From trial data to individual patients in WM

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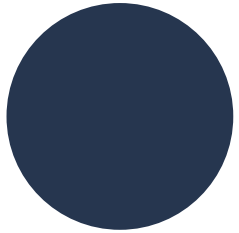
Disclosures

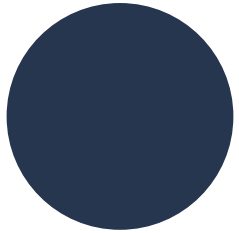
- Research support: BeiGene
- Honoraria: BeiGene, Janssen Cilag, BMS, Siemens, Sanofi

Variations on a WM case: Exploring different clinical scenarios

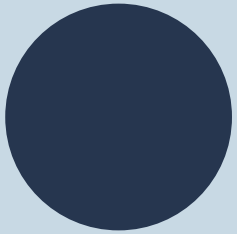
First-line



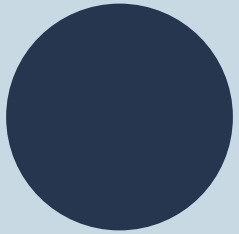
Asymptomatic WM



Blurred vision and headaches



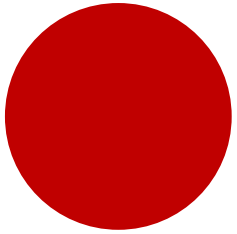
High tumor burden



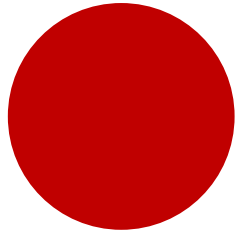
Elderly patient with comorbidities

How would you manage the patient and why?

Relapse



First relapse after BR



Second relapse on BTKi

BR, bendamustine and rituximab; BTKi, Bruton's tyrosine kinase inhibitor; WM, Waldenström's macroglobulinemia.

Patient 1A

Patient characteristics	**Male** **Age:** 64 years No prior pathology	**Mild fatigue**, and occasional **headaches** over the past few months	**First-line** **How would you manage the patient and why?**
Review of systems	• No B symptoms • No organomegaly • Several lymph nodes 1–2 cm	• No visual problems, no evidence of neuropathies, no bleeding • No cold phenomena	
Laboratory studies	**Hemoglobin:** 12.9 g/dL / 8 mmol/L **Platelets:** 220 × 10^9/L **WBC:** 6.1 × 10^9/L	**M spike:** 21 g/L **Serum IgM:** 20 g/L	
Bone marrow evaluation	**Trephine biopsy** Lymphoplasmacytic infiltration = 40%	**Flow cytometry on BM aspirate** • **22.8%** B cell clonal population CD19+, CD22+, smIgM kappa • **5.2%** kappa-positive plasma cells CD38+, CD19+, CD56−, smIgM kappa	• *MYD88*^{L265P} **positive** • *CXCR4* **normal**

This is a hypothetical patient case scenario intended for educational purposes only.

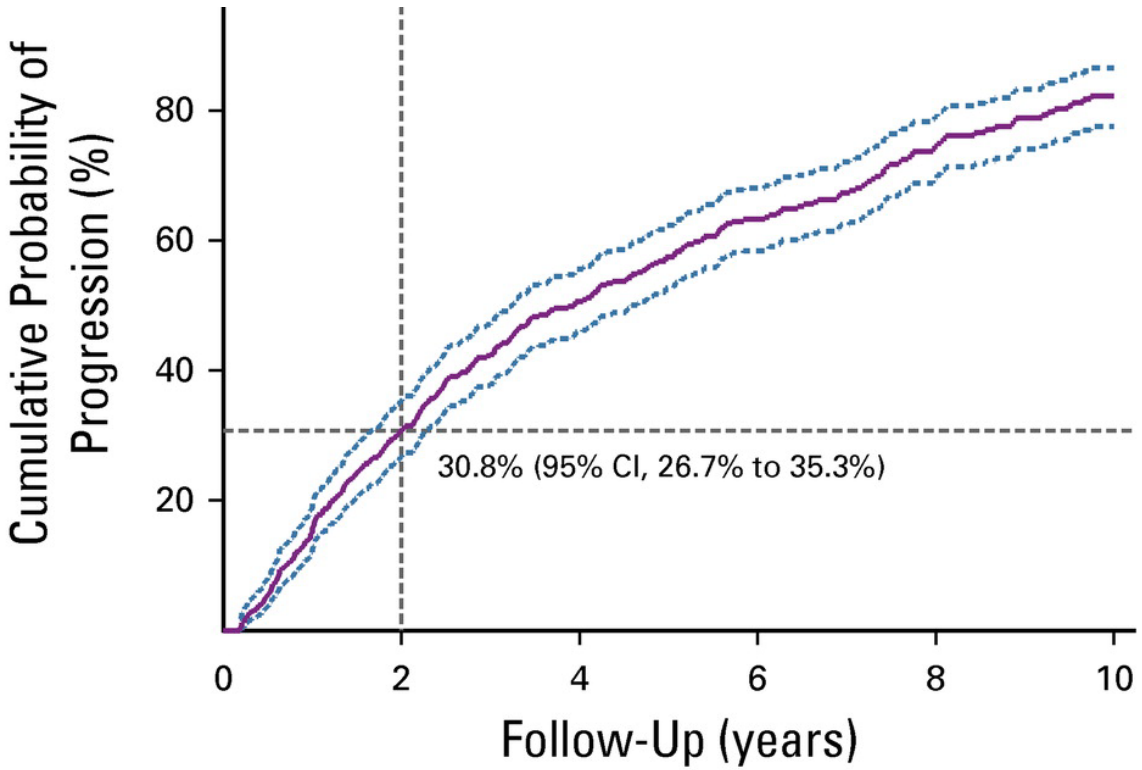
BM, bone marrow; CD, cluster of differentiation; IgM, immunoglobulin M; smIgM, surface membrane immunoglobulin M; WBC, white blood cells.

