¿Cuál es la opción óptima para el tratamiento inicial de la macroglobulinemia de Waldenström?

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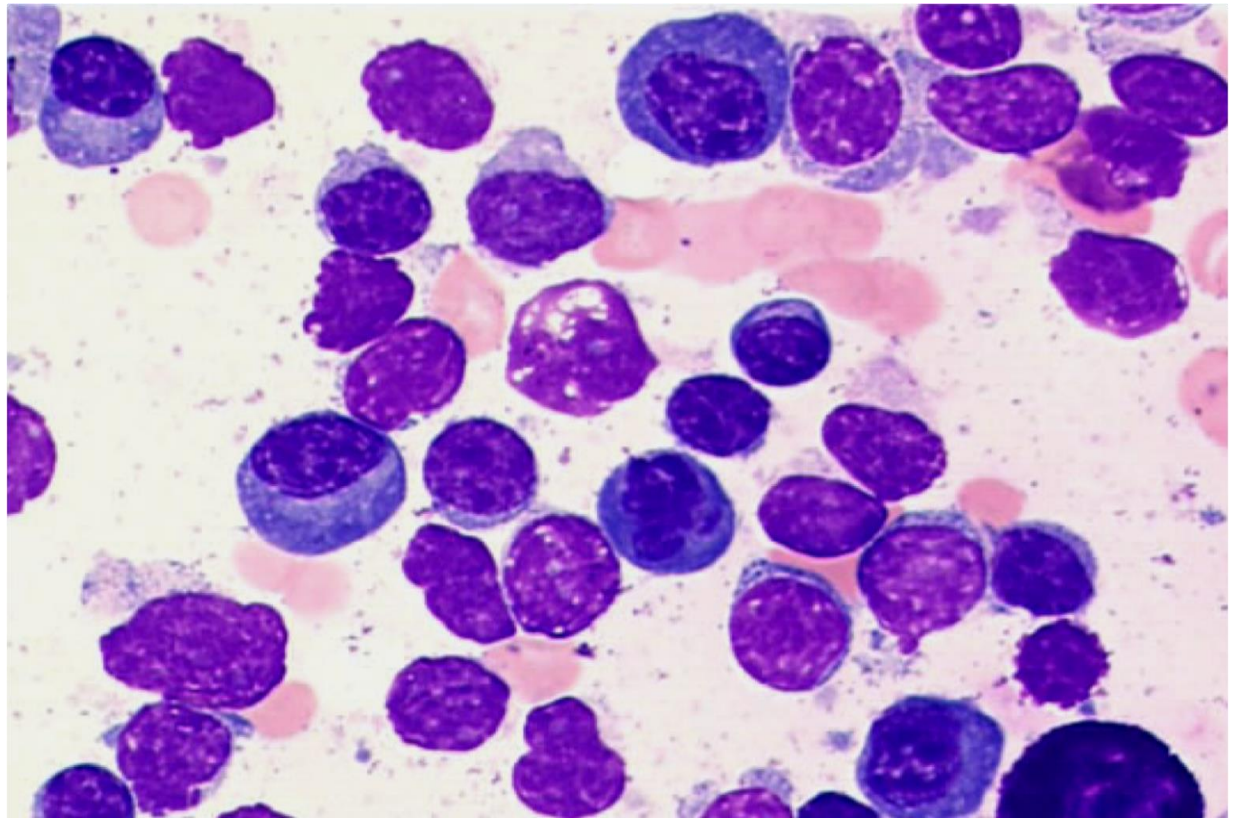
Dana-Farber
Cancer Institute

Disclosures

Company	Research	Employee	Consultant	Stockholder	Speaker's Bureau	Scientific Advisory Board
AbbVie	X					X
AstraZeneca			X			
BeOne	X					X
Cellectar	X					X
Johnson & Johnson			X			
LOXO	X					
Nurix			X			
Pharmacyclics	X					X
Schrodinger			X			

Diagnostic criteria

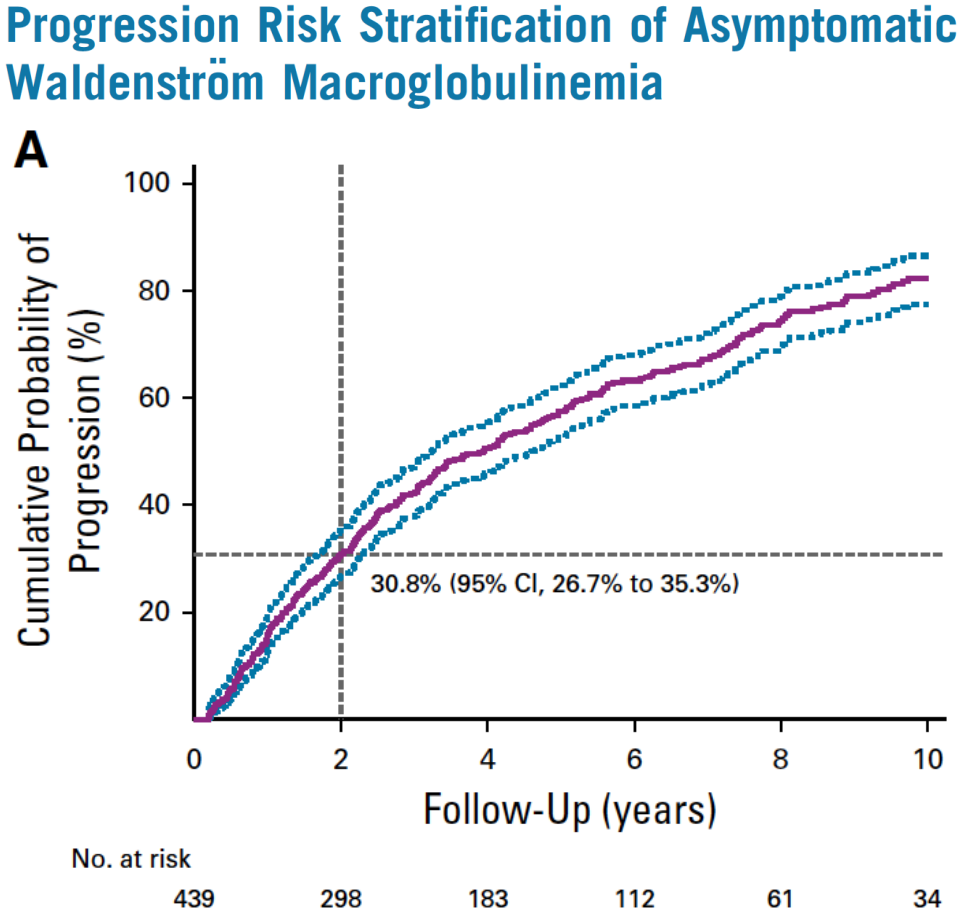
1. IgM monoclonal protein in serum protein electrophoresis and immunofixation
2. Lymphoplasmacytic lymphoma in the bone marrow
3. *MYD88 L265P* mutation by AS-PCR or NGS



