The management of Waldenström macroglobulinemia in 2024

Jorge J. Castillo, MD
Associate Professor of Medicine
Harvard Medical School
JorgeJ_Castillo@dfci.harvard.edu

Dana-Farber
Cancer Institute

Case

A 66-year-old asymptomatic man had a high serum protein level. SPEP detected an IgM *kappa* monoclonal paraprotein. CBC was normal. Serum IgM was 3500 mg/dL, serum albumin was 4 g/dL, and serum β2-microglobulin was 2.5 mg/L.

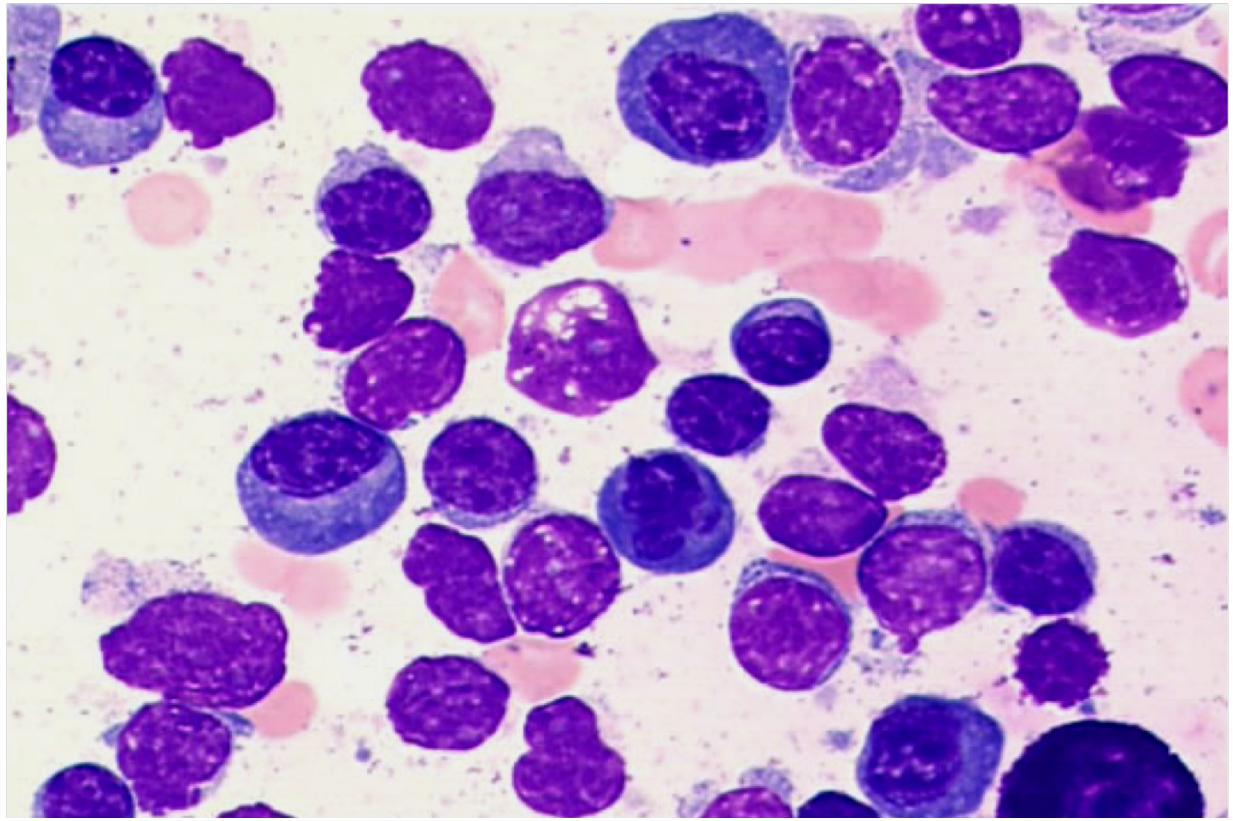
A bone marrow biopsy showed 40% involvement by κ-restricted lymphoplasmacytoid cells with positive CD20 and CD38 and negative CD5 and CD10, consistent with lymphoplasmacytic lymphoma. *MYD88 L265P* mutation was detected by PCR.

CT scans of the showed lymphadenopathy or organomegaly.

Funduscopic examination showed no evidence of hyperviscosity-related changes.

Diagnostic criteria

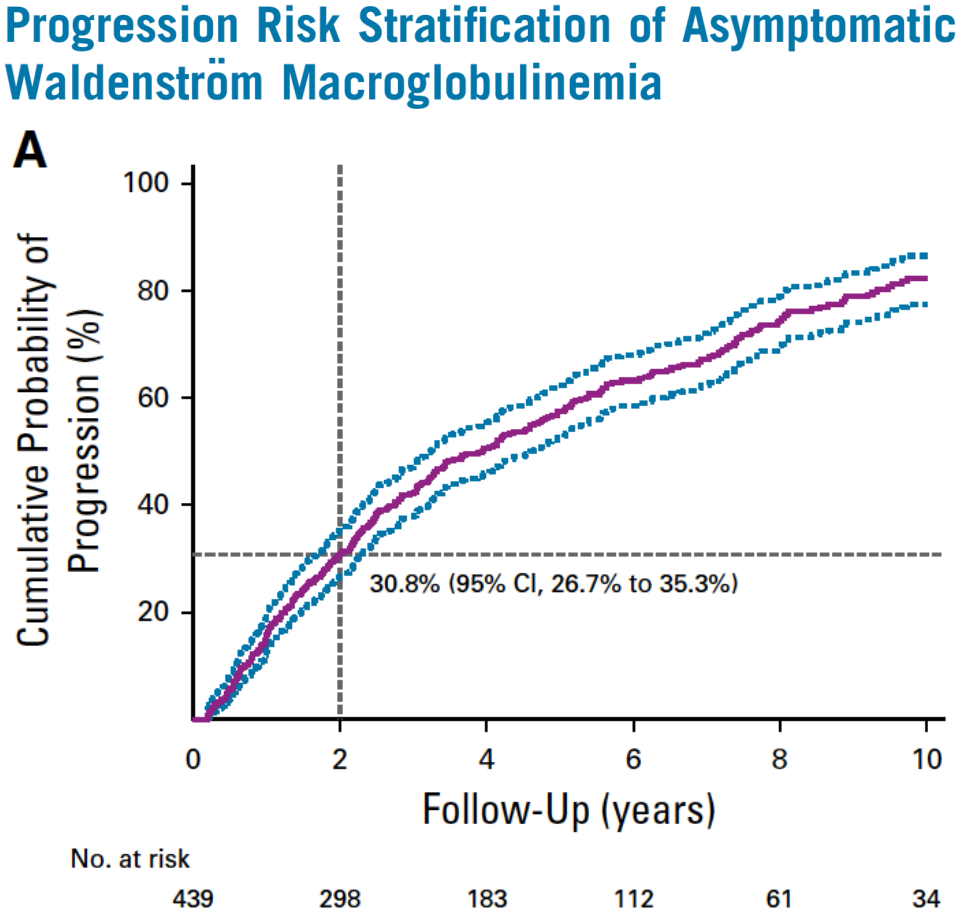
1. IgM monoclonal protein in serum protein electrophoresis and immunofixation
2. Lymphoplasmacytic lymphoma in the bone marrow
3. *MYD88 L265P* mutation by AS-PCR or NGS



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

AWM Patient Risk Calculator

Asymptomatic Waldenström Macroglobulinemia
Developed by Dana-Farber Cancer Institute

Please complete all the fields below

Note: This page does not collect or store patient data

Bone Marrow Infiltration %

40 %
Field allows 0-100%

IgM Protein Level

3500 mg/dL
Field allows 0-8000 mg/dL (reference: 37-286 mg/dL)

Beta2-Microglobulin Level

2.5 mg/L
Field allows 0-10 mg/L (reference: 0.7-1.8 mg/L)

Albumin Level

4 g/dL
Field allows 0-10 g/dL (reference: 3.5-5.5 g/dL)

Calculate Risk Score

If you are a patient diagnosed with AWM, we encourage you to enter your lab data here and share these results with your oncologist or healthcare provider. The tool may help you discuss your risks and treatment strategies.

