human body using surface electrodes (transducer arrays). The TTFields are delivered to the patient by means of surface transducer arrays that are electrically insulated, so that resistively coupled electric currents are not delivered to the patient. The transducer arrays, which incorporate a layer of adhesive hydrogel and a layer of hypoallergenic medical tape, are placed on the patient's shaved head. The transducer arrays must be replaced every three to four days and the scalp re-shaved in order to maintain optimal capacitative coupling between the transducer arrays and the patient head. All the treatment parameters are pre-set by Novocure so there are no electrical output adjustments available to the patient. The patient must learn to apply and change transducer arrays and change and recharge depleted device batteries and to connect to an external electrical outlet.

Novocure Device Support Specialists and/or Clinical Science Liaisons will be available at all clinical sites participating in the trial to train and support patients, research staff and health care professionals with the operation and management of the device. In addition, Novocure provides a 24/7 support line for patients and the health care team.

2.9. Effect of NovoTTF-100A on recurrent GBM patients – Pivotal study

A pilot study was performed enrolling 10 recurrent GBM patients treated with the NovoTTF-100A device as monotherapy[37-38]. All patients underwent surgery and radiotherapy for the primary tumor. Only 1 patient was chemotherapy naïve, the rest having received either Temozolomide or other chemotherapeutic agents, as adjuvant treatment, prior to recurrence.

All patients were treated with multiple four-week treatment courses using continuous, 24-hour a day, 200 kHz, 0.7 V/cm TTFields. TTFields were applied through two sets of opposing insulated transducer arrays and alternated at a 1 second duty cycle between two perpendicular field directions through the tumor. Patients completed between 1 and 15 treatment courses leading to maximal treatment duration of 14.5 months. Overall, more than 70, 4 week treatment courses were completed (> 7 courses per patient on average). The treatment was well tolerated with no treatment related serious adverse events seen in any of the patients. Patients received treatment on average about three quarters of the scheduled time. Considering the continuous nature of NovoTTF treatment (i.e., 24 hours a day for many months) this figure indicates that compliance with treatment, similar to the newly diagnosed pilot study was very high, with patients taking very few days off treatment and stopping only for short periods of time during treatment for personal needs. Mild to moderate contact dermatitis appeared beneath the transducer gel in 8 of the 10 patients during treatment. The skin reaction improved with use of topical corticosteroids and regular shifting of the location of the transducer arrays.

The median progression free survival (PFS) of the patients in this study exceeded historical controls[4] dramatically (26.1 weeks versus 9 weeks, respectively). The PFS at 6 months (PFS6) was 50% compared to 15% in historical controls[4]. Until the last report 7 of the 10 patients have died. The remaining 3 patients are still alive and 2 of them are progression free. Median overall survival was 62 weeks. Response rate was 25% (1 CR + 1 PR) and only two patients had progressive disease despite treatment.

Effect of NovoTTF-100A on recurrent GBM patients – Pivotal study

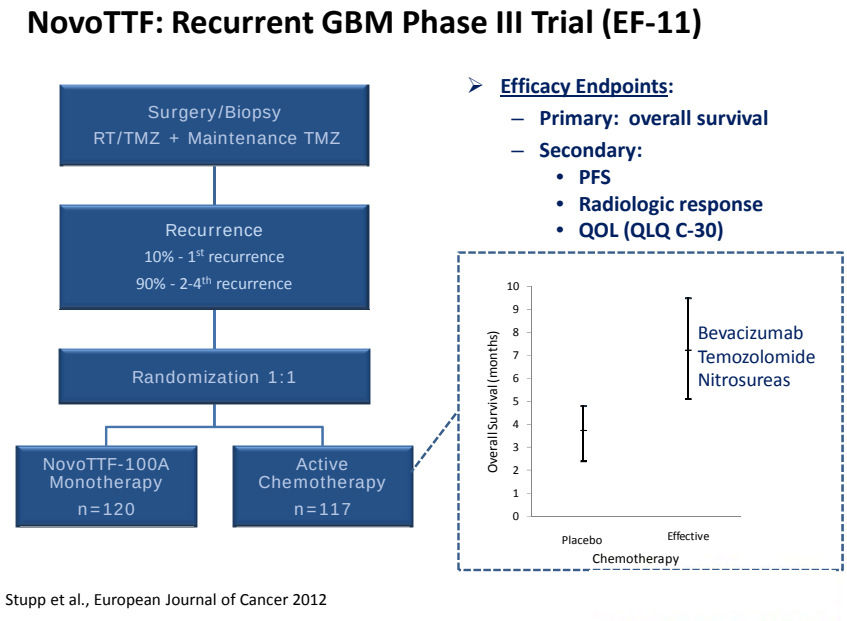
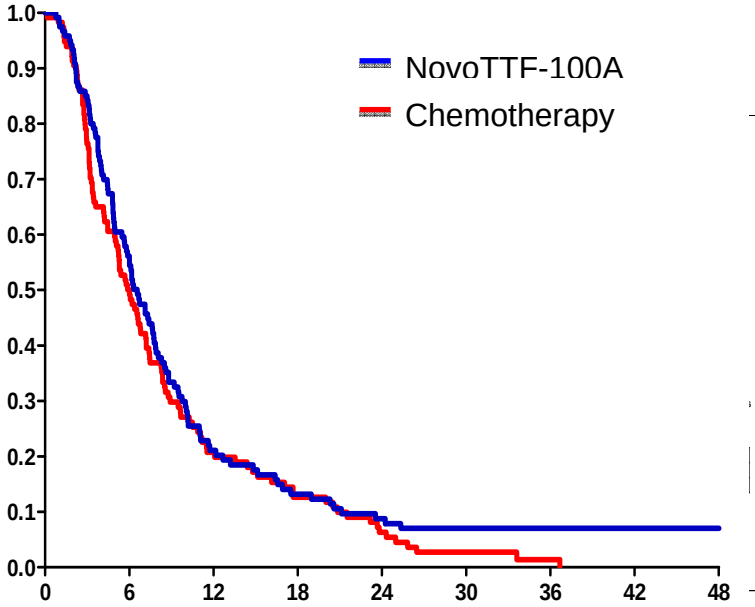


