Abstract Title (German): ASPEN: Ergebnisse einer randomisierten Phase 3 Studie mit Zanubrutinib versus Ibrutinib bei Patienten mit Morbus Waldenström (WM)

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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Introduction: 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: Patients with *MYD88* mutation–positive (*MYD88^{mut+})* WM were randomly assigned 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, received zanubrutinib, 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 WM. Primary analysis was planned to occur at ~12 months after the 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, with the exception of more elderly patients (aged >75 years, 33.3% vs 22.2%) and more anemia (hemoglobin ≤110 g/L, 65.7% vs 53.5%) in the zanubrutinib arm. At a median follow-up of 19.4 months, the rate of VGPR (no CRs were observed) was 28.4% vs 19.2% with zanubrutinib vs ibrutinib, respectively (2-sided *P*=0.09). Rates of atrial fibrillation, contusion, diarrhea, edema peripheral, hemorrhage, muscle spasms, pneumonia, and adverse events leading to discontinuation or death were lower with zanubrutinib. The rate of neutropenia was higher with zanubrutinib (**Table**), but 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, zanubrutinib was associated with a numerically higher VGPR response rate and demonstrated clinically meaningful advantages in safety and tolerability compared with ibrutinib.

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, 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		
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[b]	5.9	9.2
Atrial fibrillation/flutter	2.0	15.3

Presented as %.
[a]R/R population (n=83, zanubrutinib; n=81, ibrutinib).

[b]Includes grade ≥3 hemorrhage and central nervous system bleeding of any grade.
AE, adverse event; CI, confidence interval; OS, overall survival; PFS, progression-free survival; R/R, relapsed or refractory. VGPR, very good partial response.