**ADVL1115**: A Phase I Study of AMG 386, an Angiopoietin Neutralizing Peptibody, in Children with Relapsed or Refractory Solid Tumors, including CNS Tumors.

**PURPOSE**: This phase I trial studies the side effects and the best dose of trebananib in treating patients with relapsed or refractory solid tumors, including central nervous system tumors.

**Study Type**: Interventional  
**Masking**: Open Label  
**Primary Purpose**: Treatment

**OBJECTIVES**:  
**Primary**  
- To estimate the maximum-tolerated dose (MTD) and/or recommended Phase 2 dose (RP2D) of trebananib (AMG 386) administered as a weekly intravenous infusion to children with recurrent or refractory solid tumors.  
- To determine the tolerability of the solid tumor MTD and/or RP2D of AMG 386 in children with central nervous system (CNS) tumors.  
- To define and describe the toxicities of AMG 386 administered on this schedule.  
- To characterize the pharmacokinetics and immunogenicity of AMG 386 in children with refractory cancer.  
- To measure changes in vascular permeability relative to baseline, evaluated by magnetic resonance imaging (MRI) perfusion, following AMG 386 administration in pediatric patients with CNS tumors.

**Secondary**  
- To preliminarily define the antitumor activity of AMG 386 within the confines of a Phase 1 study.  
- To measure biologic markers of angiogenesis with potential for correlation with disease response.

**OUTLINE**: This is a multicenter, dose-escalation study (part 1) followed by a safety and imaging study (part 2).  
- Patients receive trebananib intravenously (IV) over 30-60 minutes on days 1, 8, 15, and 22. Treatment repeats every 28 days for up to 12 courses in the absence of disease progression or unacceptable toxicity.  
- Patients undergo blood sample collection at baseline and periodically during study for pharmacokinetic and immunogenicity studies. Blood may also be collected for correlative studies.
Some patients also undergo dynamic contrast-enhanced (DCE)-MRI at baseline and periodically during study.

After completion of study treatment, patients are followed up every 3 to 6 months.

AGES ELIGIBLE FOR STUDY: 1 Year to 21 Years

DISEASE CHARACTERISTICS:

- Part 1: Patients must have had histologic verification of non-CNS solid tumor malignancy at original diagnosis or relapse
- Part 2: Patients must have had histologic verification of CNS malignancy at original diagnosis or relapse except in patients with intrinsic brain stem tumors, optic pathway gliomas, or patients with pineal tumors and elevations of CSF or serum tumor markers including alpha-fetoprotein or beta-human chorionic gonadotropin (HCG)
  - Neurologic deficits in patients with CNS tumors must have been relatively stable for at least 7 days prior to study enrollment
- Patients must have either measurable or evaluable disease
- Patient's current disease state must be one for which there is no known curative therapy or therapy proven to prolong survival with an acceptable quality of life
- Patients with known bone marrow metastatic disease will be eligible for study provided they meet the required blood counts (may receive transfusions provided they are not known to be refractory to red cell or platelet transfusions)
- Patients with CNS tumors and evidence of new CNS hemorrhage of more than punctate size and/or more than three foci of punctate hemorrhage on baseline magnetic resonance imaging (MRI) obtained within 14 days prior to study enrollment are not eligible
  - Echocardiogram (ECHO) gradient MRI sequences per institutional guidelines are required for patients with CNS tumors

PATIENT CHARACTERISTICS:

- Karnofsky ≥50% for patients > 16 years of age and Lansky ≥50% for patients ≤16 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
- For patients with solid tumors without known bone marrow involvement:
  - Peripheral absolute neutrophil count (ANC) ≥1,000/mm³
- Platelet count ≥ 100,000/mm³ (transfusion independent, defined as not receiving platelet transfusions for at least 7 days prior to enrollment)

- Creatinine clearance or radioisotope GFR ≥ 70 mL/min or a serum creatinine based on age/gender as follows:
  - 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)

- Urine protein: ≤ 30 mg/dL in urinalysis or ≤ 1+ on dipstick, unless quantitative protein is < 1,000 mg in a 24-hour urine sample

- Bilirubin (sum of conjugated + unconjugated) ≤ 1.5 times upper limit of normal (ULN) for age

- Serum glutamic pyruvate transaminase (SGPT) (alanine aminotransferase [ALT]) ≤ 110 U/L; for the purpose of this study, the ULN for SGPT is 45 U/L

- Serum albumin ≥ 2 g/dL

- Shortening fraction of ≥ 27% by echocardiogram OR ejection fraction of ≥ 50% by gated radionuclide study

