Evolution of Myeloma

Myeloma Crowd Round Table

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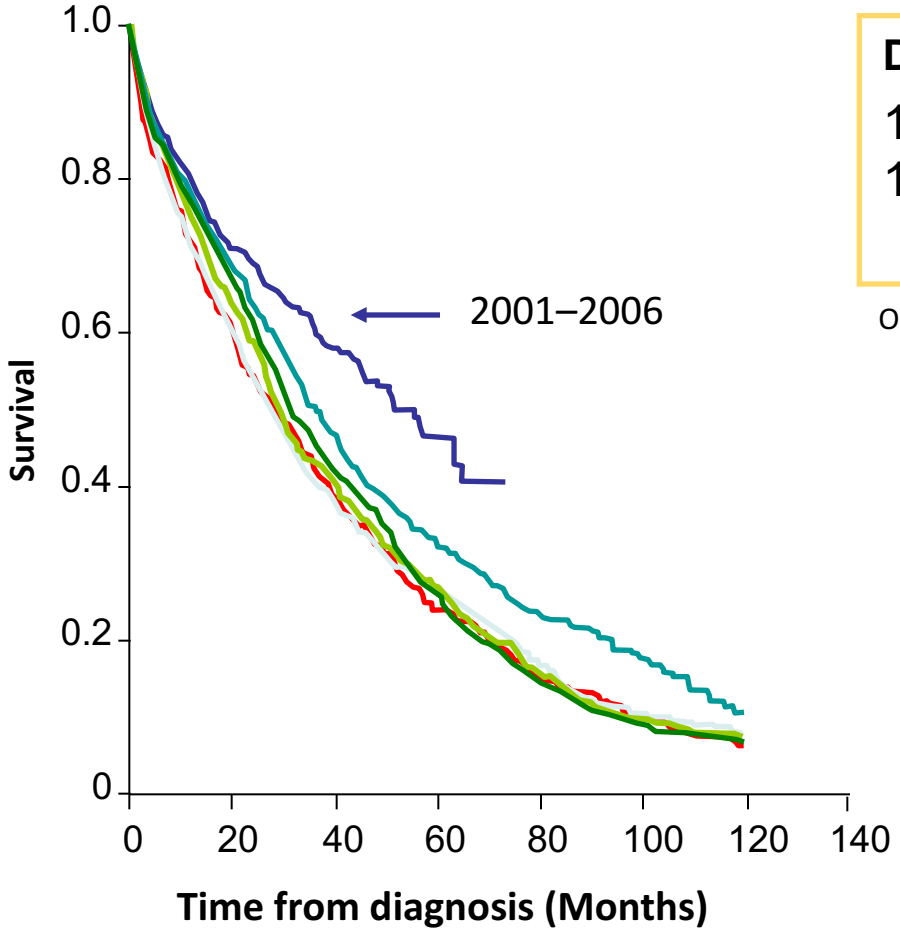
Trends in Overall Survival of MM

Overall survival 1971–2006



Diagnosis period	Median OS
1996–2006	45 months
1971–1996	30 months (P<0.001)

OS, overall survival.

1971–1976
1977–1982
1983–1988
1989–1994
1995–2000
2001–2006

Kumar SK, et al. *Blood*. 2008;111:2516-2520.

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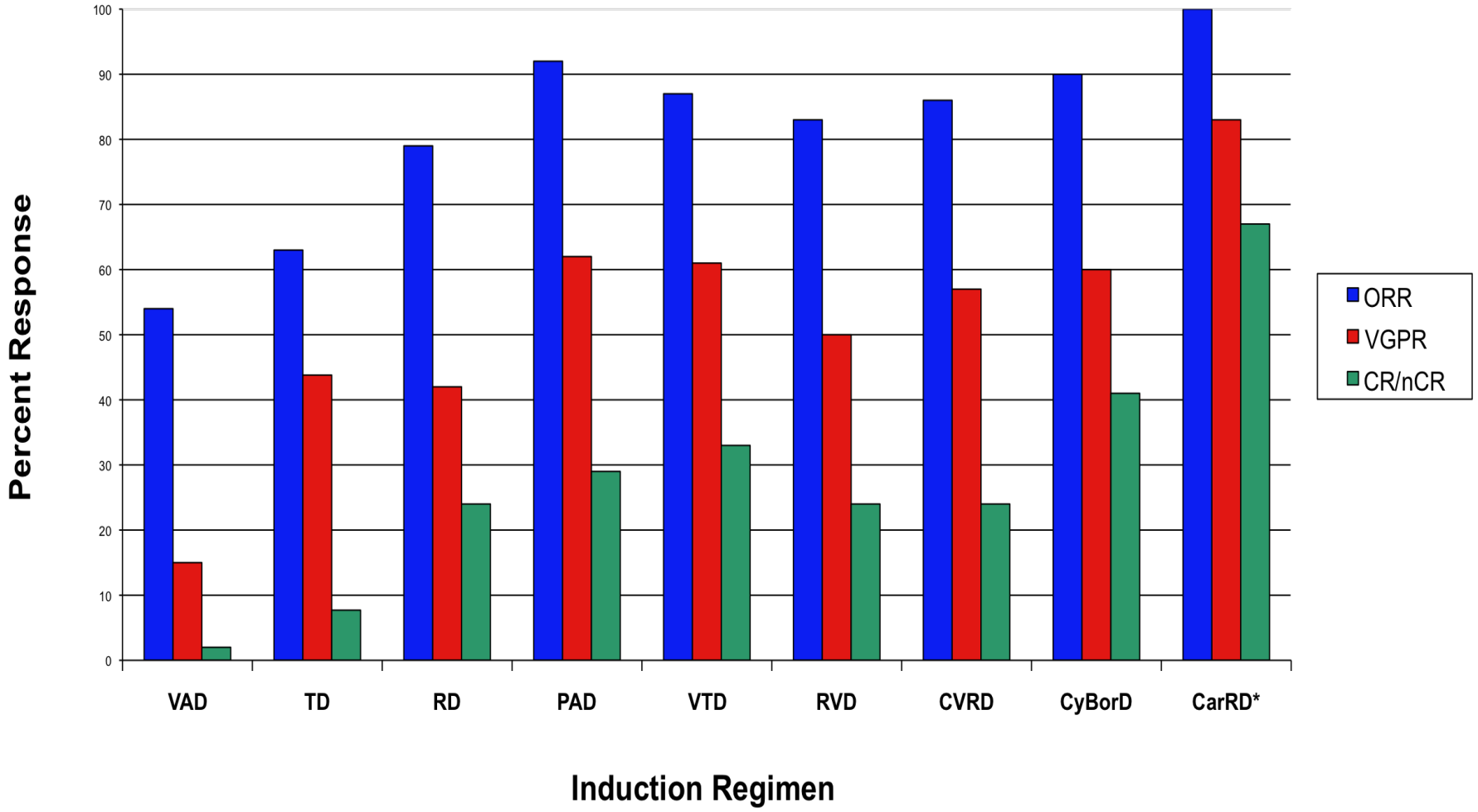
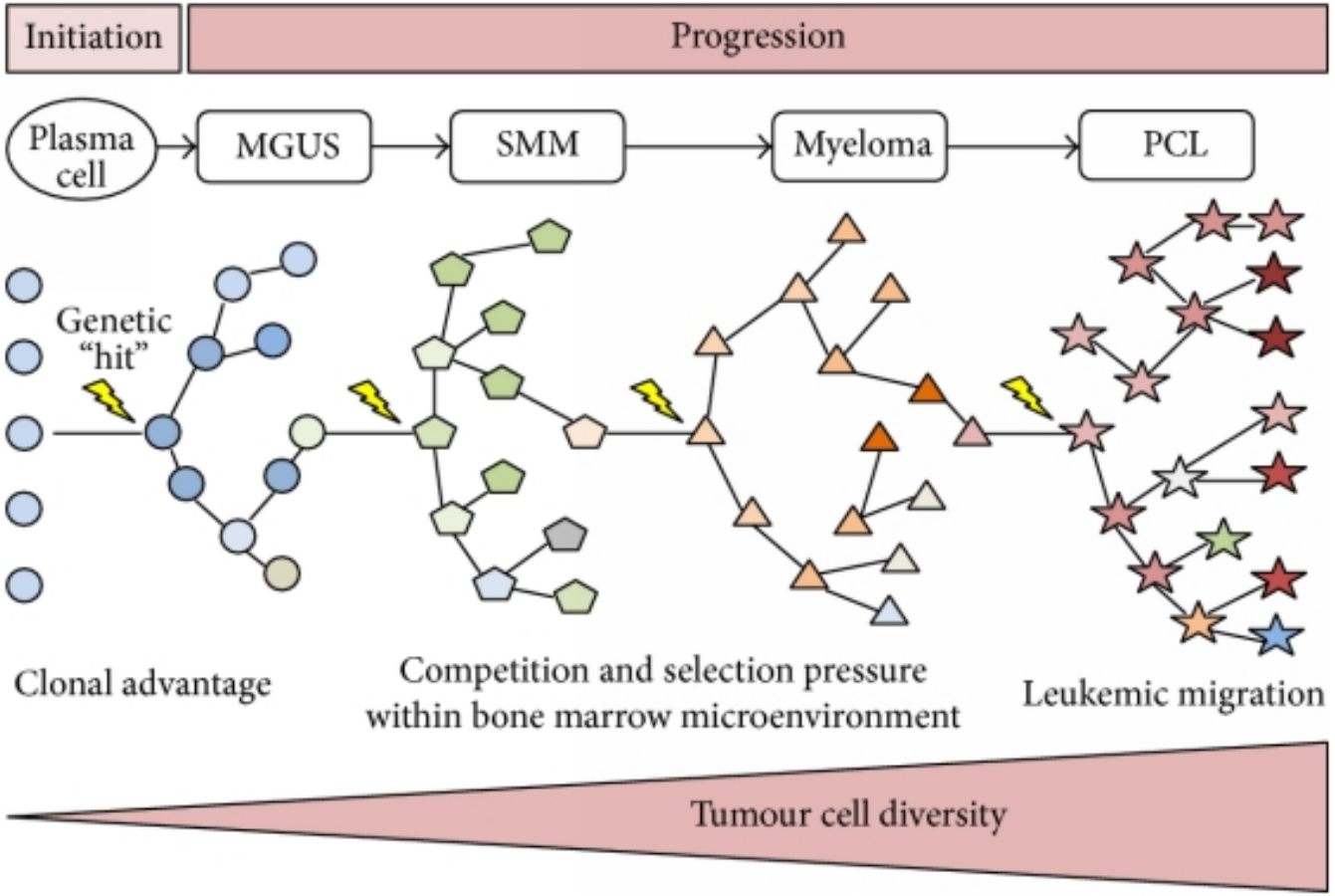
Improving Response Rates with Combination Therapies



