How I Manage IgM Disease and Systemic Impact

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

Dana-Farber
Cancer Institute

Disclosures

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

A case

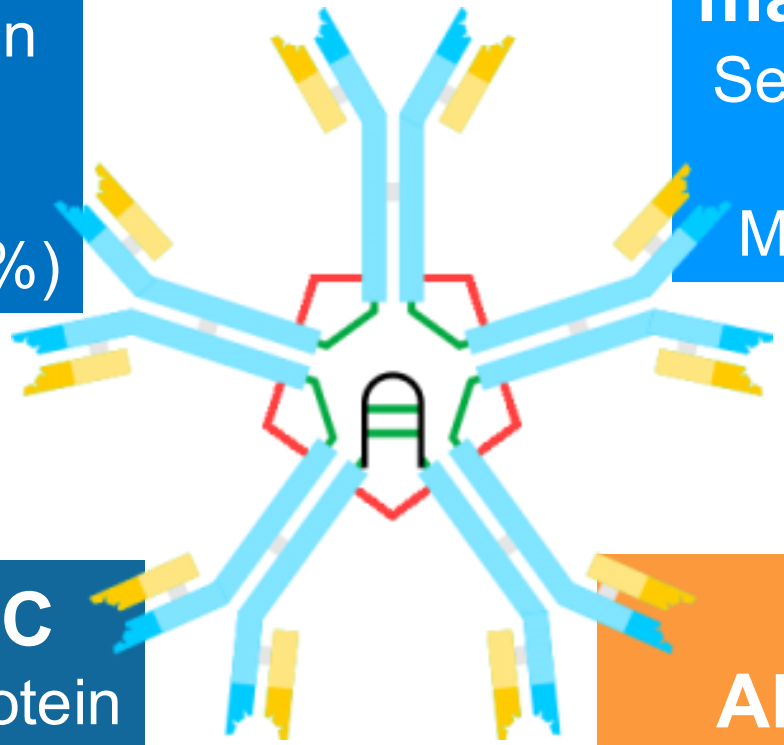
62M with irrelevant past medical history presents with asymptomatic increase in serum creatinine to 1.9 mg/dl from a baseline of 0.8 mg/dl.

24-hour urine protein quantification showed albuminuria of 800 mg.

SPEP/SIFE showed an IgM-lambda monoclonal paraprotein.

IgM MGUS, NOS
Serum IgM paraprotein
No LPL clusters
No monotypic PCs
MYD88 L265P (60-70%)

Waldenström macroglobulinemia
Serum IgM paraprotein
LPL involvement
MYD88 L265P (90%)



IgM MGUS, PC
Serum IgM paraprotein
No LPL clusters
<10% monotypic PCs
MYD88 L265P (0%)

IgM-related AL amyloidosis
Congo red stain
Mass spectrometry
Lambda>kappa restriction

Myeloma Complications: Renal disease

Light-chain cast nephropathy (60-70%)

Amyloidosis

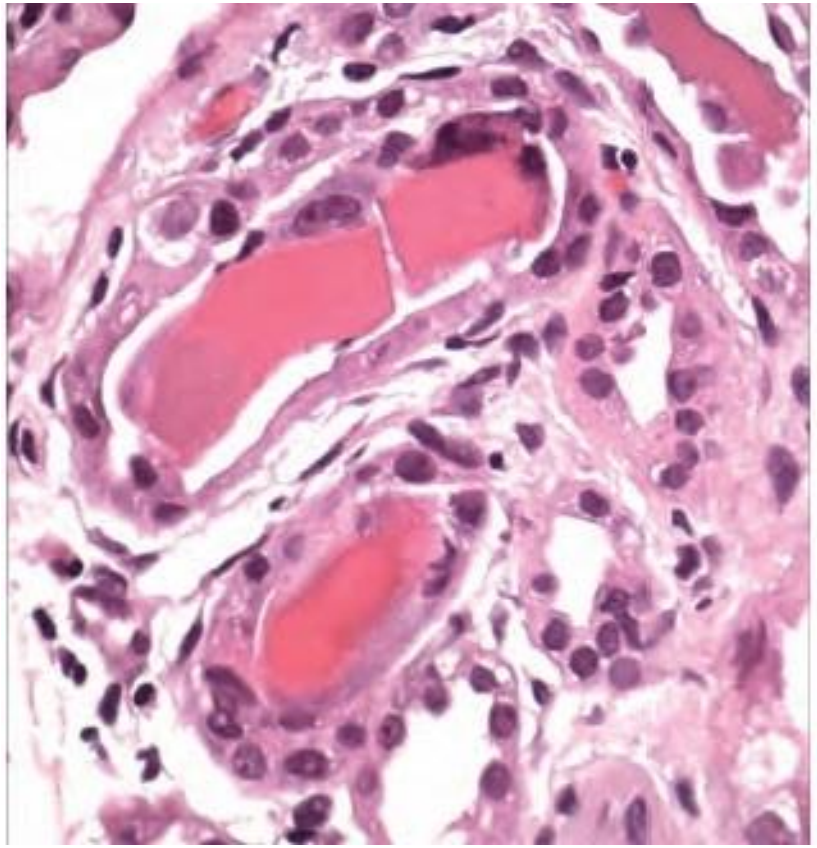
Cryoglobulinemia

Hypercalcemia

Hyperviscosity

Infiltrative interstitial nephropathy

Plasma cell infiltration

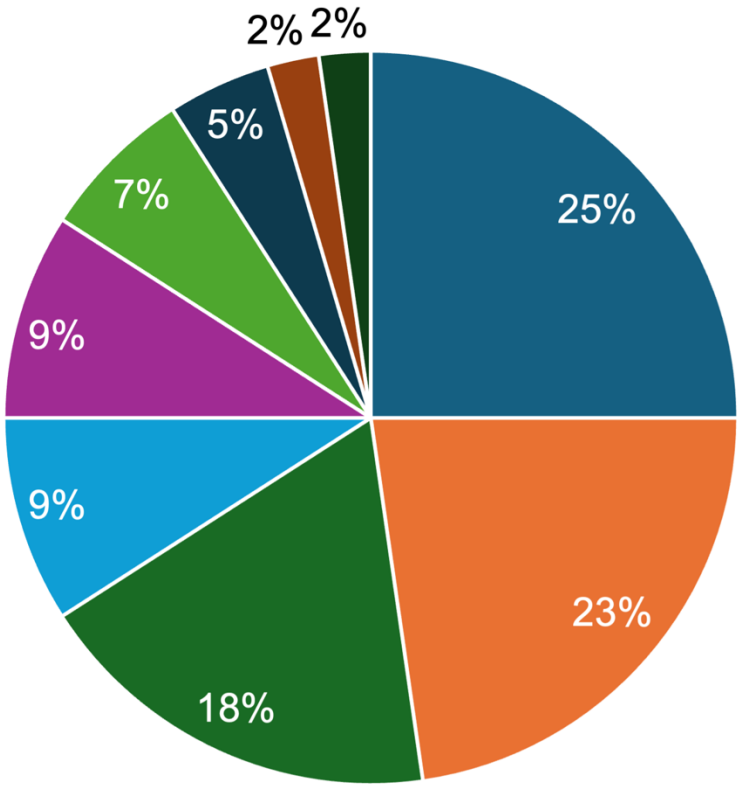


Management of Renal Disease in MM

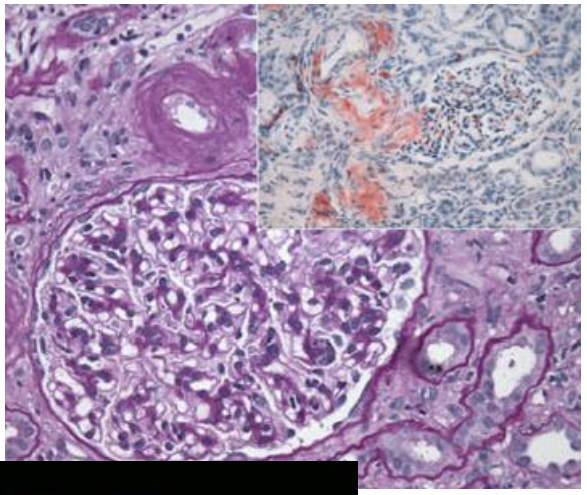
Per NCCN guidelines:

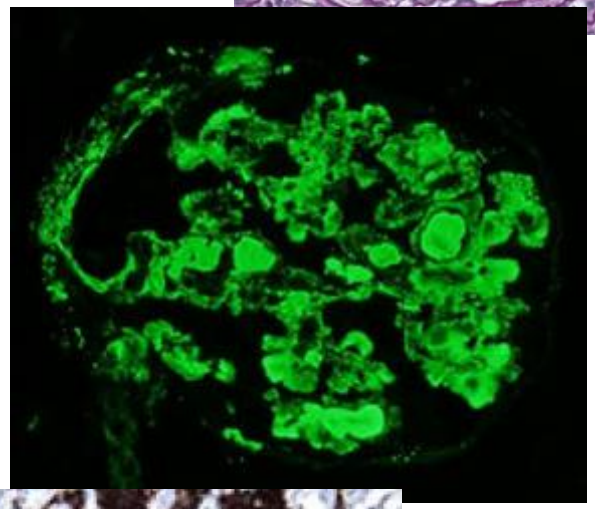
- Provide hydration to dilute tubular light chains; goal urine output is 100-150 cc/h
- Consider renal biopsy in patients with significant proteinuria
- Treat with pulse dexamethasone and regimens containing bortezomib or daratumumab

