Waldenström's Macroglobulinemia

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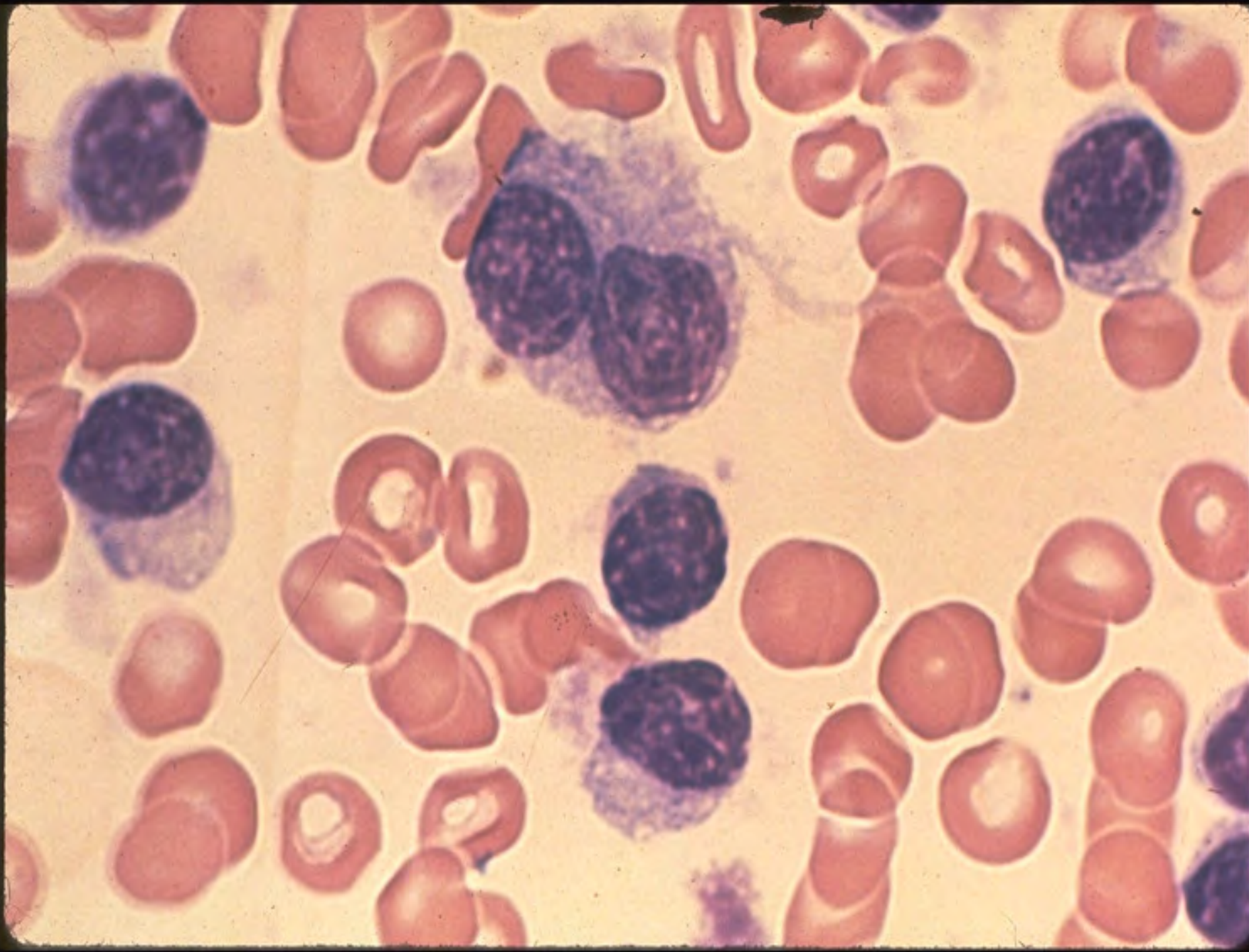
Waldenström's Macroglobulinemia

Lage frequentie
- 6% van alle MGUS
- 2-5 pt/mill. inh/yr (GEM, 3'1) 2500 patienten/jaar in Europe

