Challenges in the diagnosis, staging, and clinical work-up of Waldenström's macroglobulinemia: A practical guide to current best practice

Monday, November 9, 2020 | 17:00–18:30 (CET)

Welcome and introductions

Chair: Christian Buske

Disclaimers

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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.

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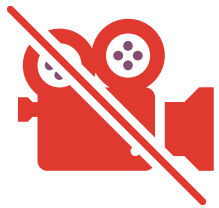
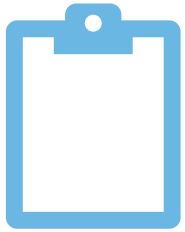
Housekeeping



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

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Aims of the webinar

To showcase the BeiGeneius webinar series as a platform for learning and exchange between hemato-oncologists

To provide a practical overview of the latest developments and best practice in the diagnosis, staging, and clinical work-up of WM

To identify and address key clinical challenges in the diagnosis and management of patients with WM

WM, Waldenström's macroglobulinemia.

Introducing the speakers

Professor Christian Buske
University Hospital of Ulm, Germany

Dr. Roger Owen
St James's Institute of Oncology, UK

Dr. Alessandra Tedeschi
Niguarda Cancer Center, Italy

BeiGeneius

Disclosures

- Honoraria: Roche, Janssen, BeiGene, Celltrion, Pfizer, AbbVie
- Research funding: Roche, Janssen, Celltrion, AbbVie, Bayer, MSD

Agenda

17:00	**Welcome and introductions** *Christian Buske*
17:10	**What are the diagnostic considerations and clinical features for patients presenting with WM symptoms?** *Roger Owen*
17:30	**Diagnosing WM: A patient's journey** *Alessandra Tedeschi*
17:50	**Should all patients undergo mutation analysis of *MYD88* and *CXCR4* as part of the WM diagnostic work-up?** *Moderator: Roger Owen* *For: Alessandra Tedeschi | Against: Christian Buske*
18:05	**Talk to the experts: What challenges do you face in diagnosing WM?** *Moderator: Christian Buske* *Panel: All*
18:25	**Summary** *Christian Buske*

CXCR4, C-X-C chemokine receptor type 4 gene; MYD88, myeloid differentiation primary response 88 gene; WM, Waldenström's macroglobulinemia.

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A guide to the meeting platform and live polling function

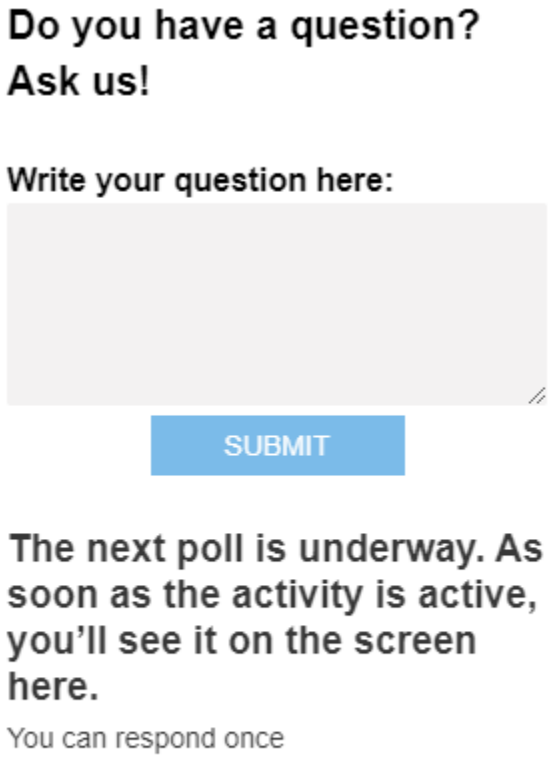
Please exit the full screen view to participate in the Q&A and live polling.

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)



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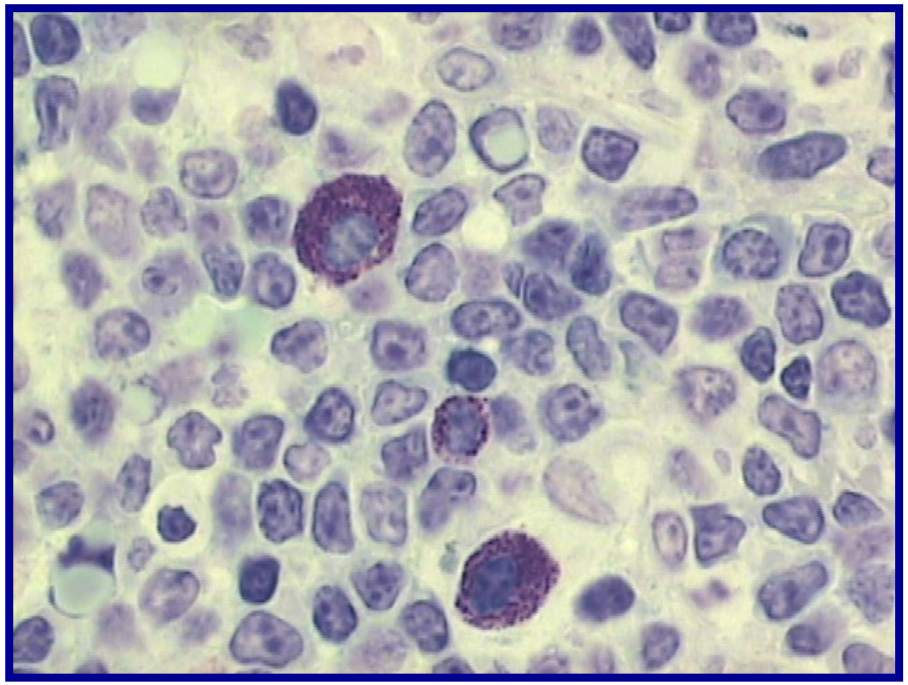
What are the diagnostic considerations and clinical features for patients presenting with WM symptoms?

Roger Owen

WM, Waldenström's macroglobulinemia.

Waldenstrom macroglobulinaemia: diagnostic considerations and clinical features

Roger G Owen
St James's Institute of Oncology, Leeds, UK.

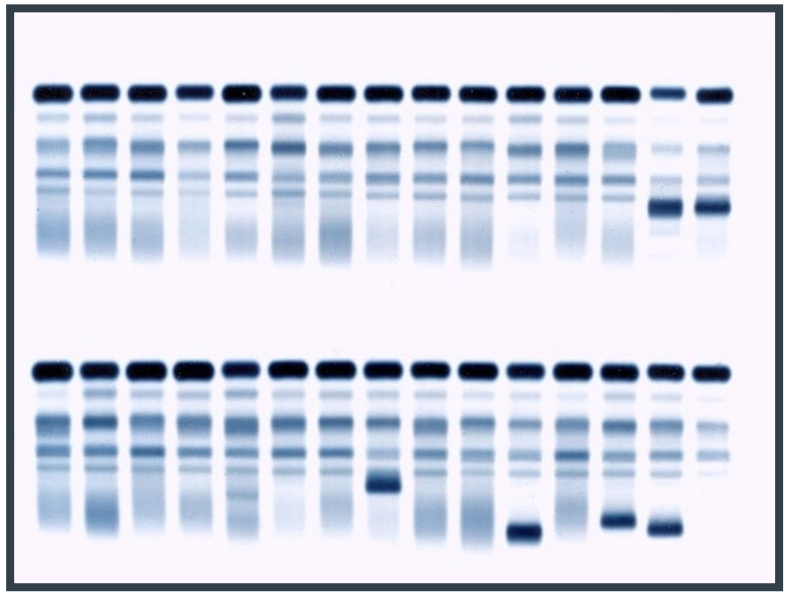


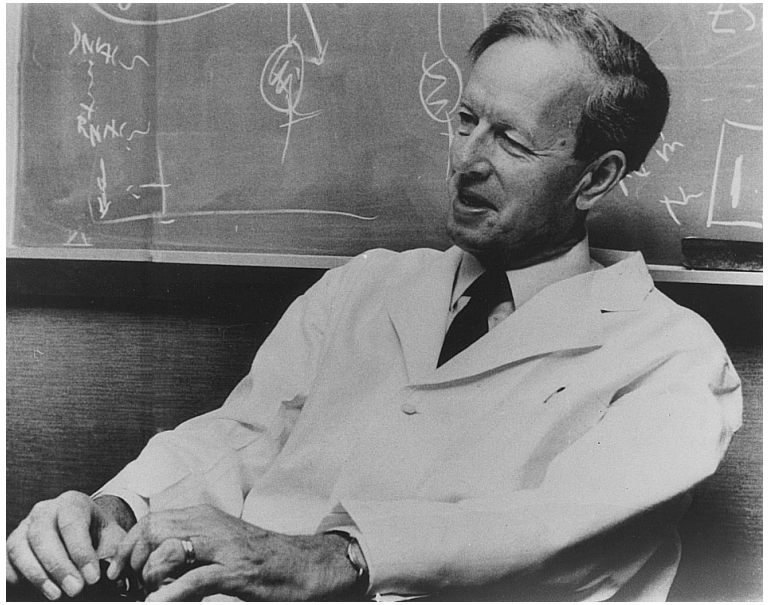
Disclosures

- AstraZeneca – honoraria
- BeiGene – honoraria, advisory board
- Celgene – honoraria
- Janssen – honoraria, advisory board

What is Waldenström's macroglobulinemia?

- IgM M protein or paraprotein
- Bone marrow infiltration by lymphoplasmacytic lymphoma

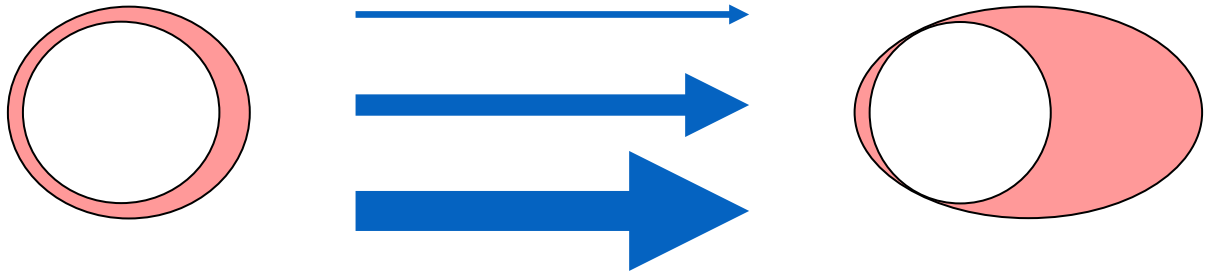




Incipient myelomatosis or "essential" hyperglobulinemia with fibrinogenopenia — a new syndrome?
J Waldenström.
***Acta Med Scand* 1944; 117 (3–4): 216–247.**

IgM, immunoglobulin M.
Waldenström J. *Acta Med Scand* 1944; 117 (3–4): 216–247.

Plasma cell differentiation in WM



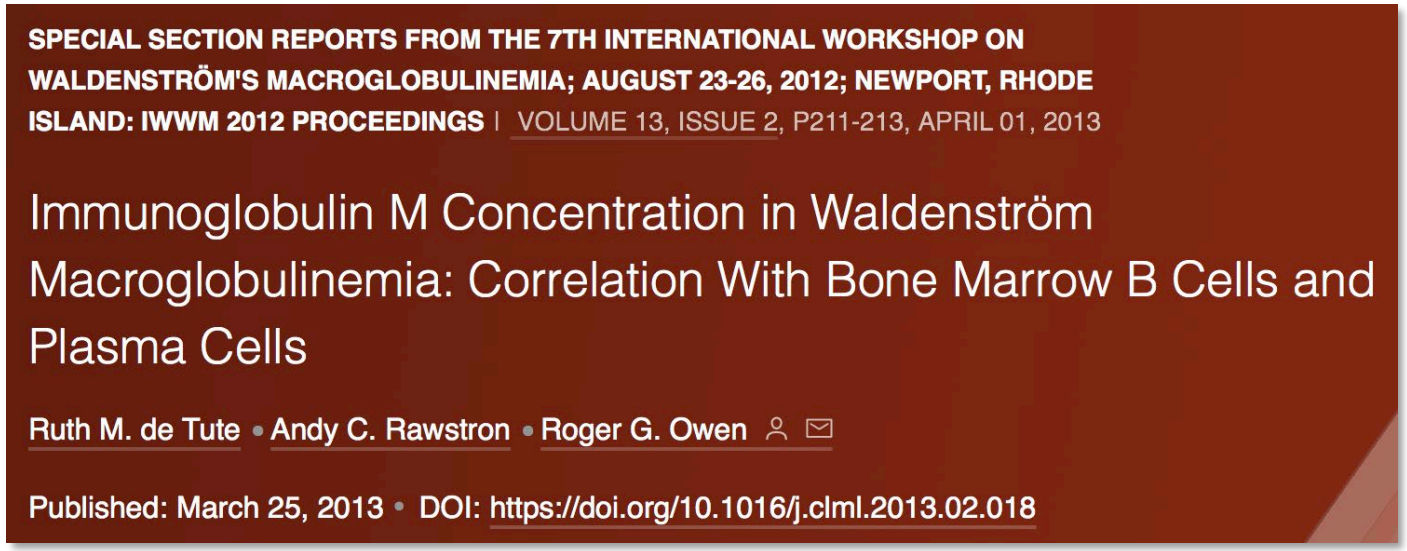
B-cell component

- Symptoms related to tumor bulk
- Anemia
- B symptoms
- Lymph nodes
- Spleen

Plasma cell component

- Symptoms attributable to M protein
- Hyperviscosity syndrome
- Neuropathy
- Hemolytic anemia
- Cryoglobulinemia
- Immunodeficiency

WM, Waldenström's macroglobulinemia.



SPECIAL SECTION REPORTS FROM THE 7TH INTERNATIONAL WORKSHOP ON WALDENSTRÖM'S MACROGLOBULINEMIA; AUGUST 23-26, 2012; NEWPORT, RHODE ISLAND: IWWM 2012 PROCEEDINGS | VOLUME 13, ISSUE 2, P211-213, APRIL 01, 2013

Immunoglobulin M Concentration in Waldenström Macroglobulinemia: Correlation With Bone Marrow B Cells and Plasma Cells

Ruth M. de Tute • Andy C. Rawstron • Roger G. Owen

Published: March 25, 2013 • DOI: https://doi.org/10.1016/j.clml.2013.02.018

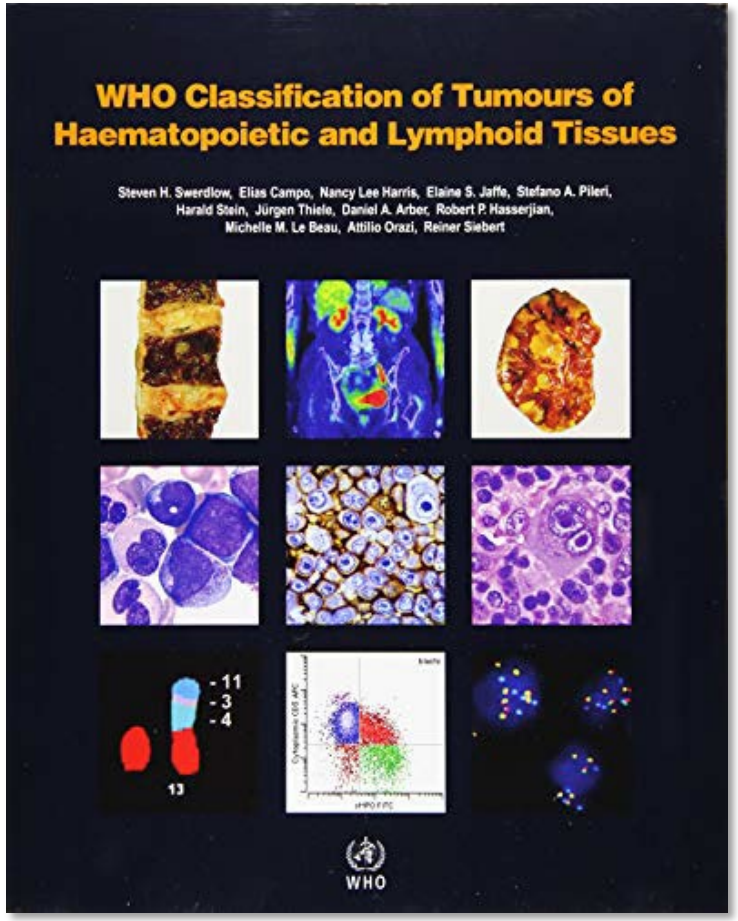
Bone-marrow plasma cell burden correlates with IgM paraprotein concentration in Waldenström macroglobulinaemia

Sant-Rayn Pasricha[1, 2], Surender K Juneja[1, 2, 3], David A Westerman[2, 3], Neil A Came[1, 2, 3]

Journal of Clinical Pathology

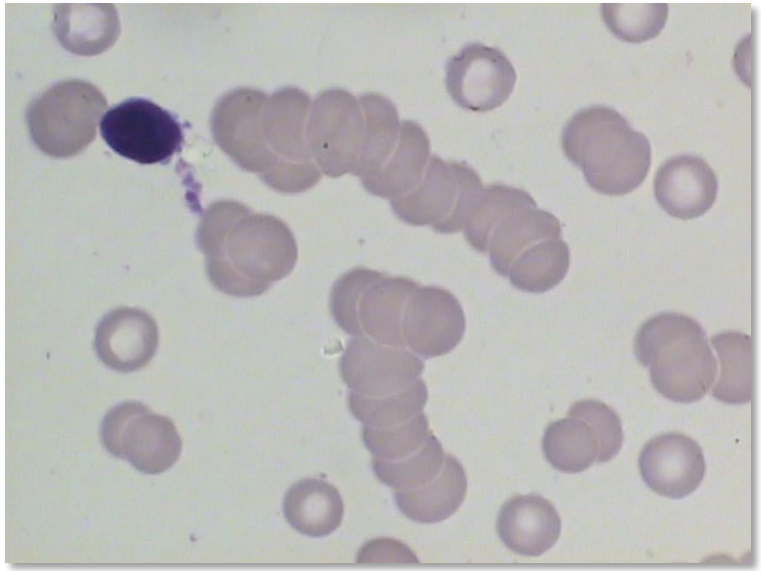
de Tute RM *et al*. *Clin Lymphoma Myeloma Leuk* 2013; 13 (2): 211–213. Pasricha S-R *et al*. *J Clin Pathol* 2011; 64 (6): 520–523.

WHO: Concept of distinct clinicopathological entities



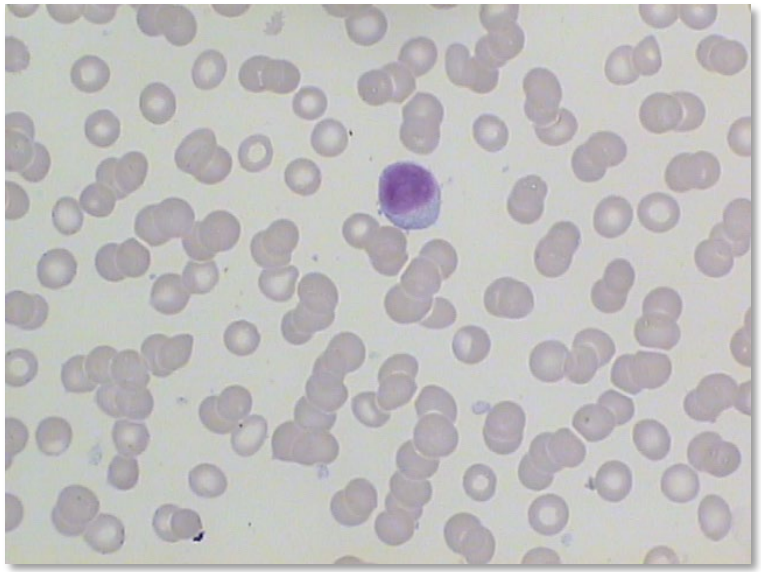
- Morphology
- Immunophenotype
- Genotype
- Clinical syndrome

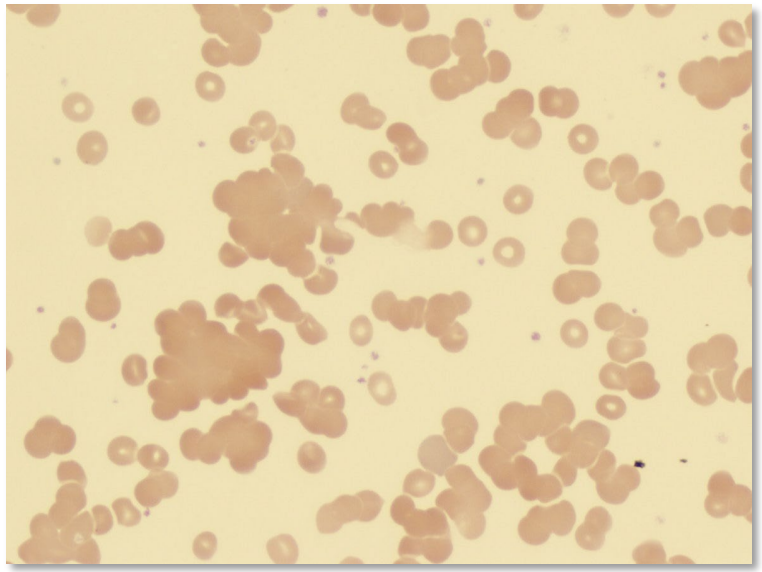
WHO, World Health Organization.

