# Clinical Efficacy of IDH Inhibitors in IDH-Mutated Relapsed/Refractory Acute Myeloid Leukemia: A Systematic Review and Meta-Analysis of RCTs

A. BINT I MUNIR[1], M. MYLAVARAPU[2], N. IYER[3], K. DOSHI[4], and R. MEDARAMETLA[5]

1. North Alabama Medical Center, Florence, AL, USA
2. Walker Baptist Medical Center, Jasper, AL, USA
3,4. Macneal Hospital, Loyola University Health System, Berwyn, IL, USA
5. Mamata Medical College, Khammam, Telangana, India

## Introduction

- Acute myeloid leukemia (AML) is a genetically heterogeneous malignancy. **IDH1 mutations** occur in ~6–10% and **IDH2 mutations** in ~9–13% of AML cases [1].
- These mutations produce the oncometabolite **2-hydroxyglutarate**, which impairs cellular differentiation and contributes to leukemogenesis [2].
- Targeted **IDH inhibitors** (Ivosidenib for IDH1, Enasidenib for IDH2) have shown clinical activity in relapsed/refractory AML.
- This systematic review and meta-analysis aim to provide an assessment and pooled evidence on the efficacy of IDH inhibitors in RR-AML.

## Methods

- A comprehensive search was conducted in PubMed/MEDLINE, CENTRAL, Embase, and ScienceDirect.
- Randomized controlled trials (RCTs) evaluating IDH inhibitors (Ivosidenib or Enasidenib) in adult patients with IDH-mutated relapsed/refractory AML were included.
- Two independent reviewers screened studies and extracted data.
- A total of 656 studies were screened; 15 underwent full-text review, and 4 RCTs were included in the final analysis.
- Efficacy endpoints: Complete Remission Rate (CRR), Overall Response Rate (ORR), and Overall Survival (OS).
- Statistical analysis performed using inverse variance weighting with logit transformation (PLOGIT).
- Pooled effect estimates were reported with 95% confidence intervals (CI) and heterogeneity ($I^2$).

## Results

- A total of 4 RCTs comprising 582 patients with IDH-mutated RR-AML were included.
- **Overall efficacy (all IDH mutations):**
  - ORR: 40% (95% CI: 0.36–0.44; $I^2$ = 0%)
  - CRR: 21% (95% CI: 0.18–0.25; $I^2$ = 0%)
  - OS: 16% (95% CI: 0.12–0.21; $I^2$ = 54%)
- **IDH2 subset (Enasidenib):**
  - ORR: 40% (95% CI: 0.35–0.45; $I^2$ = 0%)
  - CRR: 21% (95% CI: 0.17–0.25; $I^2$ = 0%)
  - OS: 17% (95% CI: 0.12–0.25; $I^2$ = 68%)
- Consistent efficacy observed across studies with low heterogeneity for response rates.

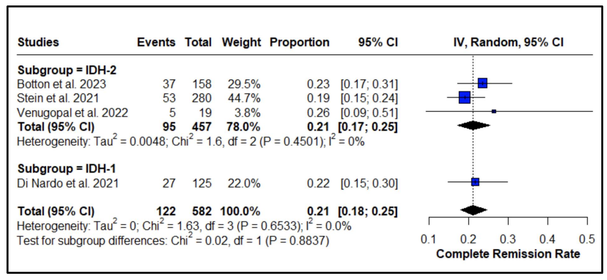



Figure 1. Forest plot – Complete Remission Rate CRR

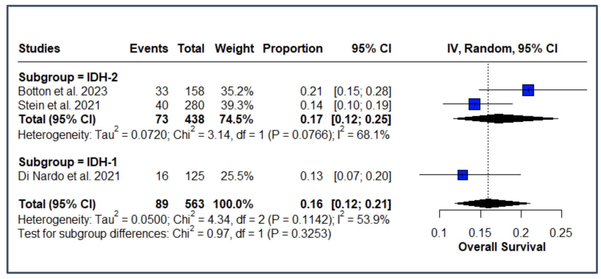



Figure 2. Forest plot – Overall Survival OS

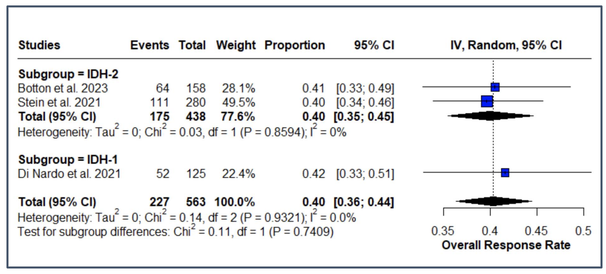



Figure 3. Forest plot – Overall Response Rate ORR

## Discussion

- Our findings suggest that IDH inhibitors demonstrate meaningful clinical efficacy in relapsed/refractory (RR) AML with IDH mutations, with a pooled ORR of 40% and CRR of 21%.
- These results are clinically relevant given the limited therapeutic options and poor prognosis associated with RR-AML.
- Enasidenib (IDH2 inhibitor) showed consistent response rates (ORR 40%, CRR 21%) across included trials, reinforcing its role as a viable treatment option for IDH2-mutated disease.
- Compared to conventional salvage chemotherapy, IDH inhibitors offer a targeted approach with favorable tolerability, supporting their incorporation into RR-AML treatment algorithms.
- Variability in overall survival highlights the need for further investigation.
- While additional randomized multicenter studies are needed to clarify the survival benefit, current evidence supports IDH inhibitors as a therapeutic option for patients with RR-AML harboring IDH mutations.

## References

1) DiNardo CD, Stein EM, de Botton S, et al. Durable Remissions with Ivosidenib in IDH1-Mutated Relapsed or Refractory AML. N Engl J Med. 2018;378(25):2386-2398. doi:10.1056/NEJMoa1716984

2) Clark O, Yen K, Mellinghoff IK. Molecular Pathways: Isocitrate Dehydrogenase Mutations in Cancer. Clin Cancer Res. 2016;22(8):1837-1842. doi:10.1158/1078-0432.CCR-13-1333