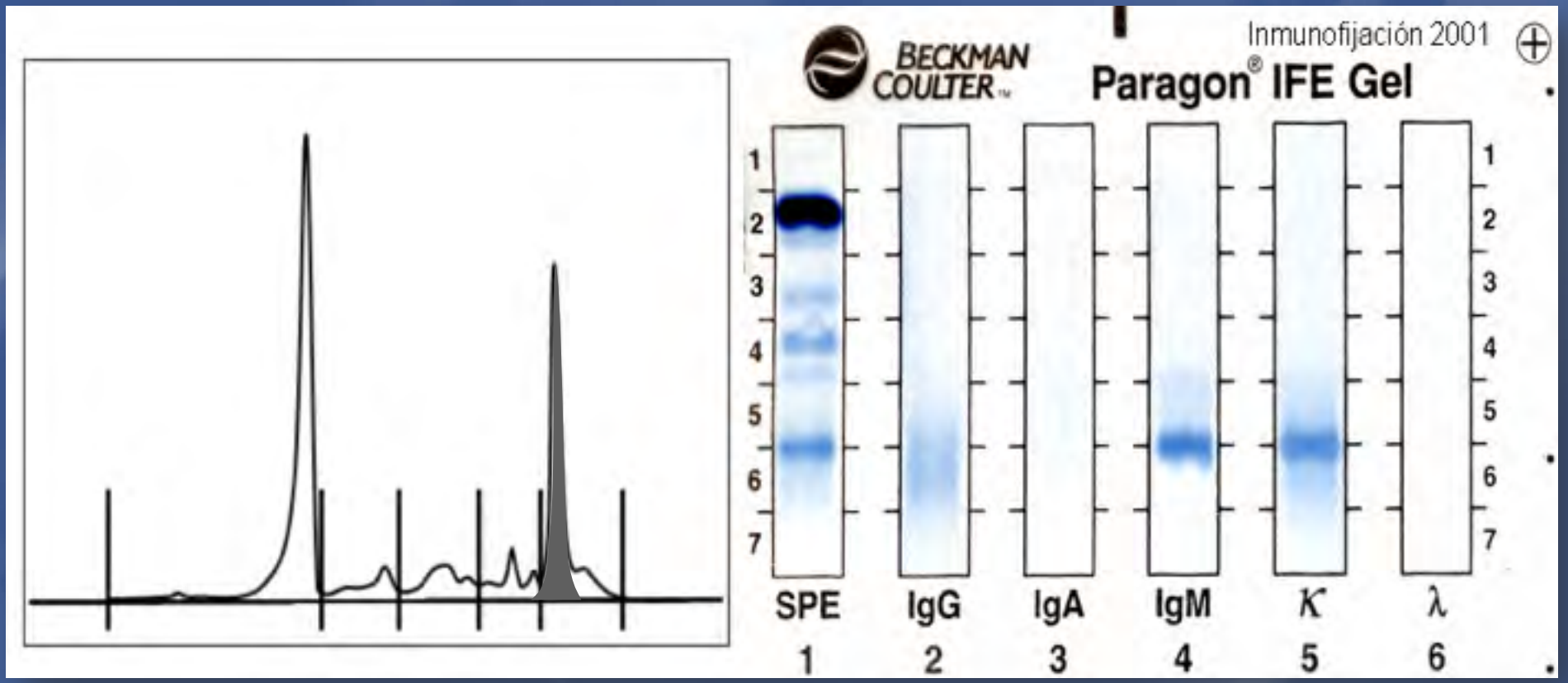
Oudere leeftijd
- Median: 71 jaar. Man/vrouw : 2:1

Natuurlijk beloop
- Traag groeiende ziekte , Mediane overleving : 11 jaar
- 1/3 pt overlijdt aan andere ziekte dan Waldenstrom



Protein Electrophoresis

Immunofixation



Definitie

Waldenström's Macroglobulinemia is een zeldzame ziekte, horend bij de non hodgkin lymfomen.
Karakteristiek is beenmerg infiltratie en IgM M proteine/ paraproteine

Beenmerg diagnose volgens WHO is; lymphoplasmacytic lymphoma.

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

Classificatie van WM en verwante ziektebeelden

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

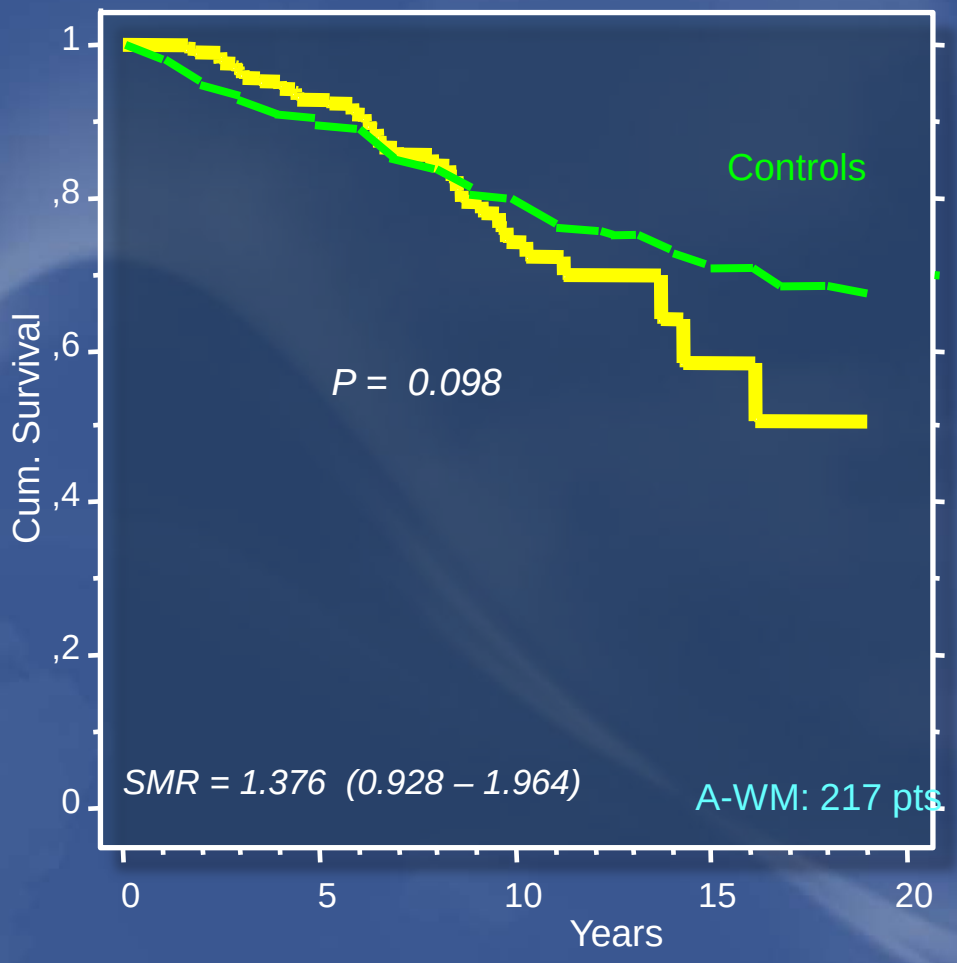
1) The panel considered to be inappropriate to define an IgM concentration to distinguish MGUS from WM. However, it should be noted that IgM concentration rarely if ever exceeds 3 g/dL in MGUS; 2) Patients with unequivocal BM infiltration by lymphoplasmocytic lymphoma will be considered to have WM, while 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

