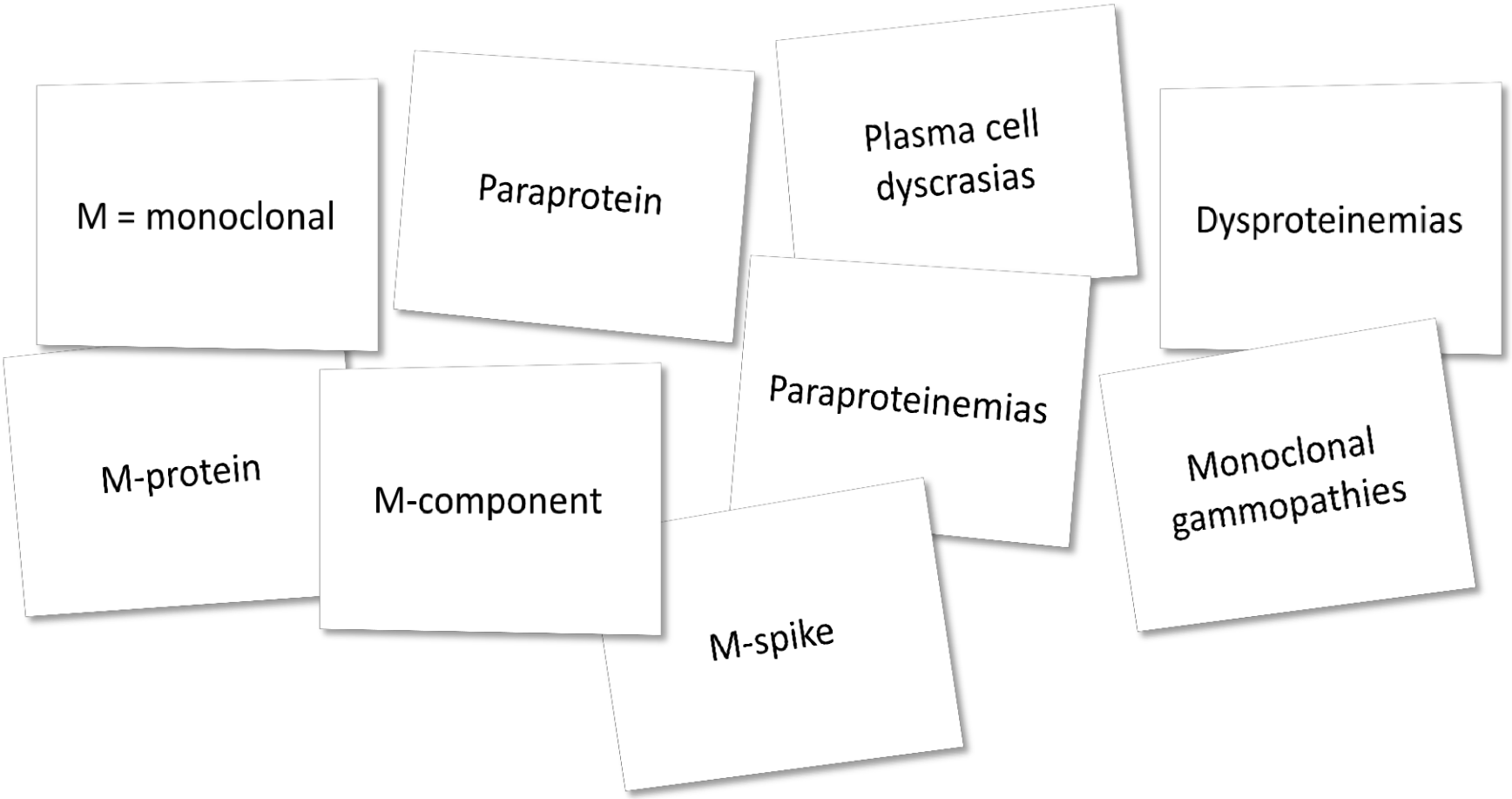
Myelomatose generelt

Dansk Myelomatose Forening

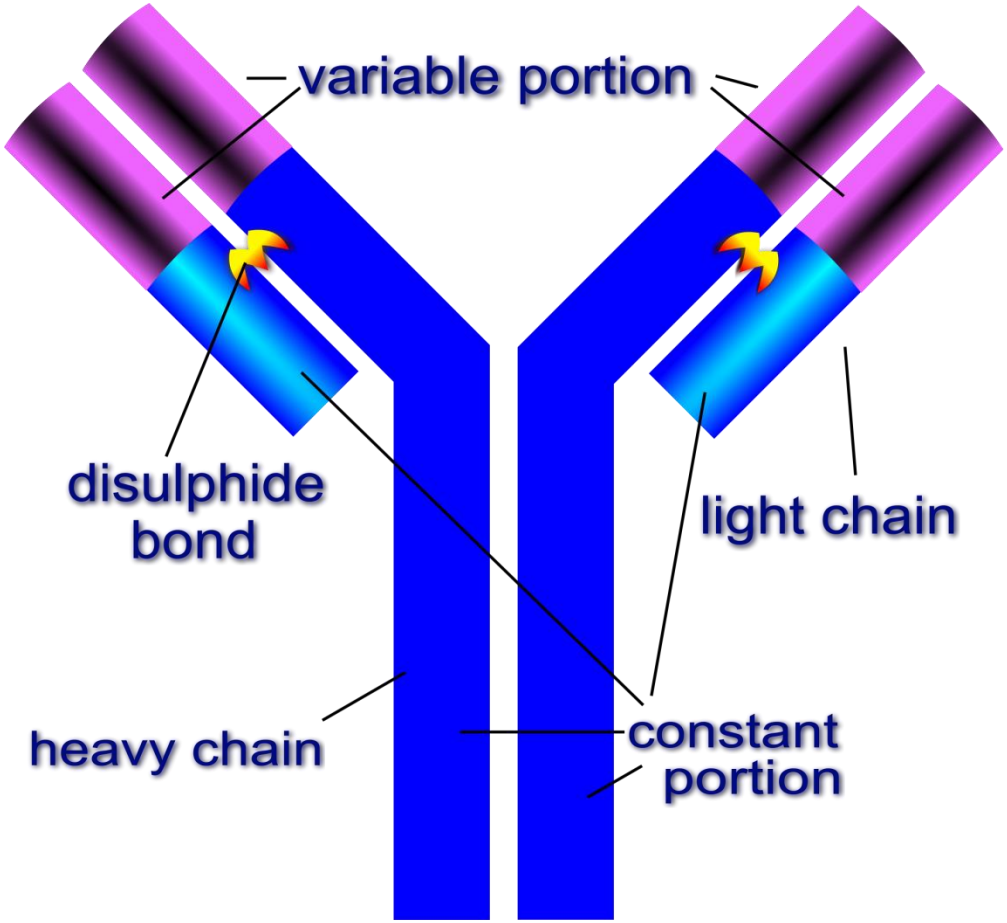
Konference, 11. marts 2017

Agoston Gyula Szabo
læge i hoveduddannelse, hæmatologi
Vejle Sygehus
agoston.gyula.szabo@rsyd.dk

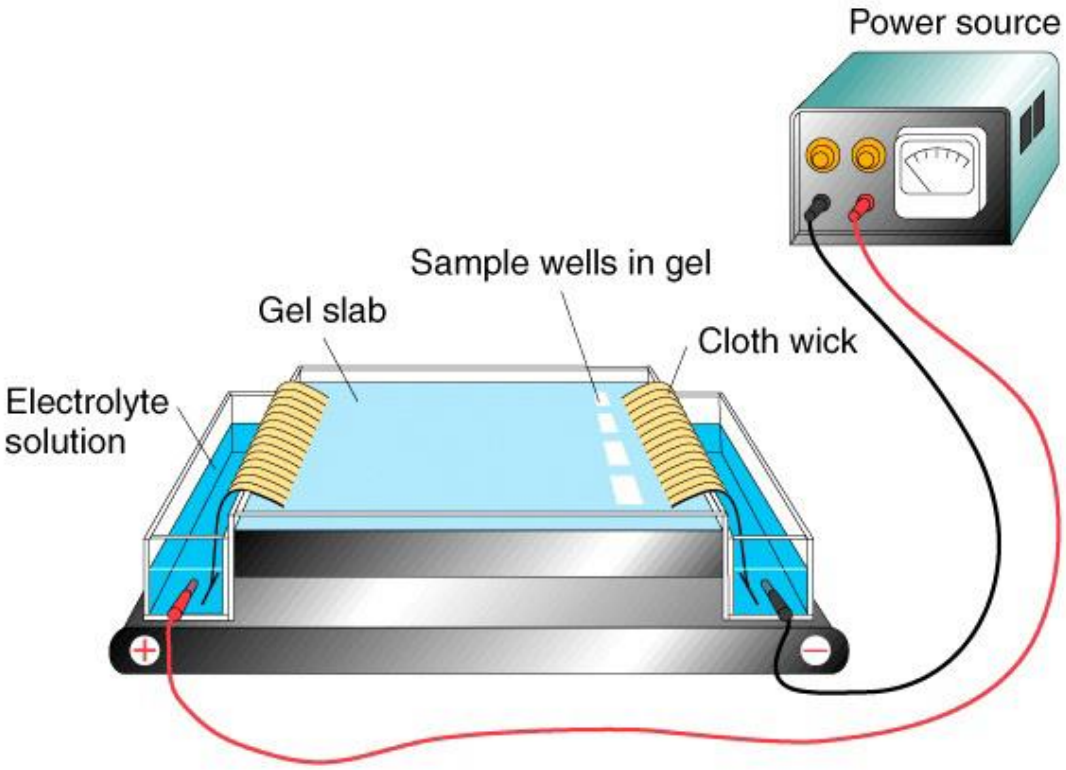
M-protein


M = monoclonal
Paraprotein
Plasma cell dyscrasias
Dysproteinemias
M-protein
M-component
Paraproteinemias
Monoclonal gammopathies
M-spike

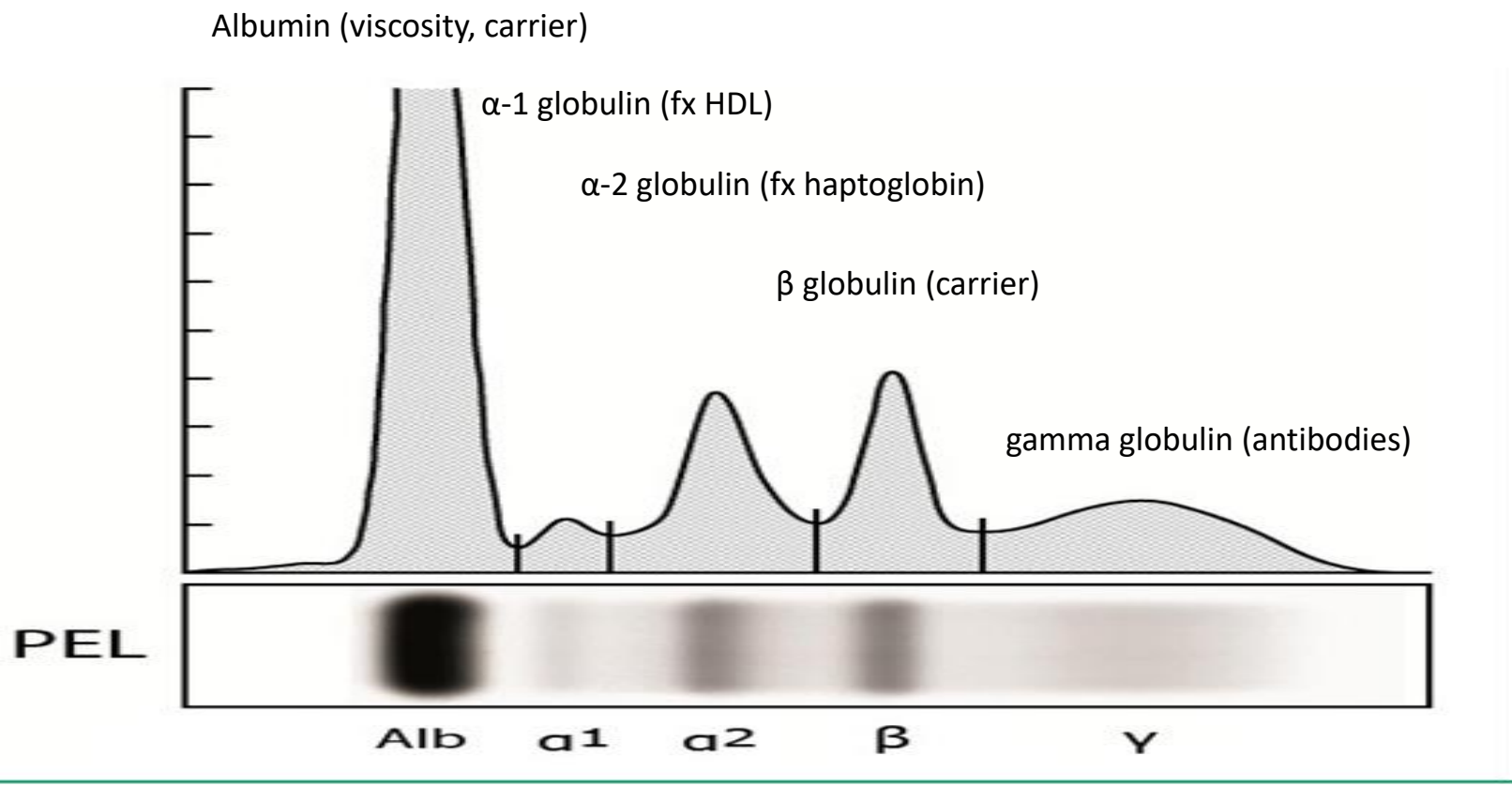
M-protein


variable portion
disulphide bond
light chain
heavy chain
constant portion

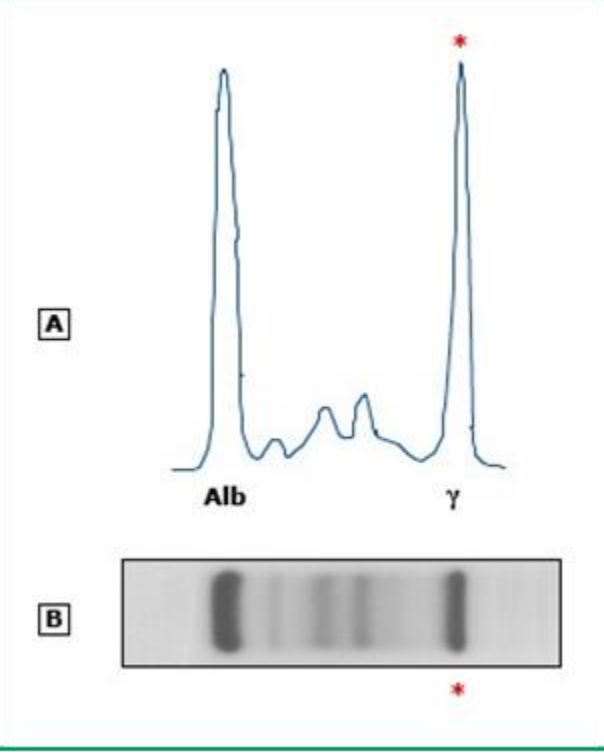
Serum protein electrophoresis (SPEP)



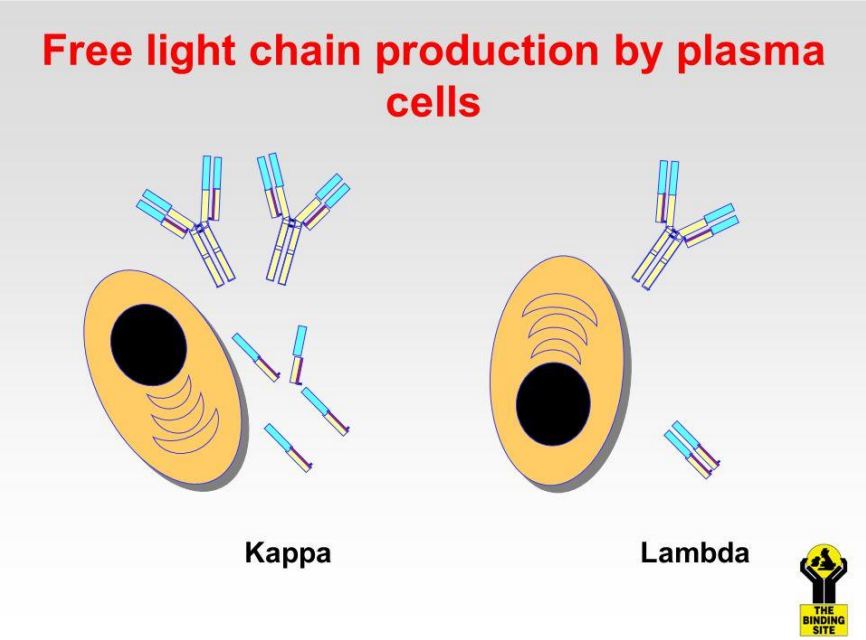
SPEP: Normal pattern



SPEP: Monoclonal gammopathy



Serum free light chain (FLC) assay



- sFLC kappa: 3.3 to 19.4 mg/L
- sFLC lambda: 5.7 to 26.3 mg/L
- Kappa/lambda 0.26 to 1.65

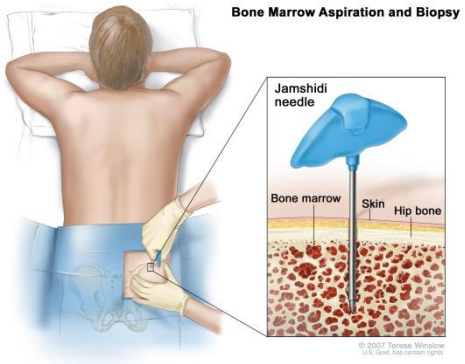
Bradwell Clin Chem. 2001 Apr;47(4):673-80.

Diagnostic workup

Blood tests

Imaging:
X-ray
Whole body low dose CT-scan
Whole body diffusion weighted MRI
PET-CT

Bone marrow biopsi



MGUS

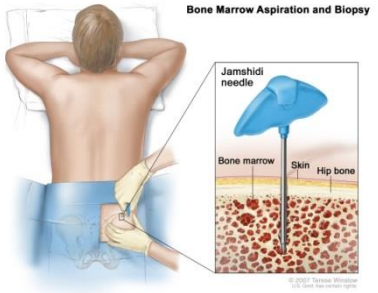
Monoclonal Gammopathy of Undetermined Significance

MGUS

ASYMPTOMATIC

Premalignant clonal disorder

M-protein < 30 g/L



< 10% plasma cells in the bone marrow

no myeloma defining event /CRAB

MGUS

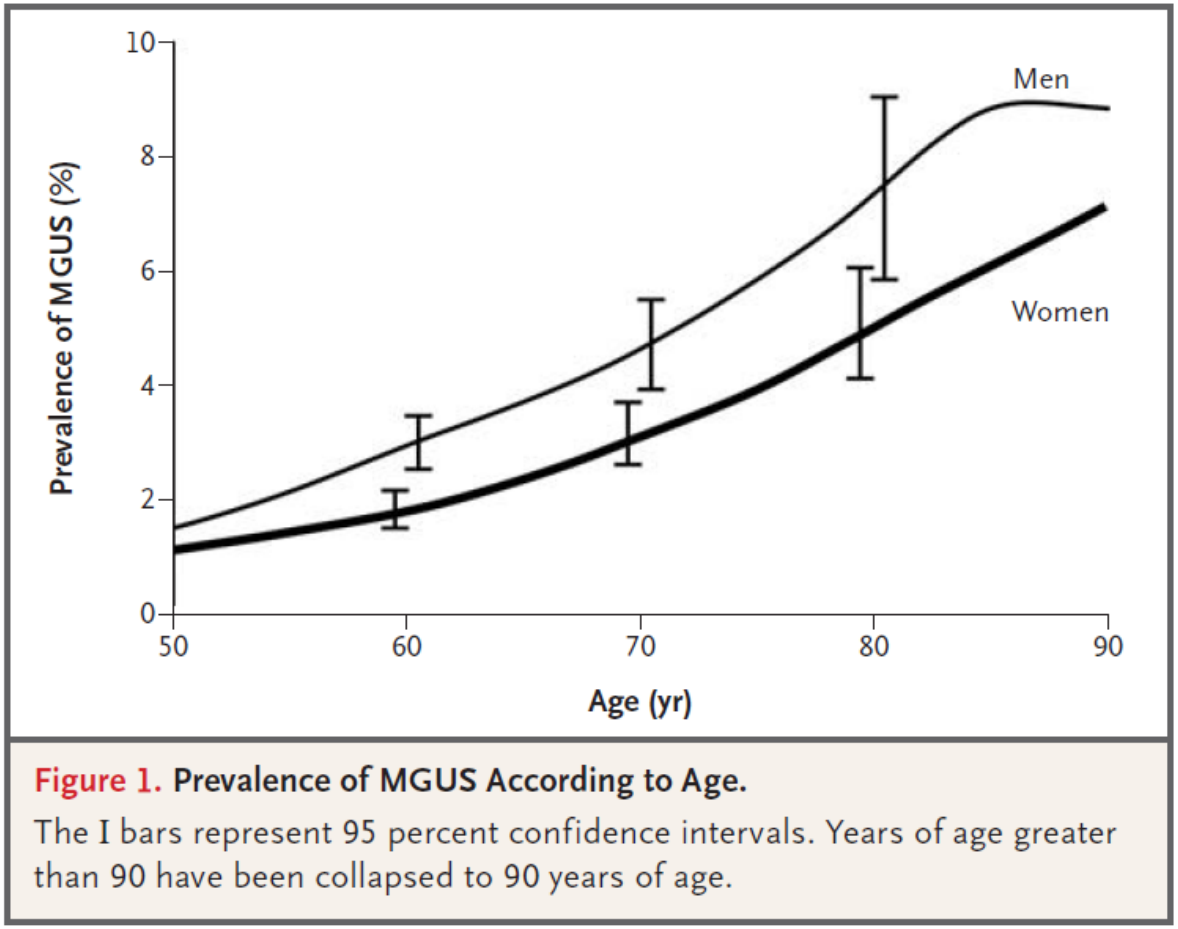


Figure 1. Prevalence of MGUS According to Age.

