Clinical-Stage Menin Inhibitor KO-539 is Synergistically Active with Multiple Classes of Targeted Agents in KMT2A/MLL-r and NPM1-Mutant AML Models.


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Introduction
KMT2A/MLL-r and NPM1-Mutant AML Models

KO-539, a monovalent fragment of the polyclonal antibody KO-139, is an inhibitor of the Menin protein and is currently being evaluated in clinical trials. Recent studies demonstrated in vitro synergy between Menin inhibition and multiple classes of targeted agents in AML cell lines and patient-derived xenograft (PDX) models. In a phase I dose finding study, 33 patients were enrolled and treated with single-agent KO-539 or in combination with Venetoclax or nivolumab. The combination arm showed greater clinical benefit compared to single-agent KO-539. Here, we report on an ongoing phase I clinical trial (NCT04358268) evaluating KO-539 in adult patients with refractory or relapsed AML and a phase II clinical trial (NCT04061955) evaluating KO-539 in adult patients with NPM1-Mutant AML.

Methods

Conclusions

KO-539 synergestically inhibits clonal and disease outgrowth in AML cells and xenograft models. These findings are consistent with the dual impairment of the Menin-TAF complex and epigenetic dysregulation and suggest that KO-539 serves as an effective combinatorial cancer therapy for patients with NPM1-Mutant AML or high-risk MLL-r AML.