A Phase 2, Multi-center, Single arm, Historically Controlled Study Testing the Combination of TTFields and Pulsed Bevacizumab Treatment in Patients with Bevacizumab-refractory Recurrent Glioblastoma

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Study Device:	NovoTTF-100A (Optune)
Study Drug:	Bevacizumab (Avastin®)
Clinical Trials.gov #:	NCT02663271

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Protocol Revision History

Initial Approval Version	**3/21/2016**
Amendment 1	**12/01/2016**
Amendment 2	**05/23/2017**
Amendment 3	**08/29/2017**
Amendment 4	**10/24/2017**
Amendment 5	**03/09/2018**
Amendment 6	**08/31/2018**
Amendment 7	**11/19/2020**
Amendment 7.1	**04/15/2022**

Summary of Protocol Changes

Version Date	Sections Revised	Purpose
3/21/2016	N/A	-Initial Protocol Release
12/01/2016	Title Page	-Individuals updated to reflect current personnel. -Version date changed.
	Schema	-Schema updated for clarity and consistency.
	Table of Contents	-Updated for pagination.
	4.1, Inclusion Criteria	-Clarified informed consent as a criterion for inclusion.
	5.0, Registration Procedures	-Clarified timing of protocol intervention in relation to consent and registration.
	6.1, Treatment with Bevacizumab	-Specified assessments and defined timeframe and window for completion. -Included reference to Appendix D, which was added to clarify bevacizumab dose modifications in event of adverse events.
	6.2, Treatment with TTFields	-Updated to clarify that compliance with TTFields will be monitored by Novocure per usual procedures.
	6.4, Potential Adverse Events: Bevacizumab	-Included reference to Appendix D, Bevacizumab Dose Modifications and Appendix E, Hypertension Management which were added to provide clarification for patient management.
	7.1.2, Quality of Life 7.1.3, Response Criteria	-Clarified timing of assessments for internal consistency.
	8.0, Dose Delays/Dose Modifications	-Updated to include reference to Appendix D, Bevacizumab Dose Modifications.
	11.0, Schedule of Events	-Updated for clarity and internal consistency. -Updated to clarify procedures (urinalysis/dipstick) and time points to monitor for proteinuria and describe modifications in bevacizumab dosing based on results.
	16.0, Statistical Considerations	-Updated to reflect the statistical plan for all objectives.
	21.0, Appendix D, Bevacizumab Modifications	-New appendix added to clarify recommendations for bevacizumab dose modifications in event of adverse events.
	22.0, Appendix E, Management of Hypertension	-New appendix added to clarify management of hypertension in patients treated with bevacizumab.

05/23/2017	11.0 Schedule of Events	-Schedule of events revised to better reflect the timing of assessments (physical exam, pregnancy test, KPS, MMSE) that should be associated with screening and registration rather than Week 0.
	12.0 Data Submission Schedule	-Data submission time points for KPS and MMSE updated from 4 to 8 weeks for consistency with schedule of events and to reflect treatment standard.
	13.3 Methods for Evaluation of Measurable Disease	-Error in verbiage corrected as brain FDG-PET coupled with head CT or brain MRI should not be used as the primary or sole method of determining response or disease status. This was an unintended error in previous protocol versions.
9/15/2017	Table of Contents	-Updated to reflect change in page numbers.
	4.1 Inclusion Criteria	-Revision to allow Bevacizumab refractory patients in the trial during any recurrence or progression of disease. A shift in use of Bevacizumab to later recurrence has become practice. Update is needed to capture Bevacizumab refractory patients.
	7.1 Imaging	-MRI should be obtained every 8 weeks +/- 7 days. Updated for continuity throughout protocol.
	13.1 Antitumor effect: Solid Tumors	-Updated response evaluation to 8 weeks +/- 7 days. Updated for continuity throughout protocol.
	11.0 Schedule of Events	-Study calendar updated to reflect what is included in survival follow up.
	13.3.5 Neurological Exam and Performance Status	-Updated evaluation every 4 weeks +/- 2 weeks. Updated for continuity throughout protocol.
	Appendix C: RANO	-Updated RANO measurement form.
	Appendix F: Guidance on Contraception	-Appendix F added .
10/24/2017	1.0, Protocol Synopsis	-Clarified number of evaluable subjects needed to complete study.

	4.1 Inclusion Criteria	-Clarified eligibility criterion #1 limiting the number of prior progressions on bevacizumab.
	7.1.3 Response Criteria	-Added provision to allow for replacement of subjects who are not evaluable.
03/09/2018	10.1 Reporting Requirements for Secondary Sites	-Reference to events that require reporting added for completeness.
	14.0 Data and Safety Monitoring	-Monitoring plan added per DSMB recommendation with onset of accrual at secondary site and event reporting clarified.
	15.0 Auditing	-Requirement for auditing better delineated.
8/31/2018	8.0 External Palliative Care	-Section added to allow for subjects to receive treatment with bevacizumab locally to decrease travel burden on patients.
11/19/2020	Title (throughout)	-Correction of typographical error.
	12.0 Schedule of Events	-MRI timeframe clarified since patients may be scanned prior to the Screening Visit, and without this revision the MRI might become asynchronous to the protocol treatment timeline.

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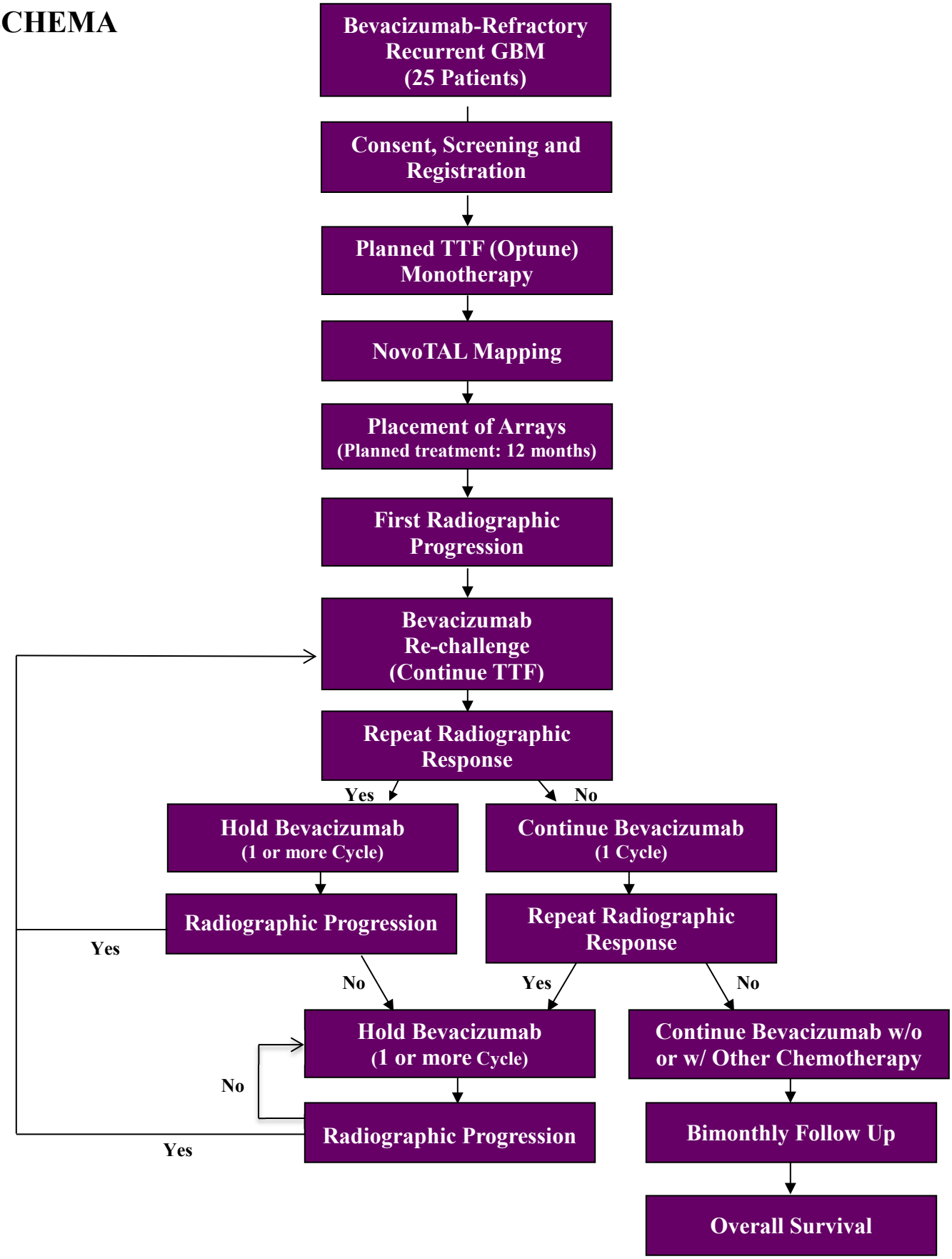
Principal Investigator Signature Page

Principal Investigator:	David Tran, M.D., PhD.	
	Signature of Investigator	Date
	Printed Name of Investigator	
	By my signature, I agree to personally supervise the conduct of this study and to ensure its conduct in compliance with the protocol, informed consent, IRB/HRPO procedures, the Declaration of Helsinki, ICH Good Clinical Practices guidelines, and the applicable parts of the United States Code of Federal Regulations or local regulations governing the conduct of clinical studies.	