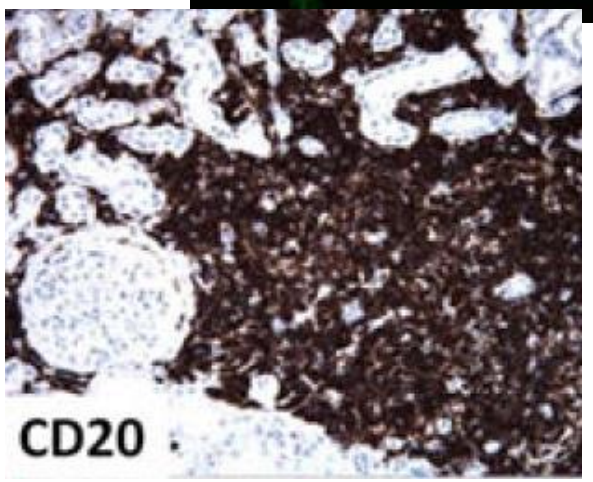
Renal disease related to Waldenström macroglobulinaemia: incidence, pathology and clinical outcomes



- AL amyloidosis
- IgM/cryo deposition
- LPL infiltration
- LC deposition
- LC cast nephropathy
- TMA
- MCD
- LC tubulopathy
- Membranous GN

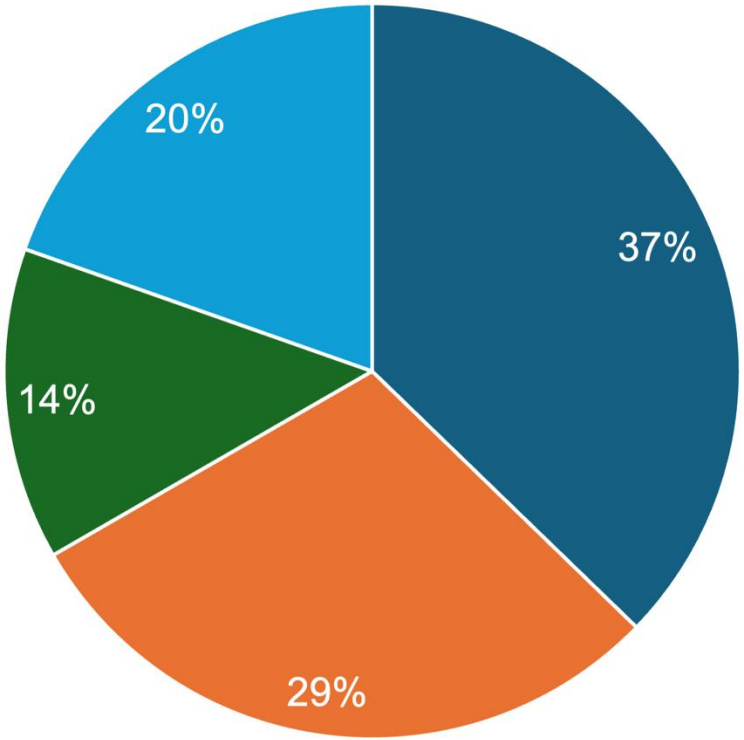




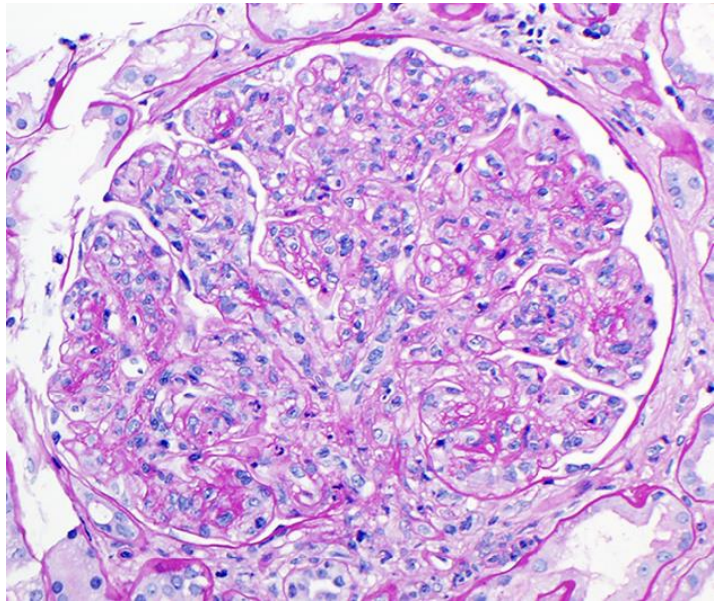


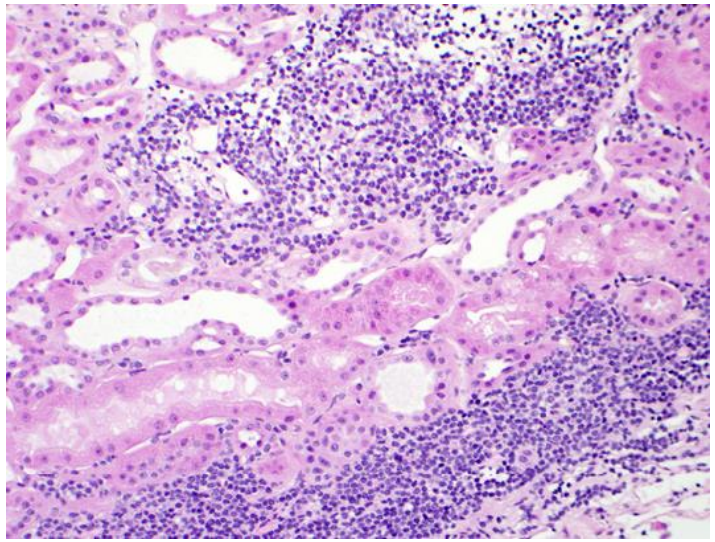
Vos et al. Br J Haematol 2016

Kidney Involvement of Patients with Waldenström Macroglobulinemia and Other IgM-Producing B Cell Lymphoproliferative Disorders



- Amyloid glomerulopathy
- Non-amyloid glomerulopathy
- Tubulointerstitial nephritides
- Non-monoclonal gammopathy related

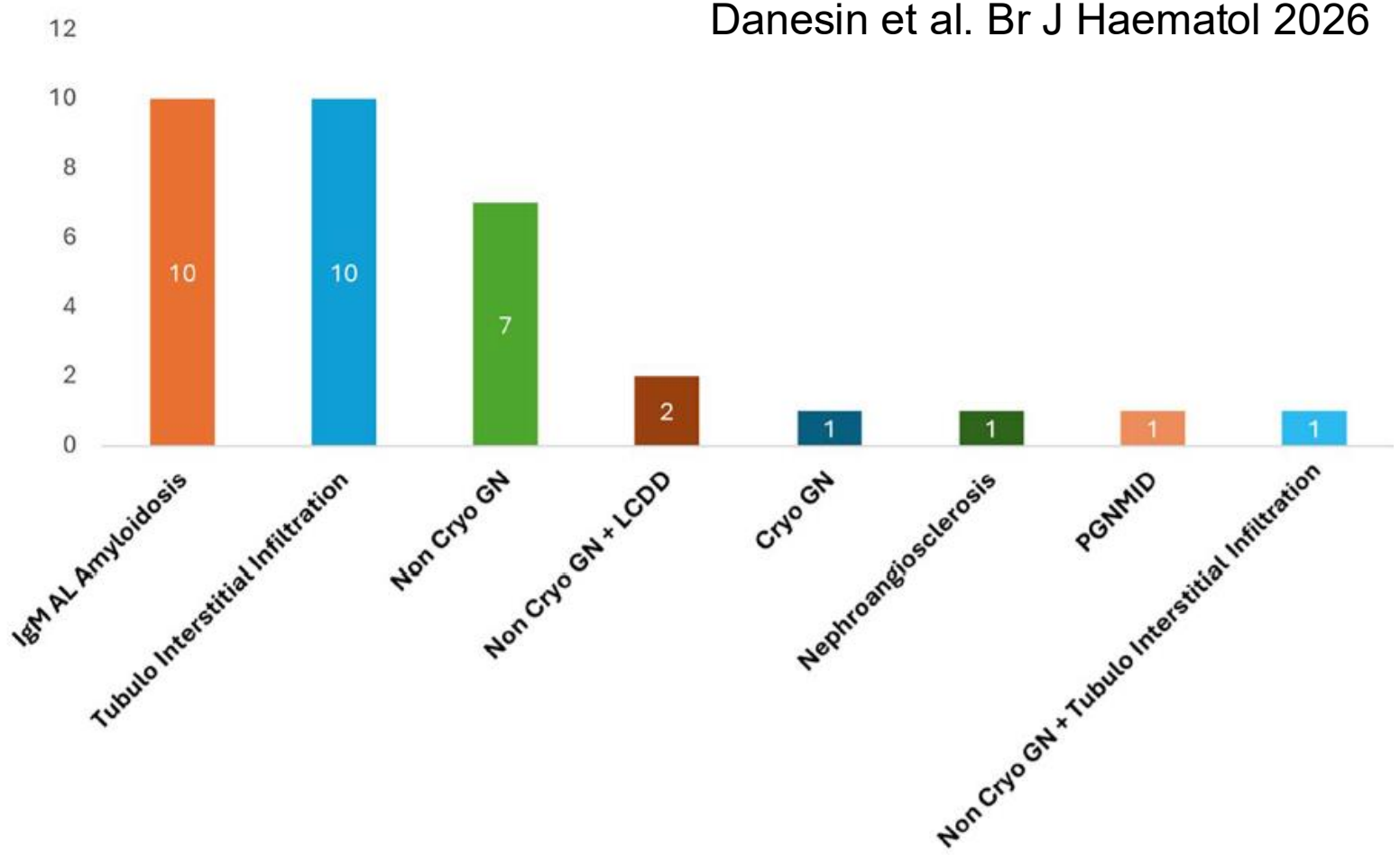




Higgins et al. Clin J Am Soc Nephrol 2018

Renal dysfunction in symptomatic Waldenström macroglobulinaemia: A nationwide Italian multicentre study