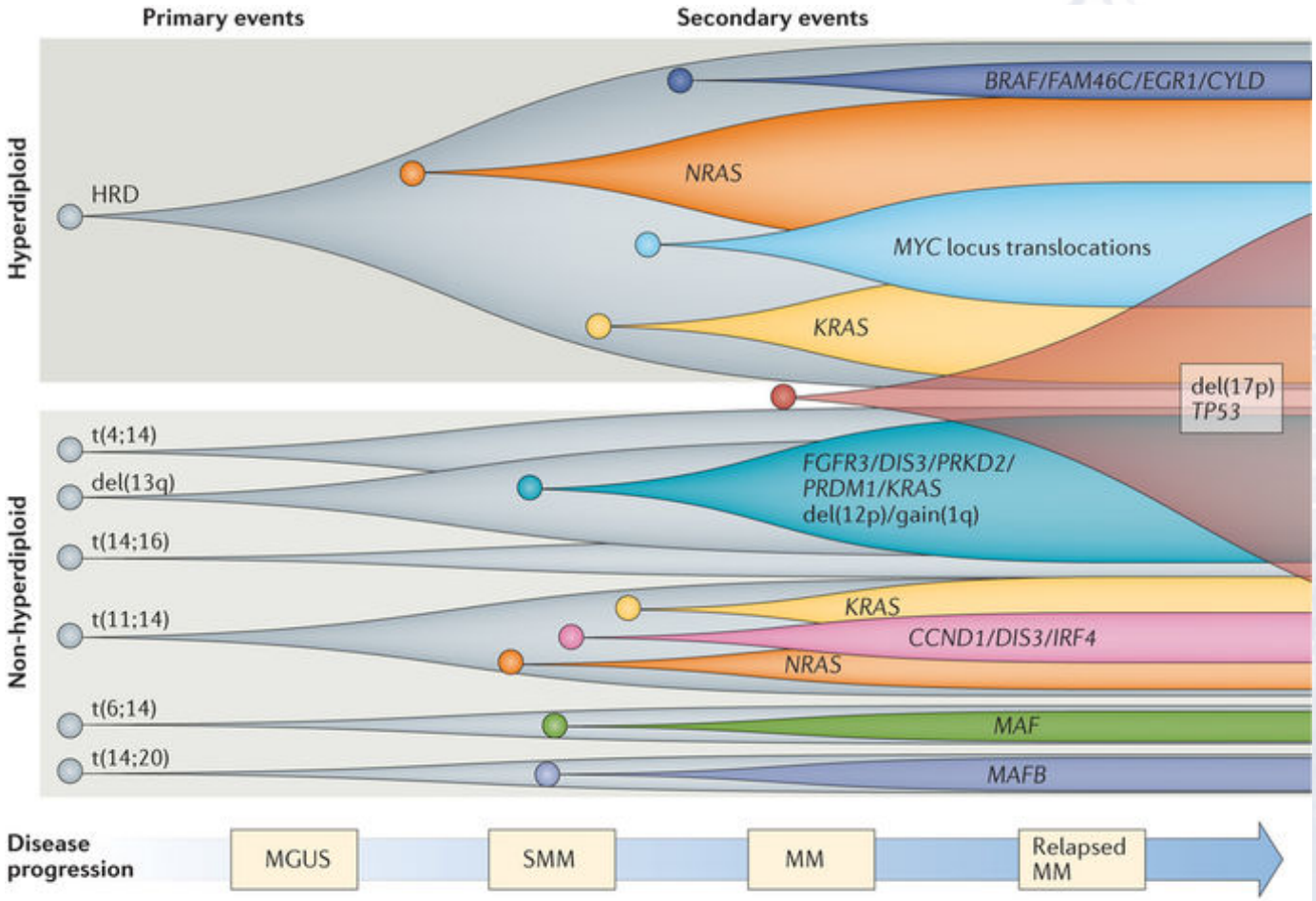
What is Multiple Myeloma?

