Real-World Effectiveness and Safety of Zanubrutinib in Waldenström Macroglobulinemia: Results From the Belgian WIZARD Study

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CONCLUSIONS

- Zanubrutinib showed **real-world efficacy** in WM (ORR, 77.5%; MRR, 64.0%; 18-month PFS, 75.9%), which included patients who progressed on ibrutinib
- Zanubrutinib was **generally well tolerated**, with mostly low-grade AEs (diarrhea, fatigue, hypertension), very few grade ≥3 events, and only one case of atrial fibrillation
- As such, the **WIZARD study confirms that zanubrutinib is a highly effective and well-tolerated treatment option for patients with WM in everyday clinical practice**

INTRODUCTION

- **Waldenström macroglobulinemia (WM)** is a rare, indolent B-cell lymphoproliferative disorder characterized by bone marrow infiltration with lymphoplasmacytic cells and secretion of monoclonal immunoglobulin M, leading to symptoms such as anemia, hyperviscosity, and neuropathy[1]
- **Bruton tyrosine kinase inhibitors (BTKis)** represent a major therapeutic breakthrough in WM by targeting B-cell receptor signaling, resulting in high response rates and durable disease control[2]
- **Zanubrutinib**, a next-generation covalent BTKi, was evaluated in the phase 3 **ASPEN trial** in patients with WM[3]
  - At 44.4 months of median follow-up, very good partial response (VGPR) + complete response (CR) rates were **36.3% with zanubrutinib versus 25.3% with ibrutinib** in patients with *MYD88*-mutated disease; in patients with *MYD88* wild-type disease in cohort 2, VGPR was 30.8% with one CR
  - At 42 months, PFS was **78.3% with zanubrutinib versus 69.7% with ibrutinib**; HR, 0.63 (95% CI, 0.36-1.12)
  - **Exposure-adjusted incidences** of atrial fibrillation/flutter, hypertension, and diarrhea were **significantly lower** with **zanubrutinib** versus ibrutinib, respectively (descriptive *P* <.05)
- **Real-world validation of clinical trial data** is essential to confirm the effectiveness, tolerability, and patterns of zanubrutinib treatment in broader, more heterogeneous WM populations
  - The **WIZARD study** collected **Belgian real-world data on the efficacy and safety of zanubrutinib in adult patients with WM**

METHODS

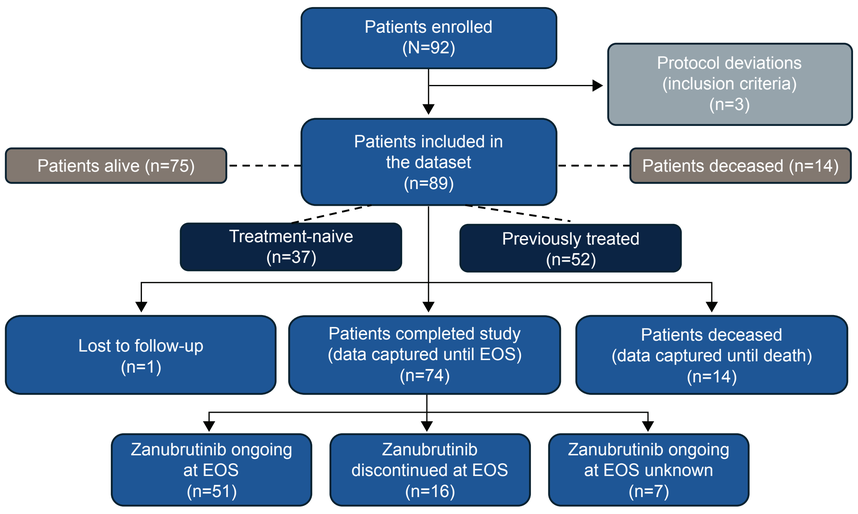
- WIZARD was a retrospective and prospective, multicenter, observational study conducted in Belgium
- Eligible participants were adult patients with symptomatic WM who had received zanubrutinib in accordance with Belgian reimbursement criteria, with treatment initiated no later than September 1, 2024
- **The primary objective** was the real-world effectiveness of zanubrutinib, as assessed by major response rate (MRR; complete, very good partial or partial response), overall response rate (ORR; MRR + minor response), best individual response, and PFS
- **Secondary objectives** were time to (patient best) response, (best) response duration, overall survival (OS), time to next treatment and safety

RESULTS

Study Population

- In total, 92 patients were recruited, of whom 89 were included in the dataset (**Figure 1**)
  - Three patients were identified as screening failures as they did not meet the inclusion criteria
  - Patients came from 14 academic and non-academic centers in Belgium (six from Flanders, six from Wallonia and two from Brussels)
- Key patient and disease characteristics are summarized in **Table 1**

Figure 1. Patient Disposition



Abbreviation: EOS, end of study.

