

Intérêt clinique de l'identification des chaînes légères libres

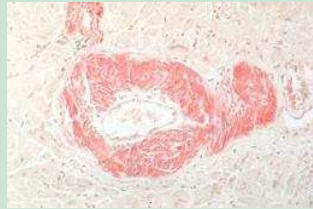
Jean-François Lambert
Hématologie - CHUV

Healthy 69 yo female

- Negative past medical history
- 2/07 acute pulmonary edema
 - Progressive SOB since a few months
 - Echo : hypertrophic cardiomyopathy with severe diastolic dysfunction
 - Coronarography : normal
 - Aggravation despite diuretics
- Labs
 - Normal CBC, Creat 80 μ mol/l, nl LFT's

Cardiac evaluation

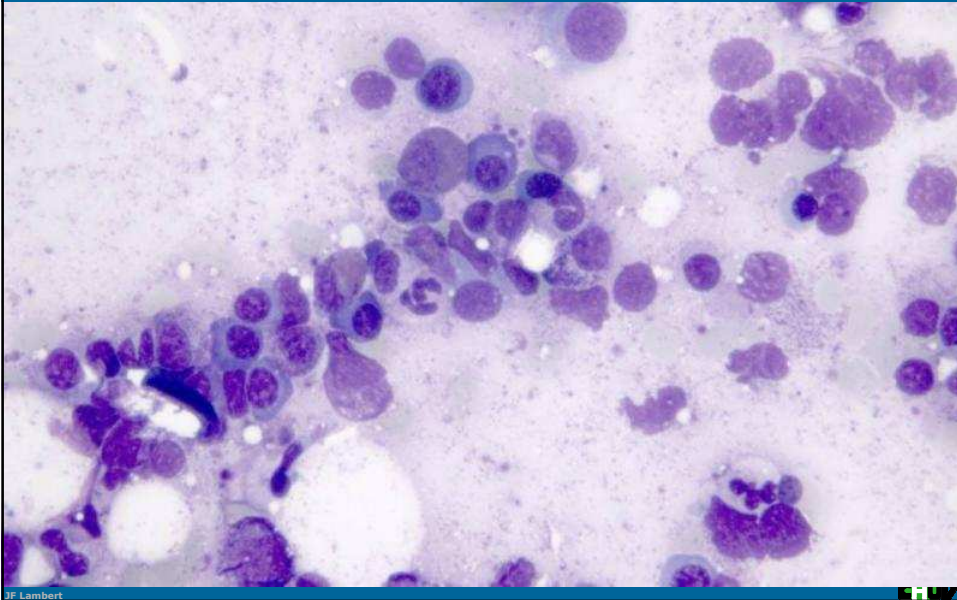
- Labs :
 - Troponin T 0.20 ug/l
 - NT-proBNP 5838 ng/l
- Echo :
 - EF 50%, concentric LV hypertrophy, increased filling pressure (amyloidosis ?)
- Cardiac biopsy
 - Interstitial and perivascular amyloidosis with light chain deposits



Immunological assessment

- Immunosubtraction : **no monoclonal peak**
- IgG 2.67g/l; IgA 0.5g/l ; IgM 0,12g/l
- 24 hrs urines : prot 6g/l, **no lamda chains**
- **Free light chains lambda 680mg/L**

