

RTOG Foundation Collaboration With Novocure

RTOG 3503

A Limited Participation Study

**PHASE II TRIAL OF OPTUNE® PLUS BEVACIZUMAB IN BEVACIZUMAB-REFRACTORY RECURRENT
GLIOBLASTOMA**

Protocol Version Date: December 12, 2017
Amendment Number 5

Sponsor: RTOG Foundation

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On behalf of the RTOG Foundation, Inc.



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Date

RTOG FOUNDATION STUDY 3503
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PHASE II TRIAL OF OPTUNE® PLUS BEVACIZUMAB IN BEVACIZUMAB-REFRACTORY RECURRENT GLIOBLASTOMA

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Protocol Agents

<u>Agent/Device</u>	<u>Supply</u>	<u>IND/IDE #</u>
Optune®	Novocure*	IDE #G150275
Bevacizumab	Commercial	Exempt

*Obtained through commercial prescription process, with forms submitted to Novocure; see Protocol Section 7.3 for details.

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RTOG FOUNDATION STUDY 3503

Phase II Trial of Optune® Plus Bevacizumab in Bevacizumab-Refractory Recurrent Glioblastoma

SCHEMA

Recurrent GBM That Has
Progressed on
Bevacizumab

Bevacizumab continuation every 2 weeks + Optune*

*See Section 7 for full treatment details.

Patient Population: (See Section 3.0 for Eligibility)

- Histologically proven diagnosis of glioblastoma or other grade IV malignant glioma (including variants of glioblastoma ie, gliosarcoma, giant cell glioblastoma, etc.).
- Confirmation of tumor recurrence or progression on contrast MRI (with and without gadolinium contrast) as determined by RANO criteria within 14 days prior to registration for patients who did not have recent resection of their glioblastoma or only had a stereotactic biopsy
- Failure on bevacizumab (either as a monotherapy or a combination) as most recent regimen confirmed by tumor recurrence on MRI. The patient must have failed no more than one regimen of bevacizumab. The patient must not have received bevacizumab as an upfront treatment in newly diagnosed glioblastoma

Required Sample Size: 85 patients

1.0 INTRODUCTION

Despite advances in surgery, radiation therapy, and chemotherapy, including establishment of concurrent radiation and temozolomide followed by temozolomide as standard of care, GBM remains an incurable disease with a dismal median overall survival (OS) of 15-18 months (Stupp 2005).

Bevacizumab (Avastin; Genentech, South San Francisco, CA) is a humanized monoclonal antibody that inhibits VEGF and is the first antiangiogenic therapy to be approved for use in patients with cancer. The BRAIN study, a phase II randomized trial, evaluated the role of bevacizumab (alone or in combination with irinotecan) in 167 patients with recurrent GBM (Friedman 2009). The progression-free survival (PFS) at 6 months (PFS-6) was 42.6% and 50.3%, objective response rate (ORR) was 28.2% and 37.8% and median overall survival (OS) was 9.2 months and 8.7 months in the monotherapy and combination arms, respectively. In a study done at the National Cancer Institute (NCI), 48 patients with recurrent glioblastoma multiforme (GBM) were treated with bevacizumab, producing a response rate (RR) of 35%, PFS-6 of 29% and a median OS of 31 weeks (Kreisl 2009). Clinical benefit was evident with decreasing cerebral edema, tapering steroid doses, and improvement in neurological function in nearly half of the patients. Addition of irinotecan to patients who progressed following bevacizumab did not provide any additional benefit.

The results of these two studies compared favorably to historic controls of PFS-6 of 15% for GBM (Wong 1999), and the FDA approved bevacizumab for patients with recurrent GBM in May 2009 as a monotherapy. However, the duration of effect of bevacizumab appears to be limited and there are growing concerns about the long-term efficacy of bevacizumab. To date, clinical trials with bevacizumab with recurrent GBM have shown an improvement of PFS without substantial improvement in OS. There is no effective therapy for patients with recurrent GBM after progression on bevacizumab. Various studies have reported PFS of 5 to 8 weeks and OS of 3 to 5 months, emphasizing the dismal prognosis of these patients and an urgent need for options in this setting of bevacizumab-refractory recurrent GBM (Kreisel 2009; Iwamoto 2009; Norden 2008; Quant 2009; Hovey 2015; Magnuson 2014).

Studies of Patients With Recurrent GBM Who Have Progressed on Bevacizumab

Author	N	Treatment	Median PFS, Wks	6-Mo PFS, %	Median OS, (months)
Norden 2008	23	Bevacizumab + a different chemotherapy (most often carboplatin)	7	2	NS
Kreisl 2009	19	Bevacizumab + irinotecan	4	0	NS
Hovey 2015	23	Bevacizumab + carboplatin	7	3	3.4
Iwamoto 2009	19	Bevacizumab + chemotherapy	8	0	5.2

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

Novocure (Haifa, Israel) has developed a novel therapy (Optune) utilizing alternating electric fields and has shown that when properly tuned, very low intensity, intermediate frequency electric fields (TTFields Therapy) inhibit the proliferation of tumor cells (including glioma). Given its mechanism of action, Optune is not dependent on the BBB for its efficacy (explained in detail with both preclinical and clinical data

provided below). The inhibitory effect with TTFields Therapy has been demonstrated in all proliferating cancer cell types tested, whereas non-proliferating cells and normal tissues were unaffected. Promising clinical results have been demonstrated in pilot studies of both newly diagnosed GBM in combination with temozolomide as well as recurrent GBM when treated with the Optune System. In a phase III trial Optune monotherapy demonstrated comparable efficacy to chemotherapy with a more favorable safety profile and quality of life benefit in the recurrent GBM setting, resulting in FDA approval of Optune. A subset post-hoc analysis generated the hypothesis that survival could putatively be lengthened in bevacizumab-refractory recurrent GBM (data presented below).

1.1 Introduction to Electric Fields

In the laboratory setting and in clinical practice, alternating electric fields show a wide range of effects on living tissues. At very low frequencies (under 1 kHz), alternating electric fields stimulate excitable tissues through membrane depolarization. (Palti 1966; Polk 1995) The transmission of such fields by radiation is insignificant and therefore they are usually applied directly by contact electrodes, though some applications have also used insulated electrodes. Some well-known examples of such effects include nerve, muscle, and heart stimulation by alternating electric fields. (Palti 1966; Polk 1995) In addition, low frequency pulsed electric fields have been claimed to stimulate bone growth and accelerate fracture healing. (Basset 1985). However, as the frequency of the alternating electric field increases above 1 kHz, the stimulatory effect diminishes. Under these conditions although a greater fraction of the fields penetrates the cells, due to the parallel resistor-capacitor nature of all biological membranes, the stimulatory power greatly diminishes as the alternating cell membrane hyper-depolarization cycles are integrated such that the net effect is nulled.

At very high frequencies (i.e., above many MHz), while the integration becomes even more effective, a completely different biological effect is observed. At these frequencies tissue heating becomes dominant due to dielectric losses. This effect becomes more intense as field intensity or tissue dissipation factor increase. (Elson 1995) This phenomenon serves as the basis for some commonly used medical treatment modalities including diathermy and radiofrequency tumor ablation, which can be applied through insulated electrodes. Chou 1995)

Intermediate frequency electric fields (i.e., tens of kHz to MHz) alternate too fast to cause nerve-muscle stimulation and involve only minute dielectric losses (heating). Such fields, of low to moderate intensities, are commonly considered to have no biological effect. (Elson 1995) However, a number of non-thermal effects of minor biological consequence have been reported even at low-field intensities. These effects include microscopic particle alignment (i.e., the pearl chain effect [Takashima 1985]) and cell rotation. Holzapfel 1982) With pulsed relatively strong electric fields, $> 10^3$ V/cm and 100 ms pulse length, reversible pore formation appears in the cell membrane, a phenomenon usually called electroporation. (Pawlowski 1993)

The relevance of electric fields in oncology may not be immediately obvious but under closer examination it is apparent that biological molecules are dipoles (composed of positive and negative charges), and with the application of an external electric field, dipole movement can occur. In situations where biological processes require precise spatial alignment, such as mitosis, externally applied electric fields can disrupt this process. This was the hypothesis that led to the initial work to evaluate the ability of electric fields to disrupt mitosis in cancer cells.

1.2 Novocure's Tumor Treating Electric Fields (TTFields) or TTFields Therapy

Preclinical studies have shown that when properly tuned, very low intensity, intermediate frequency electric fields (TTFields Therapy) inhibit the growth of tumor cells (Figure1) (Kirson 2004). This inhibitory effect was demonstrated in all proliferating cancer cell types tested, whereas non-proliferating cells and normal tissues were unaffected. Interestingly, different cell types showed specific intensity and frequency dependencies of TTField inhibition. It has been shown that two main processes occur at the cellular level during exposure to TTFields Therapy: arrest of proliferation and dividing cell destruction. The damage caused by TTFields Therapy to these replicating cells was dependent on the orientation of the division process in relation to the field vectors, indicating that this effect is non-thermal. Indeed, temperature measurements made within culture dishes during treatment and on the skin above treated tumors in vivo, showed no significant elevation in temperature compared to control cultures/mice. Also, TTFields Therapy caused the dividing cells to orient in the direction of the applied field in a manner similar to that described in cultured human corneal epithelial cells exposed to constant electric fields. (Zhao 1999) At the sub-

cellular level it was found that TTFields Therapy disrupt the normal polymerization-depolymerization process of microtubules during mitosis. Indeed, the described abnormal mitotic configurations seen after exposure to TTFields Therapy (Figure 2) are similar to the morphological abnormalities seen in cells treated with agents that interfere directly (Jordan 1992; Rowinsky 1995) or indirectly (Kline-Smith 2002; Kapoor 2000; Maiato 2002) with microtubule polymerization (e.g., paclitaxel).

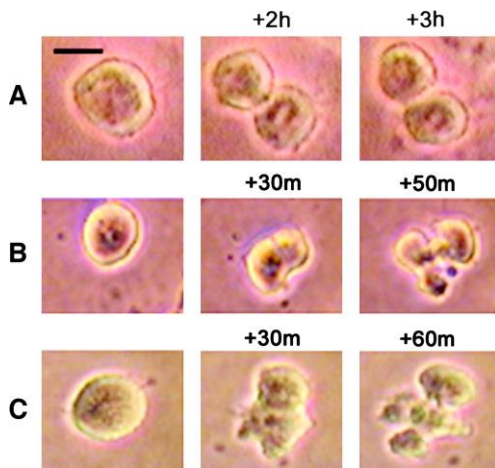


Figure 1. Time-lapse microphotography of malignant melanoma cells exposed to TTFields Therapy. *A*, an example of a cell in mitosis arrested by TTFields Therapy. Contrary to normal mitosis, the duration of which is less than 1 h, the depicted cell is seen to be stationary at mid-cytokinesis for 3 h. *B* and *C*, two examples of disintegration of TTFields Therapy-treated cells during cytokinesis. Three consecutive stages are shown: cell rounding (*left*); formation of the cleavage furrow (*middle*); and cell disintegration (*right*). Scale bar = 10 μ m.

