

Acalabrutinib vs. Chemoimmunotherapy in CLL: A Systematic Review and Meta-Analysis of Randomized Controlled Trials



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Introduction

- CLL treatment has shifted from chemoimmunotherapy to targeted agents.
- Acalabrutinib, a BTK inhibitor, shows efficacy advantages over traditional therapy.
- Its toxicity profile is not yet fully addressed.
- Aim:** To compare acalabrutinib with chemoimmunotherapy in CLL and fill this evidence gap.

Methods and Materials

Search strategy: Systematic search of multiple databases (PRISMA flow diagram).

Inclusion criteria: RCTs comparing acalabrutinib vs. chemoimmunotherapy in CLL (6 RCTs included).

Outcomes: Overall response rate (ORR), overall survival (OS), progression-free survival (PFS), treatment exposure, adverse events (AEs).

Analysis: Random-effects model; RR for dichotomous outcomes, SMD for continuous outcomes.

Quality assessment: Risk of bias, GRADE, and trial sequential analysis (TSA).

Results

Studies included: 6 RCTs; 1036 acalabrutinib vs. 1032 chemoimmunotherapy

Risk of bias: 3 low, 1 some concerns, 2 high (open-label follow-ups)

PFS: RR 0.48 (0.22–1.04), non-significant trend favoring acalabrutinib

OS (immediate): RR 0.59 (0.42–0.83), significantly better with acalabrutinib

OS (longer-term): RR 1.09 (0.93–1.28), no difference

ORR: RR 1.13 (1.04–1.23), significantly higher with acalabrutinib; TSA information size reached