Patient Results

Patient's Risk Score **1.4426**

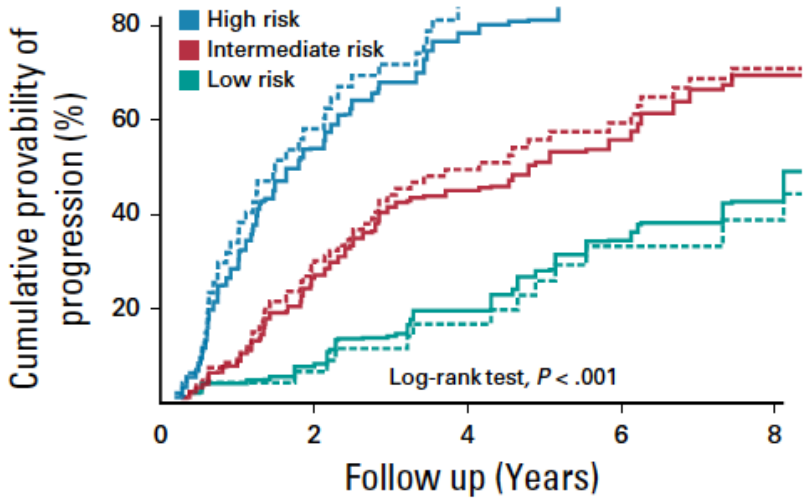
Patient's Risk Group

Low	< 0.535
Medium	0.536 - 1.802
High	>= 1.802

Median Time to Progression **4.8 years**

as determined by risk group

Re-Enter Fields

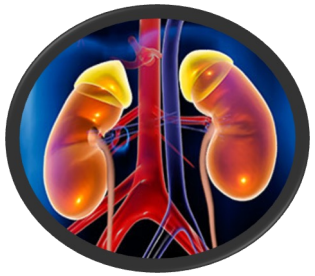


No at risk:					
High-risk:	47	19	6	1	1
Intermediate-risk:	93	66	36	22	11
Low-risk:	47	40	29	16	11

Bustoros et al. JCO 2019

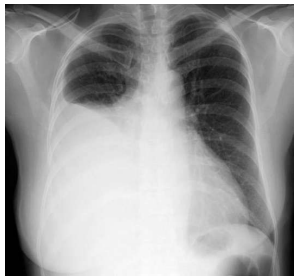
https://awmrisk.com

Manifestations of Waldenstrom Macroglobulinemia

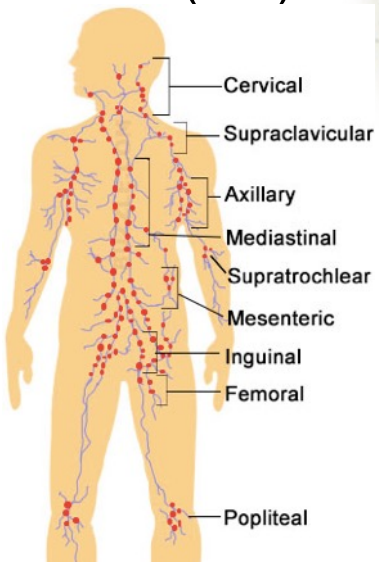


Renal involvement
(2-3%)

Bing Neel
Syndrome (1%)



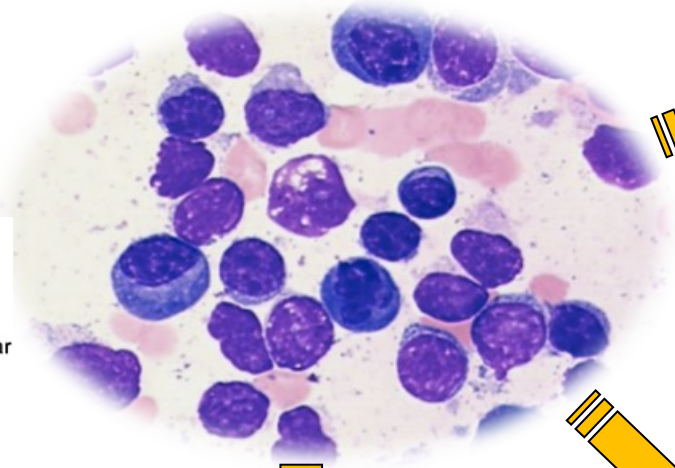
Pleural effusions
(1-2%)

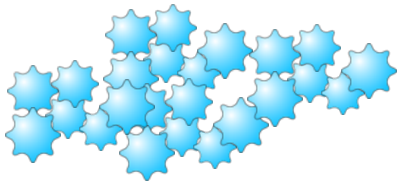


Extramedullary
disease (20-50%)

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

Dana-Farber Cancer Institute

Adapted from Derman et al. ASCO Ed Book 2022

Case

The patient was followed expectantly. Three years later, the patient presented with recurrent nosebleeds and progressive fatigue.

Hemoglobin was 9.2 g/dL, platelets were 115 K/uL, and serum IgM was 5500 mg/dL. Fundoscopy revealed engorged retinal vessels and scattered retinal hemorrhages.

A bone marrow biopsy showed 80% involvement by LPL. *MYD88 L265P* was detected by PCR, and *CXCR4 T318fs* (frameshift) by NGS.

CT scans showed generalized lymphadenopathy, with maximum diameter of 3 cm, without hepatosplenomegaly.

TREATMENT OPTIONS

Rituximab combination regimens

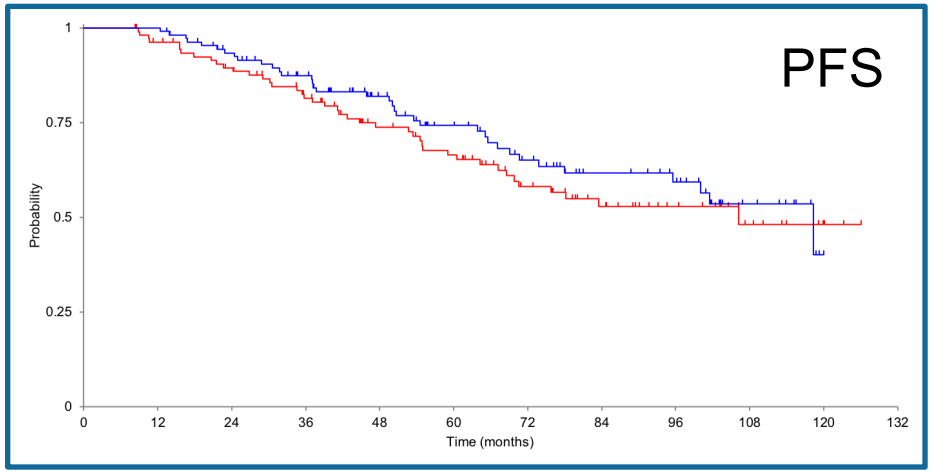
Regimen	n	ORR	Major	PFS (mo)
Cyclophosphamide-dex-R	72	83%	76%	35
Fludarabine-R	43	95%	86%	51
Bendamustine-R	69	97%	96%	69
Bortezomib-dex-R	59	85%	68%	42
Carfilzomib-dex-R	31	87%	68%	46
Ixazomib-dex-R	26	96%	77%	40

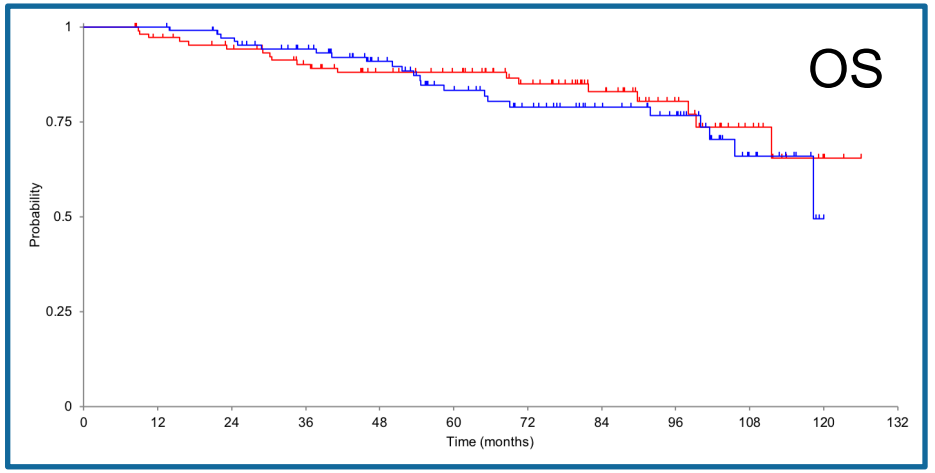
Dimopoulos et al. Blood 2014; Treon et al. Blood 2015; Laribi et al. Br J Haematol 2019; Dimopoulos et al. Blood 2013; Treon et al. Blood 2014; Castillo et al. Blood Adv 2020

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

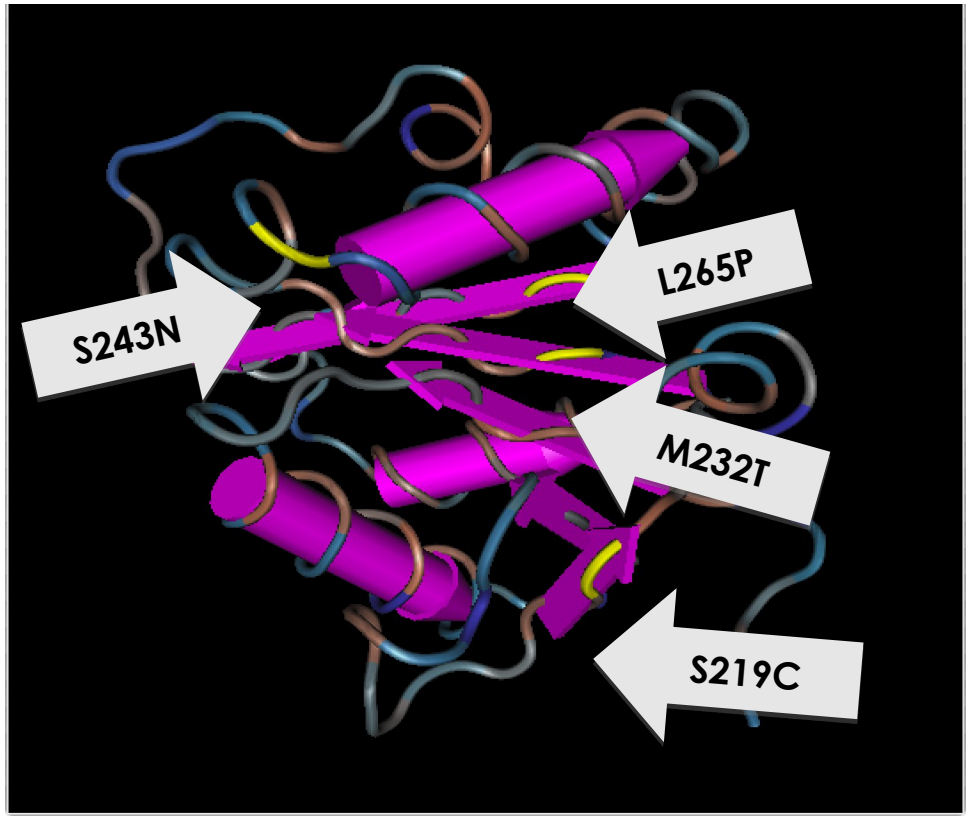
	All	R +	R-
Total (n)	218	109	109
Age (median)	66	67	65
Hemoglobin <11 g/dl	149 (68%)	70 (64%)	79 (72%)
IgM g/l (median)	32.7	32.7	31.3
β_2-Microglobulin	3.5	3.3	3.7
B-symptoms	75 (34%)	43 (39%)	32 (29%)

