Health-related quality of life (HRQOL) in patients with Waldenström macroglobulinemia (WM) treated with zanubrutinib or ibrutinib: results from long-term follow-up of the phase 3 ASPEN trial

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Aim: HRQOL outcomes were evaluated in patients with WM who received zanubrutinib, a next-generation Bruton tyrosine kinase inhibitor, or ibrutinib in the randomized, open-label, phase 3 ASPEN (NCT03053440) study. Data from cohort 1 (*MYD88* mutations) in the intention-to-treat (ITT) population and in patients who achieved complete response (CR), or very good partial response (VGPR) are reported.

Method: Patient-reported outcomes (PROs) were assessed as exploratory endpoints via EORTC QLQ-C30 and EQ-5D-5L VAS scores. Patients completed questionnaires at baseline (cycle 1 day 1), every 3 cycles up to cycle 13, and then every 6 cycles (28-day cycles). Differences in PRO endpoints of global health status, physical and role functioning, and symptoms of fatigue, diarrhea, and nausea/vomiting were assessed between arms.

Results: Cohort 1 enrolled 201 patients (zanubrutinib, n=102; ibrutinib, n=99). Adverse events leading to dose holds or reductions, drug discontinuation, or death were higher with ibrutinib vs zanubrutinib. Adherence rates were high (zanubrutinib, 92%-97%; ibrutinib, 89%-98%). In the ITT population, diarrhea and nausea/vomiting scores were stable from baseline through all key clinical cycles with zanubrutinib; patients receiving ibrutinib had worsening of diarrhea and nausea/vomiting from baseline. In other key PRO endpoints, improvements from baseline were observed with both treatments but were not significantly different (**Table**). Median time to VGPR was shorter with zanubrutinib vs ibrutinib (8 vs 17 mo; CR+VGPR response rate, 38.2% vs 25.3%; *P*=.0374). Patients who achieved VGPR by cycle 25 with zanubrutinib (n=31) had generally better PRO endpoint outcomes than those receiving ibrutinib (n=17). Among patients achieving VGPR, differences between arms were clinically meaningful at cycles 7 and 25 for physical functioning and fatigue. Outcomes were worse with ibrutinib vs zanubrutinib in cycle 4 for diarrhea and nausea/vomiting.

Conclusions: Zanubrutinib was associated with greater improvements in HRQOL vs ibrutinib in patients with WM and *MYD88* mutations in ASPEN.

Table. Treatment Difference in Key PRO Endpoints (ITT Population) at Key Clinical Cycles[a]

PRO	Treatment difference between zanubrutinib and ibrutinib arms (95% CI)			
	Cycle 4	**Cycle 7**	**Cycle 13**	**Cycle 25**
GHS/QOL	−2.35 (−8.53 to 3.84)	−0.65 (−6.10 to 4.80)	−2.37 (−7.58 to 2.84)	−1.07 (−7.11 to 4.97)
Physical functioning	−0.18 (−5.37 to 5.00)	1.76 (−3.59 to 7.11)	−2.80 (−8.09 to 2.48)	0.53 (−4.23 to 5.29)
Role functioning	−2.85 (−10.36 to 4.67)	−1.81 (−9.27 to 5.65)	1.53 (−5.80 to 8.86)	3.02 (−3.73 to 9.83)
Diarrhea	**−7.26 (−12.62 to −1.90)[b]**	−4.90 (−10.63 to 0.84)[c]	−3.37 (−8.67 to 1.93)	0.57 (−4.76 to 5.91)
Fatigue	−1.76 (−8.14 to 4.62)	0.34 (−5.52 to 6.20)	1.10 (−4.81 to 7.01)	−0.05 (−6.34 to 6.24)
Nausea/vomiting	**−5.57 (−9.49 to −1.66)[d]**	0.80 (−1.62 to 3.21)	−1.52 (−3.85 to 0.81)	−0.33 (−3.13 to 2.47)

Descriptive analysis was performed using all scales. Differences between arms were assessed with a linear mixed-effects model for repeated measures. The model includes repeated measurements of the PRO endpoints up to cycle 25 as the dependent variable and the baseline score and treatment arm by timepoint interaction as covariates. An unstructured covariance matrix was used. Clinically meaningful differences (defined as a ≥5 point difference from baseline) are in bold.

GHS, global health status; ITT, intention to treat; PRO, patient-reported outcome; QOL, quality of life.

[a] Key clinical cycles corresponding to the median time to major response; [b] P=.008; [c] P=.093; [d] P=.0055.