The I bars represent 95 percent confidence intervals. Years of age greater than 90 have been collapsed to 90 years of age.

Kyle N Engl J Med. 2006 Mar 30;354(13):1362-9.

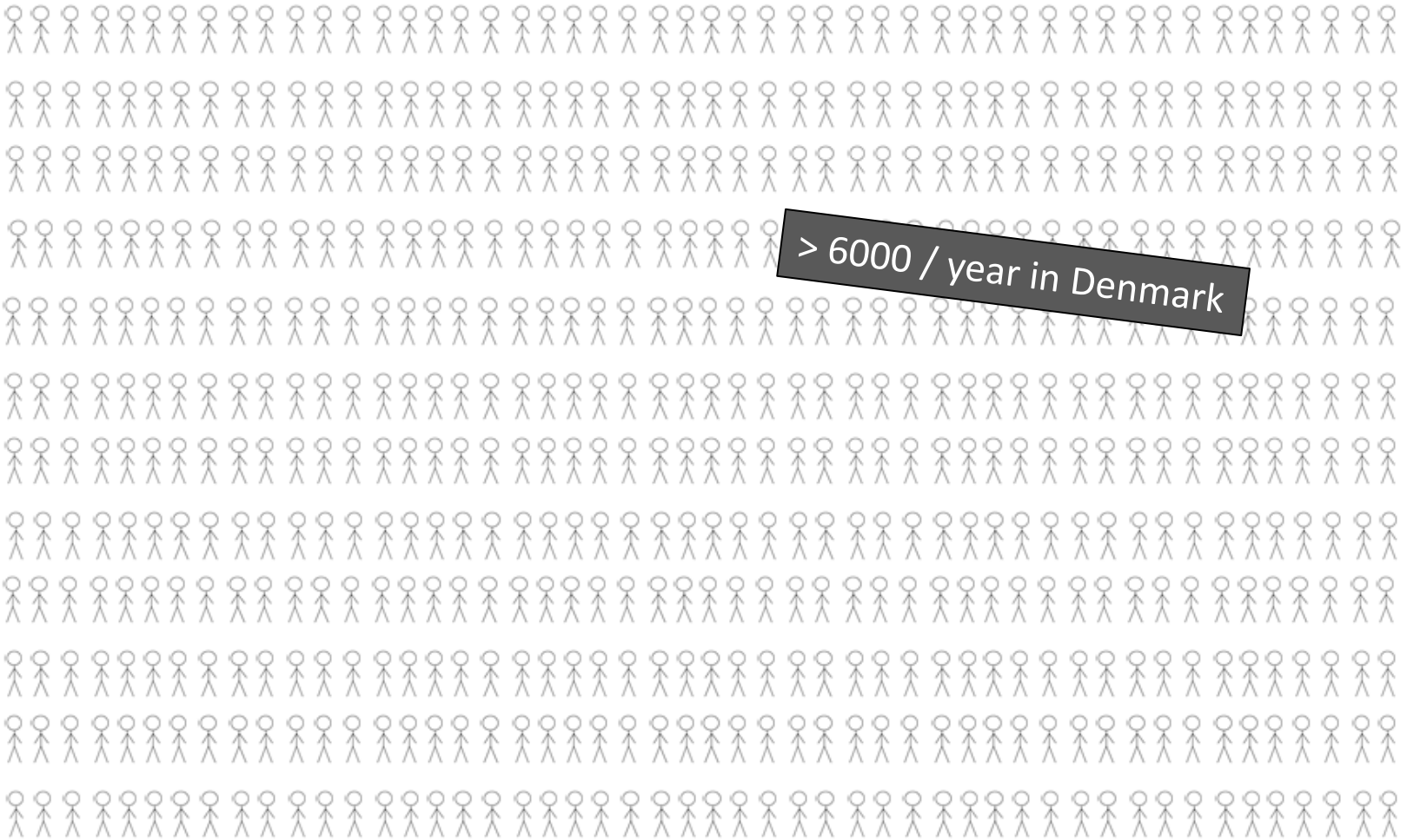
MGUS

Premalignant clonal disorder

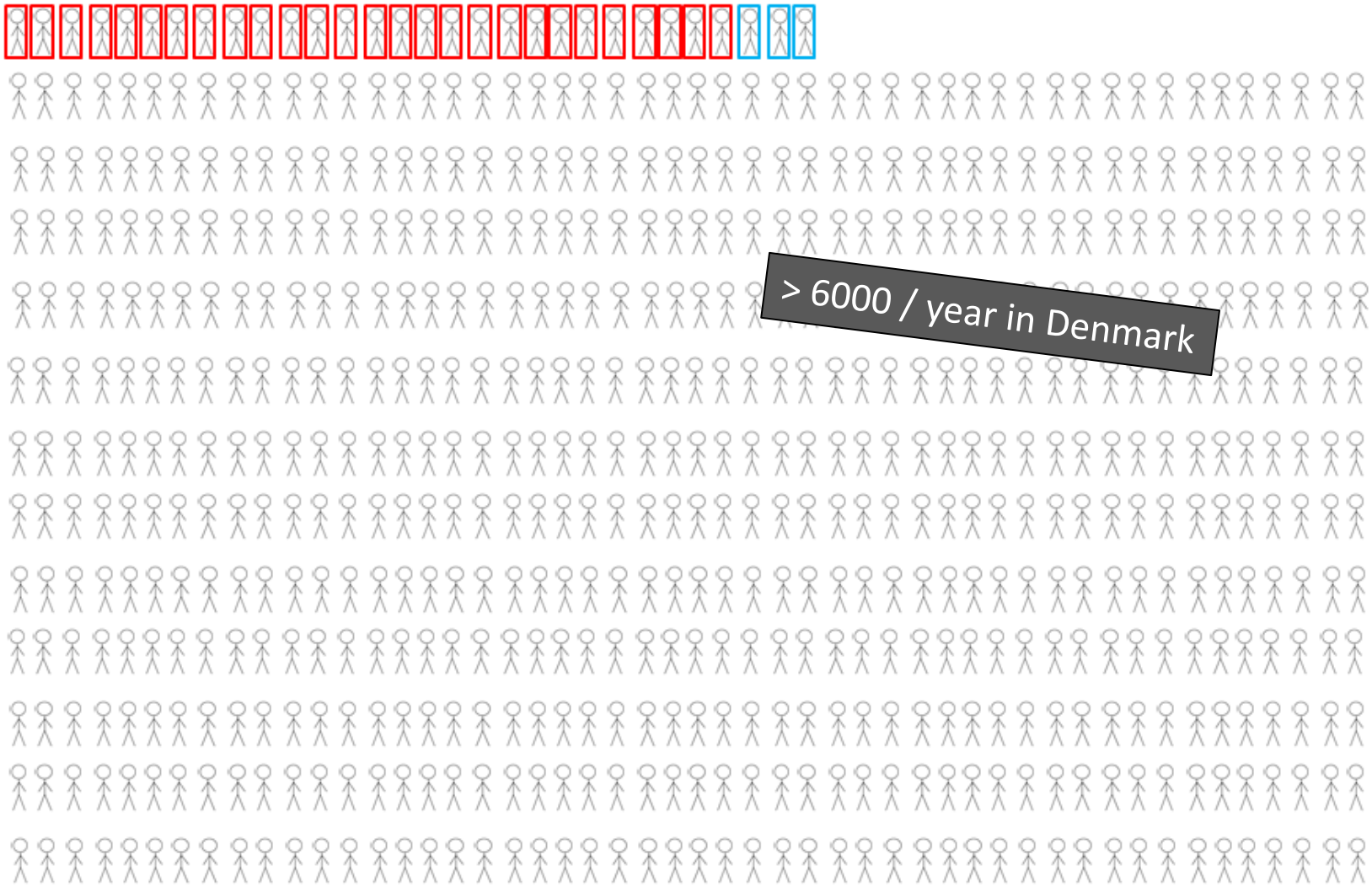
AGE AND PREVALENCE OF MGUS	
≥ 50 years	3,2 %
≥ 70 years	5,3 %
≥ 85 years	7,5 %

Kyle N Engl J Med. 2006 Mar 30;354(13):1362-9.

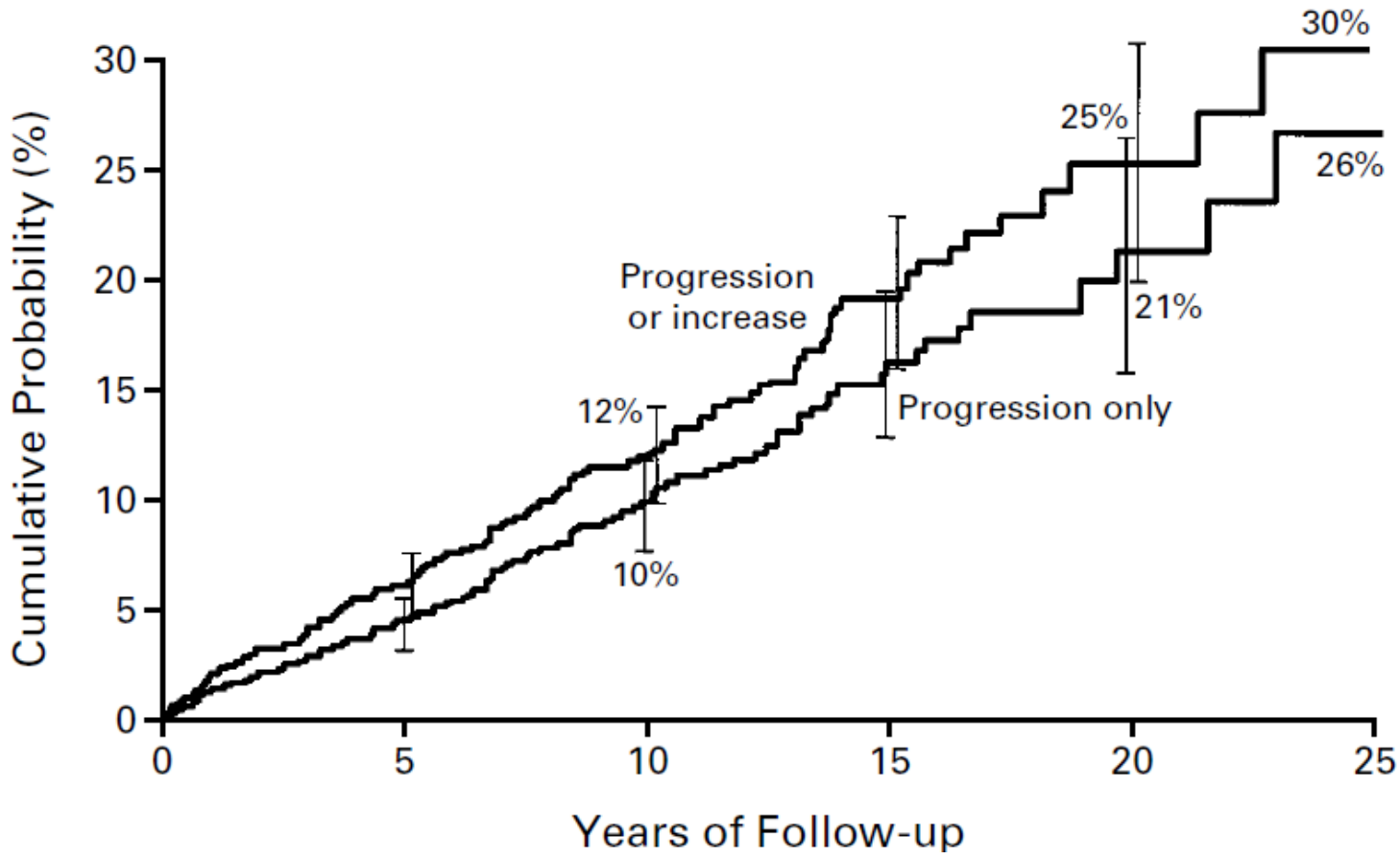
MGUS



MGUS

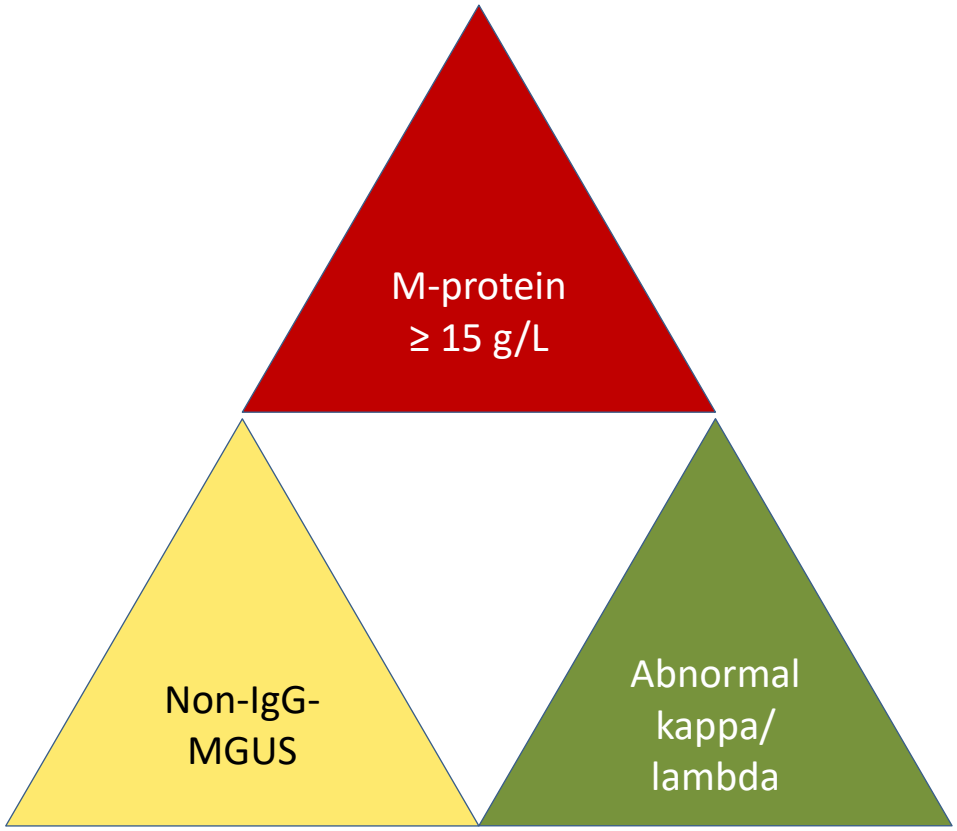


MGUS



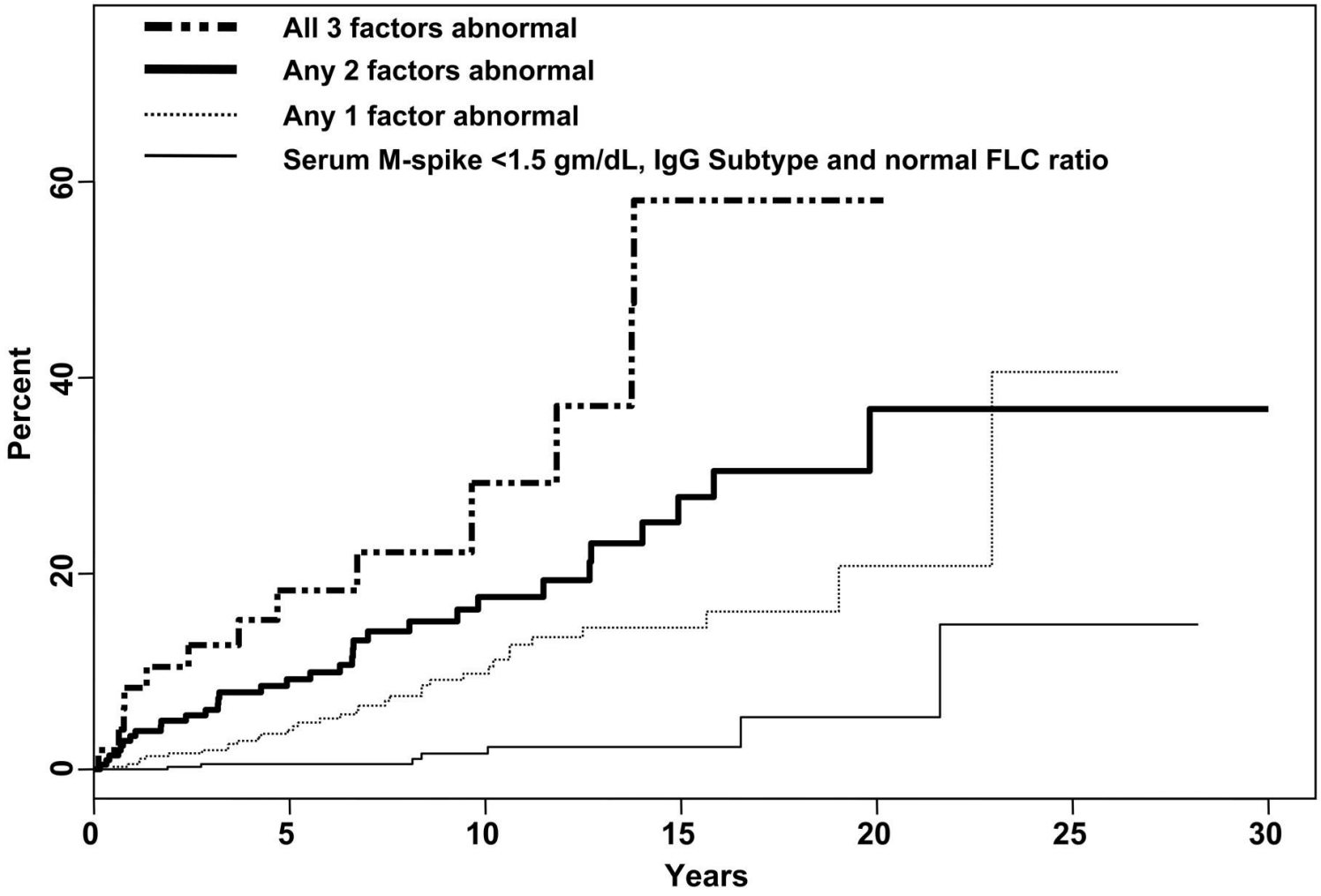
Kyle N Engl J Med. 2002 Feb 21;346(8):564-9.

MGUS



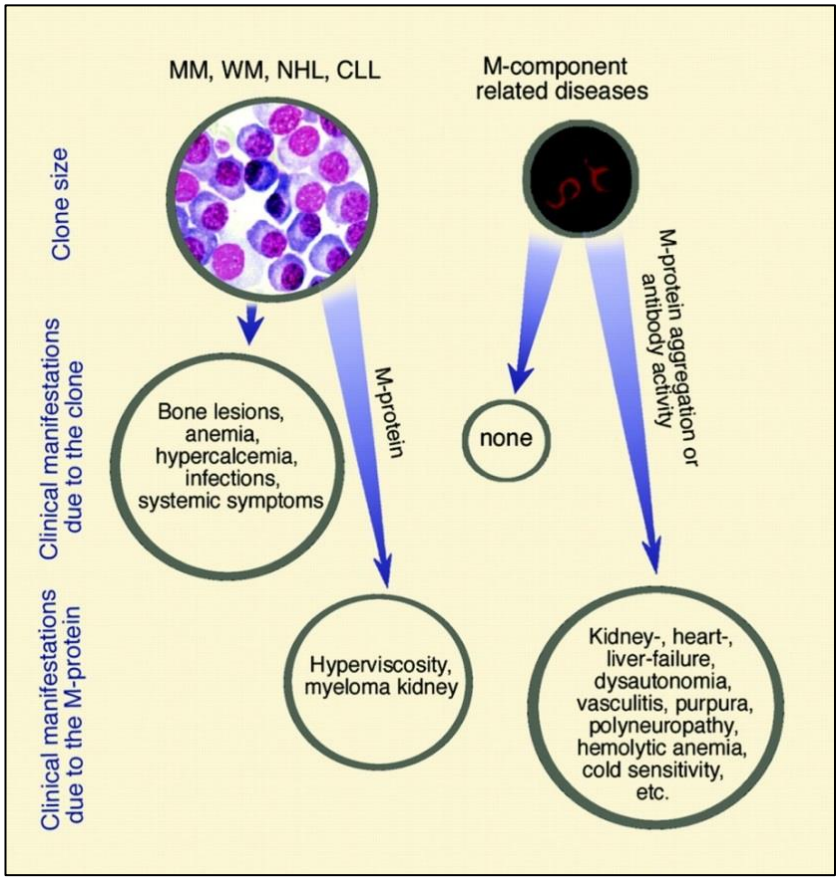
No. of risk factors	absolute risk of disease progression over 20 years
0	5 %
1	21 %
2	37 %
3	58 %

MGUS


All 3 factors abnormal
Any 2 factors abnormal
Any 1 factor abnormal
Serum M-spike <1.5 gm/dL, IgG Subtype and normal FLC ratio
Percent
0
20
40
60
0
5
10
15
20
25
30
Years

MGUS

SYMPTOMATIC



Dangerous small B-cell clones

Giampaolo Merlini and Marvin J. Stone

The detection of a monoclonal immunoglobulin in serum or urine usually raises concerns about the size of the underlying B-cell–derived clone and possible systemic effects caused by its expansion. However, a small clone can synthesize a very toxic protein, producing devastating systemic damage and protean clinical presentations. The resulting "monoclonal component-related diseases," although difficult to diagnose, may be progressive and even fatal. The monoclonal protein can aggregate and deposit systemically as occurs in light-chain amyloidosis, monoclonal immunoglobulin deposition disease, crystal-storing histiocytosis, and monoclonal cryoglobulinemia. Alternatively, some monoclonal proteins possess antibody activity toward autogenous antigens and cause chronic cold agglutinin disease, mixed cryoglobulinemia, and peripheral neuropathies. Other humoral mediators may contribute to neuropathy in variant disorders such as the POEMS (polyneuropathy, organomegaly, endocrinopathy, M protein, and skin changes) syndrome. The clone synthesizing the noxious monoclonal proteins is often small, and sensitive techniques may be required to detect these immunoglobulins. A delay in diagnosis can allow irreversible organ damage and dramatically shorten survival. Prompt recognition of suggestive signs and symptoms should trigger a thorough diagnostic approach to reach the correct diagnosis quickly, because this is the key to effective therapy. Although the treatment of these conditions is not optimal, significant advances have been made, improving the duration and quality of life. (Blood. 2006;108:2520-2530)

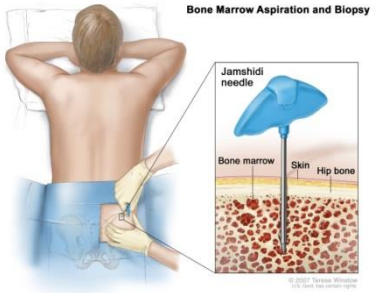
Merlini Blood. 2006 Oct 15;108(8):2520-30.

