KOMET-008: A Phase 1 Study to Determine the Safety and Tolerability of Ziftomenib Combinations for the Treatment of KMT2A-rearranged or NPM1-mutant Relapsed/Refractory Acute Myeloid Leukemia

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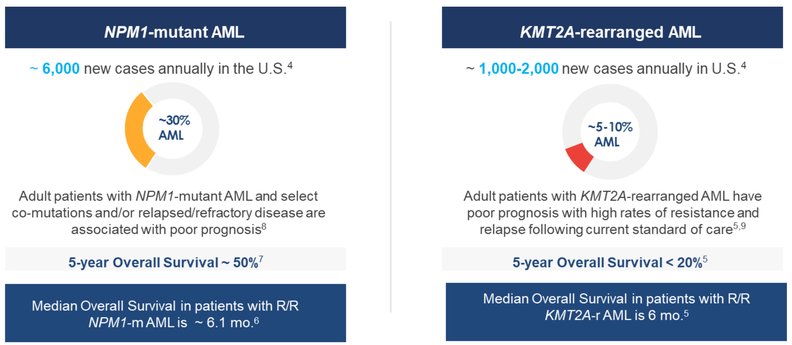
komet-008
ACUTE LEUKEMIAS
KURA KO-MEN-008

BACKGROUND

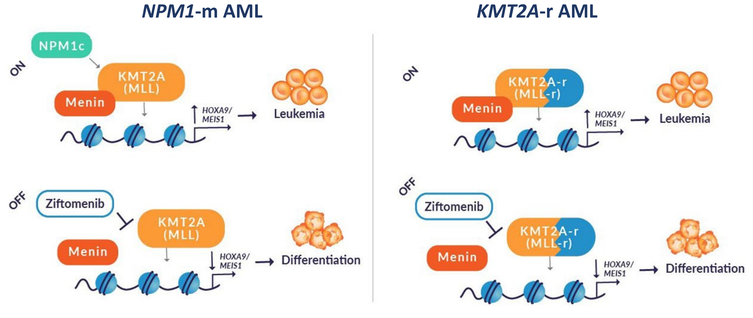
- Relapsed/refractory (R/R) acute myeloid leukemia (AML) with nucleophosmin 1 (*NPM1*) mutations or lysine[K]-specific methyltransferase 2A (*KMT2A*) rearrangements represent a high unmet need, with no currently approved targeted therapies (**Figure 1**).[1-3]
- There are approximately 6,000 new cases of *NPM1*-mutant (*NPM1*-m) AML and 1,000 to 2,000 new cases of *KMT2A*-rearranged (*KMT2A*-r) AML each year in the United States.[4]
- Adult R/R AML patients harboring *NPM1* mutations or *KMT2A* rearrangements have poor prognoses, with median overall survivals of approximately 6 months (**Figure 1**).[5,6]

FIGURE 1. *NPM1*-m AND *KMT2A*-r AML



- *NPM1*-m and *KMT2A*-r AML subtypes are dependent on the protein-protein interaction between menin and histone-lysine-N-methyltransferase 2A (KMT2A), a central regulator of target genes driving leukemic transformation in AML subtypes (**Figure 2**).[10-12]
- Ziftomenib is an oral investigational drug that is a potent and selective inhibitor of the protein-protein interaction between menin and KMT2A (**Figure 2**).[10-12]
- Preclinical studies have demonstrated that ziftomenib effectively triggers myeloid differentiation and produces anti-leukemic effects in *NPM1*-m and *KMT2A*-r AML cellular and in vivo models.[13,14]
- Furthermore, the antitumor activity of menin inhibitors in preclinical models of *KMT2A*-r and *NPM1*-m AML is enhanced by the addition of FLT3 inhibitors such as gilteritinib.[15,16]
- In an ongoing Phase 1/2 study (KO-MEN-001; NCT04067336) in patients with heavily pre-treated R/R AML, ziftomenib 600 mg monotherapy was well tolerated and demonstrated meaningful clinical activity in *NPM1*-m AML, with a complete remission (CR) rate of 35.0% (n=20), and in *KMT2A*-r AML, with a composite CR rate of 16.7% (n=18).[17]
- This encouraging preliminary clinical activity and safety/tolerability profile of ziftomenib support its clinical investigation in combination with standard therapies, which may lead to improved outcomes for these genetically defined AML patients.
- KOMET-008 (KO-MEN-008; NCT06001788) is a Phase 1 clinical trial being conducted to evaluate the safety and preliminary clinical activity of ziftomenib in combination with standard-of-care (SOC) therapies in patients with R/R *NPM1*-m or *KMT2A*-r AML.

FIGURE 2. ZIFTOMENIB MECHANISM OF ACTION



AML, acute myeloid leukemia; *KMT2A-r*, lysine[K]-specific methyltransferase 2A-rearranged; *HOXA9*, homeobox A9; *MEIS1*, meis homeobox 1; *MLL*, menin-mixed-lineage leukemia; MLL-r, *MLL*-rearranged; NPM1c, cytoplasmic NPM1; NPM1c, cytoplasmic nucleophosmin 1; *NPM1*-m, nucleophosmin 1-mutant; XPO1, exportin 1.