WM not yet requiring treatment

Asymptomatic WM is defined as:[1,2]

- ≥30 g/L serum monoclonal IgM protein **and/or** ≥10% bone marrow lymphoplasmacytic infiltration
- No evidence of end-organ damage or complications attributed to a plasma cell proliferative disorder, e.g:
  - Symptomatic anemia
  - Constitutional symptoms
  - Hyperviscosity
  - Lymphadenopathy
  - Hepatosplenomegaly
  - Neuropathy

Cumulative probability of progression among patients with asymptomatic WM[3]



*Attributed to a plasma cell proliferative disorder.
CI, confidence interval; IgM, immunoglobulin M; WM, Waldenström's macroglobulinemia.
1. Kyle RA *et al*. *Blood* 2012; 119 (19): 4462–4466. 2. Haematolymphoid Tumours. WHO Classification of Tumours, 5th Edition, Volume 11. Available at: https://publications.iarc.fr/Book-And-Report-Series/Who-Classification-Of-Tumours/Haematolymphoid-Tumours-2024. Accessed: February 2025. 3. Bustoros M *et al*. *J Clin Oncol* 2020; 37 (16): 1403–1411.

Indications to initiate treatment of WM

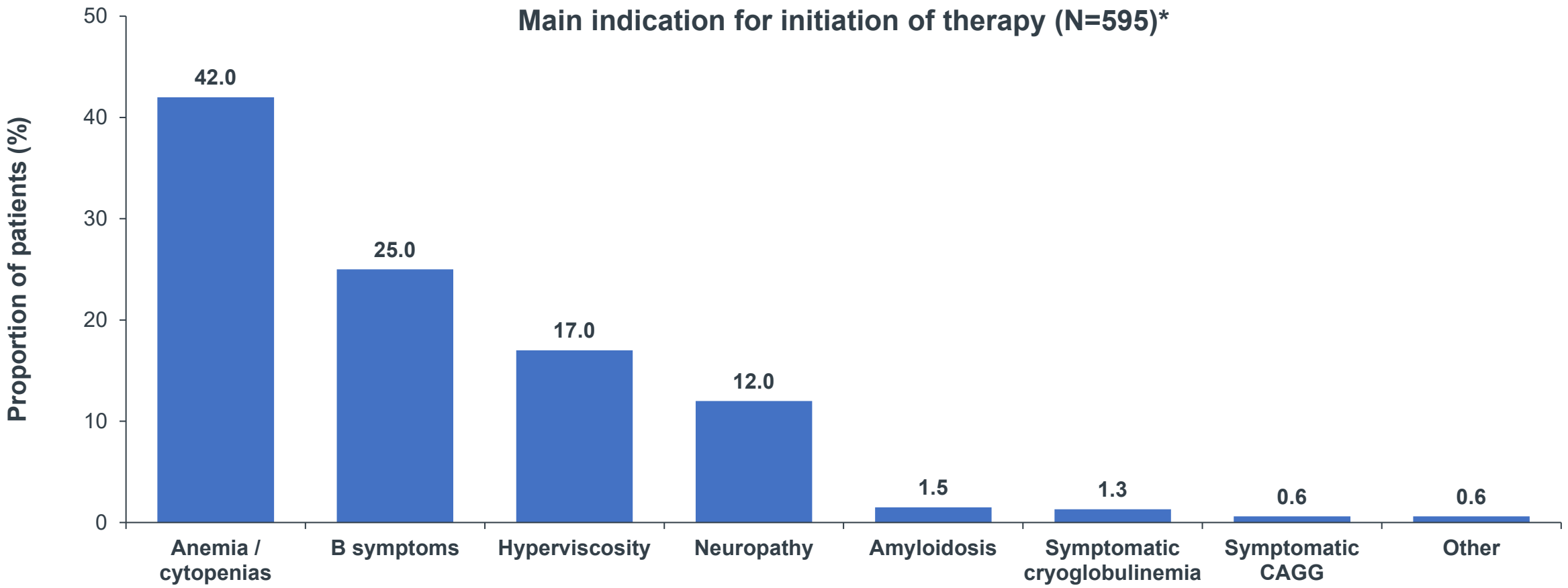
Clinical indications
Recurrent fever, night sweats, weight loss, fatigue
Lymphadenopathy: Either symptomatic or bulky (≥5 cm in maximum diameter)
Symptomatic hepatomegaly and/or splenomegaly
Symptomatic organomegaly and/or organ or tissue infiltration
Hyperviscosity
Peripheral neuropathy due to IgM

Laboratory indications
Hemoglobin ≤10 g/dL
Platelets $<100 \times 10^9$/L
IgM levels >60 g/L
Nephropathy related to WM
Symptomatic cryoglobulinemia
Symptomatic cold agglutinin anemia
Autoimmune hemolytic anemia and/or thrombocytopenia
Amyloidosis related to WM

IgM, immunoglobulin M; WM, Waldenström's macroglobulinemia.

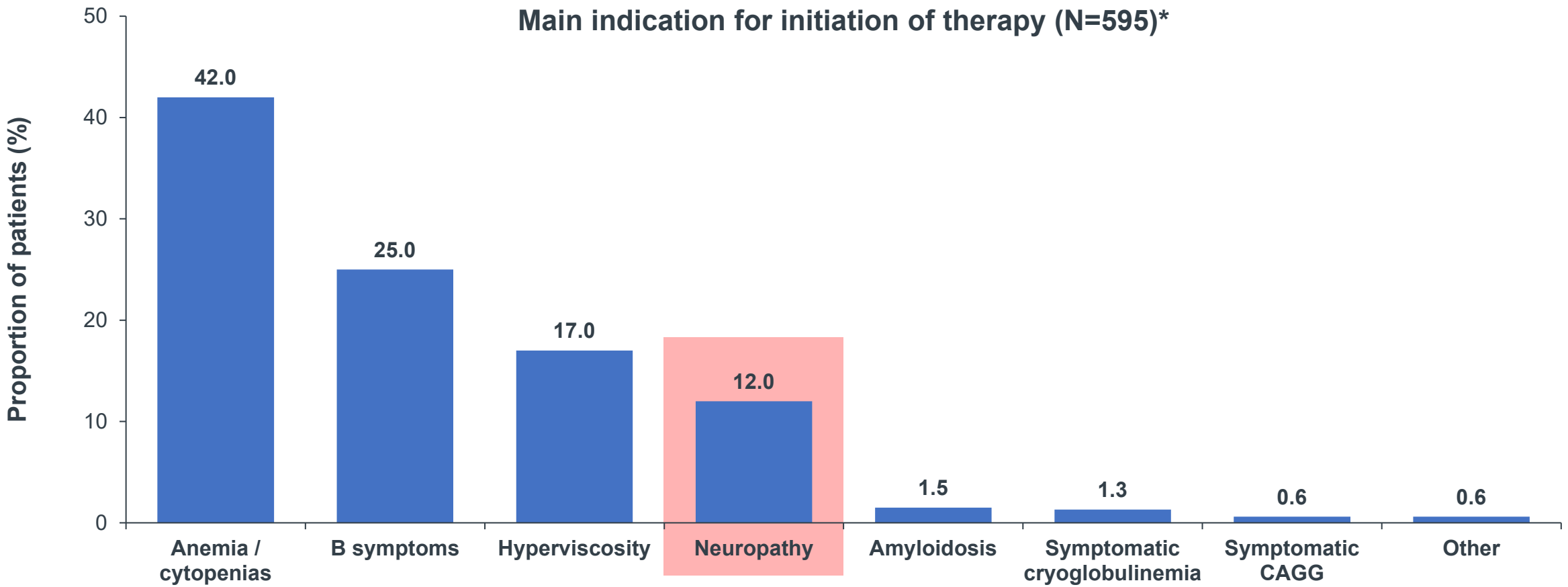
Kastritis E *et al*. *Ann Oncol* 2018; 29 (Suppl 4): iv41–iv50.

