Comparative efficacy and safety of zanubrutinib versus pirtobrutinib in US adults with relapsed/refractory CLL/SLL (as of December 2025)

Scope and key questions

This report compares the efficacy and safety of zanubrutinib (a covalent BTK inhibitor) and pirtobrutinib (a non-covalent BTK inhibitor) for adults with relapsed/refractory (R/R) chronic lymphocytic leukemia (CLL) or small lymphocytic lymphoma (SLL) in the United States. It prioritizes progression-free survival (PFS) and evaluates overall response rate (ORR), complete response (CR), duration of response (DOR), overall survival (OS), time to next treatment (TTNT), and minimal residual disease (MRD) when reported. Safety comparisons include overall and grade ≥3 adverse events (AEs), treatment discontinuation and dose modification, atrial fibrillation/flutter (AF), other cardiac events, bleeding, hematologic toxicities, hypertension, and infections. Findings are stratified by line of therapy, prior covalent BTK inhibitor (cBTKi) or venetoclax exposure, high-risk biology (del[17p]/TP53, IGHV status if available), and age/comorbidity subgroups when reported. Where direct head-to-head data are lacking, indirect comparisons are made with attention to study design and population differences.

US indications, dosing, and positioning in practice

Zanubrutinib (Brukinsa) received US approval for CLL/SLL on January 19, 2023. [1] The US label recommends 160 mg orally twice daily or 320 mg orally once daily until disease progression or unacceptable toxicity, with a reduced dose of 80 mg twice daily for severe hepatic impairment. [2] [2]

Pirtobrutinib (Jaypirca) received accelerated US approval on December 1, 2023 for adults with CLL/SLL after at least two prior lines of therapy, including a BTK inhibitor and a BCL-2 inhibitor. [4] The recommended dose is 200 mg orally once daily until disease progression or unacceptable toxicity. [5]

Within NCCN-derived educational materials for 2025, first-line CLL/SLL category 1 options include acalabrutinib ± obinutuzumab, venetoclax + obinutuzumab, and zanubrutinib. [6] [7] [8] In second-line and later settings, category 1 options include ibrutinib, venetoclax + rituximab (no del[17p]), acalabrutinib, and zanubrutinib; pirtobrutinib is listed as useful for BTKi resistance or intolerance. [9] For multi-refractory disease after BTKi and BCL-2 inhibitor exposure, preferred regimens include CAR-T (liso-cel) and pirtobrutinib if not previously given. [10]

Mechanisms of action and pharmacologic class context

Zanubrutinib is a next-generation covalent BTK inhibitor designed for high BTK occupancy and improved selectivity compared with first-generation agents; its clinical positioning is supported by head-to-head efficacy and safety advantages over ibrutinib in R/R CLL/SLL (ALPINE). [11]

Pirtobrutinib is a highly selective, non-covalent (reversible) BTK inhibitor that inhibits both wild-type and C481-mutant BTK with equal low-nanomolar potency, enabling activity after cBTKi failure driven by BTK C481 resistance mutations. [12]

Efficacy evidence in relapsed/refractory CLL/SLL

Zanubrutinib: randomized head-to-head data versus ibrutinib (ALPINE)

In the global phase 3 ALPINE trial (R/R CLL/SLL; n=652), zanubrutinib 160 mg twice daily demonstrated superior PFS versus ibrutinib 420 mg once daily at a median follow-up of 29.6 months (HR 0.65). [11] [13] [14] ORR was also higher with zanubrutinib (83.5% vs 74.2%). [15]

With extended follow-up of 42.5 months, the PFS benefit was sustained (HR 0.68), with a 36-month PFS of 65.4% versus 54.4%. [16] [17] Response depth improved over time, with

CR/CRi rates of 11.6% versus 7.7%. [18] The PFS advantage extended to patients with del(17p)/TP53 alterations (HR 0.51). [19]

Time-to-next-treatment was not a primary outcome in ALPINE and was not consistently reported across public summaries; thus, no definitive TTNT comparison to pirtobrutinib is available from ALPINE.

