Waldenström's Macroglobulinemia

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Waldenström's Macroglobulinemia

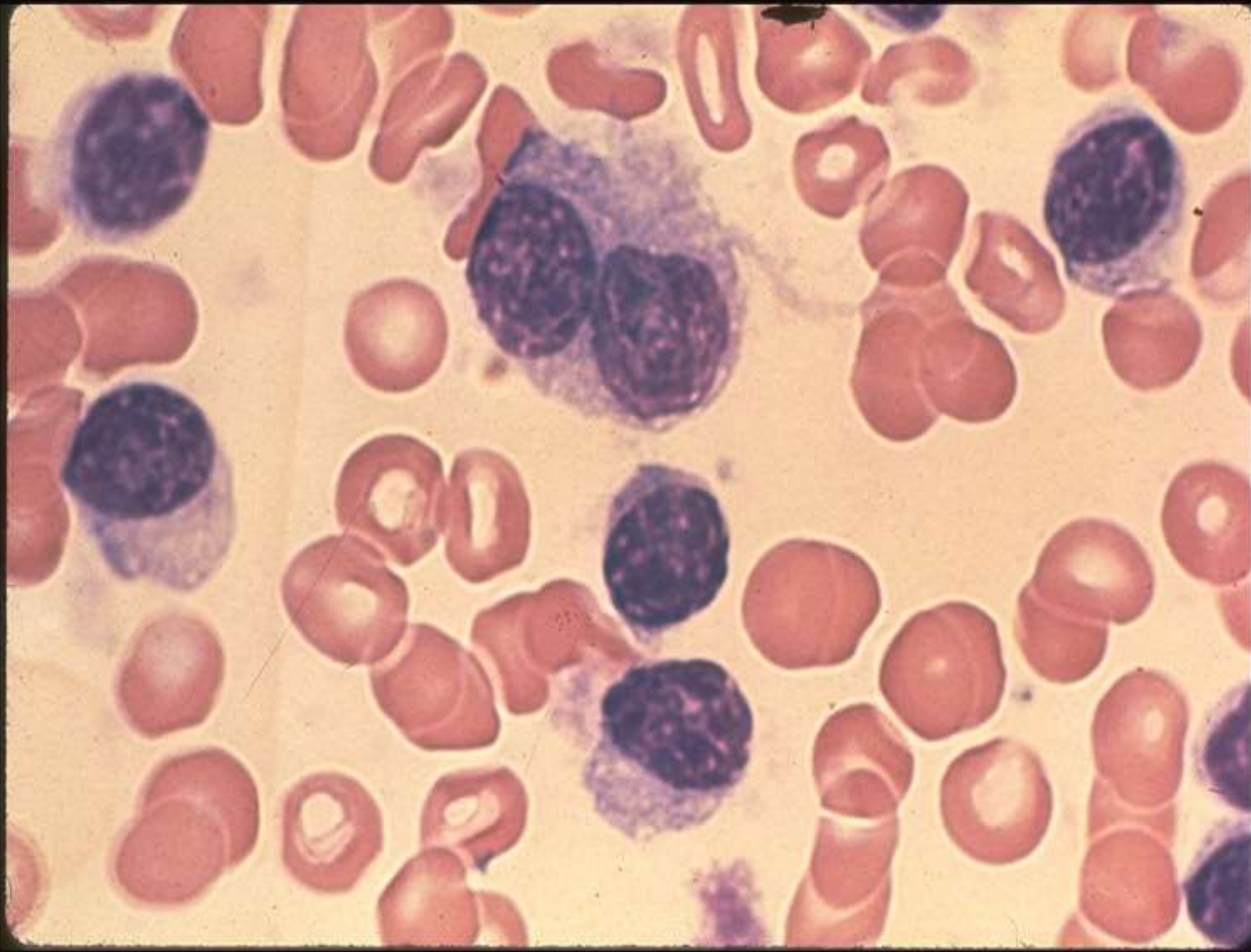
Low frequency
- 6% of all M-gammopathies:
- 2-5 cases/mill. inh/yr (GEM, 3'1) 2500 cases/yr in Europe

Advanced age
- Median: 71. Male/Female: 2:1

Natural history
- Indolent disease, Median survival: 11 years
- 1/3 die for other causes; 2/3 die of WM