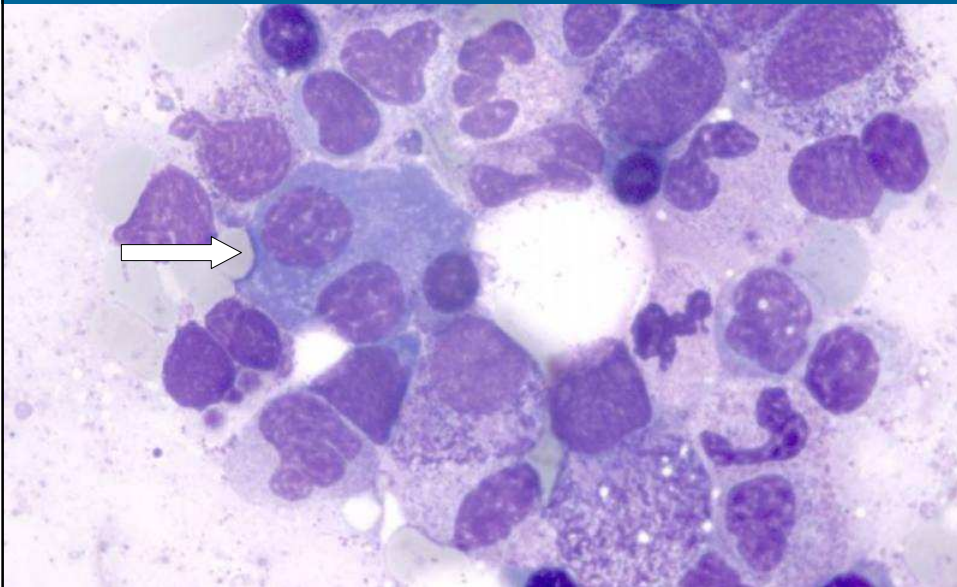
Bone marrow



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H&E

Bone marrow



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H&E

Diagnosis

- Non secretory multiple myeloma stage II
- AL amyloidosis
 - with severe cardiac and kidney involvement
- Orthostatic hypotension

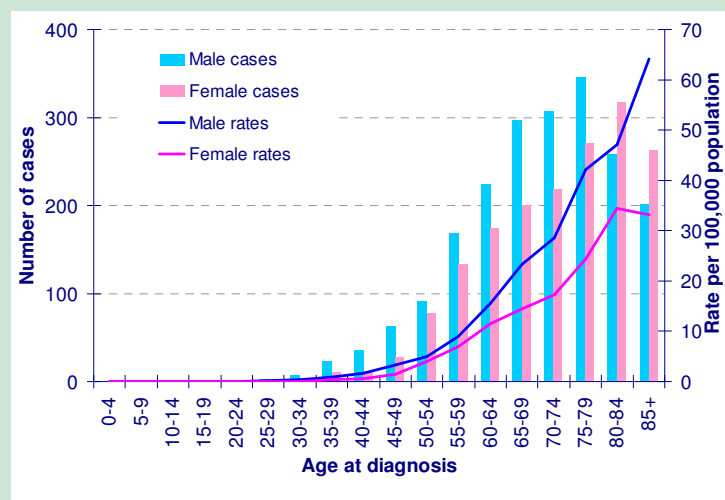
Evolution

- Lenalidomine 25mg 21/28, dexamethasone 20mg/wk
- Lambda FLC
 - 680 (28.2) → 325 (13.4) after first cycle
 - **Partial response**
- NT pro BNP
 - 5838 (28.2) → 22715 (13.4)
 - **Cardiac aggravation**
- Died on 19.5.07

