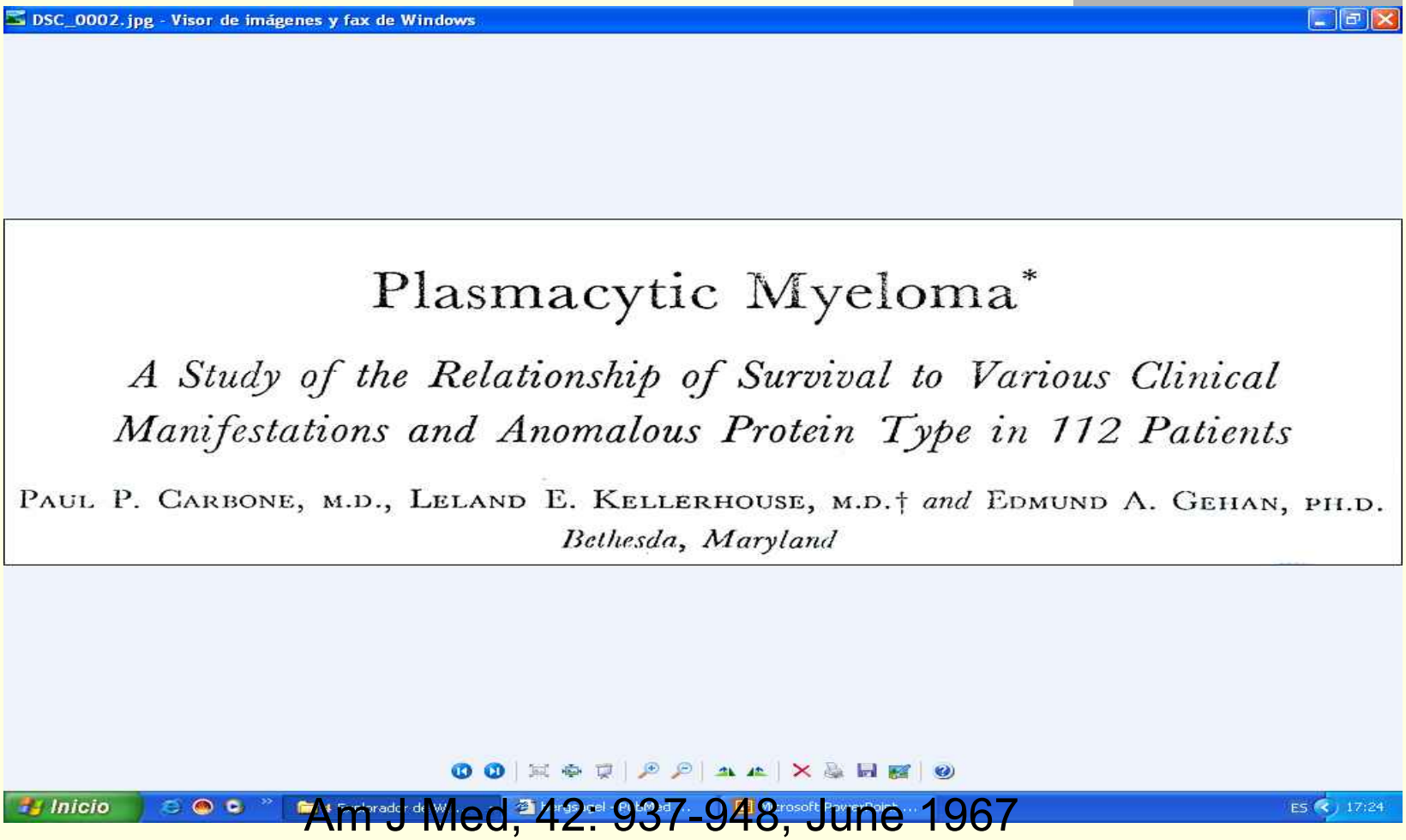
Which are the relevant prognostic factors in the current management of multiple myeloma with novel agents?

