AGILITY: A Phase 3, Randomized, Double-Blind, Placebo-Controlled Study to Assess the Efficacy and Safety of Entospletinib in Combination With Intensive Induction and Consolidation Chemotherapy in Adults With Newly Diagnosed *Nucleophosmin 1*–Mutated Acute Myeloid Leukemia

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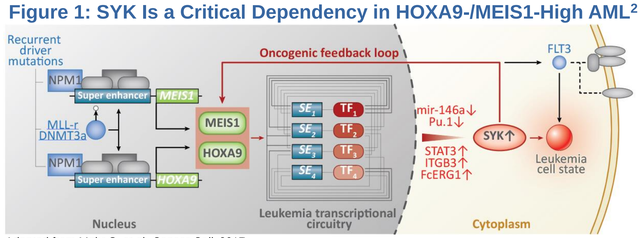
Background

- Spleen tyrosine kinase (SYK) has been implicated in the pathogenesis of a subset of acute myeloid leukemia (AML) 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 AML patients and correlate with poor prognosis.[3,4]
- Sensitivity to entospletinib (ENTO), an oral, potent, and selective SYK inhibitor, in AML strongly correlates with the presence of the *NPM1* mutation (*NPM1*m),[4] and *NPM1*m is associated with aberrant expression of HOXA9 and MEIS1.[5] (Figure 1)
- While newly diagnosed patients treated with ENTO plus standard induction chemotherapy achieved an overall composite complete response (CR) rate of 70%, a subset of patients with *NPM1*m 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.[4]
- The current phase 3 AGILITY trial (NCT05020665) is investigating whether the addition of ENTO to standard induction/consolidation in newly diagnosed patients with *NPM1*m AML will improve the rate of CR without evidence of measurable residual disease (MRD-negative CR) post-induction and improve the duration of event-free survival (EFS).

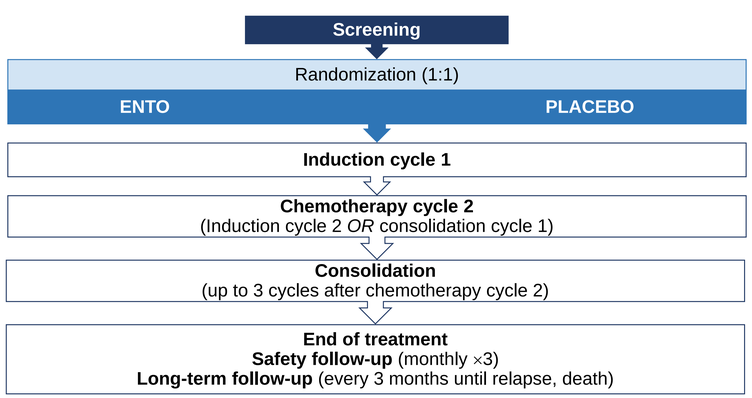
Figure 1: SYK Is a Critical Dependency in HOXA9-/MEIS1-High AML[2]



Adapted from Mohr S, et al. *Cancer Cell*. 2017.

Study Design

- Previously untreated patients with *NPM1*m 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 anthracycline administered during induction (daunorubicin vs idarubicin)
- Two-step screening procedure:
  1. Testing procedure for presence of *NPM1/FLT3* mutations (bone marrow aspirate and/or peripheral blood assessed in a central laboratory)
  2. Patients harboring *NPM1*m can be further screened for eligibility, if *FLT3* wild-type or *FLT3*-mutated without access to midostaurin.



Objectives

- Evaluate the efficacy of ENTO when added to chemotherapy in patients with previously untreated *NPM1*m AML as defined by MRD-negative CR
- Evaluate the efficacy of ENTO when added to chemotherapy in patients with previously untreated *NPM1*m AML as defined by EFS, relapse-free survival (RFS), overall survival (OS), and CR rates
- Evaluate the safety of ENTO when added to induction chemotherapy using standard safety metrics

Treatment (through Chemotherapy Cycle 2)

	Induction Cycle 1	Induction Cycle 2 *(Patients with ≥5% blasts post-induction cycle 1)*
Cytarabine	100 mg/m^2 CI, days 1–7	1.0 g/m^2 BID days 1–6
Anthracycline	Daunorubicin 60 mg/m^2 IV days 1–3 *or* idarubicin 12 mg/m^2 IV days 1–3	*(For patients age <60 years)* Daunorubicin 60 mg/m^2 IV days 1–3 *or* idarubicin 12 mg/m^2 IV days 1–3
Study medication	ENTO (400 mg BID) or placebo	
	Consolidation Cycle 1 *(Patients with <5% blasts [CR, CRi, CRh, MLFS] post-induction cycle 1)*	
Cytarabine	3 g/m^2 BID, days 1, 3, 5* for patients <60 years 1.5 g/m^2 BID, days 1, 3, 5* for patients ≥60 years	
Study medication	ENTO (400 mg BID) or placebo	

BID, twice daily; CI, continuous infusion; CRi, complete response with incomplete blood count recovery; CRh, complete response with hematologic improvement; IV, intravenous; MLFS, morphologic leukemia-free state.
*Every 28–35 days; all CR, CRh or CRi patients are eligible to receive up to 3 cycles of age-adjusted high-dose cytarabine after chemotherapy cycle 2 + ENTO/placebo.