SCHEMA


Bevacizumab-Refractory Recurrent GBM (25 Patients)
Consent, Screening and Registration
Planned TTF (Optune) Monotherapy
NovoTAL Mapping
Placement of Arrays (Planned treatment: 12 months)
First Radiographic Progression
Bevacizumab Re-challenge (Continue TTF)
Repeat Radiographic Response
Yes
No
Hold Bevacizumab (1 or more Cycle)
Continue Bevacizumab (1 Cycle)
Radiographic Progression
Repeat Radiographic Response
Yes
No
Yes
No
Hold Bevacizumab (1 or more Cycle)
Continue Bevacizumab w/o or w/ Other Chemotherapy
No
Radiographic Progression
Bimonthly Follow Up
Yes
Overall Survival

Glossary of Abbreviations

AE	Adverse event
ALT (SGPT)	Alanine transaminase (serum glutamate pyruvic transaminase)
ANC	Absolute neutrophil count
AST (SGOT)	Aspartate transaminase (serum glutamic oxaloacetic transaminase)
BBB	Blood brain barrier
B-HCG	Beta human chorionic gonadotropin
CBC	Complete blood count
CFR	Code of Federal Regulations
CNS	Central nervous system
CRF	Case report form
CT	Computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CTEP	Cancer Therapy Evaluation Program
DLTs	Dose Limiting Toxicities
DSM	Data and Safety Monitoring
ECI	Event of clinical interest
FDA	Food and Drug Administration
FNA	Fine needle aspiration
FWA	Federal wide assurance
GBM	Glioblastoma multiforme
HIV	Human Immunodeficiency Virus
HRPO	Human Research Protection Office (IRB)
IB	Investigator's brochure
IHC	Immunohistochemistry
IND	Investigational New Drug
INR	International normalized ratio
irAE	Immune-related adverse event
IRB	Institutional Review Board
IULN	Institutional upper limit of normal
IV	Intravenous (i.v.)
MRI	Magnetic resonance imaging
NCI	National Cancer Institute
NIH	National Institutes of Health
NSCLC	Non-small cell lung cancer

OHRP	Office of Human Research Protections
OS	Overall survival
PFS	Progression-free survival
PI	Principal investigator
PK	Pharmacokinetic
PT	Prothrombin time
PTT	Partial thromboplastic time
QASMC	Quality Assurance and Safety Monitoring Committee
RANO	Response Assessment in Neuro-Oncology
SAE	Serious adverse event
SUSAR	Suspected unexpected serious adverse reaction
TIL	Tumor-infiltrating lymphocytes
TSH	Thyroid stimulating hormone
TTFields	Tumor-treating fields
UPN	Unique patient number

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1.0 PROTOCOL SYNOPSIS

Title	A Phase 2, Multi-center, Single arm, Historically Controlled Study Testing the Combination of TTFields and Pulsed Bevacizumab Treatment in Patients with Bevacizumab-refractory Recurrent Glioblastoma
Study Device & Drug	NovoTTF-100A (Optune); Bevacizumab (Avastin®)
Study Objectives	To determine whether or not TTFields combined with pulsed bevacizumab treatment increases overall survival in patients with bevacizumab-refractory GBM compared to historical controls treated with continuous bevacizumab alone or in combination with standard chemotherapy.
Study Design	Phase 2, single-arm, open-labeled, historically controlled
Study Hypothesis	Successive cycles of on/off (or pulsed) bevacizumab dosing will produce peaks and troughs, respectively, in mitotic activities of glioma cells that render glioma cells more sensitive to the antimitotic activity of TTFields during peak growth rates, thus lowering disease burden and increasing survival.
Sample Size	25 evaluable adult patients with bevacizumab-refractory recurrent primary or secondary GBM, WHO Grade IV
Study population	Male or female patients with bevacizumab-refractory recurrent GBM (WHO grade IV) who are ≥ 22 years of age
Primary endpoint	Overall survival
Secondary endpoint	Rate of repeat response to bevacizumab re-challenge after at least 1 cycle
Disease assessment	Per RANO criteria
Sponsor	NovoCure Ltd. PO Box 15022 MATAM Center Haifa, 31905, Israel

2.0 BACKGROUND AND RATIONALE

2.1 Glioblastoma Multiforme

Glioblastoma multiforme (GBM) is the most common and deadliest primary malignant neoplasm of the central nervous system in adults. Despite aggressive multimodality treatment approach including surgery, radiation therapy and chemotherapy, the median overall survival (OS) reaches only 14.6 months (*1*), and increasing to 19.6 months with the addition of TTFields in newly diagnosed GBM (ASCO Abstract 2015). Recurrent GBM has an even more dismal prognosis with a median overall survival of ~25 weeks (*2*).

2.2 Bevacizumab (Avastin®)

Bevacizumab (Avastin®, Genentech, Inc., South San Francisco, CA) is an anti-VEGF recombinant humanized monoclonal antibody approved in the United States as a single agent for recurrent GBM (*3, 4*). Although radiographic responses are observed on MRI following treatment with bevacizumab, to date, no direct comparison between bevacizumab and cytotoxic chemotherapy has been conducted, and it remains unclear if bevacizumab improves OS in patients with recurrent GBM (*3, 4*). Once refractory to bevacizumab, patients are unlikely to respond to subsequent regimens, whether they contain bevacizumab or not and inevitably relapse. Median OS after bevacizumab failure has ranged from approximately 1.1 to 4.5 months regardless of treatment (*5-7*).

2.3 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 depolarization (*8*). The transmission of such fields by radiation is insignificant and therefore they are usually applied directly by contact electrodes, though some applications have also used insulated electrodes. Some well-known examples of such effects include nerve, muscle, and heart stimulation by alternating electric fields (*8, 9*). In addition, low frequency pulsed electric fields have been claimed to stimulate bone growth and accelerate fracture healing (*10*). 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 (*11*). 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 (*12*).

Intermediate frequency electric fields (i.e., tens of kHz to MHz) alternate too fast for causing 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 (*11*). 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) and cell rotation (*13-15*). 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 (*16, 17*).

2.4 Novocure's Tumor-treating Fields (TTFields™)

Novocure has shown that when properly tuned, very low intensity, intermediate frequency electric fields (TTFields) stunt the growth of tumor cells (*18*). This inhibitory effect was demonstrated in all proliferating cell types tested, whereas non-proliferating cells and tissues were unaffected. Interestingly, different cell types showed specific intensity and frequency dependences 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 (*19*). 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 (*20, 21*) or indirectly (*22-25*) with microtubule polymerization (e.g., Taxol).

2.5 The Optune System

The Optune system (NovoTTF™ Therapy) is a portable battery operated device, which produces TTFields within the human body by means of surface transducer arrays (*26, 27*). The TTFields are applied 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 change and recharge depleted service batteries and to connect to an external battery pack overnight.

Optune is currently FDA-approved as a single modality treatment for recurrent GBM when both surgical and radiotherapy options have been exhausted as well as combination with adjuvant temozolomide for newly diagnosed GBM. In the pivotal EF-11 trial in recurrent GBM, overall survival (OS) of patients treated with the device was equivalent to those treated with standard chemotherapy alone (*27*). Six-month progression-free survival (6PFS) analysis favored the TTFields arm compared to the chemo arm, although not statistically significant. Safety and toxicity profile favored the Optune arm compared to the chemotherapy control arm. No device-specific grade 3 and 4 toxicities were identified for hematologic, gastrointestinal, vascular, renal and respiratory disorders. There was also no increased grade 3 and 4 central nervous system adverse events. The most common device specific adverse event was skin rash due to the transducer arrays.

2.6 Study Rationale

A post hoc subgroup analysis of the EF-11 study data revealed that patients with bevacizumab-refractory GBM achieved median OS of 6.3 months when treated with TTFields monotherapy compared to 3.3 months when standard bevacizumab-based chemotherapy was continued (HR 0.39, 95% CI 0.19-0.79, p=0.01). This preliminary data suggest that bevacizumab-refractory GBM may be particularly sensitive to the anti-mitotic activity of TTFields (*28, 29*) after bevacizumab withdrawal. Rapid tumor regrowth and radiographic tumor rebound phenomenon has been reported after withdrawal of bevacizumab in patients with recurrent high-grade glioma, leading to an accelerated clinical decline (*30*). For this reason, many practitioners are reluctant to discontinue bevacizumab even when bevacizumab failure is well documented, and thus this approach represents a potential overtreatment. Molecularly, acquired resistance to bevacizumab in high grade gliomas is thought to result from a meschymal transition characterized by an enrichment of slow-cycling, highly invasive, and treatment-resistant glioma stem-like cells (GSCs) (*31, 32*). After discontinuation of bevacizumab, the microhypoxic stress and pro-GSC environment are removed and presumably GSCs exit cell cycle arrest and reactivate rapid proliferation. This is during bevacizumab withdrawal that we hypothesis that GBM cells, especially GSCs reentering rapid cycling, are most sensitive to the anti-mitotic activities of TTFields. Bevacizumab treatment may be resumed temporarily for subsequent radiographic progression or worsening symptoms, due to either further disease progression or inflammatory responses to TTFields-induced cell death. Once inflammation is controlled, bevacizumab is again withdrawn and this cycle can be repeated many times. We hypothesize that successive cycles of on/off (or pulsed) bevacizumab dosing will produce peaks and troughs in mitotic activities of GSCs that allows TTFields to work at slowly reducing the GSC fraction in tumors, and thus lowering disease infiltration and increasing survival.

We recently conducted a case series study describing the outcomes for 8 patients with bevacizumab-refractory GBM, who were treated with TTFields monotherapy first, then with concomitant re-challenge with bevacizumab upon subsequent radiographic progression in 5 of these patients (*33*). The 8 patients had a median OS of 216 days (7.2 months) from first day of treatment with TTFields therapy, which was significantly longer than historical data of 1-4 months and consistent with the subgroup analysis of EF-11 data. Of the 5 patients re-challenged with bevacizumab, median OS from first dose of bevacizumab re-challenge was

172 days (5.7 months), although they all had developed resistance to bevacizumab after having received a median time of 236.5 days (7.9 months) of bevacizumab prior to starting TTFields. Patients highly adherent to treatment -- who were also those who received pulse dose bevacizumab -- had the longest OS. Patient # 4 had an adherence rate of 92.9%; her time from first day of TTFields therapy to death was 276 days (9.2 months) and, from first dose of bevacizumab re-challenge until death, 150 days (5.0 months). Patient # 7, with an adherence rate of 73.2%, had a time from first day of TTFields to death of 406 days (13.5 months) and, from first dose of bevacizumab re-challenge until death, of 349 days (11.6 months) (Fig. 1).

In this case series, we describe 8 patients with recurrent glioblastoma in whom we discontinued treatment with bevacizumab successfully - despite the concern of possible rapid disease progression upon bevacizumab withdrawal, effectively used TTFields therapy, and then re-challenged them with bevacizumab once patients developed symptoms and/or had evidence of radiographic progression. This "pulsed dosing" approach to bevacizumab administration, combined with TTFields therapy, has not been described in this patient population, and although the results from this small study is encouraging this novel approach will need to be formally tested in a focused prospective clinical study.