- Disease of increased plasma cells
- Disease of the bone marrow microenvironment
- Disease of a genetically altered plasma cell

Clonal Heterogeneity



Acquired Genetic Mutations with Disease Progression



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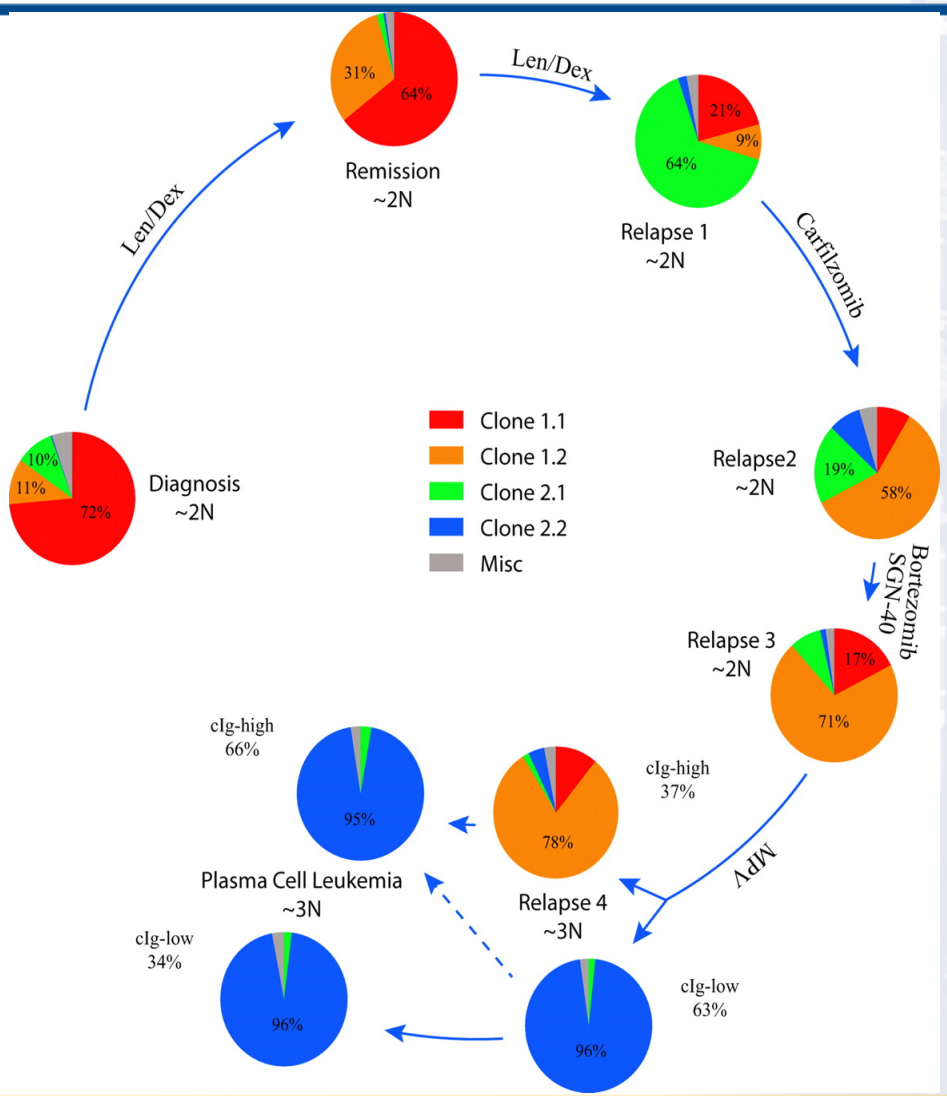
Clonal Evolution of Myeloma Throughout Treatment Cycle



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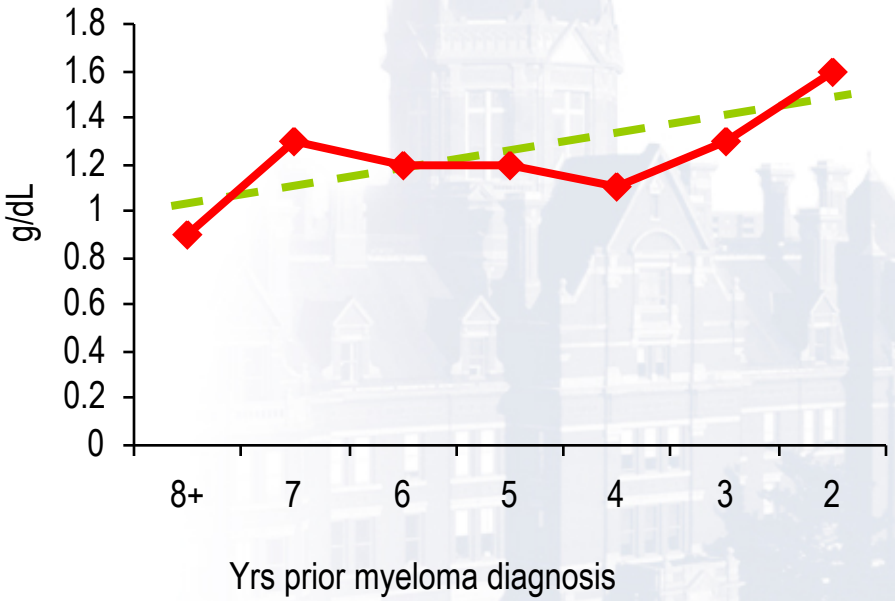
Abnormalities in M-Spike Found Several Years Prior to Developing Myeloma

Yrs prior myeloma dx	N	Median (range) concentration
2	**24**	**1.6 (0.4–3.7)**
3	**47**	**1.3 (0.5–3.1)**
4	**37**	**1.1 (0.5–3.9)**
5	**26**	**1.2 (0.6–3.8)**
6	**20**	**1.2 (0.6–3.6)**
7	**11**	**1.3 (0.7–3.5)**
8+	**10**	**0.9 (0.5–1.8)**



$P_{trend} = 0.025$

Landgren et al. *Blood 2009*

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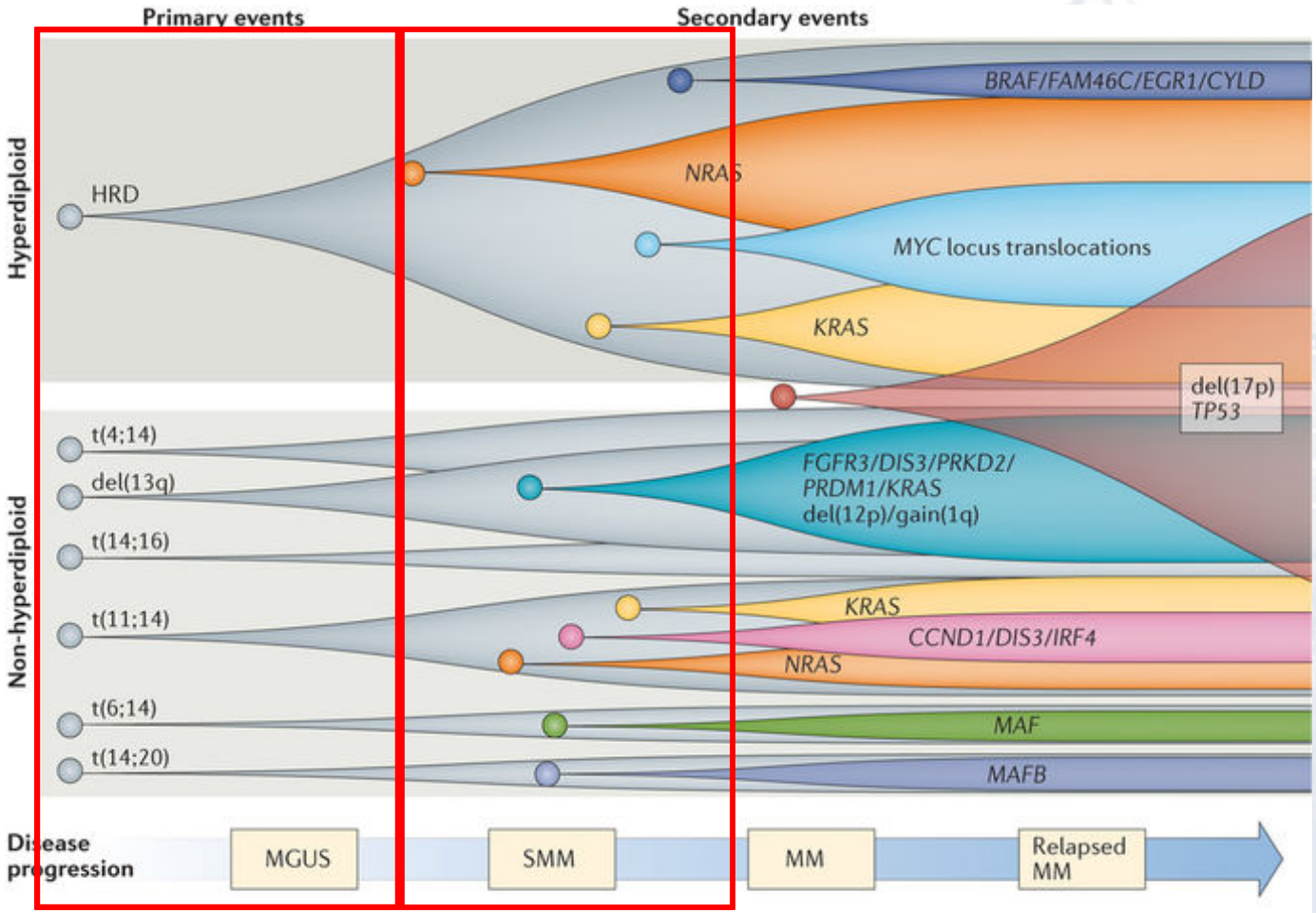
Acquired Genetic Mutations with Disease Progression



