

## **ADV0912: A Phase I/II study of PF-02341066, an Oral Small Molecule Inhibitor of Anaplastic Lymphoma Kinase (ALK) and c-MET, in children with Relapsed/Refractory Solid Tumors, Primary CNS Tumors, and Anaplastic Large Cell Lymphoma**

### **Rationale**

Crizotinib may stop the growth of cancer cells by blocking some of the enzymes needed for cell growth.

### **Purpose**

This phase I/II trial is studying the side effects and best dose of Crizotinib and to see how well it works in treating young patients with relapsed or refractory solid tumors or anaplastic large cell lymphoma.

### **Study Type**

Interventional

### **Study Design**

Masking: Open Label

Primary Purpose: Treatment

### **Objectives**

#### **Primary**

- To estimate the maximum tolerated dose and recommended phase II dose of Crizotinib administered orally twice daily to children with relapsed or refractory solid tumors or anaplastic large cell lymphoma (ALCL).
- To define and describe the toxicities of this drug when administered on this schedule.
- To characterize the pharmacokinetics of this drug in these patients.

#### **Secondary**

- To preliminarily define the antitumor activity of this drug within the confines of a phase I study.
- To obtain initial phase II data on the antitumor activity of this drug in children with relapsed or refractory neuroblastoma or ALCL.
- To preliminarily examine the relationship between response to treatment and anaplastic lymphoma kinase gene status (e.g., the presence of a mutation, duplication, amplification, and/or translocation) in children with relapsed or refractory neuroblastoma or ALCL.
- To preliminarily examine the relationship between minimal residual disease status and clinical response to treatment in children with ALCL.

### **Outline**

This is a multicenter, phase I dose-escalation study followed by a phase II study.

Patients receive oral Crizotinib twice daily on days 1-28. Treatment repeats every 28 days for up to 24 courses in the absence of disease progression or unacceptable toxicity.

Plasma and whole blood samples are collected for pharmacokinetic and pharmacogenomic analysis. Tumor tissue (from patients with neuroblastoma) and bone marrow and/or peripheral blood (from patients with anaplastic large cell lymphoma) samples are collected for further correlative laboratory studies.

After completion of study treatment, patients are followed up periodically.

## Ages Eligible for Study

1 year to 21

## Disease Characteristics

- Histologically confirmed\* malignancy at original diagnosis or relapse, including the following:
  - Solid tumors (phase I)
  - CNS tumors (phase I)
    - Neurologic deficits must have been relatively stable for  $\geq 1$  week before study enrollment
  - Anaplastic large cell lymphoma (ALCL) (phase I or II)
    - No primary cutaneous ALCL
  - Confirmed anaplastic lymphoma kinase (ALK) fusion proteins ALK mutations, or ALK amplification (defined as  $> 4$ -fold increase in the ALK signal number as compared to reference signal number on chromosome 2q arm (phase I)
  - Neuroblastoma (phase I or II) NOTE: \*Histologic confirmation is not required for patients with diffuse intrinsic brain stem tumors, optic pathway tumors, or pineal region tumors with elevations of serum or CSF tumor markers (e.g., alpha-fetoprotein or beta-HCG).
- Relapsed or refractory disease
- Measurable and/or evaluable disease
  - Patients with neuroblastoma must have measurable tumor on MRI, CT scan, or x-ray obtained within the past 2 weeks and/or evaluable tumor by MIBG scan or bone marrow involvement with tumor cells seen on routine morphology
  - Patients with ALCL enrolled in the phase II portion of the trial must have measurable disease
- No known curative therapy or therapy proven to prolong survival with an acceptable quality of life exists

## Patient Characteristics

- Karnofsky performance status (PS) 50-100% (for patients  $> 16$  years of age) or Lansky PS 50-100% (for patients  $\leq 16$  years of age)
  - Patients who are up in a wheelchair and are unable to walk due to paralysis will be considered ambulatory for the purpose of assessing PS
- ANC  $\geq 1,000/\text{mm}^3$  ( $\geq 750/\text{mm}^3$  in patients with metastatic bone marrow disease)
- Platelet count  $\geq 75,000/\text{mm}^3$  (transfusion independent, defined as no platelet transfusions within the past 7 days) in patients without bone marrow involvement OR  $\geq 25,000/\text{mm}^3$  (platelet transfusions allowed) in patients with metastatic bone marrow disease
- Hemoglobin  $\geq 8.0$  g/dL (RBC transfusions allowed)
- Creatinine clearance or radioisotope GFR  $\geq 70$  mL/min/1.73m<sup>2</sup> OR serum creatinine based on age/gender as follows:
  - $\leq 0.6$  mg/dL (for patients 1 year of age)
  - $\leq 0.8$  mg/dL (for patients 2 to 5 years of age)
  - $\leq 1.0$  mg/dL (for patients 6 to 9 years of age)