Pirtobrutinib: single-arm BRUIN and randomized BRUIN CLL-321

In the phase 1/2 BRUIN study (R/R CLL/SLL; n=317; majority cBTKi-pretreated), pirtobrutinib produced an ORR of 73.3% (82.2% including PR with lymphocytosis) and a median PFS of 19.6 months. [20] [21] [22]

In the randomized, open-label BRUIN CLL-321 trial (post-cBTKi), pirtobrutinib monotherapy improved PFS versus investigator's choice of idelalisib + rituximab or bendamustine + rituximab: median 14.0 versus 8.7 months (HR 0.54), at a median follow-up of 17.2 months. [23] [24] TTNT was also significantly longer: 24.0 versus 10.9 months (HR 0.37). [25] Investigator-assessed ORR (including PR-L) was 69% versus 50% for the control arm. [26] Effective crossover from control to pirtobrutinib occurred in 76% of eligible patients after progression, potentially diluting OS differences. [27]

Safety and tolerability profiles

Zanubrutinib

In ALPINE, zanubrutinib had a lower incidence of any-grade AF/flutter (5.2% vs 13.3%), fewer cardiac disorders overall (21.3% vs 29.6%), and fewer discontinuations due to AEs (15.4% vs 22.2%) than ibrutinib. [11] With longer follow-up, AF/flutter remained lower (7.1% vs 17.0%), with fewer cardiac events (25.9% vs 35.5%) and no cardiac deaths on zanubrutinib versus six with ibrutinib, despite similar hypertension rates. [31] [32] [33]

From the US label pooled safety population, key warnings include hemorrhage with grade ≥3 events in 3.8% (fatal 0.2%), serious infections with grade ≥3 events in 26% (fatal 3.2%), and atrial fibrillation/flutter in 4.4%. [34] [35] [36]

Pirtobrutinib

In BRUIN (phase 1/2), commonly observed AEs included infections (71%), bleeding (42.6%), and neutropenia (32.5%); grade ≥3 infections occurred in 28.1% and grade ≥3 neutropenia in 26.8%. [37] AF/flutter (3.8%), major hemorrhage (2.2%), and hypertension (14.2%) were infrequent, and 2.8% discontinued for treatment-related AEs. [38]

In BRUIN CLL-321, grade ≥3 treatment-emergent AEs were lower with pirtobrutinib (57.7%) than with idelalisib/rituximab or bendamustine/rituximab (73.4%), and discontinuations due to AEs were less frequent (17.2% vs 34.9%). [39] The pirtobrutinib US label further notes major hemorrhage in 3% (fatal 0.3%) and grade ≥3 infections in 24% (fatal 4.4%) in the pooled safety population. [40] [41]

Stratified findings by setting, prior therapies, risk biology, and age/comorbidity

Prior BTK inhibitor and venetoclax exposure strongly influence clinical choices. Pirtobrutinib has randomized evidence specifically after cBTKi exposure and is FDA-authorized after prior BTKi and BCL-2 inhibitor in the US. [23] [4] In BRUIN, median PFS was longer in patients without prior BCL-2 inhibitor exposure (23.0 months) than in those previously exposed (15.9 months), supporting a role earlier in the post-cBTKi sequence when BCL-2 therapy is still ahead. [12]

For high-risk biology, zanubrutinib's superiority over ibrutinib extends to del(17p)/TP53 subgroups (HR 0.51), strengthening its position among covalent BTKi options for genetically high-risk R/R disease. [19] IGHV-stratified outcomes are not consistently reported across these BTK monotherapy trials; however, in practice materials, second-generation BTK inhibitors such as zanubrutinib are favored in unmutated IGHV or TP53-aberrant disease contexts. [42]

Older age is common in CLL; zanubrutinib's broader development program included many older patients.

Cardiac comorbidity often influences BTK inhibitor choice. In ALPINE, no cardiac deaths occurred with zanubrutinib versus six in the ibrutinib arm, and AF/flutter was consistently lower with zanubrutinib, informing selection in patients at AF risk. [44] [11]

Study design differences affecting indirect comparisons

Cross-trial comparisons between zanubrutinib and pirtobrutinib must be interpreted cautiously due to differences in comparators, prior therapy exposure, and follow-up. ALPINE compared zanubrutinib to ibrutinib in R/R CLL/SLL and enrolled many BTKi-naïve patients, with follow-up now beyond 42 months. [11] [16] By contrast, BRUIN CLL-321 enrolled exclusively cBTKi-pretreated patients and used chemoimmunotherapy or PI3K-based control arms, with median follow-up of 17.2 months and substantial crossover to pirtobrutinib at progression. [45] [24] [27] These differences preclude valid indirect estimation of superiority between zanubrutinib and pirtobrutinib; rather, they support complementary roles at different points in the US treatment sequence.