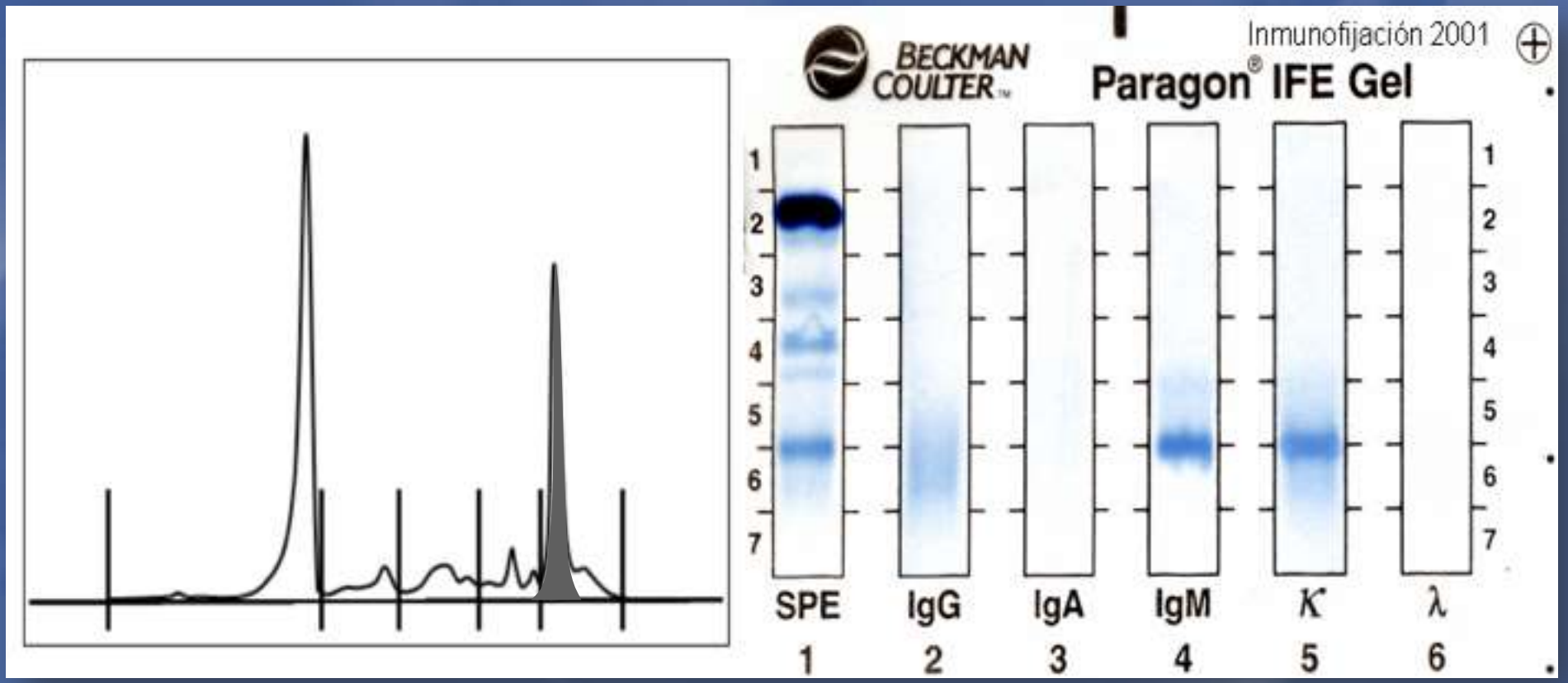
Therapeutic efficacy

Biological interest



Protein Electrophoresis

Immunofixation



Definition

Waldenström's Macroglobulinemia is an uncommon lymphoproliferative disorder characterized primarily by bone marrow infiltration and IgM monoclonal gammopathy.

The underlying pathological diagnosis in WM is lymphoplasmacytic lymphoma as defined by the World Health Organization (WHO) and Revised European-American Lymphoma (REAL) classification criteria.

Owen et al, Sem Hematol 2003, 30:110-115
WHO Classification of Tumors of hematopoietic and Lymphoid Tissues, 2008

Classification of WM and related disorders

	IgM monoclonal protein[1]	Bone Marrow infiltration[2]	Symptoms Attributable to IgM	Symtoms due to tumor infiltration[3]
Symptomatic WM	+	+	+ (4)	+ (4)
Asymptomatic WM	+	+	–	–
IgM-related disorders[5]	+	–	+	–
IgM MGUS	+	–	–	–

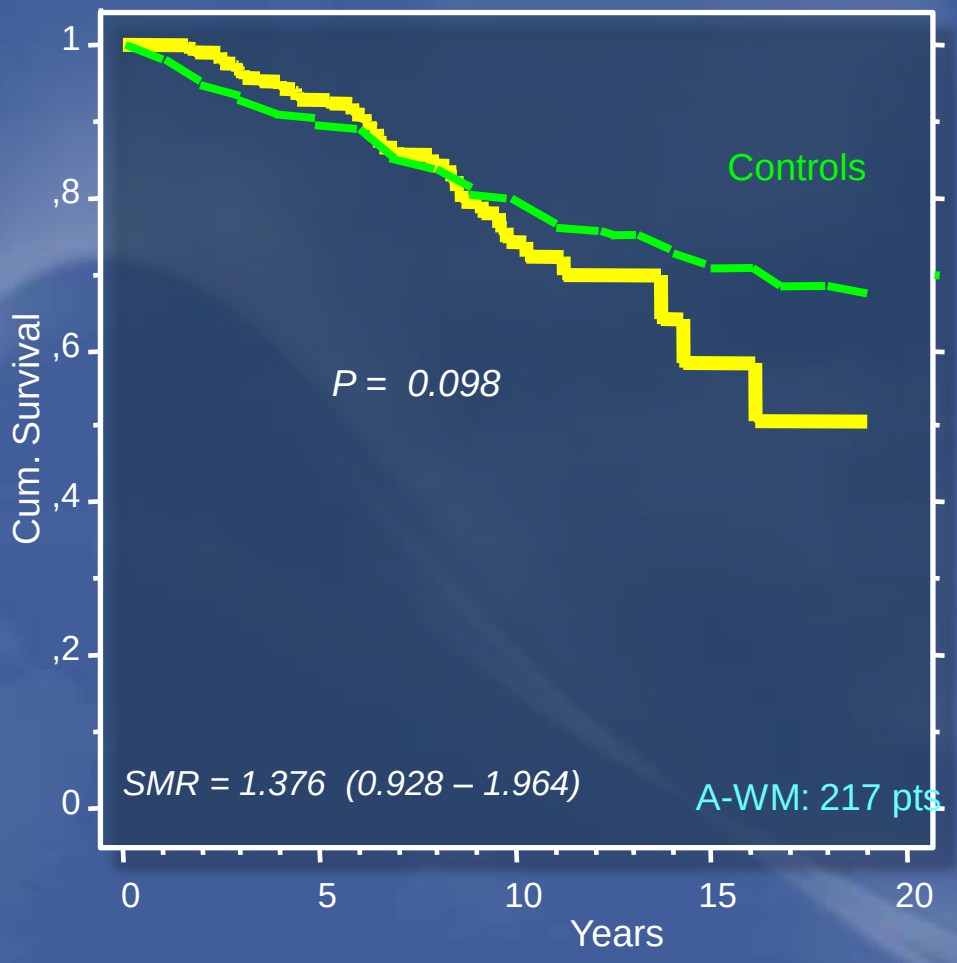
1) The panel considered to be inappropriate to define an IgM concentration to distinguish MGUS from WM. However, it should be noted that IgM concentration rarely if ever exceeds 3 g/dL in MGUS; 2) Patients with unequivocal BM infiltration by lymphoplasmocytic lymphoma will be considered to have WM, while patients without evidence of infiltration will be considered to have MGUS. However, it is acknowledged that in some patients equivocal evidence of BM infiltration is demonstrable. This may be manifest in a number of ways and includes the detection of clonal B-cells by flow cytometry or PCR in the absence of morphological evidence of BM infiltration. Alternatively, patients may have equivocal bone marrow infiltrates without confirmatory phenotypic studies. It is considered that these patients should be classified as MGUS until further data become available. 3) Symptoms attributable to tumor infiltration will include any of the following manifestations: constitutional symptoms, cytopenia(s), or organomegaly. 4)It is required the presence of one or both groups of symptoms. (5) It is well recognized that a population of patients exist who have symptoms attributable to the IgM monoclonal protein but no overt evidence of lymphoma. Such patients may present with symptomatic crioglobulinemia, amyloidosis, or autoimmune phenomena such as peripheral and coll agglutinin disease. It is appropriate to consider these patients as a clinically distinct group and the term "IgM-relates disorders is proposed".

