

Protocol Abstract and Schema

Phase I and Pharmacokinetic Trial of PTC299 in Pediatric Patients with Refractory or Recurrent CNS Tumors

Description:

This is a Phase I and pharmacokinetic (PK) trial of PTC299, a novel, orally bioavailable, small molecule which selectively inhibits tumor vascular endothelial growth factor (VEGF) protein expression at the post-transcriptional level. The study will be conducted in pediatric patients with refractory or recurrent central nervous system (CNS) tumors. PTC299 will be given 2 times per day (BID) or 3 times per day (TID), every day, continuously. The total dose to be administered to each patient will be based on milligrams of drug per kilogram of actual patient body weight. Four consecutive weeks will constitute 1 course and subsequent courses will immediately follow, with no break in administration. The dose escalation is designed to achieve dose levels comparable to those being used in trials of PTC299 in adults.

Rationale:

Tumor growth and metastasis are believed to be dependent, at least in part, on the ability of a tumor to induce neovascularization. Angiogenesis inhibitors may play a role either in prevention of tumor growth or in decreasing tumor propensity for metastasis of childhood CNS tumors. There is marked angiogenic activity in astrocytic as well as embryonal tumors. In some studies the degree of angiogenesis inversely correlates with patient survival. Angiogenesis inhibitors have been demonstrated to result in tumor control in adults with high-grade gliomas and children with low-grade gliomas.

The mechanisms involved in tumor-induced angiogenesis are complex and involve paracrine signaling by VEGF, basic fibroblast growth factor (bFGF), Platelet Derived Growth Factor and a variety of other cytokines. VEGF is one of the most common angiogenic factors found in tumor-induced angiogenesis. Treatment of CNS tumors by angiogenesis inhibitors has been found to be relatively safe. However, there are potentially significant risks, including systemic and intracranial hemorrhage and clotting.

It is known that VEGF production by tumors is controlled post-transcriptionally by sequences in both the 5'- and 3'-untranslated regions (UTRs) of its encoding messenger ribonucleic acid (mRNA). PTC299 is a novel, orally bioavailable small molecule designed to control tumor growth by selectively inhibiting VEGF protein expression at the post-transcriptional level. PTC299 suppresses tumor overproduction of all 4 VEGF isoforms and inhibits production of other angiogenic cytokines. It also induces a parallel interruption of tumor cell division at G1/S phase of cell cycle, offering a potential additional mechanism of action. In vitro studies demonstrate that PTC299 preferentially inhibits VEGF production in cells stimulated by stressors such as hypoxia. In vivo studies show that single-agent PTC299 reduces tumor and plasma VEGF concentrations, decreases tumor microvessel density, and induces tumor regression or substantially impedes tumor progression in multiple xenograft models of human cancer, including gliomas. In vitro studies in cultured tumor cells demonstrate that PTC299 inhibits VEGF production in multiple tumor types. Evaluation of drug disposition has indicated that PTC299 penetrates the blood-brain barrier.

Safety and pharmacology studies and Phase I studies in adult healthy volunteers and patients with cancer have indicated that PTC299 in capsule form is generally well tolerated by adults at doses through 120 mg/dose 3 times daily (TID) (approximately equivalent to 1.8 mg/kg/dose TID). Preliminary drug metabolism studies have shown that PTC299 is metabolized by cytochrome P450 isoenzyme 2C19 but not 3A4, and is unlikely to be affected by enzyme-inducing anticonvulsants.

The planned starting doses are based on the established safety and PK profiles from previous nonclinical experience and from prior Phase I studies of healthy adult volunteers and other Phase I studies in adult patients with cancer. Dosing levels offer the potential to achieve target plasma trough concentrations associated with PTC299 anti-tumor activity in pre-clinical xenograft models. Body-weight-based dosing using capsule strengths of 10 mg and 20 mg will be used to accommodate the variations in body size in pediatric patients. Four dose levels will be evaluated to reach dosing levels that are projected to achieve plasma exposures similar to those observed in adult patients.

Schema:

PTC299 Dose Escalation Schedule

Dose Level	Dose
0	0.6 mg/kg/dose BID
1 (Starting Dose)	1.2 mg/kg/dose BID
2	1.2 mg/kg/dose TID
3	1.5 mg/kg/dose TID
4	2.0 mg/kg/dose TID

PTC299 will be administered orally BID or TID continuously in 28-day courses with no interruptions between courses. Patients may continue to receive study drug until the patient experiences disease progression or unacceptable toxicity.

OBJECTIVES

Primary Objectives

1. To estimate the maximum tolerated dose (MTD) and to recommend a Phase II dose of PTC299 for children with recurrent or progressive CNS tumors.
2. To evaluate and characterize the adverse events associated with PTC299 administration in children with recurrent or progressive CNS tumors.
3. To evaluate and characterize the pharmacokinetics and pharmacodynamics of PTC299 in children with recurrent and progressive CNS tumors.

Secondary Objectives

4. To investigate the relationships between PTC299 plasma exposure and other outcome measures.
5. To evaluate the anti-tumor activity of PTC299 within the confines of a Phase I study.
6. To evaluate changes in angiogenic and inflammatory markers in the blood and to investigate the relationships between these changes and other outcome measures.
7. To obtain preliminary evidence of biologic activity of PTC299 by using MR diffusion to assess tumor cellularity.

