Protocol Abstract and Schema

Phase II study of Bevacizumab plus Irinotecan (Camptosar™) in Children with Recurrent, Progressive, or Refractory Malignant Gliomas, Diffuse/Intrinsic Brain Stem Gliomas, Medulloblastomas, Ependymomas, and Low Grade Gliomas

Description:

A phase II study of bevacizumab in combination with irinotecan (CPT-11) will be performed in children with recurrent malignant glioma, diffuse brain stem glioma, medulloblastoma, ependymoma and low grade glioma. Therapy will begin with single-agent bevacizumab 10 mg/kg given intravenously (i.v) on day 1 and day 15 (+/- 24 hours) followed by MR-perfusion/diffusion imaging within 24-48 hours following the 2nd dose of bevacizumab to assess whether there is reduction in permeability since VEGF mediates tumor angiogenesis and vascular permeability and bevacizumab directly inhibits VEGF. The first dose of irinotecan will be given i.v following this MR-perfusion scan. Subsequently, bevacizumab and irinotecan will be given every two weeks. The irinotecan dose will depend on whether the patient is on an enzyme-inducing anticonvulsant drug (EIACD). The irinotecan dose will be 250 mg/m2 (~ 80 % of dose tolerated by adults in the Duke Phase II study of bevacizumab plus irinotecan) every two weeks for those on EIACDs. If the patient is not on an EIACD, the starting dose will be 125 mg/m2. These doses are routinely used when irinotecan is administered as a single-agent for malignant glioma in adults and children. Treatment will continue on study until tumor progression, unacceptable toxicity, or for a maximum of two years. Standard MRI scan of brain +/- spine, rapid perfusion and diffusion MRI of the brain, and FDG-PET scans prior to treatment and at periodic intervals will be obtained to study the effects of bevacizumab + irinotecan in these tumors. In addition, biology correlates will be studied including serum pharmacokinetics of bevacizumab and the expression of vascular endothelial growth factor receptor-2 (VEGF-R2) on peripheral blood mononuclear cells (PBMC) and the effect of bevacizumab on VEGF-R2 phosphorylation. In the latter would be correlated with tumor responses and MR perfusion changes in tumor following bevacizumab therapy. In addition, immunochemistry (IHC) expression of Hypoxia inducible factor-2α, carbonic anhydrase IX (CA9), vascular endothelial growth factor (VEGF-A), and (VEGF-R2) will be studied on paraffin sections of medulloblastoma, ependymoma, and low grade glioma and intensity of expression will be correlated with rate of sustained tumor response and distribution of progression-free survival.

Objectives:

Primary Objectives

1. To estimate the rates of objective response (sustained for 8 weeks) observed prior to disease progression during the ***first four courses of treatment*** with i.v bevacizumab plus irinotecan (CPT-11) given every 2 weeks in patients with (1) recurrent/progressive/refractory malignant glioma (Stratum A), and recurrent/progressive/refractory intrinsic brain-stem glioma (Stratum B). ***(The accrual goal for these two strata has been met)***

2. To estimate the rates of objective response (sustained for 8 weeks) observed prior to disease progression during the first four courses of treatment with i.v bevacizumab plus irinotecan (CPT-11) given every 2 weeks in patients with recurrent or progressive medulloblastoma (Stratum C), and (4) recurrent or progressive ependymoma (Stratum D).

3. To estimate the sustained disease stabilization rate associated with i.v bevacizumab plus irinotecan (CPT-11) given every 2 weeks in patients with recurrent or progressive low grade glioma (stratum E). In this stratum, disease stabilization is defined as PR or CR observed during the first four courses of treatment and sustained for 8 weeks; or SD sustained for 6 courses characterized by SD at the end of course 2, at the end of course 4 and at the end of course 6.

Secondary Objectives

4. To document changes in the brain tumor on MR perfusion and diffusion scans obtained within 24-48 hours following the 2nd dose of bevacizumab as compared to baseline and correlate with response in the same tumor as well as with PFS.

