PBTC-041: A Phase I Trial of p28 (NSC745104), a Non-HDM2 Mediated Peptide Inhibitor of p53 Ubiquitination in Pediatric Patients With Recurrent or Progressive CNS Tumors

PURPOSE: This phase I trial studies the side effects and best dose of azurin-derived cell-penetrating peptide p28 (p28) in treating patients with recurrent or progressive central nervous system tumors. Drugs used in chemotherapy, such as azurin-derived cell-penetrating peptide p28, work in different ways to stop the growth of tumor cells, either by killing the cells or by stopping them from dividing.

Study Type: Interventional
Primary Purpose: Treatment

AGES ELIGIBLE FOR STUDY: 3 to 21 Years

Objectives

Primary

- To establish whether the adult recommended phase II dose of 3x/week bolus infusions of p28 is safe for pediatric patients with recurrent/refractory central nervous system (CNS) tumors.
- To describe dose-limiting toxicities of 3x/week bolus infusions of p28 in pediatric patients with recurrent/refractory CNS tumors.
- To evaluate and characterize the plasma pharmacokinetics of p28 in children with recurrent/refractory CNS tumors.

Secondary

- To describe in the context of a phase I trial any observed antitumor activity of p28.
- To investigate levels of p53 in clinical tumor specimens of patients with pediatric gliomas and other pediatric CNS tumors treated with p28.
- To document the type/site(s) of p53 mutation in tumor tissue specimens. IV. To evaluate and characterize the intratumoral pharmacokinetics of p28 in children with recurrent/refractory CNS tumors, if available.

OUTLINE: This is a dose-escalation study. Patients receive azurin-derived cell-penetrating peptide p28 intravenously (IV) over 15 minutes thrice weekly for 4 weeks. Treatment repeats every 6 weeks for up to 10 courses in the absence of disease progression or unacceptable toxicity.

After completion of study treatment, patients are followed up for at least 30 days.

Criteria

Inclusion Criteria:

- Patients must have histologically confirmed primary progressive, recurrent or refractory CNS tumors with no known curative therapies limited to high grade glioma, such as glioblastoma multiforme, medulloblastoma, primitive neuroectodermal tumor, atypical
teratoid/rhabdoid tumor, anaplastic astrocytoma, high-grade astrocytoma not otherwise specified (NOS), anaplastic oligodendroglioma, or choroid plexus carcinoma; or diffuse intrinsic pontine glioma; the requirements for histological verification are waived for diffuse intrinsic pontine glioma

- Patients must not have received myelosuppressive chemotherapy or immunotherapy within 3 weeks of registration (6 weeks if prior nitrosourea)
- Patients must have received their last dose of biologic agent >= 7 days prior to study registration
- Steroid dose should be stable or decreasing for at least 1 week prior to registration
- If prior therapy was monoclonal antibody, 30 days or 3 half-lives must have elapsed (whichever is longer), prior to registration
- Patient must be off all colony stimulating factors > 1 week prior to registration (filgrastim [GCSF], sargramostim [GM CSF], erythropoietin)
- Any craniospinal irradiation must have taken place >= 3 months prior to registration >= 8 weeks for local irradiation to primary tumor; >= 2 weeks prior to study entry for focal irradiation for symptomatic metastatic sites
- Karnofsky performance scale (KPS) (for > 16 years [yrs] of age) or Lansky performance score (LPS) (for =< 16 years of age) >= 50 assessed within two weeks prior to registration
- Patients with neurological deficits should have deficits that are stable for a minimum of 1 week prior to registration
- Absolute neutrophil count >= 1000/ mm^3 (unsupported)
- Platelets >= 100,000/ mm^3 (unsupported)
- Hemoglobin >= 8g/dL (with or without packed red blood cells [PRBC] transfusion)
- Total bilirubin =< 1.5 times upper limit of normal for age
- Alanine aminotransferase (ALT) (serum glutamate pyruvate transaminase [SGPT]) =< 3.0 times institutional upper limit of normal for age
- Aspartate aminotransferase (AST) (serum glutamic oxaloacetic transaminase [SGOT]) =< 3.0 times institutional upper limit of normal for age
- Blood glucose within normal limits for age (If above institutional normal limits must be repeated as fasting and then within normal limits [WNL] for age)
- Creatinine clearance or nuclear glomerular filtration rate (GFR) >= 70 mL/min/1.73 m^2 or a serum creatinine based on age as follows:
  - <= 5 years: 0.8 mg/dL
  - > 5 to <= 10 years: 1 mg/dL
  - > 10 to <= 15 years: 1.2 mg/dL
  - > 15 years: 1.5 mg/dL
- Albumin =< 2 g/dL
- 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
- 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 and for 6 months after the last drug administration
- Ability of subject or parent/guardian to understand and the willingness to sign a written informed consent document
Exclusion Criteria:

- Patients who are receiving any other investigational agents
- Patients with known inability to return for follow-up visits or obtain follow-up studies required to assess toxicity to therapy
- Only tumor types listed above are allowed; low grade gliomas (with and without neurofibromin 1 [NF1]) and ependymomas are excluded
- History of hypersensitivity reactions attributed to compounds of similar chemical or biologic composition to murine protein-containing products
- Uncontrolled intercurrent illness including, but not limited to, ongoing or active infection, symptomatic congestive heart failure, unstable angina pectoris, cardiac arrhythmia, or psychiatric illness/social situations that would limit compliance with study requirements
- Pregnant women are excluded from this study; breastfeeding should be discontinued if the mother is treated with p28

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