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A Phase I Trial of the Optune NovoTTF-200A System in Combination with Temozolomide and Bevacizumab in Pediatric Patients with High-grade Glioma and Ependymoma

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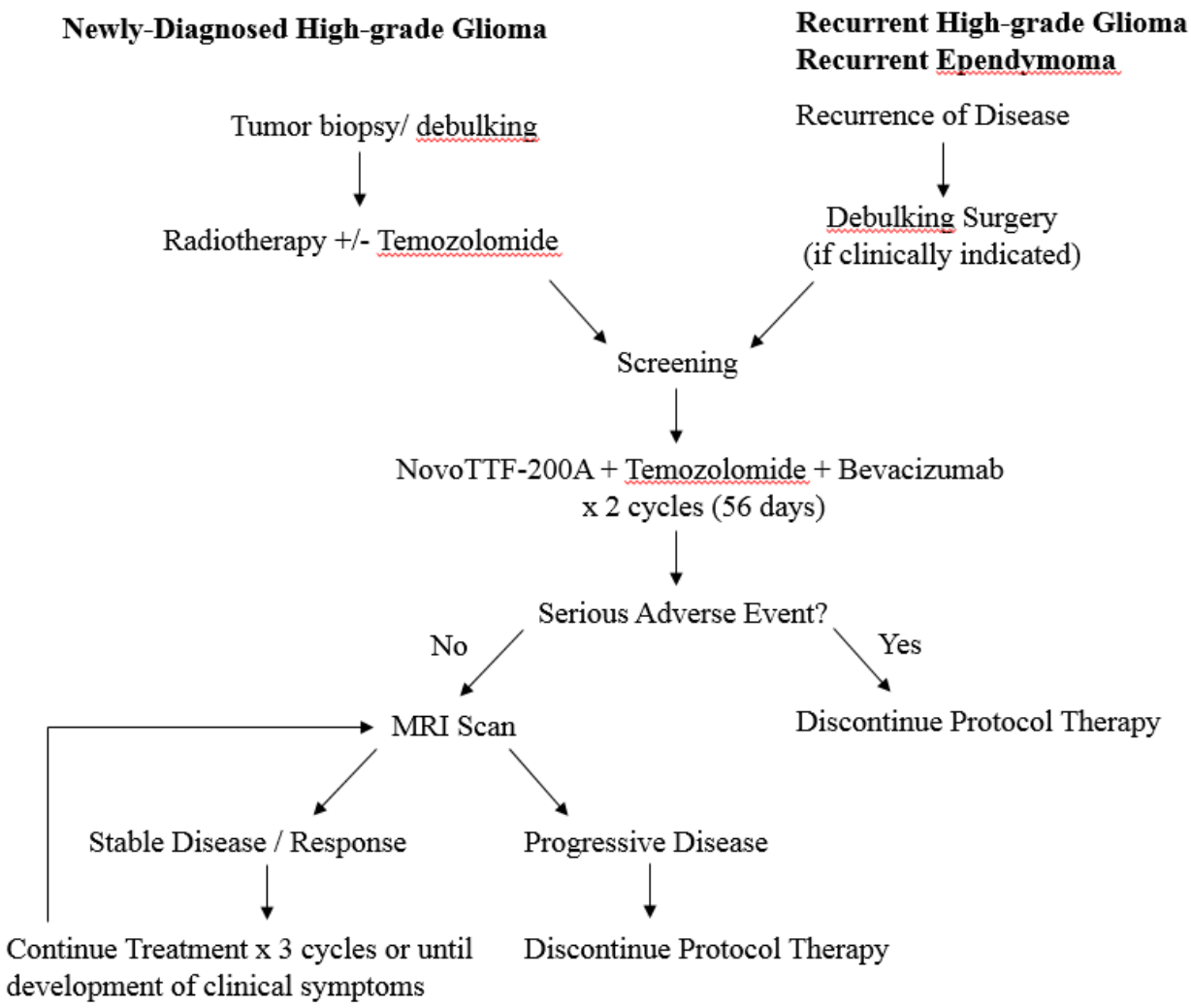
1. PROTOCOL SUMMARY AND SCHEMA

1.1 SUMMARY

Title:	A Phase I Trial of the Optune NovoTTF-200A System in Combination with Temozolomide and Bevacizumab in Pediatric Patients with High-grade Glioma and Ependymoma
Device:	Optune NovoTTF-200A System
Study Objectives:	To determine the safety and tolerability of the Optune NovoTTF-200A System when used in combination with temozolomide and bevacizumab in pediatric patients with newly-diagnosed and recurrent high-grade gliomas and recurrent ependymomas. .
Study Design:	Phase I - Prospective, non-randomized, open label
Study Hypothesis:	The hypothesis of this study is that the Optune NovoTTF-200A System is a safe and well-tolerated treatment for pediatric patients when used in combination with temozolomide and bevacizumab for the treatment of high-grade gliomas and ependymomas.
Sample Size:	Up to 6 pediatric patients with newly-diagnosed or recurrent high-grade glioma or recurrent ependymoma for the phase I safety analysis; Up to 6 patients for the expansion cohort
Study Population:	Patients with a tissue-based diagnosis of newly-diagnosed or recurrent high-grade glioma or ependymoma greater than 5 and less than 21 years of age, of both genders.
Primary Endpoint:	This study's safety endpoint will assess the safety and tolerability of the Optune NovoTTF-200A System when used in combination with temozolomide and bevacizumab for the treatment of pediatric high-grade glioma and ependymoma. This safety endpoint will be determined using the rules of a standard 3+3 phase I study design.
Secondary Endpoint:	There are no efficacy endpoints for this study. However, patients will be followed to assess their progression-free and overall survival. While the study is not powered to provide an efficacy evaluation, the efficacy data gained from this study may be useful in designing future phase II/III investigations.
Device Provided by:	NovoCure Ltd. POB 15022 MATAM Center Haifa, 31905, Israel

Sponsor:	Hackensack University Medical Center Children's Cancer Institute Joseph M. Sanzari Children's Hospital Hackensack University Medical Center 30 Prospect Ave Hackensack, NJ 07601

1.2 PROTOCOL SCHEMA



2. OBJECTIVES AND SCIENTIFIC AIMS

2.1 PRIMARY OBJECTIVE

- To determine the safety and tolerability of the Optune NovoTTF-200A System when used in combination with temozolomide and bevacizumab in pediatric patients with newly-diagnosed and recurrent high-grade gliomas and recurrent ependymomas.

2.2 SECONDARY OBJECTIVES

- To assess the event-free and overall survival of patients treated on this study protocol to aid in the future development of pediatric phase II/III studies using the Optune NovoTTF-200A System.

2.3 EXPLORATORY OBJECTIVES

- To assess the effects of treatment with the Optune NovoTTF-200A System on pediatric brain development.

3. BACKGROUND AND RATIONALE

3.1 PEDIATRIC HIGH-GRADE GLIOMA

High-grade gliomas (HGG) are relatively rare forms of pediatric brain tumors, constituting only 8–12% of primary central nervous system (CNS) tumors in children.[1] These tumors include astrocytomas of either WHO grade 3 (anaplastic astrocytoma) or grade 4 (glioblastoma multiforme) pathology. The management of these tumors involves surgical resection to the extent feasible, as well as adjuvant radiation and chemotherapy.

Surgery provides insight into histologic diagnosis, but the impact of the extent of resection on outcome varies. Although there is debate about extensive tumor resection in adults, there is agreement that the extent of resection is directly related to outcome in children. Campbell et al demonstrated retrospectively a relationship between complete resection and long-term prognosis in cases of well-circumscribed hemispheric malignant gliomas in children.[2] However, surgery by itself rarely cures patients because regional tumor infiltration beyond the primary tumor prevents complete resections unless the tumor is confined to polar locations, which is uncommon.

For older children and adults, radiation therapy is the most commonly used treatment for HGG. All patients are candidates for RT after surgery, except for very young children where an attempt

has been made to eliminate or delay the use of RT because of fears regarding neuro-developmental morbidity. Newer techniques, such as conformal RT, which permit more precise treatment to the tumor bed are being investigated to reduce treatment related morbidity.

Even with these interventions, the prognosis for patients with these tumors is poor, with most patients succumbing to their disease within 12–18 months.[3] These outcomes are far below what has been achieved in the treatment of other pediatric cancers. As a result, new therapies must be investigated to improve clinical outcomes for this population.

3.2 HISTORICAL TREATMENTS FOR PEDIATRIC HIGH-GRADE GLIOMA

Children with high-grade gliomas continue to have poor outcomes despite multi-modal therapy with surgical resection, radiation therapy, and chemotherapy. While surgical resection has a clear benefit and radiation does slightly prolong time to progression, to date, chemotherapy, in particular, has had little impact on the survival outcomes of these children.

The Children's Cancer Group (CCG) conducted the first prospective, randomized study of adjuvant chemotherapy in children with high-grade astrocytoma, CCG 943.[4] In this study, 58 patients were randomized following surgery to radiation therapy with or without chemotherapy consisting of chloroethyl-cyclohexyl nitrosourea (CCNU), vincristine, (VCR), and prednisone. The 5-year EFS for the radiotherapy and chemotherapy group was 46%, compared to 18% for the radiotherapy-only group. In patients with GBM, specifically, and at least a partial resection, the 5-year EFS for the combined radiotherapy and chemotherapy group was clearly superior at 42%, compared to 6% for the radiotherapy-only group (P=0.001).

Study CCG 945 randomized 172 patients to receive an 8-in-1 chemotherapy regimen or the CCNU/VCR/prednisone regimen used in CCG943.[5] The 8-in-1 regimen showed no improvement in patient outcomes when compared to the CCNU/VCR/prednisone regimen. The five-year progression-free survival (PFS) and OS were 33% and 39%, respectively for the 8-in-1 group, where the CCNU/VCR/prednisone group had a PFS of 26% and an OS of 29%. Of note, the patients receiving CCNU/VCR/prednisone in the CCG 945 study did not respond as well as the patients receiving the same regimen in the CCG 943 study. The 5-year PFS in CCG for the CCNU/VCR/prednisone arm was 46% vs. 26% for the same regimen in protocol CCG 945.

CCG protocol 9933 studied three different high-dose chemotherapy regimens prior to radiation.[6] Seventy six patients were enrolled and received four courses of either etoposide with carboplatin, or ifosfamide, or cyclophosphamide. Patients then received radiotherapy followed by CCNU and VCR. The five-year EFS and OS were 8% (±3%) and 24% (±5%), respectively, without any difference in response rates between the three regimens. These high-dose regimens carried a significant amount of morbidity with 29% of patients experiencing severe non-hematologic toxicities.

The Pediatric Oncology Group (POG) conducted a phase III study which randomized patients to either cisplatin and BCNU or VCR and cyclophosphamide prior to radiotherapy. Outcomes of this study were poor with a 5-year survival of 20% for the cisplatin/BCNU arm and 5% for the VCR/cyclophosphamide arm.[7]

Children's Oncology Group study ACNS0126 used temozolomide (TMZ) as a radiosensitizer followed by 10 cycles of TMZ (200 mg/m^2/day x 5 days of every 28 day cycle). 107 patients with a diagnosis of anaplastic astrocytoma (AA), GBM, or gliosarcoma were enrolled. Ninety patients were eligible (31 AA, 55 GBM, and 4 other). The three-year EFS and OS were 11% (±3%) and 22% (±5%), respectively. Although this study did not demonstrate an improved survival rate compared to CCG 945, the study did demonstrate comparable survival with less toxicity than in studies utilizing nitrosurea-based regimens.

In a safety and feasibility study, twelve children and young adults with newly diagnosed HGG received radiotherapy with bevacizumab and temozolomide followed by bevacizumab, irinotecan and temozolomide. The most common ≥grade 3 toxicities included lymphopenia, neutropenia and leukopenia. Grade 3 hypertension occurred in 2 patients. No intracranial hemorrhages occurred. In HGG patients, 3-year progression free survival and OS were 33 % and 50 %, respectively. The authors concluded that a bevacizumab-based regimen is feasible and tolerable in newly diagnosed children and young adults with HGG.[8]

As demonstrated by the results of the multiple studies detailed above, there is currently no effective chemotherapy regimen for pediatric high-grade gliomas that can be considered a true "standard of care". Due to its increased tolerability and similar efficacy to nitrosurea-containing regimens, temozolomide is currently one of the more common chemotherapy agents used in these tumors and has thus been incorporated into the second portion of this study. Likewise, bevacizumab, which also has a relatively favorable side effect profile and is commonly used in pediatric high-grade glioma, has been selected as the second standard of care agent. Temozolomide and bevacizumab in combination has demonstrated safety and efficacy on par with other regimens in both adults and pediatric high-grade glioma studies.[8,9] As such, they are felt to be reasonable backbone drugs in the second portion of this study combining Optune NovoTTF-200A treatment with chemotherapy.

3.3 PEDIATRIC EPENDYMOMA

Ependymoma is the third most common pediatric CNS tumor accounting for 8-10% of all diagnoses.[10] Unfortunately, outcomes for these tumors are suboptimal with the five-year progression-free and overall survival being 50-64% and 23-45%, respectively.[11-14] The standard of care for ependymoma is maximal feasible surgical resection followed by radiotherapy to the primary site. However, the use of radiotherapy in young children remains controversial, particularly in those children with supratentorial tumors. Chemotherapy is typically reserved for patients with residual tumor post-operatively and administered prior to radiotherapy.[15] The benefit of post-radiation maintenance chemotherapy is currently being evaluated in the Children's Oncology Group ACNS0831 study.