Table 1. Patient and Disease Characteristics

Characteristic	Patients (N=89)
Sex, n (%)	
Male	48 (53.9)
Age, median (range), years	76 (49-91)
≤65 years, n (%)	13 (14.6)
66-74 years, n (%)	30 (33.7)
≥75 years, n (%)	46 (51.7)
BMI, median (range), kg/m²	23.7 (0-33.5)[a]
ECOG performance status, n (%)	
0/1	38 (42.2)
≥2	6 (6.6)
Unknown/missing	45 (50.6)
Concomitant infection at Tx initiation, n (%)	
Yes	23 (25.8)
No	66 (74.2)
Comorbidities at Tx initiation, n (%)	
Yes	80 (89.9)
No	3 (3.4)
Unknown	6 (6.7)
Extramedullary disease, n (%)	
No	45 (50.6)
Yes	24 (27.0)
NA/unknown	20 (22.5)
***MYD88* mutation status, n (%)**	
Mutated (L256P)	56 (62.9)
Wild type	5 (5.6)
NA/unknown	28 (31.5)
Serum IgM	
Median (range), g/L	29 (1.2-114.2)
≥70 g/L, n (%)	5 (5.6)
<70 g/L, n (%)	73 (82.0)
Unknown/missing, n (%)	11 (12.4)
Hemoglobin	
Median (range), g/L	105.5 (65-326)
≤110 g/L, n (%)	51 (57.3)
>110 g/L, n (%)	37 (41.6)
Unknown/missing, n (%)	1 (1.1)
No. of prior treatment lines, median (range)	2 (0-7)
0, n (%)	37 (41.6)
1, n (%)	17 (19.1)
≥2, n (%)	32 (36.0)
Unknown/missing, n (%)	3 (3.4)
Prior ibrutinib treatment, n (%)	20 (22.5)

[a]Missing BMI result may have been recorded as 0

Abbreviations: BMI, body mass index; ECOG, Eastern Cooperative Oncology Group; IgM, immunoglobulin M; NA, not available; Tx, treatment.

Efficacy

- The MRR and ORR were 64% (95% CI, 53.2%-73.9%) and 77.5% (95% CI, 67.4%-85.7%), respectively
  - MRR and ORR were consistent across investigated subgroups (**Table 2**)
- Overall, 23 patients (25.8%) achieved a VGPR or better as their best response

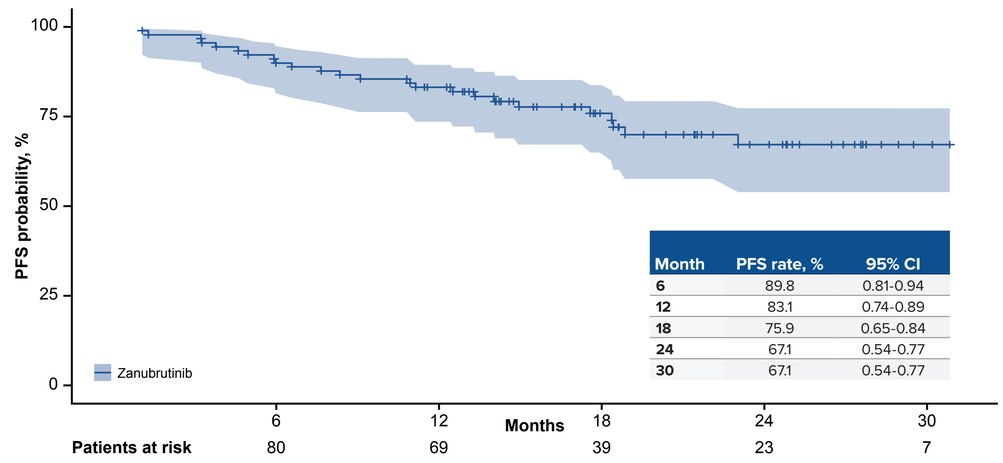
Table 2. MRR and ORR in Overall Study Population and Across Selected Subgroups

Subgroup	n	MRR, %	ORR, %
Overall	89	64.0 (95% CI, 53.2-73.9)	77.5 (95% CI, 67.4-85.7)
Age			
≤65 years	13	61.5	76.9
66-75 years	30	60.0	76.7
≥76 years	46	67.4	78.3
Baseline ECOG performance status			
0/1	38	73.7	84.2
≥2	6	66.7	66.7
Zanubrutinib Tx			
First	35	71.4	85.7
Second	17	58.8	64.7
Later	18	66.7	83.3
Treatment status			
Treatment naive	37	67.6	81.1
Previously treated	52	61.5	75.0
Prior ibrutinib treatment	20	45.0	60.0
***MYD88* mutation status**			
Mutant	56	64.3	80.4
Wild type/unknown	33	63.6	72.7

Abbreviations: ECOG, Eastern Cooperative Oncology Group; MRR, major response rate; ORR, overall response rate; Tx, treatment.