Outline

- **Myeloma**
- Diagnostic methods
- Treatment and follow-up evaluation

Age specific incidence

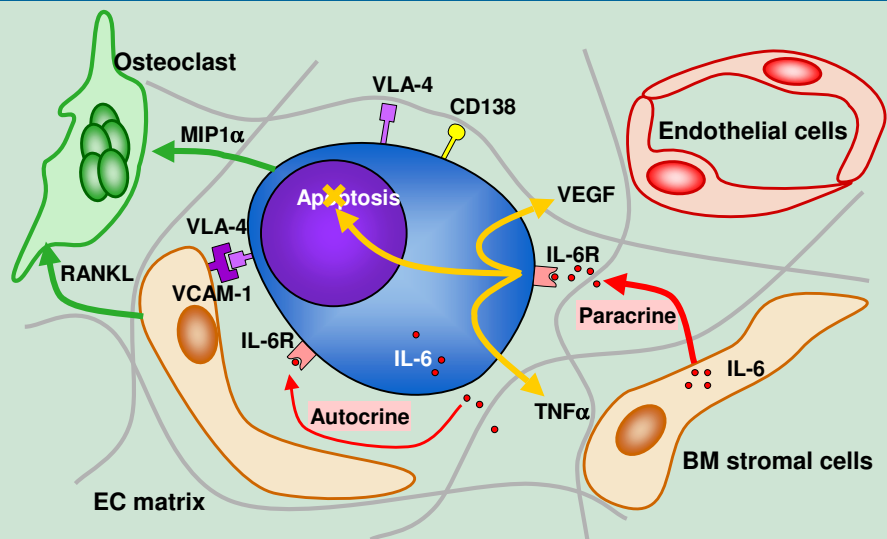


3% MGUS in >70 years old

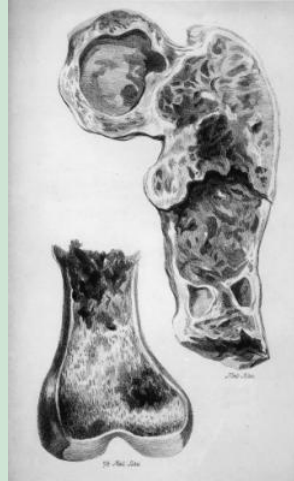
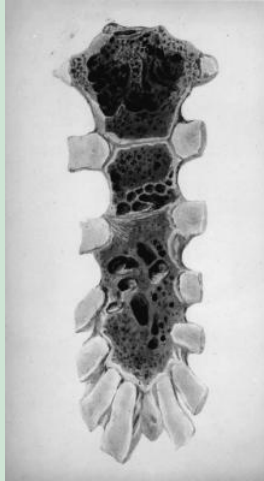
Etiology

- Farm workers
 - Herbicides 3-4x
 - Animal exposure ?
- Chronic antigen stimulation
 - Rheumatoid arthritis
 - Chronic HCV infection
 - HIV
- Genetics
 - Low incidence in Japanese and Chinese even in US immigrants
 - Rare familial associations

Myeloma cell and its environment



Sarah Newbury, 39 yo female



Solly, S. Remarks on the pathology of mollities ossium with cases. Medical and Chirurgical Transactions of London, 1844:27:435-461

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Diagnostic criteria

Multiple myeloma

- Major criteria:
 - M protein: IgG >3.5 g/dL; IgA >2.0 g/dL
 - Marrow plasmacytosis >30%
 - Plasmacytoma
- Minor criteria:
 - Lytic bone lesions
 - Marrow plasmacytosis 10–30%
 - M protein less than level defined above
 - Decreased level of normal immunoglobulins

Diagnosis of multiple myeloma requires one major and one minor criterion or three minor criteria

Smoldering myeloma

- Marrow plasmacytosis <30%
- M protein: IgG <7 g/dL; IgA <5 g/dL
- No bone lesions or limited bone lesions (<3)

MGUS

- M protein: IgG <3.5 g/dL; IgA <2.0 g/dL
- Urine light chains <1 g/24 h
- Marrow plasmacytosis <10%
- No lytic bone lesions or organ damage

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Prognosis tools

Durie Salmon

- Stage I
 - Hb >100 g/L
 - Ca normal or ≤ 3 mmol/L
 - N skeletal survey or solitary plasmacytoma
 - IgG <50 g/L or IgA <30 g/L
 - BJ protein <4 g/24h
- Stage II
 - Neither stage I nor stage III
- Stage III (one of the following)
 - Hb <85 g/L
 - Calcium > 3 mmol/L
 - Multiple lytic lesions
 - IgG >70 g/L or IgA >50 g/L
 - BJ protein >12 g/24h

median survival

5 y

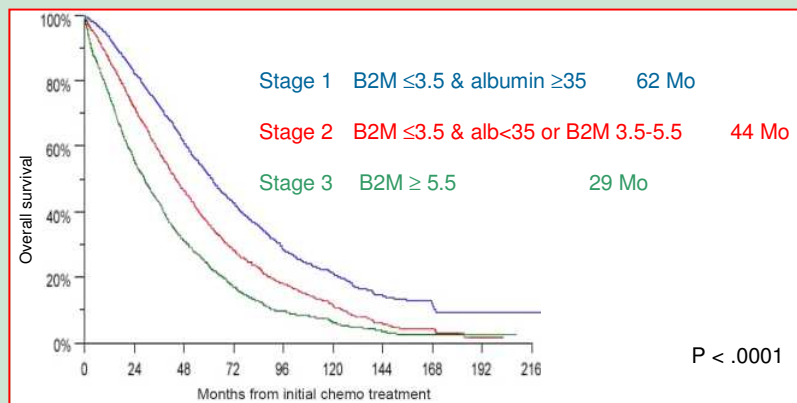
3.7 y

2.4 y

ISS - International Staging System

- Stage I
 - B2M ≤ 3.5 & albumin ≥ 35
 - And
 - C-reactive protein ≤ 4.0
 - Plasma cell labeling index <1%
 - Absence of del(13)
 - Low serum IL-6 receptor levels
 - Long duration of initial plateau
 - Chemo/steroid-sensitive disease
- Stage II
 - B2M ≤ 3.5 & alb <35 or B2M 3.5-5.5
- Stage III
 - B2M ≥ 5.5