There is currently no standard of care for recurrent ependymoma in children. Children who receive incomplete resections of their tumor are at much higher risk for recurrence than those

who receive a gross-total resection. Treatment strategies for children with recurrent ependymoma include re-resection and re-irradiation when feasible.[16] Chemotherapy has typically not demonstrated significant benefit in patients with recurrent tumor.[17] There have been documented

long-term responses to metronomic anti-angiogenic regimens, but these treatments are generally not felt to be curative.[18,19] Many families of children with recurrent ependymomas seek experimental treatment due to the lack of proven therapeutic options. Given the tremendous need for investigations of new therapies for children with recurrent ependymoma it is felt that including this patient population for enrollment in this phase I study is both reasonable and ethical.

3.4 INTRODUCTION TO ELECTRIC FIELDS

In the laboratory setting and in clinical practice, alternating electric fields show a wide range of effects on living tissues. At very low frequencies (under 1 kHz), alternating electric fields stimulate excitable tissues through membrane depolarisation.[20] 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.[20,21] In addition, low frequency pulsed electric fields have been claimed to stimulate bone growth and accelerate fracture healing.[22]

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.[23] 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.[24]

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.[23] 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[25]) and cell rotation.[26, 27] With pulsed relatively strong electric fields, $> 10^3$ V/cm and 100 ms pulse length, reversible pore formation appears in the cell membrane, a phenomenon usually called electroporation.[28]

3.5 NOVOCURE'S TUMOR TREATING ELECTRIC FIELDS (*TTFIELDS*)

NovoCure has shown[29] that when properly tuned, very low intensity, intermediate frequency electric fields (TTFields) stunt the growth of tumor cells. This inhibitory effect was demonstrated in all proliferating cell types tested, whereas, non-proliferating cells and tissues were unaffected. Interestingly, different cell types showed specific intensity and frequency dependences of

TTField inhibition. It has been shown that two main processes occur at the cellular level during exposure to TTFields: arrest of proliferation and dividing cell destruction. The damage caused by TTFields to these replicating cells was dependent on the orientation of the division process in relation to the field vectors, indicating that this effect is non-thermal. Indeed, temperature measurements made within culture dishes during treatment and on the skin above treated tumors in-vivo, showed no significant elevation in temperature compared to control cultures/mice. Also, TTFields caused the dividing cells to orient in the direction of the applied field in a manner similar to that described in cultured human corneal epithelial cells exposed to constant electric fields.[30] 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[31, 32] or indirectly[33-35] with microtubule polymerization (e.g., Taxol).

3.6 MODELING THE MECHANISM OF ACTION OF TTFIELDS

In order to explain how TTFields cause orientation dependent damage to dividing cells and disrupt the proper formation of the mitotic spindle NovoCure modeled the forces exerted by TTFields on intracellular charges and polar particles using finite element simulations. Two main mechanisms by means of which the electric fields may affect dividing cells were recognized. The first relates to the field effect on polar macromolecule orientation. Within this framework, during the early phases of mitosis, i.e., in pre-telophase, when tubulin polymerization-depolymerization drives the proliferation process, the electric field forces any tubulin dimers, positioned further than 14nm away from the growing end of a microtubule, to orient in the direction of the field. This force moment, (10^{-5} pN) acting on the dimers, is sufficient to interfere with the proper process of assembly and disassembly of microtubules that is essential for chromosome alignment and separation.[36] This effect can explain the mitotic arrest of TTField treated cells.[37]

The second mechanism, which interferes with cell division, and is most likely to play an important role in cell destruction, becomes dominant during cleavage. As seen in simulations, the electric field within quiescent cells is homogenous, whereas the field inside mitotic cells, during cytokinesis, is not homogenous. An increased field line concentration (indicating increased field intensity) is seen at the furrow, a phenomenon that highly resembles the focusing of a light beam by a lens. This in-homogeneity in field intensity exerts a unidirectional electric force, on all intracellular charged and polar entities (including induced dipoles), pulling them towards the furrow (regardless of field polarity). For example, for a cleavage furrow that reached a diameter of 1μm in an external field of only 1 V/cm, the force exerted on the microtubules is in the order of 5pN. This magnitude is compatible with the reported forces necessary to stall microtubule polymerization which is 4.3 pN.[38] 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).

3.7 IN VIVO EFFECTS OF TTFIELDS

NovoCure has shown[39] 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.

3.8 THE NOVOTTF-200A DEVICE

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.

Of note, the NovoTTF-200A is a second generation device and has received approval by the FDA in adults. The first generation device, the NovoTTF-100A, was used to conduct many of the initial clinical trials for the device in adults.

3.9 CLINICAL STUDIES OF NOVOTTF SYSTEM IN ADULT PATIENTS

3.9.1 A PHASE III STUDY OF MAINTENANCE THERAPY WITH TUMOR-TREATING FIELDS PLUS TEMOZOLOMIDE VS TEMOZOLOMIDE ALONE FOR GLIOBLASTOMA

A phase III study was performed to evaluate the efficacy and safety of TTFields used in combination with temozolomide maintenance treatment after chemoradiation therapy for patients with glioblastoma. After completion of chemoradiotherapy, patients with glioblastoma were randomized (2:1) to receive maintenance treatment with either TTFields plus temozolomide (n = 466) or temozolomide alone (n = 229). The study enrolled 695 of the planned 700 patients between July 2009 and November 2014 at 83 centers in the United States, Canada, Europe, Israel, and South Korea.

Treatment with TTFields was delivered continuously (>18 hours/day) via 4 transducer arrays placed on the shaved scalp and connected to a portable medical device. Temozolomide (150-200 $mg/m^2/d$) was given for 5 days of each 28-day cycle.

The trial was terminated based on the results of this planned interim analysis. The interim analysis included 210 patients randomized to TTFields plus temozolomide and 105 randomized to temozolomide alone, and was conducted at a median follow-up of 38 months (range, 18-60 months). Median progression-free survival in the intent-to-treat population was 7.1 months (95% CI, 5.9-8.2 months) in the TTFields plus temozolomide group and 4.0 months (95% CI, 3.3-5.2 months) in the temozolomide alone group (hazard ratio [HR], 0.62 [98.7% CI, 0.43-0.89]; $P = .001$). Median overall survival in the per-protocol population was 20.5 months (95% CI, 16.7-25.0 months) in the TTFields plus temozolomide group (n = 196) and 15.6 months (95% CI, 13.3-19.1 months) in the temozolomide alone group (n = 84) (HR, 0.64 [99.4% CI, 0.42-0.98]; $P = .004$).

In this interim analysis of 315 patients with glioblastoma who had completed standard chemoradiation therapy, adding TTFields to maintenance temozolomide chemotherapy significantly prolonged progression-free and overall survival. [40]

3.9.2 EFFECT OF NOVOTTF-100A ON NEWLY DIAGNOSED GLIOBLASTOMA PATIENTS – CLINICAL PILOT STUDY

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

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

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

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

The median progression free survival (PFS) of the patients in this study exceeded concurrent and historical controls[41] dramatically (greater than 18 months versus 7.1 months, respectively). = Median overall survival from diagnosis was greater than 26 months (compared to 14.6 months in historical controls[41]). Although the number of patients in this pilot trial is small, the excellent safety profile of this treatment modality and the highly promising efficacy data gathered so far indicate the potential of the NovoTTF system treatment as an effective therapy for newly diagnosed GBM patients.

3.9.3 EFFECT OF NOVOTTF-100A ON RECURRENT GLIOBLASTOMA PATIENTS – CLINICAL PILOT STUDY

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

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

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

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

The median progression free survival (PFS) of the patients in this study exceeded historical controls2 dramatically (26.1 weeks versus 9 weeks, respectively). The PFS at 6 months (PFS6) was 50% compared to 15% in historical controls.[42] Median overall survival was 62 weeks. Response rate was 25% (1 CR + 1 PR) and only two patients had progressive disease despite treatment.

3.9.4 EFFECT OF NOVOTTF-100A ON RECURRENT GLIOBLASTOMA PATIENTS – PIVOTAL STUDY

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

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

3.10 CLINICAL STUDIES OF NOVOTTF SYSTEM IN PEDIATRIC PATIENTS

The Pediatric Brain Tumor Consortium study PBTC-048 is an ongoing trial examining the feasibility and device-related toxicity of TTFields in children 5–21 years of age with recurrent supratentorial HGG and ependymoma.[43] Feasibility is defined in this trial as the ability of pediatric subjects to wear Optune ≥18 hours/day for at least 23/28 days of cycle one.

The study's planned interim analysis included 11 patients (seven males and four females) with supratentorial tumors (ten high-grade glioma and one ependymoma). Ten patients were evaluable (one patient had progressive disease during the feasibility period) and four remained on study through 4 cycles. One grade 5 intracranial hemorrhage not associated with the device and no grade IV toxicities occurred. Three patients had seizures (grade 1–3), fatigue, scalp pain, localized rash, and headache (none greater than grade 3). Of the 10 evaluable patients, 7 satisfied the feasibility criteria for the Optune therapy, which was above the prespecified threshold of at least 6/11. These preliminary results were determined to indicate feasibility of monotherapy with Optune in the pediatric population with minimal toxicity.

Quality of life assessments were performed as part of the interim analysis.[44] Participating patients and one of their parents completed the following measures at baseline and prior to each intervention cycle: PROMIS Fatigue, Anger, Anxiety, Depressive Symptoms, Mobility, Upper Extremity Function, and Peer Relationships and Neuro-QOL Stigma. Participants also completed an exit survey when they were off the study regarding their experiences wearing the device.

Patients reported worse HRQOL than the norms on all domains. Six of eleven patients completed the exit survey. No significant changes ($p< 0.05$) between the baseline and the final assessment were found except for Stigma. Patients perceived less stigma at baseline than at the final assessment ($t=2.82$, $p=0.0370$). Of these 6 parents who completed the exit survey, most considered wearing the device to be easy (n=5). Patient reminders were unnecessary (n=5), patients rarely/didn't complain (n=4) or refuse (n=5) to wear the device, there was rare/no (n=4) difficulty with daily activities because of the device, and patients were not (n=4) or sometimes (n=2) embarrassed to wear the device. These preliminary results indicate Optune-delivered TTFields therapy is feasible and accepted by children and parents with no evidence of negatively impacting patients' quality of life

3.11 STUDY RATIONALE

Pediatric high-grade gliomas are aggressive tumors that carry a poor prognosis. In the recurrent setting, the outcomes for children with ependymomas are equally dismal. There is currently no standard-of-care for these tumors and patients are in desperate need of improved and innovative new therapies. TTFields have proven to be a safe and efficacious approach to the treatment of adult high-grade gliomas and the Optune device is currently FDA-approved for this indication. Preliminary pediatric investigations have demonstrated the safety and feasibility of delivering TTFields to children with high-grade glioma and ependymoma. Given these positive results, further exploration into the use of TTFields for pediatric high-grade glioma and ependymoma are warranted.

TTFields, temozolomide, and bevacizumab each have a track record of tolerability in children and have non-overlapping toxicity profiles. Historically, most improvement in pediatric cancer outcomes have been achieved with the use of combination therapy. With this in mind, the proposed study regimen combining TTFields with the chemotherapy agents temozolomide and bevacizumab is felt to be a rational next-step in the investigation of the Optune NovoTTF-200A system in children.

4.0 STUDY DESIGN

4.1 PHASE 1 DESIGN

This proposed phase I trial will utilize a standard 3+3 design to determine the safety and tolerability of the Optune NovoTTF-200A System in combination with temozolomide and bevacizumab in pediatric high-grade glioma and ependymoma patients. The phase I safety evaluation period will encompass the first two cycles (56 days) of treatment. If one or fewer serious adverse events related to treatment are observed in the first three patients of this cohort, then an additional three patients will be enrolled. If fewer than two adverse events related to treatment are noted following the phase I safety evaluation period for all six patients, then the study will conclude that treatment with the Optune NovoTTF-200A System in combination with temozolomide and bevacizumab is well-tolerated for pediatric patients with high-grade gliomas and ependymomas. If at any point two or more patients experience a serious adverse event related to treatment, then the study will close.

Once a patient is enrolled it is planned that they will continue to receive treatment in cycles of 28 days (4 weeks), which may be repeated continuously without therapy interruption for 12 cycles or until any criterion for discontinuation (clinical or radiological progression of disease, clinically unacceptable toxicity, completion of treatment, etc.) is met. Patients who appear to benefit from this treatment will be allowed to continue treatment beyond 12 cycles if approved by the study Principle Investigator.

Following the completion of enrollment for the phase I cohort, enrollment will open for an expansion cohort of an additional six patients. The expansion cohort will allow for the collection of additional safety and efficacy data of the study regimen and also allow eligible patients access to TTFields treatment while a phase II protocol is being developed. Patients in the expansion cohort will follow the eligibility guidelines and treatment plan as outlined in the protocol.

4.2 TREATMENT PLAN

Enrolled subjects will receive TTField treatment with the Optune NovoTTF-200A system, administered at 200kHz for a minimum of 18 hours per day in 28 day cycles. Patients will also receive temozolomide 200mg/m^2/dose orally on Days 1-5, as well as bevacizumab 10mg/kg/dose intravenously on Days 1 and 15 of each 28 day cycle. Phase I safety evaluation will take place over the initial two cycles (56 days) of treatment. Following the completion of the safety evaluation period, patients will continue to receive treatment in 28 day cycles, which may be repeated continuously without therapy interruption until any criterion for discontinuation is met.

