CCF IRB CC578 NABTT 0703

Full Title
Phase I/II study of poly (ADP-ribose) polymerase-1 (PARP-1) inhibitor BSI-201 in patients with newly diagnosed malignant glioma

Principal Investigator
David Peereboom, M.D.

Contact Information
Cathy Schilero, RN, BSN
Research Nurse
216.444.4068

Objectives

Phase I Primary Objectives:

- Study Group I: To determine the Maximum Tolerated Dose (MTD) of BSI-201, administered as an IV infusion in patients with newly diagnosed malignant glioma when given with standard dose temozolomide (TMZ) after the completion of standard radiation therapy and concomitant TMZ.
- Study Group II: To determine the Maximum Tolerated Dose (MTD) of BSI-201, administered as an IV infusion in patients with newly diagnosed malignant glioma when given with metronomic temozolomide (TMZ) after the completion of standard radiation therapy and concomitant TMZ.

Phase I Secondary Objectives:

- To assess the toxicity associated with the two treatment regimens.
- To assess and describe the pharmacokinetics of BSI-201 in these two treatment regimens and potentially correlate with biologic markers of PARP1 inhibition.

Phase II Primary Objective:

- To estimate the overall survival for adult patients with newly diagnosed glioblastoma multiforme (GBM) treated with BSI-201 at the MTDs during RT with concurrent and adjuvant TMZ.

Phase II Secondary Objective:

- To estimate the frequency of toxicity associated with this treatment regimen.

Eligibility

1. Patients must be at least 18 years of age.
2. Patients must have a Karnofsky performance status ≥ 60% (i.e. the patient must be able to care for himself/herself with occasional help from others).
3. Patients must have the following hematologic, renal and liver function (i.e. Absolute neutrophil count > 1500/mm3, Platelets > 100,000/mm3, creatinine ≤ 1.7 mg/dl, total bilirubin ≤ 1.5 mg/dl, transaminases ≤ 4 times above the upper limits of the institutional normal.

4. Patients must be able to provide written informed consent.
5. Patients with the potential for pregnancy or impregnating their partner must agree to follow acceptable birthcontrol methods to avoid conception. Women of childbearing potential must have a negative pregnancy test. The anti-proliferative activity of this experimental drug as well as the standard drug (temozolomide) may be harmful to the developing fetus or nursing infant.
6. Patients must have a Mini Mental Status Exam score of ≥ 15.
7. Patients must have tumor tissue form completed and signed by a pathologist.

Additional Phase I Eligibility

1. Phase I Patients ONLY: Patients must have histologically proven supratentorial malignant glioma (anaplastic astrocytoma, anaplastic oliogodendroglioma or glioblastoma multiforme).
2. Phase I Patients ONLY: Patients must have received at least 80% of planned temozolomide and radiation therapy with no grade 3 or grade 4 toxicity attributed to the temozolomide.
3. Phase I Patients ONLY: Patients must have received planned treatment with radiation therapy and concomitant temozolomide at least 28 days but no more than 49 days prior to starting treatment on this study.
4. Phase I Patients ONLY: Patients must have Gadolinium MRI or contrast CT scan within 28 days of starting treatment.

Additional Phase II Eligibility

1. Phase II Patients ONLY: Patients must have histologically confirmed supratentorial grade IV astrocytoma (glioblastoma multiforme).
2. Phase II Patients ONLY: Patients must not have received prior radiation therapy, chemotherapy, immunotherapy or therapy with biologic agent (including immunotoxins, immunoconjugates, antisense, peptide receptor antagonists, interferons, interleukins, TIL, LAK or gene therapy), or hormonal therapy for their brain tumor. Glucocorticoid therapy is allowed.
3. Phase II Patients ONLY: Patients must have recovered from the immediate post-operative period and be maintained on a stable corticosteroid regimen (no increase for 5 days) prior to the start of treatment.
4. Phase II Patients ONLY: Patients must have Gadolinium MRI or contrast CT scan within 14 days of starting treatment.

Exclusions

1. Patients with serious concurrent infection or medical illness, which would jeopardize the ability of the patient to receive the treatment outlined in this protocol with reasonable safety.
2. Patients who are pregnant or breast-feeding. The anti-proliferative activity of this experimental drug and temozolomide may be harmful to the developing fetus or nursing infant.
3. Patients receiving concurrent therapy for their tumor (i.e. chemotherapeutics or investigational agents).

4. Patients with a concurrent or prior malignancy are ineligible unless they are patients with curatively treated carcinoma-in-situ or basal cell carcinoma of the skin. Patients who have been free of disease (any prior malignancy) for ≥ five years are eligible for this study.
5. Patients cannot be receiving cytochrome P450-inducing anticonvulsants (EIAEDs; *e.g.*, phenytoin, carbamazepine, phenobarbital, primidone, oxcarbazepine) and must not have taken them for at least 10 days.

Additional Phase I Exclusions:

1. Phase I Patients ONLY: Patients who have had repeat craniotomy for tumor therapy after receiving RT and TMZ treatment.
2. Phase I Patients ONLY: Patients who received other chemotherapeutics or investigational agents in addition to their radiation therapy and concomitant temozolomide treatment. Patients who have received Gliadel wafers are eligible for this study.