A Multi-Institutional Pilot Study of Prophylactic Cranial Tumor-Treating Fields for Patients with Extensive-stage Small Cell Lung Cancer

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Investigators	See Appendix E
Sponsor:	Albert Attia M.D., Vanderbilt University Medical Center

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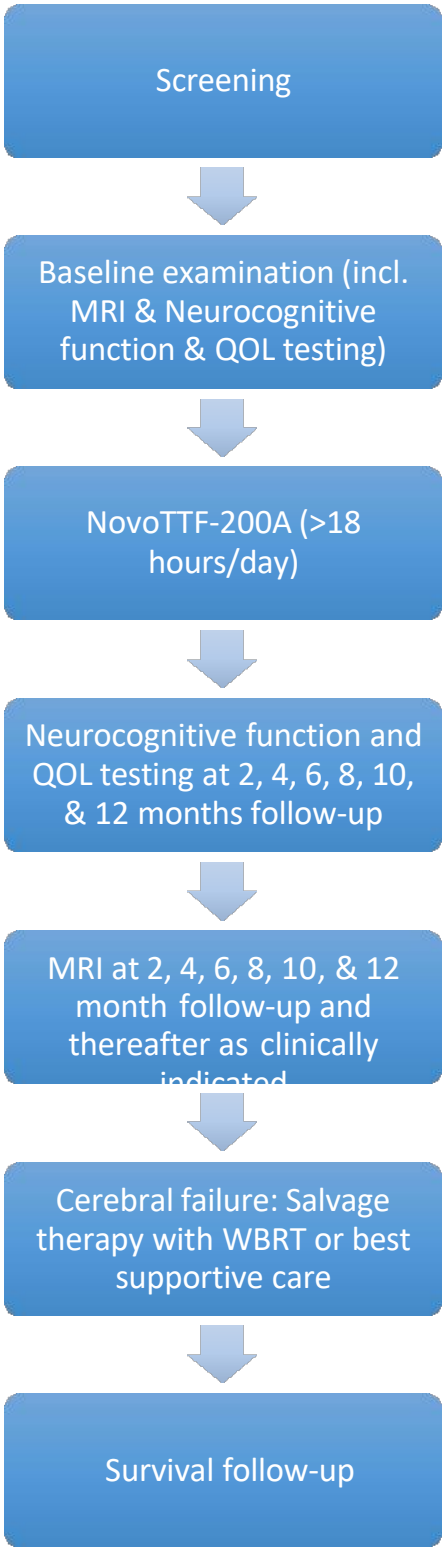
List of abbreviations

AE: Adverse Event
ADE: Adverse Device Effect
B16F10: Mouse Malignant Melanoma cell line
BM: Brain metastases
CI: Confidence Interval
CIP: Clinical Investigational Plan
cm: Centimeter
CR: Complete Response
CRF: Case Report Form
DLT: Dose Limiting Toxicity
DSS: Device Support Specialist
ES-SCLC: Extensive Stage Small Cell Lung Cancer
EORTC: European Organisation for Research and Treatment of Cancer ERP: Enterprise Resource Planning system
GBM: Glioblastoma
HR: Hazard Ratio
HVLT: Hopkins Verbal Language Test
kHz: kilohertz
LS-SCLC: Limited Stage Small Cell Lung Cancer
mA: miliamper
RMS: Root Mean Square
MRI: Magnetic Resonance Imaging
MST: Mean Survival Time
NSCLC: Non-Small-Cell Lung Cancer
PCI: Prophylactic Cranial Irradiation
PFS: Progression Free Survival
PR: Partial Response
QLQ C-30: EORTC's Quality of life Questionnaire
QOL: Quality of Life
SADE: Serious Adverse Device Effect
SAE: Serious Adverse Event
SCLC: Small Cell Lung Cancer
SD: Standard Deviation
TTF: Tumor Treatment Fields
USADE: Unanticipated Serious Adverse Device Effect
V/cm: Volt/centimeter
VX-2: Rabbit Carcinoma cell line
WBRT: Whole Brain Radiation Therapy

1. OVERALL SYNOPSIS OF THE CLINICAL INVESTIGATION

Title:	A Multi-Institutional Pilot Study of Prophylactic Cranial Tumor-Treating Fields for Patients with Extensive-stage Small Cell Lung Cancer
Device:	NovoTTF-200A System (200kHz output frequency)
Study Objectives:	To test the feasibility and compliance of TTF therapy to the brain in patients with extensive-stage small cell lung cancer with no evidence of brain metastasis. Secondary endpoints include overall survival, development of brain metastases, neurocognitive function, and QOL outcomes.
Study Design:	Prospective open label pilot study
Study Hypothesis:	The hypothesis of this study is that NovoTTF-200A will reduce the risk of developing brain metastases for ES-SCLC patients.
Sample Size:	25 patients treated with NovoTTF-200A
Study Population:	Patients with histologically proven small cell lung cancer who have undergone at least four cycles of first-line chemotherapy with a partial or complete response, above 22 years of age, no evidence of intracranial metastasis.
Primary Endpoint:	Feasibility, as measured by tolerability of TTFs (% patients continuing TTF therapy until intracranial tumor progression, discontinuation due to DLT, or 6 months).
Secondary Endpoints:	• Time to intracranial failure • Overall survival • Rates of intracranial failure at 2, 4, 6, 8, 10, 12 months after NovoTTF-200A • Intracranial failure free survival • Rate of decline in HVLT-R free recall, delayed recall and delayed recognition, COWAT and TMT Parts A and B at 2, 4, 6, 8, 10, 12 months after NovoTTF-200A • Time to neurocognitive failure • Neurocognitive failure-free survival • Quality of Life using the EORTC QLQ C30 with BN20 addendum • Adverse events, severity and frequency based on CTCAE V5.0
Sponsor:	Albert Attia M.D., Vanderbilt University Medical Center

STUDY SCHEMA



2. IDENTIFICATION AND DESCRIPTION OF THE INVESTIGATIONAL DEVICE

a) Description of the Investigational Device and its Intended Purpose

The NovoTTF-200A System is an investigational medical device for the prophylactic cranial treatment of ES-SCLC patients with no evidence of brain metastases. It is intended to be used exclusively by patients in a clinical trial.

The device is a portable, battery operated system which delivers TTFields to the patient by means of insulated Transducer Arrays (INE transducer arrays). NovoTTF-200A produces electric forces intended to disrupt cancer cell division.

b) Details Concerning the Manufacturer of the Investigational Device

The NovoTTF-200A System is manufactured by Novocure Ltd., Topaz Building, MATAM center, Haifa 31905, Israel. Novocure Ltd. is a 21CFR820 compliant medical device company developing electric field based therapy for cancer patients. Novocure's headquarters are located in Israel. Novocure GmbH is a 21CFR820 compliant Novocure Ltd global distribution center. Novocure GmbH is based in Switzerland.

c) System Parts and Their Identification

The NovoTTF-200A System is composed of several parts, which are shown in the picture below.

1. Electric Field Generator (the device)
2. Portable Batteries
3. Charger for Portable Batteries
4. Plug In Power Supply
5. Connection Cable and Box (CAD)
6. Transducer Arrays
7. Power Cords
8. Shoulder Bag and Strap
9. Portable Battery Case

d) Traceability

All parts of the NovoTTF-200A 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	ENISO13485 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 Investigation

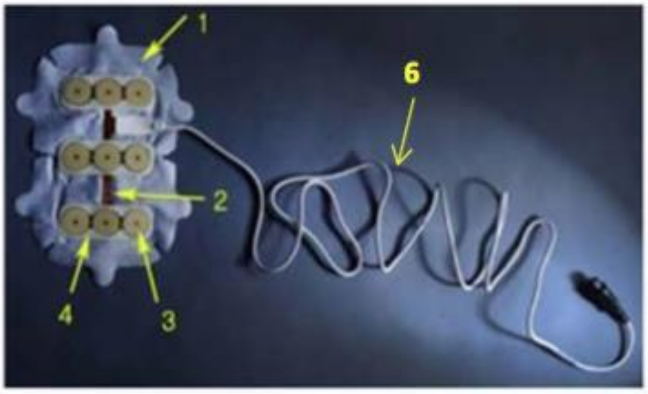
The NovoTTF-200A System is intended to test the feasibility and compliance of TTF therapy to the brain in patients with extensive-stage small cell lung cancer with no evidence of brain metastasis. Secondary endpoints include overall survival, development of brain metastases, neurocognitive function, and QOL outcomes.

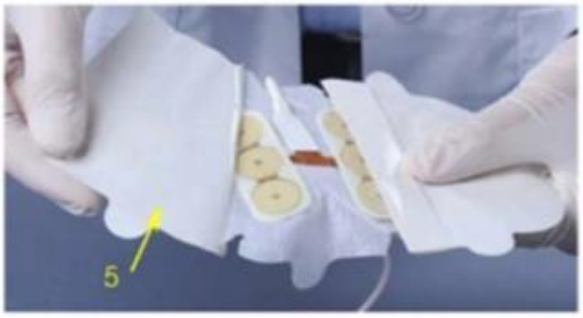
f) The Populations and Indications for Which the Investigational Device is Intended

Patients with histologically proven small cell lung cancer who have undergone at least four cycles of first-line chemotherapy with a partial or complete response, above 22 years of age, no evidence of intracranial metastasis.

g) 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

h) Training and Specific Medical or Surgical Procedures Involved in the Use of the Investigational Device

The NovoTTF-200A 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. JUSTIFICATION FOR THE DESIGN OF THE CLINICAL INVESTIGATIONAL PLAN

a) Prophylactic Cranial Treatment for ES-SCLC patients

Small cell lung cancer (SCLC) is a neuroendocrine tumor which encompasses approximately 15% of all lung cancers. The majority of patients present with extensive stage disease, which includes patients with bulky disease, extensive nodal involvement, and/or distant metastases. Patients with extensive-stage small cell lung cancer (ES-SCLC) have disease that is too large to treat with definitive chemoradiation, and are thus initially treated with systemic chemotherapy alone.

