ASPEN: Results of a phase III 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. ASPEN is a randomized phase 3 study comparing zanubrutinib (ZANU), a potent and selective BTK inhibitor, versus ibrutinib (IBR), a first generation BTK inhibitor, in WM patients.

Methods:
Patients with WM and *MYD88* mutation 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, received ZANU, and are reported separately. Randomization was stratified by CXCR4 mutational status and the number of 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 (R/R) WM. Primary analysis was planned to occur at~12 months after last patient enrolled.

Results:
In total, 201 patients were randomized from Jan 2017 to Jul 2018. The treatment groups were well balanced for important baseline factors, except in the ZANU arm there were more elderly patients (aged >75 years, 33.3% vs 22.2%) and more anemia (hemoglobin ≤110 g/L, 65.7% vs 53.5%). At a median follow-up of 19.4 months, the rate of CR+VGPR was 28.4% vs 19.2% with ZANU vs IBR, respectively (2-sided *P*=0.09). Rates of atrial fibrillation, contusion, diarrhea, edema peripheral, hemorrhage, muscle spasms, pneumonia, and adverse events (AEs) leading to discontinuation or death were lower with ZANU. The rate of neutropenia was higher with ZANU (Table); however, grade ≥ 3 infection rates were similar (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 CR+VGPR response rate, and demonstrated clinically meaningful advantages in safety and tolerability compared to IBR. Clinical trial information: NCT03053440.

Assessment, %	ZANU (n=102)	IBR (n=99)
CR+VGPR Rate	28.4	19.2
12-mo PFS/OS – overall population	89.7/97.0	87.2/93.9
12-mo PFS/OS – R/R population (n=83 vs 81)	92.4/98.8	85.9/92.5
AEs ≥Grade 3 / Grade 5	58.4 /1.0	63.3/4.1
AEs leading to discontinuation	4.0	9.2
Atrial fibrillation/flutter	2.0	15.3
Hypertension	10.9	17.3
Major bleeding[a]	5.9	9.2
Neutropenia	29.7	13.3

PFS/OS, progression-free survival/overall survival.

[a]Includes grade ≥3 hemorrhage and central nervous system bleeding of any grade.