UCI 16-56: PHASE II, SINGLE ARM STUDY OF NOVOTTF-200A IN BEVACIZUMAB-NAÏVE SUBJECTS WITH RECURRENT WHO GRADE III MALIGNANT ASTROCYTOMA

INVESTIGATIONAL PRODUCT (IP): NovoTTF-200A

IDE: G170145

PI Information
Name: Daniela A. Bota, M.D., Ph.D.
Title: Associate Professor, Neurology Medical Director, Comprehensive Brain Tumor Center Program University of California, Irvine Medical Center
Address: University of California, Irvine Medical Center Chao Family Comprehensive Cancer Center 101 The City Drive South Building 23 Orange, CA 92868
Phone: (714) 456-7032
Email: dbota@uci.edu

PROTOCOL VERSION DATE: 11/27/17

Protocol SYNOPSIS

Proposed Title	**Phase II, Single Arm Study Of NOVOTTF-200A In Bevacizumab-Naïve Subjects with Recurrent WHO Grade III Malignant Astrocytoma**
Study No.	UCI 16-56
Sponsor	University of California, Irvine / NovoCure Ltd.
Phase	2
Indication	WHO Grade III Malignant Astrocytoma (G3 MG) in bevacizumab-naïve subjects
No. of Sites	Single center study in the United States.
Background and Study Rationale	The study population includes subjects with histologically confirmed recurrent/progressive anaplastic astrocytoma (G3 astrocytoma). The population includes patients who had progressive disease after treatment with radiation, followed by either temozolomide chemotherapy or CCNU or PCV or other clinically available agents (cyclophosphamide, etoposide). These patients must not have previously received any bevacizumab (BEV) or any experimental agents. At the time of recurrence after temozolomide, the patients have no standard of care choices. They are treated with a variety of different treatments based on the treating physician choice. Most frequently, the chosen regimen includes bevacizumab based on the published data showing a 6-month progression-free survival of 55% (95% CI, 36-70%) and 6-month overall survival of 79% (95% CI, 61-89%). Additional treatment options are needed for these subjects. Published literature indicates that targeting mitosis via tumor treating fields (TTF) in rapidly dividing cancer cells by disrupting both spindle formation and normal cytokinesis selectively kills or arrests growth in glioma cell lines. The NovoTTF-200A® system is a novel antimitotic cancer therapy approved in 2011 by the FDA for the treatment of recurrent (supratentorial) glioblastoma (G4 astrocytoma) based on the results of a Phase 3 trial comparing NovoTTF® therapy with best active chemotherapy according to physician choice. No data are currently available on the response of anaplastic astrocytoma to this technology. In addition, no biomarker is yet available in order to predict which patients will have a better response to the NovoTTF® technology. The NovoTTF device-related adverse effect most commonly cited involves skin irritation and heat sensations on the scalp below the transducer arrays.

	Patients described these as "warm," "tingling" sensations, none of which were associated with injury to the patient. Systemic events which were often associated with chemotherapy (gastrointestinal, hematologic and infectious adverse events) are rarely reported with use of NovoTTF.
Objectives	Primary Objective: The primary objective will be to determine the efficacy of NOVOTTF-200A in recurrent anaplastic astrocytoma patients (6-month progression-free survival) Secondary Objectives: • To evaluate the safety of NOVOTTF-200A in the subject population. • To evaluate efficacy of NOVOTTF-200A in the subject population. • To see if the presence of ATRX, TERT promoter, IDH1 mutations and/or MGMT promoter methylation, confers a better response to NOVOTTF-200A. • To determine if the treatment significantly modifies the patient's quality of life. We will use the Functional Assessment of Cancer Therapy (FACT) questionnaires: o FACT-Brain (FACT-Br) o FACT-Cognitive Function (FACT-Cog) Exploratory Objectives: • To determine if the presence of proneural or mesenchymal phenotype (Cytoscan analysis) confers a better response to NovoTTF. • To determine if the *in vitro* sensitivity of the glioma cells derived from patient specimens before and after the NOVOTTF-200A treatment correlates with the patient's response to treatment.
Study Design	This is a Phase 2 study in subjects with WHO Grade III Anaplastic Astrocytoma (G3 astrocytoma) who had progressive disease during first or second line treatment and who have not previously received any BEV or any experimental agents. Up to 36 subjects will be enrolled and will be used to assess efficacy. Given the nature of the NOVOTTF-200A device, no cohort will be needed to assess maximum tolerated dose (MTD) as it does not apply.
Study Treatments	NOVOTTF-200A has received FDA approval for other indications and will be available through a commercial use program by NovoCure.

	NOVOTTF-200A will be administered under appropriate guidelines. Monthly adherence rate >= 75% (>= 18 hours/day) over a 4-week cycle (28 days) will be strongly encouraged.
No. Subjects	Up to 36 subjects will be enrolled in the study (26 evaluable needed).
Study Population	The study population includes subjects with G3 astrocytoma who had progressive disease after radiation, temozolomide and/or PCV (up to two recurrences) and who have not previously received any anti-angiogenic agents including BEV. **Key Inclusion Criteria** Subjects must meet the following criteria to be eligible for study participation: 1. Understand and voluntarily sign and date an informed consent document prior to any study related assessments/procedures are conducted. 2. Males and females > the age of 21 years at the time of signing of the informed consent document. 3. All subjects must have histologic evidence of anaplastic astrocytoma and radiographic evidence of recurrence or disease progression (defined as either a greater than 25% increase in the largest bidimensional product of enhancement, a new enhancing lesion or significant increase in T2 FLAIR) after first-line treatment. 4. Subjects with archival tumor tissue suitable for genetic testing must give permission to access and test the tissue. 5. No prior treatment with any anti-angiogenic agents including BEV. 6. At least 4 weeks from surgical resection and 12 weeks from end of radiotherapy prior to enrollment in this study, unless relapse is confirmed by tumor biopsy or new lesion outside of radiation field, or if there are two MRIs confirming progressive disease that are 8 weeks apart. 7. All AEs resulting from prior chemotherapy, surgery or radiotherapy must have resolved to NCI-CTCAE (v. 4.03) Grade ≤1 (except for laboratory parameters outlined below). 8. Laboratory results within 7 days prior to NovoTTF® administration (transfusions and/or growth factor support may be used at the discretion of the Investigator during Screening): • Hemoglobin ≥9 g/dL. • Absolute neutrophil count (ANC) ≥1.5 × 10^9/L. • Platelet count ≥100 × 10^9/L. • Serum bilirubin ≤1.5 × upper limit of normal (ULN) or ≤3 × ULN if Gilbert's disease is documented.

	• Aspartate transaminase (AST) ≤ 2.5 ULN. • Serum creatinine ≤1.5 × ULN. • Urine protein: creatinine ratio ≥1.0 at screening 9. Karnofsky Performance Status (KPS) score ≥70%. 10. For women of child-bearing potential and for men with partners of child-bearing potential, subject must agree to take contraceptive measures for duration of treatments 11. Willing and able to adhere to the study visit schedule and other protocol requirements. **Key Exclusion Criteria:** Subjects with any of the following will be excluded from participation in the study: 1. The presence of 1p19q LOH which is diagnostic for anaplastic oligodendroglioma (AO). 2. Co-medication that may interfere with study results, e.g., immunosuppressive agents other than corticosteroids. (Steroid therapy for control of cerebral edema is allowed at the discretion of the investigator. Subjects should be on a stable dose of steroids for at least 1 week prior to study beginning. 3. Chemotherapy administered within 4 weeks (6 weeks for an IV nitrosoureas and 12 weeks for an implanted nitrosoureas wafer) prior to Day 1 of study treatment. 4. Pregnancy or breastfeeding. 5. Uncontrolled intercurrent illness including, but not limited to, ongoing or active infection requiring IV antibiotics & psychiatric illness/social situations that would limit adherence with study requirements, or disorders associated with significant immunocompromised state. 6. Known previous/current malignancy requiring treatment within ≤ 3 years except for cervical carcinoma *in situ*, squamous or basal cell skin carcinoma and superficial bladder carcinoma. 7. Any comorbid condition that confounds the ability to interpret data from the study as judged by the Investigator or Medical Monitor.
Length of Study Participation	Subjects may continue on study treatment until disease progression, unacceptable toxicity, and withdrawal of consent or termination of the study. For subjects who discontinue study treatment for reasons other than disease progression, whenever possible tumor assessment will continue as per protocol until disease progression. After disease progression, subjects will be followed for survival and the start of new anti-glioma therapy and its outcome.
Investigational Product/ Background	NOVOTTF-200A will be administered with a monthly adherence rate goal of >= 75% (>= 18 hours daily) of therapy over a 4-week cycle in subjects with recurrent G3 MG who have not previously been treated with any anti-

Therapy/ Route/ Regimen	angiogenic agent including BEV.
Procedures	Study visits and procedures will be performed as outlined in Table 1. The study will consist of Screening, Treatment and Follow-Up periods. Screening: The screening period may not exceed a 28-day window prior to start of study treatment (Cycle 1, Day 1). Assessments will include medical history, cancer history including previous treatments, physical examination and tumor assessments. Tumor assessment must have a baseline MRI scan with contrast within 14 (+3) days prior to first treatment with investigational product. Vital signs measurement and laboratory tests are to be conducted within 7 days prior to Cycle 1, Day 1. Treatment: Subjects may continue on study treatment until disease progression, unacceptable toxicity, withdrawal of consent or termination of the study. Assessment will include MRI scans at the end of every even numbered cycle (± 7 days) using RANO (2010) criteria for assessment. Subjects who discontinue study therapy for reasons other than disease progression whenever possible will continue tumor assessment as per protocol schedule until progression. Safety Follow-Up (End-of-Treatment Visit): Subject will be followed for safety for 28 (+3) days after discontinuation of trial therapy (NOVOTTF-200A) Survival Follow-Up: All subjects will be followed in the long-term survival follow-up period for as long as they are alive. Long-term follow-up will occur every 3 months (±7 days) after the 28-day post-treatment discontinuation visit. Telephone contact will be sufficient to document survival status. During the follow-up period, the following information will be collected: survival, and subsequent anti-malignant glioma regimens (regimen, start and end date and treatment outcome).
Overview of Assessments	Efficacy Assessments Tumor response, including progressive disease, will be assessed with MRI every 2 cycles (at the end of each even-numbered cycle of therapy) according to the RANO 2010 criteria, including: • Radiographic Response Rate • Progression-free Survival (PFS) • Overall Survival (OS) Quality of Life (QoL)Assessments

