

Title: Real-world outcomes with Bruton's Tyrosine Kinase inhibitors in patients with Waldenstrom macroglobulinemia

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Background: Bruton's tyrosine kinase inhibitors (BTKis) are effective therapies for Waldenström macroglobulinemia (WM), particularly in *MYD88*L265P-mutated disease, but comparative real-world data are limited. We evaluated the survival and toxicity outcomes of BTKi therapy in routine clinical practice.

Methods: We retrospectively reviewed patients with WM treated with ibrutinib or zanubrutinib monotherapy between January 2015 and December 2025 in the treatment-naïve (TNWM) or relapsed/refractory (RRWM) settings. We collected data regarding progression-free survival (PFS), event-free survival (EFS; defined as time to progression, death or drug discontinuation from any cause) and treatment-related toxicities. Patients stopping due to toxicity but not progressed were censored for PFS calculation at the date of stopping.

Results: A total of 402 patients (462 BTKi treatment initiations) were identified. Median follow-up from BTKi initiation was 6.0 years for ibrutinib and 1.9 years for zanubrutinib. Ibrutinib was used more frequently than zanubrutinib (249 vs 213 initiations), whereas zanubrutinib was more commonly used in TNWM (40.8% vs 25.7%, $p < 0.001$). Among those tested, 87.7% (292/333) harbored *MYD88*L265P mutations and 33.6% (44/131) had *CXCR4* mutations. Baseline clinical characteristics were similar between treatment groups.

Response data were available for 215 patients. In TNWM, ORR was 91.7% with ibrutinib and 91.3% with zanubrutinib. In RRWM, ORR was 85.9% and 83.5%, respectively. With ibrutinib, the 2- and 4-year PFS rates were 72.6% and 54.8%, respectively, with a median PFS of 4.8 years. Corresponding PFS rates with zanubrutinib were 76.9% and 64.5%, with median PFS not reached ($p = 0.21$). Median EFS was longer with zanubrutinib vs. ibrutinib (2.8 vs 1.5 years; $p = 0.033$).

In TNWM, the 2-year PFS rate was numerically higher with zanubrutinib than ibrutinib (84.4% vs 69.1%; $p=0.06$), whereas median PFS was similar in RRWM (4.4 vs 4.8 years; $p=0.89$). No significant differences in PFS were observed between ibrutinib and zanubrutinib within *MYD88*^{L265P}, *MYD88*^{WT}, *CXCR4*^{MUT} or *CXCR4*^{WT} subgroups.

Within the ibrutinib cohort, median PFS was numerically longer in *MYD88*^{L265P} versus *MYD88*^{WT} WM (4.7 vs 2.0 years; $p=0.38$) and in *CXCR4*^{WT} versus *CXCR4*^{MUT} WM (5.6 vs 3.4 years; $p=0.07$). In the zanubrutinib cohort, median PFS was not reached in *MYD88*^{L265P} versus 3.3 years in *MYD88*^{WT} WM ($p=0.087$) and was not reached irrespective of *CXCR4* status.

Overall, 39.2% (181/462) treatments were stopped due to toxicity, more frequently with ibrutinib than zanubrutinib (47.8% vs 29.1%). The most common reasons for discontinuation were cardiovascular events (24.4% vs 11.3%), bleeding/bruising (9.2% vs 15.5%), and infection (11.8% vs 11.3%) for ibrutinib and zanubrutinib, respectively. Atrial fibrillation occurred more often with ibrutinib than zanubrutinib (21.7% vs 4.7%; $p<0.001$), whereas rates of hypertension (11.2% vs 7.0%), infection requiring hospitalization (10.8% vs 8.9%), and bleeding requiring treatment interruption (6.3% vs 6.1%) were similar between ibrutinib and zanubrutinib, respectively.

Conclusion:

In this real-world cohort, both ibrutinib and zanubrutinib achieved high response rates and demonstrated comparable PFS, although zanubrutinib was associated with longer EFS, fewer treatment discontinuations, and less cardiovascular toxicity, particularly atrial fibrillation. These findings support individualized BTKi selection based on toxicity profile and patient comorbidities.

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