

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

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Background:

Inhibitors of Bruton tyrosine kinase (BTK) have shown significant activity in patients with 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). The ASPEN trial evaluated zanubrutinib (ZANU), a potent and selective BTK inhibitor, in WM patients.

Methods:

In the ASPEN trial, bone marrow *MYD88* mutations were assessed at study entry by a central laboratory (NeoGenomics). 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. The objective was to assess the safety and efficacy of ZANU in patients with *MYD88*^{WT} WM.

Results:

In total, 28 patients with 26 *MYD88*^{WT} WM were enrolled into cohort 2. The median age was 72 years; 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 the 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. The overall response rate was 80.8%, with a major response rate of 50.0%, including a very good partial response (VGPR) rate of 26.9% (Table). Progression-free survival event-free rate at 12 months was 72.4%. The most frequently reported adverse events (AEs) were diarrhea, anemia, contusion, pyrexia, and upper respiratory tract infection. Major hemorrhage was reported in 2 patients, and atrial fibrillation was reported in 1 patient. There were no fatal AEs.

Conclusions:

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. ZANU demonstrated efficacy regardless of *MYD88* mutational status in WM. Clinical trial information: [NCT03053440](https://clinicaltrials.gov/ct2/show/study/NCT03053440).

	TN (n = 5)	R/R (n = 21)	Overall (n = 26)
Median follow-up, mo	19.3	17.1	17.9
Best Overall Response, n (%)	TN (n = 5)	R/R (n = 21)	Overall (n = 26)
Complete response	0	0	0
VGPR	1 (20.0)	6 (28.6)	7 (26.9)
PR	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)