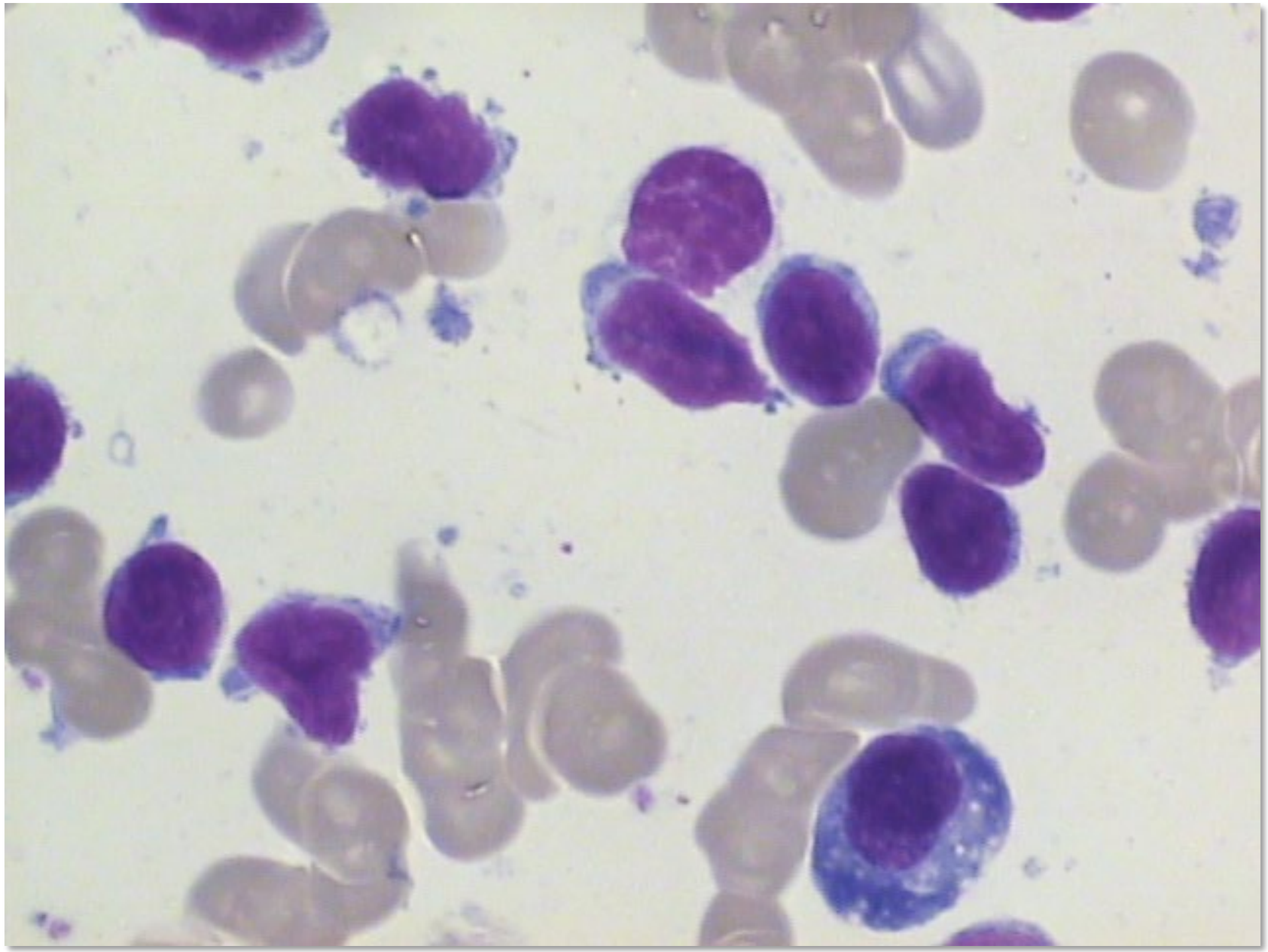


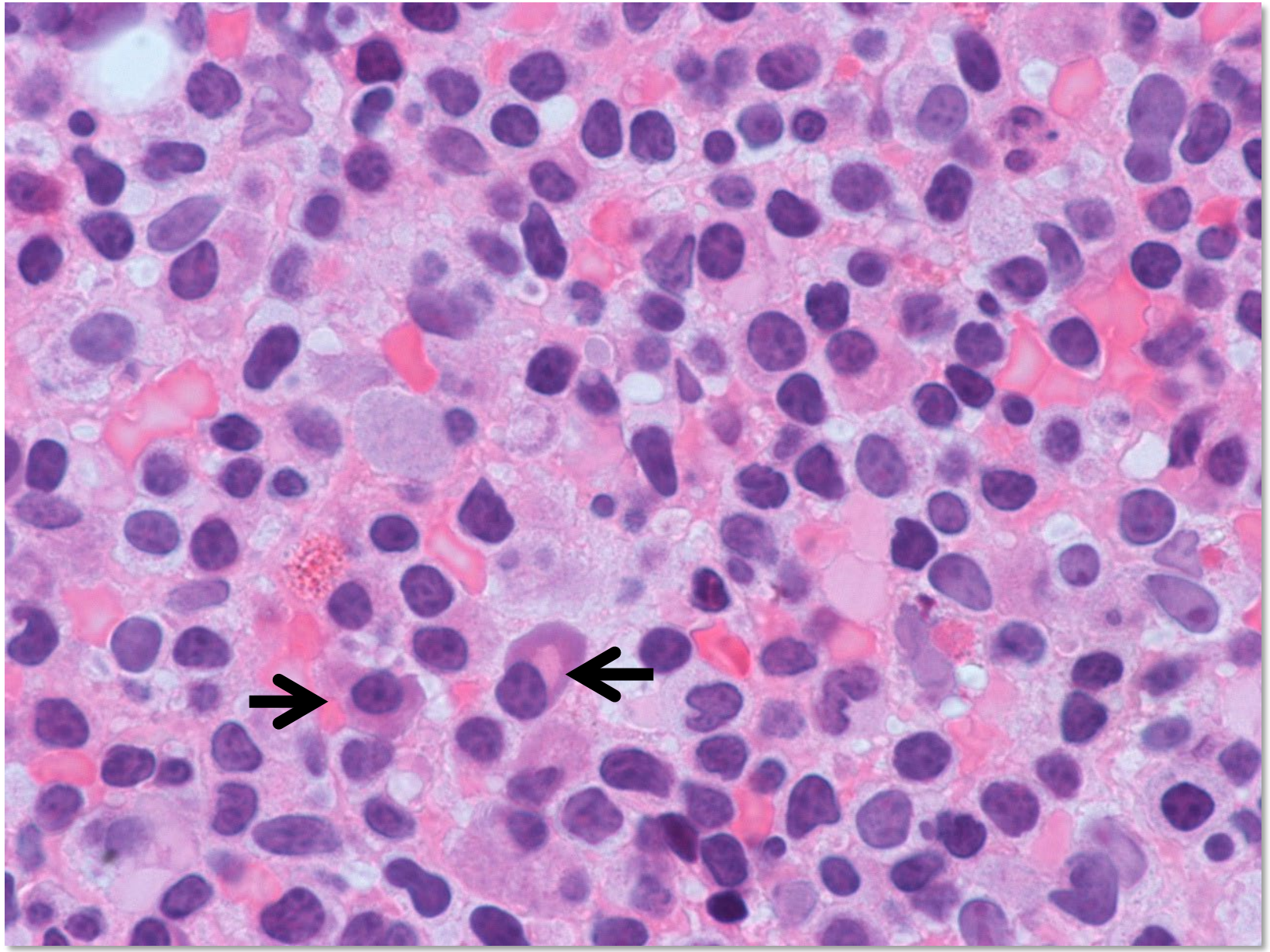
Blood morphology

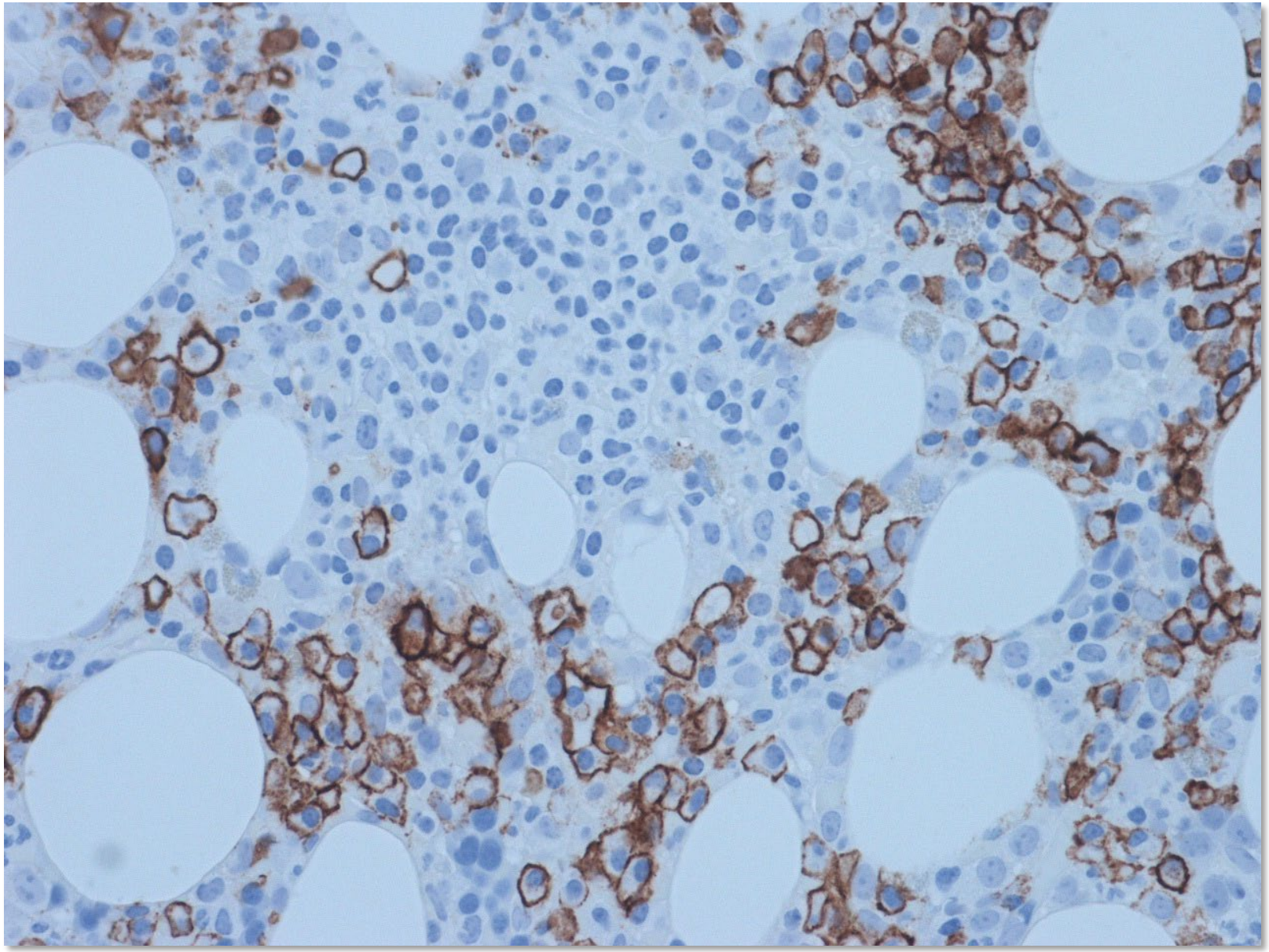
- Anemia
- Film can be normal
- Rouleaux
- Cold agglutination
- Circulating cells

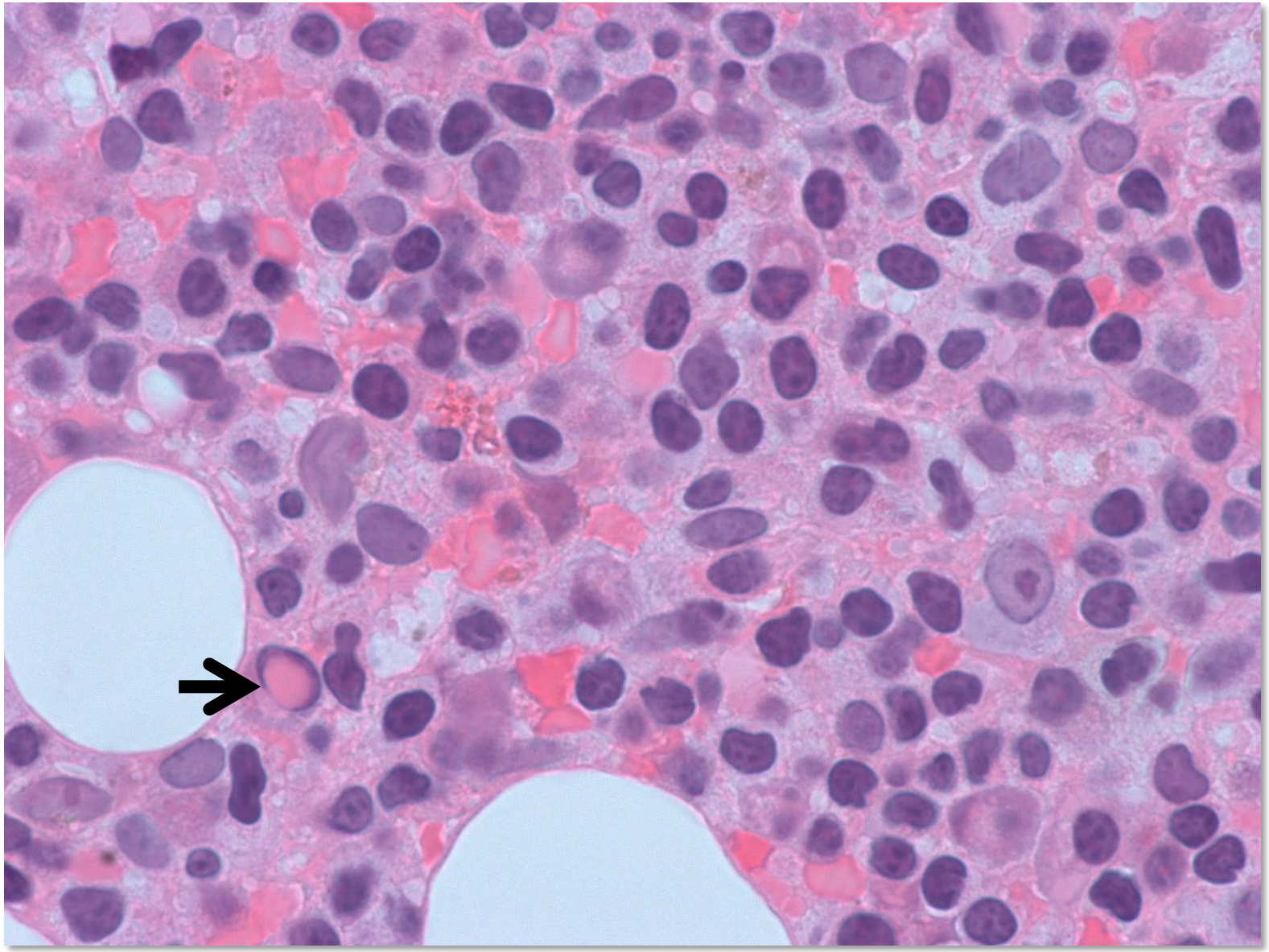


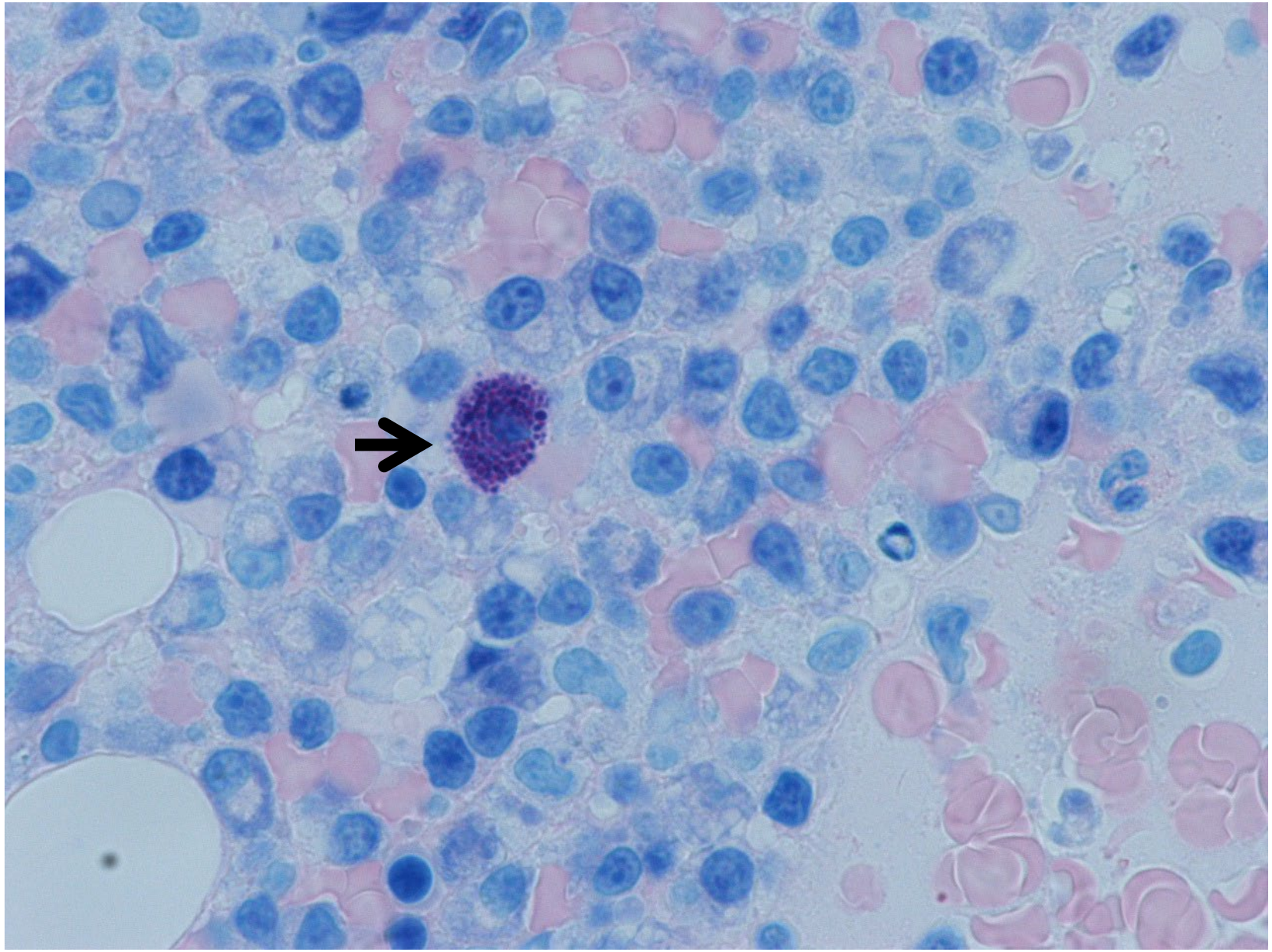






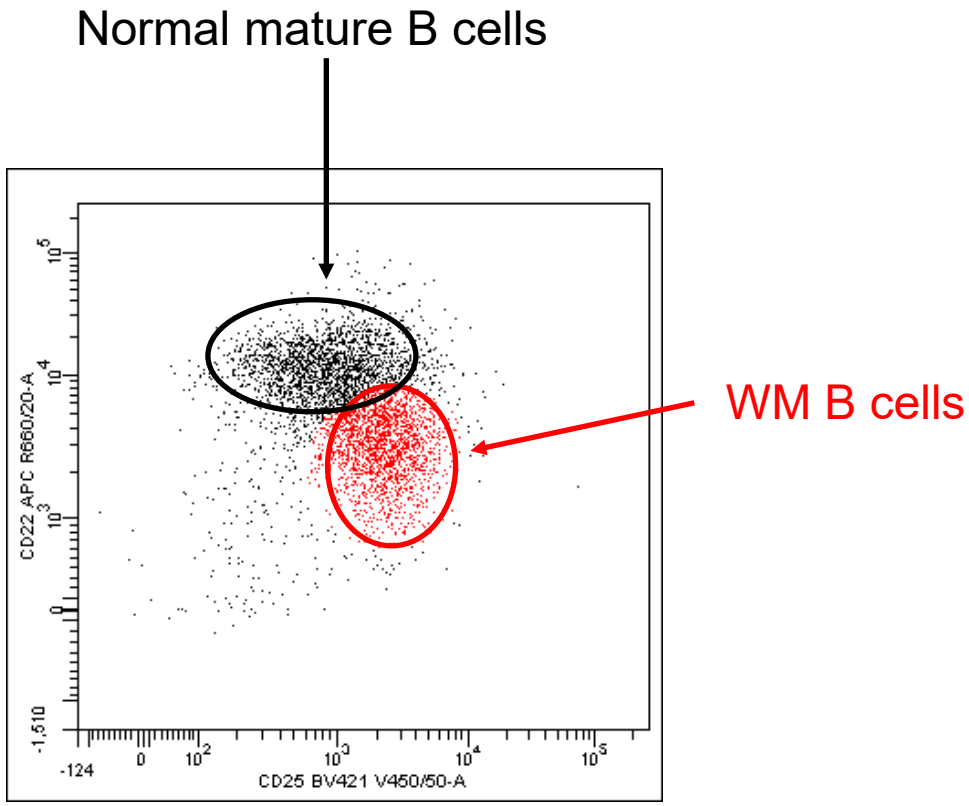






Multiparameter flow cytometry for the identification of the Waldenström's clone in IgM-MGUS and Waldenström's Macroglobulinemia: new criteria for differential diagnosis and risk stratification

B Paiva[1,2], MC Montes[1], R García-Sanz[1,2], EM Ocio[1,2], J Alonso[1], N de las Heras[3], F Escalante[3], R Cuello[4], AG de Coca[4], J Galende[5], J Hernández[6], M Sierra[7], A Martin[1], E Pardal[8], A Bárez[9], J Alonso[10], L Suarez[11], TJ González-López[12], JJ Perez[1], A Orfao[2,13], M-B Vidríales[1,2] and JF San Miguel[1,2]

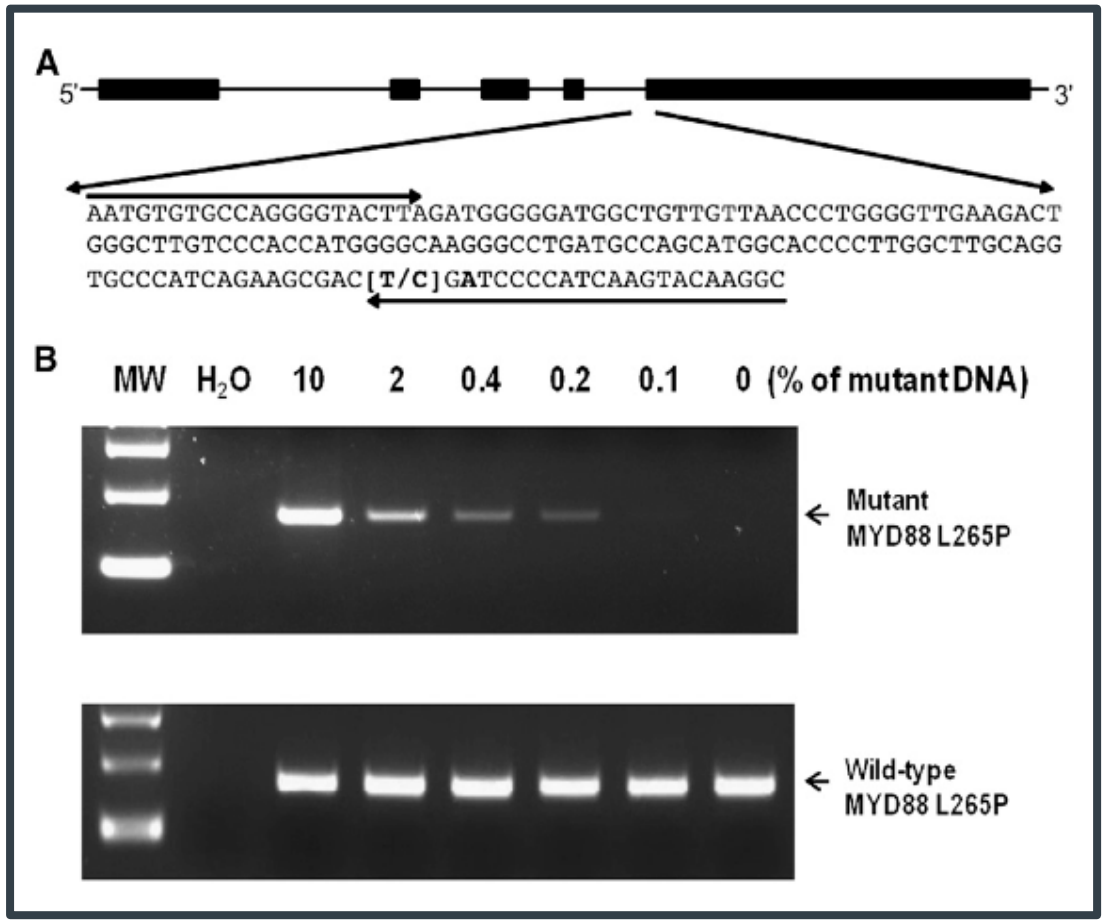


WM B-cells: CD22 (+wk) CD25+ CD27+ IgM+ CD305wk/-

IgM, immunoglobulin M; MGUS, monoclonal gammopathy of undetermined significance; wk, weak; WM, Waldenström's macroglobulinemia.
Paiva B *et al*. *Leukemia* 2014; 28 (1): 166–173.

LYMPHOID NEOPLASIA

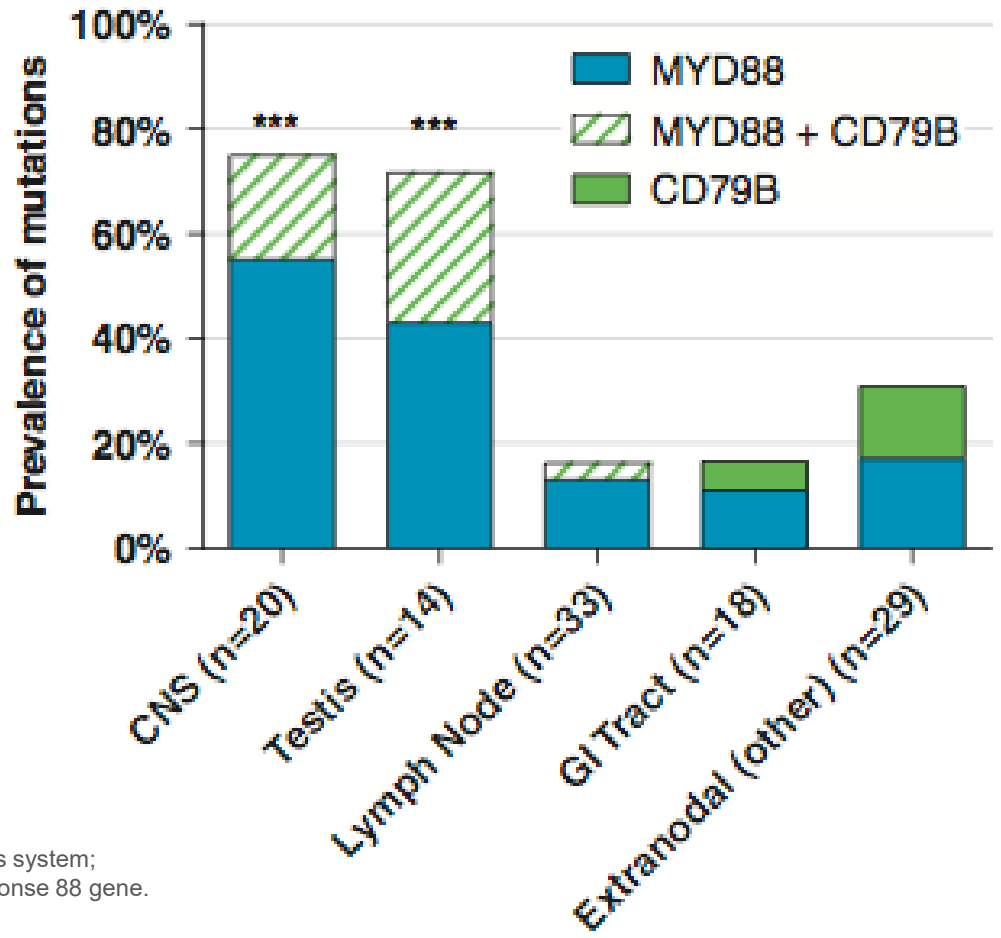
MYD88 L265P in Waldenström macroglobulinemia, immunoglobulin M monoclonal gammopathy, and other B-cell lymphoproliferative disorders using conventional and quantitative allele-specific polymerase chain reaction



Xu L *et al*. *Blood* 2013; 121 (11): 2051–2058.

