RAD 1704/UAB 1793: A Pilot and Feasibility Trial to Determine the Rate of Brain Relapse in Small Cell Lung Cancer (SCLC) Patients with Brain Metastases Treated with Stereotactic Radiosurgery (SRS) Followed by Tumor Treating Fields (TTF)

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1.0 OBJECTIVES

1.1 Primary:

1.1.1 To determine the rate of distant brain metastases at 6 months in patients with SCLC brain metastases receiving SRS followed by Novo TTF-200A.

1.2 Secondary:

1.2.1 Determine the feasibility of SRS in patients SCLC brain metastases followed by Novo TTF-200A.

1.2.2 Determine the rate of distant brain metastases (outside the 100% isodose volume) at 1 year in patients with SCLC brain metastases receiving SRS followed by Novo TTF-200A.

- Determine the rates of toxicity from SRS for patients with brain metastases followed by Novo TTF-200A.
- Determine the rate of CTCAE physician reported toxicity.
- Determine the rate of neurocognitive toxicity using neurocognitive tests.

1.2.3 Characterize quality of life using standardized metrics

1.2.4 Determine the rate of local control of targeted lesions.

1.2.5 Determine the rate of overall survival

2.0 BACKGROUND AND RATIONALE

2.1 Small Cell Lung Cancer Brain Metastases Overview

SCLC, representing 10-15% of all lung cancers, grows rapidly and spreads to distant organs early in the disease course. SCLC spreads to the brain in approximately 40% of all patients. Without treatment, the median survival for a patient with brain metastases is less than 3 months [1-5]. Historically, whole brain radiation therapy (WBRT) has been used to treat brain metastases with a median survival on the order of 6 months [2-5]. For patients with a limited number of brain metastases, focal treatment with surgery or SRS is associated with an increase in survival [6]. Multiple studies have shown that the addition of WBRT to SRS for brain metastases does not improve survival [7]. However the rate of distant brain failures with omission of WBRT is approximately 50%. To reduce this intracranial relapse risk while sparing the patient the toxic effects of whole brain radiotherapy, the METIS trial is investigating the addition of NovoTTF-100M to SRS in non-small cell lung cancer patients [8]. Due to the perceived high intracranial relapse rate for small cell lung cancer patients, most physicians advocate WBRT for any amount of measurable brain metastases.

2.2 Neurocognitive Sequelae of Whole Brain Radiation

WBRT includes a large volume of normal tissue that may not need to be irradiated to therapeutic doses. Investigators from Memorial Sloan-Kettering Cancer Center have described dementia in 11% of long-term survivors after

whole brain radiation. Lower grade neurocognitive complications are even more common [9,10]. In an effort to avoid this long-term toxicity, there has been increased interest in avoiding WBRT in patients with brain metastases. More recently, Chang et al reported a randomized trial at MD Anderson including 58 patients randomized to SRS alone or SRS plus WBRT in NSCLC patients [11]. In this study detailed neuro-cognitive and quality of life (QOL) assessments were performed including the Functional Assessment of Cancer Therapy- Brain (FACT-BR) and Hopkins Verbal Learning Test-revised (HVLT-R). Accrual to the study was stopped early when an interim analysis revealed a difference in total recall at 4 months, the primary endpoint of the trial, in favor of the group that was treated with SRS alone. This outcome was observed despite the use of an adjuvant WBRT dose that was relatively modest at 30 Gy in 12 fractions of 2.5 Gy. The mean probability of decline was 52% with combination therapy vs. 24% with SRS alone. Delayed recall and delayed recognition also favored the SRS alone arm. Within the limitations of a small study, QOL as measured by FACT-BR did not differ between the two groups. Local control of the treated tumors strongly favored the group that received combined therapy (100% vs. 67%), and there was a lower risk of developing tumors elsewhere in the brain. Paradoxically, preventing recurrences in the brain did not lead to an improvement in overall survival. In fact, overall survival favored the group that received SRS alone. This confounding observation brings into question whether other differences between the groups might be contributing not only to survival but also to the neuro-cognitive outcomes.

2.3 Role of Radiosurgery Without Whole Brain Radiation for SCLC Brain Metastases

No prospective trials have been conducted to evaluate local control, patterns of relapse, and toxicity with SRS for SCLC brain metastases specifically. Many physicians continue to give WBRT for SCLC brain metastases with the assumption that rates of relapse within the brain are higher than in other malignancies. However, limited retrospective studies of salvage SRS after WBRT show 6 and 12 month relapse rates of 25% and 47%, respectively [12]. In comparison, relapse rates after upfront SRS alone in other malignancies are 35% at 6 months and 49.5% at 12 months [13]. Patients managed initially with SRS alone do have a higher incidence of developing subsequent brain metastases, but retrospective and prospective studies suggest no decrement to neurologic outcome in these patients, mostly due to successful salvage with WBRT [14].

2.4 Rationale for the Use of Tumor Treating Fields (TTFields)

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 [15,16]. 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 [17], NSCLC at 150kHz [18]; breast carcinoma at 120kHZ [19]; melanoma at 100kHz [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 [15,17]. 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 [21], 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 [22]. 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 [23] showed Optune™ 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 Optune™ 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 [24], without the addition of high grade toxicity and without decline in quality of life.

2.5 Preclinical Results with TTFields

Human squamous cell carcinoma (HTB 182), human adenocarcinoma (H1299, A549, HCC827) murine squamous cell carcinoma (KLN 205) and murine Lewis lung carcinoma (LLC1) cells have been subjected to low intensity TTFields in preclinical studies. These experiments showed that TTFields significantly inhibit culture proliferation. A frequency dependency was clearly demonstrated, with an optimal inhibitory frequency of 150 kHz for these cultures. A reduction of 31-57% in the number of viable cancer cells,

compared to control cultures, was seen following 72 hours of continuous TTFields treatment in these cell lines ($p<0.05$). TTFields were found to significantly impair the colony-forming ability of all tested cell lines in culture [17,18].

In addition, two animal models were used to test the in vivo application of continuous TTFields for the treatment of NSCLC. In an autologous model of C57BL/6 mice, LLC1 tumors were implanted in the left lung of the mice 11 days prior to treatment initiation. Bi-directional, 150 kHz TTFields were applied for 6 days by means of two pairs of insulated transducer arrays placed on the animal's chest skin overlaying the lung area, so that two perpendicular field directions were delivered sequentially to the lungs. TTFields were applied for at least 90% of the duration of the experimental treatment. Following treatment, mice were sacrificed and tumors excised. TTFields reduced tumor volume by 36%±38% compared to control mice tumors ($p<0.05$) [25,26].

In addition, KLN-205-T1 cells were used to establish an orthotopic, syngeneic animal model for testing the effects of TTFields in lung squamous cell carcinoma. The cells were injected into the left lung lobe of DBA/2 mice. Seven days after tumor inoculation, mice were treated with TTFields. Tumor volume and weight were determined post mortem. KLN-205-T1 tumors demonstrated a 47±17% reduction in tumor volume as compared to control animals, after treatment with TTFields ($P=0.04$). Similarly, the weight of the left lung lobe carrying the KLN-205-T1 tumors was reduced after treatment with TTFields to 72±6% of controls ($P=0.01$) [25,26].

A meta-analysis of cancer cell lines found that DMS 114 (biopsied tumor from a patient with small cell lung cancer) responded optimally to TTFields at a frequency of 200mHz, which will be used for our study [32].

2.6 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 [27]: (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).