Metastases from SCLC have a predilection for the brain, with up to 24% of SCLC patients presenting with brain metastases at time of diagnosis [1]. Furthermore, up to 50% of patients who present with no evidence of brain metastasis at diagnosis will ultimately develop intracranial metastatic disease [2]–[4]. This high incidence of brain metastases is likely due to the low permeability of the blood-brain barrier to

systemic therapies and existence of subclinical intracranial disease at time of diagnosis. Prophylactic cranial irradiation (PCI) has been widely adopted as standard of care to reduce the incidence of brain metastases in limited stage SCLC patients who have had a response of their thoracic disease to definitive chemoradiation. PCI has been demonstrated to reduce the incidence of brain metastases (relative risk 0.56; 95% CI, 0.38-0.57) and portends a 5.4% improvement in survival at three years [5].

However, the role of PCI in ES-SCLC patients who have a good response to initial systemic therapy remains unclear. To date, there have been two randomized multicenter trials which evaluated PCI in ES-SCLC. An EORTC phase III trial by Slotman et al., randomized ES-SCLC patients with a response to chemotherapy to either PCI or observation. The primary end point for this study was symptomatic brain metastases. Of note, intracranial screening by MRI was not utilized prior to PCI. When compared to observation, PCI was associated with a lower risk of symptomatic brain metastases (hazard ratio [HR], 0.27; 95% confidence interval [CI], 0.16 to 0.44; P < 0.001), higher median disease-free survival (14.7 weeks vs 12.0 weeks), and higher median overall survival (6.7 months vs 5.4 months). The cumulative risk of brain metastases within 1 year was 14.6% in the irradiation group (95% CI, 8.3 to 20.9) vs 40.4% in the control group (95% CI, 32.1 to 48.6), and the 1-year survival rate was 27.1% (95% CI, 19.4 to 35.5) in the irradiation group vs 13.3% (95% CI, 8.1 to 19.9) in the control group [6].

Another phase III trial was performed in Japan, in which ES-SCLC patients with some response to initial chemotherapy were randomized to either PCI or observation. Unlike the EORTC trial, this trial required MRI screening prior to randomization. Preliminary interim analysis, presented at the American Society of Clinical Oncology annual meeting in 2014, demonstrated a trend towards worse overall survival with PCI (10.1 months vs 15.1 months, HR 1.38; 95% CI, 0.95 to 2.01; stratified log-rank test, p = 0.091). Compared to observation, PCI significantly reduced the risk of brain metastases (32.4% vs 58.0% at 12 months; Gray's test, p < 0.001) and had comparable PFS (median, 2.2 vs 2.4 months; HR 1.12; 95%CI, 0.82 to 1.54) [7].

Both the EORTC and Japanese trials confirm the impact of PCI on reducing the incidence of brain metastases in ES-SCLC patients. However, these trials provide conflicting data on whether PCI provides a survival benefit. Moreover, PCI adversely affects short term quality of life with side effects such as fatigue and hair loss [6]. In addition, there is concern for long-term radiation-induced neurological morbidity [8], [9]. As treatment for ES-SCLC becomes more successful, efforts to minimize neurotoxicity from PCI will be of paramount importance.

b) Tumor Treating Fields (TTFields) Overview

TTFields are a non-invasive, regional antimitotic treatment modality with minimal toxicity which have been approved for the treatment of recurrent and newly diagnosed glioblastoma (GBM) by the Food and Drug Administration (FDA) in the United States and have obtained a CE mark in Europe for the same indications. 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 predominantly during two phases of mitosis: 1) during metaphase, by disrupting the formation of the mitotic spindle, and 2) during cytokinesis, by dielectrophoretic dislocation of intracellular constituents resulting in apoptosis [10], [11]. 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 primary brain tumor cell lines and cell lines from other tumors which commonly metastasize to the brain (glioblastoma at 200 kHz [12], NSCLC at 150kHz [13], breast carcinoma at 120kHZ [14], and melanoma at 100kHz [10]). For SCLC, maximal cell death has been found to occur at 200 kHz [15].

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 [10], [12]. 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. Using two directional TTFields in pilot clinical testing demonstrated TTFields to be biologically active in human tumors. In a pilot trial [16], TTFields were shown to decrease the size of skin metastases from breast cancer and from malignant melanoma. In addition, in a phase I/II trial in 42 pretreated advanced NSCLC patients TTFields were applied to the chest and upper abdomen together with systemic pemetrexed [17]. This trial demonstrated that TTFields therapy were well tolerated by NSCLC patients without any detectable increase in systemic toxicity due to pemetrexed. Interestingly, patients in this trial showed promising local disease control in the lungs and median survival time when compared to historical data in advanced NSCLC with pemetrexed alone. In addition, a phase III trial of TTFields as monotherapy compared to active chemotherapy in recurrent glioblastoma patients [18] showed OptuneTM to be equivalent to active chemotherapy in extending survival, associated with minimal toxicity, good quality of life, and activity within the brain (14% response rate). Finally, a phase III trial of OptuneTM combined with maintenance temozolomide compared to maintenance temozolomide alone has shown that that combined therapy led to a significant improvement in both PFS and OS in patients with newly diagnosed GBM [19], without the addition of high grade toxicity and without decline in quality of life.

c) Metastasis Prevention Using TTFields

In addition to the impact on the primary tumor, TTFields have been tested for their potential to inhibit metastatic spread of solid tumors to the lungs in two animal models [20]: (1) Mice injected with malignant melanoma cells (B16F10) into the tail vein, (2) New Zealand white rabbits implanted with VX-2 tumors within the kidney capsule. The mice and rabbits were treated using two-directional TTFields at 100–200 kHz. Animals were either monitored for survival, or sacrificed for pathological and histological analysis of the lungs. The total number of lung surface metastases and the absolute weight of the lungs were both significantly lower in TTFields treated mice than in sham control mice ($p < 0.05$). TTFields treated rabbits survived significantly longer than sham control animals. This extension in survival was found to be due to an inhibition of metastatic spread, seeding or growth in the lungs of TTFields treated rabbits compared to controls. Histologically, extensive peri- and intra-tumoral immune cell infiltration were seen in TTFields treated rabbits only (Figure 1).

Rabbits with VX2 Tumors in the Kidney ***Mice with Melanoma Injected into the Tail Vein***

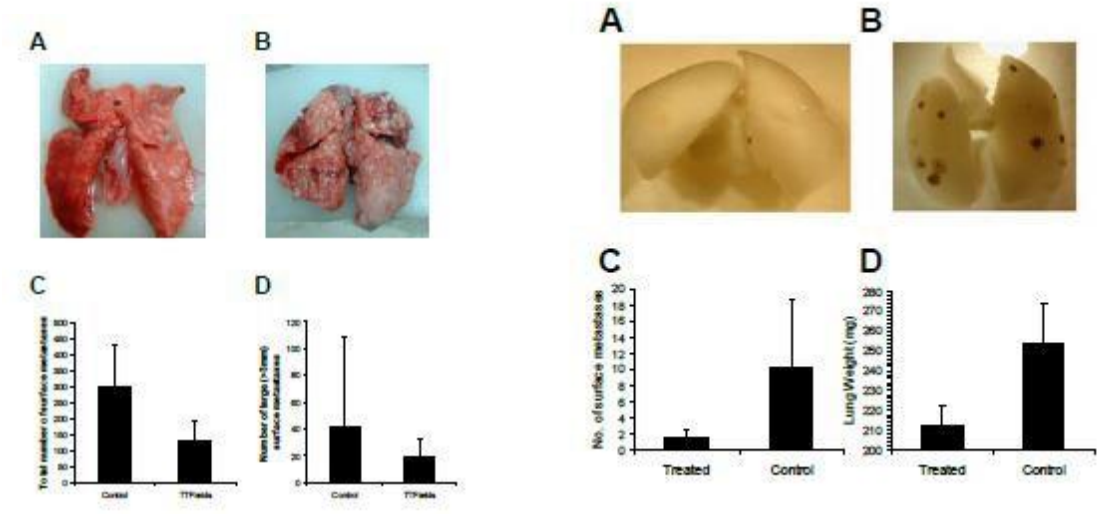


Fig. 1
Right Panel Malignant melanoma metastases as seen on the surface of the lungs of mice treated with TTFields. Exemplary photos of lungs of mice treated with TTFields (A) or sham control (B) are shown after removal of the pulmonary blood by perfusion with saline. Average number of surface metastases (±SD) in treated and control mice (C). Average lung weight (±SD) of treated and control mice (D)
Left Panel Exemplary photos of surface lung metastases in TTFields treated (A) versus sham control rabbits (B). Treatment was initiated on day 12 from implantation of the kidney tumor. The average total number (±SD) of surface metastases (C) and the average number of large metastases (±SD) (D) in control versus treated rabbits

d) Clinical Results with OptuneTM 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 [18]**.** 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). Active chemotherapy control arm included “physician choice” 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 (HR 0.86; 95% CI, 0.66 to 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 OptuneTM 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 [21], [22]. The 2-year survival rate in this population was 30% (compared to 9% in OptuneTM-treated patients on the clinical trial). Compliance was a clear predictor of survival on OptuneTM, 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 OptuneTM was skin reaction.

