

Protocol Abstract and Schema

A Phase I Study of ABT-888, an Oral Inhibitor of Poly(ADP-ribose) Polymerase, and Temozolomide in Children with Recurrent/Refractory CNS Tumors

Description and Rationale for the Study:

Temozolomide, an oral alkylating agent, has shown modest activity in recurrent pediatric CNS tumors, including high-grade gliomas, medulloblastoma/PNET, and low-grade gliomas. Given the low rate of objective response to temozolomide (< 20%), it is probable that most pediatric CNS tumors have *de novo* or acquired resistance to temozolomide or other alkylating agents. Temozolomide induces single-stranded DNA breaks, the majority of which are repaired by the base excision repair (BER) pathway. Poly(ADP-ribose) polymerase, or PARP, is a critical nuclear enzyme that binds to DNA breaks, recruits and activates key proteins in the BER and other DNA repair pathways, halts DNA replication, and facilitates repair of damaged DNA. High levels of PARP proteins and/or enzymatic activity have been detected in pediatric malignant gliomas and medulloblastomas and represent a likely mechanism of tumor resistance to alkylating agents. Pre-clinical studies have shown that PARP inhibition enhances the sensitivity of malignant gliomas' to temozolomide. ABT-888 is a potent and orally bioavailable PARP inhibitor that has been shown to enhance cytotoxicity of temozolomide and other chemotherapy agents in several pre-clinical models of human tumors. We have demonstrated that ABT-888 crosses the blood-brain barrier effectively, accumulates preferentially in intracranial xenografts of pediatric medulloblastoma and glioblastoma multiforme in mice, potently inhibits PARP activity and other DNA repair pathways, and improves tumor response to temozolomide. Phase 1 clinical trials of ABT-888 and temozolomide have been completed in adults with recurrent/progressive solid tumors, and the recommended phase 2 doses of ABT-888 and temozolomide are 40 mg bid and 200 mg/m²/day x 5 days every 28 days respectively. In this phase 1 trial we will estimate the maximum tolerated dose (MTD) or recommend Phase 2 doses of the combination of ABT-888 and temozolomide in children with recurrent/progressive CNS tumors.

Schema:

ABT-888 will be given twice daily on day 1-5, and temozolomide will be given once daily on day 1-5, every 28 days. The morning dose of ABT-888 will be given 60-90 minutes prior to temozolomide.

Each Course	Up to 13 courses of protocol therapy					
Day	1	2	3	4	5	6-28
ABT-888, BID	x,x	x,x	x,x	x,x	x,x	Rest/Evaluation
Temozolomide, Morning only	x	x	x	x	x	

The study design in estimating the MTD of the combination of ABT-888 and temozolomide is to maximize the dose of temozolomide and adjust the dose of ABT-888 as tolerated. Using an estimated adult body surface area of 1.73 m² and starting with approximately 80% of the recommended adult phase 2 dose of 40 mg BID, the starting dose of ABT-888 (Dose Level 1) for this study is 20 mg/m² BID (approximately equal to an adult dose of 30mg BID). Since a significant number of patients with recurrent/refractory CNS tumors will have received craniospinal irradiation previously, the starting dose of temozolomide will be 180 mg/m²/day x 5 days every 28 days for all patients, as this dose was previously well tolerated in a COG phase 2 study in children with recurrent pediatric CNS tumors who have received prior CSI.

Revised Treatment Schema, PBTC 027

Dose Level	ABT-888 Dose, mg/m ² /dose BID x 5 days	TMZ Dose, mg/m ² /day x 5 days
0	15 mg/m ² /dose BID	135 mg/m ² /day
1 (starting dose level)	20 mg/m ² /dose BID	135 mg/m ² /day
2	25 mg/m ² /dose BID	135 mg/m ² /day

The starting Dose Level will be Dose Level 1. There will be no intra-patient dose escalations. Patients with dose limiting toxicities will be de-escalated to the next lower dose level. The traditional Phase I design will be used to estimate the maximum tolerated dose (MTD) using doses up to and including dose level 2. Once the MTD or the recommended Phase II dose has been determined, six additional patients will be treated at that dose to reach a total of 12 patients treated at the MTD in order to better understand the toxicity profile of the regimen. A reasonable attempt will be made to control accrual at the MTD or the recommended dose to ensure that 6 of these 12 patients will be younger than 12 years of age and 6 will be 12 or older.