Clinical presentation of patients with symptomatic WM



*In many patients, more than one indication was present.
CAGG, cold agglutinin anemia; WM, Waldenström's macroglobulinemia.
Dimopoulos MA *et al*. *Blood* 2019; 134 (23): 2022–2035.

Clinical presentation of patients with symptomatic WM



*In many patients, more than one indication was present.
CAGG, cold agglutinin anemia; WM, Waldenström's macroglobulinemia.
Dimopoulos MA *et al*. *Blood* 2019; 134 (23): 2022–2035.

Patient 1B

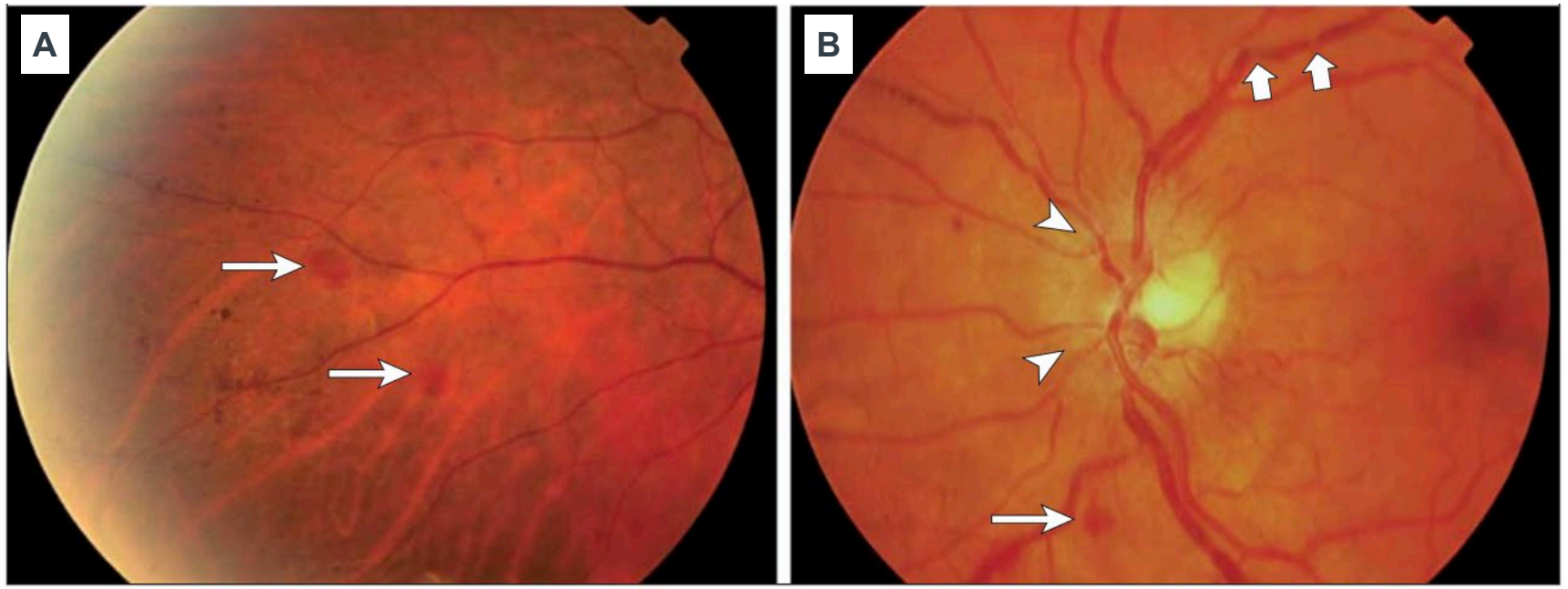
Patient characteristics	**Male** **Age:** 64 years No prior pathology	Patient returns to your clinic after a 2-week holiday abroad, having experienced **blurred vision** and **frequent headaches**	**First-line** **How would you manage the patient and why?**
Review of systems	• No B symptoms • No organomegaly • Several lymph nodes 1–2 cm	No evidence of neuropathies, no bleeding	
Laboratory studies	**Hemoglobin:** 11.6 g/dL / 7.2 mmol/L **Platelets:** 164 × 10^9/L **WBC:** 5.1 × 10^9/L	**M spike:** 54 g/L **Serum IgM:** 82 g/L	
Bone marrow evaluation	**Trephine biopsy** Lymphoplasmacytic infiltration = 70%	**Flow cytometry on BM aspirate** • **44%** B cell clonal population CD19+, CD22+, smIgM kappa • **12%** kappa-positive plasma cells CD38+, CD19+, CD56−, smIgM kappa	*CXCR4* **wild type**

This is a hypothetical patient case scenario intended for educational purposes only.

BM, bone marrow; CD, cluster of differentiation; IgM, immunoglobulin M; smIgM, surface membrane immunoglobulin M; WBC, white blood cells.

Diagnosing hyperviscosity-related retinopathy in WM

Fundus images of eyes of patients with WM



A) Peripheral retinal hemorrhages (arrows).

B) Central retinal hemorrhage (thin arrow); optic disc edema (arrowheads); and venous sausaging (thick arrows).

