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Each year approximately 17,000 people are diagnosed with primary malignant brain tumors in the United States (CBTRUS, 2000). Malignant glial tumors, including anaplastic astrocytoma and glioblastoma multiforme (GBM) exact a tremendous toll on patients because of the severe neurological disability they produce. Despite optimum treatment modalities of maximal tumor removal, radiation, and adjuvant chemotherapy, the prognosis for these tumors is bleak with survival rates of 12 to 18 months (Neurosurgery, 1991).

The overexpression (more of the substance than is normally present) of epidermal growth factor receptor (EGFR – a protein that causes cells to divide and multiply quickly) and tyrosine kinase (an amino acid enzyme) activity has been correlated with cell proliferation (growth) and an extremely poor prognosis in GBM. Since pre-clinical and clinical studies have demonstrated that pharmacologic inhibition (repression) of EGFR results in anti-tumor effects, new cancer therapies have targeted EGFR. A small molecule, Gefitinib (Iressa, ZD 1839), is a potent EGFR inhibitor. While its clinical efficacy in GBM has been demonstrated, monotherapy (single treatment therapy) with Gefitinib is insufficient. Rapamycin blocks a protein called mTOR, which plays a critical role in tumor growth. Recognizing that GBM is a heterogeneous (consisting of dissimilar elements) disease and that multiple strategic growth-promoting pathways must be inhibited for optimal and effective control, a clinical trial of Gefitinib and Rapamycin in the treatment of recurrent and progressive GBM is proposed.

Our primary endpoints are to evaluate the safety and toxicity of Gefitinib and Rapamycin in patients with progressive or recurrent GBM. Our secondary endpoints are to determine the efficacy of Gefitinib and Rapamycin in patients with progressive or recurrent GBM, particularly with regard to time to tumor progression and overall survival. In addition, assessments of quality of life will be made.

Gefitinib will be dosed at 500 mg/day with those receiving dexamethasone (a steroid that helps decrease swelling in the brain) and/or an enzyme inducing (CYP3A4) agents, for example: carbamazepine, dexamethasone, ethosuximide, phenobarbital, phenytoin, primidone and rofecoxib, escalated to a dose of 1000 mg.

Rapamycin will be administered at a dose of 2 mg/day and adjusted to obtain whole blood trough (cumulative) concentrations of 4-12 nanograms/mL (by chromatographic – a method of chemical analysis - assay). Drug dosing will be modified pending additional pharmacokinetic (the study of the action of a drug in the body over a period of time) data.

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Physical and neurologic exams, including a mental status exam and Karnofsky performance scores, will be performed at screening and every other month thereafter.

Laboratory parameters, including a complete blood count and complete metabolic panel, and screening for toxicities using the NCI Common Toxicity Criteria will be obtained every 2 weeks for one month and then every other month. MRI scans of the brain and quality of life parameters using the Functional Assessment of Cancer Therapy (FACT)-Br scale will be performed at entry and every two months thereafter.

If tumor progression is observed, the patient will be removed from the study. Those patients with stable disease, partial or complete responses will continue study medications until tumor progression or dose-limiting toxicities occur.