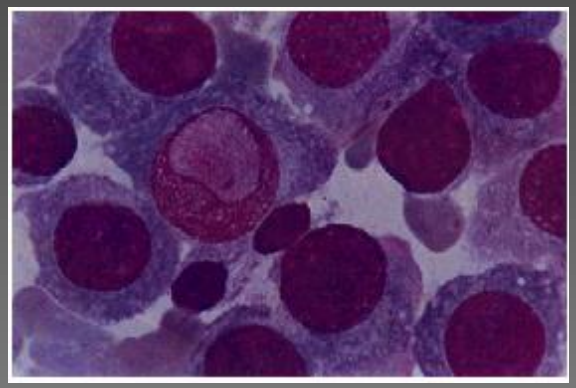


Mieloma Mùltiple

Valdivia, Mayo 2017

Dr. Mauricio Ocqueteau T

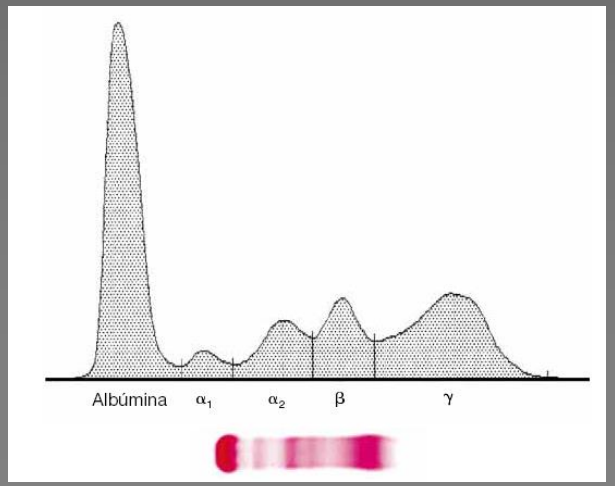
PROGRAMA DE CANCER

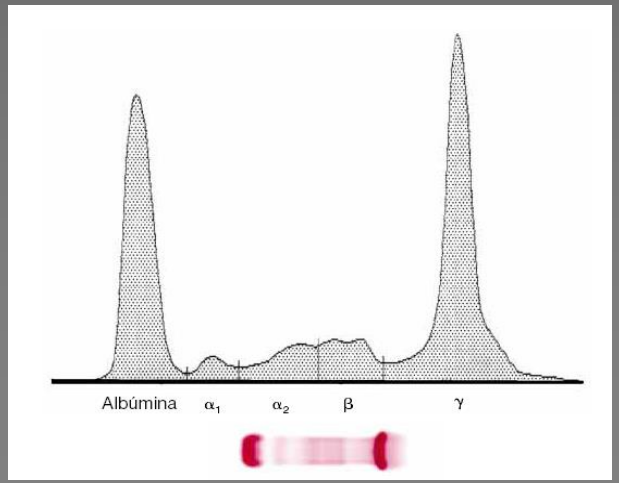
PONTIFICIA UNIVERSIDAD CATOLICA DE CHILE

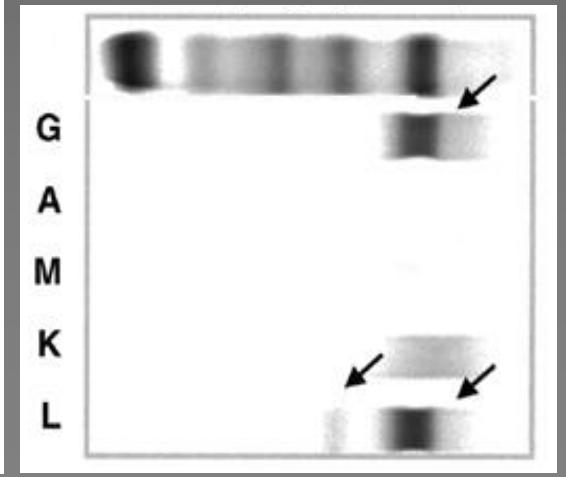
Gammapatías Monoclonales

Las gammapatías monoclonales (GM) constituyen un grupo de trastornos caracterizados por la proliferación clonal de células linfoides B en los últimos estadios madurativos (células plasmáticas y/o linfoplasmocitos) que producen una Ig homogénea de carácter monoclonal (componente M o CM)

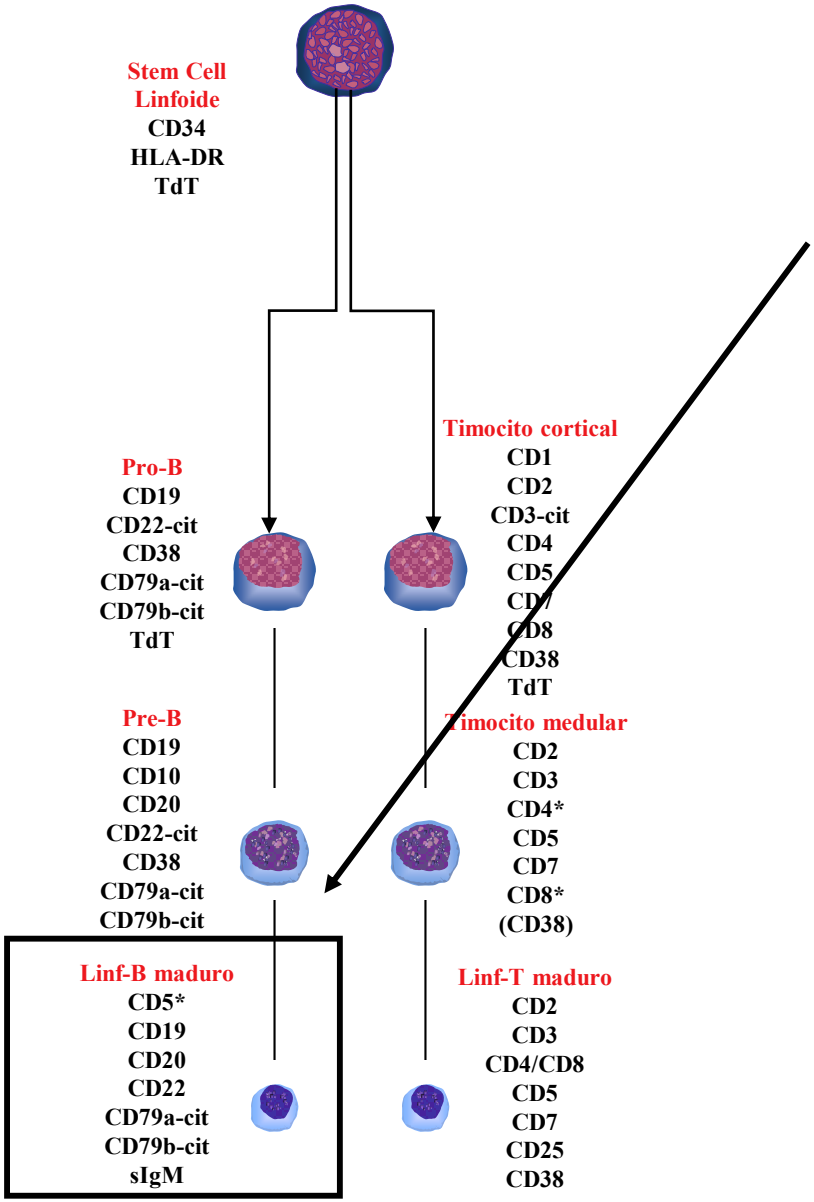
El carácter monoclonal lo define la expresión de un solo tipo de cadena ligera (κ o λ) (restricción de cadena ligera) y, cuando la paraproteína es completa, un solo tipo de cadena pesada



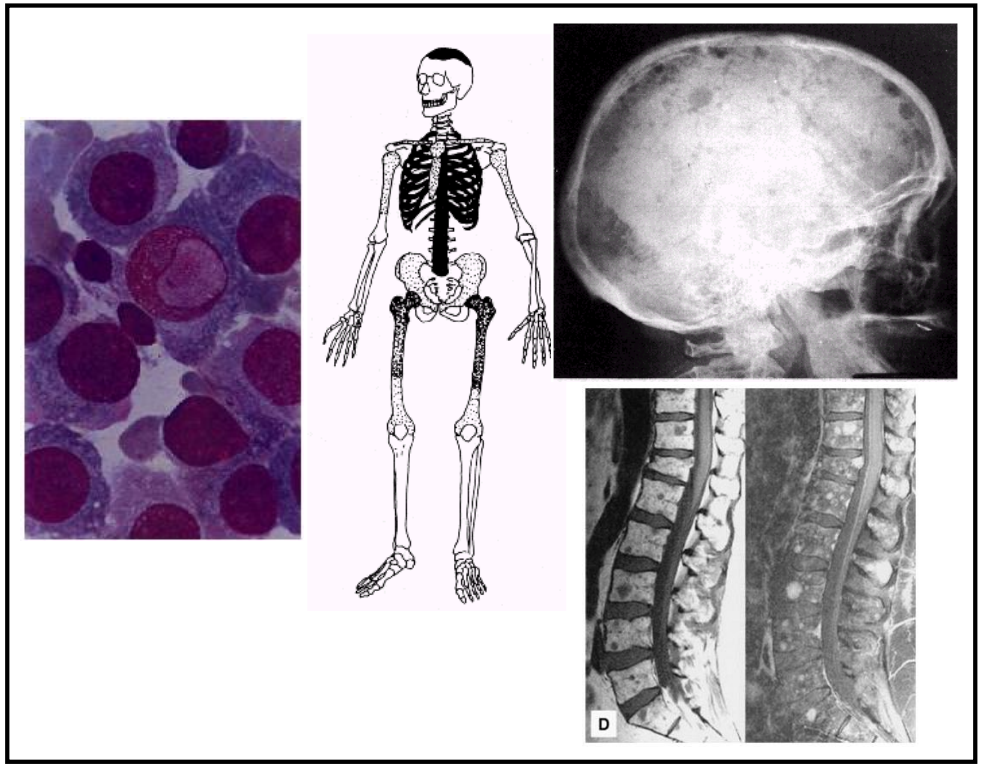




Alteraciones Genómicas y Enfermedades



Gammapatías Monoclonales



Gammapatías Monoclonales

Aumento C. Plasmáticas → ***Proteína Monoclonal***

GMSI

Mieloma

Osteolisis
Anemia
Falla Renal
Hipercalcemia
etc.

25%

"Benigna"

Muerte

Gammapatías Monoclonales

Gammapatías monoclonales malignas
- Mieloma múltiple (IgG, IgA, IgD, IgE y cadenas ligeras)
- Formas especiales de mieloma múltiple (mieloma quiescente, leucemia de células plasmáticas, mieloma no secretor, mieloma osteosclerótico, mieloma en pacientes jóvenes)
- Plasmocitomas localizados
  - Plasmocitoma óseo solitario
  - Plasmocitoma extramedular
- Macroglobulinemia de Waldenström
- Enfermedades de las cadenas pesadas (γ, α, μ, δ)
- Amiloidosis (primaria o asociada a mieloma)

Gammapatías monoclonales de significado desconocido
- Gammapatía monoclonal idiopática (IgG, IgA, IgM y rara vez cadenas ligeras)
- Gammapatías monoclonales transitorias (infecciones, trasplante de médula ósea, trasplante renal)

Gammapatía maligna más frecuente:
- 4 casos/100,000 habs.
- 1% todas las neoplasias
- 10% hematológicas
- Edad: 60-65 años

Gammapatía más frecuente
1-5% Población

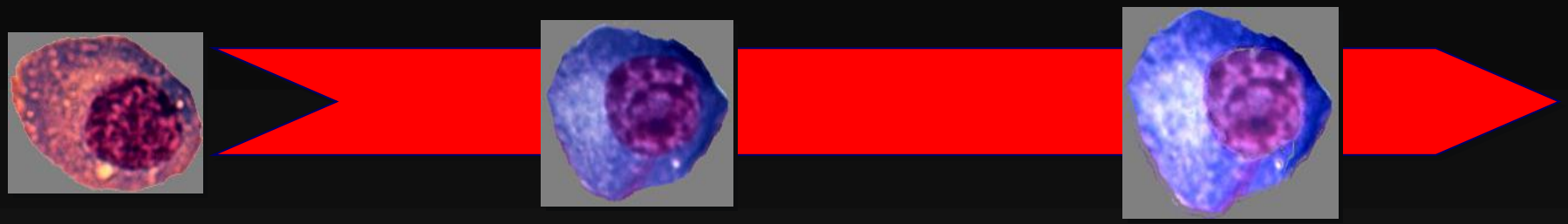
BM stromal cell/IL6 dependence

Increased DNA index

Inmortalization
Non malignant acumulation

Malignant
Transformation

Aggressive growth
Stromal independent



Normal **MGUS** **MM**

Primary IGH Translocatios

11q13
6p21
16q23
20q11
4p16

Karyotypic inestability

Trisomies **del 13/p16**

Secondary IGH Translocations:C-MYC

Mutations of N, K-RAS, FGFR3

Mutaciones de p53

Plasma cell discrasias: diagnostic criteria

	Monoclonal Gammopathy of uncertain significance (MGUS)	Smouldering Multiple Myeloma (SMM)	Multiple Myeloma
Monoclonal component	< 3 g/dL serum	≥3 g/dL serum	Present (*serum/urine*)
	AND	AND/OR	AND
Bone Marrow Plasma Cells (%)	< 10%	> 10%	> 10%[b]
	AND	AND	AND
Myeloma-defining event[a]	Absent	Absent	Present

Hypercalcaemia: serum calcium >0.25 mmol/L (>1 mg/dL) higher than the upper limit of normal or >2.75 mmol/L (>11 mg/dL)

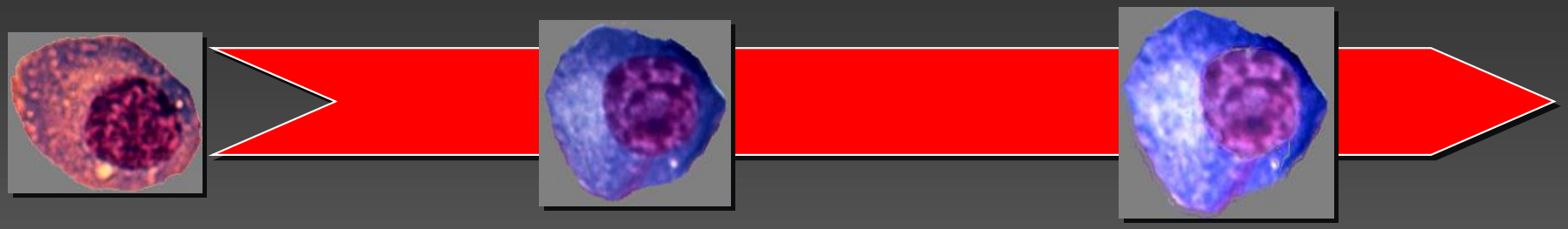
Renal insufficiency: serum creatinine >177 µmol/L (>2 mg/dL)

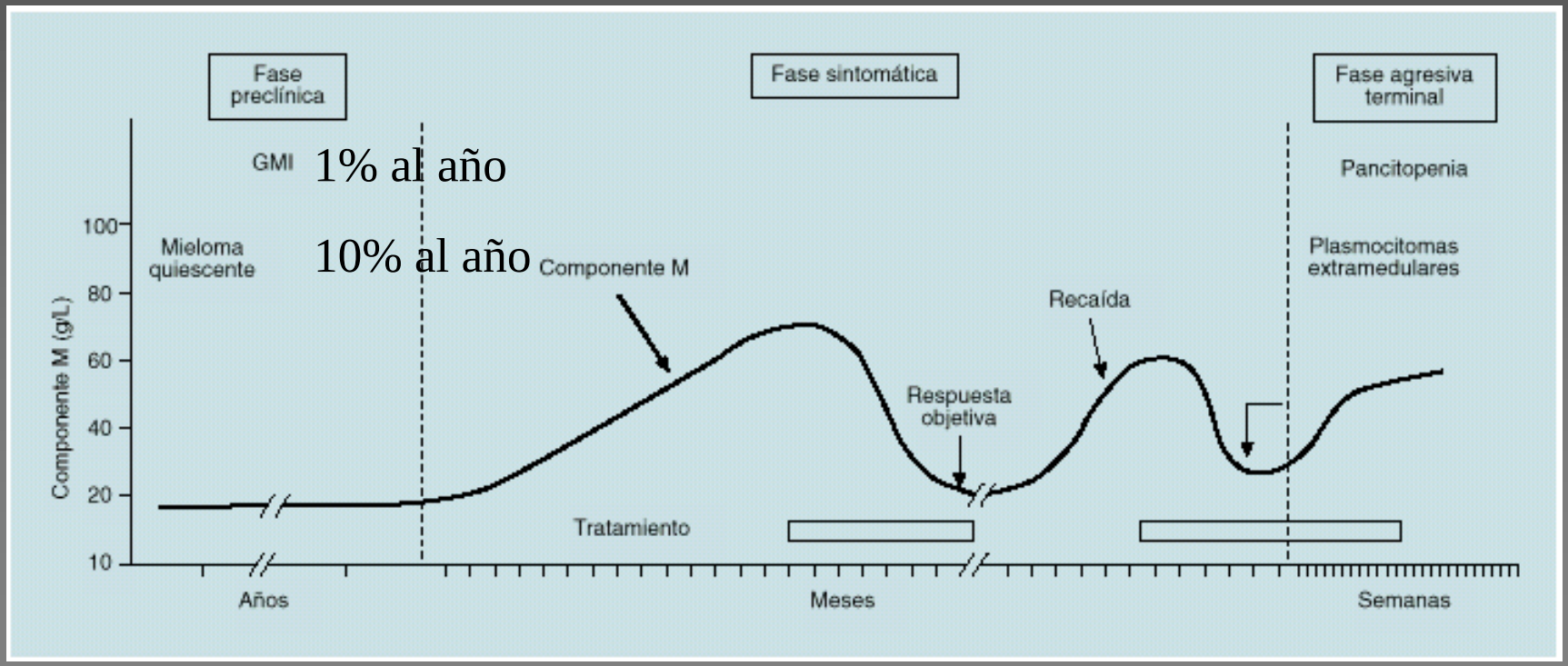
Anaemia: haemoglobin value of >20 g/L below the lower limit of normal, or a haemoglobin value <100 g/L