ORIGINAL ARTICLE

High prevalence of oncogenic *MYD88* and *CD79B* mutations in diffuse large B-cell lymphomas presenting at immune-privileged sites

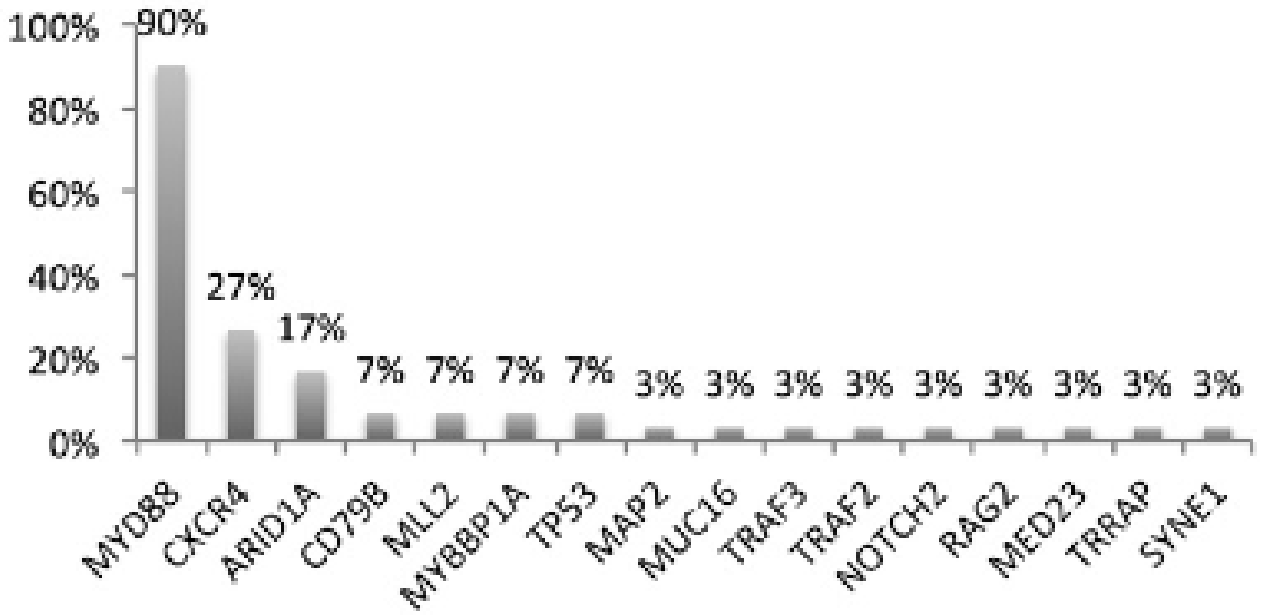


***P<0.001 by Fisher's exact test.
CD79B, cluster of differentiation 79B gene; CNS, central nervous system; GI, gastrointestinal; *MYD88*, myeloid differentiation primary response 88 gene.
Kraan W *et al*. *Blood Cancer J* 2013; 3 (9): e139.

LYMPHOID NEOPLASIA

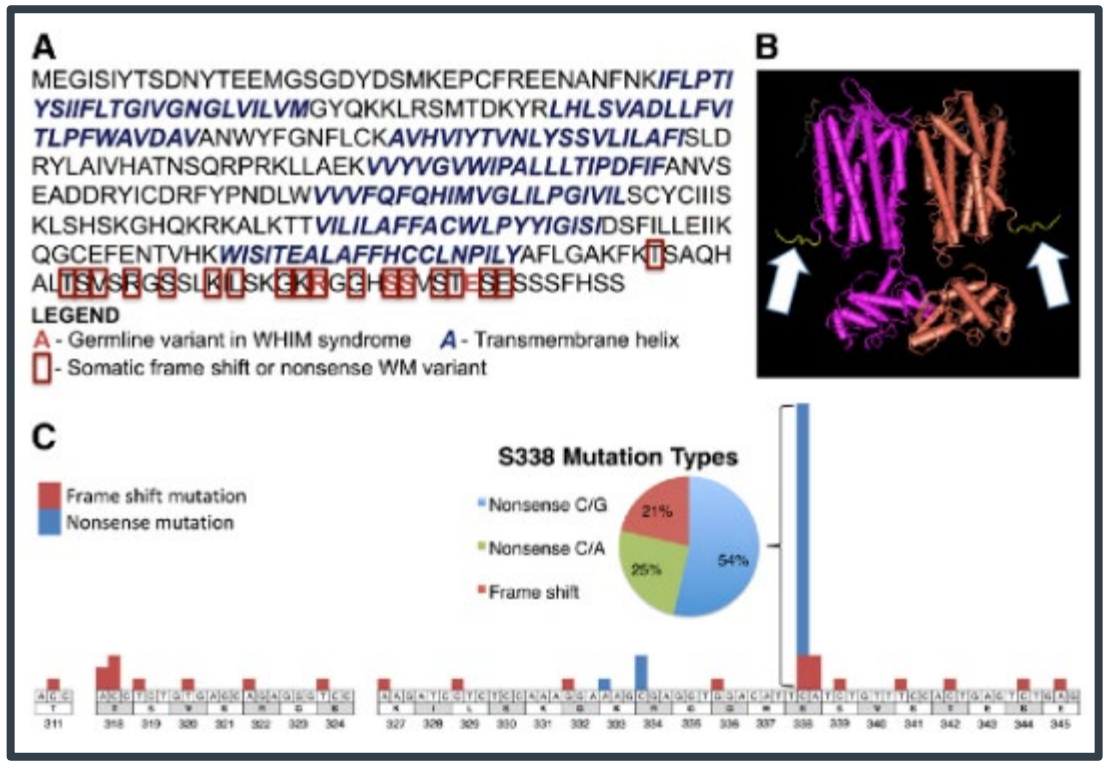
The genomic landscape of Waldenström macroglobulinemia is characterized by highly recurring MYD88 and WHIM-like CXCR4 mutations, and small somatic deletions associated with B-cell lymphomagenesis

Zachary R. Hunter,[1,2] Lian Xu,[1] Guang Yang,[1] Yangsheng Zhou,[1] Xia Liu,[1] Yang Cao,[1] Robert J. Manning,[1] Christina Tripsas,[1] Christopher J. Patterson,[1] Patricia Sheehy,[1] and Steven P. Treon[1,3]



ARID1A, AT-rich interactive domain–containing protein 1A gene; *CD79B*, cluster of differentiation 79B gene; *CXCR4*, C-X-C chemokine receptor type 4 gene; *MAP2*, microtubule-associated protein 2 gene; *MED23*, mediator complex subunit 23 gene; *MLL2*, histone-lysine N-methyltransferase 2D gene; *MUC16*, mucin 16 gene; *MYBBP1A*, Myb-binding protein 1a gene; *MYD88*, myeloid differentiation primary response 88 gene; *NOTCH2*, neurogenic locus notch homolog protein 2 gene; *RAG2*, recombination activating 2 gene; *SYNE1*, spectrin repeat containing nuclear envelope protein 1 gene; *TP53*, tumor protein p53 gene; *TRAF2*, TNF receptor–associated factor 2 gene; *TRAF3*, TNF receptor–associated factor 3 gene; *TRRAP*, transformation/transcription domain–associated protein gene; WHIM, warts, hypogammaglobulinemia, infection, and myelokathexis.
Hunter ZR *et al*. *Blood* 2014 13; 123 (11): 1637–1646.

CXCR4: Mutations

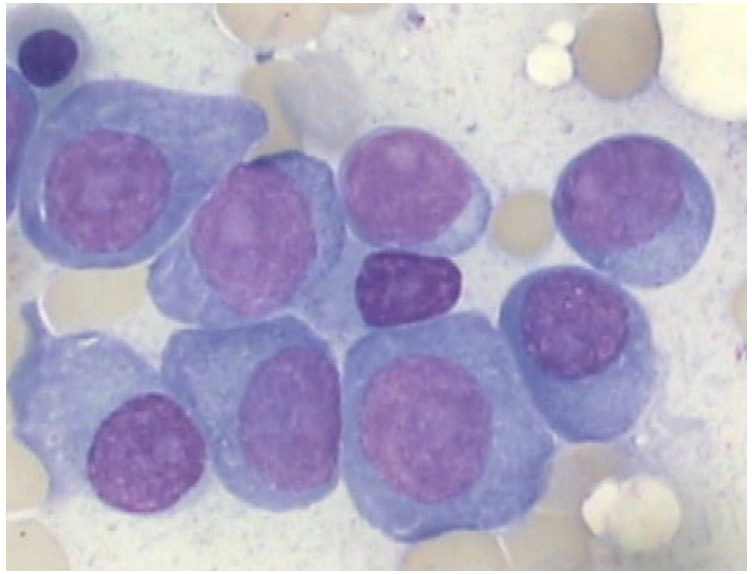


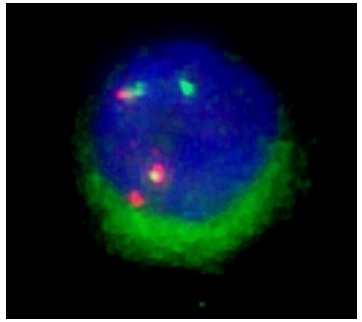
- ~40% patients with WM (only *MYD88*^{MUT})
- MGUS
- C terminus – SDF1a (CXCL12) signaling
- WHIM syndrome
- NS/FS mutations
- ‘Hotspot’ at S338
- Subclonal – Multiple mutations in some patients
- Methodology – ASO/sorting/NGS

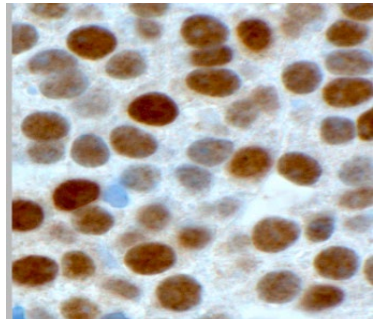
ASO, allele-specific oligonucleotide; *CXCR4*, C-X-C chemokine receptor type 4 gene; FS, frameshift; NS, nonsense; NGS, next-generation sequencing; MGUS, monoclonal gammopathy of undetermined significance; MUT, mutation; *MYD88*, myeloid differentiation primary response 88 gene; WHIM, warts, hypogammaglobulinemia, infection, and myelokathexis; WM, Waldenström’s macroglobulinemia.

Hunter ZR *et al*. *Blood* 2014 13; 123 (11): 1637–1646.

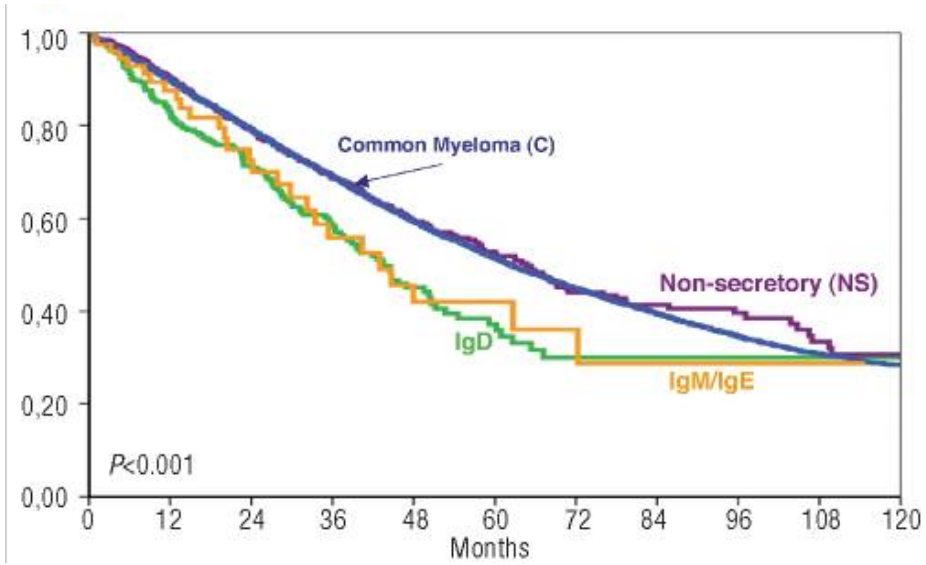
What about IgM myeloma?





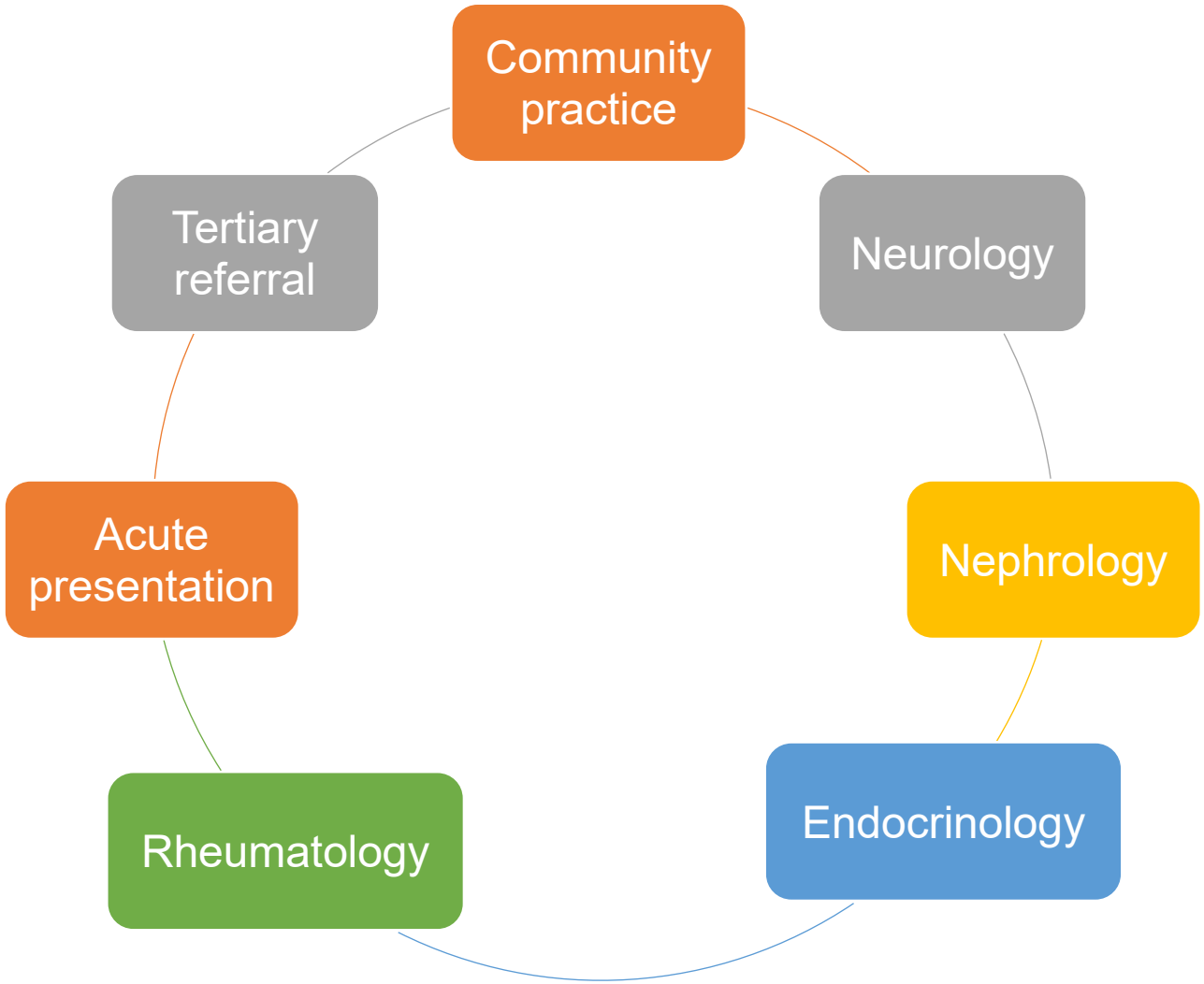


- No B-cell component
- Plasma cells have an abnormal phenotype, typically: $CD19^{-}$ $CD45^{-}$ $CD56^{-}$ $CD117^{-}$
- High incidence of *IGH* translocations, particularly the t(11;14)
- Poor outcome
- Absence of *MYD88*^{L265P}



IgD, immunoglobulin D; IgE, immunoglobulin E; *IGH*, immunoglobulin heavy chain gene; IgM, immunoglobulin M; *MYD88*, myeloid differentiation primary response 88 gene; t, translocation.

Feyler S *et al*. *Br J Haematol* 2008; 140 (5): 547–551. Owen RG *et al*. *Br J Haematol* 2011; 155 (3): 402–403. Owen RG *et al*. *Am J Hematol* 2011; 86 (8): 717.
Morris C *et al*. *Haematologica* 2010; 95 (12): 2126–2133.


Community practice
Neurology
Nephrology
Endocrinology
Rheumatology
Acute presentation
Tertiary referral

Key diagnostic assessments for WM

- Blood count, chemistry, LDH, β2-microglobulin
- Plasma viscosity
- M protein quantitation, uninvolved Ig, sFLC
- Tetanus, pneumococcal, haemophilus titers
- Hepatitis B, hepatitis C, HIV
- DAT
- MAG / cold agglutinins / cryoglobulin, according to history, etc.
- BM aspirate and trephine – flow cytometry, ASO PCR for *MYD88*^{L265P} (NGS coming!)
- CT pre-RX / PET-suspected transformation

ASO PCR, allele-specific oligonucleotide polymerase chain reaction; BM, bone marrow; CT, computed tomography; DAT, direct antiglobulin test; Ig, immunoglobulin; LDH, lactate dehydrogenase; MAG, myelin-associated glycoprotein; *MYD88*, myeloid differentiation primary response 88 gene; NGS, next-generation sequencing; PET, positron emission tomography; RX, rotating X-ray; sFLC, serum free light chain; WM, Waldenström's macroglobulinemia.

Classification of WM and IgM-related disorders

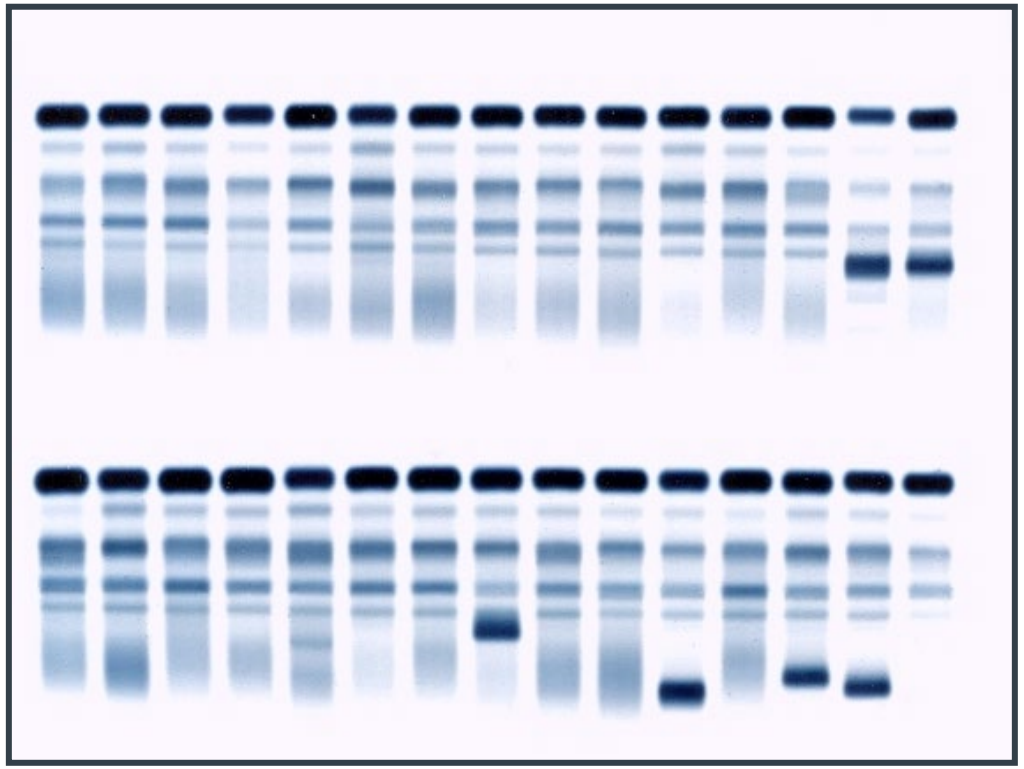
	IgM	Bone marrow	Symptoms
Symptomatic WM	Yes	Yes	Yes
Asymptomatic WM	Yes	Yes	No
IgM-MGUS	Yes	No	No
IgM-related disorders	Yes	No	Yes

IgM, immunoglobulin M; MGUS, monoclonal gammopathy of undetermined significance; WM, Waldenström's macroglobulinemia.

Owen RG *et al. Semin Oncol* 2003; 30 (2): 110–115.

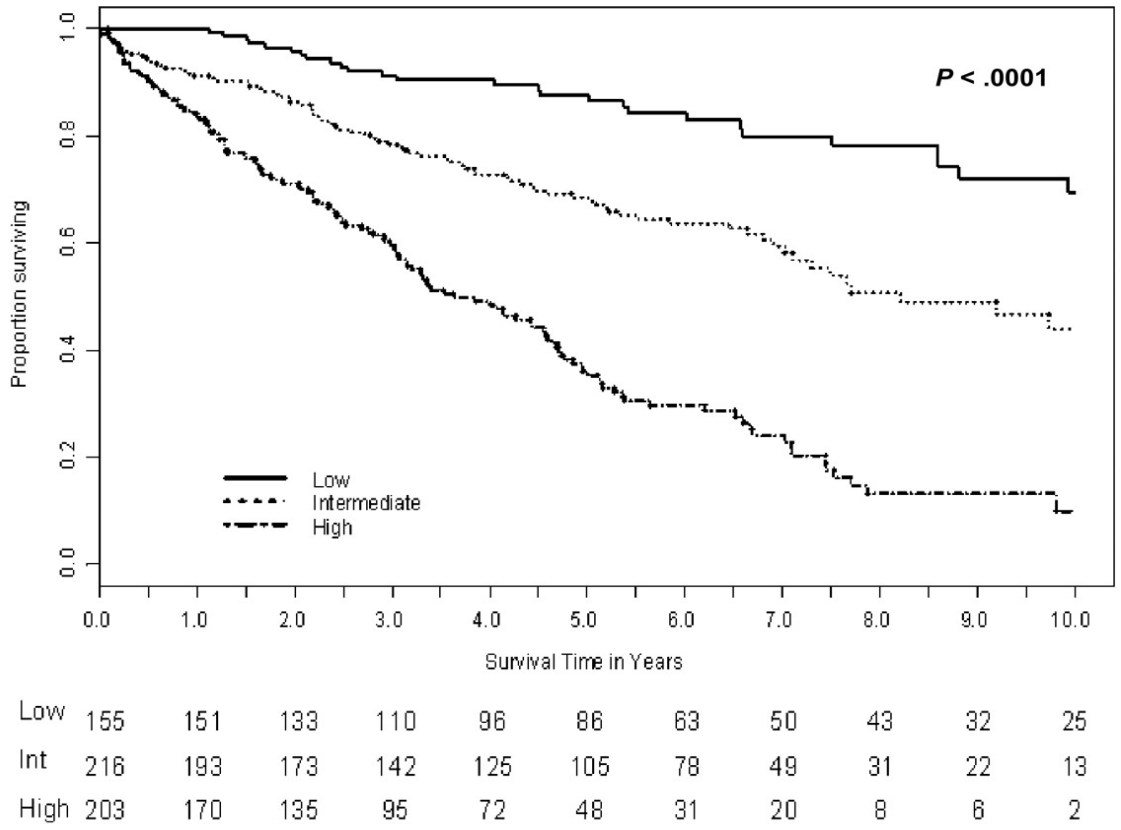
IgM-related disorders

- Anti-MAG peripheral neuropathy
- Cold agglutinin disease
- Cryoglobulinemia
- Amyloidosis
- Schnitzler syndrome
- Acquired vWD
- MGRS



IgM, immunoglobulin M; MAG, myelin-associated glycoprotein; MGRS, monoclonal gammopathy of renal significance; vWD, von Willebrand disease.

