Abstract Title (German): Aktualisierte Ergebnisse der ASPEN Studie für die Patientenkohorte mit *MYD88*-wildtyp Morbus Waldenström (*MYD88*^{WT} WM)

Abstract Title (English): Updated results of the ASPEN trial from a cohort of patients with wild-type *MYD88* Waldenström macroglobulinemia (*MYD88*^{WT} WM)

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Introduction: Inhibitors of Bruton's tyrosine kinase (BTK) have shown significant activity in patients with *MYD88* mutation–positive (*MYD88*$^{mut+}$) WM. However, lower response rates and shorter progression-free survival have been reported in patients with WM who lack such mutations (*N Engl J Med*. 2015;372:1430). The ASPEN trial (NCT03053440) evaluated zanubrutinib, a potent and selective BTK inhibitor, in patients with *MYD88*^{WT} WM. Here, we present the safety and efficacy of zanubrutinib in these patients.

Methods: At study entry, bone marrow *MYD88* mutations were assessed by a central laboratory (NeoGenomics). Based on these results, patients were assigned to cohort 1 (*MYD88*$^{mut+}$) or cohort 2 (*MYD88*^{WT} or unknown mutation status). Patients received zanubrutinib 160 mg twice daily until disease progression.

Results: In total, 28 patients were enrolled in cohort 2, of which 26 were centrally confirmed as *MYD88^{WT}*. Median age of patients was 72 years; five patients were treatment-naïve and 23 patients had relapsed/refractory (≥1 prior therapy) WM. Most patients had intermediate-risk (39.3%) or high-risk (42.9%) disease, as defined by the International Prognostic Scoring System for WM. At median follow-up of 17.9 months, two patients discontinued zanubrutinib due to adverse events (AEs), and six experienced disease progression; there were no cases of disease transformation. In patients with confirmed *MYD88*^{WT}, the overall response rate by independent review was 80.8%, with a major response rate of 50.0%, including a very good partial response rate of 26.9%. The progression-free survival event-free rate at 12 months was 72.4%. The most frequently reported AEs were diarrhea, anemia, contusion, pyrexia, and upper respiratory tract infection. Major hemorrhage was reported in two patients, and atrial fibrillation was reported in one patient. There were no fatal AEs.

Conclusions: Zanubrutinib showed clinically meaningful antitumor activity, including achieving major responses and durability of responses, and was considered well tolerated with a low discontinuation rate due to AEs in patients with *MYD88^{WT}* WM.

Table. Best Overall Response by Independent Central Review in Patients with *MYD88^{WT}* WM

	Treatment-naïve WM (n=5)	Relapsed/refractory WM (n=21)	Overall (N=26)
Median follow-up, mo	19.3	17.1	17.9
Best overall response, n (%)			
Complete response	0	0	0
Very good partial response	1 (20.0)	6 (28.6)	7 (26.9)
Partial response	1 (20.0)	5 (23.8)	6 (23.1)
Minor response	2 (40.0)	6 (28.6)	8 (30.8)
Stable disease	1 (20.0)	3 (14.3)	4 (15.4)
Progressive disease	0	1 (4.8)	1 (3.8)

WM = Waldenström macroglobulinemia.