Advances in the understanding and treatment of multiple myeloma

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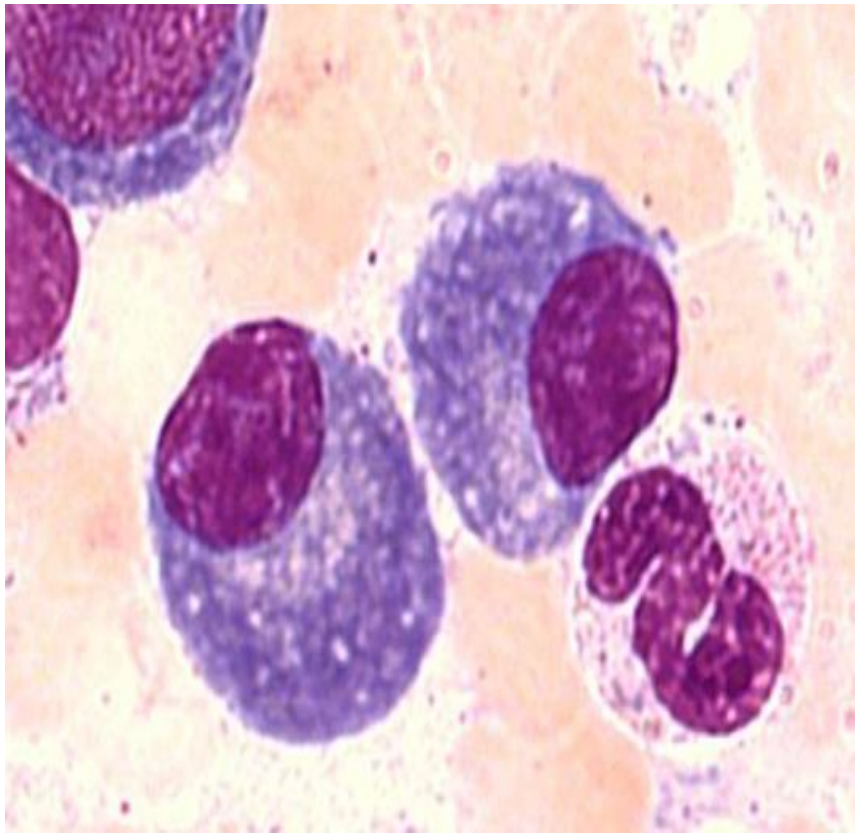
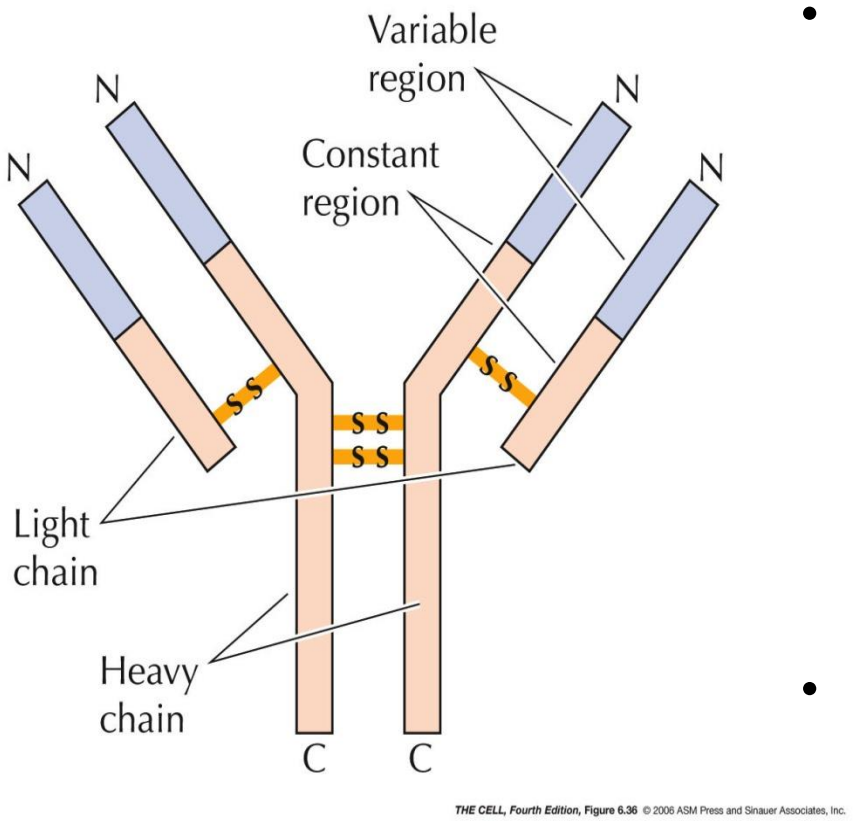
Immunoglobulin Structure

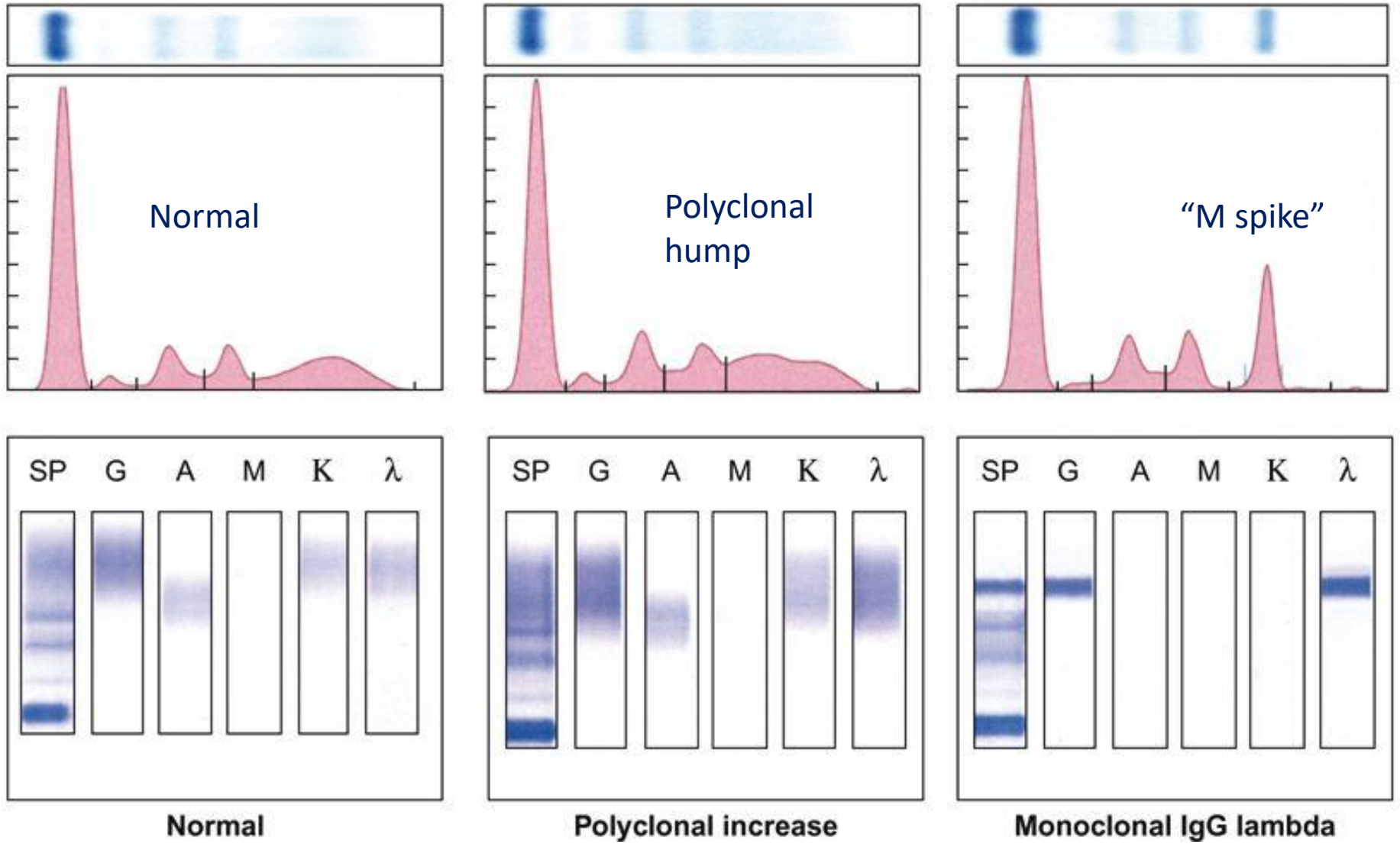




- The immunoglobulin protein consists of two heavy polypeptide chains of the same class designated by a Greek letter and a corresponding latin capital letter:
  - Gamma in IgG
  - Alpha in IgA
  - Mu in IgM
  - Delta in IgD
  - Epsilon in IgE
- Associated with two light chains of the same type, either kappa or lambda, but not both.

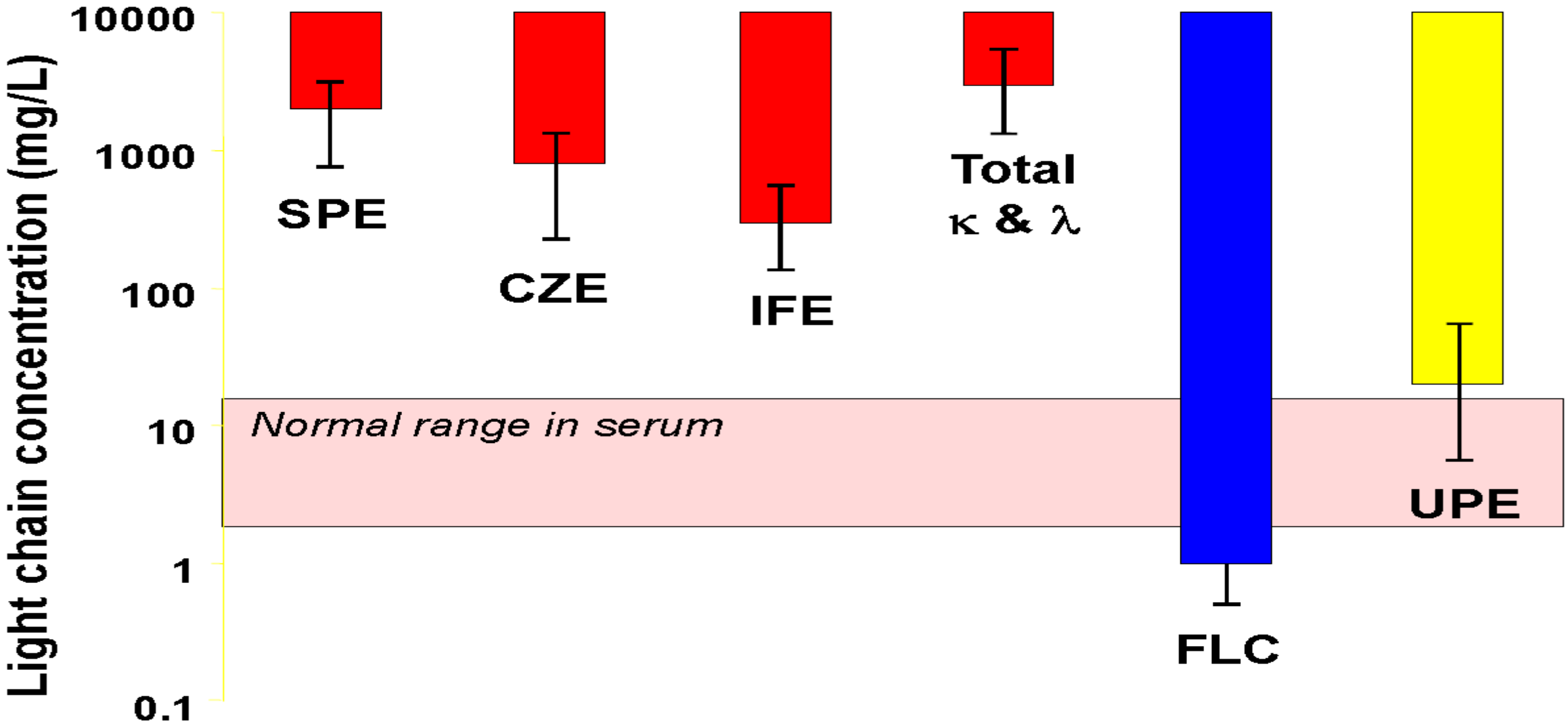
Monoclonal plasma cells produce abnormal monoclonal immunoglobulin (M protein)

How to diagnose Monoclonal Gammopathy? Serum Protein Electrophoresis (SPEP) and Immunofixation Electrophoresis (IFE)

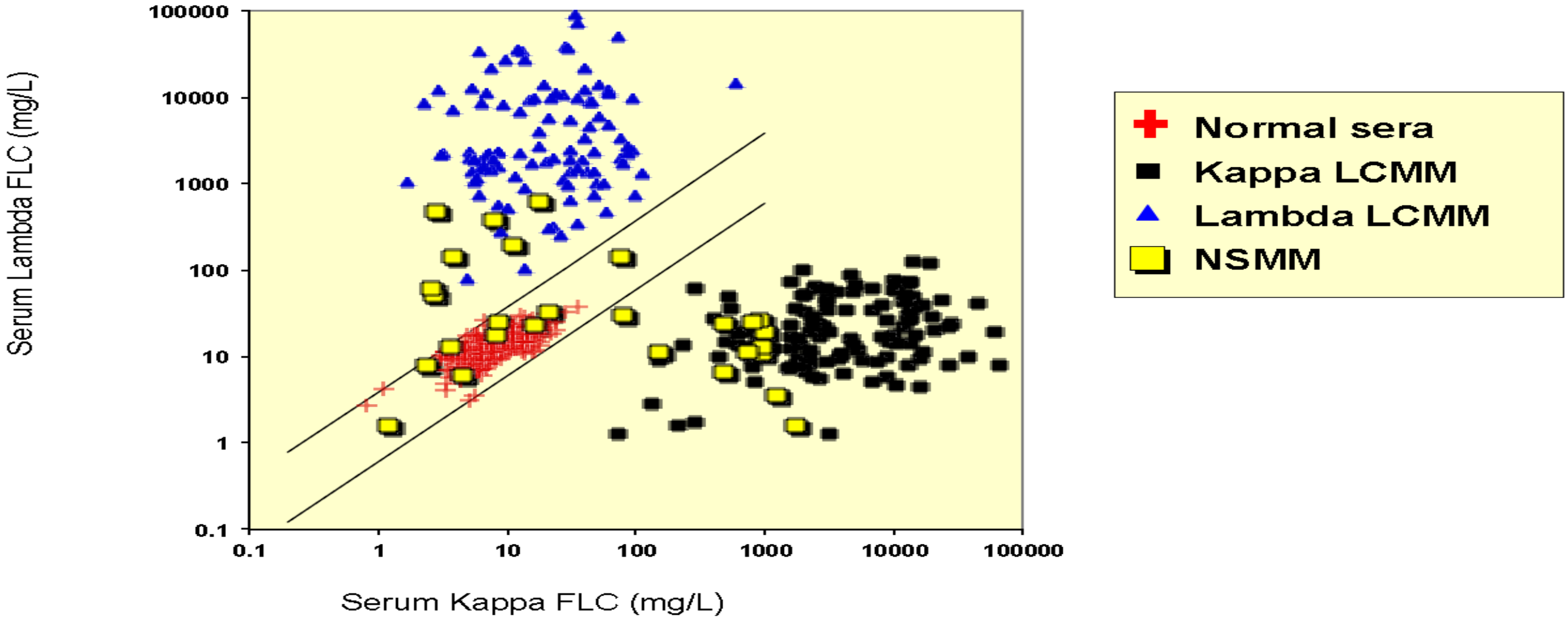


Munshi N et al, Harrison's Principles of Internal Medicine, 18th Edition

Sensitivity of methods for detection of FLC



Serum FLCs in light chain myeloma and non secretory myeloma



Drayson Blood 2001; 97: 2900 – 2902

Serum Free Light Chain (FLC) Assay

- The normal kappa/lambda FLC ratio is 0.26 to 1.65
- Abnormal FLC ratios are seen in clonal plasma cell disorders when there is excess production of one type of light chain
- Abnormal FLC ratio predicts higher risk of progression in MGUS and SMM
- Up to 20 percent of myeloma is characterized by only a light chain in the serum or urine, lacking expression of the immunoglobulin heavy chain
- Useful in AL amyloidosis (AL)

Differential Diagnosis

- Monoclonal Gammopathy of Uncertain Significance (MGUS)
- Smoldering multiple myeloma (SMM)
- Multiple myeloma
- Solitary Plasmacytoma
- Light chain Amyloidosis (AL amyloidosis)
- Waldenström macroglobulinemia
- Polyneuropathy, Organomegaly, Endocrinopathy, M-protein and Skin abnormalities (POEMS) syndrome
- Light chain deposition disease, Heavy chain deposition disease
- Cryoglobulinemia

MGUS

Smoldering MM

Active Myeloma

Diagnostic criteria

Patient Criteria	MGUS[1,2]	Smoldering Myeloma[1]	Symptomatic Myeloma[1]
M-protein	< 3 g/dL spike	≥ 3g/dL spike and/or	In serum and/or urine[2]
Monoclonal plasma cells in bone marrow, %	< 10	≥ 10	Usually ≥ 10[2]
End-organ damage	None	None	≥ 1 CRAB* feature[3]

*C: Calcium elevation (> 10.5 mg/L or ULN)
R: Renal dysfunction (serum creatinine > 2 mg/dL)
A: Anemia (Hb < 10 g/dL or 2 g < normal)
B: Bone disease (lytic lesions)

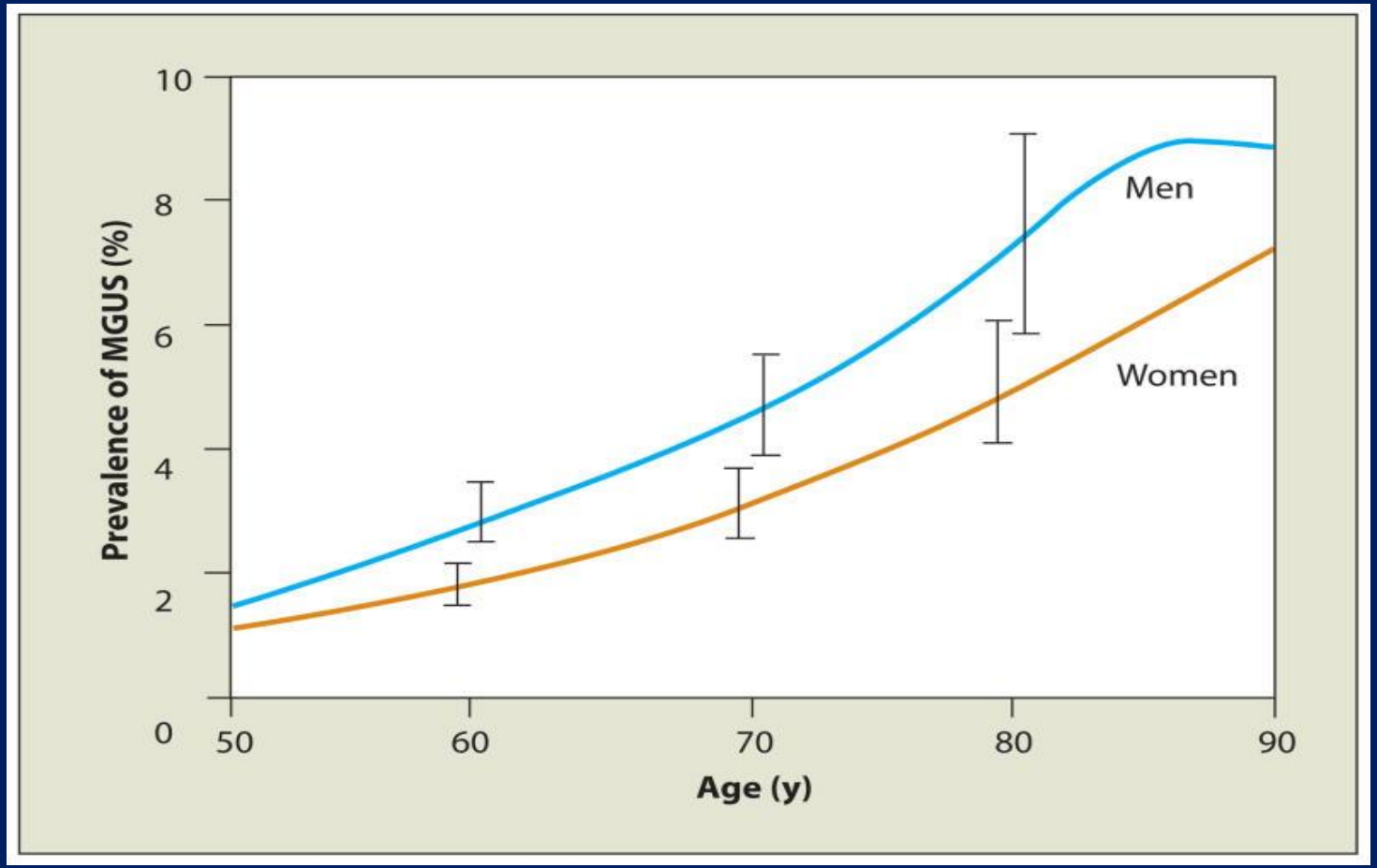
1. IMWG. Br J Haematol. 2003;121:749-757. 2. Kyle RA, et al. Leukemia. 2009;23:3-9.
3. Durie BG, et al. Hematol J. 2003;4:379-398.

Prevalence of MGUS

- Population based study from Olmsted county, MN, serum samples obtained from 77% of residents, 50 years or older

- Age >50 3.2%
- Age >70 5.3%
- Age >85 7.5%

- Two-three fold higher in AA compared with whites (same as MM)



Kyle, R. et al. N Engl J Med 2006;354:1362-1369

ORIGINAL ARTICLE

A Long-Term Study of Prognosis in Monoclonal Gammopathy of Undetermined Significance

Robert A. Kyle, M.D., Terry M. Therneau, Ph.D., S. Vincent Rajkumar, M.D., Janice R. Offord, B.S., Dirk R. Larson, M.S., Matthew F. Plevak, B.S., and L. Joseph Melton, III, M.D.

N Engl J Med 2002; 346:564-569 | February 21, 2002 | DOI: 10.1056/NEJMoa01133202

TABLE 1. RISK OF PROGRESSION AMONG 1384 RESIDENTS OF SOUTHEASTERN MINNESOTA IN WHOM MONOCLONAL GAMMOPATHY OF UNDETERMINED SIGNIFICANCE WAS DIAGNOSED IN 1960 THROUGH 1994.*

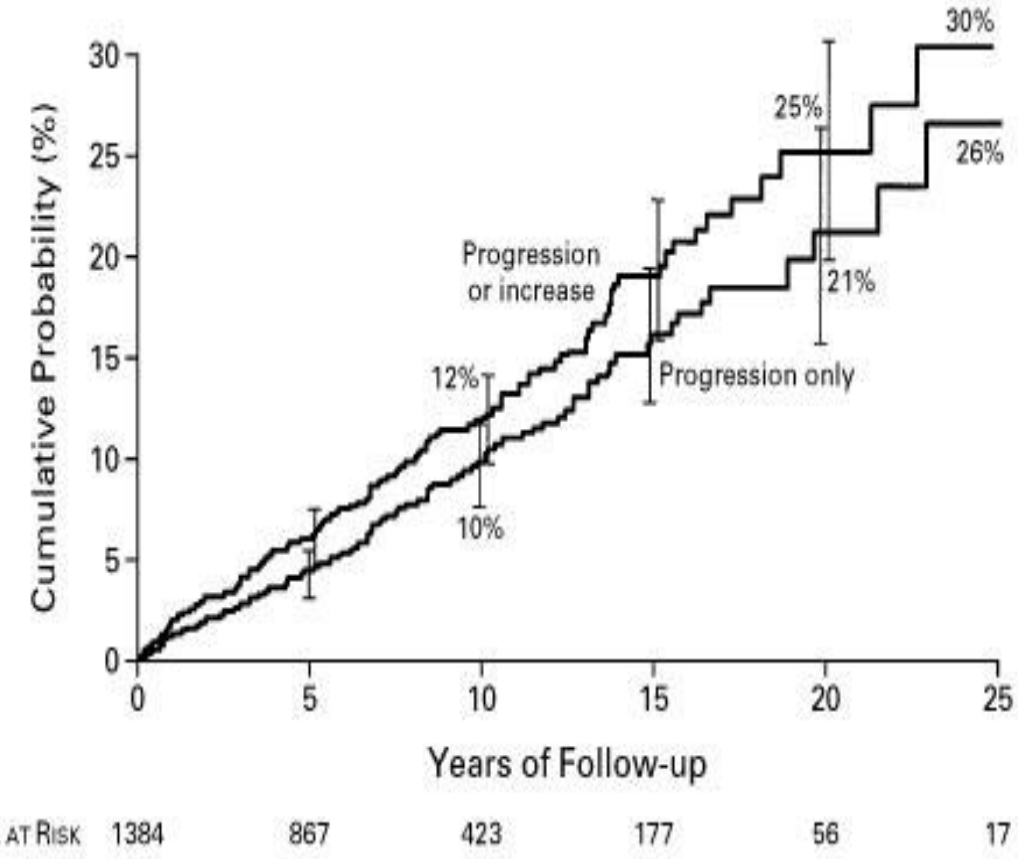
TYPE OF PROGRESSION	OBSERVED NO. OF PATIENTS	EXPECTED NO. OF PATIENTS†	RELATIVE RISK (95% CI)
Multiple myeloma	75	3.0	25.0 (20–32)
Lymphoma	19‡	7.8	2.4 (2–4)
Primary amyloidosis	10	1.2	8.4 (4–16)
Macroglobulinemia	7	0.2	46.0 (19–95)
Chronic lymphocytic leukemia	3§	3.5	0.9 (0.2–3)
Plasmacytoma	1	0.1	8.5 (0.2–47)
Total	115	15.8	7.3 (6–9)

*CI denotes confidence interval.

