Peripheral Neuropathy in Phase 3 ASPEN Study of Bruton Tyrosine Kinase Inhibitors for Waldenström Macroglobulinemia

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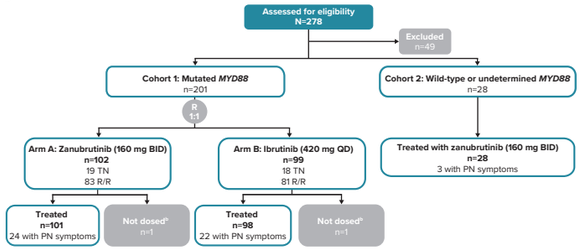
INTRODUCTION

- Peripheral neuropathy (PN) is commonly experienced by patients with Waldenström macroglobulinemia (WM) and is a cause of morbidity[1]
- Treatment options for WM-associated PN remain limited by lack of therapeutic benefit and/or toxicities[2-4]
- Covalent Bruton tyrosine kinase (BTK) inhibitors zanubrutinib (next generation) and ibrutinib (first generation) are approved for the treatment of WM, but data on whether BTK inhibitors are effective at managing WM-associated neuropathy are limited[5-7]
- The phase 3, open-label ASPEN study (NCT03053440) compared the efficacy and safety of zanubrutinib and ibrutinib in patients with WM[4,7]
  - Both zanubrutinib and ibrutinib were effective in treating patients with WM (very good partial response rate, 28% vs 19%, respectively; *P*=.09)[7]
  - Zanubrutinib-treated patients had fewer discontinuations due to adverse events and less cardiovascular toxicity than ibrutinib-treated patients[7]
- This ad hoc analysis examined the outcomes of treatment with zanubrutinib or ibrutinib on PN symptoms in patients with WM in the ASPEN study

METHODS

- The ASPEN study design, methods, and results of primary and long-term follow-up analyses have been described[4,7]
  - Patients with relapsed/refractory WM or treatment-naive WM unsuitable for chemoimmunotherapy were eligible
  - In cohort 1, patients with mutated *MYD88* (*MYD88*^{MUT}) were randomly assigned 1:1 to receive either zanubrutinib 160 mg twice daily or ibrutinib 420 mg once daily in 28-day cycles
  - In cohort 2, patients with wild-type *MYD88* (*MYD88*^{WT}) or undetermined *MYD88* mutation status received zanubrutinib 160 mg twice daily
- All enrolled patients who had symptomatic PN assessed by the investigator as related to WM at study enrollment were included in this ad hoc analysis (**Figure 1**)
- WM responses were assessed by the investigators per modified IWWM-6 criteria[8]
  - Formal objective assessments of PN, such as electromyography or diagnosis by neurologist, were not required per protocol
- Resolution of treatment-precipitating symptoms (per IWWM-7 guidelines[9]) was a predefined secondary endpoint of the ASPEN study. All enrolled patients were followed up for resolution of treatment-precipitating symptoms, including PN symptoms, throughout study treatment on day 1 of each cycle through cycle 13 and every 3 cycles after that until the end of treatment; patients with baseline WM-associated PN symptoms were followed to resolution
- Logistic regression models were used to assess the relationship between PN symptom resolution and potential predictors of resolution
- HRQOL was assessed using the validated European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30 (EORTC-QLQ-C30)

Figure 1. Patients Enrolled in the ASPEN Study[a]



[a] Final study data cutoff: June 21, 2022; patients enrolled between January 2017 and July 2018. [b] Did not receive treatment due to acute kidney injury and central nervous system lymphoma.
BID, twice daily; *MYD88*, myeloid differentiation primary response 88; PN, peripheral neuropathy; QD, once daily; R, randomized; R/R, relapsed/refractory; TN, treatment naive.