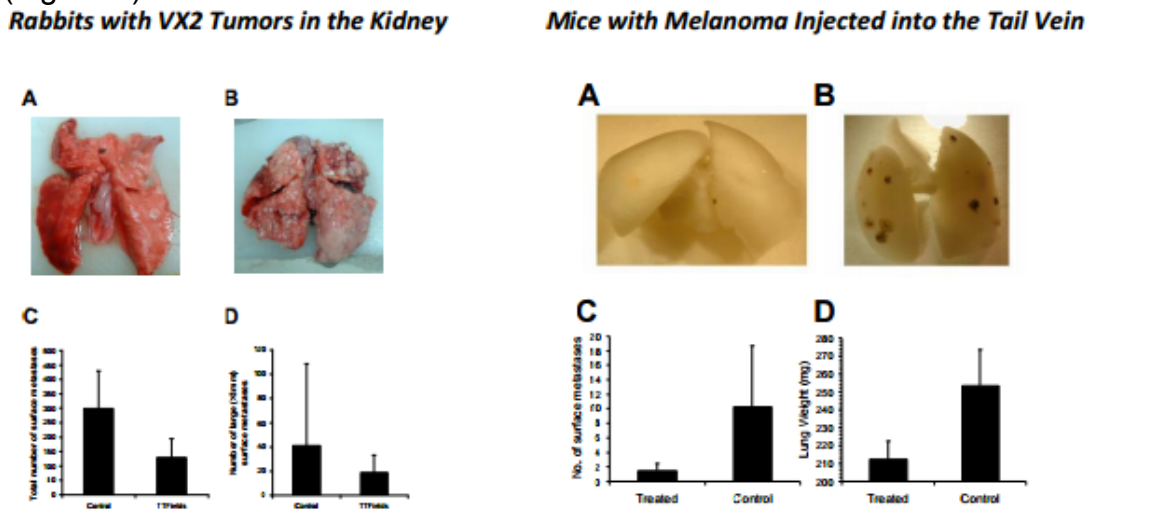


Fig. 1

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)

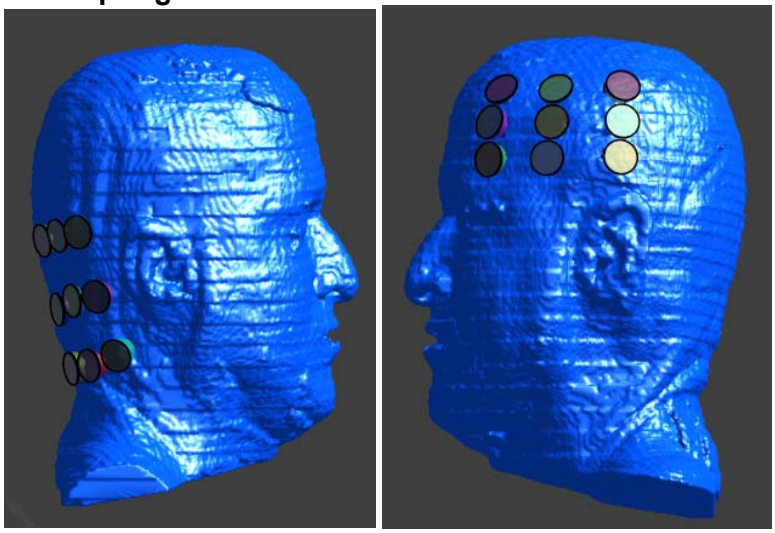
Left Panel Exemplary photos of surface lung metastases in TTFields treated (A) versus sham control rabbits (B). Treatment was initiated on day 12 from implantation of the kidney tumor. The average total number (±SD) of surface metastases (C) and the average number of large metastases (±SD) (D) in control versus treated rabbits

2.6.1 Delivery TTFields to the Infratentorial Region

Computational simulations on a phantom model were conducted in order to examine the distribution of TTFields in the infratentorial region. The same treatment parameters were assumed for these simulations as the NovoTTF-100M delivers to patients treated on the EF-25 study. These simulations were performed using the Sim4Life 1.2 Software package (ZMT, Zurich, Switzerland) on several models. The permittivity and conductivity were assigned to the tissues of the phantom based on the Gabriel Model [37]. Electric field distributions were calculated using the Sim4Life quasi-static low frequency finite element solver. The simulations performed demonstrated for the first time that by placing a pair of arrays on the lateral aspects of the occipital plane of the scalp, or placing a pair of arrays on the vertex of the scalp and on the posterior-inferior aspect of the neck, respectively, a therapeutic distribution of TTFields is obtained throughout the cerebellum and brain stem. Importantly, at the same time, these layouts also still provide therapeutic TTFields levels in the supratentorial region, demonstrating the feasibility of treating both supra- and infratentorial regions in cases where metastases affect both regions of the brain.

2.6.2 Combined Infra- & Supratentorial Array Layout

***Left Up Right Behind Ear**



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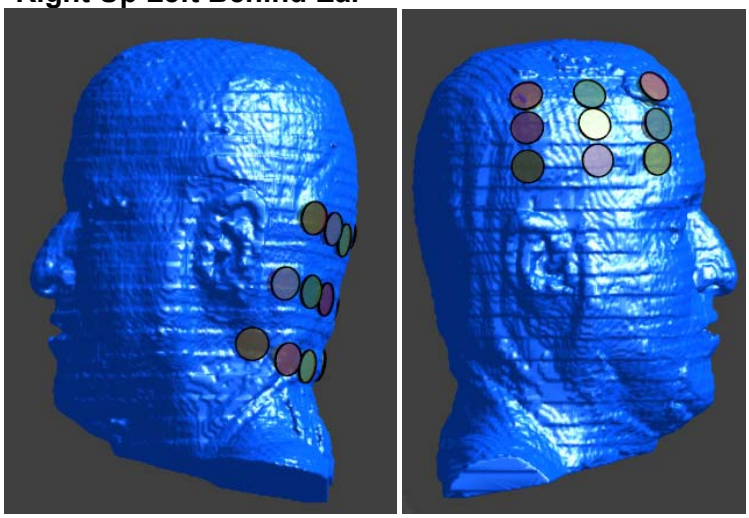

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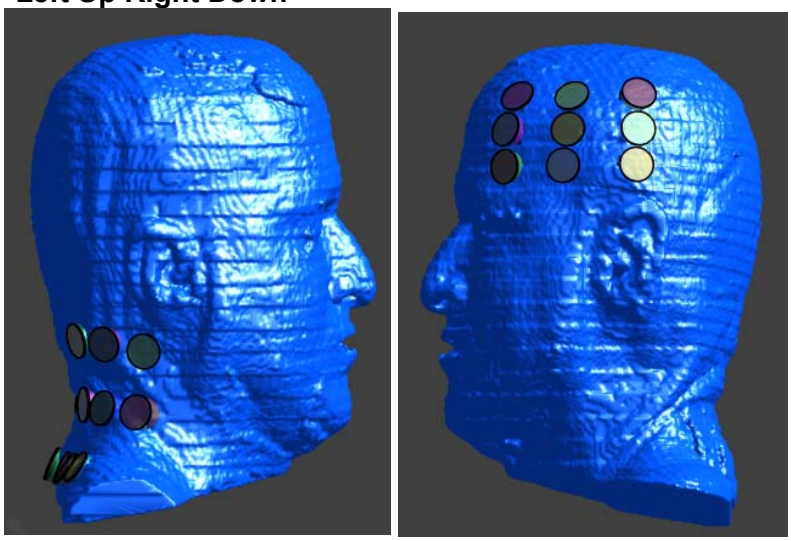