†Expected numbers of cases were derived from the age- and sex-matched white population of the Surveillance, Epidemiology, and End Results program in Iowa,[18] except for primary amyloidosis, for which data are from Kyle et al.[20]

‡All 19 patients had serum IgM monoclonal protein. If the 30 patients with IgM, IgA, or IgG monoclonal protein and lymphoma were included, the relative risk would be 3.9 (95 percent confidence interval, 2.6 to 5.5).

§All three patients had serum IgM monoclonal protein. If all six patients with IgM, IgA, or IgG monoclonal protein and chronic lymphocytic leukemia were included, the relative risk would be 1.7 (95 percent confidence interval, 0.6 to 3.7).



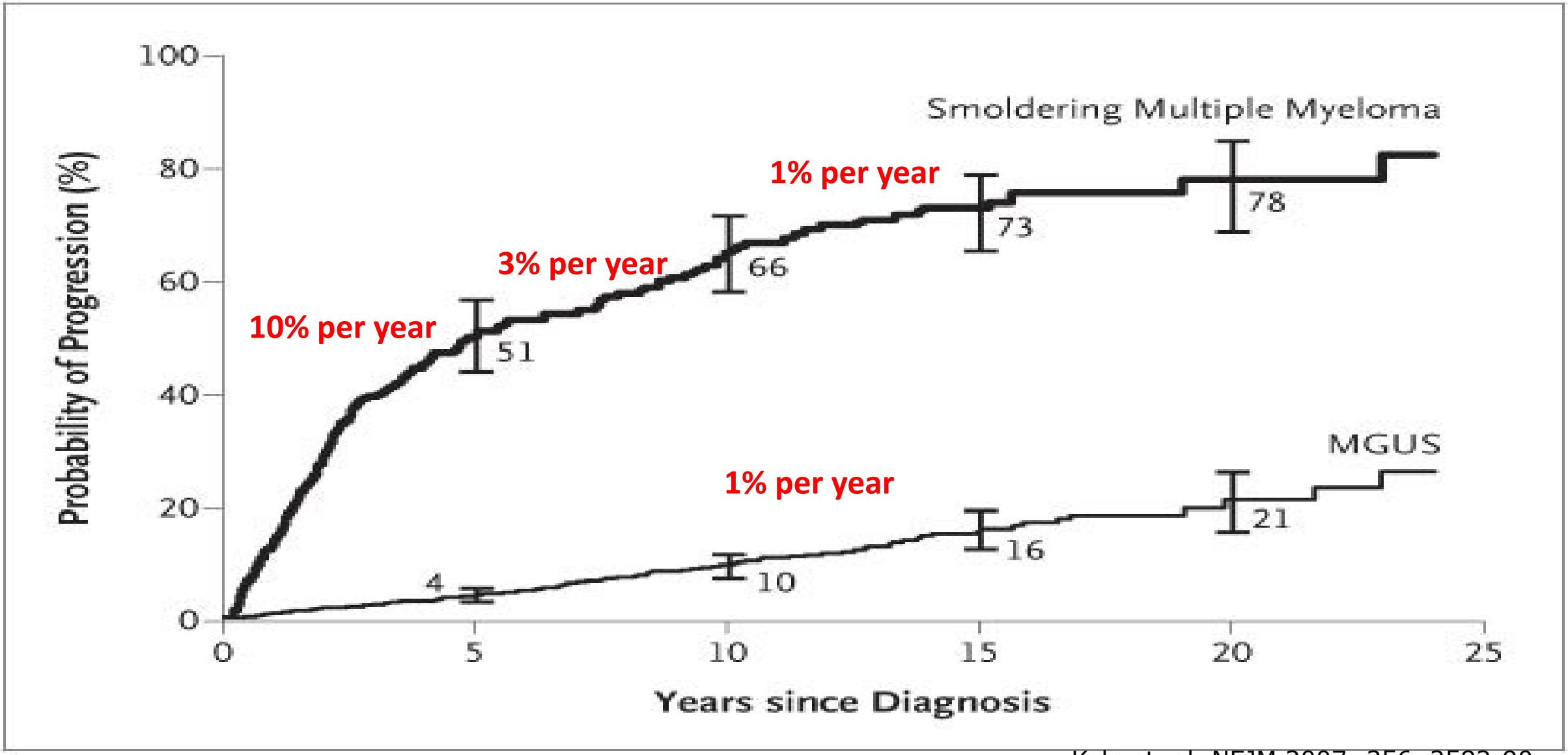
MGUS

- One of the most common premalignant disorder in western countries
- Constant risk of progression of 1% per year persists even after 25 to 30 years of diagnosis
- Majority of MGUS will not progress
- Does not require any form of therapy, only regular follow up is necessary.

MGUS: ‘Red Flags’

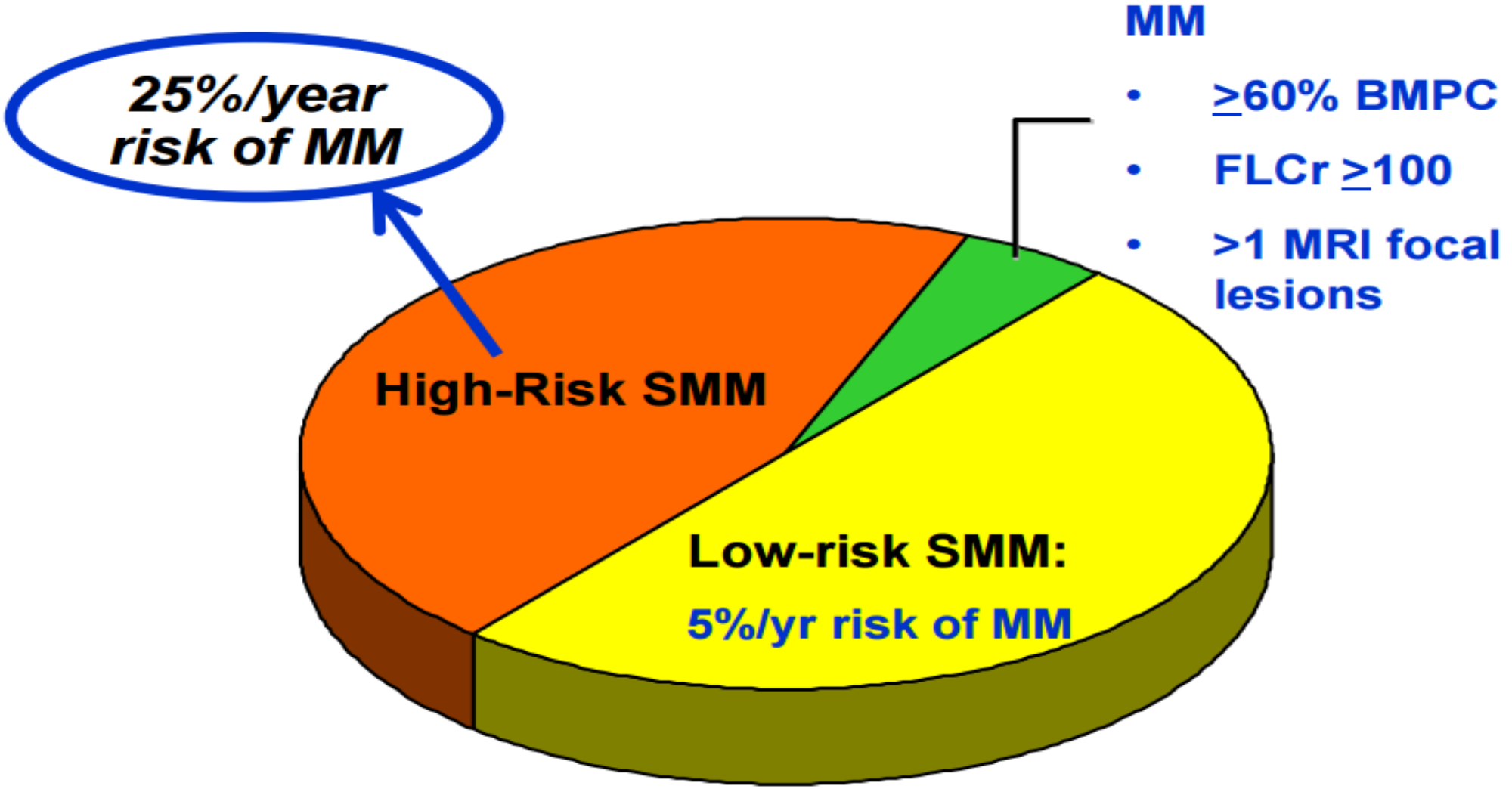
- Bone pain
- Fatigue/generalized weakness
- Abnormal labs
- Constitutional “B” symptoms
- Neurologic symptoms
- Amyloid symptoms

Risk of Progression: MGUS vs Smoldering Myeloma



Kyle et. al. NEJM 2007; 356, 2582-90

Smoldering Multiple Myeloma



Diagnosis of Myeloma
Revised Definition of Multiple Myeloma

Classical Definition

- Hyper**C**alcemia
- **R**enal insufficiency
- **A**nemia
- **B**one disease

Expanded Definition: Myeloma defining events

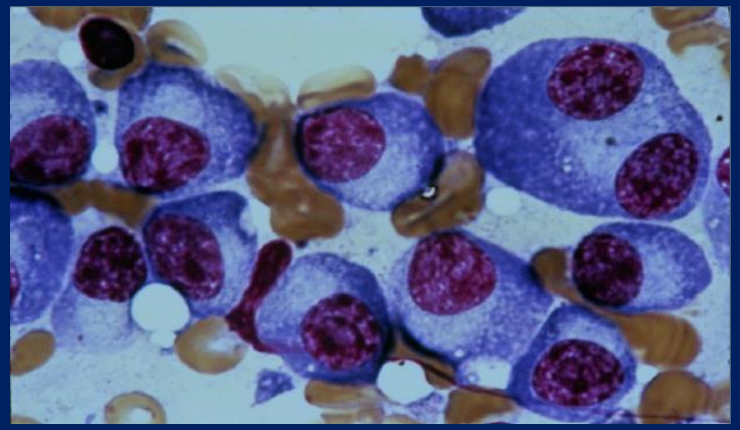
- Clonal BMPC ≥ 60%
- > 1 focal lesion on MRI
- Involved/uninvolved serum FLC ratio > 100

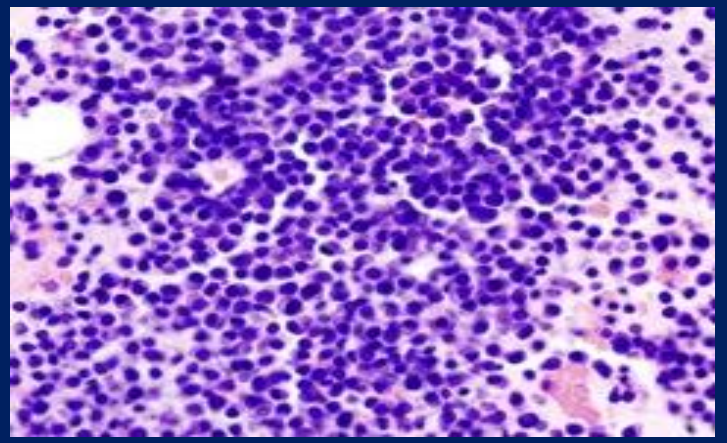
Predicts ≥ 80% probability of progression from smoldering to active disease within 2 yrs

Rajkumar SV, et al. Lancet Oncol. 2014;15:e538-548.

Multiple Myeloma *by the numbers*

- 2nd most common hematologic malignancy
- More than 30,000 new cases in US every year
- Approximately 12,000 deaths in US every year
- *African Americans 2X*
- *Hispanics 1.6X*
- *Male: Female: 1.4:1*
- Median age at diagnosis 69 years
- 5 year relative survival 50-65% (2006-2012)



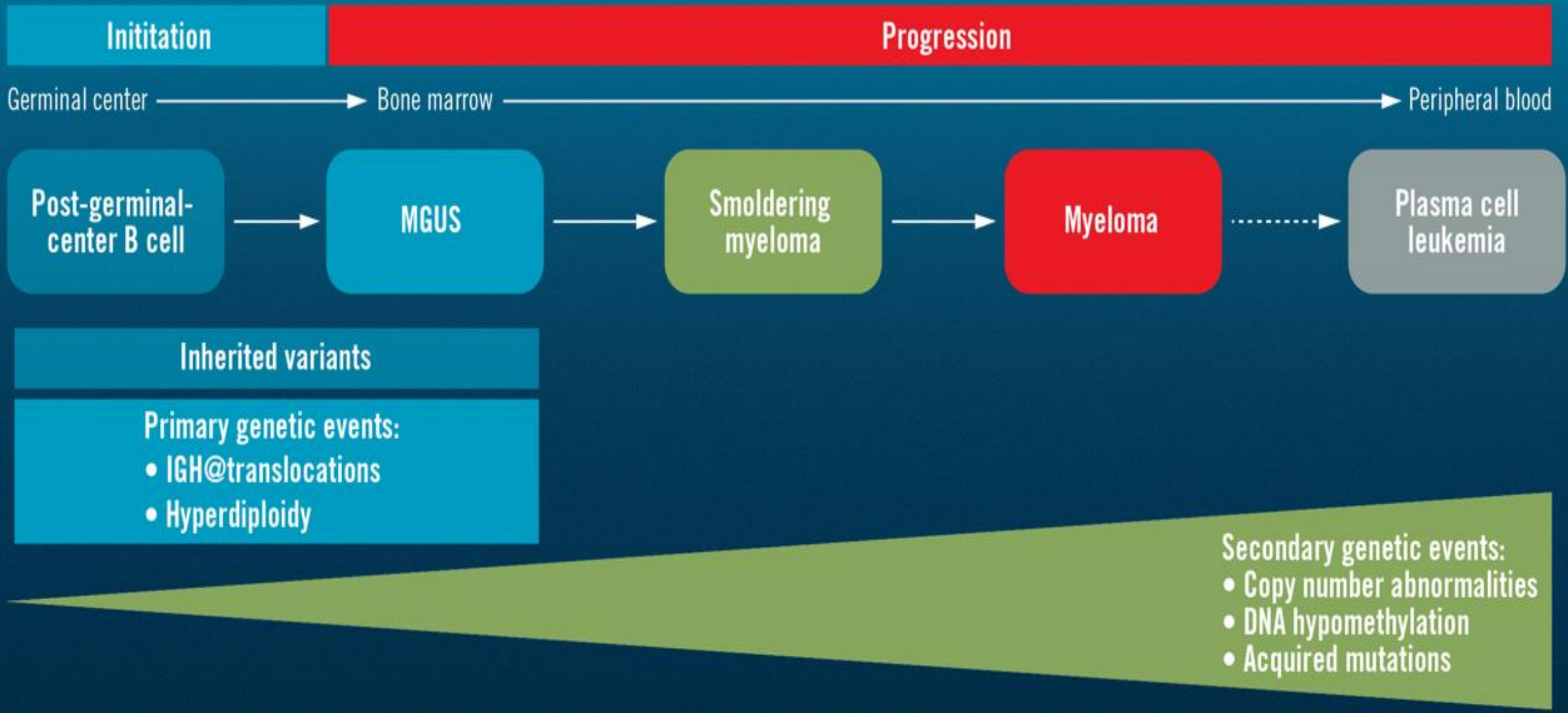


1. American Cancer Society. Cancer facts & figures. 2014. 2. SEER stat fact sheet: myeloma. 2016.

Cause of multiple myeloma is not well established

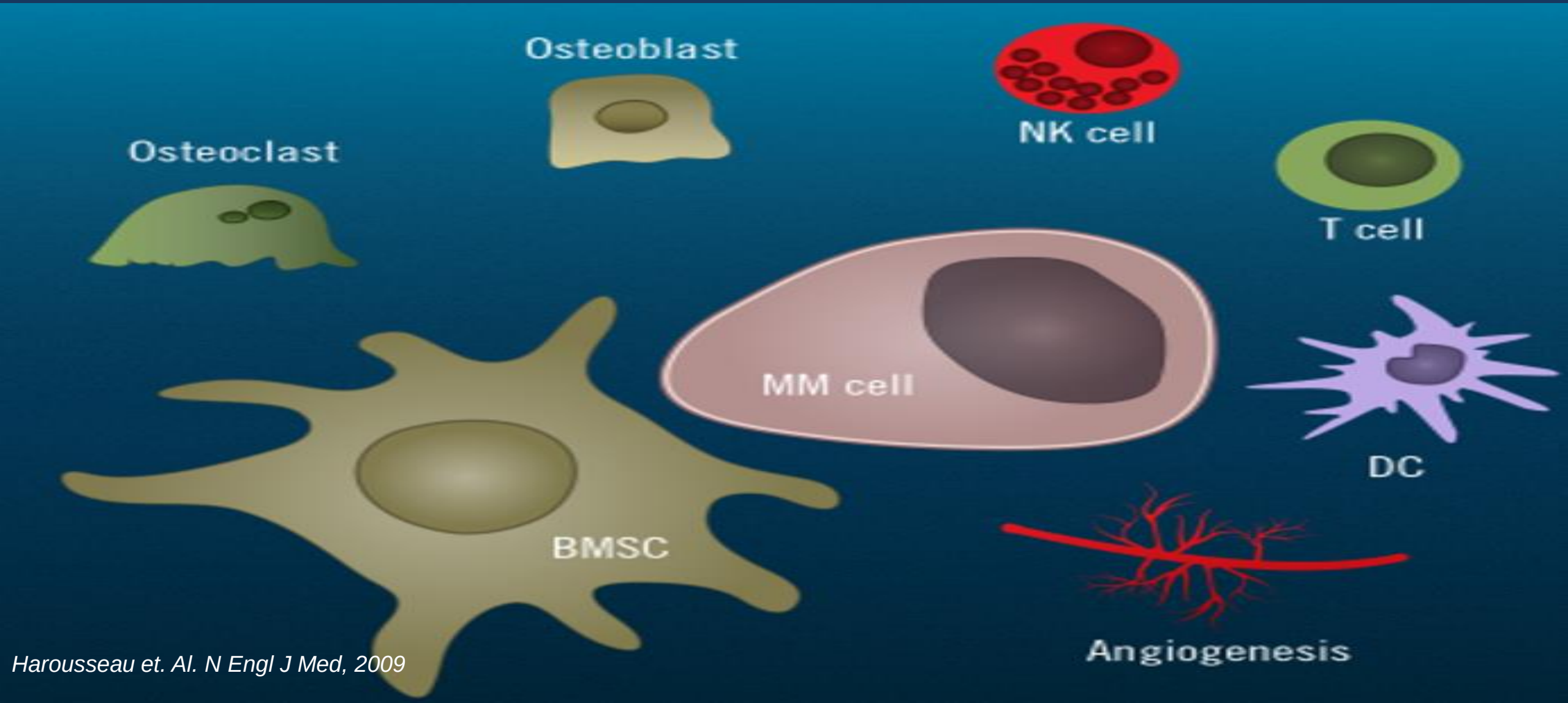
Accepted Risk Factors
Increasing Age
Male Sex
African American
History of MGUS
Possible Risk Factors
Obesity
Pesticides, Insecticides
Family History (small number of cases)
Not risk Factors
Smoking
Alcohol
Radiation

Progression to multiple myeloma involves numerous genetic events



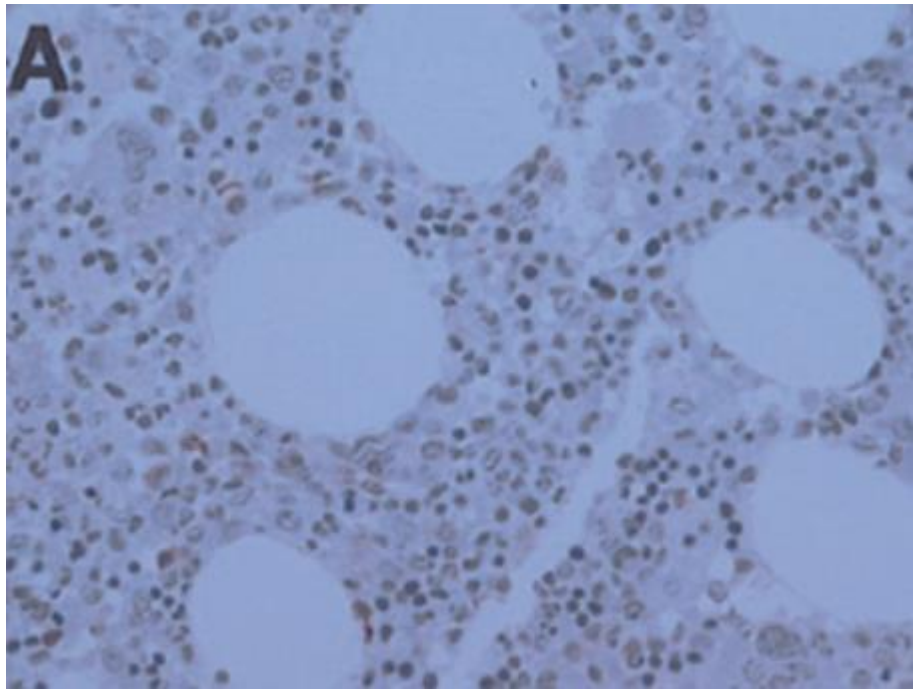
Morgan et al. nature review cancer 2012; 12 (5): 335-348

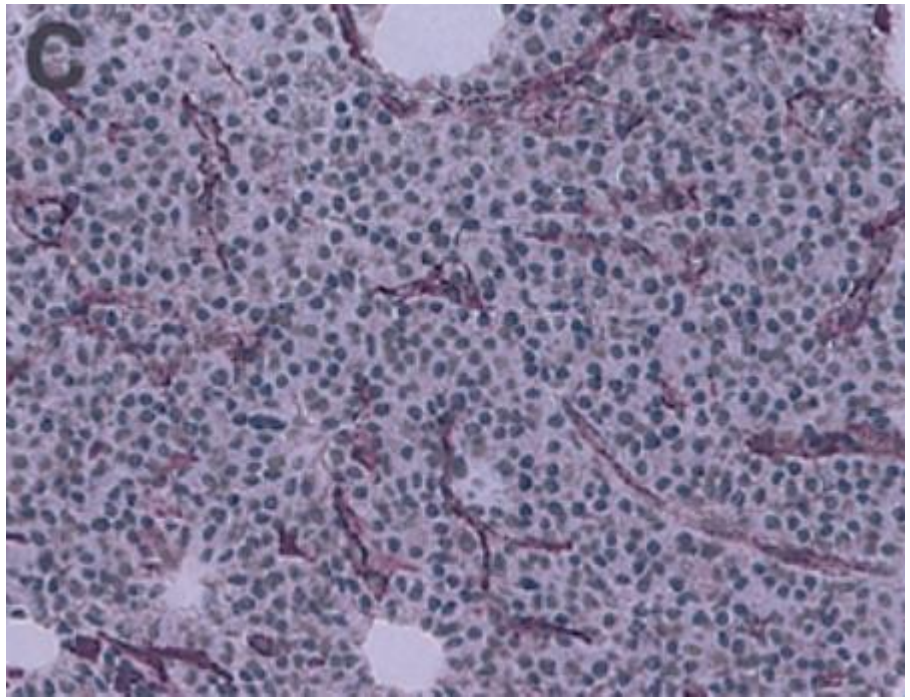
Cellular and non-cellular components in bone marrow microenvironment are important for myeloma pathogenesis



Harousseau et. Al. N Engl J Med, 2009

Bone marrow angiogenesis in MM compared with earlier stages of disease





Rajkumar SV et. al. Clin Cancer Res 2002; 8(7): 2210-2216

Clinical Presentations

How do patients present?

