Protocol #: LCI-NEU-NOV-001

TITLE: A PHASE II STUDY OF OPTUNE™ SYSTEM IN COMBINATION WITH BEVACIZUMAB (BEV) AND TEMOZOLOMIDE (TMZ) IN SUBJECTS WITH NEWLY DIAGNOSED UNRESECTABLE GLIOBLASTOMA (GBM)

LAY TITLE: A PHASE II STUDY OF OPTUNE™, A DEVICE WORN ON THE HEAD IN COMBINATION WITH CHEMOTHERAPY TO TREAT GLIOBLASTOMA IN ADULTS

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Investigational device: Optune™ System
Commercial agents: Bevacizumab and Temozolomide

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SCHEMA

Phase II Study of Optune™ System in Combination with Bevacizumab (BEV) and Temozolomide (TMZ) in Patients with Newly Diagnosed Unresectable Glioblastoma (GBM)

PI: Sumrall

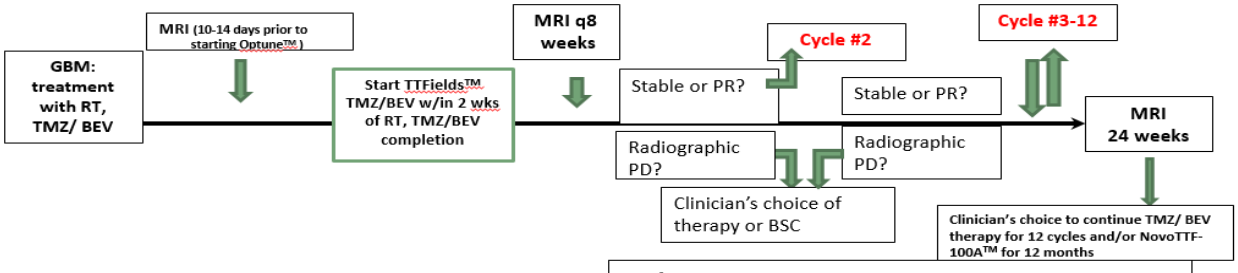
Objectives:

Primary: 1) Assess OS of subjects while receiving regimen that involves the administration of TMZ/ BEV with concurrent use of TTFields™ (Tumor Treating Fields) for subjects with newly diagnosed unresectable GBM.

Secondary: 1) Evaluate PFS 2) Evaluate ORR and DCR 3) Evaluate DOR and disease control

Inclusion Criteria:

- ❑ ≥22 years of age
- ❑ KPS ≥60
- ❑ Biopsy proven, supratentorial GBM
- ❑ Confirmed path for WHO grade IV
- ❑ Women of childbearing age must use contraception
- ❑ Signed informed consent, approved by IRB
- ❑ Intervention starts between 2-4 weeks out from biopsy/subtotal resection



Endpoints:

Primary: Assess OS.

Secondary:
a) PFS
b) ORR
c) DOR
d) Duration of disease control

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1. OBJECTIVES

1.1. Primary Objective

The primary objective of this phase II study is to assess the efficacy of a treatment regimen that involves the administration of temozolomide and bevacizumab with concurrent use of the medical device, Optune™ System, by evaluating the percentage of newly diagnosed unresectable glioblastoma (GBM) subjects who are alive at 12 months and compare to relevant historical controls.

1.2. Secondary Objective

The secondary objectives are to:

- Evaluate progression free survival (PFS)
- Evaluate objective response rate (ORR) and disease control rate (DCR)
- Evaluate duration of response and disease control

1.3. Safety Objectives

The safety objectives are to evaluate:

- Adverse events (AE) assessed by NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0
- Serious adverse events (SAE) and unanticipated adverse device effects (UADEs) including death on study

2. BACKGROUND

2.1. Study Disease

Despite decades of intensive investigation, the prognosis for most patients with primary anaplastic, central nervous system (CNS) neoplasms remains very poor. Most high grade CNS tumors are highly resistant to currently available therapy. The addition of temozolomide to radiation therapy has improved survival compared to radiation therapy alone, but improvements are modest.[1] Median survival for adults with the most common form of CNS tumor, glioblastoma, has been reported as 9-15 months after diagnosis. Most recently, addition of Optune™ to therapy for newly diagnosed glioblastoma (GBM) has demonstrated improved survival. In a cohort that included patients with resectable and unresectable glioblastoma, median progression-free survival from randomization was 6.7 months in the TTFields + temozolomide group and 4.0 months in the temozolomide group (HR, 0.63; 95% CI, 0.52-0.76; P < .001). Median overall survival was 20.9 months in the TTFields + temozolomide group vs 16.0 months in the temozolomide-alone group (HR, 0.63; 95% CI, 0.53-0.76; P < .001). [2]. It has been documented that patients with unresectable disease have an even shorter survival. In the landmark EORTC study, patients who received diagnostic biopsy followed by temozolomide and radiation had a median OS of 5.1 months (95% CI: 4.47, 8.84). [1] Attempts to improve outcomes in the newly diagnosed setting by novel interventions have proven to be disappointing. In one study using

ultrafractionated radiotherapy for unresectable tumors, an improvement in OS was not observed. [3, 4] Other attempts to improve survival have been modest. [4]

Occasional responses to single or multiple agent chemotherapy are observed in the setting of recurrent tumor, but these responses are generally short in duration, and long-term survival is rare. Bevacizumab has been FDA-approved for recurrent glioblastoma, based on a randomized phase II trial. This led to additional work to evaluate bevacizumab in the newly diagnosed setting. In a small cohort of newly diagnosed patients, it was deemed safe to be administered with concurrent temozolomide and radiation therapy. In a phase II study examining patients with newly-diagnosed glioblastoma, the addition of bevacizumab to standard radiation therapy and daily temozolomide followed by the addition of bevacizumab and irinotecan to adjuvant temozolomide showed an improvement median overall survival to 21.2 months (95% CI: 17.2-25.4), and 65% of the patients were alive at 16 months (95% CI: 53.4-74.9). The median progression-free survival was 14.2 months (95% CI: 12-16). [5] This prompted larger, randomized studies. The mature PFS and OS results from AVAglio, a phase III trial evaluating bevacizumab added to standard radiation and temozolomide for newly-diagnosed GBM, were recently presented at the 2013 American Society of Clinical Oncology Annual Meeting. Unresectable tumors were included in this study. A 36% risk reduction in progression or death was observed. An improvement in median PFS by 4.4 months was observed (HR 0.64, $p<0.0001$) in the bevacizumab treatment arm, and PFS in the control arm was 6.2 months. Stability or improvement in quality-of-life was also observed in the bevacizumab treatment arm, as well as maintenance of functional independence. Overall survival (OS) was not significantly prolonged.[6] RTOG 0825 also failed to demonstrate an improvement in OS. Of note, multifocal tumors were excluded from this study. In addition, 60% of the enrolled patients underwent gross total resection of glioblastoma.[7] From these studies, one can garner that bevacizumab appears to improve PFS and quality of life. The subset analyses from these studies are eagerly anticipated.

Due to the dilemma of markedly poor prognosis for patients with unresectable disease, a novel approach is needed to improve long-term survival. An attempt to prolong survival in this cohort was documented by the efforts of Lou, Peters, Sumrall, et al. By administering upfront bevacizumab and temozolomide to patients with unresectable glioblastoma, OS was observed to be 11.7 months (95% CI: 7.4, 15.6). Minimal toxicities were observed.[8]

2.2. Study Device: Optune™ System

The portable, battery-operated medical device, the Optune™ System, delivers low intensity, intermediate frequency, alternating electric fields (TTFields (Tumor Treating Fields)) to the region of the malignant tumor.[9] 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. This novel approach uses arrest of cell division in anaphase to augment cell death. It has been studied in combination with temozolomide and deemed safe for concurrent administration with chemotherapy in preclinical and clinical settings.[9]

Patients are evaluated for treatment with Optune™ System by a qualified physician who has been specifically trained by Novocure. The device is to be worn for 18 hours on average each day for maximum effect. It has been FDA-approved for use as a treatment for adult patients with both newly-diagnosed and recurrent GBM after receiving chemotherapy and radiation therapy.

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 device batteries and to connect to an external battery pack overnight.

2.3. Study Rationale

Typical patients with newly diagnosed, unresectable glioblastoma receive concurrent temozolomide and radiation therapy for approximately 6 weeks (Appendix A). Most of our patients without contraindications will also receive bevacizumab dosed at 10 mg/kg IV every 2 weeks in this setting. Four weeks after completion of this phase, they will move forward to receive 12 months of adjuvant temozolomide and bevacizumab.

Optune™ Therapy has been studied in combination with temozolomide and deemed safe for concurrent administration with chemotherapy in preclinical and clinical settings.[10],[11] Based on the phase III trial evaluating the use of Optune™ Therapy for recurrent GBM, an improved PFS-6 rate, improved response rate, and trend toward reduction of risk of death were observed. [12] This led to the FDA approval of the device. Furthermore, this treatment has been evaluated in the EF-14 trial, a randomized trial evaluating the efficacy of Optune™ Therapy in combination with temozolomide in newly diagnosed, unresectable GBM patients. At the American Society of Clinical Oncology Annual Meeting in June 2015, analysis of this data was initially shared. A pre-specified, interim analysis of the first 315 subjects concluded that the trial met its endpoints of superior PFS and OS. Analysis of the full trial cohort of 700 subjects confirmed this. Subjects treated with TTFields and temozolomide demonstrated a significant increase in PFS compared to temozolomide alone (median PFS of 7.1 months compared to 4.2 months, hazard ratio=0.69, p=0.001). Longer follow-up showed impressive results with an improvement in median progression-free survival from randomization of 2.7 months in the TTFields + temozolomide group. Median overall survival was improved by 4.9 months in the TTFields + temozolomide group (HR, 0.63; 95% CI, 0.53-0.76; P < .001). [2] It is now FDA-approved for use in the adjuvant setting.

