Abstract and Schema:

Description and Rationale:
Pediatric high grade gliomas have a progressive initial course and high risk of relapse/ progression; making the 5-year overall survival rate 15-35% with current therapeutic options. Surgical debulking is the initial therapy of choice for high-grade gliomas and may lead to improvement of symptoms and prolong survival. Localization in eloquent areas (e.g., primary motor cortex) or infiltration of the corpus callosum may allow for only partial tumor debulking. Therefore, surgical resection is usually attempted prior to initiation of adjuvant therapy. However, due to the infiltrative growth pattern, residual tumor cells persist even despite an apparent complete resection. Although recent research has revealed molecular, genetic, and biological distinctions between adult and pediatric gliomas, the current treatment options for children with these tumors remain ineffective. Novel therapeutic approaches, such as oncolytic viral therapy, warrant clinical investigation.

HSV is one of the best characterised human viruses and the entire 150kb genome of HSV-1 strain 17 (the parent strain from which HSV1716 was derived) has been sequenced. Researchers have isolated a mutant form of Herpes Simplex Virus type 1 (HSV-1) identified as HSV1716 (SEPREHVIR®) which is unable to replicate in the brain. It is also thought not to replicate in other types of normal, terminally differentiated cells. The mutant virus, HSV1716, is based on the selective ability of herpes simplex virus lacking ICP34.5 to kill only dividing cells. HSV1716 replicates in and lyses dividing cells of tumors such as glioblastoma but fails to replicate normal post-mitotic brain cells.

This is a phase I study to estimate the MTD or recommended Phase II dose of a single intratumoral/peritumoral injection of HSV1716. Patients with recurrent high grade glioma amenable to surgical resection are eligible for this study.

Schema:
HSV1716 dosing will begin at one dose level below the adult maximum tested dose. The HSV1716 dose will be increased as shown in Table 4 below, until the MTD is reached.

HSV1716 Dose levels and Cohort size		
Dose level	**No of Patients**	**HSV1716 Dosage**
1*	3 to 6	1 ml of 1 x 10^5 infectious units HSV1716 per ml
2	3 to 6	1 ml of 2 x 10^6 infectious units HSV1716 per ml
3	3 to 6	1 ml of 1 x 10^7 infectious units HSV1716 per ml

*starting dose level

Objectives:

1.1 Primary Objectives

1.1.1 To determine whether intratumoral/peritumoral injection of HSV1716 is safe in children with recurrent high-grade gliomas amenable to resection.
1.1.2 To estimate the maximum tolerated dose (MTD) or a Recommended Phase II dose of intratumoral/peritumoral injection of HSV1716.
1.1.3 To describe any dose-limiting toxicities (DLT) of intratumoral/peritumoral injection of HSV1716 at the doses given to children with high-grade gliomas.
1.1.4 To evaluate changes in tumor enhancement, quantitative MR measures of tumor perfusion (relative cerebral blood volume (rCBV), ktrans, Vp and Ve values and apparent diffusion coefficient (ADC) in response to HSV1716 injection

1.2 Secondary Objectives
1.2.1 To measure antiviral immune response in patients with refractory high-grade gliomas injected with HSV1716.
1.2.2 To measure the systemic viremia and viral shedding following intratumoral/peritumoral administration of HSV1716.
1.2.3 To preliminarily describe the antitumor activity of HSV1716 injection within the confines of a Phase I study.
1.2.4 To evaluate anti-tumor immune cellular and humoral immune responses
1.2.5 To evaluate changes in FDG-PET uptake in response to HSV1716 injection.
1.2.6 To evaluate changes in tumor choline values using MR spectroscopy in response to HSV1716 injection and further delineate from progressive disease versus pseudo-progression post therapy.

Eligibility Criteria
Tumor
Patients must have a histologically-confirmed primary diagnosis of HGG (such as glioblastoma multiforme, gliosarcoma, anaplastic oligodendroglioma, anaplastic ganglioglioma, high grade astrocytoma, NOS) that is recurrent or refractory to conventional therapy. **Patients with metastatic disease are not eligible.** If there is evidence of the tumor arising from the ventricular system, patient is NOT eligible.

Patients must be those for whom surgical resection is clinically indicated. The intent of surgical resection may include debulking or attempt to resect as much of the tumor as safely feasible; if a gross total or near total resection is not feasible, HSV1716 injection into the wall of the resection cavity, encompassing residual tumor, is permissible.

Patients must be amenable to receiving 1 dose of HSV1716 intra-operatively with planned HSV1716 injection sites ≥1 cm from the ventricular system AND meet at least one of the criteria below based upon pre-surgical MRI:

- Tumor is ≥1 cm from the ventricular system
- Patients whose tumors that are < 1 cm from the ventricular system are eligible if there is sufficient space within the tumor cavity and/or residual tumor to perform the HSV 1716 injections that are ≥1 cm from the ventricular system

An intraoperative MRI upon resection will confirm the distance of the planned injection sites from the ventricular system prior to the HSV1716 injection. Intra-operatively, the neurosurgeon may decide to not inject the HSV1716 or may revise the sites of HSV1716 injection if injection cannot be guaranteed ≥1 cm from the ventricular system. Patient will be removed from the study if there are not sufficient areas in the tumor cavity to guarantee injection of HSV1716 ≥1cm from the ventricular system.