RESULTS

Patient Population

- At screening, 49 patients (21.4% of study population) had WM-associated PN symptoms, per investigator assessment, as the reason for initiation of WM-directed therapy (**Figure 1**)
- Most patients with PN symptoms had relapsed/refractory WM (78%), and most had *CXCR4* wild type disease (73%) (**Table 1**)

Table 1. Demographic and Disease Characteristics of Patients With PN Symptoms

	Cohort 1 (*MYD88*^{MUT})		Cohort 2 (*MYD88*^{WT})	
	Zanubrutinib (n=24)	Ibrutinib (n=22)	Zanubrutinib (n=3)	Total (N=49)
Age, median (range), years	69.5 (50-87)	68.0 (57-83)	70.0 (57-85)	69.0 (50-87)
Male, n (%)	15 (62.5)	14 (63.6)	3 (100)	32 (65.3)
Prior lines of therapy, n (%)				
0	6 (25.0)	4 (18.2)	1 (33.3)	11 (22.4)
1-3	15 (62.5)	16 (72.7)	2 (66.7)	33 (67.3)
>3	3 (12.5)	2 (9.1)	0	5 (10.2)
Genotype by NGS, n (%)				
CXCR4^{WT}	18 (75.0)	15 (68.2)	3 (100)	36 (73.5)
CXCR4^{MUT}	6 (25.0)	5 (22.7)	0	11 (22.4)
CXCR4^{FS}	4 (16.7)	3 (13.6)	0	7 (14.3)
CXCR4^{NS}	2 (8.3)	2 (9.1)	0	4 (8.2)
Unknown	0	2 (9.1)	0	2 (4.1)
Baseline [IgM] (central lab), median (range), g/L	32.4 (6.7-68.9)	21 (6.8-54.9)	24 (13.8-42.5)	26 (6.72-68.9)
Baseline anti-MAG Ab, median (range), TU	70 (1 to >70,000)	138 (9 to >70,000)	70 (44 to 1,545)	85 (1 to >70,000)
Anti-MAG Ab elevation (>999 TU) at baseline, n (%)	2 (8.3)	7 (31.8)	1 (33.3)	10 (20.4)

Ab, antibody; FS, frameshift; IgM, immunoglobulin M; MAG, myelin-associated glycoprotein; MUT, mutated; NGS, next-generation sequencing; NS, nonsense; PN, peripheral neuropathy; TU, titer units; WT, wild type.

PN Symptom Resolution

- Overall, 35 patients (71.4%) experienced PN symptom resolution
- The median time to PN symptom resolution and PN symptom resolution rate in patients with major response are shown in **Table 2**

Table 2. PN Symptom Resolution

	Cohort 1 (*MYD88*^{MUT})		Cohort 2 (*MYD88*^{WT})	
	Zanubrutinib (n=24)	Ibrutinib (n=22)	Zanubrutinib (n=3)	Total (N=49)
Time to PN symptom resolution, median (range), months	4.6 (1-47)	14.1 (1-44)	28.6 (14-43)	10.1 (1-47)
Patients with major response who had PN symptom resolution, n/N (%)	14/18 (78)	16/19 (84)	2/2 (100)	32/39 (82)

MUT, mutated; PN, peripheral neuropathy; WT, wild type.

Predictors of PN Symptom Resolution

- **Table 3** shows logistic regression modeling of predictors of PN symptom resolution, with a strong, significant relationship between PN symptom resolution and major response (*P*<.01)
- Lower baseline anti-MAG antibody level was also associated with PN symptom resolution (*P*<.05)
- Normalization of IgM (cutoff: minimum IgM ≤ upper limit of normal) and IgM maximum percent reduction from pretreatment baseline were associated with increased likelihood of PN symptom resolution, but neither was statistically significant (*P*=.0526 and *P*=.0546, respectively) (**Table 3**)

Table 3. Logistic Regression of Predictors of PN Symptom Resolution

Variable	HR (95% CI)	*P* value[a]
Multivariate model variables		
Medical history of PN	0.6509 (0.1516-2.7945)	.56357
Major response	11.2122 (2.0557-61.1531)	**.00523**
Medical history pertinent to PN	2.0375 (0.3362-12.3484)	.43887
Prior antineoplastic therapy	0.9000 (0.1213-6.6759)	.91788
Pertinent concomitant medication	0.6509 (0.1516-2.7945)	.56357
Univariate models		
Major response	10.6664 (2.1958-51.8132)	**.00333**
Baseline anti-MAG antibody value (10^{-4} TU)	0.7198 (0.5192-0.9979)	**.048649**
Binary baseline anti-MAG antibody (≤999 TU)	1.9332 (0.4512-8.2838)	.375
Maximum IgM reduction	0.9772 (0.9315-1.0251)	.344
Maximum IgM percent reduction	1.0314 (0.9994-1.0644)	.0546
IgM reduction at the latest measurement at or prior to PN symptom resolution[b]	1.0146 (0.9707-1.0606)	.52
IgM reduction at the next measurement after PN symptom resolution[b]	1.0088 (0.9638-1.0558)	.7074
Minimum IgM	0.9771 (0.9112-1.0478)	.5161
Normalized minimum IgM ≤ ULN[c]	5.0526 (0.9821-25.9942)	.0526
Normalized minimum IgM ≤1.5 × ULN[c]	2.6469 (0.696-10.0658)	.153
Normalized minimum IgM ≤2 × ULN[c]	1.5001 (0.4311-5.2198)	.524