International Prognostic Scoring System for WM



- Age >65
- Hb ≤11.5 g/dL
- Platelets ≤100 × 10^9/L
- β2M >3 mg/L
- M protein >7.0 g/L

0 or 1 (except age) = low risk

Age or 2 = intermediate risk

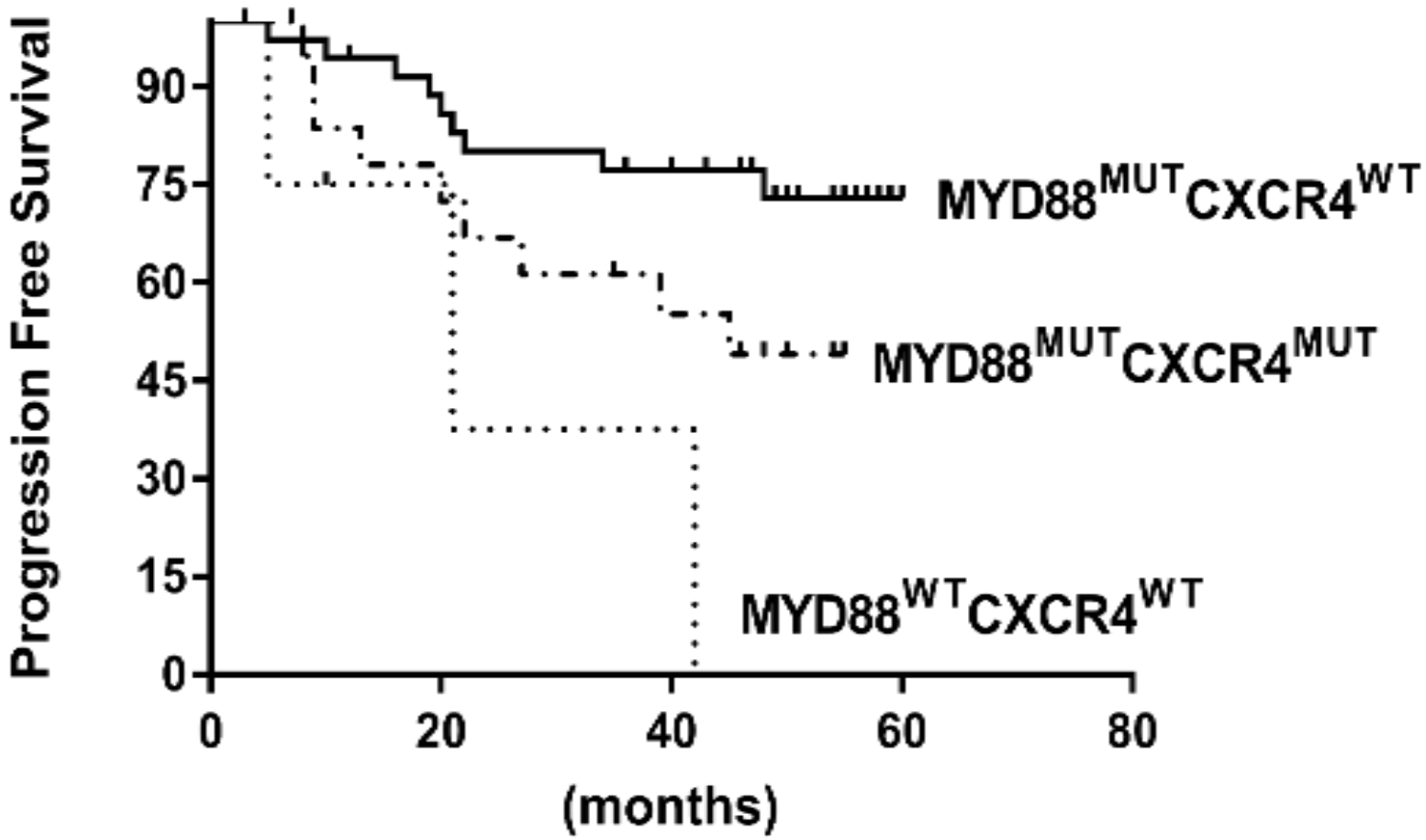
≥3 = high risk

blood

β2M, β2–microglobulin; Hb, hemoglobin; WM, Waldenström's macroglobulinemia.

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

Impact of genomics on outcome



Adapted from Treon *et al*. *Blood* 2017.

Median study follow-up 47.1 months; N=63.
Treon SP *et al. Blood*. 2017;130(suppl 1):2766.

Executive summary

- WM is a B-cell disorder characterized by plasma cell differentiation, and clinical features can be considered in this context
- *MYD88*^{L265P} and WM-specific B-cell phenotype allows for a definitive pathological diagnosis

MYD88, myeloid differentiation primary response 88 gene; WM, Waldenström's macroglobulinemia.


"That's all Folks!"

Diagnosing WM: A patient's journey

Alessandra Tedeschi

WM, Waldenström's macroglobulinemia.

Disclosures

- Consulting services for AbbVie, AstraZeneca, BeiGene and Janssen-Cillag SpA

Initial case presentation

Patient characteristics

- 64-year-old male
- Good overall health, no comorbidities
- No medications
- No known family history of B-cell lymphoproliferative disorders
- Routine blood test performed before a surgical intervention

Initial case presentation

Patient characteristics

- 64-year-old male
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Laboratory studies

Hemoglobin:	11.6 g/dL
Platelets:	230 × 10^9/L
WBC:	4 × 10^9/L
PMN:	65%
Serum creatinine:	1.2 mg/dL
LFTs:	Normal
Serum protein electrophoresis:	Monoclonal component in γ region (M spike 0.4 g/dL)
Immunofixation:	IgM kappa

IgM, immunoglobulin M; LFT, liver function test; PMN, polymorphonuclear leukocytes; WBC, white blood cells.

Which tests are essential at this point?

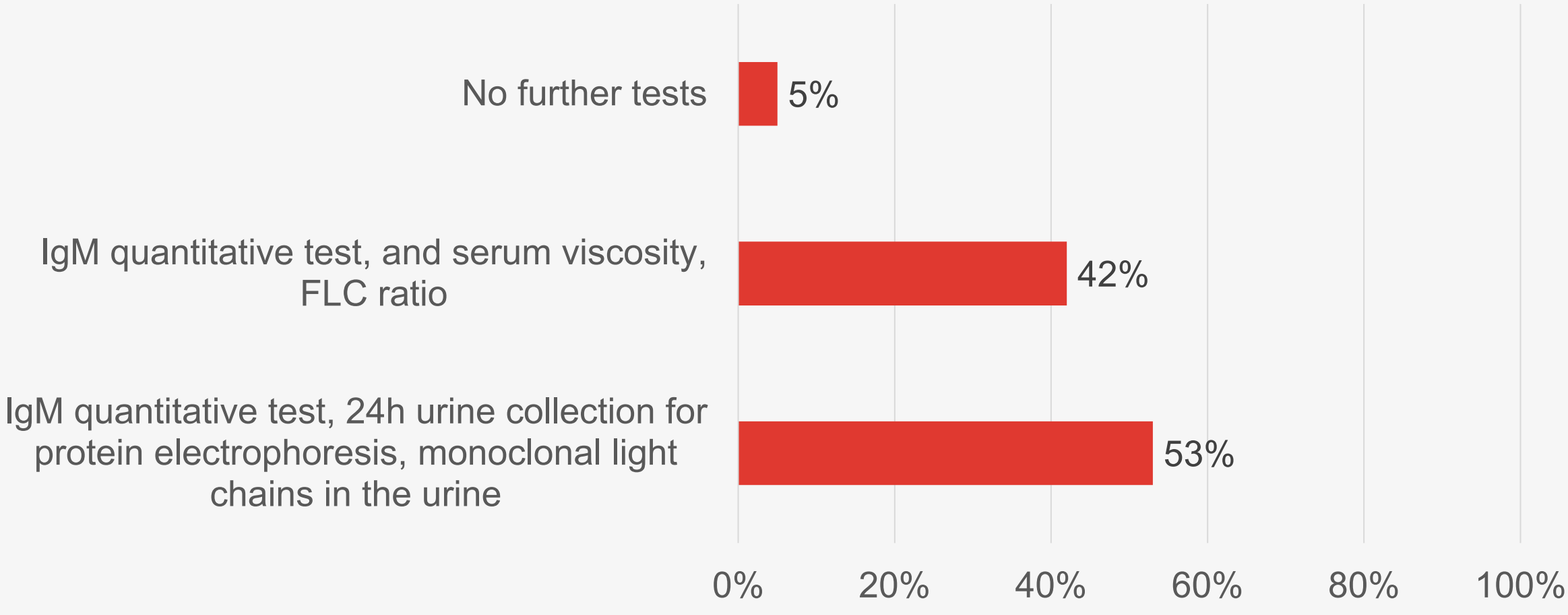
A No further tests

B IgM quantitative test, and serum viscosity, FLC ratio

C IgM quantitative test, 24h urine collection for protein electrophoresis, monoclonal light chains in the urine

FLC, free light chain; IgM, immunoglobulin M.

Which tests are essential at this point?



BeiGeneius

According to guidelines, when would you perform a bone marrow evaluation in an asymptomatic patient?

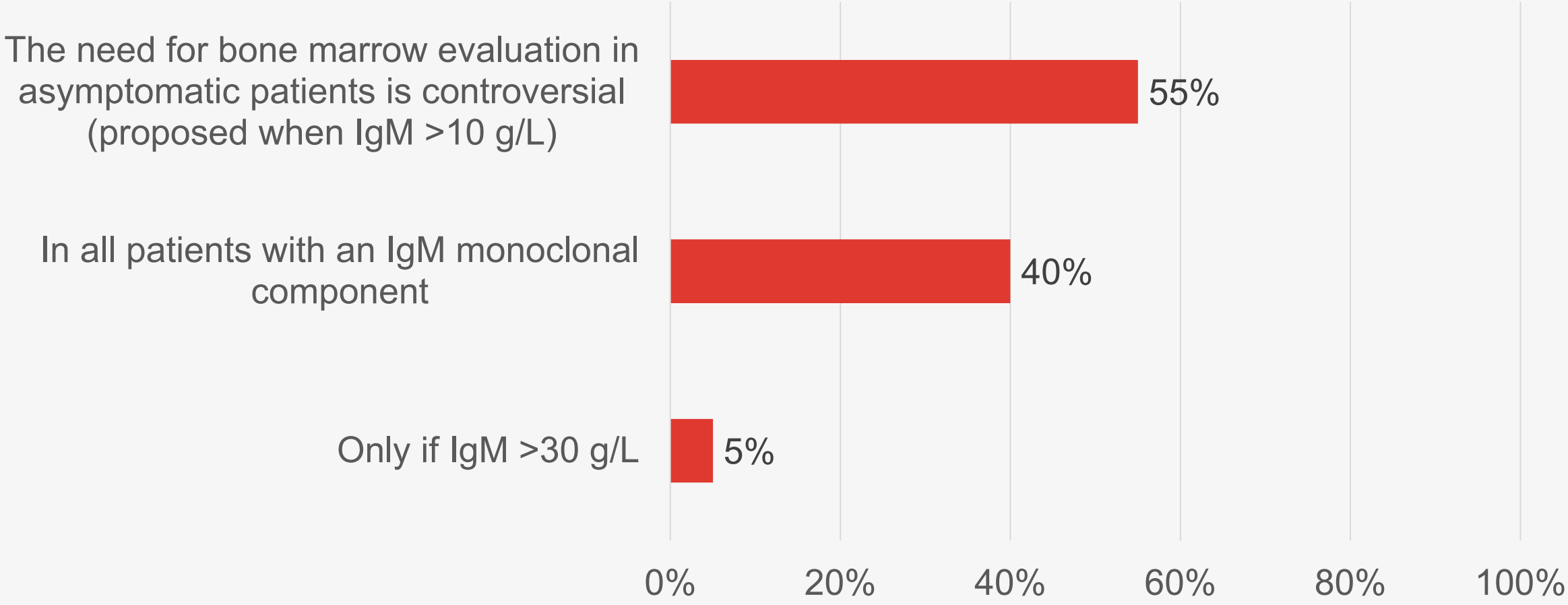
A. The need for bone marrow evaluation in asymptomatic patients is controversial (proposed when IgM >10 g/L)

B. In all patients with an IgM monoclonal component

C. Only if IgM >30 g/L

IgM, immunoglobulin M.

According to guidelines, when would you perform a bone marrow evaluation in an asymptomatic patient?



BeiGeneius

Bone marrow evaluation in patients with IgM paraprotein

YES in case of:

- Symptomatic patients
- Cytopenias, lymphadenopathy, or splenomegaly
- Suspected IgM-related syndrome, such as peripheral neuropathy, CHAD, or AL

> “Its value in the assessment of asymptomatic individuals with an IgM paraprotein is not established but **an arbitrary IgM monoclonal protein threshold of 10 g/L has been proposed in some guidelines**[1]”

87 asymptomatic patients with an IgM M protein <10 g/L [2]
- 65 patients (75%) IgM MGUS [2]
- 22 (25%) asymptomatic WM [2]

AL, amyloidosis, light chain; CHAD, cold hemagglutinin disease; IgM, immunoglobulin M; MGUS, monoclonal gammopathy of undetermined significance; WM, Waldenström’s macroglobulinemia.

1. Owen RG *et al*. *Br J Haematol* 2014; 165 (3): 316–333. 2. Varettoni M *et al. Br J Haematol* 2015; 168 (2): 301–313.

Bone marrow evaluation was not performed. What is the patient's diagnosis?

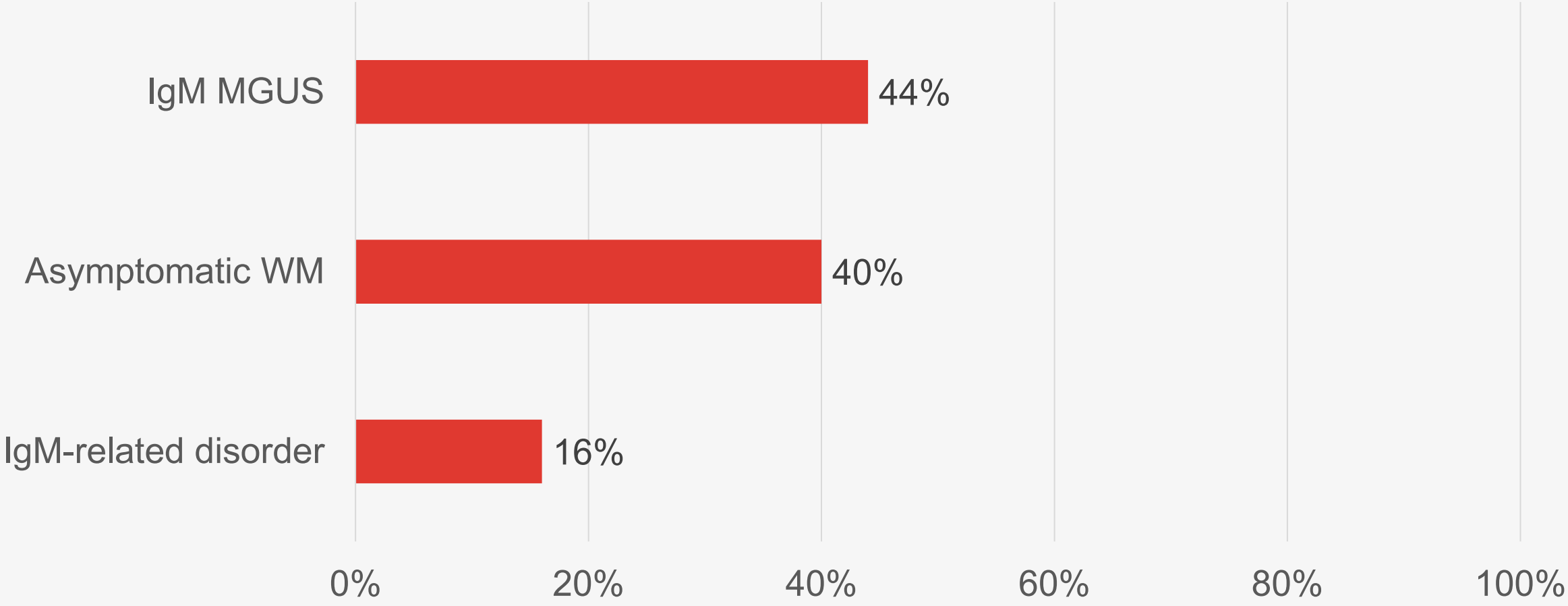
A IgM MGUS

B Asymptomatic WM

C IgM-related disorder

IgM, immunoglobulin M; MGUS, monoclonal gammopathy of undetermined significance; WM, Waldenström's macroglobulinemia.

Bone marrow evaluation was not performed. What is the patient's diagnosis?



BeiGene

Definitions of IgM-related phenomena

	IgM monoclonal protein	Bone marrow infiltration	Symptoms attributed to IgM*	Symptoms attributed to tumor infiltration†
MGUS	+	–	–	–
IgM-related disorders	+	–	+	–
WM asymptomatic	+	+	–	–
WM symptomatic	+	+	+	+

*Neuropathy, cold agglutinin-related anemia, autoimmune thrombocytopenia, cryoglobulinemia, amyloidosis. †Systemic symptoms, cytopenia, lymphoadenopathy, hepatosplenomegaly.
IgM, immunoglobulin M; MGUS, monoclonal gammopathy of undetermined significance; WM, Waldenström's macroglobulinemia.
Owen RG *et al*. *Semin Oncol* 2003; 30 (2): 110–115.

Patient follow-up: 64-year-old asymptomatic patient with IgM MGUS (M spike 0.4 g/dL)

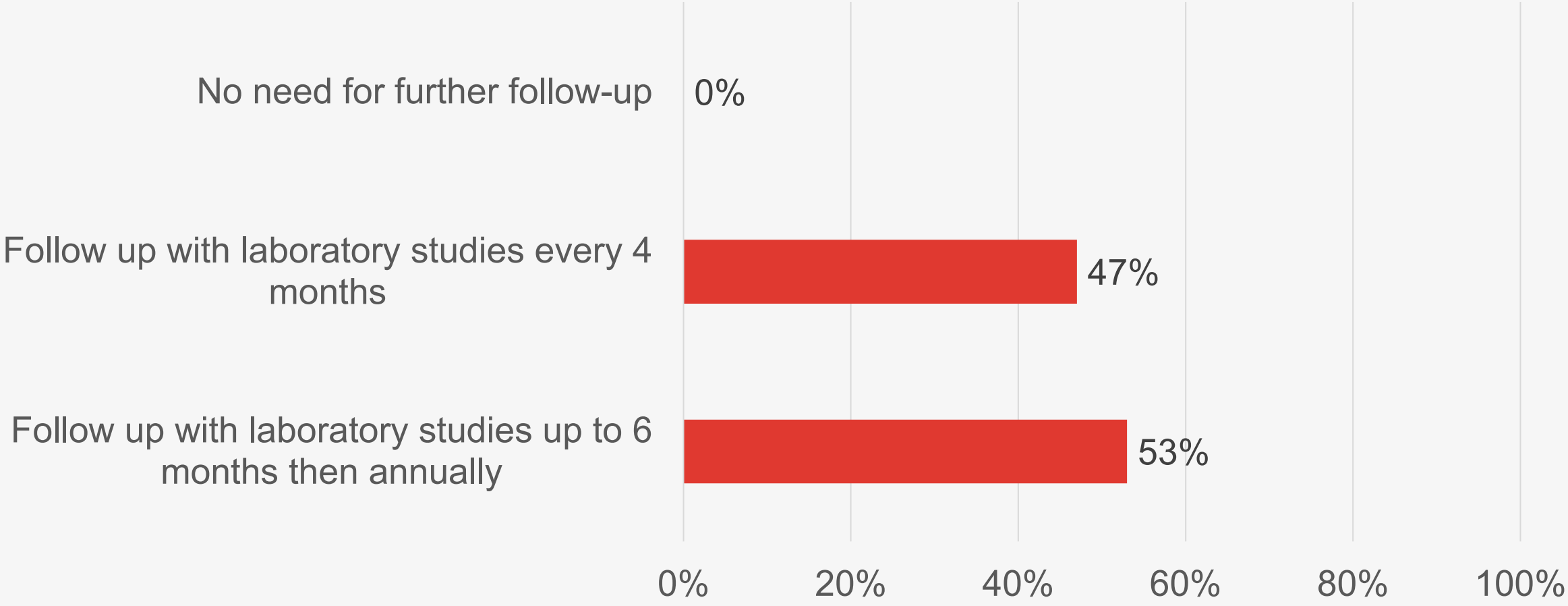
A No need for further follow-up

B Follow up with laboratory studies every 4 months

C Follow up with laboratory studies up to 6 months then annually

IgM, immunoglobulin M; MGUS, monoclonal gammopathy of undetermined significance.

Patient follow-up: 64-year-old asymptomatic patient with IgM MGUS (M spike 0.4 g/dL)



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After 3 years

Patient characteristics

- 67-year-old male
- Asymptomatic

Laboratory studies

Hemoglobin:	10.8 g/dL
Platelets:	180 × 10^9/L
WBC:	5.7 × 10^9/L
PMN:	72%
Serum creatinine:	1.19 mg/dL
LFTs:	Normal
M spike:	2.1 g/dL
IgM:	1980 mg/dL
24h urinary protein:	Normal
Bence Jones K:	Positive

IgM, immunoglobulin M; LFT, liver function test; PMN, polymorphonuclear leukocytes; WBC, white blood cells.

Bone marrow evaluation:

- No evidence of bone marrow infiltration
- 5% B-cell clonal population CD19+ CD22+ smIgM kappa
- *MYD88* mutated

What is the patient's diagnosis?

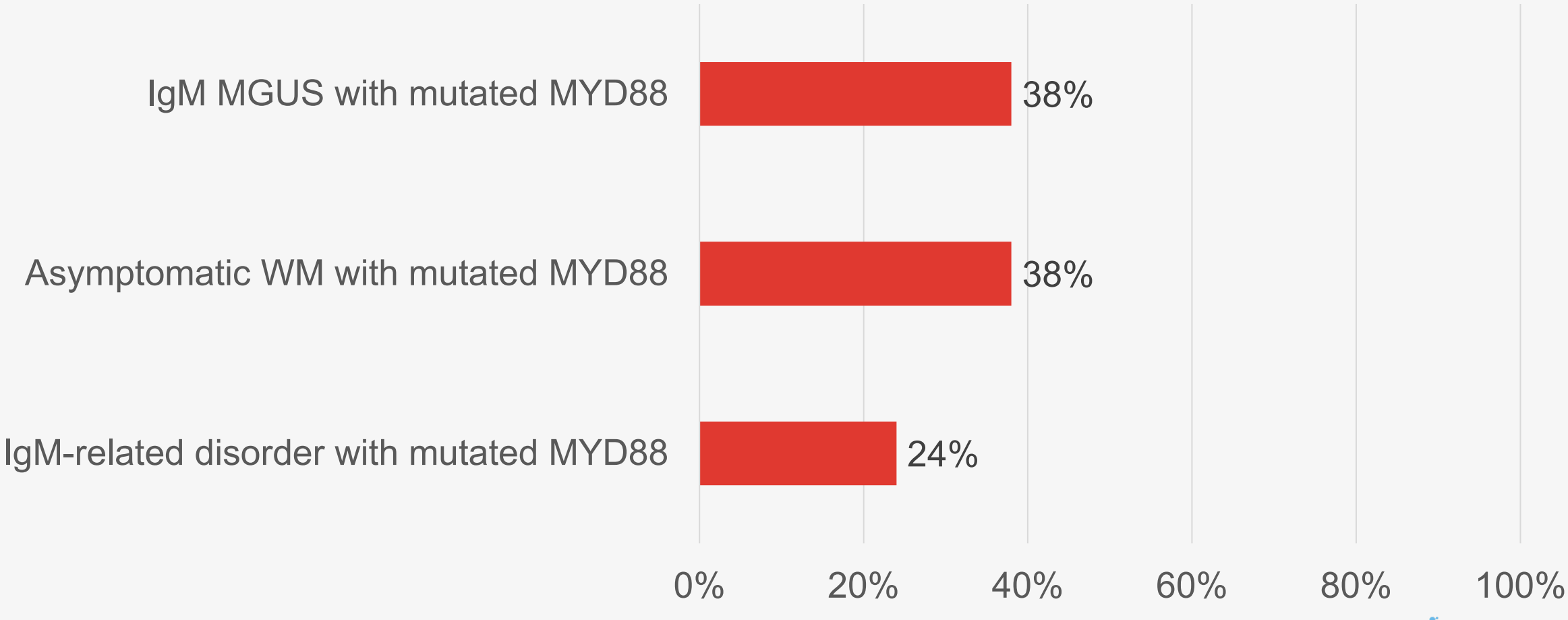
A IgM MGUS with mutated *MYD88*

B Asymptomatic WM with mutated *MYD88*

C IgM-related disorder with mutated *MYD88*

IgM, immunoglobulin M; MGUS, monoclonal gammopathy of undetermined significance; smIgM, surface membrane immunoglobulin M; MYD88, myeloid differentiation primary response 88 gene; WM, Waldenström's macroglobulinemia.

What is the patient's diagnosis?



