

Protocol Abstract and Schema

Phase I study of the Smoothed (SMO) antagonist GDC-0449 for recurrent or refractory medulloblastoma

Description

This is a multicenter, phase I trial for children with recurrent or refractory medulloblastoma to recommend daily dose of GDC-0449 for a subsequent Phase II trial, evaluate toxicity and characterize the pharmacokinetics and biologics of the GDC-0449.

Primary Objectives

- To select, based on safety and pharmacokinetics, a daily dose of GDC-0449 to recommend for a subsequent PBTC Phase II trial of children with recurrent or refractory medulloblastoma

Secondary Objectives

- To document and describe toxicities associated with GDC-0449 administered on a daily schedule.
- To characterize the pharmacokinetics (plasma and cerebrospinal fluid) of GDC-0449 in children/adolescents with refractory medulloblastoma
- To document preliminary antitumor activity in patients with recurrent or refractory medulloblastoma treated with GDC-0449
- To identify Medulloblastoma that belong to the subset of tumors that have an activated PTCH/SHH pathway using pathologic and genomic methods

Eligibility Criteria

Age: Patients must be at least 3 years of age (≥ 3 and ≤ 21 yrs) on the date of registration.

Tumor: Patients with a histologically confirmed diagnosis of medulloblastoma that is recurrent, progressive, or refractory to standard therapy and for which there is no known curative therapy.

Neurological Status: Patients with neurological deficits should have deficits that are stable for a minimum of 1 week prior to registration. This is to be documented in the database.

Performance Status: Karnofsky Performance Scale (KPS for > 16 yrs of age) or Lansky Performance Score (LPS for ≤ 16 years of age) ≥ 60 assessed within two weeks prior to registration

Prior/Concurrent Therapy

- Must have recovered from prior treatment-related toxicity. No other myelosuppressive chemotherapy or immunotherapy within 4 weeks prior to study entry (6 weeks if prior nitrosurea).
- Decadron dose should also be stable or decreasing for at least 1 week (7days) prior to starting therapy.
 - XRT ≥ 3 months prior to study entry for craniospinal irradiation (≥ 23 Gy); ≥ 8 weeks for local irradiation to primary tumor; ≥ 2 weeks prior to study entry for focal irradiation for symptomatic metastatic sites.
 - Off all colony stimulating factors > 1 week prior to study entry (GCSF, GM CSF, erythropoietin).

Organ dysfunction

- Adequate bone marrow functions for patients without bone marrow involvement:
 - ANC $\geq 1000 \mu\text{L}$
 - Platelet count $\geq 100,000/\mu\text{L}$ (transfusion independent)
 - Hemoglobin $\geq 8.0 \text{ gm/dL}$ (may receive RBC transfusions)
- Adequate Renal Function defined as:
 - Creatinine clearance or radioisotope GFR $\geq 70 \text{ ml/min/1.73 m}^2$ or
 - A serum creatinine based on age as follows:

| Age (Years) | Maximum Serum Creatinine (mg/dL) |
|---------------------------|----------------------------------|
| ≤ 5 | 0.8 |
| $5 < \text{age} \leq 10$ | 1.0 |
| $10 < \text{age} \leq 15$ | 1.2 |
| > 15 | 1.5 |

- Adequate Liver Function defined as:
 - Total bilirubin $\leq 1.5 \times$ upper limit of normal (ULN) for age,
 - SGPT (ALT) $\leq 5 \times$ institutional upper limit of normal (ULN) for age
 - SGOT (AST) ≤ 5 times institutional upper limit of normal for age
 - Serum albumin $\geq 2.5 \text{ g/dL}$

Baseline Adverse Events: Patient must have recovered from the significant acute toxicities of all prior therapy before entering this study and meet all other eligibility criteria specified in the Inclusion and Exclusion Criteria.

Growth factors: Off all colony forming growth factor(s) for at least 1 week prior to registration (filgrastim, sargramostim, erythropoietin).

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

Pregnancy Prevention 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.

Informed Consent: Signed informed consent according to institutional guidelines must be obtained.

Exclusion Criteria

Concurrent Illness:

- Patients with diagnosis of Atypical Teratoid / Rhabdoid Tumor (ATRT); supratentorial PNET
- Patients with any clinically significant unrelated systemic illness (serious infections or significant cardiac, pulmonary, hepatic or other organ dysfunction), that would compromise the patient's ability to tolerate protocol therapy or would likely interfere with the study procedures or results.

Current Therapy: Patients receiving any other anticancer or investigational drug therapy

Inability to Participate: Patients with inability to return for follow-up visits or obtain follow-up studies required to assess toxicity to therapy.

Other: below given criteria are confirmed by the patient history

- Inability to swallow capsules
- Malabsorption syndrome or other condition that would interfere with enteral absorption
- History of congestive heart failure
- History of ventricular arrhythmia requiring medication.
- History of congenital long QT syndrome

- Uncontrolled hypocalcemia, hypomagnesemia, hyponatremia or hypokalemia defined as less than the lower limit of normal for the institution despite adequate electrolyte supplementation.
- Clinically important history of liver disease, including viral or other hepatitis or cirrhosis.

Study Rationale

GDC -0449 is a novel molecule that inhibits aberrant downstream signaling in the *PTCH /SHH* pathway. Preclinical studies in mouse models that spontaneously develop medulloblastoma have demonstrated that treatment of the mice with GDC 0449 will suppress tumor formation and will induce reduction in tumors of tumor bearing mice.

Phase I studies in adults with basal cell carcinoma have demonstrated that the drug is well tolerated in adults and has minimal toxicity. Patients with basal cell carcinoma demonstrated complete and partial responses. More importantly *Gli-1* expression in these tumors decreased > 2 times from their baseline values.

Based on the strong preclinical rational and encouraging data from the adult phase I study we propose a Phase I type study with GDC-0449. The initial dose for the trial will be 85 /m² (89% of the adult MTD). Initially, dose-limiting toxicity will comprise toxicities attributable to drug administration occurring during the first course. Therapy may continue as long as the patient's disease remains stable. Although safety will be based on toxicities observed during the first course, toxicities observed during course 2 will be classified according to whether they are dose limiting and any chronic grade 3/4 toxicities that occur after the first course will be documented and may warrant a review of the treatment regimen.

In consenting patients, serial plasma samples will be collected during therapy with GDC-0449 to allow the estimation of pharmacokinetic parameters in children with recurrent medulloblastoma. In children with Omayo reservoirs, simultaneous cerebrovascular fluid (CSF) and plasma samples will be collected to assess GDC-0449 CSF penetration. Archival tissue samples will be collected from patients to evaluate whether diagnostic reagents under development can detect HH pathway activation in archival tumor tissue

Schema

The drug will be administered orally on a once a day schedule continuously for 28 days in patients with recurrent or refractory medulloblastoma. 28 days defines one course of therapy and there are no breaks between courses. Patients may continue to receiving the protocol therapy up to 13 courses if patient doses not meet 'off treatment' criteria per protocol and there are no unacceptable toxicities.