Brief report

Translocation t(14;16) and multiple myeloma: is it really an independent prognostic factor?

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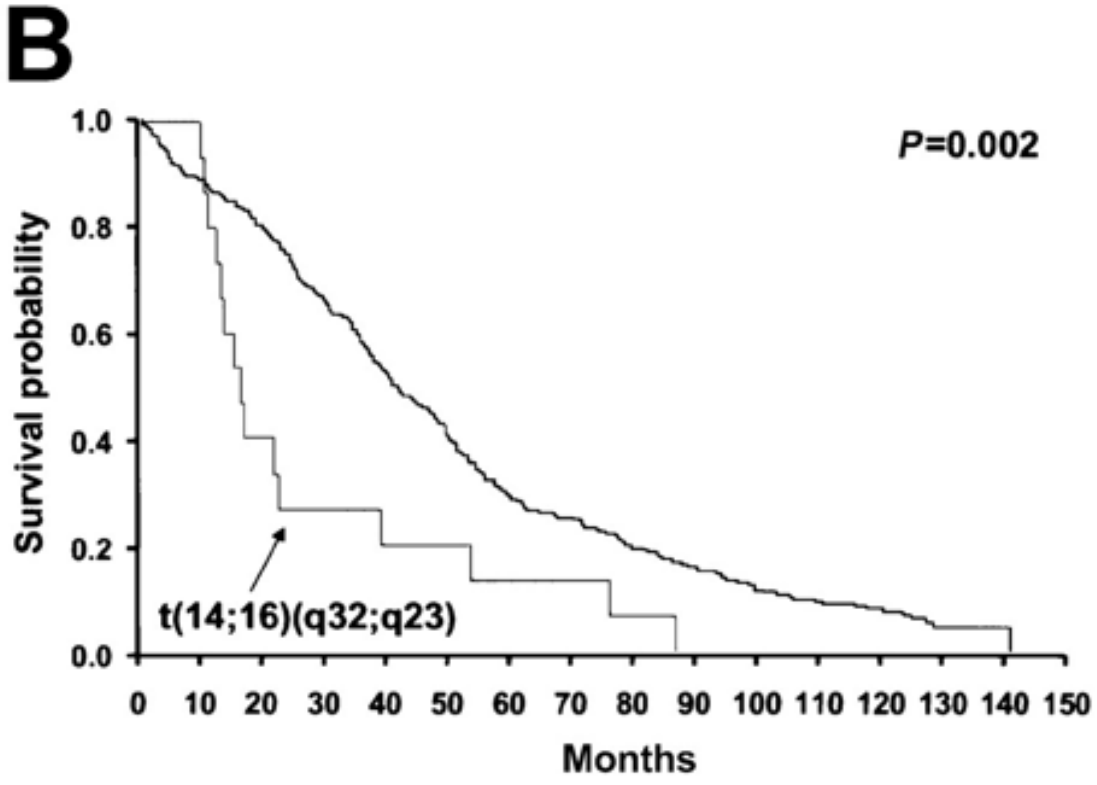

