Comparative Cardiac Safety of Covalent and Non-Covalent Bruton Tyrosine Kinase Inhibitors in Mantle Cell Lymphoma- A Multi-Center Retrospective Cohort Study

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INTRODUCTION

- Second-generation BTKi (Acalabrutinib and Zanubrutinib) and the non-covalent BTKi Pirtobrutinib are increasingly used in mantle cell lymphoma (MCL).
- Much of their safety data has been extrapolated from trials in other B-cell malignancies (ELEVATE-RR, ALPINE, ASPEN).
- We evaluated the comparative cardiovascular, infectious, and bleeding risks of BTKi therapy in MCL patients in a real-world setting.

AIM

To compare the 1-year risks of cardiac, infectious, and major bleeding events among different BTKi regimens in MCL patients.

METHODS

- **Design:** Multicenter retrospective cohort study using the TriNetX Global Collaborative Network.
- **Population:** Adult MCL patients diagnosed between 2018 and 2025.
- **Exposure:** Stratified by first BTKi exposure with no prior exposure to alternative BTKi agents within 1 year prior to index date.
- **Comparisons (1:1 PSM):**
  (1) Acalabrutinib vs Ibrutinib
  (2) Zanubrutinib vs Ibrutinib
  (3) Acalabrutinib vs Zanubrutinib
  (4) Pirtobrutinib vs pooled 2nd-generation BTKi
- **PSM Factors:** Demographics, co-morbidities, and prior medication use.

RESULTS

Post-PSM matched cohort sizes (per comparison)

- Acalabrutinib vs Ibrutinib: **531 vs 531**
- Zanubrutinib vs Ibrutinib: **254 vs 254**
- Acalabrutinib vs Zanubrutinib: **475 vs 475**
- Pirtobrutinib vs pooled 2nd-gen BTKi: **190 vs 190**

Hazard Ratios (HR) with 95% Confidence Intervals for 1-Year Outcomes

Comparison	Cardiac Composite (Primary Outcome) HR (95% CI)	Infections (Secondary Outcome) HR (95% CI)	Major Bleeding (Secondary Outcome) HR (95% CI)
Acalabrutinib vs Ibrutinib (n=531 vs 531)	**0.86** (0.73 – 1.02)	**0.88** (0.67 – 1.16)	**0.82** (0.53 – 1.29)
Zanubrutinib vs Ibrutinib (n=254 vs 254)	**0.95** (0.75 – 1.20)	**0.83** (0.56 – 1.23)	**0.97** (0.54 – 1.73)
Acalabrutinib vs Zanubrutinib (n=475 vs 475)	**0.84** (0.71 – 1.00)	**0.97** (0.72 – 1.31)	**0.70** (0.42 – 1.14)
Pirtobrutinib vs Pooled 2nd-gen BTKi (n=190 vs 190)	**1.33** (1.00 – 1.77)	**1.56** (1.03 – 2.36)	**1.66** (0.78 – 3.56)

HR >1 favors comparator; HR <1 favors first agent.

CONCLUSIONS

- Second-generation BTKi (Acalabrutinib and Zanubrutinib) did not demonstrate significantly improved cardiovascular, infectious, or bleeding safety profiles compared with Ibrutinib in MCL patients within one year of therapy initiation.
- Pirtobrutinib was associated with higher cardiac and infectious complications compared with pooled second-generation BTKi.
- Interpretation is limited by small sample size and shorter follow-up for Pirtobrutinib.

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