Danesin et al. Br J Haematol 2026



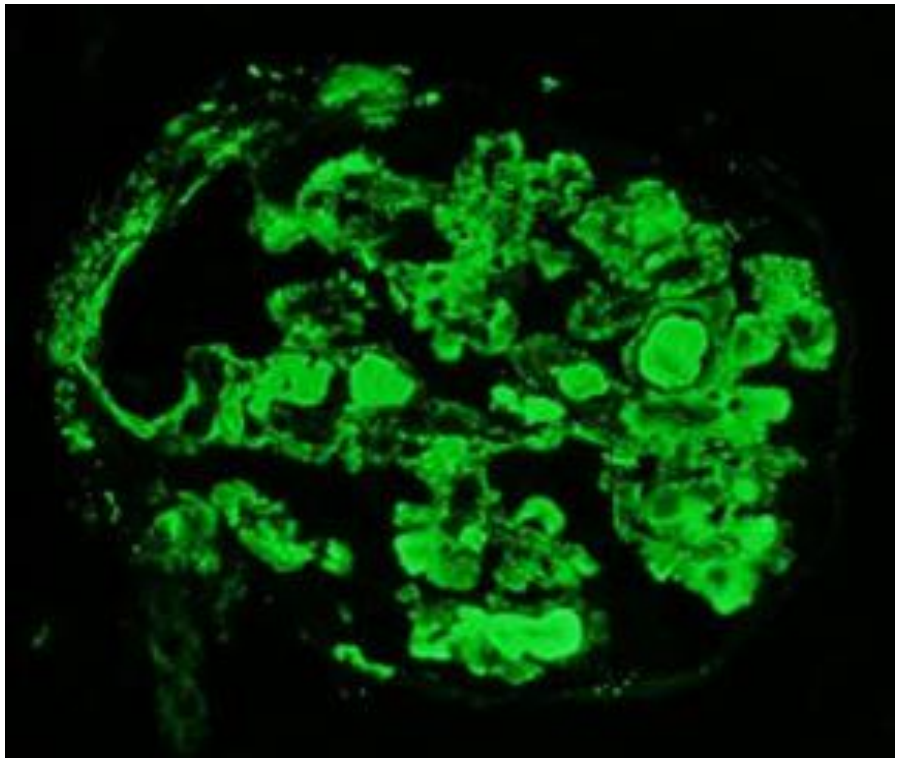
Case continuation

Bone marrow biopsy:

- Polytypic B cells (10%), polytypic plasma cells (5%)
- MYD88 L265P detected by PCR

Kidney biopsy:

- MONOCLONAL IMMUNOGLOBULIN DEPOSITION DISEASE, WITH IgM/LAMBDA SPECIFICITY



Diagnosis: IgM MGRS, NOS

Management of IgM MGRS

MONOCLONAL GAMMOPATHY OF RENAL SIGNIFICANCE

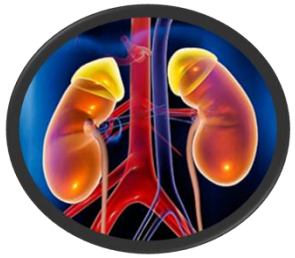
TREATMENT

For lymphoplasmacytic-related MGRS, see NCCN Guidelines for Waldenström Macroglobulinemia/Lymphoplasmacytic Lymphoma[a]

RESPONSE ASSESSMENT

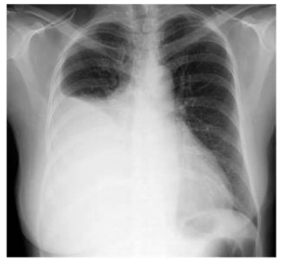
For IgM-associated MGRS, use the response criteria for WM (See NCCN Guidelines for Waldenström Macroglobulinemia/Lymphoplasmacytic Lymphoma)

Manifestations of Waldenström Macroglobulinemia

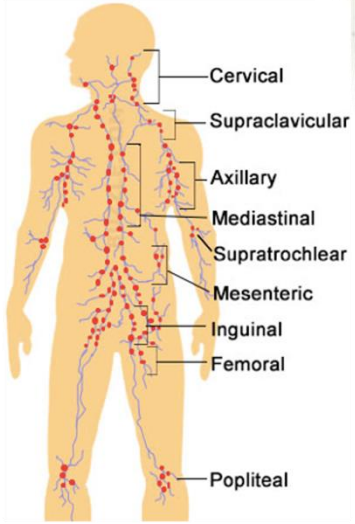


Renal involvement
(2-3%)

Bing Neel
Syndrome (1%)

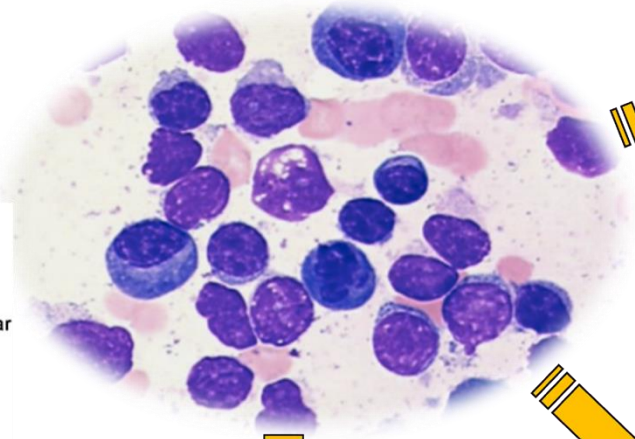


Pleural effusions
(1-2%)



Extramedullary
disease (20-50%)

Bone Marrow
↓HB>> ↓PLT> ↓WBC



Hyperviscosity Syndrome (15%)
Epistaxis, Headaches
Impaired vision

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

Hepcidin
↓Fe Anemia

Adapted from Derman et al. ASCO Ed Book 2022

Rituximab combination regimens

Regimen	n	ORR	Major	PFS (mo)
Cyclophosphamide-dex-R	72	83%	76%	Median: 35
Bortezomib-dex-R	59	85%	68%	Median: 42
Carfilzomib-dex-R	31	87%	68%	Median: 46
Ixazomib-dex-R	26	96%	77%	Median: 40
Bortezomib-Cyclophosphamide-dex-R	102	95%	85%	24-month: 81%

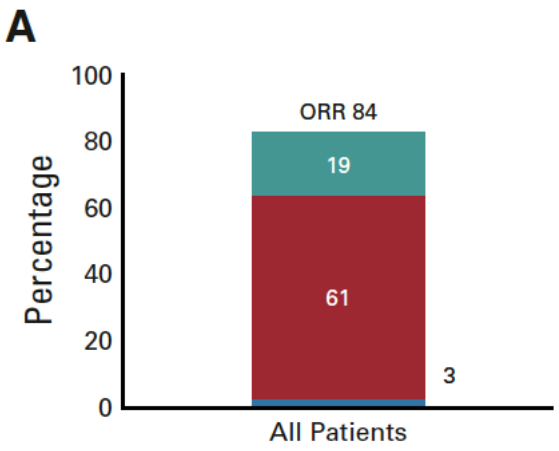
Dimopoulos et al. Blood 2014; Dimopoulos et al. Blood 2013; Treon et al. Blood 2014; Castillo et al. Blood Adv 2022; Buske et al. J Clin Oncol 2023

BTK inhibitors

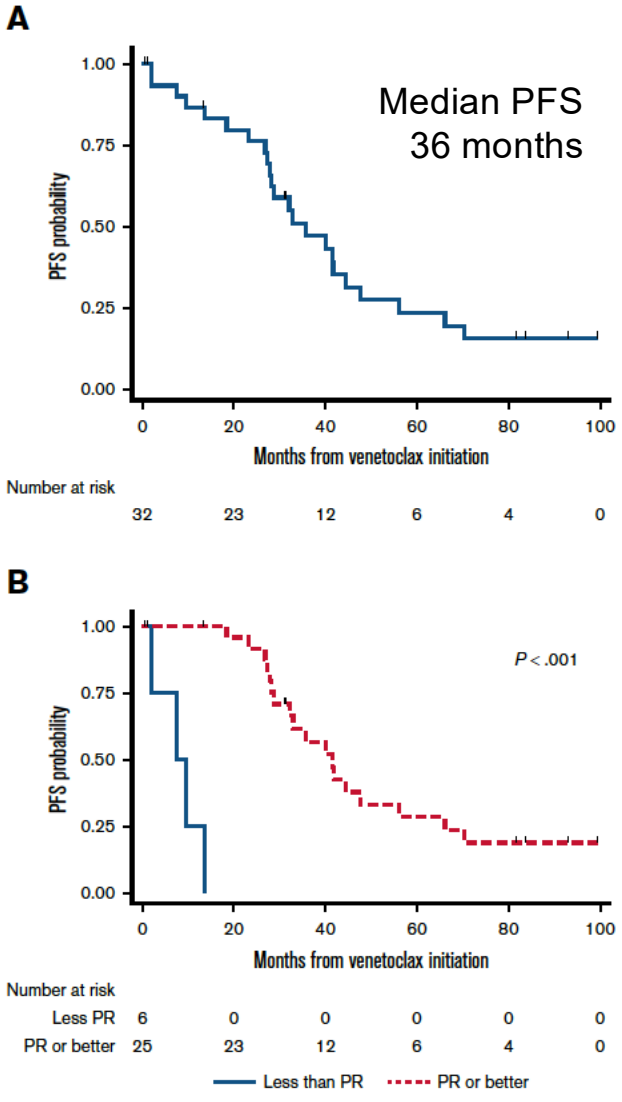
Regimen	N	ORR	Major	PFS
Ibrutinib (RR)	63	91%	73%	54% at 5 years
Ibrutinib (R-refractory)	31	90%	71%	Median 39 months
Ibrutinib (TN)	30	100%	87%	76% at 4 years
Ibrutinib-R (INNOVATE)	75	92%	76%	68% at 4.5 years
Zanubrutinib (ASPEN)	101	94%	77%	78% at 42 months