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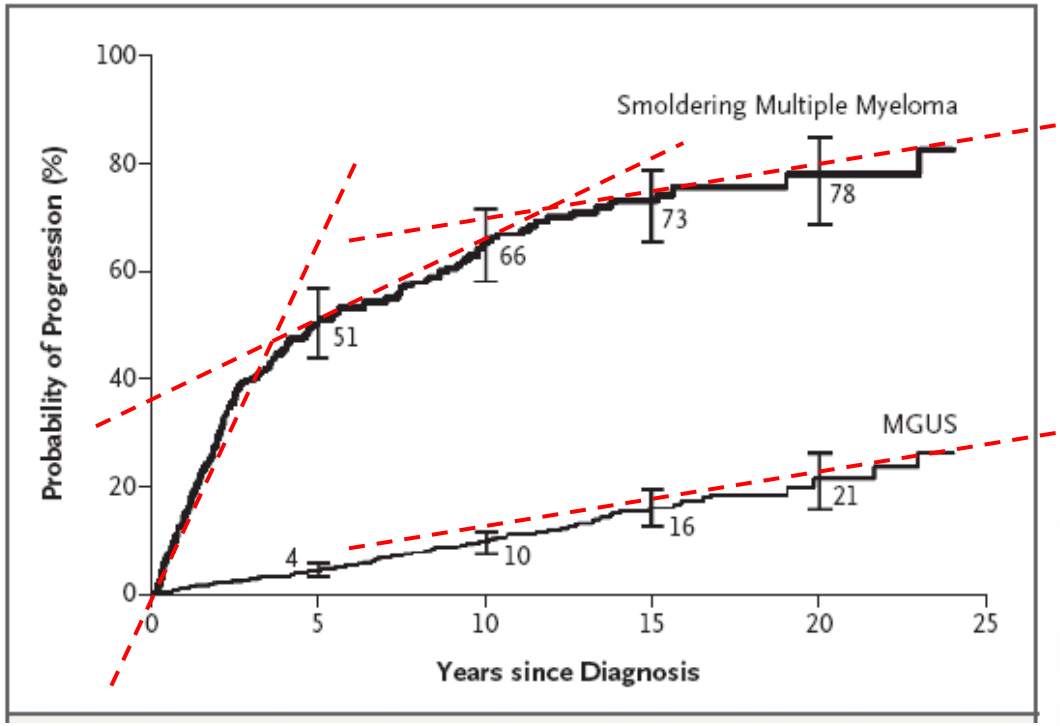
Smoldering myeloma (SMM) Subsets: the Mayo Clinic experience



- 276 SMM patients diagnosed 1970-1995
- 163 (59%) progressed
  - 158 multiple myeloma
  - 5 amyloidosis
- Overall risk of progression (per year):
  - 10% the first 5 years
  - 3% the next 5 years
  - 1% the last 10 years

Kyle et al. *NEJM 2007*

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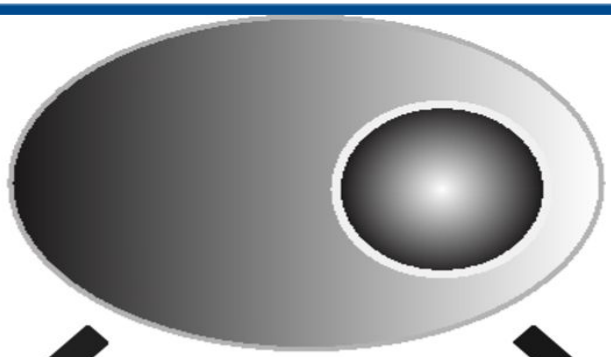
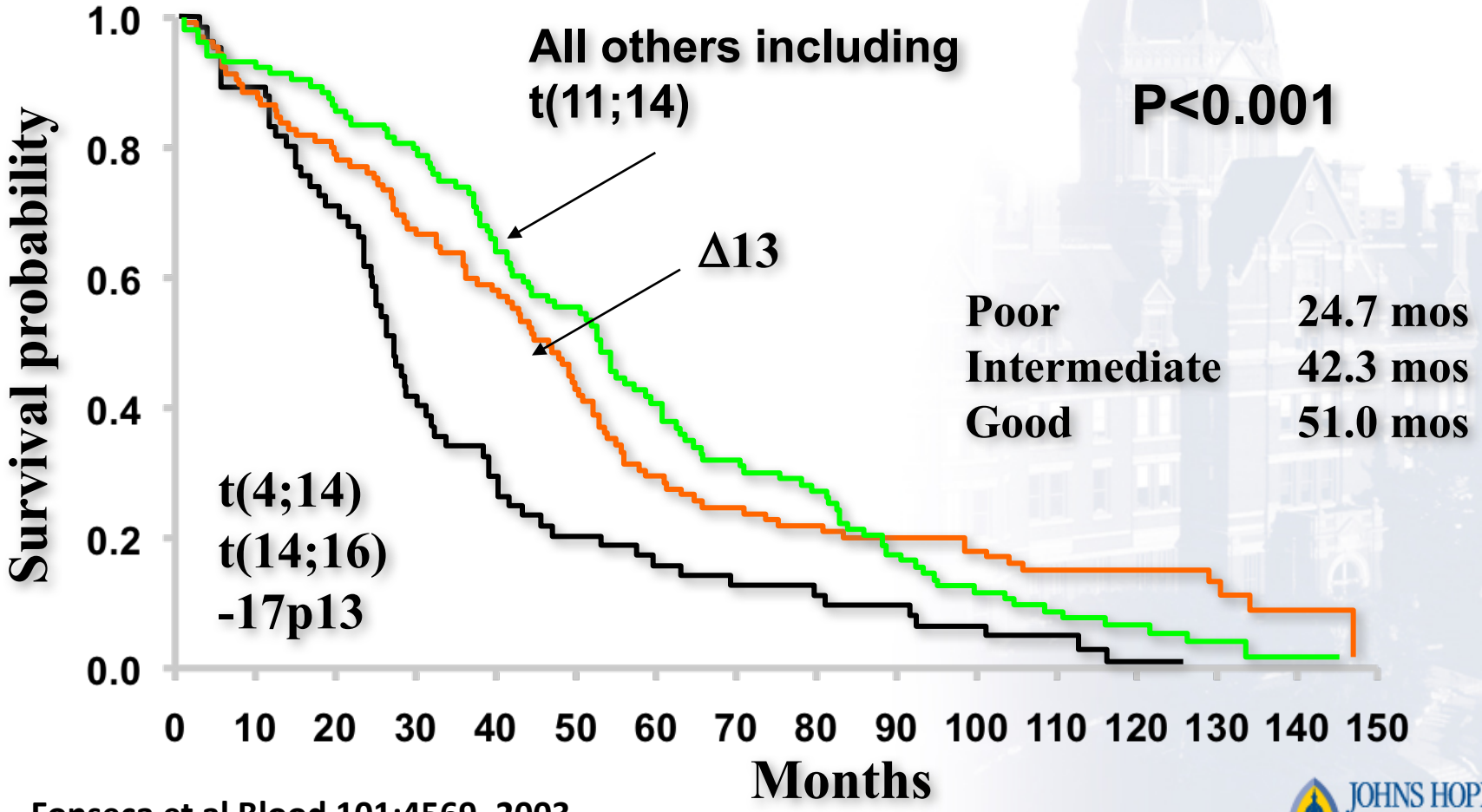
Chromosomal Abnormalities



