PROTOCOL ABSTRACT AND SCHEMA

Phase I/II Trial of Intracerebral IL13-PE38QQR Infusion in Pediatric Patients with Recurrent Malignant Glioma

Schema		
Phase I - Flow Rate Escalation	**Phase I - Concentration Escalation**	**Phase II**
Estimate the Maximum Total Flow Rate using fixed concentration of 0.25 µg/mL.	Estimate the Maximum Tolerated Infusion Concentration (MTiC) using flow rate from previous step	Treat at MTiC and maximum total flow rate, based on Phase I Concentration and Flow Rate evaluations
Increase total flow rate from 500 µL/hr to 750 µL/hr.*	Increase concentration to 0.5 µg/mL using maximum total flow rate determined in previous step.	

*An option to decrease the total flow rate to 400 µL/hr is provided if the starting total flow rate of 500 µL/hr is not well tolerated.

Treatment Plan	
Day of Resection	Resect tumor (planned gross, total resection)
Day after Resection	MRI scan to determine extent of resection and plan catheter placement. NOTE: A second scan may be needed if catheter placement is delayed 3-7 days.
Catheter Placement (CP) 2 to 7 days after Resection	Stereotactically place 2-4 peritumoral catheters. Confirm placement with non-contrast CT scan prior to starting infusion.
Day 1ACP**	Start Infusion of IL13-PE38QQR within 24 hours (maximum 48 hours) post CP if patient is neurologically stable. Infuse for 96 hours.
Day 5ACP	Complete infusion

** ACP = After Catheter Placement

Description: Patients will be registered prior to planned gross total resection (≥95% resection of the solid, contrast-enhancing tumor component). On the day of Catheter Placement (CP, 2 days after Resection preferred, up to 7 days allowed), if the patient is neurologically stable, 2 to 4 catheters will be stereotactically placed. Placement of the catheters will be primarily based upon the post-operative MRI and clinical judgment. If Catheter Placement is delayed (up to 7 days after Resection); an additional planning MRI may be required. A non-contrast CT scan will be performed to confirm adequate catheter positioning prior to starting the infusion. On Day 1 After Catheter Placement (Day 1ACP), infusion of IL13-PE38QQR will begin if the patient is neurologically stable, and infusion will continue for 96 hours. In Phase I, the total flow rate and the concentration of IL13-PE38QQR will be determined by the dose-escalation plan. In the Phase II evaluations of safety and efficacy, patients will be treated at the flow rate and concentration identified in the Phase I portion of this trial.

In Phase I, the total flow rate (all catheters combined) will be escalated based on a traditional Phase I design, to a maximum of 750 μL/hr given over 4 days to deliver a total of 72.0 mL, to assess the tolerability of these infusion flow rates in pediatric patients. Subsequently, the IL13-PE38QQR concentration will be escalated to 0.5 μg/mL (maximum of 36.0 μg, assuming 750 μL/hr flow rate). A traditional Phase I design will be used to determine the maximum tolerated infusion concentration (MTiC) based on escalation of concentration as shown in the following tables:

Table 1. Phase I IL13-PE38QQR Infusion – Total Flow Rate Escalation

Dose Level	Total Flow Rate ALL CATHETERS COMBINED (μL/hr)	Total Duration of Infusion (hours)	Total Volume of Infusate (mL)	IL13-PE38QQR Concentration (μg/mL)	Total Infusion Dose (μg)	Increment (%)
0*	400	96	38.4	0.25	9.6	-20
1**	500	96	48	0.25	12	—
2	750	96	72	0.25	18	+50

* Patients will be enrolled at Dose Level 0 only if Dose Level 1 (the starting dose level for the study) is deemed unsafe

** Starting Dose Level

Table 2. Phase I IL13-PE38QQR Infusion at Maximum Total Flow Rate (as Determined in Dose Levels 0-2) – Concentration Escalation

Dose Level	Total Flow Rate ALL CATHETERS COMBINED (μL/hr)	Total Duration of Infusion (hours)	IL13-PE38QQR Concentration (μg/mL)	Total Infusion Dose (μg)	Increment (%)***
3	TBD	96	0.5	TBD	100

TBD = To Be Determined. Will be determined based on maximum tolerated total flow rate as determined in Dose Levels 0-2.