	QoL will be assessed at baseline and every two cycles (at the end of each even-numbered cycle of therapy). Our chosed instruments are the Functional Assessment of Cancer Therapy (FACT) questionnaires: o FACT-Brain (FACT-Br) o FACT-Cognitive Function (FACT-Cog) <u>Exploratory Assessments:</u> • To determine if the presence of proneural or mesenchymal phenotype (Cytoscan analysis) confers a better response to NovoTTF. • To determine if the *in vitro* sensitivity of the glioma cells derived from patient specimens before and after the NovoTTF-200A treatment correlates with the patient's response to treatment.
Statistical Analyses	Primary Objective: The primary objective is to estimate the proportion of participants showing no evidence of disease progression six months after initiating treatment with the device (PFS6). We will compute interval estimates of this proportion. This information will inform decisions about further research on this device (or similar approaches). We will also document issues of intolerability and all adverse events. Primary Efficacy Endpoint: The primary efficacy endpoint is disease status six months from initiation of treatment with the device. Assessment is per RANO (2010) criteria. The primary efficacy measure is the 90-percent interval estimate of PFS6. Primary Adverse Event Measures. Adverse events will be recorded, including time-on-treatment and an assessment of likely relation to device use. Reasons for discontinuing use of the device will be recorded to the fullest extent possible. Analysis Data Sets for Efficacy: The primary efficacy analyses will be conducted on the intent-to-treat data set (ITT), defined as including all participants receiving at least one exposure to the active device. Supplemental analyses will be performed on the per-protocol data set (PP), defined as including only those participants meeting the minimum prescription for device use (>= 18 hours daily over a four-week cycle). Variables to be Collected. In addition to adverse events, reasons for discontinuation, disease trajectory, mutation status (viz., ATRX, TERT, IDH1, MGMT), Karnofsky performance status, and psychometrics (viz., FACT-Br, FACT-Cog), information on patient demographics, host factors, and co-morbidities will be collected for use in exploratory analyses.

	Survival will be tracked until death or the end of the project. Information on further anti-glioma treatments received after patients are off of this study will be sought. Design: This is a single-center, single-arm, open-label, Phase-IIA clinical trial to estimate PFS6 under the conditions of the trial and to gather information on safety and tolerability associated with the device in clinical use.

Table 1: Schedule of Assessments and Procedures, All Cycles

	Screen [1]	Baseline [1]	Cycle 1	Cycle 2+	End of Treatment [15]	Post Study Follow-up [16]
Study Day	**-28 to -1**	**-7 to -1**	**1**	**1**		
Window	**Up to Dayyatm**			**±1**	**+7**	**±14**
Informed consent [1]	**X**					
Medical history/Demographics [1]	**X**					
Concomitant medications [1]	**X**	**X**	**X**	**X**	**X**	**X**
Physical examination, height [2]		**X**				
Targeted physical, weight, BSA, KPS [2]		**X**	**X**	**X**	**X**	
Toxicity evaluation [3]			**X**	**X**		
Vital signs (HR, temp, BP) [4]		**X**	**X**	**X**	**X**	
ECG [5]		**X**			**X**	
CBC, Diff, Platelets [6]		**X**		**X**	**X**	
Serum Chemistry [7]		**X**		**X**	**X**	
PT/PTT [8]		**X**			**X**	
Urinalysis [9]		**X**			**X**	
NovoTTF-200AoTTF-isis [10]			**X**	**X**		
Pregnancy test [11]		**X**			**X**	
Tumor measurement [12]	**X (-14 to -1)**			**End of even numbered cycle**		
Tumor gene signature profiling [13]	**X**					
Quality of Life Questionnaires [14]	**X**			**End of even numbered**		

1. Within 7 days of starting treatment except consent, demographics, medical history, concomitant medications, complete physical examination, radiographic/tumor assessments, and consent to acquire and test archival tumor tissue samples which can be obtained within 28 days prior to the start of treatment.
2. Height measured at baseline only. Physical Examination is a complete physical as per institutional guidelines (genitourinary examination not required unless there are related signs or symptoms) at baseline but thereafter as directed by signs and symptoms (focused physical examination). Karnofsky Performance Status (KPS) is according the Karnofsky scale (see Appendix A).
3. Toxicity evaluation is an assessment of reported and observed adverse events following the NOVOTTF-200A administrations compared to pre-treatment findings.
4. Vital Signs: (blood pressure, heart rate and temperature) Day 1 of every cycle. Vital signs are also collected as part of the physical examination.
5. ECG: to be done at the baseline and the end-of-treatment visit.
6. Hemoglobin (Hgb), hematocrit (Hct), red blood cell (RBC) count, white blood cell (WBC) count with differential and platelets as per standard of care.
7. Sodium, potassium, chloride, bicarbonate, calcium, magnesium, glucose, BUN, serum creatinine, uric acid, ALT, AST, alkaline phosphatase, total protein, albumin and total bilirubin as per standard of care.
8. Prothrombin time (PT) or International Normalized Ratio (INR) and partial thromboplastin time (PTT) may be performed if clinically indicated.
9. Urinalysis: to be done at the baseline and the end-of-treatment visit.
10. NOVOTTF-200A: therapy: To initiate on Day 1, Cycle 1 and be continued from Cycle 2 on with monthly adherence rate >= 75% (>= 18 hours daily) of therapy over each 4-week cycle in subjects until progression.
11. Pregnancy test (serum or urine) to be performed at Baseline and at End-of-Treatment visit and more frequently if clinically indicated.
12. Tumor assessment: Baseline tumor assessments are to be made within 14 days prior to Cycle 1, Day 1. Response should be assessed (RANO 2010) every 2 cycles. If a subject is determined to have an overall disease response of CR or PR, then disease assessments should be repeated approximately 4 (±2 days) weeks later to confirm the response. If tumor assessments have not been performed in the 4 weeks prior to the End-of-Treatment Visit, then tumor assessments are to be done at the End-of-Treatment Visit.
13. For subjects with archived blocks of glioma tumor, genomic analysis and transcriptional profiling will be conducted.
14. Quality of Life: The Quality of Life Questionnaires [the Functional Assessment of Cancer Therapy (FACT) questionnaires FACT-Brain (FACT-Br) and FACT-Cognitive Function (FACT-Cog)] will be administered within 14 days prior to Cycle 1, Day 1. The QoL questionnaires should be administered every 2 cycles. If the QoL assessments

have not been performed in the 4 weeks prior to the End-of-Treatment Visit, then QoL are to be done at the End-of-Treatment Visit.

15. Subjects with treatment-related Adverse Events of Grade ≥2 observed at the End-of Treatment assessment should be followed up at least monthly until the Adverse Event has resolved to Grade 1, the event is believed to be chronic or the subject receives other anti-cancer therapy.
16. Post-Study Follow-Up visits may be made in person or other means of communication. Purpose of the follow-up, which should occur every 3 months (±7 days), is to determine survival and the start of any new anti-glioma treatment and its outcome.

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1. BACKGROUND AND RATIONALE

1.1. WHO Grade 3 Malignant Astrocytoma: Current Clinical Outcome: There is an unmet clinical need for the therapy of progressive or recurrent malignant gliomas (MG) with a median survival of < 12 months despite available chemotherapy. Recurrence following current "standard of care" surgery, radiation therapy and adjuvant chemotherapy, is nearly universal. The traditional therapies rely on DNA damage and disruption of mitotic machinery with limited effect in prolonging subject survival (Stupp 2005). The reported data show a 6 month progression-free-survival of 15% and median progression-free survival of only 9 weeks among 225 subjects with recurrent glioblastoma (GBM) (Wong 1999). Upon progression, these subjects typically develop progressive physical and mental debilitation culminating in death 40 to 50 weeks from diagnosis. Novel therapies are being developed in an attempt to target specific molecular mechanisms involved in abnormal signaling and resistance to apoptosis.

Anaplastic astrocytomas are more common and more aggressive then than anaplastic oligodedrogliomas (Central Brain Tumor Registry of the United States, 2008). Overall survival is lower in patients with astrocytomas tumors than oligodendroglial of the same WHO grade. The diagnosis of anaplastic astrocytoma mandates treatment with radiation therapy, followed by temozolomide treatment (which is FDA approved for recurrent AA). The 1p19q codeletion which characterize the anaplastic oligodendroglioma tumors (AO) is both predictive of response to treatment and prognostic for improved survival (Smith, 2000). The malignant gliomas with the codeletion (AO) have a median overall survival of 6 to 7 years compared with 2 to 3 years for those without the codeletion - AA (Ino, 2001). As such, the prognosis for WHO grade 3 glioma, and especially for AA is very poor – and the need for new therapies is extremely high.

The efficacy and safety of BEV in combination with irinotecan was also evaluated in an open-label, small study of subjects with previously treated grade III and grade IV gliomas (Vredenburgh 2007). Only nine grade III patients were included, seven of them with AA. Subjects received BEV plus irinotecan until disease progression or until unacceptable toxicity. All subjects received prior radiotherapy (completed at least 8 weeks prior to receiving BEV) and temozolomide. Subjects with active brain hemorrhage were excluded. The 6-month PFS in the WHO grade III astrocytoma patients was 56% (95% CI, 31-99%).

