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PILOT STUDY OF COMBINED OPTUNE (NOVOTTF-100A), BEVACIZUMAB, AND HYPOFRACTIONATED STEREOTACTIC IRRADIATION FOR BEVACIZUMAB-NAIIVE, RECURRENT GLIOBLASTOMA

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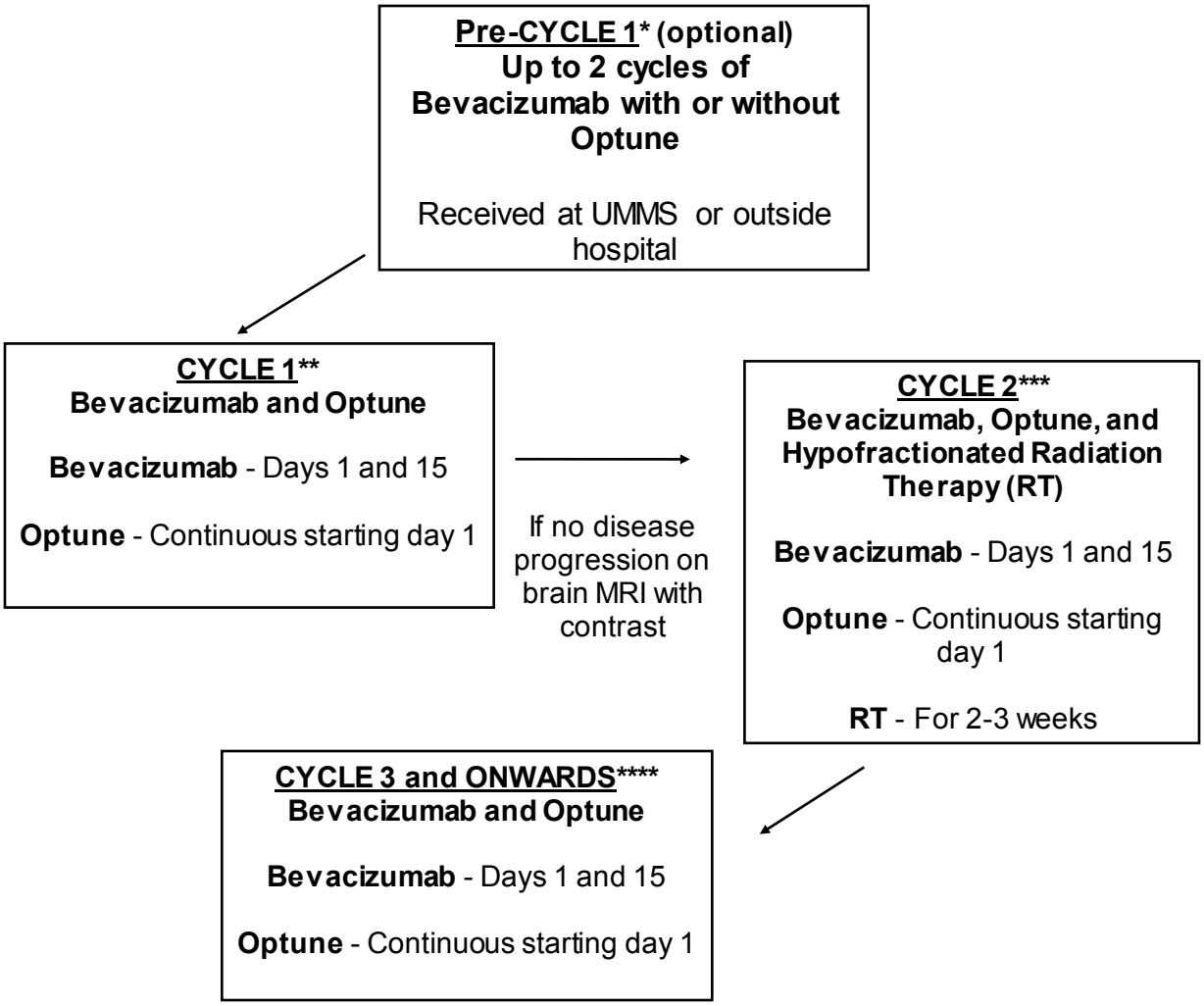
SCHEMA



* Pre-Cycle 1 treatment is optional and can consist of up to 2 cycles of bevacizumab administered at University of Maryland Medical System or an outside institution.

** Cycle 1 of treatment will consist of bevacizumab and Optune and will be 28 days. Bevacizumab will be given on days 1 and 15 (+/- 3 days). Optune will be worn continuously (or as tolerated by the patient) and will begin before Cycle 1, day 1 infusion of bevacizumab. Upon completion of Cycle 1, patients will have a brain MRI with contrast to evaluate for disease progression; if there is no disease progression the patient will proceed to Cycle 2.

*** Cycle 2 of bevacizumab and Optune will include hypofractionated radiation therapy (RT). The duration of this cycle will also be 28 days. Cycle 2 will begin on day 29 (+/- 3 days) of treatment. Bevacizumab will be given on days 1 and 15 (+/- 3 days). Optune will be worn continuously (or as tolerated by the patient). RT will be initiated within the

first 10 days of Cycle 2 and will continue for 2-3 weeks based on which regimen the treating radiation oncologist selects; either 30 Gy in five fractions of 6 Gy each (given at least 48 hours apart) or 35 Gy in ten consecutive fractions of 3.5 Gy each.

**** Cycle 3 treatment and any subsequent cycles (28 days +/- 3 days) will mirror Cycle 1 treatment with bevacizumab and Optune. Patients will be evaluated by a physician prior to starting each new cycle and will continue treatment until disease progression.

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ELIGIBILITY CHECKLIST

(Y) 1. Does the patient have histologically proven diagnosis of original glioblastoma or other variant of WHO grade IV malignant glioma?

(Y) 2. Does the patient have disease progression on contrast-enhanced brain MRI within 30 days prior to registration?

(N) 3. Does the patient have a recurrent or persistent enhancing tumor greater than 8 cm in maximum diameter?

(N) 4. Does the patient have any significant CNS hemorrhage (greater than 1 cm in diameter) seen on the brain MRI with contrast?

(Y/N) 5. Has the patient had prior therapy with bevacizumab or an inhibitor of VEGF or VEGFR?

(Y/NA) Has the patient received two or less cycles of bevacizumab?

(N/NA) Has the patient received a different inhibitor of VEGF or VEGFR?

(Y) 6. Was a history and physical with neurological examination obtained within 30 days prior to registration?

(Y) 7. Is the Karnofsky performance status greater than or equal to 70% within 30 days prior to registration?

(Y) 8. Is the patient's age greater than or equal to 22?

(Y) 9. Was a CBC with differential, CMP, and Urinalysis obtained within 14 days prior to registration showing adequate bone marrow, liver, and renal function as defined in the eligibility criteria?

- Absolute neutrophil count (ANC) ≥ 1.5 x 10^9/L.
- Platelets ≥ 100 x 10^9/L.
- Hemoglobin (Hgb) ≥ 9.0 g/dL (Note the use of transfusion or other intervention to achieve Hgb ≥ 9.0 is acceptable).
- Serum total bilirubin ≤ 1.5 x ULN.
- ALT and AST ≤ 3.0 x ULN.
- Adequate Renal Function: BUN and Cr < 2 x ULN.

(Y) 10. Is there an interval of 12 weeks or greater between completion of prior radiotherapy and registration?

(Y) 11. Does the patient have a prior history of CNS radiation as defined in the eligibility criteria?

(Y/N) 12. Did the patient have a recent resection, major surgery (e.g. intra-thoracic, intra-abdominal or intra-pelvic), open biopsy or significant traumatic injury in the last 4 weeks prior to registration?

(Y/NA) Has the patient recovered from the effects of surgery?

(Y/N) 13. Did the patient have a minor procedure, percutaneous biopsy or placement of vascular access device in the last 1 week prior to registration?

(Y/NA) Has the patient recovered from the effects of the procedure?

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ELIGIBILITY CHECKLIST

(Y/N) 14. Did the patient receive prior investigational agent(s) and/or prior cytotoxic drug therapy?

(Y/NA) Was there a minimum time of 3 weeks since last non-cytotoxic therapy?

