The menin inhibitor zitomiben (KO-539) synergizes with agents targeting chromatin regulation or apoptosis and sensitizes AML with MLL rearrangement or NPM1 mutation to venetoclax.


1. Department of Hematology and Medical Oncology, University Medical Center, Johannes Gutenberg-University, Mainz, Germany; 2. Department of Medical Oncology, Dana-Farber Cancer Institute, Boston, MA; 3. Kura Oncology, Inc., San Diego, CA, USA; 4. Department of Systems Biology, Beckman Research Institute, City of Hope, Duarte, CA, USA; 5. University Cancer Center Mainz, Mainz, Germany; 6. Department of Pediatric Oncology, Dana-Farber Cancer Institute, Boston, MA; 7. Division of Hematology/Oncology, Boston Children’s Hospital, Harvard Medical School, Boston, MA.

CONCLUSIONS

- Zitomiben has significant activity against NPM1mut and MLL-AML, suppresses specific leukemic gene expression, and induces differentiation.
- Zitomiben exhibits synergistic leukemic cell killing in combination with drugs from various classes, targeting chromatin regulation & DNA damage (LSD1, PRMT5, PARP) and apoptosis & cell cycle (BCL2, AKT, CDK4/6).
- The combination with venetoclax has profound anti-apoptotic activity. Zitomiben-induced cellular priming may contribute to the synergistic effects.
- The combination of venetoclax and zitomiben exhibits synergistic anti-leukemic activity, and these data support clinic evaluation of the combination in the treatment of acute leukemias.

REFERENCES


INTRODUCTION

NPM1 mutated (NPM1mut) and MLL-rearranged Acute Myeloid Leukemia (AML) are dependent on the interaction of the methyltransferase MLL and its cofactor menin to express a particular leukemogenic transcriptional program. This includes the aberrant expression of the self-renewal associated MEIS1, PBX3 and homeobox (HOX) transcription factor genes and their targets FLT3 and BCL2. Small-molecule inhibitors blocking the menin-MLL interaction reverse this gene expression program, induce differentiation, and have profound anti-leukemic activity against NPM1mut and MLL-leukemia models in vivo and in vitro. Zitomiben is one of five menin inhibitors currently assessed in a clinical phase II trial with reported explorative single-agent efficacy in relapsed or refractory AML.

AIMS & METHODS

To date, no single therapy has resulted in sustainable remission in AML. We designed a synergetic drug screen to identify effective combination partners to zitomiben and aimed to characterize the highly synergistic effects with the BCL2 inhibitor venetoclax.

1. In vitro single-agent efficacy of zitomiben was assessed by cell viability assays. To characterize treatment effects, differentiation was measured by CD11b surface expression, gene expression changes by RNA sequencing.
2. A drug synergy screen evaluated single and combined effects of zitomiben and 37 targeted compounds with known preclinical or clinical efficacy in AML.
3. Dose-dependent killing and IC50 values of single and combined zitomiben and venetoclax treatment was determined on various MLL- and NPM1mut cell lines in vitro. Treatment-induced apoptosis was assessed by Annexin V staining and Bcl2 profiling.
4. The drug combination was then validated in NPM1mut primary AML samples and in vivo in a MLL- in MLL411 xenograft model.

RESULTS

1. Zitomiben has profound and selective in vitro activity against MLL-r and NPM1mut AML and induces transcriptional downregulation of MEIS1, PBX3, FLT3, and BCL2.

2. Synergistic drug screen of zitomiben with 37 targeted drugs detects strong activity in MLL-r and NPM1mut AML.

3. The combination of zitomiben and venetoclax leads to synergistic anti-proliferative activity and pronounced apoptosis in vitro.

4. Combined treatment with zitomiben and venetoclax improves anti-leukemic effects in NPM1mut primary samples and NPM1 leukemia in vivo.

CONCLUSIONS

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