Bone lesions: one or more osteolytic lesions on skeletal radiography

IMWG 2006

Mieloma Múltiple: evolución





MM: Impacto en Sobrevida

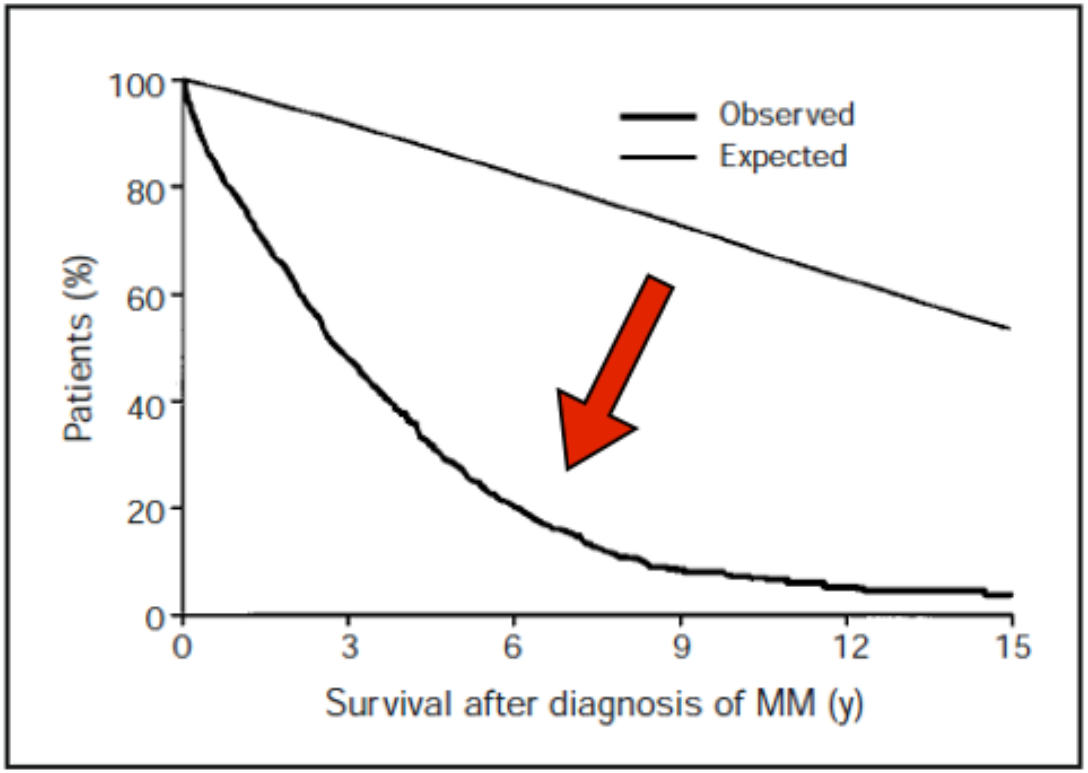
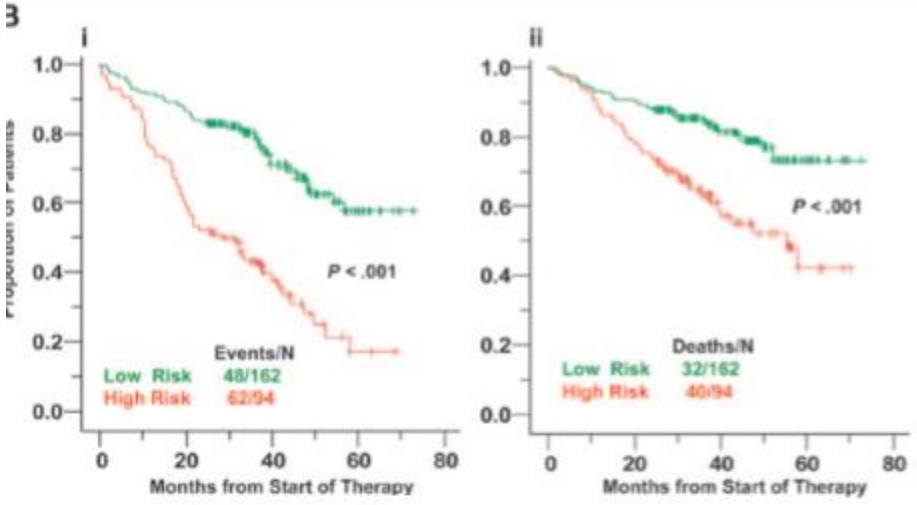


Figure 5. Duration of survival after diagnosis of multiple myeloma (MM) in 1027 patients and expected survival. Median of observed and expected survival, 2.8 years and 16.6 years, respectively.

Kyle, MCP 2003

Table 2 | Risk stratification of multiple myeloma

Category	Risk factors	Approximate frequency (%)
Low-risk multiple myeloma	Absence of intermediate-risk or high-risk factors	75
Intermediate-risk multiple myeloma	t(4;14) plus absence of 17p deletion or high-risk gene-expression-profiling signature	10
High-risk multiple myeloma	Presence of 17p deletion or high-risk gene-expression-profiling signature	15



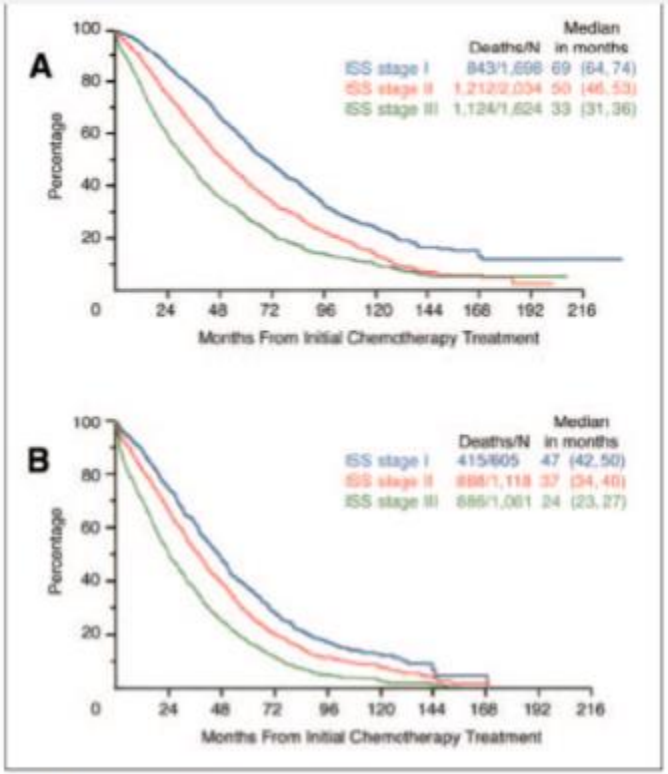


Fig 3. International Staging System (ISS); staging by age. A is patient's age < 65 years; B is patient's age ≥ 65 years.

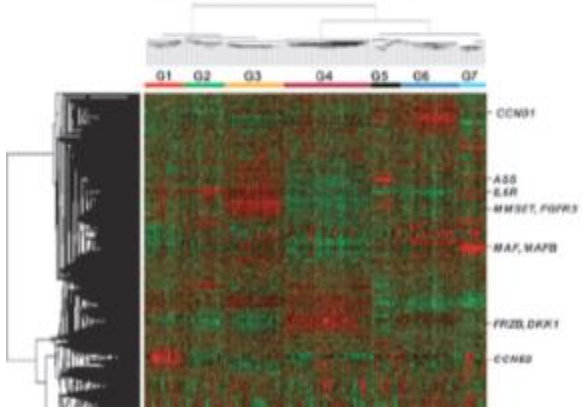
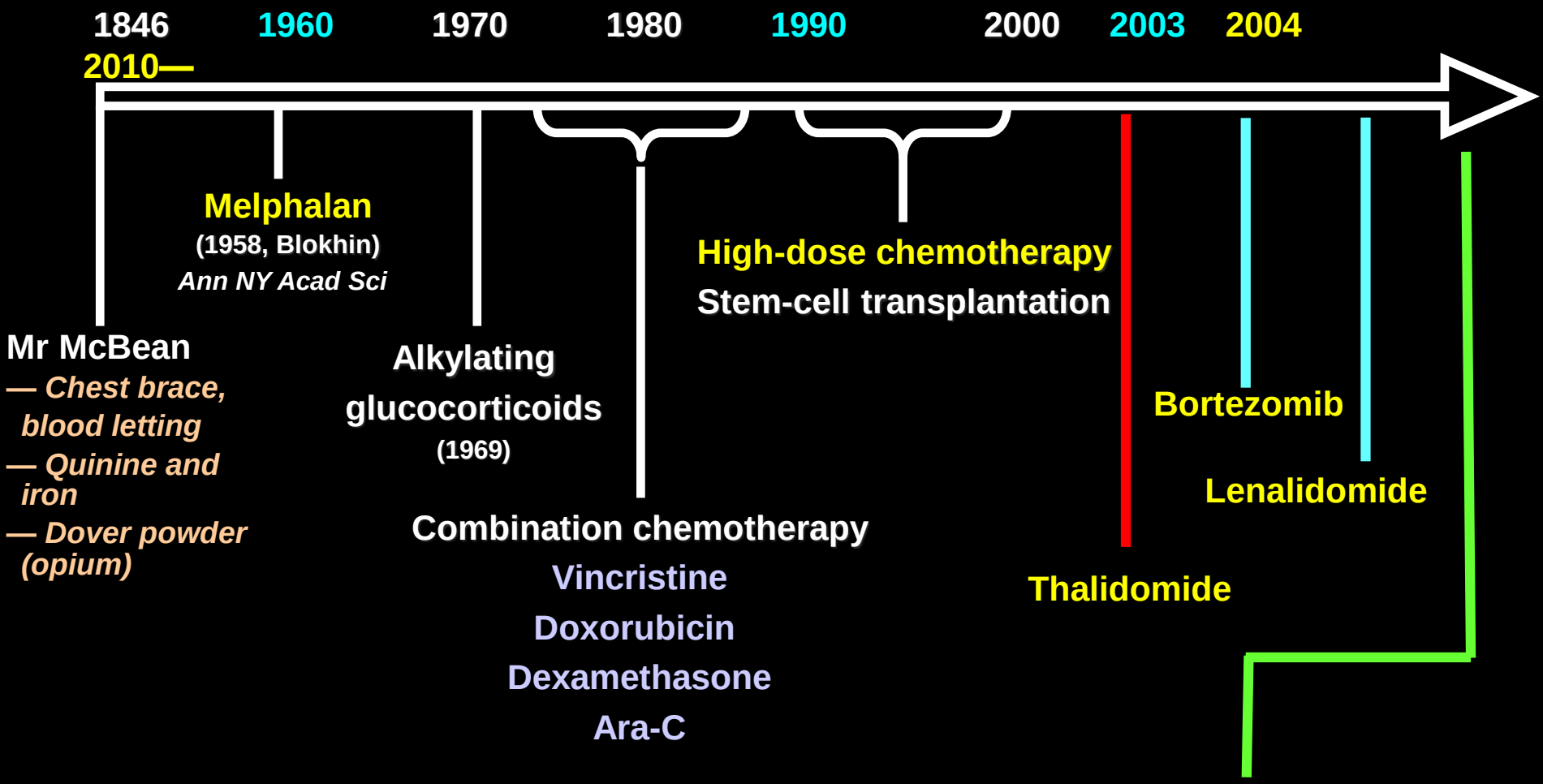


Table 4 Concordance between TC and UAMS GEP-derived classification

Subtypes	*4p16*	*MAF*	*6p21*	*11q13*	*D1*	*D1+D2*	*D2*	*None*	*All cases*
MS	68								68
MF		37							37
CD-1			2	22	2		1		27
CD-2		1	3	50	4	1	2		61
HY			1	1	106	5	2	1	116
LB			1	1	8	8	39	1	58
PR	6	2		4	10	9	13	3	47
All cases	74	40	7	78	130	23	57	5	414

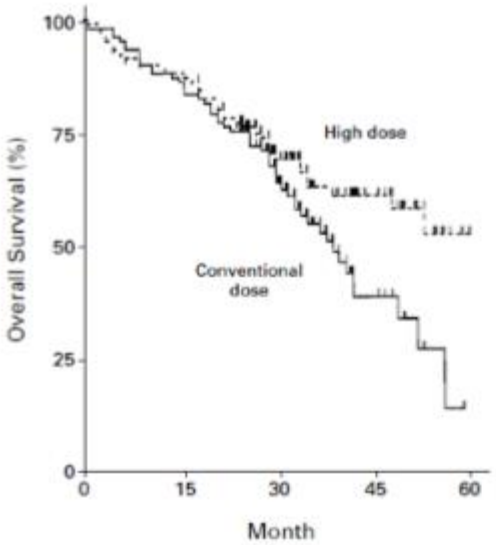
Myeloma treatment in the last century



HDACs, Histone deacetylases; IMiDs, immunomodulatory drugs; mAbs, monoclonal antibodies; PIs, proteasome inhibitors

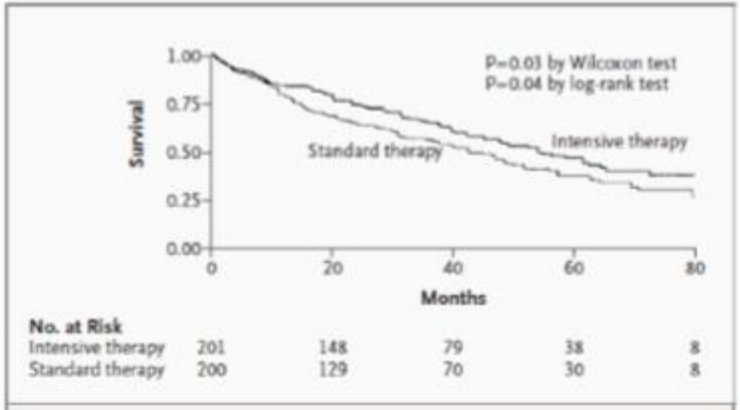
TMO en MM

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



Conventional dose	63 (53–73)	35 (22–50)	12 (1–40)	
High dose	69 (58–78)	61 (50–71)	52 (36–67)	

High-Dose Chemotherapy with Hematopoietic Stem-Cell Rescue for Multiple Myeloma



No. at Risk					
Intensive therapy	201	148	79	38	8
Standard therapy	200	129	70	30	8

Figure 2. **Kaplan–Meier Estimates of Overall Survival in the Intention-to-Treat Population.**

Overall, there was an improvement in median survival of 11.8 months in the intensive-therapy group (median survival, 54.1 months; 95 percent confidence interval, 44.9 to 65.2) as compared with the standard-therapy group (42.3 months; 95 percent confidence interval, 33.1 to 51.6; P=0.04 by the log-rank test and P=0.03 by the Wilcoxon test).

Attal, NEJM 1996
Child, NEJM 2003

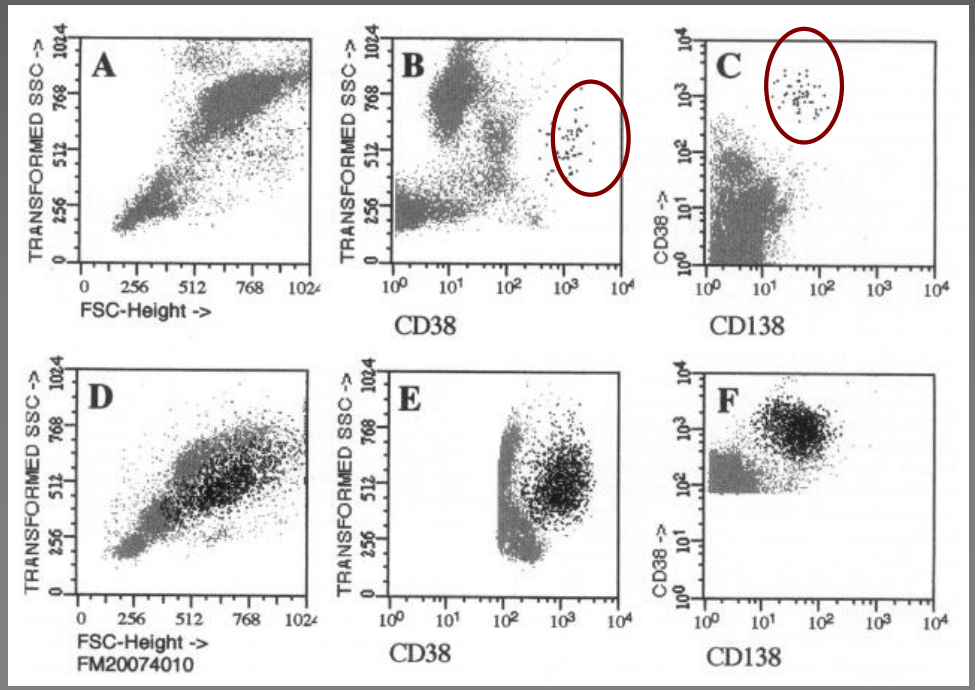
American Journal of Pathology, Vol. 152, No. 6, June 1998

Immunophenotypic Characterization of Plasma Cells from Monoclonal Gammopathy of Undetermined Significance Patients

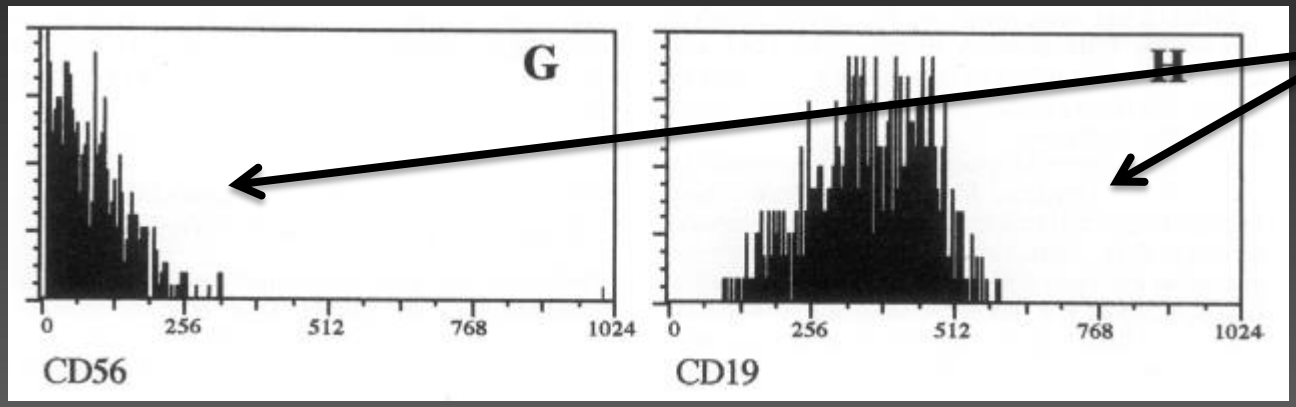
Implications for the Differential Diagnosis between MGUS and Multiple Myeloma

CP en MO Normal: Proporciones bajas

Mauricio Ocqueteau,* Alberto Orfao,†
Julia Almeida,* Joan Bladé,‡ Marcos González,*
Ramón García-Sanz,* Consuelo López-Berges,*
María J. Moro,§ José Hernández,¶ Luis Escribano,‖
Dolores Caballero,* María Rozman,‡ and
Jesús F. San Miguel*



Gammapatías Monoclonales



CP Normales

Antigen	CPN	CPP	MM, Myelomatous PCs
CD38-FITC	1,299,650 ± 396,251*	694,067 ± 367,668*	467,801 ± 158,652
CD19-PE	50,985 ± 35,224†	2002 ± 2906†	3457 ± 5222
CD56-PE	14,316 ± 16,243‡	55,792 ± 73,808‡	67,679 ± 62,478

Results are expressed as mean ± SD in MESF units. There were no significant differences between clonal BMPCs and myelomatous PCs. For the CD56-PE antigen, for polyclonal BMPCs, MESF values refer exclusively to CD56+ cells.