Access to ophthalmologist and apheresis services… during the weekend?

WM, Waldenström's macroglobulinemia.
Menke MN *et al. Arch Opthalmol* 2006; 124 (11): 1601–1606.

Management of monoclonal IgM–related symptoms
Plasmapheresis

Indications:

- Hyperviscosity syndrome
- Cryoglobulinemia

Temporary management of symptoms

↓

Should be followed by fast-acting systemic therapy

IgM, immunoglobulin M.

Dimopoulos MA *et al*. *Blood* 2019; 134 (23): 2022–2035.

Patient 2

Patient characteristics	**Male** **Age:** 64 years No prior pathology	Patient has experienced **fever**, **night sweats**, and **loss of body weight**	**First-line** **How would you manage the patient and why?**
Review of systems	• Several lymph nodes >5 cm • Splenomegaly 17 cm	• No visual problems, no evidence of neuropathies, no bleeding	
Laboratory studies	**Hemoglobin:** 10.8 g/dL / 6.7 mmol/L **Platelets:** 158 × 10^9/L **WBC:** 5.8 × 10^9/L	**M spike:** 42 g/L **Serum IgM:** 55 g/L	
Bone marrow evaluation	**Trephine biopsy** Lymphoplasmacytic infiltration = 75%	**Flow cytometry on BM aspirate** • **54%** B cell clonal population CD19+, CD22+, smIgM kappa • **15%** kappa-positive plasma cells CD38+, CD19+, CD56−, smIgM kappa	• *MYD88*^{L265P} **positive** • *CXCR4* **mutated**

This is a hypothetical patient case scenario intended for educational purposes only.

BM, bone marrow; CD, cluster of differentiation; IgM, immunoglobulin M; smIgM, surface membrane immunoglobulin M; WBC, white blood cells.

Ask the audience

How would you treat this patient?

- Rituximab monotherapy
- Bendamustine and rituximab
- Dexamethasone, rituximab, and cyclophosphamide
- Bortezomib and rituximab
- Bortezomib, rituximab, and dexamethasone
- Zanubrutinib or ibrutinib (± rituximab)
- Oral fludarabine ± rituximab
- Chlorambucil ± rituximab

Patient 3

Patient characteristics	**Male** | **Age:** 84 years • Diabetes, non-insulin–dependent • Arthritic hips (walking problems) • Hypertension • Mild aortic valve stenosis	Patient has experienced **fatigue**, **night sweats**, and **loss of body weight**	**First-line** **How would you manage the patient and why?**
Review of systems	• Several lymph nodes >5 cm • Splenomegaly 17 cm	• No visual problems, no evidence of neuropathies, no bleeding	
Laboratory studies	**Hemoglobin:** 11.9 g/dL / 7.4 mmol/L **Platelets:** 173 × 10^9/L **WBC:** 4.9 × 10^9/L	**M spike:** 22 g/L **Serum monoclonal IgM:** 26 g/L	
Bone marrow evaluation	**Trephine biopsy** Lymphoplasmacytic infiltration = 75%	**Flow cytometry on BM aspirate** • **58%** B cell clonal population CD19+, CD22+, smIgM kappa • **19%** kappa-positive plasma cells CD38+, CD19+, CD56−, smIgM kappa	• *MYD88*^{L265P} **positive** • *CXCR4* **wild type**

This is a hypothetical patient case scenario intended for educational purposes only.

BM, bone marrow; CD, cluster of differentiation; IgM, immunoglobulin M; smIgM, surface membrane immunoglobulin M; WBC, white blood cells.

Ask the audience

How would you treat this patient?

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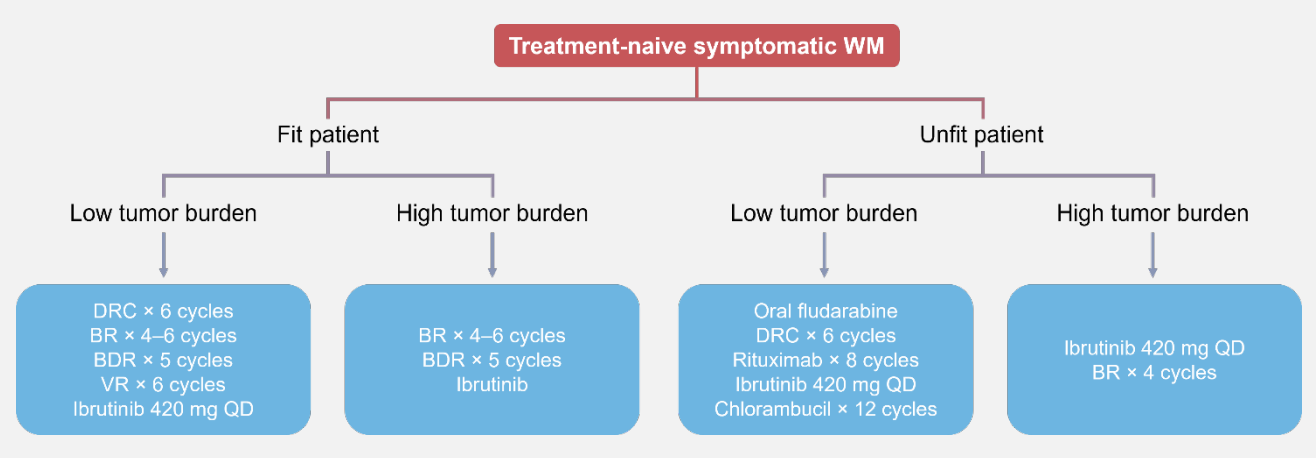
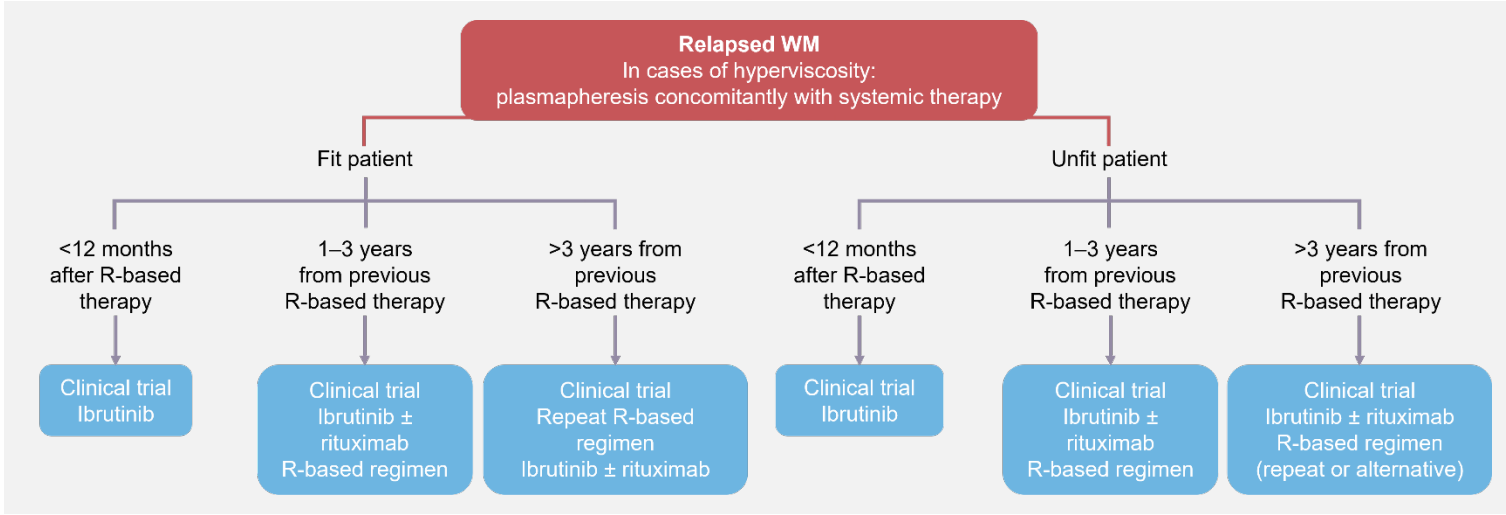
- Oral fludarabine ± rituximab
- Chlorambucil ± rituximab

