PBTC-002 Abstract for Health Professionals

Study Title: A Phase I Study of SU5416 in Pediatric Patients With Recurrent or Progressive Poor Prognosis Brain Tumors

Description:

This is a phase I trial for patients 21 years of age or less, with recurrent or progressive brain tumors. It is a collaborative study of the Pediatric Brain Tumor Consortium.

Patients will receive intravenous SU5416 twice weekly for up to two years. Cohorts of 3 to 6 patients will receive escalating doses of SU5416 until the maximum tolerated dose (MTD) is established.

SU5416 Dose Escalation Table		
Dose Level	**Patients not on enzyme-inducing anticonvulsant drugs** **Dose (mg/m^2)**	**Patients taking enzyme-inducing anticonvulsant drugs** **Dose (mg/m^2)**
1	110	48
2	145	65
3	190	85
4	250	110
5	330	145
6	-	190
7	-	250
8	-	330

Pharmacokinetic analysis and biological activity studies will be conducted using standard pharmacokinetic tests and *in vitro* endothelial proliferation and inhibition assays and sera from patients pre-drug and post-drug. Standard 3-D MRI, multi-voxel MRS, rapid perfusion/diffusion MRI and PET (where available) imaging will be obtained.

Objectives:

1. To determine the maximum-tolerated dose (MTD) and toxicity profile of SU5416 in pediatric patients with refractory brain tumors, stratified by concurrent use of enzyme-inducing anticonvulsant drugs.

- To obtain preliminary information about the efficacy of SU5416 and investigate the relation among tumor imaging characteristics, surrogate markers of tumor angiogenesis, and reported toxicities.

Rationale:

The traditional role of chemotherapy has been to directly disrupt the division of cancerous cells; however, tumor cells with high mutation rates quickly develop resistance to the therapy so that further treatment by the same agent no longer slows the growth of the tumor. One alternative to targeting tumor cells themselves is disrupting the supply of blood (and therefore oxygen and nutrients) to the malignancy.

This study utilizes SU5416 (Semoxind), which may inhibit the proliferation of cancerous cells indirectly by interfering with the activity of tyrosine kinase receptors on the surfaces of endothelial cells, which help to support blood flow to the tumor. SU5416 inhibits endothelial cell proliferation *in vitro* but does not inhibit normal or tumor cell growth, proliferation, or differentiation, which are targets of standard chemotherapy. SU5416 has been tested on numerous mouse and human tumors in a murine *in vivo* system and has shown regression of some tumors. Extensive testing of this agent in mice, and preliminary toxicity data in adults has shown limited drug induced toxicity, even when used at high doses.

Eligibility Criteria:

- Patients 21 years of age or younger.
- Patients with malignant recurrent or progressive brain tumors. Patients must have a histologically proven diagnosis either from initial presentation, or at the time of recurrence or progression. For patients with brainstem gliomas, the requirement for histologic verification may be waived.
- Evidence of recovery from prior chemotherapy. No myelosuppressive chemotherapy within 3 weeks (6 weeks if a nitrosourea agent) of entry onto study. Bone Marrow Transplant > 6 months prior to study entry
- XRT: > 3 months prior to study entry for craniospinal irradiation (>24Gy) or total body irradiation; and > 2 weeks prior to study entry for focal irradiation to symptomatic metastatic sites.
- Performance Status: Karnofsky/Lansky >= 60%, life expectancy > 8 weeks.
- Nutrition status: > 3rd percentile weight for height; Albumin > 3g/dl.
- Patient has adequate organ function as defined by the following parameters: ANC >1000/µl; Platelets > 75,000/µl; Hgb > 9 g/dl; Creatinine <= 1.5X N or GFR > 70 ml/min/1.73m^2; Bilirubin within normal range; SGPT (ALT) and SGOT (AST) < 2.5X N; PT/PTT <= 120% upper limit of normal. Patient has no overt renal, hepatic, cardiac or pulmonary disease.
- Off growth factors > 1 week and if receiving dexamethasone, must be on a stable dose for at least 1 week prior to study entry.
- Signed informed consent according to institutional guidelines must be obtained and patient must begin therapy within fourteen days of registration.

Contact:

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