Protocol Abstract and Schema

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

Description and Rationale

Recurrent, progressive pediatric CNS tumors generally have a poor prognosis under current treatment regimens. Although disease control can sometimes be achieved after surgery, radiotherapy, and chemotherapy, for children with medulloblastoma and high-grade gliomas, once recurrence occurs most patients exhibit rapid disease progression. The lack of long-term response to therapy has prompted detailed analyses of the molecular genetic origins and response of CNS tumors.

Consensus findings from these analyses indicate substantial differences in the molecular features underlying pediatric and adult CNS tumors. These findings are exemplified in high grade gliomas (HGG), and suggest that findings in adult tumors cannot be simply extrapolated to younger patients. Much research has led to the belief of the centrality of structural alterations in the tumor suppressor protein TP53 (p53) to the course and outcome of CNS tumors. p53 (tp53) is central to the regulation of the cell cycle, DNA repair, development and programmed cell death (apoptosis) through a myriad of signaling pathways. As such, it has been characterized as the Guardian of the Genome. The p53 gene is mutated in ~ 50% of all p53+ human solid tumors. p53 is expressed in most major types of solid tumors including those of the CNS and hematologic malignancies. These tumors can express constitutively high levels of their mutant p53 due to a lack of feedback control of p53 protein levels. Mutations are concentrated within the p53 DNA binding domain (DBD) of ~200 amino acids, a domain that is central to the function of p53 as a transcription factor. Mutations within p53 are reportedly associated with a poorer Progression-Free Survival (PFS) and a strong trend toward a shorter Overall Survival (OS). Though p53 mutation and overexpression are significantly less frequent in tumors from children younger than 4 when compared to older children, p53 remains important. Although more recent observations suggest that the association between individual mutations within p53 may not be predictive of outcome, overexpression of p53 in malignant gliomas during childhood is strongly associated with an adverse outcome, independent of clinical prognostic factors and histologic findings. Moreover, the association between age and frequency of p53 mutations among pediatric malignant gliomas indicates the probable existence of two distinct pathways of molecular tumorigenesis in younger versus older children.

p53-dependent apoptosis mediates the DNA damaging, cytotoxic effects of irradiation and chemotherapy. As high-grade gliomas are notoriously insensitive to radiation and genotoxic drugs, p53 status might be associated with outcome in childhood malignant gliomas. We know that resistance to genotoxic modalities in p53-positive gliomas is generally attributed to attenuation of p53 functions by mutations of other components within the p53 signaling axis, such as p14(Arf), MDM2, ATM and the central nervous system (CNS)-restricted transcription factor Olig2, which antagonizes the interaction of p53 with promoter elements of multiple target genes.

Single and combination chemotherapy(s) that damage DNA in gliomas suggest that p53 mediates an initial response and that its regulation is intimately involved in resistance to these agents,

reducing the target response rate in pediatric patients with recurrent or progressive HGG and BSG. To date, strategies for restoration of p53 functions in tumors have focused on targeting wild-type p53 with the aim of protecting p53 from degradation by a major endogenous regulator, HDM2, a ubiquitin protein ligase that suppresses the transcriptional activity of p53 and accounts for a majority of p53 ubiquitination and subsequent proteasomal degradation.

A small molecule or peptide targeting overexpressed mutant or wild type p53 in cancer cells should not affect wild-type p53 in normal cells because wild type p53 is properly folded and expressed at low levels kept in check by HDM2. Since mutant p53 is already activated in tumor cells, downstream pathways regulated by p53 are likely to remain intact. This suggests restoration of p53 function should have a therapeutic effect at any point in tumor development without an adverse effect on normal cells.

Schema

This is a multicenter Phase I trial of p28 in pediatric recurrent/progressive CNS tumors to establish whether the adult recommended dose is safe for children. Patients will receive a 15 minute infusion of p28 3 times per week for 4 consecutive weeks, followed by two weeks of break, which constitutes one course. These 6 week courses may be repeated up to 10 times.
Dose level 1 (adult recommended dose) will be the starting dose and dose de-escalation will be governed by the Rolling-6 design as outlined below and in the statistics section.

