A Phase 3, Randomized Study of Pracinostat in Combination with Azacitidine (AZA) Versus Placebo in Patients ≥18 years with Newly Diagnosed Acute Myeloid Leukemia (AML) Unfit for Standard Induction Chemotherapy

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BACKGROUND
- AML is associated with poor survival rates in those ineligible for intensive induction chemotherapy (IC) or stem cell transplant due to advanced age, comorbidities, and/or disease risk factors.
- Non-intensive therapies are frequently used in this setting; however, response rates and survival remain dismal.
- Studies have shown that AML cells demonstrate widespread hypermethylation of DNA promoter regions and that such hypermethylation leads to selective gene silencing. The development of hypomethylating agents, such as azacitidine (AZA) and decitabine, were designed to reverse hypermethylation and normalize gene expression.
- Histone deacetylases (HDACs) are enzymes involved in the remodeling of chromatin and therefore have a key role in the epigenetic regulation of gene expression. The reduction of acetylation status of histones is one mechanism for the abnormal epigenetic silencing of important regulatory genes. HDAC inhibitors, which can induce G1 or G2 cell cycle arrest leading to apoptosis and/or cell death, have been extensively studied in both hematologic and solid tumors.
- Preclinical studies in myeloid malignancies indicate that inhibition of histone deacetylation and DNA hypermethylation induces re-expression of silenced genes in a synergistic fashion and that the combination of hypomethylating agents like AZA with HDAC inhibitors could be synergistic in vivo.1,2
- Pracinostat is a potent oral HDAC inhibitor selective for Class I, II, and IV isoforms.
- In a Phase 2 study, pracinostat in combination with AZA showed promising efficacy results in patients ≥65 years with AML eligible for IC (Table). The overall response rate (all complete/partial remissions) was 64% and the median overall survival was 19.1 months.3
- Based on these favorable Phase 2 findings, a randomized, double-dummy Phase 3 study was designed to evaluate pracinostat in combination with AZA, compared with AZA alone, in AML patients unfit for intensive treatment.

Methods

Study Design

Randomization (1:1) N ~ 500

Statified by WBC and cytogenetic risk group (intermediate vs unfavorable) and ECOG performance status (0-1 vs 2)

All patients are followed every 3 months for disease progression and survival until death or end of study

Pharmacokinetic and Pharmacodynamic Endpoints

Pracinostat: 60 mg capsule (QD) followed by 3 weeks (prior to AZA) followed by 1 week rest
AZA: 75 mg per day (7/3/7) x 11 x 7 days followed by 3 week rest

Placebo: blinded placebo capsule (QD) followed by 3 weeks (prior to AZA) followed by 1 week rest
AZA: 75 mg per day (7/3) x 9 x 7 days followed by 3 week rest

Key Inclusion and Exclusion Criteria

Inclusion Criteria

Male or female patients ≥ 18 years of age with newly diagnosed, histologically confirmed AML, including de novo, secondary to antecedent hematologic disorders, or treatment related disease with intermediate or unfavorable-risk cytogenetics

Unable to receive intensive chemotherapy regimens at enrollment, due to older age (≥75 years) or if <75 years due to comorbidities such as ECOG performance status of 2, clinically significant cardiovascular or pulmonary disease, diabetes mellitus with symptomatic end-organ damage, autoimmune inflammatory conditions, Class III obesity, or renal impairment

Peripheral white blood cell (WBC) count <3,000/μL

ECOG performance status ≤ 2

Exclusion Criteria

AML-associated inv(16)/t(16;16)/del(16q), t(15;17) (i.e., promyelocytic leukemia) with/without secondary aberrations: t(8;21) lacking del (9q) or lacking complex karyotypes

Presence of an active malignant disease within the last 12 months, with the exception of adequately treated cervical cancer in situ, non-melanoma skin cancer and superficial bladder tumors

Life-threatening illnesses other than AML, uncontrolled medical conditions or organ system dysfunction that, in the Investigator’s opinion, could compromise the patient’s safety or put the study outcomes at risk

Uncontrolled arrhythmias; any Class 3 or 4 cardiac diseases as defined by the New York Heart Association functional classification

Enrollment & Registration

Enrollment of this international study began in July 2017 with ~140 sites planned in North & South America, Europe, Asia and Australia. Recruitment is ongoing in 13 countries (see map).

The study is registered at ClinicalTrials.gov (NCT03151408).

REFERENCES