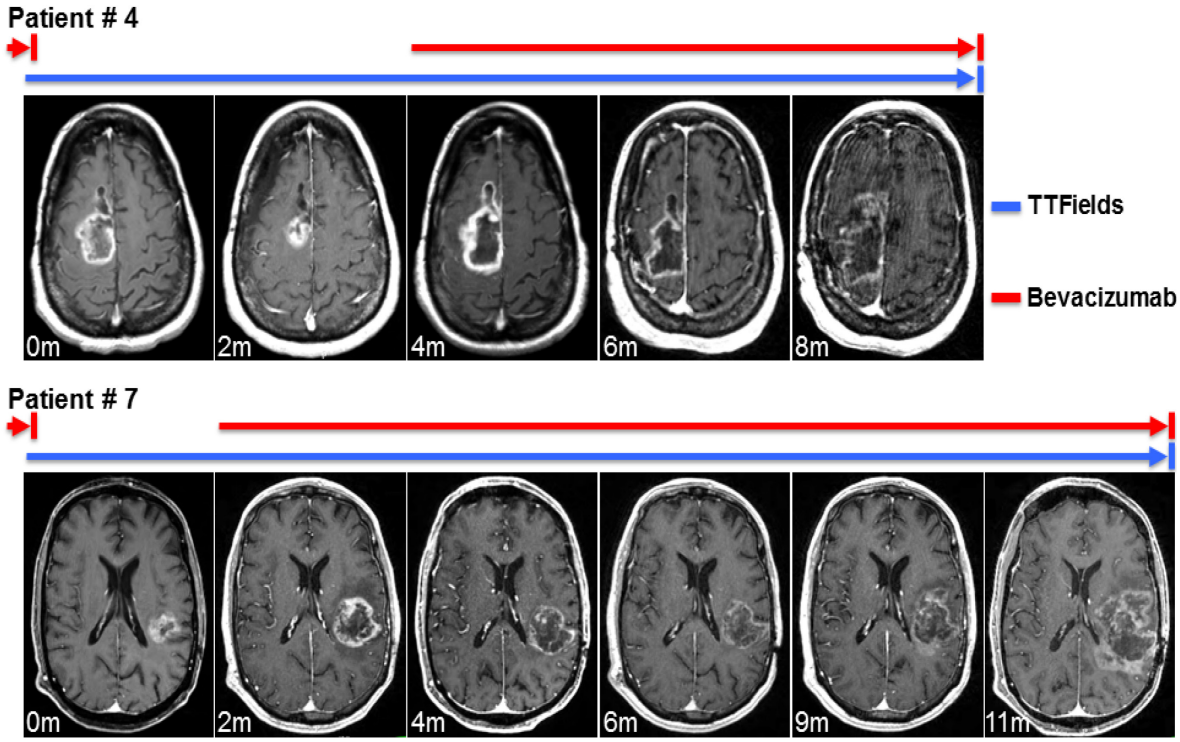


Figure 1: Radiographic appearance of bevacizumab-refractory GBM treated with TTFields and subsequently re-challenged with bevacizumab. Representative pictures of serial gadolinium contrast-enhanced brain MRI scans of Patients # 4 and # 7 are shown. Colored bars denote time line of TTFields and bevacizumab re-challenge in months, starting from the first documented radiographic diagnosis of bevacizumab-refractory GBM per RANO criteria. Patient # 4 demonstrated an initial response to TTFields at 2 months but progressed radiographically at 4 months. Upon re-challenge with bevacizumab, this patient's GBM demonstrated a radiographic response again. Patient # 7 did not have a radiographic response to TTFields in the first 2 months. However, this patient had a durable radiographic response to bevacizumab re-challenge while continuing on with TTFields.

3.0 OBJECTIVES

3.1 Primary Objectives

1. To determine whether or not TTFields combined with pulsed bevacizumab treatment increases overall survival in patients with bevacizumab-refractory GBM compared to historical controls treated with continuous bevacizumab alone or in combination with other chemotherapy.

3.2 Secondary Objectives

1. To determine whether or not TTFields combined with pulsed bevacizumab treatment re-sensitizes bevacizumab-refractory GBM to bevacizumab re-challenge.

2. To determine whether or not TTFields combined with pulsed bevacizumab treatment is safe in patients with bevacizumab-refractory GBM.

4.0 PATIENT SELECTION

4.1 Inclusion Criteria

1. Patients must have histologically confirmed GBM, WHO grade IV (GBM variants or secondary GBM is allowed) in any recurrence on any therapy, except that only one prior tumor progression on bevacizumab is permitted. Prior therapy must include radiation and chemotherapy, which includes, but not limited to, temozolomide, PCV, bevacizumab, CCNU or BCNU.

2. Unequivocal evidence of tumor progression during prior bevacizumab treatment per RANO criteria.

3. Patient is a candidate for, and agrees to proceed with additional bevacizumab treatment.

4. Male or female at least 22 years of age or older.

5. Karnofsky Performance Scale (KPS) $\geq$ 60%.

6. Planned treatment with TTFields therapy.

7. Women of childbearing potential must have a negative serum or urine pregnancy test within 14 days of treatment.

8. Participants of childbearing/reproductive potential must use effective contraception as outlined in Appendix F.

9. Participants must be able to understand and willing to comply with protocol requirements as assessed by the investigator**.**

10. Signed informed consent according to institutional guidelines must be obtained prior to registration.

4.2 Exclusion Criteria

1. Inability to undergo brain MRI due to medical or personal reasons.

2. Currently receiving investigational agents that are intended as treatments of recurrent GBM.

3. Skull defect such as missing bone or bullet fragments.

4. Uncontrolled intercurrent illness including, but not limited to symptomatic congestive heart failure, unstable angina pectoris, heart attack within the previous 12 months, stroke (except for TIA) within the previous 6 months, or psychiatric illness/social situations that would limit compliance with study requirements.

5. Intracranial hemorrhage except for tumor associated micro hemorrhage.

6. Women who are pregnant or breastfeeding.

7. Implanted pacemaker, programmable shunts, defibrillator, deep brain stimulator, vagus nerve stimulator, and other implanted electronic devices in the brain or the spinal cord.

8. Tumor located entirely in the infratentorium.

9. History of hypersensitivity to hydrogel.

4.3 Inclusion of Women and Minorities

Both men and women and members of all races and ethnic groups are eligible for this trial.

5.0 REGISTRATION PROCEDURES

Patients must not start any protocol intervention prior to consent and registration with the University of Florida.

The following steps must be taken before registering patients to this study:

1. Confirmation of patient eligibility by University of Florida
2. Registration of patient in OnCore, the University of Florida Cancer Center's Clinical Trial Management System
3. Assignment of unique patient number (UPN)

Once the patient has been entered in OnCore, the study coordinator will forward verification of enrollment and the UPN via email.

5.1 Confirmation of Patient Eligibility

Confirm patient eligibility by collecting the information listed below and scanning and emailing it to the University of Florida research coordinator at least one business day prior to registering patient:

1. Your name and contact information (telephone/fax numbers and email address)
2. Your site PI's name, the registering MD's name, and your institution name
3. Patient's race, sex, and DOB
4. Three letters (or two letters and a dash) for the patient's initials
5. Currently approved protocol version date
6. Copy of signed consent form (patient name may be blacked out)
7. Planned date of enrollment
8. Completed eligibility checklist, signed and dated by a member of the study team
9. Copy of appropriate source documentation confirming patient eligibility

5.2 Patient Registration in the University of Florida Cancer Center Database

Registrations may be submitted Monday through Friday between 8am and 5pm EST. Urgent late afternoon or early morning enrollments should be planned in advance and coordinated with the University of Florida research coordinator. Registration will be confirmed by the research coordinator or his/her delegate by email within one business day. Verification of eligibility and registration should be kept in the patient chart.

All patients at all sites must be registered through OnCore at the University of Florida.

5.3 Assignment of UPN

Each patient will be identified with a unique patient number (UPN) for this study. Patients will also be identified by first, middle, and last initials. If the patient has no middle initial, a dash will be used on the case report forms (CRFs). All data will be recorded with this identification number on the appropriate CRFs.

6.0 TREATMENT PLAN

6.1 Treatment with Bevacizumab

Patients with unequivocal evidence of bevacizumab-refractory GBM per RANO criteria will be eligible. Patients will undergo 12 months of planned continuous treatment with TTFields followed by pulsed bevacizumab treatment when there is evidence of further progression per RANO, with the option of extending treatment up to a total of 24 months in patients who have not progressed and/or have adequate performance status at the 12 month mark. Pulsed bevacizumab dosing is defined by at least one cycle on and at least one cycle off. A cycle is defined as 8 weeks in length (Fig. 2). If after one cycle on, there is no evidence of a repeat response bevacizumab will be continued for one more cycle. If after two cycles on, there is no repeat response bevacizumab will be continued with or without other standard chemotherapy until death. If after at least one cycle on, there is evidence of repeat response, bevacizumab will be discontinued for at least one cycle or until progression is noted again per RANO, whichever is later, at which time pulsed bevacizumab will be restarted as above. Bevacizumab will be given at 10mg/kg IV every 2 weeks. Physical examination, KPS and MMSE will be performed within 28 days (+/- 7) of starting treatment with TTFields and every 8 (+/- 2) weeks thereafter. Brain MRI will be performed at screening and every 8 weeks (+/- 7) days thereafter.

Dose modifications for bevacizumab will be in accordance with guidelines in Appendix D.

Patients may be infused locally at the discretion of the enrolling investigator.

