EFFICACY AND SAFETY OF FLT3 INHIBITORS IN FLT3-MUTATED ACUTE MYELOID LEUKEMIA: A SYSTEMATIC REVIEW AND META-ANALYSIS OF RCTS

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INTRODUCTION

FLT3 mutations occur in ~25–30% of adults with acute myeloid leukemia (AML) and confer poor prognosis. Three FLT3 inhibitors — sorafenib, gilteritinib, and quizartinib — have demonstrated clinical activity across disease settings, but no head-to-head randomized trials exist.
This systematic review and meta-analysis evaluates their comparative efficacy and safety versus non-FLT3-based regimens in FLT3-mutated AML.

AIM

To evaluate the comparative efficacy and safety of FLT3 inhibitors — sorafenib, gilteritinib, and quizartinib, as monotherapy or in combination — versus chemotherapy, placebo, or best supportive care in FLT3-mutated AML.

Settings assessed: newly diagnosed (ND), relapsed/refractory (R/R), and post-transplant (post-HCT) maintenance.

METHOD

Systematic search for RCTs enrolling adults/adolescents with FLT3-mutated AML receiving sorafenib, gilteritinib, or quizartinib vs. chemotherapy, placebo, or best supportive care.

- Primary outcomes: overall survival (OS), event-free/relapse-free survival (EFS/RFS), and complete remission (CR/CRc) rates.
- Safety outcomes: grade ≥3 adverse events, QT prolongation, myelosuppression, and treatment discontinuation.
- Hazard ratios (HRs) and risk ratios (RRs) with 95% CIs pooled using a **DerSimonian-Laird random-effects model**.

CONCLUSIONS

FLT3 inhibitors significantly improve OS, remission rates, and relapse-free survival across all AML disease settings. Gilteritinib and quizartinib demonstrate superior FLT3 selectivity and efficacy versus sorafenib in the ND and R/R settings. MRD status emerges as a critical modifier of post-HCT maintenance benefit. Direct head-to-head trials are needed to define the optimal FLT3 inhibitor strategy.

RESULTS

Study population

Ten RCTs (n=2280) were included, spanning newly diagnosed (4 trials), relapsed/refractory (3 trials), and post-HCT maintenance (3 trials) settings.

Survival and remission

Pooled OS favored FLT3 inhibition over control (HR 0.71; 95% CI 0.61–0.82; P<0.001), strongest in R/R disease (HR 0.66) and moderate in ND patients (HR 0.82). Post-HCT RFS was markedly improved, driven by sorafenib (HR 0.47). Gilteritinib (MORPHO) narrowly missed its overall RFS endpoint (HR 0.679; P=0.052) but showed significant benefit in MRD-positive patients (HR 0.515; P=0.007). CRc rates nearly doubled with FLT3 inhibition in R/R AML (RR 1.96).

Safety

QT prolongation was a class-specific concern with quizartinib. Sorafenib was distinguished by hand-foot skin reaction and broader off-target toxicity.

10
Randomized Controlled Trials

2,280
Patients Analyzed

ND • R/R • Post-HCT
Disease Settings Covered

Outcome	Setting / Agent	Estimate
Overall survival	Overall (pooled)	HR 0.71
Overall survival	Relapsed / refractory	HR 0.66
Overall survival	Newly diagnosed	HR 0.82
Relapse-free survival, post-HCT	Sorafenib (pooled)	HR 0.47
RFS post-HCT (MORPHO)	Gilteritinib, overall	HR 0.679
RFS post-HCT (MORPHO)	Gilteritinib, MRD-positive	HR 0.515
Complete remission (CRc)	Relapsed / refractory	RR 1.96
QT prolongation	Quizartinib	Class-specific safety signal
Hand-foot skin reaction	Sorafenib	Distinguishing off-target toxicity

Table 1. Pooled effect estimates for efficacy and safety outcomes of FLT3 inhibitors vs. control across disease settings, derived from random-effects meta-analysis of 10 RCTs.

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