Joan Bladé

Athens Conference on Plasma Cell Dyscrasias

Athens, September 2009



Am J Med, 42: 937-948, June 1967

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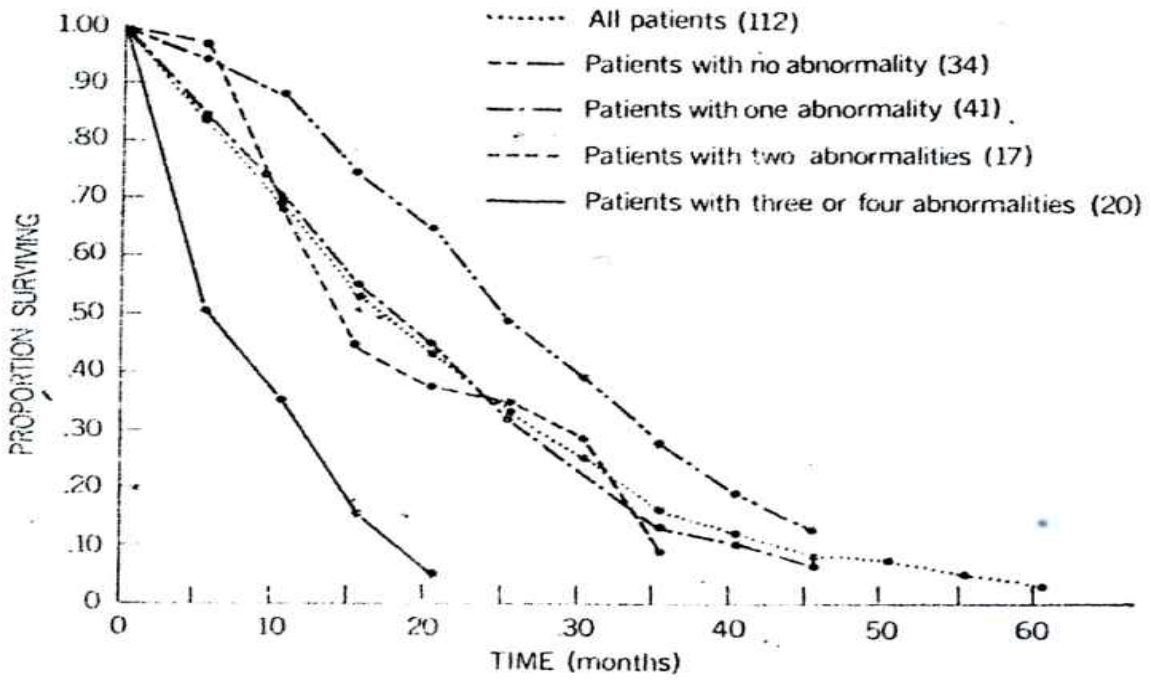

FIG. 2. Survival curves for patients with plasmacytic myeloma.

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Microsoft Po...
ES
17:19

Prognostic Factors in MM

- Prognostic value…
- A new prognostic factor…
- A simple reliable marker…
- An easily available parameter…
- An independent prognostic factor…
- A new staging system…
- Proposal for a novel prognostic index…

Prognostic Factors in MM

- Clinical and laboratory features
- Staging systems
- Malignant clone: molecular genetic status
- Response to therapy
- Mechanisms of disease control/progression

Prognostic Factors in MM
Clinical and Laboratory Features

- Host characteristics
  - Age
  - PS
- Tumor burden
  - β_2-microglobulin
- Organ damage
  - Renal function
  - Hb

Main Staging Systems in MM

Author, year	Parameters	Other
Durie and Salmon, 1975	Hb, Ca, M-protein, bone lesions	Renal function
Merlini et al, 1980	%PC, Cr, and Ca (IgG) Hb, Ca, M-protein (IgA)	
MRC, 1980	Hb, urea, PS	
Cavo et al, 1989	D & S, platelet count	
Greipp et al, 1988	β2-microglobulin, LI	
Bladé et al, 1989	Albumin, urea	
San Miguel et al, 1989	Hb, Cr, PS, PI	
San Miguel et al, 1995	S-phase, β2-microglobulin, age, PS	
IMWG, 2005	**β2-microglobulin, albumin**	

MRC: Medical Research Council; IMWG: International Myeloma Working Group; Hb: haemoglobin; Ca: calcium; PC: plasma cells; Cr: creatinine; Ig: Immunoglobulin; PS: performance status; LI: labelling index; PI: paraprotein index.

International Prognostic System (IPS)

