Safety and tolerability of tumor treating fields (TTFields) combined with chemoradiation in newly diagnosed glioblastoma (UNITY)

Protocol number:	UNITYGBM01
Phase:	I
Investigators:	Ricky Chen, MD (PI) Nicholas Butowski, MD Steve Braunstein, MD Manju Sharma, PhD Eric Hansen, MD
Protocol version:	4.0
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Revision history:

Version Number	Version Date	List of Changes
1.0	25SEP2017	N/A
2.0	30JAN2018	Given that some patients likely will not have their MGMT result by the time of enrollment into the study, MGMT status will not be a cause for exclusion. MGMT results will be used for stratification only. In addition to the first safety lead in cohort, an additional safety stop will be incorporated when half of the study (15 patients) have completed trimodal therapy with TTF, temozolomide, and radiation phase, with another interim analysis before proceeding to the complete enrollment of 30 patients. Revised eligibility criteria to patients 22 years of age or older to match Optune indications (as opposed to age 18 and above). Removed from eligibility: Neurologically stable for at least 14 days prior to first use of TTField therapy. This is vague and already represented by performance status. As long as a potential subject has KPS 70 or greater, they are able to participate. Added consistency: Patients with other significant cancer within the prior 3 years are excluded. Clarified compliance requirement: Patients who are using the TTField treatment less than 75% of the minimum recommended usage of 18 hours a day on average as assessed monthly (13 hours a day or less) unless per officially instituted dose

		reduction may be discontinued from therapy at the discretion of the investigator or sponsor. Changed schema to show RT dose remodeling BEFORE enrollment and now includes the 2 safety lead-ins. RT should be started within 2 weeks of starting TTF therapy (to give more flexibility to logistics of starting RT). Corrected inconsistency with steroid dosing requirements: Patients can be on high dose steroids after surgery but must have tapered down to 8mg or less of dexamethasone or bioequivalent within 7 days after enrollment. During the study, patients can be discontinued from study therapy at the discretion of the investigator, if they are requiring more than 8mg daily of dexamethasone (or bioequivalent dose) for 7 consecutive days at any given time. Dosimetry start date: March 1st, 2018. Screening start Date April 15th, 2018. PJP prophylaxis will be a recommendation only, and each site may opt to follow their institution protocols. Added clause to allow for initiation of TMZ up to 7 days after start of RT to not count as deviation. Corrected – Neuro exams at week 3 and 6 will be done alongside weekly skin exams during RT phase. Clarified use of novocure device support specialist. This is not a study procedure per se, but is standard practice for all patients on TTField therapy to have access to a device support specialist to troubleshoot use of the device and extract compliance data from the device. Given that the safety and tolerability of adjuvant therapy with ttfields combined with temozolomide was reported in EF-14, this will not be reproduced here. DLT and TRAEs will be monitored and analyzed in the window of greatest concern from start of trimodal therapy to 8 weeks after completion. The use of adjuvant TTFields with temozolomide after that will proceed as per the standard of care. Secondary endpoints (imaging response, PFS at 6 months, median OS overall and at 2 years and duration and compliance of TTF use) will continue to be monitored beyond the trimodal therapy phase. Added statement that transducer arrays must be off the skin during

		weekly skin checks in trimodal therapy to make the logistics explicitly clear.
2.1	31JAN2018	Updates to Day 1 of Cycle 2 to allow for final toxicity monitoring 8 weeks after trimodal therapy phase. Statistical considerations updated to remove redundancies and address intention-to-treat analyses.
2.2	23MAY2018	Corrected DLT review of 15 subjects to read second review instead of initial review. Added language to allow for continued enrollment in trial if study treatment is withdrawn for observational purposes to perform the intention-to-treat analysis. Corrected inclusion #13A to 3-4 weeks (21 to 28 days) for resection, 2-4 weeks (14-28 days) for biopsy. Also corrected this in the pre-treatment period text. Corrected inclusion #13B to include timing of RT start from biopsy date. Added HIV+ to exclusion #2. Clarified that both MGMT and IDH to be reviewed at each subsequent visit post screening until resulted. Removed text from study enrollment visit and treatment period that stated all study related treatments must be initiated no later than 14 days after the Day 1 clinic visit. This could be 21 days after Day 1 if all treatments started on the last day of each window in the sequence of initiating trimodal therapy section. Removed disease assessment/extent of measurable disease from Day 1 of trimodal therapy due to lack of MRI at this time point. Clarifying text added that adjuvant therapy phase falls 4 weeks after the completion of radiation therapy. Updated text to read “criteria for removal of study therapy” from “withdrawal from therapy” to reference correct protocol section title. Clarified that disease assessment/extent of measurable disease and objective response assessments at Day 1 of Cycle 2 will be based on MRI completed at Day 1 Cycle 1 due to absence of MRI at Day 1 Cycle 2, as this is the last visit of the Study Period. Added clarifying text that disease assessment/extent of measurable disease with clinical response or deterioration and objective response

		assessments to be completed during the Long-Term Follow-up Period only when an MRI was completed since last review/contact. Removed ORR assessment from Long-Term Follow-up Period since this will be calculated during data analysis, not collected per patient. Added text to dose modifications during TTField therapy to clarify when to up-titrate due to non-hematologic toxicity events and allow for investigator discretion. Appendix 3 updated to reflect above noted changes.
3.0	28AUG2018	The following revisions were made per FDA recommendations: Study Objectives: the secondary objective have been revised. Study Design: Exploratory analysis of radiation dosimetry has been clarified to occur prior to any patient enrollment Eligibility Criteria: Inclusion criterion #9 has been revised to limit consenting permissions to the patient. Exclusion criterion #16 has been added to prohibit patients allergic or unable to have gadolinium contrast dye with MRI. Exclusion criterion #17has been added to prohibit patients with aneurysm clips or implanted metal objects in the brain. Exclusion criterion #18 has been added to prohibit patients with significant skin breakdown. Clinical Trial Related Procedures; Treatment Modalities: Training of the patient on the use of Transducer Array Layout map, and the placement of arrays has been added. Dose Modifications: Guidance on skin toxicity has been updated. Radiation Therapy without interruptions: text has been updated per updated skin toxicity guidance.
3.1	10SEP2018	The following revisions were made to incorporate the clarifications from the Protocol Clarification Letter (PCL) dated 06JUN2018 that accompanied protocol version 2.2. These edits did not make it into the 3.0 version of the protocol inadvertently: Removal of PI, Ricky Chen, MD, as the Data Safety Monitoring Committee Chair. Chair responsibility will be shared by the three committee members. Clarification that the PI and study manager will facilitate the DSMC meetings as non-members.

		The lead-in phase report will be reviewed by all of the DSMC members due to the removal of the Chair. Death events will be reported to the PI, Ricky Chen, MD, or designee, Regulatory Manager, Mark Schuster, due to the removal of the DSMC Chair. Death due to disease progression need not be reported to the PI or designee, not the study monitor, as the study monitor is not the designee. The following additional edits were made: Corrected Data Safety Monitoring Board to Data Safety Monitoring Committee for consistency throughout protocol. Removed INC#8, as EXC#10 describes a different steroid taper timeframe that is more appropriate as eligibility criteria. INC#8 described discontinuation criteria. Removed INC#13B, as this describes timing of events after enrollment, so not true eligibility criteria. Timing of surgery or biopsy to enrollment and initiation of TTField, RT, and TMZ after enrollment already described. INC#13A changed to INC#13 (A and B no longer necessary).
4.0	19MAY2020	Added co-investigator from UCSF who replaced a prior co-investigator who was removed. Clarified that biopsy may be done alone without resection of GBM. Added that a post-procedure cranial CT may be used instead of an MRI if biopsy completed alone without resection if there was a MRI within 14 days pre-biopsy. This is more in line with potential imaging used as part of standard care. Removed window that this imaging must be done within 72 hours, as this is not realistic per standard care. This language also reflected in the updates made to INC#11. INC#8 changed to allow for a legally authorized representative. INC#12 window changed for surgery from 3-4 weeks to 3-6 weeks (21-28 days to 21 to 42 days). This is more in line with standard care. EXC#2 updated to include active Hepatitis B and active Hepatitis C, and clarified that these illnesses noted in criteria are by history only (not testing for them during trial, removed Hepatitis B labs from screening procedures).

		EXC#5 updated to add the language regarding prior cancer history exceptions that were previously noted in EXC#13 (now #14), as this is the more appropriate criteria to list these items. Removed from EXC#14. EXC#10 updated to clarify timeframe is calculated off of Day 1. Removed "baseline" throughout text, as this was confusing when this occurred. Moved third bullet from EXC#11 to a new criteria (new EXC#12), as non-hematological toxicity did not fit in lab abnormalities criteria. EXC#14 (prior #13) updated to clarify that significance and stability are per investigator discretion. EXC#16 (prior #15) updated since legally authorized representative now allowed. Added text that patient must be willing and able to complete study procedures, per investigator discretion. INC#19 (prior #18) updated to clarify that the significant skin breakdown is being monitored on the scalp. Added INC#20 to clarify that patients need to be able to receive standard care radiation therapy and can only receive hypofractioned radiation due to age and poor performance status, per investigator discretion. Updated anticipated start dates, as there were contract delays that delayed being able to start dosemetric testing and analysis and site activations. Reworded the screening window period for clarity, window is unchanged. Added typical turnaround time for treatment planning from Novocure (5 business days) to screening for clarity. Clarified that radiation oncology initial clinical visit and planning for therapy must be scheduled during the screening period, if not already completed at the time of screening. Scheduling required only during this time period, may occur post Day 1. Clarified that Day 1 the clinic visit, not necessarily the day TTField is started. Day 1 is when enrollment occurs. Rearranged order of treatments (TTField therapy, RT, TMZ) language from the Study Enrollment section to the Treatment Period section, as this is less confusing this way and does not need to be repeated twice in

		the protocol. Added language to the Treatment Modalities section and Clinical Trial-Related Procedures section specifying that the transducer arrays will need to be replaced at study visits that require them to be removed to complete a protocol required procedure (MRIs and skin exams at specified visits). Added language to the Treatment Period section that was present in the treatment modalities section for consistency. Added a diagram depicting the sequence of starting trimodal therapy for added clarity. Added that the procedures listed in the Trimodal Therapy, Day 1 section are to be completed before initiating TTField. Added text so order of events is clear. CBC and chemistry labs at Day 1 do not need to be repeated if these screening labs were collected within 14 days of Day 1. This eliminates the need for duplicate testing when there is not anticipated to be a significant change in that short of a timeframe. Removed phosphorus from the chemistry labs, as this is not a standard part of the site's chemistry panel and needs to be ordered separately. This is not ordered for standard care, so removed. Removed details of toxicity from TTField from skin exam at Day 1, as therapy will not have been initiated and this is not an applicable assessment at this time point. Clarified that the device support specialist may visit the patient in the clinic, not just at their home. Removed text from Day 8 that was redundant regarding when to start RT/TMZ and regarding offsetting calendar procedures, as this was not accurate considering there are windows for when to start study treatment. Removed language regarding PJP prophylaxis from the Day 8 visit and moved it to the treatment modalities TMZ section. This is a more appropriate section, as it is a recommendation and not required at a specific study visit. Added a +7 day window for continuing RT and TMZ past day 49, as clinically appropriate. This follows standard treatment.

		Clarified that the TTField compliance assessment is to be completed monthly and may not be available at each visit for review. Edit made that radiation therapy must be given within 4-6 weeks of resection or 2-4 weeks of biopsy. Added a window to each time point. Added an unscheduled visit to allow the investigator to bring patients in in case of a safety concern or the need for an additional exam. Added an early termination phone visit to in order to collect final adverse event, concomitant medication, and TTF compliance data. Updated Section 7a reference in the Evaluation of Safety section to the correct section header title. Updated contacts for serious and unexpected AE reporting, as the Regional Research Regulatory Office manager has changed, and the study manager also tracks these reports. Removed text stating protocol version number and effective date would be added to amendment after IRB review, as this is inaccurate. These items are added pre-review. Appendix 2 language updated to be reflective of the standard of care counseling for adequate birth control methods for the treatments being used in the study. Also rearranged text to list all of the methods in one section instead of being embedded across the text and list. Changed requirement to qualify as post-menopausal to natural spontaneous amenorrhea for ≥1 year only. Appendix 3 updated to reflect changes noted in main text. CTCAE updated to version 5.0 from 4.03.

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Table of Contents

List of abbreviations

A-172: Human Glioma Cell Line

CRF: Case Report Form

DSS: Device Support Specialist

ERP: Enterprise Resource Planning system

FDA: Food and Drug Administration

GBM: Glioblastoma

HR: Hazard Ratio

IR: Irradiation

IRB: Institutional Review Board

ITT: Intent To Treat

kHz: Kilo Herz

LN-18: Human Glioma Cell Line

LN-229: Human Glioma Cell Line

mA: mili Amper

NSCLC: Non-Small-Cell Lung Cancer

ORR: Objective Response Rate

OS: Overall Survival

PFS: Progression Free Survival

PR: Partial Response

RMS: Root Mean Square

SD: Stable Disease

TTFields: Tumor Treating Fields

TMZ: Temozolomide

U-87 MG: Human Glioma Cell Line

U-118 MG: Human Glioma Cell Line

V/cm: Volt/centimeter

1. OVERALL SYNOPSIS OF THE CLINICAL TRIAL

Title:	Safety and tolerability of tumor treating fields (TTFields) combined with chemoradiation in newly diagnosed glioblastoma (UNITY)
Device:	Optune™ (200kHz output frequency)
Study Objectives:	**Primary Objective:** The primary objective is to determine the safety and tolerability of using TTFields concurrent with standard fractionated radiotherapy and temozolomide (TMZ) chemotherapy followed by adjuvant therapy. **Secondary Objective:** The secondary objective is to report clinical outcomes (overall survival, progression free survival, imaging response, and duration and compliance of TTF use) after the tri-modal therapy. **Exploratory Objectives:** 1. To explore dosimetric influences of radiation delivery on dose distribution with TTFields arrays as a representation of normal treatment conditions. 2. To explore the feasibility of producing a high-quality mask for radiation planning with TTFields arrays in position. 3. To explore the source of skin toxicity.
Study Design:	The study is an open-label pilot study in newly diagnosed GBM patients following surgery. Patients (≥22 years) with histologically confirmed GBM in the supratentorial region and a KPS ≥70% are eligible to participate. Patients must have had MGMT testing performed locally for stratification purposes to participate, but specific MGMT result (positive, negative, or indeterminate) shall not be a cause for exclusion. Eligible patients will be receiving treatment with TTFields starting about 1 week prior to radiation. In addition to TTFields, they will receive radiation and temozolomide at a dose and schedule conforming to the standard of care. The expected toxicity is skin related and patients will be followed closely for weekly skin and neurological examination during the DLT window throughout radiation therapy and then for 8 weeks afterwards to capture any delayed toxicity as they begin adjuvant therapy per the standard of care. As long as tolerated and their conditions remain stable, patients shall continue the experimental therapy up to 24 months per the standard of care. The study incorporates three stages of recruitment to confirm the safety of combining TTFields therapy with concurrent chemoradiation: a safety lead-in cohort of the first 6 patients enrolled, a second safety lead-in cohort of the first 15 patients enrolled (half of the total enrollment), and an expansion cohort with 15 additional patients. For the lead-in cohorts, a safety interim analysis will be performed 4 weeks after radiation of the

	last patient and will need to pass a pre-specified stopping rule before the next stage of recruitment can begin. Safety within the DLT window and efficacy analyses will be performed on all subjects at the end of the study. An exploratory analysis of radiation dosimetry will be performed by phantom modeling incorporating the TTFields electrode arrays prior to any patients being enrolled.
Study Hypothesis:	TTFields has been shown to be safe and efficacious in large trials with glioblastoma patients in combination with adjuvant temozolomide but concurrent use together with trimodal therapy has not been examined in clinical trials. Our primary hypothesis is that the TTFields treatment, if initiated concurrently along with radiation and temozolomide therapy, would not significantly alter the safety profile. Secondarily, continuation of early initiated TTF along with adjuvant temozolomide treatment as per the standard of care would increase progression and overall survival. The primary hypothesis is safety and will be tested directly in this trial, but the secondary hypothesis would be assessed only with preliminary observations and need validation in a larger trial that is statistically powered for that investigation.
Sample Size:	30 patients total, 6 included in the first safety lead-in and 15 in the second safety lead-in.
Study Population:	Patients with newly diagnosed histologically confirmed glioblastoma after maximally safe resection, with MGMT methylation status in process, are eligible for enrollment.
Primary Endpoint:	The primary endpoint is safety and tolerability of the combined use of TTFields added to standard chemoradiation and TMZ.
Secondary Endpoints:	Our secondary endpoints will be progression-free and overall survival, imaging response by RANO criteria, and duration and compliance of TTF use.

