Phase 2 Trial of G207 + 5 Gy Radiation for Children with High-Grade Gliomas

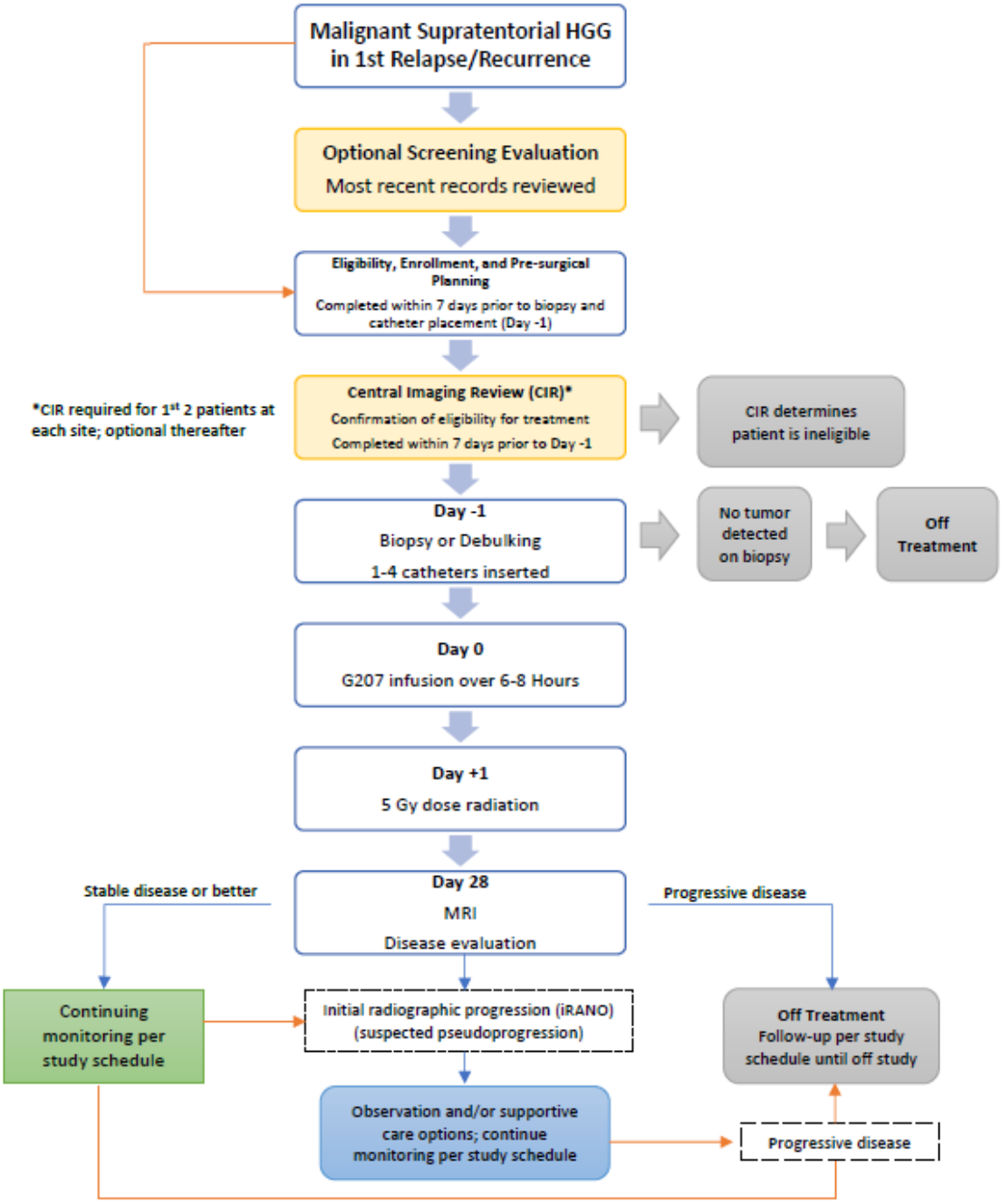
ABSTRACT

This is a Phase II Clinical Trial of HSV G207 with a Single 5 Gy Radiation Dose in Children with Recurrent High-Grade Glioma. Outcomes for children with recurrent or progressive high-grade glioma are extremely poor. G207 was safe and tolerable and demonstrated evidence of radiographic, neuropathologic, and clinical responses in a Phase I trial in children with recurrent malignant supratentorial brain tumors.