Figure 2: Schema of the EF-11 trial- Effect of NovoTTF-100A in Recurrent Glioblastoma Multiforme (GBM)

Based on the promising data from the pilot trial, Novocure conducted a prospective, randomized, open label, active parallel control trial to compare the effectiveness and safety outcomes of recurrent GBM subjects treated with NovoTTF-100A monotherapy (n=120) to those treated with an effective best standard of care chemotherapy (including bevacizumab; n=117). Best standard of care chemotherapy was investigator chosen with the most common treatments as follows: 31% bevacizumab based regimens, 31% irinotecan and 25% nitrosureas. Patient characteristics were well balanced between treatment arms and 90% of patients were at their second or beyond recurrence (Figure 2). NovoTTF-100A subjects had comparable overall survival to subjects receiving the best available chemotherapy (OS 6.6 vs. 6.0 months; HR 0.86; p=0.98, shown in Figure 3)[39]. Similar results showing comparability of NovoTTF-100A to chemotherapy were seen in all secondary endpoints (e.g., PFS6 = 21.4% for NovoTTF-100A vs. 15.2% for chemotherapy). In addition, objective response rates were seen with NovoTTF-100A monotherapy 14 vs. 9.6% for chemotherapy (p = 0.19).



Median survival (months)	
NovoTTF-100A Svstem	6.6
Chemotherapy (n = 117)	6.0
Cox Proportional Model	
Hazard Ratio	0.86
P value	0.27
95% CI of ratio	0.66 –

Figure 3: Overall survival (Kaplan Meier curves)

NovoTTF-100A subjects experienced fewer adverse events in general, significantly fewer treatment related adverse events, and significantly lower gastrointestinal, hematological and infectious adverse events compared to chemotherapy controls. The only device-related adverse events seen were a mild to moderate skin irritation beneath the device transducer arrays, which was easily treated with topical ointments. Finally, quality of life measures (EORTC – QLQ C30 symptom and general scales) were better in NovoTTF-100A subjects as a group when compared to subjects receiving effective best standard of care chemotherapy.

Given the clinical interest in bevacizumab in the setting of recurrent GBM two exploratory survival analyses were performed in a subset of bevacizumab treated patients: 1) NovoTTF-100A treatment versus patients that had received bevacizumab-based regimens on the chemotherapy arm of the trial and 2) NovoTTF-100A versus chemotherapy in the subset of patients that had progressed on prior bevacizumab (~20%). In the first exploratory analysis, median OS was significantly longer for the NovoTTF-100A treated patients than for those treated with a bevacizumab based regimen (6.6 vs. 5.0 months; HR 0.65, p = 0.048; CI 0.51 to 0.90)[40] (Figure 3). In the second exploratory analysis, median OS in patients who had progressed on bevacizumab, was significantly longer when treated with NovoTTF-100A compared to chemotherapy (6.3 vs. 3.3 months; HR 0.39; p = 0.01; CI 0.19 to 0.79) (Figure 4).

Treatment options for patients with recurrent GBM progressing on bevacizumab remains a significant clinical challenge and an important area of study. Given the single agent activity of NovoTTF, especially in patients who have progressed on bevacizumab, coupled with the fact that the mechanism of action of NovoTTF not being limited by normalization of the BBB by use of concomitant bevacizumab makes a rational and compelling case for evaluation of the combination of Novocure TTF and bevacizumab in patients with recurrent GBM who progress

on bevacizumab. In addition, the favorable safety profile of NovoTTF suggests that the combination will add little additional toxicity.

In summary, a combination of NovoTTF-100A and bevacizumab is promising:

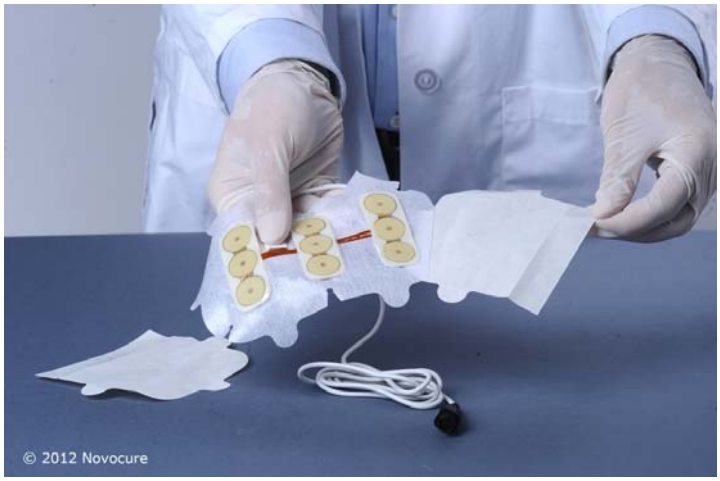
1. The mechanism of action of NovoTTF-100A is not limited by normalization of the blood brain barrier by use of bevacizumab
2. Two approaches have non overlapping toxicities.
3. Both approaches demonstrated efficacy and have been approved by the FDA.

Hence we propose a trial of a combination of NovoTTF-100A and bevacizumab in patients with recurrent GBM who are bevacizumab naive.

2.10. NovoTTF-100A Treatment

1. Treatment planning: Transducer array layout will be determined based on the location of the patient's tumor(s) on MRI. Patient training: Patients will be trained in the use of the device by the investigator, a designated health care provider (eg. Nurse) or device technician trained by Novocure. Novocure is currently validating the software used for external use. Once validated, the investigator using the NovoTAM™ software supplied by Novocure will determine the transducer array layout. Investigators will be trained in the utilization of this software by a Novocure representative. In the meantime, investigators will forward MRIs to Novocure for array layout planning.
2. Treatment initiation: NovoTTF-100A treatment will be initiated by the investigator as per protocol. All patients will be required to shave their heads to initiate array placement and TTField therapy. Array placement will be performed based on the transducer array map calculated during treatment planning.
3. Treatment duration: Treatment with the device will be continuous with breaks allowed for personal needs (eg. showering, array exchange). Patients must use the device for at least 18 hours a day on average. Treatment will be continued until disease progression in the brain, death, or unacceptable side effects to patient.
4. The NovoTTF-100A device will be programmed by Novocure to deliver 200kHz TTFields in two sequential, perpendicular field directions at a maximal intensity of 707mA RMS. There will be no adjustments made to the device by investigators or patients/caregivers.