Smouldering Myeloma

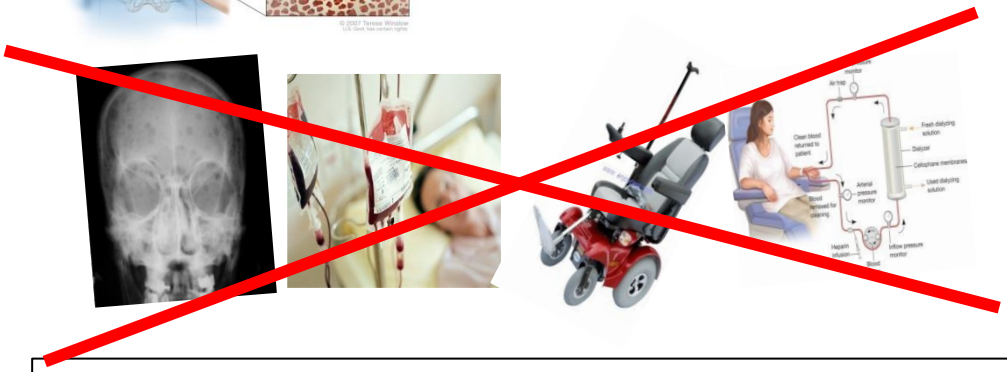
Smouldering myeloma

Ulmende knoglemarvskræft / asymptomatisk myelomatose

M-protein ≥ 30 g/L and/or

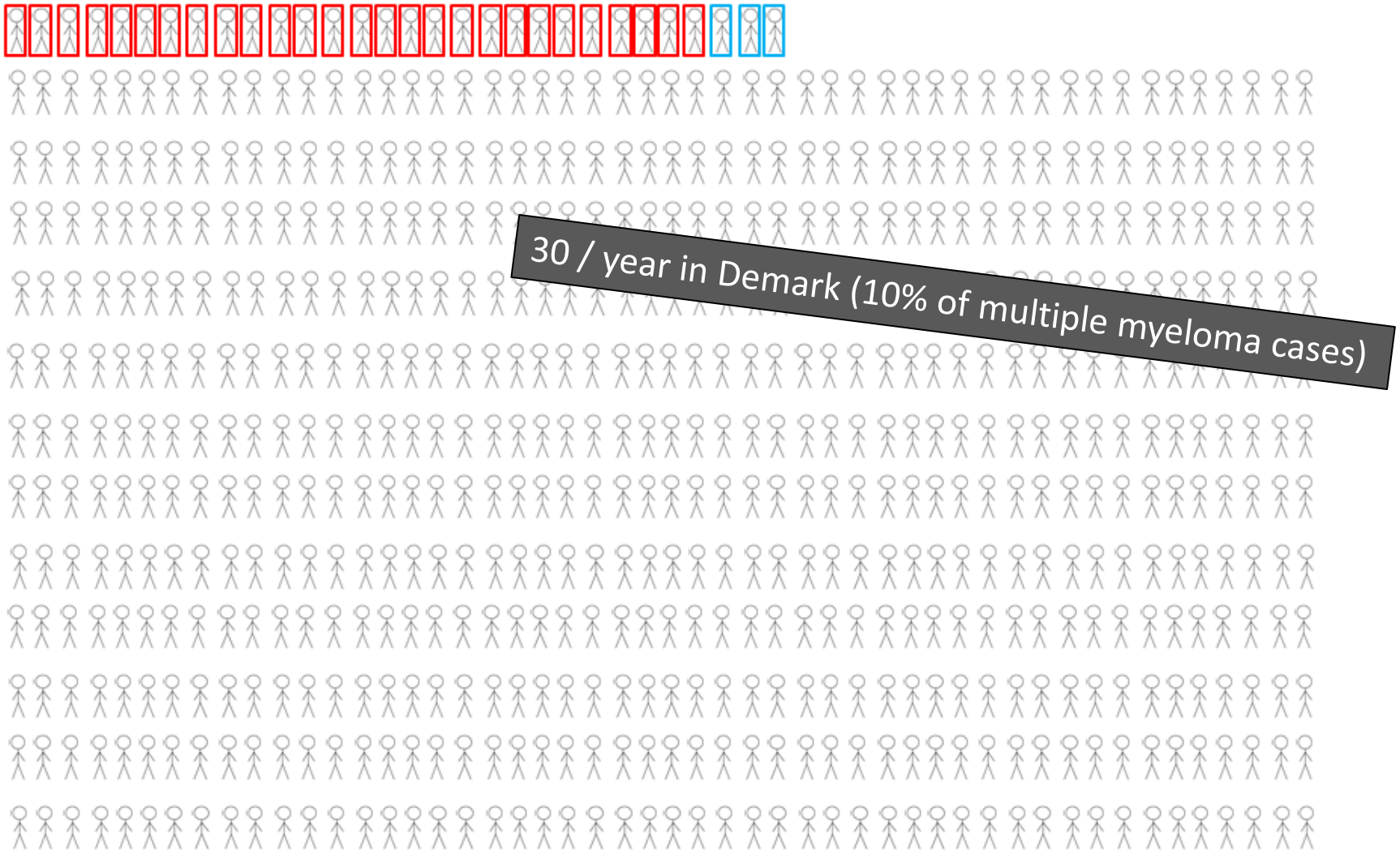


10% ≤ plasma cells in the bone marrow < 60%

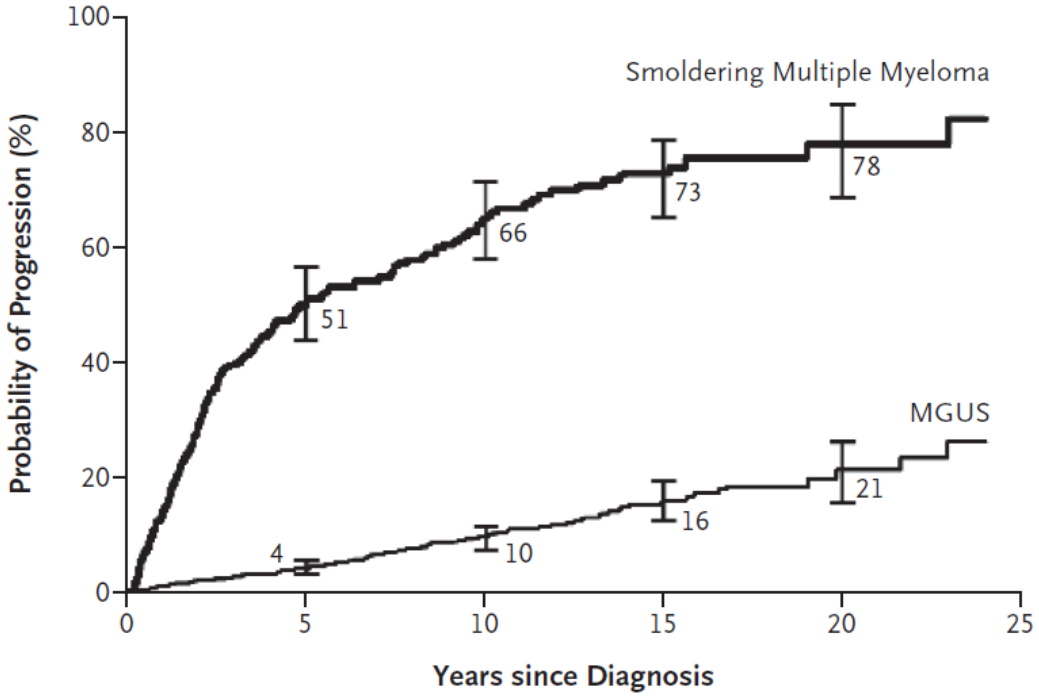


no myeloma defining event /CRAB

Smouldering myeloma

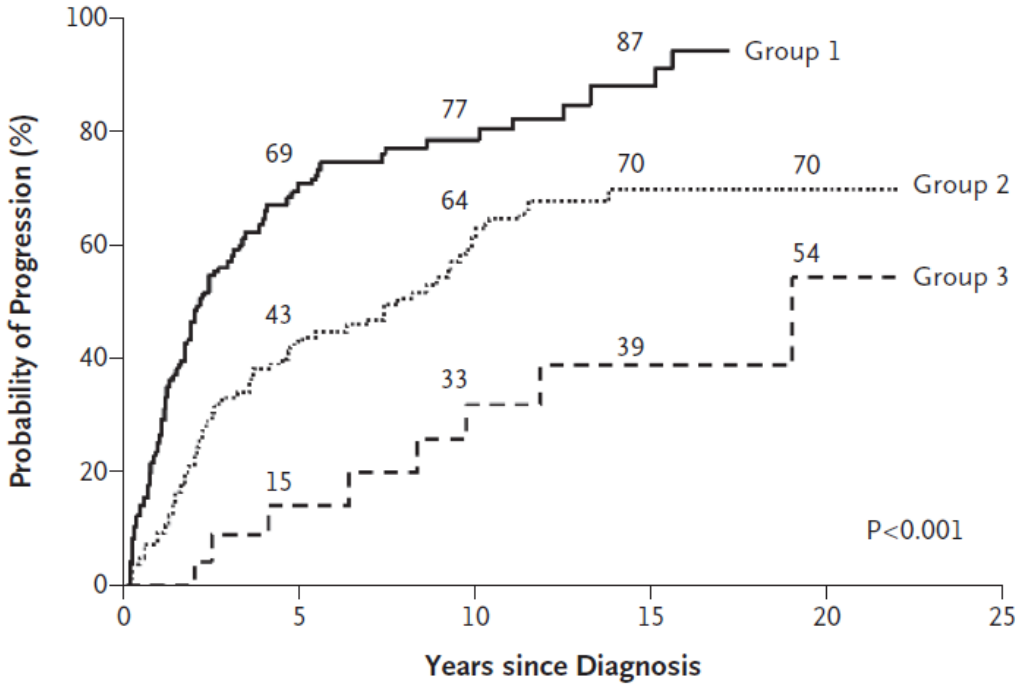


Smouldering myeloma



Kyle N Engl J Med. 2007 Jun 21;356(25):2582-90.

Smouldering Multiple Myeloma



RISK-STRATIFICATION MODEL

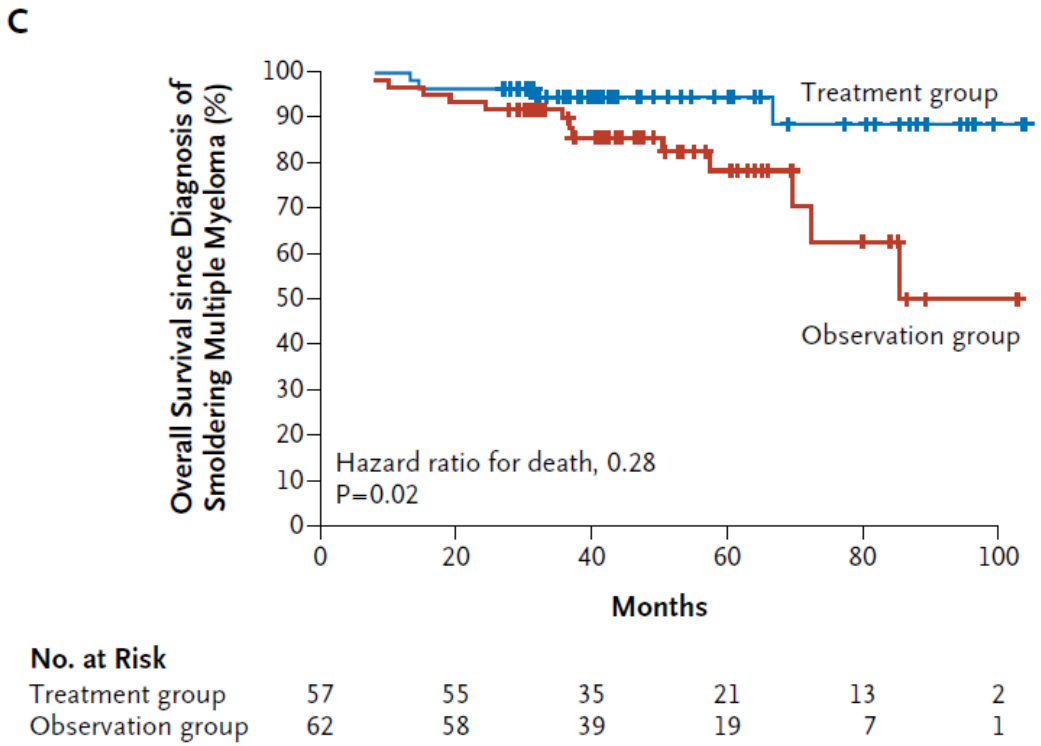
group 1
- bone marrow plasma cells, ≥10%;
- M-protein ≥30 g/L

group 2
- plasma cells, ≥10%
- M-protein <30 g/L

group 3
- plasma cells, <10%;
- M-protein ≥30 g/L

Smouldering Multiple Myeloma

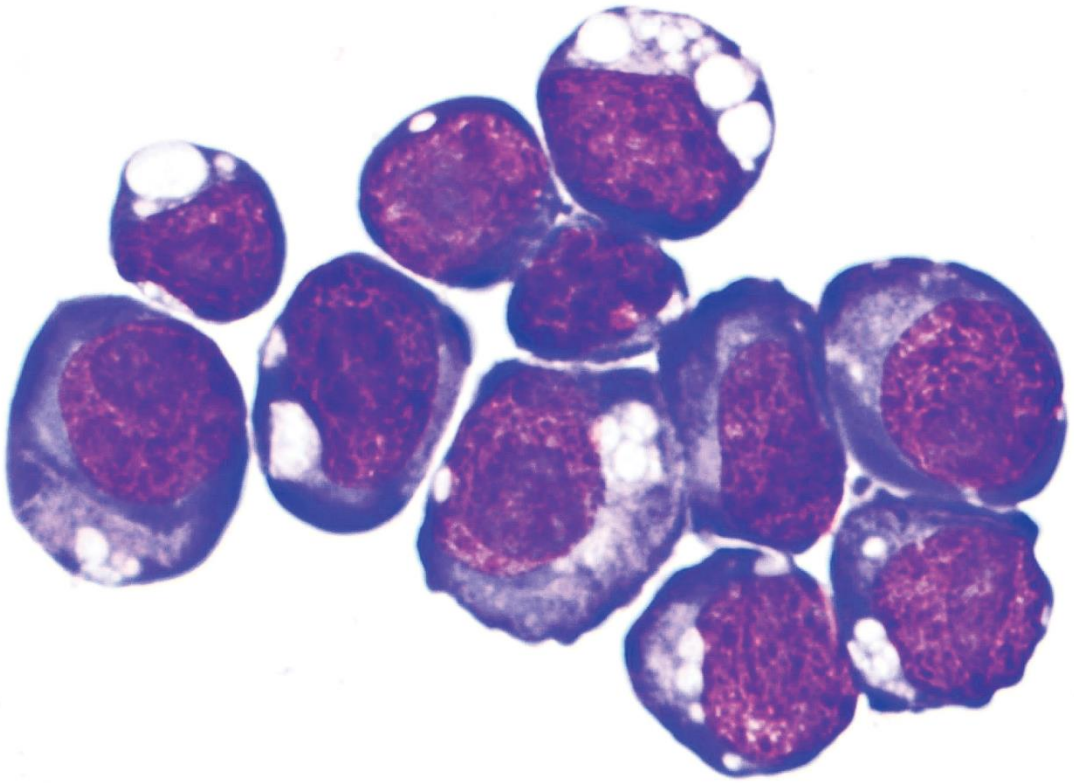
Lenalidomide plus Dexamethasone for High-Risk Smoldering Multiple Myeloma



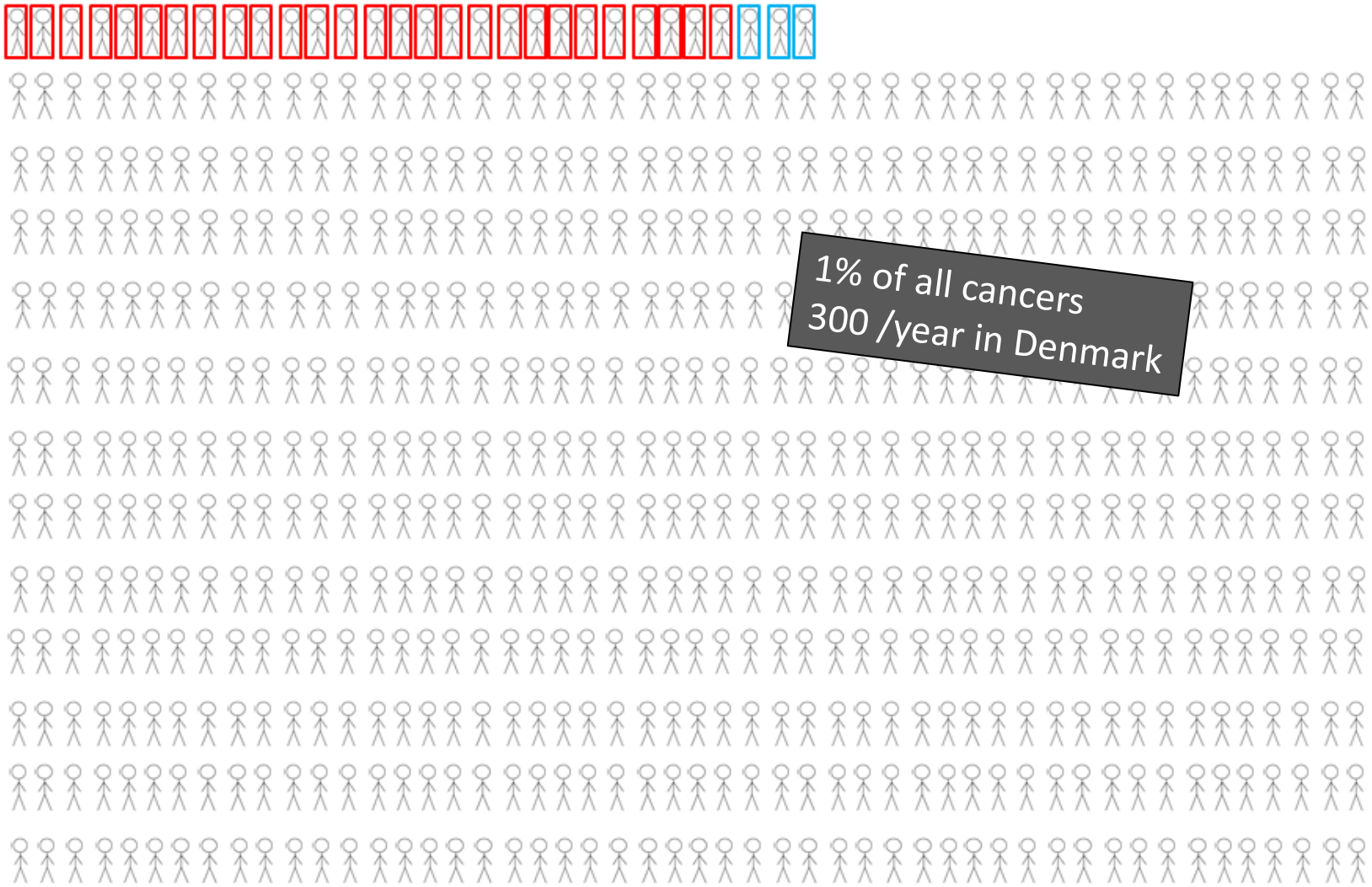
Mateos N Engl J Med. 2013 Aug 1;369(5):438-47

Symptomatic / Active Multiple Myeloma

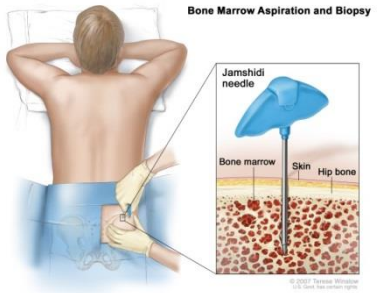
Multiple myeloma



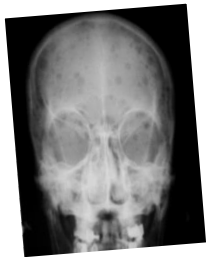
Multiple Myeloma



Multiple myeloma



10% ≤ clonal plasma cells in the bone marrow



myeloma defining event /CRAB present

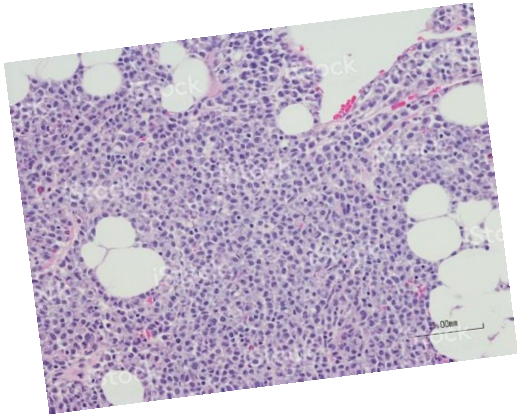
Rajkumar Lancet Oncol. 2014 Nov;15(12):e538-48.