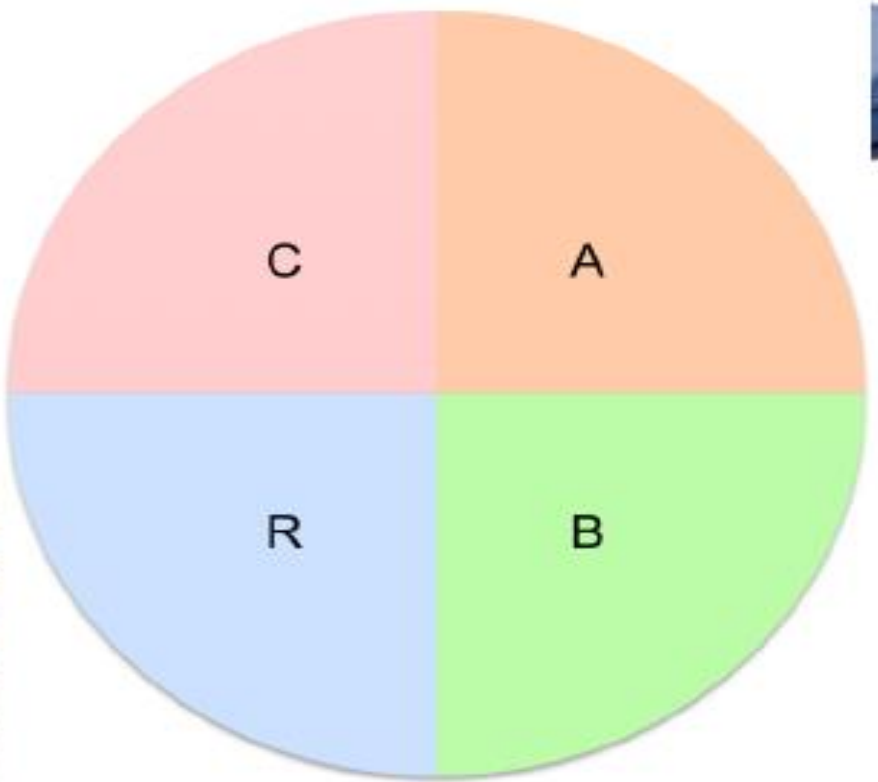
- Bone Pain
- Fatigue/generalized weakness
- Fractures
- Infection
- Constitutional Symptoms
- Renal failure
- Spinal cord compression

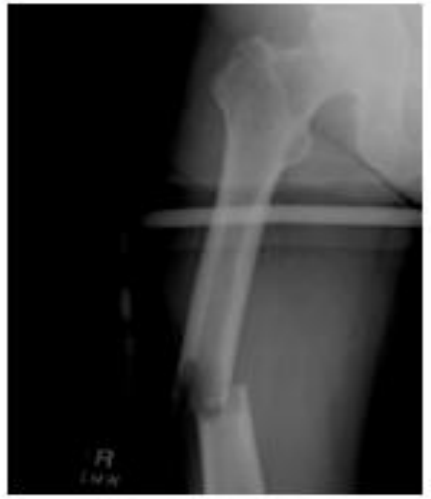
Most common findings

- Anemia (normochromic normocytic): 73%
- Lytic bone lesions: 70%
- Serum creatinine >2: 20%
- Hypercalcemia: 13%
- Increased plasma cells in marrow: 95%

Kyle RA Mayo Clinic Proc 2003; 78(1):21

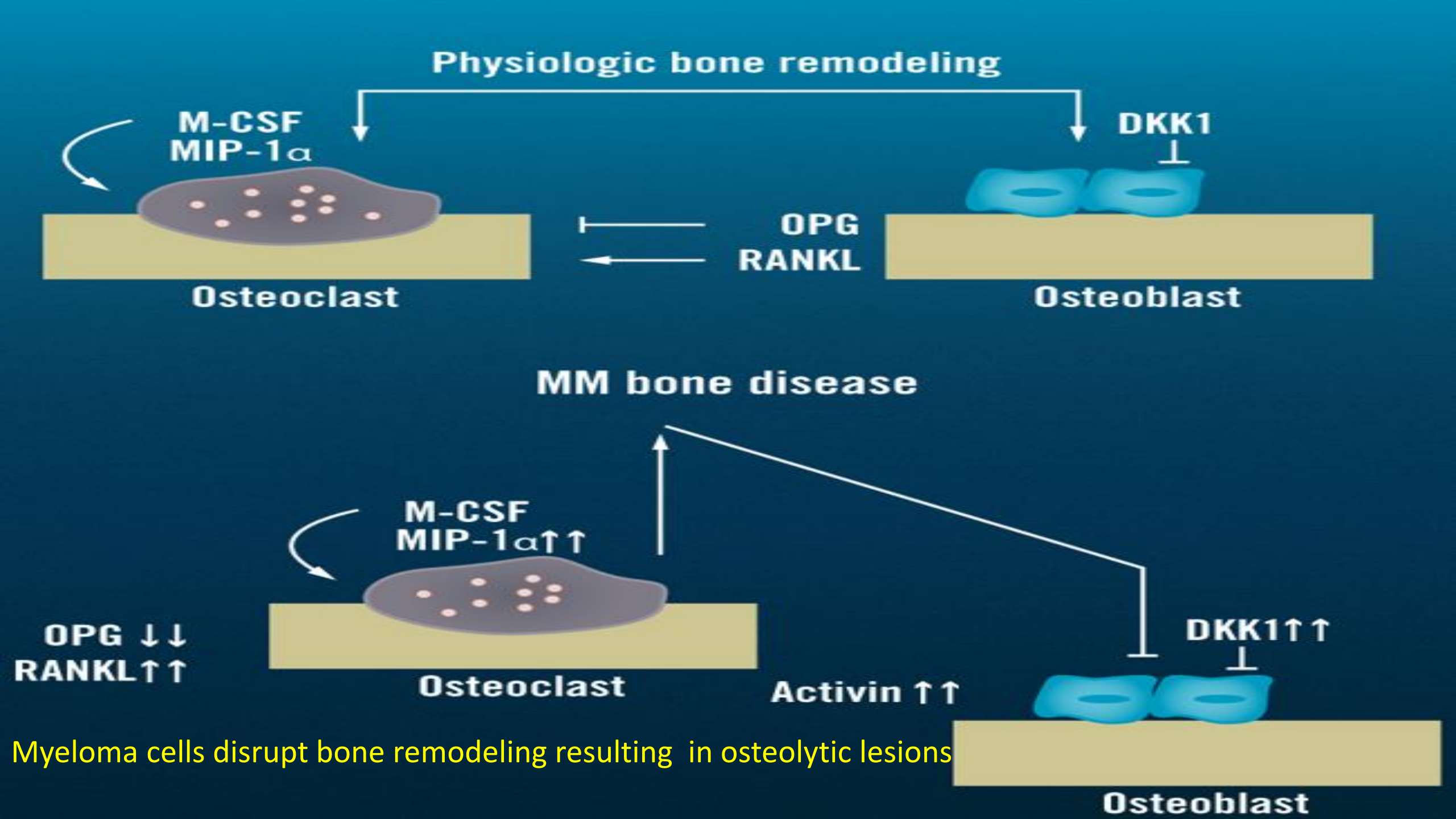
How does myeloma affect the patient?





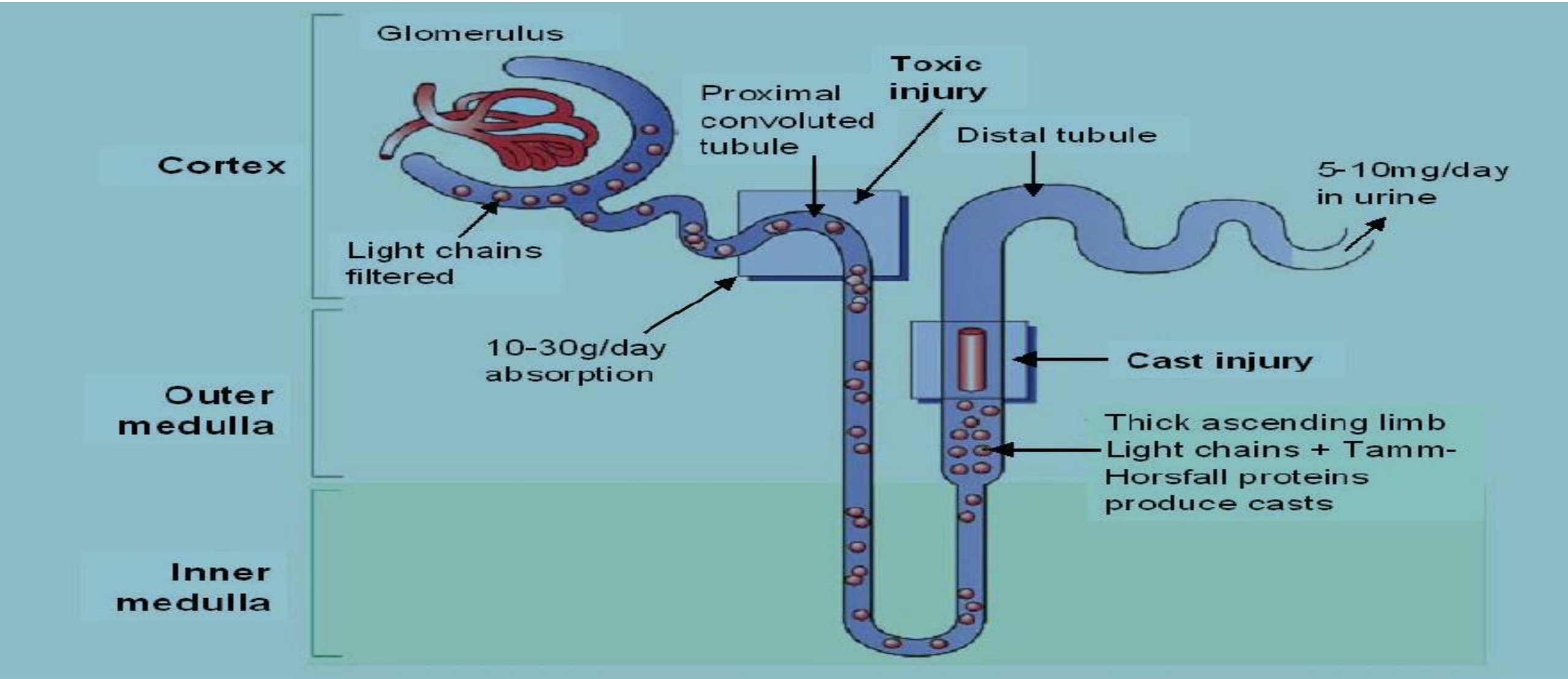
‘CRAB’ criteria

Courtesy Rafael Fonseca MD

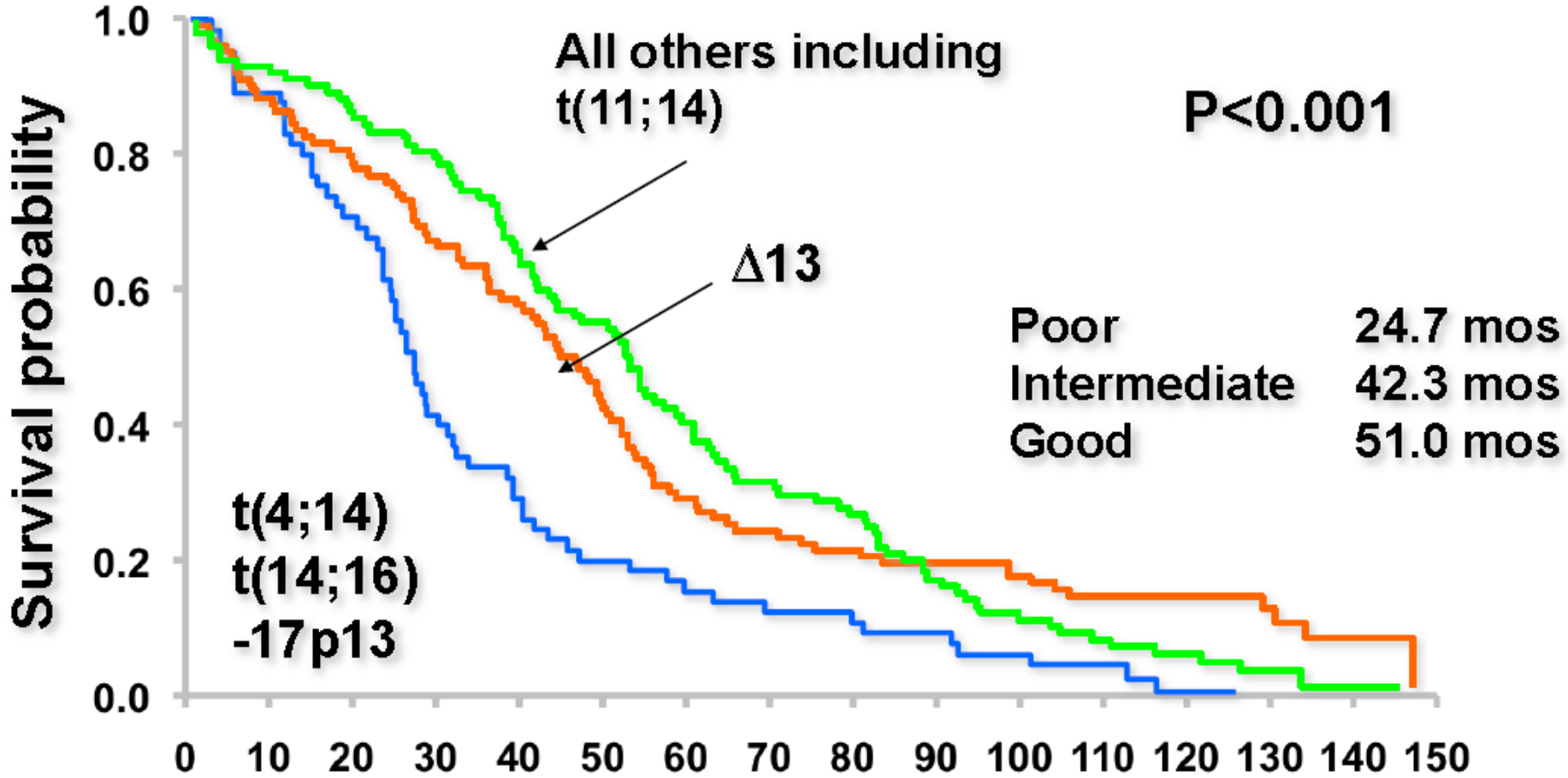


Myeloma cells disrupt bone remodeling resulting in osteolytic lesions

Renal Metabolism of Serum Free Light Chains



Molecular Prognostic Model



Fonseca et. Al Blood 2003; 101, 4569

MM Risk Categories

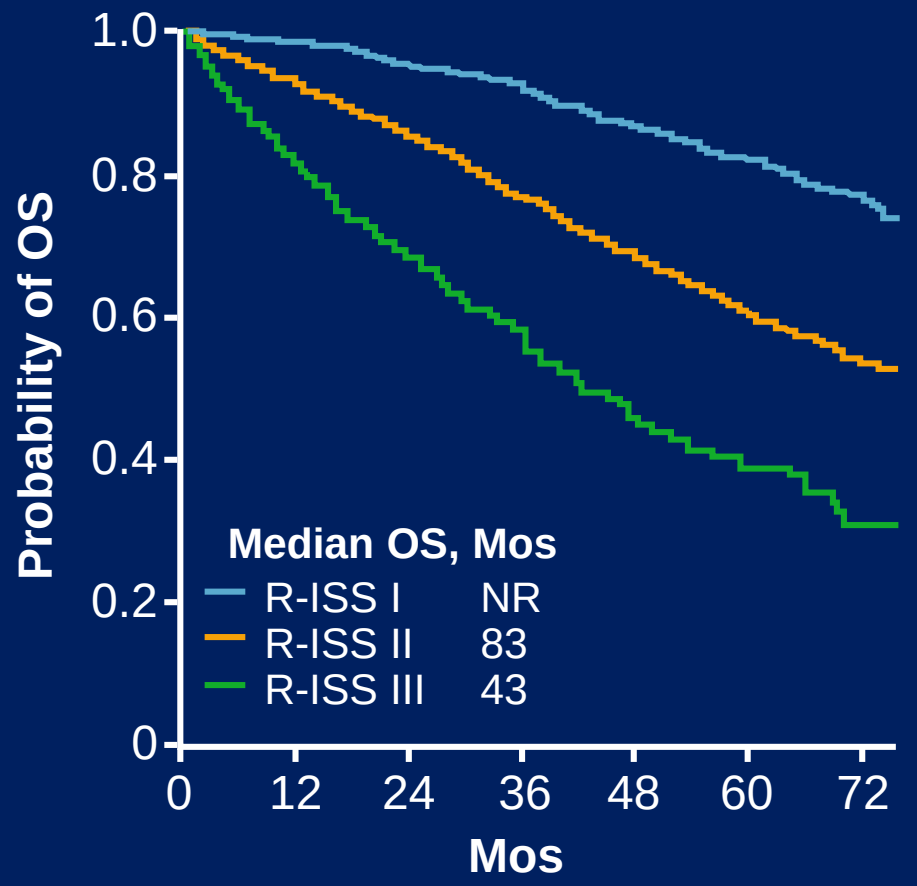
Risk Factors	Standard Risk (80%) (Expected OS: 7-10 Yrs)	High Risk (20%) (Expected OS: 2-3 Yrs)
FISH	t(11;14), t(6;14)	del(17p), t(4;14)* t(14;16), +1q21
Cytogenetics	Hyperdiploidy	Hypodiploidy del(13q)
β_2-microglobulin*	Low (< 3.5 mg/L)	High (≥ 5.5 mg/L)
PCLI	< 3%	High (≥ 3%)
LDH	--	> 2 times ULN
Gene expression profile	Good risk	High risk

*Pts with t(4;14), β_2-microglobulin < 4 mg/L, and Hb ≥ 10 g/dL may have intermediate-risk disease. Host factors such as age, PS, comorbidities, renal failure need to be considered

Dispenzieri A, et al. Mayo Clin Proc. 2007;82:323-341. Kumar SK, et al. Mayo Clin Proc. 2009;84:1095-1110. Mikhael JR, et al. Mayo Clin Proc. 2013;88:360-376. NCCN. Clinical practice guidelines in oncology: multiple myeloma. v.1.2015. Chng WJ, et al. Leukemia. 2014;28:269-277.

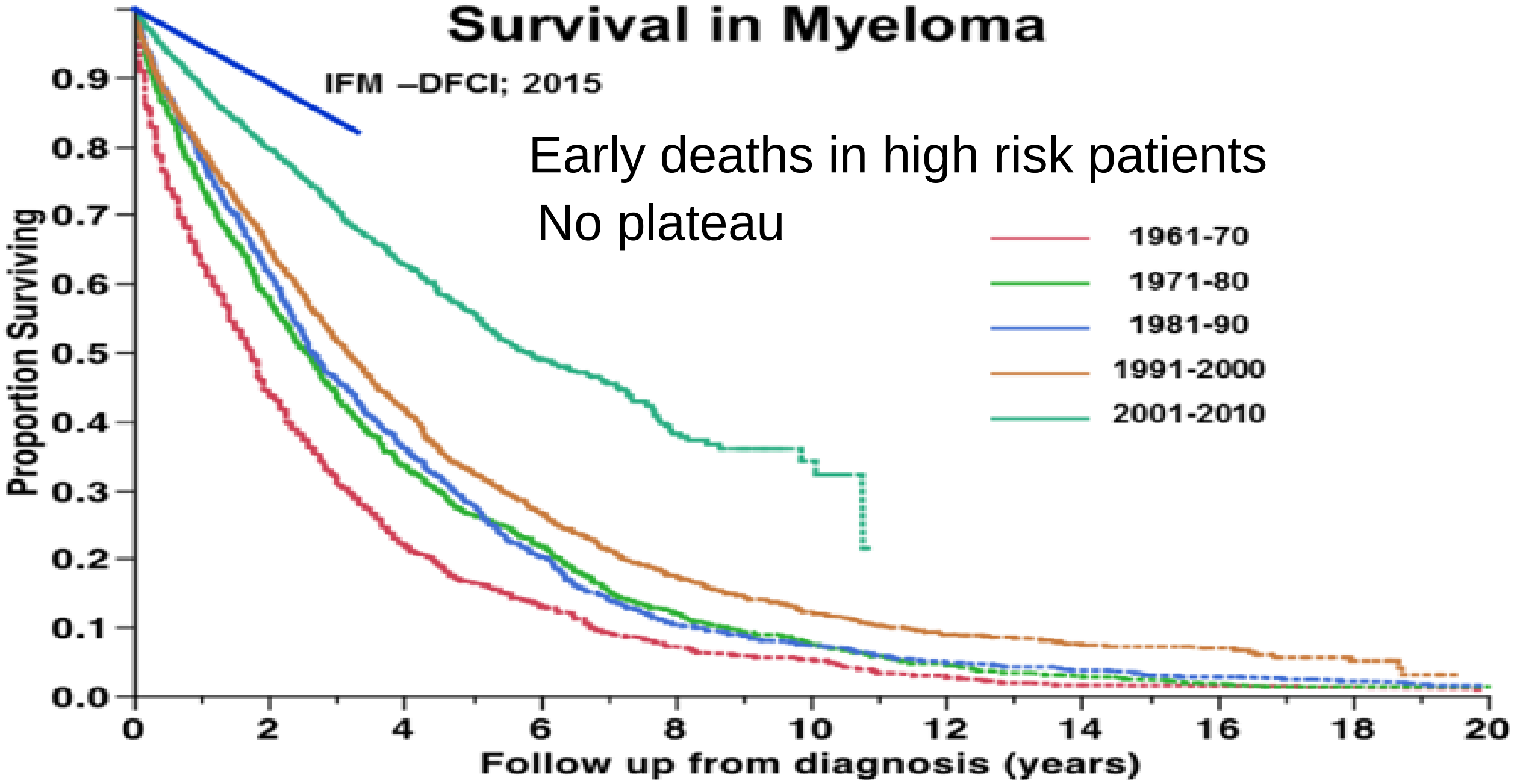
Revised ISS Staging System

ISS Stage	Definition
I	▪ Serum albumin ≥ 3.5 g/dL *AND* ▪ β_2-M < 3.5 mg/L
II	▪ Not stage I or III
III	▪ β_2-M ≥ 5.5 mg/dL
R-ISS Stage	**Definition**
I	▪ ISS stage I *AND* ▪ Normal LDH ▪ No t(4;14), t(14;16), or del(17p)
II	▪ Not stage I or III
III	▪ ISS stage III *AND* ▪ Serum LDH > ULN *OR* ▪ With t(4;14), t(14;16), or del(17p)



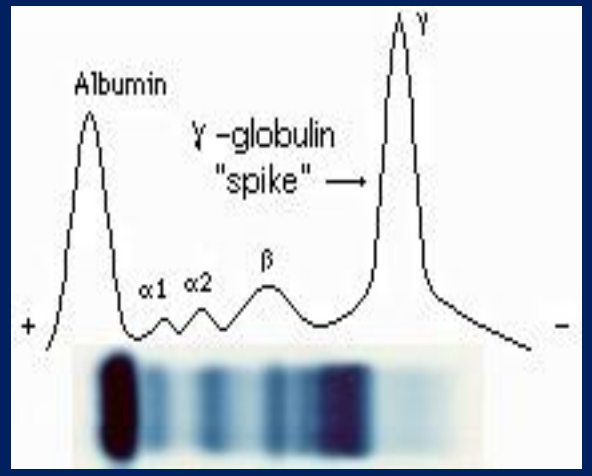
Palumbo A, et al. J Clin Oncol. 2015;33:2863-2869.

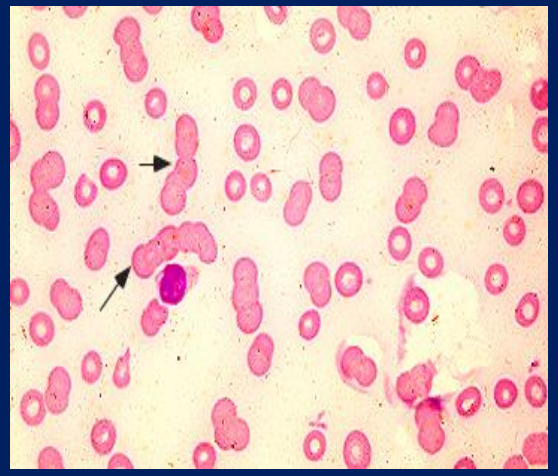
Survival in Myeloma

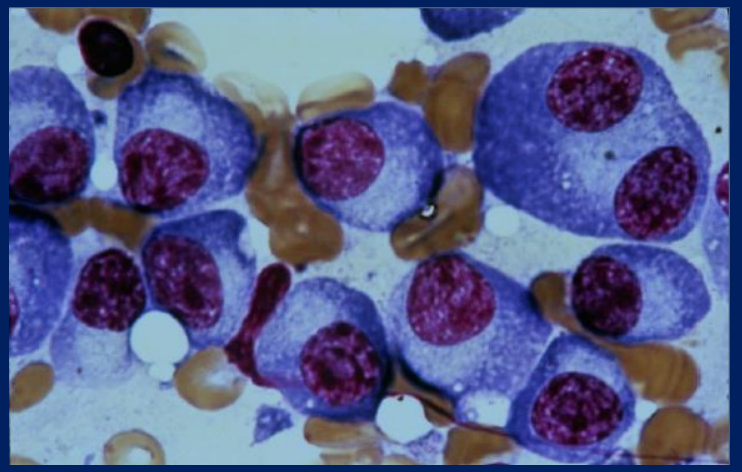


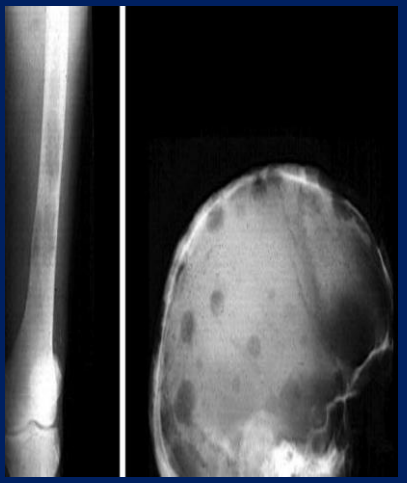
Kumar S. Blood 2008;111: 2516– 2520; Kumar S. Leukemia (2014) 28, 1122–1128.