ISS staging

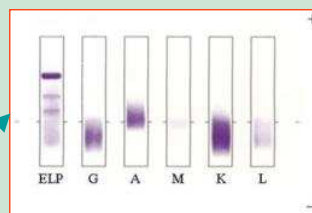
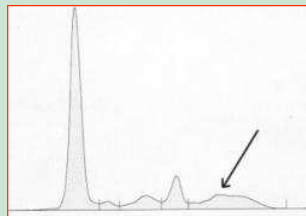


Age > 60 predicts independently for lower survival

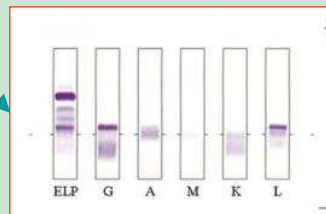
Outline

- Myeloma
- **Diagnosis**
- Treatment

Immuno-fixation

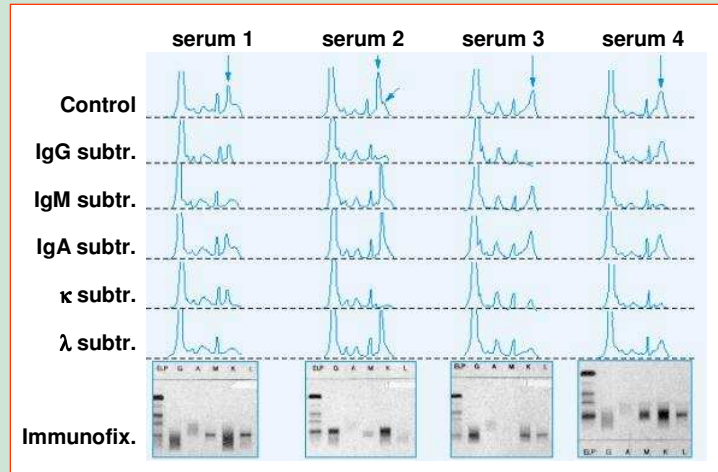


Normal

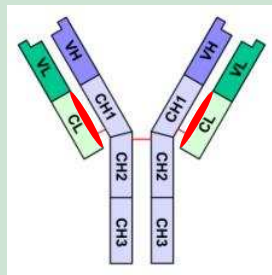


Monoclonal IgG λ

Immuno-subtraction

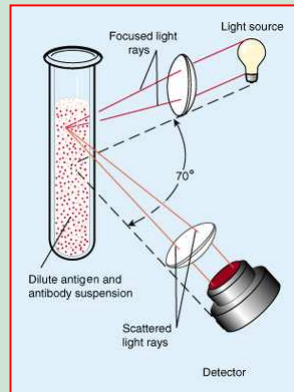


Identification of free light chains



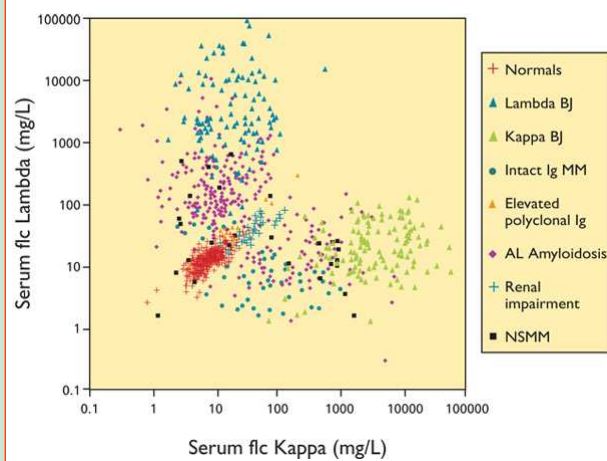
Monoclonal IgG

Identificaton of free light chains



Nephelometry

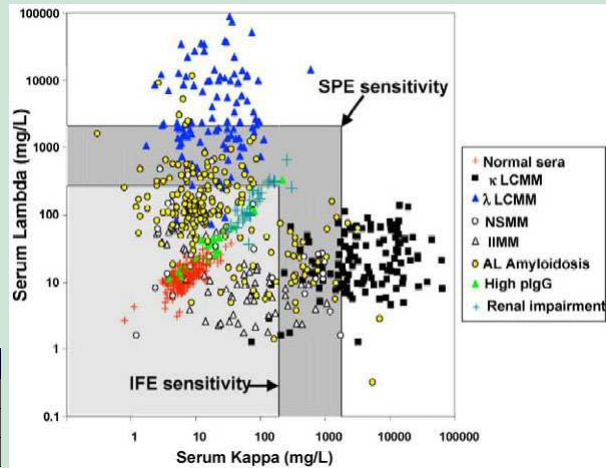
free light chains and differential diagnosis



Mead GP et al. BJH 2004

Overall sensitivity of FLC assay

	Kappa	Lambda
SPE	500-2000 mg/L	500-2000 mg/L
IFE	150-500 mg/L	150-500 mg/L
FLC	0.3 mg/L	0.5 mg/L

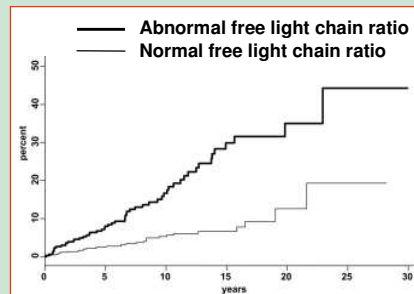


