Real-World Evidence on Bruton Tyrosine Kinase Inhibitors in Treatment-Naive Chronic Lymphocytic Leukemia or Small Lymphocytic Lymphoma: An Artificial Intelligence–Assisted Literature Review

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CONCLUSIONS

- Comparative RWE in TN CLL/SLL is limited; however, emerging data consistently favor zanubrutinib over ibrutinib for survival, treatment durability, and inpatient burden, while acalabrutinib shows lower effectiveness with reduced emergency department utilization relative to ibrutinib
- Future evidence synthesis will be needed to further characterize differences among BTK inhibitors as new RWE emerges
- This study also demonstrated that use of AI in the literature review helped increase efficiency, which will allow future updates to more easily capture emerging RWE in CLL/SLL

INTRODUCTION

- Covalent Bruton tyrosine kinase (BTK) inhibitors (zanubrutinib, acalabrutinib, and ibrutinib) have transformed the treatment landscape for chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL) and are now established as standard-of-care regimens[1,2]
- In the absence of head-to-head clinical trials directly comparing these treatments in treatment-naive (TN) patients, real-world evidence (RWE) is essential to assess comparative effectiveness and fully understand real-world clinical outcomes across diverse patient populations
- This review synthesizes current RWE on clinical outcomes and healthcare resource utilization (HCRU) with BTK inhibitor monotherapies in TN CLL/SLL

METHODS

- Comprehensive search strings were developed using Smart Search, an artificial intelligence (AI)–assisted search tool within the Nested Knowledge (NK) platform, and subsequently reviewed and refined prior to execution
- Searches were conducted in Medline (via API with PubMed) and translated to Embase, capturing literature published between 2018 and 2025 to reflect recent evidence following the wider adoption of BTK inhibitor use in clinical practice
- Studies were considered eligible if they had a comparative real-world design evaluating two or more BTK inhibitor therapies in patients with TN CLL/SLL and reported at least one outcome of interest, including measures of clinical effectiveness, safety, or HCRU (**Table 1**)

Table 1. PICOS Eligibility Criteria

	Inclusion criteria	Exclusion criteria
Population	• Adult patients (aged ≥18 years) diagnosed with CLL/SLL *At least 10 patients per treatment group*	• Pediatric populations • Treatment settings or conditions other than TN CLL/SLL
Interventions	Zanubrutinib or acalabrutinib monotherapy	Other treatments
Comparators	Any	N/A
Outcomes	• OS • TTNT, TTD • AEs • HCRU	Other outcomes
Study design	Comparative RWE (eg, prospective or retrospective cohort, case-control)	Clinical trials, single-arm studies, reviews, case reports, etc
Timeframe	Publication dates: 2018-2025	Publication prior to 2018

Abbreviations: AE, adverse event; CLL chronic lymphocytic leukemia; HCRU, healthcare resource utilization; N/A, not available; OS, overall survival; PICOS, population, intervention, comparison, outcomes, and study design; RWE, real-world evidence; SLL, small lymphocytic lymphoma; TN, treatment naive; TTD, time to discontinuation; TTNT, time to next treatment.

- Screening was performed within NK using a human-in-the-loop approach: large language models were deployed on human-configured screening criteria and elements for data extraction
- All AI decisions were expert curated, and data were extracted using AI recommendations with human validation

RESULTS

- The searches identified 1256 citations, of which 24 records (13 unique studies) were included (**Table 2**)
- Most studies were from 2024-2025 (21/24 [88%]) and were presented at conferences (20/24 [83.3%]) rather than published as full manuscripts; nearly all studies (12/13 [92%]) were retrospective cohort studies conducted in the United States
- Ten studies (77%) reported effectiveness outcomes, two (15%) reported safety outcomes, and five (38%) reported HCRU, with only four (31%) reporting more than one type of outcome. However, data reporting was heterogeneous across studies, and common data types were limited

Table 2. Characteristics of Included Studies[a]