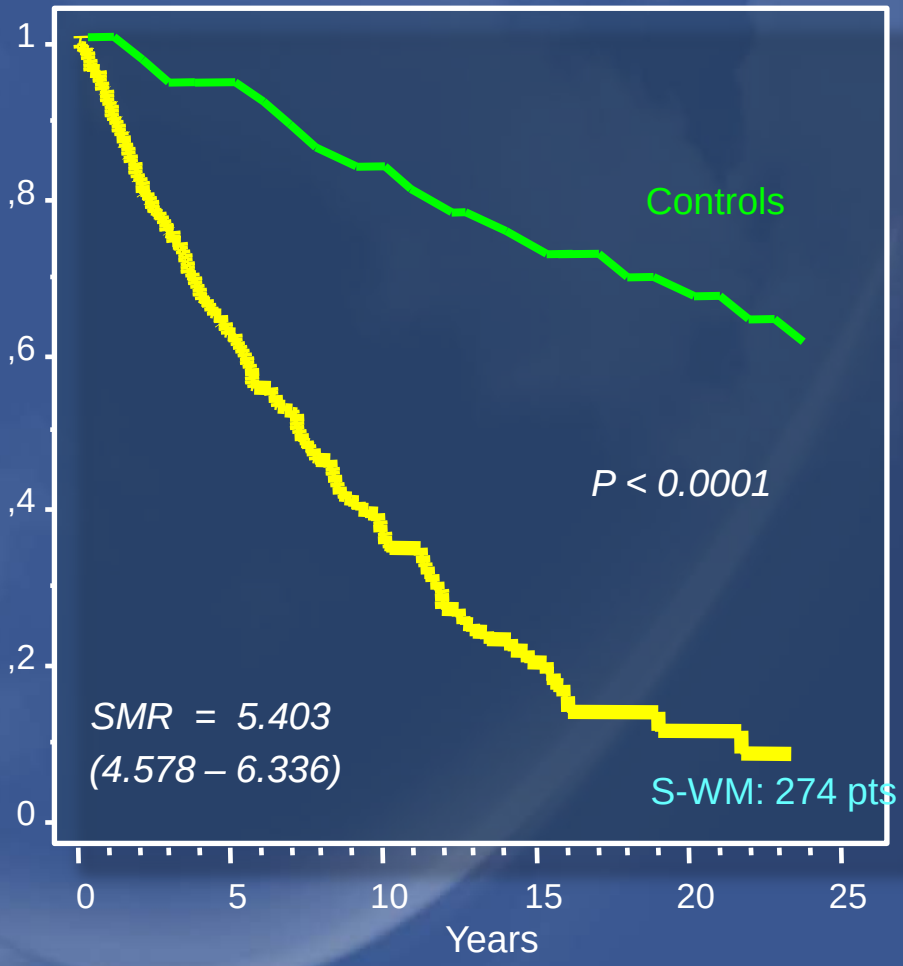
Beenmerg biopsie is noodzakelijk

Overleving

Asymptomatic WM



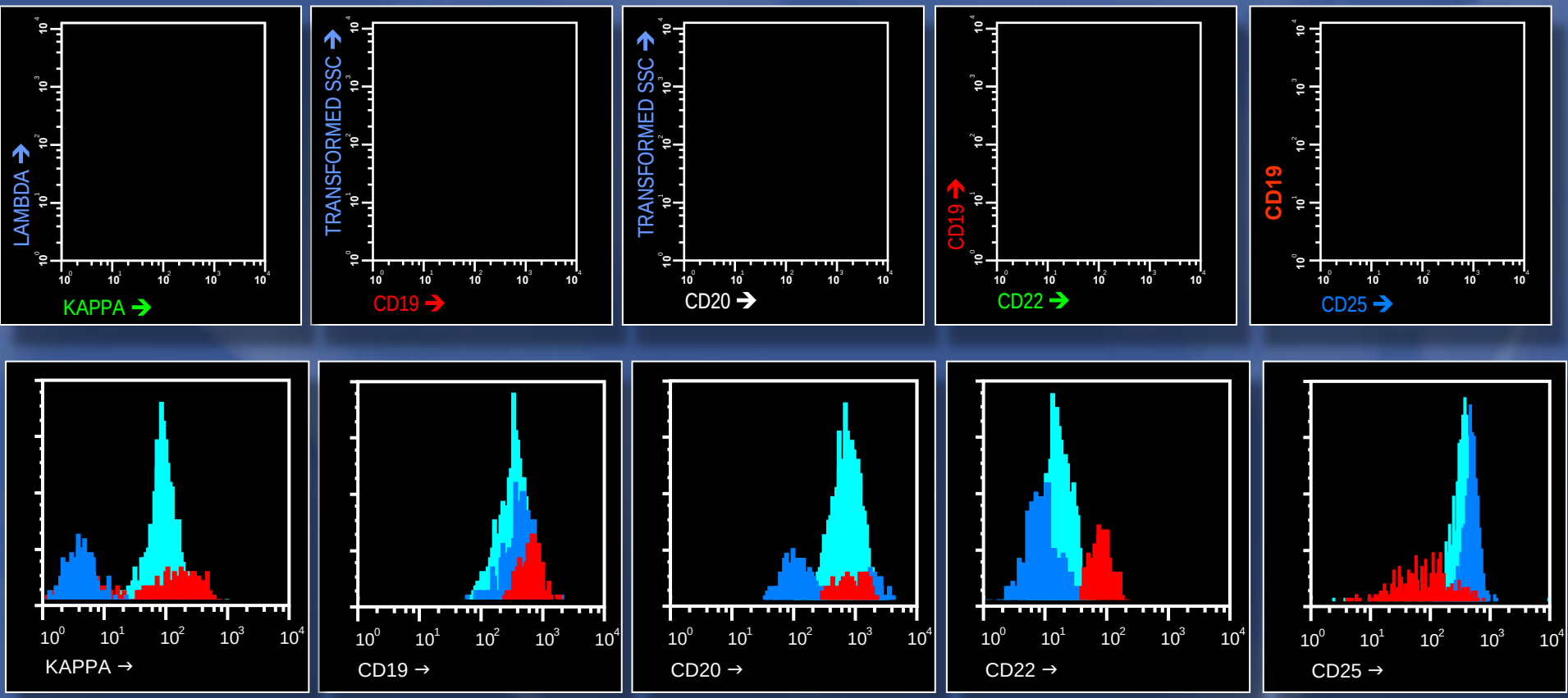
Symptomatic WM



Morel et al, IMWG 2009

Pan B cell eiwitten op cel oppervlak

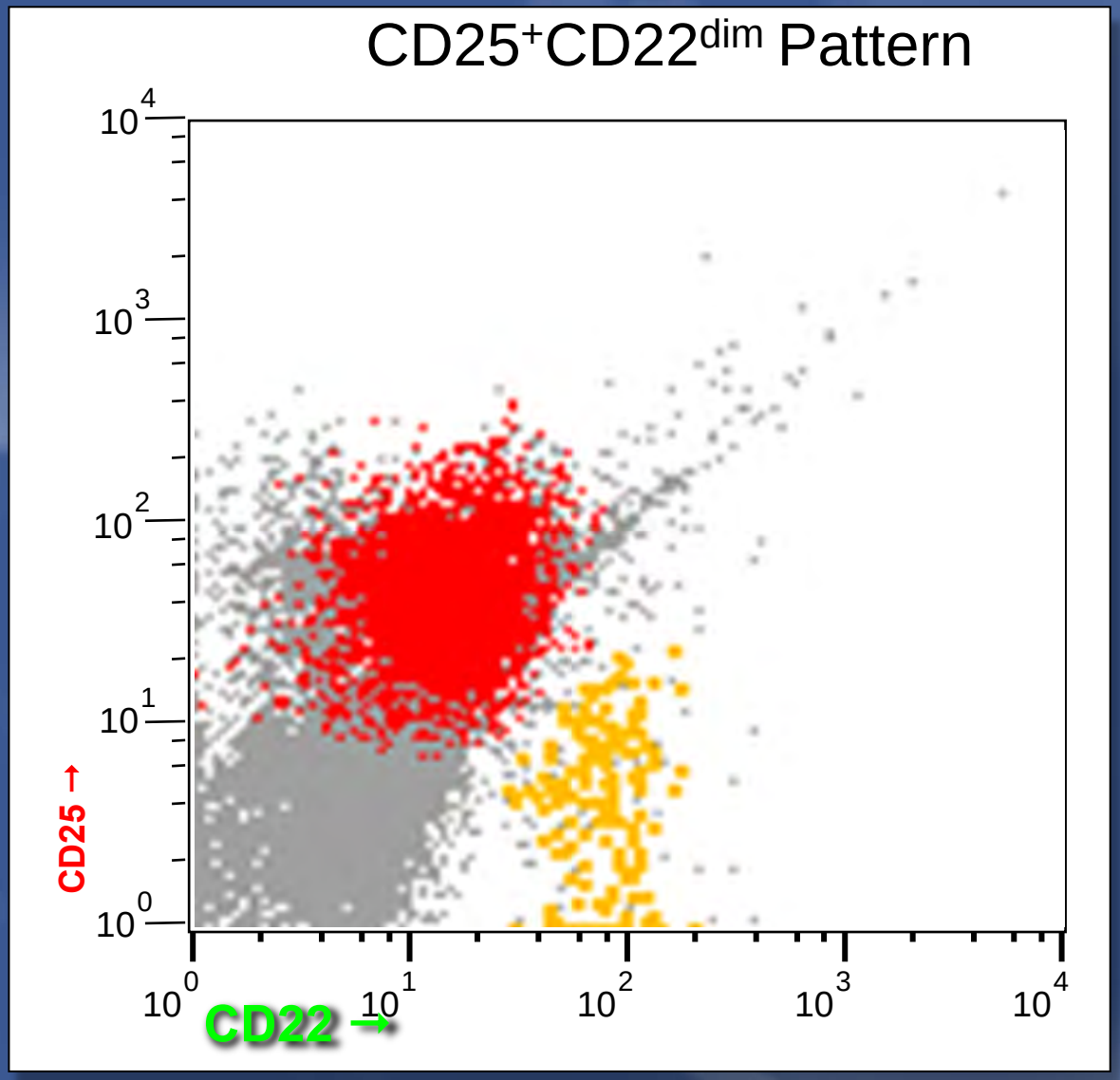
sIg$^{+/homog.}$	CD19$^{+/homog.}$	CD20$^{++/homog.}$	CD22$^{+lo/homog.}$	CD25 $^{(+)}$



sIg κ:sIg λ ratio= 5:1

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

Eiwit combinaties gebruikt voor de diagnose



WM Lymphoid cells

Normal Lymphoid cells

88% WM *versus* 21% SMZL

Genetische afwijkingen in WM cellen

	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*

Resultaten

Betrokken gen	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%)