Proposed Amendment, PBTC 027, Version 6.0

Based on PK and biological activity data from the patients treated on the revised schema, Version 3.0, it appears that ABT-888 at 25 mg/m² bid will lead to more optimal drug exposure and PARP inhibition in the PBMC compared to 20 mg/m² bid. Assuming that no more than 1 out of our additional 3 patients who are currently receiving ABT-888 at 20 mg/m² bid experience any DLTs, we propose to enroll 3 additional patients at Dose Level 2 (ABT-888 at 25 mg/m² bid, TMZ 135 mg/m²/day) with the aims of optimizing drug exposure and PARP inhibition. CNS toxicity will be closely monitored. If another patient experiences a dose-limiting toxicity, expansion of Dose Level 2 cohort will be terminated. If 3 additional patients at Dose Level 2 do not experience any DLT, then we propose to expand the cohort to enroll six additional patients (for a total of 12 patients) to gather additional data on tolerability, PK, and PD profiles.

Pharmacokinetic and pharmacodynamic studies will continue to be **REQUIRED** for all patients to be enrolled onto the amended protocol to allow determination of optimal drug exposure and PARP inhibition and appropriate planning of a subsequent phase II study.

Objectives

Primary Objectives

1. To estimate the maximum tolerated dose (MTD) of ABT-888 in combination with temozolomide in children with recurrent or refractory CNS tumors.
2. To study the plasma pharmacokinetics (PK) of ABT-888 and PARP inhibition in peripheral blood mononuclear cells (PBMC) in order to recommend a Phase 2 dose of ABT-888 in combination with temozolomide in children with recurrent or refractory CNS tumors.
3. To describe the toxicities of the combination of ABT-888 and temozolomide in children with recurrent or refractory CNS tumors.

Secondary Objectives

1. To measure non-homologous end-joining (NHEJ) activity in peripheral blood mononuclear cells (PBMC) prior to and following ABT-888 administration.
2. To assess PARP expression and/or activity in tumor tissue obtained at either initial diagnosis or relapse.
3. To determine expression and/or activity of DNA repair pathways, including MGMT and mismatch repair, in tumor tissues, when available.
4. To document, within the confines of this phase 1 trial, radiographic tumor response to ABT-888 and temozolomide.

PATIENT SELECTION

All clinical and laboratory studies required to determine eligibility (excluding diagnosis of recurrent tumor) must be performed within 14 days prior to enrollment unless otherwise indicated. Imaging studies are required within 3 weeks prior to registration.

If more than 7 calendar days elapse between the date eligibility studies outlined in Section 6.0 were obtained and the start date of treatment, then the following studies must be repeated prior to treatment:

- CBC with differential
- Bilirubin
- ALT (SGPT)
- Serum Creatinine

If any of these repeat laboratory studies are outside the parameters required for eligibility or the patient's clinical condition worsens so they no longer meet eligibility requirements (labs may again be repeated within 48-72 hours), then the patient will not be eligible for protocol therapy.

Important note: The eligibility criteria listed below are to be interpreted literally and cannot be waived. All clinical and laboratory data required for determining eligibility of a patient enrolled on this trial must be available in the patient's medical or research record which will serve as the source document for verification at the time of audit.

Inclusion Criteria

Age

Patients must be ≤ 21 years of age at the time of study enrollment.

- At the time the MTD or the dose to be recommended for future trials is identified, up to 12 additional patients will be enrolled at that dose level to further define the toxicity profile. . Per Section 12.2, six of these patients will be <12 years of age and the other half will be ≥ 12 years.

Tumor

Patients with a diagnosis of a primary CNS malignancy (including low-grade glioma) that is recurrent or refractory to standard therapy and for which there is no known curative therapy. All patients must have had histological verification of malignancy at initial diagnosis or relapse, excluding patients with diffuse intrinsic brain stem tumors, optic pathway tumors or CNS germ cell tumors with elevations of reliable serum or CSF tumor markers (alpha-fetoprotein or beta-HCG). Patients with intrinsic pontine gliomas or optic pathway tumors do not require histological confirmation of disease but should have clinical and/or radiographic evidence of progression.

Performance Status

Patients must have Karnofsky Performance Score (for patients > 16 years of age) or Lansky Performance Score (for patients ≤ 16 years of age) $\geq 50\%$ assessed within two weeks of study enrollment.