Based on this clinical data in recurrent GBM and a pilot trial in newly diagnosed GBM with OptuneTM 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 OptuneTM in combination with temozolomide maintenance after surgery and chemoradiation versus temozolomide alone was conducted. In the final analysis (n = 695), progression-free survival was 7.1 months for OptuneTM/temozolomide vs 4.2 months for temozolomide alone (HR 0.694; 95% CI, 0.558 to 0.863; log rank p = 0.0010) and overall survival was 19.4 months for OptuneTM/temozolomide vs 16.6 months for temozolomide alone (HR 0.754; 95% CI, 0.595 to 0.955; p = 0.0229). This translates into 2-year survival rates of 43% (95% CI, 36 to 50) vs 29% (95% CI, 21 to 38). No significant added toxicity was seen in the temozolomide /OptuneTM arm. Quality of life and gross cognitive function were also comparable in the 2 arms.

Based on the data submitted to FDA from this newly diagnosed GBM study, FDA approved OptuneTM in combination with temozolomide for the treatment of adult patients with newly diagnosed GBM on October 5, 2015. In the US, OptuneTM 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 Investigation

TTFields are a novel, non-invasive regional anti-mitotic treatment modality. Pre-clinical studies and clinical data in glioblastoma have demonstrated a favorable safety profile and clinical superiority when treating the brain with TTFields. In addition, durable responses have been demonstrated with 200 kHz TTFields monotherapy for supratentorial tumors of the brain.

Brain metastases are a common occurrence in patients diagnosed with SCLC. PCI has been showed to improve survival in patients with LS-SCLC and potentially in patients with ES-SCLC as well. However, it has detrimental effects on quality-of-life, requiring the investigation of alternative strategies which allow for intracranial control while minimizing the risk of neurocognitive adverse effects. As such, prophylactic cranial TTFields may allow for sufficient intracranial control. Due to the favorable safety profile seen in recent phase III glioblastoma trials, NovoTTF-200A to the brain may be an appealing alternative to PCI. If TTFs can treat microscopic disease in the brain and prevent the formation of brain metastases with minimal to no late cognitive effects, then this would potentially improve survival and quality of life for patients with small cell lung cancer. Thus, the safety and efficacy of prophylactic cranial TTF in SCLC patients should be studied.

We hypothesize that prophylactic cranial TTF for patients with ES-SCLC with no evidence of brain metastases will be well tolerated. We anticipate that at least 75% of patients will tolerate treatment for 6 months or greater.

If the safety and tolerability of TTF is achieved, then a phase 2 study will be considered to test the efficacy. The ultimate goal would be for TTF to replace PCI as a safe and efficacious treatment modality to prevent brain metastasis in ES-SCLC. A second potential step would be for this modality to be tested in limited stage SCLC patients.

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

The risks associated with use of the NovoTTF-200A are the same as those associated with use of the approved Optune System. Principally, the risks are electrical or mechanical failure leading to electrical shock or 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. Other risks include headaches, fatigue, falls, and muscle twitching. 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.

Approximately 25 patients will be enrolled in the proposed study and will receive Novo-TTFA treatment. Participants are considered enrolled after their eligibility is confirmed and the coordinating center sends the enrollment confirmation to the site. Considering the minimal toxicity and promising efficacy seen in the GBM studies, the number of patients exposed to this treatment in the proposed study and the risks associated with the alternative treatments for these patients, the company believes that the possible benefits of NovoTTF-200A treatment clearly exceed its potential risks.

5. OBJECTIVES AND HYPOTHESES OF THE CLINICAL INVESTIGATION

a) Purpose and Objectives

Purpose
To test the feasibility of prophylactic cranial TTF therapy in preventing brain metastases in ES-SCLC patients who have a partial or complete response of extracranial disease after at least 4 cycles of first line chemotherapy.

Primary Objective
To measure the feasibility and compliance of NovoTTF-200A as prophylactic cranial TTF therapy, determined by % of patients continuing TTF therapy until intracranial tumor progression, discontinuation due to DLT, or 6 months.

Secondary Objectives

1. To evaluate time to intracranial failure after NovoTTF-200A.
2. To evaluate overall survival after NovoTTF-200A.
3. To evaluate the rates of intracranial failure at 2, 4, 6, 8, 10, 12 months after NovoTTF-200A.
4. To evaluate intracranial failure free survival after NovoTTF-200A.
5. To evaluate the rate of decline in HVLT-R free recall, delayed recall and delayed recognition, COWAT and TMT Parts A and B at 2, 4, 6, 8, 10, 12 months after NovoTTF-200A.
6. To evaluate time to neurocognitive failure after NovoTTF-200A.
7. To evaluate neurocognitive failure-free survival after NovoTTF-200A.
8. To evaluate Quality of Life using the EORTC QLQ C30 with BN20 addendum after NovoTTF-200A.
9. To assess adverse events, severity, and frequency associated with NovoTTF-200A using the CTCAE version 5.0.

b) Hypotheses
The hypothesis of this study is that NovoTTF-200A will reduce the risk of developing brain metastases for ES-SCLC patients.

c) Intended Performance of the Investigational Device
This prospective open label pilot study is designed to study the safety, tolerability and feasibility of NovoTTF-200A to the brain as prophylactic cranial therapy for ES-SCLC patients.

d) Risks and Anticipated Adverse Device Effects That are to be Assessed
See **Section 4** (Risks and Benefits of the Investigational Device and Clinical Investigation).

6. DESIGN OF THE CLINICAL INVESTIGATION

1. General

a) Description of the Type of Clinical Investigation to be Performed
This is a prospective, single-arm, open-label multicenter pilot study. All patients will undergo TTFs using the NovoTTF-200A System set to an output frequency of 200 kHz. Patients on the study may receive chest irradiation at the discretion of the treating physician. Moreover, should the patient develop progressive extracranial disease, then the patient may receive systemic therapy at the discretion of the treating physician. All oncology therapies will be recorded in the clinical trial record.

NovoTTF-200A will be discontinued in patients who develop intracranial failure while on therapy. All patients who develop intracranial failure may undergo WBRT or best supportive care at the discretion of the treating physician.

All study follow-up procedures should continue according to the study's protocol until death, or until one of the other criteria for removal from the study is met (see **Section 3.C** below).

b) Outcome Measures

Primary Outcome Measure:
Feasibility, as measured by tolerability of TTFs, will be recorded as percentage of patients continuing TTF therapy until intracranial tumor progression, discontinuation due to DLT, or continuation of therapy for at least 6 months.

Secondary Outcome Measures:

1. Time to intracranial failure, as measured from date of starting NovoTTF-200A to intracranial failure as a first event. Death prior to evidence of intracranial failure is treated as a competing risk and will be censored on the time to intracranial failure curves.
2. Overall survival, defined from the date of starting NovoTTF-200A to death, or censored at the date of last follow-up.
3. Rate of intracranial failure at 2, 4, 6, 8, 10, 12 months after starting NovoTTF-200A
4. Intracranial failure free survival, defined from the date of starting NovoTTF-200A to the first intracranial failure or death (whichever occurs first) or, otherwise, censored at the last MRI imaging assessment date on which the patient was reported alive without intracranial failure.
5. Rate of decline in cognitive function as measured by HVLT-R free recall, delayed recall, and delayed recognition; COWAT; and TMT Parts A and B at 2, 4, 6, 8, 10, 12 months follow-up.
6. Time to neurocognitive failure, as measured by cognitive decline on a battery of tests: HVLT-R free recall, delayed recall, and delayed recognition; COWAT; and TMT Parts A and B.
7. Neurocognitive failure-free survival, defined from the date of starting NovoTTF-200A to neurocognitive failure (as measured by HVLT-R free recall, delayed recall, and delayed recognition; COWAT; and TMT Parts A and B) or death (whichever occurs first), censored at the last neurocognitive assessment on which the patient was reported alive without neurocognitive failure.
8. Quality of Life using the EORTC QLQ C30 with BN20 addendum.
9. Toxicity during NovoTTF-200A treatment based on incidence and severity of treatment emergent adverse events as evaluated using the CTCAE version 5.0

c) Methods and Timing for Assessing, Recording, and Analyzing Variables.
See under Statistical Considerations (**Section 9**).

2. Investigational Device(s) and Comparator(s)
The investigational device and comparators are described as part of the study treatments below.

3. Subjects

Inclusion Criteria:

1. 22 years of age and older
2. Life expectancy of > 3 months
3. Histologically proven ES-SCLC (any T any N and any M stage) within 6 months prior to start of study treatment with the NovoTTF-200A, with a partial or complete response to at least four cycles of first-line chemotherapy
4. Karnofsky performance status (KPS) > 70 (see **Appendix A**)
5. Adequate hematological, hepatic and renal function, defined as: Neutrophil count > 1.5 x 10^9/L and platelet count > 100 x 10^9/L; bilirubin < 1.5 x ULN; AST and/or ALT < 2.5 x ULN or < 5 x ULN if patient has documented liver metastases; and serum creatinine < 1.5 x ULN.

