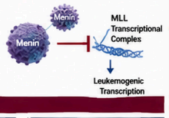
Comparative Efficacy and Safety of FDA-Approved Menin Inhibitors in Relapsed/Refractory NPM1-Mutated Acute Myeloid Leukemia: A Systematic Review and Meta-analysis

Mishal Tariq[1], Akshaya Junnuthula[2], Zahra Nawaz[3], Sushmitha Venkata Annadatha[4], Harshawardhan Dhanraj Ramteke[5], Sourav hazra[6], Rakhshanda khan[7]

[1]Rawalpindi Medical University, Rawalpindi, Pakistan; [2]Siddhartha Medical College, Hyderabad, India; [3]Cmh lahore medical and dental college, Lahore, Pakistan; [4]University of Perpetual Help system dalta - Jonelta Foundation School of Medicine, Philippines; [5]Rhythm heart and critical care hospitals, Nagpur, Maharashtra India; [6]College of Medicine and Sagore Dutta Hospital, Kolkata, India; [7]Ayaan institute of medical sciences, moinabad, Telangana, India;



INTRODUCTION

- NPM1 mutations occur in ~30% of AML and define a distinct molecular subgroup.
- Relapsed/refractory (R/R) NPM1-mutated AML has historically poor outcomes with limited effective targeted options.
- Menin inhibitors target the menin–MLL interaction, disrupting leukemogenic transcription.
- In 2025, revumenib and ziftomenib received FDA approval, marking a new era of targeted therapy.
- Comparative evidence on efficacy, molecular depth, and safety between these agents is limited.

OBJECTIVE

To compare the efficacy and safety of FDA-approved menin inhibitors in patients with relapsed/refractory NPM1-mutated acute myeloid leukemia through a systematic review and meta-analysis.

METHODS

Study Design: Systematic review and meta-analysis of registrational clinical trials of FDA-approved menin inhibitors in R/R NPM1-mutated AML.

Data Sources: Comprehensive search of PubMed, Embase, Web of Science, Cochrane Library up to May 2025.

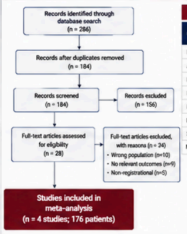
Inclusion Criteria: Clinical trials enrolling adults with R/R NPM1-mutated AML treated with revumenib or ziftomenib and reporting efficacy or safety outcomes.

Outcomes: CR/CRh rate (primary); MRD negativity among responders; key adverse events (QTc prolongation, differentiation syndrome); bridge to allogeneic hematopoietic stem-cell transplantation (allo-HCT).

Statistical Analysis: Random-effects pooled proportion models using Stata v18.0. Results reported as pooled proportions with 95% CI.

Risk of Bias: Assessed using Cochrane Risk of Bias tool (RoB 2.0).

STUDY FLOW & PATIENT DISPOSITION



RESULTS (N = 176 PATIENTS; 4 STUDIES)

BASELINE CHARACTERISTICS (N = 176)

Characteristic	Revumenib (n = 86)	Ziftomenib (n = 90)	Total (N = 176)
Median age, years (range)	61 (34–75)	60 (29–74)	60 (29–75)
Age ≥65 years, n (%)	36 (41.9)	37 (41.1)	73 (41.5)
Male, n (%)	53 (61.6)	55 (61.1)	108 (61.4)
ECOG PS 0–1, n (%)	62 (72.1)	64 (71.1)	126 (71.6)
Prior venetoclax exposure, n (%)	74 (86.0)	78 (86.7)	152 (86.4)
Median prior lines of therapy (range)	2 (1–6)	2 (1–5)	2 (1–6)
Secondary AML, n (%)	22 (25.6)	21 (23.3)	43 (24.4)
Median bone marrow blasts, % (range)	38 (10–90)	36 (12–88)	37 (10–90)

CR/CRh RATE (POOLED)

Revumenib	Ziftomenib
23.4% (95% CI: 13.5%–35.2%)	21.4% (95% CI: 14.2%–30.2%)

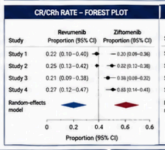
MRD NEGATIVITY AMONG RESPONDERS (POOLED)

Revumenib	Ziftomenib
45.0% (95% CI: 32.1%–58.2%)	61.0% (95% CI: 45.1%–74.3%)

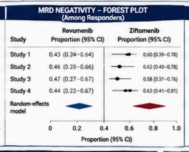
BRIDGED TO ALLO-HCT (POOLED)

20.0% (95% CI: 14.3%–26.8%)

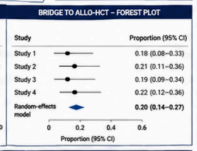
CR/CRh RATE – FOREST PLOT



MRD NEGATIVITY – FOREST PLOT (Among Responders)



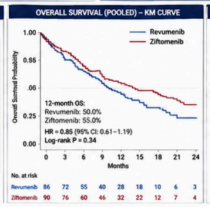
BRIDGE TO ALLO-HCT – FOREST PLOT



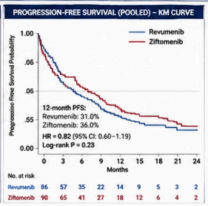
KEY SAFETY OUTCOMES (POOLED INCIDENCE)

	Revumenib (n = 86)	Ziftomenib (n = 90)
QTc Prolongation (Any Grade)	43.0% (95% CI: 31.4%–55.3%)	5.0% (95% CI: 2.0%–11.5%)
QTc Prolongation (Grade ≥3)	23.0% (95% CI: 18.2%–28.4%)	1.0% (95% CI: 0.2%–4.2%)
Differentiation Syndrome (Any Grade)	5.0% (95% CI: 2.0%–11.0%)	25.0% (95% CI: 17.1%–34.2%)
Infection (Any Grade)	38.0% (95% CI: 27.0%–50.0%)	36.0% (95% CI: 25.0%–48.0%)
Treatment Discontinuation Due to AEs	12.0% (95% CI: 6.0%–22.0%)	9.0% (95% CI: 4.0%–18.0%)

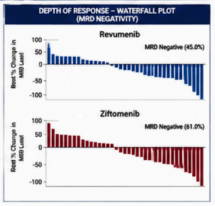
OVERALL SURVIVAL (POOLED) – KM CURVE



PROGRESSION-FREE SURVIVAL (POOLED) – KM CURVE



DEPTH OF RESPONSE – WATERFALL PLOT (MRD NEGATIVITY)



CONCLUSION

FDA-approved menin inhibitors demonstrated significant efficacy in relapsed/refractory NPM1-mutated AML. Both revumenib and ziftomenib achieved comparable CR/CRh rates, while ziftomenib produced deeper molecular responses and minimal clinically significant cardiac toxicity. Differentiation syndrome was more frequent with ziftomenib but was manageable. Approximately 20% of patients successfully bridged to allo-HCT. These findings support ziftomenib as a next-generation targeted therapeutic backbone in R/R NPM1-mutated AML.

RoB 2.0 assessment demonstrated an overall low-to-moderate risk of bias across included studies.