Neurological Status

Patients must be able to take oral medications (either capsules or liquid). Patients with neurologic deficits must have been stable for a minimum of 1 week prior to study entry. Patients who are unable to walk because of paralysis, but who are up in a wheelchair, will be considered ambulatory for the purpose of assessing the performance score.

Prior/Concurrent Therapy

Patients must have fully recovered from the acute toxic effects of all prior chemotherapy, immunotherapy, or radiotherapy prior to entering this study. Recovery is defined as all AE's, attributable to prior therapy, having improved to grade 2 or better or as outlined below.

Myelosuppressive chemotherapy:

- Patients must have received their last dose of known myelosuppressive anticancer chemotherapy at least three (3) weeks prior to study registration.
- Patients must have received their last dose of nitrosourea (including Gliadel) at least six (6) weeks prior to study registration.

Biologic agent (anti-neoplastic): Patient must have received their last dose of other 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. The duration of this interval must be discussed with the study chair.

Monoclonal antibody treatment: Patient must have received their last dose of monoclonal antibody ≥ 4 weeks prior to registration.

Radiation - Patients who have had prior radiation must have had their last fraction of:

- Craniospinal irradiation or total body irradiation > 3 months prior to registration
- Local irradiation to the primary tumors or other sites (cumulative dose ≥ 40 Gy) > 3 months prior to registration
- Palliative irradiation delivered to symptomatic metastatic sites > 4 weeks prior to registration.

Stem Cell Transplant: Patient must be:

- ≥ 6 months since allogeneic stem cell transplant prior to registration
- ≥ 3 months since autologous stem cell transplant prior to registration.

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

Growth factors:

- Off all colony forming growth factor(s) that support platelet or white blood cell count, number or function for at least 1 week prior to registration (filgrastim, sargramostim, erythropoietin).
- Off Pegylated G-CSF and/or Erythropoiesis Stimulating Protein for at least 14 days prior to registration.

Temozolomide: Patients who have received temozolomide previously are eligible for this study if they meet all other inclusion and exclusion criteria.

Organ Function: Documented within 14 days of registration and within 7 days of starting treatment.

Bone Marrow:

- Hgb > 8 gm/dL (transfusion independent)
- Platelet count $> 100,000/mm^3$ (transfusion independent)
- Absolute neutrophil count (ANC) $> 1,500/mm^3$

Hepatic:

- Total Bilirubin (sum of conjugated + unconjugated) ≤ 1.5 times institutional upper limit of normal (ULN) for age
- SGPT (ALT) ≤ 2.5 times institutional ULN for age
- Serum albumin ≥ 2 g/dL

Renal:

- Creatinine clearance or radioisotope GFR ≥ 70 ml/min/1.73m² or a serum creatinine based on age as follows:

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

Pregnancy or Breast-feeding:

Patients must not be pregnant or breast-feeding. Females of reproductive potential must have a negative serum or urine pregnancy test (within 72 hours prior to enrollment). Males or females of reproductive potential may not participate unless they have agreed to use an effective contraceptive method, which includes abstinence.

Signed Informed consent according to institutional guidelines must be obtained.

Exclusion Criteria

Concomitant Medications:

Patients receiving any of the following medications are not eligible for study entry:

- Anti-cancer therapy
- Investigational agents

Concurrent Illness

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.

Seizures

Patients with uncontrolled seizures are not eligible for study entry.

Hypertension:

- Patients with inadequately controlled systemic hypertension (SBP and/or DBP > 95 th percentile for age and height (see Appendix XI)
- Patients with a prior history of hypertensive crisis and/or hypertensive encephalopathy

If a BP measurement prior to registration is > 95 th percentile for age and height, it must be rechecked and documented to be < 95 th percentile for age and height prior to registration. If a patient falls between the height or weight percentiles, site should average the value as appropriate. For patients ≥ 18 years the normal blood pressure should be $< 140/90$ mm of Hg. Patients with hypertension are eligible if their blood pressures become < 95 th percentile for age and height after anti-hypertensive medications.

Prior CNS ischemia and/or infarction

Patients with documented CNS ischemia and/or infarction, whether symptomatic or discovered incidentally without clinical symptoms, will be excluded from study participation.

Inability to Participate

Patients with an inability to return for follow-up visits or obtain follow-up studies required to assess toxicity to therapy.