ADVL1121: A Phase II trial of the Raf Kinase and Receptor Tyrosine Kinase Inhibitor Sorafenib(IND# 69896) in Children and Young Adults with Relapsed/Refractory Rhabdomyosarcomas, Wilms Tumors, Hepatocellular Carcinoma, and Papillary Thyroid Carcinoma

Type of Trial	Study Design	Age Range (yrs.)	Primary Purpose	Protocol ID
Interventional	Open Label	3 to 30 years	Treatment	ADVL1121

Purpose

This Phase II trial will study how well sorafenib tosylate works in treating younger patients with relapsed or refractory Rhabdomyosarcoma, Wilms Tumors, Liver cancer or Thyroid cancer

Objectives

Primary

- To determine the objective response rate to sorafenib tosylate (sorafenib) in children with relapsed or refractory Rhabdomyosarcoma, Wilms tumor, Hepatocellular Carcinoma (HCC), or Papillary Thyroid Carcinoma (PTC).

Secondary

- To further define and describe the toxicities of sorafenib administered on an oral, twice-daily continuous schedule
- To further characterize the pharmacokinetics of sorafenib in children with refractory cancer.
- To estimate the progression-free survival on sorafenib for rhabdomyosarcoma, Wilms tumor, and hepatocellular carcinoma and compare to a group of patients enrolled on selected closed Phase II studies of Children Oncology Group (COG).
- To assess the biologic activity of sorafenib on vascular endothelial growth factor (VEGF) and soluble vascular endothelial growth factor receptor-2 (VEGFR-2) in peripheral blood samples.
- To evaluate the presence of BRAF mutations and RET/PTC rearrangements in patients with PTC.

Outline

This is a multicenter study. Patients are stratified according to diagnosis (rhabdomyosarcoma vs Wilms tumor vs hepatocellular carcinoma vs papillary thyroid carcinoma).

Patients receive sorafenib tosylate orally (PO) twice daily (BID) on days 1-28. Treatment repeats every 28 days for up to 24 courses in the absence of disease progression or unacceptable toxicity.

Patients undergo blood sample collection at baseline and periodically during study for pharmacokinetic studies, and VEGF and VEGFR-2 analysis by ELISA. Previously collected formalin-fixed paraffin-embedded tissue samples, from patients with papillary thyroid carcinoma, are also analyzed for BRAF mutation and RET/PTC rearrangements by PCR.

After completion of study treatment, patients are followed up for up to 5 years.

Eligibility

Ages eligible for study: 3 to 30 years

Disease Characteristics

- Patients must have had histologic verification of one of the malignancies listed below at original diagnosis or at relapse:
    - Rhabdomyosarcoma (RMS)
    - Wilms tumor
    - Hepatocellular carcinoma (HCC)
    - Papillary thyroid carcinoma (PTC)
- Patients must have relapsed or refractory disease (RMS, Wilms tumor, HCC, PTC)
    - Patients must have radiographically measurable disease; measurable disease is defined as the presence of at least one lesion on magnetic resonance imaging (MRI) or computed tomography (CT) scan that can be accurately measured with the longest diameter a minimum of 10 mm in at least one dimension (CT scan slice thickness no greater than 5 mm)
        - The following do not qualify as measurable disease:
            - Malignant fluid collections (e.g., ascites, pleural effusions)
            - Bone marrow infiltration
            - Lesions only detected by nuclear medicine studies (e.g., bone, gallium, or positron emission tomography [PET] scans)
            - Elevated tumor markers in plasma or cerebrospinal fluid (CSF)
            - Previously radiated lesions that have not demonstrated clear progression post radiation
            - Leptomeningeal lesions that do not meet the requirements noted above
- Patients with HCC must be relapsed or refractory to conventional chemotherapy
- Patients with PTC must be refractory to radioactive iodine (RAI)
- 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 metastasis to the brain will be excluded from trial participation unless treated surgically or with radiotherapy and stable with no recurrent lesions for at least 3 months