2. IDENTIFICATION AND DESCRIPTION OF THE INVESTIGATIONAL DEVICE

a) Description of the Investigational Device and its Intended Purpose

Optune™ is intended as a treatment for adult patients (22 years of age or older) with histologically-confirmed glioblastoma multiforme (GBM).

Optune™ with temozolomide is indicated for treatment of adult patients with newly diagnosed, supratentorial glioblastoma following maximal debulking surgery and completion of radiation therapy together with concomitant standard of care chemotherapy.

For the treatment of recurrent GBM, Optune™ is indicated following histologically or radiologically-confirmed recurrence in the supratentorial region of the brain after receiving chemotherapy. The device is intended to be used as a monotherapy, and is intended as an alternative standard medical therapy for GBM after surgical and radiation options have been exhausted.

Under this clinical trial, Optune™ is also intended to be used for the treatment of newly diagnosed glioblastoma following maximal debulking surgery, however, the treatment will be initiated concurrent with (not after completion of) radiation therapy along with temozolomide.

The device is a portable, battery operated system which delivers TTFields to the patient by means of insulated Transducer Arrays (INE transducer arrays). Optune™ produces electric forces intended to disrupt cancer cell division.

b) Details Concerning the Manufacturer of the Investigational Device

The Optune™ System is manufactured by Novocure Ltd., Topaz Building, MATAM center, Haifa 31905, Israel. Novocure Ltd. is an EN ISO 13485 approved and 21CFR820 compliant medical device company developing electric field based therapy for cancer patients. Novocure's headquarters are located in Israel. Novocure GmbH is the EN ISO 13485 approved and 21CFR820 compliant Novocure Ltd global distribution center. Novocure GmbH is based in Switzerland.

c) System Parts and Their Identification

The Optune™ System is composed of several parts, which are shown in the picture below.

1 Power supply
2 Charger
3 Insulated transducer arrays
4 Device carrying bag
5 Optune™ electric field generator (the device)
6 Portable battery
7 Connection cable & box

d) Traceability

All parts of the Optune™ System are identified by a unique and personal serial number. Transducer arrays are identified by lot number. Novocure maintains traceability of all parts through paper documentation and SAP ERP:

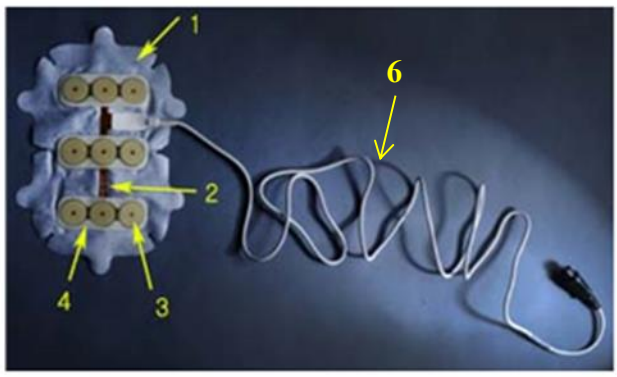
Steps	Traceability ensured by
Manufacturing	EN ISO 13485 Vendor Quality System
Receiving	SOP-USOC-002 Incoming Inspection and SAP ERP
Storage	SOP-USOC-004 Stockroom and SAP ERP
Shipping	SOP-USOC-003 Shipping- Final release and SAP ERP
Use	SAP ERP

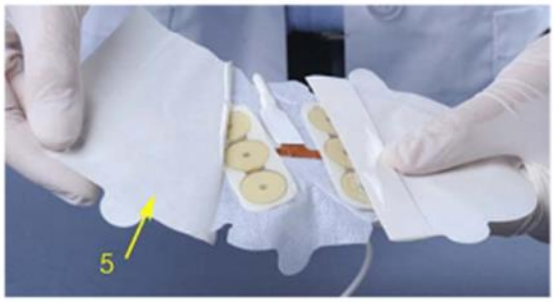
e) Intended Purpose of the Investigational Device in the Proposed Clinical Trial

The Optune™ System is intended for the treatment of newly diagnosed glioblastoma following maximal debulking surgery concurrent with chemoradiation therapy.

f) Materials That Will Be in Contact with Tissues

The INE transducer arrays are applied directly to the skin.





These arrays are sterile single use devices and incorporate the following:

	Part name	Functions
1	Cover tape	Provides adhesion of the array to patients' skin
2	INE transducer array	The array delivers the treatment to the patient and measures the temperature
3	Conductive gel layers and ceramic discs (beneath)	Gel: Ensures electric contact between the transducer array and the skin Ceramic disc: Used for the TTFields transmission
4	Mid-pads	Mechanically stabilizes the gel over the array
5	Overlapping liner	Covers the gel and the cover tape
6	Applied part cable with black connector or white connector	Connects the transducer array to the connection box

g) Training Procedures Involved in the Use of the Investigational Device

The Optune™ System is easy to use and a simple training by the Device Support Specialist (DSS) is sufficient for patients and the study team to apply the investigational device according to its intended use. No specific medical/surgical procedures are needed for the use of the investigational device.

3. SCIENTIFIC BACKGROUND RELEVANT FOR THE DESIGN OF THE CLINICAL TRIAL

a) Glioblastoma multiforme (GBM)

GBM, a malignant form of astrocytoma, is the most common of all malignant primary brain and CNS tumors. The incidence rate of GBM is 3.2 per 100,000 population. Incidence increases steadily above 45 years of age with 12,120 cases predicted in 2016 in the US. GBM is the most lethal brain tumor. Despite numerous attempts to improve the outcome of patients with GBM, only one-third of patients survive for one year and the 5-year survival rate is only 5.1 %[1].

Before the introduction of TTFields, treatment of newly diagnosed GBM was based on surgical resection with or without Gliadel Wafer implantation, radiotherapy, and temozolomide. Patients with newly diagnosed GBM who were treated with maximal surgical resection, 60 Gy radiotherapy together with temozolomide, followed by maintenance temozolomide for 6 months, had a median survival of 14.6 months[2].

Each of these treatments is briefly described below:

1. Surgical resection - Treatment of patients with GBM usually begins with resection or biopsy, with maximal safe debulking of the tumor as the main goal because curative resection is exceedingly rare.
2. Radiation therapy - Post-surgical radiation therapy has been shown to improve survival, though even with maximal treatment, survival after RT alone is still limited to about one year[2].
3. Temozolomide – Adjuvant temozolomide and radiation therapy following surgery has been shown to improve survival by about 20%. According to the temozolomide package insert adjuvant temozolomide treatment delays disease progression (from 5 to 6.9 months) and improves overall survival (from 12.1 to 14.6 months)[2].

Unfortunately, nearly all glioblastoma cases recur. At recurrence the management depends on the extent of the disease and patient's performance status. Treatment options include re-resection with or without wafer placement in the surgical bed, systemic chemotherapy, re-irradiation and TTFields.

b) Tumor Treating Fields (TTFields) Overview

TTFields are a non-invasive, regional antimitotic treatment modality with which has been approved for the treatment of recurrent and newly diagnosed GBM by the Food and Drug Administration (FDA) in the United States. The instructions for use of Optune™ can be found at: https://www.optune.com/Content/pdfs/Optune_IFU_8.5x11.pdf

TTFields act by delivering low intensity (1-3 V/cm), intermediate frequency (100-300 kHz) alternating electric fields to the tumor using non-invasive transducer arrays placed on the skin around the region of the body containing the tumor. TTFields act during mitosis by disrupting the formation of the mitotic spindle during metaphase, by impeding the normal midline

localization of septin complex in cells which have entered anaphase, inducing violent cytoplasmic blebbing and mitotic failure, and by dielectrophoretic dislocation of intracellular constituents during cytokinesis, resulting in apoptosis[3–7]. The efficacy of TTFields is frequency dependent on specific cell types. The anti-mitotic effect of TTFields has been shown in multiple cell lines when the appropriate frequency was utilized. This includes but not limited to the following tumor models: glioblastoma at 200 kHz[7], NSCLC at 150kHz[8]; breast carcinoma at 120kHz[9]; melanoma at 100kHz[10]).

The effect of TTFields is directional, i.e., TTFields are most effective when applied in the direction of the division axis of the dividing cell[3,7]. In order to increase the efficacy of TTFields, two sequential field directions can be applied to tumors by using two perpendicular pairs of transducer arrays.

c) Preclinical Results with TTFields

TTFields and Radiation Therapy

TTFields have demonstrated significant activity in *in vitro* and *in vivo* glioma preclinical models both as a single modality treatment and in combination with irradiation. Radiation therapy (RT) has significantly greater efficacy when combined with TTFields according to an evaluation that compared the surviving fraction of U-87 MG and U-118 MG cultures glioma cell cultures[11]. The combination therapy was found to be most effective when TTFields were applied immediately after exposure to RT. Aberrant DNA damage repair and extended retention of γH2AX and Rad51 nuclear foci in cells 24 hours after exposure to both modalities. Combining TTFields treatment and IR led to a further decrease in the surviving fraction for all tested radiation doses in both cell lines. Additionally, TTFields delayed DNA damage repair following irradiation induced damage[11, 19, 20]. This was achieved through inhibition of double stand DNA damage repair by homologous recombination.

Investigations using an ion chamber connected to a unidos dosemeter demonstrated that the TTFields transducer arrays absorb only a small fraction of the irradiation energy, but lead to a dramatic increase in the energy directly below the ceramic arrays that could potentially abolish the "skin sparing" effect[12]. Further experiments showed that no additional skin adverse events were observed when single irradiation dose of 10 Gy was applied to the rat head through the transducers. Skin screening revealed that irradiation through the ceramic arrays did not lead to adverse skin reactions when rats were irradiated with 2 Gy, five times a week for two weeks through ceramic arrays placed on the rat's dorsal skin.

Effects of the tumor suppressor gene p53 on TTFields

The surviving fractions of glioma cell lines expressing either wild-type p53 (A-172 and U-87 MG) or mutant p53 (U-118 MG and F-98 rat glioma) demonstrated that the application of TTFields led to a significant reduction in cell count and clonogenic potential as compared to untreated cells in both p53 wt and p53 mutant cell lines[13]. Analysis of Annexin V and Propidium Iodide expression revealed that TTFields-induced apoptosis is independent of p53 status. Caspase activity was increased in wt p53 cells following TTFields application, however no increase was

observed in mutant p53 cells. This demonstrates that TTFields exposure induces apoptosis by both p53-dependent and p53-independent pathways.

TTFields effects on cell migration

Application of TTFields in-vitro led to a significant reduction in both migratory and invasive phenotype in multiple glioma cell lines[14]. Specifically, cell migration velocity, as assessed by the wound healing assay, was significantly reduced in U-87 MG (31%, P<0.001), and in A-172 (27%, P<0.001) compared with untreated control cells. The number of invading cells, as assessed by the modified Boyden chamber assay, was reduced in U-87 MG (54%, P<0.05), A-172 (68%, P<0.05), LN-229 (38%, P<0.01) and in LN-18 (55%, P<0.05) compared with untreated control cells. These results suggest that human glioma cell motility is impaired by exposure to TTFields.

d) Clinical Results with Optune™ in Glioblastoma

Based on promising pilot data in both recurrent and newly diagnosed glioblastoma, a phase III trial was conducted in the United States and Europe to test the safety and efficacy of 200 kHz TTFields alone versus active chemotherapy in patients with recurrent glioblastoma[15]**.** The primary endpoint was overall survival. Patients (median age 54 years (range 23-80), Karnofsky performance status 80% (range 50-100)) were randomized to 200 kHz TTFields alone (n=120) or active chemotherapy control (n=117). The treatment of control arm was based on physician-selected active chemotherapy that predominantly included bevacizumab based regimens, irinotecan or nitrosurea. The median number of prior treatments was 2 (range 1-6).
Median overall survival was 6.6 vs. 6.0 months (hazard ratio 0.86 [95% CI 0.66-1.12]; p=0.27), 1-year survival rate was 20% and 20% and progression-free survival rate at 6 months was 21.4% and 15.1% (p=0.13), respectively in TTFields versus chemotherapy treated patients. Responses were more frequent in the TTFields arm (14% vs. 9.6%, p=0.19). The most common TTFields-related adverse event was mild (14%) to moderate (2%) skin irritation beneath the transducer arrays, which was again expected with use of the transducer arrays. These adverse events were effectively treated with topical hydrocortisone. Patients receiving chemotherapy had significantly more gastrointestinal, hematological and infectious complications. Quality of life analyses favored TTFields in most domains. Specifically, cognitive and emotional function were reported to be much better in the TTFields treated patients than with chemotherapy.
The results of this phase III trial demonstrated comparable efficacy with this chemotherapy-free treatment (200 kHz TTFields) to chemotherapy (including bevacizumab) in recurrent glioblastoma with a more favorable safety profile and quality of life and supported FDA approval of TTFields in recurrent glioblastoma in 2011 and a CE mark in Europe.

