A novel small molecule menin-MLL inhibitor for potential treatment of MLL-rearranged leukemias and NPM1/DNMT3A-mutant AML

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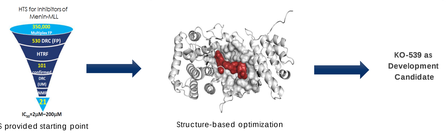
Introduction and background

Patients with MLL-rearranged leukemia typically have a poor prognosis and no targeted therapies are yet available. As the leukemogenic activity of MLL fusion proteins is dependent on their direct interaction with menin, development of small molecules that block the menin-MLL interaction is a promising therapeutic strategy for this disease. In addition, recent reports have implicated menin-MLL signaling in some forms of MLL wild-type AML, including those bearing oncogenic mutations in NPM1 and DNMT3A – which together represent 45% of cases of AML – suggesting that menin-MLL inhibitors could provide clinical benefit in a broader population of AML patients than originally envisioned.

We have recently reported a novel, potent, and selective small molecule menin-MLL inhibitor, KO-539, that effectively treats MLL leukemias in in vivo models, demonstrating its potential clinical utility. The compound potently inhibits the growth of MLL-rearranged cell lines, displays favorable PK properties, and is remarkably effective in both the MV4;11 and MOLM13 disseminated leukemia models.

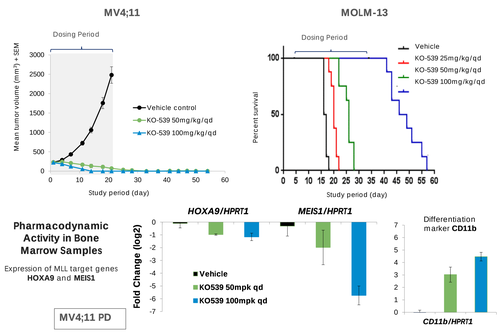
Here we report that KO-539 is highly effective in two independent models of MLL wild-type AML, displaying robust and persistent antitumor activity when dosed orally daily at well-tolerated doses.

KO-539 is a potent & selective menin-MLL inhibitor with robust activity in models of MLL-rearranged AML

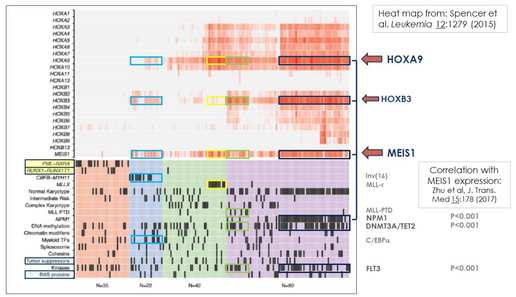


Cell Lines with MLL Fusions as drivers (GI_{50})		Biochemical Assay (IC_{50})	
Murine BM Cell Line (rMLL-AF9)	7 nM	MLL(4-43)/Menin Binding	22 nM
MV4;11 (MLL-AF4 AML)	15 nM	**Control Cell Lines without MLL Fusions (GI_{50})**	
MOLM13 (MLL-AF9 AML)	16 nM	REH	1.5 µM
KOPN8 (MLL-ENL AML)	20 nM	U937	> 6 µM
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 >50 fold selectivity over non-MLL fusion cell lines



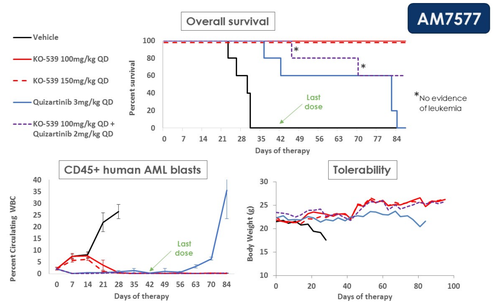
Overexpression of menin-MLL target genes HOXA9 and MEIS1 is strongly linked to several mutationally-defined subsets of AML



Characteristics of AML PDX models

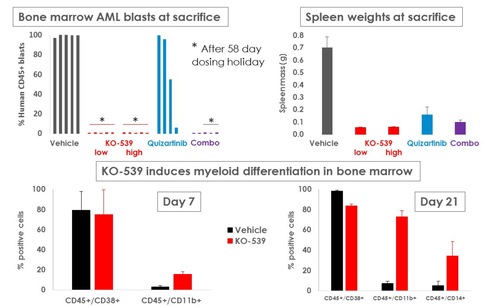
Model	Vendor	Genotype				SOC data
		NPM1	DNMT3A	IDH1/2	FLT3	
AM7577	Crown Bio	L287fs	R882H	IDH2 R140Q	ITD	Resistant to Ara-C
LEXFAM 2734	CRL Oncotest	L287fs	WT	IDH1 R132H	N841K	Resistant to decitabine