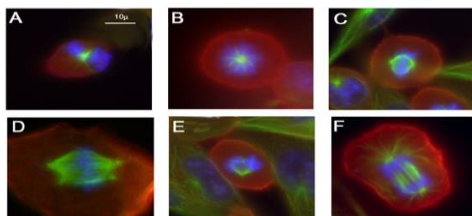


Figure 2. Immunohistochemical staining of abnormal mitotic figures in TTFields Therapy-treated cultures. Malignant melanoma cultures ($n = 4$) were treated for 24 h at 100 kHz and then stained with monoclonal antibodies for microtubules (*green*), actin (*red*), and DNA (*blue*). The photomicrographs show exemplary abnormal mitoses including: polyploid prophase (*A*); rosette (*B*); ill separated metaphase (*C*); multispindled metaphase (*D*); single-spindled metaphase (*E*); and asymmetric anaphase (*F*).

1.3 Mechanisms of Action of TTFields Therapy

In order to explain how TTFields Therapy cause orientation-dependent damage to dividing cells and disrupt the proper formation of the mitotic spindle Novocure modeled the forces exerted by TTFields Therapy on intracellular charges and polar particles using finite element simulations. Two main mechanisms by which the electric fields may affect dividing cells were recognized. The first relates to the field effect on polar macromolecule orientation. Within this framework, during the early phases of mitosis, i.e., in pre-telophase, when tubulin polymerization-depolymerization drives the proliferation process, the electric field forces any tubulin dimers, positioned further than 14 nm away from the growing end of a microtubule, to orient in the direction of the field (Figure 3). This force moment, (10^{-5} pN) acting on the dimers, is sufficient to interfere with the proper process of assembly and disassembly of microtubules that

is essential for chromosome alignment and separation. (Gagliardi 2002) This effect can explain the mitotic arrest of TTField treated cells. (Fishkind 1996)

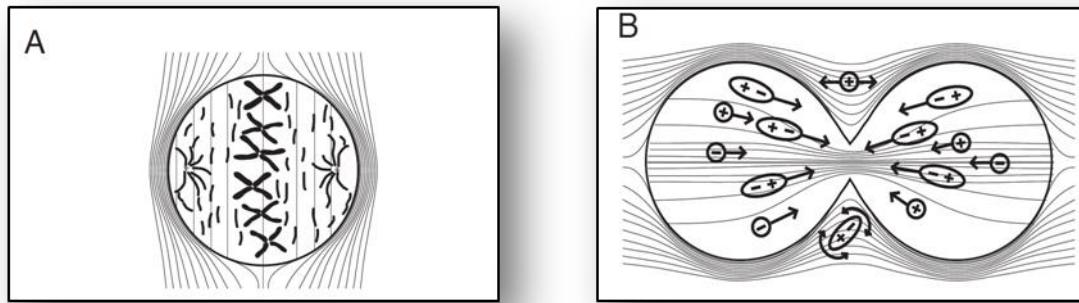


Figure 3. Tumor treating fields mechanism of action: (A) Disruption of the formation of the mitotic spindle in metaphase, and (B) Positive dielectrophoresis during anaphase.

The second mechanism, which interferes with cell division and is most likely to play an important role in cell destruction, becomes dominant during cleavage. As seen in simulations, the electric field within quiescent cells is homogenous, whereas the field inside mitotic cells, during cytokinesis, is not homogenous. An increased field line concentration (indicating increased field intensity) is seen at the furrow, a phenomenon that highly resembles the focusing of a light beam by a lens. This in-homogeneity in-field intensity exerts a unidirectional electric force on all intracellular charged and polar entities (including induced dipoles), pulling them towards the furrow (regardless of field polarity). For example, for a cleavage furrow that reached a diameter of 1 μm in an external field of only 1 V/cm, the force exerted on the microtubules is in the order of 5 pN. This magnitude is compatible with the reported forces necessary to stall microtubule polymerization that is 4.3 pN. (Dogterom 1997) With regards to other particles, such as cytoplasmic organelles, they are polarized by the field within dividing cells. Once polarized, the forces acting on such particles may reach values up to an order of 60 pN, resulting in their movement towards the furrow at velocities that may approach 0.03 m/sec. At such velocity, cytoplasmic organelles would pile up at the cleavage furrow within a few minutes, interfering with cytokinesis and possibly leading to cell destruction. It has also been found that the electric forces acting on intracellular particles are maximal when the axis of division is aligned with the external field. This is consistent with the dependence of the destructive effect of TTFields Therapy on the angle between division axis and the field, as demonstrated experimentally. The calculated dependence of the magnitude of this force on frequency is consistent with the experimentally determined frequency dependence of the inhibitory effect of TTFields Therapy on melanoma and glioma cell proliferation (120 kHz vs. 200 kHz, respectively). Finally, cells that progress to anaphase show evidence of structural disruption and violent membrane blebbing (Figure 4).

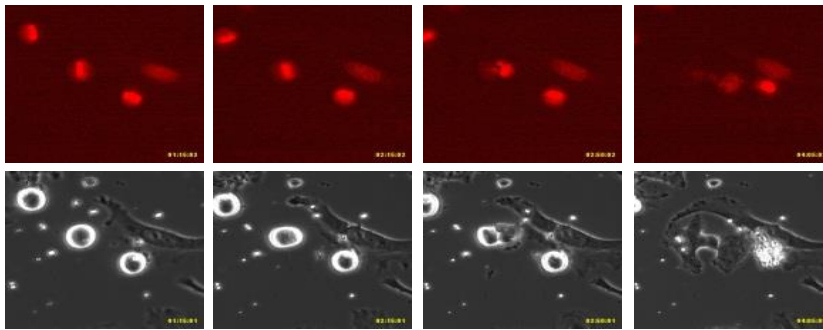


Figure 4. Microscopic evidence of membrane blebbing. HeLa cells treated with TTFields during mitosis exhibit both moderate and violent membrane blebbing soon after the appearance of metaphase plates within the cells. (Lee 2011)

1.4 In Vivo Effects of TTFields Therapy

Novocure has shown that TTFields Therapy can be applied effectively to animals through electrodes (transducer arrays) placed on the surface of the body. (Kirson 2004; Kirson 2007) Using a special type of electrically insulated transducer array, significant inhibition of the growth of both intradermal melanoma (B16F1, Figure 5 A-F) in mice and intracranial glioma (F-98, Figure 5 G-H) in rats was seen after less than one week of treatment. This growth inhibition was accompanied by a decrease in angiogenesis within the tumor, due to inhibition of endothelial cell proliferation.

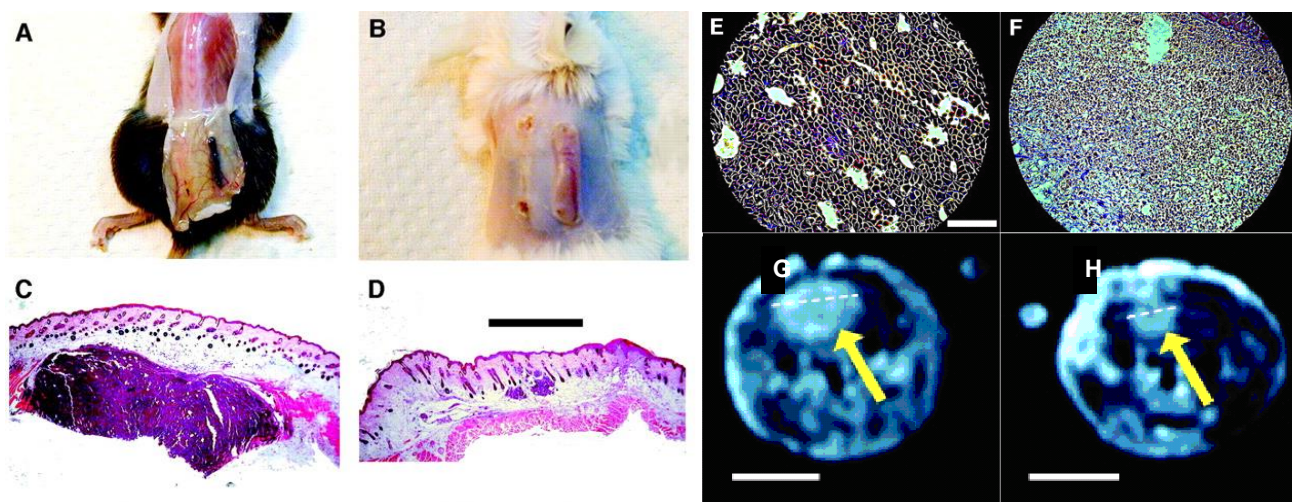


Figure 5 A-F. In vivo effects of TTFields on intradermal tumors in mice. Malignant melanoma (A) and adenocarcinoma (B) tumor cells were injected in two parallel locations intradermally on the back of each mouse. Only the tumor on the left side of the mouse was treated. After 4 days of TTFields treatment (at 100 kHz), no tumor can be discerned on the treated side, whereas on the untreated side a large tumor has grown. C–F, histological sections of TTFields-treated intradermal melanoma *versus* a control (untreated) melanoma on the same mouse. C, after H&E staining, a large (5 mm diameter) nodule of melanoma cells can be seen in the dermis of the control tumor ($\times 40$). Note that due to the large size of the tumor, its deep portion has been lost in preparation. D, treated tumor; only two small (< 0.4 mm diameter) nodules are present (scale bar = 0.5 mm). The nontumor structures of the dermis are morphologically intact. E, control tumor, malignant melanoma cells appear intact and viable ($\times 200$). (Scale bar = 100 μ m). F, only necrotic tissue and cellular debris are seen in the treated tumor.

Figure 5 G-H. TTFields inhibition of the growth of intracranial glioma. (G and H) Exemplary T1 weighted coronal MRI sections (after IV injection of Gd-DTPA) of the heads of a control and a TTFields treated (200 kHz, two-directional TTFields) rat, respectively. In both examples, the section shown is that with the largest diameter tumor. Head simulations are 3.1×1.9 cm ellipsoid; skin thickness, 0.4 mm ($\sigma = 0.00045$ S/m; $\epsilon = 1,120$); skull thickness, 1.1 mm ($\sigma = 0.015$ S/m; $\epsilon = 16$); thickness of the CSF surrounding the brain, 0.5 mm ($\sigma = 2$ S/m; $\epsilon = 109$); and brain itself has the properties of a uniform white matter ($\sigma = 0.15$ S/m; $\epsilon = 3,200$). The electrodes placed over a 0.5-mm layer of hydrogel. Note the almost uniform field intensity in most brain volume. (Scale bars, 1 cm.)