5. Transducer array replacement: Patients will replace the transducer arrays twice to three times per week with the help of a caregiver. At each array replacement the patient's scalp will be re-shaved and skin treated according to the guidelines set out below.



6. Compliance assessment: The device will be interrogated on a monthly basis to assess patient compliance with therapy. Novocure is currently validating the software for investigator use, using the NovoPCA™ . Until this is available Novocure device technicians will conduct the monthly compliance assessment.
7. The following skin care guidelines should be closely adhered to:
    a. If the skin beneath the transducer arrays is inflamed a hydrocortisone ointment should be prescribed to the patient. The patient or caregiver should apply the ointment after removing the arrays and cleaning the scalp with baby oil and medical alcohol. The ointment should be left on the scalp for at least 30 minutes prior to washing the skin with a mild shampoo and applying a new set of arrays.
    b. At each array replacement, the new set of arrays should be shifted by approximately 2 cm compared to the previous layout so that the array discs are placed between the areas of skin irritation. At the next array replacement the arrays should be shifted back to their original location.
    c. If the dermis is breached (ulcers, open sores, punctate lesions, cuts, etc.) an antibiotic ointment (e.g. mupiricin) should be prescribed and used in place of the hydrocortisone ointment.
    d. There will be no "dose" adjustments to the device for adverse events. Reasons for breaks in treatment for longer than 24 hours will be documented in the CRFs.

2.11. Potential Adverse Events:

NovoTTF-100A

Treatment with the NovoTTF-100A is not expected to cause any serious side effects. However, it is possible that treatment may cause any of the following:

1. Local warmth and tingling "electric" sensation beneath the transducer array
2. Allergic reaction to the adhesive or to the gel
3. Skin irritation or skin breakdown

4. Infection at the sites of transducer array contact with the skin
5. Transducer array overheating leading to pain and/or local skin burns
6. Headache
7. Fatigue

In the phase III trial of NovoTTF-100A monotherapy vs. physician's choice chemotherapy in recurrent GBM the following moderate to severe adverse events (regardless of causality) were seen:

		TTF (n=116)	**Active Control (n=91)**
System	**Adverse event term**	**% (% gr. 3+4)**	**% (% gr. 3+4)**
Hematological		3 (0)	17 (4)
	Leukopenia	0 (0)	5 (1)
	Neutropenia	0 (0)	2 (1)
	Thrombocytopenia	1 (1)[†]	7 (2)
Gastrointestinal disorders		4 (1)	17 (3)
	Abdominal pain	0 (0)	3 (0)
	Diarrhea	0 (0)	6 (2)
	Nausea / Vomiting	2 (0)	7 (0)
General deterioration and malaise		5 (1)	6 (1)
Infections		4 (0)	8 (1)
Skin rash (transducer arrays)		2 (0)	0 (0)
Metabolism and nutrition disorders		4 (1)	6 (3)
Musculoskeletal Disorders		2 (0)	5 (0)
Nervous system disorders		30 (7)	28 (7)
	Brain edema	0 (0)	2 (0)
	Cognitive disorder	2 (1)	2 (1)
	Convulsion	7 (2)	5 (2)
	Dysphasia	2 (0)	1 (0)
	Headache	8 (1)	6 (0)
	Hemianopsia	1 (0)	3 (1)
	Hemiparesis	3 (1)	2 (1)
	Neuropathy peripheral	2 (0)	2 (0)
Psychiatric disorders		5 (0)	4 (0)

Renal and urinary disorders		3 (1)	3 (0)
Respiratory Disorders		1 (0)	3 (1)
Vascular disorders		3 (1)	4 (3)
	Pulmonary embolism	1 (1)	2 (2)
	Hypertension	1 (0)	1 (1)
	Deep vein thrombosis	1 (0)	1 (0)
† thrombocytopenia from prior chemotherapy, normalized subsequently.			

3. SELECTION AND WITHDRAWL OF PATIENTS

3.1. ELIGIBILITY CRITERIA:

Inclusion criteria:

1. Patients with histologically confirmed glioblastoma or other grade IV malignant glioma (i.e. gliosarcoma, small cell glioblastoma, etc.), recurrent after prior external-beam fractionated radiotherapy and temozolomide chemotherapy.
2. Patients with upto two prior recurrences are allowed.
3. Karnofsky performance status ≥ 70%.
4. Age ≥ 22 years old.
5. Patients must have the following laboratory values:
    - Absolute neutrophil count (ANC) ≥ 1.5 x 109/L
    - Platelets ≥ 100 x 109/L
    - Hemoglobin (Hgb) > 9 g/dL
    - Serum total bilirubin: ≤ 1.5 x ULN
    - ALT and AST ≤ 3.0 x ULN
    - Serum creatinine ≤ 1.5 x ULN
    - Blood coagulation parameters: INR ≤ 1.5
6. Minimum interval since completion of radiation treatment is 12 weeks
7. Minimum interval since last drug therapy:
    - 3 weeks since last non-cytotoxic therapy
    - 3 weeks must have elapsed since the completion of a non-nitrosourea-containing chemotherapy regimen
    - 6 weeks since the completion of a nitrosourea-containing chemotherapy regimen.

8. Patients must have signed an approved informed consent and authorization permitting release of personal health information.
9. Patients with the potential for pregnancy or impregnating their partner must agree to follow acceptable birth control methods to avoid conception. The effects of bevacizumab on developing fetus or nursing infant are not known. Female patients of child-bearing potential must have a negative pregnancy test.
10. Patients must have no concurrent malignancy except curatively treated basal or squamous cell carcinoma of the skin or carcinoma in situ of the cervix and breast, adequately treated stage I or II cancer from which the patient is in complete remission. Patients with other prior malignancies must be disease-free for ≥ three years.
11. Patients must be maintained on a stable corticosteroid regimen from the time of their baseline scan until the start of treatment and/or for at least 5 days before starting treatment.

