**Health-Related Quality of Life in Patients (Pts) With Waldenström Macroglobulinemia (WM) Treated With Zanubrutinib (ZANU) vs Ibrutinib (IBR): Results from the Phase 3 ASPEN Trial Long-Term Follow-Up**

**Authors**: Alessandra Tedeschi,[1] Constantine S. Tam,[2] Roger G. Owen,[3] Christian Buske,[4] Véronique Leblond,[5] Meletios Dimopoulos,[6] Ramón Garcia-Sanz,[7] Jorge J. Castillo,[8] Judith Trotman,[9] Steven P. Treon,[8] Keri Yang,[10] Boxiong Tang,[10] Heather Allewelt,[10] Sheel Patel,[10] Wai Y. Chan,[10] Aileen Cohen,[10] Jingjing Schneider,[10] and Gisoo Barnes[10]

**Affiliations**: [1]ASST Grande Ospedale Metropolitano Niguarda, Milan, Italy; [2]Alfred Health and Monash University, Melbourne, Victoria, Australia[3]St. James University Hospital, Leeds, United Kingdom; [4]Institute of Experimental Cancer Research, CCCU, University Hospital Ulm, Baden-Württemberg, Germany; [5]Sorbonne University, Pitié Salpêtrière Hospital, Paris, France; [6]Department of Clinical Therapeutics, National and Kapodistrian University of Athens, Athens, Greece; [7]Hospital Universitario de Salamanca, Salamanca, Spain; [8]Dana-Farber Cancer Institute, Boston, MA, USA; [9]Concord Repatriation General Hospital, Sydney, New South Wales, Australia; and [10]BeiGene USA, Inc., San Mateo, CA, USA.

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

**Aims:** Health-related quality of life (HRQoL) outcomes were evaluated in Cohort 1 (pts with activating mutations in *MYD88*) in both the intention-to-treat (ITT) population and pts achieving a complete response or very good partial response (CR + VGPR).

**Methods**: Patient-reported outcomes (PROs) were exploratory endpoints assessed using the EORTC QLQ-C30 and EQ-5D-5L VAS scores. Patients in Cohort 1 completed the questionnaires at baseline (Cycle 1, Day 1), every 3 cycles up to Cycle 13, and every 6 cycles thereafter. Each cycle was 28 days for both arms. Descriptive analysis was performed using all the scales. A linear mixed-effects model for repeated measures analysis assessed the differences between arms for PRO endpoints of global health status (GHS), physical and role functioning, and symptoms of fatigue, diarrhea, and nausea/vomiting. Key clinical cycles in ITT and VGPR populations (pts who achieved a VGPR by Cycle 25) included Cycles 4, 7, 13, and 25; key cycles corresponded to the median times to major response. Clinically meaningful difference was defined as ≥5 points difference from baseline.

**Results**: Overall, 201 pts (102 ZANU; 99 IBR) were enrolled in Cohort 1. Baseline characteristics were similar between arms except for pts aged >75 years (33.3% vs 22.2%), and pts with anemia (hemoglobin ≤110 g/L, 65.7% vs 53.5%) in the ZANU vs IBR arms, respectively. Adverse events (AEs) leading to dose holds or reductions, drug discontinuation, and deaths were higher in the IBR vs ZANU arm. Compliance rates were high (ZANU: 92%–97%; IBR: 89%–98%). In the ITT population, diarrhea, and nausea/vomiting symptom scores were stable from baseline through all key clinical cycles in the ZANU arm; pts on IBR experienced worsening of diarrhea and nausea/vomiting from baseline. In other key PRO endpoints, improvements from baseline for both treatments were observed, but were not significantly different (Table). There was no CR. Median time to VGPR was achieved faster in pts on ZANU (8 months [mo]) vs IBR (17 mo) (CR + VGPR response rate: 38.2% vs 25.3% (*P*=0.0374), respectively; 31 pts on ZANU who were VGPR responders by Cycle 25 had generally better outcomes in PRO endpoints compared with 17 pts on IBR. Among VGPR responders, the differences between arms were clinically meaningful at Cycle 7 for physical functioning (10.42 [95% CI: 0.57, 20.28]; *P*=0.0387) and fatigue (-11.76 [95% CI: -22.24, -1.28]; *P*=0.0288); and again at Cycle 25, (10.45 [95% CI: 0.12, 20.79]; *P*= 0.0476) for physical functioning

and (-13.53 [95% CI: -25.00, -2.06]; *P*=0.0220) fatigue. Pts on IBR had worse outcomes compared with ZANU in Cycle 4 for diarrhea (-19.83 [95% CI: -33.43, -6.24]; *P*=0.0053) and nausea/vomiting (-10.98 [95%CI: -22.21, 0.24], *P*=0.0549).

**Conclusions/Summary**: In the ASPEN trial, treatment with ZANU was associated with greater improvements in HRQoL vs IBR in pts with WM and *MYD88* mutations. Clinically meaningful differences were observed in diarrhea and nausea/vomiting in both ITT and VGPR populations in earlier cycles of treatment as well as in long-term physical functioning and fatigue in patients achieving VGPR. For pts who achieved a VGPR by Cycle 25, treatment with ZANU compared with IBR led to an earlier and lasting improvement of HRQoL, consistent with a shorter median time to VGPR.

**Table:** Treatment Difference in Key PRO Endpoints (ITT Population)

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

[a]*P*=0.008. [b]*P*=0.093. [c]*P*=0.0055

*Based on a linear mixed-effect model for repeated measures (MMRM). The model includes the repeated measurements of the PRO endpoints up to Cycle 25 as the dependent variable with the baseline score and the treatment arm by timepoint interaction as covariates. An unstructured covariance matrix was used. Clinically meaningful differences are in **bold**.