

Gruppo di Ricerca Geriatrica

Brescia, 25 gennaio 2008

GAMMAPATIE MONOCLONALI E MIELOMA

Giuseppe Rossi

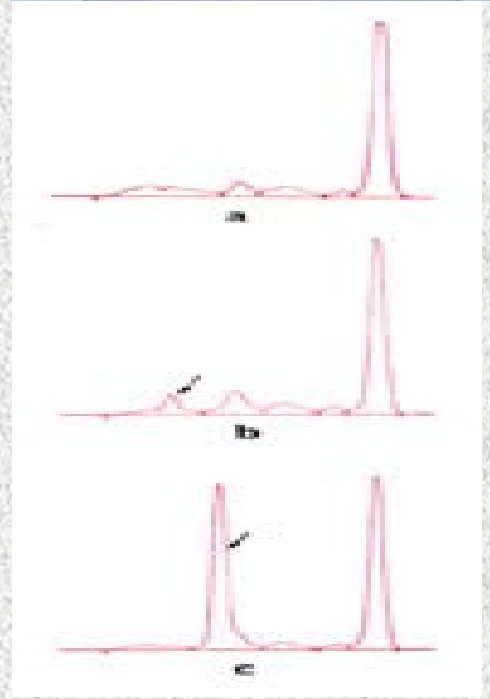
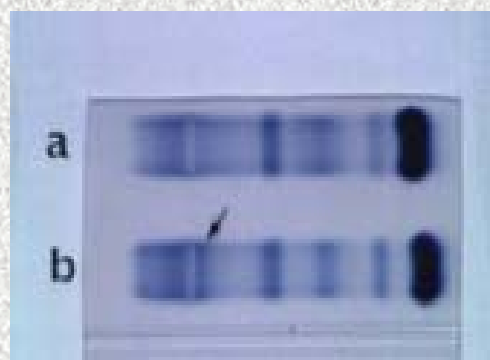
Divisione di Ematologia

Spedali Civili - Brescia

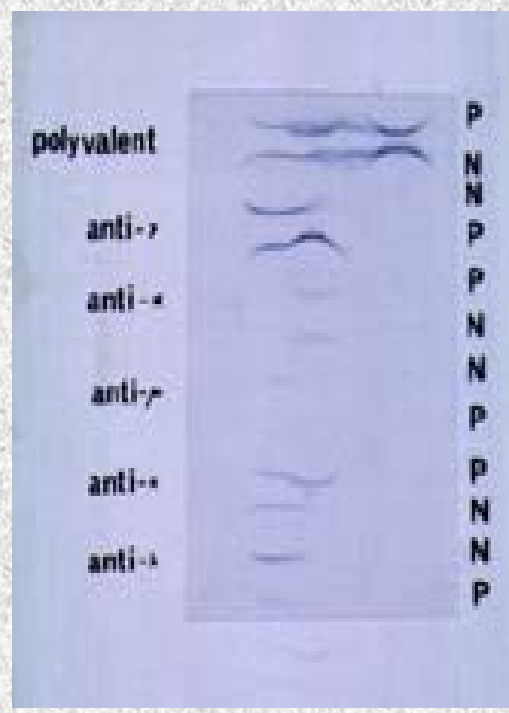


Paraproteinemia monoclonale: diagnosi

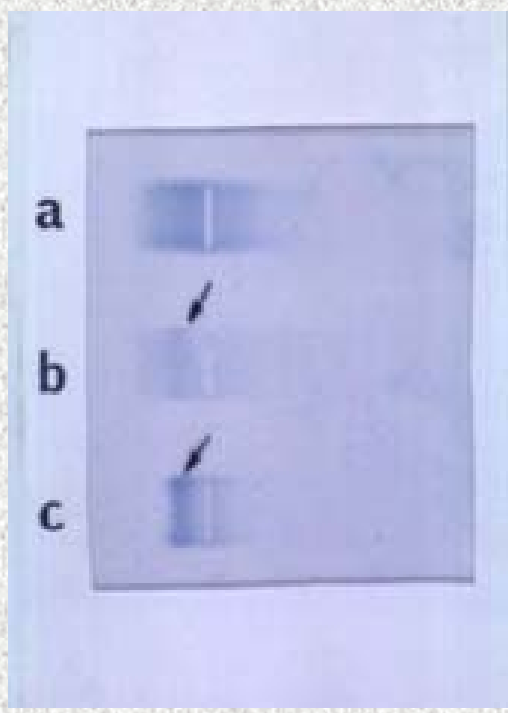
Elettroforesi



Immuno-elettroforesi



Immunofissazione



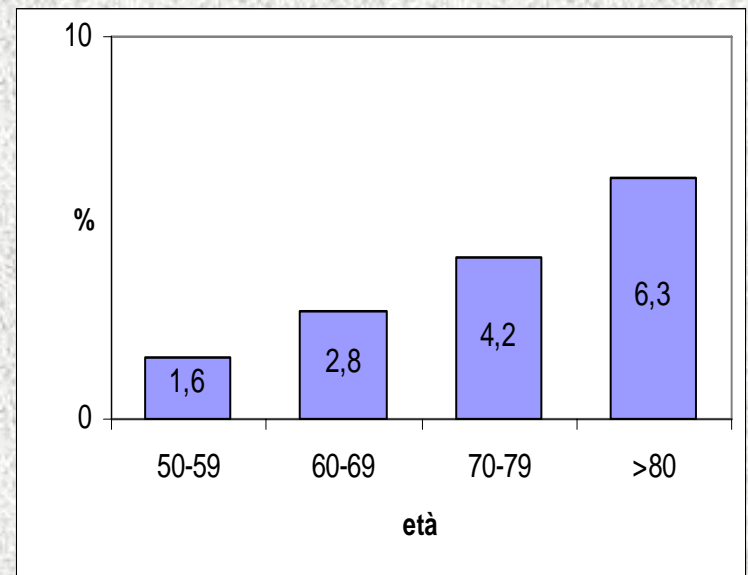
Sensibilità:
Siero: 200 mg/dL
Urine: 40 mg/L

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%

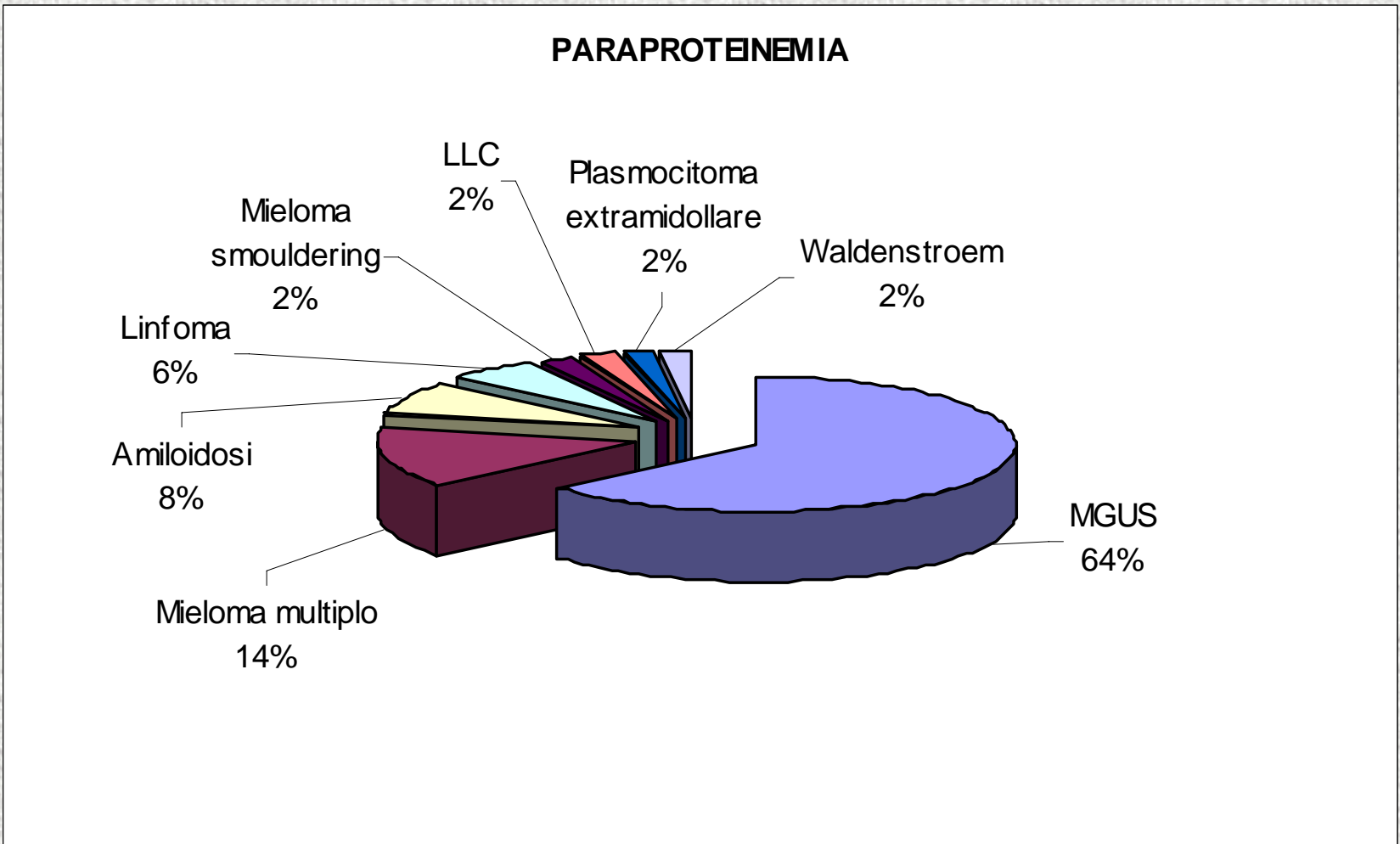
Il rischio sembra mantenere un ritmo costante dopo i 50 anni



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

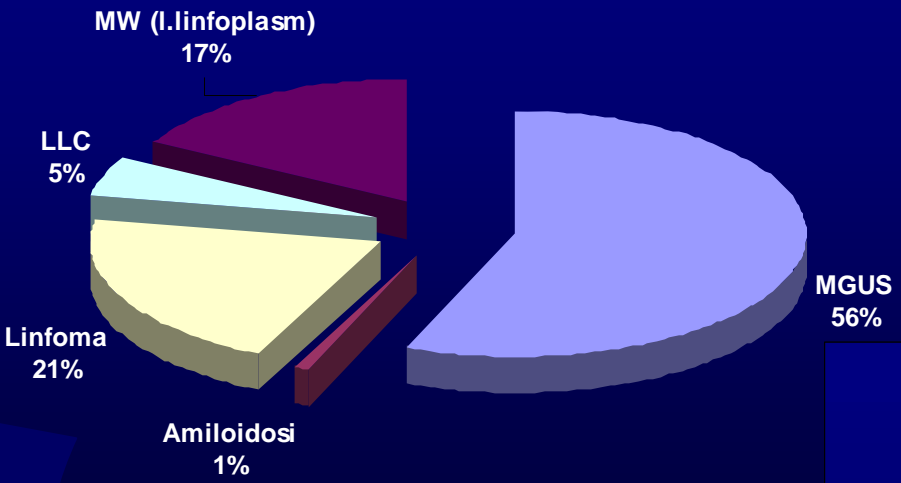
La paraproteinememia monoclonale è una delle condizioni di rischio neoplastico più frequenti nella popolazione generale di età > a 50 anni

Patologie associate alla presenza di paraproteinemia monoclonale



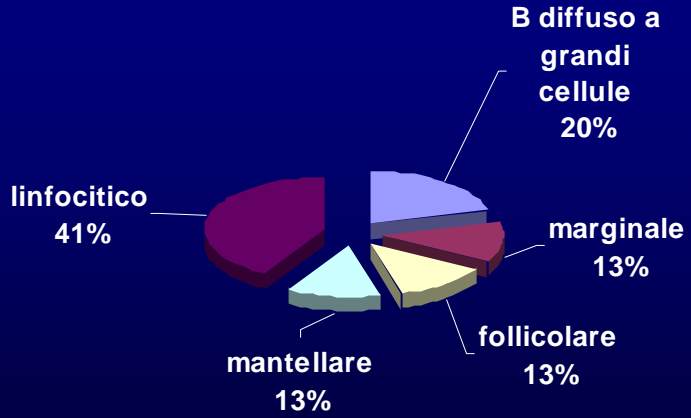
Patologie associate a paraproteinemia monoclonale IgM

Paraproteinemie IgM



Mayo Clin Cases, 1987

Patologia linfoproliferativa



Owen, Clin Lymphoma, 2000

MGUS: definizione

MGUS: monoclonal gammopathy of undetermined significance

MGUS: gammopatia 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 \leq 3,5g/dL, IgA \leq 2,0 g/dL; BJ \leq 1,0 g/dL
- c) osteolisi
- d) ridotti livelli delle Ig non clonali

Combinazioni diagnostiche

Ib, Ic, Id,

IIb IIc, II d

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

Criteria maggiori:

- I plasmacitoma alla biopsia
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- c) osteolisi
- d) ridotti livelli delle Ig non clonali

Mieloma "indolente"

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

Mieloma "smouldering"

- non lesioni osteolitiche
- plasmacellule \leq 30%
- non sintomi

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

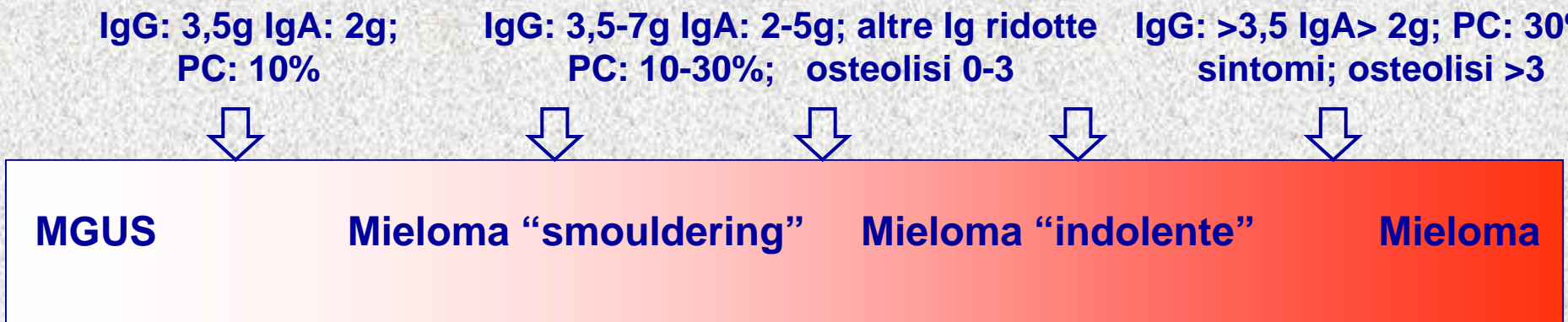


GAMMAPATIA MONOCLONALE

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- non lesioni osteolitiche
- plasmacitosi midollare < 10%

