A Prospective, Multi-center Trial of NovoTTF-100A Together With Temozolomide Compared to Temozolomide Alone in Patients with Newly Diagnosed GBM

THERAPEUTIC PROTOCOL

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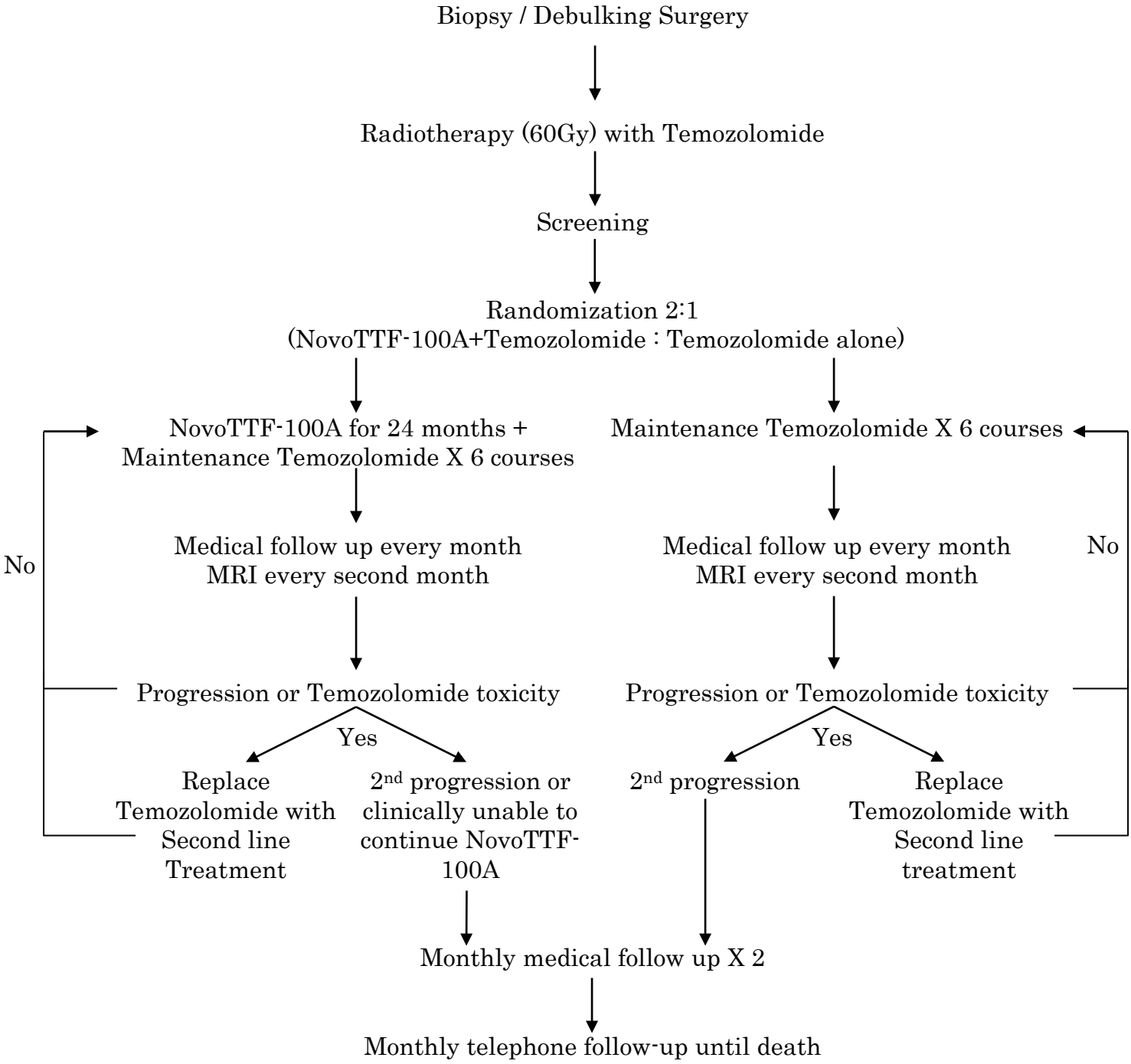
I. PROTOCOL SUMMARY AND SCHEMA

1. SUMMARY

Title:	A Prospective, Multi-center Trial of NovoTTF-100A Together With Temozolomide Compared to Temozolomide Alone in Patients with Newly Diagnosed GBM
Device:	NovoTTF-100A
Study Objectives:	To compare the efficacy and safety outcome of newly diagnosed GBM patients treated with NovoTTF-100A concomitant to Temozolomide to those treated with Temozolomide alone
Study Design:	Prospective, Randomized, Open Label, Standard of Care Control
Study Hypothesis:	The hypothesis of this study is that addition of NovoTTF-100A treatment to maintenance Temozolomide will significantly increase progression free survival of newly diagnosed GBM patients compared to patients treated with Temozolomide alone
Sample Size:	283 patients with newly diagnosed GBM
Study Population:	Patients with tissue based diagnosis of GBM, above 18 years of age, of both genders after surgery or biopsy followed by radiation therapy with adjuvant Temozolomide (Stupp protocol[23])
Primary endpoint:	Progression free survival time
Secondary endpoints:	• Overall survival (OS) • Progression free survival at 6 months (PFS6) • % 1 and 2-year survival • Radiological response (Macdonald criteria) • Quality of life assessment (EORTC QLQ-C30) • Adverse events severity and frequency
Sponsor:	NovoCure Ltd. POB 15022 MATAM Center Haifa, 31905, Israel

2. PROTOCOL SCHEMA



II. OBJECTIVES AND SCIENTIFIC AIMS

- To prospectively compare the progression free survival time of newly diagnosed GBM patients treated with NovoTTF-100A together with Temozolomide to those treated with Temozolomide alone.
- To prospectively compare the overall survival time of newly diagnosed GBM patients treated with NovoTTF-100A together with Temozolomide to those treated with Temozolomide alone.
- To prospectively determine %6-month progression free survival, % 1 and 2-year survival and quality of life (TAB H) of patients treated with NovoTTF-100A together with Temozolomide to those treated with Temozolomide alone.
- To collect evidence of the safety of the NovoTTF-100A device applied together with Temozolomide to patients with newly diagnosed GBM.

III. BACKGROUND AND RATIONALE

Glioblastoma multiforme (GBM), a malignant form of astrocytoma, is the most common primary intracranial neoplasm. The incidence of GBM increases steadily above 45 years of age with a prevalence of approximately 7500 cases in the USA. Despite numerous attempts to improve the outcome of patients with GBM, the 3-year survival of these patients is only 6% with median survival of 14.6 months[1].

Patients with newly diagnosed GBM who are treated with maximal surgical resection, 60 Gy radiotherapy together with Temozolomide, followed by maintenance Temozolomide for 6 months, have a median survival of 14.6 months[23]. Thus, there is a critical need for new therapeutic options for treatment of GBM. TTFields are a new experimental modality for the treatment of malignant tumors. Pre-clinical studies[12,22] have shown this treatment modality to effectively inhibit the growth of experimental tumors both in-vitro and in-vivo without any systemic side effects.

The currently accepted treatment of newly diagnosed GBM is based on: surgical resection with or without Gliadel Wafer implantation, radiotherapy, and Temozolomide. Each of these treatments is briefly described below:

1. Surgical resection - Treatment of patients with GBM usually begins with resection (in conjunction with the biopsy or after it), with maximal debulking of the tumor as the main goal because curative resection is very rare.

2. Radiation therapy - Post-surgical radiation therapy has been shown to improve survival, though even with maximal treatment, survival after RT alone is still limited to about one year[23].

3. Temozolomide – Adjuvant Temozolomide and radiation therapy following surgery has been shown to improve survival by about 20%. According to the Temozolomide package insert adjuvant Temozolomide treatment delays disease progression (from 5 to 6.9

months) and improves overall survival (from 12.1 to 14.6 months)[23]. In the past, Temozolomide was also approved for recurrent anaplastic astrocytoma.

4. GLIADEL® Wafer in combination with surgical resection – Gliadel Wafer delivers carmustine (BCNU) directly to the bed of the resected tumor. The package insert indicates that for newly diagnosed GBM, Gliadel increased median overall survival from 11.6 to 13.9 months compared to placebo. No data is presented regarding the effect of Gliadel wafers on progression free survival.

In conclusion, despite the immense effort made over the years with different treatment modalities, the survival of patients with newly diagnosed GBM is still very poor; no treatment is curative; and the quality of life of patients with this tumor is compromised significantly, not only by their disease but also by side effects of these rigorous treatment plans. A treatment modality is needed that will improve the results of standard treatments without further impairing the quality of life of these patients for their limited life span.

Introduction to electric fields

In the laboratory setting and in clinical practice, alternating electric fields show a wide range of effects on living tissues. At very low frequencies (under 1 kHz), alternating electric fields stimulate excitable tissues through membrane depolarisation[3]. The transmission of such fields by radiation is insignificant and therefore they are usually applied directly by contact electrodes, though some applications have also used insulated electrodes. Some well known examples of such effects include nerve, muscle and heart stimulation by alternating electric fields[3,4]. In addition, low frequency pulsed electric fields have been claimed to stimulate bone growth and accelerate fracture healing[5]. However, as the frequency of the alternating electric field increases above 1 kHz, the stimulatory effect diminishes. Under these conditions although a greater fraction of the fields penetrates the cells, due to the parallel resistor-capacitor nature of all biological membranes, the stimulatory power greatly diminishes as the alternating cell membrane hyper –depolarization cycles are integrated such that the net effect is nulled.

At very high frequencies (i.e., above many MHz), while the integration becomes even more effective, a completely different biological effect is observed. At these frequencies tissue heating becomes dominant due to dielectric losses. This effect becomes more intense as field intensity or tissue dissipation factor increase[6]. This phenomenon serves as the basis for some commonly used medical treatment modalities including diathermy and radio frequency tumor ablation, which can be applied through insulated electrodes[7].

Intermediate frequency electric fields (i.e., tens of kHz to MHz), alternate too fast for causing nerve-muscle stimulation and involve only minute dielectric losses (heating). Such fields, of low to moderate intensities, are commonly considered to have no biological effect[6]. However, a number of non-thermal effects, of minor biological consequence, have been reported even at low field intensities. These include microscopic particle alignment (i.e., the pearl chain effect[8]) and cell rotation[9,10]. With pulsed relatively strong electric fields, $> 10^3$ V/cm and 100 ms pulse length, reversible pore formation appears in the cell membrane, a phenomenon usually called electroporation[11].

NovoCure's Tumor treating electric fields (*TTFields*)

NovoCure has shown[12] that when properly tuned, very low intensity, intermediate frequency electric fields (TTFields) stunt the growth of tumor cells. This inhibitory effect was demonstrated in all proliferating cell types tested, whereas, non-proliferating cells and tissues were unaffected. Interestingly, different cell types showed specific intensity and frequency dependences of TTField inhibition. It has been shown that two main processes occur at the cellular level during exposure to TTFields: arrest of proliferation and dividing cell destruction. The damage caused by TTFields to these replicating cells was dependent on the orientation of the division process in relation to the field vectors, indicating that this effect is non-thermal. Indeed, temperature measurements made within culture dishes during treatment and on the skin above treated tumors in-vivo, showed no significant elevation in temperature compared to control cultures/mice. Also, TTFields caused the dividing cells to orient in the direction of the applied field in a manner similar to that described in cultured human corneal epithelial cells exposed to constant electric fields[13]. At the sub-cellular level it was found that TTFields disrupt the normal polymerization-depolymerization process of microtubules during mitosis. Indeed, the described abnormal mitotic configurations seen after exposure to TTFields are similar to the morphological abnormalities seen in cells treated with agents that interfere directly[14,15] or indirectly[16-18] with microtubule polymerization (e.g., Taxol).

Modeling the mechanism of action of *TTFields*

In order to explain how TTFields cause orientation dependent damage to dividing cells and disrupt the proper formation of the mitotic spindle NovoCure modeled the forces exerted by TTFields on intracellular charges and polar particles using finite element simulations. Two main mechanisms by means of which the electric fields may affect dividing cells were recognized. The first relates to the field effect on polar macromolecule orientation. Within this framework, during the early phases of mitosis, i.e., in pre-telophase, when tubulin polymerization-depolymerization drives the proliferation process, the electric field forces any tubulin dimers, positioned further than 14nm away from the growing end of a microtubule, to orient in the direction of the field. This force moment, (10^{-5} pN) acting on the dimers, is sufficient to interfere with the proper process of assembly and disassembly of microtubules that is essential for chromosome alignment and separation[19]. This effect can explain the mitotic arrest of TTField treated cells[20].

The second mechanism, which interferes with cell division, and is most likely to play an important role in cell destruction, becomes dominant during cleavage. As seen in simulations, the electric field within quiescent cells is homogenous, whereas the field inside mitotic cells, during cytokinesis, is not homogenous. An increased field line concentration (indicating increased field intensity) is seen at the furrow, a phenomenon that highly resembles the focusing of a light beam by a lens. This in-homogeneity in field intensity exerts a unidirectional electric force, on all intracellular charged and polar entities (including induced dipoles), pulling them towards the furrow (regardless of field polarity). For example, for a cleavage furrow that reached a diameter of 1μm in an external field of only 1 V/cm, the force exerted on the microtubules is in the order of 5pN. This magnitude is compatible with the reported forces necessary to stall microtubule polymerization which is 4.3 pN[21]. With regards to other particles, such as cytoplasmatic

organelles, they are polarized by the field within dividing cells. Once polarized, the forces acting on such particles may reach values up to an order of 60 pN resulting in their movement towards the furrow at velocities that may approach 0.03 μm/sec. At such velocity, cytoplasmatic organelles would pile up at the cleavage furrow within a few minutes, interfering with cytokinesis and possibly leading to cell destruction. It has also been found that the electric forces acting on intracellular particles are maximal when the axis of division is aligned with the external field. This is consistent with the dependence of the destructive effect of TTFields on the angle between division axis and the field, as demonstrated experimentally. In addition, the calculated dependence of the magnitude of this force on frequency is consistent with the experimentally determined frequency dependence of the inhibitory effect of TTFields on melanoma and glioma cell proliferation (120 kHz vs. 200 kHz, respectively).

In Vivo effects of TTFields

NovoCure has shown[22] that TTFields can be applied effectively to animals through electrodes placed on the surface of the body. Using a special type of electrically insulated electrodes, significant inhibition of the growth of both intradermal melanoma (B16F1) in mice and intracranial glioma (F-98) in rats was seen after less then one week of treatment. This growth inhibition was accompanied by a decrease in angiogenesis within the tumor, due to inhibition of endothelial cell proliferation.

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

Secondly, the anti-mitotic effect of TTFields might be expected to damage the replication of rapidly dividing normal cells within the body (bone marrow, small intestine mucosa). Surprisingly, no treatment related toxicities were found in any of the animal safety trials performed by NovoCure, even when field intensities 3 fold higher than the effective anti-tumoral dose were used. The lack of damage to intestinal mucosa in TTField-treated animals is probably a reflection of the fact that the small intestine mucosal cells have a slower replication cycle than neoplastic cells and that the intestine itself most likely changes its orientation in relation to the applied field quite often, lowering the efficacy of TTField mediated mitotic disruption. Bone marrow, on the other hand, is naturally protected from TTFields by the high electric resistance of both bone and bone marrow compared to most other tissues in the body. To test the later assumption, the TTField intensity within the bone marrow of a long bone was modeled using the finite element mesh (FEM) method. It was found that the intensity of TTFields was 100-fold

lower within the bone marrow compared to the surrounding tissues (including within solid tumors). Thus, hematopoietic cell replication should not be affected even when TTField intensities 10-fold higher than necessary to inhibit tumor growth are applied.

The NovoTTF-100A Device

The NovoTTF-100A device is a portable battery operated device which produces TTFields within the human body by means of surface electrodes. The TTFields are applied to the patient by means of surface electrodes that are electrically insulated, so that resistively coupled electric currents are not delivered to the patient. The electrodes, which incorporate a layer of adhesive hydrogel and a layer of hypoallergenic medical tape, are placed on the patient's shaved head. The electrodes must be replaced every three to four days and the scalp re-shaved in order to maintain optimal capacitative coupling between the electrodes and the patient head. All the treatment parameters are pre-set by NovoCure so there are no electrical output adjustments available to the patient. The patient must learn to change and recharge depleted device batteries and to connect to an external battery pack overnight.

Effect of NovoTTF-100A on newly diagnosed GBM patients – clinical pilot study

A pilot study was performed so far on ten newly diagnosed GBM patients treated with the NovoTTF-100A device. All patients underwent surgery and radiotherapy for the primary tumor. All patients received Temozolomide as adjuvant chemotherapy, in addition to NovoTTF-100A treatment.

All patients were treated with multiple four-week treatment courses using continuous, 24-hour a day, 200 kHz, 0.7 V/cm TTFields. TTFields were applied through two sets of opposing insulated electrode arrays and alternated at a 1 second duty cycle between two perpendicular field directions through the tumor. Patients completed between 1 and 17 treatment courses leading to maximal treatment duration of 16.5 months. Overall, more than 96, 4 week treatment courses were completed to date (> 9.6 courses per patient on average).

The treatment was well tolerated with no treatment related serious adverse events seen in any of the patients. Patients received treatment on average about 80% of the scheduled time. Considering the continuous nature of NovoTTF treatment (i.e., 24 hours a day for many months) this figure indicates that compliance with treatment was very high, with patients taking very few days off treatment and stopping only for short periods of time during treatment for personal needs.

Mild to moderate contact dermatitis appeared beneath the electrode gel in all patients during treatment. In most cases this dermatitis appeared for the first time during the second treatment course. The skin reaction improved with use of topical corticosteroids. Regular relocation of the electrode arrays was necessary in order to allow for continuous treatment.

The median progression free survival (PFS) of the patients in this study exceeded concurrent and historical controls[23] dramatically (greater than 18 months versus 7.1 months, respectively). So far 2 of the 10 patients have died. The remaining 8 patients are still alive and 5

of them are progression free. Median overall survival from diagnosis is greater than 26 months at the moment (compared to 14.6 months in historical controls[23]).

Although the number of patients in this pilot trial is small, the excellent safety profile of this treatment modality and the highly promising efficacy data gathered so far indicate the potential of NovoTTF-100A treatment as an effective therapy for newly diagnosed GBM patients.

Effect of NovoTTF-100A on recurrent GBM patients – clinical pilot study

A pilot study was performed on ten recurrent GBM patients treated with the NovoTTF-100A device. All patients underwent surgery and radiotherapy for the primary tumor. Only 1 patient was chemotherapy naïve, the rest having received either Temozolomide or other chemotherapeutic agents, as adjuvant treatment, prior to recurrence.

All patients were treated with multiple four-week treatment courses using continuous, 24-hour a day, 200 kHz, 0.7 V/cm TTFields. TTFields were applied through two sets of opposing insulated electrode arrays and alternated at a 1 second duty cycle between two perpendicular field directions through the tumor. Patients completed between 1 and 15 treatment courses leading to maximal treatment duration of 14.5 months. Overall, more than 70, 4 week treatment courses were completed to date (> 7 courses per patient on average).

The treatment was well tolerated with no treatment related serious adverse events seen in any of the patients. Patients received treatment on average about three quarters of the scheduled time. Considering the continuous nature of NovoTTF treatment (i.e., 24 hours a day for many months) this figure indicates that compliance with treatment was very high, with patients taking very few days off treatment and stopping only for short periods of time during treatment for personal needs.

Mild to moderate contact dermatitis appeared beneath the electrode gel in 8 of the 10 patients during treatment. In most cases this dermatitis appeared for the first time during the second treatment course. The skin reaction improved with use of topical corticosteroids. Regular relocation of the electrode arrays was necessary in order to allow for continuous treatment.

The median progression free survival (PFS) of the patients in this study exceeded historical controls[2] dramatically (26.1 weeks versus 9 weeks, respectively). The PFS at 6 months (PFS6) was 50% compared to 15% in historical controls[2]. So far 7 of the 10 patients have died. The remaining 3 patients are still alive and 2 of them are progression free. Median overall survival was 62 weeks. Response rate was 25% (1 CR + 1 PR) and only two patients had progressive disease despite treatment.

Although the number of patients in this pilot trial was small, the excellent safety profile of this treatment modality and the highly promising efficacy data gathered led to IDE approval (G03091) to test the efficacy of NovoTTF-100A treatment for recurrent GBM patients. This pivotal clinical trial is currently ongoing in 23 centers in the US and Europe.

Effect of NovoTTF-100A on patients with locally advanced and/or metastatic solid tumors – a phase I study

Six patients with locally advanced or metastatic solid tumors were treated so far with the NovoTTF-100A device in this study. The first two patients, who suffered from metastatic skin lesions, were treated for two weeks using 100 kHz TTFields. The third patient, who suffered from an advanced pleural mesothelioma, was treated for four weeks using 120 kHz TTFields. The fourth patient, who also suffered from metastatic skin lesions, was treated continuously for 4 weeks using 100 kHz TTFields. The fifth patient having a rapidly progressive GBM was treated for four weeks using 200 kHz, 3 directional fields. Finally, the sixth patient who also had metastatic skin tumors was treated for six weeks using 100 kHz TTFields until systemic progression.

The treatment was well tolerated with no treatment related serious adverse events in any patient. Two patients developed mild skin reactions to the electrode hydrogel and the medical grade plasters used to fix the electrodes to the torso. All other adverse events were related either to concomitant medication or disease progression.

In the first two patients, previously progressive lesions were stabilized for two to three weeks and then resumed growth. In the third patient, local minimal regression of the mesothelioma was seen in the treated area (the abdomen) while in the chest and pelvis the disease was stable and progressive, respectively. The fourth patient showed a partial response to treatment with a 51% decrease in tumor area after 4 weeks of treatment. The fifth patient progressed during treatment. Finally, the sixth patient showed a 20% decrease in tumor size before systemic progression occurred.

These results indicate the complete lack of systemic toxicity of NovoTTF-100A treatment when applied to the head, chest, abdomen, and limbs of advanced cancer patients. In addition, promising initial efficacy results were observed in these patients.

IV. STUDY DESIGN

A prospective, randomly controlled pivotal study will be conducted on 283 patients (randomized at a 2:1 ratio in favor of the NovoTTF-100A group) with tissue diagnosis of GBM who have completed 60 Gy radiation therapy together with adjuvant Temozolomide. The control group will receive standard Temozolomide maintenance therapy. The primary endpoint will be time to disease progression (TTP). The sample size was chosen based on the log-rank test comparing time to event (i.e., recurrence) assuming patients treated with the NovoTTF-100A together with maintenance Temozolomide will have a median TTP significantly greater than controls (10.7 months compared to 7 months, respectively; with an overall 5% 2-sided type I error and 80% power). This sample size also has adequate power (80%) to detect a minimum of 8.9 month increase in median overall survival in NovoTTF-100A treated patients compared with control patients.

The following will be considered disease progression for determination of TTP (based on the Macdonald criteria; Tab D):

1. Tumor growth > 25% compared to the smallest tumor area measured in this patient during the trial.
2. Appearance of 1 or more new tumors in the brain (diagnosed radiologically as GBM).

Final determination of progression will be made by CORE radiology review, in cases where an MRI is available (which should be the great majority of cases). In cases where an MRI is not available, clinical progression will be diagnosed according to the following criteria:

1. Decline in functional status as indicated by a decrease in KPS of > 10, and
2. Decline in neurological function as indicated by a decrease of 2 points or more in MRC scale (TAB H), and
3. ≥50% increase in steroid dose.

The determination of whether to stop treatment due to progression will be based on the investigator's evaluation of the patient's clinical condition. NovoTTF-100A treatment will be continued for 24 months unless the patient's clinical condition prohibits this. In the case of radiological progression based on local evaluation, Temozolomide treatment will be stopped and a second line treatment chosen instead. The following treatments or any combination of these treatments are considered second line therapy in this protocol:

1. Re-operation (NovoTTF-100A treatment will be interrupted for at least 2 weeks after reoperation or until wound healing).
2. Local radiation therapy (e.g. gamma knife)
3. Second line chemotherapy
4. Combination of the above.

Patients will be recruited to the study by the principal investigator (PI) or one of the co-investigators (CI) in 25 centers (at least half of the centers will be in the USA). Immediately following screening, patients will be randomized at a 2:1 ratio to receive either NovoTTF-100A treatment together with maintenance Temozolomide or maintenance Temozolomide alone.

Patient accrual is expected to continue for 24 months. Patient follow-up for time to progression will continue until 12 months from accrual of the last patient. Follow up for overall survival will continue for 18 months from accrual of the last patient.

Treatment arm

NovoTTF-100A treatment will be given together with maintenance Temozolomide (according to the standard maintenance dosing described below in section XII). At treatment initiation patients will be seen at an outpatient clinic. During this visit baseline examinations will be performed and NovoTTF-100A treatment will be initiated under medical supervision. The patients will also be instructed on the operation of the NovoTTF-100A and battery replacement. Once the patients are trained in operating the device they will be released to continue treatment

at home. The patients will receive multiple 1 month courses of continuous NovoTTF-100A treatment. NovoTTF-100A treatment will be stopped in the following cases:

1. Treatment will be stopped in the case of device related serious adverse events
2. Clinical and functional deterioration considered by the investigator to be prohibitive of continuing treatment.
3. Toxicity due to Temozolomide treatment will not be cause for stopping NovoTTF-100A treatment.
4. Radiological progression alone will not lead to termination of NovoTTF-100A treatment, but to replacement of the Temozolomide treatment with best standard of care second line therapy:
   a. Re-operation (NovoTTF-100A treatment will be interrupted for at least 2 weeks after reoperation or until wound healing).
   b. Local radiation therapy (e.g. gamma knife)
   c. Second line chemotherapy
   d. Combination of the above.

Control arm

Patients will be treated with maintenance Temozolomide according to the standard dosing regimen described below in section XII. Following radiological progression or unacceptable toxicity, Temozolomide will be replaced with best standard of care second line therapy:

a. Re-operation (NovoTTF-100A treatment will be interrupted for at least 2 weeks after reoperation or until wound healing)..
b. Local radiation therapy (e.g. gamma knife)
c. Second line chemotherapy
d. Combination of the above

Follow-up Evaluations

As long as the patients are receiving any treatment (NovoTTF-100A or chemotherapy), all patients will be seen once every month at an outpatient clinic where they will undergo medical follow-up and routine laboratory exams. An MRI will be performed every second month following the baseline MRI. In the case of clinical progression an unscheduled MRI will be obtained within 1 week of the investigator becoming aware of the clinical progression. No additional MRIs will be required after progression. Central MRI review will be performed by a neuro-radiologist blinded to the treatment group of each patient. Medical follow-up will continue for 2 months after treatment termination in order to capture treatment related toxicities. After these visits, mortality will be assessed based on monthly telephone interviews with the patients or the patients' caregivers.

Core MRI review

All MRI's will be sent to an independent radiologist, blinded to the treatment groups of the patients. Either digital (DICOM) images or analog films can be used for this purpose. Contrast agent and dose per body weight must be kept constant between scans for each patient.

V. CRITERIA FOR PATIENT ELIGIBILITY

Any patient with a histological diagnosis of GBM who meets all of the specific eligibility criteria listed below may by enrolled on this study. Operable patients must undergo surgery prior to randomization. All patients must have received maximal radiation therapy with concomitant Temozolomide prior to randomization. Patients receiving steroids to control edema may be included in the trial, however, any change in steroid dose must be documented during the follow-up visits. An increase in steroid dose will preclude a diagnosis of partial or complete response (as suggested by Macdonald et al; TAB D). Patients who have progressive disease at screening (compared to the immediate post-surgical MRI) are not candidates for this study. In the case of local radiological suspicion of radiation necrosis the study PI will be consulted.

1) PATIENT INCLUSION CRITERIA:

a. Pathological evidence of GBM using WHO classification criteria.
b. ≥ 18 years of age.
c. Received maximal debulking surgery and radiotherapy with Temozolomide.
e. Karnofsky scale ≥ 70
f. Life expectancy at least 3 months
g. Participants of childbearing age must use effective contraception.
h. All patients must sign written informed consent.
i. Treatment start date at least 4 weeks out from surgery.
j. Treatment start date at least 4 weeks out but not more than 7 weeks from last dose of adjuvant Temozolomide.
k. Treatment start date at least 4 weeks out from radiation therapy.

2) PATIENT EXCLUSION CRITERIA:

a. Progressive disease (according to MacDonald Criteria).
b. Actively participating in another clinical treatment trial
c. Pregnant
d. Significant co-morbidities at baseline which would prevent maintenance Temozolomide treatment:
    1. Thrombocytopenia (platelet count < 100 x $10^3/\mu L$)
    2. Neutropenia (absolute neutrophil count < 1.5 x $10^3/\mu L$)
    3. CTC grade 4 non-hematological Toxicity (except for alopecia, nausea, vomiting)
    4. Significant liver function impairment - AST or ALT > 3 times the upper limit of normal
    5. Total bilirubin > upper limit of normal
    6. Significant renal impairment (serum creatinine > 1.7 mg/dL)
e. Implanted pacemaker, defibrillator or deep brain stimulator, or documented clinically significant arrhythmias.

f. Infra-tentorial tumor
g. Evidence of increased intracranial pressure (midline shift > 5mm, clinically significant papilledema, vomiting and nausea or reduced level of consciousness)
h. History of hypersensitivity reaction to Temozolomide or a history of hypersensitivity to DTIC.

VI. RECRUITMENT PLAN

Patients will be recruited to this study from either the outpatient clinic or inpatient hospital setting at each center. All patients will be seen by the corresponding investigator. Every effort will be made to encourage eligible women and minorities to participate. All patients will be required to sign a written informed consent prior to being registered on this protocol. Every effort will be made to answer questions raised by the patient and their family or advocate regarding the protocol and alternative therapies prior to asking the patient to sign the consent form.

VII. RANDOMIZATION

Patients who meet the above inclusion/exclusion criteria will be randomized at a 2:1 ratio either to the treatment group who will receive NovoTTF-100A treatment together with maintenance Temozolomide, or to the control group who will receive maintenance Temozolomide alone. Randomization will be performed centrally and not within in each center to allow for the following stratifications:

1. Extent of Resection – Biopsy; Partial Resection; Gross total resection
2. MGMT (O^6-benzylguanine, O^6BG) methylation status – Positive, Negative, Unknown

Randomization will be performed with randomly varying block sizes (e.g., 3, 6, or 9 patients) within each stratum.

These classifications are expected to have a stronger impact on disease outcome than the treatment variability between centers, since standard of care for newly diagnosed GBM, worldwide, is based on the Stupp protocol.

VIII. PRE-TREATMENT EVALUATION (SCREENING AND BASELINE) (TAB A)

Within one week prior to beginning treatment all patients will undergo the following studies:

- Baseline contrast enhanced MRI of the brain (within 2 weeks of beginning treatment).
- Complete physical examination
- Neurological status and KPS (Karnofsky performance scale).
- Complete blood count (CBC) and differential
- Biochemistry panel (Electrolytes, BUN, creatinine, bilirubin, liver enzymes, albumin, total protein, glucose, cholesterol)

- Coagulation study (PTT, INR)
- Quality of life questionnaire (EORTC QLQ-C30)

IX. TREATMENT PLAN – NOVOTTF-100A+TEMOZOLOMIDE GROUP

All patients will begin treatment within 1 week from screening/baseline evaluation. Treatment will be initiated in an outpatient clinic by the investigator at each center. In addition to clinical evaluation (as elaborated in section VIII), the investigator will perform the following actions for the treatment arm patients:

- Train the patient in using the device:
    - Battery replacement and recharging
    - Turning the device on and off
    - Disconnecting and reconnecting the electrodes from the device for personal needs
    - How to handle device error messages (see trouble shooting section in User manual)
    - What adverse events can be expected during the treatment.
    - How to handle irritated skin
    - What to do in case of new or worsening clinical signs (call investigator)
- Review the baseline MRI and decide where to place the electrodes (according to the guidelines elaborated in section X below).
- Shave the patients scalp (can be performed by other medical staff in the hospital or by a barber prior to coming to the hospital)
- Place the electrodes
- Connect the electrodes to the device (through the connection cable)
- Turn on the device

The device will be set in advance by a device technician with the following treatment parameters:

- Frequency – 200 kHz
- Output current – 707 mA RMS
- Number of field directions – 2
- Duty cycle – 1 sec in each direction

The patients will continue treatment at home after being trained in device use.

The treatment group patients will receive multiple 1 month courses of continuous NovoTTF-100A treatment together with standard maintenance Temozolomide. The decision to add each additional treatment course will depend on the lack of treatment related serious adverse events which reappear upon re-challenge and lack of clinical disease progression. After initiation of treatment by the physician in the outpatient clinic, maintenance of NovoTTF-100A treatment will be performed by technicians trained by the sponsor. All technical aspects of the treatment are handled by these technicians at technical clinics or at the patients' homes. Technical clinics are situated in close proximity to each center. Patients in the treatment arm will report to these clinics twice per week for treatment maintenance and immediately following a monthly follow up visit (to replace the electrodes). The following actions are performed by the technician:

- Periodic electrode replacement (twice per week) – patients will come to technical clinics for this purpose. Electrodes will be placed in the same locations every time, according to the locations originally decided upon by the investigator during treatment initiation.
- Periodic download of device log (once every 2 weeks)
- Replacement of faulty equipment
- Device, electrode and accessory accountability tracking, and requests for replacements from NovoCure
- Problem solving – by phone between visits to the technical clinic or directly during these visits
- For technical support the patient will contact the local technical clinic. A list of clinics and their contact information will be supplied to the patients separately. If the patient is unable to get a hold of the local device technician or if the patient has technical problems with the device beyond working hours he/she should call the following Toll free number for NovoCure's international support center: 011 - 800 – NOVOCURE (for USA) and 00 - 800 – NOVOCURE (for Europe)

During NovoTTF-100A treatment the patient will be permitted to interrupt treatment for periods of up to an hour twice a day for personal needs. Any pause in treatment beyond this must be coordinated in advance with the principal investigator or one of the co-investigators. Patients will be allowed an additional 1-3 days off treatment between courses according to personal needs.

Once every month from baseline, until treatment termination, all patients will report to an outpatient clinic where they will be assessed clinically and undergo routine laboratory examinations. The follow-up window for these visits is +/- 7 days if the visit occurs prior to the 6 month follow-up window and +/- 14 days on or after the 6 month visit window. Follow up window from the 12 month visit onward will be +/- 1 month. During these visits the investigator will remove the electrodes and examine the skin beneath them. Electrode replacement will be performed at the local technical clinic after the follow-up visit. Medical follow-up and routine laboratory exams for all patients will continue once per month for 2 months following end of

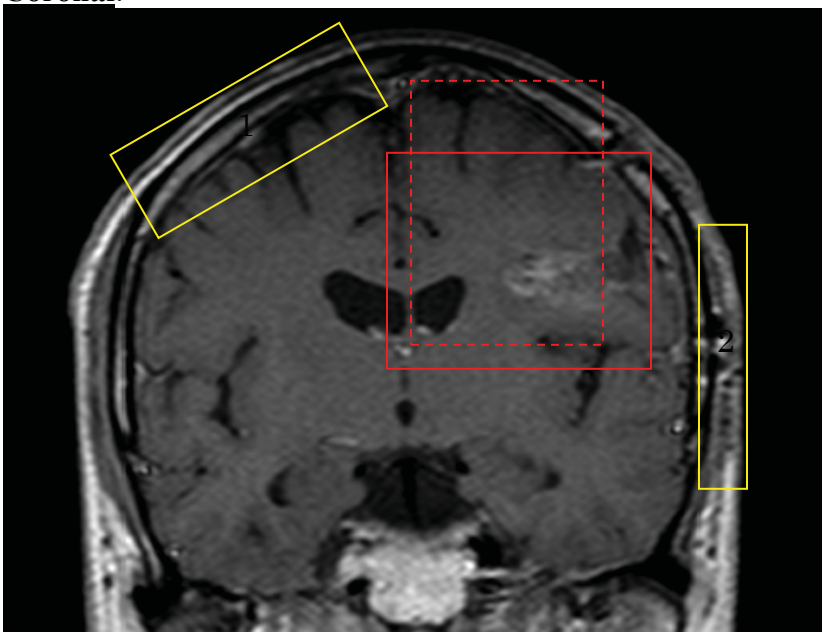
treatment. After this post-progression follow up period, patients will be followed by monthly telephone interview until death.

X. ELECTRODE PLACEMENT PROTOCOL:

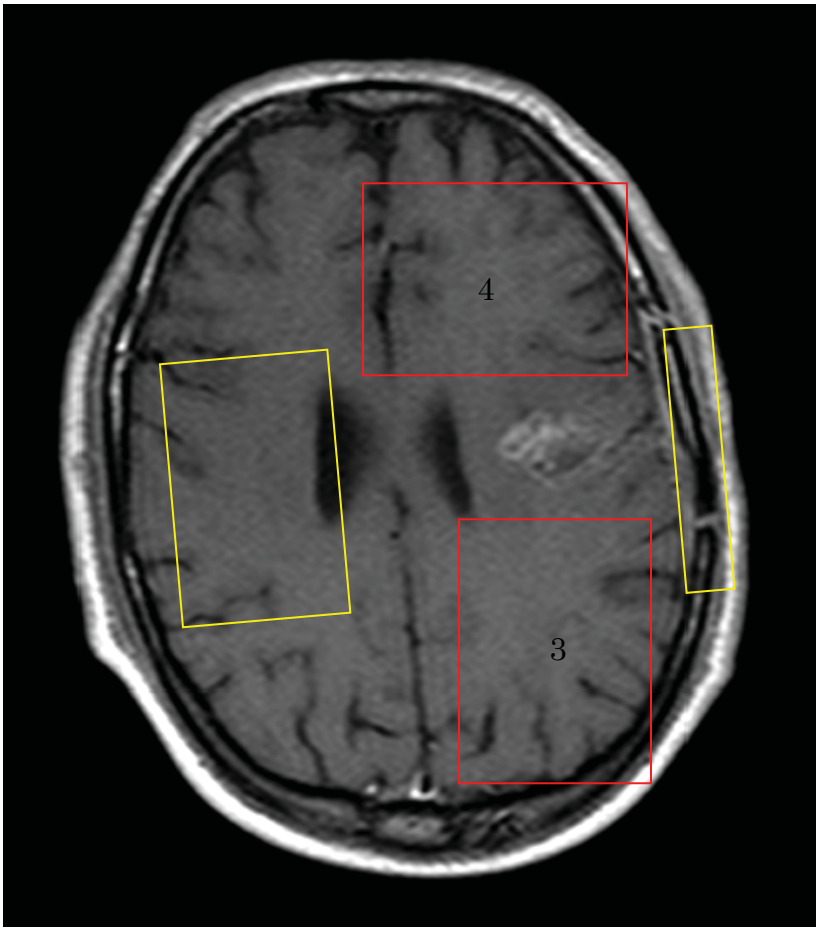
The specific locations of each electrode set will be determined by the treating investigator according to tumor location as follows: the electrode locations will be determined so as to minimize the distance between each electrode set and the center of the tumor, while maintaining a distance of at least one tumor diameter between the electrode sets. This means that the closer the tumor is to the calvarium, the closer the electrode sets will be to each other, and the closer the tumor is to the center of the brain, the further the electrode sets will be from each other. At all times a right angle will be maintained between the imaginary lines connecting each pair of electrode sets.