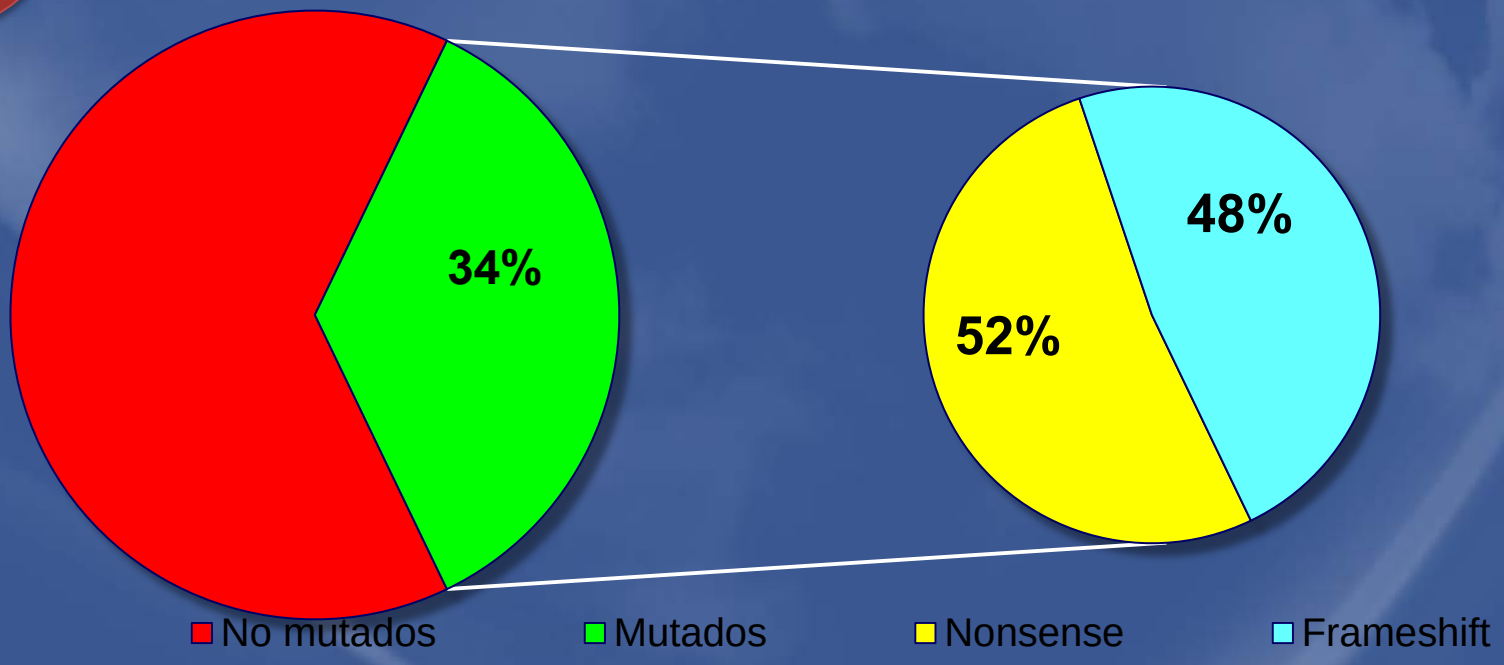
MYD88 L265P mutatie in B-cell NHL

Entity	N	MYD88 L265P
Waldenström's Macroglobulinemia	221	182 (82%)
IgM MGUS	53	37 (70%)
Agressief lymfoom	10	77 (19%)
Marginale Zone Lymphoom	36	3 (8%)
B-CLL (18 with IgM M-component)	358	11 (3%)
Hairy cell Leukemie	53	0 (0%)
Lymphoplasmocytic lymphoma	11	0 (0%)
Multipel Myeloma (3 IgM)	67	0 (0%)
MGUS IgG/IgA	72	0 (0%)
Gezonde vrijwilligers	38	0 (0%)
CXCR4 mutations (WM)	76	26 34%

Garcia Sanz, IWWM 2016

CXCR4 mutaties

CD19+ cells from 76 WM pts



Jiménez et al, ASH 2015

Klachten

Bij diagnose

- *moeheid (toenemende lichaamszwakte)*
  - *bloedarmoede (38%)*
  - *Hyperviscositeit (31%)*
- *vergrote lymfeklieren (25%)*
- *B Symptomen; koorts, gewichtsverlies, nachtzweten (23%)*
- *Bloedingen (23%)*
- *Neurologische klachten [PNP] (22%)*
- *geen klachten (27%)*

Oorzaak van klachten

