

**Abstract Title:** ASPEN: RESULTS OF A PHASE 3 RANDOMIZED TRIAL OF ZANUBRUTINIB VERSUS IBRUTINIB FOR PATIENTS WITH WALDENSTRÖM MACROGLOBULINEMIA

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**Introduction:** Bruton's tyrosine kinase (BTK) inhibition is an emerging standard of care for Waldenström macroglobulinemia (WM). Zanubrutinib is a potent, specific next-generation BTK inhibitor with higher selectivity for BTK compared with TEC- and EGFR-family kinases, which may be related to off-target toxicities. ASPEN (NCT03053440) is a randomized phase 3 study comparing zanubrutinib, a potent and selective BTK inhibitor, versus ibrutinib, a first-generation BTK inhibitor, in patients with WM.

**Methods:** At ASPEN study entry, *MYD88* gene mutations were assessed by a central laboratory (NeoGenomics). Patients with *MYD88*-mutation-positive (*MYD88*<sup>mut+</sup>) WM were randomized (1:1) to receive zanubrutinib (160 mg twice daily) or ibrutinib (420 mg once daily). Patients without *MYD88* mutations were assigned to a separate cohort to receive

zanubrutinib; these results are reported separately. Randomization was stratified by *CXCR4* mutational status and prior lines of therapy (0 vs 1-3 vs >3). The primary endpoint was the proportion of patients achieving very good partial response (VGPR) or better. Sample size was calculated to provide 81% power to detect a 35% versus 15% difference in rates of VGPR or better in the subset of patients with relapsed or refractory WM. Primary analysis was planned to occur at ~12 months after the last patient enrolled.

**Results:** Overall, 201 patients with *MYD88*<sup>mut+</sup> WM were randomized to receive zanubrutinib (n=102) or ibrutinib (n=99). While the treatment groups were well balanced for most baseline factors, more elderly patients (>75 years, 33.3% vs 22.2%) and more patients with anemia (hemoglobin ≤110 g/L, 65.7% vs 53.5%) were randomized to receive zanubrutinib than ibrutinib. At a median follow-up of 19.4 months, VGPR rate was higher with zanubrutinib than ibrutinib (28.4% vs 19.2%; 2-sided *P*=0.09). No complete responses were observed. Rates of atrial fibrillation, contusion, diarrhea, peripheral edema, hemorrhage, muscle spasms, pneumonia, and adverse events leading to discontinuation or death were lower with zanubrutinib compared with ibrutinib. Although the rate of neutropenia was higher with zanubrutinib (29.7% vs 13.3%) (Table), grade ≥3 infection rates were similar between treatments (17.8% vs 19.4%).

**Conclusions:** ASPEN is the largest phase 3 trial of BTK inhibitors in WM and the first head-to-head comparison of BTK inhibitors in any disease. Although not statistically significant, compared with ibrutinib, zanubrutinib was associated with a higher VGPR response rate and demonstrated clinically meaningful advantages in safety and tolerability in patients with WM.

**Table.**

	<b>Zanubrutinib (N=102)</b>	<b>Ibrutinib (N=99)</b>
<b>Efficacy (overall population) (%)</b>		
VGPR rate	28.4	19.2
12-month PFS	89.7	87.2
12-month OS	97.0	93.9
<b>Efficacy (R/R population)<sup>a</sup> (%)</b>		
12-month PFS (95% CI)	92.4 (83.8-96.5)	85.9 (75.9-91.9)
12-month OS (95% CI)	98.8 (91.6-99.8)	92.5 (84.1-96.6)
<b>Safety/tolerability profile<sup>b</sup> (%)</b>		
AEs leading to discontinuation	4.0	9.2
≥Grade 3 AEs	58.4	63.3
Grade 5 AEs	1.0	4.1
<b>AEs of interest (%)</b>		

Neutropenia	29.7	13.3
Hypertension	10.9	17.3
Major bleeding <sup>c</sup>	5.9	9.2
Atrial fibrillation/flutter	2.0	15.3
<p>Data presented as %, unless otherwise designated.</p> <p><sup>a</sup>R/R population (n=83, zanubrutinib; n=81, ibrutinib).</p> <p><sup>b</sup>Safety population included 101 patients treated with zanubrutinib and 98 treated with ibrutinib.</p> <p><sup>c</sup>Includes grade ≥3 hemorrhage and central nervous system bleeding of any grade.</p> <p>AE, adverse event; CI, confidence interval; OS, overall survival; PFS, progression-free survival; R/R, relapsed or refractory; VGPR, very good partial response.</p>		