

Initial dose drives efficacy and subsequent reductions manage toxicity with zanubrutinib in Waldenström macroglobulinemia

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Background: Zanubrutinib is the preferred Bruton tyrosine kinase inhibitor (BTKi) for Waldenström macroglobulinemia and is endorsed by NCCN and IWWM-12 guidelines. However, the landmark ASPEN trial evaluated only the 160 mg twice-daily schedule and did not address alternative dosing patterns commonly used in routine practice. We evaluated initial dosing strategies and subsequent dose reductions in a large cohort of consecutive WM patients treated with zanubrutinib monotherapy.

Methods: We evaluated 236 consecutive WM patients who received zanubrutinib monotherapy between 2018 and 2025. Responses were assessed per IWWM-11 criteria. The primary exposures were (1) initial dosing (standard: 160 mg twice-daily or 320 mg daily vs. sub-standard: <320 mg daily) and (2) subsequent dose reductions. The primary outcomes were very good partial response (VGPR) and progression-free survival (PFS). Multivariable logistic and Cox regression models identified independent predictors of VGPR and PFS, adjusted for age, sex, *MYD88*, *CXCR4*, *TP53*, ECOG performance status, prior therapy, and MSS-WM risk category.

Results: Among 236 patients (median age 72, 42% female, 56% treatment naïve), 193 (82%) initiated 160 mg twice-daily (BID), 22 (9%) initiated 320 mg once-daily (QD), and 21 (9%) initiated sub-standard dosing (<320 mg daily). With a median follow-up of 33 months (95% CI 30.4-35.2), standard-dose regimens produced comparable outcomes: VGPR 39% (71/184) with 160 mg twice-daily vs. 40% (8/20) with 320 mg once-daily ($p=0.90$), and 30-month PFS rate 89% vs. 89% ($p=0.86$). Sub-standard initiation yielded inferior efficacy, with VGPR of 14% (3/21; $p=0.03$) and a 30-month PFS rate of 54% ($p<0.001$). In multivariable analysis, sub-standard initiation independently predicted lower VGPR attainment (OR 0.10;

95% CI 0.01-0.86; $p=0.04$) and worse PFS (HR 11.09; 95% CI 2.62-46.99; $p=0.001$). Among patients who started at standard dose, 51/215 (24%) required a subsequent dose reduction at a median of 5.02 months (range, 0.26-48.3). With a median follow-up after dose reduction of 32.7 months, 17/38 patients (45%) experienced a deepened response over time, 20/38 (53%) maintained the same categorical response, and only 1 (3%) remained without a response. Subsequent dose reductions did not impact outcomes (VGPR 49% vs. 36%, $p=0.09$; 30-month PFS rate 95% vs. 88%, $p=0.13$), an observation confirmed in multivariable analysis (OR for VGPR 2.33, $p=0.16$; HR for PFS 0.40, $p=0.29$). Dose reductions improved symptoms in 36/51 patients (67%). The lowest daily dose reached after reduction was not associated with symptom improvement, but the type of toxicity was with the highest improvement rates for gastrointestinal (9/10; 90%), rheumatologic (11/14; 79%), and cardiac (7/11; 64%) adverse events, and limited improvement for bleeding (2/6; 33%) and edema (1/5; 20%). Overall, 19 patients (9%) discontinued therapy due to toxicity, most commonly in the context of bleeding (6/8; 75%), edema (5/6; 83%), and fatigue (5/9; 56%).

Conclusions: In this largest off-trial WM cohort, the 160 mg twice-daily and 320 mg once-daily schedules produced equivalent efficacy, while sub-standard initiation independently worsened outcomes and subsequent toxicity-driven dose reductions preserved efficacy and improved symptoms. These findings support standard-dose zanubrutinib initiation with either schedule and dose reductions only after standard-dose initiation for toxicity management in WM.

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