Alaggio et al. Leukemia 2022; ASH Image Bank 2022

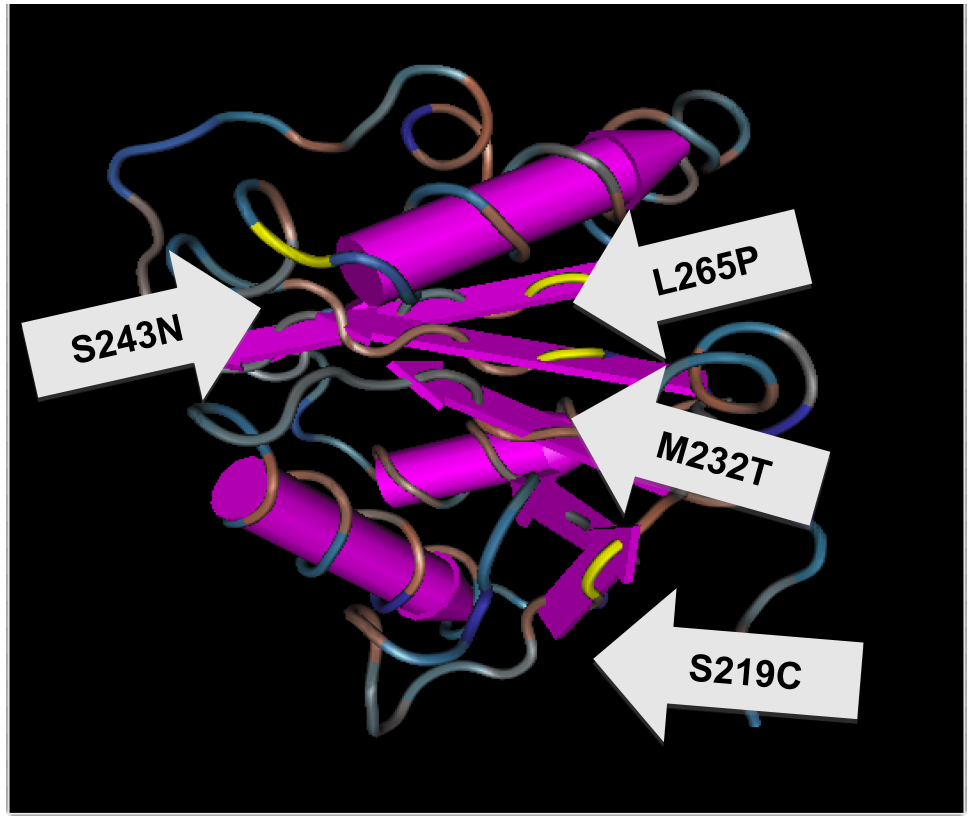
Why not treat everybody at diagnosis?

- WM is incurable
- Treatment promotes resistance
- Treatment comes with toxicity
- No evidence that treating early prolongs survival
- WM patients enjoy decades of life



Bustoros et al. JCO 2019

MYD88 mutations

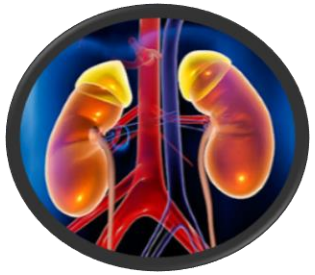


2% non-L265P MYD88 mutations

Treon et al. N Engl J Med 2012
Xu et al. Blood 2013

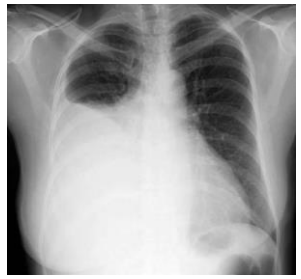
Study	Method	%
Xu	AS-PCR	93%
Gachard	PCR	70%
Varettoni	AS-PCR	100%
Landgren	Sanger	90%
Jimenez	AS-PCR	86%
Poulain	PCR	80%
Argentou	PCR-RFLP	92%
Willenbacher	Sanger	86%
Mori	AS-PCR	80%
Ondrejka	AS-PCR	100%
Ansell	WES/AS-PCR	97%
Patkar	AS-PCR	85%
Cao	AS-PCR	92%
Giuliani	AS-PCR	95%
Riva	AS-PCR	89%

Manifestations of Waldenstrom Macroglobulinemia

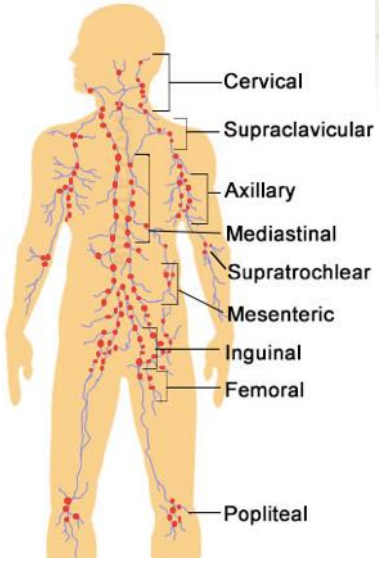


Renal involvement
(2-3%)

Bing Neel
Syndrome (1%)



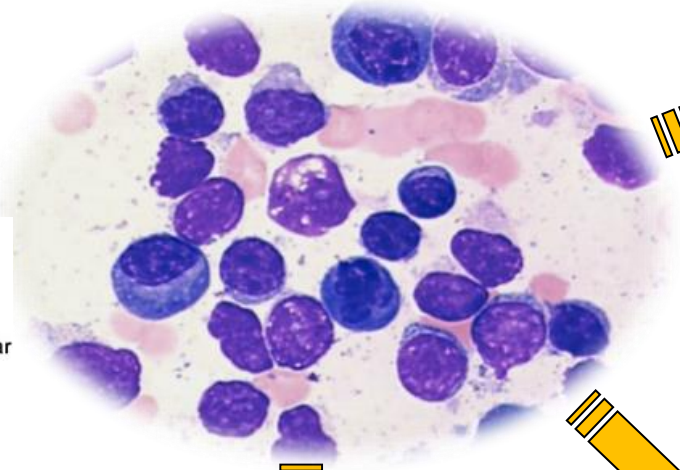
Pleural effusions
(1-2%)