ESMO treatment guidelines for WM were published in 2018



The guidelines predate EMA approval of zanubrutinib in 2021



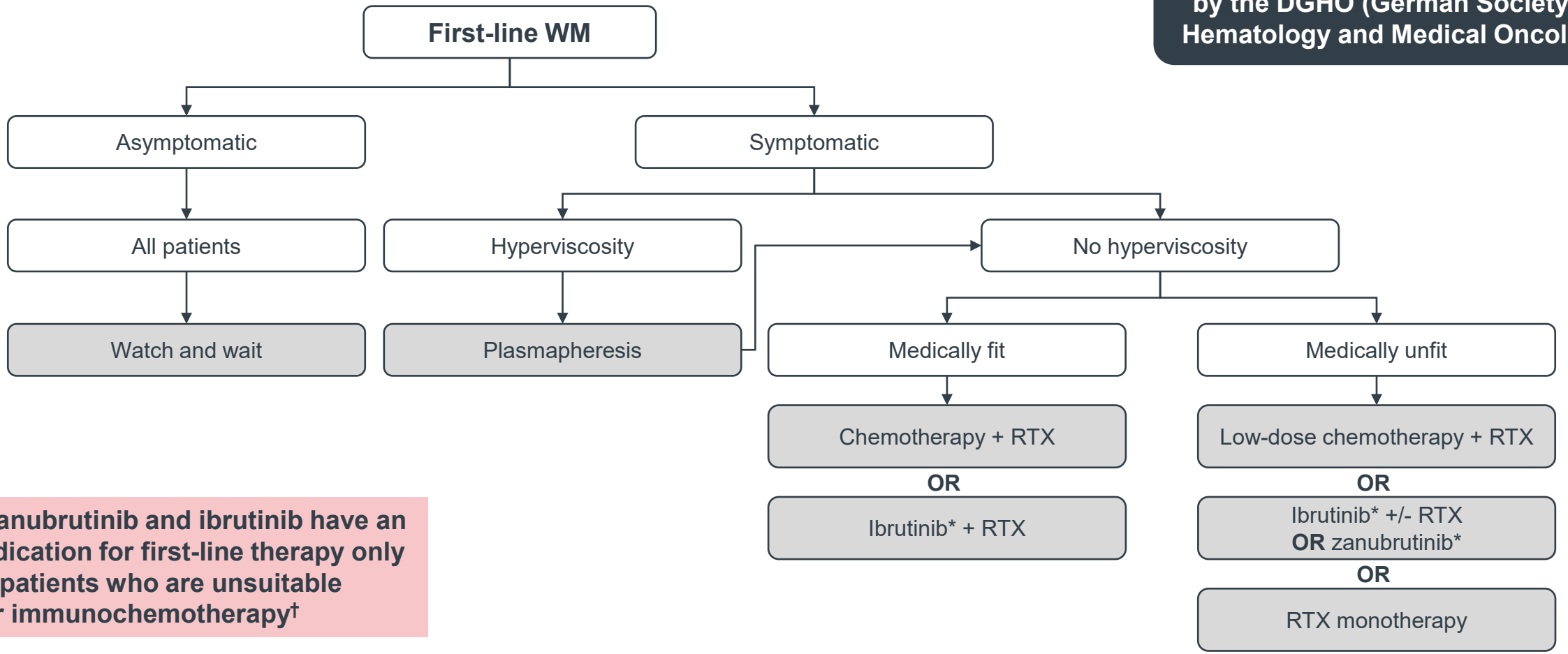
BDR, bortezomib, dexamethasone, and rituximab; BR, bendamustine and rituximab; DRC, dexamethasone, rituximab, and cyclophosphamide; EMA, European Medicines Agency; ESMO, European Society for Medical Oncology; QD, once daily; R, rituximab; VR, bortezomib and rituximab; WM, Waldenström's macroglobulinemia.

Kastritis E *et al*. *Ann Oncol* 2018; 29 (Suppl 4): iv41–iv50.

Recent WM treatment guidelines

Onkopedia first-line WM

Onkopedia guidelines are developed by the DGHO (German Society for Hematology and Medical Oncology)



***Zanubrutinib and ibrutinib have an indication for first-line therapy only in patients who are unsuitable for immunochemotherapy†**

RTX, rituximab; WM, Waldenström's macroglobulinemia.
†Applies in the EU and other markets where they are approved for use in WM.
Buske C *et al*. Onkopedia. Waldenström's disease (lymphoplasmocytic lymphoma). Available at: https://www.onkopedia.com/de/onkopedia/guidelines/morbus-waldenstroem-lymphoplasmozytisches-lymphom/@@guideline/html/index.html. Accessed November 2024.