4.3. CONCOMITANT THERAPY RESTRICTIONS

4.3.1 No other cancer chemotherapy or immunomodulating agents will be used.

4.3.2 Filgrastim (G-CSF) may be used at the treating physician's discretion to enhance neutrophil recovery when clinically indicated (e.g., for culture proven bacteremia or invasive fungal infection). Routine use of filgrastim in clinically well patients awaiting count recovery is not recommended.

4.3.3 Appropriate antibiotics, blood products, antiemetics, fluids, electrolytes and general supportive care are to be used as necessary.

4.3.4 Corticosteroid therapy is permissible only for treatment of increased intracranial pressure. The lowest dose consistent with good medical management should be used. Patients receiving corticosteroids must be on a stable or decreasing dose prior to study enrollment. Corticosteroids should NOT be used as an antiemetic due to their effect on the blood brain barrier.

4.4 DEFINITIONS OF SERIOUS ADVERSE EVENTS

Serious adverse events are based on Version 5.0 of the NCI Common Terminology Criteria for Adverse Events (CTCAE). A copy of the CTCAE version 5.0 can be downloaded from the CTEP website at: https://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_5x7.pdf.

Serious adverse events are defined as:

a) The development of new seizures or an increase in the grade of seizures based on CTCAE 5.0 criteria for those patients with baseline seizures

c) Any grade 4 non-hematological toxicity

d) Any grade 3 non-hematological toxicity with the specific exception of

i. Grade 3 nausea and vomiting of less < 5 days duration responsive to antiemetic therapy;

ii. Grade 3 increased alanine aminotransferase (ALT or SGPT) that return to levels that meet initial eligibility criteria within 7 days of treatment interruption and that do not recur upon study re-challenge with treatment

iii. Grade 3 fever or infection < 5 days duration.

iv. Grade 3 hypokalemia, hypophosphatemia, hypocalcemia and/or hypomagnesemia responsive to oral supplementation

e) Any grade 2 non-hematological toxicity that persists for ≥ 7 days and is considered sufficiently medically significant or sufficiently intolerable by patients that it requires treatment interruption

f) Any Grade 2 or higher adverse event requiring interruption of protocol treatment for > 7 days or which recurs upon treatment re-challenge.

g) Skin breakdown or evidence of infection, either of which requires a break in NovoTTF-200A treatment greater than 3 days

When a serious adverse events is identified, treatment with Optune NovoTTF- should be discontinued until resolution of the toxicity. Treatment with Optune NovoTTF-200A should then be restarted, if felt to be clinically appropriate, by the investigator.

4.4.1 **Management of Adverse Events, Serious Adverse Events, and Special Reporting Situations**

4.4.2 Adverse events (AE) will be graded according to the CTC AE criteria, version 5.0. CTC AE version 5.0 may be downloaded from the CTEP web site (http://ctep.cancer.gov).

4.4.3 Grade 3 (non-hematologic) and all higher adverse events will be reported to the Protocol Chair within 5 days of the occurrence using the form in except as specified in section 14.5.3.

4.4.4 **Grade 4 and grade 5 adverse events specified in the table require expedited reporting as detailed below.**

Attribution	Grade 4		Grade 5[#]		Protocol-Specific Requirements
	Unexpected	Expected	Unexpected	Expected	
Unrelated or Unlikely			SAE Report		Report to Study Chair by phone within 24 hours of occurrence and by fax or email using the form within 5 calendar days.
Possible, Probable, Definite	SAE Report		SAE Report	SAE Report	

[#]This includes all deaths within 30 days of the last dose of treatment with a commercial agent regardless of attribution. Any death that occurs more than 30 days after the last dose of treatment with a commercial agent(s) and is attributed (possibly, probably, or definitely) to the agent(s) and is not due to cancer recurrence must be reported according to the instructions above.

4.4.5 **Reporting to Novocure.**

In general, the Investigator or study personnel must immediately report to Novocure any serious adverse event and Special Reporting Situations, whether or not considered device related. Study endpoints that are serious adverse events (e.g., all-cause mortality) must be reported in accordance with the protocol unless there is evidence suggesting a causal relationship between the device and the event (e.g., death as a result of anaphylactic reaction or fatal hepatic necrosis). In that case, the investigator must immediately report the event to Novocure. The sponsor must record non-serious adverse events and report them to Novocure according to the timetable for reporting as specified either in the protocol or to fulfill regulatory reporting requirements.

For each subject, AEs, SAEs, and Special Reporting Situations should be recorded after informed consent is obtained until the subject has completed participation in the study as follows:

A Serious Adverse Event or Special Reporting Situations must be reported if it occurs from the receipt of a signed and dated ICF until **30 days** of receiving the study device.

Any serious adverse event or Special Reporting Situation that is ongoing when a subject completes his/her participation in the Study must be followed until any of the following occurs:

- the event resolves or stabilizes;
- the event returns to baseline condition or value (if a baseline value is available);
- the event can be attributed to agents(s) other than the Study Device, or to factors unrelated to Study conduct.

4.4.6 **Recording of Adverse Events, Serious Adverse Events and Special Reporting Situations**

Recording should be done in a concise manner using standard, acceptable medical terms.

The adverse event recorded should not be a procedure or a clinical measurement (i.e. a laboratory value or vital sign) but should reflect the reason for the procedure or the diagnosis based on the abnormal measurement, if known.

Preexisting conditions that worsen in severity or frequency during the Study should also be recorded (a preexisting condition that does not worsen is not an adverse event).

Further, a procedure or surgery is not an adverse event; rather, the event leading to the procedure or surgery is considered an adverse event. Any event requiring in-patient hospitalization that occurs during the course of a subject's participation in a trial must be reported as an SAE. Hospitalizations that do not meet the criteria for SAE reporting are:

A: Reasons described in the Protocol, e.g. drug administration, Protocol-required testing
B. Surgery or procedure planned prior to entry into the Study.

If, in the Sponsor Investigator's judgment, a clinical significant worsening from baseline is observed in any laboratory or other test parameter (e.g. electrocardiogram (ECG), angiogram), physical exam finding, or vital sign, a corresponding clinical adverse event should be recorded.

If a specific medical diagnosis has been made, that diagnosis or syndrome should be recorded as the adverse event, whenever possible. However, a complete description of the signs, symptoms and investigations which led to the diagnosis should be provided. For example, if clinically significant elevations of liver function tests are known to be secondary to hepatitis, "hepatitis" and not "elevated liver function tests" should be

recorded. If the cause is not known, the abnormal test or finding should be recorded as an adverse event, using appropriate medical terminology (e/g/ thrombocytopenia, peripheral edema, QT prolongation).

4.5 PRIMARY EVALUATIONS

During the first two cycles (56 days) of treatment, patients will be closely monitored for adverse events related to treatment. They will undergo frequent physical examination and laboratory evaluations as needed to assess the safety and tolerability of the treatment regimen.

Patients will be recommended to undergo an MRI scan of the brain with and without contrast following the completion of Cycle 2 of treatment to assess the tumor's response to therapy, and then every additional three cycles. MRI scans may be done more frequently as clinically indicated.

4.6 CORE MRI REVIEW

All MRI scans for study patients will be reviewed by a neuro-radiologist at Hackensack University Medical Center or Arnold Palmer Children's Hospital. Either digital (DICOM) images or analog films can be used for this purpose. Contrast agent and dose per body weight must be kept constant between scans for each patient.

5.0 ELIGIBILITY CRITERIA

5.1 INCLUSION CRITERIA

5.1.1 Age ≥ 5 years and < 22 years

5.1.2 Patients must have a minimum head circumference of 44 cm

5.1.3 Diagnosis:
Patients must have either a histologically- or cytologically-confirmed supratentorial high-grade glioma or supratentorial ependymoma.

Patients with metastatic disease involving the infratentorium or spinal cord are eligible providing that they have a supratentorial tumor that is able to be targeted with TTFields.

Eligible pathologic diagnoses include:

<u>High-grade Glioma (WHO Grade III or IV):</u>
Anaplastic Astrocytoma
Astroblastoma
Diffuse Midline Glioma
Glioblastoma
Gliosarcoma

Ependymoma (WHO Grade II or III):
Ependymoma
Anaplastic Ependymoma

Patients with high-grade glioma must be newly-diagnosed or have a tumor that is progressive or recurrent following standard treatment. Patients with ependymoma must have a tumor that is progressive or recurrent following standard treatment.

5.1.4 Patients must have received the maximal feasible resection of their tumor and radiation therapy (unless contraindicated due to patient age) as part of their initial treatment prior to study enrollment.

5.1.5 Timing of therapy

5.1.5.1 Patients must be enrolled before treatment begins. Treatment must start within 14 days of study enrollment.

5.1.5.2 All clinical and laboratory studies to determine eligibility must be performed within 7 days prior to enrollment unless otherwise indicated in the eligibility section.

5.1.5.3 Newly-diagnosed patients must begin therapy within six weeks of the completion of radiotherapy, or within six weeks of surgical resection if radiotherapy is contraindicated.

To provide adequate time for study enrollment and initiation of Optune treatment, patients in the expansion cohort may receive one cycle (28 days) of treatment with temozolomide and bevacizumab prior to beginning therapy with Optune. This pre-study cycle of treatment should begin within six weeks of the completion of radiotherapy, or within six weeks of surgical resection if radiotherapy is contraindicated. Study therapy should then begin within ten weeks of the completion of radiotherapy or surgical resection.

5.1.5.4 Recurrent high-grade glioma or ependymoma patients must begin therapy within six weeks of documented tumor progression by MRI scan.

5.1.6 Patients must have a Lansky or Karnofsky performance status score of ≥ 50%, corresponding to ECOG categories of 0, 1 or 2. Use Karnofsky for patients > 16 years of age and Lansky for patients ≤ 16 years of age. Patients who are unable to walk because of paralysis, but who are up in a wheelchair will be considered ambulatory for the purpose of assessing the performance score.

5.1.7 Able to undergo adequate tumor imaging, via magnetic resonance imaging (MRI) scan to evaluate disease evolution.

5.1.8 Adequate hematologic, renal, liver function as demonstrated by laboratory values:

5.1.8.1 ANC ≥ 1,000/ul
5.1.8.2 Hemoglobin ≥8.0 gm/dl
5.1.8.3 Platelet count ≥ 100,000/ul
5.1.8.4 Adequate Liver Function Defined As
• Total bilirubin ≤ 1.5 x upper limit of normal (ULN) for age, and
• SGPT (ALT) < 2.5 x upper limit of normal (ULN) for age.
5.1.8.5 Adequate Renal Function Defined As Either
• Creatinine clearance or radioisotope GFR ≥ 70ml/min/1.73m^2
• or a serum creatinine less than or equal to the institutional normal for age

5.1.9 Negative pregnancy test in women of childbearing potential within 7 days of initiating investigational therapy

5.1.10 Recent mothers must agree not to breast feed while receiving medications on study.

5.1.11 Patient or legal guardian must give written, informed consent or assent (when applicable).

5.1.12 Able to swallow and ingest oral medication or have a NG or G-tube for drug administration

5.1.13 Urine protein should be screened by urine analysis. If protein ≥ 2+ on urinalysis, then Urine Protein Creatinine (UPC) ratio should be calculated. If UPC ratio > 0.5, 24-hour urine protein should be obtained and the level should be < 1000 mg for patient enrollment.

Note: UPC ratio of spot urine is an estimation of the 24 urine protein excretion – a UPC ratio of 1 is roughly equivalent to a 24-hour urine protein of 1000 mg. UPC ratio is calculated using one of the following formula:

- [urine protein]/[urine creatinine] – if both protein and creatinine are reported in mg/dL
- [(urine protein) x0.088]/[urine creatinine] – if urine creatinine is reported in mmol/L

5.1.14 Adequate Coagulation Defined As

– PT/INR ≤ 1.5 x upper limit of normal

5.2 EXCLUSION CRITERIA

5.2.1 Age <5 years or ≥ 21 years

5.2.2 Head circumference < 44 cm

5.2.3 Absence of supratentorial tumor.

5.2.4 Use of any other investigational drug within five half-lives of that drug prior to the initiation of protocol therapy

5.2.5 Anti-cancer therapy within 4 weeks prior to the initiation of protocol therapy (6 weeks for mitomycin and nitrosureas, 4 weeks for curative-intent radiotherapy, and 2 weeks for palliative radiotherapy)

5.2.6 Any National Cancer Institute (NCI) Common Toxicity Criteria for Adverse Events (CTCAE version 5.0) >Grade 1 toxicities from prior chemotherapy or radiotherapy that could impact on safety outcome assessment

5.2.7 Any surgery within 14 days prior to initiation of protocol therapy (excluding shunt or line insertion)

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

5.2.9 Evidence of increased intracranial pressure (clinically significant papilledema, vomiting and nausea or reduced level of consciousness). Patients receiving escalating doses of corticosteroids to control symptoms of increased intracranial pressure (e.g., require a stable or decreasing dose of corticosteroids for at least 7 days prior to enrollment) will also be excluded.

5.2.10 Known > Grade 1 intracranial or intratumoral hemorrhage either by CT or MRI scan within the last 1 month. Patients with resolving hemorrhage changes, punctate hemorrhage or hemosiderin may enter the study

5.2.11 Pregnant female patients are not eligible for this study. Pregnancy tests with a negative result must be obtained in all post-menarchal females.

5.2.12 Lactating females must agree they will not breastfeed a child while on this study.

5.2.13 Males and females of reproductive potential may not participate unless they agree to use an effective contraceptive method and continue to do so for at least 6 months after the completion of therapy.

