Efficacy and Safety of Triplet Targeted Therapy for FLT3-Mutated Relapsed/Refractory AML: A Systematic Review and Proportion Meta-Analysis

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Introduction

- FLT3 mutations occur in ~30% of AML cases and are associated with increased relapse rate and reduced survival. Outcomes remain poor in relapsed/refractory (R/R) AML, particularly after prior FLT3-directed therapy. FLT3 inhibitors and venetoclax-based regimens have expanded therapeutic options, but durable responses remain limited.
- We performed a systematic review and meta-analysis assessing triplet therapy with a hypomethylating agent (HMA), venetoclax, and an FLT3 inhibitor in FLT3-mutated R/R AML.

Aim

- To evaluate the efficacy and safety of HMA + venetoclax + FLT3 inhibitor triplet therapy in adults with FLT3-mutated relapsed/refractory AML with median age of 42 to 68 years.

Methodology

Conducted according to **PRISMA 2020** guidelines. PROSPERO ID: **CRD420261329046**

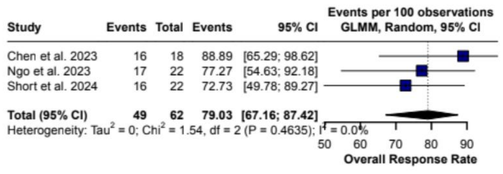
DATABASES: Pubmed, Embase, Cochrane, Scopus. Literature search through February 2026

104 patients | **2 prospective clinical trials** | **3 retrospective studies**

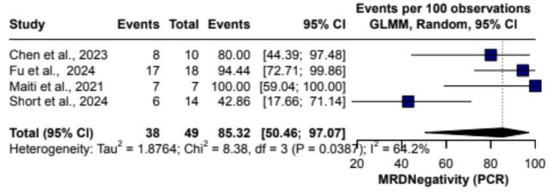
Primary Outcome: Overall Response Rate (ORR)
Secondary Outcome: Composite Complete Remission (CRc), bridge to Allogeneic Hematopoietic Stem Cell Transplantation (allo-HSCT), Measurable Residual Disease (MRD) negativity, Infections, Sepsis, and ≥ 30-Day Mortality

Outcomes	Pooled ratio	CI	P-value	I²
ORR	79.1	67.2-87.4	0.4635	0%
CRc	39.6	24.0-69.1	0.0116	69.10%
allo-HSCT	36.9	23.0-53.4	0.0163	67.10%
MRD	70.6	48.4-86.0	0.0387	0%
Infections	45.1	35.2-55.3	0.3137	15.60%
Sepsis	12.5	5.3-26.7	0.2552	22.80%
≥ 30-day Mortality	19.1	12.0-28.98	0.3571	8.70%

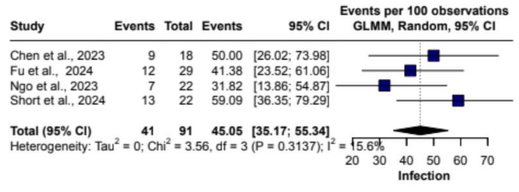
ORR



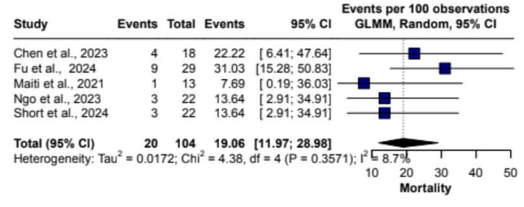
MRD



Infections



≥ 30-Day Mortality



Pooled proportions with 95% confidence intervals (CI) were estimated using a random-effects model.

Results

- 5 studies comprised of 104 patients with median age of 42 to 68 years were included. Around 43/104 (40%) patients had prior exposure to FLT3 inhibitors.
- Pooled estimates demonstrated substantial variability across endpoints, with I² ranging from 0% to 69.1%. No heterogeneity was observed for ORR or MRD negativity (I²=0%), whereas greater heterogeneity was observed for CRc and bridge to allo-HSCT (I²=69.1% and 67.1%, respectively). Heterogeneity was low for infections, sepsis, and ≥30-day mortality (I²=15.6%, 22.8%, and 8.7%, respectively).

Conclusion

- HMA + venetoclax + FLT3 inhibitor triplet therapy demonstrated encouraging clinical activity in FLT3-mutated R/R AML, with a pooled ORR of 79.1% and MRD negativity of 70.6%.
- Approximately 37% of patients were bridged to allo-HSCT, supporting the potential role of triplet therapy as a remission-induction strategy before transplantation.
- However, infections and early mortality remained clinically relevant.
- Given the small number of studies, limited sample size, and heterogeneity in CRc and transplant-bridging outcomes, larger prospective studies are needed to validate efficacy, define the optimal triplet regimen, and clarify its role in the treatment pathway and transplantation.

Acknowledgements

Access full references via QR code:

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AML-1336 | **Topic: Acute Myeloid Leukemia**

Abbreviations: FLT3: FMS-like Tyrosine Kinase 3, AML: Acute Myeloid Leukemia, HMA: Hypomethylating Agent, R/R: Relapsed/Refractory, ORR: Overall Response Rate, CRc: Composite Complete Remission, allo-HSCT: Allogeneic Hematopoietic Stem Cell Transplantation, MRD: Measurable Residual Disease, CI: Confidence Interval