6.2 Treatment with TTFields

Patients will undergo 12 months of planned treatment with TTFields. Therapy will be given as per standard of care (see Section 6.2.1 for recommended use of the TTFields). 3D mapping and placement maps of recurrent tumors will be completed by the principal investigator. Placement of transducer arrays will be provided by Novocure. Scalp shaving, array placement and all device support services (including patients' and families' education of device operation, downloading and processing of technical and compliance data, and troubleshooting device malfunction) will be provided by device support specialists employed by Novocure. The minimum treatment compliance required for this study is wearing the system for an average of no less than 60% of the time over each 4-week period with the goal of achieving 75% or more of the time over each 4-week period. Compliance with TTFields will be monitored by Novocure per usual procedures. If a patient's compliance drops below 60% over any given 4-week period, the patient will be trained on the importance of compliance and any barriers to compliance will be addressed. If a patient's compliance is below 60% for 2 consecutive 4-week periods, the patient will be removed from study. At the discretion of treating investigators, patients can have an additional treatment break during

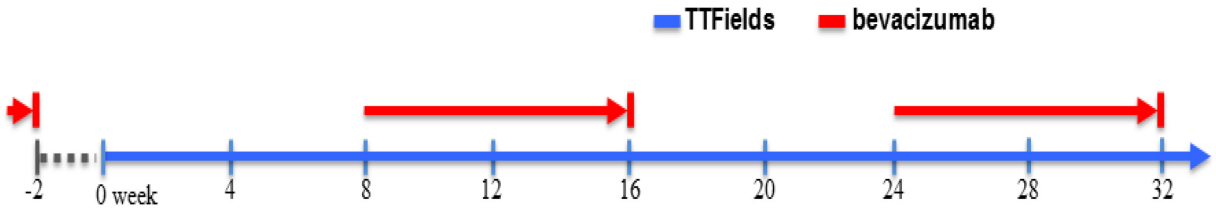


Figure 2: Schematics of Treatment Plan

each 4 week period of no more than 3 consecutive days as needed for personal reasons as long as the overall compliance for any 4 week period does not drop below 60% because of the additional break.

6.2.1 Recommendations for Use of Optune

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. It is recommended that treatment with the device be continuous with breaks allowed for personal needs (e.g., showering, array exchange). Breaks should be no more than 1 hour twice daily. Use compliance is aimed at a minimum of 60% (14.4 hours) with the goal of achieving at least 75% (18 hours) of the time per day on average. In addition, investigators may grant brief breaks in device treatment that last no more than 3 days in any 30 day period at the investigator's discretion.

Optune is programmed by Novocure to deliver 200 kHz TTFields in two sequential, perpendicular field directions at a maximal intensity of 707mARMS. There will be no adjustments made to the device by investigators or patients/caregivers.

It is recommended that patients replace the transducer arrays 2-3 times per week with the help of a caregiver. At each array replacement, it is recommended that the patient's scalp be re-shaved and skin treated according to the guidelines in section 6.2.2.

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.

6.2.2 Skin Care Guidelines

If the skin beneath the transducer arrays is inflamed, it is recommended that a prescription strength steroid ointment (e.g. 3% hydrocortisone or 0.05-0.1% Clobetasol) 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.

At each array replacement, it is recommended that the new set of arrays 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.

If the dermis is breached (ulcers, open sores, punctate lesions, cuts, etc.), it is recommended that an antibiotic ointment (e.g. bactroban) be prescribed and used in place of the steroid ointment.

6.3 Potential Adverse Events: Optune

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

- Local warmth and tingling "electric" sensation beneath the transducer array
- Allergic reaction to the adhesive or the gel
- Skin irritation or skin breakdown
- Infection at the sites of transducer array contact with the skin
- Transducer array overheating leading to pain and/or local skin burns
- Headache
- Fatigue

Treatment with Optune is FDA approved and standard of care.

6.4 Potential Adverse Events: Bevacizumab

See Appendix D for bevacizumab dose modifications.

In initial Phase I and Phase II clinical trials, the following four potential bevacizumab-associated safety signals were identified:

- Hypertension (See Appendix E for guidelines on hypertension management)
- proteinuria
- thromboembolic events
- hemorrhage

Additional completed Phase II and Phase III studies of bevacizumab as well as spontaneous reports have further defined the safety profile of this agent. Bevacizumab-associated adverse events identified in phase III trials include:

- congestive heart failure (CHF) primarily in metastatic breast cancer
- gastrointestinal perforations
- wound healing complications
- arterial thromboembolic events (ATE)
- visceral arterial ischemia
- disseminated intravascular coagulation resulting in death was reported in a single case recently

7.0 STUDY ASSESSMENTS

7.1 Imaging

Patients will undergo standard brain MRI scans without then with gadolinium contrast every 8 weeks (+/- 7) days) while on study as per routine care. Information from these scans will be

recorded in the study database. If a patient develops symptoms that are potentially indicative of disease progression, scans may be done sooner than every 8 weeks as per standard practice.

7.1.1 Lab Work

No additional lab work is required during study treatment. Labs are to be performed as clinically indicated during bevacizumab treatment as per standard practice.

7.1.2 Quality of Life

Quality of life will be assessed every 8 weeks (+/- 2 weeks) by way of the MMSE (Appendix B) and assessment of Karnofsky Performance Scale (Appendix A), as performed as a part of routine standard-of-care assessments.

7.1.3 Response Criteria

All patients are evaluable for response and for assessment of QoL after completing at least 8 weeks of treatment with the Optune device with compliance rate $\geq$ 60% in at least one 4-week period. Subjects failing to meet these criteria will be replaced.

7.1.4 Duration of Therapy

If at any time the constraints of this protocol are considered to be detrimental to the patient's health and/or the patient no longer wishes to continue protocol therapy, the protocol therapy should be discontinued and the reason(s) for discontinuation documented in the case report forms.

In the absence of treatment delays due to adverse events, subjects will be removed from the study for the following reasons:

- GI perforation
- Documented and confirmed disease progression after bevacizumab re-challenge
- Death
- Adverse event(s) that in the judgment of the investigator may cause severe or permanent harm or which rule out continuation of study treatment
- General or specific changes in the patient's condition render the patient unacceptable for further treatment in the judgment of the investigator
- Pregnancy
- Less than 60% compliance with the TTFields Therapy for 2 consecutive 4-week periods
- Other serious noncompliance with the study protocol, e.g. missed appointments without valid reason
- Lost to follow-up
- Patient withdraws consent

- Investigator removes the patient from study
- The Coordinating or participating site decides to close the study

7.1.5 Duration of Follow-up

Patients will have one follow-up visit 30 days (+/- 7 days) after stopping treatment. Patients will then be followed every 8 weeks (+/- 2 weeks) for up to 2 years for survival. Survival information can be obtained by telephone or from clinic notes.

8.0 EXTERNAL PALLIATIVE CARE

Subjects enrolled in this trial may receive bevacizumab at an institution (e.g. local hospital, clinic, infusion center or other appropriate administration site) not selected as a research site for this study, if a trial investigator determines that it would be in the subject's best interest to receive treatment in a local setting. The trial investigators will retain responsibility for overseeing protocol-related activities, ensuring the study interventions are administered in accordance with the IRB-approved protocol and ensuring any applicable protocol-related data, including but not limited to, safety data and adverse events are reported to trial investigators.

9.0 DOSE DELAYS/DOSE MODIFICATIONS

The standard dose for bevacizumab is 10mg/kg IV every 2 weeks. If adverse events occur during the bevacizumab cycle, the standard dose can be adjusted at the principal investigator's discretion and per accepted standard practice, for example, decrease dose (7.5 mg/kg every 2 weeks), or maintain standard dose but increase the time frame between doses (10mg/kg every three weeks), or hold for toxicities as outlined in Appendix D, Bevacizumab Dose Modifications. 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.

10.0 REGULATORY AND REPORTING REQUIREMENTS

10.1 Adverse Events (AEs)

Definition: any unfavorable medical occurrence in a human subject including any abnormal sign, symptom, or disease.

Grading: the descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 will be utilized for all toxicity reporting. A copy of the CTCAE version 4.0 can be downloaded from the CTEP website.

Attribution (relatedness), Expectedness, and Seriousness: the definitions for the terms listed that should be used are those provided by the Department of Health and Human Services' Office for Human Research Protections (OHRP). A copy of this guidance can be found on OHRP's website:

http://www.hhs.gov/ohrp/policy/advevntguid.html

10.2 Serious Adverse Events (SAEs)

Definition: any adverse event that results in any of the following:

- Death
- A life-threatening adverse event
- Inpatient hospitalization or prolonging existing hospitalization
- A persistent or significant disability/incapacity
- A congenital anomaly/birth defect

Note: The term "life-threatening" refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if it were more severe.

10.3 Unanticipated Problems

Definition:

- unexpected (in terms of nature, severity, or frequency) given (a) the research procedures that are described in the protocol-related documents, such as the IRB-approved research protocol and informed consent document; and (b) the characteristics of the subject population being studied;
- related or possibly related to participation in the research ("possibly related" means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); and
- suggests that the research places subjects or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

10.4 Noncompliance

Definition: failure to follow any applicable regulation or institutional policies that govern human- subject's research or failure to follow the determinations of the IRB. Noncompliance may occur due to lack of knowledge or due to deliberate choice to ignore regulations, institutional policies, or determinations of the IRB.

10.5 Serious Noncompliance

Definition: noncompliance that materially increases risks that result in substantial harm to subjects or others, or that materially compromises the rights or welfare of participants.

10.6 Protocol Exceptions

Definition: A planned deviation from the approved protocol that are under the research team's control. Exceptions apply only to a single participant or a singular situation.

Local IRB approval of all protocol exceptions must be obtained prior to the event. For all sites, the UF PI will issue approval of the exception, but it must be submitted to the local IRB with documentation of local approval forwarded to UF. UF IRB approval is not required for protocol exceptions occurring at secondary sites.

11.0 Reporting to the IRB and UFHCC Data and Safety Monitoring Board

Each PI is required to promptly notify their IRB of the following events:

- Any unanticipated problems involving risks to participants or others
- Non-compliance with federal regulations or the requirements of the IRB
- Receipt of new information that may impact the willingness of participants to participate or continue participation in the research study.

These events must be reported to the institution's IRB of record within **10 working days** (or in accordance with local IRB policies) of the occurrence of the event or notification to the PI of the event. The death of a research participant that qualifies as a reportable event should be reported **within 1 working day** of the occurrence (or in accordance with the local IRB policies) of the event or notification to the PI of the event.

11.1 Reporting Requirements for Secondary Sites

The research team at each secondary site is required to promptly notify the UF PI and research coordinator of all reportable events (as described above 9.2 to 9.6) within **1 working day** of the occurrence of the event or notification of the secondary site's PI of the event. This notification may take a place via email if there is not yet enough information for a formal written report (using either an FDA MedWatch form if required or an institutional SAE reporting form). A formal written report must be sent to the UF PI and research coordinator within **4 calendar days (**for fatal or life-threatening adverse experiences) or **11 calendar days** (for serious, unexpected adverse experiences).