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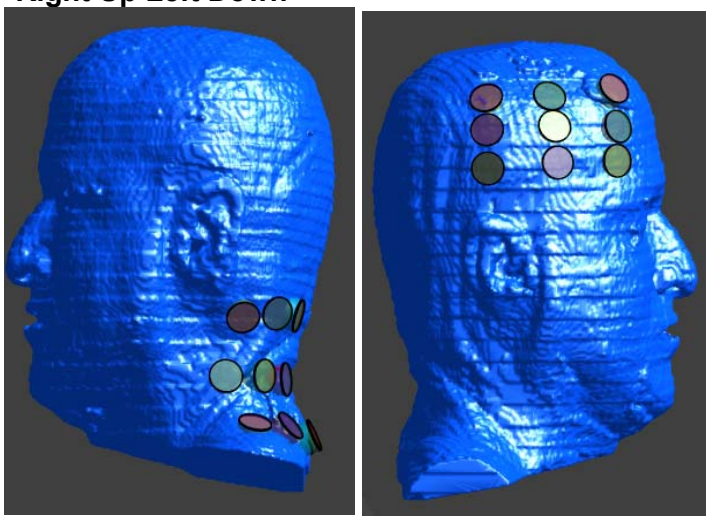


2.7 Clinical Results with TTFields in Glioblastoma

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 [16]. 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 (hazard ratio 0.86 [95% CI 0.66-1.12]; p=0.27), 1-year survival rate was 20% and 20% and progression-free survival

rate at 6 months was 21.4% and 15.1% (p=0.13), respectively in TTFields versus chemotherapy treated patients. Responses were more frequent in the TTFields arm (14% vs. 9.6%, p=0.19). The most common TTFields-related adverse event was mild (14%) to moderate (2%) skin irritation beneath the transducer arrays, which was again expected with use of the transducer arrays. These adverse events were effectively treated with topical hydrocortisone. Patients receiving chemotherapy had significantly more gastrointestinal, hematological and infectious complications. Quality of life analyses favored TTFields in most domains. Specifically, cognitive and emotional function were reported to be much better in the TTFields treated patients than with chemotherapy.

The results of this phase III trial demonstrated comparable efficacy with this chemotherapy-free treatment (200 kHz TTFields) to chemotherapy (including bevacizumab) in recurrent glioblastoma with a more favorable safety profile and quality of life and supported FDA approval of TTFields in recurrent glioblastoma in 2011 and a CE mark in Europe.

Registry data from 457 recurrent GBM patients who started Optune™ prescribed by the treating physician in the US between October 2011 and November 2013 showed an even higher median overall survival of 9.6 months, with baseline characteristics similar to those of patients treated under the pivotal clinical trial [28,29]. The 2-year survival rate in this population was 30% (compared to 9% in Optune™-treated patients on the clinical trial). Compliance was a clear predictor of survival on Optune™, and patients treated with the device for at least 18 hours per day had significantly longer survival time. No new safety signals have been detected in this registry dataset and the only common adverse event related to Optune™ was skin reaction.

Based on this clinical data in recurrent GBM and a pilot trial in newly diagnosed GBM with Optune™ in combination with temozolomide that demonstrated favorable safety profile and promising efficacy, an international phase III trial in newly diagnosed GBM, evaluating the role of Optune™ in combination with temozolomide maintenance after surgery and chemoradiation versus temozolomide alone was conducted. In the final analysis (n=695), progression-free survival was 7.1 months for Optune™/temozolomide vs. 4.2 months for temozolomide alone (hazard ratio (HR) 0.694 (95% CI: 0.558- 0.863), log rank p = 0.0010) and overall survival was 19.4 months for Optune™/temozolomide vs. 16.6 months for temozolomide alone (HR 0.754 (95% CI: 0.595-0.955), p = 0.0229). This translates into 2-year survival rates of 43% (95% CI: 36-50%) vs. 29% (95% CI: 21-38%). No significant added toxicity was seen in the temozolomide /Optune™ 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 Optune™ in combination with temozolomide for the treatment of adult patients with newly diagnosed GBM on October 5, 2015. In the US, Optune™ with temozolomide is indicated for the treatment of adult patients with newly diagnosed, supratentorial glioblastoma following maximal debulking surgery and completion of radiation therapy together with concomitant standard of care chemotherapy.

2.8 Clinical Results with TTFields in Brain Metastasis from Non-Small Cell Lung Cancer (NSCLC)

A prospective, randomized controlled phase II study is currently being conducted in Europe to study the efficacy of 150 kHz TTFields in brain metastasis from NSCLC. Sixty (60) NSCLC patients (randomized at a 1:1 ratio) with 1-5 brain metastases who underwent optimal standard local treatment (Stereotactic Radio Surgery (SRS) / Neurosurgery / combination of both) are to be included in this trial. The treatment group receives TTFields therapy using the NovoTTF-100M System and the control group receives supportive care alone. Patients also receive the best standard of care treatment for their systemic disease. The primary endpoint is time to local and distant progression in the brain. Sixteen (16) patients have been enrolled in the study to date. There have been no device-related serious adverse events (SAE) reported nor has there been any unanticipated serious adverse device effects (USADE). Expected contact dermatitis was reported in around 25% of the patients to date. The study is ongoing and enrollment continues. Another prospective, randomized trial is also currently being conducted internationally to directly compare observation and NovoTTF-100M after SRS for NSCLC brain metastases. This study is ongoing and enrollment continues.

