

## **Feasibility Trial of Optune for Children with Recurrent or Progressive Supratentorial High-Grade Glioma and Ependymoma**

### **ABSTRACT**

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.

This is a multicenter feasibility trial of the Optune device to examine the feasibility and to describe the device-related toxicity in children with supratentorial HGG and ependymoma. The primary objectives of this study are: 1) to evaluate the feasibility of treatment with Optune in pediatric patients with recurrent/refractory/progressive supratentorial malignant glioma and ependymoma, and 2) to describe the Optune device treatment-related toxicities in children with recurrent/refractory/progressive supratentorial malignant glioma and ependymoma.

The secondary objectives of this study 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 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.

The 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 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 for the monitoring of unexpected later developing toxicities and to document disease progression and event-free survival.

Patients will have Brain MRI with and without contrast performed prior to therapy, after cycles 2, 4, 6, 9, then every 3 cycles thereafter until time of progression or completion of treatment. For those patients who complete at least 9 cycles of therapy, an MRI will be performed every 3 cycles for 2 years then every 4 months after completion of treatment.

The therapy will be deemed feasible for patients who are able to use the device for  $\geq 18$  hours/day for at least 23 days out of 28 days of cycle one. 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. We will also estimate the rates of confirmed sustained objective responses (CR+PR) observed during treatment. All PROMIS and Neuro-QoL scores will be reported using T-score matrix (mean=50 and SD=10).

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The projected accrual rate is 1.5-2.5 patients per month. The total sample size and the study duration are expected to be 25 and about 1.5-2.0 years, respectively.

## **OBJECTIVES**

### **Primary Objectives**

- To establish the feasibility of treatment with the Optune device in pediatric patients with recurrent/refractory/progressive supratentorial malignant glioma and ependymoma
- To describe the Optune device treatment-related toxicities in children with recurrent/refractory/progressive supratentorial malignant glioma and ependymoma

### **Secondary Objectives**

- 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
- To assess the association of anti-tumor activity with compliance in Optune device use within the context of a small feasibility study
- 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
- To explore the association of apparent diffusion coefficient (ADC) values within the tumor and correlate with response to Optune treatment and EFS

## **PATIENT SELECTION**

All patients must meet the following inclusion and exclusion criteria.

### **Inclusion Criteria**

- **Diagnosis:** Patients must have a histologically confirmed diagnosis of supratentorial high-grade glioma or supratentorial ependymoma that is recurrent, progressive or refractory.
  - Patients must have failed standard therapy and at the time of study entry have recurrent, progressive or refractory disease with no known curative options.
- **Disease Status:** Patients must have bi-dimensionally measureable disease, defined as at least one lesion that can be accurately measured in at least two planes
  - This disease must be located primarily in the supratentorial region
  - Patients with significant disease that is metastatic outside of the supratentorial region are ineligible
- **Age:** Patients must be  $\geq 5$  but  $\leq 21$  years of age at the time of enrollment.

- **Prior Therapy:** Patients must have recovered from the acute treatment related toxicities (defined as  $\leq$  grade 1) of all prior chemotherapy, immunotherapy, or radiotherapy prior to entering this study.
- **Myelosuppressive Chemotherapy:** Patients must have received last dose of known myelosuppressive chemotherapy  $>21$  days prior to enrollment;  $>42$  days if nitrosurea.
- **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: At least three half-lives must have elapsed prior to enrollment.
    - Note: A list of the half-lives of commonly used monoclonal antibodies is available on the PBTC webpage under Generic Forms and Templates. For monoclonal antibody therapies with unknown half-lives not included on this list, contact study chair.
- **Radiation:** Patients must have had their last fraction of:
  - Craniospinal irradiation ( $>24\text{Gy}$ )  $> 3$  months prior to enrollment
  - Focal irradiation  $> 42$  days prior to enrollment
  - Local palliative irradiation (small port)  $> 14$  days
- **Surgery:** 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.
- **Inclusion of Women and Minorities:** Both males and females of all races and ethnic groups are eligible for this study.
- **Neurologic Status:** Patients with neurological deficits should be stable for a minimum of 1 week prior to enrollment.
- **Performance Status:** Karnofsky Performance Scale (KPS for  $> 16$  years of age) or Lansky Performance Score (LPS for  $\leq 16$  years of age) assessed within two weeks of enrollment must be  $\geq 60$ . 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.

- Organ Function: Patients must have organ and marrow function as defined below:
  - Absolute neutrophil count  $\geq 1.0 \times 10^9/L$
  - Platelets  $\geq 100 \times 10^9/L$  (transfusion independent)
  - Hemoglobin  $\geq 8g/dl$  (may receive transfusions)
  - Total bilirubin  $\leq 1.5$  times institutional upper limit of normal (ULN)
  - ALT(SGPT)  $\leq 3$  times institutional upper limit of normal
  - AST(SGOT)  $\leq 3$  times institutional upper limit of normal
  - Albumin  $\geq 2$  g/dl
  - Serum creatinine based on age/gender as noted in Table 1. Patients that do not meet the criteria in Table 1 but have a 24 hour Creatinine Clearance or GFR (radioisotope or iothalamate)  $\geq 70$  ml/min/1.73 m<sup>2</sup> are eligible.

**Table 1**

Serum Creatinine for age/gender		
Age	Maximum Serum Creatinine (mg/dL)	
	Male	Female
3 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
$\geq 16$ 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.

- Head circumference: Patients must have minimum head circumference of 44 cm.
- Compliance in Optune Device Usage: Patients must be willing to use the Optune device  $\geq 18$  hours/day for at least 23 days in a 28-day cycle, and keep head shaved throughout treatment.
- Pregnancy Status: Female patients of childbearing potential must have a negative serum or urine pregnancy test.
- 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.
- 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.
- Steroids: If patient is on corticosteroids, the dose must be stable or decreasing for at least 5 days prior to enrollment.

## **Exclusion Criteria**

- **Systemic Illness:** 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.
- **Other Malignancy:** Patients with a history of any other malignancy.
- **Concurrent Therapy:** Patients who are receiving any other anticancer or investigational drug therapy are not eligible.
- **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 device usage plan, other study procedures, and study restrictions.
- **Tumor Location:** Patients with primarily infra-tentorial or spinal cord tumor are not eligible.
- **Tumor Dissemination:** Patients for who clinical suspicion is present 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. Patients with CSF that is positive for tumor cells or metastatic disease found on MRI are ineligible.
- **Skull Defects:** Patients with major skull defects (such as missing bone without replacement) are not eligible.
- **Neurological Disorder:** Patients with active implanted electronic devices in the brain or spinal cord such as programmable VP shunts, deep brain stimulators, vagus nerve stimulators, are not allowed.
- **Cardiac Disorder:** Patients with pacemaker, defibrillator, or documented significant arrhythmia, are not allowed.
- **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.
- **Allergy:** Patients with history of hypersensitivity to conductive hydrogel are not eligible.