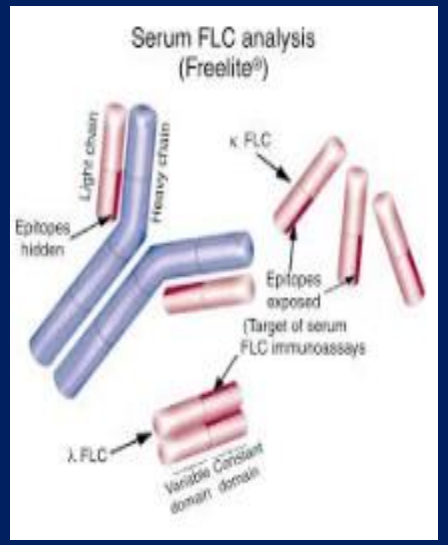
Multiple Myeloma: Diagnostic Advances



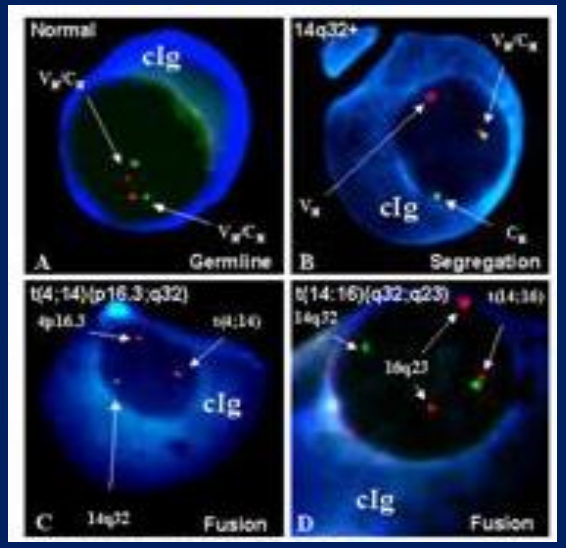




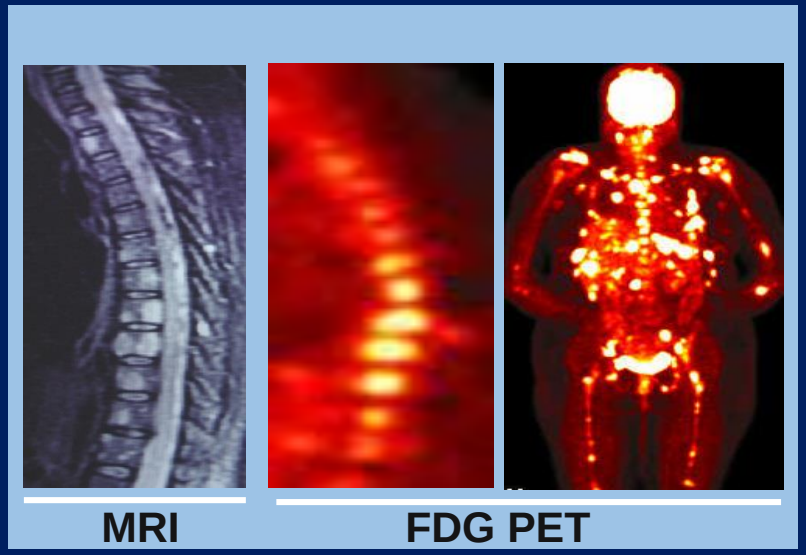


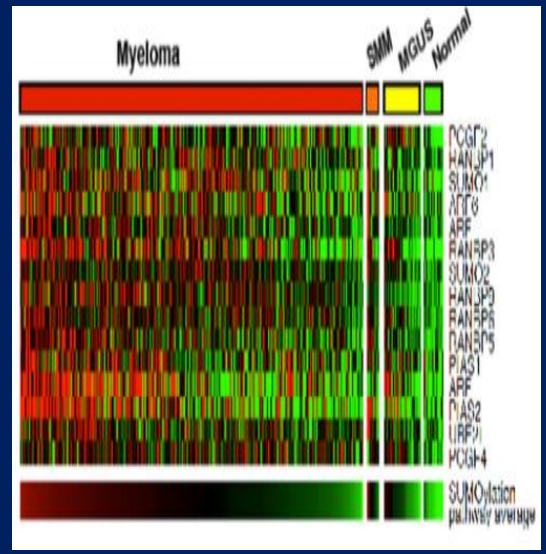


FLC



FISH





GEP

Multiple Myeloma: Work Up

Blood Specimen

- CBC
- Chemistry: serum calcium, creatinine, albumin, LDH , beta-2 microglobulin
- Serum protein electrophoresis (SPEP) and Immunofixation
- Quantitative Igs – G,A,M
- Serum free light chain (FLC) assay
- Peripheral blood smear

Urine

- Urinalysis and a 24-hour urine collection for Bence Jones Proteins

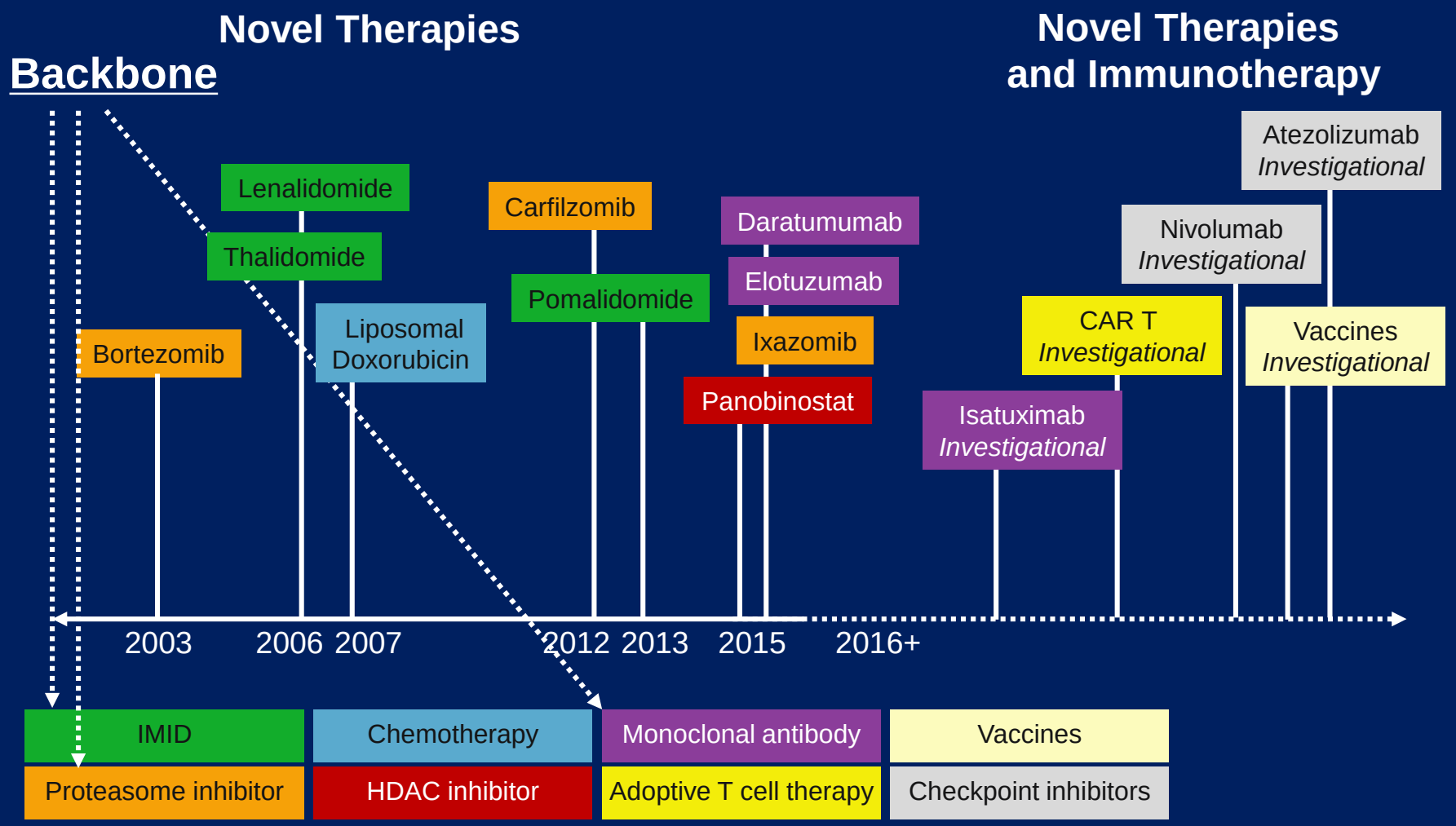
Bone marrow aspiration and biopsy

Histology, conventional cytogenetics and fluorescence in situ hybridization (FISH)

Plain X rays

MRI, CT, or PET/CT as indicated

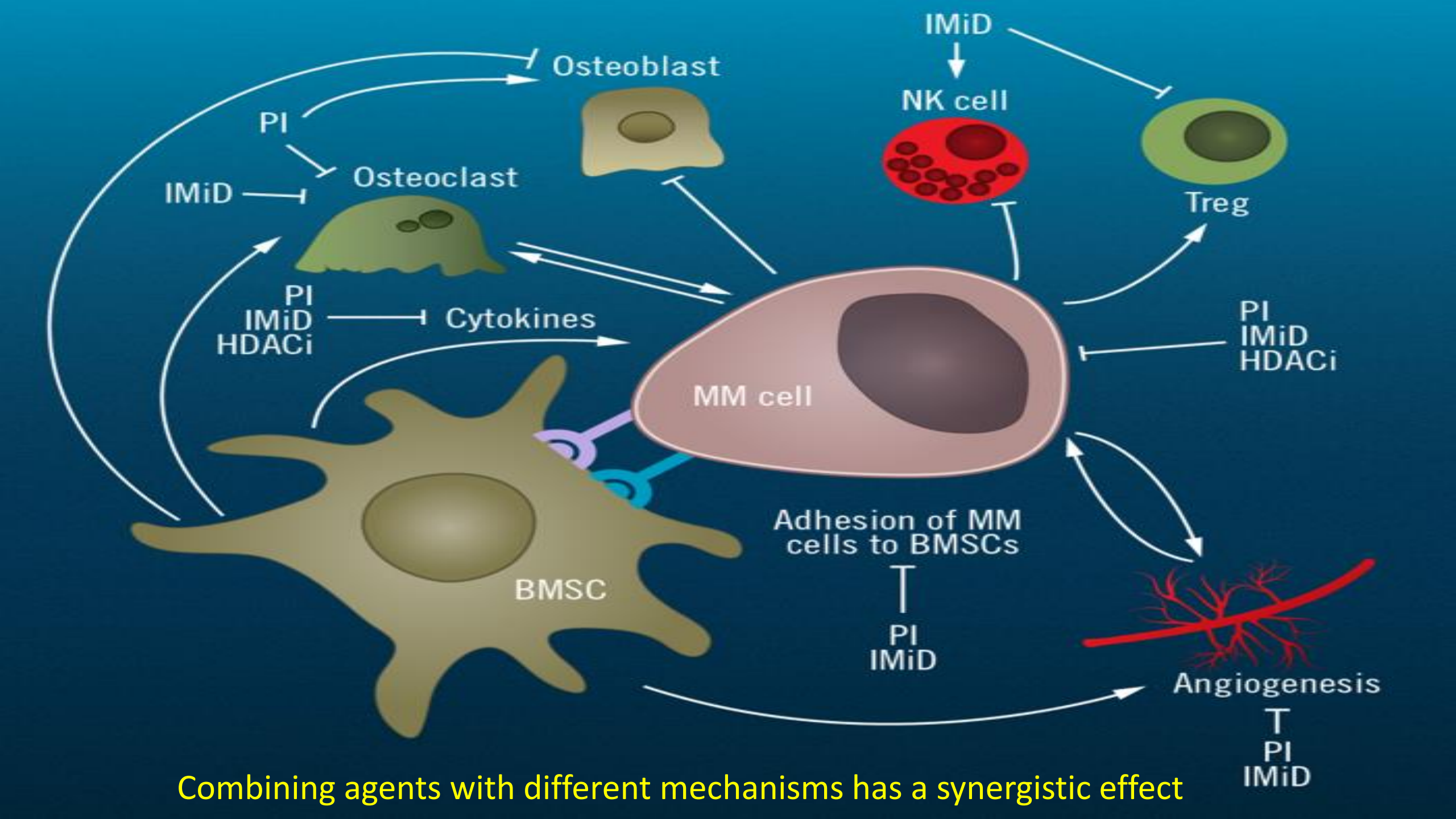
Novel Myeloma Therapy Development



Changing the Treatment Landscape of MM (2000-2018)

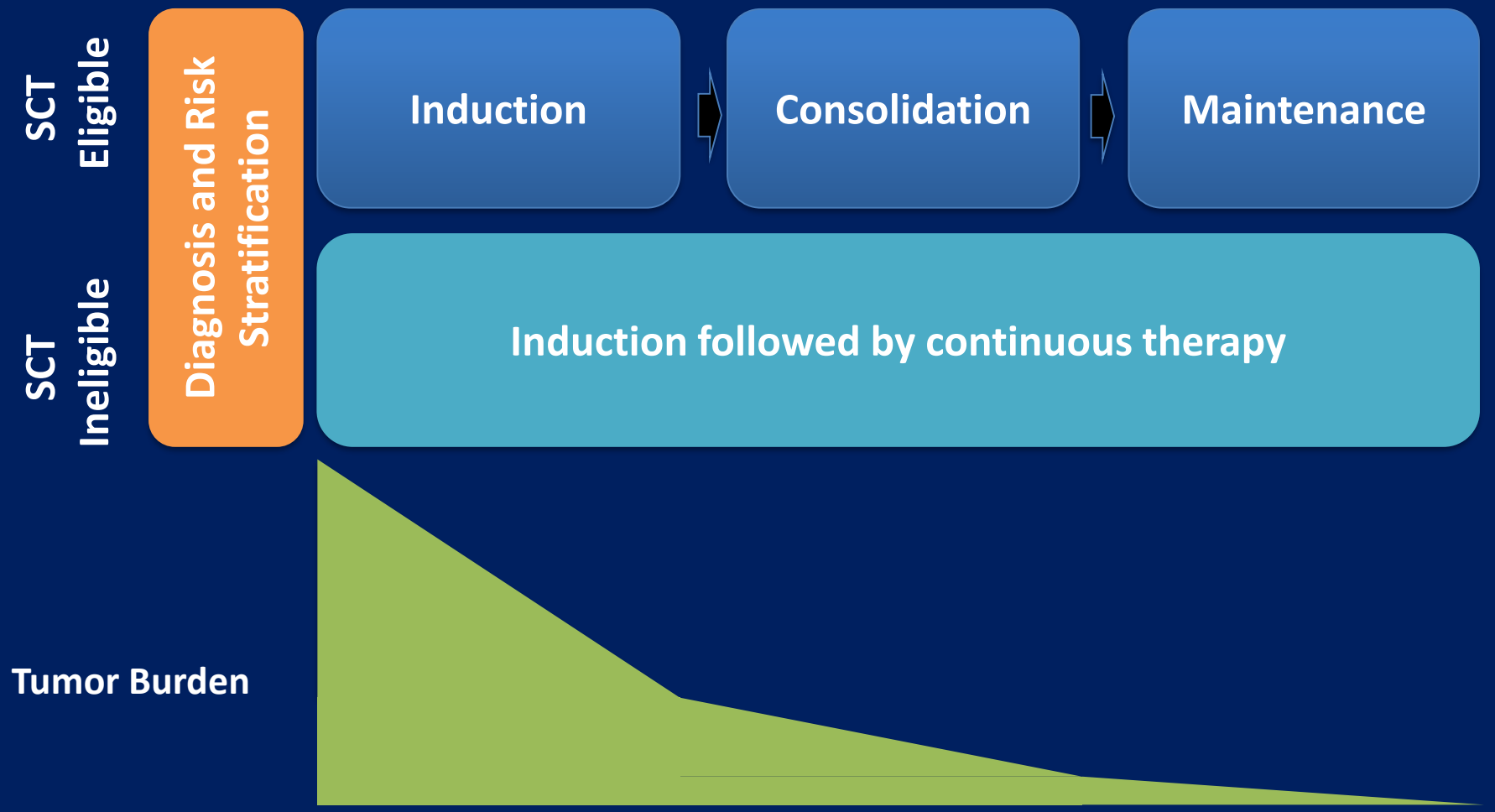
Active Drugs and Combinations

1. Bortezomib
2. Thalidomide/dexamethasone (TD)
3. Lenalidomide/dexamethasone (Rd)
4. Bortezomib + liposomal doxorubicin
5. Bortezomib + melphalan/prednisone (VMP)
6. Revlimid + Melphalan/prednisone (MPR)
7. Bortezomib/dexamethasone (Vd)
8. Bortezomib/lenalidomide/dexamethasone (VRD)
9. Bortezomib/thalidomide/dexamethasone (VTD)
10. Cytoxan/bortezomib/dexamethasone (CyBorD)
11. Cytoxan/Revlimid/Dexamethasone (CyRevD)
12. Carfilzomib/Dex
13. Carfilzomib/Revlimid/dex (KRd)
14. Pomalidomide/dexamethasone
15. Carfilzomib/Pomalidomide/dex
16. Carfilzomib/Cytoxan/dex
17. Panobinostat/bortezomib/dexamethasone
18. Ixazomib/lenalidomide/dex
19. Elotuzumab/lenalidomide/dex
20. Daratumumab/bortezomib/dex



Combining agents with different mechanisms has a synergistic effect

Myeloma Treatment Paradigm

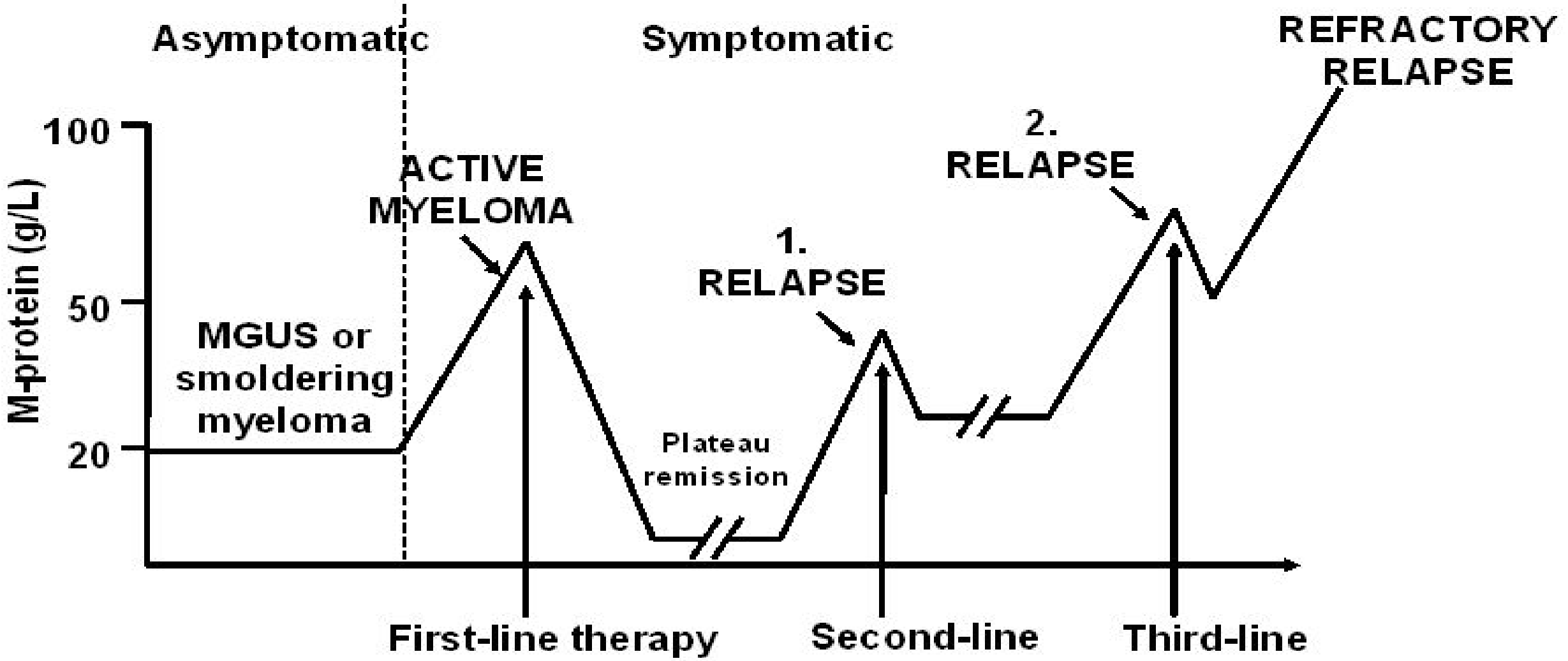


Current Treatment of Myeloma Bone Disease

- Bisphosphonates[1]
  - Pamidronate 90 mg IV over 4 hours
  - Zoledronic acid 4 mg IV over 15 minutes
  - Denosumab subcutaneous
  - Decreases bone pain and skeletal events
  - Not currently indicated in SMM or MGUS
  - Monitor for renal dysfunction and ONJ
  - Current recommendation to use for 2 years

1. NCCN. Clinical practice guidelines in oncology: multiple myeloma. v.2.2014.
2. ClinicalTrials.gov. NCT01345019.

Natural history of myeloma



Durie B; concise review of the disease and treatment options 2011/2012

Solitary Plasmacytoma

- Single bony (or extramedullary lesion)
- Small M protein may be present
- Bone marrow: negative or minimal involvement
- No CRAB features
- PET/CT should be performed
- Treatment: Radiation Therapy
- More than 50% will progress to myeloma
- Median time to progression approximately 2 years

Case 1

- 62-year-old male, asymptomatic
- Total protein elevated to 9.4.
- 1.0 g/dL IgG kappa
- Normal FLC ratio
- Skeletal survey no lytic lesions
- Diagnosis?

- 62-year-old male, asymptomatic
- Total protein elevated to 10.2
- 2.3 g/dL IgA kappa
- Abnormal FLC ratio 10
- Skeletal survey no lytic lesions
- Next step?

Case 2

- 52-year-old male, asymptomatic. Total protein elevated to 10.4. SPEP shows 3.6 g/dL IgG lambda, abnormal FLC ratio 0.08. Urine PEP shows 190 mg/day BJP. 30% BMPC, standard risk cyto/FISH. No anemia, renal failure. Normal Calcium
- PET-CT scan no lytic lesions
- Diagnosis?

Case 3

63-year-old man with a past medical history of diabetes and congestive heart failure who presents with increasing fatigue. His laboratory results are as follows:

- Elevated total serum protein: 10.3 g/dL
- Hemoglobin: 11.5 g/dL
- Serum creatinine: 2.1 mg/dL
- Serum IgGκ monoclonal protein: 3.5 g/dL
- Serum free light-chain kappa/lambda ratio: 70
- β_2-microglobulin: 2.0 mg/L
- A bone marrow biopsy reveals 40% monoclonal plasma cells. Fluorescence in situ hybridization (FISH) and cytogenetic analysis on the marrow are normal. A skeletal survey is also normal. Whole body MRI shows 2 large lytic lesion in the pelvis and femur.
- Diagnosis?
- Treatment Recommendations?

Case 4

- 51 yo male
- CBC, CMP wnl
- Skeletal survey: negative
- PET-CT: negative
- SPEP: 1.1 gm IgG kappa
- FLC ratio = 101
- Bone marrow: 20% plasma cells
- Diagnosis?

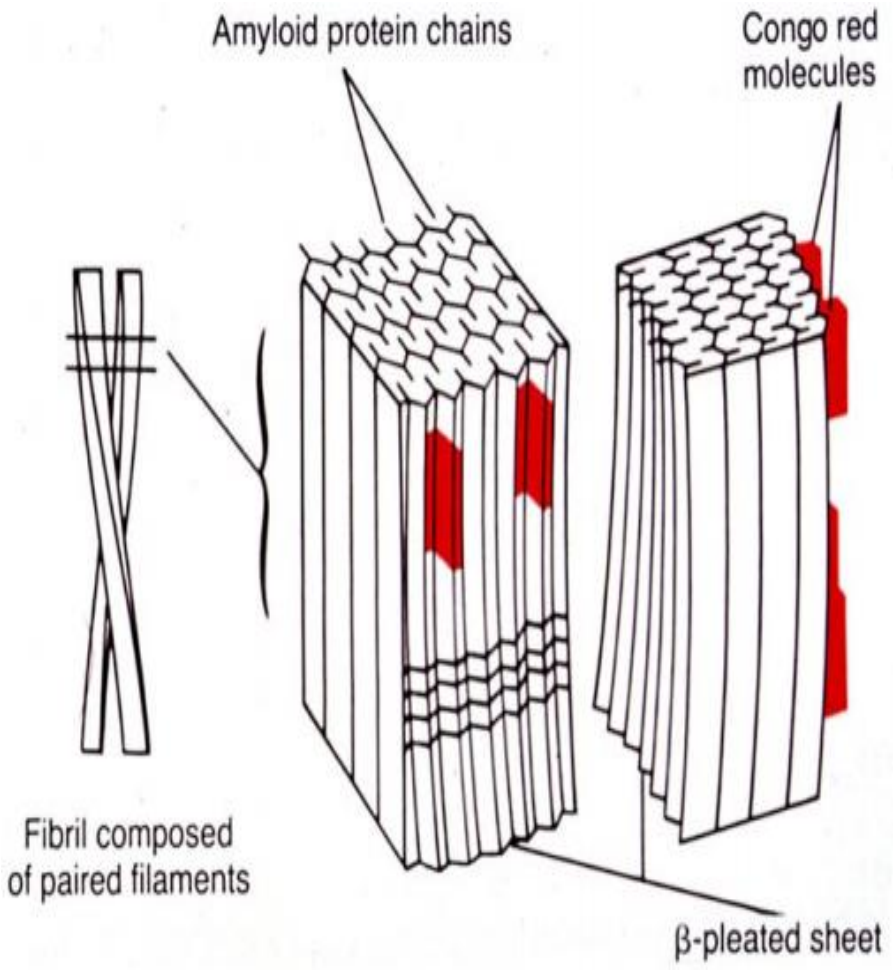
Case 5

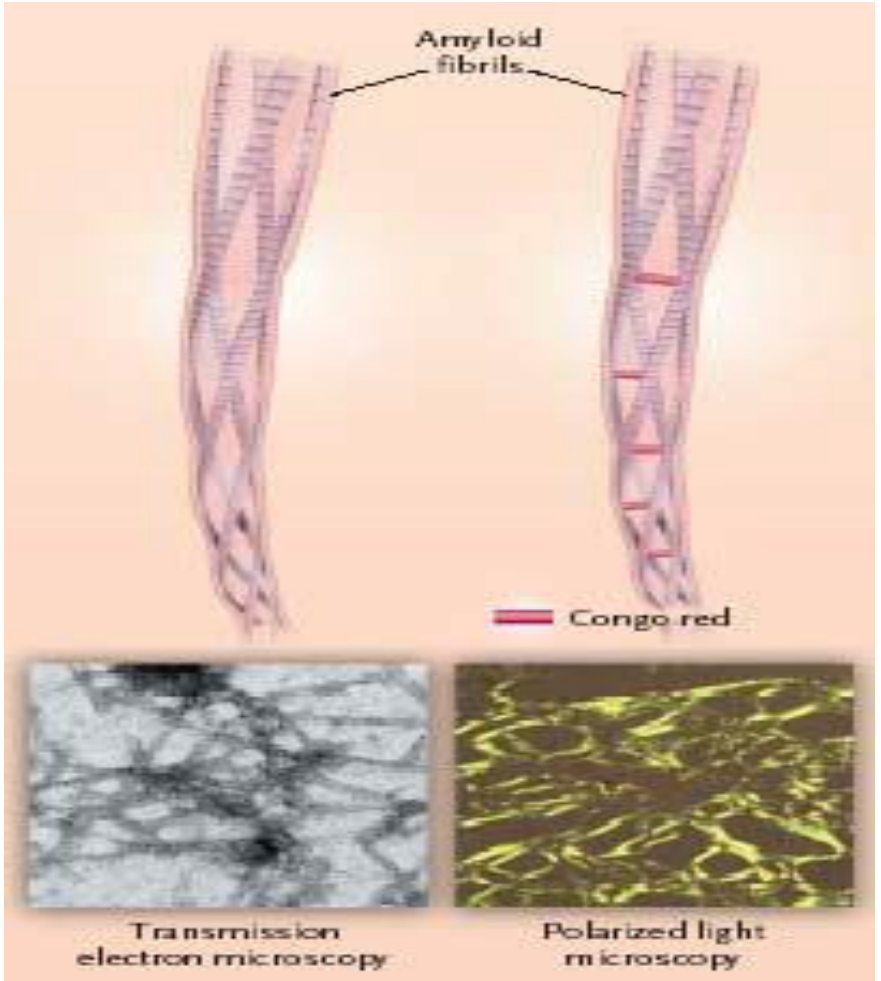
- 55-year-old male who was diagnosed with multiple myeloma when he presented to his primary care physician with increased fatigue. Initial work-up showed a hemoglobin level of 10.2 g/dL,
- Serum creatinine: 2.1 mg/dL
- Serum calcium: 10.2 mg/dL
- IgA kappa monoclonal protein: 2.6 g/dL
- Serum kappa free light-chain: 1700 mg/L
- Serum lambda free light-chain: 12 mg/L
- 24-hour urine test: M spike 1230 mg/day, all kappa light-chain
- A skeletal survey showed scattered small lucencies in the femur and humerus. A bone marrow biopsy showed 40% to 50% monoclonal plasma cells, and FISH studies showed the t(4;14) translocation.
- The patient was started on Velcade-Revlimid-Dex. After 4 cycles of therapy, which he tolerated well, his testing reveals:
- Serum M spike: 0.2 g/dL
- Kappa free light-chain: 160 mg/L
- Lambda free light-chain: 5 mg/L
- 24-hour urine test: 120 mg/d M-spike
- Next step?