The progression-free and overall survivals are not well characterized for AA patients who relapsed on bevacizumab. In a small, mixed, patient population (both grade IV and grade III tumors), the continuation of bevacizumab together with third and fourth line chemotherapy options including carmustine, lomustine, etoposide, temozolomide and erlotinib resulted in a median time to radiologic progression of only 7 weeks.

1.2. Tumor Treating Fields

Figure 1: NOVOTTF-200A Device (http://www.virtualtrials.com/pdf/novocure/novottf.jpg)

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. 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. In addition, low frequency pulsed electric fields have been claimed to stimulate bone growth and accelerate fracture healing5. 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. 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

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.
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) and cell rotation. With pulsed relatively strong electric fields, > 103 V/cm and 100 ms pulse length, reversible pore formation appears in the cell membrane, a phenomenon usually called electroporation.

NovoCure has shown that when properly tuned, very low intensity, intermediate frequency electric fields (TTFields) stunts 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. 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 or indirectly with microtubule polymerization (e.g., Taxol).

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. This effect can explain the mitotic arrest of TTField treated cells.

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 pN21. 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).

NovoCure has shown 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 than one week of treatment. This growth inhibition was accompanied by a decrease in angiogenesis within the tumor, due to inhibition of endothelial cell proliferation.

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-200A 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.

A pilot study was performed on ten recurrent GBM patients treated with the NovoTTF- 200A 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 (> 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 (26.1 weeks versus 9 weeks, respectively). The PFS at 6 months (PFS6) was 50% compared to 15% in historical controls. Median overall survival was 62 weeks.

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-200A treatment for recurrent GBM patients. A prospective, randomized, open-label, phase III clinical trial of NovoTTF-200A versus best standard of care chemotherapy was conducted between in patients with recurrent glioblastoma (Stupp, 2012). 237 pts were randomized (28 centers in the United States and Europe) to either TTF alone (120 pts) or BSC (117 pts). Patient characteristics were balanced, median age was 54 years (range 23-80), median KPS 80% (50-100). All had prior TMZ/RT, and the majority at least one prior therapy for recurrence. One-quarter had surgery for recurrence. Mean treatment duration was 4.4 mo (0-40) vs. 2.3 mo (0-15). Median survival was 6.6 versus 6.0 months (hazard ratio 0.86 [95% CI 0.66–1.12]; p = 0.27), 1-year survival rate was 20% and 20%, progression-free survival rate at 6 months was 21.4% and 15.1% (p = 0.13), respectively in TTF and active control patients. Responses were more common in the TTF arm (14% versus 9.6%, p = 0.19). The TTF-related adverse events were mild (14%) to moderate (2%) skin rash beneath the transducer arrays. Severe adverse events occurred in 6% and 16% (p = 0.022) of patients treated with TTF and chemotherapy, respectively. Quality of life analyses favored TTF therapy in most domains. Treatment compliance with TTF was excellent with a median duration 20 hours/day.

The risks associated with use of the NovoTTF-200A 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 the initial 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.

2. STUDY OBJECTIVES

2.1. Primary Objective

The primary objective of the study is:

- To determine the efficacy of NOVOTTF-200A in recurrent anaplastic astrocytoma patients (6-month progression-free survival).

2.2. Secondary Objectives

The secondary objectives of the study are:

- To evaluate the safety of NOVOTTF-200A in the subject population.
- To evaluate efficacy of NOVOTTF-200A in the subject population.
- To see if the presence of ATRX, TERT promoter, MGMT methylation and/or IDH1mutation, confers a better response to NOVOTTF-200A.
- To determine if the treatment significantly modifies the patient's quality of life. We will use the Functional Assessment of Cancer Therapy (FACT) questionnaires:
    - FACT-Brain (FACT-Br)
    - FACT-Cognitive Function (FACT-Cog)

2.3. Exploratory Objectives

The exploratory objectives of the study are:

- To determine if the presence of proneural or mesenchymal phenotype (Cytoscan analysis) confers a better response to NOVOTTF-200A.
- To determine if the *in vitro* sensitivity of the glioma cells derived from patient specimens before and after the NOVOTTF-200A treatment correlates with the patient's response to treatment.

3. OVERALL STUDY DESIGN

3.1. Study Design

This is a Phase 2, single arm study in subjects with AA who had progressive disease during first-line treatment or who are in first or second relapse and who have not previously received any bevacizumab (BEV) or other anti-angiogenic agent, including sorafenib, sunitinib, axitinib, pazopanib or cilengitide. Up to 36 subjects will be enrolled with 26 evaluable patients needed.

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-200A treatment may be continued until disease progression, unacceptable toxicity, withdrawal of consent, or termination of the study. . In the case of radiological progression, NOVOTTF-200A treatment will be stopped and a different treatment will be chosen instead by the investigator.

Patients will be recruited to the study by the principal investigator (PI) or one of the coinvestigators (CI) at UC Irvine. Patient accrual is expected to continue for 24-36 months.

NovoTTF-200A treatment will be given alone for this single arm study. At treatment initiation patients will be seen at an outpatient clinic. During this visit baseline examinations will be performed and NovoTTF-200A treatment will be initiated under medical supervision. The patients will also be instructed on the operation of the NovoTTF-200A 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-200A treatment.

NovoTTF-200A 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. Radiological progression
4. Re-operation, for the patients where the pathology is consistent with necrosis (pseudo-progression). NovoTTF-200A treatment will be interrupted for at least 2 weeks after reoperation or until wound healing).

As long as the patients are receiving treatment (NovoTTF-200A), 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.

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.

3.2. Study Design Rationale

The study is a single arm design that is often used in Phase 2 cancer studies. Standard evaluations for safety and efficacy are employed.

3.3. Study Duration

Subjects may continue on study treatment until disease progression, unacceptable toxicity, withdrawal of consent, or termination of the study. Once discontinued from the study treatment, subjects will enter a long-term follow-up period for documentation of survival and the start of first new anti-glioma therapy and its outcome. Long-term follow-up will occur every 3 months (±7 days) after the 28-day post-treatment discontinuation visit.

3.4. End of Trial

The End of Trial is defined as the date of receipt of the last data point from the last remaining subject that is required for primary, secondary and/or exploratory analysis.

4. PROCEDURES

Study visits and procedures will be performed as outlined in Table 1.

The study will consist of Screening, Treatment, and Follow-up periods.

Screening:

Screening procedures may not be done prior to the signing and dating of the Informed Consent document. However, the results of tumor assessments done as part of standard of care that are within the 14-day screening period do not have to be repeated. However, if results are not available, then tumor assessments are to be conducted within 14 days prior to Cycle 1 Day 1. The screening period may not exceed a 28 day (with a 3 day window for scheduling conflicts) window prior to start of study treatment (Cycle 1 Day 1) for assessments that include medical history including demographics and cancer history, prior medications and procedures. Physical examination including height, weight, and vital signs, electrocardiograms, laboratory tests including hematology, coagulation, chemistry, urinalysis, and, as appropriate, pregnancy tests are to be done within 7 days prior to Cycle 1 Day 1.

Treatment:

Safety tests and procedures will be performed according to the Schedule of Assessments and Procedures (Table 1). Assessments will include MRI scans at the end of every even numbered cycle using RANO 2010 criteria for assessment.

Subjects may continue on study treatment until disease progression, unacceptable toxicity, withdrawal of consent, or termination of the study.

End-of-Treatment Visit:

An End-of-Treatment Visit should occur when a subject discontinues study treatment 28 (+7) days after NOVOTTF-200A. Tests are primarily to ensure there are no late occurring AEs and that AEs have resolved or have stabilized. Additional follow up visits may be conducted to follow ongoing that are resolving. If a subject cannot or will not make this visit, attempts to gather information on the status of AEs should be made by telephone or other means.

Post Study Follow-up:

All subjects will be followed for survival during the follow-up period for as long as they are alive. Post Study follow-up will occur every 3 months (±7 days) after the End-of-Treatment Visit. During long-term follow-up, the following information will be collected: survival, subsequent anti-glioma regimens, and treatment outcomes.

Efficacy Assessments

Tumor response, including progressive disease, will be assessed with MRI at the end of every 2 cycles of therapy according to the RANO criteria (Wen 2010), including:

- Radiographic Overall Response Rate
- Progression-free Survival (PFS)
- Overall Survival (OS)

Assessments

Gene Profiling

For AA subjects with available tissue, gene signature profiling will be performed, using the Cytoscan analysis. We will determine the GBM phenotype (mesenchymal versus neuronal) and will see how that the particular gene phenotypes associate with response to treatment

In-vitro Sensitivity of glioma cells derived from patient specimens

For AA subjects resected in our center, primary cell cultures will be produced. The response to TTF fields in the Inovitro system will be compared between patients, before and after the NOVOTTF-200A treatments – for the patients that also have surgery after progression.

Quality of Life Assessments

- FACT-Cog

  The Functional Assessment of Cancer Therapy-Cognitive Function (FACT-Cog) is a 37-item validated subjective neuropsychological instrument designed to evaluate cancer patients' perceived cognitive deterioration on their quality of life. A 6.9 to 10.6 points reduction of the FACT-Cog score corresponds to the smallest clinically-relevant perceived cognitive deterioration. These estimates are important as they can facilitate the interpretation of patient-reported cognitive changes and sample size estimation (Chan 2013). The FACT-Cog questionnaire is provided in Appendix B.

