PHASE 1 STUDY OF ZIFTOMENIB IN COMBINATION WITH VENETOCLAX, VENETOCLAX/AZACITIDINE, OR STANDARD INDUCTION (7+3) CHEMOTHERAPY IN PATIENTS WITH ACUTE MYELOID LEUKEMIA

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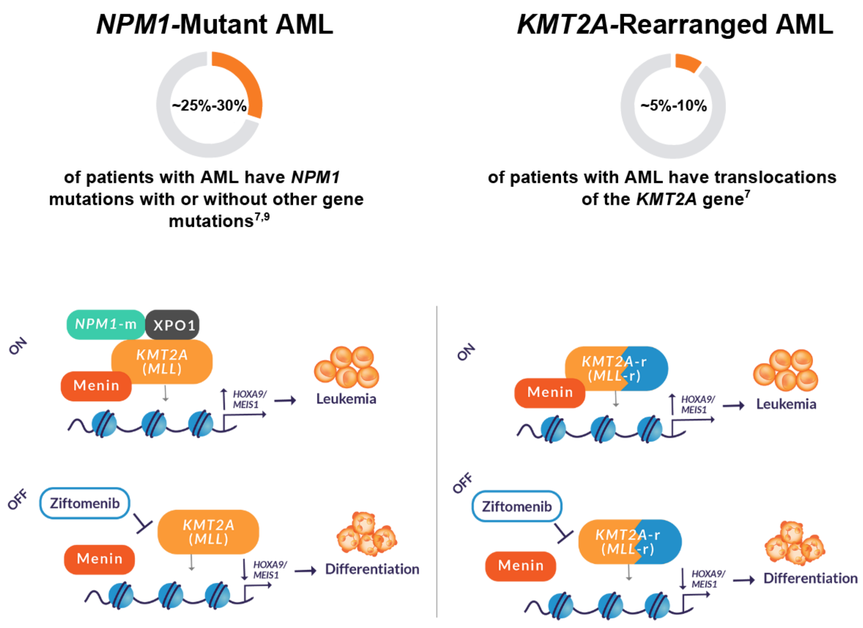
BACKGROUND

- Acute myeloid leukemia (AML) with nucleophosmin 1-mutations (*NPM1*-m) or lysine[K]-specific methyltransferase 2A-rearrangment (*KMT2A*-r) represent a high unmet need, as no Food and Drug Administration-approved targeted therapies exist today[1-3]
- There are approximately 6000 new cases of *NPM1*-m and 1000 to 2000 new cases of *KMT2A*-r each year in the United States
- Adult patients harboring *NPM1*-m or *KMT2A*-r mutations have a poor prognosis, with a 5-year overall survival of about 50% and <20%, respectively[4,5]
- Ziftomenib is an investigational, potent, selective inhibitor that targets the menin-mixed-lineage leukemia (MLL) *KMT2A* interaction, which drives leukemogenesis in these subtypes (**Figure 1**)[6-8]

FIGURE 1. MECHANISM OF ACTION



AML, acute myeloid leukemia; *KMT2A*-r, lysine[K]-specific methyltransferase 2A-rearrangment; *HOXA9*, homeobox A9; *MEIS1*, meis homeobox 1; *MLL*, menin-mixed-lineage leukemia; *NPM1*-m, nucleophosmin 1-mutations; XPO1, exportin 1.

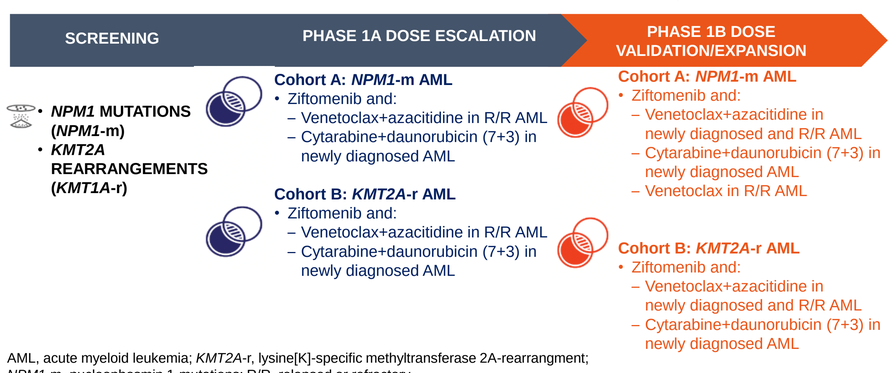
- Aberrant *HOXA9/MEIS1* expression results from epigenetic changes caused by perturbation of the menin-*KMT2A* (*MLL*) complex, which leads to proliferation, stemness, and differentiation block of bone marrow cells[7,10]
- Rearrangements involving *KMT2A (MLL*) alter the gene's normal histone methyltransferase function, maintaining elevated HOX expression and sustaining the hematopoietic differentiation blockade[7,10,11]
- The leukemic gene expression program is dependent on mutant *NPM1 (NPM1*-m) interacting with menin and wild-type *KMT2A (MLL)*[1,2,7]
- In an ongoing Phase 1/2 study (KO-MEN-001; NCT04067336) in patients with heavily pre-treated R/R AML, ziftomenib 600 mg monotherapy demonstrated meaningful clinical activity in *NPM1*-m AML with complete response (CR) of 30.0% (n=20), and in *KMT2A-r* AML, the ORR was 16.7% (n=18), with manageable toxicities
  - Ziftomenib 600mg was deemed the recommended Phase 2 dose
- In preclinical testing, ziftomenib combined with venetoclax induced synergistic lethality in *KMT2A*-r and *NPM1*-m human AML cell lines and patient-derived cells[12]
- Moreover, treatment with ziftomenib plus venetoclax/azacitidine has induced prolonged durable remissions in mice with *KMT2A*-r AML xenografts
- Therefore, administration of ziftomenib in combination with standard-of-care (SOC) therapies may provide additional clinical benefit for patients with newly diagnosed or R/R *NPM1*-m and *KMT2A*-r menin-dependent AML

