A PHASE II CLINICAL TRIAL EVALUATING THE EFFICACY AND SAFETY OF GDC-0449 IN CHILDREN WITH RECURRENT OR REFRACTORY MEDULLOBLASTOMA

PROTOCOL ABSTRACT AND SCHEMA

Description

This is a multicenter, phase II type trial for children with recurrent or refractory medulloblastoma, to estimate the efficacy of GDC-0449 treatment for pediatric patients with recurrent or refractory medulloblastoma, as measured by the objective response rates for patients without (Stratum A) and with (Stratum B) evidence of activation of Hedgehog (Hh) signaling pathway in their tumors.

Schema

BSA Range	Mg Dose	Frequency
≥0.67-1.33	150 mg	Once daily (QD)
>1.33-2.21	300 mg	Once daily (QD)
>2.21-2.50	450 mg	Once daily (QD)

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 receive the protocol therapy for up to 26 courses if the patient does not meet 'off treatment' criteria per protocol and there are no unacceptable toxicities.

Primary Objective

- To estimate the efficacy of GDC-0449 treatment for pediatric patients with recurrent or refractory medulloblastoma, as measured by the sustained objective response rates for patients without (Stratum A) and with (Stratum B) evidence of activation of Hedgehog (Hh) signaling pathway in their tumors.
- To characterize the pharmacokinetics (plasma) of GDC-0449 in children/adolescents with refractory medulloblastoma
- To document pathologic and genomic methods to identify medulloblastomas with activation of the Hh signaling pathway

Secondary Objectives

- To document and describe toxicities associated with GDC-0449 administered on a daily schedule
- To estimate the duration of objective response and progression-free survival (PFS)
- To characterize the pharmacokinetics (cerebrospinal fluid) of GDC-0449 in children/adolescents with refractory medulloblastoma

PATIENT SELECTION

Inclusion Criteria

Age

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

Tumor Tissue

Patient must have archival formalin fixed, paraffin embedded (FFPE) primary tumor material for biology studies.

*Patient has Immunohistochemical (IHC) evidence of Hh pathway activated tumor

**This eligibility criterion will be used now that stratum A is closed to accrual. At this time, a screening consent is used to confirm the Hh pathway activation. The Stratum A Closed to Accrual eligibility criteria are now operative.*

Evaluable Tumor on Imaging

Patients must have bi-dimensionally measureable disease in the brain or spinal cord defined as at least one lesion that can be accurately measured in at least 2 planes in order to be eligible for this study.

BSA

Patients must have a BSA of $\geq 0.67 m^2$ and at most $2.5 m^2$.

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 status of ≥ 50% in patients > 16 years, or Lansky performance status of ≥ 50% in patients ≥ 3 yrs and ≤ 16 years, 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; ≥ 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).
- Prior therapy will include primary therapy (including radiation therapy and chemotherapy) and a maximum of 2 additional salvage therapies. Patients can enroll on the protocol after failure on primary therapy.

Organ dysfunction

- **Adequate bone marrow functions for patients without bone marrow involvement:**
  - ANC ≥ 1000 μL
  - Platelet count ≥ 50,000/μL (transfusion independent)
  - Hemoglobin ≥ 8.0 gm/dL (may receive RBC transfusions)

- **Adequate Renal Function defined as**:
  - Creatinine clearance or radioisotope GFR ≥ 70ml/min/1.73 m^2 or
  - A serum creatinine ≤1.5 mg/dL

- **Adequate Liver Function defined as:**
  - Total bilirubin ≤ 1.5 x upper limit of normal (ULN) for age,
  - SGPT (ALT) ≤ 2.5 x institutional upper limit of normal (ULN) for age
  - SGOT (AST) ≤ 2.5 times institutional upper limit of normal for age
  - Alkaline Phosphatase ≤ 1.5x institutional upper limit of normal
  - Serum albumin ≥ 2.5 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.

Pregnancy Status

Pregnancy should be avoided for 12 months after the last dose of GDC-0449 for females of child-bearing potential. 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 within 24 hours prior to beginning treatment (see section 3.16.6 for details about the contraception for females and males and patient counseling).

Pregnancy Prevention

Women of childbearing potential are required to have a negative serum pregnancy test (with a sensitivity of at least 25 mIU/mL) within 10-14 days and within 24 hours prior to the first dose of GDC-0449 (serum or urine). A pregnancy test (serum or urine) will be administered every 4 weeks if their menstrual cycles are regular or every 2 weeks if their cycles are irregular while on study within the 24-hour period prior to the administration of GDC-0449. **Prior to dispensing GDC-0449, the investigator must confirm and document the patient's use of two contraceptive methods, dates of negative pregnancy test, and confirm the patient's understanding of the of GDC-0449 to cause spontaneous abortion or birth defects.**

Female patients are required to use two forms of acceptable contraception, including one barrier method **during participation in the study and for the 12 months following the last dose**. All patients should receive contraceptive counseling either by the investigator, or by an obstetrician (OB)/ gynecologist or other physician who is qualified in this area of expertise. If a woman of childbearing potential believes that her contraceptive method has failed, emergency contraception should be considered.

If a patient is suspected to be pregnant, GDC-0449 should be immediately discontinued. In addition, a positive urine test must be confirmed by a serum pregnancy test. If it is confirmed that the patients is not pregnant, the patient may resume dosing with GDC-0449.

If a female patient becomes pregnant during therapy or within 12 months after the last dose of GDC-0449, or if the female partner of a male patient exposed to the drug becomes pregnant while the male patient is receiving GDC-0449 or within 12 months after the last dose of GDC-0449, the investigator must be notified in order to facilitate outcome follow-up.

Abortion, whether accidental, therapeutic, or spontaneous, should always be classified as serious. Any congenital anomaly/birth defect in a child conceived during the study or within 12 months after the last dose of GDC-0449 to a female patient or to a female partner of a male patient exposed to the agent during treatment or within 12 months after the last dose of GDC-0449 should be recorded and reported as an SAE.

- Female patients should not breastfeed a baby while on this study.

- Female patients must NEVER donate ova while being treated with GDC-0449.

- All sexually active male subjects (including those who have undergone vasectomy) should utilize a barrier form of contraception **during study treatment and for 12 months after the last dose** as it is not known whether GDC-0449 that may be present in seminal fluid would cause serious or life-threatening birth defects in a fetus born to the female partner of a male subject. Males should also not donate sperm during treatment or up to 12 months after the last dose.

Informed Consent

Signed informed consent must be obtained including for pharmacokinetic study according to institutional guidelines.

Exclusion Criteria

CNS embryonal tumor other than medulloblastoma

Patients with diagnosis of Atypical Teratoid / Rhabdoid Tumor (ATRT), PNET from a non-cerebellar site within the central nervous system, ependymoblastoma, and medulloepithelioma

Concurrent Illness

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
- 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