BeiGeneius

MYD88 in IgM MGUS

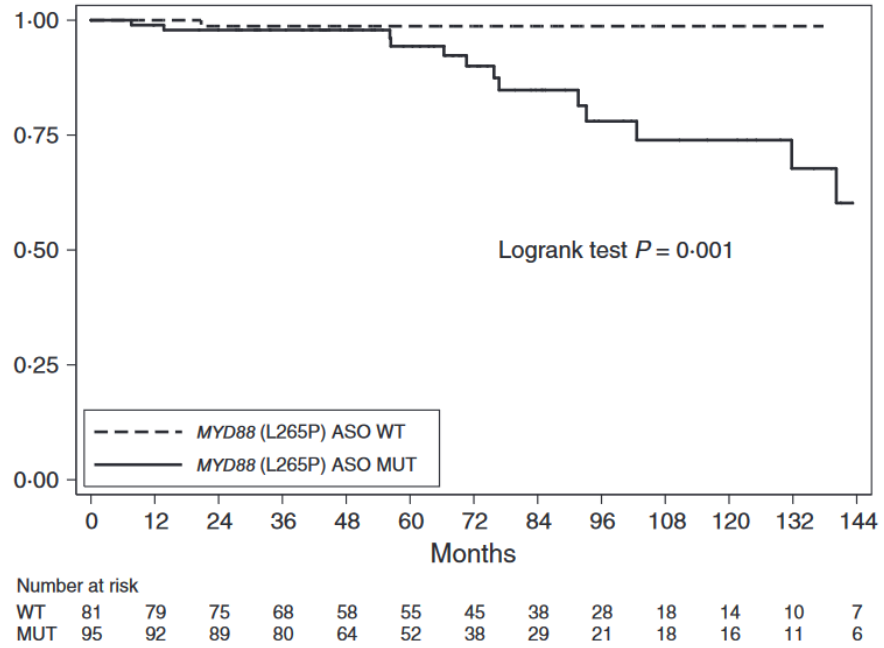
MYD88^{L256P} in WM and IgM MGUS

	Method	Tissue	WM	IgM MGUS
Treon[2]	WGS/Sanger	BM CD19+	91%	10%
Xu[3]	AS-PCR	BM CD19+	93%	56%
Gachard[4]	PCR	BM	67%	
Varettoni[5]	AS-PCR	BM CD19+	100%	47%
Landgren[6]	Sanger	BM		54%
Jiménez[7]	AS-PCR	BM	86%	87%

bjh research paper

A risk-stratification model based on the initial concentration of the serum monoclonal protein and *MYD88* mutation status identifies a subset of patients with IgM monoclonal gammopathy of undetermined significance at high risk of progression to Waldenström macroglobulinaemia or other lymphoproliferative disorders

IgM MGUS with an M protein ≥10 g/L harboring *MYD88* at diagnosis are at high risk of progression, with a cumulative incidence of 38% at 10 years[1]



AS-PCR, allele-specific polymerase chain reaction; BM, bone marrow; IgM, immunoglobulin M; MGUS, monoclonal gammopathy of undetermined significance; MYD88, myeloid differentiation primary response 88 gene; PCR, polymerase chain reaction; WGS, whole genome sequencing; WM, Waldenström's macroglobulinemia.

1. Varettoni M *et al*. *Blood* 2019; 134: 1539; 2. Treon S *et al. N Engl J Med* 2012; 367: 826–833; 3. Xu L *et al. Blood* 2013; 121: 2051–2058; 4. Gachard N *et al. Leukemia* 2013; 27: 183–189; 5. Varettoni M *et al. Blood* 2013; 121 :2522–2528; 6. Landgren O & Staudt L. *N Engl J Med* 2012; 367: 2255–2257; 7. Jiménez C *et al. Leukemia* 2013; 27: 1722–1728.

After 16 months

Patient characteristics

- 69-year-old male
- Complains of fatigue

Physical examination

- No lymphadenopathies
- Splenomegaly

Abdomen ultrasound

- Confirmed splenomegaly of 17 cm
- No adenopathies
- Liver: Normal

Laboratory studies

Hemoglobin:	10.6 g/dL
Platelets:	180 × 10^9/L
WBC:	5.7 × 10^9/L
PMN:	72%
Serum creatinine:	1.19 mg/dL
LFTs:	Normal
M spike:	2.4 g/dL
IgM:	2300 mg/dL
24h urinary protein:	Normal
Bence Jones K:	Positive

IgM, immunoglobulin M; LFT, liver function test; PMN, polymorphonuclear leukocytes; WBC, white blood cells.

Differential diagnosis

- Small lymphocytic lymphoma
- Follicular lymphoma
- Mantle cell lymphoma
- Marginal zone lymphoma
- Multiple myeloma

Bone marrow evaluation: Immunophenotype

Patient

$CD19^{+}$
$CD22^{low+}$
$CD20^{+}$
$CD25^{+}$
$CD27^{+/-}$
$CD5^{-}$
$CD23^{-}$
$CD10^{-}$
$CD11c^{-}$
$CD38^{-/+}$
$sIgM^{bright}$

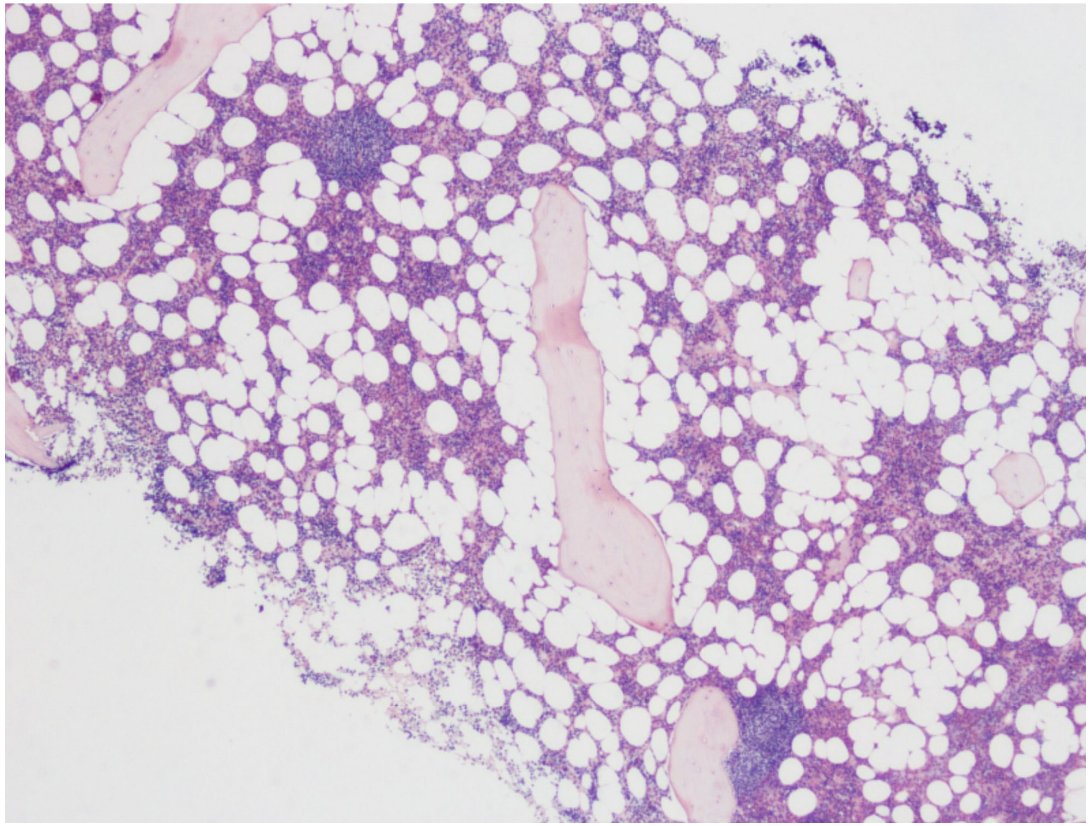
DD

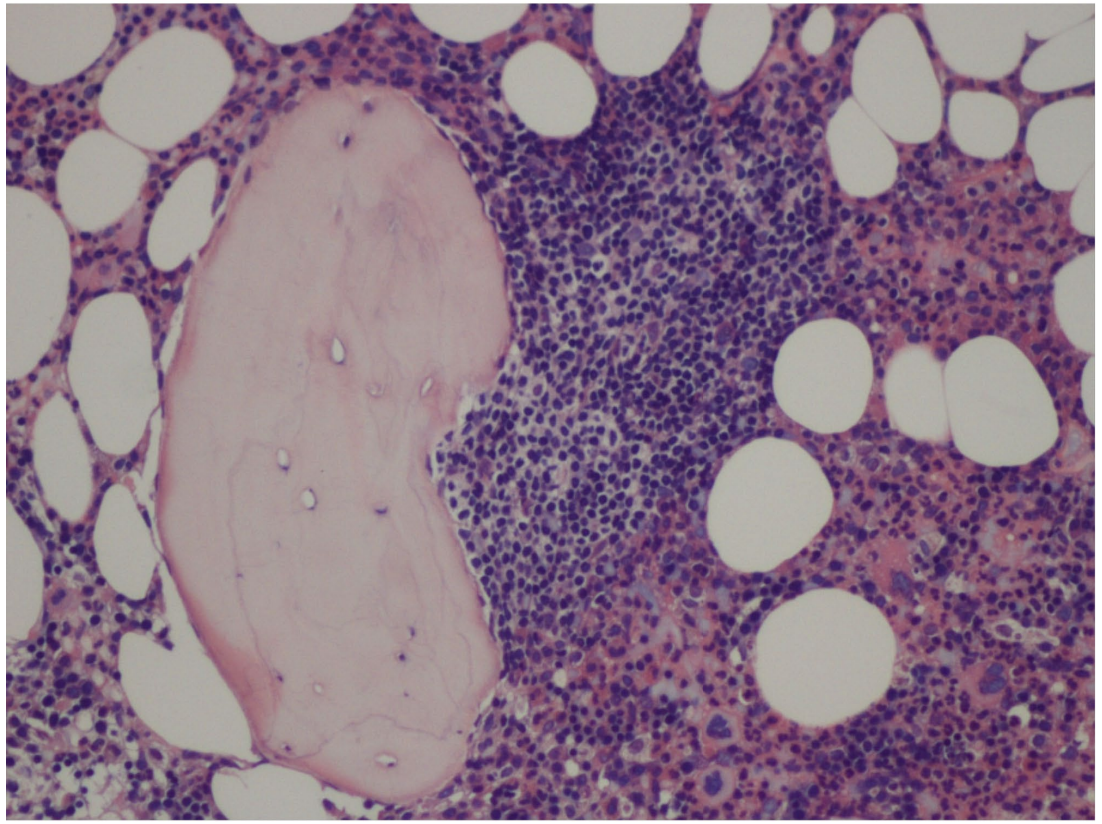
CLL/SLL:	$CD5^{+}$ $CD23^{+}$ Surface Ig^{DIM}
MCL:	$CD5^{+}$
FL:	$CD10^{+}$

Antigen	WM B Cell	MZL
CD5	–	–
CD10	–	–
CD11C	–	+/–
CD19	++	++
CD20	++	++
CD22	Low+	Low+
CD23	+/–	+/–
CD25	+	+/–
CD27	+/–	–
CD38	–/+	–/+
CD305	–	+
SIG	+	+

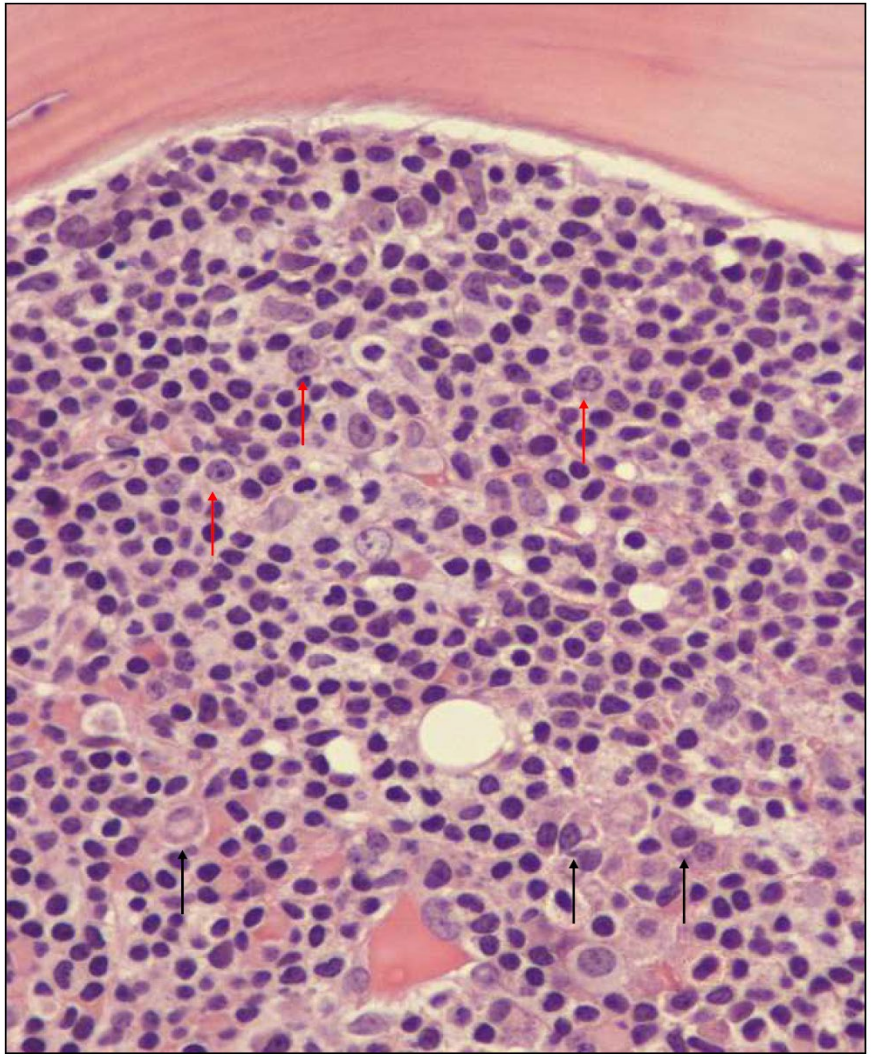
CLL, chronic lymphocytic leukemia; DD, differential diagnosis; FL, follicular lymphoma; MCL, mantle cell lymphoma; MZL, marginal zone lymphoma; SLL, small lymphocytic lymphoma; WM, Waldenström's macroglobulinemia.

Bone marrow evaluation: Histology

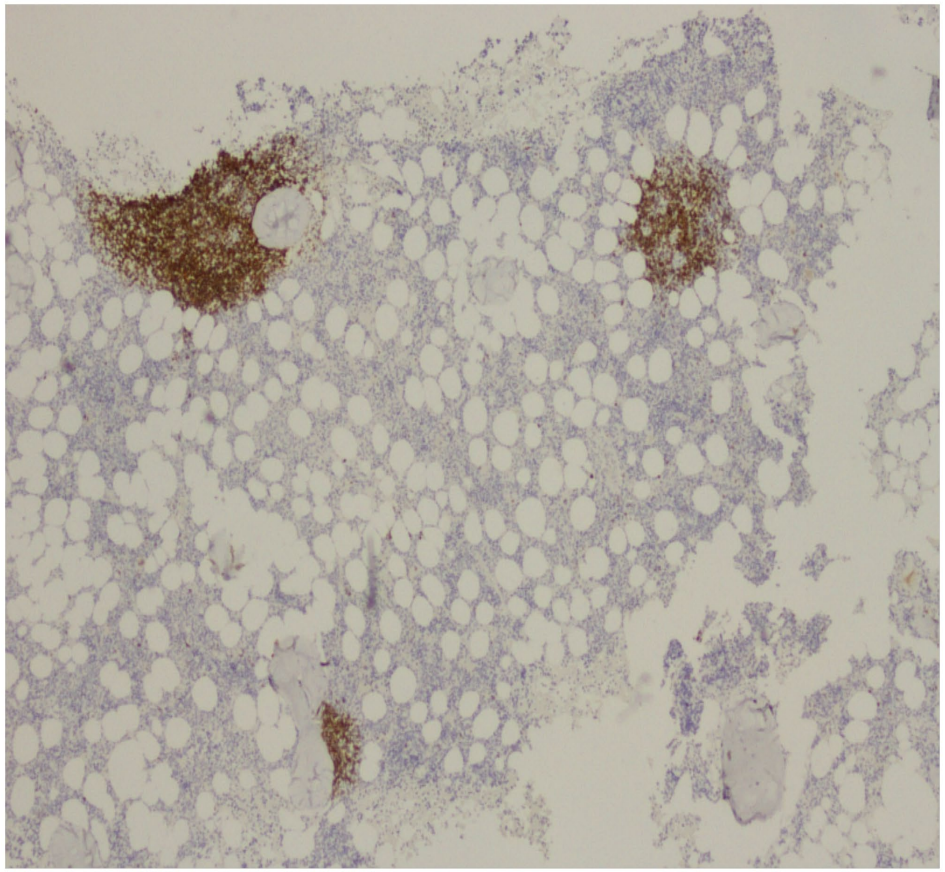




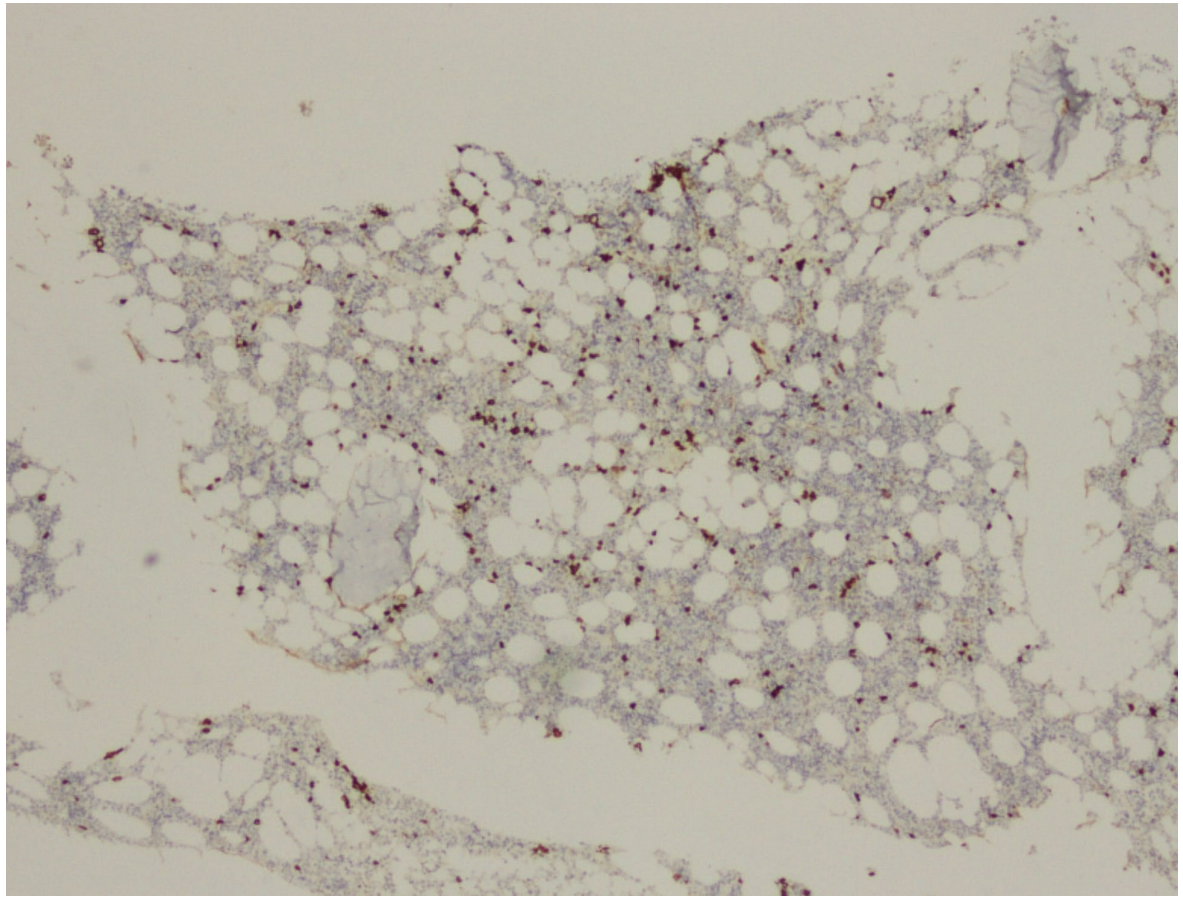
Bone marrow evaluation: Histology



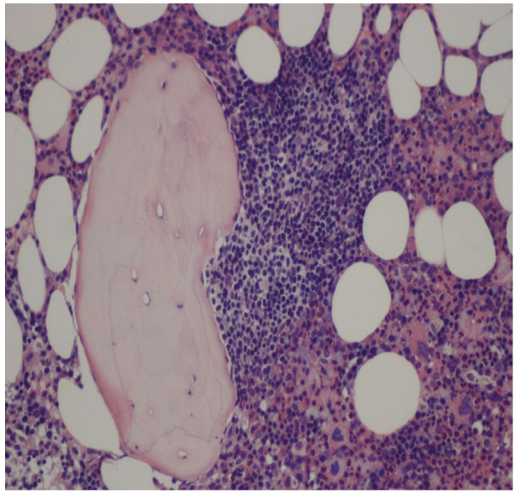
CD20

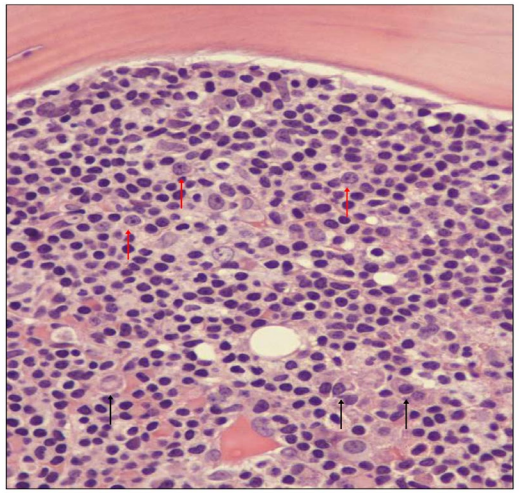


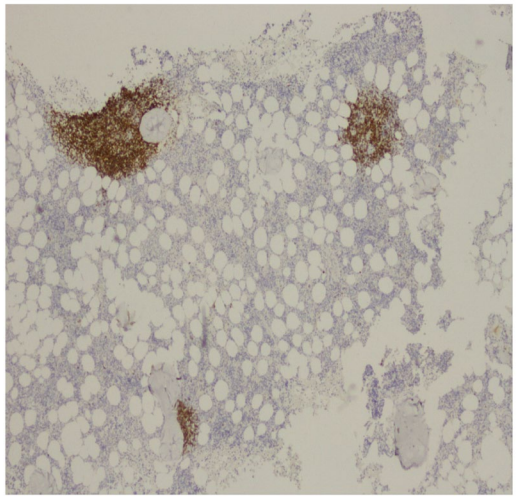
CD138

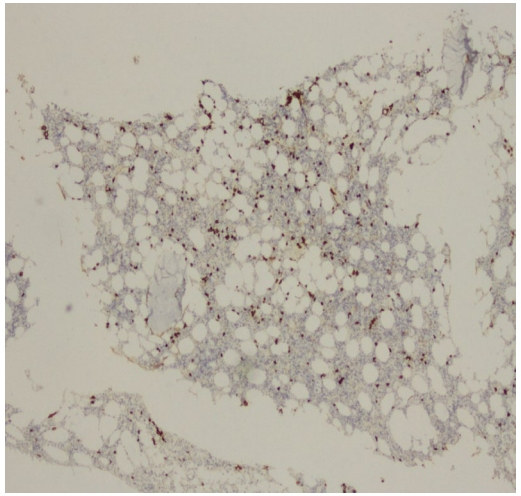


Conclusion









Mature B-cell lymphoproliferative disorder – small lymphocytes with minimal plasmacytic differentiation (*MYD88* mutated)

$CD19^{+}$
$CD22^{low+}$
$CD20^{+}$
$CD25^{+}$
$CD27^{+/-}$
$CD5^{-}$
$CD23^{-}$
$CD10^{-}$
$CD11c^{-}$
$CD38^{-/+}$
$sIgM^{bright}$

$MYD88^{mut}$

MZL?
WM?

Splenomegaly:
WM: 10%–20%
MZL: 80%–100% in splenic MZL

MYD88, myeloid differentiation primary response 88 gene; MZL, marginal zone lymphoma; WM, Waldenström's macroglobulinemia.

Bone marrow evaluation: *MYD88* confirmed to be positive

MYD88^{L265P} mutation in lymphoid B malignancies	
WM	90%–100%
IgM-MGUS	41%–56%
SMZL	7%–13%
MALT	9%
CLL	3%–10%
ABC-DLBCL	29%

ABC-DLBCL, activated B-cell-like diffuse large B-cell lymphoma; CLL, chronic lymphocytic leukemia; IgM, immunoglobulin M; MALT, mucosa-associated lymphoid tissue; MGUS, monoclonal gammopathy of undetermined significance; MYD88, myeloid differentiation primary response 88 gene; SMZL, splenic marginal zone lymphoma; WM, Waldenström's macroglobulinemia.

Treon SP *et al*. *N Engl J Med* 2012; 367 (9): 826–833. Landgren O & Tageja N. *Leukemia* 2014; 28: 1799–1803. Dimopoulos MA *et al*. *Blood* 2019; 134 (23): 2022–2035.

