**AGILITY: A Phase 3, Randomized, Double-Blind, Placebo-Controlled Study of the Efficacy and Safety of Entospletinib Added to Standard Induction Chemotherapy in Newly Diagnosed NPM1-Mutated AML**

*John C. Byrd¹, Jorge E. Cortes², Mark D. Minden³, Thomas Oellerich⁴, Eytan M. Stein⁵, Jenna Elder⁶, Pavan Kumar⁷, Gordon Bray⁸, Jorge DiMartino⁹, Wendy Stock⁹*

¹The University of Cincinnati, Cincinnati, Ohio, USA; ²Georgia Cancer Center at Augusta University, Augusta, GA, USA; ³Princess Margaret Cancer Centre, Toronto, Ontario, Canada; ⁴Frankfurt Cancer Institute, Frankfurt am Main, Germany; ⁵Memorial Sloan Kettering Cancer Center, New York, NY, USA; ⁶PharPoint Research, Inc., Durham, NC, USA; ⁷Kronos Bio, Inc., San Mateo, CA, USA; ⁸University of Chicago Medicine, Chicago, IL, USA

---

**Background**

- **Splen tyrosine kinase (Syk)** has been implicated in the pathogenesis of a subset of acute myeloid leukemias (AMLs), as defined by dysregulated expression of the HOXA9 and MEIS1 transcription factors. ¹⁻²
- **Syk** protein expression and activity are modulated by HOXA9 and MEIS1, homeodomain-containing transcription factors that are overexpressed in ~30% to 40% of patients with AML and correlate with poor prognosis. ¹⁻²
- **Sensitivity to entospletinib (ENTO)**, an oral, potent, and selective Syk inhibitor, in AML strongly correlates with the presence of the nucleophosmin 1 mutation (NPM1m),³ and NPM1m is associated with aberrant expression of HOXA9 and MEIS1 (Figure 1). ¹⁻²
- **Although newly diagnosed patients treated with ENTO plus standard induction chemotherapy achieved an overall complete composite response (CR) rate of 70%, a sub-set of patients with NPM1m and MLL rearrangements achieved higher CR rates of 87% and 90%, respectively.⁴
- **The adverse event (AE) profile of ENTO in combination with 7+3 induction was largely consistent with AEs expected with 7+3 alone.**

---

**Objectives**

- **Evaluate the efficacy of ENTO when added to chemotherapy in patients with previously untreated NPM1m AML as defined by MRD-negative CR.**
- **Evaluate the efficacy of ENTO when added to chemotherapy in patients with previously untreated NPM1m AML as defined by EFS, relapse-free survival (RFS), overall survival (OS), and CR rates.**
- **Evaluate the safety of ENTO when added to intensive chemotherapy using standard safety metrics.**

---

**Study Design**

- **Previously untreated AML patients with NPM1m and eligible for 7+3 induction randomized 1:1 to receive induction/consolidation chemotherapy in combination with either ENTO or placebo.**
- **Randomization stratified by age (<60 vs ≥60 years), and antracycline administered during induction (daunorubicin vs idarubicin).**
- **Screening includes bone marrow aspiration for confirmation of diagnosis, morphologic assessment (viable prep), detection of cytogenetic abnormalities by cytogenetic fluorescence in situ hybridization (FISH), and biomarker assessments (including NPM1 and FLT3 mutation status).**

---

**Endpoints**

- **Primary Endpoint**
  - MRD-negative CR rates after completion of 2 cycles of chemotherapy plus ENTO or placebo
- **Secondary Endpoints**
  - EFS
  - RFS
  - OS
  - **Exploratory Endpoints**
  - MRD assessment
  - Safety assessments
  - Pharmacogenomics

---

**Key Assessments and Timing**

- **1:1 randomization**
- **ENTO vs placebo**
- **Induction cycle 4**
- **Post-chemotherapy cycle 2**
- **Consolidation cycle 3**
- **End-of-study follow-up**

---

**Patient Eligibility**

- **Key Inclusion Criteria**
  - Adults 18–74 years with previously untreated de novo AML, AML with MDS features, or therapy-related AML
  - Known active COVID-19
  - Adequate hepatic and renal functions
  - LVEF ≥50%
  - PT, aPTT, and INR ≤1.5x ULN, unless receiving therapeutic anticoagulation
  - Candidate for intensive induction therapy
- **Key Exclusion Criteria**
  - Isolated myeloid sarcoma, acute promyelocytic leukemia, or known CNS involvement with leukemia
  - Concurrent FLT3 mutation (either TKD or ITD)
  - Active infection with hepatitis B, C, or HIV
  - Known active COVID-19
  - Disseminated intravascular coagulation with active bleeding or signs of thrombosis
  - Gastrointestinal hemorrhage
  - Neutropenic fever
  - History of severe, persistent, or frequent fevers in the setting of appropriate antimicrobial therapy
  - Treatment with proton pump inhibitors (H₂ receptor antagonists and histamine-2 blockers are allowed)

---

**Treatment (Through Chemotherapy Cycle 2)**

- **Induction Cycle 1**
  - Cytarabine: 100 mg/m² CI days 1–7
  - Anthracycline
- **Induction Cycle 2**
  - Cytarabine: 100 mg/m² CI days 1 and 3
  - Anthracycline: Daunorubicin 60 mg/m² IV days 1–3 or Idarubicin 12 mg/m² IV days 1–3 (for patients ≥60 years)
  - Idarubicin 12 mg/m² IV days 1–3 (for patients <60 years)

---

**Study Medication**

- **ENTO** (400 mg bid) or placebo
  - **Chemotherapy Cycle 2**
  - (Patients with ≥5% blasts post-induction cycle 1)
  - (Patients with ≤5% blasts post-induction cycle 1)

---


---

**References**