Owen et al, Sem Hematol 2003, 30:110-115

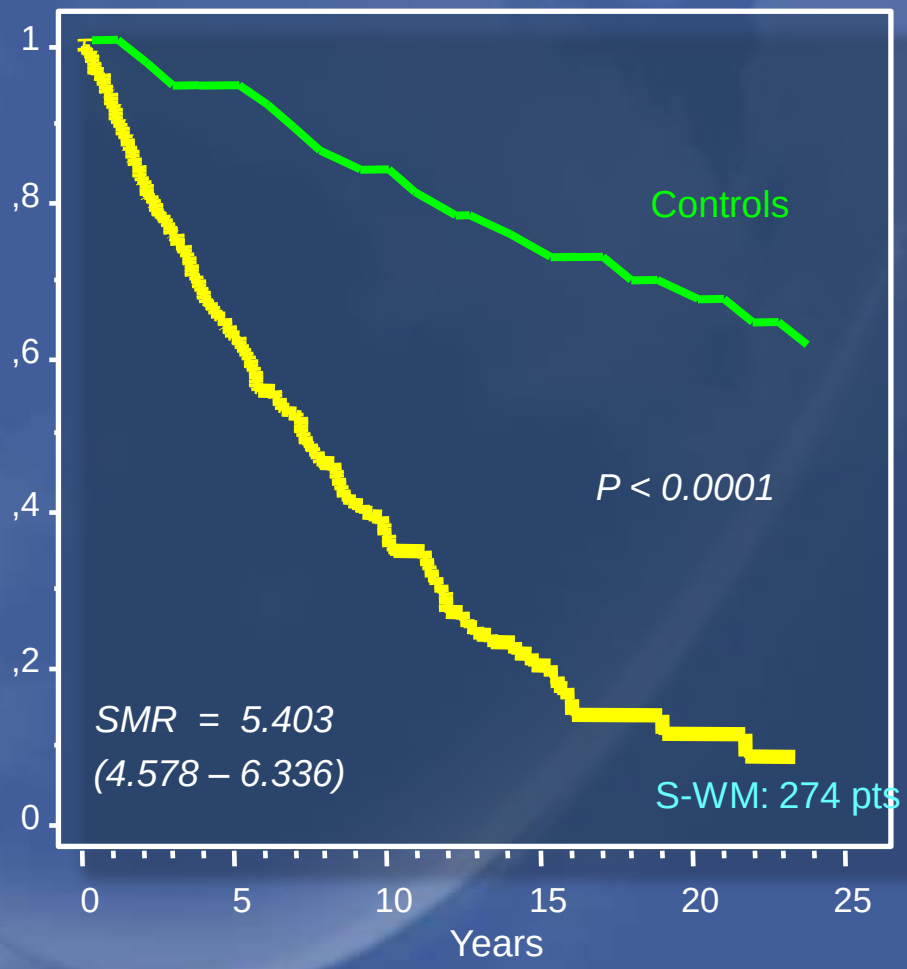
BONE BIOPSY IS MANDATORY

Overall survival

Asymptomatic WM



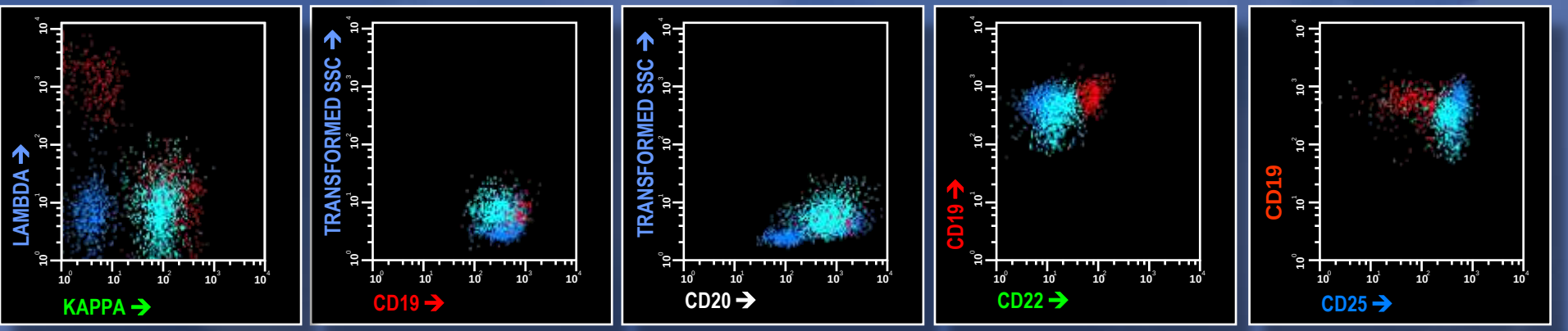
Symptomatic WM

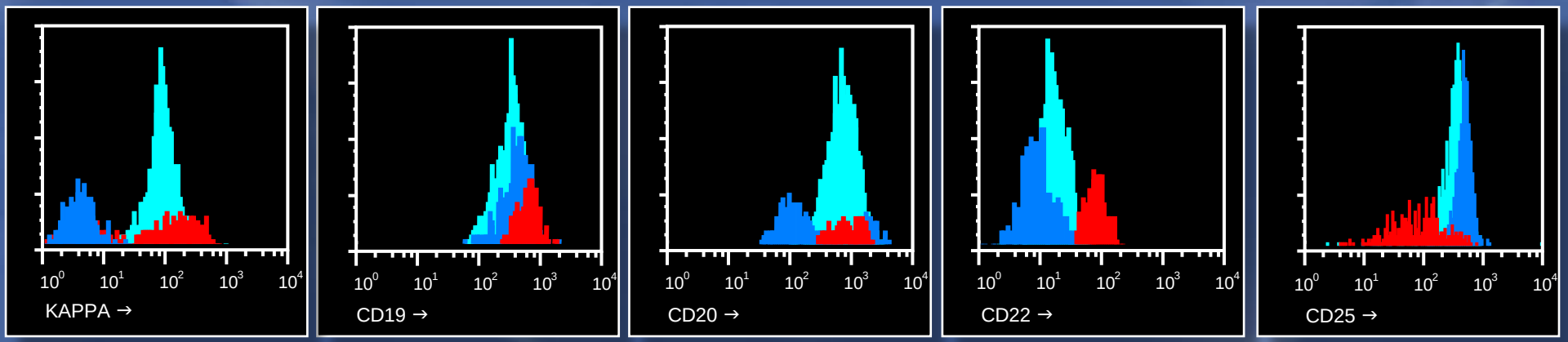


