Initiation of treatment for Waldenström's macroglobulinemia: Practical guidance for starting treatment and managing complications

Wednesday, January 20, 2021 | 17:00–18:30 (CET)

Welcome and introductions

Chair: Prof. Véronique Leblond

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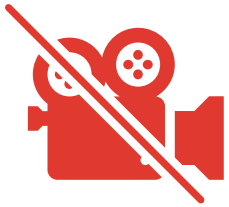
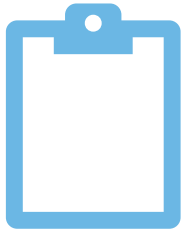
- Zanubrutinib is not approved for use outside the United States and China. Zanubrutinib is not approved for the treatment of Waldenström’s macroglobulinemia.

Housekeeping



Please note that personal recording of this meeting is not permitted

Please use the Q&A function throughout the meeting to submit questions you wish to ask the speaker panel



A post-meeting survey will be shared at the end of the webinar; we would greatly appreciate your feedback

Q&A, question and answer.

Introducing the speakers

Véronique Leblond
Pitié-Salpêtrière Hospital, France

Meletios A. Dimopoulos
National and Kapodistrian University of Athens School of Medicine, Greece

Ramón García-Sanz
University Hospital of Salamanca, Spain

Wojciech Jurczak
Maria Skłodowska-Curie National Research Institute of Oncology, Poland

Disclosures

- **Speaker bureau:** Roche, Gilead, Janssen, AbbVie, BeiGene, GSK
- **Board:** Roche, Pharmacyclics, Janssen-Cilag, GSK, Gilead, AstraZeneca, AbbVie
- **Honoraria:** Roche, Pharmacyclics, Janssen-Cilag, GSK, Gilead, Lilly, Amgen, AstraZeneca, BeiGene

Agenda

17:00	**Welcome and introductions**	Véronique Leblond
17:05	**How do I treat patients with WM?**	Meletios A. Dimopoulos
17:25	**Challenges from the clinic: Initiation of treatment in WM**	Ramón García-Sanz
17:45	**Open panel discussion:** What are the greatest difficulties we face in initial treatment of WM?	**Moderator:** Wojciech Jurczak **Panel:** All
18:00	**Panel debate:** Should chemotherapy-free regimens play a greater role when initiating treatment for WM?	**Moderator:** Meletios A. Dimopoulos **For:** Wojciech Jurczak **Against:** Véronique Leblond
18:15	**Talk to the experts: What challenges do you face in treating WM?**	**Moderator:** Véronique Leblond **Panel:** All
18:25	**Summary**	Véronique Leblond

WM, Waldenström's macroglobulinemia.

A guide to the meeting platform and live polling function

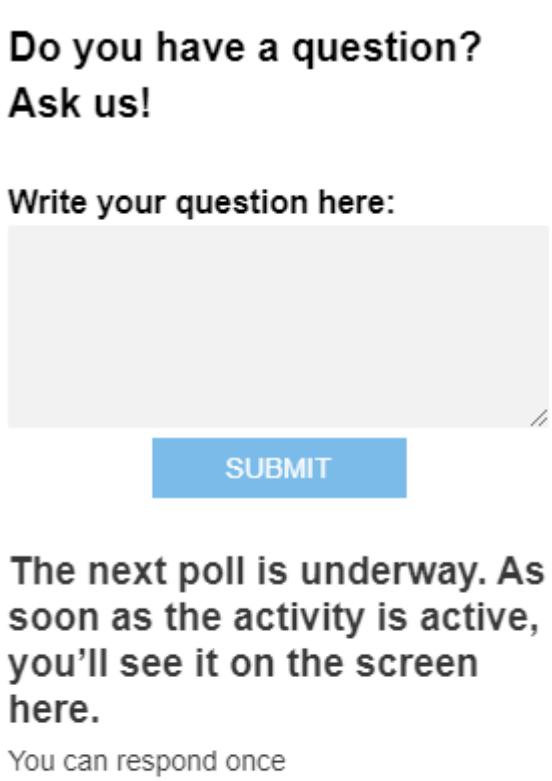
Please exit the full screen view to participate in the Q&A and live polling.

Q&A function:

- Please enter your questions in the Q&A submission box
- Because of the volume of questions expected today, some questions received might not be answered during the session

Live polling function:

- When an audience poll is active, please answer the questions in the poll section
- Please select your response (note that responses will be shown on the screen and remain anonymous)



Q&A, question and answer.

How do I treat patients with WM?

Prof. Meletios A. Dimopoulos
National and Kapodistrian University of Athens
School of Medicine, Greece

WM, Waldenström’s macroglobulinemia.

Disclosures

- Honoraria from participation in advisory boards
  - Amgen, BeiGene, Bristol Myers Squibb, Janssen, Takeda

Overview

1. Symptomatic and asymptomatic WM
   - Definitions and risk assessment
2. Symptomatic therapy
   - Plasmapheresis
3. Disease-targeted therapy
   - Treatment options and recommendations
   - Assessing treatment response
   - ‘Fit’ and ‘unfit’ patients
   - Pros and cons of immunochemotherapy
4. How I start treatment for WM

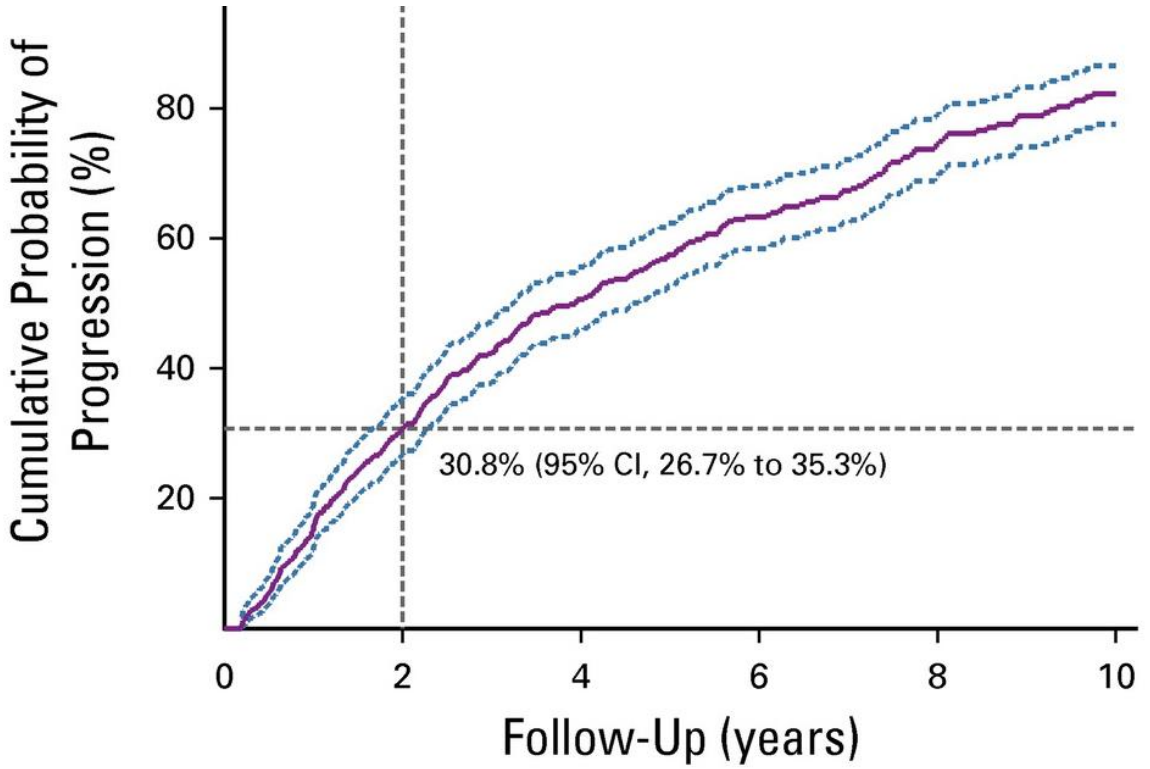
WM, Waldenström’s macroglobulinemia.

Asymptomatic WM

Asymptomatic WM is defined as[1]:

- ≥3 g/dL serum monoclonal IgM protein **and/or** ≥10% bone marrow lymphoplasmacytic infiltration
- No evidence of end-organ damage*, e.g.
  - Symptomatic anemia
  - Constitutional symptoms
  - Hyperviscosity
  - Lymphadenopathy
  - Hepatosplenomegaly

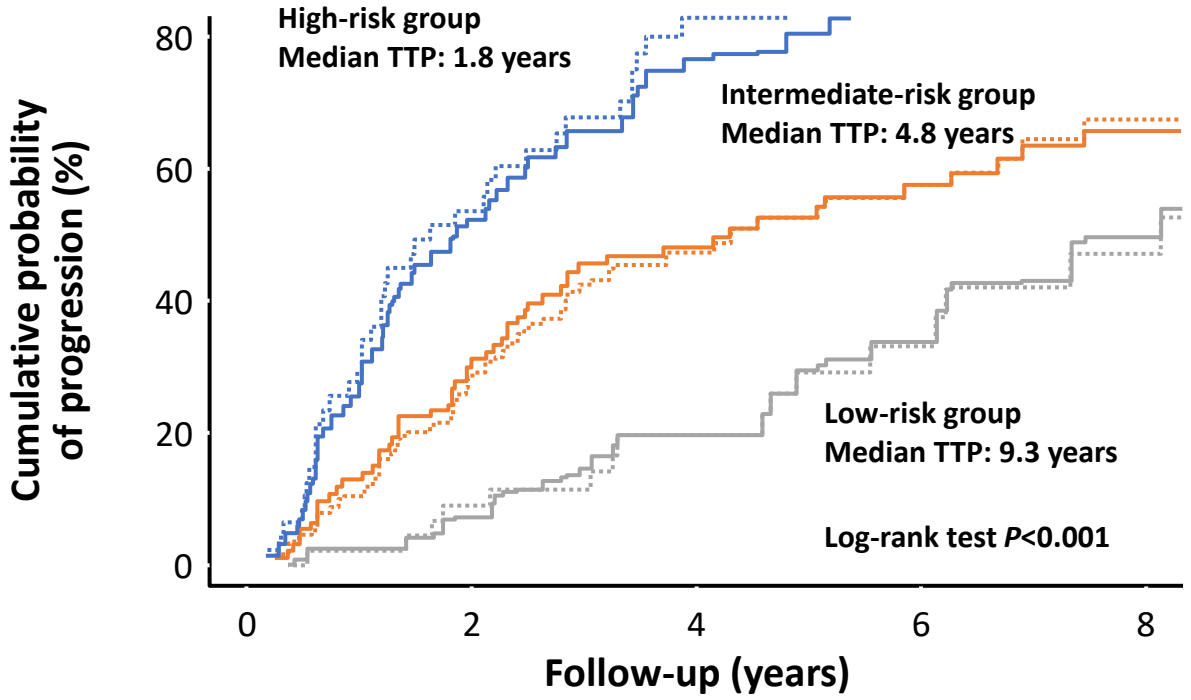
Cumulative probability of progression among patients with asymptomatic WM[2]



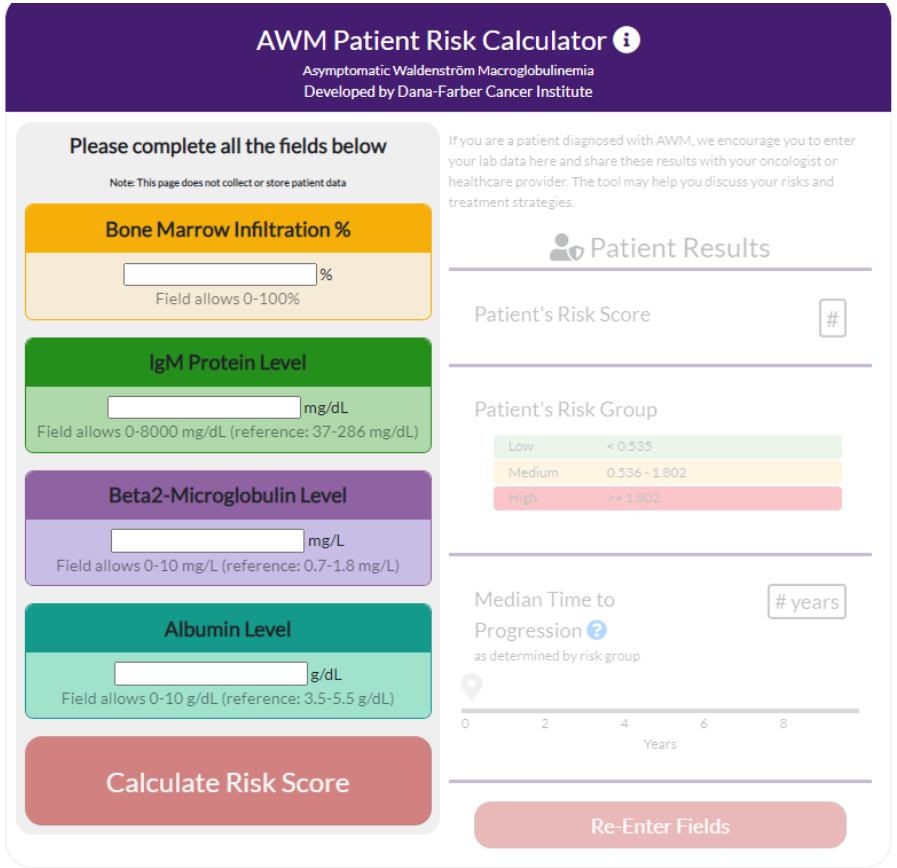
*Attributed to a plasma cell proliferative disorder; CI, confidence interval; IgM, immunoglobulin M; WM, Waldenström's macroglobulinemia.

1. Kyle RA *et al*. *Blood* 2012; 119 (19): 4462–4466. 2. Bustoros M *et al*. *J Clin Oncol* 2020; 37 (16): 1403–1411.

Asymptomatic WM Patient Risk Calculator*



Dashed lines represent the results of training set.
Solid lines represent the results of cross-validation.



IgM, immunoglobulin M; TTP, time to progression; WM, Waldenström's macroglobulinemia.
Bustoros M *et al*. *J Clin Oncol* 2020; 37 (16): 1403–1411.

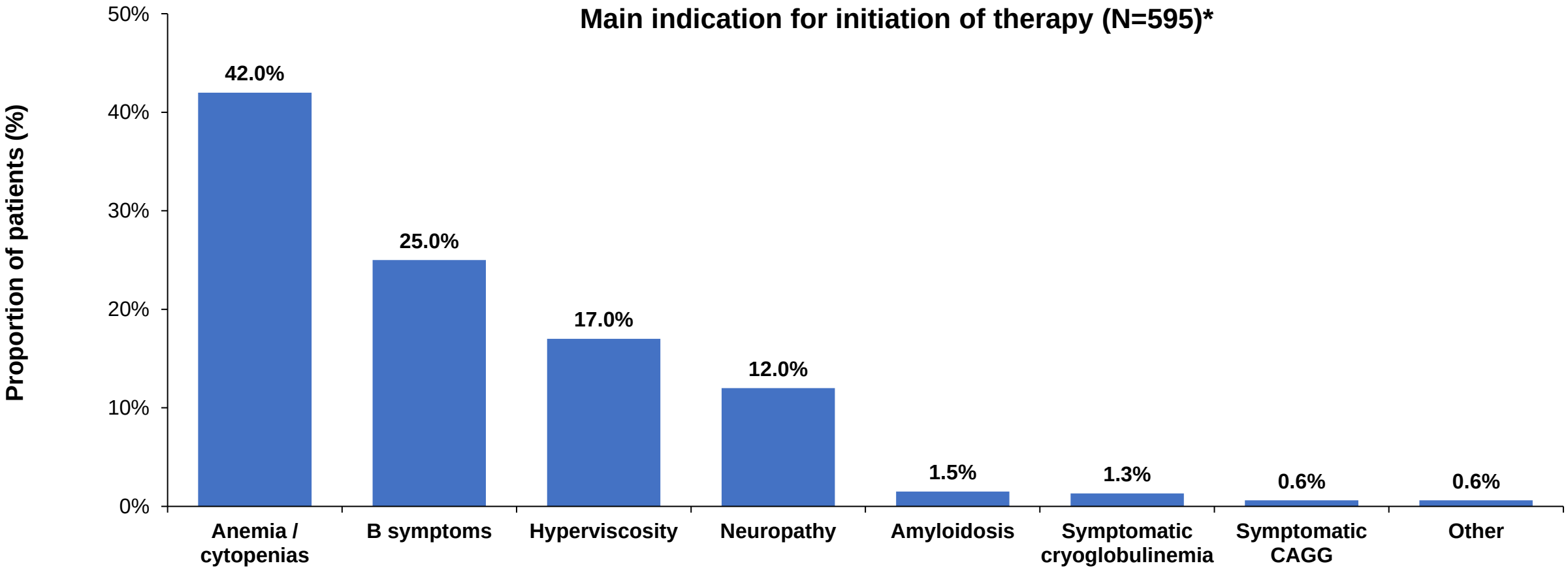
Indications to initiate treatment of WM

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

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

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

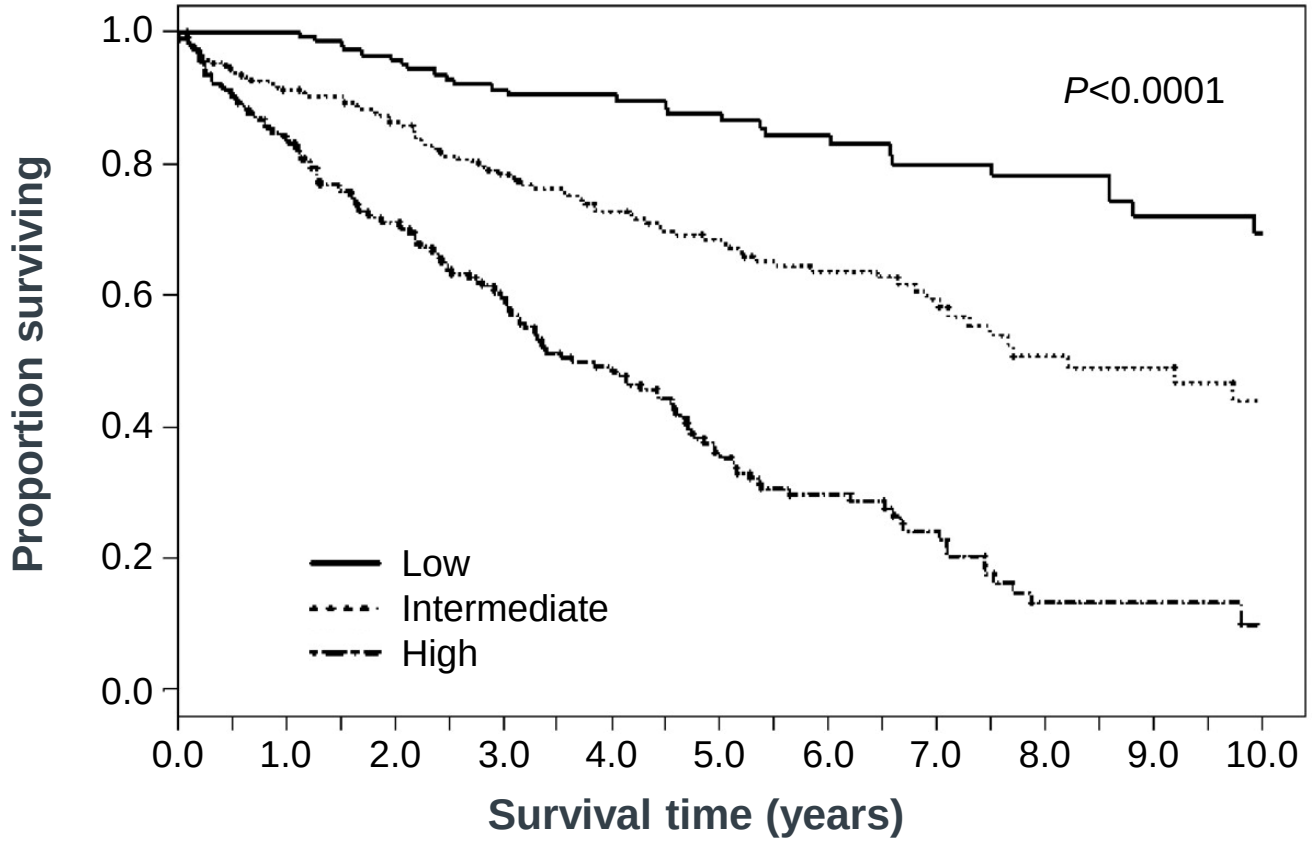


*In many patients, more than one indication was present.
CAGG, cold agglutinin anemia; WM, Waldenström's macroglobulinemia.
Dimopoulos MA *et al*. *Blood* 2019; 134 (23): 2022–2035.

Prognosis of the symptomatic patient

The International Prognostic Scoring System for WM

Survival after treatment initiation according to the ISSWM



- Age >65 years
- Hemoglobin ≤11.5 g/dL
- Platelets ≤100 × 10^9/L
- β2-microglobulin >3 mg/L
- M protein >7.0 g/dL

Low risk = 0 or 1 (except age)

Intermediate risk = age or 2

High risk = ≥3

ISSWM, International Prognostic Scoring System for Waldeström's macroglobulinemia; WM, Waldenström's macroglobulinemia.

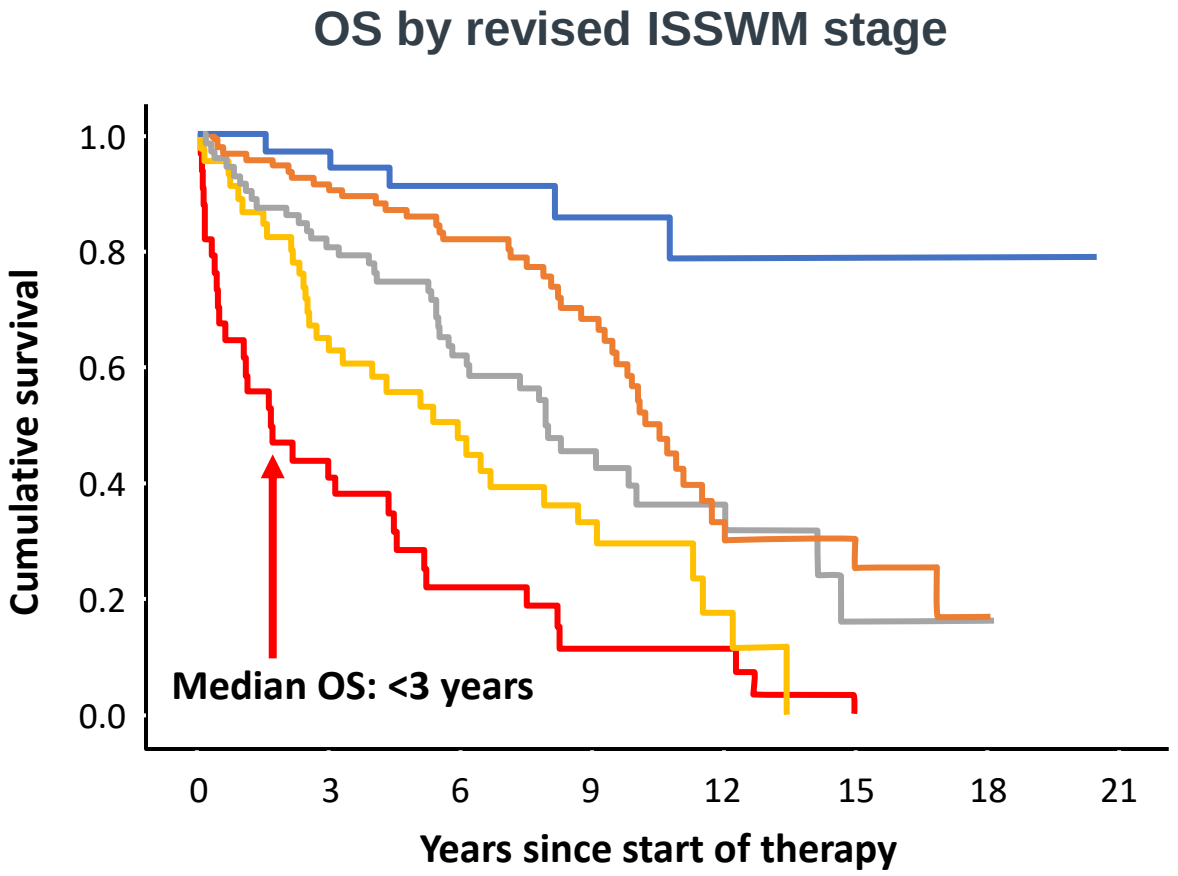
Morel P *et al*. *Blood* 2009; 113 (18): 4163–4170.

Prognosis of the symptomatic patient

The *Revised* International Prognostic Scoring System for WM

		Points
Age	<65 years 66–75 years >75 years	0 1 2
Serum β2-microglobulin >4 mg/L		1
LDH >250 IU/L		***1***
Serum albumin <3.5 g/dL		***1***

Stage	Score	Patients (%)	5-year OS (%)	10-year OS (%)	Median OS (years)
Very low	0	13	95	84	NR
Low	1	33.5	86	59	10.4
Intermediate	2	25.5	78	37	7.8
High	3	16	47	19	6.1
Very high	4–5	12	36	9	2.9



ISSWM, International Prognostic Scoring System for Waldeström's macroglobulinemia; IU, International Units; LDH, lactate dehydrogenase; NR, not reported; OS, overall survival; WM, Waldenström's macroglobulinemia.

Kastritis E *et al*. *Leukemia* 2019; 33 (11): 2654–2661.

Management of monoclonal IgM–related symptoms

Plasmapheresis

Indications:

- Hyperviscosity syndrome
- Peripheral neuropathy (?)
- Cryoglobulinemia

Temporary management of symptoms

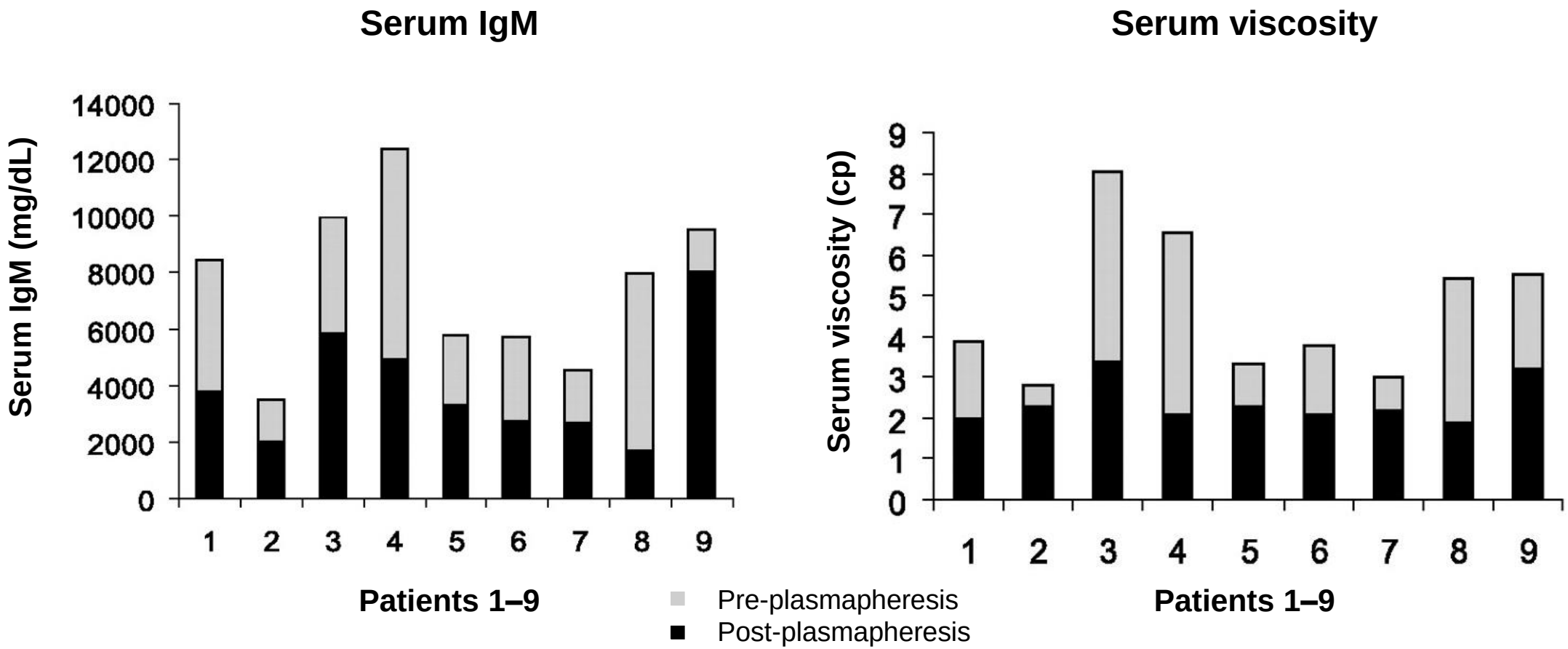
↓

Should be followed by systemic therapy

IgM, immunoglobulin M.