KO-539 produces lasting complete remissions in a NPM1/DNMT3A/IDH2/FLT3-mutant AML model



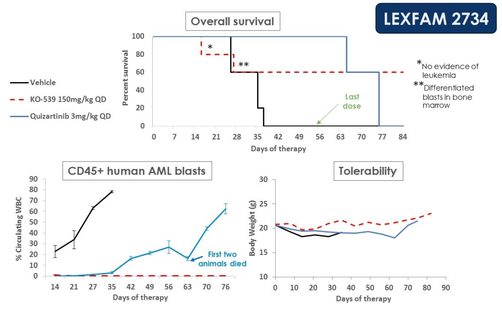
- 10/10 single-agent KO-539-treated animals at both dose levels cleared their leukemia and became long-term survivors
- Tumor growth inhibition was durable - no leukemia was detectable in blood or bone marrow two months after cessation of dosing
- KO-539 was well tolerated at tested dose levels
- Comparator compound was initially active but all animals eventually relapsed

KO-539 clears bone marrow blasts and induces myeloid differentiation in AM7577 AML model



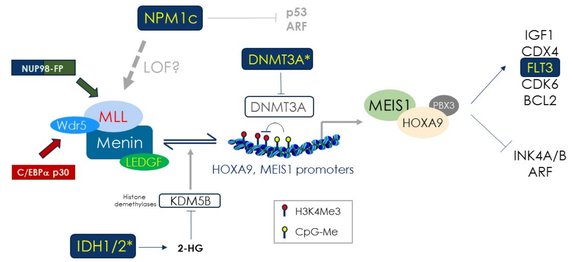
- The bone marrow of all KO-539-treated animals was cleared of AML blasts, even two months after cessation of therapy
- Spleen weights were within the normal range in KO-539-treated mice
- Myeloid lineage differentiation of AML blasts was detectable within 7 days of treatment initiation and largely complete within 21 days

KO-539 produces lasting complete remissions in a NPM1/IDH1/FLT3-mutant AML model



- Three of five KO-539-treated animals were long-term survivors with no evidence of peripheral leukemia
- Of the two KO-539-treated animals that did not survive, one succumbed early with no evidence of leukemia and the other contained differentiated blasts in the bone marrow
- Comparator compound was initially active but all animals eventually relapsed

A central role for menin-MLL in epigenetic dysregulation in AML



Lu et al *Cancer Cell* 30:92 (2017); Ferreira et al *Oncogene* 35:3079 (2016); Jeong et al *Nat. Genet.* 46:17 (2014); Wang et al *Blood* 106:245 (2005); Chowdhury et al *EMBO Rep.* 12:463 (2011); Greblen et al *Nat. Chem. Biol.* 11:471 (2015); Xu et al *Cancer Cell* 30:1 (2016); Collins et al *Curr. Opin. Hematol.* 23:534 (2016)

Conclusions

- KO-539 is a potent, selective small molecule menin-MLL inhibitor designed for therapy of MLL-rearranged AML, but…
- Robust antitumor activity of KO-539 is also observed in disseminated $NPM1^{mut}$ /$DNMT3A^{mut}$/$IDH2^{mut}$/FLT3-ITD and $NPM1^{mut}$/$IDH1^{mut}$/$FLT3^{mut}$ AML PDX models
- Preliminary PD data suggests that KO-539 exerts antileukemic activity by induction of myeloid differentiation in AML blasts
- The menin-MLL complex appears to be a central node in epigenetic dysregulation driven by several distinct oncogenic driver mutations known to be important in diverse leukemias and myeloproliferative disorders
- Oncogenic HOXA9/MEIS1 overexpression may be driven by MLL fusions in MLL-r AML or by wild-type menin-MLL in NPM1, DNMT3A and IDH1/2 mutants
- Menin-MLL inhibitors could provide clinical benefit in a broader population of AML patients than originally envisioned
- Potential indications include AML, ALL, MDS, CMML and CML

Acknowledgements

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