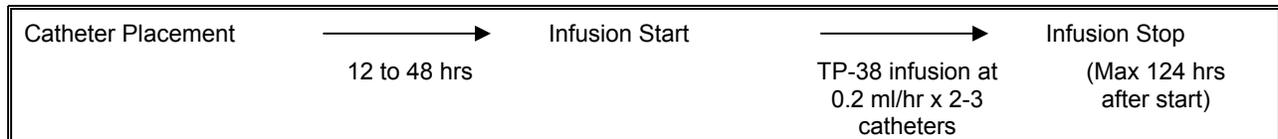


Protocol Abstract and Schema

Title: A Phase I/II Study of a Recombinant Chimeric Protein Composed of Transforming Growth Factor (TGF)- α and a Mutated Form of the Pseudomonas Exotoxin Termed PE38 (TP-38) in Pediatric Patients with Recurrent or Progressive Supratentorial High Grade Gliomas

Phase I - Flow Volume Escalation	Phase I - Concentration Escalation	Phase II
<i>Estimate the Maximum Total Flow Volume at a fixed concentration of 50 ng/mL</i>	<i>Estimate the Maximum Tolerated Infusion Concentration (MTiC) using flow volume from Step 1</i>	<i>Treat at MTiC based on Phase I Concentration</i>
Increase total flow volume (20, 30, 40 ml)	Increase concentration using flow volume from step 1: infusions: 50, 75, 100 ng/mL;	



Description:

This is a Phase I/II study of a recombinant, chimeric protein composed of transforming growth factor (TGF)- α , which is the epidermal growth factor receptor binding ligand, and a genetically engineered form of pseudomonas exotoxin, TP-38, in children between 3 and 21 years of age with recurrent or progressive high grade gliomas. Initially, in the dose-finding (Phase I) study, an escalation of flow volume with a stable concentration will be undertaken, followed by escalation of concentration at the maximum safe flow volume. In the safety and efficacy (Phase II) study, the efficacy of TP-38 will be estimated by survival post-infusion.

Objectives:

Phase I Objectives:

Primary Objective

- To describe the toxicities and estimate the maximum safe flow volume and maximum tolerated infusion concentration of TP-38, in children with recurrent or progressive malignant supratentorial high grade gliomas.

Secondary Objectives

- To estimate the prevalence of EGFR expression and phosphorylation (activity) in pediatric recurrent or progressive malignant supratentorial high grade gliomas.
- To correlate EGFR expression with qualitative measures (histology, grade and other tumor characteristics) and tumor response.

Phase II Objectives:

Primary Objective

- To estimate the efficacy of TP-38 as measured by survival post-infusion.

Secondary Objectives

- To estimate the objective response rate and progression-free survival distribution of recurrent and progressive malignant gliomas to therapy.
- To estimate the prevalence of EGFR expression and phosphorylation (activity) in pediatric recurrent or progressive malignant supratentorial high grade gliomas.
- To correlate EGFR expression with qualitative measures (histology, grade and other tumor characteristics), tumor response, survival and progression-free survival.

Eligibility Criteria:

1. Prior to enrollment patients must have a previous pathologic diagnosis of supratentorial malignant glioma and are believed not amenable for a gross total resection. Histologic documentation of apparently active tumor is required for treatment. This will be documented by frozen section compatible with glial tumor on tissue obtained by stereotactic biopsy or resection performed immediately prior to catheter placement.
2. Patients must have recurrent or progressive supratentorial malignant glioma. Baseline tumor measurements must be determined ≤ 7 days prior to study entry.
3. Tumor must have a single solid portion ≥ 1 cm and ≤ 5 cm in maximum diameter.
4. Age: Patients must be 3 – 21 years of age, inclusive. If there is a competing adult study within an institution then the upper age limit may be lowered to 18 for that institution
5. Patients must have received external beam radiotherapy, with tumor dose of ≥ 45 Gy, completed ≥ 8 weeks prior to study entry
6. Performance status: Karnofsky Performance Scale (KPS, for > 16 yrs of age) or Lansky Performance Score (LPS, for ≤ 16 years of age) ≥ 60 assessed within two weeks prior to registration.
7. Organ function: Adequate hepatic, renal and bone marrow function as outlined in protocol, assessed within two weeks prior to registration and confirmed, if necessary, to document organ function within one week prior to catheter placement. The required assessments are:
 - a. Absolute neutrophil count of $\geq 1,500/\text{mm}^3$,
 - b. Platelet count $\geq 100,000/\text{mm}^3$,
 - c. Hgb ≥ 9 gm/dl
 - d. PT/PTT \leq institutional upper limit of normal
 - e. Serum creatinine < 1.5 x normal for age or GFR > 70 ml/min/1.73m²
 - f. SGPT (ALT) and SGOT (AST) < 2.5 X upper limit of normal for age
8. Patients must have recovered from toxicity of prior therapy prior to registration. Minimum intervals required: ≥ 6 months after Gliadel® wafer, ≥ 8 weeks from hematopoietic stem cell transplant or brain radiotherapy, ≥ 4 weeks after any cytotoxic chemotherapy or any investigational agent, ≥ 6 weeks after nitrosoureas, and ≥ 2 weeks after vincristine or non-cytotoxic chemotherapy.
9. Patient (if > 18 yrs.) or patient's legal guardian must sign an IRB-approved informed consent prior to treatment. Patient's assent will be obtained as indicated by institutional guidelines.
10. Patients of child-bearing or child-fathering potential must be willing to practice an effective method of birth control during the study. Female patients must not be pregnant or breast-feeding.