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

Effect of plasmapheresis



cp, centipoises; IgM, immunoglobulin M.

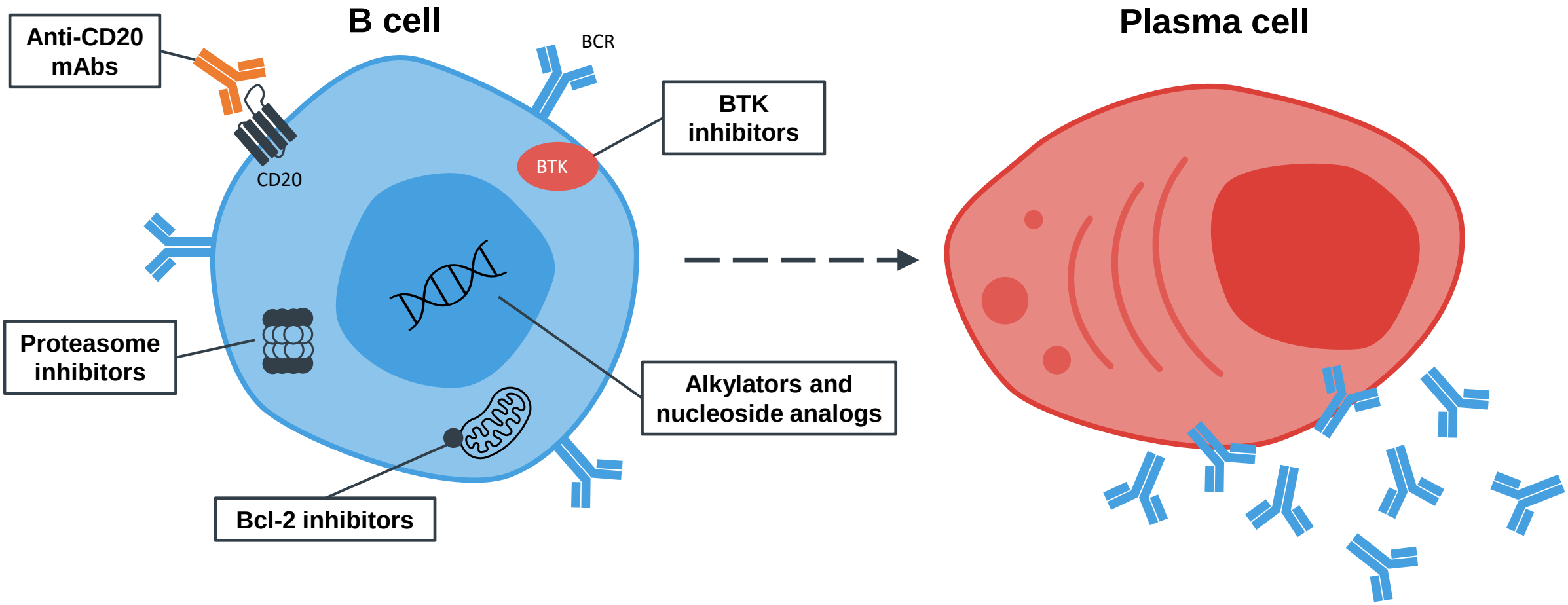
Menke MN *et al*. *Invest Ophthalmol Vis Sci* 2008; 49 (3): 1157–1160.

Disease-targeted therapy for WM

What is available?

IMiDs
mTOR inhibitors

New options



Bcl-2, B-cell lymphoma 2; BCR, B-cell receptor; BTK, Bruton's tyrosine kinase; IMiDs, immunomodulatory imide drugs; mAb, monoclonal antibody; mTOR; mammalian target of rapamycin; WM, Waldenström's macroglobulinemia. Adapted from Imhof BA *et al*. *Swiss Med Wkly* 2017; 147: w14487.

Consensus treatment recommendations

Update from the 10th International Workshop on WM[1]

- Treatment should be personalized based on:
  - Toxicity profile
  - Administration route and schedule
  - Drug access
  - Patient preference

Preferred initial treatment options

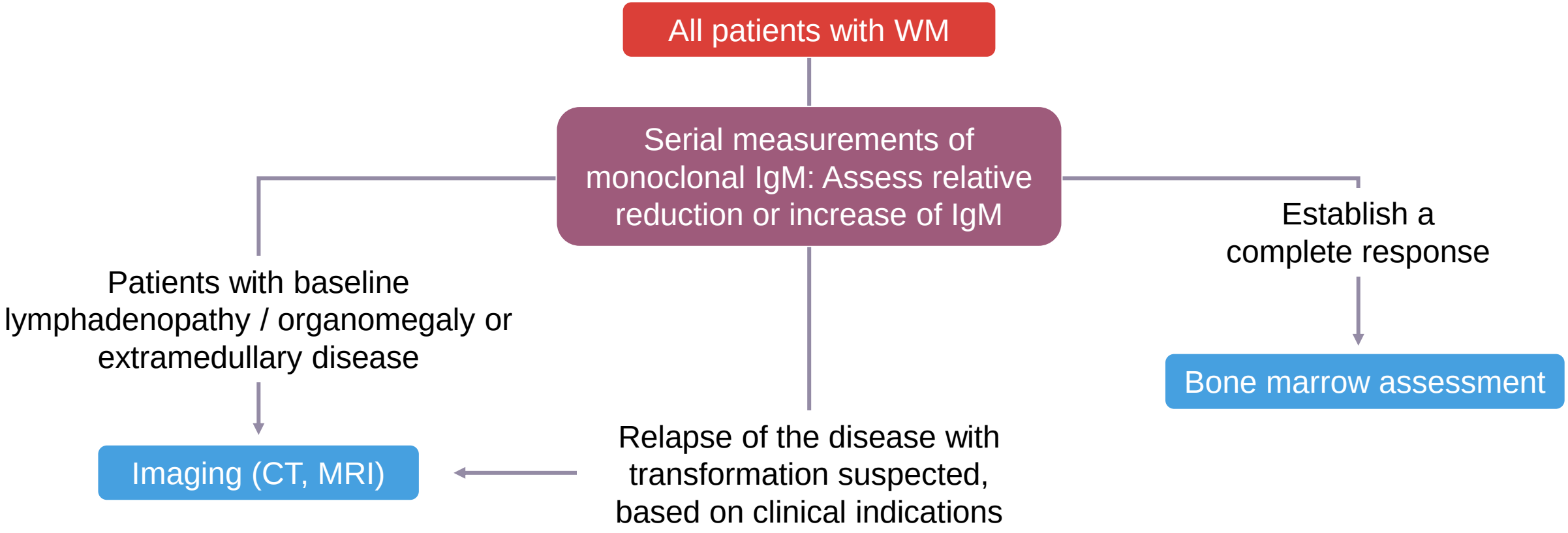
- Bendamustine plus rituximab
- Bortezomib, dexamethasone, and rituximab
- Cyclophosphamide, dexamethasone, and rituximab
- Ibrutinib (with or without rituximab)

Treatment recommendations

- Avoid bortezomib and vincristine in patients with neuropathy
- Avoid carfilzomib* in patients with cardiac disease or patients >65 years of age
- Avoid nucleoside analogues in patients who are candidates for SCT
- Consider delaying rituximab if serum IgM concentrations are >40 g/L
- Consider ofatumumab* in patients who are intolerant to rituximab

*Not approved in Europe for the treatment of patients with WM.
IgM, immunoglobulin M; SCT, stem cell transplantation; WM, Waldenström's macroglobulinemia.
1. Castillo JJ *et al*. *Lancet Haematol* 2020; 7 (11): e827–e837.

WM response evaluation



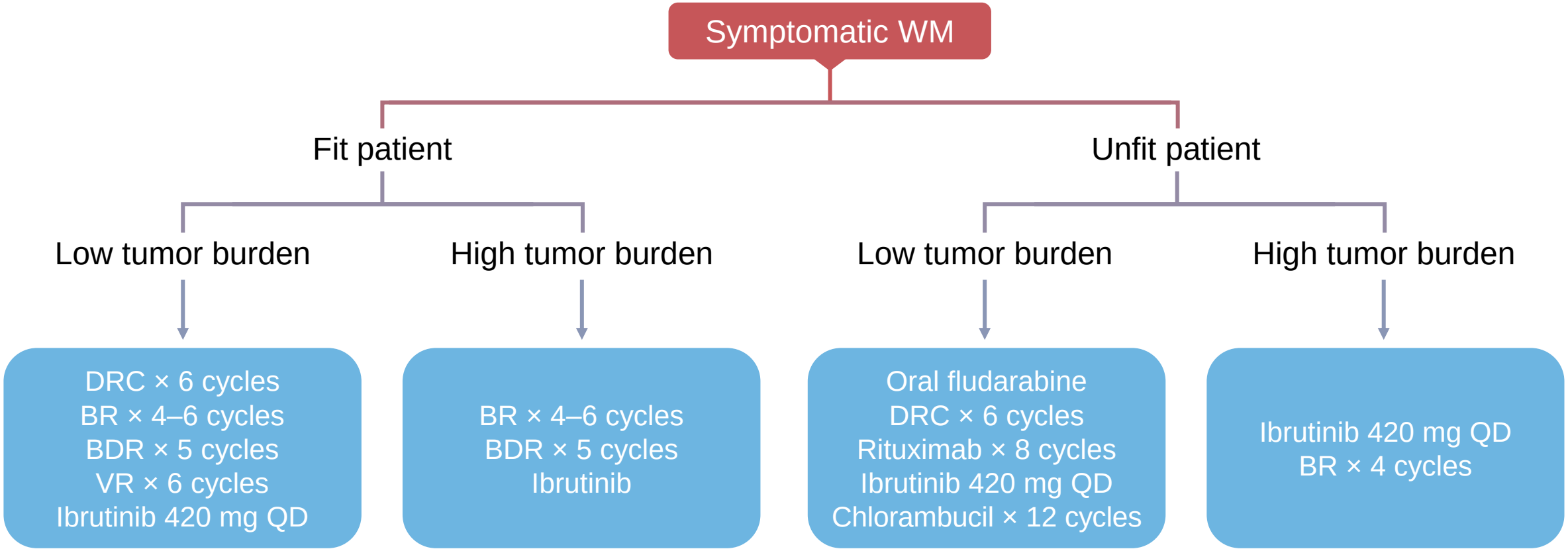
CT, computed tomography; IgM, immunoglobulin M; MRI, magnetic resonance imaging; WM, Waldenström's macroglobulinemia.
Kastritis E *et al*. *Ann Oncol* 2018; 29 (Suppl 4): iv41–iv50.

Response assessment in WM:
Update from the 6th International Workshop on WM[1]

Response category	IgM	Extramedullary disease (i.e. lymphadenopathy/ splenomegaly)	New signs and symptoms of active disease	Other
Complete response (CR)	Absence of serum monoclonal IgM protein by immunofixation and normal serum IgM level	Complete resolution	None	Morphologically normal bone marrow aspirate and trephine biopsy
Very good partial response (VGPR)†	Monoclonal IgM is detectable ≥90% baseline reduction in serum IgM*	Complete resolution	None	–
Partial response (PR)	Monoclonal IgM is detectable ≥50% but <90% baseline reduction in serum IgM*	Reduction	None	–
Minor response (MR)	Monoclonal IgM is detectable ≥25% but <50% baseline reduction in serum IgM*	–	None	–
Stable disease (SD)	Monoclonal IgM is detectable <25% reduction and <25% increase in baseline serum IgM*	No progression	None	–
Progressive disease (PD)‡	≥25% increase in serum IgM* level from lowest nadir (requires confirmation)	Progression of disease-related clinical features		–

*Sequential changes in IgM levels may be determined either by M protein quantitation by densitometry or total serum IgM quantitation by nephelometry †VGPR was added at the 6th International Workshop on WM.
‡Either condition sufficient for PD. IgM, immunoglobulin M; WM, Waldenström's macroglobulinemia.
1. Owen RG *et al*. *Br J Haematol* 2013; 160 (2): 171–176.

ESMO guidelines: Treatment of newly diagnosed WM



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

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

How I define ‘fit’ and ‘unfit’ patients with WM

- Age alone is not a criterion of fitness

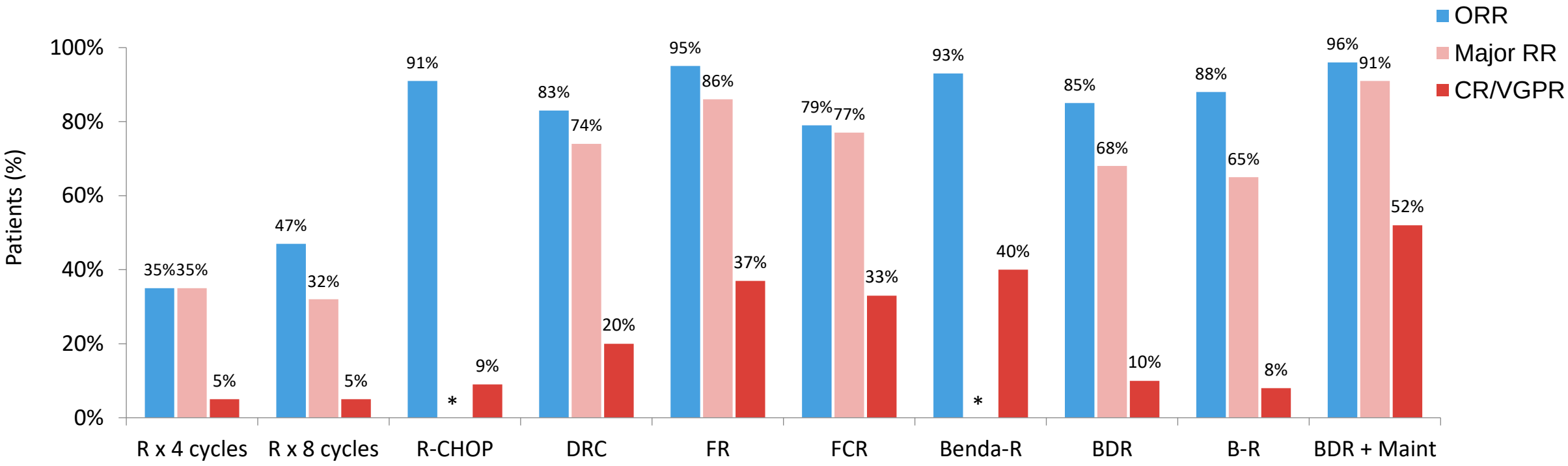
- Presence of comorbidities (CIRS score?)
  - Cardiac comorbidities are a key criterion when using potentially cardiotoxic therapies
  - History of recent and prior infections
  - Access to medical care and ability to control and adhere to oral medication

- WM-related complications: How do they affect overall ‘fitness’?
  - Cytopenias
  - Neuropathy
  - Amyloidosis

CIRS, Cumulative Illness Rating Scale; WM, Waldenström’s macroglobulinemia..

mAb-based therapy in WM:
Efficacy of commonly used rituximab-based regimens

- Rituximab-based treatment is the most commonly used in Europe across all lines of therapy[1]

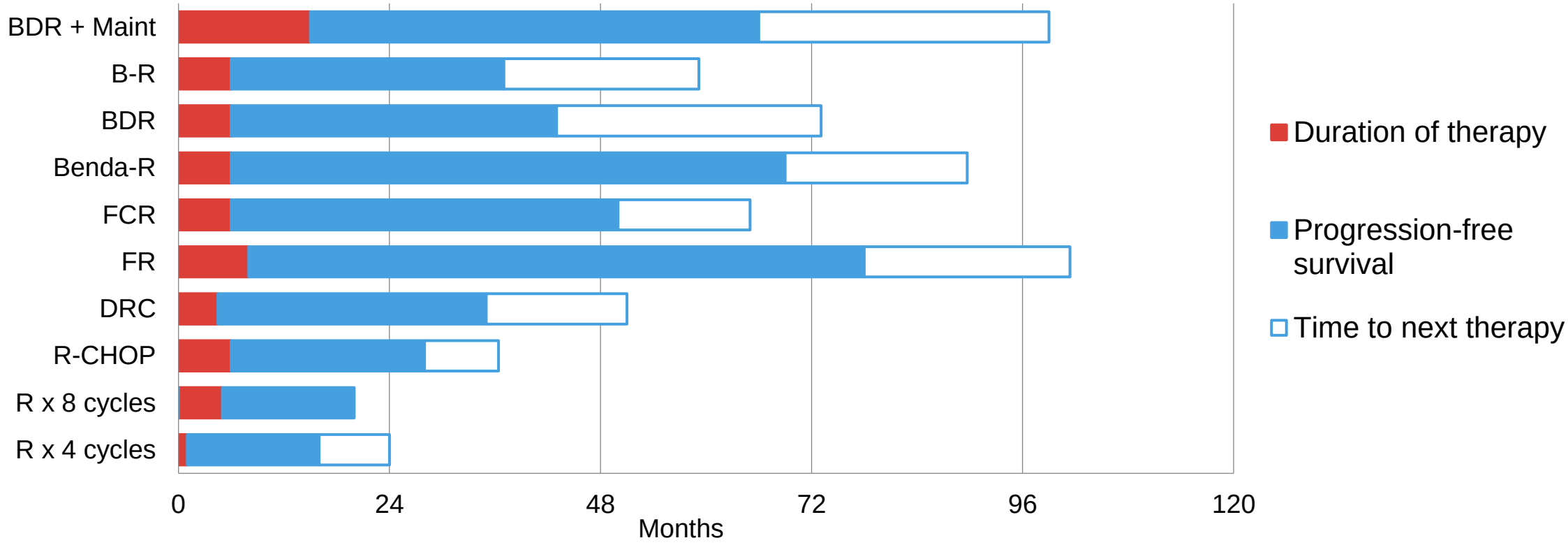


*Not reported; B, bortezomib; Benda, bendamustine; C, cyclophosphamide; CR, complete response; D, dexamethasone; F, fludarabine; H, doxorubicin; mAb, monoclonal antibody; Maint, maintenance therapy; O, vincristine; ORR, overall response rate; P, prednisone; R, rituximab; RR, response rate; VGPR, very good partial response; WM, Waldenström's macroglobulinemia.

1. Buske C et al. Lancet Haematol. 2018;5(7):e299-e309; 2. Treon SP, et al. Blood. 2015;126(23) Abstract #1833; 3. Ghobrial IM, et al Am J Hematol 2010;85:670-4; 4. Dimopoulos MA, et al Blood 2013;122:3276-82; 5. Gavriatopoulou M, et al Blood 2017;129:456-9; 6. Rummel MJ, et al Lancet 2013;381:1203-10; 7. Tedeschi A, et al Cancer 2012;118:434-43; 8. Treon SP, et al Blood 2009;113:3673-8; 9.Dimopoulos MA, et al J Clin Oncol 2007;25:3344-9; 10. Kastritis E, et al Blood 2015;126:1392-4; 11. Buske C, et al Leukemia. 2009;23(1):153-61; 12. Dimopoulos MA, et al. New Engl J Med 2018;378:2399-410; 13. Dimopoulos MA, et al Clin Lymphoma. 2002 Dec;3(3):163-6.

Efficacy of commonly used rituximab-based regimens for WM

Duration of therapy, PFS and time to next therapy



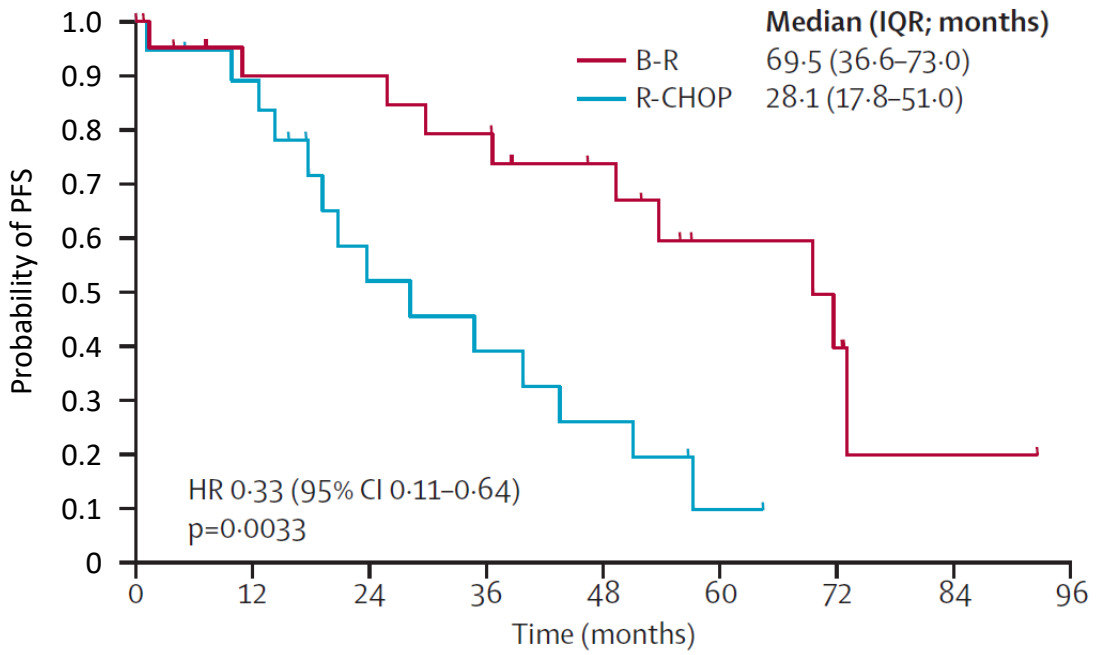
B, bortezomib; Benda, bendamustine; C, cyclophosphamide; CR, complete response; D, dexamethasone; F, fludarabine; H, doxorubicin; Maint, maintenance therapy; O, vincristine; ORR, overall response rate; P, prednisone; R, rituximab; VGPR, very good partial response; TFI, treatment-free interval; WM, Waldenström's macroglobulinemia.

1. Treon SP, et al. Blood. 2015;126(23) Abstract #1833; 2. Ghobrial IM, et al Am J Hematol 2010;85:670-4; 3. Dimopoulos MA, et al Blood 2013;122:3276-82; 4. Gavriatopoulou M, et al Blood 2017;129:456-9; 5. Rummel MJ, et al Lancet 2013;381:1203-10; 6. Tedeschi A, et al Cancer 2012;118:434-43; 7. Treon SP, et al Blood 2009;113:3673-8; 8.Dimopoulos MA, et al J Clin Oncol 2007;25:3344-9; 9. Kastritis E, et al Blood 2015;126:1392-4; 10. Buske C, et al Leukemia. 2009;23(1):153-61; 11. Dimopoulos MA, et al J Clin Oncol 2002;20:2327-33; 12. Dimopoulos MA, et al. New Engl J Med 2018;378:2399-410; 13. Dimopoulos MA, et al Clin Lymphoma. 2002 Dec;3(3):163-6.

Immunochemotherapy

Benda-R versus R-CHOP

PFS in patients with TN WM (N=41)



% adverse events in the total population (N=514)

	Benda-R (n=261)	R-CHOP (n=253)	*P* value
Hematologic adverse events (grade 3–4)			
Leukocytopenia	37%	72%	<0.0001
Neutropenia	29%	69%	<0.0001
Lymphocytopenia	74%	43%	–
Anemia	3%	5%	–
Thrombocytopenia	5%	6%	–
Non-hematologic adverse events (any grade)			
Alopecia	0	100%*	<0.0001
Paresthesia	7%	29%	<0.0001
Stomatitis	6%	19%	<0.0001
Skin (erythema)	16%	9%	0.024
Skin (allergic reaction)	15%	6%	0.0006
Infectious episodes	37%	50%	0.0025
Sepsis	<1%	3%	0.019

*Includes only 245 patients who received three or more cycles.

Benda-R, bendamustine plus rituximab; HR, hazard ratio; IQR, interquartile range; PFS, progression-free survival; R-CHOP, rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone; TN, treatment naive; WM, Waldenström's macroglobulinemia.

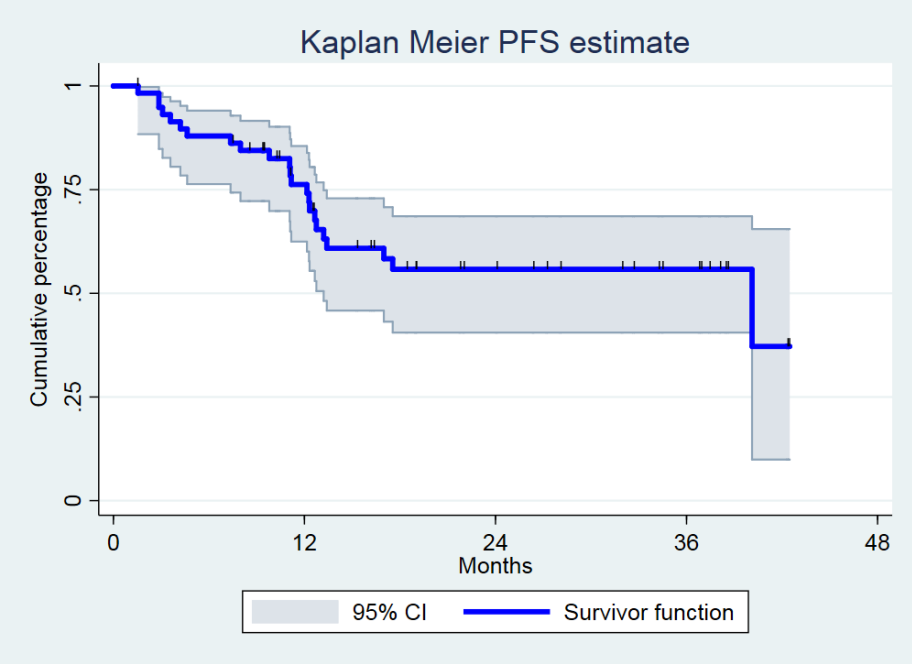
Rummel MJ, et al. Lancet. 2013;381:1203–10.