BACKGROUND (CONT)

ZIFTOMENIB MECHANISM OF ACTION

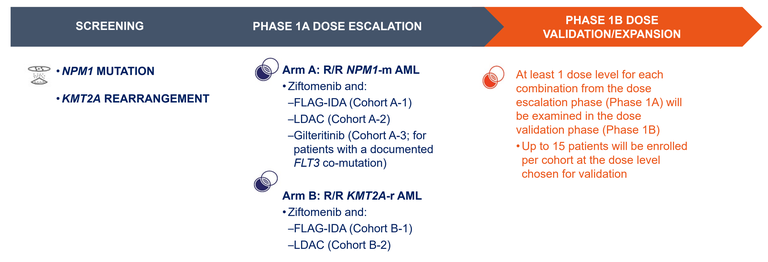
- Genetic rearrangements of *KMT2A* lead to aberrant expression of homeobox (*HOX*) genes and their DNA-binding cofactor *MEIS1*, which leads to proliferation, stemness and differentiation block of bone marrow cells.[11,18,19]
- Rearrangements involving *KMT2A* alter the gene's normal histone methyltransferase function, maintaining elevated HOX expression and sustaining the hematopoietic differentiation blockade, while the menin-binding motif is preserved throughout all KMT2A fusion proteins.[11,18,20] Likewise, the leukemic gene expression program is dependent on NPM1-m interacting with menin and wild-type KMT2A.[1,2,11]
- Inhibition of the menin–KMT2A interaction disrupts the assembly of oncogenic KMT2A wild-type or fusion complexes on chromatin and studies have demonstrated that menin inhibition downregulates *HOX* and *MEIS1* transcription leading to differentiation of leukemic blasts.[10,18]

STUDY DESIGN

- KOMET-008 is a 2-part dose-escalation (Phase 1A) and expansion (Phase 1B) clinical trial to evaluate the safety, tolerability, and preliminary clinical activity of ziftomenib when combined with SOC regimens for the treatment of either *NPM1*-m or *KMT2A*-r R/R AML.
- During Phase 1A, the ziftomenib dose will be escalated with gilteritinib, FLAG-IDA, or LDAC in separate genetically-defined cohorts (*NPM1*-m and *KMT2A*-r). Initially, 6 patients will be treated at DL1 within the respective cohort. Dose escalation within each cohort will occur independently following a rule-based approach based on a i3+3 design to select ziftomenib doses for expansion/validation in Phase 1B (**Figure 3**).
- Study objectives/endpoints and key inclusion and exclusion criteria are shown in Table 1 and Table 2, respectively.

FLAG-IDA, fludarabine, cytarabine (Ara-C), granulocyte-colony stimulating factor (G-CSF), and idarubicin; LDAC, low-dose cytarabine.

FIGURE 3. KOMET-008 STUDY DESIGN



AML, acute myeloid leukemia; FLAG-IDA, fludarabine, cytarabine, granulocyte-colony stimulating factor, and idarubicin; *KMT2A-r*, lysine[K]-specific methyltransferase 2A-rearranged; LDAC, low-dose cytarabine; *NPM1*-m, nucleophosmin 1-mutant; R/R, relapsed or refractory.

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STUDY DESIGN (CONT)

TABLE 1. KEY OBJECTIVES AND ENDPOINTS

Objectives	Endpoints
Primary	
Determine safety and tolerability	• Rate of DLT per dose level • Descriptive statistics of AEs per the NCI-CTCAE v 5.0
Secondary	
Evaluate clinical activity	• CR for FLAG-IDA, LDAC combinations in patients with *KMT2A*-r or *NPM1*-m R/R AML • CR/CRh in combination with gilteritinib in *NPM1*-m patients with a documented *FLT3* mutation
Evaluate survival and disease control outcomes	• CRc (CR+CRi+CRh) and MLFS rates[15] • OS and 6-month OS • Median EFS and 6-month EFS • Duration of remission • MRD assessment in BM by flow cytometry and molecular analysis (PCR, NGS) • Proportion of patients that undergo HSCT • Rate of transfusion independence
Characterize the PK of ziftomenib and metabolites when administered in combination	• Cmax, Tmax, AUC(0-last), AUC(tau)
Evaluate the PK of gilteritinib when administered concurrently with ziftomenib	• Cmax, Tmax, AUC(0-last), AUC(tau)

[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; 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; zifto, ziftomenib.

TABLE 2. KEY INCLUSION AND EXCLUSION CRITERIA

Inclusion Criteria

- Adults (≥18 years of age) diagnosed with AML[a] who relapsed following or were refractory (R/R) to ≥1 prior line of therapy
- Documented *NPM1*-m or *KMT2A*-r AML
- For gilteritinib combination only: documented *FLT3* mutation (internal tandem duplication [ITD] or tyrosine kinase domain mutation) in BM or peripheral blood following completion of immediate prior therapy, as measured by the established threshold of the chosen assay (polymerase chain reaction [PCR], next-generation sequencing [NGS], etc).
- ECOG performance status: 0, 1, or 2
- Adequate and stable renal, hepatic, and cardiac function

Exclusion Criteria

- Diagnosis of promyelocytic leukemia or blast chronic myeloid leukemia
- Clinically active CNS leukemia
- Active and uncontrolled infection
- Mean corrected QT interval by Fredericia's formula (QTcF) >480 ms on triplicate 12-lead ECGs performed within approximately 5 minutes of each other
- Clinical signs/symptoms of leukostasis or WBC >25×10^9/L.
- Has received prior stem cell transplant and has not adequately recovered
- Has received radiation, chemotherapy, immunotherapy, or any other anticancer therapy including investigational therapy <14 days or within 5 drug half-lives (whichever is shorter) prior to the first dose of study intervention

[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-rearranged; MDS, myelodysplastic syndromes; *NPM1*-m, nucleophosmin 1-mutant; R/R, relapsed/refractory; WHO, World Health Organization.

SUMMARY

- KOMET-008 will determine the safety, tolerability, and preliminary clinical activity of ziftomenib in combination with gilteritinib, FLAG-IDA, and LDAC SOC regimens for the treatment of *NPM1*-m and *KMT2A*-r R/R AML.