(Y/NA) Was there a minimum time of 3 weeks since the completion of a non-nitrosourea-containing chemotherapy regimen?

(Y/NA) Was there a minimum time of 6 weeks since the completion of a nitrosourea-containing chemotherapy regimen?

(Y/NA) 15. Has patient recovered from the toxic effects of any prior surgery/procedure and/or investigational agent/drug/cytotoxic therapy so that in the opinion of the treating physician the patient could tolerate study treatment?

(Y) 16. Did the patient provide informed consent prior to registration?

(Y) 17. Is the patient willing to practice effective contraception while on study treatment and for 6 months after?

Questions 18-19 pertain only to female patients

(N) 18. Is the patient pregnant or breast-feeding?

(Y/NA) 19. Was a negative pregnancy test obtained within 14 days prior to registration for women of child-bearing potential?

(Y/N) 20. Has the patient had prior invasive malignancy (except non-melanomatous skin cancer; does not apply to glioblastoma or recurrent glioblastoma)?

(Y/NA) Has the patient been disease free for a minimum of 1 year?

(Y) 21. Is the patient maintained on a stable or decreasing corticosteroid regimen from the time of their baseline scan until registration?

(Y/N) 22. Is the patient on full dose anticoagulants?

(Y/NA) Is there an in-range INR (usually between 2 and 3) on a stable dose of oral anticoagulant or on a stable dose of low molecular weight heparin?

(N/NA) Does the patient have active bleeding or a pathological condition that carries a high risk of bleeding (e.g. tumor involving major vessels or known varices)?

(N) 23. Does the patient have severe active co-morbidity as defined in the eligibility criteria (e.g. cardiac impairment, cirrhosis, viral issues, HIV, GI issues, infection, uncontrolled diabetes, etc.)?

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ELIGIBILITY CHECKLIST

(N) 24. Does the patient have an active implanted medical or electronic device, or bullet fragments? (Examples of implanted devices include: deep brain stimulators, spinal cord stimulators, vagus nerve stimulators, pacemakers, defibrillators, and programmable shunts.)

(N) 25. Is there evidence of multifocal, infratentorial or leptomeningeal spread of disease?

(N) 26. Does the patient have a history of allergy or sensitivity to conductive hydrogels like the gel used on electrocardiogram (ECG) stickers or TENS (transcutaneous electrical nerve stimulation) electrodes?

(N) 27. Was the patient treated on any other therapeutic clinical protocols within 3 weeks of registration?

(Y/N) 28. Does the patient have data regarding MGMT methylation status?

What was the result of the MGMT analysis?

(N) 29. Has the patient had gastrointestinal bleeding or any other hemorrhage/bleeding event (CTCAE v.4) grade 3 or greater within 30 days prior to registration?

This Eligibility Checklist must be completed in its entirety prior to registration. The completed, signed, and dated checklist used for study registration must be retained in the patient's study file.

For use during screening of subjects:

_____ _____
Name of Subject

Reviewed and subject acceptable for study: ___ YES ___ NO

_____ _____
Signature of Principal Investigator Date

1.0 INTRODUCTION

This protocol is designed to generate and provide preliminary data to determine the safety and activity of combination therapy using Optune (tumor treating fields (TTFields; NovoTTF-100A; Novocure, Haifa, Israel)), a novel FDA-approved therapy utilizing alternating electric fields to inhibit tumor cell growth, along with bevacizumab (Avastin; Genentech, San Francisco, CA), a humanized monoclonal antibody that inhibits vascular endothelial growth factor (VEGF), and hypofractionated stereotactic radiotherapy, a highly-focal abbreviated course of brain irradiation, in the treatment of patients with bevacizumab-naive recurrent glioblastoma (GBM). Each of these individual therapies, and also several combinations in doublets, has already demonstrated safety and efficacy but prospective clinical data for the concurrent combination of all three therapies are lacking.

1.1 Background Information

Glioblastoma remains the most prevalent primary malignant brain tumor in adults. Despite optimal treatment, median survival is only < 15 months with the majority of patients developing recurrence at a median of < 8 months post treatment (Stupp 2005). At the time of disease recurrence, treatment options for glioblastoma patients are limited and prognosis is poor. Various treatment modalities have been evaluated in the recurrent setting including resection, chemotherapy, targeted agents, irradiation, and combinations of modalities.

Bevacizumab for the treatment of recurrent glioma

After initial progression, phase II trials of chemotherapy have resulted in 6-month progression-free survivals of 9-19% and median survivals of 6-8 months (Wong 1999, Chang 2003). Bevacizumab (BVZ), a humanized monoclonal antibody targeting VEGF, was approved by the FDA as a single agent for recurrent glioblastoma. Vascular proliferation is a common feature in glioblastoma and anti-VEGF therapy can inhibit new vessel growth, lead to vascular regression and vascular normalization, as well as directly affect tumor cell function (Ellis 2008). Antiangiogenic therapies may decrease vasogenic edema as well as corticosteroid use and has been shown to be effective in the treatment of radiation necrosis (Levin 2011). Several phase II trials using Bevacizumab have shown promising results with 6-month progression-free survival rates ranging from 29-42%[1]. In spite of this improvement in PFS, clinical trials of bevacizumab for recurrent glioblastoma to date have not shown a substantial improvement in overall survival (OS).

Hypofractionated Stereotactic Radiation Therapy for Recurrent Glioma

Salvage re-irradiation is another well-studied treatment modality with historical results conferring 6-month progression-free survival ranging from 28-39% and a median 1-year overall survival of 26%, ranging from 18-46% (Combs 2005, Nieder 2008). Hypofractionated stereotactic radiotherapy (HFSRT) offers an acceptable safety profile and abbreviated schedule while exploiting several radiobiological advantages of an increase in dose-per-fraction and accelerated time course of radiotherapy. One recent retrospective analysis of one hundred forty seven patients with recurrent HGG treated with HFSRT (median dose 35 Gy in 3.5 Gy fractions) reported median survival of 11

months and found 1/3 of patients able to reduce corticosteroid dose (Fogh 2010). Patients with shorter-interval recurrence and those receiving > 35 Gy re-irradiation may stand to benefit more from treatment. While toxicities have been associated with an increased rate of radiation necrosis and subsequent re-operation, previous studies of HFSRT have resulted in comparable and possibly increased survival rates[2].

Combination Bevacizumab and HFSRT for Recurrent Glioma

Putative benefits to the combination of bevacizumab and hypofractionated stereotactic radiotherapy include the ability of anti-angiogenic agents to sensitize tumor endothelium to RT, targeting of radio-resistant cancer stem cells by disrupting vascular niches, and vascular stabilization leading to reduced toxicity by reducing risk of radiation necrosis (Gutin 2009). This combination has recently been evaluated in a phase II study as treatment for recurrent malignant gliomas. Gutin et al. reported on twenty-five patients with recurrent grade III-IV glioma who received bevacizumab concurrently with HFSRT and found a 6-month progression-free survival of 65% and median overall survival of 12.5 months; results which compare very favorably to historic controls. Additionally, an overall response rate of 50% for the GBM cohort was seen. This treatment was well tolerated with no incidence of radiation necrosis and no additional need for corticosteroids following radiation.

Single institution retrospective data also suggests a benefit to the addition of bevacizumab to highly focal radiation (Cuneo 2012). In patients with Grade IV glioma, SRS with adjuvant bevacizumab resulted in 1-year OS of 50% vs. 22% for patients not receiving adjuvant bevacizumab ($p = 0.005$). Median progression-free survival (PFS) for patients who received adjuvant bevacizumab was 5.2 months vs. 2.1 months for patients who did not ($p = 0.014$). Treatment-related Grade 3/4 toxicity for patients receiving and not receiving adjuvant BVZ was 10% and 14%, respectively ($p = 0.58$).

Tumor Treatment Fields

Optune (formerly NovoTTF) represents a novel, promising therapeutic option for patients with recurrent glioblastoma as well as other malignancies. This FDA-approved therapy utilizes low-intensity intermediate-frequency alternating electric fields delivered via non-invasive transducer arrays to inhibit tumor cell growth. These fields physically interfere with microtubule subunit polymerization in the mitotic spindle and alter intracellular macromolecule movement during telophase leading to disturbance in chromosome segregation and cell death (Lee 2011). The morphological abnormalities seen after exposure to TTFields are analogous to those seen in cells treated with agents that interfere directly or indirectly with microtubule polymerization, e.g. paclitaxel, with well-studied safety and efficacy data when used in concert with other chemotherapies (Rowinsky 1995). Indeed, favorable combination and dose reduction indices from combination of paclitaxel and NovoTTF suggest similarity and synergism in a pre-clinical study (Kirson 2009).