- *Tumor groei (infiltratie orgaan)*
- *Paraproteine effecten*

García-Sanz, BJH 2001, 115:575-582

Tekenen van tumor groei; cellen

Beenmerg afwijkingen:

- ***bloedarmoede***
- ***toename lymfocyten***
- ***lage afweercellen***
- ***lage bloedplaatjes***

Andere orgaan van lymfestelsel:

- ***vergrote lymfeklieren***
- ***vergrote lever en milt***

Buiten lymfatische stelsel:

- ***long en longbladen***
- ***nier***
- ***huid***
- ***darmen***
- ***zenuwstelsel***

García-Sanz, BJH 2001, 115:575-582

Tekenen van toename M proteine

Hyperviscositeit syndroom :

- ***Neurologisch***
- ***Cardiaal***
- ***bloedingen***

Cryoglobulinemie & Cryoaglutininemie

Remming door antistof activiteit :

- ***Neurologisch***
- ***Nier***
- ***Amyloidosis***
- ***gewrichtsklachten***
- ***Van willebrand ziekte***

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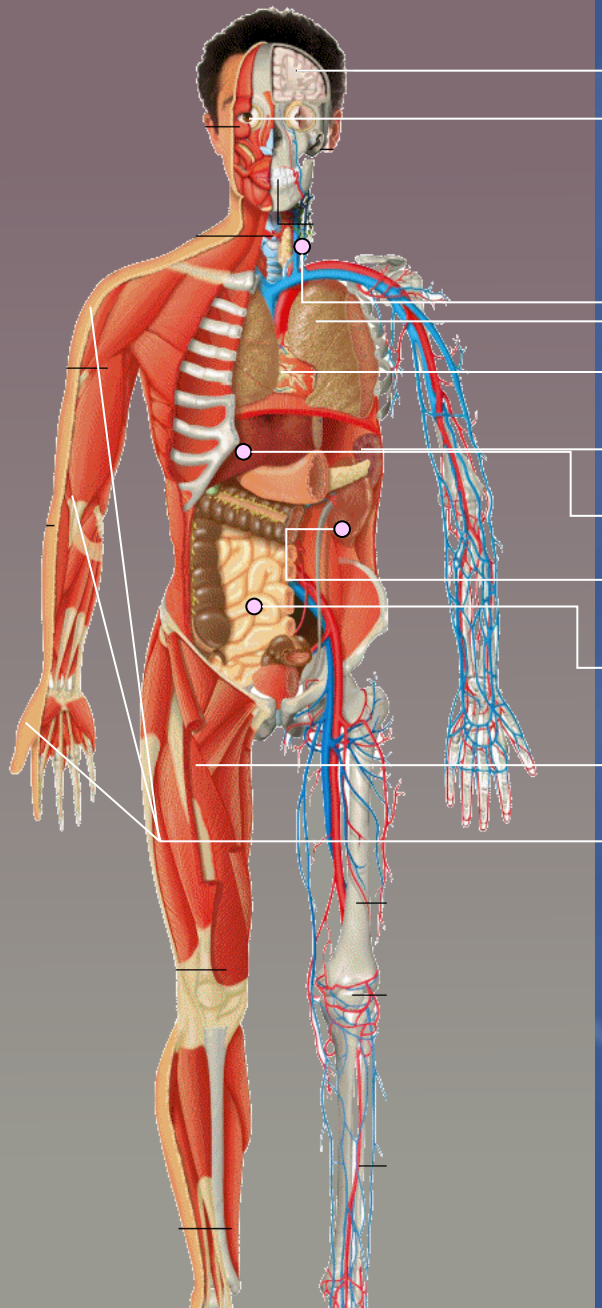