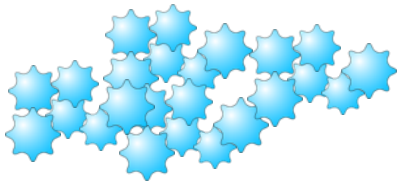


Extramedullary
disease (20-50%)

Bone Marrow

↓HB>> ↓PLT> ↓WBC





Hyperviscosity Syndrome (15%)
Epistaxis, Headaches
Impaired vision

IgM Neuropathy (20%)
Cryoglobulinemia (10%)
Cold Agglutinemia (5%)
AL amyloidosis (5%)

Hepcidin
↓Fe Anemia

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Adapted from Derman et al. ASCO Ed Book 2022

Rituximab combination regimens

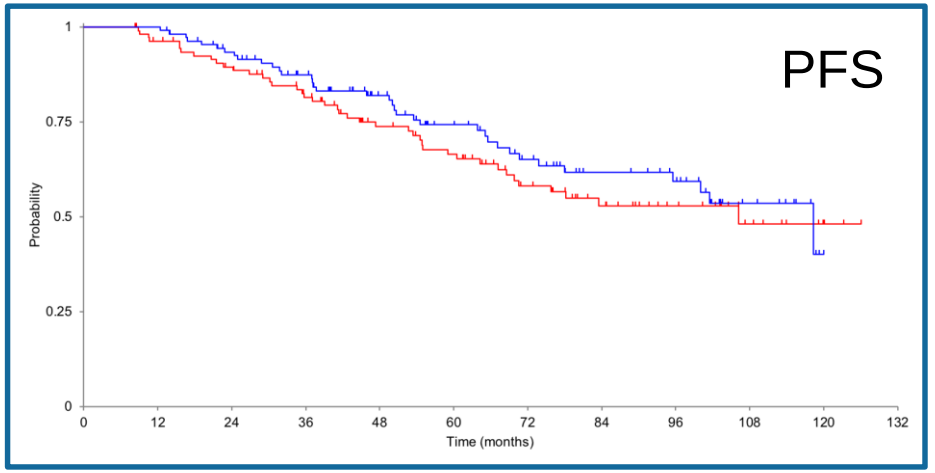
Regimen	n	ORR	Major	PFS (mo)
Cyclophosphamide-dex-R	72	83%	76%	35
Fludarabine-R	43	95%	86%	51
Bendamustine-R	69	97%	96%	69
Bortezomib-dex-R	59	85%	68%	42
Carfilzomib-dex-R	31	87%	68%	46
Ixazomib-dex-R	26	96%	77%	40

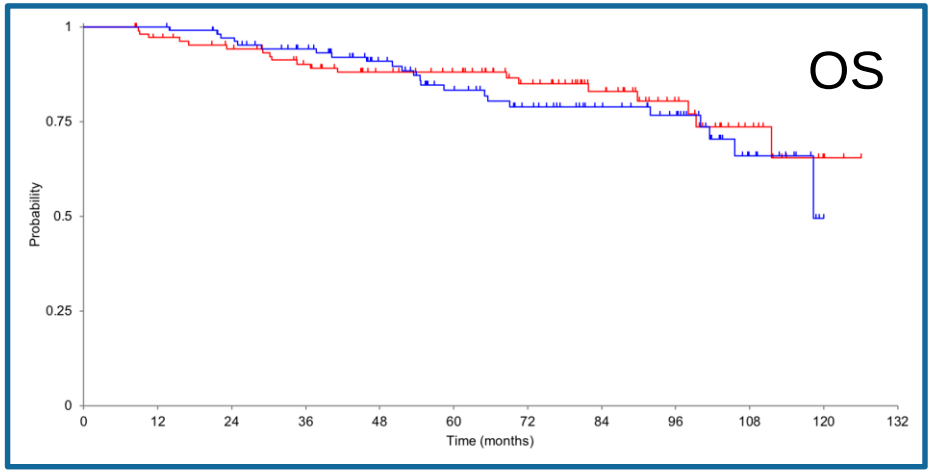
Dimopoulos et al. Blood 2014; Treon et al. Blood 2015; Laribi et al. Br J Haematol 2019; Dimopoulos et al. Blood 2013; Treon et al. Blood 2014; Castillo et al. Blood Adv 2022

Two years Rituximab maintenance versus observation after first line treatment with Bendamustine plus Rituximab in patients with Waldenström Macroglobulinemia

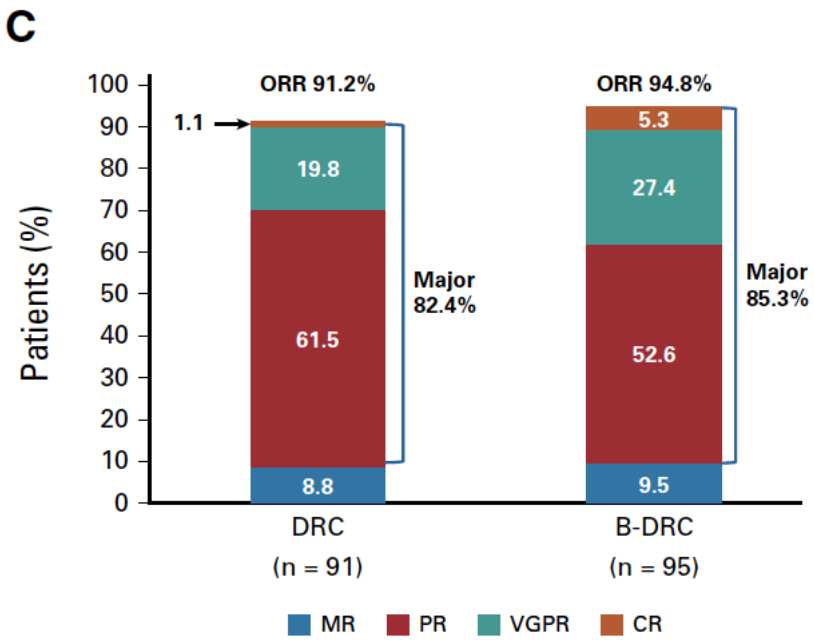
	All	R maint	Obs
Total (n)	218	109	109
Age (median)	66	67	65
Hemoglobin <11 g/dl	68%	64%	72%
IgM g/l (median)	32.7	32.7	31.3
β_2-Microglobulin	3.5	3.3	3.7
B-symptoms	34%	39%	29%