2.9 Rationale for Conducting the Clinical Investigation

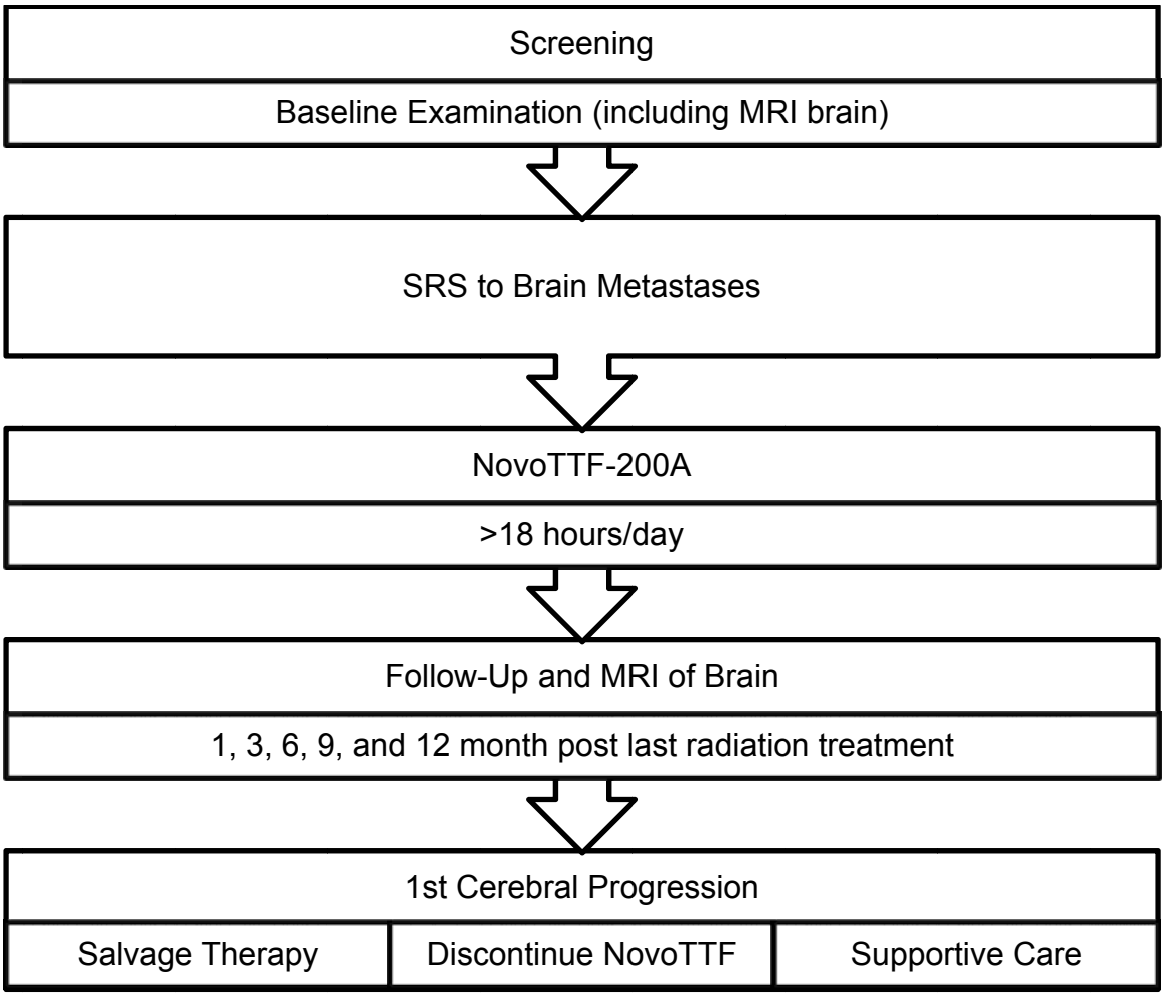
TTFields are a novel, non-invasive regional anti-mitotic treatment modality. Pre-clinical studies and clinical data in Glioblastoma Multiforme have demonstrated a favorable safety profile and clinical superiority when treating the brain with TTFields. In addition, durable responses have been demonstrated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

The development of brain metastases is devastating for SCLC patients and their families. Treatment options in this setting are limited to SRS or WBRT or a combination thereof. Few clinicians treat SCLC brain metastases with SRS alone because intracranial recurrence is high due to the fact that the entire brain is not treated. WBRT treats the entire brain and improves intracranial control, but at the risk of neurocognitive complications. Thus, new therapeutic options are needed, particularly ones that allow for greater intracranial control while minimizing the risk of neurocognitive adverse events. As such, TTFields following SRS may allow for sufficient regional treatment of the brain to

eliminate any remaining tumor cells following radiosurgery as well as micro-metastases that remain untreated, and ultimately prolong intracranial control. Due to the favorable safety profile seen in phase III recurrent and newly diagnosed glioblastoma trials and in which the patients reported improved neurocognitive and emotional functioning, NovoTTF-200A is not expected to have neuro-toxic effects seen with WBRT.
Thus, we hypothesize that the use of NovoTTF-200A applied to the brain following SRS for SCLC brain metastases will have cerebral control comparable to WBRT with less neurocognitive effects.

3.0 SCHEMA

3.1 Initiation of NovoTTF will occur within **1** month of SRS treatment.
3.2 NovoTTF will continue for 1 year or until first progression.
3.3 MRI will be obtained at 1, 3, 6, 9, and **1**2 months after the last radiation treatment.



4.0 PATIENT SELECTION CRITERIA

4.1 Inclusion Criteria

4.1.1 All subjects must have history of histologically confirmed small cell lung cancer. Brain biopsy is not required unless diagnosis is judged to be in doubt by the treating physician.

4.1.2 Brain metastases must be amenable to SRS.

- Longest diameter < 4 cm

4.1.3 Prior prophylactic cranial irradiation (PCI) or whole brain radiotherapy (WBRT) is allowed.

4.1.4 Prior Metastatic lesions in the brain are allowed. Patients must have new or progressing lesions after prior brain directed therapy.

4.1.5 Prior systemic therapy is allowed after diagnosis of brain metastases provided that restaging MRI shows measurable intracranial disease.

4.1.6 Karnofsky performance status (KPS) of greater than or equal to 70 (Appendix B)

4.1.7 Age greater than or equal to 18 years.

4.1.8 Life expectancy greater than 3 months.

4.1.9 Must receive optimal therapy for extracranial disease and may continue on systemic therapy during TTF administration.

4.1.10 Ability to operate the NovoTTF-200A device independently or with caregiver aid.

4.1.11 Previous clinical trial enrollment is allowed.

4.1.12 Subjects given written informed consent.

4.2 Exclusion Criteria

4.2.1 Patients with significant edema leading to risk of brain herniation.

4.2.2 Diffuse Leptomeningeal metastases with radiographic involvement in the brain and/or spinal cord. This does not include local leptomeningeal involvement which is defined as leptomeningeal enhancement within direct contact of targetable metastases.

4.2.3 Implantable electronic device in the brain.

4.2.4 Implanted pacemaker, programmable shunts, defibrillator, deep brain stimulator, other implanted electronic devices in the brain, or documented clinically significant arrhythmias.

4.2.5 Evidence of increased intracranial pressure (midline shift > 5mm, clinically significant papilledema, vomiting and nausea, or reduced level of consciousness).

4.2.6 Known allergies to medical adhesives or hydrogel.

4.2.7 Currently pregnant or breastfeeding.

4.2.8 Insufficient recovery from all active toxicities of prior therapies.

4.2.9 Women of childbearing potential who are not using an effective method of contraception are excluded.

5.0 DEVICE INFORMATION

5.1 Description of the Investigational Device and its Intended Purpose

The NovoTTF-200A System is an investigational medical device for the treatment of brain metastases from small cell lung cancer (SCLC). It is intended to be used exclusively by patients in a clinical trial. The device is a portable battery or power supply operated system which produces alternating electrical fields, called tumor treating fields (TTFields) within the human body. TTFields are applied to the patient by electrically-insulated surface transducer arrays. NovoTTF-200A disrupts the rapid cell division exhibited by cancer cells.

5.2 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 an EN ISO 13485 approved and 21CFR820 compliant medical device company developing electric field based therapy for cancer patients. Novocure's headquarters are located in Israel. Novocure GmbH is the EN ISO 13485 approved and 21CFR820 compliant Novocure Ltd global distribution center. Novocure GmbH is based in Switzerland.

5.3 System Parts and their Identification

The NovoTTF-200A System is composed of several parts, which are shown in the picture below. 1) NovoTTF-200A 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, and 9) Portable Battery Case.

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

5.5 Intended Purpose of the Investigational Device in the Proposed Clinical Investigation

The NovoTTF-200A System is intended for the treatment of patients 18 years of age or older with recently diagnosed brain metastases from small cell lung cancer (SCLC) following treatment of the metastases using stereotactic radiosurgery (SRS).

5.6 The Populations and Indications for which the Investigational Device is Intended

Patients with histology or cytology based diagnosis of SCLC, above 18 years of age, with brain metastases amenable to SRS.

5.7 Materials that will be in Contact with Tissues

The transducer arrays are adhesive bandages that hold insulated ceramic discs that are needed to deliver treatment. The transducer arrays should be used with NovoTTF-200A only. Four transducer arrays are used at one time. There are two different color transducer arrays, one type has a white connection end and one has a black connection end. The patient will need two transducer arrays with white connection ends, and two transducer arrays with black connection ends every time they change their arrays. Put the transducer arrays on a clean, shaven scalp. The patient will put them on their scalp in the place where the study doctor and/or Device Support Specialist (DSS) instructed them, based on their tumor location. The transducer arrays are disposable. They will be changed at least two times per week (every 4 days at most).

