Protocol Abstract and Schema

Phase 1 Trial of Panobinostat in Children with Diffuse Intrinsic Pontine Glioma

DESCRIPTION AND RATIONALE

Diffuse Intrinsic Pontine Glioma (DIPG) is a devastating, aggressive brain tumor of childhood arising in the ventral pons. Though brainstem tumors are rare among adults, they comprise approximately 10-15% of pediatric brain tumors, with half of all pediatric malignant gliomas occurring in the brainstem[1]. DIPG is the most common tumor subtype in this anatomical region, constituting 80% of brainstem gliomas[2]. With an estimated 200-400 children affected by DIPG annually in the United States, it is the second most common malignant brain tumor of childhood [3]. The prognosis is bleak: in the absence of effective therapies, DIPG is uniformly fatal and is the leading cause of childhood brain tumor death. Median age at diagnosis is 6-7 years, with median survival of 9 months; 90% of children will die from the disease within 2 years of initial diagnosis, with less than 1% surviving after 5 years[4].

Because DIPG grows diffusely and infiltrates critical brainstem structures, surgical resection is not possible. Radiation therapy has remained the mainstay of treatment for the past three decades since its introduction. At most treatment centers, the standard recommendation is conventionally fractionated local field radiotherapy with dose range of 54-60 Gy for a period of 6 weeks[5]. Radiotherapy provides temporary improvement or stabilization of symptoms and extends overall survival by an average of 3 months; median survival is less than 5 months without radiation[6]. Though both clinical and radiographic responses are initially observed, local recurrence invariably occurs. (See protocol for references).

SCHEMA

Description
This is a multicenter, phase 1 trial of Panobinostat (LBH589) for children with diffuse intrinsic pontine glioma tumors.

Panobinostat is a pan-HDAC inhibitor of Class I, II and IV histone deacetylases (HDACs) involved in the deacetylation of histone and non-histone cellular proteins. Panobinostat inhibits purified total cellular histone deacetylase activity (IC_{50} = 0.03 uM) and activities of most HDAC isoforms (IC_{50} <10nM). In addition, panobinostat induces expression of the cell-cycle control genes including CDKN1A (p21), and selectively inhibits the proliferation of a variety of tumor cells compared to normal cells. It has been extensively profiled for its *in vitro* and *in vivo* pharmacological activity on a variety of tumor cell lines and tumor xenograft mice models.

Based on the *in vitro* and *in vivo* activity of panobinostat in preclinical models using DIPG cell cultures and orthotopic xenograft model systems, and the potentially important role of histone deacetylases and histone 3 K27M mutations in relation to pontine malignancies, we are conducting a Phase 1 study of panobinostat in children with recurrent/progressive DIPG.

The primary objectives of the study are to (1) describe the toxicity profile and define the dose-limiting toxicities of panobinostat in children with recurrent/progressive DIPG; (2) estimate the maximum tolerated dose and/or the recommended Phase 2 dose of panobinostat in children with

recurrent/progressive DIPG; and (3) evaluate and characterize the plasma pharmacokinetics of panobinostat in children with recurrent/progressive DIPG.

Schema
Only patients with recurrent or progressive DIPG will be enrolled initially. Panobinostat will be administered every other day, 3 times/week, p.o. preferably on a Monday/Wednesday/Friday schedule for three weeks, followed by a rest period. Three weeks of therapy plus the one week rest period (total 4 weeks) will constitute one course. Treatment will continue for up to two years (26 courses) unless the patient experiences progressive disease, unacceptable toxicity or any of the off-study criteria.

The starting dose (dose level 1) is 10 mg/m^2/day. The table below lists the proposed dose levels to be studied:

Dose level #	***panobinostat oral dose (mg)***	***Minimum BSA Restriction***
*0**	5 mg/m^2/day MWF, three weeks on, one week off (1 course = 28 days)	Patients must have a BSA $\geq$ 0.80 m^2
1 (starting dose level)	10 mg/m^2/day MWF, three weeks on, one week off, (1 course = 28 days)	Patients must have a BSA $\geq$ 0.65 m^2
2	16 mg/m^2/day MWF, three weeks on, one week off, (1 course = 28 days)	Patients must have a BSA $\geq$ 0.65 m^2
3	22 mg/m^2/day MWF, three weeks on, one week off, (1 course = 28 days)	Patients must have a BSA $\geq$ 0.65 m^2
4	28 mg/m^2/day MWF, three weeks on, one week off, (1 course = 28 days)	Patients must have a BSA $\geq$ 0.50 m^2
5	36 mg/m^2/day MWF, three weeks on, one week off, (1 course = 28 days)	Patients must have a BSA $\geq$ 0.50 m^2
	Panobinostat will be administered as a single agent *** Dose level 0 represents a potential treatment dose for patients requiring a dose reduction from dose level 1 and may be used as a contingency dose level if the starting dose level of panobinostat is not tolerated in the initial cohort.**	

OBJECTIVES

Primary Objectives

- To describe the toxicity profile and define the dose-limiting toxicities of panobinostat in children with recurrent/progressive DIPG
- To estimate the maximum-tolerated dose and/or the recommended-phase 2 dose of panobinostat in children with recurrent/progressive DIPG
- To evaluate and characterize the plasma pharmacokinetics of panobinostat in children with recurrent/progressive DIPG

Secondary Objectives

- To describe the progression-free survival (PFS) and overall survival (OS) of children with recurrent or progressive DIPG who are treated with panobinostat
- To identify histone 3 K27M mutations in peripheral blood and urine, and evaluate changes with treatment

PATIENT SELECTION

All patients must meet the following inclusion and exclusion criteria.