After 16 months

Patient characteristics

- 69-year-old male
- Complains of fatigue
- Splenomegaly (17 cm)
- No adenopathies

- Mature B-cell lymphoproliferative disorder
  - Small lymphocytes with minimal plasmacytic differentiation
  - *MYD88* mutated

Laboratory studies

Hemoglobin:	10.6 g/dL
Platelets:	180 × 10^9/L
WBC:	5.7 × 10^9/L
PMN:	72%
Serum creatinine:	1.19 mg/dL
LFTs:	Normal
M spike:	2.8 g/dL
IgM:	1800 mg/dL
24h urinary protein:	Normal
Bence Jones K:	Positive

IgM, immunoglobulin M; LFT, liver function test; MYD88, myeloid differentiation primary response 88 gene; PMN, polymorphonuclear leukocytes; WBC, white blood cells.

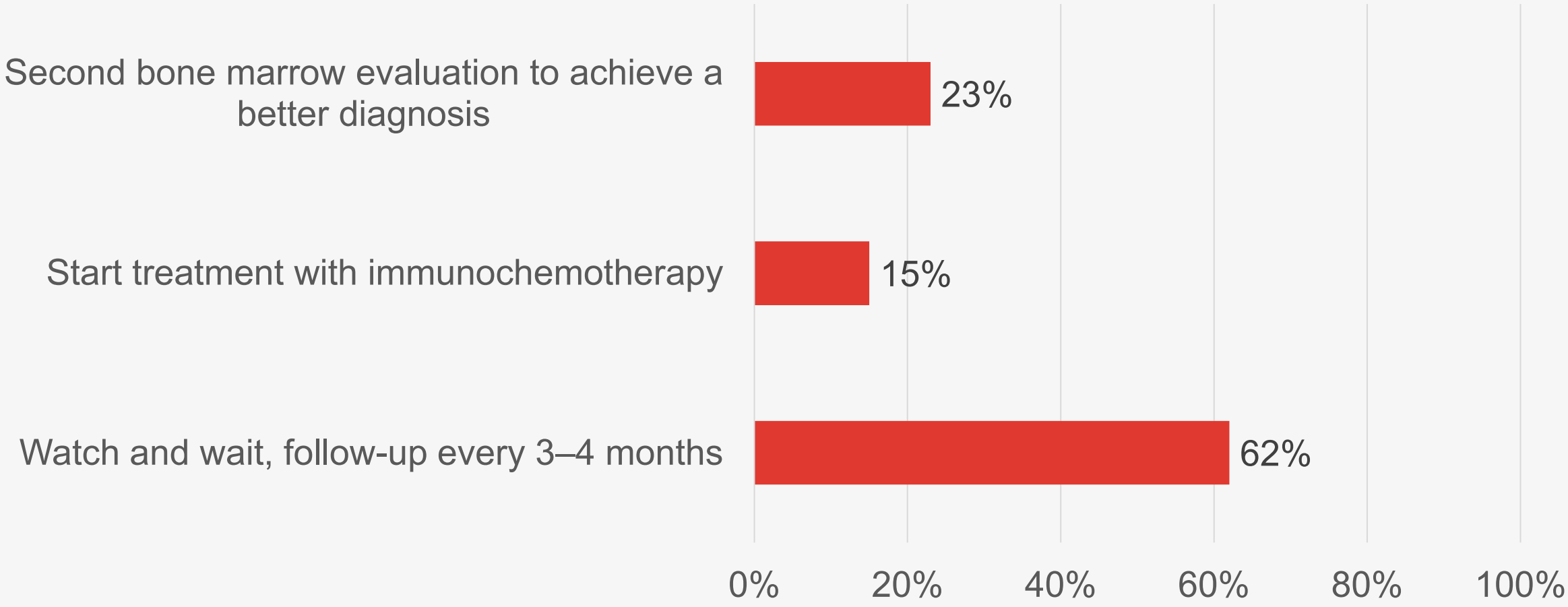
Patient follow-up

A Second bone marrow evaluation to achieve a better diagnosis

B Start treatment with immunochemotherapy

C Watch and wait, follow-up every 3–4 months

Patient follow-up



BeiGeneius

After 12 months

Patient characteristics

- 70-year-old male
- Fatigue increased, sometimes shortness of breath

Physical examination

- Two small palpable adenopathies of about 2 cm LC
- Splenomegaly

Abdomen ultrasound

- Splenomegaly of 18 cm
- Liver: Normal

Laboratory studies

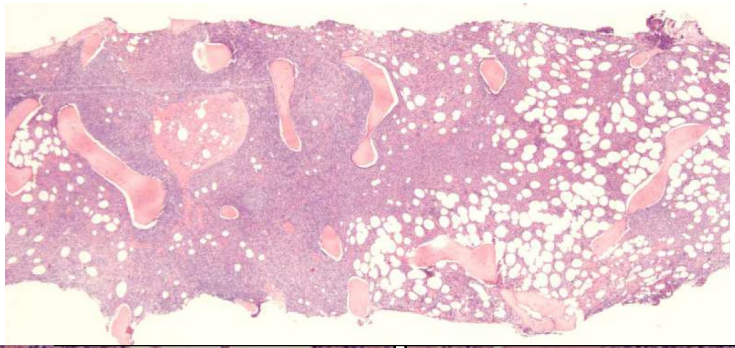
Hemoglobin:	8.9 g/dL
Platelets:	120 × 10^9/L
WBC:	3.7 × 10^9/L
PMN:	62%
Serum creatinine:	1.3 mg/dL
LFTs:	Normal
M spike:	4.2 g/dL
IgM:	3220 mg/dL
24h urinary protein:	Normal
Bence Jones K:	Positive

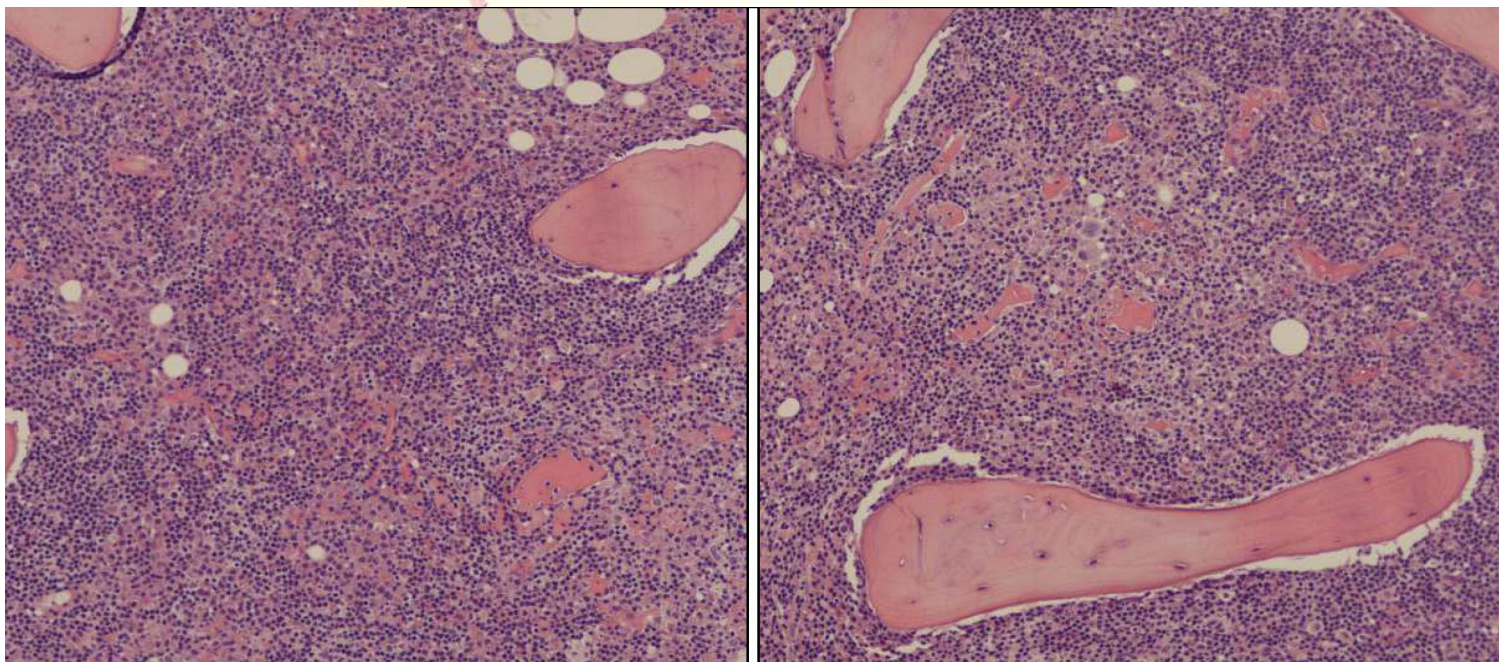
→ Considering the possibility of BTKi treatment in WM diagnosis needed

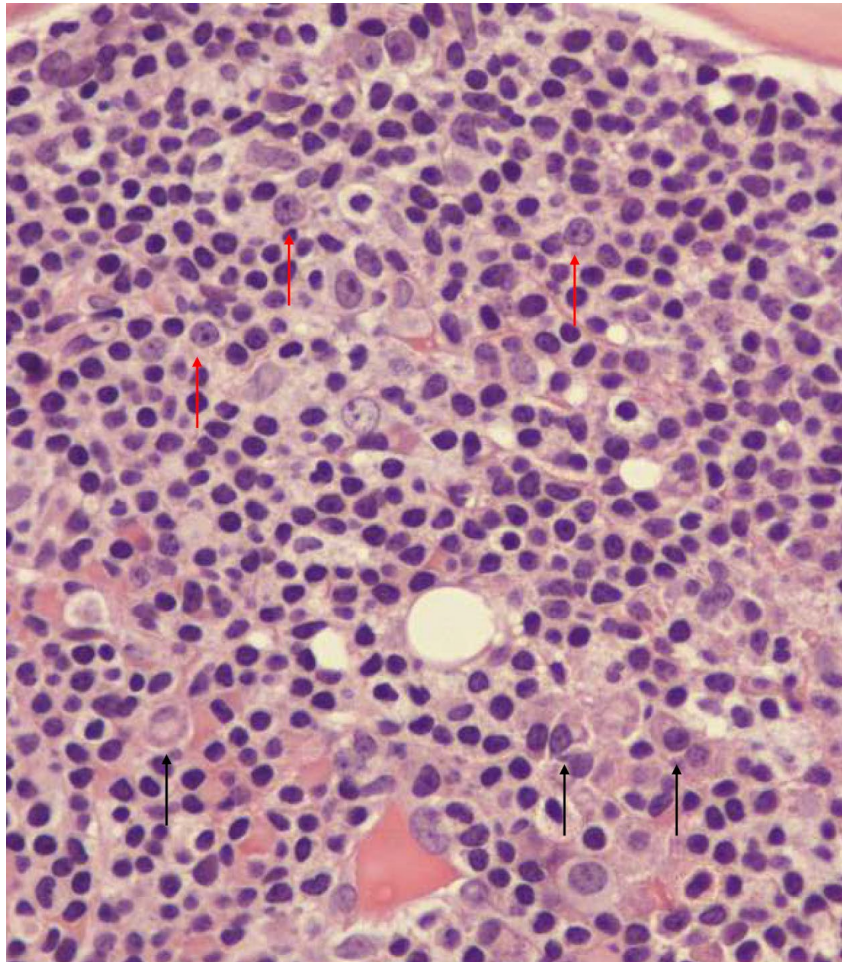
→ Bone marrow and lymph node histology

BTKi, Bruton tyrosine kinase inhibitor; IgM, immunoglobulin M; LC, Langerhans cells; LFT, liver function test; PMN, polymorphonuclear leukocytes; WBC, white blood cells.

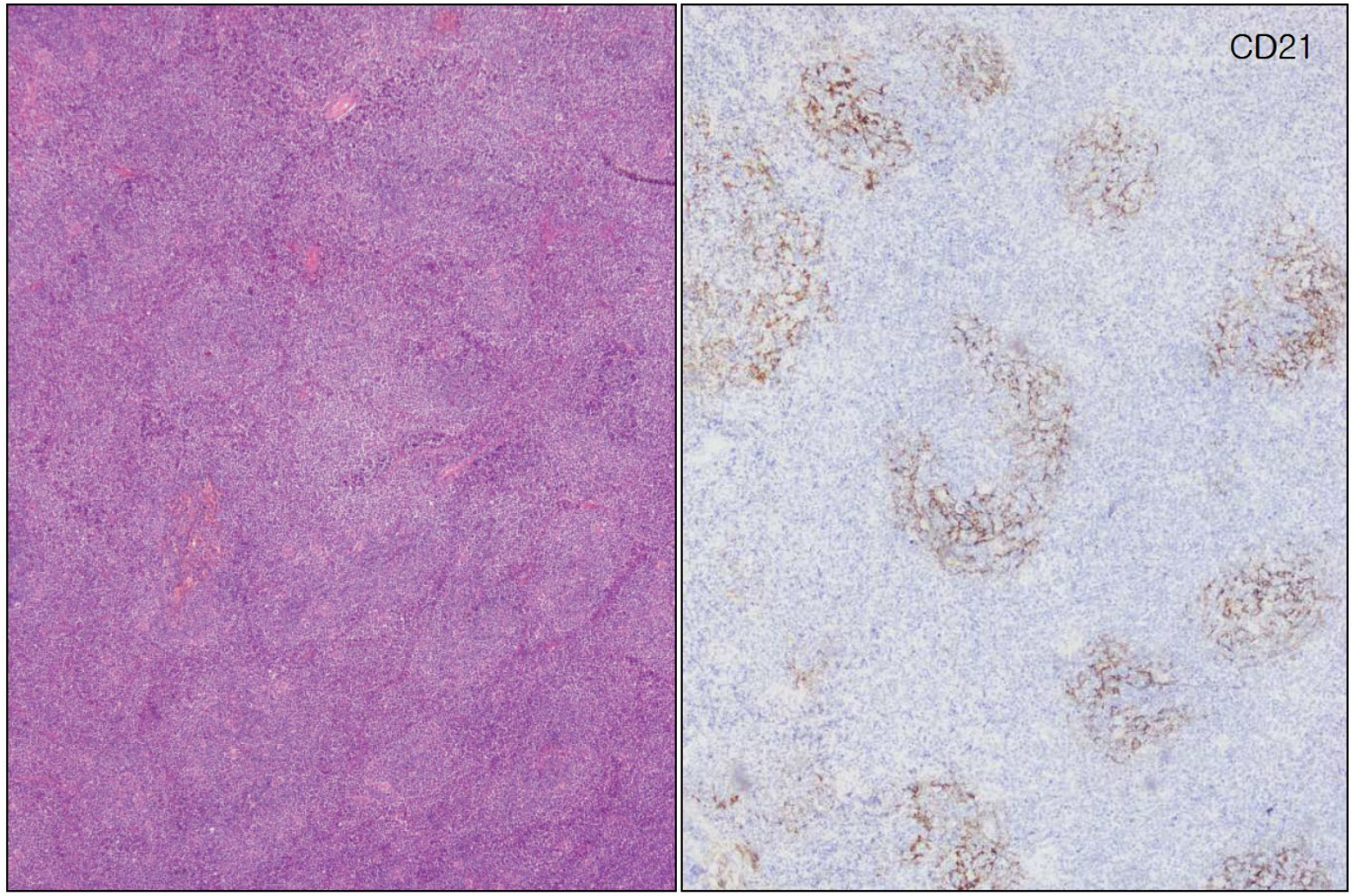
Bone marrow evaluation: Histology

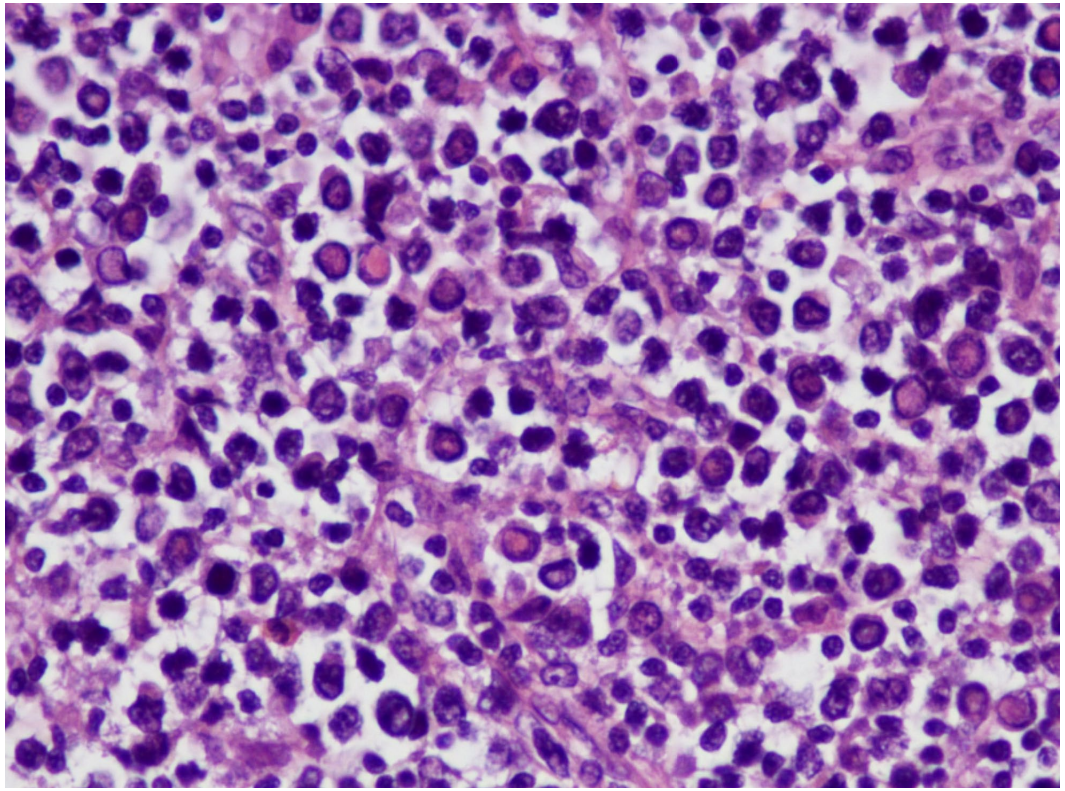


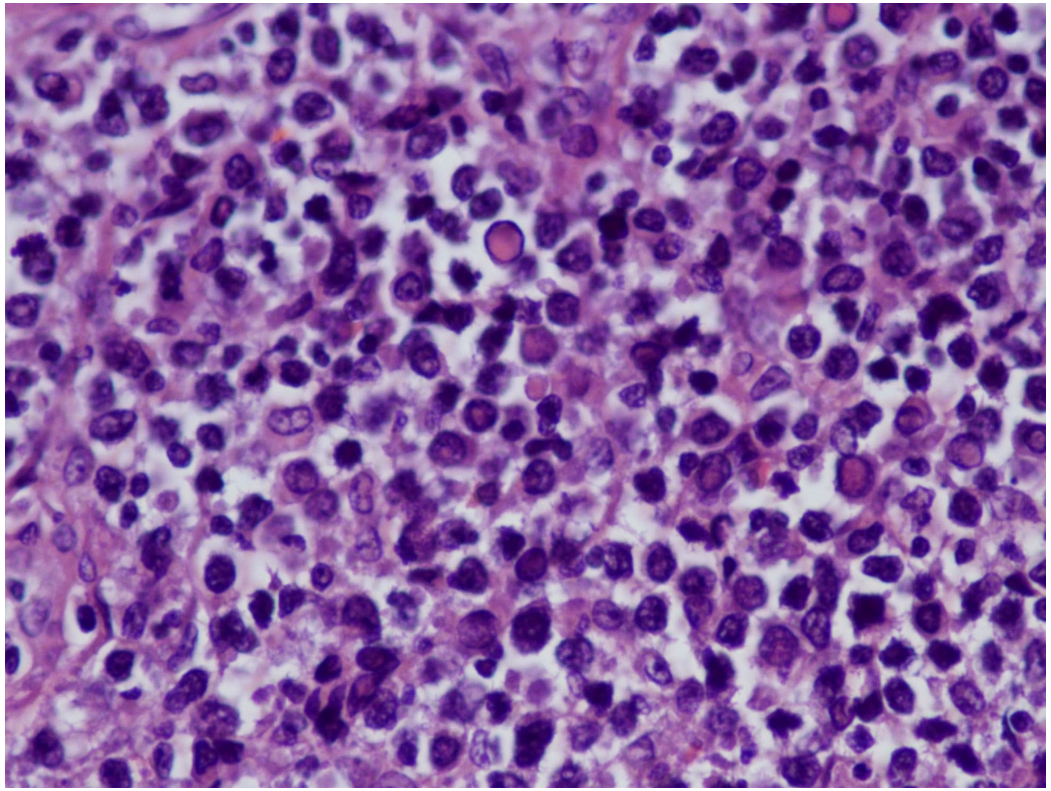




Lymph node: Histology







Conclusion

- Waldenström's macroglobulinemia
- Symptomatic, in need of treatment for anemia and splenomegaly

Should all patients undergo mutation analysis of *MYD88* and *CXCR4* as part of the WM diagnostic work-up?

Moderator: Roger Owen

For: Alessandra Tedeschi | *Against:* Christian Buske

CXCR4, C-X-C chemokine receptor type 4 gene; *MYD88*, myeloid differentiation primary response 88 gene; WM, Waldenström's macroglobulinemia.

Should all patients undergo mutation analysis of *MYD88* and *CXCR4* as part of the WM diagnostic work-up?

A Yes

B No

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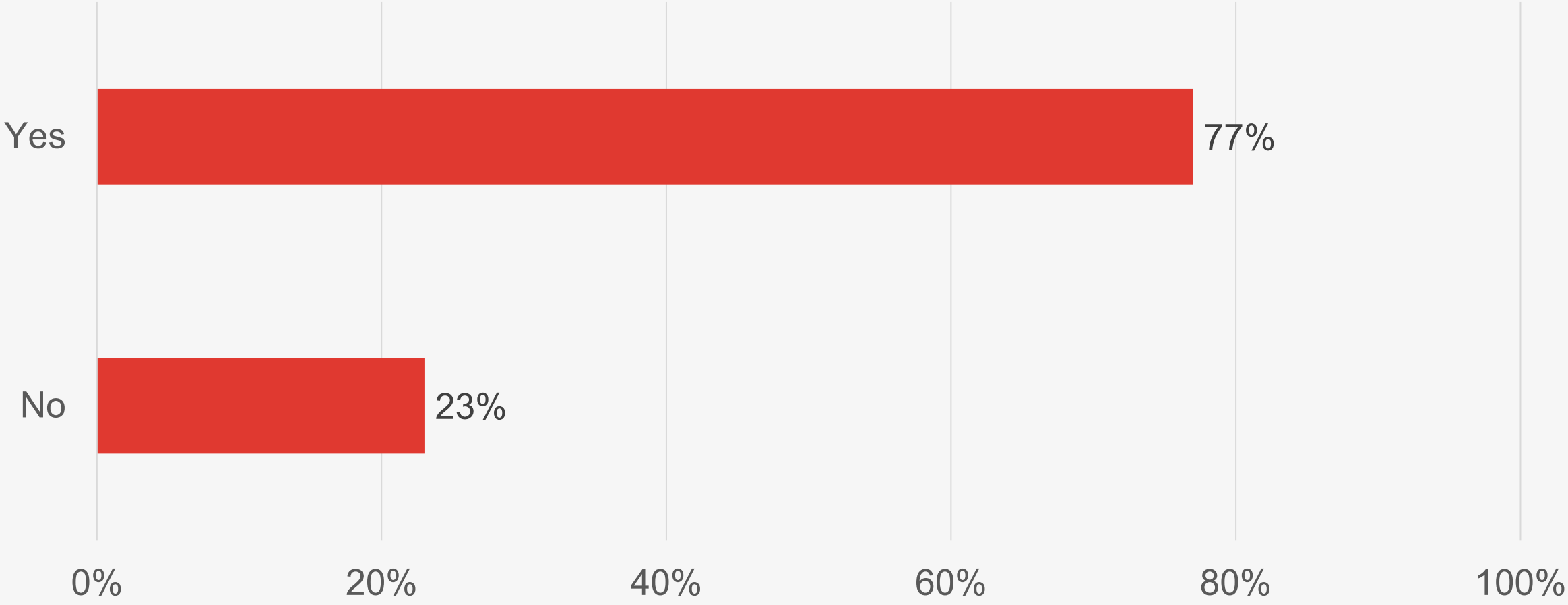
Should all patients undergo mutation analysis of *MYD88* and *CXCR4* as part of the WM diagnostic work-up?