Exclusion criteria:

1. Patients who have had previous treatment with either bevacizumab and/ or NovoTTF 100A system.
2. Patients who have undergone major surgery (e.g. intra-thoracic, intra-abdominal or intra-pelvic), open biopsy or significant traumatic injury ≤ 4 weeks prior to starting study drug, or patients who have had minor procedures, percutaneous biopsies or placement of vascular access device ≤ 1 week prior to starting study drug, or who have not recovered from side effects of such procedure or injury
3. Patients with impaired cardiac function or clinically significant cardiac diseases, including any of the following:
    - History or presence of serious uncontrolled ventricular arrhythmias
    - Any of the following within 6 months prior to starting study drug: myocardial infarction (MI), severe/unstable angina, Coronary Artery Bypass Graft (CABG), Congestive Heart Failure (CHF), Cerebrovascular Accident (CVA), Transient Ischemic Attack (TIA), Pulmonary Embolism (PE)
    - Uncontrolled hypertension (defined by a SBP ≥ 160 mm Hg or DBP ≥ 100 mm Hg while on anti-hypertensive medications)
4. Patients with cirrhosis, or active viral or nonviral hepatitis.
5. Implanted pacemaker, shunts, defibrillator or deep brain stimulator, other implanted electronic devices in the brain or documented clinically significant arrhythmias.
6. Infra-tentorial tumor
7. Evidence of increased intracranial pressure (clinically significant papilledema, vomiting and nausea or reduced level of consciousness)
8. Known sensitivity to conductive hydrogels
9. Known diagnosis of human immunodeficiency virus (HIV) infection (HIV testing is not mandatory)

10. Other concurrent severe and/or uncontrolled concomitant medical conditions (e.g. active or uncontrolled infection, uncontrolled diabetes) that could cause unacceptable safety risks or compromise compliance with the protocol
11. Pregnant or breast-feeding women
12. Patients unwilling or unable to comply with the protocol
13. Patients with leptomeningeal disease

3.2. Duration of Treatment and Patient Withdrawal Criteria

Patients are eligible for treatment with the combination of bevacizumab and NovoTTF-100A until disease progression or unacceptable toxicity. A patient should be withdrawn from study treatment if, in the opinion of the Investigator, it is medically necessary, or if it is the wish of the patient. If a patient does not return for a scheduled visit, every effort should be made to contact the patient. In any circumstance, every effort should be made to document patient outcome. Data to be collected at the end of study visit are described in the Schedule of Assessments (Table). Patients will be followed for at least 28 days after the last dose of bevacizumab and removal of NovoTTF-100A for adverse events. If the patient withdraws consent, no further evaluations should be performed, and no attempts should be made to collect additional data. In addition, patients will be withdrawn from treatment in the case of:

- Modified RANO criteria defined disease progression. In cases where Modified RANO criteria cannot be applied, progression should be based on unequivocal evidence of progressive disease sufficient to require a change in therapy.
- A need for surgery, radiation, or for other anticancer therapy not specified in the protocol.
- Lost to follow-up or noncompliant.
- Pregnancy. Pregnant patients should be followed for the duration of the pregnancy and the outcome of the pregnancy should be documented.

4. ENDPOINTS

4.1. Primary Endpoint:

1. Efficacy of combination of bevacizumab and NovoTTF-100A in bevacizumab-naïve patients with recurrent GBM as measured by 6-month progression-free survival (PFS6)

4.2. Secondary Endpoints:

1. Safety and tolerability of combination of bevacizumab and NovoTTF-100A in this population by CTCAE version 4.0.
2. Median overall survival (OS) by KM methodology
3. Objective response rate (ORR) using modified RANO criteria.
4. To assess time-to-progression in this population
5. To assess neurocognitive function (NCF) and quality of life (QOL) in this population.

5. STATISTICAL CONSIDERATIONS

In the randomized Phase II trial of bevacizumab with or without irinotecan in recurrent GBM participants in first or second relapse. Participants were treated with bevacizumab 10 mg/kg every 2 weeks, alone or in combination with irinotecan[2]. In the bevacizumab monotherapy arm (n=85), the response rate was 28% and PFS6 43%[2]. In reviewing this trial for purposes of approval, the FDA conducted an independent imaging review and determined that the response rate was 26% and the PFS6 was 36%[41].

This trial will enroll enough participants to discriminate between a 36% and 56% PFS6 rate. The trial will accrue 40 participants. The trial will be declared successful if at least 20 achieve PFS6. This design assumes an exact type I error of 5% (one-sided) and a maximum type II error of 20%.

5.1. Sample Size/Accrual Rate

This trial will be a single arm multicenter phase II and will accrue 40 participants. The trial will be declared successful if at least 20 achieve PFS6. The trial will be conducted at Cleveland Clinic, Ohio State University and University of Cincinnati. Every year 125-150 patients with recurrent GBM are seen at Cleveland Clinic. Approximately 3-4 patients per month will be entered onto the study and accrual will be completed in 12 months. All patients will be followed until progression.

5.2 Data Analysis

Since all patients will have the potential for at least six months of follow-up PFS will be summarized both as the simple proportion of patients progression-free at 6 months and using the method of Kaplan and Meier. Secondary endpoints such as response, toxicity, neurocognitive function and QOL (based on the FACT-Br) will be summarized using frequency counts and proportions or medians and ranges as appropriate. Changes from baseline at a particular timepoint will be assessed using methods such as chi-square tests and the Wilcoxon signed rank test, while the overall time to neurocognitive decline and overall survival will be assessed using the Kaplan-Meier method. Exploratory comparisons of time-to-event data such as overall PFS, overall survival, and neurocognitive decline will be conducted using methods such as the logrank test and proportional hazards model. Tests of significance of secondary endpoints will generally be two-sided and no adjustment will be made for multiple comparisons due to the exploratory nature of these studies.

6. DRUG THERAPY

6.1. Bevacizumab

Bevacizumab will be administered intravenously on days 1 and 15 of each 28 day cycle. 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 10 mg/kg of actual body weight. The dose will be determined using body weight determined at the beginning of each treatment cycle.