- FACT-Br

  The Functional Assessment of Cancer Therapy-Brain (FACT-Br) is a commonly used instrument measuring general quality of life (QOL) that reflects symptoms or problems associated with brain malignancies across 5 scales. The measure yields information about total QOL, as well as information about the dimensions of physical well-being, social/family well-being, emotional well-being, functional well-being, and disease specific concerns. The FACT-Br is written at the 4th grade reading level, and subjects can filled out it in 5-10 minutes. The self-report of quality of life can be completed by the subject or with little or no assistance in subjects who are not neurologically incapacitated. Subjects rate all 5 items using a five-point Likert scale ranging from 0 (not at all) to 4 (very much). Overall, higher ratings suggest higher QOL. Items are totaled to produce the following subscales, along with an overall QOL score: physical well-being (7 items); social/family well-being (7 items); emotional well-being (6 items); functional well-being (7 items); and concerns relevant to subjects with brain tumors (23 items). The FACT-Br questionnaire is provided in Appendix C (Cella 1993).

5. STUDY POPULATION

The study population includes subjects with AA who had progressive disease during first-line treatment or who are in first or second relapse and who have not previously received any bevacizumab (BEV) or other anti-angiogenic agent, including sorafenib, sunitinib, axitinib, pazopanib, everolimus or cilengitide.

5.1. Number of Subjects and Sites

Approximately 36 subjects will be enrolled in the study 26 evaluable patients needed.

5.2. Inclusion Criteria

Any patient with a histological diagnosis of AA who meets all of the specific eligibility criteria listed below may be enrolled on this study.

1. Understand and voluntarily sign and date an informed consent document before any study related assessments/procedures are conducted.
2. Males and females > the age of 21 years at the time of the signing of the informed consent document.
3. All subjects must have histologic evidence of G3 MG and radiographic evidence of recurrence or disease progression (defined as either a greater than 25% increase in the largest bi-dimensional product of enhancement, a new enhancing lesion or a significant increase in T2 FLAIR).
4. Subjects with archival tumor tissue suitable for genetic testing must give permission to access and test the tissue; subjects without archival tumor tissue are eligible.
5. No prior treatment with BEV or any anti-angiogenesis agents.
6. At least 4 weeks from surgical resection and 12 weeks from end of radiotherapy prior to enrollment in this study, unless relapse is confirmed by tumor biopsy or new lesion outside of radiation field, or if there are two MRIs confirming progressive disease that are 8 weeks apart.
7. All AEs resulting from prior chemotherapy, surgery or radiotherapy must have resolved to NCI-CTCAE (v. 4.03) Grade ≤1 (except for laboratory parameters outlined below).
8. Laboratory results within 7 days prior to NOVOTTF-200A administration (transfusions and/or growth factor support may be used at the discretion of the Investigator during Screening):
    - Hemoglobin ≥9 g/dL.
    - Absolute neutrophil count (ANC) $\geq 1.5 \times 10^9$/L.
    - Platelet count $\geq 100 \times 10^9$/L.
    - Serum bilirubin ≤1.5 × upper limit of normal (ULN) or ≤3 × ULN if Gilbert's disease is documented.
    - Aspartate transaminase (AST) ≤ 2.5 ULN.
    - Serum creatinine ≤1.5 × ULN.
9. Karnofsky Performance Status (KPS) score ≥70%.
10. Willing and able to adhere to the study visit schedule and other protocol requirements.

5.3. Exclusion Criteria

The presence of any of the following will exclude a subject from enrollment:

1. The presence of 1p19q LOH which is diagnostic for anaplastic oligodendroglioma (AO).
2. Co-medication that may interfere with study results, e.g., immunosuppressive agents other than corticosteroids. (Steroid therapy for control of cerebral edema is allowed at the discretion of the investigator. Subjects should be on a stable dose of steroids for at least 1 week prior to study beginning.)
3. Chemotherapy administered within 4 weeks (6 weeks for an IV nitrosoureas and 12 weeks for an implanted nitrosoureas wafer) prior to Day 1 of study treatment.
4. Pregnancy or breastfeeding.
5. Uncontrolled intercurrent illness including, but not limited to, ongoing or active infection requiring IV antibiotics & psychiatric illness/social situations that would limit adherence with study requirements, or disorders associated with significant immunocompromised state.
6. Known previous/current malignancy requiring treatment within ≤ 3 years except for cervical carcinoma *in situ*, squamous or basal cell skin carcinoma and superficial bladder carcinoma.
7. Any comorbid condition that confounds the ability to interpret data from the study as judged by the Investigator.

6. DESCRIPTION OF STUDY TREATMENTS

6.1. Description of Investigational Product

NOVOTTF-200A is an investigational device that will be available through a commercial use program by NovoCure.

6.2.1. Pre-Treatment Evaluation (Screening and Baseline)

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 [the Functional Assessment of Cancer Therapy (FACT) questionnaires FACT-Brain (FACT-Br) and FACT-Cognitive Function (FACT-Cog)]

6.2.2. Treatment Administration and Schedule

All patients will begin treatment within 1 week from screening/baseline evaluation. Treatment will be initiated in an outpatient clinic by the investigator. In addition to clinical evaluation, 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
    - 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
- Place the electrodes
- Connect the electrodes to the device (through the connection cable)
- Turn on the device

The device will be set in advance 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 patients will receive multiple 1 month courses of continuous NovoTTF-200A treatment. 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-200A treatment will be performed by NOVOTTF-200A technicians. All technical aspects of the treatment are handled by these technicians at the patients' homes.

The following actions are performed by the technician:

- Periodic download of device log
- 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).

Once every month from baseline, until treatment termination, all patients will be seen in the 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.

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.

The specific locations of each electrode set will be determined by the treating investigator using the NovoTal software.

6.2.3. Ongoing Evaluation and Periodic Evaluation

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). 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-200A 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 –

a. 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.

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

- Physical examination
- Neurological status
- Quality of life questionnaire (the Functional Assessment of Cancer Therapy (FACT) questionnaires FACT-Brain (FACT-Br) and FACT-Cognitive Function (FACT-Cog)) – every two months until treatment
- termination
- Blood exams (CBC, Chemistry, Coagulation – for patients receiving anti-coagulants)
- Steroid dose *if applicable*
- 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.

6.2.4. 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.

6.3. Method of Treatment Assignment

Single arm study. All the patients will receive NOVOTTF-200A treatment.

6.4. Packaging and Labeling

The label(s) for Investigational Product (IP) NOVOTTF-200A will include manufacturer name, address and telephone number, the protocol number, IP name, device identification/kit number, instructions, storage conditions, technician contact information, and required caution statements and/or regulatory statements as applicable. Additional information may be included on the label as applicable per local regulations.

6.5. Investigational Product Accountability and Disposal

Designee of the study team will review with the subject the process for Investigational Product return.

7. Concomitant Medications and Procedures

7.1. Permitted Concomitant Medications and Procedures

Concomitant medications to treat comorbid conditions and adverse events are permitted. Enzyme-inducing anti-epileptic drugs (EIAEDs) are allowed. Steroids are allowed and dosing is at the discretion of the investigator.

7.2. Prohibited Concomitant Medications and Procedures

Medications to treat the underlying malignancy are not permitted and their use constitutes progressive disease and subjects must discontinue study treatment. Investigational agents of any kind are not permitted.

7.3. Required Concomitant Medications and Procedures

There are no required concomitant medications or procedures.

8. STATISTICAL CONSIDERATIONS

Efficacy: Tumor response, including PD, progression-free survival (PFS), and overall survival (OS) will be assessed. Tumor response will be assessed by the Investigators using RANO 2010 criteria. The overall confirmed response rate will be presented. Primary outcome variable will be 6-month PFS. In addition, response rate will also be measured taking into account partial response and complete response.
Primary Objective: The primary objective is to estimate the proportion of participants showing no evidence of disease progression six months after initiating treatment with the device (PFS_6). We will compute interval estimates of this proportion. This information will inform decisions about further research on this device (or similar approaches). We will also document issues of intolerability and all adverse events.

Primary Efficacy Endpoint: The primary efficacy endpoint is disease status six months from initiation of treatment with the device. Assessment is per RANO (2010) criteria. The primary efficacy measure is the 90-percent interval estimate of PFS_6.

Primary Adverse Event Measures. Adverse events will be recorded, including time-on-treatment and an assessment of likely relation to device use. Reasons for discontinuing use of the device will be recorded to the fullest extent possible.

Analysis Data Sets for Efficacy: The primary efficacy analyses will be conducted on the intent-to-treat data set (ITT), defined as including all participants receiving at least one exposure to the active device. Supplemental analyses will be performed on the per-protocol data set (PP), defined as including only those participants meeting the minimum prescription for device use (>= 18 hours daily over a four-week cycle).

Variables to be Collected. In addition to adverse events, reasons for discontinuation, disease trajectory, mutation status (viz., ATRX, TERT, IDH1, MGMT), Karnofsky performance status, and psychometrics (viz., FACT-Br, FACT-Cog), information on patient demographics, host factors, and co-morbidities will be collected for use in exploratory analyses. Survival will be tracked until death or the end of the project. Information on further anti-glioma treatments received after patients are off of this study will be sought.

Design: This is a single-center, single-arm, open-label, Phase-IIA clinical trial to estimate PFS_6 under the conditions of the trial and to gather information on safety and tolerability associated with the device in clinical use.

8.1. Sample Size: Justification of Sample Size: Data from 36 participants will yield a 90-percent interval estimate of PFS_6 with sufficient precision for our purposes. Table 1 shows the probability of observing a 90-percent confidence interval from 34 participants at various levels of the population proportion and confidence-interval half widths. The table is based on 34 rather than 36 participants, anticipating some loss of participants to the exigencies of research.

The table shows over 90-percent power to estimate PFS_6 to plus or minus 16 percent at all levels of the population proportion shown. The power to estimate PFS_6 to plus or minus 15

percent is adequate for the more extreme levels of population proportion, but perhaps not when the latter is near 50 percent.