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Risk of progression of MGUS to myeloma

- 2% of MGUS evolve to myeloma each year with a 15% and 30% risk at 10 and 15 years respectively.
- M-Protein >15g/L
- non-IgG subtype
- abnormal free light chain ratio (<0.26 or >1.65)
- 0 to 3 factors confer a absolute risk of progression of 5, 21, 37 and 58% at 20 years respectively

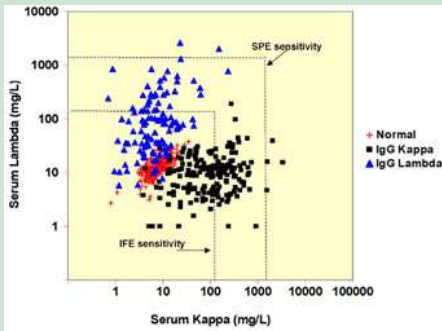


Rajkumar et al. Blood 2005;106:812-7

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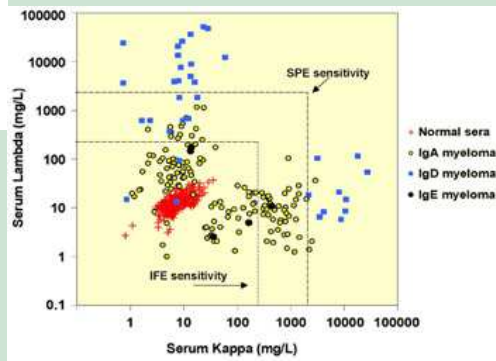
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Diagnosis of standard Ig myeloma

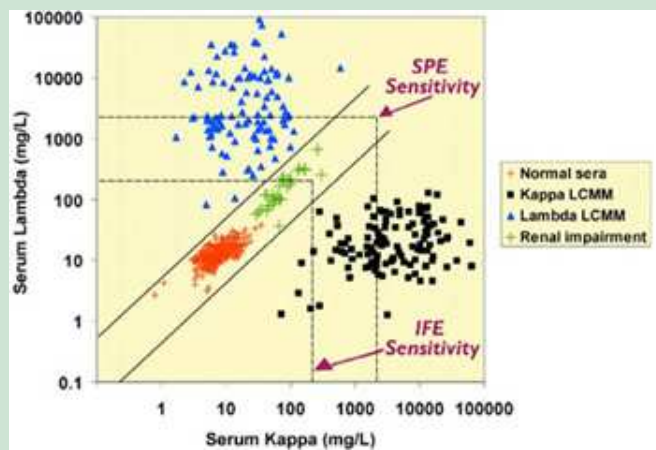


Concentrations of serum free light chains in 314 patients with IgG Myeloma compared with 282 normal sera.

Concentrations of serum free light chains in 142 IgA, 36 IgD and 5 IgE Myeloma patients compared with 282 normal sera.