6.2. General:

Prior to each treatment, the patient should be carefully assessed with special attention to blood pressure, proteinuria, bleeding and cardiovascular events, as well as symptoms or signs of bowel perforation and reversible posterior leukoencephalopathy syndrome (RPLS). Infusional reactions: Routine premedication is not required for the first dose of bevacizumab. If infusional reactions occur, acetaminophen, diphenhydramine, steroids or other medications may be given for symptom control and for premedication as needed. Anaphylactic precautions should be observed during bevacizumab administration.

- Hypertension: Patients should have blood pressure monitored prior to each infusion of bevacizumab. Hypertensive medication should be initiated or increased for optimal blood pressure control according to standard public heath guidelines.
- Surgery and wound complication issues and surgery: The appropriate interval from discontinuation of bevacizumab to subsequent elective surgery required to reduce the risk of impaired wound healing has not been determined. Decision on such an interval should take into consideration the half-life of bevacizumab. It is generally recommended that bevacizumab should be discontinued at least 4-8 weeks prior to major elective surgery. In addition, bevacizumab should not be restarted until at least 4 weeks after major surgery provided that the wound has adequately healed; in cases of high risk procedures such as liver resection, thoracotomy or neurosurgery, it is recommended that bevacizumab be resumed no earlier than 8 weeks after surgery.

Bevacizumab Dose Modifications

The dose of bevacizumab will be 10 mg/kg delivered intravenously. There will be no dose reduction for bevacizumab. Treatment should be interrupted or discontinued for certain adverse events, as described below. If bevacizumab is interrupted for ANY reason for > 8 weeks, the patient should discontinue bevacizumab therapy on protocol. If the bevacizumab therapy is discontinued and the patient is maintained on the protocol on only NovoTTF 100A system, then the laboratory tests pertaining to bevacizumab may be discontinued and the patient need to be followed only once every 4 weeks and can discontinue bevacizumab related labs such as urine analysis.

Treatment Modification for Bevacizumab- Related Adverse Events

Event	CTCAE.v4.0 Grade	Action To Be Taken
Allergic reactions or Acute infusional reactions/ cytokine release syndrome	Grade 1-3	If infusion-related or allergic reactions occur, premedications should be given with the next dose and infusion time may not be reduced for the subsequent infusion. Follow the guidelines in Section 7.3 for bevacizumab administration. **For patients with grade 3 reactions**, bevacizumab infusion should be stopped and not restarted on the same day. At the physicians' discretion, bevacizumab may be permanently discontinued or re-instituted with premedications and at a rate of 90+15 min. **If bevacizumab is re-instituted, the patient should be closely monitored for a duration comparable to or longer than the duration of the previous reactions**.

	Grade 4	Discontinue bevacizumab
Arterial Thrombosis -Cardiac ischemia/ infraction **-**CNS ischemia (TIA, CVA) **-**any peripheral or visceral arterial ischemia/thrombosis	Grade 2 (if new or worsened since bevacizumab therapy)	Discontinue bevacizumab
	Grade 3-4	Discontinue
Venous Thrombosis		
	Grade 3 OR asymptomatic grade 4	Hold bevacizumab treatment. If the planned duration of full-dose anticoagulation is < 2 weeks, bevacizumab should be held until the full-dose anticoagulation period is over. ⓾ If the planned duration of full-dose anticoagulation is >2 weeks, bevacizumab (or placebo) may be resumed during the period of full-dose anticoagulation **IF** all of the criteria below are met: -The subject must have an in-range INR (usually 2-3) on a stable dose of warfarin or be on a stable dose of heparin prior to restarting bevacizumab -The subject must not have pathological conditions that carry high risk of bleeding (eg, tumor involving major vessels or other conditions) -The subject must not have had hemorrhagic events while on study. If thromboemboli worsen/recur upon resumption of study therapy, discontinue bevacizumab
	Grade 4 (symptomatic)	Discontinue bevacizumab
Hypertension*	[Treat with antihypertensive medication as needed. The goal of BP control should be consistent with general medical practice]	
	Grade 1	Consider increased BP monitoring
	Grade 2 asymptomatic **but** diastolic BP < 100 mmHg	Begin anti-hypertensive therapy and continue bevacizumab
	-Grade 2-3 Symptomatic **OR** -Diastolic BP > 100 mmHg	• Hold bevacizumab until symptoms resolve **AND** BP < 160/90mmHg*
	Grade 4	Discontinue bevacizumab
Congestive Heart Failure	Grade 3	• Discontinue bevacizumab
	Grade 4	Discontinue Bevacizumab
	Grade 4	Discontinue bevacizumab
Proteinuria	[Proteinuria should be monitored by urine analysis for urine protein creatinine (UPC) ratio prior to every other dose of bevacizumab	
	UPC ratio < 3.5	Continue bevacizumab
	UPC ratio > 3.5	Hold bevacizumab (or placebo)until UPC recovers to < 3.5
	Grade 4 or nephrotic syndrome	Discontinue bevacizumab
Hemorrhage (CNS or pulmonary)	Grade 2-4	• Discontinue bevacizumab

Hemorrhage (non-CNS; non-pulmonary)	Grade 3	• Patients receiving full-dose anticoagulation should discontinue bevacizumab • For patients not on full-dose anticoagulation, hold bevacizumabuntil ALL of the following criteria are met: -the bleeding has resolved and Hb is stable -there is no bleeding diathesis that would increase the risk of therapy -there is no anatomic or pathologic condition that could increase the risk of hemorrhage recurrence. • Patients who experience recurrence of grade 3 hemorrhage should discontinue study therapy
	Grade 4	Discontinue bevacizumab
RPLS (reversible posterior leukoencephalopathy syndrome **or PRES** (posterior reversible encephalopathy syndrome)	**• Hold bevacizumab in patients with symptoms/signs suggestive of RPLS; subsequent management should include MRI scans and control of HTN • Discontinue bevacizumab upon diagnosis of RPLS**	
Wound dehiscence requiring medical or surgical intervention	**•Discontinue bevacizumab**	
GI perforation, GI leak or fistula	Discontinue bevacizumab	
Bowel obstruction	Grade 2 requiring medical intervention	• Hold bevacizumab until complete resolution, with a minimum of 4 weeks after surgery.
	Grade 3-4	• Hold bevacizumab until complete resolution • If surgery is required, patient may restart bevacizumab after full recovery from surgery, and at investigator's discretion
Other unspecified bevacizumab-related AEs (except controlled nausea/vomiting).	Grade 3	Hold bevacizumab until symptoms resolve to < grade 1
	Grade 4	• Discontinue bevacizumab**• Upon consultation with the study chair,** resumption of bevacizumab may be considered if a patient is benefiting from therapy and the grade 4 toxicity is transient, has recovered to < grade 1 and unlikely to recur with retreatment

6.3. OTHER THERAPY

Permitted Supportive 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.