Table 1. Probability of Observing a 90-Percent Binomial Confidence Interval Given 34 Subjects for the Indicated Underlying True Proportions and Interval Half Widths

Population Proportion	Interval Half-Width		
	13%	15%	16%
25%	0.36	0.99	0.99
35%	0.05	0.83	0.99
45%	0.00	0.47	0.99
55%	0.00	0.47	0.99
65%	0.05	0.83	0.99
75%	0.36	0.99	0.99

Rounded to nearest one hundredth, exact method, 2-sided, SAS Power and Sample Size v3.1

Futility Assessment. If none of the first nine participants is progression-free at six months from initial use of the device, then serious consideration will be given to stopping the project for futility. This criterion is adopted from the Simon, two-stage, optimal design (null-hypothesis rate of 5% v alternate- hypothesis rate of 25%). A formal decision to stop the trial will depend upon the clinical judgment of the medical director.

Intolerability Assessment. Intolerability and adverse events will be closely monitored by the treating physicians. A decision to stop the project for intolerability will be based on clinical judgment of the medical director.

Primary Analyses for Efficacy: The 90-percent interval estimate of PFS6 is the primary summary of efficacy in this project. Exact methods will be used.

Secondary Analyses for Efficacy: We will examine the data in many ways to inform decisions about further research, including plots, tables, and statistical tests, accounting for repeated measures where appropriate. Participants will be described by sex, age, and other host or clinical factors, using means, medians, and percentiles for continuous variables and counts and percentages for categorical variables. The FACT-Br and FACT-Cog will be scored in the standard way (Weitzner et al, 1995). Both progression-free and overall survival will be estimated by Kaplan-Meier methods, both overall and by strata of interest. Differences in survival between or among groups will be evaluated by the log-rank test. If the assumptions are reasonably met, then Cox proportional-hazards models will examine the effects on survival of covariates adjusting for other covariates. Ties in survival time will be broken by the subtracting a small, randomly generated amount from each tied observation (Borucka, 2014). Secondary analyses will be performed on both the ITT and PP data sets, as seems warranted. For secondary analyses, the probability values from statistical tests will be used as a guide to interpretation, which will also depend on clinical judgment. Therefore, we will not be concerned with overall, study-wise, type-1 error rates for the secondary analyses.

Analyses for Intolerability or Toxicity: We will examine the data to discover factors that may predict adverse reactions to the study treatment. We will proceed in the same way as outlined

above for secondary analyses for efficacy. As the goals of these analyses are to inform decisions about future research, no formal statistical hypothesis testing will be done, probabilities from statistical tests will augment clinical judgment in interpretation, and we will not regard overall, study-wise, error rates.

8.2. Background and Demographic Characteristics

Subjects' age, height, weight, and baseline characteristics will be summarized using descriptive statistics, while gender, race and other categorical variables will be provided using frequency tabulations. Medical history data including cancer history will be listed.

8.3. Subject Disposition

Subject disposition (analysis population allocation, entered, discontinued, along with primary reason for discontinuation) will be summarized using frequency and percent for both treatment and follow-up phases. A summary of subjects enrolled by site will be provided. Protocol deviations will be summarized using frequency tabulations.

9. OUTCOME MEASURES

9.1. Efficacy Analysis

Tumor response including PD, progression-free survival (PFS), and overall survival (OS) will be assessed by the investigators using RANO 2010 criteria. The overall confirmed response rate will be examined.

Efficacy analysis:

Primary Endpoint

- *The primary endpoint of the study will be* 6-month progression-free survival

Secondary Outcome Measures

- *Safety*
- *Overall survival time*
- *Correlations with established molecular markers* (ATRX, TERT promoter and/or IDH1 mutation and MGMT promoter methylation)
- *Quality of Life*

9.2. Safety Analysis

All subjects will be evaluated for safety analysis if they receive NOVOTTF-200A. The safety data will be presented in individual listings and summary tables, including frequency tables for adverse events and listings of abnormalities for laboratory variables.

Safety analysis:

- *Safety and tolerability of* NOVOTTF-200A*treatment will be based on the incidence and severity of adverse events and toxicities. Toxicities will be assessed according to the "Common toxicity criteria (CTC), version 4.03".*

10. ADVERSE EVENTS

10.1. Monitoring, Recording and Reporting of Adverse Events

Data and Safety Monitoring Plan

This is a risk level 1 study, as defined in the Chao Family Comprehensive Cancer Center (CFCCC) Data and Safety Monitoring Plan (DSMP) because this is a high risk UCI investigator-initiated interventional trial where the PI holds the IDE.

The Principal Investigator (PI), co-investigator, clinical research coordinator, and statistician are responsible for monitoring of data and safety for this study, including implementation of the stopping rules for safety and efficacy.

The CFCCC Data and Safety Monitoring Board (DSMB) is an independent body responsible for the safety of study subjects as well as the data integrity of the protocol. Data and safety will be reported to the DSMB with submission of progress reports that include aggregated reports of adverse events, serious adverse events, deviations/violations, and unanticipated problems. In addition, certain adverse events and deviations/violations, and unanticipated problems will be reported promptly to the DSMB for review according to the tables below.

Risk Levels

Risk Level	Definition	Monitoring
Level 1	**High Risk** - UCI investigator-initiated interventional trials where the PI holds Investigational New Drug (IND) or Investigation Device Exemption (IDE). Example: Gene therapy, dendritic cell products from GMP suite, phase I/II development and phase I studies, first in human, etc.	Two months after subject enrollment
Level 2	**Medium Risk** - UCI investigator-initiated interventional trials for which IND/IDE is exempt by FDA. Example: Use of commercially available agents for an unapproved indication.	Six months after subject enrollment
Level 3	**Low Risk –** UCI investigator-initiated interventional trials that is minimal risk. Example: Phase III clinical studies, dietary intervention trials, and after-market studies.	Twelve months after subject enrollment
Exempt	Studies that are industry-sponsored, NCTN-sponsored, and/or trials that are monitored by an external DSMB.	

Recording of Events

All investigator initiated treatment trials require that adverse events, serious adverse events, deviations, and unanticipated problems be entered into the clinical trial management system (CTMS), OnCore. All entries must be entered in OnCore within five (5) days of being aware of

the adverse event, serious adverse event, violation, deviation, or unanticipated problem. Serious violations, deviations/violations, and unanticipated problems that require prompt reporting to the DSMB must be entered into OnCore within 24 hours of knowing of the event. Definitions of events are provided below.

Definitions

Adverse event (AE) - An adverse event is any untoward medical experience or change of an existing condition that occurs during or after treatment, whether or not it is considered to be related to the protocol intervention.

Unexpected Adverse Event [21 CFR 312.32 (a)] – An adverse event is unexpected if it is not listed in the investigator's brochure and/or package insert; is not listed at the specificity or severity that has been observed; is not consistent with the risk information described in the protocol and/or consent; is not an expected natural progression of any underlying disease, disorder, condition, or predisposed risk factor of the research participant experiencing the adverse event.

Expected Adverse Event - Any event that does not meet the criteria for an unexpected event OR is an expected natural progression of any underlying disease, disorder, condition, or predisposed risk factor of the research participant experiencing the adverse event.

Serious Adverse Event (SAE) [21 CFR 312.32] - defined as *any expected or unexpected adverse event* that result in any of the following outcomes:

- Death
- Is life-threatening experiences (places the subject at immediate risk of death from the event as it occurred)
- Unplanned hospitalization equal or greater than 24 hours)) or prolongation of existing hospitalization
- A persistent or significant disability/incapacity
- A congenital anomaly/birth defect
- Any other adverse event that, based upon appropriate medical judgment, may jeopardize the subject's health and may require medical or surgical intervention to prevent one of the outcomes listed above (examples of such events include allergic bronchospasm requiring intensive treatment in the emergency room or at home, blood dyscrasias of convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse).

Unanticipated problem (UP) - Any incident, experience or outcome that **meets all three** of the following criteria:

1. Unexpected (in term nature, severity, or frequency) given the following: a) the research procedures described in the protocol-related documents such as the IRB approved research protocol, informed consent document or Investigator Brochure (IB); and b) the characteristics of the subject population being studied; **AND**

2. Related or possibly related to participation in the research (possibly related means there is a reasonable possibility that the incident, experience, or outcomes may have been caused by the drugs, devices or procedures involved in the research); **AND**
3. Suggests that the research places subjects or others at greater risk of harm (including physical, psychological, economic, or social harm) than previously known or recognized.

Protocol Violation- A protocol violation is an accidental or unintentional change to or noncompliance with the IRB-approved protocol that increases risk or decreases benefit and/or affects the subject's rights, safety, welfare, and/or the integrity of the data. Examples of incidents that may be considered violations include: enrolling a participant who does not meet the inclusion criteria; obtaining verbal consent before the initiation of study procedures when the IRB requires signed, written informed consent; and failure to collect screening labs before initiation of study procedures.

Protocol Deviation- A deviation is an unintentional change to or noncompliance with the research protocol that does not have a significant effect on the subject's rights, safety or welfare, and/or on the integrity of the data. Deviations may result from the action of the participant, researcher, or research staff. Examples of deviations include: a rescheduled visit; an incomplete study visit; and failure to collect ancillary study measures (e.g., questionnaire, baseline BP).

Reporting Requirements to the CFCCC DSMB

ADVERSE EVENT/ SERIOUS ADVERSE EVENTS

Event Type	Reporting Timeframe
• Unexpected SAE, all attributions (unrelated, unlikely, possibly, probably, definite) • Grades 3-5	5 days from date the PI is aware of the event
• Expected AE/SAE, all attributions (unrelated, unlikely, possibly, probably, definite) • Grades 1-5	Progress review as aggregate report

DEVIATIONS/VIOLATIONS

Event Type	Reporting Timeframe
An incident that significantly affects subject safety or data integrity (e.g. wrong dosage of drug administered, safety procedures not being conducted at specific time points).	5 days from the date the PI is aware of the event
All incidents that occurred during the study	At the time of progress review as aggregate reports

UNANTICIPATED PROBLEMS

Unanticipated problems that are adverse events must be reported within 24 hours of reporting to the IRB for review.