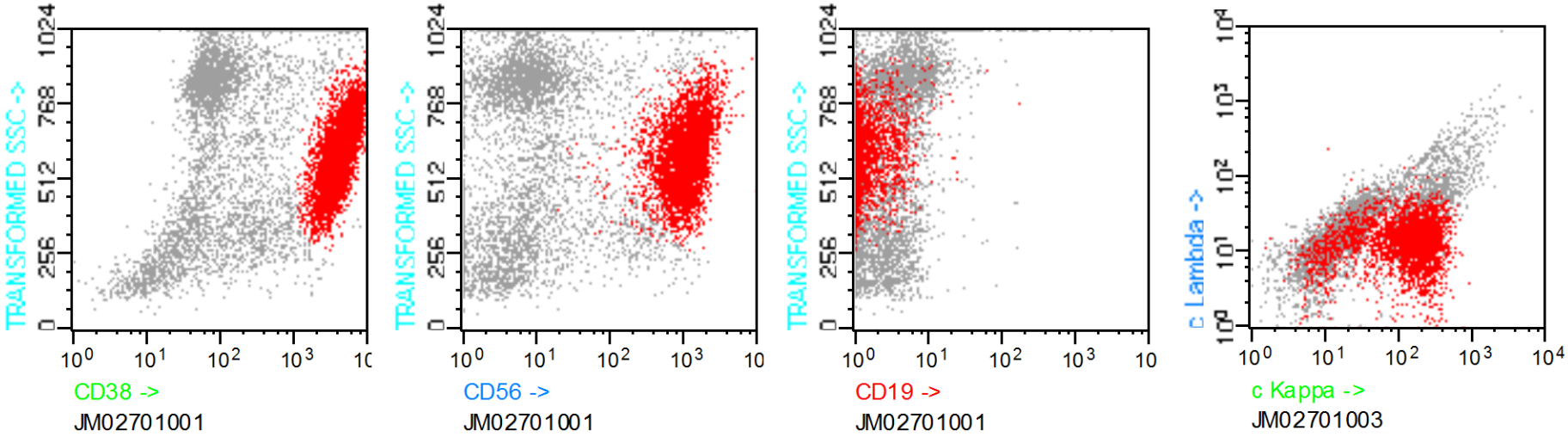
*$P = 0.001$.

†$P = 0.007$.

‡$P = 0.008$.

Gammapatías Monoclonales
Patrón de Citometría de Flujo

Mieloma Múltiple

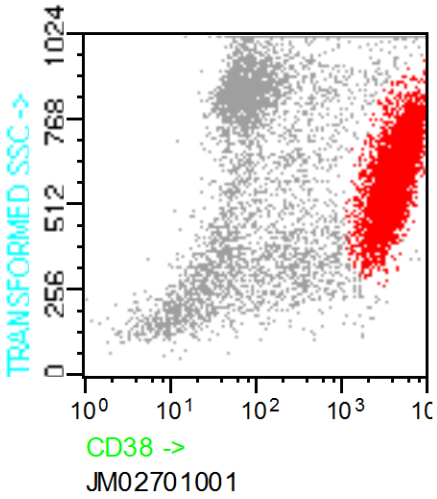


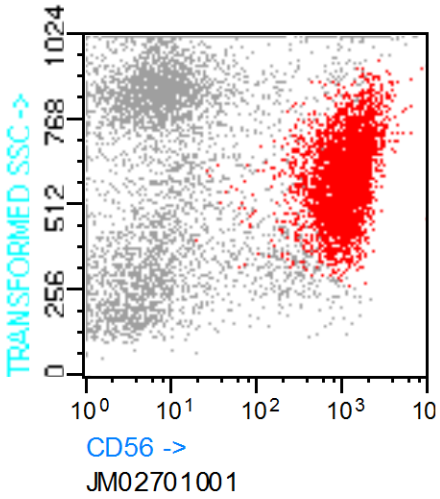
Patrón CP Clonales

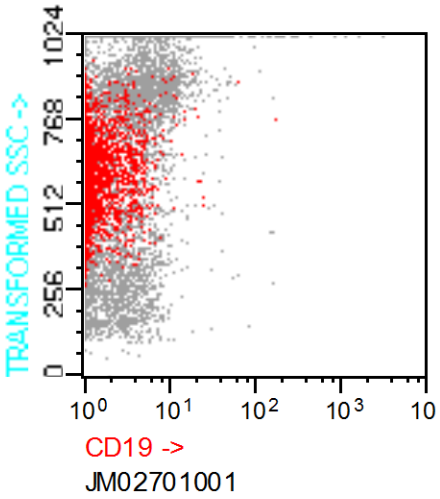
Antigen	MGUS population A	Control BMPCs	MGUS population B	MM BMPCs
CD38*	100	100	100	100
CD19	100	100	6	3
CD56†	0	0	69	67
CD28	0	0	47	41
CD117	0	0	23	27
sIg	0	0	28	31

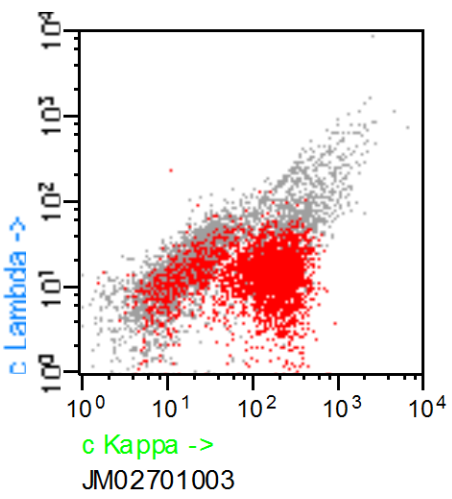
Gammapatías Monoclonales
Patrón de Citometría de Flujo

Mieloma Múltiple

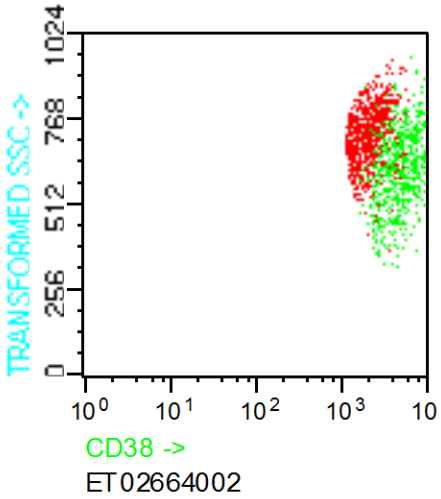


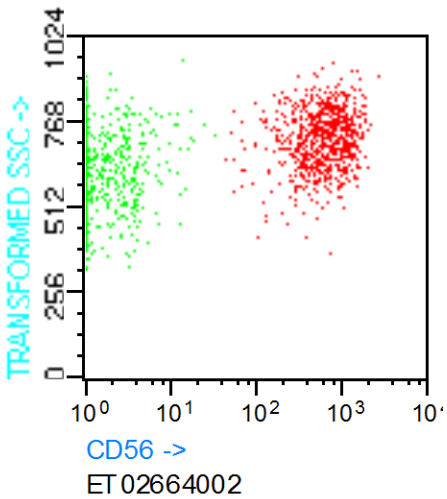


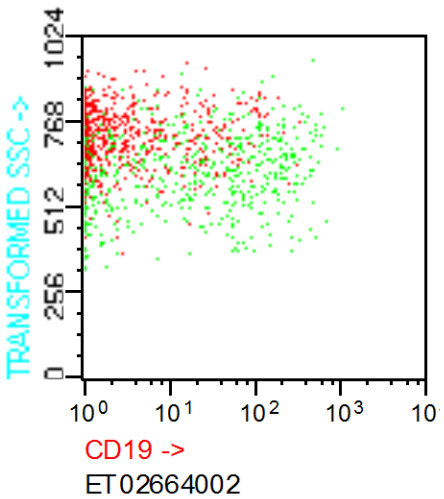


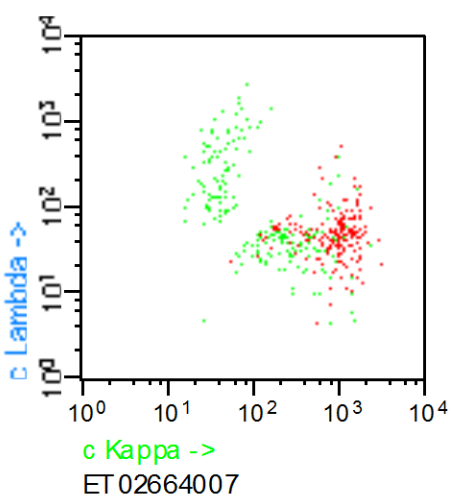


MGUS

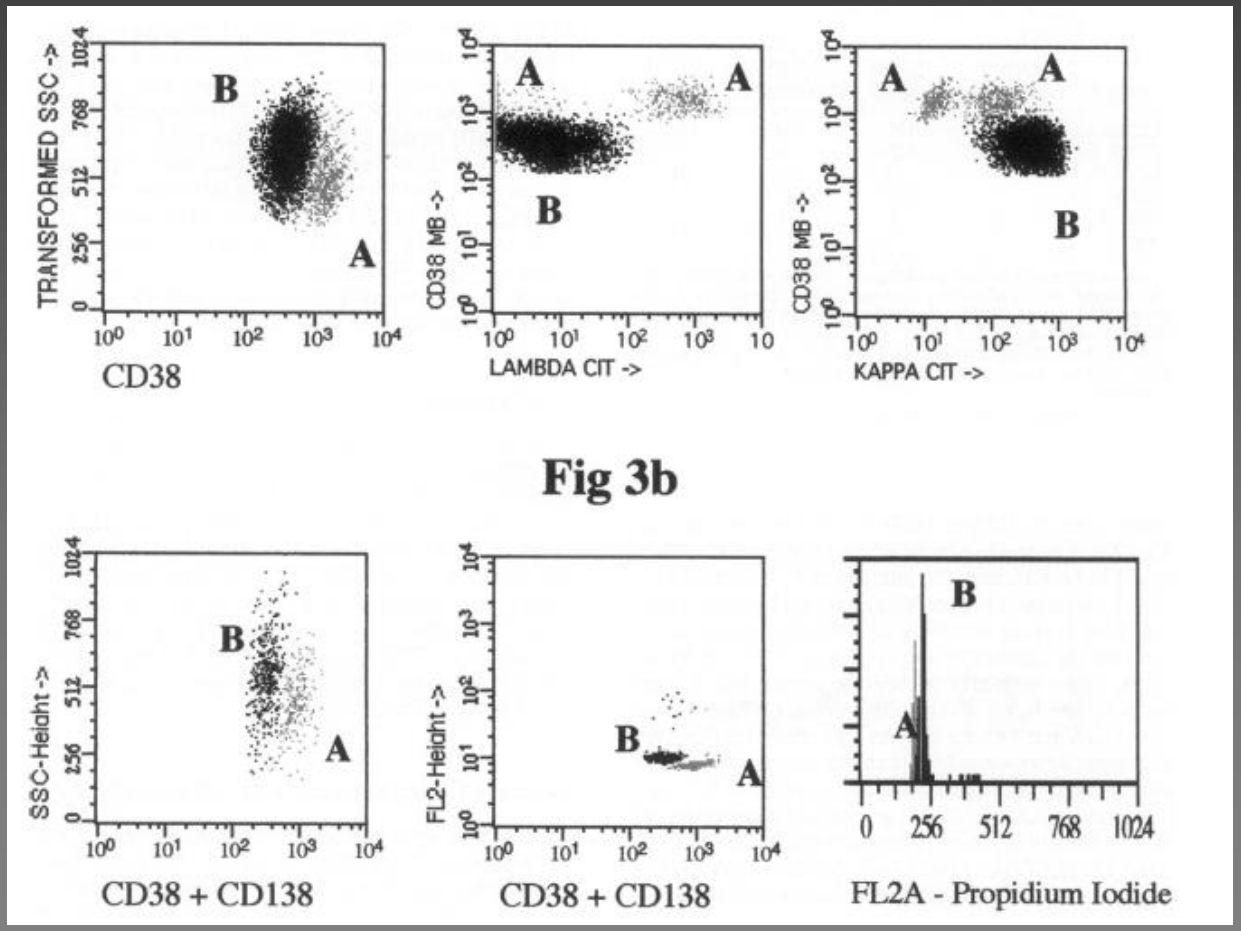


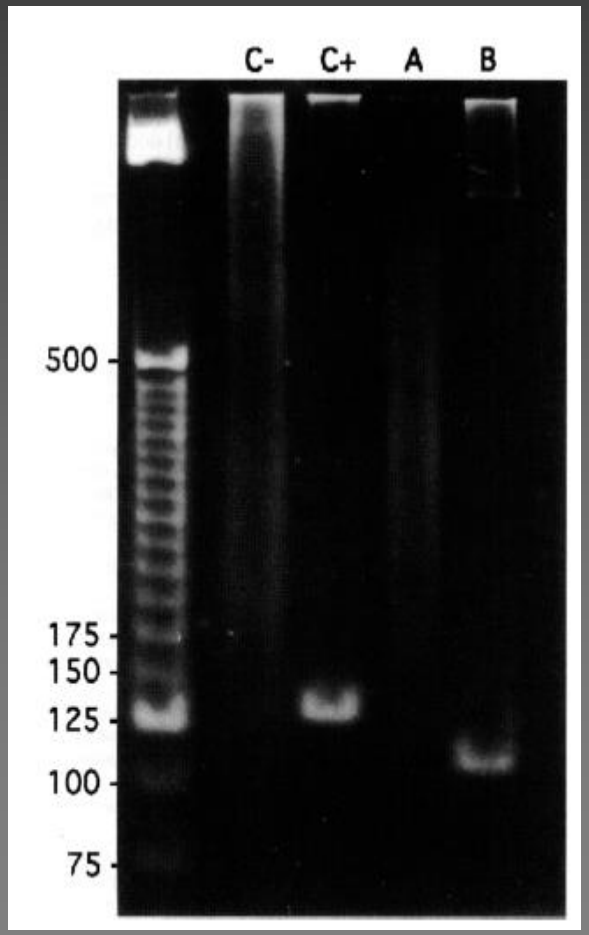






Gammapatías Monoclonales





Patrón Inmunofenotípico en Dco Diferencial

Table 4. Clinical and Biological Features in MGUS and MM Patients

Parameter	MM	MGUS	*P* value
Age (years)	61 ± 12	66 ± 11	0.04
Osteolytic bone lesions	66%	0%	0.0001
Hemoglobin (g/dl)	10.5 ± 3.0	13.7 ± 1.6	0.0001
Total protein (g/L)	9.1 ± 2.1	7.5 ± 0.	0.0001
Amount of MC (g/dl)	4658 ± 2526	1541 ± 550	0.0001
Ca^{2+} (mg/dl)	9.7 ± 1.3	9.5 ± 0.6	NS
β2-microglobulin (mg/L)	4.8 ± 5.3	2.3 ± 1.0	0.005
LDH (IU/L)	311 ± 103	342 ± 88	NS
CRP (mg/dl)	3.1 ± 3.6	2.1 ± 4.0	NS
% BMPCs by morphology	43.3 ± 26.1	5.4 ± 4.2	0.0001
% BMPCs by immunophenotype	14.5 ± 14.1	1.8 ± 1.2	0.0001
% S-phase BMPCs	1.8 ± 2.2	1.4 ± 2.0	NS
% INPCs	0.25 ± 0.76	32.8 ± 31.4	0.0001
% Cases with >3% INPCs	1.5	98	0.0001

% INPCs, percentage of immunophenotypically normal BMPCs; CRP, C-reactive protein; LDH, lactic dehydrogenase; MC, monoclonal component; NS, statistically nonsignificant.