5.8 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.

5.9 Risks and Benefits of the Investigational Device

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, electromagnetic interference, etc., as well as the risk that the treatment will not be effective in delaying tumor progression or causing regression. Additional risks include skin irritation, and skin breakdown or infection at electrode sites. Technical failure is extremely unlikely due to stringent compliance with all standard design and manufacturing safety protocols. In addition, appropriate measures have been taken to minimize the risk to study subjects, including preclinical in vitro and in vivo testing to ensure safe operation of the device. Furthermore, there have been no device-related serious adverse events or unanticipated serious adverse device effects reported in the 16 patients who have been enrolled in the ongoing pilot study to date.

6.0 TREATMENT PLAN

6.1 Stereotactic Radiosurgery Timing

6.1.1 SRS must be delivered within 21 days of enrollment and ideally after discussion at a multi-disciplinary radiosurgery tumor board/conference.

6.2 Localization and Immobilization

6.2.1 A frameless radiosurgery approach will be utilized. A thermoplastic mask will be used to immobilize the head during treatment.

6.2.2 All patients will have a brain MRI (3T) with and without contrast suitable for SRS planning. T1-weighted, T2 and/or FLAIR MRI of the brain (maximum slice thickness 5mm). FLAIR imaging is preferred.

6.2.3 A treatment planning MRI, ideally within 10 days of radiosurgery, may be obtained in addition to the screening MRI.

6.3 Stereotactic Radiosurgery Dose Specifications

6.3.1 For all tumors, the dose will be prescribed to the minimum isodose volume that covers the gross target volume (GTV), typically 40-85% line.

6.3.2 Tumors with volume < 4 mL will be prescribed 18-22 Gy at the lesion periphery. Tumors 4-10 mL will be prescribed 15-20 Gy at the periphery. Additional increase or decrease in dose by up to 2 Gy is allowed.

6.3.3 Tumors over 2cm may be treated with a 5 fraction approach at the discretion of the physician. Typical doses per fraction are 5-6Gy per fraction for a total of 25 or 30Gy.

6.3.4 The goal of treatment planning will be to obtain conformity such that the conformity index (CI, ratio of planning isodose volume to target volume) does not exceed 2:1.

6.4 SRS Target Volume Delineations

6.4.1 Target volume delineation will be based on a three-dimensional spoiled gradient (3D-SPGR) multi-plane MRI scan (or similar sequences suitable for target delineation) fused with the treatment planning CT scan. The CT should not be exclusively used for target volume delineation.

6.4.2 **Definition of the GTV**: The GTV includes the contrast-enhancing tumor, but not surrounding edema.

6.4.3 **Definition of the PTV:** The PTV equals the GTV.

6.4.4 No margin for microscopic spread or setup error is allowed.

6.5 Critical Structures

6.5.1 The maximum allowed doses to brainstem, optic nerves, and optic chiasm for single fraction treatments are as follows:

Table 6.5.1: Critical Structure Dose Constraints	
Structure	Maximum Point Dose (Gy)
Brainstem	14
Optic Nerves	10
Optic Chiasm	10

6.5.2 The dose to a small volume of the target may be reduced below the prescription to meet these constraints at the discretion of the treating radiation oncologist.

6.6 Technical Factors

6.6.1 SRS will be delivered using FDA-approved stereotactic localization and linear accelerators.

6.7 Tumor Treating Fields (TTFields)

6.7.1 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.

6.7.2 Patient training: Patients will be trained in the use of the device by the Device Support Specialist (DSS) trained by Novocure or can be done by the investigator and/or a designated health care provider (e.g. nurse). .

6.7.3 Treatment initiation: NovoTTF-200A may be initiated by the Device Support Specialist (DSS) or the investigator within 7 days of SRS. 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, avoiding areas of skin damage as a result of SRS.

6.7.4 Treatment duration: Treatment with the device will be continuous with breaks allowed for personal needs (e.g. showering, array exchange). Patients must use the device for at least 18 hours a day on average. Treatment will be continued until first cerebral progression in the brain (as defined in 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 in NovoTTF-200A every month is allowed. However, the patient should use the device for at least 18 hours a day on average as stated above.

6.7.5 The NovoTTF-200A System will be programmed by Novocure to deliver 200kHz TTFields. There will be no adjustments made to the device by investigators or patients/caregivers.

6.7.6 Transducer Array replacement: Patients will replace the Transducer Arrays twice to three times per week with the help of a caregiver. At each array replacement the patient's scalp will be reshaved and skin treated according to the guidelines set out below.

6.7.7 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.

6.7.8 The following skin care guidelines should be closely adhered to:

- 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.
- 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 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. 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 is 3 weeks.

6.8 Systemic and Supportive Therapy

6.8.1 Optimal systemic therapy for existing extracranial disease should be given to all patients on the study according to physician discretion. Systemic therapy may continue throughout NovoTTF-200A treatment. Understanding that most of these patients will receive chemotherapy and immunotherapy as part of their standard regimen, it is not possible to completely control for the effect of systemic therapy on brain metastases. To attempt to account for this in the reporting of our data, chemotherapy, including dosing and regimen changes, will be prospectively recorded in the study CRFs.

6.8.2 Patients should also receive the best supportive care available at each site including steroids for brain edema. Steroid dosing throughout the trial will be documented. Patients should not receive any intrathecal chemotherapy while on study (outside of protocol treatment). In addition, supportive care will include standard of care treatments for the treatment of each patient’s symptoms as determined by the treating physician. For example: anti-epileptic drugs, anticoagulants, pain control medications, and nausea control medications. The supportive care prescribed by the physician to each patient will be recorded in the study CRFs.

6.8.3 Previous clinical trial enrollment pertaining to the patient’s small cell lung cancer will be documented in the CRFs, including description of trial and intervention received.

6.9 Salvage Therapy

6.9.1 If distant cerebral progression (not within 100% isodose volume) is noted at time of follow-up, salvage therapy may be undertaken as follows:

- If the patient develops new metastases and no previous PCI, whole brain RT may be offered if reasonable life expectancy and discontinuation of TTF.
- If previous whole brain radiotherapy or declining performance status, consider supportive care versus repeat whole brain RT with discontinuation of TTF.
- Discontinue NovoTTF-200A after sign of 1st progression.

- If an enlarging lesion is found on follow-up MRI that was not initially treated with SRS due to small size or uncertainty on the pretreatment MRI, this will not constitute an intracranial failure. Such lesions may receive SRS and the patient can stay on trial.

7.0 THERAPY MODIFICATIONS

7.1 Non-Study Treatment

7.1.1 All medications and other treatments taken by the subject during the study, including those treatments initiated prior to the start of the study, must be recorded on the medical record.

7.1.2 The use of corticosteroids to manage symptoms of disease or treatment is allowed at the discretion of the treating physician.

7.2 Concomitant Medication

7.2.1 All medications since protocol enrollment will be recorded in the medical record.

7.2.2 Non-cytotoxic systemic therapies such as hormonal agents or bisphosphonates may be administered during the study evaluation period.