Morel et al, IMWG 2009

Pan B Markers

sIg$^{+/homog.}$ CD19$^{+/homog.}$ CD20$^{++/homog.}$ CD22$^{+lo/homog.}$ CD25 $^{(+)}$

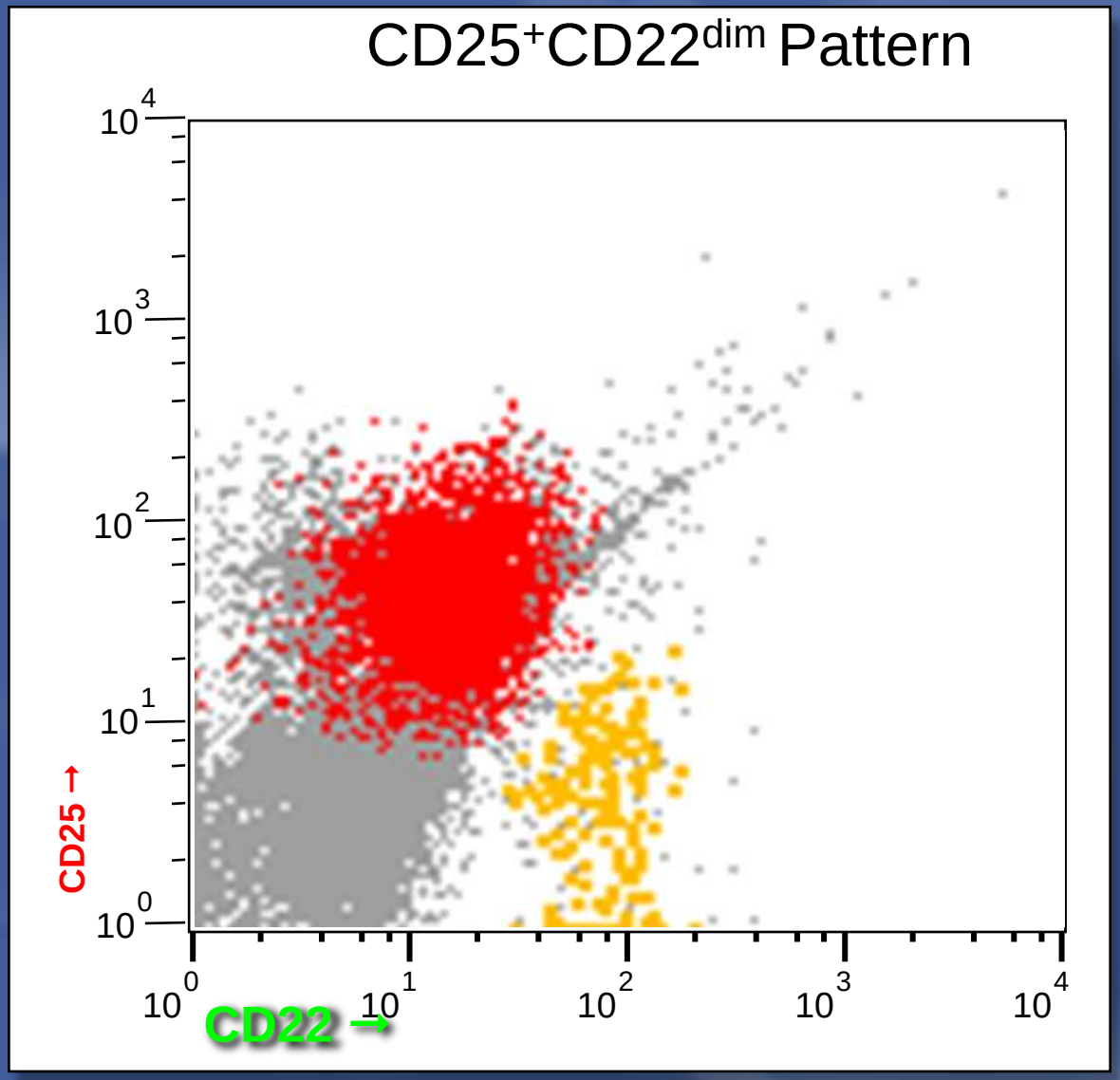




sIg κ:sIg λ ratio= 5:1

B-WM lymph B-precursors B-normal lymph.