- No known cardiac disease

- No history of myocardial infarction, severe or unstable angina, peripheral vascular disease, or familial QTc prolongation

- Patients with seizure disorder may be enrolled if on anticonvulsants and well controlled

- Nervous system disorders (CTCAE v. 4) resulting from prior therapy must be ≤ Grade 2

- No evidence of active bleeding

- Prothrombin time (PT) and partial thromboplastin time (PTT) ≤ 1.2 times ULN and an INR ≤ 1.2

- A blood pressure (BP) ≤ the 95th percentile for age, height, and gender, and not receiving medication for treatment of hypertension

- Pregnant or breast-feeding women will not be entered on this study due to risks of fetal and teratogenic adverse events as seen in animal/human studies; pregnancy tests must be obtained in girls who are post-menarchal; males or females of reproductive potential may not participate unless they have agreed to use an effective contraceptive method for the duration of study participation, and for 6 months after completion of AMG 386 administration
Patients who have an uncontrolled infection are not eligible

Patients with evidence of active bleeding: intratumoral hemorrhage by current imaging, or bleeding diathesis are not eligible

Patients with a history (within 180 days prior to study enrollment) of arterial thromboembolic events including transient ischemic attack (TIA) or cerebrovascular accident (CVA) are not eligible

Patients with a history of hemoptysis within 42 days prior to study enrollment are not eligible

Patients who have a history of serious or non-healing wound, abdominal fistula, gastrointestinal ulcer or perforation, bone fracture, or intra-abdominal abscess within 28 days of study enrollment are not eligible

Patients with known cardiac or peripheral vascular disease are not eligible

Patients who, in the opinion of the investigator, may not be able to comply with the safety monitoring requirements of the study are not eligible

PRIOR CONCURRENT THERAPY:

Patients must have fully recovered from the acute toxic effects of all prior anti-cancer chemotherapy

At least 21 days after the last dose of myelosuppressive chemotherapy (42 days if prior nitrosourea)

At least 14 days after the last dose of a long-acting growth factor (e.g., Neulasta) or 7 days for short-acting growth factor; for agents that have known adverse events occurring beyond 7 days after administration, this period must be extended beyond the time during which adverse events are known to occur; the duration of this interval must be discussed with the study chair

At least 7 days after the last dose of a biologic agent; for agents that have known adverse events occurring beyond 7 days after administration, this period must be extended beyond the time during which adverse events are known to occur; the duration of this interval must be discussed with the study chair

At least 42 days after the completion of any type of immunotherapy, e.g., tumor vaccines

At least 3 half-lives of the antibody after the last dose of a monoclonal antibody

At least 14 days after local palliative radiotherapy (XRT) (small port)

At least 150 days must have elapsed if prior total-body irradiation (TBI), craniospinal XRT, or radiation to 50% of pelvis

At least 42 days must have elapsed if other substantial bone marrow radiation delivered
- No evidence of active graft-vs-host disease and at least 56 days must have elapsed after transplant or stem cell infusion
- Patients receiving corticosteroids who have not been on a stable or decreasing dose of corticosteroid for at least 7 days prior to enrollment are not eligible
- Patients who are currently receiving another investigational drug are not eligible
- Patients who are currently receiving other anticancer agents are not eligible
- Patients who are receiving cyclosporine, tacrolimus, or other agents to prevent graft-versus-host disease post bone marrow transplant are not eligible for this trial
- Patients who are currently receiving therapeutic anticoagulation with heparin, low-molecular weight heparin, or coumadin are not eligible for this trial
- Patients who are currently receiving aspirin, ibuprofen, or other non-steroidal anti-inflammatory drugs or anti-platelet agents are not eligible
- Patients who are receiving anti-hypertensive medications for control of blood pressure at the time of enrollment are not eligible for this trial
- Patients who have received a prior solid organ transplantation are not eligible
- Patients who have had or are planning to have the following invasive procedures are not eligible:
  - Major surgical procedure, laparoscopic procedure, open biopsy, or significant traumatic injury within 28 days prior to enrollment
  - Central line placement or subcutaneous port placement is not considered major surgery but must be placed at least 3 days prior to enrollment for external lines (e.g., Hickman or Broviac) and at least 7 days prior to enrollment for subcutaneous port
  - Core biopsy within 7 days prior to enrollment
  - Fine-needle aspirate within 7 days prior to enrollment
- Concurrent cancer therapy, including chemotherapy, radiation therapy, immunotherapy, or biologic therapy may NOT be administered to patients receiving study drug

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