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Advances in the frontline treatment of Waldenström macroglobulinemia

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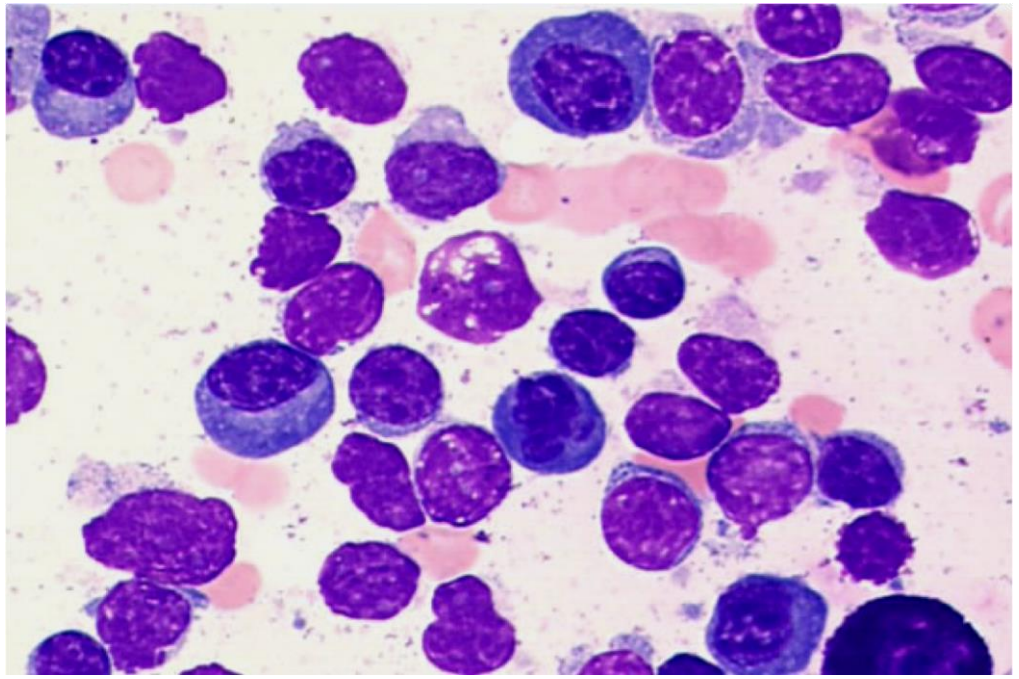
Disclosures

Research Support	Abbvie, Beigene, Janssen, Millennium, Pharmacyclics, TG Therapeutics
Employee	N/A
Consultant	Janssen, Pharmacyclics, Roche, Vical
Major Stockholder	N/A
Speakers Bureau	N/A
Honoraria	N/A
Scientific Advisory Board	Abbvie, Pharmacyclics

Diagnostic criteria

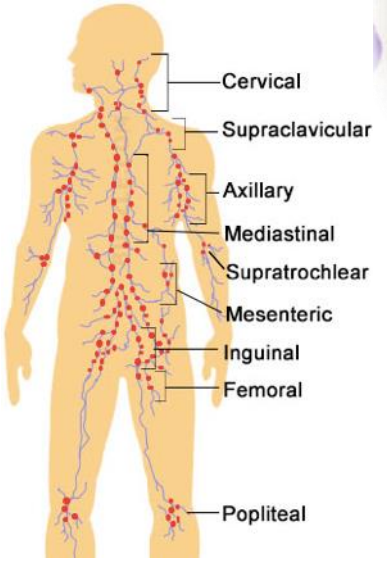
- Lymphoplasmacytic lymphoma in the bone marrow
- IgM monoclonal paraprotein in serum protein electrophoresis
- MYD88 L265P mutation



Swerdlow et al. WHO Classification of Lymphomas, 2018

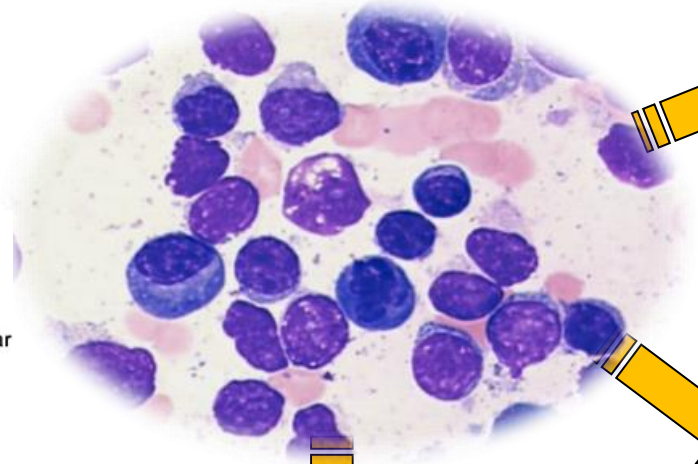
Manifestations of Waldenström Macroglobulinemia

Bing Neel Syndrome (1%)

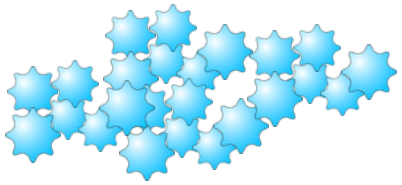


≤20% at diagnosis;
50-60% at relapse.

Anemia (60-70%)
Thrombocytopenia (10-20%)
Leukopenia (<5%)



Hepcidin
↓Fe Anemia (20%)

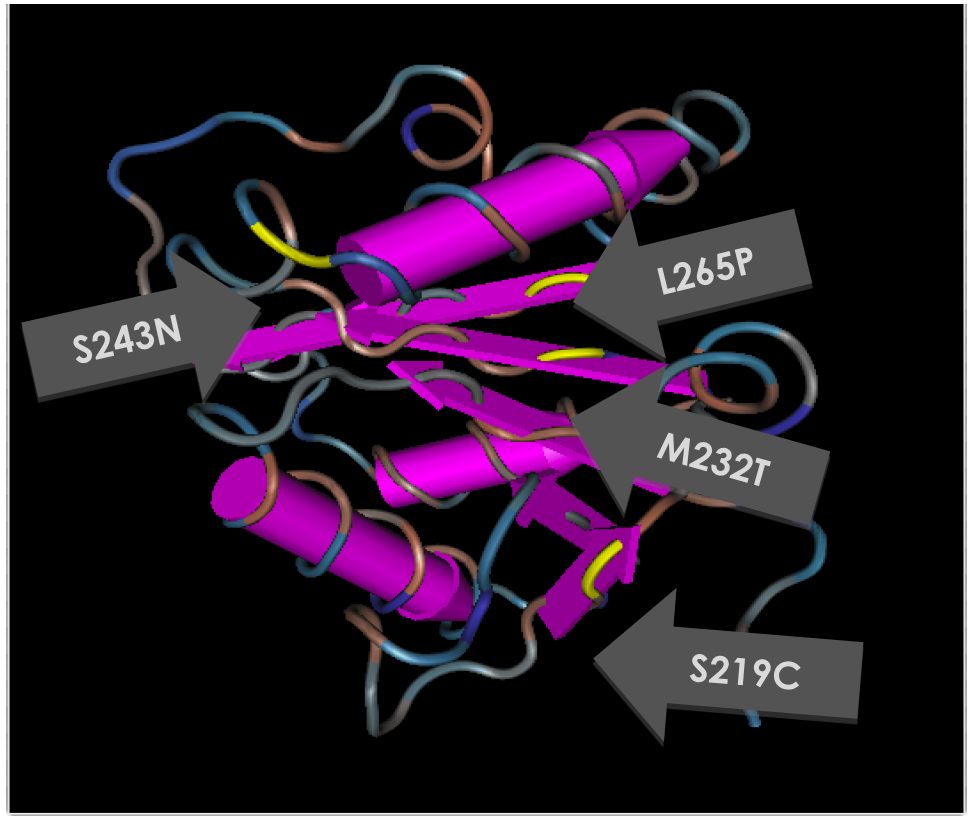


Hyperviscosity Syndrome (10%):
Epistaxis, Headaches
Impaired vision
>6,000 mg/dL or >4.0 CP

Cold Agglutinemia (5%)
Cryoglobulinemia (10%)
IgM Neuropathy (20%)
Amyloidosis (10%)