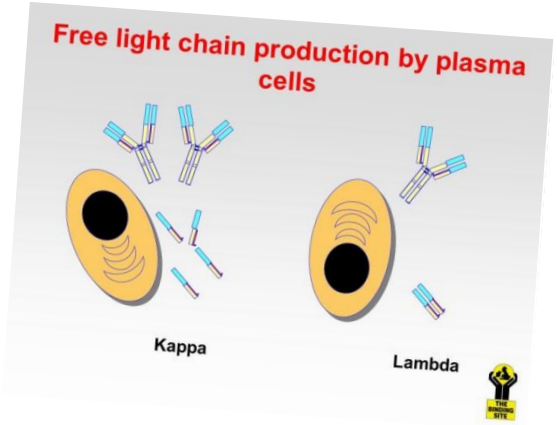
Multiple myeloma

Presence of a biomarker associated with inevitable progression to end-organ damage

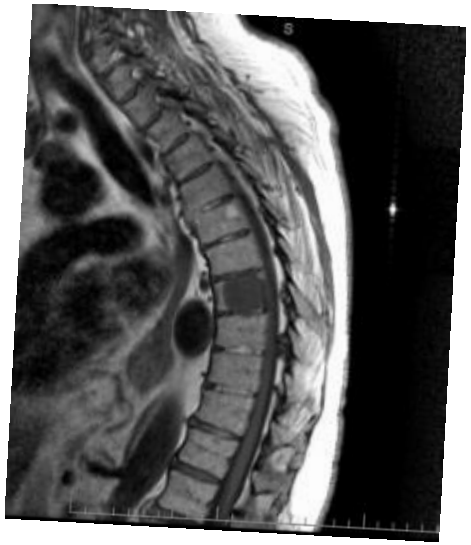
involved uninvolved FLC ratio ≥ 100

≥ 60% clonal plasma cells in the bone marrow



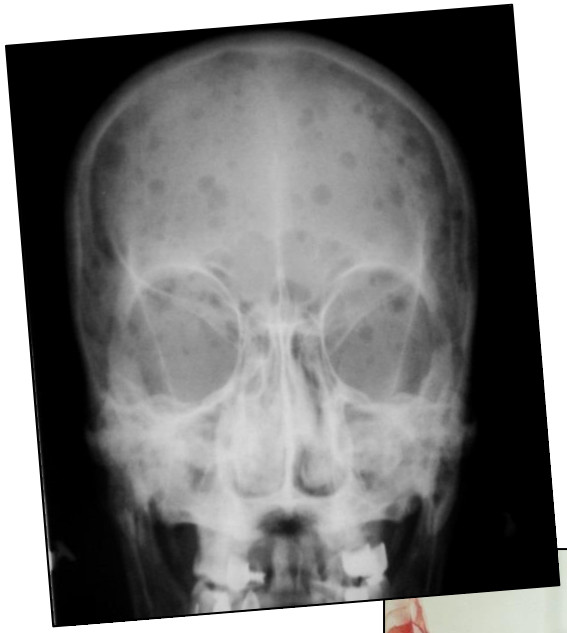


MRI with ≥ focal lesion

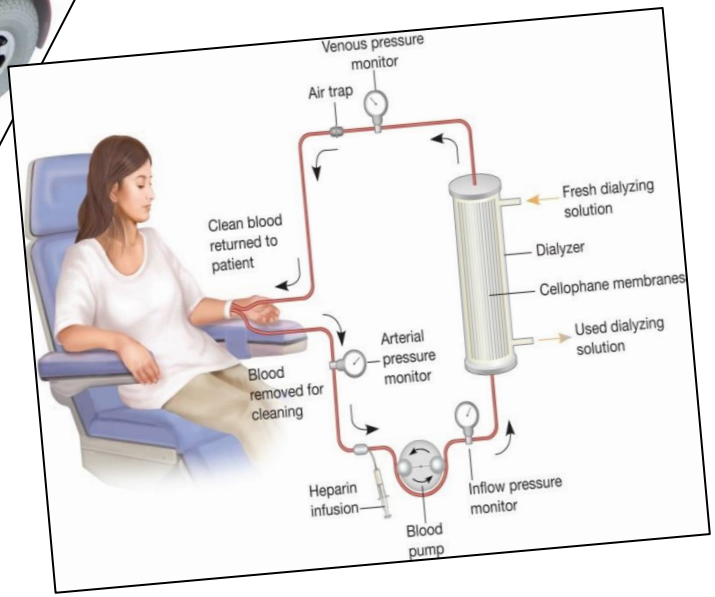


Rajkumar Lancet Oncol. 2014 Nov;15(12):e538-48.

CRAB




www. enjoycare.com


Venous pressure monitor
Air trap
Fresh dialyzing solution
Clean blood returned to patient
Dialyzer
Cellophane membranes
Used dialyzing solution
Arterial pressure monitor
Blood removed for cleaning
Heparin infusion
Inflow pressure monitor
Blood pump

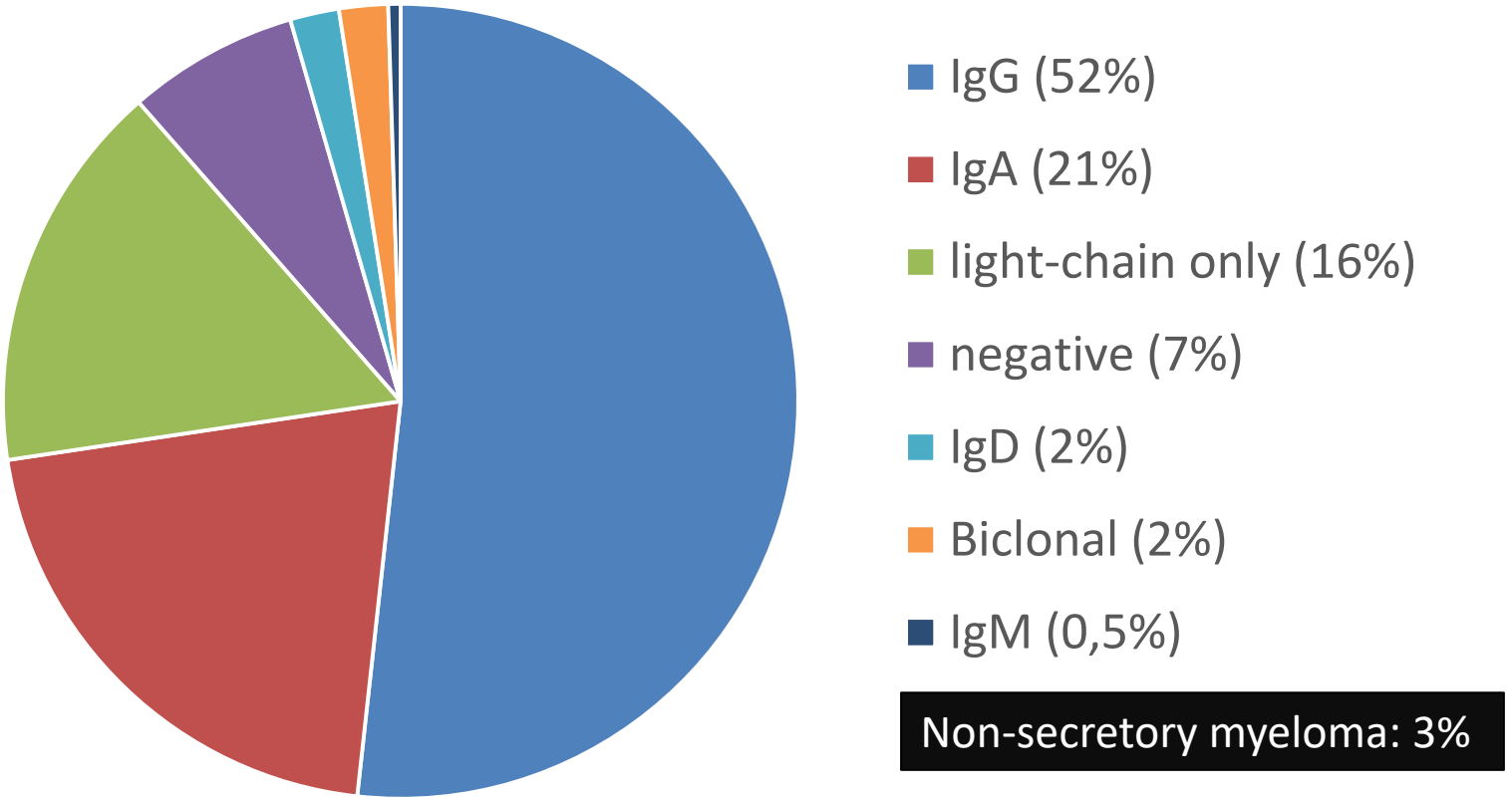
symptome	present at diagnosis
bone pain	58%
fatigue / generalized weakness	32%
weight loss	24%

M-protein serum/urine	93%
lytic lesions on X-ray	80%

pathologic finding	present at diagnosis
anemia	73%
renal failure	20-48%
hypercalcemia	28%
Haemodialysis dependent acute renal failure	3-9%
cord compression	5%
infection	↑

Kyle Mayo Clin Proc. 2003 Jan;78(1):21-33.

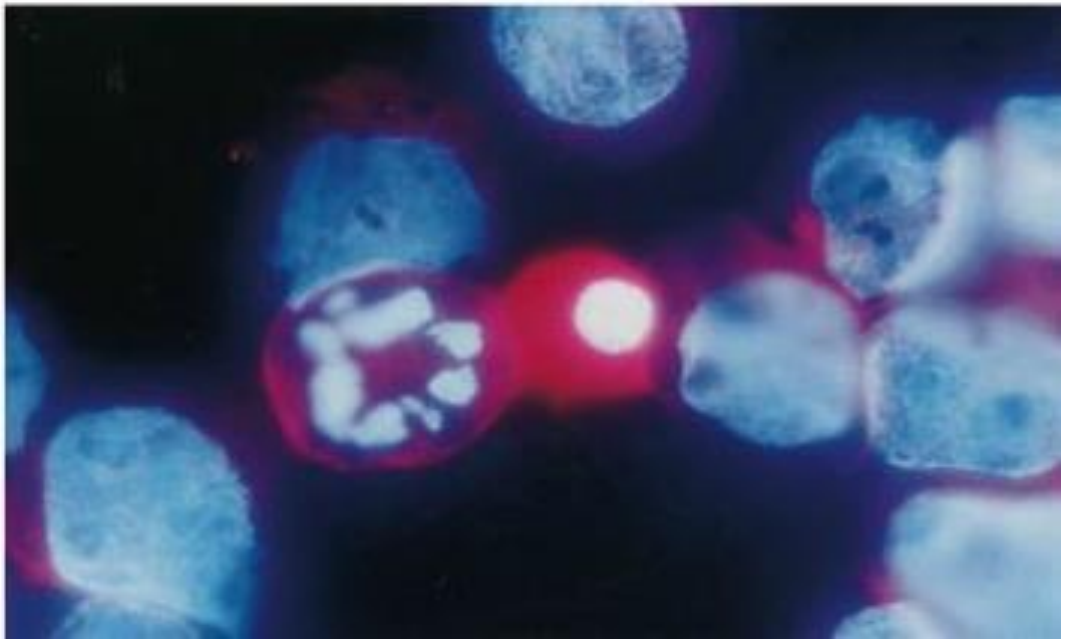
Serum monoclonal proteins



Kyle Mayo Clin Proc. 2003 Jan;78(1):21-33.

Anemia

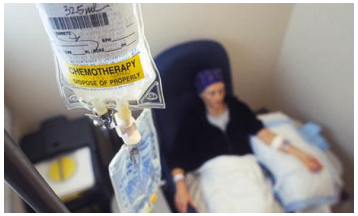
cytotoxic mechanisms exerted by myeloma cells
chronic inhibition of erythropoiesis



Silvestris et al. Blood. 2002 Feb 15;99(4):1305-13

Anemia: treatment

1. anti-myeloma treatment



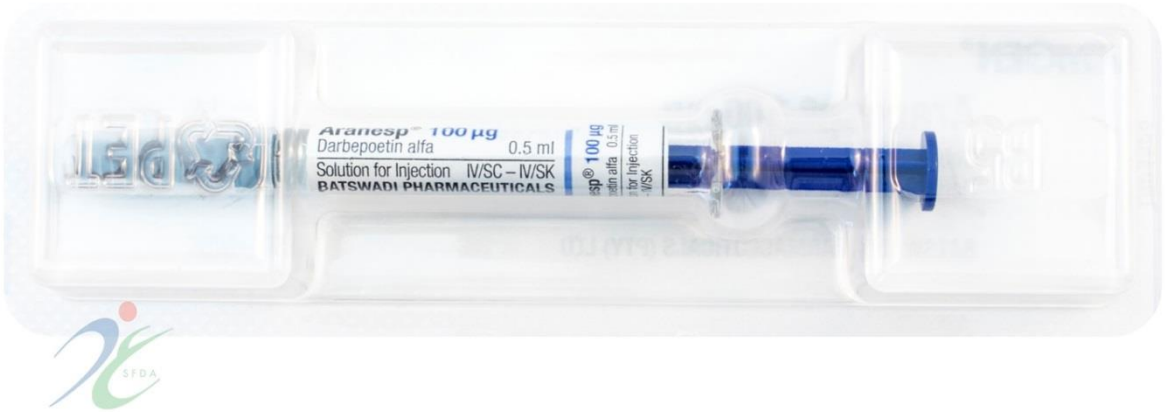
2. Stimulation of red blood cell production

3. Transfusion of red blood cells

Kyle et al. Mayo Clin Proc. 2003 Jan;78(1):21-33.

Anemia: treatment

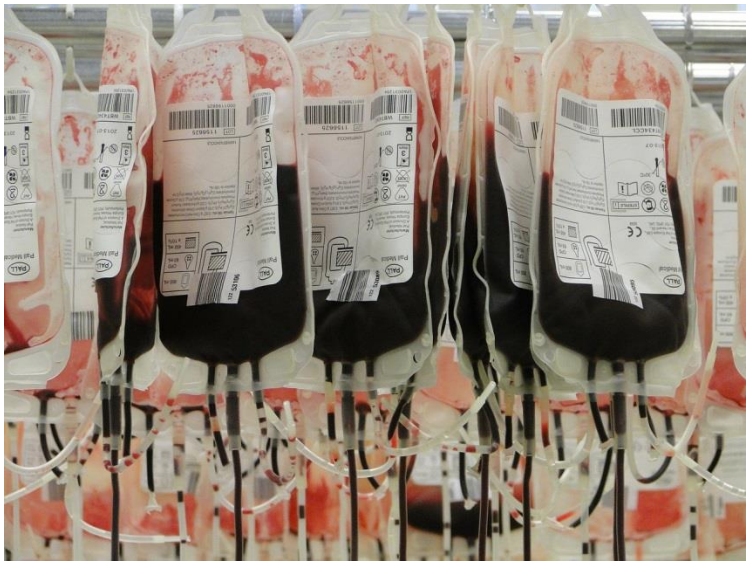
recombinant human erythropoietin (EPO)
increasees of hemoglobin levels over an extended time without the risks of blood transfusions



Ludwig et al. N Engl J Med. 1990 Jun 14;322(24):1693-9.

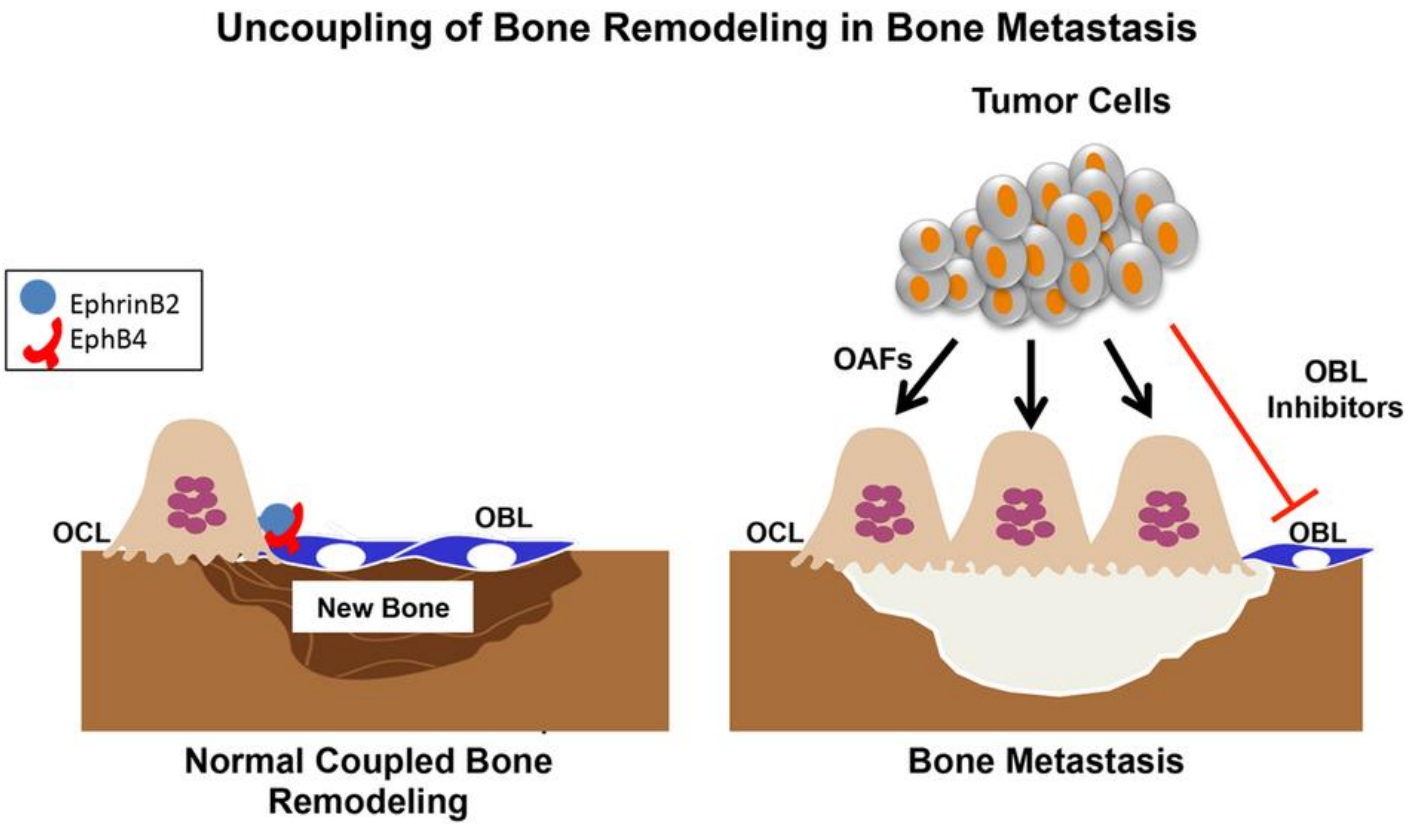
Anemia: treatment

risks of viral infections
iron overload
allergic reactions
sensitization to histocompatibility antigens



Ludwig et al. N Engl J Med. 1990 Jun 14;322(24):1693-9.

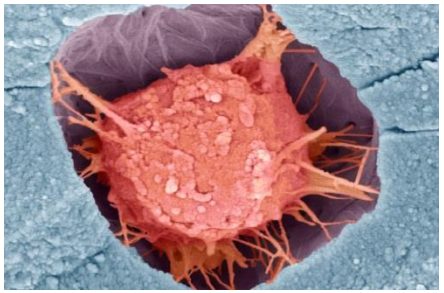
Bone disease



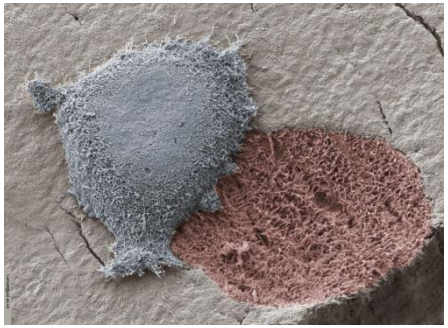
Roodman et al. Leukemia. 2009 Mar;23(3):435-41.

