

CLINICAL TRIALS Broadcast

In Focus: Acute Myeloid Leukemia

E2902

A Phase III Randomized Study of Farnesyl Transferase Inhibitor R115777 in Acute Myeloid Leukemia Patients in Second or Subsequent Remission or in Remission After Primary Induction Failure or Patients Over Age 60 in First Remission

Background

Although significant advances have been made in the treatment of acute myeloid leukemia (AML), the majority of patients relapse, and remissions following relapse are generally shorter than those following initial treatment. Approximately 80% of patients relapse within 12 months. Efforts to prolong remission duration have so far not been successful.

Targeting farnesyl transferase may be an effective approach to treating AML. Farnesylation of proteins (eg, adding a 15-carbon unsaturated polymer derived from the lipid pathway) appears to play a critical role in cell signaling, proliferation, and differentiation.^{1,2} In particular, the *Ras* proto-oncogene appears to rely on this process. *Ras* proteins, activated downstream of protein tyrosine kinases, begin a cascade of phosphorylation events via pathways crucial to the survival of hematopoietic cells. Mutated *Ras* proteins are present in a variety of tumor types, including 15–25% of AML.³ Thus, it is hypothesized that inhibiting the farnesylation process linked to *Ras* could be effective in the treatment of AML.⁴

Farnesyl transferase (FT), the catalyst of protein farnesylation, appears to have two binding sites, one for farnesyl diphosphate and one for the target protein. Zinc is a required cofactor. The initial development of FT inhibitors (FTIs) were based on the possibility of preventing *Ras* processing and thus transduction of proliferative signals.⁵⁻⁷ Additional studies have found that the cytotoxic action of these inhibitors may also rely on targets other than *Ras*.^{1,2}

Tipifarnib (R115777, Zarnestra; Johnson & Johnson), an oral agent that is a highly potent and selective inhibitor of farnesylation, was the first FTI to be studied in leukemia patients.⁷⁻⁹ Single-agent phase I and II studies in adults and children with advanced malignancies

demonstrated oral bioavailability. The most frequently observed side effects were nausea, fatigue, and anemia, and prolonged therapy is associated with grade 3 and 4 granulocytopenia and thrombocytopenia at doses exceeding 400 mg twice daily. Phase I and II trials in patients with leukemia have demonstrated activity in patients with both relapsed as well as untreated disease. A phase II study has evaluated the use of tipifarnib as maintenance therapy in patients with poor-risk AML in first complete remission. The median duration of remission in these patients was 14 months, compared to 8.75 months for similar patients who refused tipifarnib.¹⁰ Based on the preclinical and Phase I and II studies done to date, the Eastern Cooperative Oncology Group (ECOG) has initiated a phase III trial, E2902, which is studying tipifarnib as maintenance therapy for patients with AML who have achieved complete remission (CR) following salvage therapy or patients over the age of 60 in first remission. Patients are eligible to enter the study once they have recovered from salvage therapy and, if desired, postremission therapy. Younger patients who will undergo allogeneic transplantation will be excluded from this study. Thus, the expected study population includes younger and older patients who are not allogeneic transplant candidates.

References

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Objectives

- Primary: To compare tipifarnib maintenance therapy to observation only with respect to disease-free survival in patients with AML in second or subsequent CR or in CR following primary induction failure or patients over the age of 60 in first remission.
- Secondary:
 - To compare overall survival of patients in both arms
 - To evaluate the long-term safety and toxicity of extended administration of tipifarnib in AML patients in remission

Basic Eligibility Criteria

- First remission following primary induction failure, having received at least two chemotherapy induction regimens
- Second or subsequent remission
- >60 years old in first remission
- CR or morphologic remission, with confirmatory bone marrow performed ≤ 2 weeks prior to randomization
- Platelets $\geq 50,000$
- Morphologic proof of AML of any of the following types: acute myeloblastic leukemia (M0, M1, M2);

acute myelomonocytic leukemia (M4), acute monocytic leukemia (M5), acute erythroleukemia (M6), acute megakaryocytic leukemia (M7), refractory anemia with excess blasts in transformation (RAEB-T). (Patients with acute promyelocytic leukemia are not eligible.)

- No allogeneic transplant during current remission. Patients who have had an allogeneic transplant in a previous remission and are currently in remission after subsequent relapse are eligible.
- ≥ 18 years of age
- ECOG performance status 0–2

Targeted Accrual

139 patients (69–70 per treatment arm)

Contact Information

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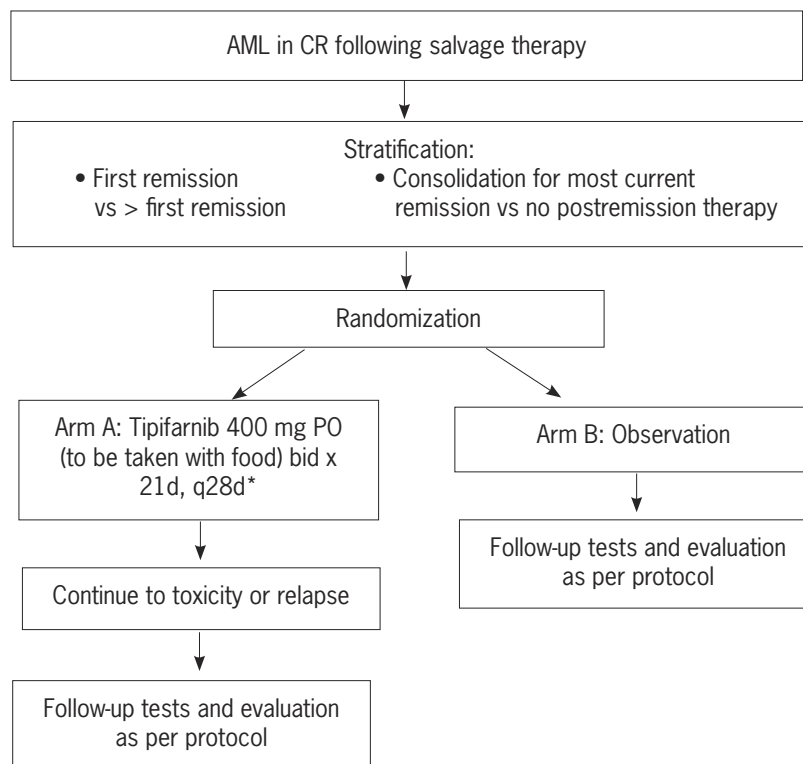
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Schema



* 1 cycle = 28 days. Dose modifications as needed.