Treatment with the NOVOTTF-200A 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

Adverse events and complications associated with the underlying AA disease process, which are unlikely but unknown if related to treatment with NOVOTTF-200A might include the following adverse events:

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

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 4.03 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 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, the site is 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 local IRB within 10 days of the investigator learning of the event. The investigator will investigate whether the adverse event is a UADE and, if so, report the UADE to the manufacturer, as soon as possible but no later than 3 days after first learning of the event. Expedited report for FDA submission to follow within 10 working days after the investigator first learning of the event.
The report will contain the following:

- The initials of the subject, subject ID #, 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-200A
- 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 subject 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-200A device. 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.

An adverse event (AE) is any noxious, unintended, or untoward medical occurrence that may appear or worsen in a subject during the course of a study. It may be a new intercurrent illness, a worsening concomitant illness, an injury, or any concomitant impairment of the subject’s health, including laboratory test values, regardless of etiology. Any worsening (i.e., any clinically significant adverse change in the frequency or intensity of a pre-existing condition) should be considered an AE. A diagnosis or syndrome should be recorded on the AE page of the CRF rather than the individual signs or symptoms of the diagnosis or syndrome.

All subjects will be monitored for AEs during the study. Assessments may include monitoring of any or all of the following parameters: the subject’s clinical symptoms, laboratory,

pathological, radiological or surgical findings, physical examination findings, or findings from other tests and/or procedures.

All SAEs will be recorded by the Investigator from the time the subject signs informed consent until 28 days after the last NovoTTF-200A treatment and those SAEs made known to the investigator at any time thereafter that are suspected of being related to study treatment. AEs are recorded from the start of the initial treatment. AEs occurring before the treatment are considered medical history and should be recorded on the medical history CRF. AEs and serious adverse events (SAEs) will be recorded on the AE page of the CRF and in the subject's source documents. All SAEs must be reported to NovoCure within 24 hours of the Investigator's knowledge of the event by facsimile, or other appropriate method, using the SAE Report Form, or approved equivalent form.

10.2.1. Evaluation of Adverse Events

The Investigator will evaluate all adverse events.

10.2.2. Seriousness

A serious adverse event (SAE) is any AE occurring at any dose that:

- Results in death;
- Is life-threatening (i.e., in the opinion of the Investigator, the subject is at immediate risk of death from the AE);
- Requires inpatient hospitalization or prolongation of existing hospitalization (hospitalization is defined as an inpatient admission, regardless of length of stay);
- Results in persistent or significant disability/incapacity (a substantial disruption of the subject's ability to conduct normal life functions);
- Is a congenital anomaly/birth defect;
- Constitutes an important medical event.

Important medical events are defined as those occurrences that may not be immediately life threatening or result in death, hospitalization, or disability, but may jeopardize the subject or require medical or surgical intervention to prevent one of the other outcomes listed above. Medical and scientific judgment should be exercised in deciding whether such an AE should be considered serious.

Events **not considered** to be SAEs are hospitalizations for:

- A standard procedure for protocol treatment administration. However, hospitalization or prolonged hospitalization for a complication of treatment administration will be reported as an SAE.
- Routine treatment or monitoring of the studied indication not associated with any deterioration in condition.
- The administration of blood or platelet transfusion as routine treatment of studied indication. However, hospitalization or prolonged hospitalization for a complication of such transfusion remains a reportable SAE.

- A procedure for protocol/disease-related investigations (e.g., surgery, scans, endoscopy, sampling for laboratory tests, bone marrow sampling). However, hospitalization or prolonged hospitalization for a complication of such procedures remains a reportable SAE.
- Hospitalization or prolongation of hospitalization for technical, practical, or social reasons, in absence of an AE.
- A procedure that is planned (i.e., planned prior to starting of treatment on study); must be documented in the source document and the CRF. Hospitalization or prolonged hospitalization for a complication remains a reportable SAE.
- An elective treatment of or an elective procedure for a pre-existing condition unrelated to the studied indication.
- Emergency outpatient treatment or observation that does not result in admission, unless fulfilling other seriousness criteria above.

If an AE is considered serious, both the AE page of the CRF and the SAE Report Form must be completed.

For each SAE, the Investigator will provide information on severity, start and stop dates, relationship to study treatment, action taken regarding study treatment, and outcome.

10.2.3. Severity / Intensity

For both AEs and SAEs, the Investigator must assess the severity / intensity of the event.

The term "severe" is often used to describe the intensity of a specific event (as in mild, moderate or severe myocardial infarction); the event itself, however, may be of relatively minor medical significance (such as severe headache). This criterion is *not* the same as "serious" which is based on subject/event *outcome* or *action* criteria associated with events that pose a threat to a subject's life or functioning.

Seriousness, not severity, serves as a guide for defining regulatory obligations.

10.2.4. Causality

The Investigator must determine the relationship between the administration of study treatment and the occurrence of an AE/SAE as Not Suspected or Suspected as defined below:

Not suspected:	Means a causal relationship of the adverse event to study treatment administration is **unlikely or remote**, or other medications, therapeutic interventions, or underlying conditions provide a sufficient explanation for the observed event.
Suspected:	Means there is a **reasonable possibility** that the administration of study treatment caused the adverse event. 'Reasonable possibility' means there is evidence to suggest a causal relationship between the study treatment and the adverse event.

Causality should be assessed and provided for every AE/SAE based on currently available information. Causality is to be reassessed and provided as additional information becomes available. For regulatory purposes, it is the Sponsor that is responsible for making the final causality assessment.

10.2.5. Duration

For both AEs and SAEs, the Investigator will provide a record of the start and stop dates of the event. For AEs that become SAEs, the start date of the SAE will be when the seriousness criteria are met. The original AE will have a stop date the same as the start date of the SAE. The SAE will have a stop date of when the seriousness criteria are no longer met. If the AE continues after the seriousness criteria are no longer met, then a new AE will be recorded with a start date the same as the SAE stop date and a stop date when the AE is completely resolved. In all cases, the AE must have the same verbatim term throughout. Within the duration of the SAE or AE, the maximum grade should be used to categorize severity.

10.2.6. Action Taken

The Investigator will report the action taken with each study treatment as a result of an AE or SAE, as applicable (e.g., discontinuation, interruption, or reduction of study treatment, as appropriate) and report if concomitant and/or additional treatments were given for the event.

10.2.7. Outcome

All SAEs that have not resolved upon discontinuation of the subject's participation in the study must be followed until recovered, recovered with sequelae, returned to baseline, stabilized, or died (due to the SAE or due to another cause).

10.3. Abnormal Laboratory Values

An abnormal laboratory value is considered to be an AE if the abnormality:

- results in discontinuation from the study;
- requires treatment, modification/ interruption of treatment, or any other therapeutic intervention; or
- is judged to be of significant clinical importance.

Regardless of severity grade, only laboratory abnormalities that fulfill a seriousness criterion need to be documented as a serious adverse event.

If a laboratory abnormality is one component of a diagnosis or syndrome, then only the diagnosis or syndrome should be recorded on the AE page of the CRF. If the abnormality was not a part of a diagnosis or syndrome, then the laboratory abnormality should be recorded as the AE. If possible, the laboratory abnormality should be recorded as a medical term and not simply as an abnormal laboratory result (e.g., record thrombocytopenia rather than decreased platelets).

10.4.1. Pregnancy

All pregnancies or suspected pregnancies occurring in either a female subject or partner of a male subject are immediately reportable events.

10.4.2 Females of Childbearing Potential

Pregnancies and suspected pregnancies (including a positive pregnancy test regardless of age or disease state) of a female subject occurring while the subject is on study treatment or within 28 days of the subject's last TTF therapy are considered immediately reportable events. Study treatment is to be discontinued immediately. The pregnancy, suspected pregnancy, or positive pregnancy test must be reported to NovoCure immediately by facsimile, or other appropriate method, using the Pregnancy Initial Report Form, or approved equivalent form.

The female subject should be referred to an obstetrician-gynecologist, preferably one experienced in reproductive toxicity for further evaluation and counseling.

The Investigator will follow the female subject until completion of the pregnancy, and must notify NovoCure immediately about the outcome of the pregnancy (either normal or abnormal outcome) using the Pregnancy Follow-up Report Form, or approved equivalent form.

If the outcome of the pregnancy was abnormal (e.g., spontaneous abortion), the Investigator should report the abnormal outcome as an AE. If the abnormal outcome meets any of the serious criteria, it must be reported as an SAE to NovoCure by facsimile, or other appropriate method, within 24 hours of the Investigator's knowledge of the event using the SAE Report Form, or approved equivalent form.

All neonatal deaths that occur within 28 days of birth should be reported, without regard to causality, as SAEs. In addition, any infant death after 28 days that the Investigator suspects is related to the in utero exposure to the IP should also be reported to NovoCure by facsimile, or other appropriate method, within 24 hours of the Investigator's knowledge of the event using the SAE Report Form, or approved equivalent form.

10.4.3. Male Subjects

If a female partner of a male subject taking investigational product becomes pregnant, the male subject taking study treatment should notify the Investigator, and the pregnant female partner should be advised to call her healthcare provider immediately.

10.5.1. Reporting of Serious Adverse Events

Any AE that meets any criterion for an SAE requires the completion of an SAE Report Form in addition to being recorded on the AE page of the CRF. All SAEs must be reported to NovoCure or its designee within 24 hours of the Investigator's knowledge of the event by facsimile, or other appropriate method, using the SAE Report Form, or approved equivalent form. This instruction pertains to initial SAE reports as well as any follow-up reports.

The Investigator is required to ensure that the data on these forms is accurate and consistent. This requirement applies to all SAEs (regardless of relationship to study treatment) that occur during the study (from the time the subject signs informed consent until 28 days after the last dose of study treatment) or any SAE made known to the Investigator at any time thereafter that are suspected of being related to study treatment. SAEs occurring prior to treatment (after signing the ICF) will be captured.