Bone disease

Decreased osteoblast activity



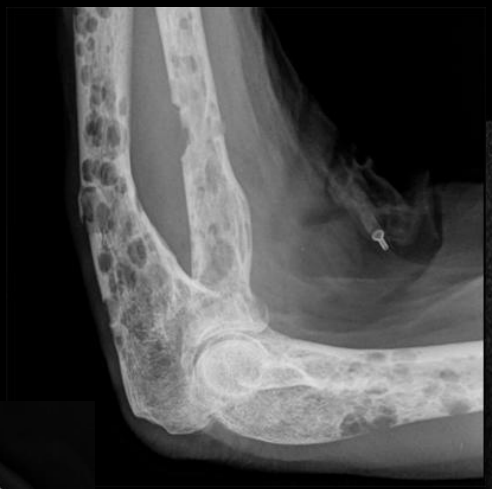
Increased osteoclast activity

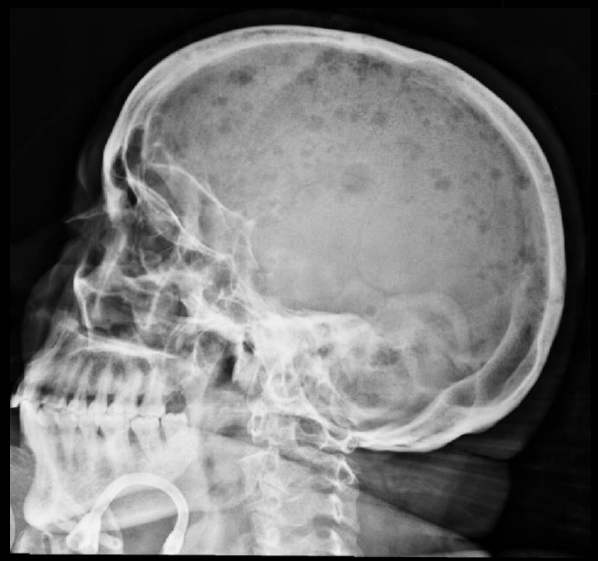


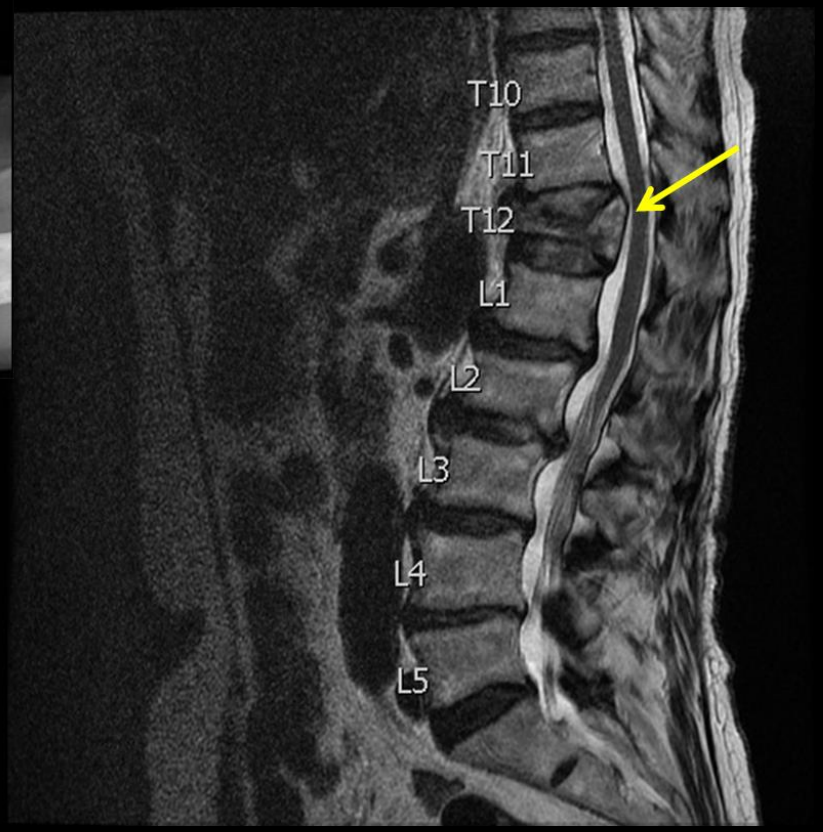
Roodman et al. Leukemia. 2009 Mar;23(3):435-41.

Bone disease

Lytic lesions
Severe bone pain
Pathologic fractures
Hypercalcemia

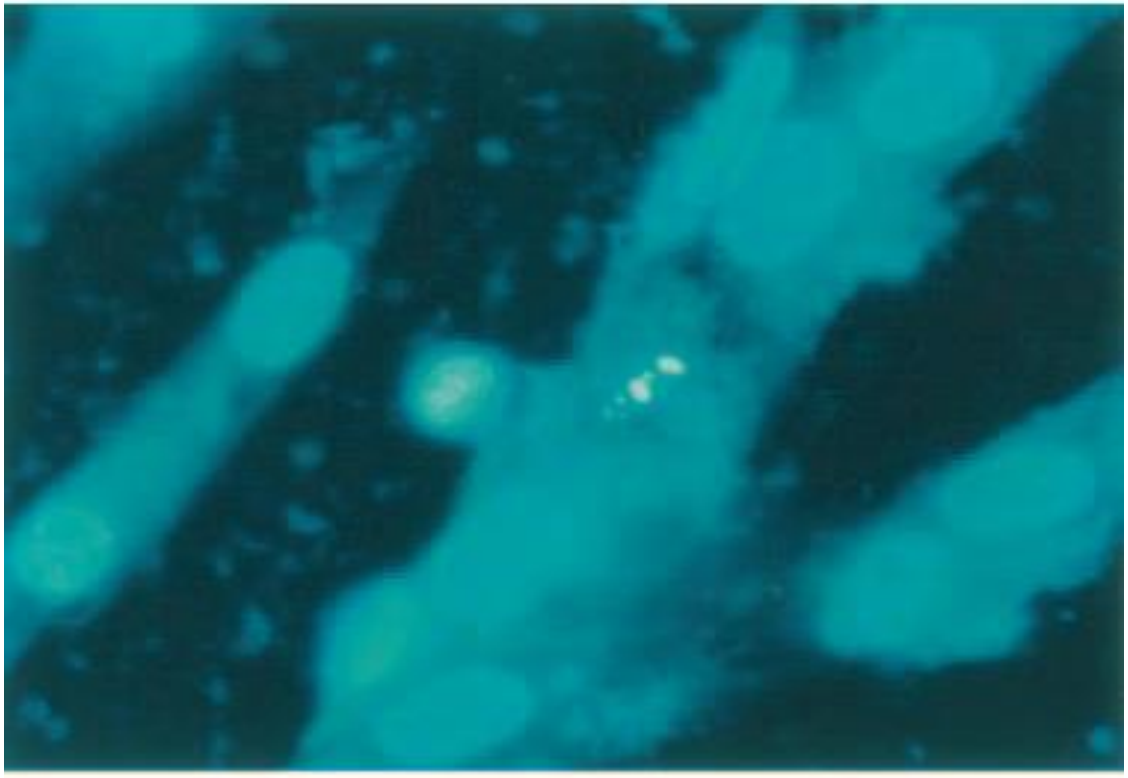






Bone disease

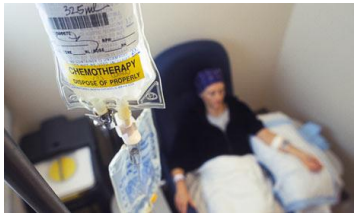
adhesion of the myeloma cell to the osteoblast undergoing nuclear fragmentation



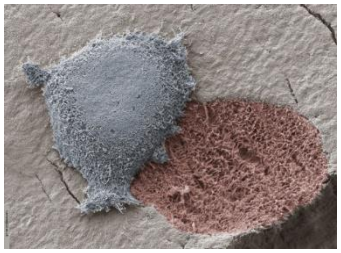
Silvestris et al. Br J Haematol. 2004 Aug;126(4):475-86.

Bone disease: treatment

1. anti-myeloma treatment



2. inhibition of bone resorption



Roodman et al. Leukemia. 2009 Mar;23(3):435-41.

Bone disease: treatment

1

anti-myeloma treatment

Bortezomib
Increases osteoblast activity

Lenalidomide
Inhibits osteoclast formation

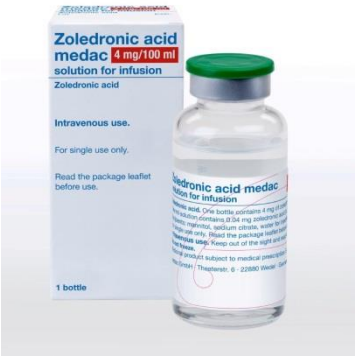
Roodman et al. Leukemia. 2009 Mar;23(3):435-41.

Bone disease

2

inhibition of bone resorption

Zolendronic acid (Zometa)



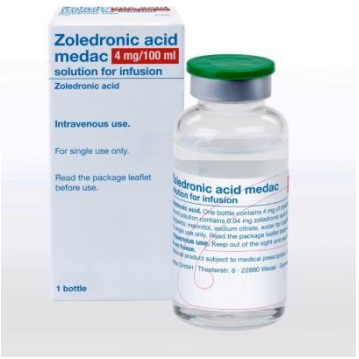
Denosumab

Roodman et al. Leukemia. 2009 Mar;23(3):435-41.

Bone disease: treatment

Zolendronic acid (Zometa)

i.v. infusion every 3-4 weeks

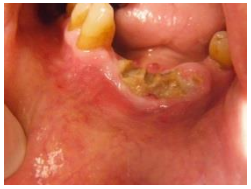


releives pain

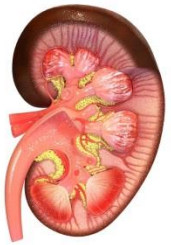
decreases incidence of fractures

extends overall survival

osteonecrosis of the jaw (4%)



acute renal failure (6%)



Morgan Lancet Oncol. 2011 Aug;12(8):743-52.

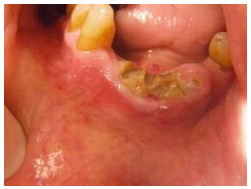
Bone disease

Denosumab

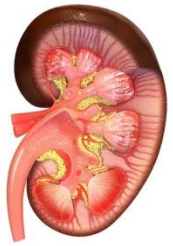
s.c. injection

Non-iferior to Zometa

Similar incidence of osteonecrosis of the jaw 1.1% (at 3 years)



Similar incidence of renal failure (2.3%)

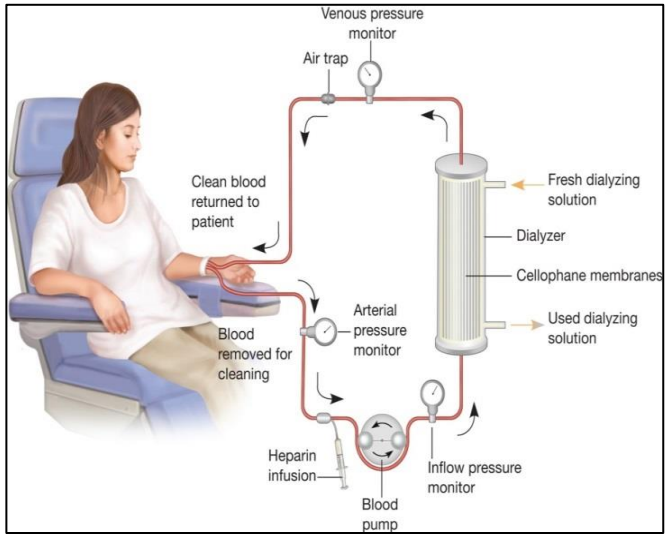


Henry J Clin Oncol. 2011 Mar 20;29(9):1125-32.

Renal disease

20-50% of patients at the time of diagnosis

Hemodialysis dependent acute renal failure occurs in 3-9% at diagnosis



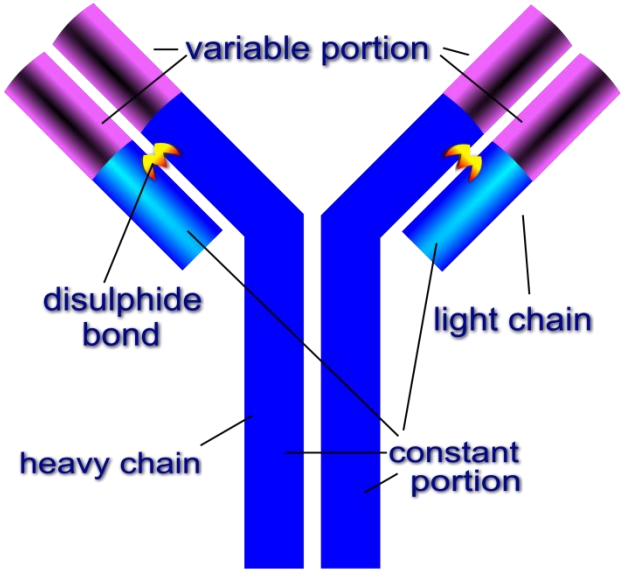
dialysis dependent end-stage renal disease
life expectancy: 26 months

Knudsen Eur J Haematol. 1994 Oct;53(4):207-12.
Gonsalves Blood Cancer J. 2015 Mar 20;5:e296.
Vonesh Kidney Int. 2004 Dec;66(6):2389-401.
Bloembergen J Am Soc Nephrol. 1995 Aug;6(2):184-91.

Renal disease

M-protein related: 73%

Non-M-protein related: 27%



Hypercalcemia

Volume depletion

Infection

Nephrotoxic drugs

Hyperuricemia

Intravenous contrast media

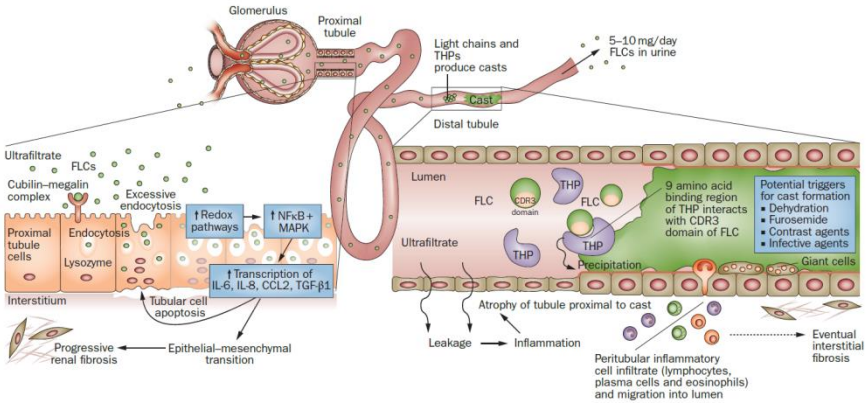
Hypertensive kidney disease

Diabetic kidney disease

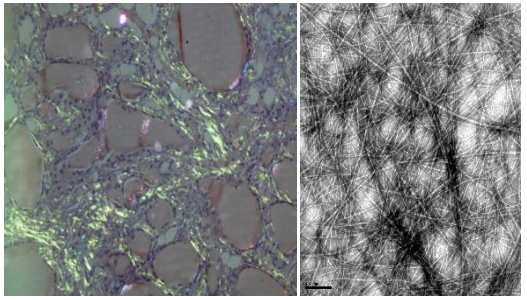
Nasr Am J Kidney Dis. 2012 Jun;59(6):786-94.
Montseny Nephrol Dial Transplant. 1998 Jun;13(6):1438-45.

M-protein related renal disease

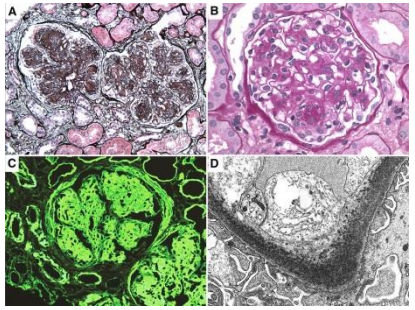
Cast nephropathy
(33-41%)



AL
Amyloidosis
(21-30%)



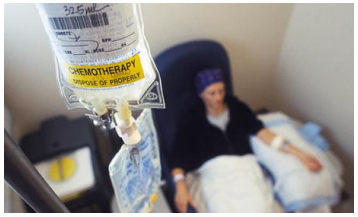
Monoclonal immunoglobulin deposition disease
(19-22%)



Nasr Am J Kidney Dis. 2012 Jun;59(6):786-94.
Montseny Nephrol Dial Transplant. 1998 Jun;13(6):1438-45.
Hutchison Nat Rev Nephrol. 2011 Nov 1;8(1):43-51.

Renal disease: treatment

1. anti-myeloma treatment



2. artificial removal of monoclonal free light chains (controversial)

Renal disease: MYRE trial

98 Patients with cast nephropathy

High cut-off hemodialysis (HCO-HD)

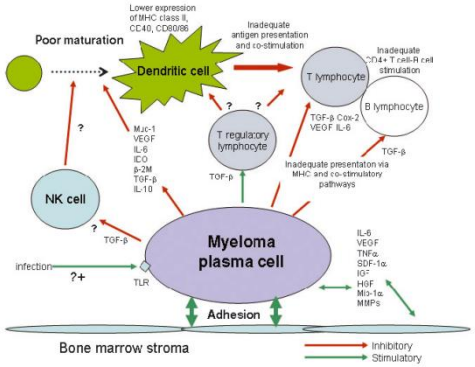
bortezomib- dexamethasone (cyclophosphamide reinforcement)

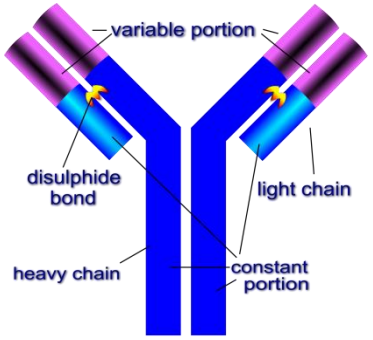
End-point	HCO-HD	Standard HD
3 months HD independence	41%	33%
6 months HD independence	57%	35%
12 months HD independece	61%	37,5%
12 months survival	52%	35%

Bridoux Blood 2016 128:978

Infections

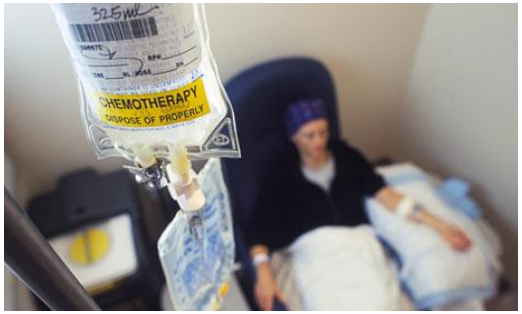
complex immunodeficiency





Hypogammaglobulinemia and decreased vaccination responses

therapy-related immunosuppression



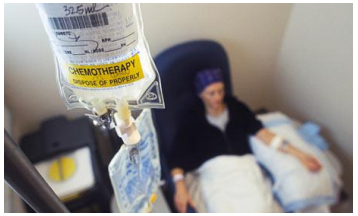
advanced age and co-morbidities

Blimark Haematologica. 2015 Jan; 100(1): 107–113.
Nucci Clin Infect Dis. 2009 Oct 15;49(8):1211-25.
Pratt Br J Haematol. 2007 Sep;138(5):563-79.

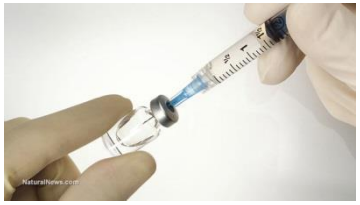
Kastritis Leukemia. 2014 Oct;28(10):2075-9.
Karlsson Clin Vaccine Immunol. 2016 Apr; 23(4): 379–385.
Rapezzi Eur J Haematol. 2003 Apr;70(4):225-30.

Infections

1. anti-myeloma treatment



2. vaccination



3. immunoglobulin replacement therapy

4. prophylactic antibiotics

Pause

Questions?