Patrón Inmunofenotípico en Dco Diferencial

Table 5. Stage IA MM Patients: Individual Distribution According to Conventional Diagnostic Criteria

Patient	% BMPCs by morphology	Amount/type of MC	% INPCs
1	27	2700/IgA	0
2	21	1350/IgG	0
3	25	3680/IgG	0
4	15	3100/IgA	0
5	11	3710/IgA	1.7
6	12	4500/IgA	0

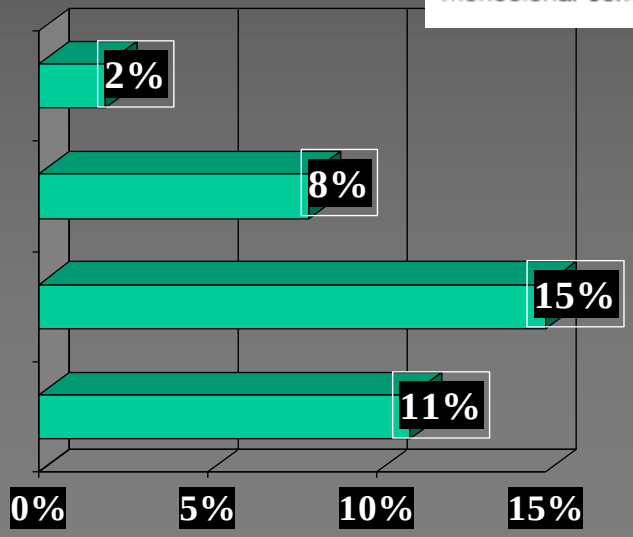
% INPCs, percentage of immunophenotypically normal BMPCs; MC, monoclonal component.

%INPC

CP Morfología

Osteolisis

C.Monoclonal

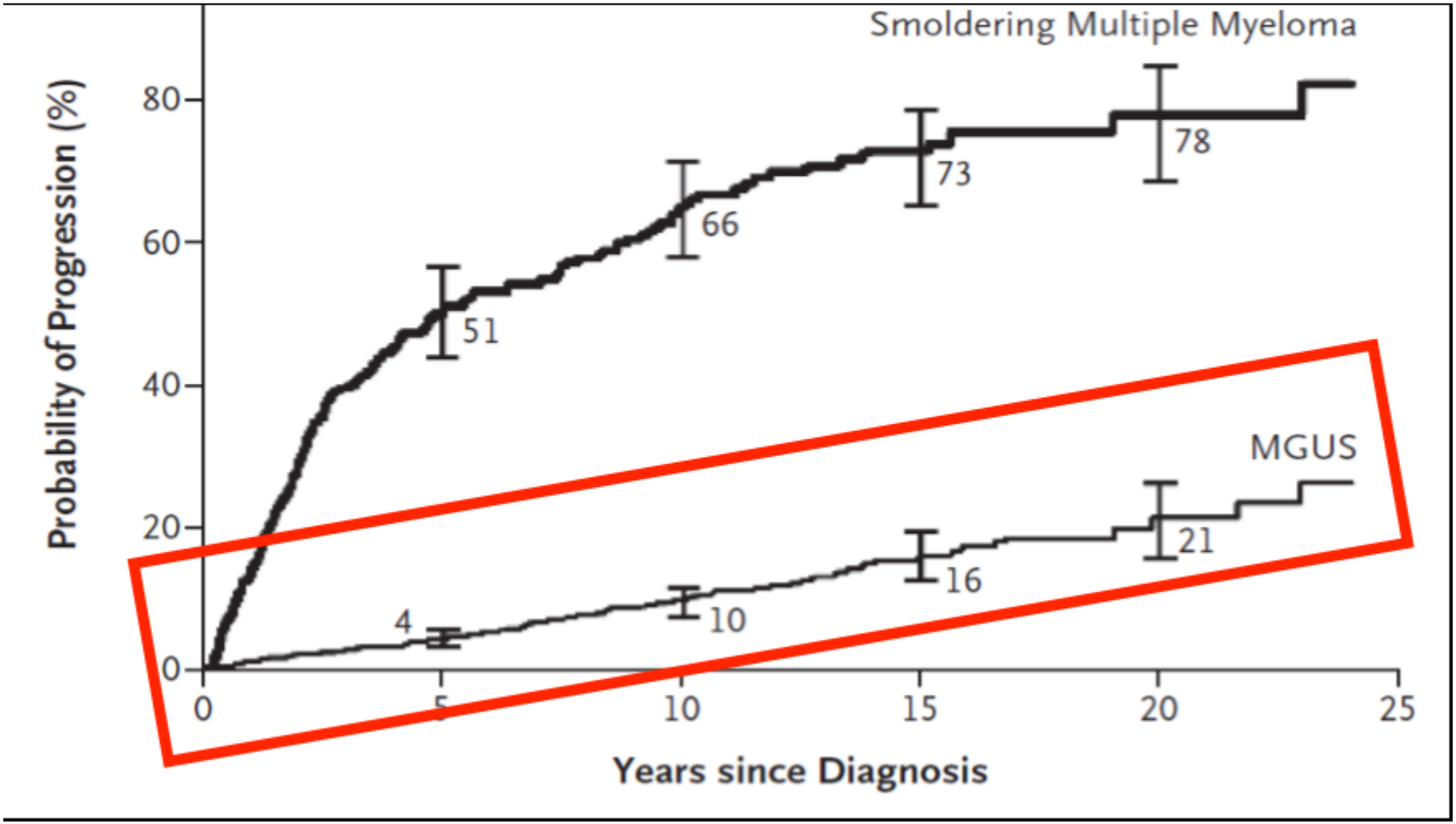


% Casos

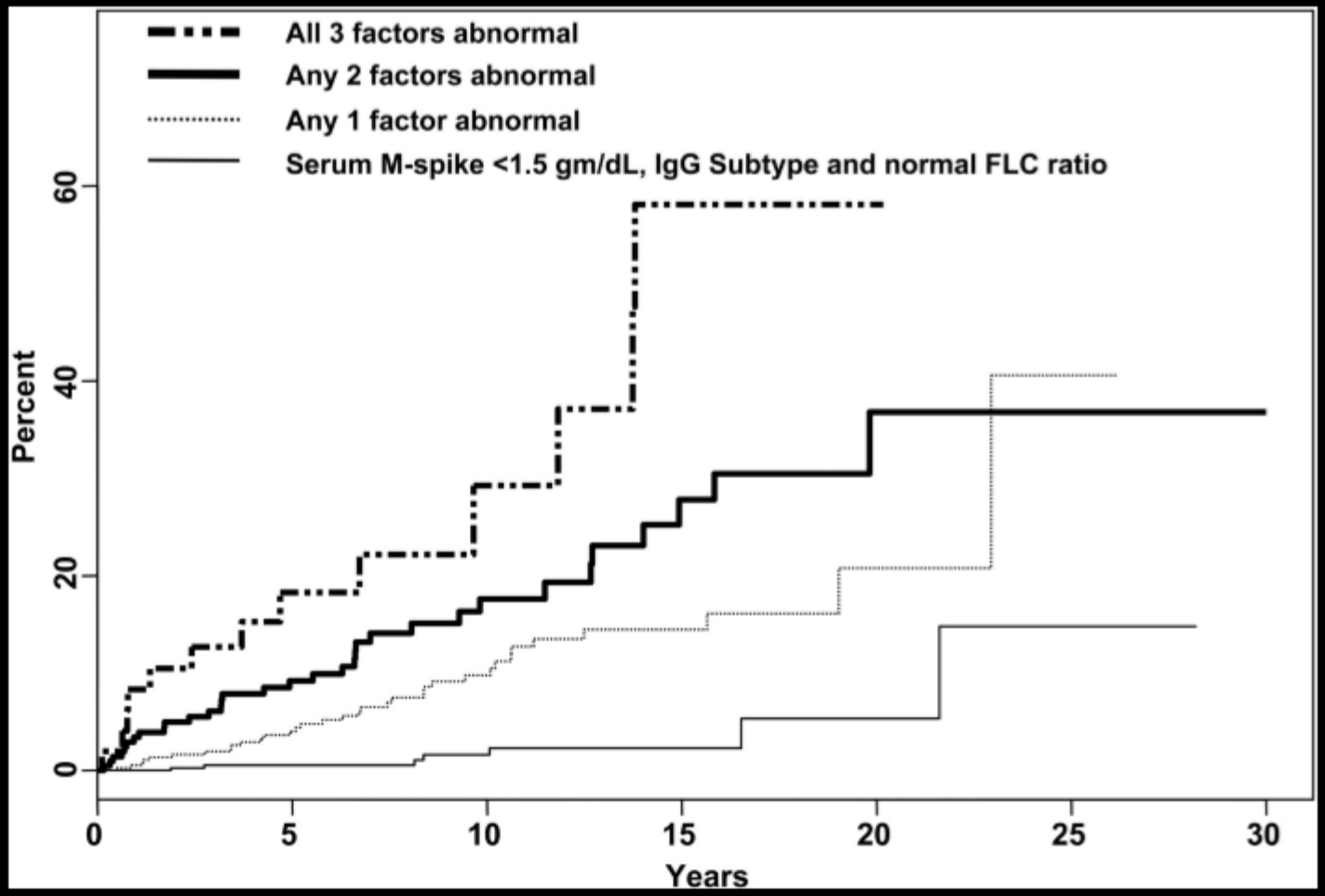
MGUS: 76 casos

MM: 65 casos

Progresión a MM Sintomático



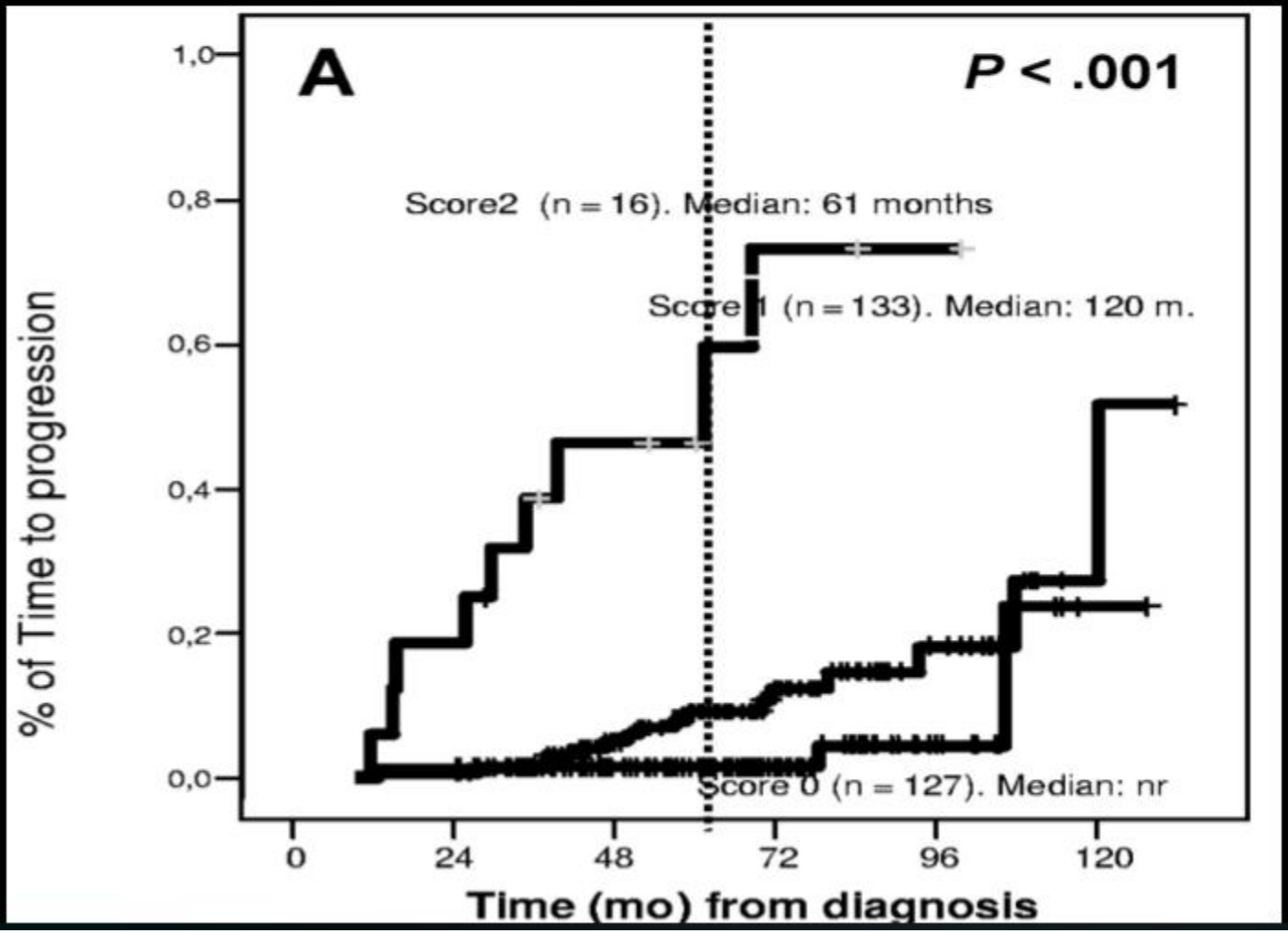
- non IgG MGUS
- M-protein ≥ 15 g/L
- Abnormal serum kappa/lambda FLC ratio



Rajkumar Blood 2005

-DNA aneuploidy

-Multiparameter flow cytometry of bone marrow plasma cells (≥95% aberrant BM plasma cells)



New criteria to identify risk of progression in monoclonal gammopathy of uncertain significance and smoldering multiple myeloma based on multiparameter flow cytometry analysis of bone marrow plasma cells

Ernesto Pérez-Persona,[1] María-Belén Vidriales,[1,2] Gema Mateo,[1] Ramón García-Sanz,[1,2] Maria-Victoria Mateos,[1] Alfonso García de Coca,[3] Josefina Galende,[4] Guillermo Martín-Nuñez,[5] José M. Alonso,[6] Natalia de las Heras,[7] José M. Hernández,[8] Alejandro Martín,[9] Consuelo López-Berges,[1] Alberto Orfao,[2,10] and Jesús F. San Miguel[1,2]

MGUS SMM

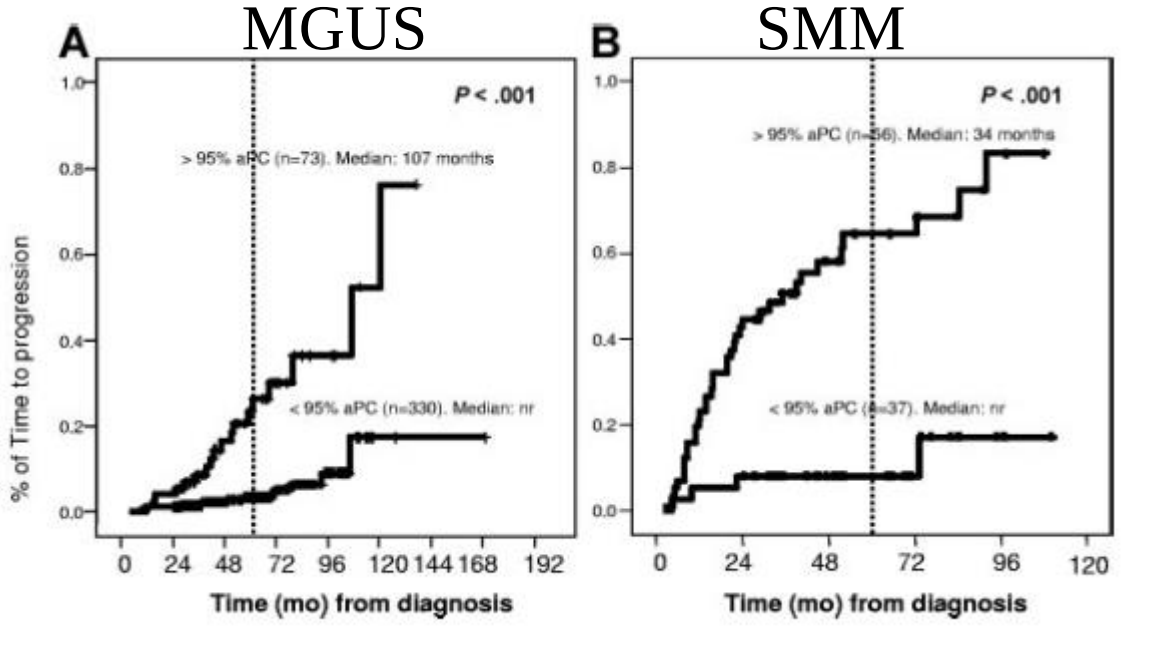
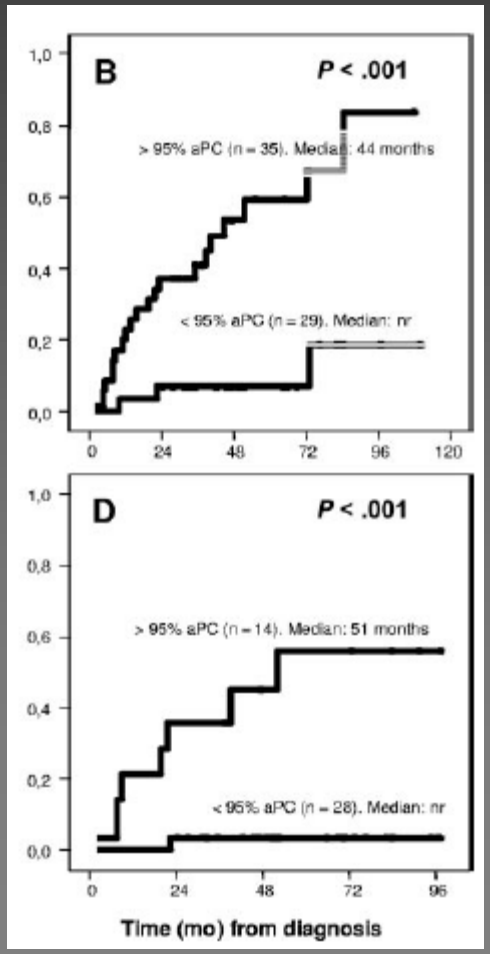


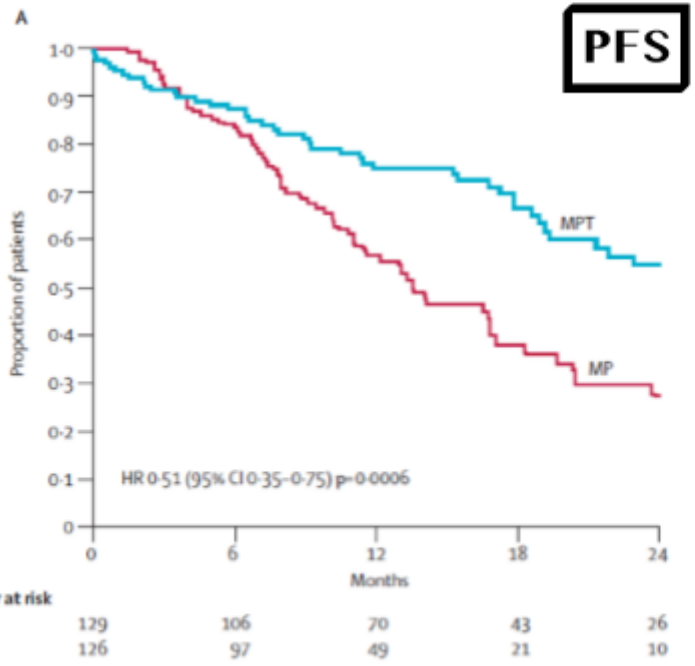
Figure 2. Time to progression in MGUS and SMM according to the percentage of immunophenotypically aberrant plasma cells. (A) For MGUS, the median time to progression (TTP) was 107 months versus not reached (nr) for patients with 95% or greater versus less than 95% aberrant PC, respectively ($P < .001$). (B) For SMM, the median TTP was 34 months vs not reached for patients with 95% or greater versus less than 95% aberrant PC, respectively ($P < .001$).