5.2.14 Any serious and/or unstable pre-existing medical, psychiatric or other condition which in the Investigator's opinion could interfere with subject safety, obtaining written informed consent, or compliance with the study protocol

5.2.15 Known hypersensitivity to temozolomide or bevacizumab

5.2.16 Patients who are unable to take oral medications because of significant uncontrolled vomiting will be excluded.

5.2.17 Patients must not have a history of myocardial infarction, severe or unstable angina, clinically significant peripheral vascular disease, Grade 2 or greater heart failure, or serious and inadequately controlled cardiac arrhythmia.

5.2.18 Patients must not have a known clinically significant bleeding diathesis or coagulopathy

5.2.19 Patients who have experienced arterial thromboembolic events, including transient ischemic attacks or cerebrovascular accidents are excluded from participation.

5.2.20 Patients must not have been previously diagnosed with a deep venous thrombosis (including pulmonary embolism) and must not have a known thrombophilic condition (e.g., protein S, protein C, antithrombin III deficiency, Factor V Leiden or Factor II G202`0A mutation, homocysteinemia, or antiphospholipid antibody syndrome).

5.2.21 Patients must not have a history of an abdominal fistula, gastrointestinal perforation, or intra-abdominal abscess within the last 6 months prior to study entry.

5.2.22 Patients with a serious or non-healing wound, ulcer, or bone fracture are not eligible for this study.

5.2.23 Patients with a history of allergic reaction to Chinese hamster ovary cell products, or other recombinant human antibodies are ineligible.

6.0 RECRUITMENT PLAN

6.1 PATIENT POPULATION

The initial cohort of patients will include children (≥ 5 years of age and <21 years of age) with newly-diagnosed or recurrent supratentorial high-grade gliomas (either WHO Grade III anaplastic astrocytoma or WHO Grade IV glioblastoma multiforme) or recurrent supratentorial ependymomas (either WHO Grade II ependymoma or WHO Grade III anaplastic ependymoma).

6.2 PATIENT SELECTION

Patients will primarily be accrued from the pediatric brain tumor population treated at and referred to Hackensack University Medical Center as well as Arnold Palmer Children's Hospital. While the lower age limit for this study is 5 years of age, the patient's head circumference will need to meet the minimum requirement of 44 cm for the Optune NovoTTF-200A device.

Patients will be expected to have received the maximal feasible resection of their tumor and radiation therapy (unless contraindicated due to patient age) as part of their initial treatment prior to study enrollment.

Newly-diagnosed patients must begin therapy within six weeks of the completion of radiotherapy, or within six weeks of surgical resection if radiotherapy is contraindicated. Recurrent patients must begin therapy within six weeks of documented tumor progression by MRI scan.

There is no prior therapy restriction for recurrent high-grade glioma or ependymoma patients receiving treatment with the Optune NovoTTF-200A System.

Patients will be screened for acceptable performance status and bone marrow and organ function prior to enrollment. Females of childbearing age will receive pregnancy screening prior to enrollment.

7.0 PRE-TREATMENT EVALUATIONS

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

- Baseline contrast enhanced MRI of the brain (within 6 weeks of beginning treatment).
- Complete physical examination
- Neurological status exam
- Performance Status (Lansky or Karnofsky)
- Complete blood count (CBC) and differential
- Biochemistry panel (Electrolytes, BUN, creatinine, bilirubin, liver enzymes, albumin, total protein, glucose)
- Coagulation study (PTT, INR)
- Urinalysis (See Section 5.1.13)

8.0 TREATMENT PLAN

All patients will begin treatment with NovoTTF-200A within 7 days from screening/baseline evaluation (See Section 7.0). Newly-diagnosed high-grade glioma patients must begin therapy within six weeks of the completion of radiotherapy, or within six weeks of surgical resection if radiotherapy is contraindicated. Recurrent high-grade glioma and ependymoma patients must begin therapy within six weeks of documented tumor progression by MRI scan.

Patients will report weekly during Cycle 1 of treatment and bi-weekly during Cycle 2 and subsequent cycles to the outpatient clinic where they will be assessed clinically and undergo routine laboratory examinations. . The follow-up window for these visits is +/- 3 days if the visit occurs prior to the 6 month follow-up window and +/- 7 days on or after the 6 month visit window..

Criteria to start Cycle 2 and subsequent cycles include:

- Peripheral absolute neutrophil count (ANC) ≥ 1000/µl
- Platelet Count > 100,000/µl (without transfusion within the last 7 days)
- Serum creatinine ≤ 1.5 x normal for age
- Total bilirubin ≤ 1.5 x normal for age, and SGPT (ALT) < 2.5 x normal for age
- Urinalysis demonstrating < 2+ protein
- The patient has no evidence of progressive disease as assessed clinically and/or by imaging studies
- The patient did not experience a bevacizumab-related targeted toxicity that requires discontinuation or withholding of bevacizumab as listed in Section 9.3

If a patient does not meet criteria to begin a cycle of treatment, treatment with Optune NovoTTF-200A may continue. Temozolomide and bevacizumab administration should be held until the patient meets criteria to begin the next cycle.

8.1 OPTUNE NOVOTTF-200A SYSTEM TREATMENT

The NovoTTF-200A treatment will be initiated in an outpatient clinic by the investigator at each center. In addition to clinical evaluation (see Section 7.0), the investigator will perform the following actions for patients:

- Train the patient in using the device:
    - Battery replacement and recharging
    - Turning the device on and off
    - Disconnecting and reconnecting the electrodes from the device for personal needs
    - How to handle device error messages (see trouble shooting section in User manual)
    - Adverse events that can be expected during the treatment
    - How to handle irritated skin
    - What to do in case of new or worsening clinical signs (call investigator)
- Review of the baseline MRI and decide where to place the electrodes (according to the guidelines elaborated in Section 11.0 below).
- Shave the patients scalp (can be performed by other medical staff in the hospital or by a barber prior to coming to the hospital)
- Place the electrodes
- Connect the electrodes to the device (through the connection cable)
- Turn on the device

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

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

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

The treatment group patients will receive 12 28-day 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. Patients who appear to benefit from this treatment will be allowed to continue treatment beyond 12 cycles if approved by the study Principle Investigator.

Periodic electrode replacement (twice per week) – patients will be trained to replace electrodes independently. Electrodes will be placed in the same locations every time, according to the locations originally decided upon by the investigator unless the patient experiences skin irritation, in which case, they are alternated (see Section 12.0 below).

The following actions are performed by the technician:

- Periodic download of device log (once every 2 weeks)
- Replacement of faulty equipment
- Device, electrode and accessory accountability tracking, and requests for replacements from NovoCure
- Problem solving – by phone between visits to the technical clinic or directly during these visits
- For technical support the patient will contact the local technical clinic. A list of clinics and their contact information will be supplied to the patients separately. If the patient is unable to get a hold of the local device technician or if the patient has technical problems with the device beyond working hours he/she should call the following Toll free number for NovoCure's international support center: 011 - 800 NOVOCURE.

During NovoTTF-200A treatment the patient will be permitted to interrupt treatment for periods that should not, in total, exceed six hours per day (resulting in a minimum of 18 hours of treatment per day) for personal needs. Any pause in treatment beyond this must be coordinated in advance with the principal investigator or one of the co-investigators. Patients will be encouraged to minimize treatment interruptions as the adult study data suggests that treatment exposures of more than 18 hours per day correlated with improved outcomes. Patients will be allowed an additional 1-3 days off treatment between courses according to personal needs.

8.2 TEMOZOLOMIDE TREATMENT

Dose: 200 mg/m^2/day

Administration: Given daily by mouth on Days 1, 2, 3, 4, and 5 of each cycle.

If a patient vomits within 30 minutes after the dose of temozolomide is administered and the capsule is visible, that dose should be repeated. If a patient vomits after 30 minutes, the dose will not be repeated. Patients who have taken a suspension of temozolomide should not be redosed.

8.3 BEVACIZUMAB TREATMENT

Dose: 10 mg/kg/dose

Days: Given intravenously over 90 Minutes on Days 1 and 15 of each cycle. A platelet count of 75,000/μL, with or without platelet transfusion, is required to administer bevacizumab.

Note: Infuse first dose over 90 minutes. If tolerated without infusion-related side effects, the second dose may be given over 60 minutes. If tolerated, may shorten subsequent infusions to 30 minutes. Check vital signs prior to infusion and monitor for infusion-related reactions every 30 minutes and at the end of the infusion. Monitor every 15 minutes while the infusion rate is being adjusted. Routine premedication is not required for the first dose of bevacizumab. If infusion reactions occur, acetaminophen [10-15 mg/kg (max 650 mg)], diphenhydramine [1 mg/kg (max

50 mg)], or other medications may be given for symptom control and for premedication as needed. (See Section 4.3 for concomitant therapy restrictions.) Anaphylactic precautions should be observed during bevacizumab administration. If an infusion reaction occurs, subsequent doses of bevacizumab should be administered over the shortest period that was well-tolerated. Bevacizumab is incompatible with D5W (the drug is inactivated).

Special precautions: Black box warning includes risk of gastrointestinal perforation and wound healing complications (fatal results have occurred). Suspend dosing at least 28 days prior to elective surgery. Do not initiate bevacizumab for at least 28 days after a major surgery (e.g., organ resection, exploratory laparotomy, thoracotomy) or 14 days after intermediate surgical procedure (e.g., paracentesis or thoracocentesis) and until the surgical wound is fully healed. Minor surgical procedures (e.g., biopsies, infusaport, or Broviac line placement) need to have fully healed and occurred > 7 days prior to initiation of bevacizumab.

8.4 THERAPY DELIVERY MAP

Treatment is given in cycles. Each cycle lasts 28 days.
Use a copy of this page once for each cycle. *(Please note cycle number below.)*
This Therapy Delivery Map is on **one (1) page**

_____
Patient Name

_____
DOB

Criteria to start cycle 1: ANC ≥1000/µl, platelets > 100,000/µl (transfusion independent), serum creatinine ≤1.5 x normal for age , total bilirubin ≤1.5 x normal for age, and SGPT (ALT) < 2.5 x normal for age.
Criteria to start cycles 2 through 12: ANC ≥1000/µl, platelets > 100,000/µl (transfusion independent), serum creatinine ≤ 1.5 x normal for age, total bilirubin ≤ 1.5 x normal for age, SGPT (ALT) < 2.5 x normal for age, no bevacizumab-related targeted toxicity that requires discontinuation or withholding of bevacizumab as listed in Section 9.3, and no progressive disease.

Drug	Route	Dose	Days	Important Notes	Observations
Bevacizumab (BEVA)	IV over 90 minutes*	10 mg/kg/dose	Days 1 and 15	*Second infusion may be given over shorter duration if well tolerated. See admin. guidelines in Section 8.3.	a. Hx/PE, Performance status b. CBC/diff/platelets c. BUN/Creatinine/AST/ ALT/bilirubin d. Electrolytes (Ca++, PO4, Mg++) e. Urinalysis for Protein (urine dipstick or UPC ratio) f. MRI of the Head with and without gadolinium **Obtain other studies as required for good patient care**
Temozolomide (TEM)	PO	200 mg/m^2	Days 1-5		

Cycle:_____ Ht:_____cm Wt:_____kg BSA:_____m2

Date Due	Date Given	Week	Day	BEVA	TEM	Studies	Observations
		1	1	_____mg	_____mg	a, b, c, d, e, f*	
			2		_____mg		
			3		_____mg		
			4		_____mg		
			5		_____mg		
			6				
			7				
		2	8				
		3	15	_____mg		a, b, c, d, e	
		4	22				
			29	Begin next cycle on Day 29 or when criteria to begin cycle are met (whichever occurs later). See Section 8.1 for end of therapy evaluations.			

Observation Notes:
* Obtain prior to cycle 1, 3, 6 and then every subsequent 3rd cycle.
+ If urine dipstick is 2+ or greater from protein, hold bevacizumab and obtain UPC ratio within 3 days of Day 1 dose of bevacizumab. See bevacizumab dose modifications for proteinuria (Section 9.3). If UPC ratio is > 1, collection of 24 hour urine for measurement of urine protein level is recommended but not required.

9.0 DOSE MODIFICATIONS FOR TOXICITY

The following dose modifications for toxicities are for use during the study. Notify the Study Chair at the time of removing a patient from protocol therapy for toxicity.

9.1 HEMATOLOGIC TOXICITY

Every cycle of therapy containing temozolomide should begin when ANC ≥ 1000/µL and platelet count ≥ 100,000/µL. If either ANC and/or platelet count is lower than the above parameters chemotherapy should be held. Then repeat counts should be drawn a twice weekly until counts reach the required levels. If there is a greater than 2 week delay in the resumption of temozolomide, then decrease the dose of the drug in the previous course by 25%.

9.2 – NON-HEMATOLOGIC TOXICITY

Patients with toxicity attributed to bevacizumab but not listed in Section 9.3 may continue on study provided the toxicity is reversible to eligibility requirements within 14 days after the planned start of the next treatment course. Patients who have any Grade 3 or 4 non-hematologic toxicity that does not resolve to meet starting criteria by 14 days after the planned start of the next cycle must be removed from protocol therapy.

9.2.1 Hepatotoxicity

If grade 3-4 toxicity develops, hold chemotherapy until toxicity is less than grade 2. For the purposes of the phase I study, grade 3-4 hepatotoxicity would be considered a dose-limiting toxicity. If the etiology of the toxicity is unexplained, then the dose of temozolomide, should be reduced by 25%.

9.3 BEVACIZUMAB DOSE MODIFICATIONS

There will be no dose reductions made for toxicity related to bevacizumab. Treatment should be interrupted or discontinued for certain adverse events, as described in the table below. If bevacizumab is held and a patient cannot resume treatment before the stipulated time for the particular toxicity, the patient will be taken off protocol therapy.

