ACNS0822: A Randomized Phase II/III Study of Vorinostat (IND# 71976) and Local Irradiation OR Temozolomide and Local Irradiation OR Bevacizumab (IND# 7921) and Local Irradiation Followed by Maintenance Bevacizumab and Temozolomide in Children With Newly Diagnosed High-Grade Gliomas

Type	Status	Age Range	Sponsors	Protocol ID
Interventional	Open	3 to 21 years	CCHMC	ACNS0822

Rationale

Vorinostat may stop the growth of tumor cells by blocking some of the enzymes needed for cell growth. Drugs used in chemotherapy, such as temozolomide, work in different ways to stop the growth of tumor cells, either by killing the cells or by stopping them from dividing. Monoclonal antibodies, such as bevacizumab, can block tumor growth in different ways. Some block the ability of tumor cells to grow and spread. Others find tumor cells and help kill them or carry tumor-killing substances to them. Radiation therapy uses high-energy x-rays to kill tumor cells. It is not yet known whether giving vorinostat is more effective then temozolomide or bevacizumab when given together with radiation therapy in treating glioma.

Purpose

This randomized phase II/III trial is studying vorinostat, temozolomide, or bevacizumab to see how well they work compared with each other when given together with radiation therapy followed by bevacizumab and temozolomide in treating young patients with newly diagnosed high-grade glioma.

Objectives

Primary

- Dose-limiting toxicity of vorinostat when given with radiotherapy (feasibility study) [Designated as safety issue: Yes]
- Toxicity of vorinostat, bevacizumab, or temozolomide when given in combination with radiotherapy [Designated as safety issue: Yes]

Secondary

- Event-free survival of patients in each treatment arm [Designated as safety issue: No]
- Overall survival of patients in each treatment arm [Designated as safety issue: No]
- Progression-free survival of patients in each treatment arm [Designated as safety issue: No]

Eligibility

Ages Available for Study: 3 - 21 years of age

Disease Characteristics

- Newly diagnosed high-grade glioma
  - Anaplastic astrocytoma
  - Glioblastoma multiforme
  - Gliosarcoma
  - Primary spinal cord malignant glioma allowed
  - No oligodendroglioma or oligoastrocytoma
- Patient must have histological verification of diagnosis
  - No M+ disease (defined as evidence of neuraxis dissemination)
  - No positive CSF cytology

Patient Characteristics

- ECOG performance status (PS) 0-2
  - Karnofsky PS 50-100% (patients > 16 years of age)
  - Lansky PS 50-100% (patients ≤ 16 years of age)
- ANC ≥ 1,000/µL
- Platelet count ≥ 100,000/µL
- Hemoglobin ≥ 8.0 mg/dL (transfusion independent)
- Creatinine clearance or radioisotope GFR ≥ 70 mL/min/1.73m^2 OR serum creatinine based on age and/or gender as follows:
  - 0.4 mg/dL (1 month to < 6 months of age)
  - 0.5 mg/dL (6 months to < 1 year of age)
  - 0.6 mg/dL (1 to < 2 years of age)
  - 0.8 mg/dL (2 to < 6 years of age)
  - 1.0 mg/dL (6 to < 10 years of age)
  - 1.2 mg/dL (10 to < 13 years of age)
  - 1.5 mg/dL (male) or 1.4 mg/dL (female) (13 to < 16 years of age)
  - 1.7 mg/dL (male) or 1.4 mg/dL (female) (≥ 16 years of age)
- Proteinuria < 2+ OR urine:protein ratio (UPC) ≤ 0.5
  - If UPC > 0.5, a 24-hour urine protein should be obtained and level should be < 1,000 mg of protein
- Total bilirubin ≤ 1.5 times upper limit of normal (ULN)
- ALT < 2.5 times ULN
- Serum albumin ≥ 2 g/dL
- PT INR ≤ 1.5 times ULN
- Not pregnant or nursing

- Negative pregnancy test
- Fertile patients must use effective contraception during all study therapy and for ≥ 6 months after completion of bevacizumab

- Hypertension well controlled (≤ 95th percentile for age and height if patient is ≤ 17 years) by stable doses of medication allowed

  - For patients > 17 years, systolic blood pressure (BP) ≤ 150 mm Hg or diastolic BP ≤ 100 mm Hg)
- Seizure disorder allowed provided patient is well-controlled and on nonenzyme-inducing anticonvulsants
- No history of myocardial infarction, severe or unstable angina, clinically significant peripheral vascular disease, ≥ grade 2 heart failure, or serious and inadequately controlled cardiac arrhythmia
- No known bleeding diathesis or coagulopathy
- No prior arterial thromboembolic events, including transient ischemic attacks or cerebrovascular accidents
- No prior diagnosis of a deep venous thrombosis, including pulmonary embolism, and no known thrombophilic condition (e.g., protein S, protein C, antithrombin III deficiency, Factor V Leiden or Factor II G202`0A mutation, homocysteinemia, or antiphospholipid antibody syndrome)
- No history of an abdominal fistula, gastrointestinal perforation, or intra-abdominal abscess within the past 6 months
- No serious or non-healing wound, ulcer, or bone fracture
- No evidence of significant postoperative intracranial hemorrhage, defined as > 1 cm of blood on postoperative MRI scan (potentially in addition to the postoperative scan) obtained within the past 14 days
- No history of allergic reaction to Chinese hamster ovary cell products or other recombinant human antibodies

Prior Concurrent Therapy

- No more than 31 days since definitive surgery
- Must not have received any prior chemotherapy, radiotherapy, immunotherapy, or bone marrow transplant
- More than 7 days since major surgical procedure and recovered
  - For patients scheduled to receive bevacizumab:
    - More than 28 days since major procedure
    - More than 14 days since intermediate procedure
    - More than 7 days since minor procedure (lumbar picture or placement of PICC lines are not considered minor procedures
- No other current anti-cancer agents
- No concurrent nonsteroidal anti-inflammatory medications known to inhibit platelet function or known to selectively inhibit cyclooxygenase activity
- No concurrent enzyme inducing anticonvulsants
- No concurrent HDAC inhibitors (e.g., valproic acid)
- No concurrent anticoagulants including systemic thrombolytic agents, heparin, low molecular weight heparins, or warfarin except as required to maintain patency of pre-existing permanent vascular catheters or for prevention of thrombosis in the post-operative period

For more information contact:

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