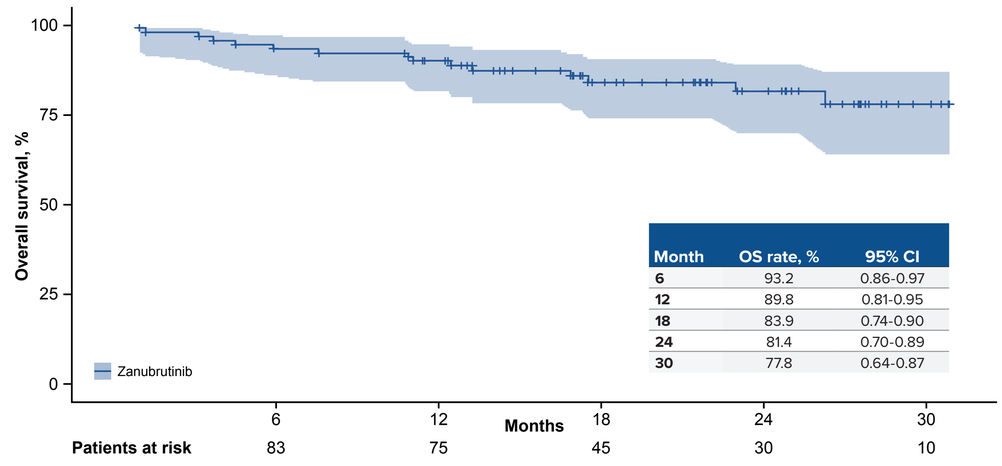
- Median PFS was not reached, with 1- and 2-year PFS rates of 83.1% and 67.1%, respectively (**Figure 2**)
- Median OS was not reached, with 1- and 2-year OS rates of 89.8% and 81.4%, respectively (**Figure 3**)

Figure 2. PFS



Abbreviation: PFS, progression-free survival.

Figure 3. OS



Abbreviation: OS, overall survival.

- PFS and OS rates at 12 and 24 months were consistent across the investigated subgroups (**Table 3**)
- Responses were durable, with 77% of patients maintaining their response for at least 12 months
- Responses occurred relatively fast, with 58.1% of the responding patients having their best response after 6 months of therapy

Table 3. PFS and OS Rates at 12 and 24 months Across Investigated Subgroups

Subgroup	OS, %		PFS, %	
	12 months	24 months	12 months	24 months
Age				
≤65 years	100	100	100	74.1
66-75 years	96.7	81.8	80.0	64.4
≥76 years	82.5	77.6	80.3	66.7
Baseline ECOG performance status				
0/1	94.7	90.9	92.1	81.6
≥2	66.7	50.0	50.0	33.0
Zanubrutinib treatment line				
First	91.4	79.9	82.9	58.4
Second	88.2	77.2	76.5	65.5
Later	100	93.3	94.4	79.7
Treatment status				
Treatment naive	86.5	75.2	78.4	53.7
Previously treated	92.2	85.9	86.4	74.5
***MYD88* mutation status**				
MYD88 mutant	89.3	80.4	82.1	63.9
Time since last treatment				
<2 years	91.9	83.5	83.4	67.6
≥2 years	92.9	92.9	92.9	92.9
Treatment discontinuation				
Yes	74.7	61.6	49.5	28.3
No	94.2	88.7	92.8	80.1

Abbreviation: ECOG, Eastern Cooperative Oncology Group.

Safety

- The median treatment duration with zanubrutinib was 400 days (range, 1-925)
- Overall, 40 patients (44.9%) reported at least one adverse event (AE) during treatment with zanubrutinib
  - The most common AEs observed in this study were hematoma (n=5) and muscle cramps/pain (n=4)
  - Other AEs occurring in more than one patient were diarrhea (n=3), fatigue (n=3), hypertension (n=3), epistaxis (n=2), neutropenia (n=2), joint joint pain (n=2) and thrombocytopenia (n=2)
  - One patient in the study developed grade 1 atrial fibrillation
- Eight patients in the study experienced a grade ≥3 AE
  - Two patients developed grade ≥3 neutropenia
  - Grade ≥3 acute hepatitis, bronchopneumonia, hematologic toxicity, hepatotoxicity, infectious colitis, intestinal problems, thrombocytopenia and urosepsis occurred in one patient each
- Serious AEs were observed in 9 zanubrutinib-treated patients; there were no fatal AEs
- AEs leading to permanent zanubrutinib discontinuation were abdominal pain, acute hepatitis, intestinal problems, neutropenia and thrombocytopenia (n=1 each)
- AEs leading to dose reduction were abdominal cramps with diarrhea, anorexia, ecchymosis on the limbs, hematologic toxicity, hepatotoxicity, dermatitis, muscle cramps, and onychodystrophy of the upper limbs (n=1 each)

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DISCLOSURES

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