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; Dimopoulos et al. J Clin Oncol 2023

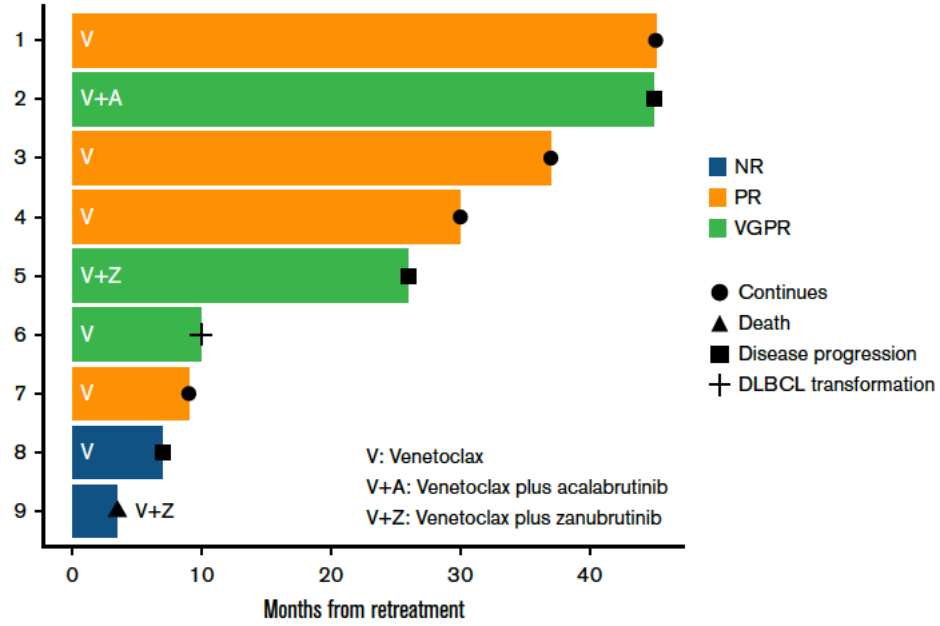
Long-term follow-up of venetoclax monotherapy in previously treated patients with Waldenström macroglobulinemia



Castillo et al. JCO 2022

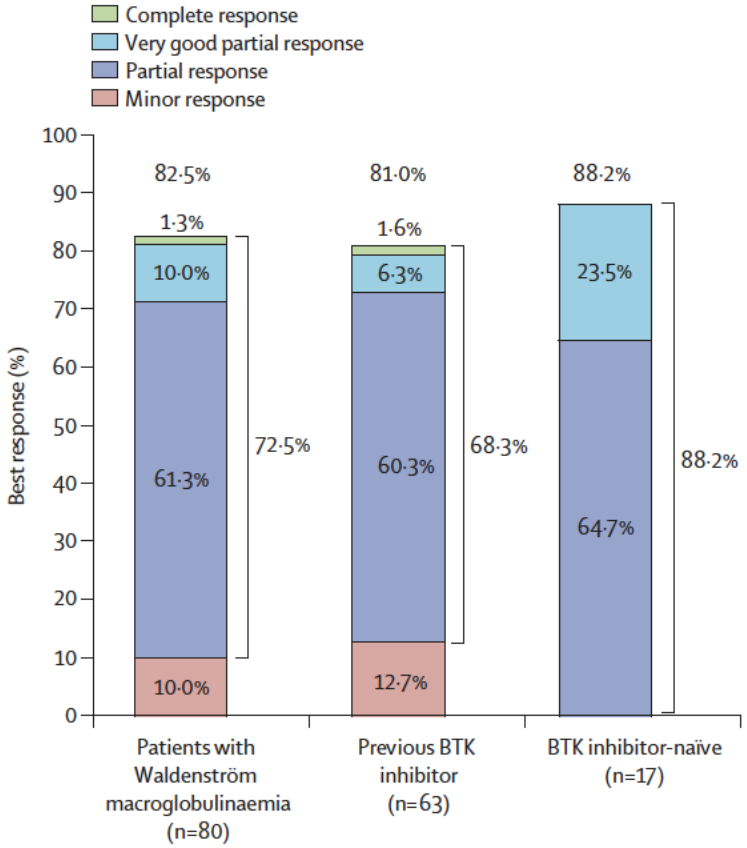


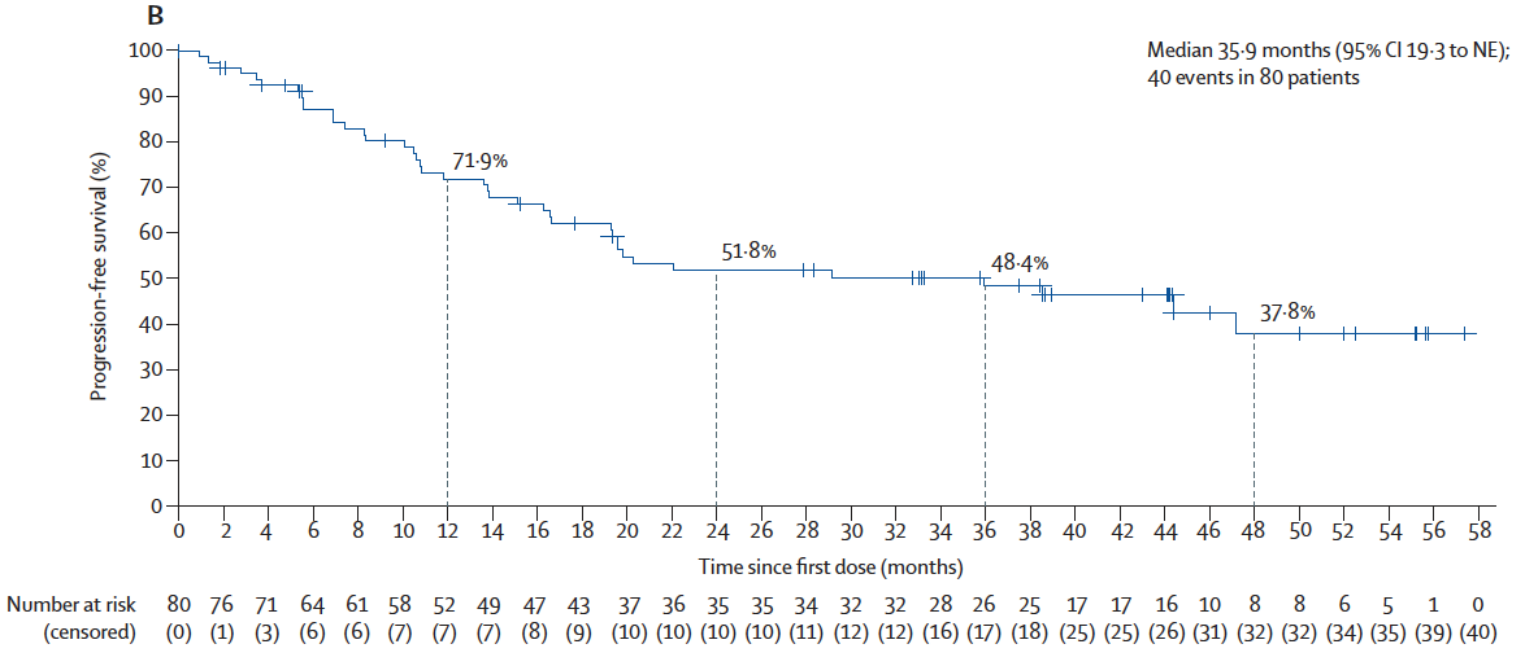
Venetoclax re-treatment



Castillo et al. Blood Adv 2025

Safety and activity of pirtobrutinib in patients with relapsed or refractory Waldenström macroglobulinaemia: 5-year follow-up of the open-label, multicentre, phase 1/2 BRUIN trial





