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| <i>Confidential</i> | PBTC-023 v1.0 |
| | Version Date: 06/04/2007 |

Description

This is a multicenter, Phase I trial to estimate the maximum tolerated dose and describe dose limiting toxicities of enzastaurin (LY317615) administered orally for 28 consecutive days to children and adolescents with refractory primary CNS tumors. Pharmacokinetic, imaging and biology correlative studies will be performed in all consenting patients.

Primary Objectives

1. To estimate the maximum tolerated dose (MTD) and/or recommend a Phase II dose of enzastaurin administered as a once daily oral dose to children with recurrent or refractory CNS tumors who are not receiving enzyme-inducing anticonvulsants.

Secondary Objectives

2. To characterize the pharmacokinetics of enzastaurin in children when administered on this schedule.
3. To document and describe toxicities associated with enzastaurin administered on this schedule.
4. To document antitumor activity in children with recurrent or refractory CNS tumors that may be apparent in a phase I, dose escalation trial of enzastaurin.
5. To explore changes in MR perfusion and diffusion scans obtained within 15 ± 2 days after initiation of enzastaurin therapy as compared to baseline and to correlate these changes with clinical outcome, as applicable.
 - 5.1. Results of imaging studies will be also be combined across similar PBTC protocols to increase the power for detecting correlations among scans and with outcome.
6. To evaluate a panel of biological surrogate markers in this patient population at baseline and following enzastaurin administration.

Eligibility criteria

- **Age:** Patient must be ≤ 21 years of age at registration.
- **Tumor:** Patients with a histologically confirmed diagnosis of a primary CNS malignancy (including low-grade glioma) that is recurrent, progressive, or refractory to standard therapy and for which there is no known curative therapy. All tumors except intrinsic brain stem and diffuse optic pathway tumors must have histological verification at either the time of diagnosis or recurrence. Patients with intrinsic brain stem or diffuse optic pathway tumors must have clinical and/or radiographic evidence of progression.
- **Performance Score:** Karnofsky Performance Scale (KPS for > 16 yrs of age) or Lansky Performance Score (LPS for ≤ 16 years of age) ≥ 60 assessed within two weeks prior to registration (Appendix III).
- **Prior/Concurrent Therapy:**
Recovery from Prior Therapy: Patient must have recovered from the acute toxic effects of all prior therapy before entering this study.

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Recovery is defined as a toxicity grade ≤ 2 , using CTCAE v. 3.0, unless otherwise specified in the Inclusion and Exclusion Criteria.

- Chemotherapy:
 - Myelosuppressive chemotherapy: Must not have received within 3 weeks of entry onto this study (6 weeks if prior nitrosourea).
 - Hematopoietic growth factors: At least 7 days since the completion of therapy with a hematopoietic growth agent (filgrastim, sargramostim, and erythropoietin) and 14 days for long-acting formulations.
 - Biologic (anti-neoplastic agent): At least 7 days since the completion of therapy with a biologic agent. 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. These patients must be discussed with the Study Chair on a case-by case basis.
- Radiation:
 - ≥ 2 wks for local palliative XRT (small volume)
 - ≥ 6 months must have elapsed after prior total body irradiation (TBI), or craniospinal XRT
 - ≥ 6 wks must have elapsed after other substantial bone marrow irradiation
- Bone Marrow Transplant: Patient must be:
 - ≥ 6 months since allogeneic bone marrow transplant prior to registration
 - ≥ 3 months since autologous bone marrow/stem cell prior to registration
 - No evidence of active graft versus host disease
- Corticosteroids: Patients who are receiving dexamethasone must be on a stable or decreasing dose for at least 1 week prior to registration
- Anticonvulsants: If taking anticonvulsants, patients must be on anticonvulsants which are not considered enzyme inducing (See appendix IV).
- **Organ Function**
 - Adequate Bone Marrow Function:
 - Peripheral absolute neutrophil count (ANC) $\geq 1000/\mu\text{L}$
 - Platelet count $\geq 100,000/\mu\text{L}$ (transfusion independent)
 - Hemoglobin ≥ 8.0 gm/dL (may receive RBC transfusions)

- Adequate Renal Function:
 - Creatinine clearance or radioisotope GFR \geq 70ml/min/1.73 m² or
 - A serum creatinine based on age as follows:

| Age (Years) | Maximum Serum Creatinine (mg/dL) |
|--------------------|----------------------------------|
| 5 | 0.8 |
| 5 < age \leq 10 | 1.0 |
| 10 < age \leq 15 | 1.2 |
| > 15 | 1.5 |

- Adequate Liver Function:
 - Total bilirubin \leq 1.5 x upper limit of normal (ULN) for age, and
 - SGPT (ALT) \leq 5 x upper limit of normal (ULN) for age
 - Serum albumin \geq 2.5 g/dL
- Adequate Cardiac Function: Patients must have a normal QTc for age and no evidence of a clinically significant arrhythmia on ECG.
- Birth Control: 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: Signed informed consent according to institutional guidelines must be obtained.

Exclusion Criteria

- Patients with BSA less than 0.5 m².
- Patients with any clinically significant unrelated systemic illness that would compromise the patient's ability to tolerate protocol therapy or would likely interfere with the study procedures or results.
- Patients receiving any other anticancer or investigational drug therapy.
- Patients receiving enzyme inducing anticonvulsant therapy.
- Patients with known hypersensitivity to enzastaurin or its components.
- Patients who are pregnant or lactating.
- Patients with inability to return for follow-up visits or obtain follow-up studies required to assess toxicity to therapy.

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Rationale

Central nervous system tumors (CNS) are the most common solid malignancy of childhood and the second most common pediatric cancer. There are approximately 2000 new childhood brain tumors diagnosed each year.¹ There have been modest improvements in the treatment of childhood CNS tumors over the past several decades using multi-modality therapy including surgery, radiation and chemotherapy. Nevertheless, deaths caused by CNS tumors are the highest among pediatric cancers.² In addition, the morbidity associated with CNS tumors and currently available therapeutic strategies may be profound with regard to physical deficits as well as neuro-psychological and neuroendocrine sequelae. Thus, new agents and treatment strategies are needed for the effective treatment of these challenging malignancies.

Neovascularization is important for tumor growth and metastases and therefore chemotherapeutic agents that inhibit angiogenesis pathways are an important emerging class of agents that warrant further study and characterization in pediatric patients with malignancies. Studies of the role of angiogenesis in CNS tumors from both children and adults have shown that there is marked angiogenic activity in astrocytic as well as embryonal tumors.³⁻⁶ In some studies, the degree of angiogenesis inversely correlates with patient survival, particularly for patients with high-grade tumors.⁷ In addition, preliminary studies evaluating VEGF concentrations in the cerebrospinal fluid of patients with leptomeningeal metastasis reveal that CSF VEGF levels mirror the patient's clinical course with a marked reduction in response to therapy and an increase at relapse. This suggests that markers of angiogenesis may serve as predictors of response to therapy and outcome.⁸

Schema

Enzastaurin will be given once daily. Drug will be taken orally, ideally within 30 min following a meal and at the same time each day. Dosing will be based on the BSA determined within a week prior to the start of each course.