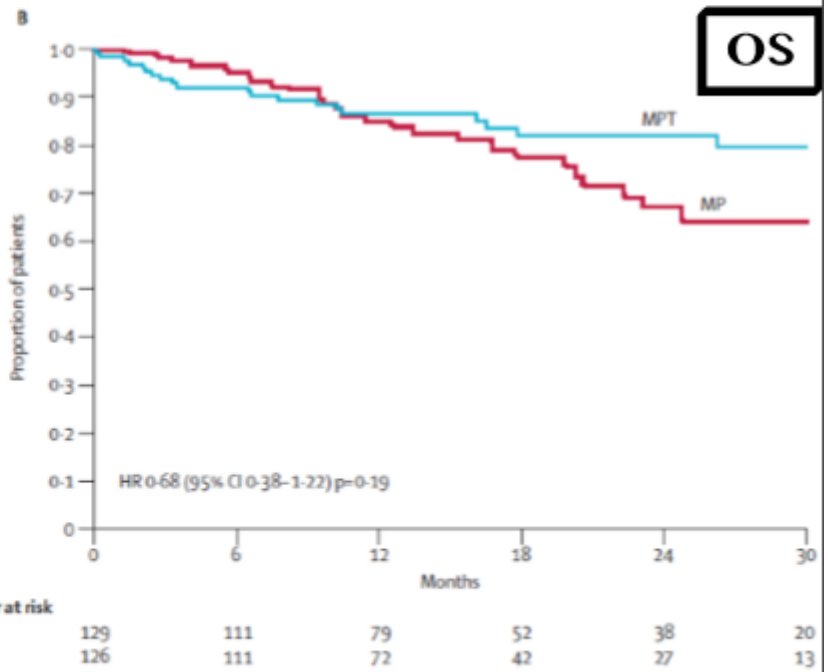
SMM baja masa

Oral melphalan and prednisone chemotherapy plus thalidomide compared with melphalan and prednisone alone in elderly patients with multiple myeloma: randomised controlled trial

Melfalan Prednisona Talidomida



Number at risk					
MPT	129	106	70	43	26
MP	126	97	49	21	10

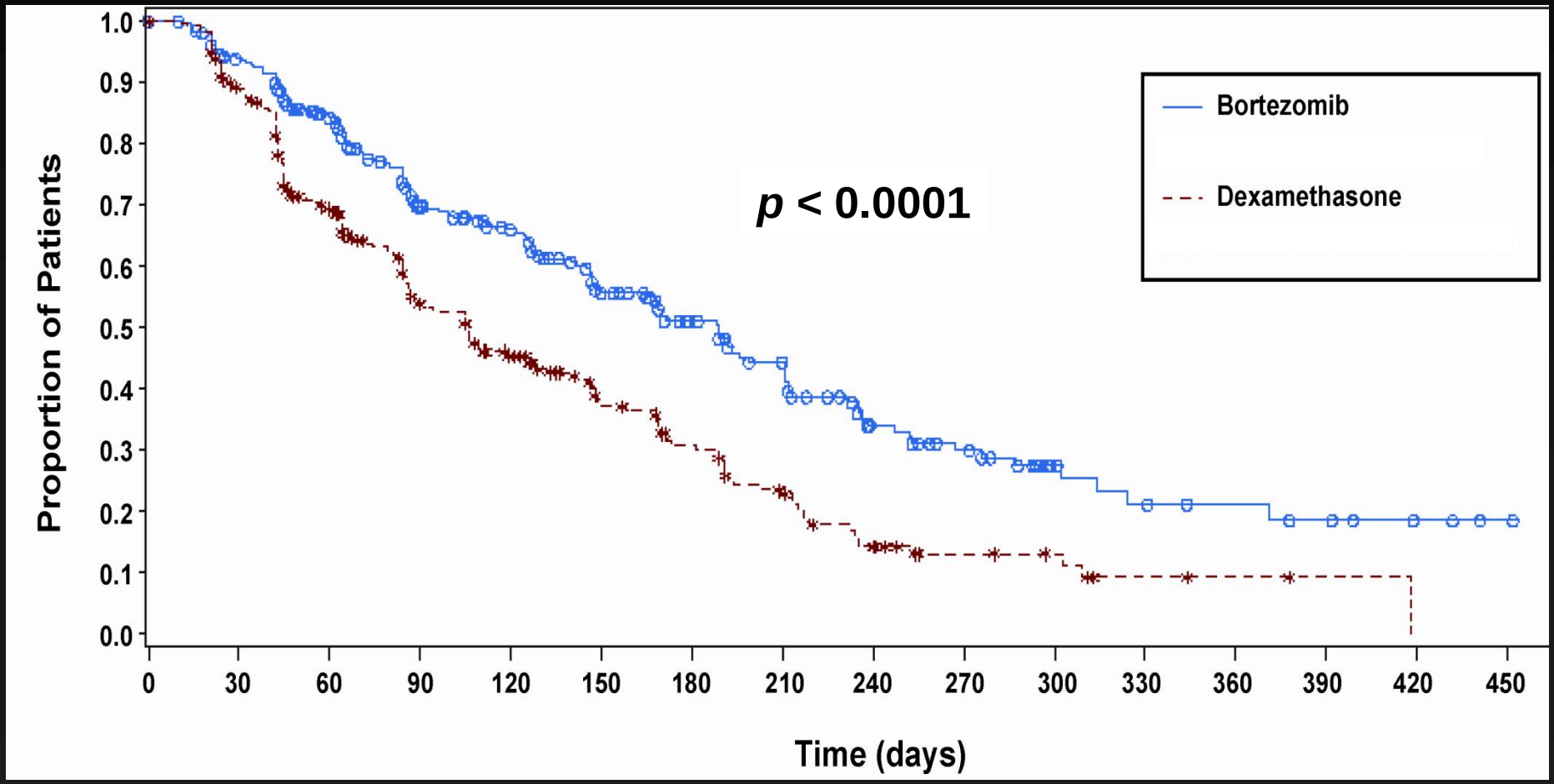


Number at risk						
MPT	129	111	79	52	38	20
MP	126	111	72	42	27	13


complete-response
prednisone
melphalan
myeloma
orally
lenalidomide
thalidomide
bortezomib
dexamethasone
treatment
total
autologous
therapies
factor
bone
growth
age
risk
pain
diagnosed
response
years
multiple
induction
infusion
consolidation
marrow
diagnosis
transplantation
overall-survival
progression-free-survival
randomized
protein
tumor
staging
factors
adhesion
trials
intravenous
monoclonal
abnormalities
renal
newly
younger
drug
clinical
study
cyclophosphamide
toxic
anemia
relapse
bolus
high
maintenance
combination

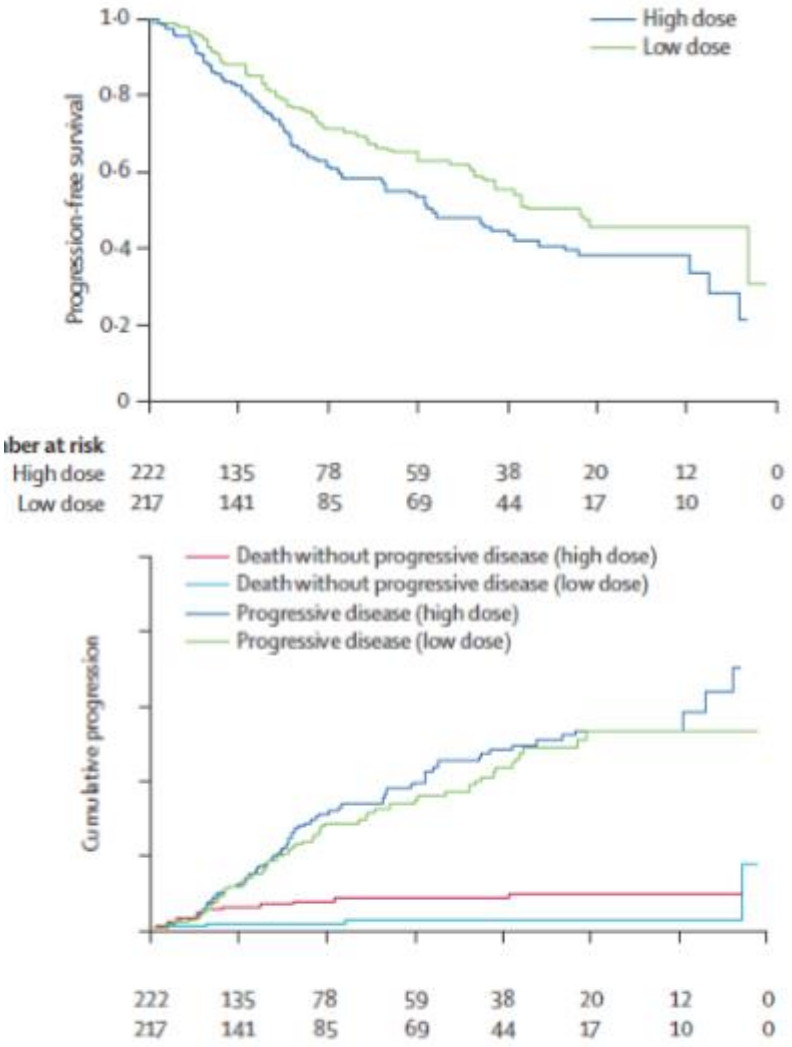
Time to progression (*n* = 669)

78% improvement in median TTP with bortezomib



Median TTP: bortezomib 6.2 months; dexamethasone 3.5 months

Lenalidomide plus high-dose dexamethasone versus lenalidomide plus low-dose dexamethasone as initial therapy for newly diagnosed multiple myeloma: an open-label randomised controlled trial



	High dose (n=223)	Low dose (n=220)*	p value
Haematological			
Haemoglobin	18 (8)	15 (7)	0·72
Platelets	13 (6)	11 (5)	0·83
Neutrophils	26 (12)	44 (20)	0·02
Non-haematological			
Deep-vein thrombosis or pulmonary embolism	57 (26)	27 (12)	0·0003
Infection or pneumonia	35 (16)	20 (9)	0·04
Hyperglycaemia	25 (11)	14 (6)	0·09
Cardiac ischaemia	7 (3)	1	0·07
Atrial fibrillation or flutter	6 (3)	1	0·12
Fatigue	33 (15)	20 (9)	0·08
Neuropathy	5 (2)	4 (2)	0·1
Non-neuropathic weakness	25 (11)	9 (4)	0·01
Summary			
Any grade 3 or higher in first 4 months	117 (52)	76 (35)	0·0001
Any grade 3 or higher non-haematological toxicity at any time during therapy	146 (65)	106 (48)	0·0002
Any grade 4 or higher non-haematological toxicity at any time during therapy	46 (21)	18 (14)	0·0002
Early mortality (first 4 months)	12 (5)	1	0·003

Data are number (%). *Data unavailable for two patients.

Table 4: **Major grade 3 or higher toxicity**

Rajkumar, Lancet 2010

Daratumumab: MM refractario/Recaida

EJM 2016.pdf Abrir con

The NEW ENGLAND JOURNAL of MEDICINE

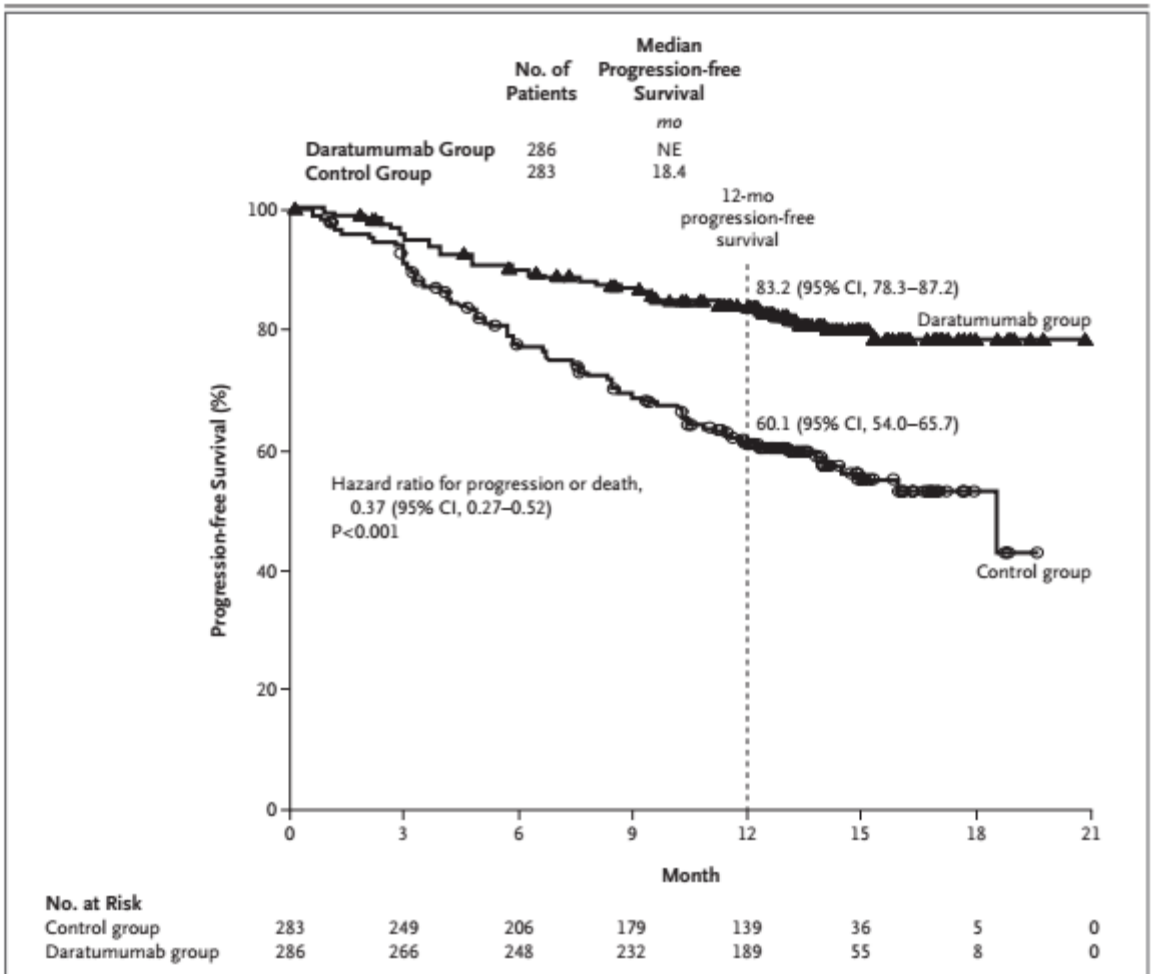
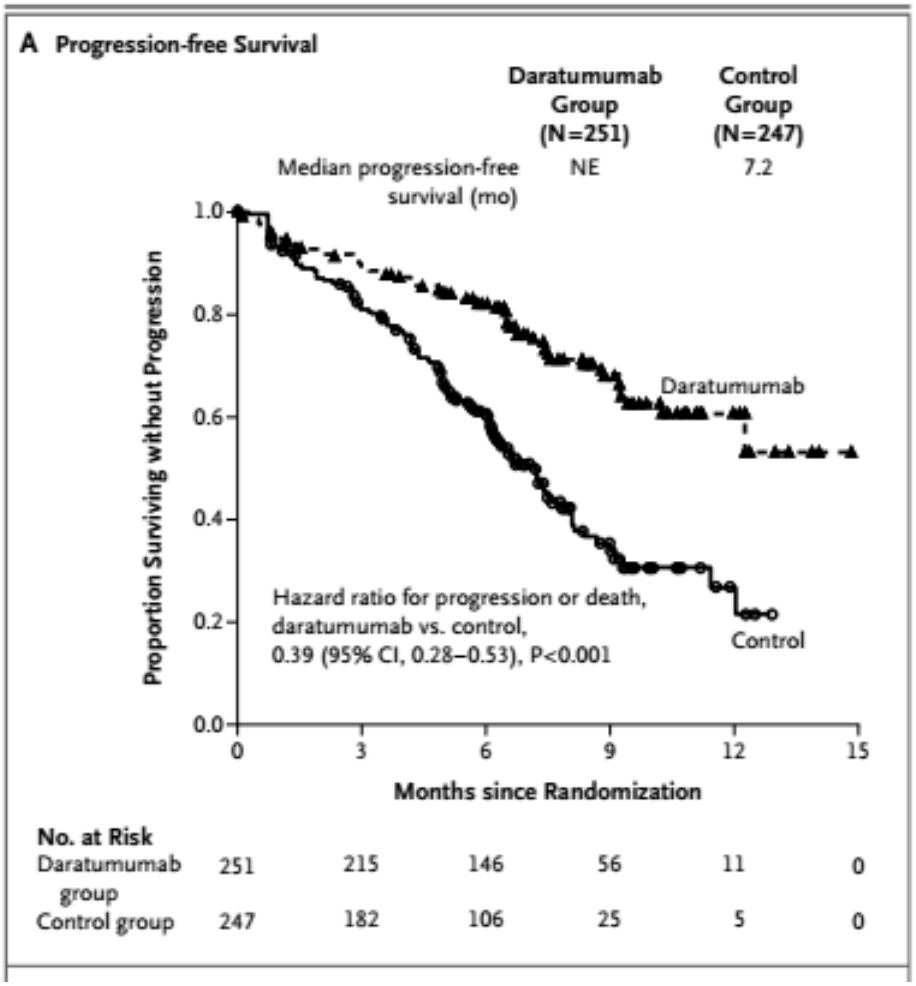