Rummel et al. ASH 2019





MYD88 mutations

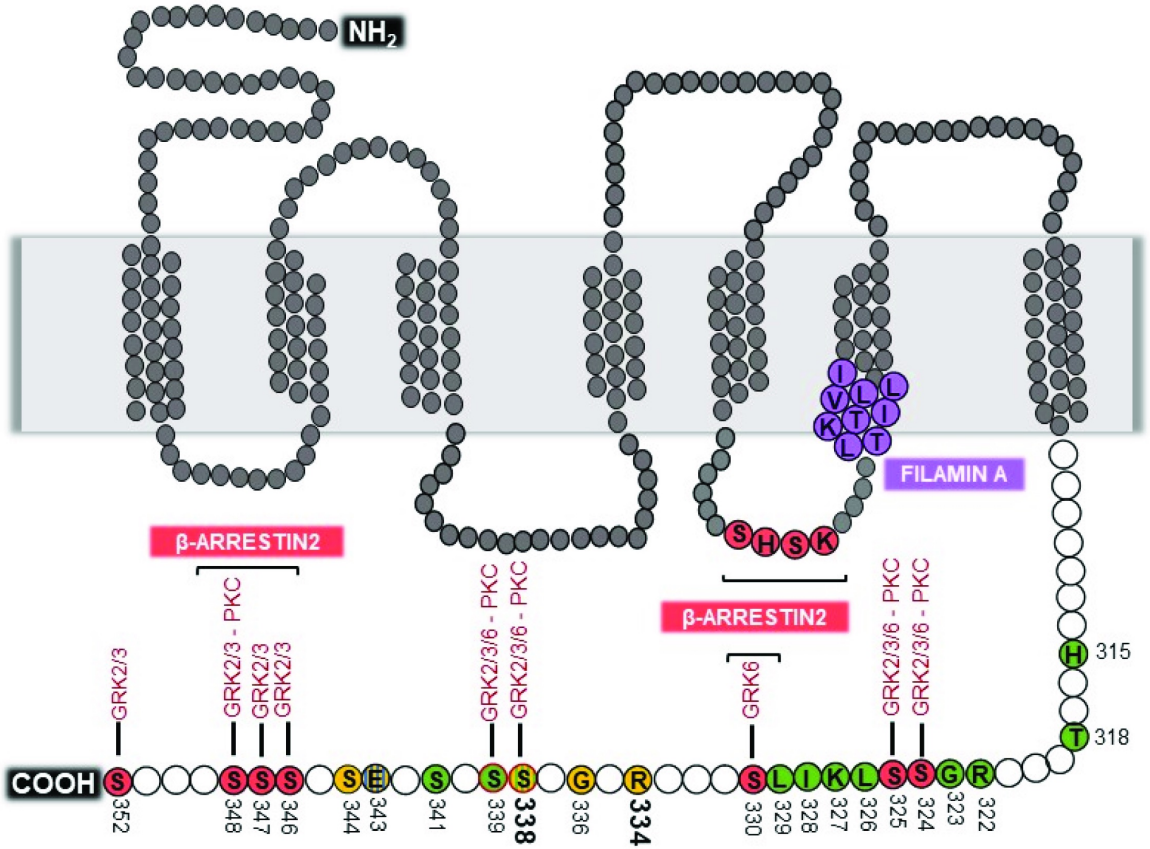


2% non-L265P MYD88 mutations

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

Study	Method	%
Xu	AS-PCR	94%
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%

CXCR4 mutations



Milanesi et al. Int J Mol Sci 2020

Study	Method	%
Hunter	WGS	27%
Roccaro	AS-PCR	28%
Poulain	NGS/Sanger	25%
Schmidt	Sanger	36%
Xu	AS-PCR/Sanger	40%
Ballester	Sanger	25%
Cao	Sanger	24%
Shin	Target capture	19%

BTK inhibitors

Regimen	N	ORR	Major	PFS
Ibrutinib (RR)	63	91%	73%	54% at 5 years
Ibrutinib (R-refractory)	31	90%	71%	Median 39 months
Ibrutinib (TN)	30	100%	87%	76% at 4 years
Ibrutinib-R (INNOVATE)	75	92%	76%	68% at 4.5 years
Acalabrutinib	106	93%	80%	Median 68 months
Zanubrutinib (ASPEN)	101	94%	77%	78% at 42 months

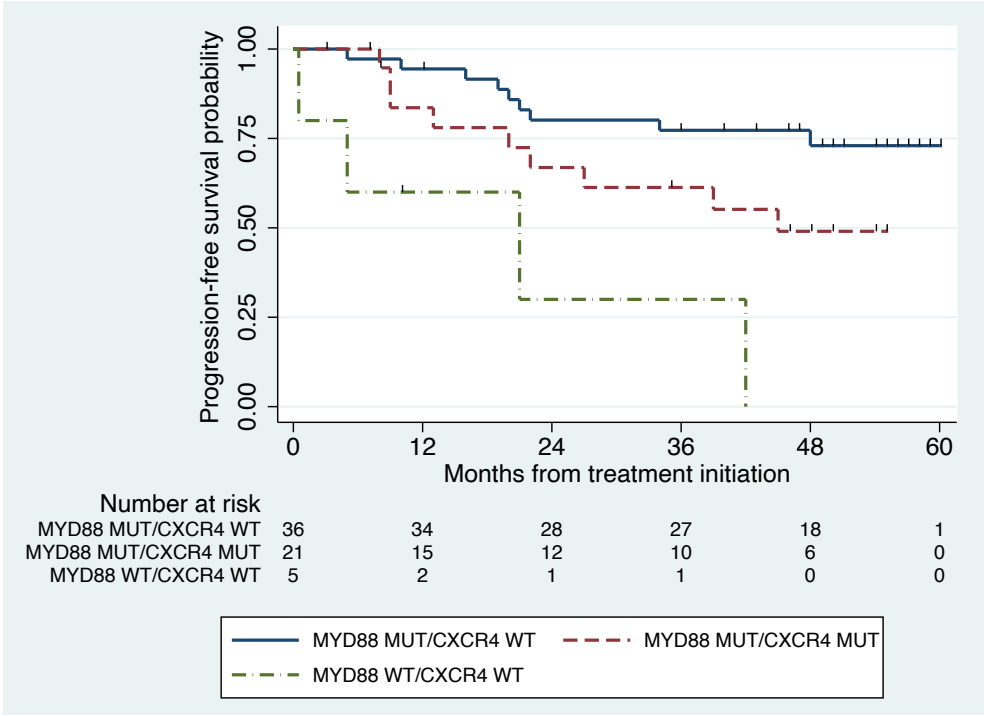
Treon et al. J Clin Oncol 2021; Trotman et al. Clin Cancer Res 2021; Castillo et al. Leukemia 2022; Buske et al. J Clin Oncol 2022; Owen et al. EHA 2022; Dimopoulos et al. J Clin Oncol 2023

Phase II
RR

FDA

Long-Term Follow-Up of Ibrutinib Monotherapy Symptomatic, Previously Treated Patients With Waldenström Macroglobulinemia

	MYD88^{MUT} CXCR4^{WT}	MYD88^{MUT} CXCR4^{MUT}	MYD88^{WT} CXCR4^{WT}
N=	36	21	5
ORR	100%	86%	60%
Major (>PR)	97%	68%	0%
VGPR	47%	9%	0%
TTR (mos.)	1.0	1.0	1.0
TTMR (mos.)	2.0	6.0	N/A

