PBTC-009 Abstract for Health Professionals

Study Title: Phase I Trial of GLIADEL® and O^6-Benzylguanine in Pediatric Patients with Recurrent Malignant Gliomas

Two days before surgery for tumor debulking in children with progressive unifocal supratentorial malignant gliomas that require tumor resection for relief of mass effect, patients will receive 120 mg/m^2 of O^6-benzylguanine (O^6-BG) intravenously over one hour followed immediately by the initiation of a continuous intravenous infusion of 30 mg/m^2/24 hours, which will be continued for a total of nine days. After 48 hours ($\pm$ 8 hours is permissible) of the infusion, patients will go to the operating room to have their tumors resected as extensively as deemed safely feasible by the operating neurosurgeon. Gliadel wafers will then be implanted. Immediately before wafer implantation, tumor tissue will be obtained for the determination of alkylguanine-DNA alkyltransferase (AGT) level. If at least 11 of 14 patients have complete suppression of AGT levels, this will confirm this dose as the recommended Phase II O^6-BG dose for continuous infusion. If at any time during the accrual of the 14 patients, 4 or more patients have measurable AGT levels, then the O^6-BG continuous infusion dose will be increased by 10 mg/m^2/24 hours in the next cohort of 14 patients. Escalation of doses in this manner will continue until at least 11 of 14 patients in a cohort meet the target of complete suppression of AGT levels. All patients will continue to receive the O^6-BG infusion postoperatively for seven days.

Objectives:

1. To define the dose of O^6-BG when infused continuously for 48 ($\pm$ 8) hours that will reliably inhibit AGT activity in recurrent malignant gliomas.
2. To characterize toxicities associated with the administration of O^6-BG and Gliadel wafers.
3. To document anti-tumor response in patients when treated with O6-BG and Gliadel wafers.
4. To characterize the pharmacokinetics of O6-BG when administered continuously over a 9-day period.
5. To characterize the presence of TP53 mutations, EGFR amplification, p16 deletions, and chromosome 1p and 19q deletion in tissue from relapsed malignant gliomas.

Eligibility Criteria:

- Age $\geq$ 3 and $\leq$ 21
- Progressive supratentorial anaplastic astrocytoma or glioblastoma multiforme mass measuring at least 1 cm in diameter, confirmed by previous histology, without current or previous evidence of multifocal disease,without extension across the midline, with no more than minimal intraventricular involvement, and judged by the operating neurosurgeon and non-neurosurgical neuro-oncologist to be in need of (and amenable to) extensive debulking sufficient to ameliorate tumor-induced mass effect
- Karnofsky Score or Lansky Score >= 60%; Life expectancy > 8 weeks
- Neurological Deficits: None or stable for a minimum of 1 week prior to study entry
- Prior Therapy: *Chemo*: $\leq$ 2 cytotoxic regimens, $\leq$3 regimens total. Evidence of recovery from prior chemotherapy. No myelosuppresive chemotherapy within 3 weeks (6 weeks if a nitrosourea). If patient has had prior nitrosourea, must not have had non–hematopoietic Grade III/IV toxicity associated with this therapy. No myeloblative therapy within 6 months prior to study entry. *XRT*: Completed >= 3 months prior to study entry for local therapy; patients that required craniospinal irradiation are excluded
- Other medications: *Anti-convulsants*: No limitations. *Growth factors*: Off all colony stimulating growth factor(s) > 2 weeks prior to study entry. *Dexamethasone*: Patients who are receiving dexamethasone must be on a stable dose for at least 1 week prior to study entry. However, subsequent dose modifications during the perioperative period are at the discretion of the treating neurosurgeon and/or non-neurosurgical neuro-oncologist.
- Organ function: *Bone marrow*: ANC > 1,000/µl, Platelets > 100,000/µl; Hemoglobin> 8g/dl (may be transfused). ANC and platelet counts must be transfusion independent. *Renal*: creatinine clearance <= 1.5

times institutional normal for age or GFR > 70 ml/min/1.73m^2. *Hepatic*: bilirubin <= 1.5 times institutional normal for age; SGPT (ALT) and SGOT (AST) < 3X institutional normal. Albumin >= 2 g/dL. No overt renal, hepatic, cardiac or pulmonary disease.

- Female patients of childbearing potential must have negative serum or urine pregnancy test. Patient must not be pregnant or breast-feeding. 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.

Rationale:

While clinical studies have established that GLIADEL® 3.85% is well tolerated and prolongs survival after surgery in adults with malignant gliomas, the clinical benefits remain somewhat modest. There are ample preclinical experimental data to suggest that O^6-BG enhances the therapeutic effect of BCNU by reversing AGT-mediated drug resistance. However, the clinical utility of a strictly systemic approach to combination BCNU/O^6-BG therapy is limited by the fact that depletion of AGT can potentially enhance not only the antitumor efficacy, but also the systemic toxicity, of the alkylator. In contrast, the combination of local delivery of BCNU with intravenous administration of O^6-BG has a strong theoretical rationale as a way to enhance the therapeutic effectiveness of the locally delivered BCNU.

In the proposed trial, the O^6-BG will be administered continuously in order to completely inhibit the AGT protein during the time of maximum BCNU release from the polymer. Preliminary confirmation of the safety of this approach as well as the doses of O^6-BG required to deplete tumor AGT have been obtained in an ongoing NABTT adult trial. Because previous pediatric studies with O^6-BG have demonstrated that the doses required to deplete AGT are comparable to those that are effective in adults (Friedman et al., personal communication), the current study will adopt the dosing strategy employed in the NABTT study, which has proven to be effective and well tolerated. To confirm AGT depletion at the time of wafer implantation, after the two-day preoperative infusion of O^6-BG, tumor tissue from all patients enrolled in this study will be obtained for analysis of AGT levels immediately prior to the wafer implantation step. Based on the preclinical data that 100% of the BCNU within GLIADEL® Wafers is released within a 5-day period, we will continue the postoperative continuous infusion for 7 days.

Schema:

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Treatment Schema		
Day on Treatment	***Day from surgery***	***Treatment***
1	-2	120 mg/m^2 for 1 hr followed by CIV* O^6-BG
2	-1	CIV O^6-BG
3	0	Surgery + Gliadel + CIV O^6-BG *Tumor sample for AGT testing prior to Gliadel placement*
4	1	CIV O^6-BG
5	2	CIV O^6-BG
6	3	CIV O^6-BG
7	4	CIV O^6-BG
8	5	CIV O^6-BG
9	6	CIV O^6-BG

*CIV = Continuous intravenous infusion over 24 hours. CIV O^6-BG will be dose escalated in 10mg/m^2/24 hours increments, if indicated, beginning with the 30 mg/m^2/24 hours dose used in the NABTT adult trial

Contact:

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