PBTC-006 Abstract for Health Professionals

Study Title: A Phase I/II Trial of STI571 in Children with Newly Diagnosed Poor Prognosis Brainstem Gliomas and Recurrent Intracranial Malignant Gliomas

Description:

Dose Finding: During the dose-finding component of the trial, children with newly diagnosed localized poor prognosis brainstem gliomas and recurrent intracranial malignant gliomas, including recurrent brainstem gliomas will be studied.

In **Stratum 1**, children with newly diagnosed localized brainstem tumors will receive STI-571 twice daily, starting 2 weeks (+ 1 week) after completion of a standard 6-week interval of radiation therapy, beginning at a dose of 350 mg/m^2/day, provided that there is no evidence of intratumoral hemorrhage at the completion of irradiation. The modified CRM method will be used to estimate the MTD. Toxicity will be evaluated after two 28-day courses of therapy. In the absence of disease progression or dose-limiting toxicity, treatment will continue for 1 year. Daily doses of STI571 to be studied are 350 mg/m^2, 465 mg/m^2, 620 mg/m^2, and 800 mg/m^2. De-escalation of the starting dose (between patients) will be permitted, in the event of dose-limiting toxicity. The dose-limiting toxicity observation period for the purpose of establishing the MTD will be the first two 28-day courses of STI-571 treatment.

In **Stratum 2**, children with recurrent intracranial malignant gliomas will receive STI-571 twice daily, as described above. As in Stratum 1, the modified CRM method will be used to estimate the MTD independently in both substrata. Patients have already been accrued at the 350, 465, and 620 mg/m^2 dose levels and dose levels for subsequent patients will start at a dose of 465 as determined by the CRM, using the same range of dose levels included in stratum 1. Toxicity will be evaluated after two 28-day courses (eight weeks) of therapy. Patients will be stratified based on concurrent use of EIACDs into substrata 2A (not receiving) and 2B (receiving EIACD).

Safety and Efficacy–Phase II. When the MTD is determined, efficacy will be investigated further in Stratum 1 by enrolling additional patients at the MTD established for this stratum. The efficacy endpoints will be 1-year progression-free survival among children with newly diagnosed brainstem glioma. For Stratum 2, a total of 12 patients in each substratum will be treated at the MTD, and no formal analysis of efficacy will be performed.

Objectives:

Primary Objectives:

1. To define the maximal tolerated dose of STI571 administered beginning 2 weeks + 1 week after completion of involved field irradiation in children with newly diagnosed poor prognosis brainstem gliomas.

2. To define the maximal tolerated dose of STI571 in children with recurrent high-grade intracranial gliomas, stratified according to use of enzyme inducing anticonvulsant drugs (EIACD).

3. To assess the efficacy of STI571 in children newly diagnosed with a poor prognosis brainstem glioma.

Secondary Objectives:

1. To develop exploratory data concerning surrogate endpoints of therapeutic activity, using physiological neuroimaging studies and correlative biological studies.

2. To characterize the pharmacokinetics of STI571 in the above patient groups and determine the effects of EIACD on the pharmacokinetics.

Rationale:

STI-571 is a pharmacological inhibitor of selected tyrosine kinase receptors, and was initially found to have preclinical activity in inhibiting the BCR-Abl fusion protein expressed in Ph+ leukemias as well as evidence of clinical efficacy. More recent studies have demonstrated that this agent also inhibits platelet-derived growth factor receptor (PDGFR), a dominant mitogen signaling pathway of malignant gliomas, and exhibits significant anti-tumor activity in preclinical glioma model systems. The current study will evaluate the safety and, in a preliminary way, the efficacy of this agent in recurrent high-grade gliomas and in newly diagnosed brainstem gliomas (given as adjuvant therapy following radiotherapy), tumors that have a generally poor prognosis with conventional therapies.

Eligibility Criteria:

Age: 3 – 21 years

Tumor type: Stratum 1: Newly diagnosed localized intrinsic diffuse brainstem glioma without imaging evidence of intratumoral hemorrhage during or prior to standard irradiation.

Stratum 2: Recurrent anaplastic astrocytoma, glioblastoma multiforme, or other high-grade glioma, including recurrent brainstem glioma.

Performance status: Karnofsky $\geq$ 50; Lansky $\geq$ 50

Laboratory: *Bone marrow*: ANC > 1,000/µl, Platelets > 100,000/µl (transfusion independent); Hemoglobin> 8g/dl (may be transfused). *Renal:* creatinine < 1.5x normal for age or GFR = 70 ml/min/1.73m2. *Hepatic*: bilirubin <= 1.5 times institutional normal for age; SGPT (ALT) < 3X institutional normal for age and albumin >= 2 g/dL. *No overt renal, hepatic, cardiac or pulmonary disease.*

Schema:

STI571 is given orally twice a day with no interruptions in the absence of dose limiting toxicity. Each 28-day period is defined as a course. STI571 therapy will continue without interruption for up to 13 courses (52 weeks) in the absence of progression or serious toxicity. The dose limiting toxicity evaluation period is the first 8 weeks of STI571 therapy.

	Stratum 1 **Newly Diagnosed Localized Brain Stem Gliomas**	**Stratum 2** **Recurrent or Refractory Intracranial High Grade Gliomas**
	Patients must not be taking enzyme inducing anticonvulsants	Patients are stratified according to those not using enzyme inducing anticonvulsants (Stratum 2A) and those using enzyme-inducing anticonvulsants (Stratum 2B). Dose escalation will be conducted independently in both strata.

Radiation Therapy:	Patients receive a standard 6-week course of radiation therapy. An MRI evaluation will be given post irradiation to ensure there is no evidence of intratumoral hemorrhage.	None
STI571 Therapy:	Patients start 2 weeks ± 1 week after completion of radiation.	Patients within 10 days of registration.

STI571 Dose Escalation Table – Total Daily Dose

	Stratum 1	Stratum 2A	Stratum 2B
Dose Level	Dose (mg/m^2)	Dose (mg/m^2)	Dose (mg/m^2)
-1	100		
0	150		
1	200*		
2	265	265	265
3	350**	350	350
4	465	465**	465**
5	620	620	620
6	800	800	800

*** Original Starting Doses.**
**** Starting doses for new post-irradiation escalation of Stratum 1 and Stratum 2 .**

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