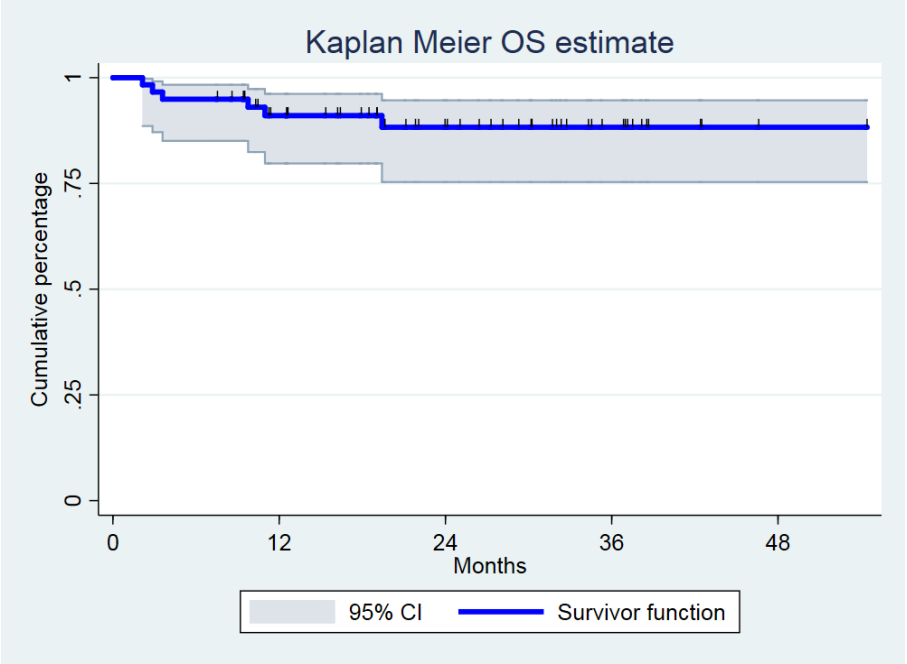
Oral proteasome inhibitor plus anti-CD20 mAb

Ixazomib, rituximab and dexamethasone in R/R WM: median follow-up 24 months

At 24 months:

- PFS = 56%
- DoR = 60%
- OS = 88%



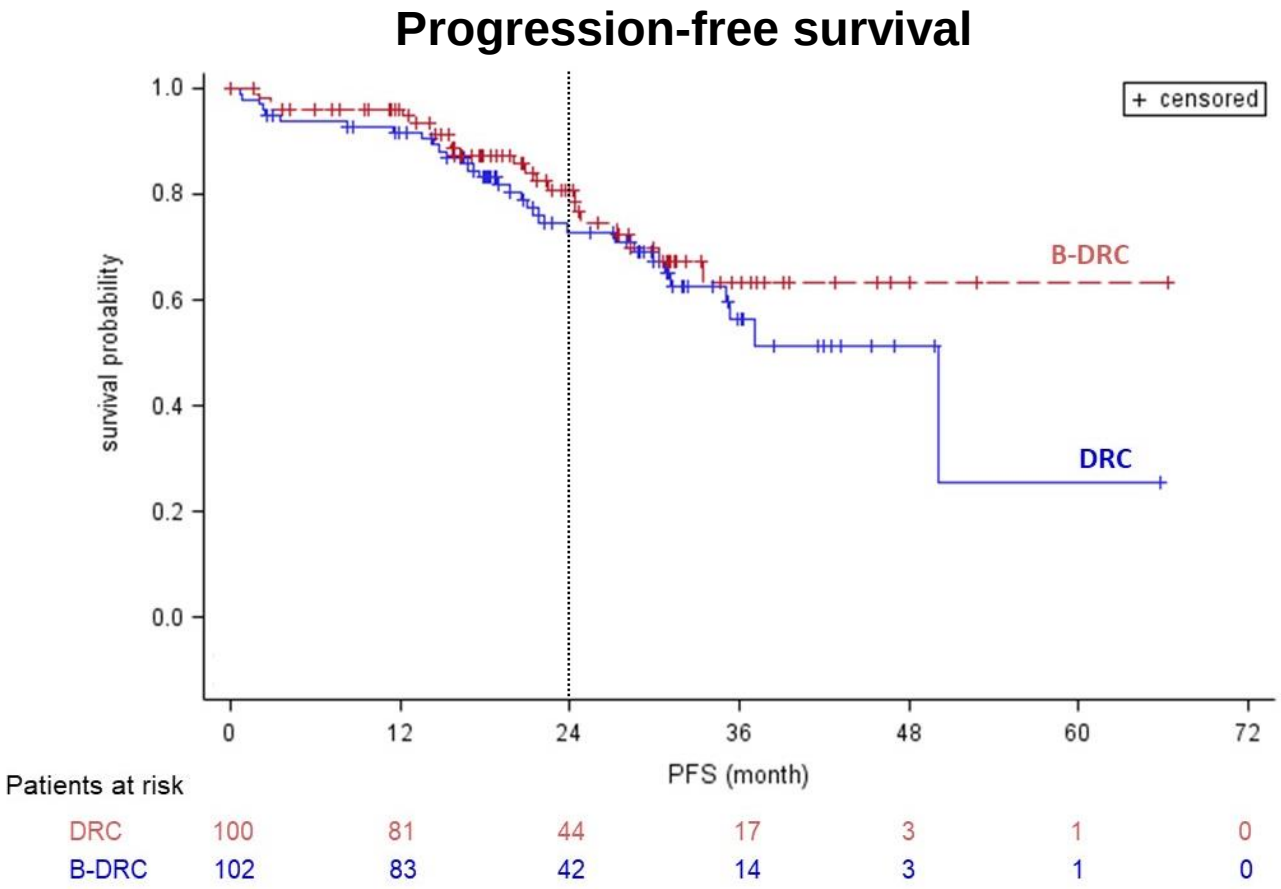


DoR, duration of response; OS, overall survival; PFS, progression-free survival; R/R, relapsed/refractory; WM, Waldenström's macroglobulinemia.

Kersten MJ, et al. Blood 2019; 134(Supplement_1):344. Presented at the American Society of Hematology (ASH) annual meeting; December 7–10, 2019.

Adding bortezomib to immunochemotherapy

ECWM-1 study: B-DRC vs DRC in TN WM

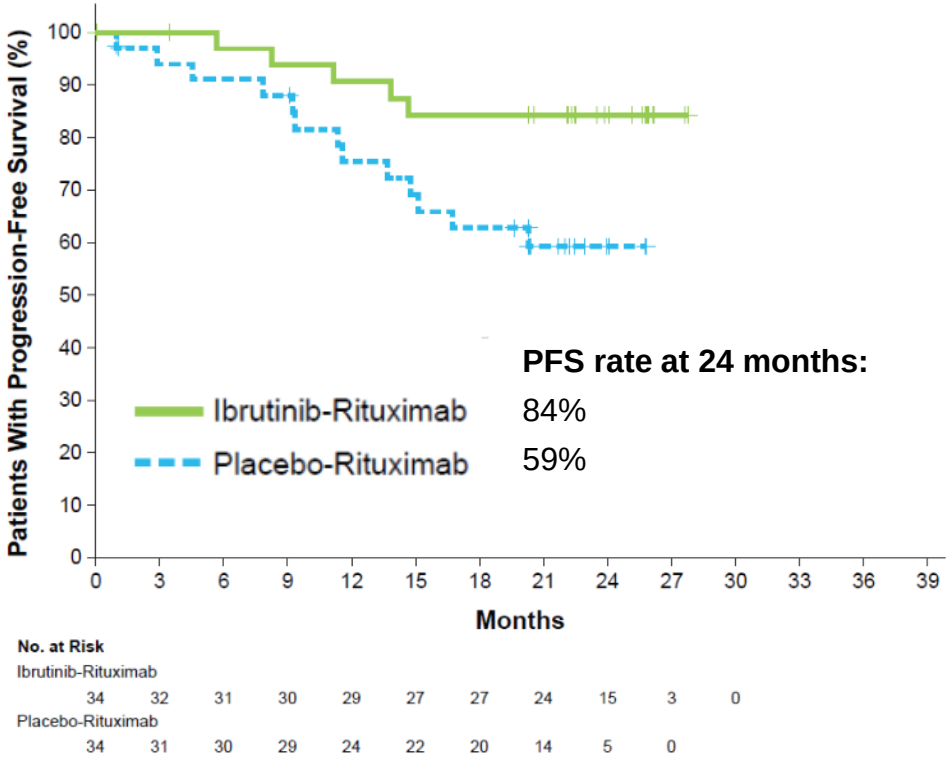


B, bortezomib; DRC, dexamethasone, rituximab and cyclophosphamide; ECWM, European consortium for WM; TN, treatment-naive; WM, Waldenström's macroglobulinemia.
Buske C *et al*. *Blood* 2020; 136(Supplement 1): 26. Presented at the American Society of Hematology (ASH) annual meeting; December 5–8, 2020

BTK inhibitors

Ibrutinib with or without rituximab

PFS with ibrutinib plus rituximab in TN WM (N=68)[1]

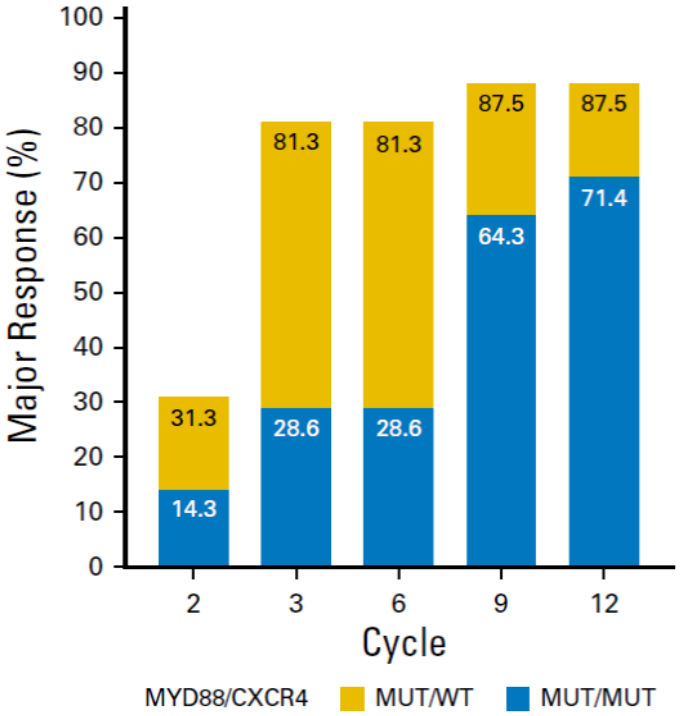


PFS rate at 24 months:

84%

59%

MR rate with ibrutinib monotherapy in TN WM (N=30)[2]



PFS at 18 months:

92%

(95% CI, 73–98)

MR, major response (complete, very good partial or partial response); MUT, mutant; PFS, progression-free survival; TN, treatment naive; WM, Waldenström's macroglobulinemia; WT, wild type.

1. Dimopoulos MA, et al. N Engl J Med 2018;378:2399–410; 2. Treon SP, et al. JCO 2018;36:2755–2761.

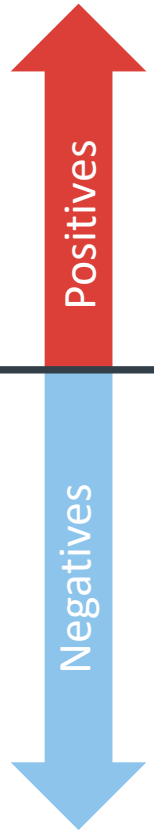
Treatment options: “old” and “new” standards

Immunochemotherapy

- Fixed duration of therapy
- Treatment-free interval
- Extensive experience
- Low cost
- Toxicity (+/-)

BTK inhibitor-based therapy

- Oral therapy
- Efficacy
- Toxicity (+/-)
- Rapid activity
- Penetrates CNS



- Toxicity: short / long term (+/-)
- Low CR rates
- Slower response with some combinations
- Parenteral therapy (IV/SC)

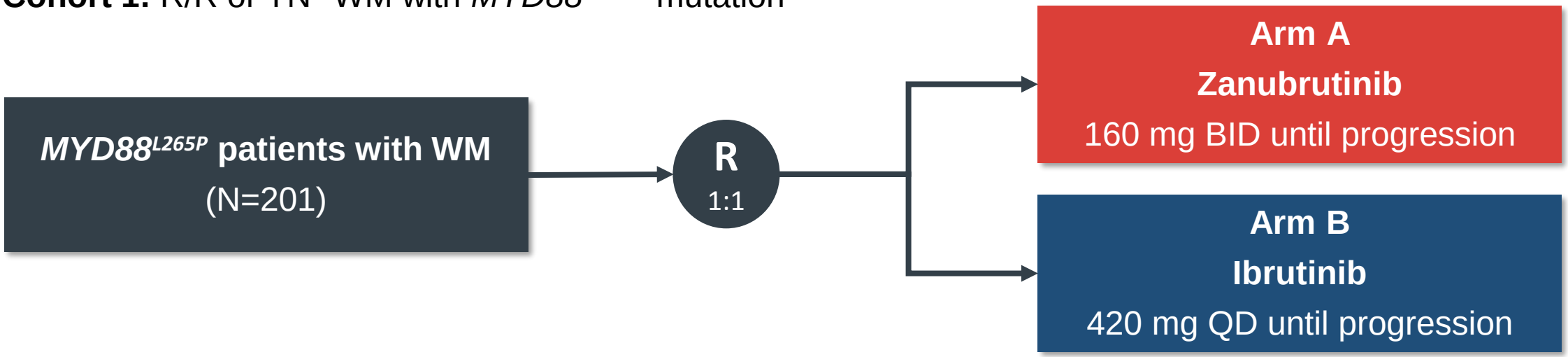
- Continuous therapy
- No CRs (or low rate)
- Some toxicities (AF, HTN, interactions)
- High cost
- Long-term experience (?)
- Affected by genotype (?)
- Risk of infections (?)

AF, atrial fibrillation; BTK, Bruton’s tyrosine kinase; CNS, central nervous system; CR, complete response; HTN, hypertension; IV, intravenous; SC, subcutaneous.

BTK inhibitors

ASPEN trial: zanubrutinib versus ibrutinib

Cohort 1: R/R or TN* WM with *MYD88*^{L265P} mutation



Cohort 2: R/R or TN* WM with *MYD88*^{WT}

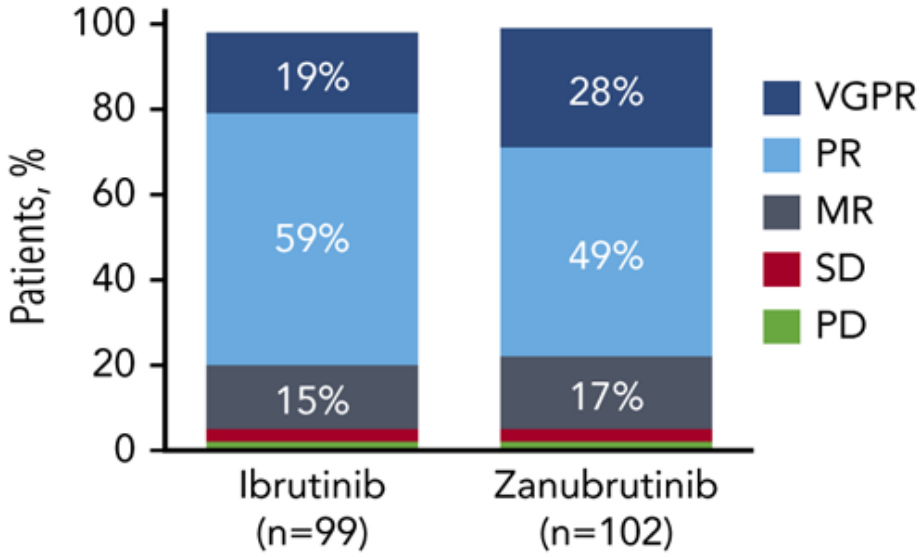
*Unsuitable for standard immunochemotherapy because of comorbidities and/or other risk factors

BID, twice daily; *MYD88*, myeloid differentiation primary response 88 gene; QD, once daily; R, randomized; R/R, relapsed/refractory; TN, treatment naïve; WM, Waldenström's macroglobulinemia; WT, wild type.

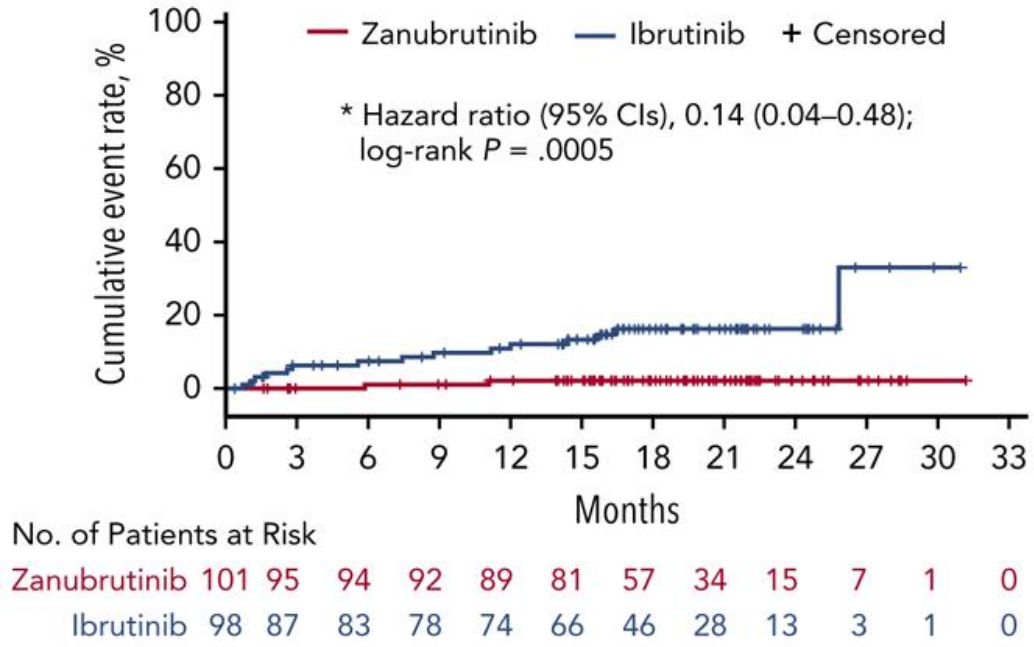
Tam CS, et al. Blood 2020;136 (18):2038–2050; Dimopoulos MA, et al. HemaSphere 2020;4(Supplement 1):550 Abstract EP1180.

BTK inhibitors
ASPEN trial Cohort 1

Best overall response* in R/R or TN† WM



Time-to-event analysis of atrial fibrillation/flutter



*Determined by an Independent Review Committee;†Unsuitable for standard immunochemotherapy due to comorbidities and/or other risk factors
CI, confidence interval; MR, minimal response; PD, progressive disease; PR, partial response; R/R, relapsed/refractory; SD, stable disease; TN, treatment naïve; VGPR, very good partial response; WM, Waldenström's macroglobulinemia.
Tam CS, et al. Blood 2020;136 (18):2038–2050.

BTK inhibitors

ASPEN trial Cohort 1

	Ibrutinib (n=98)		Zanubrutinib (n=101)	
	All grade	Grade ≥3	All grade	Grade ≥3
Non-hematologic AEs (%)*				
Diarrhea	32	1	21	3
Upper respiratory tract infection	29	1	24	0
Contusion	24	0	13	0
Muscle spasms	24	1	10	0
Epistaxis	19	0	13	0
Peripheral edema	19	0	9	0
Cough	17	0	13	0
Rash	16	0	13	0
Hypertension	16	11	11	6
Arthralgia	16	0	13	3
Fatigue	15	1	19	1
Constipation	7	0	16	0

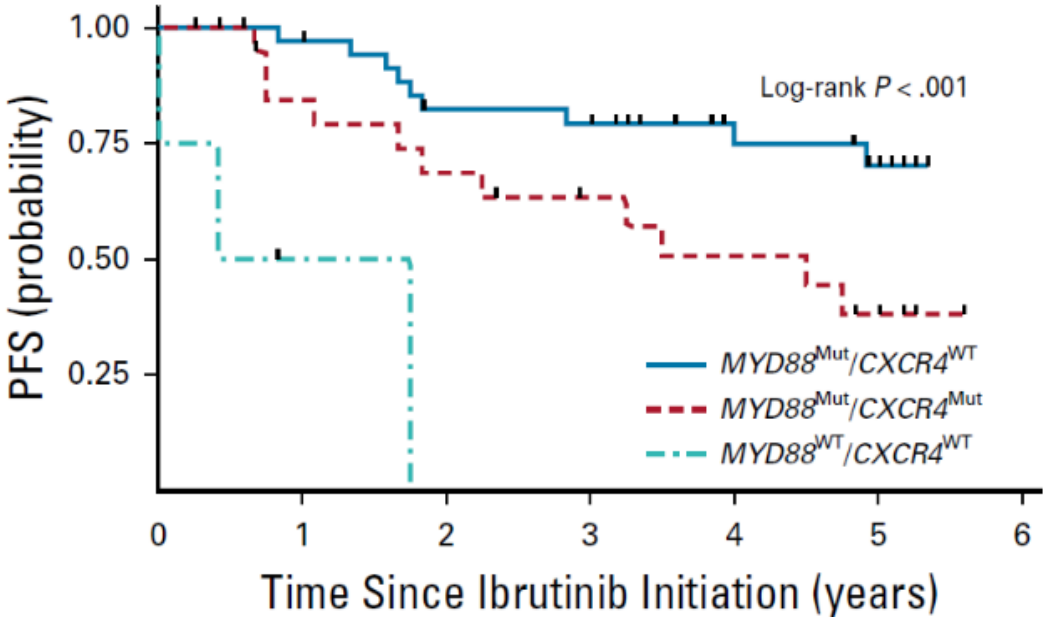
	Ibrutinib (n=98)		Zanubrutinib (n=101)	
	All grade	Grade ≥3	All grade	Grade ≥3
Hematologic AEs (%)				
Neutropenia	13	8†	29	20†
Febrile neutropenia	0	0	4	4
Thrombocytopenia	10	3	10	6
Anemia	10	5	12	5
AEs of interest, events/100 person-months				
Infections Opportunistic infections	8.3 0.1	1.2 0	7.9 0.1	1.1 0.1
Bleeding Major hemorrhage	7.0 0.6	0.5 0.5	4.4 0.3	0.3 0.3
Hypertension	1.2	0.8	0.7	0.3
Atrial fibrillation/flutter	1.0	0.2	0.1	0
Neutropenia	0.9	0.5	2.1	1.3
Thrombocytopenia	0.8	0.2	0.6	0.3
Second primary malignancy Skin cancers	0.7 0.6	0.1 0	0.7 0.5	0.1 0
Anemia	0.6	0.3	0.7	0.3
Tumor lysis syndrome	0	0	0	0

*Occurring in >15% of patients in either group; †Includes the MedDRA–preferred term “neutrophil count decreased” in 1 and 4 patients in the ibrutinib and zanubrutinib arms, respectively. AE, adverse events.

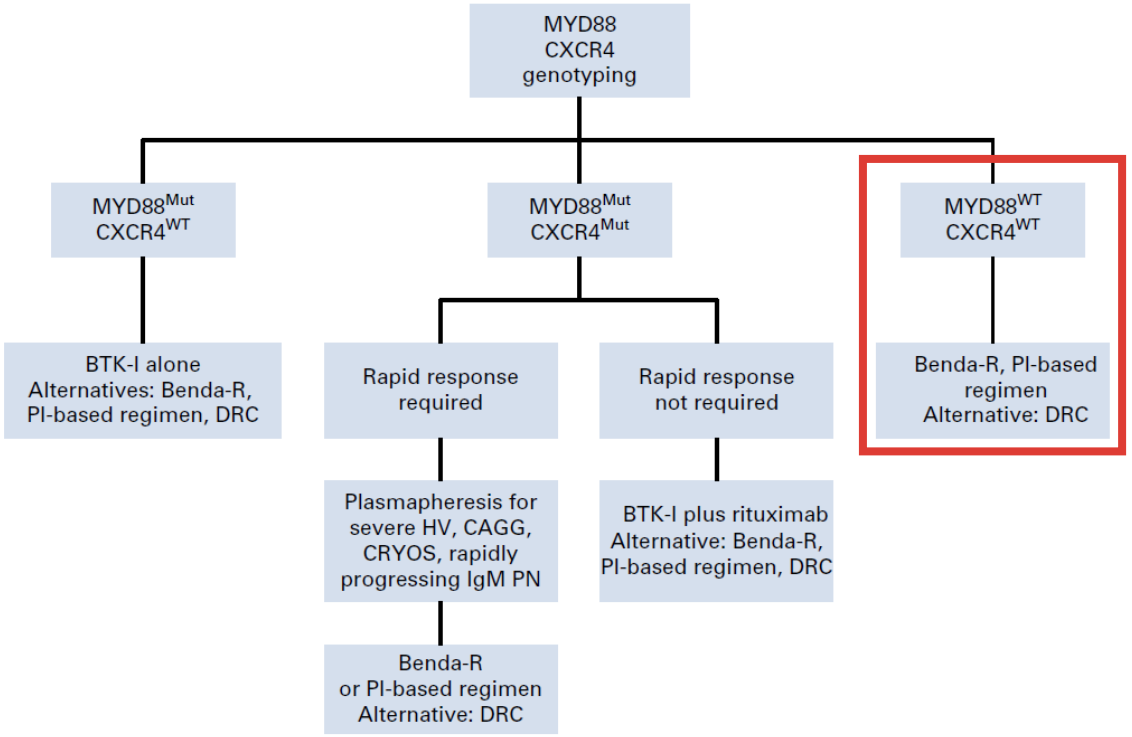
Tam CS, et al. Blood 2020;136 (18):2038–2050.

Impact of genotype on ibrutinib outcomes

PFS with ibrutinib monotherapy in R/R WM[1]



Genomic-based treatment algorithm for TN WM[2]

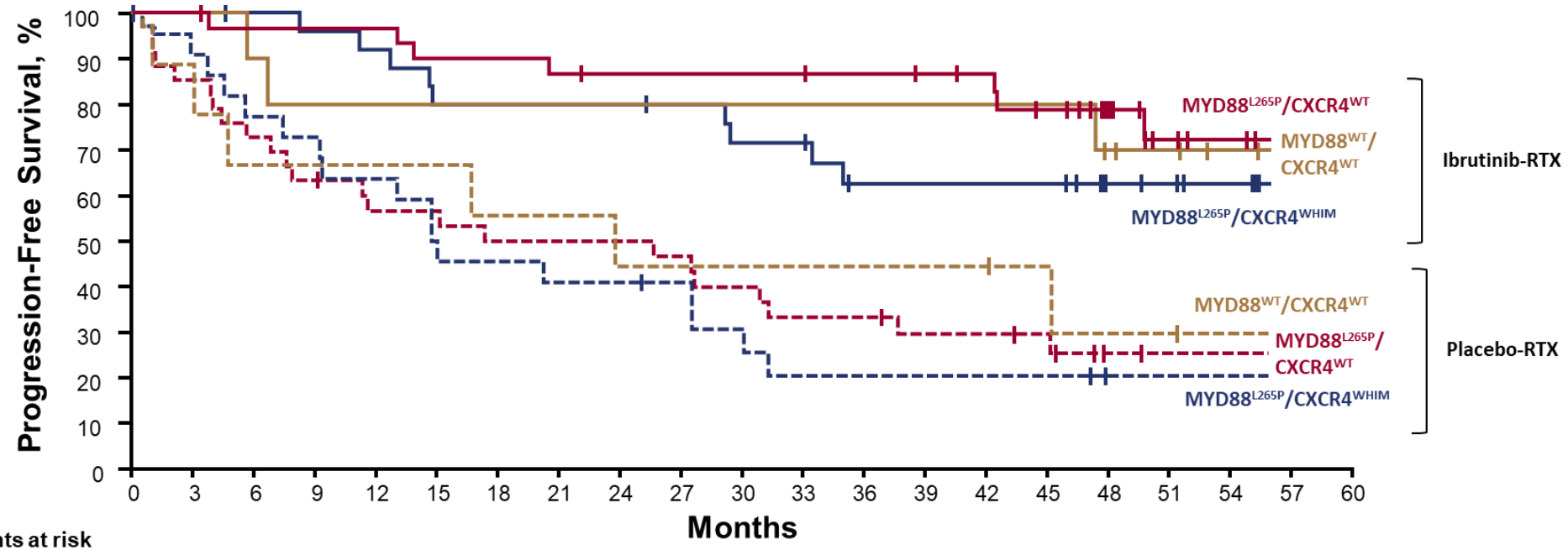


Benda-R, bendamustine and rituximab; BTK-I, Bruton tyrosine kinase inhibitor; CAGG, cold agglutinemia; CRYOS, cryoglobulinemia; DRC, dexamethasone, rituximab, and cyclophosphamide; HV, hyperviscosity; IgM, immunoglobulin M, Mut, mutation; PI, proteasome inhibitor; PN, peripheral neuropathy; R/R, relapsed/refractory; TN,treatment naïve; WT, wild-type.