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

Secondly, the antimitotic effect of TTFields Therapy might be expected to damage the replication of rapidly dividing normal cells within the body (bone marrow, small intestine mucosa). Surprisingly, no treatment-related toxicities were found in any of the animal safety trials performed by Novocure, even when field intensities, 3-fold higher than the effective antitumoral dose were used. The lack of damage to

intestinal mucosa in TTField-treated animals is probably a reflection of the fact that the small intestine mucosal cells have a slower replication cycle than neoplastic cells and that the intestine itself most likely changes its orientation in relation to the applied field quite often, lowering the efficacy of TTField-mediated mitotic disruption. Bone marrow, on the other hand, is naturally protected from TTFields Therapy by the high electric resistance of both bone and bone marrow compared to most other tissues in the body. To test the later assumption, the TTField intensity within the bone marrow of a long bone was modeled using the finite element mesh (FEM) method. It was found that the intensity of TTFields Therapy was 100-fold lower within the bone marrow compared to the surrounding tissues (including within solid tumors). Thus, hematopoietic cell replication should not be affected even when TTField intensities 10-fold higher than necessary to inhibit tumor growth are applied.

1.5 The Optune Device

The Optune is a portable battery-operated device that produces TTFields within the human body using surface electrodes (transducer arrays). The TTFields Therapy is delivered to the patient by means of surface transducer arrays that are electrically insulated, so that resistively coupled electric currents are not delivered to the patient. The transducer arrays, which incorporate a layer of adhesive hydrogel and a layer of hypoallergenic medical tape, are placed on the patient's shaved head. The transducer arrays must be replaced every 3 to 4 days and the scalp re-shaved in order to maintain optimal capacitive coupling between the transducer arrays and the patient's head. All the treatment parameters are pre-set by Novocure so there are no electrical output adjustments available to the patient. The patient must learn to apply and change transducer arrays and change and recharge depleted device batteries and to connect to an external electrical outlet.

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

1.6 Effect of Optune on Newly Diagnosed GBM Patients – Clinical Pilot Study

A pilot study was performed enrolling 10 newly diagnosed GBM patients treated with the Optune device. (Kirsan 2009) All patients underwent surgery and chemoradiotherapy for the primary tumor. All patients received temozolomide as adjuvant chemotherapy, in addition to Optune treatment. Patients were treated with multiple 4-week treatment courses using continuous, 24-hour a day, 200 kHz, 0.7 V/cm TTFields Therapy. TTFields Therapy were applied through two sets of opposing insulated transducer arrays and alternated at a 1 second duty cycle between two perpendicular field directions through the tumor. Patients completed between 1 and 17 treatment courses, leading to maximal treatment duration of 16.5 months. Overall, more than 96, 4-week treatment courses were completed (> 9.6 courses per patient on average). The treatment was well tolerated with no treatment-related serious adverse events seen in any patients. Patients received treatment on average about 80% of the scheduled time. Despite the continuous nature of TTFields treatment (i.e., 24 hours a day for many months) the compliance with treatment was very high, with patients taking very few days off treatment and stopping only for short periods of time during treatment for personal needs.

Mild to moderate contact dermatitis appeared beneath the transducer array gel in all patients during treatment. In most cases this dermatitis appeared for the first time during the second treatment course. The skin reaction improved with use of topical corticosteroids. Slight back and forth shifting of the location of the transducer arrays was necessary in order to allow for continuous treatment and allow the skin to recover.

The median PFS of the patients in this study exceeded concurrent and historical controls¹ (greater than 18 months versus 7.1 months, respectively). At the time of the last report, 2 of the 10 patients had died and the remaining 8 patients were still alive, of which 5 were progression free. Median OS from diagnosis is greater than 39 months at the time of the last report [compared to 14.6 months in historical controls (Stupp 2005)].

Although the number of patients in this pilot trial is small, the excellent safety profile of this treatment modality and the highly promising efficacy data gathered so far indicate the potential of Optune treatment as an effective therapy for newly diagnosed GBM patients. As result of this pilot study Novocure is conducting an international phase III clinical trial in newly diagnosed GBM. Patients will be randomized

2:1 following surgery and chemoradiation to temozolomide alone or temozolomide and Optune. Out of the planned enrollment of 700 patients, over 300 patients have been enrolled to date.

1.7 Effect of Optune on Recurrent GBM Patients – Clinical Pilot Study

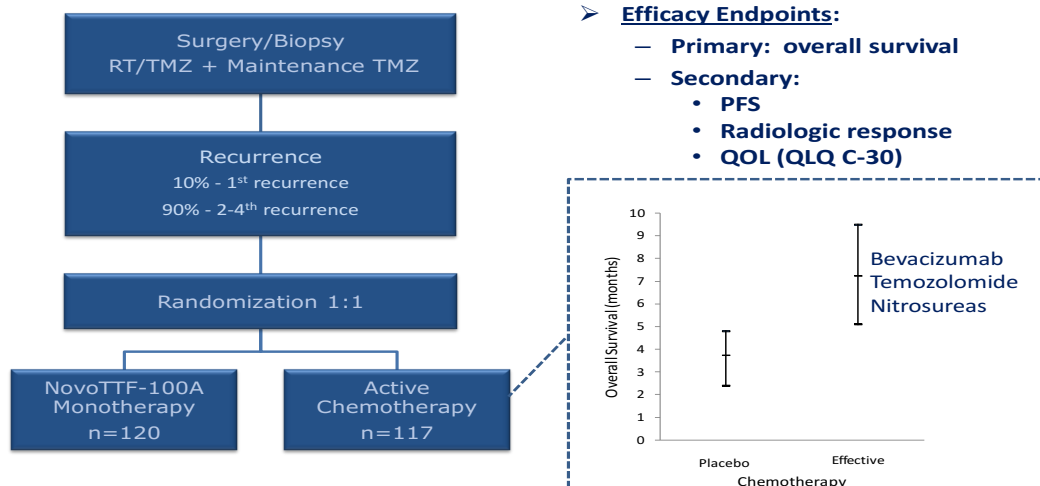
A pilot study was performed enrolling 10 recurrent GBM patients treated with the Optune device as monotherapy. (Kirson 2007; Kirson 2009) All patients underwent surgery and radiotherapy for the primary tumor. Only 1 patient was chemotherapy naïve, the rest having received temozolomide or other chemotherapeutic agents, as adjuvant treatment, prior to recurrence.

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

The PFS of the patients in this study exceeded historical controls (26.1 weeks versus 9 weeks, respectively) (Wong 1999). The PFS at 6 months (PFS6) was 50% compared to 15% in historical controls (Wong 1999). At the time of the last report, 7 of the 10 patients had died. The remaining 3 patients were still alive and 2 of them were progression free. Median OS was 62 weeks. Response rate was 25% (1 CR and 1 PR) and only 2 patients had progressive disease despite treatment.

1.8 Effect of Optune on Recurrent GBM Patients – Pivotal Study

NovoTTF: Recurrent GBM Phase III Trial (EF-11)

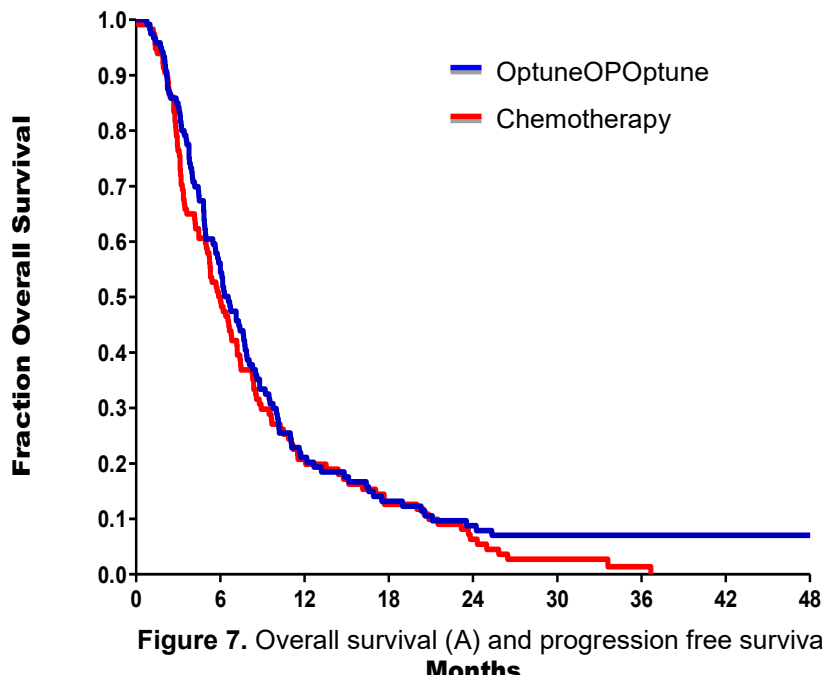


Stupp et al., European Journal of Cancer 2012

Figure 6. Schema of the EF-11 trial, Optune versus physician choice chemotherapy in recurrent GBM

Based on the promising data from the pilot trial, Novocure conducted a prospective, randomized, open-label, active parallel control trial to compare the effectiveness and safety outcomes of recurrent GBM subjects treated with Optune monotherapy (n=120) to those treated with an effective best standard of

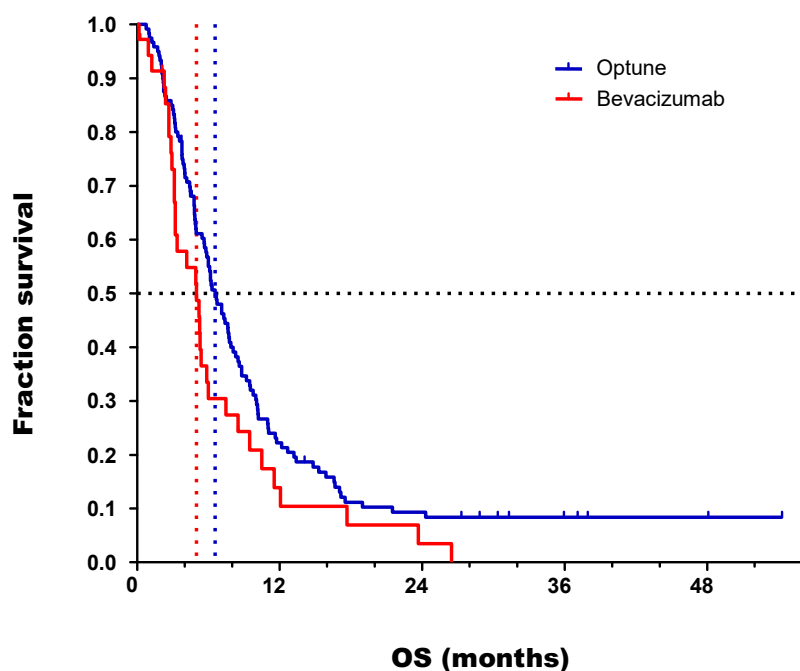
care chemotherapy (including bevacizumab; n=117). Best standard of care chemotherapy was investigator chosen, with the most common treatments as follows: 31% bevacizumab-based regimens, 31% irinotecan and 25% nitrosoureas. Patient characteristics were well balanced between treatment arms and 90% of patients were at their second or beyond recurrence (Figure 6). Optune subjects had comparable OS to subjects receiving the best available chemotherapy in the US today (OS 6.6 vs. 6.0 months; HR 0.86; p=0.98, shown in Figure 7) (Stupp 2012). Similar results showing comparability of Optune to chemotherapy were seen in all secondary endpoints (e.g., PFS6 = 21.4% for Optune vs. 15.2% for chemotherapy). In addition, objective response rates of 14% were seen with Optune monotherapy vs. 9.6% for chemotherapy (p = 0.19). Responses on the Optune arm were durable as demonstrated by the tail end of the PFS curve in Figure 7.