Optune™ therapy has also been shown to be safe when administered with bevacizumab. [13] To evaluate the effectiveness of the Optune™ System, referencing a study in newly diagnosed unresectable GBM patients using the combination of temozolomide and bevacizumab for the historical controls is necessary. One such study was conducted by Lou, Peters, and Sumrall, showing a median overall survival of 11.7 months (95% CI: 7.4, 15.6).[8]

2.4. Literature

2.4.1. Pre-clinical studies

In preclinical studies in vitro and in vivo, TTFields (Tumor Treating Fields) have been shown to safely and effectively slow tumor growth as an independent treatment modality, and in conjunction with chemotherapeutic agents.[9-11, 14, 15] In 2004, TTFields (Tumor Treating Fields) were first evaluated in over 500 culture dishes containing 11 different cancer cell lines, including human and rat glioma, as well as other human cancer cell types. [10] TTFields (Tumor Treating Fields) were delivered over a 24 hour period in a homogeneous manner. Two mechanisms of action were identified: 1) interference with the proper formation of the mitotic spindle and 2) rapid disintegration of dividing cells. [14] TTFields (Tumor Treating Fields) frequency was delivered by internally implanted electrodes and optimal levels were found to vary by cancer type. Optimal TTFields (Tumor Treating Fields) frequency was identified as 200k Hz in both human and rat glioma.[14]

Building on this research, Kirson et al examined the effects of TTFields (Tumor Treating Fields) on additional human lung and breast carcinoma cell lines, as well as animal tumor models (melanoma and glioma), using externally applied transducer arrays.[11] Mechanisms of action and optimal TTFields (Tumor Treating Fields) frequency was consistent with previously reported research. In this study, 40 Fischer rats (inoculated intracranially with glioma cells) were treated with TTFields (Tumor Treating Fields) (200 kHz at 2 V/cm) for 6 days using external electrodes. In comparison to a control arm, a 42.6% inhibition of tumor growth was observed with two directional TTFields (Tumor Treating Fields) ($p < 0.01$) and a 53.4% inhibition of tumor growth was observed with three directional TTFields (Tumor Treating Fields) ($p < 0.01$). The TTFields (Tumor Treating Fields) were positioned between 45 and 90˚ of each other. [10]

Next, the result of TTFields (Tumor Treating Fields) in conjunction with chemotherapeutic agents (paclitaxel, doxorubicin, cyclophosphamide, and dacarbazine (DTIC) treatments) were examined in human breast and glioma cell lines. [11] Four sets of experiments were conducted: control, TTFields (Tumor Treating Fields), chemotherapeutic agents, and TTFields (Tumor Treating Fields) with chemotherapy. Combined treatment (chemotherapeutic agent and TTFields (Tumor Treating Fields) treatment at 1.75 V/cm) over 72 hours resulted in 50% decrease in cell proliferation compared to controls in the breast cancer cell lines. [11]

In human glioma cell lines, a reduction in percent of viable cells was observed when adding TTFields (Tumor Treating Fields) treatment to DTIC. Dose Reduction Indexes were calculated and indicated a reduction in dose in combination with TTFields (Tumor Treating Fields) delivery could be used to achieve the same level of efficacy.[11] As temozolomide is an imidazotetrazine derivative of the alkylating agent DTIC and has a similar in vivo mechanism, this data correlates well to those patients treated with temozolomide.

2.4.2 Clinical studies

Due to the promising data from the preclinical studies, a small pilot sample was identified. Twenty patients with histologically confirmed GBM (ten newly diagnosed and ten recurrent) were included. They were treated for an average of 12 months (2.5 to 24 months) with Optune™ therapy. The ten newly-diagnosed patients had completed surgical resection and concurrent chemoradiotherapy with standard of care temozolomide and RT. Optune™ therapy was administered with maintenance temozolomide. No serious adverse effects were observed. No additional toxicity was observed when temozolomide and Optune™ therapy were combined. All patients were treated with multiple four-week treatment courses using continuous, 24-hour a day, 200 kHz, 0.7 V/cm TTFields. TTFields were applied through two sets of opposing insulated electrode arrays and alternated at a 1 second duty cycle between two perpendicular field directions through the tumor. Patients completed between 1 and 17 treatment courses leading to maximal treatment duration of 16.5 months. Overall, more than 96, 4 week treatment courses were completed to date (> 9.6 courses per patient on average). The treatment was well tolerated with no treatment related serious adverse events seen in any of the patients. Patients received treatment on average about 80% of the scheduled time. Considering the continuous nature of Optune™ therapy (i.e., 24 hours a day for many months) this figure indicates that compliance with treatment was very high, with patients taking very few days off treatment and stopping only for short periods of time during treatment for personal needs. Mild to moderate contact dermatitis appeared beneath the electrode gel in all patients during treatment. In most cases this dermatitis appeared for the first time during the second treatment course. The skin reaction improved with use of topical corticosteroids. Regular relocation of the electrode arrays was necessary in order to allow for continuous treatment. Although the number of patients in this pilot trial was small, the excellent safety profile of this treatment modality and the highly promising efficacy data gathered so far indicate the potential of Optune™ therapy as an effective therapy for newly diagnosed GBM patients. It is noted that the patients involved had a Karnofsky performance score ≥ 70 and were required to wear the externally applied transducer arrays for 18 hours (on average) each day. Median time to disease progression and overall survival of the patients was 26.1 months (range 3.0-124.0) and 62.2 months (range 20.3-124.0), respectively, with two patients remaining progression free and three patients still alive at the end of the study period. One-year survival rate was 67.5%.[11] Treatment related adverse events included mild to moderate contact dermatitis in 18 of 20 patients (with good response to steroid cream and electrode relocation). In those ten newly diagnosed patients, the median progression free survival (PFS) exceeded concurrent and historical controls dramatically (greater than 18 months versus 7.1 months, respectively). Median overall survival from diagnosis is greater than 26 months at the moment (compared to 14.6 months in historical controls).[14]

Subsequent early clinical studies examined the addition of Optune™ therapy to existing chemotherapy regimens. When Optune™ therapy is used in conjunction with existing chemotherapy regimens, an additive effect was observed among 20 GBM subjects.[14] Half the subjects were newly diagnosed and received surgery, radiation,

and temozolomide (TMZ) and were then treated with Optune™ therapy concurrently with maintenance TMZ. The remaining 10 subjects were recurrent and received only Optune™ therapy. Progression free survival (PFS) and overall survival (OS) were increased in subjects treated with Optune™ therapy. Median PFS of subjects with the combined treatment (TMZ/Optune™ therapy) was 155 weeks compared to 31 weeks for concurrent controls receiving TMZ alone. OS was >39 months for subjects receiving the combined treatment, compared to 14.7 months in matched historical controls receiving TMZ alone.[14] No serious adverse events were reported, however dermatitis occurred in most (n=18) subjects, typically by the second month of treatment. Dermatitis resolved completely within weeks of treatment termination.[14]

The most recent study of Optune™ therapy in cancer patients, a phase III multi-institutional trial, examined 237 patients with recurrent glioblastoma, who were randomized in a 1:1 ratio to receive either Optune™ therapy monotherapy or best standard of care chemotherapy.[12] Patients randomized to Optune™ therapy (n=120) wore 4 transducer arrays on their shaved scalp that delivered 200 kHz TTFields to the brain at a field intensity of > 0.7 V/cm. Patients wore the device, on average 20.6 hours each day.[12] Of the patients randomized to the best standard of care (n=117), 31% received a regimen containing bevacizumab or irinotecan (31%), followed by nitrosoureas (25%), carboplatin (13%), temozolomide (11%) or other regimen (5%). Patients were followed for OS, PFS, quality of life and safety endpoints. Median survival was slightly higher in the Optune™ therapy group compared to the chemotherapy only group (6.6 vs. 6.0 months, respectively).[12] One-year survival was equal in both groups (20%), however 2 and 3 year survival was slightly higher for the Optune™ therapy treatment group compared to the chemotherapy only group (2-year: 8% vs. 4%; 3-year: 5% vs. 1%).[12] Those treated with Optune™ therapy were 14% less likely to die compared to those treated with chemotherapy only (HR=0.86, 95% CI: 0.66-1.12, p=0.27). This hazard ratio demonstrates that Optune™ therapy alone may be at least as good as best standard of care chemotherapy in the treatment of recurrent glioblastoma.[12]Minimal adverse events were experienced by the Optune™ therapy group and included grade 1 or grade 2 contact dermatitis on the scalp underneath the transducer arrays (16%), however this was completely resolved with corticosteroid treatment after treatment was stopped.[12] Quality of life measures (cognitive and emotional functioning) were better for the Optune™ therapy treated group. While increased pain and fatigue was reported in the chemotherapy group, these symptoms were not reported in the Optune™ therapy group.[12]

3. SUBJECT SELECTION

3.1. Inclusion Criteria

a. At least 22 years of age
b. Have undergone a brain biopsy via stereotactic or open technique. Biopsy is defined as less than 20% excision of the tumor.
c. Pathological evidence of GBM using WHO classification criteria

d. Planned concurrent chemoradiotherapy post-biopsy concomitant with temozolomide (45-70Gy)
e. Karnofsky scale ≥ 60
f. Life expectancy at least 3 months
g. Baseline hemoglobin of ≥ 8.0 gm/dL
h. Signed informed consent
i. Able to start bevacizumab at least 2 weeks but no more than 4 weeks from date of biopsy
j. Able to tolerate MRI of brain and have measurable disease
k. Participants of childbearing potential must use effective contraception for at least 6 months following completion of treatment. Acceptable forms of contraception are listed in section 4.4.1.

3.2. Exclusion Criteria

a. Enrolled in another clinical treatment trial
b. Pregnant or breast-feeding
c. No active malignancy within the past 2 years except for: 1) basal cell or squamous cell carcinoma of the skin, 2) a malignancy that requires hormonal therapy alone for management, and/or 3) an early-stage cancer that was cured by surgery
d. Significant co-morbidities at baseline which would prevent maintenance temozolomide
e. Platelet count < 100 x 10^3/μL
f. Absolute neutrophil count < 1.5 x 10^3/μL
g. CTC grade 4 non-hematological toxicity (except for alopecia, nausea, vomiting)
h. AST or ALT > 3 times the upper limit of normal
i. Total bilirubin > 2 times the upper limit of normal
j. Serum creatinine> 1.7 mg/dL
k. Implanted pacemaker, programmable shunts, defibrillator, deep brain stimulator, other implanted electronic devices in the brain, or documented clinically significant arrhythmias.
l. Infra-tentorial tumor
m. Clinical evidence of increased intracranial pressure
n. History of hypersensitivity reaction to temozolomide or a history of hypersensitivity to DTIC or hydrogel
o. Inability to adequately cover treatment area with TTFields (Tumor Treating Fields)
p. Unwillingness to wear Optune™ System for an average of 18 hours per 24 hours
q. Currently taking cytotoxic medications, non-steroidal anti-inflammatory drugs (NSAIDs), or enzyme inducing anticonvulsants.
r. Currently taking anticoagulants or blood-thinners (Coumadin)
s. Subjects meeting any of the following bevacizumab-specific contraindications are ineligible for study entry:
    - Inadequately controlled hypertension (defined as systolic blood pressure >150 and/or diastolic blood pressure > 100 mmHg)
    - Prior history of hypertensive crisis or hypertensive encephalopathy
    - New York Heart Association (NYHA) Grade II or greater congestive heart failure
    - History of myocardial infarction or unstable angina within 6 months prior to study

enrollment
- History of stroke or transient ischemic attack within 6 months prior to study enrollment
- Significant vascular disease (e.g., aortic aneurysm, requiring surgical repair or recent peripheral arterial thrombosis) within 6 months prior to study enrollment
- History of hemoptysis (≥ ½ teaspoon of bright red blood per episode) within 1 month prior to study enrollment
- Evidence of bleeding diathesis or coagulopathy (in the absence of therapeutic anticoagulation)
- Major surgical procedure or significant traumatic injury within 28 days prior to 1st bevacizumab infusion or anticipation of need for major surgical procedure during the course of the study
- Core biopsy or other minor surgical procedure, excluding placement of a vascular access device, within 7 days prior to study enrollment
- History of abdominal fistula, gastrointestinal perforation within 6 months prior to study enrollment
- Serious, non-healing wound, active ulcer, or untreated bone fracture
- Proteinuria at screening as demonstrated by either urine protein: creatinine (UPC) ratio ≥ 1.0 at screening OR urine dipstick for proteinuria ≥ 2+ (subjects discovered to have ≥2+ proteinuria on dipstick urinalysis at baseline should undergo a 24-hour urine collection and must demonstrate ≤ 1g of protein in 24 hours to be eligible).
- Known hypersensitivity to any component of bevacizumab

3.3. Inclusion of Women and Minorities

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

3.4. Prerequisites for Initiation of Optune™ Therapy:

After successful completion of chemoradiation, the following criteria must be met:
1. Adequate compliance of chemoradiation as documented by the investigator.
2. Subject must be able to continue bevacizumab and maintenance temozolomide.
3. Post-radiation MRI of the brain must be completed and fit to use for treatment planning for array placement.
4. Subject must not have prohibitive skin changes which would not permit Optune™ placement.