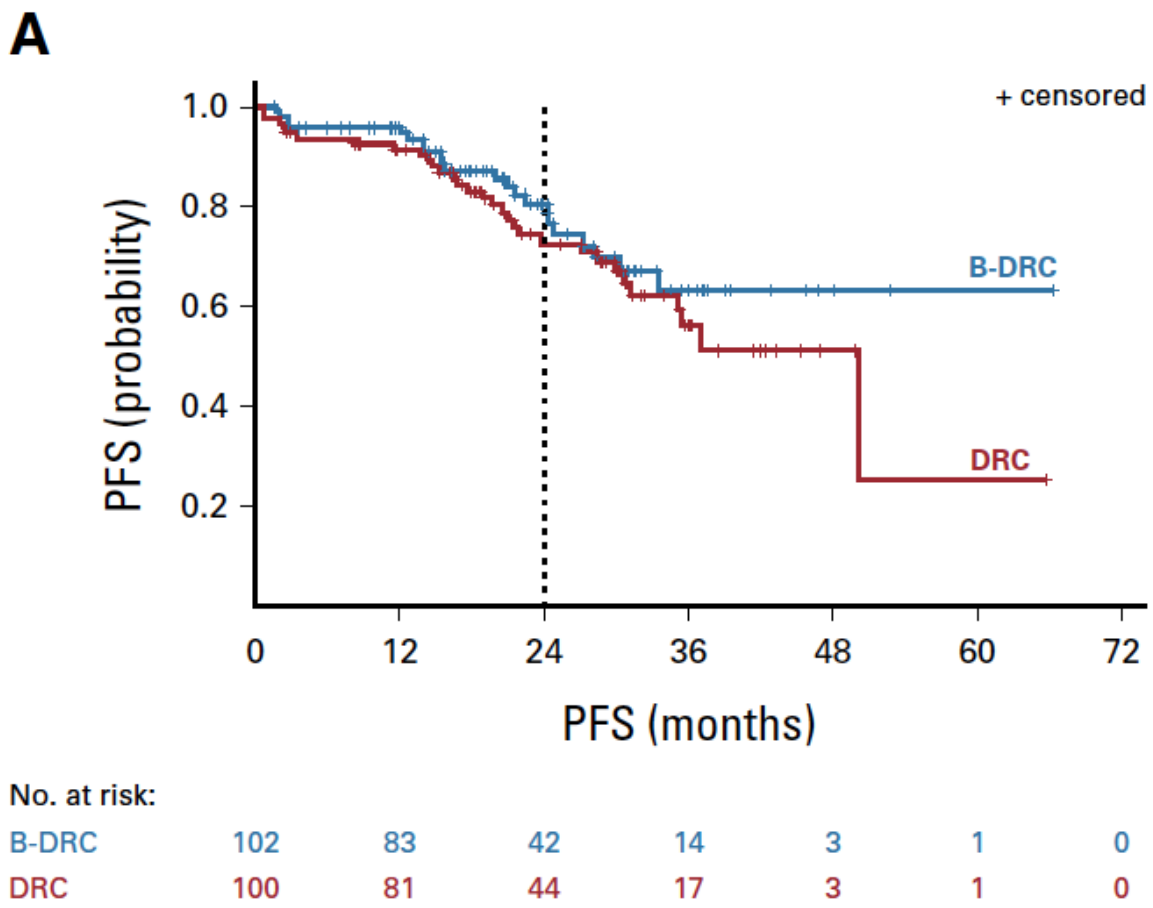
Rummel et al. ASH 2019





Bortezomib-Dexamethasone, Rituximab, and Cyclophosphamide as First-Line Treatment for Waldenström's Macroglobulinemia: A Prospectively Randomized Trial of the European Consortium for Waldenström's Macroglobulinemia





Buske et al. J Clin Oncol 2023

Bortezomib-Dexamethasone, Rituximab, and Cyclophosphamide as First-Line Treatment for Waldenström's Macroglobulinemia: A Prospectively Randomized Trial of the European Consortium for Waldenström's Macroglobulinemia

	DRC	B-DRC
Any AE	91%	92%
≥3 grade AE	49%	50%
Anemia	23%	21%
Neutropenia	28%	27%
Infections	15%	32%
≥3 grade infections	3%	4%
Neuropathy	3%	18%
≥ 3 grade neuropathy	0%	2%
Fever	5%	1%

