# UPDATED RESULTS OF THE ASPEN TRIAL FROM A COHORT OF PATIENTS WITH MYD88 WILD-TYPE WALDENSTRÖM MACROGLOBULINEMIA

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**Background**

Inhibitors of Bruton tyrosine kinase (BTK) have shown significant activity in patients with Waldenström macroglobulinemia (WM) harboring a mutation in the *MYD88* gene. 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). Zanubrutinib (BGB-3111; ZANU) is an investigational, next-generation BTK inhibitor designed to maximize BTK occupancy and minimize off-target inhibition of TEC-and EGFR-family kinases. The ASPEN trial evaluated ZANU, a potent and selective BTK inhibitor, in patients with WM.

**Aims**

To evaluate the efficacy and safety of ZANU in patients who have WM with *MYD88* wild-type ($MYD88^{WT}$) mutation status.

**Methods**

In the ASPEN trial, bone marrow *MYD88* mutations were assessed at study entry by a central laboratory (NeoGenomics) using a wild-type–blocking polymerase chain reaction method. This *MYD88* mutation assay detects all mutations in the region encompassing amino acid $Ala^{260}$-$Pro^{278}$, which includes the predominant mutation in WM ($MYD88^{L265P}$), with enhanced sensitivity (*Int J Lab Hematol*. 2016;38:133). Based on the results of the *MYD88* mutation assay, patients were assigned to cohort 1 (*MYD88* mutation) or cohort 2 ($MYD88^{WT}$ or mutation unknown). All cohort 2 patients received ZANU 160 mg twice daily until disease progression.

**Results**

In total, 28 patients (n=26 $MYD88^{WT}$; n=2 *MYD88* mutation status unknown) were enrolled into cohort 2. The median age was 72 years and 42.9% were >75 years old; 5 patients were treatment-naïve (TN), and 23 patients were relapsed/refractory (R/R; ≥1 prior therapy). Most patients had intermediate- (39.3%) or high-risk (42.9%) disease by International Prognostic Scoring System for WM. With a median follow-up of 17.9 months, 2 patients discontinued ZANU due to adverse events, and 6 patients experienced disease progression; there were no cases of disease transformation. In 26 confirmed $MYD88^{WT}$ patients, the overall response rate was 80.8%, with a major response rate of 50.0%, including a very good partial response rate of 26.9% (Table). Progression-free survival event-free rate at 12 months was 72.4%. The 2 patients with unknown *MYD88* mutation status achieved best overall response of partial response. In cohort 2 patients (n=28), the most frequently reported adverse events (AEs) were diarrhoea, anaemia, contusion, pyrexia, and upper respiratory

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

| | Modified Owen, 6th IWWM,[a] n (%) | | |
|---|---|---|---|
| | TN | R/R | Overall |
| | n=5 | n=21 | 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) |
| **Overall response rate, n (%)** | 4 (80.0) | 17 (81.0) | 21 (80.8) |

IWWM, International Workshop on Waldenström macroglobulinemia; TN, treatment naïve; R/R, relapsed/refractory.
[a] Owen et al. *Br J Haematol*. 2013;160:171.

**Conclusion**

ZANU 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. ClinicalTrials.gov: NCT03053440