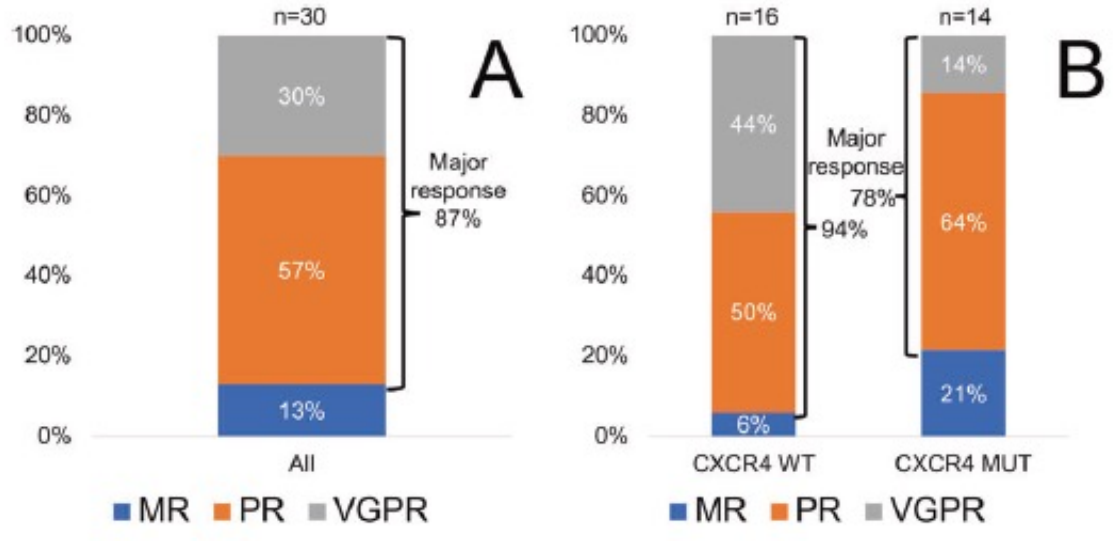


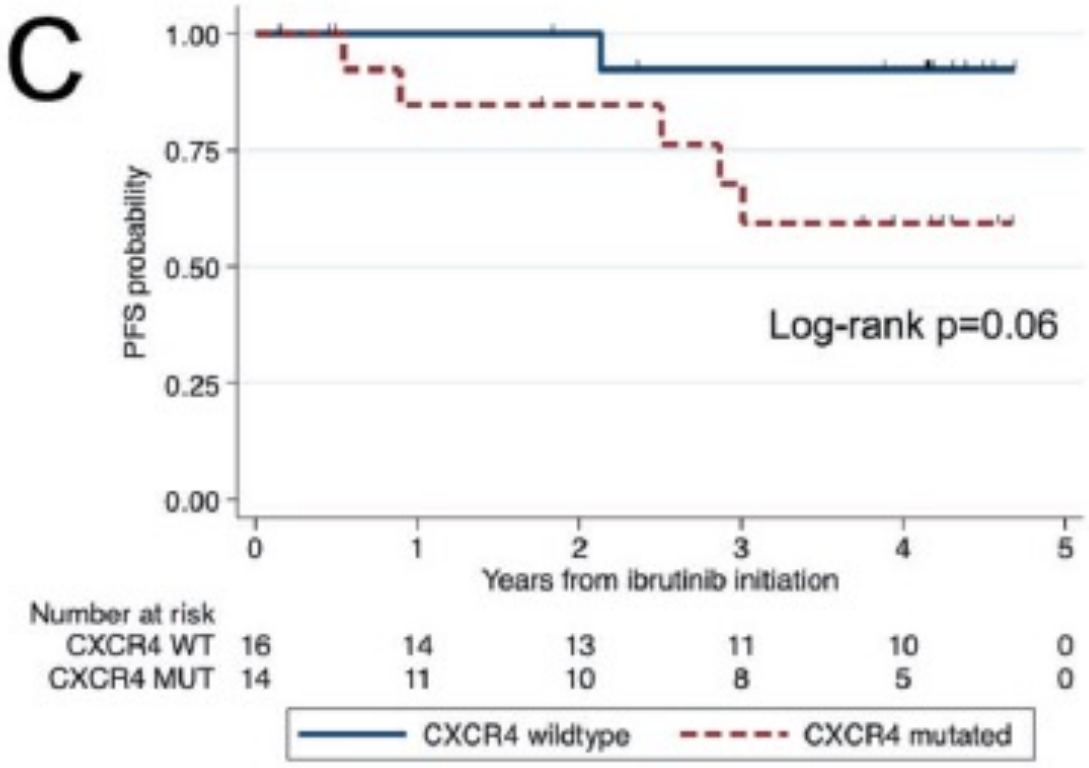
Treon et al. J Clin Oncol 2020

Phase II TN

FDA

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



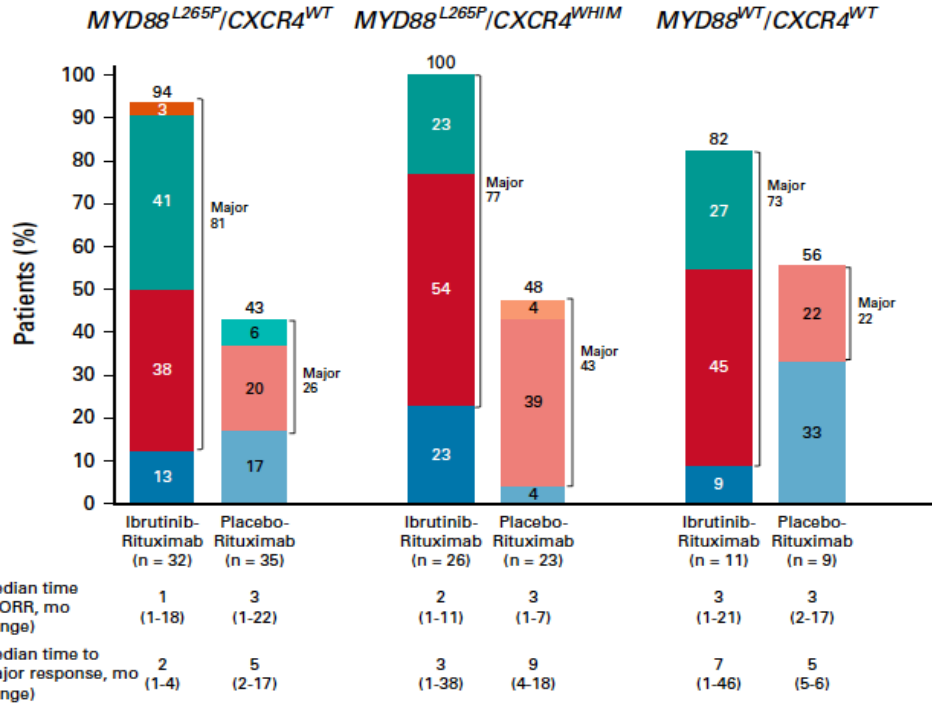


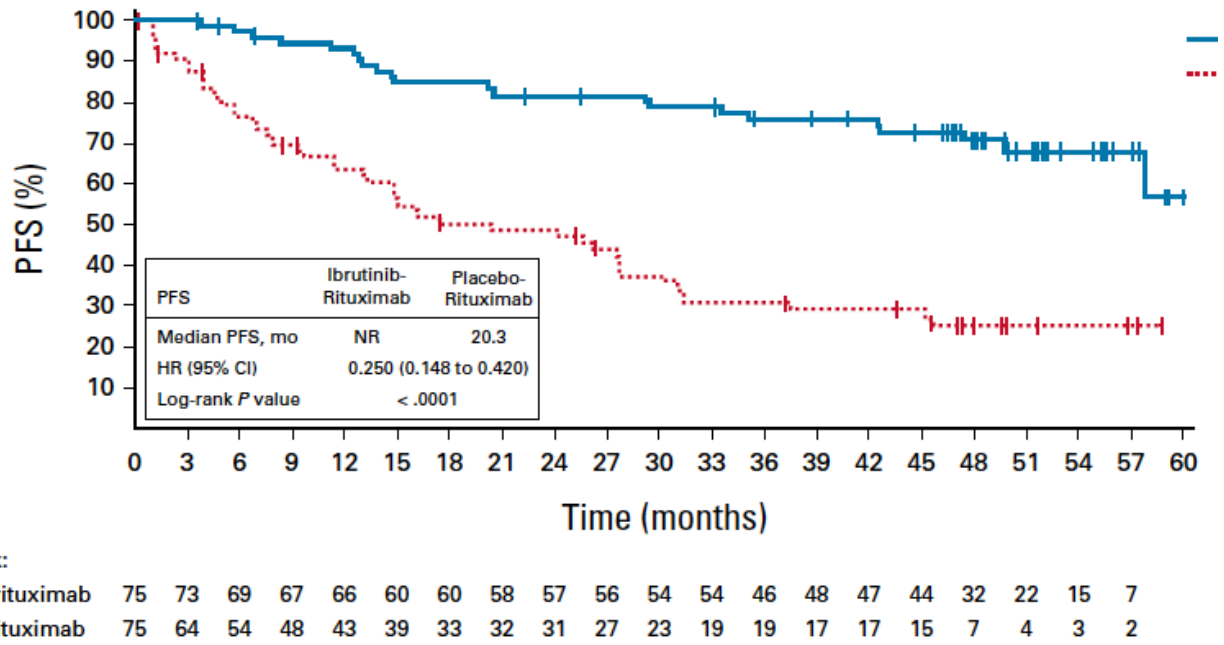
Castillo et al. Leukemia 2022

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

Phase III TN/RR

FDA



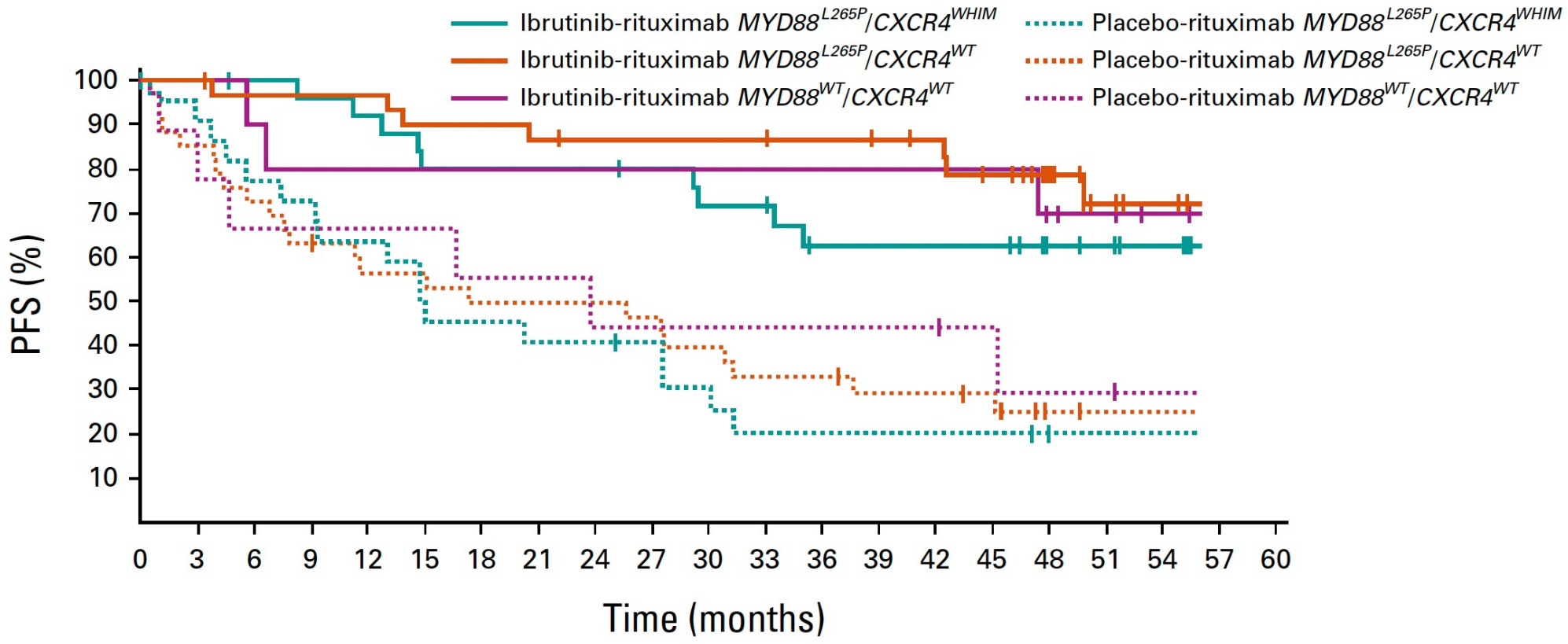


Buske et al. J Clin Oncol 2022

Phase III
TN/RR

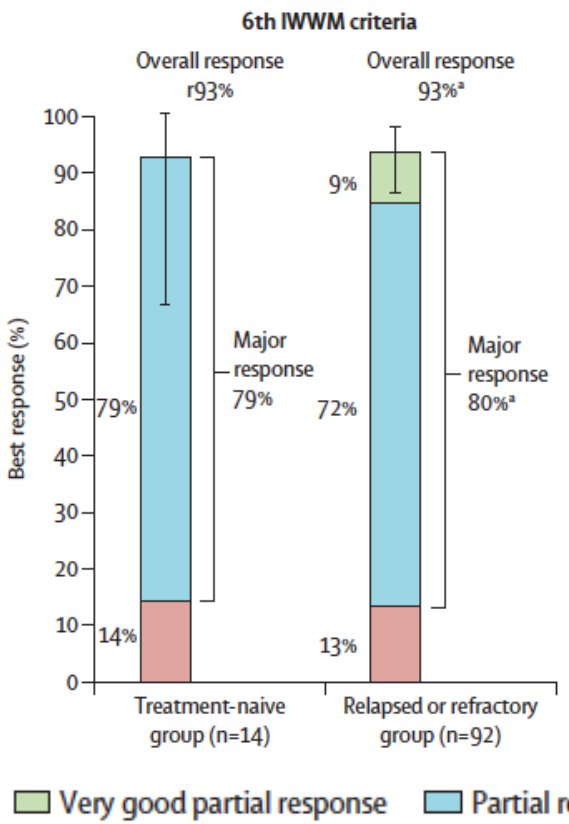
FDA

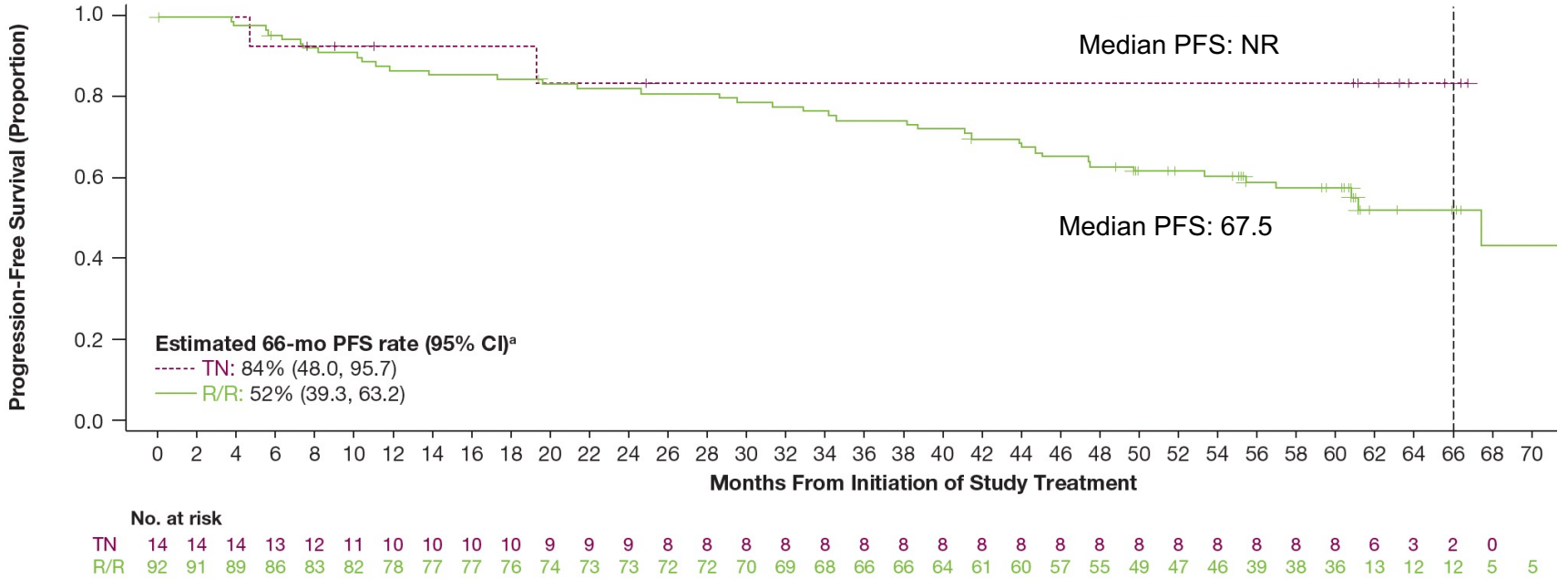