- $\leq 1.2$  mg/dL (for patients 10 to 12 years of age)
- $\leq 1.4$  mg/dL (for female patients  $\geq 13$  years of age)
- $\leq 1.5$  mg/dL (for male patients 13 to 15 years of age)
- $\leq 1.7$  mg/dL (for male patients  $\geq 16$  years of age)
- Bilirubin (sum of conjugated and unconjugated)  $\leq 1.5$  times upper limit of normal for age
- SGPT  $\leq 110$  U/L
- Serum albumin  $\geq 2$  g/dL
- Not pregnant or nursing
- Negative pregnancy test
- Fertile patients must use effective contraception
- Body surface area  $\geq 0.4$  m<sup>2</sup> (for patients enrolled at dose levels 0 and 1 only)
- Able to swallow capsules or a liquid suspension
- Able to comply with the safety monitoring requirements of the study, in the opinion of the investigator
- No uncontrolled infection
- No evidence of active graft vs host disease
- Not refractory to red cell or platelet transfusion (in patients with metastatic bone marrow disease)

### Prior Recurrent Therapy

- Recovered from prior chemotherapy, immunotherapy, or radiotherapy
- No prior Crizotinib
- At least 6 months since prior total-body radiotherapy (TBI), craniospinal radiotherapy, or radiotherapy to  $\geq 50\%$  of the pelvis
- At least 3 months since prior bone marrow or stem cell transplant (Without TBI) ( $\geq 6$  weeks for patients with neuroblastoma or patients with confirmed ALK fusion proteins, ALK mutations, or ALK amplification)
  - No evidence of active graft vs host disease
- At least 6 weeks since prior therapeutic doses of MIBG
- At least 6 weeks since other prior substantial bone marrow radiotherapy
- At least 2 weeks since prior local palliative radiotherapy (small port)
- More than 3 weeks since prior myelosuppressive chemotherapy (6 weeks for nitrosoureas) for patients with solid tumors
- At least 14 days since prior cytotoxic therapy for patients with ALCL who relapse while receiving cytotoxic therapy
  - Patients with lymphoma who relapse during standard maintenance therapy are eligible at time of relapse
  - Cytoreduction with hydroxyurea may be initiated and continued for up to 24 hours before the start of study treatment
- At least 7 days since prior growth factor therapy
- At least 7 days since prior biological agents
- At least 7 days or 3 half-lives (whichever is longer) since prior monoclonal antibody

- More than 12 days since prior and no concurrent potent CYP3A4 inducers including, but not limited to carbamazepine, phenobarbital, phenytoin, rifabutin, rifampin, tipranavir, ritonavir, or St. John's wort
- More than 7 days since prior and no concurrent potent CYP3A4 inhibitors including, but not limited to ketoconazole, itraconazole, miconazole, clarithromycin, erythromycin, ritonavir, indinavir, nelfinavir, saquinavir, amprenavir, delavirdine, nefazodone, diltiazem, verapamil, or grapefruit juice
- No concurrent medications known to be metabolized by CYP3A4 with narrow therapeutic indices, including pimozide, aripiprazole, triazolam, ergotamine, and halofantrine
- No other concurrent anticancer therapy (including chemotherapy, radiotherapy, immunotherapy, or biologic therapy), except for hydroxyurea for patients with ALCL or decadron for patients with CNS tumors
- No other concurrent investigational drugs
- Concurrent corticosteroids for CNS tumors allowed provided the dose has been stable or decreasing for the past 7 days

### **For More Information Contact**

Cincinnati Children's Hospital Medical Center  
Division of Hematology/Oncology  
3333 Burnet Ave., Cincinnati, OH 45229-3039  
Phone: 513-636-2799  
[cancer@cchmc.org](mailto:cancer@cchmc.org)