AZACITIDINE MAINTENANCE VS OBSERVATION IN AML IN FIRST REMISSION: A Systematic Review and Meta-Analysis of Randomized Trials

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BACKGROUND

Relapse is the dominant cause of failure after first remission in AML, especially when allogeneic transplantation is not planned.

Azacitidine maintenance has been evaluated using both parenteral and oral formulations, with oral azacitidine (CC-486) demonstrating an overall survival benefit in the pivotal QUAZAR AML-001 trial.

We performed a systematic review and meta-analysis of randomized trials evaluating azacitidine maintenance versus observation or placebo after intensive chemotherapy.

OBJECTIVE

Identify randomized evidence evaluating azacitidine maintenance versus placebo/observation after intensive therapy in adults with AML in first remission.

Distinguish the **direct evidence for oral azacitidine (CC-486)** from contextual randomized evidence for **injectable azacitidine**.

Pool compatible trial-level hazard ratios for **overall survival (OS)** and **relapse-/disease-free survival (RFS/DFS)** and quantify between-study heterogeneity.

METHODS

Search: PubMed/MEDLINE, ClinicalTrials.gov, and ASH/EHA conference

Eligibility: Randomized phase 3 trials evaluating oral or injectable azacitidine versus placebo/observation following intensive AML-directed therapy in patients achieving CR/CRi.

Analysis: Trial-level hazard ratios were pooled using **random-effects meta-analysis**; OS and RFS/DFS were analyzed separately, and heterogeneity was assessed using **I^2**.

CONCLUSION

Oral azacitidine: QUAZAR AML-001 demonstrated significant **OS and RFS benefit** in AML patients in first CR/CRi not proceeding to HSCT.

Pooled evidence: Azacitidine maintenance improved RFS/DFS (**HR 0.64**), while the pooled OS effect across formulations was not statistically significant (**HR 0.82; 95% CI, 0.66–1.02**).

Clinical implication: Oral CC-486 remains the evidence-based maintenance strategy; **oral and injectable azacitidine are not interchangeable**, and an OS class effect cannot be assumed.

RESULTS

Eligible Randomized Evidence:
4 phase III RCTs; N=1,172 randomized participants

1 oral trial: QUAZAR AML-001
3 injectable trials: HOVON97, UK NCRI AML16, QoLESS AZA-AMLE

Cross-Formulation Synthesis:
Overall Survival:
3 trials; N=1,118
HR 0.82 (95% CI, 0.66–1.02); I^2=50%

RFS/DFS:
2 trials; N=588
HR 0.64 (95% CI, 0.53–0.78); I^2=0%

QoLESS AZA-AMLE was included in the systematic review but not pooled for OS or DFS because a compatible overall time-to-event HR was not reported.

Safety — Direct Oral Evidence
In QUAZAR AML-001, common grade 3–4 adverse events included:
Neutropenia: 41% vs 24%
Thrombocytopenia: 22% vs 21%

DIRECT ORAL EVIDENCE

QUAZAR AML-001

N = 472

Median OS

24.7 vs 14.8 mo

HR 0.69 (0.55–0.86)

Median RFS

10.2 vs 4.8 mo

HR 0.65 (0.52–0.81)

300 mg PO days 1–14, q28d

Oral and injectable azacitidine are not interchangeable; cross-formulation pooling is exploratory.

Trial	Formulation / schedule	N	OS HR (95% CI)	RFS/DFS HR (95% CI)
QUAZAR AML-001	Oral 300 mg d1–14 q28d	472	0.69 (0.55–0.86)	RFS 0.65 (0.52–0.81)
HOVON97	SC 50 mg/m² d1–5 q28d	116	0.91 (0.58–1.44)	DFS 0.62 (0.41–0.95)
UK NCRI AML16	SC 75 mg/m² d1–5 q6wk ×9	530	0.93 (0.76–1.14)	Not reported
QoLESS AZA-AMLE	SC/IV 50→75 mg/m²	54	Not poolable	Overall difference NS
POOLED OS	**Random effects; 3 trials**	**1,118**	**0.82 (0.66–1.02); I^2 50%**	—
POOLED RFS/DFS	**Random effects; 2 trials**	**588**	—	**0.64 (0.53–0.78); I^2 0%**

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