FRONTLINE BTK INHIBITOR STRATEGIES IN MANTLE CELL LYMPHOMA: A PHASE 3 NETWORK META-ANALYSIS WITH CROSS-TRIAL SYNTHESIS ACROSS TRANSPLANT-ELIGIBLE AND -INELIGIBLE POPULATIONS

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INTRODUCTION

- Frontline treatment of mantle cell lymphoma (MCL) remains heterogeneous, with no universal standard of care.
- Bruton tyrosine kinase inhibitors (BTKis) have been integrated into chemoimmunotherapy, chemotherapy-free, and transplant-based approaches.
- Their comparative efficacy across transplant-eligible and -ineligible populations remains unclear.
- We performed a systematic review and network meta-analysis (NMA) of phase 3 trials evaluating BTKi-containing regimens in previously untreated MCL.

2,388
patients pooled across 4 phase 3 trials

AIM

To compare progression-free survival and treatment rankings of frontline BTKi-containing regimens in previously untreated MCL, and to synthesize efficacy and safety across transplant-eligible and -ineligible populations.

TRIALS INCLUDED

SHINE | ECHO | TRIANGLE | ENRICH

METHOD

Study Design
- Systematic review and network meta-analysis
- Phase 3 randomized controlled trials
- Frontline BTKi-containing regimens in MCL

Primary Outcome
- Progression-free / failure-free survival (hazard ratio)

Statistical Analysis
- Frequentist random-effects network meta-analysis
- Treatment ranking by P-score
- Structured cross-trial synthesis for non-connected trials
- Stratified by transplant eligibility and treatment backbone

CONCLUSIONS

- BTKi-containing regimens consistently improve disease control in frontline MCL.
- Acalabrutinib and ibrutinib show comparable efficacy when added to chemoimmunotherapy in older, transplant-ineligible patients.
- Chemotherapy-free BTKi approaches and BTKi-integrated strategies in younger patients may reduce the need for ASCT.
- Grade ≥3 adverse event rates were comparable across arms.

Bottom line: Individualize frontline BTKi strategy by age, fitness, and toxicity profile.

RESULTS

Key Efficacy Comparisons Across Trials

Comparison	HR	95% CI	Interpretation
IBR + BR vs BR (older, transplant-ineligible)	HR 0.75	0.59–0.96	✓ Significant benefit
ACA + BR vs BR (older, transplant-ineligible)	HR 0.73	0.57–0.94	✓ Significant benefit
IBR-R vs standard chemo (ENRICH, chemo-free)	HR 0.69	0.52–0.90	✓ Significant benefit
BTKi-containing vs chemo +ASCT (TRIANGLE, younger)	HR ≈0.54	0.52–0.56	✓ Significant benefit

No significant difference between ACA+BR and IBR+BR (HR 0.97, 95% CI 0.69–1.38) in older patients; ACA+BR ranked highest overall (P-score 0.78).

4 phase 3 trials • 2388 patients • older + younger populations

Four phase 3 trials (SHINE, ECHO, TRIANGLE, ENRICH) comprising 2388 patients were included.

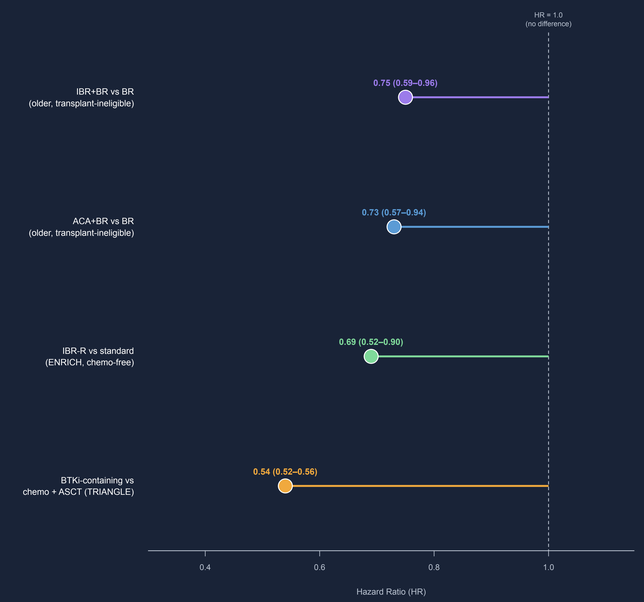
In older, transplant-ineligible patients, **IBR+BR and ACA+BR each significantly improved PFS vs BR alone** (HR 0.75 and 0.73), with no significant difference between them.

Cross-trial synthesis: **chemotherapy-free ibrutinib-rituximab (ENRICH) showed the longest PFS** (median 65.3 vs 42.4 months; HR 0.69).

In younger, transplant-eligible patients (TRIANGLE), **BTKi-containing regimens improved failure-free survival vs chemoimmunotherapy + ASCT** (HR ≈0.52–0.56), with no clear added benefit of ASCT when a BTKi was used.

- Grade ≥3 adverse event rates were comparable across treatment arms.

PFS / FFS Hazard Ratios Across BTKi Comparisons



◄ *Lower HR favors BTKi-containing regimen*