Each secondary site is responsible for reporting events to their local IRB in accordance with institutional guidelines.

11.2 Reporting to Secondary Sites

The University of Florida PI (or designee) will notify the research team at each secondary site, of all reportable events that have occurred at other sites (as described above) within **10 working days** of the occurrence of the event or notification of the PI of the event. This includes events that take place both at the University of Florida and at other secondary sites, if applicable.

12.0 SCHEDULE OF EVENTS

	Screening and Registration	Week 0	Week 8	On-Treatment Management	30-day Post-Tx Follow-up	Survival Follow-up
Informed consent[1]	X					
Medical history[2]	X					
Concomitant medications	X	X	X	X		
Physical examination	X[3]		X[3]	X[3]		
Pregnancy test	X[4]					
Urine Dipstick/Urinalysis			X[11]	X[11]		
Pulsed bevacizumab[5]			X[8]	X[8]		
MRI	X[6]		X[6]	X[6]		
Optune		X[7]	X[7]	X[7]		
Karnofsky Performance Scale	X[3]		X[3]	X[3]		
MMSE	X[3]		X[3]	X[3]		
AE Monitoring	X	X	X	X	X	
Post treatment follow-up					X[9]	
Survival contact						X[10]

1. No study-specific procedures are to be performed prior to obtaining informed consent. However, assessments performed according to SOC prior to consent may be used to fulfill the screening requirement, if completed within the window for screening. Study treatment should start within 14 (+/-3) days after informed consent is obtained.
2. Medical history may be performed at any time prior to registration.
3. Physical exam, KPS and MMSE will be performed within 28(+/-7) days of Optune treatment and every 8 (+/- 2) weeks thereafter.
4. Urine or serum pregnancy test is required for women of child-bearing potential only within 14 (+/- 3) days of treatment.
5. Bevacizumab infusions will be given at 10mg/kg as per SOC.
6. Patients will undergo SOC brain MRI scans with RANO response evaluation at screening, and then every 8 weeks (+/- 7 days) from Week 0 (Optune treatment start)
7. Optune treatment will begin at week 0 [14 (+/- 3) days from day of consent] and will be continuous throughout the study.
8. Pulsed bevacizumab dosing will begin at the time of progression. If repeat response is determined after 1 cycle, bevacizumab will be discontinued for at least 1 cycle; however if after one cycle, there is no evidence of a repeat response (progression continues) bevacizumab will be given for another cycle. If progression continues after the second cycle, the patient will be withdrawn from the study and will continue SOC treatment until death.
9. Patients will undergo a 30-day post treatment follow-up visit after treatment discontinuation or study withdrawal. Post treatment follow-up can take place via telephone if the patient is no longer being seen in clinic.

10. All patients will have their survival status documented every 8 weeks (+/- 1 month) for up to two years. Survival follow up is defined as: alive status or date of death. Survival information can be obtained via telephone or from clinic notes.
11. Urinalysis or urine dipstick will be performed prior to each dose of bevacizumab as per standard of care. Monitor proteinuria by urine dipstick for development or worsening proteinuria with serial analyses during therapy. Patients with 2+ or greater urine dipstick reading should undergo further assessment with 24h urine collection. Suspend administration for $\geq$ 2g/24hrs and resume when < 2g/24 hrs. Discontinue in patients with nephrotic syndrome.

13.0 DATA SUBMISSION SCHEDULE

Case report forms with appropriate source documentation will be completed according to the following schedule:

Case Report Form	Submission Schedule
Original Consent Form	Prior to registration
Registration Form Eligibility Form On-Study Form	Prior to starting treatment
Treatment Summary Form for TTFields	Every 4 weeks until completion of treatment
Treatment Summary Form for Bevacizumab	Every 2 weeks while patient is on the cycle
MRI Form	Baseline and every 2 months thereafter until completion of treatment
KPS Form MMSE	Every 8 weeks until completion of treatment
Survival Information	Every 8 weeks after withdrawal or 30-day post treatment follow-up
Adverse Events Form	As per Section 9.0

Participating site(s) must respond to queries generated by the University of Florida within 28 days of request. The University of Florida may institute corrective action measures for any site with delinquent or poor quality data.

14.0 MEASUREMENT OF EFFECT

14.1 Antitumor Effect- Solid Tumors

For the purposes of this study, patients should be re-evaluated for response every 8 weeks +/- 7 days. In addition to a baseline scan, confirmatory scans should also be obtained 8 weeks +/- 7 days following initial documentation of objective response. If a patient develops symptoms that are potentially indicative of disease progression, scans may be done sooner than every 8 weeks as per standard practice.

Response and progression will be evaluated in this study using the updated response assessment criteria for high-grade gliomas: Response Assessment in Neuro-Oncology (RANO) working group guideline (*34*).

Criteria for Determining First Progression Depending on Time from Initial Chemoradiotherapy

First Progression	Definition
Progressive disease < 12 weeks after completion of chemoradiotherapy	Progression can only be defined using diagnostic imaging if there is new enhancement outside of the radiation field (beyond the high-dose region or 80% isodose line) or if there is unequivocal evidence of viable tumor on histopathologic sampling (e.g., solid tumor areas [i.e., > 70% tumor cell nuclei in areas], high or progressive increase in MIB-1 or Ki67proliferation index compared with prior biopsy, or evidence for histologic progression or increased anaplasia in tumor). Note: Given the difficulty of differentiating true progression from pseudoprogression, clinical decline alone, in the Absence of radiographic or histologic confirmation of progression, will not be sufficient for definition of progressive disease in the first 12 weeks after completion of concurrent chemoradiotherapy.
Progressive disease ≥ 12 weeks after chemoradiotherapy completion	1. New contrast-enhancing lesion outside of radiation field on decreasing, stable, or increasing doses of corticosteroids. 2. Increase by ≥ 25% in the sum of the products of perpendicular diameters between the first postradiotherapy scan, or a subsequent scan with smaller tumor size, and the scan at 12 weeks or later on stable or increasing doses of corticosteroids. 3. Clinical deterioration not attributable to concurrent medication or comorbid conditions is sufficient to declare progression on current treatment but not for entry onto a clinical trial for recurrence. 4. For patients receiving antiangiogenic therapy, significant increase in T2/FLAIR non-enhancing lesion may also be considered progressive disease. The increased T2/FLAIR must have occurred with the patient on stable or increasing doses of corticosteroids compared with baseline scan or best response after initiation of therapy and not be a result of comorbid events (e.g., effects of radiation therapy, demyelination, ischemic injury, infection, seizures, postoperative changes, or other treatment effects).

Criteria for Response Assessment Incorporating MRI and Clinical Factors (Adapted from JCO 2010)

Response	Criteria
Complete response	Requires all of the following: • Complete disappearance of all enhancing measurable and non-measurable disease sustained for at least 4 weeks. • No new lesions; stable or improved non-enhancing (T2/FLAIR) lesions. • Patients must be off corticosteroids (or on physiologic replacement doses only) and stable or improved clinically. Note: Patients with non-measurable disease only cannot have a complete response; the best response possible is stable disease.
Partial response	Requires all of the following: • ≥ 50% decrease compared with baseline in the sum of products of perpendicular diameters of all measurable enhancing lesions sustained for at least 4 weeks. • No progression of non-measurable disease. • No new measureable lesion. • Stable or improved non-enhancing (T2/FLAIR) lesions on same or lower dose of corticosteroids compared with baseline scan; the corticosteroid dose at the time of the scan evaluation should be no greater than the dose at time of baseline scan. • Stable or improved clinically. Note: Patients with non-measurable disease only cannot have a partial response; the best response possible is stable disease.
Stable disease	Requires all of the following: • Does not qualify for complete response, partial response, or progression. • Stable non-enhancing (T2/FLAIR) lesions on same or lower dose of corticosteroids compared with baseline scan. In the event that the corticosteroid dose was increased for new symptoms and signs without confirmation of disease progression on neuroimaging, and subsequent follow-up imaging shows that this increase in corticosteroids was required because of disease progression, the last scan considered to show stable disease will be the scan obtained when the corticosteroid dose was equivalent to the baseline dose.
Progression	Defined by any of the following: • ≥ 25% increase in sum of the products of perpendicular diameters of enhancing lesions (with the absolute increase of at least 1 dimension of at least 5 mm) compared with the smallest tumor measurement obtained either at baseline (if no decrease) or best response, on stable or increasing doses of corticosteroids*. • Significant increase in T2/FLAIR nonenhancing lesion on stable or increasing doses of corticosteroids compared with baseline scan or best response after initiation of therapy* not caused by comorbid events (e.g. radiation therapy, demyelination, ischemic injury, infection, seizures, postoperative changes, or other treatment effects). • Any new measureable lesion (at least 10mm in at least 2 perpendicular dimensions). • Clear clinical deterioration not attributable to other causes apart from the tumor (e.g. seizures, medication adverse effects, complications of therapy, cerebrovascular events, infection, and so on) or changes in corticosteroid dose. • Failure to return for evaluation as a result of death or deteriorating condition; or clear progression of nonmeasurable disease.

NOTE. All measurable and nonmeasurable lesions must be assessed using the same techniques as at baseline.
Abbreviations: MRI, magnetic resonance imaging; FLAIR, fluid-attenuated inversion recovery.
* Stable doses of corticosteroids include patients not on corticosteroids.

14.2 Disease Parameters

Measurable disease: Bi-dimensionally measurable lesions with clearly defined margins by MRI scan. All tumor measurements must be recorded in millimeters (or decimal fractions of centimeters).

Non-measurable or evaluable disease: Uni-dimensionally measurable lesions or lesions with margins not clearly defined such as areas of T2/FLAIR signal abnormality or poorly defined enhancing abnormality.

Note: For cystic lesions, the only measurable part is any enhancement area around the cyst that is clearly defined and bi-dimensionally measurable. The cyst itself should not be considered measurable or non-measureable disease.