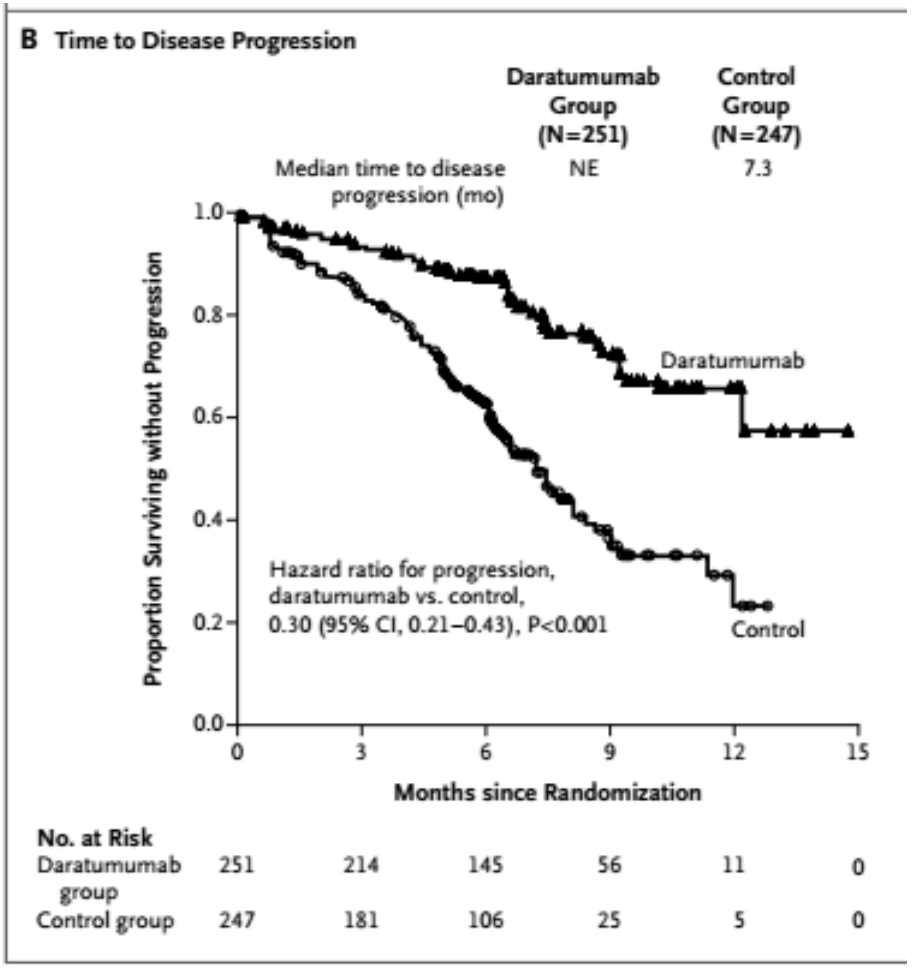
Figure 1. Progression-free Survival.

Shown are the results of the Kaplan–Meier analysis of progression-free survival among patients in the intention-to-treat population, which included all patients who underwent randomization. The P value is based on a stratified log-rank test. The daratumumab group received daratumumab, lenalidomide, and dexamethasone, and the control group received lenalidomide and dexamethasone. NE denotes could not be estimated.

Página 6 de 13

Daratumumab: MM refractario/Recaida






complete-response
prednisone
melphalan
dexamethasone
bortezomib
myeloma
orally
risk
lenalidomide
treatment
total
therapies
autologous
factor
bone
thalidomide
induction
response
growth
transplantation
progression-free-survival
overall-survival
maintenance
combination

Table 5 International Myeloma Working Group uniform response criteria: CR and other response categories

Response subcategory	*Response criteria*[a]
sCR	CR as defined below plus Normal FLC ratio and Absence of clonal cells in bone marrow[b] by immunohistochemistry or immunofluorescence[c]
CR	Negative immunofixation on the serum and urine and Disappearance of any soft tissue plasmacytomas and $\leqslant$5% plasma cells in bone marrow[b]
VGPR	Serum and urine M-protein detectable by immunofixation but not on electrophoresis or 90% or greater reduction in serum M-protein plus urine M-protein level $<$100 mg per 24 h
PR	$\geqslant$50% reduction of serum M-protein and reduction in 24-h urinary M-protein by $\geqslant$90% or to $<$200 mg per 24 h If the serum and urine M-protein are unmeasurable,[d] a $\geqslant$50% decrease in the difference between involved and uninvolved FLC levels is required in place of the M-protein criteria If serum and urine M-protein are unmeasurable, and serum free light assay is also unmeasurable, $\geqslant$50% reduction in plasma cells is required in place of M-protein, provided baseline bone marrow plasma cell percentage was $\geqslant$30% In addition to the above listed criteria, if present at baseline, a $\geqslant$50% reduction in the size of soft tissue plasmacytomas is also required
SD (not recommended for use as an indicator of response; stability of disease is best described by providing the time to progression estimates)	Not meeting criteria for CR, VGPR, PR or progressive disease

Abbreviations: CR, complete response; FLC, free light chain; PR, partial response; SD, stable disease; sCR, stringent complete response; VGPR, very good partial response.

[a]All response categories require two consecutive assessments made at anytime before the institution of any new therapy; all categories also require no known evidence of progressive or new bone lesions if radiographic studies were performed. Radiographic studies are not required to satisfy these response requirements.

[b]Confirmation with repeat bone marrow biopsy not needed.

[c]Presence/absence of clonal cells is based upon the k/λ ratio. An abnormal k/λ ratio by immunohistochemistry and/or immunofluorescence requires a minimum of 100 plasma cells for analysis. An abnormal ratio reflecting presence of an abnormal clone is k/λ of $>$4:1 or $<$1:2.

[d]Refer to Table 4 for definitions of measurable disease.

Durie, Leuk & Lymph 2006

blood

2010 115: 1343-1350
Prepublished online December 11, 2009;
doi:10.1182/blood-2009-08-239046

LEN - DEX

Lenalidomide plus dexamethasone versus thalidomide plus dexamethasone in newly diagnosed multiple myeloma: a comparative analysis of 411 patients

A

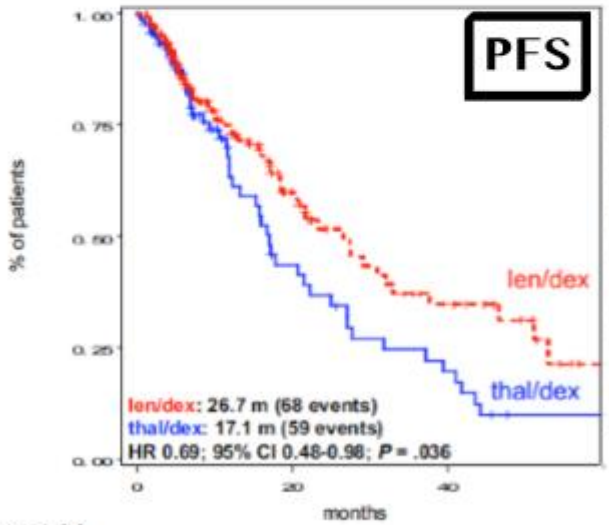


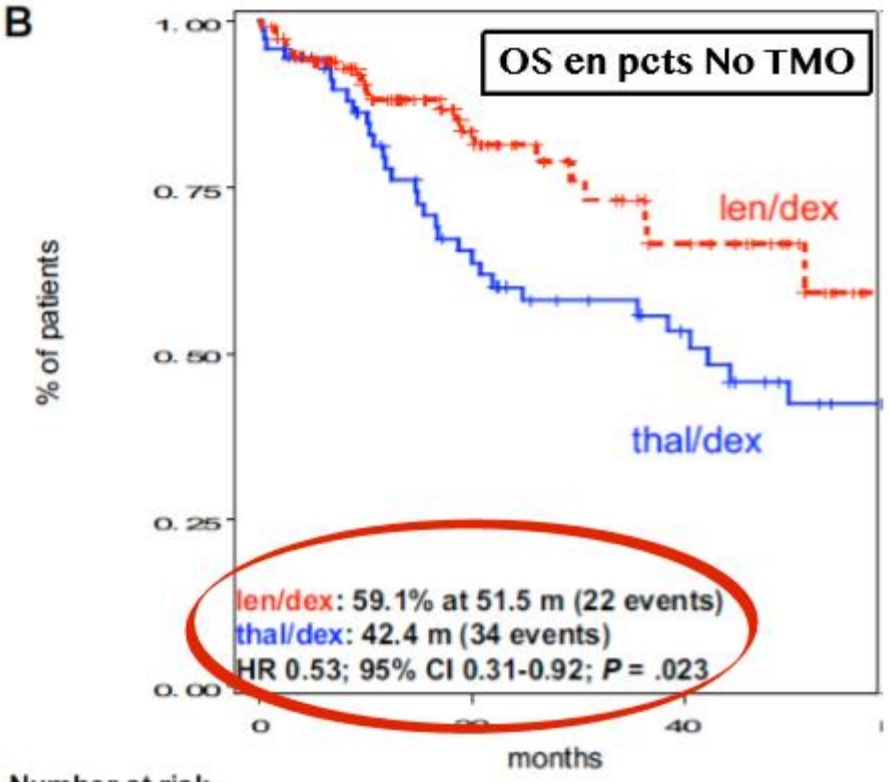
Table 3. Best responses to treatment

	All patients		
Response	thal/dex (n = 183), n (%)	len/dex (n = 228), n (%)	*P*
CR or VGPR	22 (12.0)	78 (34.2)	< .001
PR or better	112 (61.2)	183 (80.3)	< .001
CR	6 (3.3)	31 (13.6)	< .001
VGPR	16 (8.7)	47 (20.6)	< .001
PR	90 (49.2)	105 (46.1)	.528
SD	42 (22.9)	26 (11.4)	.002
PD	1 (0.6)	5 (2.2)	.232
NA	28 (15.3)	14 (6.1)	—

blood
2010 115: 1343-1350
Prepublished online December 11, 2009;
doi:10.1182/blood-2009-08-239046

LEN - DEX

Lenalidomide plus dexamethasone versus thalidomide plus dexamethasone in newly diagnosed multiple myeloma: a comparative analysis of 411 patients



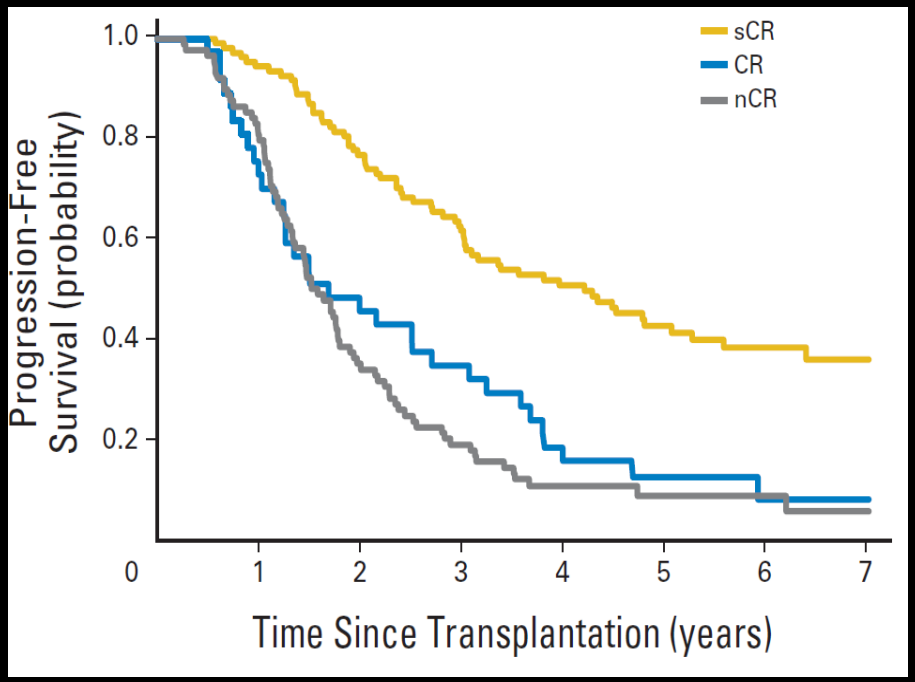
Conclusión

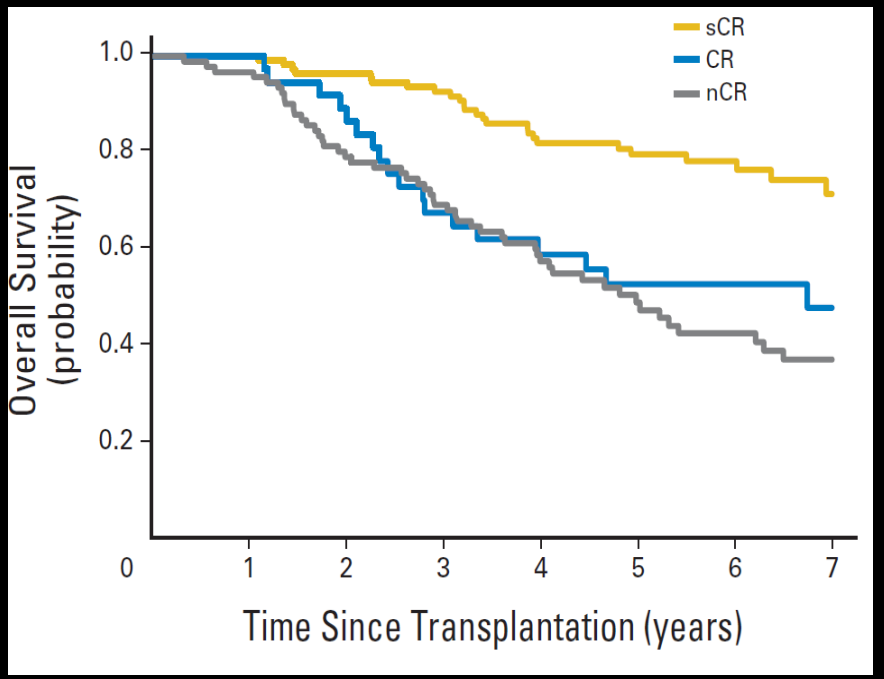
- Serie retrospectiva
- Dosis altas de Dexa en la mayoría

  (mejor >PR, menor OS)
- Len-Dex mejor

Importance of achieving stringent CR after ASCT in multiple myeloma

- Fully defined stringent CR using sFLC+IHC discriminates different outcomes among patients in CR



