MRD-Adjusted Therapeutic Index of Menin Inhibitors in NPM1-Mutated and KMT2A-Rearranged Acute Myeloid Leukemia: A Genotype-Stratified Systematic Review and Meta-Analysis

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INTRODUCTION

- Menin inhibitors are targeted therapies for **NPM1-mutated (NPM1m)** and **KMT2A-rearranged (KMT2Ar)** acute myeloid leukemia (**AML**).
- Response rate alone may not fully capture treatment benefit.
- **Measurable residual disease (MRD)** clearance, toxicity, and **hematopoietic stem-cell transplantation (HSCT)** bridging provide additional measures of therapeutic value.

AIM

- To evaluate the **efficacy, MRD response, and toxicity** of menin inhibitors in NPM1m/KMT2Ar AML.
- To assess the balance between **molecular response depth and treatment-related toxicity**.

OUTCOMES

- CR/CRh
- MRD negativity
- Differentiation syndrome
- QTc prolongation
- Bridge to HSCT

METHODS

- Genotype-stratified systematic review with interim pooled analysis.
- Included prospective trial and regulatory-reported cohorts.
- Extractable numerator/denominator data were pooled.
- Random-effects models were used for pooled proportions.
- Different treatment settings/endpoints were analyzed separately.
- **CR/CRh:** complete remission/complete remission with partial hematologic recovery
- **DS:** differentiation syndrome

RESULTS

- **293 R/R patients** across 4 monotherapy cohorts.
- **NPM1m CR/CRh: 22.2% | KMT2Ar CR/CRh: 22.8%**.
- **CR/CRh: 24.0%; among MRD-evaluable CR/CRh responders, MRD negativity: 74.8%.**
- **Frontline Combination Signal**
- **Revumenib + azacitidine/venetoclax (AZA/VEN):**
- **Composite complete remission (CRc): 81.4% (35/43)**
- **MRD negativity: 100% (37/37 evaluable)**

Analyzed separately from R/R monotherapy.

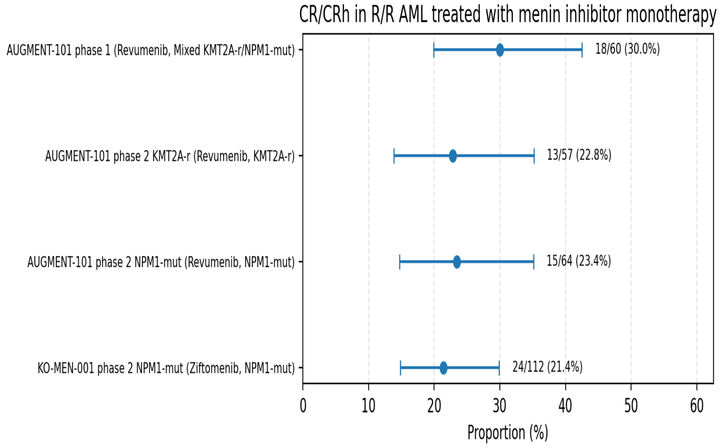

Figure 1. CR/CRh was consistent across R/R monotherapy cohorts, with a pooled rate of **24.0% (95% CI 19.5–29.3%; I^2=0%)**.

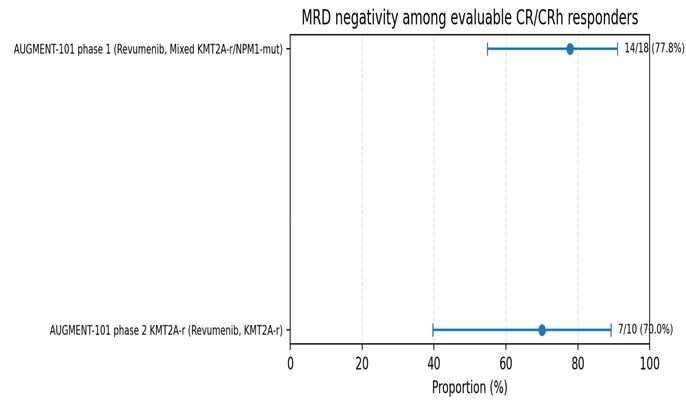

Figure 2. Among MRD-evaluable CR/CRh responders, pooled MRD negativity was **74.8% (95% CI 55.7–87.5%; I^2=0%)**.

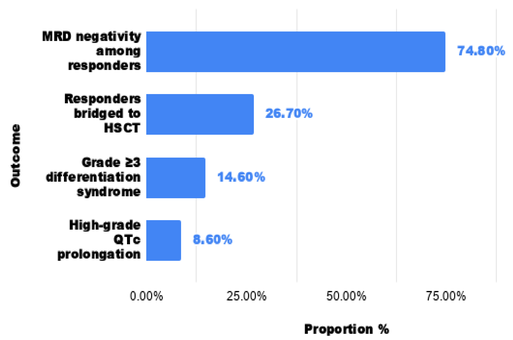

Figure 3. MRD-adjusted benefit–risk profile. MRD negativity occurred in **74.8% of evaluable responders**, compared with **14.6% grade ≥3 DS** and **8.6% high-grade QTc prolongation**; **26.7% proceeded to HSCT**. **Pooled component estimates use outcome-specific denominators.** *A uniform numerical MRD-adjusted therapeutic index was not estimable because early-mortality and matched efficacy–toxicity data were inconsistently reported across cohorts.*

CONCLUSIONS

- R/R menin inhibitor monotherapy achieved **CR/CRh in ~1 in 4 patients**.
- Nearly **3 in 4 MRD-evaluable responders achieved MRD negativity**, indicating **substantial molecular remission depth**.
- **Grade ≥3 differentiation syndrome occurred in ~15%**; **QTc prolongation** and **HSCT-bridging estimates showed substantial between-study heterogeneity**.
- Early frontline revumenib + AZA/VEN demonstrated high CRc and MRD-clearance rates but was analyzed separately from R/R monotherapy.
- **Standardized reporting of MRD, toxicity, early mortality, and transplant outcomes** is needed to enable robust validation of an **MRD-adjusted therapeutic index**.

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