5. To estimate the rate of treatment-related toxicity with i.v bevacizumab + irinotecan given every 2 weeks in patients with (1) recurrent/progressive/refractory malignant glioma (Stratum A), (2) recurrent/progressive/refractory intrinsic brain-stem glioma (Stratum B), (3) recurrent or progressive medulloblastoma (Stratum C), (4) recurrent or progressive ependymoma (Stratum D), and (5) recurrent or progressive low grade glioma (stratum E).

6. To estimate the cumulative incidence of sustained objective responses as a function of courses of treatment with i.v bevacizumab plus irinotecan given every 2 weeks in patients with (1) recurrent/progressive/refractory malignant glioma (Stratum A), (2) recurrent/progressive/refractory intrinsic brain-stem glioma (Stratum B), (3) recurrent or progressive medulloblastoma (Stratum C), (4) recurrent or progressive ependymoma (Stratum D), and (5) recurrent or progressive low grade glioma (stratum E).

7. To estimate the distributions of progression-free survival (PFS) in patients with (1) recurrent/progressive/refractory malignant glioma (Stratum A), (2) recurrent/progressive/refractory intrinsic brain-stem glioma (Stratum B), (3) recurrent or progressive medulloblastoma (Stratum C), and (4) recurrent or progressive ependymoma (Stratum D), who are treated with at least one dose of i.v bevacizumab in the context of this phase II trial for recurrent patients.

8. To estimate the distributions of progression-free survival (PFS) and overall survival in patients with recurrent or progressive low grade glioma (stratum E) who are treated with at least one dose of i.v bevacizumab in the context of this phase II trial for recurrent patients.

9. To correlate functional changes in tumor with PFS and with responses to treatment with bevacizumab + irinotecan using MR perfusion/diffusion imaging, and Fluoro-deoxyglucose (FDG) positron emission tomography (PET).

10. To obtain serum pharmacokinetics of bevacizumab in children with high grade glioma, brain stem glioma, medulloblastoma, ependymoma, and low grade glioma.

11. To estimate vascular endothelial growth factor receptor-2 (VEGF-R2) expression in peripheral blood mononuclear cells (PBMC) prior to treatment and its down-regulation

following two doses of single-agent bevacizumab and correlate this finding with permeability changes in the tumor on MR perfusion imaging obtained 24-48 hours following the 2nd dose bevacizumab.

12. To estimate expression of Hypoxia inducible factor-2α, carbonic anhydrase IX (CA9), VEGF-A, and VEGF-R2 by immunohistochemistry of paraffin sections of medulloblastoma, ependymoma, and low grade glioma and correlate intensity of expression with sustained tumor response and distribution of progression-free survival (in the context of therapy for recurrent/ progressive/ refractory disease).

Inclusion Criteria

- Patient must be ≤ 21 years of age at registration.

- Patients must have:
  - Stratum A: recurrent/progressive/refractory malignant glioma (i.e., anaplastic astrocytoma, glioblastoma multiforme [including giant cell and gliosarcoma types], anaplastic oligodendroglioma, anaplastic oligoastrocytoma or anaplastic ganglioglioma) within the brain with or without spinal cord disease
  - Stratum B: recurrent/progressive/refractory intrinsic brain-stem glioma
  - Stratum C: recurrent or progressive medulloblastoma within the brain with or without spinal cord disease
  - Stratum D: recurrent or progressive ependymoma within the brain with or without spinal cord disease
  - Stratum E: recurrent low grade glioma at any site within the brain with or without spinal cord disease
  - Prior histologic diagnosis is required for high-grade glioma, medulloblastoma, ependymoma, and low grade glioma; histologic confirmation of diffuse intrinsic brainstem glioma or visual pathway tumors is not required.

- Patients must have bi-dimensionally measurable disease in the brain, defined as at least one lesion that can be accurately measured in at least two planes in order to be eligible for this study. If there is spinal cord disease as well, response assessment will be based only upon the measureable tumor in the brain.

