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

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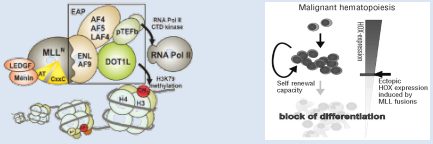
Introduction

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 40%. 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.

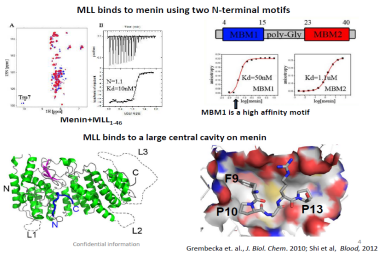
We describe KO-539, a menin-MLL inhibitor with optimized drug-like properties that demonstrates potential clinical utility in preclinical models of MLL leukemias. The compound is currently under further preclinical evaluation.

Background

- MLL-r 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

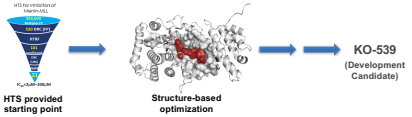


Characterization of the menin-MLL complex



Grembecka et. al., *J. Biol. Chem.* 2010; Shi et al, *Blood*, 2012

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

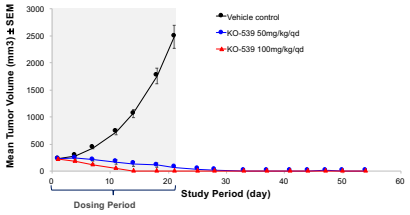


Cell Lines with MLL Fusions as drivers (GI_{50})		Biochemical Assay (IC_{50})	
Murine BM Cell Line (rMLL-AF9)	7 nM	MLL(4-43)/Menin Binding	22 nM
MV4;11 (MLL-AF4 AML)	15 nM	Control Cell Lines without MLL Fusions (GI_{50})	
MOLM13 (MLL-AF9 AML)	16 nM	REH	1.5 μM
KOPN8 (MLL-ENL AML)	20 nM	U937	> 6 μM
RS4;11 (MLL-AF4 ALL)	23 nM	K562	> 6 μM
SEM (MLL-AF4 ALL)	17 nM	KG-1	> 4.5 μM

- KO-539 shows good biochemical and cellular activity
- KO-539 displays greater than 50-fold selectivity over cell lines without the MLL fusion

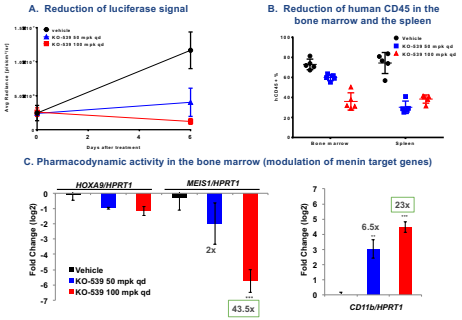
KO-539 demonstrates robust efficacy and a durable response in subcutaneous MV4;11 leukemia xenograft model in mice

Subcutaneous MV4;11 model



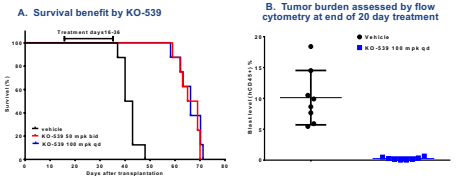
- Tumor regression was observed at 50 and 100 mpk (oral dosing)
- Durable tumor growth inhibition: tumors were undetectable 30 days after cessation of dosing
- KO-539 is well tolerated at tested dose levels

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



- Dosing initiated 19 days post tumor implantation and continued for 6 days
- KO-539 reduces tumor burden relative to the vehicle in the bone marrow and the spleen
- KO-539 dose dependently modulated expression of menin-MLL associated PD markers

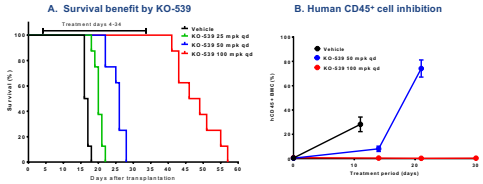
KO-539 displays survival benefit in the disseminated MV4;11 leukemia model



	Vehicle	KO-539 @ 50 mpk bid	KO-539 @ 100 mpk qd
Mean Survival	41.5 days	67 days	66 days

- KO-539 significantly prolongs mouse survival compared to the vehicle control group
- Survival benefit correlates with reduction of human leukemia blasts (hCD45+) in the mice

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



	Dose	Median Survival	Survival Benefit
Vehicle	-	16.5 days	-
KO-539	25 mpk qd	20 days	3.5 days
	50 mpk qd	26 days	9.5 days
	100 mpk qd	47.5 days	31 days

- KO-539 provides dose-dependent survival benefit in the aggressive disseminated MOLM13 leukemia model
- The observed survival benefit correlates with human blasts reduction

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-r 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 hematological malignancies and solid tumor indications

Acknowledgements

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