7. TREATMENT PLAN

Treatment will be administered on an outpatient basis.

No investigational or commercial agents or therapies other than those described below may be administered with the intent to treat the participant's malignancy.

7.1. Duration of Therapy & Criteria for Removal from Study Treatment

Duration of therapy will depend on individual response, evidence of disease progression and tolerance. In the absence of treatment delays due to adverse events, treatment may continue until one of the following criteria applies:

- Disease progression,
- Intercurrent illness that prevents further administration of treatment,
- Unacceptable adverse event(s)
- Participant demonstrates an inability or unwillingness to comply with protocol
- Participant becomes pregnant,
- Participant decides to withdraw from the treatment phase of the study, or
- General or specific changes in the participant's condition render the participant unacceptable for further treatment in the opinion of the treating investigator.

1. Table: Schedule of Assessments

Protocol Activities	Screening	*Cycle 1		*Cycles 2		*Cycles 3+		End of Study [3]	**Post Treatment Follow-up
	Day -28	Day 1 [1,2]	Day 15	Day 1 [1]	Day 15	Day 1 [1]	Day 15		28 Days
Baseline Documentation									
Informed Consent [4]	X								
Medical and Oncology History	X								
Physical Examination [5]	X	X		X		X		X	X
Vital Signs [6]	X	X	X	X	X	X	X	X	
Laboratory Studies									
Pregnancy Test [7]	Day -7								
Hematology [8]	X	X		X		X			
Coagulation	X								
Blood Chemistry [8]	X	X		X		X			
Urinalysis [9]	X	X		X		X			
Treatment w/ Drug or Device									
Bevacizumab		X	X	X	X	X	X		
NovoTTF-100A		Device***							
Tumor Assessments									
CT or MRI Scans [10]	X					X		X	
Other Clinical Assessments									
12-Lead ECG [11]	X								
Neurocognitive function [12]	X			X		X†			X
Quality of Life [13]	X	X		X		X			X
Concomitant Medications/Treatments [14]	X	X		X		X		X	X
Adverse Events [15]		X	X	X	X	X	X	X	X

*Each cycle is 28 days in duration. The allowable window for each visit within the cycle is +/- 4 days unless otherwise stated.
**Allowable window Post Treatment Follow-up is ±2 weeks
*** Allowable window for device placement is 14 days
† Cognitive function to be assessed every even numbered cycle.

Schedule of Assessments Footnotes	
1	**Days of Treatment:** All assessments should be performed prior to dosing unless otherwise indicated.
2	**Cycle 1 Day 1:** Hematology, coagulation, blood chemistry, urinalysis, physical examination, pregnancy test not required if acceptable screening assessment is performed within 7 days prior to the start of treatment with Bevacizumab.
3	**End of Study:** Assessments only need to be completed if not completed during the previous 2 weeks on study (during the last 8 weeks on study for radiologic tumor assessments).
4	**Informed Consent:** Must be obtained prior to undergoing any study specific procedure and may occur prior to the 28-day screening period.
5	**Physical Examination:** Examination of major body systems, karnofsky performance status, and vital signs (heart rate, temperature, blood pressure, weight). The physical examination will include evaluation of skin under transducer arrays.
6	**Vital Signs:** Heart rate, temperature, blood pressure, weight (only needed for day 1 of every cycle and weight not required for day 15 of every cycle).
7	**Pregnancy Test:** Testing to be performed locally. All female patients of childbearing potential must have a negative serum or urine pregnancy test within 7 days of Cycle 1 Day 1 in order to be enrolled in the trial.
8	**Hematology and Chemistry:** Testing to be performed locally. In addition to the assessments scheduled for the clinical trial, patients should undergo assessment as appropriate to ensure safe treatment. Hematology: CBC with differential and platelet count Coagulation Prothrombin Time (PT) or Internalized Normalized Ration (INR) Serum Chemistry: Total bilirubin, alanine transaminase (ALT), aspartate transaminase (AST), alkaline phosphatase, total protein, albumin, sodium, potassium, bicarbonate, chloride, calcium, phosphorus, blood urea nitrogen, creatinine, and glucose
9	**Urinalysis:** urine analysis for urine protein creatinine (UPC) ratio prior to every other dose of bevacizumab
10	**CT or MRI Tumor Imaging:** MRI will be performed every 8 weeks. Assessments should be performed whenever disease progression is suspected. Allowable window for tumor imaging studies is +/- 7 days.
11	**12-Lead ECG:** Single tracing 12-lead ECG will be performed at screening.
12	**Neurocognitive Function (NCF):** Testing to be completed by trained study staff within 7 days of day 1, every other cycle (e.g., every 2 months) after baseline.
13	**Quality of Life (QOL):** To be completed within 7 days of day 1 of each cycle.
14	**Concomitant Medications and Treatments:** Concomitant medications and treatments will be recorded from 28 days prior to the start of study treatment and up to 28 days following the last dose of study treatment.
15	**Adverse Events:** Baseline Emergent Adverse Events/Adverse Events: Patients must be followed for safety from the day of informed consent until at least 28 days after the last dose of study treatment, or until all serious or NOVOCURE TTF related toxicities have resolved or are determined to be "chronic" or "stable", whichever is later.

8. Assessment of Safety

8.1. Safety Parameters

Safety will be characterized in terms of the incidence, timing, severity (graded by the National Cancer Institute [NCI] Common Terminology Criteria for Adverse Events [CTCAE],

Version 4.0), seriousness, and relatedness of adverse events and laboratory abnormalities. In addition, physical examination, vital signs, and Karnofsky performance status will be serially monitored. Laboratory safety analyses will be based on the local laboratory data, and will include hematology, serum chemistry (including liver and kidney function), urinalysis, serum or urine pregnancy testing, and coagulation profile.