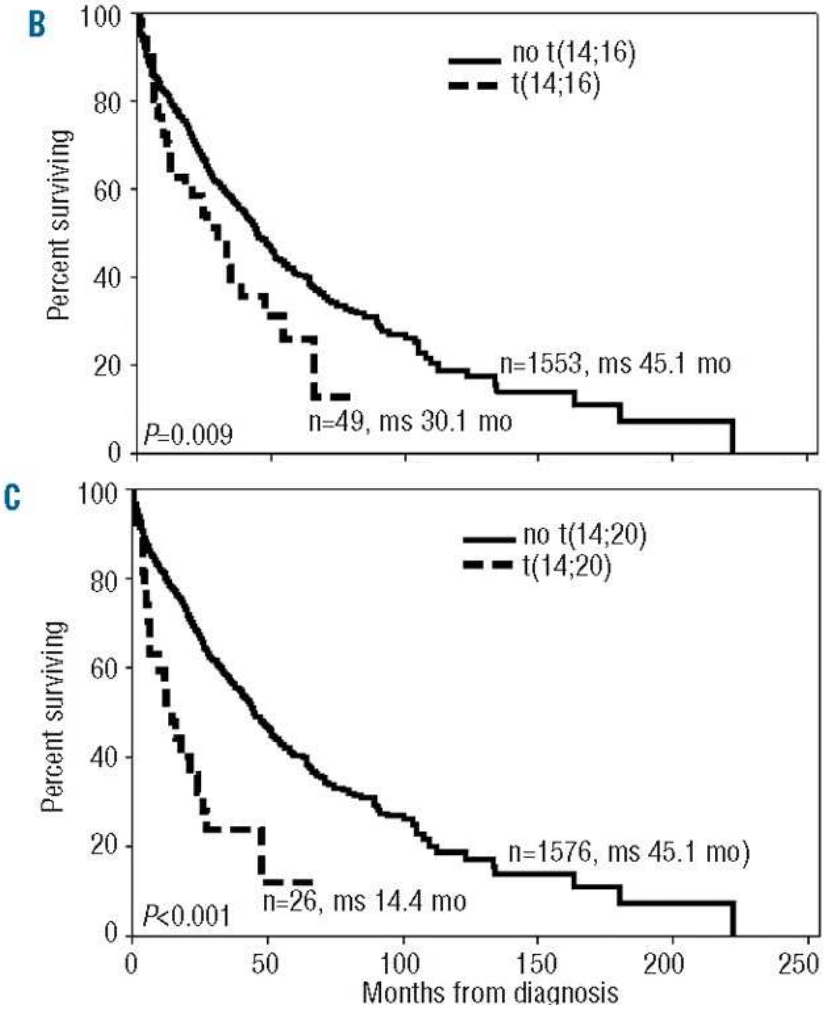

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