HEALTH-RELATED QUALITY OF LIFE IN PATIENTS (PTS) WITH WALDENSTRÖM MACROGLOBULINEMIA (WM) TREATED WITH ZANUBRUTINIB (ZANU) VS IBRUTINIB (IBR): PHASE 3 ASPEN TRIAL LONG-TERM FOLLOW-UP RESULTS

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Introduction: The randomized, open-label, phase 3 ASPEN (NCT03053440) study compared ZANU, a potent and selective next-generation Bruton tyrosine kinase inhibitor, with IBR in pts with WM.

Aim: To present health-related quality of life (HRQOL) outcomes in cohort 1 (pts with *MYD88* mutations) in the intention-to-treat (ITT) population and in pts who achieved complete response (CR) or very good partial response (VGPR).

Material or Patients and Method: Patient-reported outcomes (PROs) were exploratory endpoints assessed via EORTC QLQ-C30 and EQ-5D-5L VAS scores. Pts completed questionnaires at baseline (BL; cycle 1 day 1), every 3 cycles up to cycle 13, and then every 6 cycles. Differences between arms in PRO endpoints of global health status, physical and role functioning, and symptoms of fatigue, diarrhea, and nausea/vomiting (N/V) were assessed. The VGPR population was defined as pts who had VGPR by cycle 25.

Results: Cohort 1 enrolled 201 pts (102 ZANU; 99 IBR). BL characteristics were similar in ZANU vs IBR groups, except for pts aged >75 y (33.3% vs 22.2%) or with anemia (65.7% vs 53.5%). Adverse events leading to dose holds or reductions, drug discontinuation, or death were higher with IBR vs ZANU. Adherence rates were high (ZANU, 92%-97%; IBR, 89%-98%). In the ITT population, diarrhea and N/V symptom scores were stable from BL through all key clinical cycles in the ZANU arm; pts on IBR had worsening of diarrhea and N/V from BL. In other key PRO endpoints, improvements from BL were observed with both treatments but were not significantly different (Table). Median time to VGPR was shorter in pts on ZANU vs IBR (8 vs 17 mo). CR + VGPR response rates with ZANU vs IBR were 38.2% vs 25.3% (*P*=.0374). Pts on ZANU (n=31) vs IBR (n=17) who were VGPR responders by cycle 25 generally had better outcomes in PRO endpoints. Among pts with VGPR, differences between arms were clinically meaningful at cycle 7 for physical functioning (10.42; 95% CI, 0.57-20.28; *P*=.0387) and fatigue (−11.76; 95% CI, −22.24 to −1.28; *P*=.0288) and at cycle 25 for physical functioning (10.45; 95% CI, 0.12-20.79; *P*=.0476) and fatigue (−13.53; 95% CI, −25.00 to −2.06; *P*=.0220). Outcomes were worse with IBR vs ZANU in cycle 4 for diarrhea (−19.83; 95% CI, −33.43 to −6.24; *P*=.0053) and N/V (−10.98; 95% CI, −22.21 to 0.24; *P*=.0549).

Conclusions: Treatment with ZANU showed greater improvements in HRQOL vs IBR in pts with WM and *MYD88* mutations.

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

PRO	Treatment difference between ZANU and IBR arms (95% CI)*			
	Cycle 4[a]	**Cycle 7[a]**	**Cycle 13[a]**	**Cycle 25[a]**
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)

GHS, global health status; IBR, ibrutinib; ITT, intention-to-treat; PRO, patient-reported outcome; QOL, quality of life; ZANU, zanubrutinib

[a] Key clinical cycles corresponding to the median time to major response (28-day cycles); [b] P=.008;[c] P=.093;[d] P=.0055;*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.