Treon. Hematol Oncol 2013

MYD88 L265P

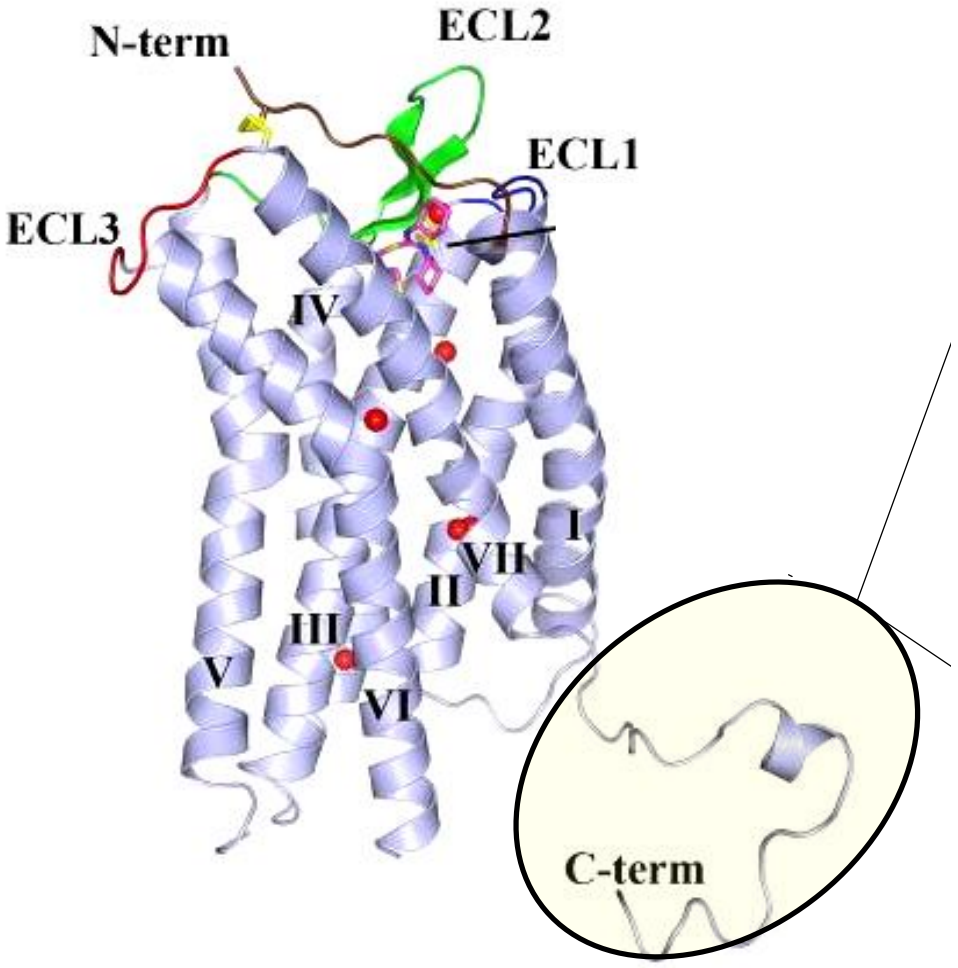


2% non-L265P MYD88 mutations

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%

CXCR4 mutations in Waldenström macroglobulinemia



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%

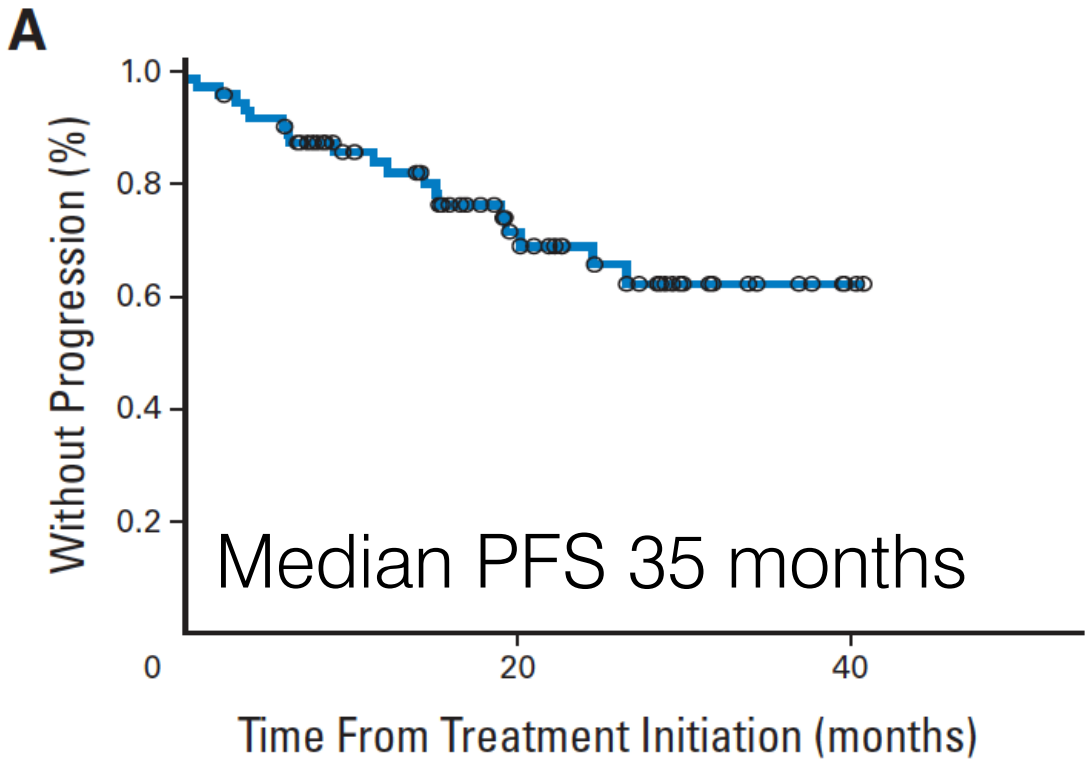
Hunter et al. Blood 2014
Xu et al. Br J Haematol 2017

FRONTLINE TREATMENT OPTIONS

Primary Treatment of Waldenström Macroglobulinemia With Dexamethasone, Rituximab, and Cyclophosphamide

Response:

- CR 7%
- PR 67%
- MR 9%
- ORR 83%



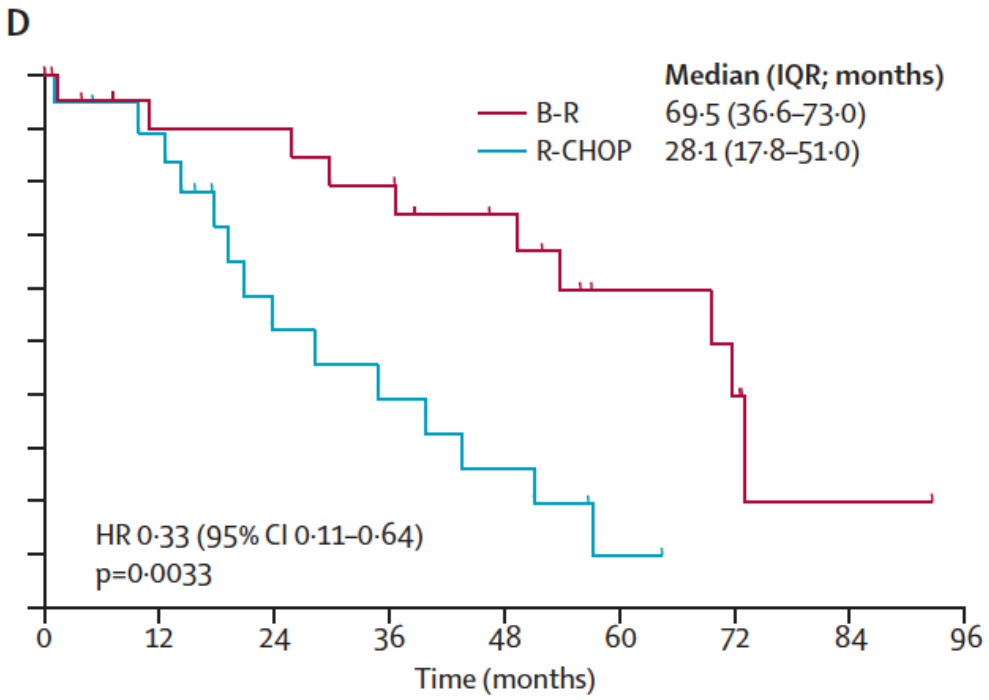
Grade ≥3 adverse events:

- Neutropenia 9%
- Hypotension 4%
- Headache 2%

Dimopoulos et al. J Clin Oncol 2007
Kastritis et al. Blood 2015

Bendamustine plus rituximab versus CHOP plus rituximab as first-line treatment for patients with indolent and mantle-cell lymphomas: an open-label, multicentre, randomised, phase 3 non-inferiority trial

	B-R (n=261)	CHOP-R (n=253)
Age (years)	64 (34–83)	63 (31–82)
<60	94 (36%)	90 (36%)
61–70	107 (41%)	105 (42%)
>70	60 (23%)	58 (23%)
Stage		
II	9 (3%)	9 (4%)
III	50 (19%)	47 (19%)
IV	202 (77%)	197 (78%)
Histology		
Follicular	139 (53%)	140 (55%)
Mantle cell	46 (18%)	48 (19%)
Marginal zone	37 (14%)	30 (12%)
Lymphoplasmacytic*	22 (8%)	19 (8%)
Small lymphocytic	16 (6%)	11 (4%)

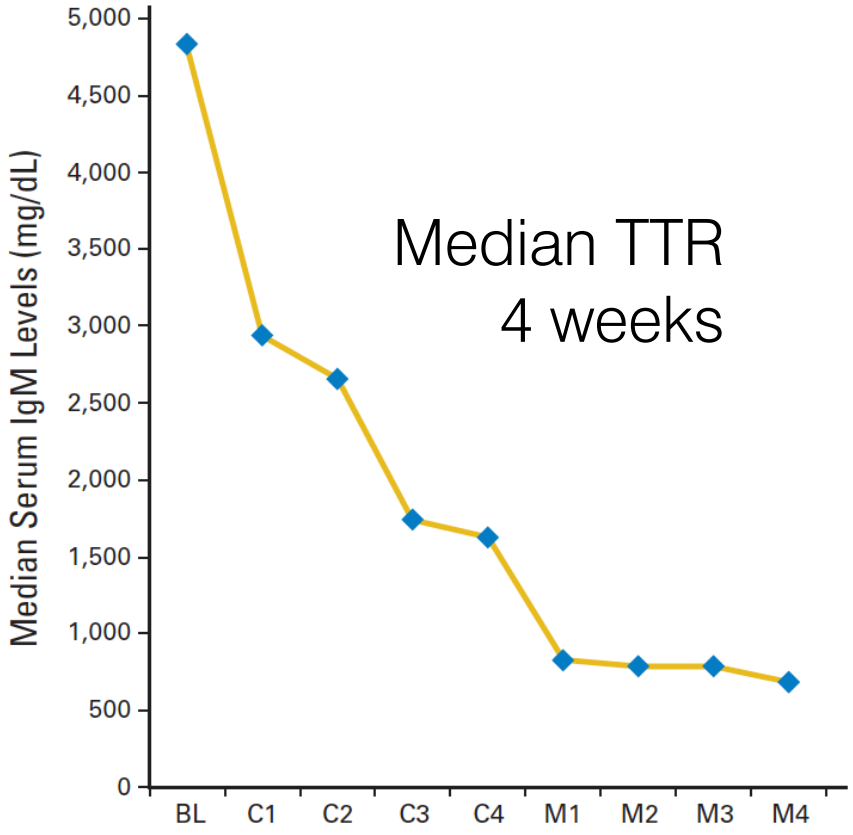


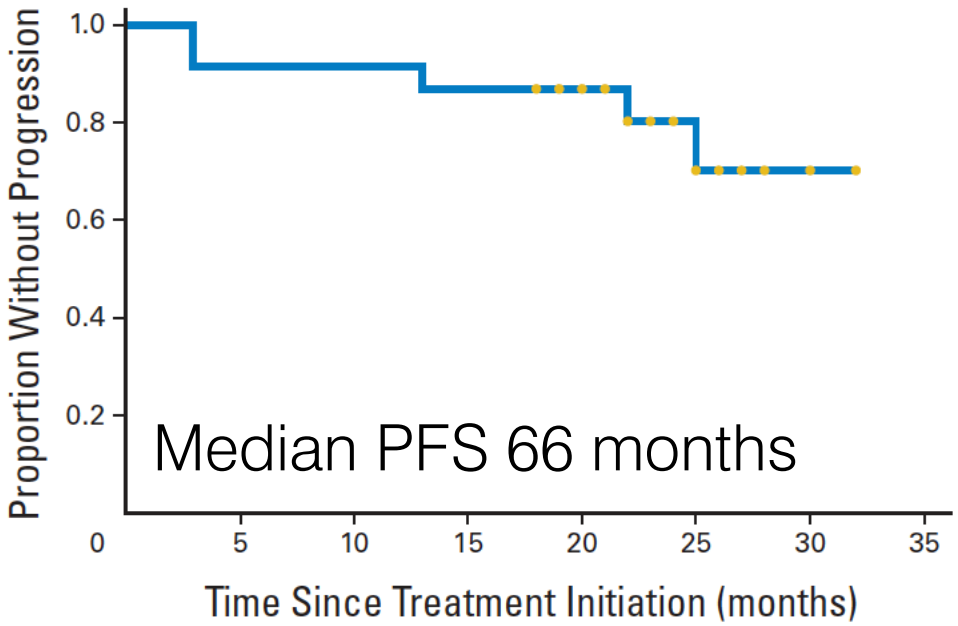
Grade ≥3 adverse events:

- Neutropenia 29%
- Anemia 3%
- Thrombocytopenia 5%

Rummel et al. Lancet Oncol 2013

Primary Therapy of Waldenström Macroglobulinemia With Bortezomib, Dexamethasone, and Rituximab: WMCTG Clinical Trial 05-180