Patient Characteristics

- Rhabdomyosarcoma and Wilms strata: patients must be ≥ 24 months and ≤ 30 years of age at study enrollment
- Hepatocellular carcinoma (HCC): patients must be ≥ 24 months and < 18 years of age at study enrollment
- Papillary thyroid carcinoma (PTC): patients must be ≥ 24 months and ≤ 21 years of age at study enrollment
- Patients must have a Lansky or Karnofsky performance status score of ≥ 50%, corresponding to ECOG categories 0, 1, or 2
    - Use Karnofsky for patients > 16 years of age and Lansky 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
- Peripheral absolute neutrophil count (ANC) ≥ 1,000/μL
- Platelet count ≥ 75,000/μL (transfusion independent, defined as not receiving platelet transfusions within a 7-day period prior to enrollment)
- Hemoglobin 8.0 g/dL (may receive red blood cell [RBC] transfusions)
- Creatinine clearance or radioisotope glomerular filtration rate (GFR) 70 ml/min/1.73m2 OR a serum creatinine based on age/gender as follows:
    - 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)
- Total bilirubin ≤ 1.5 times upper limit of normal (ULN) for age
- SGPT (ALT) ≤ 135 U/L (for the purpose of this study, the ULN for SGPT is 45 U/L)
- PT, PTT, and INR < 1.5 times ULN
- Normal serum lipase and amylase (per institutional normal values)
- No evidence of dyspnea at rest, no exercise intolerance, and a pulse oximetry > 94% if there is clinical indication for determination
- A blood pressure (BP) ≤ the 95^th percentile for age, height, and gender; and not receiving medication for treatment of hypertension
- Patients who are pregnant or breast-feeding are not eligible
- Negative 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 beginning at the signing of the informed consent until at least 30 days after the last dose of the study drug
- Patients with clinical symptoms of hepatic encephalopathy or ascites are not eligible
- Patients who have an uncontrolled infection are not eligible
- Patients with evidence of bleeding diathesis are not eligible
- Patients with known Gilbert syndrome 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

- See Disease Characteristics
- Patients must have fully recovered from the acute toxic effects of all prior chemotherapy, immunotherapy, or radiotherapy prior to entering this study
- Patients with solid tumors must not have received myelosuppressive chemotherapy within 3 weeks of enrollment onto this study (6 weeks if prior nitrosourea)
- At least 7 days must have elapsed since the completion of therapy with a growth factor (at least 14 days must have elapsed after receiving pegfilgrastim)
- At least 7 days must have elapsed since completion of therapy with a biologic agent;
  - For agents that have known adverse events occurring beyond 7 days after administration, this period prior to enrollment must be extended beyond the time during which adverse events are known to occur
- At least 3 half-lives must have elapsed since prior therapy that included a monoclonal antibody
- At least 2 weeks must have elapsed since local palliative radiotherapy (XRT) (small port); ≥ 3 months must have elapsed if prior craniospinal XRT was received, if ≥ 50% of the pelvis was irradiated, or if TBI was received; ≥ 6 weeks must have elapsed if other substantial bone marrow irradiation was given
- No evidence of active graft-vs-host disease and ≥ 2 months must have elapsed since transplant (stem cell transplant or rescue without total-body irradiation)
- For patients with papillary thyroid carcinoma (PTC) only: ≥ 3 weeks from prior radioiodine (RAI) treatment
- Patients requiring corticosteroids that have not been on a stable or decreasing dose of corticosteroid for 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 either graft-versus-host disease post bone marrow transplant or organ rejection post transplant are not eligible for this trial
- Patients who take cytochrome P450 enzyme-inducing anti-epileptic drugs (phenytoin, carbamazepine, or phenobarbital), rifampin, grapefruit juice, or St. Johns wort will not be eligible for the trial
- Patients who have received prior treatment with sorafenib are not eligible
- Patients must not be on therapeutic anti-coagulation;
    - Prophylactic anticoagulation (i.e., low-dose warfarin) of venous or arterial devices is allowed provided that the requirements for prothrombin time (PT), partial thromboplastin time (PTT), and international normalized ratio (INR) are met
- No concurrent chemotherapy, radiation therapy, immunomodulating agents, or other investigational agents

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