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

KO-539 is a potent, selective small molecule menin-MLL inhibitor designed to target MLL-rearranged leukemias and NPM1/DNMT3A-mutant AML. KO-539 displays >50 fold selectivity over non-MLL fusion cell lines and is remarkably effective in both the MV4;11 and MOLM13 disseminated wild-type AML, displaying robust and persistent antitumor activity when dosed orally daily at well-tolerated doses.

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

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

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

KO-539 is a potent, selective small molecule menin-MLL inhibitor designed for therapy of MLL-rearranged AML, but…

Conclusions

- KO-539 is a potent, selective small molecule menin-MLL inhibitor designed for therapy of MLL-rearranged AML.
- Robust antitumor activity of KO-539 is also observed in disseminated NPM1mut/DNMT3Amut/IDH2mut/FLT3-ITD and NPM1mut/DNMT3Amut/IDH2mut/FLT3mut 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 HDX9/BBS1 overexpression may be driven by MLL fusions in NPM1mut/AML or by wild-type menin-MLL in NPM1mut/DNMT3A or IDH2mut 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

- We would like to thank Mengmeng Yang, Shiqiang Li and Jinping Liu from Crown Bio (China) and Eva Oswald and Natalie Kuhn from Charles River Laboratories/Oncology (Germany) for their sterling work on the technically challenging disseminated AML PDX models.