Myelomatose behandling

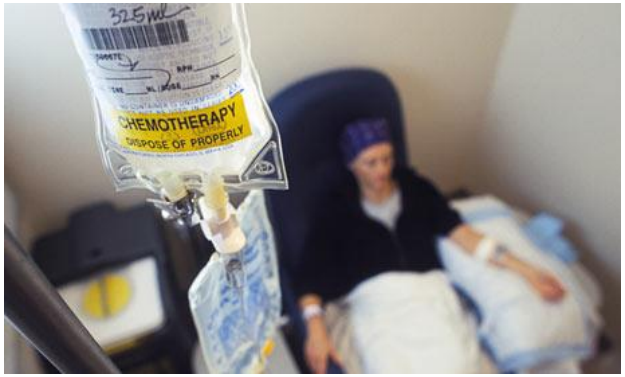
Dansk Myelomatose Forening

Konference, 11. marts 2017

Anti-myeloma treatment

Incurable disease

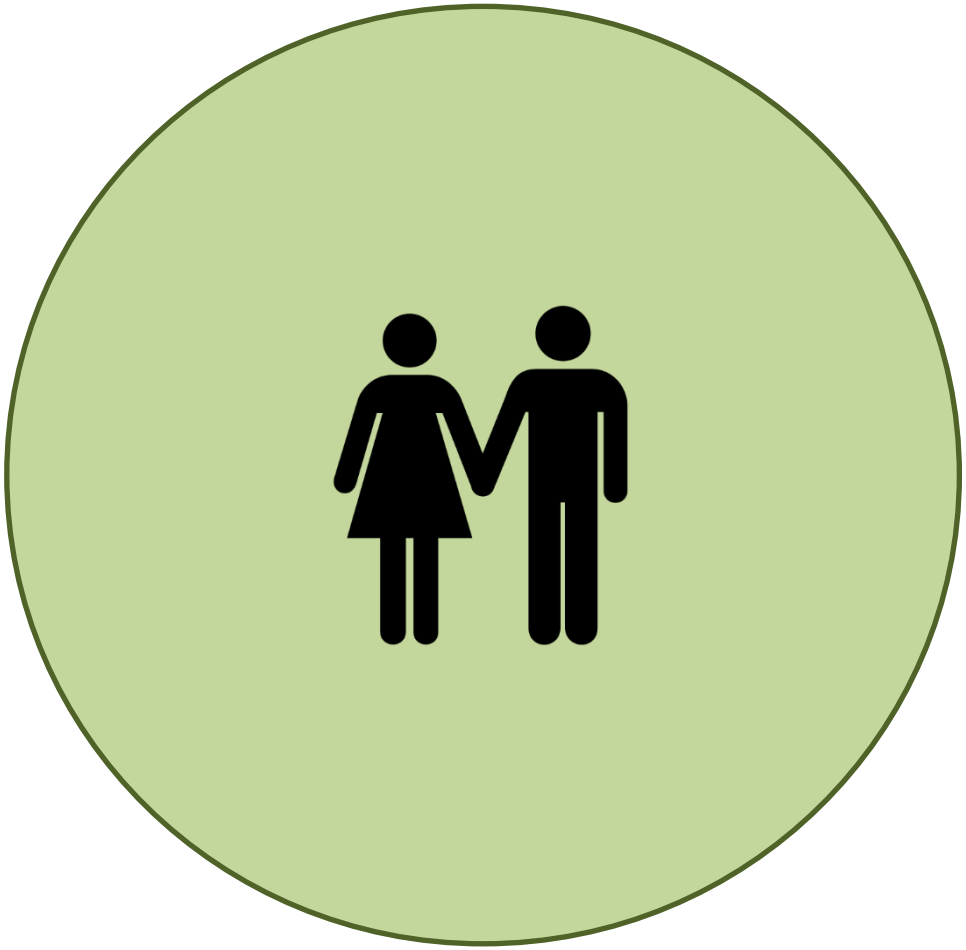
treatment



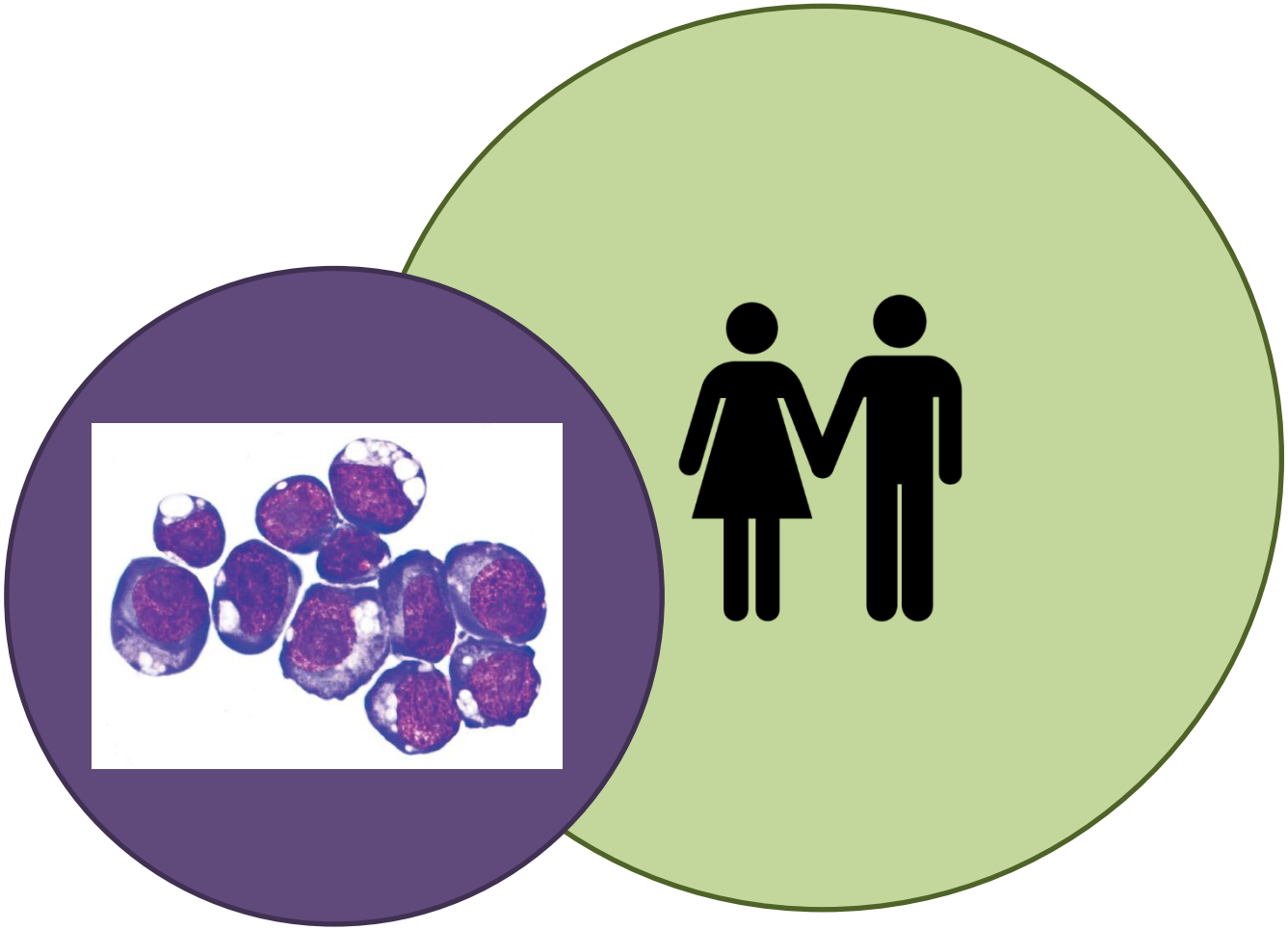
longer survival

side effects

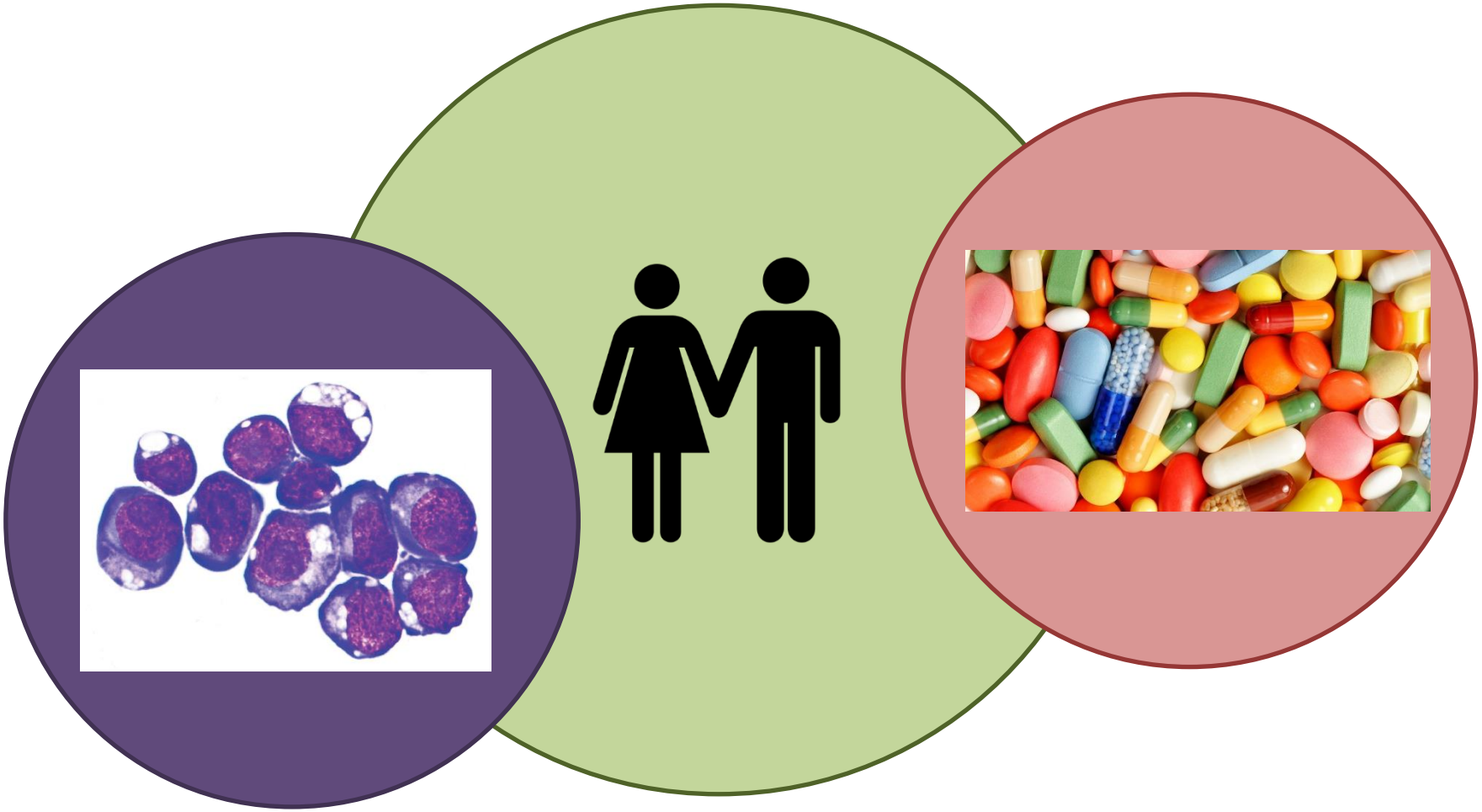
Anti-myeloma treatment



Anti-myeloma treatment

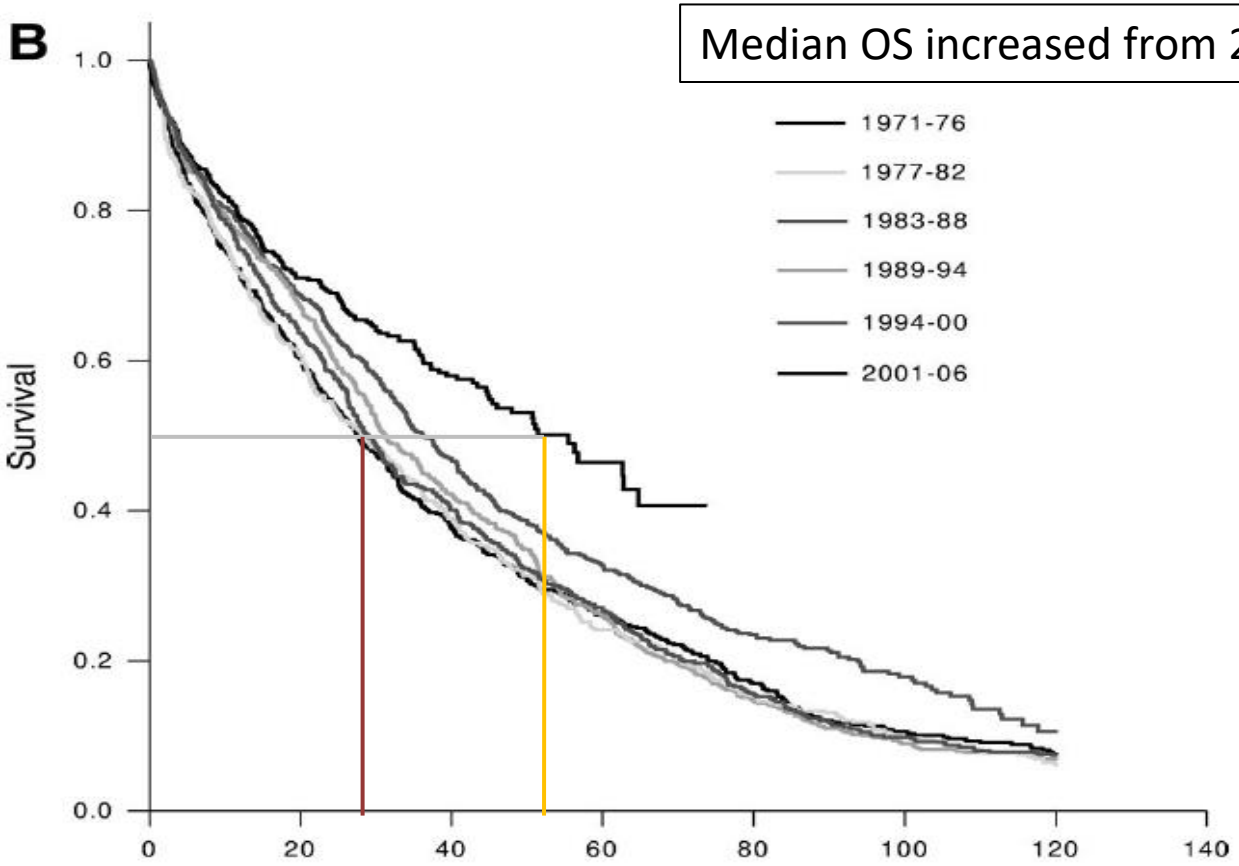


Anti-myeloma treatment



Anti-myeloma treatment outline

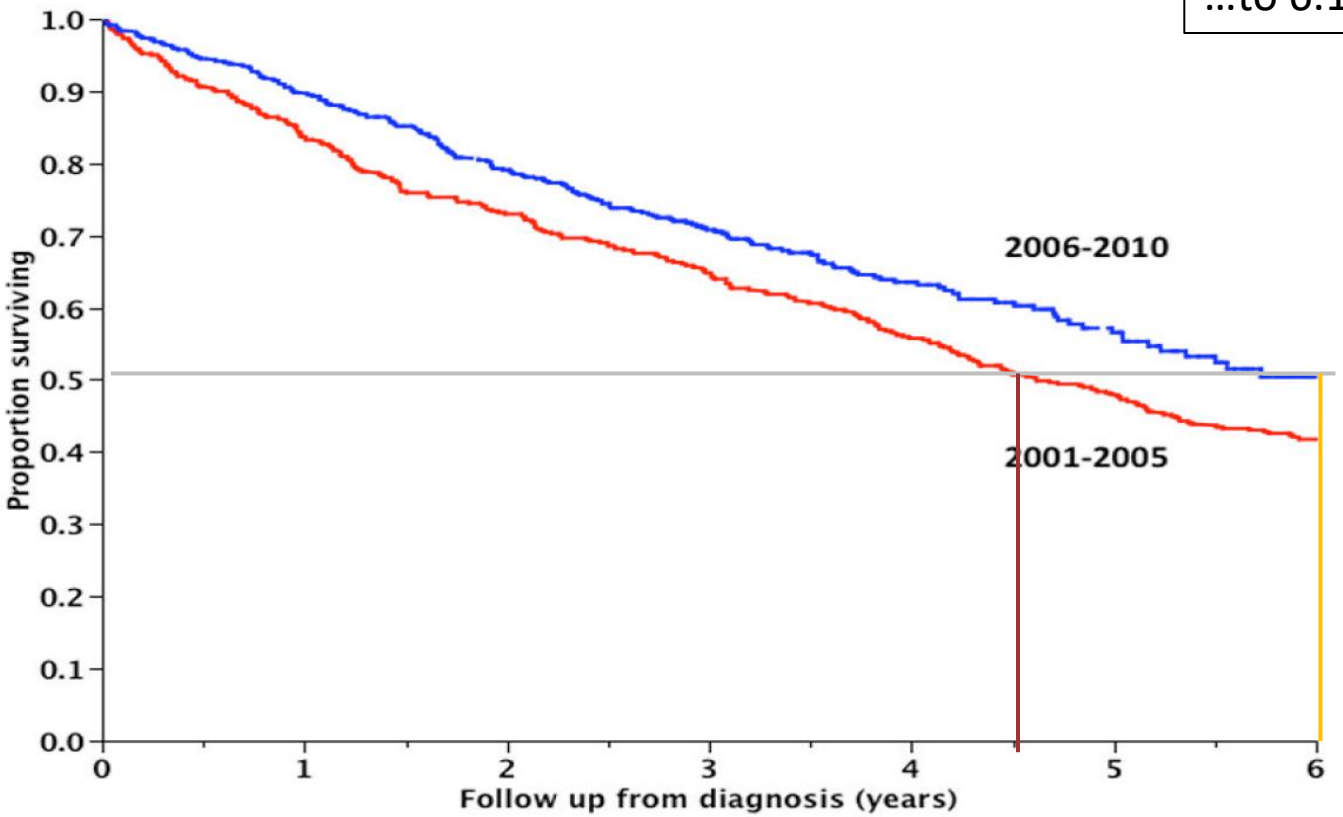
Median OS increased from 29.9 months…



Kumar, Blood. 2008;111(5):2516–20.

Anti-myeloma treatment outline

Figure 1A



…to 6.1 years.

Kumar, Leukemia. 2014;28(5):1122–8.

Anti-myeloma treatment outline

"Chemotherapy":
Vincristine
Adriamycin
Melphalan

Steroids:
Prednisolone
Dexamethasone

Anti-myeloma treatment outline

"Chemotherapy":
Vincristine
Adriamycin
Melphalan

Steroids:
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Dexamethasone

"Novel agents"

IMIDS:
Thalidomide
Lenalidomide (Revlimid)

Proteasome inhibitor
Bortezomib (Velcade)

Anti-myeloma treatment outline

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Vincristine
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Thalidomide
Lenalidomide (Revlimid)

Proteasome inhibitor
Bortezomib (Velcade)

2nd generation IMID:
Pomalidomide

2nd generation proteasome inhibitor:
Carfilzomib

Oral proteasome inhibitor:
Ixazomib

Anti-myeloma treatment outline

"Chemotherapy":
Vincristine
Adriamycin
Melphalan

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Prednisolone
Dexamethasone

"Novel agents"

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Bortezomib (Velcade)

2nd generation IMID:
Pomalidomide (Imnovid)

2nd generation proteasome inhibitor:
Carfilzomib (Kyprolis)

Oral proteasome inhibitor:
Ixazomib (Ninlaro)

Histone deacetylase inhibitors:
Panobinostat (Farydak)

Anti-myeloma treatment outline

"Chemotherapy":
Vincristine
Adriamycin
Melphalan

Steroids:
Prednisolone
Dexamethasone

"Novel agents"

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Thalidomide
Lenalidomide (Revlimid)

Proteasome inhibitor
Bortezomib (Velcade)

2nd generation IMID:
Pomalidomide (Imnovid)

2nd generation proteasome inhibitor:
Carfilzomib (Kyprolis)

Oral proteasome inhibitor:
Ixazomib (Ninlaro)

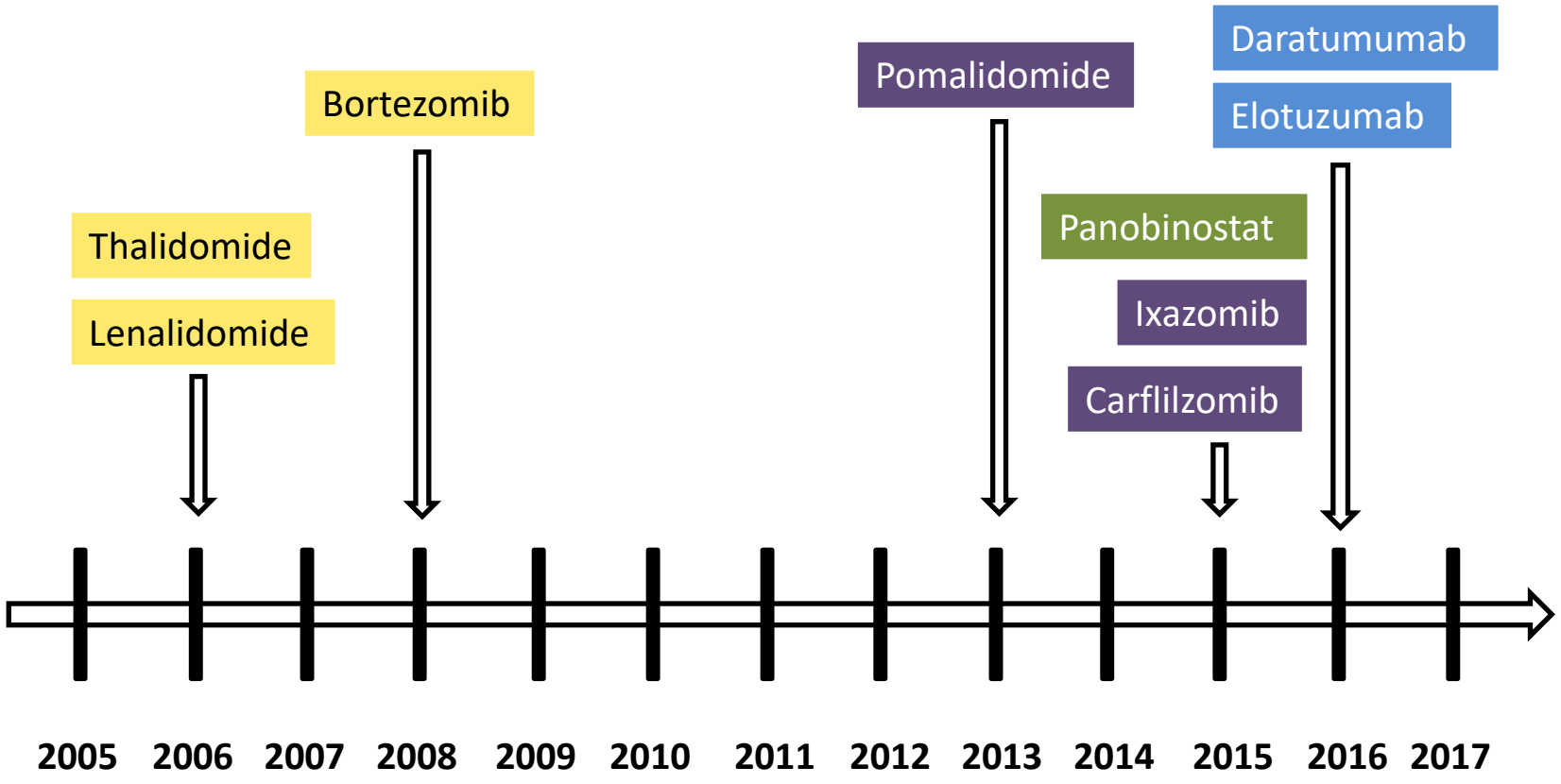
Histone deacetylase inhibitors:
Panobinostat (Farydak)