Registry data from 457 recurrent GBM patients who started Optune™ prescribed by the treating physician in the US between October 2011 and November 2013 showed an even higher median overall survival of 9.6 months, with baseline characteristics similar to those of patients treated under the pivotal clinical trial[17]. The 2-year survival rate in this population was 30% (compared to 9% in Optune™-treated patients on the clinical trial). Compliance was a clear predictor of survival on Optune™, and patients treated with the device for at least 18 hours per

day had significantly longer survival time. No new safety signals have been detected in this registry dataset and the only common adverse event related to Optune™ was dermatitis. Based on this clinical data in recurrent GBM and a pilot trial in newly diagnosed GBM with Optune™ in combination with temozolomide that demonstrated favorable safety profile and promising efficacy, an international phase III trial in newly diagnosed GBM, evaluating the role of Optune™ in combination with temozolomide maintenance after surgery and chemoradiation versus temozolomide alone was conducted[14]. An interim analysis included 210 patients randomized to TTFields plus temozolomide and 105 randomized to temozolomide alone, and was conducted at a median follow-up of 38 months (range, 18-60 months). Median progression-free survival in the intent-to-treat population was 7.1 months (95% CI, 5.9-8.2 months) in the Optune™ plus temozolomide group and 4.0 months (95% CI, 3.3-5.2 months) in the temozolomide alone group (hazard ratio [HR], 0.62 [98.7% CI, 0.43-0.89]; P = .001). Median overall survival in the per-protocol population was 20.5 months (95% CI, 16.7-25.0 months) in the Optune™ plus temozolomide group (n = 196) and 15.6 months (95% CI, 13.3-19.1 months) in the temozolomide alone group (n = 84) (HR, 0.64 [99.4% CI, 0.42-0.98]; P = .004). Quality of life and gross cognitive function were also comparable in the 2 arms[18].

Based on the data submitted to FDA from this newly diagnosed GBM study, FDA approved Optune™ in combination with temozolomide for the treatment of adult patients with newly diagnosed GBM on October 5, 2015. In the US, Optune™ with temozolomide is indicated for the treatment of adult patients with newly diagnosed, supratentorial glioblastoma following maximal debulking surgery and completion of radiation therapy together with concomitant standard of care chemotherapy.

e) Rationale for Conducting the Clinical Trial

Glioblastoma is the most common and deadly of the primary brain cancers in adults with a prevalence of 50,000 patients currently living with the disease[21]. Despite aggressive treatment with maximal surgical resection, radiotherapy and temozolomide, overall survival for most patients is limited on average to 14.6 months from diagnosis[22.] Tumor treating fields (TTFields) is a novel therapy that was initially approved by the FDA for recurrent glioblastoma in place of standard medical therapy in 2011 based on the results of an open-label phase III trial (EF-11) showing comparable survival to physician's choice chemotherapy[23]. Subsequently, another open-label phase III trial (EF-14)[24] showed a survival benefit of adding TTFields therapy to adjuvant temozolomide chemotherapy after standard chemoradiation. The mature data was presented recently[25]; the group that received maintenance TTFields therapy in addition to temozolomide had a median overall survival (OS) from diagnosis of 24.5 months compared to 19.8 months with temozolomide alone; 2-year OS rates were 42.5% and 30% respectively. This effect was statistically significant and irrespective of MGMT methylation status, age, extent of resection, or performance status. Investigators have demonstrated the mechanism of TTFields' antineoplastic effect involving disruption of microtubule polymerization and formation of mitotic spindles, leading to mitotic catastrophe, aneuploidy, and subsequent cell death.[26] However, TTFields also appears to induce apoptosis via activation of multiple immunogenic molecular pathways.[27] Given the apparent improvement in survival using this device in newly

diagnosed patients with glioblastoma post radiation and the potential synergy with radiation in preclinical studies, this study aims to investigate the safety and tolerability of using the TTField therapy concurrent with chemoradiation.

4. RISKS AND BENEFITS OF THE INVESTIGATIONAL DEVICE AND CLINICAL TRIAL

The risks associated with use of the Optune™ System are principally electrical or mechanical failure leading to electrical shock, electromagnetic interference, as well as the risk that the treatment will not be effective in delaying tumor progression or causing regression. Additional risks include skin irritation, and skin breakdown or infection at electrode sites. Technical failure is extremely unlikely due to stringent compliance with all standard design and manufacturing safety protocols. In addition, appropriate measures have been taken to minimize the risk to study subjects, including preclinical *in vitro* and *in vivo* testing to ensure safe operation of the device.

The use of TTFields in glioblastoma has been used safely in combination with temozolomide after radiation therapy in EF-14. Although mild to moderate skin irritation was common (43%), severe reactions were rare (2%). Other mild anxiety, confusion, headache, and insomnia were more frequent with the addition of TTFields to temozolomide but occurred mostly at initiation of therapy[24]. The risk of seizures was not increased with the addition of TTFields. Thus, TTFields has been shown to be safe in large trials with glioblastoma patients in combination with adjuvant temozolomide. However, in EF-14, the patients did not start TTFields until after radiation therapy. There have been no clinical trials to date using TTFields during radiotherapy with concurrent temozolomide. In preclinical studies, glioma cells that had been treated with the combination of radiation therapy (RT) and TTFields exhibited a greater fraction of double strand breaks with aberrant DNA damage repair compared with either modality alone[28]. Given the synergism with RT, combined treatment may increase the efficacy of TTFields therapy to enhance its proven survival benefit for patients with newly diagnosed GBM.

There are certain technical and safety considerations if patients are to be treated with electrodes in place. During TTFields therapy, patients are allowed brief periods unplugged from the device. In the general course of radiation therapy, the actual delivery of radiation dose at each treatment visit is no more than 15 minutes. Patients can thus turn off and unplug their TTFields device while undergoing radiotherapy with the electrodes remaining in place to prevent possible interference and damage to their device. Studies of radiation therapy in patients with cardiac devices, such as pacemakers and defibrillators, have shown that we can expect a certain amount of electromagnetic noise created by RT delivery, that while potentially detrimental to circuit boards, RAM, and transistors[29,30], are unlikely to produce permanent damage to simpler components such as wiring and electrodes. With the array adherent to the scalp, one has to consider potential interference with the radiation dosimetry (See *Study Design*) and possible interference with the sculpting of a high-quality radiation mask. Given that a small degree of attenuation is likely, we will perform measurements for reference.

Treatment-associated inflammation, edema, or necrosis is a known risk of radiation therapy and temozolomide, occurring in a percentage of patients with newly-diagnosed glioblastoma undergoing standard therapy, with some series reporting 14 out of 51 patients having MRI or pathological evidence of this phenomenon (the true incidence remains uncertain due to difficulties in imaging interpretation).[31] This is often an asymptomatic and self-limited process which can be mitigated with corticosteroids. The addition of TTFields to concurrent radiation and temozolomide chemotherapy has not been tested. However, per the EF-14 trial, in which TTFields was started only 4 weeks after radiation and combined with adjuvant temozolomide, there was no significant increase in treatment associated effects. The standard of care requires a post-radiation therapy MRI scan approximately 4 weeks after completing initial chemoradiation, included also in our study, which can identify treatment-related effects that can be treated with corticosteroid therapy. If this process is excessive, requiring more than 8mg of dexamethasone daily for 7 consecutive days or produce significant neurologic dysfunction, then treatment may be discontinued per investigator judgment for patient safety. Beyond the risks of study therapy exposure, other risks of study participation include additional visits and examinations, vital signs, blood draws for screening and for toxicity evaluation during the radiation period. Otherwise, MRI scans and quantity of subsequent visits, radiation and temozolomide chemotherapy received are the same as the standard of care.

Alternatives to this intervention include proceeding with the standard of care treatments and procedures for glioblastoma. Although the use of TTFields in the adjuvant setting has improved the survival for newly diagnosed patients, the prognosis remains poor, which is the rationale for conducting this trial.

The potential benefits of the therapy are promising. Tumor treating fields have improved survival for patients with newly diagnosed glioblastoma when added to temozolomide as maintenance therapy after standard chemoradiation. This has led to a modest but true benefit in overall survival on the order of months, leading to FDA approval of the device for use in newly diagnosed patients. Emerging preclinical data suggests that TTFields acts not only through disruption of mitotic apparatus but may lead to impairment of DNA repair and increased DNA double strand breaks in tumors after recent irradiation. TTFields has been used concurrently with TMZ and proven to be safe and well-tolerated as a maintenance therapy after radiation, but has not been used in combination with TMZ during radiation.

5. OBJECTIVES OF THE CLINICAL TRIAL

Purpose and Objectives

Purpose

The results from the proposed study will lay a necessary foundation from which to launch a large phase II clinical trial to determine the efficacy of tumor treating fields in synergy with standard chemoradiation for newly diagnosed glioblastoma. If successful, this may eventually lead to a more meaningful enhancement of survival prolongation in this devastating cancer.

Primary Objective

1. To determine the safety and tolerability of using TTFields with standard fractionated radiotherapy and temozolomide in newly diagnosed glioblastoma patients.

Secondary Objective

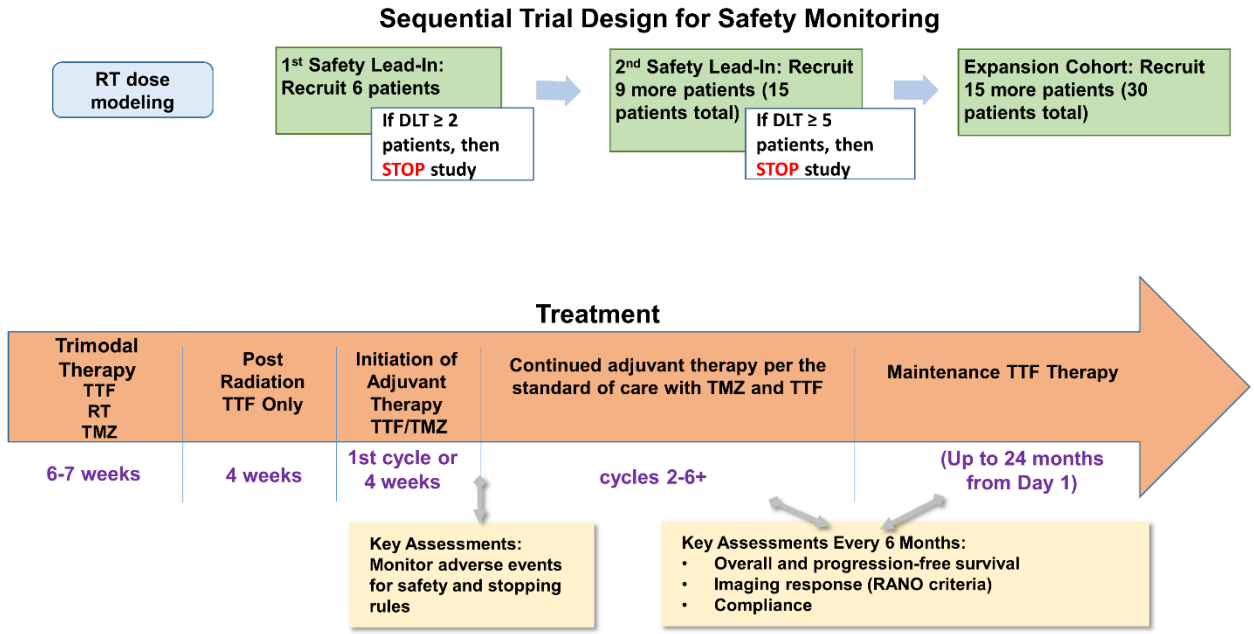
1. To observe clinical outcomes (overall survival, progression-free survival, imaging response, and duration and compliance of TTF use) of using TTFields and temozolomide in the upfront setting with concurrent radiotherapy followed by maintenance therapy with TTFields and temozolomide.

Exploratory Objectives

1. To explore dosimetric influences of radiation delivery on dose distribution with TTFields arrays as a representation of normal treatment conditions.
2. To explore the feasibility of producing a high-quality mask for radiation planning with TTFields arrays in position.
3. To explore the source of skin toxicity.

6. DESIGN OF THE CLINICAL TRIAL

Schema



General Study Design

This is a dual institution open-label, single arm, 3 stage, phase I trial of a medical device (TTFields) in newly diagnosed glioblastoma after maximal safe resection with the primary objective of determining safety.

Radiation dosimetry and mask modeling

Prior to the start of the study, a radiation dosimetry assessment and trial mask production will be performed. This serves as a preliminary safety and quality check. Using a phantom with a TTFields array in place on a medical linear accelerator, we will model the dosimetric impact of having the TTFields electrodes on the scalp at the time of RT delivery, as well as impact on the device operation. There may also be a small amount of scatter that may draw out dose superficially and cause increased skin toxicity. However, whether this would result in increased graded toxicity from routine use of TTFields therapy is unclear.

In the process of radiation planning, CT simulation involves production of a high-quality immobilization mask and acquisition of a non-contrast head CT from which to overlay the treatment maps for precise targeted radiation delivery. The presence of the scalp electrodes is expected to have minimal impact on the production of an immobilization mask, as the position of the electrodes would most likely not change from day to day. The immobilization setup can readily accommodate patients with long and dense hair, and will be able to accommodate the thin electrode pads on a shaved head. We perform daily image guidance with cone-beam CT for setup adjustment, so we can compensate for small variations in daily patient position in the mask. Finally, the presence of the electrodes may introduce image signal artifact in the planning CT scan. Prior to the study, we will analyze CT scans acquired on the phantom model for evidence of artifact and measure the signal to noise ratio and the change, if any, on Hounsfield units of normal tissues and structures imaged.

Safety Lead-ins

To form a reasonable basis of safety for enrolling the expansion cohort of patients, this study will incorporate two safety lead-ins using the first 6 patients and the first 15 patients (50% of the expected total number of patients) to assess the feasibility, safety and tolerability of combining TTFields therapy with concurrent chemoradiation (concurrent enrollment allowed). The safety cohorts will receive TTFields therapy in addition to standard of care. Variations in daily patient positioning will be recorded. Any treatment related adverse effects will be measured, assessed, and graded during the dose-limiting toxicities (DLT) period, from the beginning of therapy until 8 weeks after completion of radiation therapy to capture any potential delayed toxicity following combination (Trimodal) therapy with radiation, temozolomide, and TTFields therapy. DLT include any severe or life-threatening treatment-related adverse effects that preclude further administration of the study treatments, such as radiation, temozolomide, or continuation of TTFields therapy. The DLT assessment period will be limited to the time from start of TTFields through 8 weeks after RT's completion.

The first lead-in cohort will include the first 6 patients to finish the DLT period and be assessed by investigators. If a DLT occurs in 2 or more of the 6 patients, then the study will not move forward and may re-consider the goal dose of TTFields therapy in the main cohort to be reduced by 50% (one out of every two weeks off) and only increased to the standard usage of

continuous treatment 4 weeks after completion of radiation therapy. If a DLT occurs in less than two patients, the study will proceed with the second safety lead-in.