Antigenic combinations useful for differential diagnosis



WM Lymphoid cells

Normal Lymphoid cells

88% WM *versus* 21% SMZL

Cytogenetic Abnormalities in WM

	Schop 2002	Ocio 2006	Fonseca 2006	Chang 2004	Nguyen-Khac 2010 N=132
Deletion of 6q21	42%	33%	47%	-	22%
Deletion of 13q14	16%	3%	-	9%	13%
Deletion of 17p23*	15%	7%	-	9%	8%
IgH translocations	0%	13%	2%	14%	3%
Deletion of 11q22	-	-	-	-	8%
Trisomy 4	-	-	-	-	8%
Trisomy 12	-	-	-	-	3%
Complex Karyotype (25/79)	-	-	-	-	32%
Trisomy 18	-	-	-	-	11%

** Poor prognosis*

Results

Involved Gene	Frequency
Myeloid differentiation primary response (MYD88) gene (38182641 in chromosome 3p22.2): 265 leucine → proline (L265P)	26/30 (86.7%) 4/26 (15%) Homozygous, due to CNLOH
Transporter 2, ATP-binding cassette, sub-family B (TAP2) gene	7/30 (23%)
Chemokine (C-X-C motif) receptor 4 (CXCR4) gene	6/30 (20%)
Low density lipoprotein receptor-related protein 1B (LRP1B) gene	5/30 (17%)
Mesothelin (MSLN) gene	4/30 (13%)
AT rich interactive domain 1A (ARID1A)	3/30 (10%)
Histone cluster 1, H1e (HIST1H1E)	3/30 (10%)
Rap guanine nucleotide exchange factor 3 (RAPGEF3)	3/30 (10%)

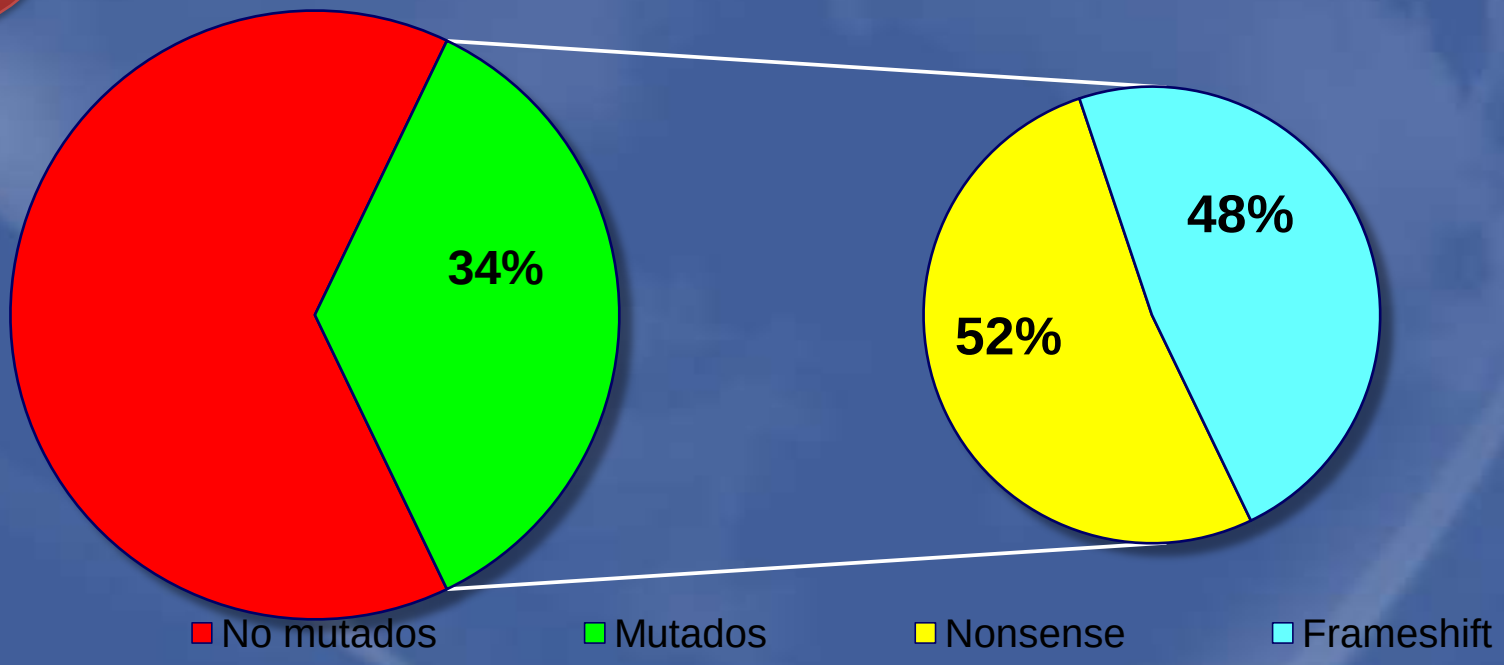
MYD88 L265P mutation in B-cell LPD

Entity	N	MYD88 L265P	
Waldenström's Macroglobulinemia	221	182	(82%)
IgM MGUS	53	37	(70%)
Diffuse Large Cell Lymphoma	10	77	(19%)
Marginal Zone Lymphomas	36	3	(8%)
B-CLL (18 with IgM M-component)	358	11	(3%)
Hairy cell Leukemia	53	0	(0%)
Lymphoplasmocytic lymphoma	11	0	(0%)
Multiple Myeloma (3 IgM)	67	0	(0%)
MGUS IgG/IgA	72	0	(0%)
Healthy volunters	38	0	(0%)
CXCR4 mutations (WM)	76	26	34%

Garcia Sanz, IWWM 2016

CXCR4 mutations

CD19+ cells from 76 WM pts



Jiménez et al, ASH 2015

Clinical Picture

Presentation

- *Fatigue (Progressive asthenia)*
  - *Anemia (38%)*
  - *Hyperviscosity (31%)*
- *Lymphadenopathy (25%)*
- *B Symptoms [fever, weight loss, sweet nights] (23%)*
- *Bleeding (23%)*
- *Neurological symptoms [PNP] (22%)*
- *Asymptomatic (27%)*

Clinical characteristics

- *Tumor growth (organ infiltration)*
- *Paraprotein effects*

García-Sanz, BJH 2001, 115:575-582

Sings and Symptoms: Tumor Growth

Bone Marrow Dysfunction:

Anemia

lymphocytosis

neutropenia

thrombocytopenia

Secondary Lymphoid organs:

adenopathy,

hepatic and spleen enlargement

Extranodal Infiltration:

Pleura & Lungs
Kidney
Skin
Gastrointestinal
Nervous system

García-Sanz, BJH 2001, 115:575-582

Sings and Symptoms: M-component

Hyperviscosity syndrome:

- ***Neurological***
- ***Cardiac***
- ***Hemorrhagic***

Cryoglobulinemia & Cryoaglutininemia

Interfering Antibody Activity:

- ***Neurological***
- ***Renal***
- ***Amyloidosis***
- ***Arthropaty***
- ***VWF disease***

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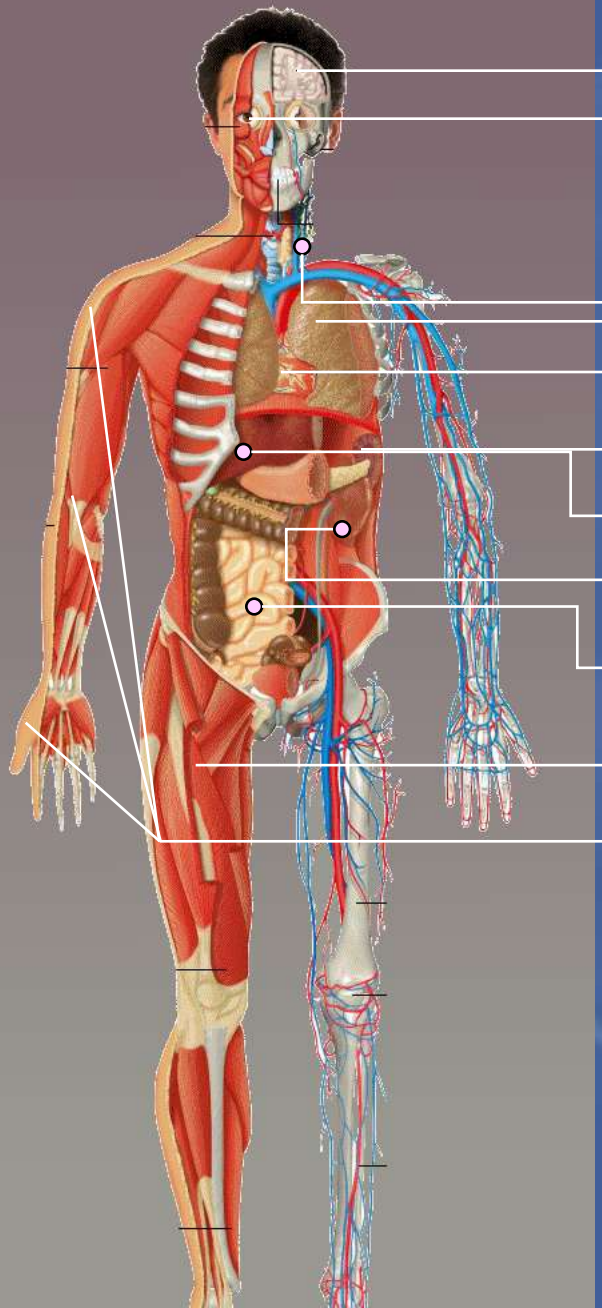


- HS: dizziness, stupor, drowsiness (31%)
- Oftalmologic alterations (34%)
- Lymphademnopathy (25%)
- Lung alterations, 4%
- Heart failure (rare)
- Splenomegaly (19%)
- Hepatomegaly(24%)
- Renal dysfunction (4%)
- Gastro-intestinal problems (3%)
- Peripheral neuropathy (25%)
- Skin (3%)

Anemia	38%	Antiglobuline test+	10%
Lymphocytosis	9%	Hemolysis	3%
Neutropenia	4%	Cold agglutinines	3%
Trombopenia	2%	LDH increase	11%
Coagulation disorders	2%	ß2M increase	54%

Prognosis: Uni/Multivariate analyses: n=587

Characteristics	No of patients	Median survival	95%CI	p value
• Age				
≤ 65	254	141	120-153	
> 65	333	56	49-63	<0.0001
• B2M (mg/L)				
≤ 3	251	122	103-141	
> 3	326	63	55-83	<0.0001
• Hemoglobin (g/L)				
≤ 11.5	381	123	110-179	
> 11.5	205	72	62-84	<0.0001
• Platelets (109/L)				
≤ 100	54	51	32-59	
> 100	531	90	83-116	<0.0001
• Absolute neutrophil count (109/L)				
≤ 1.5	53	46	27-74	
> 1.5	512	89	80-103	0.0018
• Serum monoclonal protein (g/L)				
< 70	541	90	82-110	
> 70	43	49	37-62	0.0016
• Serum albumin (g/L)				
< 35	197	79	55-89	
> 35	354	106	92-137	0.0012