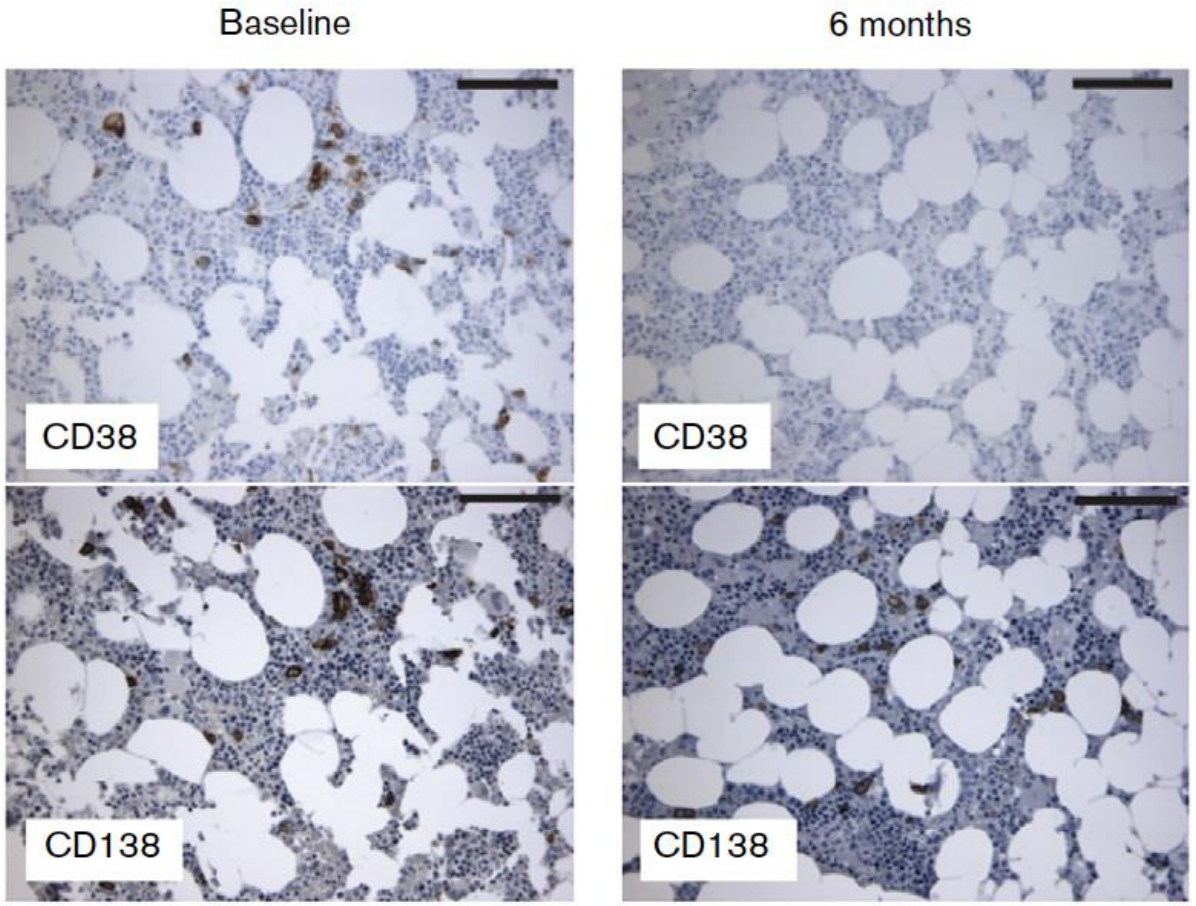
Palomba et al. Lancet Haematol 2026

Multicenter phase 2 study of daratumumab monotherapy in patients with previously treated Waldenström macroglobulinemia

Between July 2018 and May 2019, 13 patients with previously treated WM were enrolled in the study.

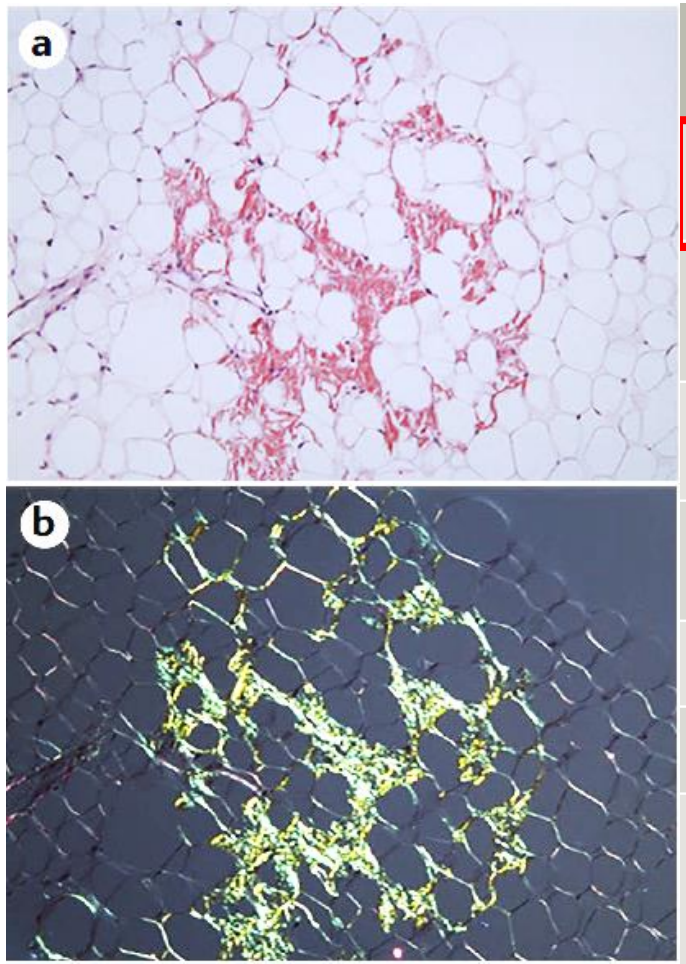
At best response, ORR was 23%, and major response rate 15%.

Given the suboptimal response to daratumumab, the study was terminated because of futility.



Castillo et al. Blood Adv 2020

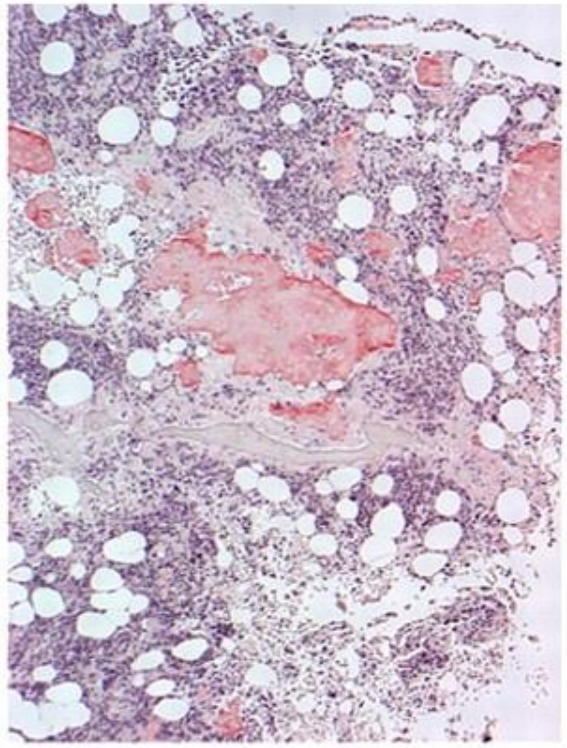
There are multiple types of amyloidosis

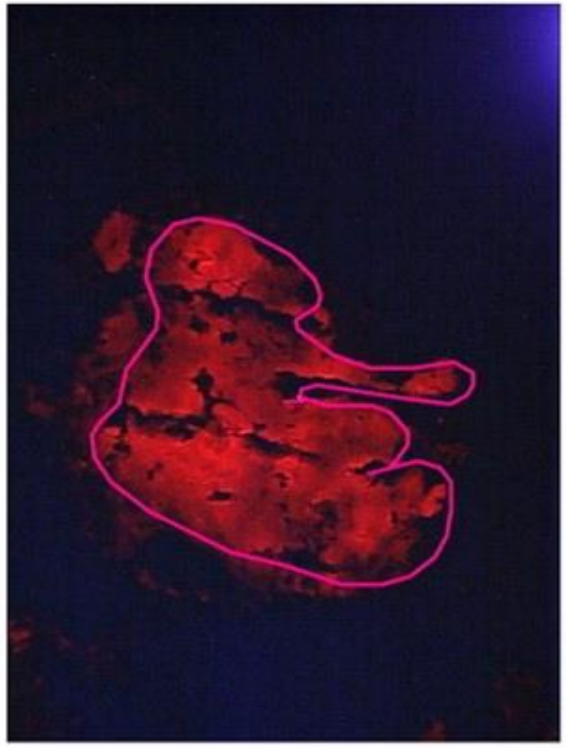


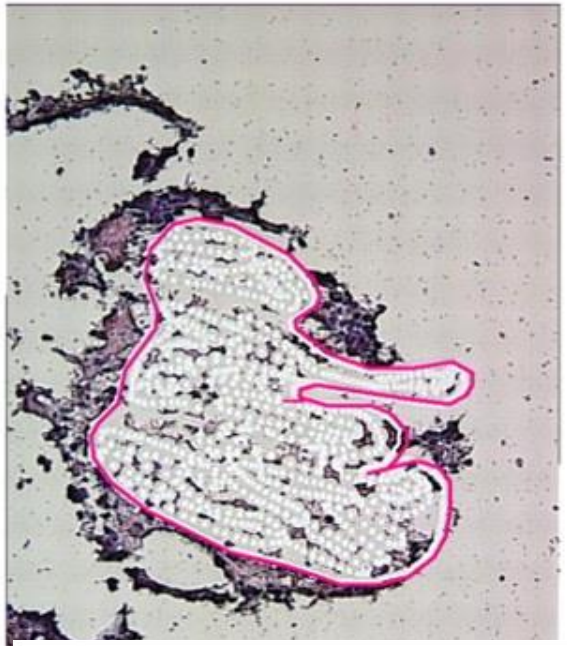
Designation[a]	Parent protein	Systemic and/or localized	Acquired or hereditary	Organs involved
AL	Immunoglobulin light chain[b]	Systemic or localized	Acquired (hereditary[c])	Heart, kidney, liver, soft tissues, peripheral nervous system (including the autonomic nervous system) and gastrointestinal tract
ATTR	Transthyretin	Systemic	Hereditary	Peripheral nervous system (including the autonomic nervous system), heart, eye, kidney and leptomeninges
		Systemic	Acquired	Heart and ligaments
AA	Serum amyloid A protein	Systemic	Acquired	Predominantly kidney, but may involve liver, gastrointestinal tract and occasionally heart, thyroid and autonomic nervous system
ALECT2	Leukocyte chemotactic factor 2	Systemic	Acquired	Kidney, liver, spleen, adrenals and lungs
AApoAI	Apolipoprotein AI	Systemic	Hereditary	Heart, liver, kidney, peripheral nervous system, testis, larynx and skin
AFib	Fibrinogen α chain	Systemic	Hereditary	Kidney, primarily, with obliterative glomerular involvement
$A\beta_2m$	β_2-microglobulin, wild type	Systemic	Acquired (haemodialysis related)	Musculoskeletal system
	β_2-microglobulin	Systemic	Hereditary	Autonomic nervous system

Merlini et al. Nat Rev Dis Primers 2018

Amyloid typing (mass spectrometry)







