Real-World Safety Comparison of BTK Inhibitors in Chronic Lymphocytic Leukemia: A Propensity Score–Matched Analysis of Acalabrutinib, Ibrutinib, and Zanubrutinib

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INTRODUCTION

BTK inhibitors (BTKi) are foundational, continuously administered therapies for chronic lymphocytic leukemia (CLL).

As treatment duration increases, off-target toxicities such as infections, cardiotoxicity, and hepatotoxicity become increasingly relevant. Next-generation BTKis (acalabrutinib and zanubrutinib) were developed to improve on ibrutinib's safety profile, but comparative real-world data across all three agents remain limited.

AIM

Objective: To compare real-world safety outcomes: mortality, cardiotoxicity, infection, and hepatotoxicity, among adults with CLL treated with first-line single-agent ibrutinib, acalabrutinib, or zanubrutinib, using propensity score-matched cohorts from the TriNetX network.

METHOD

- **Design:** Retrospective, propensity score–matched cohort study using the TriNetX database.
- **Population:** Adults with CLL receiving first-ever single-agent ibrutinib, acalabrutinib, or zanubrutinib; excluded if prior BTKi or concurrent anti-CD20 therapy.
- **Matching:** 1:1 PSM for age, sex, comorbidities, infection-related diagnoses, immunomodulating medication use, and baseline labs (cell counts, creatinine, albumin).
- **Comparisons:** Ibrutinib vs. zanubrutinib; acalabrutinib vs. zanubrutinib; acalabrutinib vs. ibrutinib.
- **Outcomes (30–365 days):** Death; cardiotoxicity (atrial/ventricular arrhythmia, heart failure); infection (sepsis, pneumonia, bacteremia); hepatotoxicity (transaminase elevation).

CONCLUSIONS

Zanubrutinib demonstrated the most favorable real-world safety profile, significantly reducing cardiotoxic, infectious, and hepatic complications compared with ibrutinib and acalabrutinib.

Acalabrutinib remains safer than ibrutinib, which exhibited the highest toxicity burden.

Although both next-generation agents are superior to ibrutinib, they are not safety-interchangeable, findings that can help guide treatment selection for patients at high risk for off-target complications.

RESULTS

Three pairwise, 1:1 propensity score–matched comparisons were performed:

- Ibrutinib vs. zanubrutinib (n = 1,622 each)
- Acalabrutinib vs. zanubrutinib (n = 1,618 each)
- Acalabrutinib vs. ibrutinib (n = 3,132 each)

Outcomes were assessed 30–365 days after treatment initiation: death, cardiotoxicity, infection, and hepatotoxicity.

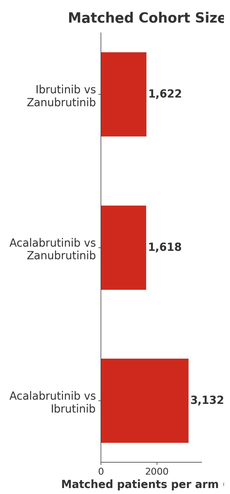

Figure 1. Patients per arm in each 1:1 matched comparison.

Outcome	Ibrutinib vs. Zanubrutinib (n=1,622 each)	Acalabrutinib vs. Zanubrutinib (n=1,618 each)	Ibrutinib vs. Acalabrutinib (n=3,132 each)
Death	32.0% vs 11.8% P<0.001	16.0% vs 11.9% P=0.001	31.6% vs 15.4% P<0.001
Infection	44.1% vs 18.3% P<0.001	29.0% vs 18.3% P<0.001	45.9% vs 28.4% P<0.001
Heart failure	16.0% vs 5.7% P=0.004	8.4% vs 5.6% P=0.004	16.1% vs 7.9% P<0.001
Atrial fibrillation	20.5% vs 4.9% P<0.001	9.7% vs 4.9% P<0.001	19.9% vs 8.9% P<0.001
Ventricular arrhythmia	4.9% vs 1.4% P<0.001	2.1% vs 1.3% P=0.101 (NS)	4.3% vs 2.0% P<0.001
Transaminase elevation	4.7% vs 2.1% P<0.001	3.5% vs 2.1% P=0.015	4.4% vs 3.0% P=0.003

ACKNOWLEDGEMENTS

Analysis conducted using the TriNetX Research Network.

ABBREVIATIONS

BTKi = Bruton tyrosine kinase inhibitor
CLL = chronic lymphocytic leukemia
CD20 = cluster of differentiation 20
PSM = propensity score matching