Abstract Title (English): ASPEN: RESULTS OF A PHASE 3 RANDOMIZED TRIAL OF ZANUBRUTINIB VERSUS IBRUTINIB FOR PATIENTS WITH WALDENSTRÖM MACROGLOBULINEMIA (WM)

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Background: Bruton tyrosine kinase (BTK) inhibition is an emerging standard of care for WM.

Aim/Objective: ASPEN (NCT03053440) is a randomized phase 3 study comparing zanubrutinib (ZANU), a potent and selective BTK inhibitor, versus ibrutinib (IBR), a first generation BTK inhibitor, in patients with WM.

Methods: Patients with *MYD88* mutation–positive (*MYD88^{mut+})* WM were randomly assigned 1:1 to receive ZANU (160 mg twice daily) or IBR (420 mg once daily). Patients without *MYD88* mutations were assigned to a separate cohort to receive ZANU; these results are reported separately. Randomization was stratified by *CXCR4* mutational status and lines of prior therapy (0 vs 1-3 vs >3). The primary end point was the proportion of patients achieving a complete response or very good partial response (CR+VGPR). Sample size was calculated to provide 81% power to detect a difference in CR+VGPR rate of 35% vs 15% 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: In total, 201 patients were randomized to receive ZANU (n=102) or IBR (n=99) between Jan 2017 and Jul 2018. While the treatment groups were well balanced for most of the important baseline factors, more elderly patients (aged >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 ZANU. At a median follow-up of 19.4 months, the rate of VGPR was 28.4% with ZANU and 19.2% with IBR (2-sided *P*=.09; Table). No CRs were observed. Rates of atrial fibrillation, contusion, diarrhea, edema peripheral, hemorrhage, muscle spasms, pneumonia, and adverse events leading to discontinuation or death were lower with ZANU compared with IBR. Although the rate of neutropenia was higher with ZANU (Table), grade ≥3 infection rates were similar between treatment arms (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 IBR, ZANU was associated with a higher VGPR response rate and demonstrated clinically meaningful advantages in safety and tolerability.

Table.

	Zanubrutinib (N=102)	Ibrutinib (N=99)
Efficacy (overall population)		
CR+VGPR rate	28.4	19.2
12-mo PFS	89.7	87.2
12-mo OS	97.0	93.9
Efficacy (R/R population)[a]		
12-mo PFS, n (95% CI)	92.4 (83.8-96.5)	85.9 (75.9-91.9)
12-mo OS, n (95% CI)	98.8 (91.6-99.8)	92.5 (84.1-96.6)
Safety/tolerability profile[b]		
AEs leading to discontinuation	4.0	9.2
≥Grade 3 AEs	58.4	63.3
Grade 5 AEs	1.0	4.1
Neutropenia	29.7	13.3
Hypertension	10.9	17.3
Major bleeding[c]	5.9	9.2
Atrial fibrillation/flutter	2.0	15.3

Data presented as %, unless otherwise designated.
[a]R/R population (n=83, zanubrutinib; n=81, ibrutinib).
[b]Safety population included 101 patients treated with zanubrutinib and 98 treated with ibrutinib.
[c]Includes grade ≥3 hemorrhage and central nervous system bleeding of any grade.
AE, adverse event; CR+VGPR, complete response or very good partial response; OS, overall survival; PFS, progression-free survival; R/R, relapsed or refractory.