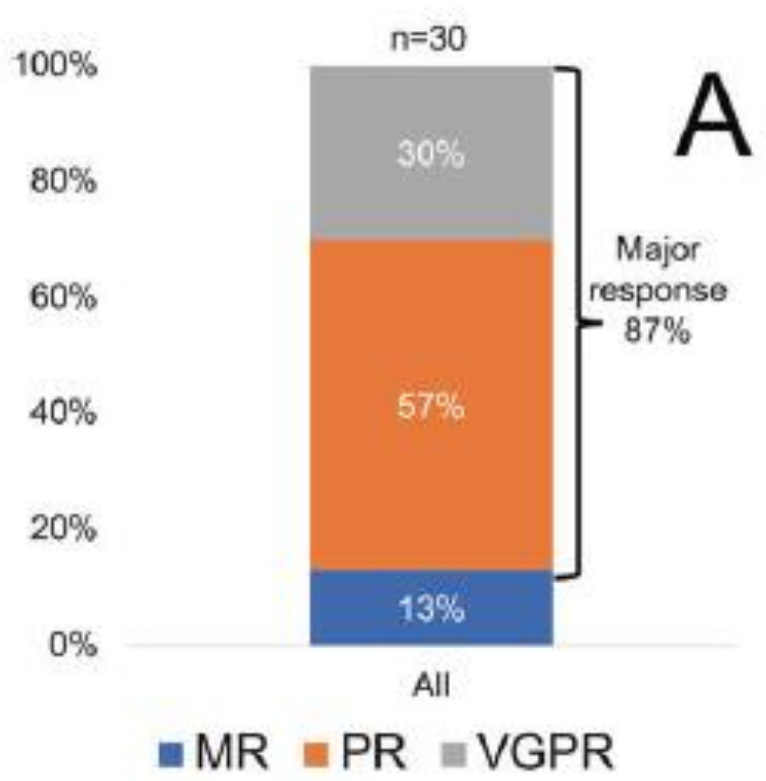
Buske et al. J Clin Oncol 2023

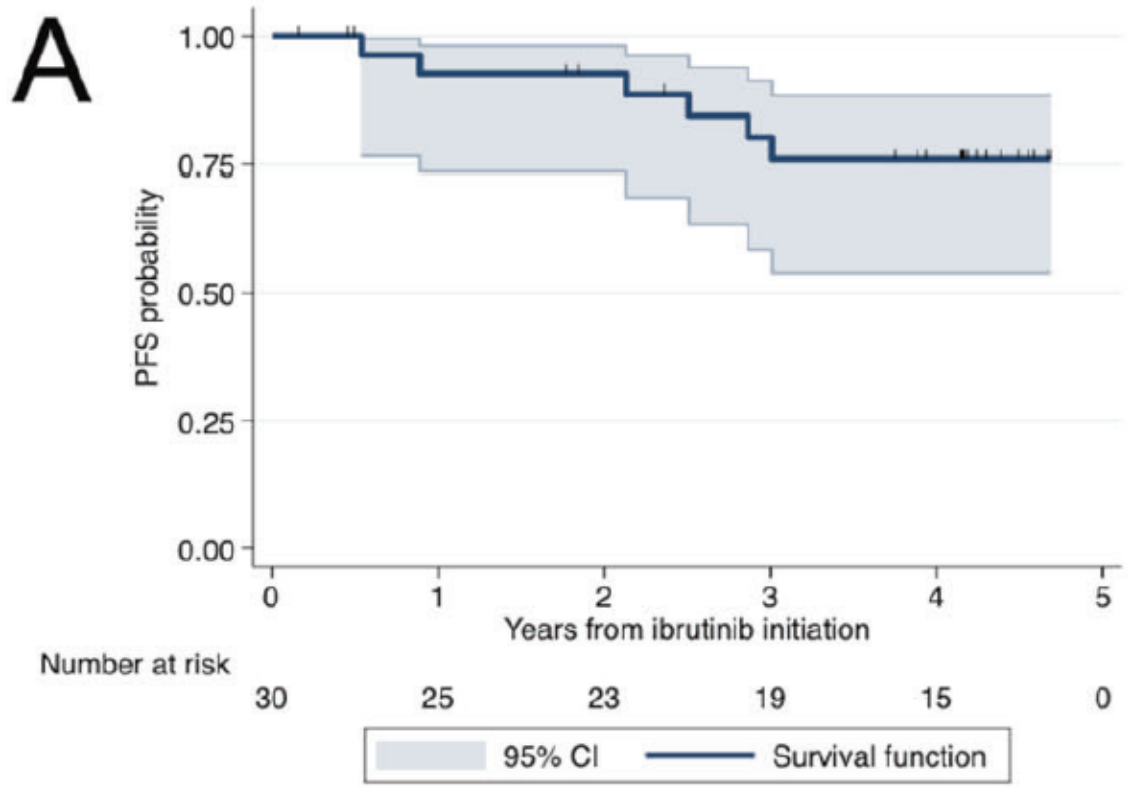
BTK inhibitors

Regimen	N	ORR	Major	PFS
Ibrutinib (TN)	30	100%	87%	76% at 4 years
Ibrutinib-R (INNOVATE)	75	91%	76%	68% at 4.5 years
Acalabrutinib	106	93%	80%	Median 68 months
Zanubrutinib (ASPEN)	101	94%	77%	78% at 42 months

Castillo et al. Leukemia 2022; Buske et al. J Clin Oncol 2022;
Owen et al. EHA 2022; Dimopoulos et al. J Clin Oncol 2023

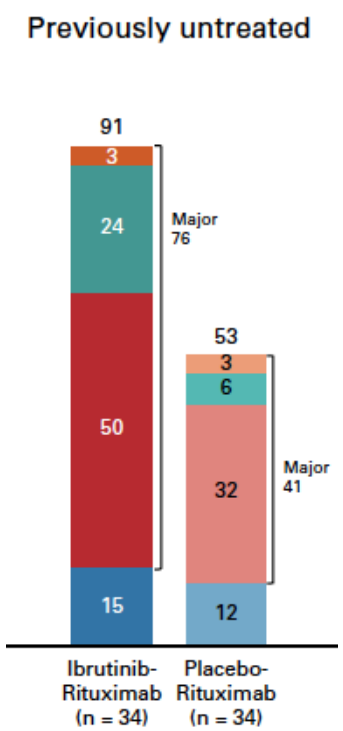
Long-term follow-up of ibrutinib monotherapy in treatment-naive patients with Waldenstrom macroglobulinemia

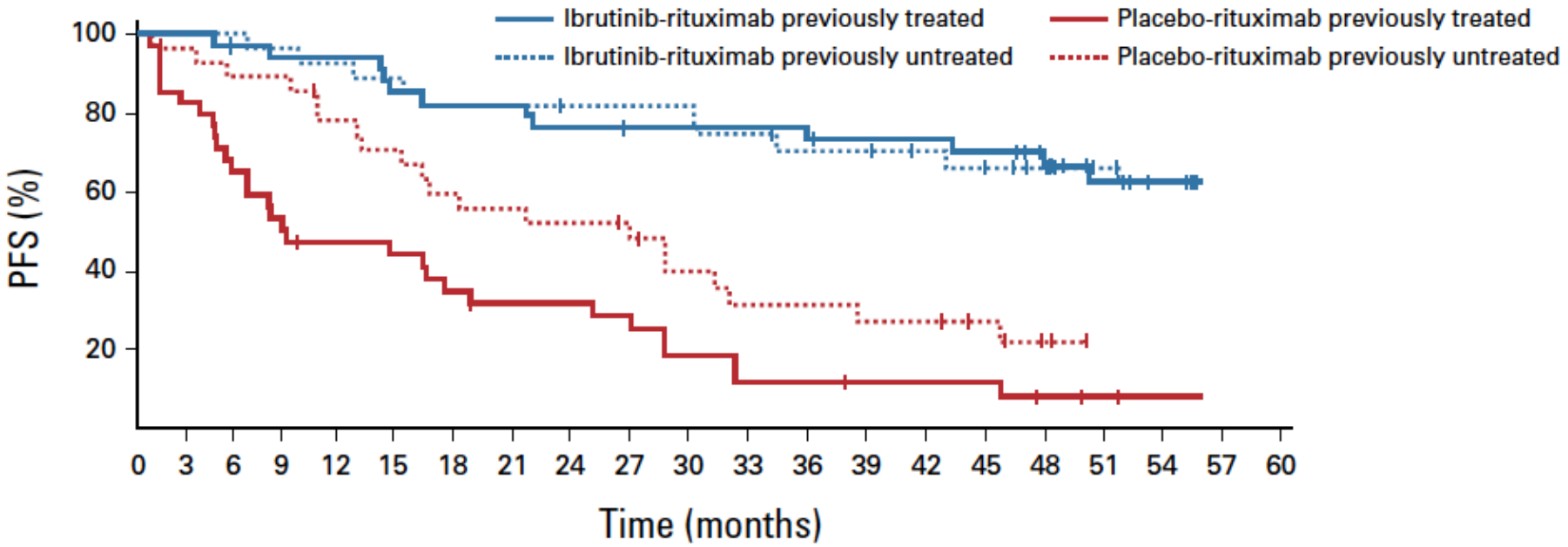




Castillo et al. Leukemia 2022

Ibrutinib Plus Rituximab Versus Placebo Plus Rituximab for Waldenström's Macroglobulinemia: Final Analysis From the Randomized Phase III iNNOVATE Study