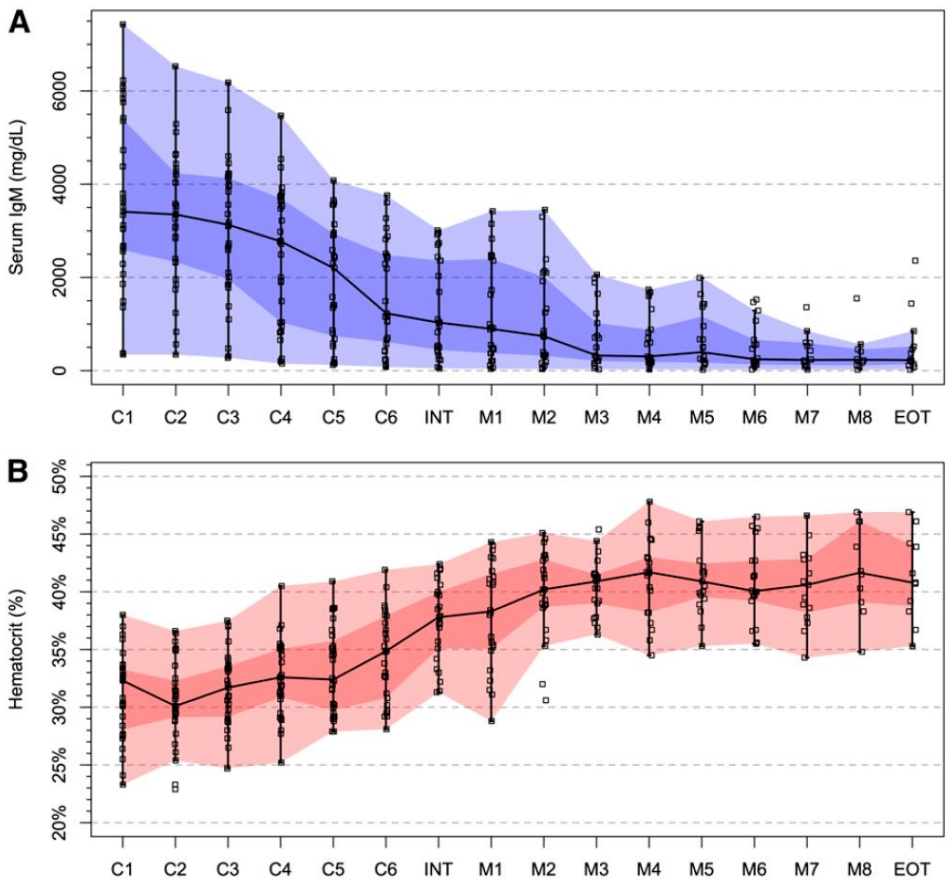


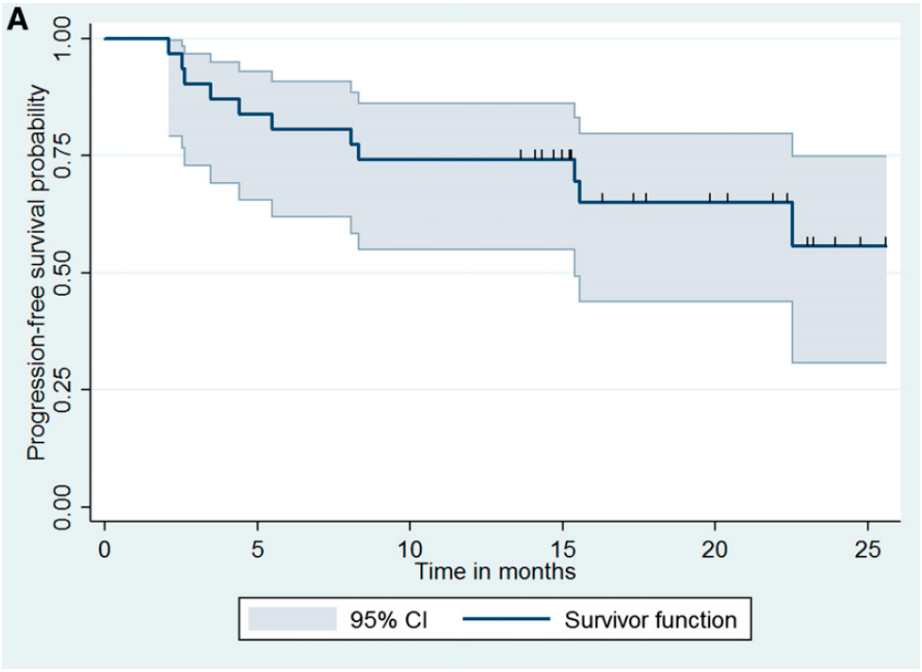
Grade ≥3 adverse events:

- Neutropenia 30%
- Neuropathy 30%
- Thrombocytopenia 9%
- Anemia 4%
- Arrhythmia 4%
- Pneumonia 4%

Treon et al. J Clin Oncol 2009

Carfilzomib, rituximab, and dexamethasone (CaRD) treatment offers a neuropathy-sparing approach for treating Waldenström's macroglobulinemia



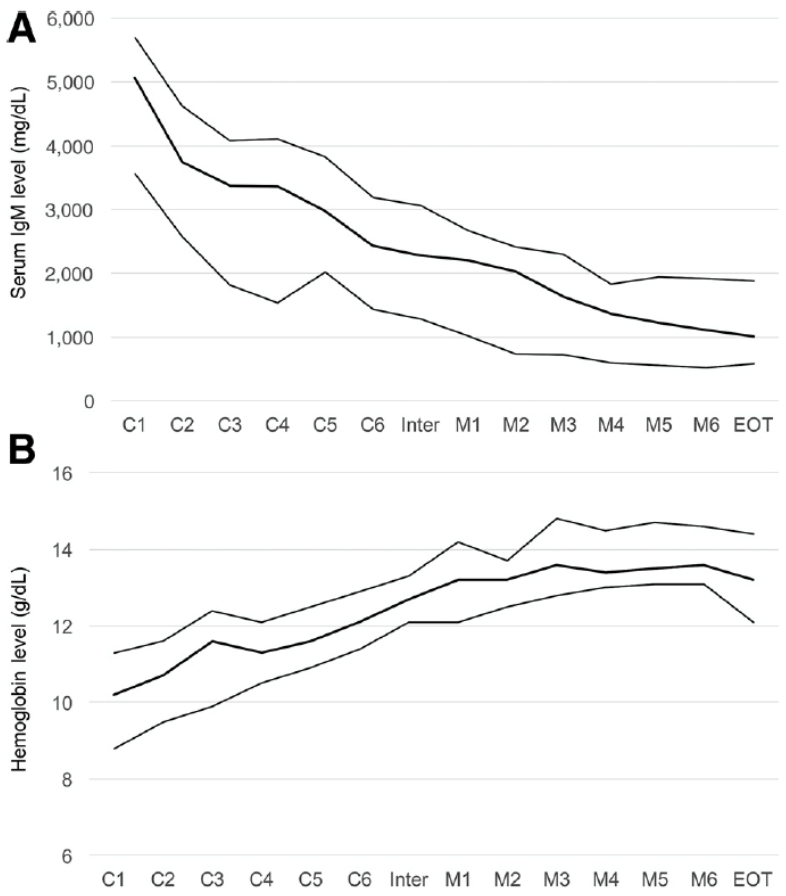


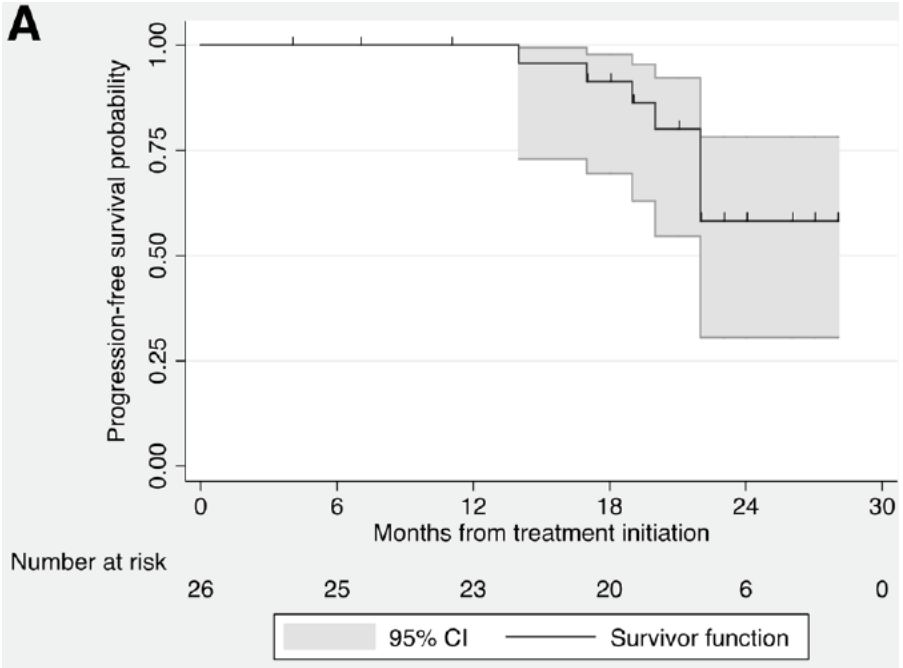
Grade ≥3 adverse events:

- Fatigue 23%
- Hyperlipasemia 16%
- Neutropenia 10%
- Rash 10%
- Hyperbilirubinemia 7%
- Azotemia 7%

Treon et al. Blood 2014

Prospective Clinical Trial of Ixazomib, Dexamethasone, and Rituximab as Primary Therapy in Waldenström Macroglobulinemia



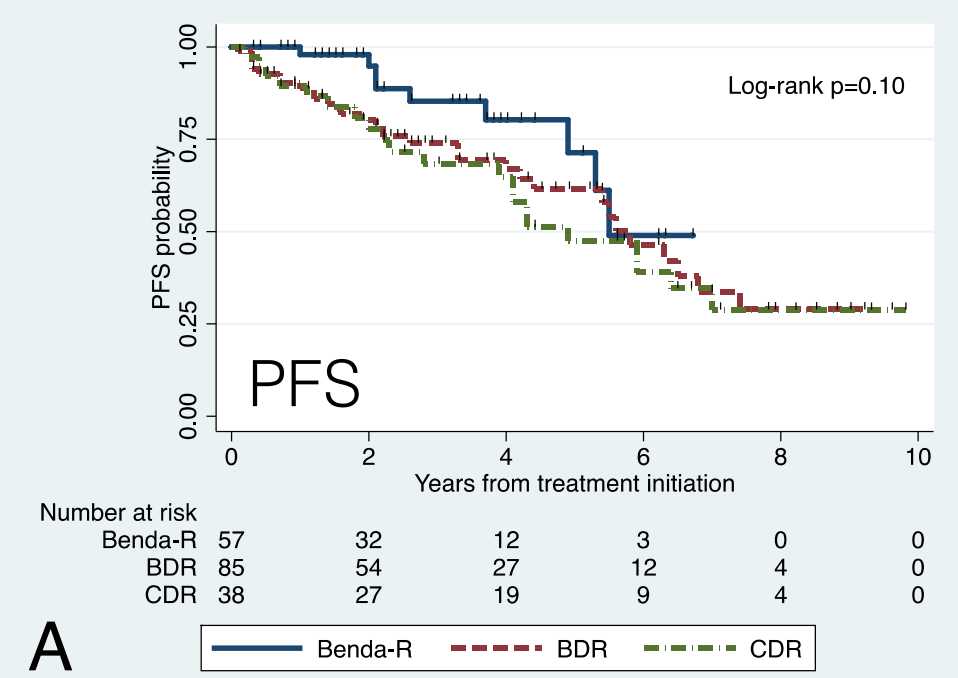


Grade ≥3 adverse events:

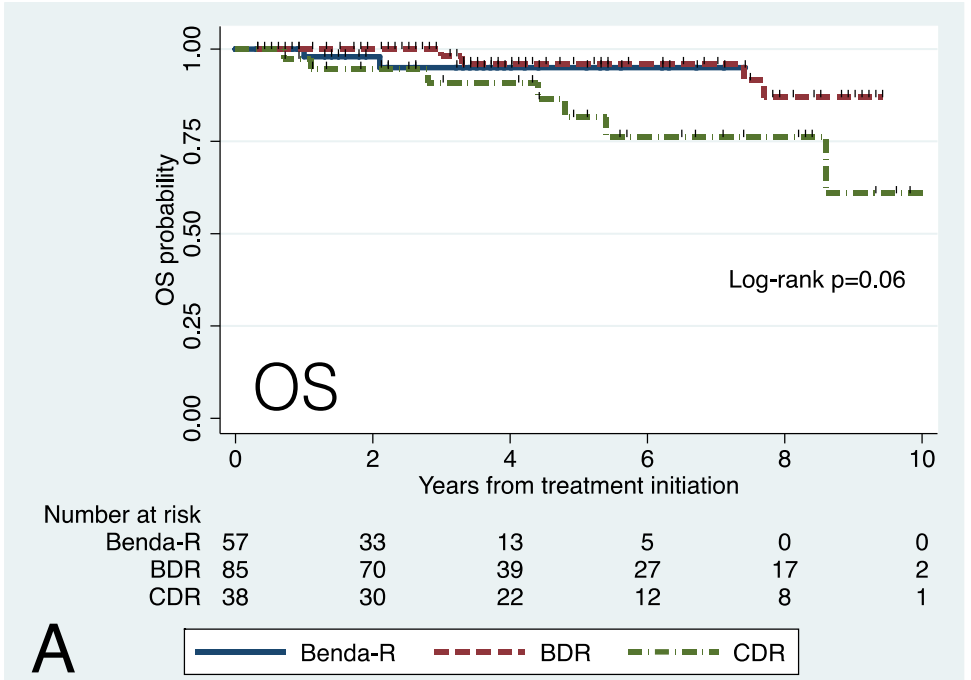
- Neuropathy 4%
- Sepsis 4%
- Pneumonia 4%

Castillo et al. Clin Cancer Res 2018

Response and survival for primary therapy combination regimens and maintenance rituximab in Waldenström macroglobulinaemia



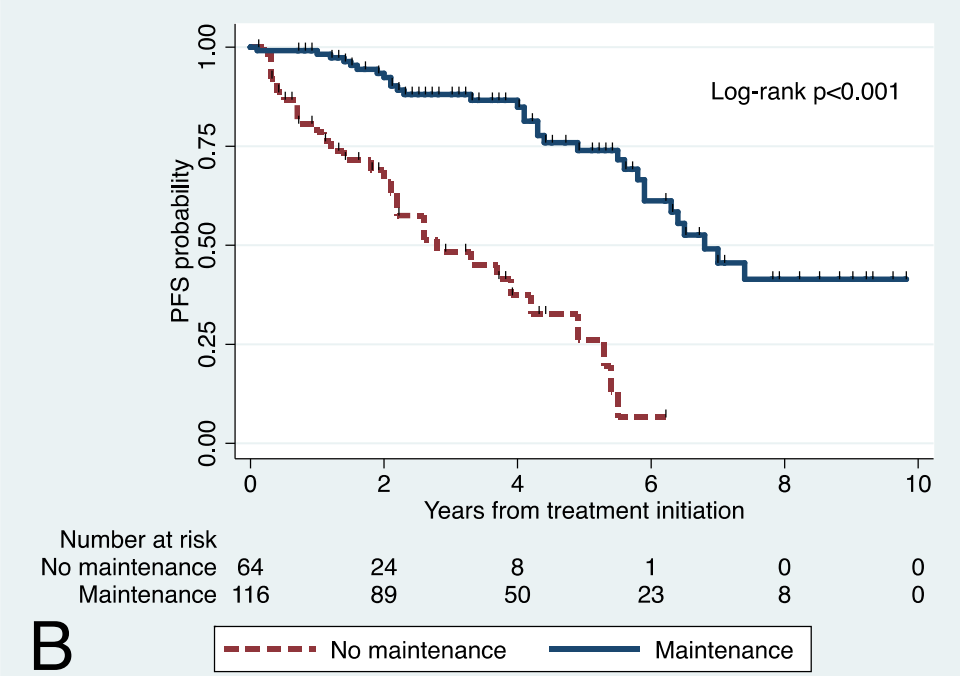
Regimen	HR (95% CI)	P
CDR	1.00 (Ref)	
Benda-R	0.18 (0.07-0.43)	<0.001
BDR	0.55 (0.30-0.99)	0.046



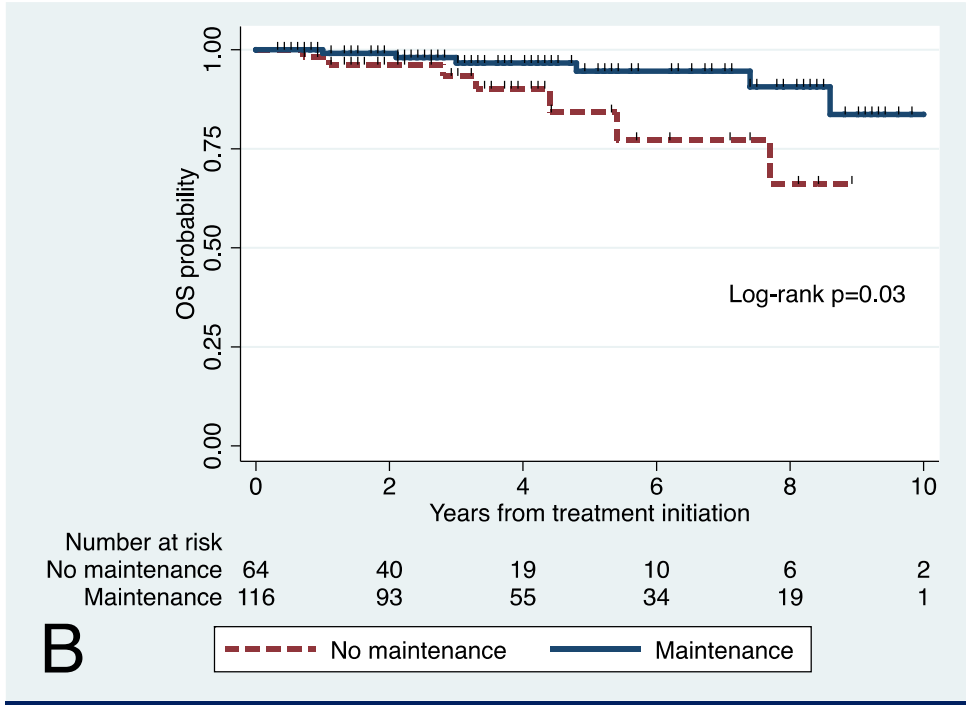
Regimen	HR (95% CI)	P
CDR	1.00 (Ref)	
Benda-R	0.24 (0.05-1.27)	0.09
BDR	0.14 (0.03-0.61)	0.009

Castillo et al. Br J Haematol 2018

Response and survival for primary therapy combination regimens and maintenance rituximab in Waldenström macroglobulinaemia



Regimen	HR (95% CI)	P
Observation	1.00 (Ref)	
Maintenance	0.54 (0.45-0.66)	<0.001