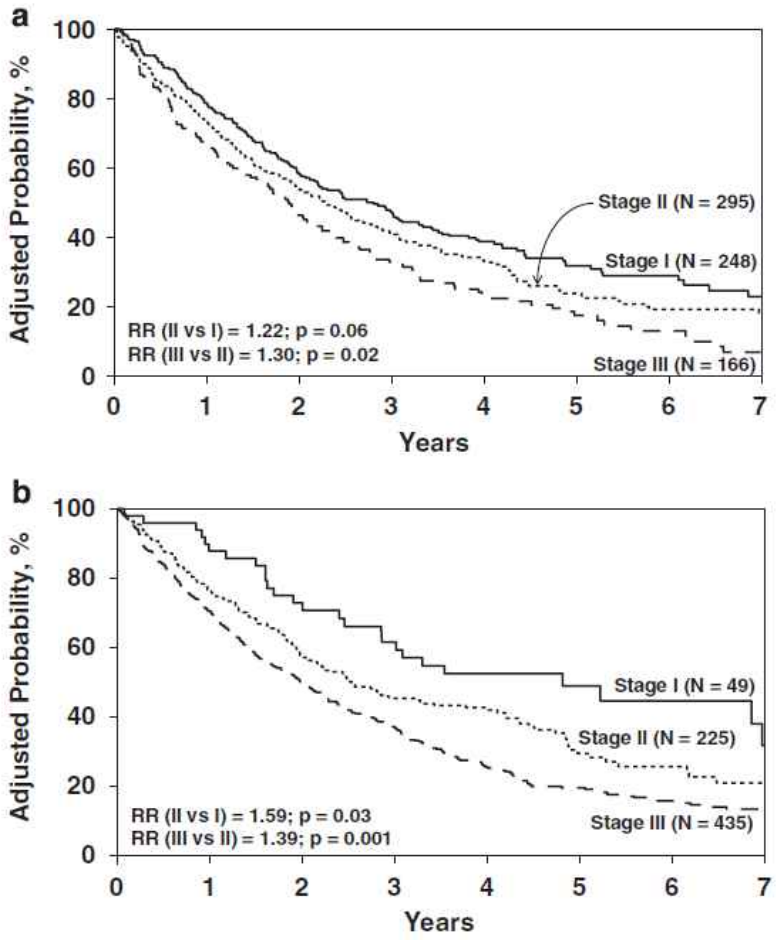
Stage		Overall Survival (months)
I	β-2M < 3.5 mg/L and albumin ≥ 3.5 g/dL	62
II	β-2M < 3.5 mg/L and albumin < 3.5 g/dL or β-2-m 3.5 – 5.4 mg/L	44
III	β-2M ≥ 5.5 mg/L	29

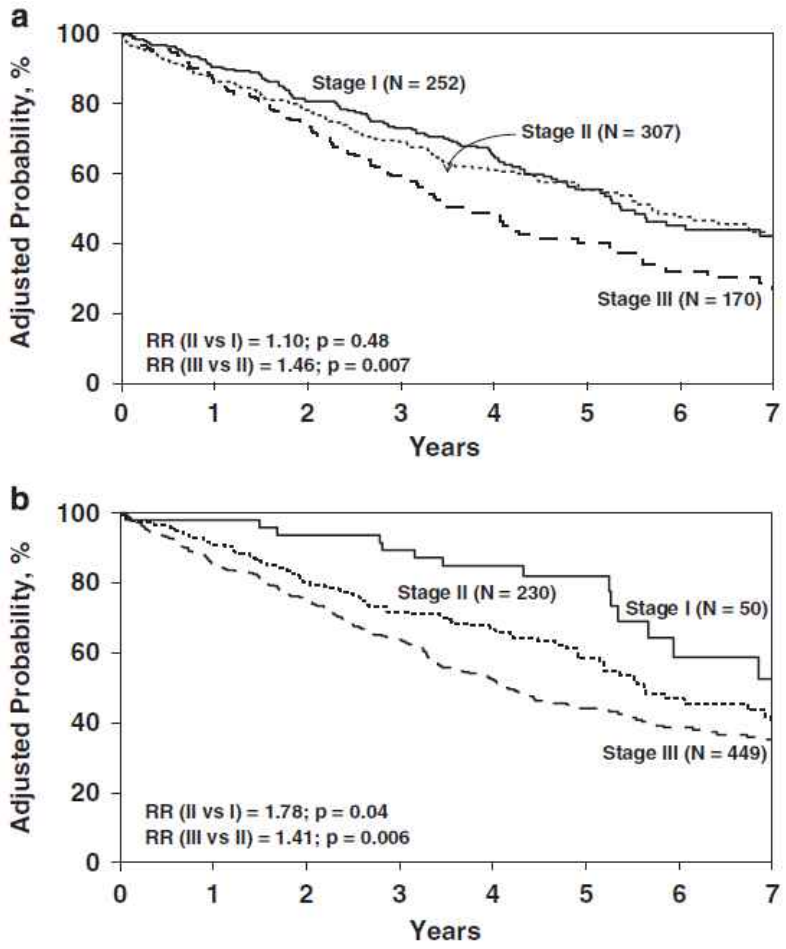
Greipp P et al. J Clin Oncol 2005; 23: 3412-20.

Is the ISS Superior to the Durie & Salmon SS?

- CIBMTR results in 729 patients who underwent up-front ASCT

Hari PN, *et al*. Leukemia 2009;23:1528-1534.


a
Adjusted Probability, %
100
80
60
40
20
0
0
1
2
3
4
5
6
7
Years
Stage II (N = 295)
Stage I (N = 248)
Stage III (N = 166)
RR (II vs I) = 1.22; p = 0.06
RR (III vs II) = 1.30; p = 0.02
b
Adjusted Probability, %
100
80
60
40
20
0
0
1
2
3
4
5
6
7
Years
Stage I (N = 49)
Stage II (N = 225)
Stage III (N = 435)
RR (II vs I) = 1.59; p = 0.03
RR (III vs II) = 1.39; p = 0.001


a
Adjusted Probability, %
100
80
60
40
20
0
Stage I (N = 252)
Stage II (N = 307)
Stage III (N = 170)
RR (II vs I) = 1.10; p = 0.48
RR (III vs II) = 1.46; p = 0.007
0
1
2
3
4
5
6
7
Years
b
Adjusted Probability, %
100
80
60
40
20
0
Stage II (N = 230)
Stage I (N = 50)
Stage III (N = 449)
RR (II vs I) = 1.78; p = 0.04
RR (III vs II) = 1.41; p = 0.006
0
1
2
3
4
5
6
7
Years