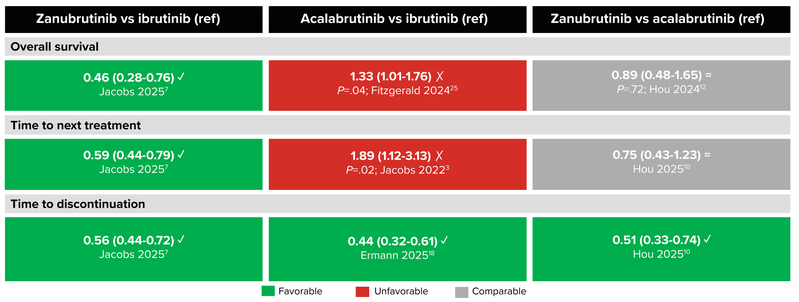
Author and year	Study design	Country	Data source	Population	BTKi	Reported outcomes
Jacobs 2022[3,b] (related reports[4-6])	Retrospective cohort	🇺🇸	Acentrus database	CLL: first-line treatment with BTKi	**Acalabrutinib** **Ibrutinib**	✓ Effectiveness ⊕ HCRU[6,b]
Jacobs 2025[7,b]	Retrospective cohort	🇺🇸	Flatiron Health	CLL: first-line BTKi monotherapy	**Zanubrutinib** **Acalabrutinib** **Ibrutinib**	✓ Effectiveness
Pinilla-Ibarz 2024[8,b] (related report[9])	Retrospective cohort	🇺🇸	Integra Connect PrecisionQ	CLL/SLL: BTKi as first-line or second-line treatment	**Zanubrutinib** **Acalabrutinib** **Ibrutinib**	✓ Effectiveness
Hou 2025[10,b] (related reports[11,12])	Retrospective cohort	🇺🇸	Integra Connect PrecisionQ	CLL/SLL: first-line treatment with BTKi	**Zanubrutinib** **Acalabrutinib**	✓ Effectiveness
Hou 2023[13,b] (related report[14])	Retrospective cohort	🇺🇸	Integra Connect PrecisionQ	CLL/SLL: treated with BTKi	**Zanubrutinib** **Acalabrutinib** **Ibrutinib**	✓ Effectiveness
Rogers 2025[15]	Retrospective cohort	🇺🇸	IQVIA PharMetrics Plus and Acentrus	CLL/SLL: first-line BTKi monotherapy	**Acalabrutinib** **Ibrutinib**	⊕ HCRU
Krackeler 2025[16]	Retrospective cohort	🇺🇸	KPNC	CLL/SLL	**Zanubrutinib** **Ibrutinib**	✓ Effectiveness Safety
Huntington 2025[17,b]	Retrospective cohort	🇺🇸	Medicare	CLL: Medicare beneficiaries aged ≥66 years initiating oral targeted therapies	**Acalabrutinib** **Ibrutinib**	✓ Effectiveness
Ermann 2025[18,b] (related reports[19-21])	Retrospective cohort	🇺🇸	ONCare Alliance Network	CLL/SLL: Medicare-eligible patients receiving BTKi monotherapy	**Acalabrutinib** **Ibrutinib**	✓ Effectiveness ⊕ HCRU[18,b]
Yang 2025[22,b] (related report[23])	Retrospective cohort	🇺🇸	Symphony Integrated Dataverse	CLL: first-line BTKi therapy, with a focus on patients aged ≥65 years	**Zanubrutinib** **Acalabrutinib** **Ibrutinib**	✓ Effectiveness ⊕ HCRU
Fan 2025[24]	Retrospective cohort	🇨🇳	The Affiliated Hospital of Qingdao University	CLL: receiving treatment with BTKi	**Zanubrutinib** **Ibrutinib**	Safety
Fitzgerald 2024[25,b]	Retrospective cohort	🇺🇸	VHA	CLL: veterans initiating first-line treatment with BTKis	**Zanubrutinib** **Acalabrutinib** **Ibrutinib**	✓ Effectiveness
Fitzgerald 2025[26]	Retrospective cohort	🇺🇸	VHA	CLL/SLL: initiating and remaining on first-line BTKi monotherapy	**Acalabrutinib** **Ibrutinib**	⊕ HCRU