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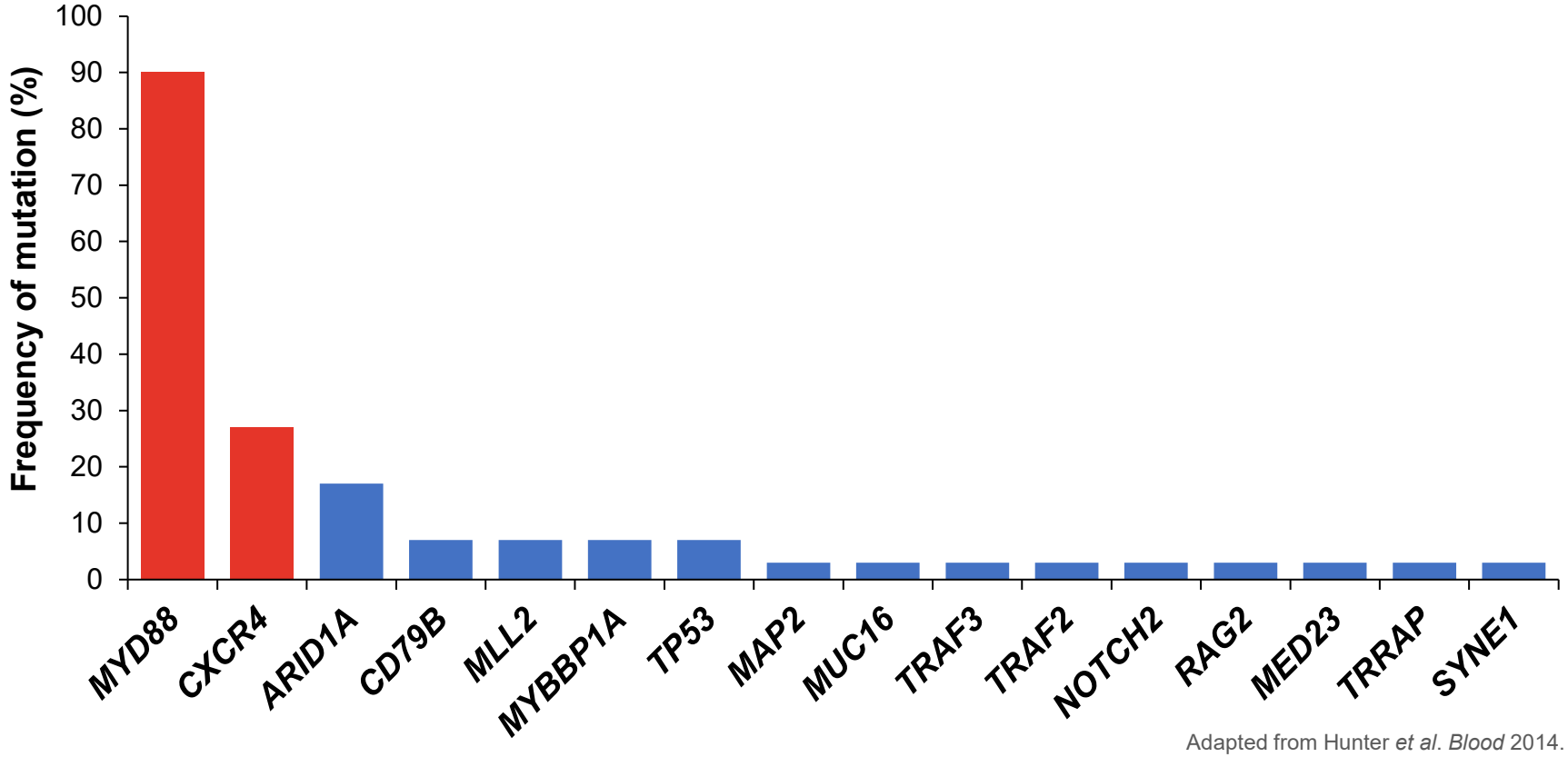
Should all patients undergo mutation analysis of *MYD88* and *CXCR4* as part of the WM diagnostic work-up?

For: Dr. Alessandra Tedeschi

Mutations occur in a very high proportion of patients with WM

- *MYD88* and *CXCR4* variants are the most frequent somatic mutations identified in WM

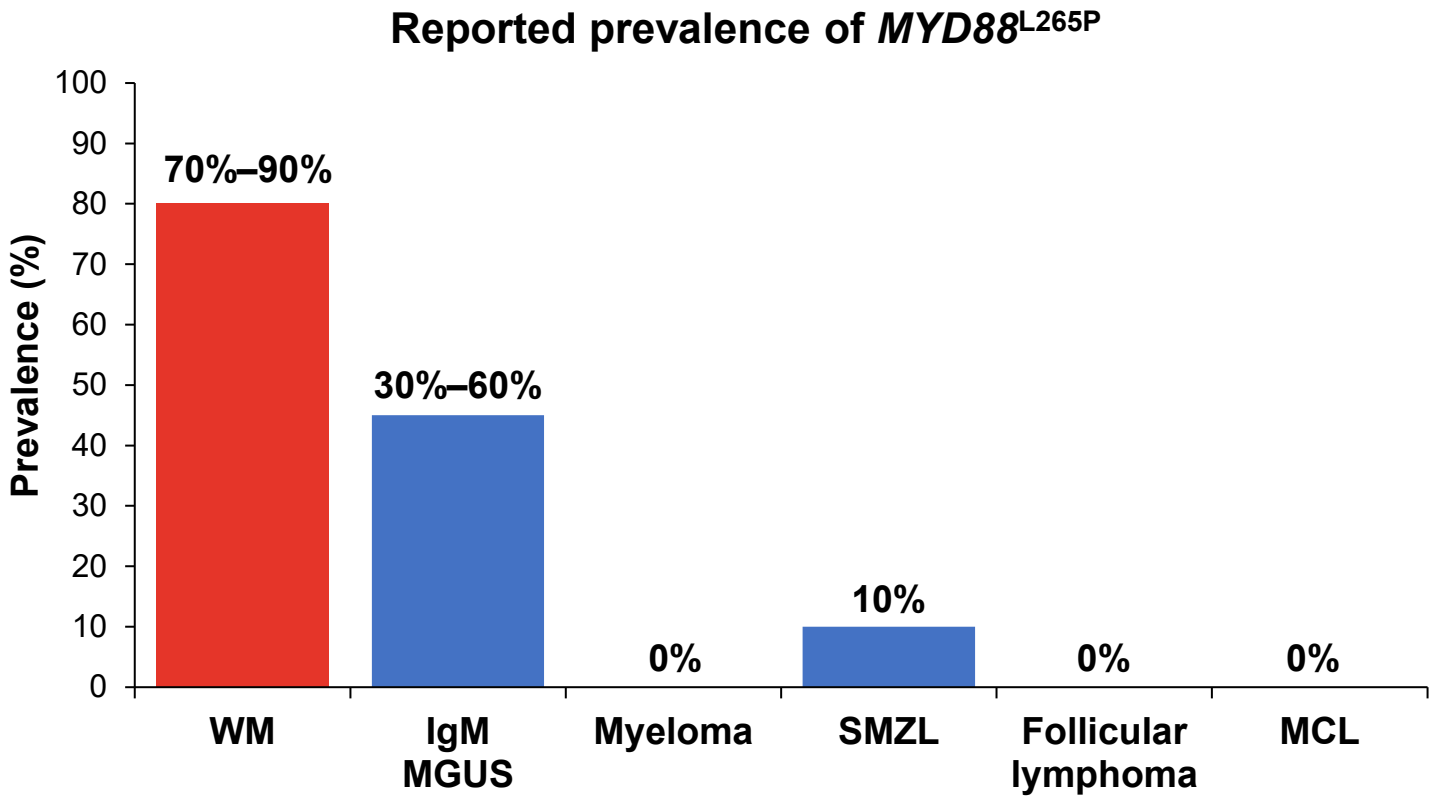


Adapted from Hunter *et al*. *Blood* 2014.

CXCR4, C-X-C chemokine receptor type 4 gene; *MYD88*, myeloid differentiation primary response 88 gene; WM, Waldenström's macroglobulinemia.
Hunter ZR *et al*. *Blood* 2014; 123 (11): 1637–1646.

MYD88^{L265P} may support a WM diagnosis

- *MYD88*^{L265P} is much more frequent in WM than in other B-cell malignancies that may share a similar phenotype



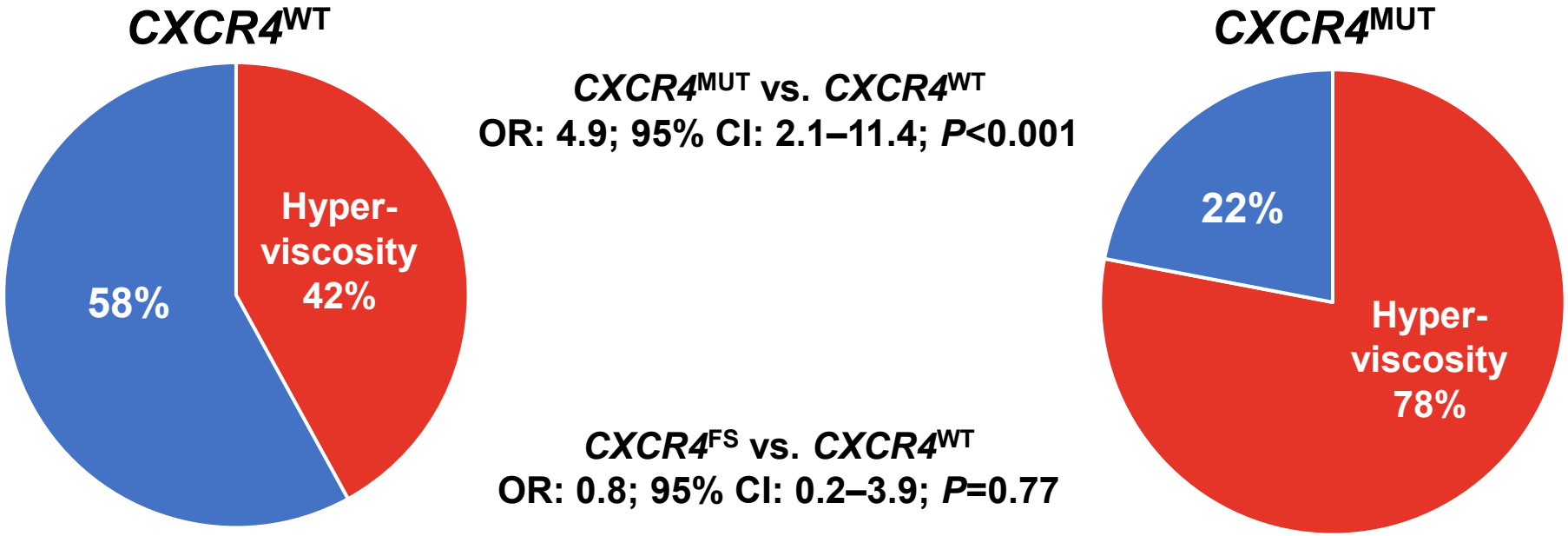
Adapted from Dimopoulos *et al*. *Blood* 2019.

IgM, immunoglobulin M; MCL, mantle cell lymphoma; MGUS, monoclonal gammopathy of undetermined significance; *MYD88*, myeloid differentiation primary response 88 gene; SMZL, splenic marginal zone lymphoma; WM, Waldenström's macroglobulinemia.

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

Clinical impact of *CXCR4*^{MUT}

- Higher BM disease burden
- Higher serum IgM level
- Lower rates of extramedullary disease
- Symptomatic disease at presentation



BM, bone marrow; CI, confidence interval; *CXCR4*, C-X-C chemokine receptor type 4 gene; FS, frameshift; IgM, immunoglobulin M; MUT, mutation; OR, odds ratio of presenting with hyperviscosity; WT, wild-type.

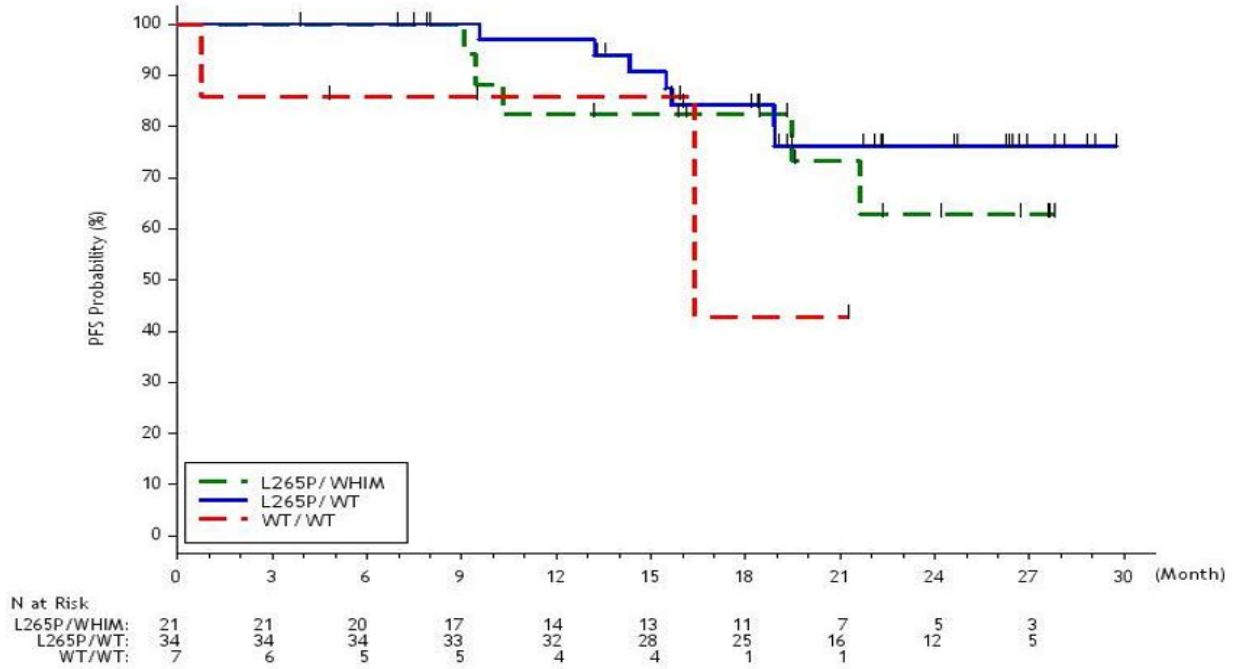
Treon SP *et al. Blood* 2014;123: 2791–2796. Gustine *et al*. *Br J Haematol* 2017; 177: 717–725.

MYD88 and *CXCR4* status are relevant to treatment outcomes with ibrutinib monotherapy

Response to ibrutinib monotherapy in R/R (median: 19.1 months of treatment)[1]

	MYD88^{L265P} *CXCR4*^{WT}	*MYD88*^{L265P} *CXCR4*^{WHIM}	*MYD88*^{WT} *CXCR4*^{WT}	*P*-value
N	**34**	**21**	**7**	
Overall RR	**100%**	**85.7%**	**71.4%**	**<0.01**
Major RR	**91.2%**	**61.9%**	**28.6%**	**<0.01**

Progression-free survival

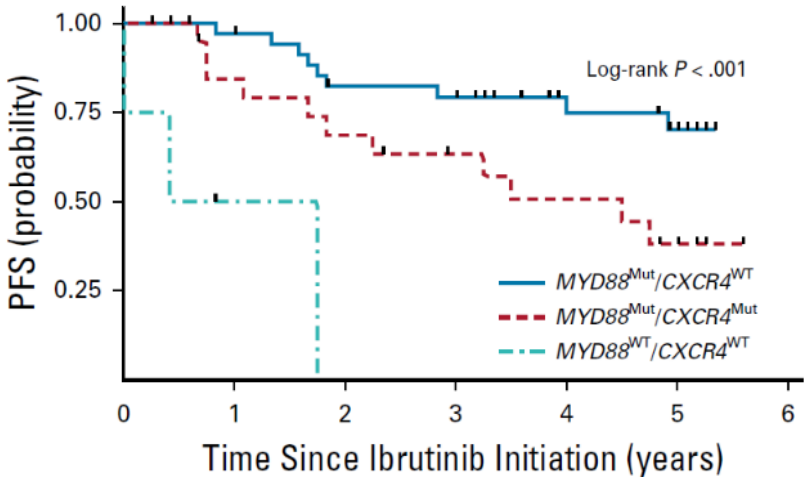


CXCR4, C-X-C chemokine receptor type 4 gene; *MYD88*, myeloid differentiation primary response 88 gene; PFS, progression-free survival; RR, response rate; R/R, relapsed/refractory; WHIM, warts, hypogammaglobulinemia, infection, and myelokathexis; WT, wild-type.

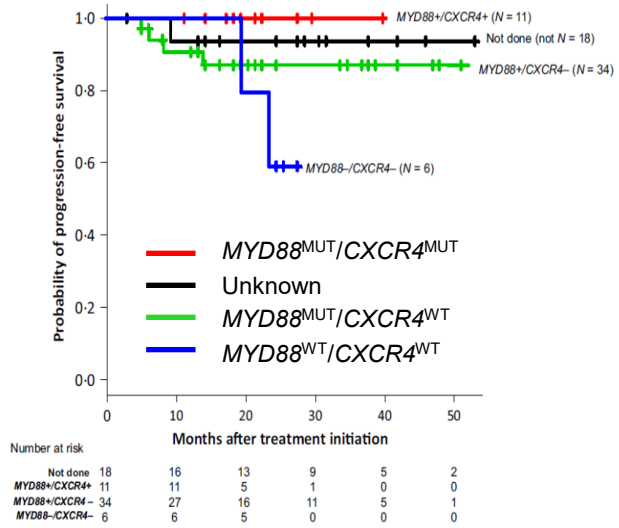
1. Treon SP *et al. N Engl J Med* 2015; 372 (15): 1430–1440.

Survival outcomes according to *CXCR4* mutational status

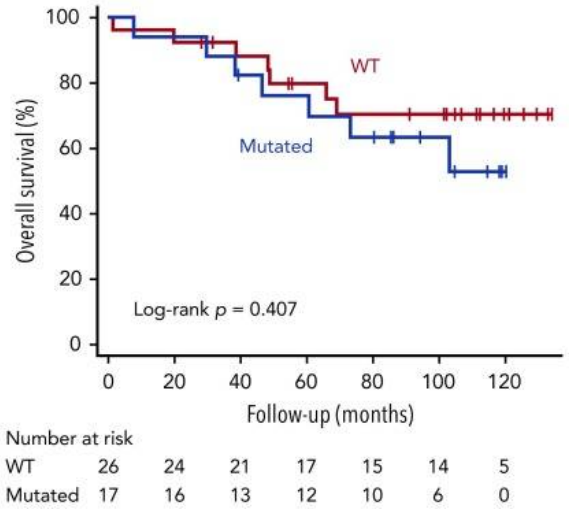
Ibrutinib monotherapy R/R PFS
Long-term follow-up (median: 59 months)[1]



Bendamustine-rituximab
first line PFS[2]



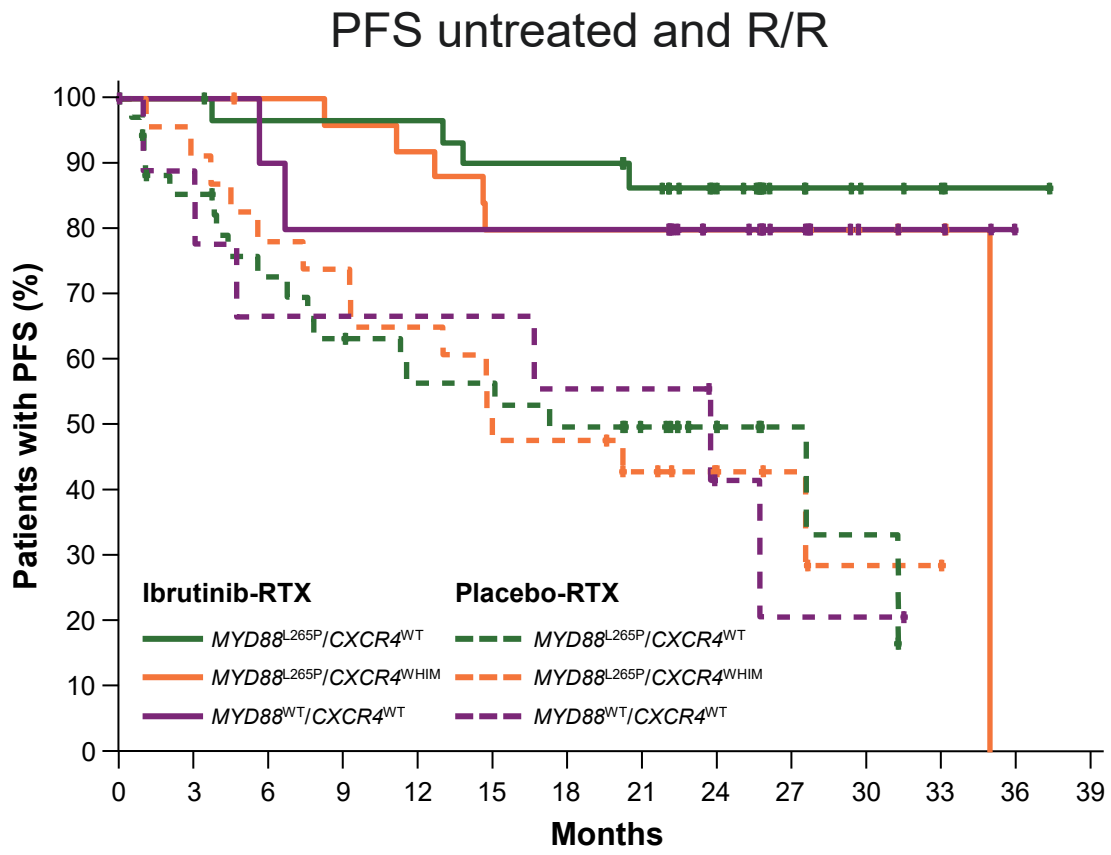
OS with bortezomib-based
treatment[3]



CXCR4, C-X-C chemokine receptor type 4 gene; MUT, mutation; *MYD88*, myeloid differentiation primary response 88 gene; OS, overall survival; PFS, progression-free survival; R/R, relapsed/refractory; WT, wild-type.

1. Treon SP *et al. J Clin Oncol* 2020; Epub ahead of print (DOI: 10.1200/JCO.20.00555). 2. Laribi K *et al. Br J Haematol* 2019; 186 (1): 146–149.
3. Sklavenitis-Pistofidis R *et al. Blood* 2018; 132 (24): 2608–2612.

Phase 3 trial of ibrutinib plus rituximab



CXCR4, C-X-C chemokine receptor type 4 gene; *MYD88*, myeloid differentiation primary response 88 gene; PFS, progression-free survival; R/R, relapsed/refractory; RTX, randomized treatment; WHIM, warts, hypogammaglobulinemia, infection, and myelokathexis; WT, wild-type.
Dimopoulos MA *et al*. *N Engl J Med* 2018; 378 (25): 2399–2410.