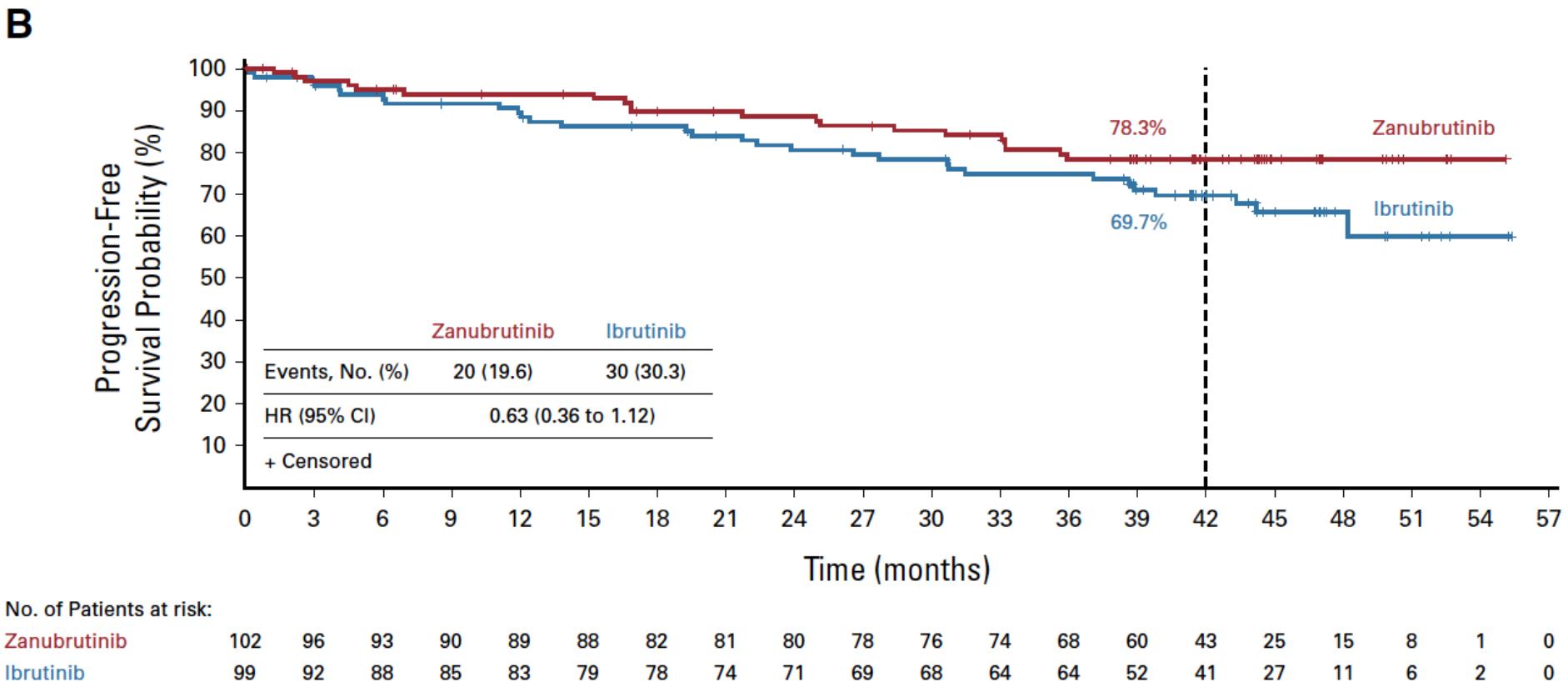




Buske et al. J Clin Oncol 2022

Zanubrutinib Versus Ibrutinib in Symptomatic Waldenström Macroglobulinemia: Final Analysis From the Randomized Phase III ASPEN Study