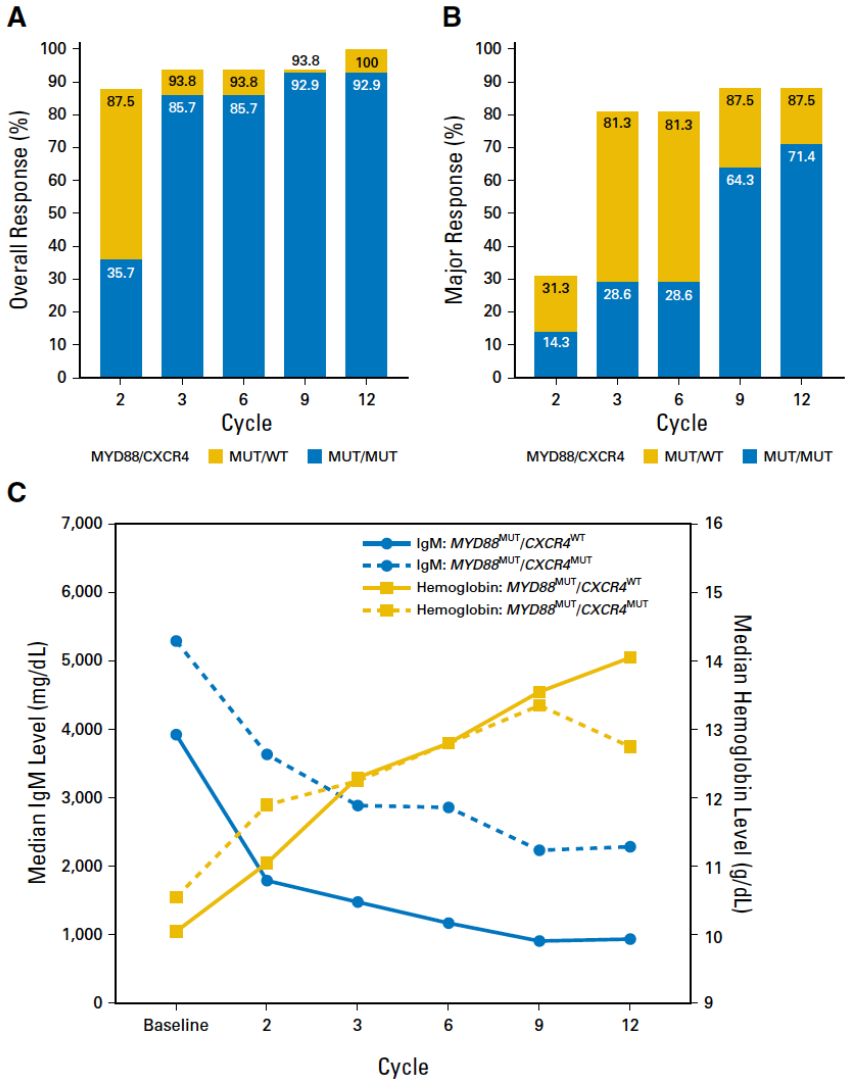
Regimen	HR (95% CI)	P
Observation	1.00 (Ref)	
Maintenance	0.72 (0.55-0.93)	0.01

Castillo et al. Br J Haematol 2018

Ibrutinib Monotherapy in Symptomatic, Treatment-Naïve Patients With Waldenström Macroglobulinemia

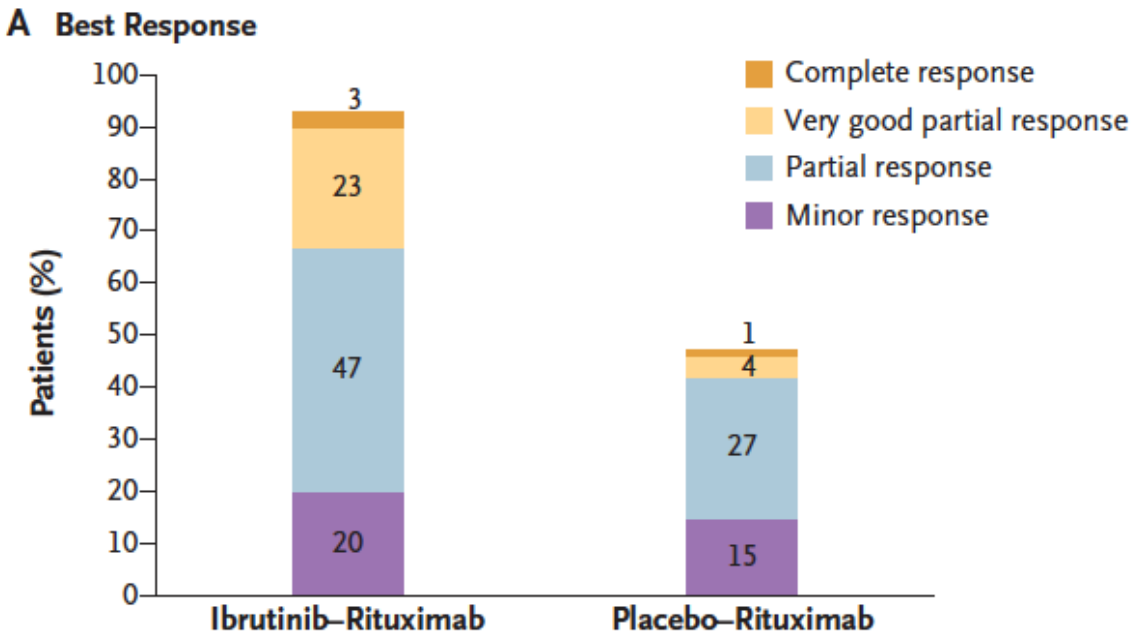
	All	MYD88+ CXCR4-	MYD88+ CXCR4+	p
ORR	100%	100%	100%	1.00
Major	83%	94%	71%	0.16
VGPR	20%	31%	7%	0.18
TTR	1	0.9	1.7	0.07
TTMR	1.9	1.8	7.3	.01