4. INVESTIGATIONAL PLAN

4.1. Milestone Date Definitions

Eligibility date: the date of the last documented criterion that confirmed subject eligibility prior to initiation of treatment with radiation, temozolomide, and bevacizumab.
Enrollment date: the date of initiation of treatment with radiation, temozolomide, or bevacizumab. If radiation, temozolomide, and bevacizumab is not initiated on the same date, the enrollment date will be defined as the initiation of the first study treatment administered.

Treatment discontinuation date: the date the Investigator decides to discontinue the subject from Optune™ therapy (subjects who have Optune™ device placed) or the date the Investigator decides that the subject will not have Optune™ device placed (subjects who do not have Optune™ placed).

4.2. Overall Study Design and Plan

This is an open label, single-arm, phase II protocol.

All subjects will complete standard of care radiation, temozolomide, and bevacizumab (approximately 6 weeks). A post-radiation MRI of the brain will be completed within 2 weeks after conclusion of radiation. Within 2 weeks of completion of this initial treatment period, study subjects will be fitted with the Optune™ System and treated continuously. Planning for this therapy will be completed using the post-radiation MRI of the brain. They will be treated with TTFields for 12 months for an average of 18 hours per day. The subject may elect to take a treatment break for a total of 3 days per month, for each month and still be in compliance. This will consist of wearing four electrically insulated electrode arrays on the head. The subjects will also continue with maintenance temozolomide/ bevacizumab for 12 cycles.

Upon completion of the Optune™ therapy intervention phase, subjects will be followed for evaluation of PFS, OS, and safety objectives.

This study will be carried out in two stages. The first stage will enroll a cohort of 22 subjects. The Stage 1 analysis will be completed after all subjects in the first stage (n=22) have at least 12 months of follow-up time from the initiation of chemoradiation therapy (or have died). The second stage will enroll a cohort of 24 subjects (a total of 46 subjects). Study data will be collected and stored in the Clinical Trials Management System (CTMS).

4.3. Pre-Treatment

4.3.1. Registration Process

Written informed consent will be obtained prior to any protocol specific pre-treatment assessments.

Following informed consent, subjects will be registered in the CTMS and assigned a Study ID number. The Study ID number will begin with “LCI” and include a two digit number sequentially assigned to the subject (e.g. “LCI01” will be the Study ID number assigned to the first subject).

After completion of chemoradiation, subjects will need to meet eligibility criteria as described in section 3.4 in order to continue participation in the study.

Eligible subjects who receive the initial placement of the Optune™ transducer arrays will be considered evaluable for efficacy analyses.

4.4. Treatment

4.4.1. Study Procedures

Refer to the study calendar in Section 5 for when the following assessments will occur.

Demographics and Medical History

Demographics and information on baseline conditions will be collected during the screening visit. Medical history (oncological and relevant non-oncological) will be collected and recorded as standard in the medical record. GBM history will be obtained during screening and the following information will be recorded inthe medical record:

- Date of first histological/cytological diagnosis
- Primary tumor site
- Tumor histology and characteristics, including analysis for MGMT and IDH1 testing

Physical Examination

A physical exam should include the following:

- Cardiopulmonary examination
- Examination of the abdomen
- Skin examination
- Assessment of the mental and neurological status
- Neurological exam to include cranial nerve, motor, and sensory examination

Additional symptoms, which have not been reported during a previous examination, should be clarified. Wherever possible the same investigator should perform this examination. Physical exams will occur at the time points specified in the Study Calendar inSection 5.

Performance Status

Evaluation of KPS will be performed at the time points specified in the Study Calendar in Section 5. The KPS is found in Appendix B.

Vital Signs and Body Weight

Vital signs (blood pressure and pulse) and body weight will be recorded at the screening visit and at the time points specified in the Study Calendar in Section 5**. Height will only be recorded at Screening.**

Compliance Assessment

A device compliance report will be downloaded by Novocure and submitted to the prescribing physician monthly. Subject compliance will be assessed by the prescribing physician. Subjects will be considered non-compliant if their average monthly compliance rate is < 75% or if they take a treatment break for more than 3 days in a month. Any non-compliance will be addressed with the subject and re-education will occur as appropriate. Subjects who experience adverse events that result in the interruption of Optune^{TM} therapy will not be considered to be non-

compliant. See Section 6 for additional information.

Concomitant Therapies and Diagnoses

Concomitant diagnoses and/or therapies present during trial participation (between the Screening visit and at least until 28 days after the last administration of study device) will be recorded in the medical record. In case of medical or surgical procedures that would affect the assessment of the radiology findings, the Investigator has to describe the type and location of intervention as well as the results from biopsy or cytology assessment in the medical record. Any anti-cancer therapy administered after treatment discontinuation, including but not exclusive of RT, chemotherapy, targeted therapy, will be recorded in the medical record.

MRI

An MRI of the brain will be performed according to the schedule outlined in the Study Calendar in Section 5.

Serum Pregnancy B-HCG

A serum pregnancy B-HCG test for women of child-bearing potential will be performed during Screening. Subjects and partners of male subjects must use an effective form of contraception.

Effective forms of contraception include:

- True abstinence
- Male sterilization (with appropriate post-vasectomy documentation of the absence of sperm in the ejaculate). For female subjects, the vasectomized male partner should be the sole partner.
- Placement of non-hormonal intrauterine device or intrauterine system
- Condom with spermicidal foam/gel/film/cream/suppository
- Occlusive cap (diaphragm or cervical/vault caps) with spermicidal foam/film/cream/suppository

Note: Unacceptable methods of contraception include: Periodic abstinence (e.g., calendar, ovulation, symptothermal post-ovulation methods), withdrawal, and tubal ligation.

Adverse event assessment

Adverse events listed in Section 7 will be monitored throughout the study as described in Section 8.

Labs

Labs will be performed per the Study Calendar in Section 5.

4.5. End of Treatment

The end of treatment (EOT) visit is done when the subject discontinues study treatment, for any reason. The decision to discontinue study treatment due to tumor progression must be based on the evaluation of imaging. If the decision to permanently discontinue study treatment is made during a scheduled visit, then the EOT visit should be performed instead of the scheduled visit. If the decision is made between scheduled visits, an EOT visit should be performed no later than 7 days after the last study treatment administration.

4.6. Follow-Up

Follow-up beyond the safety follow- up period is only required for subjects in the evaluable population for efficacy (subjects who have the Optune™ device placed). These subjects should have the first follow-up visit (FUV1) 28 days (+/-7 days) after the EOT visit. Subsequent FUVs will take place monthly in the allowed window (+/- 7 days) outlined in the Study Calendar in Section 5. It is of utmost importance that subjects continue the imaging schedules until tumor progression. At a minimum the following information should be collected at FUVs:

- Survival status
- Imaging
- KPS
- Initial subsequent anti-cancer therapy

For subjects in the evaluable population for efficacy (subjects who have the Optune™ device placed) who end treatment due to disease progression, monthly FUVs as described above will not be required. However, these subjects should be contacted (phone contact is acceptable) to assess survival every 3 months (+/- 14 days).

Death information from public sources, e.g. death registry, obituary listing, etc. can also be used when it is available and verifiable. Refer to section 6.6 for duration of follow-up.

4.7. Off Study

Subjects will be removed from the study when any of the criteria listed in Section 6.7 applies. The reason for study removal and the date the subject was removed will be documented.

5. STUDY CALENDAR

	Screening (4 weeks)[l]	XRT/TMZ/ BEV (Concurrent Chemoradiation Phase) (6 weeks +/- 7 days)	Pre-Optune™ System Treatment (up to 2 weeks)	Optune™ System Treatment[n] /TMZ/BEV maintenance	End of Treatment[j]	Follow-Up[i]
Optune™ System planning and initial placement			X			
Informed consent/ Registration	X					
Demographics	X					
Medical history[m]	X					
Physical exam[a]	X	X	X	X[f]	X	X
Optune™ System compliance				X[f]	X[p]	
Concomitant medications: documentation	X	X	X	X[f]	X	
Height	X					
Blood pressure and pulse[k]	X	X	X	X	X	
Performance status (KPS)[a]	X	X	X	X[f]	X	X
MRI[b]	X		X	X[g]		X[g]
Serum Pregnancy B-HCG[c]	X					
Adverse event assessment[o]		X	X	X	X	
Labs	X[e]	X[h]	X[h]	X[h]	X[h]	
Confirmation of Prerequisites to Initiate Optune™ Therapy[d]			X[d]			

a: Physical exam must include weight, neurologic exam and KPS (every 2 weeks [± 3 days] during chemoradiotherapy and every 4 weeks [±3 days] during Optune™ System Treatment) and required assessments as referenced in Section 4.4.1.
b: Including tumor measurements
c: In women of childbearing potential
d: Confirm prerequisites for initiation of Optune™ therapy per section 3.4
e: CBC with diff, lipid profile, CMP, U/A, PT, PTT, INR
f: Every 4 weeks (+/- 3 days)
g: Every 8 weeks +/- 7 days or as clinically indicated. Frequency to be based from previous MRI.
h: CBC with diff weekly (+/- 2 days) during chemoradiotherapy. CBC with diff, CMP, and U/A every two weeks (+/- 3 days) of each bevacizumab infusion and at the End of Treatment visit. CBC with diff day 21 (+/- 3 days) of every 28 day maintenance cycle.