Tumor Treatment Fields for Recurrent Glioma

In upfront setting, NovoTTF-100A has been preliminarily evaluated with concurrent maintenance temozolomide for patients with newly-diagnosed glioblastoma following

resection and chemoradiation. In a study of 10 patients with median follow-up of 40 months, concurrent electric field therapy and maintenance temozolomide resulted in actuarial median PFS of 155 weeks and median OS of > 39 months without serious adverse event and with no change from the expected toxicity of temozolomide alone (Kirson 2009). These results, in albeit a small and well-selected population, are profoundly heartening when compared to historic controls of 31 week PFS and 14.7 month OS with temozolomide alone.

In a phase III trial of patients with recurrent grade IV glioma, NovoTTF-100A as monotherapy demonstrated comparable efficacy to chemotherapy with a more favorable safety profile and quality of life benefit (Stupp 2012)[3]. In a cohort of heavily pretreated patients, NovoTTF use afforded a median overall survival of 6.6 months, 1-year survival rate of 20%, and a PFS-6 of 21.4%; an effect equal to that of physician's-choice chemotherapy without many of the attendant, often severe, treatment-limiting side effects of chemotherapy. 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.

Based on these data, and the continued overall poor outcomes for this population, combinations of the various therapies demonstrating activity are logically being pursued in various formats. For example, for newly diagnosed GBM the combination of temozolomide and NovoTTF as adjuvant therapy following initial post-resection radiotherapy with concomitant temozolomide is the thrust of a major international ongoing phase III trial. Within the Radiation Therapy Oncology Group (RTOG), two randomized phase II trials are either ongoing or planned to specifically test the survival advantage from combinations of these therapies (hypofractionated RT plus bevacizumab for recurrent, bev-naïve GBM; and NovoTTF plus bevacizumab for recurrent bev-refractory GBM). However, the three-modality combination, although used off-label, has not been evaluated in a prospective trial.

1.2 Rationale for Multimodality Therapy: NovoTTF-100A, Bevacizumab, and HFSRT

The population of patients with recurrent glioblastoma represents a diverse group, with subsets of both salvage-naïve patients and patients who have exhausted numerous therapeutic options. The combination of hypofractionated RT and bevacizumab in bevacizumab-naïve recurrent glioblastoma is currently the subject of a randomized prospective phase II trial (RTOG 1205). Phase III data of the clinical impact of tumor treatment fields has to date been evaluated in patients toward the end of their clinical course, often having progressed on multiple regimens. In the pivotal multinational trial published by Stupp, 91% of patients had progressed 2 or more times with 43% on their

3rd or greater recurrence. Patients who retain salvage-naiveté may harbor the potential for a more substantial benefit from this promising new modality.

Combination of NovoTTF-100A and Bevacizumab

NovoTTF has already demonstrated safety and efficacy in combination with multiple chemotherapeutic regimens. Dose-reduction was possible in vitro with addition of NovoTTF to paclitaxel, doxorubicin, and cyclophosphamide (Kirson 2009). The potential combination of TTFields with bevacizumab is enhanced by the fact that the mechanism of action of NovoTTF is not limited by the normalization of the blood-brain barrier caused by use of concomitant bevacizumab, a factor that limits the potential combinatorial effect of bevacizumab and traditional systemic chemotherapies. Studies of bevacizumab in concert with paclitaxel (like NovoTTF an inhibitor of normal microtubular function with similar mitotic effects) have shown improvements in PFS in randomized controlled trials of multiple disease sites including non-small-cell lung cancer, ovarian cancer, and metastatic breast cancer (Perren 2011).

Given the clinical interest and widespread use of bevacizumab in the setting of recurrent GBM, an exploratory survival analysis of the phase III NovoTTF trial was performed in a subset of patients who had progressed on prior bevacizumab (20% of patients evaluated). In patients with bevacizumab-refractory disease, median OS was significantly longer when treated with NovoTTF-100A compared to chemotherapy (6.3 vs. 3.3 months; hazard ratio (HR) 0.39; p = 0.01). Building on these exploratory results, the RTOG has a developing phase II randomized trial (RTOG 1301) to test the hypothesis that combination of tumor treating fields with bevacizumab will improve survival compared with treatment using bevacizumab and pre-specified investigator choice chemotherapy for patients with bevacizumab-refractory recurrent GBM. There is without doubt great promise to the combination of systemic therapy and TTF; however the full potential for benefit from concurrent therapy alongside TTF will require testing the right combination of modalities in the right populations. It is an unfortunate reality of this disease process that patients who have progressed to the point at which they would be eligible for this trial likely represent those who harbor treatment-resistant clonogens or in whom multiple treatments have selected a more aggressive phenotype. Patients with recurrence that maintain the therapeutic option of bevacizumab represent a key first step in transitioning NovoTTF therapy earlier in this disease course and offer the possibility of enhanced therapeutic effect for those in such great need of improved outcomes.

Combination of NovoTTF-100A and Radiation Therapy

NovoTTF may sensitize cells to the effects of irradiation. The mitotic arrest seen with electric field therapy and the mechanism of interrupted microtubule assembly create two avenues for radiosensitization. Arrest in M phase increases the proportion of cells in G2 and M phases and thus in radiosensitive portions of the cell cycle, enhancing the therapeutic ratio. This effect may be more dramatically realized at the increased doses per fraction seen with HFSRT. Additionally, interruption of tubule polymerization (in the form of taxol-based chemotherapy) is a well-established radiosensitizing mechanism. Phase III randomized evidence from a myriad of disease sites have demonstrated

improvement with the addition of taxol-based regimens to radiation therapy. Hypofractionated stereotactic radiation has been evaluated with concurrent paclitaxel in patients with recurrent glioblastoma (Lederman 2000). The regimen was well tolerated and suggested benefit for patients with small tumors (< 30 cm^3).

NovoTTF may potentiate the effects of irradiation. Radiation therapy is known to exert a large portion of its antitumor effects via double-strand DNA damage. DNA acts as an inducible dipole in the presence of electric fields. Double-strand breakage fragments produced by ionizing radiation, in the presence of TTFields, experience both rotational and migrational forces. These mechanical forces can interfere with DNA repair mechanisms such as homologous and non-homologous end joining pathways resulting in decreased potentially lethal damage repair and enhanced biologic effect. Preclinical data support the concept of delayed repair[4]. COMET assays were performed on MCF-7 breast cancer cells after 8 Gy single dose irradiation, 1, 2, or 24-hour TTF exposure, and the combination. Irradiation alone was associated with DNA fragmentation which returned to near control-levels within two hours. As compared to control, TTF alone, and RT alone, cells exposed to TTFields within 5 minutes following irradiation demonstrated persistence of fragmentation for the duration of TTF use. The persistence of radiation-induced DNA fragmentation suggests delayed or inhibited repair mechanisms raising the potential for enhanced biologic effect.

Radiation therapy may also enhance the effects of NovoTTF use. Chromosomal abnormalities caused by irradiation may enhance the cytotoxic mechanisms of TTF, again by altered dipole moment and differential in centripetal migration of intracellular components during cytokinesis. The potential for therapeutic benefit with concurrent TTFields and irradiation is promising, especially when considered with NovoTTF's track record of safety without significant additive toxicity.

<u>Novel multimodality therapy: NovoTTF-100A, Bevacizumab, and HFSRT</u>
The combination of NovoTTF with the active regimen of bevacizumab and hypofractionated stereotactic radiotherapy bases the addition of an effective new treatment in the setting of a safe regimen with favorable survival reports. To date, no clinical data are available on the interaction of concomitant tumor treating fields with radiation therapy either with or without bevacizumab. TTF and radiation both have the potential to enhance the other's therapeutic ratio though synergistic mechanisms of action. The addition of bevacizumab to this regimen has both therapeutic and improved-toxicity implications. A trial combining NovoTTF-100A with the proven regimen of HFSRT and bevacizumab for recurrent glioblastoma affords an avenue to demonstrate safety in a population who may more readily derive a benefit from novel multimodality therapy and explore the great potential for synergistic effect. The endpoint of efficacy would clearly need to be more definitively addressed in a future categorical trial, which would be the logical positive outcome of this pilot study.