Light chain MM - comparative sensitivity



Outline

- Myeloma
- Diagnosis
- **Treatment**

Bortezomib

Lenalidomide

**Arsenic
trioxyde**



**Farnesyltransferase
inhibitors**

DKK1 inhibitors

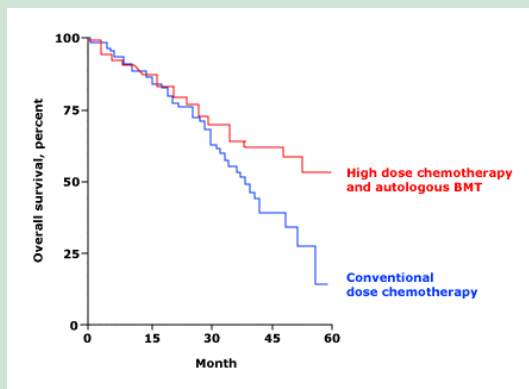
Treatment questions

- **Which induction is best ?**
 - VAD, MP, MP-Thal, Bortezomib, Lenalido
- **Stem cell transplant ?**
 - Single/double transplant, mini-allo
- **Is maintenance appropriate**
 - Thalidomide

“Standard treatment”

- Over 65 yo (not suitable for transplant)
 - MPT: more infections, neutropenia, DVT, neuropathy
 - Continue to plateau, maintenance Thal 200-400
- < 65 yo - transplant eligible
 - Induction: VAD or Thal-dex
 - SC harvest for 2 transplant
 - Mel 200 - auto SCT
 - If less than CR of VGPR ad second auto-SCT
- High risk ISS or poor cytogenetic
 - Investigational induction treatment - Miniallo

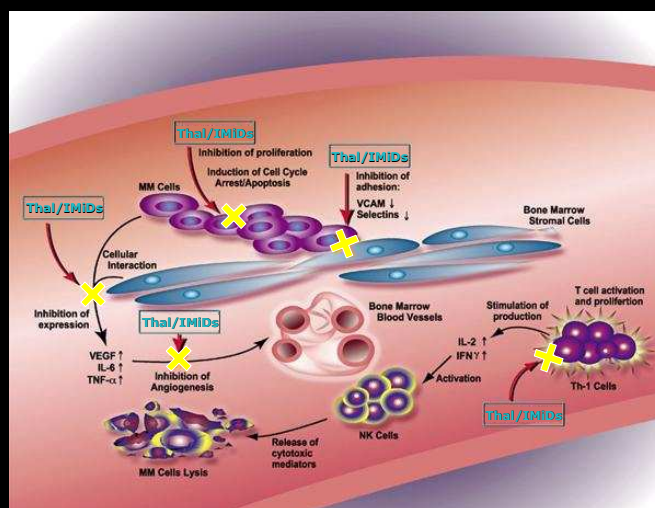
Autologous SCT



5-year OS : 52% vs 12 %

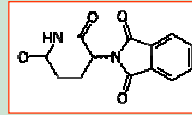
Attal M. NEJM 1996

Activity of Thalidomide and IMiDs

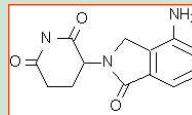


Lenalidomide

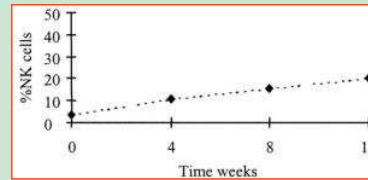
- 1950 Thalidomide
- 1960 used for it's anti-TNF effect in Leprae
- 1994 RA, Crohn, GVHD
- Lenalidomide
 - improved TNF α blocking
 - more specific antiproliferation and anti-cytokine
 - no neuropathy
 - T-cell stimulation inducing NK



