ABSTRACT

PBTC-048: Feasibility Trial of Optune for Children with Recurrent or Progressive Supratentorial High-Grade Glioma or Ependymoma, and Feasibility and Efficacy Trial of Optune in Conjunction with Radiation Therapy for children with Newly Diagnosed DIPG

Recurrent or progressive pediatric CNS tumors generally have a poor prognosis under current treatment regimens. For children with high-grade gliomas (HGG), once progression occurs, most patients cannot be cured, and median survival remains no greater than 1-2 years. The overall survival of recurrent/progressive ependymoma is also poor in children. Children with diffuse intrinsic pontine gliomas (DIPG) have a 1- and 3-year overall survival (OS) of ~40% and <10%, respectively. Other than radiation therapy, no other therapy has demonstrated benefit for these patients.

With amendment v7.0, the NovoTTF-200A System was rebranded as Optune™ Gio. Prior to amendment v7.0, the NovoTTF-200A System was referred to as the Optune™ System. Throughout the protocol the NovoTTF-200A System is referred to as the Optune System or Optune.

The Optune System produces alternating electrical fields, called tumor treatment fields (TTFields) by means of 4 transducer arrays placed on the shaved scalp. The very low intensity (1-3V/cm), intermediate frequency electric fields impair the growth of tumor cells through the arrest of cell division and inducing apoptosis. Preclinical studies have demonstrated TTFields synergistically enhance the efficacy of irradiation in glioma cell lines.

This is a multicenter trial of the Optune device to examine the feasibility and to describe the device-related toxicity in children with supratentorial HGG or ependymoma (Stratum 1) and to examine the feasibility and efficacy of concurrent Optune and standard focal radiation therapy (RT) in children with newly diagnosed DIPG (Stratum 2).

The primary objectives of Stratum 1 are: 1) to evaluate the feasibility of treatment with Optune in pediatric patients with recurrent/refractory/progressive supratentorial malignant glioma or ependymoma, and 2) to describe the Optune device treatment-related toxicities in children with recurrent/refractory/progressive supratentorial malignant glioma or ependymoma.

The primary objectives of Stratum 2 are: 1) to describe the safety and tolerability of concurrent Optune therapy and RT (Phase I component), 2) to evaluate the feasibility of treatment with concurrent Optune and RT (Phase II component), and 3) to estimate the overall survival (Phase II component) in children and adolescents with newly diagnosed DIPG treated with concurrent Optune therapy and standard RT.

The secondary objectives of for Stratum 1 are: 1) to estimate the response rate and Event-Free Survival (EFS) as markers of anti-tumor activity of the Optune device, and 2) to assess the

association of anti-tumor activity with compliance in Optune device use, and 3) to explore the impact of the Optune device on the Quality of Life (QoL) of children (aged 8+) and families undergoing this therapy.

The secondary objectives for Stratum 2 are: 1) to estimate the response rate and EFS of concurrent therapy, 2) to assess the association of anti-tumor activity with compliance with Optune treatment in patients treated with combination therapy, 3) to explore the impact of concurrent therapy on the Quality of Life (QoL) of children (aged 8+) and families undergoing this therapy, and to explore the association between demographic (e.g., SES, gender), treatment, and behavioral variables with health-related QoL changes, and 4) to evaluate the patterns of imaging disease progression after concurrent treatment with Optune and RT in children and adolescents with newly diagnosed DIPG.

Optune will be worn for a minimum of 18 hours a day, with a recommendation of 22 hours/day for at least 23 days in a 28-day cycle. Treatment may continue up to 26 cycles in Stratum 1 and Optune treatment may continue for up to 5 years in Stratum 2 if the participant is deriving benefit and in the absence of significant treatment-related toxicity. Patients will be followed for 2 years from the cessation of protocol treatment in Stratum 1, and for 5 years from the initiation of protocol treatment in Stratum 2 for the monitoring of unexpected later developing toxicities and to document disease progression, event-free and overall survival.

For patients in Stratum 1, the therapy will be deemed feasible for patients who are able to use the device for ≥ 18 hours/day for at least 23 days out of 28 days of cycle one (feasibility assessment period). A total of 20 patients need to be assessed with an interim analysis to be conducted after the first 11 patients. Kaplan-Meier estimates of EFS for all eligible patients who use the device for at least 1 day will be provided separately for the two histology-based cohorts i.e. HGG and Ependymoma.

For patients in Stratum 2, the study will consist of two parts: a phase I portion to evaluate the safety and tolerability of concurrent Optune and RT; and a phase II portion to evaluate the feasibility and efficacy of concurrent Optune and standard RT. The therapy will be deemed feasible for patients who are able to use the device for ≥ 18 hours/day for at least 40 of the 49 days of the feasibility assessment period of cycle one, which consists of concurrent Optune and RT. Up to 18 evaluable patients may need to be assessed for the phase I component. A total of 30 patients need to be assessed for the phase II component (6 of whom will be counted from the phase I component). The design also incorporates 2 interim analyses for futility assessed when 9 and 14 events are observed.