Thank you for your attention!

Amyloidosis

- Protein misfolding disorder
- Conversion of peptide from soluble state to highly organized aggregate
- Fibril formation
- Cellular injury
- Organ dysfunction





N Engl J Med 2003;349:583

Light chain (AL) Amyloidosis: Background

- AL is the most common type of systemic amyloidosis
- Approximately 3000 new cases annually in US
- Median age at diagnosis 65 years
- Male predominance (70%)
- AL is a low tumor burden plasma cell disorder
- Multi-systemic involvement (heart, kidney, liver, GI, ANS, PNS) with dominant site of involvement
- Lambda light chain more commonly involved 2:1

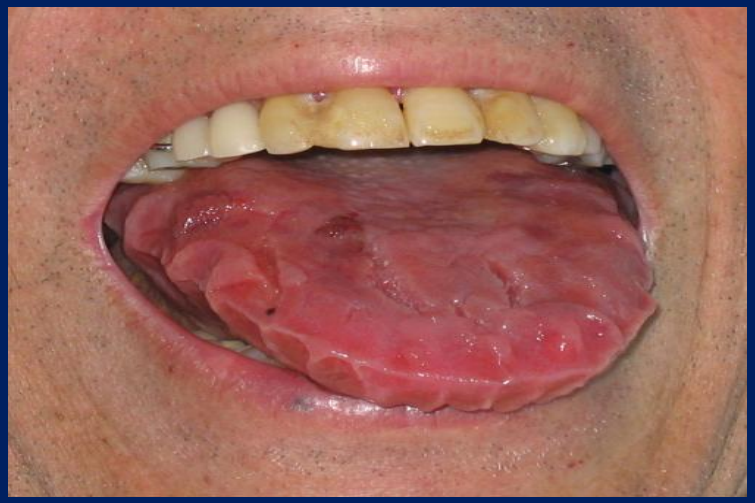
Learning objectives

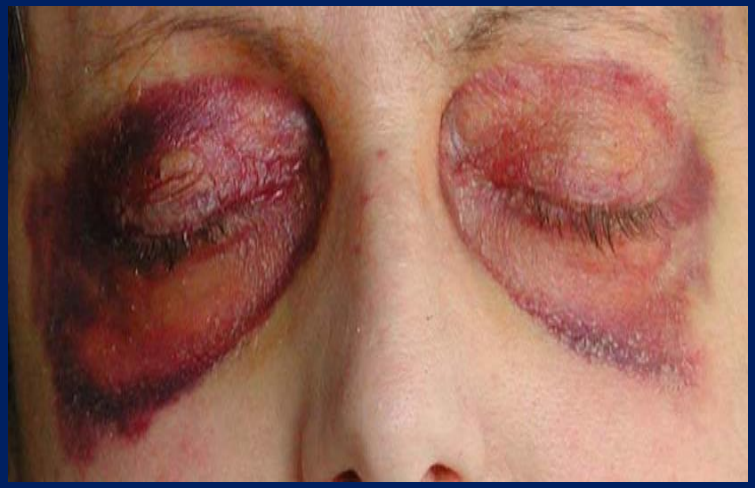
- **When should I suspect Amyloidosis & initiate screening?**
- **How do I screen when I suspect AL?**
- **How is the diagnosis confirmed when my index of suspicion is high?**
- **How do I assess the prognosis?**
- **Therapy Options**

AL Amyloidosis: Consider the Diagnosis

Clinical presentation in 868 patients with AL

Features	%
Fatigue	68
Peripheral edema	62
Weight loss (kg), median 8 kg	43
Exertional dyspnea	40
Orthostatic hypotension	27
Paresthesias	23
Dysgeusia	18
Macroglossia	14
Purpura	11
Diarrhea	9





Think of Amyloidosis when

- Unexplained progressive proteinuria (albuminuria) with or without renal dysfunction
- Unexplained hepatomegaly with elevated alk phosphatase
- No HTN, Restrictive CM, thickened IVS, PW, LV hypertrophy, diastolic or systolic dysfunction
- Autonomic nervous system involvement: orthostatic hypotension, early satiety due to delayed gastric emptying
- Painful, bilateral, symmetric, distal sensory neuropathy that progresses to motor neuropathy
- Macroglossia, submandibular gland enlargement, Purpura around the eyes/neck
- MGUS or MM and any of the above

AL Amyloidosis: Diagnosis

- Screen for monoclonal protein
- Tissue biopsy (Organ > Fat > Bone Marrow)
- Positive amyloid staining with Congo red stain
- Establish amyloid is light chain related *{Typing the amyloid protein-with direct sequencing, laser microdissection and mass spectrometry}*

Screen for monoclonal protein

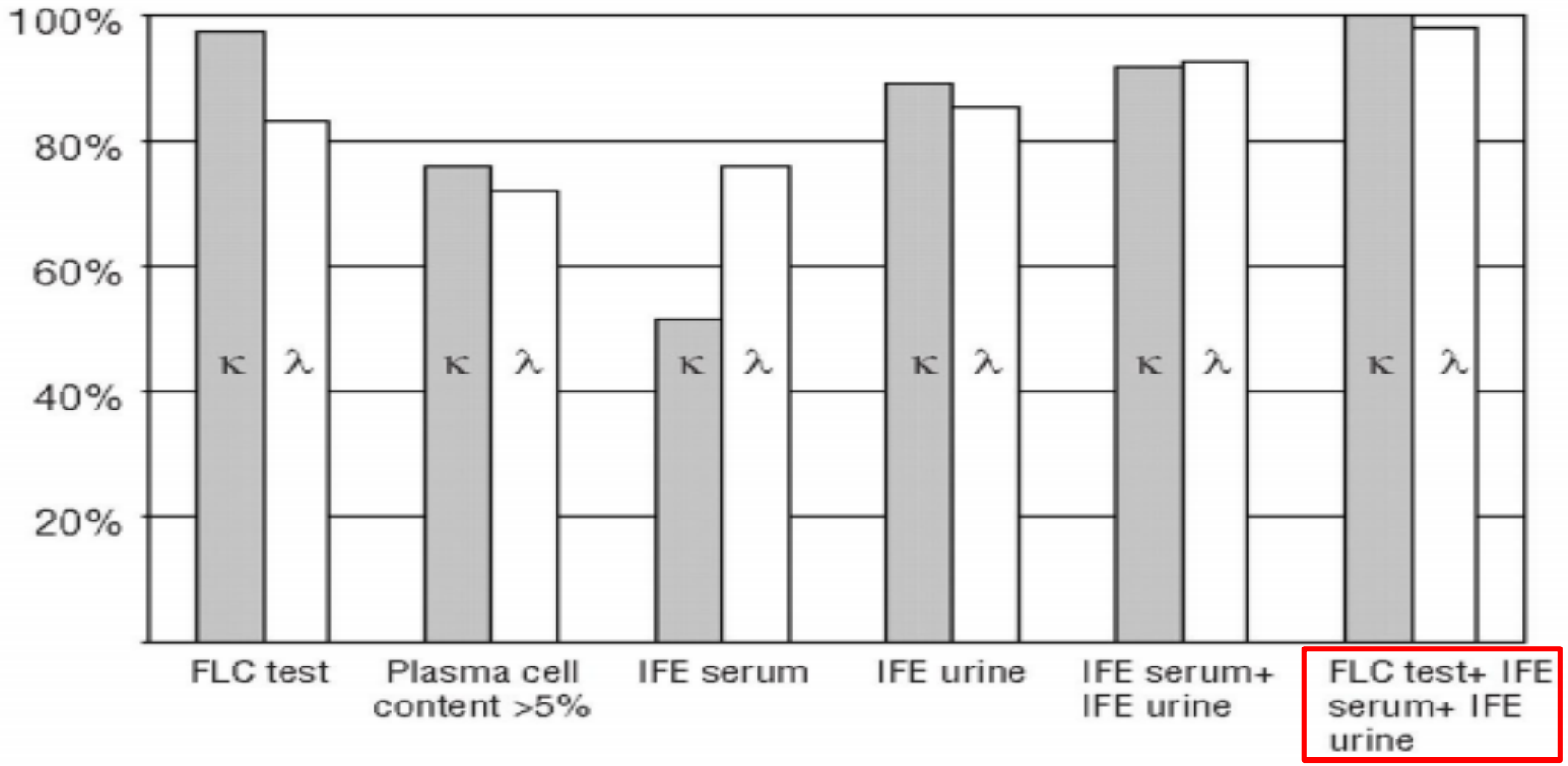
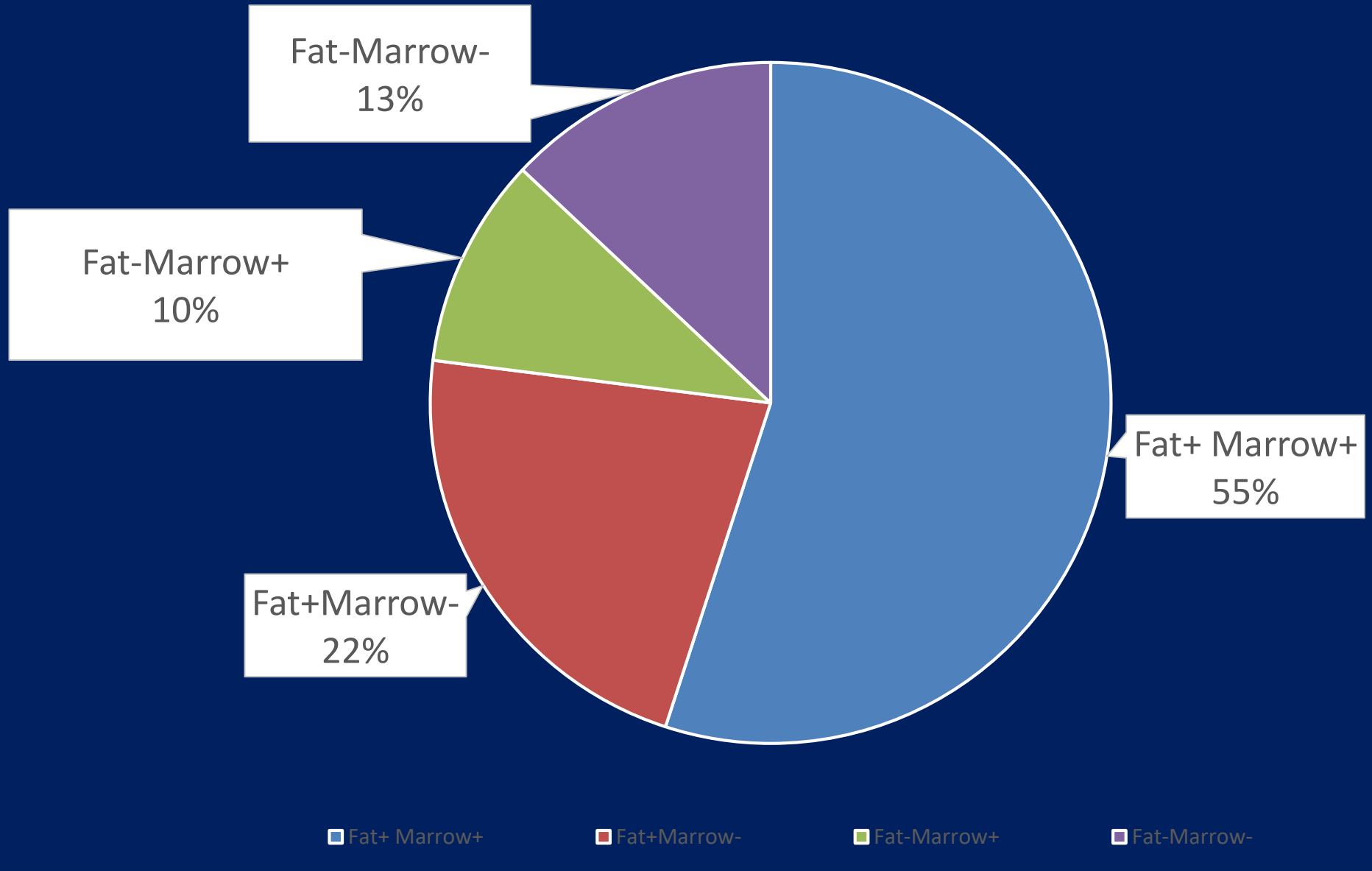


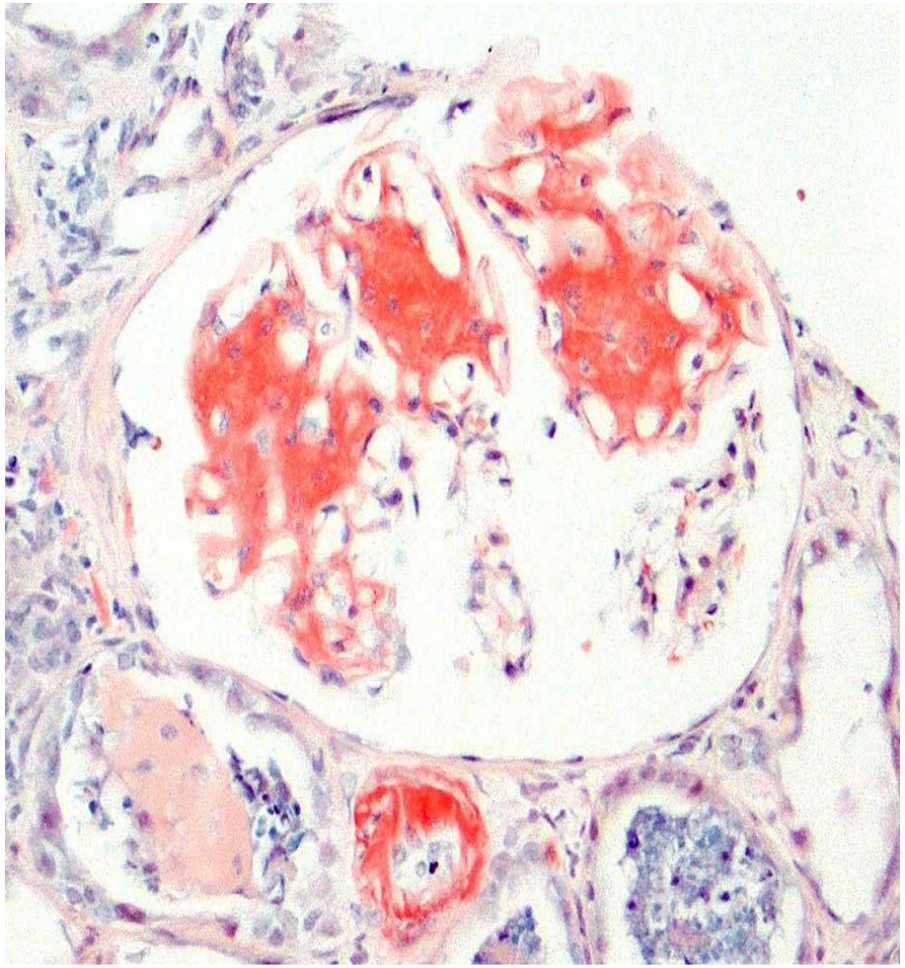
Figure 1. Sensitivities of the FLC test compared with bone marrow plasmocytosis and immunofixation specified according to light chain restriction: the FLC test has a higher sensitivity than serum immunofixation ($p<0.001$). IFE: immunofixation

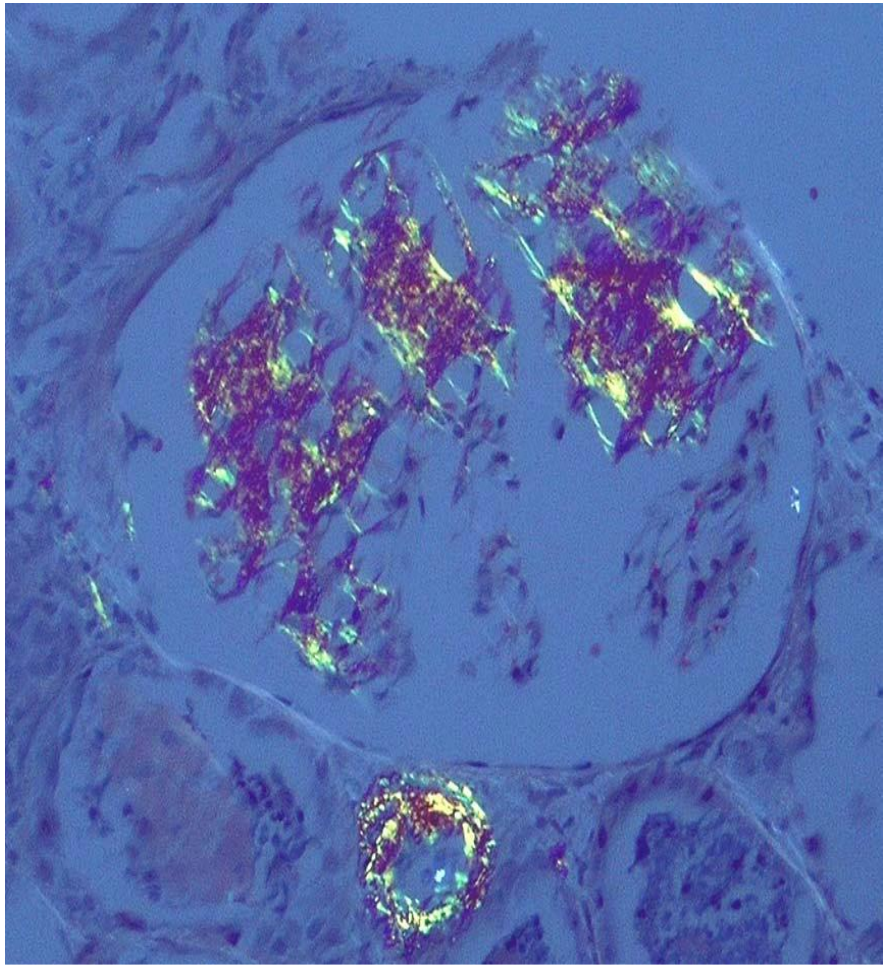
Bochtler, T. et al. Haematologica 2008;93:459-462

Tissue biopsy



Congo Red Stain (Renal Biopsy)

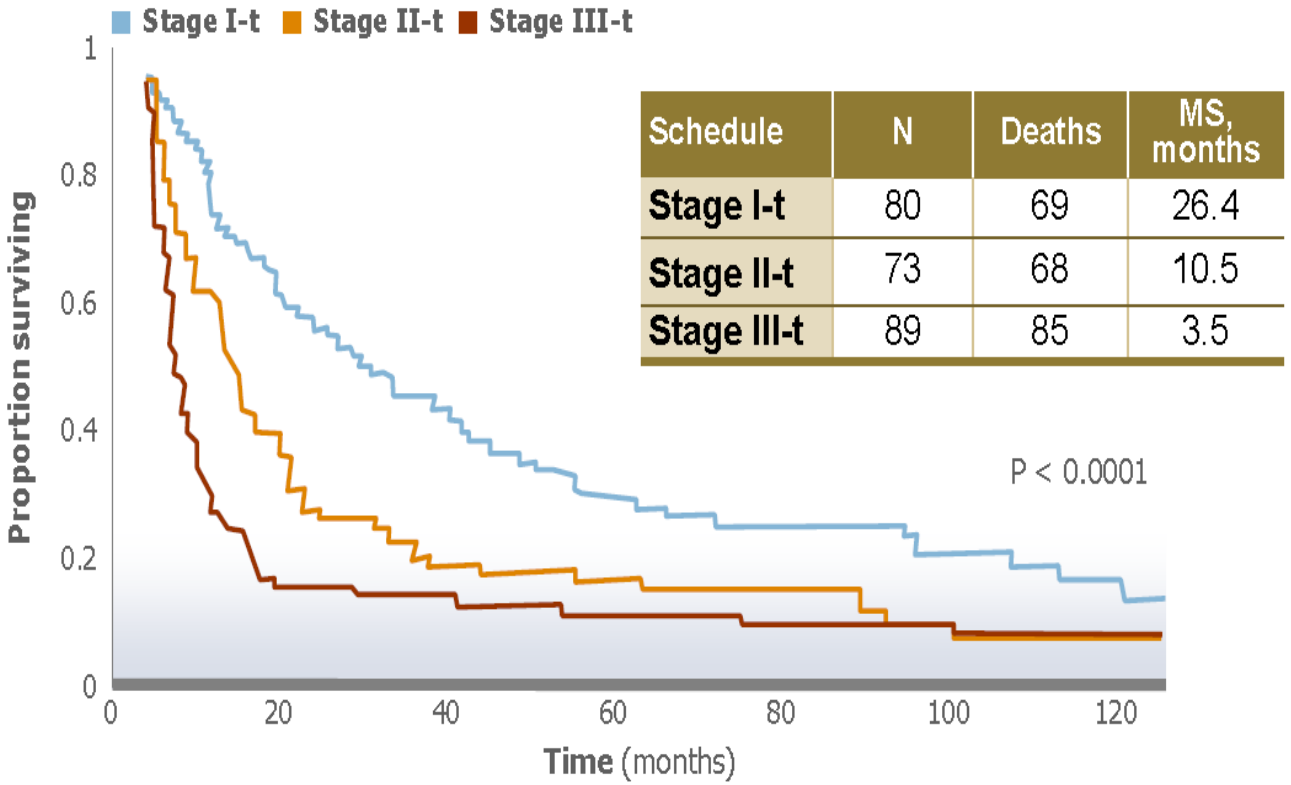




Blood 2009;114:3147

AL Amyloidosis: Defining disease extent
Staging using TropT and NT-ProBNP

In newly diagnosed AL patients

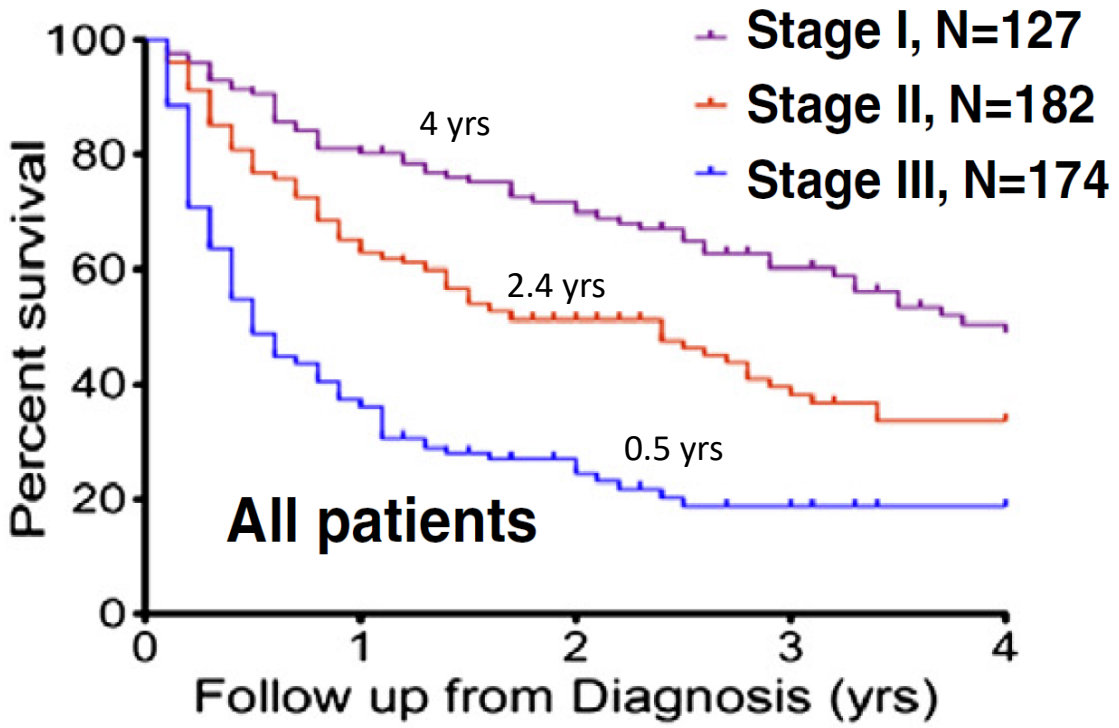


Schedule	N	Deaths	MS, months
Stage I-t	80	69	26.4
Stage II-t	73	68	10.5
Stage III-t	89	85	3.5