STUDY DESIGN

- KO-MEN-007 (NCT05735184) is a 2-part dose escalation (Phase 1a) and expansion (Phase 1b) study to evaluate the safety, tolerability, and preliminary clinical activity of ziftomenib in combination with non-intensive chemotherapy (NIC) and intensive chemotherapy (IC) in patients with *NPM1*-m and *KMT2A*-r AML
- During Phase 1a, the ziftomenib dose will be escalated with standard doses of either venetoclax and azacitidine (zifto/ven/aza) or cytarabine and daunorubicin (zifto/7+3) in defined genetic cohorts (*NPM1*-m and *KMT2A*-r) using a rule-based approach (n=6 per cohort/dose level) to select ziftomenib doses for expansion/validation in Phase 1b (**Figure 2**)
- The Phase 1b portion will also evaluate zifto/ven/aza in newly diagnosed AML (*KMT2A*-r and *NPM1*-m) and zifto/ven in R/R AML (*NPM1*-m only) (**Figure 2**)

FIGURE 2. STUDY DESIGN

PHASE 1 ZIFTOMENIB COMBINATION CLINICAL TRIAL IN PATIENTS WITH *NPM1*-MUTANT OR *KMT2A*-REARRANGEMENT 1L OR R/R AML



AML, acute myeloid leukemia; *KMT2A*-r, lysine[K]-specific methyltransferase 2A-rearrangment; *NPM1*-m, nucleophosmin 1-mutations; R/R, relapsed or refractory.

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STUDY DESIGN (CONT)

TABLE 1. KEY OBJECTIVES AND ENDPOINTS

Objectives	Endpoints
Primary	
Determine the safety and tolerability	• Rate of DLT per dose level • Descriptive statistics of AEs per the NCI-CTCAE v 5.0
Determine the preliminary clinical activity	• CR[a]
Secondary	
Evaluate survival, disease control outcomes, markers for clinical activity	• CRc (CR, CRi, or CRh)[a] or MLFS rate[a] • MRD by MFC and molecular analyses (NGS, PCR) • Median OS, median EFS, EFS at 1 year • Proportion of patients alive at 1 year • Median duration of remission • Proportion of patients who undergo HSCT • Rate of transfusion independence
Evaluate pharmacokinetics and pharmacodynamics	• Multiple dose: C_{max}, T_{max}, $AUC_{(0\text{-last})}$, $AUC_{(tau)}$, accumulation ratio
Exploratory	
Assess biomarkers for efficacy, resistance, and pharmacodynamics, and for activity in isolated myeloid sarcoma	• Prevalence and analysis of biochemical, cytogenetic, and molecular biomarkers in blood and BM collected at diagnosis, on-treatment, and at relapse • Characterization of Bcl-2 family members and gene expression from blood and BM collected before and after administration of the ven/aza/zifto combination • Investigator assessed treatment responses per institutional guidelines

