

## Long-Term Follow-Up Results of a Phase 3 Randomized Trial of Zanubrutinib vs Ibrutinib in Patients With Waldenström Macroglobulinemia (WM)

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### Abstract:

**Introduction:** ASPEN is a randomized, open-label, phase 3 study comparing zanubrutinib, a potent and selective Bruton tyrosine kinase inhibitor (BTKi), with the first-generation BTKi, ibrutinib, in Waldenström macroglobulinemia (WM).

**Objective:** Here, data with a median follow-up of 43 months are presented.

**Materials and Methods:** In cohort 1, patients with *MYD88* mutations were randomized 1:1 to receive zanubrutinib 160 mg twice daily or ibrutinib 420 mg once daily; stratification factors were *CXCR4* mutation status and prior lines of therapy. In cohort 2, patients without *MYD88* mutations received zanubrutinib 160 mg twice daily. The primary endpoint was the proportion of patients with complete response or very good partial response (CR+VGPR).

**Results:** Cohort 1 enrolled 201 patients (zanubrutinib: n=102; ibrutinib: n=99) and cohort 2 enrolled 28 patients. More cohort 1 patients in the zanubrutinib vs ibrutinib arm had *CXCR4* mutations (32% [33/98] vs 20% [20/92] with next-generation sequencing data) and were aged >75 years (33% vs 22%). With median treatment durations of 42 (zanubrutinib) and 41 (ibrutinib) months, 67% and 58% of patients remain on treatment, respectively. The investigator-assessed CR+VGPR rate was 36% vs 22% for zanubrutinib vs ibrutinib ( $P=.02$ ) in cohort 1 and 31% in cohort 2, which included 1 CR. The CR+VGPR rates for patients with wild-type *CXCR4* were 45% vs 28% (zanubrutinib vs ibrutinib;  $P=.04$ ) and 21% vs 5% ( $P=.15$ ) for patients with mutated *CXCR4*. Median progression-free survival and overall survival were not yet reached. Rates of atrial fibrillation, diarrhea, hypertension, localized infection, hemorrhage, muscle spasms, pneumonia, Grade  $\geq 3$  infection, and adverse events leading to discontinuation/death were lower for zanubrutinib vs ibrutinib, as were exposure-adjusted incidence rates of atrial fibrillation/flutter and hypertension (0.2 vs 0.8 and 0.5 vs 1.0 persons/100 person-months;  $P<.05$ ); the neutropenia rate was higher for zanubrutinib. Safety outcomes were similar for zanubrutinib between cohorts.

**Conclusion:** ASPEN is the largest phase 3 WM trial with a head-to-head BTKi comparison. At a median follow-up of 43 months, zanubrutinib had higher CR+VGPR rates and clinically meaningful advantages in long-term safety/tolerability vs ibrutinib.