Stage III: NT-proBNP > 332 ng/L and cTnT > 0.035 ug/L

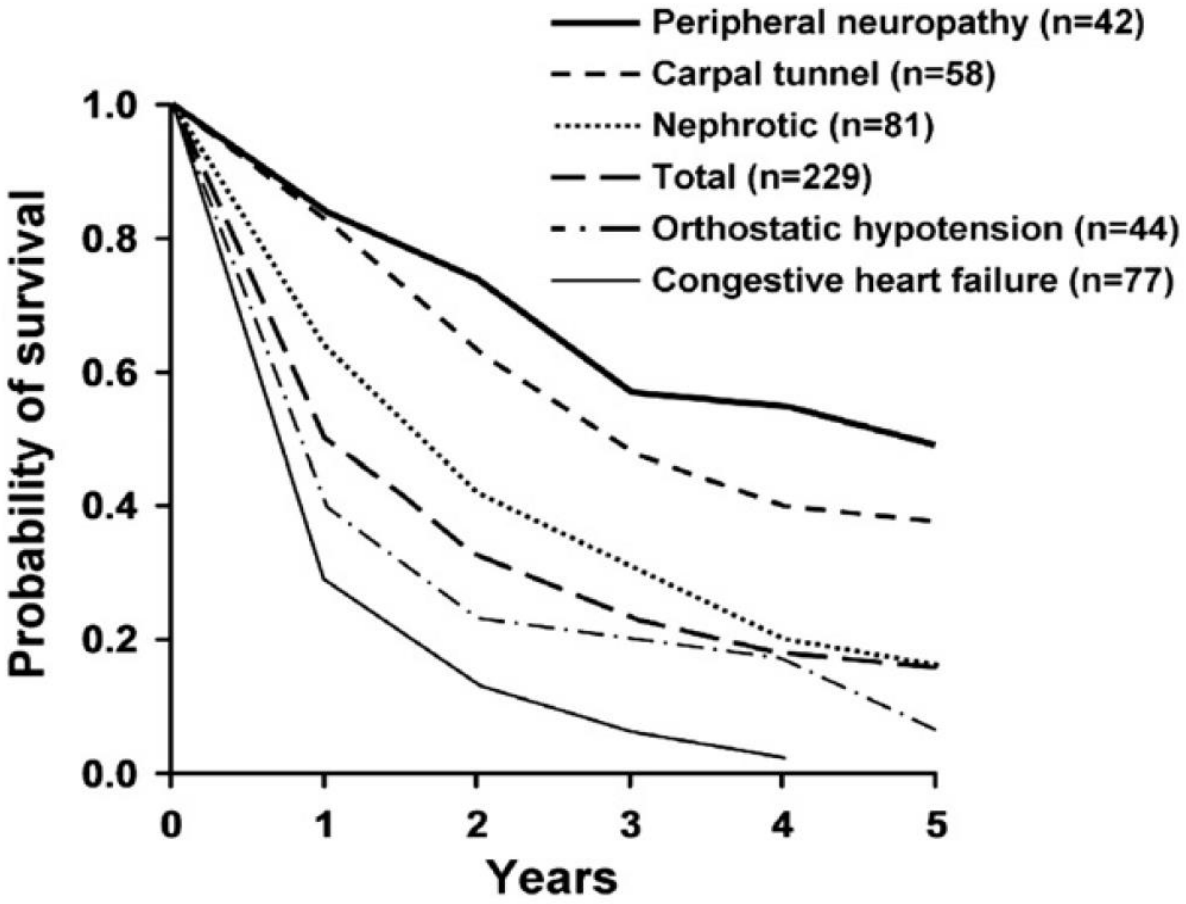
Dispenzieri A et al. JCO 2004;22:3751-3757

In AL patients undergoing transplant

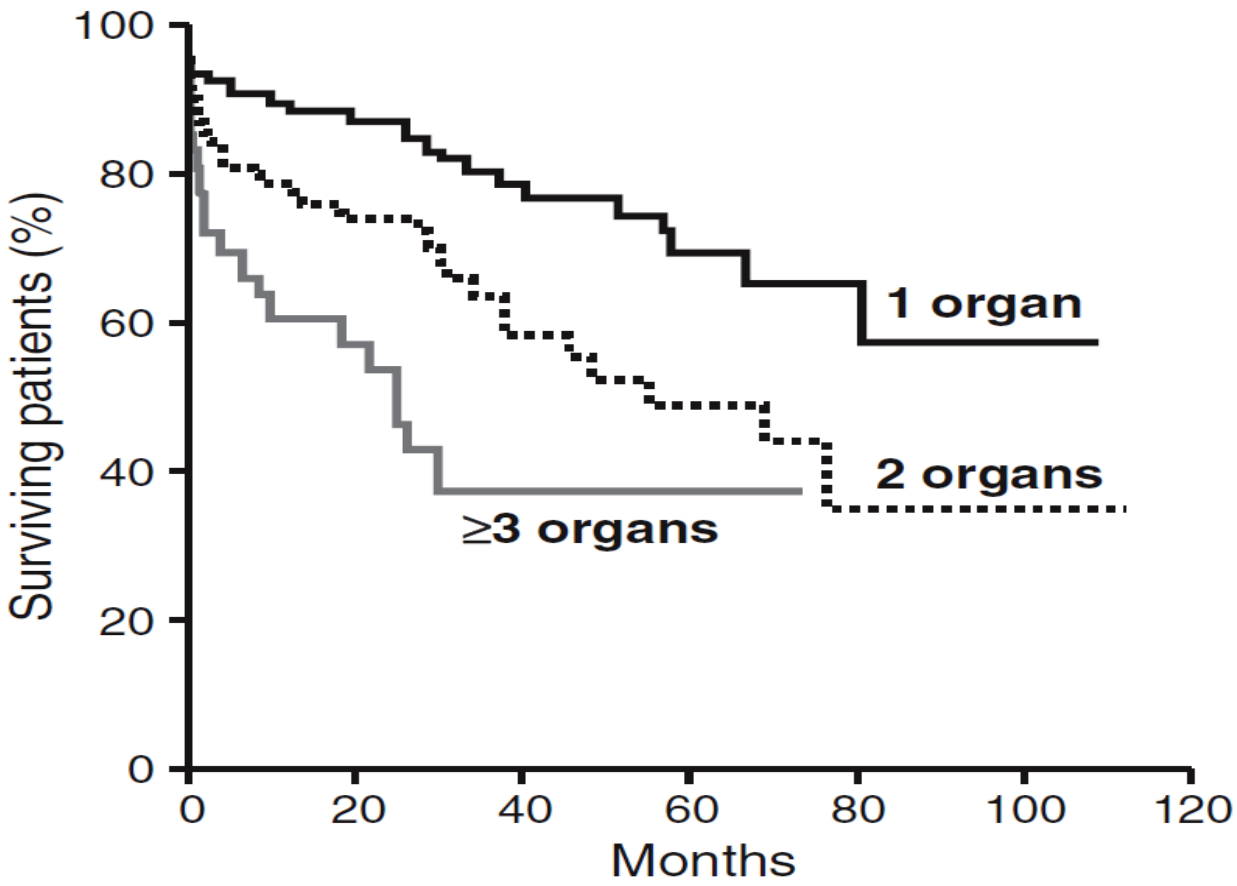


Blood 2004;104(6):1881-7

AL amyloidosis: Organ involvement and Survival

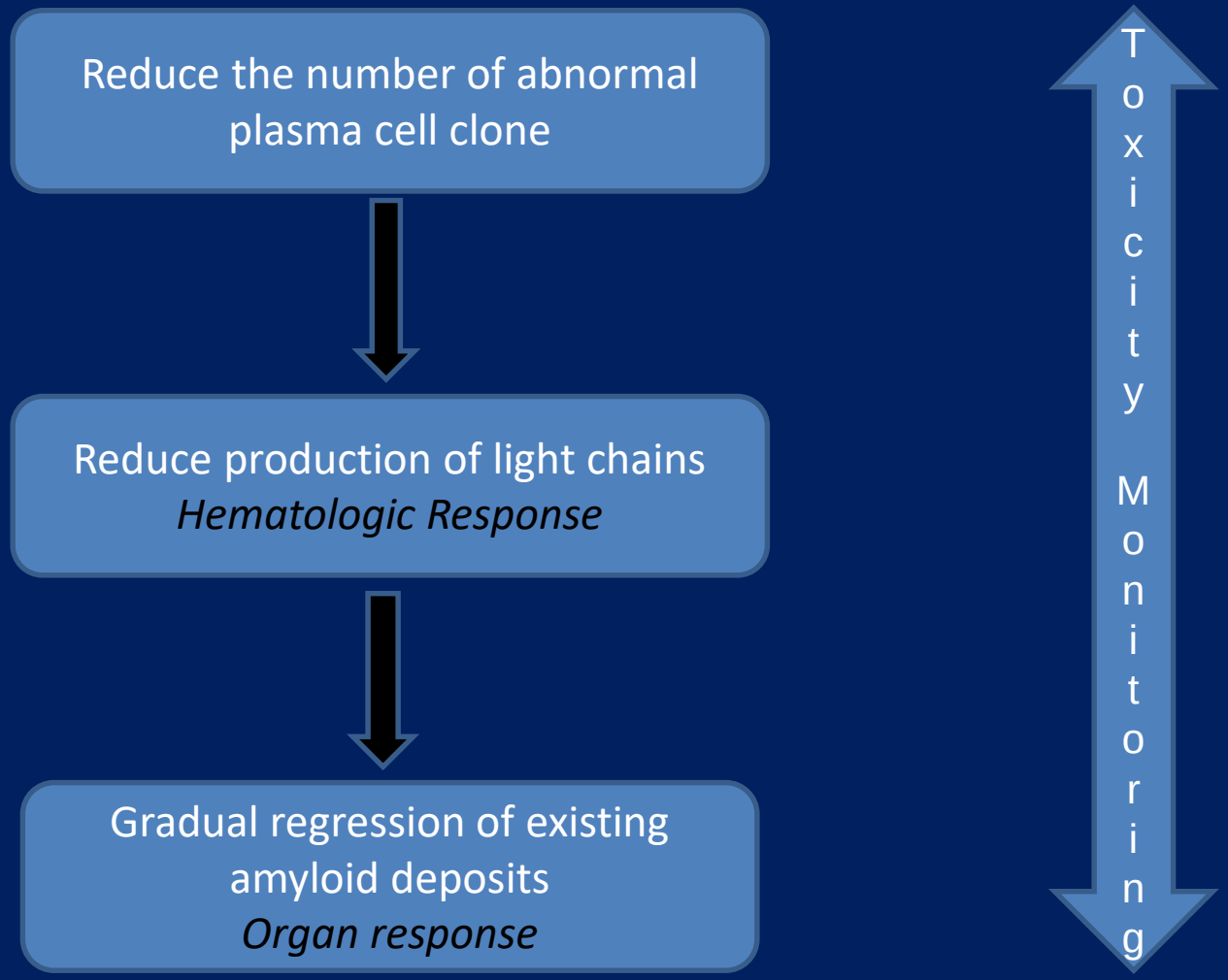


Gertz et. al. Curr Opin Oncol. 2007;19:136-141



Kyle et. al. Seminars in Hematology. 1995;32:45–59

Goal of Therapy

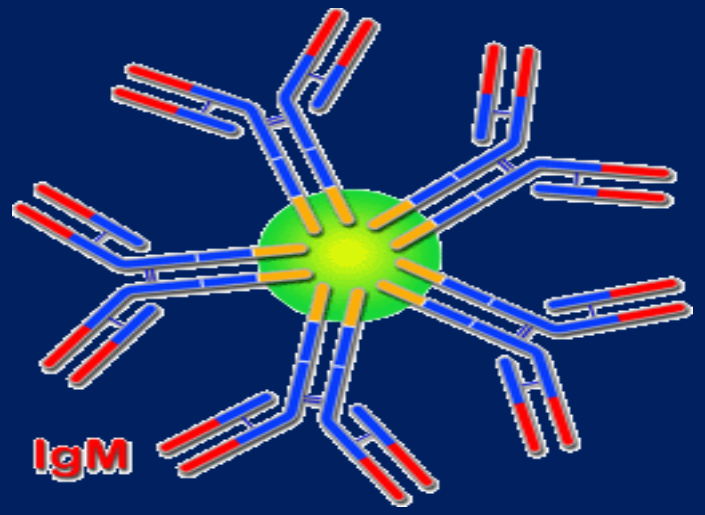


Treatment

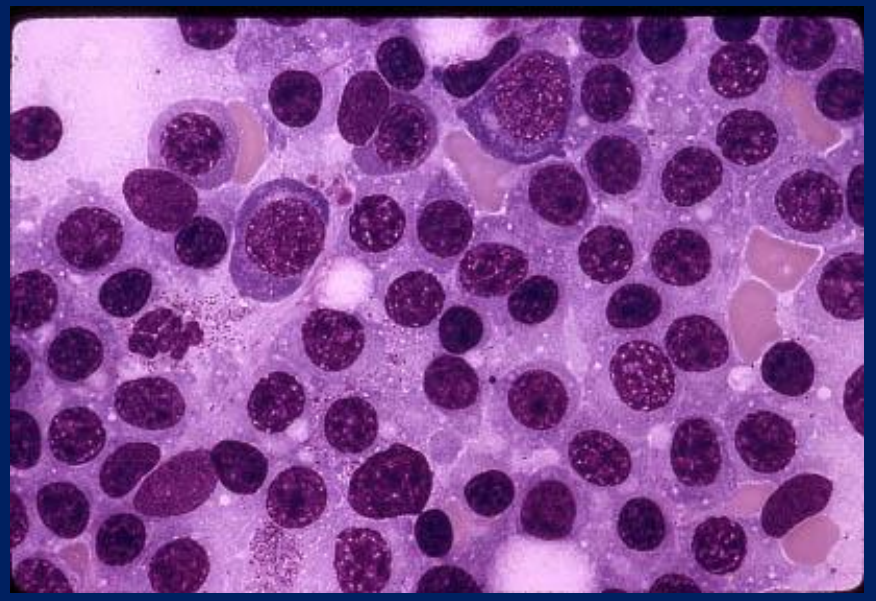
- High-dose melphalan and autologous stem cell transplant
- Oral melphalan and dexamethasone
- Dexamethasone
- Bortezomib
- Cytoxan, Bortezomib and dexamethasone
- Lenalidomide and dexamethasone
- Best supportive care
- Clinical trials: phase 3 randomized study of NEOD001 plus standard of care versus placebo plus standard of care

Waldenström Macroglobulinemia

- IgM monoclonal protein (80% time kappa)
- Lymphoplasmacytic infiltration of bone marrow (>10%)



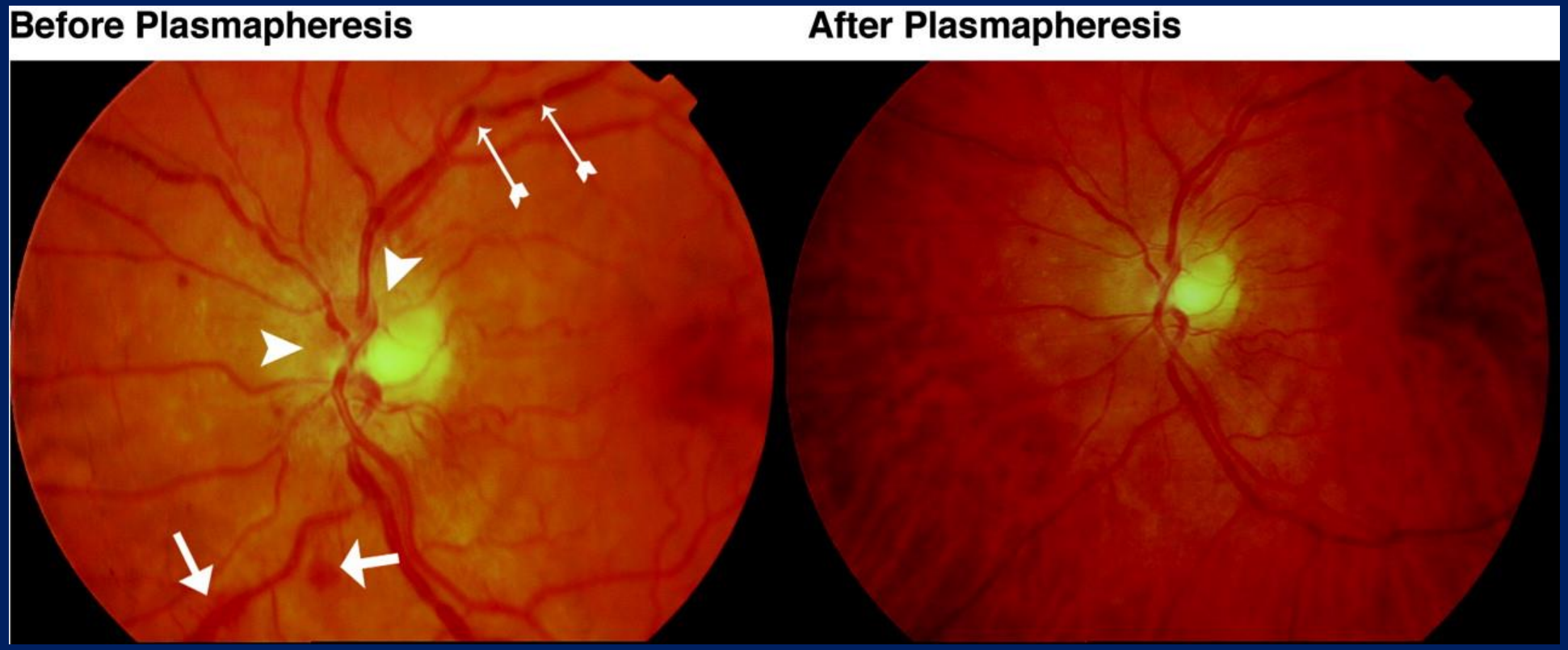
www.sanidadanimal.info/cursos/inmun/cuarto3.htm



Waldenström Macroglobulinemia

- Anemia
- Hyperviscosity syndrome
- Lymphadenopathy
- Neuropathy
- Hepatosplenomegaly
- Cryoglobulinemia
- Somatic MYD88 mutation

Hyperviscosity-Related Retinopathy in a Patient with Waldenström Macroglobulinemia



Menke MN et al, Invest. Ophthalmol. Vis. vol. 49 no. 3

- 70 year old with PMHx of HTN diagnosed with smoldering myeloma with 12% plasma cells in the bone marrow in 2006
- 09/2008 developed ARF creatinine 6.5. Hgb 10.
- FLC ratio showed lambda LC proliferation with a depressed ratio <.01. BM showed 80% PC, monosomy 13/13q deletion, ISS-3. Multiple lucent lesions throughout the axial and proximal appendicular skeleton.
- Started on Velcade and dexamethasone while undergoing dialysis. He achieved a stringent CR. Came off dialysis and went on to receive high-dose chemotherapy followed by autologous stem cell transplantation in April 2009.
- Relapsed disease in March 2012 worsening FLC ratio along with decline in renal function. Started on renally dosed Revlimid, Cytoxan and dex. Responded but developed diarrhea, and then developed a right lower limb DVT and self discontinued his medication in January 2013.
- Reported pain x 2 months to intrascapular region in 11/2013. Skeletal survey with T5 compression fracture and new lesions to clavicles.
- Received XRT for pain and started on Phase 2 clinical trial with weekly carfilzomib and dexamethasone and achieved a response.
- Relapsed/Refractory disease in 02/2016, started pomalidomide-bortezomib-dexamethasone and is currently in complete remission and stabilization of creatinine at 2.0. Remains on pamidronate and supportive care.

Multiple Myeloma Clinical Trials at CTRC

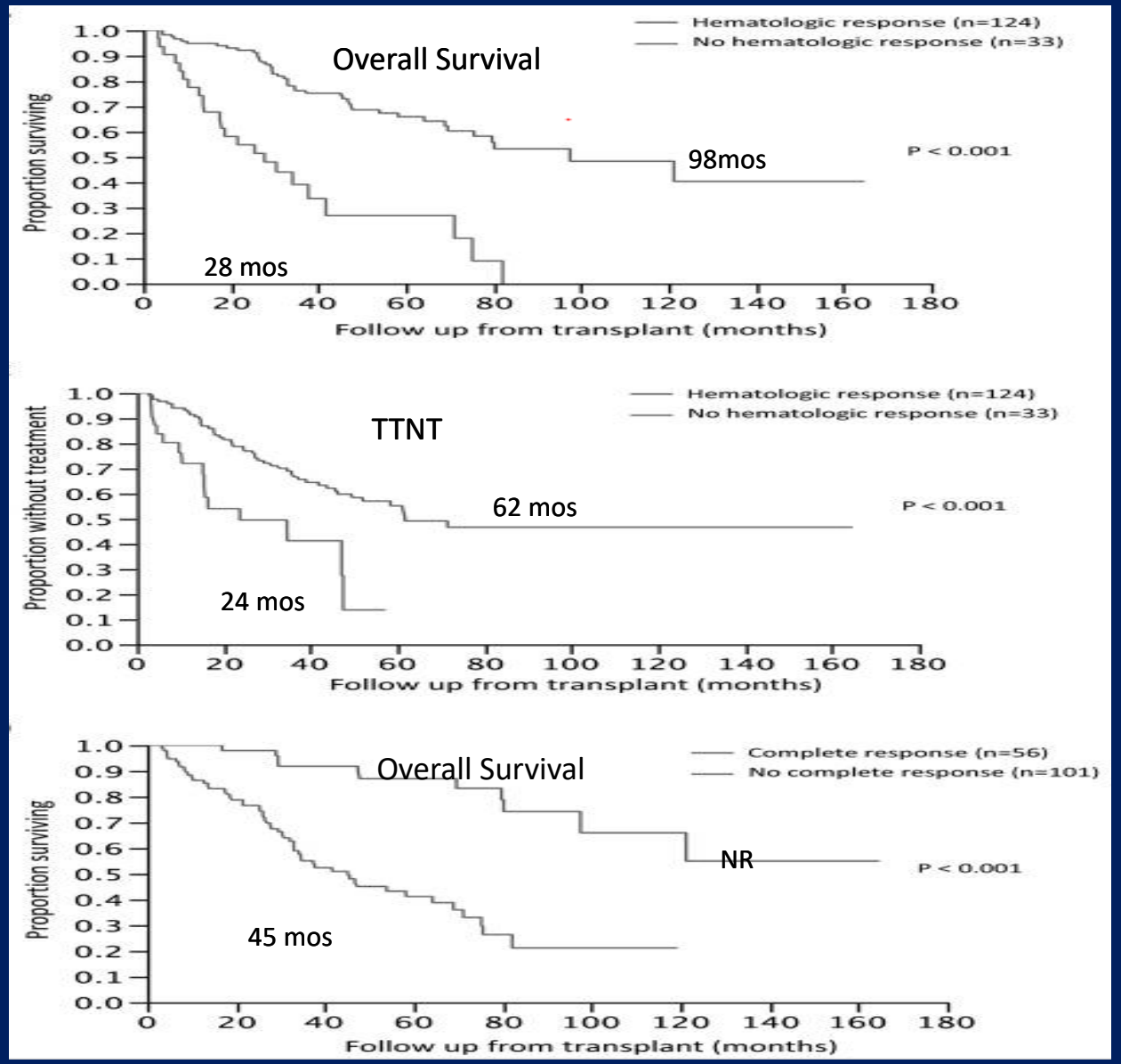
Relapsed/Refractory Multiple Myeloma

- An Open-Label, Randomized Phase 3 Trial of Combinations of Nivolumab, Elotuzumab, Pomalidomide and Dexamethasone in Relapsed and Refractory Multiple Myeloma
- **ACY-241:** A selective oral HDAC6 inhibitor given with Pomalidomide and dexamethasone. All oral regimen.

