

PBTC-030 Protocol Abstract and Schema

A Phase II Trial of Capecitabine Rapidly Disintegrating Tablets and Concomitant Radiation Therapy in Children with Newly Diagnosed Brainstem Gliomas

Description:

This is a phase II protocol for children with newly diagnosed, diffuse intrinsic brain stem gliomas. Capecitabine RDT dosing during the radiation phase will be 650 mg/m² administered twice daily and is based on the pediatric MTD of capecitabine with concomitant RT from the phase I pediatric trial. There should be no interruptions in capecitabine administration in the absence of unacceptable adverse event. Oral capecitabine RDT will continue for a total of nine weeks, followed by a two-week break. Post-RT therapy will begin after the two week break. Post radiation therapy, patients will receive twice daily oral capecitabine for 3 courses. During each course, capecitabine will be administered for 14 consecutive days followed by a 7-day rest period.

Capecitabine will be provided as a flavored, film coated, rapidly disintegrating tablet that may be swallowed intact or dispersed in water for patients unable to swallow tablets.

1.0 OBJECTIVES

1.1 Primary Objectives:

- 1.1.1 To estimate the progression-free survival distribution for newly diagnosed patients with diffuse intrinsic brainstem gliomas treated with the combination of capecitabine and radiation therapy and compare to PBTC historical controls.

1.2 Secondary Objectives

- 1.2.1 To estimate the overall survival distribution and to summarize the best tumor responses observed prior to failure.
- 1.2.2 To further characterize the safety profile of capecitabine administered concomitantly with radiation therapy in this pediatric patient population.
- 1.2.3 To further characterize the pharmacokinetics of capecitabine and its metabolites as delivered by Capecitabine Rapidly Disintegrating Tablets (RDT) in this pediatric population.
- 1.2.4 To explore the exposure-response relationship for measures of safety and effectiveness using pharmacokinetic and pharmacodynamic (PK/PD) models.
- 1.2.5 Describe diffusion tensor imaging (DTI) findings at diagnosis and explore early post-irradiation changes as a response measure in brainstem gliomas.

2.0 PATIENT SELECTION

All patients must meet the following inclusion and exclusion criteria. NO EXCEPTIONS WILL BE GIVEN.

Both men and women of all races and ethnic groups are eligible for this study.

2.1 Inclusion Criteria

2.1.1 **Age:** Patient must be ≥ 3 and <18 years of age.

2.1.2 **Tumor:** Patients must have newly diagnosed non-disseminated intrinsic infiltrating brainstem glioma. Histopathologic diagnosis is not required.

2.1.3 **Performance status:** Karnofsky Performance Scale (if > 16 yrs) or Lansky Performance Score (if ≤ 16 years) $\geq 50\%$ assessed within two weeks prior to registration.

2.1.4 **Prior/Concurrent therapy:** Patients must not have received any prior chemotherapy, radiation therapy, immunotherapy or bone marrow transplant for the treatment of brainstem glioma. Prior dexamethasone and/or surgery are allowed.

2.1.5 **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.

2.1.5.1 Bone marrow:

- i. Absolute Neutrophil Count (ANC) $\geq 1,000/\text{mm}^3$
- ii. Platelets $\geq 100,000/\text{mm}^3$ (transfusion independent)
- iii. Hemoglobin $\geq 8 \text{ g/dl}$ (transfusion independent)

2.1.5.2 *Renal:* Creatinine clearance or radioisotope GFR $\geq 70 \text{ ml/min/1.73m}^2$ or a serum creatinine based on age as follows:

Age (years)	Maximum Serum Creatinine (mg/dL)
< 5	0.8
5 and < 10	1
10 and < 15	1.2
>15	1.5

2.1.5.3 *Hepatic:* Bilirubin $\leq 1.5\text{x}$ institutional upper limit of normal for age; SGPT (ALT) $\leq 5\text{x}$ institutional upper limit of normal for age.

2.1.6 **Birth control:** 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.

2.1.7 **Consent:** Signed informed consent according to institutional guidelines must be obtained prior to study entry.