{Example: Direction 1 = set 1 versus set 2; Direction 2 = set 3 versus set 4}

Coronal:



Horizontal:



XI. EVALUATION DURING NOVOTTF-100A TREATMENT

During electrode replacement, the skin below the electrode will be inspected by the physician (during follow up visits) and by the patient himself or herself (at home or technical center). In the event of significant skin breakdown (leading to pain or bleeding) or evidence of infection, the electrode will be moved to an alternate site. Skin breakdown and/or infection will be treated according to the treating physician's clinical judgment based on a dermatologist's recommendation. Skin breakdown or evidence of infection, either of which requires a break in NovoTTF-100A treatment greater than 3 days, will be captured as an Adverse Event. Mild to moderate contact dermatitis is expected to appear beneath the electrode gel during the first or second treatment course. This condition will be treated as follows:

1. Electrode location will be shifted between two alternate sites at every electrode change.
2. If skin is inflamed – apply 0.1% hydrocortisone ointment.
3. If skin is breached (abrasions, micro-ulcerations, oozing, open sores) or infected – Discontinue hydrocortisone and prescribe a Mupiricin (e.g. Bactroban) ointment.
4. In the case of skin blistering – apply Silver Sulfadiazine (e.g. Silverdine ointment). In the case of known hypersensitivity to sulfa containing compounds the treatment outlined will not be offered and a dermatologist will be consulted.
5. In any case where the patient does not notice an improvement in skin sores, infection or blistering within 2 weeks of starting one of the treatments outlined above, the patient will inform the investigator and a dermatological consult will be obtained.
6. Oral antihistamines and analgesics will be prescribed at the investigators' discretion to control pruritus and pain.

XII. TREATMENT PLAN – MAINTENANCE TEMOZOLOMIDE

Patients randomized to the control group will be treated with maintenance Temozolomide according to the approved dosing scheme as follows:

Maintenance Phase Cycle 1: Four weeks after completing the Temozolomide + RT phase, Temozolomide is administered for an additional 6 cycles of maintenance treatment. Dosage in Cycle 1 (maintenance) is 150 mg/m^2 once daily for 5 days followed by 23 days without treatment.

Cycles 2-6: At the start of Cycle 2, the dose is escalated to 200 mg/m2, if the CTC non-hematologic toxicity for Cycle 1 is Grade ≤2 (except for alopecia, nausea and vomiting), absolute neutrophil count (ANC) is ≥ 1.5 x 10^9/L, and the platelet count is ≥ 100 x 10^9/L. The dose remains at 200 mg/m^2 per day for the first 5 days of each subsequent cycle except if toxicity occurs. If the dose was not escalated at Cycle 2, escalation should not be done in subsequent cycles.

Temozolomide dose reduction or discontinuation during maintenance:
Dose reductions during the maintenance phase should be applied according to tables 1 and 2. During treatment a complete blood count should be obtained on day 22 (21 days after the first

dose of Temozolomide) or within 48 hours of that day, and weekly until the ANC is above 1.5 x 10^9/L (1,500/μL) and the platelet count exceeds 100 x 10^9/L (100,000/μL). The next cycle of Temozolomide should not be started until the ANC and platelet count exceed these levels. Dose reductions during the next cycle should be based on the lowest blood counts and worst non-hematologic toxicity during the previous cycle. Dose reductions or discontinuations during the maintenance phase should be applied according to tables 1 and 2.

Table 1 Temozolomide Dose Levels for Maintenance Treatment

Dose Level	Dose (mg/m^2/day)	Remarks
–1	100	Reduction for prior toxicity
0	150	Dose during Cycle 1
1	200	Dose during Cycles 2-6 in absence of toxicity

Table 2 Temozolomide Dose Reduction or Discontinuation During Maintenance Treatment

Toxicity	Reduce TMZ by 1 Dose Level[a]	Discontinue TMZ
Absolute Neutrophil Count	<1.0 x 10^9/L	See footnote b
Platelet Count	<50 x 10^9/L	See footnote b
CTC Non-hematological Toxicity (except for alopecia, nausea, vomiting)	CTC Grade 3	CTC Grade 4[b]

[a]: TMZ dose levels are listed in table 1.
[b]: TMZ is to be discontinued if dose reduction to <100 mg/m2 is required or if the same Grade 3 non-hematological toxicity (except for alopecia, nausea, vomiting) recurs after dose reduction.
TMZ = Temozolomide; CTC = Common Toxicity Criteria.

Treatment after Temozolomide discontinuation:

Following Temozolomide discontinuation due to toxicity or radiological disease progression (based on local interpretation of MRI), patients in both arms will be offered second line therapy for their disease. The following treatment options will be chosen from based on the patient's clinical condition:

1. Re-operation (NovoTTF-100A treatment will be interrupted for at least 2 weeks after reoperation or until wound healing).
2. Local radiation therapy (e.g. gamma knife)
3. Second line chemotherapy
4. Combination of the above

XIII. PERIODIC EVALUATION UNTIL TREATMENT TERMINATION

Patients in both groups will undergo the following studies or review every month until treatment termination:

- Physical examination

- Neurological status
- Quality of life questionnaire (EORTC QLQ-C30) – every three months until treatment termination
- Blood exams (CBC, Chemistry, Coagulation – for patients receiving anti-coagulants)
- Steroid dose
- Record of Adverse Events

The patients will have a contrast MRI of the head performed after every two months. In case of clinical progression an MRI will be performed within a week. Contrast agent type and dose will be kept constant for each patient between scans. Central MRI review will be performed by a neuro-radiologist blinded to the treatment group of each patient.

XIV. POST-TREATMENT EVALUATION

After treatment termination the patient will be seen at an outpatient clinic every month for two additional visits. Physical and neurological examination, blood tests (CBC and Chemistry panel) will be performed during these visits. Patient mortality and adverse events will be documented on the case report forms. After the two post treatment monthly follow up visits, patients will not be required to return to the clinic for follow-up but will be followed monthly until death by telephone to monitor their status.

XV. MGMT METHYLATION STATUS ASSESSMENT

MGMT methylation - will be assessed by polymerase chain reaction (PCR) methylation status of the promoter region of MGMT.

Randomization will be stratified according to MGMT methylation status based on local analysis performed at institutions where this examination of brain tissue is performed as a standard examination for all GBM patients.

All patients with paraffin embedded brain tissue available for additional analysis will have MGMT methylation status assessed by a central laboratory (blinded to the treatment group of the patients).

Methylation status will be adjusted for during final analysis as a covariate (see statistical analysis section).

The following materials will be required for tissue evaluation:

- Representative tissue blocks that contain diagnostic tumor. A block that, when sectioned, yields at least 1 square centimeter of viable tumor must be present on the H&E slide.
- An accompanying H&E section.

- A Pathology Report documenting that the submitted material contains tumor; the report must include the protocol number, patient case number, and the patient's initials. The patient's name and/or other identifying information should be removed from the report.
- A Specimen Transmittal Form listing pathology materials being submitted for Central Tissue Evaluation must be included in the pathology submission.

Send pathology material by FedEx directly to:
XXXXXXXXXXXXXXX
TBD
XXXXXXXXXXXXXXX

All samples will be sent for Central PCR Analysis of MGMT methylation status at the following laboratory:
XXXXXXXXXXXXXXX
TBD
XXXXXXXXXXXXXXX

Reimbursement
The sponsor will reimburse pathologists from submitting institutions on a per case basis if a block or core of material is submitted.

XVI. POTENTIAL ADVERSE EFFECTS

Treatment with the NovoTTF-100A is not expected to cause any serious side effects. However, it is possible that investigational treatment will cause any of the following:

- Local warmth and tingling sensation beneath the electrodes
- Allergic reaction to the plaster or to the gel
- Skin breakdown
- Infection at the sites of electrode contact with the skin
- Electrode overheating leading to pain and/or local skin burns
- Headache
- Fatigue
- Seizures

Treatment with temozolomide commonly (>20%) causes the following adverse events:

- Leukopenia
- Headache
- Fatigue
- Nausea
- Vomiting or Constipation

Adverse events and complications associated with the underlying GBM disease process, which are unlikely but unknown if related to treatment with NovoTTF-100A together with maintenance Temozolomide include the following adverse events:

- Seizure, including Status Epilepticus
- Neurological and functional decline
- Headaches, nausea and/or vomiting
- Death

XVII. ADVERSE EVENT REPORTING

Definition of Adverse Events

As defined by the ICH Guidelines for Good Clinical Practice E2A (CPMP/ICH/377/95), an adverse event (AE) is any untoward medical occurrence in a patient administered a medicinal product and which does not necessarily have to have a causal relationship with this treatment. An adverse event can therefore be any unfavorable and unintended sign (for example, an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to this medicinal product. Adverse events include the following:

- All suspected medication adverse reactions
- All reactions from medication overdose, abuse, withdrawal, sensitivity, or toxicity.
- Apparently unrelated illnesses, including the worsening of a preexisting illness
- Injury or accidents. Note that if a medical condition is known to have caused the injury or accident (a fall secondary to dizziness), the medical condition (dizziness) and the accident (fall) should be reported as 2 separate adverse events.
- Abnormalities in physiological testing or physical examination findings that require clinical intervention or further investigation (beyond ordering a repeat [confirmatory] test).
- Laboratory abnormalities that require clinical intervention or further investigation (beyond ordering a repeat [confirmatory] test) unless they are associated with an already reported clinical event. Laboratory abnormalities associated with a clinical event (elevated liver enzymes in a patient with jaundice) should be captured in the source documents.

Each adverse event is to be classified by the investigator as serious or non-serious. This classification of the gravity of the event determines the reporting procedures to be followed.

Grading of an Adverse Event:

The descriptions and grading scales found in the revised NCI Common Toxicity Criteria (CTC) version 3.0 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	Transient or minimal symptoms, no change in activity or need for medication
MODERATE	Grade 2	Symptomatic change, interferes to some extent with patient's usual function
SEVERE	Grade 3	Incapacitating, significantly interferes with patient's usual function

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

Serious Adverse Events

An adverse event that meets one or more of the following criteria/outcomes is classified as serious:

Death
Life-threatening (i.e., at immediate risk of death)
Inpatient hospitalization or prolongation of existing hospitalization

Persistent or significant disability/incapacity
Congenital anomaly/birth defect

Important adverse events that may not result in death, may not be life-threatening, or do not require hospitalization may be considered serious when, based upon appropriate medical judgment, they may acutely jeopardize the patient without immediate medical intervention to prevent one of the outcomes listed above. Serious may also includes any other event that the investigator or company judges to be serious. In addition, sites are responsible for reporting serious adverse events to their local IRB according to their institutional requirements. Death due to disease progression need not be reported to the study monitor. These SAEs will be captured in the CRFs as described for regular AEs.

Routine Adverse Event Reporting

All adverse events must be reported in the source documentation and CRFs with appropriate information, including severity and rating of causality to the study drug/treatment. Adequate source documentation must be available to characterize the severity, duration and causality of each reported adverse event.

Unanticipated Adverse Device Effect Event (UADE) Reporting

Any potential unanticipated adverse device effect (UADE) will be reported to the study monitor and local IRB within 10 days of the investigator learning of the event. The medical monitor will investigate whether the adverse event is a UADE and, if so, report the UADE to the Sponsor, as soon as possible but no later than 3 days after first learning of the event. Expedited report for FDA submission and reporting to other IRBs to follow within 10 working days after first learning of the event by the medical monitor.

The report will contain the following:

- The initials of the subject, patient MRN #, protocol # and title
- The date the event occurred
- A description of the UADE
- An explanation of how the UADE was handled
- A description of the subject's condition
- Indication if the subject remains on the study
- Indication if the event is considered related to the NovoTTF-100A
- Indication if an amendment to the protocol and/or consent form is recommended as a result

Eliciting Adverse Event Information

The investigator is to report 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?”

Adverse Event Reporting Period

The adverse event reporting period will begin immediately following initiation of treatment with the NovoTTF-100A device or BSC chemotherapy. Adverse events will be collected for two months 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 CRFs, 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.

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.

XVIII. STUDY OUTCOME MEASURES

1. Efficacy analysis:

a. Primary Endpoint

- The primary endpoint of the study will be time to disease progression

b. Secondary Outcome Measures

- Overall survival time
- Progression free survival at 6 months (PFS6)
- One and two year survival rate (%1 year survival)
- Quality of life (EORTC QLQ-C30 questionnaire; TAB H)
- The radiological response of the tumor will be assessed by the MRI studies according to Macdonald criteria for progressive disease, stable disease, partial response or complete response (see TAB D). All patients will have their tumor measurements recorded at baseline and at the time of each MRI scan. Lesions must be measured in two dimensions. The dose and type of contrast agent must be held constant from scan to scan for each patient.

2. Safety analysis:

- Safety and tolerability of NovoTTF-100A treatment based on the incidence and severity of adverse events and toxicities. Toxicities will be assessed according to the "Common toxicity criteria (CTC), version 3.0" (see TAB B).

XIX. CRITERIA FOR REMOVAL FROM STUDY

- 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 for the patient. Patient follow up will continue as for the control arm after such an event.
- The investigator may remove a patient from the study in case of not complying with study protocol.
- Patients will be able to withdraw from the trial at their own request .

XX. STATISTICAL CONSIDERATIONS

A. Sample Size Calculation

Based on the insignificant side effects of NovoTTF-100A treatment observed in the pilot studies performed so far in Europe, we assume that any significant increase in progression free survival compared to the control group would justify use of the NovoTTF-100A device in newly diagnosed GBM patients, concomitant to maintenance Temozolomide.

The sample size of 283 patients (80 Control patients + 160 NovoTTF-100A patients + 15% loss to follow up) was determined based on the log-rank test comparing time to event (i.e., recurrence) between patients treated with the NovoTTF-100A together with maintenance Temozolomide and controls (maintenance Temozolomide alone). The null hypothesis is that the recurrence rate is the same in the two study groups, *i.e.*, hazard ratio=1. The alternative hypothesis is that the recurrence rate is not the same, *i.e.*, hazard ratio≠1. The expected hazard ratio was estimated from the expected median time to progression in the two study groups as follows:

- Expected median time to progression on control treatment is 7 months (see Stupp et al., NEJM, 2005[23] and Temozolomide package insert)
- Expected median time to progression on NovoTTF-100A treatment is 10.7 months.
- Expected accrual time during which patients are recruited: 24 months
- Additional follow-up time after end of recruitment: 12 months for time to progression and 18 months for overall survival.
- Ratio of control to experimental patients: 1:2
- Type I error: 0.0475%; 2-sided
- Power: 80%

An alpha level of 0.0475 was chosen based on the O'Brien-Fleming alpha spending method[24,25] to allow for a single interim analysis. The alpha level used for the interim analysis will be 0.0187 for PFS and 0.006 for OS. The interim analysis will be performed on the PFS and OS data available for the first 120 evaluable patients with a minimum of 18 months follow up.

This sample size also has adequate power (80%) to detect a minimum of 8.9 month increase in median overall survival in NovoTTF-100A treated patients compared with control patients. This amount of improvement in overall survival is consistent with the results currently observed in the pilot study (the median overall survival is over 26 months in NovoTTF-100A treated patients and 14.6 months in historical controls).

B. Statistical analysis

1. The primary endpoint will be achieved if the time to disease progression is significantly greater in the treatment group than in the control group. In order to allow for two analyses in the trial the alpha level used at each time point will be calculated based on the O'Brien-Fleming method[24,25] (i.e., approximately 0.0187 at the interim analysis and 0.0475 at the final analysis).

2. The primary analysis will be an intent-to-treat (ITT) analysis including all randomized patients according to their assigned treatment. For analysis of time to disease progression, patients will be censored at the time that they are last known to be recurrence free (if withdrawn or lost to follow-up) or at study closeout. For patients without any follow-up data, a sensitivity analysis will be performed that will include various imputation methods, such as treating all missing data as failures, treating all missing data as successes, treating all missing data in the treatment group as failures but all successes in the control group ("Worst Case") and treating all missing data in the control group as failures but all successes in the treatment group ("Best Case"). Baseline characteristics of patients who withdrawal or are lost to follow-up will be compared with patients who remain in the study to evaluate the potential for informative censoring. A sensitivity analysis will be conducted to evaluate the assumption for interval censoring (i.e., event time is assumed at the time of the visit). A sensitivity analysis will also be conducted excluding patients without MRI documented disease progression

3. Secondary analyses will be performed based on the per protocol population

C. Covariates

A Cox proportional hazards model will be used to evaluate covariates. The effect of the following covariates will be compared and adjusted for between the treatment and control groups:

1. Age
2. Extent of surgery (biopsy, partial, or total resection)
3. MGMT methylation status (positive, negative, unknown)
4. Baseline Karnofsky performance scale score
5. Tumor size
6. Tumor location
7. Percent of the total treatment time in which the NovoTTF-100A treated patients actually received treatment (will be calculated by analyzing the internal computerized log file of each NovoTTF-100A device and dividing the total device ON time by the prescribed number of 1 month treatment courses).

D. Additional variables

The following parameters will be also recorded and compared between the treatment and control groups

- Overall survival time (Log Rank Test). In order to allow for two analyses in the trial the alpha level used at each time point will be calculated based on the O'Brien-Fleming method[24,25] (i.e., approximately 0.006 at the interim analysis and 0.0475 at the final analysis)..
- % 6-month progression free survival
- % 1 and 2-year survival
- Quality of life (EORTC QLQ-C30 questionnaire)
- Radiological response rates
- Incidence and severity of adverse events

In addition, the correlation will be measured between the percent of time patients received NovoTTF-100A treatment and their progression free survival and overall survival.

XXI. RISK/BENEFIT ANALYSIS

The risks associated with use of the NovoTTF-100A are principally the risk of 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. The 26 patients treated to date as part of pilot studies suffered no treatment related serious adverse events after > 180 months of treatment (cumulatively). In fact the only complication seen was a mild to moderate skin irritation beneath the electrode gel.

In the pilot trial performed on 10 newly diagnosed GBM patients, median TTP in NovoTTF-100A treated patients was >14 months. Although these results are not statistically significant due to the small number of patients in the trial, they raise the possibility that the NovoTTF-100A device will benefit patients in the current study with regards to OS. Up to 174 patients will be exposed to NovoTTF-100A treatment during the current trial. Considering the minimal toxicity and promising efficacy seen in the pilot trials, the small number of patients exposed to this treatment in the current study and the and the poor outcome of these patients despite Temozolomide treatment – we conclude that the possible benefits of NovoTTF-100A treatment drastically exceed its potential risks.

XXII. STUDY MONITORING AND QUALITY ASSESSMENT

Study monitoring will be performed by a CRO assigned this responsibility by the sponsor. Study monitoring functions will be in compliance with recognized Good Clinical Practices, 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: on-site visits and review of study documents and results. The CRO will operate under written procedures to ensure compliance with the protocol.

On-site monitoring visits will take place at each center prior to study initiation and at least once during the course of the study, and a final visit at the close of the study. The pre-study visit is intended to provide an opportunity for the monitor to review the Investigational Plan with the Investigators and to ensure that the Investigators:

- have appropriate training, facilities, patient load, time, and willingness to comply with study requirements;
- have the approval of the supervising Institutional Review Board (IRB) for the Investigational Plan;
- have all study documentation and required records on site; and
- assume responsibility for the investigation at their center.

Visits during the study are 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. During these in-study visits, 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 monitor's final on-site visit at completion of the study is intended to assure that all the data have been properly completed and to have a closing meeting with the Investigators and their staff members. Reports of the on-site visits will be made by the monitor and 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.

An independent Data and Monitoring Committee (DMC), comprised of a neurosurgeon, neuro-oncologist and statistician will be formed to monitor the safety data from the study. Although there are no anticipated significant safety issues with the device, the adverse event data will be reviewed by the DMC to determine if there are any unexpected safety concerns with the device that warrant study termination or if the study should be stopped for futility purposes. Specifically, DMC review will be performed after 12 and 24 months from first patient recruited to determine if:

- there is clear evidence of unacceptably harmful side-effects of NovoTTF-100A treatment together with maintenance temozolomide; or

- there is no likelihood of demonstrating treatment benefit or equivalence.

- It is unethical to withhold NovoTTF-100A treatment from patients

The DMC will base their recommendation to the Sponsor on an evaluation of data such as:

- All adverse events, including serious adverse events and device or drug related AEs
- Time to disease progression and overall survival

XXIII. PROTECTION OF HUMAN SUBJECTS

A. Privacy

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. The use and disclosure of protected health information will be limited to the individuals described in the Research Authorization form. A Research Authorization form must be completed by the Principal Investigator and approved by the IRB and Privacy Board.

XXIV. INFORMED CONSENT PROCEDURES

RESEARCH AUTHORIZATION

Procedures for obtaining Research Authorization: Prior to carrying out any protocol-specific procedures, investigators or designated staff will explain fully 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. The Research Authorization requires a separate signature from the patient. The original signed documents will become part of the patient's medical record, and each patient will receive a copy of the signed documents. All patients must provide written informed consent prior to registration and treatment.

XXV. REFERENCES

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XXVI. PROTOCOL SIGNATURE PAGE

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Investigator Name - _____

Signature - _____

Date - _____/_____/_____

Sponsor:

NovoCure Ltd.

Name - _____

Signature - _____

Date - _____/_____/_____

TAB A
Study Procedure Matrix

	T=-7 (baseline)	T=1 month (±7 days)	T=2 months (±7 days)	T=3 months (±7 days)	T=4 months (±7 days)	T=5 months (±7 days)	T=6 months (±14 days)	T=every month until treatment stop+	T=Progression	T=1 month From treatment stop+	T=2 months From treatment stop+	Monthly thereafter+
MRI of the head	X*		X*		X*		X*	X*	X*			
Physical examination	X	X	X	X	X	X	X	X	X	X	X	
Neurological status	X	X	X	X	X	X	X	X	X	X	X	
Complete blood count (CBC) and differential	X	X	X	X	X	X	X	X	X	X	X	
Chemistry panel (SMAC)	X	X	X	X	X	X	X	X	X	X	X	
Coagulation study	X	X	X	X	X	X	X	X	X	X	X	
Quality of life questionnaire	X			X			X	X&				
Telephone interview												X

* MRI of the head will be performed routinely at baseline and again every 2 months until treatment termination or progression whichever is later. An MRI of the head will be obtained in the event of clinical signs of progression.

&Every third month until treatment termination.

+ Visit window of ± 7 days if visit occurs prior to the 6 month follow-up window, ± 14 days if visit occurs on or after the 6 month follow-up window, ± 1 month if visit occurs on or after the 12 month follow-up window.

TAB B
Common Toxicity Criteria (v 3.0)

TAB C - Karnofsky scale

The *Karnofsky Scale* has been adapted for use in many areas, including hospices, cancer clinics, etc., as well as used by various CFS researchers and physicians (Leonard Jason, PhD; Jay A. Goldstein, MD).

The 10-point scale is a quick and easy way to indicate how you are feeling on a given day, without going through several multiple choice questions or symptom surveys.

100	Able to work. Normal; No complaints; No evidence of disease.
90	Able to work. Able to carry on normal activity; Minor symptoms.
80	Able to work. Normal activity with effort; Some symptoms.
70	Independent; not able to work. Cares for self; Unable to carry on normal activity.
60	Disabled; dependent. Requires occasional assistance; cares for most needs.
50	Moderately disabled; dependent. Requires considerable assistance and frequent care.
40	Severely disabled; dependent. Requires special care and assistance.
30	Severely disabled. Hospitalized, death not imminent.
20	Very sick. Active supportive treatment needed.
10	Moribund. Fatal processes are rapidly progressing

Tab D
Macdonald Criteria

Tab E
Informed Consent

Tab F

Case Report Forms

Tab G
EORTC QLQ C30

EORTC QLQ-C30 (version 3)

We are interested in some things about you and your health. Please answer all of the questions yourself by circling the number that best applies to you. There are no "right" or "wrong" answers. The information that you provide will remain strictly confidential.

Please fill in your initials: |_|_|_|_|
Your birthdate (Day, Month, Year): |_|_|_|_|_|_|_|_|
Today's date (Day, Month, Year): 31 |_|_|_|_|_|_|_|_|

		Not at All	A Little	Quite a Bit	Very Much
1.	Do you have any trouble doing strenuous activities, like carrying a heavy shopping bag or a suitcase?	1	2	3	4
2.	Do you have any trouble taking a long walk?	1	2	3	4
3.	Do you have any trouble taking a short walk outside of the house?	1	2	3	4
4.	Do you need to stay in bed or a chair during the day?	1	2	3	4
5.	Do you need help with eating, dressing, washing yourself or using the toilet?	1	2	3	4

During the past week:

		Not at All	A Little	Quite a Bit	Very Much
6.	Were you limited in doing either your work or other daily activities?	1	2	3	4
7.	Were you limited in pursuing your hobbies or other leisure time activities?	1	2	3	4
8.	Were you short of breath?	1	2	3	4
9.	Have you had pain?	1	2	3	4
10.	Did you need to rest?	1	2	3	4
11.	Have you had trouble sleeping?	1	2	3	4
12.	Have you felt weak?	1	2	3	4
13.	Have you lacked appetite?	1	2	3	4
14.	Have you felt nauseated?	1	2	3	4
15.	Have you vomited?	1	2	3	4

Please go on to the next page

During the past week:		Not at All	A Little	Quite a Bit	Very Much
16.	Have you been constipated?	1	2	3	4
17.	Have you had diarrhea?	1	2	3	4
18.	Were you tired?	1	2	3	4
19.	Did pain interfere with your daily activities?	1	2	3	4
20.	Have you had difficulty in concentrating on things, like reading a newspaper or watching television?	1	2	3	4
21.	Did you feel tense?	1	2	3	4
22.	Did you worry?	1	2	3	4
23.	Did you feel irritable?	1	2	3	4
24.	Did you feel depressed?	1	2	3	4
25.	Have you had difficulty remembering things?	1	2	3	4
26.	Has your physical condition or medical treatment interfered with your family life?	1	2	3	4
27.	Has your physical condition or medical treatment interfered with your social activities?	1	2	3	4
28.	Has your physical condition or medical treatment caused you financial difficulties?	1	2	3	4

For the following questions please circle the number between 1 and 7 that best applies to you

29. How would you rate your overall health during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

30. How would you rate your overall quality of life during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

TAB H

Medical research council (MRC) scale for neurological status

1	No neurological deficit
2	Some neurological deficit but function adequate for useful work
3	Neurological deficit causing moderate functional impairment e.g. ability to move limbs only with difficulty, moderate dysphasia moderate paresis, some visual disturbances (e.g. field detect)
4	Neurological deficit causing major functional impairment e.g. inability to use limb/s gross speech or visual disturbances No useful function - inability to make conscious responses

novocure

A Prospective, Multi-center Trial of NovoTTF-100A Together With Temozolomide Compared to Temozolomide Alone in Patients with Newly Diagnosed GBM

THERAPEUTIC PROTOCOL

Protocol EF-14

Version 2.0

IDE G070228

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Release date:

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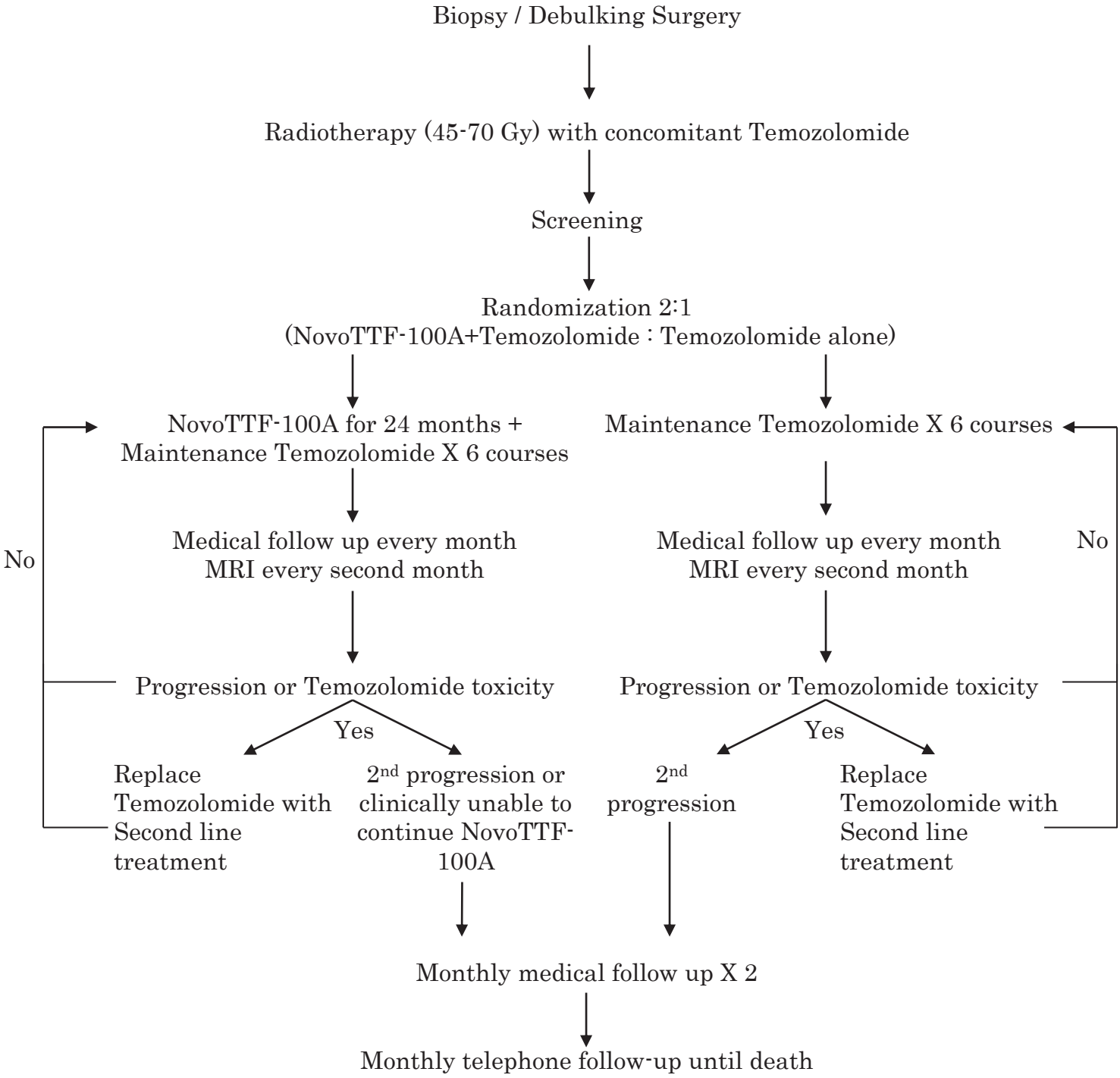
I. PROTOCOL SUMMARY AND SCHEMA

1. SUMMARY

Title:	A Prospective, Multi-center Trial of NovoTTF-100A Together With Temozolomide Compared to Temozolomide Alone in Patients with Newly Diagnosed GBM
Device:	NovoTTF-100A
Study Objectives:	To compare the efficacy and safety outcome of newly diagnosed GBM patients treated with NovoTTF-100A concomitant to Temozolomide to those treated with Temozolomide alone
Study Design:	Prospective, Randomized, Open Label, Standard of Care Control
Study Hypothesis:	The hypothesis of this study is that addition of NovoTTF-100A treatment to maintenance Temozolomide will significantly increase progression free survival of newly diagnosed GBM patients compared to patients treated with Temozolomide alone
Sample Size:	700 patients with newly diagnosed GBM
Study Population:	Patients with tissue based diagnosis of GBM, above 18 years of age, of both genders after surgery or biopsy followed by radiation therapy with adjuvant Temozolomide (Stupp protocol[23])
Primary endpoint:	Progression free survival time
Secondary endpoints:	• Overall survival (OS) • Progression free survival at 6 months (PFS6) • % 1 and 2-year survival • Radiological response (Macdonald criteria) • Quality of life assessment (EORTC QLQ-C30) • Adverse events severity and frequency
Sponsor:	NovoCure Ltd. POB 15022 MATAM Center Haifa, 31905, Israel

2. PROTOCOL SCHEMA



II. OBJECTIVES AND SCIENTIFIC AIMS

- To prospectively compare the progression free survival time of newly diagnosed GBM patients treated with NovoTTF-100A together with Temozolomide to those treated with Temozolomide alone.
- To prospectively compare the overall survival time of newly diagnosed GBM patients treated with NovoTTF-100A together with Temozolomide to those treated with Temozolomide alone.
- To prospectively determine %6-month progression free survival, % 1 and 2-year survival and quality of life (TAB H) of patients treated with NovoTTF-100A together with Temozolomide to those treated with Temozolomide alone.
- To collect evidence of the safety of the NovoTTF-100A device applied together with Temozolomide to patients with newly diagnosed GBM.

III. BACKGROUND AND RATIONALE

Glioblastoma multiforme (GBM), a malignant form of astrocytoma, is the most common primary intracranial neoplasm. The incidence of GBM increases steadily above 45 years of age with a prevalence of approximately 7500 cases in the USA. Despite numerous attempts to improve the outcome of patients with GBM, the 3-year survival of these patients is only 6% with median survival of 14.6 months[1].

Patients with newly diagnosed GBM who are treated with maximal surgical resection, 60 Gy radiotherapy together with Temozolomide, followed by maintenance Temozolomide for 6 months, have a median survival of 14.6 months[23]. Thus, there is a critical need for new therapeutic options for treatment of GBM. TTFields are a new experimental modality for the treatment of malignant tumors. Pre-clinical studies[12,22] have shown this treatment modality to effectively inhibit the growth of experimental tumors both in-vitro and in-vivo without any systemic side effects.

The currently accepted treatment of newly diagnosed GBM is based on: surgical resection with or without Gliadel Wafer implantation, radiotherapy, and Temozolomide. Each of these treatments is briefly described below:

1. Surgical resection - Treatment of patients with GBM usually begins with resection (in conjunction with the biopsy or after it), with maximal debulking of the tumor as the main goal because curative resection is very rare.

2. Radiation therapy - Post-surgical radiation therapy has been shown to improve survival, though even with maximal treatment, survival after RT alone is still limited to about one year[23].

3. Temozolomide – Adjuvant Temozolomide and radiation therapy following surgery has been shown to improve survival by about 20%. According to the Temozolomide package insert adjuvant Temozolomide treatment delays disease progression (from 5 to 6.9 months) and improves overall survival (from 12.1 to 14.6 months)[23]. In the past, Temozolomide was also approved for recurrent anaplastic astrocytoma.

4. GLIADEL® Wafer in combination with surgical resection – Gliadel Wafer delivers carmustine (BCNU) directly to the bed of the resected tumor. The package insert indicates that for newly diagnosed GBM, Gliadel increased median overall survival from 11.6 to 13.9 months compared to placebo. No data is presented regarding the effect of Gliadel wafers on progression free survival.

In conclusion, despite the immense effort made over the years with different treatment modalities, the survival of patients with newly diagnosed GBM is still very poor; no treatment is curative; and the quality of life of patients with this tumor is compromised significantly, not only by their disease but also by side effects of these rigorous treatment plans. A treatment modality is needed that will improve the results of standard treatments without further impairing the quality of life of these patients for their limited life span.

Introduction to electric fields

In the laboratory setting and in clinical practice, alternating electric fields show a wide range of effects on living tissues. At very low frequencies (under 1 kHz), alternating electric fields stimulate excitable tissues through membrane depolarisation[3]. The transmission of such fields by radiation is insignificant and therefore they are usually applied directly by contact electrodes, though some applications have also used insulated electrodes. Some well known examples of such effects include nerve, muscle and heart stimulation by alternating electric fields[3,4]. In addition, low frequency pulsed electric fields have been claimed to stimulate bone growth and accelerate fracture healing[5]. However, as the frequency of the alternating electric field increases above 1 kHz, the stimulatory effect diminishes. Under these conditions although a greater fraction of the fields penetrates the cells, due to the parallel resistor-capacitor nature of all biological membranes, the stimulatory power greatly diminishes as the alternating cell membrane hyper –depolarization cycles are integrated such that the net effect is nulled.

At very high frequencies (i.e., above many MHz), while the integration becomes even more effective, a completely different biological effect is observed. At these frequencies tissue heating becomes dominant due to dielectric losses. This effect becomes more intense as field intensity or tissue dissipation factor increase[6]. This phenomenon serves as the basis for some commonly used medical treatment modalities including diathermy and radio frequency tumor ablation, which can be applied through insulated electrodes[7].

Intermediate frequency electric fields (i.e., tens of kHz to MHz), alternate too fast for causing nerve-muscle stimulation and involve only minute dielectric losses (heating). Such fields, of low to moderate intensities, are commonly considered to have no biological effect[6]. However, a number of non-thermal effects, of minor biological consequence, have been reported even at low field intensities. These include microscopic particle alignment (i.e., the pearl chain effect[8]) and cell rotation[9,10]. With pulsed relatively strong electric fields, $> 10^3$ V/cm and 100 ms pulse length, reversible pore formation appears in the cell membrane, a phenomenon usually called electroporation[11].

NovoCure's Tumor treating electric fields (*TTFields*)

NovoCure has shown[12] that when properly tuned, very low intensity, intermediate frequency electric fields (TTFields) stunt the growth of tumor cells. This inhibitory effect was demonstrated in all proliferating cell types tested, whereas, non-proliferating cells and tissues were unaffected. Interestingly, different cell types showed specific intensity and frequency dependences of TTField inhibition. It has been shown that two main processes occur at the cellular level during exposure to TTFields: arrest of proliferation and dividing cell destruction. The damage caused by TTFields to these replicating cells was dependent on the orientation of the division process in relation to the field vectors, indicating that this effect is non-thermal. Indeed, temperature measurements made within culture dishes during treatment and on the skin above treated tumors in-vivo, showed no significant elevation in temperature compared to control cultures/mice. Also, TTFields caused the dividing cells to orient in the direction of the applied field in a manner similar to that described in cultured human corneal epithelial cells exposed to constant electric fields[13]. At the sub-cellular level it was found that TTFields disrupt the normal polymerization-depolymerization process of microtubules during mitosis. Indeed, the described abnormal mitotic configurations seen after exposure to TTFields are similar to the morphological abnormalities seen in cells treated with agents that interfere directly[14,15] or indirectly[16-18] with microtubule polymerization (e.g., Taxol).

Modeling the mechanism of action of *TTFields*

In order to explain how TTFields cause orientation dependent damage to dividing cells and disrupt the proper formation of the mitotic spindle NovoCure modeled the forces exerted by TTFields on intracellular charges and polar particles using finite element simulations. Two main mechanisms by means of which the electric fields may affect dividing cells were recognized. The first relates to the field effect on polar macromolecule orientation. Within this framework, during the early phases of mitosis, i.e., in pre-telophase, when tubulin polymerization-depolymerization drives the proliferation process, the electric field forces any tubulin dimers, positioned further than 14nm away from the growing end of a microtubule, to orient in the direction of the field. This force moment, (10^{-5} pN) acting on the dimers, is sufficient to interfere with the proper process of assembly and disassembly of microtubules that is essential for chromosome alignment and separation[19]. This effect can explain the mitotic arrest of TTField treated cells[20].

