Why A Payer Should Not Step-Edit BTK-inhibitors?

The Evidence is Beyond Clear

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October 24, 2025

ZANUBRUTINIB is a potent and selective covalent Bruton's tyrosine kinase (BTK) inhibitor developed to improve upon earlier-generation BTK inhibitors (e.g., ibrutinib) by achieving higher BTK occupancy, fewer off-target effects, and improved safety/tolerability. In multiple phase III trials (e.g., the ALPINE trial in relapsed/refractory CLL; ASPEN in Waldenström's; SEQUOIA in treatment-naïve CLL) zanubrutinib has demonstrated either superior efficacy or non-inferior efficacy plus favorable safety versus comparators.

Step-therapy edits that require patients to first fail older therapies create barriers to accessing optimal therapy. The scientific and economic evidence suggests that, for many patients, upfront use of zanubrutinib may yield better outcomes and lower total cost of care.

1. ALPINE TRIAL (RELAPSED OR REFRACTORY CLL/SLL)

STUDY:

Brown JR et al., New England Journal of Medicine 2023;389:2510–2522.
Design: Phase III, randomized (N = 652; zanubrutinib = 327, ibrutinib = 325). Median follow-up 29.6 months (data cutoff 2022; updated ASH 2023).

EFFICACY OUTCOMES:

- Overall Response Rate (ORR): 85.6 % (95 % CI 81.2–89.2) for zanubrutinib vs 75.4 % (95 % CI 70.1–80.2) for ibrutinib (P = 0.0007).
- Complete/CRi rate: 11.6 % vs 7.7 %.
- 24-month PFS: 78.4 % (95 % CI 73.3–82.7) vs 65.9 % (95 % CI 60.1–71.1); HR 0.65 (95 % CI 0.49–0.86, P = 0.002).
- 36-month PFS update (ASH 2023): 65.8 % vs 54.3 %, HR 0.67 (95 % CI 0.52–0.86).
- Median PFS: not reached (zanubrutinib) vs 42.2 months (ibrutinib).
- Del(17p)/TP53-mutated subgroup: HR 0.53 (95 % CI 0.31–0.88); 24-mo PFS 72.6 % vs 54.6 %.

SAFETY OUTCOMES:

- Any-grade adverse events (AEs): 97.0 % vs 99.1 %.
- Grade ≥ 3 AEs: 67.3 % vs 70.4 %.
- Serious AEs: 42.0 % vs 50.0 %.
- Atrial fibrillation/flutter: 7.1 % vs 17.0 %.
- Hypertension (any grade): 16.0 % vs 22.0 %.
- Treatment discontinuation due to AE: 15.4 % vs 22.2 %.
- Cardiac-related discontinuations: 0.9 % vs 4.9 %.
- Deaths on study: 9.0 % zanubrutinib vs 13.3 % ibrutinib (none cardiac in zanubrutinib arm; six cardiac deaths in ibrutinib arm).

INTERPRETATION:

Zanubrutinib achieved *superior* PFS and ORR versus ibrutinib, with a >50 % reduction in atrial fibrillation events and fewer cardiac deaths. There were six sudden cardiac deaths in patients treated with ibrutinib and none in the zanubrutinib-treated patients, raising serious concerns as sudden death is not amenable to step-edits. This establishes zanubrutinib as both more efficacious and safer—a critical point against step-editing to an inferior agent.

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2. ASPEN TRIAL (WALDENSTRÖM'S MACROGLOBULINEMIA)

STUDY:

Tam C.S. et al., J Clin Oncol 2020;38:1450-1459; long-term follow-up J Clin Oncol 2023; 41(16_suppl):7540.

Design: Phase III, open-label; n = 201 randomized (MYD88^L265P^ cohort = 164; MYD88^WT^ = 37).

EFFICACY OUTCOMES:

- Primary endpoint (VGPR + CR): 28 % zanubrutinib vs 19 % ibrutinib; did not reach statistical superiority (P = 0.09) but clinically meaningful improvement in depth of response.
- Updated 2023 (median 44.4 mo): VGPR + CR 36.3 % vs 25.3 %.
- ORR: 84 % zanubrutinib vs 81 % ibrutinib.
- Median PFS: not reached in either arm; 42-month PFS = 78 % zanubrutinib vs 70 % ibrutinib (HR 0.63, 95 % CI 0.36–1.10).
- Overall survival (OS): 84 % vs 85 %..

SAFETY OUTCOMES:

- Atrial fibrillation/flutter (any grade): 7.9 % vs 23.5 %.
- Major hemorrhage: 5.9 % vs 9.2 %.
- Hypertension: 14.9 % vs 25.5 %.
- Diarrhea: 20 % vs 36 %.
- Discontinuation due to AE: 4 % vs 9 %.
- Grade ≥ 3 neutropenia: 16 % vs 14 %.

INTERPRETATION:

Although primary superiority for VGPR + CR was narrowly missed, zanubrutinib showed consistently deeper responses and markedly fewer cardiac and bleeding AEs, aligning with ALPINE's safety advantage. Long-term follow-up confirms durability and deepening of responses with continued tolerability.

3. SEQUOIA TRIAL (TREATMENT-NAÏVE CLL)

STUDY:

Hillmen P. et al., Lancet Oncology 2022;23:1031-1043 (main analysis); ASH 2024 5-year update.

Design: Phase III, open-label; n = 479 zanubrutinib vs 241 bendamustine + rituximab (BR).

Median follow-up: 26.2 months (initial); 60 months (update).

