PIRTOBRUTINIB VERSUS COVALENT BTK INHIBITORS IN TREATMENT-NAÏVE CLL: A SYSTEMATIC REVIEW AND NETWORK META-ANALYSIS

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INTRODUCTION

Pirtobrutinib is a non-covalent (reversible) BTK inhibitor with proven efficacy in treatment-naïve (TN) CLL. It has never been compared head-to-head against second-generation covalent BTK inhibitors (zanubrutinib, acalabrutinib) in a randomised trial, leaving clinicians without direct evidence to guide first-line selection.

AIM

To indirectly compare pirtobrutinib against all approved BTK inhibitors in TN CLL by synthesising randomised evidence in a single connected network meta-analysis (NMA).

METHOD

- Search: MEDLINE, EMBASE and Cochrane Central through May 2026
- Eligibility: Phase II/III RCTs in TN CLL/SLL
- Network: 6 trials (CLL-313, CLL-314, SEQUOIA, A041202, ELEVATE-TN, iLLUMINATE) linked through two chemotherapy anchors (BR, ClbObi) and one direct BTKi comparison → a single 7-node network
- Analysis: Bayesian random-effects NMA (primary) and fixed-effects (sensitivity), R/gemtc
- Outcomes: PFS (primary, via NMA); safety descriptive; OS exploratory (immature)

CONCLUSIONS

First NMA to connect pirtobrutinib with all approved covalent BTK inhibitors in one unified network.

PFS comparisons vs covalent BTKis were directionally favourable but non-significant; the only significant efficacy signal was vs ibrutinib (HR 0.57)

A favourable cardiovascular safety profile was seen in direct comparison with ibrutinib

Findings are limited by indirect estimation and short pirtobrutinib follow-up; OS remains immature

Definitive conclusions await mature follow-up from CLL-313 and CLL-314

RESULTS

Class effect confirmed: pairwise meta-analysis of BTKis vs BR gave pooled HR 0.30 (95% CI 0.24–0.38; I²=11.5%), supporting network transitivity

Consistency: node-splitting confirmed a coherent network (all p>0.97; I²=11%) (Fig A)

Ranking (SUCRA): pirtobrutinib ranked highest at 75.4%, ahead of acalabrutinib–obinutuzumab (73.7%), zanubrutinib (60.0%), acalabrutinib (52.2%) and ibrutinib (51.3%); all BTKis ranked well above chemotherapy (Fig B)

PFS (fixed-effects): pirtobrutinib significantly better only vs ibrutinib — HR 0.57 (95% CrI 0.41–0.79); comparisons vs zanubrutinib (0.70, 0.43–1.17) and acalabrutinib (0.59, 0.31–1.12) were directionally favourable but non-significant.(Fig C). OS data were too immature for formal analysis

Safety (direct, CLL-314): vs ibrutinib, pirtobrutinib had markedly less atrial fibrillation (2.4% vs 13.5%) and less hypertension (10.6% vs 15.1%) (Fig D)

Fig A

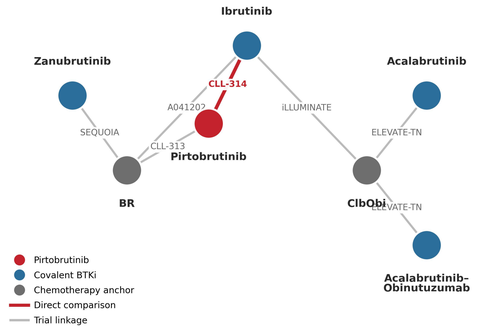


Fig B

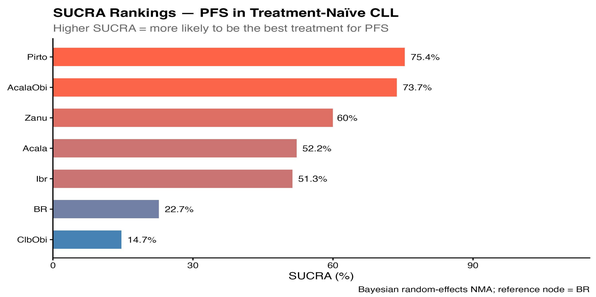


Fig C

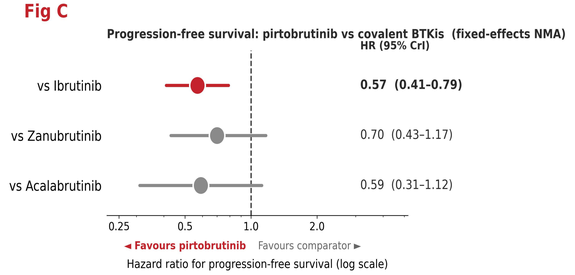
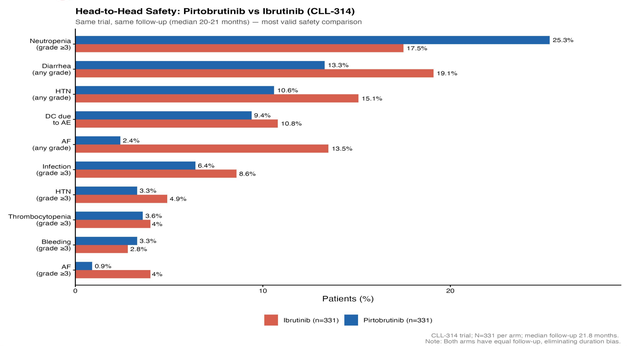


Fig D



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