The second lead-in cohort will include the first 15 patients (6 from the first lead-in and 9 additional) to finish the DLT period and be assessed by the Data Safety Monitoring Committee (DSMC). If a DLT occurs in 5 or more of the 15 patients in the second safety cohort, then the study will not move forward with the expansion cohort and may re-consider the goal dose of TTFields therapy in the main cohort to be reduced by 50% (one out of every two weeks off) and only increased to the standard usage of continuous treatment 4 weeks after completion of radiation therapy. If a DLT occurs in less than five patients, the study will proceed with the final expansion cohort.

After screening and enrollment, the expanded cohort of subjects will be treated with radiation, temozolomide, and TTField therapy for 6 weeks akin to the safety lead-ins. The primary endpoint of treatment related adverse event (TRAE) rate and severity will be recorded and graded based on the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 and DLT as defined in this protocol. The CTCAE v5.0 criteria can be found at: https://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_5x7.pdf Building on the already published long term safety data of combining TTField therapy with adjuvant TMZ after radiation therapy, this phase I study aims to assess the safety and tolerability of the device when used with concurrent radiation and TMZ at the initial postoperative or postbiopsy setting. Thus, the toxicity window for the primary endpoints of this study will start when subjects begin combined trimodal therapy (TTFields, RT, and TMZ) and end 8 weeks after completion of the trimodal therapy. After this time, TRAEs and DLTs are not monitored as part of the study endpoints because long term safety of adjuvant TTFields along with TMZ after radiation has been established in the preceding EF-14 trial. After completion of the DLT window, we will analyze and report on the safety and tolerability of combining TTField therapy with radiation and temozolomide prior to adjuvant therapy. We will report on those findings as well as preliminary survival trends that were observed after final completion of the study.

During the initial trimodal therapy phase, all subjects will receive weekly skin exams along with repeat neurologic exams at Day 22 and Day 43 while chemoradiation is underway. After completion of initial chemoradiation, they will have a 4-week hiatus from TMZ chemotherapy but will continue TTField therapy. After the hiatus, an MRI will be performed and TMZ will then be resumed for a minimum of 6 cycles of adjuvant therapy (along with continued TTField therapy for up to 2 years as tolerated) with appropriate laboratory monitoring per the standard of care.

Two weeks after trimodal therapy, patients will receive a skin exam, scalp assessment and neurologic exam at Day 64 and will also be monitored at 4 weeks (Day 1 of Cycle 1 of adjuvant TMZ) and 8 weeks (Day 1 of Cycle 2 of adjuvant TMZ) after trimodal therapy to assess for post treatment toxicity that may be delayed. After conclusion of the DLT window, the treatment of

patients will be carried out per the standard of care in addition to continued TTFields therapy, as outlined in the clinical trial-related procedures section. The trial will then follow the clinical outcomes including duration of TTF use, completion of 6 cycles of temozolomide, and progression free survival at 6 months, and median overall survival and overall survival at 2 years.

Primary Study Endpoints

- Rate of treatment-related adverse events (TRAE)
- Rate of treatment-related severe adverse events (TRSAE)
- Rate of Dose-limiting toxicity (DLT)

Given that the primary objective of this study is to determine the safety and tolerability of adding TTField therapy to combined chemoradiation, our primary endpoints are related to safety as follows: Identify the rate of treatment-related adverse events as well as the rate of any severe adverse events during the combined treatment period and up to 8 weeks afterwards. For the same time frame, we will also document and assess the rate of dose-limiting toxicities. Safety of combined adjuvant treatment with TTFields and TMZ chemotherapy outside of the initial radiation is not a primary objective and will not be formally assessed in this study. The above endpoints will be assessed initially in the interim safety analyses involving the safety lead-in cohorts and then also in the main expanded cohort for the final analysis. See statistical methods for further details of the planned analysis. For any skin toxicity grade II or greater, we will also investigate and document, if apparent, whether this was related to the adhesive vs the ceramic disc component of the device.

Secondary Study Endpoints

- PFS6
- Overall survival (median OS and rate of OS at 2 years)
- Objective response by modified RANO criteria
- Median duration of TTFields use and rate of TTF compliance

Secondary endpoints of this study will provide a preliminary assessment of clinical outcomes by estimating the PFS6 of TTField therapy plus radiation and TMZ chemotherapy followed by adjuvant TMZ for at least 6 cycles and continuous TTField therapy for up to 24 months. Since use of TTField therapy has been deemed safe and is FDA approved in the post-radiation adjuvant therapy setting, treatment will be pursued using standard of care, as outlined in the treatment modalities section. Median OS and rate of OS at 2 years will be analyzed for all subjects that start the TTField therapy along with radiation and chemotherapy. Objective response to therapy will also be assessed by modified RANO criteria (see appendix). The rate of TTFields compliance will be the percentage of patients who used TTFields at least 75% of the minimum recommended usage of 18 hours a day on average, as assessed monthly. Given the limitations of this small phase I study, these secondary endpoints will not be powered for statistical significance but will provide basic trends as a foundation for further study of efficacy

in future phase II/III trials. The above endpoints will be assessed for all patients in the final analysis.

Subject Selection and Withdrawal

The study will enroll subjects with newly-diagnosed glioblastoma (GBM), following surgical resection of the tumor. After informed consent is obtained, subjects will be screened for eligibility based on the outlined inclusion and exclusion criteria. Prospective participants must have had a contrast-enhanced brain MRI post-tumor resection procedure. If the subject had a biopsy alone without resection, a cranial CT may be used instead of a MRI, provided they had a preoperative MRI scan within 14 days of biopsy. Screening can occur after this post-operative imaging is completed.

If a subject stops study treatment on or before Day 1 of Cycle 2 of the Adjuvant TMZ Therapy Phase, they many continue in the trial for observational purposes, if willing, in order to perform the intention-to-treat analysis.

Eligibility Criteria

Patients with the following characteristics will be eligible in the clinical trial:

<u>Inclusion Criteria:</u>

1. GBM or Gliosarcoma by histology
2. MGMT methylation status and IDH mutation status must be assessed at the study site or patient's referral center. MGMT status will be used for stratification purposes but will not exclude patients from this study if they are either methylated, unmethylated, or indeterminate, or in process at the time of enrollment. Similarly, subjects with tumors that are IDH mutated or wild type are both eligible.
3. Supratentorial location
4. Maximum safe resection (including patients who can only safely be biopsied)
5. 22 years of age or older
6. Estimated survival of at least 12 weeks
7. KPS 70% or greater at time of entry to study
8. Patient provided written informed consent, or provided by a legally authorized representative
9. Willingness to comply with all procedures, including visits or evaluations, imaging, laboratory tests and rescue measures
10. Acceptable method of birth control (see appendix)
11. Have had a contrast-enhanced brain MRI after tumor resection procedure. If biopsy alone performed, cranial CT may be used in place of MRI, only if the patient had a preoperative MRI scan within 14 days of the biopsy.

12. The following time period must have elapsed prior to study enrollment: 3-6 weeks (21-42 days) from time of definitive surgery or 2-4 weeks (14-28 days) from the time of biopsy, for those who were only able to safely have a biopsy and not full resection.

Exclusion Criteria:

1. Craniotomy or stereotactic biopsy wound dehiscence or infection
2. Known by history to be HIV positive or to have an AIDS-related illness, active Hepatitis B, or active Hepatitis C (testing not required)
3. Presence of skull defects (bullets, metal fragments, missing bone)
4. Patients with implanted electronic medical devices (including but not limited to: pacemaker, vagal nerve stimulator, or pain stimulator)
5. Prior invasive malignancy, unless disease free for 3 or more years, with the exception of basal cell carcinoma, cervical carcinoma in situ, or melanoma in situ
6. Recurrent malignant gliomas or higher grade gliomas transformed from previous low grade (II) glioma
7. Patients with any current Primary brain stem or spinal cord tumor
8. Prior use of temozolomide
9. Prior treatment with Avastin
10. Individuals requiring >8mg of dexamethasone per day within 7 days prior to Day 1 (high dose steroid taper following craniotomy with >8mg of dexamethasone is allowed during the screening period, but subjects must taper down to 8mg or less of dexamethasone (or bioequivalent) within 7 days prior to Day 1).
11. Clinically significant lab abnormalities at screening showing bone marrow, hepatic, and renal dysfunction:
    - Thrombocytopenia (platelet count < 100 x 10^3/µL)
    - Neutropenia (absolute neutrophil count < 1.5 x 10^3/µL)
    - Significant liver function impairment - AST or ALT > 3 times the upper limit of normal
    - Total bilirubin > upper limit of normal
    - Significant renal impairment (serum creatinine > 1.7 mg/dL)
12. CTC grade 4 non-hematological Toxicity (except for alopecia, nausea, vomiting) at screening
13. Inability to swallow pills
14. Clinically significant or unstable comorbid medical condition, per investigator discretion (for example, active or uncontrolled infection requiring systemic therapy, including known HIV or hepatitis B or C virus)

15. Known current alcohol or drug abuse, per investigator discretion. Prior history of substance abuse is permissible if subject has been sober for the past 3 years.
16. Any clinically significant psychiatric condition that would prohibit patient willingness or ability to successfully complete study procedures, per investigator discretion
17. Patients with an allergy to or an inability to have gadolinium contrast dye administered with MRI
18. Patients with aneurysm clips or implanted metal objects in the brain
19. Patients with significant skin breakdown on the scalp
20. Patients who cannot receive standard of care radiation therapy and can only receive hypofractionated radiation due to age and poor performance status , per investigator discretion

Criteria for Removal from Study Therapy

Criteria for removal from study therapy include:

1. **Patient request** - The patient may withdraw from the study at any time.
2. **Intolerable toxicity** - Patients may discontinue therapy for intolerable adverse events attributable to the device. Any serious adverse event deemed life threatening by the treating physician that is definitely related to the study device will be cause for immediate cessation of treatment.
3. **Investigator judgment, progression** – Investigator confirmed tumor progression by study criteria.
4. **Investigator judgment, safety** – Investigator may discontinue treatment due to concerns of safety. This includes significant neurological decline during treatment or requirement of steroids beyond the daily limit of 8mg of dexamethasone or bioequivalent dose for more than 7 consecutive days.
5. **Lack of compliance** - The Sponsor or investigator may remove a patient from study therapy for lack of compliance to the study protocol. Patients who are using the TTField treatment less than 75% of the minimum recommended usage of 18 hours a day on average, as assessed monthly (13 hours a day or less), unless per officially instituted dose reduction, may be discontinued at the discretion of the investigator or sponsor.
6. **Inter-current illness** – Illness that prevents further administration of treatment.

<u>Enrollment Plan</u>

a) Anticipated Start Date

- Dosimetric testing and analysis planned for September, 2019.
- Screening planned to begin November, 2019.

b) Total Expected Duration of the Clinical Trial

Anticipated duration of the trial will be 36 months from start of screening to completing two year long-term follow of the last patient enrolled.

c) Expected Duration of Each Subject's Participation
Up to 24 months from subject screening date to the point of study discontinuation based on specified criteria above or completion of the clinical trial.

e) Estimated Time Needed to Select the Required Number of Subjects (*i.e.,* Enrollment Period)
The anticipated initial enrollment period for the 6 subjects in the lead-in cohort will be 4-8 weeks, with 3 subjects from each of the 2 study sites.

Following the interim analysis of safety for the lead-in cohort, there will be an expansion of enrollment to 15 patients, followed by another safety stop and interim analysis. The final cohort will comprise a total of 30 patients between the 2 participating sites. At least 1/3 of the subjects will be enrolled from each of the 2 study sites to ensure even enrollment (i.e., at least 10 subjects at each site). Anticipated duration for subject enrollment will be 6 to 12 months from start of screening to last subject enrolled in study.

Clinical Trial-Related Procedures
The study-specific assessments are detailed in this section and outlined in the Appendix 3 Study Calendar. Screening assessments must be performed within 21 days prior to the first treatment with investigational product. Any results falling outside of the reference ranges may be repeated at the discretion of the investigator. All study visit procedures are allowed a window of ±7 days unless otherwise noted. Treatment or visit delays for public holidays or weather conditions do not constitute a protocol violation.
A written, signed, informed consent form (ICF) must be obtained before any study-specific assessments are initiated. A signed copy of the signed ICF will be given to the subject and a copy will be filed in the medical record. The original will be kept on file with the study records. All patients who are consented will be entered in the Providence Brain and Spine Institute's password protected clinical trial management system (CTMS), Velos. Velos will also be used by the study sites as an electronic data capturing system to enter study data.

Pretreatment Period

Subject Recruitment & Screening
Potential subjects will be recruited from the investigators' and subinvestigators' clinical practices. Every effort will be made to preserve subject confidentiality according to each site's policies and limit the use of protected health information in accordance with the requirements of the Health Insurance Portability and Accountability Act of 1996 (HIPAA). The study sites will also make efforts to recruit and retain women and members of minority groups in order to reflect the composition of the adult U.S. population as closely as possible with regard to age, gender, ethnicity and race.

Pre-Study
Prospective participants must have had a contrast-enhanced MRI post-tumor resection procedure. If the subject had a biopsy alone without resection, a cranial CT may be used

instead of a MRI, provided they had a preoperative MRI scan within 14 days of biopsy. Screening can occur after this post-operative imaging is completed.

1. Screening can occur after this post-operative MRI.
2. Have had tumor resection surgery at day -42 to day -21 or stereotactic biopsy at day -14 to day -28. Patients who were only able to have a biopsy safely and not full resection have a shorter window from procedure date to Day 1.
3. Prospective participants will be pre-screened for the above inclusion and exclusion criteria. They will then undergo a screening pretreatment evaluation.

Screening

The following Screening procedures and assessments will start between Day -21 and Day 0.

- Obtain informed consent
- Vital signs: height (only at screening), weight, temperature, pulse, respiration rate, and resting blood pressure
- Demographic collection. To include: date of birth, gender, race, ethnicity, and education level
- Physical examination including neurologic exam and head and neck exam to evaluate surgical healing and contraindications to radiation and TTField therapy
- Complete medical history, including all prior and current conditions at the time of screening
- Smoking, alcohol, and substance use history
- Documentation of pathology proven glioblastoma or gliosarcoma
- Documentation of disease assessment, status and extent of measurable disease on imaging
- KPS (performance) assessment
- History of prior treatments and any residual toxicity relating to prior treatment
- Concomitant medication review and prior medications taken within 7 days of Day 1
- Confirmation of MGMT testing in process. If results are in process at time of screening, review at each subsequent visit until resulted.
- Documentation of IDH mutation status by immunohistochemistry or genetics. This is for classification of the tumors but not an exclusion criteria. If results in process at time of screening, review at each subsequent visit until resulted.
- Complete blood count (CBC) with differential and platelet count
- Blood chemistry assessment, including:
    - Alkaline phosphatase, aspartate aminotransferase/alanine aminotransferase (ALT/AST), total bilirubin, calcium, blood urea nitrogen (BUN), creatinine, total protein, albumin, fasting glucose, potassium, sodium, chloride, bicarbonate

- Coagulation assessment, including prothrombin time, partial thromboplastin time, international normalized ratio (PT/PTT/INR)
- Serum or urine pregnancy test (for women of childbearing potential)
- Confirmation of imaging (MRI) of the brain for tumor/lesion completed during pre-study period
- Review of Imaging (MRI) of the brain for tumor/lesion assessment, including collection and review of prior relevant brain MRIs
- Patient imaging will be sent to Novocure for treatment planning using NovoTAL™ and determining the appropriate transducer array layout. This must be done within 14 days prior to Day 1 (typically requires 5 business days). Patients will be trained by the investigator or the device specialist on the placement of the arrays.
- Electrocardiogram (ECG) at screening only. To be collected and read by cardiology department.
- Documentation of seizure frequency along with type of seizure (generalized or partial) and/or headache severity and frequency
- Scheduling of radiation oncology initial clinical visit and planning for therapy, if not already completed at the time of screening. Radiation oncology clinical visit is per standard of care.
- Adverse events to be assessed beginning after time of informed consent
- Eligibility assessment

Study Enrollment

Once the subject has been scheduled for radiation oncology planning and all eligibility criteria are met, the subject will be able to move to the Day 1 clinic visit for enrollment into the trial.

