Study Synopsis

Title of Study:	Phase I Clinical Trial of HSV G207 Alone or With a Single Radiation Dose in Children with Recurrent Supratentorial Brain Tumors
Principal Investigator:	Gregory K. Friedman, M.D., Department of Pediatrics, Division of Pediatric Hematology/Oncology, Neuro-Oncology Program
Study Center:	University of Alabama at Birmingham
Clinical Phase:	Phase I
Study Rationale:	Outcomes for children with recurrent supratentorial brain tumors are extremely poor. Novel innovative treatments are greatly needed. One promising new approach is the use of a genetically engineered, conditionally replicating herpes simplex virus (HSV) that has shown tumor specific tropism and potential efficacy in the treatment of malignant brain tumors.
Study Objectives:	Primary: To assess the safety and tolerability of G207 administered intratumorally via stereotactic infusion alone or followed by a single dose of radiation within 24 hours of G207 administration in children with recurrent or progressive malignant supratentorial brain tumors. To establish a maximum tolerated dose (MTD) or maximal planned dose if no dose-limiting toxicity is observed. Secondary: To obtain preliminary information concerning the potential efficacy of and biological response to G207 alone or combined with a single dose of radiation in pediatric patients with recurrent or progressive malignant brain tumors by assessing radiographic response, performance scale, progression-free and overall survival, immune response, and presence of G207 in blood, saliva, and conjunctiva.
Investigational Drug:	G207 is a genetically altered HSV that has been demonstrated to be aneurovirulent secondary to deletions of both copies of the $\gamma_1$34.5 gene. After stereotactic biopsy to confirm tumor recurrence, up to 4 silastic catheters will be passed to predefined coordinates of enhancing tumor, if present. Catheters may be placed in non-enhancing regions if residual tumor is confirmed in those locations. Subsequently, patients will be inoculated with 2.4 ml of G207 at one of two doses over 6 hours alone or followed by a single 5 Gy fraction of radiation within 24 hours of virus inoculation.
Subject Population:	Up to 24 pediatric patients, ages 3 to 18 years, with recurrent/progressive malignant supratentorial brain tumors will be enrolled in this study.
Treatment Indication:	Progressive or recurrent growth of malignant supratentorial brain tumor after initial surgery, radiotherapy, and/or chemotherapy. Patients with brainstem, cerebellar or intraventricular tumors will not be eligible.
Inclusion Criteria:	1) Age ≥ 36 months and < 19 years 2) Pathologically proven malignant supratentorial brain tumor

(including glioblastoma multiforme, giant cell glioblastoma, anaplastic astrocytoma, primitive neuroectodermal tumor, ependymoma, atypical teratoid/rhabdoid tumor, germ cell tumor, or other high-grade malignant tumor) which is progressive or recurrent despite standard care including surgery, radiotherapy, and/or chemotherapy. A pathologically proven secondary malignant tumor without curative treatment options is eligible.

3) Lesion must be ≥ 1.0 cm in diameter and surgically accessible as determined by MRI

4) Patients must have fully recovered from acute treatment related toxicities of all prior chemotherapy, immunotherapy or radiotherapy prior to entering this study.

5) Myelosuppressive chemotherapy: patients must have received their last dose at least 3 weeks prior (or at least 6 weeks if nitrosurea)

6) Investigational/Biologic agents: patients must have recovered from any acute toxicities potentially related to the agent and received last dose ≥ 7 days prior to entering this study (this period must be extended beyond the time during which adverse events are known to occur for agents with known adverse events ≥ 7 days). For viral therapy, patients must have received viral therapy ≥ 3 months prior to study entry and have recovered from all acute toxicities potentially related to the agent

7) Monoclonal antibodies: For bevacizumab, the patient must have received last dose ≥ 28 days prior. At least 3 half-lives must have elapsed prior to study entry for other monoclonal antibodies.

8) Radiation: Patients must have received their last fraction of craniospinal radiation (>24 Gy) or total body irradiation ≥ 3 months prior to study entry. Patients must have received focal radiation to symptomatic metastatic sites or local palliative radiation > 28 days prior to study entry.

9) Autologous bone marrow transplant: Patients must be ≥ 3 months since transplant prior to study entry.

10) Normal hematological, renal and liver function (Absolute neutrophil count > 1000/mm^3, Platelets > 100,000/mm^3, PT or PTT < 1.3 x control, Creatinine within normal institutional limits OR creatinine clearance >60 mL/min/1.73 m^2 for patients with creatinine levels above institutional normal, Total Bilirubin < 1.5 mg/dl, Transaminases < 3 times above the upper limits of the institutional norm)

11) Patients < 10 years, Modified Lansky score ≥ 60; patients ≥ 10 years, Karnofsky score ≥ 60

12) Patient life expectancy must be at least 8 weeks

13) Written informed consent in accordance with institutional and FDA guidelines must be obtained from patient or legal guardian

Exclusion Criteria:

1) Acute infection, granulocytopenia or medical condition precluding surgery

2) Pregnant or lactating females

3) Prior history of encephalitis, multiple sclerosis, or other CNS infection

4) Tumor involvement which would require ventricular, cerebellar or brainstem inoculation or would require access through a ventricle in order to deliver treatment

5) Required steroid increase within 1 week prior to injection

6) Known HIV seropositivity

7) Concurrent therapy with any drug active against HSV (acyclovir, valacyclovir, penciclovir, famciclovir, gancyclovir, foscarnet, cidofovir) or any immunosuppressive drug therapy (except dexamethasone or prednisone).

Study Design:

This study is a Phase 1, open-label study of HSV G207 to assess its safety and tolerability. A traditional 3 + 3 design will be used. The following dose escalation scheme will be used:

Dose Level	Patients	Dose (pfu)	Volume	# Loci
-1	3	$1x10^6$	2.4 ml	1-4
1	3 (+3)	$1x10^7$	2.4 ml	1-4
2	3 (+3)	$1x10^8$	2.4 ml	1-4
3	3 (+3)	$1x10^7$ + 5 Gy radiation	2.4 ml	1-4
4	3 (+3)	$1x10^8$ + 5 Gy radiation	2.4 ml	1-4

Safety Analysis:

Patient monitoring will be appropriately tapered from the initial intensive monitoring in the Pediatric Intensive Care Unit immediately after biopsy and catheter placement, to an inpatient room at Children's of Alabama, and then to regular clinic follow-up visits. In addition to regularly scheduled screening tests looking specifically for G207 shedding and viremia, other routine evaluations will include vital sign measurements, neurological exams, neurological performance measurements, magnetic resonance imaging studies (MRIs), chemistry and hematology laboratories, urinalysis, neuropsychological testing, and quality of life questionnaires (quality of life measures are optional consent).

Study Duration:

Patients will have close scheduled follow-up for 24 months following treatment with G207. Outpatient visits will be scheduled at day 7, 14, and 28, and month 3, 5, 7, 9, 12, 18, and 24 after G207 inoculation. Annual follow-up appointments will be made for patients who survive longer than 24 months. Patients whose tumor shows radiographic and clinical evidence of progression will be declared a treatment failure and may be considered as candidates for any other available therapy.