2.0 OBJECTIVES

The study will enroll 32 patients, expecting to accrue 27 evaluable patients. The assumption is that at least 16 patients (60%) will receive the proposed tri-modality treatment without undue treatment related toxicity. After 9 patients have been enrolled the study will be evaluated to determine whether the treatment is feasible and safe. If at least 6 out of the 9 patients have completed the tri-modality treatment without undue treatment related toxicity, the trial will move on to the second stage so that a total of 27 patients will be evaluable. For evaluation purposes, patients who initiate therapy with bevacizumab and Optune, but experience disease progression before initiating radiotherapy will be deemed not evaluable. In addition, patients without undue treatment related toxicity who do not initiate tri-modality treatment will be deemed not evaluable. If the total number of patients completing the tri-modality treatment without undue treatment related toxicity is at least 16 of 27, the treatment will deemed safe and will be considered for further study. If 3 or fewer patients of the first 9, or 15 or fewer patients total, complete the tri-modality treatment without undue treatment related toxicity respectively, then modification of the protocol will be considered, including possibly proceeding to the tri-modality phase earlier.

2.1 Primary Objective

The ability to complete protocol treatment (i.e. tri-modality treatment) without undue treatment related acute toxicity as defined below:

2.1.1 Safety: < 40% rate of Grade 3 or higher non-hematologic treatment related toxicity.

2.1.2 Safety: < 15% rate of Grade 4 or higher non-hematologic treatment related toxicity.

2.1.3 Safety: < 5% rate of Grade 4+ scalp dermatitis.

2.1.4 Safety: < 50% rate of Grade 2-3 scalp dermatitis.

2.1.5 Early stopping rules: Two or more Grade 2 or higher symptomatic CNS hemorrhages; Eight treatment-related Grade 3 or higher non-hematologic or Grade 4 or higher hematologic treatment related toxicities.

2.2 Secondary Objectives

2.2.1 Progression-Free Survival at 6 months.

2.2.2 Median Progression-Free Survival.

2.2.3 Median Overall Survival.

2.2.4 1-year Overall Survival.

2.2.5 Overall Response Rate.

2.2.6 Quality of Life assessment.

3.0 ELIGIBILITY

3.1 Inclusion criteria

3.1.1 Patients with recurrent or progressive glioblastoma or other grade IV malignant glioma (e.g. glioblastoma, gliosarcoma, giant cell glioblastoma, etc.) who have failed prior radiation but who have not progressed/recurred on bevacizumab.

Patients will be eligible if the original histology was lower-grade glioma and subsequent diagnosis of glioblastoma or gliosarcoma is made.

3.1.2 Patients with any number of recurrences are allowed.

3.1.3 Brain MRI with contrast demonstrates an enhancing tumor ≤ 8 cm in largest diameter within 30 days prior to registration.

3.1.4 History and physical including neurological exam, height, weight, cranial skin exam, and Karnofsky performance status ≥ 70% within 30 days prior to registration.

3.1.5 Age ≥ 22 years old.

3.1.6 Patients must have the following laboratory values within 14 days prior to registration (by CBC w/ differential, CMP, Urinalysis, and PT/INR for patients on anticoagulants):

- Absolute neutrophil count (ANC) ≥ 1.5 x 10^9/L.
- Platelets ≥ 100 x 10^9/L.
- Hemoglobin (Hgb) ≥ 9.0 g/dL (Note the use of transfusion or other intervention to achieve Hgb ≥ 9.0 is acceptable).
- Serum total bilirubin ≤ 1.5 x ULN.
- ALT and AST ≤ 3.0 x ULN.
- Adequate Renal Function: BUN and Cr < 2 x ULN.

3.1.7 Minimum interval since completion of radiation treatment is 12 weeks.

3.1.8 History of CNS radiotherapy: radiation of 60 Gy in 30 fractions, 59.4 Gy in 1.8 Gy fractions, 75 Gy in 30 fractions or equivalent or lower doses.

3.1.9 Minimum interval since last major surgery (e.g. intra-thoracic, intra-abdominal or intra-pelvic), open biopsy, or significant traumatic injury is 4 weeks prior to registration. Minimum interval since minor procedures, percutaneous biopsies or placement of vascular access device is 1 week prior to registration. Patients must have recovered from side effects of such procedure or injury prior to registration.

3.1.10 Minimum interval since last investigational agent and/or prior cytotoxic drug therapy (patient must have also recovered from the toxic effects of any prior 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.

3.1.11 Patients must have signed an approved informed consent.

3.1.12 Patients with the potential for pregnancy or impregnating their partner must agree to practice effective contraceptive methods to avoid conception while on study and for 6 months after study completion.

3.1.13 Female patients of child-bearing potential must have a negative pregnancy test within 14 days prior to study registration.

3.1.14 Patients with history of prior invasive malignancy (except non-melanomatous skin cancer and glioblastoma diagnosis) must have been disease free for a minimum of 1 year.

3.1.15 Patients must be maintained on a stable or decreasing corticosteroid regimen from the time of their baseline scan until registration.

3.1.16 Patients on full-dose anticoagulants (e.g., warfarin or LMW heparin) must meet both of the following criteria:

- No active bleeding or pathological condition that carries a high risk of bleeding (e.g., tumor involving major vessels or known varices).
- In-range INR (max ≤ 3) on a stable dose of oral anticoagulant for greater than 1 month or on a stable dose of low molecular weight heparin.

3.2 Exclusion criteria

3.2.1 Greater than two cycles of bevacizumab or any prior therapy with an inhibitor of VEGF or VEGFR.

3.2.2 Any significant CNS hemorrhage defined as > 1 cm diameter of blood seen on the pre-registration brain MRI with contrast scan. If > 1 cm of acute blood is detected, the patient will be ineligible for this trial.

3.2.3 Patients with impaired cardiac function or clinically significant cardiac diseases, including any of the following:

- History or presence of serious uncontrolled ventricular or significant arrhythmias.
- Any of the following within 6 months prior to registration: 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 mmHg or DBP ≥ 100 mmHg while on anti-hypertensive medications) or history of hypertensive crisis or hypertensive encephalopathy, stroke, TIA, symptomatic peripheral vascular disease, or grade 2 CHF.

3.2.4 Patients with cirrhosis, or active viral or non-viral hepatitis.

3.2.5 Patients with peptic ulcer, abdominal fistula, gastrointestinal perforation, intra-abdominal abscess within 6 months of registration.

3.2.6 Patients with active implanted medical or electronic device or bullet fragments including pacemakers, defibrillators, deep brain stimulators, spinal cord stimulators, vagus nerve stimulators, and programmable shunts.

3.2.7 Infratentorial, leptomeningeal, or multifocal tumor.

3.2.8 Known sensitivity or allergy to conductive hydrogels (like the gel used on electrocardiogram (ECG) stickers or TENS (transcutaneous electrical nerve stimulation) electrodes).

3.2.9 Known diagnosis of human immunodeficiency virus (HIV) infection (please note that HIV testing is not mandatory).

3.2.10 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.

3.2.11 Pregnant or breast-feeding women.

3.2.12 Patients treated on any other therapeutic clinical protocols within 3 weeks of registration.

3.2.13 Patients with gastrointestinal bleeding or any other hemorrhage/bleeding event (CTCAE v.4) grade 3 or greater within 30 days prior to registration will be ineligible.

4.0 TRIAL DESIGN

4.1 Treatment Overview

Patients with recurrent or progressive grade IV malignant glioma who have failed prior radiation but who have not progressed/recurred on bevacizumab and who meet the specified inclusion/exclusion criteria will be eligible for participation.

The date of registration/enrollment is considered to be the day the Eligibility Checklist is signed by the verifying physician. Once a patient is enrolled, a unique case number will be assigned to the patient.

