01-C-0196: A Phase I Trial and Pharmacokinetic Study of R115777 in Pediatric Patients with Refractory Leukemias

R115777 is a farnesyltransferase inhibitor that inhibits the post-translational isoprenylation of *ras* and other farnesylated proteins. The *ras* proteins are integral in cell signaling pathways, and farnesylation is essential for the function of both mutant and non-mutant *ras* proteins. *Ras* mutations have been documented in hematologic malignancies with high frequency, and a 30% response rate to R115777 was observed in adult patients with refractory leukemias. On this trial R115777 will be administered orally twice daily for cycles of 21 days followed by a 7 day rest period. This trial will define the toxicities, maximum tolerated dose, and pharmacokinetics of R115777 in pediatric patients with refractory leukemias. In addition biologic studies (*ras* mutation and expression status, inhibition of farnesyltransferse) will be performed on bone marrow/peripheral blood mononuclear cell (PBMC) samples.

ELIGIBILITY CRITERIA:

Age: Patients must be ≤21 years of age.

Histological Diagnosis: Patients must have histologically-confirmed acute lymphoblastic leukemia (ALL), acute non lymphoblastic leukemia (ANLL), juvenile myelomonocytic leukemia (JMML), or chronic myelogenous leukemia (CML) in blast crisis.

Prior Therapy:

- The leukemia must be refractory to standard curative treatment regimens. Patients with acute promyelocytic leukemias (APL) must be refractory to treatment with retinoic acid and arsenic trioxide. Patients with Philadelphia (Ph) chromosome positive CML must be refractory to STI571.
- Patients must have had their last dose of radiation therapy at least four weeks prior to study entry, their last dose of chemotherapy at least two weeks prior to study entry, and their last dose of retinoids or corticosteroids 7 days prior to study entry. Patients who previously received myeloablative therapy followed by a bone marrow or stem cell transplant are eligible if the transplant was performed at least 3 months before study entry.
- Patients must be off colony stimulating factors (with the exception of erythropoietin) such as filgrastim (granulocyte colony-stimulating factor), and GM-CSF for at least one week prior to study entry.
- Patients must have recovered from the non-hematologic toxic effects of all prior therapy before entry onto this trial. The Cancer Therapy Evaluation Program Common Toxicity Criteria (CTC) Version 2.0 will be used for toxicity assessment. A copy of the CTC version 2.0 can be downloaded from the CTEP home page (http://ctep.info.nih.gov). Recovery is defined as a toxicity grade <2, unless otherwise specified in the Inclusion and Exclusion Criteria.

Disease Status: Patients must have greater than 25% blasts in the bone marrow (M3 bone marrow). Active extramedullary disease (except for leptomeningeal disease) may also be present. Patients with JMML have to meet diagnostic criteria for JMML (Appendix 1B), and the requirement of greater than 25% blasts in the bone marrow does not apply to these patients.

Performance Status: Patients > 10 years must have a Karnofsky performance level ≥ 50, and children ≤ 10 years must have a Lansky performance level ≥ 50. (See Appendix 1A).

Hepatic Function: Patients must have adequate liver function, defined as bilirubin, SGPT, and SGOT within normal limits, and no recent history (within 1 month of trial entry) of significant elevation in bilirubin, SGPT, or SGOT to grade ≥3.

Renal Function: Patients must have an age-adjusted normal serum creatinine (see Table below) OR a creatinine clearance ≥60 mL/min/1.73 m^2.

Age (Years)	**Maximum Serum Creatinine** (mg/dl)
< 5	0.8
5 ≤ age <10	1.0
10 ≤ age <15	1.2
≥15	1.5

Hematologic Function: Blood counts not required to be normal prior to entry on this trial.

Informed Consent: All patients or their legal guardians (if the patient is <18 years old) must sign a document of informed consent indicating their understanding of the investigational nature and the risks of this study before any protocol related studies are performed (this does not include routine laboratory tests or imaging studies required to establish eligibility). When appropriate, pediatric patients will be included in all discussions in order to obtain verbal assent.

Birth Control: Subjects of childbearing or child-fathering potential must be willing to use a medically acceptable form of birth control, which includes abstinence, while they are being treated on this study.

Durable Power of Attorney (DPA): Assignment of DPA to a family member or guardian should be offered to all patients 18-21 years of age.

EXCLUSION CRITERIA

- Patients with active leptomeningeal leukemia (CSF WBC >5/μL and unequivocal confirmation of leukemic blasts in the CSF by morphologic demonstration on a CSF cytocentrifuge specimen).
- Patients with persistent grade >2 (as defined by Common Toxicity Criteria) sensory or motor neuropathy.
- Patients with history of grand mal seizures (grade ≥3) other than febrile seizures. Patients taking anti-convulsant medications, for any reasons, are not eligible for the trial.
- Clinically significant unrelated systemic illness (serious infections or significant cardiac, pulmonary, hepatic, renal or other organ dysfunction) which in the judgement of the Principal or Associate Investigator would compromise the patient's ability to tolerate R115777 or are likely to interfere with the study procedures or results.
- Pregnant or breast feeding females are excluded from this trial due to unknown effects of R115777 to the developing fetus or nursing child.
- Patients currently receiving other investigational agents.
- Inability to return for follow up visits.
- Patients with an allergy to azoles (for example clotrimazole, fluconazole, ketoconazole, voriconazole).
- Patients requiring total parenteral nutrition.

PRETREATMENT EVALUATION:

- History and physical examination, including complete neurologic exam and documentation of measurable extramedullary disease, performance status.
- Blood tests within 72 hours prior to enrollment, including hematology, chemistries, urinalysis and urine pregnancy test.
- Ophthalmologic evaluation prior to or within 3 days of starting treatment, including visual fields & examination of lens for opacification
- Lumbar puncture for cell count and morphology of CSF cytocentrifuge specimen within 14 days prior to study entry.

- Bone marrow aspiration for morphology, flow cytometry, and cytogenetics within 14 days prior to study entry.

GENERAL TREATMENT PLAN:

- Patients will receive R115777 orally as tablets every 12 hours for 21 days followed by a 7 day rest period (28 day treatment cycle). The starting dose for the trial is 300 mg/m^2/dose. Patients can expect to stay in the area for approximately 1 week when enrolling onto the study. Treatment is outpatient unless otherwise clinically indicated.

PHARMACOKINETICS/BIOLOGIC STUDIES:

- Blood samples will be obtained for pharmacokinetics on days 1 and 2, and 1 sample between day 6 and 10 of treatment. A bone marrow or PBMC sample will be obtained for biologic studies prior to and between day 6 and 10.

ACCRUAL:

- The trial is open to accrual at the POB and COG phase I institutions.