#	Accession	MW	Control	1	2	3	4
1	ALBU_HUMAN	69 kDa		100% (36)	100% (35)	100% (36)	100% (35)
2	APOE_HUMAN	36 kDa		100% (19)	100% (17)	100% (18)	100% (17)
3	VTNC_HUMAN	54 kDa		100% (13)	100% (13)	100% (17)	100% (14)
4	KAC_HUMAN	12 kDa		100% (7)	100% (8)	100% (7)	100% (8)
5	APOA4_HUMAN	45 kDa		100% (15)	100% (19)	100% (17)	100% (13)
6	SAMP_HUMAN	25 kDa		100% (8)	100% (9)	100% (9)	100% (9)
7	C4BP_HUMAN	67 kDa		100% (11)	100% (10)	100% (12)	100% (10)
8	HBB_HUMAN	16 kDa		100% (4)	100% (8)	100% (9)	100% (7)
9	CLUS_HUMAN	52 kDa		100% (10)	100% (7)	100% (8)	100% (8)
10	CO6A3_HUMAN	344 kDa		100% (6)	100% (13)	100% (17)	100% (10)

Merlini et al. Nat Rev Dis Primers 2018

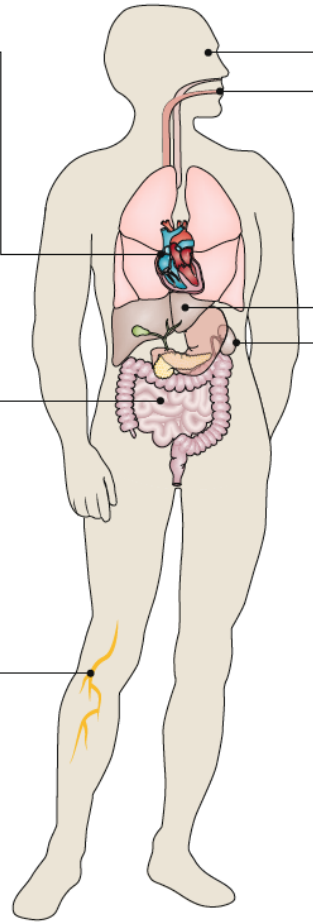
Organ involvement in AL amyloidosis

Heart
- Heart failure with preserved ejection fraction
- Thickened ventricular walls and low voltages on electrocardiography
- Dysponea at rest or exertion, fatigue
- Hypotension or syncope
- Peripheral oedema

Gastrointestinal tract
- Malabsorption and weight loss
- Bleeding (factor X)

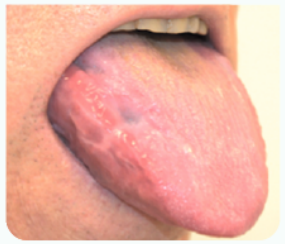
Nervous system
Peripheral
- Symmetric lower extremity sensorimotor polyneuropathy

Carpal tunnel syndrome (bilateral)
Autonomic
- Postural hypotension
- Erectile dysfunction (males)
- Gastrointestinal motility alterations



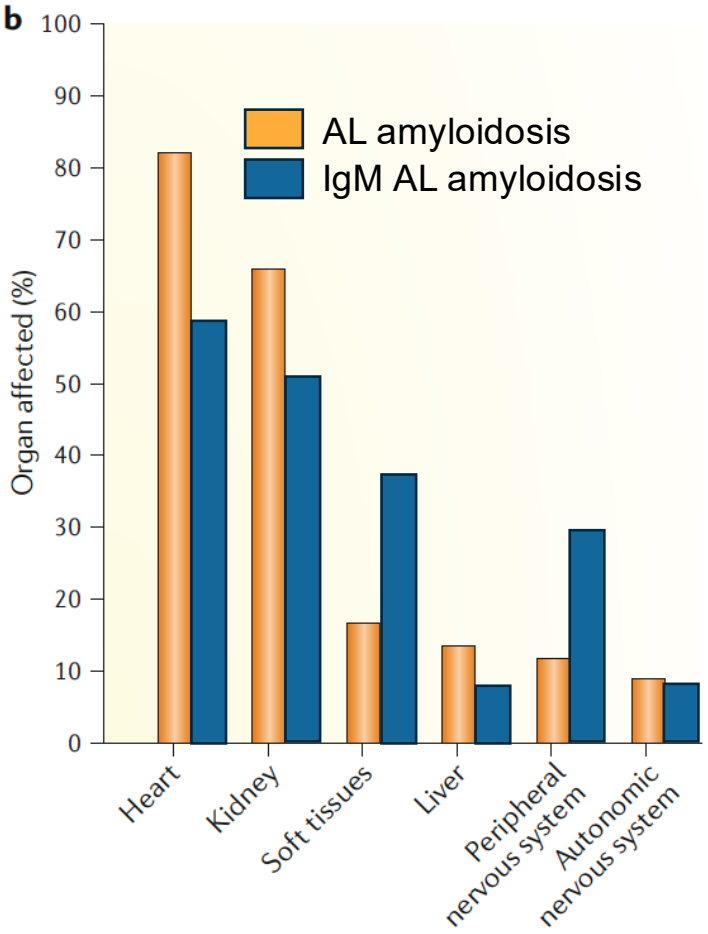
Periorbital purpura

Macroglossia



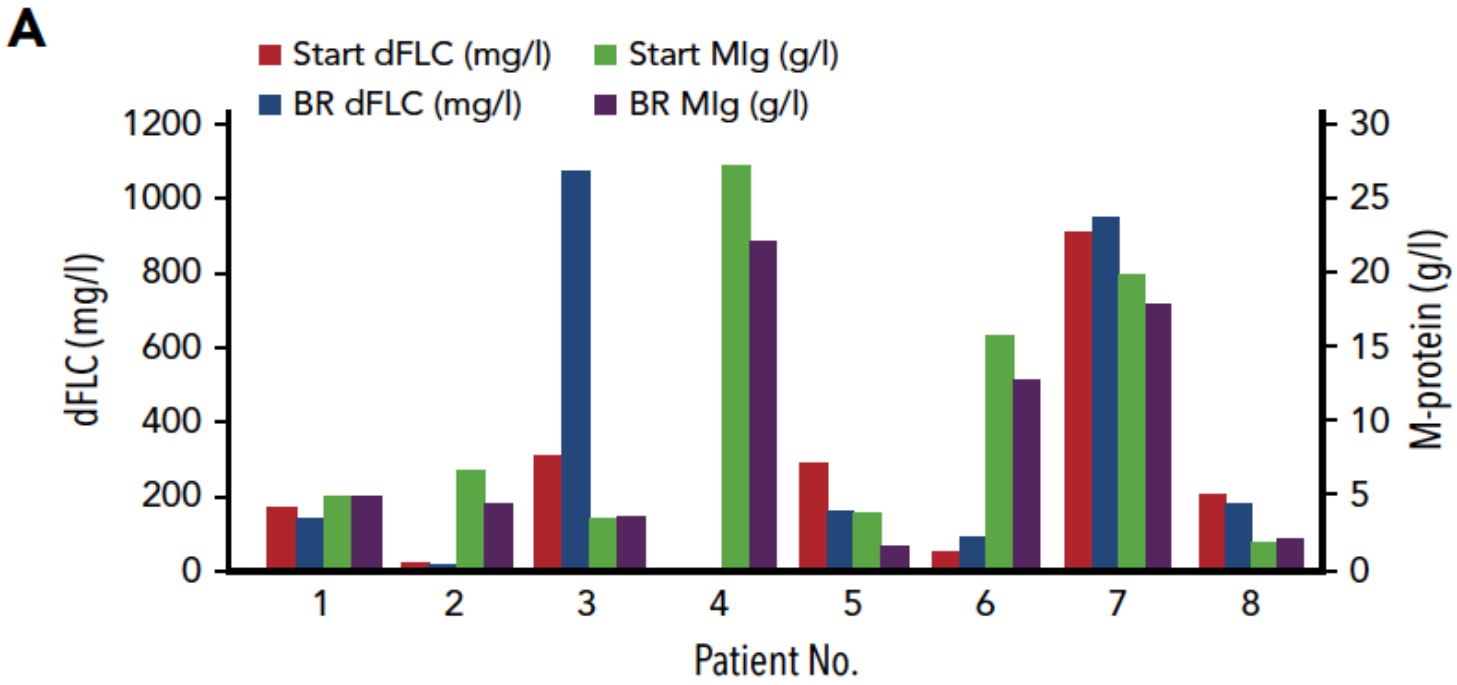
Liver
- Increased alkaline phosphatase
- Hepatomegaly

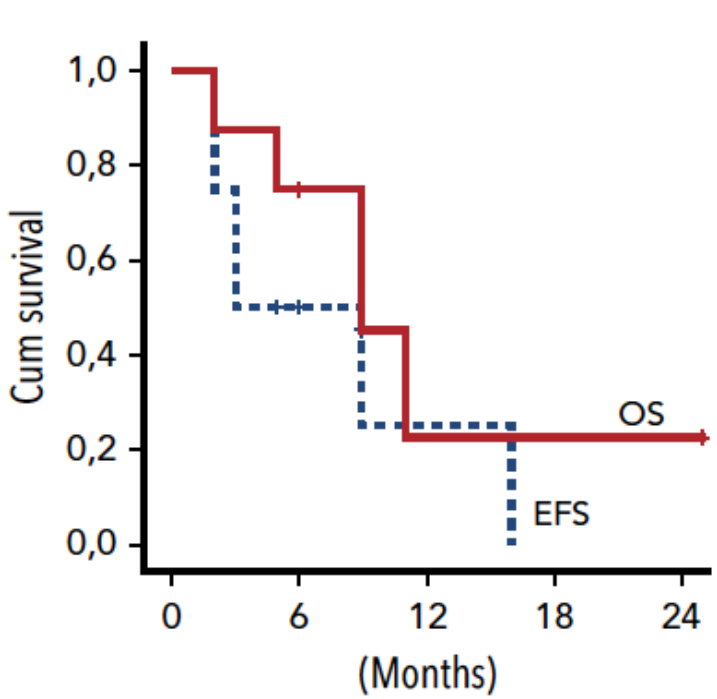
Kidney
- Nephrotic range proteinuria
- Renal failure
- Peripheral oedema



