Comparing Ibrutinib with Acalabrutinib and Zanubrutinib in B-Cell Malignancies: A Real-World Study of Mortality and Toxicity

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INTRODUCTION

Covalent Bruton tyrosine kinase (BTK) inhibitors are widely used to treat B-cell malignancies. Second-generation BTK inhibitors have demonstrated improved tolerability in clinical trials, but comparative real-world data on mortality and major toxicities remain limited.

AIM

To compare all-cause mortality and major cardiopulmonary and bleeding toxicities in patients receiving Ibrutinib versus Acalabrutinib or Zanubrutinib for B-cell malignancies in a large real-world cohort.

METHOD

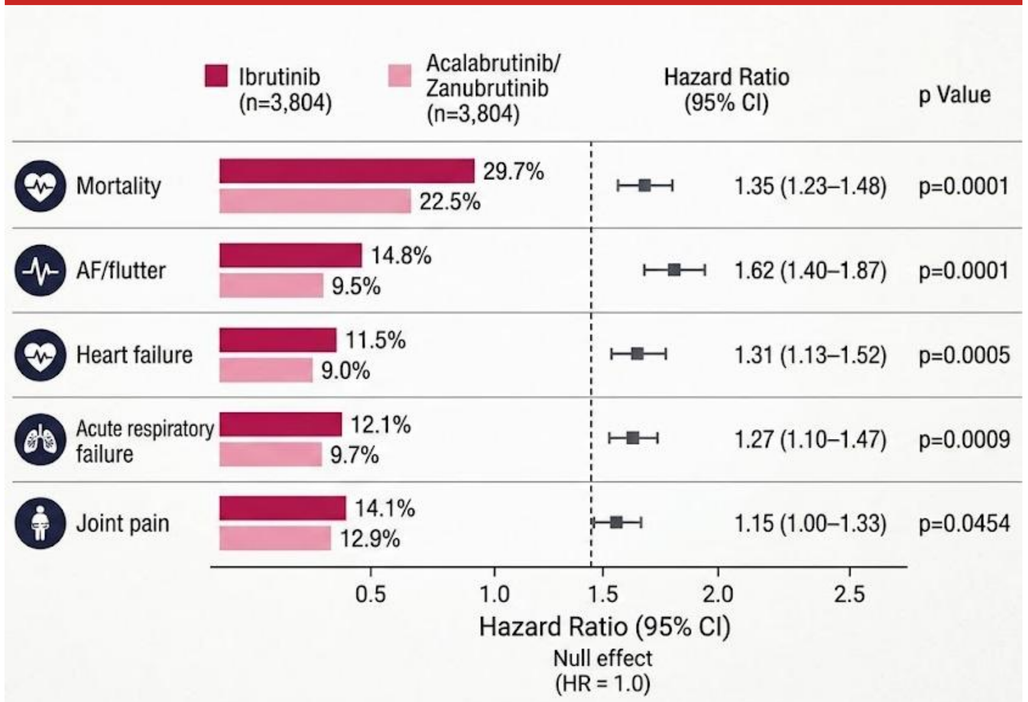
- Retrospective cohort study using the TriNetX Global Collaborative Network.
- Adults with chronic lymphocytic leukemia, Waldenström macroglobulinemia, or mantle cell lymphoma.
- Compared Ibrutinib with Acalabrutinib/Zanubrutinib; patients with prior BTK inhibitor exposure were excluded.
- 1:1 propensity-score matching balanced demographics, cardiovascular comorbidities, bleeding-risk factors, and anticoagulant/antiplatelet use.
- Matched cohorts: 3,804 patients per group.
- Primary outcome: all-cause mortality.
- Secondary outcomes: atrial fibrillation/flutter, heart failure, gastrointestinal hemorrhage, acute respiratory failure, emergency endotracheal intubation, arthralgia, myalgia, and other hemorrhage.
- Analyses: Kaplan–Meier methods and Cox proportional-hazards models.

RESULTS

Key finding : Ibrutinib was associated with a 35% higher risk of all-cause mortality versus Acalabrutinib/Zanubrutinib.

29.7% vs 22.5% | HR 1.35 (95% CI, 1.23–1.48) | p < 0.0001

Median survival: 2,642 vs 4,306 days.



Gastrointestinal hemorrhage, emergency endotracheal intubation, myalgia, and nonspecific hemorrhage were similar between groups.

CONCLUSION

Ibrutinib was associated with higher all-cause mortality and greater cardiopulmonary toxicity than second-generation BTK inhibitors.

The excess mortality may reflect off-target kinase inhibition in an older, comorbid population.

These findings support consideration of Acalabrutinib or Zanubrutinib when clinically appropriate and underscore the importance of careful cardiovascular risk assessment for patients receiving ibrutinib.

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DISCLOSURES

The authors have no relevant conflicts of interest to disclose.

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