The SAE report should provide a detailed description of the SAE and include a concise summary of hospital records and other relevant documents. If a subject died and an autopsy has been

performed, copies of the autopsy report and death certificate are to be sent to NovoCure as soon as these become available. Any follow-up data should be detailed in a subsequent SAE Report Form, or approved equivalent form, and sent to Novocure.

Where required by local legislation, the Investigator is responsible for informing the IRB of the SAE and providing them with all relevant initial and follow-up information about the event. The Investigator must keep copies of all SAE information on file including correspondence with NovoCure and the IRB.

10.5.2. Safety Queries

Queries pertaining to SAEs will be communicated from NovoCure to the site via facsimile or electronic mail. The response time is expected to be no more than five (5) business days. Urgent queries (e.g., missing causality assessment) may be handled by phone.

10.6. Expedited Reporting of Adverse Events

For the purpose of regulatory reporting, NovoCure will determine the expectedness of events suspected of being related to NOVOTTF-200A.

In the United States, all suspected unexpected serious adverse reactions (SUSARs) will be reported in an expedited manner in accordance with 21 CFR 312.32.

NovoCure or its authorized representative shall notify the Investigator of the following information:

- Any AE suspected of being related to the use of IP in this study or in other studies that is both serious and unexpected (i.e., SUSAR);
- Any finding from tests in laboratory animals that suggests a significant risk for human subjects including reports of mutagenicity, teratogenicity, or carcinogenicity.

Where required by local legislation, the Investigator shall notify his/her IRB promptly of these new serious and unexpected AE(s) or significant risks to subjects.

The Investigator must keep copies of all pertinent safety information on file including correspondence with NovoCure and the IRB. (See Section 0 for record retention information).

NovoCure Device Safety Contact Information:

For NovoCure Device Safety contact information, please refer to the Serious Adverse Event Report Form Completion Guidelines or to the Pregnancy Report Form Completion Guidelines.

11. 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 after the 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 study at their own request .

The following events are considered sufficient reasons for discontinuing a subject from the investigational product and/or from the study:

- Protocol Violation
- Non-Compliance
- Adverse Event
- Subject Developed a DLT
- Subject Decision
- Withdrew Consent
- Investigator Decision
- Disease Progression
- Pregnancy
- Death
- Other

The reason for discontinuation should be recorded in the CRF and in the source documents.

12. EMERGENCY PROCEDURES

12.1. Emergency Contact

In emergency situations, the subject and/or study team should contact the investigator or designee by telephone at the number(s) listed on the Emergency Contact Information page of the protocol (after title page).

13. REGULATORY CONSIDERATIONS

13.1. Good Clinical Practice

The procedures set out in this study protocol pertaining to the conduct, evaluation, and documentation of this study are designed to ensure that NovoCure, its authorized representative, and Investigator abide by Good Clinical Practice (GCP), as described in International Conference on Harmonization (ICH) Guideline E6 and in accordance with the general ethical principles outlined in the Declaration of Helsinki. The study will receive approval from an IRB/EC prior to commencement. The Investigator will conduct all aspects of this study in accordance with applicable national, state, and local laws of the pertinent regulatory authorities.

13.2. Investigator Responsibilities

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.

Investigator responsibilities are set out in the ICH Guideline for Good Clinical Practice and in the local regulations. NovoCure staff or an authorized representative will evaluate and approve all Investigators who in turn will select their staff.

The Investigator should ensure that all persons assisting with the study are adequately informed about the protocol, amendments, study treatments, as well as study-related duties and functions. The Investigator should maintain a list of Sub-investigators and other appropriately qualified persons to whom he or she has delegated significant study-related duties.

The Investigator is responsible for keeping a record of all subjects who sign an informed consent document and are screened for entry into the study. Subjects who fail screening must have the reason(s) recorded in the subject's source documents.

The Investigator, or a designated member of the Investigator's staff, must be available during monitoring visits to review data, resolve queries and allow direct access to subject records (e.g., medical records, office charts, hospital charts, and study-related charts) for source data verification. The Investigator must ensure timely and accurate completion of CRFs and queries.

13.3. Subject Information and Informed Consent

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.

The Investigator must obtain informed consent of a subject and/or a subject's legal representative prior to any study related procedures.

Documentation that informed consent occurred prior to the study subject's entry into the study and of the informed consent process should be recorded in the study subject's source documents including the date. The original informed consent document signed and dated by the study subject and by the person consenting the study subject prior to the study subject's entry into the study, must be maintained in the Investigator's study files and a copy given to the study subject. In addition, if a protocol is amended and it impacts on the content of the informed consent, the informed consent document must be revised. Study subjects participating in the study when the amended protocol is implemented must be re-consented with the revised version of the informed consent document. The revised informed consent document signed and dated by the study subject and by the person who consented the study subject must be maintained in the Investigator's study files and a copy given to the study subject.

13.4. Confidentiality

NovoCure affirms the subject's right to protection against invasion of privacy and to be in compliance with ICH and other local regulations (whichever is most stringent). NovoCure requires the Investigator to permit NovoCure's representatives and, when necessary, representatives from regulatory authorities, to review and/or copy any medical records relevant to the study in accordance with local laws.

Should direct access to medical records require a waiver or authorization separate from the subject's signed informed consent document, it is the responsibility of the Investigator to obtain such permission in writing from the appropriate individual.

13.5. Protocol Amendments

Any amendment to this protocol must be approved by the Sponsor and submitted by the investigator to the FDA. Amendments will be submitted to the IRB for written approval. Written approval must be obtained before implementation of the amended version occurs. The written signed approval from the IRB should specifically reference the Investigator name, protocol number, study title and amendment number(s) that is applicable. Amendments that are administrative in nature do not require IRB approval but will be submitted to the IRB for information purposes.

13.6. Institutional Review Board Review and Approval

Before the start of the study, the study protocol, informed consent document, and any other appropriate documents will be submitted to the IRB with a cover letter or a form listing the documents submitted and their dates of issue. Study treatment can only be supplied to an Investigator by NovoCure or its authorized representative after documentation on all ethical and legal requirements for starting the study has been received by NovoCure or its authorized representative. Before the first subject is enrolled in the study, all ethical and legal requirements must be met.

The IRB must be informed of all subsequent protocol amendments in accordance with local legal requirements. Amendments must be evaluated to determine whether formal approval must be sought and whether the informed consent document should also be revised.

The Investigator must keep a record of all communication with the IRB. This statement also applies to any communication between the Investigator and regulatory authorities.

Any advertisements used to recruit subjects for the study must be reviewed by NovoCure and the IRB prior to use.

13.7. Ongoing Information for Institutional Review Board

If required by legislation or the IRB, the Investigator must submit to the IRB:

- Information on serious or unexpected adverse events as soon as possible;
- Periodic reports on the progress of the study;
- Deviations from the protocol or anything that may involve added risk to subjects.

13.8. Closure of the Study

NovoCure reserves the right to terminate this study at any time for reasonable medical or administrative reasons. Any premature discontinuation will be appropriately documented according to local requirements (e.g., regulatory authorities, etc...).

In addition, the Investigator or NovoCure has the right to discontinue the study for medical or administrative reasons such as:

- Unsatisfactory enrollment;
- GCP noncompliance;
- Inaccurate or incomplete data collection;
- Falsification of records;
- Failure to adhere to the study protocol.

14. DATA HANDLING AND RECORDKEEPING

14.1. Data/Documents

The Investigator must ensure that the records and documents pertaining to the conduct of the study and the distribution of the investigational product are complete, accurate, filed and retained. Examples of source documents include: hospital records; clinic and office charts; laboratory notes; memoranda; subject's diaries or evaluation checklists; dispensing records; recorded data from automated instruments; copies or transcriptions certified after verification as being accurate copies; microfiche; x-ray film and reports; and records kept at the pharmacy, and the laboratories, as well as copies of CRFs or CD-ROM.

14.2. Data Management

Data will be collected via CRF and entered into the clinical database per UC Irvine SOPs, or if delegated to a vendor, according to the vendor's SOPs. This data will be electronically verified through use of programmed edit checks specified by the clinical team. Discrepancies in the data will be brought to the attention of the clinical team, and investigational site personnel, if necessary. Resolutions to these issues will be reflected in the database. An audit trail within the system will track all changes made to the data.

14.3. Record Retention

Essential documents must be retained by the Investigator for a minimum of 2 years. The investigator must retain these documents for the time period described above or according to local laws or requirements, whichever is longer. Essential documents include, but are not limited to, the following:

- Signed informed consent documents for all subjects;
- Subject identification code list, screening log (if applicable), and enrollment log;
- Record of all communications between the Investigator and the IRB
- Composition of the IRB
- Record of all communications between the Investigator, NovoCure, and their authorized representative(s);
- List of Sub-investigators and other appropriately qualified persons to whom the Investigator has delegated significant study-related duties, together with their roles in the study, curriculum vitae, and their signatures;
- Copies of CRFs (if paper) and of documentation of corrections for all subjects;
- IP accountability records;
- Record of any body fluids or tissue samples retained;
- All other source documents (subject records, hospital records, laboratory records, etc.);

- All other documents as listed in Section 8 of the ICH consolidated guideline on GCP (Essential Documents for the Conduct of a Clinical Trial).

The Investigator must notify NovoCure if he/she wishes to assign the essential documents to someone else, remove them to another location or is unable to retain them for a specified period. The Investigator must obtain approval in writing from NovoCure prior to destruction of any records. If the Investigator is unable to meet this obligation, the Investigator must ask NovoCure for permission to make alternative arrangements. Details of these arrangements should be documented.

All study documents should be made available if required by relevant health authorities. Investigator/Institution should take measures to prevent accidental or premature destruction of these documents.