7.3 Adverse Events (AE's), Adverse Device Effects, Serious Adverse Events (SAE's), and Device Deficiencies

7.3.1 **Definition of AE**: Any untoward medical occurrence, which does not necessarily have a causal relationship with the study treatment. This includes any physical or clinical change experienced by the subject, whether or not considered related to the study treatment. An AE can therefore be any unfavorable or unintended sign (including an abnormal laboratory finding, for example), symptom or disease (including the onset of new illness and the exacerbation of pre-existing conditions) temporally associated with the study treatment. Progressive disease is not considered to be an AE. All AE's will be recorded in the medical record.

An adverse event (AE) 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 procedures in the clinical investigation plan).

- **Possible Adverse Events (AEs)**
  a. <u>Stereotactic Radiosurgery (SRS).</u> The following are possible side effects of SRS:

-Bleeding from the points where an immobilization frame was attached to the skull.
-Tingling or itching where the frame was attached.
-Skin Irritation
-Pain
-Nausea and vomiting
-Headache
-Dizziness
-Hair Loss (rare)
-Fatigue
-Radiation necrosis
-Brain Edema
-Seizure
-Claustrophobia

b. <u>Novo TTF-220A System (200 kHz TTFields)</u>
In the phase III trial in patients with recurrent GBM device-related adverse events (grades 1 and 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. Treatment with the NovoTTF-200A is not expected to cause any serious side effects. However, it is possible that investigational treatment may cause any of the following:
-Local heat and tingling "electric" sensation beneath the transducer array
-Allergic reaction to the adhesive or to the gel
-Skin irritation or skin breakdown
-Infection at the sites of transducer array contact with the skin
-Open sores, ulceration or blisters underneath transducer arrays
-Headache
-Fatigue
-Seizures
-Falls
-Muscle twitching

7.3.2 <u>Definition of SAE</u>: Any event occurring during the study evaluation period that results in any of the following outcomes:

- Death (i.e. any grade 5 AE)
- Inpatient hospitalization

All SAE's must be recorded in the medical record. The onset and end dates, severity, duration, effect on study treatment administration (e.g., discontinuation/cancellation), relationship to

study treatment, and administration of any drug(s) to treat this event will be recorded for each SAE.

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. All SAE's must be recorded in the patient's medical record. The onset and end dates, severity, duration, effect on study treatment administration (e.g., discontinuation/cancellation), relationship to study treatment, and administration of any drug(s) to treat this event will be recorded for each SAE.

7.3.3 Serious Adverse Device Effect (SADE)**:** A SADE is any adverse device effect that has resulted in any of the consequences characteristic of a serious adverse events.

7.3.4 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 the current version of the risk analysis report. Anticipated SADEs are effects whose nature, incidence, severity or outcome has been previously identified in the risk analysis report. Any potential USADEs will be reported to the Principal Investigator (Dr. Hunter Boggs) or their designee by calling (205) 975-5581. A written report should be submitted to the local IRB and UAB Clinical Trials Monitoring Committee per institutional policy, within 10 days of the investigator learning of the event. The PI will investigate the events are USADEs and, if so, report them to the Company (Novocure), as soon as possible but no later than the next business day after learning of the event. Expedited report for FDA submission to follow within 10 working days after first learning of the event by the PI, in accordance with 21 CFR Part 812.

7.3.5 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.

7.4 Guidelines for Adverse Event Evaluations and Reporting

7.4.1 Grading of an AEs and SAEs: The descriptions and grading scales found in the revised NCI Common Toxicity Criteria (CTC) version 4.0 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 observation 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; limited self-care ADL**
POTENTIALLY LIFE-THREATENING	**Grade 4**	**Life-threatening consequences; urgent intervention indicated.**
DEATH	**Grade 5**	**Death related to AE.**

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

<u>Grade 1</u>- 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.**
<u>Grade 2</u> – Moderate symptoms AND Systemic Therapy required OR event is requiring interruption of NovoTTF-200A for more than 3 days.
<u>Grade 3</u> – Severe or medically significant but not immediately life threatening AND hospitalization OR prolongation of existing hospitalization indicated
<u>Grade 4-</u> Life threatening consequences AND urgent intervention indicated

7.4.2 <u>Determination of Causality of Adverse Events:</u> The investigator must assess the relationship of any AE or SAE to the use of study treatment using the following guidelines noted in Table 7.4.2.

Table 7.4.2: ATTRIBUTION OF ADVERSE EVENTS		
Code	**Descriptor**	**Definition**
5	Definite	The adverse event is clearly related to the investigational treatment(s)
4	Probable	The adverse event is likely related to the investigational treatment(s)
3	Possible	The adverse event may be related to the investigational treatment(s)
2	Unlikely	The adverse event is doubtfully related to the investigational treatment(s)

1	Unrelated	The adverse event is clearly not related to the investigational treatment(s)

7.5 Monitoring of Adverse Events

7.5.1 Subjects having AE's or SAE's will be monitored with relevant clinical assessments and laboratory tests as determined by the subject's treating physicians. ALL adverse events must be followed to satisfactory resolution or stabilization of the event(s).

7.5.2 Any actions taken and follow-up results must be recorded in the subject's medical record.

7.5.3 For all AE's or SAE's which require the subject to be discontinued from the study, relevant clinical assessments and laboratory tests will be repeated as clinically indicated, until final resolution or stabilization of the event(s).

7.6 Adverse Event Reporting and Other Reportable Events

7.6.1 For the purpose of this guidance and based on the definitions above, the following events are considered reportable events:

- Any SAE,
- Any investigational device deficiency that might have left 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/updated relation to already report events,
- USADEs.

The PI will notify the company (Novocure), by the next business day, after becoming aware of any of the above reportable events. Notification will be sent to Novocure, by email, to support@novocure.com.

The company (Novocure) will promptly advise Dr. Boggs of adverse reactions or side effects related to NovoTTF-200A which may become known to them during the course of the study.

7.6.2 Notification of all events must be reported to Principal Investigator (Dr. Hunter Boggs) or their designee by calling (205) 975-5581. A written report should be submitted to the appropriate Institutional Review Board (IRB) and UAB Clinical Trials Monitoring Committee per institutional policy.

7.6.3 Adverse events and other reportable events will be reported to the UAB Clinical Trials Monitoring Committee.

7.7 Data Safety Monitoring Plan

7.7.1 This protocol will follow the UAB Data and Safety Monitoring Plan maintained by the UAB Comprehensive Cancer Center.

7.7.2 Serious adverse events will be reviewed in the UAB Radiosurgery Conference and the Department of Radiation Oncology Quality Assurance committees.

7.8 Early Termination

Patients may be discontinued from study prior to completion of study requirements for any of the following reasons:

7.8.1 The patient has a clinically significant adverse event as determined by the Principal Investigator.

7.8.2 The patient requests to be withdrawn from the study.

7.8.3 The patient fails to comply with the requirements for study evaluations/visits.

7.8.4 The development of circumstances that prevent study evaluations/visits.

7.8.5 Other conditions for which, in the investigator's opinion, it is in the patient's best interest to be withdrawn from the study.

7.8.6 Patient did not meet eligibility requirements.

7.9 Premature Termination or Suspension of Study

This study may be temporarily suspended or prematurely terminated if there is sufficient reasonable cause. Written notification, documenting the reason for study suspension or termination, will be provided by the suspending or terminating party to the investigators, funding agency, and regulatory authorities. If the study is prematurely terminated or suspended, the PI will promptly inform the IRB and will provide the reason(s) for the termination or suspension. Circumstances that may warrant termination or suspension include, but are not limited to:

- Determination of unexpected, significant, or unacceptable risk to participants.
- Demonstration of lack of efficacy that would warrant stopping defined as rapid (1 month) intracranial failure in > 5 patients.
- Insufficient compliance to NovoTTF-200A protocol requirements defined as > 5 patients unable to meet device compliance of wearing NovoTTF-200A at least 12 hours a day on average over the course of a month. Noncompliance is also defined as failure to wear this device at least 20 out of 30 days.
- Data that is not sufficiently complete and/or evaluable.
- Determination of futility.

