ADVL1111: A Phase 1 Study of the c-Met Inhibitor, Tivantinib (ARQ 197, IND# 112603) in Children With Relapsed or Refractory Solid Tumors

PURPOSE: This phase I trial studies the side effects and best dose of tivantinib in treating younger patients with relapsed or refractory solid tumors. Tivantinib may stop the growth of tumor cells by blocking some of the enzymes needed for cell growth

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

OBJECTIVES

PRIMARY OBJECTIVES

- To estimate the maximum tolerated dose (MTD) and/or recommended phase 2 dose of tivantinib administered orally twice daily to children with refractory solid tumors.
- To define and describe the toxicities of tivantinib administered on this schedule.
- To characterize the pharmacokinetics of tivantinib (capsule as well as powder formulation) in children with refractory cancer.

SECONDARY OBJECTIVES:

- To preliminarily define the antitumor activity of tivantinib within the confines of a phase 1 study.
- To preliminarily investigate whether cytochrome P450 (CYP450) polymorphisms impact pharmacokinetics or toxicity of tivantinib.
- To preliminarily investigate whether tumor c-Met and/or hepatocyte growth factor (HGF) expression or downstream c-Met signaling correlate with clinical response to tivantinib.

OUTLINE: This is a dose-escalation study.

Patients receive tivantinib orally (PO) twice daily (BID) on days 1-28. Treatment repeats every 28 days for up to 12 courses in the absence of disease progression or unacceptable toxicity.

After completion of study treatment, patients are followed up for 30 days.

AGES ELIGIBLE FOR STUDY: 13 Months to 21 Years

CRITERIA

INCLUSION CRITERIA:

- PART A: Patients on dose levels -1 or 1 must have a body surface area (BSA) >= 0.65 m^2 at the time of study enrollment; patients on dose levels 2 or 3 must have a BSA >= 0.45 m^2 at the time of study enrollment
- PART B: There is no minimum body surface area requirement for patients in part B
- Patients with relapsed or refractory solid tumors including central nervous system (CNS) tumors are eligible; patients must have had histologic verification of 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 cerebrospinal fluid (CSF) or serum tumor markers including alpha-fetoprotein or beta-human chorionic gonadotropin (HCG)
- 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
- Karnofsky >= 50% for patients > 16 years of age and Lansky >= 50 for patients =< 16 years of age; note: neurologic deficits in patients with CNS tumors must have been stable or improving for at least 7 days prior to study enrollment; 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
- Patients must have fully recovered from the acute toxic effects of all prior anti-cancer chemotherapy:
    - Myelosuppressive chemotherapy: At least 21 days after the last dose of myelosuppressive chemotherapy (42 days if prior nitrosourea)
    - Hematopoietic growth factors: 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
    - Biologic (anti-neoplastic agent): 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
    - Immunotherapy: At least 42 days after the completion of any type of immunotherapy, e.g. tumor vaccines

  - Monoclonal antibodies: At least 3 half-lives of the antibody after the last dose of a monoclonal antibody
  - Radiation therapy (XRT): At least 14 days after local palliative XRT (small port); at least 150 days must have elapsed if prior total-body irradiation (TBI), craniospinal XRT or if >= 50% radiation of pelvis; at least 42 days must have elapsed if other substantial bone marrow (BM) radiation
  - Stem cell infusion without TBI: No evidence of active graft vs. host disease and at least 84 days must have elapsed after transplant or stem cell infusion
  - Patients may not have received prior therapy with tivantinib
- Peripheral absolute neutrophil count (ANC) >= 1000/mm^3
- Platelet count >= 100,000/mm^3 (transfusion independent, defined as not receiving platelet transfusions for at least 7 days prior to enrollment)
- Patients with known bone marrow involvement will be eligible for study provided they meet the blood counts above (may receive transfusions provided they are not known to be refractory to red cell or platelet transfusions); these patients will not be evaluable for hematologic toxicity; at least 5 of every cohort of 6 patients with a solid tumor must be evaluable for hematologic toxicity for the dose escalation part of the study; if dose-limiting hematologic toxicity is observed, all subsequent patients enrolled must be evaluable for hematologic toxicity
- Creatinine clearance or radioisotope glomerular filtration rate (GFR) >= 70ml/min/1.73 m^2 or a serum creatinine based on age/gender as follows:
  - 1 to < 2 years: 0.6 mg/dL
  - 2 to < 6 years: 0.8 mg/dL
  - 6 to < 10 years: 1.0 mg/dL
  - 10 to < 13 years: 1.2 mg/dL
  - 13 to < 16 years: 1.5 mg/dL (males); 1.4 mg/dL (females)
  - >= 16 years: 1.7 mg/dL (males); 1.4 mg/dL (females)
- Bilirubin (sum of conjugated + unconjugated) =< 1.5 x 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
- All patients and/or their parents or legally authorized representatives must sign a written informed consent; assent, when appropriate, will be obtained according to institutional guidelines

EXCLUSION CRITERIA:

- Pregnant or breast-feeding women will not be entered on this study; 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
- 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 anti-cancer 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 must not be receiving any of the following for at least 24 hours prior to enrollment: omeprazole, esoprazole, lansoprazole, pantoprazole, rifampin, omeprazole, fluvoxamine, or moclobemide
- Patients must not be receiving any of the following for at least 24 hours prior to enrollment: atazanavir, clarithromycin, indinavir, itraconazole, ketoconazole, nefazodone, nelfinavir, ritonavir, saquinavir, telithromycin, troleandomycin (TAO), voriconazole, rifampicin, rifabutin, rifapentine, phenytoin, carbamazepine, phenobarbital, or St. John's Wort
- Nasogastric or G tube administration is not allowed; patients in part A must be able to swallow capsules
- Patients who have an uncontrolled infection are not eligible
- Patients who have received a prior solid organ transplantation 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
- Patients with >= grade 2 bradycardia or with a known history >= grade 2 cardiac arrhythmia are not eligible

For more information contact:

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