i: Follow-up beyond the safety follow-up period is only required for subjects in the evaluable population for efficacy (subjects who have the Optune™ device placed). The first follow-up visit will be 28 days (+/- 7 days) from EOT visit per Section 4.6. Subsequent visits are monthly (+/- 7 days). For subjects who have disease progression, the only follow-up requirement is to contact to assess survival every 3 months (+/- 14 days).
j: If the decision to permanently discontinue the device treatment is made during a scheduled visit, then the EOT visit should be performed instead of the scheduled visit. If the decision is made between scheduled visits, an EOT visit should be performed no later than 7 days after the last Optune™ treatment administration.
k: Vital signs (blood pressure and pulse) to be documented during screening and then every two weeks (+/- 2 days) prior to bevacizumab infusion
l. All screening procedures to be performed within 4 weeks of study treatment initiation unless otherwise noted
m. To include documentation of baseline conditions
n. Optune™ System placement will occur after completion of chemoradiation and Pre-Optune™ System Procedures (per the study calendar). TMZ and bevacizumab to be administered currently with Optune™ System as 28 day cycles (12 cycles total during maintenance) with a +/- 3 day variation allowed for Day 1.
o. Adverse event assessment to occur beginning with initiation of study treatment through 30 days after Optune™ device is discontinued (or last dose of study treatment for subjects who do not have the Optune™ device placed).
p. Only required for subjects who had the Optune™ System placed

6. TREATMENT PLAN

6.1. Temozolomide Administration

Concurrent Chemoradiation Phase: Subjects will receive temozolomide at 75 mg/m2 daily concurrently with radiation therapy and bevacizumab.

Maintenance Phase : At least four weeks after completing concurrent TMZ + RT + BEV, TMZ will be administered (with bevacizumab) for an additional 12 cycles (cycle = 28 days; ± 3 day window allowed for Day 1). Dosage for cycle 1 will be TMZ 150 mg/m^2 daily on days 1-5, followed by 23 days of rest. At the start of cycle 2, the dose will be escalated to 200 mg/m^2 if the following criteria are met:

- CTC non-hematologic toxicities for Cycle 1 have resolved to Grade ≤2 (except for alopecia, nausea and vomiting),
- Absolute neutrophil count (ANC) is ≥ 1.5 x 109/L, and
- Platelet count is ≥ 100 x 109/L

If the dose was not escalated at cycle 2, it may be escalated at cycle 3. After cycle 3, no dose escalations will be allowed.

In the event of a treatment delay at the scheduled Day 1 of a cycle during maintenance, Day 1 of that cycle will be delayed until TMZ is re-started. This may cause a cycle to extend to longer than 28 days. Day 1 will be defined as the day TMZ is re-started.

If treatment is delayed for a TMZ-related toxicity, treatment with bevacizumab may continue per investigator discretion. If TMZ is held for greater than 4 weeks, the subject will be discontinued from study treatment.

Dose delays or modifications not defined above will be done according to the most recent package insert.

6.2. Bevacizumab Administration

Concurrent Chemoradiation Phase: Bevacizumab will be administered every 2 weeks (+/- 3 days) as an IV infusion dosed at 10 mg/kg concurrently with TMZ and radiation therapy. Every effort will be made to initiate bevacizumab and TMZ on the same day that radiation starts. Bevacizumab will only be administered if any existing surgical wound has fully healed. A maximum of 4 weeks after biopsy will be permitted.

Dosing calculations should be based on body weight unless the subject's weight on the day of dosing differs > 10% from the weight used to calculate the dose, then the dose must be recalculated. All doses should be rounded to the nearest milligram.

The first infusion should be administered over 90 minutes. If the subject tolerates the first infusion, the second infusion will be administered over 60 minutes. All subsequent infusions will be administered over 30 minutes if the 60 minute infusion is tolerated.

Refer to the package insert for recommended treatment modifications and supportive care for the following bevacizumab-related toxicities.

Bevacizumab will be temporarily held for:

- Elective surgery (hold at least 4 weeks prior to surgery and until wound is fully healed)
- Severe hypertension defined as SBP > 160 and/or DBP > 100 mm Hg
- Moderate to severe proteinuria
    - Hold for 3+ or greater urine dipstick reading
    - Resume when proteinuria is < 3+ on urine dipstick reading. A 24 hour urine may be ordered per investigator discretion.
- Severe infusion reactions

Bevacizumab will be permanently discontinued for:

- Gastrointestinal perforation, including fistula formation involving an internal organ and intra-abdominal abscess
- Surgery and wound healing complications including dehiscence and nectrotizing fasciitis
- Serious hemorrhage
- Severe arterial thromboembolic events
- Grade 4 venous thromboembolic events, including pulmonary embolism that are determined to be life-threatening by the treating investigator
- Hypertensive crisis or hypertensive encephalopathy
- Posterior Reversible Encephalopathy Syndrome
- Nephrotic syndrome

Maintenance: After completing concurrent TMZ + RT + BEV, bevacizumab (with TMZ) will be administered every 2 weeks (+/-3 days) as an IV infusion dosed at 10 mg/kg for an additional 12 cycles (cycle = 28 days).

If treatment is delayed for a bevacizumab-related toxicity, treatment with TMZ may continue per investigator discretion.

In the event of a treatment delay at the scheduled Day 1 of a cycle during maintenance, Day 1 of that cycle will be delayed until TMZ is re-started. This may cause a cycle to extend to longer than 28 days. Day 1 will be defined as the day the treatment is re-started.

Missed doses will not be made up. If bevacizumab is held for greater than 4 weeks, the subject will be discontinued from study treatment.

6.3. Radiation Therapy

Intensity Modulated RT (IMRT) is allowed. Radiation therapy must begin ≤ 4 weeks after surgery. The modality chosen at registration MUST be used for the entire course of treatment

6.3.1. Dose Specifications

For both IMRT and 3D-CRT plans, one treatment of 2 Gy will be given daily 5 days per week for a total of 60 Gy over 6 weeks.

6.3.2. Localization, Simulation, and Immobilization

The subject shall be treated in the supine or other appropriate position for the location of the lesion. A head-holding device to ensure adequate immobilization during therapy and ensure reproducibility is strongly recommended.

6.3.3. Initial Target Volume

Target volumes will be based upon postoperative-enhanced MRI. Preoperative imaging should be used for correlation and improved identification. Two planning target volumes (PTV) will be defined, as outlined below. The initial gross tumor volume (GTV1) will be defined by either theT2 or the FLAIR abnormality on the post-operative MRI scan. The initial clinical target volume (CTV1) will be the GTV plus a margin of 2 cm.

6.3.4. Boost Target Volume

The boost gross tumor volume (GTV2) will be defined by the contrast-enhanced T1 abnormality on the post-operative MRI scan. This must also include the surgical cavity margins. The boost clinical target volume (CTV2) will be the GTV plus a margin of 2.0 cm. The CTV2 margin maybe reduced to 0.5 cm around natural barriers to tumor growth such as the skull, ventricles, falx, etc, and also to allow sparing of the optic nerve/chiasm, if necessary.

6.3.5. Dose Guidelines

The initial target volume will be treated to 46 Gy in 23 fractions. After 46 Gy, the conedown or boost volume will be treated to a total of 60 Gy, with seven additional fractions of 2 Gy each (14Gy boost dose).

6.3.5.1. Treatment Interruption

Up to 5 days of treatment interruption are permitted for any reason. Interruptions of 6 to 7 treatment days will be considered an acceptable protocol deviation. For interruptions of 8 days or greater, an unacceptable deviation will be assigned.

6.3.6. Radiation Therapy Adverse Events

6.3.6.1. Acute

Expected acute radiation-induced toxicities include hair loss, fatigue, and erythema or soreness of the scalp. Potential acute toxicities include nausea and vomiting as well as temporary aggravation of brain tumor symptoms such as headaches, seizures, and weakness. Dry mouth or altered taste has been occasionally reported.

6.3.6.2. Early Delayed

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

6.3.6.3. Late Delayed

Possible late delayed effects of radiotherapy include radiation necrosis, endocrine dysfunction, and radiation-induced neoplasms. In addition, neurocognitive deficits, which could lead to mental slowing and behavioral change, are possible. Cataracts can be encountered.

6.4. Optune™ System Administration

6.4.1. Treatment Planning of TTFields (Tumor Treating Fields)

Once the chemoradiation has been completed, the post-radiation MRI of the brain will be used for treatment planning of the transducer array layout. Only investigators trained by Novocure are involved in this study and training will be documented. The treatment planning of the TTFields (Tumor Treating Fields) will be performed by the investigator via the NovoTAL™ system. The investigator will plan the location of the treatment transducer arrays by using 3D software to encompass the target volume of tumor, and/or resection bed within the fields.

6.4.2. Subject Preparation Prior to the Placement of Optune™ System

The subjects (and/or caregiver) will be trained in the use of the device by the investigator, a designated health care provider (eg. nurse), or a Novocure device support specialist. All subjects will be required to shave their heads prior to initiating array placement and **Optune™** therapy. Array placement will be performed based on the transducer array map calculated during treatment planning.

6.4.3. Placement of Optune™System

Upon completion of the treatment planning, the subject will have an appointment with the prescribing physician for the initial placement of the transducer arrays. Furthermore, the subject and caregiver(s) will be provided with educational material. They will receive extensive teaching in regard to usage and daily wear of the **Optune™** System.

6.4.3.1. Transducer Array Placement Protocol

The specific locations of each transducer array set will be pre-calculated by the investigator based on the post-radiation MRI of the brain. The transducer array layout will be approved by the treating investigator and determined according to tumor location. After transducer array placement, the **Optune™** System will be activated with pre-defined parameters which will be supplied by Novocure.

6.4.3.2. Transducer Replacement

During transducer array replacement, the skin below the transducer array will be inspected by the physician (during treatment visits) and by the subject himself or herself (or caregiver). In the event of significant skin breakdown (leading to pain or bleeding) or evidence of infection, the transducer array will be moved to an alternate site. Skin breakdown and/or infection will be treated according to the treating physician's clinical judgment or based on a dermatologist's recommendation. Adverse Events (AEs) of skin breakdown or evidence of infection, either of which requires a break in **Optune™** System treatment greater than 3 days, will be reported on the eCRF. Mild to moderate contact dermatitis is expected to appear beneath the transducer array gel during the first or second treatment course. This condition will be treated per instructions outlined under section 6.4.6.

- Transducer array location will be shifted between two alternate sites at every transducer array change. At each array placement, the new set of arrays should be shifted by approximately 2 cm compared to the previous layout so that the array discs are placed between the areas of skin irritation. At the next array replacement, the arrays should be shifted back to their original location.
- Subjects will replace the transducer arrays two to three times per week with the help of a caregiver. At each array replacement, the subject's

scalp will be re-shaved and skin treated according to the guidelines specified in this protocol.