Exclusion Criteria:

1. Evidence of brain metastases on MRI of brain with and without contrast
2. History of other prior malignancy within the past 5 years except for superficial skin cancers
3. No severe comorbidities:
    a. History of significant cardiovascular disease unless the disease is well controlled.

Significant cardiac disease includes second/third degree heart block; significant ischemic heart disease; poorly controlled hypertension; congestive heart failure of the New York Heart Association (NYHA) Class II or worse (slight limitation of physical activity; comfortable at rest, but ordinary activity results in fatigue, palpitation or dyspnea).

b. History of arrhythmia that is symptomatic or requires treatment. Patients with atrial fibrillation or flutter controlled by medication are not excluded from participation in the trial.
c. History of cerebrovascular accident (CVA) within 6 months prior to start of study treatment
d. Active infection or serious underlying medical condition that would impair the ability of the patient to received protocol therapy.
e. History of any psychiatric condition that might impair patient's ability to understand or comply with the requirements of the study or to provide consent.

4. Active implantable electronic medical devices in the brain; a skull defect, a shunt, or bullet fragments
5. Known allergies to medical adhesives or hydrogel
6. Unable to operate the NovoTTF-200A device independently or with the help of a caregiver
7. If a female, currently pregnant, breastfeeding, or unwilling to avoid pregnancy while on study treatment.
8. Concurrent brain directed therapy (beyond NovoTTF-200A as per protocol)
9. Prior clinical trial participation with brain directed therapy
10. Concurrent treatment clinical trials

4. 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. Lack of compliance – The Sponsor or investigator may remove a patient from the study for lack of compliance to the study protocol.
3. Intolerable toxicity - Patients may be removed from study treatment 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.
4. Intracranial failure – As defined in section 9(a) of the protocol
5. Death

5. Enrollment Plan

a) Start Date of Enrollment

Enrollment of the first patient is expected during the second quarter of 2017.-

b) Total Expected Duration of the Clinical Investigation

The study is expected to last for 36 months.

c) Expected Duration of Each Subject's Participation

Subject participation in the trial is anticipated to be 10-15 months.

d) Number of Subjects Required to be Included in the Clinical Investigation

A total of 25 patients will be accrued for this study at up to three institutions. Any patients deemed screen failures may be replaced with a new patient.

e) Estimated Time Needed to Select this Number (*i.e.,* Enrollment Period).
It is assumed that the accrual will take place over 24 months.

Enrollment Procedures

Guidelines for VICC and Participating Institutions

Prior to enrollment, a copy of the IRB approval at the site will be requested and kept on file at the Vanderbilt-Ingram Cancer Center (VICC) Coordinating Center. Eligible participants will be entered on study centrally at the VICC Coordinating Center. All sites should email the Coordinating Center at Coordinating.Center@vumc.org to verify treatment availability prior to enrollment.

All patients MUST be enrolled with the VICC prior to the start of protocol treatment. Enrollment can only be conducted during the business hours of 8AM – 5PM Monday through Friday.

1) All sites should email the **VICC Coordinating Center coordinating.center@vumc.org**to notify of upcoming enrollment and slot availability. The following information should be included in your email:
    - Study Number
    - Patient Initials
    - Anticipated Consent Date
    - Anticipated Start Date

2) To enroll, email the following documents to the Coordinating Center for eligibility review and patient enrollment (**VICC Coordinating Center coordinating.center@vumc.org):**
    - Copy of the patient's signed and dated Informed Consent, including documentation of the consent process.
    - HIPAA authorization form (if separate from the main consent form)
    - VICC Patient Enrollment Form
    - Copies of supporting source documentation including any laboratory, imaging and pathology reports or EMR access
    - Completed Eligibility Checklist. **To be eligible for the study, the participant must meet each inclusion criterion listed in the eligibility checklist.**

Note: VICC Coordinating Center requests that sites **send eligibility documents 24-48 hours prior to planned enrollment.** Same day treatment enrollments will only be accepted with prior notice and discussion with the Coordinating Center. Please email the Coordinating Center if enrollment is needed sooner.

Once enrollment confirmation from Coordinating Center is received, proceed with protocol procedures.

Please contact the assigned Study Contact with any questions regarding this process. You can also reach out to your assigned CRA once the study is activated.

The VICC Coordinating Center will assign subject IDs to all patients in screening. Only patients deemed eligible will be registered to investigational treatment. Sequence numbers will not be re-used if a patient screen fails unless the same patient re-screens at a later point. Following enrollment confirmation by the coordinating center, eligible participants should begin study treatment consistent with the protocol no later than 21 days after the baseline/screening MRI.

Issues that would cause treatment delays should be discussed with the Protocol Chair. If a participant does not receive protocol therapy following enrollment within allowed time period, the participant will become ineligible and will be removed from the study. Such patients will have to undergo re-screening in order to participate in the study. Any requests for eligibility exceptions and/or deviations must be approved in writing by the Protocol Chair and the VICC DSMC.

As is generally accepted, standard of care procedures performed prior to consent, but within the protocol defined screening window for each assessment, can be used for study purposes. All research-only procedures must be performed after the patient consents.

6. Clinical Investigation-related Procedures

a) NovoTTF-200A System Treatment

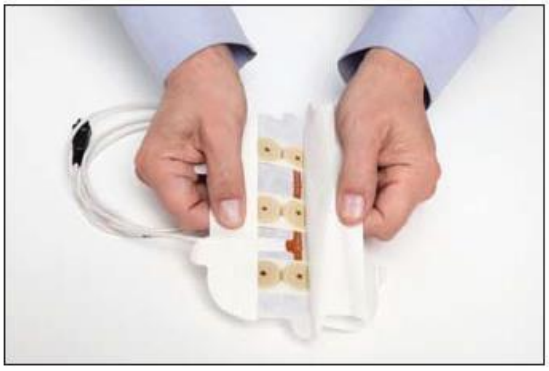
1. Treatment planning: Transducer array layout will be determined by the investigator or Novocure using the NovoTALTM software supplied by Novocure. NovoTAL can be used for multiple tumors as is often the case with GBM (the approved indication for the Optune System). There is no difference in the field mapping algorithm based on histology of the tumor or frequency of the TTFields.

2. Patient training: Patients will be trained in the use of the device by the investigator, a designated health care provider (e.g. nurse) or Device Support Specialist (DSS) trained by Novocure.
3. Treatment initiation: NovoTTF-200A will be initiated by the investigator within 4 weeks of completion of chemotherapy. All patients will be required to shave their heads to initiate array placement and TTFields. Array placement will be performed based on the Transducer Array Layout

map calculated during treatment planning.

4. Treatment duration: Treatment with the device will be continuous with breaks allowed for personal needs (e.g. showering, array exchange) and for MRI imaging assessments. Patients must use the device for at least 18 hours a day on average. Treatment will be continued until intracranial failure (as defined in section 9(a) of the protocol), 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 per month in NovoTTF-200A is allowed. However, the patient should use the device for at least 18 hours a day on average as stated above.
5. The NovoTTF-200A System will be programmed by Novocure to deliver 200 kHz 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.
6. Transducer Array replacement: Patients will replace the Transducer Arrays twice to three times per week independently or with the help of a caregiver. At each array replacement the patient's scalp will be re- shaved and skin treated according to the guidelines set out below.





7. Compliance assessment: The device will be inspected either by the investigator or by a

Novocure representative on a monthly basis to assess patient compliance with therapy.

8. The following skin care guidelines should be closely adhered to:
    1. If the skin beneath the Transducer Arrays is inflamed, a high potency topical steroid (e.g. clobetasol) should 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.
    2. 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.
    3. If the dermis is breached (skin erosions, ulcers, open sores, punctate lesions, etc.) an antibiotic ointment (e.g. mupiricin) should be prescribed and used in place of the steroid ointment. Any evidence of infection should result in bacterial cultures being taken. There will be no "dose" adjustments to the device for adverse events. Compliance data will be reviewed biweekly. Review of the compliance data and the reasons for breaks in treatment for longer than 24 hours will be documented in the eCRFs. The maximum duration of treatment break allowed for adverse events related to TTFields is 3 weeks.

b) Systemic Therapy

Patients should have completed 4 to 6 cycles of first-line chemotherapy prior to the start of study treatment. If patients develop progressive extracranial disease during study, then the patient may receive systemic therapy at the discretion of the treating physician while on NovoTTF-200A. Systemic therapy utilized will be documented in the CRFs.

c) Chest irradiation

Patients may receive chest irradiation at the discretion of the treating physician while on NovoTTF-200A. Radiation therapy utilized will be documented in the CRFs.

c) Salvage Therapy

Following intracranial failure, patients may be offered salvage therapy based on local practice at each site including, but not limited to:

1. WBRT
2. Best supportive care

7. PATIENT EVALUATIONS AND FOLLOW UP PLAN

A table of the study procedure calendar for this study is provided in **Appendix C**.

a) Pre-treatment Evaluation (Baseline)

The following will be performed within 21 days prior to registration (start of study treatment with the NovoTTF-200A System):

1. Verify informed consent is signed
2. A high resolution, isovolumetric T1-weighted post-gadolinium MRI of the brain using a 3T MR scanner. **Treatment with the NovoTTF-200A System is to begin no later than 21 days after the baseline MRI.** Additional parameters include:
    a) FOV: 256 mm x 256 mm

b) Matrix: 256x256
c) Slice thickness: 1 mm
d) Full brain coverage

The same slice thickness and contrast material type & dose should be maintained throughout the entire study. The NovoTTF-200A System and all components including the transducer arrays must be removed and cannot be brought into the MR environment.