The second mechanism, which interferes with cell division, and is most likely to play an important role in cell destruction, becomes dominant during cleavage. As seen in simulations, the electric field within quiescent cells is homogenous, whereas the field inside mitotic cells, during cytokinesis, is not homogenous. An increased field line concentration (indicating increased field intensity) is seen at the furrow, a phenomenon that highly resembles the focusing of a light beam by a lens. This in-homogeneity in field intensity exerts a unidirectional electric force, on all intracellular charged and polar entities (including induced dipoles), pulling them towards the furrow (regardless of field polarity). For example, for a cleavage furrow that reached a diameter of 1μm in an external field of only 1 V/cm, the force exerted on the microtubules is in the order of 5pN. This magnitude is compatible with the reported forces necessary to stall microtubule polymerization which is 4.3 pN[21]. With regards to other particles, such as cytoplasmatic organelles, they are polarized by the field within dividing cells. Once polarized, the forces acting on such particles may reach values up to an order of 60 pN resulting in their movement towards

the furrow at velocities that may approach 0.03 μm/sec. At such velocity, cytoplasmatic organelles would pile up at the cleavage furrow within a few minutes, interfering with cytokinesis and possibly leading to cell destruction. It has also been found that the electric forces acting on intracellular particles are maximal when the axis of division is aligned with the external field. This is consistent with the dependence of the destructive effect of TTFields on the angle between division axis and the field, as demonstrated experimentally. In addition, the calculated dependence of the magnitude of this force on frequency is consistent with the experimentally determined frequency dependence of the inhibitory effect of TTFields on melanoma and glioma cell proliferation (120 kHz vs. 200 kHz, respectively).

In Vivo effects of TTFields

NovoCure has shown[22] that TTFields can be applied effectively to animals through electrodes placed on the surface of the body. Using a special type of electrically insulated electrodes, significant inhibition of the growth of both intradermal melanoma (B16F1) in mice and intracranial glioma (F-98) in rats was seen after less then one week of treatment. This growth inhibition was accompanied by a decrease in angiogenesis within the tumor, due to inhibition of endothelial cell proliferation.

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

Secondly, the anti-mitotic effect of TTFields might be expected to damage the replication of rapidly dividing normal cells within the body (bone marrow, small intestine mucosa). Surprisingly, no treatment related toxicities were found in any of the animal safety trials performed by NovoCure, even when field intensities 3 fold higher than the effective anti-tumoral dose were used. The lack of damage to intestinal mucosa in TTField-treated animals is probably a reflection of the fact that the small intestine mucosal cells have a slower replication cycle than neoplastic cells and that the intestine itself most likely changes its orientation in relation to the applied field quite often, lowering the efficacy of TTField mediated mitotic disruption. Bone marrow, on the other hand, is naturally protected from TTFields by the high electric resistance of both bone and bone marrow compared to most other tissues in the body. To test the later assumption, the TTField intensity within the bone marrow of a long bone was modeled using the finite element mesh (FEM) method. It was found that the intensity of TTFields was 100-fold lower within the bone marrow compared to the surrounding tissues (including within solid tumors). Thus, hematopoietic cell replication should not be affected even when TTField intensities 10-fold higher than necessary to inhibit tumor growth are applied.

The NovoTTF-100A Device

The NovoTTF-100A device is a portable battery operated device which produces TTFields within the human body by means of surface electrodes. The TTFields are applied to the patient by means of surface electrodes that are electrically insulated, so that resistively coupled electric currents are not delivered to the patient. The electrodes, which incorporate a layer of adhesive hydrogel and a layer of hypoallergenic medical tape, are placed on the patient's shaved head. The electrodes must be replaced every three to four days and the scalp re-shaved in order to maintain optimal capacitative coupling between the electrodes and the patient head. All the treatment parameters are pre-set by NovoCure so there are no electrical output adjustments available to the patient. The patient must learn to change and recharge depleted device batteries and to connect to an external battery pack overnight.

Effect of NovoTTF-100A on newly diagnosed GBM patients – clinical pilot study

A pilot study was performed so far on ten newly diagnosed GBM patients treated with the NovoTTF-100A device. All patients underwent surgery and radiotherapy for the primary tumor. All patients received Temozolomide as adjuvant chemotherapy, in addition to NovoTTF-100A treatment.

All patients were treated with multiple four-week treatment courses using continuous, 24-hour a day, 200 kHz, 0.7 V/cm TTFields. TTFields were applied through two sets of opposing insulated electrode arrays and alternated at a 1 second duty cycle between two perpendicular field directions through the tumor. Patients completed between 1 and 17 treatment courses leading to maximal treatment duration of 16.5 months. Overall, more than 96, 4 week treatment courses were completed to date (> 9.6 courses per patient on average).

The treatment was well tolerated with no treatment related serious adverse events seen in any of the patients. Patients received treatment on average about 80% of the scheduled time. Considering the continuous nature of NovoTTF treatment (i.e., 24 hours a day for many months) this figure indicates that compliance with treatment was very high, with patients taking very few days off treatment and stopping only for short periods of time during treatment for personal needs.

Mild to moderate contact dermatitis appeared beneath the electrode gel in all patients during treatment. In most cases this dermatitis appeared for the first time during the second treatment course. The skin reaction improved with use of topical corticosteroids. Regular relocation of the electrode arrays was necessary in order to allow for continuous treatment.

The median progression free survival (PFS) of the patients in this study exceeded concurrent and historical controls[23] dramatically (greater than 18 months versus 7.1 months, respectively). So far 2 of the 10 patients have died. The remaining 8 patients are still alive and 5 of them are progression free. Median overall survival from diagnosis is greater than 26 months at the moment (compared to 14.6 months in historical controls[23]).

Although the number of patients in this pilot trial is small, the excellent safety profile of this treatment modality and the highly promising efficacy data gathered so far indicate the

potential of NovoTTF-100A treatment as an effective therapy for newly diagnosed GBM patients.

Effect of NovoTTF-100A on recurrent GBM patients – clinical pilot study

A pilot study was performed on ten recurrent GBM patients treated with the NovoTTF-100A device. All patients underwent surgery and radiotherapy for the primary tumor. Only 1 patient was chemotherapy naïve, the rest having received either Temozolomide or other chemotherapeutic agents, as adjuvant treatment, prior to recurrence.

All patients were treated with multiple four-week treatment courses using continuous, 24-hour a day, 200 kHz, 0.7 V/cm TTFields. TTFields were applied through two sets of opposing insulated electrode arrays and alternated at a 1 second duty cycle between two perpendicular field directions through the tumor. Patients completed between 1 and 15 treatment courses leading to maximal treatment duration of 14.5 months. Overall, more than 70, 4 week treatment courses were completed to date (> 7 courses per patient on average).

The treatment was well tolerated with no treatment related serious adverse events seen in any of the patients. Patients received treatment on average about three quarters of the scheduled time. Considering the continuous nature of NovoTTF treatment (i.e., 24 hours a day for many months) this figure indicates that compliance with treatment was very high, with patients taking very few days off treatment and stopping only for short periods of time during treatment for personal needs.

Mild to moderate contact dermatitis appeared beneath the electrode gel in 8 of the 10 patients during treatment. In most cases this dermatitis appeared for the first time during the second treatment course. The skin reaction improved with use of topical corticosteroids. Regular relocation of the electrode arrays was necessary in order to allow for continuous treatment.

The median progression free survival (PFS) of the patients in this study exceeded historical controls[2] dramatically (26.1 weeks versus 9 weeks, respectively). The PFS at 6 months (PFS6) was 50% compared to 15% in historical controls[2]. So far 7 of the 10 patients have died. The remaining 3 patients are still alive and 2 of them are progression free. Median overall survival was 62 weeks. Response rate was 25% (1 CR + 1 PR) and only two patients had progressive disease despite treatment.

Effect of NovoTTF-100A on recurrent GBM patients – Pivotal study

In a prospective, randomized, open label, active parallel control trial to compare the effectiveness and safety outcomes of recurrent GBM subjects treated with NovoTTF-100A (n=120) to those treated with an effective best standard of care chemotherapy (including bevacizumab; n=117), NovoTTF-100A subjects had comparable overall survival to subjects receiving the best available chemotherapy in the US today (OS 6.3 vs. 6.4 months; HR 1.0; p=0.98). Similar results showing comparability of NovoTTF-100A to BSC chemotherapy were seen in all secondary endpoints (e.g., PFS6 = 21.4% for NovoTTF-100A vs. 15.2% for chemotherapy).

NovoTTF-100A subjects experienced fewer adverse events in general, significantly fewer treatment related adverse events, and significantly lower gastrointestinal, hematological and infectious adverse events compared to BSC controls. The only device-related adverse events seen were a mild to moderate skin irritation beneath the device electrodes, which was easily treated with topical ointments. Finally, quality of life measures were better in NovoTTF-100A subjects as a group when compared to subjects receiving effective best standard of care chemotherapy.

Effect of NovoTTF-100A on patients with locally advanced and/or metastatic solid tumors – a phase I study

Six patients with locally advanced or metastatic solid tumors were treated so far with the NovoTTF-100A device in this study. The first two patients, who suffered from metastatic skin lesions, were treated for two weeks using 100 kHz TTFields. The third patient, who suffered from an advanced pleural mesothelioma, was treated for four weeks using 120 kHz TTFields. The fourth patient, who also suffered from metastatic skin lesions, was treated continuously for 4 weeks using 100 kHz TTFields. The fifth patient having a rapidly progressive GBM was treated for four weeks using 200 kHz, 3 directional fields. Finally, the sixth patient who also had metastatic skin tumors was treated for six weeks using 100 kHz TTFields until systemic progression.

The treatment was well tolerated with no treatment related serious adverse events in any patient. Two patients developed mild skin reactions to the electrode hydrogel and the medical grade plasters used to fix the electrodes to the torso. All other adverse events were related either to concomitant medication or disease progression.

In the first two patients, previously progressive lesions were stabilized for two to three weeks and then resumed growth. In the third patient, local minimal regression of the mesothelioma was seen in the treated area (the abdomen) while in the chest and pelvis the disease was stable and progressive, respectively. The fourth patient showed a partial response to treatment with a 51% decrease in tumor area after 4 weeks of treatment. The fifth patient progressed during treatment. Finally, the sixth patient showed a 20% decrease in tumor size before systemic progression occurred.

These results indicate the complete lack of systemic toxicity of NovoTTF-100A treatment when applied to the head, chest, abdomen, and limbs of advanced cancer patients. In addition, promising initial efficacy results were observed in these patients.

IV. STUDY DESIGN

A prospective, randomly controlled pivotal study will be conducted on 700 patients (randomized at a 2:1 ratio in favor of the NovoTTF-100A group) with tissue diagnosis of GBM who have completed radiation therapy together with adjuvant Temozolomide. The control group will receive standard Temozolomide maintenance therapy. The primary endpoint will be progression free survival (PFS). The sample size was chosen based on the log-rank test comparing time to event (i.e., progression or death prior to progression) assuming patients treated with the NovoTTF-100A together with maintenance Temozolomide will have a median PFS significantly greater than controls (9 months compared to 7 months, respectively; with an overall 5% 2-sided type I error and 80% power). This sample size also has adequate power (80%) to detect a minimum of 4.5 month increase in median overall survival in NovoTTF-100A treated patients compared with control patients (expected control group median OS = 14.6 months, Stupp et al, NEJM 2005).

The following will be considered disease progression for determination of PFS (based on the Macdonald criteria; Tab D):

1. Tumor growth > 25% compared to the smallest tumor area measured in this patient during the trial.
2. Appearance of 1 or more new tumors in the brain (diagnosed radiologically as GBM).

Final determination of progression will be made by CORE radiology review, in cases where an MRI is available (which should be the great majority of cases). In cases where an MRI is not available, clinical progression will be diagnosed according to the following criteria:

1. Decline in functional status as indicated by a decrease in KPS of > 10, and
2. Decline in neurological function as indicated by a decrease of 2 points or more in MRC scale (TAB H), and
3. ≥50% increase in steroid dose.

The determination of whether to stop treatment due to progression will be based on the investigator's evaluation of the patient's clinical condition. NovoTTF-100A treatment will be continued for 24 months or until second progression whichever occurs first unless the patient's clinical condition prohibits this. In the case of radiological progression based on local evaluation, Temozolomide treatment will be stopped and a second line treatment chosen instead. The following treatments or any combination of these treatments are considered second line therapy in this protocol:

1. Re-operation
2. Local radiation therapy (e.g. gamma knife)
3. Second line chemotherapy
4. Combination of the above.

Patients will be recruited to the study by the principal investigator (PI) or one of the co-investigators (CI) in up to 40 US centers and at up to 25 OUS centers . Immediately following screening, patients will be randomized at a 2:1 ratio to receive either NovoTTF-100A treatment together with maintenance Temozolomide or maintenance Temozolomide alone.

Patient accrual is expected to continue for 48 months. Patient follow-up for PFS and OS will continue for 18 months from accrual of the last patient.

Treatment arm

NovoTTF-100A treatment will be given together with maintenance Temozolomide (according to the standard maintenance dosing described below in section XII). At treatment initiation patients will be seen at an outpatient clinic. During this visit baseline examinations will be performed and NovoTTF-100A treatment will be initiated. The patients will also be instructed on the operation of the NovoTTF-100A and battery replacement. Once the patients are trained in operating the device they will be released to continue treatment at home. The patients will receive multiple 1 month courses of continuous NovoTTF-100A treatment. NovoTTF-100A treatment will be stopped in the following cases:

1. The occurrence of device related serious adverse events
2. Clinical and functional deterioration considered by the investigator to be prohibitive of continuing treatment.
3. After 24 months or after second progression whichever occurs first.

Treatment with the NovoTTF-100A device does not need to be terminated in the following situations:

1. Toxicity due to Temozolomide treatment
2. Radiological progression alone will not lead to termination of NovoTTF-100A treatment, but to replacement of the Temozolomide treatment with best standard of care second line therapy:
    a. Re-operation
    b. Local radiation therapy (e.g., gamma knife)
    c. Second line chemotherapy
    d. Combination of the above.

Control arm

Patients will be treated with maintenance Temozolomide according to the standard dosing regimen described below in section IX. Following radiological progression or unacceptable toxicity, Temozolomide will be replaced with best standard of care second line therapy:

a. Re-operation
b. Local radiation therapy (e.g., gamma knife)
c. Second line chemotherapy
d. Combination of the above

Follow-up Evaluations

As long as the patients are receiving any treatment (NovoTTF-100A or chemotherapy), all patients will be seen once every month at an outpatient clinic where they will undergo medical follow-up and routine laboratory exams (see Tab A). An MRI will be performed every second month following the baseline MRI until second progression (when treatment on both arms of the study will be terminated). In the case of clinical progression an unscheduled MRI

will be obtained within 1 week of the investigator becoming aware of the clinical progression. No additional MRIs will be required after second progression. Central MRI review will be performed by a neuro-radiologist blinded to the treatment group of each patient. Medical follow-up will continue for 2 months after treatment termination in order to capture treatment related toxicities. After these visits, mortality will be assessed based on monthly telephone interviews with the patients or the patients' caregivers.

Core MRI review

All MRI's will be sent to an independent radiologist, blinded to the treatment groups of the patients. Either digital (DICOM) images or analog films can be used for this purpose. Contrast agent and dose per body weight must be kept constant between scans for each patient.

V. CRITERIA FOR PATIENT ELIGIBILITY

Any patient with a histological diagnosis of GBM who meets all of the specific eligibility criteria listed below may by enrolled on this study. Operable patients must undergo surgery prior to randomization. All patients must have received maximal radiation therapy with concomitant Temozolomide prior to randomization. Patients receiving steroids to control edema may be included in the trial; however, any change in steroid dose must be documented during the follow-up visits. An increase in steroid dose will preclude a diagnosis of partial or complete response (as suggested by Macdonald et al; TAB D). Disease status will be determined by comparing screening MRI to the immediate post-surgical MRI. If unavailable, an immediate post-surgical CT can be used for the same purpose. Patients who have progressive disease at screening (compared to the immediate post-surgical MRI) are not candidates for this study. In the case of local radiological suspicion of pseudoprogression a PET scan or other imaging modality (in addition to T1 weighted MRI) will be obtained to assess biological activity of the tumor.

1) PATIENT INCLUSION CRITERIA:

a. Pathological evidence of GBM using WHO classification criteria.
b. ≥ 18 years of age.
c. Received maximal debulking surgery and radiotherapy concomitant with Temozolomide (45-70Gy):
    1. Patients may enroll in the study if received Gliadel wafers before entering the trial
    2. Any additional treatments received prior to enrollment will be considered an exclusion.
    3. Minimal dose for concomitant radiotherapy is 45 Gy
d. Karnofsky scale ≥ 70
e. Life expectancy at least 3 months
f. Participants of childbearing age must use effective contraception.
g. All patients must sign written informed consent.
h. Treatment start date at least 4 weeks out from surgery.
i. Treatment start date at least 4 weeks out but not more than 7 weeks from the later of last dose of concomitant Temozolomide or radiotherapy.

2) PATIENT EXCLUSION CRITERIA:

a. Progressive disease (according to MacDonald Criteria). If pseudoprogression is suspected, additional imaging studies must be performed to rule out true progression.
b. Actively participating in another clinical treatment trial
c. Pregnant
d. Significant co-morbidities at baseline which would prevent maintenance Temozolomide treatment:
    1. Thrombocytopenia (platelet count < 100 x $10^3/\mu L$)
    2. Neutropenia (absolute neutrophil count < 1.5 x $10^3/\mu L$)
    3. CTC grade 4 non-hematological Toxicity (except for alopecia, nausea, vomiting)
    4. Significant liver function impairment - AST or ALT > 3 times the upper limit of normal
    5. Total bilirubin > upper limit of normal
    6. Significant renal impairment (serum creatinine > 1.7 mg/dL)
e. Implanted pacemaker, programmable shunts, defibrillator, deep brain stimulator, other implanted electronic devices in the brain, or documented clinically significant arrhythmias.
f. Infra-tentorial tumor
g. Evidence of increased intracranial pressure (midline shift > 5mm, clinically significant papilledema, vomiting and nausea or reduced level of consciousness)
h. History of hypersensitivity reaction to Temozolomide or a history of hypersensitivity to DTIC.

VI. RECRUITMENT PLAN

Patients will be recruited to this study from either the outpatient clinic or inpatient hospital setting at each center. All patients will be seen by the corresponding investigator. Every effort will be made to encourage eligible women and minorities to participate. All patients will be required to sign a written informed consent prior to being registered on this protocol. Every effort will be made to answer questions raised by the patient and their family or advocate regarding the protocol and alternative therapies prior to asking the patient to sign the consent form.

VII. RANDOMIZATION

Patients who meet the above inclusion/exclusion criteria will be randomized at a 2:1 ratio either to the treatment group who will receive NovoTTF-100A treatment together with maintenance Temozolomide, or to the control group who will receive maintenance Temozolomide alone. Randomization will be performed centrally and not within in each center to allow for the following stratifications:

a. Extent of Resection – Biopsy; Partial Resection; Gross total resection (only if immediate post surgical MRI is available)

b. MGMT (O^6-benzylguanine, O^6BG) methylation status – Positive, Negative, Unknown

Randomization will be performed with randomly varying block sizes (e.g., 3, 6, or 9 patients) within each stratum.

These classifications are expected to have a stronger impact on disease outcome than the treatment variability between centers, since standard of care for newly diagnosed GBM, worldwide, is based on the Stupp protocol.

VIII. PRE-TREATMENT EVALUATION (SCREENING AND BASELINE) (TAB A)

Within one week prior to beginning treatment all patients will undergo the following studies:

- Baseline contrast enhanced MRI of the brain (within 2 weeks of beginning treatment).
- Complete physical examination
- Neurological status and KPS (Karnofsky performance scale).
- Complete blood count (CBC) and differential
- Biochemistry panel (Electrolytes, BUN, creatinine, bilirubin, liver enzymes, albumin, total protein, glucose, cholesterol)
- Coagulation study (PTT, INR)
- Quality of life questionnaire (EORTC QLQ-C30)
- MMSE

IX. TREATMENT PLAN – NOVOTTF-100A+TEMOZOLOMIDE GROUP

All patients will begin treatment with temozolomide and NovoTTF-100A within 1 week from screening/baseline evaluation, and no later than 7 weeks from last dose of concomitant temozolomide or radiation therapy (the latter of the two).

a. Maintenance Temozolomide treatment

Maintenance Phase Cycle 1: Approximately four weeks after completing the Temozolomide + RT phase, Temozolomide is administered for an additional 6 cycles of maintenance treatment. Dosage in Cycle 1 (maintenance) is 150 mg/m^2 once daily for 5 days followed by 23 days without treatment.

Cycles 2-6: At the start of Cycle 2, the dose is escalated to 200 mg/m^2, if the CTC non-hematologic toxicity for Cycle 1 is Grade ≤ 2 (except for alopecia, nausea and vomiting), absolute neutrophil count (ANC) is $\geq 1.5 \times 10^9/L$, and the platelet count is $\geq 100 \times 10^9/L$. The dose remains at 200 mg/m^2 per day for the first 5 days of each subsequent cycle except if toxicity occurs. If the dose was not escalated at Cycle 2, escalation should not be done in subsequent cycles.

Patients who completed all 6 cycles of maintenance temozolomide will be treated per investigator discretion, concomitant with the TTF treatment, until second progression.

Temozolomide dose reduction or discontinuation during maintenance:

Dose reductions during the maintenance phase should be applied according to Tables 1 and 2 below. During treatment a complete blood count should be obtained on day 22 (21 days after the first dose of Temozolomide) or within 48 hours of that day, and weekly until the ANC is above 1.5 x 10^9/L (1,500/µL) and the platelet count exceeds 100 x 10^9/L (100,000/µL). The next cycle of Temozolomide should not be started until the ANC and platelet count exceed these levels. Dose reductions during the next cycle should be based on the lowest blood counts and worst non-hematologic toxicity during the previous cycle. Dose reductions or discontinuations during the maintenance phase should be applied according to tables 1 and 2.

Table 1 Temozolomide Dose Levels for Maintenance Treatment

Dose Level	Dose (mg/m^2/day)	Remarks
–1	100	Reduction for prior toxicity
0	150	Dose during Cycle 1
1	200	Dose during Cycles 2-6 in absence of toxicity

Table 2 Temozolomide Dose Reduction or Discontinuation During Maintenance Treatment

Toxicity	Reduce TMZ by 1 Dose Level[a]	Discontinue TMZ
Absolute Neutrophil Count	<1.0 x 10^9/L	See footnote b
Platelet Count	<50 x 10^9/L	See footnote b
CTC Non-hematological Toxicity (except for alopecia, nausea, vomiting)	CTC Grade 3	CTC Grade 4[b]

[a]: TMZ dose levels are listed in table 1.
[b]: TMZ is to be discontinued if dose reduction to <100 mg/m2 is required or if the same Grade 3 non-hematological toxicity (except for alopecia, nausea, vomiting) recurs after dose reduction.
TMZ = Temozolomide; CTC = Common Toxicity Criteria.

Treatment after Temozolomide discontinuation:

Following Temozolomide discontinuation due to toxicity or radiological disease progression (based on local interpretation of MRI), patients in both arms will be offered second line therapy for their disease. The following treatment options will be chosen from based on the patient's clinical condition:

1. Re-operation (NovoTTF-100A treatment will be interrupted for at least 2 weeks after reoperation or until wound healing).
2. Local radiation therapy (e.g., gamma knife)
3. Second line chemotherapy
4. Combination of the above

TTF treatment will continue concomitantly with second line treatments until second disease progression for NovoTTF-100A + temozolomide arm patients.

b. NovoTTF Treatment

The NovoTTF-100A treatment will be initiated in an outpatient clinic by the investigator at each center. In addition to clinical evaluation (as elaborated in section VIII), the investigator will perform the following actions for the treatment arm patients:

- Train the patient in using the device:
  - Battery replacement and recharging
  - Turning the device on and off
  - Disconnecting and reconnecting the electrodes from the device for personal needs
  - How to handle device error messages (see trouble shooting section in User manual)
  - What adverse events can be expected during the treatment.
  - How to handle irritated skin
  - What to do in case of new or worsening clinical signs (call investigator)
- Review of the baseline MRI and decide where to place the electrodes (according to the guidelines elaborated in section X below).
- Shave the patients scalp (can be performed by other medical staff in the hospital or by a barber prior to coming to the hospital)
- Place the electrodes
- Connect the electrodes to the device (through the connection cable)
- Turn on the device

The device will be set in advance by a device technician with the following treatment parameters:

- Frequency – 200 kHz
- Output current – 707 mA RMS
- Number of field directions – 2
- Duty cycle – 1 sec in each direction

The patients will continue treatment at home after being trained in device use.

The treatment group patients will receive multiple 1 month courses of continuous NovoTTF-100A treatment together with standard maintenance Temozolomide. The decision to

add each additional treatment course will depend on the lack of treatment related serious adverse events which reappear upon re-challenge and lack of clinical disease progression. After initiation of treatment, maintenance of NovoTTF-100A treatment will be performed by technicians trained by the sponsor. All technical aspects of the treatment are handled by these technicians at technical clinics or at the patients' homes. Technical clinics are situated in close proximity to each center. Patients in the treatment arm will visit these clinics for treatment maintenance, technical support and assistance in electrode replacement. The following actions are performed by the technician:

- Periodic electrode replacement (twice per week) – patients will come to technical clinics for this purpose or be trained to replace electrodes independently. Electrodes will be placed in the same locations every time, according to the locations originally decided upon by the investigator unless the patient experiences skin irritation, in which case, they are alternated (see Section XI below).
- Periodic download of device log (once every 2 weeks)
- Replacement of faulty equipment
- Device, electrode and accessory accountability tracking, and requests for replacements from NovoCure
- Problem solving – by phone between visits to the technical clinic or directly during these visits
- For technical support the patient will contact the local technical clinic. A list of clinics and their contact information will be supplied to the patients separately. If the patient is unable to get a hold of the local device technician or if the patient has technical problems with the device beyond working hours he/she should call the following Toll free number for NovoCure's international support center: 011 - 800 NOVOCURE (for USA) and 00 - 800 – NOVOCURE (for Europe)

During NovoTTF-100A treatment the patient will be permitted to interrupt treatment for periods of up to an hour twice a day for personal needs. Any pause in treatment beyond this must be coordinated in advance with the principal investigator or one of the co-investigators. Patients will be allowed an additional 1-3 days off treatment between courses according to personal needs.

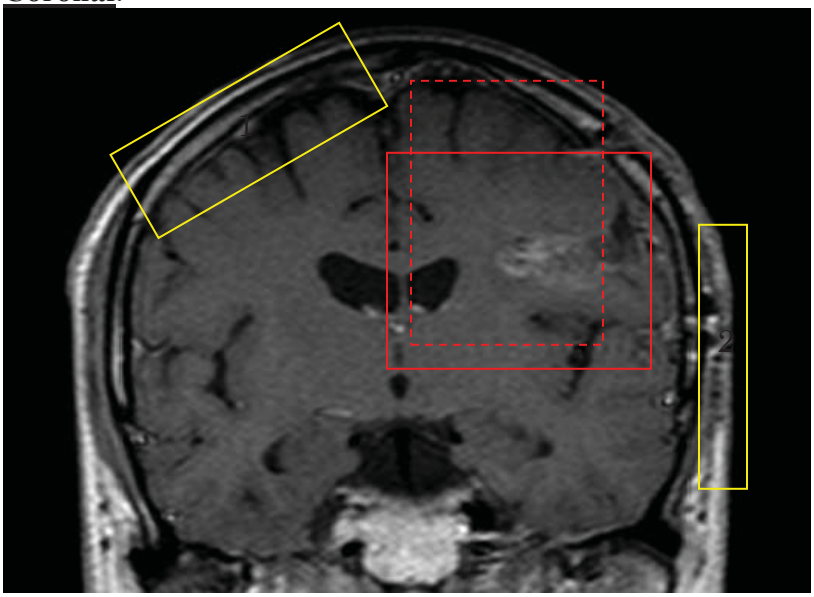
Once every month from baseline, until treatment termination, all patients will report to an outpatient clinic where they will be assessed clinically and undergo routine laboratory examinations. The follow-up window for these visits is +/- 7 days if the visit occurs prior to the 6 month follow-up window and +/- 14 days on or after the 6 month visit window. Follow up window from the 12 month visit onward will be +/- 1 month. During these visits the investigator will remove the electrodes and examine the skin beneath them. Electrode replacement will be performed at the local technical clinic or at the patient's home after the follow-up visit. Medical follow-up and routine laboratory exams for all patients will continue once per month for 2 months following end of treatment. After this post-progression follow up period, patients will be followed by monthly telephone interview until death.

X. ELECTRODE PLACEMENT PROTOCOL:

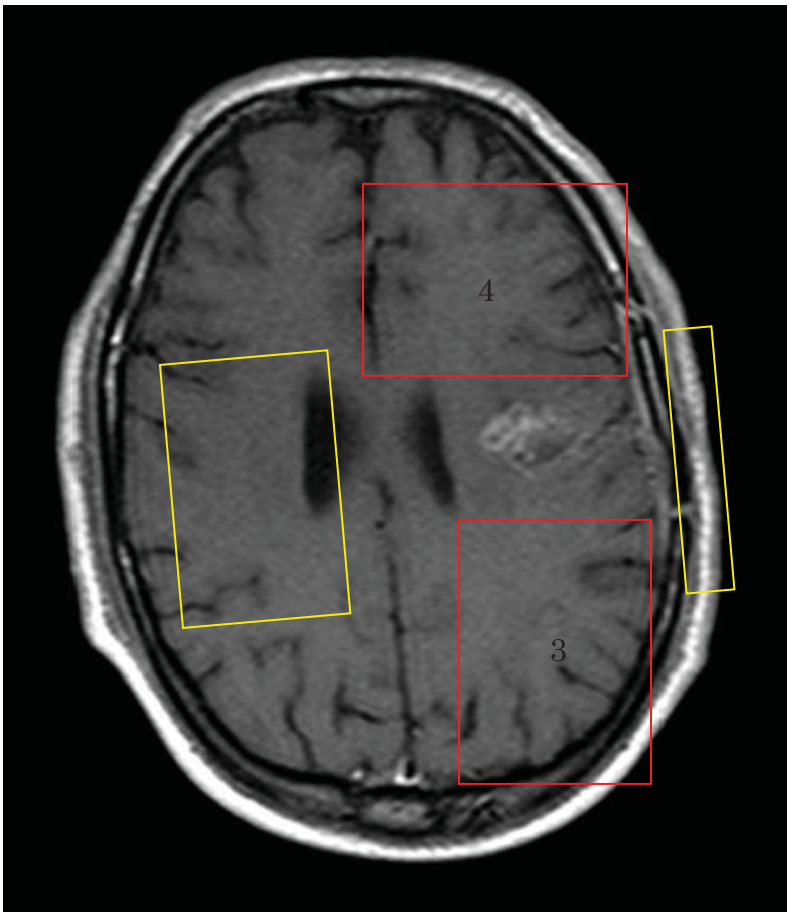
The specific locations of each electrode set will be approved by the treating investigator and determined according to tumor location as follows: the electrode locations will be determined so as to minimize the distance between each electrode set and the center of the tumor, while maintaining a distance of at least one tumor diameter between the electrode sets. This means that the closer the tumor is to the calvarium, the closer the electrode sets will be to each other, and the closer the tumor is to the center of the brain, the further the electrode sets will be from each other. At all times a right angle will be maintained between the imaginary lines connecting each pair of electrode sets. If needed, adjustments to electrode placement will be made following first progression.

{Example: Direction 1 = set 1 versus set 2; Direction 2 = set 3 versus set 4}

Coronal:



Horizontal:



XI. EVALUATION DURING NOVOTTF-100A TREATMENT

During electrode replacement, the skin below the electrode will be inspected by the physician (during follow up visits) and by the patient himself or herself (at home or technical center). In the event of significant skin breakdown (leading to pain or bleeding) or evidence of infection, the electrode will be moved to an alternate site. Skin breakdown and/or infection will be treated according to the treating physician's clinical judgment based on a dermatologist's recommendation. Skin breakdown or evidence of infection, either of which requires a break in NovoTTF-100A treatment greater than 3 days, will be captured as an Adverse Event. Mild to moderate contact dermatitis is expected to appear beneath the electrode gel during the first or second treatment course. This condition will be treated as follows:

1. Electrode location will be shifted between two alternate sites at every electrode change.
2. If skin is inflamed – apply 0.1% hydrocortisone ointment.
3. If skin is breached (abrasions, micro-ulcerations, oozing, open sores) or infected – Discontinue hydrocortisone and prescribe a Mupiricin (e.g. Bactroban) ointment.
4. In the case of skin blistering – apply Silver Sulfadiazine (e.g. Silverdine ointment). In the case of known hypersensitivity to sulfa containing compounds the treatment outlined will not be offered and a dermatologist will be consulted.
5. In any case where the patient does not notice an improvement in skin sores, infection or blistering within 2 weeks of starting one of the treatments outlined above, the patient will inform the investigator and a dermatological consult will be obtained.
6. Oral antihistamines and analgesics will be prescribed at the investigators' discretion to control pruritus and pain.

XII. TREATMENT PLAN – MAINTENANCE TEMOZOLOMIDE

Patients randomized to the control group will be treated with maintenance Temozolomide as described above (see IX a.). Treatment will start within 1 week from screening/baseline evaluation, and no later than 7 weeks from last dose of concomitant temozolomide or radiation therapy (the latter of the two).

XIII. PERIODIC EVALUATION UNTIL TREATMENT TERMINATION

Patients in both groups will undergo the following studies or review every month until treatment termination:

- Physical examination
- Neurological status
- Quality of life questionnaire (EORTC QLQ-C30) – every three months until treatment termination
- Blood exams (CBC, Chemistry, Coagulation – for patients receiving anti-coagulants)
- Steroid dose
- Record of Adverse Events
- Mini Mental State Exam (MMSE)

The patients will have a contrast MRI of the head performed after every two months until second progression. In case of clinical progression an MRI will be performed within a week. Contrast agent type and dose will be kept constant for each patient between scans. Central MRI review will be performed by a neuro-radiologist blinded to the treatment group of each patient.

XIV. POST-TREATMENT EVALUATION

Treatment will continue according to the protocol until second progression or 24 months (the earlier of the two). After treatment termination the patient will be seen at an outpatient clinic every month for two additional visits. Physical and neurological examination, blood tests (CBC and Chemistry panel) will be performed during these visits. Patient mortality and adverse events will be documented on the case report forms. After the two post treatment monthly follow up visits, patients will not be required to return to the clinic for follow-up but will be followed monthly until death by telephone to monitor their status.

XV. MGMT METHYLATION STATUS ASSESSMENT

MGMT methylation - will be assessed by polymerase chain reaction (PCR) methylation status of the promoter region of MGMT.

Randomization will be stratified according to MGMT methylation status based on local analysis performed at institutions where this examination of brain tissue is performed as a standard examination for all GBM patients.

All patients with paraffin embedded brain tissue available for additional analysis will have MGMT methylation status assessed by a central laboratory (blinded to the treatment group of the patients).

Methylation status will be adjusted for during final analysis as a covariate (see statistical analysis section).

The following materials will be required for tissue evaluation:

- Representative tissue blocks that contain diagnostic tumor. A block that, when sectioned, yields at least 1 square centimeter of viable tumor must be present on the H&E slide.
- An accompanying H&E section.
- A Pathology Report documenting that the submitted material contains tumor; the report must include the protocol number, patient case number, and the patient's initials. The patient's name and/or other identifying information should be removed from the report.
- A Specimen Transmittal Form listing pathology materials being submitted for Central Tissue Evaluation must be included in the pathology submission.

All samples will be sent for Central PCR Analysis of MGMT methylation status at

MDxHealth Inc.
US Office
2505 Meridian Parkway
Suite 310
Durham, NC 27713

Belgium Office
Tour 5 GIGA niveau +3
Av. de l'Hopital 11
4000 Liege

Reimbursement

The sponsor will reimburse pathologists from submitting institutions on a per case basis if a block or core of material is submitted.

XVI. ADDITIONAL TUMOR GENETIC ASSESSMENTS

In addition to MGMT, all patients with paraffin embedded brain tissue available for additional analysis, recruited to the trial after approval of Version 2.0 of this protocol, will also have the following genetic analyses of their tumor tissue performed and the results correlated with OS results in the final analysis:

- EGFR amplification, over expression or rearrangement
- Chromosomes 1p/19q deletion status
- IDH1 mutation

XVII. POTENTIAL ADVERSE EFFECTS

Treatment with the NovoTTF-100A is not expected to cause any serious side effects. However, it is possible that investigational treatment will cause any of the following:

- Local warmth and tingling sensation beneath the electrodes
- Allergic reaction to the plaster or to the gel
- Skin breakdown
- Infection at the sites of electrode contact with the skin
- Electrode overheating leading to pain and/or local skin burns
- Headache
- Fatigue
- Seizures

Treatment with temozolomide commonly (>20%) causes the following adverse events:

- Leukopenia
- Headache
- Fatigue
- Nausea
- Vomiting or Constipation

Adverse events and complications associated with the underlying GBM disease process, which are unlikely but unknown if related to treatment with NovoTTF-100A together with maintenance Temozolomide include the following adverse events:

- Seizure, including Status Epilepticus
- Neurological and functional decline
- Headaches, nausea and/or vomiting
- Death

XVIII. ADVERSE EVENT REPORTING

Definition of Adverse Events

As defined by the ICH Guidelines for Good Clinical Practice E2A (CPMP/ICH/377/95), an adverse event (AE) is any untoward medical occurrence in a patient administered a medicinal product and which does not necessarily have to have a causal relationship with this treatment. An adverse event can therefore be any unfavorable and unintended sign (for example, an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to this medicinal product. Adverse events include the following:

- All suspected medication adverse reactions
- All reactions from medication overdose, abuse, withdrawal, sensitivity, or toxicity.
- Apparently unrelated illnesses, including the worsening of a preexisting illness
- Injury or accidents. Note that if a medical condition is known to have caused the injury or accident (a fall secondary to dizziness), the medical condition (dizziness) and the accident (fall) should be reported as 2 separate adverse events.
- Abnormalities in physiological testing or physical examination findings that require clinical intervention or further investigation (beyond ordering a repeat [confirmatory] test).
- Laboratory abnormalities that require clinical intervention or further investigation (beyond ordering a repeat [confirmatory] test) unless they are associated with an already reported clinical event. Laboratory abnormalities associated with a clinical event (elevated liver enzymes in a patient with jaundice) should be captured in the source documents.

Each adverse event is to be classified by the investigator as serious or non-serious. This classification of the gravity of the event determines the reporting procedures to be followed.

Grading of an Adverse Event

The descriptions and grading scales found in the revised NCI Common Toxicity Criteria (CTC) version 3.0 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	Transient or minimal symptoms, no change in activity or need for medication
MODERATE	Grade 2	Symptomatic change, interferes to some extent with patient's usual function
SEVERE	Grade 3	Incapacitating, significantly interferes with patient's usual function

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

Serious Adverse Events

An adverse event that meets one or more of the following criteria/outcomes is classified as serious:

Death
Life-threatening (i.e., at immediate risk of death)
Inpatient hospitalization or prolongation of existing hospitalization
Persistent or significant disability/incapacity
Congenital anomaly/birth defect

Important adverse events that may not result in death, may not be life-threatening, or do not require hospitalization may be considered serious when, based upon appropriate medical judgment, they may acutely jeopardize the patient without immediate medical intervention to prevent one of the outcomes listed above. Serious may also includes any other event that the investigator or company judges to be serious. In addition, sites are responsible for reporting serious adverse events to their local IRB/EC according to their institutional requirements. Death due to disease progression need not be reported to the study monitor. These SAEs will be captured in the CRFs as described for regular AEs.