Merlini et al. Nat Rev Dis Primers 2018; Sidana et al. Leukemia 2020

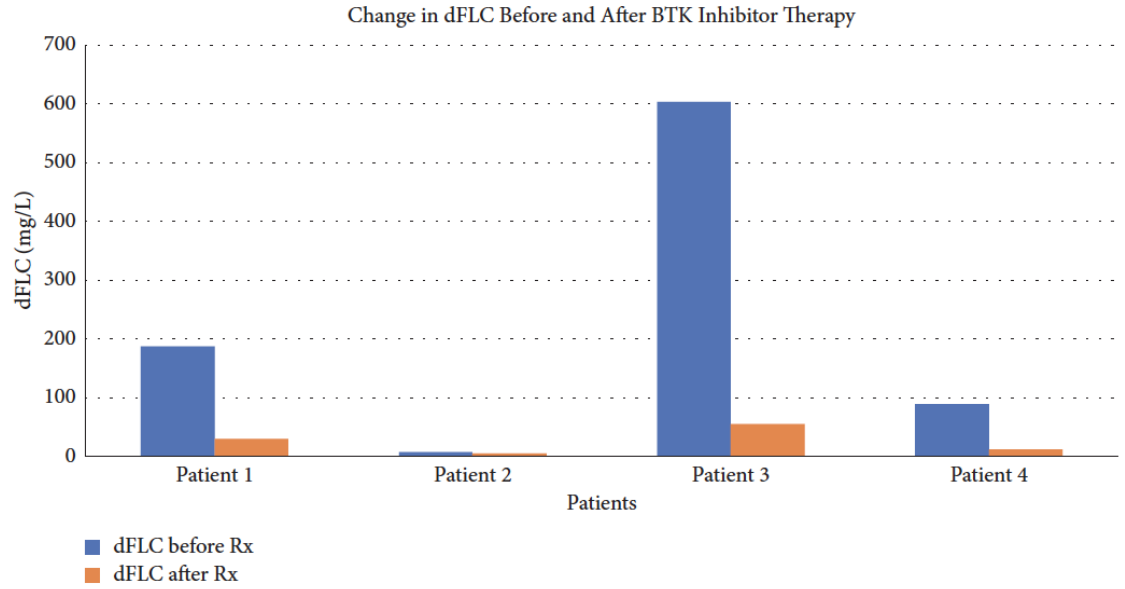
First report of ibrutinib in IgM-related amyloidosis: few responses, poor tolerability, and short survival

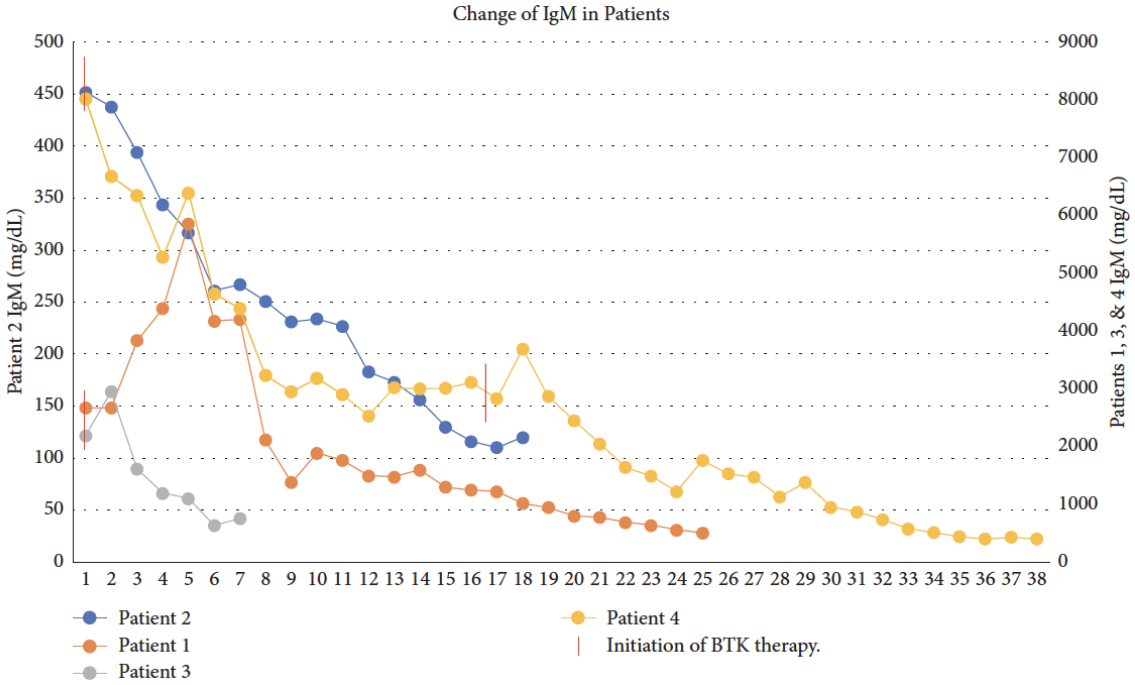




Pika et al. Blood 2018

Utility of Bruton's Tyrosine Kinase Inhibitors in Light Chain Amyloidosis Caused by Lymphoplasmacytic Lymphoma (Waldenström's Macroglobulinemia)

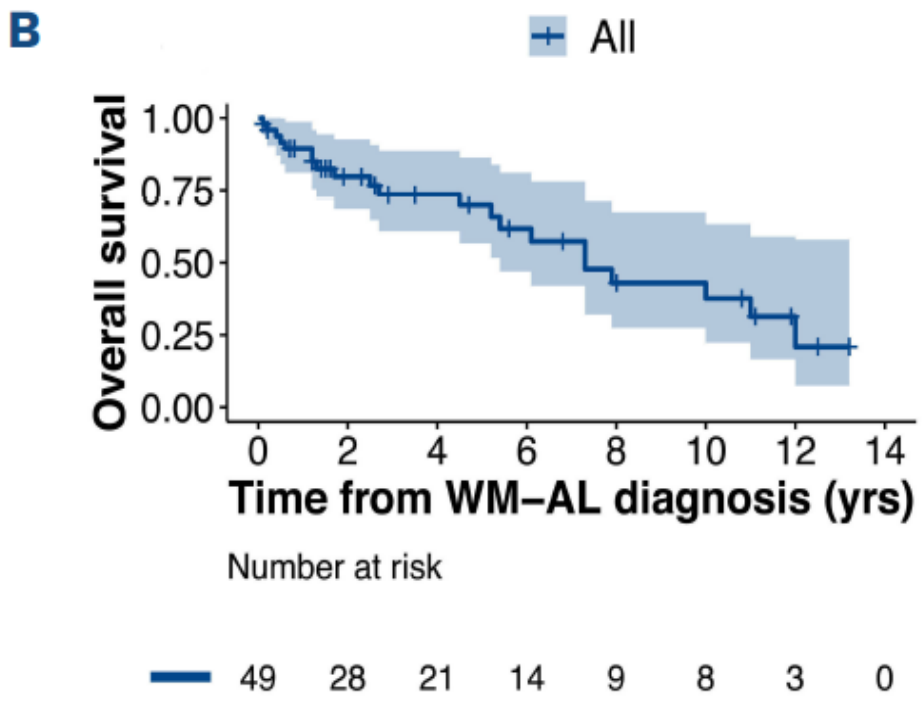


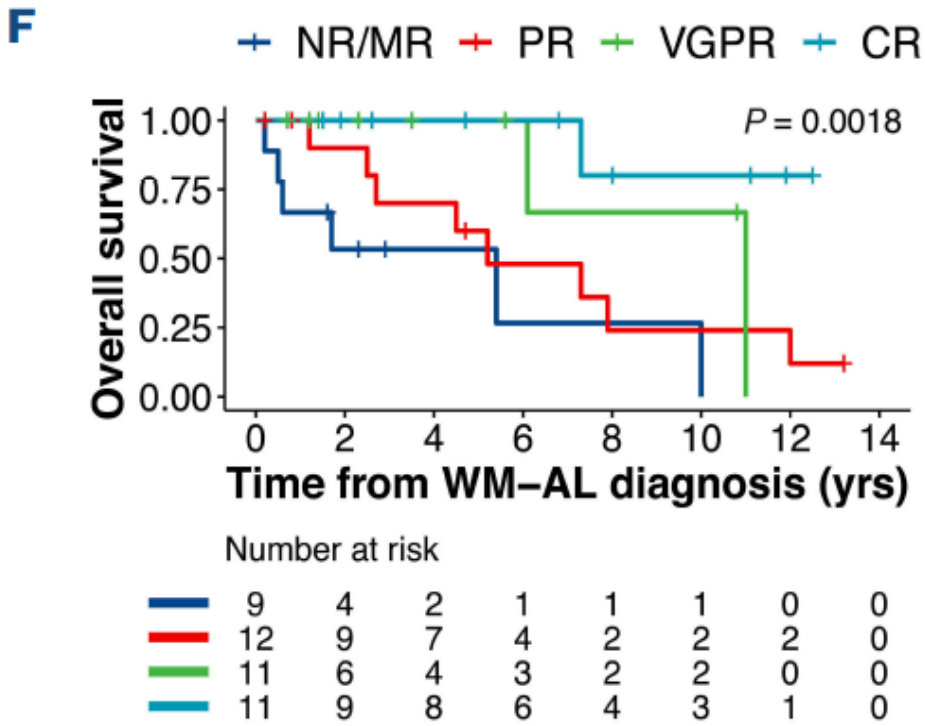


Bou Zerdan et al. Adv Hematol 2022

Light chain amyloidosis associated with Waldenström macroglobulinemia: treatment and survival outcomes