We will also summarize the rates of confirmed sustained objective responses (CR+PR) observed during treatment. While the association of radiologic responses with OS is not clear, responses may be associated with better QOL. All PROMIS and Neuro-QoL scores will be reported using T-score matrix (mean=50 and SD=10). The projected accrual rate is 1-2 patients per month. The total sample size and the study duration are expected to be 25 and about 3-4 years for Stratum 1, and up to 50 and about 3-4 years for Stratum 2, respectively.

1. OBJECTIVES

1.1 Primary Objectives

Stratum 1 recurrent, progressive or refractory supratentorial high-grade glioma or ependymoma

1.1.1 To establish the feasibility of treatment with the Optune device in pediatric patients with recurrent/refractory/progressive supratentorial malignant glioma and ependymoma.

1.1.2 To describe the Optune device treatment-related toxicities in children with recurrent/refractory/progressive supratentorial malignant glioma and ependymoma.

Stratum 2 newly diagnosed DIPG

1.1.3 To evaluate the safety and tolerability of concurrent Optune treatment and radiation therapy (RT) in children and adolescents with newly diagnosed DIPG.

1.1.4 To establish the feasibility of treatment with concurrent Optune treatment and (RT) in children and adolescents with newly diagnosed DIPG.

1.1.5 To estimate the overall survival in children and adolescents with newly diagnosed DIPG treated concurrently with the Optune device and standard focal RT.

1.2 Secondary Objectives

Stratum 1 recurrent, progressive or refractory supratentorial high-grade glioma or ependymoma

1.2.1 To estimate the response rate and Event-Free Survival (EFS) as markers of anti-tumor activity of the Optune device within the context of a feasibility trial.

1.2.2 To assess the association of anti-tumor activity with compliance in Optune device use within the context of a small feasibility study.

1.2.3 To explore the impact of the Optune device on the children and families undergoing this therapy, and to explore the association between demographic (e.g., SES, gender), disease (e.g., risk status), treatment, and behavioral variables with health-related quality of life (QoL) changes.

1.2.4 To explore the association of apparent diffusion coefficient (ADC) values within the tumor and correlate with response to Optune treatment and EFS.

Stratum 2 newly diagnosed DIPG

1.2.5 To estimate the response rate (RR) and Event-Free Survival (EFS) as descriptive markers of anti-tumor activity of concurrent RT and Optune therapy in DIPG.

1.2.6 To assess the association of anti-tumor activity with compliance with Optune treatment in children and adolescents with newly diagnosed DIPG treated concurrently with Optune and RT.

1.2.7 To explore the impact of concurrent RT and Optune therapy on the children undergoing this therapy, their families, and to explore the association between demographic (e.g., SES, gender), treatment, and behavioral variables with health-related QoL changes.

1.2.8 To evaluate the patterns of imaging disease progression after concurrent treatment with Optune and RT in children and adolescents with newly diagnosed DIPG.

2. PATIENT SELECTION

All subjects must meet the following inclusion and exclusion criteria. No exceptions will be given. Imaging studies to establish eligibility must be done within two weeks prior to enrollment. All other clinical evaluations to establish eligibility must be done within 7 days prior to enrollment.

2.1 Eligibility Criteria for Enrollment

2.1.1 Diagnosis

- Stratum 1: Patients must have a histologically confirmed diagnosis of supratentorial high-grade glioma or supratentorial ependymoma that is recurrent, progressive or refractory.

- Stratum 2: Patients with newly diagnosed DIPG
    - Patients with a typical DIPG on MR imaging, defined as a tumor with a pontine epicenter and diffuse involvement of more than 2/3 of the pons, are eligible without histologic confirmation.
        - Note: Patients with typical DIPG who undergo a biopsy are eligible provided the tumor is a diffuse glioma WHO Grade II-IV with OR without H3 K27M mutation.

    - Patients with pontine lesions that do not meet these MR imaging criteria will be eligible if there is histologic confirmation diffuse glioma WHO Grade II-IV with H3 K27M-mutation.

2.1.2 Disease Status

Subjects must have bi-dimensionally measurable disease, defined as at least one lesion that can be accurately measured in at least two planes.

- Stratum 1: This disease must be located primarily in the supratentorial region
    - Patients with significant disease that is metastatic outside of the supratentorial region are ineligible
- Stratum 2: This disease must be located primarily in the pons (see definition in Section 3.1.1).

2.1.3 Age

- Stratum 1: Patient must be ≥ 5 but ≤ 21 years of age at the time of enrollment.
- Stratum 2: Patient must be ≥ 3 but ≤ 21 years of age at the time of enrollment.

