REAL-WORLD COMPARATIVE OUTCOMES OF SECOND-GENERATION (ZANUBRUTINIB/ACALABRUTINIB) VERSUS FIRST-GENERATION (IBRUTINIB) BTK INHIBITORS IN WALDENSTRÖM MACROGLOBULINEMIA: A PROPENSITY-MATCHED COHORT STUDY

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Introduction

- Bruton tyrosine kinase (BTK) inhibitors have transformed the management of Waldenström macroglobulinemia (WM).
- Ibrutinib, the first-in-class BTK inhibitor, improves response rates but is limited by off-target toxicities.
- Second-generation agents, zanubrutinib and acalabrutinib offer greater BTK selectivity and potentially improved tolerability, yet head-to-head randomized evidence in WM is scarce and real-world comparative data remain limited.
- To inform everyday practice, we leveraged a large EHR network to compare survival and safety outcomes between second-generation BTK inhibitors and ibrutinib in routine care.

Aim

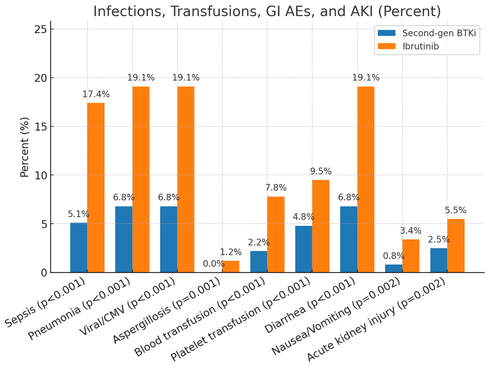
- To evaluate real-world effectiveness and safety of second-generation BTK inhibitors (zanubrutinib/acalabrutinib) versus first-generation ibrutinib in patients with WM.

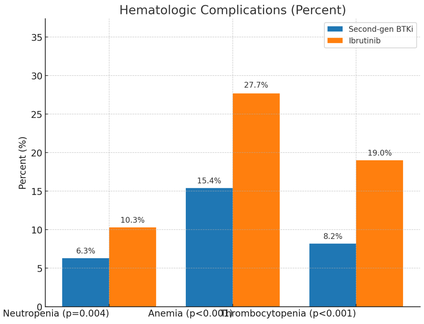
Objectives

- Primary objective: compare all-cause mortality and 5-year survival probability between treatment cohorts after propensity score matching.
- Key secondary objectives: compare hematologic toxicities, infectious complications, gastrointestinal events, acute kidney injury, transfusion requirements, thromboembolic events (DVT/PE), major cardiac events (cardiac arrest, heart failure, myocardial infarction), and rates of secondary malignancies.

Methods

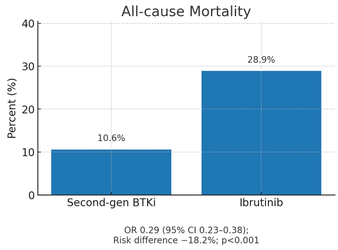
- We conducted a retrospective cohort study using the TriNetX global federated network. Adults (18–99 years) with WM who initiated a BTK inhibitor were identified and grouped as second-generation (zanubrutinib or acalabrutinib) versus first-generation (ibrutinib).
- Patients with overlapping systemic therapies were excluded. Propensity score matching (1:1; n=847 per group) balanced baseline characteristics.
- Outcomes were assessed over a maximum of 5 years. Effectiveness was evaluated using Kaplan–Meier estimates (5-year survival probability) and Cox proportional hazards models (hazard ratios [HR]); event risks were compared using odds ratios (OR), risk differences, and two-sided p-values with 95% confidence intervals (CI)





Results

- Second-generation BTK inhibitors were associated with significantly lower all-cause mortality than ibrutinib (10.6% vs 28.9%; risk difference −18.2%; OR 0.29, 95% CI 0.23–0.38; p<0.001).
- Five-year survival probability was higher with second-generation agents (82.5% vs 53.5%; HR 0.68, 95% CI 0.53–0.87; p=0.002).
- Second-generation therapy had lower neutropenia (6.3% vs 10.3%; p=0.004), anemia (15.4% vs 27.7%; p<0.001), thrombocytopenia (8.2% vs 19.0%; p<0.001), sepsis (5.1% vs 17.4%; p<0.001), pneumonia (6.8% vs 19.1%; p<0.001), and viral/CMV infections (6.8% vs 19.1%; p<0.001).
- Aspergillosis occurred only with ibrutinib (0% vs 1.2%; p=0.001).
- Transfusion needs were reduced with second-generation agents (blood: 2.2% vs 7.8%; p<0.001; platelets: 4.8% vs 9.5%; p<0.001).
- Gastrointestinal events were less frequent (diarrhea: 6.8% vs 19.1%; p<0.001; nausea/vomiting: 0.8% vs 3.4%; p=0.002) and acute kidney injury was lower (2.5% vs 5.5%; p=0.002).
- No statistically significant differences were observed in pulmonary embolism, deep vein thrombosis, cardiac arrest, heart failure, myocardial infarction, or secondary malignancies (AML, MDS, breast, lung, thyroid, colorectal).



OR 0.29 (95% CI 0.23–0.38);
Risk difference −18.2%; p<0.001

Summary

- In this large, propensity-matched real-world cohort of patients with WM, second-generation BTK inhibitors (zanubrutinib/acalabrutinib) were associated with improved survival and a substantially more favorable safety profile compared with ibrutinib.
- Hematologic suppression, serious infections, gastrointestinal toxicity, transfusion requirements, and acute kidney injury were all lower with second-generation therapy, while cardiovascular and secondary malignancy risks were similar between groups.

Discussion

- These findings support preferential use of second-generation BTK inhibitors in routine WM practice, aligning pharmacologic selectivity with clinically meaningful gains in tolerability and survival.
- The absence of excess thrombotic, cardiac, or secondary malignancy signals suggests that improved selectivity does not trade off long-term safety in these domains.
- Clinically, lower infection and cytopenia rates may reduce treatment interruptions, transfusions, and hospitalizations, thereby enhancing quality of life and care efficiency.
- Limitations include the retrospective design, reliance on coded EHR data, potential for unmeasured confounding, and lack of granular disease metrics (e.g., MYD88/CXCR4 status, IgM response depth, prior BTK exposure details) in all sites. While propensity matching mitigates imbalance, causal inference cannot be confirmed.
- Future work should validate these results in molecularly annotated cohorts, explore time-to-event toxicity and dose-modification patterns, and assess cost-effectiveness and patient-reported outcomes across BTK inhibitor generations.

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