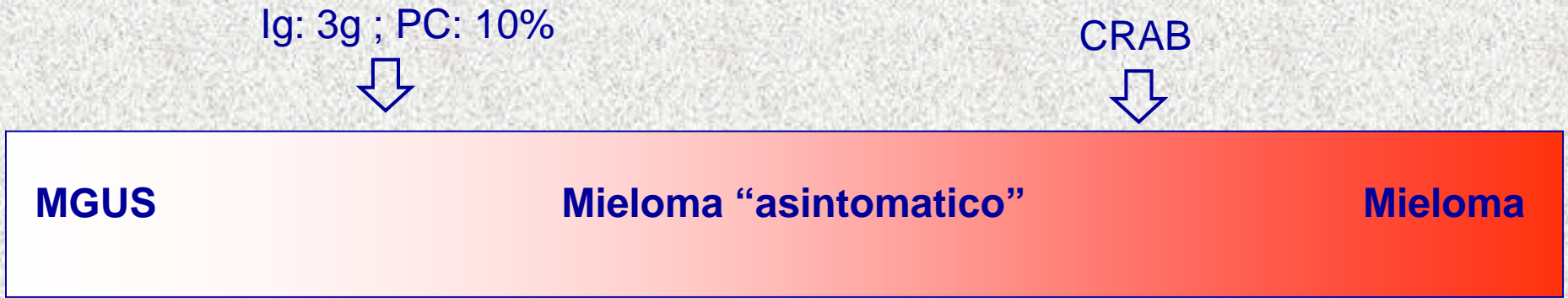
- non sintomi, PS (iK) >70, non infezioni
- Hgb > 10g, creatinina < 2 mg/dl, calcemia normale

MGUS: diagnosi differenziale vs mieloma



?Terapia

Terapia



CRAB

Terapia

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, Renal insufficiency, Anaemia, Bone (CRAB)]

MIELOMA ASINTOMATICO (smouldering)

paraproteina monoclonale ≥ 3.0 g/dL

e/o

plasmacellule clonali midollari $\geq 10\%$

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 ?*

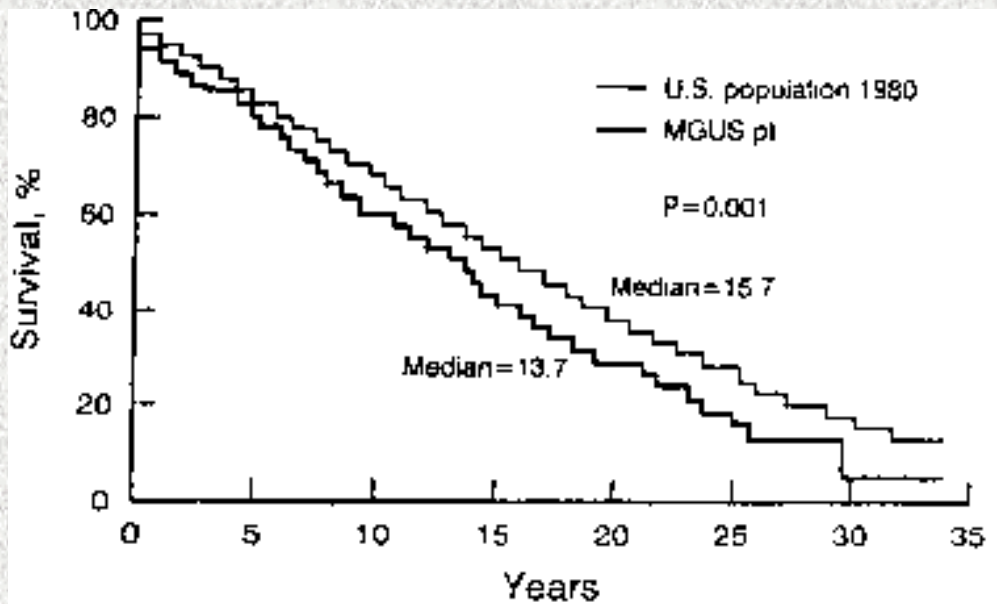
Work-up diagnostico allargato:

crioglobuline, complementemia, HCV?
viscosimetria plasmatica
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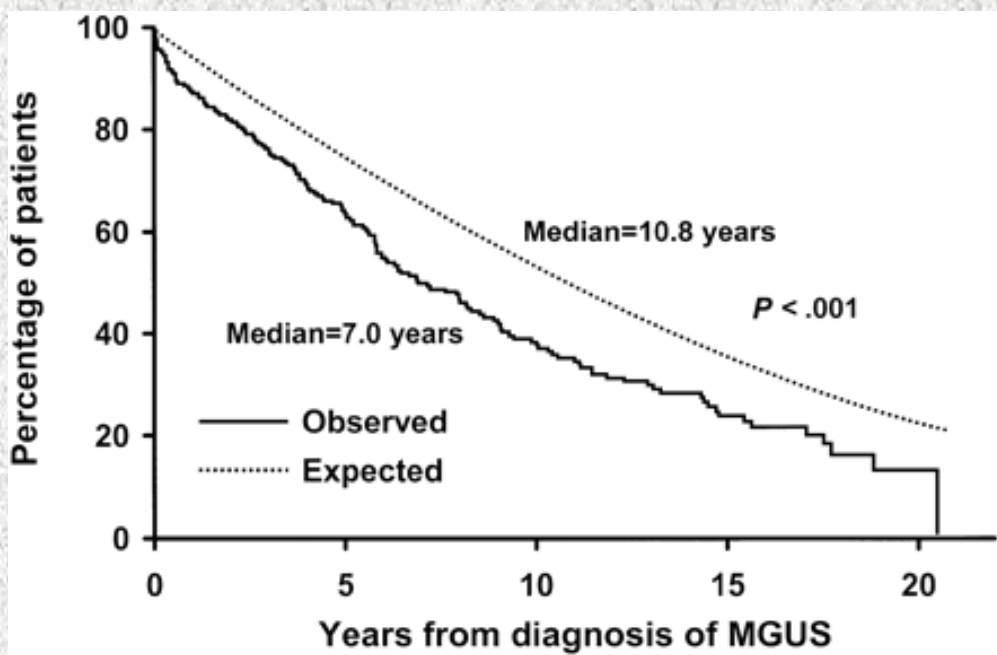
ISS (International Staging System)

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

MGUS: prognosis

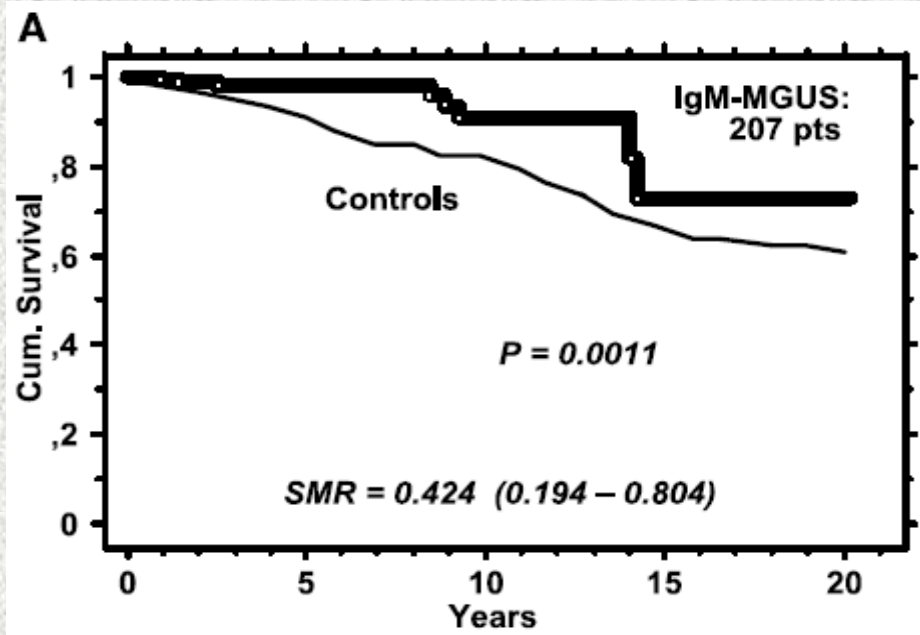


Semin Hematol 26: 176, 1989;
Mayo Clin Proc 68: 26, 1993

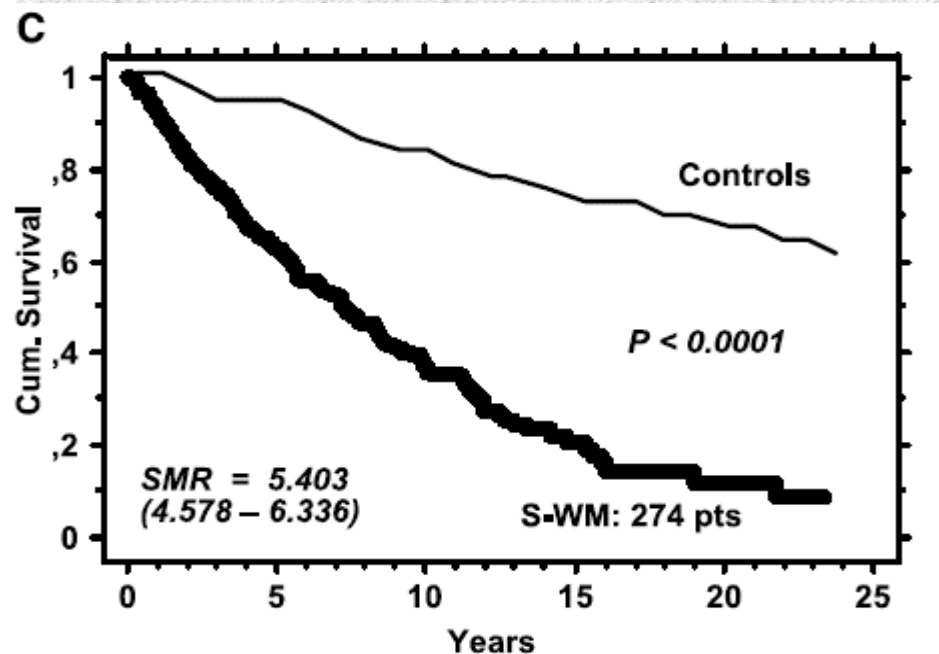
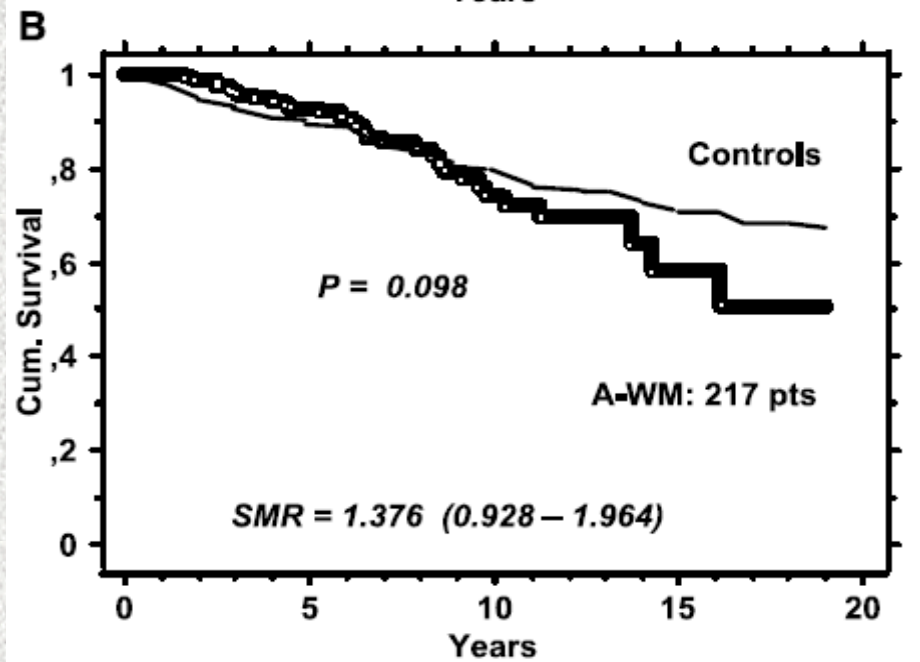


Blood, 102:3759, 2003

MGUS IgM: prognosi

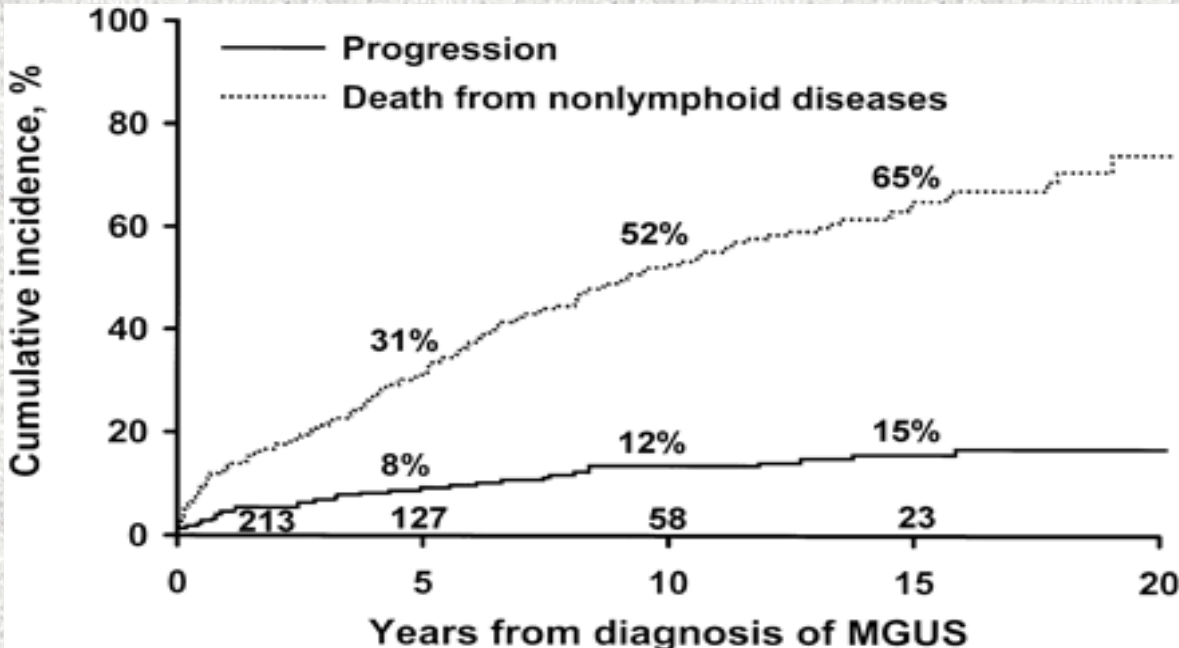
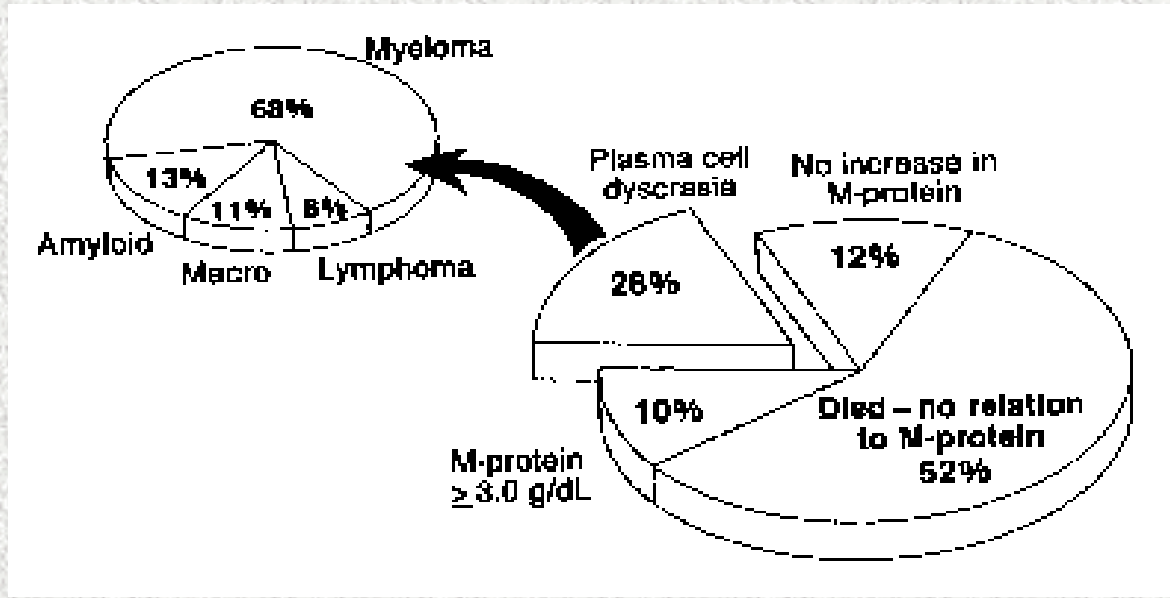


Clin Cancer Res, 137:49, 2005



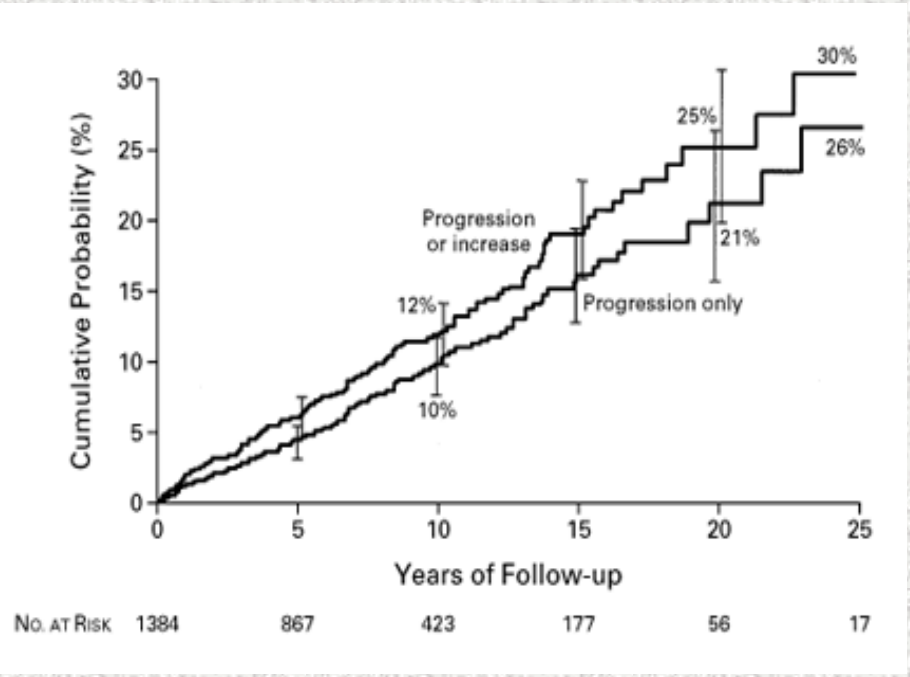
MGUS: evoluzione e prognosi

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

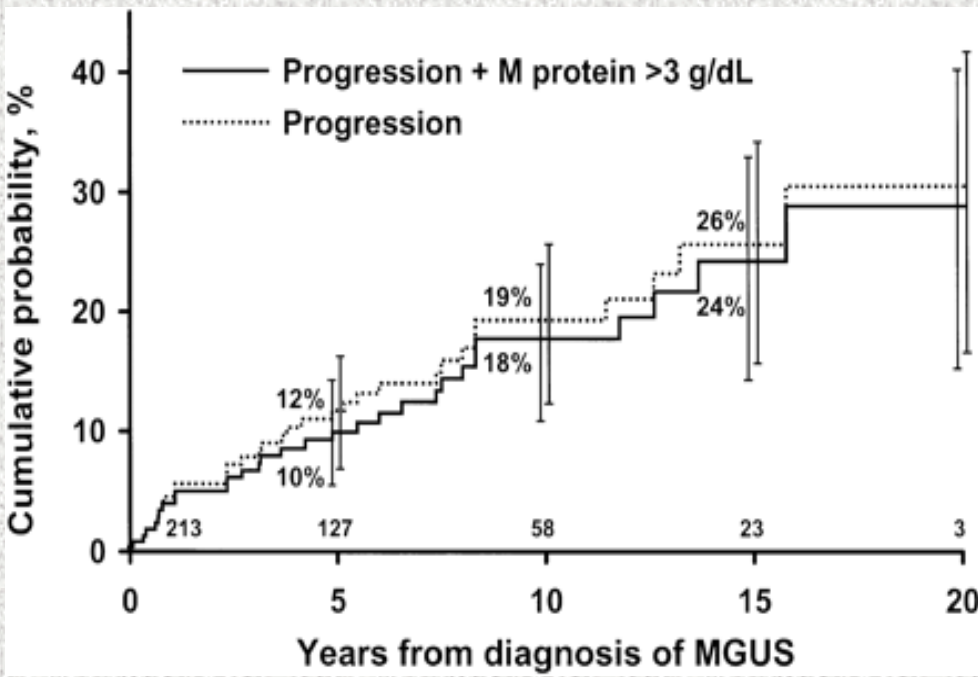


Blood, 102:3759, 2003

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	Kyle	Cesana	Baldini	Ucci	Gregersen
N° pazienti	1384	1231	386	684	1247
Mesi f-up mediano	185	72	70	36	
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

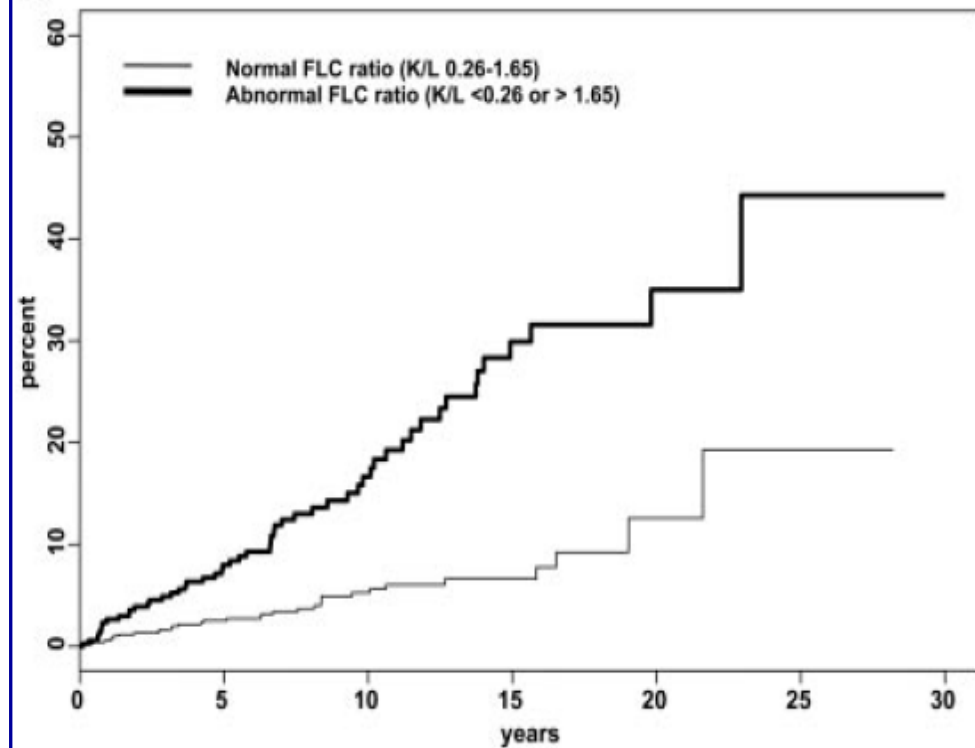
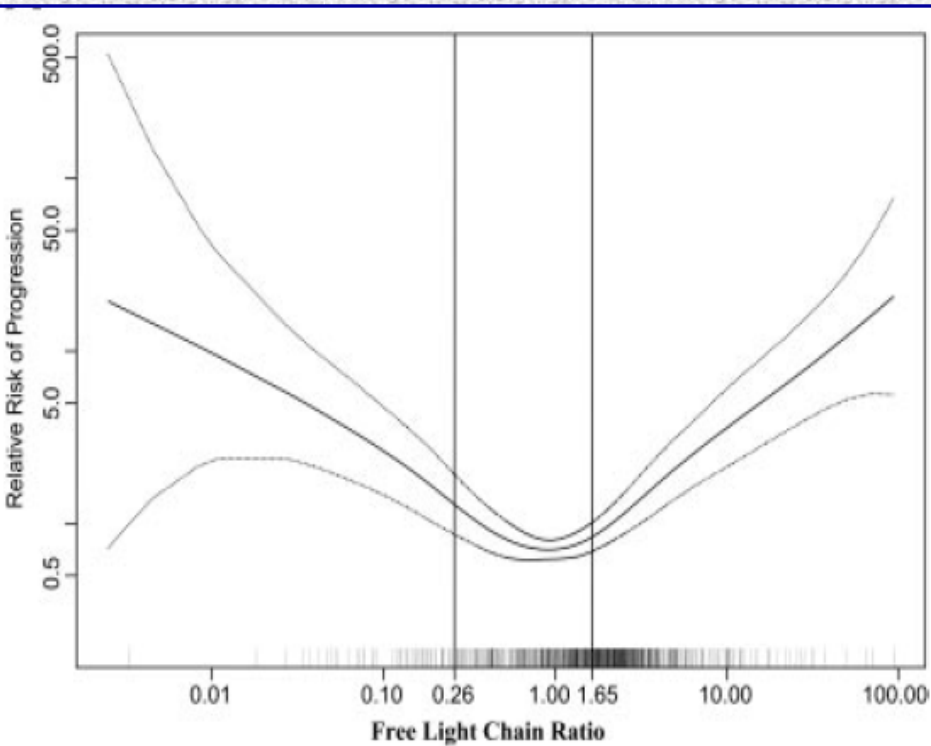
Livelli di Ig iniziali	Rischio di progressione a mieloma multiplo a 10 anni	
0.5 g/dL	6%	
1.0 g/dL	7%	
1.5 g/dL	11%	
2.0 g/dL	20%	P<0.001
2.5 g/dL	24%	
3.0 g/dL	34%	

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).

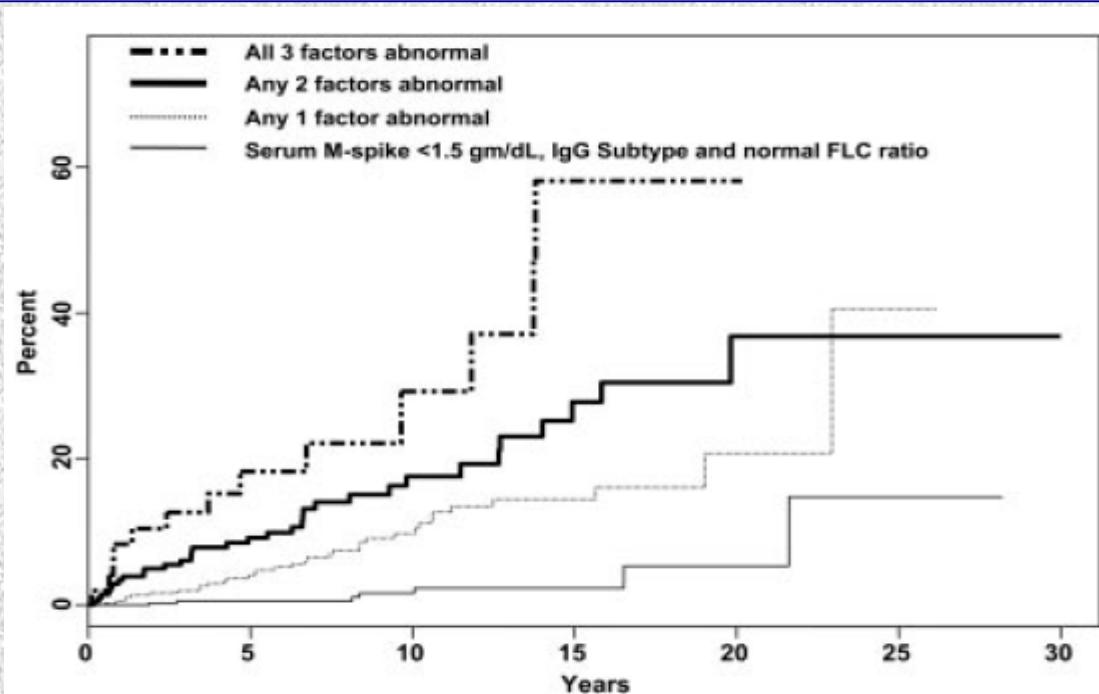
Tuttavia nessuna combinazione di fattori di rischio giustifica l'inizio di una terapia specifica in pazienti asintomatici (**International Consensus Conference, Atene, 2002**)

Serum FLC ratio e prognosi MGUS



MGUS: fattori prognostici per evoluzione a mieloma

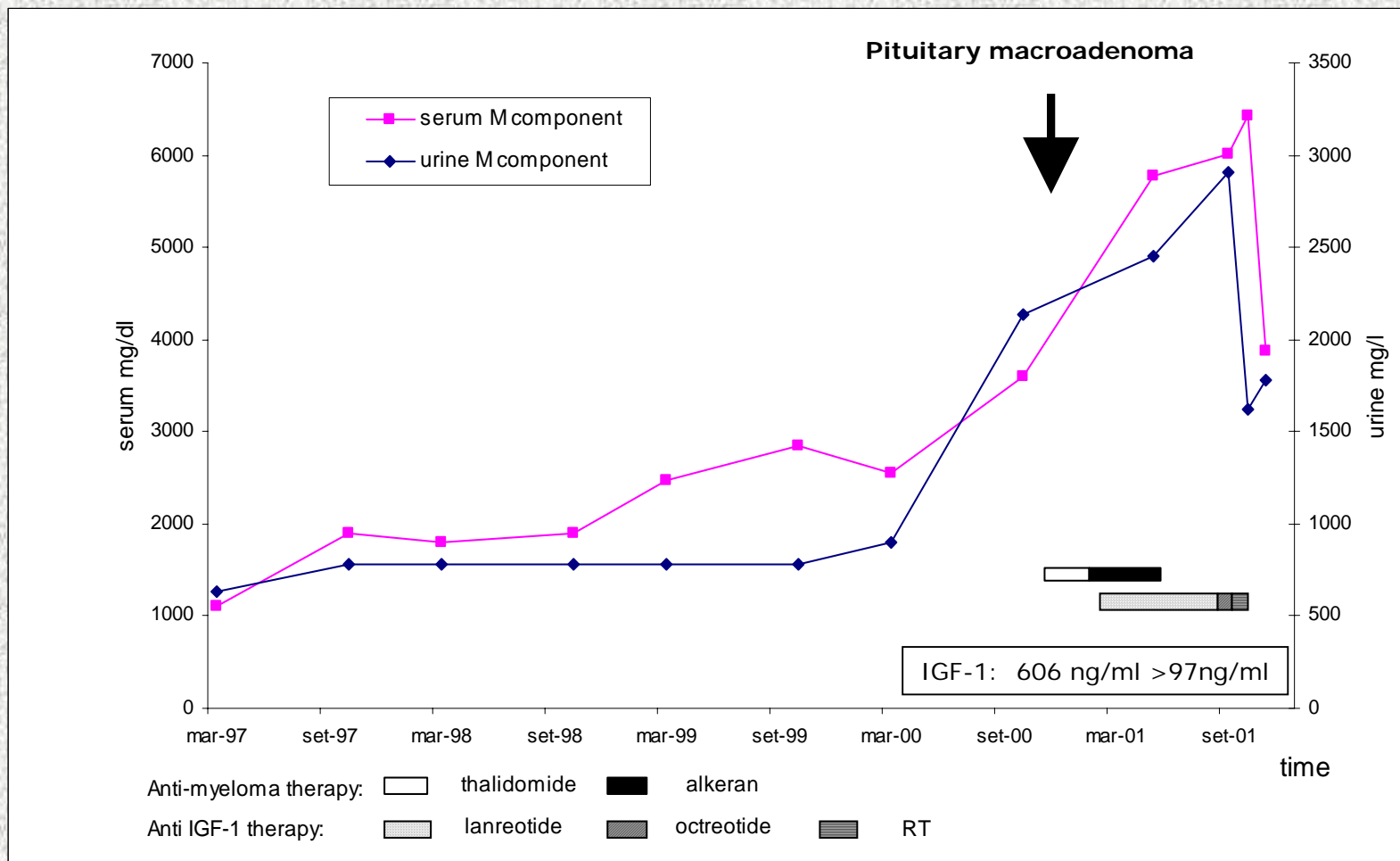
Il rapporto fra i livelli di **catene leggere libere nel siero** come fattore prognostico indipendente di progressione da MGUS a mieloma



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%

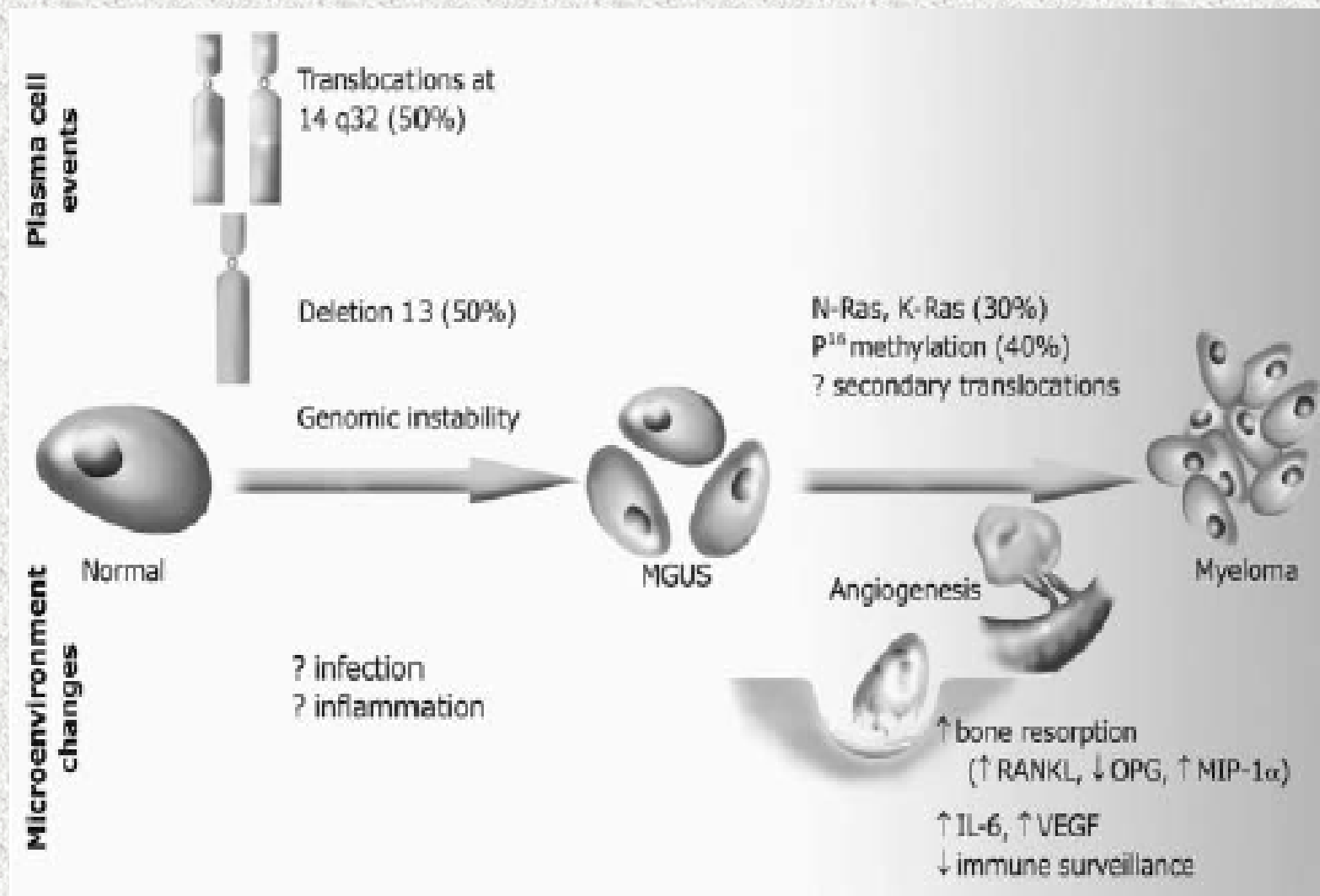
S. Vincent Rajkumar, et al
Blood. 2005;106:812-817

Quando una gammapatia monoclonale diventa mieloma multiplo?

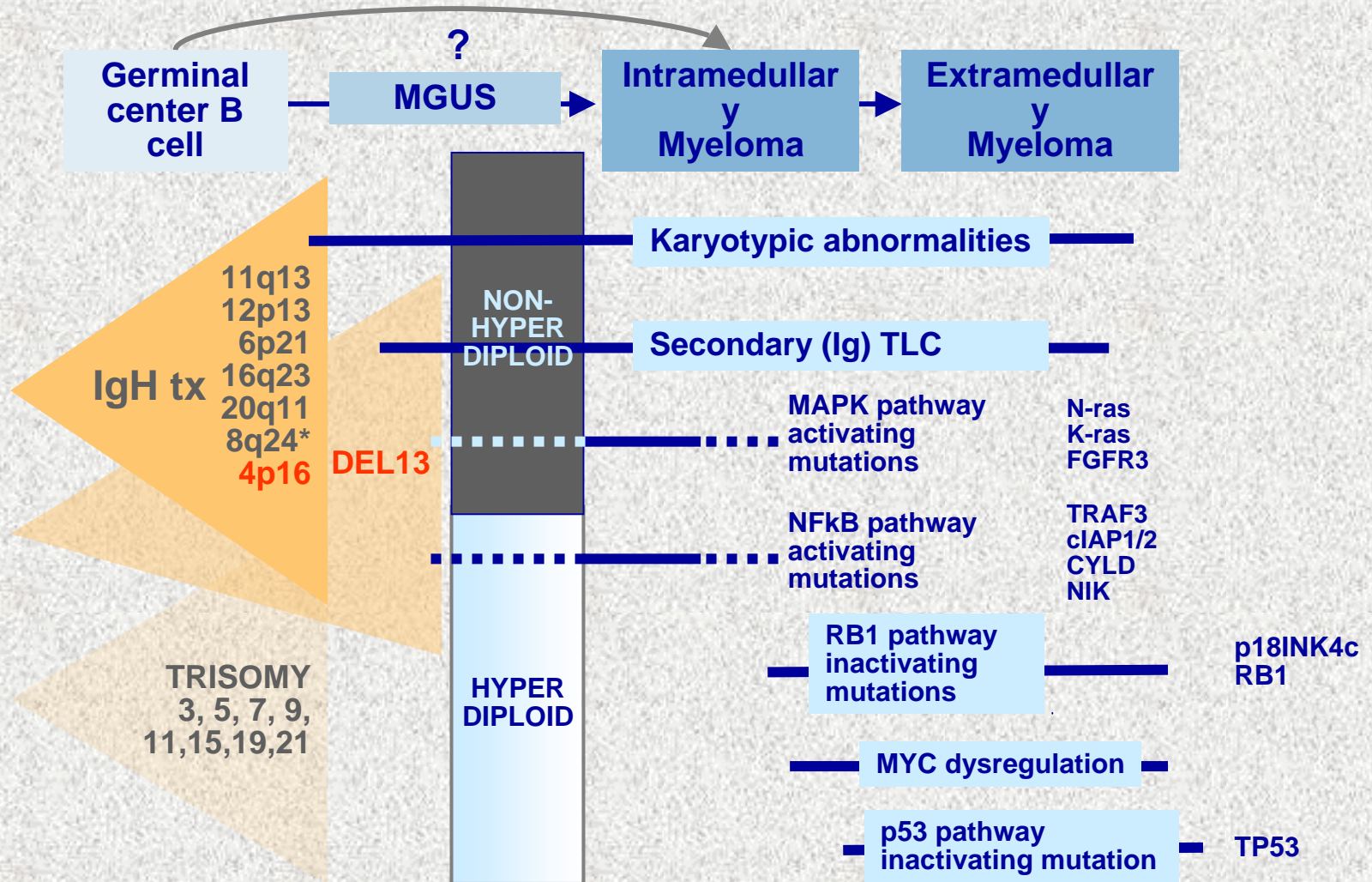


In un modello murino di mieloma, la terapia con NVP-ADW742, un inibitore specifico della kinasi IGF1-R correlata ha dimostrato un significativo effetto antitumorale in vivo. (Mitsiades, Cancer Cell, 2004)

Quando una gammapatia monoclonale diventa mieloma multiplo?

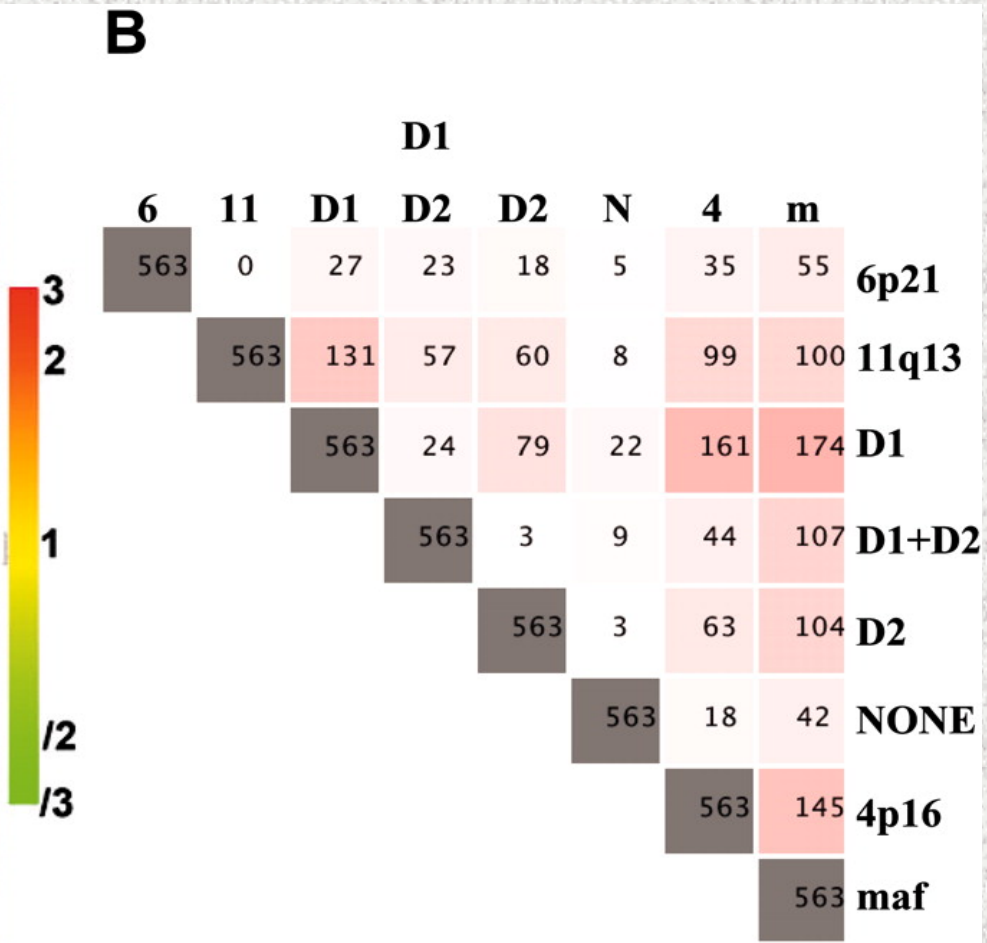
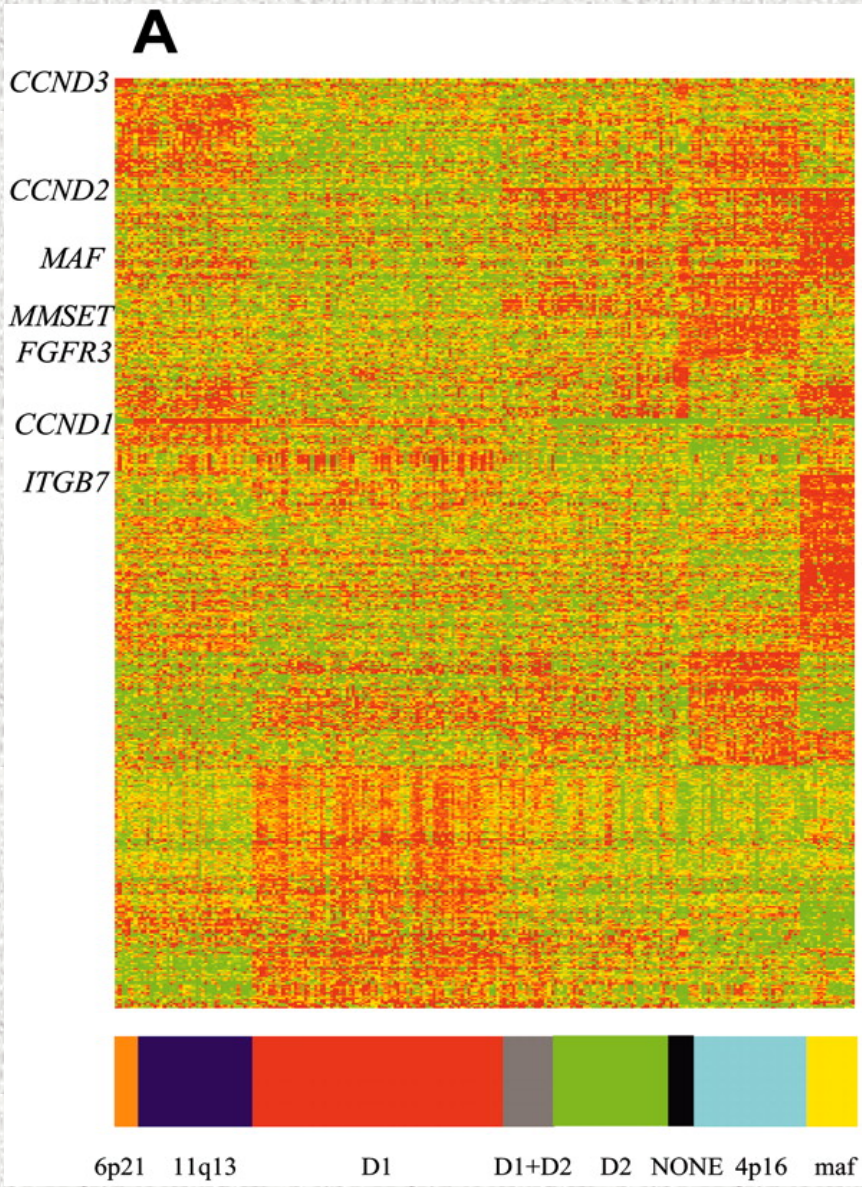