Practical implications for US treatment sequencing

In R/R patients without prior BTKi, covalent BTK inhibitors remain standard options; within this class, zanubrutinib offers superior PFS and a more favorable cardiac safety profile versus ibrutinib in R/R CLL/SLL. [11] After prior cBTKi exposure, pirtobrutinib provides randomized PFS and TTNT advantages versus idelalisib/rituximab or bendamustine/rituximab, with fewer grade ≥3 AEs and discontinuations. [23] [25] [39] In multi-refractory patients previously treated with both BTKi and venetoclax, pirtobrutinib has an FDA-authorized role; CAR-T therapy (liso-cel) is an additional NCCN-listed option for appropriate candidates. [4] [10]

Summary table: efficacy and safety highlights by agent and setting

Agent	Trial/ setting	Population/ comparator	Efficacy	Safety/ tolerability
Zanubrutinib	ALPINE, R/R randomized vs ibrutinib	160 mg BID vs ibrutinib 420 mg QD; n=652; global R/R, many BTKi-naïve	PFS HR 0.65 at 29.6 mo; 24-mo PFS 78.4% vs 65.9%; ORR 83.5% vs 74.2%; sustained PFS HR 0.68 at 42.5 mo; 36-mo PFS	Any-grade AF/ flutter 5.2% vs 13.3%; cardiac disorders 21.3% vs 29.6%; AE discontinuations 15.4% vs 22.2%;

Agent	Trial/ setting	Population/ comparator	Efficacy	Safety/ tolerability
			65.4% vs 54.4%; CR/ CRi 11.6% vs 7.7%; HR 0.51 in del(17p)/ TP53	AF/flutter 7.1% vs 17.0% at longer follow-up; cardiac deaths 0 vs 6; similar hypertension rates [11] [14] [15] [16] [17] [18] [19] [11] [31] [33]
Pirtobrutinib	BRUIN (phase 1/2), single-arm	R/R CLL/SLL; n=317; majority post-cBTKi	ORR 73.3% (82.2% incl. PR-L); median PFS 19.6 mo; 12-mo OS 86.0%	Grade ≥3 infections 28.1%, grade ≥3 neutropenia 26.8%; AF/ flutter 3.8%; major hemorrhage 2.2%; HTN 14.2%; 2.8% discontinued for treatment-related AEs [21] [22] [20] [37] [38]
Pirtobrutinib	BRUIN CLL-321, randomized post-cBTKi	200 mg QD vs idelalisib+rituximab or bendamustine+rituximab	Median PFS 14.0 vs 8.7 mo (HR 0.54); median TTNT 24.0 vs 10.9 mo (HR 0.37); investigator-assessed ORR (incl. PR-L) 69% vs 50%; median follow-up 17.2 mo	Grade ≥3 TEAEs 57.7% vs 73.4%; discontinuations due to AEs 17.2% vs 34.9%; 76% effective crossover from control to pirtobrutinib after PD [23] [25] [26] [24] [39] [27]

Notes: PR-L = partial response with lymphocytosis; HTN = hypertension; PD = progressive disease. Cross-trial comparisons are limited by differences in prior therapies, comparators, and follow-up.

Safety class effects and label-level cautions relevant in US practice

Zanubrutinib carries class warnings for hemorrhage, serious infections, cytopenias, second primary malignancies, and cardiac arrhythmias, with label-reported grade ≥3 hemorrhage in 3.8% (fatal 0.2%) and grade ≥3 infections in 26% (fatal 3.2%). [34] [35] Pirtobrutinib labeling identifies major hemorrhage in 3% (fatal 0.3%) and grade ≥3 infections in 24% (fatal 4.4%) in pooled clinical experience. [40] [41] These data underscore the importance of infection prophylaxis/monitoring, bleeding risk mitigation, and cardiac assessment when selecting among BTK inhibitors in US practice.

Conclusions

- In R/R CLL/SLL without prior BTKi, zanubrutinib offers superior PFS and improved cardiac safety compared with ibrutinib, with sustained benefit into high-risk del(17p)/TP53 subgroups and lower AF/flutter and cardiac events over long-term follow-up. [11] [19] [31]
- In the post-cBTKi setting, pirtobrutinib demonstrates significant improvements in PFS and TTNT against idelalisib/rituximab or bendamustine/rituximab controls, with fewer grade ≥3 AEs and discontinuations; it is FDA-authorized after both BTKi and venetoclax and is recognized in NCCN-derived materials as a preferred option in multi-refractory disease if not previously given. [23] [25] [39] [4] [10]
- There is no head-to-head trial of zanubrutinib versus pirtobrutinib; their roles are complementary in US practice: zanubrutinib is a preferred covalent BTKi in earlier R/R lines, and pirtobrutinib is an active, well-tolerated option after cBTKi (and per FDA label, after both BTKi and venetoclax), with randomized evidence against non-BTKi controls. [8] [9] [23]

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