Median survival (months)	
Optune System (n = 120)	6.6
Chemotherapy (n = 117)	6.0
Cox Proportional Model	
Hazard Ratio	0.86
P value	0.27
95% CI of ratio	0.66 – 1.12

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

Given the clinical interest in bevacizumab in the setting of recurrent GBM two exploratory survival analyses were performed in a subset of bevacizumab treated patients: 1) Optune treatment versus patients that had received bevacizumab-based regimens on the chemotherapy arm of the trial, and 2) Optune versus chemotherapy in the subset of patients that had progressed on bevacizumab prior to entering the trial (~20%). In the first exploratory analysis, median OS was significantly longer for the Optune-treated patients than for those treated with a bevacizumab-based regimen (6.6 vs. 5.0 months; HR 0.65, $p = 0.048$; CI 0.51 to 0.90)²⁸ (Figure 8). In the second exploratory analysis, median OS in patients who had progressed on bevacizumab was significantly longer when treated with Optune compared to chemotherapy (6.3 vs. 3.3 months; HR 0.39; $p = 0.01$; CI 0.19 to 0.79) (Figure 9).



Median survival	
Optune System (n = 120)	6.6 m
Bevacizumab (n = 36)	5.0 m
Cox Proportional Model	
Hazard Ratio	0.65
P value	0.048
95% CI of ratio	0.51 to 0.90

Figure 8. Exploratory analysis of overall survival: Optune vs. subset of bevacizumab treated patients

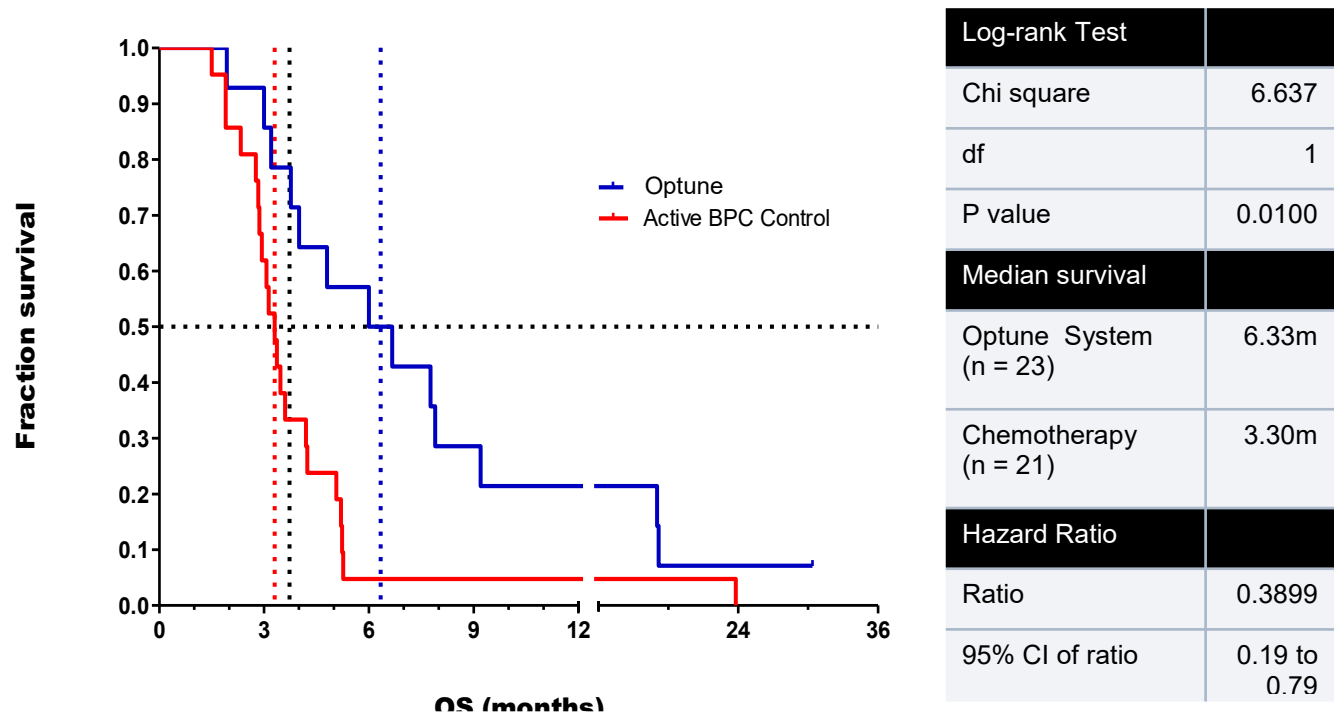


Figure 9. Exploratory analysis of overall survival: Optune vs. active BPC control (best physicians choice chemotherapy) in bevacizumab failures

Treatment options for patients with recurrent GBM progressing on bevacizumab remains a significant clinical challenge and an important area of study. The post hoc analysis of the EF-11 trial demonstrated single-agent activity of TTFields, especially in patients who have progressed on bevacizumab. In addition the mechanism of action of TTFields is not limited by normalization of the BBB by use of concomitant bevacizumab. This makes a rational and compelling case for evaluation of the combination of TTFields and bevacizumab in patients with recurrent GBM who progress on bevacizumab. In addition, the favorable safety profile of TTFields suggests that the combination will add little additional toxicity.

2.0 OBJECTIVES

2.1 Primary Objective

To determine the efficacy of TTFields Therapy with bevacizumab as measured by the overall survival rate at 6 months from time of registration

2.2 Secondary Objectives

2.2.1 To determine the efficacy of TTFields Therapy with bevacizumab as measured by overall survival from time of registration

2.2.2 To determine the efficacy of TTFields Therapy with bevacizumab as measured by progression-free survival from time of registration

2.2.3 To determine the response rate of TTFields Therapy with bevacizumab

2.2.4 To evaluate and record the toxicities of TTFields Therapy with bevacizumab

3.0 PATIENT SELECTION

For questions concerning eligibility, contact the study Data Managers (see the title page for contact information).

3.1 Conditions for Patient Eligibility

3.1.1 Histologically proven diagnosis of glioblastoma or other grade IV malignant glioma (including variants of glioblastoma ie, gliosarcoma, giant cell glioblastoma, etc.).

3.1.2 Confirmation of tumor recurrence or progression on contrast MRI (with and without gadolinium contrast) as determined by RANO criteria within 14 days prior to registration for patients who did not have recent resection of their glioblastoma or only had a stereotactic biopsy.

3.1.3 Patients having undergone recent resection (within 5 weeks prior to registration) of their glioblastoma to treat current recurrence prior to study treatment must have recovered from the effects of surgery (including patient's skin having fully recovered from the surgical wound) Note: a 4-week window is required after surgery prior to starting treatment per protocol Section 7.0. For CNS-related stereotactic biopsies, a minimum of 7 days must have elapsed prior to registration.

- Residual disease of recurrent glioblastoma is not mandated for eligibility into the study. To best assess the extent of residual disease post-operatively, a post-operative MRI scan must be performed prior to registration and is recommended to be within 96 hours post-surgery (although 24-48 hours would be optimum). Note: Patients who did have surgery with a post-operative contrast-enhanced scan falling outside the 5-week window prior to registration, per definition of recent surgery in 3.1.3, must have a repeat MRI scan within 14 days prior to registration.

3.1.4 Patients with up to two recurrences are allowed.

3.1.5 Failure on bevacizumab (either as a monotherapy or a combination) as most recent regimen confirmed by tumor recurrence on MRI as described in Section 3.1.2.

- The patient must have failed no more than one regimen of bevacizumab.
- The patient must not have received bevacizumab as an upfront treatment in newly diagnosed glioblastoma.
- There must be a minimum of 14 days (i.e., an interval equal to or greater than 14 days) since last treatment with bevacizumab and registration

3.1.6 History/physical examination within 14 days prior to registration;

3.1.7 Karnofsky performance status ≥ 70 within 14 days prior to registration;

3.1.8 Age ≥ 22 ;

3.1.9 CBC/differential obtained within 14 days prior to registration, with adequate bone marrow function defined as follows:

- Absolute neutrophil count (ANC) $\geq 1,000$ cells/mm³;
- Platelets $\geq 75,000$ cells/mm³;
- Hemoglobin ≥ 9.0 g/dl (Note: The use of transfusion or other intervention to achieve Hgb ≥ 9.0 g/dl is acceptable.);

3.1.10 Adequate renal function within 14 days prior to registration, as defined below:

- Creatinine ≤ 1.5 mg/dl
- Urine protein: creatinine (UPC) ratio < 1.0 within 14 days prior to registration **OR** urine dipstick for proteinuria $\leq 2+$ (patients discovered to have $> 2+$ proteinuria on dipstick urinalysis at baseline must have a UPC ratio done that is < 1.0 to be eligible. If the UPC ratio is ≥ 1.0 then the patients should undergo a 24-hour urine collection and must demonstrate ≤ 1 g of protein in 24 hours to be eligible).