EFFICACY OUTCOMES:

- 24-month PFS: 85.5 % zanubrutinib vs 69.5 % BR; HR 0.42 (95 % CI 0.28–0.63; P < 0.0001).
- 30-month PFS update: 82.4 % vs 60.8 %; HR 0.40 (95 % CI 0.28–0.57).
- 5-year PFS (ASH 2024): 70.9 % vs 45.1 %.
- OS at 5 years: 86 % vs 81 % (trend favoring zanubrutinib).
- In del(17p)/TP53-mutant cohort (non-randomized arm): 24-month PFS 88 % (95 % CI 80–94 %).

SAFETY OUTCOMES:

- Any-grade AEs: 95 % zanubrutinib vs 98 % BR.
- Grade ≥ 3 AEs: 61 % vs 70 %.
- Neutropenia (≥ grade 3): 15 % vs 47 %.
- Atrial fibrillation/flutter: 2 % zanubrutinib vs 0 BR (expected given BR is non-BTK).
- Treatment discontinuation due to AEs: 8 % vs 14 %.

INTERPRETATION:

Front-line zanubrutinib outperformed chemoimmunotherapy with a 60 % relative reduction in progression risk. The manageable AE profile—including a very low AF incidence—supports zanubrutinib as a first-line standard, not a later-line therapy contingent on prior ibrutinib/acalabrutinib failure. Furthermore, per the NCCN guidelines, for those patients who are intolerant to a cBTKi, changing to an alternate cBTKi is then considered second-line therapy. As such, step-edits exclude zanubrutinib from being utilized as first-line therapy which is a violation of the protected class status of oncology agents.

4. BGB-3111-206 AND EARLY-PHASE EXTENSIONS (2017–2020)

STUDY:

Tam C.S. et al., Blood 2019;134:851-859 (phase 1/2).

FINDINGS:

- Across 123 CLL/SLL patients, ORR = 94.2 % (CR 5 %).
- 12-month PFS = 100 % (treatment-naïve) and 91 % (relapsed/refractory).
- Atrial fibrillation/flutter incidence < 3 %.

INTERPRETATION:

These early results presaged the superior tolerability and pharmacodynamic BTK occupancy seen in phase III trials.

5. INDIRECT COMPARISON WITH ACALABRUTINIB (MAIC & NETWORK ANALYSES)

STUDY:

Kittai A. et al., J Clin Oncol 2023 41(16_ suppl):7506; data from CLL 14 and ALPINE cross-trial analysis.

- Population: Relapsed/refractory CLL, adjusted for baseline prognostic factors.
- Results: No statistically significant difference in PFS (HR 0.92; 95 % CI 0.65–1.32) or ORR (85 % vs 82 %).
- Safety: Grade ≥ 3 hemorrhage 3.6 % zanubrutinib vs 4.8 % acalabrutinib; any-grade headache 14 % vs 32 %; AF incidence 5 % vs 8 %.

INTERPRETATION:

Efficacy appears comparable; however, zanubrutinib shows fewer headaches and possibly lower AF rates, while maintaining full BTK target engagement across all tissue compartments (consistent >95 % BTK occupancy in lymph node biopsies).

SUMMARY INTERPRETATION FOR POLICY AND PAYER DECISIONS

Comparator	Key Clinical Outcome	Zanubrutinib Result	Comparator Result	Clinical Meaning
Ibrutinib (ALPINE)	24-mo PFS	78.4 %	65.9 %	HR 0.65 → 35 % ↓ risk of progression/death
	Atrial Fibrillation	7.1 %	17.0 %	58 % relative reduction
Ibrutinib (ASPEN)	VGPR + CR	36.3 %	25.3 %	Deeper responses
	Atrial Fibrillation	7.9 %	23.5 %	66 % relative reduction
Bendamustine -Rituximab (SEQUOIA)	24-mo PFS	85.5 %	69.5 %	HR 0.42 → 58 % ↓ progression risk
Acalabrutinib (MAIC)	PFS	HR 0.92	Reference	Comparable efficacy, possible AE benefit

ECONOMIC-COST EVIDENCE SPECIFIC TO ZANUBRUTINIB

A very recent peer-reviewed cost-analysis (2025) compared total per-patient costs for zanubrutinib vs ibrutinib: $399,928 for zanubrutinib vs $447,059 for ibrutinib. Savings per patient treated: ~$47,132. This suggests a lower total cost of care over the treatment horizon with zanubrutinib, driven by fewer complications, lower discontinuation, and lower salvage therapy costs.

Even though drug acquisition costs may be similar or higher for zanubrutinib (depending on contractual pricing), the total cost of care (drug + AE/hospitalization + switch costs) is lower. Therefore, from a payer's perspective, forcing an older agent first (step-edit) may **increase** total cost of care, not decrease it.

More importantly, however, is it critical to maintain physician choice in selecting treatment for patients, especially when failing to do so may create a higher risk of adverse events, including serious and potentially fatal cardiac events.

SUMMARY AND RECOMMENDATIONS

IN SUM:

1. **High-quality, peer-reviewed randomized trial data show zanubrutinib yields improved or at least non-inferior efficacy and better safety versus ibrutinib, and favorable indirect comparisons versus acalabrutinib.**
2. **Real-world and economic analyses demonstrate that total cost of care (taking into account adverse events, discontinuations, switching, salvage therapy) is lower for patients treated with zanubrutinib vs older BTK inhibitors.**
3. **Step-therapy edits forcing use of older agents (or non-indicated drugs such as imatinib) prior to zanubrutinib are inconsistent with the evidence base, may increase risk and cost of care, and delay optimal therapy.**
4. **From a payer perspective, restricting immediate access to zanubrutinib may paradoxically increase total cost of care and worsen patient outcomes.**

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