Menin Inhibitors in KMT2A-Rearranged and NPM1-Mutated Acute Leukemia: A Scoping Review of Safety and Efficacy

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Background

Menin inhibitors represent a promising class of targeted agents for patients with acute myeloid leukemia (AML), acute lymphoblastic leukemia (ALL), and mixed phenotype acute leukemia (MPAL) harboring KMT2A rearrangements or NPM1 mutations. The development of Menin inhibitors represents a landmark advancement in treating these challenging leukemia subtypes. Early-phase trials have substantiated Revumenib's therapeutic potential, demonstrating both safety and efficacy in patients with relapsed or refractory leukemias harboring KMT2Ar or mutated NPM1 (1,2)

Aim

To systematically review and critically analyze the current clinical evidence on emerging Menin inhibitors in acute leukemias, particularly KMT2A-rearranged and NPM1-mutated subtypes

Objectives

Examine the clinical development and implementation of menin inhibitors including its safety profile and clinical efficacy

Methods

- A scoping review of clinical trials investigating Menin inhibitors in acute leukemias was conducted, systematically searching peer-reviewed publications, conference abstracts, and clinical trial registries.
- Thirteen trials evaluating six agents (Revumenib, Ziftomenib, Bleximenib, BMF-219, DS-1594, and DSP-5336) were included
- Data were extracted for trial design, patient characteristics, mutation subtypes, response rates, MRD negativity, and treatment-related adverse events (TRAEs)

Summary

Menin inhibitors represent a promising targeted therapy for acute leukemias with KMT2A rearrangements and NPM1 mutations, disrupting leukemogenic HOX/MEIS1 transcriptional programs. Early clinical trials, highlighted by the FDA approval of Revumenib, demonstrate meaningful responses but also reveal challenges with resistance and durability, underscoring the need for optimized combination strategies

Results

- **Revumenib** achieved the first FDA approval for R/R KMT2A-rearranged AML, showing a 23% CR+CRh rate and frequent MRD-negative remission (1)
- **Ziftomenib** demonstrated strong efficacy in NPM1-mutated AML, with the 200 mg dose (3) showing the most promising outcomes.
- **Bleximenib** reported an overall response rate (ORR) of 93% (4)
- Early-phase agents (**BMF-219, DS-1594, DSP-5336**) are in development with limited but encouraging preliminary results
- Differentiation syndrome and resistance mutations were identified as key clinical challenges across trials

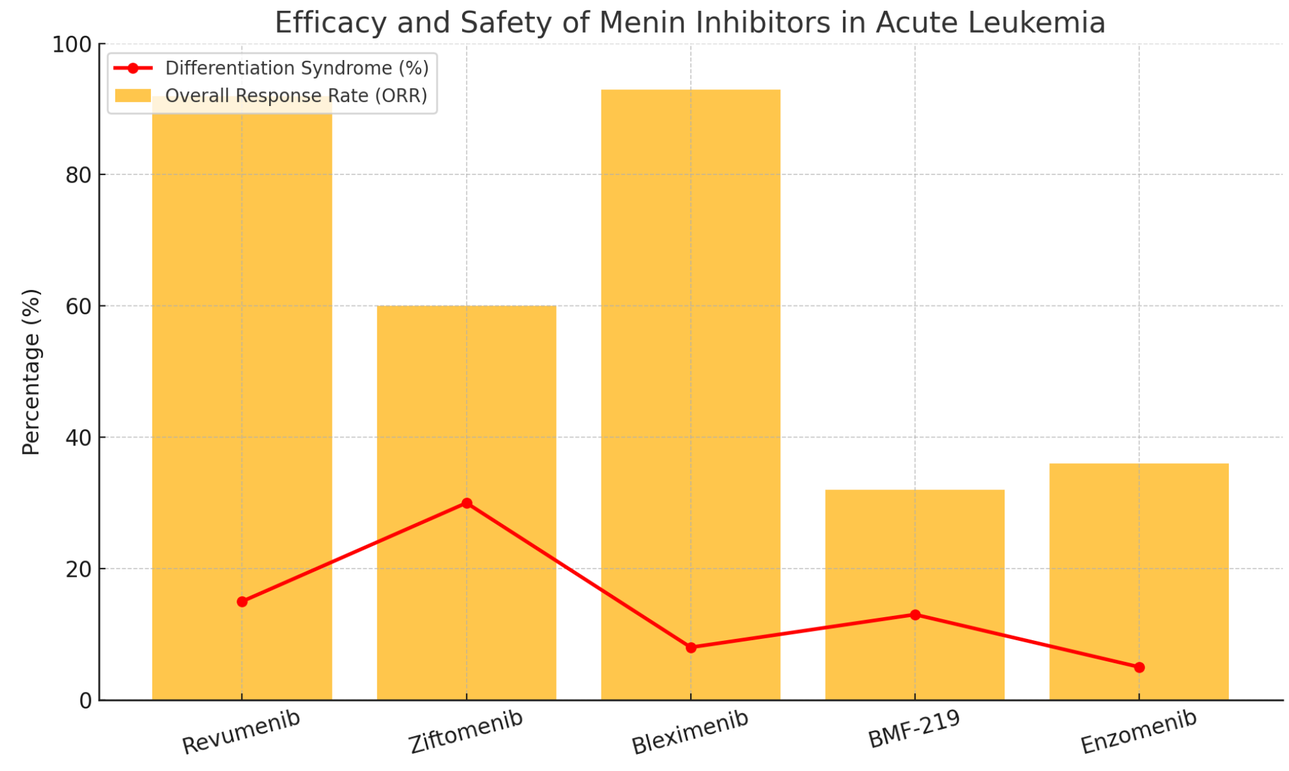


Figure 1. Comparison of Overall Response Rate (ORR) and Differentiation Syndrome (DS) incidence across Menin inhibitor trials.

Discussion

- Menin inhibitors target the critical Menin–KMT2A interaction, disrupting HOX/MEIS1-driven transcriptional programs in KMT2Ar and NPM1-mutated leukemias.
- Revumenib is the first FDA-approved Menin inhibitor, achieving MRD-negative remissions across pediatric and adult populations with KMT2A-rearranged AML.
- Ziftomenib shows strong activity in NPM1-mutated AML, while emerging agents (Bleximenib, BMF-219, DS-1594, DSP-5336) remain in earlier phases of development.
- Resistance mutations and limited durability highlight the need for combination strategies and ongoing clinical trials to optimize Menin inhibitor therapy
- Sustained suppression of HOX and MEIS1 expression emerges as a critical determinant of durable responses to Menin inhibition, reinforcing their role as central nodes in leukemic transcriptional addiction (5)

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