ISS versus Durie & Salmon SS

- Durie & Salmon superior when adjusting with Brier Score

- Neither staging system strongly predictive of outcomes

⇓

Need for incorporation other prognostic markers (cytogenetics, GEP, imaging-MRI/PET)

Hari PN, *et al*. Leukemia 2009; 23: 1528-1534

Cytogenetic Prognostic Subgroups in Multiple Myeloma

- Good/average prognosis
  - Hyperdiploidy
  - t(11;14)(q32;q32): cyclin D1 upregulation
- Bad prognosis
  - Hypodiploidy
  - t(4;14)(p16.3;q32): FGFR3&MMSET upregulation
  - t(14;16)(q32;q23): c-MAF upregulation
  - Chromosome 1 abnormalities: 1q gains (overexpression CKS1B)
  - 17q deletions, 13q deletions

13q Deletion as Single Abnormality

- No independent prognostic impact*

* Gutiérrez N et al. Leukemia 2007; 21: 541-9.

* Avet-Loiseau H et al. Blood 2007; 109: 3489-95.

Molecular Myeloma Subgroups
Gene Expression Profiling

- "**T**ranslocation/**C**yclin D" classification*:
  - 8 groups
- Recurrent translocations/hyperdiploidy**:
  - 7 entities

* Bergsagel PL et al. Blood 2005; 106: 296-303.

** Zhan F et al. Blood 2006; 108: 2020-8.

High-resolution Genomic Profiles*
(aCGH/mRNA microarray/FISH/novel bioinformatics)

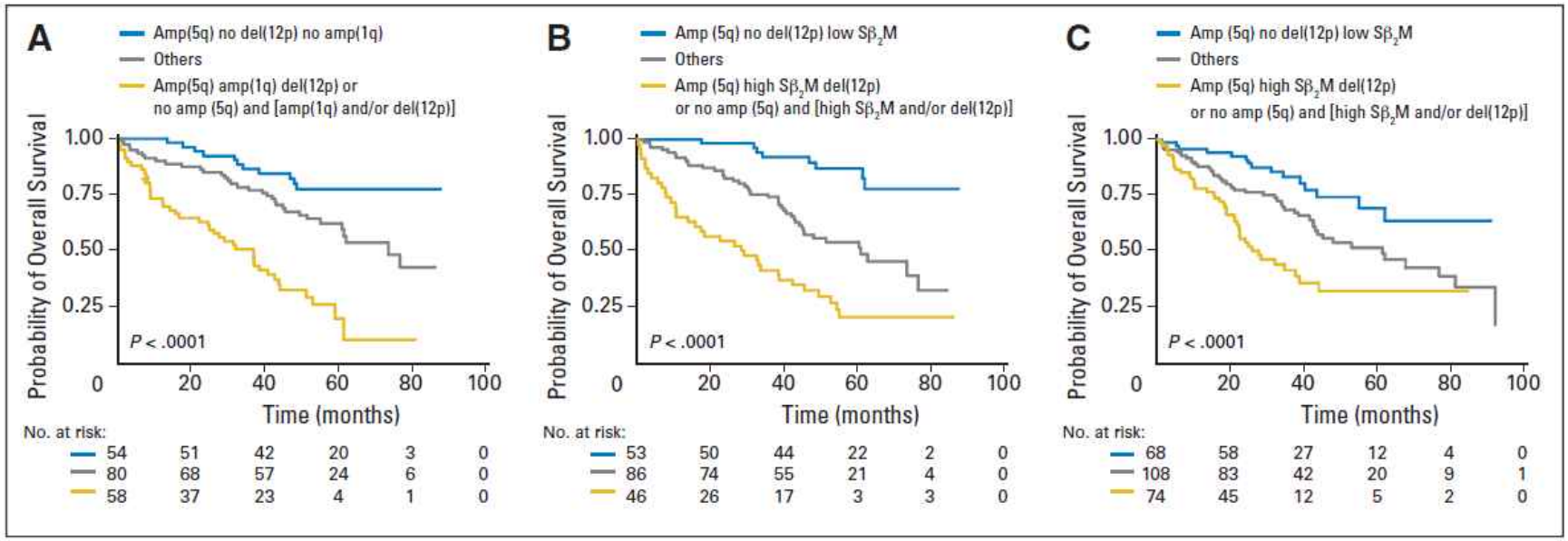
- 4 different MM subtypes
  (recurrent DNA copy number changes), i.e.:
  - Hyperdiploid, 11q gains: good outcome
  - Hyperdiploid, 1q gains and/or 13 losses: poor outcome

* Carrasco R et al. Cancer Cell 2006; 4: 313-25.