Routine Adverse Event Reporting

All adverse events must be reported in the source documentation and CRFs with appropriate information, including severity and rating of causality to the study drug/treatment. Adequate source documentation must be available to characterize the severity, duration and causality of each reported adverse event.

Unanticipated Adverse Device Effect Event (UADE) Reporting

Any potential unanticipated adverse device effect (UADE) will be reported to the study monitor and local IRB/EC within 10 days of the investigator learning of the event. The medical monitor will investigate whether the adverse event is a UADE and, if so, report the UADE to the Sponsor, as soon as possible but no later than 3 days after first learning of the event. Expedited report for FDA submission and reporting to other IRBs/ECs to follow within 10 working days after first learning of the event by the medical monitor.

The report will contain the following:

- The initials of the subject, patient MRN #, protocol # and title
- The date the event occurred
- A description of the UADE
- An explanation of how the UADE was handled
- A description of the subject's condition
- Indication if the subject remains on the study
- Indication if the event is considered related to the NovoTTF-100A
- Indication if an amendment to the protocol and/or consent form is recommended as a result

Eliciting Adverse Event Information

The investigator is to report 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?"

Adverse Event Reporting Period

The adverse event reporting period will begin immediately following initiation of treatment with the NovoTTF-100A device or BSC chemotherapy. Adverse events will be collected for two months 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 CRFs, 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.

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.

XIX. STUDY OUTCOME MEASURES

1. Efficacy analysis:

a. Primary Endpoint

- The primary endpoint of the study will be progression free survival

b. Secondary Outcome Measures

- Overall survival time
- Progression free survival at 6 months (PFS6)
- One and two year survival rate (%1 and %2 year survival)
- Quality of life (EORTC QLQ-C30 questionnaire; TAB H)
- The radiological response of the tumor will be assessed by the MRI studies according to Macdonald criteria for progressive disease, stable disease, partial response or complete response (see TAB D). All patients will have their tumor measurements recorded at baseline and at the time of each MRI scan. Lesions must be measured in two dimensions. The dose and type of contrast agent must be held constant from scan to scan for each patient.

2. Safety analysis:

- Safety and tolerability of NovoTTF-100A treatment based on the incidence and severity of adverse events and toxicities. Toxicities will be assessed according to the "Common toxicity criteria (CTC), version 3.0" (see TAB B).

XX. CRITERIA FOR REMOVAL FROM STUDY

- 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 for the patient. Patient follow up will continue as for the control arm after such an event.
- The investigator may remove a patient from the study in case of not complying with study protocol.
- Patients will be able to withdraw from the trial at their own request.

XXI. STATISTICAL CONSIDERATIONS

A. Sample Size Calculation

Based on the insignificant side effects of NovoTTF-100A treatment observed in the pilot studies of newly diagnosed GBM performed so far in Europe and in the pivotal trial in recurrent GBM, we assume that any significant increase in progression free survival compared to the control group would justify use of the NovoTTF-100A device in newly diagnosed GBM patients, concomitant to maintenance Temozolomide.

The sample size of 700 patients (210 Control patients + 420 NovoTTF-100A patients + 10% loss to follow-up) was determined using NCSS/PASS11 software based on the log-rank test comparing time to event (i.e., progression or death prior to progression) between patients treated with the NovoTTF-100A together with maintenance Temozolomide and controls (maintenance Temozolomide alone). The null hypothesis is that the recurrence rate is the same in the two study groups, *i.e.*, hazard ratio=1. The alternative hypothesis is that the recurrence rate is not the same, *i.e.*, hazard ratio≠1. The expected hazard ratio was estimated from the expected median progression free survival in the two study groups as follows:

- Expected median progression free survival on control treatment is 7 months (see Stupp et al., NEJM, 2005[23] and Temozolomide package insert)
- Expected median progression free survival on NovoTTF-100A treatment is 9 months.
- Expected accrual time during which patients are recruited: 48 months
- Additional follow-up time after end of recruitment: 18 months.
- Ratio of control to experimental patients: 1:2
- Type I error: 0.05%; 2-sided
- Power: 80%

This sample size also has adequate power (80%) to detect a minimum of 4.5 month increase in median overall survival in NovoTTF-100A treated patients compared with control patients (who have an expected median OS of 14.6 months).

One interim analysis will be performed on the PFS and OS data available for the first 315 patients accrued with a minimum of 18 months follow up. The assumptions used in the sample size calculations will be evaluated at the interim analysis. If it appears that the event rate and/or the treatment effect may be smaller than expected, the company may request a sample size increase to achieve the desired study power. The company will not request a sample size decrease based on the results of this assessment.

B. Statistical analysis

1. The primary endpoint will be achieved if the progression free survival is significantly greater in the treatment group than in the control group. In order to allow for two analyses in the trial the alpha level used at each time point will be calculated according to

the Lan-DeMets method using the O'Brien and Fleming spending function[24,25] (approximately 0.01394 at the interim analysis and 0.04574 at the final analysis).

2. The primary analysis will be an intent-to-treat (ITT) analysis including all randomized patients according to their assigned treatment. For analysis of progression free survival, patients will be censored at the time that they are last known to be alive and recurrence free (if withdrawn or lost to follow-up) or at study closeout. For patients without any follow-up data, a sensitivity analysis will be performed that will include various imputation methods, such as treating all missing data as failures, treating all missing data as successes, treating all missing data in the treatment group as failures but all successes in the control group ("Worst Case") and treating all missing data in the control group as failures but all successes in the treatment group ("Best Case"). Baseline characteristics of patients who withdraw or are lost to follow-up will be compared with patients who remain in the study to evaluate the potential for informative censoring. A sensitivity analysis will be conducted to evaluate the assumption for interval censoring (i.e., event time is assumed at the time of the visit). A sensitivity analysis will also be conducted excluding patients without MRI documented disease progression

3. Secondary analyses will be performed based on the per protocol population. The specific tests to be used for secondary outcome measures are described below:
    - Overall survival time – This endpoint will be achieved if the overall survival is significantly greater in the treatment group than in the control group using a log-rank test. In order to allow for two analyses in the trial the alpha level used at each time point will be calculated according to the Lan-DeMets method using the O'Brien and Fleming spending function[24,25] (approximately 0.00598 at the interim analysis and 0.0481 at the final analysis).
    - Progression free survival at 6 months (PFS6) – This endpoint will be tested with a one-sided chi-square test, assuming the NovoTTF-100A arm will have a higher PFS6 than the control arm of the study. No analysis will be performed at the interim analysis.
    - One and two year overall survival rates - These secondary endpoints will be tested with a one-sided chi-square test, assuming the NovoTTF-100A arm will have higher 1- and 2-year survival rates than the control arm of the study. No analysis will be performed at the interim analysis.
    - Quality of life (EORTC QLQ-C30 questionnaire; TAB H) – Change from baseline (CFB) to 3, 6, 9 and 12 months will be calculated for each subscale domain and symptom scale in the questionnaire. Results will be presented descriptively as a ratio in CFB at each of the above time points in the treatment arm compared to the control arm of the study.
    - Radiological response rate – This endpoint will compared between groups using a one-sided chi-square test assuming the NovoTTF-100A arm will have a higher response rate than the control arm of the study. No analysis will be performed at the interim analysis.

Preservation of the type I error –

1. The company only plans to make efficacy claims on the first secondary endpoint, the overall survival, due to its importance and also the fact that it is a powered secondary endpoint in the trial. No efficacy claims are planned based on PFS6, 1- and 2-year survival, quality of life analysis or radiological response rate. Thus, the entire alpha of 0.05 will be allocated to the overall survival endpoint and no adjustment will be made for multiple hypothesis testing.
2. A hierarchical approach will be used to first test the primary endpoint of PFS and then the secondary endpoint of overall survival to avoid problems with statistical multiplicity. Specifically, overall survival will be tested at the proposed significance levels for the interim and final analyses if the primary endpoint of progression free survival also meets its significance levels at the respective time points.

C. Covariates

A Cox proportional hazards model will be used to evaluate covariates. The effect of the following covariates will be compared and adjusted for between the treatment and control groups:

1. Age
2. Extent of surgery (biopsy, partial, or total resection)
3. MGMT methylation status (positive, negative, unknown)
4. Additional genetic markers:
    a. EGFR amplification, over expression or rearrangement
    b. Chromosomes 1p/19q deletion status
    c. IDH1 mutation
5. Baseline Karnofsky performance scale score
6. Tumor size
7. Tumor location
8. Percent of the total treatment time in which the NovoTTF-100A treated patients actually received treatment (will be calculated by analyzing the internal computerized log file of each NovoTTF-100A device and dividing the total device ON time by the prescribed number of 1 month treatment courses).

D. Additional variables

The following parameters will be also recorded and compared between the treatment and control groups:

- Overall survival time (Log Rank Test). In order to allow for two analyses in the trial the alpha level used at each time point will be calculated based on the O'Brien-Fleming method[24,25] (i.e., approximately 0.0089 at the interim analysis and 0.0475 at the final analysis). For analysis of overall survival, patients will be censored at the time that they are last known to be alive (if withdrawn or lost to follow-up) or at study closeout.
- % 6-month progression free survival
- % 1 and 2-year survival

- Quality of life (EORTC QLQ-C30 questionnaire)
- Radiological response rates
- MMSE scores
- Incidence and severity of adverse events

In addition, the correlation will be measured between the percent of time patients received NovoTTF-100A treatment and their progression free survival and overall survival.

XXII. RISK/BENEFIT ANALYSIS

The risks associated with use of the NovoTTF-100A are principally the risk of 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. The 26 patients treated to date as part of pilot studies suffered no treatment related serious adverse events after > 180 months of treatment (cumulatively). In fact the only complication seen was a mild to moderate skin irritation beneath the electrode gel. In the pivotal study in recurrent GBM, 116 patients were treated with the NovoTTF-100A device without unexpected device events.

In the pilot trial performed on 10 newly diagnosed GBM patients, median TTP in NovoTTF-100A treated patients was >14 months. Although these results are not statistically significant due to the small number of patients in the trial, they raise the possibility that the NovoTTF-100A device will benefit patients in the current study with regards to OS. Up to 467 patients will be exposed to NovoTTF-100A treatment during the current trial. Considering the minimal toxicity and promising efficacy seen in the pilot trials, the small number of patients exposed to this treatment in the current study and the and the poor outcome of these patients despite Temozolomide treatment – we conclude that the possible benefits of NovoTTF-100A treatment drastically exceed its potential risks.

XXIII. STUDY MONITORING AND QUALITY ASSESSMENT

Study monitoring will be performed by a CRO assigned this responsibility by the sponsor. Study monitoring functions will be in compliance with recognized Good Clinical Practices, 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: on-site visits and review of study documents and results. The CRO will operate under written procedures to ensure compliance with the protocol.

On-site monitoring visits will take place at each center prior to study initiation and at least once during the course of the study, and a final visit at the close of the study. The pre-study

visit is intended to provide an opportunity for the monitor to review the Investigational Plan with the Investigators and to ensure that the Investigators:

- have appropriate training, facilities, patient load, time, and willingness to comply with study requirements;
- have the approval of the supervising Institutional Review Board (IRB) or Ethics Committee (EC) for the Investigational Plan;
- have all study documentation and required records on site; and
- assume responsibility for the investigation at their center.

Visits during the study are 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. During these in-study visits, 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 monitor's final on-site visit at completion of the study is intended to assure that all the data have been properly completed and to have a closing meeting with the Investigators and their staff members. Reports of the on-site visits will be made by the monitor and 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.

An independent Data and Monitoring Committee (DMC), comprised of a neurosurgeon, neuro-oncologist and statistician will be formed to monitor the safety data from the study. Although there are no anticipated significant safety issues with the device, the adverse event data will be reviewed by the DMC to determine if there are any unexpected safety concerns with the device that warrant study termination or if the study should be stopped for futility purposes. Specifically, DMC review will be performed annually from first patient recruited, or more often if necessary, to determine if:

- There is clear evidence of unacceptably harmful side-effects of NovoTTF-100A treatment together with maintenance temozolomide; or
- There is no likelihood of demonstrating treatment benefit or equivalence.
- It is unethical to withhold NovoTTF-100A treatment from patients

Additionally, a formal statistical analysis of the interim efficacy results will be reviewed by the DMC to determine whether early stopping for efficacy or any modifications to the study design should be recommended.

The DMC will base their recommendation to the Sponsor on an evaluation of data such as:

- All adverse events, including serious adverse events and device or drug related AEs
- Progression free survival and overall survival

XXIV. PROTECTION OF HUMAN SUBJECTS

A. Privacy

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. The use and disclosure of protected health information will be limited to the individuals described in the Research Authorization form. A Research Authorization form must be completed by the Principal Investigator and approved by the IRB/EC and Privacy Board.

XXV. INFORMED CONSENT PROCEDURES

RESEARCH AUTHORIZATION

Procedures for obtaining Research Authorization: Prior to carrying out any protocol-specific procedures, investigators or designated staff will explain fully the details of the protocol, study procedures, and the aspects of patient privacy concerning research specific information. In addition to signing the IRB/EC Informed Consent, all patients must sign the Research Authorization component of the informed consent form. The Research Authorization requires a separate signature from the patient. The original signed documents will become part of the patient's medical record, and each patient will receive a copy of the signed documents. All patients must provide written informed consent prior to registration and treatment.

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XXVII. PROTOCOL SIGNATURE PAGE

Investigator:

Center - _____

Investigator Name - _____

Signature - _____

Date - _____/_____/_____

Sponsor:

NovoCure Ltd.

Name - _____

Signature - _____

Date - _____/_____/_____

TAB A

STUDY PROCEDURE MATRIX

	T=-7 (baseline)	T=1 month (±7 days)	T=2 months (±7 days)	T=3 months (±7 days)	T=4 months (±7 days)	T=5 months (±7 days)	T=6 months (±14 days)	T=every month until treatment stop+	T=Progression	T=1 month From treatment stop+	T=2 months From treatment stop+	Monthly thereafter+
MRI of the head	X*		X*		X*		X*	X*	X*			
Physical examination	X	X	X	X	X	X	X	X	X	X	X	
Neurological status	X	X	X	X	X	X	X	X	X	X	X	
Complete blood count (CBC) and differential	See adjacent table											
Chemistry panel (SMAC)												
Coagulation study												
Mini Mental State Exam (MMSE)	X	X	X	X	X	X	X	X	X	X	X	
Quality of life questionnaire	X			X			X	X^				
Telephone interview												X

* screening MRI should be done within 2 weeks before study start. MRI of the head will be performed routinely at baseline and again every 2 months until treatment termination or second progression, whichever is later. An MRI of the head will be obtained in the event of clinical signs of progression.

^ Every third month until treatment termination.

+ Visit window of ± 7 days if visit occurs prior to the 6 month follow-up window, ± 14 days if visit occurs on or after the 6 month follow-up window, ± 1 month if visit occurs on or after the 12 month follow-up window.

	Test	Screening	Follow-up	Progressions 1&2	1 month from treatment stop	2 months from treatment stop
Hematology	Hemoglobin	+	+	+	+	+
	Hematocrit	+	+	+	+	+
	RBC	+	+	+	+	+
	MCV	+	+	+	+	+
	WBC	+	+	+	+	+
	Neutrophils	+	+	+	+	+
	Eosinophils	+	#	#	#	#
	Basophils	+	#	#	#	#
	Lymphocytes	+	+	+	+	+
	Monocytes	+	#	#	#	#
	Platelets	+	+	+	+	+
Chemistry						
	Sodium	+	+	+	+	+
	Potassium	+	+	+	+	+
	Calcium	+	+	+	+	+
	Glucose	+	+	+	+	+
	BUN/Urea	+	+	+	+	+
	Creatinine	+	+	+	+	+
	Total Protein	+	+	+	+	+
	Total Bilirubin	+	+	+	+	+
	Alk. Phosphatase	+	+	+	+	+
	Albumin	+	+	+	+	+
	ALT	+	+	+	+	+
	AST	+	#	#	#	#
	Total	+	#	#	#	#
	Cholesterol					
Coagulation						
	PTT	+	&	&	&	&
	INR	+	&	&	&	&

+ Required tests
# - only when clinically indicated
& - only for patients with coagulation problems / on anti-coagulants

TAB B

COMMON TOXICITY CRITERIA (V 3.0)

TAB C - KARNOFSKY SCALE

The *Karnofsky Scale* has been adapted for use in many areas, including hospices, cancer clinics, etc., as well as used by various CFS researchers and physicians (Leonard Jason, PhD; Jay A. Goldstein, MD).

The 10-point scale is a quick and easy way to indicate how you are feeling on a given day, without going through several multiple choice questions or symptom surveys.

100	Able to work. Normal; No complaints; No evidence of disease.
90	Able to work. Able to carry on normal activity; Minor symptoms.
80	Able to work. Normal activity with effort; Some symptoms.
70	Independent; not able to work. Cares for self; Unable to carry on normal activity.
60	Disabled; dependent. Requires occasional assistance; cares for most needs.
50	Moderately disabled; dependent. Requires considerable assistance and frequent care.
40	Severely disabled; dependent. Requires special care and assistance.
30	Severely disabled. Hospitalized, death not imminent.
20	Very sick. Active supportive treatment needed.
10	Moribund. Fatal processes are rapidly progressing

TAB D

MACDONALD CRITERIA

TAB E

INFORMED CONSENT

TAB F

CASE REPORT FORMS

TAB G

EORTC QLQ C30

EORTC QLQ-C30 (version 3)

We are interested in some things about you and your health. Please answer all of the questions yourself by circling the number that best applies to you. There are no "right" or "wrong" answers. The information that you provide will remain strictly confidential.

Please fill in your initials: _____

Your birthdate (Day, Month, Year): _____

Today's date (Day, Month, Year): 31 _____

		Not at All	A Little	Quite a Bit	Very Much
1.	Do you have any trouble doing strenuous activities, like carrying a heavy shopping bag or a suitcase?	1	2	3	4
2.	Do you have any trouble taking a long walk?	1	2	3	4
3.	Do you have any trouble taking a short walk outside of the house?	1	2	3	4
4.	Do you need to stay in bed or a chair during the day?	1	2	3	4
5.	Do you need help with eating, dressing, washing yourself or using the toilet?	1	2	3	4

During the past week:

		Not at All	A Little	Quite a Bit	Very Much
6.	Were you limited in doing either your work or other daily activities?	1	2	3	4
7.	Were you limited in pursuing your hobbies or other leisure time activities?	1	2	3	4
8.	Were you short of breath?	1	2	3	4
9.	Have you had pain?	1	2	3	4
10.	Did you need to rest?	1	2	3	4
11.	Have you had trouble sleeping?	1	2	3	4
12.	Have you felt weak?	1	2	3	4
13.	Have you lacked appetite?	1	2	3	4
14.	Have you felt nauseated?	1	2	3	4
15.	Have you vomited?	1	2	3	4

Please go on to the next page

During the past week:	Not at All	A Little	Quite a Bit	Very Much
16. Have you been constipated?	1	2	3	4
17. Have you had diarrhea?	1	2	3	4
18. Were you tired?	1	2	3	4
19. Did pain interfere with your daily activities?	1	2	3	4
20. Have you had difficulty in concentrating on things, like reading a newspaper or watching television?	1	2	3	4
21. Did you feel tense?	1	2	3	4
22. Did you worry?	1	2	3	4
23. Did you feel irritable?	1	2	3	4
24. Did you feel depressed?	1	2	3	4
25. Have you had difficulty remembering things?	1	2	3	4
26. Has your physical condition or medical treatment interfered with your family life?	1	2	3	4
27. Has your physical condition or medical treatment interfered with your social activities?	1	2	3	4
28. Has your physical condition or medical treatment caused you financial difficulties?	1	2	3	4

For the following questions please circle the number between 1 and 7 that best applies to you

29. How would you rate your overall health during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

30. How would you rate your overall quality of life during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

TAB H

MEDICAL RESEARCH COUNCIL (MRC) SCALE FOR NEUROLOGICAL STATUS

1	No neurological deficit
2	Some neurological deficit but function adequate for useful work
3	Neurological deficit causing moderate functional impairment e.g. ability to move limbs only with difficulty, moderate dysphasia moderate paresis, some visual disturbances (e.g. field detect)
4	Neurological deficit causing major functional impairment e.g. inability to use limb/s gross speech or visual disturbances No useful function - inability to make conscious responses

A Prospective, Multi-center Trial of NovoTTF-100A Together With Temozolomide Compared to Temozolomide Alone in Patients with Newly Diagnosed GBM

THERAPEUTIC PROTOCOL

Protocol EF-14

Version 2.1

IDE G070228

Investigators: (see TAB I)

Release date: 14 December, 2012

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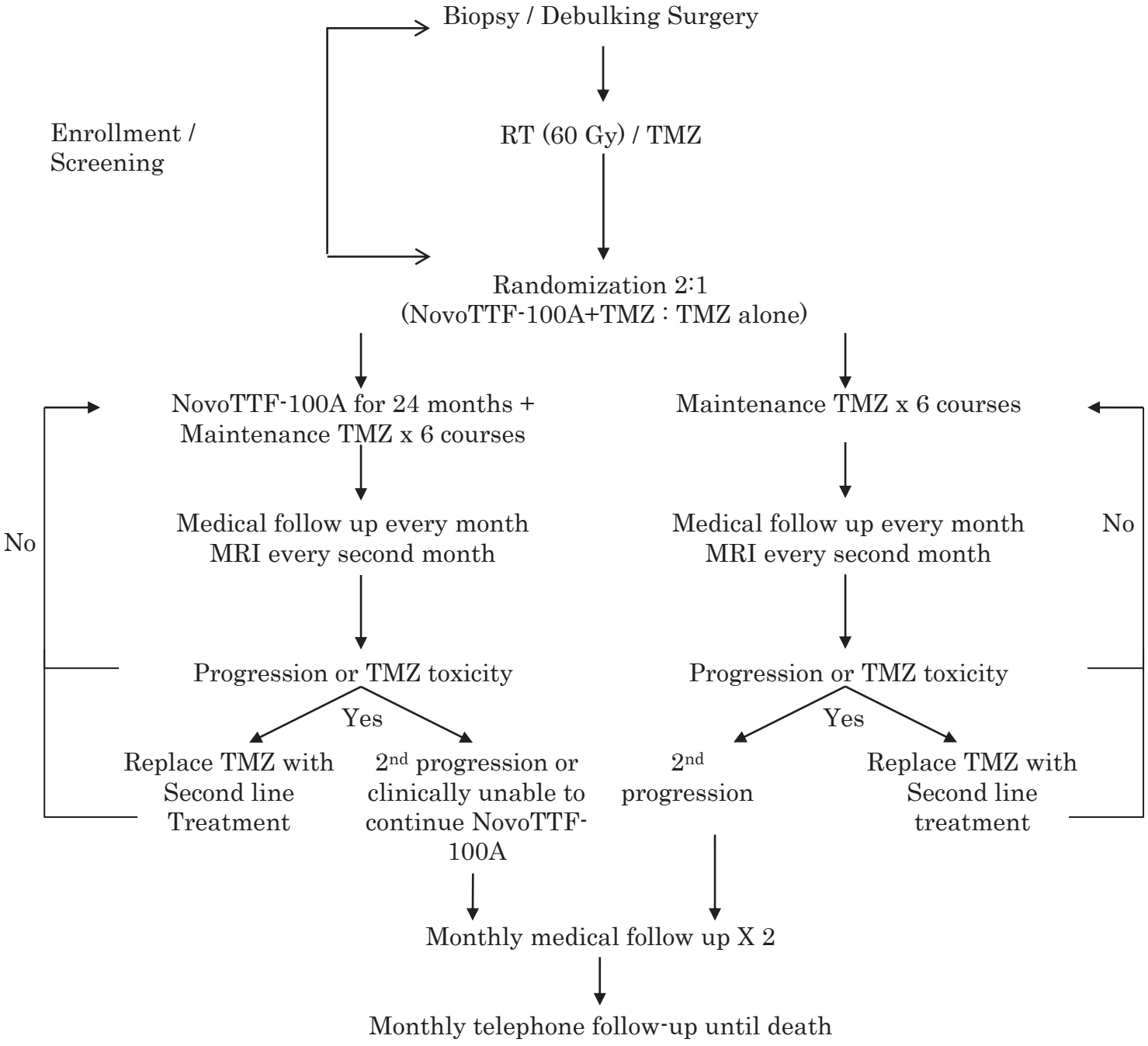
I. PROTOCOL SUMMARY AND SCHEMA

1. SUMMARY

Title:	A prospective, multi-center trial of NovoTTF-100A together with temozolomide (TMZ) compared to TMZ alone in patients with newly diagnosed glioblastoma (GBM)
Device:	NovoTTF-100A
Study Objectives:	To compare the efficacy and safety outcome of newly diagnosed GBM patients treated with NovoTTF-100A concomitant to TMZ to those treated with TMZ alone
Study Design:	Prospective, randomized, open label, standard of care control
Study Hypothesis:	The hypothesis of this study is that addition of NovoTTF-100A treatment to maintenance TMZ will significantly increase progression free survival of newly diagnosed GBM patients compared to patients treated with TMZ alone
Sample Size:	700 patients with newly diagnosed GBM
Study Population:	Patients with tissue based diagnosis of GBM, above 18 years of age, of both genders after surgery or biopsy followed by radiation therapy (RT) with adjuvant TMZ (Stupp protocol[23])
Primary endpoint:	Progression free survival time
Secondary endpoints:	• Overall survival (OS) • Progression free survival at 6 months (PFS6) • 1 and 2-year survival rates • Radiological response (Macdonald criteria) • Quality of life assessment (EORTC QLQ-C30) • Adverse events severity and frequency
Sponsor:	Novocure Ltd. POB 15022 MATAM Center Haifa, 31905, Israel

2. PROTOCOL SCHEMA



II. OBJECTIVES AND SCIENTIFIC AIMS

- To prospectively compare the progression free survival time of newly diagnosed GBM patients treated with NovoTTF-100A together with TMZ to those treated with TMZ alone.
- To prospectively compare the overall survival time of newly diagnosed GBM patients treated with NovoTTF-100A together with TMZ to those treated with TMZ alone.
- To prospectively determine % of patients alive and progression-free at 6-months (PFS6), survival rate at 1 and 2-years.
- Quality of life (EORTC QLQ-30 + BCM20, TAB H)
- Safety of the NovoTTF-100A device applied together with TMZ to patients with newly diagnosed GBM.

III. BACKGROUND AND RATIONALE

Glioblastoma (GBM), a malignant form of astrocytoma, is the most common primary intracranial neoplasm in adults. The incidence of GBM increases steadily above 45 years of age with a prevalence of approximately 7500 cases in the USA. Despite numerous attempts to improve the outcome of patients with GBM, the 3-year survival of these patients is only 6% with median survival of 14.6 months[1].

Patients with newly diagnosed GBM who are treated with maximal surgical resection when feasible, 60 Gy radiotherapy (RT) together with concomitant temozolomide (TMZ) (RT/TMZ), followed by maintenance (adjuvant) TMZ for 6 months, have a median survival of approx. 15 months only [23]. Thus, there is a critical need for new therapeutic options for treatment of GBM. TTFields are a new investigational modality for the treatment of malignant tumors. Pre-clinical studies[12,22] have shown this treatment modality to effectively inhibit the growth of experimental tumors both in-vitro and in-vivo without any systemic side effects.

The currently accepted standard treatment of newly diagnosed GBM is based on: surgical resection to the extent safely feasible, with or without Gliadel™ wafer implantation (in the US), followed by RT, and concomitant and adjuvant TMZ chemotherapy. Each of these treatments is briefly described below:

1. Surgical resection - Treatment of patients with GBM usually consists of tumor resection (to the extent safely feasible) or diagnostic biopsy.
2. Radiotherapy (RT) - Post-surgical RT improves survival, though even with maximal treatment, survival after RT alone is still limited to about one year[23].
3. Temozolomide (TMZ) – Concomitant TMZ chemotherapy during RT and adjuvant (maintenance) TMZ for 6 cycles has been shown to significantly improve survival (HR 0.63). This combined modality treatment is considered the standard of care.
    a. According to the TMZ (Temodar®, Temodal®) package insert adjuvant TMZ treatment delays disease progression (from 5 to 6.9 months) and improves overall survival (from 12.1 to 14.6 months)[23].

b. In the recently presented RTOG0525/EORTC Intergroup trial where patients were randomized after the end of TMZ/RT (similar to the current EF-14 trial), progression-free survival was also only 6-7 months (estimated from curve)[26]

4. GLIADEL™ Wafers in combination with surgical resection – Gliadel™ Wafers deliver carmustine (BCNU) directly to the bed of the resected tumor. Gliadel has been approved for GBM after surgical resection, based on trials performed before TMZ therapy was established.
    a. The package insert indicates that for newly diagnosed GBM, Gliadel™ increased median overall survival from 11.6 to 13.9 months compared to placebo. Progression-free survival with Gliadel™ wafers has been reported as 5.9 months[27]. No prospective data of Gliadel™ in combination with TMZ has been reported.

In conclusion, despite the immense effort made over the years with different treatment modalities, the survival of patients with newly diagnosed GBM remains poor; no treatment is curative; and the quality of life of patients with this tumor is compromised significantly,. A treatment modality is needed that will improve the results of standard treatments without further impairing the quality of life of these patients for their limited life span.

Introduction to electric fields

In the laboratory setting and in clinical practice, alternating electric fields show a wide range of effects on living tissues. At very low frequencies (under 1 kHz), alternating electric fields stimulate excitable tissues through membrane depolarisation[3]. The transmission of such fields by radiation is insignificant and therefore they are usually applied directly by contact electrodes, though some applications have also used insulated electrodes. Some well known examples of such effects include nerve, muscle and heart stimulation by alternating electric fields[3,4]. In addition, low frequency pulsed electric fields have been claimed to stimulate bone growth and accelerate fracture healing[5]. However, as the frequency of the alternating electric field increases above 1 kHz, the stimulatory effect diminishes. Under these conditions although a greater fraction of the fields penetrates the cells, due to the parallel resistor-capacitor nature of all biological membranes, the stimulatory power greatly diminishes as the alternating cell membrane hyper –depolarization cycles are integrated such that the net effect is nulled.

At very high frequencies (i.e., above many MHz), while the integration becomes even more effective, a completely different biological effect is observed. At these frequencies tissue heating becomes dominant due to dielectric losses. This effect becomes more intense as field intensity or tissue dissipation factor increase[6]. This phenomenon serves as the basis for some commonly used medical treatment modalities including diathermy and radio frequency tumor ablation, which can be applied through insulated electrodes[7].

Intermediate frequency electric fields (i.e., tens of kHz to MHz), alternate too fast for causing nerve-muscle stimulation and involve only minute dielectric losses (heating). Such fields, of low to moderate intensities, are commonly considered to have no biological effect[6]. However, a number of non-thermal effects, of minor biological consequence, have been reported

even at low field intensities. These include microscopic particle alignment (i.e., the pearl chain effect[8]) and cell rotation[9,10]. With pulsed relatively strong electric fields, > 10^3 V/cm and 100 ms pulse length, reversible pore formation appears in the cell membrane, a phenomenon usually called electroporation[11].

Tumor treating electric fields (*TTFields*)

Novocure has shown[12] that when properly tuned, very low intensity, intermediate frequency electric fields (TTFields) stunt the growth of tumor cells. This inhibitory effect was demonstrated in all proliferating cell types tested, whereas, non-proliferating cells and tissues were unaffected. Interestingly, different cell types showed specific intensity and frequency dependences of TTField inhibition. It has been shown that two main processes occur at the cellular level during exposure to TTFields: arrest of proliferation and dividing cell destruction. The damage caused by TTFields to these replicating cells was dependent on the orientation of the division process in relation to the field vectors, indicating that this effect is non-thermal. Indeed, temperature measurements made within culture dishes during treatment and on the skin above treated tumors in-vivo, showed no significant elevation in temperature compared to control cultures/mice. Also, TTFields caused the dividing cells to orient in the direction of the applied field in a manner similar to that described in cultured human corneal epithelial cells exposed to constant electric fields[13]. At the sub-cellular level it was found that TTFields disrupt the normal polymerization-depolymerization process of microtubules during mitosis. Indeed, the described abnormal mitotic configurations seen after exposure to TTFields are similar to the morphological abnormalities seen in cells treated with agents that interfere directly[14,15] or indirectly[16-18] with microtubule polymerization (e.g. paclitaxel).

Modeling the mechanism of action of *TTFields*

In order to explain how TTFields cause orientation dependent damage to dividing cells and disrupt the proper formation of the mitotic spindle Novocure modeled the forces exerted by TTFields on intracellular charges and polar particles using finite element simulations. Two main mechanisms by means of which the electric fields may affect dividing cells were recognized. The first relates to the field effect on polar macromolecule orientation. Within this framework, during the early phases of mitosis, i.e., in pre-telophase, when tubulin polymerization-depolymerization drives the proliferation process, the electric field forces any tubulin dimers, positioned further than 14nm away from the growing end of a microtubule, to orient in the direction of the field. This force moment, (10^{-5} pN) acting on the dimers, is sufficient to interfere with the proper process of assembly and disassembly of microtubules that is essential for chromosome alignment and separation[19]. This effect can explain the mitotic arrest of TTField treated cells[20].

The second mechanism, which interferes with cell division, and is most likely to play an important role in cell destruction, becomes dominant during cleavage. As seen in simulations, the electric field within quiescent cells is homogenous, whereas the field inside mitotic cells, during cytokinesis, is not homogenous. An increased field line concentration (indicating increased field intensity) is seen at the furrow, a phenomenon that highly resembles the focusing of a light beam by a lens. This in-homogeneity in field intensity exerts a unidirectional electric force, on all intracellular charged and polar entities (including induced dipoles), pulling them towards the

furrow (regardless of field polarity). For example, for a cleavage furrow that reached a diameter of 1μm in an external field of only 1 V/cm, the force exerted on the microtubules is in the order of 5pN. This magnitude is compatible with the reported forces necessary to stall microtubule polymerization which is 4.3 pN[21]. With regards to other particles, such as cytoplasmatic organelles, they are polarized by the field within dividing cells. Once polarized, the forces acting on such particles may reach values up to an order of 60 pN resulting in their movement towards the furrow at velocities that may approach 0.03 μm/sec. At such velocity, cytoplasmatic organelles would pile up at the cleavage furrow within a few minutes, interfering with cytokinesis and possibly leading to cell destruction. It has also been found that the electric forces acting on intracellular particles are maximal when the axis of division is aligned with the external field. This is consistent with the dependence of the destructive effect of TTFields on the angle between division axis and the field, as demonstrated experimentally. In addition, the calculated dependence of the magnitude of this force on frequency is consistent with the experimentally determined frequency dependence of the inhibitory effect of TTFields on melanoma and glioma cell proliferation (120 kHz vs. 200 kHz, respectively).

In vivo effects of TTFields

Novocure has shown[22] that TTFields can be applied effectively to animals through transducer array placed on the surface of the body. Using a special type of electrically insulated electrodes (transducer arrays), significant inhibition of the growth of both intradermal melanoma (B16F1) in mice and intracranial glioma (F-98) in rats was seen after less then one week of treatment. This growth inhibition was accompanied by a decrease in angiogenesis within the tumor, due to inhibition of endothelial cell proliferation.

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

Secondly, the anti-mitotic effect of TTFields might be expected to damage the replication of rapidly dividing normal cells within the body (bone marrow, small intestine mucosa). Surprisingly, no treatment related toxicities were found in any of the animal safety trials performed by Novocure, even when field intensities 3 fold higher than the effective anti-tumoral dose were used. The lack of damage to intestinal mucosa in TTField-treated animals is probably a reflection of the fact that the small intestine mucosal cells have a slower replication cycle than neoplastic cells and that the intestine itself most likely changes its orientation in relation to the applied field quite often, lowering the efficacy of TTField mediated mitotic disruption. Bone

marrow, on the other hand, is naturally protected from TTFields by the high electric resistance of both bone and bone marrow compared to most other tissues in the body. To test the later assumption, the TTField intensity within the bone marrow of a long bone was modeled using the finite element mesh (FEM) method. It was found that the intensity of TTFields was 100-fold lower within the bone marrow compared to the surrounding tissues (including within solid tumors). Thus, hematopoietic cell replication should not be affected even when TTField intensities 10-fold higher than necessary to inhibit tumor growth are applied.

The NovoTTF-100A device

The NovoTTF-100A device is a portable battery operated device which produces TTFields within the human body by means of surface transducer arrays. The TTFields are applied to the patient by means of surface transducer arrays that are electrically insulated, so that resistively coupled electric currents are not delivered to the patient. The transducer arrays, which incorporate a layer of adhesive hydrogel and a layer of hypoallergenic medical tape, are placed on the patient's shaved head. The transducer arrays must be replaced every three to four days and the scalp re-shaved in order to maintain optimal capacitative coupling between the transducer arrays and the patient head. All the treatment parameters are pre-set by Novocure so there are no electrical output adjustments available to the patient. The patient must learn to change and recharge depleted device batteries and to connect to an external battery pack overnight.

Effect of NovoTTF-100A on newly diagnosed GBM patients – clinical pilot study

A pilot study was performed on ten newly diagnosed GBM patients treated with the NovoTTF-100A device. All patients underwent surgery and RT for the primary tumor. All patients received TMZ as adjuvant chemotherapy, in addition to NovoTTF-100A treatment.

All patients were treated with multiple four-week treatment courses using continuous, 24-hour a day, 200 kHz, 0.7 V/cm TTFields. TTFields were applied through two sets of opposing insulated transducer arrays and alternated at a 1 second duty cycle between two perpendicular field directions through the tumor. Patients completed between 1 and 17 treatment courses leading to maximal treatment duration of 16.5 months. Overall, more than 96, 4 week treatment courses were completed to date (> 9.6 courses per patient on average).

The treatment was well tolerated with no treatment related serious adverse events seen in any of the patients. Patients received NovoTTF treatment on average about 80% of the scheduled time. Considering the continuous nature of NovoTTF therapy (i.e., 24 hours a day for many months) this figure indicates that compliance with treatment was high, with patients taking very few days off treatment and stopping only for short periods of time during treatment for personal needs.

Mild to moderate contact dermatitis appeared beneath the transducer array gel in all patients during treatment. In most cases this dermatitis appeared for the first time during the

second treatment course (> 4 weeks of NovoTTF treatment). The skin reaction improved with use of topical corticosteroids. Regular relocation of the transducer arrays was necessary in order to allow for continuous treatment.

The median progression free survival (PFS) of the patients in this study exceeded concurrent and historical controls[23] dramatically (greater than 18 months versus 7.1 months, respectively). So far 2 of the 10 patients have died. The remaining 8 patients are still alive and 5 of them are progression free. Median overall survival from diagnosis is greater than 26 months at the moment (compared to 14.6 months in historical controls[23]).

Although the number of patients in this pilot trial is small, the excellent safety profile of this treatment modality and the highly promising efficacy data gathered so far indicate the potential of NovoTTF-100A treatment as an effective therapy for newly diagnosed GBM patients.

