

ADVL1112: A Phase I Study of Imetelstat, a Telomerase Inhibitor, in Children With Refractory or Recurrent Solid Tumors and Lymphomas

Type	Study Design	Age Range (yrs.)	Primary Purpose
Interventional	Open Label	1 - 21	Treatment

Rationale

Imetelstat sodium may stop the growth of tumor cells by blocking some of the enzymes needed for cell growth.

Purpose

This phase I clinical trial is studying the side effects and best dose of imetelstat sodium in treating young patients with refractory or recurrent solid tumors or lymphoma.

Objectives

Primary

- To estimate the maximum-tolerated dose (MTD) and/or recommended phase II dose of imetelstat sodium in children with refractory or recurrent solid tumors or lymphoma.
- To define and describe the toxicities of imetelstat sodium.
- To characterize the pharmacokinetics of imetelstat sodium in children with refractory or recurrent solid tumors or lymphoma.

Secondary

- To determine, in a preliminary manner, the antitumor effects of imetelstat sodium in children with refractory or recurrent solid tumors or lymphoma. (exploratory)
- To provide preliminary assessment of the biological activity of imetelstat sodium in children with recurrent or refractory malignancies by assessing telomerase activity, telomere length, hTERT protein, hTERT mRNA, and hTR levels in patient peripheral blood mononuclear cells (PBMNC) samples pretreatment and on treatment. (Exploratory)
- To assess telomerase activity, hTERT expression, telomere length, hTERT protein, hTERT mRNA, and hTR levels in patients' pretreatment tumor samples. (Exploratory)

Eligibility

Ages available for study: 1 to 21 years

Disease Characteristics

- Diagnosis of refractory or recurrent solid tumors, including lymphoma
 - No CNS tumors or known CNS metastases (Part A, dose escalation)

- CNS tumors or known CNS metastases allowed (Part B, maximum-tolerated dose or recommended phase II dose)
 - No prior or concurrent CNS hemorrhage on a baseline MRI within the past 14 days
- All patients must have histologic verification of malignancy at original diagnosis or relapse except for:
 - Intrinsic brain stem tumors
 - Optic pathway gliomas
 - Pineal tumors and elevations of CSF or serum tumor markers including alpha-fetoprotein or beta-HCG
- Measurable or evaluable disease
- Disease for which there is no known curative therapy or therapy proven to prolong survival with an acceptable quality of life
- Patients with known bone marrow metastatic disease will be eligible for study provided they meet the blood count criteria and they are not known to be refractory to red cell or platelet transfusions

Patient Characteristics

- Karnofsky performance status (PS) 50-100% (patients > 16 years of age) OR Lansky PS 50-100% (patients ≤ 16 years of age)
- ANC ≥ 1,000/mm³
- Platelet count ≥ 100,000/mm³ (transfusion-independent, defined as not receiving platelet transfusion within the past 7 days prior to enrollment)
- Creatinine clearance or radioisotope GFR ≥ 70 mL/min/1.73m² OR a serum creatinine based on age and/or gender as follows:
 - 0.6 mg/dL (1 to < 2 years of age)
 - 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)
- Bilirubin (sum of conjugated and unconjugated) ≤ 1.5 times upper limit of normal (ULN)
- ALT ≤ 110 U/L (ULN for ALT is 45 U/L)
- Serum albumin ≥ 2 g/dL
- aPTT < 1.2 times ULN
- Not pregnant or nursing
- Negative pregnancy test
- Fertile patients must use an effective contraception method
- No uncontrolled infection
- 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

- Recovered from acute toxic effects of all prior anti-cancer chemotherapy, immunotherapy, or radiotherapy
- At least 3 weeks since prior myelosuppressive chemotherapy (6 weeks for nitrosourea)
- At least 14 days since prior long-acting growth factor (e.g., Neulasta) or ≥ 7 days since prior short-acting growth factor
- At least 7 days since prior biologic or anti-neoplastic agent
- At least 6 weeks since any type of prior immunotherapy (e.g., tumor vaccines)
- At least 3 half-lives since last dose of a monoclonal antibody

- At least 2 weeks since prior local palliative radiotherapy (small port)
 - At least 24 weeks since prior total-body irradiation, craniospinal radiotherapy, or radiation to $\geq 50\%$ of the pelvis
 - At least 6 weeks since prior substantial bone marrow radiation
- At least 12 weeks since prior transplantation or stem cell infusion with no evidence of active graft vs host disease
- Prior and concurrent stable or decreasing dose of corticosteroids within the past 7 days allowed
- No prior allogeneic transplant
- No other concurrent investigational drug
- No other concurrent anticancer agents including chemotherapy, radiotherapy, immunotherapy, or biologic therapy
- No concurrent cyclosporine, tacrolimus, or other agents to prevent either graft-versus-host disease post-bone marrow transplant or organ rejection post-transplant

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