1. Treon SP *et al*. *J Clin Oncol* 2020; 15;JCO2000555; 2. Treon SP *et al*. *J Clin Oncol* 2020; 38 (11): 1198–1208.

Ibrutinib/rituximab vs placebo/rituximab

Progression-free survival according to genotype



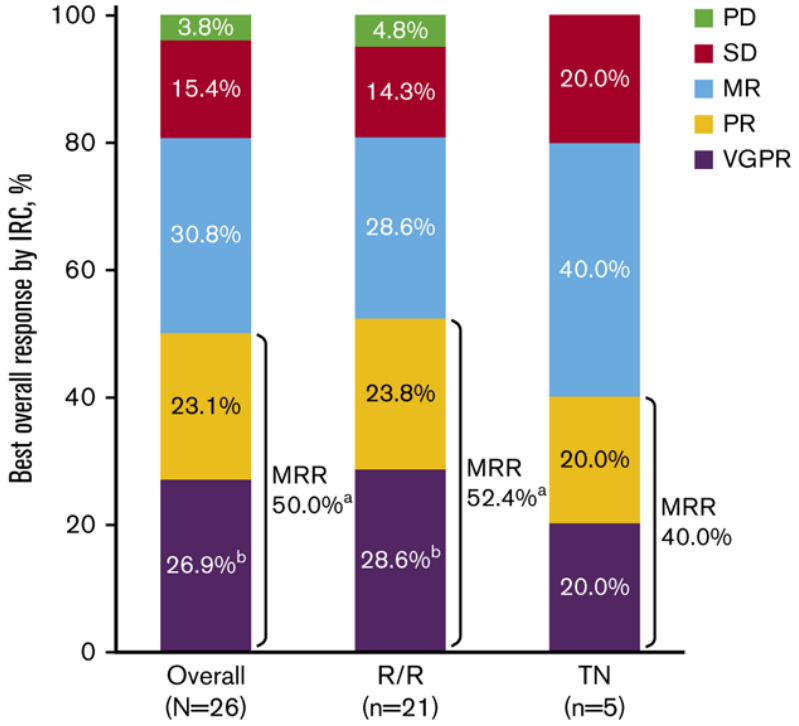
Patients at risk																			
Ibrutinib-RTX MYD88^{L265P}/CXCR4^{WHIM}	26	26	25	24	23	20	20	20	20	19	17	17	13	13	13	13	8	7	5
Ibrutinib-RTX MYD88^{L265P}/CXCR4^{WT}	32	31	29	29	29	27	27	26	25	25	25	25	24	23	22	19	15	8	5
Ibrutinib-RTX MYD88^{WT}/CXCR4^{WT}	11	10	9	8	8	8	8	8	8	8	8	8	8	8	8	8	6	5	3
Placebo-RTX MYD88^{L265P}/CXCR4^{WHIM}	23	20	17	16	14	11	10	9	9	8	6	4	4	4	4	4	2	1	1
Placebo-RTX MYD88^{L265P}/CXCR4^{WT}	35	28	23	20	17	17	15	15	15	14	12	10	10	8	8	7	3	1	1
Placebo-RTX MYD88^{WT}/CXCR4^{WT}	9	8	6	6	6	6	5	5	4	4	4	4	4	4	4	3	2	2	1

Kaplan–Meier curves for subgroups are shown for timepoints with ≥10 patients at risk.
RTX, rituximab; WHIM, warts, hypogammaglobulinemia, immunodeficiency, and myelokathexis; WT, wild type.
Buske C, et al. Blood 2020; 136(Supplement 1):24–26.

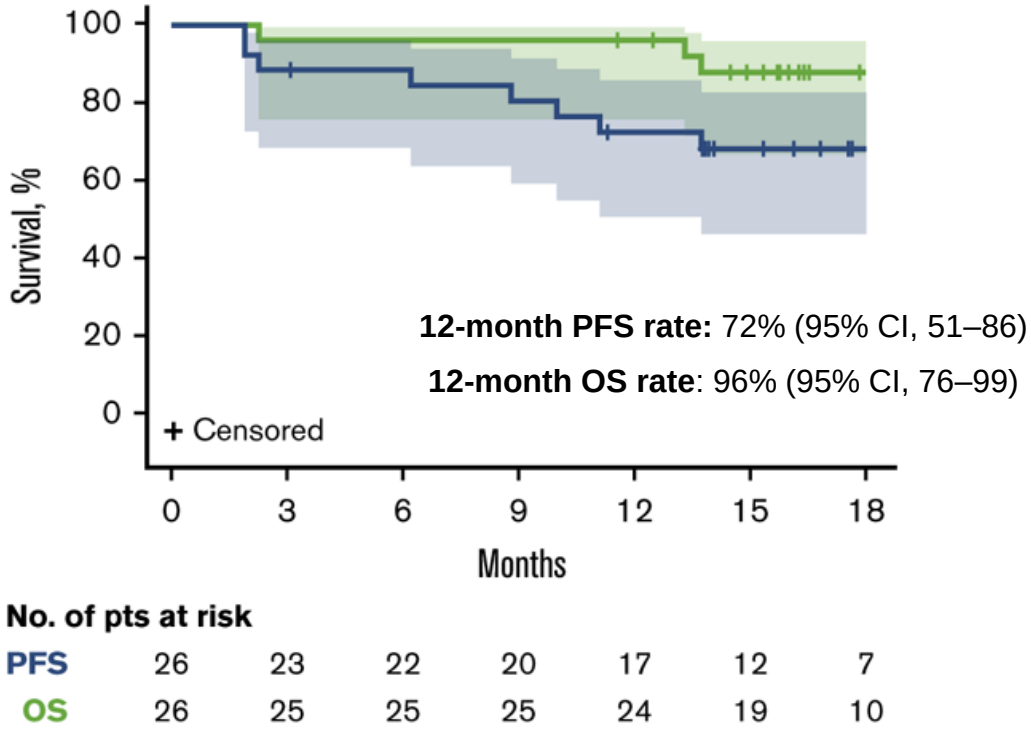
Zanubrutinib in *MYD88*^{WT} WM

ASPEN trial Cohort 2

Best overall response* in R/R or TN† WM



Survival in R/R or TN† WM



12-month PFS rate: 72% (95% CI, 51–86)

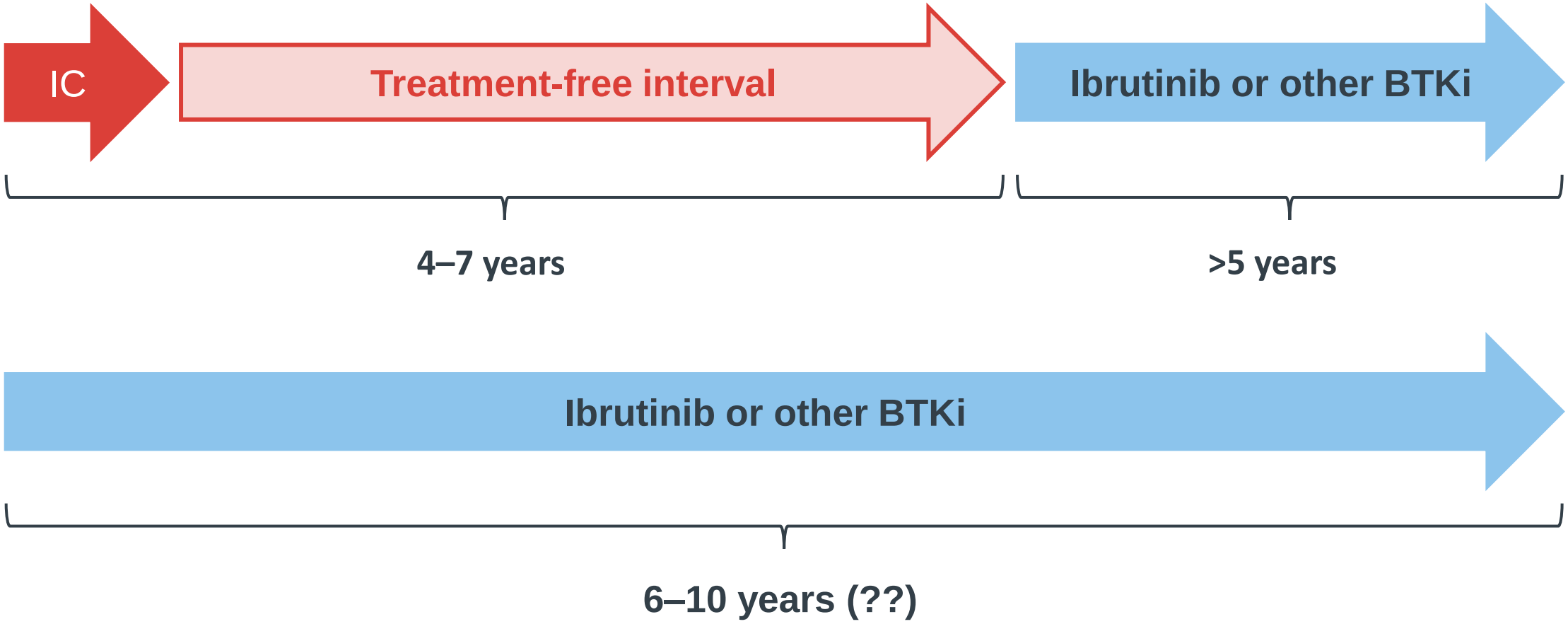
12-month OS rate: 96% (95% CI, 76–99)

*Determined by an Independent Review Committee;†Unsuitable for standard immunochemotherapy.

CI, confidence interval; IRC, independent review committee; MR, minimal response; MRR, major response rate; MYD88, myeloid differentiation primary response 88 gene; OS, overall survival; PD, progressive disease; PFS, progression-free survival; PR, partial response; pts, patients; R/R, relapsed/refractory; SD, stable disease; TN, treatment-naive; VGPR, very good partial response; WM, Waldenström's macroglobulinemia; WT, wild-type.

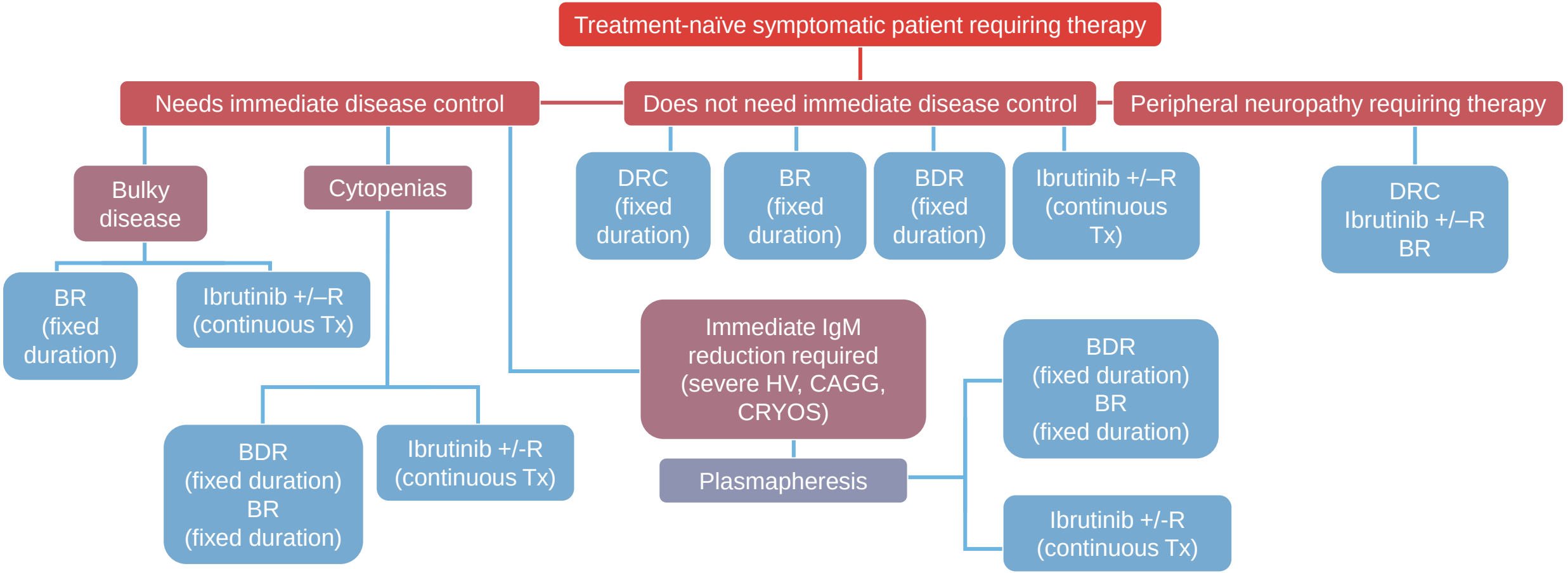
Dimopoulos MA, et al. HemaSphere 2020;4(Supplement 1):550 Abstract EP1180. Presented at the European Hematology Association (EHA) annual meeting; June 11–22, 2020.

How to start therapy:
Immunochemotherapy or BTK inhibitor



BTKi, Bruton's tyrosine kinase inhibitor; IC, immunochemotherapy.

How I start treatment for WM



BDR, Bortezomib-Dexamethasone-Rituximab; BR, Bendamustine-Rituximab, BTK-I, Bruton tyrosine kinase inhibitor; CAGG, cold agglutinemia; CRYOS, cryoglobulinemia; *CXCR4*, C-X-C chemokine receptor type 4 gene; DRC, Dexamethasone-Rituximab-Cyclophosphamide; HV, hyperviscosity; IgM, immunoglobulin M, Mut, mutation; *MYD88*, myeloid differentiation primary response 88 gene; PI, proteasome inhibitor; PN, peripheral neuropathy; R, Rituximab; Tx, treatment; WM, Waldenström's macroglobulinemia; WT, wild-type.

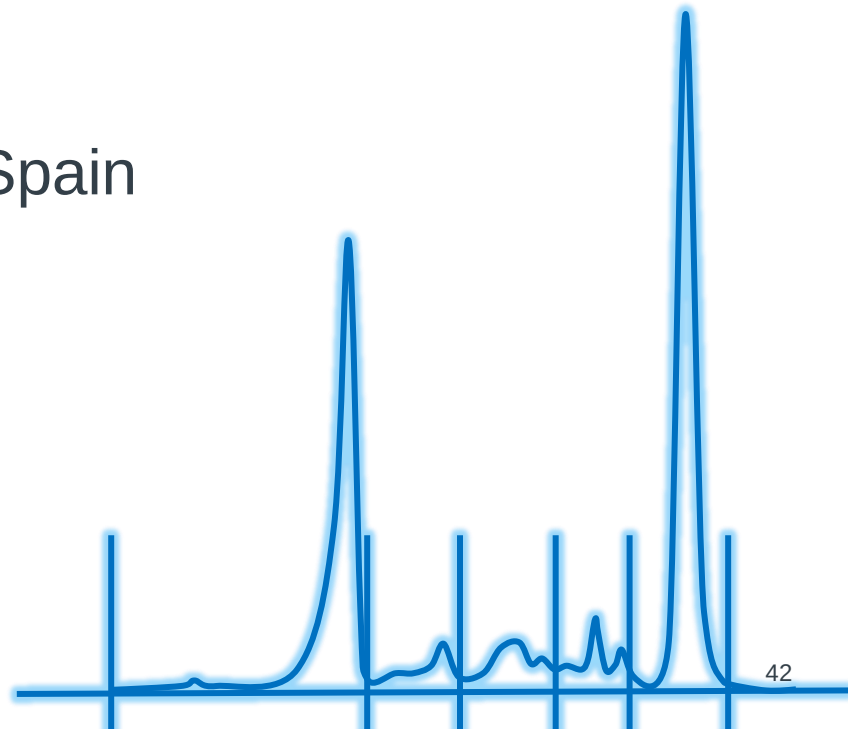
Dimopoulos MA & Kastritis E. Blood 2019; 134(23): 2022–2035.

First-line treatments for WM disease: challenges

- Development of active, low-toxicity combinations providing high probability of complete response and in a fixed duration of therapy
  - Need to optimize available options, especially targeted therapies
- Treatment options for patients who relapse on ibrutinib and/or discontinue due to toxicity
- Treatment options for patients wild-type for *MYD88* and *CXCR4*
- Access to new therapies
  - Physicians are often reliant on clinical trials to access better treatments for their patients

Challenges from the clinic: Initiation of treatment in WM

Dr. Ramón García-Sanz
University Hospital of Salamanca, Spain



Disclosures

- Honoraria
  - Amgen, Astellas, Beigene, BMS, Janssen, Takeda

- Speakers bureau/scientific advisory board
  - Takeda

Patient 1: Initial presentation (1)

Patient characteristics

- Male, 41 years
- No prior pathology
- Progressive asthenia, several months, certain sensitivity to low temperature, no B symptoms, no lymphadenopathy, no organomegaly
- Many failed biological studies
- High ESR, hyperproteinemia not very high

Review of systems

- Fatigue: no anemia
- Occasional headache
- No somnolence, no visual alterations
- No fever, weight loss or night sweats
- No bleeding
- No Raynaud's disease, no acrocyanosis

Laboratory studies

- Hemoglobin 12.9 g/dL
- Platelets 320 x 10^9/L
- WBC: 5.8 x 10^9/L
  - ANC: 3.01, ALC: 1.21, AMC: 0.8 x 10^9/L
- Serum creatinine 0.81 mg/dL
- LDH 207 U/L (max 260)
- β_2-microglobulin 2.32 µg/mL (max 2.6)
- Albumin: 4.1 g/L
- Serum monoclonal IgM 3.1 g/dL
- sFLC (mg/dL), κ/λ: **400/**23.

ALC, absolute lymphocyte count; AMC, absolute monocyte count; ANC, absolute neutrophil count; ESR, erythrocyte sedimentation rate; LDH, lactate dehydrogenase; sFLC, serum free light chains; WBC, white blood cells.

Patient 1: Initial presentation (2)

Laboratory studies

- Serum Fe: 59.3 mg/dl
- Ferritin: 86 ng/ml
- Transferrin: 429 mg/dl (Sat: 11%)

Bone marrow examinations

- Bone marrow biopsy: paratrabecular interstitial infiltration by lymphocytes, lymphoplasmocytes and plasma cells (33%); abundant mastocytes
- Flow cytometry:
  - Bone marrow: **48%** monoclonal lymphoid B cells with phenotype: $CD19^{+}$, $CD5^{-}$, $CD20^{++}$, $FMC7^{\pm}$, $CD22^{w+}$, $sIgk^{+}$, $CD25^{+}$, $CD10^{-}$, $CD103^{-}$
    0.98% kappa plasma cells, with no aberrancies
  - Peripheral blood: 0.015% monoclonal B cells
- BM FISH studies: 6q21, normal *TP53* & *IgH*
- BM Molecular studies:
  - $MYD88^{L265P}$: positive (Ct: 30.3^{MUT}; vs 28.1^{WT})
  - *CXCR4* (CD19+ cells & Sanger): normal

Total body CT scan

- No organomegaly
- Several lymph nodes between 1 & 2 cm

Funduscopy

- Normal

Cryoagglutinins

- Positive

Cryoglobulins

- Negative

BM, bone marrow; CT, computerized tomography; CXCR4, C-X-C chemokine receptor type 4; Ct, 1st cycle threshold; MUT: mutant; WT: wild type; Fe, iron; FISH, fluorescence in situ hybridization; IgH, immunoglobulin heavy-chain; MYD88, myeloid differentiation primary response 88; TP53, tumor protein P53; WM, Waldenström's macroglobulinemia.

Review of systems in patients with WM[1]

Symptom/complaint	Implications	Action
Fatigue, lack of energy	Anemia	Evaluate for anemia, including iron, folate or cobalamin deficiency, haemolytic anaemia (warm and cold antibodies), etc. Patients with iron deficiency may benefit from parenteral iron.
Constitutional symptoms	Disease progression	Obtain serum IgM levels and SPEP. Evaluate other causes of fever, night sweats and unintentional weight loss.
Recurrent sinus and bronchial infections	Hypogammaglobulinemia	Antibiotic support. If patient refractory to antibiotics, required hospitalization, or infections were life threatening, consider IVIG replacement.
Headaches, blurry vision or visual loss, confusion, epistaxis	Hyperviscosity	Funduscopic examination, obtain serum IgM and serum viscosity levels. Consider emergent plasmapheresis for symptomatic hyperviscosity.
Easy bruising, bleeding diathesis	Thrombocytopenia; acquired VWD; acquired coagulation factor deficiency	Complete blood count, evaluate for immune thrombocytopenia or hypersplenism if indicated; consider evaluation for VWD; consider amyloidosis. Evaluate other bleeding diathesis with INR, PTT and coagulation factor levels, as clinically indicated.
Progressive symmetrical numbness, tingling, burning, pain feet and hands	IgM-related neuropathy; amyloidosis	Obtain EMG studies and neurology consultation. Obtain anti-MAG, and if negative anti-GM1 and anti-sulfatide IgM antibody studies. Consider fat pad biopsy and Congo red stain for amyloidosis. Evaluate other causes of neuropathy: diabetes, thyroid dysfunction, HIV infection, cobalamin deficiency, etc.
Raynaud-like symptoms, acrocyanosis, ulcers on extremities	Cryoglobulinemia; cold agglutinemia	Obtain cryoglobulins and cold agglutinins. In patients suspected of having cryoglobulins, IgM should be obtained in a warm bath to avoid cryoprecipitation. Consider emergent plasmapheresis
Diarrhoea, gastrointestinal cramping	Malabsorption	Endoscopy to evaluate small bowel, biopsy to evaluate for amyloidosis, IgM deposition, tumour involvement. Evaluate other causes of diarrhoea.
Foamy urine, bipedal oedema	Kidney dysfunction	Obtain serum free light chains, 24-h urine protein, and consider kidney biopsy. Evaluate other causes of kidney dysfunction.
Urticaria, papules, dermatitis	Schnitzler syndrome, IgM/tumor cell infiltration, amyloid deposits	Skin biopsy, histological examination for tumour cell infiltration, stain for IgM, Congo-red staining for amyloid. Evaluate other causes of rash.

Anti-MAG, anti-myelin-associated globulin; EMG, electromyography; HIV, human immunodeficiency virus; IgM, immunoglobulin M; INR, International normalized ratio; IVIG, intravenous immunoglobulin; PTT, partial thromboplastin time; SPEP, serum protein electrophoresis; VWD, von Willebrand disease.

1. Castillo JJ *et al. Br J Haematol* 2016, 175, 77–86.

Classification of WM and related disorders[1]

	IgM monoclonal protein*	Bone Marrow infiltration**	Symptoms Attributable to IgM	Symptoms due to tumor infiltration†
Symptomatic WM	+	+	+ (‡)	+ (‡)
Asymptomatic WM	+	+	–	–
IgM-related disorders§	+	–	+	–
IgM MGUS	+	–	–	–

* The panel considered it to be inappropriate to define an IgM concentration to distinguish MGUS from WM. However, it should be noted that IgM concentration rarely if ever exceeds 3 g/dL in MGUS. ** Patients with unequivocal BM infiltration by lymphoplasmocytic lymphoma will be considered to have WM, while patients without evidence of infiltration will be considered to have MGUS. However, it is acknowledged that in some patients equivocal evidence of BM infiltration is demonstrable. This may be manifest in a number of ways and includes the detection of clonal B cells by flow cytometry or PCR in the absence of morphological evidence of BM infiltration. Alternatively, patients may have equivocal bone marrow infiltrates without confirmatory phenotypic studies. It is considered that these patients should be classified as MGUS until further data become available. † Symptoms attributable to tumor infiltration will include any of the following manifestations: constitutional symptoms, cytopenia(s), or organomegaly. ‡ It is required the presence of one or both groups of symptoms. § It is well recognized that a population of patients exist who have symptoms attributable to the IgM monoclonal protein but no overt evidence of lymphoma. Such patients may present with symptomatic cryoglobulinemia, amyloidosis, or autoimmune phenomena such as peripheral and cold agglutinin disease. It is appropriate to consider these patients as a clinically distinct group and the term “IgM-related disorders” is proposed.

BM, bone marrow; IgM, immunoglobulin M; MGUS, monoclonal gammopathy of undetermined significance; PCR, polymerase chain reaction; WM, Waldenström’s macroglobulinemia.

1. Owen RG *et al. Sem Hematol* 2003; 30: 110–115.

Patient 1: Staging and risk assessment

- **Conventional IPSS**
  - Hb: 0
  - Age: 0
  - Platelet: 0
  - IgM: 0
  - B2M: 0
- **Revised IPSS:**
  - Age 0
  - B2M 0
  - sAlbumin 0
  - LDH 0

- However: Our case is asymptomatic
- IPSS is not valid. Use risk assessment for evolution to symptomatic disease:

http://www.awmrisk.com

B2M, beta-2 microglobulin; Hb, hemoglobin; IgM, immunoglobulin M; IPSS, International Prognostic Scoring System; LDH, lactate dehydrogenase; sAlbumin, serum albumin.

Patient 1: Staging and risk assessment

- **Conventional IPSS**
  - Hb: 0
  - Age: 0
  - Platelet: 0
  - IgM: 0
  - B2M: 0
- **Revised IPSS:**
  - Age 0
  - B2M 0
  - sAlbumin 0
  - LDH 0

- However: Our case is asymptomatic
- IPSS is not valid. Use risk assessment for evolution to symptomatic disease:

http://www.awmrisk.com

Bone Marrow Infiltration: 33%

IgM protein level: 3.1 mg/L

B2M Level: 2.32 mg/L

Albumin level: 4.1 mg/L

0

B2M, beta-2 microglobulin; Hb, hemoglobin; IgM, immunoglobulin M; IPSS, International Prognostic Scoring System; LDH, lactate dehydrogenase; sAlbumin, serum albumin.

Patient 1: Key treatment considerations

- Asymptomatic
  - Asthenia, weak, with no correspondence to Hb level
  - Cold sensitivity: too weak, too subjective
  - No symptoms attributable to WM
- New scoring system for asymptomatic patients
- Very young, relative high IgM monoclonal peak
- No therapy, close follow-up

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

Treatment criteria: Symptomatic disease[1]

1. Recurrent fever, night sweats, weight loss, fatigue
2. Hyperviscosity
3. Lymphadenopathy which is either symptomatic or bulky (≥5 cm in maximum diameter)
4. Symptomatic hepatomegaly and/or splenomegaly
5. Symptomatic organomegaly and/or organ or tissue infiltration
6. Peripheral neuropathy due to WM
7. Symptomatic cryoglobulinemia
8. Cold agglutinin anemia
9. Immune hemolytic anemia and/or thrombocytopenia
10. Nephropathy related to WM
11. Amyloidosis related to WM
12. Hemoglobin ≤10 g/dL
13. Platelet count <100 x 10^9/L

WM, Waldenström's macroglobulinemia.

