ADVL1011: A Phase I Study of JAK Inhibition (INCB018424) in Children With Relapsed or Refractory Solid Tumors, Leukemias, and Myeloproliferative Neoplasms

Type	Status	Age Range (yrs.)	Sponsor	Protocol ID
Interventional	Active	1 year to 21 years	CCHMC	ADVL1011

Purpose

This phase I clinical trial is studying the side effects and best dose of INCB18424 in treating young patients with relapsed or refractory solid tumor, leukemia, or myeloproliferative disease.

Objectives

Primary

- To estimate the maximum-tolerated dose and/or recommended phase II dose of oral JAK inhibitor INCB18424 administered continuously, twice daily to pediatric patients with relapsed or refractory solid tumors.
- To define and describe the toxicities of this treatment administered on this schedule in pediatric patients with relapsed or refractory solid tumors, leukemias, or myeloproliferative neoplasms (MPNs).
- To characterize the pharmacokinetics of this treatment in pediatric patients with relapsed or refractory solid tumors, leukemias, or MPNs.

Secondary

- To preliminarily define the antitumor activity of this treatment within the confines of a phase I study.
- To assess the biologic activity of oral JAK inhibitor INCB18424 upon JAK-STAT signaling in pediatric patients with relapsed or refractory solid tumors, leukemias, or MPNs.
- To assess the cytotoxicity and biologic activity of oral JAK inhibitor INCB18424 upon phosphosignaling and mutation burden in pediatric patients whose leukemias or MPNs have known CRLF2 and/or JAK mutations.

Outline

This is a multicenter, dose-escalation study.

Patients receive oral JAK inhibitor INCB18424 twice daily on days 1-28. Courses repeat every 28 days in the absence of disease progression or unacceptable toxicity.

Patients with relapsed or refractory leukemia may receive intrathecal chemotherapy in course 2 and subsequent courses at the discretion of the treating physician.

Plasma, bone marrow, and blood samples may be collected at baseline, during course 1, and before subsequent courses

for pharmacokinetic analysis and correlative biology studies.

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

Eligibility

Ages available for study: 1 to 21 years

Disease Characteristics

- Histologically confirmed diagnosis of one of the following:
  - Relapsed or refractory Extracranial solid tumor
  - Relapsed or refractory Leukemia
    - At least 25% blasts in the bone marrow (M3) with the exception of patients with acute myeloid leukemia (AML), who must have > 20% blasts in the bone marrow
  - Relapse or refractory Myeloproliferative neoplasm (MPN)
    - At original diagnosis or relapse
    - Current diagnostic criteria for MPNs include polycythemia vera, essential thrombocythemia, juvenile myelomonocytic leukemia, myelofibrosis, and atypical chronic myeloid leukemia
  - Relapsed or refractory leukemia or MPN that have confirmed JAK mutations and/or positive TSLPR surface staining
    - Testing for JAK mutations and/or confirmed positive flow cytometry surface staining for the thymic stromal lymphopoietin receptor (TSLPR; encoded by CRLF2) must be performed by a CLIA-approved laboratory
- Measurable or evaluable disease (for patients with solid tumors)
- Current disease state is one for which there is no known curative therapy or therapy proven to prolong survival with an acceptable quality of life
- No known active CNS involvement (radiographic or cytologic)

Patient Characteristics

- Karnofsky performance status (PS) 50-100% (for patients > 16 years old) or Lansky PS 50-100% (for patients ≤ 16 years old)
  - Patients who are unable to walk because of paralysis, but who can actively sit up in a wheelchair, will be considered ambulatory for the purpose of assessing the performance status
- Patients with solid tumors* must meet the following criteria:
  - Peripheral ANC ≥ 1,000/mm^3
  - Platelet count ≥ 100,000/mm^3 (transfusion-independent, defined as > 7 days since prior platelet transfusions)
  - Hemoglobin ≥ 8.0 g/dL (may receive RBC transfusions)
    - Not refractory to to red cell or platelet transfusion
  - ALT ≤ 110 U/L NOTE: *Patients with solid tumors and known bone marrow metastatic disease are eligible for study, but not evaluable for hematologic toxicity. These patients must not be known to be refractory to RBC or platelet transfusions.
- Patients with leukemia or MPNs must meet the following criteria:
  - Platelet count ≥ 20,000/mm^3 (may receive platelet infusions)
  - Hemoglobin ≥ 8.0 g/dL (may receive RBC transfusions)