ASPEN: A global Phase 3 study of zanubrutinib* vs. ibrutinib in WM Cohort 2 *MYD88*^{WT}

***MYD88*^{WT} patients with WM**
(N=26)

→

Arm C
Zanubrutinib
160 mg BID
until progression

Characteristic	Total (N=26)
Median age, years (range)	72
Treatment naive, n (%)	5 (19.2)
R/R, n (%)	21 (80.8)
Median no. of prior Tx, (range)	1 (1–5)
MYD88^{WT}/*CXCR4*^{WT}, n (%)	23 (88.5%)

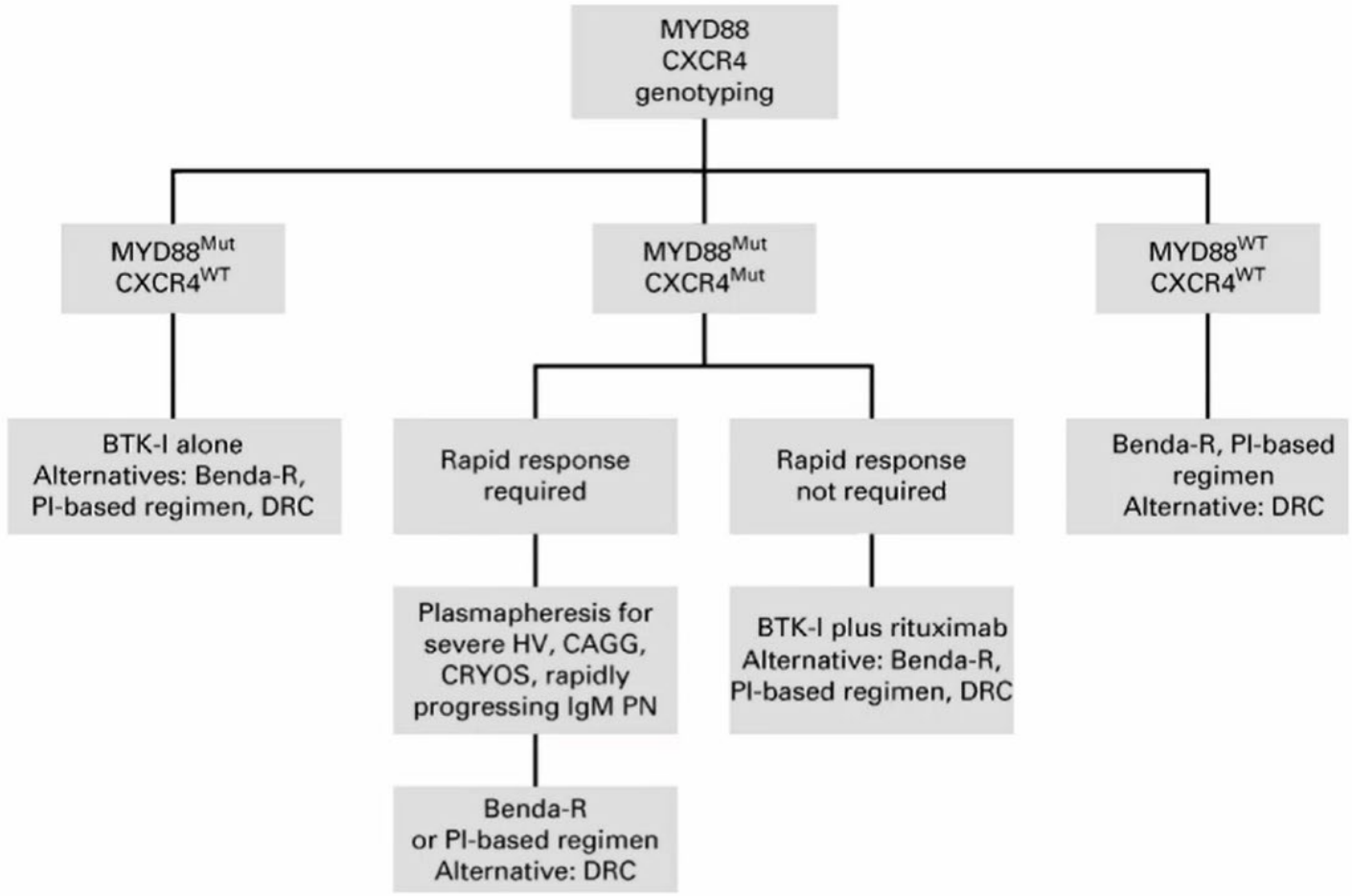
Best response, n (%)	Total (N=26)
Overall RR	21 (80.8)
Major RR (PR or better)	13 (50.0)
VGPR	7 (26.9)
PR	6 (23.1)
Minor response	8 (30.8)
Stable disease / progressive disease	4 (15.4) / 1 (3.8)
Time to first major response (≥PR), median (range), months	2.9 (1.9–16.1)
Study follow-up time, median (range) months	17.9 (2.3–27.8)

*Zanubrutinib is not approved for the treatment of patients with Waldenström's macroglobulinemia. Zanubrutinib is approved by the FDA for use in the US for the treatment of adult patients with mantle cell lymphoma who have received at least one prior therapy and is marketed in the US under the brand name BRUKINSA™. This indication is approved under accelerated approval based on overall response rate. Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial.

BID, twice daily; *CXCR4*, C-X-C chemokine receptor type 4 gene; *MYD88*, myeloid differentiation primary response 88 gene; PR, partial response; RR, response rate; R/R, relapsed/refractory; VGPR, very good partial response; Tx, treatment; WM, Waldenström's macroglobulinemia; WT, wild-type.

Dimopoulos M *et al. EHA Library* 2020; Abstract EP1180, available at library.ehaweb.org/eha/2020/eha25th/293669. Eposter available at beigenemedical.eu/publications

MYD88 and *CXCR4* status can guide treatment decisions



Benda-R, bendamustine and rituximab; BTK-I, Bruton tyrosine kinase inhibitor; CAGG, cold agglutinemia; CRYOS, cryoglobulinemia; *CXCR4*, C-X-C chemokine receptor type 4 gene; DRC, dexamethasone, rituximab, and cyclophosphamide; HV, hyperviscosity; IgM, immunoglobulin M, Mut, mutation; *MYD88*, myeloid differentiation primary response 88 gene; PI, proteasome inhibitor; PN, peripheral neuropathy; WT, wild-type.

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

Summary

All patients **should** undergo mutation analysis of *MYD88* and *CXCR4*

The mutations are biologically relevant

- Affect patient presentation
- Can influence patient responses to treatment
- Can guide treatment decisions

WHEN YOU KNOW BETTER YOU DO BETTER !!!

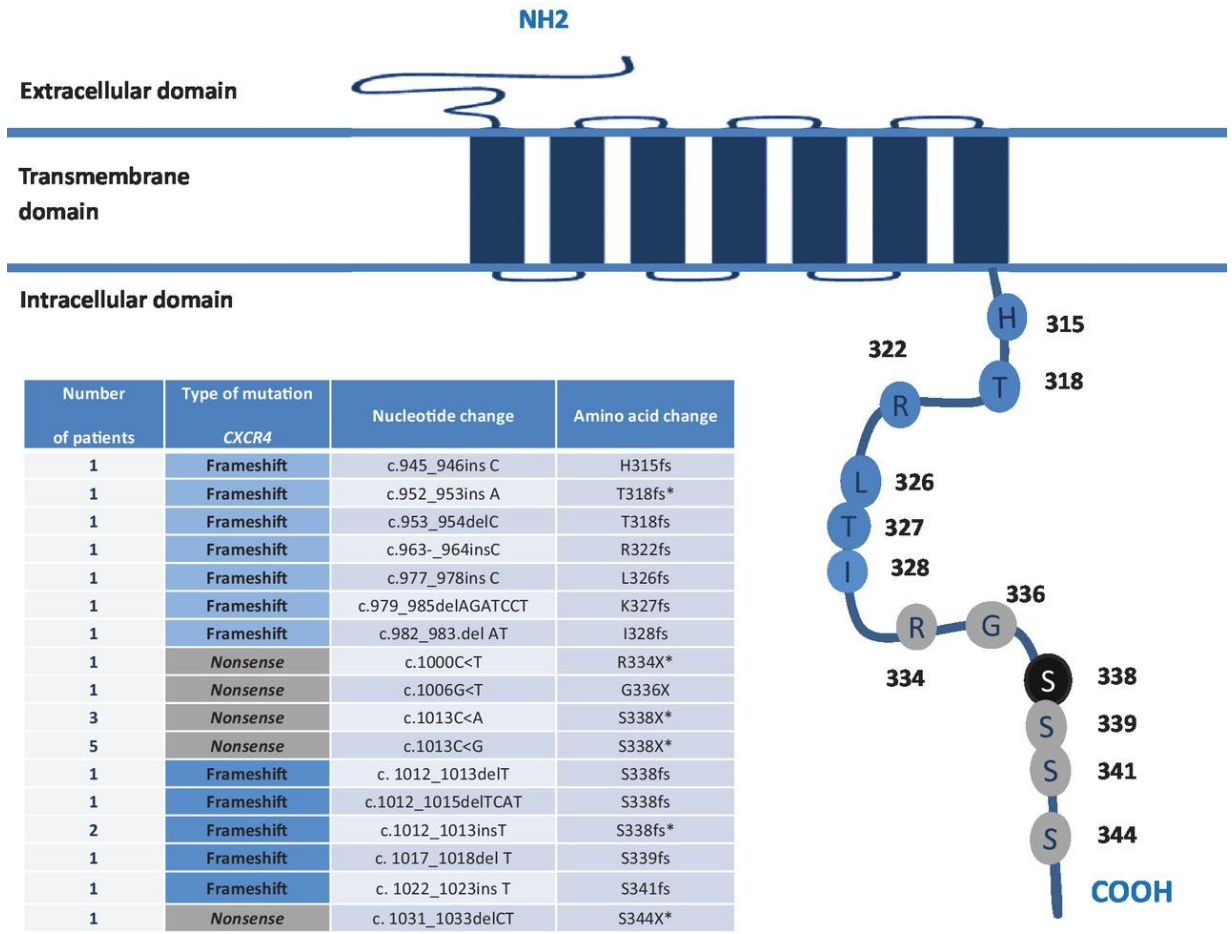
CXCR4, C-X-C chemokine receptor type 4 gene; *MYD88*, myeloid differentiation primary response 88 gene.

Should all patients undergo mutation analysis of *MYD88* and *CXCR4* as part of the WM diagnostic work-up?

Against: Professor Christian Buske

The *CXCR4* mutational landscape is complex

- In a cohort of 98 patients with WM, 17 *CXCR4* mutations were identified, of which 12 were novel
- A clinician might see a new *CXCR4* mutation with every diagnosis

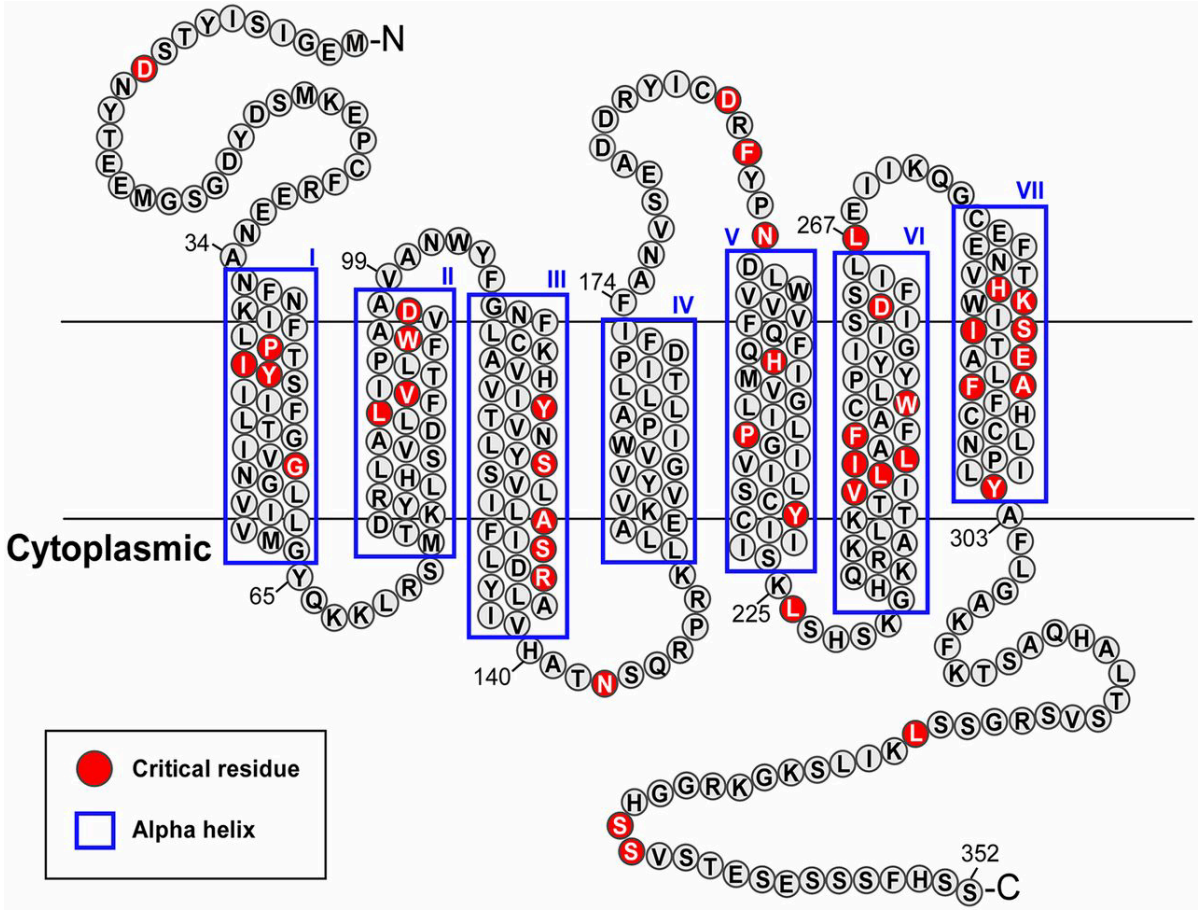


Number of patients	Type of mutation *CXCR4*	Nucleotide change	Amino acid change
1	Frameshift	c.945_946ins C	H315fs
1	Frameshift	c.952_953ins A	T318fs*
1	Frameshift	c.953_954delC	T318fs
1	Frameshift	c.963-_964insC	R322fs
1	Frameshift	c.977_978ins C	L326fs
1	Frameshift	c.979_985delAGATCCT	K327fs
1	Frameshift	c.982_983.del AT	I328fs
1	*Nonsense*	c.1000C<T	R334X*
1	*Nonsense*	c.1006G<T	G336X
3	*Nonsense*	c.1013C<A	S338X*
5	*Nonsense*	c.1013C<G	S338X*
1	Frameshift	c. 1012_1013delT	S338fs
1	Frameshift	c.1012_1015delTCAT	S338fs
2	Frameshift	c.1012_1013insT	S338fs*
1	Frameshift	c. 1017_1018del T	S339fs
1	Frameshift	c. 1022_1023ins T	S341fs
1	*Nonsense*	c. 1031_1033delCT	S344X*

CXCR4, C-X-C chemokine receptor type 4 gene; WM, Waldenström's macroglobulinemia.
Poulain S *et al. Clin Cancer Res* 2016; 22 (6): 1480–1488.

CXCR4 mutations are difficult to interpret

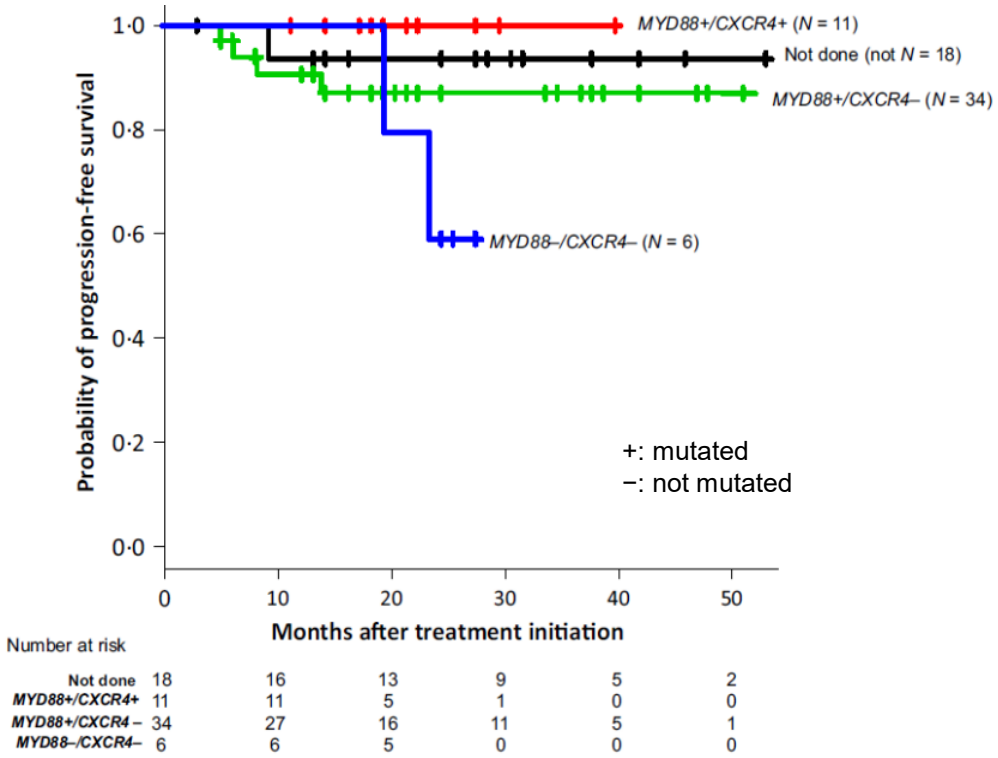
- The biological implications of many *CXCR4* mutations are unknown



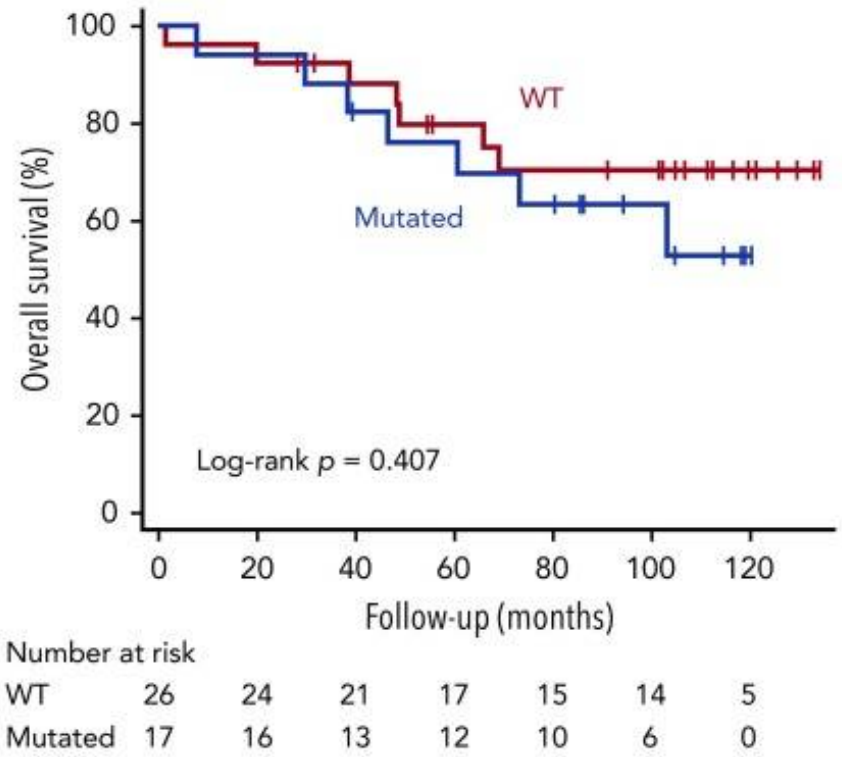
CXCR4, C-X-C chemokine receptor type 4 gene.
Wescott MP *et al. Proc Natl Acad Sci U S A* 2016; 113 (35): 9928–9933.

CXCR4 status has no impact on patient outcomes with some therapies

CXCR4 mutational status does not influence PFS with first-line R-bendamustine[1]



CXCR4 mutations have no effect on OS under bortezomib-based treatment[2]



CXCR4, C-X-C chemokine receptor type 4 gene; MYD88, myeloid differentiation primary response 88 gene; OS, overall survival; PFS, progression-free survival; R, rituximab; WT, wild-type.

1. Laribi K *et al. Br J Haematol* 2019; 186 (1): 146–149. 2. Sklavenitis-Pistofidis R *et al. Blood* 2018; 132 (24): 2608–2612.

Mutational testing can be technically challenging

- The optimal initial assay for *MYD88* is AS-PCR on bone marrow aspirates
  - Sanger sequencing or targeted NGS can be used to evaluate for non-L265P *MYD88* mutations
- Selection of CD19+ cells can improve detection rates but is not routinely performed
- Mutated *CXCR4* is subclonal, with highly variable clonality averaging approximately 35%
  - False negative results can occur
  - Ultra-deep NGS or Sanger sequencing may be required

AS-PCR, allele-specific polymerase chain reaction; CXCR4, C-X-C chemokine receptor type 4 gene; MYD88, myeloid differentiation primary response 88 gene; NGS, next-generation sequencing.

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

Standardization of testing and analysis must come first

- Standard protocols are needed to support clinicians and institutions testing for *MYD88* and *CXCR4* mutations, to avoid mistakes and promote continuity

CXCR4, C-X-C chemokine receptor type 4 gene; MYD88, myeloid differentiation primary response 88 gene

Summary

All patients should not undergo mutation analysis of *MYD88* and *CXCR4* as part of the WM diagnostic work-up:

- *MYD88*^{L265P} may support a WM diagnosis and should be evaluated
- The argument for *CXCR4* analysis is less strong
  - Mutations are highly variable, and their biological implications are unclear at present
  - Effects on treatment outcomes are not consistent across different therapies
  - *CXCR4* mutation analysis can be technically challenging
- Clinicians must be supported with standard protocols for mutation testing for both *MYD88* and *CXCR4*

CXCR4, C-X-C chemokine receptor type 4 gene; MYD88, myeloid differentiation primary response 88 gene; WM, Waldenström's macroglobulinemia.

Should all patients undergo mutation analysis of *MYD88* and *CXCR4* as part of the WM diagnostic work-up?

Moderator: Roger Owen

For: Alessandra Tedeschi | *Against:* Christian Buske

CXCR4, C-X-C chemokine receptor type 4 gene; *MYD88*, myeloid differentiation primary response 88 gene; WM, Waldenström's macroglobulinemia.

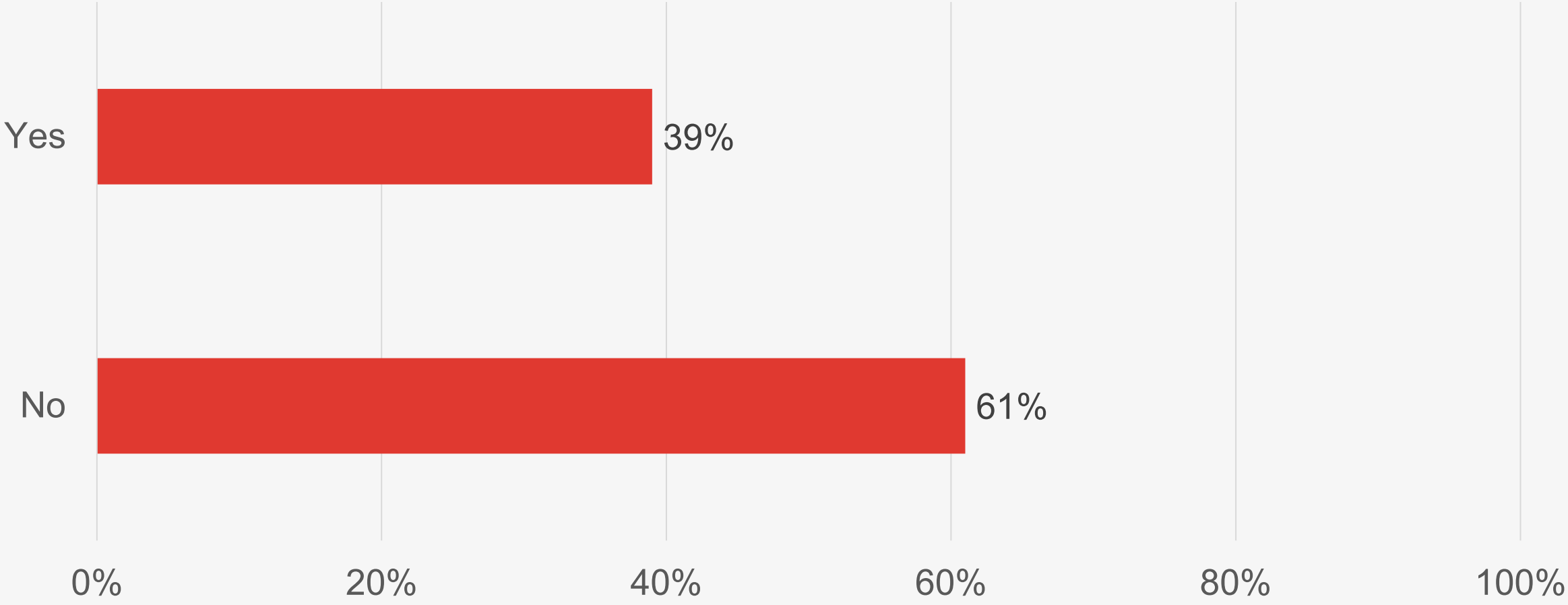
Should all patients undergo mutation analysis of *MYD88* and *CXCR4* as part of the WM diagnostic work-up?

A Yes

B No

BeiGeneius

Should all patients undergo mutation analysis of *MYD88* and *CXCR4* as part of the WM diagnostic work-up?



BeiGeneius

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

Moderator: Christian Buske
Panel: All

WM, Waldenström's macroglobulinemia.

Summary

Chair: Christian Buske

Summary

WM is a B-cell disorder characterized by variable presentation due to involvement of both lymphoid and plasmacytic cell compartments. Histomorphology, immunophenotyping, and *MYD88*^{L256P} mutation analysis can enable a definitive diagnosis.[1]

Monoclonal gammopathies are relatively common in older people; MGUS affects up to 3% of individuals aged >50 years.[2] Careful investigation and regular follow-up is required to manage the risk of malignant progression, including progression to WM.

MYD88 mutation analysis may support diagnostic differentiation and should form part of the WM clinical work-up for all patients; the implications of *CXCR4* testing need further assessment.[1]

CXCR4, C-X-C chemokine receptor type 4 gene; MGUS, monoclonal gammopathy of undetermined significance; *MYD88*, myeloid differentiation primary response 88 gene; WM, Waldenström's macroglobulinemia.

1. Kastritis E *et al*. *Ann Oncol* 2018; 29 (Suppl 4): iv41–iv50. 2. Kyle RA *et al*. *N Engl J Med* 2006; 354 (13): 1362–1369.

Save the date!

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

Join us in **January 2021** for the second installment in the BeiGeneius webinar series in which we will explore the practical aspects of initiating WM treatment and managing associated complications

BeiGeneius

WM, Waldenström's macroglobulinemia.

We would appreciate your feedback!

Please complete the post-meeting survey.

BeiGeneius

Thank you for your attention