3. Medical history
4. Concomitant medications
5. Karnofsky Performance Status (KPS) score recording
6. Physical examination and vital signs
7. Neurological examination
8. Neurocognitive testing: Hopkins Verbal Learning Test (HVLT-R) for free recall, delayed recall and delayed recognition, Controlled Oral Word Association Test (COWAT); and Trail Making Tests (TMT) Parts A and B
9. Quality of Life questionnaire (EORTC QLQ C30 with BN20 addendum)
10. Serum Pregnancy test (if applicable) within 14 days
11. Complete blood count including differential
12. Serum chemistry panel, including:
    1. BUN, Creatinine
    2. Sodium, Potassium
    3. ALT, AST, Bilirubin
13. Coagulation tests (PT, PTT)

b) Follow-up until Intracranial Failure

Once every 8 weeks until intracranial failure the following examinations will be performed:

1. Physical examination and vital signs
2. KPS score recording
3. Neurological examination
4. Complete blood count including differential
5. Serum chemistry panel, including:
    1. BUN, Creatinine
    2. Sodium, Potassium
    3. ALT, AST, Bilirubin
6. Coagulation tests (PT, PTT) as clinically indicated
7. Adverse event collection and recording
8. Concomitant medication recording
9. A high resolution, isovolumetric T1-weighted post-gadolinium MRI of the brain using a 3T MR scanner. Additional parameters include:
    a) FOV: 256 mm x 256 mm
    b) Matrix: 256x256
    c) Slice thickness: 1 mm
    d) Full brain coverage

    The same slice thickness and contrast material type & dose should be maintained throughout the entire study. The NovoTTF-200A System and all components including the transducer arrays must be removed and cannot be brought into the MR environment.
10. Device compliance (if applicable)

Once every 8 weeks, for one year or until intracranial failure (whichever comes first) the following

neurocognitive tests will be performed:

1. HVLT-R
2. TMT Part A and B
3. COWAT

Once every 8 weeks, for one year or until intracranial failure (whichever comes first) the following Quality of Life questionnaires will be performed:

1. EORTC QLQ C30
2. EORTC BN20 addendum

c) Follow up 8 weeks from treatment termination

1. KPS score recording
2. Physical examination and vital signs
3. Neurological examination
4. Complete blood count including differential
5. Serum chemistry panel, including:
    1. BUN, Creatinine
    2. Sodium, Potassium
    3. ALT, AST, Bilirubin
6. Adverse event collection and recording
7. Concomitant medication recording
8. A high resolution, isovolumetric T1-weighted post-gadolinium MRI of the brain using a 3T MR scanner. Additional parameters include:
    a) FOV: 256 mm x 256 mm
    b) Matrix: 256x256
    c) Slice thickness: 1 mm
    d) Full brain coverage

    The same slice thickness and contrast material type & dose should be maintained throughout the entire study. The NovoTTF-200A System and all components including the transducer arrays must be removed and cannot be brought into the MR environment.

Please see **Section 9.a** and **Appendix B** for details about the neurocognitive function assessments.

Following Study Treatment Discontinuation

Patients will have additional follow-up outside of scheduled study follow-up at the discretion of the treating physician.

Post Intracranial Failure Follow-up

Following intracranial failure, patients will be followed every 4 weeks for survival (this can include telephone call follow-up and does not require a clinical visit). Patient death date will be captured in the CRFs.

Foreseeable Factors That May Compromise the Outcome of the Clinical Investigation or the Interpretation of Results

There are no foreseeable factors that may compromise the outcome of the clinical investigation or the interpretation of the study results.

8. MONITORING PLAN

Study monitoring will be performed by the coordinating center assigned this responsibility by the Sponsor. Study monitoring functions will be in compliance with recognized Good Clinical Practices, EN-ISO-14155, FDA's IDE guidance documents, and as outlined in 21 C.F.R. § 812.43(d) and 21 C.F.R. § 812.46. The principal function of the clinical monitor is to observe and assess the quality of the clinical study. The monitor's duties include: remote monitoring of study documents and results. The coordinating center will operate under written procedures to ensure compliance with the protocol.

Remote monitoring will take place every 8-16 weeks during the course of the study (as long as there are patients in follow up at the site), and final remote monitoring at the close of the study.

Remote monitoring during the study is intended to assess Investigators' adherence to the Investigational Plan, maintenance of records, reports and investigational devices, and review of source documents for accuracy, completeness, and legibility. The monitor is required to assess the progress of the study toward meeting study objectives, and to identify any concerns that stem from observations of device performance and/or review of the Investigator's patient records, study management documents, and informed consent documents, and to ensure accountability of all patients that have been treated under the study.

The remote monitoring at completion of the study is intended to assure that all the data have been properly completed Monitoring reports should include resolution of concerns, completion of appropriate follow-up activities, completion of assigned tasks, and any necessary corrective actions. At the close of the study, the monitor will prepare a final report.

The Vanderbilt-Ingram Cancer Center (VICC) oversees patient safety and data monitoring for its investigator-initiated and NIH-NCI funded clinical trials through its Data and Safety Monitoring Committee (DSMC). The purpose of the DSMC is to ensure the efficient implementation and management of VICC Data and Safety Monitoring Plan (DSMP). The Committee maintains authority to intervene in the conduct of studies as necessary to ensure clinical research performed at VICC achieves the highest quality standards.

The VICC DSMC meets on a quarterly basis and ad hoc to discuss data and safety monitoring of clinical trials and to oversee the VICC DSMP. Internal audits for compliance with adverse event reporting, regulatory and study requirements, and data accuracy and completion are conducted according to the VICC DSMP according to study phase and risk. The committee reviews all serious adverse events (SAE) on Vanderbilt sponsored investigator-initiated studies on a quarterly basis and provides DSMC SAE review reports to the Vanderbilt IRB.

9. STATISTICAL CONSIDERATIONS

a) Study Endpoints

The primary endpoint is feasibility, measured as percentage of patients continuing TTF therapy until

intracranial tumor progression, discontinuation due to DLT, or 6 months. Death prior to evidence of intracranial failure is treated as a competing risk and the patient is censored at time of death. Death will not be considered as an event and patients who have not had intracranial failure will be censored at the time of death.

Secondary endpoints include:

- Time to intracranial failure, as measured from date of starting NovoTTF-200A to intracranial failure as a first event. Death prior to evidence of intracranial failure is treated as a competing risk and will be censored on the time to intracranial failure curves.
    - Intracranial Failure will be diagnosed based on ONE of the following criteria:
        - New lesion seen on two consecutive axial slices
        - New lesion seen on at least one slice in two separate planes
        - MRI used to diagnose intracranial failure must meet requirements mentioned in inclusion criteria, specifically, the MRI must be a high resolution, isovolumetric T1-weighted post-gadolinium MRI of the brain using a 3T MR scanner. Additional parameters include:
            - FOV: 256 mm x 256 mm
            - Matrix: 256x256
            - Slice thickness: 1 mm
            - Full brain Coverage
    - A lesion is designated "Undetermined" as long as it does not comply with the definition of intracranial failure above. If on a subsequent scan or on an additional imaging modality it is deemed as intracranial failure according to the criteria above, the date of intracranial failure diagnosis will be documented as the first time a new lesion was evident on a scan (i.e., backdated).
- Overall survival, defined from the date of starting NovoTTF-200A to death due to any causes, or censored at the date of last follow-up.
- Rate of intracranial failure at 2, 4, 6, 8, 10, 12 month after starting NovoTTF-200A
- Intracranial failure free survival, defined from the date of starting NovoTTF-200A to the first intracranial failure or death (whichever occurs first) or, otherwise, censored at the last MRI imaging assessment date on which the patient was reported alive without intracranial failure.
- Rate of decline in cognitive function as measured by HVLT-R free recall, delayed recall, and delayed recognition; COWAT; and TMT Parts A and B at 2, 4, 6, 8, 10, 12 months follow-up.
- Time to neurocognitive failure, as measured by cognitive decline on a battery of tests: HVLT-R free recall, delayed recall, and delayed recognition; COWAT; and TMT Parts A and B.
- Neurocognitive failure-free survival, defined from the date of starting NovoTTF-200A to neurocognitive failure (as measured by HVLT-R free recall, delayed recall, and delayed recognition; COWAT; and TMT Parts A and B) or death (whichever occurs first), censored at the last neurocognitive assessment on which the patient was reported alive without neurocognitive failure.
- Quality of Life using the EORTC QLQ C30 with BN20 addendum.
- Toxicity during NovoTTF-200A treatment based on incidence and severity of treatment emergent adverse events as evaluated using the CTCAE version 5.0 (**Appendix D**).