1. Kyle RA et al. Semin. Oncol. 2003; 30: 116–120.

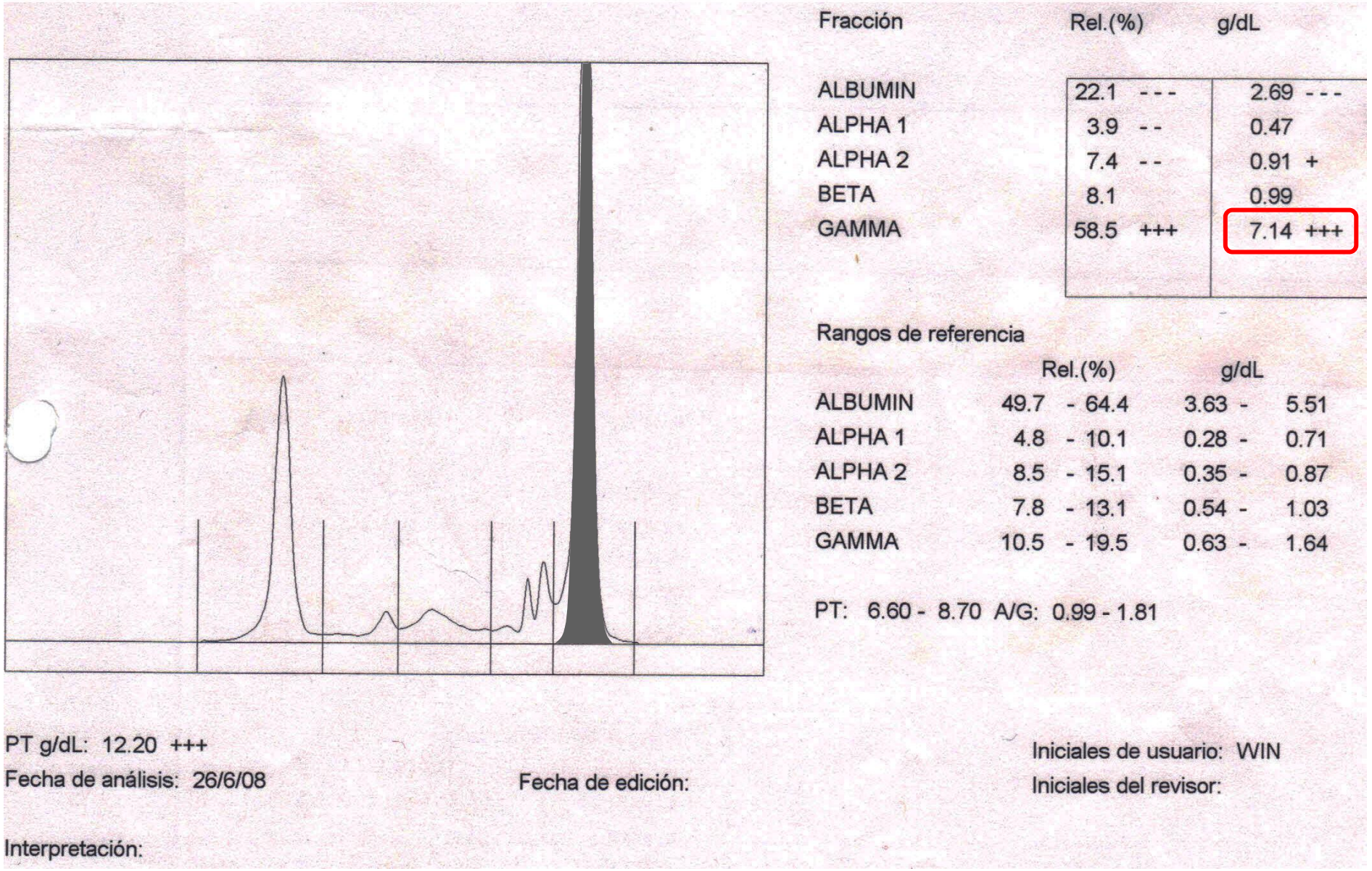
Patient 1: Follow-up

- In one year, progressive increase of the M component
- Anemia: Hb 11.2 g/dL, without the appearance of lymphadenopathy or B symptoms
- Almost impossible analytics due to tube agglutination
- Very frequent headaches
- In the last visit incipient signs of bloating: slow thinking, prolonged sleep
  - Funduscopy: small isolated hemorrhages, which were not seen previously

- Now: very young patient, symptomatic disease, quick progression

Hb, hemoglobin.

One year later…



Fracción	Rel.(%)	g/dL
ALBUMIN	22.1 - - -	2.69 - - -
ALPHA 1	3.9 - -	0.47
ALPHA 2	7.4 - -	0.91 +
BETA	8.1	0.99
GAMMA	58.5 +++	7.14 +++

Rangos de referencia

	Rel.(%)	g/dL
ALBUMIN	49.7 - 64.4	3.63 - 5.51
ALPHA 1	4.8 - 10.1	0.28 - 0.71
ALPHA 2	8.5 - 15.1	0.35 - 0.87
BETA	7.8 - 13.1	0.54 - 1.03
GAMMA	10.5 - 19.5	0.63 - 1.64

PT: 6.60 - 8.70 A/G: 0.99 - 1.81

PT g/dL: 12.20 +++

Fecha de análisis: 26/6/08

Fecha de edición:

Iniciales de usuario: WIN

Iniciales del revisor:

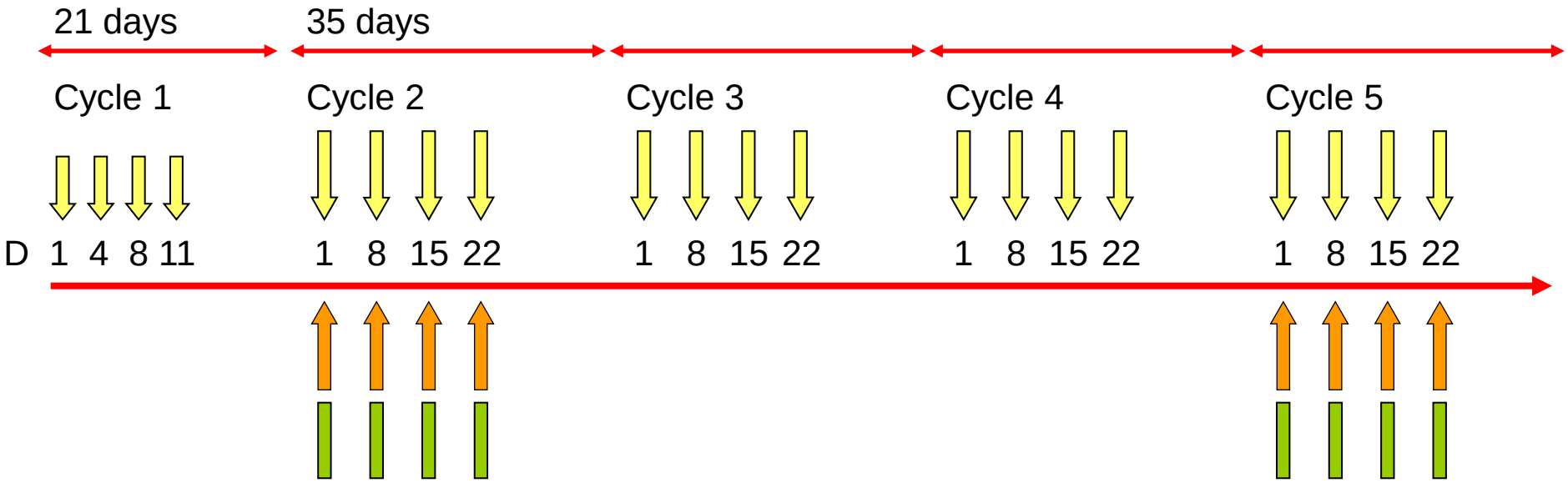
Interpretación:

Patient 1: Patient outcome

- BDR, European protocol
- Well tolerated: completion of the protocol, no delays, no dose reductions
- Minor response, low symptomatic improvement
- Early progression
- Refractory disease

BDR, Bortezomib-Dexamethasone-Rituximab.
Dimopoulos MA *et al*. *Blood* 2013; 122(19): 3276–82.

European Myeloma Network Multicenter BDR protocol



Bortezomib — 1.3mg/m^2 IV – cycle 1; 1.6mg/m^2 IV – cycle 2–5

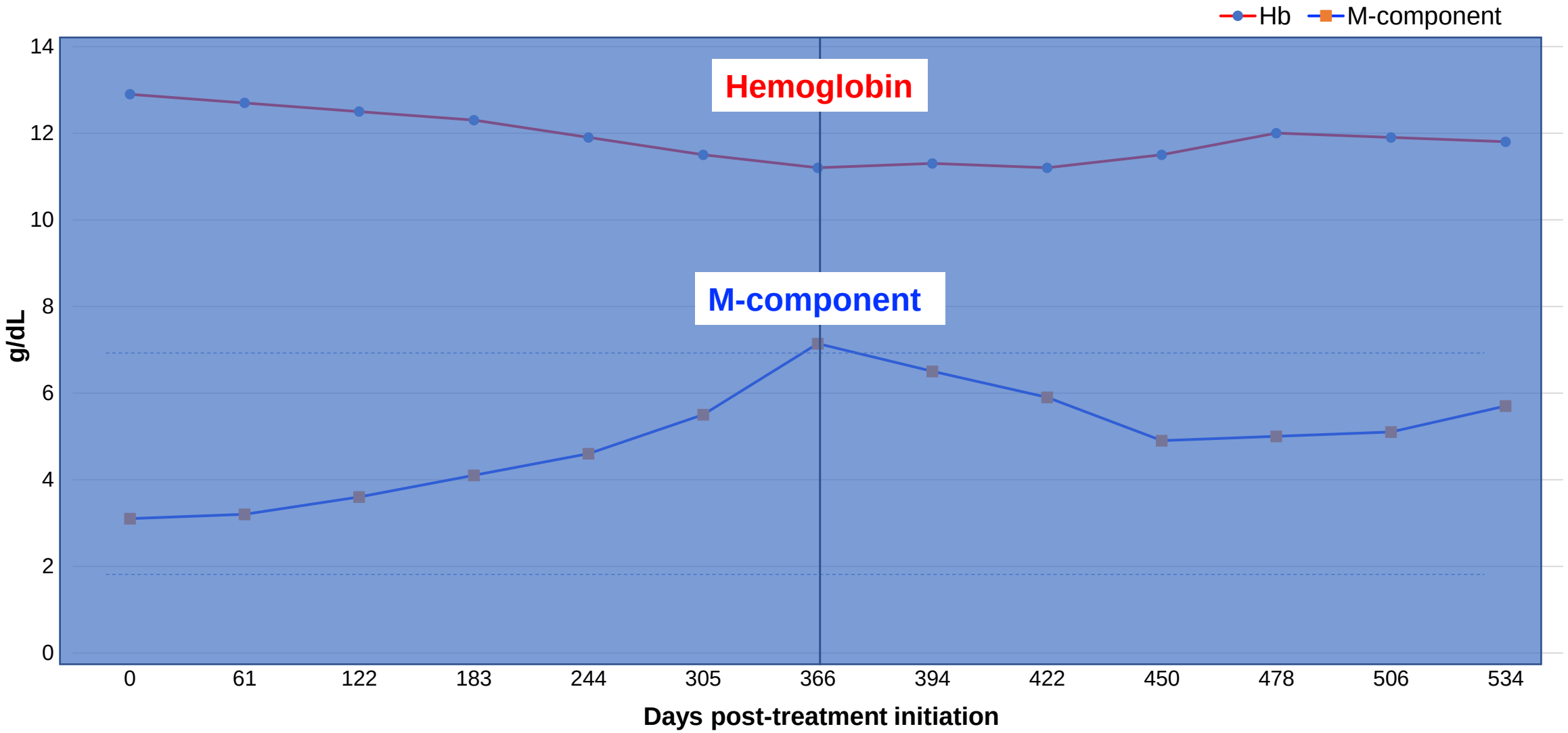
Rituximab — 375 mg/m^2 IV

Dexamethasone — 40 mg orally or IV

BDR, boretezomib, dexamethasone and rituximab; IV, intravenous.

Dimopoulos MA *et al*. *Blood* 2013; 122(19): 3276–82.

Patient 1: Hb and M-component outcomes



Hb, hemoglobin.

Patient 2: Initial presentation

Patient characteristics

- Female, 81 years
- Type 2 diabetes: under control
- Hypertension, 2 drugs; prior angina
- Progressive asthenia
- Occasional mucosal bleeding, gums & nose
- Isolated ecchymosis in both legs

Review of systems

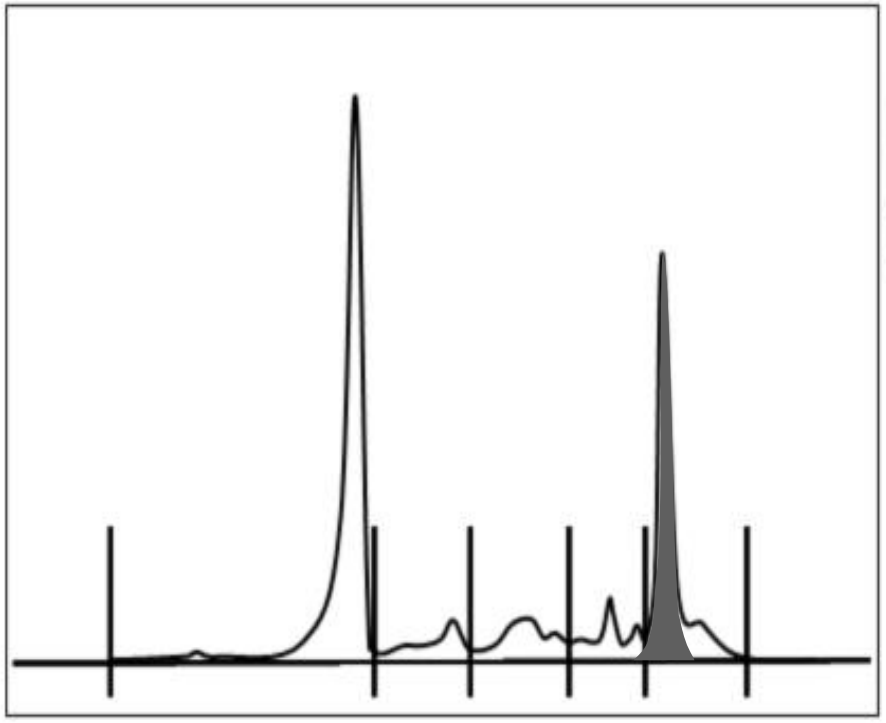
- No fatigue, no B symptoms
- 3 kg weight loss
- No Raynaud, no acrocyanosis
- Feet paresthesia, bilateral weakness inferior extremities
- Electrophysiology: symmetrical reduction of conduction velocities, prolonged distal motor latency
- No intestinal, skin or kidney alterations

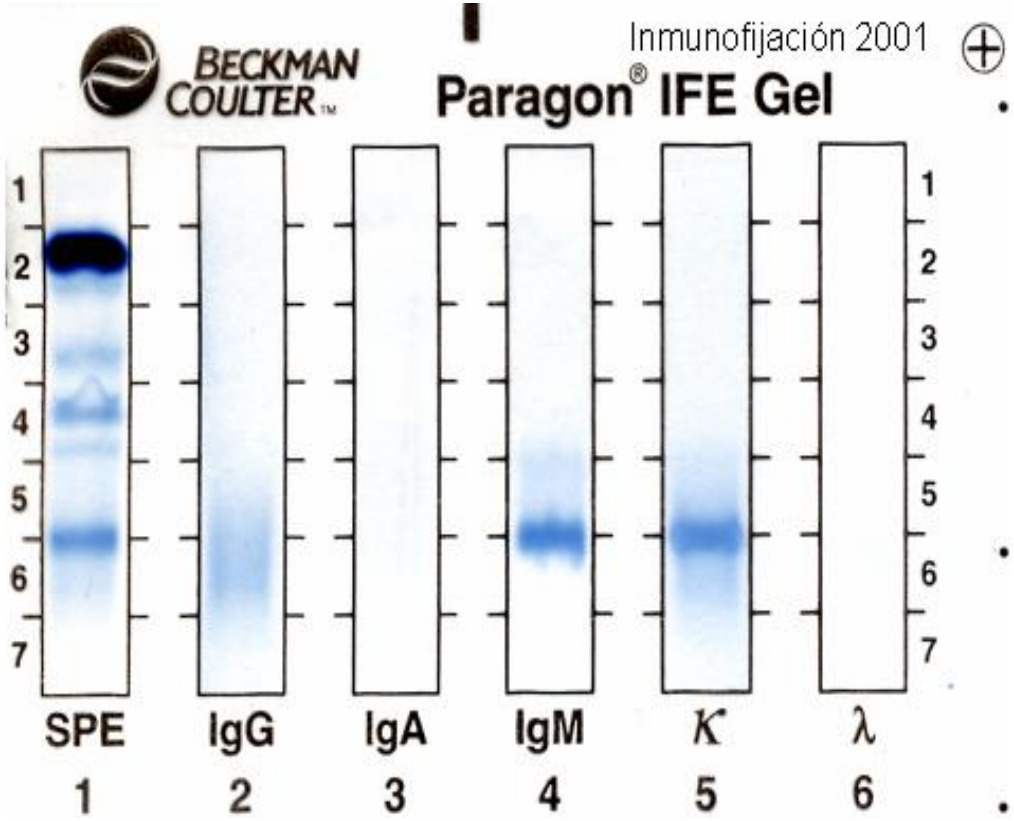
Laboratory studies

- Hemoglobin 11.7 g/dL
- Platelets 23 x 10^9/L
- WBC: 3.3 x 10^9/L
  - ANC: 2.01, ALC: 0.62, AMC: 0.37 x 10^9/L
- Serum creatinine 1.36 mg/dL
- LDH 214 U/L (max 260)
- β2-microglobulin 4.56 µg/mL (max 2.6)
- Albumin: 3.4 g/L
- Serum monoclonal IgM 2.74 g/dL
- sFLC (mg/dL), κ/λ: **241**/17.

WBC: White blood cell count; ANC: absolute neutrophil count; ALC: absolute Lymphocyte count; AMC: absolute monocyte count; ESR, erythrocyte sedimentation rate; LDH, lactate dehydrogenase; sFLC, serum free light chain.

Protein electrophoresis and immunofixation





IgA, immunoglobulin A; IgG, immunoglobulin G; IgM, immunoglobulin M; SPE, serum protein electrophoresis.

Patient 2: Initial presentation (2)

Laboratory studies

- Serum Fe: 33.7 mg/dL
- Ferritin: 19 ng/mL
- Transferrin: 329 mg/dL (Sat: 10.2%)

Bone marrow examinations

- Bone marrow biopsy: mixed nodular-interstitial infiltration by lymphoplasmocytes (63%)
- Flow cytometry:
  - Bone marrow: 56% monoclonal lymphoid B cells with phenotype: $CD19^{+}$, $CD5^{-}$, $CD20^{++}$, $FMC7^{\pm}$, $CD22^{w+}$, $sIgk^{+}$, $CD25^{+}$, $CD10^{-}$, $CD103^{-}$
    0.23% kappa plasma cells, with no aberrancies
  - Peripheral blood: No monoclonal B cells
- BM FISH studies: del(6q21); normal *TP53* & *IgH*
- BM Molecular studies:
  - $MYD88^{L265P}$: positive (Ct: 31.6^{MUT}; vs 28.2^{WT})
  - *CXCR4* (CD19+ cells & Sanger): normal

Total body CT scan

- No organomegaly
- No lymphadenopathy

Funduscopy

- Normal

Cryoagglutinins

- Negative

Cryoglobulins

- Negative

BM, bone marrow; CT, computerized tomography; CXCR4, C-X-C chemokine receptor type 4; Ct, 1st cycle threshold; mut: mutates; wt: wild type; Fe, iron; FISH, fluorescence in situ hybridization; IgH, immunoglobulin heavy-chain; MYD88, myeloid differentiation primary response 88; TP53, tumor protein P53; WM, Waldenström's macroglobulinemia.

Patient 2: Staging and risk assessment

- **Conventional IPSS**
  - Hb: 0
  - Age: 2
  - Platelet: 1 IPSS = 4
  - IgM: 0
  - B2M: 1

- **Revised IPSS:**
  - Age 2
  - B2M 1 rIPSS = 4
  - sAlbumin 1
  - LDH 0

GAH scale[1]:

- 4 = Frail patient

CIRS-G

- 13 = Frail patient

B2M, beta-2 microglobulin; CIRS-G, Cumulative Illness Rating Scale-Geriatric; GAH: Geriatric Assessment in Hematological malignancies; Hb, hemoglobin; IgM, immunoglobulin M; IPSS, International Prognostic Scoring System; LDH, lactate dehydrogenase; rIPSS, revised International Prognostic Scoring System; sAlbumin, serum albumin.

1. Bonanad S et al. J Geriatr Oncol. 2015; 6(5): 353–361.

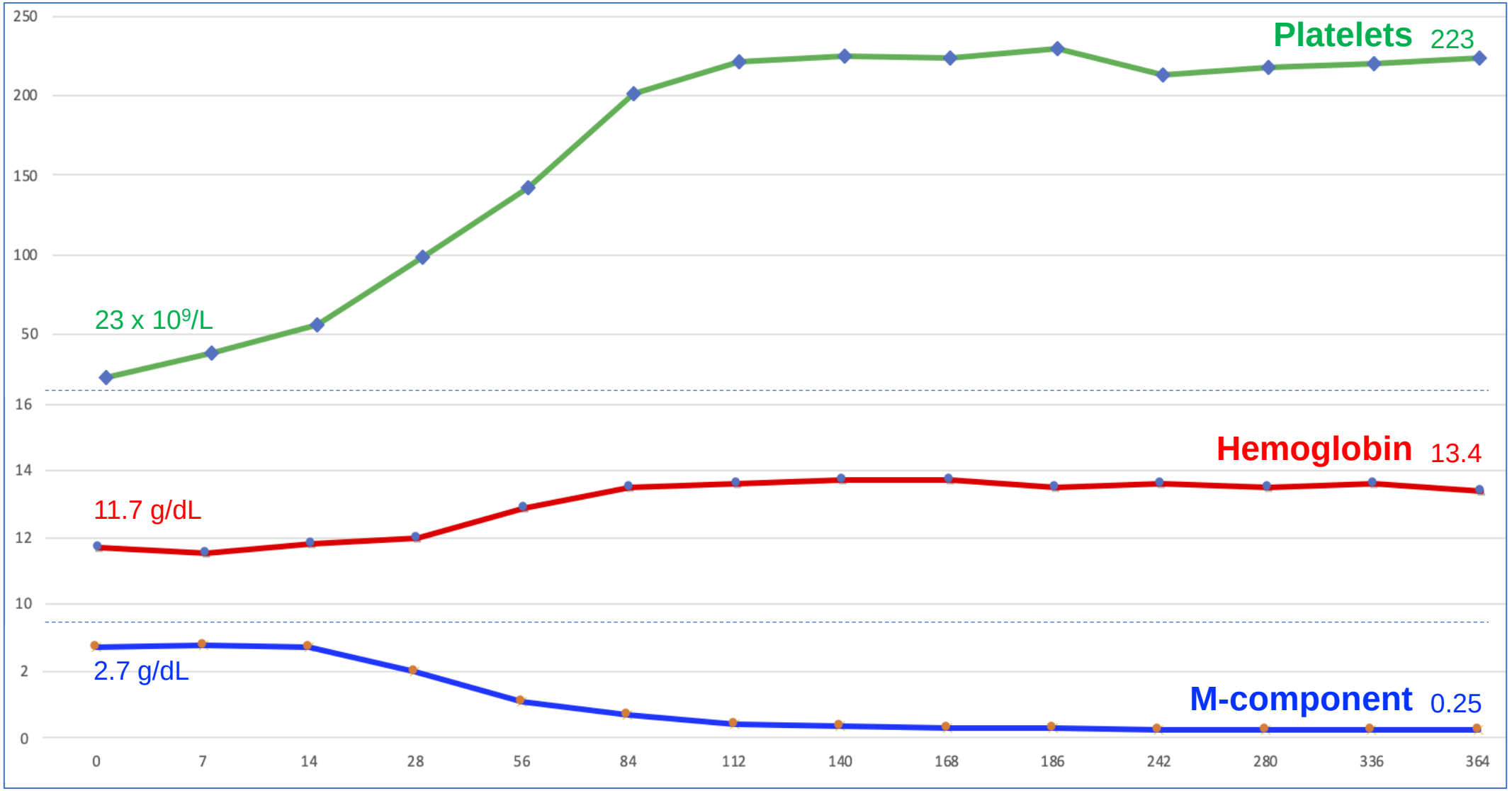
Patient 2: Key treatment considerations

- Old patient – avoid intensive therapy
- Geriatric Scales: Frail patient – avoid intensive therapy
- Relevant thrombocytopenia: Grade 3 – avoid bendamustine, cyclophosphamide, bortezomib
- Type 2 diabetes: Insulin controlled – difficulties with steroids
- Long distance to hospital: 90 min driving – favor oral therapy

Patient 2: Initiation of therapy and patient management

- Ibrutinib 420 mg/day (approved)
- Pay special attention to:
  - Hypertension: possible increase in drug requirements
  - Cardiac rhythm: atrial fibrillation / flutter can be difficult to manage
  - Bleeding: until platelet recovery, bleeding can be a problem
- Initial close follow-up

Patient 2: Outcome at year 1



Conclusions

- Accurate initial evaluation at diagnosis is necessary for all WM patients
- A careful review of systems is necessary for all patients, especially when treatment criteria are not clear
- Review of systems should include a detailed evaluation of comorbidities
  - Geriatric scales are helpful
- There are some clues derived from molecular findings that could help in the treatment decision-making process
- Possible adverse events should be taken into account when selecting the appropriate therapy

Panel discussion

- Criteria to start therapy
- Influence of age in therapeutic decision-making
- Comorbidities: scales
- Accessory circumstances influencing therapy:
  - Way of living
  - Distance to hospital
  - Risk of adverse events

What are the greatest difficulties we face in initial treatment of WM?

Moderator: Prof. Wojciech Jurczak
Panel: All

What are the greatest difficulties we face in initial treatment of WM?

1. When should we initiate treatment in the COVID era?
2. How do we identify patients appropriate for chemotherapy-free treatment?
3. How do we manage the risk of treatment-related complications?
4. How do we define and treat “unfit” versus “fit” patients?
5. What is the impact of MYD88 / CXCR4 mutation status on first-line treatment?

Should chemotherapy-free regimens play a greater role when initiating treatment for WM?

Moderator: Prof. Meletios A. Dimopoulos

Yes: Prof. Wojciech Jurczak | *No:* Prof. Véronique Leblond

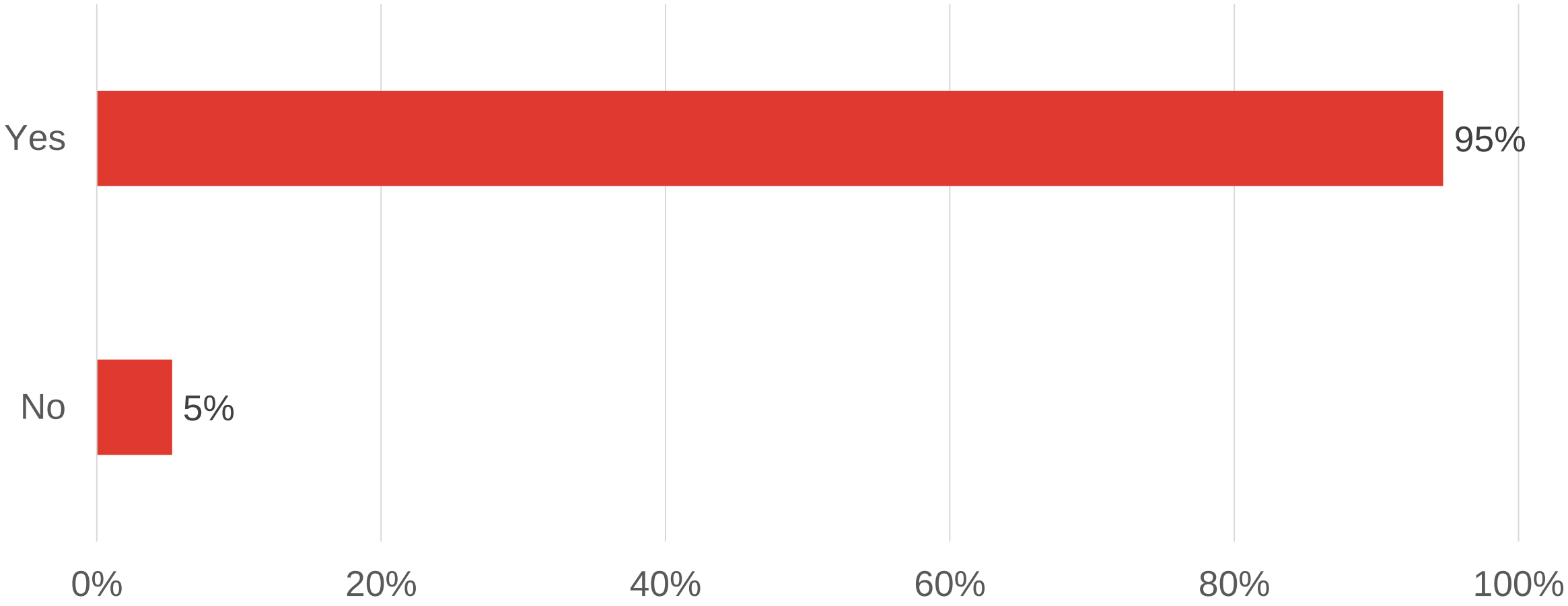
Should chemotherapy-free regimens play a greater role when initiating treatment for WM?

A Yes

B No

Please vote now!