Ibrutinib Plus Rituximab Versus Placebo Plus Rituximab for Waldenström's Macroglobulinemia: Final Analysis From the Randomized Phase III iNNOVATE Study



Buske et al. J Clin Oncol 2022

Acalabrutinib monotherapy in patients with Waldenström macroglobulinemia: a single-arm, multicentre, phase 2 study





Owen et al. Lancet Haematol 2020; Owen et al. EHA 2022

Phase III
TN/RR

FDA

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

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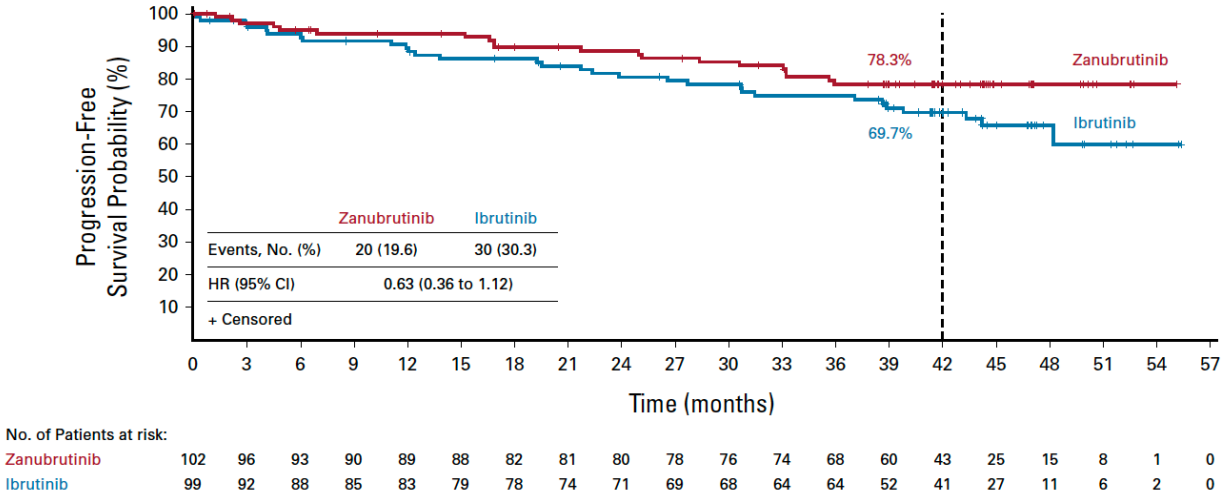