Target lesions: Target lesions should be selected on the basis of their size (lesions with the longest diameter), but in addition should be those that lend themselves to reproducible repeated measurements. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement in which circumstance the next largest lesion, which can be measured reproducibly should be selected. When there are too many measurable lesions, choose the largest 3 lesions as target lesions to follow. The other measurable lesions should be considered evaluable for the purpose of objective status determination.

Non-target lesions: All non-measurable lesions should be identified as non-target lesions and should also be recorded at baseline. Measurements of these lesions are not required, but the presence, absence, or in rare cases unequivocal progression of each should be noted throughout follow-up.

14.3 Methods for Evaluation of Measurable Disease

All measurements should be taken and recorded in metric notation using a ruler. All baseline evaluations should be performed as closely as possible to the beginning of treatment and never more than 2 weeks before the beginning of the treatment.

Clinical lesions: Clinical lesions will only be considered measurable on brain MRI when they are ≥ 5 mm diameter as assessed using a ruler.

Histology: This technique can be used to differentiate between partial responses (PR) and complete responses (CR) in rare cases when biopsy or surgical resection of a measureable lesion is clinically indicated.

Perfusion/CBV: This advanced brain MRI technique can be used as an adjunct test to determine treatment response or disease status. However, it should not be used as the primary or sole method to determine response or disease status.
Brain FDG-PET coupled with head CT or brain MRI: This advanced metabolic imaging technique can be used as an adjunct test to determine response or disease status. However it should not be used as the primary or sole method of determining response or disease status.

14.3.1 Evaluation of Target Lesions

Complete Response (CR): Disappearance of all target lesions.

Partial Response (PR): ≥ 50% decrease compared with baseline in the sum of products of perpendicular diameters of all target lesions sustained for at least 4 weeks.

Progressive Disease (PD): At least a 25% increase in the sum of products of perpendicular diameters of at least 1target lesion, taking as reference the smallest sum of products of perpendicular diameters on study (this includes the baseline sum if that is the smallest on study).

Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum of products of perpendicular diameters while on study.

14.3.2 Evaluation of Non-Target Lesions

Complete Response (CR): Disappearance of all non-target lesions.

Non-CR/Non-PD: Persistence of one or more non-target lesion(s).

Progressive Disease (PD): Appearance of one or more new lesions and/or unequivocal progression of existing non-target lesions on stable or increasing doses of corticosteroids compared with baseline scan or best response after initiation of therapy* not caused by comorbid events (e.g. radiation therapy, demyelination, ischemic injury, infection, seizures, postoperative changes, or other treatment effects). Unequivocal progression should not normally trump target lesion status. It must be representative of overall disease status change, not a single lesion increase.

Although a clear progression of "non-target" lesions only is exceptional, the opinion of the treating physician should prevail in such circumstances, and the progression status should be confirmed at a later time by the review panel (or Principal Investigator).

14.3.3 Evaluation of Best Overall Response

The best overall response is the best response recorded from the start of the treatment until disease progression/recurrence (taking as reference for progressive disease the smallest measurements recorded since the treatment started). The patient's best response assignment will depend on the achievement of both measurement and confirmation criteria.

Summary of the RANO Response Criteria

Criterion	CR	PR	SD	PD
T1 gadolinium enhancing disease	None	≥ 50% ↓	< 50% ↓ but < 25% ↑	≥ 25% ↑*

Criterion	CR	PR	SD	PD
T2/FLAIR	Stable or ↓	Stable or ↓	Stable or ↓	↑*
New measureable lesion	None	None	None	Present*
Corticosteroids	None	Stable or ↓	Stable or ↓	NA†
Clinical status	Stable or ↑	Stable or ↑	Stable or ↑	↓*
Requirement for response	All	All	All	Any*

Abbreviations: RANO, Response Assessment in Neuro-Oncology; CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; FLAIR, fluid-attenuated inversion recovery; NA, not applicable.
* Progression occurs when this criterion is present.
† Increase in corticosteroids alone will not be taken into account in determining progression in the absence of persistent clinical deterioration.

14.3.4 Duration of Response

Duration of overall response: The duration of overall response is measured from the time measurement criteria are met for CR or PR (whichever is first recorded) until the first date that recurrent or progressive disease is objectively documented (taking as reference for progressive disease the smallest measurements recorded since the treatment started).

The duration of overall CR is measured from the time measurement criteria are first met for CR until the first date that progressive disease is objectively documented.

Duration of stable disease: Stable disease is measured from the start of the treatment until the criteria for progression are met, taking as reference the smallest measurements recorded since the treatment started, including the baseline measurements.

14.3.5 Neurological Exam and Performance Status

Patients will be graded using the Karnofsky Performance Status scale and their neurological function evaluated as improved, stable or deteriorated in addition to objective measurement of tumor size. These parameters will be used to determine the overall response assessment and will be collected every 4 weeks (+/- 2 weeks).

14.3.6 Progression-Free Survival

PFS is defined as the duration of time from start of treatment to time of progression or death, whichever occurs first.

15.0 DATA AND SAFETY MONITORING

The study principal investigator and clinical research coordinator will monitor for serious toxicities on an ongoing basis. Once the principal investigator or clinical research coordinator becomes aware of an adverse event, the AE will be reported to the IRB and DSMB, if applicable, according to institutional guidelines.

Adverse events meeting the definition of an SAE must be reported to the Coordinating Center within 1 working day of the investigator's discovery by e-mail and entered into OnCore within 72 hours. These events will be assessed by the Protocol Chair and reported to the IRB and DSMB per institutional requirements, FDA as applicable and other participating investigators as outlined in the protocol.

Data and safety monitoring will be performed by the UF Health Cancer Center (UFHCC) Data Integrity and Safety Committee (DISC). The UFHCC SRMC conducts initial review of IITs and determines the level of risk which corresponds with DISC review requirements. Given the risk level assigned to this protocol, this trial will undergo review by the DISC annually to review study and toxicity data. The UFHCC DISC will also conduct monitoring and audit activities as outlined in the DISC Charter. Any study subject enrolled on the trial, regardless of enrollment site, may be subject to DISC monitoring or audit. Audit activities are done to verify data accuracy, assess protocol compliance and adherence to GCP and ensure timely and complete reporting of safety data. Consent documents, treatment records and regulatory documents, among others, may be reviewed. Once notified of an impending audit, the UF coordinator will notify secondary sites of the audit date and date by which applicable source documentation must be provided to the Coordinating Center (usually within 72 hours from the site notification). The results of DISC activities will be provided to the PI, IRB and secondary sites.

The Coordinating Center will periodically review data entry in OnCore and notify sites of missing, incomplete or inconsistent data as applicable.

16.0 AUDITING

The University of Florida is the Coordinating Center and will also be responsible for auditing this study as described above. Any reports of local audits performed at secondary sites should be provided to the Coordinating Center.

17.0 STATISTICAL CONSIDERATIONS

Statistical Considerations for the Primary Objective of the Proposed Trial

For primary endpoint OS, Kaplan-Meier Curve will be generated. Median survival and its 95% confidence interval (CI) will be calculated if applicable. One-sample log-rank test will be used to compare OS between study intervention vs. historical control.
Statistical details of the clinical trial design and assumptions/results of a power analysis of the proposed trial sample size follow:

Accrual and follow-up:
Patient accrual rate: 2 patients per month
Accrual period: 12 months (10 to 18 months considered)
Follow-up after the end of accrual: 6 months

Historical control group (EF-11): N=21
In the pivotal EF-11 trial in recurrent GBM, a post hoc subgroup analysis of the data revealed that patients with bevacizumab-refractory GBM achieved median OS of 6.3 months when treated with TTFields monotherapy compared to 3.3 months when standard bevacizumab-based chemotherapy was continued (HR 0.39, 95% CI 0.19-0.79, p=0.01). The length of follow-up was 24 months and the median survival time was 3.3 months.

Testing scenario
The Wald test statistic will be used to test the following null (H0) and alternative (H1) hypotheses:
H0: HR >= 1 (log (HR) >= 0)
H1: HR < 1 (log (HR) < 0)
(The HR is the ratio of the experimental group hazard rate to the control group hazard rate)
1-tailed alpha-level: 0.05
Power level: 80%, 90%, 95%

Assumptions:
Survival times in both the historical control group and the experimental group are assumed to follow Weibull distributions(*35*). Given the observed historical control group median survival time and the trajectory of the survival curve from the Novocure EF11 post-hoc analysis, the Weibull shape parameter k appears to fall somewhere between 1.5 and 2.5:

k=1.5 (accelerating hazard function, probability of dying in the next instant increases over time)

k=2.5 (hazard function accelerating more rapidly, probability of dying in the next instant increases more rapidly over time).

For Weibull-distributed survival times, the hazard ratio (experimental vs control) is equal to the ratio of the control group median survival time (m1) to the experimental group median survival time (m^2), raised to the power of the shape parameter k: $HR = (m1/m^2)^k$

This is why the minimum detectable m2 for fixed m1 and fixed detectable HR decreases as the shape parameter k increases (a more rapidly accelerating hazard function will result in more observable deaths in a fixed period of time).

Largest hazard ratio (HR) < 1 (or smallest median survival time > 3.3 months) that can be detected at 80%, 90%, or 95% power and a 1-tailed significance level of 0.05, by sample size (N=20 to 36, or 10 to 18 months of accrual at 2 patients per month) and shape parameter k=1.50, 2.50:

Weibull Shape Parameter k = 1.5			
	80% Power	**90% Power**	**95% Power**

Sample Size	N Months Accrual	HR	LD50	HR	LD50	HR	LD50
20	10	0.43	5.8	0.37	6.4	0.32	7.1
22	11	0.45	5.7	0.38	6.3	0.33	6.9
24	12	0.46	5.6	0.39	6.2	0.35	6.6
26	13	0.47	5.5	0.40	6.1	0.36	6.5
28	14	0.47	5.5	0.41	6.0	0.37	6.4
30	15	0.48	5.4	0.42	5.9	0.37	6.4
32	16	0.48	5.4	0.42	5.9	0.38	6.3
34	17	0.49	5.3	0.43	5.8	0.39	6.2
36	18	0.49	5.3	0.43	5.8	0.39	6.2

Table 5: Weibull Shape Parameter k = 2.5							
		80% Power		90% Power		95% Power	
Sample Size	N Months Accrual	HR	LD50	HR	LD50	HR	LD50
20	10	0.45	4.5	0.39	4.8	0.35	5.0
22	11	0.46	4.5	0.40	4.8	0.36	5.0
24	12	0.47	4.5	0.41	4.7	0.36	5.0
26	13	0.47	4.5	0.42	4.7	0.37	4.9
28	14	0.48	4.4	0.42	4.7	0.38	4.9
30	15	0.49	4.4	0.43	4.6	0.38	4.9
32	16	0.49	4.4	0.43	4.6	0.39	4.8
34	17	0.49	4.4	0.44	4.6	0.39	4.8
36	18	0.50	4.4	0.44	4.6	0.40	4.8

Statistical Considerations for the Secondary Objectives of the Proposed Trial

To address our secondary objectives, we will generate point estimates with 95% confidence intervals (CI) for the proportion of patients demonstrating repeat response after one cycle of Bevacizumab, after two cycles, and after greater than two cycles. We will also use proportion point estimates with 95% CI's to characterize the rates of various adverse events observed during the course of the trial. Although we will have no historical data to serve as a basis for comparison of repeat response rates associated with pulsed Bevacizumab treatment, we will contrast our observed adverse event rates with those that have been established for standard treatment with Bevacizumab.