Effect of NovoTTF-100A on recurrent GBM patients – clinical pilot study

A pilot study was performed on ten recurrent GBM patients treated with the NovoTTF-100A device. All patients underwent surgery and RT for the primary tumor. Only 1 patient was chemotherapy naïve, the rest having received either TMZ or other chemotherapeutic agents, as adjuvant treatment, prior to recurrence.

All patients were treated with multiple four-week treatment courses using continuous, 24-hour a day, 200 kHz, 0.7 V/cm TTFields. TTFields were applied through two sets of opposing insulated transducer arrays and alternated at a 1 second duty cycle between two perpendicular field directions through the tumor. Patients completed between 1 and 15 treatment courses leading to maximal treatment duration of 14.5 months. Overall, more than 70, 4 week treatment courses were completed to date (> 7 courses per patient on average).

The treatment was well tolerated with no treatment related serious adverse events seen in any of the patients. Patients received treatment on average about three quarters of the scheduled time. Considering the continuous nature of NovoTTF treatment (i.e., 24 hours a day for many months) this figure indicates that compliance with treatment was very high, with patients taking very few days off treatment and stopping only for short periods of time during treatment for personal needs.

Mild to moderate contact dermatitis appeared beneath the transducer array gel in 8 of the 10 patients during treatment. In most cases this dermatitis appeared for the first time during the second treatment course. The skin reaction improved with use of topical corticosteroids. Regular relocation of the transducer arrays was necessary in order to allow for continuous treatment.

The median progression free survival (PFS) of the patients in this study exceeded historical controls[2] dramatically (26.1 weeks versus 9 weeks, respectively). The PFS at 6 months (PFS6) was 50% compared to 15% in historical controls[2]. So far 7 of the 10 patients have died. The remaining 3 patients are still alive and 2 of them are progression free. Median overall

survival was 62 weeks. Response rate was 25% (1 CR + 1 PR) and only two patients had progressive disease despite treatment.

Effect of NovoTTF-100A on recurrent GBM patients – Pivotal study

In a prospective, randomized, open label, active parallel controlled trial to compare the effectiveness and safety outcomes of recurrent GBM subjects treated with NovoTTF-100A alone (n=120) to those treated with an effective best standard of care chemotherapy (according to physicians best choice [e.g. CCNU, BCNU, bevacizumab]; n=117), NovoTTF-100A subjects had comparable overall survival to subjects receiving the best available chemotherapy nowadays (median overall survival 6.3 vs. 6.4 months; HR 1.0; p=0.98)[28]. Importantly, secondary endpoints favored the NovoTTF treated patients (e.g. PFS6 = 21.4% for NovoTTF-100A vs. 15.2% for chemotherapy, p=0.14, response rate 14% vs 9.6%, p=0.24, for NovoTTF and the active control group, respectively).

Expectedly, the chemotherapy-free NovoTTF-100A patients experienced fewer adverse events in general, significantly fewer treatment related adverse events, and significantly lower gastrointestinal, hematological and infectious adverse events compared to the best standard of care active controls. The main device-related adverse events seen were a mild to moderate skin irritation beneath the device transducer arrays, which was easily treated with topical ointments. Finally, quality of life measures were better in NovoTTF-100A subjects as a group when compared to subjects receiving effective best standard of care[28].

IV. STUDY DESIGN

A prospective, randomly controlled pivotal study will be conducted on 700 patients (randomized at a 2:1 ratio in favor of the NovoTTF-100A group). Patients with histologically confirmed GBM will be randomized after having completed RT/TMZ to either maintenance TMZ and NovoTTF for up to 24 months (experimental arm), or maintenance TMZ chemotherapy alone (control). The primary endpoint will be progression free survival (PFS), overall survival is clinically an equally important secondary endpoint. The sample size was chosen based on the log-rank test comparing time to event (i.e., progression or death prior to progression) assuming patients treated with the NovoTTF-100A together with maintenance TMZ will have a median PFS significantly greater than controls (9 months compared to 7 months, hazard ratio < 0.78), respectively; with an overall 5% 2-sided type I error and 80% power). This sample size also has adequate power (80%) to detect a minimum of 4.5 month increase in median overall survival (hazard ratio < 0.76) in NovoTTF-100A treated patients compared with control patients (expected control group median OS = 14.6 months, Stupp et al, NEJM 2005).

The following will be considered disease progression for determination of PFS (based on the Macdonald criteria; Tab D):

1. Tumor growth > 25% of the product of 2 perpendicular diameters compared to the smallest tumor area measured in this patient during the trial.
2. Appearance of 1 or more new tumors in the brain (diagnosed radiologically as GBM).

Final determination of progression will be made by independent radiology review, in cases where an MRI is available (which should be the great majority of cases). In cases where an MRI is not available, clinical progression will be diagnosed according to the following criteria:

1. Decline in functional status as indicated by a decrease in KPS of ≥ 20 points, or
2. Decline in neurological function as indicated by a decrease of 2 points or more in MRC scale (TAB H), or
3. ≥50% increase in steroid dose.

The determination of whether to stop treatment due to progression will be based on the investigator's evaluation of the patient's clinical condition. NovoTTF-100A treatment shall be continued for 24 months or until (or beyond) second progression, at the investigators discretion. In the case of radiological progression based on local evaluation, TMZ treatment will be stopped and a second line therapy initiated, at the investigators discretion, while NovoTTF may be continued. The following treatments or any combination of these treatments are considered second line therapy in this protocol:

1. Re-operation (in cases where viable tumor cannot be demonstrated histologically [pseudoprogression], this will not be considered progression and a second-line therapy)
2. Local RT (e.g. gamma knife)
3. Second line chemotherapy
4. Any combination of the above.

Patients will be recruited to the study by the principal investigator (PI) or one of the co-investigators (CI) in up to 40 medical centers in the United States, and approximately 25 centers in the rest of the world. Following informed consent and screening, non-progressive patients who have completed TMZ/RT will be randomized at a 2:1 ratio to receive either NovoTTF-100A treatment together with maintenance TMZ or maintenance TMZ alone.

The estimated recruitment duration is 48 months. Patient follow-up for PFS and OS will continue for at least 18 months from accrual of the last patient.

Experimental treatment arm

NovoTTF-100A treatment will be given together with maintenance TMZ (according to the standard maintenance dosing described below in section IX). At treatment initiation patients will be seen at an outpatient clinic. During this visit baseline examinations will be performed and NovoTTF-100A treatment will be initiated. The patients will also be instructed on the operation of the NovoTTF-100A and battery replacement. Once the patients are trained in operating the device they will be released to continue treatment at home. The patients will receive multiple 1 month courses of continuous NovoTTF-100A treatment. NovoTTF-100A treatment will be stopped in the following cases:

1. The occurrence of device related serious adverse events

2. Clinical and functional deterioration considered by the investigator to be prohibitive of continuing treatment.

Treatment with the NovoTTF-100A device does not need to be terminated in the following situations:

1. Toxicity due to TMZ treatment
2. Radiological progression and initiation of second line therapy; e.g.
   i. Re-operation
   ii. Local RT (e.g., gamma knife)
   iii. Second line chemotherapy
   iv. Combination of the above.

Control arm

Patients will be treated with standard maintenance TMZ according to the standard dosing regimen described below in section IX. Following radiological progression or unacceptable toxicity, TMZ will be replaced with best standard of care second line therapy:

a. Re-operation
b. Local RT (e.g., gamma knife)
c. Second line chemotherapy
d. Combination of the above

Follow-up Evaluations

As long as the patients are receiving any protocol treatment (NovoTTF-100A and/or first and second-line chemotherapy), monthly outpatient clinic visits are required, including medical exam and follow-up, and routine laboratory exams (see Tab A). An MRI is to be performed every two months until second progression. In the case of clinical progression an unscheduled MRI will be obtained within 1 week of the investigator becoming aware of the clinical progression. After second progression imaging is performed at the investigators discretion. Monthly medical follow-up visit shall be scheduled for 2 months after termination of protocol therapy in order to capture potential treatment related toxicities. All patients will be followed for survival by either direct contact or regular telephone interviews with the patient or the patient's caregiver.

Independent MRI review

Independent MRI review will be performed by a neuro-radiologist blinded to the treatment group of each patient. All MRI's will be sent to an independent radiologist, blinded to the treatment groups of the patients. Either digital (DICOM) images or analog films can be used for this purpose. Contrast agent and dose per body weight must be kept constant between scans for each patient.

V. CRITERIA FOR PATIENT ELIGIBILITY

Patients with newly diagnosed and histologically confirmed GBM after initial therapy with surgery if applicable, followed by standard concomitant chemoradiotherapy (TMZ/RT according to Stupp et al) are to be considered. Patients may be enrolled at any time, randomization will be performed only after completion of TMZ/RT, provided the following criteria are met.

1) PATIENT INCLUSION CRITERIA:

a. Histologically confirmed diagnosis of GBM according to WHO classification criteria.
b. Supratentorial tumor location
c. age ≥ 18 years
d. Recovered from maximal debulking surgery, if applicable (gross total resection, partial resection and biopsy-only patients are all acceptable)
   - Patients may enroll in the study if received Gliadel wafers before entering the trial
e. have completed standard adjuvant chemoradiotherapy of approx. 60 Gy of RT, or biologically equivalent dose, according to local practice, and concomitant TMZ chemotherapy (75mg/m^2 daily)
   - Any other cytotoxic or biologic anti-tumor therapy received prior to enrollment will be considered an exclusion.
f. Planned treatment with adjuvant/maintenance TMZ (150-200 mg/m2 daily x 5 d, q28 days)
g. All patients must have had tissue submitted for *MGMT* Promoter Methylation determination prior to randomization, following an analysis performed by a central lab on a paraffin-embedded tissue block from the surgical procedure used for GBM diagnosis (tissue slides are not desirable but optional),
h. Karnofsky performance status ≥ 70%
i. Life expectancy ≥ least 3 months
j. Participants of childbearing age must use effective contraception.
k. All patients must sign written informed consent.
l. Study start date at least 4 weeks out from brain surgery.
m. Study start after the end of RT/TMZ (admissible Study start date of TTF and/or temozolomide should be between day 29 and day 49 after last dose of irradiation).
n. Stable or decreasing dose of corticosteroids for the last 7 days prior to randomization, if applicable.

2) PATIENT EXCLUSION CRITERIA:

o. Early progressive disease after the end of TMZ/RT. If pseudoprogression is suspected, additional imaging studies should be performed to rule out true progression. The sponsor should be contacted in case of doubt.
p. Participation in another clinical treatment trial
q. Pregnancy
r. Significant co-morbidities at baseline which would preclude maintenance TMZ treatment:
   i. Thrombocytopenia (platelet count < 100 x 10^3/ µ L)
   ii. Neutropenia (absolute neutrophil count < 1.5 x 10^3/µL)
   iii. CTC grade 4 non-hematological Toxicity (except for alopecia, nausea, vomiting)
   iv. Significant liver function impairment - AST or ALT > 3 times the upper limit of normal
   v. Total bilirubin > 1.5 x upper limit of normal
   vi. Significant renal impairment (serum creatinine > 1.7 mg/dL, or > 150 µmol/l)
s. Implanted pacemaker, programmable shunts, defibrillator, deep brain stimulator, other implanted electronic devices in the brain, or documented clinically significant arrhythmias.
t. Infra-tentorial tumor location
u. Evidence of increased intracranial pressure (midline shift > 5mm, clinically
   - significant papilledema, vomiting and nausea or reduced level of consciousness)
v. History of hypersensitivity reaction to TMZ or a history of hypersensitivity to DTIC.

VI. RECRUITMENT PLAN

Patients will be recruited locally at each center. All patients will be seen by the corresponding local investigator or sub-investigator. Every effort will be made to encourage eligible women and minorities to participate. All patients will be required to sign a written informed consent prior to being registered on this protocol. Patients will be extensively informed both orally and in writing, patient will have sufficient time for reflection and consideration of alternative treatments. The local investigator will be available to answer any questions the patient or his entourage may have.

VII. RANDOMIZATION

Patients who meet the above inclusion/exclusion criteria will be randomized at a 2:1 ratio either to the treatment group who will receive NovoTTF-100A treatment together with maintenance TMZ, or to the control group who will receive standard maintenance TMZ alone. Randomization will be performed centrally using a web based software. Stratification for the following prognostic factors will be performed:

a. Extent of Resection – Biopsy; Partial Resection; Gross total resection (only if immediate post surgical MRI is available)

b. *MGMT* methylation status as provided by the central lab – Positive, Negative, Indeterminate

Randomization will be performed with randomly varying block sizes (e.g., 3, 6, or 9 patients) within each stratum.

VIII. PRE-TREATMENT EVALUATION (SCREENING AND BASELINE) (TAB A)

Within one week prior to beginning treatment all patients will undergo the following studies:

- Baseline contrast enhanced MRI of the brain (within 2 weeks before beginning treatment).
- Complete physical examination, including vital signs
- Neurological status, MRC scale (see TAB H) and KPS (Karnofsky performance status – see TAB C).
- Complete blood count (CBC) and differential
- Biochemistry panel (Electrolytes, BUN, creatinine, bilirubin, liver enzymes, albumin, total protein, glucose, cholesterol)
- Quality of life questionnaire (EORTC QLQ-C30 + BCM20)
- MMSE

IX. TREATMENT PLAN – NOVOTTF-100A+TMZ GROUP

All patients will begin treatment with TMZ and NovoTTF-100A within 1 week from screening/baseline evaluation, and no later than 7 weeks from last dose of concomitant TMZ/RT (the latter of the two).

a. Maintenance TMZ treatment

All patients are to receive standard maintenance TMZ chemotherapy according to the established regimen (Stupp et al., NEJM 2005 and TMZ package insert). Maintenance treatment is to begin about 4 weeks after the end of TMZ/RT. TMZ is administered at the conventional dosing regimen for 5 days, every 28 days (i.e.. 5 days of therapy, 23 days of rest). Cycle 1 is to be given at a dose of 150 mg/m2 p.o. daily x 5 days, dose to be escalated to 200 mg/m2 in the absence of toxicity. TMZ administration and dosing guidelines are available from the manufacturer and are summarized in the TMZ package insert.

Patients who completed all 6 cycles of maintenance TMZ will be treated per investigator discretion, concomitant with the TTF treatment, until second progression. Prolonged maintenance TMZ treatment is admissible as per local practice and physician's discretion.

b. Treatment after TMZ discontinuation:

Following TMZ discontinuation due to toxicity or radiological disease progression (based on local interpretation of MRI), patients in both arms may be offered second line therapy for their disease. The following treatment options may be considered based on the patient's clinical condition:

1. Re-operation (NovoTTF-100A treatment shall be interrupted for at least 2 weeks after reoperation, but may be restarted after adequate wound healing).
2. Re-irradiation or radiosurgery (e.g., gamma knife)
3. Second line chemotherapy
4. Combination of the above

TTF treatment will continue concomitantly with second line treatments until second disease progression for NovoTTF-100A + TMZ arm patients.

c. NovoTTF Treatment

The NovoTTF-100A treatment will be initiated in an outpatient clinic by the investigator at each center. In addition to baseline clinical evaluation (as elaborated in section VIII), the investigator will perform the following actions for the treatment arm patients:

- Train the patient in using the device:
  - Battery replacement and recharging
  - Turning the device on and off
  - Disconnecting and reconnecting the transducer arrays from the device for personal needs
  - How to handle device error messages (see trouble shooting section in User manual)
  - What adverse events can be expected during the treatment.
  - How to handle irritated skin
  - What to do in case of new or worsening clinical signs (call investigator)
- Review of the baseline MRI and decide where to place the transducer arrays (according to the guidelines elaborated in section X below).
- Shave the patients scalp (can be performed by other medical staff in the hospital or by a barber prior to coming to the hospital)
- Place the transducer arrays
- Connect the transducer arrays to the device (through the connection cable)
- Turn on the device

The device will be set in advance by a device technician with the following treatment parameters:

- Frequency – 200 kHz
- Output current – 707 mA RMS
- Number of field directions – 2
- Duty cycle – 1 sec in each direction

The patients will continue treatment at home after being trained in device use.

The NovoTTF treatment group patients will receive multiple 1 month courses of continuous NovoTTF-100A treatment together with standard maintenance TMZ. In the absence of treatment related serious adverse events, NovoTTF will continue up to 24 monhts or second progression. Instructions and surveillance of technical aspects of the treatment are handled by specialized technicians trained by the sponsor. The technicians will see the patients at specific technical clinics or at the patients' homes. Patients in the treatment arm will visit these clinics for treatment maintenance, technical support and assistance in transducer array replacement. The following actions are performed by the technician:

- Periodic transducer array replacement (twice per week) – patients will come to technical clinics for this purpose or be trained to replace transducer arrays independently. Transducer arrays will be placed in the same locations every time, according to the locations originally decided upon by the investigator unless the patient experiences skin irritation, in which case, they are alternated (see Section XI below).
- Periodic download of device log (once every 2 weeks)
- Replacement of faulty equipment
- Device, transducer array and accessory accountability tracking, and requests for replacements from Novocure
- Problem solving – by phone between visits to the technical clinic or directly during these visits
- For technical support the patient will contact the local technical clinic. A list of clinics and their contact information will be supplied to the patients separately. If the patient is unable to get a hold of the local device technician or if the patient has technical problems with the device outside regular working hours he/she should call the following Toll free number for Novocure's international support center:
  - USA: 1 - 800 NOVOCURE (1-800-6686-2873)
  - Europe: 00 - 800 – NOVOCURE (00-800-6686-2873)

During NovoTTF-100A treatment the patient is advised to interrupt treatment for periods of up to an hour twice a day for personal needs and to give the skin a short period of rest. Longer treatment breaks for personal reasons or in order to allow for recovery from toxicity should ideally be coordinated in advance with the local investigator and the technician. Treatment

breaks of up to 3 days per month are considered planned according to the protocol, longer breaks need to be justified and explained in the CRF.

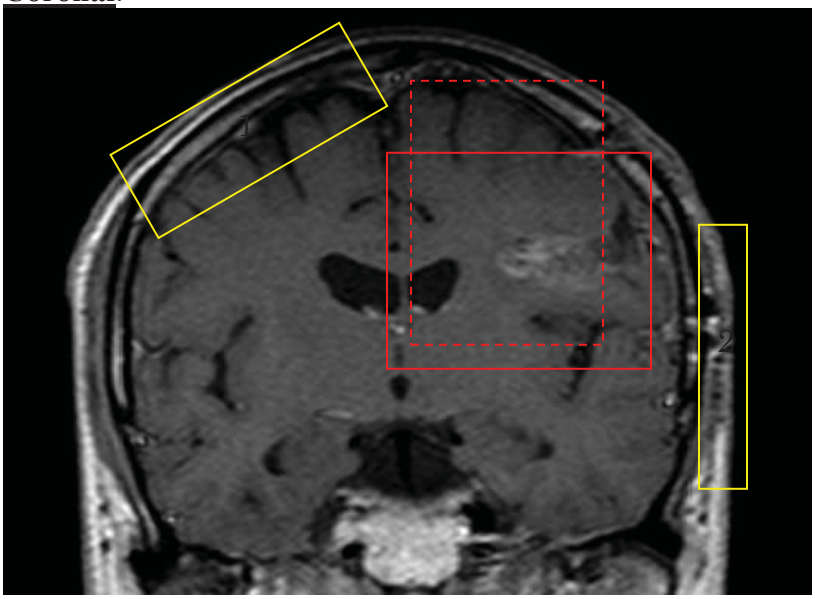
Clinical follow-up includes monthly medical visits and appropriate laboratory and/or imaging investigations as needed and is described in detail in TAB A and TAB B. During these visits the investigator will remove the transducer arrays and examine the skin beneath them.

X. TRANSDUCER ARRAY PLACEMENT PROTOCOL:

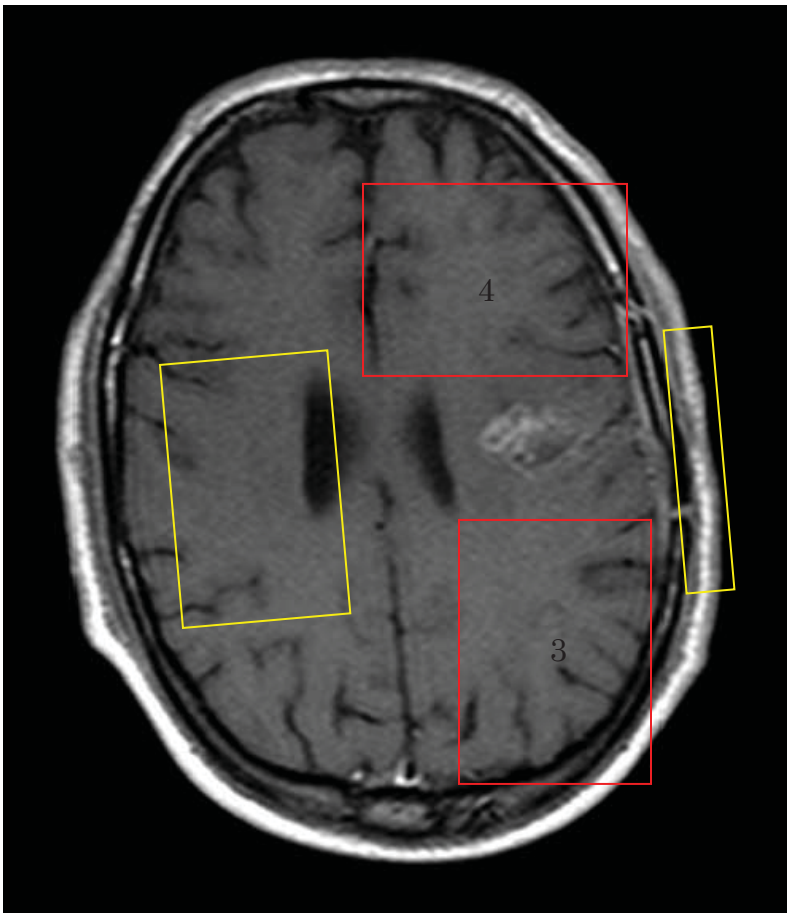
The specific locations of each transducer array set will be determined according to tumor location as follows: the transducer array locations will be determined so as to minimize the distance between each transducer array set and the center of the tumor, while maintaining a distance of at least one tumor diameter between the transducer array sets. This means that the closer the tumor is to the calvarium, the closer the transducer array sets will be to each other, and the closer the tumor is to the center of the brain, the further the transducer array sets will be from each other. At all times a right angle will be maintained between the imaginary lines connecting each pair of transducer array sets. If needed, adjustments to transducer array placement will be made following first progression.

{Example: Direction 1 = set 1 versus set 2; Direction 2 = set 3 versus set 4}

Coronal:



Horizontal:



XI. EVALUATION DURING NovoTTF-100A TREATMENT

During transducer array replacement, the skin below the transducer array will be inspected. In the event of significant skin breakdown (leading to pain or bleeding) or evidence of infection, the transducer array will be moved to an alternate site. Skin breakdown and/or infection will be treated according to the treating physician's clinical judgment, preferably based on a dermatologist's recommendation. Skin breakdown or evidence of infection, either of which requires a break in NovoTTF-100A treatment greater than 3 days, will be captured as an Adverse Event. Mild to moderate contact dermatitis is expected to appear beneath the transducer array gel during the first or second treatment course. This condition will be treated as follows:

1. Transducer array location will be shifted between two alternate sites at every transducer array change.
2. If skin is inflamed – apply 0.1% hydrocortisone ointment.
3. If skin is breached (abrasions, micro-ulcerations, oozing, open sores) or infected – Discontinue hydrocortisone and prescribe a Mupiricin (e.g. Bactroban®) ointment.
4. In the case of skin blistering – apply Silver Sulfadiazine (e.g. Silverdine ointment). In the case of known hypersensitivity to sulfa containing compounds the treatment outlined will not be offered and a dermatologist will be consulted.
5. In any case where the patient does not notice an improvement in skin sores, infection or blistering within 2 weeks of starting one of the treatments outlined above, the patient will inform the investigator and a dermatological consult will be obtained.
6. Oral antihistamines and analgesics will be prescribed at the investigators' discretion to control pruritus and pain.

XII. TREATMENT PLAN – MAINTENANCE TMZ

Patients randomized to the control group will be treated with maintenance TMZ as described above (see IX a.). Treatment will start within 1 week from screening/baseline evaluation, and no later than 7 weeks from last dose of concomitant TMZ/RT (the latter of the two).

XIII. PERIODIC EVALUATION UNTIL TREATMENT TERMINATION

Patients in both groups will undergo the following studies or review every month until treatment termination:

- Physical examination, including vital signs
- Neurological status and MRC score (TAB H).
- Quality of life questionnaire (EORTC QLQ-C30 + BCM-20) – every three months until treatment termination
- Blood exams (CBC, Chemistry)
- Steroid type and dose, if applicable
- Concomitant medication
- Record of Adverse Events
- Mini Mental State Exam (MMSE)

The patients will have a contrast MRI of the head performed after every two months until second progression. In case of clinical progression an MRI shall be performed without undue delay (ideally within a week). Contrast agent type and dose will be kept constant for each patient between scans. Central MRI review will be performed by a neuro-radiologist blinded to the treatment group of each patient.

XIV. POST-TREATMENT EVALUATION

Treatment will continue according to the protocol until second progression or 24 months (the earlier of the two). Monthly medical follow-up visit shall be scheduled for 2 months after termination of protocol therapy in order to capture potential treatment related toxicities. All patients will be followed for survival by either direct contact or regular telephone interviews with the patient or the patient's caregiver. Physical and neurological examination, blood tests (CBC and Chemistry panel) will be performed during these visits. Adverse events and date of last patient contact or date of death will be documented on the case report forms. Subsequently, all patients will be followed for survival by either direct contact or regular telephone interviews with the patient or the patient's caregiver.

XV. MGMT METHYLATION STATUS ASSESSMENT

MGMT methylation status - will be assessed centrally by polymerase chain reaction (PCR) methylation status of the promoter region of *MGMT* gene.

Randomization will be stratified according to *MGMT* methylation status based on central lab analysis performed prior to randomization. The laboratory will be blinded to the treatment group of the patients. The name of the laboratory used for *MGMT* determination will be recorded.

All patients enrolled in the study must have paraffin embedded brain tissue available for central pathology review and MGMT determination. Additional molecular tests as described below will be performed separately in a central lab and may not be available at time of randomization.

Adjustments for *MGMT* methylation status will be performed for during final analysis (see statistical analysis section).

Submission of the following material is required for tissue evaluation:

- Representative formalin-fixed and paraffin-embedded (FFPE) tumor tissue blocks. Slides are not desirable but optional in case no tissue blocks are available for testing.
- Samples will be kept at the Central Pathologist site until the molecular testing has been performed. After the end of the study, the tissue blocks will be returned to the local pathologists or centers.

- On specific request for medical reasons by the investigator or pathologist the block is shipped promptly back to the site.
- All fixed tissue for *MGMT* analysis should preferably be fixed in 10% v/v neutral buffered formalin where possible. To preserve the quality of the tissue and increase the likelihood of a valid *MGMT* methylation assay result, acidic formalin, zinc or mercuric chloride should be avoided where possible.
- Samples fixed in formalin for longer than 18 hours yield low quality DNA due to cross linking. Fixation times of greater than 24 hours should preferably be avoided.
- Shipping supplies and lab detailed specifications will be provided by Novocure for each site
- An accompanying H&E slide is encouraged for rapid diagnosis, but is not required. The shipment should be accompanied by an anonymized copy of the local pathology report or a completed Local Pathology Form documenting and identifying the submitted material. This will include protocol number, local institution information, patient identifier and pathological data. The patient's name and/or other identifying information should be removed from the form.
- Any effort should be made to obtain FFPE tumor tissue block from a referral center in case the EF-14 patient candidate was not operated at an EF-14 trial center, in order to allow patient enrollment.
- All patients with submitted tissue samples for MGMT analysis will be considered eligible for randomization as long as they comply with all other eligibility criteria.

All samples for pathology review, experimental and translational neuro-oncology will be collected at the central Laboratory at CHUV in Lausanne. Send all samples to:

Lab of Brain Tumor Biology and Genetics (Prof. Monika Hegi)
Neurosurgery Department
University Hospital (CHUV BH19-110)
Rue du Bugnon 46
Lausanne 1011
Switzerland

Phone: +41-21 314 25 81
Fax: +41-21 314 25 87
Email: NCH.LABOLN@chuv.ch

Reimbursement of shipping

The sponsor will reimburse pathologists on a per case basis for biological material and tumor blocks submitted. Novocure will also reimburse sites for obtaining FFPE tumor tissue blocks from referral patients, if applicable.

XVI. ADDITIONAL TUMOR GENETIC ASSESSMENTS

- In addition to *MGMT*, all patients with paraffin embedded brain tissue available for additional analysis, will also have the following molecular analyses of their tumor tissue performed by the central lab:
- EGFR amplification, over expression or rearrangement
- Chromosomes 1p/19q deletion status
- IDH1 mutation

XVII. POTENTIAL ADVERSE EFFECTS

Treatment with the NovoTTF-100A is not expected to cause any serious side effects. However, it is possible that investigational treatment will cause any of the following:

- Local warmth and tingling sensation beneath the transducer arrays
- Allergic reaction to the plaster or to the gel
- Skin breakdown
- Infection at the sites of transducer array contact with the skin
- Transducer array overheating leading to pain and/or local skin burns
- Headache
- Fatigue
- Seizures

Treatment with TMZ may cause the following adverse events:

- Myelosuppression, in particular thrombocytopenia and leukopenia
- Fatigue
- Nausea and vomiting
- Headache (often due to prophylactic antiemetics)
- Vomiting or Constipation (often due to prophylactic antiemetics)

Adverse events and complications that are often associated with the underlying brain tumor but could theoretically be exacerbated by the NovoTTF-100A treatment:

- Seizures
- Neurological and functional decline
- Headaches

XVIII. ADVERSE EVENT REPORTING

Definition of Adverse Events

As defined by the ICH Guidelines for Good Clinical Practice E2A (CPMP/ICH/377/95), an adverse event (AE) is any untoward medical occurrence in a patient administered a medicinal product and which does not necessarily have to have a causal relationship with this treatment. An

adverse event can therefore be any unfavorable and unintended sign (for example, an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to this medicinal product. Adverse events include the following:

- All suspected medication adverse reactions
- All reactions from medication overdose, abuse, withdrawal, sensitivity, or toxicity.
- Apparently unrelated illnesses, including the worsening of a preexisting illness
- Injury or accidents. Note that if a medical condition is known to have caused the injury or accident (a fall secondary to dizziness), the medical condition (dizziness) and the accident (fall) should be reported as 2 separate adverse events.
- Abnormalities in physiological testing or physical examination findings that require clinical intervention or further investigation (beyond ordering a repeat [confirmatory] test).
- Laboratory abnormalities that require clinical intervention or further investigation (beyond ordering a repeat [confirmatory] test) unless they are associated with an already reported clinical event. Laboratory abnormalities associated with a clinical event (elevated liver enzymes in a patient with jaundice) should be captured in the source documents.

Each adverse event is to be classified by the investigator as serious or non-serious. This classification of the gravity of the event determines the reporting procedures to be followed.

Grading of an Adverse Event

The descriptions and grading scales found in the revised NCI Common Toxicity Criteria (CTC) version 3.0 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	Transient or minimal symptoms, no change in activity or need for medication
MODERATE	Grade 2	Symptomatic change, interferes to some extent with patient's usual function
SEVERE	Grade 3	Incapacitating, significantly interferes with patient's usual function

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

Serious Adverse Events

An adverse event that meets one or more of the following criteria/outcomes is classified as serious:

Death
Life-threatening (i.e., at immediate risk of death)
Inpatient hospitalization or prolongation of existing hospitalization
Persistent or significant disability/incapacity
Congenital anomaly/birth defect

Important adverse events that may not result in death, may not be life-threatening, or do not require hospitalization may be considered serious when, based upon appropriate medical judgment, they may acutely jeopardize the patient without immediate medical intervention to prevent one of the outcomes listed above. Serious may also include any other event that the investigator or company judges to be serious. In addition, sites are responsible for reporting serious adverse events to their local IRB/EC according to their institutional requirements. Death due to disease progression need not be reported to the study monitor. These SAEs will be captured in the CRFs as described for regular AEs.

Routine Adverse Event Reporting

All adverse events must be reported in the source documentation and CRFs with appropriate information, including severity and rating of causality to the study drug/treatment. Adequate source documentation must be available to characterize the severity, duration and causality of each reported adverse event.

Unanticipated Adverse Device Effect Event (UADE) Reporting

Any potential unanticipated adverse device effect (UADE) will be reported to the study monitor and local IRB/EC within 10 days of the investigator learning of the event. The medical monitor will investigate whether the adverse event is a UADE and, if so, report the UADE to the Sponsor, as soon as possible but no later than 3 days after first learning of the event. Expedited report for FDA submission and reporting to other IRBs/ECs to follow within 10 working days after first learning of the event by the medical monitor.

The report will contain the following:

- The initials of the subject, patient MRN #, protocol # and title
- The date the event occurred
- A description of the UADE
- An explanation of how the UADE was handled
- A description of the subject's condition
- Indication if the subject remains on the study
- Indication if the event is considered related to the NovoTTF-100A
- Indication if an amendment to the protocol and/or consent form is recommended as a result

Eliciting Adverse Event Information

The investigator is to report 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?”

Adverse Event Reporting Period

The adverse event reporting period will begin immediately following initiation of treatment with the NovoTTF-100A device or BSC chemotherapy. Adverse events will be collected for two months 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 CRFs, 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.

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.

XIX. STUDY OUTCOME MEASURES

1. Efficacy analysis:

a. Primary Endpoint

- The primary endpoint of the study will be progression free survival

b. Secondary Outcome Measures

- Overall survival
- Progression free survival at 6 months (PFS6)
- One and two year survival rate
- Quality of life (EORTC QLQ-C30 + BN20 questionnaire; TAB H)
- The radiological response of the tumor will be assessed by the MRI studies according to Macdonald criteria for progressive disease, stable disease, partial response or complete response (see TAB D). All patients will have their tumor measurements recorded at baseline and at the time of each MRI scan. Lesions must be measured in two dimensions. The dose and type of contrast agent must be held constant from scan to scan for each patient.

2. Safety analysis:

- Safety and tolerability of NovoTTF-100A treatment based on the incidence and severity of adverse events and toxicities. Toxicities will be assessed according to the "Common toxicity criteria (CTC), version 3.0" (see TAB B).

XX. CRITERIA FOR REMOVAL FROM STUDY

- 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 for the patient. Patient follow up will continue as for the control arm after such an event.
- The investigator may remove a patient from the study in case of not complying with study protocol.
- Patients will be able to withdraw from the trial at any time at their own request. All data collected until treatment discontinuation, follow-up and outcome data will remain in the database, unless the patient formally withdraws the consent for collecting further follow-up and survival data.

XXI. STATISTICAL CONSIDERATIONS

A. Sample Size Calculation

Based on the insignificant side effects of NovoTTF-100A treatment observed in the pilot studies of newly diagnosed GBM performed so far in Europe and in the pivotal trial in recurrent GBM, we assume that any significant increase in progression free survival compared to the control group would justify use of the NovoTTF-100A device in newly diagnosed GBM patients, concomitant to maintenance TMZ.

The sample size of 700 patients (210 Control patients + 420 NovoTTF-100A patients + 10% loss to follow-up) was determined using NCSS/PASS11 software based on the log-rank test comparing time to event (i.e., progression or death prior to progression) between patients treated with the NovoTTF-100A together with maintenance TMZ and controls (maintenance TMZ alone). The null hypothesis is that the recurrence rate is the same in the two study groups, *i.e.*, hazard ratio=1. The alternative hypothesis is that the recurrence rate is not the same, *i.e.*, hazard ratio≠1. The expected hazard ratio was estimated from the expected median progression free survival in the two study groups as follows:

- Expected median progression free survival on control treatment is 7 months (see Stupp et al., NEJM, 2005[23] and TMZ package insert), and similar PFS was also seen in the recently reported RTOG0525-EORTC Intergroup trial[26]
- Expected median progression free survival on NovoTTF-100A treatment is 9 months.
- This increase in median PFS is equivalent to a Hazard Ratio of 0.78 for the NovoTTF-100A patients compared to control patients.
- Expected accrual time during which patients are recruited: 48 months
- Additional follow-up time after end of recruitment: 18 months.
- Ratio of control to experimental patients: 1:2
- Type I error: 0.05%; 2-sided
- Power: 80%

This sample size also has adequate power (80%) to detect a minimum of 4.5 month increase in median overall survival in NovoTTF-100A treated patients compared with control patients (who have an expected median OS of 14.6 months). This increase in survival is equivalent to a Hazard Ratio of 0.76 for the NovoTTF-100A patients compared to control patients.

Recently, the results of RTOG0525-EORTC Intergroup trial[26] have been presented. Similar to the current protocol, in the RTOG trial non-progressive patients were randomized only after TMZ/RT (however the RTOG trial included only patients who had undergone prior tumor resection). In that trial median survival was 18 months. In our trial powered to achieve a hazard ratio of 0.76 for OS, this would translate to a 6-months increase in median survival to 24 months, a difference that would be considered clinically meaningful.

One interim analysis will be performed on the PFS and OS data available on the first 315 patients with a minimum of 18 months follow up. The assumptions used in the sample size calculations will be evaluated at the interim analysis. If it appears that the event rate and/or the

treatment effect may be smaller than expected, adaptation of the sample size may be considered in order to allow for adequate study power. The company will not request a sample size decrease based on the results of this assessment.

B. Statistical analysis

1. The primary endpoint will be achieved if the progression free survival is significantly greater in the treatment group than in the control group. In order to allow for two analyses in the trial the alpha level used at each time point will be calculated according to the Lan-DeMets method using the O'Brien and Fleming spending function[24,25] (approximately 0.01394 at the interim analysis and 0.04574 at the final analysis).

2. The primary analysis will be an intent-to-treat (ITT) analysis including all randomized patients according to their assigned treatment. For analysis of progression free survival, patients will be censored at the time that they are last known to be alive and recurrence free (if withdrawn or lost to follow-up) or at study closeout. For patients without any follow-up data, a sensitivity analysis will be performed that will include various imputation methods, such as treating all missing data as failures, treating all missing data as successes, treating all missing data in the treatment group as failures but all successes in the control group ("Worst Case") and treating all missing data in the control group as failures but all successes in the treatment group ("Best Case"). Baseline characteristics of patients who withdraw or are lost to follow-up will be compared with patients who remain in the study to evaluate the potential for informative censoring. A sensitivity analysis will be conducted to evaluate the assumption for interval censoring (i.e., event time is assumed at the time of the visit). A sensitivity analysis will also be conducted excluding patients without MRI documented disease progression

3. Secondary analyses will be performed based on the per protocol population. The specific tests to be used for secondary outcome measures are described below:
    - Overall survival time – This endpoint will be achieved if the overall survival is significantly greater in the treatment group than in the control group using a log-rank test. In order to allow for two analyses in the trial the alpha level used at each time point will be calculated according to the Lan-DeMets method using the O'Brien and Fleming spending function[24,25] (approximately 0.00598 at the interim analysis and 0.0481 at the final analysis).
    - Progression free survival at 6 months (PFS6) – This endpoint will be tested with a one-sided chi-square test, assuming the NovoTTF-100A arm will have a higher PFS6 than the control arm of the study. No analysis will be performed at the interim analysis.
    - One and two year overall survival rates - These secondary endpoints will be tested with a one-sided chi-square test, assuming the NovoTTF-100A arm will have higher 1- and 2-year survival rates than the control arm of the study. No analysis will be performed at the interim analysis.
    - Quality of life (EORTC QLQ-C30 + BN20 questionnaire; TAB H) – Change from baseline (CFB) to 3, 6, 9 and 12 months will be calculated for each subscale domain and symptom scale in the questionnaire. Results will be presented

descriptively as a ratio in CFB at each of the above time points in the treatment arm compared to the control arm of the study.

