Abstract Title: ASPEN: Results of a phase 3 randomized trial of zanubrutinib versus ibrutinib for patients with Waldenström macroglobulinemia (WM)

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Background: Bruton's tyrosine kinase (BTK) inhibition is an emerging standard of care for WM. The ASPEN trial (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, mutations in the gene for *MYD88* were assessed by a central laboratory (NeoGenomics). Patients with *MYD88* mutation–positive (*MYD88*$^{mut+}$) WM were randomized (1:1) to receive zanubrutinib (160 mg twice daily) or ibrutinib (420 mg once daily). 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 a complete response or very good partial response (CR+VGPR).

Results: Overall, 201 patients with *MYD88*$^{mut+}$ 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*=.09). 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 zanubrutinib compared with ibrutinib. Although the rate of neutropenia was higher with zanubrutinib, 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 *MYD88*$^{mut+}$ WM.