Data on TN patients were not reported



Dimopoulos et al. J Clin Oncol 2023

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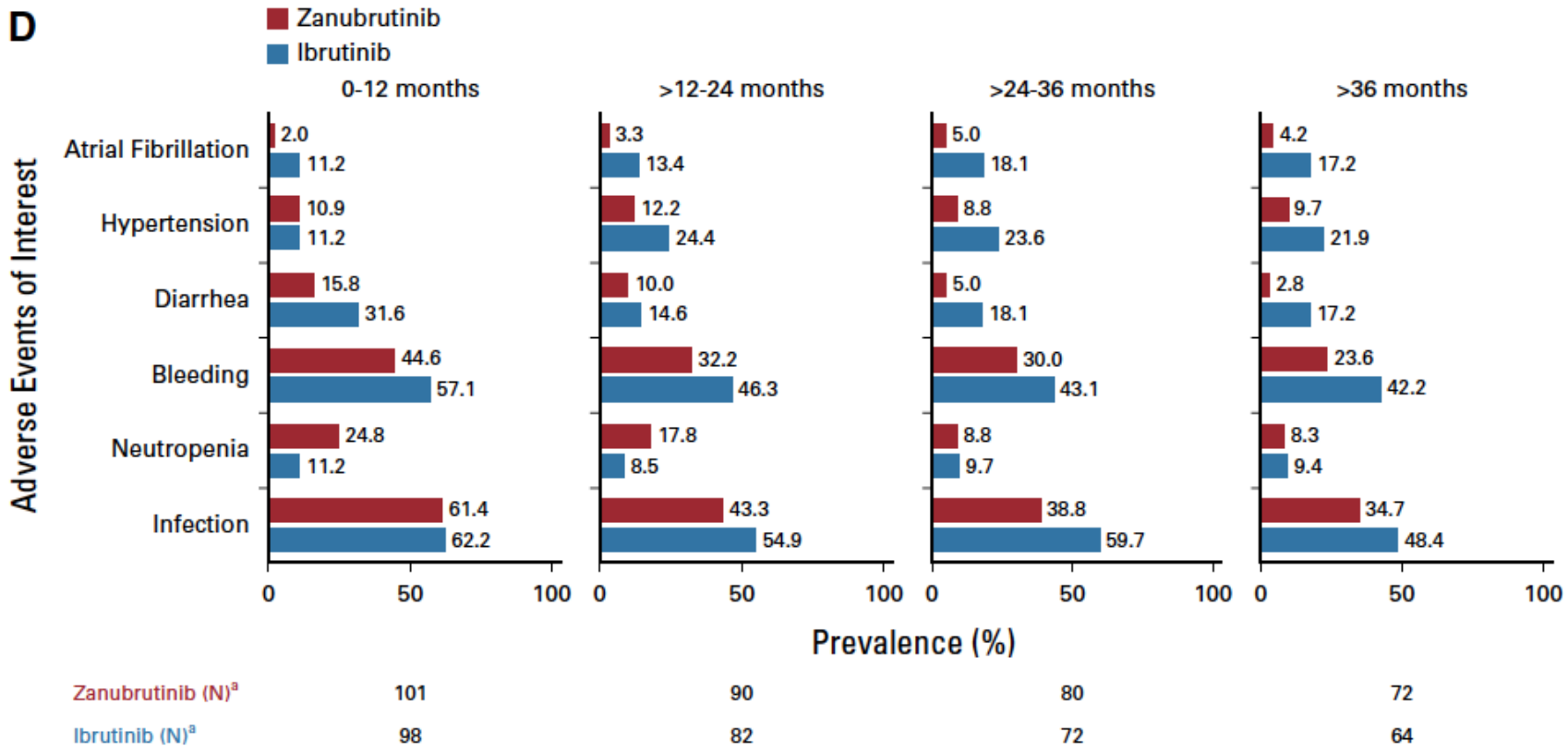
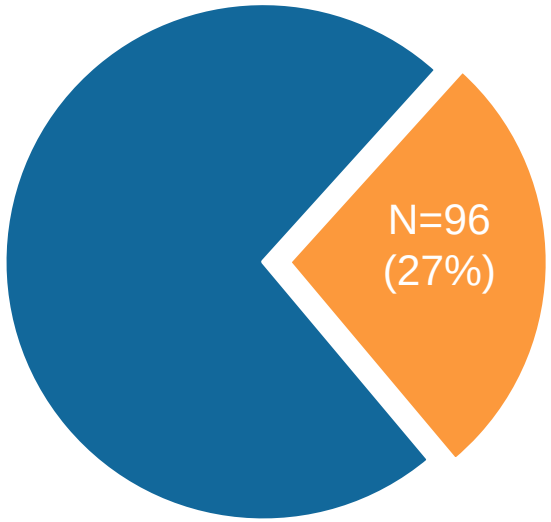
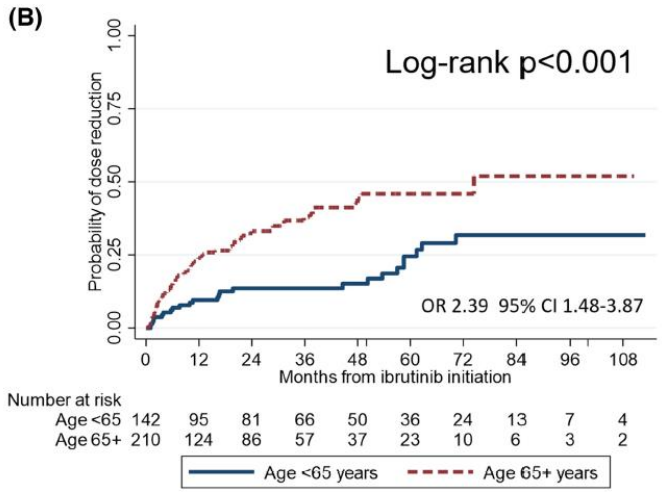


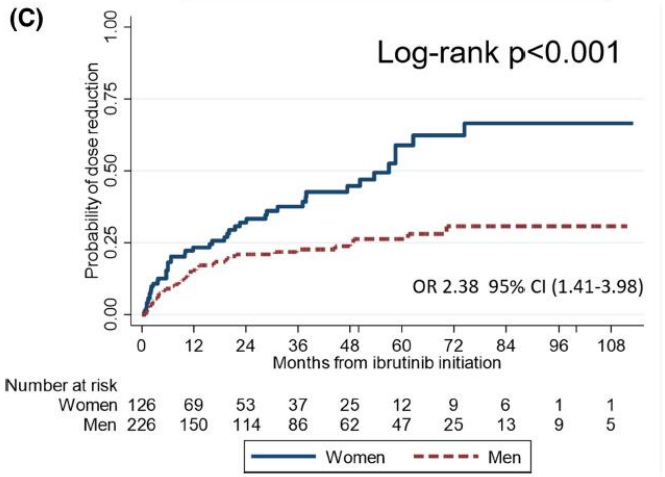
Dimopoulos et al. J Clin Oncol 2023

Dose reductions in patients with Waldenström macroglobulinaemia treated with ibrutinib