Study may resume once concerns about safety, protocol compliance, data quality are addressed and satisfy the sponsor, IRB and/or FDA.

8.0 STUDY PARAMETERS

8.1 In the absence of symptoms requiring earlier evaluation, the Day 30 MRI and physical exam will be used to determine if toxicity has developed. Acute and Late Toxicity are defined in Section 11.3.

8.2 Day 0 is defined as the day of radiosurgery.

8.3 Baseline evaluations must take place within 3 weeks (21 days) of study enrollment.

8.4 "1 Month" evaluation may be done within 7 days of the specified day. "3 Month" evaluation may be done within 14 days of the specified day.

8.5 Six month evaluations (6mo) may take place six months from the day of SRS, plus or minus 30 days. Similarly, the twelve month evaluations (12mo) will take place 12 months from the day of SRS, plus or minus 30 days

Table 8.1: Required evaluations and therapies

	Baseline	Day of SRS (D0)	Day 1-7	1mo (+/- 7 days)	3mo (+/- 14 days)	6mo (+/- 30 days)	9mo (+/- 30 days)	12mo (+/- 30 days)
MRI	x			X	x	x	x	x
H & P	x[1]			x[1]	x[1]	x[1]	x[1]	x[1]
Neurological Exam	x			X	x	x	x	x
Toxicity				X	x	x	x	x
GPA*	x							
KPS*	x			X	x	x	x	x
βHCG	X[2]							
Measurement of Brain Mets (RANO)	x			X	x	x	x	x
Placement of TTF device			x					
Con Meds	x			X	x	x	x	x
Neurocognitive Testing	x			X	x	x	x	x
Quality of Life Questionnaire	x			X	x	x	x	x
CBC with diff	x				x	x	x	x
CMP	x				x	x	x	x
PT/PTT	x							
Device Compliance				Monthly				

*See Appendices
[1] record medications
[2] If applicable, per Section 4.2.12

9.0 EVALUATION CRITERIA

9.1 Pretreatment Evaluations (Baseline)

9.1.1 The following will be performed within 21 days:

- Verify informed consent is signed.
- Gadolinium enhanced T1-weighted, T2 and/or FLAIR MRI (3T) of the brain (maximum slice thickness 5mm). FLAIR imaging is preferred.
  - 9.1.1..1 Treatment planning MRI may be repeated if diagnostic MRI is outside of the 21 day window
- Measurement of brain metastases per protocol.
- Medical history.
- Concomitant medications.
- Graded prognostic assessment (GPA) score recording.
- Karnofsky performance status (KPS) score recording.
- Physical examination and vital signs.
- Neurological examination.
- 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.
- Quality of Life questionnaire (EORTC QLQ C30 with BN20 addendum)
- Pregnancy test (if applicable) within 14 days.
- Complete blood count including differential.
- Serum chemistry panel, including: BUN, Creatinine, Sodium, Potassium, ALT, AST, Bilirubin, PT, and PTT.

9.2 Treatment Phase (Day 0)

9.2.1 Radiosurgery

9.3 Follow-Up

9.3.1 At the one, three, six, nine, and twelve month evaluations, the following will be performed:

- Medical history, physical examination, and vital signs.
- Neurological examination.
- Toxicity and Adverse Events.
- Karnofsky performance status (KPS) score recording.
- Concomitant medications.
- Contrast-enhanced T1-weighted, T2 and/or FLAIR MRI (3T) using similar sequences and slice thickness obtained for SRS planning (maximum slice thickness 5mm). FLAIR imaging is preferred.

- Measurement of brain metastases per protocol.
- 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.
- Quality of Life questionnaire (EORTC QLQ C30 with BN20 addendum).

9.3.2 At the three, six, nine, and twelve month evaluations, the following will be performed:

- Complete blood count including differential.
- Serum chemistry panel, including: BUN, Creatinine, Sodium, Potassium, ALT, AST, and Bilirubin.

9.3.3 Device compliance will be evaluated monthly.

10.0 PATIENT REGISTRATION

10.1 Patients can be registered by calling 205-975-2879.

11.0 STATISTICAL CONSIDERATIONS

11.1 Study Endpoints

11.1.1 **Primary endpoint:** The primary endpoint is rate of distant CNS progression at 6 months. Distant progression is defined as development of a new metastases outside of the previously treated 100% isodose volume. The 6 month time interval will be defined from the day of SRS to the time of the 6 month follow-up MRI. We estimate no more than 50% of patients will suffer distant brain relapses during time period. In Takahashi's study, the rate of development of brain metastases in patients with small cell lung cancer who did not have whole brain radiation was 70% [34]. Also in this study, the estimated rate of failure in the brain after prophylactic cranial irradiation (radiotherapy delivered to the whole brain) was approximately 50%. As WBRT is the current standard of care for patients with small cell lung cancer, a 50% intracranial relapse rate would be similar to the historical control of whole brain radiotherapy in Takahashi's study. This would signal that SRS combined with NovoTTF-200A may be as efficacious as whole brain RT and warrants further investigation in larger studies.

11.1.2 **Secondary endpoints**: overall survival, local tumor control, and distant CNS progression (outside of the previously treated 100% isodose volume) at one year, neurological death, time to first brain directed radiation, change in neurocognitive metric, and change in quality of life at 6 months and one year.

11.1.3 Selection of Lesions for the Assessment of Cerebral Response:

- When more than one lesion is measurable lesion is present at the SRS planning MRI, all lesions up to a maximum of five lesions should be identified as target lesions and will be recorded and measured at the SRS planning MRI.
- Target lesions should be selected on the basis of their size (longest diameter) and as those that can be measured reproducibly.

11.1.4 Assessment of Cerebral Response:

- A sum of the diameters for all target lesions will be calculated and reported as the baseline sum of longest diameters, taken from the SRS planning MRI.
- All other lesions should be identified as non-target lesions and should also be recorded at baseline (SRS planning MRI). Measurements are not required and these lesions should be classified as present, absent, or unequivocal progression, and followed up.
- All target lesions should have their actual measurement recorded, even if very small. If the lesion disappears, the value should be recorded as 0 mm. However, if the lesion is sufficiently small (but still present) to be assigned an exact measure; a default value of 5 mm should be recorded on the case report form.
- The definition of clinical deterioration is left to the discretion of the treating physician, but it is recommended that patients who have a decrease in score on the Karnofsky performances scale from 100 or 90 to 70 points or less, a decrease of minimum 20 points from 80 or less, or a decrease from any baseline to 50 points or less, for at least 7 days, be considered as having neurological deterioration, unless this functional impairment is attributable to comorbid events, treatment-related toxicity, or changes in corticosteroid dose.

11.1.5 Special cases of cerebral response

- **Coalescing lesions**: Lesions might coalesce during treatment. As lesions coalesce, a plane between them may be maintained that would aid in obtaining maximum longest diameter of each individual lesion. If the lesions have truly coalesced such that they are no longer separable, the vector of the longest diameter in this instance should be the maximum longest diameter for the coalesced lesion.