6.4.4. Device Compliance

The subject and caregiver(s) will be instructed on the length of daily wear (on average 18 hours or more a day), the procedure for shaving subject's scalp for preparation, and continued wearing of the device. Treatment with the device will be continuous, with breaks allowed for personal needs (eg: showering, array exchange). The subject may elect to take a treatment break for a total of 3 days per month (may be non-consecutive), for each month and still be in compliance. The treatment will be continued until disease progression, 12 months, a non-acceptable side effect to the subject, or consent withdrawal. Compliance with the **Optune™** System will be assessed through the use of a log generated by the device and will be assessed by the investigator or Novocure representative. Subjects who experience adverse events that result in the interruption of **Optune™** therapy will not be considered to be non-compliant.

6.4.5. Delivery of Optune™ Therapy

Optune™ System will be programmed by Novocure to deliver 200kHz TTFields in two sequential, perpendicular field directions at a maximal intensity of 707mA RMS (otherwise known as the output current). There will be no adjustments made to the device by investigators or subjects/caregivers.

6.4.6. Skin Care/Dose Modification for Optune™ Therapy

If the skin is inflamed and shows signs of allergic or irritant contact dermatitis, a topical corticosteroid such as triamcinolone 0.1% or clobetasol, at the physician's discretion, will be applied to the irritated area twice daily, left on the scalp for 15 minutes, and wiped away before the arrays are replaced.

- In cases of irritant contact dermatitis, ceramide creams and/or bland emollients/moisturizers such as Eucerin Original Moisturizing fragrance-free lotion or cream (applied twice daily) or topical Aquaphor (applied once daily) may be recommended at the physician's discretion. If a superficial infection develops, a topical antibiotic ointment may be added to the treatment regimen.
- In cases of allergic contact dermatitis, calamine lotion or antipruritic lotions (i.e. topical diphenhydramine) may be recommended at the physician's discretion. Severe cases of allergic contact dermatitis will be treated with a 2-week course of systemic corticosteroids or corticosteroid injections. Topical immunomodulators may be used in cases where topical corticosteroids are unsafe. If a superficial infection develops, a topical antibiotic ointment may be added to the treatment regimen.
- For folliculitis, topical antibiotic is recommended. Oral antibiotic may be advised if severe. Warm compresses or medicated shampoos may be advised.

- For erosions (incomplete loss of epidermis), topical antibiotic is recommended. Oral antibiotics may be added for severe cases. Avoidance of erosions when placing arrays is recommended. The wounds may be dressed with gauzes, hydrogels, or hydrocolloids. Arrays will be removed from the site of the skin breach and bandages may be trimmed.
- If the epidermis appears to be lost and dermis is affected, those lesions will be described as ulcers. Topical antibiotic is recommended. Oral antibiotics may be added for severe cases. Avoidance of erosions when placing arrays is recommended. Culture of open wound may be advised. The wounds may be dressed with gauzes, hydrogels, or hydrocolloids. Arrays will be removed from the site of the skin breach and bandages may be trimmed.

If skin blistering occurs, silver sulfadiazine may be recommended to be applied to the affected areas. In subjects with sulfa allergy, a dermatology consult will be obtained to seek alternative courses of treatment. The subject or caregiver(s) may also apply cold, moist compresses for 20 minutes 3x a day.

In any case where the subject does not notice an improvement in the skin reaction within 2 weeks of starting one of the treatments outlined above, the subject will be instructed to inform the investigator and a dermatological consult will be obtained.

For all types of skin irritation (pruritis, erosion, ulcer, infection, or blister), the physician may determine that a temporary hold on the Optune™ treatment may be necessary.

There will be no "dose" adjustments to the device for adverse events. Reasons for breaks in treatment for longer than 3 days will be documented.

6.4.7. Technical Support of the Optune™ System

The subject/caregiver(s) will be trained by a Novocure device support specialist and/or prescribing physician or other Novocure trained designee. The subject/caregiver(s) will learn how to turn the device on/off and how to connect/disconnect the transducer arrays (through the connection cable). The subject/caregiver(s) will also learn how to recharge and replace the device battery.

The subject's caregiver(s) will learn how to handle device error messages/device malfunctions themselves (using the troubleshooting section of the **Optune™** Patient Information and Operation Manual provided by Novocure) and will learn how to contact the Novocure device support specialist (or Novocure Technical Support Line) for issues they cannot resolve themselves. They will also be instructed on when to contact the Novocure device support specialists versus when to call the prescribing physician.

The subject/caregiver(s) will also be given extensive instruction on the treatment of expected adverse events.

All technical aspects of treatment can be handled by the Novocure device support specialists. Examples of technical issues include, but are not limited to: technical support of device for the subject (by phone or in person), training/re-training on correct use of the device, periodic download of device compliance log file (once every four weeks), replacement of faulty equipment, requests for replacements from Novocure and device, electrode and accessory accountability tracking.

6.5. Duration of Therapy

Study treatment will continue until one of the following criteria applies:

- Completion of protocol therapy which is defined as completion of 12 months of Optune™ therapy
- Disease progression
- Intercurrent illness that prevents further administration of treatment
- Unacceptable adverse event(s)
- Subject decides to withdraw study consent
- General or specific changes in the subject's condition render the subject unacceptable for further treatment in the judgment of the investigator
- Study subject becomes pregnant

NOTE: In the event the criteria for the final analysis are met, and there are subjects who have not yet been discontinued from study treatment, they will continue to receive therapy until one of the above criteria applies.

6.6. Duration of Follow-Up

Subjects in the evaluable population for efficacy (subjects who have the Optune™ device placed) will be followed until all subjects have been on study five years from the date of enrollment, have died, or until the censoring rate reduces to 20%, whichever occurs first. Subjects who do have the Optune™ device placed will be followed for the 30 day safety follow-up period as described in Section 8.2.1 and then removed from the study.

6.7. Criteria for Removal from Study

When subjects are removed from the study, the reason for study removal and date the subject was removed should be documented. Reasons a subject may be removed from the study include, but are not limited to:

- Subject withdraws study consent
- Investigator's decision to withdraw the subject
- Subject is lost to follow-up after three consecutive months of attempted contact
- Death
- Study completion

Any subject removed from the study will remain under medical supervision until discharge or transfer is medically acceptable. Subjects that are Off Study will not participate in any

study related procedures, including data collection.

7. TREATMENT- RELATED ADVERSE EVENTS

7.1. Adverse Event Characteristics

CTCAE term (AE description) and grade: The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 will be utilized for AE reporting.

Attribution of the AE:
Definite – The AE *is clearly related* to the study treatment.
Probable – The AE *is likely related* to the study treatment.
Possible – The AE *may be related* to the study treatment.
Unlikely – The AE *is doubtfully related* to the study treatment.
Unrelated – The AE *is clearly NOT related* to the study treatment.

7.2. Adverse Events Considered Related to Optune™ System

Mild to moderate (grade 1 and grade 2) dermatitis has been reported on the scalp underneath the transducer arrays in patients receiving Optune™ therapy. This typically occurs by the second month of treatment and resolves with use of topical steroids and shifting of the arrays "back and forth" at each transducer array exchange. Sometimes short treatment interruptions are required. Treatment with the Optune™ System is not expected to cause any serious side effects. However, it is possible that investigational treatment may cause any of the following:

- Local heat and tingling "electric" sensation beneath the transducer array
- Allergic reaction to the adhesive or to the gel
- Skin irritation or skin breakdown
- Infection at the sites of transducer array contact with the skin
- Open sore, ulceration or blisters underneath the transducer arrays
- Headache
- Fatigue

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

Table 1

		Optune™ Therapy (n=116)	**Active Control (n=91)**
System	**Adverse event term**	**% (% gr. 3+4)**	**% (% gr. 3+4)**

Hematological		3 (0)	17 (4)
	Leukopenia	0 (0)	5 (1)
	Neutropenia	0 (0)	2 (1)
	Thrombocytopenia	1 (1)†	7 (2)
Gastrointestinal disorders		4 (1)	17 (3)
	Abdominal pain	0 (0)	3 (0)
	Diarrhea	0 (0)	6 (2)
	Nausea / Vomiting	2 (0)	7 (0)
General deterioration and malaise		5 (1)	6 (1)
Infections		4 (0)	8 (1)
Skin rash (transducer arrays)		2 (0)	0 (0)
Metabolism and nutrition disorders		4 (1)	6 (3)
Musculoskeletal Disorders		2 (0)	5 (0)
Nervous system disorders		30 (7)	28 (7)
	Brain edema	0 (0)	2 (0)
	Cognitive disorder	2 (1)	2 (1)
	Convulsion	7 (2)	5 (2)
	Dysphasia	2 (0)	1 (0)
	Headache	8 (1)	6 (0)
	Hemianopsia	1 (0)	3 (1)
	Hemiparesis	3 (1)	2 (1)
	Neuropathy peripheral	2 (0)	2 (0)
Psychiatric disorders		5 (0)	4 (0)
Renal and urinary disorders		3 (1)	3 (0)
Respiratory Disorders		1 (0)	3 (1)
Vascular disorders		3 (1)	4 (3)
	Pulmonary embolism	1 (1)	2 (2)
	Hypertension	1 (0)	1 (1)
	Deep vein thrombosis	1 (0)	1 (0)
† thrombocytopenia from prior chemotherapy, normalized subsequently.			

7.3. Adverse Events Considered Related to Temozolomide

Temozolomide has been well-tolerated by adults with the most common toxicity being mild myelosuppression. Other, less likely, potential toxicities include nausea and vomiting,

constipation, headache, alopecia, rash, burning sensation of skin, esophagitis, pain, diarrhea, lethargy, and hepatotoxicity. Hypersensitivity reactions have not yet been noted with temozolomide. As is the case with many anti-cancer drugs, temozolomide may be carcinogenic.

7.4. Adverse Events Considered Related to Bevacizumab

Patients receiving bevacizumab have experienced the following adverse events:

- Grade 3/4 hypertension (including RPLS (confirmed by MRI) or hypertensive encephalopathy)
- Grade ≥ 1 pulmonary or CNS hemorrhage
- Grade 3 non-pulmonary and non-CNS hemorrhage
- Grade 4 hemorrhage
- Grade 3/4 asymptomatic venous thrombosis
- Grade 4 symptomatic venous thrombosis
- Any grade arterial thromboembolic
- Grade 3/4 congestive heart failure (left ventricular systolic dysfunction)
- Grade 3/4 proteinuria
- GI perforation
- Bowel obstruction
- Wound dehiscence

8. SAFETY DATA COLLECTION, RECORDING, AND REPORTING

Safety assessments will consist of monitoring and recording all adverse events and serious adverse events, the regular monitoring of hematology, blood chemistry values, regular measurement of vital signs and the performance of physical examinations. Safety and tolerability will be assessed according to the Common Terminology Criteria for Adverse Events (CTCAE) version 4.0. All adverse events (Grades 1 – 5) will be recorded.