The above battery of neurocognitive instruments has been selected based on accepted standardization and psychometric principles, published normative data relative to routine demographics, relevance to general neurocognitive status, minimal practice effects, and brevity of the overall battery. Additionally, similar variations of this neurocognitive testing battery have been utilized in multiple cooperative group trials including RTOG 0212, RTOG 0214, RTOG 0424, RTOG 0525, RTOG 0933, ACOSOG Z0933,

NCCTG N0574, NCCTG N0577, RTOG 0825, ECOG E3F05, NCCTG N0874/ABTC 09-0, and N107C. Assessments will be conducted every 8 weeks for the first year or until intracranial failure, whichever occurs first. The HVLT-R test has been used and validated in multiple prior phase III trials of patients with brain metastases [9, 21]. HVLT-R incorporates 6 different forms, helping to mitigate practice effects of repeated administrations. Each form includes 12 nouns (targets) with 4 words drawn from 3 semantic categories, which differ across the 6 forms. The test involves memorizing a list of 12 targets for 3 consecutive trials (immediate recall), recalling the 12 targets after a 20-minute delay (delayed recall), and identifying the 12 targets from a list of semantically related or unrelated items (delayed recognition). In COWAT [Johnson SC et al, *Clin Neuropsychol.* 2012; 26(7):1230-41, Johnson DR et al, *Neuro Oncol.* 2012;14(6):808-16], the patient produces as many words as possible in 1 minute for a specific letter and the test assesses language and executive/frontal skills. The test is widely used and is part of the Halstead-Reitan Neuropsychological Battery. Impairment in the understanding of language or the motor expression of language will impair the results in this trial. Since such functions are affected by brain-directed therapies such as WBRT, the test could be sensitive to the experimental treatment effects on those functions. TMT [Bowie CR and Harvery PD, *Nat Protoc.* 2006; 1(5):2277-81] is a measure of visuospatial scanning, attention, sequencing and cognitive processing speed (Part A) and executive function (Part B). Those neurocognitive functions could be affected both by brain metastasis and by therapies directed to the brain, and will therefore be used in the trial. Patients must "connect the dots" either in a numbered sequence or alternating letters and numbers.

b) Sample Size Determination: Because the primary endpoint is feasibility, the proposed sample size is not driven by statistical hypotheses. Rather, we propose the sample size of 25 so that we will have precise enough information for planning the next phase of treatment development. The following table summarizes the point estimate and 95% confidence interval when n=25.

# patients continuing therapy	10	15	18	20
Point estimate	40%	60%	72%	80%
95% confidence interval	23% - 59%	41% - 77%	52% - 86%	61% - 91%

c) Statistical Analysis – Primary Endpoint: Since this is a feasibility study, we will not attempt a strict control of multiplicity in analyses of the primary and secondary endpoints. Proportion of patients continuing TTF will be estimated using Wilson's method and a one-sided 95% confidence interval will be reported. We will also summarize this measure for those who had PR and CR separately.

d) Statistical Analysis – Secondary Endpoints

Secondary endpoints for statistical testing: Time to intracranial failure with death as a competing risk will be estimated using cumulative incidence function (CIF) and reported with a one-sided 95% confidence interval. Rate of intracranial failure at a given time will be estimated using the CIF. Overall survival will be estimated using the Kaplan-Meier method. Other time-to-events data (with or without competing risks) will be analyzed similarly. Quality of life will be treated as a continuous endpoint; its mean will be estimated and reported with a 95% confidence interval. Toxicity (CTCAE 0-4) will be tabulated.

10. DATA MANAGEMENT

Participating institutions will be collaborating with Vanderbilt in patient accrual. Data will be collected using a centralized electronic case report form called ON-line Clinical Oncology Research Environment = Oncore (http://www.vicc.org/ct/research/oncore.php). Oncore is a highly secure, web based, cancer

specific, and customizable system that provides fully integrative clinical data management and study administration capabilities developed in an ongoing collaborative effort with NCI designated Comprehensive Cancer Centers. It fully integrates study administration functionality including protocol tracking, patient registration, NCI reporting, review committee tracking, and SAE tracking, with clinical data management functionality including electronic case report forms (eCRF) design, clinical data capture, protocol and regulatory compliance monitoring. Also the system is capable in storing basic protocol information (e.g., IRB approval dates, dates for annual renewals,) and clinical trials research data. Oncore allows the investigator to define specific protocol requirements and generate data collection forms. Creation of the data collection form is done with a single button click after the parameters of an individual protocol have been specified. Oncore permits specification of study protocols, management of patient enrollment, clinical data entry and viewing, and the generation of patient or study-specific reports based on time stamping. OnCore is embedded with a comprehensive domain repository of standard reference codes and forms to promote standardization. The sources for the repository include CDUS, CTC, CDEs from NCI, ICD, MedDRA and various best practices from contributing NCI-designated Comprehensive Cancer Centers. OnCore provides several reporting features specifically addressing NCI Summary 3 and Summary 4 and other reporting requirements. Data may also be exported in a format suitable for import into other database, spreadsheets or analysis systems (such as SPSS). This system will be used to manage all VICCC clinical trials data. OnCore is maintained and supported in the VICC Clinical and Research Informatics Resource.

Specified members at each participating site will submit all pertinent regulatory documents to the Coordinating Center, who will store it in a secure location.

Sites will retain organized subject, laboratory, and study device inventory records relating to the study for the period of time required by applicable federal law or regulation. The site will not destroy such records without giving the Sponsor prior written notice and the opportunity to further store such records, at the Sponsor's cost and expense.

11. AMENDMENTS TO THE CIP

All protocol amendments will be submitted to the Institutional Review Boards (IRBs), FDA and other Competent Authorities by the coordinating center on behalf of the sponsor-investigator when any revision is made to the original protocol or subsequent version of the protocol that significantly affects 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.
The final approved amended protocol will be distributed to participating investigator(s) at each site for local IRB approval.

12. DEVIATIONS FROM CLINICAL INVESTIGATIONAL PLAN

Investigators are not allowed to deviate from the clinical investigation plan. Deviations from the CIP necessary to protect the rights, safety and well-being of human subjects may proceed without prior approval of the Sponsor and the IRB. Such deviations shall be documented and reported to the Sponsor and the IRB as soon as possible, but in no event later than 5 working days after the deviation occurred.

CIP deviations are to be reported in the eCRF. Sites should report deviations to their IRB as per institutional guidelines. At the discretion of the Sponsor, Investigators not complying with the protocol may be disqualified to continue participation in the clinical trial.

13. DEVICE ACCOUNTABILITY

Device accountability is ensured by the Sponsor-investigator and the funder, 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

14. STATEMENTS OF COMPLIANCE

The clinical investigation evaluated under this protocol shall be conducted at each participating site in accordance with ethical principles. The clinical investigation will also be conducted in compliance with national or regional regulations as appropriate.

The clinical investigation shall not begin before IRB and Competent Authority approval is obtained for the participating sites accordingly. The appropriate insurance for subjects participating in this clinical trial shall be arranged for each participating site.

15. INFORMED CONSENT PROCESS

It is the responsibility of the Research Staff to ensure that protocol patients have received the Center's Notice of Privacy Practices. If the subject has not already done so, personnel of the relevant participating Center must try to obtain acknowledgment before the patient participates in this study.

The Center's Privacy Office may allow the use and disclosure of protected health information pursuant to a completed and signed Research Authorization form or a signed informed consent form that contains the authorization to use/disclose protected health information. The use and disclosure of protected health information will be limited to the individuals described in the Research Authorization form or section of the consent form. A Research Authorization form or section of the consent must be completed by the Principal Investigator or designee and have prior approval of the IRB of record for that institution.

Prior to carrying out any protocol-specific procedures, investigators or designated staff will fully explain the details of the protocol, study procedures, and the aspects of patient privacy concerning research specific information. In addition to signing the IRB Informed Consent, all patients must sign the Research Authorization component of the informed consent form where applicable. The Research Authorization requires a separate signature from the patient. Each patient will receive a copy of the signed documents. All patients must provide written informed consent prior to enrollment and registration totreatment.

The following points will be observed during the informed consent process:
a) The Principal Investigator or his/her authorized designee conducts the informed consent process
b) All aspects of the clinical investigation that are relevant to the subject's decision to participate will be included
c) Any coercion or undue improper influence on, or inducement of, the subject to participate will be avoided
d) The study does not waive or appear to waive the subject's legal rights
e) Native non-technical language that is understandable to the subject will be used
f) Ample time for the subject to read and understand the informed consent form and to consider participation in the clinical investigation will be given.
g) Personally dated signatures of the subject and the Principal Investigator or an authorized designee responsible for conducting the informed consent process will be included in the informed consent form
h) The subject will be provided with a copy of the signed and dated informed consent form and any other pertinent study documents will be provided
i) Important new information will be provided to new and existing subjects throughout the clinical investigation.

Subjects that are unable to provide consent by their own will not be included.

Informed consent will comply with regional and national laws as applicable.

16. ADVERSE EVENTS, ADVERSE DEVICE EFFECTS AND DEVICE DEFICIENCIES

As defined by MEDDEV 2.7/3 Revision 3 (May 2015), an adverse event is any untoward medical occurrence, unintended disease or injury or any untoward clinical signs (including an abnormal laboratory finding) in subjects, users or other persons whether or not related to the investigational medical device. This includes events related to the investigational device or the comparator, events related to the procedures involved (any procedure in the clinical investigation plan). For users or other persons, this is restricted to events related to the investigational medical device.