Patients will have baseline contrast-enhanced brain MRI within 30 days prior to registration. MR diffusion and spectroscopy studies may be performed to better define and characterize areas of recurrent disease, as per physician discretion and institutional guidelines. Patients will also undergo complete physical and neurological exam within 30 days prior to registration, and blood and urine tests within 14 days prior to registration.

Patients will receive bevacizumab at a dose of 10 mg/kg IV every 14 days on days 1 and 15 (+/- 3 days) of 28 day cycles until treatment failure (disease progression). Bevacizumab is standard of care for recurrent GBM and can be administered at an outside institution.

Starting on or before day 1 of cycle 1, patients will initiate Optune with frequency of 200 kHz electric fields and field intensity set at > 0.7 V/cm (at the center of the brain) in 2 perpendicular directions, 1 second in each direction sequentially, with goal use of greater than 18 hours/day. Optune therapy will consist of 28 day courses of continuous Optune treatment until progression. Patients will be permitted to take 2-3 days off treatment near the end of each 28 days of treatment but should resume Optune therapy with the start of radiotherapy.

At the end of the first cycle of concurrent bevacizumab and Optune (ideally days 21-28 or as close as is reasonably possible), patients will undergo a repeat contrast-enhanced brain MRI as well as repeat physical and neurological exam. If patients have a response or stable findings on MRI they will proceed to radiation therapy. Patients with progressive disease will come off study and will not be evaluable for protocol therapy and endpoints.

Hypofractionated Stereotactic Radiation Therapy (HFSRT) will be determined at the discretion of the treating physician from one of the following regimens:

A. Contrast enhancing lesion: 6 Gy x 5 = 30 Gy
   Residual FLAIR after 1st cycle of bevacizumab, Optune: 4 Gy x 5 =20

OR

B. Contrast enhancing lesion: 3.5 Gy x 10 = 35 Gy
Residual FLAIR after 1st cycle of bevacizumab, Optune: 2.5 Gy x 10 =25

Radiation treatments will start within the first 10 days of cycle 2 of concurrent bevacizumab and Optune and will be delivered over a 2-3 week period. During radiotherapy, patients will remove Optune treatment arrays immediately prior to radiation treatments and will resume as soon as is reasonably possible on each day following completion of radiation treatment.

After completion of cycle 2 with the tri-modality treatment, patients will resume 28 day cycles of bevacizumab and Optune until disease progression. These subsequent cycles will mirror cycle 1.

Please note that dose modifications, delays, and discontinuations of bevacizumab, Optune, and radiotherapy are at the physician's discretion and per institution guidelines. If bevacizumab is interrupted, treatment with Optune and radiotherapy will continue as planned, and this follows for the other treatment modalities.

5.0 RADIATION THERAPY

5.1 Dose Specifications

Choice of radiation therapy regimen is at the treating physician's discretion. For an enhancing tumor greater than 5 cm in maximum diameter, Regimen B should be followed.

Regimen A: 30 Gy in five fractions of 6 Gy each delivered to the contrast enhancing lesion, with 20 Gy in five fractions of 4 Gy each delivered to the residual FLAIR signal abnormality remaining after the initial cycle of bevacizumab and Optune. Treatments will be delivered with at least 48 hours between fractions; maximum of 3 fractions per 5 day treatment week.

OR

Regimen B: 35 Gy in ten fractions of 3.5 Gy each delivered to the contrast enhancing lesion, with 25 Gy in ten fractions of 2.5 Gy each delivered to the residual FLAIR signal abnormality remaining after the initial cycle of bevacizumab and Optune. Treatments will be delivered once daily on consecutive treatment days (typically 5 fractions per week).

Radiation treatments will start within the first 10 days of cycle 2 of concurrent bevacizumab and Optune and will be delivered over a 2-3 week period.

5.2 Coverage Goals

Volume of PTV (planning target volume) covered by the prescription dose: Greater than or equal to 95% of the PTV should receive greater than or equal to 100% of the planned

total prescription dose. Acceptable deviation will include greater than or equal to 90% of the PTV receiving greater than or equal to 100% of the planned total prescribed dose.

Minimum dose to the PTV (0.03 cc): Greater than or equal to 90% of the planned total prescription dose. Acceptable deviations will include minimum PTV dose greater than or equal to 80% of the prescription dose as well as minimum PTV doses less than 80% of the prescription dose if these areas occur due to OAR-PTV overlap.

Maximum dose to the PTV (0.03 cc): Less than or equal to 110% of the prescription dose. Acceptable deviation will include maximum dose less than or equal to 115% of the prescription dose.

5.3 Localization, Immobilization, Simulation, and Imaging

MRI with contrast is required for treatment planning. CT simulation of the patient immobilized in treatment position should have image resolution of no worse than 1.5 mm slice thickness. Immobilization must be rigid (e.g. thermoplastic mask, with bite block preferred if patient able to tolerate). For daily treatment, localization will include the steps of a) immobilization with the same device used for simulation, and b) daily image guidance using at a minimum orthogonal pairs of radiographs aligned to digitally reconstructed radiographs (DRRs) (use of CBCT alignment is permitted as well but not mandatory).

Image fusion of both the pre-study-entry MRI: “MRI-1” and the pre-RT (ideally end of cycle 1) MRI: “MRI-2” will be made with the planning CT simulation scan and used for target delineation per protocol and institutional guidelines.

5.4 Technical Factors

Treatment shall be delivered with megavoltage machines of a minimum energy of 6 MV photons. Selection of the appropriate photon energy(ies) should be based on optimizing the radiation dose distribution within the target volume and minimizing dose to non-target normal tissue. Source skin distance for SSD techniques or source axis distance for SAD techniques must be at least 80 cm. Electron, particle, planned radiosurgery or implant boost is not permissible. Intensity-modulated Radiation Therapy (IMRT) is required; any of the methods of IMRT may be used. Proton therapy is permitted at the discretion of the treating physician.

5.5 Treatment Planning/Target Volumes

5.5.1 Initial Target Volume (PTV1): Treatment volumes will be defined by the pre-RT MRI (MRI-2). Gross tumor volume (GTV1) will be equal to clinical tumor volume (CTV1). CTV1 will be defined by either the T2 or the FLAIR abnormality on MRI-2. This must also include any volume included in GTV2 (described below). The initial planning target volume (PTV1) is an additional margin of 3 to 5 mm, depending upon localization method and reproducibility, however, this may be reduced to as low as 0 cm around natural barriers to tumor growth or to allow sparing of normal tissues.

The dose to PTV1 for regimen A will be 4 Gy per fraction for 5 fractions, total dose 20 Gy. The dose to PTV1 for regimen B will be 2.5 Gy per fraction for 10 fractions, total dose 25 Gy.

5.5.2 Boost Target Volume (PTV2): In order to account for the described phenomena of pseudo-response seen with bevacizumab and pseudo-progression seen with NovoTTF, the gross tumor volume (GTV2) will represent a composite of the pre-study-entry MRI (MRI-1) and the pre-RT MRI (MRI-2). GTV2 will be defined by the contrast-enhancing T1 abnormality according to the following provisions:

a) if the contrast-enhancing lesion on MRI-2 is smaller than MRI-1, the extent of disease on MRI-1 will be used
b) if the contrast-enhancing lesion on MRI-2 is reasonably larger than MRI-1 (but not meeting the criteria for progressive disease), the extent of disease on MRI 2 will be used
c) if the contrast-enhancing lesion on MRI-2 is significantly larger than MRI-1 (but not meeting the criteria for progressive disease), the portion of enhancement felt to represent pseudo-progression will be excluded and the extent of disease on MRI-2 will be edited to include, at a minimum, the extent of disease on MRI-1.

The post-operative resection cavity will be outlined if no residual enhancing tumor is noted. The boost clinical target volume (CTV2) will be the gross tumor volume (GTV2) plus an optional margin of no more than 5 mm if this is a new lesion. The CTV2 margin may be reduced to as low 0 cm around natural barriers to tumor growth such as the skull, ventricles, falx, etc, and also to allow sparing of the normal tissues, if necessary. The boost planning target volume (PTV2) is an additional margin of 3 to 5 mm, depending upon localization method and reproducibility, however this may be reduced to as low as 0 cm around natural barriers to tumor growth or to allow sparing of normal tissues.