- **Radiation necrosis**: If radiographical evidence of progression exists, but clinical evidence indicates that the radiological changes are due to treatment effect and not to progression of brain metastases (e.g. radiation necrosis), patients should undergo perfusion MRI, magnetic resonance spectroscopy, or 18FLT or 18FDG PET imaging if available at the treating institution to help distinguish between treatment effects and recurrent tumor. All additional imaging studies must be shared with the central radiology lab. Patients can be continued on protocol therapy while true disease progression is being ruled out. If subsequent testing shows that progression has occurred for a lesion that has previously been suspected as radiation necrosis, all previous unidimensional measurements of that lesion should be added to the total sum of diameters calculated for response assessment from the date of the scan this issue was first raised.

- **Use of Corticosteroids**: In the absence of clinical deterioration related to the tumor, an increase in corticosteroid dose alone should not be used as a sole determinant of progression. Patients with stable imaging results and whose corticosteroid dose has increased for reasons other than clinical deterioration related to the tumor do not qualify as having stable disease or progression.

11.1.6 Cerebral Response for Target Lesions:

- **Complete response**: Disappearance of all target lesions; with no new lesions, no use of corticosteroids, and patient is stable or improved clinically.
- **Partial response**: At least a 30% decrease in the sum longest diameter of target lesions, taking as reference the baseline sum longest diameter (from SRS planning MRI); no new lesions; stable to decreased corticosteroid dose; stable or improved clinically.
- **Progressive disease**: At least a 20% increase in the sum longest diameter of target lesions, taking as reference the smallest sum on study (this includes the SRS planning MRI if that is the smallest on study). In addition to the relative increase of 20%, at least one lesion must increase by an absolute value of 5 mm or more to be considered progression.
- **Stable disease**: neither sufficient shrinkage to qualify for partial response nor sufficient increase to qualify for progressive disease, taking as reference the smallest sum longest diameter while on study.

11.1.7 Cerebral Response for <u>Non-Target</u> Lesions:

- **Non-target lesions** should be assessed qualitatively at each of the time points specified in the protocol.
- **<u>Complete response</u>**: Requires all of the following: disappearance of all enhancing non-target lesions, no new CNS lesions.
- **<u>Non-complete response or non-progressive disease</u>** Persistence of one or more non-target lesion or lesions.
- **<u>Progressive disease</u>**: Any of the following: unequivocal progression of existing enhancing non-target lesions, new lesion(s) (except while on immunotherapy-based treatment), or unequivocal progression of existing tumor related non-enhancing (T2/FLAIR) lesions.
- **Summary of response criteria adapted from RANO-BM**:

	Complete response	Partial response	Stable disease	Progressive disease
Target lesions	None	≥30% decrease in sum longest distance relative to SRS planning MRI	<30% decrease relative to SRS planning MRI but <20% increase in sum longest distance relative to nadir	≥20% increase in sum longest distance relative to nadir*
Non-target lesions	None	Stable or improved	Stable or improved	Unequivocal progressive disease*
New lesion(s)†	None	None	None	Present*
Clinical status	Stable or improved	Stable or improved	Stable or improved	Worse*
Requirement for response	All	All	All	Any‡

- **<u>Secondary endpoints include</u>** acute toxicity, late toxicity, local control, neurocognitive change, overall survival, distant brain progression, quality of life, and adverse events associated with SRS and/or TTFields.

11.2 Sample Size

11.2.1 We plan to enroll 20 patients up to a 3 year time period.

11.2.2 Data will be collected according to the following proportions:

- No. of patients meeting eligibility criteria / No. of patients evaluated
- No. of patients enrolled / No. of patients meeting eligibility criteria
- No. of patients completing 6 months of follow-up/No. of patients enrolled
- No. of patients compliant to Novo-TTF use/No. of patients enrolled.

11.2.3 We estimate that 80% of patients will meet compliance criteria for Novo-TTF.

11.3 Toxicity Evaluations

11.3.1 Acute and late toxicity will be graded according to the CTCAE v 4.0 criteria [30].

11.3.2 Definition of acute toxicity: Any possible, probable, or definite treatment-related AE or SAE occurring within six months or less from the date of SRS.

11.3.3 Definition of late toxicity: Any possible, probable, or definite treatment-related AE or SAE occurring more than six months from date of SRS.

11.4 Efficacy Evaluations

11.4.1 Distant intracranial recurrence will be defined as a measurable lesion deemed likely to be a brain metastasis found outside of the previously treated 100% isodose volume.

- **Exception: An enlarging lesion that was not treated on the initial SRS course due to uncertainty of imaging characteristics.**

11.4.2 Local Recurrence will be defined as a measurable lesion deemed likely to be a brain metastasis found within the previously treated 100% isodose volume.

11.4.3 Contrast-enhanced MRI's obtained at 2-3 month intervals will be used to evaluate local control and incidence of intracranial recurrence.

11.4.4 Imaging performed at the discretion of the treating physician (i.e. in response to new or progressive symptoms) may be used to evaluate for local control or leptomeningeal dissemination. Such studies can substitute for the required 6 and 12 month evaluations if either occurs within plus or minus 30 days of the specified date.

11.5 Data Management: Data collection will be coordinated by the research nurse and overseen by the Radiation Oncology Research Committee.

11.6 Statistical Analysis

11.6.1 Primary endpoints: the primary endpoint is rate of distant CNS progression at 6 months, which will be calculated as the total number patients with such events divided by the total number of patients. Its 95% confidence interval will also be provided. Distant progression is defined as development of a new metastases outside of the previously treated 100% isodose volume. The 6 month time interval will be defined from the day of SRS to the time of the 6 month follow-up MRI.

11.6.2 Secondary endpoints. Overall survival will be measured as time from first SRS treatment to date of death, or censored as the last follow up. Overall survival rates will be analyzed using the Kaplan-Meier (KM) method. Time to other events such as local recurrence, distant CNS progression, neurological death, or first brain directed radiation will be measured as time from first SRS treatment to date of such events, or death, whichever occurs first. All the time-to-

events will be analyzed using KM method. Neurocognitive function raw scores will be derived for HVLT-R free recall, delayed recall, and delayed recognition; COWAT; and TMT Parts A and B at each assessment point. The following summary statistics will be estimated: mean, median, quartiles, and variance of all measurements. The changes over time at different assessment points will also be graphically presented through scatter plots, and scatterplot matrices. Quality of life will be presented descriptively over time for each of the general and symptom scales of EORTC QLQ C30 and BN20 addendum according to the EORTC coding manual.

11.6.3 **Toxicity and AE**. Acute toxicity during NovoTTF-200A treatment based on incidence and severity of treatment emergent adverse events will be evaluated using the CTCAE version 4.0. Adverse events will be presented as overall incidence, incidence by severity and incidence by relatedness to therapy.

12.0 REFERENCES

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APPENDIX A: Graded Prognostic Assessment (GPA)

	Score		
	0	0.5	1
Age	>60	50-59	<50
KPS	<70	70-80	90-100
# of CNS metastases	>3	2-3	1
Extracranial Metastasis	Present	-	None

APPENDIX B: Karnofsky Performance Status (KPS)

100	Normal. No complaints; No evidence of disease
90	Able to carry on normal activity; minor signs or symptoms of disease
80	Normal activity with effort; some signs or symptoms of disease
70	Cares for self; unable to carry on normal activity or 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; hospital admission is indicated although death is not imminent
20	Very sick; hospital admission necessary, active supportive treatment necessary
10	Moribund; fatal processes progressing rapidly
0	Dead