THAL

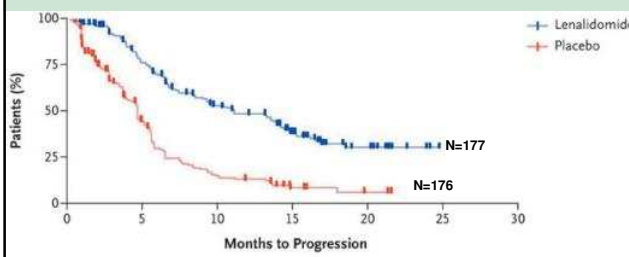


LEN



Davies. Blood 2001

Lenalidomide 2nd line

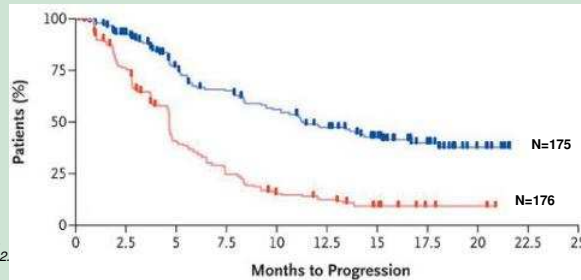


OS 29.6 vs 20.0 Mo

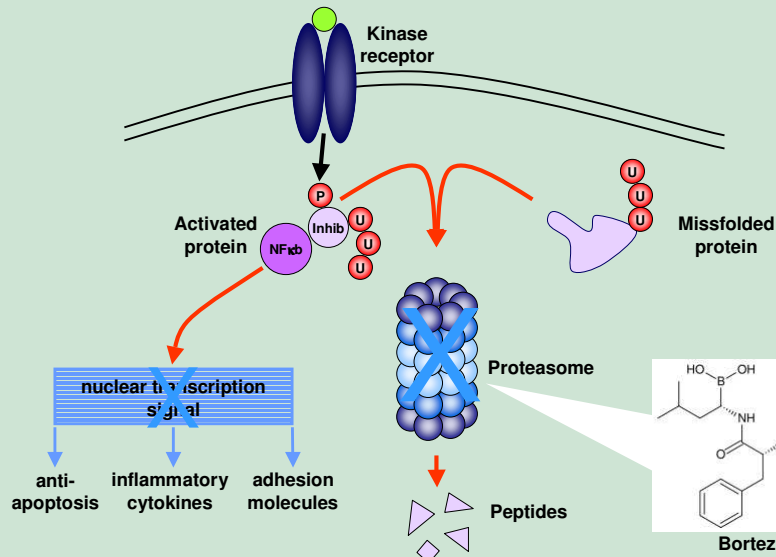
Weber DM et al.
Multiple Myeloma (009).
NEJM 2007;37:2133-42

OS not reached vs 20.6 Mo

Dimopoulos M et al.
Multiple Myeloma (010).
NEJM 2007;357:2123-32.



NF- κ b activation pathway

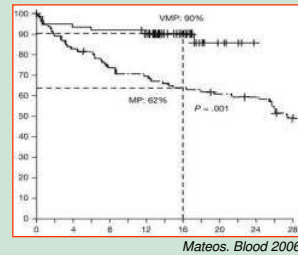


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Bortezomib

- Induction
 - Bortezomib OR 40% alone
 - V-Dex combination OR 90%
 - VMP vs PM in elderly, CR 32%
- 2nd or 3rd line
 - Doxil-Bortezomib in refractory MM
- HD regimen
 - IFM
Bortezomib 1mg/m² -6-3+1+4, Mel 200 -2
CR 31%, VGPR 46%, OR 77%



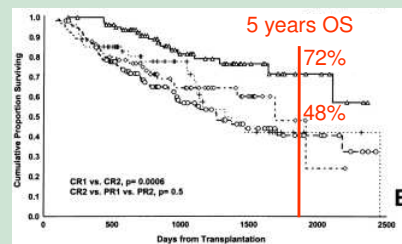
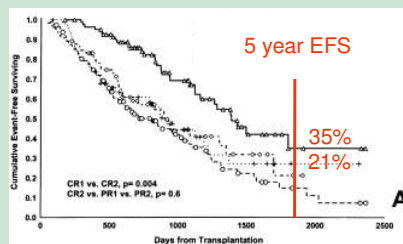
Mateos. Blood 2006

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Importance of obtaining a “complete” CR

- CR: no monoclonal protein by SPEP and immunofixation, marrow PC < 5%
- nCR: near CR, negative SPEP, positive immunofixation
- VGPR: >90% decrease in M-component or marrow PC