Patient 4A

Patient characteristics	**Female** **Age:** 72 years • No prior pathology • **Two years' remission following 1st line bendamustine-rituximab**	Patient has experienced **tingling** in the **hands** and **feet**, **pain** is present at night	**First-line** **How would you manage the patient and why?**
Review of systems	• No enlarged lymph nodes • Splenomegaly 15 cm	• No visual problems, no bleeding • No cold phenomena	
Laboratory studies	**Hemoglobin:** 12.9 g/dL / 8 mmol/L **Platelets:** 220 × 10^9/L **WBC:** 6.1 × 10^9/L	**M spike:** 23 g/L [rising] **Serum IgM:** 28 g/L **Anti-MAG:** ++	
Bone marrow evaluation	**Trephine biopsy** Lymphoplasmacytic infiltration = 20%	**Flow cytometry on BM aspirate** • **14%** B cell clonal population CD19+, CD22+, smIgM kappa • **2%** kappa-positive plasma cells CD38+, CD19+, CD56−	• *MYD88*^{L265P} **positive** • *CXCR4* **wild type**

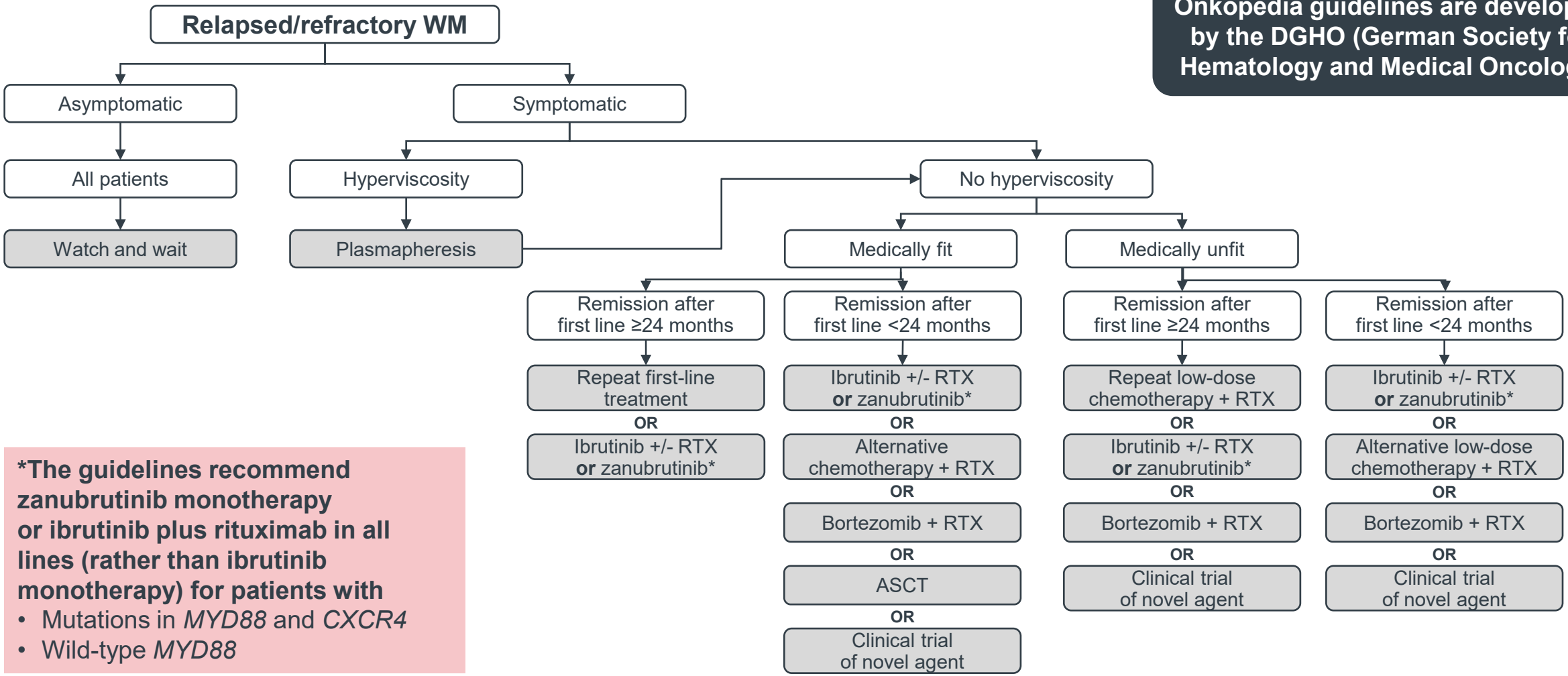
This is a hypothetical patient case scenario intended for educational purposes only.

BM, bone marrow; CD, cluster of differentiation; IgM, immunoglobulin M; smIgM, surface membrane immunoglobulin M; WBC, white blood cells.

Recent WM treatment guidelines

Onkopedia relapsed/refractory WM

Onkopedia guidelines are developed by the DGHO (German Society for Hematology and Medical Oncology)



***The guidelines recommend zanubrutinib monotherapy or ibrutinib plus rituximab in all lines (rather than ibrutinib monotherapy) for patients with**