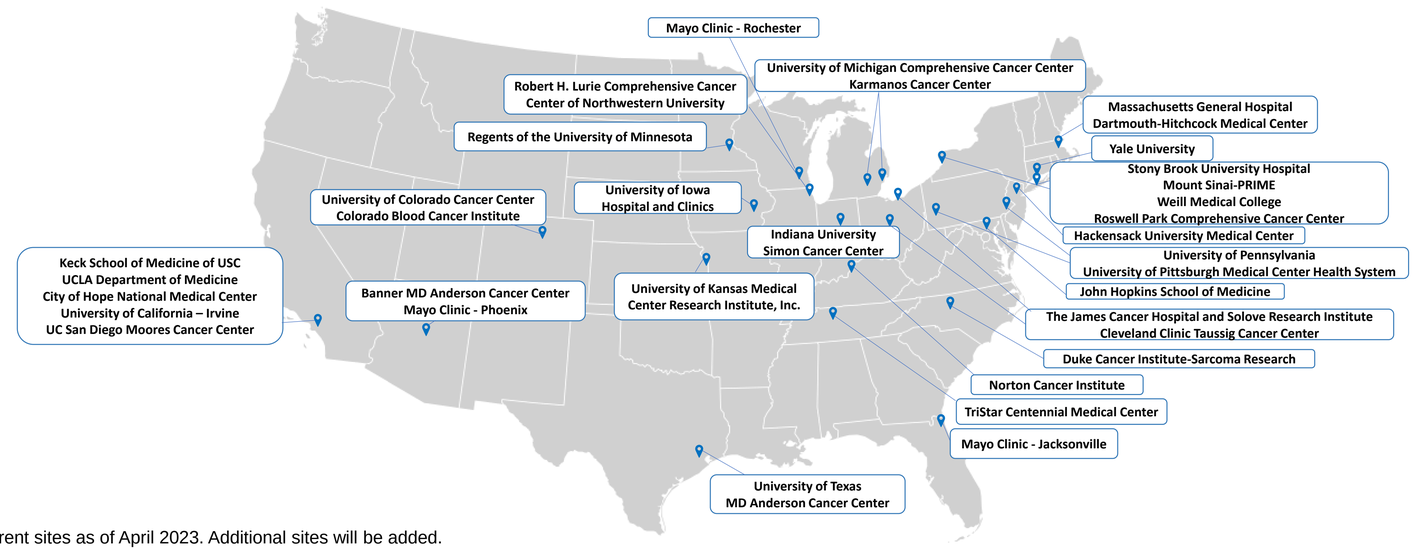
[a]CR, CRc, or MLFS rate determined using the ELN 2022 criteria.
AE, adverse event; $AUC_{(0\text{-last})}$, area under the concentration-time curve from time zero to the time of the last quantifiable concentration after dosing; $AUC_{(tau)}$, area under the concentration-time curve over a dosing interval; aza, azacytidine; Bcl-2, B-cell lymphoma 2; BM, bone marrow; C_{max}, maximum plasma concentration; CR, complete remission; CRc, composite complete remission; CRh, complete remission with partial hematologic recovery; CRi, complete remission with incomplete hematologic recovery; DLT, dose-limiting toxicity; EFS, event-free survival; ELN, European Leukemia Network; HSCT, hematopoietic stem cell transplant; MFC, multiparameter flow cytometry; MLFS, morphologic leukemia-free state; MRD, measurable residual disease; NCI-CTCAE, National Cancer Institute Common Terminology for Adverse Events; NGS, next-generation sequencing; OS, overall survival; PCR, polymerase chain reaction; T_{max}, time to maximum plasma concentration; ven, venetoclax; zifto, ziftomenib.

TABLE 2. KEY INCLUSION AND EXCLUSION CRITERIA

Inclusion Criteria	Exclusion Criteria
• ≥18 years of age diagnosed with AML[a] with documented *NPM1*-m or *KMT2A*-r • Newly diagnosed *NPM1*-m patients must also be *FLT3* wild-type, not eligible for *FLT3* targeted treatment • R/R cohorts: relapsed or refractory to prior therapy or development of new extramedullary disease and have failed at least one prior line of therapy	• Diagnosis of promyelocytic leukemia or blast chronic myelomonocytic leukemia; history of *BCR-ABL* alteration
• ECOG performance status: 0, 1, or 2	• For newly diagnosed cohorts: has received prior chemotherapy for leukemia, except hydroxyurea and/or leukapheresis to control leukocytosis, prior treatment with all-transretinoic acid for initially suspected acute promyelocytic leukemia, or non-HMA therapy for prior myelodysplastic syndrome • For R/R cohorts: has received chemotherapy, immunotherapy, radiotherapy (unless if given for management of CNS leukemia), or any ancillary therapy that is considered to be investigational (ie, used for non-approved indications[s] and in the context of a research investigation) <14 days prior to the first dose of ziftomenib or within 5 drug half-lives prior to the first dose of study drug
• Adequate and stable renal, hepatic, and cardiac function	• Active CNS involvement • Active HIV, Hepatitis B or C infection, or other active and uncontrolled infection • Unstable or uncontrolled cardiac conditions

[a]Per WHO Classification of Hematolymphoid Tumors (5th Edition). AML, acute myeloid leukemia; APML, acute promyelocytic leukemia; CNS, central nervous system; ECOG, Eastern Cooperative Oncology Group; ELN, European Leukemia Network; *FLT3*, FMS-like tyrosine kinase 3; HIV, human immunodeficiency virus; HMA, hypomethylating agents; *KMT2A*-r, lysine[K]-specific methyltransferase 2A rearrangement; MDS, myelodysplastic syndromes; *NPM1*-m, nucleophosmin 1 mutation; R/R, relapsed/refractory; WHO, World Health Organization.

FIGURE 3. ENROLLMENT MAP[a]



[a]Current sites as of April 2023. Additional sites will be added.

SUMMARY

- KO-MEN-007 will determine the safety, tolerability, and preliminary clinical activity of ziftomenib in combination with NIC and IC in newly diagnosed or R/R patients with *NPM1*-m and *KMT2A*-r AML

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