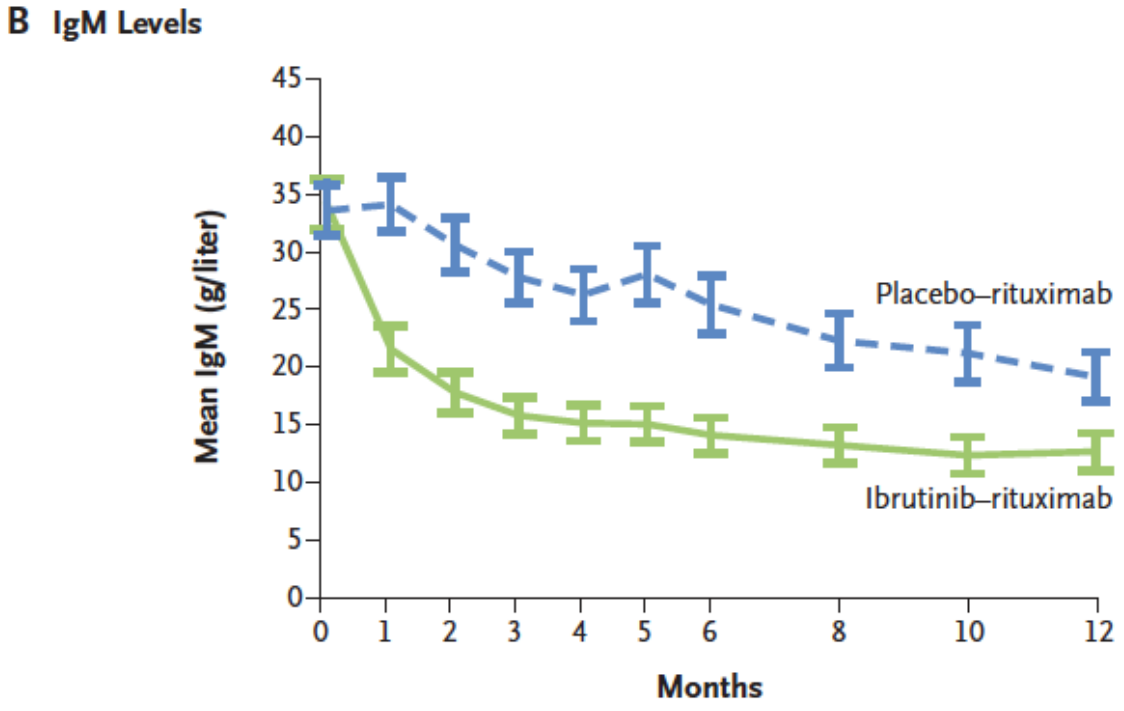
18-month PFS: 92%



Treon et al. J Clin Oncol 2018

Phase 3 Trial of Ibrutinib plus Rituximab in Waldenström's Macroglobulinemia



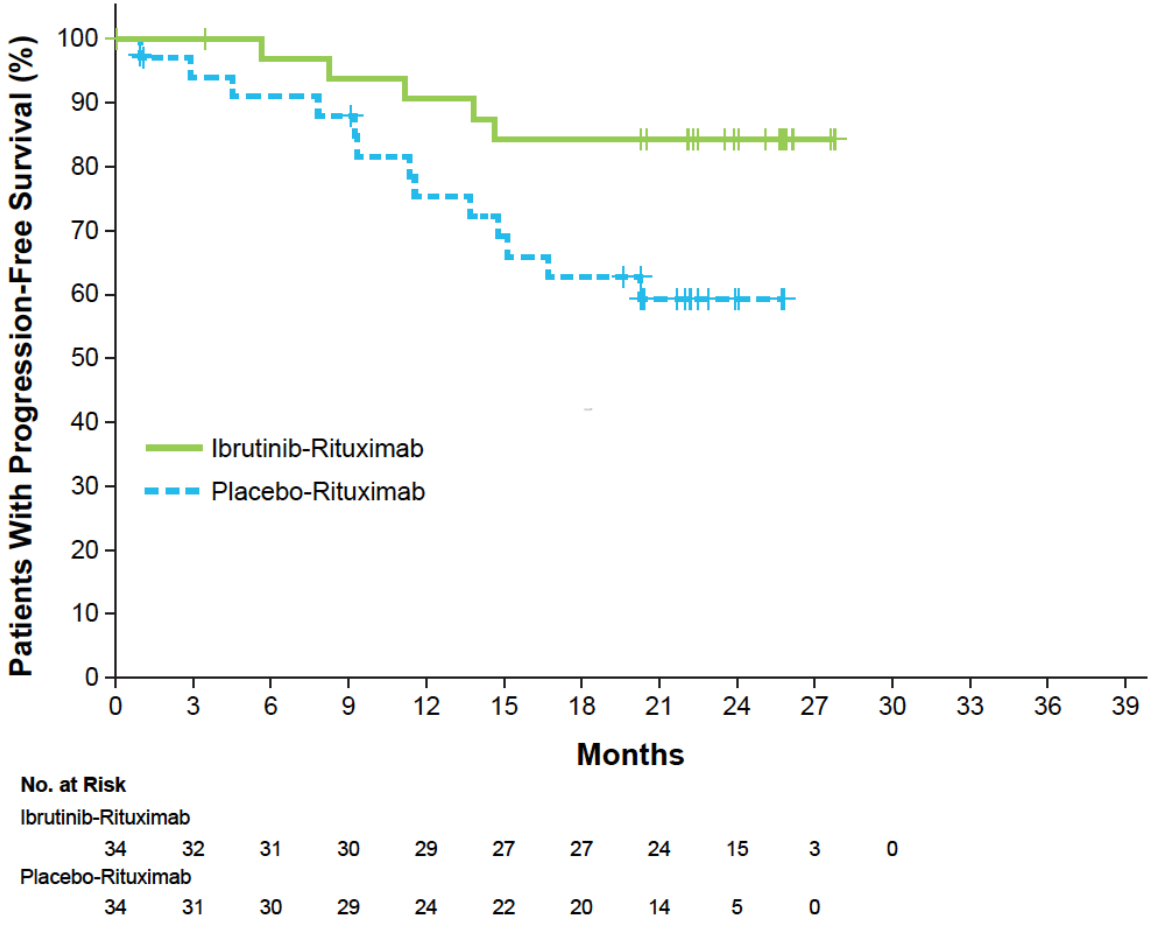


No. of Patients

Placebo–rituximab	75	67	64	63	61	57	54	54	46	44
Ibrutinib–rituximab	75	71	71	72	73	71	71	71	70	70

Dimopoulos et al. N Engl J Med 2018

Phase 3 Trial of Ibrutinib plus Rituximab in Waldenström's Macroglobulinemia



Grade ≥3 adverse events:

- Hypertension 13%
- Atrial fibrillation 12%
- Anemia 11%
- Neutropenia 9%
- Pneumonia 9%
- Hyponatremia 5%
- Infusion reaction 1%

Dimopoulos et al. N Engl J Med 2018

Is ibrutinib-rituximab better than ibrutinib alone?

	Ibrutinib + rituximab	Ibrutinib alone
N previously untreated	34	30
N previously treated	41	-
ORR	92%	100%
MRR	72%	83%
VGPR	23%	20%
PFS	30-mo: 82%	18-mo: 92%

Dimopoulos et al. N Engl J Med 2018; Treon et al. J Clin Oncol 2018

CLINICAL TRIALS

Efficacy of First Line DRC +/- Bortezomib for Patients With Waldenström Macroglobulinemia

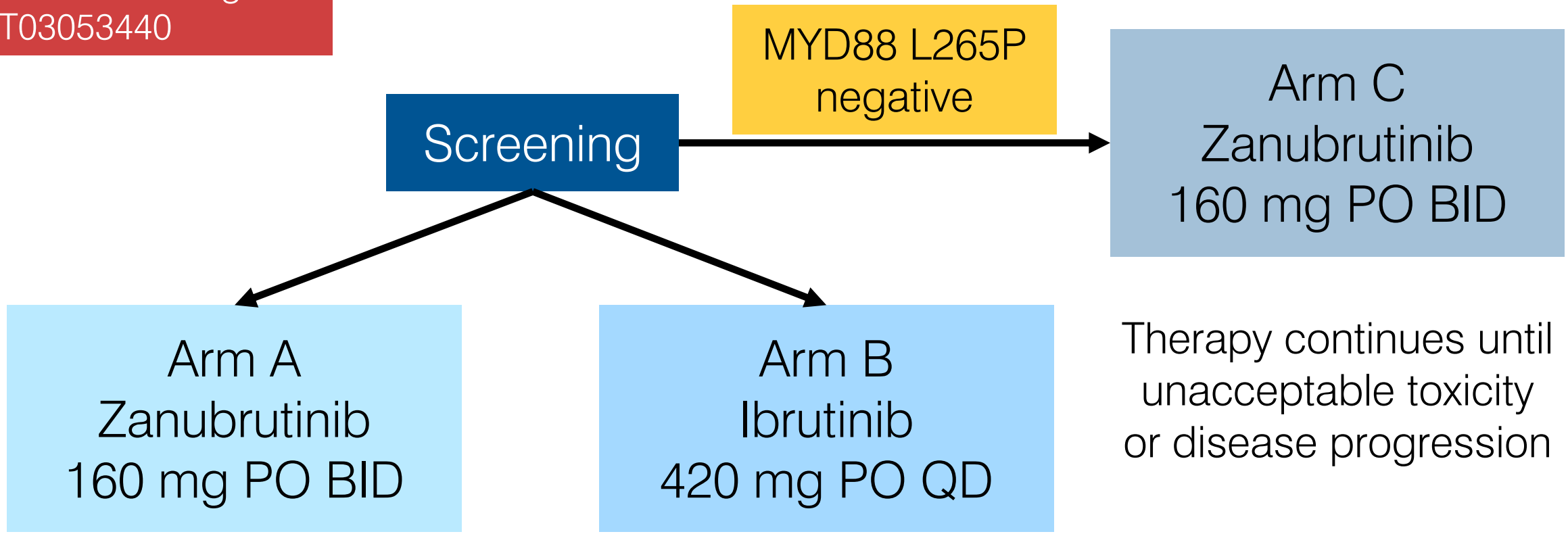
- Sponsor: University of Ulm
- N=202 (1:1)
- Primary outcome: PFS
- Secondary outcomes: CR, TTF, OS, ORR
- ID: NCT01788020

Rituximab and Ibrutinib Versus DRC as Initial Therapy for Waldenström Macroglobulinemia (RAINBOW)

- Sponsor: University College London
- N=148 (1:1)
- Primary outcomes: PFS
- Secondary outcomes: Safety & tolerability, ORR, TNT, DOR, OS, QOL
- ID: NCT04061512

A Study Comparing BGB-3111 and Ibrutinib in Subjects With Waldenström Macroglobulinemia