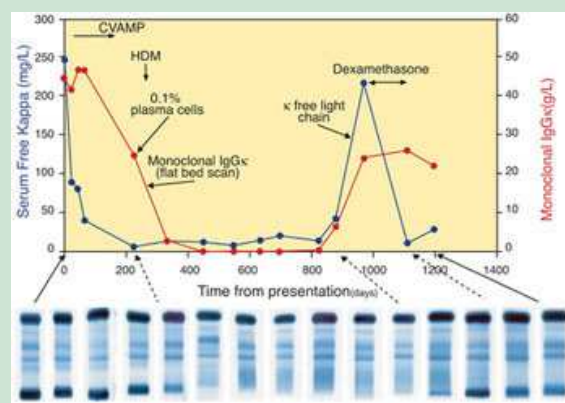


Lahuerta JJ. BJH 2000

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Standard Ig myeloma – tt follow-up

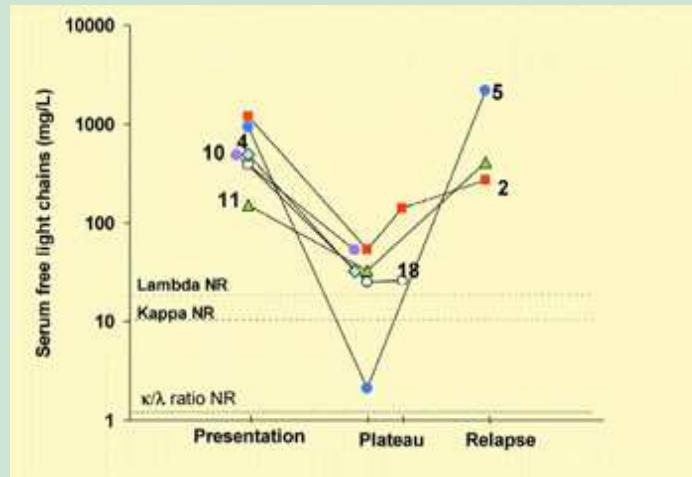


Monitoring of one of the 17 Myeloma patients using IgGκ and free κ. Electrophoresis gels are shown for each sample. CVAMP = cyclophosphamide, vincristine, adriamycin, melphalan, prednisolone; HDM: high dose melphalan and stem cell transplant.

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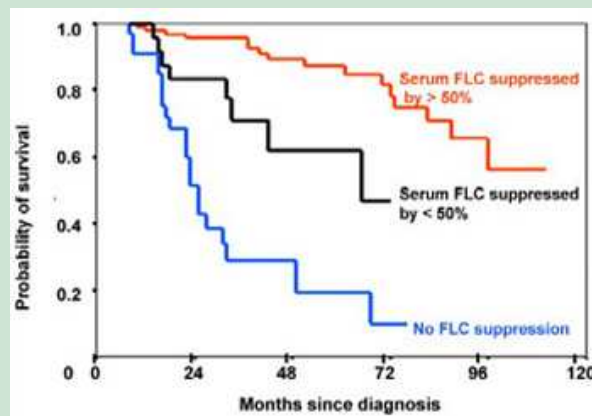
Follow up of treated non secretory myeloma



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Prognostic factor in AL amyloidosis



H J Lachmann et al. *BJH* 2003;122:78-84

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New way of accurate response evaluation

Response	Criteria
Stringent Complete Response (sCR)	Normal serum FLC ratio
Measurable disease*	Abnormal serum FLC ratio and involved serum FLC > 100 mg/L
Partial Response*	> 50% decrease in the difference between involved and uninvolved FLC levels
Progressive disease*	Increase > 25% from baseline in the difference between involved and uninvolved Free Light Chain levels and the absolute increase > 100mg/L

* where immeasurable by SPE, 24h UPE or quantitative immunoglobulin analysis

International uniform response criteria for multiple myeloma
BGM Durie *et al.* Leukemia (2006) 20: 1467-1473¹

Expert panel recommendations

Disease	For Diagnosis	For Monitoring
Nonsecretory MM	Important	Important
AL Amyloidosis	Important	Important
Light Chain MM	Important	Important
Intact immunoglobulin MM	Important	Useful/Important
MGUS	Important	Important
Light Chain Deposition Disease	Important	Important
Waldenstroms macroglobulinaemia	Insufficient data	Insufficient data
Plasmacytoma	Insufficient data	Insufficient data
Lymphoma/Leukaemia	Insufficient data	Insufficient data
Smouldering MM	Insufficient data	Insufficient data

The panel was Robert Kyle, Michel Attal, Philip Greipp, Helen Lachman and Jo Bradwell