Inclusion Criteria

- Diagnosis: Patients with progressive DIPG, as defined by progressive neurologic abnormalities or worsening neurologic status not explained by causes unrelated to tumor progression (e.g., anticonvulsant or corticosteroid toxicity wean, electrolyte disturbances, sepsis, hyperglycemia, etc.), OR an increase in the bi-dimensional measurement, taking as a reference the smallest disease measurement recorded since diagnosis, OR the appearance of a new tumor lesion since diagnosis.
    - Please note: patients with a radiographically typical DIPG, defined as a tumor with a pontine epicenter and diffuse involvement of more than 2/3 of the pons, are eligible without histologic confirmation.
    - Patients with pontine lesions that do not meet these radiographic criteria will be eligible if there is histologic confirmation of malignant glioma WHO II-IV.
- Age: Patients must be ≥ 2 but < 22 years of age at the time of enrollment.
- BSA:
  Patients must have a BSA ≥ 0.80 m2 for dose 5mg/m2.
  Patients must have a BSA ≥ 0.65 m2 for doses of 10mg/m2 - 22 mg/m2.
  Patients must have a BSA ≥ 0.50 m2 for doses of 28 mg/m2 - 36 mg/m2.

- Neurologic Status: Patients must be able to swallow whole capsules.

- Performance Status: Karnofsky Performance Scale (KPS for > 16 years of age) or Lansky Performance Score (LPS for ≤ 16 years of age) assessed within 7 days of enrollment must be ≥ 50%. 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.

- Prior Therapy: Patients must have received a minimum of 54 Gy focal irradiation administered over approximately 42 days prior to enrollment. 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.

- Myelosuppressive Chemotherapy: Patients must have received their last dose of known myelosuppressive anticancer therapy or immunotherapy at least 21 days prior to enrollment (42 days if prior nitrosourea).

- Investigational/Biologic Agent: Biologic or investigational agent (anti-neoplastic):
  Patient must have recovered from any acute toxicity potentially related to the agent and received their last dose of the investigational or 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, and discussed with the principal investigator.

- Investigational/Biologic Agent: 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.

- Radiation Therapy: Patients must have had their last fraction of:
  - Craniospinal irradiation or radiation to ≥ 50% of pelvis > 3 months prior to enrollment.
  - Focal irradiation to the primary site > 42 days prior to enrollment
  - Local palliative irradiation other than previously irradiated primary site (small port) ≥ 14 days

- Organ Function: Patients must have organ and marrow function as defined below:
  - Absolute neutrophil count ≥ 1,000/mm3
  - Platelets ≥ 100,000/ mm3 (unsupported, defined as no platelet transfusion within 7 days and recovery from nadir)
  - Hemoglobin ≥ 8 g/dL (may receive transfusions)
  - Total bilirubin ≤ 1.5 times institutional upper limit of normal (ULN)
  - ALT (SGPT) ≤ 3 x institutional upper limit of normal
  - Albumin ≥ 3 g/dL
  - Potassium ≥ LLN

- Serum total calcium (correct for serum albumin) or ionized calcium ≥ LLN
- Serum creatinine based on age/gender as noted in the table below. Patients that do not meet the criteria in the table below but who have a 24-hour Creatinine Clearance or GFR (radioisotope or iothalamate) ≥ 70 ml/min/1.73 m2 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
≥ 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.		

- Cardiac Function
  - Left ventricular ejection fraction ≥ 50 by gated radionuclide study OR shortening fraction of ≥ 27% by echocardiogram
  - Patient has no ventricular arrhythmias except for benign premature ventricular contractions.
  - Patient has a QTc interval < 450 ms.

- Growth Factors: Patients must be off all colony-forming growth factor(s) for at least 7 days prior to enrollment (i.e. filgrastim, sargramostim or erythropoietin). 14 days must have elapsed if patients received PEG formulations.

- Fruit: Patients must agree to avoid grapefruit or grapefruit juice and Seville (sour) oranges during the entire study.

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

- Breastfeeding: Female patients with an infant must agree not to breastfeed their infants while on this study.

- 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 and for 3 months after the last dose of panobinostat.

- 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.

Exclusion Criteria

- Prior Therapy:
  - Patients who have had > 60 Gy total radiation to the pons (e.g. patients who have received re-irradiation).
  - Patients have had prior HDAC, DAC, HSP90 inhibitors for the treatment of their DIPG.
  - Patients have had valproic acid within 28 days prior to enrollment.
  - Patients have had prior bone marrow transplant.

- Neurological Status: Patients have significant acute deterioration in neurologic status in 72 hours prior to enrollment, in the opinion of the treating physician.

- Gastrointestinal
  - Patients have impairment of GI function or GI disease that may significantly alter the absorption of panobinostat; for example severe inflammatory bowel disease.
  - Patients have diarrhea > CTCAE grade 2.

- Systemic Illness: Patients have 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 ability of the patient to tolerate protocol therapy or put them at additional risk for toxicity or would interfere with the study procedures or results.

- Other Malignancy: Patients have a history of any other malignancy.

- Transfusions: Patients are known to be refractory to red blood cell or platelet transfusions.

- Concurrent Therapy
  - Patients who are receiving any other anticancer or investigational drug therapy
  - Patients who are required to receive any medication which can prolong the QTc interval. Please see Protocol Appendix B: Medications Which May Cause QTc Prolongation.

- 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 drug administration plan, other study procedures, and study restrictions