Pirtobrutinib Following Covalent BTK Inhibitor Exposure in Relapsed/Refractory Chronic Lymphocytic Leukemia: A Systematic Review and Pooled Analysis

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INTRODUCTION

- Covalent Bruton tyrosine kinase inhibitors (cBTKi) have substantially improved outcomes in chronic lymphocytic leukemia (CLL), but treatment discontinuation due to disease progression or intolerance remains common.
- Patients who progress after cBTKi therapy, particularly those previously treated with both cBTKi and BCL2 inhibitor therapy, have limited treatment options and historically poor outcomes.
- Pirtobrutinib is a highly selective, non-covalent BTK inhibitor designed to overcome common resistance mechanisms associated with covalent BTK inhibition while maintaining a favorable safety profile.
- Multiple clinical studies have demonstrated promising activity for pirtobrutinib following prior cBTKi therapy; however, outcomes across sequencing populations have not been systematically synthesized.
- Objective: To systematically evaluate the efficacy and safety of pirtobrutinib following prior covalent BTK inhibitor exposure in relapsed/refractory CLL.

AIM

To characterize clinical outcomes with pirtobrutinib after prior covalent BTK inhibitor therapy in relapsed/refractory chronic lymphocytic leukemia, with particular emphasis on patients previously exposed to both covalent BTK and BCL2 inhibitor therapy.

KEY FINDINGS

✓ Pooled overall response rate (ORR): 72% (95% CI, 67–76%)
✓ Double-exposed patients (prior cBTKi + BCL2 inhibitor): ORR 70% (95% CI, 60–79%)
✓ BRUIN CLL-321 demonstrated improved progression-free survival (14.0 vs 8.7 months; HR 0.54) and prolonged time to next treatment (24.0 vs 10.9 months).
✓ Pooled atrial fibrillation/flutter incidence: 3% (95% CI, 1–5%), supporting a favorable

METHOD

- A systematic literature review was conducted using PubMed, Embase, Cochrane Library, and major hematology conference proceedings (ASH and EHA).
- Studies evaluating pirtobrutinib in relapsed/refractory chronic lymphocytic leukemia following prior covalent BTK inhibitor (cBTKi) exposure were eligible for inclusion.
- Primary outcomes included overall response rate (ORR), progression-free survival (PFS), time to next treatment (TTNT), and treatment-related adverse events.
- Pooled analyses of response and safety outcomes were performed using random-effects meta-analysis of proportions in R (meta package).
- Randomized and early-phase studies were synthesized, while overlapping cohorts were identified and accounted for to avoid duplicate patient inclusion.

CONCLUSIONS

- Pirtobrutinib demonstrates meaningful clinical activity following prior covalent BTK inhibitor therapy in patients with relapsed/refractory CLL, including those previously exposed to both covalent BTK and BCL2 inhibitor therapy.
- Pooled analyses showed consistently high response rates with a favorable safety profile, supporting the role of non-covalent BTK inhibition after covalent BTKi failure.
- Randomized phase III evidence further demonstrates improved progression-free survival and prolonged time to next treatment compared with currently available treatment options.
- These findings support pirtobrutinib as an important component of treatment sequencing in relapsed/refractory CLL and provide a foundation for future studies evaluating optimal sequencing and combination strategies.

RESULTS

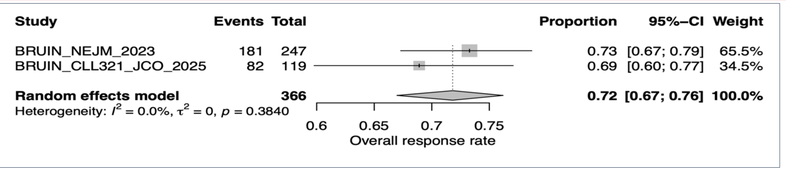


Figure 1. Pooled overall response rate following prior covalent BTK inhibitor exposure.
Random-effects pooled analysis of the BRUIN phase 1/2 and randomized phase III BRUIN CLL-321 studies demonstrated an overall response rate of 72% (95% CI, 67–76%) among patients with relapsed/refractory chronic lymphocytic leukemia previously treated with covalent BTK inhibitors, with no significant between-study heterogeneity (I^2 = 0%).

