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 (ZANU) is a potent, specific, next-generation BTK inhibitor with higher selectivity for BTK than TEC- and EGFR-family kinases; the latter may be related to off-target toxicities.

Objective: ASPEN (NCT03053440), a randomized phase 3 study, compared the efficacy and safety of ZANU vs ibrutinib (IBR; first-generation BTK inhibitor) in patients (pts) with WM.

Material and Methods: At study entry, *MYD88* gene mutations were assessed by a central laboratory (NeoGenomics). Pts with *MYD88*-mutation–positive (*MYD88*$^{mut+}$) WM were randomized (1:1) to receive ZANU (160 mg BID) or IBR (420 mg QD). Results from pts without *MYD88* mutations 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 pts achieving very good partial response (VGPR) or better. Sample size was calculated to provide 81% power to detect a 35% vs 15% difference in rates of VGPR or better in the subset of pts with relapsed or refractory WM. Primary analysis was planned at ~12 mos after the last pt enrolled.

Results: Overall, 201 pts with *MYD88*$^{mut+}$ WM were randomized to ZANU (n=102) or IBR (n=99). While well balanced for most baseline factors, more elderly (>75 yr, 33.3% vs 22.2%) and pts with anemia (hemoglobin ≤110 g/L, 65.7% vs 53.5%) were randomized to ZANU. At a median follow-up of 19.4 mos, VGPR rate was higher with ZANU than IBR (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 ZANU. The rate of neutropenia was higher with ZANU (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, ZANU was associated with a higher VGPR response rate than IBR and demonstrated clinically meaningful advantages in safety and tolerability.

Some authors declare conflicts of interest. This study was sponsored by BeiGene, Ltd. Editorial assistance was provided by Peloton Advantage, LLC, an OPEN Health company, Parsippany, NJ, and funded by the sponsor.

Table.

	Zanubrutinib (N=102)	Ibrutinib (N=99)
Efficacy (overall population) (%)		
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 (95% CI)	92.4 (83.8-96.5)	85.9 (75.9-91.9)
12-mo OS (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
AEs of interest (%)		
Neutropenia	29.7	13.3
Hypertension	10.9	17.3
Major bleeding[c]	5.9	9.2
Atrial fibrillation/flutter	2.0	15.3