Exclusion Criteria

1. Patients with tumor crossing the midline (note: tumors which have invaded the corpus callosum but not in the contralateral hemisphere are eligible), more than one foci of tumor, tumors

involving the brainstem or cerebellum, or tumor dissemination (subependymal or leptomeningeal).

2. Patients with impending herniation (including midline shift >0.5 cm), uncontrolled seizures or requirement for immediate palliative treatment.
3. Patients who have received any localized anti-tumor therapy for malignant glioma, either intracerebral chemotherapy (other than Gliadel®) or focal radiation therapy (e.g., gamma knife radiosurgery, single-fraction stereotactic radiosurgery, brachytherapy).
4. Patients who are receiving any concurrent chemotherapy (other than steroids) or any other investigational agent or who have received any investigational agent within 4 weeks of study entry.
5. Patients with known or suspected allergies to local anesthetics.
6. Patients with active infection requiring treatment or having an unexplained febrile illness.
7. Patients who have systemic diseases or other conditions that may be associated with unacceptable anesthetic/operative risk and/or that would not allow safe completion of the study protocol.
8. Patients with prior or concurrent malignancy (curatively treated carcinoma-in-situ or basal cell carcinoma, or patients, who have been disease free after therapy for earlier malignant disease for at least 5 years, are eligible).

Rationale:

Outcome for children with malignant gliomas is extremely poor and, at the time of recurrence, long-term survival is uncommon. Human malignant gliomas have been shown to express high levels of epidermal growth factor receptors relative to normal brain. In pediatric malignant gliomas, this often occurs despite a low frequency of epidermal growth factor receptor amplification. Targeted toxins are a new therapeutic modality with significant potential; there is both pre-clinical and clinical evidence in adults that TP-38, a recombinant chimeric protein composed of the epidermal growth factor receptor binding ligand and a genetically engineered form of pseudomonas exotoxin, may be an effective approach for patients with recurrent high-grade gliomas. There is also evidence that intraparenchymal, convection-enhanced delivery of therapeutic agents to brain tumors is both safe and feasible in adults. However, to date, there is no safety data utilizing this approach in children with malignant gliomas. Preliminary results in adults, however, support the feasibility of such an approach.

Schema:

TP-38 will be delivered via a micro-infusion pump/catheter connection system with 2-3 (preferably 3) catheters placed at investigator-determined areas within or adjacent to the enhancing tumor area. When possible, the catheters will be placed at least 0.5 cm into the enhancing tumor and preferably 2 cm apart and 2 cm from either a brain surface or contact with cerebrospinal fluid or tumor cyst fluid. Patients will be entered into the Phase I portion of the study in sequential groups of three patients. Each group will receive a different dose level as determined initially by an increasing flow volume with a fixed concentration until documentation of the maximum tolerated volume. Subsequently a fixed volume (at the maximum tolerated volume) will be administered including increasing concentration of TP-38. Total volume will be infused over a duration of 33 to 100 hours depending on the dose level and at least three patients will be entered at each dose level.

After evaluation of the Phase I portion of the study, if the study is deemed to be both safe and demonstrating potential efficacy, the Phase II portion of the study may be initiated. The highest tolerated combination of volume and concentration will be utilized.