ASPEN: Long-Term Follow-Up Results of a Phase 3 Randomized Trial of Zanubrutinib vs Ibrutinib in Patients With Waldenström Macroglobulinemia

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Abstract

Context: 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). Data with a median follow-up of 43 months are presented.

Design: In cohort 1, patients with *MYD88* mutations were randomized 1:1 to receive zanubrutinib 160 mg twice daily or ibrutinib 420 mg once daily; stratifications were *CXCR4* mutations and prior lines of therapy. In cohort 2, patients without *MYD88* mutations received zanubrutinib 160 mg twice daily.

Main Outcomes Measures: The primary endpoint was the proportion of patients with complete response/very good partial response (CR+VGPR).

Results: In cohorts 1 and 2, 201 (zanubrutinib=102; ibrutinib=99) and 28 patients were enrolled, respectively. More cohort 1 patients in the zanubrutinib versus 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% remain on treatment, respectively. Investigator-assessed CR+VGPR rate was 36% versus 22% (zanubrutinib vs ibrutinib; *P*=0.02) and 31% in cohort 2 (1 CR). CR+VGPR rates for wild-type *CXCR4* were 45% versus 28% (zanubrutinib vs ibrutinib; *P*=0.04) and were 21% versus 5% (*P*=0.15) for 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 ≥3 infection, and adverse events leading to discontinuation/death were lower for zanubrutinib versus 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*<0.05); neutropenia rate was higher. Zanubrutinib safety outcomes were similar between cohorts.

Conclusions: ASPEN is the largest phase 3 WM trial with 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 versus ibrutinib.