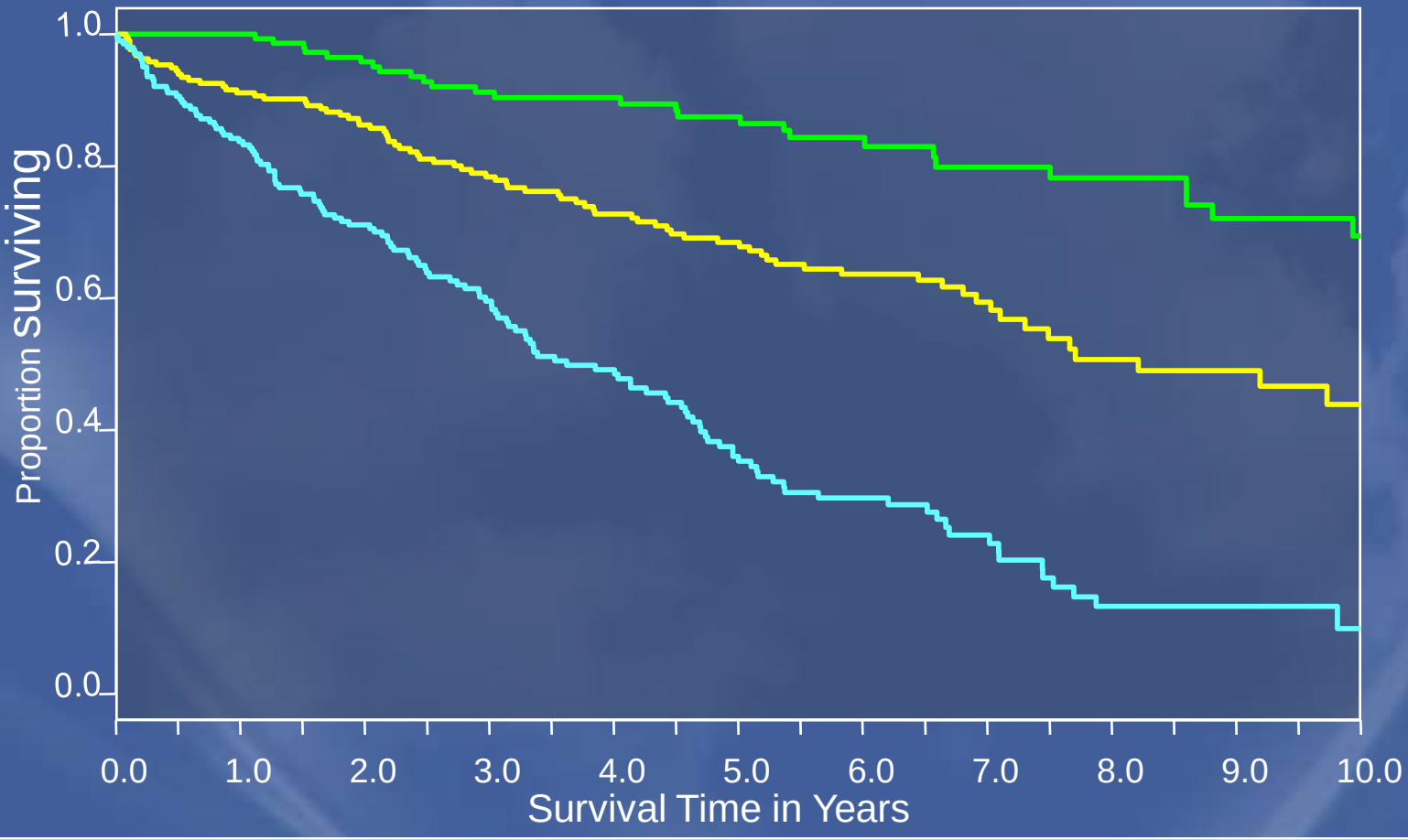
Morel et al, Blood 2009;113:4163-4170

The Prognostic Index: ISSWM

Stratum	Score	Total	Failed	Median	0.95lcl	0.95ucl
Low	0 or 1 (except age)	155 (27%)	38	142.5	120.3	195.7
Intermediate	Age>65 or 2	216 (38%)	87	98.6	81.7	137.2
High	>2	203 (35%)	134	43.5	36.6	55.1

Morel et al, Blood 2009;113:4163-4170

The Prognostic Index: ISSWM



Number at risk	Years									
Low	155	152	133	110	96	87	64	51	43	33	25
Inte	216	194	174	143	126	106	79	50	32	23	14
High	203	170	136	95	73	48	31	20	9	6	3