The dose to PTV2 for regimen A will be be 6 Gy per fraction for 5 fractions, total dose 30 Gy. The dose to PTV2 for regimen B will be 3.5 Gy per fraction for 10 fractions, total dose 35 Gy.

5.6 Critical Structures

Normal tissues to be contoured will include the brainstem, optic nerves, chiasm, retina, cochlea, lenses, and lacrimal gland. The treatment parameters should be modified to optimize the conformity of the prescription isodose volume to the target volume while minimizing dose to critical structures. The dose limits for both regimens A and B are given below.

Normal Tissue Dose Limits

Regimen A

Critical Structure	Dose Constraint	Acceptable Deviation

Maximum Dose to Optic Nerves and Chiasm (0.03 cc)	Less than or equal to 15 Gy	Greater than 15 Gy but less than or equal to 18 Gy
Maximum Dose to Brainstem (0.03 cc)	Less than or equal to 17 Gy	Greater than 17 Gy but less than or equal to 22 Gy
Mean Dose to Cochlea	Less than or equal to 22 Gy	Greater than 22 Gy
Maximum Dose to Lens	Less than or equal to 5 Gy	Greater than 5 Gy
Mean Dose Lacrimal Gland	Less than or equal to 12 Gy	Greater than 12 Gy

Regimen B

Critical Structure	Dose Constraint	Acceptable Deviation
Maximum Dose to Optic Nerves and Chiasm (0.03 cc)	Less than or equal to 20 Gy	Greater than 20 Gy but less than or equal to 25 Gy
Maximum Dose to Brainstem (0.03 cc)	Less than or equal to 24 Gy	Greater than 24 Gy but less than or equal to 30 Gy
Mean Dose to Cochlea	Less than or equal to 30 Gy	Greater than 30 Gy
Maximum Dose to Lens	Less than or equal to 7 Gy	Greater than 7 Gy
Mean Dose Lacrimal Gland	Less than or equal to 20 Gy	Greater than 20 Gy

6.0 BEVACIZUMAB THERAPY

6.1 Drug Definition, Description, and Storage

Bevacizumab (human-mouse monoclonal rhuMAb-VEGF γ-chain anti-human vascular endothelial growth factor) is a humanized IgG1 monoclonal antibody (MAb) that binds biologically active isoforms of human VEGF (VEGF-A) and prevents interaction of VEGF with its receptors (Flt-1, KDR) on the surface of endothelial cells resulting in inhibition of angiogenesis. The antibody consists of human IgG1 framework regions and murine complementarity-determining antigen-binding regions. Vials contain bevacizumab with phosphate, trehalose, polysorbate 20, sterile water for injection, USP. Vials contain 25 mg/mL concentrate and should be diluted in 0.9% sodium chloride. Do not administer or mix with dextrose solutions. Vials contain no preservative and are suitable for single use only. Diluted solution may be stored at 2-8°C for up to 8 hours, do not freeze; protect from light.

6.2 Dose Administration

Bevacizumab will be administered at a dose of 10 mg/kg every 2 weeks (+/- 3 days). Doses will be adjusted if there is a > 10% change in weight. Bevacizumab should be administered as a continuous intravenous infusion using a rate-regulating device per institutional guidelines with associated pre-medications and not as an IV push or bolus. Administer the initial dose over a minimum of 90 minutes. If no adverse reactions occur, administer the second dose over a minimum of 60 minutes. If no adverse reactions occur after the second dose, administer subsequent doses over a minimum of 30 minutes. Bevacizumab has been administered safely over shorter infusion times

(0.5 mg/kg per minute), but is not recommended to be administered in shorter than 30 minutes. If infusion-related adverse reactions occur, all subsequent infusions should be administered over the shortest period that was well tolerated. Dose modifications, delays, and discontinuations are at the discretion of the treating medical oncologist and per institutional standards.

6.3 Timing of Therapy

The initial cycle of bevacizumab (concurrent with Optune initiation) must start within 14 days of registration. A cycle will consist of a dose on day 1 and day 15 (+/- 3 days). Subsequent cycles will be administered every 28 days (+/- 3 days) until disease progression.

7.0 OPTUNE THERAPY

7.1 Description

The Optune (formerly NovoTTF-100A) System is an FDA (Food and Drug Administration) approved device developed by Novocure. It is a portable battery or power supply operated device which produces alternating electric fields (tumor treatment fields or TTF) which are applied to the patient by electrically-insulated surface transducer arrays. The Optune System is comprised of two main components: an Electric Field Generator (the Optune device) and INE Insulated Transducer Arrays (the transducer arrays). In addition, the following components are also included in the Optune Treatment Kit: power supply, portable battery, battery rack, battery charger, connection cable and carrying case. The patient must change and recharge depleted device batteries and connect unit to an external power supply overnight. In addition, the transducer arrays need to be replaced once to twice a week and the scalp re-shaved at least weekly in order to maintain optimal contact.

7.2 Treatment Parameters

Treatment parameters are preset by Novocure such that there are no electrical output adjustments available to the patient. Electric field intensity will be set at > 0.7 V/cm at the center of the brain and frequency set at 200 kHz. Two intersecting field directions will be used with transducer array arrangements designed by Novocure to encompass the highest proportion of treatable orientations. Each field will operate in alternating sequence at 1 second duty cycles.

7.3 Treatment Application

As is standard clinical practice, patients will be supplied with multiple sterile transducer arrays as well as the Optune treatment unit and associated cables, equipment, and instruction. Patients will have four transducer arrays placed on the shaved scalp in an arrangement pattern specified by Novocure and connected to a portable, battery or power supply operated device (Optune) set to sequentially generate perpendicular alternating electric fields. Patients will be trained on how to operate the device and will then continue treatment at home. Treatment will be continuous while maintaining normal daily activity. Transducer arrays are to be replaced by the patients, their caregivers or device technicians once or twice a week. Prior to placement, the scalp

will be carefully re-shaved as needed with an electric razor in order to avoid skin irritation or wounding. Uninterrupted treatment is recommended with goal treatment time of greater than 18 hours per day. Patients will remove transducer arrays immediately prior to each radiotherapy treatment and will resume therapy as soon as is reasonably possible (ideally within about 30 minutes) following completion of that day's radiation treatment. Patients will be allowed to take treatment breaks of up to an hour, twice per day, for personal needs (e.g. shower). In addition, patients will be allowed to take 2-3 days off treatment at the end of each 28 day cycle of treatment.

8.0 ASSESSMENTS

8.1 Clinical Follow-Up

Patients will undergo clinical assessments including neurologic exam and blood and urine tests prior to each cycle of treatment. Patients will be evaluated for toxicities weekly for the duration of radiotherapy as well as prior to each new cycle. NCI Common Toxicity Criteria version 4 scoring will be used for toxicity grading.

8.2 Imaging Assessment

8.2.1 Imaging Schedule

Patients will undergo contrast-enhanced brain MRI scanning after the first cycle of treatment with bevacizumab and Optune. After completion of radiotherapy, MRIs will be performed every 2-3 months (+/- 2 weeks). MRIs may be performed earlier if clinically warranted.

8.2.2 Measurement of Response

Response to treatment will be determined by contrast-enhanced brain MRI and neurological status according to three pre-defined scales: RECIST, Macdonald, and RANO (in expectation that the utilization of the appropriate scale for recurrent GBM will likely change in the near-future); however, for "actionable" results, only the Macdonald criteria will be utilized for this trial.

- Complete Response (CR) requires all of the following: Complete disappearance of the measurable enhancing lesion sustained for at least 4 weeks; no new lesions; and on a stable or reduced corticosteroid dose.
- Partial Response (PR) requires all of the following: ≥ 50% decrease compared with baseline in the sum of products of perpendicular diameters of the measurable enhancing lesion sustained for at least 4 weeks; no new lesions; and stable or reduced corticosteroid dose.
- Stable Disease (SD) requires all of the following: Does not qualify for complete response, partial response, or progression and is receiving stable or decreasing doses of steroids. This will not require a confirmatory scan.
- Progression (P) is defined by any of the following: ≥ 25% increase in sum of the products of perpendicular diameters of enhancing lesions provided that the patient has not had his/her dose of steroids decreased since the last evaluation period; and any new lesions. A concomitant decrease in steroid dose will rule out progression during the initial 12 weeks after completion of RT.