Note: UPC ratio of spot urine is an estimation of the 24-hour urine protein excretion; a UPC ratio of 1 is roughly equivalent to a 24-hour urine protein of 1 gm. UPC ratio is calculated using one of the following formulas:

- ☐ [urine protein]/[urine creatinine]: if both protein and creatinine are reported in mg/dL
- ☐ [(urine protein) x 0.088]/[urine creatinine]: if urine creatinine is reported in mmol/L

3.1.11 Serum total bilirubin $\leq 1.5 \times$ ULN within 14 days prior to registration

3.1.12 ALT and AST $\leq 3.0 \times$ ULN within 14 days prior to registration

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

1. No active bleeding or pathological condition that carries a high risk of bleeding (e.g., tumor involving major vessels or known varices) within 14 days prior to registration
2. One of the below criteria must be met based on patient's therapy:

- a) Warfarin: In-range INR (usually between 2 and 3) within 14 days prior to registration
- b) Low molecular weight heparin or Novel oral anti-coagulant: stable dose within 14 days prior to registration

- 3.1.14** Patients must have recovered from the toxic effects of prior therapy at the time of registration as follows:
- 28 days from the administration of any investigational agent
 - 28 days from administration of prior cytotoxic therapy with the following exceptions:
 - 14 days from administration of vincristine or irinotecan
 - 42 days from administration of nitrosoureas
 - 21 days from administration of procarbazine
 - 7 days from administration of non-cytotoxic agents [e.g., interferon, tamoxifen, thalidomide, cis-retinoic acid, etc. (radiosensitizer does not count)]. Any questions related to the definition of non-cytotoxic agents should be directed to the study chair.
- 3.1.15** Female patients of child-bearing potential must have a negative serum pregnancy test within 14 days prior to registration.
- 3.1.16** Patient must be maintained on a stable or decreasing dose of corticosteroid for at least 5 days before the baseline scan.
- 3.1.17** Minimum interval since completion of radiation treatment at the time of registration is 90 days.
- 3.1.18** Patient must provide study specific informed consent prior to study entry.

3.2 Conditions for Patient Ineligibility (10/31/16)

- 3.2.1** Prior invasive malignancy (except non-melanomatous skin cancer) unless disease free for a minimum of 3 years. (For example, carcinoma in situ of the breast, oral cavity, or cervix are all permissible);
- 3.2.2** Infra-tentorial tumor.
- 3.2.3** > 1 cm diameter of blood seen on the MRI described in Section 3.1.2.
- 3.2.4** Severe, active co-morbidity, defined as follows:
- Major surgery such as intra-thoracic, intra-abdominal or intra-pelvic (with the exception of craniotomy unless craniotomy was performed ≤ 4 weeks prior to protocol treatment), open biopsy or significant traumatic injury ≤ 4 weeks prior to registration, or patients who have had minor procedures, percutaneous biopsies or placement of vascular access device ≤ 1 week prior to registration, or who have not recovered from side effects of such procedure or injury.
 - Non-healing surgical incisions or wounds on the scalp where the transducers will be placed.
 - Implanted pacemaker, defibrillator or deep brain stimulator, other implanted electronic devices in the brain
 - Unstable angina and/or congestive heart failure requiring hospitalization within the last 6 months prior to registration;
 - Transmural myocardial infarction within the last 6 months prior to registration;
 - Cerebrovascular accident (CVA), transient ischemic attack (TIA) within the last 6 months prior to registration
 - Pulmonary embolism (PE) within the last 6 months prior to registration
 - Uncontrolled hypertension (defined by a SBP ≥ 160 mm Hg or DBP ≥ 100 mm Hg while on anti-hypertensive medications) within 14 days prior to registration
 - Acute bacterial or fungal infection requiring intravenous antibiotics at the time of registration;
 - Chronic lung disease or Chronic Obstructive Pulmonary Disease exacerbation or other respiratory illness requiring hospitalization or precluding study therapy at the time of registration;
 - Severe hepatic disease, defined as a diagnosis of Child-Pugh Class B or C hepatic disease.
 - Known HIV positive patients. Note also that HIV testing is not required for eligibility for this protocol.
 - Other concurrent severe and/or uncontrolled concomitant medical conditions (e.g. active or uncontrolled infection, uncontrolled diabetes) that could cause unacceptable safety risks or compromise compliance with the protocol.
 - Skull defects such as missing bone flap, a shunt, or bullet fragments.
 - Significant intracranial pressure as per treating physician that may require surgical intervention.
- 3.2.5** Pregnancy or women of childbearing potential and men who are sexually active and not willing/able to use medically acceptable forms of contraception; this exclusion is necessary because the treatment involved in this study may be significantly teratogenic. **Note:** Contraception is required during treatment with bevacizumab and for 180 days after the last dose for women of childbearing potential and 90 days after the last dose for males.

- 3.2.6 Women who are breast feeding
- 3.2.7 Prior allergic reaction to bevacizumab or severe adverse event with bevacizumab.
- 3.2.8 Known sensitivity to conductive hydrogels
- 3.2.9 Prior treatment with the Optune system.
- 3.2.10 Active treatment on another clinical trial.

4.0 PRETREATMENT EVALUATIONS/MANAGEMENT

NOTE: This section lists baseline evaluations needed before the initiation of protocol treatment that do not affect eligibility.

4.1 Recommended Evaluations/Management

Albumin, alkaline phosphatase, BUN, calcium, chloride, glucose, potassium, total protein, and sodium chloride are recommended within 30 days prior to treatment start.

5.0 REGISTRATION PROCEDURES

Note: This is a limited institution study; see participating institutions on the RTOG web site.

5.1 Regulatory Requirements (12-DEC-2017)

5.1.1 Please refer to the study-specific guide for investigators and research staff for detailed procedures regarding the following: requirements for regulatory collection and patient enrollment. The RTOG Foundation 3503 Study Guide is posted on the RTOG website: <https://www.rtog.org/ClinicalTrials/RTOGFoundationStudies/RTOGFoundationStudy3503.aspx>

5.1.2 Patient Enrollment

See the study specific guide on the RTOG Foundation 3503 protocol page of the RTOG website, www.rtog.org for details.

5.1.3 Pre-Registration Requirements for Investigator Certification

All investigators must successfully complete the training provided by Novocure for clearance to submit prescriptions for the Optune device. (Training can be arranged directly with Novocure at 855-281-9301 or support@novocure.com). Novocure will issue a Certified Prescriber Certificate after investigator training is completed. This certificate is required in order to receive the device.

6.0 RADIATION THERAPY

Not applicable.

7.0 DRUG AND DEVICE THERAPY (12-DEC-2017)

Protocol treatment must begin within 14 calendar days after registration for all patients. In addition, patients who had recent resection of their GBM must start treatment ≥ 4 weeks post-surgery.

7.1 **Treatment: Bevacizumab Plus Optune** (see section 12.0 for details on treatment form collection)

Patients will receive bevacizumab at a dose of 10 mg/kg every 2 weeks over 30 minutes on a 4-week cycle and Optune will be worn continuously. Treatment will be given until progression or development of adverse events that require complete discontinuation. Bevacizumab should start on the first day (+/- 1 day) of Optune therapy.

7.2 **Bevacizumab Treatment Guidelines**

Refer to the package insert for detailed pharmacologic and safety information.

7.2.1 Bevacizumab is administered intravenously as a continuous infusion. The initial dose can be administered over a minimum of 30 minutes if no adverse reactions occurred during previous infusions of bevacizumab. If infusion-related adverse reactions occur, all subsequent infusions should be administered over the shortest period that was well tolerated.

Patients will receive bevacizumab at a dose of 10 mg/kg every 2 weeks.

7.3 Optune Treatment Guidelines (12-DEC-2017)

Optune is an FDA approved device. Optune is being made available under an IDE sponsored by the RTOG Foundation and distributed by Novocure.

Prescription Process and Supply

Please see study specific guide on the RTOG website, www.rtog.org.

7.3.1 Treatment Planning

Transducer array layout will be determined based on the location of the patient's tumor(s) on MRI. Investigators are required to send the baseline MRI scans to Novocure for NovoTAL™ array layout planning **no later than one day from submitting the prescription** (shipping labels are provided at certification). Novocure will acknowledge receipt of the prescription form and the MRI. An array layout will be supplied prior to treatment start. Investigator may modify the transducer array layout at any time during the trial based on radiological data analysis and clinical considerations. NovoTAL™ software supplied by Novocure for layout planning may be used **ONLY** by study investigators who are NovoTAL™ certified by Novocure and wish to use it on this trial. The NovoTAL™ certified sites must send the NovoTAL-generated array layout PDFs to support@novocure.com **within 1-5 days of submission of the Rx**.

Patients will receive an instructional call from Novocure prior to training to highlight important items such as the need to shave the head and to answer any technical or logistics questions the patient or caregiver may have. All other Patient training: Patients will be trained on the technical aspects of using the device by a Novocure Device Support Specialist in their home.

7.3.2 Treatment Initiation

Optune treatment will be initiated by the investigator as per protocol. All patients will be required to shave their heads to initiate array placement and TTField therapy. Array placement will be performed based on the transducer array map calculated during treatment planning.

7.3.3 Treatment Duration

Treatment with the device will be continuous with breaks allowed for personal needs (eg. showering, array exchange). Patients must use the device for at least 18 hours a day on average. Patients will be allowed an additional 1-3 days off treatment between courses (one course is 4 weeks) according to personal needs. Treatment will be continued until disease progression in the brain, death, or unacceptable side effects to patient.

7.3.4 Treatment Programming

The Optune device will be programmed by Novocure to deliver 200kHz TTFields Therapy 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.

7.3.5 Transducer Array Replacement

Patients will replace the transducer arrays twice to 3 times per week with the help of a caregiver. At each array replacement the patient's scalp will be re-shaved and skin treated according to Section 7.3.7. Instructions for replacing the arrays will be part of the initial training. Novocure Device Support Specialists will be available to provide support as needed.

Technical Support: Technical support is available 24/7 by Novocure through a toll free number (855-281-9301).

7.3.6 Compliance Assessment

The device will be interrogated on a monthly basis to assess patient compliance with therapy. Novocure device technicians will conduct the monthly compliance assessment. Compliance reports will be provided to the investigators by Novocure's technical support center.

The Investigator will anonymize the monthly patient compliance reports and send to RTOG Headquarters via fax 215-940-8926. Please see the study specific guide for further details.

7.3.7 Skin Care Guidelines

The following skin care guidelines should be closely adhered to:

- If the skin beneath the transducer arrays is inflamed, a high potency topical steroid should be prescribed to the patient. The patient or caregiver should apply the ointment after removing the arrays, removing remaining array adhesive from the skin with baby oil and cleaning the skin with medical alcohol. The ointment should be left on the skin for at least 30 minutes prior to washing the skin with a mild soap and applying a new set of arrays.
- 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.
- If the epidermis is breached (skin erosions, punctate lesions, cuts, open sores etc.) an antibiotic ointment (e.g. mupirocin) should be prescribed and used in place of the topical steroid treatment. Any evidence of infection should result in bacterial cultures being taken.
- There will be no “dose” adjustments to the device for adverse events. Reasons for breaks in treatment for longer than 24 hours will be documented in the CRFs. The maximum duration of treatment break allowed for adverse events related to TTFIELDS Therapy is 4 weeks.