IgH translocations	Genomic imbalances
t(4;14)*	Hyperdiploid
t(14;16)*	Non-hyperdiploid*
t(14;20)*	1q gains*
t(11;14)	Monosomy 13
t(6;14)	17p deletions*

*Unfavorable prognosis

Chromosomal Prognostic Models



Fonseca et al Blood 101:4569, 2003

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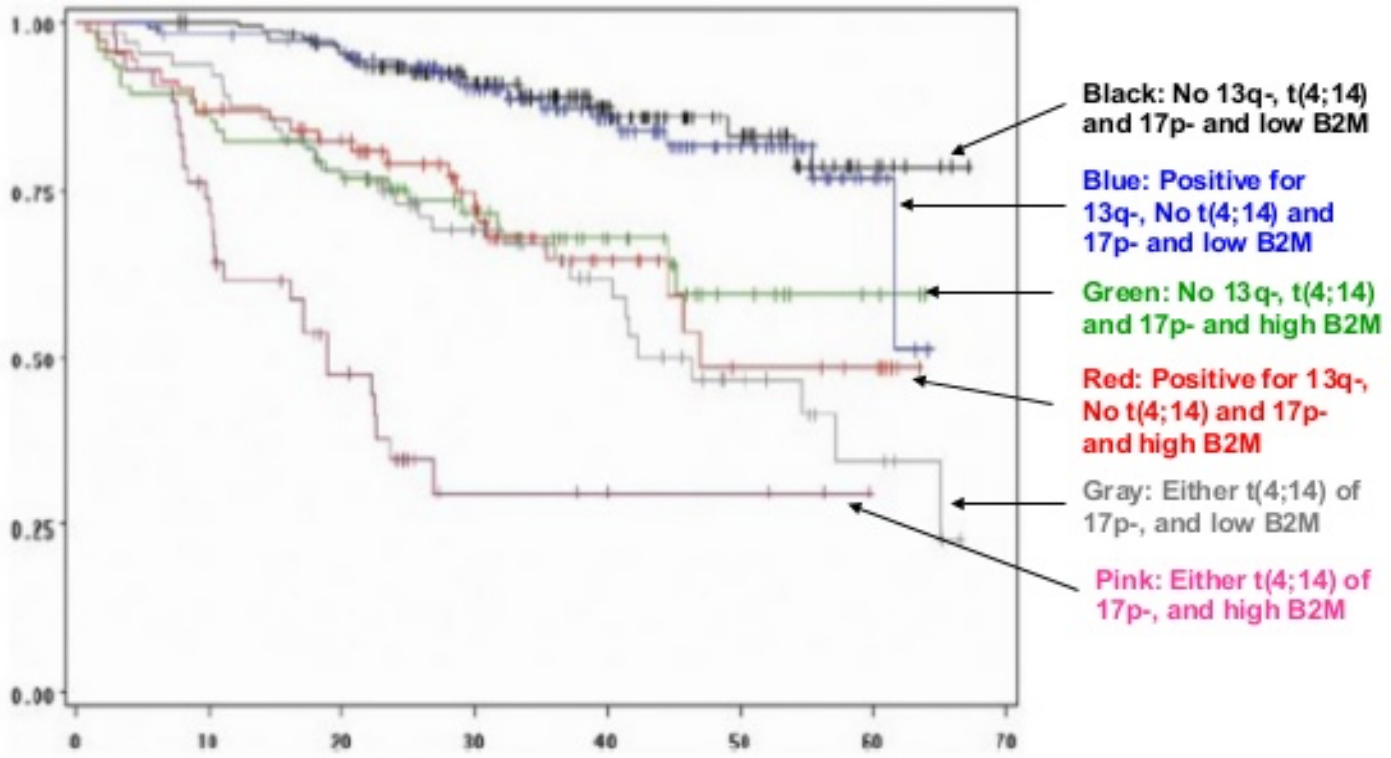
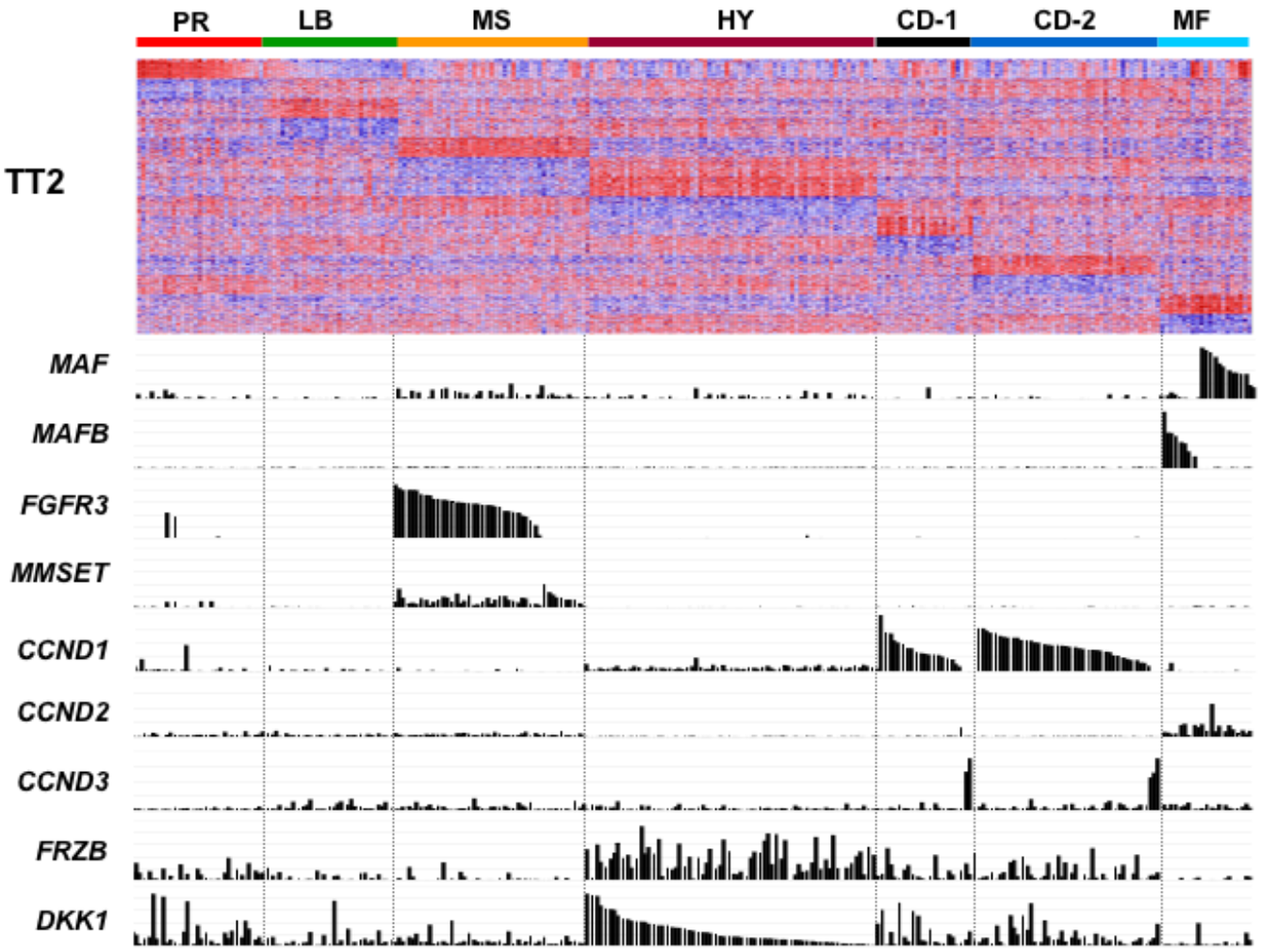
Prognostic Significance of Chromosomal Abnormalities