[a] *P* values in red represent statistically significant associations with PN symptom resolution at *P*<.05. [b] Or the maximum IgM reduction if the patient did not have PN symptom resolution. [c] ULN for IgM was defined as 2.3 g/L.
HR, hazard ratio; IgM, immunoglobulin M; MAG, myelin-associated glycoprotein; PN, peripheral neuropathy; TU, titer units; ULN, upper limit of normal.

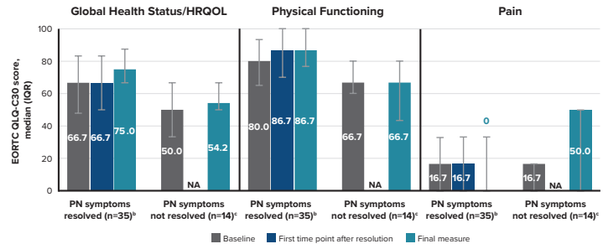
Patient-Reported HRQOL Outcomes

- Median global health status/HRQOL was improved from baseline in patients with and without PN symptom resolution, and greater improvement was observed in those with PN symptom resolution (**Figure 2**)
- Median pain score improved from baseline in patients with PN symptom resolution, whereas worsening from baseline was observed in those without PN symptom resolution
- Modest improvement in median physical functioning score from baseline occurred in patients with PN symptom resolution but not in patients without PN symptom resolution

CONCLUSIONS

- In this ad hoc analysis of data from the phase 3 ASPEN study, BTK inhibitors zanubrutinib and ibrutinib effectively treated PN symptoms in patients with WM
- Achievement of WM major response and lower baseline anti-MAG antibody levels were associated with PN symptom resolution
- Patients with PN symptom resolution had greater improvement in median HRQOL and pain scores compared with those without PN symptom resolution
- While further evaluation, including detailed neurophysiological investigations, is required, this analysis supports the use of BTK inhibitors to treat PN symptoms in patients with WM

Figure 2. EORTC-QLQ-C30 Patient-Reported Outcomes[a] by Resolution of PN Symptoms



[a] Higher scores correspond to improved global status, improved physical functioning, and worsening of pain. [b] Patients with PN symptom resolution who completed the EORTC QLQ-C30 questionnaire at baseline (n=32), the first time point after PN symptom resolution (n=31), and the final time point (n=35). [c] Patients without PN symptom resolution who completed the EORTC QLQ-C30 questionnaire at baseline (n=13) and the final time point (n=14).
EORTC-QLQ-C30, European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30; HRQOL, health-related quality of life; IQR, NA, not applicable; PN, peripheral neuropathy.

REFERENCES

1. Levine T, et al. *J Neurol Neurosurg Psychiatry.* 2006;77(2):224-228.
2. Lunn MP, Nobile-Orazio E. *Cochrane Database Syst Rev.* 2016;10(10):CD002827.
3. Treon SP, et al. *Ann Oncol.* 2004;15(10):1481-1483.
4. Dimopoulos MA, et al. *N Engl J Med.* 2018;378(25):2399-2410.
5. Brukinsa (zanubrutinib). Prescribing Information. BeiGene, Ltd; 2024.
6. Dimopoulos MA, et al. *N Engl J Med.* 2018;379(20):1975-1976.
7. Tam CS, et al. *Blood.* 2020;136(18):2038-2050.
8. Owen RG, et al. *Br J Haematol.* 2013;160(2):171-176.
9. Dimopoulos MA, et al. *Blood.* 2014;124(9):1404-1411.

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