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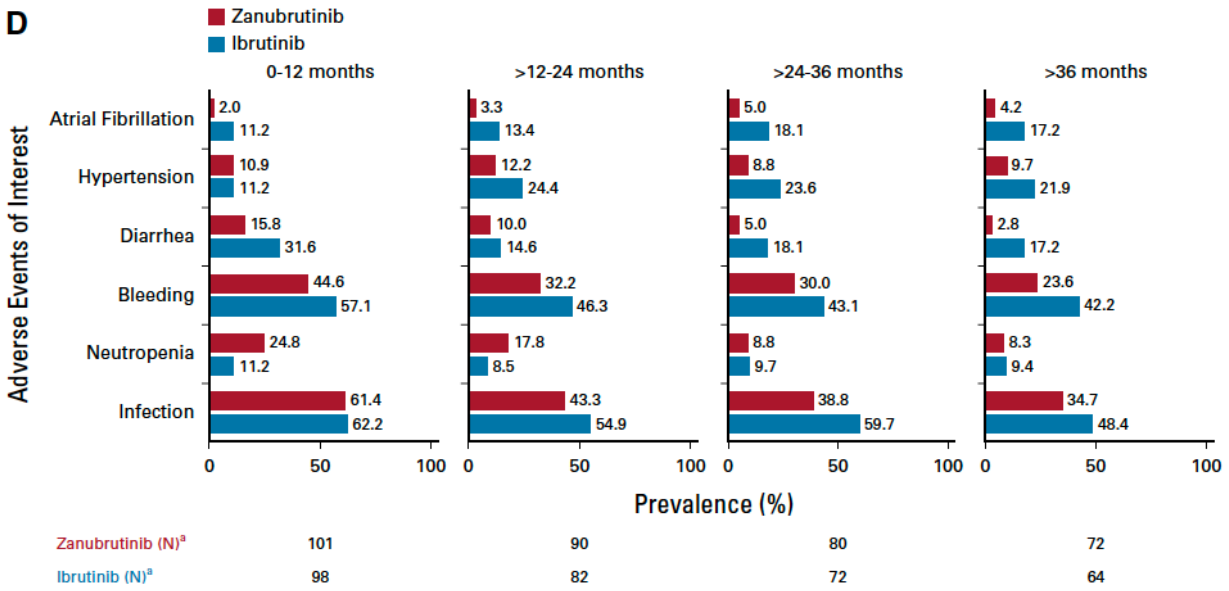


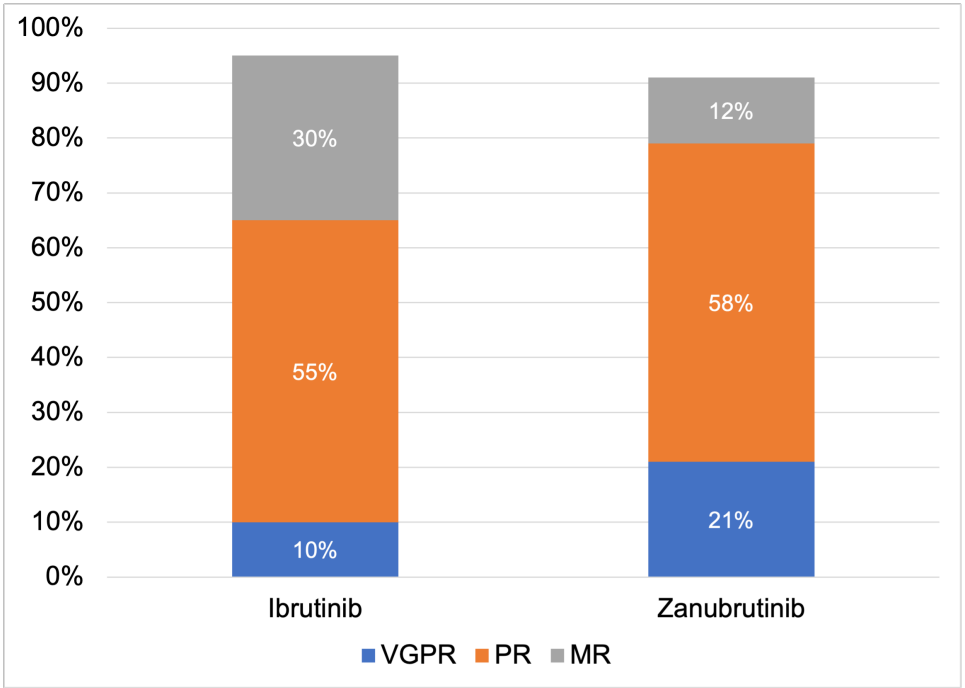
Dimopoulos et al. J Clin Oncol 2023

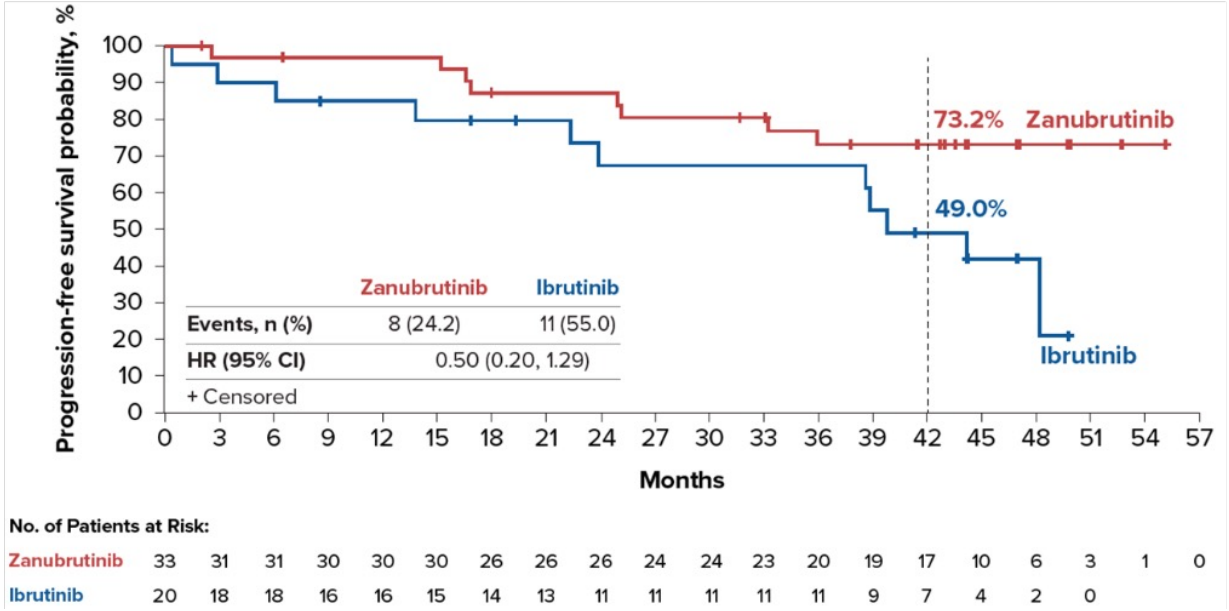
Phase III
TN/RR

FDA

A randomized phase 3 trial of zanubrutinib vs ibrutinib in symptomatic Waldenström macroglobulinemia: the ASPEN study

Patients with CXCR4 mutations

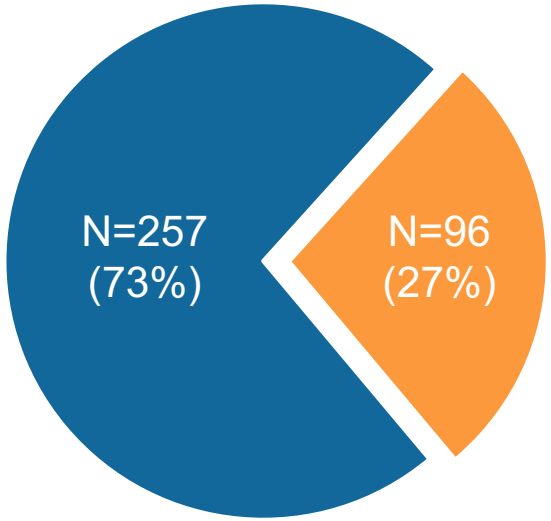


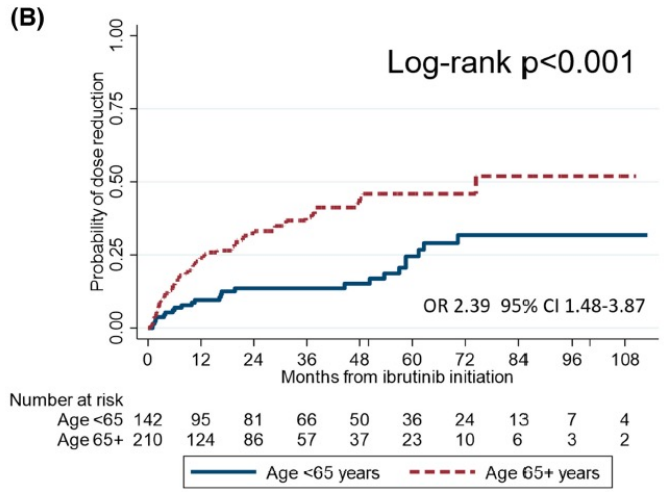


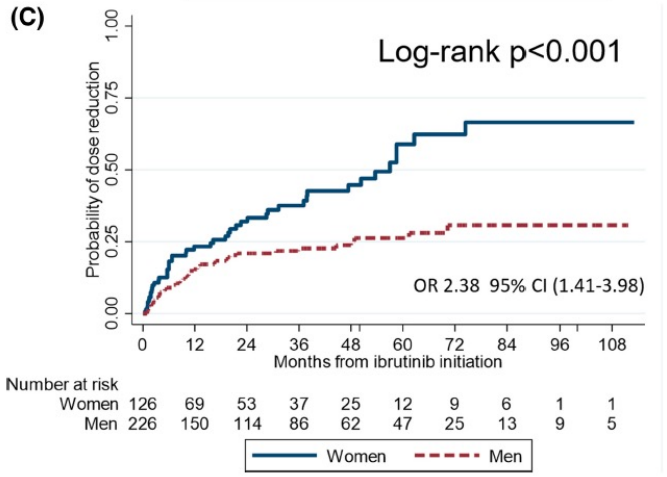
Tam et al. ASCO 2022: 7521

Dose reductions in patients with Waldenström macroglobulinaemia treated with ibrutinib