- HS: dizziness, stupor, drowsiness (31%)
- Oftalmologic alterations (34%)
- Lymphademnopathy (25%)
- Lung alterations, 4%
- Heart failure (rare)
- Splenomegaly (19%)
- Hepatomegaly(24%)
- Renal dysfunction (4%)
- Gastro-intestinal problems (3%)
- Peripheral neuropathy (25%)
- Skin (3%)

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%

Prognose : 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

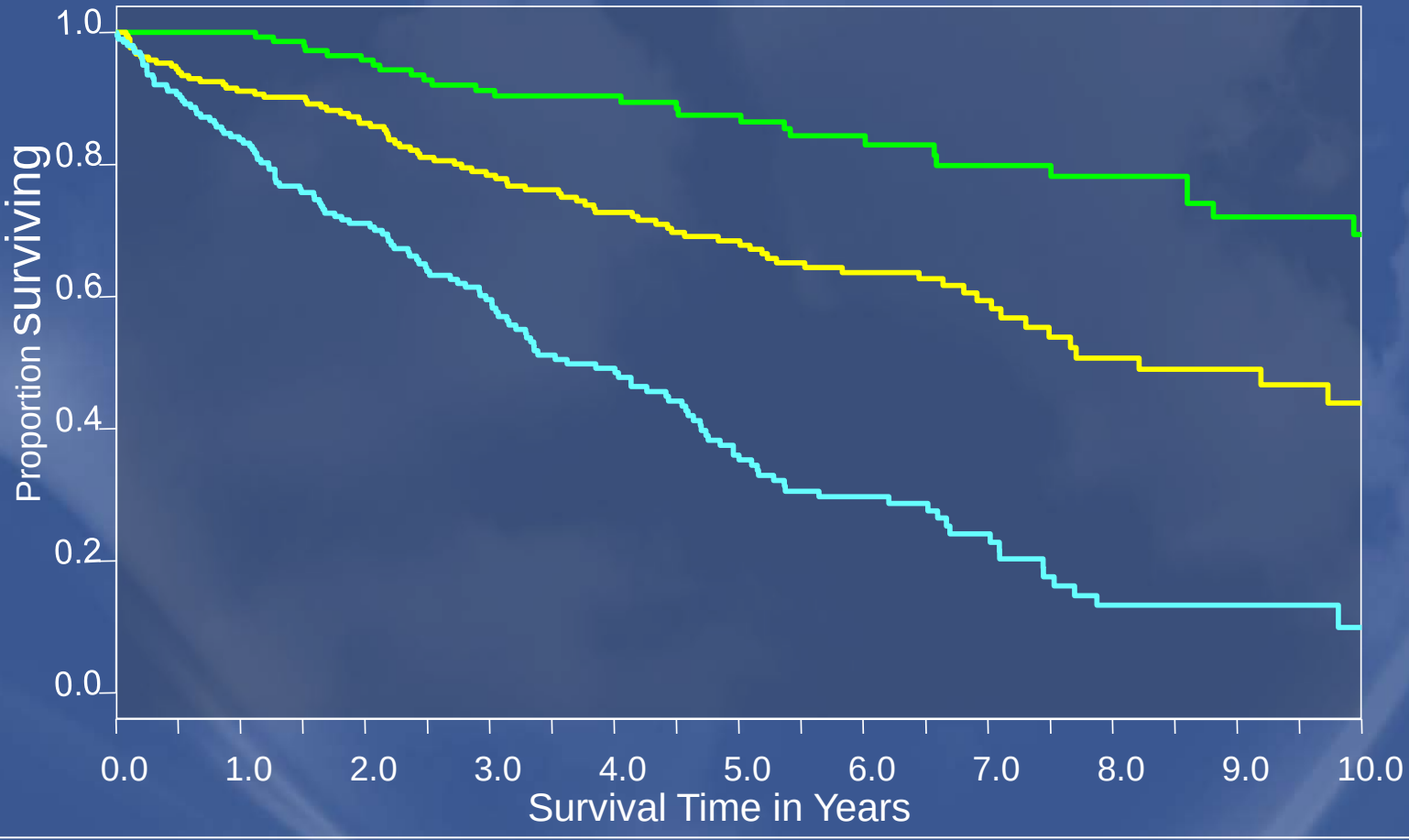
Morel et al, Blood 2009;113:4163-4170

Prognostische classificatie: 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