2.2 Exclusion Criteria

- 2.2.1 Patients receiving any other anticancer or experimental drug therapy
- 2.2.2 Patients with uncontrolled infection
- 2.2.3 Patients with significant cardiac, hepatic, gastrointestinal, renal, pulmonary, or other systemic disease
- 2.2.4 Patients with a known hypersensitivity to capecitabine or any of its components
- 2.2.5 Patients with known dihydropyrimidine dehydrogenase (DPD) deficiency
- 2.2.6 Patients who are receiving any of the following medications: warfarin, sorivudine or chemically related analogues, such as brivudine.
- 2.2.7 Patients who are pregnant and/or lactating,
- 2.2.8 Patients who in the opinion of the investigator will be unable to comply with study follow-up or procedures

2.3 Criteria to Start Therapy

- 2.3.1 Pre-treatment MRIs must be obtained within two (2) weeks prior to the start of therapy.
- 2.3.2 Laboratory values used to assess eligibility in Section 4.1.5 must be no older than seven (7) days at the start of therapy. Laboratory tests need not be repeated if therapy starts within seven (7) days of obtaining labs to assess eligibility. If a post-registration lab value is outside the limits for eligibility, it must be rechecked prior to the start of therapy. If recheck is outside the limits of eligibility, the patient may not receive protocol therapy and will be considered off study.

3.0 TREATMENT PLAN AND MODIFICATIONS

3.1 Treatment Plan

3.1.1 Radiation Phase

Capecitabine RDT dosing during the radiation phase will be 650 mg/m² administered twice daily and is based on the pediatric MTD of capecitabine with concomitant RT from the PBTC021 trial. There should be no interruptions in capecitabine administration in the absence of unacceptable adverse events. (**Note:** The dose of Capecitabine RDT post-RT is different than the dose during radiation.)

3.1.2 Drug Initiation

Treatment must be initiated within seven (7) working days of registration and within 24 hours of the start of radiation therapy. See Section 4.3 for criteria to start therapy.

3.1.3 Drug Administration

3.1.3.1 *Radiation Phase:* Capecitabine RDT will be given orally twice daily approximately 12 hours apart, beginning within 24 hours of the start of radiation therapy and continuing for 9 weeks. Patients will have a two-week break following the completion of this 9 week course of capecitabine prior to starting the Post RT phase. It is anticipated that it will take approximately 6 weeks to deliver the prescribed radiation therapy dose (Section 6.0). This entire 11-week period is the radiation phase.

Drug should continue during interruptions of radiation therapy not due to toxicity. For non-anesthetized patients, Capecitabine RDT should ideally be taken within 30 minutes of a meal and 1 hour prior to radiation therapy. For patients requiring anesthesia, Capecitabine RDT should be taken as close to radiation therapy as practical.

3.1.3.2 *Post Radiation Therapy:* Post RT therapy with Capecitabine RDT will begin after the completion of the 11 week radiation phase including the two week break. During the Post RT phase, patients will receive twice daily oral capecitabine, approximately 12 hours apart, for a total of 3 courses. During each course, capecitabine will be administered for 14 consecutive days followed by a 7-day rest period (Total 21 days). The total duration of the Post RT phase will be 9 weeks.

Note: If vomiting occurs during a course of treatment, no re-dosing of capecitabine should occur prior to the next scheduled dose.

Schema

Capecitabine Schedule			
Radiation Phase		Weeks	Protocol Therapy
	Course 1	Weeks 1 through 3	Capecitabine + RT
	Course 2	Weeks 4 through 6	Capecitabine + RT
	Course 3	Weeks 7 through 9	Capecitabine ± RT*
	Break	Weeks 10 and 11	None
Post Radiation Phase	Course 4	Weeks 12 and 13 Week 14	Capecitabine None
	Course 5	Weeks 15 and 16 Week 17	Capecitabine None
	Course 6	Weeks 18 and 19 Week 20	Capecitabine None

* Patients who did not complete radiation as planned at the end of week 6 will continue to receive radiation during course 3 to complete the prescribed radiotherapy dose.

Patients will be followed for three years from the initiation of the protocol treatment for monitoring of unexpected later developing toxicities, other morbidity and to document disease progression and survival.