- RT and TMZ are to be initiated after the clinic visit. **TTField therapy can be initiated either that same day or no more than 7 days from the Day 1 clinic visit.**
- For this purpose, the staff will also coordinate with Novocure for a Device Support Specialist (DSS) trained by Novocure to initiate treatment either in clinic or at the subject's home within the above time frame.

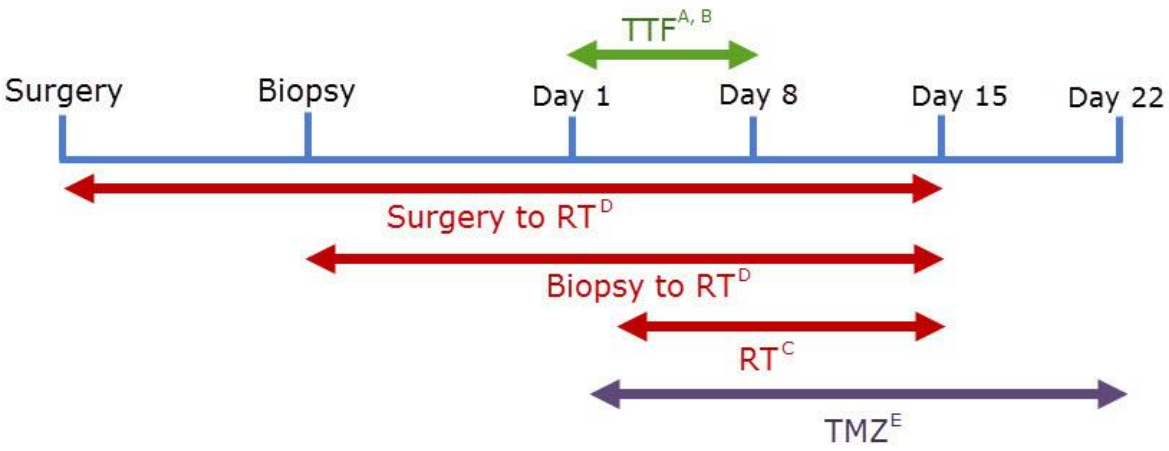
Treatment Period

Study Procedures, Trimodal therapy phase – Day 1 of treatment is marked by the Day 1 clinic visit, just prior to initiation of trimodal therapy.

- The following guidelines should be observed regarding the **sequence of initiating trimodal therapy:**
    - TTField therapy can start as soon as the same day as the day 1 clinic visit, no more than 7 days after the day 1 visit, and up to 14 days before RT/TMZ initiation.

- **TTField therapy must be initiated prior to RT simulation and mask preparation.**
  - Preferably, patients would have the TTF initiated for a few days **prior to** radiation therapy to adjust for user errors and patient issues.
- RT should be initiated no more than 14 days after the day 1 visit. Subjects will receive radiation therapy within 4-6 weeks of their surgical resection or 2-4 weeks of their biopsy for the purpose of ensuring proper wound-healing.
- TMZ treatment should also be coordinated to start on the first day of RT, but starting no more than 7 days after start of RT is acceptable and will not be recorded as a treatment delay. TMZ may start within 24 hours before RT, per investigator discretion.

Sequence of Starting Trimodal Therapy



[A] TTField therapy can start as soon as the same day as the day 1 clinic visit, no more than 7 days after the day 1 visit (Day 1 to Day 8), and up to 14 days before RT/TMZ initiation.

[B] TTField therapy must be initiated prior to RT simulation and mask preparation. Preferably, patients would have the TTF initiated for a few days prior to radiation therapy to adjust for user errors and patient issues.

[C] RT should be initiated no more than 14 days after the day 1 visit (by Day 15).

[D] Subjects will receive radiation therapy within 4-6 weeks of their surgical resection or 2-4 weeks of their biopsy for the purpose of ensuring proper wound-healing.

[E] TMZ treatment should also be coordinated to start on the first day of RT, but starting no more than 7 days after start of RT is acceptable and will not be recorded as a treatment delay (by Day 22). TMZ may start within 24 hours before RT, per investigator discretion.

During this phase, study procedures should be completed +/- 7 days from the Day specified unless otherwise noted.

During this phase, patients will undergo weekly skin checks by radiation oncology or neuro-oncology. Transducer arrays must be off the skin in order to perform a careful examination of the skin for toxicity. The patient and physician needs to time the changing of transducer arrays such that the arrays are not worn during weekly visits. The same practice applies to skin checks after the trimodal therapy phase and during adjuvant treatment per the standard of care.

Trimodal therapy, Day 1 (21-42 days from surgery or 14-28 days from stereotactic biopsy)

The following procedures are to be completed on Day 1 prior to TTField initiation:

- Vital signs: weight, temperature, pulse, respiration rate, and resting blood pressure.
- Physical examination including neurologic exam, head and neck exam, and scalp exam to evaluate surgical healing and contraindications to radiation and TTField therapy.
- Adverse event assessment
- Concomitant medication review
- KPS (performance) assessment
- Complete blood count (CBC) with differential and platelet count (if completed for screening within 14 days of Day 1, does not need to be repeated)
- Blood chemistry assessment, including (if completed for screening within 14 days of Day 1, does not need to be repeated):
    - Alkaline phosphatase, aspartate aminotransferase/alanine aminotransferase (ALT/AST), total bilirubin, calcium, blood urea nitrogen (BUN), creatinine, total protein, albumin, fasting glucose, potassium, sodium, chloride, bicarbonate
- Documentation of seizure frequency along with type of seizure (generalized or partial) and/or headache severity and frequency.
- Eligibility assessment
- Skin examination by investigator or subinvestigator

When the above procedures are completed, TTField therapy may be initiated:

- TTField therapy (see treatment modalities for detailed description of treatment and parameters) will be initiated by the investigator by calling the device support specialist to confirm the patient is ready. The Device Support Specialist (DSS) will visit the patient in their home or in the clinic and initiate treatment with TTField therapy (Accounting for scheduling, treatment initiation within 7 days from the Day 1 visit is acceptable and will not be marked as treatment delay).

Day 8 of Trimodal therapy

- Skin examination by investigator or subinvestigator in Radiation Oncology or Neuro-Oncology (document attribution, grade of toxicity, and if there is apparent correlation with the ceramic disc or adhesive gel on the transducer arrays). Treatment of mild skin toxicity as appropriate. If there are concerns of worsening skin toxicity, treatment break from Optune or consider referral to dermatologist for specialist evaluation (transducer arrays will need to be removed/replaced for exam).
- Complete blood count (CBC) with differential and platelet count
- Adverse event assessment

- Concomitant medication review
- Continuation of TTField Therapy
- Initiate radiation therapy in accordance with standard of care as detailed under treatment modalities.
- Initiate daily TMZ chemotherapy ideally on the same day as radiation in accordance with standard of care as detailed under treatment modalities. TMZ initiation up to 7 days after start of RT is permissible and will not be deemed a deviation.
- In addition to clinic visits and instruction, the patient also has access to device support specialist for routine skin care issues as part of the standard of care for patients on active treatment with tumor treating field therapy. In between visits, the patient will be asked to report any notable skin toxicity to their neuro-oncologist office.

Day 15 (±7 days)

- Skin examination by investigator or subinvestigator in Radiation Oncology or Neuro-Oncology (document attribution, grade of toxicity, and if there is apparent correlation with the ceramic disc or adhesive gel on the transducer arrays). Treatment of mild skin toxicity as appropriate. If there are concerns of worsening skin toxicity, referral to dermatologist for specialist evaluation (transducer arrays will need to be removed/replaced for exam).
- Complete blood count (CBC) with differential and platelet count
- Adverse event assessment
- Concomitant medication review
- Continuation of TTField Therapy
- Continuation of RT
- Continuation of TMZ therapy

Day 22 (±7 days)

- Skin examination by investigator or subinvestigator in Radiation Oncology or Neuro-Oncology (document attribution, grade of toxicity, and if there is apparent correlation with the ceramic disc or adhesive gel on the transducer arrays). Treatment of mild skin toxicity as appropriate. If there are concerns of worsening skin toxicity, referral to dermatologist for specialist evaluation (transducer arrays will need to be removed/replaced for exam).
- Neurological examination by investigator or subinvestigator in Radiation oncology or Neuro-oncology.
- Complete blood count (CBC) with differential and platelet count
- Adverse event assessment
- Concomitant medication review

- Continuation of TTField Therapy
- Continuation of RT
- Continuation of TMZ therapy

Day 29 (±7 days)

- Skin examination by investigator or subinvestigator in Radiation Oncology or Neuro-Oncology (document attribution, grade of toxicity, and if there is apparent correlation with the ceramic disc or adhesive gel on the transducer arrays). Treatment of mild skin toxicity as appropriate. If there are concerns of worsening skin toxicity, referral to dermatologist for specialist evaluation (transducer arrays will need to be removed/replaced for exam).
- Complete blood count (CBC) with differential and platelet count
- Adverse event assessment
- Concomitant medication review
- Continuation of TTField Therapy
- Continuation of RT
- Continuation of TMZ therapy

Day 36 (±7 days)

- Skin examination by investigator or subinvestigator in Radiation Oncology or Neuro-Oncology (document attribution, grade of toxicity, and if there is apparent correlation with the ceramic disc or adhesive gel on the transducer arrays). Treatment of mild skin toxicity as appropriate. If there are concerns of worsening skin toxicity, referral to dermatologist for specialist evaluation (transducer arrays will need to be removed/replaced for exam).
- Complete blood count (CBC) with differential and platelet count
- Adverse event assessment
- Concomitant medication review
- Continuation of TTField Therapy
- Continuation of RT
- Continuation of TMZ therapy

Day 43 (±7 days) Final week of Trimodal therapy

- Skin examination by investigator or subinvestigator in Radiation Oncology or Neuro-Oncology (document attribution, grade of toxicity, and if there is apparent correlation with the ceramic disc or adhesive gel on the transducer arrays). Treatment of mild skin toxicity as appropriate. If there are concerns of worsening skin toxicity, referral to

dermatologist for specialist evaluation (transducer arrays will need to be removed/replaced for exam).

- Neurological examination by investigator or subinvestigator in Radiation oncology or Neuro-oncology.
- Complete blood count (CBC) with differential and platelet count
- Adverse event assessment
- Concomitant medication review
- Continuation of TTField Therapy
- Continuation of RT until Day 49 + 7 days, as clinically appropriate
- Continuation of TMZ therapy until Day 49 + 7 days, as clinically appropriate

Day 64 (±7 days) Post initial chemoradiation continued DLT window

This is marked by continued TTField therapy alone for 4 weeks with the following procedures for continued monitoring of DLTs and TRAEs. One visit to be conducted in the middle of the 4 weeks with the following procedures.

- Vital signs: weight, temperature, pulse, respiration rate, and resting blood pressure.
- Skin examination by investigator or subinvestigator in Neuro-Oncology (document attribution, grade of toxicity, and if there is apparent correlation with the ceramic disc or adhesive gel on the transducer arrays). Treatment of mild skin toxicity as appropriate. If there are concerns of worsening skin toxicity, referral to dermatologist for specialist evaluation (transducer arrays will need to be removed/replaced for exam).
- Physical examination including neurologic exam, skin and scalp assessment.
- Complete blood count (CBC) with differential and platelet count
- Adverse event assessment
- Concomitant medication review
- Continue TTField therapy

Study procedures, Adjuvant therapy phase and monitoring of delayed toxicities until 8 weeks after completion of trimodal therapy.

This would fall 4 weeks after completion of radiation therapy and marked by initiation of TMZ chemotherapy on a 5 out of 28-day cycle along with continued TTField therapy per the standard of care. MRIs are recommended every 2 months during temozolomide therapy. Day 1 of cycle 1 and cycle 2 are marked by continued treatment per the standard of care along with assessments for delayed TRAEs following trimodal therapy and continued DLT window (4 weeks and 8 weeks after completion of trimodal therapy).

Adjuvant TMZ therapy, Day 1 of Cycle 1 (Study Day 78 ± 5 days) with delayed toxicity monitoring.

- MRI of the brain with and without contrast (transducer arrays will need to be removed/replaced for imaging)
- Vital signs: weight, temperature, pulse, respiration rate, and resting blood pressure.
- Physical examination including neurologic exam, skin and scalp assessment.
- Skin examination by investigator or subinvestigator in Neuro-Oncology (document attribution, grade of toxicity, and if there is apparent correlation with the ceramic disc or adhesive gel on the transducer arrays). If there are concerns of worsening skin toxicity, referral to dermatologist for specialist evaluation (transducer arrays will need to be removed/replaced for exam).
- Adverse event assessment
- Concomitant medication review
- Documentation of disease assessment, clinical response or deterioration, status and extent of measurable disease on imaging
- Objective response assessment
- KPS (performance) assessment
- Complete blood count (CBC) with differential and platelet count
- Blood chemistry assessment, including:
    - Alkaline phosphatase, aspartate aminotransferase/alanine aminotransferase (ALT/AST), total bilirubin, calcium, blood urea nitrogen (BUN), creatinine, total protein, albumin, fasting glucose, potassium, sodium, chloride, bicarbonate
- Initiate Cycle 1, day 1 treatment of adjuvant TMZ on a 5 out of 28-day cycle as detailed under treatment modalities. Dosing will start at 150mg/m^2/day for the first cycle and then increased if tolerated to 200mg/m^2/day for all subsequent cycles.
- Continue TTField therapy. Total duration of treatment will be 24 months from the start of therapy (including back to trimodal treatment day 1) unless discontinued for other reasons (see criteria for removal of study therapy).
- In addition to clinic visits and assessments, the subject also has access to a device support specialist for routine skin care issues as part of the standard of care for patients on active treatment with tumor treating field therapy. In between visits, the patient will be asked to report any notable skin toxicity to their neuro-oncologist office.
- TTField compliance assessment (to be completed monthly, may not be available at each visit)

Day 22 (± 3 days) of Cycle 1

- Complete blood count (CBC) with differential and platelet count
- Continue TTField therapy

- Adverse event assessment
- Concomitant medication review
- Access to device support specialist
- TTField compliance assessment (to be completed monthly, may not be available at each visit)

Day 1 of Cycle 2, Day 1 (Study Day 106 ± 5 days) with delayed toxicity monitoring.

