Second-Generation BTK Inhibitors vs Ibrutinib in CLL: A Systematic Review of Efficacy and Safety

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INTRODUCTION

Chronic lymphocytic leukemia (CLL) is the most common adult leukemia in Western countries, characterized by the accumulation of mature B-lymphocytes and variable progression based on cytogenetic factors. Treatment options have evolved from traditional chemoimmunotherapy to targeted therapies, specifically Bruton tyrosine kinase inhibitors (BTKI), with significant improvement in tolerance of treatment and survival benefits, especially for those with poor prognostic factors. Initial clinical trials evaluating the safety profiles and efficacy of second-generation BTKIs over first-generation ibrutinib and older treatment regimens demonstrated superiority in relapsed or refractory cases. This systematic review aims to assess the impact of these medications with more recent data from studies that utilize second-generation BTKIs in treatment-naive cases.

METHODS

Electronic databases (PubMed, Embase, Cochrane Library, Web of Science, and Scopus)were searched for randomized controlled trials (RCTs) or comparative observational studies utilizing second-generation BTKIs, acalabrutinib or zanubrutinib, in CLL. Exclusion criteria consisted of single-arm studies, case reports and case series, preclinical studies, and studies comparing BTKIs with non-BTKI regimens only.

Of the 14 studies included, seven were RCTs that formed the base of primary evidence for meta-analytic synthesis, and seven were comparative observational studies (six retrospective cohorts and one prospective cohort) that contributed supplemental and real-world evidence.

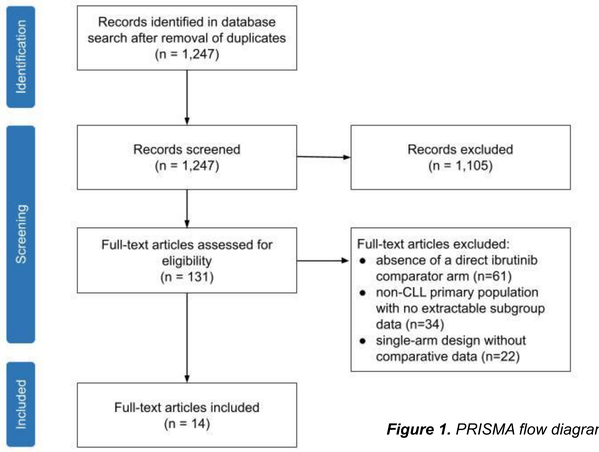

Figure 1. *PRISMA flow diagram.*

RESULTS

- Included studies were published from 2020 to 2026 and assessed a combined total of 19,819 patients across multiple countries.
- Seven studies evaluated zanubrutinib vs ibrutinib, six studies compared acalabrutinib with ibrutinib, and one study evaluated both second-generation agents against ibrutinib.
- Overall low risk of bias using the Cochrane risk-of-bias tool for randomized trials (RoB 2) tool.
- Across all randomized controlled trials, second-generation BTKIs consistently demonstrated either superiority or non-inferiority to ibrutinib for progression-free survival (PFS). (Table 1)
- In multiple studies, median overall survival (OS) has not been yet. In those reporting OS data, the majority of results show a non-significant benefit favoring second-generation agents. (Table 1)
- Overall response rates (ORR) are consistently higher in groups treated with second-generation BTKIs than those treated with ibrutinib. Significantly greater responses are seen in R/R settings. (Table 1)

Author (year)	Drug	Atrial Fibrillation (%)		Hypertension (%)		Major Bleeding (%)		Diarrhea (%)	
		Study Drug	Ibrutinib	Study Drug	Ibrutinib	Study Drug	Ibrutinib	Study Drug	Ibrutinib
Brown, JR. (2024)	Zanubrutinib	7.1	17.0	27.2	25.3	NR	NR	18.8	25.6
Byrd, JC. (2021)	Acalabrutinib	9.4	16.0	9.4	23.2	4.5	5.3	34.6	46.0
Zhou, K. (2024)	Zanubrutinib	0.0	4.7	15.6	14.0	0	0	13.3	16.3
Woyach, JA. (2020)	Acalabrutinib	5.0	10.0	9.0	23.0	4.0	7.0	10.0	16.0
Fan, F. (2025)	Zanubrutinib	1.0	0.0	0.01	0	3.0	3.0	NR	NR
Dranitsaris. (2025)	Acalabrutinib	7.8	13.9	5.6	13.9	7.8	11.7	NR	NR

Table 2. *Safety outcomes assessed by rates of common adverse drug events in studies comparing second-generation BTKIs directly to ibrutinib. All grades of adverse events included, except for major bleeding, which is consider grade 3 or greater hemorrhage. NR=not reported.*

- Treatment discontinuation rates were consistently lower in second-generation BTKI groups than those treated with ibrutinib across all studies included.
- Rates of atrial fibrillation, diarrhea, and any grade of bleeding reported in all studies included were consistently lower in groups treated with second-generation BTKIs.
- Studies evaluating acalabrutinib found lower rates of new-onset hypertension, while rates of hypertension were comparable between groups treated with zanubrutinib and ibrutinib.
- Rates of neutropenia and infections were comparable between the two drug groups.

Author (year)	Drug	Setting	PFS HR (95% CI)	OS HR (95% CI)	ORR	ORR Ibrutinib
Brown, JR. (2024)	Zanubrutinib	R/R	0.68 [0.54–0.84]	0.77 [0.55–1.06]	85.6%	75.4%
Byrd, JC. (2021)	Acalabrutinib	R/R	1.00 [0.79–1.27] (NI)	0.82 [0.59–1.15]	81%	77%
Zhou, K. (2024)	Zanubrutinib	R/R	0.34 [0.15–0.77]	0.45 [0.14–1.50]	80.9%	72.1%
Tam, CS.(2026)	Zanubrutinib	R/R	0.56 [0.36–0.88]	0.73 [0.41–1.29]	89.3%	76.0%
Gill, S. (2022)	Zanubrutinib	TN	0.40 [0.23–0.69]	NR	88%	78%
Woyach, JA. (2020)	Acalabrutinib	TN	0.31 [0.20–0.49]	NR	81%	77%
Fitzgerald, L. (2026)	Acalabrutinib & Zanubrutinib	TN	NR	1.33 [1.00–1.74]	NR	NR

Table 1. *Primary efficacy outcomes in studies comparing second-generation BTKIs directly to ibrutinib. PFS=progression-free survival; HR=hazard ratio; OS=overall survival; ORR=overall response rate; NI=non-inferior; NR=not reported; R/R=relapsed/refractory disease; TN=treatment-naive.*

CONCLUSIONS

Growing evidence from more trials evaluating use of second-generation BTKIs compared to ibrutinib shows overall PFS and ORR outcomes, as well as lower rates of many adverse effects and treatment discontinuation, favoring second-generation agents with moderate certainty of evidence. Data for overall survival benefits remain immature, and continued assessment will be needed. Statistical heterogeneity could not be formally calculated due inconsistent reporting of variance estimates in observational studies. This study is also limited with insufficient volume of studies per outcome to perform all regressions otherwise indicated. These findings highlight the importance of assessing ongoing trial data and identifying drug-specific, rather than drug class, conclusions for clinical applications moving forward.

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