BACKGROUND

Relapsed/refractory (RR) acute myeloid leukemia (AML) with nucleophosmin 1 (NPM1) mutations or tyrosine kinase domain (TKD) specific methylationtransferase 2A (KMT2A) rearrangements represent a high unmet need, with currently approved targeted therapies (Figure 1a).1,2

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.3

Adult R/R AML patients harboring NPM1 mutations or KMT2A rearrangements have poor prognoses, with median overall survivals of approximately 6 months (Figure 1b).1,3

Ziftomenib (KOMET-008) is a Phase 1/2 clinical trial being conducted to evaluate the safety and tolerability of ziftomenib in combination with standard of care (SOC) therapies in patients with NPM1-m or KMT2A-r AML (Figure 2).

Figure 2. ZIFTOMENIB MECHANISM OF ACTION

• 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 2a).4

• Ziftomenib is an oral investigational drug that is a potent and selective inhibitor of the protein-protein interaction between menin and KMT2A (Figure 2b).4

Pharmacodynamic studies have demonstrated that ziftomenib effectively targets myeloid differentiation and produces anti-leukemic effects in NPM1-m and KMT2A-r AML cellular and in vivo models.5,6

Furthermore, the antitumor activity of menin inhibitors in preclinical models of NPM1-m and KMT2A-r AML is enhanced by the addition of FLT3 inhibitors such as gilteritinib.7

In an ongoing Phase 1/2 study (KO-MEN-004; NCT04047361) in patients with heavily pre-treated R/R AML, ziftomenib 850 mg mouthwash 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 complete CR rate of 16.7% (n=10).8

This encouraging preliminary activity and tolerability profile of ziftomenib supports its clinical investigation in combination with standard-of-care treatments, which may lead to improved outcomes for these genetically defined AML patients.9

KOMET-008 (KO-MEN-008; NCT06001788) is a Phase 1 clinical trial being conducted to evaluate the safety and tolerability of ziftomenib in combination with standard of care (SOC) therapies in patients with R/R AML (Figure 3).

Figure 3. KOMET-008 STUDY DESIGN

• Genetic rearrangements of KMT2A lead to abnormal expression of homeobox (HOX) genes and their DNA-binding cofactor MEIS1, which leads to proliferation, stemness and differentiation block of bone marrow cells.9,10

• Rearrangements involving KMT2A alter the gene’s normal histone methylation transferase function, maintaining elevated HOX expression and sustaining the hematopoietic differentiation blockade, while the menin-binding motif in the menin target diagent interacts with KMT2A fusion proteins.11,12

• Inhibition of the mutant-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.9,10

STUDY DESIGN

DEFINITIONS

• CR: Complete remission (CR); CRi: complete remission with incomplete hematologic rescue; CRh: complete remission with partial hematologic recovery; CRp: complete remission with partial hematologic recovery; CR with complete remission with partial hematologic recovery; CRp/h: complete remission with partial hematologic recovery; CR with partial response; CR with hematologic improvement; MRC: Medical Research Council; PR: partial response; CRp: complete remission with partial hematologic recovery; CRi: complete remission with incomplete hematologic recovery; CRh: complete remission with partial hematologic recovery.

• KMT2A-r AML: AML with KMT2A rearrangements have poor prognoses, with median overall survivals of approximately 6 months (Figure 2).10-12

• FLT3-ITD: Internal tandem duplication of FLT3

• NPM1-m: NPM1 bi-allelic mutations in both AML alleles

• NPM1c: Cytoplasmic NPM1

• NPM1-m: NPM1 mutant (nucleophosmin 1-mutant); R/R, relapsed or refractory.

• KMT2A-r: KMT2A-rearranged; NPM1c, cytoplasmic nucleophosmin 1; NPM1c, cytoplasmic

• AML, acute myeloid leukemia; FLAG-IDA, Fludarabine, cytarabine, daunorubicin, and mitoxantrone; LDAC, low-dose cytarabine; NPM1, nucleophosmin 1; KMT2A, lysine [K]-specific methyltransferase 2A; R/R, relapsed or refractory.

REFERENCES


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.

TABLE 2. KEY INCLUSION AND EXCLUSION CRITERIA

Inclusion Criteria

• Adults (≥18 years of age) diagnosed with AML 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 [TKD] mutation) in a 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 prolymphocytic leukemia or blast chronic myeloid leukemia.

• Clinically active CNS leukemia.

• Active and uncontrolled infection.

• Mean corrected QT interval by Fridericia’s formula (QTf) >460 ms on trilapide-12 lead ECGs performed within approximately 5 minutes of each other.

• Clinical signs/symptoms of leukostasis or WBC ≥10^10/L.

• Has received prior stem cell transplant and has not adequately recovered.

• Has active radiation, chemotherapy, immunotherapy, or any other anticancer therapy including investigational therapy <4 days or within 5 drug half-lives (whichever is shorter) prior to the first dose of study intervention.