PBTC-007 Abstract for Health Professionals

Study Title: A Phase I/II Trial of ZD1839 (Iressa™) and Radiation in Pediatric Patients Newly Diagnosed with Brain Stem Tumors or Incompletely Resected Supratentorial Malignant Gliomas with Phase II Limited to Brain Stem Tumors

Children with newly diagnosed intrinsic brain stem gliomas (BSG) and incompletely resected supratentorial malignant gliomas (STMG) with residual tumor on imaging will be eligible for this study.

The study will consist of an initial dose finding (phase I) component, and a subsequent efficacy (phase II) component for patients with brain stem gliomas. For the purpose of dose finding, two strata will be identified. 1) BSG and STMG not receiving enzyme inducing anticonvulsant drugs (EIACD) and 2) STMG receiving anticonvulsants. In each stratum, the beginning dose of ZD1839 will be 100 mg/m^2/day commencing with the beginning of radiation therapy.

In the absence of disease progression or dose-limiting toxicity, treatment will continue for one year. Treatment may continue longer if drug is benefiting the patients and continues to be available. Daily doses of ZD1839 to be studied subsequently are 250 mg/m^2, 375 mg/m^2, 500 mg/m^2, 650 mg/m^2 and 850 mg/m^2. De-escalation of the starting dose to 75 mg/m^2 will be permitted, in the event of a dose-limiting toxicity at the first dose level. The dose-limiting toxicity observation period for the purpose of establishing safety during radiotherapy will be the first two 28-day courses of treatment (eight weeks). Pharmacokinetics will be evaluated for each patient and if the blood levels obtained at 850 mg/m^2/day are substantially less than obtained in adults at the adult MTD further dose levels may be studied unless a MTD has been reached.

When the MTD is determined or the highest dose level reached (whichever is lowest), efficacy will be investigated further in patients with BSG by enrolling additional patients at that dose for Stratum 1. The efficacy endpoints will be 1-year progression-free survival. For Stratum 2, a total of 12 patients will be treated at the highest dose evaluated or at the MTD, and no formal analysis of efficacy will be performed.

Primary Objectives:

1. To define the safety of ZD1839 administered in conjunction with irradiation in children with newly diagnosed brainstem gliomas and incompletely resected STMG not receiving EIACDs.
2. To define the safety of ZD1839 in children with newly diagnosed, incompletely resected STMG receiving EIACDs.
3. To assess the efficacy of ZD1839 given with radiation therapy in children newly diagnosed with a poor prognosis brainstem glioma.

Secondary Objectives:

1. To compare hemodynamic MR parameters to metabolic FDG-PET scanning and correlate both with clinical response or progression in this population.
2. To characterize the expression of ErbB1 receptors in tissue from STMG patients using immunohistochemistry and western blot assays.
3. To characterize the pharmacokinetics of ZD1839 in the above patient groups and determine the effects of EIACD on the pharmacokinetics.
4. To explore the pharmacogenetic polymorphisms for ZD1839 (e.g., CYP3A4/5 and BCRP) and relate them to ZD1839 pharmacokinetics and pharmacodynamics (phenotype-genotype).

Age: $\geq$ 3 and $\leq$ 21 years

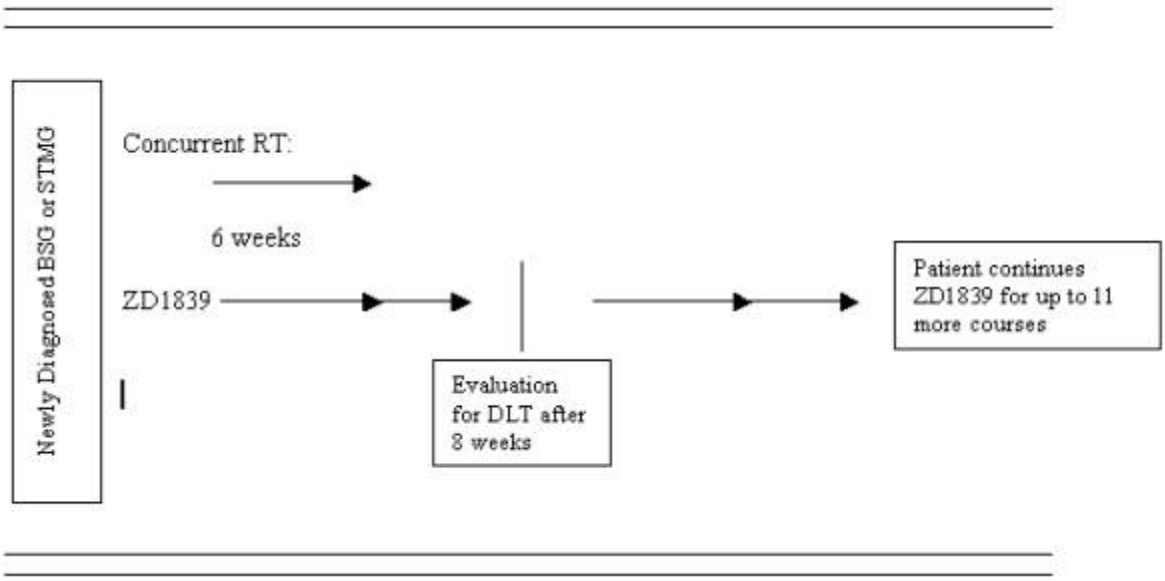
Tumor type: Newly diagnosed localized intrinsic diffuse brainstem glioma.
Newly diagnosed anaplastic astrocytoma, glioblastoma multiforme or other high-grade glioma with incomplete resections

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

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

Schema:

ZD1839 is given orally once a day with no interruptions in the absence of dose limiting toxicity. Each 28 day period is defined as a course. ZD1839 therapy will continue for up to 13 courses (52 weeks) in the absence of progression or serious toxicity.



ZD1839 Dose Escalation Table ***Round dose to the nearest 5 mg***		
	Stratum 1	**Stratum 2**
Dose Level	**Dose (mg/m^2)**	**Dose (mg/m^2)**
0	75	75
1	100*	100*
2	250	250

3	375	375
4	500	500
5	650	650
6	850	850

*Starting Dose

Note: If pharmacokinetic studies demonstrate substantially lower blood levels of ZD1839 than seen in adults at 850 mg/m^2 further dose levels will be studied.

Contact:

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