2.1.4 Prior Therapy

Stratum 1: Patients must have recovered from the acute treatment related toxicities (defined as ≤ Grade 1) of all prior chemotherapy, immunotherapy, or radiotherapy prior to entering this study.

Stratum 2: Patients may not have had any prior antitumor therapy except surgery and/or steroids.

2.1.4.1 Myelosuppressive chemotherapy

Patient must have received last dose of known myelosuppressive chemotherapy >21 days prior to enrollment; >42 days if nitrosourea

2.1.4.2 Biologic Agent/Immunotherapy

- Biologic agent - must have recovered from any acute toxicity potentially related to the agent and received their last dose of the biologic agent > 7 days prior to study enrollment.
    - For agents that have known adverse events occurring beyond 7 days after administration, this period must be extended beyond the time during which adverse events are known to occur.

- Immunomodulatory treatment - Patient must have received the last dose >21 days prior to enrollment.
- Monoclonal antibody treatment and agents with known prolonged half-lives: Patient must have recovered from any acute toxicity potentially related to the agent and received their last dose of the agent ≥ 28 days prior to study enrollment.

2.1.4.3 Radiation

- Stratum 1: Patients must have had their last fraction of:
    - Craniospinal irradiation (>24Gy) or total body irradiation or radiation to ≥ 50% of pelvis ≥ 42 days prior to enrollment
    - Focal irradiation ≥ 14 days prior to enrollment
    - Local palliative irradiation (small port) ≥ 14 days
- Stratum 2: Patients must not have received any radiotherapy prior to enrollment. If clinically indicated, enrolled patients may receive up to 5 fractions of radiotherapy prior to starting Optune therapy.

2.1.4.4 Surgery

- Stratum 1: Optune device application start date must be at least 4 weeks (28 days) from CNS surgical procedure. Excluding VP shunts, Endoscopic Third Ventriculostomy (ETV) for which treatment could start 10 days post procedure. Non-CNS surgical procedures such as but not limited to central venous catheter insertion at the discretion of treating physician and study chair.

- Stratum 2: Radiation therapy and Optune device application start date must be at least 5 days after the date of a tumor biopsy if obtained.
  The Optune device application start date must be at least 5 days after the date of a VP shunt or ETV procedure. For patients starting Optune therapy within 10 days of VP shunt or ETV procedure, neurosurgical sign off to start therapy is required.

2.1.5 Inclusion of Women and Minorities

Both males and females of all races and ethnic groups are eligible for this study.

2.1.6 Neurologic Status

- Stratum 1: Patients with neurological deficits should be stable for a minimum of 1 week prior to enrollment.

- Stratum 2: Stable neurologic deficits are not an eligibility criterion for Stratum 2.

2.1.7 Performance Status

Stratum 1:

Karnofsky Performance Scale (KPS for > 16 years of age) or Lansky Performance Score (LPS for ≤ 16 years of age) assessed within two weeks of enrollment must be ≥ 50 (Appendix A). Patients who are unable to walk because of neurologic deficits, but who are up in a wheelchair, will be considered ambulatory for the purpose of assessing the performance score.

There are no performance status requirements for Stratum 2 patients.

2.1.8 Organ Function

Patients must have adequate organ and marrow function as defined below:

- Absolute neutrophil count ≥ 1.0 X 10^9/L
- Platelets ≥ 100 X 10^9/L (transfusion independent)
- Hemoglobin ≥8g/dl (may receive transfusions)
- Total bilirubin ≤1.5 times institutional upper limit of normal (ULN)
- ALT(SGPT) ≤3 times institutional upper limit of normal
- AST(SGOT) ≤3 times institutional upper limit of normal
- Albumin ≥2 g/dl

Serum creatinine based on age/gender as noted in Table 3. Patients that do not meet the criteria in Table 3 but have a 24 hour Creatinine Clearance or GFR (radioisotope or iothalamate) ≥ 70 ml/min/1.73 m^2 are eligible.

Table 3

Serum Creatinine for age/gender		
Age	**Maximum Serum Creatinine (mg/dL)**	
	Male	**Female**
2 to < 6 years	0.8	0.8
6 to < 10 years	1	1
10 to < 13 years	1.2	1.2
13 to < 16 years	1.5	1.4
≥ 16 years	1.7	1.4
The threshold creatinine values in this Table were derived from the Schwartz formula for estimating GFR (Schwartz et al. J. Peds,		

106:522, 1985) utilizing child length and stature data published by the CDC.

2.1.9 Head Circumference (Strata 1 & 2)
Patients must have a minimum head circumference of 44 cm.

2.1.10 Compliance in Optune Device Usage

- Stratum 1: Patients must be willing to use the Optune device ≥18 hours/day for at least 23 days in a 28-day cycle, and keep head shaved throughout treatment.