DOSE MODIFICATIONS FOR BEVACIZUMAB-RELATED ADVERSE EVENTS

Event	CTCAE v 5.0 Grade	Action to be Taken
Allergic reactions, **Or** **Infusion-related reactions** **OR** **Anaphylaxis**	Grade 1-2	Infusion of bevacizumab should be interrupted for subjects who develop dyspnea or clinically significant hypotension. For infusion-associated symptoms not specified above, infusion should be slowed to 50% or less or interrupted. Upon complete or resolution of the symptoms, infusion may be continued at no more than 50% of the rate prior to the reaction and increased in 50% increments every 30 minutes if well tolerated. Infusions may be restarted at the full rate during the next cycle. If infusional reactions occur, acetaminophen [10-15 mg/kg (max 650 mg)], diphenhydramine [1 mg/kg (max 50 mg)], or other medications may be given for symptom control and for premedication as needed. (See Section 4.2 for concomitant therapy restrictions.) Subjects who experience bronchospasm (regardless of grade) should discontinue bevacizumab.
	Grade 3-4	Discontinue bevacizumab.
Thromboembolic Event (Arterial); arterial ischemia • Cardiac ischemia • Myocardial infarction • CNS ischemia (TIA, CVA) • Any peripheral or visceral arterial ischemia/thrombosis	Grade 2 (if new or worsened since bevacizumab therapy)	Discontinue bevacizumab.
	Grade 3-4	Discontinue bevacizumab.

Event	CTCAE v 5.0 Grade	Action to be Taken
Thromboembolic Event (Venous)	Grade 3 OR asymptomatic Grade 4	Hold bevacizumab treatment. If the planned duration of full-dose anticoagulation is < 2 weeks, bevacizumab should be held until the full-dose anticoagulation period is over. If the planned duration of full-dose anticoagulation is > 2 weeks, bevacizumab may be resumed during the period of full-dose anticoagulation **IF** all of the criteria below are met: - The subject must not have pathological conditions that carry high risk of bleeding (e.g. tumor involving major vessels or other conditions). - The subject must not have had hemorrhagic events while on study. - The subject must be on stable dose of heparin or have an in-range INR (usually 2-3) on a stable dose of warfarin prior to restarting bevacizumab. If thromboemboli worsen/recur upon resumption of study therapy, discontinue bevacizumab.
	Grade 4 (symptomatic)	Discontinue bevacizumab.
Hypertension* **Use age and height appropriate normal values** **> 95th percentile ULN for pediatric patients** **(see Appendices I and II)**	[Treat with anti-hypertensive medication as needed. The goal of BP control should be consistent with general medical practice.]	
	Grade 1 If age ≤ 17 years: Asymptomatic, transient (< 24 hrs) BP increase >ULN; intervention not indicated. If age > 17 years: (SBP 120-139 mmHg or DBP 80-89 mm Hg)	Consider increased BP monitoring; start antihypertensive medication if appropriate
	Grade 2 asymptomatic: If age ≤ 17 years: Recurrent or persistent (≥ 24 hrs) BP > ULN; If age > 17 years: (SBP 140-159 mmHg or DBP 90-99 mm Hg)	If age ≤ 17 years: monotherapy indicated continue bevacizumab. If age > 17 years: Begin anti-hypertensive therapy and continue bevacizumab.
	Grade 2 symptomatic: **OR** Grade 3: (>17 years: SBP >160mmHg or DBP >100mmHg) requiring more than one drug or more intensive therapy than previously (all ages)	- Start or adjust anti-hypertensive therapy - Hold bevacizumab until symptoms resolve **AND** BP < 95th percentile ULN for age and height, if age ≤ 17 years; or

		BP < 160/90mmHg if age > 17 years.
	Grade 4: (all ages) life threatening (e.g. hypertensive crisis or malignant hypertension)	Discontinue bevacizumab.
Event	**CTCAE v 5.0 Grade**	**Action to be Taken**
Heart Failure or LV dysfunction	Heart failure ≥ grade 2 LV dysfunction ≥ grade 3	Discontinue bevacizumab.
Proteinuria Proteinuria will be monitored by urine analysis for urine protein creatinine (UPC) ratio, or dipstick If Dipstick ≥ 2+ proteinuria or UPC ratio ≥ 1, 24 hour urine protein should be obtained	If 24-h urine protein < 2.0gm	- Hold bevacizumab until 24-h urine protein < 2 gm. - Discontinue bevacizumab if urine protein does not recover to < 2 after 8 weeks of bevacizumab interruption
	Grade 4 or nephrotic syndrome	Discontinue bevacizumab.
Hemorrhage (intracranial or pulmonary)	Grade 3	-Patients receiving full-dose anticoagulation should discontinue bevacizumab . - For patients not on full-dose anticoagulation, hold bevacizumab until ALL of the following criteria are met: - the bleeding has resolved and Hb is stable; - there is no bleeding diathesis that would increase the risk of therapy; - there is no anatomic or pathologic condition that could increase the risk of hemorrhage recurrence. - Patients who experience recurrence of Grade 3 hemorrhage should discontinue study therapy.
	Grade 4	Discontinue bevacizumab.
RPLS (Reversible Posterior Leukoencephalopathy syndrome **or PRES** (Posterior Reversible Encephalopathy Syndrome)		▪ Hold bevacizumab in patients with symptoms/signs suggestive of RPLS; subsequent management should include MRI scans and control of HTN. ▪ Discontinue bevacizumab upon diagnosis of RPLS.
Wound dehiscence requiring medical or surgical intervention or wound complications	Grade 2	Hold bevacizumab until healing
	Grade 3-4	Discontinue bevacizumab.
Perforation (GI or any other organ)		Discontinue bevacizumab.
Fistula (GI, pulmonary or any other organ)		Discontinue bevacizumab.
Obstruction of GI tract	Grade 2 requiring medical intervention	▪ Hold bevacizumab until complete resolution.

	Grade 3-4	▪ Hold bevacizumab until complete resolution. ▪ If surgery is required, patient may restart bevacizumab after full recovery from surgery, and at investigator's discretion.
Other Unspecified bevacizumab-related AEs (except controlled nausea/vomiting).	Grade 3	▪ Hold bevacizumab until symptoms resolve to ≤ grade 1
	Grade 4	Discontinue bevacizumab.

9.3.1 GUIDELINES FOR CNS HEMORRHAGE (PUNCTUATE LESIONS)

Definition of punctate hemorrhage identified by neuroimaging:

Punctate hemorrhage on neuroimaging refers to:
1. Small (< 2mm) foci of presumed hemorrhagic signal within the lesion often demonstrated by GRE techniques, without associated mass effect.

2. Curvilinear areas of hemorrhagic signal (< 2 mm thickness) surrounding the lesion, often seen with high grade glial tumors. This would include areas identified only on GRE sequences (presumably related to hemosiderin deposition).

Patients with punctate hemorrhage will be allowed to continue bevacizumab therapy but will be closely monitored for signs and symptoms of worsening hemorrhage. In such an event, repeat neuroimaging studies should be obtained including CT scan of head followed by MRI scan of brain with GRE sequences. Patients with worsening hemorrhage should be taken off bevacizumab. This action would also apply to those who are asymptomatic and are found to have worsening hemorrhage on a subsequent routine MRI scan of the brain.

9.3.2 SURGICAL PROCEDURES

Patients may not have had a planned major surgical procedure (such as resection of recurrent disease) within 28 days of initiating bevacizumab. If major surgery for local control is planned during study therapy for a patient on bevacizumab, then the bevacizumab should be held for one cycle prior and for 28 days post definitive resection, unless the patient has had a significant post-operative wound complication that, in the opinion of the investigator, would preclude bevacizumab administration. In this clinical situation post-operative bevacizumab should be withheld for longer. These restrictions are due to concerns of delayed wound healing and hemorrhage. Minor surgical procedures (e.g., biopsies, vascular catheter placement, G-tube) need to have fully healed and occurred > 7 days prior to initiating bevacizumab.

10.0 DRUG INFORMATION

Drugs are listed in alphabetical order.

10.1 BEVACIZUMAB (rhuMAb VEGF, Avastin®) NSC# 704865 IND # 7921 (11/08/11)

Source and Pharmacology:

Bevacizumab is a recombinant humanized anti-vascular endothelial growth factor (anti-VEGF) monoclonal antibody, consisting of 93% human and 7% murine amino acid sequences. The agent is composed of human IgG framework and murine antigen-binding complementarity-determining regions. Bevacizumab approximate molecular weight is 149,000 daltons. Bevacizumab blocks the binding of VEGF to its receptors resulting in inhibition of angiogenesis.

The estimated half-life of bevacizumab is approximately 20 days (range 11-50 days). The predicted time to reach steady state was 100 days in 491 patients who received 1 to 20 mg/kg weekly, every 2 weeks, or every 3 weeks. The clearance and the central volume of distribution are higher in males than females. Clearance was higher in those patients with a higher tumor volume.

Toxicity:

Comprehensive Adverse Events and Potential Risks list (CAEPR) For Bevacizumab (rhuMAb VEGF, NSC 704865)

The Comprehensive Adverse Event and Potential Risks list (CAEPR) provides a single list of reported and/or potential adverse events (AE) associated with an agent using a uniform presentation of events by body system.

Adverse Events with Possible Relationship to Bevacizumab (rhuMAb VEGF) (CTCAE 5.0 Term)		
Likely (> 20%)	**Less Likely (≤ 20%)**	**Rare but Serious (< 3%)**
BLOOD AND LYMPHATIC SYSTEM DISORDERS		
	• Anemia • Febrile neutropenia	• Blood and lymphatic system disorders – Other (renal thrombotic microangiopathy)
CARDIAC DISORDERS		
	• Supraventricular tachycardia	• Acute coronary syndrome • Heart failure • Left ventricular systolic dysfunction • Myocardial infarction • Ventricular arrhythmia • Ventricular fibrillation
EAR AND LABYRINTH DISORDERS		
	• Vertigo	

GASTROINTESTINAL DISORDERS		
	• Abdominal pain • Colitis • Constipation • Diarrhea • Dyspepsia • Gastrointestinal hemorrhage[2] • Gastrointestinal obstruction[3] • Ileus • Mucositis oral • Nausea • Vomiting	• Gastrointestinal fistula[1] • Gastrointestinal perforation[4] • Gastrointestinal ulcer[5]
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS		
	• Fatigue • Infusion related reaction • Non-cardiac chest pain • Pain	
IMMUNE SYSTEM DISORDERS		
	• Allergic reaction	• Anaphylaxis
INFECTIONS AND INFESTATIONS		
	• Infection[6] • Infections and infestations - Other (peri-rectal abscess) • Wound dehiscence	• Gastrointestinal anastomotic leak
INVESTIGATIONS		

	• Alanine aminotransferase increased • Alkaline phosphatase increased • Aspartate aminotransferase increased • Blood bilirubin increased • Cardiac troponin I increased • Neutrophil count decreased • Weight loss • White blood cell decreased	
METABOLISM AND NUTRITION DISORDERS		
	• Anorexia	
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS		
	• Arthralgia • Musculoskeletal and connective tissue disorder - Other (bone metaphyseal dysplasia)[7] • Myalgia • Osteonecrosis of jaw[8]	
NERVOUS SYSTEM DISORDERS		
	• Dizziness • Headache • Peripheral sensory neuropathy[9] • Syncope	• Intracranial hemorrhage • Ischemia cerebrovascular • Reversible posterior Leukoencephalopathy syndrome
RENAL AND URINARY DISORDERS		
	• Hematuria • Proteinuria	• Acute kidney injury • Renal and urinary disorders – Other (Nephrotic Syndrome) • Urinary fistula
REPRODUCTIVE SYSTEM AND BREAST DISORDERS		

• Reproductive system and breast disorders - Other (ovarian failure)[10]	• Vaginal hemorrhage	• Vaginal fistula
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS		
	• Allergic rhinitis • Cough • Dyspnea • Epistaxis • Hoarseness	• Bronchopleural fistula • Bronchopulmonary hemorrhage • Respiratory, thoracic and mediastinal disorders - Other (nasal-septal perforation) • Respiratory, thoracic and mediastinal disorders - Other (tracheoesophageal fistula)
SKIN AND SUBCUTANEOUS TISSUE DISORDERS		
	• Pruritus • Rash maculo-papular • Urticaria	
VASCULAR DISORDERS		
• Hypertension	• Thromboembolic event	• Vascular disorders – Other (arterial thromboembolic event)[11]

[1]Gastrointestinal fistula may include: Anal fistula, Colonic fistula, Duodenal fistula, Esophageal fistula, Gastric fistula, Gastrointestinal fistula, Rectal fistula, and other sites under the GASTROINTESTINAL DISORDERS SOC.
[2]Gastrointestinal hemorrhage may include: Colonic hemorrhage, Duodenal hemorrhage, Esophageal hemorrhage, Esophageal varices hemorrhage, Gastric hemorrhage, Hemorrhoidal hemorrhage, Intraabdominal hemorrhage, Oral hemorrhage, Rectal hemorrhage, and other sites under the GASTROINTESTINAL DISORDERS SOC.
[3]Gastrointestinal obstruction may include: Colonic obstruction, Duodenal obstruction, Esophageal obstruction, Ileal obstruction, Jejunal obstruction, Rectal obstruction, Small intestinal obstruction, and other sites under the GASTROINTESTINAL DISORDERS SOC.
[4]Gastrointestinal perforation may include: Colonic perforation, Duodenal perforation, Esophageal perforation, Gastric perforation, Jejunal perforation, Rectal perforation, Small intestinal perforation, and other sites under the GASTROINTESTINAL DISORDERS SOC.
[5]Gastrointestinal ulcer may include: Duodenal ulcer, Esophageal ulcer, Gastric ulcer, and other sites under the GASTROINTESTINAL DISORDERS SOC.
[6]Infection may include any of the 75 infection sites under the INFECTIONS AND INFESTATIONS SOC.
[7]Metaphyseal dysplasia was observed in young patients who still have active epiphyseal growth plates.
[8]Cases of osteonecrosis of the jaw (ONJ) have been reported in cancer patients in association with bevacizumab treatment, the majority of whom had received prior or concomitant treatment with i.v. bisphosphonates.
[9]Increased rate of peripheral sensory neuropathy has been observed in trials combining bevacizumab and chemotherapy compared to chemotherapy alone.
[10]Ovarian failure, defined as amenorrhea lasting 3 or more months with follicle-stimulating hormone (FSH) elevation (≥30 mIU/mL), was increased in patients receiving adjuvant bevacizumab plus mFOLFOX compared to mFOLFOX alone (34% vs. 2%). After discontinuation of bevacizumab, resumption of menses and an FSH level <30 mIU/mL was demonstrated in 22% (7/32) of these women. Long term effects of bevacizumab exposure on fertility are unknown.
[11]Arterial thromboembolic event includes visceral arterial ischemia, peripheral arterial ischemia, heart attack, and stroke.

