ADVL0413: A Phase I/II Study of the Raf Kinase and Receptor Tyrosine Kinase Inhibitor Sorafenib (BAY 43-9006, NSC# 724772, IND# 69896) in Children With Refractory Solid Tumors or Refractory Leukemias

Type of Trial	Study Design	Primary Purpose	Age Range (yrs.)	Protocol ID
Interventional	Open Label	Treatment	2 to 21 years	ADVL0413

Rationale

Sorafenib may stop the growth of cancer cells by blocking some of the enzymes needed for cell growth and by blocking blood flow to the cancer.

Purpose

This phase I trial is studying the side effects and best dose of sorafenib in treating young patients with relapsed or refractory solid tumors or leukemia.

Objectives

Primary

- Maximum-tolerated dose and recommended phase II dose [Designated as safety issue: Yes]
- Toxicity effects [Designated as safety issue: Yes]
- Pharmacokinetics [Designated as safety issue: No]

Secondary

- Preliminary antitumor activity [Designated as safety issue: No]
- Pharmacodynamics [Designated as safety issue: No]
- Gene expression, proteomic profile, and ERK phosphorylation [Designated as safety issue: No]

Eligibility

Ages Eligible for Study: 2 to 21 years

Disease Characteristics

- Diagnosis of 1 of the following:
  - Histologically confirmed malignant solid tumor at original diagnosis or relapse
    - Measurable or evaluable disease by CT scan or MRI
  - Histologically confirmed leukemia, including 1 of the following:
  - Acute lymphoblastic leukemia (ALL)
    - Greater than 25% blasts in the bone marrow (M3 bone marrow)
  - Acute myeloid leukemia (AML)
    - Greater than 25% blasts in the bone marrow (M3 bone marrow)

- AML and FLT3-ITD mutation
  - Patients must have ≥ 5% blasts in the bone marrow
  - Active extramedullary disease (except leptomeningeal disease) allowed
- Juvenile myelomonocytic leukemia (JMML) meeting the following criteria:
- Peripheral blood monocytosis > 1,000/mm^3
- Blasts (including promonocytes) are < 20% of the WBCs in the blood and of the nucleated bone marrow cells
- No Philadelphia chromosome (Ph) or BCR/ABL fusion gene
- Has ≥ 2 of the following additional diagnostic criteria:
  - Hemoglobin F increased for age
  - Immature granulocytes in the peripheral blood
  - WBC > 10,000/mm^3
  - Clonal chromosomal abnormality (e.g., may be monosomy 7)
  - Sargramostim (GM-CSF) hypersensitivity of myeloid progenitors in vitro
- Chronic myelogenous leukemia (CML) in blast crisis
  - Greater than 25% blasts in the bone marrow (M3 bone marrow)
  - Patients with Ph-positive CML must be refractory to imatinib mesylate
- Relapsed or refractory disease
  - Patients with acute promyelocytic leukemia (APL) must be refractory to treatment with tretinoin and arsenic trioxide
- Standard curative therapies or therapies proven to prolong survival with an acceptable quality of life do not exist
- Active extramedullary disease, except active leptomeningeal leukemia, allowed
- No brain tumors or known brain metastases

Patient Characteristics

- Karnofsky performance status (PS) 50-100% (for patients > 10 years of age)
- Lansky PS 50-100% (for patients ≤ 10 years of age)
- Patients with solid tumors must have adequate bone marrow function, as defined by the following:
  - Absolute neutrophil count ≥ 1,000/mm^3
  - Platelet count ≥ 75,000/mm^3 (transfusion independent)
  - Hemoglobin ≥ 8.0 g/dL (red blood cell [RBC] transfusions allowed)
- Patients with leukemia may have abnormal blood counts but must meet the following criteria:
  - Platelet count ≥ 20,000/mm^3 (platelet transfusions allowed)
  - Hemoglobin ≥ 8.0 g/L (RBC transfusions allowed)
- Patients with acute myeloid leukemia and FLT3-ITD mutation
  - Platelet count ≥ 20,000/mm^3
- Lipase and amylase normal
- Creatinine clearance or radioisotope glomerular filtration rate ≥ 70 mL/min OR creatinine normal based on age as follows:
  - No greater than 0.8 mg/dL (for patients 5 years of age and under)
  - No greater than 1.0 mg/dL (for patients 6-10 years of age)
  - No greater than 1.2 mg/dL (for patients 11-15 years of age)
  - No greater than 1.5 mg/dL (for patients over 15 years of age)