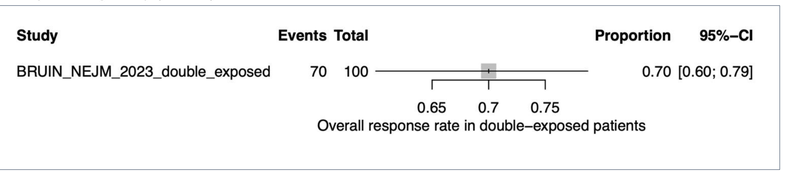


Figure 2. Overall response rate among patients previously exposed to both covalent BTK and BCL2 inhibitor therapy. ***Pooled analysis demonstrated an overall response rate of 70% (95% CI, 60–79%) in heavily pretreated, double-exposed patients with relapsed/refractory chronic lymphocytic leukemia, supporting continued clinical activity of pirtobrutinib in this high-risk population.***

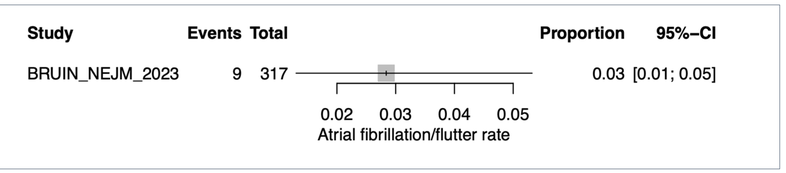
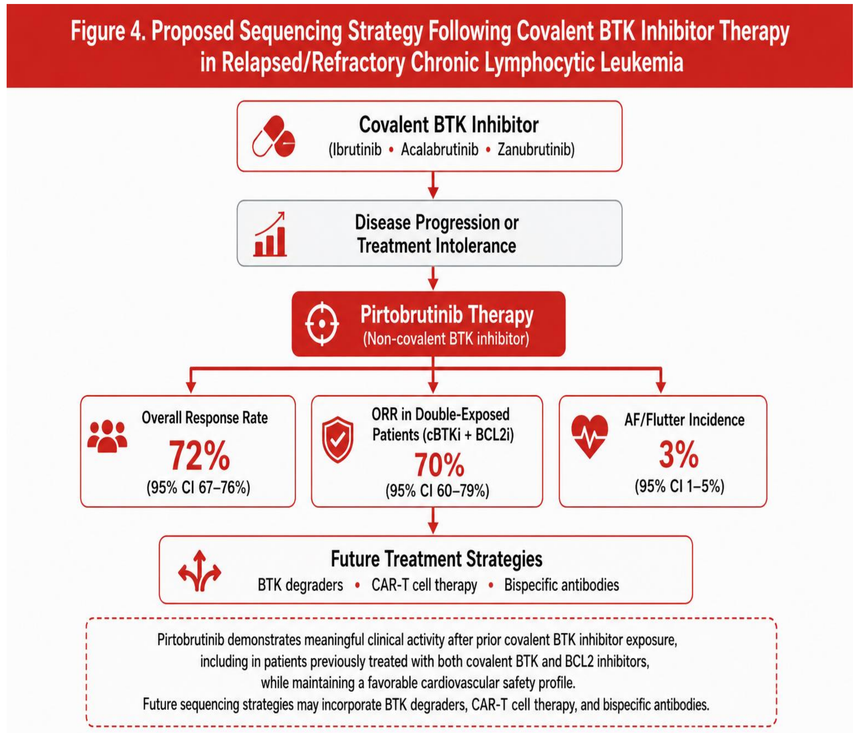


Figure 3. Pooled Incidence of Atrial Fibrillation/Flutter With Pirtobrutinib Following Prior Covalent BTK Inhibitor Therapy
Pooled atrial fibrillation/flutter incidence was 3% (95% CI, 1–5%), supporting the favorable cardiovascular safety profile of pirtobrutinib following prior covalent BTK inhibitor exposure.



Study	Design	Population	Prior cBTKi Exposure	Prior BCL2i Exposure	Median Prior Lines of Therapy	Key Findings
BRUIN Phase 1/2	Phase 1/2, multicenter	Relapsed/refractory CLL/SLL	121 efficacy-evaluable patients	45 patients	4	ORR 62%; ORR 64% in prior BTKi + BCL2i; favorable safety profile
BRUIN (Updated NEJM 2023)	Phase 1/2, multicenter	Relapsed/refractory CLL/SLL after prior cBTKi	247 patients	100 patients (41%)	3	ORR 73%; median PFS 19.6 months; double-exposed ORR 70%; median PFS 16.8 months
BRUIN CLL-321	Randomized Phase III	Relapsed/refractory CLL/SLL after prior cBTKi	238 randomized patients	Prior BCL2i permitted	4	Median PFS 14.0 vs 8.7 months; HR 0.54; TTNT 24.0 vs 10.9 months

Table 1. Characteristics of Studies Included in the Pooled Analysis

Abbreviations: *BTKi, Bruton tyrosine kinase inhibitor; BCL2i, B-cell lymphoma 2 inhibitor; CLL, chronic lymphocytic leukemia; SLL, small lymphocytic lymphoma; ORR, overall response rate; PFS, progression-free survival; TTNT, time to next treatment.*

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