- Radiological response rate – This endpoint will compared between groups using a one-sided chi-square test assuming the NovoTTF-100A arm will have a higher response rate than the control arm of the study. No analysis will be performed at the interim analysis.

Preservation of the type I error –

1. Overall survival is the most important secondary endpoint. Prolongation of survival is considered to correlate with a clinical benefit for the patient. Thus, this trial has been sufficiently powered to allow for definitive conclusions with regards to overall survival after adequate follow-up.
2. No efficacy claims are planned based on PFS6, 1- and 2-year survival, quality of life analysis or radiological response rate. Thus, the entire alpha of 0.05 will be allocated to the overall survival endpoint and no adjustment will be made for multiple hypothesis testing.
3. A hierarchical approach will be used to first test the primary endpoint of PFS and then the secondary endpoint of overall survival to avoid problems with statistical multiplicity. Specifically, overall survival will be tested at the proposed significance levels for the interim and final analyses if the primary endpoint of progression free survival also meets its significance levels at the respective time points.

C. Covariates

A Cox proportional hazards model will be used to evaluate covariates. The effect of the following covariates will be compared and adjusted for between the treatment and control groups:

1. Age
2. Extent of surgery (biopsy, partial, or total resection)
3. *MGMT* methylation status (positive, negative, indeterminate)
4. Additional genetic markers:
    a. EGFR amplification, over expression or rearrangement
    b. Chromosomes 1p/19q deletion status
    c. *IDH1* mutation
5. Baseline Karnofsky performance scale score
6. Tumor size
7. Tumor location
8. Percent of the total treatment time in which the NovoTTF-100A treated patients actually received treatment (will be calculated by analyzing the internal computerized log file of each NovoTTF-100A device and dividing the total device ON time by the prescribed number of 1 month treatment courses).
9. Duration of temozolomide therapy
10. Gliadel wafers administration

D. Additional variables

The following parameters will be also recorded and compared between the treatment and control groups:

- Overall survival time (log Rank Test). In order to allow for two analyses in the trial the alpha level used at each time point will be calculated based on the O'Brien-Fleming method[24,25] (i.e., approximately 0.00598 at the interim analysis and 0.0481 at the final analysis). For analysis of overall survival, patients will be censored at the time that they are last known to be alive (if withdrawn or lost to follow-up) or at study closeout.
- Percentage alive and progression-free at 6-month
- Actuarial survival at 1 and 2-years
- Quality of life (EORTC QLQ-C30 + BN20 questionnaire)
- Radiological response rates
- MMSE scores
- Incidence and severity of adverse events

In addition, the correlation will be measured between the percent of time patients received NovoTTF-100A treatment (treatment compliance) and their progression free survival and overall survival.

XXII. RISK/BENEFIT ANALYSIS

The risks associated with use of the NovoTTF-100A are principally the risk of 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 transducer array sites. Technical failure is extremely unlikely due to stringent compliance with all standard design and manufacturing safety protocols. In addition, appropriate measures have been taken to minimize the risk to study subjects, including preclinical *in vitro* and *in vivo* testing to ensure safe operation of the device. The 20 recurrent and newly diagnosed GBM patients treated to date as part of pilot studies (10 patients with the combination of TMZ and NovoTTF-100A) suffered no treatment related serious adverse events after > 180 months of treatment (cumulatively). In fact the only complication seen was a mild to moderate skin irritation beneath the transducer array gel. In the pivotal study in recurrent GBM, 116 patients were treated with the NovoTTF-100A device without unexpected device events[28].

XXIII. STUDY MONITORING AND QUALITY ASSESSMENT

Study sites will be monitored by an independent clinical research organization (CRO). The sponsor will mandate one or several CRO's for this task. Study monitoring functions will be in compliance with recognized Good Clinical Practices, 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:

on-site visits and review of study documents and results. The CRO will operate under written procedures to ensure compliance with the protocol.

On-site monitoring visits will take place at each center prior to study initiation and at least once during the course of the study, and a final visit at the close of the study. The pre-study visit is intended to provide an opportunity for the monitor to review the Investigational Plan with the Investigators and to ensure that the Investigators:

- have appropriate training, facilities, patient load, time, and willingness to comply with study requirements;
- have the approval of the supervising Institutional Review Board (IRB) or Ethics Committee (EC) for the Investigational Plan;
- have all study documentation and required records on site; and
- assume responsibility for the investigation at their center.

Visits during the study are 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. During these in-study visits, 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 monitor's final on-site visit at completion of the study is intended to assure that all the data have been properly completed and to have a closing meeting with the Investigators and their staff members. Reports of the on-site visits will be made by the monitor and 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.

An independent Data and Monitoring Committee (DMC), comprised of at least a neurosurgeon, a neuro-oncologist and a statistician will be formed to monitor the safety data from the study. Although there are no anticipated significant safety issues with the device, the adverse event data will be reviewed by the DMC to determine if there are any unexpected safety concerns with the device that warrant study termination or if the study should be stopped for futility purposes. Specifically, DMC review will be performed annually from first patient recruited, or more often if necessary, to determine if:

- There is clear evidence of unacceptably harmful side-effects of NovoTTF-100A treatment together with maintenance TMZ; or
- There is no likelihood of demonstrating treatment benefit or equivalence.
- It is unethical to withhold NovoTTF-100A treatment from patients

Additionally, a formal statistical analysis of the interim efficacy results will be reviewed by the DMC to determine whether early stopping for efficacy or any modifications to the study design should be recommended.

The DMC will base their recommendation to the Sponsor on an evaluation of data such as:

- All adverse events, including serious adverse events and device or drug related AEs
- Progression free survival and overall survival

XXIV. PROTECTION OF HUMAN SUBJECTS

A. Privacy

It is the responsibility of the Research Staff to ensure that protocol patients have received the Center's Notice of Privacy Practices.

The Center's Privacy Office may allow the use and disclosure of protected health information pursuant to a completed and signed Research Authorization form. The use and disclosure of protected health information will be limited to the individuals described in the Research Authorization form. A Research Authorization form must be completed by the Principal Investigator and approved by the IRB/EC and Privacy Board.

XXV. INFORMED CONSENT PROCEDURES

RESEARCH AUTHORIZATION

Procedures for obtaining Research Authorization: Prior to carrying out any protocol-specific procedures, investigators or designated staff will explain fully the details of the protocol, study procedures, and the aspects of patient privacy concerning research specific information. In addition to signing the IRB/EC Informed Consent, all patients must sign the Research Authorization component of the informed consent form. The Research Authorization requires a separate signature from the patient. The original signed documents will become part of the patient's medical record, and each patient will receive a copy of the signed documents. All patients must provide written informed consent prior to registration and treatment.

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XXVII. PROTOCOL SIGNATURE PAGE

Investigator:

Center - _____

Investigator Name - _____

Signature - _____

Date - _____/_____/_____

Sponsor:

Novocure Ltd.

Name – _____

Signature - _____

Date –_____

TAB A

STUDY PROCEDURE MATRIX

	T=-7 (baseline)	T=1 month (±7 days)	T=2 months (±7 days)	T=3 months (±7 days)	T=4 months (±7 days)	T=5 months (±7 days)	T=6 months (±14 days)	T=every month until treatment stop+	T=Progression	T=1 month From treatment stop+	T=2 months From treatment stop+	Monthly thereafter+
MRI of the head	X*		X		X		X		X			
Physical examination	X	X	X	X	X	X	X	X	X	X	X	
Neurological status	X	X	X	X	X	X	X	X	X	X	X	
Complete blood count (CBC) and differential	See adjacent table											
Chemistry panel												
Coagulation												
Mini Mental State Exam (MMSE)	X	X	X	X	X	X	X	X	X	X	X	
Quality of life Questionnaire	X			X			X	X^				
Survival follow-up												X

* screening MRI should be done within 2 weeks before study start. MRI of the head will be performed routinely at baseline and again every 2 months until treatment termination or second progression, whichever is later. An MRI of the head will be obtained in the event of clinical signs of progression.

^ Every third month until treatment termination.

+ Visit window of ± 7 days if visit occurs prior to the 6 month follow-up window, ± 14 days if visit occurs on or after the 6 month follow-up window, ± 1 month if visit occurs on or after the 12 month follow-up window.

	Test	Screening	Follow-up	Progressions 1&2	1 month from treatment stop	2 months from treatment stop
Hematology	Hemoglobin	+	+	+	+	+
	Hematocrit	+	+	+	+	+
	RBC	+	+	+	+	+
	MCV	+	+	+	+	+
	WBC	+	+	+	+	+
	Neutrophils	+	+	+	+	+
	Eosinophils	+	#	#	#	#
	Basophils	+	#	#	#	#
	Lymphocytes	+	+	+	+	+
	Monocytes	+	#	#	#	#
	Platelets	+	+	+	+	+
Chemistry						
	Sodium	+	+	+	+	+
	Potassium	+	+	+	+	+
	Calcium	+	+	+	+	+
	Glucose	+	+	+	+	+
	BUN/Urea	+	+	+	+	+
	Creatinine	+	+	+	+	+
	Total Protein	+	+	+	+	+
	Total Bilirubin	+	+	+	+	+
	Alk. Phosphatase	+	+	+	+	+
	Albumin	+	+	+	+	+
	ALT	+	+	+	+	+
	AST	+	#	#	#	#
	Total Cholesterol	+	#	#	#	#
Coagulation						
	PTT	+	&	&	&	&
	INR	+	&	&	&	&

+ Required tests
# - only when clinically indicated
& - only for patients with coagulation problems / on anti-coagulants

TAB B

COMMON TOXICITY CRITERIA (V 3.0)

TAB C - KARNOFSKY SCALE

The *Karnofsky Scale* has been adapted for use in many areas, including hospices, cancer clinics, etc., as well as used by various CFS researchers and physicians (Leonard Jason, PhD; Jay A. Goldstein, MD).

The 10-point scale is a quick and easy way to indicate how you are feeling on a given day, without going through several multiple choice questions or symptom surveys.

100	Able to work. Normal; No complaints; No evidence of disease.
90	Able to work. Able to carry on normal activity; Minor symptoms.
80	Able to work. Normal activity with effort; Some symptoms.
70	Independent; not able to work. Cares for self; Unable to carry on normal activity.
60	Disabled; dependent. Requires occasional assistance; cares for most needs.
50	Moderately disabled; dependent. Requires considerable assistance and frequent care.
40	Severely disabled; dependent. Requires special care and assistance.
30	Severely disabled. Hospitalized, death not imminent.
20	Very sick. Active supportive treatment needed.
10	Moribund. Fatal processes are rapidly progressing

TAB D

MACDONALD CRITERIA

TAB E

INFORMED CONSENT

TAB F

CASE REPORT FORMS

TAB G

EORTC QLQ C30

EORTC QLQ-C30 (version 3)

We are interested in some things about you and your health. Please answer all of the questions yourself by circling the number that best applies to you. There are no "right" or "wrong" answers. The information that you provide will remain strictly confidential.

Please fill in your initials: ____
Your birthdate (Day, Month, Year): ____
Today's date (Day, Month, Year): 31 ____

		Not at All	A Little	Quite a Bit	Very Much
1.	Do you have any trouble doing strenuous activities, like carrying a heavy shopping bag or a suitcase?	1	2	3	4
2.	Do you have any trouble taking a long walk?	1	2	3	4
3.	Do you have any trouble taking a short walk outside of the house?	1	2	3	4
4.	Do you need to stay in bed or a chair during the day?	1	2	3	4
5.	Do you need help with eating, dressing, washing yourself or using the toilet?	1	2	3	4

During the past week:

		Not at All	A Little	Quite a Bit	Very Much
6.	Were you limited in doing either your work or other daily activities?	1	2	3	4
7.	Were you limited in pursuing your hobbies or other leisure time activities?	1	2	3	4
8.	Were you short of breath?	1	2	3	4
9.	Have you had pain?	1	2	3	4
10.	Did you need to rest?	1	2	3	4
11.	Have you had trouble sleeping?	1	2	3	4
12.	Have you felt weak?	1	2	3	4
13.	Have you lacked appetite?	1	2	3	4
14.	Have you felt nauseated?	1	2	3	4
15.	Have you vomited?	1	2	3	4

Please go on to the next page

During the past week:	Not at All	A Little	Quite a Bit	Very Much
16. Have you been constipated?	1	2	3	4
17. Have you had diarrhea?	1	2	3	4
18. Were you tired?	1	2	3	4
19. Did pain interfere with your daily activities?	1	2	3	4
20. Have you had difficulty in concentrating on things, like reading a newspaper or watching television?	1	2	3	4
21. Did you feel tense?	1	2	3	4
22. Did you worry?	1	2	3	4
23. Did you feel irritable?	1	2	3	4
24. Did you feel depressed?	1	2	3	4
25. Have you had difficulty remembering things?	1	2	3	4
26. Has your physical condition or medical treatment interfered with your family life?	1	2	3	4
27. Has your physical condition or medical treatment interfered with your social activities?	1	2	3	4
28. Has your physical condition or medical treatment caused you financial difficulties?	1	2	3	4

For the following questions please circle the number between 1 and 7 that best applies to you

29. How would you rate your overall health during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

30. How would you rate your overall quality of life during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

EORTC BCM20 ADDENDUM

TAB H

MEDICAL RESEARCH COUNCIL (MRC) SCALE FOR NEUROLOGICAL STATUS

1	No neurological deficit
2	Some neurological deficit but function adequate for useful work
3	Neurological deficit causing moderate functional impairment e.g. ability to move limbs only with difficulty, moderate dysphasia moderate paresis, some visual disturbances (e.g. field detect)
4	Neurological deficit causing major functional impairment e.g. inability to use limb/s gross speech or visual disturbances No useful function - inability to make conscious responses

TAB I

PARTICIPATING INVESTIGATORS AND CENTERS (LAST UPDATED JULY 2012)

1.	Dr. Thomas C. Chen	(University of Southern California, CA)
2.	Dr. Santosh Kesari	(University of California San diego, CA)
3.	Dr. Nicholas G. Avgeropoulos	(MD Anderson Cancer Center Orlando, FL)
4.	Dr. Herbert H. Engelhard	(University of Illinois at Chicago, IL)
5.	Dr. Rajiv Desai	(Maine Medical Center, Maine)
6.	Dr. Eric T. Wong	(Beth Israel Deaconess Medical Center, MA)
7.	Dr. Joseph C. Landolfi	(New Jersey Neuroscience Center, NJ)
8.	Dr. Susan Pannullo	(Weill Cornell Medical College, NY)
9.	Dr. Gene Barnett	(Cleveland Clinic Taussig Cancer Center, OH)
10.	Dr. Frank S. Lieberman	(University of Pittsburgh Medical Center, PA)
11.	Dr. Steven A. Toms	(Geisinger Health System, PA)
12.	Dr. Karen L. Fink	(Baylor Medical Center, TX)
13.	Dr. John S. Nystrom	(Tufts Medical Center, MA)
14.	Dr. Surbhi Jain	(Moffitt Cancer Center, FL)
15.	Dr. Jung Wu	(University of North Carolina, NC)
16.	Dr. John W. Henson	(Swedish Neuroscience Institute, WA)
17.	Dr. Pamela Z. New	(Methodist Neurological Institute, TX)
18.	Dr. Yvonne Kew	(Methodist Hospital, TX)
19.	Dr. Carlos David	(Lahey Clinic, MA)
20.	Dr. Jay Jinguang-Zhu	(University of Texas Health Sciences Ctr, TX)
21.	Dr. Andrew Lassman	(Columbia University Medical Center, NY)
22.	Dr. John Villano	(University of Kentucky, KY)
23.	Dr. Tobias Walbert	(Henry Ford Health System, MI)
24.	Dr. Samuel Goldlust	(Hackensack University Medical Center, NJ)
25.	Dr. Steven Brem	(Hospital of the University of Pennsylvania, PA)
26.	Dr. David Tran	(Washington University Barnes-Jewish Hospital, MO)
27.	Dr. Allessandro Olivi	(Johns Hopkins University School, MD)
28.	Dr. Herbert Newton	(Ohio State University, OH)
29.	Dr. Isabelle Germano	(Mount Sinai School of Medicine, NY)
30.	Dr. William Read	(Emory University Hospital, GA)
31.	Dr. Roger Stupp	University Hospital (CHUV), Lausanne, Switzerland)
32.	Dr. Michael Weller	University Hospital (USZ), Zurich, Switzerl.
33.	Dr. Franz Payer	(University Hospital Graz, Austria)
34.	Dr. Sophie Taillibert	(Group Hospitals Pitie-Salpetriere, France)

35.	Dr. Jerome Honnorat	(Hospital of Neurology Lyon, France)
36.	Dr. Alexandra Benouaich-Amiel	(Hospitalo-Universitaire de Toulouse Purpan, France)
37.	Dr. Maximillian Mehdorn	(University Hospital of Schleswig-Holstein, Germany)
38.	Dr. Manfred Westphal	(University Medical Center Hamburg-Eppendorf, Germany)
39.	Dr. Andrew Kanner	(Tel Aviv Sourasky Medical Center, Israel)
40.	Dr. Antonio Silvani	(C. Besta Neurological Institute, Italy)
41.	Dr. Andrea Salmaggi	(Ospedale Lecco, Italy)
42.	Dr. Manuela Caroli	(Foundation Hospital Greater Policlinico, Italy)
43.	Dr. Carmine Carapella	(National Institution Regina Helena, Italy)
44.	Prof. Christine Marosi	(Medical University Hospital Vienna, Austria)
45.	Dr. Jordi Bruna Escuer	(Bellvitge Hospital Universitari, Spain)
46.	Dr. Pedro Perez Segura	(Hospital Clinico San Carlos, Spain)
47.	Prof. Massimo Scerrati	(Ospedaliero-Universitaria - Ospedali Riuniti, Ancona, Italy)
48.	Dr. Jan Sroubek	(Homolce Hospital, Czech Republic)
49.	Dr. Wolfgang Wick	(Medical University Heidelberg, Germany)

novocure

EF-14 Protocol Amendment (V1.3 → V2.0) – List of major changes

Section	Protocol V1.3	Protocol V2.0	Rationale
List of PI's	Partial list of investigators	List of investigators included (see Appendix 1)	The change reflects the requirement to include this information as set forth in ICH guideline for GCP E6(R1) 6.1.5.
I, IV	283 patients with newly diagnosed GBM	700 patients with newly diagnosed GBM	To power the statistical analysis taking into consideration the expected crossover from BSC arm, following FDA approval for recurrent GBM patients. Also in view of the requirement to collect additional genetic data from tumors.
I	Radiotherapy (60 Gy)	Radiotherapy (45-70 Gy)	To reflect common variations in standard of care treatment between individual patients/centers
III	N/A	Pivotal Study (NovoTTF for recurrent GBM compared to BSC) data	To include all clinical data available and relevant for the current study per GCP requirements
IV, XIX	The primary endpoint will be time to disease progression (TTP). The sample size was chosen based on the log-rank test comparing time to event (i.e., recurrence) assuming patients treated with the NovoTTF-100A together with maintenance Temozolomide will have a median TTP significantly greater than controls (10.7 months compared to 7 months, respectively; with an overall 5% 2-sided type I error and 80% power).	The primary endpoint will be progression free survival (PFS). The sample size was chosen based on the log-rank test comparing time to event (i.e., progression or death prior to progression) assuming patients treated with the NovoTTF-100A together with maintenance Temozolomide will have a median PFS significantly greater than controls (9 months compared to 7 months, respectively; with an overall 5% 2-sided type I error and 80% power).	To clarify the correct primary endpoint in the trial (progression or death prior to progression) and modify expected outcome according to the current statistical considerations.
IV	This sample size also has adequate power (80%) to detect a minimum of 8.9 month increase in median overall survival in NovoTTF-100A treated patients compared with control patients.	This sample size also has adequate power (80%) to detect a minimum of 4.5 month increase in median overall survival in NovoTTF-100A treated patients compared with control patients (expected control group median OS = 14.6 months, Stupp et al, NEJM 2005).	To reflect expected outcomes according to current statistical considerations.

IV	NovoTTF-100A treatment will be continued for 24 months unless the patient's clinical condition prohibits this.	NovoTTF-100A treatment will be continued for 24 months or until second progression whichever occurs first unless the patient's clinical condition prohibits this.	To emphasize treatment time per protocol, which was already clarified on Letter of Clarifications to EF-14 Protocol, No. 2 (1 March, 2010)
IV	Patients will be recruited to the study by the principal investigator (PI) or one of the co-investigators (CI) in 25 centers (at least half of the centers will be in the USA). Immediately following screening, patients will be randomized at a 2:1 ratio to receive either NovoTTF-100A treatment together with maintenance Temozolomide or maintenance Temozolomide alone. Patient accrual is expected to continue for 24 months. Patient follow-up for time to progression will continue until 12 months from accrual of the last patient. Follow up for overall survival will continue for 18 months from accrual of the last patient.	Patients will be recruited to the study by the principal investigator (PI) or one of the co-investigators (CI) in up to 40 US centers and at up to 25 OUS centers . Immediately following screening, patients will be randomized at a 2:1 ratio to receive either NovoTTF-100A treatment together with maintenance Temozolomide or maintenance Temozolomide alone. Patient accrual is expected to continue for 48 months. Patient follow-up for PFS and OS will continue for 18 months from accrual of the last patient.	To clarify the actual maximal number of centers allowed in this clinical trial, and updated time to accrual.
V	Patients who have progressive disease at screening (compared to the immediate post-surgical MRI) are not candidates for this study. In the case of local radiological suspicion of radiation necrosis the study PI will be consulted.	Disease status will be determined by comparing screening MRI to the immediate post-surgical MRI. If unavailable, an immediate post-surgical CT can be used for the same purpose. Patients who have progressive disease at screening (compared to the immediate post-surgical MRI) are not candidates for this study. In the case of local radiological suspicion of pseudoprogression a PET scan or other imaging modality (in addition to T1 weighted MRI) will be obtained to assess biological activity of the tumor.	To clarify imaging studies required for screening patients in this study, prior to enrollment, in order to comply with the eligibility criteria
V	Received maximal debulking surgery and radiotherapy with Temozolomide.	Received maximal debulking surgery and radiotherapy concomitant with Temozolomide (45-70Gy): 1. Patients may enroll in the study if received Gliadel wafers before entering the trial 2. Any additional treatments received prior to enrollment will be considered an exclusion. 3. Minimal dose for concomitant radiotherapy is 45 Gy	To clarify and standardize the pre-study treatment of the study population according to current best standard of care (see for example NCCN Practice Guidelines in Oncology – v.2.2009, and Stupp, 2005)
V	i. Treatment start date at least 4 weeks out from surgery. j. Treatment start date at least 4 weeks out but not more than 7 weeks from last dose of adjuvant Temozolomide.	h. Treatment start date at least 4 weeks out from surgery. i. Treatment start date at least 4 weeks out but not more than 7 weeks from the later of last dose of concomitant Temozolomide or	To simplify time window definitions for inclusion in this trial

	k. Treatment start date at least 4 weeks out from radiation therapy.	radiotherapy. … Progressive disease (according to MacDonald Criteria). If pseudoprogression is suspected, additional imaging studies must be performed to rule out true progression.	
V	Implanted pacemaker, defibrillator or deep brain stimulator, or documented clinically significant arrhythmias.	Implanted pacemaker, programmable shunts, defibrillator, deep brain stimulator, other implanted electronic devices in the brain, or documented clinically significant arrhythmias.	To broaden the definition of implants that become commonly used by the study population, and which might raise a safety concern, as set forth in ICH guideline for GCP E6(R1)
VI	N/A	TTF treatment will continue concomitantly with second line treatments until second disease progression for NovoTTF-100A + temozolomide arm patients.	To clarify the protocol requirement to continue TTF treatment following first progression and until second progression.
VI	No additional MRIs will be required after progression.	No additional MRIs will be required after second progression.	To clarify that MRI follow up scans will continue until second progression per protocol.
VII	Extent of Resection – Biopsy; Partial Resection; Gross total resection	Extent of Resection – Biopsy; Partial Resection; Gross total resection (only if immediate post surgical MRI is available)	To clarify that extent of resection cannot be a stratification criterion if no post surgical MRI is available (see Section V) per MacDonald criteria (MacDonald, 1990)
XII	N/A	as described above (see IX a.). Treatment will start within 1 week from screening/baseline evaluation, and no later than 7 weeks from last dose of concomitant temozolomide or radiation therapy (the latter of the two).	To simplify time window definitions for treatment start.
XVII	N/A	**ADDITIONAL TUMOR GENETIC ASSESSMENTS** In addition to MGMT, all patients with paraffin embedded brain tissue available for additional analysis, recruited to the trial after approval of	To comply with FDA requirement to add genetic profile tests of tumors in addition to MGMT methylation status.

		Version 2.0 of this protocol, will also have the following genetic analyses of their tumor tissue performed and the results correlated with OS results in the final analysis: • EGFR amplification, over expression or rearrangement • Chromosomes 1p/19q deletion status • IDH1 mutation	
XXI	The sample size of 283 patients (80 Control patients + 160 NovoTTF-100A patients + 15% loss to follow up) was determined based on the log-rank test comparing time to event (i.e., recurrence) between patients treated with the NovoTTF-100A together with maintenance Temozolomide and controls (maintenance Temozolomide alone). The null hypothesis is that the recurrence rate is the same in the two study groups, *i.e.*, hazard ratio=1. The alternative hypothesis is that the recurrence rate is not the same, *i.e.*, hazard ratio≠1. The expected hazard ratio was estimated from the expected median time to progression in the two study groups as follows: • Expected median time to progression on control treatment is 7 months (see Stupp et al., NEJM, 2005[23] and Temozolomide package insert) • Expected median time to progression on NovoTTF-100A treatment is 10.7 months. • Expected accrual time during which patients are recruited: 24 months • Additional follow-up time after end of recruitment: 12 months for time to progression and 18 months for overall survival. • Ratio of control to experimental patients: 1:2 • Type I error: 0.0475%; 2-sided • Power: 80% An alpha level of 0.0475 was chosen based on the O'Brien-Fleming alpha spending method[24,25] to allow for a single interim analysis. The alpha level used for the interim analysis will be 0.0187 for PFS and 0.006 for OS. The interim analysis will be performed on the PFS and OS data available for the first 120 evaluable patients with a minimum of 18 months follow up.	The sample size of 700 patients (210 Control patients + 420 NovoTTF-100A patients + 10% loss to follow-up) was determined using NCSS/PASS11 software based on the log-rank test comparing time to event (i.e., progression or death prior to progression) between patients treated with the NovoTTF-100A together with maintenance Temozolomide and controls (maintenance Temozolomide alone). The null hypothesis is that the recurrence rate is the same in the two study groups, *i.e.*, hazard ratio=1. The alternative hypothesis is that the recurrence rate is not the same, *i.e.*, hazard ratio≠1. The expected hazard ratio was estimated from the expected median progression free survival in the two study groups as follows: • Expected median progression free survival on control treatment is 7 months (see Stupp et al., NEJM, 2005[23] and Temozolomide package insert) • Expected median progression free survival on NovoTTF-100A treatment is 9 months. • Expected accrual time during which patients are recruited: 48 months • Additional follow-up time after end of recruitment: 18 months. • Ratio of control to experimental patients: 1:2 • Type I error: 0.05%; 2-sided • Power: 80% This sample size also has adequate power (80%) to detect a minimum of 4.5 month increase in median overall survival in NovoTTF-100A treated patients compared with control patients (who have an expected median OS of 14.6 months). One interim analysis will be performed on the PFS and OS data available for all patients after the first 315 patients accrued have a minimum of 18 months follow up. The assumptions used in the sample size calculations will be evaluated at the interim analysis. If it appears that the event rate and/or the treatment effect may be smaller than expected, the company may request a sample size increase to achieve the desired study power. The company will not request a sample size decrease based on the results of this assessment.	To adjust current statistical considerations to the study endpoints for the total number of patients.

XXI	Secondary analyses will be performed based on the per protocol population	Secondary analyses will be performed based on the per protocol population. The specific tests to be used for secondary outcome measures are described below: • Overall survival time – This endpoint will be achieved if the overall survival is significantly greater in the treatment group than in the control group using a log-rank test. In order to allow for two analyses in the trial the alpha level used at each time point will be calculated according to the Lan-DeMets method using the O'Brien and Fleming spending function[24,25] (approximately 0.00598 at the interim analysis and 0.0481 at the final analysis). • Progression free survival at 6 months (PFS6) – This endpoint will be tested with a one-sided chi-square test, assuming the NovoTTF-100A arm will have a higher PFS6 than the control arm of the study. No analysis will be performed at the interim analysis. • One and two year overall survival rates - These secondary endpoints will be tested with a one-sided chi-square test, assuming the NovoTTF-100A arm will have higher 1- and 2-year survival rates than the control arm of the study. No analysis will be performed at the interim analysis. • Quality of life (EORTC QLQ-C30 questionnaire; TAB H) – Change from baseline (CFB) to 3, 6, 9 and 12 months will be calculated for each subscale domain and symptom scale in the questionnaire. Results will be presented descriptively as a ratio in CFB at each of the above time points in the treatment arm compared to the control arm of the study. • Radiological response rate – This endpoint will compared between groups using a one-sided chi-square test assuming the NovoTTF-100A arm will have a higher response rate than the control arm of the study. No analysis will be performed at the interim analysis. Preservation of the type I error – 1. The company only plans to make efficacy claims on the first secondary endpoint, the overall survival, due to its importance and also the fact that it is a powered secondary endpoint in the trial. No efficacy claims are planned based on PFS6, 1- and 2-year survival, quality of life analysis or radiological response rate. Thus, the entire alpha of 0.05 will be allocated to the overall survival endpoint and no	To specify the statistical tests used for the analysis of secondary outcome measures.

		adjustment will be made for multiple hypothesis testing. 2. A hierarchical approach will be used to first test the primary endpoint of PFS and then the secondary endpoint of overall survival to avoid problems with statistical multiplicity. Specifically, overall survival will be tested at the proposed significance levels for the interim and final analyses if the primary endpoint of progression free survival also meets its significance levels at the respective time points.	
XXI	N/A	Additional genetic markers: 1. EGFR amplification, over expression or rearrangement 2. Chromosomes 1p/19q deletion status 3. IDH1 mutation	To reflect the change in covariates evaluation following the addition of genetic tests.
XXII	Overall survival time (Log Rank Test). In order to allow for two analyses in the trial the alpha level used at each time point will be calculated based on the O'Brien-Fleming method[24,25] (i.e., approximately 0.006 at the interim analysis and 0.0475 at the final analysis)..	Overall survival time (Log Rank Test). In order to allow for two analyses in the trial the alpha level used at each time point will be calculated based on the O'Brien-Fleming method[24,25] (i.e., approximately 0.0089 at the interim analysis and 0.0475 at the final analysis). For analysis of overall survival, patients will be censored at the time that they are last known to be alive (if withdrawn or lost to follow-up) or at study closeout.	To reflect updated considerations in the calculation of Overall Survival, following the increase in total number of patients enrolled in the trial.
XXIII	DMC review will be performed after 12 and 24 months from first patient recruited to determine if:…	DMC review will be performed annually from first patient recruited, or more often if necessary, to determine if:… Additionally, a formal statistical analysis of the interim efficacy results will be reviewed by the DMC to determine whether early stopping for efficacy or any modifications to the study design should be recommended.	To adjust frequency of Data Monitoring Committee evaluations in view of the current study timeline, and clarify the purpose of DMC evaluation.

Appendix 1: list of EF-14 Primary Investigators

Investigators:

1.	Dr. Thomas C. Chen	(University of Southern California, CA)
2.	Dr. William Read	(University of California San diego, CA)
3.	Dr. Nicholas G. Avgeropoulos	(MD Anderson Cancer Center Orlando, FL)
4.	Dr. Herbert H. Engelhard	(University of Illinois at Chicago, IL)
5.	Dr. Rajiv Desai	(Maine Medical Center, Maine)
6.	Dr. Eric T. Wong	(Beth Israel Deaconess Medical Center, MA)
7.	Dr. Joseph C. Landolfi	(New Jersey Neuroscience Center, NJ)
8.	Dr. Susan Pannullo	(Weill Cornell Medical College, NY)
9.	Dr. Gene Barnett	(Cleveland Clinic Taussig Cancer Center, OH)
10.	Dr. Frank S. Lieberman	(University of Pittsburgh Medical Center, PA)
11.	Dr. Steven A. Toms	(Geisinger Health System, PA)
12.	Dr. Karen L. Fink	(Baylor Medical Center, TX)
13.	Dr. John S. Nystrom	(Tufts Medical Center, MA)
14.	Dr. Steven Brem	(Moffitt Cancer Center, FL)
15.	Dr. Jing Wu	(University of North Carolina, NC)
16.	Dr. John W. Henson	(Swedish Neuroscience Institute, WA)
17.	Dr. Pamela Z. New	(Methodist Neurological Institute, TX)
18.	Dr. Yvonne Kew	(Methodist Hospital, TX)
19.	Dr. Carlos David	(Lahey Clinic, MA)
20.	Dr. Jay Jinguang-Zhu	(University of Texas Health Sciences Ctr, TX)
21.	Dr. Roger Stupp	(University Hospital CHUV, Switzerland)
22.	Prof. Franz Payer	(University Hospital Graz, Austria)
23.	Dr. Sophie Taillibert	(Group Hospitals Pitie-Salpetriere, France)
24.	Prof. Jerome Honnorat	(Hospital of Neurology Lyon, France)
25.	Dr. Alexandra Benouaich-Amiel	(Hospitalo-Universitaire de Toulouse Purpan, France)
26.	Prof. Maximillian Mehdorn	(University Hospital of Schleswig-Holstein, Germany)
27.	Prof. Manfred Westphal	(University Medical Center Hamburg-Eppendorf, Germany)
28.	Dr. Andrew Kanner	(Tel Aviv Sourasky Medical Center, Israel)
29.	Dr. Andrea Salmaggi	(C. Besta Neurological Institute, Italy)
30.	Dr. Manuela Caroli	(Foundation Hospital Greater Policlinico, Italy)
31.	Prof. Carmine Carapella	(National Institution Regina Helena, Italy)
32.	Dr. Jan Sroubek	(Homolce Hospital, Czech Republic)
33.	Prof. Wolfgang Wick	(University Hospital Heidelberg, Germany)

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Appendix 2: Study Procedure Matrix

	T=-7 (baseline)	T=1 month (±7 days)	T=2 months (±7 days)	T=3 months (±7 days)	T=4 months (±7 days)	T=5 months (±7 days)	T=6 months (±14 days)	T=every month until treatment stop+	T=Progression	T=1 month From treatment stop+	T=2 months From treatment stop+	Monthly thereafter+
MRI of the head	X*		X*		X*		X*	X*	X*			
Physical examination	X	X	X	X	X	X	X	X	X	X	X	
Neurological status	X	X	X	X	X	X	X	X	X	X	X	
Complete blood count (CBC) and differential	See adjacent table											
Chemistry panel (SMAC)												
Coagulation study												
Mini Mental State Exam (MMSE)	X	X	X	X	X	X	X	X	X	X	X	
Quality of life questionnaire	X			X			X	X^				
Telephone interview												X

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Appendix 3: Laboratory Tests Schedule

	Test	*Screening*	*Follow-up*	*Progressions 1&2*	*1 month from treatment stop*	*2 months from treatment stop*
Hematology	Hemoglobin	+	+	+	+	+
	Hematocrit	+	+	+	+	+
	RBC	+	+	+	+	+
	MCV	+	+	+	+	+
	WBC	+	+	+	+	+
	Neutrophils	+	+	+	+	+
	Eosinophils	+	#	#	#	#
	Basophils	+	#	#	#	#
	Lymphocytes	+	+	+	+	+
	Monocytes	+	#	#	#	#
	Platelets	+	+	+	+	+
Chemistry						
	Sodium	+	+	+	+	+
	Potassium	+	+	+	+	+
	Calcium	+	+	+	+	+
	Glucose	+	+	+	+	+
	BUN/Urea	+	+	+	+	+
	Creatinine	+	+	+	+	+
	Total Protein	+	+	+	+	+
	Total Bilirubin	+	+	+	+	+
	Alk. Phosphatase	+	+	+	+	+
	Albumin	+	+	+	+	+
	ALT	+	+	+	+	+
	AST	+	#	#	#	#
	Total Cholesterol	+	#	#	#	#
Coagulation						
	PTT	+	&	&	&	&
	INR	+	&	&	&	&

+ Required tests
# - only when clinically indicated
& - only for patients with coagulation problems / on anti-coagulants

V2.0 to V2.1
14-Dec-2012

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EF-14: Major changes in protocol V2.1 compared to V2.0 (Release date 14-Dec-2012)

Section	Protocol V2.1	Protocol V2.0	Rationale
I	A prospective, multi-center trial of NovoTTF-100A together with temozolomide (TMZ) compared to TMZ alone in patients with newly diagnosed glioblastoma (GBM)	A Prospective, Multi-center Trial of NovoTTF-100A Together With Temozolomide Compared to Temozolomide Alone in Patients with Newly Diagnosed GBM	Clarification of wording, protocol intention did not change
I2	PROTOCOL SCHEMA changed	ORIGINAL PROTOCOL SCHEMA	Clarification of wording, protocol intention did not change
III	Glioblastoma (GBM), a malignant form of astrocytoma, is the most common primary intracranial neoplasm in adults. The incidence of GBM increases steadily above 45 years of age with a prevalence of approximately 7500 cases in the USA. Despite numerous attempts to improve the outcome of patients with GBM, the 3-year survival of these patients is only 6% with median survival of 14.6 months[1]. Patients with newly diagnosed GBM who are treated with maximal surgical resection when feasible, 60 Gy radiotherapy (RT) together with concomitant temozolomide (TMZ) (RT/TMZ), followed by maintenance (adjuvant) TMZ for 6 months, have a median survival of approx. 15 months only [23]. Thus, there is a critical need for new therapeutic options for treatment of GBM. TTFields are a new investigational modality for the treatment of malignant tumors. Pre-clinical studies[12,22] have shown this treatment modality to effectively inhibit the growth of experimental tumors both in-vitro and in-vivo without any systemic side effects. The currently accepted standard	Glioblastoma multiforme (GBM), a malignant form of astrocytoma, is the most common primary intracranial neoplasm. The incidence of GBM increases steadily above 45 years of age with a prevalence of approximately 7500 cases in the USA. Despite numerous attempts to improve the outcome of patients with GBM, the 3-year survival of these patients is only 6% with median survival of 14.6 months[1]. Patients with newly diagnosed GBM who are treated with maximal surgical resection, 60 Gy radiotherapy together with Temozolomide, followed by maintenance Temozolomide for 6 months, have a median survival of 14.6 months[23]. Thus, there is a critical need for new therapeutic options for treatment of GBM. TTFields are a new experimental modality for the treatment of malignant tumors. Pre-clinical studies[12,22] have shown this treatment modality to effectively inhibit the growth of experimental tumors both in-vitro and in-vivo without any systemic side effects. The currently accepted treatment of newly diagnosed GBM is based on: surgical resection with or without Gliadel Wafer implantation, radiotherapy, and Temozolomide. Each of these treatments is briefly described below: 5. Surgical resection - Treatment of patients	Clarification of wording, protocol intention did not change

	treatment of newly diagnosed GBM is based on: surgical resection to the extent safely feasible, with or without Gliadel™ wafer implantation (in the US), followed by RT, and concomitant and adjuvant TMZ chemotherapy. Each of these treatments is briefly described below: 1. Surgical resection - Treatment of patients with GBM usually consists of tumor resection (to the extent safely feasible) or diagnostic biopsy. 2. Radiotherapy (RT) - Post-surgical RT improves survival, though even with maximal treatment, survival after RT alone is still limited to about one year[23]. 3. Temozolomide (TMZ) – Concomitant TMZ chemotherapy during RT and adjuvant (maintenance) TMZ for 6 cycles has been shown to significantly improve survival (HR 0.63). This combined modality treatment is considered the standard of care. a. According to the TMZ (Temodar®, Temodal®) package insert adjuvant TMZ treatment delays disease progression (from 5 to 6.9 months) and improves overall survival (from 12.1 to 14.6 months)[23]. b. In the recently presented RTOG0525/EORTC Intergroup trial where patients were randomized after the end of TMZ/RT (similar to the current EF-14 trial), progression-free survival was also only 6-7 months (estimated from curve)[26] 4. GLIADEL™ Wafers in combination with surgical resection	with GBM usually begins with resection (in conjunction with the biopsy or after it), with maximal debulking of the tumor as the main goal because curative resection is very rare. 6. Radiation therapy - Post-surgical radiation therapy has been shown to improve survival, though even with maximal treatment, survival after RT alone is still limited to about one year[23]. 7. Temozolomide – Adjuvant Temozolomide and radiation therapy following surgery has been shown to improve survival by about 20%. According to the Temozolomide package insert adjuvant Temozolomide treatment delays disease progression (from 5 to 6.9 months) and improves overall survival (from 12.1 to 14.6 months)[23]. In the past, Temozolomide was also approved for recurrent anaplastic astrocytoma. 8. GLIADEL® Wafer in combination with surgical resection – Gliadel Wafer delivers carmustine (BCNU) directly to the bed of the resected tumor. The package insert indicates that for newly diagnosed GBM, Gliadel increased median overall survival from 11.6 to 13.9 months compared to placebo. No data is presented regarding the effect of Gliadel wafers on progression free survival. In conclusion, despite the immense effort made over the years with different treatment modalities, the survival of patients with newly diagnosed GBM is still very poor; no treatment is curative; and the quality of life of patients with this tumor is compromised significantly, not only by their disease but also by side effects of these rigorous treatment plans. A treatment modality is needed that will improve the results of standard treatments without further impairing the quality of life of these patients for their limited life span.	