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16. APPENDICES

APPENDIX A. KARNOFSKY PERFORMANCE STATUS SCALE

Activity Level	**Score**
Normal, no complaints	100
Able to carry on normal activity; minor signs or symptoms of disease	90
Normal activity with effort	80
Unable to carry on normal activity or perform active work; cares for self	70
Requires occasional assistance but is able to care for most own needs	60
Requires considerable assistance and frequent medical care	50
Disabled; requires special medical care and assistance	40
Severely disabled; hospitalization indicated although death not imminent	30
Very sick; hospitalized and requires active supportive care.	20
Moribund; fatal processes progressing rapidly	10
Dead	0

APPENDIX B. FACT COGNITIVE (FACT-COG) FUNCTION

FACT-Cognitive Function (Version 3)

Below is a list of statements that other people with your condition have said are important. **Please circle or mark one number per line to indicate your response as it applies to the past 7 days.**

	PERCEIVED COGNITIVE IMPAIRMENTS	Never	About once a week	Two to three times a week	Nearly every day	Several times a day
CogA1	I have had trouble forming thoughts	0	1	2	3	4
CogA3	My thinking has been slow	0	1	2	3	4
CogC7	I have had trouble concentrating	0	1	2	3	4
CogM9	I have had trouble finding my way to a familiar place	0	1	2	3	4
CogM10	I have had trouble remembering where I put things, like my keys or my wallet	0	1	2	3	4
CogM12	I have had trouble remembering new information, like phone numbers or simple instructions	0	1	2	3	4
CogV13	I have had trouble recalling the name of an object while talking to someone	0	1	2	3	4
CogV15	I have had trouble finding the right word(s) to express myself	0	1	2	3	4
CogV16	I have used the wrong word when I referred to an object	0	1	2	3	4
CogV17b	I have had trouble saying what I mean in conversations with others	0	1	2	3	4
CogF19	I have walked into a room and forgotten what I meant to get or do there	0	1	2	3	4
CogF23	I have had to work really hard to pay attention or I would make a mistake	0	1	2	3	4
CogF24	I have forgotten names of people soon after being introduced	0	1	2	3	4

FACT-Cog (Version 3)

Please circle or mark one number per line to indicate your response as it applies to the past 7 days.

		Never	About once a week	Two to three times a week	Nearly every day	Several times a day
CogF25	My reactions in everyday situations have been slow.....	0	1	2	3	4
CogC31	I have had to work harder than usual to keep track of what I was doing	0	1	2	3	4
CogC32	My thinking has been slower than usual	0	1	2	3	4
CogC33a	I have had to work harder than usual to express myself clearly	0	1	2	3	4
CogC33c	I have had to use written lists more often than usual so I would not forget things	0	1	2	3	4
CogMT1	I have trouble keeping track of what I am doing if I am interrupted.....	0	1	2	3	4
CogMT2	I have trouble shifting back and forth between different activities that require thinking	0	1	2	3	4

Please circle or mark one number per line to indicate your response as it applies to the past 7 days.

	COMMENTS FROM OTHERS	Never	About once a week	Two to three times a week	Nearly every day	Several times a day
CogO1	Other people have told me I seemed to have trouble remembering information	0	1	2	3	4
CogO2	Other people have told me I seemed to have trouble speaking clearly.....	0	1	2	3	4
CogO3	Other people have told me I seemed to have trouble thinking clearly	0	1	2	3	4
CogO4	Other people have told me I seemed confused	0	1	2	3	4

FACT-Cog (Version 3)

Please circle or mark one number per line to indicate your response as it applies to the <u>past 7 days</u>.

	PERCEIVED COGNITIVE ABILITIES	Not at all	A little bit	Some-what	Quite a bit	Very much
Cog PC1	I have been able to concentrate	0	1	2	3	4
Cog PV1	I have been able to bring to mind words that I wanted to use while talking to someone	0	1	2	3	4
Cog PM1	I have been able to remember things, like where I left my keys or wallet	0	1	2	3	4
Cog PM2	I have been able to remember to do things, like take medicine or buy something I needed	0	1	2	3	4
Cog PF1	I am able to pay attention and keep track of what I am doing without extra effort	0	1	2	3	4
Cog PCH 1	My mind is as sharp as it has always been	0	1	2	3	4
Cog PCH 2	My memory is as good as it has always been	0	1	2	3	4
Cog PMT 1	I am able to shift back and forth between two activities that require thinking	0	1	2	3	4
Cog PMT 2	I am able to keep track of what I am doing, even if I am interrupted	0	1	2	3	4

Please circle or mark one number per line to indicate your response as it applies to the <u>past 7 days</u>.

	IMPACT ON QUALITY OF LIFE	Not at all	A little bit	Some-what	Quite a bit	Very much
CogQ35	I have been upset about these problems	0	1	2	3	4
CogQ37	These problems have interfered with my ability to work	0	1	2	3	4
CogQ38	These problems have interfered with my ability to do things I enjoy	0	1	2	3	4
CogQ41	These problems have interfered with the quality of my life	0	1	2	3	4

APPENDIX C. FACT-BR

FACT-Br (Version 4)

Below is a list of statements that other people with your illness have said are important. **Please circle or mark one number per line to indicate your response as it applies to the past 7 days.**

	PHYSICAL WELL-BEING	Not at all	A little bit	Some-what	Quite a bit	Very much
GP1	I have a lack of energy	0	1	2	3	4
GP2	I have nausea	0	1	2	3	4
GP3	Because of my physical condition, I have trouble meeting the needs of my family	0	1	2	3	4
GP4	I have pain	0	1	2	3	4
GP5	I am bothered by side effects of treatment	0	1	2	3	4
GP6	I feel ill	0	1	2	3	4
GP7	I am forced to spend time in bed	0	1	2	3	4

	SOCIAL/FAMILY WELL-BEING	Not at all	A little bit	Some-what	Quite a bit	Very much
GS1	I feel close to my friends	0	1	2	3	4
GS2	I get emotional support from my family	0	1	2	3	4
GS3	I get support from my friends	0	1	2	3	4
GS4	My family has accepted my illness	0	1	2	3	4
GS5	I am satisfied with family communication about my illness	0	1	2	3	4
GS6	I feel close to my partner (or the person who is my main support)	0	1	2	3	4
Q1	*Regardless of your current level of sexual activity, please answer the following question. If you prefer not to answer it, please mark this box* ☐ *and go to the next section.*					
GS7	I am satisfied with my sex life	0	1	2	3	4

FACT-Br (Version 4)

Please circle or mark one number per line to indicate your response as it applies to the past 7 days.

	EMOTIONAL WELL-BEING	Not at all	A little bit	Some-what	Quite a bit	Very much
GE1	I feel sad	0	1	2	3	4
GE2	I am satisfied with how I am coping with my illness	0	1	2	3	4
GE3	I am losing hope in the fight against my illness	0	1	2	3	4
GE4	I feel nervous	0	1	2	3	4
GE5	I worry about dying	0	1	2	3	4
GE6	I worry that my condition will get worse	0	1	2	3	4

	FUNCTIONAL WELL-BEING	Not at all	A little bit	Some-what	Quite a bit	Very much
GF1	I am able to work (include work at home)	0	1	2	3	4
GF2	My work (include work at home) is fulfilling	0	1	2	3	4
GF3	I am able to enjoy life	0	1	2	3	4
GF4	I have accepted my illness	0	1	2	3	4
GF5	I am sleeping well	0	1	2	3	4
GF6	I am enjoying the things I usually do for fun	0	1	2	3	4
GF7	I am content with the quality of my life right now	0	1	2	3	4

FACT-Br (Version 4)

Please circle or mark one number per line to indicate your response as it applies to the past 7 days.

	ADDITIONAL CONCERNS	Not at all	A little bit	Some-what	Quite a bit	Very much
Br1	I am able to concentrate	0	1	2	3	4
Br2	I have had seizures (convulsions)	0	1	2	3	4
Br3	I can remember new things	0	1	2	3	4
Br4	I get frustrated that I cannot do things I used to	0	1	2	3	4
Br5	I am afraid of having a seizure (convulsion)	0	1	2	3	4
Br6	I have trouble with my eyesight	0	1	2	3	4
Br7	I feel independent	0	1	2	3	4
NTX6	I have trouble hearing	0	1	2	3	4
Br8	I am able to find the right word(s) to say what I mean	0	1	2	3	4
Br9	I have difficulty expressing my thoughts	0	1	2	3	4
Br10	I am bothered by the change in my personality	0	1	2	3	4
Br11	I am able to make decisions and take responsibility	0	1	2	3	4
Br12	I am bothered by the drop in my contribution to the family	0	1	2	3	4
Br13	I am able to put my thoughts together	0	1	2	3	4
Br14	I need help in caring for myself (bathing, dressing, eating, etc.)	0	1	2	3	4
Br15	I am able to put my thoughts into action	0	1	2	3	4
Br16	I am able to read like I used to	0	1	2	3	4
Br17	I am able to write like I used to	0	1	2	3	4
Br18	I am able to drive a vehicle (my car, truck, etc.)	0	1	2	3	4
Br19	I have trouble feeling sensations in my arms, hands, or legs	0	1	2	3	4
Br20	I have weakness in my arms or legs	0	1	2	3	4
Br21	I have trouble with coordination	0	1	2	3	4
An10	I get headaches	0	1	2	3	4

APPENDIX D. GENE SIGNATURE PROFILING

Potential gene signatures that may be evaluated from archived tumor tissue are shown below:

Gene Symbol	Gene Name
AQP1	Aquaporin 1
CHI3L1	Chitinase 3-like 1 / YKL-40
EMP3	Epithelial membrane protein 3
GPNMB	Glycoprotein nmb
IGFBP2	Insulin-like growth factor binding protein 2

Subtypes of Glioma

-proneural

-neural

-mesenchymal

-classic