8.1.1. Laboratory Safety Assessments

Abnormal and clinically significant laboratory tests should be recorded as adverse events. To meet the definition of clinically significant, the test result generally requires a change in medical management (e.g. new medication, unplanned treatment, additional tests, etc.).

8.1.1.1. Hematology, Serum Chemistry, Coagulation, Pregnancy Test

Assessments will be performed at the time points indicated in the Schedule of Assessments (Table) and analyzed at local laboratories. Investigators may have additional blood tests performed for the purpose of planning treatment administration, or for following adverse events as clinically indicated.

- Hematology: CBC with differential and platelet count
- Coagulation: Prothrombin Time (PT) or Internalized Normalized Ration (INR) will be assessed
- Serum Chemistry: Total bilirubin, alanine transaminase (ALT), aspartate transaminase (AST), alkaline phosphatase, total protein, albumin, sodium, potassium, bicarbonate, chloride, calcium, phosphorus, blood urea nitrogen, creatinine, and glucose
- Pregnancy Test: Serum or urine pregnancy tests will be performed locally on all female patients of childbearing potential. Patients must be surgically sterile (i.e.: hysterectomy) or be postmenopausal, or must agree to use effective contraception during the study and for 3 months following last dose of bevacizumab. The definition of effective contraception will be based on the judgment of the Principal Investigator or a designated associate.

8.1.1.2. Urinalysis

8.1.1.3. Urine analysis for urine protein creatinine (UPC) ratio prior to every other dose of bevacizumab Physical Examination

A physical examination including, but not limited to, general appearance, head, eyes, ears, nose, throat, neck, heart, chest, abdomen, musculoskeletal, extremities, skin, lymph nodes, neurological genitourinary (as appropriate), and rectal (as appropriate) will be assessed at time points indicated within the Schedule of Assessments (table). The physical examination will include examination of known and suspected sites of disease.

8.1.1.4. Vital Signs

Heart rate, temperature, blood pressure, respiratory rate and weight will be assessed at time points indicated within the Schedule of Assessments (table).

8.1.1.5. Performance Status

The Karnofsky performance scale will be used to assess performance status at Screening.

8.1.1.6. ECG

A single 12-lead (with a 10–second rhythm strip) tracing will be used for all ECGs. It is preferable that the machine used has a capacity to calculate standard intervals automatically. ECG will be performed according to the Schedule of Assessments (table).

8.1.1.7. Neurocognitive Function (NCF)

The following NCF tests were selected because they are widely-used standardized psychometric instruments that have been shown to be sensitive to the neurotoxic effects of cancer treatment in brain tumor clinical trials[42]. The tests have published normative data that takes into account age, and where appropriate, education and gender. The tests were also selected to minimize the effects of repeated administration. Data obtained in other studies reveals that patients tend to perform normally on tests of attention span, reflecting adequate effort is being put forth, and that mood disturbance does not correlate with the results of the cognitive portion of the battery. The memory test has six alternate forms. The other tests measure motor and information processing speed and are relatively resistant to the effects of practice.

Cognitive Function	Test	Time to Administer (min)
Memory	Hopkins Verbal Learning Test	5
Verbal fluency	Controlled Oral Word Association	5
Visual-motor speed	Trail Making Test Part A	2
Executive Function	Trail Making Test Part B	5
Motor dexterity	Grooved Pegboard	3

8.1.1.8. Quality of Life (QOL)

The assessment of QOL has become accepted as an important endpoint. There are several validated measures, including the Functional Assessment of Cancer Therapy including Brain Tumor module (FACT-Br[43]). It evaluates the self-reported impact of illness on several important domains, including self-care, social support/function, emotional state, occupational role, and specific symptom impact on daily functions. This measure is completed by the subject and takes approximately 5 minutes.

8.1.2. ADVERSE EVENT REPORTING

This study will utilize the Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 for grading of all adverse events.

8.1.2.1. Grading of Adverse Event Severity

To report adverse events on the CRFs, the Investigator will use the severity grading as described in NCI CTCAE (Version 4.0).

Every effort should be made by the Investigator to assess the adverse event according to CTCAE criteria. If the Investigator is unable to assess severity because the term is not described in NCI (Version 4.0), severity of MILD, MODERATE, SEVERE, LIFE-THREATENING, or

FATAL may be used to describe the maximum intensity of the adverse event. For purposes of consistency, these intensity grades are defined as follows:

2. Table: Adverse Event Grading

Grade	Non-CTCAE Severity	Definition
1	Mild	Does not interfere with patient's usual function
2	Moderate	Interferes to some extent with patient's usual function
3	Severe	Interferes significantly with patient's usual function
4	Life-Threatening	Results in immediate risk of patient's death
5	Fatal	Results in patient's death

Note the distinction between the severity and the seriousness of an adverse event. A severe event is not necessarily a serious event. For example, a headache may be severe (interferes significantly with patient's usual function) but would not be classified as serious unless it met one of the criteria for serious events.

Adverse Events (AEs)
Definition of an AE: Any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medical treatment or procedure regardless of whether it is considered related to the medical treatment or procedure (attribution of unrelated, unlikely, possible, probable, or definite).

Serious Adverse Events (SAEs)
Definition of an SAE: Any adverse experience occurring during any part of protocol treatment and 30 days after that results in any of the following outcomes:

- Death
- A life-threatening adverse drug experience
- Inpatient hospitalization or prolongation of existing hospitalization
- A persistent or significant disability/incapacity

A medwatch form should be completed for each SAE, Novocure (and Cleveland Clinic must be notified (refer to patient as an IST patient).

8.2. A congenital anomaly/birth defect

Important adverse events that may not result in death, may not be life-threatening, or do not require hospitalization may be considered serious when, based upon appropriate medical judgment, they may acutely jeopardize the patient without immediate medical intervention to prevent one of the outcomes listed above. Serious may also includes any other event that the investigator or company judges to be serious. In addition, serious adverse events will be reported to local IRB according to institutional requirements. Death due to disease progression need not

be reported to the study monitor. These SAEs will be captured in the CRFs as described for regular AEs.

