AAML1031: A Phase III Randomized Trial for Patients with de Novo AML using Bortezomib and Sorafenib for Patients with High Allelic Ratio

Basic Study Information

Study Type: Interventional
Study Design: Allocation: Randomized
Masking: Open Label
Primary Purpose: Treatment

Purpose

This randomized phase II/III trial is studying how well giving bortezomib and sorafenib tosylate together works in treating patients with newly diagnosed acute myeloid leukemia with or without mutations.

Objectives

Primary

- To measure event-free survival

Secondary

- To determine overall survival
- To determine remission rate after 1 and 2 courses of therapy
- To measure the proportion of patients dying in each course of therapy
- To measure the course duration
- To measure the length of hospitalization
- To measure the time to blood count recovery
- To measure relapse rate
- To measure treatment-related mortality
- To determine frequency of toxicities, including infectious and cardiac complications

Ages Eligible for Study: up to 29 Years

Disease Characteristics:

- Patients must be newly diagnosed with de novo acute myelogenous leukemia and must meet 1 of the following criteria:
  - Patients with previously untreated primary AML who meet the customary criteria for AML with ≥ 20% bone marrow blasts as set out in the 2008 WHO Myeloid Neoplasm Classification are eligible
  - Patients with cytopenias and bone marrow blasts who do not meet the customary criteria for the diagnosis of AML (patients with < 20% blasts) are eligible if they have a karyotypic abnormality characteristic of de novo AML (t(8;21)(q22;q22), inv(16)(p13q22) or t(16;16)(p13;q22) or 11q23 abnormalities), or if they have the unequivocal presence of megakaryoblasts, as set out in the 2008 WHO Myeloid Neoplasm Classification
  - Patients with biopsy-proven isolated myeloid sarcoma (myeloblastoma; chloroma, including leukemia cutis) are eligible
- Patients must meet one of the following criteria:

- Low-risk disease as defined by any of the following:
  - Presence of inv(16)/t(16;16) or t(8;21) cytogenetic features or NPM or CEBPα mutation regardless of monosomy 7, monosomy 5, or del5q and regardless of MRD at end of Induction I
  - Negative MRD (< 0.1%) at end of Induction I and no high-risk disease features
  - Patients who do not have MRD data and have non-informative molecular studies (NPM, CEBPα, and cytogenetics) will be classified as having low-risk disease
- High-risk disease as defined by any of the following:
  - FLT3/ITD+ with high allelic ratio > 0.4 (HR FLT3/ITD+) regardless of low-risk features
  - Presence of monosomy 7, monosomy 5, or del5q, without inv(16)/t(16;16) or t(8;21) cytogenetics or NPM or CEBPα mutations
  - AML without inv(16)/t(16;16), t(8;21), NPM, CEPBα mutations, monosomy 7, monosomy 5, del5q, or HR FLT3/ITD+, but with evidence of residual AML (≥ 0.1%) at end of Induction I

- Patients with juvenile myelomonocytic leukemia (JMML) are not eligible
- Patients with Philadelphia chromosome positive AML, biphenotypic or bilineal acute leukemia, or acute promyelocytic leukemia are not eligible
- High-risk patients may have a donor (bone marrow or cord blood) meeting the following criteria available:
  - Matched family donor (MFD)*
    - HLA, A, B, C, DRB1, identical, or 1 antigen or allele mismatched
      - HLA typing must be performed using molecular high-resolution technique
      - All available first-degree family members (parents and siblings) must be HLA typed
    - Use of syngeneic donors will NOT be permitted in this study NOTE: *For MFD SCT, the use of peripheral blood stem cells (PBSC) is not permitted on this study.
  - Alternative donor
    - HLA, A, B, C, DRB1 identical or 1 antigen- or allele-mismatched unrelated donor
    - HLA A, B, DRB1 4 of 6 antigen-matched unrelated donor cord blood unit with an adequate cell dose (nucleated cell dose > 3.7x10^7/kg or CD34+ cell dose > 2 x 10^5/kg)
    - Mismatched family member donor with at least one haplotype match, or 5 of 6 antigen phenotypic match

Patient Characteristics:

- Patients with any performance status are eligible
- Patients with constitutional trisomy 21 are not eligible
- Patients with any of the following are not eligible:
  - Fanconi anemia
  - Shwachman syndrome
  - Any other known bone marrow failure syndrome
  - Another concurrent malignancy
- Not pregnant or nursing
- Negative pregnancy test
- Sexually active patients of reproductive potential are not eligible unless they have agreed to use an effective contraceptive method for the duration of their study participation

Prior/Concurrent Therapy:

- Prior therapy with hydroxyurea, all-trans retinoic acid (ATRA), corticosteroids (any route), and intrathecal (IT) cytarabine given at diagnosis is allowed
    - Hydroxyurea and ATRA must be discontinued prior to initiation of protocol therapy
- No concurrent peripheral blood stem cell transplantation
- Patients who have previously received any other chemotherapy, radiation therapy, or any other antileukemic therapy are not eligible for this protocol
- Concomitant administration of strong CYP3A4 inducers and inhibitors (including clinically relevant moderate inhibitors) is prohibited on both sorafenib cohorts

Who should I contact for more information?

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