Sarosiek et al. Br J Haematol 2023



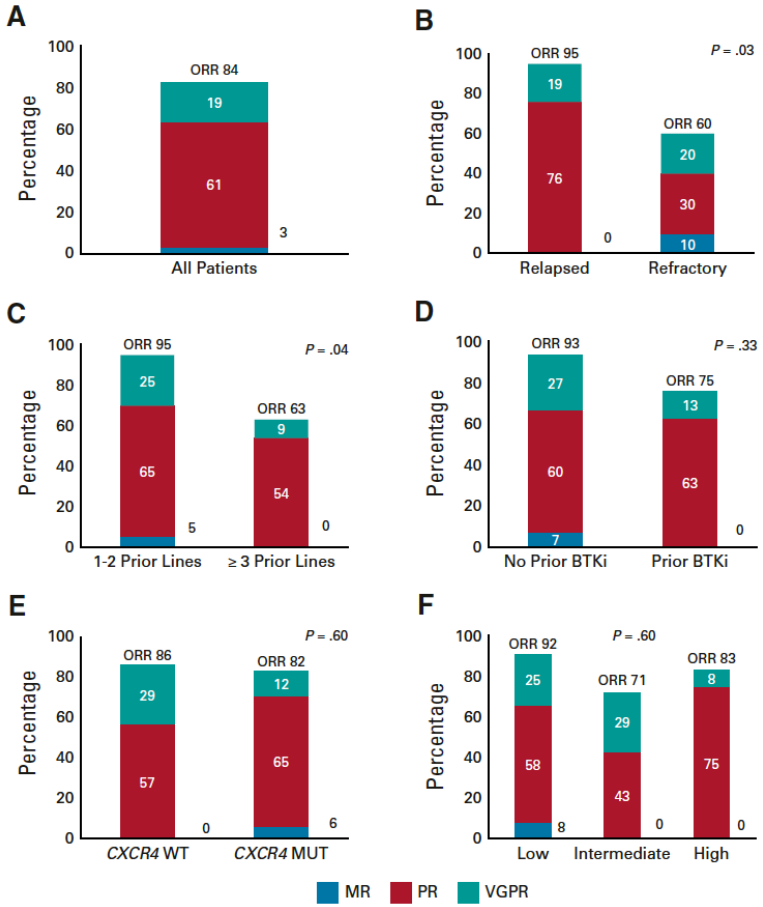


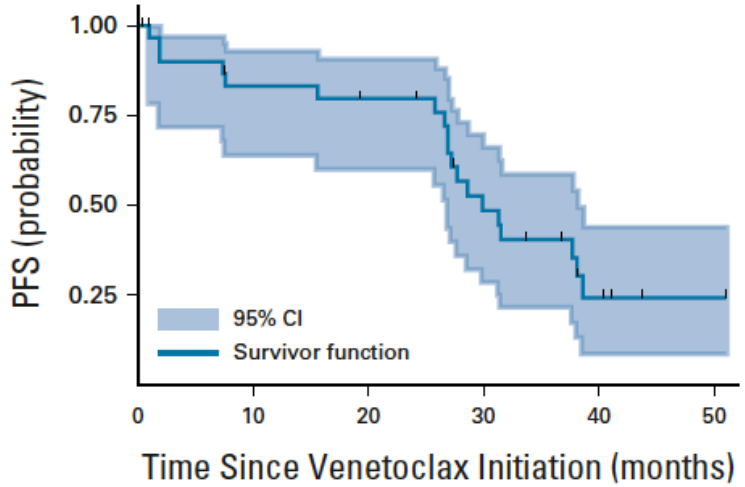


	Total (*n*)	Resolved or improved after dose reduction *n* (%)[a]
Rheumatologic (myalgias, arthralgias, muscle cramping)	28	20 (71)
Cardiac (arrhythmia, hypertension, palpitations)	17	11 (65)
Nail/skin/hair changes	16	9 (56)
Cytopenias	16	9 (56)
Gastrointestinal symptoms (diarrhoea, nausea, reflux)	13	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 79% of patients who dose-reduced ibrutinib.

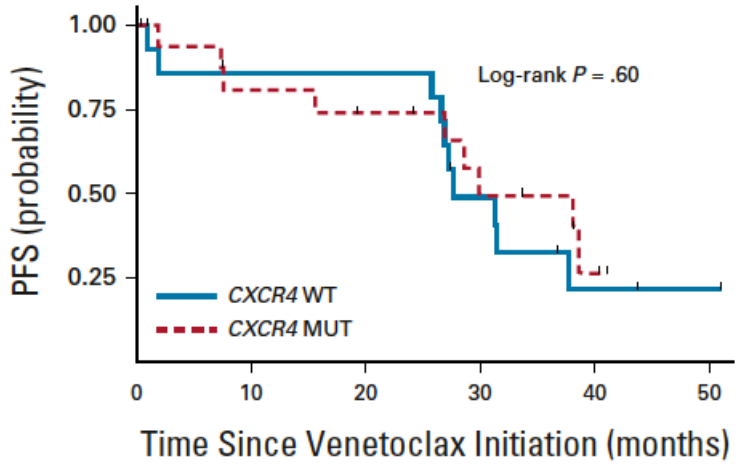
Venetoclax in Previously Treated Waldenström Macroglobulinemia





No. at risk:

	32	24	22	12	4	1

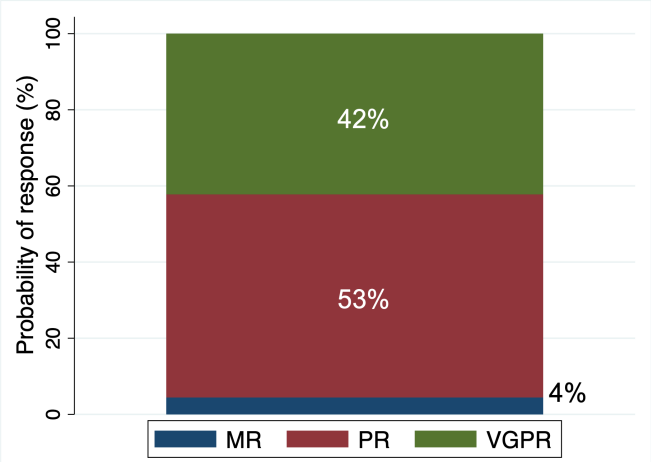


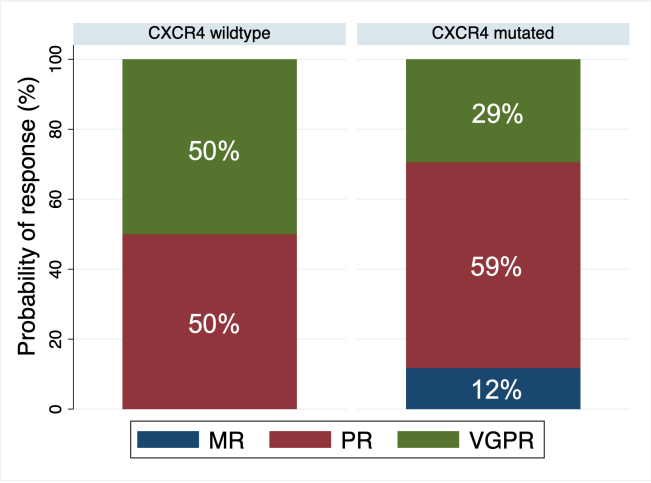
No. at risk:

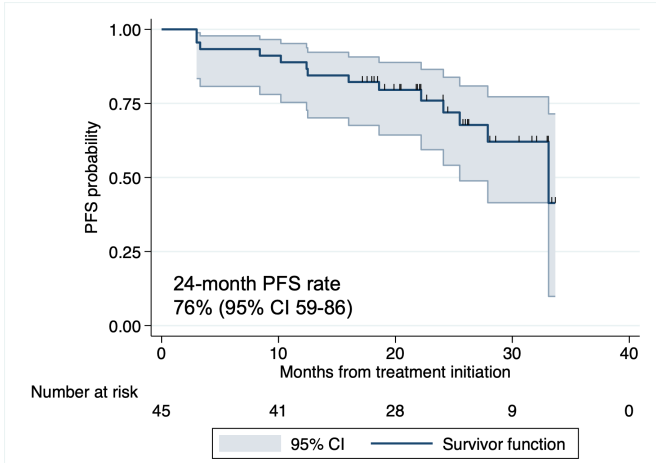
CXCR4 WT	15	12	12	6	2	1
CXCR4 MUT	17	12	10	6	2	0