1. Which tests are essential at this point?



N=19

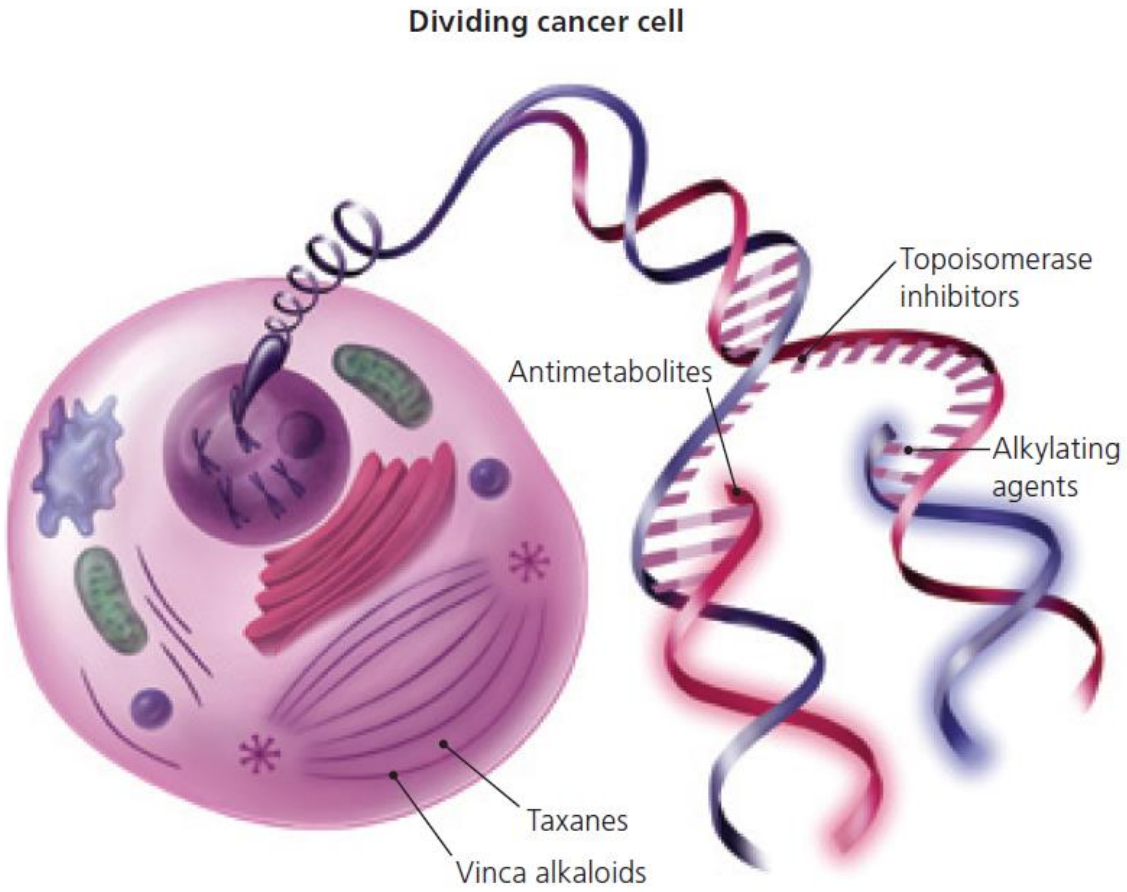
Should chemotherapy-free regimens play a greater role when initiating treatment for WM? YES

Prof. Wojciech Jurczak
National Research Institute of Oncology, Poland

National Institute of Oncology

Chemotherapy

Targeted therapies for rapidly dividing cells



Is WM an aggressive lymphoma?

Do patients like 'chemo'?

Can we cure patients?

Are chemotherapy AEs acceptable?

AE, adverse event; WM, Waldenström's macroglobulinemia.
Gerber DE. *Am Fam Physician* 2008; 77 (3): 311–319.

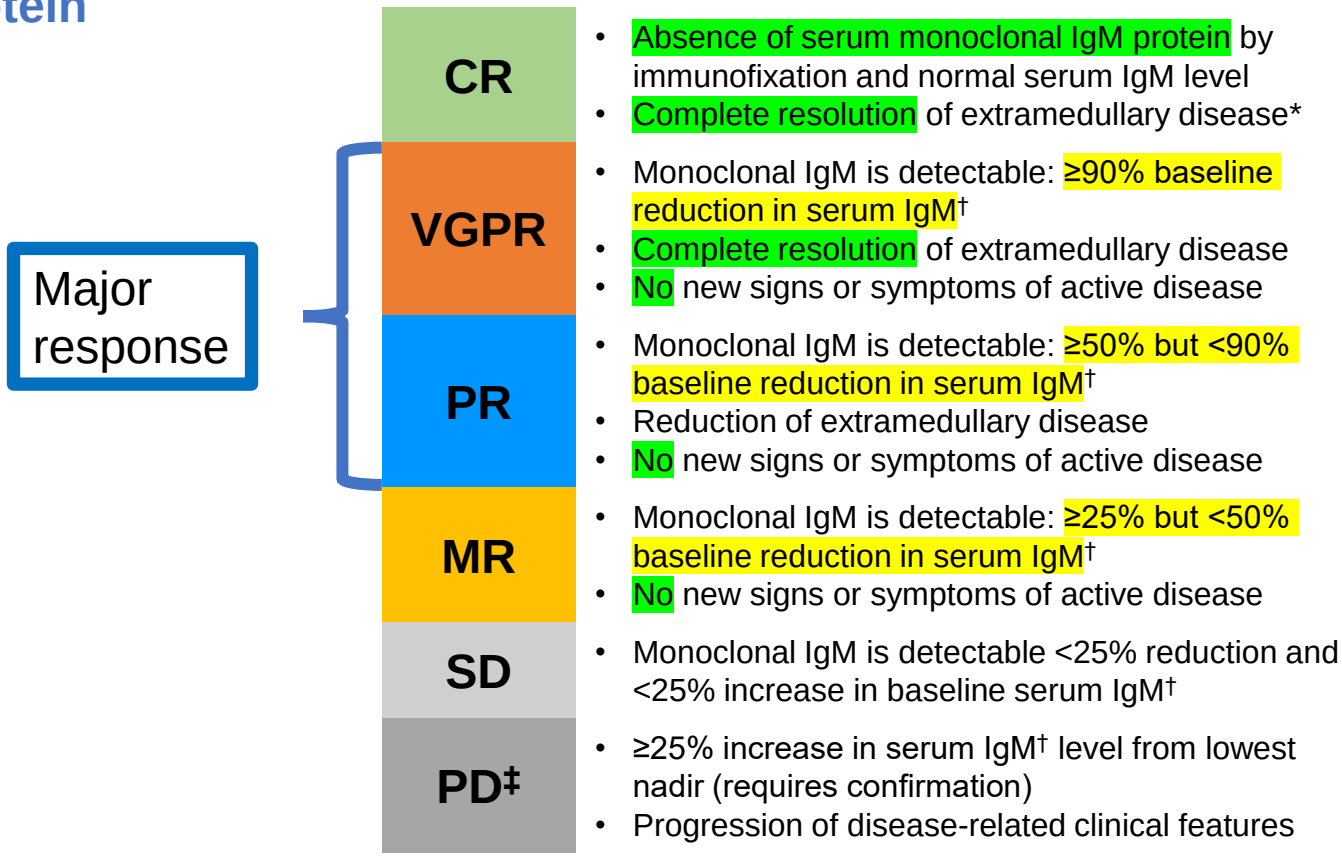
‘Non-chemo’ alternatives for WM

Recognized ‘standard of care’	Emerging therapies*
Monotherapy with anti-CD20 mAb • Rituximab • Obinutuzumab **Proteasome inhibitors (+ mAb, +/− steroids)** • Bortezomib • Carfilzomib • Ixazomib* **BTK inhibitors** • Ibrutinib • Acalabrutinib* • Tirabrutinib† • Zanubrutinib*	**BCL-2 antagonists** • Venetoclax **PI3K inhibitors** • Idelalisib **mTOR inhibitors** • Everolimus **SYK inhibitors** **CXCR4 antagonists** • Mavorixafor

*Not approved for the treatment of WM; †Not approved for the treatment of WM outside Japan.
BCL-2, B-cell lymphoma 2; BTK, Bruton’s tyrosine kinase; CXCR4, C-X-C chemokine receptor type 4; mAb, monoclonal antibody; mTOR, mammalian target of rapamycin; PI3K, phosphoinositide 3-kinase; SYK, spleen tyrosine kinase; WM, Waldenström’s macroglobulinemia.

Treatment of symptomatic patients – efficacy is required

- **Circulating monoclonal IgM paraprotein**
  - Hyperviscosity syndrome
  - Cryoglobulinemia
  - Cold agglutinin disease
  - Peripheral neuropathy
  - Amyloidosis
- **Bone marrow infiltration**
  - Peripheral cytopenias
- **Nodal or splenic involvement**



*i.e. lymphadenopathy/splenomegaly. †Sequential changes in IgM levels may be determined by M protein quantitation by densitometry or total serum IgM quantitation by nephelometry. ‡Either condition sufficient for PD.
CR, complete response; IgM, immunoglobulin M; MR, minor response; PD, progressive disease; PR, partial response; SD, stable disease; VGPR, very good partial response.
Owen RG *et al*. *Br J Haematol* 2013; 160: 171–176.

Anti-CD20 mAb monotherapy

Inferior efficacy compared with immunochemotherapy

	Drug	Treatment naive, relapsed or refractory	Overall response rate	Major response rate	Very good partial response rate or better	Progression-free survival (95% CI)
Gertz et al[8]	Rituximab	34, 35 (n=69)	36 (52%)	19 (28%)	0	Median: 23 months (NR)
Treon et al[9]	Rituximab	12, 17 (n=29)	19 (66%)	14 (48%)	0	Median: 14 months (NR)
Dimopoulos et al[10]	Rituximab	34, 41 (n=75)	35 (47%)	24 (32%)	5 (7%)	30-month: 28% (NR)
Furman et al[11]	Ofatumumab	9, 28 (n=37)	22 (59%)	15 (41%)	0	Median: 18 months (14–22)

- **IgM flares** in half of the patients
  - May worsen symptoms of hyperviscosity, neuropathy, cryoglobulinemia, or cold agglutinin disease, especially in patients with IgM >4,000 mg/dL
- Late onset neutropenia
- Infusion reactions

CI, confidence interval; IgM, immunoglobulin M; mAb, monoclonal antibody; NR, not reached.
Castillo JJ *et al*. *Lancet Haematol* 2020; 7 (11): e827–e837.

Proteasome inhibitors + anti-CD20 mAb (+ steroids)[1]

Similar efficacy to immunochemotherapy

	Drugs	Treatment naive, relapsed or refractory	Overall response rate	Major response rate	Very good partial response rate or better	Progression-free survival (95% CI)
Treon et al[26]	Bortezomib, dexamethasone, and rituximab	23, 0 (n=23)	22 (96%)	19 (83%)	8 (35%)	Median: 66 months (NR)
Ghobrial et al[27]	Bortezomib (weekly) and rituximab	0, 37 (n=37)	30 (81%)	19 (51%)	2 (5%)	Median: 16 months (11–21)
Ghobrial et al[28]	Bortezomib (weekly) and rituximab	26, 0 (n=26)	23 (88%)	17 (65%)	2 (8%)	1-year: 75% (50–89)
Dimopoulos et al[29]	Bortezomib (weekly), dexamethasone, and rituximab	59, 0 (n=59)	50 (85%)	40 (68%)	6 (10%)	Median: 42 months (NR)
Treon et al[30]	Carfilzomib, dexamethasone, and rituximab	31, 0 (n=31)	27 (87%)	21 (68%)	11 (35%)	Median: 44 months (NR)
Castillo et al[31]	Ixazomib, dexamethasone, and rituximab	26, 0 (n=26)	25 (96%)	20 (77%)	4 (15%)	Median: not reached at 22 months (NR)
Kersten et al[32]	Ixazomib, dexamethasone, and rituximab (subcutaneous)	0, 50 (n=50)	37 (74%)	26 (52%)	8 (16%)	Median: not reached at 20 months (NR)

- **Ixazomib**
  - No neuropathy
  - Taken orally

- **Bortezomib**
  - Weekly infusions
  - Grade 3 neuropathy!!
- **Carfilzomib**
  - Dose-dependent cardiovascular events, particularly if patient aged >65 years

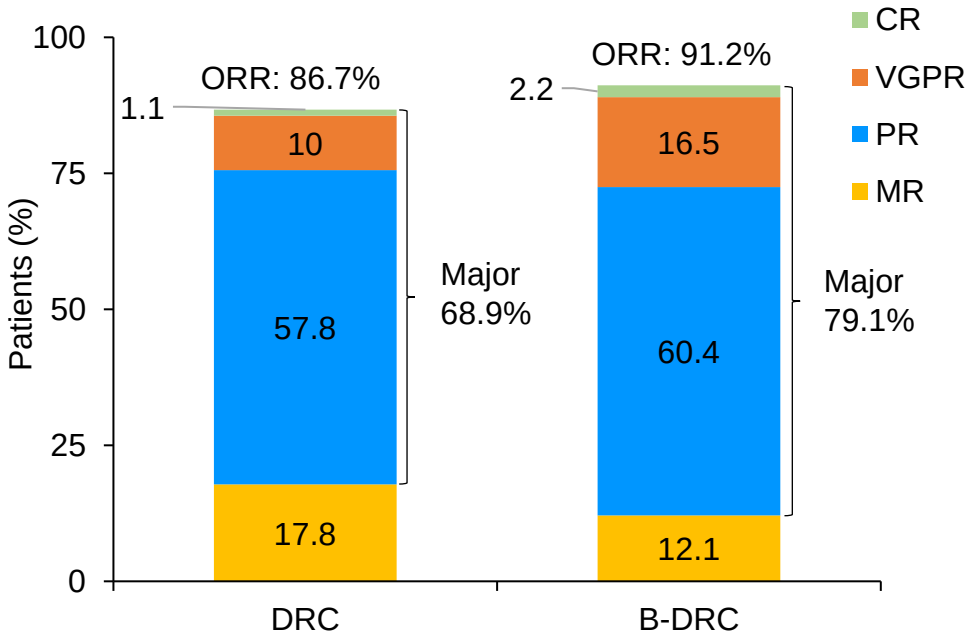
CI, confidence interval; mAb, monoclonal antibody; NR, not reached.

1. Castillo JJ *et al*. *Lancet Haematol* 2020; 7 (11): e827–e837.

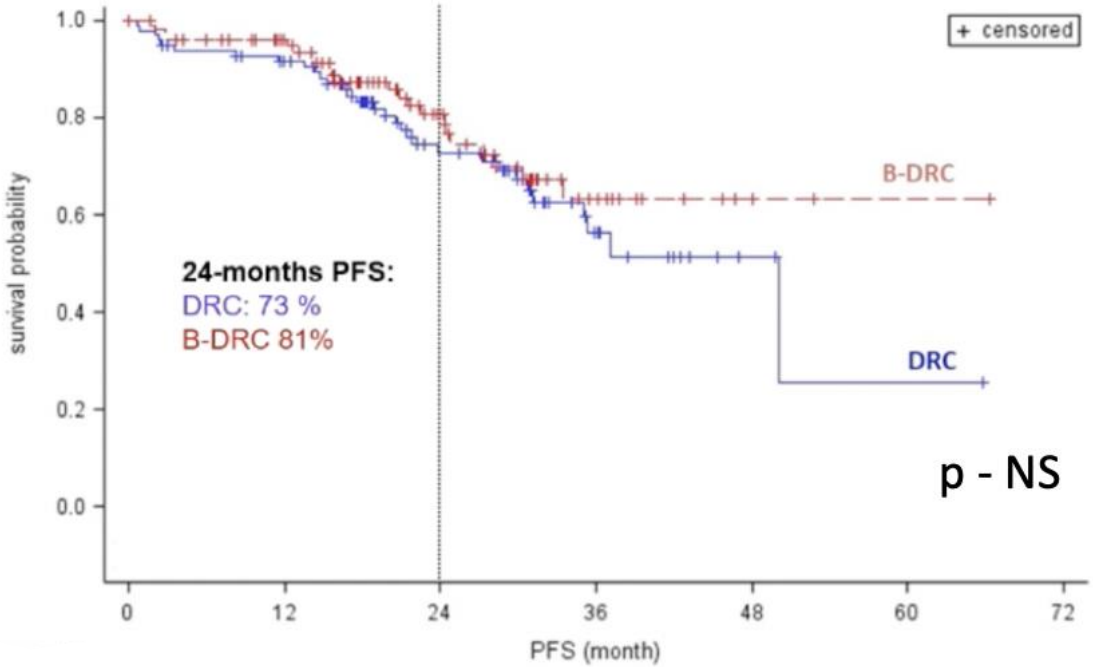
ECWM-1 Phase III study (N=202): DRC vs. B-DRC[1]

- Bortezomib 1.6 mg/m² D1, 8, 15; dexamethasone 20 mg po D1; rituximab 375 mg/m² IV D1 cycle 1 and 1400 mg SC D1 cycles 2–6; cyclophosphamide 100 mg/m² po D1–5
- Protocol was administered for six 4-week induction cycles

Response at end of induction



PFS



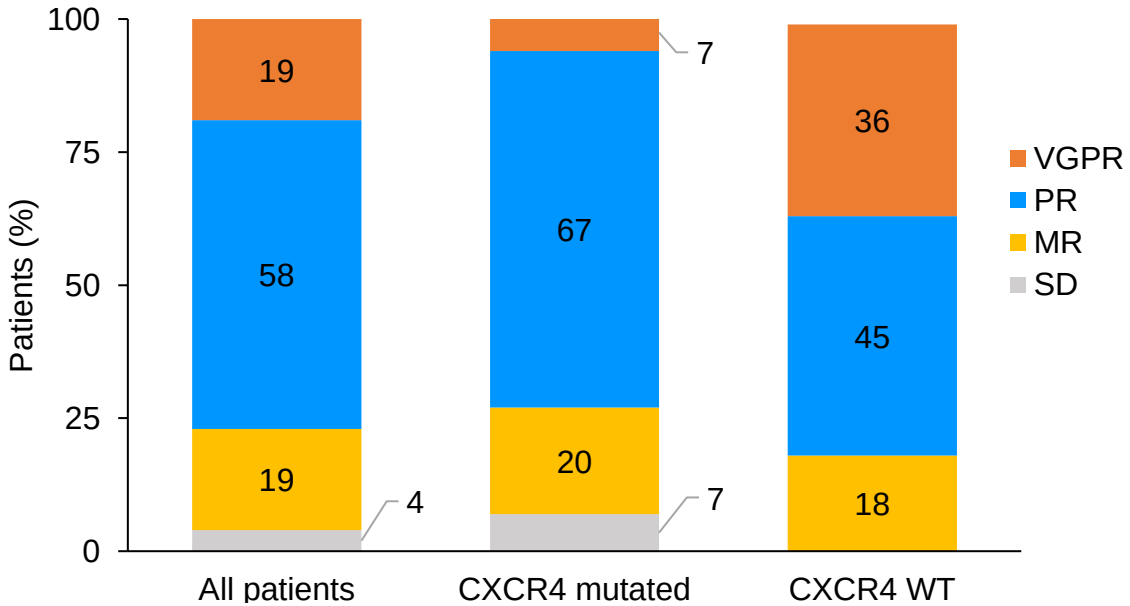
B-DRC, bortezomib, dexamethasone, rituximab, and cyclophosphamide; CR, complete response; D, Day; DRC, dexamethasone, rituximab, and cyclophosphamide; ECWM, European Consortium for Waldenström's Macroglobulinemia; IV, intravenous; MR, minor response; NS, not significant; ORR, overall response rate; PFS, progression-free survival; po, per os (taken orally); PR, partial response; SC, subcutaneous; VGPR, very good partial response.

1. Buske C *et al*. *Blood* 2020; 136(Supplement 1): 26. Oral presentation at the American Society of Hematology (ASH) annual meeting; December 5–8, 2020.

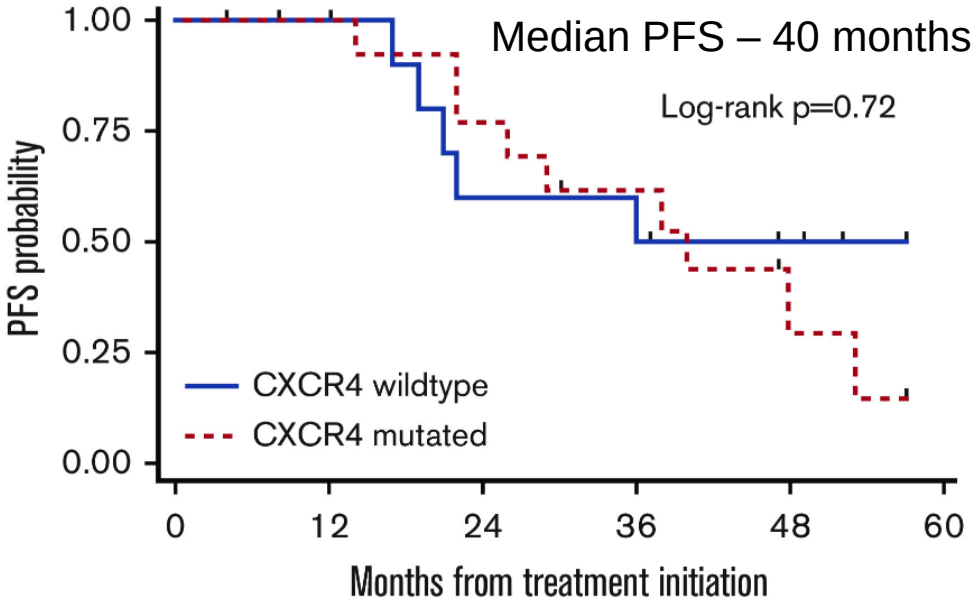
Ixazomib, dexamethasone, and rituximab Phase II study (N=26)[1]

- Ixazomib 4 mg and dexamethasone 20 mg orally on D1, 8, and 15, and 375 mg/m² rituximab IV on Day 1
- Protocol was administered for six 4-week induction cycles followed by six 8-week maintenance cycles

Response rates of 26 patients with WM treated with IDR according to CXCR4 mutational status



Kaplan-Meier estimates for PFS



CXCR4, C-X-C chemokine receptor type 4 gene; D, Day; IDR, ixazomib, dexamethasone, and rituximab; IV, intravenous; mR, minor response; MYD88, myeloid differentiation primary response 88 gene; PFS, progression-free survival; PR, partial response; SD, stable disease; VGPR, very good partial response; WT, wild-type.

1. Castillo JJ *et al*. *Blood Adv* 2020; 4 (16): 3952–3959.

BTK inhibitors (+/− anti-CD20 mAb)

Superior efficacy compared with immunochemotherapy

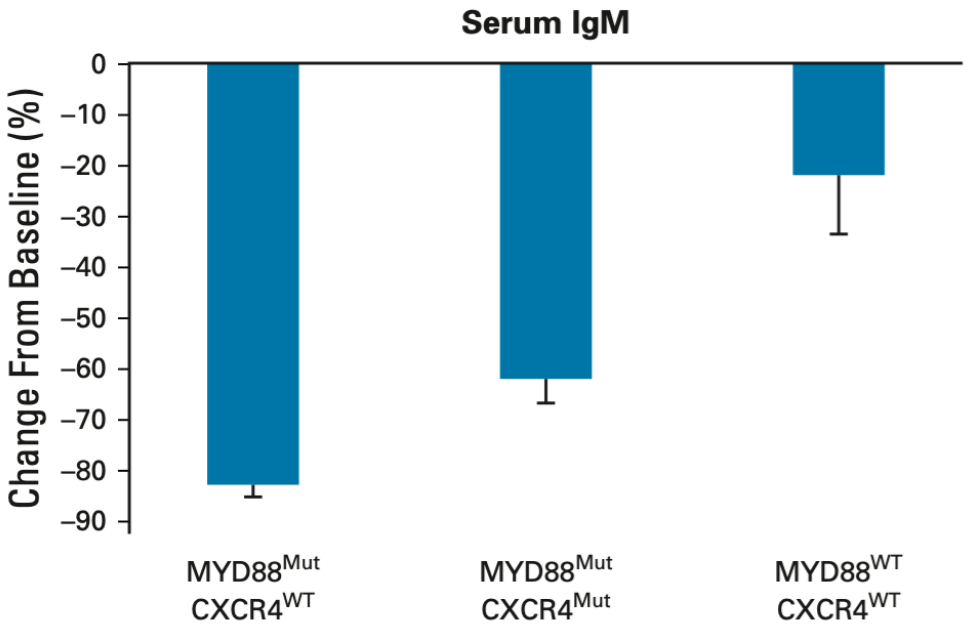
	Drugs	Treatment naive, relapsed or refractory	Overall response rate	Major response rate	Very good partial response rate or better	Progression-free surviv… (95% CI)
Treon et al[37]	Ibrutinib	0, 63 (n=63)	57 (90%)	50 (79%)	19 (30%)	5-year: 54% (95% CI 39–67%)
Dimopoulos et al[29]	Ibrutinib	0, 31 (n=31)	28 (90%)	22 (71%)	4 (13%)	18-month: 86% (66–94)
Treon et al[38]	Ibrutinib	30, 0 (n=30)	30 (100%)	25 (83%)	6 (20%)	18-month: 92% (73–98)
Dimopoulos et al[39]	Ibrutinib, rituximab	34, 41 (n=75)	70 (93%)	55 (73%)	20 (27%)	30-month: 82% (NR)
Owen et al[40]	Acalabrutinib	14, 92 (n=106)	99 (93%)	83 (78%)	8 (8%; IWWM-6) and 31 (29%; IWWM-3)	24-month: 90% (47–99, TN); 82% (72–89, RR)
Tam et al	**Zanubrutinib**	**19, 83 (n=102)**	**96 (94%)**	**79 (77%)**	**29 (28%)**	**18 months: 85%**

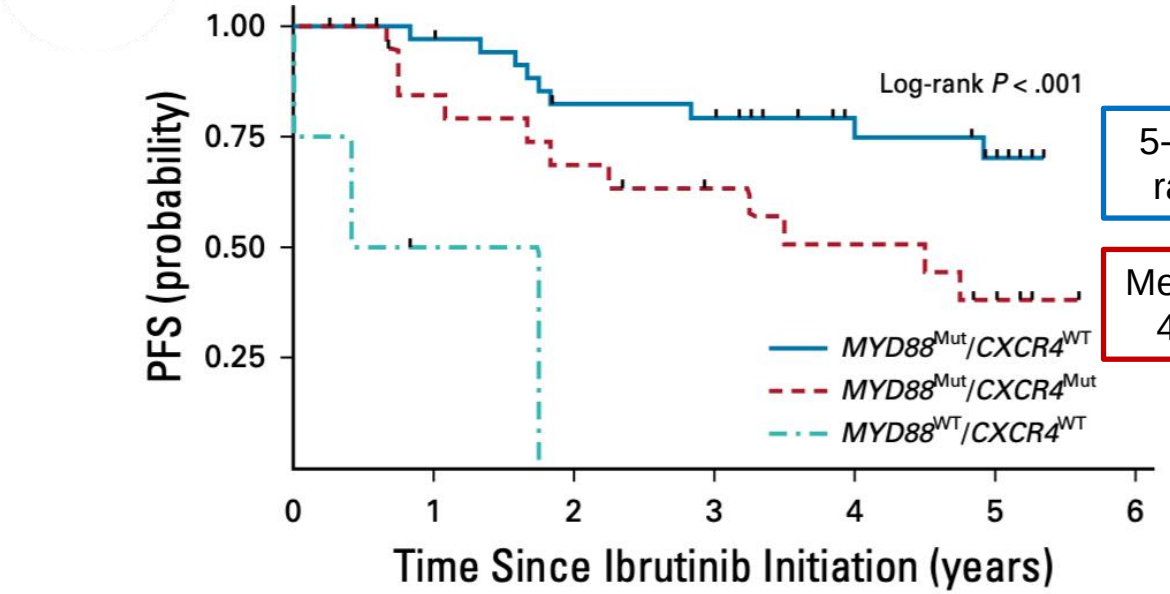
- **Highly active:** fast time to response, high rates of response, improved median PFS
- **Safety profile improved** in selective BTK inhibitors: acalabrutinib and zanubrutinib
- **Active in CNS** (patients with Bing–Neel syndrome)

- **Patients without *MYD88* mutations appear to benefit the least**
  - No patients had a major response to ibrutinib; all progressed within 2 years
- **Ibrutinib**
  - AEs leading to therapy discontinuation
  - Patients with a *CXCR4* mutation appear to benefit less

AE, adverse event; BTK, Bruton's tyrosine kinase; CI, confidence interval; CNS, central nervous system; *CXCR4*, C-X-C chemokine receptor type 4 gene; IWWM, International Workshop on Waldenström Macroglobulinemia; mAb, monoclonal antibody; *MYD88*, myeloid differentiation primary response 88 gene; NR, not reached; PFS, progression-free survival; RR, relapsed/refractory; TN, treatment-naive.
Castillo JJ *et al*. *Lancet Haematol* 2020; 7 (11): e827–e837.