Age
Patients must be ≥12 years and ≤ 21 years of age at the time of study enrollment.
Prior Therapy
Patients must have received prior therapy other than surgery and must have fully recovered from the acute treatment related toxicities of all prior chemotherapy, immunotherapy, or radiotherapy prior to entering this study.

Myelosuppressive chemotherapy:
Patients must have received their last dose of known myelosuppressive anticancer chemotherapy at least three (3) weeks prior to study registration treatment or at least six (6) weeks if nitrosourea.

Investigational / Biologic agent:

a. Biologic or investigational agent (anti-neoplastic):
   Patient must have recovered from any acute toxicity potentially related to the agent and received their last dose of the investigational or biologic agent ≥ 7 days prior to study registration.
   - 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.
b. Monoclonal antibody treatment: At least three half-lives must have elapsed prior to registration.
   Note: A list of the half-lives of commonly used monoclonal antibodies is available on the PBTC webpage under Generic Forms and Templates.

Radiation:

Patients must have had their last fraction of

a. Craniospinal irradiation (>24Gy) or total body irradiation > 3 months prior to registration.
b. Focal irradiation to symptomatic metastatic sites >4 weeks prior to registration
c. Local palliative XRT (small port) ≥ 4 weeks
d. If prior TBI, craniospinal XRT or if ≥ 50% radiation of pelvis ≥ 6 months must have elapsed
e. If other substantial BM radiation ≥ 6 weeks must have elapsed

Bone Marrow Transplant:

Patient must be:

a. ≥ 6 months since allogeneic bone marrow transplant prior to registration
b. Stem Cell Transplant or Rescue without TBI: No evidence of active graft vs. host

disease and ≥ 3 months must have elapsed since transplant.

Performance Status
Karnofsky Performance Scale (KPS for > 16 years of age) or Lansky Performance Score (LPS for ≤ 16 years of age) assessed within two weeks of registration must be ≥ 60.

Organ Function
Patients with adequate organ function as defined by the following parameters obtained within two (2) weeks prior to registration and again within seven (7) days prior to the start of therapy. Eligibility labs need not be repeated if therapy starts within 7 days of drawing labs.

a. Hemoglobin: ≥10 g/dl
b. Absolute neutrophil count **:** ≥1000/mm^3
c. Platelets: ≥100,000/mm^3 (transfusion independent defined as not receiving platelet transfusions within 7 days prior to registration)
d. Total bilirubin: <1.5 x upper limit of institutional normal for age
e. ALT (SGPT): ≤2.5 x institutional upper limit of normal
f. Creatinine clearance or radioisotope GFR ≥70 mL/min/1.73 m^2 or a serum creatinine based on age and gender as follows:

Table 3

Creatinine clearance by age and gender		
Age	**Maximum Serum Creatinine (mg/dL)**	
	Male	**Female**
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.		

g. Nutrition: Albumin ≥ 2.5 g/dL
h. Coagulation: PTT< 1.2 X institutional upper limits of normal.

Neurological Status
Patients with neurological deficits should have deficits that are stable for a minimum of 1 week prior to registration. This is to be documented at baseline.

Corticosteroids
Patients with CNS tumors who are receiving dexamethasone must have been on a stable or decreasing dose of dexamethasone for the 7 days prior to enrollment.

Growth Factors
Growth factors that support platelet or white cell number or function must not have been administered within the past 7 days. Growth factors include: GCSF (Filgrastim), PEG-GCSF (Neulasta), GMCSF (sargramostim) and erythropoietin.

Infectious Disease
Patient has documented evidence of negative tests for the presence of Hepatitis B surface antigen, Hepatitis C antibody, and HIV1/2 antibodies within the three months preceding study entry. Subjects who do not have such evidence must undergo appropriate testing prior to virus administration. HIV-positive patients on combination antiretroviral therapy are ineligible because of the potential for having an increased risk of developing an uncontrolled virus infection.

Pregnancy Status
Female patients of childbearing potential must have a negative serum or urine pregnancy test at the time of enrollment.

Informed Consent
Ability to understand and the willingness to sign a written informed consent document according to institutional guidelines.

2.1. **Exclusion Criteria**
Patients with metastatic disease i.e. Leptomeninges, multi-focal lesions in the CNS.

Patients who are receiving any other investigational agents.

Patients who are currently receiving other anti-cancer agents are excluded from this trial.

Patients with history of prior HSV encephalitis or encephalitis due to other etiologies.

Teratogenicity:
There is no available information regarding human fetal or teratogenic toxicities.

a. Pregnant women are excluded to avoid the risk of systemic intrauterine/neonatal HSV infection
b. Males or females of reproductive potential may not participate unless they have agreed to use an effective contraceptive method from the time of study entry to a period of no less than four months post the HSV1716 injection.
c. Women who participate in this study must agree not to breastfeed from study entry to a period of no less than four months post the HSV1716 injection

Anti-HSV antivirals
Subjects whose primary physicians determine that anti-HSV antiviral therapy (such as acyclovir, ganciclovir, foscarnet, etc.) cannot be safely discontinued from 2 days prior to the injection to 28 days following the injection are excluded from this study.

Patients on systemic anticoagulants are excluded from this study.

Patients with any clinically significant unrelated systemic illness (serious infections or significant cardiac, pulmonary, hepatic or other organ dysfunction), that would compromise the patient's ability to tolerate protocol therapy or would likely interfere with the study procedures or results.