High-resolution DNA copy number changes (SNP-based mapping array technology)

	HR	p
Del (12p13.31)	3.17	<0.0001
sβ2M≥5 mg/L	2.78	<0.0001
Amp (5q31.3)	0.37	0.0005

Avet-Loisseau H, *et al*. J Clin Oncol 2009 (Published ahead of print, August 17, 2009)


A
Amp(5q) no del(12p) no amp(1q)
Others
Amp(5q) amp(1q) del(12p) or
no amp (5q) and [amp(1q) and/or del(12p)]
Probability of Overall Survival
1.00
0.75
0.50
0.25
0
P < .0001
0
20
40
60
80
100
Time (months)
No. at risk:
54 51 42 20 3 0
80 68 57 24 6 0
58 37 23 4 1 0
B
Amp (5q) no del(12p) low Sβ2M
Others
Amp (5q) high Sβ2M del(12p)
or no amp (5q) and [high Sβ2M and/or del(12p)]
Probability of Overall Survival
1.00
0.75
0.50
0.25
0
P < .0001
0
20
40
60
80
100
Time (months)
No. at risk:
53 50 44 22 2 0
86 74 55 21 4 0
46 26 17 3 3 0
C
Amp (5q) no del(12p) low Sβ2M
Others
Amp (5q) high Sβ2M del(12p)
or no amp (5q) and [high Sβ2M and/or del(12p)]
Probability of Overall Survival
1.00
0.75
0.50
0.25
0
P < .0001
0
20
40
60
80
100
Time (months)
No. at risk:
68 58 27 12 4 0
108 83 42 20 9 1
74 45 12 5 2 0

High-resolution DNA copy number changes (SNP-based mapping array technology)

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Avet-Loisseau H, *et al*. J Clin Oncol 2009 (Published ahead of print, August 17, 2009)

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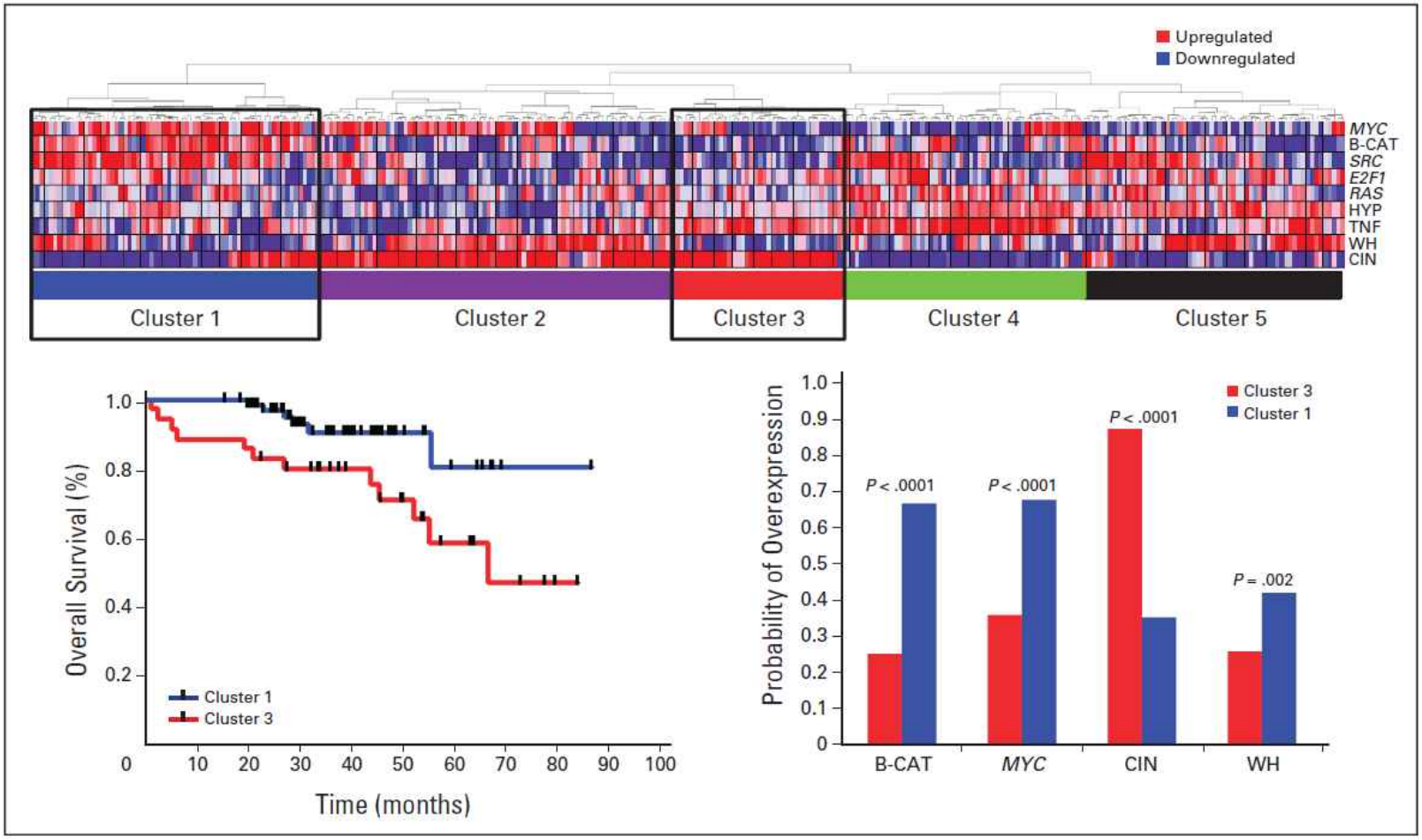
JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Gene Expression Profiles of Tumor Biology Provide a Novel Approach to Prognosis and May Guide the Selection of Therapeutic Targets in Multiple Myeloma