- Pseudo-Progression (PP): The effect of large dose per fraction as well as combined modality treatment with Optune may result in imaging changes indicative of treatment effect or pseudo-progression. As such, in the absence of neurologic decline OR a new distant area of tumor, the initial post-radiation scan should NOT be used to declare progression. Spectroscopy and perfusion sequences, as per standard clinical practice guidelines, may be used to better define imaging uncertainty. Progressive worsening on subsequent imaging studies usually distinguishes true progression from pseudo-progression; and if determined by subsequent imaging, then the date of progression returns to the earlier date with increasing mass.

8.3 Quality-of-Life Assessment

As part of a planned exploratory endpoint, patients will be given the opportunity to undergo a quality of life assessment with the M. D. Anderson Symptom Inventory - Brain Tumor (MDASI-BT) Module at the time of study entry, prior to initiating radiotherapy, upon completion of radiotherapy, at 1 month post treatment, as well as every 8 weeks (+/- 1 week) thereafter. MDASI-BT assessment may be performed by telephone interview. The MDASI-BT assessment tool is detailed in Appendix I.

9.0 SAFETY

Safety will be measured by the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0.

9.1 Radiation Therapy Related Adverse Events

Particular side effects and risks from therapy will change based on the location of recurrent disease and previous treatment specifics. The following are some commonly encountered adverse events.

9.1.1 Acute

Expected acute radiation-induced toxicities include, fatigue, hair loss, scalp or erythema or soreness. Potential acute toxicities include nausea and vomiting, temporary aggravation of brain tumor symptoms such as headaches, seizures, and weakness, as well as erythema and/or soreness of the ears or in the ear canals potentially resulting in short-term hearing impairment, dry mouth, or altered taste.

9.1.2 Early Delayed

Possible early delayed radiation effects include fatigue and lethargy as well as potential worsening of existing neurological deficits occurring 1-3 months after radiotherapy treatment.

9.1.3 Late Delayed

Possible late delayed effects of radiotherapy include risk of radiation necrosis, hormonal impairment, cataract formation, and neurocognitive deficits which could lead to mental slowing and behavioral changes. Permanent hearing impairment and visual damage are rare.

9.2 Bevacizumab Related Adverse Events Including Likely (> 20%) and Less-Likely Events (< 20% - > 3%)

9.2.1 Blood and lymphatic system disorders: Anemia, febrile neutropenia.
9.2.2 Cardiac disorders: Supraventricular tachycardia.
9.2.3 Ear and labyrinth disorders: Vertigo.
9.2.4 Gastrointestinal disorders: Abdominal pain, colitis, constipation, diarrhea, dyspepsia, gastrointestinal hemorrhage, gastrointestinal obstruction, ileus, oral mucositis, nausea, vomiting.
9.2.5 General disorders and administration site conditions: Fatigue, infusion related reaction, non-cardiac chest pain, pain.
9.2.6 Immune system disorders: Allergic reaction.
9.2.7 Infections and infestations: Infection, peri-rectal abscess.
9.2.8 Injury, poisoning and procedural complications: Wound dehiscence.
9.2.9 Investigations: Increased alanine aminotransferase, increased alkaline phosphatase, increased aspartate aminotransferase increased blood bilirubin, increased cardiac troponin i, decreased neutrophil count, weight loss, decreased white blood cell count.
9.2.10 Metabolism and nutrition disorders: Anorexia.
9.2.11 Musculoskeletal and connective tissue disorders: Arthralgia, bone metaphyseal dysplasia, myalgia, osteonecrosis of jaw.
9.2.12 Nervous system disorders: Dizziness, headache, peripheral sensory neuropathy, syncope.
9.2.13 Renal and urinary disorders: Hematuria, proteinuria.
9.2.14 Reproductive system and breast disorders: Ovarian failure, vaginal hemorrhage.
9.2.15 Respiratory, thoracic and mediastinal disorders: Allergic rhinitis, cough, dyspnea, epistaxis, hoarseness.
9.2.16 Skin and subcutaneous tissue disorders: Pruritus, maculo-papular rash, urticaria.
9.2.17 Vascular disorders: Hypertension, thromboembolic event.

9.3 Optune Related Adverse Events

Adverse events deemed as related to Optune reported in the recurrent GBM setting include: device site reaction (rash under transducer arrays), headache, malaise, muscle twitching, falls, skin ulcers, other skin and subcutaneous tissue disorders (such as skin breakdown, infections, pain, blisters), as well as other musculoskeletal and connective tissue disorders.

9.4 Adverse Event Reporting

9.4.1 Data and Safety Monitoring / Quality Assurance Committee

This study will be governed by the UMGCC Data Safety Mointoring / Quality Assurance Committee (DSMQAC). The study will be sent to the DSMQAC for a mandatory interim review after the first 9 patients have been accrued. Once the DSMQAC has reviewed and approved the initial 9 patients on the study, 23 additional patients will be enrolled. The study will be reviewed by the DSMQAC on an annual basis and a report will be uploaded in the continuing review submitted to the Institutional Review Board (IRB).

9.4.2 Anticipated Toxicities

All anticipated toxicities are listed in this protocol document (sections 9.1-9.3) and the informed consent document.

9.4.3 Toxicity Reporting

The research team and the treating physicians/PI will review the toxicities and record them in Oncore. Attribution of toxicity to protocol and clinical relevance will be reviewed.

If an undue treatment related toxicity or other significant medical event is unexpected and probably related to study treatment, then it will be submitted to the IRB via the Reportable New Information (RNI) guidelines. All AE's entered into Oncore will be submitted for review on an annual basis.

Patients that are withdrawn from protocol treatment will be followed for adverse events for 30 days after discontinuation of protocol treatment.

10.0 PATIENT PROTOCOL DISCONTINUATION

Imaging evidence confirming disease progression or occurrence of an undue treatment related toxicity (Grade 3 or higher non-hematologic adverse event or Grade 4 or greater hematologic adverse event) will serve as criteria for discontinuation of protocol treatment. If protocol treatment is discontinued, follow-up and data collection will continue at the treating physician's discretion.

11.0 STATISTICS

A two phase design will allow for evaluation after enrollment of the initial nine patients. A Grade 3 or higher non-hematologic Adverse Event or Grade 4 or greater hematologic Adverse Event as measured by the NCI Common Terminology Criteria for Adverse Events (CTCAE version 4.0) will be termed an undue toxicity. Should three or fewer patients complete the tri-modality treatment without undue toxicity, the study will be terminated and the treatment protocol modified. Should the study progress to the second phase and fifteen or fewer patients complete tri-modality treatment without undue acute toxicity, the treatment will be rejected and modification of the protocol will be considered.

If P = patient completes tri-modality treatment without undue toxicity, the two-stage design to test the null hypothesis that the probability of $P <= 0.35$ versus the alternative that $P >= 0.60$ has an expected sample size of 16 and a probability of early termination of 0.609. If the treatment is actually not feasible and/or safe there is a 0.046 probability of concluding that it is (the target for type II error being $\beta < 0.05$). If the treatment is actually feasible and safe, there is a 0.195 probability of concluding that it is not (the target for type I error $\alpha < 0.200$). After treating 9 patients in the first stage, the study will be terminated and the current treatment protocol rejected if 3 or fewer patients complete the tri-modality treatment without undue acute toxicity. If the study goes on to the second stage, a total of 32 patients will be enrolled (with at least 27 evaluable patients). If the total number of patients completing the tri-modality treatment without undue acute

toxicity is less than or equal to 15, the treatment is rejected and modification of the protocol will be considered.

