

HGG-1MF: A Study of Bevacizumab Therapy in Patients with Newly Diagnosed High-Grade Gliomas and Diffuse Intrinsic Pontine Gliomas

Type	Status	Age Range	Sponsor
Interventional	Active	3 years to 30 years	<ul style="list-style-type: none"> ▪ Cincinnati Children's Hospital ▪ Genentech

Outline

The outcome for children with high-grade glioma and diffuse intrinsic brainstem gliomas remains poor despite the use of multi-modal therapy with surgery, radiation therapy and chemotherapy. Novel therapies are needed to improve the outcome of these children. Recent studies have demonstrated very promising results of treatment with bevacizumab/irinotecan in patients with recurrent high-grade gliomas. Based on these promising results, and the tolerability of the irinotecan and bevacizumab in children with recurrent CNS malignancies both anecdotally and in a study conducted by the Pediatric Brain Tumor Consortium, we have designed a novel study incorporating concurrent radiation therapy with bevacizumab ± temozolomide followed by bevacizumab, irinotecan ± temozolomide in patients with newly diagnosed high-grade gliomas and diffuse intrinsic pontine gliomas.

Objectives

Primary

- To determine the toxicities and feasibility of the proposed treatment regimen in patients with high-grade glioma and diffuse intrinsic brainstem glioma

Secondary

- To determine the one year EFS, median PFS and median OS in newly diagnosed patients with high-grade glioma treated with radiotherapy and concurrent temozolomide, bevacizumab followed by bevacizumab, irinotecan and temozolomide for 12 courses.
- To determine the one year EFS, median PFS and median OS in newly diagnosed patients with diffuse intrinsic brainstem glioma treated with radiotherapy and concurrent bevacizumab followed by bevacizumab and irinotecan for 12 courses.
- To estimate blood levels of VEGF in circulating endothelial cells in patients at different time points
- To document changes in MR perfusion and diffusion within 24-48 hours after the 2nd dose of bevacizumab during radiotherapy.
- To correlate functional changes in tumor with responses to treatment using MR diffusion/perfusion imaging.
- To correlate the results of the biology studies in serum or tumor with PFS.
- To conduct gene expression profiling, CGH and SNP arrays in patients with high-grade gliomas.
- To assess telomerase activity, *hTert* expression, and telomere length in patients with HGG.

- To assess the health related quality of life of patients by parent report and, when possible, patient report at key points in therapy.
- To assess functional abilities and level of independence of patients during and following treatment.

Projected Accrual

- 20 patients for the high-grade glioma stratum and 15 patients for the diffuse intrinsic brainstem glioma stratum.

Mechanism of Action

Bevacizumab is a recombinant humanized monoclonal antibody directed against the vascular endothelial growth factor (VEGF), a pro-angiogenic cytokine. Bevacizumab binds to VEGF and inhibits VEGF receptor binding, thereby preventing the growth and maintenance of tumor blood vessels.

Entry Criteria

Disease Characteristics:

- Not Specified.

Patient Characteristics:

Age

- ≥ 3 years and ≤ 30 years

Performance Status

- Performance Level: Karnofsky $\geq 50\%$ for patients > 10 years of age and Lansky ≥ 50 for patients ≤ 10 years of age. 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

Life Expectancy

- > 8 weeks

Hematopoietic

- Adequate Bone Marrow Function Defined as:
 - Peripheral absolute neutrophil count (ANC) $\geq 1000/\mu\text{L}$
 - Platelet count $\geq 100,000/\mu\text{L}$ (transfusion independent, defined as not receiving platelet transfusions within a 7 day period prior to enrollment)
 - Hemoglobin ≥ 8.0 gm/dL (may receive RBC transfusions)

Hepatic

- Adequate Liver Function Defined As:
 - Bilirubin (sum of conjugated + unconjugated) ≤ 1.5 x upper limit of normal (ULN) for age
 - SGPT (ALT) ≤ 2.5 x upper limit of normal (ULN) for age
 - Serum albumin ≥ 2 g/dL

Renal

- Patients with Proteinuria with a urine protein (albumin)/creatinine ratio of ≥ 1.0 will not be enrolled in this study
- Adequate Renal Function Defined As:
 - No greater than trace protein on urine dipstick, OR < 1000 mg protein/24 hour urine collection (i.e., Grade 1 proteinuria), AND
 - Creatinine clearance or radioisotope GFR ≥ 70 ml/min/1.73 m² OR
 - Serum creatinine based on age/gender as follows:

Age	Maximum Serum Creatinine (mg/dL)	
	Male	Female
3 to < 6 years	0.8	0.8
6 to < 10 years	1	1
10 to < 13 years	1.2	1.2
13 to < 16 years	1.5	1.4
≥ 16 years	1.7	1.4

The threshold creatinine values in this Table were derived from the Schwartz formula for estimating GFR (Schwartz et al. J. Peds, 106:522, 1985) utilizing child length and stature data published by the CDC.

Cardiovascular

- Patients with uncontrolled systemic hypertension

Other

- Patients with metastatic disease (i.e. M+ disease, or disease anywhere other than primary site).
- Patients with evidence of a new intracranial hemorrhage that is larger than a punctate size on baseline MRI scan
- The use of steroids is permissible
- Must not have a history of allergic reaction to Chinese hamster ovary cell products, or other recombinant human antibodies
- Pregnant or breast feeding women will not be entered on this study
- 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
- Patients who require IV antibiotics at time of enrollment, or who are currently receiving treatment for Clostridium difficile infection are excluded
- Patients must not have been previously diagnosed with a deep venous or arterial thrombosis (including pulmonary embolism), and must not have a known thrombophilic condition
- Must not have any serious or non-healing wounds
- Adequate Blood Clotting Defined As: INR, Fibrinogen, and PTT < Grade 2
- Patients with seizures may be enrolled if the seizures are well-controlled with non-enzyme inducing anticonvulsants

Prior Concurrent Therapy:

Surgery

- Patients who have had major surgery should not receive the first dose of bevacizumab until 28 days after major surgery

Other

- No prior anticancer therapy

Trial Contact Information

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