Avet-Loiseau et al, Blood 2007; 109: 3489 - 95

Molecular Subclassifications of Myeloma



Gene Expression

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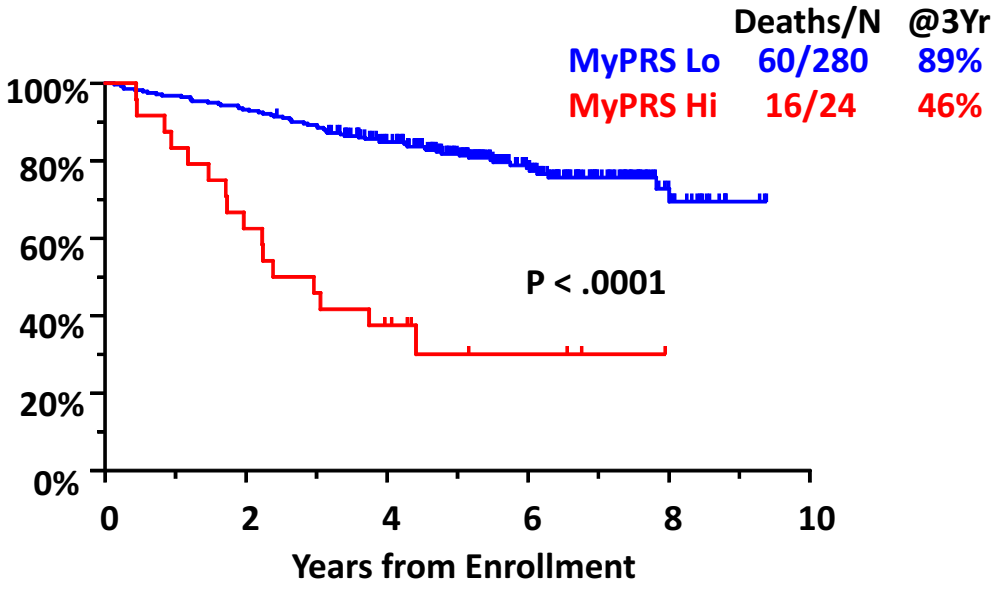
Adapted from Zhan et al., 2006

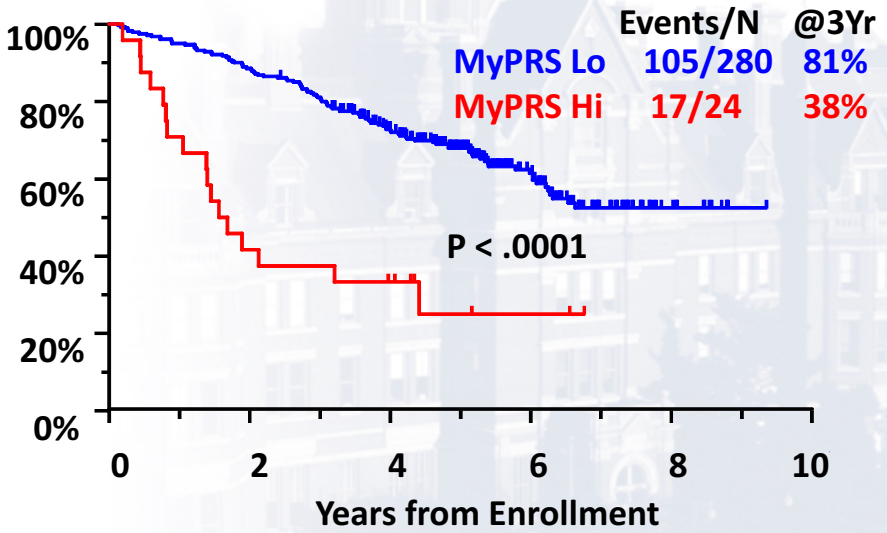
MyPRS Stratifies Risk within ISS Stages

ISS STAGE 1

Overall Survival



Progression-Free Survival



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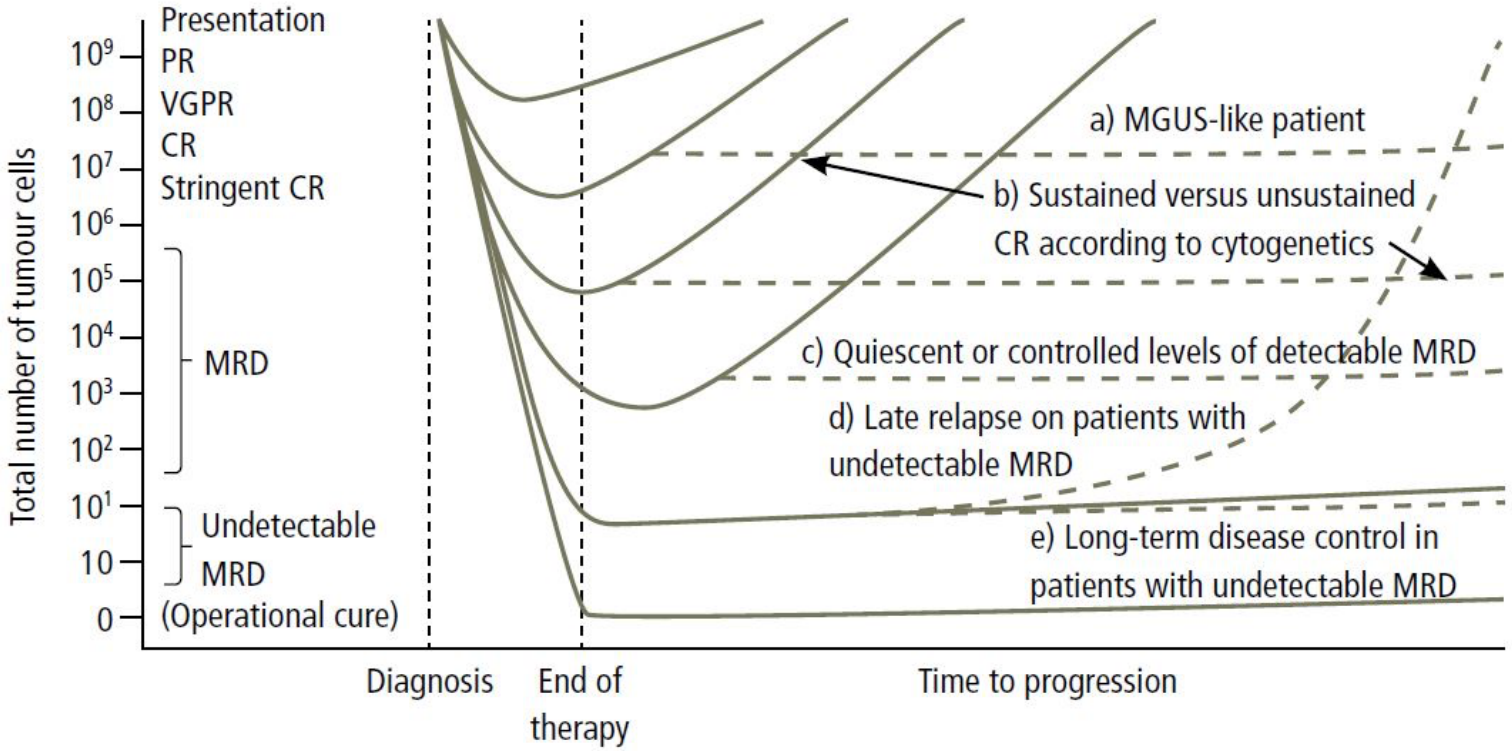


CR, complete response; MGUS, monoclonal gammopathy of unknown significance; MRD, minimal residual disease; PR, partial response; VGPR, very good partial response.