Prognostische classificatie : **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

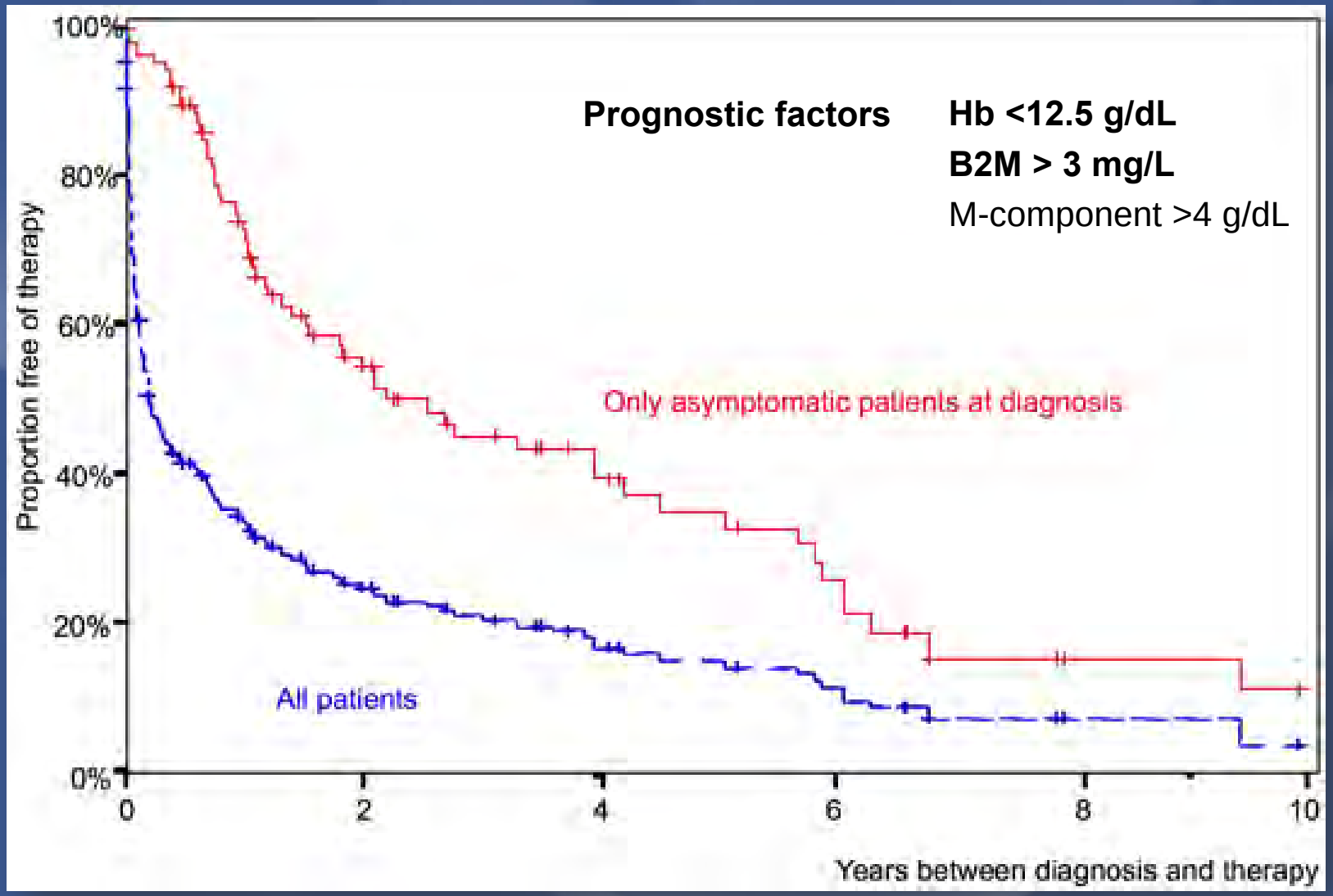
Blood 2009;113:4163-4170

Wanneer behandelen: bij deze symptomen

1. B symptomen; koorts, nachtezweten, gewichtsverlies, moeheid
2. Hyperviscositeit
3. Klachten van de vergrote lymfeklieren of klieren > 5 cm
4. Klachten van de vergrote milt en/of lever
5. Andere klachten van orgaan infiltratie
6. Periphere neuropathie door WM
7. Symptomatische cryoglobulinemie
8. Koude agglutinatie bloedarmoede
9. Immuun gemedieerde bloedarmoede of lage bloedplaatjes
10. Nierziekte door WM
11. Amyloidosis door WM
12. Ernstige Anemie
13. Bloed plaatjes $<100 \cdot 10^9/L$

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

Behandelings vrije overleving



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