	– Gliadel™ Wafers deliver carmustine (BCNU) directly to the bed of the resected tumor. Gliadel has been approved for GBM after surgical resection, based on trials performed before TMZ therapy was established. a. The package insert indicates that for newly diagnosed GBM, Gliadel™ increased median overall survival from 11.6 to 13.9 months compared to placebo. Progression-free survival with Gliadel™ wafers has been reported as 5.9 months[27]. No prospective data of Gliadel™ in combination with TMZ has been reported. In conclusion, despite the immense effort made over the years with different treatment modalities, the survival of patients with newly diagnosed GBM remains poor; no treatment is curative; and the quality of life of patients with this tumor is compromised significantly,. A treatment modality is needed that will improve the results of standard treatments without further impairing the quality of life of these patients for their limited life span.		
III	**The NovoTTF-100A device** The NovoTTF-100A device is a portable battery operated device which produces TTFields within the human body by means of surface transducer arrays. The TTFields are applied to the patient by means of surface transducer arrays that are electrically insulated, so that resistively coupled electric currents are not delivered to the patient. The transducer arrays, which incorporate a layer of adhesive hydrogel	**The NovoTTF-100A Device** The NovoTTF-100A device is a portable battery operated device which produces TTFields within the human body by means of surface electrodes. The TTFields are applied to the patient by means of surface electrodes that are electrically insulated, so that resistively coupled electric currents are not delivered to the patient. The electrodes, which incorporate a layer of adhesive hydrogel and a layer of hypoallergenic medical tape, are placed on the patient's shaved head. The electrodes must be	Clarification of wording, protocol intention did not change

	and a layer of hypoallergenic medical tape, are placed on the patient's shaved head. The transducer arrays must be replaced every three to four days and the scalp re-shaved in order to maintain optimal capacitative coupling between the transducer arrays and the patient head. All the treatment parameters are pre-set by Novocure so there are no electrical output adjustments available to the patient. The patient must learn to change and recharge depleted device batteries and to connect to an external battery pack overnight.	replaced every three to four days and the scalp re-shaved in order to maintain optimal capacitative coupling between the electrodes and the patient head. All the treatment parameters are pre-set by NovoCure so there are no electrical output adjustments available to the patient. The patient must learn to change and recharge depleted device batteries and to connect to an external battery pack overnight.	
III	In a prospective, randomized, open label, active parallel controlled trial to compare the effectiveness and safety outcomes of recurrent GBM subjects treated with NovoTTF-100A alone (n=120) to those treated with an effective best standard of care chemotherapy (according to physicians best choice [e.g. CCNU, BCNU, bevacizumab]; n=117), NovoTTF-100A subjects had comparable overall survival to subjects receiving the best available chemotherapy nowadays (median overall survival 6.3 vs. 6.4 months; HR 1.0; p=0.98)[28]. Importantly, secondary endpoints favored the NovoTTF treated patients (e.g. PFS6 = 21.4% for NovoTTF-100A vs. 15.2% for chemotherapy, p=0.14, response rate 14% vs 9.6%, p=0.24, for NovoTTF and the active control group, respectively). Expectedly, the chemotherapy-free NovoTTF-100A patients experienced fewer adverse events in general, significantly fewer treatment related adverse events, and significantly lower gastrointestinal, hematological and infectious adverse events compared to the best standard of care active controls. The main device-related adverse events seen were a mild to moderate skin irritation beneath the device transducer arrays,	In a prospective, randomized, open label, active parallel control trial to compare the effectiveness and safety outcomes of recurrent GBM subjects treated with NovoTTF-100A (n=120) to those treated with an effective best standard of care chemotherapy (including bevacizumab; n=117), NovoTTF-100A subjects had comparable overall survival to subjects receiving the best available chemotherapy in the US today (OS 6.3 vs. 6.4 months; HR 1.0; p=0.98). Similar results showing comparability of NovoTTF-100A to BSC chemotherapy were seen in all secondary endpoints (e.g., PFS6 = 21.4% for NovoTTF-100A vs. 15.2% for chemotherapy). NovoTTF-100A subjects experienced fewer adverse events in general, significantly fewer treatment related adverse events, and significantly lower gastrointestinal, hematological and infectious adverse events compared to BSC controls. The only device-related adverse events seen were a mild to moderate skin irritation beneath the device electrodes, which was easily treated with topical ointments. Finally, quality of life measures were better in NovoTTF-100A subjects as a group when compared to subjects receiving effective best standard of care chemotherapy.	Clarification of wording, correction of inaccuracies

	which was easily treated with topical ointments. Finally, quality of life measures were better in NovoTTF-100A subjects as a group when compared to subjects receiving effective best standard of care[28]		
IV	A prospective, randomly controlled pivotal study will be conducted on 700 patients (randomized at a 2:1 ratio in favor of the NovoTTF-100A group). Patients with histologically confirmed GBM will be randomized after having completed RT/TMZ to either maintenance TMZ and NovoTTF for up to 24 months (experimental arm), or maintenance TMZ chemotherapy alone (control). The primary endpoint will be progression free survival (PFS), overall survival is clinically an equally important secondary endpoint. The sample size was chosen based on the log-rank test comparing time to event (i.e., progression or death prior to progression) assuming patients treated with the NovoTTF-100A together with maintenance TMZ will have a median PFS significantly greater than controls (9 months compared to 7 months, hazard ratio < 0.78), respectively; with an overall 5% 2-sided type I error and 80% power). This sample size also has adequate power (80%) to detect a minimum of 4.5 month increase in median overall survival (hazard ratio < 0.76) in NovoTTF-100A treated patients compared with control patients (expected control group median OS = 14.6 months, Stupp et al, NEJM 2005). The following will be considered disease progression for determination of PFS (based on the Macdonald criteria; Tab D): 1. Tumor growth > 25% of the product of 2 perpendicular diameters compared to the smallest tumor area measured in this patient during the trial. 2. Appearance of 1 or more new	A prospective, randomly controlled pivotal study will be conducted on 700 patients (randomized at a 2:1 ratio in favor of the NovoTTF-100A group) with tissue diagnosis of GBM who have completed radiation therapy together with adjuvant Temozolomide. The control group will receive standard Temozolomide maintenance therapy. The primary endpoint will be progression free survival (PFS). The sample size was chosen based on the log-rank test comparing time to event (i.e., progression or death prior to progression) assuming patients treated with the NovoTTF-100A together with maintenance Temozolomide will have a median PFS significantly greater than controls (9 months compared to 7 months, respectively; with an overall 5% 2-sided type I error and 80% power). This sample size also has adequate power (80%) to detect a minimum of 4.5 month increase in median overall survival in NovoTTF-100A treated patients compared with control patients (expected control group median OS = 14.6 months, Stupp et al, NEJM 2005). The following will be considered disease progression for determination of PFS (based on the Macdonald criteria; Tab D): 3. Tumor growth > 25% compared to the smallest tumor area measured in this patient during the trial. 4. Appearance of 1 or more new tumors in the brain (diagnosed radiologically as GBM). Final determination of progression will be made by CORE radiology review, in cases where an MRI is available (which should be the great majority of cases). In cases where an MRI is not available, clinical progression will be diagnosed according to the following criteria:	Clarification of wording, protocol intention did not change

	tumors in the brain (diagnosed radiologically as GBM). Final determination of progression will be made by independent radiology review, in cases where an MRI is available (which should be the great majority of cases). In cases where an MRI is not available, clinical progression will be diagnosed according to the following criteria: 1. Decline in functional status as indicated by a decrease in KPS of ≥ 20 points, or 2. Decline in neurological function as indicated by a decrease of 2 points or more in MRC scale (TAB H), or 3. ≥50% increase in steroid dose. The determination of whether to stop treatment due to progression will be based on the investigator's evaluation of the patient's clinical condition. NovoTTF-100A treatment shall be continued for 24 months or until (or beyond) second progression, at the investigators discretion. In the case of radiological progression based on local evaluation, TMZ treatment will be stopped and a second line therapy initiated, at the investigators discretion, while NovoTTF may be continued. The following treatments or any combination of these treatments are considered second line therapy in this protocol: 1. Re-operation (in cases where viable tumor cannot be demonstrated histologically [pseudoprogression], this will not be considered progression and a second-line therapy) 2. Local RT (e.g. gamma knife)	4. Decline in functional status as indicated by a decrease in KPS of > 10, and 5. Decline in neurological function as indicated by a decrease of 2 points or more in MRC scale (TAB H), and 6. ≥50% increase in steroid dose. The determination of whether to stop treatment due to progression will be based on the investigator's evaluation of the patient's clinical condition. NovoTTF-100A treatment will be continued for 24 months or until second progression whichever occurs first unless the patient's clinical condition prohibits this. In the case of radiological progression based on local evaluation, Temozolomide treatment will be stopped and a second line treatment chosen instead. The following treatments or any combination of these treatments are considered second line therapy in this protocol: 5. Re-operation 6. Local radiation therapy (e.g. gamma knife) 7. Second line chemotherapy 8. Combination of the above. Patients will be recruited to the study by the principal investigator (PI) or one of the co-investigators (CI) in up to 40 US centers and at up to 25 OUS centers . Immediately following screening, patients will be randomized at a 2:1 ratio to receive either NovoTTF-100A treatment together with maintenance Temozolomide or maintenance Temozolomide alone. Patient accrual is expected to continue for 48 months. Patient follow-up for PFS and OS will continue for 18 months from accrual of the last patient.	

	3. Second line chemotherapy 4. Any combination of the above. Patients will be recruited to the study by the principal investigator (PI) or one of the co-investigators (CI) in up to 40 medical centers in the United States, and approximately 25 centers in the rest of the world. Following informed consent and screening, non-progressive patients who have completed TMZ/RT will be randomized at a 2:1 ratio to receive either NovoTTF-100A treatment together with maintenance TMZ or maintenance TMZ alone. The estimated recruitment duration is 48 months. Patient follow-up for PFS and OS will continue for at least 18 months from accrual of the last patient.		
IV	Treatment with the NovoTTF-100A device does not need to be terminated in the following situations: 1. Toxicity due to Temozolomide treatment 2. Radiological progression alone will not lead to termination of NovoTTF-100A treatment, but to replacement of the Temozolomide treatment with best standard of care second line therapy: a. Re-operation b. Local radiation therapy (e.g., gamma knife) c. Second line chemotherapy Combination of the above.	Treatment with the NovoTTF-100A device does not need to be terminated in the following situations: 3. Toxicity due to TMZ treatment 4. Radiological progression and initiation of second line therapy; e.g. i. Re-operation ii. Local RT (e.g., gamma knife) iii. Second line chemotherapy iv. Combination of the above.	Clarification of wording, protocol intention did not change
IV	As long as the patients are receiving any protocol treatment (NovoTTF-100A and/or first and second-line chemotherapy), monthly outpatient clinic visits are required, including medical exam and follow-up, and routine laboratory exams (see Tab A). An MRI is to be performed	As long as the patients are receiving any treatment (NovoTTF-100A or chemotherapy), all patients will be seen once every month at an outpatient clinic where they will undergo medical follow-up and routine laboratory exams (see Tab A). An MRI will be performed every second month following the baseline MRI until second progression	Clarification of wording, protocol intention did not change

	every two months until second progression. In the case of clinical progression an unscheduled MRI will be obtained within 1 week of the investigator becoming aware of the clinical progression. After second progression imaging is performed at the investigators discretion. Monthly medical follow-up visit shall be scheduled for 2 months after termination of protocol therapy in order to capture potential treatment related toxicities. All patients will be followed for survival by either direct contact or regular telephone interviews with the patient or the patient's caregiver. **Independent MRI review**	(when treatment on both arms of the study will be terminated). In the case of clinical progression an unscheduled MRI will be obtained within 1 week of the investigator becoming aware of the clinical progression. No additional MRIs will be required after second progression. Central MRI review will be performed by a neuro-radiologist blinded to the treatment group of each patient. Medical follow-up will continue for 2 months after treatment termination in order to capture treatment related toxicities. After these visits, mortality will be assessed based on monthly telephone interviews with the patients or the patients' caregivers. **Core MRI review**	
V	Patients with newly diagnosed and histologically confirmed GBM after initial therapy with surgery if applicable, followed by standard concomitant chemoradiotherapy (TMZ/RT according to Stupp et al) are to be considered. Patients may be enrolled at any time, randomization will be performed only after completion of TMZ/RT, provided the following criteria are met. 1) PATIENT INCLUSION CRITERIA: a. Histologically confirmed diagnosis of GBM according to WHO classification criteria. b. Supratentorial tumor location c. age ≧ 18 years d. Recovered from maximal debulking surgery, if applicable (gross total resection, partial resection and biopsy-only patients are all acceptable) Patients may enroll in the study if received Gliadel	Any patient with a histological diagnosis of GBM who meets all of the specific eligibility criteria listed below may by enrolled on this study. Operable patients must undergo surgery prior to randomization. All patients must have received maximal radiation therapy with concomitant Temozolomide prior to randomization. Patients receiving steroids to control edema may be included in the trial; however, any change in steroid dose must be documented during the follow-up visits. An increase in steroid dose will preclude a diagnosis of partial or complete response (as suggested by Macdonald et al; TAB D). Disease status will be determined by comparing screening MRI to the immediate post-surgical MRI. If unavailable, an immediate post-surgical CT can be used for the same purpose. Patients who have progressive disease at screening (compared to the immediate post-surgical MRI) are not candidates for this study. In the case of local radiological suspicion of pseudoprogression a PET scan or other imaging modality (in addition to T1 weighted MRI) will be obtained to assess biological activity of the tumor. 1) PATIENT INCLUSION CRITERIA: a. Pathological evidence of GBM using WHO classification criteria. b. ≥ 18 years of age.	Clarification of wording, clear and uniform description of criteria, protocol intention did not change

	wafers before entering the trial e. have completed standard adjuvant chemoradiotherapy of approx. 60 Gy of RT, or biologically equivalent dose, according to local practice, and concomitant TMZ chemotherapy (75mg/m^2 daily) Any other cytotoxic or biologic anti-tumor therapy received prior to enrollment will be considered an exclusion. f. Planned treatment with adjuvant/maintenance TMZ (150-200 mg/m2 daily x 5 d, q28 days) g. All patients must have had tissue submitted for *MGMT* Promoter Methylation determination prior to randomization, following an analysis performed by a central lab on a paraffin-embedded tissue block from the surgical procedure used for GBM diagnosis (tissue slides are not desirable but optional), h. Karnofsky performance status ≥ 70% i. Life expectancy ≥ least 3 months j. Participants of childbearing age must use effective contraception. k. All patients must sign written informed consent. l. Study start date at least 4 weeks out from brain	c. Received maximal debulking surgery and radiotherapy concomitant with Temozolomide (45-70Gy): 1. Patients may enroll in the study if received Gliadel wafers before entering the trial 2. Any additional treatments received prior to enrollment will be considered an exclusion. 3. Minimal dose for concomitant radiotherapy is 45 Gy d. Karnofsky scale ≥ 70 e. Life expectancy at least 3 months f. Participants of childbearing age must use effective contraception. g. All patients must sign written informed consent. h. Treatment start date at least 4 weeks out from surgery. i. Treatment start date at least 4 weeks out but not more than 7 weeks from the later of last dose of concomitant Temozolomide or radiotherapy. 2) <u>PATIENT EXCLUSION CRITERIA</u>: a. Progressive disease (according to MacDonald Criteria). If pseudoprogression is suspected, additional imaging studies must be performed to rule out true progression. b. Actively participating in another clinical treatment trial c. Pregnant d. Significant co-morbidities at baseline which would prevent maintenance Temozolomide treatment: 1. Thrombocytopenia (platelet count < 100 x 10^3/μL) 2. Neutropenia (absolute neutrophil count < 1.5 x 10^3/μL) 3. CTC grade 4 non-hematological Toxicity (except for alopecia, nausea, vomiting) 4. Significant liver function impairment - AST or ALT > 3	

	surgery. m. Study start after the end of RT/TMZ (admissible Study start date of TTF and/or temozolomide should be between day 29 and day 49 after last dose of irradiation). n. Stable or decreasing dose of corticosteroids for the last 7 days prior to randomization, if applicable. 2) PATIENT EXCLUSION CRITERIA: a. Early progressive disease after the end of TMZ/RT. If pseudoprogression is suspected, additional imaging studies should be performed to rule out true progression. The sponsor should be contacted in case of doubt. b. Participation in another clinical treatment trial c. Pregnancy d. Significant co-morbidities at baseline which would preclude maintenance TMZ treatment: Thrombocytopenia (platelet count < 100 x $10^3/\mu L$) Neutropenia (absolute neutrophil count < 1.5 x $10^3/\mu L$) CTC grade 4 non-hematological Toxicity (except for alopecia, nausea, vomiting) Significant liver function impairment - AST or ALT > 3 times the upper limit of	times the upper limit of normal 5. Total bilirubin > upper limit of normal 6. Significant renal impairment (serum creatinine > 1.7 mg/dL) e. Implanted pacemaker, programmable shunts, defibrillator, deep brain stimulator, other implanted electronic devices in the brain, or documented clinically significant arrhythmias. f. Infra-tentorial tumor g. Evidence of increased intracranial pressure (midline shift > 5mm, clinically significant papilledema, vomiting and nausea or reduced level of consciousness) h. History of hypersensitivity reaction to Temozolomide or a history of hypersensitivity to DTIC.	

	normal Total bilirubin > 1.5 x upper limit of normal Significant renal impairment (serum creatinine > 1.7 mg/dL, or > 150 µmol/l) e. Implanted pacemaker, programmable shunts, defibrillator, deep brain stimulator, other implanted electronic devices in the brain, or documented clinically significant arrhythmias. f. Infra-tentorial tumor location g. Evidence of increased intracranial pressure (midline shift > 5mm, clinically significant papilledema, vomiting and nausea or reduced level of consciousness) History of hypersensitivity reaction to TMZ or a history of hypersensitivity to DTIC		
VI	Patients will be recruited locally at each center. All patients will be seen by the corresponding local investigator or sub-investigator. Every effort will be made to encourage eligible women and minorities to participate. All patients will be required to sign a written informed consent prior to being registered on this protocol. Patients will be extensively informed both orally and in writing, patient will have sufficient time for reflection and consideration of alternative treatments. The local investigator will be available to answer any questions the patient or his entourage may have.	Patients will be recruited to this study from either the outpatient clinic or inpatient hospital setting at each center. All patients will be seen by the corresponding investigator. Every effort will be made to encourage eligible women and minorities to participate. All patients will be required to sign a written informed consent prior to being registered on this protocol. Every effort will be made to answer questions raised by the patient and their family or advocate regarding the protocol and alternative therapies prior to asking the patient to sign the consent form.	Clarification of wording, protocol intention did not change

VII	Patients who meet the above inclusion/exclusion criteria will be randomized at a 2:1 ratio either to the treatment group who will receive NovoTTF-100A treatment together with maintenance TMZ, or to the control group who will receive standard maintenance TMZ alone. Randomization will be performed centrally using a web based software. Stratification for the following prognostic factors will be performed: a. Extent of Resection – Biopsy; Partial Resection; Gross total resection (only if immediate post surgical MRI is available) b. *MGMT* methylation status as provided by the central lab – Positive, Negative, Indeterminate Randomization will be performed with randomly varying block sizes (e.g., 3, 6, or 9 patients) within each stratum.	Patients who meet the above inclusion/exclusion criteria will be randomized at a 2:1 ratio either to the treatment group who will receive NovoTTF-100A treatment together with maintenance Temozolomide, or to the control group who will receive maintenance Temozolomide alone. Randomization will be performed centrally and not within in each center to allow for the following stratifications: c. Extent of Resection – Biopsy; Partial Resection; Gross total resection (only if immediate post surgical MRI is available) d. MGMT (O^6-benzylguanine, O^6BG) methylation status – Positive, Negative, Unknown Randomization will be performed with randomly varying block sizes (e.g., 3, 6, or 9 patients) within each stratum. These classifications are expected to have a stronger impact on disease outcome than the treatment variability between centers, since standard of care for newly diagnosed GBM, worldwide, is based on the Stupp protocol.	Clarification of wording, clarification that MGMT results derive from a central lab only.
VIII	All patients are to receive standard maintenance TMZ chemotherapy according to the established regimen (Stupp et al., NEJM 2005 and TMZ package insert). Maintenance treatment is to begin about 4 weeks after the end of TMZ/RT. TMZ is administered at the conventional dosing regimen for 5 days, every 28 days (i.e.. 5 days of therapy, 23 days of rest). Cycle 1 is to be given at a dose of 150 mg/m2 p.o. daily x 5 days, dose to be escalated to 200 mg/m2 in the absence of toxicity. TMZ administration and dosing guidelines are available from the manufacturer and are summarized in the TMZ package insert. Patients who completed all 6 cycles of maintenance TMZ will be treated per	Temozolomide is administered for an additional 6 cycles of maintenance treatment. Dosage in Cycle 1 (maintenance) is 150 mg/m^2 once daily for 5 days followed by 23 days without treatment. **Cycles 2-6:** At the start of Cycle 2, the dose is escalated to 200 mg/m^2, if the CTC non-hematologic toxicity for Cycle 1 is Grade ≤2 (except for alopecia, nausea and vomiting), absolute neutrophil count (ANC) is ≥ 1.5 x 10^9/L, and the platelet count is ≥ 100 x 10^9/L. The dose remains at 200 mg/m^2 per day for the first 5 days of each subsequent cycle except if toxicity occurs. If the dose was not escalated at Cycle 2, escalation should not be done in subsequent cycles. Patients who completed all 6 cycles of maintenance temozolomide will be treated per	Clarification of wording, protocol intention did not change

	investigator discretion, concomitant with the TTF treatment, until second progression. Prolonged maintenance TMZ treatment is admissible as per local practice and physician's discretion.	investigator discretion, concomitant with the TTF treatment, until second progression. **Temozolomide dose reduction or discontinuation during maintenance:** Dose reductions during the maintenance phase should be applied according to Tables 1 and 2 below. During treatment a complete blood count should be obtained on day 22 (21 days after the first dose of Temozolomide) or within 48 hours of that day, and weekly until the ANC is above 1.5 x 10^9/L (1,500/μL) and the platelet count exceeds 100 x 10^9/L (100,000/μL). The next cycle of Temozolomide should not be started until the ANC and platelet count exceed these levels. Dose reductions during the next cycle should be based on the lowest blood counts and worst non-hematologic toxicity during the previous cycle. Dose reductions or discontinuations during the maintenance phase should be applied according to tables 1 and 2.	
IX	During NovoTTF-100A treatment the patient is advised to interrupt treatment for periods of up to an hour twice a day for personal needs and to give the skin a short period of rest. Longer treatment breaks for personal reasons or in order to allow for recovery from toxicity should ideally be coordinated in advance with the local investigator and the technician. Treatment breaks of up to 3 days per month are considered planned according to the protocol, longer breaks need to be justified and explained in the CRF. Clinical follow-up includes monthly medical visits and appropriate laboratory and/or imaging investigations as needed and is described in detail in TAB A and TAB B. During these visits the investigator will remove the transducer arrays and examine the skin beneath them	During NovoTTF-100A treatment the patient will be permitted to interrupt treatment for periods of up to an hour twice a day for personal needs. Any pause in treatment beyond this must be coordinated in advance with the principal investigator or one of the co-investigators. Patients will be allowed an additional 1-3 days off treatment between courses according to personal needs. Once every month from baseline, until treatment termination, all patients will report to an outpatient clinic where they will be assessed clinically and undergo routine laboratory examinations. The follow-up window for these visits is +/- 7 days if the visit occurs prior to the 6 month follow-up window and +/- 14 days on or after the 6 month visit window. Follow up window from the 12 month visit onward will be +/- 1 month. During these visits the investigator will remove the electrodes and examine the skin beneath them. Electrode replacement will be performed at the local technical clinic or at the patient's home after the follow-up visit. Medical follow-up and routine	Clarification of wording, protocol intention did not change

		laboratory exams for all patients will continue once per month for 2 months following end of treatment. After this post-progression follow up period, patients will be followed by monthly telephone interview until death.	
XIV	Treatment will continue according to the protocol until second progression or 24 months (the earlier of the two). Monthly medical follow-up visit shall be scheduled for 2 months after termination of protocol therapy in order to capture potential treatment related toxicities. All patients will be followed for survival by either direct contact or regular telephone interviews with the patient or the patient's caregiver. Physical and neurological examination, blood tests (CBC and Chemistry panel) will be performed during these visits. Adverse events and date of last patient contact or date of death will be documented on the case report forms. Subsequently, all patients will be followed for survival by either direct contact or regular telephone interviews with the patient or the patient's caregiver.	Treatment will continue according to the protocol until second progression or 24 months (the earlier of the two). After treatment termination the patient will be seen at an outpatient clinic every month for two additional visits. Physical and neurological examination, blood tests (CBC and Chemistry panel) will be performed during these visits. Patient mortality and adverse events will be documented on the case report forms. After the two post treatment monthly follow up visits, patients will not be required to return to the clinic for follow-up but will be followed monthly until death by telephone to monitor their status.	Clarification of wording, protocol intention did not change
XV	*MGMT* methylation status - will be assessed centrally by polymerase chain reaction (PCR) methylation status of the promoter region of *MGMT* gene. Randomization will be stratified according to *MGMT* methylation status based on central lab analysis performed prior to randomization. The laboratory will be blinded to the treatment group of the patients. The name of the laboratory used for *MGMT* determination will be recorded. All patients enrolled in the study must have paraffin embedded brain tissue available for central pathology review and MGMT determination. Additional molecular tests as described below will be	MGMT methylation - will be assessed by polymerase chain reaction (PCR) methylation status of the promoter region of MGMT. Randomization will be stratified according to MGMT methylation status based on local analysis performed at institutions where this examination of brain tissue is performed as a standard examination for all GBM patients. All patients with paraffin embedded brain tissue available for additional analysis will have MGMT methylation status assessed by a central laboratory (blinded to the treatment group of the patients). Methylation status will be adjusted for during final analysis as a covariate (see statistical	Clarification of wording, MGMT testing in Central lab is mandatory

	performed separately in a central lab and may not be available at time of randomization. Adjustments for *MGMT* methylation status will be performed for during final analysis (see statistical analysis section).	analysis section). **The following materials will be required for tissue evaluation:** • Representative tissue blocks that contain diagnostic tumor. A block that, when sectioned, yields at least 1 square centimeter of viable tumor must be present on the H&E slide. • An accompanying H&E section. • A Pathology Report documenting that the submitted material contains tumor; the report must include the protocol number, patient case number, and the patient's initials. The patient's name and/or other identifying information should be removed from the report. • A Specimen Transmittal Form listing pathology materials being submitted for Central Tissue Evaluation must be included in the pathology submission. **Submission of the following material is required for tissue evaluation:** • Representative formalin-fixed and paraffin-embedded (FFPE) tumor tissue blocks. Slides are not desirable but optional in case no tissue blocks are available for testing. • Samples will be kept at the Central Pathologist site until the molecular testing has been performed. After the end of the study, the tissue blocks will be returned to the local pathologists or centers. • On specific request for medical reasons by the investigator or pathologist the block is shipped promptly back to the site. • All fixed tissue for *MGMT* analysis should preferably be fixed in 10% v/v neutral buffered formalin where possible. To preserve the quality of the tissue and increase the likelihood of a valid *MGMT* methylation assay	

		result, acidic formalin, zinc or mercuric chloride should be avoided where possible. • Samples fixed in formalin for longer than 18 hours yield low quality DNA due to cross linking. Fixation times of greater than 24 hours should preferably be avoided. • Shipping supplies and lab detailed specifications will be provided by Novocure for each site • An accompanying H&E slide is encouraged for rapid diagnosis, but is not required. The shipment should be accompanied by an anonymized copy of the local pathology report or a completed Local Pathology Form documenting and identifying the submitted material. This will include protocol number, local institution information, patient identifier and pathological data. The patient's name and/or other identifying information should be removed from the form. • Any effort should be made to obtain FFPE tumor tissue block from a referral center in case the EF-14 patient candidate was not operated at an EF-14 trial center, in order to allow patient enrollment. • All patients with submitted tissue samples for MGMT analysis will be considered eligible for randomization as long as they comply with all other eligibility criteria. **All samples for pathology review, experimental and translational neuro-oncology will be collected at the central Laboratory at CHUV in Lausanne. Send all samples to:** Lab of Brain Tumor Biology and Genetics (Prof. Monika Hegi) Neurosurgery Department University Hospital (CHUV BH19-110) Rue du Bugnon 46 Lausanne 1011 Switzerland	

		Phone: +41-21 314 25 81 Fax: +41-21 314 25 87 Email: NCH.LABOLN@chuv.ch	
XVII	Treatment with TMZ may cause the following adverse events: • Myelosuppression, in particular thrombocytopenia and leukopenia • Fatigue • Nausea and vomiting • Headache (often due to prophylactic antiemetics) • Vomiting or Constipation (often due to prophylactic antiemetics) Adverse events and complications that are often associated with the underlying brain tumor but could theoretically be exacerbated by the NovoTTF-100A treatment: • Seizures • Neurological and functional decline • Headaches	Treatment with temozolomide commonly (>20%) causes the following adverse events: • Leukopenia • Headache • Fatigue • Nausea • Vomiting or Constipation Adverse events and complications associated with the underlying GBM disease process, which are unlikely but unknown if related to treatment with NovoTTF-100A together with maintenance Temozolomide include the following adverse events: • Seizure, including Status Epilepticus • Neurological and functional decline • Headaches, nausea and/or vomiting • Death	Clarification of wording, correction of inaccuracies
XX	• Patients will be able to withdraw from the trial at any time at their own request. All data collected until treatment discontinuation, follow-up and outcome data will remain in the database, unless the patient formally withdraws the consent for collecting further follow-up and survival data.	• Patients will be able to withdraw from the trial at their own request.	Clarification of wording, protocol intention did not change
XXI	Expected median progression free survival on control treatment is 7 months (see Stupp et al., NEJM, 2005[23] and TMZ package insert), and similar PFS was also seen in the recently reported RTOG0525-EORTC Intergroup trial[26] Expected median progression free	• Expected median progression free survival on control treatment is 7 months (see Stupp et al., NEJM, 2005[23] and Temozolomide package insert) • Expected median progression free survival on NovoTTF-100A treatment is 9 months. • Expected accrual time during which patients are recruited: 48 months	Clarification of wording, correction of inaccuracies.

	survival on NovoTTF-100A treatment is 9 months. This increase in median PFS is equivalent to a Hazard Ratio of 0.78 for the NovoTTF-100A patients compared to control patients. Expected accrual time during which patients are recruited: 48 months Additional follow-up time after end of recruitment: 18 months. Ratio of control to experimental patients: 1:2 Type I error: 0.05%; 2-sided Power: 80% This sample size also has adequate power (80%) to detect a minimum of 4.5 month increase in median overall survival in NovoTTF-100A treated patients compared with control patients (who have an expected median OS of 14.6 months). This increase in survival is equivalent to a Hazard Ratio of 0.76 for the NovoTTF-100A patients compared to control patients. Recently, the results of RTOG0525-EORTC Intergroup trial[26] have been presented. Similar to the current protocol, in the RTOG trial non-progressive patients were randomized only after TMZ/RT (however the RTOG trial included only patients who had undergone prior tumor resection). In that trial median survival was 18 months. In our trial powered to achieve a hazard ratio of 0.76 for OS, this would translate to a 6-months increase in median survival to 24 months, a difference that would be considered clinically meaningful. One interim analysis will be performed on the PFS and OS data available for all patients after the first 315 patients accrued have a minimum of 18 months follow up. The assumptions used in the sample size calculations will be	• Additional follow-up time after end of recruitment: 18 months. • Ratio of control to experimental patients: 1:2 • Type I error: 0.05%; 2-sided • Power: 80% This sample size also has adequate power (80%) to detect a minimum of 4.5 month increase in median overall survival in NovoTTF-100A treated patients compared with control patients (who have an expected median OS of 14.6 months). One interim analysis will be performed on the PFS and OS data available the first 315 patients accrued after a minimum of 18 months follow up. The assumptions used in the sample size calculations will be evaluated at the interim analysis. If it appears that the event rate and/or the treatment effect may be smaller than expected, the company may request a sample size increase to achieve the desired study power. The company will not request a sample size decrease based on the results of this assessment.	

	evaluated at the interim analysis. If it appears that the event rate and/or the treatment effect may be smaller than expected, adaptation of the sample size may be considered in order to allow for adequate study power. The company will not request a sample size decrease based on the results of this assessment.		
XXI	1. Overall survival is the most important secondary endpoint. Prolongation of survival is considered to correlate with a clinical benefit for the patient. Thus, this trial has been sufficiently powered to allow for definitive conclusions with regards to overall survival after adequate follow-up.	2. The company only plans to make efficacy claims on the first secondary endpoint, the overall survival, due to its importance and also the fact that it is a powered secondary endpoint in the trial. No efficacy claims are planned based on PFS6, 1- and 2-year survival, quality of life analysis or radiological response rate. Thus, the entire alpha of 0.05 will be allocated to the overall survival endpoint and no adjustment will be made for multiple hypothesis testing.	Clarification of secondary endpoint
XXI	The following parameters will be also recorded and compared between the treatment and control groups: • Overall survival time (log Rank Test). In order to allow for two analyses in the trial the alpha level used at each time point will be calculated based on the O'Brien-Fleming method[24,25] (i.e., approximately 0.00598 at the interim analysis and 0.0481 at the final analysis). For analysis of overall survival, patients will be censored at the time that they are last known to be alive (if withdrawn or lost to follow-up) or at study closeout. • Percentage alive and progression-free at 6-month • Actuarial survival at 1 and 2-years • Quality of life (EORTC QLQ-C30 + BN20 questionnaire)	The following parameters will be also recorded and compared between the treatment and control groups: • Overall survival time (Log Rank Test). In order to allow for two analyses in the trial the alpha level used at each time point will be calculated based on the O'Brien-Fleming method[24,25] (i.e., approximately 0.0089 at the interim analysis and 0.0475 at the final analysis). For analysis of overall survival, patients will be censored at the time that they are last known to be alive (if withdrawn or lost to follow-up) or at study closeout. • % 6-month progression free survival • % 1 and 2-year survival • Quality of life (EORTC QLQ-C30 questionnaire) • Radiological response rates • MMSE scores • Incidence and severity of adverse events In addition, the correlation will be measured	Clarification of analysis plan and correction of inaccuracies

	• Radiological response rates • MMSE scores • Incidence and severity of adverse events In addition, the correlation will be measured between the percent of time patients received NovoTTF-100A treatment (treatment compliance) and their progression free survival and overall survival.	between the percent of time patients received NovoTTF-100A treatment and their progression free survival and overall survival.	
XXVI	26. Gilbert et al. Proc Am Soc Clin Oncol, J Clin Oncol 29: (suppl), abstract # 2006 27. Westphal et al. A phase 3 trial of local chemotherapy with biodegradable carmustine (BCNU) wafers (Gliadel wafers) in patients with primary malignant glioma. Neuro Oncol. 2003 Apr;5(2):79-88 28. Stupp et al., NovoTTF-100A versus physician's choice chemotherapy in recurrent glioblastoma: a randomised phase III trial of a novel treatment modality. Eur J Cancer. 2012 Sep;48(14):2192-202		Additional relevant references

Novocure, Ltd.