Monoclonal antibodies:

CD38:
Daratumumab (Darzalex)

SLAMF7:
Elotuzumab (Empliciti)

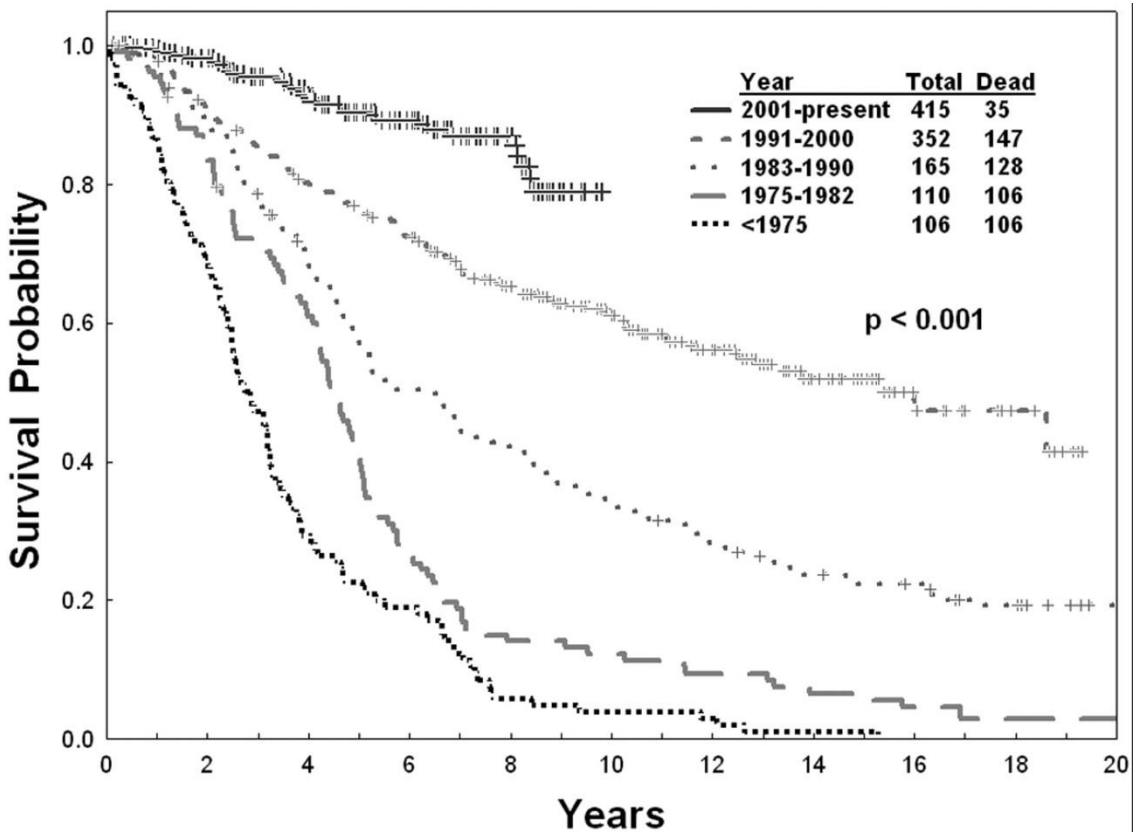
Anti-myeloma treatment outline



www.fda.gov

Anti-myeloma treatment

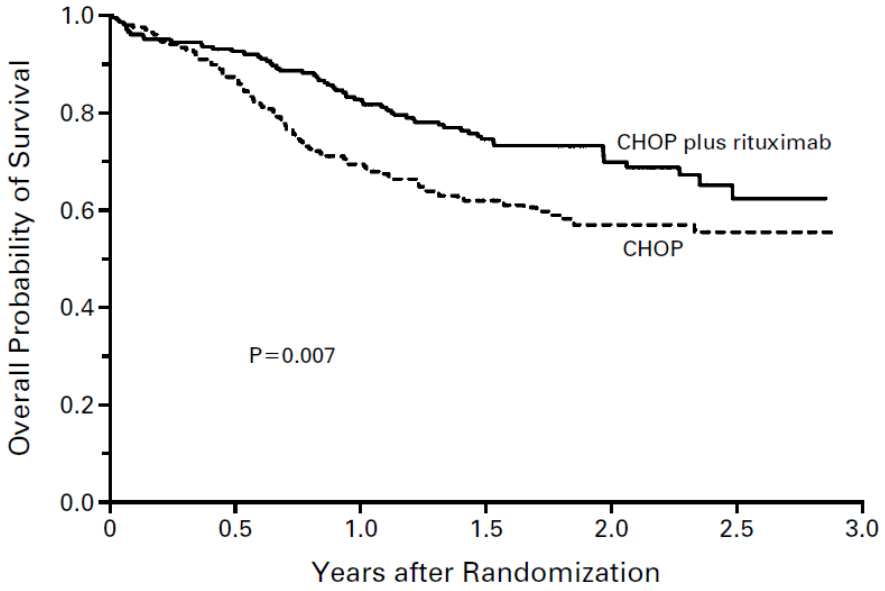
The goal: chronic myeloid leukemia since the introduction of imatinib (Gleevec) in 2001



Kantarjian Blood. 2012 Mar 1;119(9):1981-7.

Anti-myeloma treatment

The goal: Rituximab for diffuse large-B-cell lymphoma



No. at Risk						
CHOP plus rituximab	202	187	167	118	64	21
CHOP	197	171	136	96	58	16

Figure 2. Overall Survival among 399 Patients Assigned to Chemotherapy with Cyclophosphamide, Doxorubicin, Vincristine, and Prednisone (CHOP) or with CHOP plus Rituximab.

Coiffier N Engl J Med. 2002 Jan 24;346(4):235-42.

Anti-myeloma treatment

Dexamethasone

Anti-myeloma treatment

Melphalan

Anti-myeloma treatment

Thalidomide

Anti-myeloma treatment

Lenalidomide

Anti-myeloma treatment

Bortezomib

Anti-myeloma treatment

Pomalidomide

28 day cycles of pomalidomide on days 1–21

Anti-myeloma treatment

Panobinostat

3-week cycles of panobinostat 3 times per week for 2 out of 3 weeks

Anti-myeloma treatment

Carfilzomib

Anti-myeloma treatment

Ixazomib

28-day cycles, oral ixazomib on days 1, 8, and 15

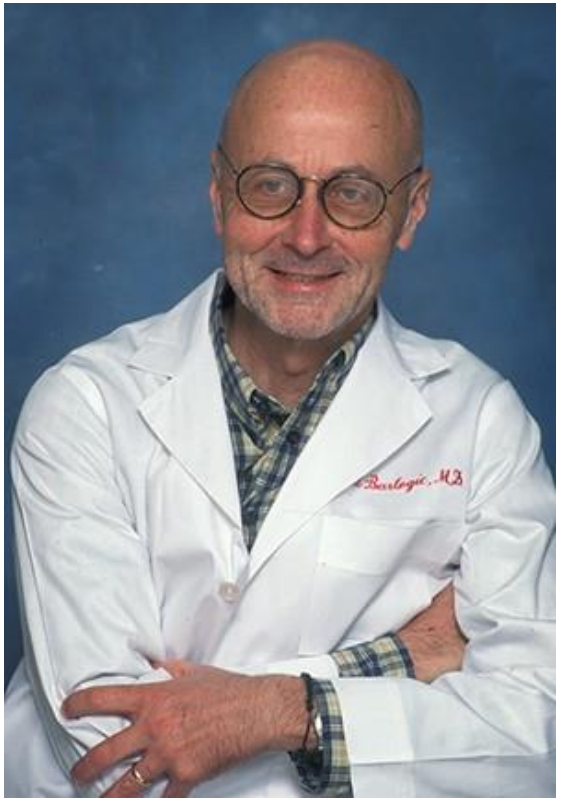
Anti-myeloma treatment

Elotuzumab

Anti-myeloma treatment

Daratumumab

Anti-myeloma treatment outline



High-dose melphalan + autologous stem cell transplantation

"Total therapy"

induction

consolidation

maintenance

tandem transplantation

Barlogie Blood. 1986 May;67(5):1298-301.

Total Therapy 1

Induction phase

Cycles 1-3, VAD

Cycle 4, HD-CTX

Cycle 5, EDAP

Transplantation pha

First transplanta

Second transp

Maintenance

Interferon

Total therapy 2

Induction

Cycle 1, VAD

Cycle 2, DCEP

Cycle 3, CAD

Cycle 4, DCEP

Transplantation

First transplantation

Second transplantation

Consolidation

Randomized arm A: DCEP

Randomized arm B

DCEP*

CAD*

DPACE

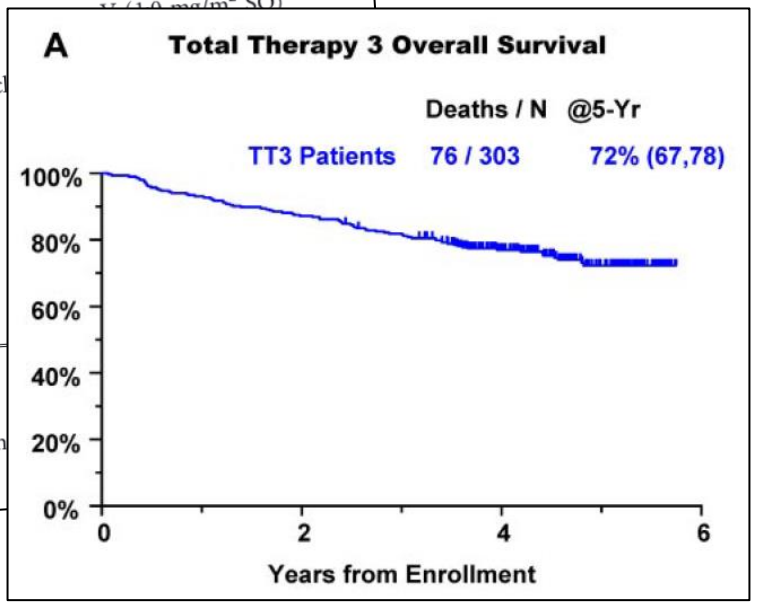
DEX

Maintenance

Interferon

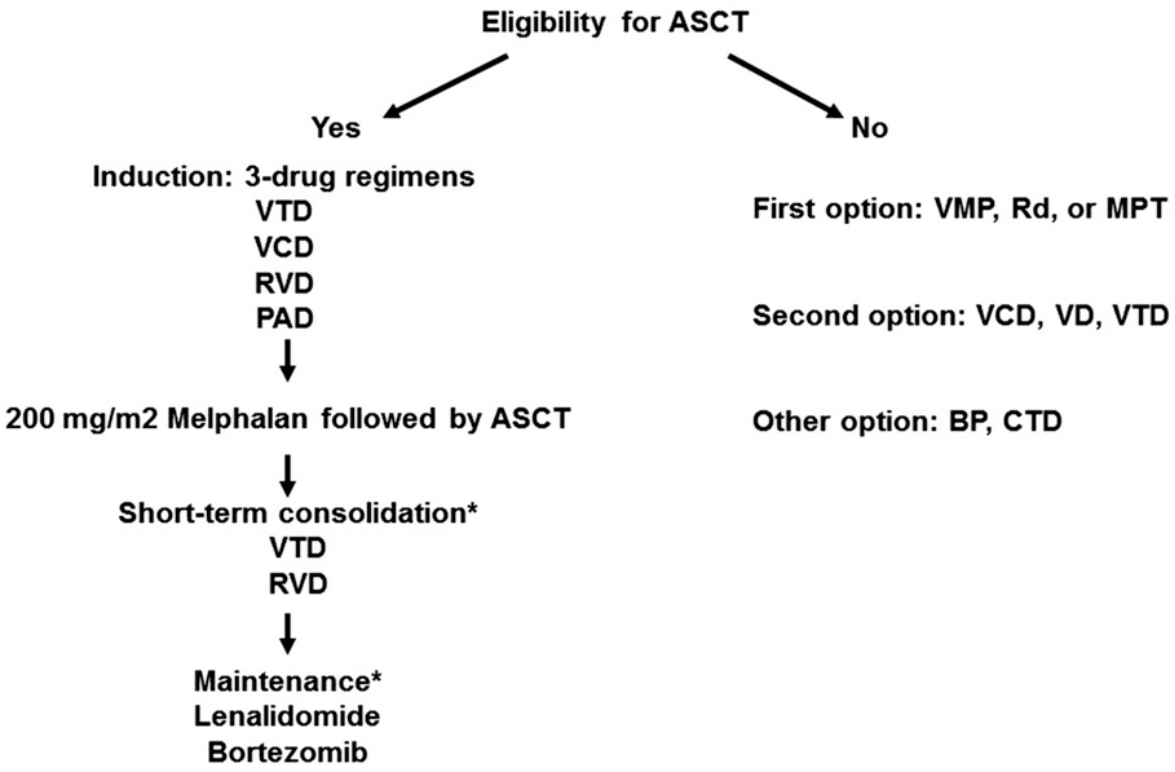
Table I. Total therapy 3 schema.

Induction (2 cycles ≤8 weeks apart)	Cycle 1 with PBSC collection VTD-PACE	Inte reco
	V (1·0 mg/m² SQ) day 1*,4,8,11 T (200 mg/d p.o.) day 4–7 D (40 mg/d p.o.) day 4–7 P (10 mg/m²/d) day 4–7 A (10 mg/m²/d) day 4–7 C (400 mg/m²/d) day 4–7 E 40 mg/m²/d) day 4–7	D (2 day T(5C
Transplant (>2 months apart but not >6 months apart)	1st transplant†	
	MEL (200 mg/m²)	
Consolidation (if platelets <50 × 10⁹/l, proceed to year 1 of maintenance)	Cycle 1 VTD-PACE	
Cycle 1: 6 weeks to 4 months after last transplant Cycle 2: 2–4 months after cycl		
Maintenance		
Year 1: 1–4 months after con		



Anti-myeloma treatment outline

Figure 1. Summary of frontline therapy. Asterisk indicates optional. BP, bendamustine-prednisone; CTD, cyclophosphamide-thalidomide-dexamethasone; MPT, melphalan-prednisone-thalidomide; Rd, lenalidomide and low-dose dexamethasone; VCD, bortezomib-cyclophosphamide-dexamethasonemide; VMP, bortezomib-melphalan-prednisone.



Moreau Blood. 2015 May 14;125(20):3076-84.

Anti-myeloma treatment dilemmas

Table 3. Risk stratification and possible therapeutic questions within each risk categories

	High-risk	*Standard-risk*	*Low-risk*
Parameters	ISS II/III and t(4;14)[a] or 17p13 del	Others	ISS I/II and absence of t(4;14), 17p13 del and +1q21 and age <55 years
Median OS	2 years	7 years	>10 years
% Patients	20%	60%	20%
Therapeutic questions	There is a need for novel therapeutic approaches e.g. Allogeneic stem cell transplant or immune therapy approaches		Do these patients benefit from maintenance therapy? Is VGPR a good enough response in these patients, as they may revert to an MGUS state

Abbreviations: ISS, International staging system; MGUS, monoclonal gammopathy of undetermined significance; OS, overall survivalVGPR, very good partial response. [a]Survival of t(4;14) patients is improved with the use of velcade-based therapy.

Chng Leukemia. 2014 Feb;28(2):269-77.

Anti-myeloma treatment dilemmas

Relapsed multiple myeloma, at least 3 prior lines of therapy, refractory to both an IMID and a proteasome inhibitor, exposed to alkylating agent

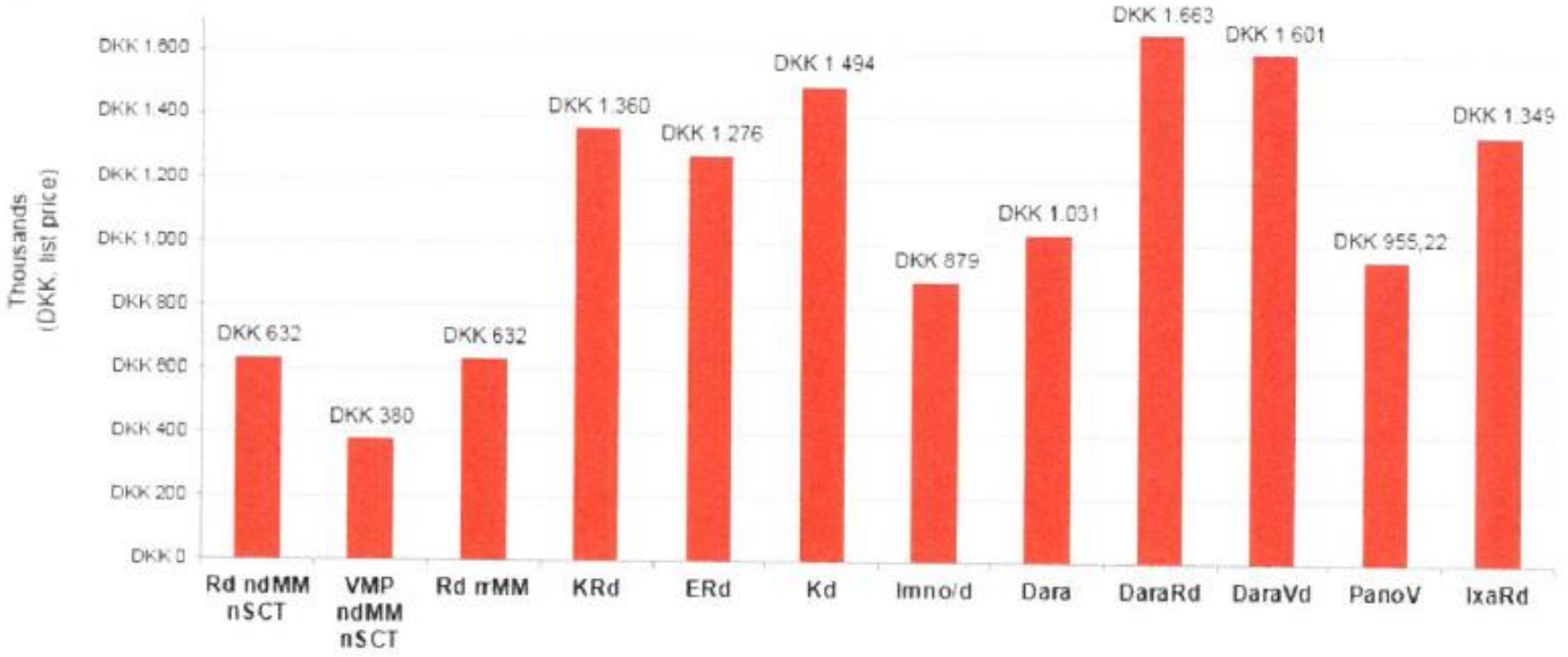
		100%	57%	52%	49%	61%
		Regimen (Post T0)				
Response		**1st**	**2nd**	**3rd**	**4th**	**5th**
Number of Subjects in Regimen	N	462	264	137	68	42
Overall Response (>=PR)	n (%)	153 (33.1)	65(24.6)	36(26.3)	20(29.4)	6(14.3)
CR	n (%)	6(1.3)	2(0.8)	2(1.5)	0(0.0)	0(0.0)
SCR	n (%)	2(0.4)	1(0.4)	1(0.7)	1(1.5)	0(0.0)
NCR/VGPR	n (%)	0(0.0)	1(0.4)	0(0.0)	0(0.0)	0(0.0)
VGPR	n (%)	44(9.5)	16(6.1)	8(5.8)	2(3.0)	1(2.4)
PR	n (%)	101(21.9)	45(17.1)	25(18.2)	17(25.0)	5(11.9)
MR	n (%)	3 (0.6)	0(0.0)	0(0.0)	0(0.0)	0(0.0)
SD	n (%)	159(34.4)	114(43.2)	53(38.7)	23(33.8)	17(40.5)
PD	n (%)	146(31.6)	85(32.2)	46(33.6)	26(38.2)	19(45.2)