REFERENCES

1. Stupp R, Mason WP, van den Bent MJ, et al. Radiotherapy plus concomitant and adjuvant temozolomide for glioblastoma. N Engl J Med 2005;352:987-96.
2. Wong ET, Hess KR, Gleason MJ, et al. Outcomes and prognostic factors in recurrent glioma patients enrolled onto phase II clinical trials. J Clin Oncol 1999;17:2572-8.
3. Chang Yi W, Allen PK, Maor MH, et al. International Journal of Radiation Oncology, Biology, Physics 2003;56(2):519-528.
4. Combs SE, Thilmann C, Schulz-Ertner D J, et al. Efficacy of fractionated stereotactic reirradiation in recurrent gliomas: long-term results in 172 patients treated in a single institution. J Clin Oncol. 2005;23(34):8863-9.
5. Stupp R, Wong ET, Gutin PH. et al. NovoTTF-100A versus physician's choice chemotherapy in recurrent glioblastoma: a randomised phase III trial of a novel treatment modality. Eur J Cancer. 2012;48(14):2192-202.
6. Lederman G, Wronski M, Wrzolek M, et al. Treatment of recurrent glioblastoma multiforme using fractionated stereotactic radiosurgery and concurrent paclitaxel. Am J Clin Oncol. 2000;23(2):155-9.
7. Kirson ED, Gurvich Z, Schneiderman R, et al. Disruption of cancer cell replication by alternating electric fields. Cancer Res 2004;64:3288-95.
8. Macdonald DR, Cascino TL, Schold SC, Jr., Cairncross JG. Response criteria for phase II studies of supratentorial malignant glioma. J Clin Oncol 1990;8:1277-80.
9. Kirson E, Dbaly V, Palti Y, et al. Alternating electric fields arrest cell proliferation in animal tumor models and human brain tumors. PNAS 2007;104:10152-57.
10. Kirson E, Schneiderman RS, Palti Y, et al. Chemotherapeutic treatment efficacy and sensitivity are increased by adjuvant alternating electric fields (TTFields). BMC Medical Physics 2009;9:1-13.
11. Gutin P, Iwamoto F, Abrey L, et al. Safety and efficacy of bevacizumab with hypofractionated stereotactic irradiation for recurrent malignant gliomas. IJROBP 2009;75:156-163.
12. Friedman H, Prados M, Cloughesy T, et al. Bevacizumab alone and in combination with irinotecan in recurrent glioblastoma. J Clin Oncol 2009;27:4733-40.
13. Simon, R. Optimal Two-Stage Designs for Phase II Clinical Trials. Controlled Clinical Trials 1989; 10:1-10.

APPENDIX I

M. D. Anderson Symptom Inventory – Brain Tumor (MDASI-BT)

Date: _____ **Institution:** _____

Participant Initials: _____ **Hospital Chart #:** _____

Participant Number: _____

M. D. Anderson Symptom Inventory - Brain Tumor (MDASI - BT)

Part I. How **severe** are your symptoms?

People with cancer frequently have symptoms that are caused by their disease or by their treatment. We ask you to rate how severe the following symptoms have been ***in the last 24 hours***. Please fill in the circle below from 0 (symptom has not been present) to 10 (the symptom was as bad as you can imagine it could be) for each item.

	Not Present 0	1	2	3	4	5	6	7	8	9	As Bad As You Can Imagine 10
1. Your **pain** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
2. Your **fatigue (tiredness)** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
3. Your **nausea** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
4. Your **disturbed sleep** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
5. Your feeling of being **distressed (upset)** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
6. Your **shortness of breath** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
7. Your problem with **remembering things** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
8. Your problem with **lack of appetite** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
9. Your feeling **drowsy (sleepy)** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
10. Your having a **dry mouth** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
11. Your feeling **sad** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
12. Your **vomiting** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
13. Your **numbness or tingling** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
14. Your **weakness** on one side of the body at its WORST?	○	○	○	○	○	○	○	○	○	○	○
15. Your difficulty **understanding** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
16. Your difficulty **speaking** (finding the words) at its WORST?	○	○	○	○	○	○	○	○	○	○	○

Page 1 of 2

APPENDIX I

M. D. Anderson Symptom Inventory – Brain Tumor (MDASI-BT)

Date: _____ Institution: _____

Participant Initials: _____ Hospital Chart #: _____

Participant Number: _____

	Not Present 0	1	2	3	4	5	6	7	8	9	As Bad As You Can Imagine 10
17. Your seizures at its WORST?	○	○	○	○	○	○	○	○	○	○	○
18. Your difficulty concentrating at its WORST?	○	○	○	○	○	○	○	○	○	○	○
19. Your vision at its WORST?	○	○	○	○	○	○	○	○	○	○	○
20. Your change in appearance at its WORST?	○	○	○	○	○	○	○	○	○	○	○
21. Your change in bowel pattern (diarrhea or constipation) at its WORST?	○	○	○	○	○	○	○	○	○	○	○
22. Your irritability at its WORST?	○	○	○	○	○	○	○	○	○	○	○

Part II. How have your symptoms **interfered** with your life?

Symptoms frequently interfere with how we feel and function. How much have your symptoms interfered with the following items **in the last 24 hours**:

	Did not Interfere 0	1	2	3	4	5	6	7	8	9	Interfered Completely 10
23. General activity?	○	○	○	○	○	○	○	○	○	○	○
24. Mood?	○	○	○	○	○	○	○	○	○	○	○
25. Work (including work around the house)?	○	○	○	○	○	○	○	○	○	○	○
26. Relations with other people?	○	○	○	○	○	○	○	○	○	○	○
27. Walking?	○	○	○	○	○	○	○	○	○	○	○
28. Enjoyment of life?	○	○	○	○	○	○	○	○	○	○	○

APPENDIX II
Tables and Figures

1. Outcomes with Bevacizumab in Recurrent GBM

Study	Pts (n)	Treatment	mOS	mPFS	PFS-6	ORR
Kreisl JCO 2009	48	Bevacizumab	7.8 mo	16 wks	29%	35%
Nagane JCO 2012	29	Bevacizumab	10.5 mo	13 wks	34%	27.6%
Gilbert JCO 2009	57	Bev + CPT11			37%	
Vrendenburgh Clin Ca Res 2007	23 GBM	Bev + CPT11	9.2 mo	20 wks	38%	61%
Friedman JCO 2009	82	Bev + CPT11	8.7 mo.	24 wks	50.2%	37.8%
Freidman JCO 2009	85	Bevacizumab	9.2 mo	18 wks	42.6%	28.2%

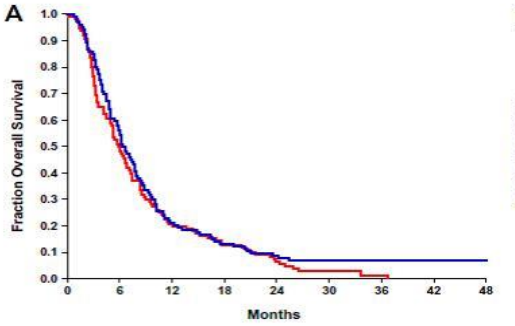
2. Outcomes of Re-irradiation in Recurrent GBM

Study	Pts (n)	Gy/Fx's	Median OS	ORR	Severe Tox/Re-op rate
Shepherd IJROBP 1997	29	20-50Gy/5 Fx	11 months		36%
Hudes IJROBP 1999	19	30Gy/10 Fx	10.5 months	22%	0%
Vordermark BMC Cancer 2005	9	30Gy/6 Fx	7.4 months		26%
Ernst-Stecken J Neuro Onc 2006	15	35Gy/5 Fx	11 months	27%	0%
Fokas 2009	52	30Gy/10 Fx	9 months		0%
Gutin IJROBP 2009	20	30Gy/5 Fx (+Bev)	12.5 months	50%	12% (Gr 4)
Fogh JCO 2010	147	35Gy/10 Fx	11 months	10%	0%

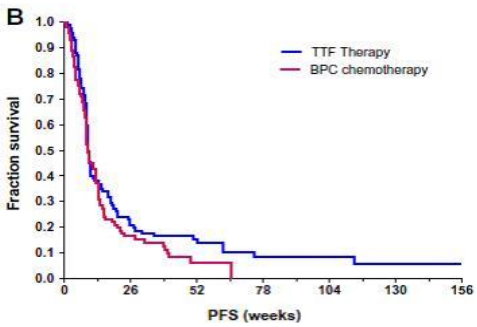
APPENDIX II

Tables and Figures

3. Overall Survival and PFS for patients treated with TTF in Stupp 2012 trial.
4.



At risk	0 m	6 m	12 m	18 m	24 m	30 m	36 m	42 m	48 m
TTF	120	63	24	15	9	7	4	2	1
BPC	117	56	22	14	6	2	1	0	0



0 m	13 w	26w	39w	52w	65 w	78 w	91 w
120	38	19	14	11	6	4	3
117	34	14	10	3	1	0	0