- Vital signs: weight, temperature, pulse, respiration rate, and resting blood pressure.
- Physical examination including neurologic exam, skin and scalp assessment.
- Skin examination by investigator or subinvestigator in Neuro-Oncology (document attribution, grade of toxicity, and if there is apparent correlation with the ceramic disc or adhesive gel on the transducer arrays). If there are concerns of worsening skin toxicity, referral to dermatologist for specialist evaluation (transducer arrays will need to be removed/replaced for exam).
- Adverse event assessment
- Concomitant medication review
- Documentation of disease assessment, clinical response or deterioration, status and extent of measurable disease on imaging, using MRI from Day 1 of Cycle 1 for assessment
- Objective response assessment, using MRI from Day 1 of Cycle 1 for assessment
- KPS (performance) assessment
- Complete blood count (CBC) with differential and platelet count
- Blood chemistry assessment, including:
    - Alkaline phosphatase, aspartate aminotransferase/alanine aminotransferase (ALT/AST), total bilirubin, calcium, blood urea nitrogen (BUN), creatinine, total protein, albumin, fasting glucose, potassium, sodium, chloride, bicarbonate
- Initiate 2nd cycle of adjuvant TMZ as detailed under treatment modalities. Note that beginning with cycle 2, the dose is increased to 200mg/m^2/day for all subsequent cycles if tolerability criteria are met.
- Continue TTField therapy
- Access to device support specialist
- TTField compliance assessment (to be completed monthly, may not be available at each visit)

Day 22 (± 3 days) of Cycle 2

To be completed as part of standard of care. Noted here for clarity, but not being collected as part of the trial.

- Complete blood count (CBC) with differential and platelet count
- Continue TTField therapy

- Adverse event assessment
- Concomitant medication review
- Access to device support specialist
- TTField compliance assessment (to be completed monthly, may not be available at each visit)

Following cycle 2, the patient will continue therapy with temozolomide and TTFields treatment per the standard of care, which is a minimum of 6 cycles. The following are not strict requirements for continued participation in the trial but recommendations per the standard of care on how to proceed through TMZ and TTField therapy with appropriate lab and MRI monitoring. For continued participation in the trial, patients must continue to follow up every 2-3 months with a repeat MRI of the brain so that clinical outcomes data can be collected for the secondary analyses (transducer arrays will need to be removed/replaced for imaging).

Subsequent cycles of adjuvant therapy

The following is recommended for patients receiving continued temozolomide and TTFields therapy. Clinical outcomes analyses based on intention-to-treat will be performed on subjects treated for at least one day per the standard of care as follows. Repeat above procedures following the protocol for cycle 1 and cycle 2 for a minimum total of 6 full cycles of TMZ with the exception that after cycle 1 (150mg/m^2/day), all cycles use a dose of 200mg/m^2/day. Otherwise, the procedures for odd-numbered cycles 3 and 5 (and potentially beyond, per standard of care) match those detailed for cycle 1 above (phase 1). The procedures for even-numbered cycles 4 and 6 (and potentially beyond, per standard of care) match those detailed for cycle 2 above (phase 2). A repeat MRI is recommended on the first day of every odd numbered cycle (cycle 1, 3, and 5) +/- 7 days, which is roughly every 2 months.

- Cycle 3: follow cycle 1 procedures (except dose remains at 200mg/m2/day)
- Cycle 4: follow cycle 2 procedures
- Cycle 5: follow cycle 1 procedures (except dose remains at 200mg/m2/day)
- Cycle 6: follow cycle 2 procedures

Cycle 6, day 28 marks the completion of the full 6 cycles of adjuvant TMZ per the standard of care. If there is no contraindication, TMZ may be discontinued at that time. If there is clinical cause, physicians may opt to continue TMZ therapy longer beyond the 6 cycles. Otherwise, TTField therapy alone will be continued for maintenance.

Maintenance TTField therapy (Long-Term Follow-up)

At the end of the adjuvant therapy, the subject will continue TTF treatment per the standard of care, and the study will follow clinical outcomes via the chart and by telephone as needed. It is recommended that the subject have a follow-up MRI, objective response assessments, physical exam, and medication review with their neuro-oncologist at least every 3 months during this time for up to 2 years. Refer to sections on evaluation of response and evaluation of pseudoresponse for criteria of assessments. Investigators at each site will document the date of confirmed progression on MRI scan and or death, and cause of death for every subject that

has been on treatment for at least 1 day (disease assessment/extend of measurable disease on imaging with clinical response or deterioration, when an MRI has been completed per standard care). Site study coordinators will review patient records at minimum every 6 months starting from the date of initial Trimodal therapy while patients remain on study to collect data on TTF compliance, treatment response, disease progression, and survival. This will provide the secondary outcomes that will be analyzed and reported at the close of the study.

Unscheduled Visit, anytime during the Study Period (Day 1-Day 106 ± 5 days)
An unscheduled visit may be used if the investigator feels they need to see the patient for a safety concern or an additional indicated exam that is outside of a specified protocol visit window. Any of the following may be completed, per investigator discretion, based on where the patient is currently in the study.

- MRI of the brain with and without contrast (transducer arrays will need to be removed/replaced for imaging)
- Vital signs: weight, temperature, pulse, respiration rate, and resting blood pressure
- Physical examination including neurologic exam, skin and scalp assessment
- Skin examination by investigator or subinvestigator in Neuro-Oncology (document attribution, grade of toxicity, and if there is apparent correlation with the ceramic disc or adhesive gel on the transducer arrays). If there are concerns of worsening skin toxicity, referral to dermatologist for specialist evaluation (transducer arrays will need to be removed/replaced for exam).
- Neurological examination by investigator or subinvestigator in Radiation oncology or Neuro-oncology
- Adverse event assessment
- Concomitant medication review
- Documentation of disease assessment, clinical response or deterioration, status and extent of measurable disease on imaging
- Objective response assessment
- KPS (performance) assessment
- Complete blood count (CBC) with differential and platelet count
- Blood chemistry assessment, including:
    - Alkaline phosphatase, aspartate aminotransferase/alanine aminotransferase (ALT/AST), total bilirubin, calcium, blood urea nitrogen (BUN), creatinine, total protein, albumin, fasting glucose, potassium, sodium, chloride, bicarbonate
- In addition to clinic visits and assessments, the subject also has access to a device support specialist for routine skin care issues as part of the standard of care for patients on active treatment with tumor treating field therapy. In between visits, the patient will be asked to report any notable skin toxicity to their neuro-oncologist office.

- TTField compliance assessment (to be completed monthly, may not be available at each visit)
- Continuation of TTField Therapy (if applicable)
- Continuation of RT Therapy (if applicable)
- Continuation of TMZ therapy (if applicable)

Early Termination Phone Visit, anytime during the Study Period (Day 1-Day 106 ± 5 days)
If a subject stops study treatment on or before Day 1 of Cycle 2 of the Adjuvant TMZ Therapy Phase, they may continue in the trial for observational purposes, if willing, in order to perform the intention-to-treat analysis. If a subject is unwilling to continue in the trial, an early termination phone visit will be conducted.

- Adverse event assessment
- Concomitant medication review
- TTField compliance assessment (to be completed monthly, may not be available at each visit)

Treatment Modalities

a) Optune™ Treatment

Treatment planning: Transducer array layout will be determined by Novocure using the NovoTAL™ software.

1. Patient training: Patients will be trained in the use of the device by the investigator, a designated health care provider (e.g. nurse, medical assistant, research coordinator) or Device Support Specialist (DSS) trained by Novocure.
2. Treatment initiation: Optune™ will be initiated by the investigator within 7 days of the day 1 clinic visit. All patients will be required to shave their heads to initiate array placement and Optune™. Array placement will be performed based on the Transducer Array Layout map calculated during treatment planning. The investigator or the device specialist will train patients on how to use the map and avoid placing the discs on protruding craniotomy plates, screws, and scars.
3. Treatment duration: Treatment with the device will be continuous with breaks allowed for personal needs (e.g. showering, array exchange). Patients must use the device for at least 18 hours a day on average. Treatment will be continued until tumor progression, death, or unacceptable side effects to patient. Patients must use the device for a minimum of 4 weeks from treatment initiation. A treatment break of 3 days in Optune™ every month is allowed. However, the patient should use the device for at least 18 hours a day on average as stated above.
4. The Optune™ System will be programmed by Novocure to deliver 200kHz TTFields in two sequential, perpendicular field directions at a maximal intensity of 707mA RMS. There will be no adjustments made to the device by investigators or patients/caregivers.
5. Transducer Array replacement: Patients will replace the Transducer Arrays twice to three times per week with the help of a caregiver. The Transducer Arrays will need to be replaced at study visits that require them to be removed to complete a protocol required procedure. At each array replacement the patient's scalp will be re-shaved and skin treated according to the guidelines set out below.

6. Compliance assessment: The device usage will be extracted by a Novocure representative and the data will be reported to the investigator on a monthly basis to assess patient compliance with therapy. Patients who are using the TTField treatment less than 75% of the minimum recommended usage of 18 hours a day on average, as assessed monthly (13 hours a day or less), unless per officially instituted dose reduction, may discontinue therapy at the discretion of the investigator or sponsor.

7. The following skin care guidelines should be closely adhered to:
    a. If the skin beneath the Transducer Arrays is inflamed, a high potency topical steroid (e.g. clobetasol) may be prescribed to the patient. The patient or caregiver should apply the ointment after removing the arrays and cleaning the scalp with baby oil and medical alcohol. The ointment should be left on the scalp for at least 30 minutes prior to washing the skin with a mild shampoo and applying a new set of arrays.
    b. At each array replacement, the new set of arrays should be shifted by approximately 2 cm compared to the previous layout so that the array discs are placed between the areas of skin irritation. At the next array replacement, the arrays should be shifted back to their original location.
    c. If the dermis is breached (skin erosions, ulcers, open sores, punctate lesions, etc.) an antibiotic ointment (e.g. mupirocin) should be prescribed and used in place of the steroid ointment. Any evidence of infection should result in bacterial cultures being taken. During radiotherapy, a break from the Optune array is mandatory if there is ulceration or open sores.
8. Expected and potential treatment-related acute adverse effects include: Localized skin toxicity, anxiety, headaches, fatigue, insomnia, seizures.

Dose modifications during TTField therapy (applies to *all phases of therapy*--trimodal therapy, adjuvant therapy, or maintenance therapy, including for the safety lead-ins):

Grade 3-4 non-hematologic toxicity (skin toxicity, neurologic symptom, etc): reduce device usage schedule to 50% or 1 week on, 1 week off to allow for recovery. If toxicity remains grade 3 or above for 1 month after reduced usage, then discontinue therapy. If non-hematologic toxicity moves to grade 2 or below, titrate up as soon as able to tolerate, per investigator discretion. If skin toxicity improves to grade 2 or below in the 1-month period, the original TTF usage can be resumed per investigator discretion. If TTF therapy could not be resumed in the 1-month period and has to be discontinued then it would be considered DLT for Optune use.

b) Concomitant chemoradiation: The use of radiation therapy and temozolomide chemotherapy for patients with newly diagnosed glioblastoma is considered standard of care. Furthermore, TTField therapy with Optune™ is also approved for post-radiation adjuvant treatment of newly diagnosed glioblastoma (see preclinical data). The use of these treatment modalities will follow established parameters and guidelines and will be briefly reviewed in this section. However, trimodal treatment at the outset with radiation, TMZ, and Optune™ (TTField) therapy has not been studied and may require adjustments for safety and tolerability.

1. Radiation therapy

Subjects will receive radiation therapy within 4-6 weeks of their surgical resection or 2-4 weeks of their biopsy for the purpose of ensuring proper wound-healing. Treatment will be mapped

and delivered by a qualified radiation oncologist to a target dose of 60 Gray (Gy) in equally divided fractions of 2 Gy to the Clinical Target Volume (CTV) delivered over 30 fractions over a period of 42 days + 7 days (about 6 weeks; to Day 49 + 7 days). At the discretion of the Radiation Oncologist, particularly for large treatment volumes, the prescription dose may be 59.4 Gy in 33 fractions of 1.8 Gy. The subject will undergo treatment mapping and production of a high-quality mask to immobilize the head for treatment. An initial CT image of the subject's head is obtained and fused to the post-surgical MRI of the brain for treatment mapping and used for conebeam CT image alignment before treatment delivery. Due to the presence of the transducer arrays on the scalp, a phantom model will be employed to investigate radiation dosimetry effects and any interference with the making of a high-quality immobilization mask. These exploratory studies will provide guidance on any necessary adjustments for subjects for safe and effective radiation treatment of tumor (See RT). Expected and potential treatment-related acute adverse effects include skin reactions, alopecia, headache, fatigue, seizure, tumor necrosis, memory impairment, and altered cognition.

Radiation therapy without interruptions

Completion of radiotherapy course uninterrupted will be prioritized. Grade 3-4 skin toxicity during RT course will result in at least 1 week break from TTF therapy (with reduced Optune dosing for up to one month as above) with resumption following physician evaluation and clearance.

2. Temozolomide chemotherapy

Subjects will receive TMZ chemotherapy as part of the trimodal therapy phase concurrently with radiation and TTField therapy. This will be administered orally by the subjects at a dose of 75mg/m^2 (of their body surface area) daily during radiation therapy (typically for 42 consecutive days including on weekends, up to 49 days is acceptable; to Day 49 + 7 days). Subjects will then discontinue the chemotherapy and have a 4-week break after radiation prior to resuming TMZ adjuvant therapy concurrent with TTField therapy alone. Doses will then be administered for 5 consecutive days out of a 28-day cycle. For the first cycle of adjuvant therapy, subjects will be dosed at 150mg/m^2/day for 5 days out of 28 days in the first cycle, and increased if tolerated to 200mg/m^2/day and continue that dose until the end of chemotherapy. The standard requirement is for 6 cycles of adjuvant treatment post-radiation but this may be extended per the judgment of the subject's treating clinician to no more than 12 cycles of adjuvant TMZ therapy. Please see package insert for full details. Expected and potential treatment-related acute adverse effects include: Nausea, fatigue, constipation, liver toxicity, myelosuppression resulting in thrombocytopenia, leukopenia (or neutropenia), anemia, or pancytopenia.

Initiation of PJP prophylaxis is recommended but each site will be given discretion to follow their institutional protocols.