*** Increment based on doubling of the concentration at the maximum tolerated total flow rate from Dose Levels 0-2.

Toxicity will be assessed using clinical signs and symptoms, neurologic examination and clinical laboratory studies. The definition of dose-limiting toxicity (DLT) includes any Grade 3 or 4 toxicity considered to be definitely or probably related to study drug that does not resolve to

Grade ≤2 within 24 hours, any neurologic toxicity of Grade 4 which is considered to be at least possibly related to study drug that does not resolve to Grade ≤2 within 24 hours, or renal toxicity that does not resolve within 24 hours (see Section 5.8 for a complete description of toxicities considered a DLT).

In Phase II, patient entry will be limited to patients experiencing their first progression or recurrence of malignant glioma.

Correlative studies will be conducted during both Phases I and II. Tumor specimens will be submitted to central laboratories for immunohistochemistry (IHC), western blot, and RT-PCR for IL13 receptor α2 chain expression status and distribution. Histopathology will be centrally reviewed.

Objectives:

Phase I

Primary

- To describe toxicities and estimate the maximum safe flow rate and maximum tolerated infusion concentration of IL13-PE38QQR, delivered after surgical resection by peritumoral infusion via 2-4 catheters positioned in brain adjacent to the resection cavity, from the start of infusion through the DLT observation period (see Section 5.8)

Secondary

- To determine the IL13 receptor α2 chain expression status and distribution in pediatric recurrent or progressive malignant gliomas
- To describe the overall safety and tolerability of IL13-PE38QQR infusion from the start of infusion through disease progression or initiation of alternative treatment

Phase II

Primary

- To estimate the survival distribution post initial progression or recurrence at the maximum safe total flow rate and MTiC established in Phase I

Secondary

- To estimate the progression-free survival distribution for patients post initial progression or recurrence at the maximum safe total flow rate and MTiC established in Phase I
- To determine the IL13 receptor α2 chain expression status and distribution in pediatric recurrent or progressive malignant gliomas
- To describe the overall safety and tolerability of IL13-PE38QQR infusion from the start of infusion through disease progression or initiation of alternative treatment

Eligibility Criteria:

Inclusion Criteria

1. Patients must have had prior surgery (or biopsy) of a supratentorial brain tumor with pathologic diagnosis of malignant (Grade 3 or 4) glioma: anaplastic astrocytoma, mixed anaplastic oligoastrocytoma, or glioblastoma multiforme. In Phase II, entry is limited to patients at first progression or recurrence of malignant glioma.
2. Patients must have radiologic evidence of recurrent or progressive supratentorial malignant glioma compared with a prior imaging study.
3. Tumor must have a solid component ≥1 cm in diameter. Baseline tumor measurements must be determined ≤2 weeks prior to registration.
4. Gross total resection must be planned with the intent of removing all contrast-enhancing components of the tumor. Histopathologic confirmation on tissue obtained during the resection of apparently active and viable tumor is required for catheter placement. This will be documented by frozen section compatible with glial tumor or a permanent section confirmation of glial tumor.
5. Age: Patient must be ≥3 and ≤21 years of age. If there is a competing adult study within an institution then the upper age limit may be lowered to 18 for that institution.
6. Patients must have received external beam radiotherapy, with tumor dose of ≥48 Gy, completed ≥8 weeks prior to registration.
7. Patients must be in adequate general condition for study.
   a. Karnofsky Performance Scale score (KPS, for >16 yrs of age) or Lansky Performance Scale score (LPS, for ≤16 years of age) ≥60 assessed within two weeks prior to registration (see Appendix III for performance scale)
   b. Adequate hematologic status:
      i. Absolute neutrophils ≥1,500/mm^3
      ii. Hemoglobin ≥10 gm/dL (transfusion independent)
      iii. Platelets ≥100,000/mm^3 (transfusion independent)
      iv. PT and aPTT ≤ institutional upper limit of normal
   c. Serum creatinine less than the institutional upper limit of normal for age

   NOTE: Hematologic and serum creatinine status are to be assessed within two weeks prior to registration and again **within 48 hours prior to resection**.

8. Patients must have recovered from toxicity of prior therapy before registration. Minimum intervals required: ≥6 months after GLIADEL® Wafer, ≥8 weeks from hematopoietic stem cell transplant, ≥4 weeks after any cytotoxic chemotherapy or any systemic investigational agent, ≥6 weeks after nitrosoureas, and ≥2 weeks after vincristine or non-cytotoxic chemotherapy.
9. Patient's legal guardian must understand the investigational nature of the study and its potential risks and benefits and 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.