Also reported on Bevacizumab (rhuMAb VEGF) trials but with the relationship to Bevacizumab (rhuMAb VEGF) still undetermined:

BLOOD AND LYMPHATIC SYSTEM DISORDERS - Blood and lymphatic system disorders – Other (idiopathic thrombocytopenia purpura); Disseminated intravascular coagulation
CARDIAC DISORDERS - Pericardial effusion
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS - Gait disturbance; Sudden death NOS
HEPATOBILIARY DISORDERS - Hepatic failure
INFECTIONS AND INFESTATIONS - Infections and infestations - Other (aseptic meningitis)
INVESTIGATIONS - Platelet count decreased
METABOLISM AND NUTRITION DISORDERS - Hyponatremia
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS - Musculoskeletal and connective tissue disorder - Other (aseptic necrotic bone); Musculoskeletal and connective tissue disorder – Other (myasthenia gravis)
NERVOUS SYSTEM DISORDERS - Dysgeusia; Peripheral motor neuropathy; Seizure
PSYCHIATRIC DISORDERS - Confusion
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS - Adult respiratory distress syndrome; Pneumonitis; Pneumothorax; Pulmonary hypertension
SKIN AND SUBCUTANEOUS TISSUE DISORDERS - Palmar-plantar erythrodysesthesia syndrome; Skin ulceration

Note: Bevacizumab (rhuMAb VEGF) in combination with other agents could cause an exacerbation of any adverse event currently known to be caused by the other agent, or the combination may result in events never previously associated with either agent.

Effect in Pregnancy and Lactation:
Bevacizumab has been shown to be teratogenic in rabbits when administered in doses that are two-fold greater than the recommended human dose on a mg/kg basis. Observed effects included decreases in maternal and fetal body weights, an increased number of fetal resorption, and an increased incidence of specific gross and skeletal fetal alterations. Adverse fetal outcomes were observed at all doses tested. Angiogenesis is critical to fetal development and the inhibition of angiogenesis following administration of Bevacizumab is likely to result in adverse effects on pregnancy. It is not known whether Bevacizumab is secreted in human milk. Because human IgG1 is secreted into human milk, the potential for absorption and harm to the infant after ingestion is unknown.

Effect on Growth and Development:
Studies of bevacizumab in animals showed a decrease in ovarian function and abnormal bone growth. These and other effects of bevacizumab may potentially impair growth and development. Abnormal changes in the bones after treatment with bevacizumab have been observed in young children with growing bones. This side effect appeared to be reversible after the treatment was stopped, but has not been assessed with long-term use of the drug.

Formulation and Stability: Bevacizumab is supplied as a clear to slightly opalescent, sterile liquid ready for parenteral administration. Each 400 mg (25mg/mL, 16 mL fill) glass vial

contains bevacizumab with phosphate, trehalose, polysorbate 20, and Sterile Water for Injection, USP. Upon receipt, refrigerate the intact bevacizumab vials at 2-8°C (36-46°F). Store in the outer carton to protect bevacizumab vials from light. Do not freeze. Do not shake.

Bevacizumab vials contain no antibacterial preservatives and are labeled for single use. Discard any unused portion left in the vial immediately after use.

Guidelines for Administration: See Treatment and Dose Modification sections of the protocol. Do not administer as an intravenous (IV) push or bolus. Prior to administration, dilute the dose in 0.9% sodium chloride for injection to a final concentration of 1.4-16.5 mg/mL. Inspect visually for particulate matter and discoloration prior to administration.

The chemical and physical stability of the diluted solution in 0.9% sodium chloride is 48 hours at 2°C- 30°C. From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions are the responsibility of the user and would normally not be longer than 24 hours at 2°C to 8°C, unless dilution has taken place in controlled and validated aseptic conditions. Bevacizumab is incompatible with D5W.
To ensure complete delivery of bevacizumab IV infusion line must be flushed with 0.9% sodium chloride. The following are two recommended methods for flushing the line:

1. When the bevacizumab infusion is complete, while maintaining a closed system, add an additional 50mL of 0.9% sodium chloride for injection to the bevacizumab infusion bag. Continue the infusion until a volume equal to that of the volume contained in the tubing has been administered.
2. Replace the empty bevacizumab infusion bag with a 50mL bag of 0.9% sodium chloride for injection and infuse a volume equal to the volume contained in the tubing. Please note: the flush is not included in the total recommended infusion times.

Supplier: Commercially available. See package insert for further information.

10.2 TEMOZOLOMIDE (Temodar TM) NSC# 362856 (082005)

Source and Pharmacology: An orally administered alkylating agent, a second generation imadazotetrazine. A prodrug of MTIC, temozolomide spontaneously decomposes to MTIC at physiologic pH. The drug exerts its effect by cross-linking DNA. This is likely a site specific alkylation at the O6-position of guanine with some effect at the N7 position. Temozolomide reaches its peak concentration in 1 hour. Food reduces the rate and extent of absorption. It has an elimination half-life of 1.13hr (intraperitoneally) and 1.29hr (orally) with an oral bioavailability of 0.98. Total apparent body clearance is 100ml/min/m^2 and plasma elimination half-life is ~100 minutes.

Toxicity:

	Common Happens to 21-100 out of every 100 children	**Occasional** Happens to 5-20 children out of every 100	**Rare** Happens to <5 children out of every 100
Immediate:	Anorexia, constipation,	abdominal pain, diarrhea,	Convulsions, anaphylaxis,

Within 1-2 days of receiving drug	nausea, vomiting	headache, rash, itching, urinary frequency and/or infection	hemiparesis, dizziness, ataxia, confusion, dysphagia, anxiety, thrombo-embolism (L)
Prompt: Within 2-3 weeks, prior to the next course	Myelosuppression	Mucositis, lethargy, peripheral edema	Prolonged lymphopenia with increased risk of infection or death, amnesia, insomnia, depression, myalgia, diplopia, visual changes
Delayed: Any time later during therapy		Alopecia, hepatotoxicity	
Late: Any time after completion of treatment			Secondary tumors or cancer

Formulation and Stability: 5mg, 20mg, 100mg, 250mg capsules, stored at room temperature

Guidelines for Administration: See Treatment and Dose Modifications sections of the protocol. There is a potential for medication errors involving Temodar capsules resulting in drug overdosages, which may have been caused by dispensing/taking the wrong number of capsules per day and/or product usage exceeding the prescribed dosing schedule. Temodar capsules are available in four different strengths, each a different size, and are color coded according to strength. All capsules are available in 5-count and 20-count packages.

Capsule Strength	**COLOR**
5 mg	Green Imprint
20 mg	Brown Imprint
100 mg	Blue Imprint
250 mg	Black Imprint

When dispensing, it is extremely important that prescribing and dispensing include clear instructions on which capsules, and how many of each capsule(s) are to be taken per day. Only dispense what is needed for the course, and clearly indicate how many days of dosing the patient will have and how many days are without Temodar dosing. When counseling patients, it is important for each patient/parent to understand the number of capsules per day and the number of days that they take Temodar. It is also important for the patient/parent to understand the number of days that they will be off the medication.

Each strength of Temodar must be dispensed in a separate vial or in its original glass bottle. Based on the dose prescribed, determine the number of each strength of Temodar capsules needed for the full course as prescribed by the physician. For example, 275 mg/day for 5 days would be dispensed as five 250-mg capsules, five 20-mg capsules, and five 5-mg capsules. Label each container with the appropriate number of capsules to be taken each day. Dispense to the patient/parent, making sure each container lists the strength (mg) per capsule and that he or she understands to take the appropriate number of capsules of Temodar from each bottle or vial to equal the total daily dose prescribed by the physician.

Supplier: Commercially available. See package insert for further information

11.0 ELECTRODE PLACEMENT PROTOCOL

The specific locations of each electrode set will be approved by the treating investigator using the NovoTAL™ system (Novocure Ltd., Haifa, Israel). The NovoTal™ system is approved in the United States to produce a personalized transducer array layout to maximize the intensity of TTFields within the tumor on the basis of morphologic measurements of the head, tumor size, and location(s). Personalized treatment planning can result in an almost doubling of field intensity directed to the tumor bed in simulation studies.

Initial morphometric head size measurements will be determined from the T1 sequences of the patient's brain MRI, using axial and coronal views. Postcontrast axial and coronal MRI slices will be selected to demonstrate the maximal diameter of enhancing lesions. Employing measures of head size and distances from predetermined fiducial markers to tumor margins, the

NovoTAL™ system will run permutations and combinations of paired array layouts in order to generate the configuration which will deliver maximal electric field intensity to the tumor site. The system will output a three-dimensional array layout map, which will be used by the physician and patient in arranging arrays on the scalp during the TTFields therapy.

In a study evaluating physician performance in conducting transducer array layout mapping using the NovoTAL System compared with mapping performed by the Novocure in-house clinical team, fourteen physicians (7 neuro-oncologists, 4 medical oncologists, and 3 neurosurgeons) evaluated five blinded cases of recurrent glioblastoma and performed head size and tumor location measurements using a standard Digital Imaging and Communications in Medicine reader.[45] Concordance with Novocure measurement and intra- and inter-rater reliability were assessed using relevant correlation coefficients. The study criterion for success was a concordance correlation coefficient (CCC) >0.80. CCC for each physician versus Novocure on 20 MRI measurements was 0.96 (standard deviation, SD ± 0.03, range 0.90–1.00), indicating very high agreement between the two groups. Intra- and inter-rater reliability correlation coefficients were similarly high: 0.83 (SD ±0.15, range 0.54–1.00) and 0.80 (SD ±0.18, range 0.48–1.00), respectively. The study concluded that physicians prescribing TTFields, when trained on the NovoTAL System, can independently perform transducer array layout mapping required for the initiation and maintenance of patients on TTFields therapy

All electrode mapping for this study will be done by a treating investigator who has been trained in NovoTAL™ mapping. In the event that a trained investigator is not available to perform the electrode mapping, the patient's MRI scans will be sent to Novocure for mapping.

12.0 EVALUATIONS DURING NOVOTTF-200A TREATMENT

During electrode replacement, the skin below the electrode will be inspected by the physician (during follow up visits) and by the patient himself or herself (at home or technical center). In the event of significant skin breakdown (leading to pain or bleeding) or evidence of infection, the electrode will be moved to an alternate site. Skin breakdown and/or infection will be treated according to the treating physician's clinical judgment based on a dermatologist's recommendation.

Skin breakdown or evidence of infection, either of which requires a break in NovoTTF-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 – Discontinue hydrocortisone and prescribe a Mupirocin (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.

13.0 SCHEDULE OF ASSESSMENTS

Timing of protocol therapy administration, response assessment studies, and surgical interventions are based on schedules derived from the experimental design or on established standards of care. Minor unavoidable departures (up to 72 hours) from protocol directed therapy and/or disease evaluations (and up to 1 week for surgery) for valid clinical, patient and family logistical, or facility, procedure and/or anesthesia scheduling issues are acceptable, except where explicitly prohibited within the protocol.

13.1 REQUIRED ASSESSMENTS BEFORE AND DURING PROTOCOL THERAPY

		Cycle 1				Cycle 2						
	Screening	**Visit 1**	**Visit 2**	**Visit 3**	**Visit 4**	**Visit 5**	**Visit 6**	**Visit 7**		**Continued Therapy**		**End of Therapy / Progression**
PROCEDURE	**Baseline**	**Wk 1 (D1)**	**Wk 2# (D8)**	**Wk 3 (D15)**	**Wk 4# (D22)**	**Wk 1 (D1)**	**Wk 3 (D15)**	**Wk 5 (D29)**		**Every 2 Weeks**		
Informed Consent	X											
Inclusion/ Exclusion Criteria	X											
Medical History	X											
Vital Signs	X	X	X	X	X	X	X	X		X		X
Physical Exam	X	X	X	X	X	X	X	X		X		X
Neurological Status	X	X	X	X	X	X	X	X		X		X
QOL Questionnaires[5]						X				X[6]		X
Concomitant Meds	X	X	X	X	X	X	X	X		X[7]		X
LOCAL LABS												
Hematology	X	X	X	X	X	X	X	X		X		X
Electrolytes, BUN, Cr, t.bili, AST, ALT ,Ca, PO4, Mg	X	X	X	X	X	X	X	X		X		X
Urinalysis 1,2	X	X		X		X	X	X		X		
PT/INR	X											
RADIOLOGY												
MRI - Brain 3	X							X		X* q 3 months		X
TREATMENT												
Temozolomide		Days 1-5				Days 1-5				Days 1-5		
Bevacizumab		Day 1		Day 15		Day 1	Day 15			Days 1 and 15		
NovoTTF-200A Study Device 4		X	X	X	X	X	X	X		X		
NovoTTF-200A Study Device TX Initiation		X										
OTHER												
Adverse Events	X	X	X	X	X	X	X	X		X		X
Concomitant Medications	X	X	X	X	X	X	X	X		X		X

* screening MRI should be done within 4 weeks of starting study, MRI of the brain is performed at the end of Cycle 2, and then routinely q 3 months or if there is a clinical change with signs of progression

Cycle 1 Week 2 and Week 4 visits are not required for patients enrolled on the expansion cohort

Screening/Baseline assessments can be done with Visit 1 prior to administration of chemotherapy and placement of electrodes.