Depth of Response Correlates with Improved Outcomes

Prognostic impact of CR vs nCR/VGPR/PR vs SD/PD after high-dose therapy plus ASCT (n=344)

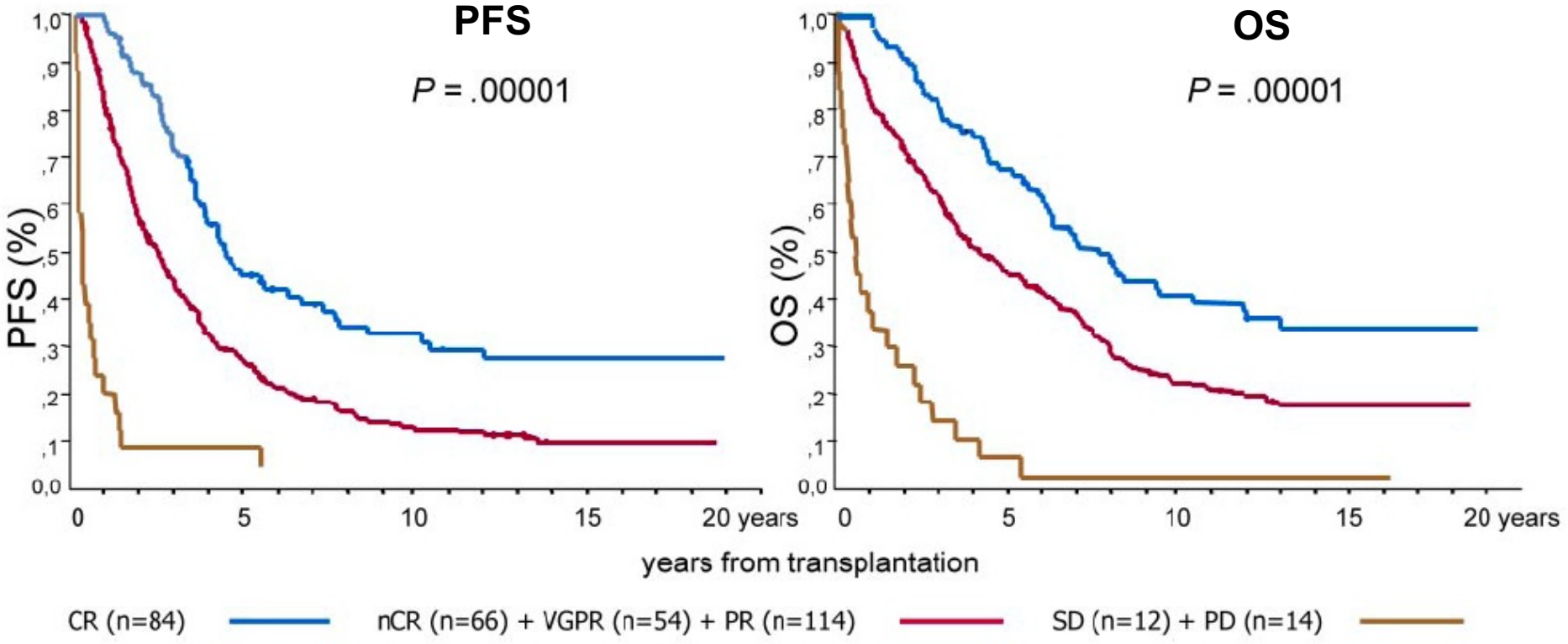
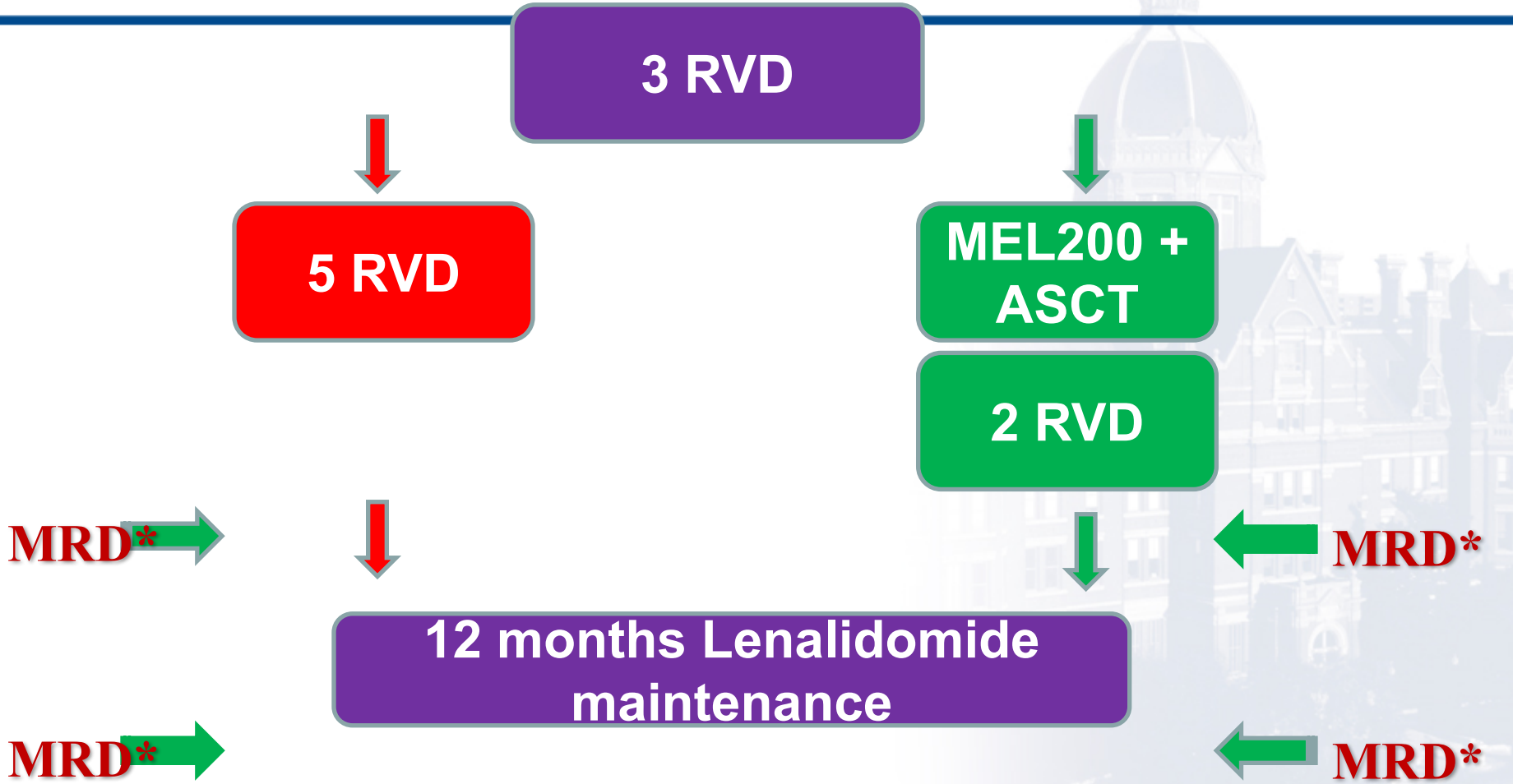


Figure 2. Prognostic effect of CR patients versus those in nCR or VGPR or PR versus patients with SD or PD after HDT/ASCT.