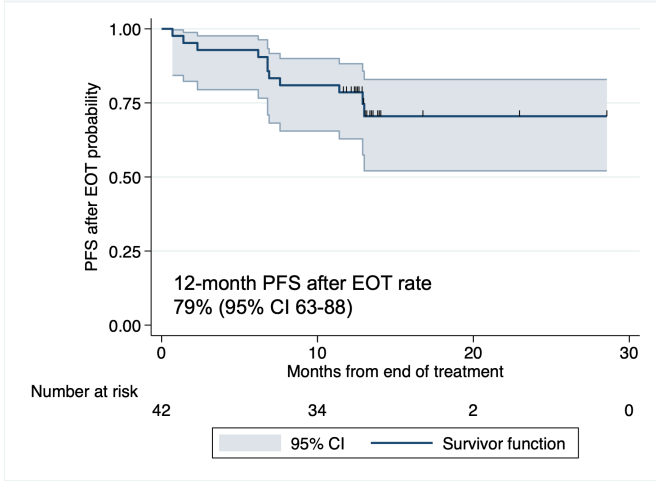
Castillo et al. J Clin Oncol 2022

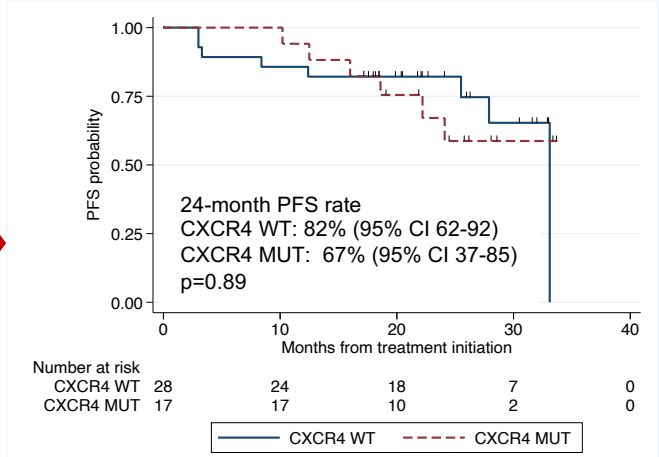
Ibrutinib and venetoclax as primary therapy in symptomatic treatment naïve Waldenström macroglobulinemia

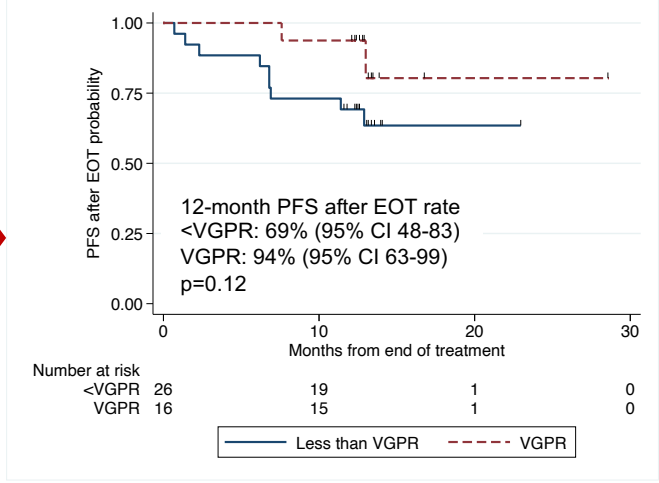












Castillo et al. Blood 2024

Ibrutinib and venetoclax as primary therapy in symptomatic treatment naïve Waldenström macroglobulinemia

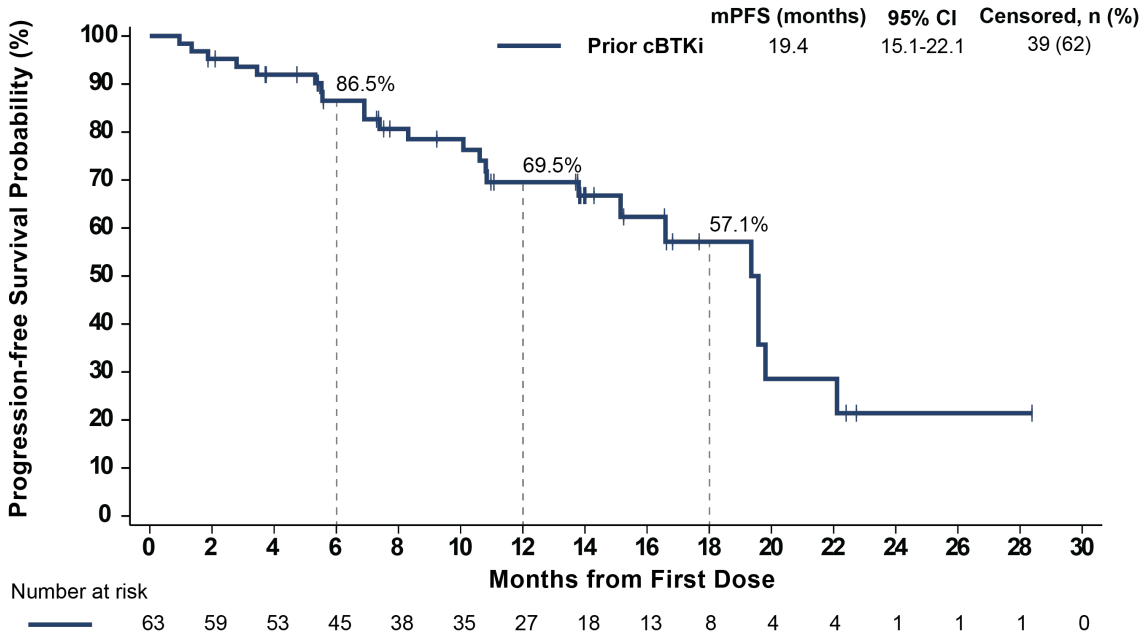
Adverse event	Grade 2	Grade 3	Grade 4	Grade 5
Alanine aminotransferase increase		1		
Arthralgia	5	1		
Atrial fibrillation	1	2		
Bruising	2			
Diarrhea	11	3		
Gastroesophageal reflux disease	12			
Hyperphosphatemia	8			
Hypertension	2	1		
Intracranial hemorrhage		1		
Lung infection	2			
Mucositis	9	4		
Nausea	5			
Neutropenia	2	13	4	
Platelet decrease		1		
Skin rash	5			
Soft tissue infection	2	1		
Tumor lysis syndrome		3		
Urinary tract infection	5			
Ventricular arrhythmia	1		1	2

Castillo et al. Blood 2024

Efficacy of Pirtobrutinib, a Highly Selective, Non-Covalent (Reversible) BTK Inhibitor in Relapsed/Refractory Waldenström Macroglobulinemia: Results from the Phase 1/2 BRUIN Study

Response Evaluable WM Patients	Prior cBTKi n=63	cBTKi Naïve n=17
Major Response Rate[a], %	67 (54-78)	88 (64-98)
CR + VGPR Rate, %	24 (14-36)	29 (10-56)
Best Response		
VGPR, n (%)	15 (23.8)	5 (29.4)
PR, n (%)	27 (42.9)	10 (58.8)
MR, n (%)	9 (14.3)	0 (0)
SD, n (%)	9 (14.3)	2 (11.8)

Palomba et al. ASH 2022: 229



The median follow-up for PFS in patients who received prior cBTKi was 14 months

Efficacy of Pirtobrutinib, a Highly Selective, Non-Covalent (Reversible) BTK Inhibitor in Relapsed/Refractory Waldenström Macroglobulinemia: Results from the Phase 1/2 BRUIN Study

	All Doses and Patients (N=773)			
	Treatment-Emergent AEs, (≥15%), %		Treatment-Related AEs, %	
Adverse Event (AEs)	Any Grade	Grade ≥ 3	Any Grade	Grade ≥ 3
Fatigue	28.7%	2.1%	9.3%	0.8%
Diarrhea	24.2%	0.9%	9.3%	0.4%
Neutropenia	24.2%	20.4%	14.7%	11.5%
Contusion	19.4%	0.0%	12.8%	0.0%
Cough	17.5%	0.1%	2.3%	0.0%
Covid-19	16.7%	2.7%	1.3%	0.0%
Nausea	16.2%	0.1%	4.7%	0.1%
Dyspnea	15.5%	1.0%	3.0%	0.1%
Anemia	15.4%	8.8%	5.2%	2.1%
AEs of Special Interest	Any Grade	Grade ≥ 3	Any Grade	Grade ≥ 3
Bruising	23.7%	0.0%	15.1%	0.0%
Rash	12.7%	0.5%	6.0%	0.4%
Arthralgia	14.4%	0.6%	3.5%	0.0%
Hemorrhage/Hematoma	11.4%	1.8%	4.0%	0.6%
Hypertension	9.2%	2.3%	3.4%	0.6%
Atrial fibrillation/flutter	2.8%	1.2%	0.8%	0.1%

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Selected clinical trials in WM

ClinicalTrials.Gov ID	Agents	Phase	Eligibility
NCT04061512	Ibrutinib, rituximab vs. DRC	II	TN
NCT04263480	Ibrutinib, carfilzomib vs. ibrutinib	II	TN
NCT04624906	Acalabrutinib, bendamustine, rituximab	II	TN
NCT05099471	Venetoclax, rituximab vs. DRC	II	TN
NCT02952508	Iopofosine 131	II	RR
NCT04728893	Nemtabrutinib	II	RR
NCT05006716	BGB-16673	I/II	RR
NCT05190705	Loncastuximab tesirine	II	RR
NCT05360238	MB-106	II	RR
NCT05734495	Pirtobrutinib, venetoclax	II	RR
NCT05952037	Sonrotoclax	II	RR

Conclusions

- Diagnosis: IgM elevation, LPL infiltration, and MYD88 mutation
- Reserve therapy for symptomatic patients
- Chemoimmunotherapy, proteasome inhibitors, BTK inhibitors, and BCL2 antagonists are safe and effective
- Clinical trials are evaluating BTKi combinations, triplets, fixed-duration regimens, and immunotherapy

The management of Waldenström macroglobulinemia in 2024

Jorge J. Castillo, MD
Associate Professor of Medicine
Harvard Medical School
JorgeJ_Castillo@dfci.harvard.edu

Dana-Farber
Cancer Institute