7.3.8 Potential Adverse Events

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

- Local warmth and tingling “electric” sensation beneath the transducer array
- Allergic reaction to the adhesive or to the gel
- Skin irritation or skin breakdown
- Infection at the sites of transducer array contact with the skin
- Transducer array overheating leading to pain and/or local skin burns
- Headache
- Fatigue
- Malaise
- Muscle twitching
- Fall, if the system interferes with walking

In the phase III trial of Optune monotherapy versus physician’s choice chemotherapy in recurrent GBM, the following moderate to severe adverse events (regardless of causality) were seen:

		TTF (n=116)	Active Control (n=91)
System	Adverse event term	% (% gr. 3+4)	% (% gr. 3+4)
Hematological		3 (0)	17 (4)
	Leukopenia	0 (0)	5 (1)
	Neutropenia	0 (0)	2 (1)
	Thrombocytopenia	1 (1) [†]	7 (2)
Gastrointestinal disorders		4 (1)	17 (3)
	Abdominal pain	0 (0)	3 (0)
	Diarrhea	0 (0)	6 (2)
	Nausea / Vomiting	2 (0)	7 (0)
General deterioration and malaise		5 (1)	6 (1)
Infections		4 (0)	8 (1)
Skin rash (transducer arrays)		2 (0)	0 (0)
Metabolism and nutrition disorders		4 (1)	6 (3)
Musculoskeletal Disorders		2 (0)	5 (0)

Nervous system disorders	30 (7)	28 (7)
Brain edema	0 (0)	2 (0)
Cognitive disorder	2 (1)	2 (1)
Convulsion	7 (2)	5 (2)
Dysphasia	2 (0)	1 (0)
Headache	8 (1)	6 (0)
Hemianopsia	1 (0)	3 (1)
Hemiparesis	3 (1)	2 (1)
Neuropathy peripheral	2 (0)	2 (0)
Psychiatric disorders	5 (0)	4 (0)
Renal and urinary disorders	3 (1)	3 (0)
Respiratory Disorders	1 (0)	3 (1)
Vascular disorders	3 (1)	4 (3)
Pulmonary embolism	1 (1)	2 (2)
Hypertension	1 (0)	1 (1)
Deep vein thrombosis	1 (0)	1 (0)
† thrombocytopenia from prior chemotherapy, normalized subsequently.		

7.4 Dose Modifications

7.4.1 Optune

There will be no “dose” adjustments to the device for adverse events. Reasons for breaks in treatment for longer than 24 hours will be documented in the CRFs. The maximum duration of treatment break allowed for adverse events related to Optune therapy is 4 weeks. However, if Optune therapy is interrupted for ANY reason for > 4 weeks, the patient must discontinue bevacizumab and the device on protocol.

7.4.2 Bevacizumab

The dose of bevacizumab will be 10 mg/kg delivered intravenously. There will be no dose reduction for bevacizumab. Treatment should be interrupted or discontinued for certain adverse events, as described below. If the treatment with bevacizumab is held, the patient can continue with the device. However if bevacizumab is interrupted for ANY reason for > 8 weeks, the patient must discontinue bevacizumab and the device on protocol.

Treatment Modification for Bevacizumab-Related Adverse Events

Event	CTCAE.v4.0 Grade	Action To Be Taken
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Event	CTCAE.v4.0 Grade	Action To Be Taken
Allergic reactions or Acute infusional reactions/ cytokine release syndrome	Grade 1-3	<p>If infusion-related or allergic reactions occur, premedications should be given with the next dose and infusion time may not be reduced for the subsequent infusion. Follow the guidelines in the package insert for bevacizumab administration.</p> <p>For patients with grade 3 reactions, bevacizumab infusion should be stopped and not restarted on the same day. At the physicians' discretion, bevacizumab may be permanently discontinued or re-instituted with premedications and at a rate of 90±15 min. If bevacizumab is re-instituted, the patient should be closely monitored for duration comparable to or longer than the duration of the previous reactions.</p>
	Grade 4	Discontinue bevacizumab
Arterial Thrombosis - Cardiac ischemia/ infraction - CNS ischemia (TIA, CVA) - any peripheral or visceral arterial ischemia/thrombosis	Grade 2 (if new or worsened since bevacizumab therapy)	Discontinue bevacizumab
	Grade 3-4	Discontinue bevacizumab
Venous Thrombosis		
	Grade 3	<ul style="list-style-type: none"> ▪ Hold bevacizumab treatment. If the planned duration of full-dose anticoagulation is < 2 weeks, bevacizumab should be held until the full-dose anticoagulation period is over. ▪ If the planned duration of full-dose anticoagulation is >2 weeks, bevacizumab may be resumed during the period of full-dose anticoagulation IF all of the criteria below are met: <ul style="list-style-type: none"> - The subject must have an in-range INR (usually 2-3) on a stable dose of warfarin or be on a stable dose of heparin prior to restarting bevacizumab - The subject must not have pathological conditions that carry high risk of bleeding (eg, tumor involving major vessels or other conditions) - The subject must not have had hemorrhagic events while on study ▪ If thromboemboli worsen/recur upon resumption of study therapy, discontinue bevacizumab
	Grade 4 =	Discontinue bevacizumab
Hypertension*	[Treat with antihypertensive medication as needed. The goal of BP control should be consistent with general medical practice]	
	Grade 1	Consider increased BP monitoring

Event	CTCAE.v4.0 Grade	Action To Be Taken
	Grade 2 asymptomatic and diastolic BP < 100 mmHg	Begin anti-hypertensive therapy and continue bevacizumab
	-Grade 2-3 Symptomatic OR -Diastolic BP > 100 mmHg	Hold bevacizumab until symptoms resolve AND BP < 160/90mmHg
	Grade 4	Discontinue bevacizumab
Congestive Heart Failure	Grade 3	Discontinue bevacizumab
	Grade 4	Discontinue bevacizumab
Proteinuria	Proteinuria should be monitored by urine dipstick or urine protein creatinine (UPC) ratio before every dose of bevacizumab, if dipstick is > 2 + then a UPC ratio should be performed.	
	UPC ratio < 3.5	Continue bevacizumab
	UPC ratio ≥ 3.5	Hold bevacizumab until UPC recovers to < 3.5
	Nephrotic syndrome	Discontinue bevacizumab
Hemorrhage (CNS or pulmonary)	Grade 2-4	Discontinue bevacizumab
Hemorrhage (non-CNS; non-pulmonary)	Grade 3	<ul style="list-style-type: none"> • Patients receiving full-dose anticoagulation should discontinue bevacizumab • For patients not on full-dose anticoagulation, hold bevacizumab until ALL of the following criteria are met: <ul style="list-style-type: none"> - the bleeding has resolved and Hb is stable - there is no bleeding diathesis that would increase the risk of therapy - there is no anatomic or pathologic condition that could increase the risk of hemorrhage recurrence. • Patients who experience recurrence of grade 3 hemorrhage should discontinue study therapy
	Grade 4	Discontinue bevacizumab
RPLS (reversible posterior leukoencephalopathy syndrome or PRES (posterior reversible encephalopathy syndrome))		<ul style="list-style-type: none"> • Hold bevacizumab in patients with symptoms/signs suggestive of RPLS; subsequent management should include MRI scans and control of HTN • Discontinue bevacizumab upon diagnosis of RPLS
Wound dehiscence requiring medical or surgical intervention		• Discontinue bevacizumab
GI perforation, GI leak or fistula		Discontinue bevacizumab
Bowel obstruction	Grade 2 requiring medical intervention	Hold bevacizumab until complete resolution, with a minimum of 4 weeks after surgery.
	Grade 3-4	<ul style="list-style-type: none"> • Hold bevacizumab until complete resolution • If surgery is required, patient may restart bevacizumab after full recovery from surgery, and at investigator's discretion
Other unspecified bevacizumab-related	Grade 3	Hold bevacizumab until symptoms resolve to ≤ grade 1

Event	CTCAE.v4.0 Grade	Action To Be Taken
AEs (except controlled nausea/vomiting).	Grade 4	<ul style="list-style-type: none"> Discontinue bevacizumab Upon consultation with the study chair, resumption of bevacizumab may be considered if a patient is benefiting from therapy and the grade 4 toxicity is transient, has recovered to \leq grade 1 and unlikely to recur with retreatment

7.5 Modality Review (12-DEC-2017)

The Principal Investigator, Manmeet Ahluwalia, MD, or Neuro-Oncology Co-chair, Karan Singh Dixit, MD, will perform a Quality Assurance Review of all patients who receive or are to receive bevacizumab and device therapy in this trial. The goal of the review is to evaluate protocol compliance. The review process is contingent on timely submission of chemotherapy treatment data as specified in Section 12.1. The scoring mechanism is: **Per Protocol, Acceptable Variation, Unacceptable Deviation, and Not Evaluable**. A report is sent to each institution once per year to notify the institution about compliance for each case reviewed in that year.

The Principal Investigator, Manmeet Ahluwalia, MD, or Neuro-Oncology Co-Chair, Karan Singh Dixit, MD, will perform a Quality Assurance Review after complete data for the first 20 cases enrolled has been received at RTOG Headquarters. Dr. Ahluwalia or Dr. Dixit will perform the next review after complete data for the next 20 cases enrolled has been received at RTOG Headquarters. The final cases will be reviewed within 3 months after this study has reached the target accrual or as soon as complete data for all cases enrolled has been received at RTOG Headquarters, whichever occurs first.

7.6 Adverse Events (12-DEC-2017)

This study will use the Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 for adverse event reporting. All appropriate treatment areas should have access to a copy of the CTCAE version 4.0.

Adverse events (AEs) that meet expedited reporting criteria defined in the table below will be reported via the SAE reporting form accessed via the RTOG website.

7.6.1 Adverse Events (AEs)

Definition of an AE: Any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related. Therefore, an AE can be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not considered related to the medicinal (investigational) product (attribution of unrelated, unlikely, possible, probable, or definite). (International Conference on Harmonisation [ICH], E2A, E6).

AEs, as defined above, experienced by patients accrued to this protocol should be reported on the AE section of the appropriate case report form (see Section 12.1).

NOTE: If the event is a Serious Adverse Event (SAE) [see next section], further reporting will be required. Reporting AEs only fulfills Data Management reporting requirements.

7.6.2 Serious Adverse Events (SAEs) –Serious Adverse Events that meet expedited reporting criteria defined in the table in Section 7.7 will be reported via the SAE report form. SAEs that require 24h notification are defined in the expedited reporting table in Section 7.7.

Definition of an SAE: Any adverse drug event (experience) occurring at any dose that results in any of the following outcomes:

- Death;
- A life-threatening adverse drug experience;
- Inpatient hospitalization or prolongation of existing hospitalization;
- A persistent or significant disability/incapacity;
- A congenital anomaly/birth defect;
- Other serious/important medical events;

- Important medical events that may not result in death, be life threatening, or require hospitalization may be considered an SAE, when, based upon medical judgment, they may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed in the definition.