2 patients were treated with ibrutinib without an FLC response





Gustine et al. Haematologica 2023

True, true unrelated? Coexistence of Waldenström macroglobulinemia and cardiac transthyretin amyloidosis

Case	Age (years) / Sex	IgM (mg/dL)	M protein (g/dL)	IgM isotype	Free K (mg/L)	Free L (mg/L)	NT-pro BNP (pg/mL)	Troponin T (ng/mL)	MYD88 mutation	PYP	IVS (mm)	Mass-spectrometry	ATTR
1	76 / M	2908	0.57	Kappa	60	30.8	2581	0.07	WT	3	17	ATTR	WT
2	80 / M	784	0.6	Lambda	32.2	55.4	2392	0.01	Unknown	2	23	ATTR	WT
3	74 / M	798	0.68	Lambda	31.8	27	3590	0.03	L265P	3	17	NP	WT
4	81 / M	706	0.34	Lambda	34	26	1664	0.04	WT	2	15	NP	WT

Singh et al. Haematologica 2018

Report of Consensus Panel 6 from the 11 th International Workshop on Waldenström's Macroglobulinemia on Management of Waldenström's Macroglobulinemia Related Amyloidosis

Early diagnosis

- Annual 24-h urine protein quant, NT-proBNP, ALKP

Diagnosis

- Typing is necessary
- Mass spectrometry preferred

Treatment

- Induce rapid VGPR/CR; ASCT as consolidation; BTKi less preferred

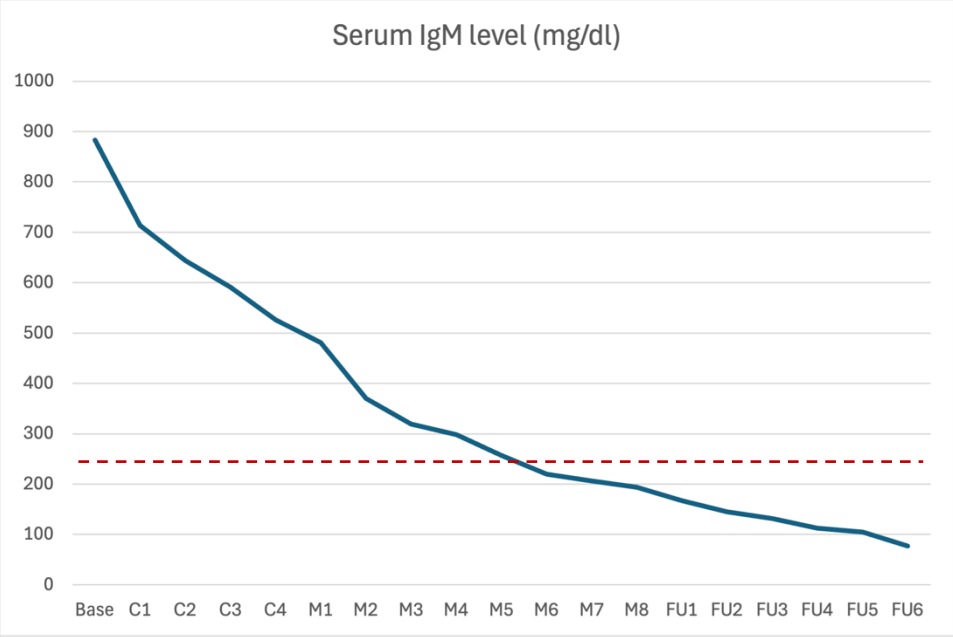
Response

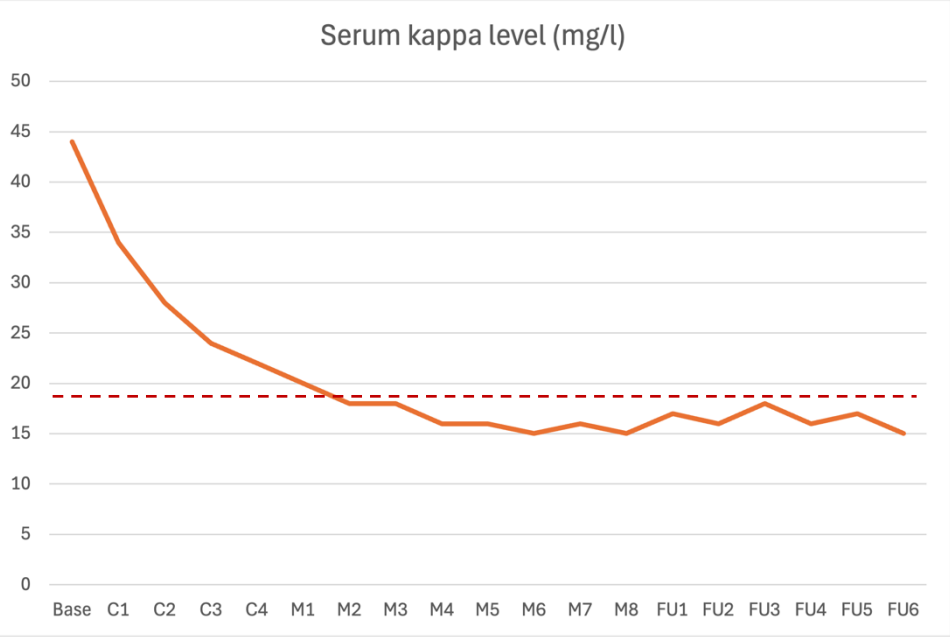
- Use criteria for AL amyloidosis
- Lymph node involvement should not be considered

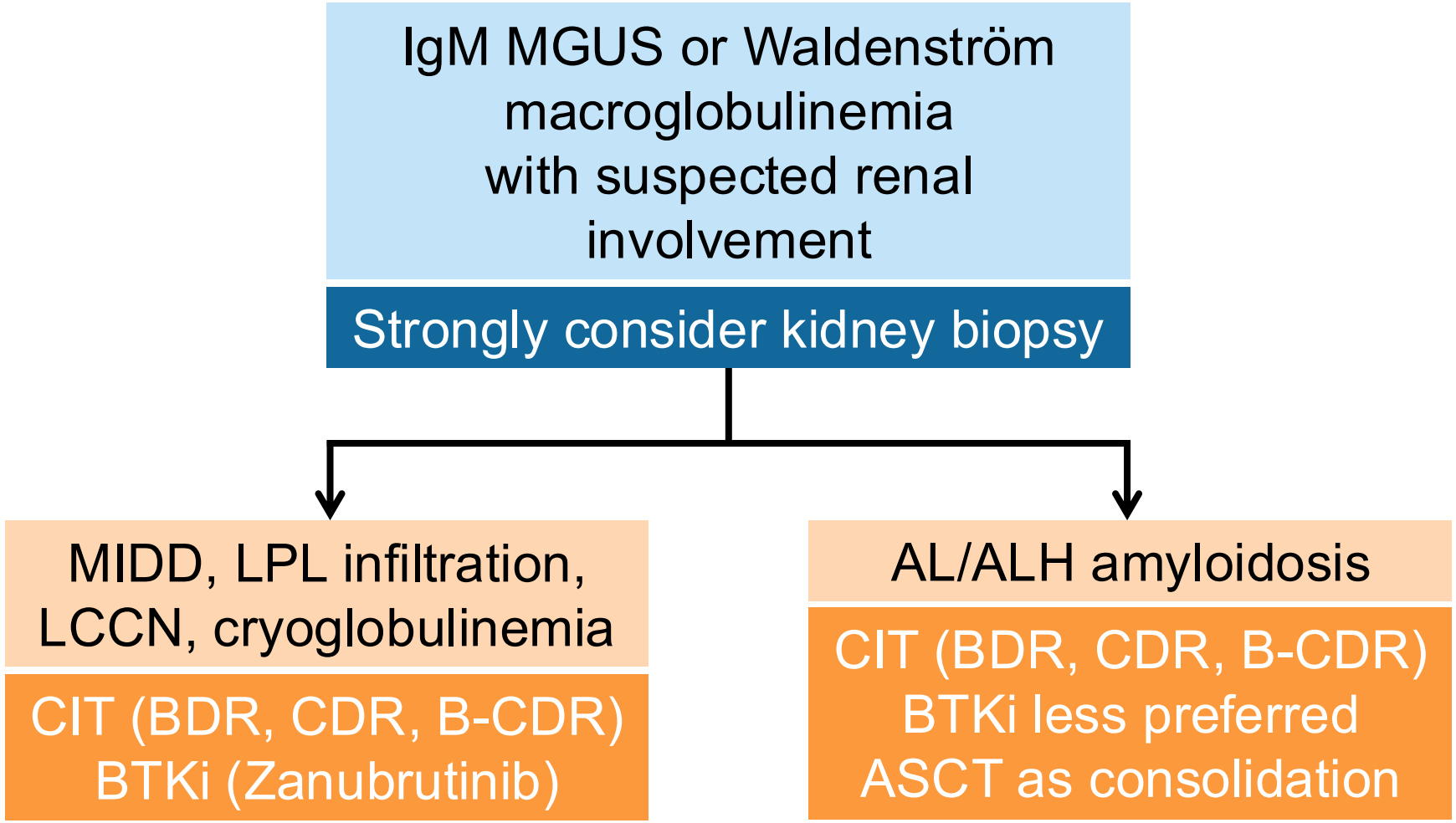
Merlini et al. Semin Hematol 2023

Case conclusion

The patient received 4 cycles of BDR followed by 8 doses of maintenance rituximab






IgM MGUS or Waldenström macroglobulinemia with suspected renal involvement
Strongly consider kidney biopsy
MIDD, LPL infiltration, LCCN, cryoglobulinemia
CIT (BDR, CDR, B-CDR)
BTKi (Zanubrutinib)
AL/ALH amyloidosis
CIT (BDR, CDR, B-CDR)
BTKi less preferred
ASCT as consolidation

How I Manage IgM Disease and Systemic Impact

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

Dana-Farber
Cancer Institute