Poster P525

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

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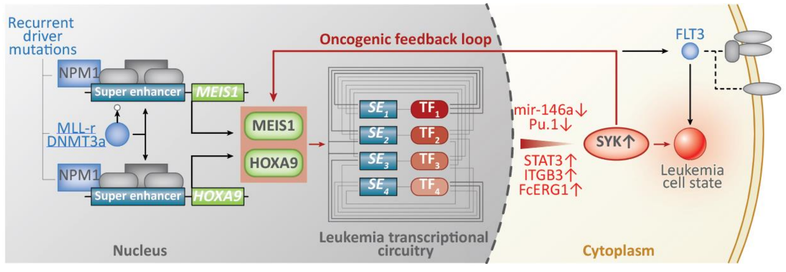
Background

- Spleen 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.[3,4]
- Sensitivity to entospletinib (ENTO), an oral, potent, and selective SYK inhibitor, in AML strongly correlates with the presence of the *nucleophosmin 1* mutation (*NPM1*m),[4] and *NPM1*m is associated with aberrant expression of HOXA9 and MEIS1[5] (**Figure 1**).
- Although 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 chemotherapy in newly diagnosed, fit 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;31(4):549-562.e11.

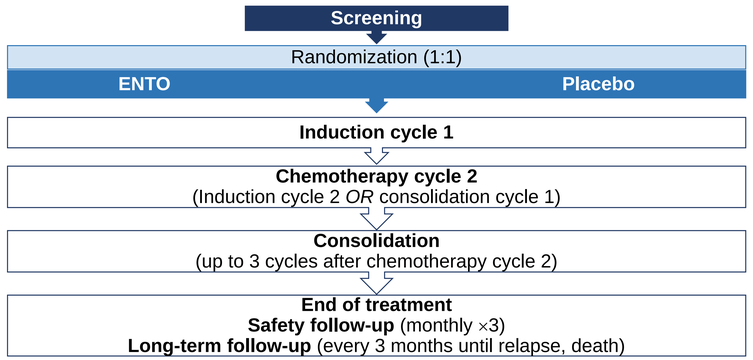
Objectives

- 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 intensive chemotherapy using standard safety metrics.

Study Design

- Previously untreated AML 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).
- Screening includes bone marrow aspiration for confirmation of diagnosis, morphology assessment (spicule prep), detection of cytogenetic abnormalities by cytogenetics/ fluorescence in situ hybridization (FISH), and biomarker assessments (including *NPM1* and *FLT3* mutation status).

Study Design (cont'd)



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 <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	
	Chemotherapy Cycle 2 *(Patients with <5% blasts 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; IV = intravenously.
*Every 28–35 days; all 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 18–74 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 • Candidate for intensive induction therapy	• 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 • Ongoing immunosuppressive therapy, including systemic chemotherapy‡ • 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)

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; ITD = internal tandem duplication; LVEF = left ventricular ejection fraction; MDS = myelodysplastic syndromes; PT = prothrombin time; TKD = tyrosine kinase domain; ULN = upper limit of normal.
*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. †Either symptomatic or asymptomatic, as determined by nasopharyngeal swab for severe acute respiratory syndrome coronavirus 2 RNA or antigen. ‡Patients may not receive AML-directed therapy prior to enrollment other than hydroxyurea or leukapheresis.

Endpoints

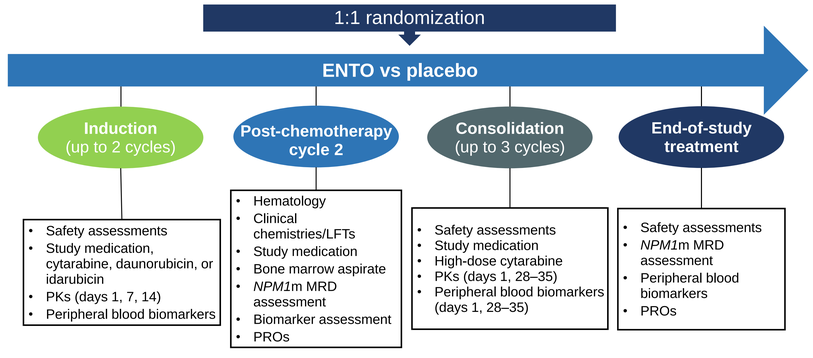
Primary Endpoint
• MRD-negative CR rates after completion of 2 cycles of chemotherapy plus ENTO or placebo

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 AEs • 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 expression profiling • ENTO target engagement • Log reduction from baseline in bone marrow *NPM1* mutant alleles • Prognostic value of MRD for morphologic relapse • Quality-of-life assessments

ECG = electrocardiogram; ECHO = echocardiogram; ELN = European LeukemiaNet; MUGA = multigated acquisition.

Key Assessments and Timing

Screening (14 Days)		
• IxRS registration	• Bone marrow evaluations	• Pharmacogenomics
• Safety assessments	• Biomarker assessments	• PROs



Long-term Follow-up
• Longitudinal *NPM1*m MRD assessments (in patients achieving MRD-negative CR post-chemotherapy cycle 2), PROs, follow-up for progression/relapse, first salvage therapy, OS

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

Enrollment

- First patient was enrolled in November 2021, and accrual is ongoing.
- Planned enrollment is approximately 180 patients.
- Additional information is available at ClinicalTrials.gov: https://clinicaltrials.gov/ct2/show/NCT05020665

References

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