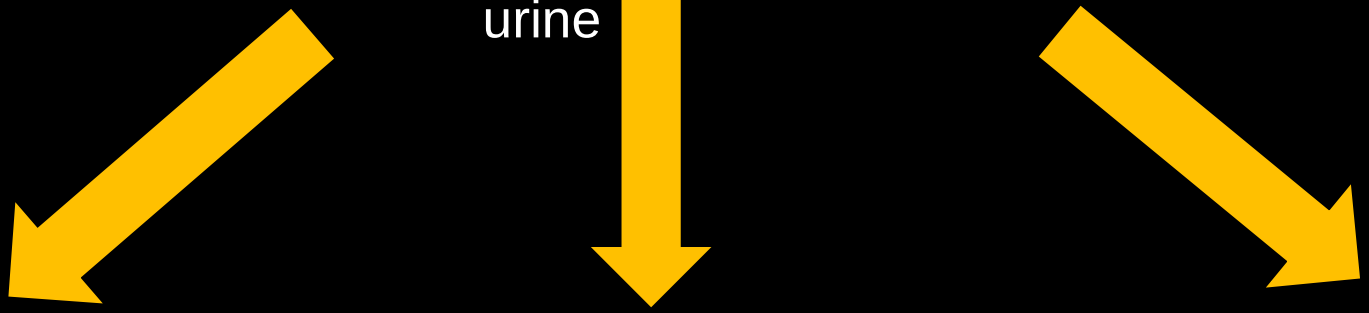


Re-defining the CR criteria in MM

< 5% PCs in bone marrow

Negative IFE of serum and urine

Disappearance of soft tissue plasmacytomas



Cellular clonality

- Immunohistochemistry
- Flow cytometry
- ASO-PCR
- NGS

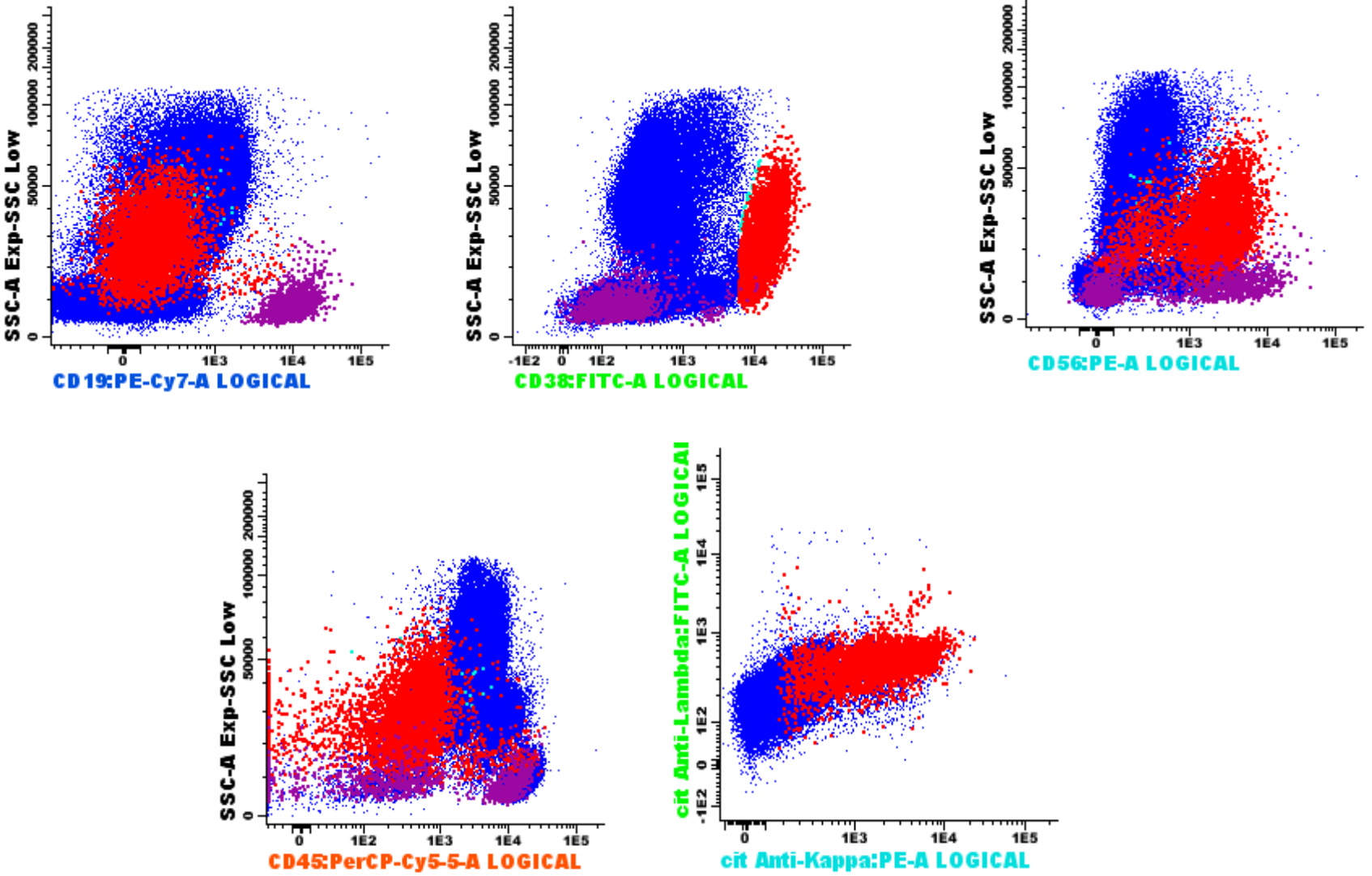
Cellular production

- sFLC
- Hevylite
- Isotype specific LC-MS/MS

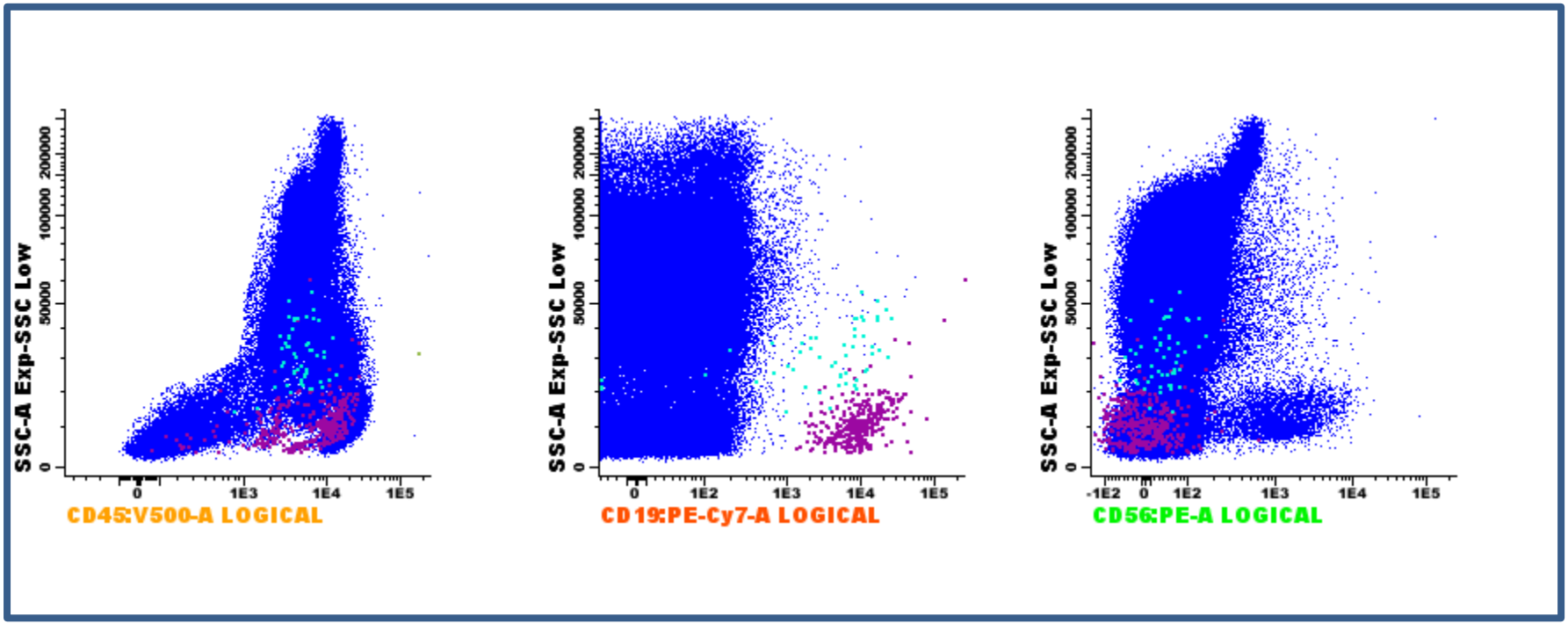
Cellular dissemination

- PET/CT
- WB-MRI

MM al Diagnóstico



EMR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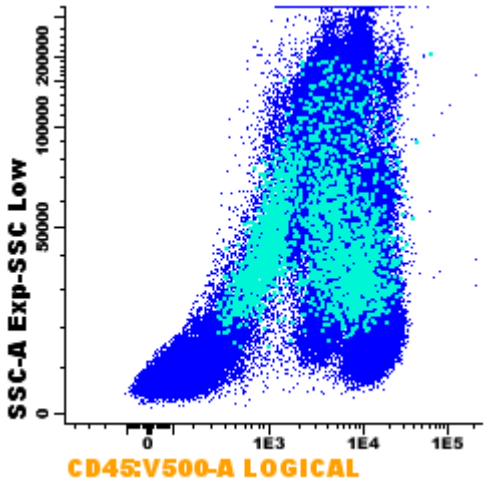
CD56:PE-A LOGICAL

MGUS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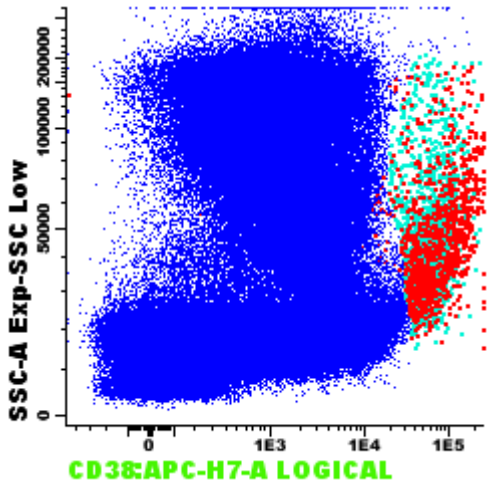
CD45:V500-A LOGICAL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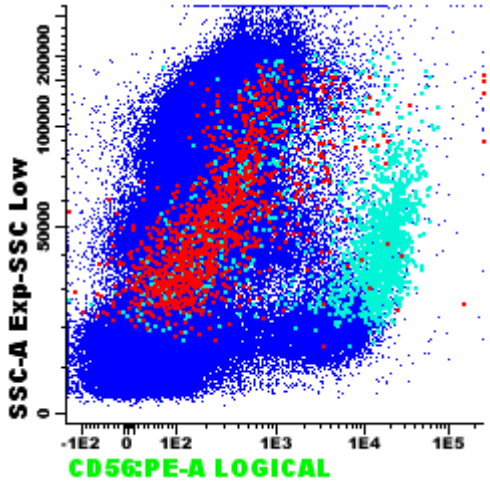
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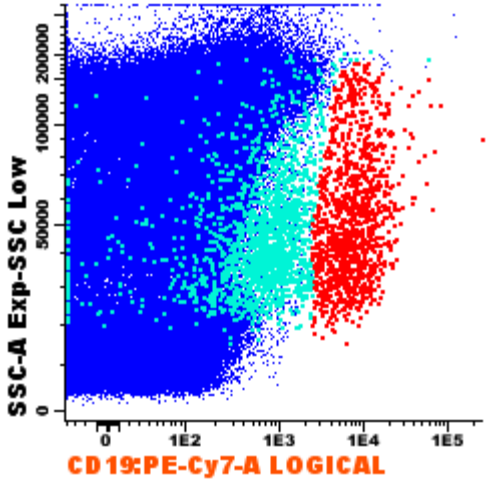
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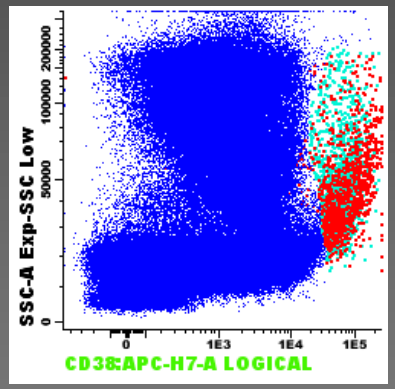
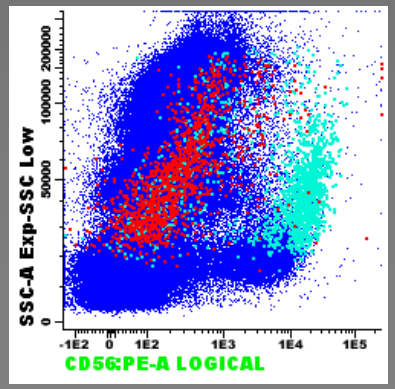
CD19:PE-Cy7-A LOGICAL

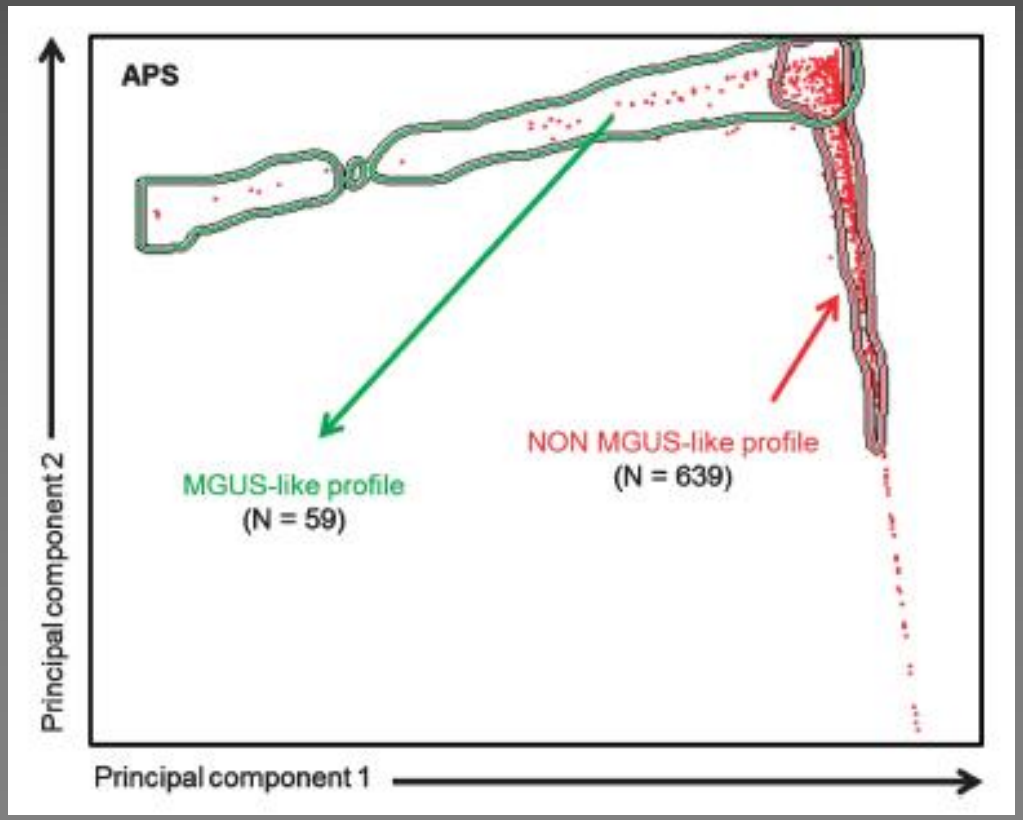
A multiparameter flow cytometry immunophenotypic algorithm for the identification of newly diagnosed symptomatic myeloma with an MGUS-like signature and long-term disease control

This article has been corrected since Advance Online Publication and a corrigendum is also printed in this issue

B Paiva[1,2], M-B Vídriales[1,2], L Rosiñol[3], J Martínez-López[4], M-V Mateos[1,2], EM Ocio[1,2], M-Á Montalbán[4], L Cordón[5], NC Gutiérrez[1,2], L Corchete[1,2], A Oriol[6], M-J Terol[7], M-A Echeveste[8], R De Paz[9], F De Arriba[10], L Palomera[11], J de la Rubia[5], J Díaz-Mediavilla[12], M Granell[13], A Gorosquieta[14], A Alegre[15], A Orfao[2,16], J-J Lahuerta[4], J Bladé[3] and JF San Miguel[1,2] on behalf of the GEM (Grupo Español de MM)/PETHEMA (Programa para el Estudio de la Terapéutica en Hemopatías Malignas) cooperative study group







MM tipo "MGUS": comportamiento post tto.