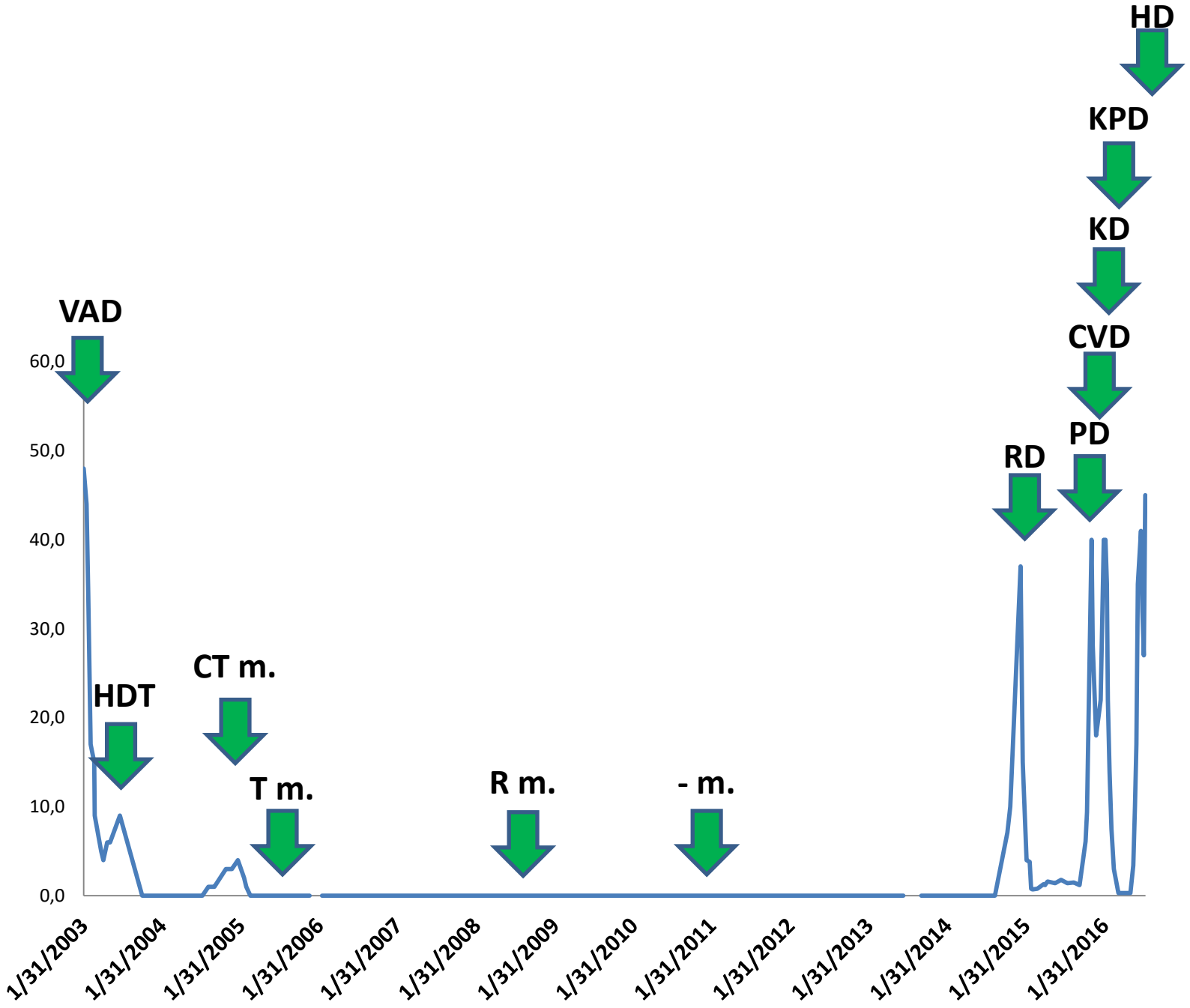
Median OS: 13 months

Median PFS: 5 months

Kumar, ASH Annual Meeting & Exposition 2016, abstract 4414

Anti-myeloma treatment dilemmas

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CVD
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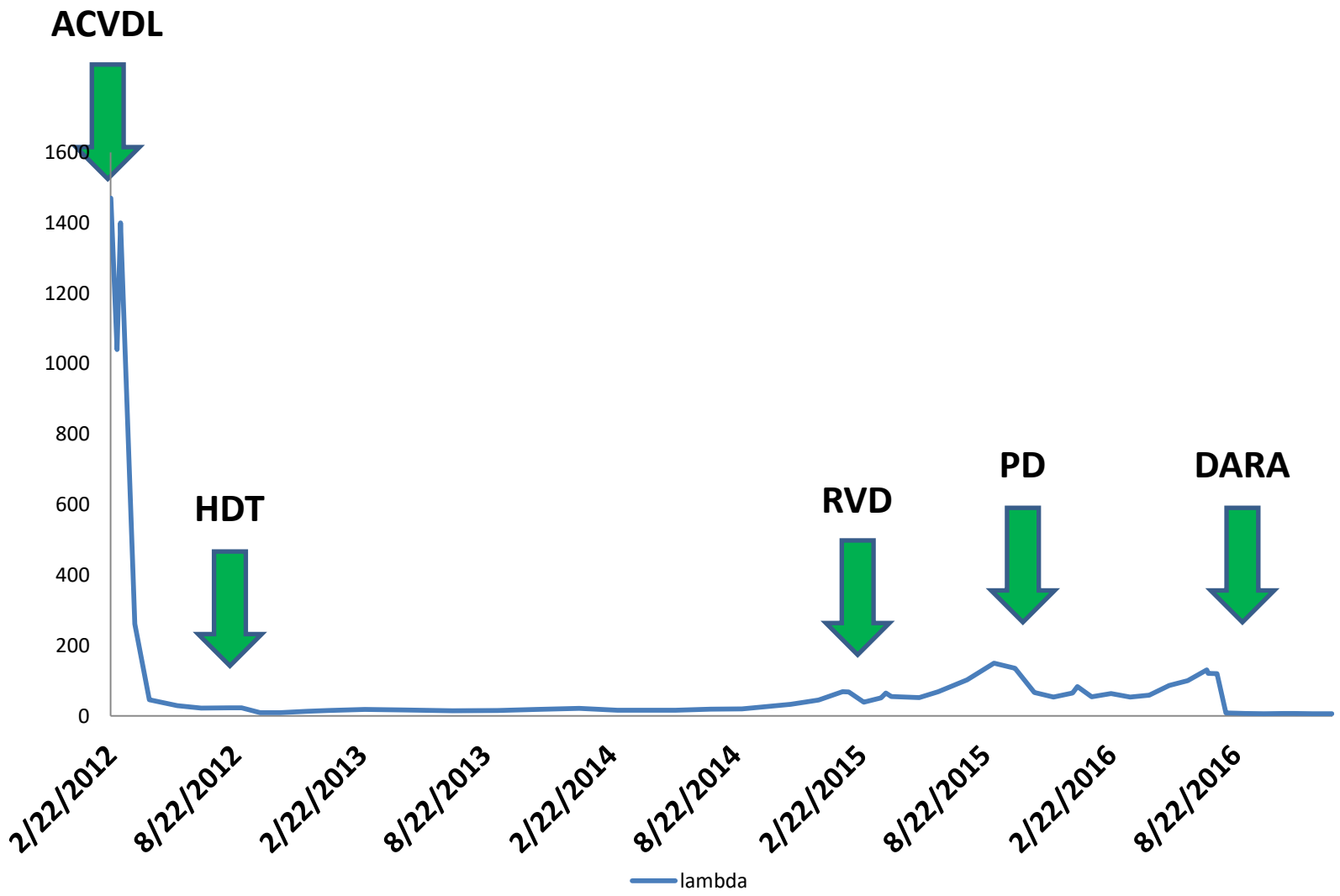
1/31/2016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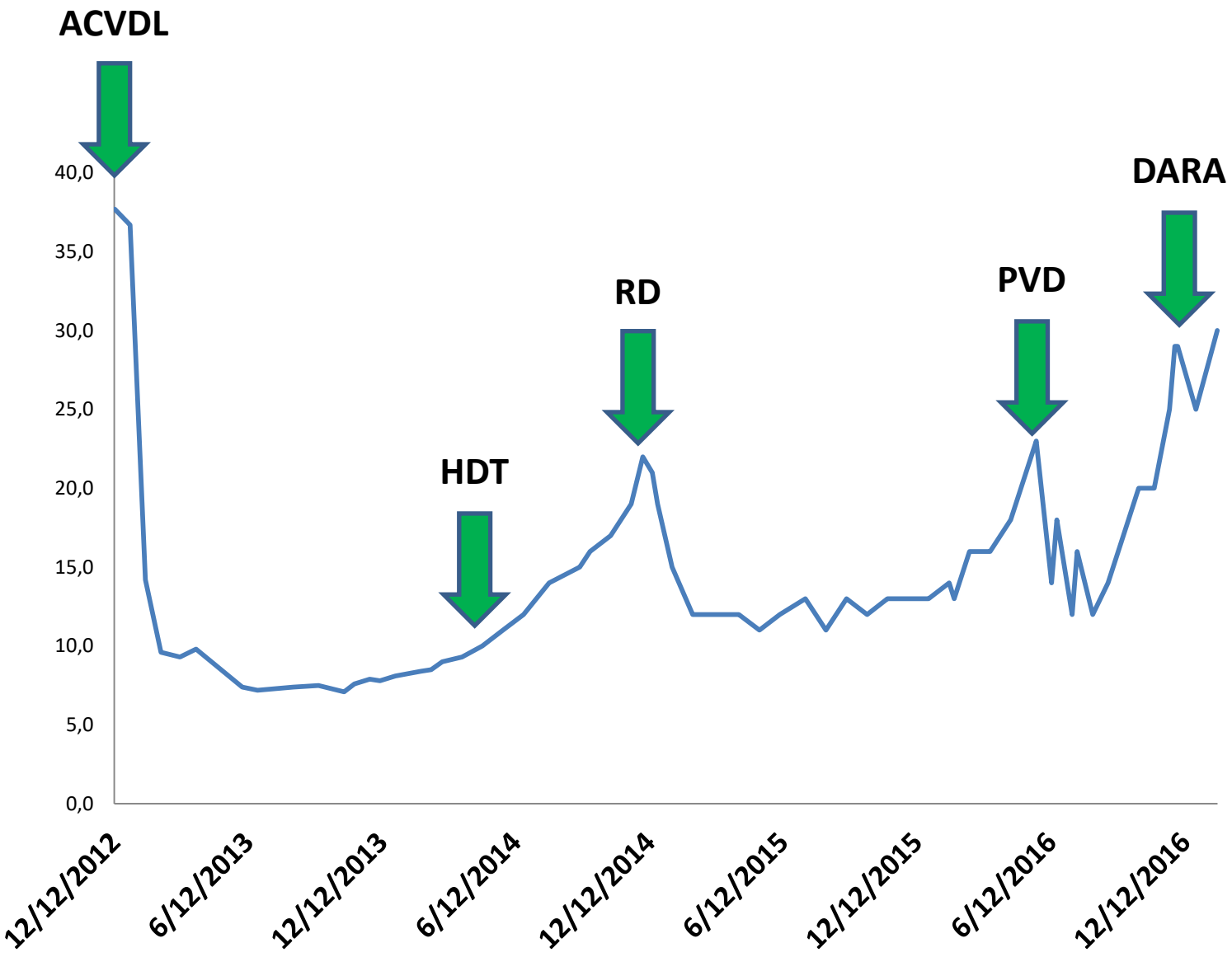
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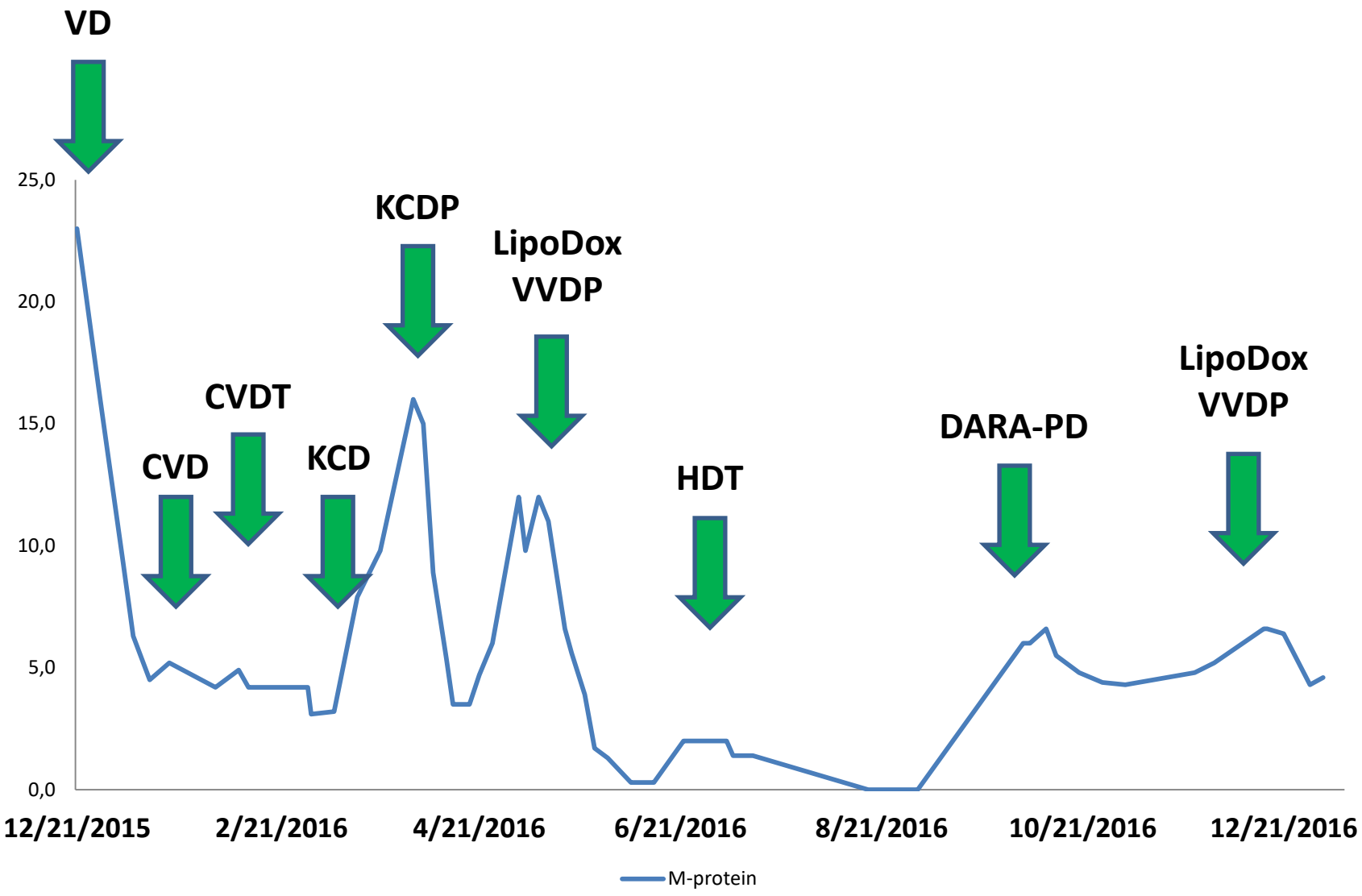
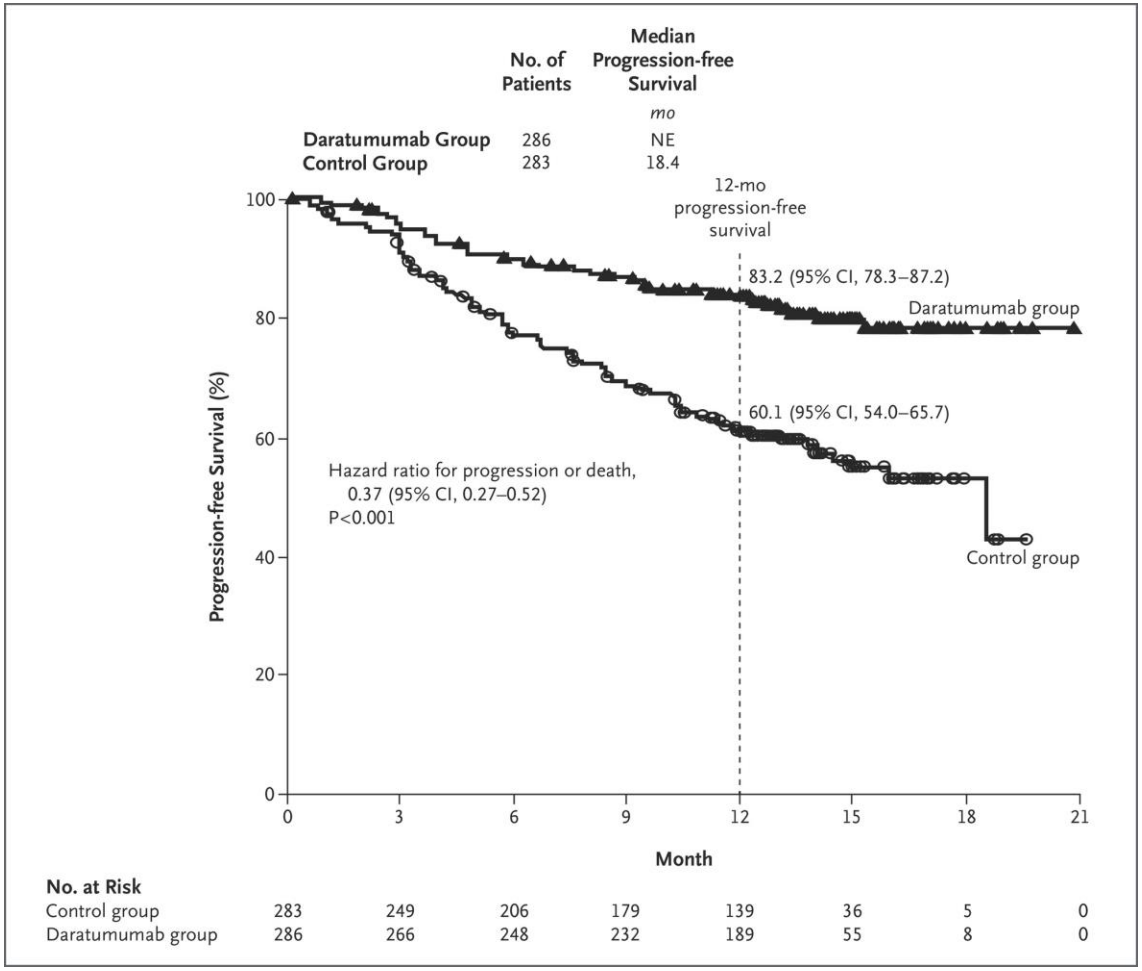
20,0
15,0
10,0
5,0
0,0
12/12/2012
6/12/2013
12/12/2013
6/12/2014
12/12/2014
6/12/2015
12/12/2015
6/12/2016
12/12/2016


VD
CVD
CVDT
KCD
KCDP
LipoDox
VVDP
HDT
DARA-PD
LipoDox
VVDP
25,0
20,0
15,0
10,0
5,0
0,0
12/21/2015
2/21/2016
4/21/2016
6/21/2016
8/21/2016
10/21/2016
12/21/2016
M-protein

The POLLUX trial



Dimopoulos N Engl J Med. 2016 Oct 6;375(14):1319-1331.

The POLLUX trial

POLLUX: Daratumumab-Lenalidomide-Dexamethasone vs. Lenalidomide-Dexamethasone in relapsed and refractory multiple myeloma

	DARA-LEN-DEX	LEN-DEX
progression-free survival at 12 months	83.2%	60.1%
Median progression-free survival	Could not be estimated	18,4 months
Overall response rate	92.9%	76.4%

Dimopoulos N Engl J Med. 2016 Oct 6;375(14):1319-1331.

The POLLUX trial

Amendment INT-3, 26 May 2016
subjects who were randomized to the lenalidomide and dexamethasone (Rd) group will be offered treatment with daratumumab monotherapy

Dimopoulos N Engl J Med. 2016 Oct 6;375(14):1319-1331.

The role of clinical trials

16.11.2015 Daratumumab monotherapy **approval** by FDA

27.5.2016 Daratumumab monotherapy **approval** by EMA

30.9.2016 Daratumumab monotherapy **approval** (KRIS) in Denmark

21.11.2016 Daratumumab-Lenalidomide-dexamethasone **approval** by FDA

23.8.2016 Daratumumab-Lenalidomide-dexamethasone **application** to EMA filed

The role of clinical trials

GEN501: Daratumumab in relapsed and refractory multiple myeloma
Recruitment at Vejle Hospital:
Part I: 11.3.2008 – 8.7.2012
Part II: 22.5.2013-8.5.2014

GEN503: Daratumumab-Lenalidomide-Dexamethasone in relapsed and refractory multiple myeloma
Recruitment at Vejle Hospital:
12.6.2012 – 7.8.2014

POLLUX: Daratumumab-Lenalidomide-Dexamethasone vs. Lenalidomide-Dexamethasone in relapsed and refractory multiple myeloma
Recruitment at Vejle Hospital:
27.11.2014-2.1.2015

ClinicalTrials.gov identifier: NCT01615029, NCT02076009

Tak for jeres opmærksomhed!

Spørgsmål?