Ariel Anguiano, Sascha A. Tuchman, Chaitanya Acharya, Kelly Salter, Cristina Gasparetto, Fenghuang Zhan, Madhav Dhodapkar, Joseph Nevins, Bart Barlogie, John D. Shaughnessy Jr, and Anil Potti

- GEP of tumor biology / chemotherapy sensitivity can refine the ISS classification


Upregulated
Downregulated
MYC
B-CAT
SRC
E2F1
RAS
HYP
TNF
WH
CIN
Cluster 1
Cluster 2
Cluster 3
Cluster 4
Cluster 5
Overall Survival (%)
1.0
0.8
0.6
0.4
0.2
0
10
20
30
40
50
60
70
80
90
100
Time (months)
Cluster 1
Cluster 3
Probability of Overexpression
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
Cluster 3
Cluster 1
P < .0001
P < .0001
P < .0001
P = .002
B-CAT
MYC
CIN
WH

Response to Therapy as Prognostic Factor

- Stabilization of disease
- Impact of CR
  - With primary therapy
  - After HDT/SCT

Imaging Techniques with Prognostic Interest

- MRI: number of focal lesions (FL)
- FDG-PET/CT:
  - FDG suppression (SUV-FL) prior ASCT
  - Metastatic spread (EMD)

Walker R, *et al*. J Clin Oncol 2007; 25:1121-1128
Bartel TB, *et al*. Blood 2009 (prepublished online, May 14)

Novel Drugs and New Molecular Targets

- Novel drugs can overcome drug resistance in poor cytogenetic subgroups
- New therapies should target specific molecular pathways

Therapy Against Cancer "Myeloma" Stem Cell

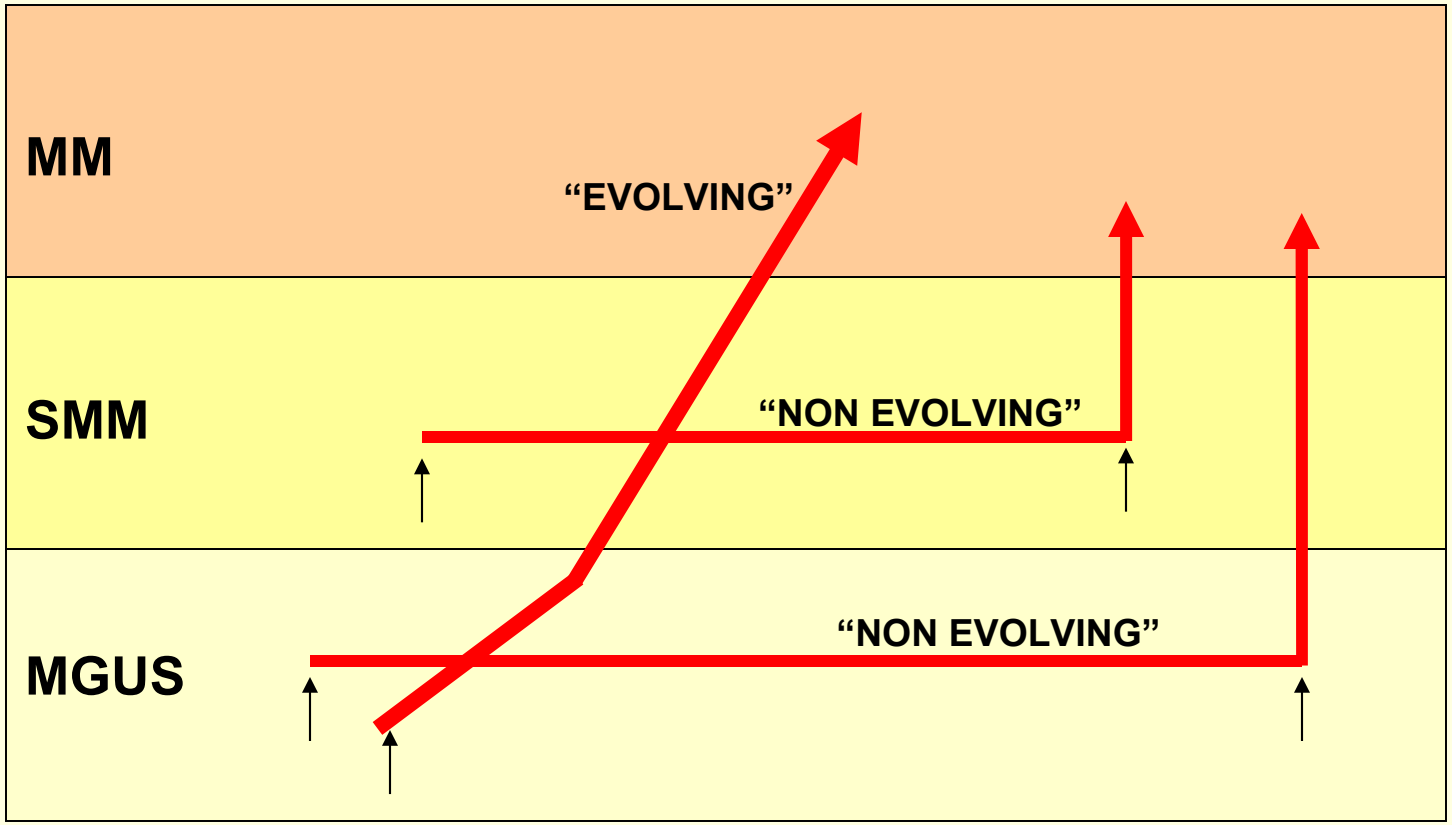
- Plasma cell killing

  → lowest possible tumor mass

- Meaning of CR achieved with novel therapies

- Different effect of old and new drugs on the **bulk of differentiated plasma cells** versus the **myeloma stem cell**?

Monoclonal Gammopathies



Rosiñol et al. Br J Haematol 2003; 123: 631-36.

Rosiñol et al. Mayo Clin Proc 2007; 82: 428-34.

Possible Impact of Influencing on Mechanisms of Disease Progression

- Evolving MGUS $\Rightarrow$ early/slowly evolving myeloma (escaping growth-restraining mechanisms)

- Avoid disease progression after decreasing tumor mass $\Rightarrow$ MGUS state (growth-restraining influences)

When Is a “Prognostic Factor” Really Prognostic?

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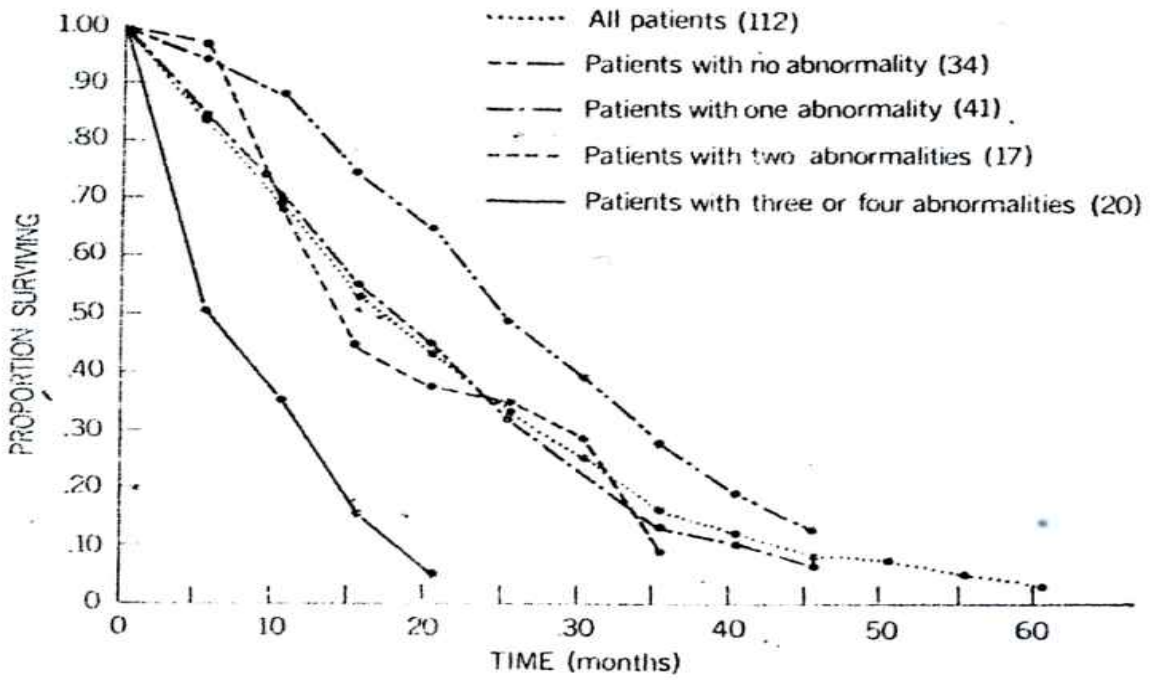

FIG. 2. Survival curves for patients with plasmacytic myeloma.