Ibrutinib in previously treated WM (N=63)





No. at risk:

MYD88^{Mut}*CXCR4*^{WT}	36	34	26	25	18	14	0
MYD88^{Mut}*CXCR4*^{Mut}	22	16	13	10	8	5	0
MYD88^{Mut}*CXCR4*^{Mut}	4	1	0	0	0	0	0

5-year PFS rate: 70%

Median PFS: 4.5 years

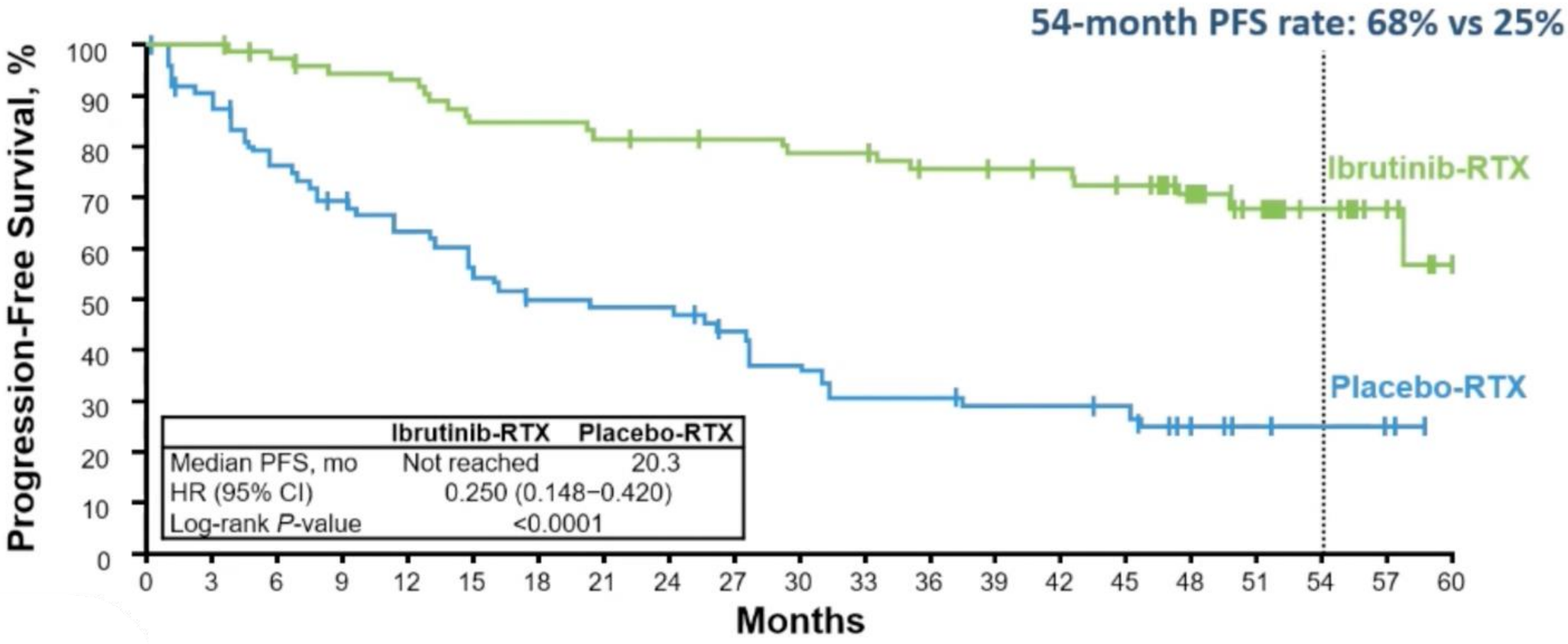
CXCR4, C-X-C chemokine receptor type 4 gene; IgM, immunoglobulin M; mut, mutated; *MYD88*, myeloid differentiation primary response 88 gene; PFS, progression-free survival; WM, Waldenström's macroglobulinemia; WT, wild-type.

Treon SP *et al*. *J Clin Oncol* 2020; 15; JCO2000555

iNNOVATE study

Ibrutinib–rituximab vs. placebo–rituximab (N=150)

- Placebo or ibrutinib 420 mg po QD until PD *and* rituximab 375 mg/m² IV QW on Weeks 1–4 and 17–20

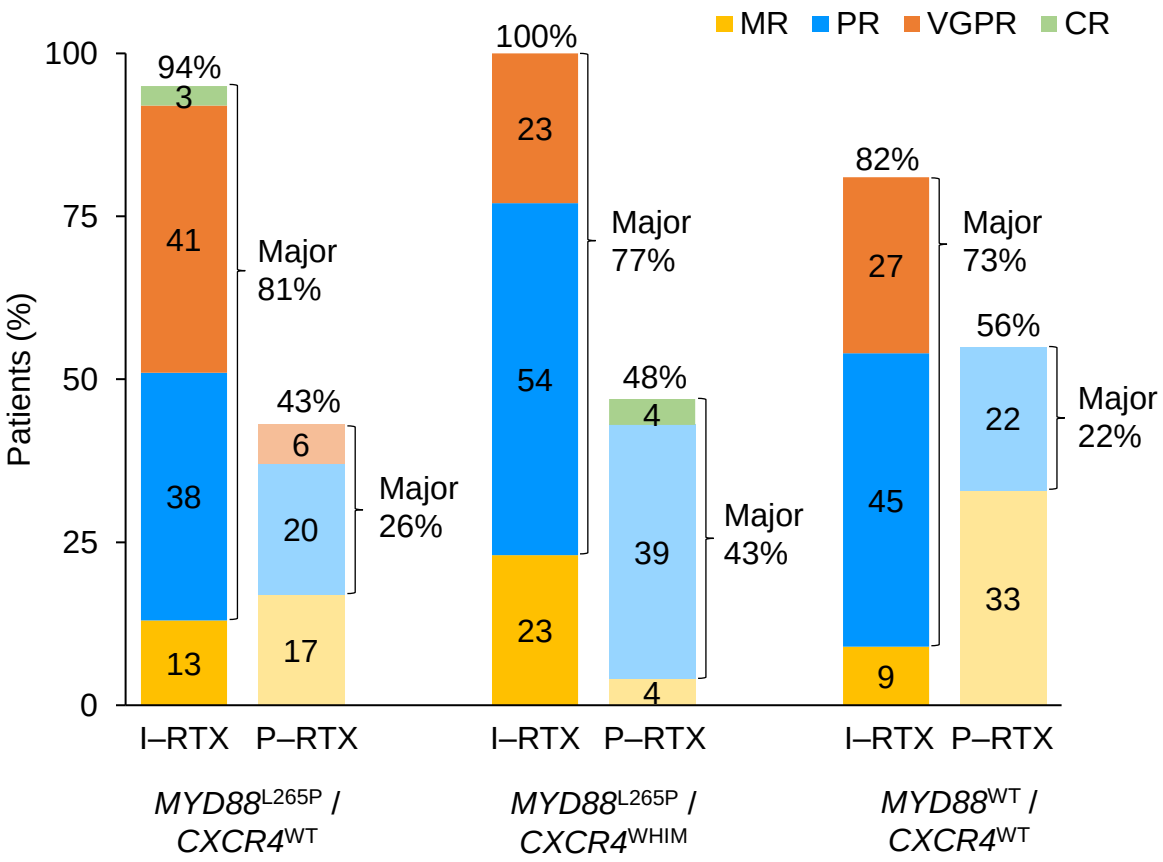


CI, confidence interval; HR, hazard ratio; IV, intravenous; PD, progressive disease; PFS, progression-free survival; po, per os (taken orally); QD, once daily; QW, once weekly; RTX, rituximab.

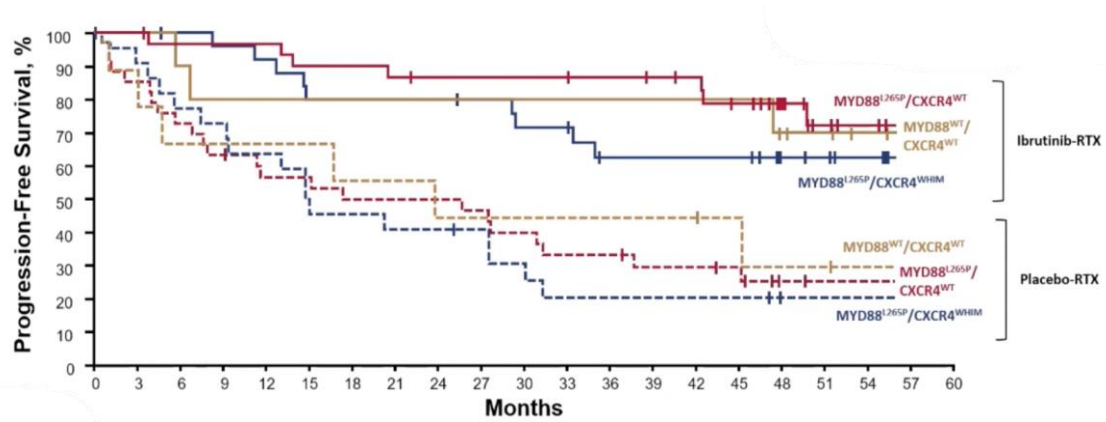
Buske C *et al*. *Blood* 2020; 136 (Suppl 1): 24–26. Dimopoulos MA *et al*. *N Engl J Med* 2018; 378 (25): 2399–2410.

iNNOVATE study

Ibrutinib–rituximab vs. placebo–rituximab (N=150)



Genotype	Ibrutinib–RTX	Placebo–RTX
MYD88^{L265P}/*CXCR4*^{WT}	43%	47%
MYD88^{L265P}/*CXCR4*^{WHIM}	35%	31%
MYD88^{WT}/*CXCR4*^{WT}	15%	12%
Unknown	8%	11%



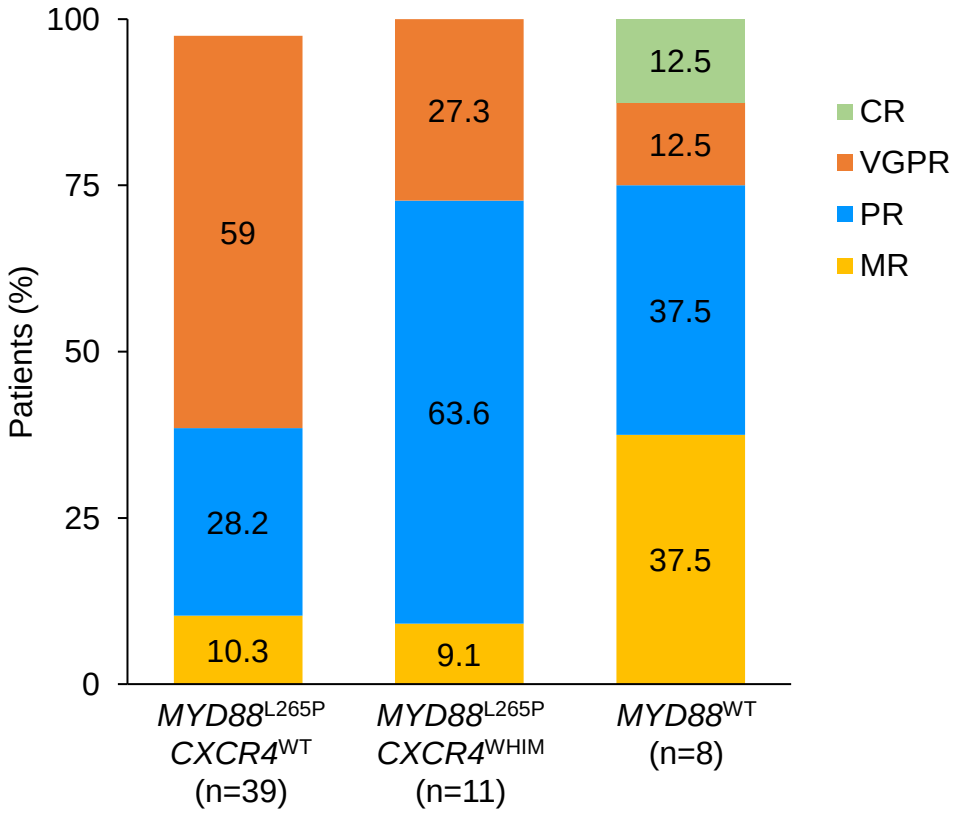
CR, complete response; I+RTX, ibrutinib and rituximab; MR, minor response; PR, partial response; P+RTX, placebo and rituximab; RTX, rituximab; VGPR, very good partial response; WHIM, warts, hypogammaglobulinemia, infections, and myelokathexis; WT, wild-type.

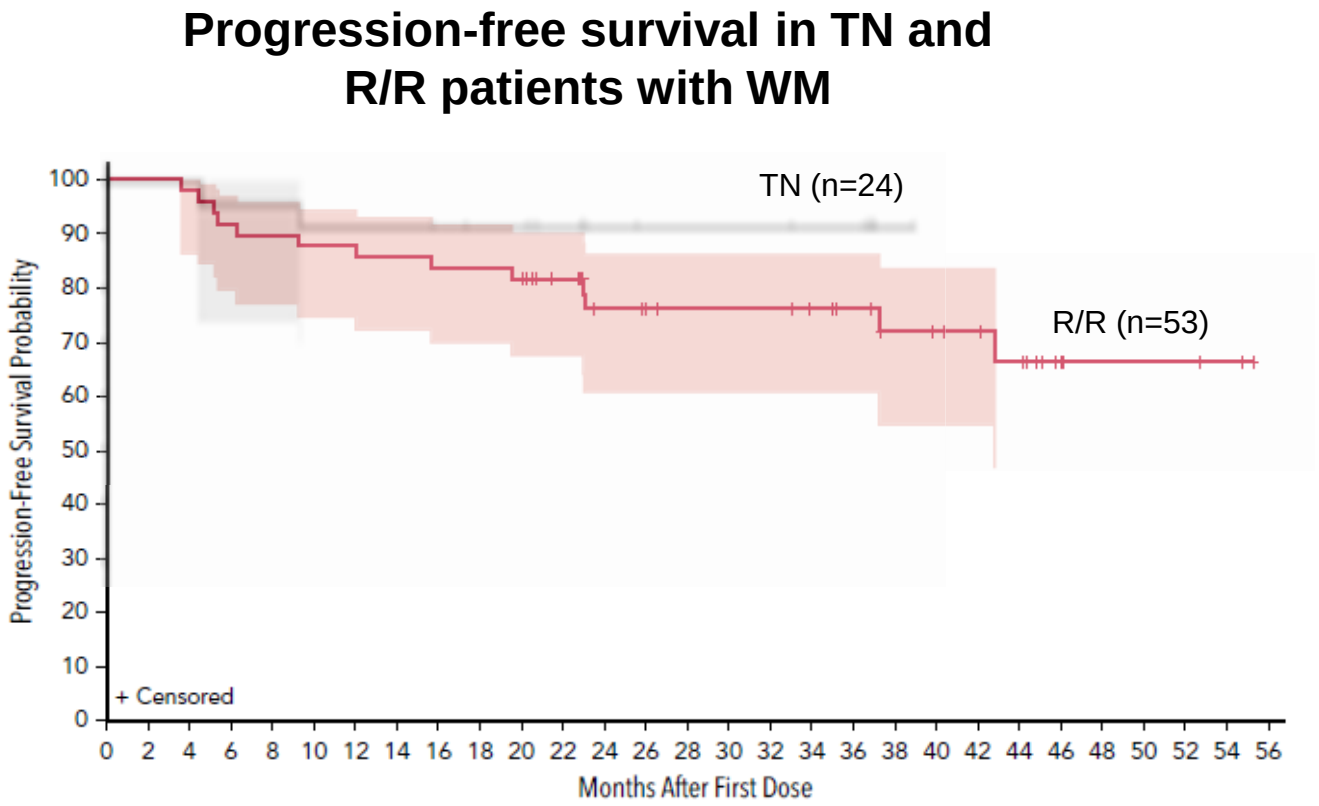
Buske C *et al*. *Blood* 2020; 136 (Suppl 1): 24–26. Dimopoulos MA *et al*. *N Engl J Med* 2018; 378 (25): 2399–2410.

Zanubrutinib monotherapy in WM

Phase I/II study long-term follow-up (N=77)

- Zanubrutinib 160 mg twice daily (n=50) or 320 mg once daily (n=23)





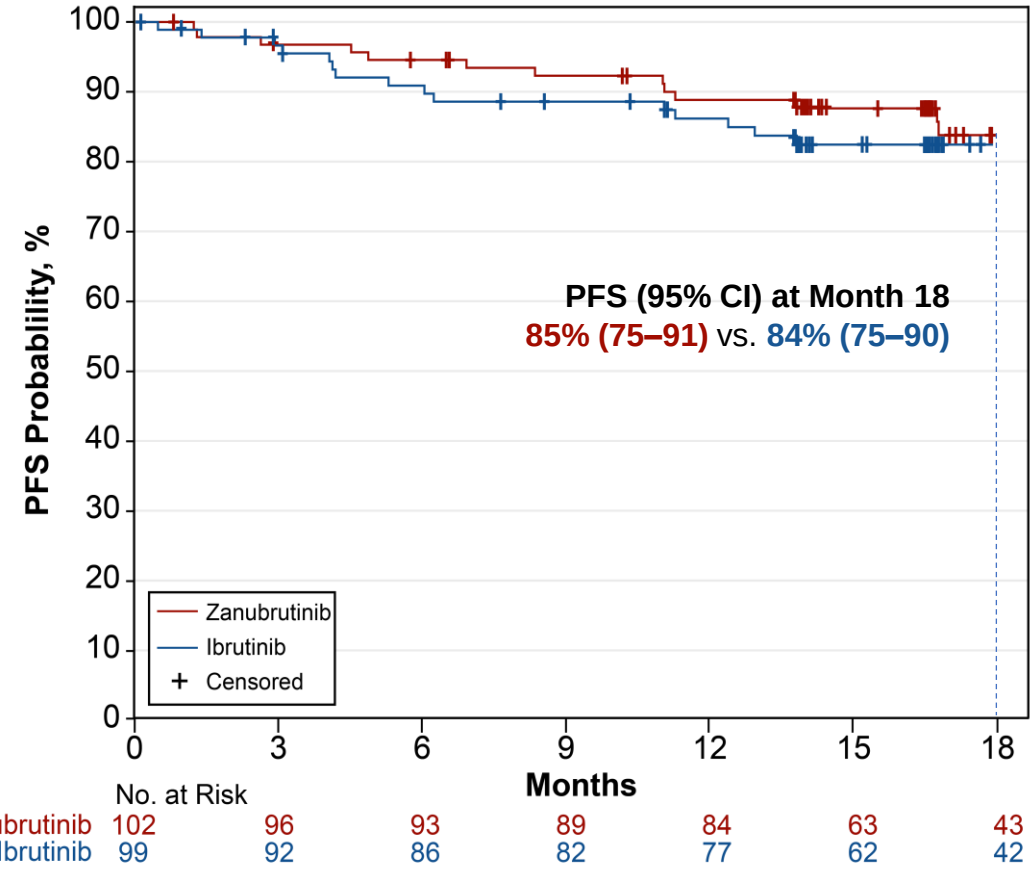
CR, complete response; *CXCR4*, C-X-C chemokine receptor type 4 gene; IgM, immunoglobulin M; MR, minimal response; *MYD88*, myeloid differentiation primary response 88 gene; PR, partial response; R/R, relapsed/refractory; TN, treatment-naïve; VGPR, very good partial response; WHIM, warts, hypogammaglobulinemia, infections, and myelokathexis; WM, Waldenström's macroglobulinemia; WT, wild-type.

Trotman J *et al*. *Blood* 2020; 136 (18): 2027–2037.

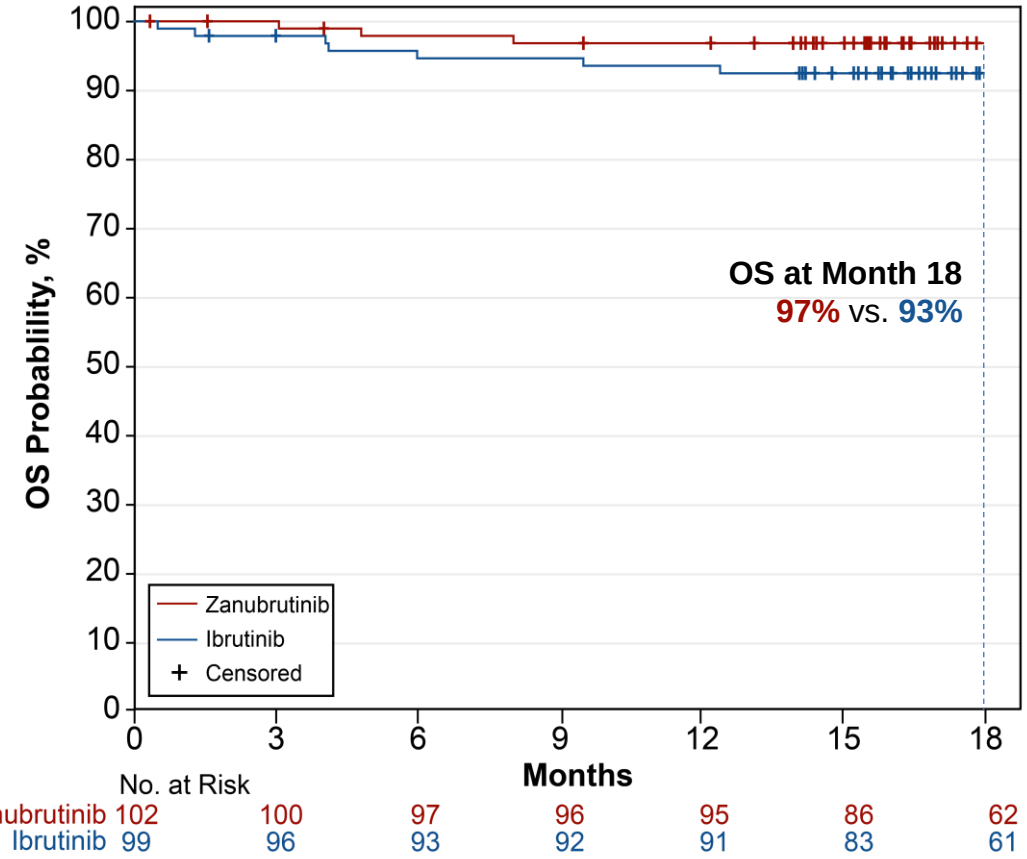
ASPEN Phase III study

Zanubrutinib vs. ibrutinib (N=201)

Progression-free survival



Overall survival



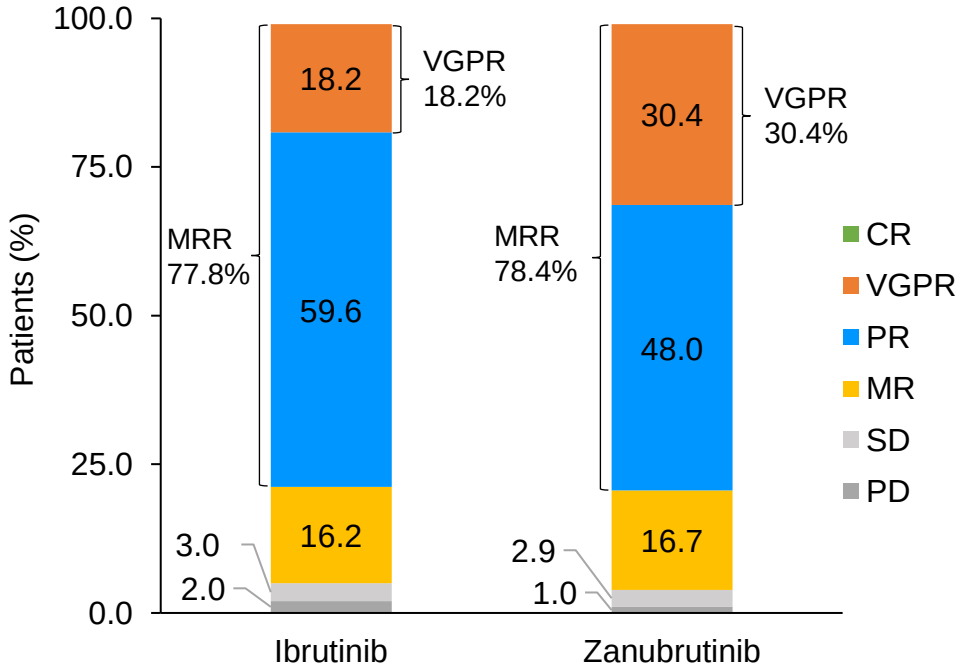
CI, confidence interval; PFS, progression-free survival; OS, overall survival.

Tam CS *et al*. *Blood* 2020; 136 (18): 2038–2050; Tam CS *et al*. Oral presentation at the 2020 American Society of Clinical Oncology (ASCO) Annual Meeting; May 29–31, 2020.

ASPEN Phase III study

Zanubrutinib vs. ibrutinib (N=201)

Investigator-assessed response*



CR + VGPR rate difference, 13.2† (1.4–25.1)

***P* = 0.0302**

Category, n (%)	Overall	
	Ibrutinib (n=98)	Zanubrutinib (n=101)
Patients with ≥1 AE	97 (99.0)	98 (97.0)
Grade ≥3	62 (63.3)	59 (58.4)
Serious	40 (40.8)	40 (39.6)
AE leading to death	4 (4.1)	1 (1.0)
AE leading to treatment discontinuation	**9 (9.2)**	**4 (4.0)**
Atrial fibrillation/flutter	**15 (15.3)**	2 (2.0)

*January 2020 data cut-off. †Adjusted for stratification factors and age group. *P*-value is for descriptive purposes only.
AE, adverse event; CI, confidence interval; CR, complete response; MR, minor response; MRR, major response rate; PD, progressive disease; PFS, progression-free survival; PR, partial response; PT, preferred term; SD, stable disease; VGPR, very good partial response.
Tam CS *et al*. Oral presentation at the 2020 American Society of Clinical Oncology (ASCO) Annual Meeting; May 29–31, 2020.