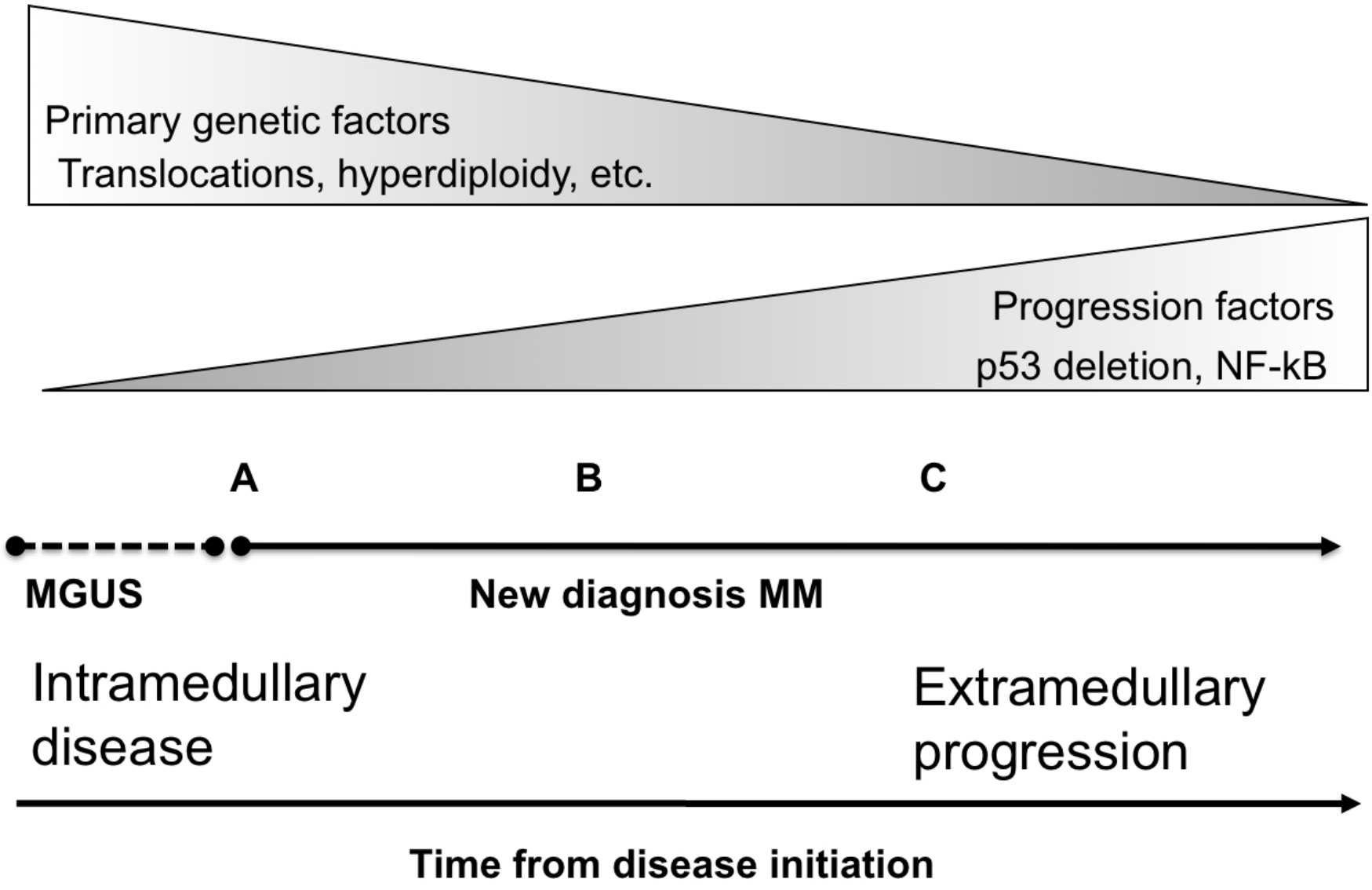
New Diagnosis MM