Serious adverse events (SAEs)/Unanticipated adverse device effects (UADEs) should be entered into the CTMS as soon as they occur, but no later than 24 hours of becoming aware of the event. Deviations should be entered into the CTMS as soon as they occur, but within no more than 5 business days of becoming aware of the event. Any additional problems, such as study drug administration, or any other problem that could affect the validity/integrity of the study data should be tracked and submitted to the Sponsor-Investigator. SAEs/UADEs are also reported to the Levine Cancer Institute Data and Safety Monitoring Committee (DSMC) as soon as they occur, but no later than 24 hours of becoming aware of the event.

8.1. Definitions

8.1.1. Unanticipated Problem (UAP) Definition

An UAP is any incidence, experience or outcome that is unexpected, given the information provided in research-related documentation (e.g investigator's brochure, informed consent) and the study population characteristics that is related or possibly

related to participation in the research study and places the participant at an increased risk.

8.1.2. Adverse Event (AE) Definition

An adverse event or adverse experience is any untoward medical occurrence in a study subject who is administered a study drug that does not necessarily have a causal relationship with this treatment. An adverse event can therefore be any unfavorable and unintended sign, symptom, or disease temporally associated with the use of the study drug, whether or not considered related to the study drug. Pre-existing conditions that increase in frequency or severity or change in nature during or as a consequence of use of a drug in human clinical trials are also considered adverse events. Adverse events may also include pre- or post-treatment complications that occur as a result of protocol mandated- procedures (e.g., invasive procedures such as biopsies).

Any continuing medical condition or clinically significant laboratory abnormality with an onset date before the first date of study drug/device administration should be considered pre-existing and should be documented at baseline. If the medical condition or clinical significant laboratory abnormality worsens while the subject is on study, it should be documented as an adverse event.

An AE does not include:

- relapse or progression of the underlying malignant disease; however, the associated signs, symptoms, or diagnoses should be recorded as adverse events (e.g., “jaundice” due to new or increasing liver metastases, or “tumor pain” or “bone pain” due to progressive disease);
- medical or surgical procedures (e.g., surgery, endoscopy, tooth extraction, transfusion). The condition that leads to the procedure is the adverse event;
- situations where an untoward medical occurrence has not occurred (e.g., hospitalization for elective surgery, social and/or convenience admissions);
- overdose of either study drug or concomitant medication without any signs or symptoms unless the subject is hospitalized for observation; or
- pregnancy.

Laboratory abnormalities are usually not recorded as adverse events; however, signs and/or symptoms that are associated with laboratory findings requiring study withdrawal, dose modification, or medical intervention (e.g., anemia requiring transfusions or hyperglycemia requiring treatment) or other abnormal assessments (e.g., ECG, radiographs, vital signs) must be recorded as adverse events if they meet the definition of an adverse event. In addition, laboratory abnormalities marked as clinically significant by the investigator should also be recorded as adverse events in the eCRF. The investigator will record the most severe grade of the clinically significant laboratory abnormality and will evaluate its relationship to the study drug and clinical condition if/when a clinically significant laboratory abnormality occurs.

The relationship to study drug therapy should be assessed using the following definitions:

Not Related: Evidence exists that the AE has an etiology other than the study drug (eg, pre-existing condition, underlying disease, intercurrent illness, or concomitant medication). This includes events that are considered remotely or unlikely related to study drug.

Related: A temporal relationship exists between the event onset and administration of the study drug. It cannot be readily explained by the subject's clinical state, intercurrent illness, or concomitant therapies. In the case of cessation or reduction of the dose, the event abates or resolves and reappears upon rechallenge. It should be emphasized that ineffective study drug treatment should not be considered as causally related in the context of AE reporting. This includes events that are considered possibly, probably, or definitely related to study drug.

All adverse events (including event name, grade, start/stop date and attribution) will be documented in the medical record and/or research chart and recorded on the electronic case report form for this protocol.

The Investigator is responsible for verifying and providing source documentation for all adverse events and assigning the attribution for each event for all subjects enrolled on the trial.

8.1.3. Suspected Adverse Reaction (SAR) Definition

A SAR is an adverse event in which there is reasonable possibility that the study drug caused the adverse event as defined by 21 CFR 312.32. The Investigator is responsible for judging whether it is a reasonable possibility that the study drug caused the adverse event.

8.1.4. Unexpected Definition

An AE or SAR is to be considered unexpected if the event is not listed in package insert, label or investigator brochure or is not listed in the severity or specificity observed.

8.1.5. Serious AE or SAR

An AE or SAR is to be considered serious if the Investigator (in consultation with the Sponsor-Investigator , if needed) deems it as such and the event results in any of the following outcomes:

- Death;
- Life-threatening situation (subject is at immediate risk of death);
- Inpatient hospitalization or prolongation of an existing hospitalization (excluding those for study drug administration, protocol-related

procedures, palliative or hospice care, or placement of an indwelling catheter, unless associated with other serious events);
- Persistent or significant disability/incapacity;
- Congenital anomaly/birth defect in the offspring of a subject who received study drug;
- Any secondary malignancy (defined as new cancers, not transformation or progression of original disease). The pathology report documenting the new malignancy should be attached.
- Other: Important medical events that may not result in death, be immediately life-threatening, or require hospitalization, may be considered an SAE when, based upon appropriate medical judgment, they may jeopardize the subject or may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such events are:
    - Intensive treatment in an emergency room or at home for allergic bronchospasm;
    - Blood dyscrasias or convulsions that do not result in hospitalization;
    - Development of drug dependency or drug abuse.

Questionable events:
Any suspected adverse reaction can and should be reported as an SAE if deemed appropriate by the Sponsor-Investigator.

Planned hospitalizations:
Elective surgeries that have been planned prior to subject enrollment in the study or for conditions existing prior to study enrollment do not need to be captured as SAEs, unless complications occur or the conditions are worse than the subject's baseline.

Hospital admission for treatment required by the protocol (overnight chemotherapy, etc.) need not be reported as an SAE, unless a complication results that fits the 21 CFR 312.32 definition of an SAE.

The Investigator is responsible for verifying and providing source documentation for all SAEs and assigning the attribution for each event for all subjects enrolled on the trial.

8.1.6. Unanticipated Adverse Device Effect (UADE)

A UADE is defined as any serious adverse effect on the health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem or death was not previously identified in nature, severity or degree of incidence. A UADE is also defined as any unanticipated serious problem associated with the device that is related to the rights, safety, or welfare of research subjects, according to 21 CFR 812.3.

8.2. Timing and Reporting

8.2.1. Adverse Events

All AEs from initiation of study treatment until 30 days after the Optune™ device is discontinued will be documented (including event name, grade, start/stop date and attribution) and recorded in the CTMS. For subjects who do not have the Optune™ device placed, AEs will be reported until 30 days after the last dose of study treatment. Study treatment is defined as protocol-directed radiation, temozolomide, bevacizumab, and Optune™ therapy. If radiation, temozolomide and/or bevacizumab are initiated on different days, the AE reporting period will start with the first study treatment administered.

8.2.2. SAEs

After informed consent but prior to initiation of study treatment, only SAEs caused by a protocol-mandated intervention will be reported (e.g. SAEs related to invasive procedures such as biopsies, medication washout).

For any other experience or condition that meets the definition of an SAE, recording of the event must begin from initiation of study treatment until 30 days after the Optune™ device is discontinued. For subjects who do not have the Optune™ device placed, SAEs will be reported until 30 days after the last dose of study treatment. Study treatment is defined as protocol-directed radiation, temozolomide, bevacizumab, and Optune™ therapy. If radiation, temozolomide and/or bevacizumab are initiated on different days, the SAE reporting period will start with the first study treatment administered.

SAEs occurring greater than 30 days after last day of study treatment and thought to be possibly, probably, or definitely related to study treatment are reportable for the duration of the subject's participation in the study.

It is the responsibility of the Sponsor-Investigator, investigators and the protocol team to ensure SAEs are reported according to the Code of Federal Regulations (CFR), GCP, the protocol guidelines, IRB, and FDA policy.

8.2.3. UADEs

Any experience or condition that meets the definition of a UADE, recording of the event must begin from Optune™ device placement and continue through the 30 days after Optune™ System treatment is discontinued.

UADEs occurring greater than 30 days after Optune™ System discontinuation and thought to be possibly, probably, or definitely related to study treatment are reportable for the duration of the subject's participation in the study.

It is the responsibility of the Sponsor-Investigator, investigators and the protocol team to ensure UADEs are reported according to the Code of Federal Regulations (CFR), GCP, the protocol guidelines, IRB, and FDA policy.

8.2.4. Reporting to the Sponsor-Investigator

All SAEs and UADEs (including event name, grade, start/stop date and attribution) must be reported to the Sponsor-Investigator within 24 hours of awareness via the CTMS.

8.2.5. Reporting to the FDA

For Investigator-sponsored studies, reporting requirements for the FDA apply in accordance with the guidance set forth in 21 CFR 812.46, 21 CFR 812.150 and 21 CFR 312.32. The following are required to be submitted to the FDA in writing within 10 calendar days after the Sponsor-Investigator becomes aware of the event:

- SAEs that are determined by the investigator to be related and unexpected to bevacizumab
- All UADEs

8.2.6. Reporting to the IRB

All events occurring during the conduct of a protocol and meeting the definition of a UAP, SAE or UADE will be reported to the IRB per IRB reporting requirements.

8.2.7. Reporting to the Funding Sponsoring Company (Novocure)

Unanticipated adverse device events (UADEs) will be reported to Novocure promptly but no later than 10 working days of the Sponsor-Investigator learning of the event.

Protocol deviations necessary to protect the safety, rights or welfare of subjects enrolled in the study will be reported to Novocure promptly but no later than 10 working days from the time of identification of the protocol deviation by the Sponsor-Investigator.

8.3. Other Reporting

Deviations from the investigational plan to protect the life or physical well-being of a subject in an emergency situation will be reported to the Sponsor-Investigator as soon as possible but no later than 5 working days after the emergency occurred and to the IRB per IRB reporting requirements. Except in emergency situations, a planned protocol deviation requires prior sponsor approval; and if the deviation may affect the scientific soundness of the investigational plan or the rights, safety or welfare of study subjects, prior FDA and IRB approval are required.

Descriptions of protocol deviations will be provided to the FDA by the Sponsor-Investigator as part of the annual progress report and/or final report, as applicable.