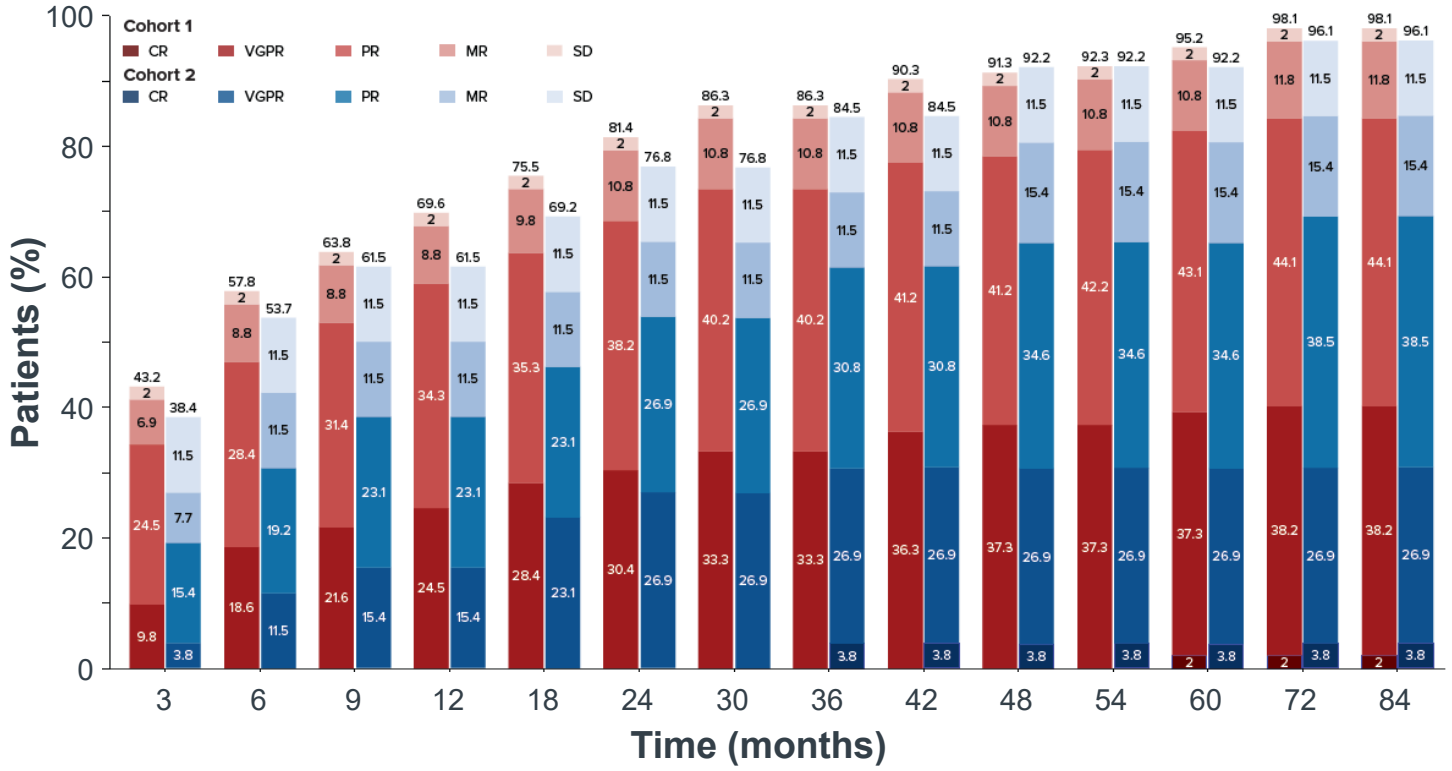
- Mutations in *MYD88* and *CXCR4*
- Wild-type *MYD88*

ASCT, autologous stem cell transplant; RTX, rituximab; WM, Waldenström's macroglobulinemia.

Buske C *et al*. Onkopedia. Waldenström's disease (lymphoplasmocytic lymphoma). Available at: https://www.onkopedia.com/de/onkopedia/guidelines/morbus-waldenstroem-lymphoplasmozytisches-lymphom/@@guideline/html/index.html. Accessed November 2024.

The ASPEN study compared zanubrutinib and ibrutinib in a head-to-head trial

Best ORR with zanubrutinib over time as assessed by investigator[1]



At a 44.4-month median follow-up, VGPR rates were 36.3% with zanubrutinib versus 25.3% with ibrutinib for *MYD88*^{MUT} patients (Cohort 1)*

In cohort 2, *MYD88*^{WT} patients treated with open-label zanubrutinib had a VGPR + CR rate of 30.8%[2]

42-month overall PFS rates were 78% with zanubrutinib and 70% with ibrutinib[2]

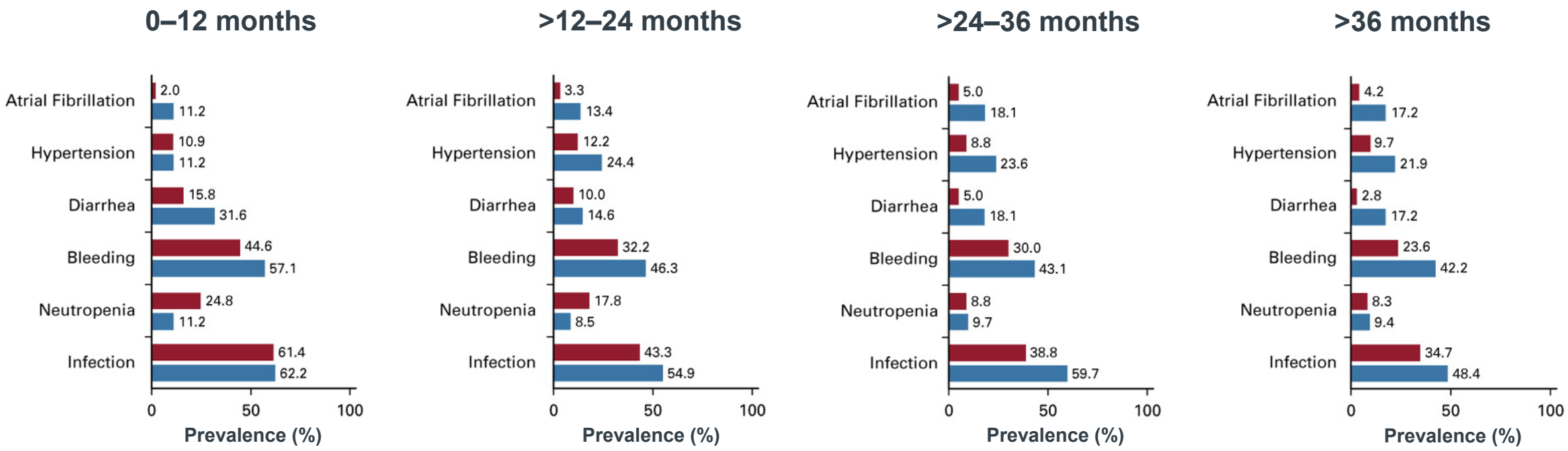
*There were no CRs in Cohort 1. CR, complete response; EFS, event-free survival; MR, minimal response; MUT, mutated; PD, progressive disease; PR, partial response; SD, stable disease; VGPR, very good partial response; WT, wild-type.