Patient Eligibility

Key Inclusion Criteria	Key Exclusion Criteria
▪ Adults 18–75 years with previously untreated de novo AML, AML with MDS features, or therapy-related AML ▪ *NPM1*m, *FLT3* wild-type*,† ▪ ECOG performance status of 0–2 ▪ Adequate hepatic and renal functions ▪ LVEF ≥45% ▪ PT, aPTT, and INR ≤1.5× ULN, unless receiving therapeutic anticoagulation	▪ Isolated myeloid sarcoma, acute promyelocytic leukemia, or known CNS involvement with leukemia ▪ Active infection with hepatitis B, C or known HIV ▪ Known active COVID-19, either symptomatic or asymptomatic‡ ▪ Disseminated intravascular coagulation with active bleeding or signs of thrombosis ▪ Ongoing immunosuppressive therapy, including systemic chemotherapy (patients may not receive AML-directed therapy prior to enrollment *other than hydroxyurea or leukapheresis*) ▪ Clinically significant heart disease ▪ Patients with a corrected QT interval >480 msec or long QT syndrome ▪ Uncontrolled systemic infection *(*including persistent fever or positive cultures in the setting of appropriate antimicrobial therapy) ▪ Treatment with proton pump inhibitors (H_2 receptor antagonists and antacids are allowed during the study*)*

aPTT, activated partial thromboplastin time; COVID-19, coronavirus disease 2019; CNS, central nervous system; ECOG, Eastern Cooperative Oncology Group; HIV, human immunodeficiency virus; INR, international normalized ratio; LVEF, left ventricular ejection fraction; MDS, myelodysplastic syndromes; PT, prothrombin time; ULN, upper limit of normal.
*Patients with concurrent *FLT3* mutation and without access to midostaurin may enroll but will not be allowed to receive a FLT3 inhibitor at any time during the study treatment period. †Patients with local test results for *NPM1*m (and/or *FLT3* mutational status) may enroll, provided that the required biosamples are sent to the central testing facility for *NPM1*m companion diagnostic development. ‡As determined by nasopharyngeal swab for severe acute respiratory syndrome coronavirus 2 RNA or antigen.

Endpoints

Primary Endpoint

- MRD-negative CR rates after completion of 2 cycles of chemotherapy plus ENTO or placebo

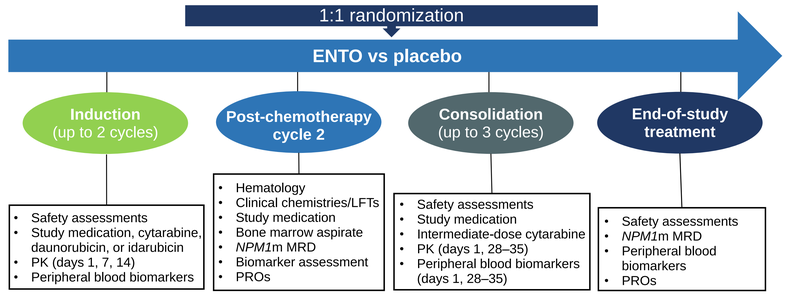
Secondary Endpoints	Exploratory Endpoints
• EFS • RFS • OS • CR rates after 2 cycles of chemotherapy, as defined by ELN 2017 criteria • Type, incidence, severity, and outcome of adverse events • Changes from baseline in safety laboratory assessments, ECGs, ECHO/MUGA scans, ECOG performance score	• *HOXA9/MEIS1* expression levels • Mutational profiling of leukemic cells • Targeted protein/phosphoprotein profiling expression levels • ENTO target engagement • Log reduction from baseline in bone marrow *NPM1* alleles • Prognostic value of MRD for morphologic relapse • Quality of life

ECG, electrocardiogram; ECHO, echocardiogram; ELN, European Leukemia Network; MUGA, multigated acquisition.

Key Assessments and Timing

Screening (14 days)

- IxRS registration
- Safety assessments
- Bone marrow evaluations
- Biomarker assessments
- Pharmacogenomics
- PROs



Long-term Follow-up

- Longitudinal *NPM1*m MRD assessments (in patients achieving MRD-negative CR), PROs, follow-up for relapse, first salvage therapy, OS

IxRS, interactive voice/web response system; LFTs, liver function tests; PK, pharmacokinetics; PROs, patient-reported outcomes.

Enrollment

- First patient enrollment is anticipated by the end of 2021.
- Planned enrollment is approximately 180 patients.
- Additional information is available at ClinicalTrials.gov: https://clinicaltrials.gov/ct2/show/NCT05020665

References

1. Hahn CK, et al. *Cancer Cell.* 2009;16(4):281-294. **2.** Mohr S, et al. *Cancer Cell.* 2017;31(4):549-562.e11. **3.** Boros K, et al. *Oncotarget.* 2015;6(28):25575-25587. **4.** Walker AR, et al. *Clin Cancer Res.* 2020;26(22):5852-5859. **5.** Brunetti L, et al. *Cancer Cell.* 2018;34(3):499-512.e9.

Disclosures

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