    NOTE: Although pharmacokinetic studies measuring serum levels of IL13-PE38QQR have not shown any detectable drug (lower limit of quantification <20-50 ng/mL), it is possible that following peritumoral infusion minute amounts of drug may reach the systemic circulation through the disrupted blood-tumor barrier. Since teratogenic effects of IL13-PE38QQR are unknown, the drug is classified as category C for pregnancy (studies in women and animals are not available). For these reasons it is felt that pregnancy should be avoided and an adequate method of contraception should be used during the study.

Exclusion Criteria

1. Patients with contrast-enhancing tumor component crossing the midline, multi-focal tumor not amenable to gross total resection, or tumor dissemination (subependymal or leptomeningeal).
2. Patients with clinically significant increased intracranial pressure (e.g., impending herniation), uncontrolled seizures, or requirement for immediate palliative treatment.
3. Patients who have received any localized antitumor therapy for malignant glioma, either intracerebral investigational agent or chemotherapy (other than GLIADEL® Wafer) or focal radiation therapy (e.g., stereotactic radiosurgery or brachytherapy), with the exception of the stereotactic radiosurgery boost part of the initial fractionated external beam radiation therapy.
4. Patients who are receiving any concurrent chemotherapy (other than steroids) or any other investigational agent.
5. Patients unwilling or unable to follow protocol requirements.

v1.1

Rationale: Although predominantly occurring in older adults, malignant glioma (glioblastoma multiforme [GBM] and anaplastic astrocytoma [AA]) also occurs in the pediatric age group; the annual incidence of supratentorial malignant gliomas is approximately 3-4 per 1,000,000 children in the U.S. Management of such patients is exceedingly complex (Johnson, 1996) and largely confined to major referral centers. Despite an aggressive, multimodal approach, no curative therapy is known for malignant glioma. Median survival expectation in adults is short: 9-12 months from diagnosis for GBM and 24-48 months for AA; and median survival rate may be slightly longer in children. Despite numerous investigational trials, patients with recurrent malignant glioma after initial radiotherapy have a very short survival (10-25 weeks). Recent advances in alkylator therapy, either systemic (Yung, 1999; Yung, 2000; Stupp, 2002) or intracavitary (Brem, 1995; Westphal, 2003) are encouraging, but new avenues of treatment are clearly needed. Systemic therapy has not improved outcome substantially; even intensive chemotherapy provided no detectable benefit in malignant glioma in the pediatric population (Heideman, 1993). NeoPharm, Inc. believes that the relative rarity of such patients requires not that such studies be deferred, but that a cooperative group approach be adopted.

IL13-PE38QQR, a tumor-targeted cytotoxin, is a potent recombinant protein consisting of human IL13 and an enzymatically-active portion of Pseudomonas Exotoxin. Malignant glioma

cells express the IL13 receptor (IL13R) at high density, while normal brain tissue expresses very low levels of IL13R, if any. Most malignant glioma cell lines are sensitive to IL13-PE38QQR at <0.01 μg/mL. There is suggestive evidence that the IL13 receptor α2 chain (which renders cells vulnerable to IL13-PE38QQR) is expressed more highly in younger adults (Joshi, 2000), although the applicability of this finding to pediatrics is not yet known.

Convection-enhanced delivery (CED) utilizes positive pressure infusion to achieve loco-regional delivery of therapeutic agents via intracerebral catheters. CED is designed to deliver anticancer agents directly into tumor or adjacent tissue, promotes much wider drug distribution than that produced by diffusion, and avoids systemic exposure. Four Phase I/II clinical trials studying CED of IL13-PE38QQR in adults with recurrent malignant glioma have completed enrollment, with only patient follow-up for survival continuing. Studies IL13PEI-001 (n=24), IL13PEI-002 (n=46), IL13PEI-103 (n=25), and IL13PEI-105 (n=8) enrolled a total of 103 patients. These studies were primarily designed to assess the safety profile of IL13-PE38QQR, identify a dose regimen for pivotal studies, and assess various parameters of administration of drug via CED. Details of the design for each of these studies are presented in the IL13-PE38QQR Investigator's Brochure. Two additional studies are currently in progress. A Phase I clinical trial (Study IL13-PE38QQR-106) examining CED of IL13-PE38QQR followed by radiation therapy with or without temozolomide is ongoing in adult patients with newly diagnosed malignant glioma. A Phase III clinical trial (Study IL13PEI-301) of IL13-PE38QQR in adult patients with recurrent glioblastoma multiforme has enrolled 100 patients as of January 1, 2005.