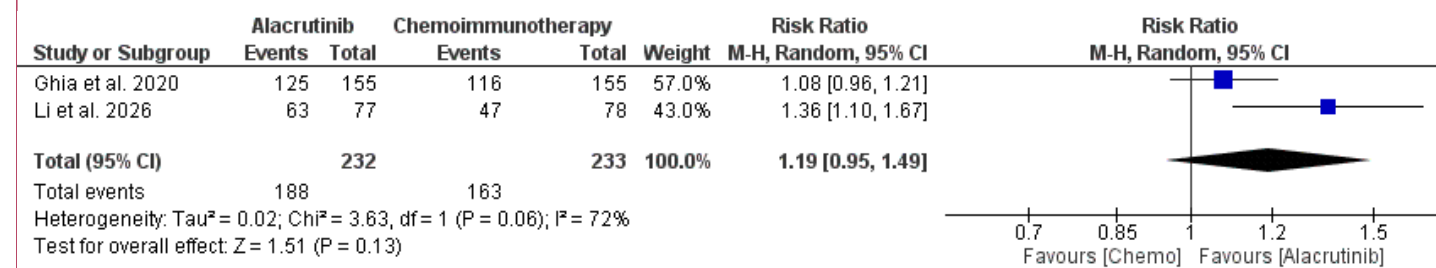
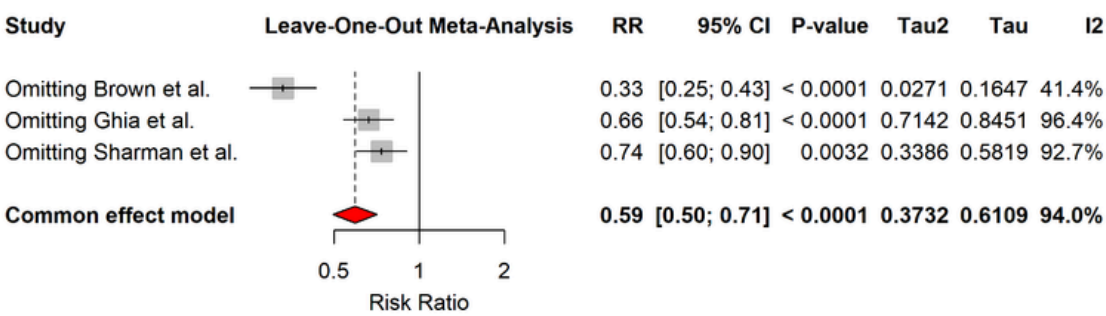
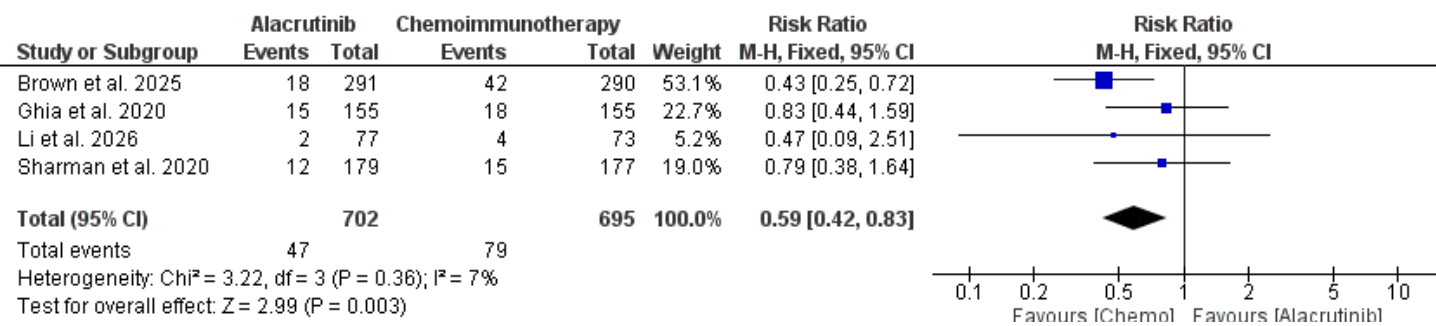
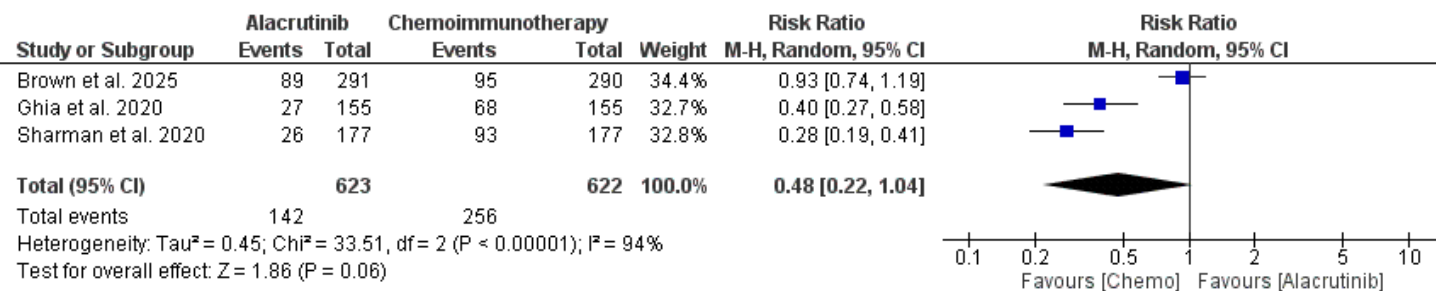
Discontinuation due to AEs: RR 0.55 (0.32–0.96), significantly lower

Total AEs: RR 0.99 (0.96–1.03), no difference

Lower with acalabrutinib: tumor lysis syndrome (RR 0.08), neutropenia (RR 0.44)

Higher with acalabrutinib: hemorrhage (RR 4.30), headache (RR 3.55), cardiac events (RR 2.83), secondary primary malignancy (RR 2.41)

No difference: thrombocytopenia, anemia, hypertension, infections, diarrhea



		Risk of bias domains					
		D1	D2	D3	D4	D5	Overall
Study	Ghia et al. 2020	+	+	+	+	+	+
	Sharman et al. 2020	+	+	+	+	+	+
	Brown et al. 2025	+	+	+	+	+	+
	Li et al. 2026	-	-	+	+	+	-
	Ghia et al. 2022	+	-	+	X	-	X
	Sharman et al. 2025	+	-	+	X	-	X
		Domains:					Judgement
		D1: Bias arising from the randomization process.					X High
		D2: Bias due to deviations from intended intervention.					- Some concerns
		D3: Bias due to missing outcome data.					+
		D4: Bias in measurement of the outcome.					
		D5: Bias in selection of the reported result.					

Conclusions

- Higher response rates and better immediate survival with acalabrutinib
- Fewer discontinuations, less tumor lysis syndrome and neutropenia
- More hemorrhage, headache, cardiac events, and secondary malignancies
- Longer-term survival similar between treatments
- TSA information size not reached for survival or most AEs; larger, longer trials needed
- Select and monitor patients carefully, especially those with cardiovascular risk or on anticoagulants

References:

