Gruppo di Ricerca Geriatrica

Brescia, 25 gennaio 2008

GAMMAPATIE MONOCLONALI E MIELOMA

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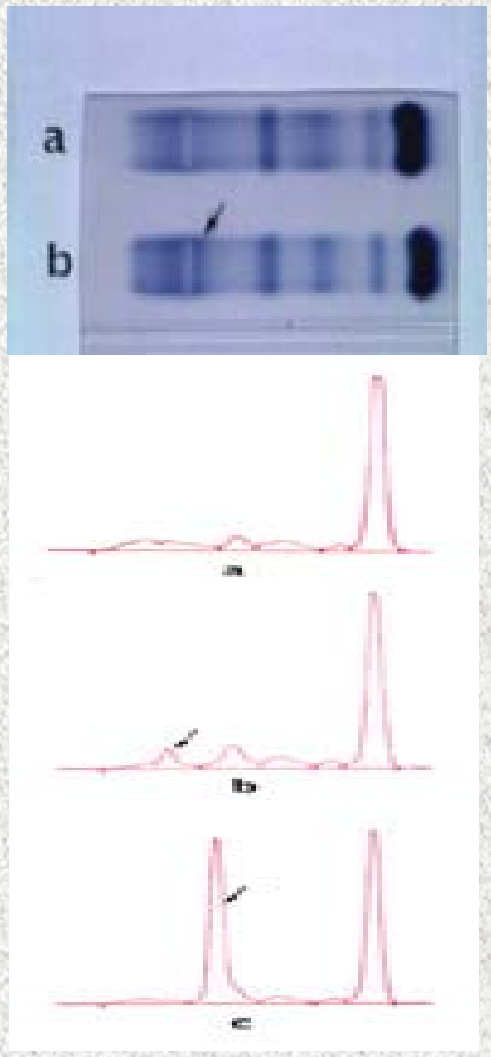
Divisione di Ematologia

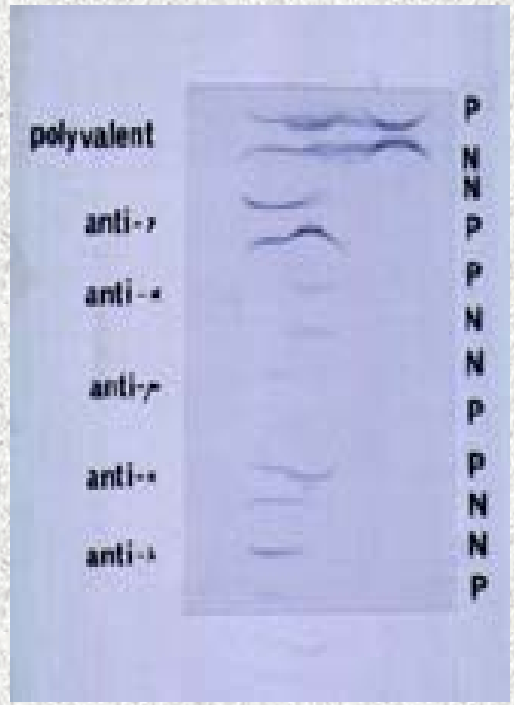
Spedali Civili - Brescia

Paraproteinemia monoclonale: diagnosi

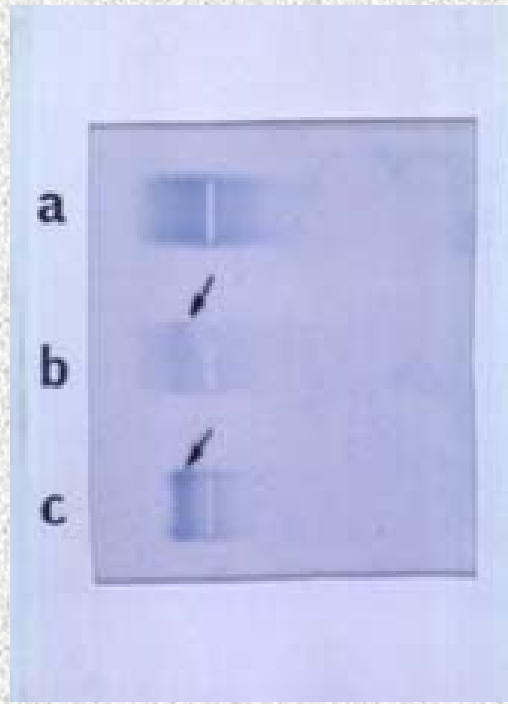
Elettroforesi



Immunoelettroforesi



Immunofissazione



Sensibilità:

Siero: 200 mg/dL

Urine: 40 mg/L

PARAPROTEINEMIE MONOCLONALI: frequenza

Studio di popolazione su 28063 residenti nella contea di Olmsted (Minnesota -USA)

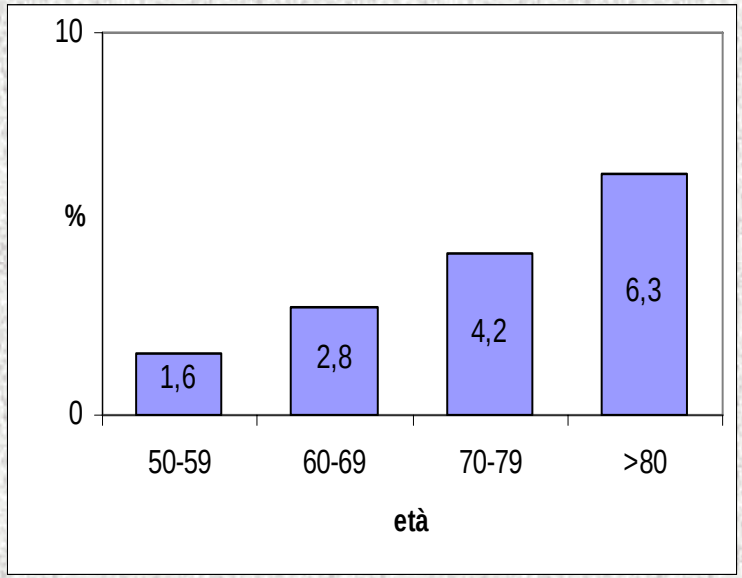
età: 50 - 59: 1,6%

60 - 69: 2,8%

70 - 79: 4,2%

≥ 80: 6,3%

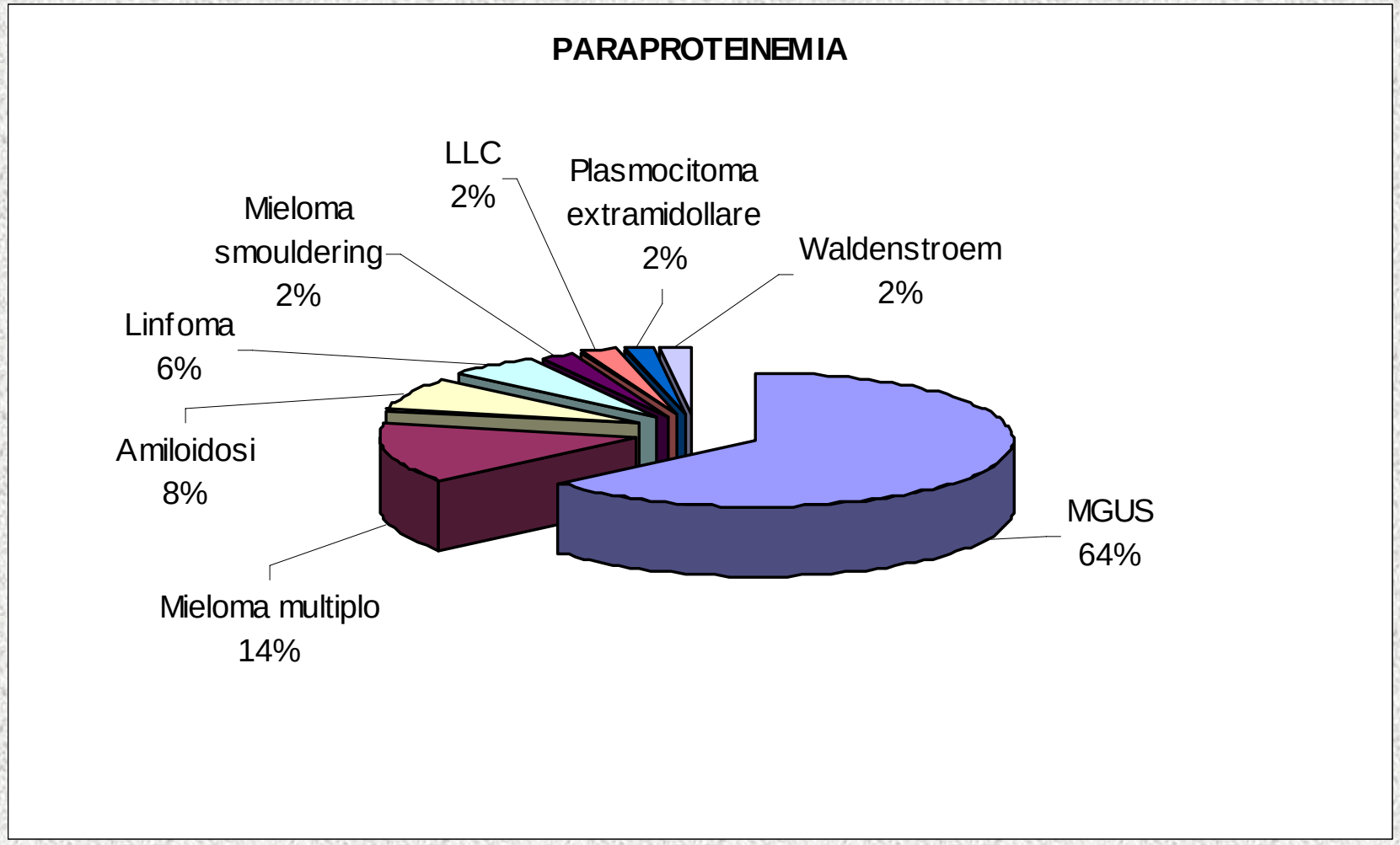
Il rischio sembra mantenere un ritmo costante dopo i 50 anni



Kyle et al. N Engl J Med 354;13, 2006

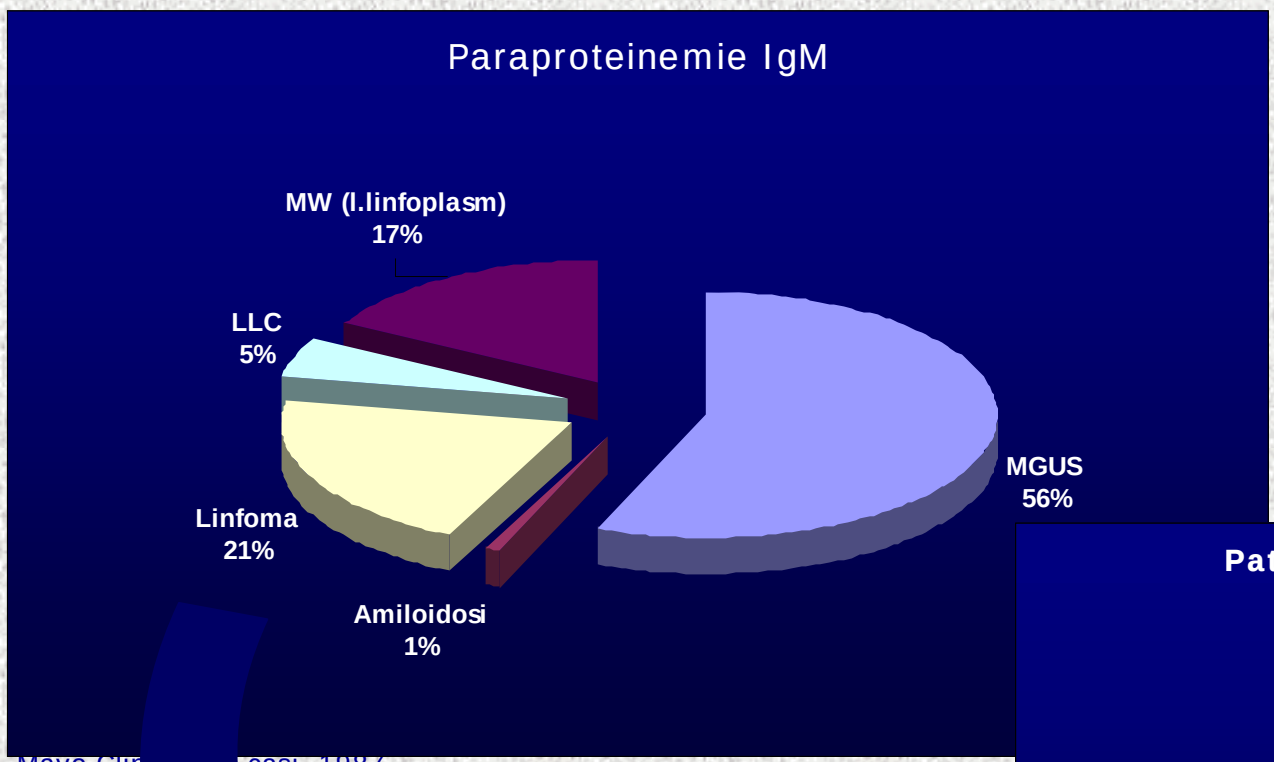
La paraproteinemia monoclonale è una delle condizioni di rischio neoplastico più frequenti nella popolazione generale di età > a 50 anni

Patologie associate alla presenza di paraproteinemia monoclonale

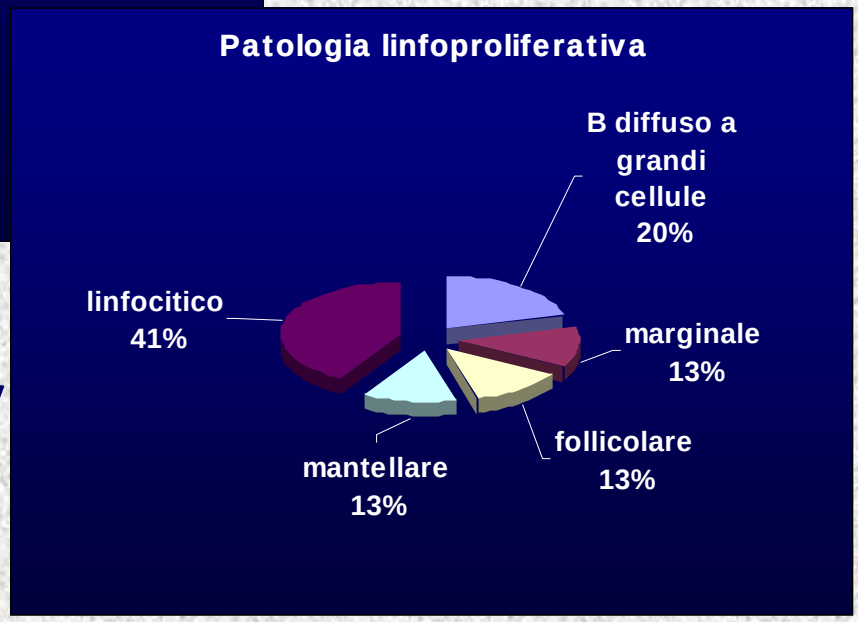


Mayo Clinic, 808 casi, 1988

Patologie associate a paraproteinemia monoclonale IgM



Mayo Clin [illegible] casi, 1987



Owen, Clin Lymphoma, 2000

MGUS: definizione

MGUS: monoclonal gammopathy of undetermined significance

MGUS: gammapatia monoclonale di incerto significato

- patogenesi non nota
- diagnosi differenziale non precisa

MGUS: paraproteinemia monoclonale non mielomatosa

MGUS: paraproteinemia monoclonale senza evidenza neoplastica

MGUS: diagnosi differenziale vs mieloma

MIELOMA

Criteri maggiori:

I plasmacitoma alla biopsia

II plasmacitosi midollare > 30%

III IgG >3,5g/dL, IgA >2,0 g/dL; BJ >1,0 g/dL

Criteri minori:

a) plasmacitosi midollare 10 - 30%

b) IgG ≤3,5g/dL, IgA ≤2,0 g/dL; BJ ≤1,0 g/dL

c) osteolisi

d) ridotti livelli delle Ig non clonali

Combinazioni diagnostiche

Ib, Ic, Id,

IIb IIc, IId

IIIa, IIIc, abc; abd;

GAMMAPATIA MONOCLONALE

- IgG <3,5g/dL, IgA <2,0 g/dL; BJ <1,0 g/L

- non lesioni osteolitiche

- plasmacitosi midollare < 10%

- non sintomi, PS (iK) >70, non infezioni

- Hgb > 10g, creatinina < 2 mg/dl, calcemia normale

IgG: 3,2 g;
plasmacellule: 15%,
non osteolisi,
IgA e IgM non ridotte
non sintomi

MGUS: diagnosi differenziale vs mieloma

MIELOMA

Criteri maggiori:

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c) osteolisi

d) ridotti livelli delle Ig non clonali

Mieloma "indolente"

- ≤ 3 lesioni osteolitiche,
- non fratture
- IgG < 7g%; IgA <5g

Mieloma "smouldering"

- non lesioni osteolitiche
- plasmacellule ≤ 30%
- non sintomi

IgG: 3,2 g;
plasmacellule: 15%,
non osteolisi,
IgA e IgM non ridotte
non sintomi

GAMMAPATIA MONOCLONALE

- IgG <3,5g/dL, IgA <2,0 g/dL; BJ <1,0 g/dL

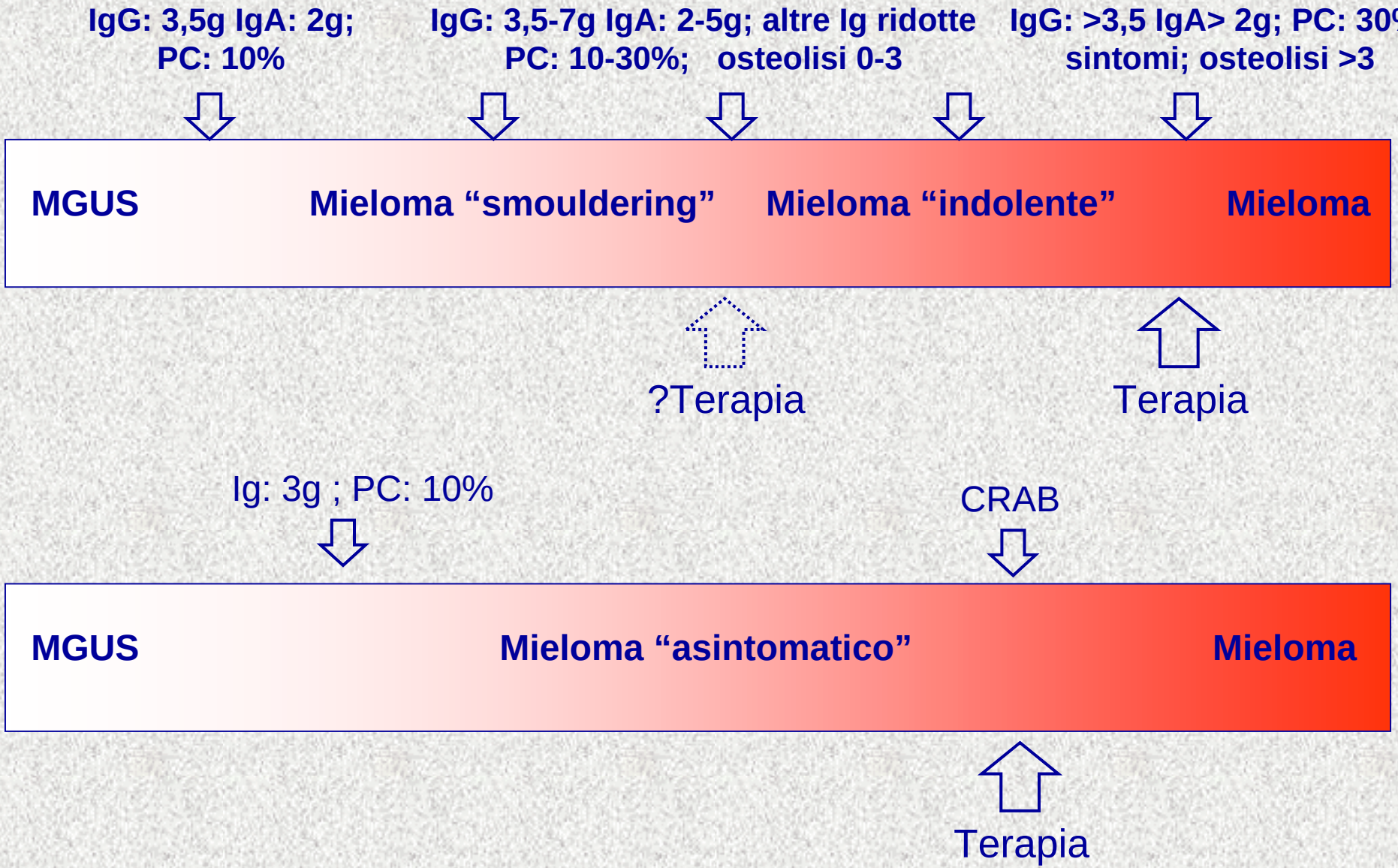
- non lesioni osteolitiche

- plasmacitosi midollare < 10%

- non sintomi, PS (iK) >70, non infezioni

- Hgb > 10g, creatinina < 2 mg/dl, calcemia normale

MGUS: diagnosi differenziale vs mieloma



MGUS: criteri diagnostici

International Myeloma Working Group – Br J Haematol, 2003

MGUS/MG(u)

paraproteina monoclonale < 3,0 g/dL

plasmacellule clonali midollari <10%; modesto infiltrato alla biopsia midollare

non evidenza di malattie linfoproliferative

non alterazioni d'organo/tessuto correlate [related organ/tissue impairment:

Calcium, **R**enal insufficiency, **A**naemia, **B**one **(CRAB)**]

MIELOMA ASINTOMATICO (smouldering)

paraproteina monoclonale ≥ 3.0 g/dL

e/o

plasmacellule clonali midollari ≥ 10%

non CRAB; non sintomi

MIELOMA MULTIPLO SINTOMATICO

paraproteina monoclonale in siero/urine

plasmacellule clonali midollari o plasmacitoma

presenza di CRAB

MGUS: criteri diagnostici per paraproteinemie IgM

II International Workshop on Waldenstroem Macroglobulinemia, Atene, 2002

MGUS - IgM:

IgM sieriche clonali (in genere < 3.0 g/dL)

infiltrazione linfoplasmacitica midollare assente o equivoca

non sintomi sistemici o correlabili a:

infiltrazione d'organo/midollare o attività anticorpale dell'IgM

MACROGLOBULINEMIA DI WALDENSTROEM ASINTOMATICA/SINTOMATICA:

IgM sieriche clonali (qualsiasi livello)

infiltrazione midollare di linfoma linfoplasmacitico (pattern intertrabecolare)

assenza/presenza di sintomi sistemici o correlabili:

- a infiltrazione d'organo o midollare
- direttamente alla presenza dell'IgM

DISORDINI IgM-CORRELATI

IgM sieriche clonali (in genere < 3.0 g/dL)

infiltrazione linfoplasmacitica midollare assente o equivoca

presenza di sintomi correlabili direttamente alla presenza dell'IgM

“Ig-M related disorders”

- Crioglobulinemie (anti-IgG)
- Neuropatie periferiche (anti-MAG)
- Sindrome da iperviscosità
- Citopenie autoimmuni (crioagglutininemia) (anti-GR)

Work-up diagnostico allargato:

crioglobuline, complementemia, HCV?

viscosimetria plasmatica

test di Coombs diretto, crioagglutinine

? coagulazione (von Willebrand)

? anticorpi antiMAG, etc

?? “Ig light chain-related disorders” ??:

- Amiloidosi AL
- Malattia da deposizione di catene leggere
- Glomerulopatia fibrillare

MGUS: caratteristiche cliniche

Mayo Clinic, Rochester, Mn; (1395 pazienti ricoverati)

• asintomatica, incidentale		
• M/F:	54/46	
• età mediana:	72	(2% <40 anni)
• tipo di Ig:	G	70%
	A	12%
	M	15%
	biclonali	3%
• catena leggera:	kappa: 61%	lambda: 39%
• riduzione Ig policlonali:	38%	
• Bence Jones:	31%	(>150mg/24h: 5%)
	kappa: 21%;	lambda: 10%
• plasmacitosi midollare:	3%	

• Emoglobina <12g/dL:	23%	(sideropenia, mielodisplasia, IRC)
• Creatinina >2mg/dl:	6%	(diabete, ipertensione,nefropatie)

MGUS IgM: caratteristiche cliniche

Mayo Clinic, Rochester, Mn; (242 pazienti ricoverati)

• M/F		58/42	
• età mediana		74	(1% < 40)
• biclonale:		1%	
• tipo di catena leggera:	kappa	70%	lambda 30%
• epatomegalia	10%		
• splenomegalia	2,5%		
• riduzione Ig policlonali:	35%		
• BenceJones:		27%	*(>150mg/24h: 5%)*
		kappa 19%	lambda 8%

Hgb <12g/L: 17% (sideropenia, mielodisplasia, IRC)

Creatinina >2mg/dl: 7% (diabete, ipertensione, nefropatie)

MGUS: caratteristiche cliniche

Divisione di Ematologia - Niguarda (1104 pazienti ricoverati)

• M/F:		52/48	
• età mediana:		63	(23 - 93)
• tipo di Ig:	G	73%	
	A	10%	
	M	12%	
	biclonali	4%	
• catena leggera:	kappa: 62%	lambda	38%
• riduzione Ig policlonali:		12,8%	
• Bence Jones:		12,6%	(mediana 0.2g/24h)
• plasmocitosi midollare:		5% (mediana)	
• *beta2-microglobulina (>N):*		*22%*	
• *VES >40 mm:*		*12%*	

Malattie concomitanti:

- neoplasie:	6,1%	(prostata, gastroenterico)
- connettiviti:	0.6%	
- sieropositività per HBV/HCV:	7,8%	*(Andreone et al, Ann Intern Med, 1998)*
- trapiantati d'organo:	1,5%	
- trapiantati di midollo:	0,6%	

Approccio clinico al paziente con paraproteinemia IgG,A,BJ o IgM

Addensamento in zona gamma
Sospetto picco monoclonale = **Possibile presenza di un clone di linfociti o plasmacellule**

Indagine di laboratorio fondamentale:
Immunofissazione sierica e urinaria

IgG, IgA, catena leggera

Devo escludere un mieloma v

IgM

Devo escludere un linfoma (M. di Waldenstroem)

Anamnesi:

- ✓**dolore osseo**
- ✓**sintomi sistemici**
- ✓**diatesi infettiva**
- ✓**anamnesi di fratture**
- ✓**sintomi IgM-correlati**

Esame obiettivo:

- ✓**patologia linfoproliferativa, ORL**
- ✓**segni di amiloidosi**
- ✓**neuropatia periferica**

(non necessaria la ricerca di neoplasie associate)

Approccio clinico al paziente con paraproteinemia IgG,A,BJ o IgM

INDAGINI DI LABORATORIO E STRUMENTALI:

- **immunofissazione siero/urine**
- **dosaggio Ig, dosaggio/elettroforesi proteinuria,**
- **Hgb, creatinina, calcio (CRAB)**
- **LDH, parametri IgM-correlati**
- **beta-2 microglobulina *(ISS)*, *VES, PCR***
- ***(sieropositività per virus epatitici, markers tumorali, ricerca HP)***
- **? Rx scheletro (cranio, rachide, bacino, emicostati, omeri, femori) (CRAB)**
- **? Rx torace, ecografia addome**
- **??? aspirato/biopsia midollare (labelling index, immunofenotipo, citogenetica)**
  - ***per indirizzo terapeutico no se asintomatico***
  - ***per indirizzo prognostico ?***

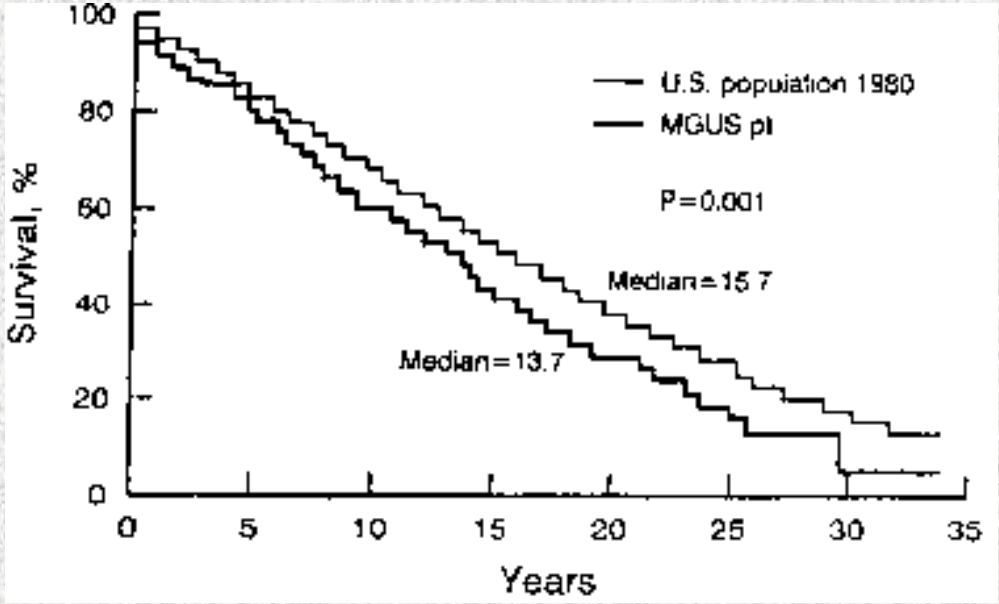
Work-up diagnostico allargato:

crioglobuline, complementemia, HCV?
viscosimetria plasmatica
test di Coombs diretto, crioagglutinine
? coagulazione (von Willebrand)
? anticorpi antiMAG, etc

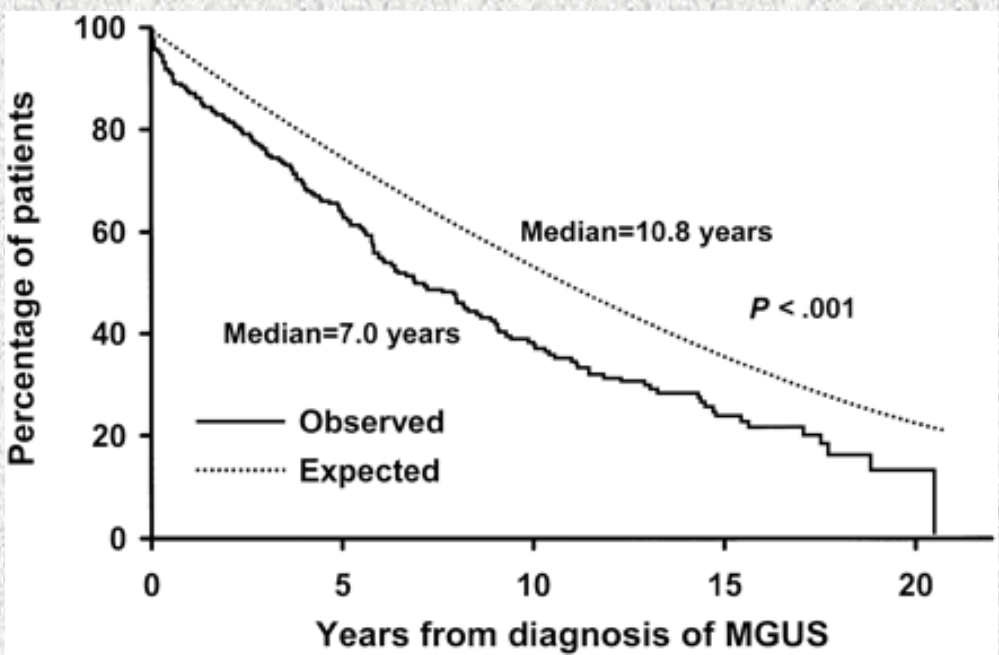
ISS (International Staging System)

- **albumina > 3,5 g/dL**
- **beta-2 microglobulina < 3,5 o > 5,5**

MGUS: prognosi

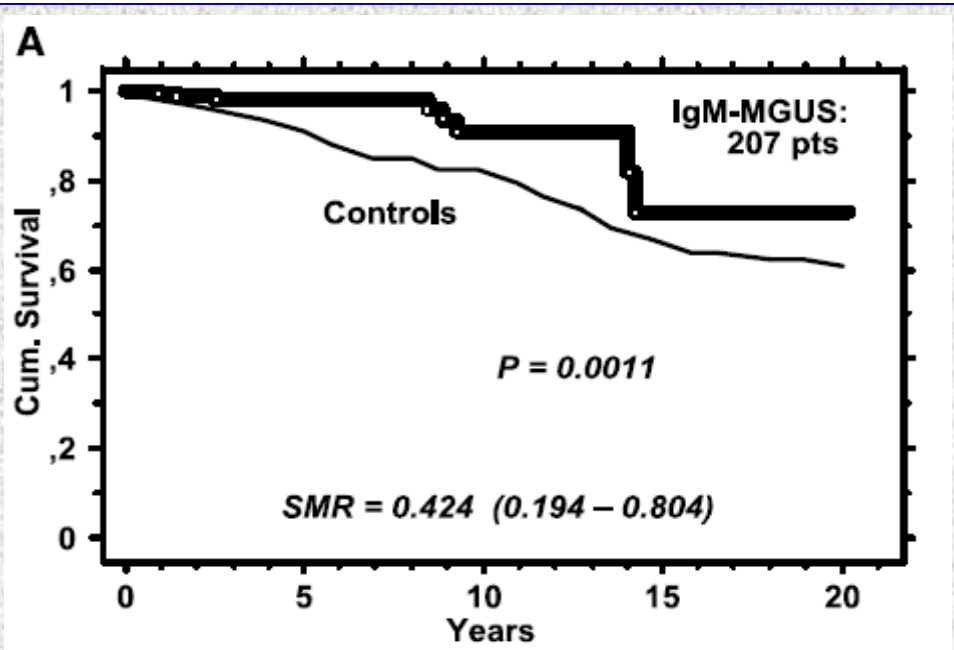


Semin Hematol 26: 176, 1989;
Mayo Clin Proc 68: 26, 1993

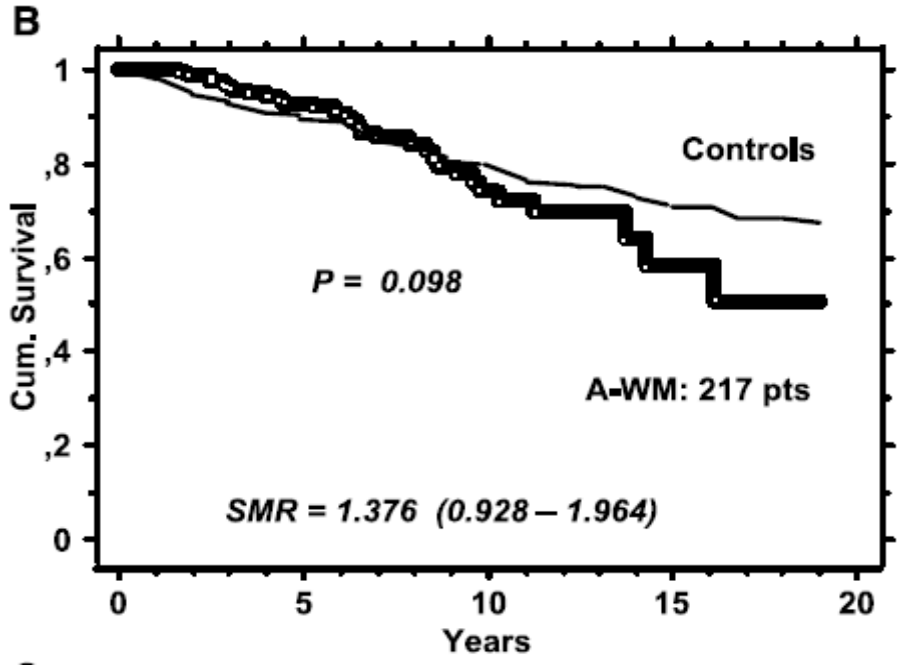


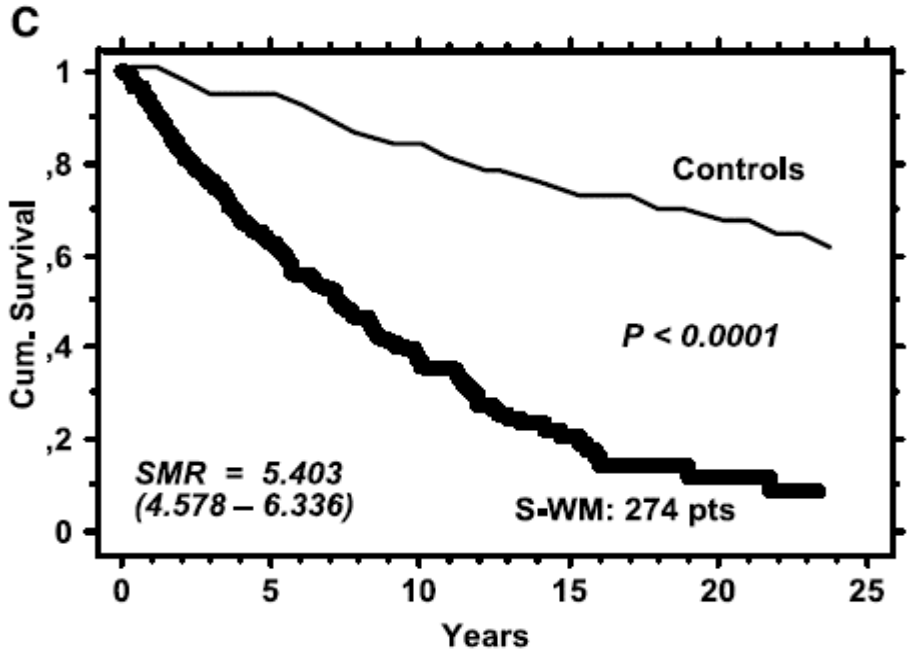
Blood, 102:3759, 2003

MGUS IgM: prognosi

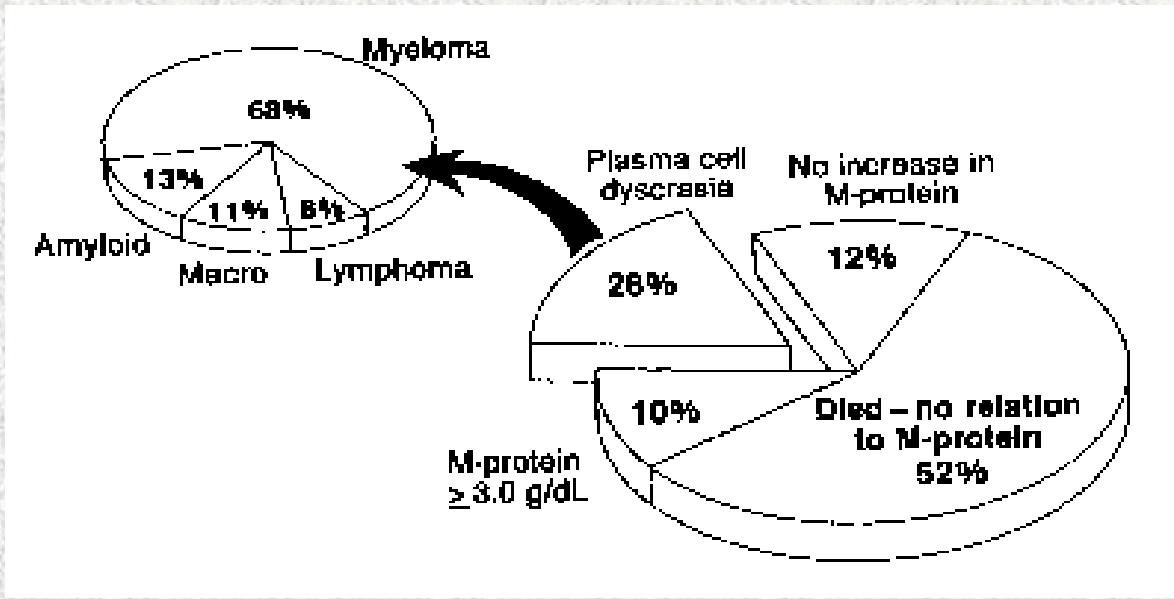


Clin Cancer Res, 137:49, 2005





MGUS: evoluzione e prognosi



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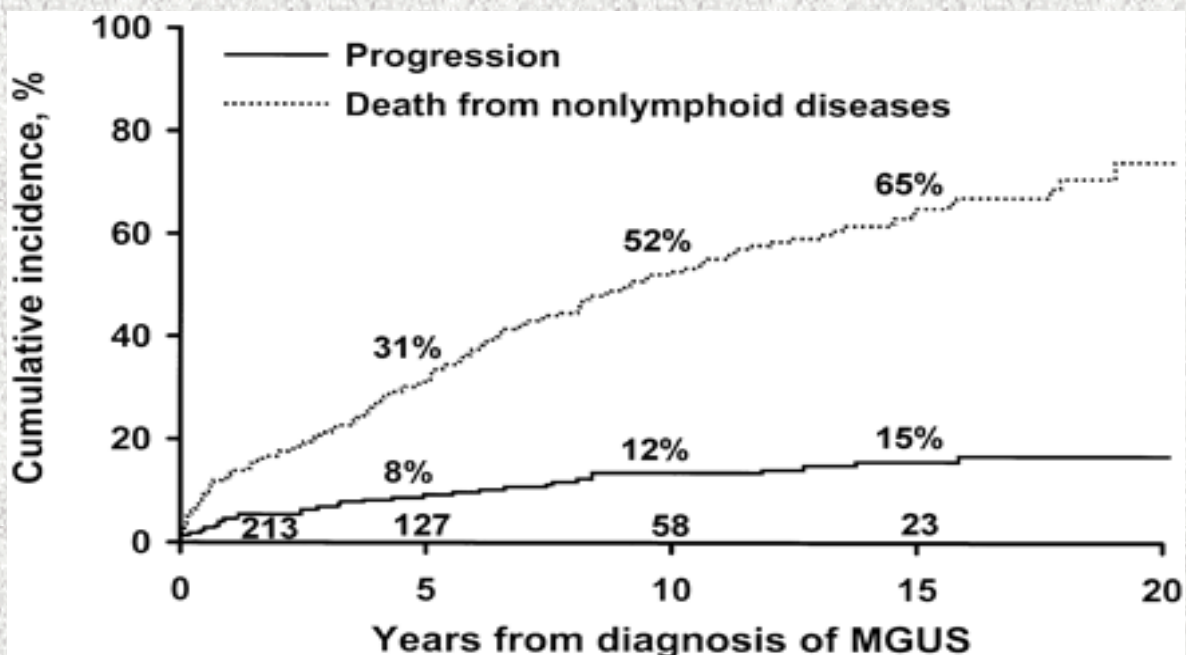
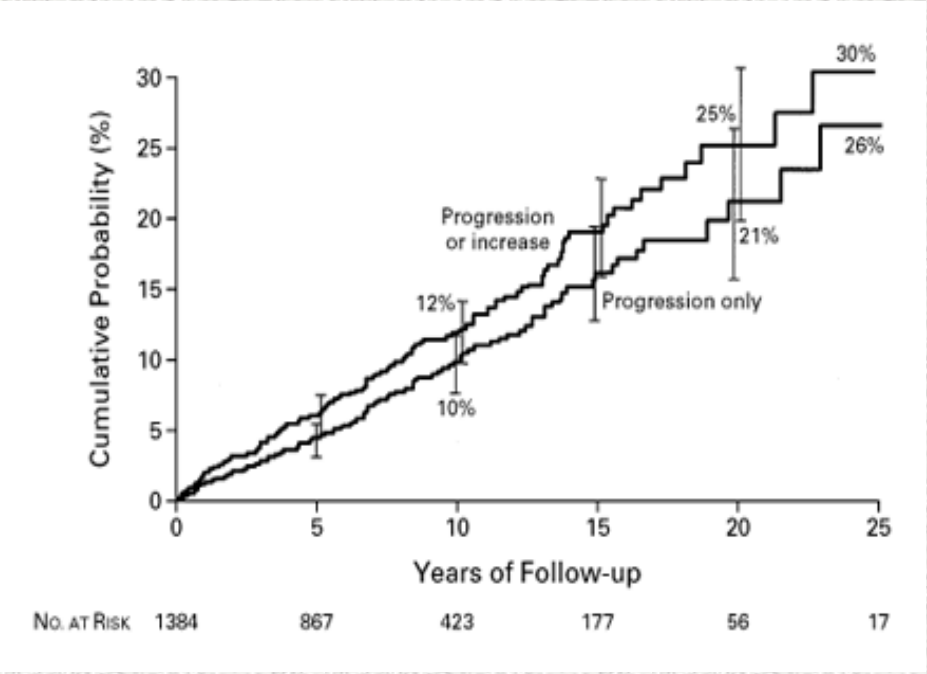
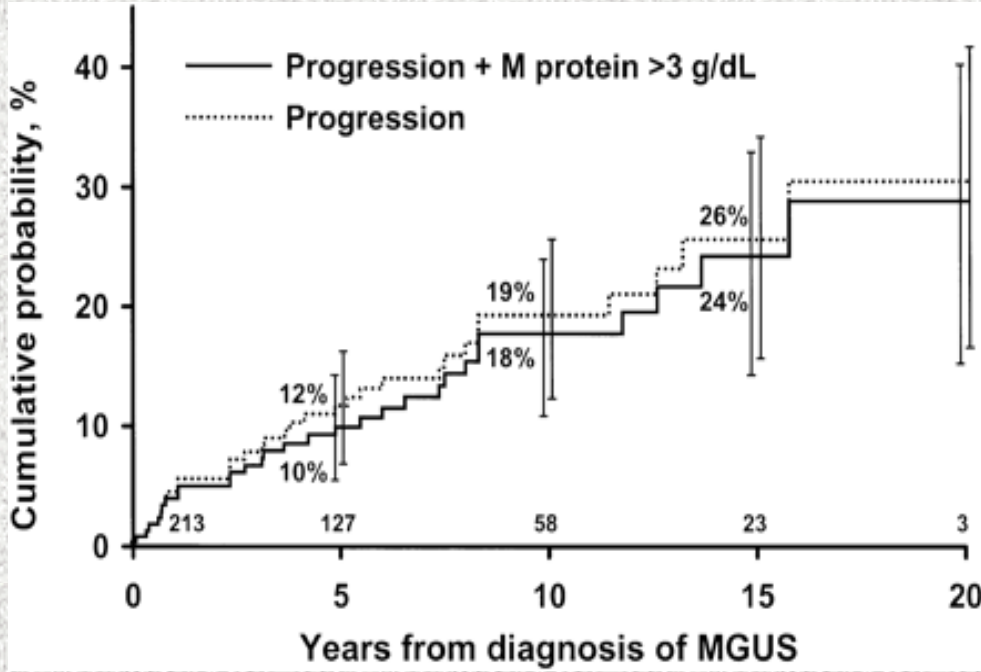


Blood, 102:3759, 2003

MGUS: evoluzione a mieloma o linfoma linfoplasmacitico



MGUS *(Kyle et al N Engl J Med, 2002)*



MGUS- IgM *(Kyle et al, Blood, 2003)*

MGUS: fattori prognostici per evoluzione a mieloma

Autore N° pazienti Mesi f-up mediano	**Kyle** **1384** **185**	**Cesana** **1231** 72	Baldini 386 70	Ucci 684 36	Gregersen 1247
Livelli del picco	**si**	no	si	si	si
Plasmacellule midollari	**NV**	si	si	si	NV
Presenza di Bence Jones	**no**	si	si	no	no
Tipo di Ig monoclonale	**IgA, IgM**	no	no	no	IgA
Riduzione Ig policlonali	**no**	si	si	si	no
VES	**NV**	si	no	si	no
Labelling index	**NV**	NV	NV	si	NV

MGUS: fattori prognostici per evoluzione a mieloma

Livelli di Ig iniziali	Rischio di progressione a mieloma multiplo a 10 anni	
0.5 g/dL	6%	
1.0 g/dL	7%	
1.5 g/dL	11%	
2.0 g/dL	20%	P<0.001
2.5 g/dL	24%	
3.0 g/dL	34%	

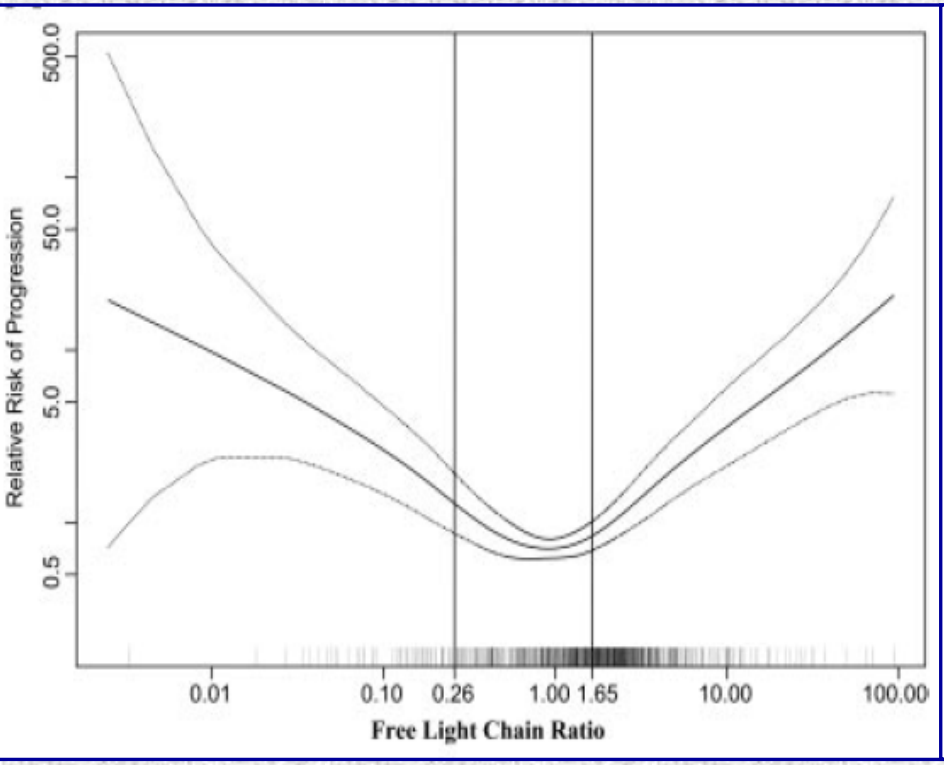
MGUS IgM:

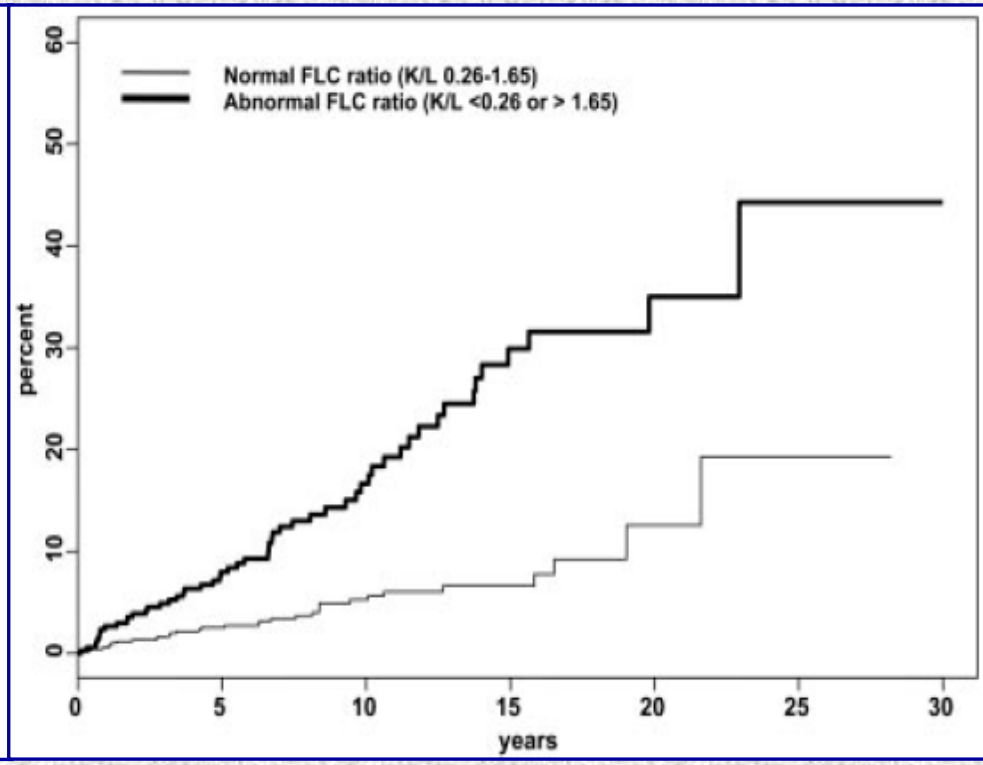
I **livelli di IgM** sono il principale fattore prognostico per l'evoluzione a linfoma, insieme all'**anemia (Hgb < 12.5g/L)** e alla **linfocitosi (>4000/mmc).**

Tuttavia nessuna combinazione di fattori di rischio giustifica l'inizio di una terapia specifica in pazienti asintomatici **(International Consensus Conference, Atene, 2002)**

Serum FLC ratio e prognosi

MGUS

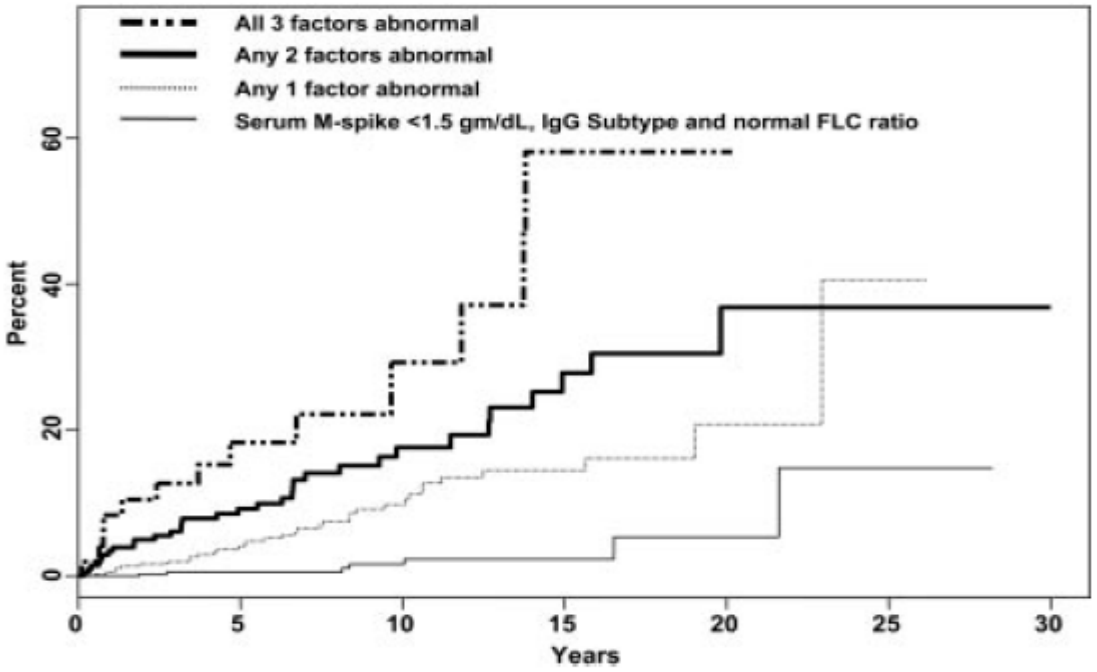




Rajkumar et al, Blood. 2005

MGUS: fattori prognostici per evoluzione a mieloma

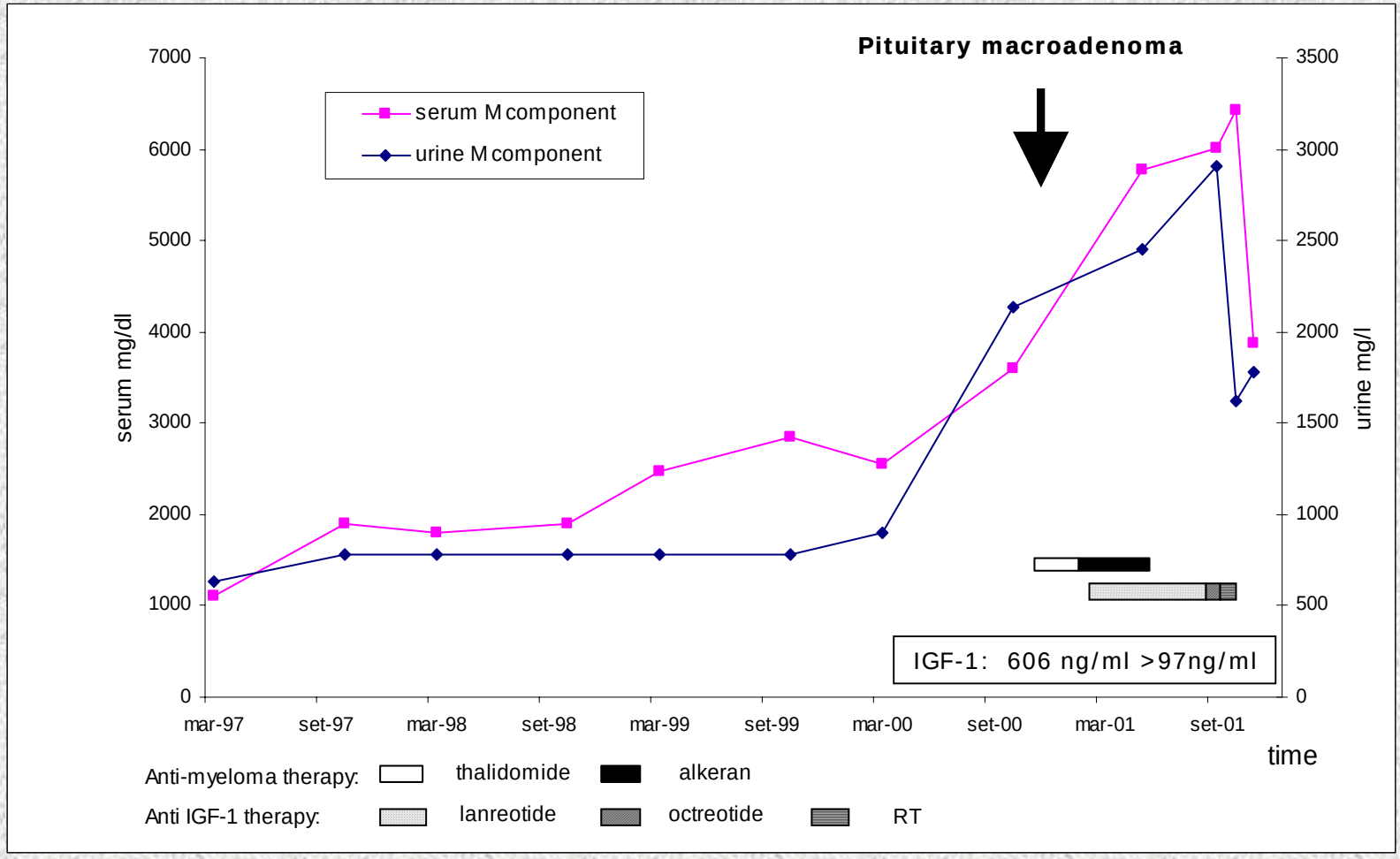
Il rapporto fra i livelli di **catene leggere libere nel siero** come fattore prognostico indipendente di progressione da MGUS a mieloma



Risk Group	No. of Patients	Relative Risk	Absolute Risk of Progression at 20 Years	Absolute Risk of Progression at 20 Years Accounting for Death as a Competing Risk
Low-risk (Serum M protein < 1.5 gm/dL, IgG subtype, normal FLC ratio (0.26–1.65)	449	1	5%	2%
Low-Intermediate-risk (Any 1 factor abnormal)	420	5.4	21%	10%
High-Intermediate-risk (Any 2 factors abnormal)	226	10.1	37%	18%
High-risk (All 3 factors abnormal)	53	20.8	58%	27%

S. Vincent Rajkumar, et al
Blood. 2005;106:812-817

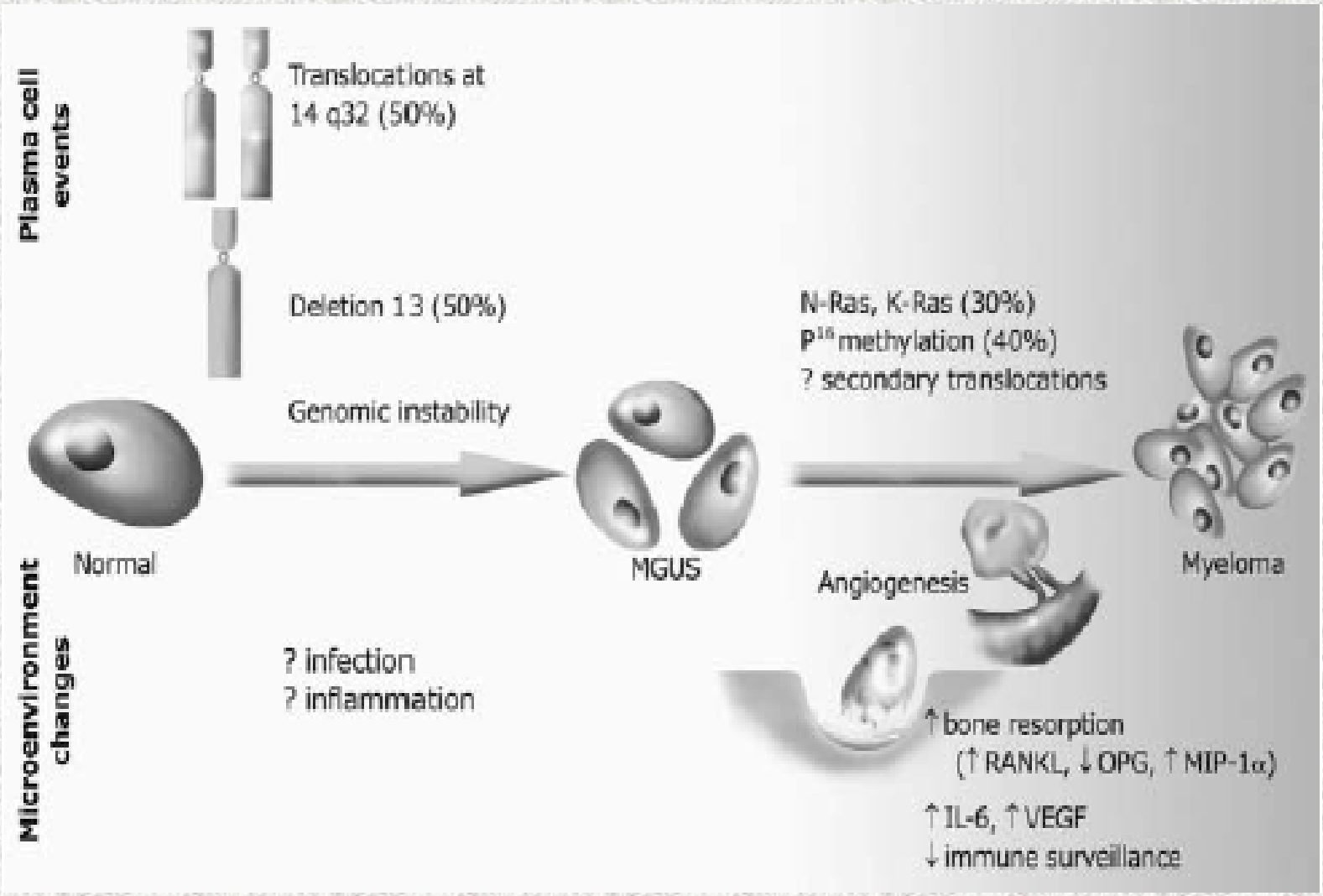
Quando una gammapatia monoclonale diventa mieloma multiplo?



In un modello murino di mieloma, la terapia con NVP-ADW742, un inibitore specifico della kinasi IGF1-R correlata ha dimostrato un significativo effetto antitumorale in vivo.
(Mitsiades, Cancer Cell, 2004)

Tucci et al..: Leukemia & Lymphoma, 2003

Quando una gammapatia monoclonale diventa mieloma multiplo?



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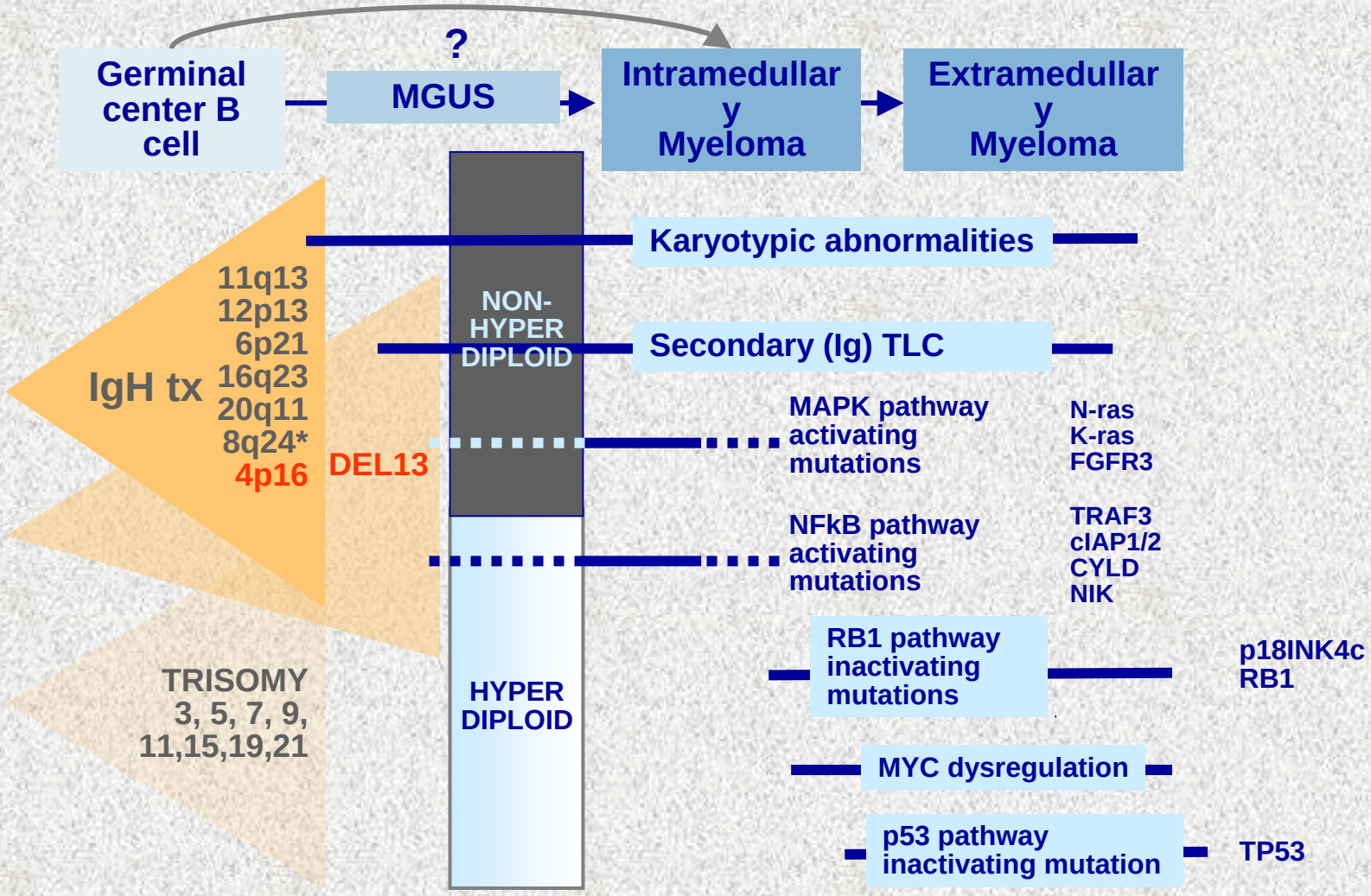
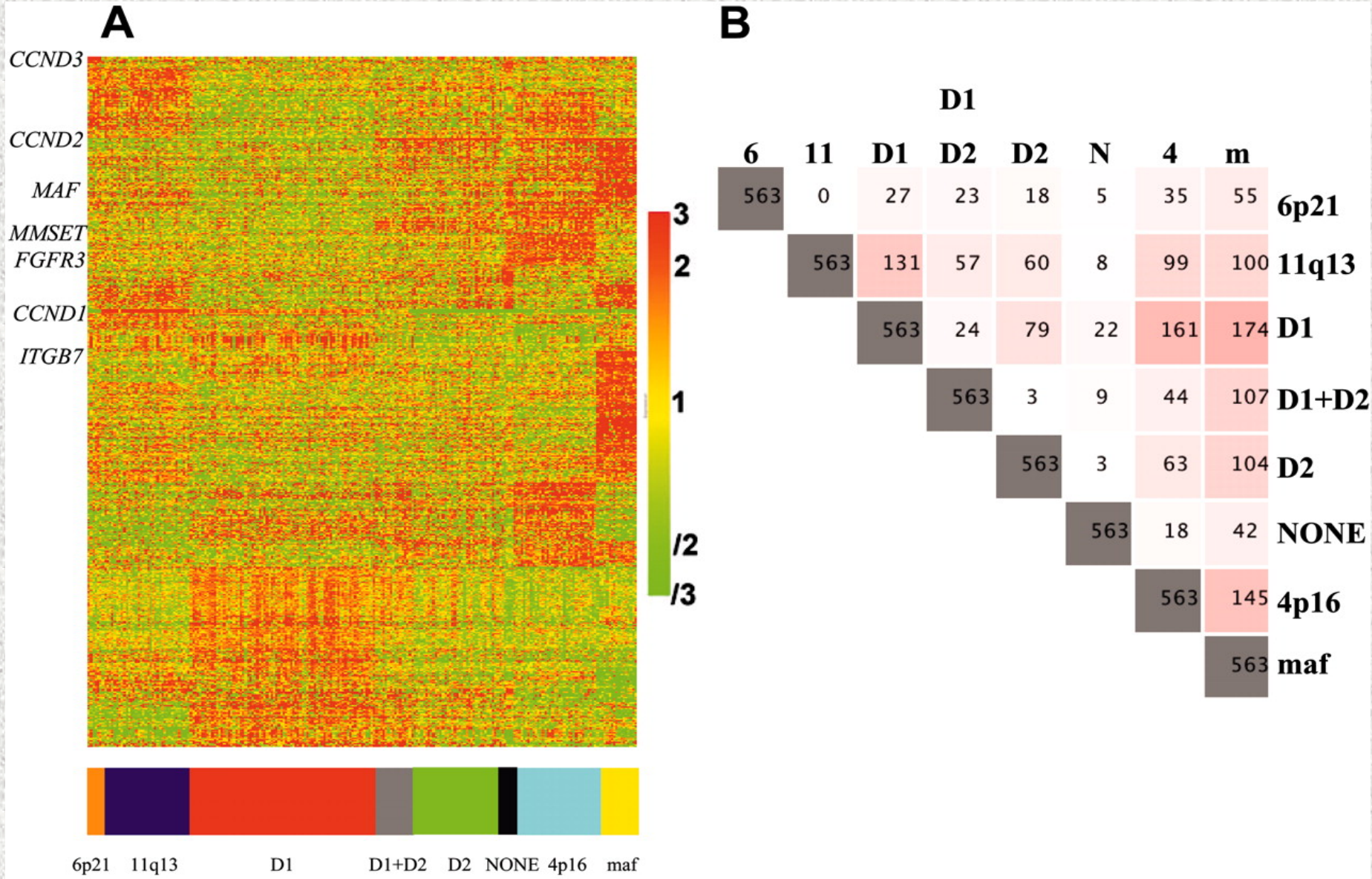
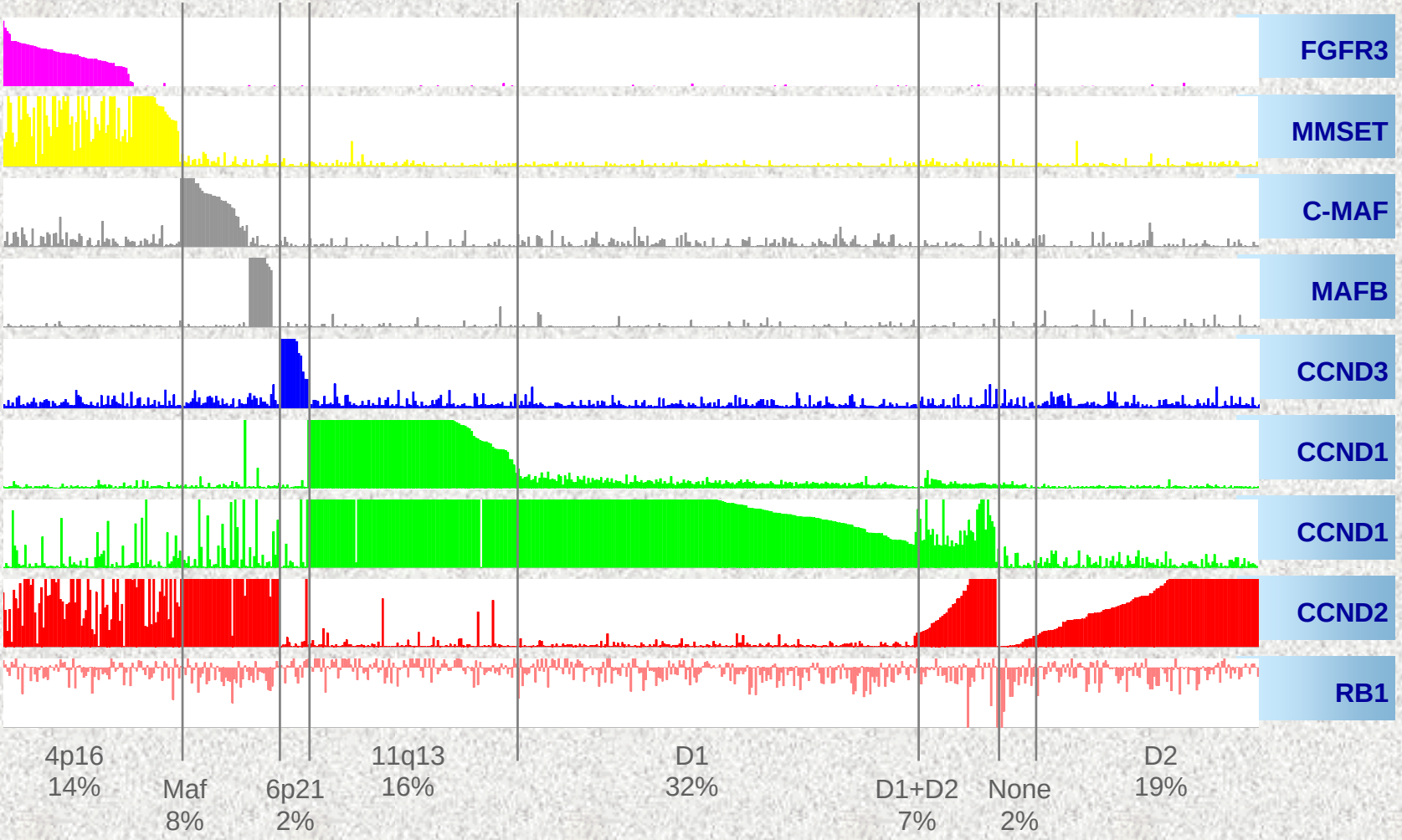


Profilo di espressione genica (GEP) del mieloma

Bergsagel, P. L. et al. Blood 2005;106:296-303

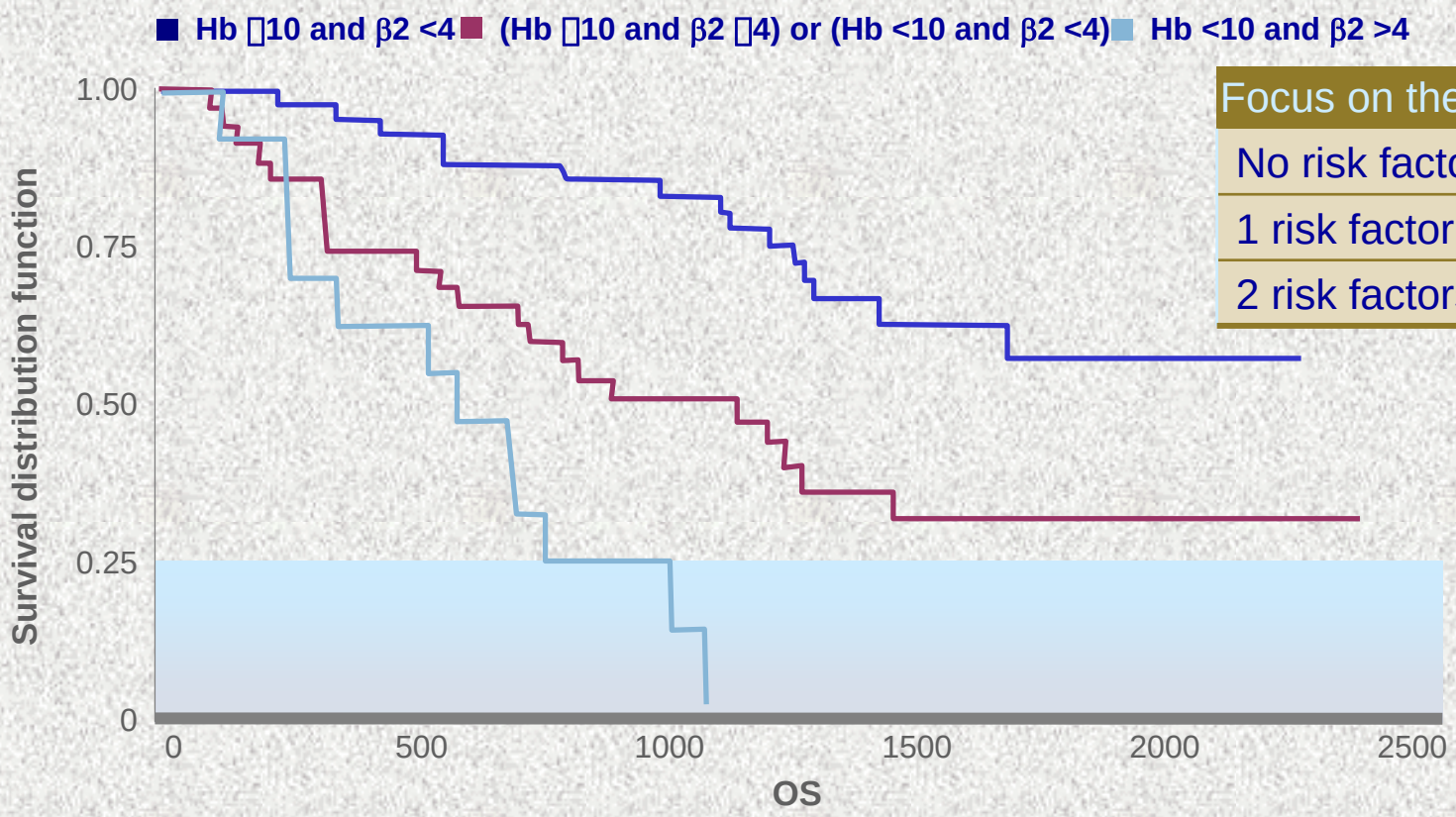


Classificazione genetica del mieloma



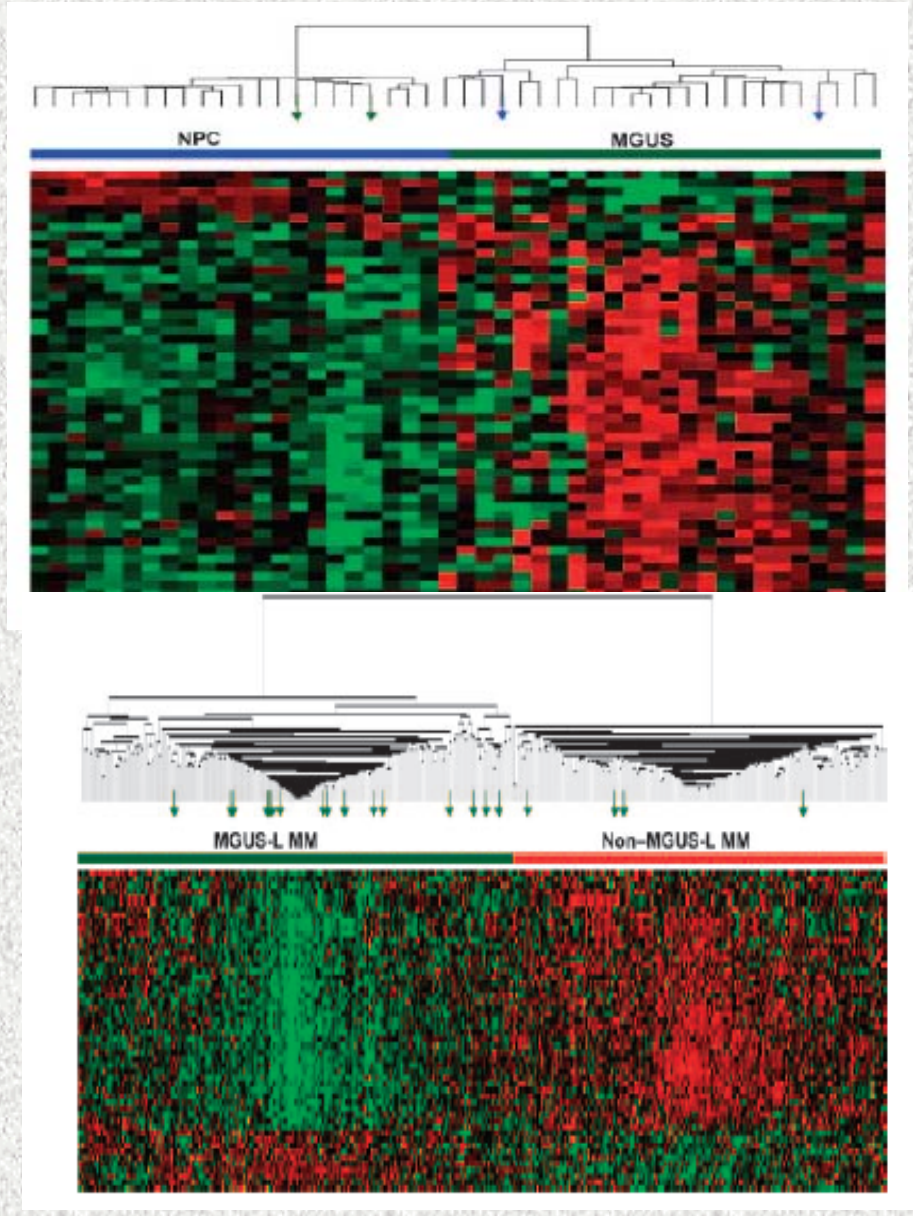
596 patients from UAMS - Shaughnessy & Barlogie

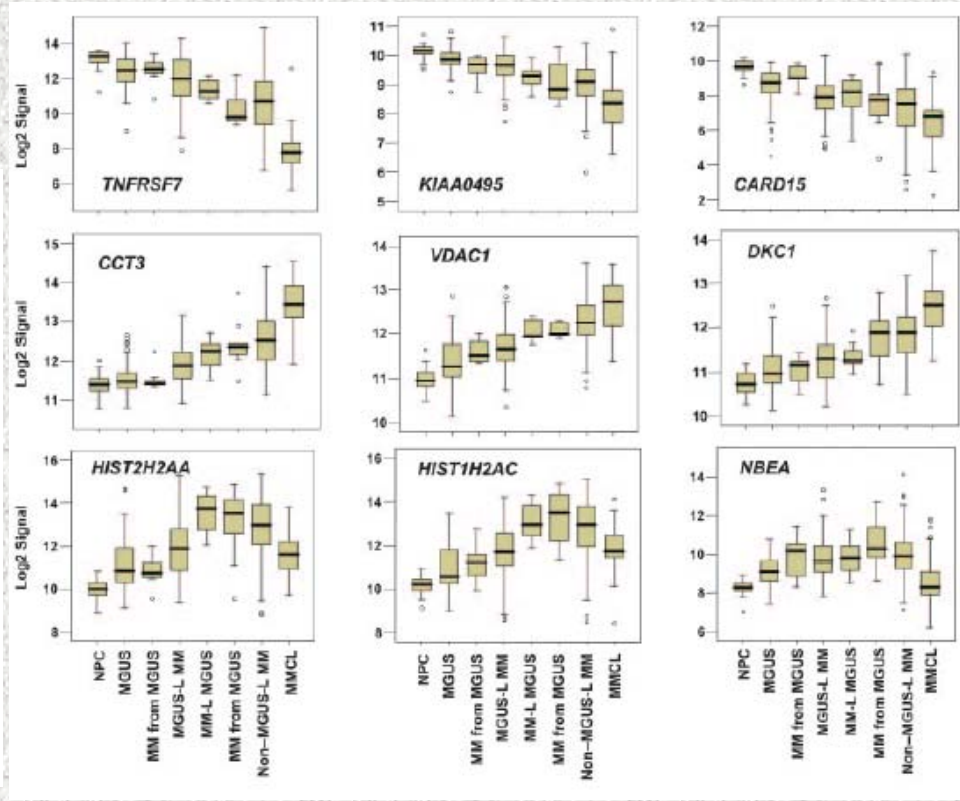
t(4;14) Survival



Focus on the 100 pts with t(4;14)	
No risk factor	**47% of pts**
1 risk factor	**39% of pts**
2 risk factors	**14% of pts**

GEP: MGUS vs nn; Mieloma MGUS-like vs MM non MGUS-like





MGUS: come seguire nel tempo i pazienti?

- **La scomparsa spontanea di una paraproteinemia monoclonale è evento eccezionale (0,4% dei casi).**
- **Il rischio di progressione persiste nel tempo, indipendentemente da età o durata del follow-up.**
- **Il controllo periodico almeno dell'elettroforesi sieroproteica, crasi ematica, creatinina, calcemia, e Bence Jones dovrebbe essere mantenuto indefinitamente, con frequenza annuale.**

Modalità evolutive delle MGUS evolute a mieloma multiplo:

Stabile, con aumento improvviso:	25%
Stabile, con aumento graduale:	12%
Aumento graduale:	12%
Aumento improvviso:	15%
Stabile:	13%
Indeterminato:	23%

Aumento graduale nell'arco di tre anni: 55% vs 10% mieloma dopo 10 anni e 80% vs 13% dopo 20 anni (Rosinol, Mayo Clin Proc 2007)

Questi MM hanno una bassa frequenza di risposta completa alla terapia (22% vs 48%) ma ciò non comporta poi una peggiore sopravvivenza (65% vs 70% a 4 anni) (Pineda-Roman, Br J Haematol, 2007)

Mieloma asintomatico

Rischio di progressione a mieloma sintomatico molto più elevato (mediana 26-48 mesi)

Fattori prognostici:
Facon, 1995; Weber, 1997

- **Livello di Ig > 3.0**
- **Plasmacellule > 25%**
- **Hb <12g**

0/3 → 50 mesi

2-3/3 → 6 mesi

- **Livello di Ig > 3.0**
- **IgA**
- **BJ > 50 mg/die**

0/3 → 95 mesi

1/3 → 39 mesi → **RM rachide**

2-3/3 → 17 mesi

Follow-up più ravvicinato:

- E.O., CRA, livelli picco e BJ, ogni 3 mesi per un anno e poi ogni 6 mesi
- Rx scheletro ogni anno (+RM rachide se un fattore di rischio)

Mieloma asintomatico

Terapia: no

Approcci sperimentali (sempre nell'ambito di studi clinici controllati):

? bifosfonati;

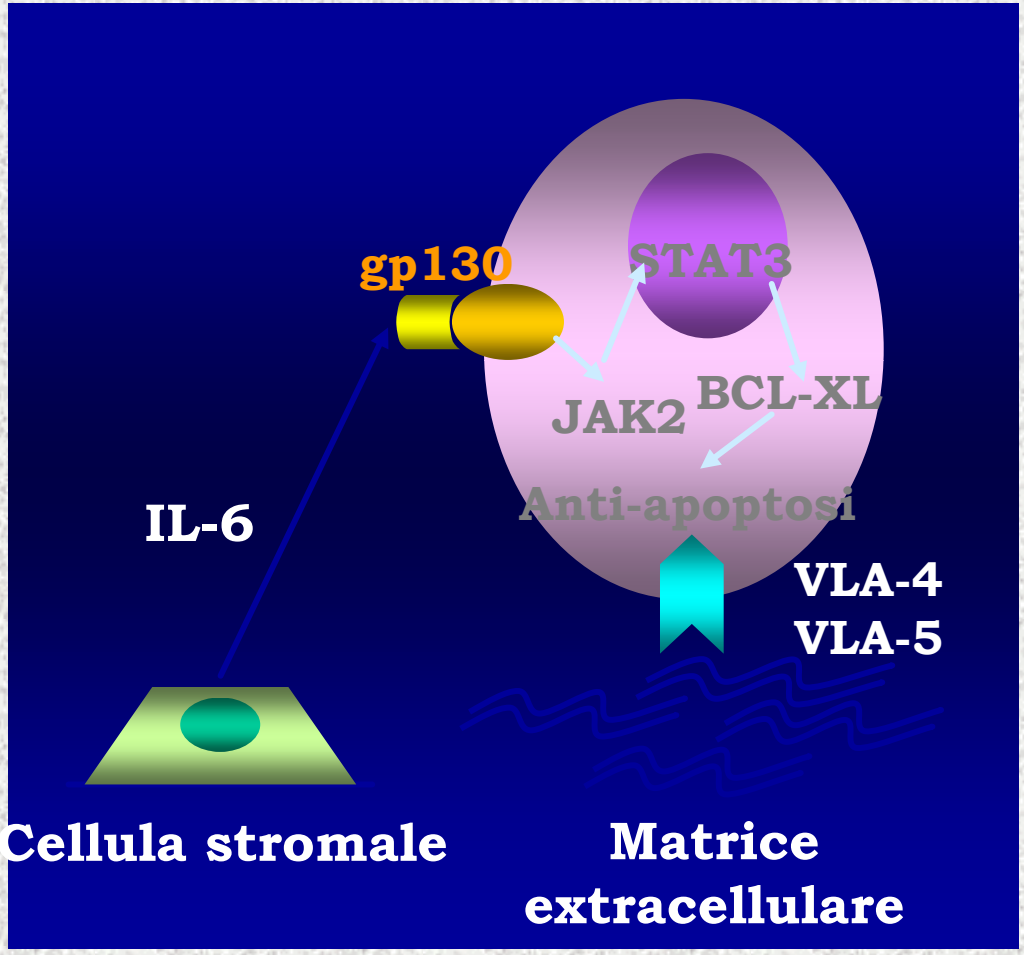
? talidomide;

??? guidata da parametri biologici

IL MICROAMBIENTE PROMUOVE LA CRESCITA DEL MM

Microambiente osteoclastico

Stroma e matrice extracellulare



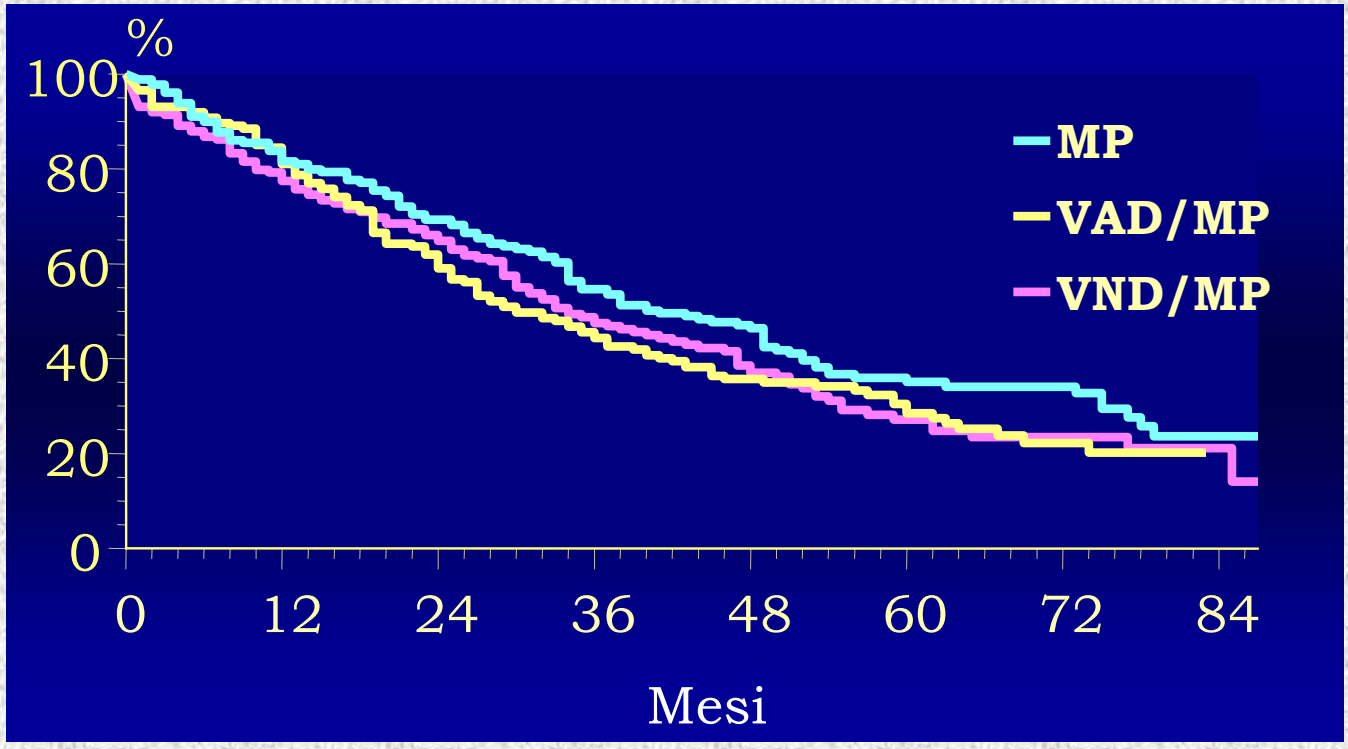
Need for New First-line Regimens for Elderly MM Patients

- Autologous transplant has become the standard of care for young MM patients
- More than 50% of all patients with MM will not receive a transplant
  - Almost half of MM patients are aged >70 years
  - Some young patients are not transplant candidates due to co-morbidities
- Melphalan and prednisone combination
  - Response rate: 40–60%, CR rare, PFS: 18 months, OS: 3 years

There is an urgent need for more active therapies for elderly patients

Reece Hematology (Am Soc Hematol Educ Program) 2005:353–9
www.nccn.org

CHEMIOTERAPIA CONVENZIONALE NEL MM



- **CR rate ≤ 5%**
- **Sopravvivenza mediana ≤ 3 aa**
- **Probabilità di sopravvivenza a lungo termine ≤ 5%**

MP vs Dexamethasone-Based Regimens (IFM 95-01 Trial)

- 488 patients aged 65-75 yr randomized to MP, MD, D, or D-IFNα (12 courses at 6-wk intervals)
- FU 82.8 mo, OS 35.0 mo (415/488), EFS 18.3 mo (473/488) for whole series
- Standard MP gold standard for treatment of older pts

Regimen	MP	MD	D	D-IFNα
n	109	110	109	101
PR↓ (P < 0.001)	51%	**74%**	40%	42%
CR (P = NS)	1%	3%	1%	1%
EFS (mo)	**21.1 ± 1.7**	**22.9 ± 2.0**	**12.2 ± 1.0***	**15.2 ± 2.7***
OS (mo)	34.0 ± 3.6	39,6 ± 3.1	33.4 ± 2.0	32.0 ± 5.3

*P < 0.001 for pts not receiving Melphalan

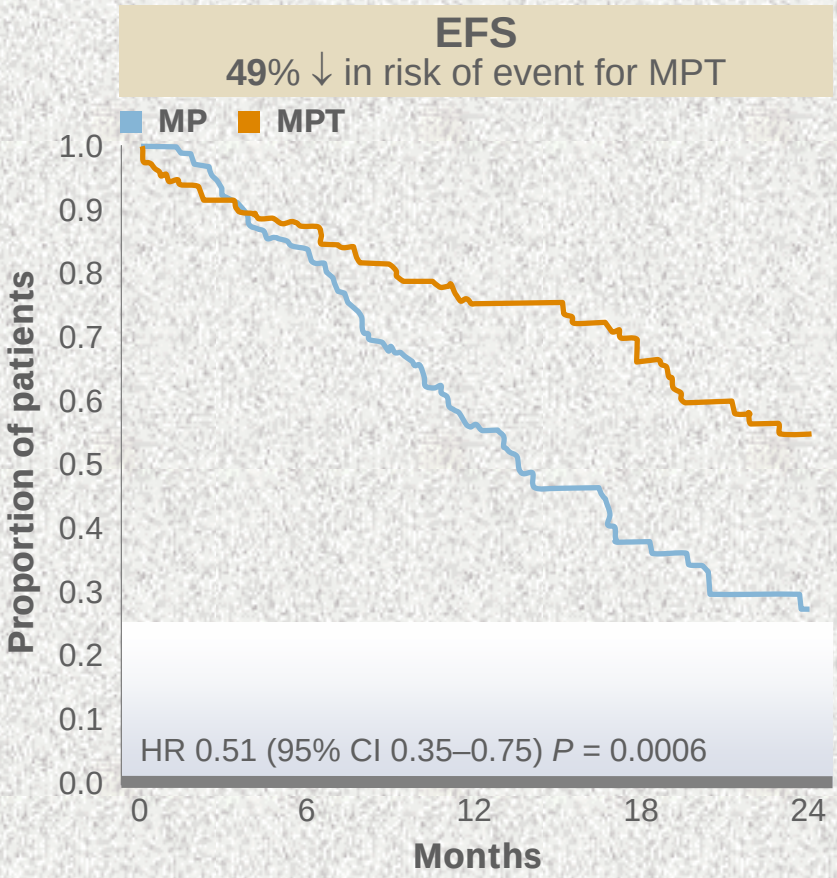
Facon T et al. Blood. 2006; 107:1292

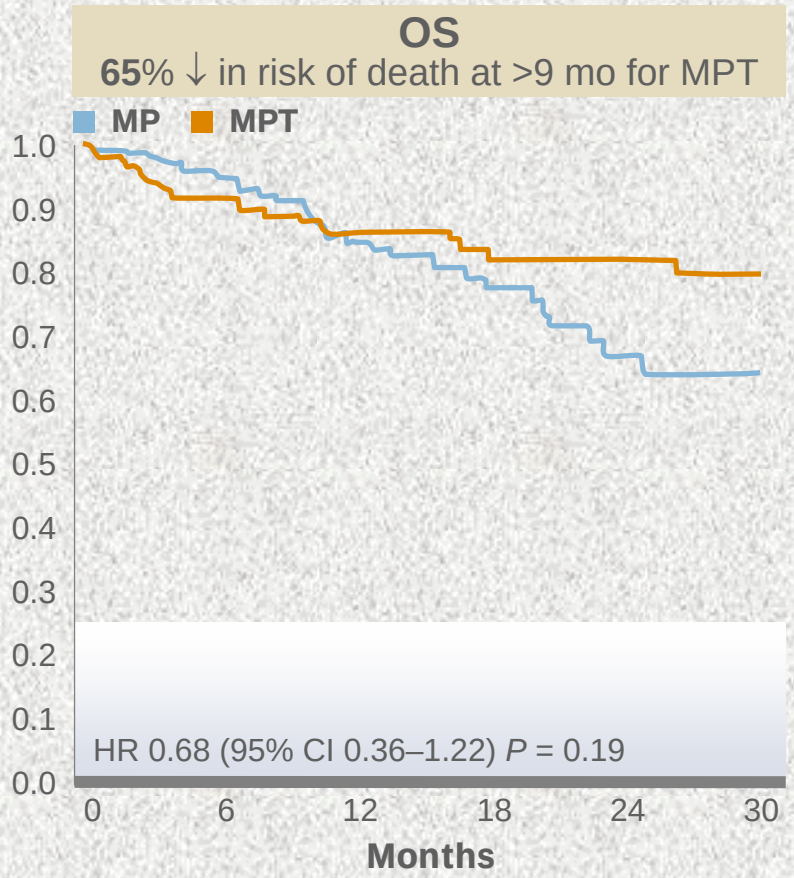
MPT vs MP in Newly Diagnosed MM Patients: EFS and OS

Age: 65-85 years

- Melphalan, 4 mg/m^2 (7 days/month) 50 mg/month
- Prednisone, 40 mg/m^2 (7 days/month) 6 cycles
- Thalidomide, 100 mg/d (continuously)

PR were 76% for MPT and 47.6% for MP



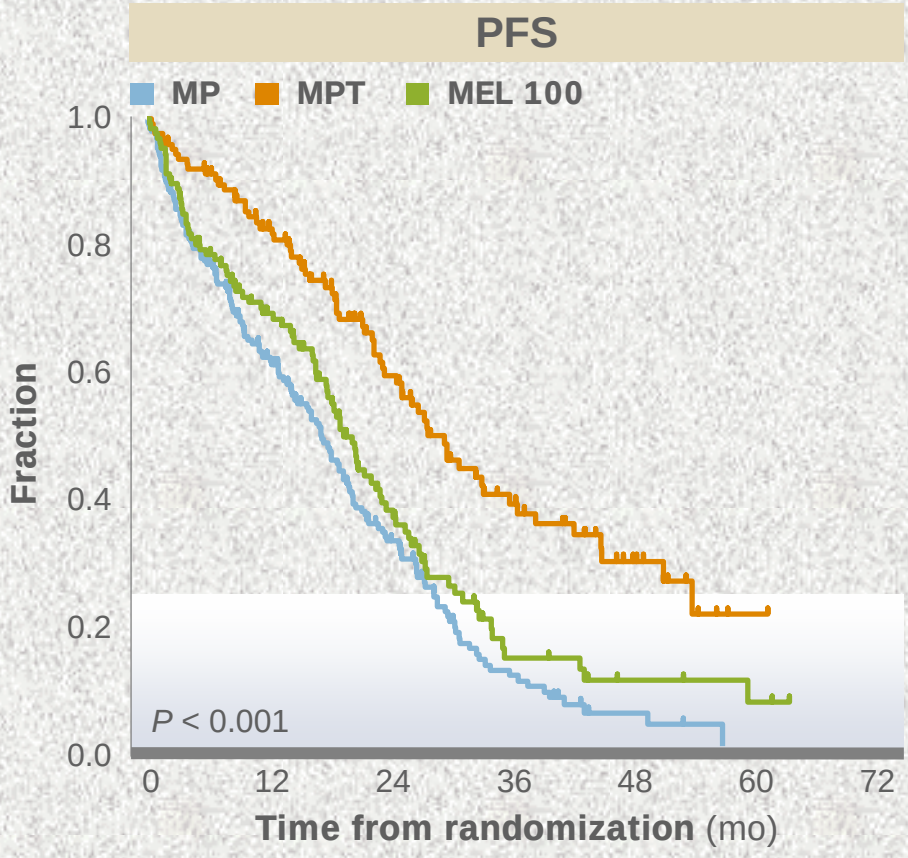


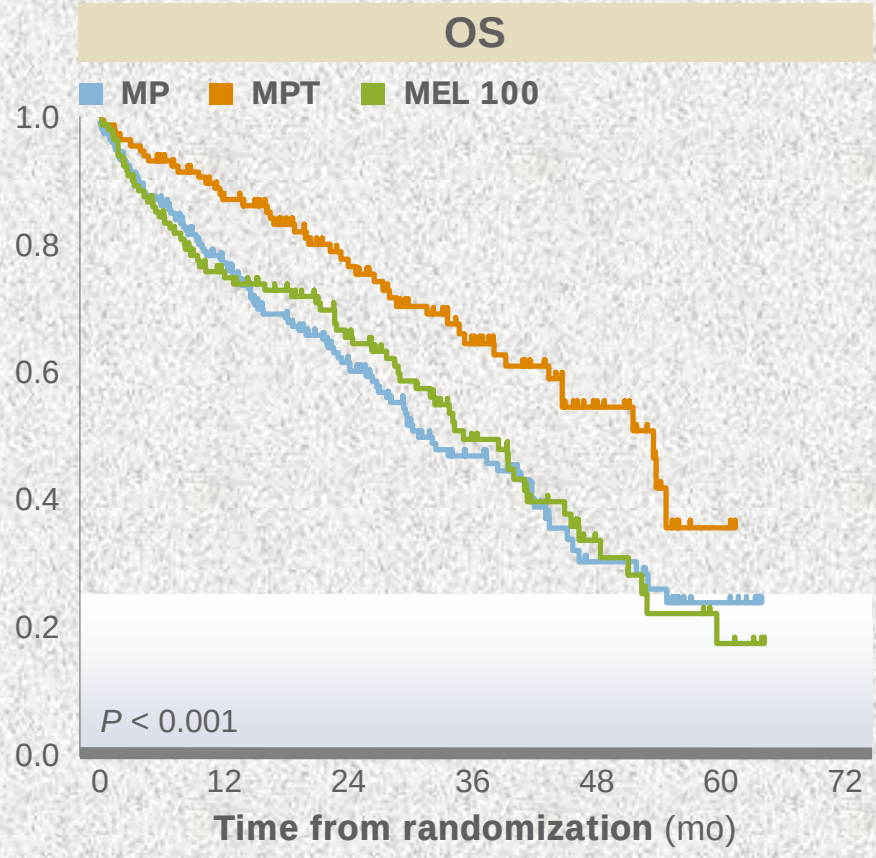
Palumbo A et al. Lancet. 2006; 367:825

MPT vs MP and MP vs MEL100/ASCT in Newly Diagnosed MM Patients: PFS and OS

Age: 65-75 years

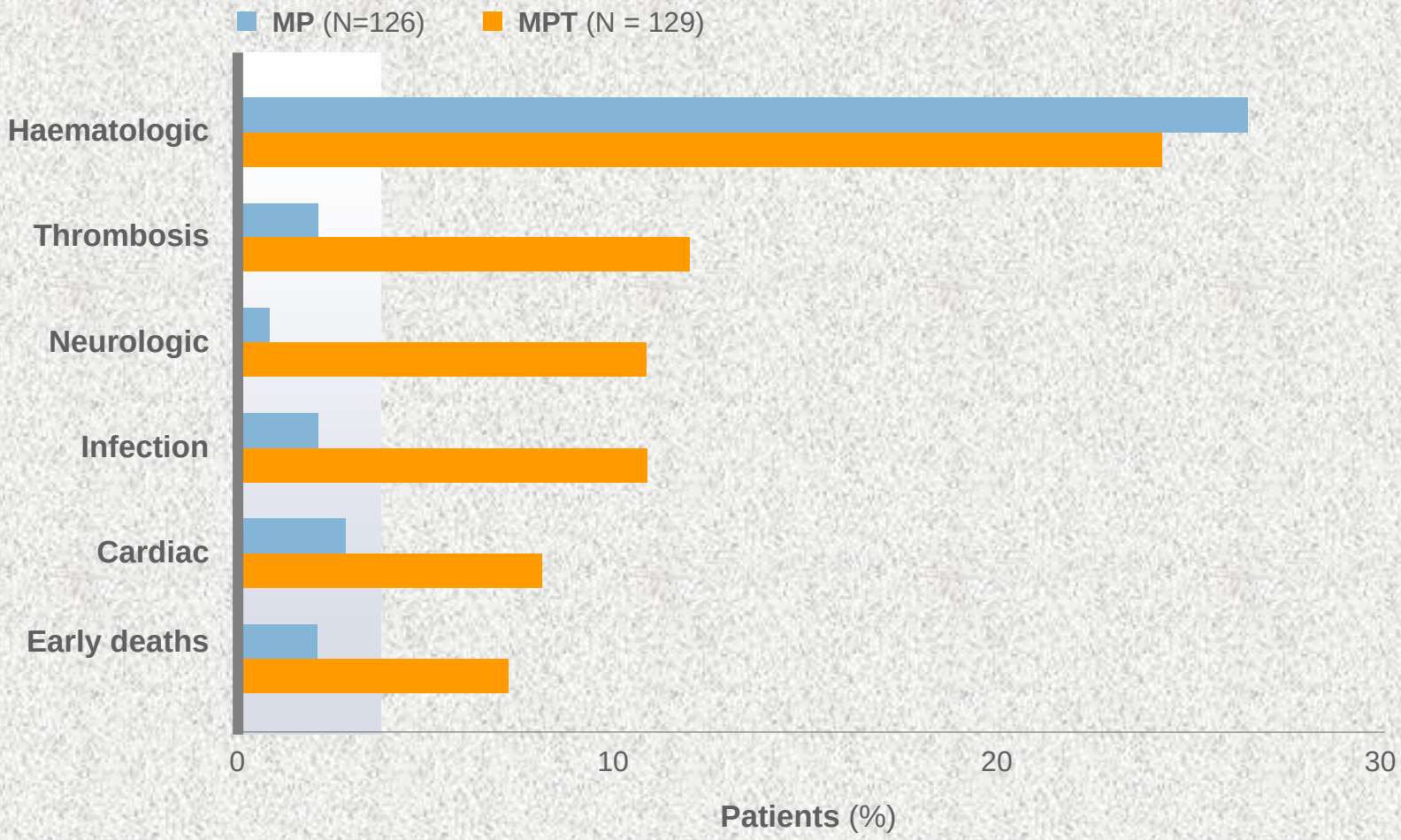
- Melphalan, 0.25 mg/kg (4 days/1.5 month) 50 mg/month
- Prednisone, 2 mg/kg (4 days/1.5 month) 12 cycles
- Thalidomide, 100-400 mg/day





Facon T et al. Presented at ASCO Annual Meeting; June 2–6, 2006; Atlanta, GA

MPT vs MP in Newly Diagnosed MM Patients: Grade 3-4 adverse events



Palumbo A et al. Lancet. 2006;367:825

Conclusions / MPT

- Three randomized studies (IFM 99-06, IFM 01-01, and GIMEMA) show the superiority of MPT in the treatment of newly diagnosed elderly patients with MM
- The superiority of MPT over MP was demonstrated based on response, including CR rate, and PFS in all studies
- In the IFM studies, the PFS advantage observed with MPT translated into a OS advantage. MPT was also found to be superior to MEL100 in the IFM 99-06 study
- MPT toxicity was acceptable but higher than the MP toxicity
- MPT could be the reference treatment for all newly diagnosed MM patients ineligible for HDT

Newly Diagnosed MM Patients
VMP vs MP: Response rates

Age: 65-85 years

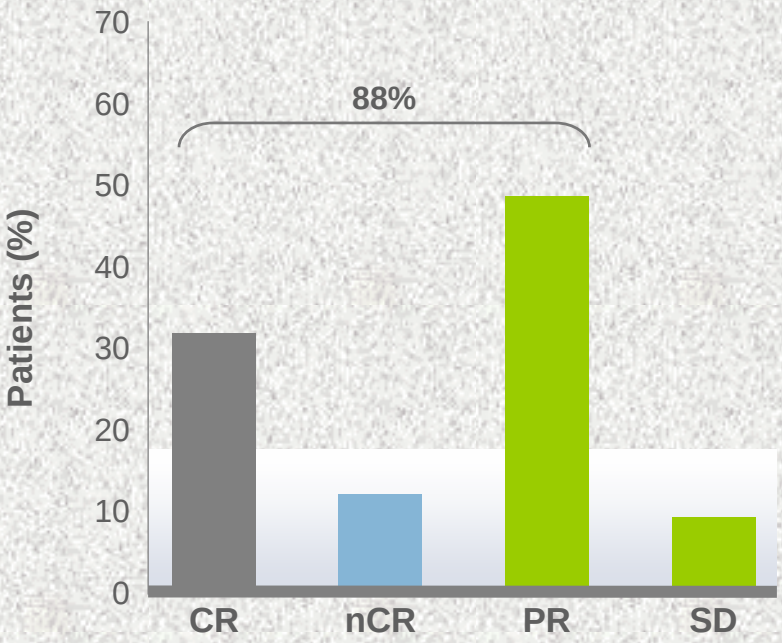
Four 6-week cycles

- Bortezomib d 1,4,8,11,22,25,29,32
- Melphalan, 9 mg/m^2 (4 days)
- Prednisone, 60 mg/m^2 (4 days)

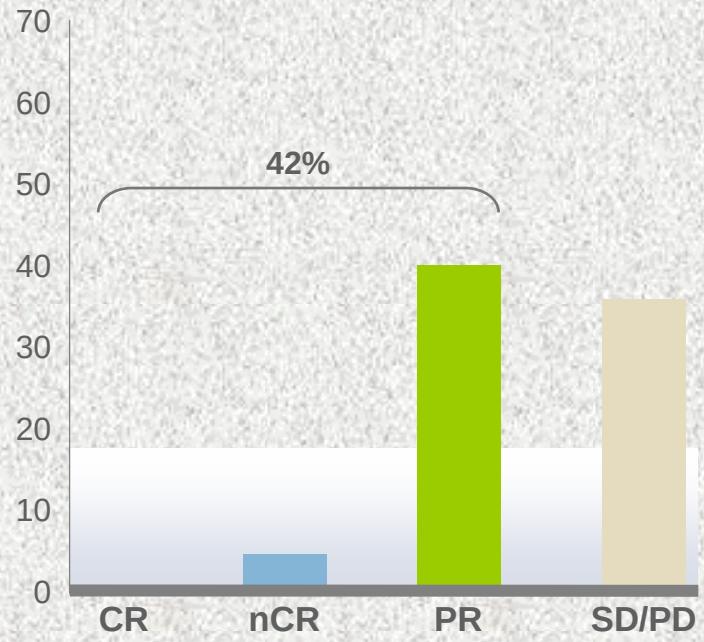
Five 5-week cycles

- Bortezomib day 1,8,15,22
- Melphalan, 9 mg/m^2 (4 days)
- Prednisone, 60 mg/m^2 (4 days)

Best response with 7 cycles of VMP[1]



Best response with 6 cycles of MP[2] (n = 87)

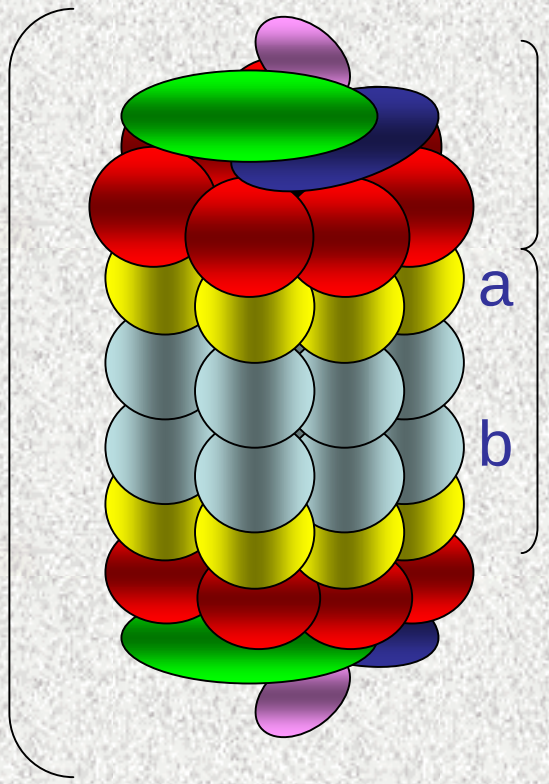


1) Mateos M-V, et al. Blood. 2006;108:2165-72

2) Hernandez JM, et al. Br J Haematol. 2004;127:159-64

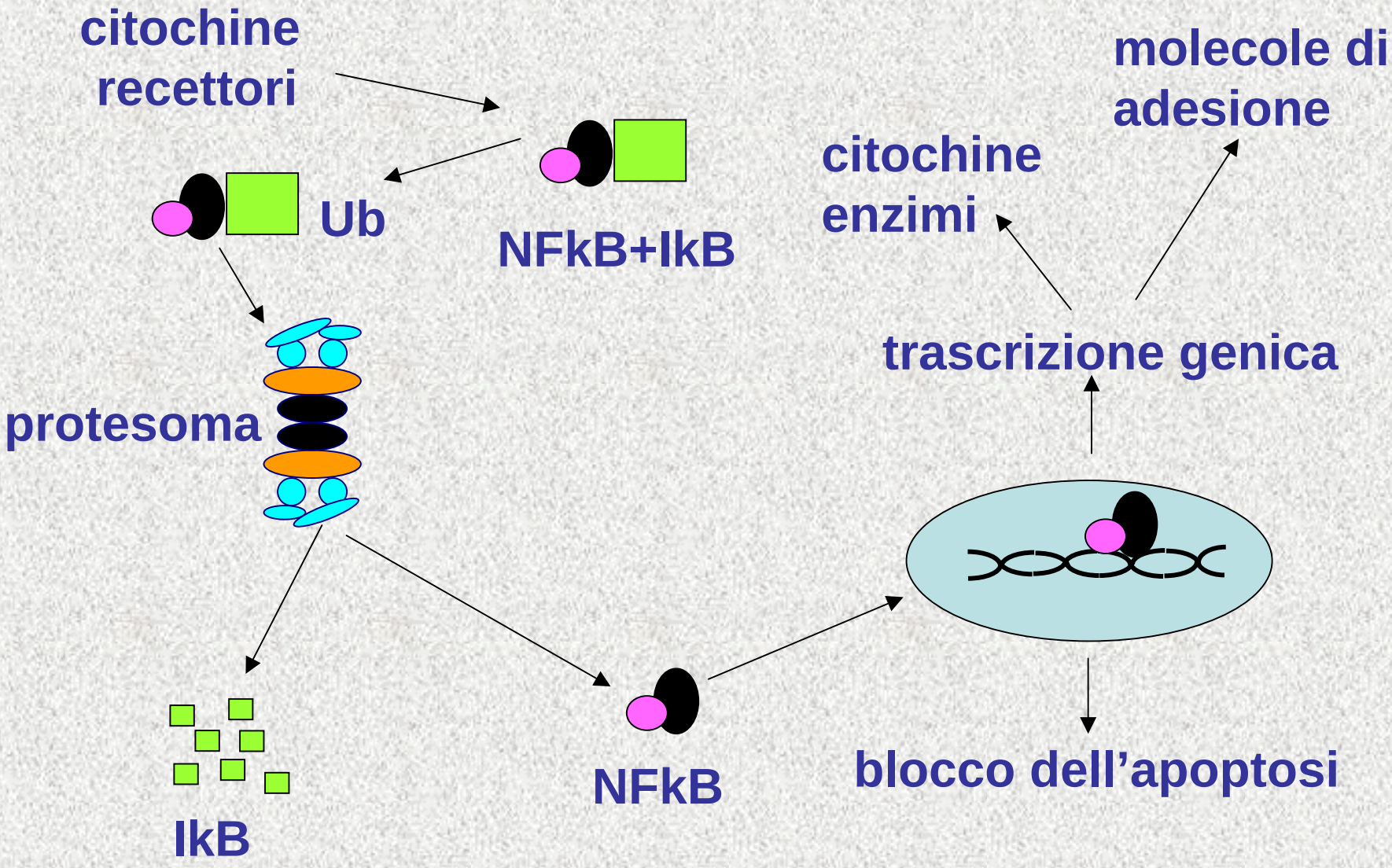
Proteasoma

26S = 20S (regione proteolitica) + 19S (regione regolatoria)

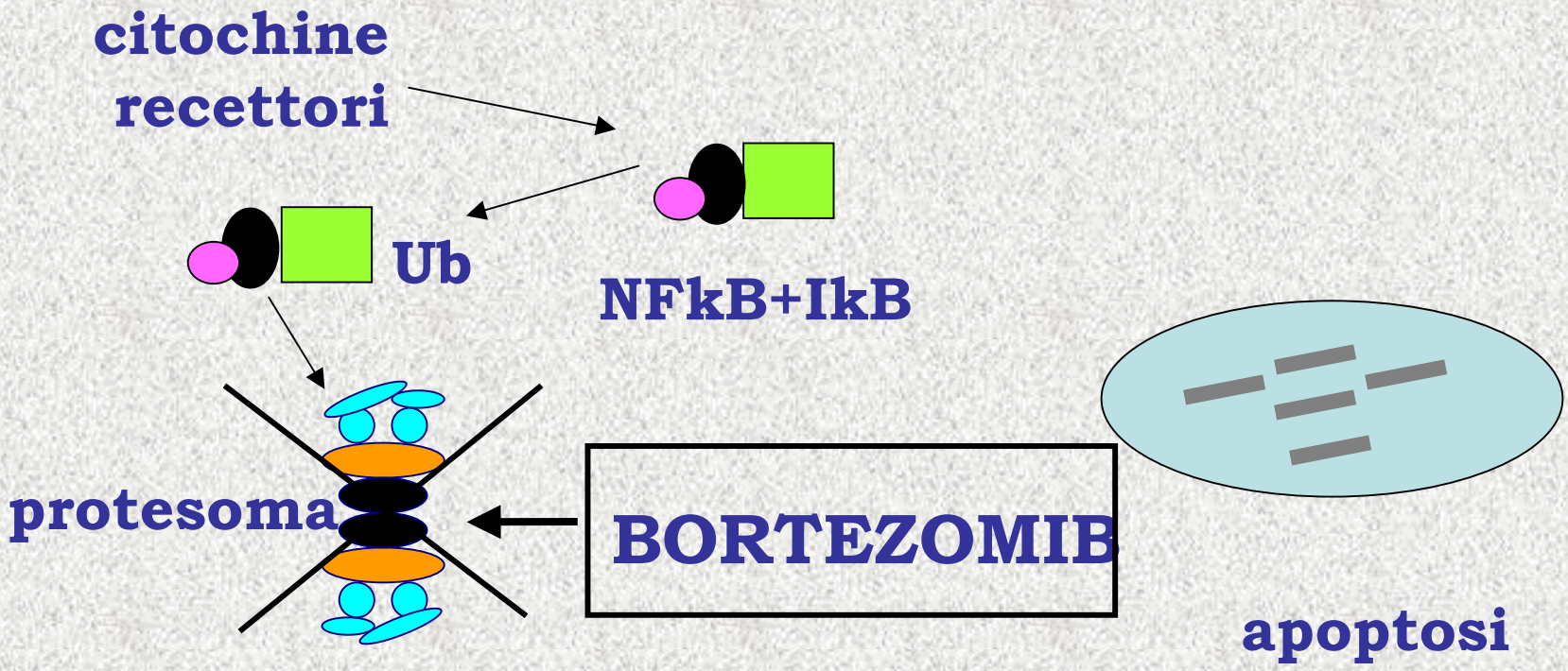


- **La regione 19S:**
  - **Riconosce le proteine ubiquitinate**
  - **Taglia la catena poliubiquitinata dalla proteina**
  - **Apre il canale degli anelli α della regione 20S permettendo l'ingresso della proteina bersaglio nella camera proteolitica**

vazione di NFkB

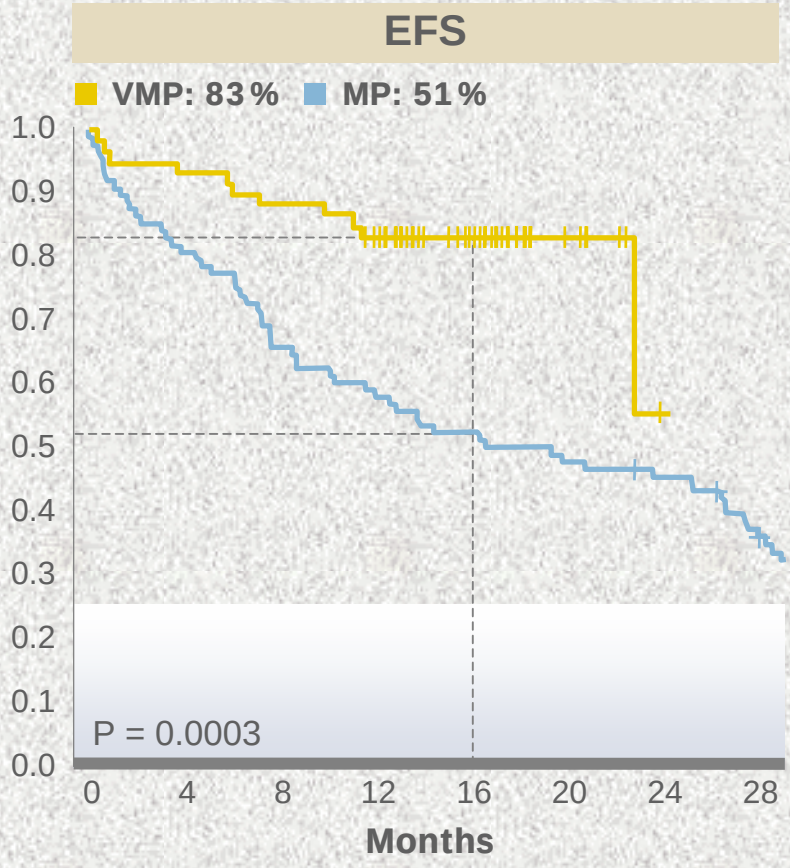


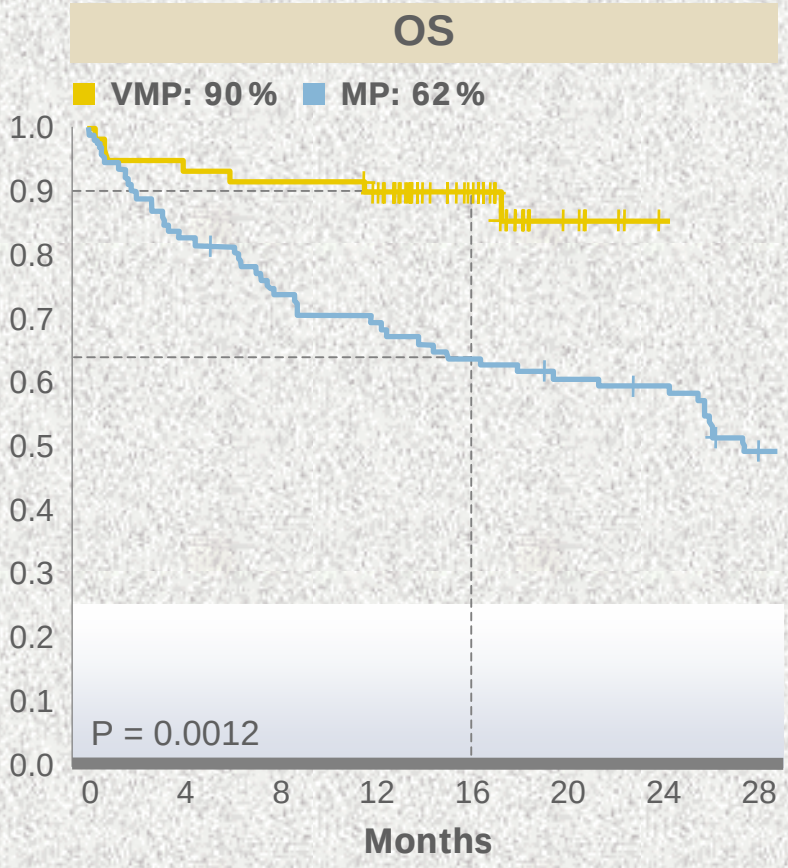
nibizione del proteasoma



Newly Diagnosed MM Patients
VMP vs MP: EFS and OS

Median follow-up: 16 months (11–24)



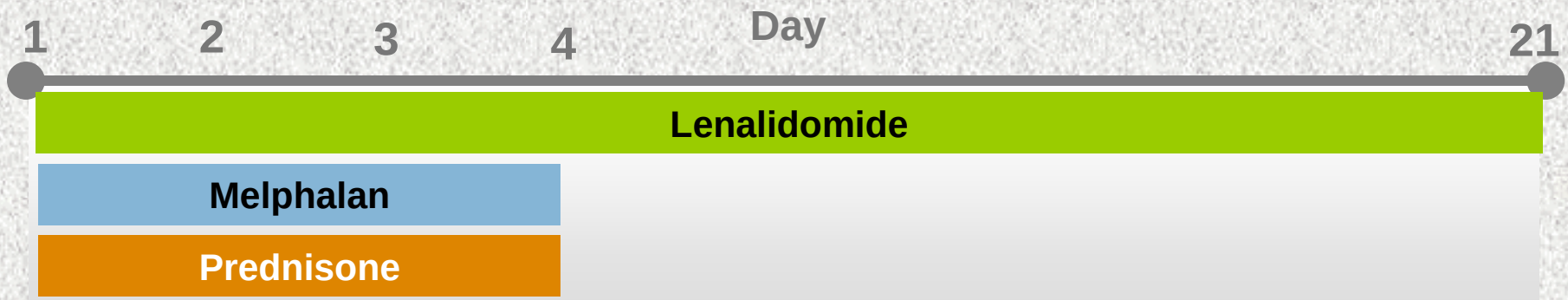


Mateos et al. Blood 2006; 108(7):2165-72

Phase I/II Trial of MPR in Newly Diagnosed MM

Median age 71 years (range, 57–77)

Cohort	**Lenalidomide** (mg/day)	**Melphalan** (mg/kg/day)	**Prednisone** (mg/kg/day)
1 (N = 6)	5	0.18	2
2 (N = 6)	5	0.25	2
3 (N = 6 + 15)	**10**	**0.18**	**2**
4 (N = 6 + 15)	10	0.25	2

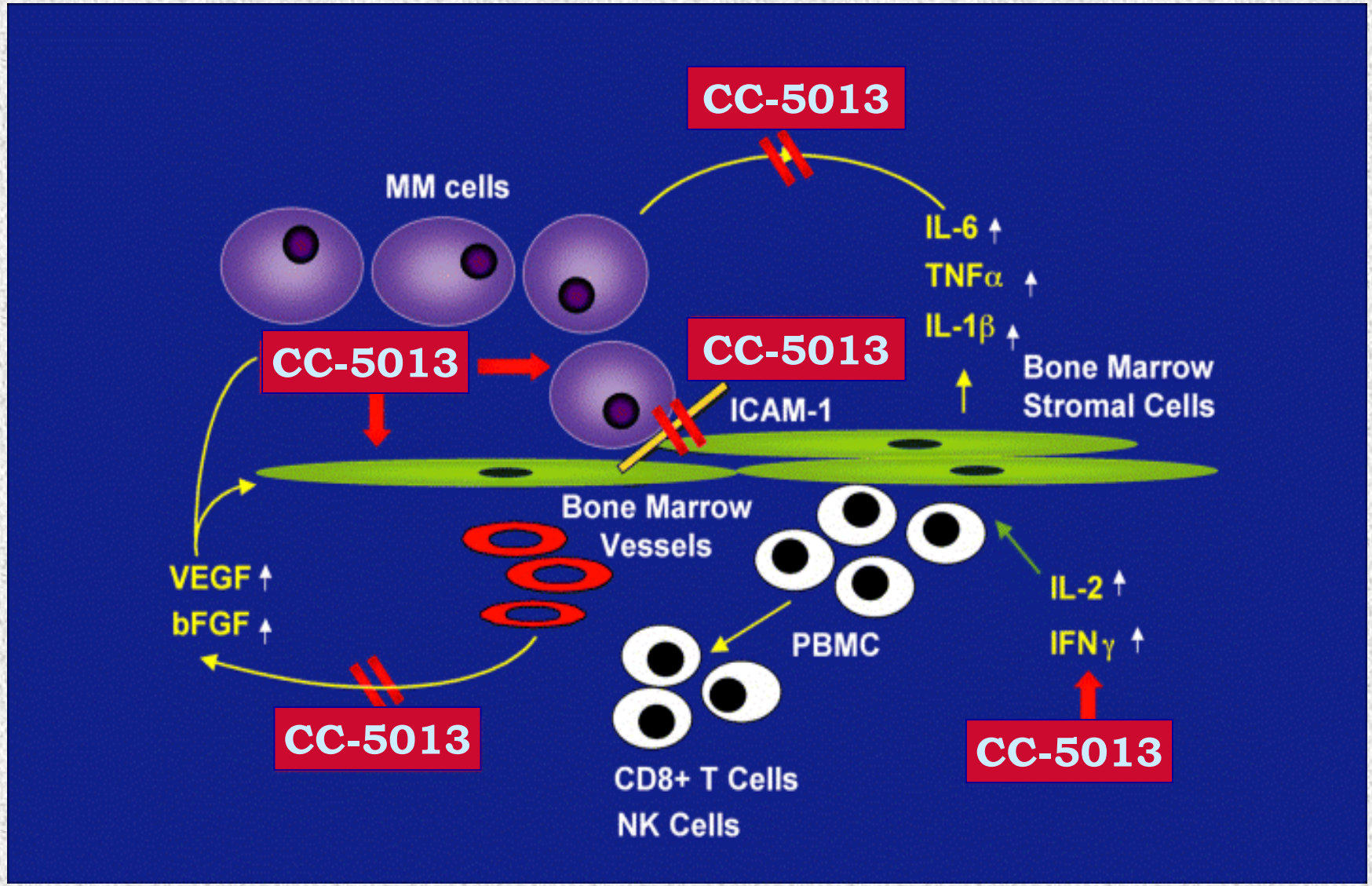


- Every 4–6 weeks for maximum of 9 cycles.
- Aspirin (100 mg/day) given as DVT prophylaxis.

MTD = Mel 0.18 mg/kg + Lenalidomide 10 mg/day

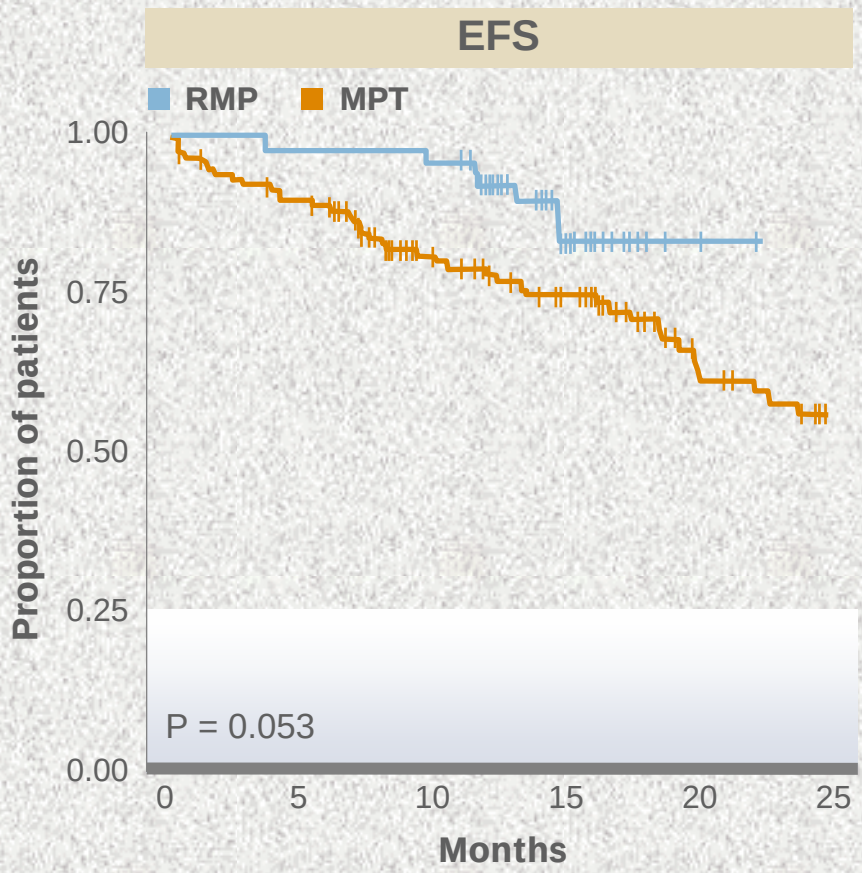
Palumbo A, et al. J Clin Oncol. 2007 [Epub ahead of print]

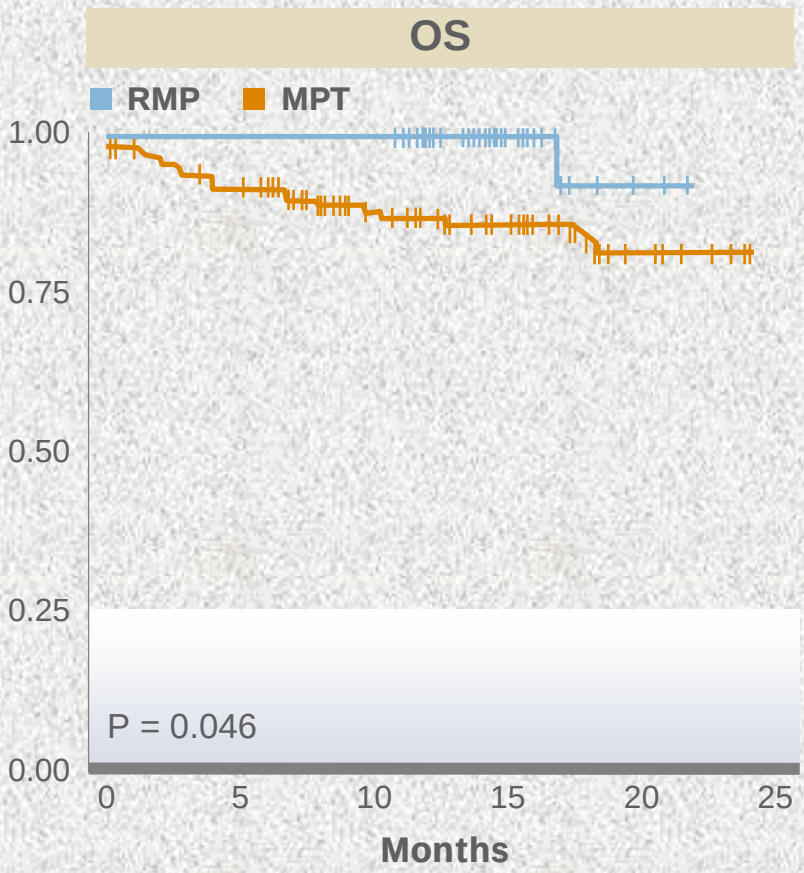
LENALIDOMIDE: MECCANISMO D'AZIONE



Newly Diagnosed MM Patients
MPR vs MPT: EFS and OS

R-MP: median follow-up 14.6 months (10.8-21.8) (N = 53)
MPT: median follow-up 17.6 months (0.23-44.3) (N = 129)*





*Historical control – Palumbo et al, Lancet 2006
Palumbo A, et al. J Clin Oncol. 2007 [Epub ahead of print]

MP + Novel Agents / Study Results

	MPT (n=124) **Facon et al.**	**MPT** (n=129) **Palumbo et al.**	**MPR** (n=21 [MTD]) **Palumbo et al.**	**VMP** (n=60) **Mateos et al.**
Age (%, >75 years)	0	25%	6%	47%
Efficacy				
• CR + PR	76%	76%	81%	88%
• CR	13%	16%	24%	32%
• EFS	28m	54% at 24m	92% at 12m	83% at 16m

Palumbo et al. Lancet 2006; 367:825–31
Facon et al. ASCO 2006 (abstract 1) Updated
Palumbo A, et al. J Clin Oncol. 2007 [Epub ahead of print]
Mateos et al. Blood 2006; 108(7):2165-72

MP + Novel Agents / Toxicity

	MPT (n=124) **Facon et al.**	**MPT** (n=129) **Palumbo et al.**	**MPR** (n=21 [MTD]) **Palumbo et al.**	**VMP** (n=60) **Mateos et al.**
Toxicity (grade 3/4, %)				
• Infections	17	10	10	16
• Neutropenia	41	22	52	43
• DVT	12	12	5	0
• Neuropathy	6	8	0	17

Palumbo et al. Lancet 2006;367:825–31
Facon et al. ASCO 2006 (abstract 1)
Palumbo A, et al. J Clin Oncol. 2007 [Epub ahead of print]
Mateos et al. Blood 2006;108:2165–72

Factors Affecting Preference for MP–Novel Combination*

- Consolidate data ..... MPT
- Antecedent or risk of DVT ..... MPV
- Antecedent PN ..... MPR
- Renal insufficiency ..... MPV
- Distance from hospital ..... MPR or MPT
- Poor patient accomplishment ..... MPV
- Cost ..... MPT

*Duration of treatment: 6 cycles

San Miguel JF. Presented at: 11th International Myeloma Workshop; June 25–30, 2007; Kos, Greece