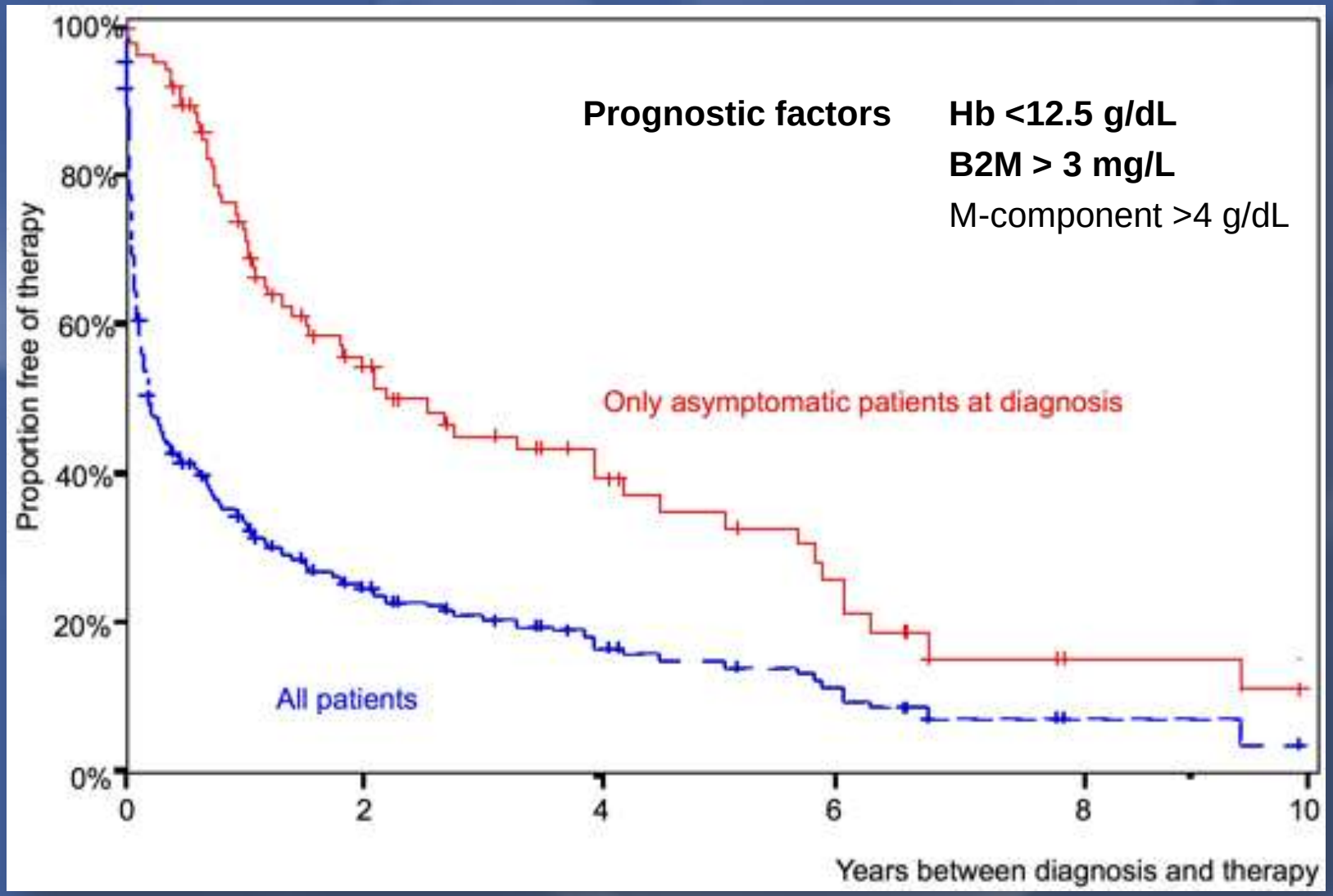
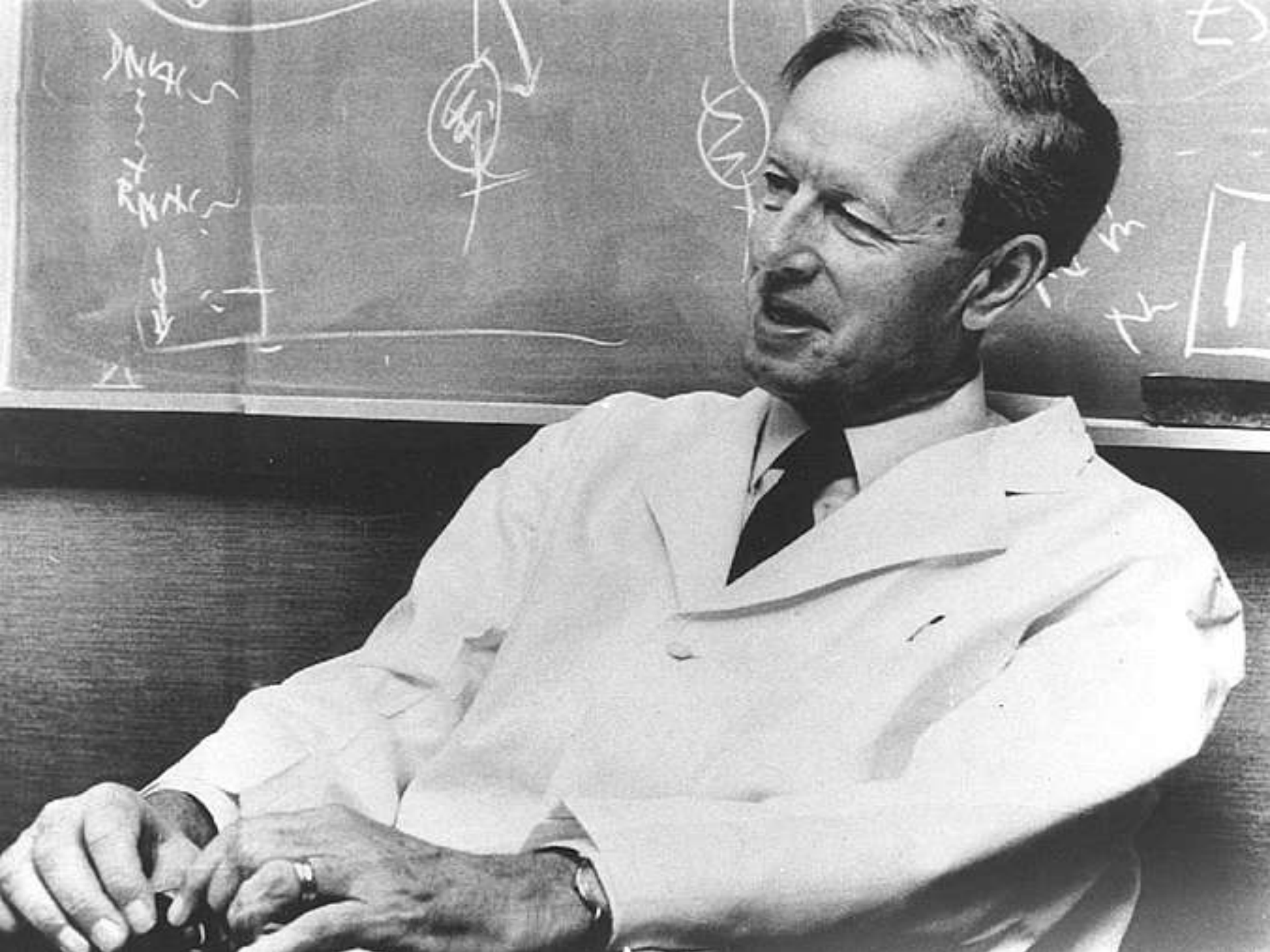
Blood 2009;113:4163-4170

Treatment Criteria: Symptomatic disease

1. Recurrent fever, night sweats, weight loss, fatigue
2. Hyperviscosity
3. Lympadenopathy which is either symptomatic or bulky (≥5cm in maximum diameter)
4. Symptomatic hepatomegaly and/or splenomegaly
5. Symptomatic organomegaly and/or organ or tissue infiltration
6. Peripheral neuropathy due to WM
7. Symptomatic cryoglobulinemia
8. Cold agglutinin anemia
9. Immune hemolytic anemia and/or thrombocytopenia
10. Nephropathy related to WM
11. Amyloidosis related to WM
12. Hemoglobin ≤10g/dL
13. Platelet count $<100 \cdot 10^9$/L

Kyle et al. Semin.Oncol 2003; 30: 116-120

Survival free of therapy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