- Patients with neurological deficits should have deficits that are stable for a minimum of 1 week prior to registration.

- Karnofsky Performance Score (KPS for > 16 yrs of age) or Lansky Performance Score (LPS for ≤ 16 years of age) ≥ 50 assessed within two weeks prior to registration.

- For patients in strata A-D (malignant glioma, diffuse brain stem glioma, medulloblastoma, and ependymoma): patient has received prior standard chemo/radiotherapy, and ≤ 2 prior chemotherapy regimens following relapse prior to study registration. For patients with secondary GBM following treatment of other brain tumors or conversion from a low grade glioma; such patients are eligible if they have had ≤ 2 prior chemotherapy regimens.

- For patients in stratum E (low grade glioma): patient has received at least one chemotherapy regimen or radiation therapy.

- Patients must have:
  - received their last dose of known myelosuppressive anticancer chemotherapy at least three (3) weeks prior to study registration or at least six (6) weeks if a nitrosourea.
  - received their last dose of other investigational or biologic agent ≥ 7 days prior to study registration.
    - In the event the patient has received another investigational or biologic agent and has experienced ≥ grade 2 myelosuppression, then at least three (3) weeks must have elapsed prior to registration.
    - If the investigational or biologic agent has a prolonged half-life then at least three (3) weeks must have elapsed prior to registration. Such patients should be discussed with the study chair prior to registration.

- Patients must have received their last fraction of craniospinal or focal irradiation to primary tumor or other sites >12 weeks (3months) prior to registration.

- Patient must be ≥ 3 months since autologous bone marrow/stem cell transplant prior to registration.

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

- All colony forming growth factor(s) have been discontinued for at least 2 week prior to registration (filgrastim, sargramostim, erythropoietin).

- Bone Marrow:
  - Absolute neutrophil count ≥ 1500/µl (unsupported)
  - Platelets ≥ 100,000/µl (unsupported)
  - Hemoglobin > 8 g/dL (may be supported).

- Renal: Serum creatinine < upper limit of institutional normal and BUN <25mg/dL.

- Hepatic:
  - Bilirubin ≤ 1.5 times upper limit of normal for age
  - SGPT (ALT) ≤ 3 times institutional upper limit of normal for age
  - SGOT (AST) ≤ 3 times institutional upper limit of normal for age

- No active renal, cardiac (congestive cardiac failure, myocarditis), or pulmonary disease.

- Female patients of childbearing potential must not be breast-feeding or pregnant as evidenced by a negative serum pregnancy test.

- 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.

- Signed informed consent according to institutional guidelines must be obtained prior to registration.

Exclusion Criteria

- Patients receiving concomitant medications that may interfere with study outcome (e.g., immunosuppressive agents other than corticosteroids).

- Patients with diffuse gliomatosis cerebri who do not have one or more discrete, measurable lesions.
- Patients who require the use of therapeutic anti-coagulation.

- Patients previously treated with either bevacizumab or irinotecan.

- Patients receiving any other concurrent anticancer or investigational drug therapy.

- Patients with evidence of new symptomatic CNS hemorrhage (> grade II) on baseline MRI obtained within 14 days prior to study registration.

- 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.

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

- Patients with central non-cerebellar PNET's (e.g., cerebral PNET or pineoblastoma).