Due to the risk of intrauterine exposure of a fetus to potentially teratogenic agents, the pregnancy of a study participant must be reported in an expedited manner.

7.7 Serious Adverse Event (SAE) Reporting Requirements (10/31/16)

It is the responsibility of the investigator to document all adverse events which occur during the study. All serious adverse events that meet expedited reporting criteria defined in the reporting table below will be reported via the RTOG SAE Report Form. The SAE Report Form and Instructions are available on the RTOG website, www.RTOG.org. RTOG Headquarters will report unexpected and related SAEs to the FDA and NovoCure via the MedWatch Form per the requirements set forth in the Code of Federal Regulations, Section 312.32.

7.7.1 Reporting SAEs

An SAE that occurs during any part of protocol treatment and 30 days after whether or not related to protocol treatment, must be reported by the investigator per the reporting table below. In addition, any SAEs which occur as a result of protocol specific diagnostic procedures or interventions also must be reported. NOTE: please see specific protocol exceptions to expedited reporting.

The SAE report should comprise a full written summary, detailing relevant aspects of the SAE in question. The SAE summary also must include the investigator's assessment of relatedness to specific protocol treatment (e.g., bevacizumab or Optune). When applicable, information from relevant hospital case records and autopsy reports should be included. Initial and follow-up information, when it becomes available, should be e-mailed to RTOG3503AE@acr.org. In the rare event when Internet connectivity is disrupted, a 24-hour notification must be made to the RTOG Operations Office by phone, (1-800-227-5463, ext. 4189). An electronic report must be submitted immediately upon re-establish of the Internet connection.

SAEs that occur during the follow-up period beginning 30 days after end of treatment and are considered by the investigator to be possibly, probably, or definitely related to protocol treatment must be reported expeditiously via the SAE Report Form.

All SAEs must be e-mailed to RTOG3503AE@acr.org within the designated timeframe outlined in the reporting table below. RTOG will complete a preliminary review of the SAE details and may contact the site with suggested revisions. RTOG will report the SAE to NovoCure and to the FDA if applicable. Note: The individual completing the SAE Report Form should remain vigilant for RTOG's review and be prepared to make recommended revisions expeditiously in order to ensure reporting within FDA-mandated timeframes.

Pregnancy

Patients who become pregnant during the study should discontinue the study immediately. Investigators should report a pregnancy, including a male participant's impregnation of his partner, expeditiously as a grade 3 SAE coded in the CTCAE v.4 as "pregnancy, puerperium and perinatal conditions, other—pregnancy" on the SAE report form and submit the Pregnancy Report Form within 14 days of notification (see Section 12.1 for data form submission). RTOG will report the pregnancy to Novocure. Patients should be instructed to notify the investigator if it is determined after completion of the study that they become pregnant, including a male participant's impregnation of his partner, either during the treatment phase of the study or within 30 calendar days after the end of treatment. The pregnancy outcome for patients on study should be reported to RTOG. RTOG will report the status to Novocure.

Late Phase 2 and Phase 3 Studies: Expedited Reporting Requirements for Adverse Events that Occur within 30 Days of the Last Administration of the Investigational Device/Commercial Agent¹

FDA REPORTING REQUIREMENTS FOR SERIOUS ADVERSE EVENTS (21 CFR Part 312)

NOTE: Investigators **MUST** immediately report to the sponsor **ANY** Serious Adverse Events, whether or not they are considered related to the investigational agent(s)/intervention (21 CFR 312.64)

An adverse event is considered serious if it results in **ANY** of the following outcomes:

- 1) Death
- 2) A life-threatening adverse event
- 3) An adverse event that results in inpatient hospitalization or prolongation of existing hospitalization for ≥ 24 hours
- 4) A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- 5) A congenital anomaly/birth defect.
- 6) Important Medical Events (IME) that may not result in death, be life threatening, or require hospitalization may be considered serious when, based upon 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. (FDA, 21 CFR 312.32; ICH E2A and ICH E6).

ALL SERIOUS adverse events that meet the above criteria **MUST** be immediately reported to RTOG via the SAE Report Form within the timeframes detailed in the table below.

Hospitalization	Grade 1 Timeframes	Grade 2 Timeframes	Grade 3 Timeframes	Grade 4 & 5 Timeframes
Resulting in Hospitalization ≥ 24 hrs	10 Calendar Days			24-Hour 5 Calendar Days
Not resulting in Hospitalization ≥ 24 hrs	Not required		10 Calendar Days	

NOTE: Protocol specific exceptions to expedited reporting of serious adverse events are found in the Specific Protocol Exceptions to Expedited Reporting (SPEER)

Expedited AE reporting timelines are defined as:

- “24-Hour; 5 Calendar Days” - The AE must initially be reported via the SAE Report Form within 24 hours of learning of the AE, followed by a complete expedited report within 5 calendar days of the initial 24-hour report.
- “10 Calendar Days” - A complete expedited report on the AE must be submitted within 10 calendar days of learning of the AE.

¹Serious adverse events that occur more than 30 days after the last administration of investigational agent/intervention and have an attribution of possible, probable, or definite require reporting as follows:

Expedited 24-hour notification followed by complete report within 5 calendar days for:

- All Grade 4, and Grade 5 AEs

Expedited 10 calendar day reports for:

- Grade 2 adverse events resulting in hospitalization or prolongation of hospitalization
- Grade 3 adverse events

Specific Protocol Exceptions to Expedited Reporting (SPEER) for Bevacizumab:

Specific Protocol Exceptions to Expedited Reporting (SPEER)
BLOOD AND LYMPHATIC SYSTEM DISORDERS
<i>Anemia (Gr 3)</i>
<i>Febrile neutropenia (Gr 3)</i>
CARDIAC DISORDERS
<i>Cardiac disorders - Other (supraventricular arrhythmias)¹ (Gr 3)</i>
GASTROINTESTINAL DISORDERS
<i>Abdominal pain (Gr 3)</i>
<i>Colitis (Gr 3)</i>
<i>Constipation (Gr 3)</i>
<i>Diarrhea (Gr 3)</i>
<i>Dyspepsia (Gr 2)</i>
<i>Gastrointestinal hemorrhage² (Gr 2)</i>
<i>Mucositis oral (Gr 3)</i>
<i>Nausea (Gr 3)</i>
<i>Vomiting (Gr 3)</i>
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS
<i>Fatigue (Gr 3)</i>
<i>Infusion related reaction (Gr 2)</i>
<i>Non-cardiac chest pain (Gr 3)</i>
<i>Pain (Gr 3)</i>
IMMUNE SYSTEM DISORDERS
<i>Allergic reaction (Gr 2)</i>
INFECTIONS AND INFESTATIONS
<i>Infection³ (Gr 3)</i>
INJURY, POISONING AND PROCEDURAL COMPLICATIONS
<i>Wound complication (Gr 2)</i>
<i>Wound dehiscence (Gr 2)</i>
INVESTIGATIONS
<i>Alanine aminotransferase increased (Gr 3)</i>
<i>Alkaline phosphatase increased (Gr 3)</i>
<i>Aspartate aminotransferase increased (Gr 3)</i>
<i>Blood bilirubin increased (Gr 2)</i>
<i>Neutrophil count decreased (Gr 3)</i>
<i>Platelet count decreased (Gr 4)</i>
<i>Weight loss (Gr 3)</i>
<i>White blood cell decreased (Gr 3)</i>
METABOLISM AND NUTRITION DISORDERS
<i>Anorexia (Gr 3)</i>
<i>Dehydration (Gr 3)</i>
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS
<i>Arthralgia (Gr 3)</i>
<i>Myalgia (Gr 3)</i>
NERVOUS SYSTEM DISORDERS
<i>Dizziness (Gr 2)</i>
<i>Headache (Gr 3)</i>

RENAL AND URINARY DISORDERS
<i>Hematuria (Gr 3)</i>
<i>Proteinuria (Gr 2)</i>
REPRODUCTIVE SYSTEM AND BREAST DISORDERS
<i>Vaginal hemorrhage (Gr 3)</i>
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS
<i>Allergic rhinitis (Gr 3)</i>
<i>Cough (Gr 3)</i>
<i>Dyspnea (Gr 2)</i>
<i>Epistaxis (Gr 3)</i>
<i>Hoarseness (Gr 3)</i>
SKIN AND SUBCUTANEOUS TISSUE DISORDERS
<i>Pruritus (Gr 2)</i>
<i>Rash maculo-papular (Gr 2)</i>
<i>Urticaria (Gr 2)</i>
VASCULAR DISORDERS
<i>Hypertension (Gr 3)</i>
<i>Thromboembolic event (Gr 3)</i>

¹Supraventricular arrhythmias may include supraventricular tachycardia, atrial fibrillation and atrial flutter.

²Gastrointestinal hemorrhage may include: Colonic hemorrhage, Duodenal hemorrhage, Esophageal hemorrhage, Esophageal varices hemorrhage, Gastric hemorrhage, Hemorrhoidal hemorrhage, Intra-abdominal hemorrhage, Oral hemorrhage, Rectal hemorrhage, and other sites under the GASTROINTESTINAL DISORDERS SOC.

³Infection may include any of the 75 infection sites under the INFECTIONS AND INFESTATIONS SOC.

8.0 SURGERY

Not applicable to this study.

9.0 OTHER THERAPY

9.1 Permitted Supportive Therapy

All supportive therapy for optimal medical care will be given during the study period at the discretion of the attending physician(s) within the parameters of the protocol and documented on each site's source documents as concomitant medication.

9.1.1 Anticonvulsants: Anticonvulsants may be used as clinically indicated. Doses at study entry and at specific time points of the treatment must be recorded (See Appendix I).

9.1.2 Corticosteroids: Corticosteroids may be administered at the treating physician's discretion. Doses at study entry and at specific time points of the treatment must be recorded.

9.2 Non-Permitted Supportive Therapy

9.2.1 Growth factors are not permitted to induce elevations in neutrophil count

9.2.2 Erythropoietin may not be administered because of possible synergistic toxicity with bevacizumab.

10.0 TISSUE/SPECIMEN SUBMISSION

Not applicable to this study.

11.0 PATIENT ASSESSMENTS

11.1 Study Parameters

See Appendix I for study assessments pre-treatment, during treatment, and follow-up assessments.

11.2 Measurement of Response/Progression/Recurrence

It is important to use the same method of assessment from one scan to the subsequent scans.

