

PBTC-032: A Phase II Clinical Trial Evaluating the Efficacy and Safety of GDC-0449 in Children with Recurrent or Refractory Medulloblastoma.

PURPOSE: This phase II trial is studying how well GDC-0449 works in treating younger patients with recurrent or refractory medulloblastoma. GDC-0449 may slow the growth of tumor cells

Study Type: Interventional
Masking: Open Label
Primary Purpose: Treatment

OBJECTIVES

PRIMARY:

- 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.
- Characterize the pharmacokinetics (plasma) of GDC-0449 in children/adolescents with refractory medulloblastoma.

SECONDARY:

- Document and describe toxicities associated with GDC-0449 administered on a daily schedule.
- Estimate the duration of objective response and progression-free survival (PFS).
- Document pathologic and genomic methods to identify medulloblastomas with activation of the Hh signaling pathway.
- Characterize the pharmacokinetics (cerebrospinal fluid) of GDC-0449 in children/adolescents with refractory medulloblastoma.

OUTLINE: This is a multicenter study. Patients are stratified according to evidence of activation of Hedgehog signaling pathway in their tumors (without vs with vs unknown).

Patients receive oral Hedgehog antagonist GDC-0449 once daily on days 1-28. Treatment repeats every 28 days for up to 26 courses in the absence of disease progression or unacceptable toxicity.

Plasma and cerebrospinal fluid samples are collected periodically for pharmacokinetic and other correlative studies.

After completion of study treatment, patients are followed up for up to 12 months.

AGES ELIGIBLE FOR STUDY: 3 Years to 21 Years

CRITERIA

Inclusion Criteria:

- 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
- Patient has immunohistochemical (IHC) evidence of Hh pathway-activated tumor (stratum B only)
- Patients must have bi-dimensionally measurable 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
- Patients with neurological deficits should have deficits that are stable for a minimum of 1 week prior to registration
- Patient must have adequate archival formalin-fixed, paraffin-embedded (FFPE) primary tumor material for biology studies
- No 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, or medulloepithelioma)
- Karnofsky performance status of $\geq 50\%$ in patients > 16 years, or Lansky performance status of $\geq 50\%$ in patients ≥ 3 yrs and ≤ 16 years
- ANC $\geq 1,000$ μL
- Platelet count $\geq 50,000/\mu\text{L}$ (transfusion independent)
- Hemoglobin ≥ 8.0 g/dL (may receive RBC transfusions)
- Creatinine clearance or radioisotope GFR ≥ 70 mL/min OR a serum creatinine 1.5 mg/dL
- Serum total bilirubin ≤ 1.5 x upper limit of normal (ULN) for age
- ALT ≤ 2.5 x institutional ULN for age
- AST ≤ 2.5 x institutional ULN for age
- Alkaline phosphatase ≤ 1.5 x institutional ULN
- Serum albumin ≥ 2.5 g/dL
- Not pregnant or nursing
- Negative pregnancy test
- Fertile patients must use 2 forms of acceptable contraception, including one barrier method, during and for 12 months after completion of study treatment
 - 100% commitment to abstinence is considered an acceptable form of birth control

- Patients must have a BSA of $\geq 0.67 \text{ m}^2$ and at most 2.5 m^2
- No 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
- No patients with inability to return for follow-up visits or obtain follow-up studies required to assess toxicity to therapy
- None of the following:
 - 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
- Male patients may not donate sperm during or for 12 months after completion of study treatment
- Female patients may not donate ova while being treated with GDC-0449
- Patients may not donate blood for 12 months after completion of study treatment
- Patient must not be receiving warfarin
- 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
- 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 (7 days) prior to starting therapy
- Radiotherapy: ≥ 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 (G-CSF, GM-CSF, erythropoietin)
- No patients receiving any other anticancer or investigational drug therapy

For more information contact:

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