[a]Studies are organized alphabetically by data source to highlight their role in the context of RWE. [b]Conference abstract.
Abbreviations: BTKi, Bruton tyrosine kinase inhibitor; CLL, chronic lymphocytic leukemia; HCRU, healthcare resource utilization; KPNC, Kaiser Permanente Northern California; RWE, real-world evidence; SLL, small lymphocytic lymphoma; VHA, Veterans Health Administration.

Effectiveness of BTK Inhibitor Agents

- Due to heterogeneity in outcome reporting, results are only presented for five real-world studies reporting hazard ratios adjusted for baseline characteristics for ease of comparison
- Zanubrutinib demonstrated significantly better overall survival, time to next treatment (TTNT), and time to treatment discontinuation vs ibrutinib (**Figure 1**)
- Compared with acalabrutinib, zanubrutinib showed significantly improved treatment durability, with no significant difference in survival or TTNT (**Figure 1**)

Figure 1. Comparative Effectiveness of BTK Inhibitor Agents[a]

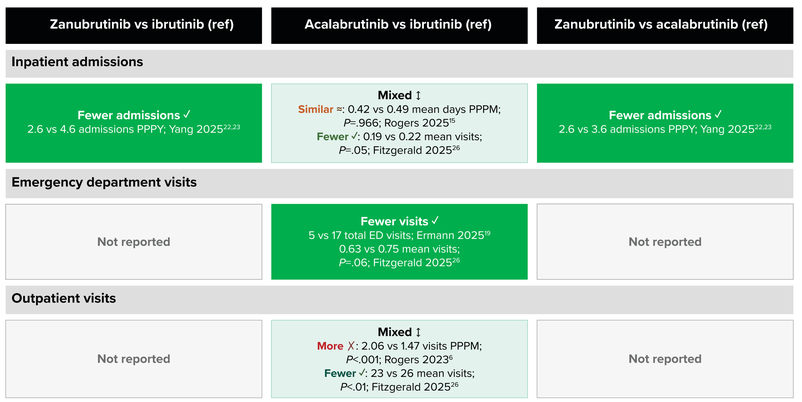


[a]Data are reported as HR and 95% CI. All HRs reflect the index treatment vs the comparator named in each column head. HR <1 favors the index treatment.
✓ significant improvement; X significant inferiority; ≈ comparable (nonsignificant).
Abbreviations: HR, hazard ratio; ref, reference.

Safety Outcomes and Healthcare Resource Utilization With BTK Inhibitor Agents

- Real-world safety data were very limited, with only two of 13 studies reporting adverse events; total adverse event rates were comparable between zanubrutinib and ibrutinib (35.2% vs 36.3%, respectively),[16] although zanubrutinib was associated with a significantly higher rate of serious adverse events (11.4% vs 4.4%; *P*=.03)[24]
- HCRU data comparing BTK inhibitors were also limited; zanubrutinib was associated with the lowest inpatient burden across BTK inhibitor agents, with significantly fewer admissions vs ibrutinib and acalabrutinib
- Mixed results were observed with acalabrutinib vs ibrutinib across studies and types of visit (**Figure 2**)

Figure 2. Comparative Healthcare Resource Utilization With BTK Inhibitor Agents[a]



[a]Results are presented for all-cause HCRU. All findings reflect the index treatment vs the comparator named in each column head.
✓ favorable; X not favorable; ≈ comparable.
Abbreviations: ED, emergency department; PPPM, per patient per month; PPPY, per patient per year; ref, reference.

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ACKNOWLEDGMENTS

This study was sponsored by BeOne Medicines, Ltd. Editorial support was provided by Nucleus Global, an Inizio company, and supported by BeOne Medicines.

DISCLOSURES

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Presented at ISPOR 2026; May 17-20, 2026; Philadelphia, PA, USA