Modified Response Assessment in Neuro-Oncology (RANO) Response Criteria will be used to define response and progression. In the past, the Macdonald criteria were used to define response and progression. This system is largely based on standardized response criteria using bi-dimensional measurements of the largest contrast-enhancing tumor area (Macdonald 1990). However, it has been demonstrated that contrast-enhanced images can be altered by agents inhibiting angiogenesis with occasional progression of T2-weighted or FLAIR abnormality as well as clinical decline despite improvement in the contrast-enhancing signal. (Batchelor 2007) In light of this, FLAIR imaging and clinical status has become part of the response criteria in addition to the widely used Macdonald criteria. Hence, the largest cross-sectional area on the T1w contrast-enhanced images will be selected and measured in 2 dimensions with linear measures on the baseline MRI axial sequence. In addition, the largest cross-sectional area of a contiguous hyperintense lesion on FLAIR sequences will be measured on the baseline MRI axial sequence. All subsequent scans will be compared against these baseline measures (for both CE and FLAIR). New foci of FLAIR signal abnormality will be recorded on each subsequent evaluation. Response will be scored based on a combination of imaging and clinical features as defined by the modified RANO criteria. (Wen 2010) Objective response rate is defined as the sum of partial responses plus complete responses.

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

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

11.3 Criteria for Discontinuation of Protocol Treatment (10/31/16)

- Progression of disease as defined in the table in section 11.2;
- A delay in protocol treatment, as specified in 7.0;
- Unacceptable adverse events; also see Section 7.0 for further information.

If protocol treatment is discontinued, follow-up and data collection will continue as specified in the protocol.

The patient may withdraw from the study at any time for any reason. The institution must notify RTOG Headquarters Data Management about this in writing and follow the guidelines set forth in the RTOG procedure manual. Follow-up and data collection will not continue in cases of patient withdrawal.

12.0 DATA COLLECTION

Data should be submitted to:

RTOG Headquarters*
1818 Market Street, Suite 1720
Philadelphia, PA 19103

***If a data form is available for web entry, it must be submitted electronically.**

Patients will be identified by initials only (first middle last); if there is no middle initial, a hyphen will be used (first-last). Last names with apostrophes will be identified by the first letter of the last name.

12.1 Summary of Data Submission (12-DEC-2017)

<u>Item</u>	<u>Due</u>
Demographic Form (A5)	Within 2 weeks after registration
Initial Evaluation Form (I1)	Within 2 weeks after registration
Pathology Report (P1, not an RTOG form but a copy of the pathology report to be faxed to RTOG Headquarters 215-940 8926). Personal health information must be removed from the report prior to faxing. Also the report must be identified with study #, case #, patient initials, and RTOG institution #.	Within 2 weeks after registration
Compliance Reports (CR, not an RTOG form but a copy of the compliance reports to be faxed to RTOG Headquarters 215-940 8926). These reports will be sent to the site by Novocure.	Monthly
Treatment Form (TF)	Arm (bevacizumab + <u>Optune</u>): At completion of each 4-week period (2 doses of bevacizumab and use of <u>Optune</u> for 4 weeks per TF Form if no protocol modification)
Follow-up Form (F1)	At the time of progression and at death. AFTER progression or treatment discontinuation: every 8 weeks for 1 year, then every 12 weeks for 1 year, then every 6 months.
Pregnancy Form (to be faxed to RTOG Headquarters: 215-940 8926)	Within 14 days of notification (see Section 7.7.1)

13.0 STATISTICAL CONSIDERATIONS

13.1 Primary Endpoint

Overall survival rate at 6 months from registration

13.2 Secondary Endpoints

13.2.1 Overall survival (OS)

13.2.2 Progression-free survival (PFS)

13.2.3 Objective response rate

13.2.4 Frequencies of treatment-related adverse events

13.3 Sample Size and Power Justification

The primary objective of this study is to determine whether the addition of TTFields Therapy with bevacizumab improves the 6m OS rate for BEV-refractory recurrent GBM patients. The data reported by Hovey (2015) and by Iwamoto (2009) are used as the historical control for this study. The null hypothesis is a 6m OS rate of 35%. The alternative hypothesis is that patients receiving TTFields Therapy plus bevacizumab will have an improved 6m OS rate at 50%, corresponding to a 33% reduction in mortality hazard (i.e. a hazard ratio of 0.67). With 80 eligible patients, there will be 85% power to detect this projected effect size at a significance level of 0.05 (1-sided). Guarding against up to a 5% ineligibility rate, the final target accrual for this study will be 85 cases.

Based on the monthly accrual for prior RTOG recurrent glioblastoma phase II studies (RTOG 0625 and 0929), this study is projected to accrue 10 cases/month. Therefore, the target accrual should be completed within 15 months of study activation, allowing slow accrual in the first 6 months. If the average monthly accrual (6 months after trial activation) is less than 5 patients, the study will be re-evaluated with respect to feasibility.

13.4 Analysis Plan

13.4.1 Statistical Methods

OS and PFS will be estimated using the Kaplan-Meier method. OS will be measured from the date of registration to the date of death or, otherwise, the last follow-up date on which the patient was reported alive. PFS will be measured from the date of registration to the date of first progression or death or, otherwise, the last follow-up date on which the patient was reported alive. The primary analysis will be conducted among all eligible patients with at least 6-month follow-up information. The following rules will be used to judge the efficacy of the treatment: out of the 80 eligible patients, if 36 or more experience 6m OS, we will reject the null hypothesis that the 6m OS rate is 35% or less and conclude that the 6m OS rate is at least 35%; If 35 or fewer patients experience 6m OS, we will not be able to reject the null hypothesis. The median OS and PFS time will be estimated, along with their respective 95% confidence interval (CI). Secondary efficacy analyses may also be conducted among patients who have had the opportunity to use the device according to requirements in Section 7.3.3 for at least 4 weeks from treatment initiation.

The objective response rate and rate of grade 3 or greater toxicities will be estimated using the exact binomial method with accompanying 95% CIs. In terms of grade 3 or greater toxicity, all eligible patients receiving any protocol treatment will be included.

13.4.2 Interim Analysis to Monitor Study Progress

Interim reports with statistical analyses are prepared every 6 months until the initial manuscript reporting the treatment results has been submitted. The reports contain:

- The patient accrual rate with a projected accrual completion date
- Accrual by institution
- The pretreatment characteristics of accrued patients
- The frequency and severity of toxicities
- The results of any completed study chair modality reviews

The interim reports will not contain the results from the treatment comparisons with respect to the efficacy endpoints (OS, PFS, treatment response). The RTOG Foundation DMC will review the accrual to the study and the rate of adverse events on the study at least twice per year until the initial results of the study have been presented to the scientific community.

13.4.3 Analysis for Reporting the Initial Treatment Results

The analysis to report the final results of treatment will be undertaken when each eligible patient has been potentially followed for a minimum of 6 months after registration (eligible patients who die within 6 months after registration will be included). All eligible patients receiving any protocol drug will be included in the efficacy analysis. Patients not included in the final analysis will be listed, with reasons for exclusion. The analysis plan is described in detail in Section 13.4.1. All information reported in the interim analyses (see Section 13.4.2) will also be included in the final report.

13.5 Gender and Minorities

In conformance with the National Institutes of Health (NIH) Revitalization Act of 1993 with regard to inclusion of women and minorities in clinical research, we aim to be inclusive, as we will also evaluate the trial for any evidence of treatment differences by gender, race, and ethnicity. The table below lists the projected accrual for each racial and ethnic group based upon previous RTOG GBM trials.

Projected Distribution of Gender and Minorities

	Gender		
Ethnic Category	Females	Males	Total
Hispanic or Latino	2	2	4
Not Hispanic or Latino	34	47	81
Ethnic Category: Total of all subjects	36	49	85
	Gender		
Racial Category	Females	Males	Total
American Indian or Alaskan Native	0	0	0
Asian	1	2	3
Black or African American	2	2	4
Native Hawaiian or other Pacific Islander	0	0	0
White	33	45	78
Racial Category: Total of all subjects	36	49	85

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APPENDIX I
STUDY PARAMETER TABLES

Pre-Treatment Assessments

Assessments	≤14 d prior to registration	≤5 d prior to baseline scan and from baseline to registration	Prior to treatment
Tumor imaging MRI/CT scan (pts without recent resection; see Section 3.1 for details)	X		
Tumor imaging MRI/CT scan (pts with recent resection; see Section 3.1 for details)	≤prior to registration and recommended to be ≤96 h post-surgery		
History/Physical/Performance Status (KPS)	X		
CBC w/ diff, ANC, platelets, Hgb	X		
Albumin, alkaline phosphatase, BUN, calcium, chloride, glucose, potassium, total protein, sodium chloride (recommended per Section 4.1)			≤30 d
Urine protein: urine dipstick or UPC ratio (If UPC >1.0 then 24 hour urine will be performed)	X		
Creatinine	X		
Serum total bilirubin	X		
ALT and AST	X		
Pregnancy test (if applicable)	X		
Steroid dose documentation and anticonvulsant dose documentation		X	
Systolic/diastolic blood pressure	X		
PT INR (pts on full-dose anticoagulants)	X		
Informed consent	X		

APPENDIX I (continued)

Assessments During Treatment (12-DEC-2017)

Assessments	d 28 (± 4d) of each cycle
Physical/ Performance Status (KPS)	X
CBC w/ diff, ANC, platelets, Hgb	X
Albumin, alkaline phosphatase, BUN, calcium, chloride, creatinine, glucose, potassium, total protein, sodium chloride	X
Urine protein: urine dipstick or UPC ratio (If UPC >1.0 then 24 hour urine will be performed)	X
Serum total bilirubin	X
ALT and AST	X
Systolic/diastolic blood pressure	X
Adverse event evaluation	X
Device compliance assessment	X*
MRI w/ and w/o contrast	Every 8 weeks

*Distributed by Novocure to site on monthly basis and to be retained in the patient's medical record. These reports also must be submitted to RTOG Headquarters monthly via fax 215-940-8926.

APPENDIX I (continued)

Assessments in Follow-Up (10/31/16)

Assessments	At progression, q 8 weeks for 1 yr, then q 12 weeks for 1 yr, then q 6 mos (+/-7days)
History/physical	X
MRI w/ and w/o contrast	X*

* After progression, MRI schedule is left at the discretion of the treating physician

APPENDIX II

KARNOFSKY PERFORMANCE SCALE

100	Normal; no complaints; no evidence of disease
90	Able to carry on normal activity; minor signs or symptoms of disease
80	Normal activity with effort; some sign or symptoms of disease
70	Cares for self; unable to carry on normal activity or do active work
60	Requires occasional assistance, but is able to care for most personal needs
50	Requires considerable assistance and frequent medical care
40	Disabled; requires special care and assistance
30	Severely disabled; hospitalization is indicated, although death not imminent
20	Very sick; hospitalization necessary; active support treatment is necessary
10	Moribund; fatal processes progressing rapidly
0	Dead