Martinez-Lopez et al *Blood*. 2011;118(3):529-534

IFM DFCI 2009 Trial
700 patients < 66y,
Newly diagnosed symptomatic MM



* Primary objective = 7-color Flow, Secondary objective = Molecular

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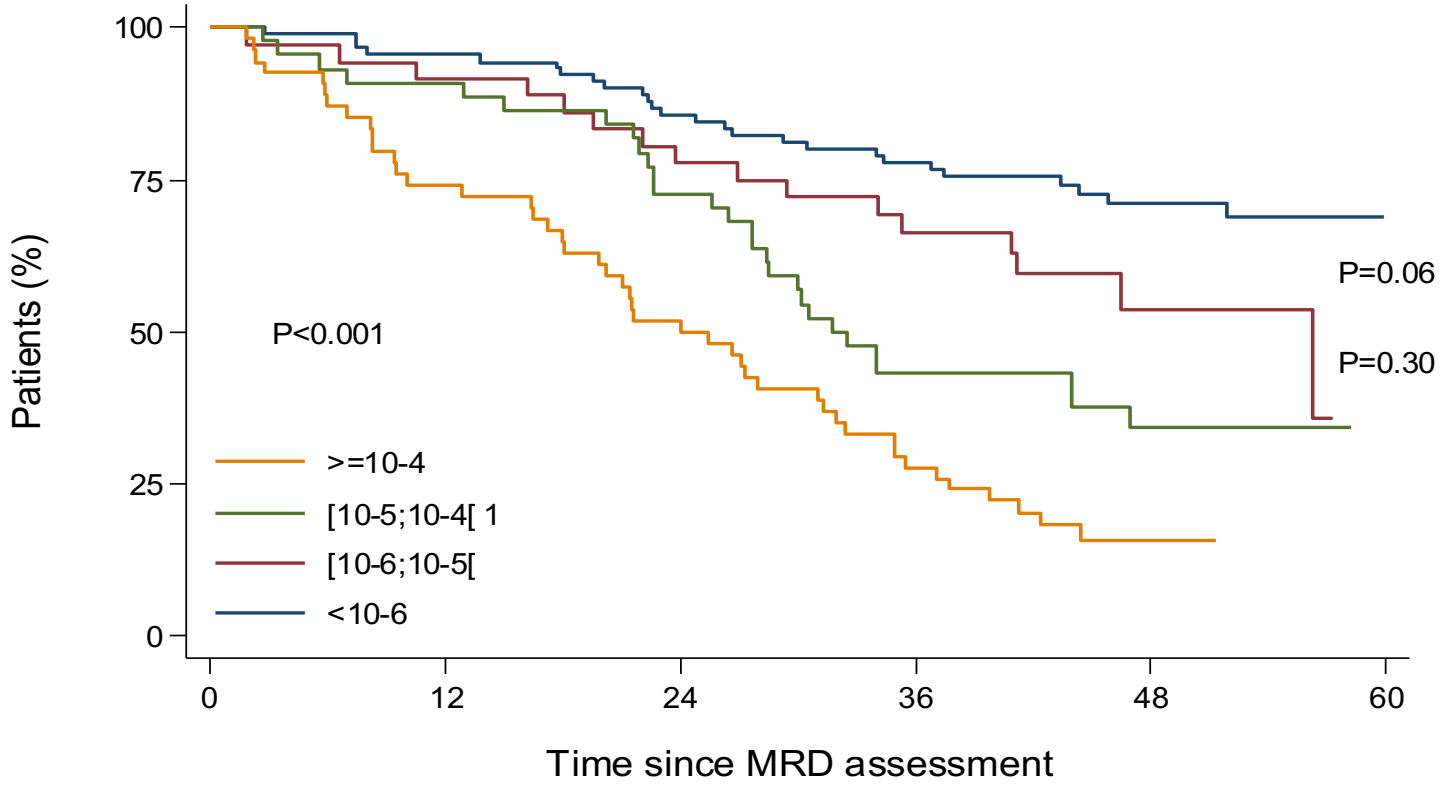
Attal M et al. NEJM 2017;376(14):1311-1320.

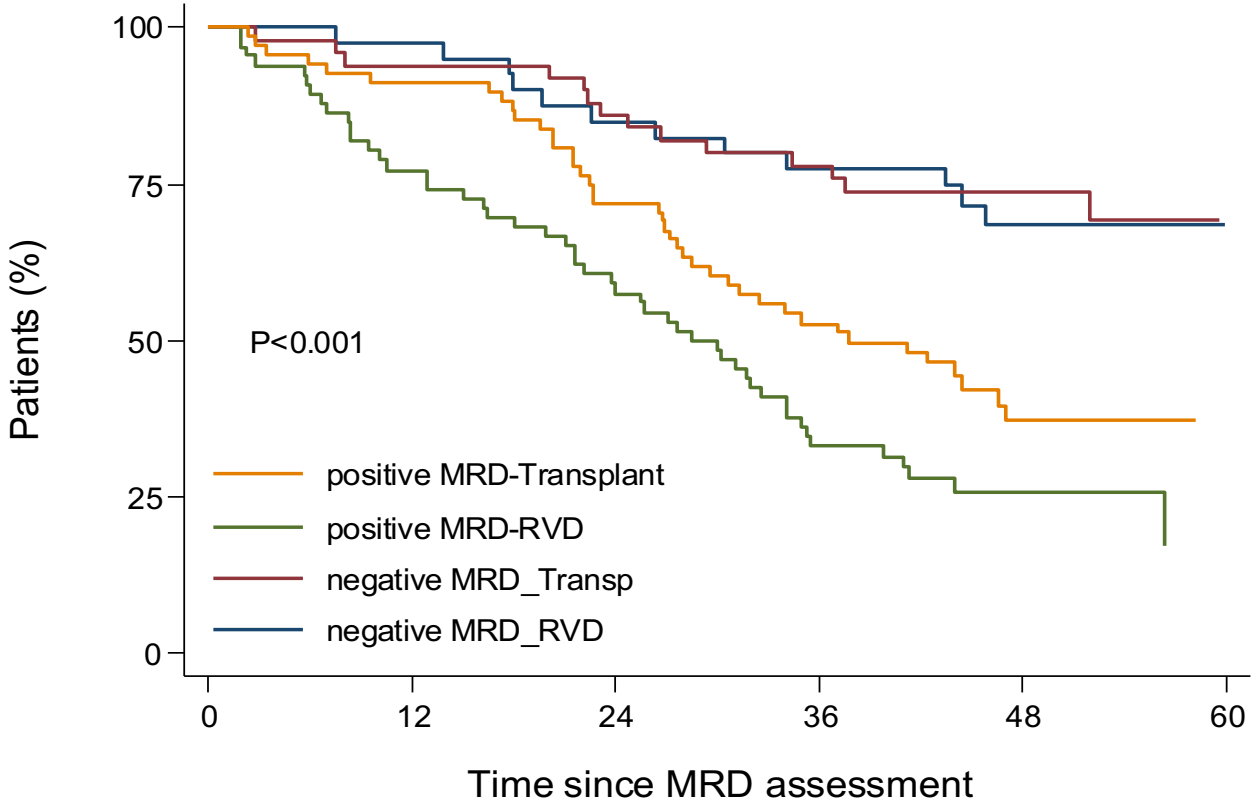
PFS according to sensitivity



N at risk						
>=10-4	54	40	27	15	7	0
[10-5;10-4[1	44	40	32	19	10	2
[10-6;10-5[	36	33	28	22	9	1
<10-6	90	86	77	69	40	5

Avet-Loiseau H et al. Oral presentation at ASH 2015 (Abstract 191).

MRD negativity and treatment arm



N at risk						
positive MRD-Transplant	68	62	49	35	15	1
positive MRD-RVD	66	51	38	21	11	2
negative MRD_Transp	50	47	43	38	23	4
negative MRD_RVD	40	39	34	31	17	1

Adapted from Avet-Loiseau H et al. Oral presentation at ASH 2015 (Abstract 191).

Conclusions

- Myeloma is a complex disease that is constantly in genetic evolution requiring an interplay of the tumor and its environment
- Disease progression and relapse is associated with clonal evolution
- Chromosomal abnormalities associated with disease progression
- MRD negativity associated with improved outcomes
- Transplant increases the likelihood of achieving MRD negativity