Sarosiek et al. Br J Haematol 2023





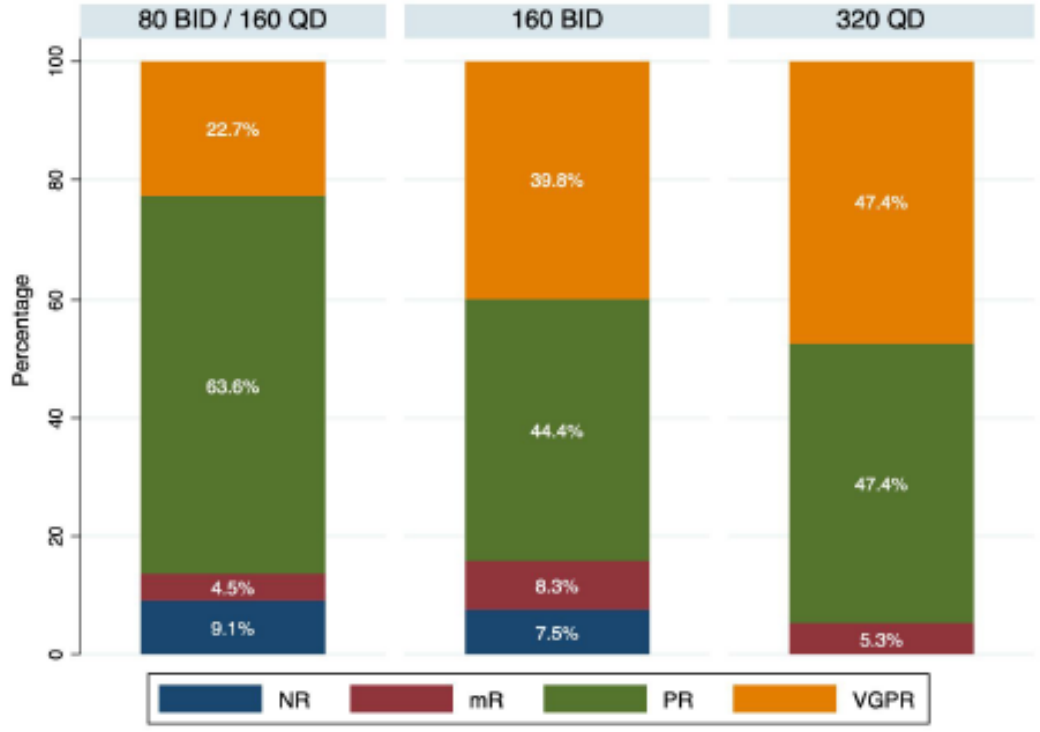


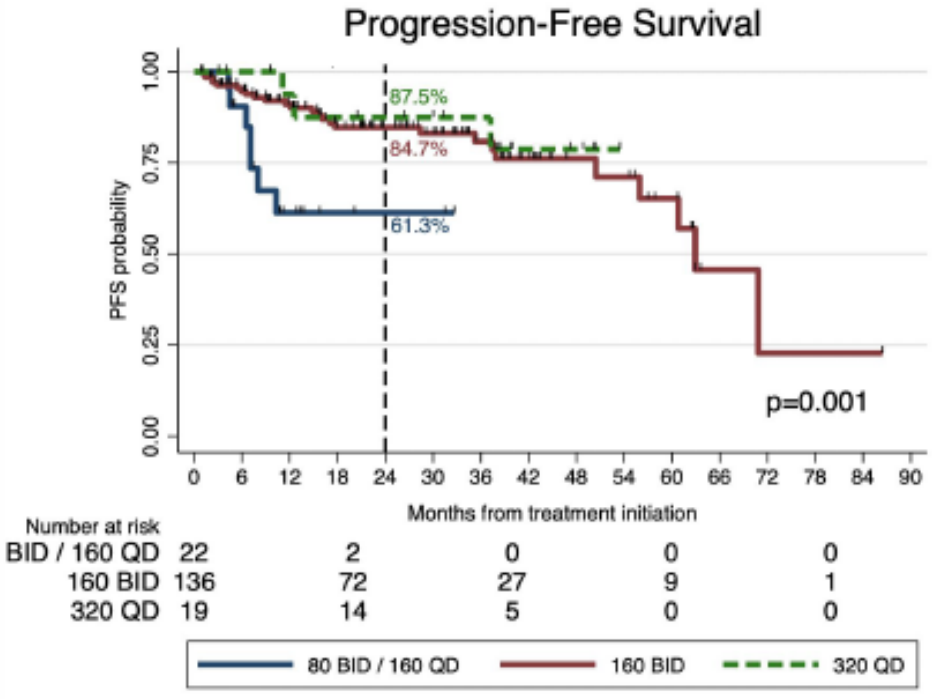
	Total (*n*)	Resolved or improved after dose reduction *n* (%)[a]
Rheumatologic (myalgias, arthralgias, muscle cramping)	28	20 (71)
Cardiac (arrhythmia, hypertension, palpitations)	17	11 (65)
Nail/skin/hair changes	16	9 (56)
Cytopenias	16	9 (56)
Gastrointestinal symptoms (diarrhoea, nausea, reflux)	13	10 (77)
Bleeding/bruising	12	4 (33)
Mucosal symptoms (dry mouth, oral ulcers, lip swelling)	8	6 (75)
Infection	8	7 (88)
Fatigue	8	5 (63)
Ocular (pemphigoid, dry eyes)	2	2 (100)

The response was maintained or deepened in 80% of patients after dose reduction

Zanubrutinib Dosing and Mutational Status Impact Response and Outcomes in Waldenström Macroglobulinemia

N=177 patients with WM treated with zanubrutinib monotherapy





Guijosa et al. SOHO 2025

Frontline clinical trials

Rituximab and Ibrutinib (RI) Versus Dexamethasone, Rituximab and Cyclophosphamide (DRC) as Initial Therapy for Waldenström Macroglobulinemia (RAINBOW)

- United Kingdom
- Randomized phase III study
- 148 participants (TN) randomized 1:1

www.clinicaltrials.gov: NCT04061512

Experimental Arm
Ibrutinib
Rituximab

Comparator Arm
Cyclophosphamide
Dexamethasone
Rituximab

Primary outcomes
Response at 24 weeks
PFS at 2 years

Secondary Outcomes
Safety and tolerability
Overall response rate
Time to next treatment
Duration of response
Overall survival (OS)
Quality of Life

Efficacy and tolerability of bendamustine, rituximab, and acalabrutinib in elderly treatment naïve Waldenström's macroglobulinemia

Study design

Prospective Phase II
9 Canadian centers
N=63 TN patients
6 cycles of bendamustine + rituximab + 12 cycles of acalabrutinib

Outcomes

VGPR/CR: 60%
PB uMRD: 78%

Acala intensity in ≥70 and <70: 78 vs. 80%
Benda intensity: 5.5 vs 5.9 cycles
Benda discontinuation: 26% vs. 9%

Suleman et al. ASH 2025: 1814

Phase II study of zanubrutinib, bendamustine and rituximab in previously untreated Waldenström macroglobulinemia

- Multicenter (DFHCC, UTSW, CBCI)
- 55 participants
- Enrolling

www.clinicaltrials.gov: NCT06561347

Experimental Arm
Zanubrutinib
15 monthly cycles
Bendamustine/rituximab
4 monthly cycles

Primary outcome
Very good partial response rate

Secondary Outcomes
MR, PR, ORR
Impact MYD88, CXCR4
PFS, OS
TLS, IgM flare
Quality of Life

Efficacy of Venetoclax in Combination With Rituximab in Waldenström Macroglobulinemia (VIWA-1)

- Germany
- Randomized phase II study
- 80 participants (TN) randomized 1:1

www.clinicaltrials.gov: NCT05099471

Experimental Arm
Venetoclax
Rituximab

Comparator Arm
Cyclophosphamide
Dexamethasone
Rituximab

Primary outcome
CR/VGPR at 12 months after randomization

Secondary Outcomes
Safety and tolerability
Overall response rate
Duration of response
Progression-free survival
Overall survival
Quality of Life

Testing the Combination of Venetoclax and Rituximab, in Comparison with Ibrutinib and Rituximab for Waldenstrom Macroglobulinemia

- United States (multicenter)
- Randomized phase II study
- 92 participants (TN) randomized 1:1

www.clinicaltrials.gov: NCT04840602

Experimental Arm
Venetoclax + Rituximab
24 months

Comparator Arm
Ibrutinib + Rituximab
24 months

Primary outcome
CR/VGPR

Secondary Outcomes
Safety and tolerability
Overall response rate
Duration of response
Progression-free survival
Overall survival
Quality of Life

Conclusions

- CIT and covalent BTK inhibitors have similar efficacy outcomes as frontline treatment in WM, but they have distinctive safety profiles.
- There are no comparative studies between CIT and covalent BTK inhibitors.
- The best frontline treatment for WM is personalized.

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