1. Urine protein should be screened by urine analysis. If 2+ on urinalysis, then Urine Protein Creatinine (UPC) ratio should be calculated. If UPC ratio > 0.5, 24-hour urine protein should be obtained and the level should be < 1000 mg for patient enrollment. See Section 5.1.13

regarding calculation of UPC ratio.
2. If urine dipstick is 2+ or greater from protein, hold bevacizumab and obtain UPC ratio within 3 days of Day 1 dose of bevacizumab. See bevacizumab dose modifications for proteinuria (Section 9.3). If UPC ratio is ≥ 1, 24 hour urine protein should be obtained.
3. MRI with or without sedation
4. Treatment is administered continuously throughout the study
5. Patient Questionnaire to be administered to patients aged 8 and above at clinicians' discretion. All patients will have completed parent questionnaires.
6. Obtain QOL Questionnaires on first day of each cycle beginning with cycle 2
7. Concomitant medication logs to be maintained on site from 30 days prior to initiation of device through 30 days safety period.

13.2 OPTIONAL ASSESSMENTS BEFORE AND DURING PROTOCOL THERAPY

The effects of TTFields on the developing brain are currently unknown. While this small phase I study is not powered or designed to evaluate effects on developmental outcomes from therapy with Optune, neuropsychological data from study subjects may provide useful information for shaping larger future studies of TTFields in the pediatric population.

Neuropsychological evaluations are routinely performed as part of the standard care for pediatric brain tumor patients. Data from the study subject's routine neuropsychological evaluations will be collected and analyzed as part of the exploratory objective of assessing the effects of Optune therapy on the developing brain. These neuropsychological evaluations are not required and should be ordered at the discretion of the subject's primary oncologist as per the routine care of the study subject.

14.0 STUDY MONITORING AND DATA COLLECTION

14.1 DATA SAFETY MONITORING BOARD (DSMB):

This study will be monitored by the DSMB at Hackensack University Medical Center, which functions independently of all other investigators associated with the conduct of this clinical trial. Safety of the investigational device will be assessed on a monthly basis once patients are enrolled.

It is envisioned that the DSMB will make 3 types of recommendations, namely:

1. No safety or ethical issues to continue the study as planned
2. Serious safety concerns precluding further study treatment, regardless of efficacy
3. Recommendation to continue the study but proposing an amendment to the protocol (ex. To incorporate additional safety assessments)

14.2 DATA COLLECTION AND MANAGEMENT:

Information about study patients will be kept confidential and managed under the applicable laws and regulations. Those regulations require a signed patient authorization informing the patient of the following:

1. What protected health information (PHI) will be collected from patients in this study
2. Who will have access to that information and why
3. Who will use or disclose that information

4. The rights of a research patient to revoke their authorization for use of their PHI.

In the event that a patient revokes authorization to collect or use PHI, the investigator, by regulation, retains the ability to use all information collected prior to the revocation of patient authorization. For patients that have revoked authorization to collect or use PHI, attempts must be made to obtain permission to collect follow-up safety information (e.g., has the patient experienced any new or worsened AEs) at the end of their scheduled study period.

Data collected during conduct of the study will be reported to Hackensack University Medical Center on Case Report Forms and sent to Study Research Nurse Coordinator via secure email. The schedule of form submission is below:

14.3 DATA FORM SUBMISSION SCHEDULE

DATA FORM SUBMISSION SCHEDULE
Forms to be submitted to Fax: (201) 968-0518
Or electronically to: Sherri.Mayans@hmhn.org

Required Form	Prior to Therapy	Within 2 Week of Study Entry	After Completion of Each Cycle	Comments and other details
Protocol Eligibility Form	X			
Demographic Form	X			
Baseline Abnormalities	X			
Copy of Signed Consent Form	X			
Baseline MRI form (with MRI report)	X			
On Study Form		X		
Neurosurgical Resection Form (with surgical and pathology reports)		X		
Initial (post-op) Neuroradiological Form (with post-op imaging reports)		X		
End of Cycle Report Form			X	
Targeted and Non-targeted Toxicity Form			X	
Adverse Event Form			X	
MRI follow up form			X	Submit at these Intervals: After cycle 2, then every 3months, end of therapy

Parent and Patient[1] QOL Questionnaires			X	Complete at the start of each cycle beginning with cycle 2
Serious Adverse Event Form				PRN
Brain Tumor Relapse Form (with imaging reports)				Submit within 10 days of disease progression/relapse
Death Registration Form				Submit within 10 days of date of death

[1] Patient Questionnaire to be administered to patients aged 8 and above at clinicians' discretion. All patients will have completed parent questionnaires.

14.4 SITE MONITORING:

Before study initiation, at a site initiation visit or at an investigator's meeting, personnel from Hackensack University Medical Center or designee will review the protocol and eCRFs with the investigators and their staff. During the study, the field monitor will visit the site regularly to check the completeness of patient records, the accuracy of entries on the CRFs, the adherence to the protocol to Good Clinical Practice, the progress of enrollment, and to ensure that study device is utilized according to specifications.

Key study personnel must be available to assist the field monitor during these visits. The investigator must maintain source documents for each patient in the study, consisting of case and visit notes (hospital or clinic medical records) containing demographic and medical information, laboratory data, electrocardiograms, and the results of any other tests or assessments. All information recorded on CRFs must be traceable to source documents in the patient's file. The investigator must also keep the original signed informed consent form (a signed copy is given to the patient). The investigator must give the monitor access to all relevant source documents to confirm their consistency with the CRF entries. Monitoring standards require full verification for the presence of informed consent, adherence to the inclusion/exclusion criteria and documentation of SAEs. Additional checks of the consistency of the source data with the CRFs are performed according to the study-specific monitoring plan.

The monitor will review the trial sites, either remotely or in person at the following time points:

1. Site initiation visit
2. After enrollment of the first study patient
3. During active enrollment at minimum once a year
4. Study close out

Monitor visits will be documented on the Monitoring Site Visit Log that will be provided to sites. Query management may be performed via email or separate written document and should be filed in the ISF.

15.0 SURGICAL GUIDELINES

The extent of surgical tumor resection will depend upon the location of the tumor within the brain, and its vascularity. Surgical debulking of recurrent tumors should be attempted as clinically indicated.

15.1 EXTENT OF RESECTION

Patients will be classified as follows:

Biopsy Only
An open surgical removal or closed removal of tissue for the purpose of establishing a pathological diagnosis, with tumor removal less than 10% of the total tumor mass.

Partial Resection
Removal of 10% to 49% of the tumor mass.

Subtotal Resection
Removal of 50% to 90% of the tumor mass.

Radical Subtotal Resection (Near Total)
Removal of >90% but less than 100% of the tumor mass.

Gross Total Resection
No visible tumor is left at the time of surgery and this is confirmed by postoperative CT or MRI.

15.2 IMAGING CONFIRMATION OF EXTENT OF RESECTION

See Section 16.0 for Neuroimaging Guidelines. All patients must have confirmation of the neurosurgical staging of the extent of resection with a postoperative MRI with and without contrast. Post-operative imaging of the brain should be done within 72 hours of surgery if possible (preferably within 24 hours of surgery), and prior to the onset of edema or gliosis which can make measurements of residual tumor difficult. If imaging cannot be obtained at this time or is difficult to interpret, the scan should be repeated 10 or more days after surgery.

15.3 PERI-OPERATIVE CORTICOSTEROIDS

Some patients with large tumors may require initiation of corticosteroid therapy pre-operatively to reduce associated cerebral edema or improve neurologic function. Usual corticosteroid dosage

is 0.25 to 1 mg/kg/day of, dexamethasone in divided doses every 4-6 hours. Corticosteroids may be continued during the peri-operative period; however, every attempt should be made to taper and discontinue corticosteroid therapy as soon as clinically feasible.

15.4 SPECIAL PRECAUTIONS FOR BEVACIZUMAB

Black box warning includes risk of gastrointestinal perforation and wound healing complications (fatal results have occurred). Suspend dosing at least 28 days prior to elective surgery. Do not initiate bevacizumab for at least 28 days after a major surgery (e.g., organ resection, exploratory laparotomy, thoracotomy) or 14 days after intermediate surgical procedure (e.g., paracentesis or thoracocentesis, ventriculoperitoneal shunt insertion) **and** until the surgical wound is fully healed. Minor surgical procedures (e.g., biopsies, infusaport, or Broviac line placement) need to have fully healed **and** occurred > 7 days prior to initiation of bevacizumab.

16.0 NEURORADIOLOGY GUIDELINES

In order to completely document the assessment of response, the three-dimensional tumor measurements for all target lesions upon which the assessments of tumor response are based should be explicitly noted in the radiology report for the baseline and all subsequent follow-up exams. Reports for the follow-up exams should reiterate the measurements obtained at baseline for each target lesion. Non-target lesions or newly occurring lesions should also be enumerated in these reports, and changes in non-target lesions should be described.

(Note: all quoted slice thickness is maximal; thinner slices are encouraged, and necessary if the lesion imaged is very small)

16.1 WHOLE BRAIN MRI WITH AND WITHOUT CONTRAST

To document the degree of residual tumor, MRI scan with and without contrast, must be done prior to starting therapy. Standard 3-dimensional MRI imaging of the head with gadolinium should be conducted within six weeks prior to the start of therapy and at the completion of Cycle 2. Patients who remain on study will continue to undergo MRI imaging every 3 months until the end of therapy or documented tumor progression.

Postoperative imaging should be done within 72 hours of surgery, prior to the onset of edema or hemorrhage, which can make measurements of residual tumor difficult. If imaging cannot be obtained at this time or is difficult to interpret, the scan should be repeated 10 or more days after surgery.

1. Sagittal T1 localizer, 5 mm skip 1 mm

2. Axial T2 and FLAIR 4 mm skip 1 (T2), 5 mm skip 0 (FLAIR) or Axial proton density/T2 if FLAIR not available, 5 mm skip 1 mm

3. Optional: Axial T1, 4mm skip 1mm (but highly recommended in post –operative imaging to help differentiate post-operative hemorrhage from enhancement)

4. Optional: sagittal or coronal T2 depending on tumor configuration/orientation

5. Post gadolinium axial T1 4mm skip 1mm

6. Post gadolinium coronal/sagittal (at least one, both preferable), 5 mm skip 1

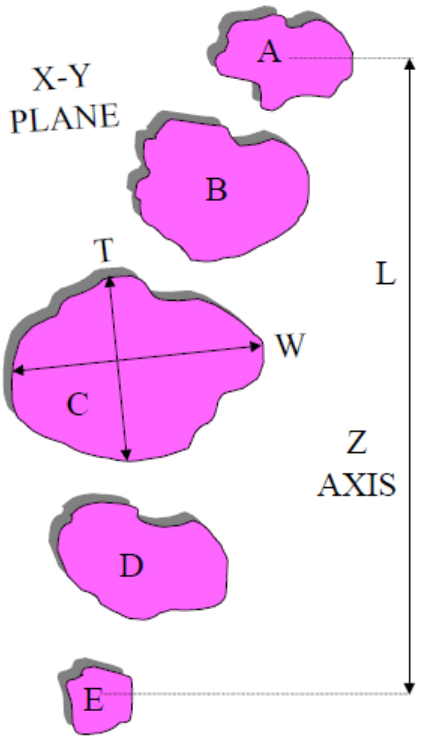
16.2 METHODOLOGY TO DETERMINE TUMOR MEASUREMENT

Tumor response criteria are determined by changes in size using all 3 dimensional measurements: width (W), transverse (T), and length (L) measurements. Thus for all tumors these 3 measurements need to be recorded, using either T1 or T2 weighted images (which ever gives the best estimate of tumor size). The following section describes the methodology. (See drawing below for illustration)

1. Longest diameter of target lesion(s) should be selected in the axial plane only for CT. For MRI imaging, the longest diameter can be measured from the axial plane or the plane in which the tumor is best seen or measured, provided the same plane is used in follow ups.

2. The longest measurement of the tumor (or width, W) should be determined.

3. The 2 perpendicular measurements should be determined (transverse (T) measurement-perpendicular to the width in the selected plane, and the length (L) – tumor extent in the plane perpendicular to the selected plane)



TUMOR SIZE MEASUREMENT BASED ON CROSS-SECTIONAL IMAGING

• A, B, C, D, & E are contiguous parallel slices in the X-Y plane (usually axial) showing the tumor

• W and T are the maximal perpendicular diameters on the slice (C in this example) showing the largest surface area

• Tumor length in the Z-axis (L) (perpendicular to X-Y plane) can be obtained either by the [a] (difference
in table position of the first and last slices showing the tumor + one slice thickness), or [b] the product of (slice
thickness + gap) and the number of slices showing the tumor

4. The cystic or necrotic components of a tumor are not considered in tumor measurements. Therefore only the solid component of cystic/necrotic tumors should be measured. If cysts/necrosis compose the majority of the lesion, the lesion may not be “measurable”. Options:

- If the cyst/necrosis is eccentric, the W, T and L of the solid portion should be measured, the cyst/necrosis excluded from measurement

- If the cyst/necrosis is central but represents a small portion of the tumor (<25%), disregard and measure the whole lesion

- If the cyst/necrosis is central but represents a large portion of the tumor, identify a solid aspect of the mass that can be reproducibly measured

5. Leptomeningeal tumor spread is usually not a target lesion, and usually cannot be measured accurately. Presence and location of leptomeningeal tumor spread should be noted, change in extent/thickness assessed on follow up studies.