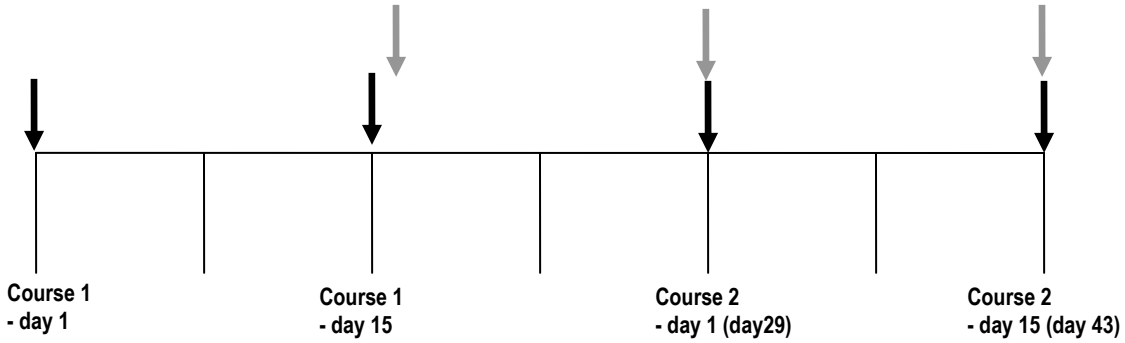
- Patients with spinal cord tumors only.

- **Bevacizumab specific concerns:**
  Subjects meeting any of the following criteria would also be ineligible for this study:
  - Uncontrolled systemic hypertension (as defined as SBP and/ or DBP > 95th percentile for age: see details in Appendix VII). If a BP reading prior to registration is > than the 95th percentile for age and height it must be rechecked and documented to be ≤the 95th percentile for age and height prior to the patient registration. Ensure patient is at rest for at least one hour prior to any BP measurement.
  - History of stroke, myocardial infarction, or unstable angina within the previous 6 months prior to registration.
  - Patients with clinically significant peripheral vascular disease.
  - Evidence of bleeding diathesis or coagulopathy.
  - PT INR value of >1.5.
  - Patients on NSAIDs, clopidrogel, or dypiridamole, or aspirin therapy > 81 mg/day.
  - Major surgical procedures ≤4 weeks prior to study enrollment.
  - Intermediate surgical procedures ≤2 weeks prior to study enrollment.

- Minor surgical procedures ≤7 days prior to study enrollment.
- Urine protein (albumin)/creatinine ratio of > 1.0.
- History of abdominal fistula or GI perforation within 6 months prior to registration.
- Serious non-healing wound, ulcer, or bone fracture.

Rationale: The prognosis of patients with recurrent high-grade glioma, diffuse brain stem glioma, medulloblastoma, ependymoma, and low grade glioma is poor and treatment failure is frequently mediated by drug resistance. Novel strategies are required for improving outcome for these patients. Tumor angiogenesis plays a major role in tumor growth, invasion, and metastasis. Vascular endothelial growth factor is a major mediator of angiogenesis and is widely expressed in brain tumors especially malignant glioma. Bevacizumab is a humanized monoclonal antibody that is specific inhibitor of VEGF and has been shown in pre-clinical and clinical studies to be safe and useful in controlling tumor growth by itself or in combination with standard chemotherapy. The combination of bevacizumab plus chemotherapy is expected to have a synergistic effect in tumor control. Randomized phase III studies have demonstrated that such a combination improves tumor response rates and survival. Bevacizumab has been shown to be safe when used in children with recurrent solid tumors. A phase II study of bevacizumab plus irinotecan was conducted in adults with recurrent malignant glioma and demonstrated a 63% objective response rate and prolongation of progression-free survival. Hence, a phase II study of bevacizumab plus irinotecan is needed in children with recurrent malignant glioma, diffuse brain stem glioma, medulloblastoma, ependymoma, and low grade glioma to assess objective response rates, survival, and toxicity of this combination.

Schema:



Bevacizumab 10mg/kg IV every 2 weeks.(Note: Day 15 bevacizumab can be given on day 15, +/-24hr)

Irinotecan 125mg/m^2 i.v every 2 weeks and increase up to a maximum of 150 mg/m^2. The first dose of irinotecan will be given after the MR perfusion diffusion scan is obtained following the second dose of bevacizumab **(within 24- 48 hours of bevacizumab dose)**. Irinotecan will always be given following bevacizumab.. Patients on EIACDs will receive irinotecan 250mg/m^2 i.v every 2 weeks and increased by 25mg/m2 every 2 weeks up to 350mg/m^2 in the absence of toxicity.