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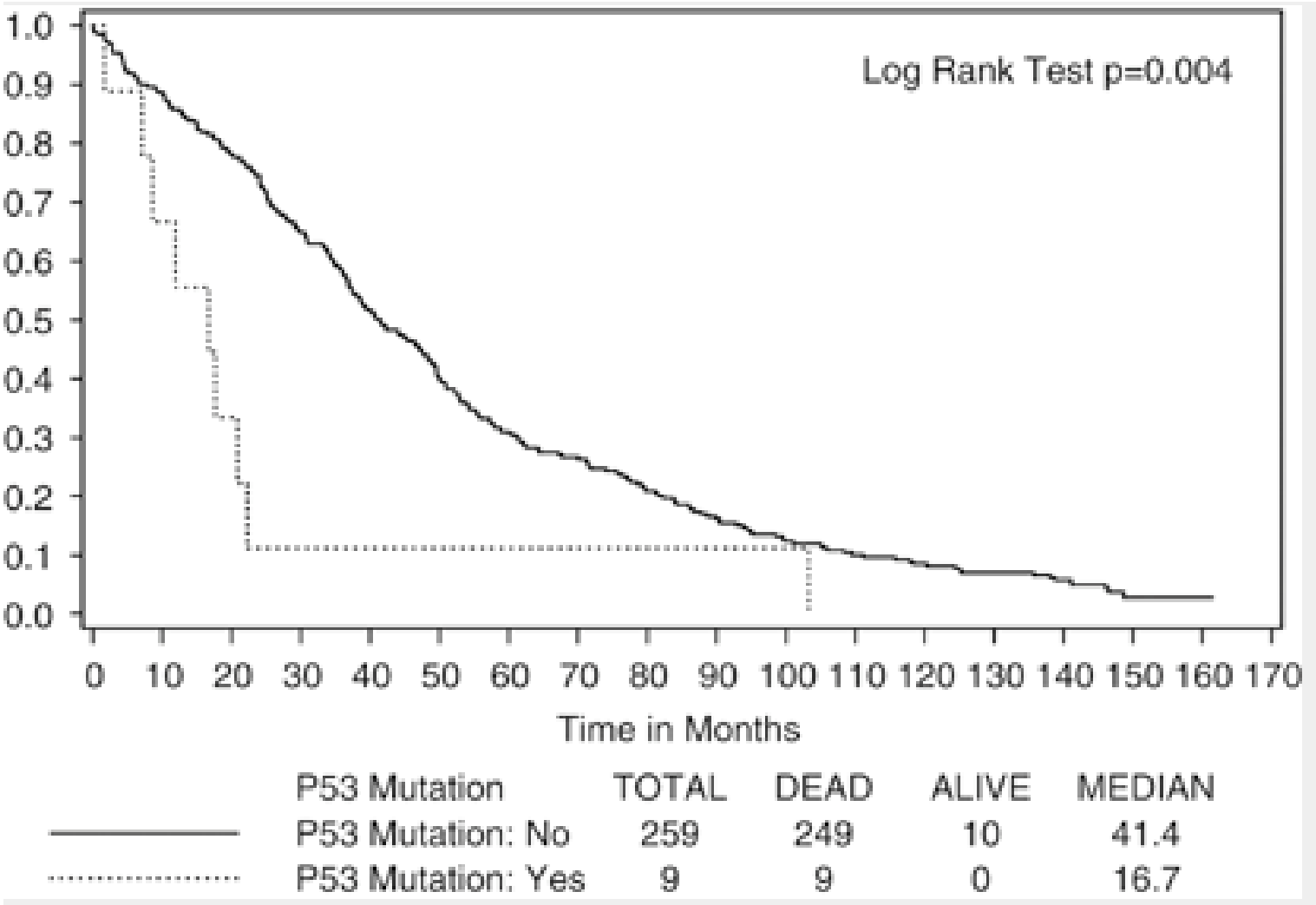
Survival by p53 mutation