G207 is a genetically altered herpes simplex virus (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 HSV G207 at the recommended Phase 2 dose (RF2D) over 6-8 hours followed by a single 5 Gy fraction of radiation within 24 hours of virus inoculation to enhance viral replication and facilitate anti-tumor innate and adaptive immune responses.

Pediatric patients ≥ 3 at initial diagnosis but < 22 years of age with recurrent or progressive high-grade glioma who have failed surgery and radiotherapy and who may or may not have had chemotherapy or other forms of treatment will be eligible for the study.

SCHEMA


Malignant Supratentorial HGG in 1st Relapse/Recurrence
Optional Screening Evaluation
Most recent records reviewed
Eligibility, Enrollment, and Pre-surgical Planning
Completed within 7 days prior to biopsy and catheter placement (Day -1)
*CIR required for 1st 2 patients at each site; optional thereafter
Central Imaging Review (CIR)*
Confirmation of eligibility for treatment
Completed within 7 days prior to Day -1
CIR determines patient is ineligible
Day -1
Biopsy or Debulking
1-4 catheters inserted
No tumor detected on biopsy
Off Treatment
Day 0
G207 infusion over 6-8 Hours
Day +1
5 Gy dose radiation
Day 28
MRI
Disease evaluation
Stable disease or better
Progressive disease
Continuing monitoring per study schedule
Initial radiographic progression (iRANO) (suspected pseudoprogression)
Off Treatment
Follow-up per study schedule until off study
Observation and/or supportive care options; continue monitoring per study schedule
Progressive disease

1.0 OBJECTIVES

1.1 Primary Objectives

1.1.1 To assess efficacy of G207 administered intratumorally followed by 5 Gy radiation within 24 hours in patients with recurrent or progressive high-grade glioma (HGG) at first progression as measured by post-progression survival compared to matched historical controls.

1.2 Secondary Objectives

1.2.1 To establish safety and characterize toxicity of G207 + 5 Gy radiation

1.2.2 To survey for virologic shedding following G207

1.2.3 To evaluate immunologic responses(s) to G207

1.2.4 To assess for radiographic changes from baseline by modified iRANO and by tumor volume, cerebral blood volume, and apparent diffusion coefficient.

1.2.5 To describe efficacy of G207 + 5 Gy radiation as measured by response rate and progression-free survival (PFS)

1.3 Exploratory Objectives

1.3.1 To assess performance status score changes over time after treatment with G207 + 5 Gy radiation

1.3.2 To evaluate pre- and post-treatment tissue for immune cell populations and checkpoint proteins in patients who are amendable to and meet criteria for resection/biopsy while on study

1.3.3 To assess OS in subgroups of patients based on therapies received after G207 + 5 Gy radiation (surgery versus no surgery; reirradiation versus no reirradiation, immunotherapy vs no immunotherapy)

3.0 PATIENT SELECTION

3.1 Eligibility Criteria for Optional Screening

Optional screening will be offered to all patients considering enrollment on this trial. Screening will allow patients to submit recent imaging (obtained within 4 weeks prior to screening) and other documentation (upon request) to be reviewed by the Study Team. The Study Team will assess if the patient is likely to meet eligibility criteria for enrollment per Section 3.2 below. See Section 4.4.3 for submission details.

3.1.1 Tumor

Recurrent or Progressive Patients:
Patients with a histologically confirmed diagnosis of high-grade glioma regardless of molecular characterization that is recurrent or progressive. All tumors must have histologic verification at either the time of diagnosis or recurrence.

Patients are only eligible after their first progression following prior surgery and radiotherapy, see Section 3.2.4.

3.1.2 Disease Status

- Supratentorial lesion must be ≥ 1.0 cm in longest dimension and surgically accessible as determined by MRI.
- For patients with tumors > 4.0 cm without an adjacent cavity, the neurosurgeon must be confident that the tumor can be debulked to ≤ 4.0 cm for eligibility.
- Multifocal disease on the ipsilateral side is eligible if at least one catheter can be placed in all multifocal areas.

3.1.3 Age

Patient must be ≥ 3 at initial diagnosis but < 22 years of age at the time of enrollment on this study.

3.1.4 Screening Consent

Participant is willing to sign a screening consent and provide their most recent imaging to determine their potential suitability for eligibility on PBTC-061. The screening consent is to be obtained according to institutional guidelines. Telephone consent is allowable as per local guidelines and approvals. Assent, when appropriate, will be obtained according to institutional guidelines.

3.1.5 Potential Eligibility for Study Enrollment

Patients screened for this trial should be expected to meet the criteria for treatment per Section 3.2 below.