The FDA, IRB and Novocure will be notified in writing of other events according to the following schedule:

Table 2

Event	Agency	Timeframe for Reporting
Minor changes to the investigational plan (prior FDA approval not required)	FDA	Within 5 working days after IRB approval/change implementation (known as 5-Day Notice of IDE Change); or, changes submitted in next progress report (non-significant changes)
	IRB	Within 90 days of S-I becoming aware of change
	Novocure	Advance notice with confirmation of Novocure approval prior to IRB submission
Major changes to the investigational plan (also known as supplements; prior approval required)	FDA	Advance notice and 30-day approval waiting period
	IRB	Prior IRB approval required after receipt of FDA approval
	Novocure	Advance notice with confirmation of Novocure approval prior to FDA submission
Recall and device disposition	FDA	30 working days
	IRB	10 working days
	Novocure	Not applicable
Withdrawal of IRB approval	FDA	5 working days after receipt of IRB withdrawal
	IRB	Not applicable
	Novocure	5 working days after receipt of IRB withdrawal
Withdrawal of IDE	FDA	Not applicable
	IRB	5 working days after receipt of IDE withdrawal
	Novocure	5 working days after receipt of IDE withdrawal
Current Investigator List	FDA	Every 6 months following FDA approval

	IRB	Only when the Principal Investigator changes
Progress Report	FDA	Annually at time of FDA approval
	IRB	Annually at time of IRB approval
Final Report	FDA	Notify FDA within 30 working days of study completion/termination. Final report submitted within 6 months.
	IRB	At time of study completion.
	Novocure	Final report submitted within 6 months.

9. DATA AND SAFETY MONITORING PLAN

This trial will be organized, performed, reported on and monitored in compliance with the study protocol, the Levine Cancer Institute (LCI) Data and Safety Monitoring Plan (DSMP), standard operating procedures (SOPs) of the LCI Clinical Trials department and Carolinas Healthcare System Office of Clinical and Translational Research, the FDA, IRB and other applicable regulations and guidelines (e.g. ICH and GCP). Ultimately, it is the responsibility of the Sponsor-Investigator to monitor the safety data for this study.

9.1. Monitoring and Review

Monitoring and review of this clinical trial will occur at 3 levels as described in the LCI Data and Safety Monitoring Plan: the Protocol Team, the Monitoring Team and the Data and Safety Monitoring Committee.

The Protocol Team will meet to review subject consents, enrollment and retention, safety data for *all* subjects [including adverse events (AE's) for all grades and attributions, serious adverse events (SAE's), unanticipated adverse device effects], drug administration, and validity/integrity of the data at all research sites. Following each Protocol Team meeting, a status report will be generated and will be kept on file.

Routine internal monitoring of subject safety and data quality at all investigational sites will also be conducted at scheduled intervals (based on protocol risk level) by the Monitoring Team at LCI according standard operating procedures. The Monitoring Team consists of members of the LCI Quality Assurance (QA) Department and other staff as needed. The Monitoring Team will be responsible for conducting initial, routine, and closeout monitoring visits according to the procedures defined in standard operating procedures. Data quality monitoring will be done by comparing source documentation to the eCRFs. The eCRFs will be reviewed and checked for omissions, apparent errors, and values requiring further clarification using computerized and manual procedures. Any variation between the

source document and the eCRF will be discussed with the Protocol Team. Data queries requiring clarification will be generated and addressed by Protocol Team. Only authorized personnel will make corrections to the protocol database and all corrections will be documented in an audit trail. At the conclusion of each routine internal monitoring visit, the Monitoring Team will provide a report to the Protocol Team and QA Manager. If at any monitoring visit subject safety risk, poor data quality or potential fraud or misconduct is identified, the Monitoring Team will notify the QA Manager and will follow the procedures outlined in the LCI standard operating procedures.

The Monitoring Team will use the CTMS, status reports, and Monitoring Visit Reports to update the DSMC on the status of the trial (including toxicity assessment and outcomes data). This information will be reviewed by the Data and Safety Monitoring Committee (DSMC) at regular intervals depending on the accrual rate, and at the time of annual review. For immediate subject safety events, the Protocol and/or Monitoring Team will notify the QA Manager upon becoming aware of the concern. Additionally, the Protocol Team will notify the DSMC within 1 business day of becoming aware of the event to allow an ad hoc meeting, if deemed necessary. Based upon DSMC review, the Sponsor-Investigator and Protocol Team may be required to develop an action plan and then notify the DSMC Chair in writing within 4 business days.

9.2. Communication Between Investigational Sites

All investigational sites will report AEs, SAEs and UADEs using eCRFs and the SAE reporting function in the CTMS. Any additional problems that could affect subject safety or data validity should be communicated with the S-I by email and/or telephone as soon as they occur, but within 1 business day.

9.3. Clinical Trial Registration

The Sponsor-Investigator is solely responsible for determining whether the trial and its results are subject to the requirements for submission to ClinicalTrials.gov (http://www.clinicaltrials.gov).

10. MEASUREMENT OF EFFECT

10.1. Antitumor Effect – Solid Tumors

In addition to a baseline scan, response and progression will be evaluated in this study using the Updated Response Assessment Criteria for High Grade Gliomas (RANO) (see section 10.1.4).

Subjects will have their response categorized as follows: 1) complete response, 2) partial response, 3) stable disease, 4) progressive disease, 5) early death from malignant disease, 6) early death from toxicity, 7) early death because of other cause, or 9) unknown (not assessable, insufficient data). [Note: By arbitrary convention, category 9 usually designates the “unknown” status of any type of data in a clinical database.]

10.1.1. Disease Parameters

Measurable disease: As defined by the Updated Response Assessment Criteria for High-Grade Gliomas: Response Assessment in Neuro-Oncology Working Group (RANO), measurable disease is defined as bi-dimensionally contrast-enhancing lesions with clearly defined margins by MRI scan, with two perpendicular diameters of at least 10 mm, visible on two or more axial slices that are preferably, at most,5 mm apart with 0-mm skip. All tumor measurements must be recorded in millimeters (or decimal fractions of centimeters).

If there are multiple contrast-enhancing lesions, a minimum of two and a maximum of five of the largest lesions should be measured, and the sum of the products of the perpendicular diameters of these lesions should be determined for response.

Note: Tumor lesions that are situated in a previously irradiated area are considered measurable if accompanying clinical deterioration and new FLAIR changes are present.[16]

Non-measurable disease: Unidimensionally measurable lesions, masses with margins not clearly defined, or lesions with maximal perpendicular diameters <10 mm are considered non-measurable disease.[16]

10.1.2. Methods of Evaluation for Measurable Disease (Target and Non-Target Lesions

All measurements should be taken and recorded in metric notation using a ruler or calipers. All baseline evaluations should be performed as closely as possible to the beginning of treatment and never more than 4 weeks before the beginning of the treatment.

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up. Imaging-based evaluation is preferred to evaluation by clinical examination when both methods have been used to assess the antitumor effect of a treatment.

Conventional MRI: These techniques should be performed with cuts of 5 mm or less in slice thickness contiguously.[16]

10.1.3. 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) (fluid-attenuated inversion recovery) lesions; subjects must be off corticosteroids (or on physiologic replacement doses only); and stable or improved clinically. (Note: Subjects with non-measurable disease only cannot have a complete response; the best response possible is stable disease.)[16]

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 lesions; 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; and stable or improved clinically. (Note: Subjects with non-measurable disease only cannot have a partial response; the best response possible is stable disease.)[16]

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.[16]

Progression:
Defined by any of the following: ≥ 25% increase in sum of the products of perpendicular diameters of enhancing lesions 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 non-enhancing lesion on stable or increasing doses of corticosteroids compared with baseline scan or best response after initiation of therapy not caused by comorbid events (eg, radiation therapy, demyelination, ischemic injury, infection, seizures, postoperative changes, or other treatment effects); any new lesion; clear clinical deterioration not attributable to other causes apart from the tumor (eg, 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 non-measurable disease. (NOTE: All measurable and non-measurable lesions must be assessed using the same techniques as at baseline.)

**Stable doses of corticosteroids include subjects not on corticosteroids.[16]

10.2. Tumor Response Review

Response will be reviewed by one neuro-oncologist and one neuro-radiologist independent of the study at the study's completion. Simultaneous review of the subjects' files and radiological images is the best approach.

11. STATISTICAL CONSIDERATIONS

11.1. Sample Size

To evaluate the effectiveness of the Optune™ System, referencing a study in newly diagnosed unresectable GBM subjects using the combination of temozolomide and bevacizumab for the historical controls is necessary. One such study was conducted by Lou, Peters, and Sumrall. The survival results for this study showed that the lower limit of the 95% CI for median OS was 7.4 months (median OS was 11.7 months). The Optune™ System will be considered worthy of further evaluation in this subject population if it is inferred that the median OS is superior to 7 months. The primary objective is to evaluate the 12-month overall survival rate. Assuming the median OS is 7 months, it is estimated that the 12-month survival rate would be 0.30. A Simon optimal 2-stage design will be used to test the hypothesis that the 12-month OS rate is less than or equal to 0.30. With treatment using the Optune™ System, an improvement in 12-month survival by 20% would be clinically notable. In the first stage, 22 subjects will be enrolled. If at least 8 subjects are surviving at 12 months, then an additional 24 subjects will be enrolled (total of 46 subjects). If at least 18 of 46 subjects are surviving at 12 months, the null hypothesis will be rejected and the addition of the Optune™ System to chemoradiation therapy may be considered for further evaluation. Assuming 1-sided alpha = 0.10 significance level, this sample size will provide 90% power to reject the null hypothesis, assuming the true 12-month survival rate is 0.50.

11.2. Endpoint Definitions

11.2.1. 12-Month Survival

Twelve-month survival will be determined for each subject as a binary variable indicating whether or not the subject is alive at 12 months. Determination of this endpoint occurs after the subject has at least 12 months of follow-up, unless they have died sooner.

11.2.2. Overall Survival

Overall survival is defined as the duration from the initiation of chemoradiation therapy to the date of death from any cause. Subjects who are alive or lost to follow-up at the time of the analysis will be censored at the last known date they were alive.

11.2.3. Progression-Free Survival

Progression-Free Survival (PFS) is defined as the duration of time from initiation of chemoradiation therapy to first occurrence of either progressive disease or death. Disease progression must be objectively determined as per Section 10.1, where the date of PD is the date of the radiologic assessment that identified progressive disease. If the subject died without documented disease progression, the date of progression will be the date of death. For surviving subjects who do not have documented disease progression, PFS will be censored at the date of last radiologic assessment. For subjects who receive subsequent anti-cancer therapy prior to documented disease progression, PFS will be censored at the date of last radiologic assessment prior to the commencement of subsequent therapy (note that this situation will not apply to cases where the subject discontinues Optune™ therapy but continues treatment with TMZ or BEV). Subjects who have an initial PFS event immediately following 2 or more consecutive missed assessments will be censored at the date of the last assessment prior to those missed assessments. For participants with only one missed assessment, the documented progressive disease status and assessment date

will be used.