Dose Schedule		
Dose Level	**Dose of *p28***	**Course**
Level -1	2.25 mg/kg/dose	3 x week for 4 weeks+ 2 week rest
Level 0	3.33mg/kg/dose	3 x week for 4 weeks+ 2 week rest
Level 1	4.16mg/kg/dose*	3 x week for 4 weeks+ 2 week rest

*The Rolling-6 Phase I design will be used to establish the safety of the adult recommended dose and dose de-escalations are planned in cohorts of 2 to 6 patients. De-escalation to dose level 0 and dose level -1 is possible in the event that dose level 1 and 0 are found to be too toxic.

Objectives

Primary Objectives

- To establish whether the adult recommended phase II dose of 3x/week bolus infusions of p28 is safe for pediatric patients with recurrent/refractory 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 Objectives

- 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
- To evaluate and characterize the intratumoral pharmacokinetics of p28 in children with recurrent/ refractory CNS tumors, if available

Patient Selection

All patients must meet the following inclusion and exclusion criteria. NO EXCEPTIONS WILL BE GIVEN.

Eligibility Criteria

- Tumor Diagnosis: 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 NOS, Anaplastic Oligodendroglioma, or Choroid Plexus Carcinoma; or Diffuse Intrinsic Pontine Glioma. The requirements for histological verification are waived for diffuse intrinsic pontine glioma.

- Myelosuppressive Chemotherapy: Patients must not have received myelosuppressive chemotherapy or immunotherapy within 3 weeks of registration (6 weeks if prior nitrosourea).

  Biological Agents: Patients must have received their last dose of biologic agent ≥ 7 days prior to study registration.

- Corticosteroids: Steroid dose should be stable or decreasing for at least 1 week prior to registration.

- Monoclonal Antibody Treatment: If prior therapy was monoclonal antibody, 30 days or 3 half-lives must have elapsed (whichever is longer), prior to registration.

- Growth Factors: Patient must be off all colony stimulating factors > 1 week prior to registration (GCSF, GM CSF, erythropoietin).

- Radiation Therapy: 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.

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

- Performance status: Karnofsky Performance Scale (KPS for > 16 yrs. of age) or Lansky Performance Score (LPS for ≤ 16 years of age) ≥ 50 assessed within two weeks prior to registration. See **Error! Reference source not found.**.

- Neurological Status: Patients with neurological deficits should have deficits that are stable for a minimum of 1 week prior to registration.

- Organ Function: Patients must have normal organ and marrow function as defined below, and documented within 14 days of registration and within 7 days of the start of treatment:

  - Absolute neutrophil count ≥ 1000/ mm^3 (unsupported)
  - Platelets ≥ 100,000/ mm^3 (unsupported)
  - Hemoglobin ≥ 8g/dL (with or without PRBC transfusion)
  - Total bilirubin ≤ 1.5 times upper limit of normal for age
  - ALT (SGPT) ≤ 3.0 times institutional upper limit of normal for age
  - AST (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 WNL for age)
  - Creatinine clearance or nuclear GFR ≥ 70 mL/min/1.73 m^2 or a serum creatinine based on age as follows:

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

  - Albumin ≥ 2 g/dL

- Pregnancy Status: 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 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 and for 6 months after the last drug administration.

- Informed Consent: Ability of subject or parent/guardian to understand and the willingness to sign a written informed consent document

Exclusion Criteria

- Current Therapy: Patients who are receiving any other investigational agents
- Inability to Participate: Patients with known inability to return for follow-up visits or obtain follow-up studies required to assess toxicity to therapy
- Tumor Diagnosis: Only tumor types listed above are allowed. Low grade gliomas (with and without NF1) and ependymomas are excluded.
- Agent Hypersensitivity: History of hypersensitivity reactions attributed to compounds of similar chemical or biologic composition to murine protein-containing products
- Concurrent Illness: 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
- Pregnancy and Breastfeeding: Pregnant women are excluded from this study because p28 is an investigational agent with unknown potential for teratogenic or abortifacient effects. Because there is an unknown but potential risk for adverse events in nursing infants secondary to treatment of the mother with p28, breastfeeding should be discontinued if the mother is treated with p28.

Inclusion of Women and Minorities:

- Both males and females of all races and ethnic groups are eligible for this trial.