  - ALT ≤ 225 U/L
- Creatinine clearance or radioisotope GFR ≥ 70 mL/min OR serum creatinine based on age/gender as follows:
  - ≤ 0.6 mg/dL (for patients 1 to < 2 years old)
  - ≤ 0.8 mg/dL (for patients 2 to < 6 years old)
  - ≤ 1 mg/dL (for patients 6 to < 10 years old)
  - ≤ 1.2 mg/dL (for patients 10 to < 13 years old)
  - ≤ 1.4 mg/dL (for female patients ≥ 13 years old)
  - ≤ 1.5 mg/dL (for male patients 13 to < 16 years old)
  - ≤ 1.7 mg/dL (for male patients ≥ 16 years old)
- Bilirubin (sum of conjugated + unconjugated) ≤ 1.5 times upper limit of normal for age
- Serum albumin ≥ 2 g/dL
- Not pregnant or nursing
- Negative pregnancy test
- Fertile patients must use effective contraception
- Able to swallow crushed or whole tablets
  - Nasogastric or G tube administration is not allowed
- Body surface area ≥ 0.65 m^2 (for patients at dose level -1, 1, and 2)
- No uncontrolled infection, including patients with known active HIV or chronic hepatitis
- No patients who, in the opinion of the investigator, may not be able to comply with the safety monitoring requirements of the study

Prior Concurrent Therapy

- Fully recovered from the acute toxic effects of all prior anticancer therapy
- At least 2 weeks since prior local palliative radiotherapy (small port)
- At least 6 months since prior total-body irradiation (TBI), craniospinal radiotherapy, or radiotherapy to ≥ 50% of the pelvis (for patients with solid tumors)
- At least 3 months since prior TBI, craniospinal radiotherapy, or radiotherapy to ≥ 50% of the pelvis (for patients with leukemia)
- At least 3 months since prior stem cell transplantation or rescue without TBI and no evidence of active graft-vs-host disease
- At least 6 weeks since other substantial bone marrow radiation
- At least 3 weeks since prior myelosuppressive therapy (6 weeks for nitrosourea) (for patients with solid tumors)
- At least 2 weeks since prior cytoxic chemotherapy (for patients with leukemia or MPNs)
  - Hydroxyurea may be initiated and continued for up to 24 hours before the start of study treatment
  - Intrathecal cytarabine (Ara-C) is not myelosuppressive chemotherapy
  - Patients with leukemia are permitted to receive intrathecal chemotherapy, including methotrexate or cytarabine, only if this is given at the time of diagnostic lumbar puncture at least 24 hours prior to the start of INCB018424
- At least 2 weeks since prior long-acting hematopoietic growth factor (e.g., Neulasta) or 1 week for a short-acting growth factor
  - For agents that have known adverse events occurring beyond 1 week, this period must be extended beyond the time during which adverse events are known to occur (as discussed with the study chair)
- At least 1 week since prior therapy with a biologic (antineoplastic) agent

    - For agents that have known adverse events occurring beyond 1 week, this period must be extended beyond the time during which adverse events are known to occur (as discussed with the study chair)
- At least 3 half-lives of antibody since prior monoclonal antibody
- No other concurrent investigational drugs
- No other concurrent anticancer agents, including chemotherapy, radiotherapy, immunotherapy, or biologic therapy
- No concurrent systemic steroids (i.e., prednisone > 10 mg)
- No concurrent aspirin > 150 mg/day
- No concurrent medications for myelofibrosis (e.g., hydroxyurea, interferon, thalidomide, busulfan, lenalidomide, or anagrelide)
- No concurrent cyclosporine, tacrolimus, or other agents to prevent graft-vs-host disease after bone marrow transplant or organ rejection after transplant

For more information contact:

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