8.2.1. Routine Adverse Event Reporting

All adverse events must be reported in the source documentation and CRFs with appropriate information, including severity and rating of causality to the study drug/treatment. Adequate source documentation must be available to characterize the severity, duration and causality of each reported adverse event.

8.2.2. Unanticipated Adverse Device Effect Event (UADE) Reporting

Any potential unanticipated adverse device effect (UADE) will be reported to the study monitor and local IRB/EC within 10 days of the investigator learning of the event. The medical monitor will investigate whether the adverse event is a UADE and, if so, report the UADE to the Sponsor, as soon as possible but no later than 3 days after first learning of the event. Expedited report for FDA submission and reporting to other IRBs/ECs to follow within 10 working days after first learning of the event by the medical monitor.
The report will contain the following:

- The initials of the subject, patient MRN #, protocol # and title
- The date the event occurred
- A description of the UADE
- An explanation of how the UADE was handled
- A description of the subject's condition
- Indication if the subject remains on the study
- Indication if the event is considered related to the NovoTTF-100A
- Indication if an amendment to the protocol and/or consent form is recommended as a result

9. DATA SAFETY MONITORING PLAN

This protocol will adhere to the policies of the Case Comprehensive Cancer Center Data and Safety Monitoring Plan that is in accordance with NCI regulations. The Data and Safety Toxicity Committee will review all serious adverse events and toxicity reports as well as annual reviews.

10. MEASUREMENT OF EFFECT

10.1. Response Assessment

Optimal guidelines for determining GBM response to therapy are not yet well established. The most accepted are the Macdonald criteria [44]. However, increasingly specific criteria are being developed by the Response Assessment in Neuro-Oncology (RANO) Group through the American Society of Clinical Oncology. Using these developing guidelines, we have designed response criteria detailed in table below. These are largely based on standardized response criteria using bi-dimensional measurements of the largest contrast-enhancing area [45]. However, it has been demonstrated that contrast-enhanced images can be altered by agents inhibiting angiogenesis with occasional progression of T2-weighted or FLAIR abnormality as well as

clinical decline despite improvement in the contrast-enhancing signal [46-47]. In light of this, FLAIR imaging and clinical status will be part of the response criteria in addition to the widely used Macdonald criteria. Hence, the largest cross-sectional area on the T1w contrast-enhanced images will be selected and measured in 2 dimensions with linear measures on the baseline MRI axial sequence. In addition, the largest cross-sectional area of a contiguous hyperintense lesion on FLAIR sequences will be measured on the baseline MRI axial sequence. All subsequent scans will be compared against these baseline measures (for both CE and FLAIR). New foci of FLAIR signal abnormality will be recorded on each subsequent evaluation. Response will be scored based on a combination of imaging and clinical features as defined by the modified RANO criteria.

3. Table: Modified RANO Response Criteria

Response	T1 Contrast Enhancement (CE)	FLAIR Images	Steroids	Neurologic Exam
Complete Response (CR)	No residual CE (complete disappearance of all enhancing measurable disease for at least 4 weeks; confirmatory MRI at 4 weeks is required to score as CR) and no new lesions.	Stable or reduced area of FLAIR signal abnormality	No steroids	Stable or improved from prior evaluation
Partial Response (PR)	>50% reduction in sum of products of the perpendicular diameters of all measurable enhancing lesions sustained for at least 4 weeks and no new lesions or progression of non-measurable lesions	Stable or reduced area of FLAIR signal abnormality	Stable or reduced glucocorticoids from baseline MRI	Stable or improved from prior evaluation
Minor response (MR)	>25% reduction in sum of products of the perpendicular diameters of all measurable enhancing lesions and no new lesions (confirmatory MRI at 4 weeks is required to score as PR)	Stable or reduced area of FLAIR signal abnormality	Stable or reduced glucocorticoids from baseline MRI	Stable or improved from prior evaluation
Stable Disease (SD)	<25% reduction in area of CE maintained for at least 4 weeks duration. Does not qualify for CR, PR or progression	Stable or reduced area of FLAIR signal abnormality	Stable or reduced glucocorticoids from baseline MRI	Stable or improved from prior evaluation

Progressive Disease	>25% in the sum of products of the perpendicular diameters of CE lesions; evidence of new lesion(s).	Measurable increase in the sum of products of the perpendicular diameters of FLAIR signal abnormality from the baseline scan or the scan representing the best response (if there was a response) following therapy and not attributable to other co-morbid events (seizure, radiation, injury, infection, ischemia, etc.) OR presence of a new focus of FLAIR signal abnormality that cannot be explained by any other pathologic process.	Stable or increased dose of glucocorticoids	Stable or worsening neurologic symptoms

Radiological tumor assessments will be performed at screening, as outlined in the Schedule of Assessments (XXX), and whenever disease progression is suspected. Another tumor assessment will be performed at the End of Study Visit if an assessment has not been performed within the prior 8 weeks. All patient files and radiological images must be available for CRF source verification.

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Appendix 1: National cancer institute (NCI) common terminology criteria for adverse events (CTCAE)

The NCI CTCAE (Version 4.0) should be used to assess Adverse Events and may be reviewed on-line at the following NCI website:

http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/ctcaev4.pdf

APPENDIX 2: KARNOFSKY PERFORMANCE SCALE AND ECOG PERFORMANCE SCALE

Status	Karnofsky	Grade	ECOG
Normal, no complaints	100	0	Fully active, able to carry on all pre-disease performance without restriction
Able to carry on normal activities. Minor signs or symptoms of disease	90	1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work
Normal activity with effort	80		
Care for self. Unable to carry on normal activity or to do active work	70	2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours
Requires occasional assistance, but able to care for most of his needs	60		
Requires considerable assistance and frequent medical care	50	3	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours
Disabled. Requires special care and assistance	40		
Severely disabled. Hospitalization indicated though death nonimminent	30	4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair
Very sick. Hospitalization necessary. Active supportive treatment necessary	20		
Moribund	10		
Dead	0		