3.2 Eligibility Criteria for Enrollment

All subjects must meet the following inclusion and exclusion criteria. No exceptions will be given. All clinical studies to establish eligibility must be done within 7 days prior to enrollment. Imaging and laboratory values must be no older than 7 days prior to the start of therapy. If more than 7 days elapse between eligibility studies and the start of therapy, studies must be redone to be within 7 days of the start of therapy. Every effort should be made to determine eligibility, enroll the patient, and start treatment in the shortest timeframe possible.

3.2.1 Diagnosis

Recurrent or Progressive Patients:
Patients with a histologically confirmed diagnosis of high-grade glioma regardless of molecular characterization that is recurrent or progressive. All tumors must have histologic verification at either the time of diagnosis or recurrence.

Patients are only eligible after their first progression following prior surgery and radiotherapy, see Section 3.2.4.

3.2.2 Disease Status

- Supratentorial lesion must be ≥ 1.0 cm in longest dimension and surgically accessible as determined by contrast-enhanced MRI.
- For patients with tumors > 4.0 cm without an adjacent cavity, the neurosurgeon must be confident that the tumor can be debulked to ≤ 4.0 cm for eligibility.
- Multifocal disease on the ipsilateral side is eligible if at least one catheter can be placed in all multifocal areas.
- Tumor size will be determined using the maximal 2-dimensional cross-sectional tumor measurements, transverse x width, using either T1 images or T2/FLAIR images for non-enhancing tumors.

Review of these MRI scans will be necessary to determine if the tumor location and size is such that the patient may undergo biopsy and catheter placement. Eligibility imaging for the first 2 patients at each site must be sent for real-time central review. If repeat imaging is required for either of the first 2 patients, central review will be required for the repeated images. After the first 2 patients, the PBTC-061 study team will be available as needed to review screening MRIs and consult with the local team. See Section 5.4.3.1 for more information.

3.2.3 Age

Patient must be ≥ 3 at initial diagnosis but < 22 years of age at the time of enrollment on this study.

3.2.4 Prior Therapy

Patients must have received prior surgery and radiotherapy and recovered from the acute treatment-related toxicities (defined as ≤ Grade 1 if not defined in eligibility criteria; excludes alopecia) prior to enrollment.

3.2.4.1 *Chemotherapy*

Patients must have received their last dose of known myelosuppressive anticancer therapy at least 21 days prior to enrollment or at least 42 days if nitrosourea.

3.2.4.2 *Investigational/Biologic Agent or Targeted therapies (non-myelosuppressive cancer therapy)*

- Biologic or investigational agent (anti-neoplastic):
  Patient must have received their last dose of the investigational or biologic agent ≥ 7 days prior to study enrollment.
  - For agents that have known adverse events occurring beyond 7 days after administration, this period must be extended beyond the time during which adverse events are known to occur.
- Monoclonal antibody treatment and agents with known prolonged half-lives:
  Patient must have received their last dose of the agent ≥ 28 days prior to study enrollment.
- Immune Effector Cell (IEC) Therapy (e.g., CAR T cells)
  For viral therapy or cellular therapy, patients must have received therapy ≥ 3 months prior to study enrollment.

3.2.4.3 *Radiation*

Patients must have had their last fraction of standard radiation ≥ 3 months prior to enrollment.

3.2.4.4 *Stem Cell Transplant*

Patient must be:

- ≥ 6 months since allogeneic stem cell transplant prior to enrollment with no evidence of active graft vs. host disease.
- ≥ 3 months since autologous stem cell transplant prior to enrollment.

3.2.5 Neurologic Status

- Patients with neurological deficits should have deficits that are stable for a minimum of 1 week prior to enrollment.
  - A baseline detailed neurological exam should clearly document the neurological status of the patient at the time of enrollment on the study.
- Patients with seizure disorders may be enrolled if seizures are well controlled.

3.2.6 Performance Status

Karnofsky Performance Scale (KPS for > 16 years of age) or Lansky Performance Score (LPS for ≤ 16 years of age) assessed within 7 days prior to enrollment must be ≥ 60 who are unable to walk because of neurologic deficits, but who are up in a wheelchair, will be considered ambulatory for the purpose of assessing the performance score. See Appendix A.