Inclusion Criteria

- Patients must be ≥ 3 years and ≤ 21 years of age on the date of registration.
- Patients must have a body weight of ≥ 15 kg and ≤ 100 kg.
- Patients must have a histologically confirmed diagnosis of a primary CNS malignancy that is recurrent, progressive, or refractory to standard therapy and for which there is no known curative therapy. All tumors must have histological verification at either the time of diagnosis or recurrence except patients with intrinsic brain stem tumors and optic pathway gliomas. These patients must have radiographic evidence of progression.
- Patients with neurological deficits should have deficits that are stable for a minimum of 1 week prior to registration.
- Patients must be able to swallow capsules
- Patients must have a Karnofsky Performance Scale (for patients >16 years of age) or Lansky Performance Score (for patients ≤ 16 years of age) ≥ 50 assessed within 2 weeks prior to registration.
- Patients must have recovered from the acute toxic effects of all prior therapy (excluding alopecia or neurotoxicity) before entering this study. For those baseline adverse events attributable to prior therapy, recovery is defined as a toxicity grade ≤ 2 , according to the Common Terminology Criteria for Adverse Events (CTCAE) version 4.0, unless otherwise specified in the Inclusion and Exclusion Criteria.
- Patients must have received their last dose of known myelosuppressive anticancer chemotherapy at least three (3) weeks prior to registration or at least six (6) weeks if nitrosourea.
- Patients must have an interval of ≥ 14 days between last dose of any investigational or biologic agent and registration.
 - For agents that have known adverse events occurring beyond 7 days after administration, this period must be extended beyond the time during which adverse events are known to occur. The duration of this interval must be discussed with the study chair prior to registration.
 - For biologic agents that have a prolonged half-life, at least three half-lives must have elapsed prior to registration. Such patients should be discussed with the study chair prior to registration.

- Patients must have completed an interval comprising ≥ 3 half-life periods between the last dose of monoclonal antibody and registration.
- Patients must have an interval of ≥ 2 weeks between local palliative XRT and registration
- An interval of ≥ 6 weeks between prior total-body irradiation, craniospinal XRT, or XRT involving irradiation of $\geq 50\%$ of the pelvis and registration
- Patients must have an interval of ≥ 90 days between allogenic bone marrow transplantation and registration. No active graft-versus-host disease may be present at the time of registration
- If receiving dexamethasone or other corticosteroids, the subject must be on a stable dose for ≥ 7 days prior to registration
- If taking antihypertensive medications, the subject must be stable on their current regimen for a minimum of 7 days prior to registration
- Patients must have normotensive blood pressure (as defined as SBP and/ or DBP ≤ 95 th percentile for age: see details in Appendix VIII, IX) for a minimum of 7 days prior to registration. If a BP reading prior to registration is > 95 th percentile for age and height it must be rechecked and documented to be \leq the 95th percentile for age and height prior to the patient registration.
- Off all colony-forming growth factor(s) (e.g. filgrastim, sargramostim, erythropoietin) for ≥ 1 week prior to registration and ≥ 14 days for long-acting formulations (e.g. pegfilgrastim).
- Documented within 14 days of study registration and within 7 days of the start of study drug administration:
- Bone Marrow
 - o Absolute neutrophil count $\geq 1,000/\mu\text{l}$ (unsupported)
 - o Platelets $\geq 100,000/\mu\text{l}$ (unsupported)
 - o Hemoglobin ≥ 8 g/dL (may be supported)
- Renal
 - o Creatinine clearance or radioisotope glomerular filtration rate (GFR) ≥ 70 ml/min/1.73 m² or a serum creatinine based on age as follows:

Age (years)	Maximum Serum Creatinine (mg/dL)
≤ 5	0.8
>5 to ≤ 10	1
>10 to ≤ 15	1.2
>15	1.5

- Urine protein/creatinine ratio < 1.0
- Hepatic
 - Serum total bilirubin ≤ 1.5 x institutional upper limit of normal (ULN) for age
 - Serum glutamic pyruvic transaminase (SGPT)/alanine aminotransferase (ALT) ≤ 2.5 x institutional ULN for age
 - Serum glutamic oxaloacetic transaminase (SGOT)/aspartate aminotransferase (AST) ≤ 2.5 x institutional ULN for age
- Nutrition
 - Albumin ≥ 2.5 g/dL
- Coagulation
 - Prothrombin time (PT) and activated partial thromboplastin time (aPTT) ≤ 1.2 x institutional ULN
- 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 test must be repeated within 48 hours prior to the start of therapy).
- 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 which includes consenting to mandatory PK and PD studies must be obtained according to institutional guidelines.

Exclusion Criteria

- 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.
- Patients receiving any other anticancer or investigational drug therapy.
- Major surgical procedures ≤ 4 weeks prior to study enrollment.
- Intermediate surgical procedures ≤ 2 weeks prior to study enrollment.
- Minor surgical procedures ≤ 7 days prior to study enrollment.
- Unwilling or unable to comply with scheduled visits, drug administration plan, laboratory tests (including PK and pharmacodynamic assessments), other study procedures, and study restrictions.
- Known coagulopathy or bleeding diathesis.
- Known history of drug-induced liver injury.
- CNS, pulmonary, gastrointestinal, or urinary bleeding within 1 month prior to registration.
- Evidence of ongoing systemic bacterial, fungal, or serious viral infection.
- Ongoing alcohol or drug addiction.
- Inability to tolerate periodic magnet resonance imaging (MRI) scans or gadolinium contrast.