- Stratum 2: During concurrent Optune therapy and RT, patients must be willing to use the Optune device ≥18 hours/day for at least 40 of the 49 days of the duration of the feasibility period. During subsequent cycles of Optune therapy alone, patients must be willing to use the Optune device ≥18 hours/day for at least 23 days in a 28-day cycle. During concurrent Optune therapy and RT and Optune therapy alone, patients must be willing to keep their head shaved throughout treatment.

2.1.11 Pregnancy Status
Female patients of childbearing potential must have a negative serum or urine pregnancy test.

2.1.12 Pregnancy Prevention
Patients of childbearing or child fathering potential must be willing to use a medically acceptable form of birth control, which includes abstinence, while being treated on this study.

2.1.13 Informed Consent
The patient or parent/guardian is able to understand the consent and is willing to sign a written informed consent document according to institutional guidelines.

2.1.14 Steroids

- Stratum 1: If patient is on corticosteroids, the dose must be stable or decreasing for at least 5 days prior to enrollment.
- Stratum 2: There are no eligibility requirements for corticosteroid dosing for Stratum 2.

2.2 Exclusion Criteria

2.2.1 Concurrent Illness

2.2.1.1 Patients with any clinically significant unrelated systemic illness (serious infections or significant cardiac, pulmonary, hepatic or other organ dysfunction), that in the opinion of the investigator would compromise the patient's ability to tolerate protocol therapy, put them at additional risk for toxicity or would interfere with the study procedures or results.

2.2.1.2 Patients with a history of any other malignancy, except patients with a secondary brain tumor if the patient's first malignancy has been in remission for at least 5 years from the end of treatment.

2.2.2 Concurrent Therapy

Patients who are receiving any other anticancer or investigational drug therapy are not eligible.

2.2.3 Inability to Participate

Patients who in the opinion of the investigator are unwilling or unable to return for required follow-up visits or obtain follow-up studies required to assess toxicity to therapy or to adhere to the device usage plan, other study procedures, and study restrictions.

2.2.4 Tumor Location

Stratum 1: Patients with primarily infra-tentorial or spinal cord tumor are not eligible.

2.2.4.1 Tumor Dissemination

- Patients with any distant intracranial or spinal metastasis on MRI or positive CSF are ineligible.
- Patients for whom there is clinical suspicion of metastatic disease in the CSF or Spine, must have MRI of Spine and CSF obtained (Lumbar puncture or through ommaya, EVD or Shunt) with negative cytology.

2.2.5 Skull Defects

Patients with major skull defects (such as missing bone without replacement) are not eligible.

2.2.6 Neurological Disorders

Patients with active implanted electronic devices in the brain or spinal cord such programmable VP shunts, deep brain stimulators, vagus nerve stimulators, are not eligible.

2.2.7 Cardiac Disorders

Patients with pacemaker, defibrillator, or documented significant arrhythmia, are not allowed.

2.2.8 Intracranial Objects

Patients with foreign body intracranially, such as bullet fragments, are not allowed, with the exception of VP-shunts (non-programmable) and Ommaya catheters.

2.2.9 Allergy

Patients with history of hypersensitivity to conductive hydrogel are not eligible.

2.3 Inclusion of Women and Minorities

NIH policy requires that women and members of minority groups and their subpopulations be included in all NIH-supported biomedical and behavioral research projects involving NIH-defined clinical research unless a clear and compelling rationale and justification establishes to the satisfaction of the funding Institute & Center (IC) Director that inclusion is inappropriate with respect to the health of the subjects or the purpose of the research. Exclusion under other circumstances must be designated by the Director, NIH, upon the recommendation of an IC Director based on a compelling rationale and justification. Cost is not an acceptable reason for exclusion except when the study would duplicate data from other sources. Women of childbearing potential should not be routinely excluded from participation in clinical research. Please see http://grants.nih.gov/grants/funding/phs398/phs398.pdf.

The PBTC remains committed to offering participation in our trials to subjects of all races and ethnic groups.

2.4 Treatment at Primary Institution

All study related imaging studies should be obtained at a PBTC institution. Laboratory studies may be performed at a CLIA certified laboratory of the investigator's choice. Imaging utilized to determine eligibility may be performed at an outside institution if all required imaging sequences are included and the study is deemed of adequate quality by the treating team. All required physical examinations, laboratory parameters need to be performed at the primary PBTC institution during the feasibility assessment period of the protocol.

2.5 Criteria to Start Treatment

- Subjects must start therapy within 10 days of enrollment.
- Laboratory values must be no older than 7 days prior to the start of therapy. If a test that is repeated post enrollment and prior to the start of therapy is outside the limits for eligibility, it must be rechecked within 48 hours prior to the start of therapy. If rechecks are still outside the limits for eligibility, the patient may not receive protocol therapy and will be considered off study.