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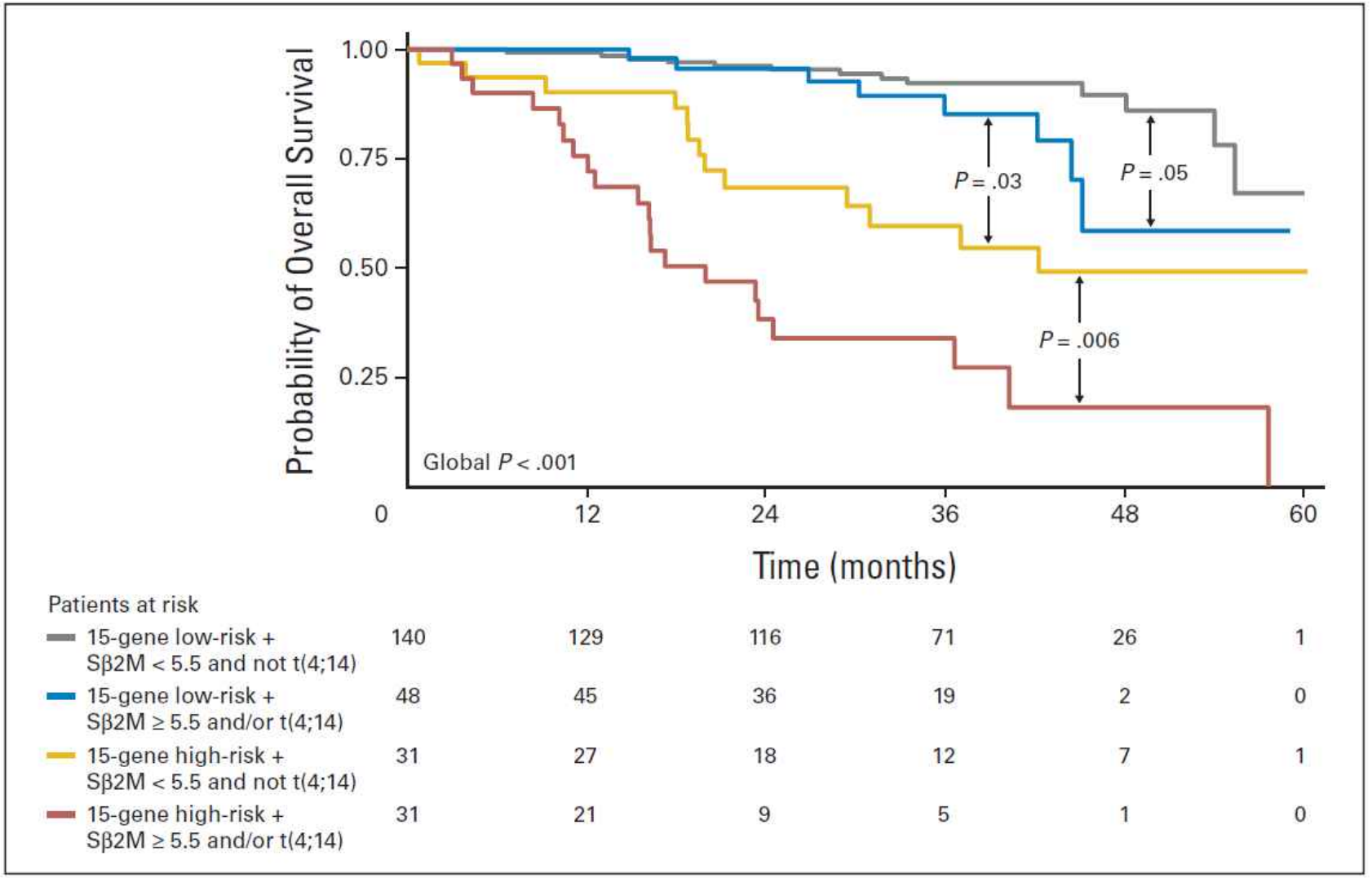

Patients at risk						
15-gene low-risk + Sβ2M < 5.5 and not t(4;14)	140	129	116	71	26	1
15-gene low-risk + Sβ2M ≥ 5.5 and/or t(4;14)	48	45	36	19	2	0
15-gene high-risk + Sβ2M < 5.5 and not t(4;14)	31	27	18	12	7	1
15-gene high-risk + Sβ2M ≥ 5.5 and/or t(4;14)	31	21	9	5	1	0