A Novel Small Molecule Menin-MLL Inhibitor for Potential Treatment of MLL-rearranged Leukemias

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Introduction
Patients with MLL-rearranged leukemia typically have a poor prognosis. With chemotherapy and stem cell transplantation as current standard of care, the 5-year survival rate is estimated to be 46%. As the leukemogenic activity of MLL fusion proteins has been shown to be dependent on their direct interaction with menin, development of small molecules that block the menin-MLL interaction is a promising therapeutic strategy for the treatment of this disease.

We describe KO-539, a menin-MLL inhibitor with optimized drug-like properties that demonstrates potential clinical utility in preclinical models of MLL leukemias. The compound is currently under further preclinical evaluation.

Background
• MLL+ leukemias are an aggressive type of blood cancer, predominantly in children and therapy-related leukemia in adults
• Chromosomal translocations in the MLL gene at 11q23 result in MLL fusions with any of more than 50 partner genes
• MLL fusion proteins drive leukemogenesis through deregulation of HOX and MEIS genes
• The leukemogenic activity of MLL fusion proteins is critically dependent on menin binding

KO-539 is a potent and selective menin inhibitor identified through structure-based optimization of a HTS hit

KO-539 demonstrates robust efficacy and a durable response in subcutaneous MV4;11 leukemia xenograft model in mice

Characterization of the menin-MLL complex

KO-539 modulates pharmacodynamic (PD) biomarkers in the disseminated MV4;11 leukemia model in mice

KO-539 extends survival in the aggressive systemic MOLM-13 leukemia model in mice

Conclusions
• KO-539 is a highly potent and selective inhibitor of the menin-MLL interaction
• KO-539 demonstrates robust, sustained tumor inhibition in subcutaneous and disseminated models of MLL-re leukemias; in vivo activity correlates with PD and target gene expression modulation
• KO-539 demonstrates acceptable tox profiles and drug-like properties
• KO-539 has been selected as a development candidate
• Additional efforts are underway to assess potential utilities of menin-MLL inhibitors in additional hematologic malignancies and solid tumor indications

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