Protocol Abstract and Schema

A Phase I, Molecular Biology and Phase II Study of Lapatinib (GW572016) in Pediatric Patients with Recurrent or Refractory Medulloblastoma, Malignant Glioma or Ependymoma

Description:

This protocol is comprised of a dose-finding Phase I study, a Molecular Biology study and a Phase II study. The Phase I component of this protocol has two aims: (i) To estimate the maximum tolerated dose (MTD) and to describe the dose limiting toxicities (DLTs) of oral lapatinib (GW572016) administered twice daily for 28 consecutive days to children with recurrent or refractory malignant CNS tumors in two strata: a) Stratum 1: those who are not receiving steroids and b) Stratum 2: those who are receiving steroids; (ii) To characterize the effect of steroids on the lapatinib (GW572016) disposition in children. Lapatinib (GW572016) will be administered twice daily for 28 days at a starting dose of 300 mg/m^2/dose bid (~80% of the adult MTD). This defines one course of therapy.

After the MTD is estimated in stratum 1, the molecular biology component of the study will commence concurrently with the phase II component of the study. The molecular biology study is designed to assess whether lapatinib (GW572016) administered at the MTD inhibits intratumoral ERBB receptor signaling. This question will be studied in children with recurrent or refractory medulloblastoma/PNET, high grade glioma or ependymoma who are undergoing a surgical resection of their tumor.

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The phase II trial will be conducted in children with recurrent or refractory medulloblastoma, malignant glioma or ependymoma who have measurable residual disease after the MTD is determined. Efficacy will be assessed independently in each of these histologically defined strata of patients. Patients with measurable residual disease enrolled on either the phase I trial and treated at the MTD or on the molecular biology trial will also be included in the phase II trial.

Primary Objectives:

1. To estimate the MTD and describe the DLT of oral lapatinib (GW572016) administered twice daily for 28 days to children with recurrent or refractory malignant brain tumors who are not receiving steroids (Stratum 1); and to describe toxicities in those patients who are receiving steroids (Stratum 2).

2. To test the ability of lapatinib (GW572016) to inhibit ERBB receptor signaling in recurrent or refractory: medulloblastoma/PNET, high-grade glioma or ependymoma.

3. To estimate the sustained objective response rates (CR plus PR) to lapatinib (GW572016) administered continuously at the MTD to children with recurrent or refractory: medulloblastoma/PNET, high-grade glioma or ependymoma. Independent estimates of the objective response rates will be made for each of these three histologically defined strata.

Secondary Objectives:

1. To characterize the plasma and tissue pharmacokinetics of lapatinib (GW572016) in children.

2. To assess the effect of steroids on the pharmacokinetics of lapatinib (GW572016).

3. To explore the pharmacogenetic polymorphisms in lapatinib (GW572016) metabolizing enzymes and relate these polymorphisms to lapatinib pharmacokinetics.

4. To estimate the incidence of ERBB1, ERBB2, ERBB3 and ERBB4 expression and pathway activation in recurrent or refractory CNS tumors of childhood, including ependymoma, medulloblastoma/PNET, and high grade glioma.

5. To identify additional genes both within and outside the canonical ERBB pathway that might act as determinants of response to lapatinib (GW572016).

Eligibility Criteria:

- **Age:** birth to ≤ 21 years.

- **Body Surface Area**: Patients enrolled during the Phase I trial must have a minimum body surface area of 0.4 m^2

- **Tumor:** Phase I Trial:
  - All patients with recurrent or refractory malignant CNS tumors. A histological diagnosis of malignant CNS tumor from either the initial presentation or at the time of recurrence is required for all patients but those with diffuse intrinsic brain stem gliomas.

  Molecular Biology Trial:
  - Patients must have recurrent or refractory: medulloblastoma/PNET, high grade glioma (anaplastic astrocytoma, glioblastoma multiforme, gliosarcoma, anaplastic oligodendroglioma), or ependymoma with a histological diagnosis from either the initial presentation or at the time of recurrence.
  - Patients for whom surgical resection is clinically indicated and are amenable to receiving GW572016 for 7 to 14 days prior to their resection.

  Phase II Trial:
  - Patients must have recurrent or refractory: medulloblastoma/PNET, high grade glioma, or ependymoma with a histological diagnosis from either the initial presentation or at the time of recurrence.
  - Patients must have measurable disease.

- **Neurological Deficits**: Neurological deficits must be stable for a minimum of 1 week prior to registration.

- **Performance Score**: Karnofsky Performance Scale (KPS for > 16 yrs of age) or Lansky Performance Score (LPS for ≤ 16 years of age) ≥ 50 assessed within two weeks prior to registration.

- **Prior/ Concurrent Therapy:**
  - Chemo: Evidence of recovery from prior chemotherapy. No myelosuppressive anticancer chemotherapy or biological therapy within 3 weeks (6 weeks if a nitrosourea or mitomycin C agent) of registration.
  - XRT: ≥ 3 months prior to registration for craniospinal irradiation (≥ 18 Gy); ≥ 4 weeks for local radiation to primary tumor; and ≥ 2 weeks prior to registration for focal irradiation to symptomatic metastatic sites.
  - Bone Marrow Transplant: ≥ 6 months prior to registration for allogeneic bone marrow transplants and ≥ 3 months prior to registration for autologous bone marrow/stem cell transplants.
  - Anti-convulsants: Patients receiving EIACD will not be eligible. Patients must be off EIACD for at least 2 weeks prior to registration.
  - Growth factors: Off all hematopoetic growth factor(s) ≥ 2 weeks prior to registration (G-CSF, GM-CSF, erythropoietin).
  - Corticosteroids: Patients who are receiving corticosteroids must be on a stable or decreasing dose for at least 1 week prior to registration.