6. Overall Response Assessment
The overall response assessment takes into account response in both target and non-target lesion, and the appearance of new lesions, where applicable, according to the criteria described in the table below. The overall response assessment is shown in the last column, and depends on the assessments of target, non-target, and new lesions in the preceding columns.

Target Lesions	Non-Target Lesions	New Lesions	Overall Response
CR	CR	No	**CR**
CR	IR/SD	No	**PR**
CR or PR	Non-PD	No	**PR**
CR	Non-PD	No	**PR**
SD	Non-PD	No	**SD**
PD	Any	Yes/No	**PD**
Any	PD	Yes/No	**PD**
Any	Any	Yes	**PD**

CR – Complete Response
PR – Partial Response
SD – Stable Disease
PD – Progressive Disease
IR – Incomplete Response

The sections that follow discuss the selection and evaluation of each of these types of lesions.

16.3 SELECTION OF TARGET AND NON-TARGET LESIONS

1. For most CNS tumors, only one lesion/mass is present and therefore is considered a "target" for measurement/follow up to assess for tumor progression/response.

2. If multiple measurable lesions are present, up to 5 should be selected as "target" lesions. Target lesions should be selected on the basis of size and suitability for accurate repeated measurements. All other lesions will be followed as non-target lesions.

3. The lower size limit of the target lesion(s) should be at least twice the thickness of the slices showing the tumor to decrease the partial volume effect (e.g. 8 mm lesion for a 4 mm slice).

4. Any change in size of non-target lesions should be noted, though does not need to be measured.

16.4 RESPONSE CRITERIA FOR TARGET LESIONS

1. Response criteria are assessed in 3 dimensions – the product of LxWxT. An elliptical model volume (=0.5LxWxT) is used.

2. To assess response/progression, the ratio is calculated:

$$\frac{\text{LxWxT (current scan)}}{\text{LxWxT (reference scan)}}$$

3. Development of new disease or progression in any established lesions is considered progressive disease, regardless of response in other lesions – e.g. when multiple lesions show

opposite responses, the progressive disease takes precedence.

4. Response Criteria for target lesions:

Complete Response (CR): Disappearance of all target lesions.

Partial response (PR): ≥65% decrease in the sum of the products of the three perpendicular diameters of all target lesions (up to 5), taking as reference the initial baseline measurements.

Stable Disease (SD): Neither sufficient decrease in the sum of the products of the three perpendicular diameters of all target lesions to qualify for PR (taking as reference the initial baseline measurements), nor sufficient increase in a single target lesion to qualify for PD, (taking as reference the smallest disease measurement since the treatment started).

Progressive Disease (PD): 25% or more increase in the product of perpendicular diameters of ANY target lesion, taking as reference the smallest product observed since the start of treatment (see exception below), OR the appearance of one or more new lesions, OR worsening neurologic status not explained by causes unrelated to tumor progression (e.g., anticonvulsant or corticosteroid toxicity, electrolyte disturbances, sepsis, hyperglycemia, presumed post-therapy swelling etc.) PLUS any increase in tumor cross-sectional area (or tumor volume).

Exception for Early Progressive Disease

Because both radiotherapy and Optune therapy may be associated with transient, reversible swelling, there may be a lag time between the initiation of therapy and maximal anti-tumor effect. Removing a patient from protocol therapy as soon as tumor area increases by 25% may result in the treatment being terminated prematurely. It is quite possible that if these patients were maintained on protocol therapy, their disease might eventually stabilize and even regress.

Therefore, patients will not be considered to have progressive disease and will not be removed from protocol therapy for radiographic worsening secondary to local tumor enlargement (LTE), defined as increase in maximal bi-dimensional tumor area of 25% or more but less than 50%, and with no new lesions on any MRI performed prior to the initiation of Cycle 3 treatment.

Thus, prior to the initiation of Cycle 3 therapy, patients should only be removed from protocol therapy for progressive disease if there is 50% or more increase in tumor area (with or without neurological worsening), OR if there is the appearance of one or more new lesions on the MRI **outside** the radiation port.

The criteria for progressive disease as defined above will commence with all MRI scans performed during Cycle 3 onwards. Patients whose tumors meet these criteria will be removed from protocol therapy.

Local progression is defined as progression of known residual tumor or the appearance of tumor at known prior sites of disease that were at some point without evidence of disease. Distant progression is defined as the appearance of tumor at sites other than known prior sites of disease.

Distant progression most often occurs in the subarachnoid space and may occur at any point within the neuraxis. Although rare, extra-CNS metastasis represents distant failure. Combined local and distant progression is defined when imaging evaluation reveals local and distant progression.

16.5 RESPONSE CRITERIA FOR NON-TARGET LESIONS

Complete Response (CR): Disappearance of all non-target lesions.

Incomplete Response/Stable Disease (IR/SD): The persistence of one or more non-target lesions.

Progressive Disease (PD): The appearance of one or more new lesions and/or unequivocal progression of existing non-target lesions.

17.0 ADVERSE EVENTS

17.1 POTENTIAL ADVERSE EVENTS

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

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

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

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

- Hypertension

Adverse events and complications associated with the underlying high-grade glioma or ependymoma disease process, which are unlikely but unknown if related to treatment with NovoTTF-200A include the following adverse events:

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

17.2 UNEXPECTED ADVERSE EVENTS

The following are descriptions of unexpected events, not listed as potential adverse events in Section 14.1. If an event occurs that meets the criteria below, it will be considered a serious adverse event for the purposes of the phase I dose escalation scheme detailed in Section 4.1 and be reported as described in protocol Section 15.0.

a) Any grade 4 non-hematological toxicity
b) Any grade 3 non-hematological toxicity with the specific exception of
    i. Grade 3 nausea and vomiting of less < 5 days duration responsive to antiemetic therapy;
    ii. Grade 3 increased alanine aminotransferase (ALT or SGPT) that return to levels that meet initial eligibility criteria within 7 days of treatment interruption and that do not recur upon study re-challenge with treatment
    iii. Grade 3 fever or infection < 5 days duration.
    iv. Grade 3 hypokalemia, hypophosphatemia, hypocalcemia and/or hypomagnesemia responsive to oral supplementation
c) Any grade 2 non-hematological toxicity that persists for ≥ 7 days and is considered sufficiently medically significant or sufficiently intolerable by patients that it requires treatment interruption.
d) Grade 2 allergic reactions that necessitate discontinuation of temozolomide or bevacizumab will not be considered dose-limiting.
e) Any Grade 2 or higher adverse event requiring interruption of protocol treatment for > 7 days or which recurs upon treatment re-challenge.

18.0 ADVERSE EVENT REPORTING

18.1 DEFINITION OF ADVERSE EVENTS

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

product, whether or not considered related to this medicinal product. Adverse events include the following:

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

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

18.2 GRADING OF AN ADVERSE EVENT

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

MILD	Grade 1	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

18.3 DETERMINATION OF CAUSALITY OF ADVERSE EVENTS

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

None: The event is clearly related to an event that may be due to environmental or accidental occurrence or other factors such as the subject’s clinical state,

therapeutic interventions, or concomitant drugs administered to the subject.

Unlikely	The event is most likely produced by other factors such as the subject's clinical condition, therapeutic interventions, or concomitant drugs administered to the subject, **and** does not follow a known response pattern to the study drug or device.
Possible	The event follows a reasonable temporal sequence from the time of drug administration or use of device, **and/or** follows a known response pattern to the study drug or device, **but** could have been produced by other factors such as the subject's clinical condition, therapeutic interventions, or concomitant drugs administered to the subject.
Probable	The event follows a reasonable temporal sequence from the time of drug administration or use of device, **and** follows a known response pattern to the study drug or device, **and** cannot be reasonably explained by other factors such as the subject's clinical condition, therapeutic interventions, or concomitant drugs administered to the subject.
Definite	The event follows a reasonable temporal sequence from the time of drug administration or use of device, **and** follows a known response pattern to the study drug or device, **and** cannot be reasonably explained by other factors such as the subject's clinical condition, therapeutic interventions, or concomitant drugs administered to the subject, **and either** occurs immediately following study drug administration or use of device **or** improves on stopping the study drug or device, **or** reappears on repeat exposure

18.4 SERIOUS ADVERSE EVENTS

When a serious adverse events is identified, treatment with Optune NovoTTF-200A and any chemotherapy should be discontinued until resolution of the toxicity. Treatment with Optune NovoTTF-200A should then be restarted, if felt to be clinically appropriate, by the investigator. Temozolomide should be restarted at 25% of the previous dose, if felt to be clinically appropriate by the investigator.

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

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

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

18.5 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.

See Section 14.0 Study Monitoring and Data Collection

18.6 UNANTICIPATED ADVERSE DEVICE EFFECT EVENT (UADE) REPORTING

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

The report will contain the following:

- The initials of the subject, patient MRN #, protocol # and title
- The date the event occurred
- A description of the UADE
- An explanation of how the UADE was handled
- A description of the subject's condition
- Indication if the subject remains on the study
- Indication if the event is considered related to the NovoTTF-200A
- Indication if an amendment to the protocol and/or consent form is recommended as a result

18.7 ELICITING ADVERSE EVENT INFORMATION

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

problems?”

18.8 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 through the final study visit. 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.

18.9 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.

19.0 STUDY OUTCOME MEASURES

19.1 SAFETY ANALYSIS

This study’s safety endpoint will be to attempt to assess the safety and tolerability of the Optune NovoTTF-200A System when used in combination with temozolomide and bevacizumab for the treatment of pediatric high-grade glioma and ependymoma. This safety endpoint will be determined using the rules of a standard 3+3 phase I study design and be based on the incidence and severity of adverse events and toxicities. Toxicities will be assessed according to the “Common toxicity criteria (CTCAE), version 5.0”

19.2 EFFICACY ANALYSIS

There are no primary efficacy endpoints for this study. However, patients will be followed to assess their progression-free and overall survival. While the study is not powered to provide an efficacy evaluation, the efficacy date gained from this study may be useful in designing future phase II/III investigations.

20.0 STATISTICAL CONSIDERATIONS

The sample size of this study will be determined by the number of severe adverse events related to therapy observed. A minimum of two and a maximum of six patients will be needed to complete the phase I portion of the study. In the event that no severe adverse events related to

therapy are observed, the study could be successfully completed with a total of five patients. The anticipated sample size for this study, including the expansion cohort, is a sample size based on feasibility and not on any formal power calculations.

21.0 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.
- The investigator may remove a patient from the study in case of not complying with study protocol.
- Patients will be able to withdraw from the trial at their own request.

22.0 RISK/BENEFIT ANALYSIS

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 most common complication seen in patients is a mild to moderate skin irritation beneath the electrode gel. In the pivotal study in recurrent GBM, 116 patients were treated with the NovoTTF-200A device without unexpected device events. The phase III trial examining the use of the NovoTTF100A in combination with temozolomide demonstrated clear improvement in both progression-free and overall survival compared to temozolomide alone. Considering the minimal toxicity in both adult and pediatric trials and the promising efficacy seen in several adult clinical trials, the small number of patients exposed to this treatment in the current study and the and the poor outcome of these patients with other treatments – we conclude that the possible benefits of combination treatment with NovoTTF-200A, temozolomide, and bevacizumab drastically exceed its potential risks.

23.0 STUDY MONITORING AND QUALITY ASSESSMENT

An independent medical monitor will be assigned to monitor the safety data from the study. This individual should be a qualified physician, other than the Principal Investigator, not associated with the protocol, able to provide medical care to research volunteers for conditions that may arise during the conduct of the study, and who will monitor the volunteers during the conduct of the study. The medical monitor plays a role in reviewing serious adverse events and unanticipated problems.

The medical monitor is required to review all unanticipated problems involving risk to subjects or others, serious adverse events and all subject deaths associated with the protocol and provide

an unbiased written report of the event. At a minimum, the medical monitor will provide the outcome of the event(s) and in case of a serious adverse event or death, provide the relationship of the event to the study device and to participation in the study. The medical monitor will also

indicate whether he/she concurs with the details of the report provided by the site principal investigator. Reports of adverse events determined by either the investigator or medical monitor to be possibly, probably, or definitely related to study participation and reports of events resulting in death will be promptly forwarded to the IRB. All adverse events, regardless of seriousness or causality must be reported. See Section 17.0 for reporting guidelines.

The medical monitor and the principal investigator, along with any co-investigators, will monitor the study data for safety and integrity. Monitoring will take place annually. Interim analysis will take place following each enrolled cohort of three patients.

24.0 PROTECTION OF HUMAN SUBJECTS

Privacy

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

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

25.0 INFORMED CONSENT PROCEDURES

Research authorization

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

26.0 REFERENCES

1. Parekh C, Jubran R, Erdreich-Epstein A, et al. Treatment of children with recurrent high grade gliomas with a bevacizumab containing regimen. J. Neurooncol. 2001 Jul; 103(3):673-80.
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