Conclusions

New ‘non-chemo’ regimens are alternative first-line options for appropriate patients

- Acceptable safety profiles
- Clinical efficacy proven in consistent results from multicenter clinical studies
- Capability to individualize therapy according to patient risk factors, genotype, comorbidities, and expected adverse reactions
- Pharmacoeconomic issues will become less relevant with time

Should chemotherapy-free regimens play a greater role when initiating treatment for WM? No

Prof. Véronique Leblond
Pitié-Salpêtrière Hospital, Paris, France

Factors in selection of first-line treatment in WM

- Patient characteristics
  - Age
  - Comorbidities[1,2]
    - >65y: 25% >2 comorbidities, 21% hypertension, 13% cardiovascular disease
    - Performance status is more relevant than age
- Disease characteristics
  - Cytopenia, need for rapid control of the disease, bulky disease, neuropathy
- Genomic profile?
  - Mutations in *MYD88*, *CXCR4*, *TP53*
- Drug availability and coverage based on respective national and/or institutional guidelines

Mean number of comorbidities in older patients with cancer

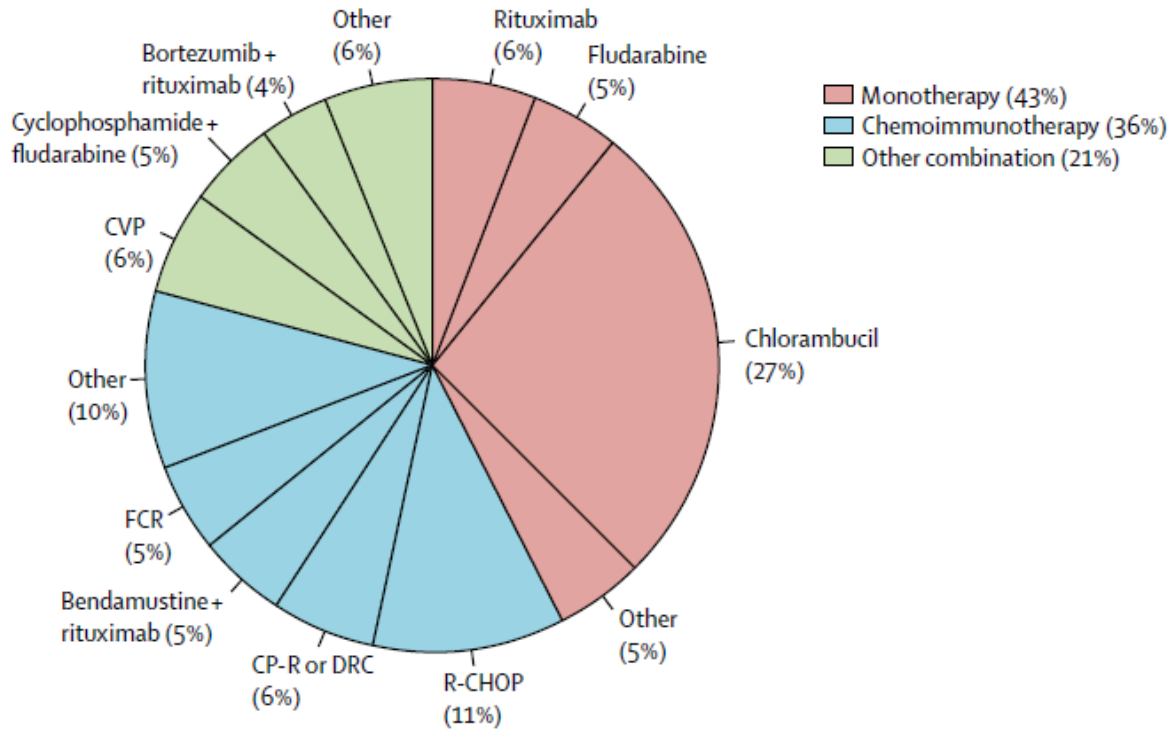
Age (years)	Patients (%)[3]	Comorbidities (mean number)[4]
≤ 54	11	N/A
55–64	19	2.9
65–74	27	3.6
75+	43	4.2

CXCR4, C-X-C chemokine receptor type 4 gene; MYD88, myeloid differentiation primary response 88 gene; N/A, not available; TP53, tumor protein P53 gene; WM, Waldenström's macroglobulinemia.

1. Stauder R et al. Ann Oncol 2017; 28 (2): 218–227. 2. Goede V et al. Haematologica 2014; 99 (6): 1095–1100. 3. Ries LA et al., editors. SEER CSR, 1975–2000. Bethesda (MD): National Cancer Institute; 2003. 4. Yancik R. Cancer 1997; 80 (7): 1273–1283.

Immunochemotherapy is a frequent option in Europe and is still an option in WM therapy guidelines

Front-line treatment choices in European patients with WM[1]



- Immunochemotherapy regimens are recommended as first-line options by both the ESMO and Mayo Clinic guidelines[2,3]
- IWWM-10 preferred options are[4]:
  - Bendamustine plus rituximab
  - Bortezomib, dexamethasone, and rituximab
  - Cyclophosphamide, dexamethasone, and rituximab
  - Ibrutinib (with or without rituximab)

CP-R, cyclophosphamide, prednisone, and rituximab; CVP, cyclophosphamide, vincristine, and prednisone; DRC, dexamethasone, rituximab, and cyclophosphamide; ESMO, European Society for Medical Oncology; FCR, fludarabine, cyclophosphamide, and rituximab; IWWM-10, 10th International Workshop on Waldenström's macroglobulinemia; R-CHOP, rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone; WM, Waldenström's macroglobulinemia.

1. Buske CB et al. Lancet Haematol. 2018 Jul;5(7):e299-e309. 2. Kastritis E et al., Ann Oncol 2018; 29:41–50. 3. Kapoor P et al., JAMA Oncol. 2017; 3(9): 1257–1265.
4. Castillo JJ et al., Lancet Haematol 2020; 11: e827–e837.

Immunochemotherapy is effective, with manageable toxicity and a fixed duration of treatment

Study	Agents	N (TN/RR)	ORR	MRR	VGPR	CR	PFS
Buske *et al*. 2009[1]	CHOP	25 (25/0)	60%	NR	NR	NR	Median: 22 months
	R-CHOP	23 (23/0)	91%	NR	NR	NR	Median: 63 months
Dimopoulos *et al*. 2007[2]	Cyclophosphamide Dexamethasone Rituximab	72 (72/0)	83%	74%	NR	7%	Median: 35 months
Rummel *et al*. 2013[3]	Bendamustine Rituximab	19 (19/0)	NR	NR	NR	NR	Median: 70 months
	R-CHOP	22 (22/0)	NR	NR	NR	NR	Median: 28 months
Laribi *et al*. 2019[4]	Bendamustine Rituximab	69 (69/0)	97%	96%	37%	19%	Median not reached: 87% at 2 years
Rummel *et al*. 2019[5]	Bendamustine Rituximab	257 (257/0)	92%	88%	4%	NR	Median: 65 months

CHOP, cyclophosphamide, doxorubicin, vincristine, and prednisone; CR, complete response; MRR, major response rate; NR, not reported; ORR, overall response rate; PFS, progression-free survival; R-CHOP, rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone; RR, relapsed/refractory; TN, treatment-naive; VGPR, very good partial response.

1. Buske C et al. Leukemia, 2009; 23(1):153–61. 2. Dimopoulos MA et al. J Clin Oncol 2007; 25: 3344–3349. 3. Rummel MJ et al. Lancet 2013; 381: 1203–1210. 4. Laribi K et al. Br J Haematol 2019; 186(1): 146–149. 5. Rummel MJ et al. Blood 2019; 134: 343.

Other chemotherapy-free options with a fixed duration regimen are often less effective and need more out-patient visits

- Rituximab with a proteasome inhibitor is another chemo-free option
- Rituximab could be used as a single agent in anti-MAG neuropathy, cryoglobulinemia or very frail WM

Study	Agents	N (TN/RR)	ORR	MRR	VGPR	CR	PFS
Ghobrial *et al*.[1]	Bortezomib Rituximab	26 (26/0)	88%	65%	4%	4%	Median not reached: 75% at 12 months
Treon *et al*.[2]	Bortezomib Dexamethasone Rituximab	23 (23/0)	96%	83%	13%	13%	Median: 66 months
Dimopoulos *et al*.[3]	Bortezomib Dexamethasone Rituximab	59 (59/0)	85%	68%	7%	3%	Median: 42 months
Castillo *et al*.[4]	Ixazomib Dexamethasone Rituximab	26 (26/0)	96%	77%	15%	NR	Median not reached at 22 months
Treon *et al.*[5]	Carfilzomib Dexamethasone Rituximab	31 (31/0)	87%	68%	35%	NR	Median: 44 months
Gertz *et al*.[6]	Rituximab monotherapy	69 (34/35)	53%	35%	0%	0%	Median: 23 months
Treon *et al*.[7]		29 (12/17)	66%	48%	0%	0%	Median: 14 months
Dimopoulos *et al*.[8]		75 (34/41)	47%	32%	4%	1%	Median: 20 months

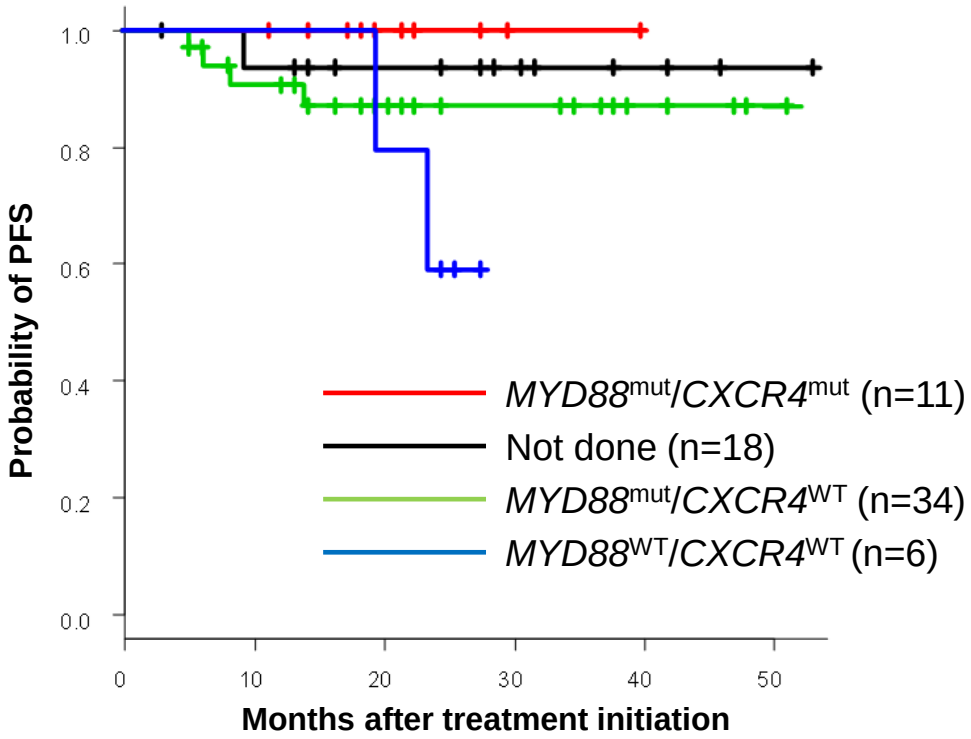
CR, complete response; MAG, myelin-associated glycoprotein; MRR, major response rate; NR, not reported; ORR, overall response rate; PFS, progression-free survival; RR, relapsed/refractory; TN, treatment-naïve; VGPR, very good partial response; WM, Waldenström's macroglobulinemia.

1. Ghobrial IM et al. Am J Hematol 2010; 85: 670–4. 2. Treon SP et al. J Clin Oncol 2009; 27(23): 3830–5. 3. Dimopoulos MA et al. Blood 2013; 122: 3276–82. 4. Castillo JJ et al. Clin Cancer Res 2018; 24: 3247–52.
5. Treon SP et al. Blood 2014; 124: 503–10. 6. Gertz MA et al. Leuk Lymphoma 2004; 45: 2047-–2055. 7. Treon SP et al. Ann Oncol 2005; 16: 132–138.
8. Dimopoulos MA et al. N Engl J Med 2018; 378: 2399–2410.

CXCR4 mutational status

No impact on PFS with bendamustine–rituximab unlike ibrutinib

PFS with bendamustine-rituximab is not influenced by *CXCR4* mutational status in TN WM[1]



CXCR4 mutations are associated with a longer median time to major response with ibrutinib in TN WM[2]

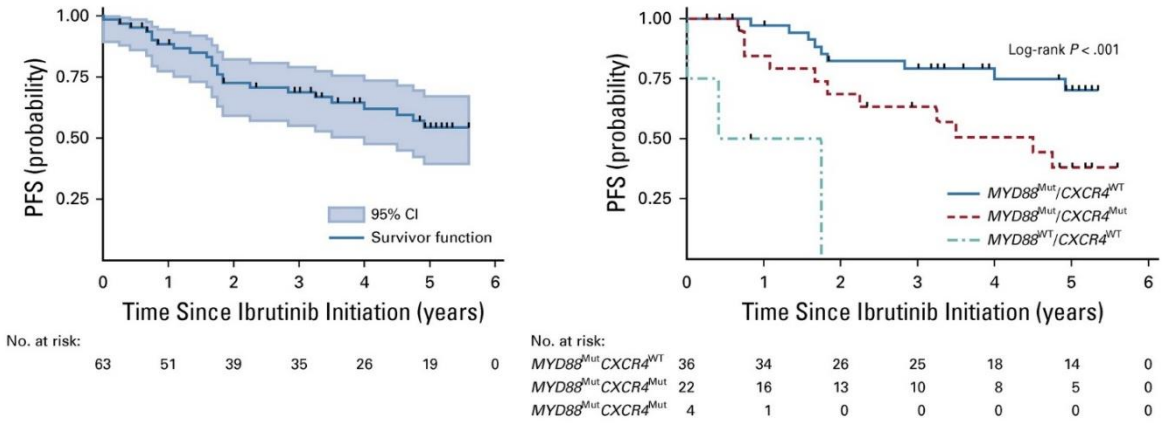
Response rate	All patients (n=30)	*MYD88*^{L265P} *CXCR4*^{WT} (n=16)	*MYD88*^{L265P} CXCR4^{mut} (n=14)	*P*-value
ORR (%)	100	100	100	NS
MRR (%)	83	94	71	NS
Median time to minor response or better (months)	1.0	0.9	1.7	NS
Median time to major response (months)	1.9	1.8	7.3	0.01

CXCR4, C-X-C chemokine receptor type 4 gene; MRR, major response rate; mut, mutated; MYD88, myeloid differentiation primary response 88 gene; NS, not significant; ORR, overall response rate; PFS, progression-free survival; TN, treatment-naïve; WM, Waldenström's macroglobulinemia; WT, wild-type. 1. Laribi et al. Br J Haematol 2019; 186: 146–149. 2. Treon et al., J Clin Oncol 2018; 36: 2755–2761.

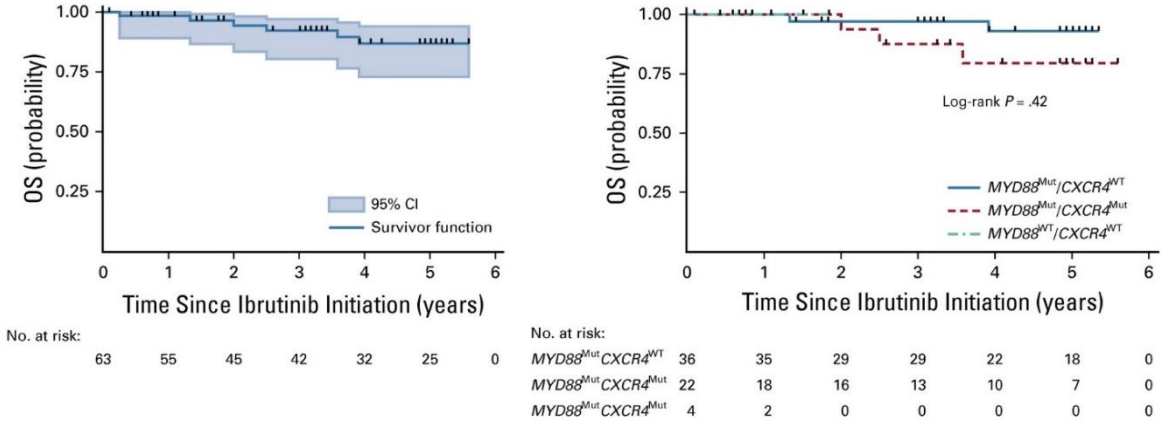
MYD88/CXCR4 mutational status

Impact on survival in R/R patients treated with ibrutinib monotherapy

PFS



OS



CI, confidence interval; CXCR4, C-X-C chemokine receptor type 4 gene; mut, mutated; MYD88, myeloid differentiation primary response 88 gene; OS, overall survival; PFS, progression-free survival; R/R, relapsed/refractory; WT, wild-type.

Treon SP et al. J Clin Oncol 2020; 15;JCO2000555.

Emergence of resistance described with BCR signaling inhibitors

- Genetic and non-genetic mechanisms of resistance to BCR signaling inhibitors have been described in B-cell malignancies[1]
- Mutations in BTK, PLCγ2, and CARD11 are associated with resistance to ibrutinib[2]

Targeted deep sequencing of *BTK*, *PLCγ2*, and *CARD11* reveals acquired mutations associated with progression on ibrutinib in WM[2]

Patient	*BTK Cys481Arg (T>C)*	*BTK Cys481Ser (T>A)*	*BTK Cys481Ser (G>C)*	*BTK Cys481Tyr (G>A)*	*PLCγ2 Tyr495His (T>C)*	*CARD11 Leu878Phe (C>T)*
WM1	ND	ND	ND	ND	ND	ND
WM2	32.4%	6.6%	5.8%	1.0%	ND	ND
WM3	0.3%	34.4%	6.5%	0.3%	ND	0.2%
WM4	ND	ND	ND	ND	ND	ND
WM5	ND	ND	ND	ND	ND	ND
WM6	ND	ND	10.3%	ND	11.9%	ND
WM7	ND	ND	1.5%	ND	ND	ND
WM8	ND	ND	0.7%	ND	ND	ND

BCR, B-cell receptor, BTK, Bruton's tyrosine kinase gene; CARD11, caspase recruitment domain family member 11 gene; PLCγ2, phosphoinositide-specific phospholipase C gene; ND, not detected; WM, Waldenström's macroglobulinemia.

1. Ondrisova L et al. Front. Oncol. 2020; 10.3389/fonc.2020.591577. 2. Xiu L et al. Blood 2017; 129(18): 2519–2525.

Is the risk of secondary malignancies higher with immunochemotherapy?

- The incidence of secondary malignancies in WM is likely to be multifactorial in the immunochemotherapy era:[1,2,3]
  - Age
  - Genetic predisposition
  - Treatment exposure
  - Immune dysfunction
- The risk of SMs was significantly higher for patients younger than 65 years (MP-SIR, 2.24; 95% CI, 1.88–2.65) vs. those who were older (MP-SIR, 1.37; 95% CI, 1.26–1.49)[4]
  - This difference was significant for solid tumors (MP-SIR for younger patients, 1.63 [95% CI, 1.31–2.00][4]
- An Italian study reported the risk of secondary **hematologic malignancies** to be 4- to 5-fold higher in treated versus untreated patients[5,6]
- The study size was small and the results were not significant for the risk of SM for patients who received chemotherapy alone as first-line treatment and treatment naïve patients[6]

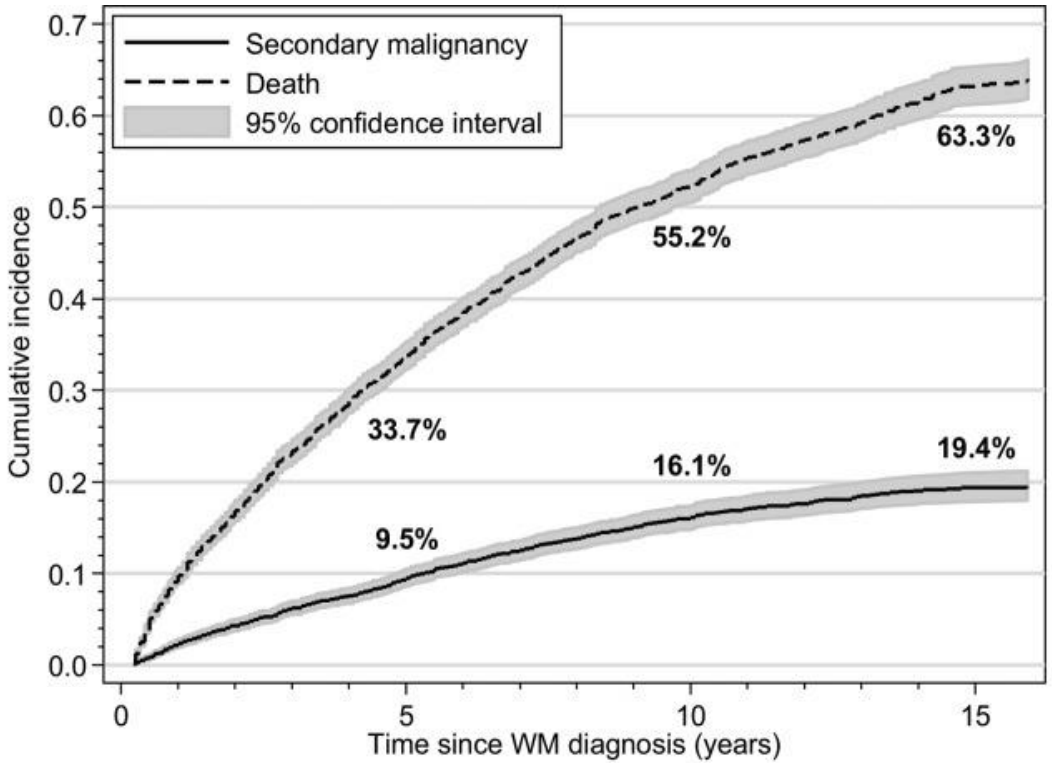
CI, confidence interval; MP-SIR, multiple primary standardized incidence ratio; SM, secondary malignancy; WWM, Waldenström's macroglobulinemia.

1. Treon SP et al. Ann Oncol. 2006; 17: 488–494. 2. Ojha RP et al. Cancer Epidemiol. 2012; 36: 294–297. 3. Greene et al. J Natl Cancer Inst. 1978; 61(2): 337–40.
4. Castillo JJ et al. Cancer 2015; 121 (13): 2230–2236. 5. Morra et al. Clin. Lymphoma Myeloma Leuk. 2013; 13(6): 700–703. 6. Varettoni M et al. Ann Oncol. 2012; 23: 411–415.

Is the risk of secondary malignancies higher with immunochemotherapy?

- Among 4676 patients with WM, 681 SMs were recorded[1]
  - SIR was 1.49 (95% CI: 1.38–1.61), and the median time to an SM was 3.7 years[1]
  - The cumulative incidence of SMs was 10% at 5 years and 16% at 10 years[1]
- Patients with CLL treated with BTKis had an observed over expected rate of SM of 2.2 (95% CI: 1.7–2.9) and remained at increased risk for SMs[2]
- Similar outcomes observed in other CLL studies
  - Large-scale, single-center study before BTKis use[3]
  - Patients treated with FCR (SIR: 2.4)[4]

Cumulative incidence of SMs and competing events (death) among patients with WM[1]



BTKi, Bruton's tyrosine kinase inhibitor; CI, confidence interval; CLL, chronic lymphocytic leukemia; FCR, fludarabine, cyclophosphamide, and rituximab; SIR, standardized incidence ratio; SM, secondary malignancy; WM, Waldenström's macroglobulinemia.

1. Castillo JJ et al. Cancer 2015; 121: 2230–2236. 2. Bond DA et al: Leukemia 2020; 34: 3197–3205. 3. Benjamini O et al. Leuk Lymphoma. 2015; 56(6): 1643–1650.
4. Tsimberidou A-M et al. J Clin Oncol 2009; 27(6): 904–910.

Conclusions

- Immunochemotherapy remains a good first-line option for the majority of patients
  - Relatively long duration of PFS and a short duration of treatment-related side effects
  - Selection of resistant clones may be less of an issue than for targeted therapy
- Risk of SMs
  - Difficult to separate treatment-related effects from other factors in retrospective studies
  - More data needed on the long-term effect of treatment with BCR inhibitors
- No consensus on the recommendations for fixed duration regimens (DRC, or bendamustine plus rituximab, or BDR) or indefinite duration regimens (ibrutinib, or ibrutinib plus rituximab, or zanubrutinib*) in first-line treated patients
- Lack of consensus because of the absence of prospective randomized trials comparing immunochemotherapy to BTK inhibitors that include cost-effectiveness evaluations

*Not approved for use outside of the United States and China.
BCR, B-cell receptor; BDR, bortezomib, dexamethasone, and rituximab; BTK, Bruton's tyrosine kinase; DRC, dexamethasone, rituximab, and cyclophosphamide; PFS, progression-free survival; SM, secondary malignancy.

Should chemotherapy-free regimens play a greater role when initiating treatment for WM?

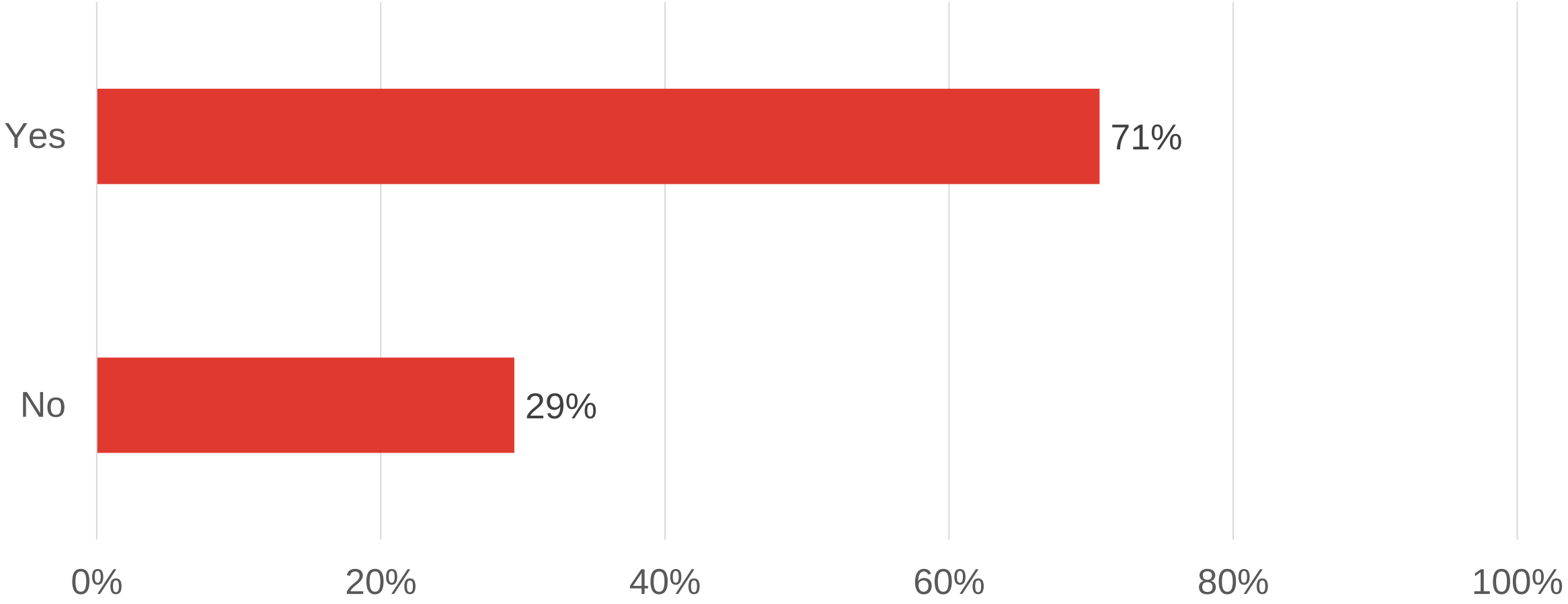
A Yes

B No

Please vote now!

WM, Waldenström's macroglobulinemia.

2. Which tests are essential at this point?



N=17

Talk to the experts: What challenges do you face in treating WM?

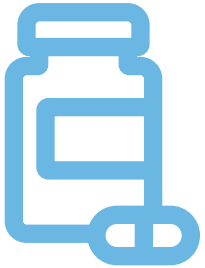
Moderator: Prof. Véronique Leblond
Panel: All

Summary

Chair: Prof. Véronique Leblond

Summary

Fixed-duration, immunochemotherapy regimens remain a good option for first-line therapy in the majority of patients with WM.



Chemotherapy-free regimens provide an effective alternative option for patients who are unsuitable for immunochemotherapy due to factors such as fitness, comorbidities, and polypharmacy.

Therapeutic decisions should reflect not only disease-relevant patient characteristics but also the patient's wider circumstances.

WM, Waldenström's macroglobulinemia.

Save the date!

Relapsed/refractory Waldenström's macroglobulinemia: Key considerations for managing pre-treated patients

Join us in **March 2021** for the third installment in the BeiGeneius webinar series in which we will explore the practical aspects of treatment of patients with relapsed and refractory WM

WM, Waldenström's macroglobulinemia.

We would appreciate your feedback!

Please complete the post-meeting survey.

Thank you for your attention