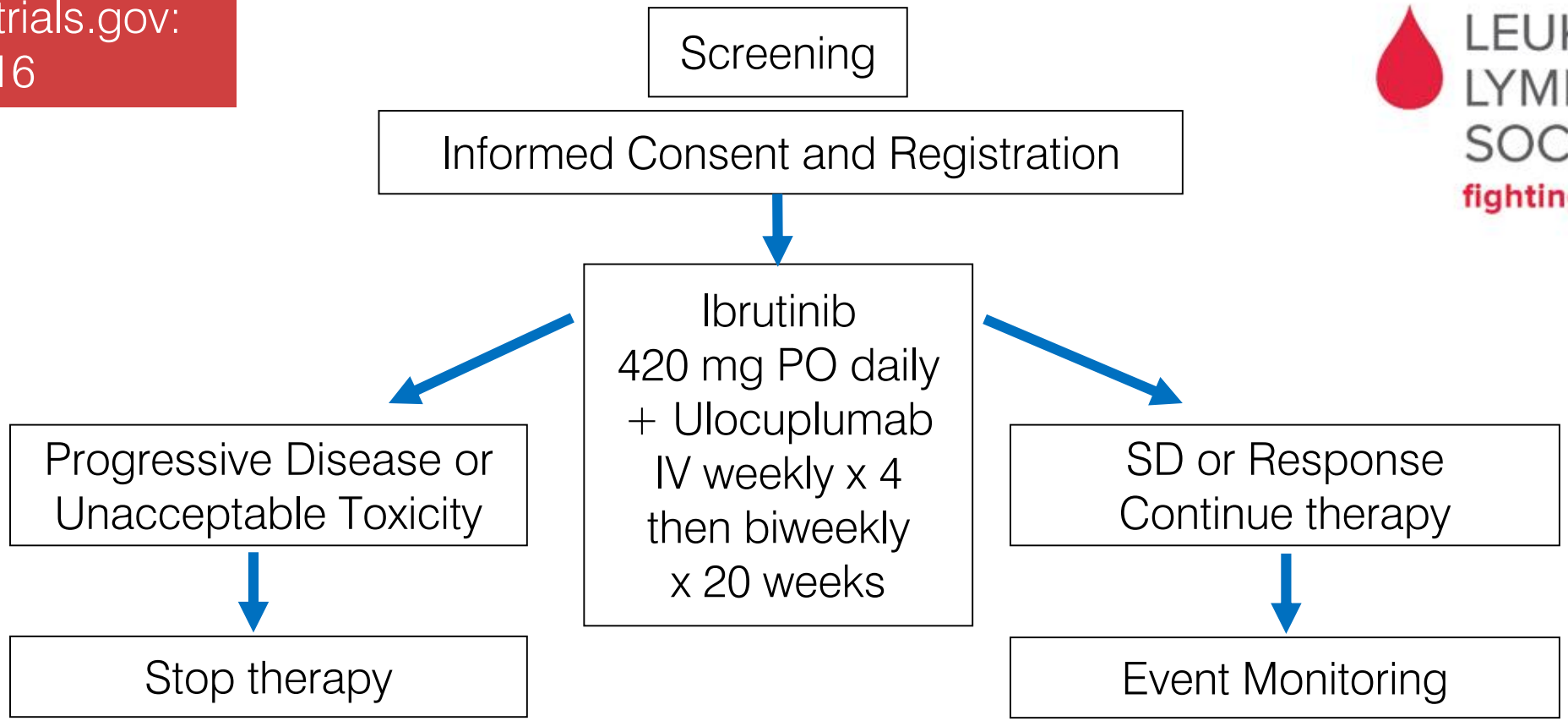
www.clinicaltrials.gov: NCT03053440



Therapy continues until unacceptable toxicity or disease progression

Phase I/II study of ibrutinib and ulocuplumab in CXCR4 mutated Waldenström macroglobulinemia patients

www.clinicaltrials.gov: NCT03225716



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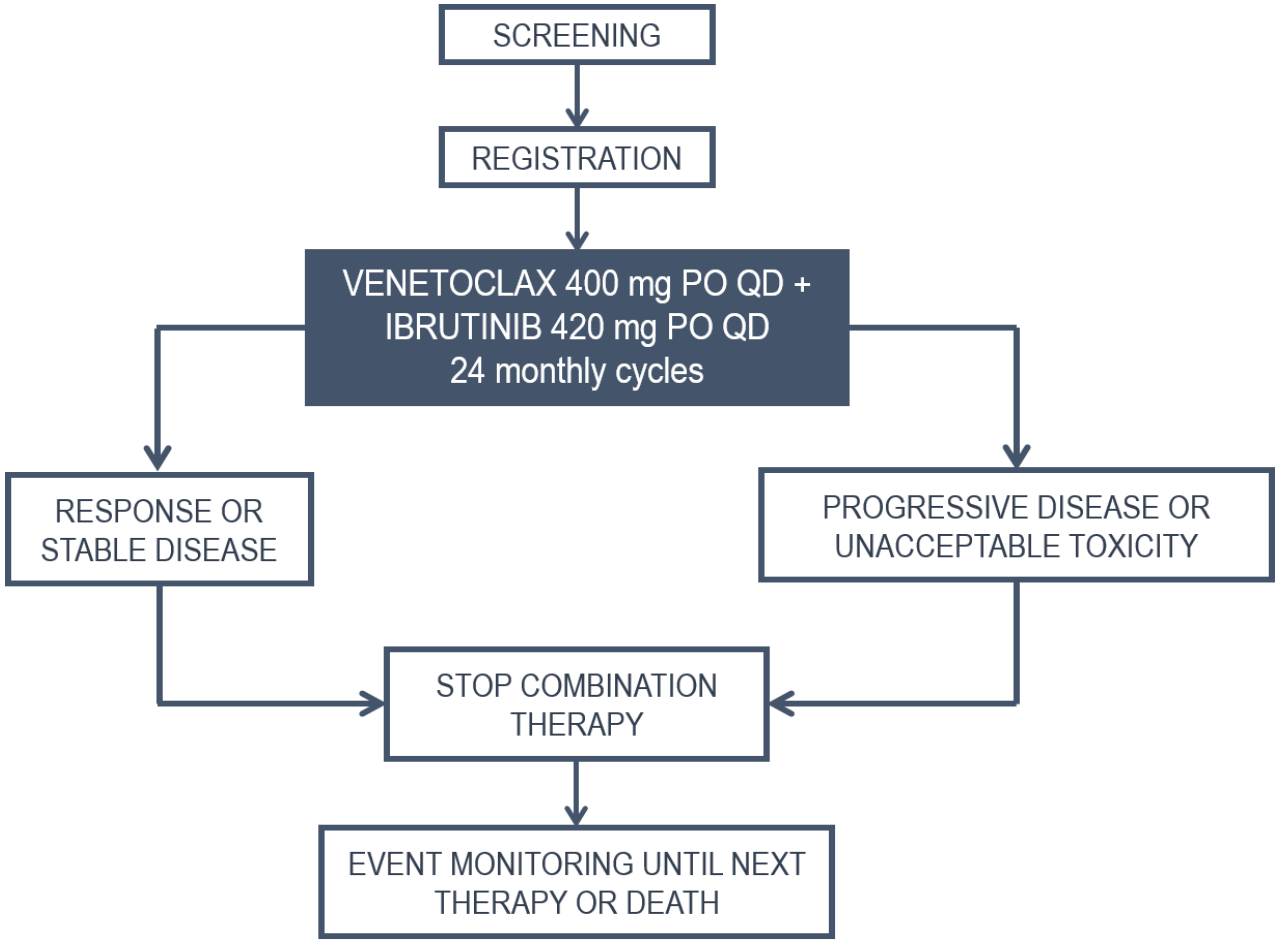
fighting blood cancers

Ibrutinib and venetoclax for patients with previously untreated Waldenström macroglobulinemia



Sample size

50 patients

Primary outcome

VGPR ≥40% at 2 years

Secondary outcomes

- Impact of genomic profiling
- Overall response rate
- Safety profile
- Ability to stop therapy

Conclusions

- Alkylators, proteasome inhibitors and BTK inhibitors with and without rituximab are standard frontline treatment options.
- The choice of therapy is largely personalized.
- Future studies should focus on deeper, longer responses and finite treatments with lower toxicity rates.
- Clinical trial referral and participation are critical.

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