1. Possible Adverse Events

a) NovoTTF-200A System (200 kHz TTFields)

In the phase III trial in patients with recurrent GBM, device-related adverse events (grade 1/2) included: medical device site reaction (skin reaction) 16%, headache 3%, malaise 2%, muscle twitching 1%, fall 1% and skin ulcer 1%. There were no serious adverse events attributed to the device. Long-term use of TTFields from EF-14 trial was associated with localized skin toxicity: Mild to moderate skin irritation was observed in 43% of patients treated with TTFields plus temozolomide and severe skin reaction (grade 3) in 2%. Mild anxiety, confusion, insomnia, and headaches were reported more frequently in the patients treated with TTFields plus temozolomide and occurred mainly at the time of therapy initiation.

Treatment with NovoTTF-200A is not expected to cause any serious side effects. However, it is possible that investigational treatment may cause any of the following:

1. Local heat and tingling “electric” sensation beneath the transducer array
2. Allergic reaction to the adhesive or to the gel
3. Skin irritation or skin breakdown
4. Infection at the sites of transducer array contact with the skin

5. Open sores, ulceration or blisters underneath transducer arrays
6. Headache
7. Fatigue
8. Falls
9. Muscle twitching
10. Electrical or mechanical failure leading to shock

b) Systemic Chemotherapy / Therapy
Patients receiving chemotherapy or biologic agents for their systemic disease are expected to experience adverse events as listed in the package insert for each agent given.

c) Supportive Medications
Supportive medications may be administered at the discretion of the investigator.

2. Adverse Event Collection and Reporting

All adverse events will be captured on a centralized electronic case report form called ON-line Clinical Oncology Research Environment = Oncore

The following will be recorded:

a) Grading of an Adverse Event
The descriptions and grading scales found in the revised NCI Common Toxicity Criteria (CTC) version 5.0 will be utilized for assessing severity of adverse events. If the toxicity is not characterized adequately by the NCI toxicity scale, the investigator will use the adjectives MILD, MODERATE, SEVERE to describe the maximum intensity of the adverse event. For purposes of consistency, these intensity grades are defined as follows:

MILD	Grade 1	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
MODERATE	Grade 2	Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental Activities of Daily Living (ADL)
SEVERE	Grade 3	Severe or medically significant but not immediately life- threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self care ADL
POTENTIALLY LIFE-THREATENING	Grade 4	Life-threatening consequences; urgent intervention indicated.
DEATH	Grade 5	Death related to AE.

Modified Grading for NovoTTF-200A-Related Skin Adverse Events:

NovoTTF-200A -Related Skin Adverse Events
Grade 1 – Asymptomatic or mild symptoms AND 1. No intervention required OR only topical treatment intervention indicated 2. Treatment interruption of less than 3 days may be required.
Grade 2 – Moderate symptoms AND Systemic therapy required OR event is requiring interruption of NovoTTF-200A for more than 3 days.
Grade 3 – Severe or medically significant but not immediately life threatening AND hospitalization OR prolongation of existing hospitalization indicated

Grade 4 – Life threatening consequences AND urgent intervention indicated

Vanderbilt University Medical Center will be responsible for the classification of adverse events and ongoing safety evaluation of the clinical investigation.

Safety evaluation and reporting will be managed through the following actions:

1. Review the investigator's assessment of all **serious adverse events** and determine and document in writing their relationship to the investigational device;
2. Review all **device deficiencies** and determine and document in writing whether they could have led to a serious adverse device effect;
3. Report or ensure the reporting to the IRB committee by the Principal Investigator(s) or designee, of all **serious adverse events** and **device deficiencies** that could have led to a serious adverse device effect, if required by federal regulations or by the IRB.
4. Report to regulatory authorities, within the required time period, all **serious adverse events** and **device deficiencies** that could have led to a serious adverse device effect, if required by federal regulations.
5. Ensure that the IRB and the regulatory authorities are informed of significant new information about the clinical investigation.
6. In case of **serious adverse device effects** and **device deficiencies** that could have led to serious adverse device effects, determine whether risk analysis needs to be updated and assess whether corrective or preventive action is required.

b) Device Deficiency

A device deficiency is defined as the inadequacy of a medical device related to its identity, quality, durability, reliability, safety or performance, such as malfunction, misuse or use error and inadequate labeling.

c) Serious Adverse Device Effect (SADE)

An SADE is any adverse device effect that has resulted in any of the consequences characteristic of a serious adverse event.

d) Serious Adverse Event (SAE)

An SAE is any adverse event that:

- led to a death,
- led to a serious deterioration in health that either:
    - resulted in a life-threatening illness or injury, or
    - resulted in a permanent impairment of a body structure or a body function, or
    - required in-patient hospitalization or prolongation of existing hospitalization, or
    - resulted in medical or surgical intervention to prevent life threatening illness or injury or permanent impairment to a body structure or a body function.
- led to fetal distress, fetal death or a congenital abnormality or birth defect.

This includes device deficiencies that might have led to a serious adverse event if

- suitable action had not been taken, or
- intervention had not been made or
- if circumstances had been less fortunate.

These are handled under the SAE reporting system.

A planned hospitalization for pre-existing condition, or a procedure required by the clinical investigation plan, without a serious deterioration in health, is not considered to be a serious adverse event.

e) Unanticipated Serious Adverse Device Effect (USADE)

A USADE is any serious adverse device effect whose nature, incidence, severity or outcome has not been identified in protocol Section 16.1a, Possible Adverse Events. Anticipated SADEs are effects whose nature, incidence, severity or outcome has been previously identified in protocol Section 16.1a, Possible Adverse Events. Any potential USADEs will be reported to the study monitor and local IRB within 10 days of the investigator learning of the event. The Sponsor will investigate and determine if the events are USADEs. Expedited reporting for FDA submission and reporting to other IRBs is to follow within 10 working days after first learning of the event by the Sponsor or their representative. If more than one USADE is observed in study patients, this will result in stopping of patient enrollment until further assessment by the data safety monitoring committee.

f) Reportable Events

For the purpose of this guidance and based on the definitions above, the following events are considered reportable events in accordance with FDA reporting requirements:

- any SAE,
- any Investigational Medical Device Deficiency that might have led to a SAE if a) suitable action had not been taken or b) intervention had not been made or c) if circumstances had been less fortunate,
- new findings/updates in relation to already reported events,
- USADEs

On this study:

1) Hospitalization duration of less than 24 hours is not considered to be a serious adverse event.
2) Death due to the primary disease (small cell lung cancer) need not be reported as an SAE. These SAEs will be captured in the CRFs as described for regular AEs.

Reportable events will be reported by the Sponsor or their designee to the appropriate regulatory authorities.

g) Reporting Timelines

Any SAE or USADE which indicates an imminent risk of death, serious injury, or serious illness and that requires prompt remedial action for other patients/subjects, users or other persons or a new finding to it will be reported immediately, but not later than 2 calendar days after awareness by Sponsor of a new reportable event or of new information in relation with an already reported event.

Any other reportable events or a new finding/updates must be reported immediately, but not later than 7 calendar days following the date of awareness by the Sponsor of the new reportable event or of new information in relation with an already reported event.

h) Determination of Causality of Adverse Events

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

None:	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.

i) Eliciting Adverse Event Information

The investigator is to record all directly observed adverse events and all adverse events spontaneously reported by the trial patient using concise medical terminology. In addition, each trial patient will be questioned about adverse events at each clinic visit following initiation of treatment. The question asked will be, "Since your last clinic visit have you had any health problems?"

j) Adverse Event Reporting Period

The adverse event reporting period will begin immediately following registration to treatment (start of use of the NovoTTF-200A device). Adverse events will be collected for 8 weeks following treatment termination. All adverse events that occur in trial patients during the adverse event reporting period specified in the protocol must be reported on the eCRFs, whether or not the event is considered study treatment-related. In addition, any known untoward event that occurs beyond the adverse event reporting period that the investigator assesses as possibly related to the investigational medication/product should also be reported as an adverse event.

k) Follow-up of Unresolved Adverse Events

All adverse events should be followed until they are resolved or the investigator assesses them as chronic or stable or the patient's participation in the trial ends.

In addition, all serious adverse events and those non-serious events assessed by the investigator as probably related to the investigational medication/product should continue to be followed even after the patient's participation in the trial is over. Such events should be followed until they resolve or until the investigator assesses them as "chronic" or "stable." Resolution of such events is to be documented on the appropriate CRF.

l) Serious Adverse Events

All serious adverse events, regardless of causality to the study treatment, will be reported to the Principal Investigator and/or the Study Coordinator at each institution, and also to the Coordinating Center.

All serious adverse events must be reported to the Coordinating Center within 24 hours of the investigator becoming aware of the event. Events should be reported using the Vanderbilt SAE form.

The Vanderbilt SAE form must be fully completed and emailed, faxed, or scanned to:

ATTN: VICC CTSR Personnel
EMAIL: coordinating.center@vumc.org
FAX: (615) 875-0040

If SAE documents are faxed, the Coordinating Center must be notified via email as well. Follow-up information must also be reported within 24 hours of receipt of the information by the investigator.

If SAE documents are faxed, the Coordinating Center must be notified via email. Follow-up information must also be reported within 24 hours of receipt of the information by the investigator.