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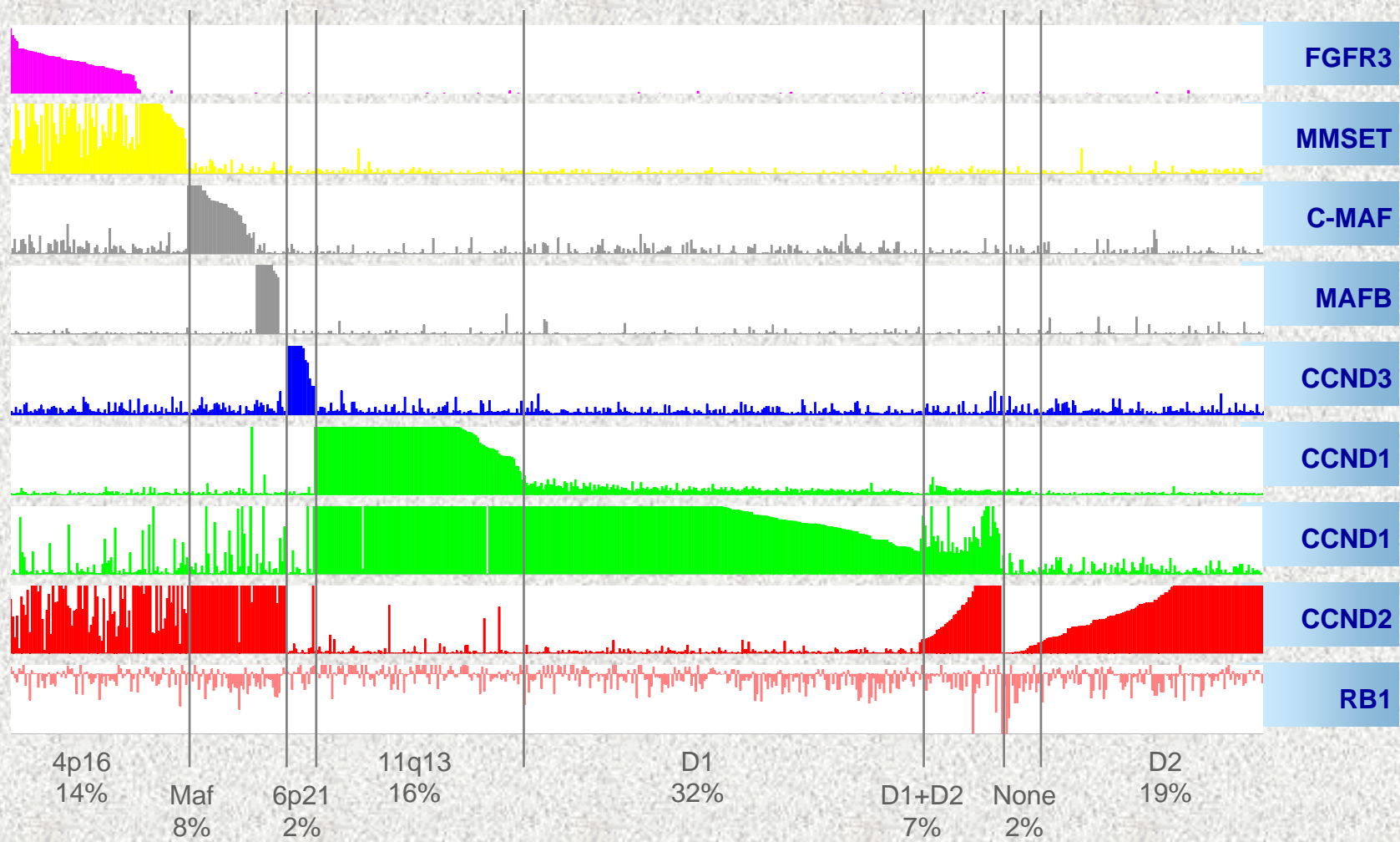


Profilo di espressione genica (GEP) del mieloma

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

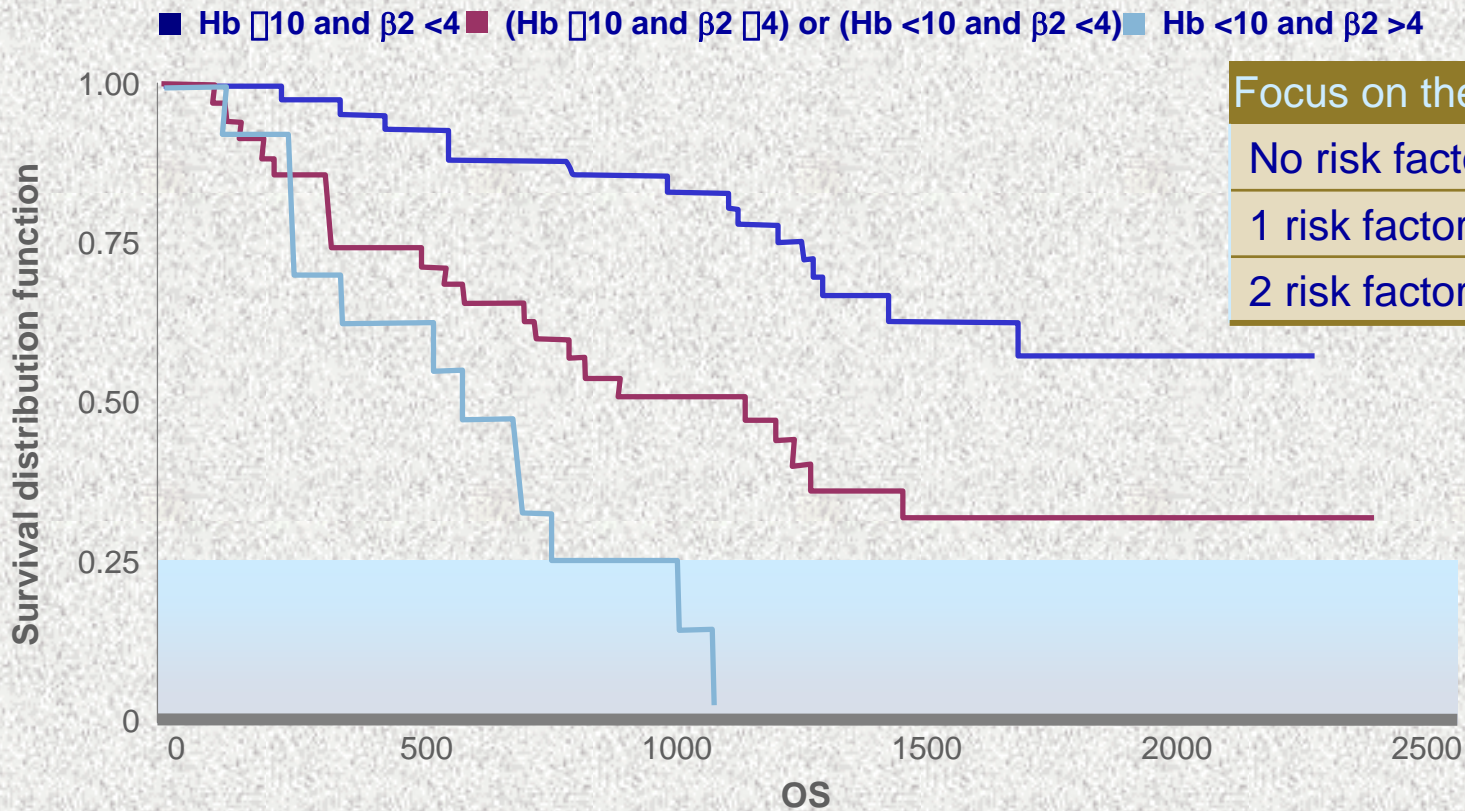


Classificazione genetica del mieloma

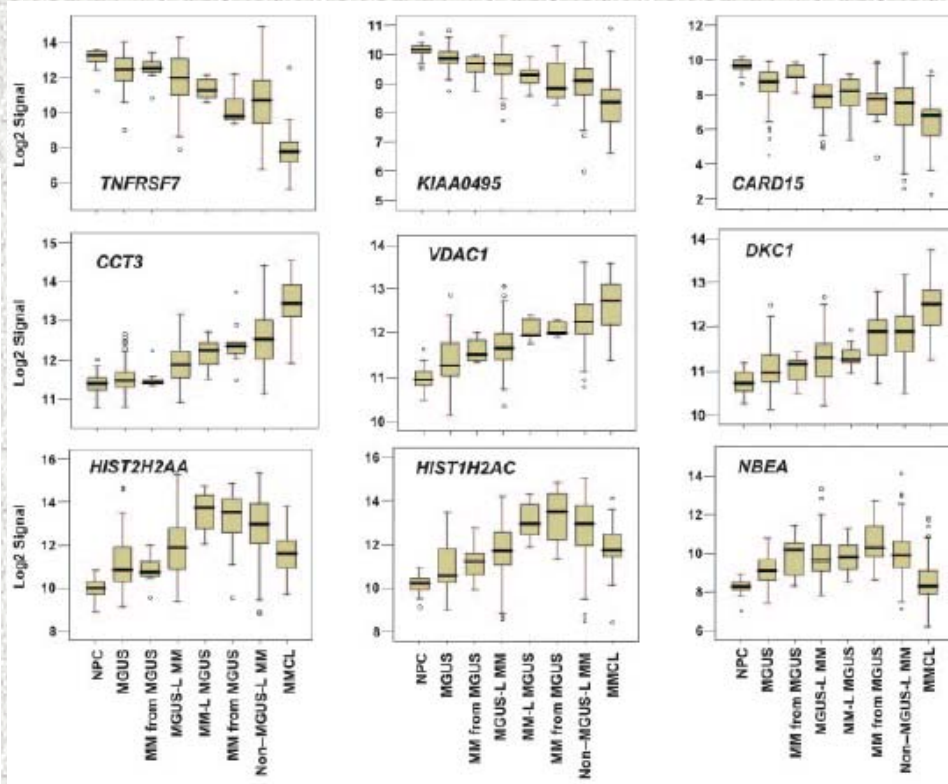
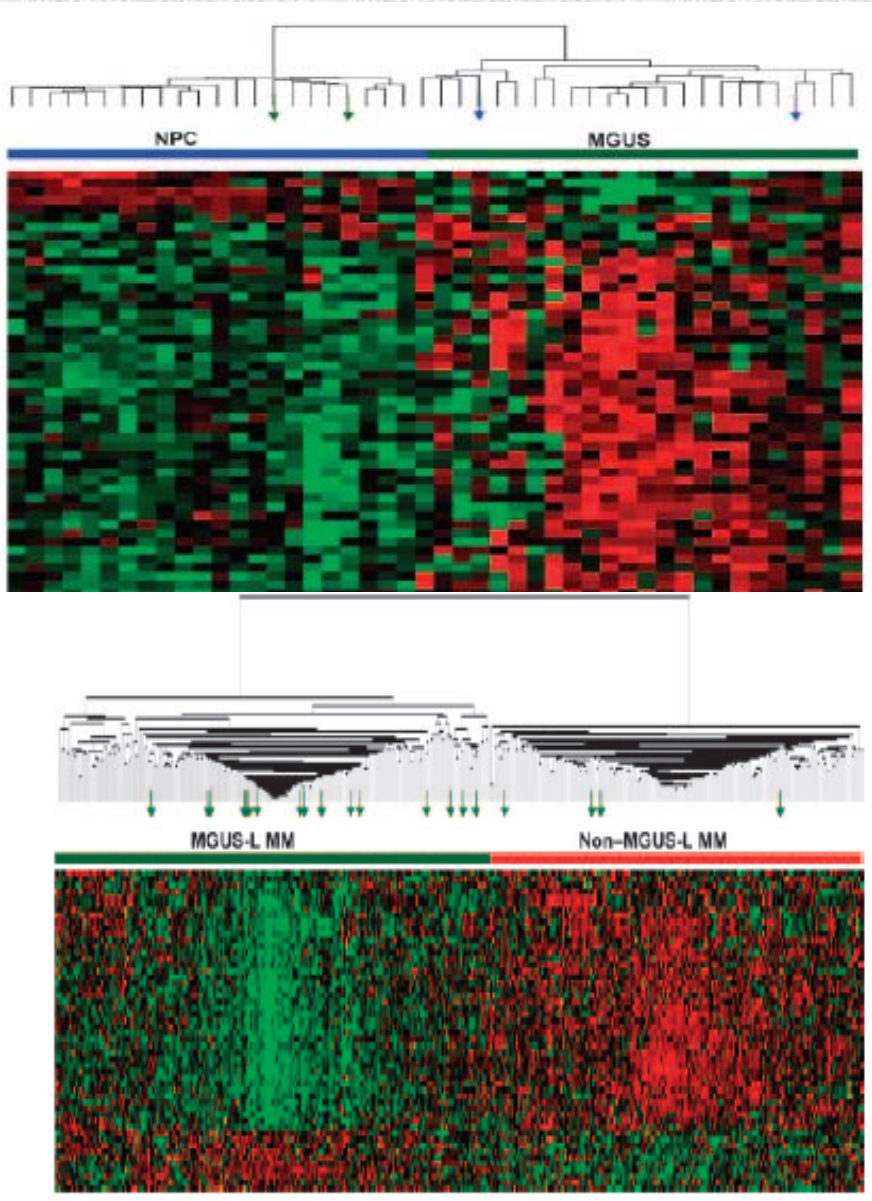


596 patients from UAMS - Shaughnessy & Barlogie

t(4;14) Survival



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)

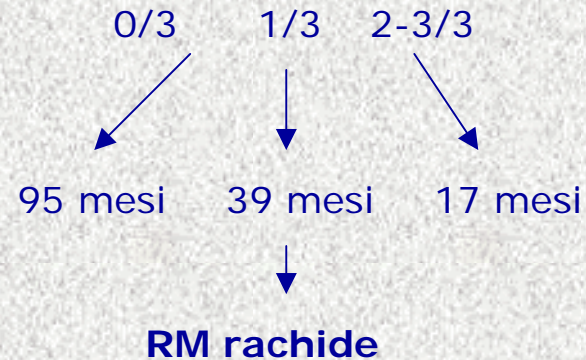
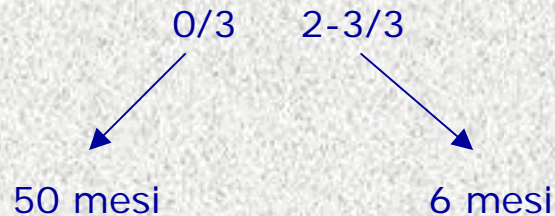
Mieloma asintomatico

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

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



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;

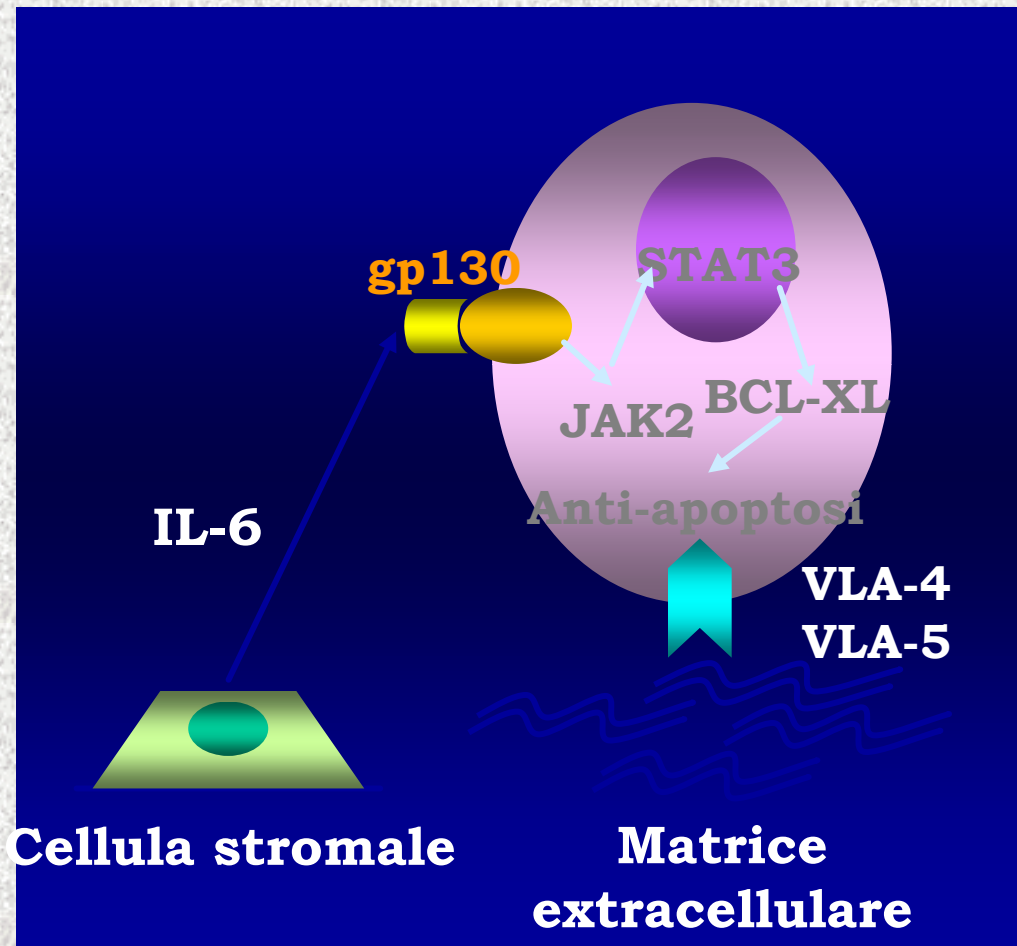
??? guidata da parametri biologici

IL MICROAMBIENTE PROMUOVE LA CRESCITA DEL MM

Microambiente osteoclastico



Stroma e matrice extracellulare

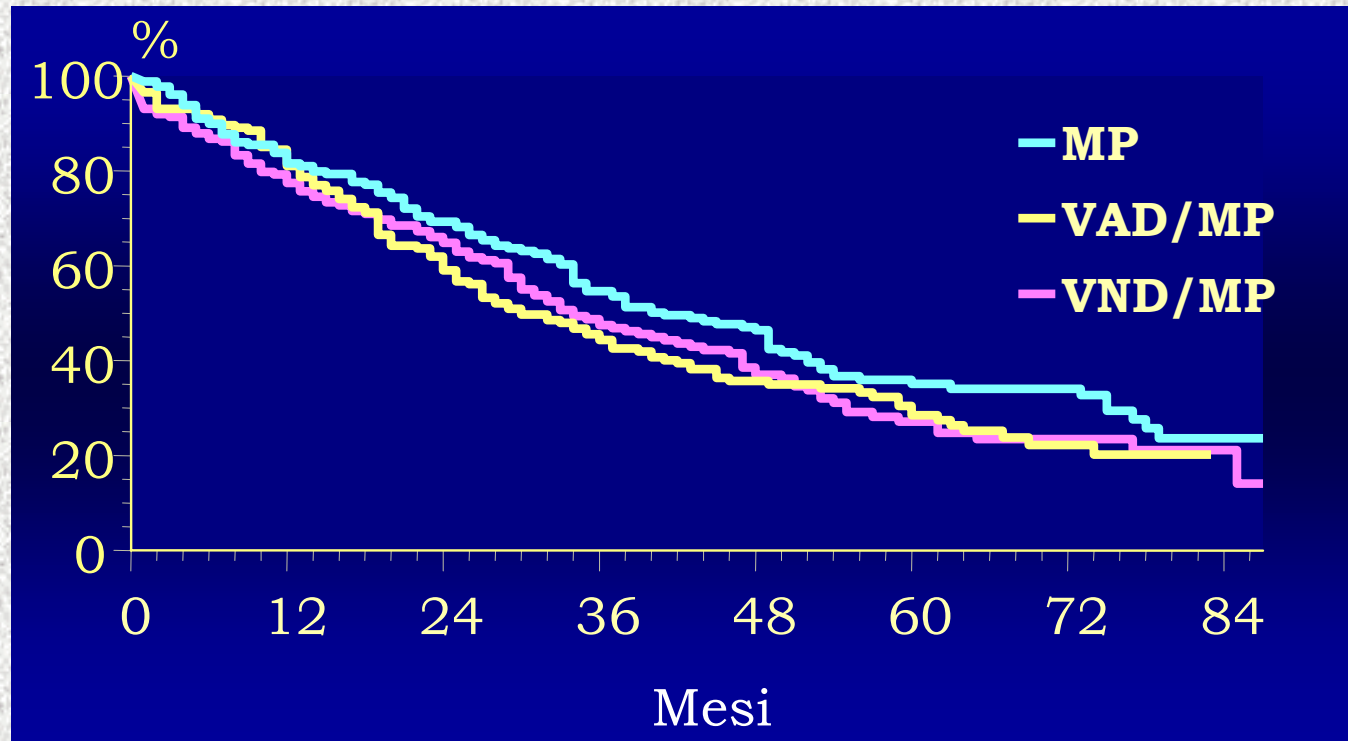


Need for New First-line Regimens for Elderly MM Patients

- 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

CHEMIOTERAPIA CONVENZIONALE NEL MM



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

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

- 488 patients aged 65-75 yr randomized to MP, MD, D, or D-IFN α (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-IFN α
n	109	110	109	101
\square PR \downarrow (P < 0.001)	51%	74%	40%	42%
CR (P = NS)	1%	3%	1%	1%
EFS (mo)	21.1 \pm 1.7	22.9 \pm 2.0	12.2 \pm 1.0*	15.2 \pm 2.7*
OS (mo)	34.0 \pm 3.6	39.6 \pm 3.1	33.4 \pm 2.0	32.0 \pm 5.3

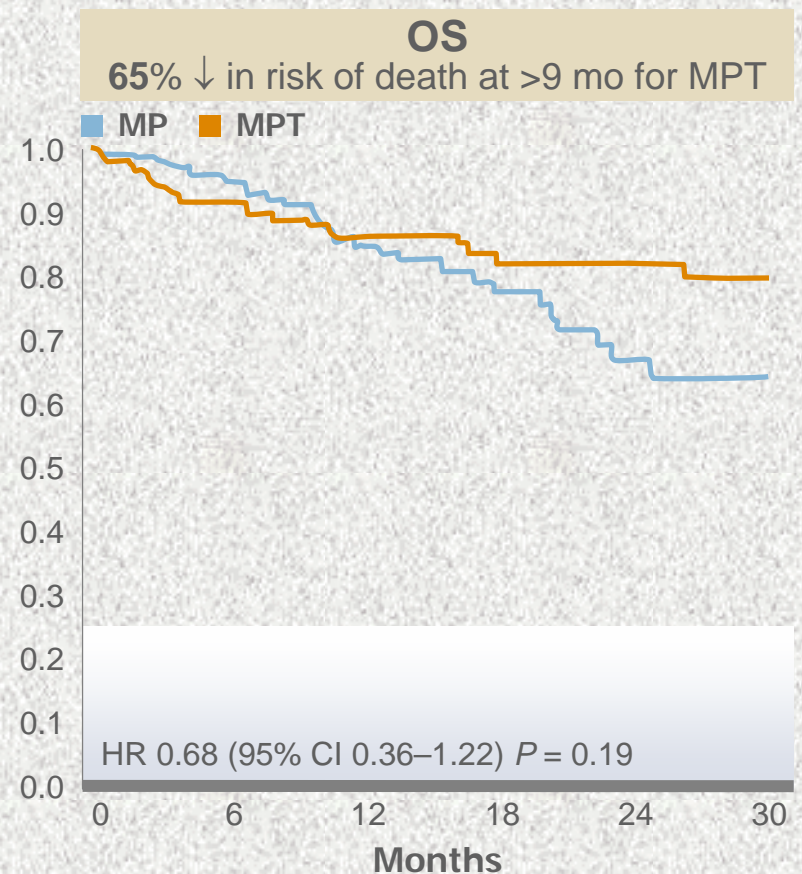
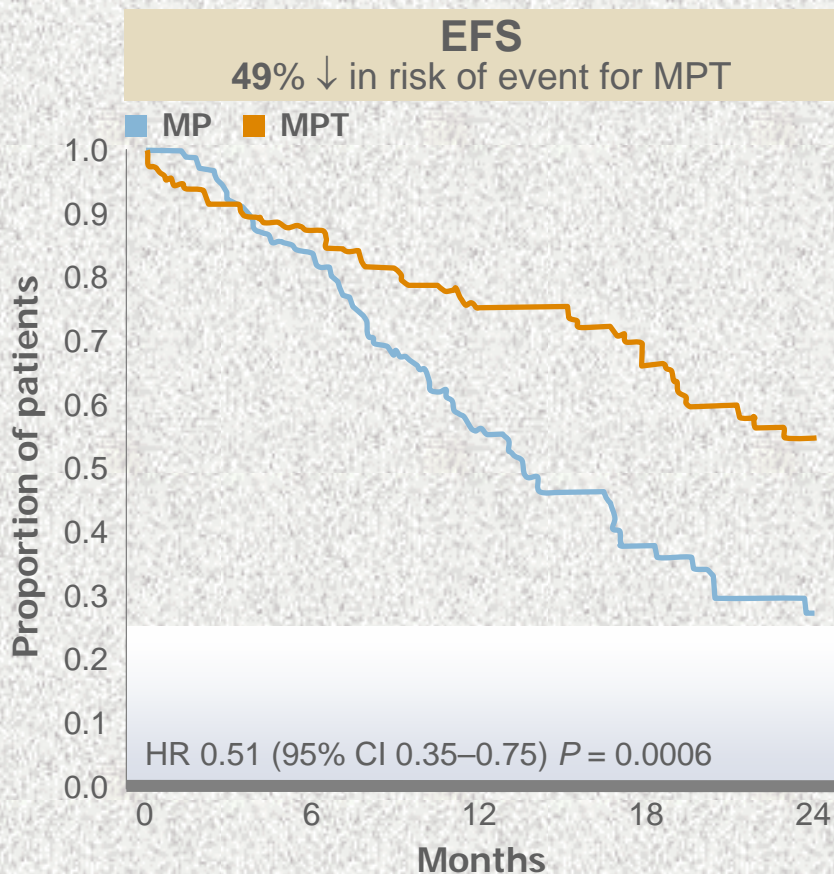
*P < 0.001 for pts not receiving Melphalan

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

Age: 65-85 years

- Melphalan, 4 mg/m² (7 days/month) 50 mg/month
- Prednisone, 40 mg/m² (7 days/month) 6 cycles
- Thalidomide, 100 mg/d (continuously)

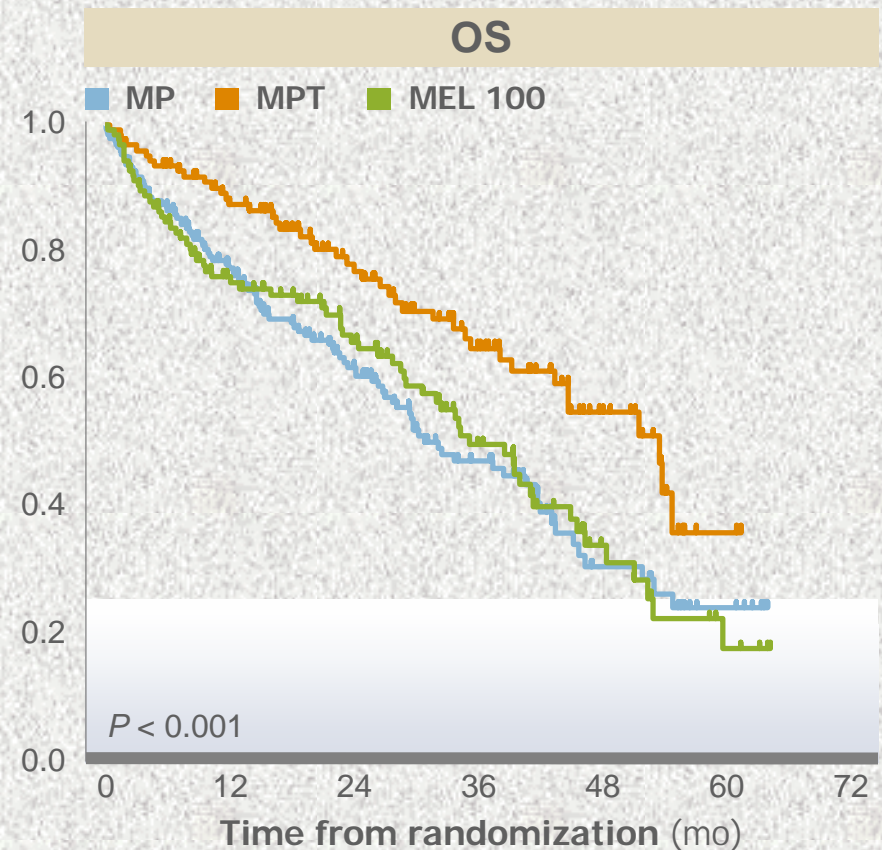
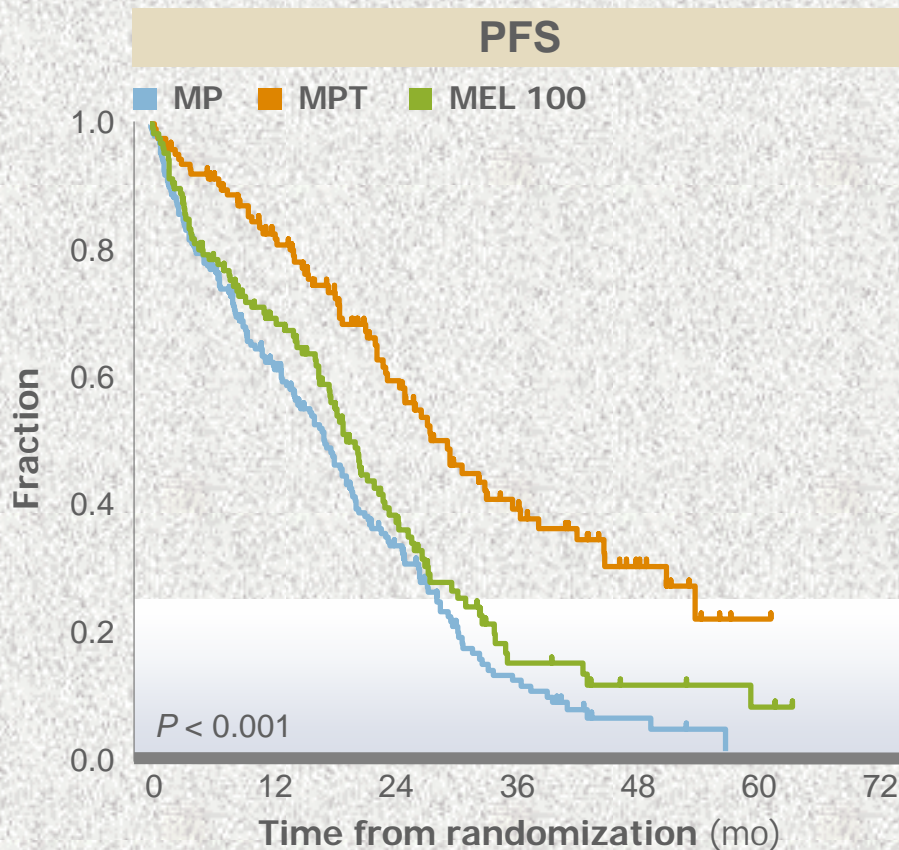
PR were 76% for MPT and 47.6% for MP



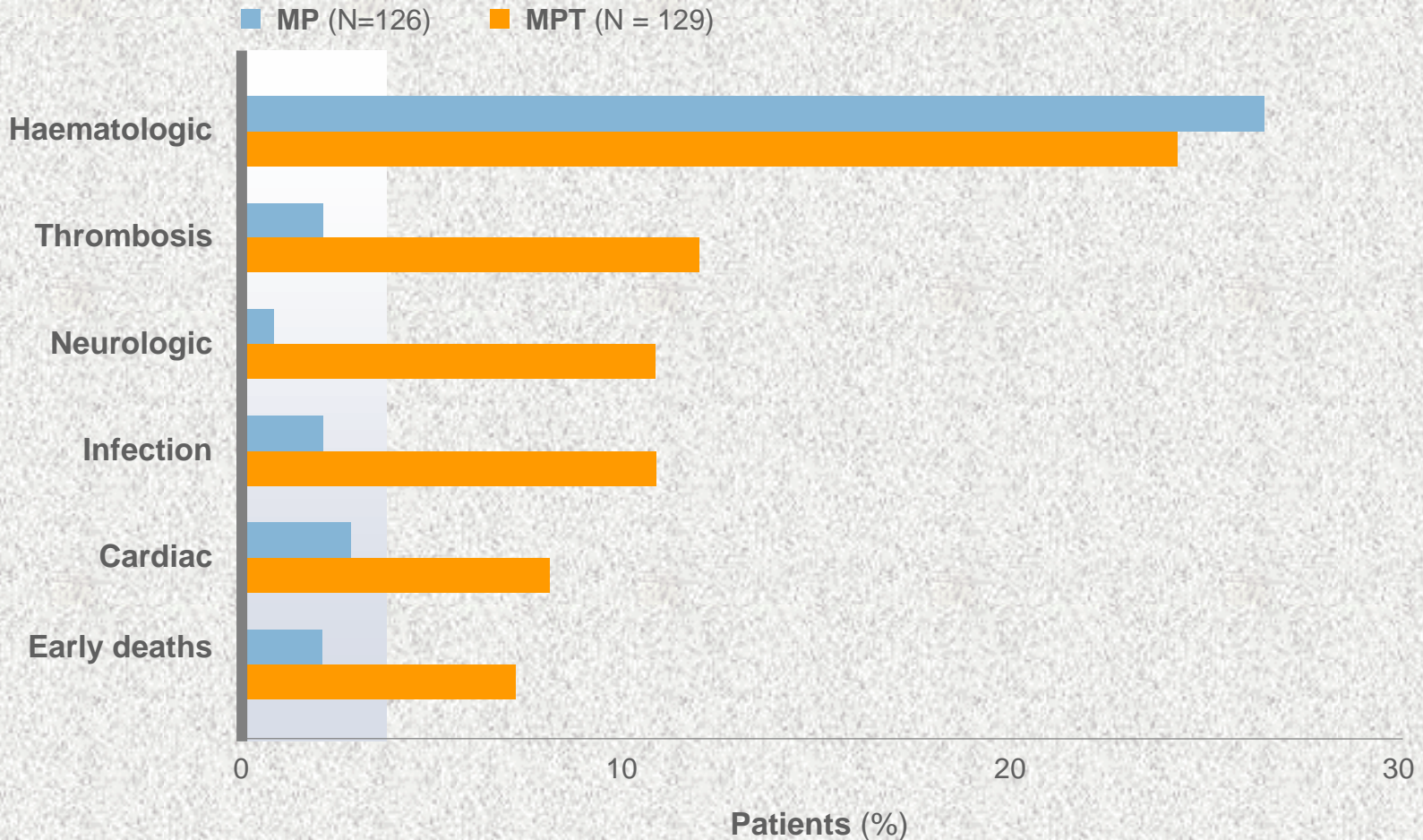
MPT vs MP and MP vs MEL100/ASCT in Newly Diagnosed MM Patients: PFS and OS

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



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



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

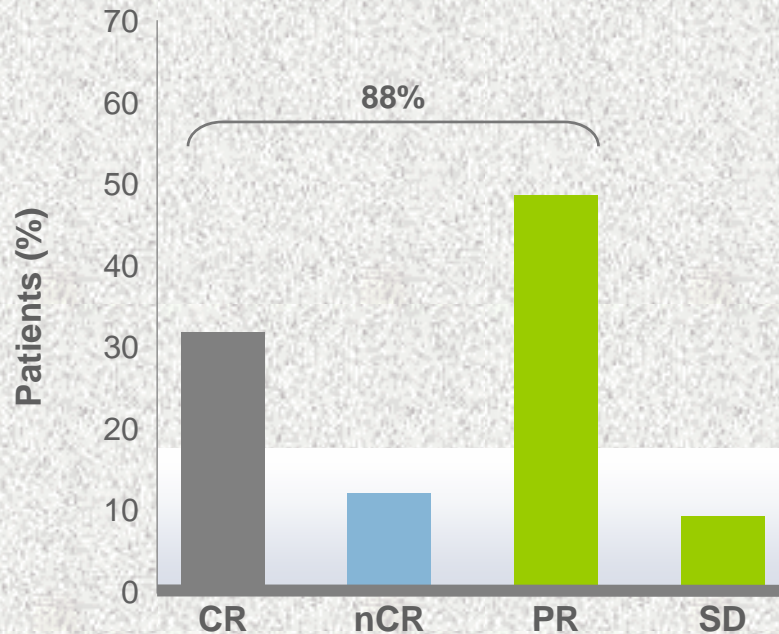
Four 6-week cycles

- Bortezomib d 1,4,8,11,22,25,29,32
- Melphalan, 9 mg/m² (4 days)
- Prednisone, 60 mg/m² (4 days)

Five 5-week cycles

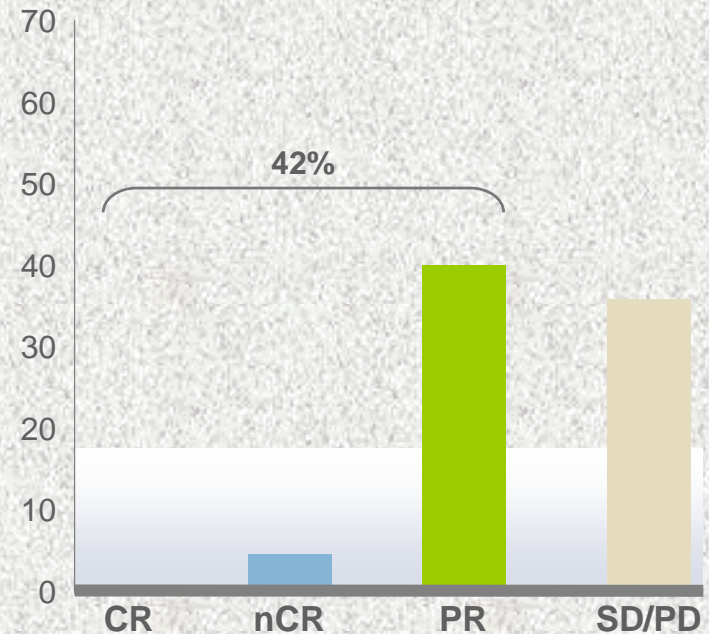
- Bortezomib day 1,8,15,22
- Melphalan, 9 mg/m² (4 days)
- Prednisone, 60 mg/m² (4 days)

Best response with 7 cycles
of VMP¹



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

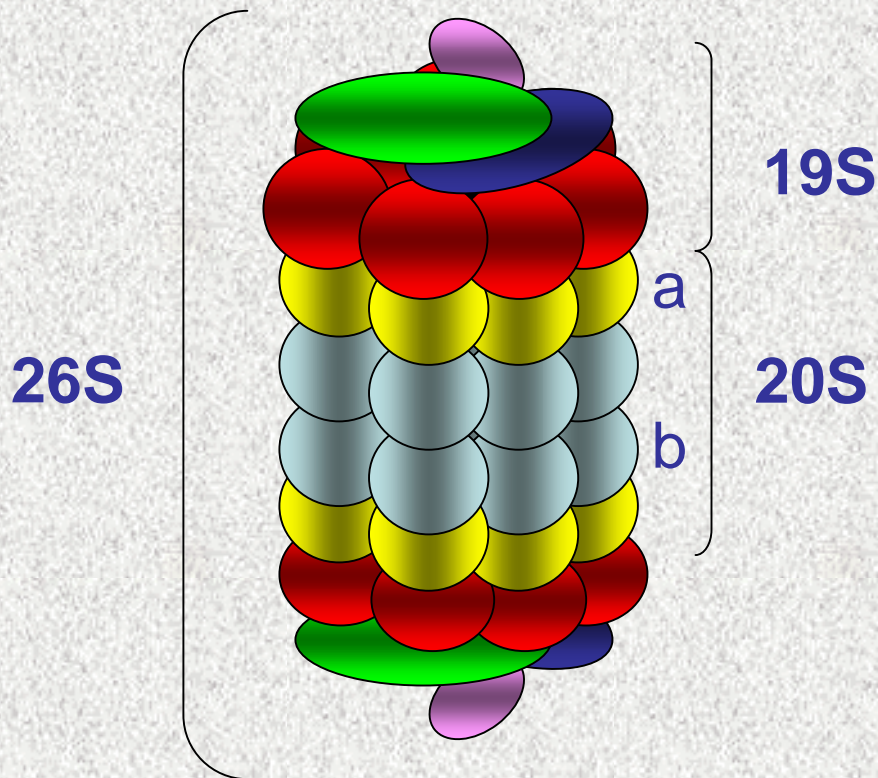
Best response with 6 cycles
of MP² (n = 87)



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

Proteasoma

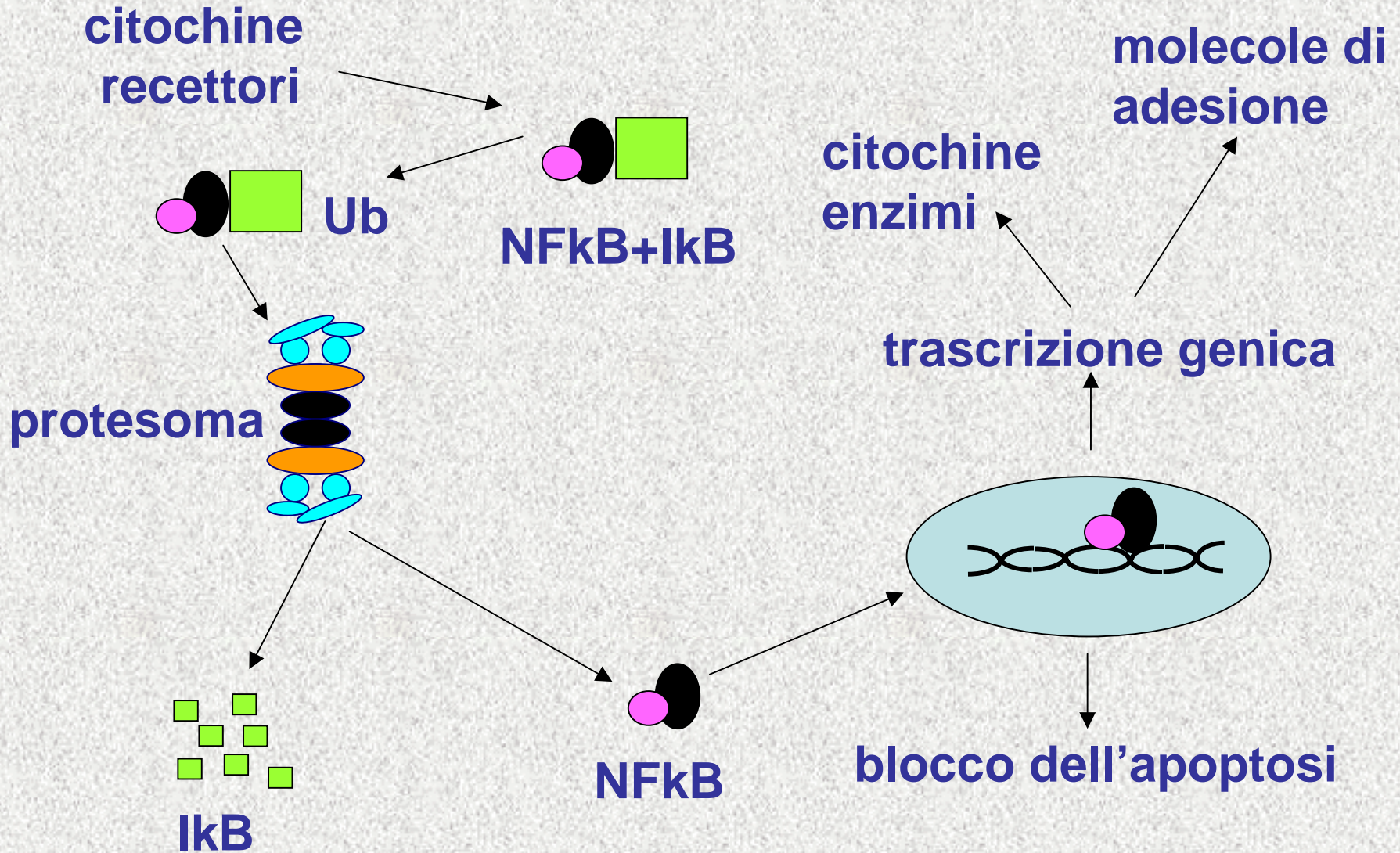
26S = 20S (regione proteolitica) + 19S (regione regolatoria)



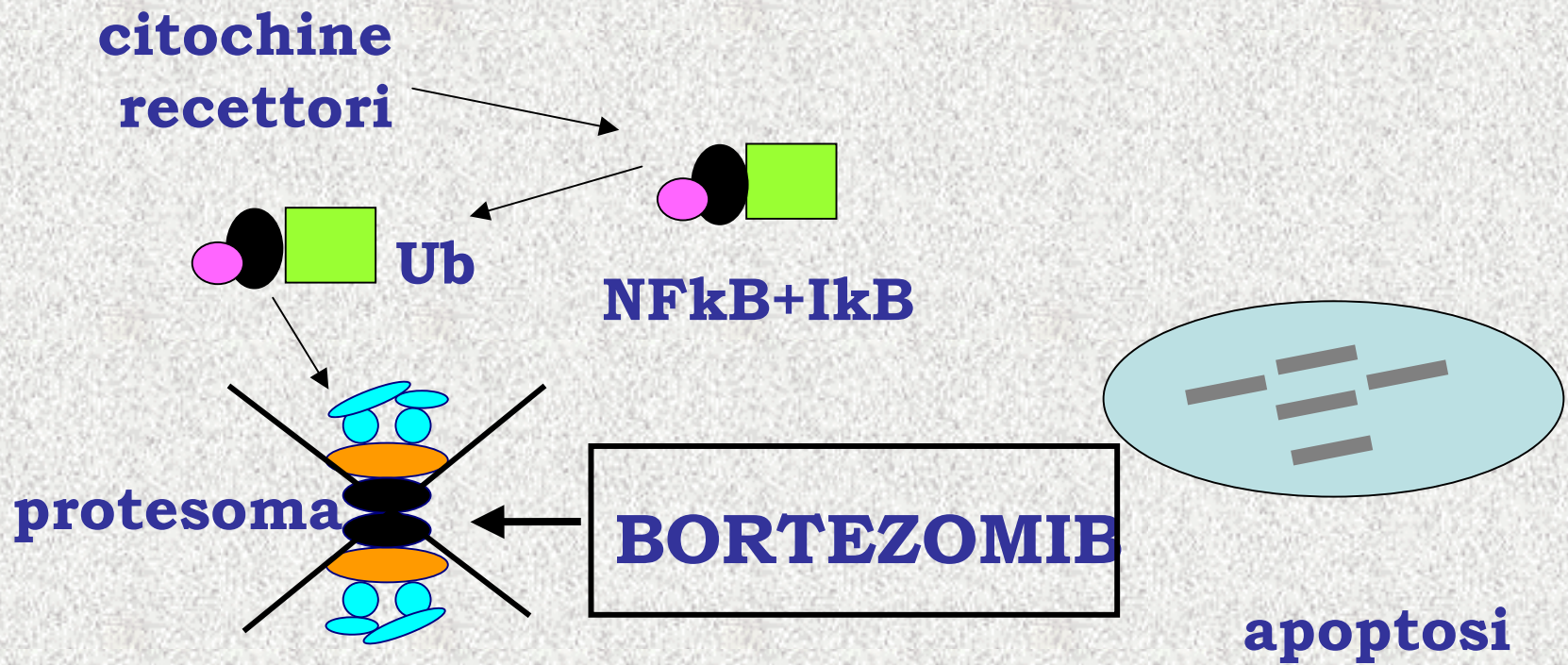
•La regione 19S:

- 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

Attivazione di NFκB

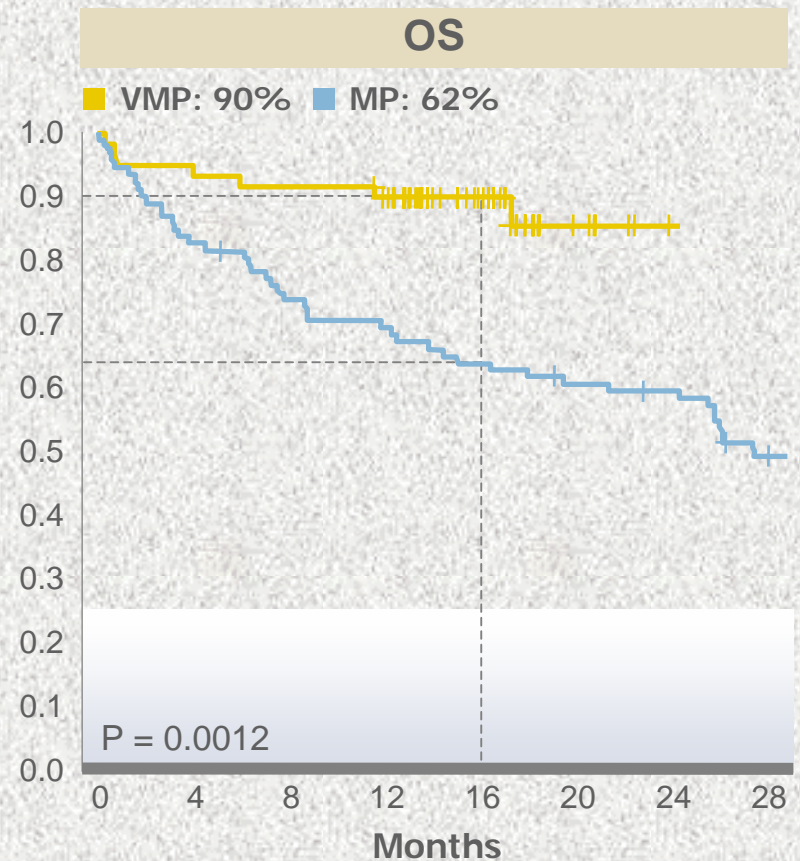
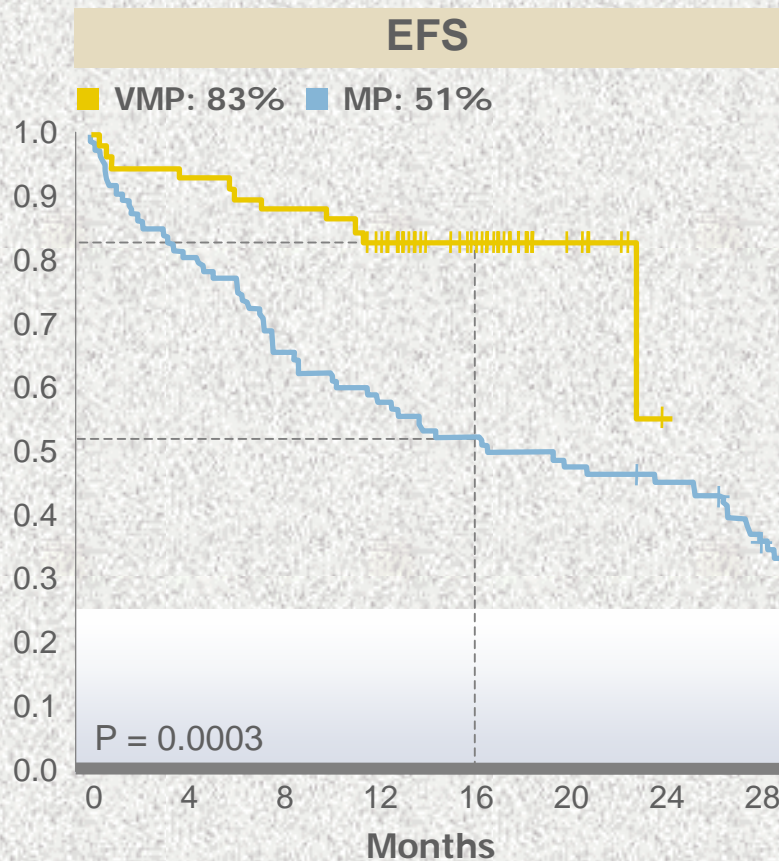


Inibizione del proteasoma



Newly Diagnosed MM Patients VMP vs MP: EFS and OS

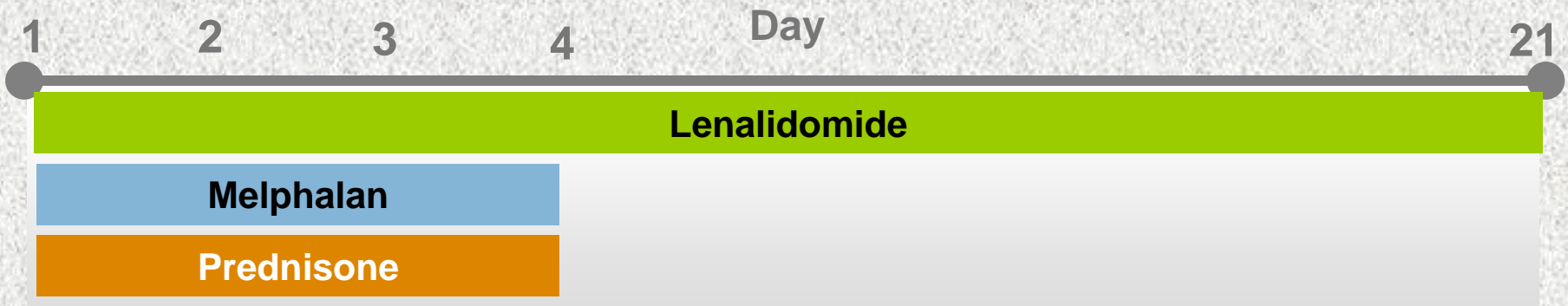
Median follow-up: 16 months (11–24)



Phase I/II Trial of MPR in Newly Diagnosed MM

Median age 71 years (range, 57–77)

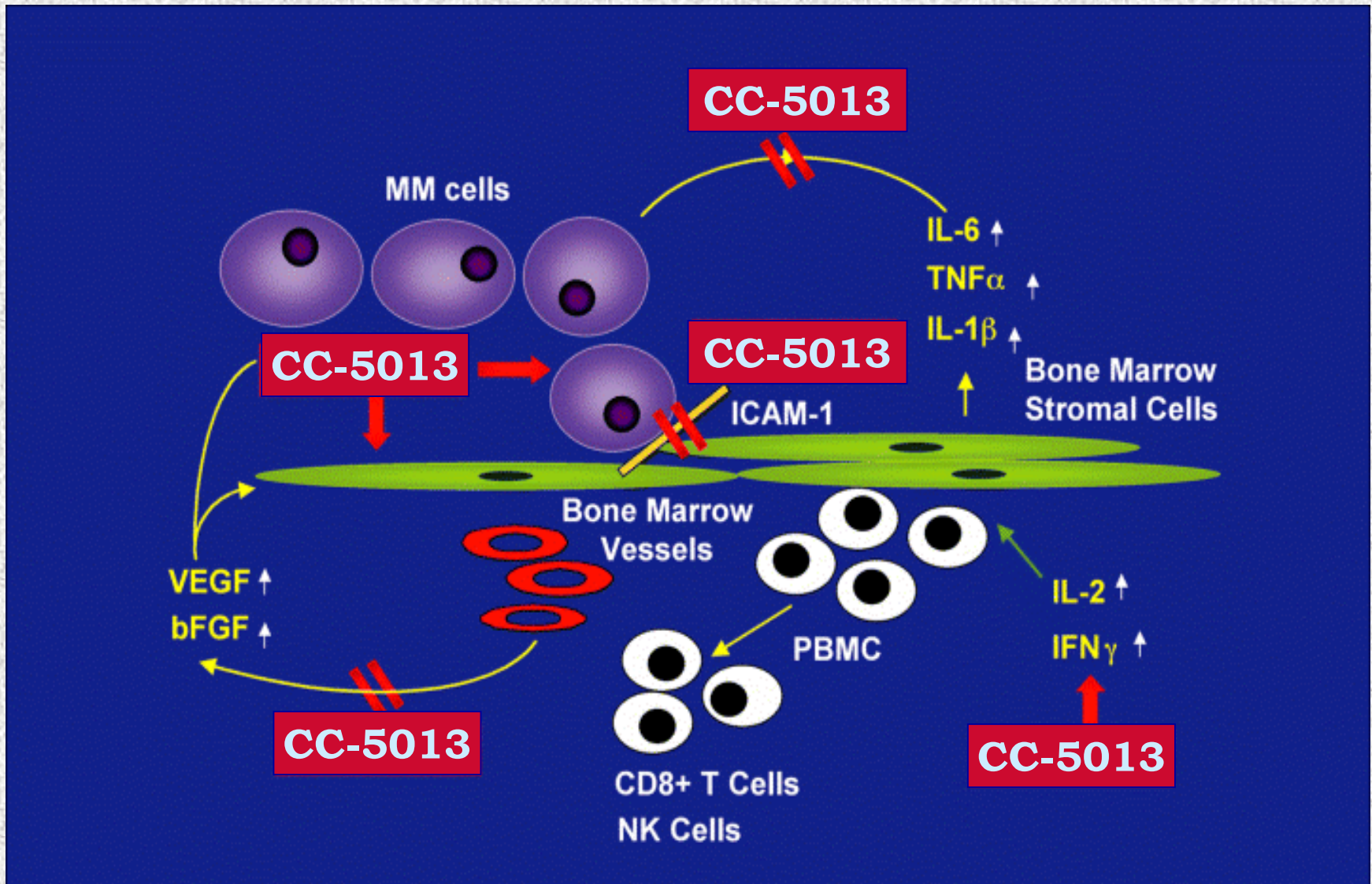
Cohort	Lenalidomide (mg/day)	Melphalan (mg/kg/day)	Prednisone (mg/kg/day)
1 (N = 6)	5	0.18	2
2 (N = 6)	5	0.25	2
3 (N = 6 + 15)	10	0.18	2
4 (N = 6 + 15)	10	0.25	2



- 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

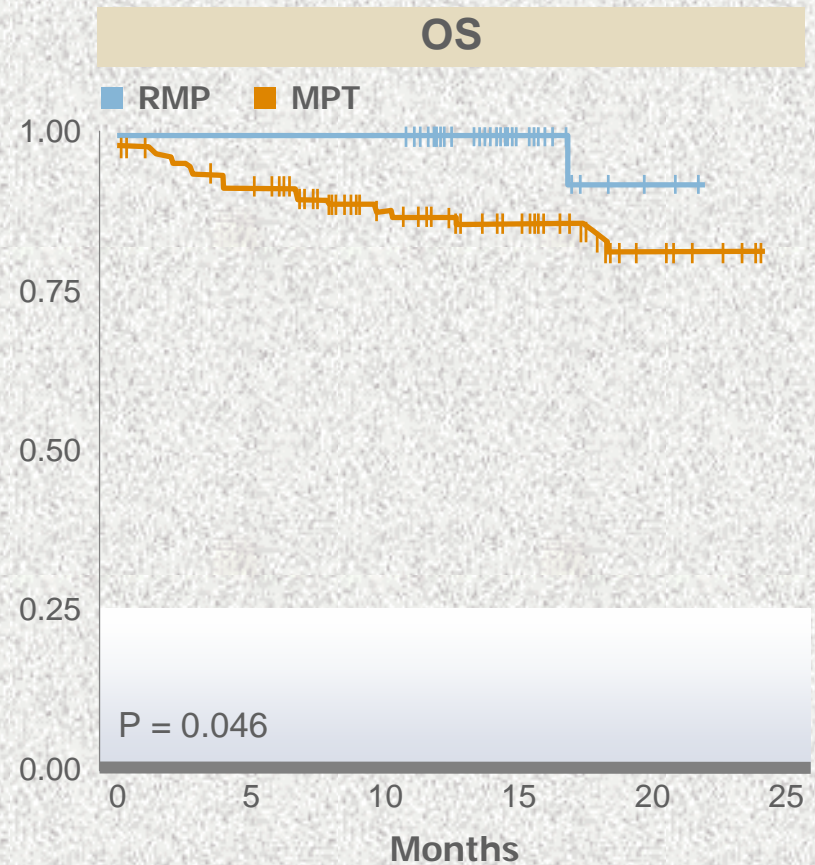
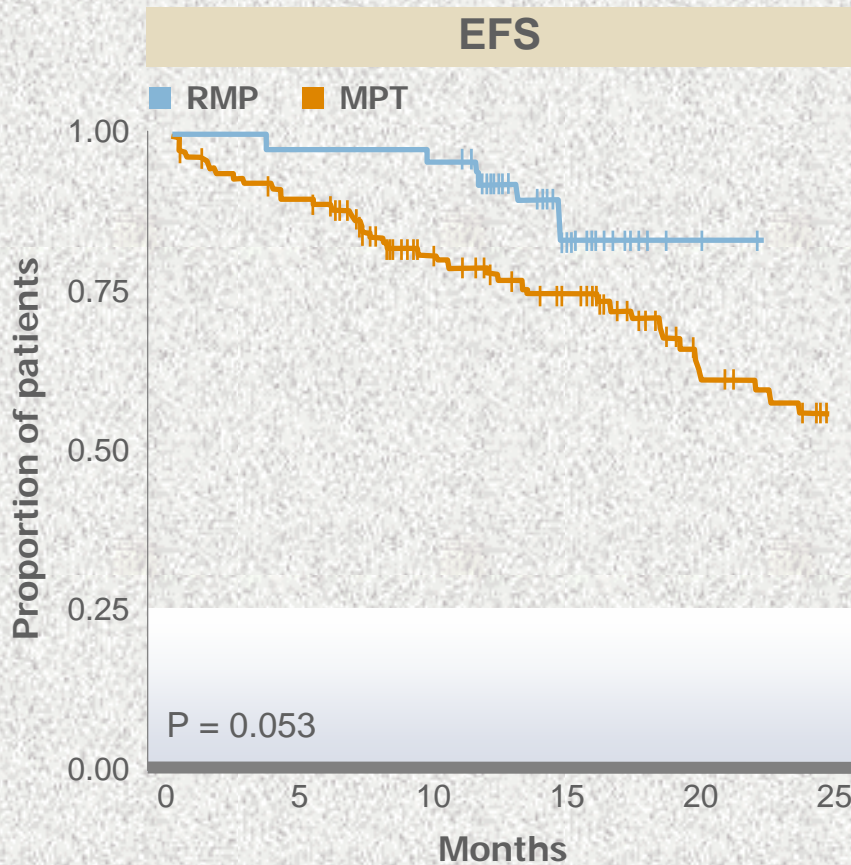
LENALIDOMIDE: MECCANISMO D'AZIONE



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

