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

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Background: 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.

Methods: The ASPEN trial (NCT03053440) evaluated zanubrutinib, a potent and selective BTK inhibitor, in patients with WM. At study entry, *MYD88* gene 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. This abstract presents the safety and efficacy of zanubrutinib in patients with *MYD88*^{WT} WM.

Results: In total, 28 patients were enrolled into cohort 2, of which 26 were *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. With the 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}, overall response rate 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.