Protocol EF-14

A Prospective, Multi-center Trial of NovoTTF-100A Together With Temozolomide Compared to Temozolomide Alone in Patients with Newly Diagnosed GBM

Statistical Analysis Plan
Version 1.0
September 3, 2014

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1. GLOSSARY OF ABBREVIATIONS

Abbreviation	Definition
AE	Adverse Event
ALT	Alanine Aminotransferase
ANC	Absolute Neutrophil Count
AST	Aspartate Aminotransferase
CEC	Clinical Endpoint Committee
CFB	Change from Baseline
CI	Confidence Interval
CT	Computed Tomography
CTCAE	Common Terminology Criteria for Adverse Events
DTIC	Dacarbazine
EORTC	European Organisation for Research and Treatment of Cancer
GBM	Glioblastoma Multiforme
GY	Gray
HR	Hazard Ratio
MedDRA	Medical Dictionary for Regulatory Activities
MGMT	O(6)-methylguanine-DNA methyltransferase
MMSE	Mini-Mental State Examination
MRC	Medical Research Council
MRI	Magnetic Resonance Imaging
NCI	National Cancer Institute
OS	Overall Survival
OUS	Outside the US
PET	Positron Emission Tomography
PFS	Progression-Free Survival
PFS-6	Progression-Free Survival at 6-months
QOL	Quality of Life

SAE	Serious Adverse Event
SD	Standard Deviation
TEAE	Treatment-Emergent Adverse Event
ULN	Upper Limit of Normal
WHO	World Health Organization

2. INTRODUCTION

The NovoTTF-100A device is a portable battery operated device which produces TTFields within the human body by means of surface transducer arrays. The TTFields are applied to the patient by means of surface transducer arrays that are electrically insulated, so that resistively coupled electric currents are not delivered to the patient. The transducer arrays, which incorporate a layer of adhesive hydrogel and a layer of hypoallergenic medical tape, are placed on the patient's shaved head. The transducer arrays must be replaced every three to four days and the scalp re-shaved in order to maintain optimal capacitative coupling between the transducer arrays and the patient head. All the treatment parameters are pre-set by Novocure so there are no electrical output adjustments available to the patient. The patient must learn to change and recharge depleted device batteries and to connect to an external battery pack overnight.

This analysis plan summarizes the planned presentation and analysis of the efficacy and safety data from Novocure, Ltd. Protocol EF-14, Version 2.0. (January 13, 2012).

Study measurements and assessments and planned statistical analysis methods for the planned statistical analyses are described in this plan. Planned tables, figures, and listings are specified and the formats of these tables, figures, and listings are presented.

3. STUDY OBJECTIVES

The objectives of this study include:

- To prospectively compare the progression free survival (PFS) time of newly diagnosed GBM patients treated with NovoTTF-100A together with Temozolomide to those treated with Temozolomide alone.
- To prospectively compare the overall survival (OS) time of newly diagnosed GBM patients treated with NovoTTF-100A together with Temozolomide to those treated with Temozolomide alone.
- To prospectively determine % 6-month progression free survival, % 1 and 2-year survival and quality of life of patients treated with NovoTTF-100A together with Temozolomide to those treated with Temozolomide alone.
- To collect evidence of the safety of the NovoTTF-100A device applied together with Temozolomide to patients with newly diagnosed GBM.

4. STUDY OVERVIEW

4.1. Study Design

This is a multi-center, prospective, randomized, controlled pivotal study trial in patients with tissue diagnosis of GBM who have completed radiation therapy together with adjuvant Temozolomide. The control group will receive standard Temozolomide maintenance therapy.

Patients who meet eligibility criteria will be randomized in a 2:1 ratio either to the treatment group who will receive NovoTTF-100A treatment together with maintenance Temozolomide, or to the control group who will receive maintenance Temozolomide alone.

4.2. Study Patients

Patients will be recruited from at least 65 clinical centers with up to 40 centers in the USA and the remainder outside the USA. Seven hundred (700) patients will be randomized into the study (see **Section 5.1** for sample size justification).

Any patient with a histological diagnosis of GBM who meets all of the specific eligibility criteria listed below may be enrolled on this study. All patients must have received debulking surgery if possible, followed by maximal radiation therapy with concomitant Temozolomide prior to randomization. Patients receiving steroids to control edema may be included in the trial; however, any change in steroid dose must be documented during follow-up visits. An increase in steroid dose will preclude a diagnosis of partial or complete response (as suggested by Macdonald et al [1]). Disease status will be determined by comparing screening MRI to the immediate post-surgical MRI. If unavailable, an immediate post-surgical CT can be used for the same purpose. Patients who have progressive disease at screening (compared to the immediate post-surgical MRI) are not candidates for this study. In the case of local radiological suspicion of pseudoprogression, a PET scan or other imaging modality (in addition to T1 weighted MRI) will be obtained to assess biological activity of the tumor.

4.2.1. Inclusion Criteria

a. Pathological evidence of GBM using WHO classification criteria.
b. $\geq$ 18 years of age.
c. Received maximal debulking surgery and radiotherapy concomitant with Temozolomide (45-70Gy):
    1. Patients may enroll in the study if received Gliadel wafers before entering the trial.
    2. Any additional treatments received prior to enrollment will be considered an exclusion.

3. Minimal dose for concomitant radiotherapy is 45 Gy.

d. Karnofsky scale ≥ 70.
e. Life expectancy at least 3 months.
f. Participants of childbearing age must use effective contraception.
g. All patients must sign written informed consent.
h. Treatment start date at least 4 weeks out from surgery.
i. Treatment start date at least 4 weeks out but not more than 7 weeks from the later of last dose of concomitant Temozolomide or radiotherapy.

4.2.2. Exclusion Criteria

a. Progressive disease (according to MacDonald Criteria). If pseudoprogression is suspected, additional imaging studies must be performed to rule out true progression.
b. Actively participating in another clinical treatment trial.
c. Pregnant.
d. Significant co-morbidities at baseline which would prevent maintenance Temozolomide treatment:
    1. Thrombocytopenia (platelet count < 100 x 10^3/μL);
    2. Neutropenia (ANC < 1.5 x 10^3/μL);
    3. CTC grade 4 non-hematological Toxicity (except for alopecia, nausea, vomiting);
    4. Significant liver function impairment - AST or ALT > 3 x upper limit of normal (ULN);
    5. Total bilirubin > ULN; or
    6. Significant renal impairment (serum creatinine > 1.7 mg/dL).
e. Implanted pacemaker, programmable shunts, defibrillator, deep brain stimulator, other implanted electronic devices in the brain, or documented clinically significant arrhythmias.
f. Infra-tentorial tumor.
g. Evidence of increased intracranial pressure (midline shift > 5mm, clinically significant papilledema, vomiting and nausea or reduced level of consciousness).
h. History of hypersensitivity reaction to Temozolomide or a history of hypersensitivity to DTIC.

4.3. Randomization and Blinding

Patients who meet eligibility criteria will be randomized in a 2:1 ratio either to the treatment group who will receive NovoTTF-100A treatment together with maintenance Temozolomide, or to the control group who will receive maintenance Temozolomide alone. Randomization will be performed across centers using an automated Interactive Web/Voice Randomization System (IxRS). A computer-generated randomization schedule will be created with randomly varying block sizes (e.g., 3, 6, or 9 patients) within each of the following strata:

- Extent of Resection – Biopsy; Partial Resection; Gross total resection (only if immediate post-surgical MRI is available).
- MGMT (O^6-benzylguanine, O^6BG) methylation status – Unmethylated, Methylated, or Unknown

These classifications are expected to have a stronger impact on disease outcome than the treatment variability between centers, since standard of care for newly diagnosed GBM, worldwide, is based on the Stupp protocol [2].

The randomization schedule will be loaded to the IxRS. Authorized site personnel will input basic demographic criteria, confirm eligibility and input strata information as detailed above within the IxRS, and the system will automatically notify the site of the patient's treatment group assignment.

The nature of the treatment precludes blinding of patients and their treating clinicians to the actual treatment received by the patients. However, central MRI review will be performed by an independent neuro-radiologist blinded to the treatment group of each patient.

4.4. Estimated Duration of Patient Participation

All patients will be followed until death. Patients will report to the clinics for evaluation during the treatment period once per month until second disease progression or 24 months (the earlier of the two). After treatment termination, patients will be seen at an outpatient clinic every month for two additional visits. Physical and neurological examination, blood tests (CBC and biochemistry panel) will be performed during these visits. After the two post treatment monthly follow up visits, patients will not be required to return to the clinic for follow-up, but will be followed monthly until death by telephone to monitor their status.

4.5. Schedule of Study Evaluations

The schedule of study evaluations is performed according to the latest approved version of the EF-14 protocol.

4.6. Study Endpoints

4.6.1. Primary Efficacy Endpoint

The primary efficacy endpoint of the study is progression free survival. The progression free survival time of newly diagnosed GBM patients treated with NovoTTF-100A together with maintenance Temozolomide will be compared to those treated with maintenance Temozolomide alone.

4.6.2. Secondary Efficacy Endpoints

Secondary efficacy endpoints include:

- Overall survival (OS) time.
- Progression free survival at 6 months (PFS-6).
- One (1) and two (2) year overall survival rates.
- Quality of life assessment (EORTC QLQ-C30) – change from baseline (CFB) to 3, 6, 9 and 12 months will be calculated for each subscale domain and symptom scale.
- Radiological response rate.

4.6.3. Safety Endpoints

Safety endpoints include:

- Incidence and severity of adverse events (AEs).
- Clinical laboratory results (hematology, serum chemistry, and coagulation).
- Physical examinations.
- Neurological status.
- Karnofsky performance status, MRC scale, and MMSE.
- Vital signs (systolic/diastolic blood pressure, heart rate, temperature, weight).

4.7. Interim Analysis

One interim analysis will be performed on the PFS and OS data available for the first 315 patients after the first 315 patients accrued have a minimum of 18 months follow up. The assumptions used in the sample size calculations will be evaluated at the interim analysis. If it appears that the event rate, is lower than expected the company may request a sample size increase or a follow up duration increase to achieve the desired study power. The company will not request a sample size decrease based on the results of this assessment.

5. STATISTICAL METHODS

5.1. Sample Size Considerations

Based on the insignificant side effects of NovoTTF-100A treatment observed in the pilot studies of newly diagnosed GBM performed so far in Europe and in the pivotal trial in recurrent GBM, we assume that any significant increase in progression free survival compared to the control group would justify use of the NovoTTF-100A device in newly diagnosed GBM patients, concomitant to maintenance Temozolomide.

The sample size of 700 patients (210 Control patients + 420 NovoTTF-100A patients + 10% loss to follow-up) was determined using NCSS/PASS11 software based on the log-rank test comparing time to event (i.e., progression or death prior to progression) between patients treated with the NovoTTF-100A together with maintenance Temozolomide and controls (maintenance Temozolomide alone). The null hypothesis is that the recurrence rate is the same in the two study groups, *i.e.*, hazard ratio=1. The alternative hypothesis is that the recurrence rate is not the same, *i.e.*, hazard ratio≠1. The expected hazard ratio was estimated from the expected median progression free survival in the two study groups as follows:

- Expected median progression free survival on control treatment is 7 months (see Stupp [2] and Temozolomide package insert).
- Expected median progression free survival on NovoTTF-100A treatment is 9 months.
- Expected Hazard Ratio = 0.78
- Expected accrual time during which patients are recruited: 48 months.
- Additional follow-up time after end of recruitment: 18 months.
- Ratio of control to experimental patients: 1:2.
- Type I error: 0.05%; 2-sided.
- Power: 80%.

This sample size also has adequate power (80%) to detect a minimum of 4.5 month increase in median overall survival in NovoTTF-100A treated patients compared with control patients (who have an expected median OS of 14.6 months), or a Hazard Ratio of 0.76.

5.2. Analysis Populations

The following analysis populations will be used in the study:

- Intent-to-Treat (ITT)

The ITT population includes all patients who were randomized to the trial. The analysis will be performed by the treatment group to which the patient was randomized. The primary efficacy analysis will use the ITT population.

- Per Protocol (PP)

The PP population includes:

- All patients who do not have any major protocol violations that would affect the endpoints being assessed.
- Patients on the control arm who cross over to NovoTTF-100A at progression will be excluded from the PP population.
- All patients randomized to NovoTTF-100A together with Temozolomide who received at least one full treatment course as defined in the protocol (1 maintenance cycle of Temozolomide and 28 days of NovoTTF-100A treatment)
- All patients randomized to maintenance Temozolomide alone treatment received at least one maintenance cycle of Temozolomide.

Note – A patient receiving the first maintenance cycle of temozolomide is defined as a patient who received the first day of the second temozolomide course (since temozolomide is given for 5 days out of every 28 days).

All secondary efficacy endpoints will use the PP population except for OS which will be calculated for the ITT in addition to PP population.

- Safety Population

The Safety population includes all patients who received at least one dose of maintenance Temozolomide or at least one day of treatment with NovoTTF device. The safety analysis will be performed by treatment group according to the treatment which the patient actually received. Only AEs occurring prior to treatment termination will be included in the summary tables because of the obvious confounding of safety analysis that may result from disease condition and/or subsequent therapy. All adverse events will be included in the listing of AEs.

5.3. Analysis Conventions

This section details general conventions to be used for the statistical analyses. Departures from these general conventions may be given in the specific detailed sections of this analysis plan. The following conventions will be applied to all data presentations and analyses.

- Summary statistics will consist of the number and percentage of responses in each level for categorical variables, and the sample size (n), mean, median, standard deviation (SD), minimum, and maximum values for continuous variables.

- In general, all means and confidence intervals will be formatted to one more decimal place than the measured value. Median values will be formatted to the same number of decimal places as the measured value, and standard deviation values will be formatted to two more decimal places than the measured value. Minimum and maximum values will be presented with the same number of decimal places as the measured value.

- The number and percentage of responses will be presented as XX (XX), with the percentage in parentheses.

- All p-values will be rounded to 4 decimal places. All p-values that round to 0.0000 will be presented as '<0.0001' and p-values that round to 1.000 will be presented as '>0.9999'.

- One month is equal to 30 days.

- All summary tables will include the analysis population sample size (i.e., number of patients) in each treatment group.

- "Enrollment Date" is the randomization date.

- "Study Start Date" for treatment emergent AE calculations (replacing the term "Treatment Start Date") will never be prior to date the patient signs the Informed Consent Form and patient randomization (enrollment). Study Start Date as defined here is synonymous with the date of data collection start, including AE/SAE reports.
    - If maintenance Temozolomide started prior to Enrollment Date, the Study Start Date will be identical to the Enrollment Date, regardless of the time of signing the Informed Consent Form.
    - When maintenance Temozolomide starts after consent and Enrollment Date, the Study Start Date is the earlier of the date of first dose of maintenance Temozolomide or date of application NovoTTF.

- The last assessment taken prior to administration of the first dose or first use of the device (whichever comes first) will be used as the baseline measurement for statistical analyses.

- Change from baseline (CFB) will be calculated as follows:

CFB = Post-baseline value – baseline value, or Post-baseline value/baseline value (as percentage)

- Missing data will not be imputed, and therefore will not be included in statistical analysis unless otherwise stated.

- Date variables will be formatted as DDMMMYYYY for presentation.

- Tables, figures, and listings will be presented in landscape orientation.

- SAS® version 9.3 [3] or higher will be the statistical software package used for all data analysis and datasets.

- All data from this study will be presented in a listing. All listings will be sorted by treatment group, site, patient number, and date where applicable.

5.4. Patient Disposition

The total number of patients enrolled in the study will be presented in the patient disposition table in addition to the following subsets of patients which will be presented by treatment group and overall:

- Number of patients randomized.
- Number of patients receiving treatment/therapy (for each course).
- Number of patients with 1st and 2nd progression according to investigators assessment.
- Number of patients discontinued from treatment.
- The primary reason for discontinuation.

5.5. Demographic and Baseline Characteristics

A summary table by treatment group will be presented showing summary statistics for age, gender, race, region (North America - NA or Rest of World - ROW), extent of resection (biopsy, partial resection, or total resection), MGMT methylation status (positive, negative, unknown), genetic markers (EGFR amplification, over-expression or rearrangement; chromosomes 1p/19q deletion status; IDH1 mutation), Karnofsky performance scale score, median time from GBM diagnosis to randomization, size and location of primary tumor (hemisphere & lobe) for the ITT, PP, and Safety populations.

Baseline characteristics of patients who withdraw or are lost to follow-up before meeting the study endpoints (OS and PFS) will be compared using descriptive statistics with patients who remain in the study to evaluate the potential for informative censoring.

GBM history, including the type of surgery, gliadel wafer use, number of wafers used, and histological diagnosis, will be collected at screening and summarized by treatment group.

Dose of prior radiation therapy (total), number of temozolomide courses per patient (one course = first 5 days of each 28 days), total temozolomide dose and schedule of subsequent chemotherapies will be listed per patient and tabulated as summary statistics per arm.

Medical history and other interventions will be collected at screening and presented in a data listing.

5.6. Primary Efficacy Analysis

The primary endpoint of the study is progression-free survival (PFS). Determination of progression will be made by core radiology review in cases where an MRI is available (which should be the great majority of cases). The following will be considered disease progression (based on the Macdonald criteria):

- Tumor growth > 25% compared to the smallest tumor area measured in this patient during the trial;
- Appearance of 1 or more new tumors in the brain (diagnosed radiologically as GBM);

In cases where an MRI is not available, clinical criteria will be used:

- Decline in functional status as indicated by a decrease in Karnofsky performance scale score > 10, and
- Decline in neurological function as indicated by a decrease of 2 points or more in MRC scale, and
- ≥50% increase in steroid dose.

In cases where progression is not determined according to one of the above methods, a clinical events committee will adjudicate the date of progression based on core radiology assessment, investigator assessment of progression, the above clinical criteria, adverse events and changes in treatment plan.

PFS is calculated from the date of randomization to the date of disease progression (defined above) or censoring. PFS will be censored at the last patient follow up visit date that the patient is known to be progression free if the patient is lost-to-follow-up, or is still under observation at the time the final analysis (administrative censoring). Specifically, PFS will be calculated as:

PFS = (Progression/Censor Date – Randomization Date + 1) / 30 days.

Disease progression may be radiological progression (as determined by an independent reviewer's assessment), clinical progression (as determined by the investigator after CEC adjudication in the absence of an MRI), or a death due to any cause. For the time from last follow up to death, if a patient dies within window for the next MRI, this will be disease progression. But if a patient dies later, the time to disease progression for that patient will be censored at the last follow up as death after 90 days (2+1 months) from last known stable disease will not be considered disease progression.

The statistical hypothesis that will be tested is:

H_0: $PFS_t = PFS_c$ versus H_A: $PFS_t \neq PFS_c$

where,

PFS_t = K-M progression free survival curve in the NovoTTF-100A treatment arm;
PFS_c =K-M progression free survival curve in the control arm.

This hypothesis will be tested using a stratified log-rank test by MGMT status and the extent of resection at randomization at a two-sided significance level of 0.01394 at the interim analysis and 0.04574 at the final analysis.

Exploratory Analyses of the primary endpoint (only at the final analysis):

At the final analysis a Cox proportional hazards model will be used, adjusting for the stratification factors (extent of resection used at randomization and MGMT methylation status) and region (NA vs ROW). Additionally, any covariates described in **Section 5.9** that may be significant predictors of PFS, will be adjusted for in the model. The number of patients at risk in each treatment group, number of patients who had an event, hazard ratio (HR), 95% confidence interval of the HR, and both the adjusted and unadjusted p-values will be presented in this table and as a forest plot.

The statistical hypothesis that will be tested is:

H_0: $\beta = 0$ versus H_A: $\beta \neq 0$

where,

$\exp(\beta) = h_1(t)/h_2(t)$;
$h_1(t)$ = the hazard at time t for the treatment arm; and
$h_2(t)$ = the hazard at time t for the control arm.

This hypothesis will be tested using a log-rank test at the nominal α=0.05 level (2-sided) for the final analysis.

5.7. Secondary Efficacy Analysis

A hierarchical approach will be used to first test the primary endpoint of PFS and then the secondary endpoint of overall survival to avoid problems with statistical multiplicity. Specifically, overall survival will be tested at the proposed significance levels for the interim and final analyses, if the primary endpoint of progression free survival also meets its significance levels at the respective time points.

5.7.1. Overall Survival (OS)

OS is measured from the date of randomization to the date of death or censoring (in months). OS will be censored at the last date when a patient is known to be alive if the patient is lost to follow up or is still under observation at the time of the final analysis (administrative censoring). Specifically, OS will be calculated as:

OS = (Death/Censor Date – Randomization Date + 1) / 30 days.

The statistical hypothesis that will be tested is:

H_0: $OS_t = OS_c$ versus H_A: $OS_t \neq OS_c$

where,

OS_t = the Kaplan Meier survival curve for the treatment arm; and
OS_c = the Kaplan Meier survival curve for the control arm.

This hypothesis will be tested using a log-rank test at an α level of 0.00598 at the interim analysis and an α level of 0.0481 level (2-sided) for the final analysis.

Exploratory analysis of OS (performed at the final analysis):
A Cox proportional hazards model will be used, adjusting for the stratification factor, and region. Additionally, any covariates described in **Section 5.9** that may be significant predictors of overall survival in the model, will be adjusted for in the model. The number of patients at risk in each treatment group, number of patients who had an event, hazard ratio (HR), 95% confidence interval of the HR, and both the adjusted and unadjusted p-values will be presented in this table.

Kaplan-Meier estimates (quartiles, median time to event, and 95% CI) of OS and corresponding survival curves will be provided by treatment group and by treatment group for each stratum.

5.7.2. Progression Free Survival at 6 Months (PFS-6)

PFS at 6 months will be analyzed in the same manner as overall PFS in **Section 5.6** including similar censoring rules.

Definition of PFS at 6 months is the proportion of patients who are progression free on the Kaplan Meier curves for PFS at the 6 month time point (1 month=30 days).

The statistical hypothesis that will be tested is:

$$H_0: P_t - P_c \leq 0 \qquad \text{versus} \qquad H_A: P_t - P_c > 0$$

where,

P_t = the K-M estimated proportion of patients who are alive and progression free at 6 months in the NovoTTF-100A treatment arm;
P_c =the K-M estimated proportion of patients who are alive and progression free at 6 months in the control arm.

This hypothesis will be tested using a chi-square test at one-sided significance level of 0.05.

No analysis will be performed on this endpoint at the interim analysis.

5.7.3. One and Two Year Overall Survival

For one-year survival, the analysis will be performed based on the Kaplan Meier estimated proportion of patients alive at 12 months (360 days) in both arms of the study. Similarly, for two-year survival, the analysis will be performed based on the Kaplan Meier estimated proportion of patients alive at 24 months (720 days) in both arms of the study.

The one-year survival and two-year survival analysis will be similar to the overall survival presented in **Section 5.7.1**, except that a one-sided chi-square test assuming the NovoTTF-100A will have higher one and two year survival rates than the control arm will be tested. The number of patients at risk, the number of patients who had an event and the survival rates will be summarized and presented by treatment group. No analysis will be performed on these endpoints at the interim analysis.

5.7.4. Quality of Life

Quality of life (EORTC QLQ-C30 questionnaire) will be assessed and completed at baseline, month 3, month 6, as well as every three months until the patient stops treatment. The mean response and change from baseline to each time point for each subscale domain and symptom scale in the questionnaire (see Appendix 1) will be summarized in tables by treatment group, showing the actual mean response as well as

the percent change from baseline. No analysis will be performed when the number of patient responses to the questionnaire drops below 70 (total in both arms).

5.7.5. Radiological Response

The radiological response rate of the tumor will be assessed by the MRI studies according to Macdonald criteria for progressive disease, stable disease, partial response or complete response. The proportion of patients by radiological response will be presented by visit and treatment group, as well as for the best overall response. The response rate will be calculated using the number of all randomized patients as the denominator.

Final radiological responses by the independent reviewer and by investigator assessment will be presented.

The two treatment groups will be compared using a one-sided chi-square test using a significance level of 0.05 assuming that NovoTTF-100A will have a higher response rate than the control group. No analysis of radiological response rate will be performed at the interim analysis.

5.7.6. Karnofsky Performance Scale Score

The Karnofsky performance score (0-100) will be assessed and completed at every scheduled visit until the patient stops treatment. The Karnofsky performance scores and change from baseline to each subsequent timepoint will be summarized in tables using descriptive statistics by treatment group, including the percent change from baseline. A graph of the longitudinal descriptive statistics will be presented as means and medians with 95%CIs.

5.7.7. Medical Research Council (MRC) Neurological Status

The MRC scale for neurological status score (1-4) will be assessed and completed at every scheduled visit until the patient stops treatment. The number and percentage of patients in each MRC scale status will be summarized at each scheduled visit.

5.7.8. Mini-Mental State Examination (MMSE)

The MMSE score (0-30) will be assessed and completed at every scheduled visit until the patient stops treatment. The MMSE scores and change from baseline to each subsequent timepoint will be summarized in tables using descriptive statistics by treatment group, including the percent change from baseline. A graph of the longitudinal descriptive statistics will be presented as means and medians with 95%CIs.

5.8. Safety Analysis

All safety analysis will be performed on the Safety population, defined in **Section 5.2**.

5.8.1. Adverse Events

All adverse events will be coded to body system and preferred term using the most current version of Medical Dictionary for Regulatory Activities (MedDRA) version 16.0. A treatment-emergent adverse event (TEAE) is defined as an AE that was not present prior to study treatment but appeared following treatment or was present at treatment initiation, but worsened during treatment. TEAEs will also include any AEs with partial onset dates, or if the stop date is after the Study Start Date (see definition in **Section 5.3**) and the dates do not definitively place the AE before the start date of study treatment, or if the AE is completely missing onset dates.

Only adverse events occurring during study treatment will be included in the summary tables of AEs. All adverse events will be presented in the data listings.

Treatment-emergent adverse events will be summarized by treatment group with respect to:

- Incidence of adverse events (the number and percent of patients reporting at least one episode of a specific adverse event) by body system and preferred term;
- Incidence of adverse events by body system, preferred term, and maximum severity Common Terminology Criteria for Adverse Events (CTCAE) version 3.0 grade (defined below);
- Incidence of adverse events by body system, preferred term, and strongest relationship to study treatment;
- Incidence of adverse events by body system, preferred term, and outcome
- Incidence of adverse events leading to study treatment withdrawal (not including tumor progression); and
- Incidence of serious treatment-emergent adverse events.

In the incidence tables by maximum severity and strongest relationship to study drug/device, if a patient experiences multiple episodes of the same adverse event, then the most severe event or the event with the strongest relationship to study drug will be used. For the incidence table by outcome, if a patient experiences multiple episodes of the same adverse event, then event with the 'worst' outcome will be used. Outcomes ordered from best to worst are:

- Resolved Without Sequelae
- Resolved With Sequelae
- Ongoing
- Death

AE severity will be graded according to the National Cancer Institute (NCI) CTCAE grades as defined below.

Grade	Degree of Severity
1	Mild, with no or mild symptoms; not interventions required
2	Moderate; minimal intervention indicated; some limitation of activities
3	Severe but not life-threatening; hospitalization required; limitation of patient's ability to care for him/herself
4	Life-threatening; urgent intervention required
5	Death related to adverse event

Sub analysis
AE rates may be normalized per treatment group by the duration on treatment per group in case if there is imbalance in the duration of treatment between the treatment groups.

5.8.2. Clinical Laboratory Results

Descriptive statistics of laboratory results and changes from baseline will be tabulated for all hematology, serum chemistry, and coagulation parameters for each clinical visit by treatment group. In addition, a summary table of CTCAE grades will be presented by treatment group for each applicable parameter.

5.8.3. Physical Examinations

A shift from baseline table will be presented for the physical examination results, showing changes between normal/abnormal findings at each clinical visit by treatment group.

5.8.4. Neurological Examinations

A shift from baseline table will be presented for the neurological examination results at each clinical visit by treatment group.

5.8.5. Vital Signs

A summary table will be presented for the reported values and for the change from baseline for all collected vital sign parameters (systolic blood pressure, diastolic blood pressure, heart rate, respiration, temperature, and weight) at each clinical visit by treatment group. Height will be summarized at baseline.

5.8.6. Exposure to Study Treatment

A summary table will be presented including the number of patients exposed to each treatment including the number of months of each treatment (NovoTTF-100A and

Temozolomide). One month of treatment is defined as 30 days. Descriptive statistics will be presented for the fraction (%) of course treated.

5.8.7. Prior and Concomitant Medications

Prior and concomitant medications will be coded using the World Health Organization (WHO) Drug Dictionary 4th Quarter 2008. Levels of summarization will include global, WHO Anatomic Therapeutic Chemical (ATC) Level II drug class, and WHO generic term. At each level of summarization, a patient will be counted only once for each concurrent medication he/she has within that level. The percentage of patients having had at least one medication at each level will be calculated.

Prior medications are defined as any medication that was started before first exposure to study treatment. Concomitant medications are defined as any medication started after first exposure to stud treatment. Medications with partial start dates that indicate usage from the beginning of the screening period and medications with completely missing stop dates will be classified as concomitant. All medications collected will be presented in the data listings and prior medications will be flagged.

5.8.8. Chemotherapy Regimen

Chemotherapy regimens will be coded using the World Health Organization (WHO) Drug Dictionary 4th Quarter 2008. Levels of summarization will include global, WHO Anatomic Therapeutic Chemical (ATC) Level II drug class, and WHO generic term. At each level of summarization, a patient will be counted only once for each concurrent medication he/she has within that level. The percentage of patients having had at least one medication at each level will be calculated.

In addition, the number of cycles of each regimen received, and the number of months of treatment will be summarized by treatment arm. One month of treatment is defined as 30 days. One cycle of chemotherapy treatment will be defined as any cycle in which at least one dose of chemotherapy was given.

5.8.9. Steroid Use for GBM

Steroids used for the treatment of GBM will be coded using the World Health Organization (WHO) Drug Dictionary 4th Quarter 2008. Levels of summarization will include global, WHO Anatomic Therapeutic Chemical (ATC) Level II drug class, and WHO generic term. At each level of summarization, a patient will be counted only once for each concurrent medication he/she has within that level. The percentage of patients having had at least one medication at each level will be calculated.

5.8.10. Ancillary Procedures

All ancillary procedures will be presented in the data listings.

5.9. Covariates

Using Cox proportional hazards as described in **Section 5.6**, the effect of the following covariates on PFS and OS will be investigated and their significance levels presented in a summary table:

- Age (continuous)
- Extent of surgery (biopsy, partial, or total resection)
- MGMT methylation status (Unmethylated, methylated or unknown)
- Additional genetic markers:
    - EGFR amplification, over-expression or rearrangement
    - Chromosomes 1p/19q deletion status
    - IDH1 mutation
- Baseline Karnofsky performance scale score
- Tumor size (continuous)
- Tumor location
- Percent of the total treatment time in which the NovoTTF-100A treated patients actually received treatment (will be calculated by analyzing the internal computerized log file of each NovoTTF-100A device and dividing the total device ON time by the prescribed number of 1 month treatment courses).

5.10. Pooling

Subgroup analysis of the primary efficacy endpoint by country and center will be used to evaluate the 'poolability' of the results. The significance of country and center variability in the treatment effect will be evaluated by including an interaction term of treatment by country or center in the Cox regression model. In the case that poolability is questionable, the reasons for differential treatment effect, such as patient and tumor characteristics, will be investigated and reported. However, no pooling of countries or centers is planned in the primary and secondary efficacy analysis models.

5.11. Subgroup Analysis

PFS and overall survival analysis will be presented for the ITT and PP population by various subgroups. Subgroups to be presented will be defined as those parameters which meet a significance of <0.20 in the cox proportional hazards model in section 5.9 above.

Subgroup analysis of the overall survival for the NovoTTF-100A treatment arm only will be conducted by maximal compliance level defined as the median compliance for each patient throughout the study period (<75% vs ≥75%).

5.12. Exploratory Analysis

The correlation between the percent of time patients received NovoTTF-100A treatment and their median PFS and OS will be presented as a scatter plot with a linear regression

An exploratory analysis of adverse events may also be conducted, investigating the number of adverse events per patient.

6. REFERENCES

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8. DEVIATIONS FROM PLANNED ANALYSIS IN PROTOCOL

None in this version of SAP.

Appendix 1 – QLQ-C30 Scoring Manual

The QLQ-C30 is composed of both multi-item scales and single-item measures. These include five functional scales, three symptom scales, a global health status / QoL scale, and six single items. Each of the multi-item scales includes a different set of items - no item occurs in more than one scale.

All of the scales and single-item measures range in score from 0 to 100. A high scale score represents a higher response level.
Thus a **high score for a functional scale** represents a *high / healthy level of functioning*,
a **high score for the global health status / QoL** represents a *high QoL*,
but a **high score for a symptom scale / item** represents a *high level of symptomatology / problems*.

The principle for scoring these scales is the same in all cases:

1. Estimate the average of the items that contribute to the scale; this is the *raw score*.

2. Use a linear transformation to standardise the raw score, so that scores range from 0 to 100; a higher score represents a higher ("better") level of functioning, or a higher ("worse") level of symptoms.

Coding of the scoring procedure is presented in Appendix 3 for three major statistical packages.

Technical Summary

In practical terms, if items $I_1, I_2, \ldots I_n$ are included in a scale, the procedure is as follows:

Raw score
Calculate the raw score
RawScore = $RS = (I_1 + I_2 + \ldots + I_n)/n$

Linear transformation
Apply the linear transformation to 0-100 to obtain the score S,

Functional scales: $S = \left\{1 - \frac{(RS-1)}{range}\right\} \times 100$

Symptom scales / items: $S = \{(RS-1)/range\} \times 100$

Global health status / QoL: $S = \{(RS-1)/range\} \times 100$

Range is the difference between the maximum possible value of RS and the minimum possible value. The QLQ-C30 has been designed so that all items in any scale take the same range of values. Therefore, the range of RS equals the range of the item values. Most items are scored 1 to 4, giving *range* = 3. The exceptions are the items contributing to the global health status / QoL, which are 7-point questions with *range* = 6, and the initial yes/no items on the earlier versions of the QLQ-C30 which have *range* = 1.

Table 1: Scoring the QLQ-C30 version 3.0

	Scale	Number of items	Item range*	**Version 3.0** Item numbers	Function scales
Global health status / QoL					
Global health status/QoL (revised)†	QL2	2	6	29, 30	
Functional scales					
Physical functioning (revised)†	PF2	5	3	1 to 5	F
Role functioning (revised)†	RF2	2	3	6, 7	F
Emotional functioning	EF	4	3	21 to 24	F
Cognitive functioning	CF	2	3	20, 25	F
Social functioning	SF	2	3	26, 27	F
Symptom scales / items					
Fatigue	FA	3	3	10, 12, 18	
Nausea and vomiting	NV	2	3	14, 15	
Pain	PA	2	3	9, 19	
Dyspnoea	DY	1	3	8	
Insomnia	SL	1	3	11	
Appetite loss	AP	1	3	13	
Constipation	CO	1	3	16	
Diarrhoea	DI	1	3	17	
Financial difficulties	FI	1	3	28	

* *Item range* is the difference between the possible maximum and the minimum response to individual items; most items take values from 1 to 4, giving *range* = 3.

† (revised) scales are those that have been changed since version 1.0, and their short names are indicated in this manual by a suffix "2" – for example, PF2.

For all scales, the *RawScore*, *RS*, is the mean of the component items:

$$RawScore = RS = (I_1 + I_2 + ... + I_n)/n$$

Then for **Functional scales**:

$$Score = \left\{1 - \frac{(RS - 1)}{range}\right\} \times 100$$

and for **Symptom scales / items** and **Global health status / QoL:**

$$Score = \{(RS - 1)/range\} \times 100$$

Examples:

Emotional functioning

$$RawScore = (Q_{21} + Q_{22} + Q_{23} + Q_{24})/4$$
$$\text{EF } Score = \{1 - (RawScore - 1)/3\} \times 100$$

Fatigue

$$RawScore = (Q_{10} + Q_{12} + Q_{18})/3$$
$$\text{FA } Score = \{(RawScore - 1)/3\} \times 100$$

Additional Analyses for the EF-14 PMA Submission

The interim analysis was limited to the primary endpoint of PFS and the powered secondary endpoint of OS. The following additional analyses for the full PMA submission will be performed:

1) A Cox proportional hazards model will be used, adjusting for the stratification factors (extent of resection used at randomization and MGMT methylation status as used in the randomization strata) and region (US vs ROW). Additionally, any covariates that may be significant predictors of PFS, will be adjusted for in the model.

   The statistical hypothesis that will be tested is:
   H_0: $\beta = 0$ versus H_A: $\beta \neq 0$
   where,
   exp(β) = h1(t)/h2(t);
   h1(t) = the hazard at time t for the treatment arm; and
   h2(t) = the hazard at time t for the control arm.
   This hypothesis will be tested using a log-rank test at the nominal alpha=0.05 level (2-sided).
2) Sensitivity Analysis for OS – Since OS was tested in a per protocol population in the interim analysis the following sensitivity analyses will be performed:
   i. A stratified log rank test between groups of OS in the ITT population (includes patients who never received therapy, received less than a full treatment cycle and patients who crossed over to the device arm).
   ii. A stratified log rank test between groups of OS in the per protocol population including patients with insufficient treatment (only crossover patients will be excluded from the per protocol population)
3) A Cox proportional hazards model of OS will be performed, adjusting for the stratification factors, and region. Additionally, any covariates that may be significant predictors of overall survival in the model, will be adjusted for in the model. The number of patients at risk in each treatment group, number of patients who had an event, hazard ratio (HR), 95% confidence interval of the HR, and both the adjusted and unadjusted p-values will be presented.
4) PFS6 - The statistical hypothesis that will be tested is:

   H_0: Pt-Pc ≤ 0 versus H_A: Pt-Pc > 0

   where,

   Pt = the K-M estimated proportion of patients who are alive and progression free at 6 months in the NovoTTF-100A treatment arm;
   Pc =the K-M estimated proportion of patients who are alive and progression free at 6 months in the control arm.

   This hypothesis will be tested using a chi-square test at one-sided significance level of 0.05.

5) OS at 12 months and OS at 24 months: For one-year survival, the analysis will be performed based on the Kaplan Meier estimated proportion of patients alive at 12 months (360 days) in both arms of the study. Similarly, for two-year survival, the analysis will be performed based on the Kaplan Meier estimated proportion of patients alive at 24 months (720 days) in both arms of the study.
   A one-sided chi-square test assuming the NovoTTF-100A will have higher one and two year survival rates than the control arm will be tested at an alpha level of 0.05.

6) Changes in mini-mental status exam (MMSE) from baseline per group: The MMSE scores and change from baseline to each subsequent time point will be summarized in tables using descriptive statistics by treatment group, including the percent change from baseline. A graph of the longitudinal descriptive statistics will be presented as means and medians with 95%CIs.

7) EORTC QLQ C30 – quality of life questionnaire: The mean response and change from baseline to each time point for each subscale domain and symptom scale in the questionnaire will be summarized in tables by treatment group, showing the actual mean response as well as the percent change from baseline. No analysis will be performed when the number of patient responses to the questionnaire drops below 70 (total in both arms).

8) Radiological response rate - The radiological response rate of the tumor will be assessed by the MRI studies according to Macdonald criteria for progressive disease, stable disease, partial response or complete response. The two treatment groups will be compared using a one-sided chi-square test using a significance level of 0.05 assuming that NovoTTF-100A will have a higher response rate than the control group.

9) Subgroup analyses: Kaplan Meier curves with descriptive statistics will be presented for the following subgroups. No Statistical hypothesis testing will be performed.
   iii. PFS and OS by region (US and ROW)
   iv. PFS and OS by MGMT methylation status
   v. PFS and OS by extent of resection
   vi. PFS and OS by Age
   vii. PFS and OS by KPS
   viii. PFS and OS by Gender

10) Subgroup analysis of the primary efficacy endpoint by region will be used to evaluate the 'poolability' of the results. The significance of regional variability in the treatment effect will be evaluated by including an interaction term of treatment by region in the Cox regression model. In the case that poolability is questionable, the reasons for differential treatment effect, such as patient and tumor characteristics, will be investigated and reported.