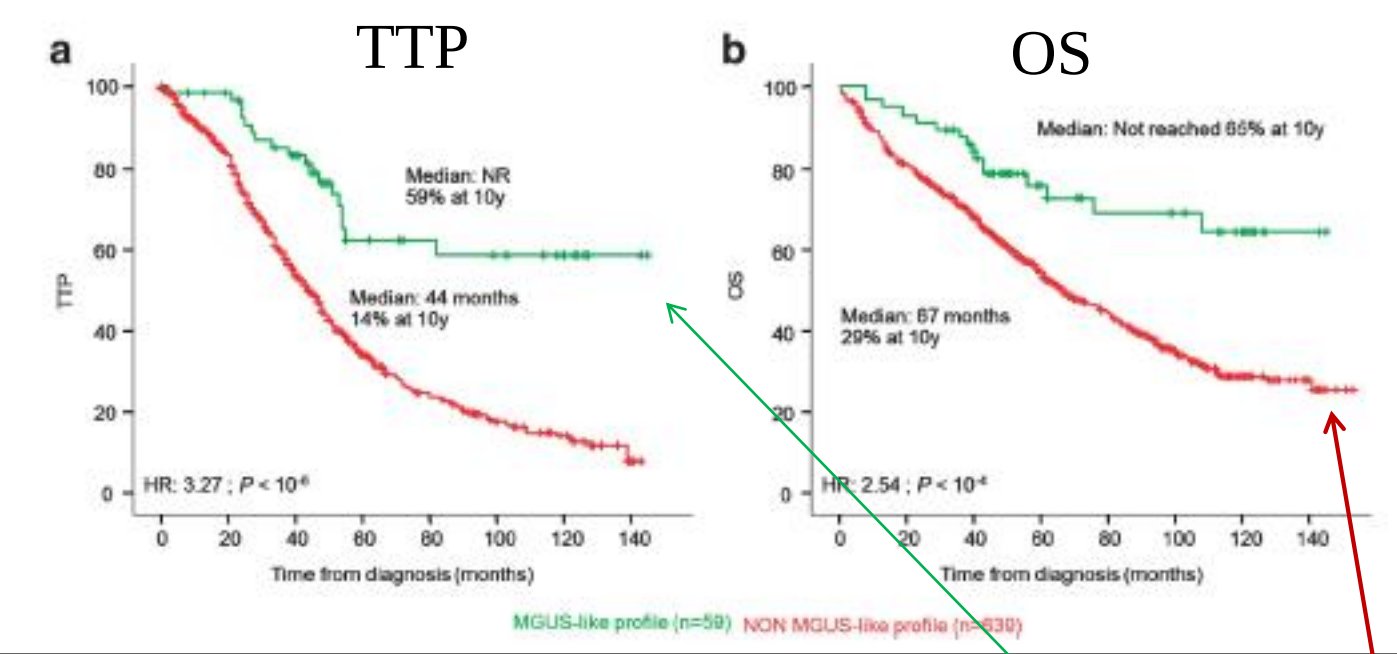
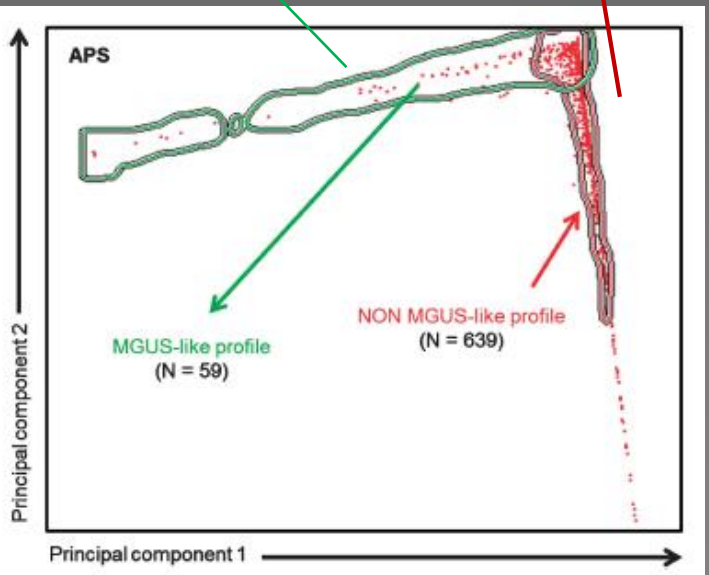
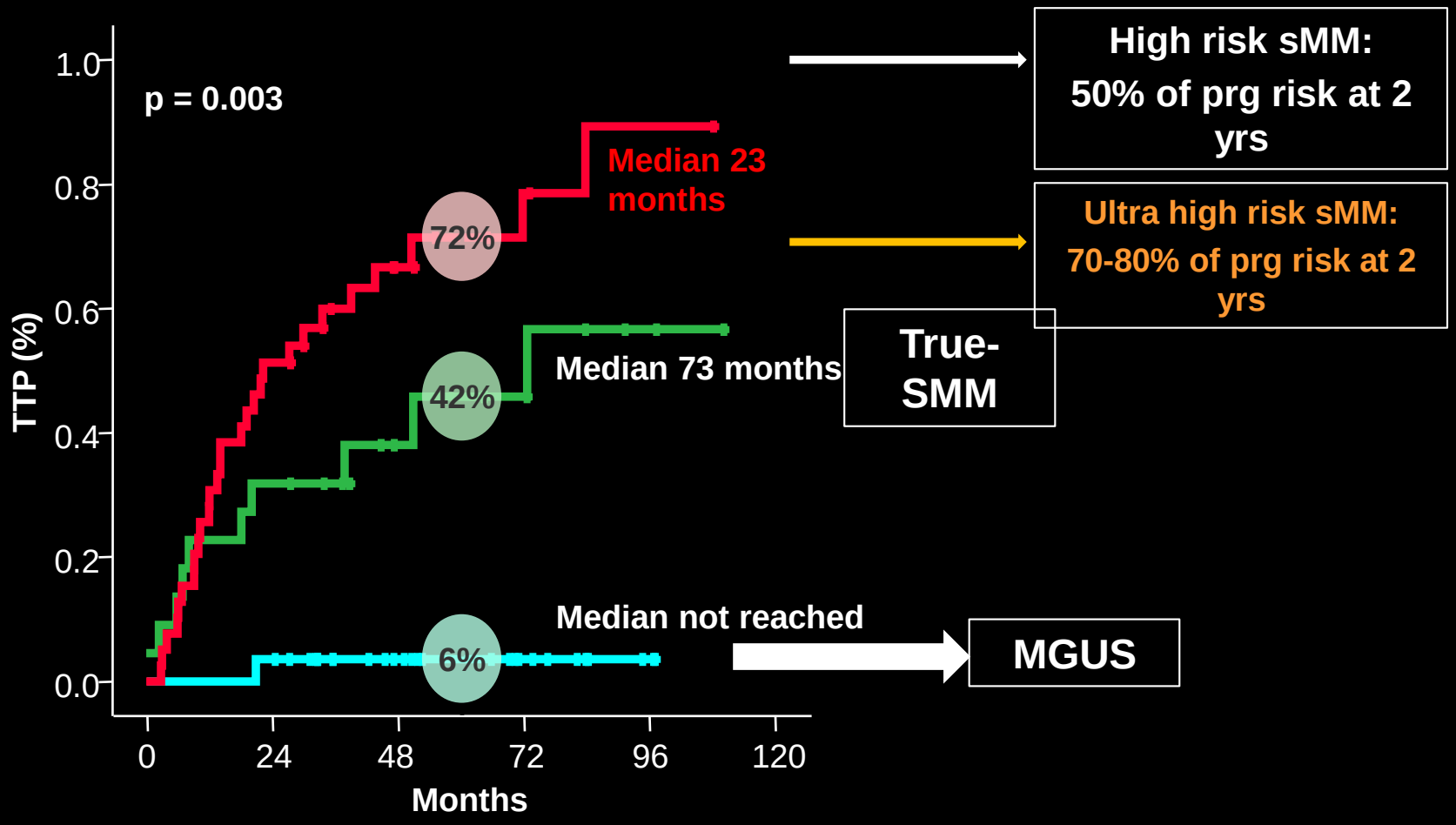


Table 2. Biological characteristics of clonal PCs in MM patients with an MGUS-like profile by computerized MFC immunophenotyping vs other symptomatic (non-MGUS-like) MM patients

Symptomatic MM	*MGUS-like*	*Non MGUS like*	*P-value*
[a]CD81 + expression on clonal PCs by MFC, %	20	51	0.06
Hyperdiploid DNA content, %	58	51	0.4
Plasma cells in S-phase, %	0.7	1.2	0.02
Cytogenetics, %			
IgH translocations	18	40	0.06
t(4;14)	0	11	0.1
t(11;14)	6	15	0.3
t(14;16)	0	4	0.4
other t(IgH)	12	10	0.8
del(13q)	6	45	0.002
del(17p)	6	7	0.9
[b]High-risk cytogenetics	6	20	0.2



Smouldering MM: Heterogeneous disease

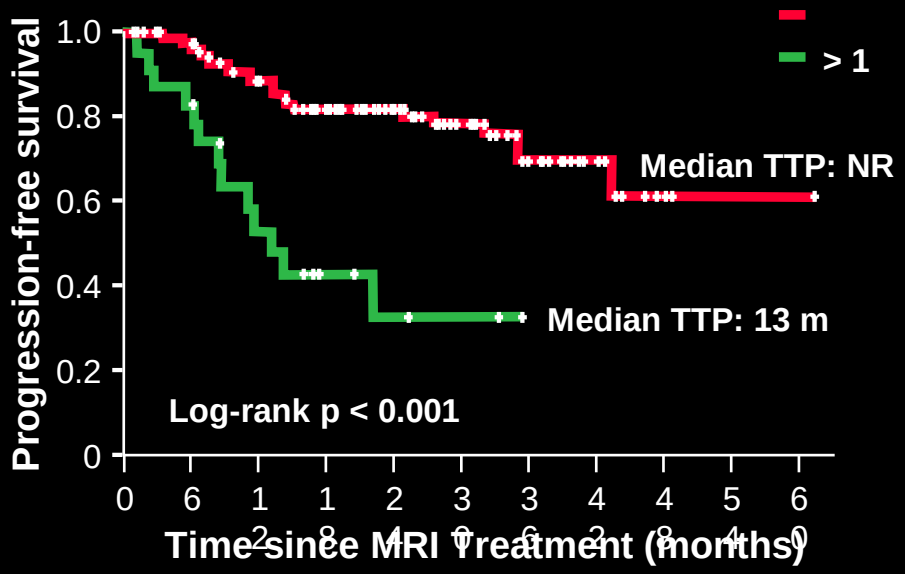


Is possible to identify this group of patients?

Smouldering Multiple Myeloma: Whole MRI

149 patients with asymptomatic MM

Whole MRI: 28% of pts: Focal lesions

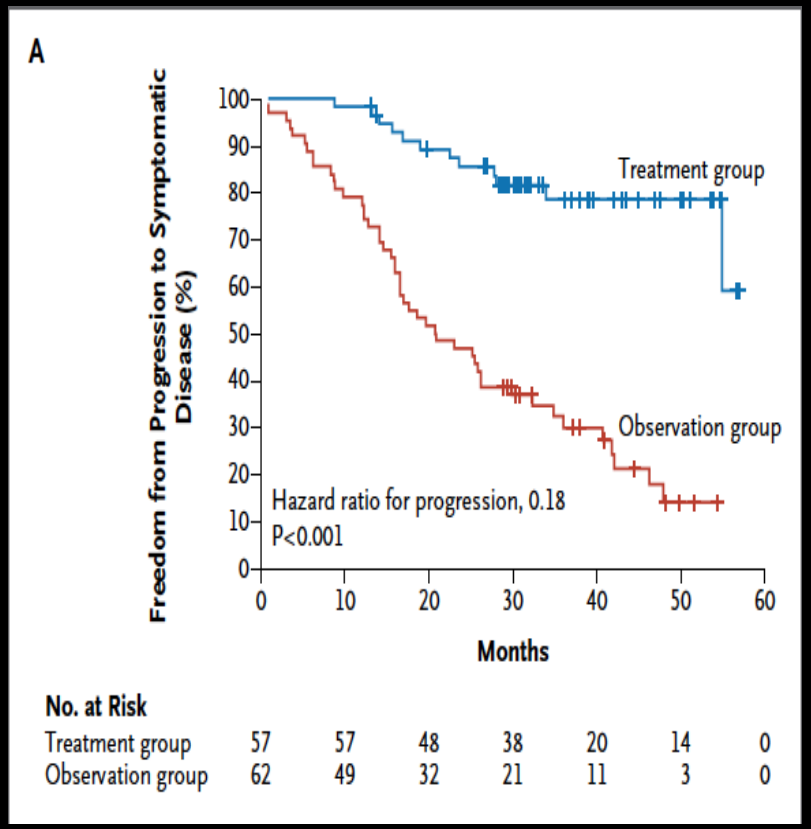


***> 1** Focal lesion plus diffuse pattern → adverse prognosis*

1. Hillengass J, et al. J Clin Oncol 2010;28:1606-1610
2. Kastritis E, et al. Leukemia. 2013 Apr;27(4):947-53

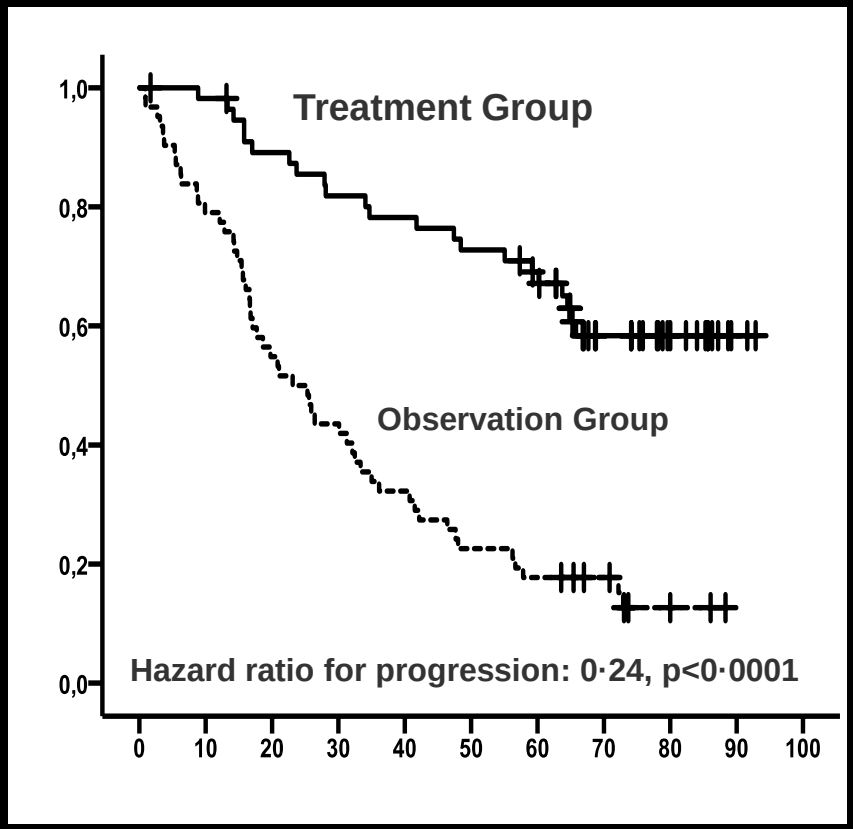
Len-dex vs no treatment: TTP to active disease
(n = 119)
Per-protocol Patients population

Median follow-up: 40 m



Mateos MV, et al. NEJM 2013

Median follow-up: 75 m



Mateos MV, et al. Lancet Oncology 2016: accepted for publication

Len-dex vs no treatment: TTP to active disease
(n = 119)
Per-protocol Patients population

Median follow-up: 40 m ***Median follow-up: 75 m***

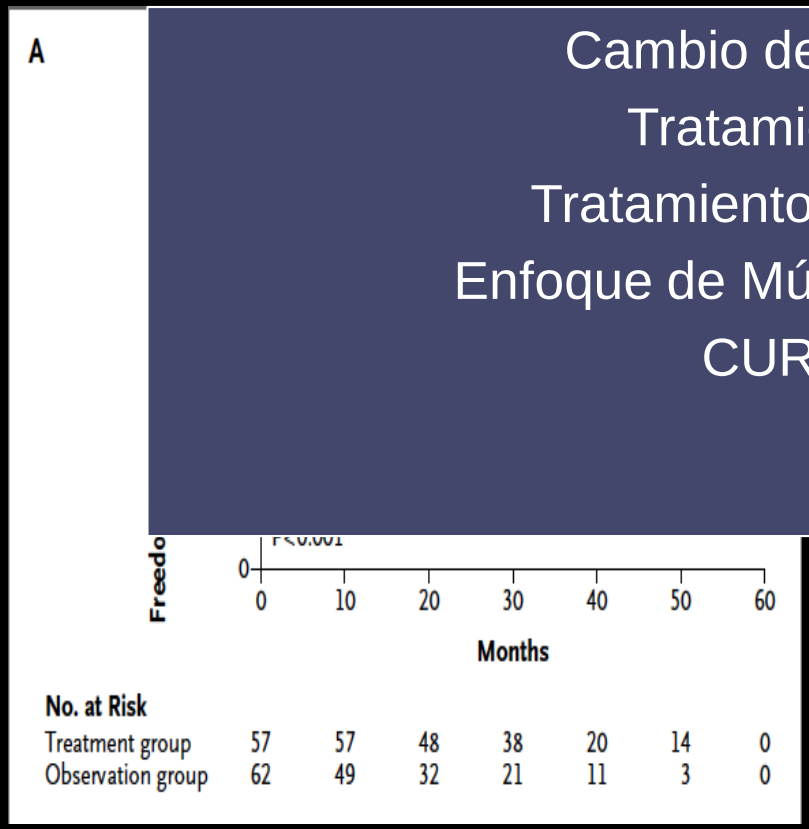
Cambio de Paradigmas?

Tratamiento Precóz

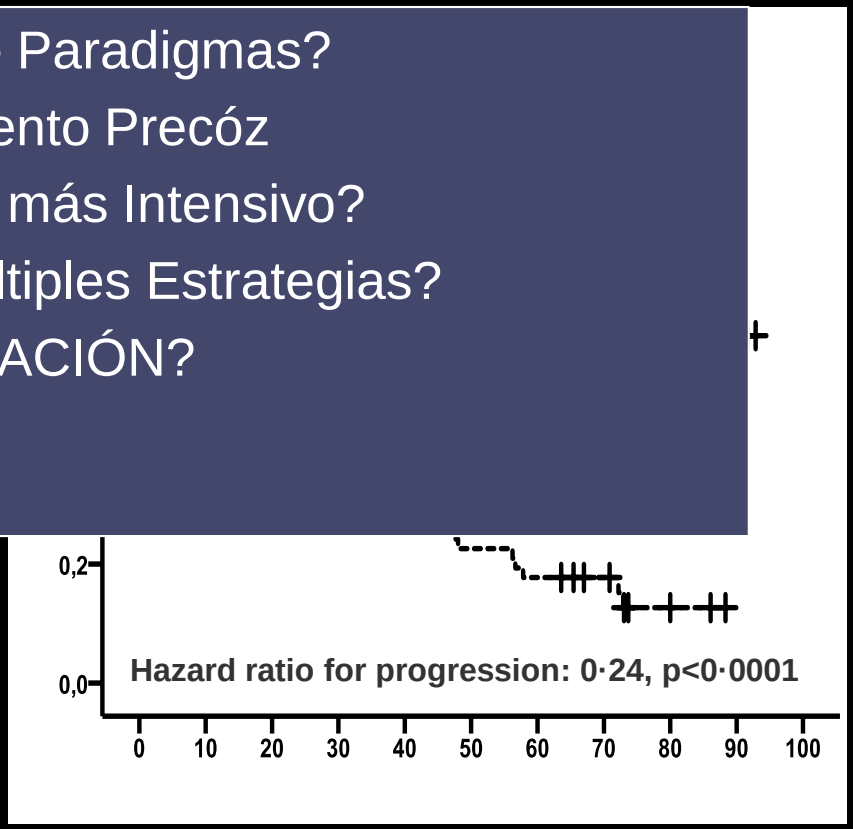
Tratamiento más Intensivo?

Enfoque de Múltiples Estrategias?

CURACIÓN?



Mateos MV, et al. NEJM 2013



Mateos MV, et al. Lancet Oncology 2016: accepted for publication