

PBTC-025B - A Phase II Clinical Trial Evaluating the Efficacy and Safety of GDC-0449 in Adults with Recurrent or Refractory Medulloblastoma

Description

This is a multicenter, phase II trial for adults with recurrent or refractory medulloblastoma to describe the efficacy, response and toxicities of the drug in patients with recurrent or refractory medulloblastoma.

Objectives

Primary Objectives

- To estimate the efficacy of GDC-0449 treatment for adult 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 Sonic Hedgehog (SHH) signaling pathway tumors.

Secondary Objectives

- To assess the safety and tolerability of GDC-0449 administered on a once daily schedule.
- To estimate the duration of objective response and progression-free survival (PFS)
- To characterize the pharmacokinetics (plasma and cerebrospinal fluid) of GDC-0449 in adults with refractory medulloblastoma
- To document pathologic and genomic methods to identify CNS tumors with activation of the PTCH/SHH pathway
- To describe the objective responses observed in patients whose pathologic assessment of tumor result in unknown (Stratum C) evidence of activation of Sonic Hedgehog (SHH) signaling pathway tumors.

Eligibility Criteria

Inclusion Criteria

Patients must meet the following criteria to be eligible for study entry:

Age

- Patients must be at least 22 years of age (≥ 22 yrs) on the date of registration

Tumor

- Patients with a histologically confirmed diagnosis of medulloblastoma (including posterior fossa PNET) that is recurrent, progressive, or refractory to standard therapy and for which there is no known curative therapy are eligible.
- The diagnosis should be confirmed at the treating institution and tissue (either from the diagnosis or relapse or preferably from both time points) must be available for biological studies

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

- ECOG performance status 0- 2 (see appendix III)

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 nitrosourea).
- 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:**
 - $ANC \geq 1000/\mu L$
 - Platelet count $\geq 100,000/\mu L$ (transfusion independent)
 - Hemoglobin ≥ 8.0 gm/dL (may receive RBC transfusions)

- **Adequate Renal Function defined as:**
 - Creatinine clearance or radio-isotope GFR ≥ 70 ml/min/1.73 m² 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)
 - SGOT (AST) ≤ 2.5 times 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 § 3.15.3 - 3.15.8 and appendix VII for details about the contraception for females and males and patient counseling).

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.

Acceptable and Unacceptable Forms of Contraception

- Acceptable forms of barrier contraception:
 - Latex condom (always used with spermicide)
 - Diaphragm (always used with spermicide)
 - Cervical cap (always used with spermicide)

- Acceptable forms of secondary contraception, when used along with a barrier method:
 - Hormonal contraception methods, including pills, patches, rings, or injections except progestin-only containing pills (i.e. “Mini-pill”)
 - Tubal ligation
 - Partner’s vasectomy
 - Intrauterine device (non-progesterone T)
 - Vaginal sponge (containing spermicide)
- Other Acceptable forms:
 - 100% commitment to abstinence
- Unacceptable forms of contraception for women of childbearing potential:
 - Oral contraception containing progestins only
 - IUD progesterone T
 - Female condom
 - Natural family planning (rhythm method) or breastfeeding
 - Fertility awareness
 - Withdrawal
 - Cervical shield

Informed Consent

Signed informed consent according to institutional guidelines must be obtained.

Exclusion Criteria

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

- Life expectancy < 12 weeks as determined by treating physician
- Inability to swallow capsules
- Prior treatment with GDC-0449 or other antagonists of the HH pathway
- 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.
- Congenital long QT syndrome
- Treatment with excluded medications as outlined in §5.4.9 and appendix VIII

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. Based on the encouraging activity of GDC-0449 in advanced BCC, a tumor that is driven by the SHH pathway, this Phase II study has been designed to demonstrate the clinical benefit of GDC-0449 in adult patients with recurrent medulloblastoma

Schema

The drug will be administered at 150 mg orally on a once a day schedule continuously for 28 days in patients with recurrent or refractory medulloblastoma. This defines one course of therapy. Therapy may continue until evidence of disease

progression, intolerable toxicities most probably attributable to GDC-0449 or withdrawal from the trial. A maximum of 26 courses of therapy will be allowed on the protocol.