11.2.4. Objective Response

Objective response will be determined for each subject as a binary variable indicating whether or not the subject achieved a best overall response of CR or PR as determined by the response criteria in Section 10.1.

11.2.5. Duration of Response

The duration of response is measured from the time measurement criteria are met for CR or PR (whichever is first recorded) until the first occurrence of either progressive disease or death. The date of PFS events and the censoring mechanism for duration of response will be the same as those described for PFS.

11.2.6. Disease Control

Disease control will be determined for each subject as a binary variable indicating whether or not the subject achieved stable disease or better (CR, PR, or stable disease) as determined by the response criteria in Section 10.1.

11.2.7. Duration of Disease Control

Duration of disease control is measured from the time of initiation of chemoradiation therapy until the first occurrence of either progressive disease or death. The date of PFS events and the censoring mechanism for duration of disease control will be the same as those described for PFS. Duration of disease control will be calculated only for those subjects with a best overall response of SD or better.

11.3. Analysis Populations

All subjects who receive the initial treatment with chemoradiation therapy will be included in the safety population. Subjects who receive initial placement of the Optune™ System transducer arrays will be included in the evaluable population for efficacy. The enrollment requirements for the 2-stage design as described in Section 11.1 apply to the evaluable population for efficacy. Subjects in the evaluable population with measurable disease will be included in the analysis of objective response, duration of response, disease control, and duration of disease control.

11.4. Analysis Methods

11.4.1. Timing of Analysis

The Stage 1 analysis will be conducted after all evaluable subjects in the first stage (n=22) have been on study for at least 12 months from the initiation of chemoradiation therapy or have died. The primary analysis of the second stage will occur after all evaluable subjects (n=46) have been on study for at least 12 months from the initiation of chemoradiation therapy or have died. An updated analysis will occur when all subjects have been on study for at least 2 years or are off study otherwise. A final analysis will occur when the OS censoring rate reaches 20%, or after all surviving subjects have been on study for at least 5 years after initiation of chemoradiation or are off study otherwise, whichever occurs first.

11.4.2. Subject Disposition

An accounting of all consenting subjects will be provided at the end of the study. This will include a breakdown of subjects who consented, were treated with chemoradiation therapy, were treated with Optune™, discontinued treatment, died, and were lost to follow-up or withdrew consent.

11.4.3. Baseline Subject and Disease Characteristics

A summary of baseline subject and disease characteristics will be completed. Counts and proportions will be used for binary and categorical variables. Means, medians, and ranges will be used for quantitative measures.

11.4.4. Efficacy Analyses

11.4.4.1. Primary Analysis

The frequency and proportions of subjects who are alive at 12 months will be summarized and corresponding 95% confidence intervals will be calculated using the Clopper-Pearson method. A one-sided test for binomial proportions using the rejection regions described in Section 11.1 will be carried out, testing the null hypothesis that the 12 months survival rate is less than 30%.

11.4.4.2. Secondary Analyses

Overall survival, progression-free survival, duration of response, and duration of disease control will be analyzed using Kaplan Meier techniques. Medians, 25th, and 75th percentiles will be estimated. Selected landmarks will be estimated using the product limit function. The frequency and proportions will be used to summarize objective response rate and disease control rate. Corresponding 95% confidence intervals will be calculated using the Clopper-Pearson method. Cox multiple regression models and logistic regression models will be used to evaluate the impact of baseline factors on outcomes.

11.4.5 Safety Analyses

The proportion of subjects experiencing AEs, SAEs, UADEs and death on study will be summarized by arm and corresponding 95% confidence intervals will be calculated using the Clopper-Pearson method. Safety data collected from date of initiation of chemoradiation therapy until the date of transducer arrays placement will be analyzed separately from safety data collected after the date of transducer arrays placement.

12. STUDY COMPLETION

The study will be considered complete when one or more of the following conditions is met:

- All subjects have completed all study visits
- All subjects have discontinued from the study
- The IRB, FDA, Sponsor-Investigator or Novocure discontinues the study because of safety considerations
- The Sponsor-Investigator defines an administrative or clinical cut-off date

13. RETENTION OF RECORDS

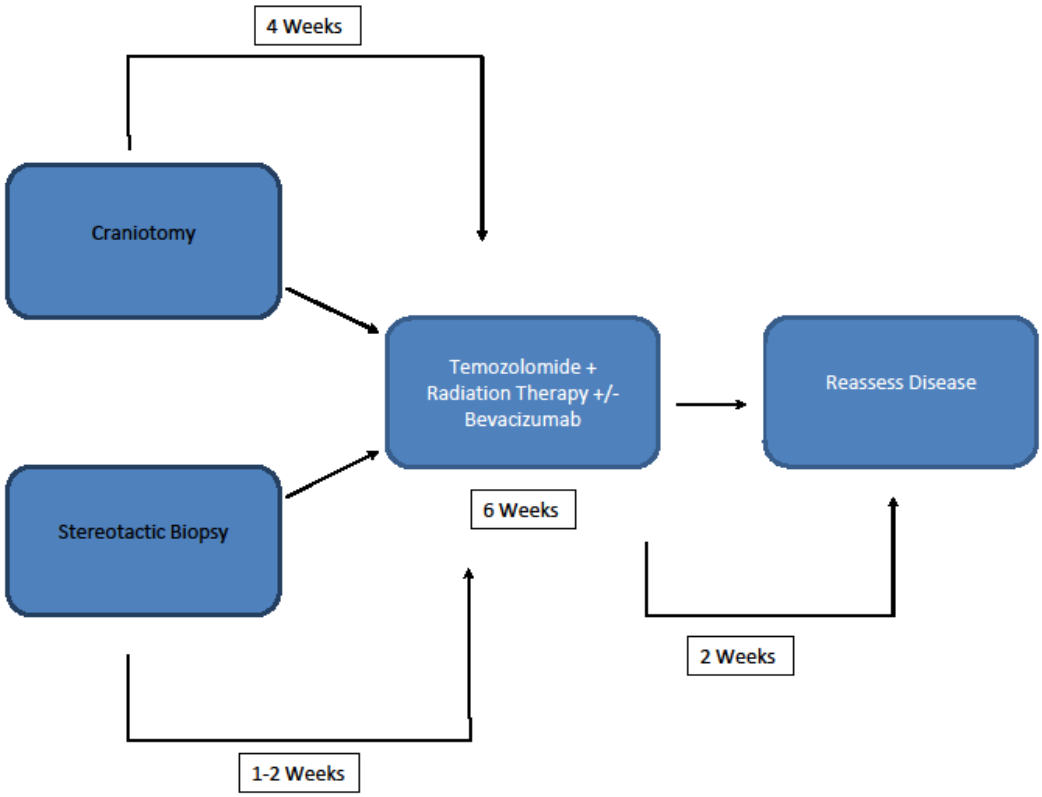
Documentation of adverse events, records of drug and device accountability, and all IRB correspondence should be retained for at least 2 years after the investigation is completed.

REFERENCES

1. Stupp, R., et al., *Radiotherapy plus concomitant and adjuvant temozolomide for glioblastoma.* N Engl J Med, 2005. **352**(10): p. 987-96.
2. Stupp, R., et al. *Effect of Tumor-Treating Fields Plus Maintenance Temozolomide vs Maintenance Temozolomide Alone on Survival in Patients With Glioblastoma: A Randomized Clinical Trial.* JAMA. 2017 Dec 19;318(23): p. 2306-2316.
3. Beauchesne, P., et al., *Prolonged survival for patients with newly diagnosed, inoperable glioblastoma with 3-times daily ultrafractionated radiation therapy.* Neuro Oncol, 2010. **12**(6): p. 595-602.
4. Nieder, C., et al., *Treatment of unresectable glioblastoma multiforme.* Anticancer Res, 2005. **25**(6C): p. 4605-10.
5. Vredenburgh, J.J., et al., *The addition of bevacizumab to standard radiation therapy and temozolomide followed by bevacizumab, temozolomide, and irinotecan for newly diagnosed glioblastoma.* Clin Cancer Res, 2011. **17**(12): p. 4119-24.
6. Fine, H. *PFS and health-related QOL in AVAglio, a phase III study of bevacizumab, temozolomide, and radiotherapy in newly diagnosed glioblastoma*. in *ASCO Annual Meeting*. 2013. Chicago, IL.
7. Gilbert, M. *RTOG 0825: Phase III double-blind placebo-controlled trial evaluating bevacizumab in patients with newly diagnosed GBM*. in *ASCO Annual Meeting*. 2013. Chicago, IL.
8. Lou, E., et al., *Phase II trial of upfront bevacizumab and temozolomide for unresectable or multifocal glioblastoma.* Cancer Med, 2013. **2**(2): p. 185-95.
9. Schneiderman, R.S., et al., *TTFields alone and in combination with chemotherapeutic agents effectively reduce the viability of MDR cell sub-lines that over-express ABC transporters.* BMC Cancer, 2010. **10**: p. 229.
10. Kirson, E.D., et al., *Disruption of cancer cell replication by alternating electric fields.* Cancer Res, 2004. **64**(9): p. 3288-95.
11. Kirson, E.D., et al., *Alternating electric fields arrest cell proliferation in animal tumor models and human brain tumors.* Proc Natl Acad Sci U S A, 2007. **104**(24): p. 10152-7.
12. Stupp, R., 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): p. 2192-202.
13. Grace Elzinga, A.C., Eric Wong, *Safety analysis of bevacizumab plus NovoTTF-100A in patients with recurrent malignant glioma*, in *ASCO Annual Meeting*2013: Chicago, IL.
14. Kirson, E.D., et al., *Alternating electric fields (TTFields) inhibit metastatic spread of solid tumors to the lungs.* Clin Exp Metastasis, 2009. **26**(7): p. 633-40.
15. Kirson, E.D., et al., *Chemotherapeutic treatment efficacy and sensitivity are increased by adjuvant alternating electric fields (TTFields).* BMC Med Phys, 2009. **9**: p. 1.
16. Wen, P.Y., et al., *Updated response assessment criteria for high-grade gliomas: response assessment in neuro-oncology working group.* J Clin Oncol, 2010. **28**(11): p. 1963-72.

APPENDICES

APPENDIX A: Standard of Care for Newly Diagnosed Glioma Patients



STANDARD OF CARE FOR NEWLY DIAGNOSED PATIENTS WITH MALIGNANT GLIOMAS (INCLUDING TIMELINE)

APPENDIX B: Karnofsky Performance Scale

Karnofsky Performance Scale	
Percent	Description
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.
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/her needs.
50	Requires considerable assistance and frequent medical care.
40	Disabled, requires special care and assistance.
30	Severely disabled, hospitalization indicated. Death not imminent.
20	Very sick, hospitalization indicated. Death not imminent.
10	Moribund, fatal processes progressing rapidly.
0	Dead.