Protocol Abstract and Schema

Phase I Study of CLORETAZINE™ (VNP40101M) in Children with Recurrent, Progressive or Refractory Primary Brain Tumors

Description:

This is a Phase I trial to estimate the maximum tolerated dose (MTD) and dose limiting toxicities (DLTs) of CLORETAZINE™ (VNP40101M) administered intravenously daily for 5 consecutive days every six weeks to children with recurrent, progressive or refractory primary brain tumors. The MTD will be estimated in two strata:

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Stratum I includes eligible patients who do not meet criteria for stratum II

Stratum II includes patients who received any one or more of the following prior therapies:

- craniospinal irradiation
- autologous bone marrow transplant
- >2 prior myelosuppressive chemotherapy or myelosuppressive biological therapy regimens

Primary Objective:

1. To estimate the MTD and describe the DLT of CLORETAZINE™ (VNP40101M) when administered intravenously daily for 5 days every 6 weeks to children with recurrent, progressive or refractory primary brain tumors.

Secondary Objectives:

1. To characterize the pharmacokinetics of CLORETAZINE™ (VNP40101M), and its active metabolite VNP4090CE, in children with recurrent, progressive or refractory primary brain tumors.

2. To estimate depletion of alkyl guanine alkyltransferase (AGT) in peripheral blood mononuclear cells (PBMC) in children with recurrent, progressive or refractory primary brain after exposure to CLORETAZINE™ (VNP40101M).

3. To obtain preliminary evidence of efficacy of CLORETAZINE™ (VNP40101M) in children with recurrent, progressive or refractory primary brain tumors.

Eligibility Criteria:

- **Age**: Patient must be ≤ 21 years of age.

- **Tumor**: Patients with a histological diagnosis of primary brain tumor (including histologically benign brain tumors (e.g. low-grade glioma)) that is recurrent, progressive, or refractory to standard therapy. Patients with intrinsic brain stem or diffuse optic pathway tumors do not require histological confirmation of disease but should have clinical and/or radiographic evidence of progression.

- **Neurological Deficits**: Patients with neurological deficits should have deficits that are not progressive for a minimum of one (1) week prior to registration.

- **Performance Score:** 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.

- **Prior therapy:**
  - Chemo: Evidence of recovery from prior chemotherapy.
    - received their last dose of known myelosuppressive anticancer chemotherapy or biological therapy at least three (3) weeks prior to study registration.
    - received their last dose of nitrosourea or mitomycin-C at least six (6) weeks prior to study registration.
    - received their last dose of other investigational agent or an anticancer drug known to be **non** myelosuppresive at least seven (7) days prior to study registration.
  - XRT: ≥ 3 months prior to registration for craniospinal irradiation (≥ 18 Gy); ≥ 2 weeks for focal irradiation radiation to primary tumor and /or symptomatic metastatic sites.
  - Bone Marrow Transplant: ≥ 6 months prior to registration for allogeneic bone marrow/stem cell transplants and ≥ 3 months prior to registration for autologous bone marrow/stem cell transplants.
  - Anti-convulsants: Patients receiving enzyme inducing anti-convulsants (EIACD) will be eligible even if they are receiving EIACDs.
  - Growth factors: Off all colony forming growth factor(s) > 1 week prior to registration (G-CSF, GM-CSF, or erythropoietin).
  - Corticosteroids: Patients who are receiving corticosteroids must be on a stable or decreasing dose for at least 1 week prior to registration.

- The following laboratory values must be assessed within two (2) weeks prior to registration and again within seven (7) days prior to the start of therapy

  - Absolute neutrophil count ≥ 1,000/mm^3 (unsupported)
  - Platelets ≥ 100,000/mm^3 (unsupported)
  - Hemoglobin ≥ 8 gm/dL (unsupported)

  - Renal: BUN < 25 mg/dl; Serum creatinine ≤ x 1.5 upper limit of institutional normal for age or GFR > 70 ml/min/1.73m^2.

  - Hepatic: Serum bilirubin ≤ 1.5 x upper limit of institutional normal. SGPT (ALT) and SGOT (AST) ≤ 2.5 times upper limit of institutional normal.

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  - Pulmonary: Adequate pulmonary function assessed within 2 weeks prior to registration, defined as DL_{CO} of ≥ 60% of predicted value. Very young patients and those who cannot reliably perform the DL_{CO} test due to neurologic dysfunction or other reasons should have a normal chest x-ray (defined as absence of pulmonary infiltrates, pneumonitis, pleural effusion, pulmonary hemorrhage, or fibrosis) and a resting pulse oximetry reading of > 94% in room air.

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  - Cardiac: Adequate cardiac function assessed within two weeks prior to registration defined as:
    1) shortening fraction ≥ 30 % assessed by echocardiogram or ejection fraction ≥50% assessed by gated radionuclide study
    2) EKG with no clinically significant cardiac arrhythmia

- No overt renal, hepatic, cardiac, or pulmonary disease.
- Female patients of childbearing potential must have negative serum pregnancy test. Patient must not be pregnant or breast-feeding.
- 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 according to institutional guidelines must be obtained prior to registration.

Exclusion Criteria

- Patients with documented bone marrow disease will not be eligible for this study. However, a bone marrow aspirate/biopsy is not required prior to study entry.
- Patient must not be receiving any other anticancer or experimental drug therapy.
- Patient must have no uncontrolled infection.
- Patients must have no known hypersensitivity to polyethylene glycol.

Rationale:

CLORETAZINE™ (VNP40101M) is a novel alkylating agent with a broad spectrum of anti-tumor activity in murine tumor models. It is believed to specifically attack the O^6 position of guanine, forming G-C DNA cross-links. CLORETAZINE™ (VNP40101M) has demonstrated in vitro and in vivo anti-tumor activity against certain selected tumor cell lines that are resistant to currently approved alkylating agents.

Schema:

CLORETAZINE™ (VNP40101M) will be given intravenously at an initial dose of 45 mg/ m^2/day for 5 consecutive days every 6 weeks up to a maximum of 8 courses of treatment.

CLORETAZINE™ (VNP40101M) Dose Escalation Table*		
CLORETAZINE™ (VNP40101M) **Dose Level**	***Stratum I*** *(mg/m^2/day)*	***Stratum II*** *(mg/m^2/day)*
-1	20	20
0	30	30
1	45**	45**
2	60	60
3	78	78
4	103	103
5	137	137
6	182	182
7	242	242

* Dose will be given daily for 5 days every 6 weeks

** Starting dose level. If the first dose level is found to be too toxic, there will be de-escalation to Dose Level 0