- The following laboratory values must be assessed within two (2) weeks prior to registration and again within seven (7) days prior to the start of therapy.

  - Absolute neutrophil count ≥ 1,000/ microliter
  - Platelets ≥ 100,000/ microliter (transfusion independent)
  - Hemoglobin ≥ 8 g/dL (transfusion independent)

  - Renal: Serum creatinine less than ≤ 1.5 times upper limit of institutional normal for age or GFR ≥ 70 ml/min/1.73m^2.

  - Hepatic: Bilirubin ≤ 1.5 times upper limit of normal for age; SGPT (ALT) ≤ 2.5x institutional upper limit of normal for age and albumin ≥ 2 g/dL.

- Adequate cardiac function, assessed within 2 weeks prior to registration, defined as: shortening fraction of ≥ 27% by echocardiogram, or ejection fraction ≥ 50% by gated radionuclide study.

- Adequate pulmonary function, assessed within 2 weeks prior to registration, defined as: no evidence of dyspnea at rest, no exercise intolerance, and a pulse oximetry > 94% if there is clinical indication for determination.

- Female patients of childbearing potential must have negative serum or urine pregnancy test. Patient must not be pregnant or breast-feeding.

- 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.

- Signed informed consent according to institutional guidelines must be obtained.

Exclusion Criteria:

- Patients with any significant medical illnesses that, in the investigator's opinion, cannot be adequately controlled with appropriate therapy or would compromise the patient's ability to tolerate this therapy
- Patients with any disease that would obscure toxicity or dangerously alter drug metabolism
- Patients receiving any other anticancer or experimental drug therapy
- Patients with uncontrolled infection
- Patients on enzyme inducing anticonvulsants

Schema:

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This study of lapatinib (GW572016) will be conducted in three separate trials: a phase I, a Molecular Biology, and a Phase II trial.

Phase I Trial

Patients will receive lapatinib (GW572016) orally twice daily. Four consecutive weeks will constitute one course and subsequent courses will immediately follow, with no break in the administration of the drug. In the absence of unacceptable toxicity or disease progression, treatment may continue for 26 courses (2 years). Lapatinib (GW572016) dosing will begin at a starting dose of 300 mg/m^2/dose twice daily and be increased in subsequent cohorts until the MTD is reached as shown below.

Lapatinib (GW572016) Dose Escalation Table

Dose Level	***Dose (mg/m^2/dose) bid***
0	210
1*	300*
2	400
3	520
4	700
*starting dose	

During the Phase I trial, patients will be stratified by use of corticosteroids.

Phase I Stratification

Stratum 1	***Stratum 2***
Patients <u>not</u> receiving corticosteroids	Patients receiving corticosteroids

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Once the MTD has been estimated, the molecular biology trial and the phase II trial will be initiated concurrently.

Molecular Biology Trial

The molecular biology trial will test the ability of lapatinib (GW572016) administered at the MTD to inhibit ERBB receptor signaling in children with recurrent or refractory: medulloblastoma/PNET, malignant glioma or ependymoma.

Patients enrolled in this component of the trial must be those for whom surgical resection is clinically indicated and be amenable to surgical resection of their recurrent or progressive tumor. Patients will be stratified by histology and randomly assigned to one of two treatment groups: 1) to receive lapatinib (GW572016) at the MTD for seven (7) to fourteen (14) days prior to surgery or 2) no GW572106 prior to surgery. Post-operatively, all patients (including those randomized to receive no drug in the pre-operative period) will then receive twice daily oral lapatinib (GW572016) in 28-day cycles at the MTD estimated in the Phase I trial. In the absence of disease progression or unacceptable toxicity drug may be continued for up to two years (26 courses).

Molecular Biology Trial Stratification

Stratum A		***Stratum B***		***Stratum C***	
recurrent or refractory medulloblastoma/PNET		***recurrent or refractory malignant glioma***		***recurrent or refractory ependymoma***	
Arm 1	***Arm 2***	***Arm 1***	***Arm 2***	***Arm 1***	***Arm 2***
Lapatinib (GW572106) 7 -14 days pre-surgery	No lapatinib (GW572106) pre-surgery	Lapatinib (GW572106) 7-14 days pre-surgery	No lapatinib (GW572106) pre-surgery	Lapatinib (GW572106) 7-14 days pre-surgery	No lapatinib (GW572106) pre-surgery

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Phase II Trial

The efficacy of lapatinib (GW572016) for the treatment of children with recurrent or refractory medulloblastoma/PNET, high-grade glioma (HGG) or ependymoma will be evaluated in terms of the objective (CR and PR) response rates in patients with measurable residual disease. Each stratum will be evaluated independently.

Patients will receive oral lapatinib (GW572016) twice daily in 28 day cycles at the MTD estimated in the Phase I component of the study. In the absence of disease progression or unacceptable toxicity drug may be continued for up to two years (26 courses).

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Phase II Trial Stratification

Stratum A	***Stratum B***	***Stratum C***
recurrent or refractory medulloblastoma/PNET	recurrent or refractory high-grade glioma	recurrent or refractory ependymoma