Dose modifications during Trimodal therapy phase

ANC ≥500/mm^3 but <1,500/mm^3 **or** platelet count ≥10,000/mm^3 but <100,000/mm^3 **or** grade 2 nonhematologic toxicity (excludes alopecia, nausea/vomiting): Interrupt therapy

ANC <500/mm^3 **or** platelet count <10,000/mm^3 **or** grade 3/4 nonhematologic toxicity (excludes alopecia, nausea/vomiting): Discontinue therapy

Dose modifications during adjuvant therapy phase (concurrent with TTField therapy only)

ANC <1,000/mm^3, platelet count <50,000/mm^3, or grade 3 nonhematologic toxicity (excludes alopecia, nausea/vomiting) during previous cycle: Decrease dose by 1 dose level (by 50 mg/m^2/day for 5 days), unless dose has already been lowered to 100 mg/m^2/day, then discontinue therapy.

If dose reduction <100 mg/m^2/day is required or grade 4 nonhematologic toxicity (excludes alopecia, nausea/vomiting), or if the same grade 3 nonhematologic toxicity occurs after dose reduction: Discontinue therapy

7. SUBJECT ASSESSMENTS FOR SAFETY AND EFFICACY

The study procedure calendar for this study is provided in **Appendix 3**.

a) Evaluation of Safety and Tolerability

Dose Limiting Toxicity

Dose limiting toxicities (DLTs) are defined as any severe or life-threatening treatment-related toxicity that precludes the use of a specified dose of any of the study treatments (TTFields, temozolomide, radiation) including continued use of Optune TTFields device at the standard treatment levels and schedule set out by prior studies. This study will prioritize preserving the standard of care for glioblastoma using approved dosing and radiation of temozolomide and radiation.

Toxicities will be graded according to the CTCAE (Version 5.0) scale. If multiple toxicities are seen, the presence of DLT should be based on the most severe toxicity experienced. Dose-limiting toxicities will be defined as any of the following events which occur during the experimental trimodal therapy with TTFields is added concurrently to radiation and temozolomide therapy or during the 8 weeks after RT is completed, and are considered by the investigator to be attributable to TTFields or the combination of TTFields with radiation and/or temozolomide:

- Any Grade >3 thrombocytopenia, and Grade 4 anemia and neutropenia.
- Any nonhematologic Grade >3 toxicity (including nausea, vomiting, or diarrhea), excluding alopecia.

- Any Grade 3-4 radiation-induced skin changes that persist for greater than 7 days and does not improve with management recommendations as outlined in toxicity management.
- Any adverse effect deemed by the investigator, patient's primary neuro-oncologist, or radiation oncologist to be life threatening in nature.

In the event of a dose-limiting toxicity, the subject will be discontinued from treatment and followed for toxicity assessment and management and a joint decision will be made by the investigator and sponsor whether to adjust the dose or schedule for other subjects or permanently close the study for safety. In the event that more than 33% of subjects experience a DLT, the study cannot continue unless a modification is made to the level of the particular treatment to which that adverse event is definitely attributable. As preliminary safety stops, the study will include two safety lead-ins receiving TTFields with concurrent chemoradiation. These initial 6 and then 15 subjects will undergo interim analyses after completion of chemoradiation to determine if the expanded cohorts should be permitted enrollment as planned or if a dose reduction in TTFields of 50% of the scheduled use is warranted for safety.

Subjects will continue to receive study treatment until confirmed tumor progression, unacceptable toxicity, or other discontinuation criteria as described; subjects MUST discontinue investigational product (and non-investigational product at the discretion of the investigator) if they meet criteria for removal from study therapy as referenced in that section.

Toxicity related to TTFields treatment: Treatment-related adverse events (TRAEs) and severe treatment-related adverse events (STRAEs) will be assessed in the following ways.

- Patients will be evaluated by a neuro-oncologist or radiation oncologist for potential skin toxicity from TTFields therapy. Routine skin care recommendations will be provided, including use clobetasol cream prior to electrode placement and adjusting array placement to avoid continued site irritation. If there are concerns by investigator, the subject will be referred to a dermatologist for specialized evaluation. Neurological and general physical evaluations as well as laboratory assessments will also be conducted by a neuro-oncologist or radiation oncologist to identify other potential toxicities.
- In addition to clinic visits and interventions, Patients will also be supported by a technician from Novocure for device troubleshooting and compliance checks.
- All other adverse effects, either mild, or serious, will be triaged by a physician in coordination with the primary investigators of the study.
- All adverse events, whether minor or serious will be reported according to protocol guidelines (see Reporting of adverse events).

b) Evaluation of Response

Patients will be evaluated for response using the Response Assessment in Neuro-Oncology (RANO) criteria[32]. Subjects who have lesions equal or less than 1cm on baseline will only be followed for assessment of progressive (PD) or stable disease (SD). SD will be marked by

the lack of observable progression on MRI. PD will be marked by any growth or recurrence of lesions consistent with tumor on MRI based on RANO criteria as follows:

Table #: RANO criteria for Response Assessment Incorporating MRI and Clinical Factors[32]	
Response	**Criteria**
Complete Response	Requires all of the following: complete disappearance of all enhancing measurable and nonmeasurable disease sustained for at least 4 weeks; no new lesions; stable or improved nonenhancing (T2/FLAIR) lesions; subjects must be off corticosteroids (or on physiologic replacement doses only); and stable or improved clinically. Note: subjects with nonmeasurable disease only cannot have a complete response; the best response possible is stable disease.
Partial Response	Requires all of the following: 50% or greater 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 nonmeasurable disease; no new lesions; stable or improved nonenhancing (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 nonmeasurable disease only cannot have a partial response; the best response possible is stable disease.
Stable Disease	Requires all of the following: does not qualify for complete response, partial response, or progression; stable nonenhancing (T2/FLAIR) lesions on same or lower dose of corticosteroids compared with baseline scan. In the event that the corticosteroid dose was increased for new symptoms and signs without confirmation of disease progression on neuroimaging, and subsequent follow-up imaging shows that this increase in corticosteroids was required because of disease progression, the last scan considered to show stable disease will be the scan obtained when the corticosteroid dose was equivalent to the baseline dose.
Progression	Defined by any of the following: Greater than or equal to 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 nonenhancing lesions on stable or increasing doses of corticosteroids compared with baseline scan or best response after

	initiation of therapy* not cause by comorbid events (eg, radiation therapy, demyelination, ischemic injury, infection, seizures, post-operative 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.

Evaluation of Pseudoprogression

Pseudoprogression is defined as worsening of the MRI lesions (enhancing lesion, T2/FLAIR hyperintense nonenhancing lesions) as a result of effects other than tumor growth. These can be the result of treatment effects from radiation, TTField therapy, or chemotherapy, or changes in the steroid dose. Pseudoprogression is typically self-limited and suggests different clinical implications from true progression of the brain tumor. However, clinically and radiographically, pseudoprogression and tumor progression are difficult to distinguish. MRIs in this study will be evaluated centrally by the principal investigator according to RANO criteria and definitions and need to account for possible pseudoprogression from any of the treatments. Therefore, in this trial, if a subject has an MRI scan concerning for progression without substantial neurological symptoms or signs within 6 months of starting TTFields therapy, it is recommended that the subject continue therapy and obtain a follow-up scan approximately 4 weeks apart to confirm progression. If that follow-up scan confirms progression, the patient shall be taken off the study treatments. If that scan is stable when compared to the prior scan, then pseudoprogression will be noted and treatment will continue. If a subject whose scan is concerning for progression also develops substantial neurological decline, or requires increasing steroid dose beyond the daily limit of 8mg dexamethasone for more than 4 weeks, then no confirmatory scan is needed; progression will be noted and that subject shall be discontinued from the study treatments. Similarly, no confirmatory scan is needed if a subject develops MRI changes concerning for progression with or without substantial neurological decline after 6 months of initiating TTFields therapy.

Reporting of Adverse Events

Evaluation of Safety

Analyses will be performed for all patients having received at least one day of TTField therapy. The study will use the CTCAE v5.0 for reporting of non-hematologic adverse events and modified criteria for hematologic adverse events, see Section 7a (Subject assessments for evaluation of safety and tolerability).

There will not be a formal Study Chair. There will be three DSMC members who will share the responsibility of monitoring study conduct and safety across participating sites.

Definitions of Adverse Events

Adverse Event

An adverse event (also known as an adverse experience) is defined as any untoward medical occurrence associated with the use of a medical device in humans, whether or not considered device related. More specifically, an adverse event (can be any unfavorable and unintended sign (e.g., an abnormal laboratory finding), symptom, or disease temporally associated with the use of a device, without any judgment about causality. An adverse event can arise from any use of the device (e.g., off-label use, use in combination with another treatment or drug).

Adverse reaction

An adverse reaction is defined as any adverse event caused by the use of a medical device. Adverse reactions are a subset of all suspected adverse reactions for which there is reason to conclude that the device use caused the event.

Suspected

A suspected adverse reaction is defined as any adverse event for which there is a reasonable possibility that the use of the device caused the adverse event. For the purposes of IDE safety reporting, "reasonable possibility" indicates that there is evidence to suggest a causal relationship between the device use and the adverse event. A suspected adverse reaction implies a lesser degree of certainty about causality than an adverse reaction.

Unexpected

An adverse event or suspected adverse reaction is considered *unexpected* if it is not listed in the investigator brochure or package insert(s), or is not listed at the specificity or severity that has been observed, or, if an investigator brochure is not required or available, is not consistent with the risk information described in the general investigational plan or elsewhere in the current application.

Adverse events that would be anticipated to occur as part of the disease process are considered *unexpected* for the purposes of reporting because they would not be listed in the investigator brochure. For example, a certain number of non-acute deaths in a cancer trial would be anticipated as an outcome of the underlying disease, but such deaths would generally not be listed as a suspected adverse reaction in the investigator brochure.

Serious

An adverse event or suspected adverse reaction is considered *serious* if, in the view of either the investigator or sponsor, it results in any of the following outcomes:

- Death
- Life-threatening adverse event
- Inpatient hospitalization or prolongation of existing hospitalization
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life function
- Congenital anomaly/birth defect

Important medical events that may not result in death, are life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to

prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

Life-threatening

An adverse event or suspected adverse reaction is considered *life-threatening* if, in the view of either the investigator or sponsor, its occurrence places the patient or subject at immediate risk of death. It does not include an adverse event or suspected adverse reaction that, had it occurred in a more severe form, might have caused death.

Recording of an Adverse Event

All grade 3 and above adverse events will be entered into the CTMS, Velos, whether or not the event is believed to be associated with use of the study device. Data about these events and their severity will be recorded using the NCI CTCAE v5.0.

All SAEs will be reviewed by a DSMC, which will consist of a panel of experts in oncology, neuro-oncology, biostatistics, or radiation oncology who are not direct investigators in this study. The PI will identify members of the DSMC and receive feedback and recommendations from the DSMC as to the safety of continuing the trial. The PI and study manager will be responsible for facilitating the proceedings as non-committee members. The committee will meet twice a year, or more if needed.

The Investigator will assess all adverse events, assign attribution of the possible association of the event with use of the investigational device, and this information will be entered into CTMS (Velos) using the classification system listed below:

Relationship	Attribution	Description
Unrelated to investigational drug/intervention	Unrelated	The AE *is clearly NOT related* to the intervention
	Unlikely	The AE *is doubtfully related* to the intervention
Related to investigational drug/intervention	Possible	The AE *may be related* to the intervention
	Probable	The AE *is likely related* to the intervention
	Definite	The AE *is clearly related* to the intervention

A more detailed definition of possible attributions is denoted in the following table:

Unrelated:	The event is clearly related to an event that may be due to environmental or accidental occurrence or other factors such as the subject's clinical state, therapeutic interventions, or concomitant drugs administered to the subject.

Unlikely	The event is most likely produced by other factors such as the subject's clinical condition, therapeutic interventions, or concomitant drugs administered to the subject, and does not follow a known response pattern to the study drug or device.
Possible	The event follows a reasonable temporal sequence from the time of drug administration or use of device, and/or follows a known response pattern to the study drug or device, but could have been produced by other factors such as the subject's clinical condition, therapeutic interventions, or concomitant drugs administered to the subject.
Probable	The event follows a reasonable temporal sequence from the time of drug administration or use of device, and follows a known response pattern to the study drug or device, and cannot be reasonably explained by other factors such as the subject's clinical condition, therapeutic interventions, or concomitant drugs administered to the subject.
Definite	The event follows a reasonable temporal sequence from the time of drug administration or use of device, and follows a known response pattern to the study drug or device, and cannot be reasonably explained by other factors such as the subject's clinical condition, therapeutic interventions, or concomitant drugs administered to the subject, and either occurs immediately following study drug administration or use of device or improves on stopping the study drug or device, or reappears on repeat exposure

The relationship of the adverse event to the study treatment must be specified using the following definitions:

Signs or symptoms reported as adverse events will be graded and recorded by the Investigator according to the CTCAE. When specific adverse events are not listed in the CTCAE they will be graded by the Investigator as *none*, *mild*, *moderate* or *severe* according to the following grades and definitions:

Grade 0	No AE (or within normal limits)
Grade 1	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated
Grade 2	Moderate; minimal, local, or noninvasive intervention (e.g., packing, cautery) indicated; limiting age-appropriate instrumental activities of daily living (ADL)
Grade 3:	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL
Grade 4:	Life-threatening consequences; urgent intervention indicated
Grade 5:	Death related to AE

Follow-up of Adverse Events

All adverse events will be followed with appropriate medical management until resolved. Patients discontinued from study therapy for unacceptable adverse events will be followed until resolution or stabilization of the adverse event and to the end of the study. For selected adverse events for which administration of the investigational device was stopped, a re-challenge of the subject with the investigational device may be conducted if considered both safe and ethical by the Investigator.

Adverse Events Monitoring

The Principal Investigator will review all adverse events and determine reportability to the DSMC and Providence's Institutional Review Board IIRB) per IRBAE reporting criteria; and, when the study is conducted under an Investigational Device Exemption (IDE), to the Food and Drug Administration (FDA) if it meets the FDA reporting criteria.

After the first 6 patients complete the lead-in phase, a written report will be submitted to the DSMC members describing the cohort, adverse events, and any Dose Limiting Toxicities observed, in accordance with the protocol. The report will be reviewed by the DSMC. Approval for the expansion cohort must be obtained from the DSMC prior to implementation.

Expedited Reporting

Reporting to the Data and Safety Monitoring Board

If a death occurs during the treatment phase of the study or within 30 days after the last administration of the study device and it is determined to be related either to the study device or to a study procedure, the Investigator or his/her designee must notify the PI, Ricky Chen, MD, or designee, Regulatory Manager, Mark Schuster, within 1 business day of knowledge of the event. The contact may be by phone or e-mail. Death due to disease progression need not be reported to the PI or designee.

Reporting to Institutional Review Board

The Principal Investigator must report events meeting the IRB definition of "Unanticipated Problem" (UP) within 5 business days of his/her awareness of the event.

