PBTC-012 Abstract for Health Professionals

Study Title: Phase I Study of Cilengitide (EMD 121974) in Children with Refractory Brain Tumors

Description: Phase I dose escalation study of the anti-angiogenesis agent, cilengitide, a potent and selective cyclized RGD pentapeptide antagonist of the integrins avβ3 and avβ5 in children with brain tumors refractory to standard therapy.

Primary Objective:

1. To describe the acute and dose-limiting toxicities (DLT) and define the maximum tolerated dose (MTD) of cilengitide (EMD 121974) when administered to children and adolescents with refractory primary brain tumors.

Secondary Objectives:

1. To obtain preliminary evidence of biologic activity by determining alterations in tissue perfusion, tumor blood flow and metabolic activity using MR perfusion, PET and MRS, and correlating these findings with changes in tumor size by volumetric MRI.

2. To characterize inter- and intra-patient variability in the pharmacokinetics of cilengitide and to estimate cilengitide renal clearance in this patient population.

3. To characterize the pharmacogenetic polymorphisms in drug transporters (e.g., MRP4, BCRP) and relate to cilengitide disposition.

4. To evaluate changes in circulating endothelial cells (CECs) and circulating endothelial precursors (CEPs) in patients treated with cilengitide, and to investigate the correlation between changes in CECs and CEPs, plasma, serum and urine levels of angiogenic proteins such as VEGF, and clinical outcome.

5. To obtain preliminary information about the efficacy of cilengitide in this patient population.

Eligibility Criteria:

- Age: Patients must be <= 21 years of age.
- Tumor: Patients with histological diagnosis of primary CNS tumor and evidence that the tumor is recurrent or progressive and refractory to standard therapy, including histologically benign CNS tumors (e.g. low-grade glioma). Clinical and radiographic evidence of a brain stem glioma is required in the absence of histologic diagnosis.
- Performance status: Karnofsky or Lansky Score >= 50
- Organ function: ANC > 1,000/µl; Platelets > 100,000/µl (transfusion independent); Hemoglobin > 8.0 g/dl (may be transfused); creatinine < 1.5 times normal range for age or GFR > 70 ml/min/1.73m^2; total bilirubin within normal range for age; SGPT (ALT) and SGOT (AST) < 2.5 times upper limit of normal.
- Prior therapy: No investigational agent, including biologic agent, within two (2) weeks of study entry; at least six (6) weeks from nitrosourea

agent to study entry; and at least four (4) weeks from any myelosuppressive therapy to study entry. Greater then six (6) months since bone marrow transplant and at least six (6) weeks from prior radiation therapy or greater than three (3) months from craniospinal irradiation (> 24 Gy) or total body irradiation or greater than two (2) weeks from local palliative irradiation to study entry.

- Exclusion Criteria: Patient must not have overt renal, hepatic, cardiac or pulmonary disease and must not be receiving any other anticancer or experimental drug therapy with the exception of corticosteroids.

Rationale:

Pre-clinical studies have demonstrated that cilengitide is a potent inhibitor of avβ3 and avβ5 -mediated cell adhesion, of *in vitro* endothelial cell migration and invasion, and of angiogenesis in the chicken chorioallantoic membrane (CAM) model. In addition, cilengitide has demonstrated *in vivo* antitumor activity in human melanoma, carcinoma, medulloblastoma and glioblastoma cell lines in the CAM model, as well as in scid and nude mouse orthotopic models, and has shown an acceptable toxicity profile in adult phase I trials for patients with CNS tumors. In view of these results, it is appropriate to evaluate this novel anti-angiogenesis agent in children with refractory primary CNS tumors.

Schema:

Cilengitide is given by intravenous infusion over 1 hour, twice weekly, with at least two days between doses and no interruptions of this schedule. Each 4-week period is defined as a course and a total of 13 courses (1 year) may be administered in the absence of unacceptable toxicity or tumor progression. Pharmacokinetic studies will be performed with the first dose of course 1 and 2. Biologic studies will be performed at baseline, on day 14 of each course, and at the discontinuation of treatment. Dose escalations will be performed using the modified CRM method as follows:

Cilengitide (EMD 121974) Dose Escalation	
Dose Level	Dose (mg/m^2)
0	100
1	120*
2	240
3	480
4	720
5	1200
6	1800
7	2400
*starting dose	

Contact:

Study Chair	**Study Co-Chair**

Tobey MacDonald, M.D., Children's National Medical Center Department of Hematology/Oncology 111 Michigan Avenue, NW Washington, DC 20010	Mark W. Kieran, M.D., Ph.D. Dana-Farber Cancer Institute Department of Pediatric Oncology 44 Binney Street Boston, MA 02115