18.0 REFERENCES

1. R. Stupp *et al.*, Effects of radiotherapy with concomitant and adjuvant temozolomide versus radiotherapy alone on survival in glioblastoma in a randomised phase III study: 5-year analysis of the EORTC-NCIC trial. *The Lancet Oncology* **10**, 459-466 (2009).
2. E. T. Wong *et al.*, Outcomes and prognostic factors in recurrent glioma patients enrolled onto phase II clinical trials. *J Clin Oncol* **17**, 2572-2578 (1999).
3. H. S. Friedman *et al.*, Bevacizumab Alone and in Combination With Irinotecan in Recurrent Glioblastoma. *Journal of Clinical Oncology* **27**, 4733-4740 (2009).
4. J. J. Vredenburgh *et al.*, Bevacizumab Plus Irinotecan in Recurrent Glioblastoma Multiforme. *Journal of Clinical Oncology* **25**, 4722-4729 (2007).
5. F. M. Iwamoto *et al.*, Patterns of relapse and prognosis after bevacizumab failure in recurrent glioblastoma. *Neurology* **73**, 1200-1206 (2009).
6. A. A. Kanner, E. T. Wong, J. L. Villano, Z. Ram, E. F. Investigators, Post Hoc analyses of intention-to-treat population in phase III comparison of NovoTTF-100A system versus best physician's choice chemotherapy. *Semin Oncol* **41 Suppl 6**, S25-34 (2014).
7. E. C. Quant *et al.*, Role of a second chemotherapy in recurrent malignant glioma patients who progress on bevacizumab. *Neuro Oncol* **11**, 550-555 (2009).
8. C. Polk, Ed., *Therapeutic Applications of Low-Frequency Sinusoidal and Pulsed Electric and Magnetic Fields*, (CRC Press, Inc, Connecticut, 1995), pp. 1404-1416.
9. Y. Palti, Stimulation of internal organs by means of externally applied electrodes. *Journal of applied physiology* **21**, 1619-1623 (1966).
10. C. A. Bassett, The development and application of pulsed electromagnetic fields (PEMFs) for ununited fractures and arthrodeses. *Clinics in plastic surgery* **12**, 259-277 (1985).
11. E. L. Elson, Ed., *Biologic Effects of Radiofrequency and Microwave Fields: In Vivo and In Vitro Experimental Results*, (CRC Press Inc, Connecticut, 1995), pp. 1424-1430.
12. C. K. Chou, Ed., *Radiofrequency Hyperthermia in Cancer Therapy*, (CRC Press Inc, Connecticut, 1995), pp. 1424-1430.
13. S. Takashima, H. P. Schwan, Alignment of microscopic particles in electric fields and its biological implications. *Biophysical journal* **47**, 513-518 (1985).
14. U. Zimmermann, J. Vienken, G. Pilwat, Rotation of cells in an alternating electric field: the occurrence of a resonance frequency. *Zeitschrift fur Naturforschung. Section C: Biosciences* **36**, 173-177 (1981).

15. C. Holzapfel, J. Vienken, U. Zimmermann, Rotation of cells in an alternating electric field: theory and experimental proof. *The Journal of membrane biology* **67**, 13-26 (1982).
16. P. Pawlowski, I. Szutowicz, P. Marszalek, M. Fikus, Bioelectrorheological model of the cell. 5. Electrodestruction of cellular membrane in alternating electric field. *Biophysical journal* **65**, 541-549 (1993).
17. P. Pawlowski, M. Fikus, Bioelectrorheological model of the cell. 4. Analysis of the extensil deformation of cellular membrane in alternating electric field. *Biophysical journal* **65**, 535-540 (1993).
18. E. D. Kirson *et al.*, Disruption of cancer cell replication by alternating electric fields. *Cancer research* **64**, 3288-3295 (2004).
19. M. Zhao, J. V. Forrester, C. D. McCaig, A small, physiological electric field orients cell division. *Proceedings of the National Academy of Sciences of the United States of America* **96**, 4942-4946 (1999).
20. M. A. Jordan, D. Thrower, L. Wilson, Effects of vinblastine, podophyllotoxin and nocodazole on mitotic spindles. Implications for the role of microtubule dynamics in mitosis. *Journal of cell science* **102 (Pt 3)**, 401-416 (1992).
21. E. K. Rowinsky, R. C. Donehower, Paclitaxel (taxol). *The New England journal of medicine* **332**, 1004-1014 (1995).
22. C. E. Walczak, E. C. Gan, A. Desai, T. J. Mitchison, S. L. Kline-Smith, The microtubule-destabilizing kinesin XKCM1 is required for chromosome positioning during spindle assembly. *Current biology : CB* **12**, 1885-1889 (2002).
23. S. L. Kline-Smith, C. E. Walczak, The microtubule-destabilizing kinesin XKCM1 regulates microtubule dynamic instability in cells. *Molecular biology of the cell* **13**, 2718-2731 (2002).
24. T. M. Kapoor, T. U. Mayer, M. L. Coughlin, T. J. Mitchison, Probing spindle assembly mechanisms with monastrol, a small molecule inhibitor of the mitotic kinesin, Eg5. *The Journal of cell biology* **150**, 975-988 (2000).
25. H. Maiato *et al.*, MAST/Orbit has a role in microtubule-kinetochore attachment and is essential for chromosome alignment and maintenance of spindle bipolarity. *The Journal of cell biology* **157**, 749-760 (2002).

26. E. D. Kirson *et al.*, Alternating electric fields arrest cell proliferation in animal tumor models and human brain tumors. *Proceedings of the National Academy of Sciences of the United States of America* **104**, 10152-10157 (2007).
27. R. Stupp *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* **48**, 2192-2202 (2012).
28. E. Fonkem, E. T. Wong, NovoTTF-100A: a new treatment modality for recurrent glioblastoma. *Expert Rev Neurother* **12**, 895-899 (2012).
29. E. T. Wong *et al.*, Response assessment of NovoTTF-100A versus best physician's choice chemotherapy in recurrent glioblastoma. *Cancer Med* **3**, 592-602 (2014).
30. R. M. Zuniga *et al.*, Rebound tumour progression after the cessation of bevacizumab therapy in patients with recurrent high-grade glioma. *J Neurooncol* **99**, 237-242 (2010).
31. Y. Piao *et al.*, Acquired Resistance to Anti-VEGF Therapy in Glioblastoma Is Associated with a Mesenchymal Transition. *Clinical Cancer Research* **19**, 4392-4403 (2013).
32. Y. Piao *et al.*, Glioblastoma resistance to anti-VEGF therapy is associated with myeloid cell infiltration, stem cell accumulation, and a mesenchymal phenotype. *Neuro-Oncology*, (2012).
33. G. Ansstas, D. D. Tran, Treatment with Tumor Treating Fields Therapy and Pulse Dose Bevacizumab in Patients with Bevacizumab-Refractory Recurrent Glioblastoma: A Case Series. *Case Reports in Neurology* **DOI: 10.1159/000442196**, (2015).
34. P. Y. Wen *et al.*, Updated response assessment criteria for high-grade gliomas: response assessment in neuro-oncology working group. *J Clin Oncol* **28**, 1963-1972 (2010).
35. J. Wu, X. Xiong, Group Sequential Design for Randomized Phase III Trials under the Weibull Model. *J Biopharm Stat*, (2014).

19.0 APPENDIX A: Karnofsky Performance Scale

Able to carry on normal activity and to work; no special care needed.	100	Normal no complaints; no evidence of disease.
	90	Able to carry on normal activity; minor signs or symptoms of disease.
	80	Normal activity with effort; some signs or symptoms of disease.
Unable to work; able to live at home and care for most personal needs; varying amount of assistance needed.	70	Cares for self; unable to carry on normal activity or to do active work.
	60	Requires occasional assistance, but is able to care for most of his personal needs.
	50	Requires considerable assistance and frequent medical care.
Unable to care for self; requires equivalent of institutional or hospital care; disease may be progressing rapidly.	40	Disabled; requires special care and assistance.
	30	Severely disabled; hospital admission is indicated although death not imminent.
	20	Very sick; hospital admission necessary; active supportive treatment necessary.
	10	Moribund; fatal processes progressing rapidly.
	0	Dead

19.0APPENDIX B: Mini-Mental Status Exam

Do you have any trouble with your memory?
May I ask you some questions about your memory?