The rationale behind the concentration proposed is based upon pre-clinical data as well as the histologically effective concentration (HEC) and the peritumoral maximum tolerated infusion concentration determined in clinical trials in adult patients. IL13-PE38QQR is a highly selective agent whose mechanism of action depends upon its binding to IL13 receptor. The mechanism of tumor cytotoxicity is mediated through an enzymatic inactivation of protein synthesis by PE. In vitro assays using similar cytotoxins have demonstrated a steep dose-response relationship curve followed by a plateau, which is consistent with the mechanism of action described above (Kunwar, 1993). A concentration of 0.5 μg/mL is at least three log units higher than the IC_{50} of most glioma cell lines but is well below the no effect level (NOEL) of 100 μg/mL obtained in rodent safety evaluations (Debinski, 1995b). Histological evidence of drug-induced tumor necrosis at concentrations of 0.5, 1.0, and 2.0 μg/mL was observed 1-2 weeks after dosing in clinical trials in patients with recurrent malignant glioma (Kunwar, 2003a; Ram, 2003). There was no apparent increased histopathological effect with increasing concentration across these concentration levels (Kunwar, 2003a). However, a post-resection MTD with a drug concentration of 0.5 μg/mL has been identified in Study IL13PEI-002 (Kunwar, 2003b). Therefore, a concentration of 0.5 μg/mL, which is within the histologically effective range of 0.5-2.0 μg/mL observed 1-2 weeks after dosing and at the post-resection/peritumoral MTD level, has been selected for Phase III development in adult patients.

v1.1

The proposed dose regimen is based upon clinical experience. Since a gross total resection of the tumor is planned, only a post-resection infusion will be performed with the catheters positioned optimally to target residual infiltrating tumor in the peritumoral region and any residual solid (contrast-enhancing) tumor. The IL13-PE38QQR dose regimen being utilized in the current Phase III study in adults includes a drug concentration of 0.5 μg/mL with a flow rate range of 187.5-375 μL/hr/catheter (3.12-6.25 μL/min/catheter) with 2-4 catheters (providing a total flow

rate of 750 µL/hr) for 96 hours with a total dose of 36.0 µg (in a total volume of 72.0 mL). This regimen for local administration of IL13-PE38QQR appears to have a favorable risk-benefit profile in the 27 patients treated in three Phase I/II studies with peritumoral (post-resection) infusion using 0.5 µg/mL for 4-6 days. This Phase III regimen also utilizes post-operative stereotactic placement of the catheters 2-7 days after resection of the tumor. Deferred catheter placement utilizing a catheter placement planning MRI appears to improve the accuracy of positioning of the catheters and minimizes the effects of resection-related post-operative edema, brain shift, and re-expansion on catheter positioning (Sampson, 2004). Such deferred placement has been evaluated by NeoPharm, Inc. in Study IL13PEI-002, Stage 4; Study IL13PEI-103, Revision 2; and Study IL13PEI-105, Stage 2. Results from these studies suggest that post-operative placement improves the accuracy of catheter positioning; catheter positioning also appears to influence patient survival (Sampson, 2004).

For comparison with studies in adults, the dosing regimen proposed for this pediatric study uses stereotactic placement of 2-4 catheters deferred until 2-7 days after resection, with a continuous peritumoral infusion of 96-hour duration (similar to the regimen being used in the Phase III study in adults). The starting total flow rate will be 500 µL/hr (vs. 750 µL/hr in the ongoing studies in the adult population). This pediatric study provides the option to increase the total flow rate to 750 µL/hr or decrease it to 400 µL/hr, depending upon the results with 500 µL/hr. The starting peritumoral IL13-PE38QQR concentration in this pediatric study will be 0.25 µg/mL (vs. 0.5 µg/mL in the ongoing adult studies), with an option to increase to a maximum concentration of 0.5 µg/mL.

Prior experience with this agent in clinical studies in adult patients using the above dosing parameters supports this proposed study. Dosing parameters outlined in this protocol have been shown to be safe and well-tolerated, with evidence of histopathological effect on tumor. In addition, the proposed starting concentration (0.25 µg/mL), flow rate (500 µL/hr for 96 hours), and total dose (12 µg) are below those shown to be safe and well tolerated in adults.