1. D'Sa S *et al*. Poster presentation at ASH 2024; San Diego, CA, USA, December 7–10, 2024. 2. Dimopoulos MD *et al*. *J Clin Oncol* 2023; 41 (33): 5099–5106.

The ASPEN study compared zanubrutinib and ibrutinib in a head-to-head trial

Adverse events of interest

Zanubrutinib | Ibrutinib



Dimopoulos MD *et al*. *J Clin Oncol* 2023; 41 (33): 5099–5106.

Zanubrutinib and ibrutinib may be effective treatments for WM-associated peripheral neuropathy (1)

Exploratory analysis of patients with WM and PN symptoms in the ASPEN study

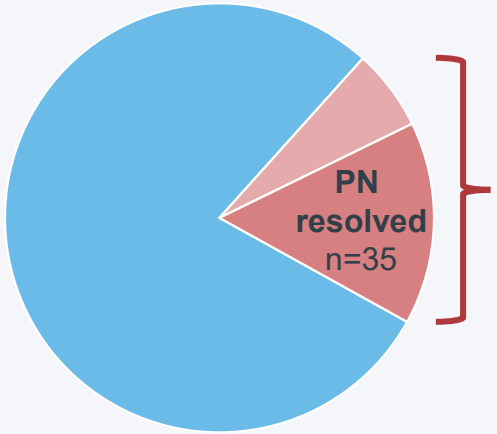
There was no formal analysis of PN and type

Anti-MAG levels at screening

10 of 49 patients with PN symptoms had elevated levels (≥1,000 TU)

4 patients had highly elevated levels (>70,000 TU) indicating an association between PN and WM

Outcomes in patients with PN symptoms in the ASPEN study (N=229)



Patients with PN (n=49; 21.4%)

71.4% experienced PN symptom resolution, as assessed by patient and hematologist

PN symptom resolution correlated with major response* and lower baseline anti-MAG level, but not IgM levels

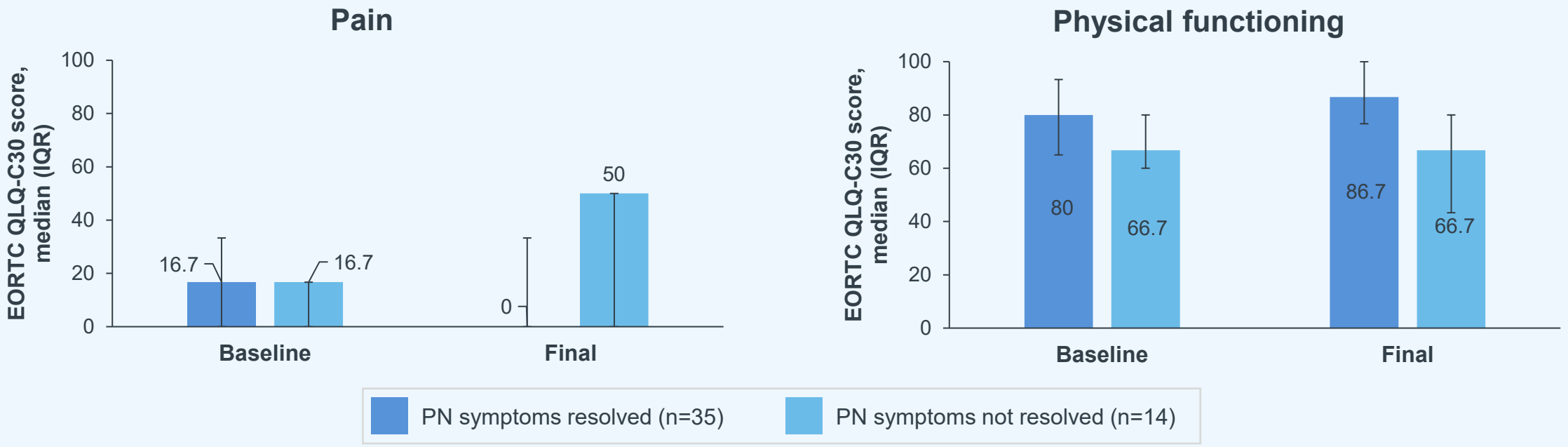
Outcomes in patients with PN per cohort and treatment (n=49)

	Cohort 1 (*MYD88*^{MUT})		Cohort 2 (*MYD88*^{WT})	Total (n=49)
	Zanu (n=24)	Ibr (n=22)	Zanu (n=3)	
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)

*PR or better. Ibr, ibrutinib; IgM, immunoglobulin M; MAG, myelin-associated glycoprotein; MUT, mutated; PN, peripheral neuropathy; PR, partial response; TU, titer units; WM, Waldenström's macroglobulinemia; WT, wild-type; Zanu, zanubrutinib.

Heyman BM *et al*. *Blood Adv* 2025; 9 (4): 722–728.

Zanubrutinib and ibrutinib may be effective treatments for WM-associated peripheral neuropathy (2)



Patients with PN resolution had improvements in pain and physical functioning

EORTC QLQ-30, European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30; IQR, interquartile range; PN, peripheral neuropathy; WM, Waldenström's macroglobulinemia.
Heyman BM *et al*. *Blood Adv* 2025; 9 (4): 722–728.

Patient 4B

Patient characteristics	**Female** **Age:** 76 years • No prior pathology • Two years' remission following first-line bendamustine-rituximab	Patient relapses 4 years into second-line treatment with continuous BTK inhibitor monotherapy	• Distal neuropathic pain, which had been manageable, has intensified • Experienced issues with balance
Review of systems	• No organomegaly • No enlarged lymph nodes	• No visual problems, no bleeding • No cold phenomena	
Laboratory studies	**Hemoglobin:** 10.0 g/dL / 7.4 mmol/L **Platelets:** 158 × 10^9/L **WBC:** 6.3 × 10^9/L	**M spike:** 12 g/L [rising] **Serum IgM: 15** g/L	
Bone marrow evaluation	**Trephine biopsy** • Not performed	**Flow cytometry on BM aspirate** • Not performed	

First-line

How would you manage the patient and why?

This is a hypothetical patient case scenario intended for educational purposes only.

BM, bone marrow; CD, cluster of differentiation; IgM, immunoglobulin M; smIgM, surface membrane immunoglobulin M; WBC, white blood cells.

Thank you for your attention