		RESPONSE	SCORE	
ORIENTATION TO TIME				
What is the …	year?	_____	0	1
	season?	_____	0	1
	month of the year?	_____	0	1
	day of the week?	_____	0	1
	date?	_____	0	1
ORIENTATION TO PLACE				
Where are we now?	state (province)?	_____	0	1
What is the …	county (or city/town)?	_____	0	1
	City/town (or part of city/neighborhood)?	_____	0	1
	Building (name or type)?	_____	0	1
	Floor of the building (room number or address)?	_____	0	1
REGISTRATION				
Listen carefully. I am going to say three words. You say them back after I stop. Ready? Here they are … APPLE [pause], PENNY [pause], TABLE [pause]. Now repeat those words back to me.				
	APPLE	_____	0	1
	PENNY	_____	0	1
	TABLE	_____	0	1
Now keep those words in mind. I am going to ask you to say them again in a few minutes.				
ATTENTION AND CALCULATION [Serial 7s]				
Now I'd like you to subtract 7 from 100. Then keep subtracting 7 from each answer until I tell you to stop.				
What is 100 take away 7?		_____	0	1
If needed, say: Keep going		_____	0	1
If needed, say: Keep going		_____	0	1
If needed, say: Keep going		_____	0	1
If needed, say: Keep going		_____	0	1

	RESPONSE	SCORE
Spell WORLD forward, then backward	D=1 L=1 R=1 O=1 W=1	

RECALL

What were those three words I asked you to remember?

APPLE		0	1
PENNY		0	1
TABLE		0	1

NAMING

What is this?	[Point to a pencil or pen.]		0	1
What is this?	[Point to a watch.]		0	1

REPETITION

Now I am going to ask you to repeat what I say. Ready? "NO IFS, ANDS, OR BUTS." Now you say that.

NO IFS, ANDS, OR BUTS.		0	1

COMPREHENSION

Listen carefully because I am going to ask you to do something.
Take this paper in your right hand [pause], fold it in half [pause], and put it on the floor (or table).

TAKE IN RIGHT HAND		0	1
FOLD IN HALF		0	1
PUT ON FLOOR		0	1

READING

Please read this and do what it says. [Show examinee the words on the stimulus form.]

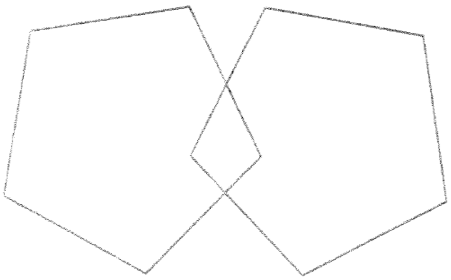
CLOSE YOUR EYES		0	1

WRITING

Please write a sentence.		0	1

DRAWING

Please copy this design.



0 1

Total Score =

Assessment of level of consciousness

Alert Drowsy Stuporous Comatose / Unresponsive

20.0 APPENDIX C: RANO Measurement Form

Study ID: **Pulsed Bevacizumab**						
Name:		DOB:		Subject ID:		
Baseline Scan Date:						
TARGETLesion(s)*	**Lesion Location/Identifier**	**Series No.**	**Image No.**	**Measurement 1 (cm)**	**Measurement 2 (cm)**	**Product(cm2)**
T1						0.00
T2						**0.00**
T3						**0.00**
T4						**0.00**
T5						0.00
Sum of Products of Diameters (SPD)						0.00
*Measurable lesions must be contrast enhancing, have 2 perpendicular diameters >10mm & no cavity or cyst in measurement. Select a minimum of 2 & a maximum of 5 lesions. Largets lesions that are suitable for reproducible measurements are preferred.						
NON-TARGETLesion(s)^	**Lesion Location/Identifier**	**Series No.**	**Image No.**	**Measurement 1 (cm)**	**Measurement 2 (cm)**	**Enhancing or Non-enhancing?**
NT1						
NT2						
NT3						
NT4						
NT5						
^Non-measurable lesions include lesions that are too small (<10 x 10mm), lesions that do not enhance, and lesions with a poorly defined margin. Non-target lesions can also include measurable lesions not included in the 5 target lesions.						
Dexamethasone Dose:	_____	**mg**	**Frequency:**	BID_____		
Indication:						
Clinical status						

Intracranial EdemaPhysiologic ReplacementOther (Specify) _____Clear deterioration due to tumorClear deterioration due to non-tumor causesOthers (specify) _____Stable ClinicallyImproved Clinically

Study ID: **Pulsed Bevacizumab**								
Name:			DOB:		Subject ID:			
Subsequent Scan Date:								
TARGETLesion(s)*	**Lesion Location/Identifier**	**Series No.**	**Image No.**	**Measurement 1 (cm)**	**Measurement 2 (cm)**	**Product(cm2)**	**SPD from Baseline or Best Response**	**% Change of SPD**
T1						0.00		
T2						**0.00**		
T3						**0.00**		
T4						**0.00**		
T5						0.00		
Sum of Products of Diameters (SPD)						0.00		#DIV/0
*Measurable lesions must be contrast enhancing, have 2 perpendicular diameters >10mm & no cavity or cyst in measurement. Select a minimum of 2 & a maximum of 5 lesions. Largets lesions that are suitable for reproducible measurements are preferred.								

NON-TARGETLesion(s)^	Lesion Location/Identifier	Series No.	Image No.	Measurement 1 (cm)	Measurement 2 (cm)	Enhancing or Non-enhancing?	
NT1							
L3							
L4							
L5							
^Non-measurable lesions include lesions that are too small (<10 x 10mm), lesions that do not enhance, and lesions with a poorly defined margin. Non-target lesions can also include measurable lesions not included in the 5 target lesions.							
Dexamethasone Dose:	_____	**mg**	**Frequency:**	BID_____			
Indication:							
Clinical status							

Intracranial EdemaPhysiologic ReplacementOther (Specify) _____Clear deterioration due to tumorClear deterioration due to non-tumor causesOthers (specify) _____Stable ClinicallyImproved Clinically

21.0 APPENDIX D: BEVACIZUMAB DOSE MODIFICATIONS

Cardiovascular	Hypertension	See Section below for management.
	Congestive heart failure Grade 3	Hold until grade ≤1 or baseline level. Then resume treatment. If second recurrence, discontinue.
	Grade 4	Discontinue
Dermatology/ Skin	Wound complication, non- infectious, Any grade	Discontinue
Gastrointestinal	Fistula or leak – Any grade	Discontinue
	Obstruction, Grade 1	Continue patient on study for partial obstruction NOT requiring medical intervention
	Grade 2	Hold until resolution. Then resume treatment.
	Grade 3-4	Hold until resolution. If surgery is necessary, patient may restart after full recovery from surgery, and at investigator's discretion.
	Perforation, Any grade	Discontinue
Hemorrhage – non CNS, non pulmonary	Grade 3	Discontinue for subjects who are also receiving full-dose anticoagulation All other subjects hold until the bleeding has resolved and hemoglobin is stable and there is no structural or pathologic condition that would increase bleeding recurrence.
		Discontinue for any recurrent Grade 3 hemorrhagic event
	Grade 4	Discontinue and go to event monitoring.
Hemorrhage – CNS or pulmonary	Grade 1	Discontinue for subjects who are also receiving full-dose anticoagulation. All other subjects hold until All other subjects hold until the bleeding has resolved and hemoglobin is stable and there is no structural or pathologic condition that would increase bleeding recurrence.
	Grade ≥ 2	Discontinue

Renal and Urinary Disorders	Proteinuria, Grade 2 (2+ proteinuria; urinary protein 1.0-3.4g/24h) Proteinuria Grade 3 (≥3.5 g/24 hr)	Check 24h urine if not already done. Suspend administration for ≥ 2g/24hrs and resume when < 2g/24 hrs. Hold until proteinuria improves to ≤ 2g/24h.. Then resume treatment
	Grade 4 (nephrotic syndrome)	Discontinue
Neurology	CNS cerebrovascular ischemia Any grade	Discontinue
	Leukoencephalopathy syndrome (radiographic findings) Any grade	Hold pending workup and management, including control of blood pressure. Discontinue if Reversible Posterior Leukoencephalopathy Syndrome (RPLS) is diagnosed.
Vascular	Thrombus/embolism Grade 3 or 4	Hold and start full dose anticoagulation for at least 2 weeks. Bevacizumab can be restarted and anticoagulation is decreased in half (only for DVT); No reduction in anti-coagulation for PE, if the subject is asymptomatic after at least 2 weeks on full dose anti-coagulation and has not had a grade 3 or 4 hemorrhagic event while on full dose
	Peripheral arterial ischemia Any grade	Discontinue
	Visceral arterial ischemia Any grade	Discontinue
All other non-hematologic adverse events (excluding alopecia)	Grade 3-4 (excludes nausea/vomiting that has not been pre-medicated)	Hold and address symptomatic relief per standard practice. Resume bevacizumab when symptoms decrease to grade <=2. If symptoms do not resolve to grde <=2 by 4 weeks, discontinue bevacizumab.

22.0 APPENDIX E: MANAGEMENT OF HYPERTENSION

Grade (CTCAE v3.0)	Antihypertensive Therapy	Blood Pressure	Bevacizumab Dose
Grade 1	None	Routine	No change
Grade 2 (asymptomatic)	Initiate monotherapy (e.g. ACE inhibitors or calcium-channel blocker)	Increase frequency and monitor per local standard until stabilized.	No change
Grade 2 (symptomatic/ persistent) **OR** diastolic BP >110 mm Hg **OR** Grade 3	Add or increase dose of agent(s): e.g. beta-blockers, diuretics, calcium channel blockers	Increase frequency and monitor per local standard and/or refer to HTN specialist for expert management until stabilized.	Hold bevacizumab until symptoms resolve and diastolic BP ≤110 mm/Hg and resume treatment at 25% dose reduction, but no less than 5mg/kg IV every 2 weeks. If HTN is not controlled to <= grade 2 in > 3 weeks, discontinue bevacizumab.
Grade 4	Urgent Treatment per local standard	Per local standard	Discontinue bevazimuab

23.0 APPENDIX F: GUIDANCE ON CONTRACEPTION

For the purposes of the proposed study, **"highly effective" contraceptive methods** are defined as those, alone or in combination, that result in a low failure rate (i.e., less than 1 percent per year) when used consistently and correctly, and include the following:

- Surgical sterilization at least 6 months before Study Drug administration
- Implants
- Levonorgestrel (LNG) and Copper T IUDs
- Sexual abstinence

Subjects who prefer methods which evidence a higher (6-9%) failure rate with typical use will be required to employ at least two methods of contraception concurrently. These methods include the following:

- Injectable hormone depos
- Oral contraceptive pill
- Hormone patch
- Vaginal ring

Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are NOT acceptable methods of contraception.

http://www.cdc.gov/reproductivehealth/unintendedpregnancy/pdf/contraceptive_methods_508.pdf for a list of contraceptive methods and effectiveness.