- Patients with solid tumors must meet the following criteria:
  - Bilirubin normal for age
  - ALT normal for age (for the purpose of this study, the upper limit of normal [ULN] for ALT is 45 μ/L)
  - Serum albumin ≥ 2 g/dL
- Patients with leukemia must meet the following criteria:
  - Bilirubin (sum of conjugated + unconjugated) ≤ 1.5 times ULN for age
  - ALT ≤ 5.0 times ULN for age (≤ 225 μ/L) (for the purpose of this study, the ULN for ALT is 45 μ/L)
  - Serum albumin ≥ 2 g/dL
- Albumin ≥ 2 g/dL
- PT, PTT, and INR normal (for patients on prophylactic anticoagulation)
- No evidence of dyspnea at rest
- No exercise intolerance
- Pulse oximetry > 94% on room air, if there is clinical indication for determination
- Diastolic blood pressure ≤ the 95th percentile for age and gender (height included for AML and FLT3-ITD mutation patients)
- Not pregnant or nursing
- Negative pregnancy test
- Fertile patients must use effective contraception
- No uncontrolled infection
- Able to swallow tablets
- No evidence of bleeding diathesis
- No other medical condition or situation that would preclude study compliance
- No known Gilbert syndrome

Prior Concurrent Therapy

- See Disease Characteristics
- Fully recovered from prior chemotherapy, immunotherapy, or radiotherapy (for patients with solid tumors)
- Recovered from the non-hematologic toxic effects of all prior therapy (for patients with leukemia)
- Recovered from acute nonhematologic toxic effects of all prior anti-cancer chemotherapy (for patients with AML and FLT3-ITD mutation)
- At least 7 days since prior hematopoietic growth factors
- At least 7 days since prior biologic agents
- At least 2 weeks since prior local palliative radiotherapy (small port)
- At least 3 months since prior total-body irradiation, craniospinal radiotherapy, or radiation to ≥ 50% of the pelvis
- At least 6 weeks since other prior substantial bone marrow radiation (e.g., skull, spine, pelvis, ribs)
- At least 3 months since prior stem cell transplantation or rescue (for patients with solid tumors)
  - No evidence of active graft-vs-host disease
- At least 3 months since prior myeloablative therapy followed by bone marrow or stem cell transplantation (for patients with leukemia)
- At least 3 weeks since prior myelosuppressive chemotherapy (6 weeks for nitrosoureas) (for patients with solid tumors)
  - At least 24 hours since prior nitrosoureas (for patients with AML and FLT3-ITD mutation)
- At least 2 weeks since prior chemotherapy (for patients with leukemia)
- At least 3 weeks since prior monoclonal antibody therapy

- No prior sorafenib
- No other concurrent investigational drugs
- No other concurrent anticancer agents or therapies, including chemotherapy, radiotherapy, immunotherapy, or biologic therapy
  - Concurrent maintenance-like chemotherapy for patients with AML and FLT3-ITD mutation allowed
- No concurrent administration of any of the following:
  - Cytochrome P450 enzyme-inducing antiepileptic drugs (e.g., phenytoin, carbamazepine, or phenobarbital)
  - Rifampin
  - Grapefruit juice
  - Hypericum perforatum (St. John wort)
- No concurrent therapeutic anticoagulation
  - Concurrent prophylactic anticoagulation (e.g., low-dose warfarin) of venous or arterial access devices allowed provided the requirements for PT, INR, or PTT are met

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