CERN 08-01: A Phase II Study of Bevacizumab and Lapatinib in Children With Recurrent or Refractory Ependymoma

Type	Status	Age Range (yrs.)	Sponsor
Interventional	Active	Up to 21 years	CCHMC

Eligibility

Ages eligible for study: Up to 21 years

Criteria

Inclusion Criteria:

- Age: Patient must be < or = 21 years of age.
- Tumor: Patients must have recurrent or refractory intracranial ependymoma, ependymoblastoma or subependymoma (including myxopapillary and clear cell and anaplastic ependymoma) with a histological diagnosis from either the initial presentation or the time of recurrence. Scrolls or paraffin embedded block from available prior brain tumor specimens must be submitted within 60 days of enrollment for central analysis.
- Patients must have measurable disease, defined as at least one measurable lesion that can be accurately measured in 2 planes. Diffuse leptomeningeal involvement will not be considered measurable disease.
- Patients may have a maximum of two prior salvage chemotherapy regimens after radiotherapy.
- Neurological Deficits: Patients with neurological deficits should have deficits that are stable or improving for a minimum of 1 week prior to registration.
- Performance Score: Karnofsky Performance Scale (KPS for > 16 years of age) or Lansky Performance Score (LPS for < or = 16 years of age) > or = 50 assessed within 2 weeks prior to registration.
- Prior/Concurrent Therapy: Chemo: Evidence of recovery from prior chemotherapy. No myelosuppressive anticancer chemotherapy or biological therapy within 3 weeks (6 weeks if a nitrosourea or mitomycin C agent) prior to registration.
- Prior/Concurrent Therapy: XRT: Patients must have had prior radiation therapy for treatment of their ependymoma. XRT must be > or = 3 months prior to registration for craniospinal irradiation (> or = 18 Gy); > or = 4 weeks for local radiation to primary tumor; and > or = 2 weeks prior to registration for focal irradiation to symptomatic metastatic sites.
- Prior/Concurrent Therapy: Bone Marrow Transplant: > or = 3 months prior to registration for autologous bone marrow/stem cell transplant.
- Prior/Concurrent Therapy: Anti-convulsants: Patients with seizure disorder may be enrolled if well controlled. Patients receiving enzyme-inducing anticonvulsants are not eligible for this study. Patients must be off EIACD for at least 2 weeks prior to registration.
- Prior/Concurrent Therapy: Corticosteroids: Patients who are receiving corticosteroids must be on a stable or decreasing dose for at least 1 week prior to registration.
- Prior/Concurrent Therapy: Growth Factors: Off all colony forming growth factor(s) > or = 2 weeks prior to registration (G-CSF, GM-CSF, Erythropoietin).

- Patients must not have received: CYP3A4 inhibitors within seven (7) days prior to registration on protocol and for the duration of the study. However, amiodarone, another CYP3A4 inhibitor, should have been discontinued 6 months prior to registration and for the duration of the study.
- Patient must not have received: CYP3A4 inducers within fourteen (14) days prior to registration and for the duration of the study.
- Patient must not have received: Cimetidine within 48 hours prior and for the duration of the study.
- Must have the following tests as defined by the following within 7 days prior to registration and again within 7 days prior to the start of therapy: Bone marrow: Absolute neutrophil count of > / = 1000/microliter, Platelets > / = 100,000/microliter (transfusion independent), Hemoglobin > or = 8.0 g/dL (transfusion independent); Renal: Serum creatinine < / = 1.5 times upper limit of institutional normal for age or GFR > / = 70 ml/min/1.73m2; Hepatic: Bilirubin < or = 1.5 times upper limit of normal for age: SGPT (ALT) < 2.5x institutional upper limit of normal for age and albumin > / = 2 g/dL.
- No overt renal, hepatic, cardiac or pulmonary disease.
- Adequate cardiac function, assessed within 2 weeks prior to registration, defined as: shortening fraction of > or = 27% by echocardiogram, or ejection fracture (LVEF) > or = 50% by gated radionuclide study.
- Adequate pulmonary function, assessed within 2 weeks prior to registration, defined as: no evidence of dyspnea at rest, no exercise intolerance, and a pulse oximetry > 94% if there is clinical indication for determination.
- Signed informed consent according to institutional guidelines must be obtained.
- Women of child-bearing potential and men must agree to use adequate contraception (hormonal or barrier method of birth control; abstinence) prior to study entry and for the duration of study participation. Should a woman become pregnant or suspect she is pregnant while participating in this study, she should inform her treating physician immediately and will be removed from the study.
- Patient must begin therapy within 7 calendar days of registration.

Exclusion Criteria:

- Patients with primary spinal cord tumors.
- Patients with any significant medical illnesses that, in the investigator's opinion, cannot be adequately controlled with appropriate therapy or would compromise the patient's ability to tolerate this therapy.
- Patients with any disease that would obscure toxicity or dangerously alter drug metabolism.
- Patients receiving any other anticancer or experimental drug therapy.
- Patients with uncontrolled infection.
- Patients on enzyme inducing anticonvulsants.
- Patients with > / = Grade 2 uncontrolled hypertension.
- History of a stroke, myocardial infarction, or unstable angina in the previous 6 months.
- Evidence of a bleeding diathesis, coagulopathy or PT INR>1.5 X ULN.
- Patients on anticoagulant drugs: Patients must not have previously been treated with anticoagulants including systemic thrombolytic agents, heparin, low molecular weight heparins, or warfarin except as required to maintain patency of preexisting permanent vascular catheters.
- Pre-existing coagulopathy or thrombosis: 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.
- Major surgical procedure(s) (e.g., tumor resection or biopsy) within 4 weeks prior to study enrollment.
- Intermediate surgical procedures (e.g. vascular access device, G-tube placement) within 14 days prior to study enrollment.

- Minor surgical procedures (e.g. incision and drainage of abscess, skin wound suture, bone marrow aspirate) within 7 days prior to study enrollment.
- History of an abdominal fistula, GI perforation, or intra-abdominal abscess within previous 6 months.
- A serious, non-healing wound, ulcer, or bone fracture.
- Evidence of a new intracranial or intratumoral hemorrhage that is larger than a punctuate size on baseline MRI obtained within 14 days prior to study registration.
- If there is proteinuria present on dipstick, patients must have a 24 hour urine collection, Patients are excluded if they have >500 mg protein on 24 hour urine collection.
- Pregnancy: Females of childbearing potential must have negative serum or urine pregnancy test within 7 days prior to study entry. The effects of lapatinib on the developing human fetus are unknown. However, bevacizumab is known to be teratogenic and detrimental to fetal development in animal models. In addition, bevacizumab may alter corpus luteum development and endometrial proliferation, thereby having a negative effect on fertility.
- Breastfeeding: Because there is an unknown but potential risk for adverse events in nursing infants secondary to treatment of the mother with lapatinib or bevacizumab, breastfeeding should be discontinued if the mother is treated on this study.

For more information contact:

Cincinnati Children's Hospital Medical Center

Cancer and Blood Diseases Institute

3333 Burnet Ave., Cincinnati, OH 45229-3039

Phone: 513-636-2799

cancer@cchmc.org