Untreated Multiple Myeloma

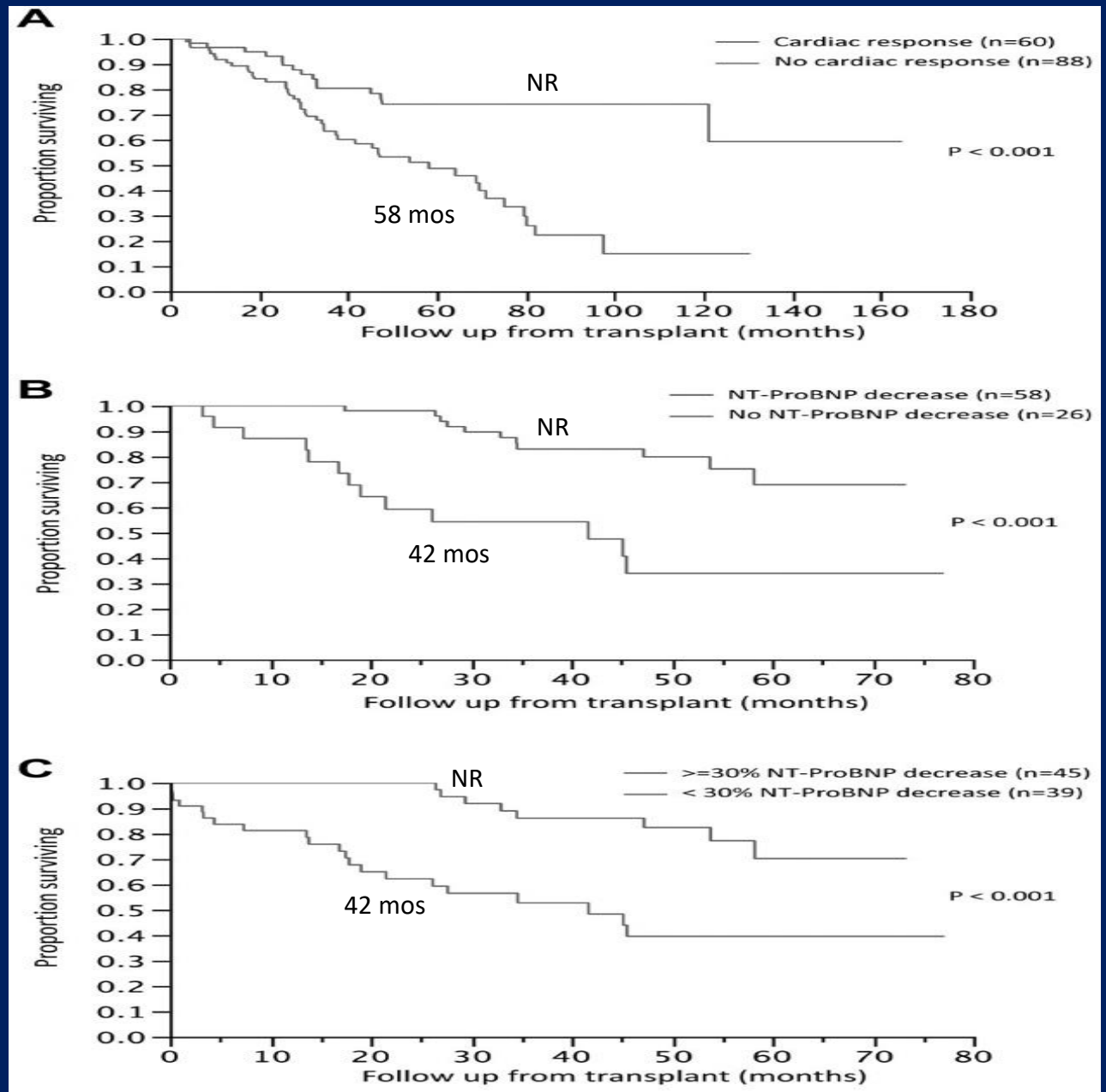
- **Phase III trial Daratumumab** in combination with Revlimid/dexamethasone vs. Revlimid/ dexamethasone.
- **E1A11 Endurance (VRd vs CRd)** – A study comparing VRd vs. CRd followed by lenalidomide maintenance in newly diagnosed MM of standard risk

Impact of hematological response on OS



Madan et. al. Blood 2012;119:1117-1122

Impact of organ response on OS

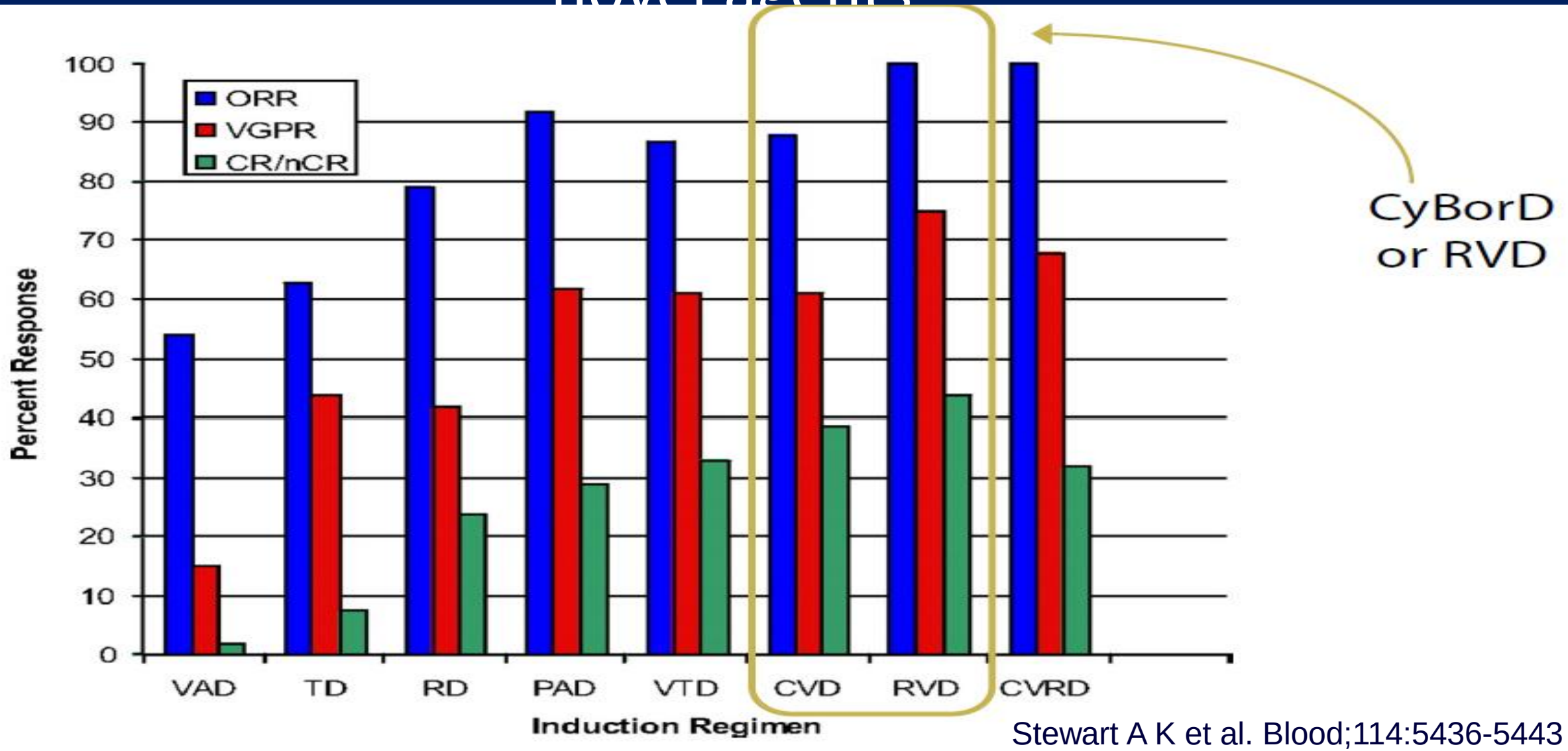


Madan et. al. Blood 2012;119:1117-1122

UT Medicine CTRC
Health Science Center San Antonio

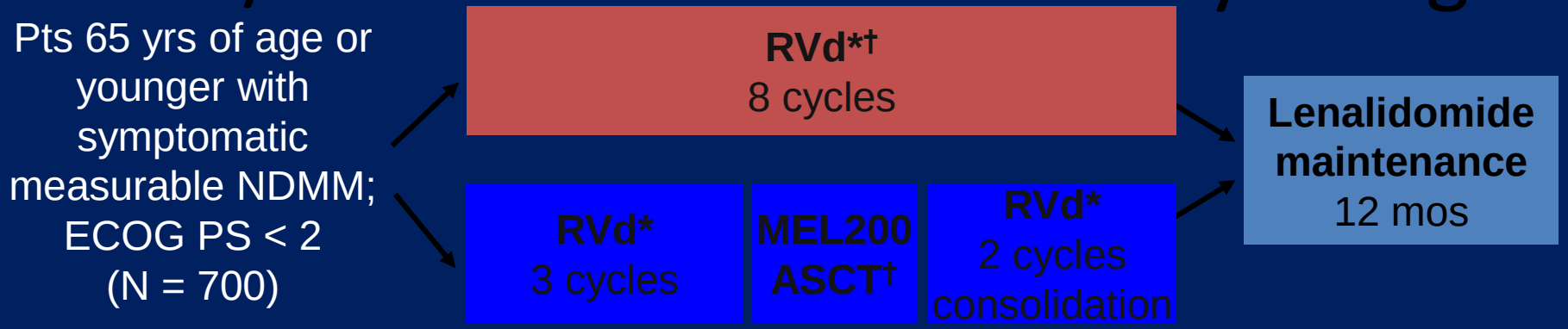
Thank you for your attention!

Induction regimen
Response rates and depth of response improved with novel agents



Stewart A K et al. Blood;114:5436-5443

What is the role of upfront transplant in the era of novel agents? IFM/DFCI 2009: Phase III Study Design

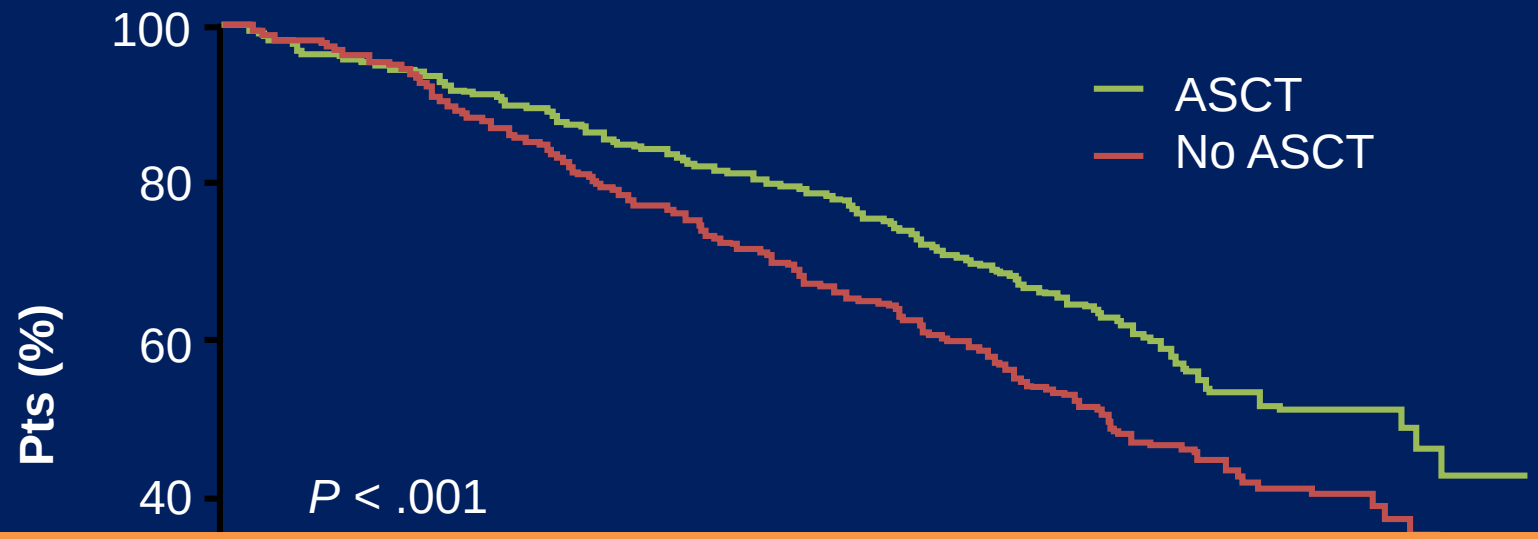


*RVD: bortezomib 1.3 mg/m^2 IV on Days 1, 4, 8, 11 + lenalidomide 25 mg on Days 1-14 + dexamethasone 20 mg on Days 1, 2, 4, 5, 8, 9, 11, 12.
†Included PBSC collection with cyclophosphamide 3 g/m^2 + G-CSF after cycle 3.

- Primary objective: PFS
- Secondary objectives: ORR, MRD, TTP, OS, safety

Attal M, et al. ASH 2015. Abstract 391.

IFM 2009: PFS



Parameter	RVD (n = 350)	Transplantation (n = 350)	*P* Value
Median follow-up, mos	41	41	
Progression or death, n	204	158	
Median PFS, mos	34	43	
4-yr PFS, %	35	47	
HR (95% CI)	1	0.69 (0.56-0.84)	< .001

Attal M, et al. ASH 2015. Abstract 391.

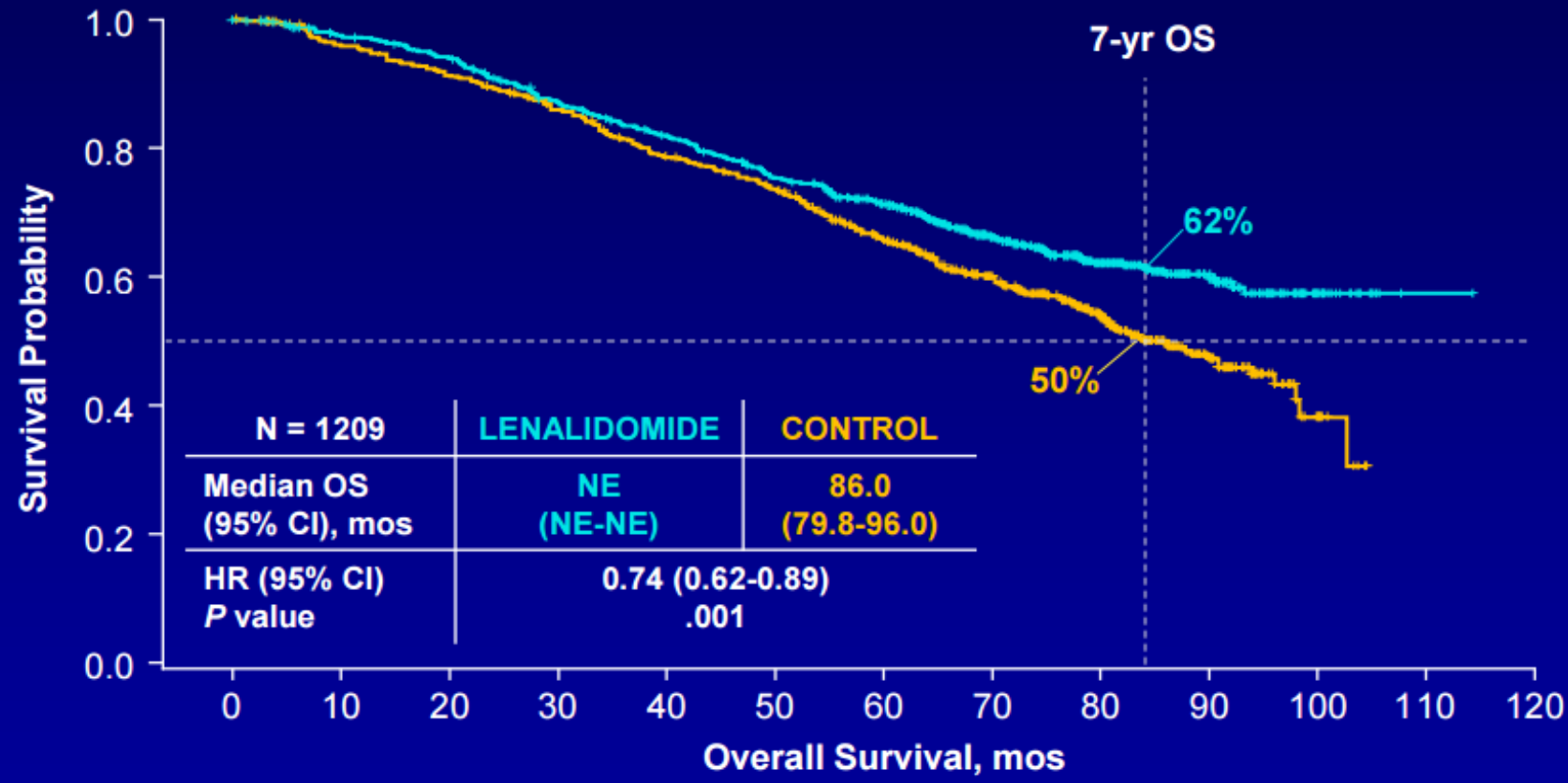
Lenalidomide Maintenance

- Upfront ASCT is the standard of care, but many patients relapse, even with complete response to ASCT
- Several maintenance trials have been published
- Meta-analysis of 3 maintenance RCT

- *Attal M et al. J Clin Oncol 2016;34(suppl):abstr 8001*

Overall Survival: Median Follow-Up of 80 Months

There is a 26% reduction in risk of death, representing an estimated 2.5-year increase in median survival[a]



N = 1209	LENALIDOMIDE	CONTROL
Median OS (95% CI), mos	NE (NE-NE)	86.0 (79.8-96.0)
HR (95% CI)	0.74 (0.62-0.89)	
P value	.001	

Patients at risk													
LENALIDOMIDE	605	578	555	509	474	431	385	282	200	95	20	1	0
CONTROL	604	569	542	505	458	425	350	271	174	71	10	0	

[a] Median for lenalidomide treatment arm was extrapolated to be 116 months based on median of the control arm and HR (median, 86 months; HR = 0.74).
HR, hazard ratio; NE, not estimable; OS, overall survival.

Attal M et al. J Clin Oncol 2016;34(suppl):abstr 8001

Doublet Vs Triplet Upfront SWOG S0777: Study Design

- Randomized phase III trial of VRd vs Rd

Stratified by ISS stage I/II/III and intent to transplant at progression

Previously untreated active MM (CRAB criteria) with measurable disease (including FLC) and CrCl > 30 cc/min (N = 525)

Lenalidomide 25 mg/day PO Days 1-21 + **Dexamethasone** 40 mg/day PO Days 1, 8, 15, 22 for six 28-day cycles (eligible n = 230)

Bortezomib 1.3 mg/m^2 IV Days 1, 4, 8, 11 + **Lenalidomide** 25 mg/day PO Days 1-14 + **Dexamethasone** 20 mg/day PO Days 1, 2, 4, 5, 8, 9, 11,12 for eight 21-day cycles (eligible n = 243)

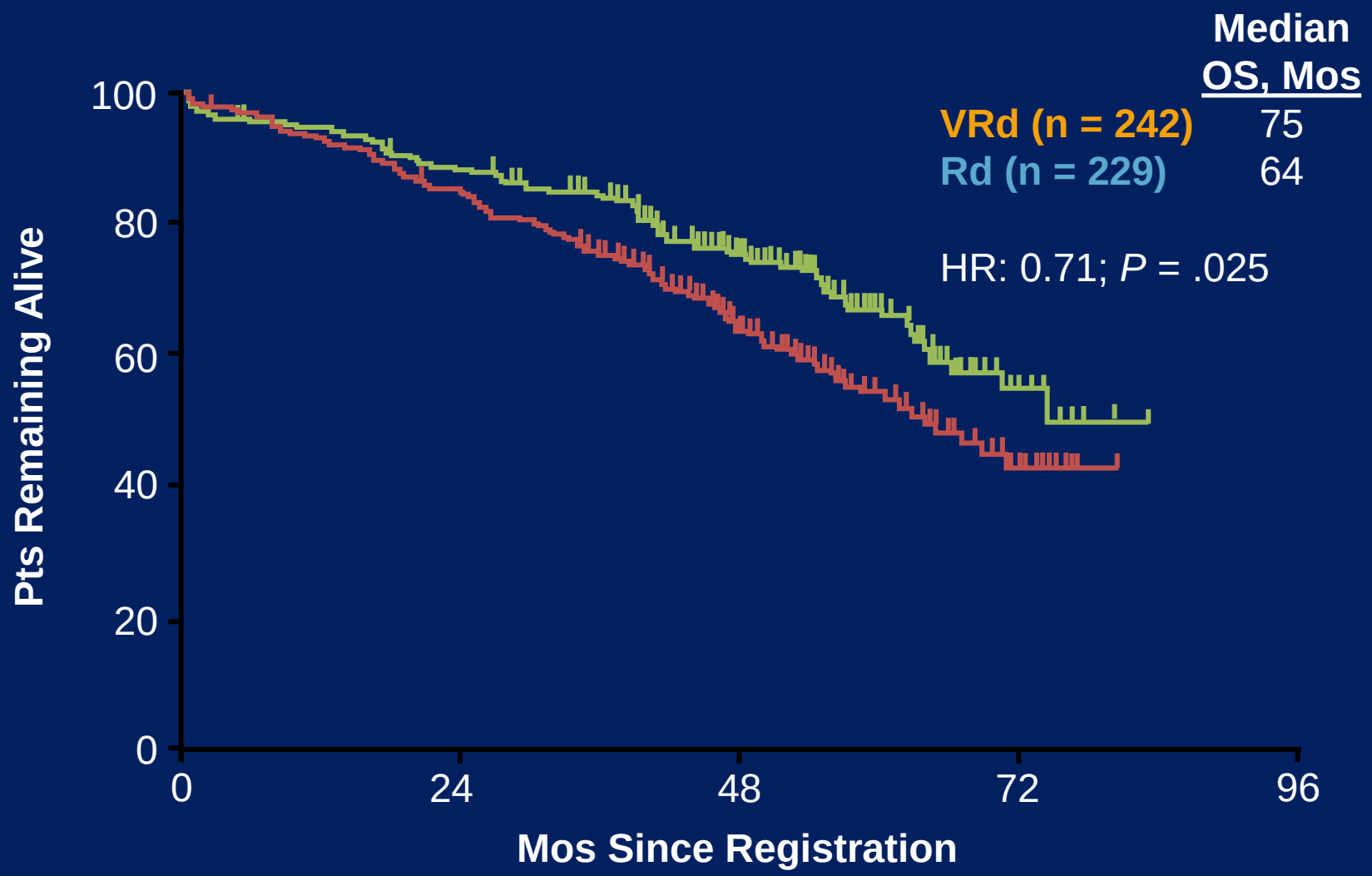
Rd maintenance until PD, unacceptable AE, or withdrawal of consent

All pts received aspirin 325 mg/day; pts in bortezomib arm received HSV prophylaxis

- Primary endpoint: PFS
- Secondary endpoints: ORR, OS, safety

Durie B, et al. ASH 2015. Abstract 25.

SWOG S0777: OS

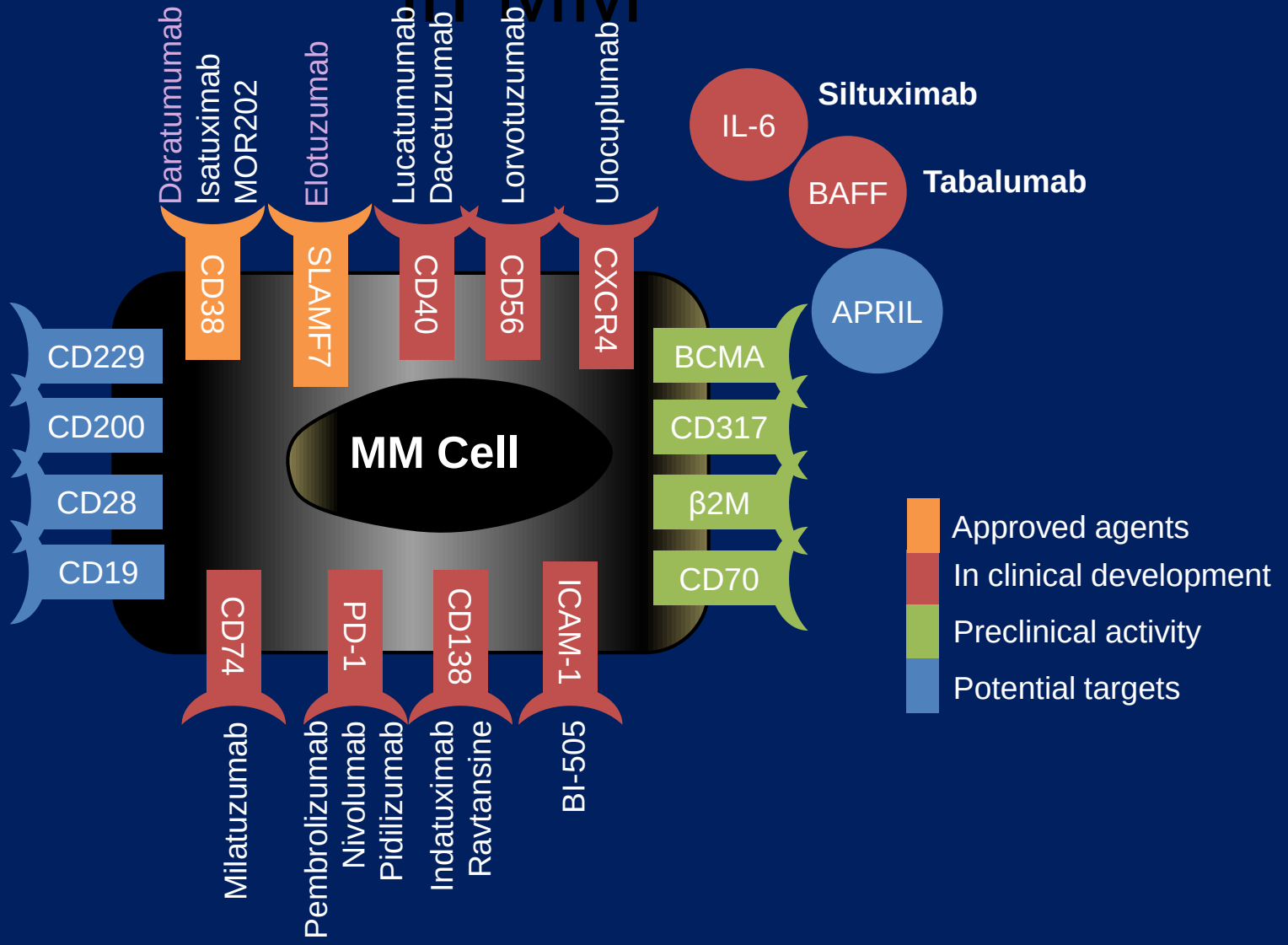


Durie B, et al. ASH 2015. Abstract 25.