Expedited Reporting to the Food and Drug Administration

If the study is being conducted under an IDE, the Sponsor-Investigator is responsible for determining whether or not the suspected adverse reaction meets the criteria for expedited reporting in accordance with Federal Regulations (21 CFR §312.32).

The Investigator must report in an IDE safety report any suspected adverse reaction that is both serious and unexpected. The Sponsor-Investigator needs to ensure that the event meets all three definitions:

- Suspected adverse reaction
- Unexpected
- Serious

Serious and unexpected AEs must be reported by the investigator to Providence Regional Research Regulatory Office and the Study Manager by email at amy.greathouse@providence.org and tiffany.gervasi-follmar@providence.org or fax to 503-215-6547 and 503-216-1039 within 24 hours of the investigator's knowledge of the event. Providence will also report the SAEs to the FDA.

If the adverse event does not meet all three of the definitions, it should not be submitted as an expedited IDE safety report.

The timeline for submitting an IDE safety report to FDA is no later than **15 calendar days** after the Investigator determines that the suspected adverse reaction qualifies for reporting (21 CFR 312.32(c)(1)). MedWatch 3500A (Mandatory Reporting) form is available at: https://www.fda.gov/Safety/MedWatch/HowToReport/DownloadForms/default.htm

Any unexpected fatal or life-threatening suspected adverse reaction will be reported to FDA no later than **7 calendar days** after the Investigator's initial receipt of the information (21 CFR 312.32(c)(2)).

Any relevant additional information that pertains to a previously submitted IDE safety report will be submitted to FDA as a Follow-up IDE Safety Report without delay, as soon as the information is available (21 CFR 312.32(d)(2)).

8. STATISTICAL CONSIDERATIONS

Interim analyses of the first and second safety lead-in cohorts will be performed using data collected from the beginning of the study to eight weeks following trimodal therapy for each patient. Patient characteristics will be summarized using means, standard deviations, medians, interquartile ranges, counts, or percentages, as appropriate. Primary endpoints will be summarized using counts and percentages of patients who experienced a treatment-related adverse event, treatment-related serious adverse event, or DLT for safety and stopping rules.

In the second interim analysis, the percentage of patients with inconclusive MGMT methylation status will also be summarized. Patients with inconclusive MGMT methylation status will be removed from the final study analysis, so we will use this percentage to assess the number of additional patients that need to be recruited to meet our sample size requirement of 30 patients. For example, if 2 out of 15 patients have an inconclusive MGMT methylation status at this stage, we will recruit 4 additional patients to meet the sample size requirement.

Using the intention-to-treat approach, the final analyses will be performed on all patients having received at least one day of use from the study device. Patients with an inconclusive MGMT methylation status will be excluded. Patient characteristics will be summarized using

means, standard deviations, medians, interquartile ranges, counts, or percentages, as appropriate.

Primary endpoints will be summarized using counts and percentages of patients who experienced a treatment-related adverse event, treatment-related serious adverse event, or DLT will be reported overall and by event type following trimodal treatment and 8 weeks thereafter to capture any later appearing toxicities. A subgroup evaluation by MGMT methylation status (methylated vs unmethylated) will also be performed.

Kaplan Meier survival analyses will be used to analyze the following secondary endpoints: 1) progression-free survival at 6 months and 2 years, 2) median time-to-death and overall survival at 2 years and 3) duration of TTF use. Log rank tests may be used in Kaplan Meier analyses to test for differences in survival curves amongst known prognostic factors such as age, duration and compliance of TTF use, KPS, extent of resection, IDH mutation status, and MGMT methylation status. The objective response by modified RANO criteria will be summarized with counts and percentages following trimodal treatment and at 2 years. The rate of TTFields compliance will be reported as the percentage of patients who used TTFields at least 75% of the minimum recommended usage of 18 hours a day on average, as assessed monthly.

The intention-to-treat analyses may be supplemented by per-protocol analyses, if the percentage of patients who did not follow standard of care recommendations as outlined for adjuvant and maintenance therapy following trimodal treatment is high.

Power Calculation

As we are expecting that patients will be more susceptible to skin irritation with concurrent therapy than with successive therapy, we focus on severe skin irritation as our endpoint for this power calculation. We expect 5% of patients will experience severe skin irritation based on a 2% rate in the Stupp et al. 2015 study (EF-14)[24] which used TTField therapy following initial chemoradiation treatment. Assuming a sample size of 30 patients of whom 5% experience severe skin irritation, we can say with 95% confidence that the true percentage of patients with severe skin irritation is no lower than 2% and no higher than 21% based on a one-sample binomial proportion. Outside of severe skin toxicity, the rate of any adverse event is not expected to differ significantly from that established by the EF-14 trial.

9. AMENDMENTS TO THE CLINICAL TRIAL PROTOCOL

All protocol amendments will be submitted to the Institutional Review Boards (IRBs) when any revision is made to the original protocol or subsequent version of the protocol that significantly affect the safety of subjects and/or any change is made that significantly affects the scope of investigation or scientific quality of the study.

The amended protocol will be reviewed, approved and documented by the same method in which the original protocol was reviewed and approved.

10. DEVICE ACCOUNTABILITY

Device accountability is ensured by Novocure through the following procedures:

- Shipping of clinical devices: SOP-USOC-003 Final release
- Use of clinical devices : SAP ERP
- Return of clinical devices : SOP-USOC-006 : Technical support-RMA Process

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12. SIGNATURE PAGE

Investigator Name (Print): _____

Study Site Name (Print): _____

Study Site Address (Print): _____

Investigator Signature: _____ **Date:** _____

13.APPENDICES

Appendix 1 Performance Status Criteria

ECOG Performance Status Scale		Karnofsky Performance Scale	
Grade	Descriptions	Percent	Description
0	Normal activity Fully active, able to carry on all pre-disease performance without restriction	100	Normal, no complaints, no evidence of disease
		90	Able to carry on normal activity; minor signs or symptoms of disease
1	Symptoms, but ambulatory Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (*e.g.*, light housework, office work)	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
2	In bed < 50% of the time Ambulatory and capable of all self-care, but unable to carry out any work activities Up and about more than 50% of waking hours	60	Requires occasional assistance, but is able to care for most of his/her needs
		50	Requires considerable assistance and frequent medical care
3	In bed > 50% of the time Capable of only limited self-care, confined to bed or chair more than 50% of waking hours	40	Disabled, requires special care and assistance
		30	Severely disabled, hospitalization indicated Death not imminent
4	100% bedridden Completely disabled Cannot carry on any self-care Totally confined to bed or chair	20	Very sick, hospitalization indicated Death not imminent
		10	Moribund, fatal processes progressing rapidly
5	Dead	0	Dead

Appendix 2 Acceptable Method of Birth Control

Women of child-bearing potential (WOCBP) and men able to father a child must agree to use highly effective contraception while on study treatment and for 60 days after the last dose of temozolomide or Optune™ use. WOCBP must have a negative pregnancy test within 28 days of initiation of study treatment. (Note: The effects of the temozolomide and Optune™ on the developing human fetus are unknown; thus, WOCBP and men able to father a child must agree to use 2 highly effective contraception methods). Highly effective contraception is defined as a method with a failure rate of less than 1 % per year, including but not limited to:

a. True Abstinence: When this is in line with the preferred and usual lifestyle of the subject. Periodic abstinence (e.g., calendar, ovulation, post-ovulation methods) and withdrawal are not acceptable methods of contraception.

b. Postmenopausal: Natural, spontaneous amenorrhea with an appropriate clinical profile for ≥1 year.

c. Female Sterilization: Surgical bilateral oophorectomy, hysterectomy, or tubal ligation at least six weeks prior.

d. Male Sterilization (provided the partner has received appropriate medical confirmation of the surgical success of the vasectomy). For female subjects on the study, the vasectomized male partner should be the sole partner for that participant.

e. Use of a combination of any two of the following:

1. Placement of an intrauterine device (IUD) or intrauterine system (IUS)

2. Barrier methods of contraception: Condom or Occlusive cap (diaphragm or cervical/vault caps) with spermicidal foam/gel/film/cream/vaginal suppository

f. Appropriate hormonal contraceptives (including any registered and marketed contraceptive agent that contains an estrogen and/or a progestational agent – including oral, subcutaneous, intrauterine, or intramuscular agents)

Appendix 3 Study Calendar

Procedure/Visit	Pre-Study	Study Period (extends 8 weeks post RT/TMZ for DLT monitoring)							Long-Term Follow-up		Any time during Study Period	Any time during Study Period
	Pre-Consent	Screening	Trimodal Therapy (6-7 weeks)		Post RT/TMZ (4 weeks)	Adjuvant TMZ Therapy (Cycles are 28 days each)			Adjuvant TMZ Therapy Cycles 3-6 and beyond, if applicable	Maintenance TTField Therapy[L]	UNS Visit	ET Phone Visit
		Day -21 to 0	Day 1	Day 8 +7 days; Day 15, 22, 29, 36, 43 ±7 days for each	Day 64 ±7 days	Cycle 1 (First cycle 1 begins on Day 78 ±5 days)		Cycle 2 (First cycle 2 begins on Day 106 ±5 days)	Minimum of 4 additional cycles	Up to 2 years (Day 720 ±30 days)	Day 1 to Day 106 ±5 days	Day 1 to Day 106 ±5 days
						Day 1 ±5 days	Day 22 ±3 days	Day 1 ±5 days	Day 180, 360, 540, 720 ±30 days (review/collect data via chart review/and or phone contact)			
Tumor Resection or Biopsy	X[DD]											
Informed Consent		X										
Demographics		X[I]										
Eligibility Review		X	X									
Medical History		X										
Treatment History/Toxicity Assessment		X[M]										
Disease Assessment/Extent of Measurable Disease		X[D]				X[P]		X[P, EE]	----------X[P, CC]----------			
Vital Signs[Q]		X[A]	X		X	X		X			X[GG]	
Physical Exam		X[B]	X[B, H]		X[K]	X[K]		X[K]			X[GG]	
Neuro Exam		X		X[X]							X[GG]	
KPS		X	X			X		X			X[GG]	
Objective Response						X		X[EE]	----------X[CC]----------		X[GG]	
CBC w/diff & Platelet Count		X	X[U]	X	X	X	X	X			X[GG]	
Blood Chemistry[S]		X	X[U]			X		X			X[GG]	
Confirm MGMT Testing		X[R]										
Documentation of IDH status		X[R]										
Coagulation Assessment[T]		X										
Serum or Urine Preg Test		X										
ECG		X[W]										
MRI of the Brain w/wo Contrast[O]	X[F]					X[HH]					X[GG, HH]	
Review of Imaging for Treatment Planning		X[C]										
Seizure & Headache Assessment[J]		X	X									
Radiation Oncology Planning		X										

Device Specialist			X[G]	X		---------- X----------						X[GG]	
TTField Compliance Review[FF]			X	X		---------- X ----------			----------X----------			X[GG]	X
TTField Therapy			X[G]	X	X	X	X	X	----------X----------			X[GG]	
Radiation Therapy (RT)			X[G]	X[BB]								X[GG]	
Temozolomide (TMZ)			X[G]	X[BB]		X[V]		X				X[GG]	
Skin Exam			X	X[N, HH]	X[N, HH]	X[N, Y, HH]		X[N, Y, HH]				X[GG, HH]	
Con meds		X[E]	----------X----------									X[GG]	X
Adverse Events[AA]		----------X----------										X[GG]	X
Survival Documentation									----------X[Z]----------				

A: To include height at screening.
B: Including neurologic exam, head exam, and neck exam.
C: Must be done within 14 days prior to Day 1.
D: At screening, to including documented pathology proven glioblastoma or gliosarcoma.
E: To include medications taken within 7 days of Day 1.
F: Confirmation of MRI completion within 3 days after tumor resection, with up to 5 additional days logistical delay being acceptable. If biopsy alone without full resection, cranial CT may be used instead of MRI, provided preoperative MRI completed within 14 days of biopsy.
G: TTF must start within 7 days of Day 1 and preferably a few days prior to beginning RT. TMZ must start within 7 days after beginning of RT. RT should be initiated no more than 14 days after Day 1.
H: To include scalp exam.
I: To include date of birth, gender, race, ethnicity, and education level.
J: Documentation of seizure frequency along with type of seizure (generalized of partial) and/or headache severity and frequency.
K: Including neurological exam, skin exam, and scalp assessment.
L: Obtained via chart review and by telephone (as needed) every 6 months until study completion.
M: To include history of prior treatments and any residual toxicity relating to prior treatment.
N: To include documentation of attribution, grade of toxicity, and if there is apparent correlation with the ceramic disc or adhesive gel on the transducer arrays.
O: With imaging assessment, status and extent of measurable disease on imaging. Repeat MRI every 2-3 months recommended.
P: Including clinical response or deterioration.
Q: Vitals to include: weight, temperature, pulse, respiration rate, and resting blood pressure.
R: MGMT methylation status and IDH mutation status must be assessed at the study site or patient's referral center. MGMT status will be used for stratification purposes but will not exclude patients from this study if they are either methylated, unmethylated, or indeterminate, or in process at the time of enrollment. Similarly, subjects with tumors that are IDH mutated or wildtype are both eligible. If results of MGMT and/or IDH are in process at time of screening, review at each subsequent visit until resulted.
S: To include alkaline phosphatase, ALT, AST, total bilirubin, calcium, blood urea nitrogen (BUN), creatinine, total protein, albumin, fasting glucose, potassium, sodium, chloride, bicarbonate.
T: To include PT, PTT, and INR.
U: If completed for screening within 14 days of Day 1, does not need to be repeated.
V: Cycle 1 day 1 dose is 150mg/m^2/day, all other cycles dose is 200mg/m^2/day.
W: To be collected and read by cardiology department.
X: To be done at Day 22 and Day 43 only.
Y: Day 1 of the first 2 cycles of adjuvant therapy will fall within the DLT window with continued skin exams (Cycle 1 Day 1 and Cycle 2 Day 1). The subsequent cycles with post-TMZ maintenance TTField therapy will proceed per the standard of care (minimum of 6 cycles, up to 2 years). For continued participation in the trial, patients must continue to follow up every 2-3 months with a repeat MRI of the brain.
Z: To include PFS and OS.
AA Monitor adverse events through 8 weeks post-RT/TMZ (through Day 1 of first cycle of Cycle 2).
BB: To be stopped post Day 43 visit on Day 49 (+ 7 days, if clinically appropriate).
CC: To be assessed if MRI completed per SOC since last review/contact.
DD: Time that must have elapsed prior to study enrollment (Day 1): 3-6 weeks (21-42 days) from time of definitive surgery or 2-4 weeks (14-28 days) from the time of biopsy for those who were only able to safely have a biopsy and not full resection.
EE: Use MRI from Day 1 Cycle 1 for assessment.
FF: To be completed monthly, may not be available at each visit.
GG: If indicated, per investigator discretion.
HH: Transducer arrays will need to be removed/replaced to complete.
Please note, the above notations can be found in the body of the protocol, but are listed here as well with the intent of making the study calendar easier to follow.