The Coordinating Center will disseminate information regarding serious adverse events to the participating sites as per FDA guidance only in the case that the event(s) is unexpected and is believed to be related (i.e., possibly, probably or definitely) to the device. The Coordinating Center will be responsible for reporting of events to the FDA and supporters, as appropriate (outlined below).

Institutional Review Board
All adverse events, serious adverse events, and adverse device effects will be reported to the IRB per current institutional standards. If an AE/ADE requires modification of the informed consent, these modifications approved by the sponsor-investigator will be provided to the IRB as soon as possible for IRB approval prior to any patient receipt of a revised consent. If an AE/ADE requires modification to the study protocol, these modifications approved by the sponsor-investigator will be provided to the IRB as soon as is possible.

Food and Drug Administration (FDA)
In this trial, serious unexpected adverse events suspected by the sponsor-investigator to be possibly, probably, or definitely related to protocol-indicated treatment will be reported to the Food and Drug Administration using the MedWatch Form FDA 3500A – Mandatory Reporting form, currently available at: http://www.fda.gov/Safety/MedWatch/HowToReport/DownloadForms/default.htm

For all participating sites, the Coordinating Center will be responsible for correspondence regarding AEs/ADEs with the FDA.

Novocure
The sponsor is responsible for reporting all UADEs to Novocure within 2 days of the Sponsor becoming aware of the UADE. UADEs are reported to Novocure via the Sponsor's SAE reporting form or by forwarding a copy of the MedWatch Form 3500A submitted to the FDA. Reports should be sent to:

Support@novocure.com or FAX 1-603-782-0219

17. VULNERABLE POPULATION

As described in the exclusion criteria, no vulnerable population will be included in this trial.

18. SUSPENSION OR PREMATURE TERMINATION OF THE CLINICAL

INVESTIGATION

Vanderbilt University Medical Center may suspend or prematurely terminate either a clinical investigation or an individual investigation site or the entire clinical investigation for significant and documented reasons. A Principal Investigator, IRB, or regulatory authority may suspend or prematurely terminate participation in a clinical investigation at the investigation sites for which they are responsible. If suspicion of an unacceptable risk to subjects arises during the clinical investigation, or when so instructed by the IRB or regulatory authorities, Vanderbilt University Medical Center shall suspend the clinical investigation while the risk is assessed. Vanderbilt University Medical Center shall terminate the clinical investigation if an unacceptable risk is confirmed.

Vanderbilt University Medical Center shall consider terminating or suspending the participation of a particular investigation site or investigator in the clinical investigation if monitoring or auditing identifies serious or repeated deviations on the part of an investigator. If suspension or premature termination occurs, the terminating party shall justify its decision in writing and promptly inform the other parties with whom they are in direct communication. The Principal Investigator and Vanderbilt University Medical Center shall keep each other informed of any communication received from either the IRB or the regulatory authority.

If, for any reason, Vanderbilt University Medical Center suspends or prematurely terminates the investigation at an individual investigation site, Vanderbilt University Medical Center shall inform the responsible regulatory authority as appropriate and ensure that the IRB is notified, by the Principal Investigator or designee. If the suspension or premature termination was in the interest of safety, Vanderbilt University Medical Center shall inform all other Principal Investigators.

If suspension or premature termination occurs,

- Vanderbilt University Medical Center shall remain responsible for providing resources to fulfill the obligations from the protocol and existing agreements for following up the subjects enrolled in the clinical investigation, and
- The Principal Investigator or authorized designee shall promptly inform the enrolled subjects at his/her investigation site, if appropriate.

When Vanderbilt University Medical Center concludes an analysis of the reason(s) for the suspension, implements the necessary corrective actions and decides to lift the temporary suspension, Vanderbilt University Medical Center shall inform the Principal Investigators, the IRBs, and, where appropriate, the regulatory authority of the rationale and provide them with the relevant data supporting this decision.

Concurrence shall be obtained from the IRBs and, where appropriate, regulatory authorities before the clinical investigation resumes. If subjects have been informed of the suspension, the Principal Investigator or authorized designee shall inform them of the reasons for resumption.

19. PUBLICATION POLICY

The results of the clinical investigation will be made publicly available in case of positive or negative results following the completion of the trial.

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21.APPENDICES

Appendix A: Performance Status Criteria ECOG Performance Status Scale

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 B: Neurocognitive Function

According to Meyers and Brown (Meyers CA 2006), for a neurocognitive test battery to be useful in clinical research it should fulfill the following 6 criteria:

a) It should be brief in order to reduce patient and clinical burden.

b) It should have alternate forms of the tests in order to reduce practice effects and therefore allow for repeated test administration.

c) It should have good psychometric properties such as validity, reliability, and population norms so that true changes in NCF above fluctuations due to situational factors can be detected.

d) It should be sensitive to changes in cognitive function.

e) It should be highly standardized and easy to administer so that no specialized psychological training is necessary in order to be able to administer the test battery.

f) Most patients should be able to complete the neurocognitive tests, even patients with significant neurocognitive problems, in order to reduce the likelihood of selection bias.

See Statistical Considerations chapter for further information regarding the evaluation of neurocognitive endpoints

Test Battery for Neurocognitive Function

Neurocognitive Parameter Measured	**Test**	**Time to Administer (Minutes)**
Auditory/verbal learning and memory	Hopkins Verbal Learning Test-Revised	**5**
Visual-Motor Scanning Speed	Trail Making Test Part A	**5**
Executive Function	Trail Making Test Part B	**5**
Verbal Fluency	Controlled Oral Word Association Test	**5**
	Total Time	**20**

Prior to initiation of TTFs, all patients will undergo baseline neurocognitive testing using these neurocognitive instruments. At that time, history regarding level of education reached will also be obtained. After completion of therapy, all patients will undergo this neurocognitive test battery, conducted by trained and certified nurses or clinical research associates, every 8 weeks until death or until one year after therapy, whichever comes first. In the analysis of neurocognitive decline, each patient will serve as his/her own control, as decline for each neurocognitive test at each follow-up time point will be compared to baseline.

Appendix C: Study Calendar

	T=(-21)-0 Days (Baseline)	T=0 days (Registration to Treatment)	T= 0 to 21 days (Registration to Treatment to 21)	T=every 8 weeks until intracranial failure (Follow-Up) (±7days)	T= 8 weeks from treatment termination (±7days)	T= every 4 weeks from treatment discontinuation (±7 days)
Signed ICF	X					
MRI of brain[1]	X			X	X	
Medical history	X					
Performance Status (KPS score)	X			X	X	
Physical examination[2]	X			X	X	
Neurological examination	X			X	X	
Complete blood count including differential	X			X	X	
Serum chemistry panel[3]	X			X	X	
Neurocognitive Testing[4]	X			X		
Quality of Life Questionnaire[4]	X			X		
Serum pregnancy test[5]	X					
Blood coagulation test[6]	X					
Registration to treatment (Start of use of NovoTTF-200A)		X				
Adverse event collection and recording[7]		X	X	X	X	
Concomitant medication recording	X	X	X	X	X	
Device compliance assessment				X		
Telephone follow-up for survival						X

1. A high resolution, isovolumetric T1-weighted post-gadolinium MRI of the brain using a 3T MR scanner. **Treatment with the NovoTTF-200A System is to begin within 21 days after this baseline MRI.** Additional parameters include:
    - FOV: 256 mm x 256 mm
    - Matrix: 256x256
    - Slice thickness: 1 mm
    - Full brain coverage

The same slice thickness should be maintained throughout the study. The NovoTTF-200A System and all components including the transducer arrays must be removed and cannot be brought into the MR environment.

2. Vital signs are included as part of the physical exam
3. Serum chemistry panel includes: BUN, Creatinine, Sodium, Potassium, ALT, AST, Bilirubin
4. Neurocognitive Testing and QOL questionnaire will be performed for one year or until second cerebral progression (whichever comes first)
5. If applicable and within 14 days
6. Coagulation tests include PT, PTT and will be performed as part of the follow up procedures only if clinically indicated
7. Reporting period will begin immediately following registration to treatment (start of use of NovoTTF-200A) and ends at the conclusion of 8 weeks following treatment termination

Appendix D: NCI Common Toxicity Criteria (CTC) version 5.0

https://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_8.5x11.pdf

Appendix E: Investigators

Principal Investigator: Albert Attia, M.D. Sub- Investigators: Sally York, M.D.,Ph.D., Michael Neuss, M.D., Kristin Ancell, M.D., Travis Osterman, D.O., Jonathan Lehman, M.D., Ph.D., Evan Osmundson, M.D., Ph.D., Leora Horn, M.D.
Name and address of the lead investigation site(s) in which the clinical investigation will be conducted. Vanderbilt University Medical Center Department of Radiation Oncology 2200 Pierce Ave., B-1003 PRB Nashville, TN 37232-5671
Names and addresses of other institutions and investigators involved in the clinical investigation. Michael Chan, M.D. Wake Forest Baptist Medical Center Department of Radiation Oncology Medical Center Boulevard Winston-Salem, NC 27157 Brandi Page, M.D. Johns Hopkins Radiation Oncology Suburban Hospital 6420 Rockledge Drive Suite 1200 Bethesda, MD 20817

Note: The Sponsor shall maintain an updated list of principal investigators, investigation sites, and institutions. This list can be kept separately from the CIP. The definitive list shall be provided with the clinical Investigation