Relapsed/Refractory myeloma

Drug	Class	Study arm	Control arm
Carfilzomib	Proteasome Inhibitor	Carfilzomib/lenalidomide/dex	Lenalidomide/dex
Ixazomib	Proteasome Inhibitor	Ixazomib/lenalidomide/dex	Lenalidomide/dex
Elotuzumab	Monoclonal Antibody	Elotuzumab/lenalidomide/dex	Lenalidomide/dex
Daratumumab	Monoclonal Antibody	Daratumumab/lenalidomide/dex	Lenalidomide/dex
Daratumumab	Monoclonal Antibody	Daratumumab/bortezomib/dex	Bortezomib/dex
Panobinostat	HDAC inhibitor	Panobinostat/bortezomib/dex	Bortezomib/dex

Targets for Monoclonal Antibodies in MM



Lonial S. ASCO 2016. New Drugs in Oncology: Ixazomib, Elotuzumab, and Daratumumab in Myeloma

Myeloma Rx: Summary

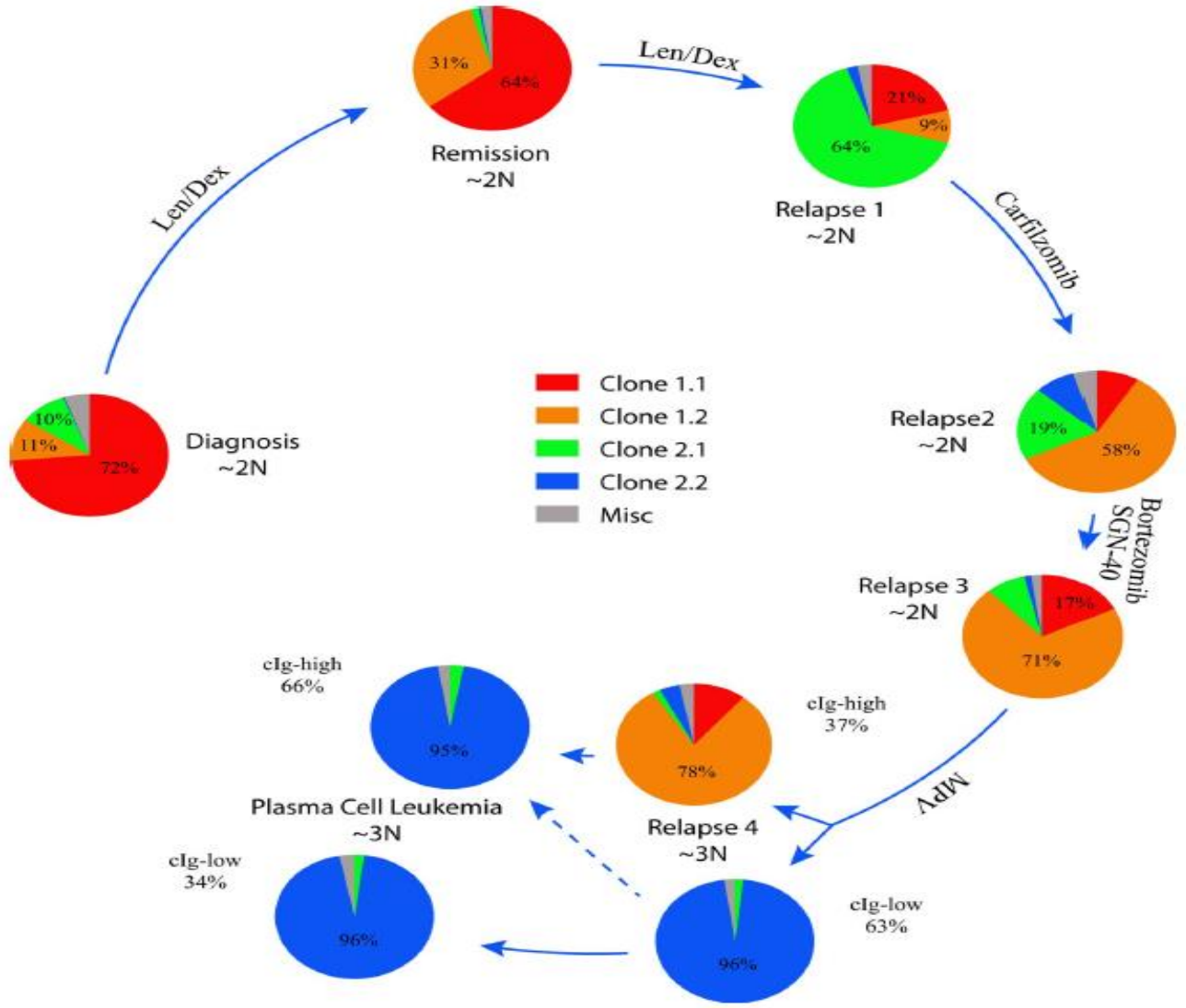
- ✓ Combination of Immunomodulatory drug and Proteasome Inhibitor is considered standard upfront regimen (Bortezomib, lenalidomide, dexamethasone)
- ✓ Upfront single autologous transplant adds benefit and is considered standard of care
- ✓ Lenalidomide maintenance is considered standard of care in standard risk
- ✓ Relapsed/Refractory disease

- 10 category 1 approved combinations in R/R myeloma (NCCN guidelines)

Genome sequencing

- Myeloma clones wax and wane in importance with time
- We will need to be craftier than the myeloma

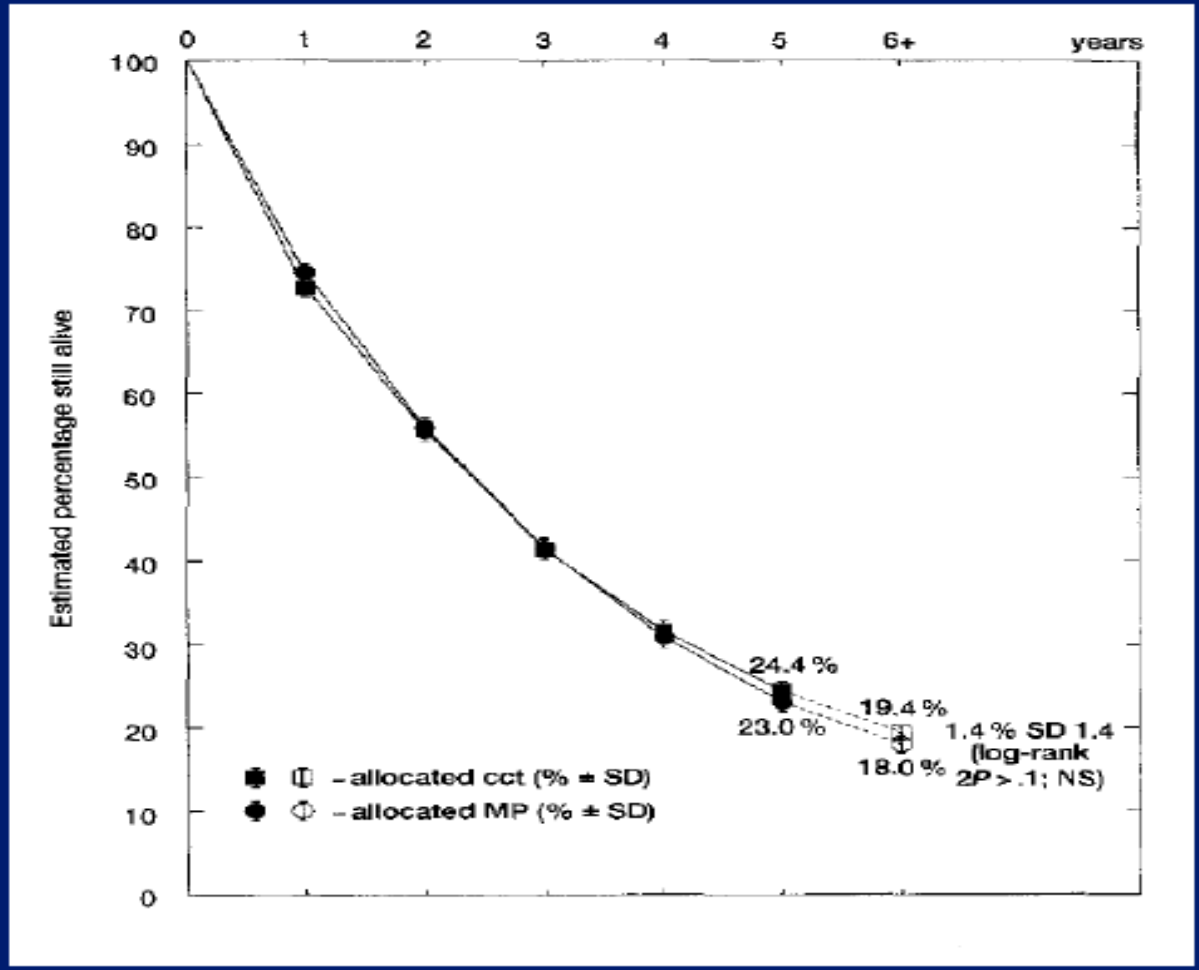
Myeloma evolution and alternating clonal dominance



Keats JJ et. Al. Blood 2012;120(5);1067-76

Melphalan Prednisone versus Conventional chemotherapy

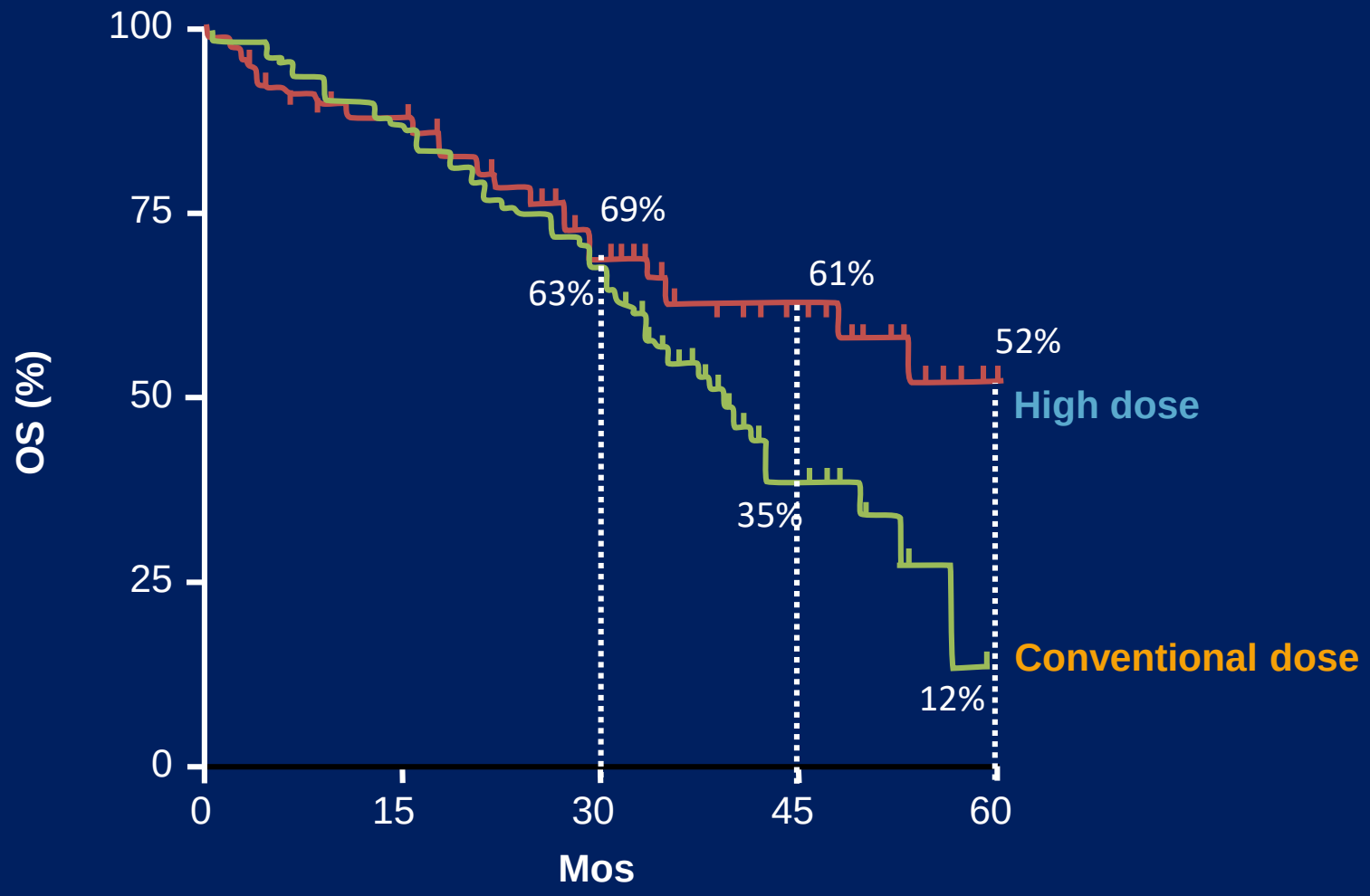
No Improvement in Therapy for Patients with Myeloma in 30 years



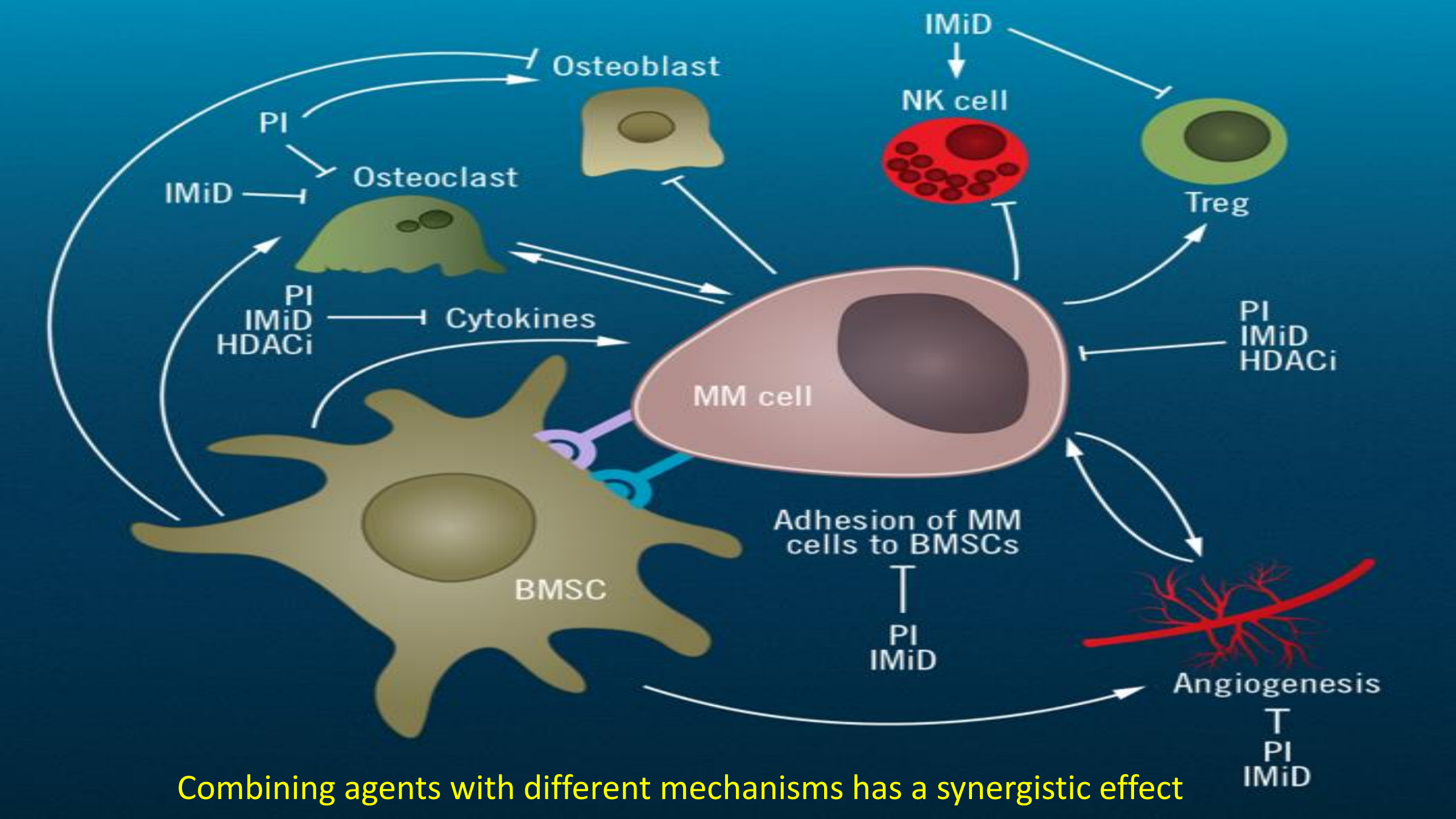
Myeloma Trialists J Clin Oncol 1998; 16: 3832-42

Transplantation vs Conventional Chemotherapy

A PROSPECTIVE, RANDOMIZED TRIAL OF AUTOLOGOUS BONE MARROW TRANSPLANTATION AND CHEMOTHERAPY IN MULTIPLE MYELOMA



Attal M, et al. N Engl J Med. 1996;335:91-97.

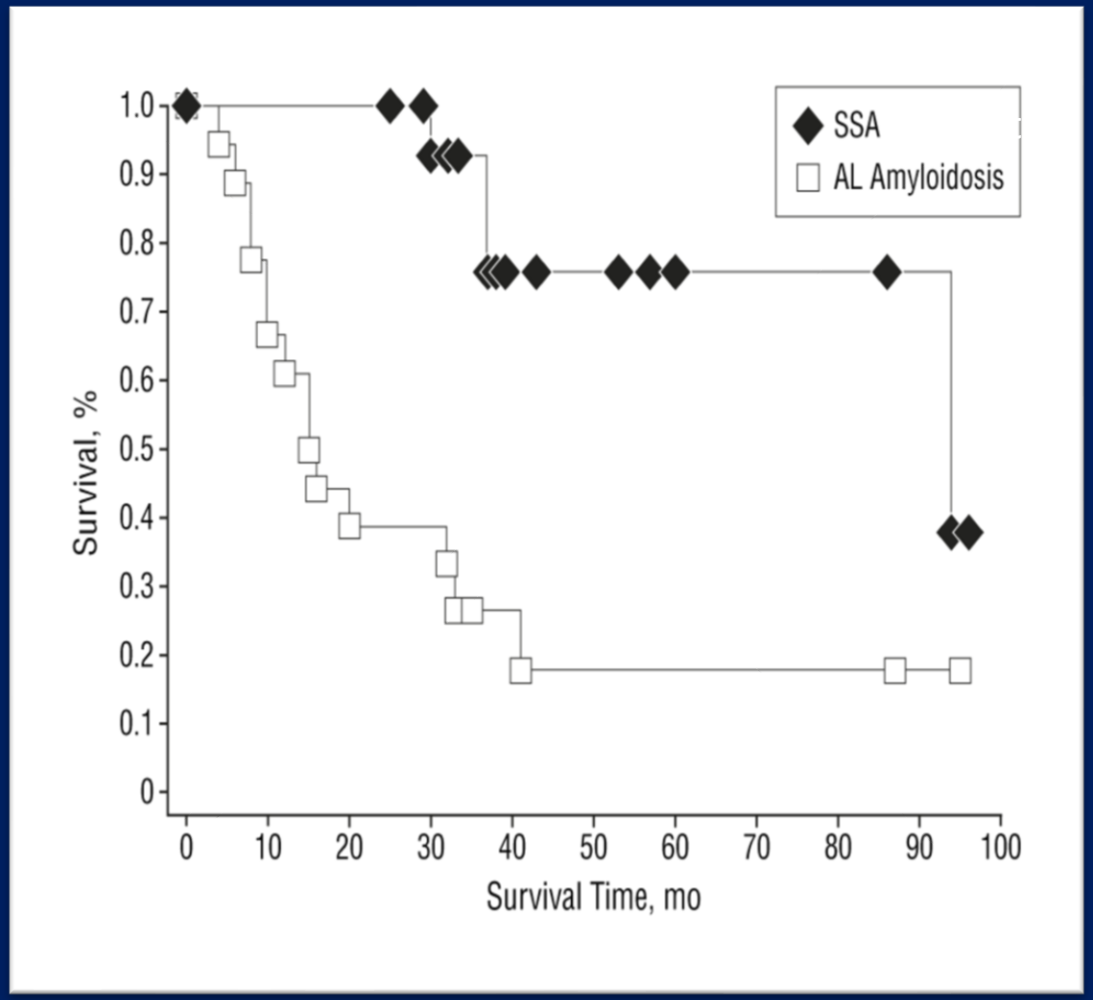


Combining agents with different mechanisms has a synergistic effect

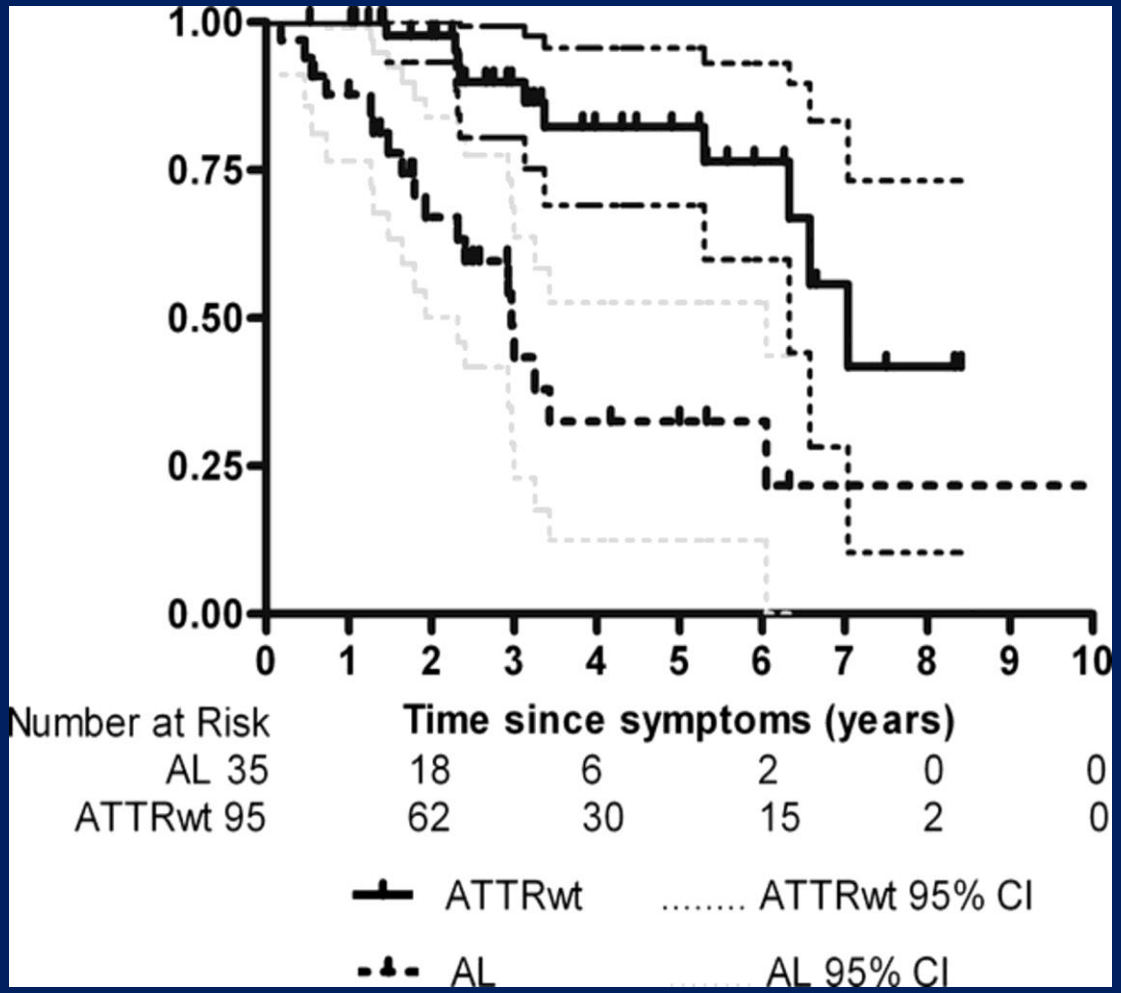
Most Common Types of Amyloidosis

Type	Abbreviation	Precursor	Site of Synthesis	Syndrome and Organs Involved	Aim of treatment	Example of treatment
Immunoglobulin light chain amyloidosis	AL	Monoclonal light chain	Bone marrow plasma cells	Primary Multi-systemic	Suppress production of monoclonal light chains	Chemotherapy Novel agents Stem cell transplant
Secondary amyloidosis	AA	Serum amyloid A	Liver	Secondary, Chronic Inflammation Kidneys	Suppress acute phase response	Anti-inflammatory Immunosuppresive Antibiotics
Senile systemic amyloidosis	SSA/TTRwt	Wild type transthyretin	Liver	Age-related Cardiomyopathy Carpal tunnel	Symptom management	Clinical Trial
Transthyretin amyloidosis	TTRm	Mutant transthyretin	Liver	Hereditary PNS, ANS, Cardiomyopathy	Eliminate source of variant protein	Orthotopic liver transplantation

Survival: SSA/ATTRwt vs AL



Belinda Ng et. Al . Arch Intern Med. 2005;165(12):1425-29



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