3.2.7 Organ Function

Patients must have adequate organ and marrow function as defined below:

- Absolute neutrophil count > 1.0 x 10^9 cells/L
- Platelets > 100 x 10^9 cells/L (unsupported, defined as no platelet transfusion within 7 days)
- Hemoglobin ≥ 8 g/dL (may receive transfusions)
- Total bilirubin ≤ 1.5 x institutional upper limit of normal (ULN)
- PT/INR, PTT ≤ 1.5 x ULN
- ALT(SGPT) and AST (SGOT) < 3 x institutional upper limit of normal (ULN)
- Albumin ≥ 3 g/dL
- Serum creatinine based on age/gender as noted in Table 2. Patients that do not meet the criteria in Table 2 but have a Cystatin C, 24-hour Creatinine Clearance or GFR (radioisotope or iothalamate) ≥ 70 mL/min/1.73 m^2 are eligible. \

Table 2. Serum Creatinine for age/gender

Age	Maximum Serum Creatinine (mg/dL)	
	Male	**Female**
1 to < 2 years	0.6	0.6
2 to < 6 years	0.8	0.8
6 to < 10 years	1	1
10 to < 13 years	1.2	1.2
13 to < 16 years	1.5	1.4
≥ 16 years	1.7	1.4
The threshold creatinine values in this Table were derived from the Schwartz formula for estimating GFR (Schwartz et al. J. Peds, 106:522, 1985) utilizing child length and stature data published by the CDC.		

3.2.8 Corticosteroids

Patients who are receiving dexamethasone must be on a stable or decreasing dose for at least 1 week prior to enrollment.

3.2.9 Growth Factors

Patients must be off all colony-forming growth factor(s) for at least 1 week prior to enrollment (e.g., filgrastim, sargramostim, or erythropoietin). Two (2) weeks must have elapsed if the patient received a long-acting formulation.

3.2.10 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.

3.2.11 Informed Consent

The patient or parent/guardian can understand the consent and is willing to sign a written informed consent document according to institutional guidelines.

3.3 **Exclusion Criteria**

3.3.1 Pregnancy

Pregnant women are excluded from this study. Female patients of childbearing potential must have a negative serum or urine pregnancy test. If the urine test is positive or cannot be confirmed as negative, a serum pregnancy test will be required.

Pregnant women are excluded from this study because G207 is an agent with the potential for teratogenic or abortifacient effects.

3.3.2 Lactation Status

Lactating females are not eligible unless they have agreed not to breastfeed their infants

- Because there is an unknown but potential risk for adverse events in nursing infants secondary to treatment of the mother with G207, breastfeeding should be discontinued if the mother is treated with G207.

3.3.3 Concurrent Illness

- Patients with any clinically significant unrelated systemic illness (serious infections or significant cardiac, pulmonary, hepatic or other organ dysfunction), that in the opinion of the investigator would compromise the patient's ability to undergo surgery and/or tolerate protocol therapy, put them at additional risk for toxicity or would interfere with the study procedures or results.
- Known HIV seropositivity.
- Patients with a prior or concurrent malignancy whose natural history or treatment has the potential to interfere with the safety or efficacy assessment of the investigational regimen for this trial.
- Patients with a secondary high-grade glioma are ineligible.
- Patient with primary tumor involving the cerebellum, brainstem or spinal cord or that would require surgical access through a ventricle in order to deliver the prescribed protocol treatment.
- Metastatic disease or diffuse, widespread, abnormal tumor pattern involving 3 or more lobes of the brain

- Tumor with evidence of clinically significant uncal herniation or midline shift, or evidence of ventricular obstruction from tumor or tonsillar herniation
- Diagnosis of encephalitis or CNS infection < 3 months prior, or receiving ongoing treatment for encephalitis, CNS infection or multiple sclerosis

3.3.4 Concomitant Medications

- Patients who are receiving any other anti-cancer or investigational drug therapy are ineligible.
- Patients who are receiving ≥ 1.5 mg of dexamethasone (or ≥ 10 mg of prednisone) daily
- Concurrent therapy with any drug active against HSV (acyclovir, valacyclovir, penciclovir, famciclovir, ganciclovir, foscarnet, cidofovir)
- Patients may not be on immunosuppressive therapy, including corticosteroids (except for patients receiving < 1.5 mg of dexamethasone or < 10 mg of prednisone daily) at time of enrollment. However, patients who require intermittent use of bronchodilators or topical steroids will not be excluded from the study.

3.3.5 Inability to participate

Patients who in the opinion of the investigator are unwilling or unable to return for required follow-up visits or obtain follow-up studies required to assess toxicity to therapy or to adhere to drug administration plan, other study procedures, and study restrictions.

3.3.6 Prior Cranial Spinal Irradiation

Patients who received cranial spinal irradiation (CSI) are ineligible.