P53 Mutation	TOTAL	DEAD	ALIVE	MEDIAN
P53 Mutation: No	259	249	10	41.4
P53 Mutation: Yes	9	9	0	16.7

Chng et al Leukemia 2007, 3:582

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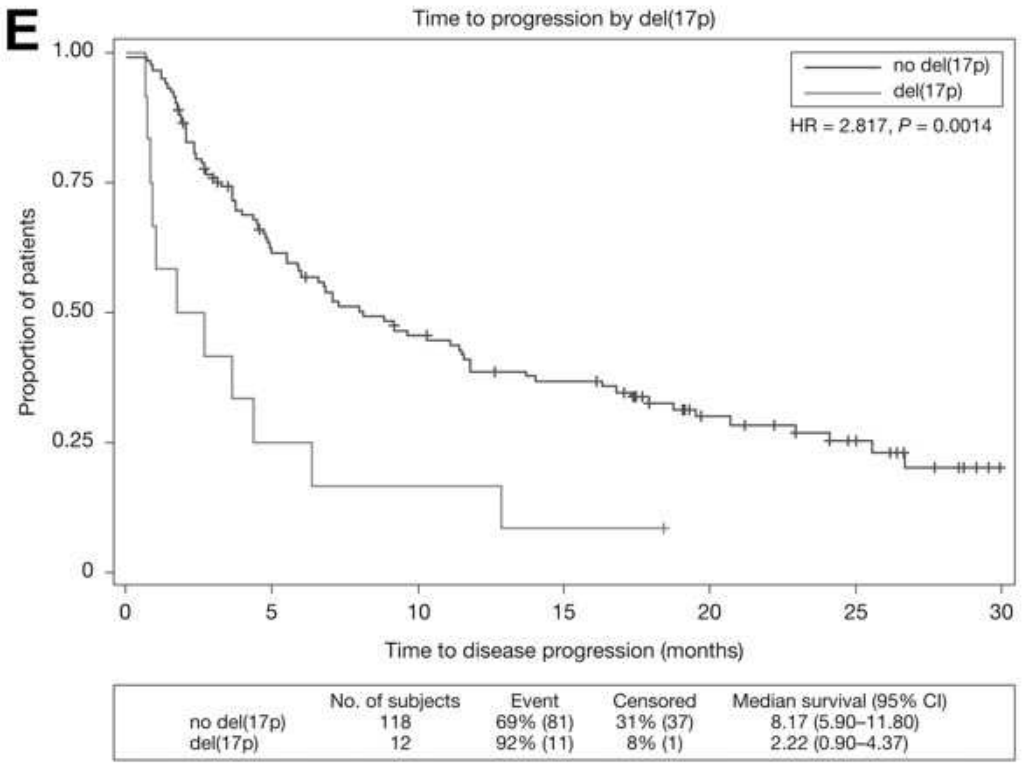
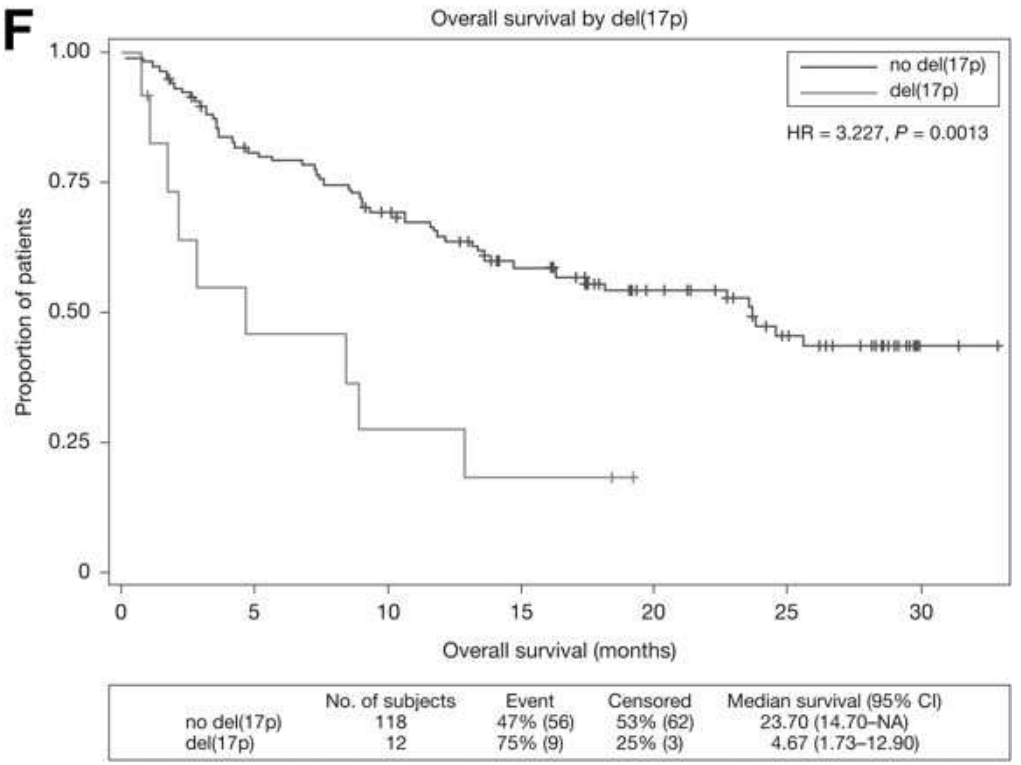
TTP and OS del 17p13



	No. of subjects	Event	Censored	Median survival (95% CI)
no del(17p)	118	69% (81)	31% (37)	8.17 (5.90–11.80)
del(17p)	12	92% (11)	8% (1)	2.22 (0.90–4.37)



	No. of subjects	Event	Censored	Median survival (95% CI)
no del(17p)	118	47% (56)	53% (62)	23.70 (14.70–NA)
del(17p)	12	75% (9)	25% (3)	4.67 (1.73–12.90)

Reece, D. et al. Blood 2009;114:522-525

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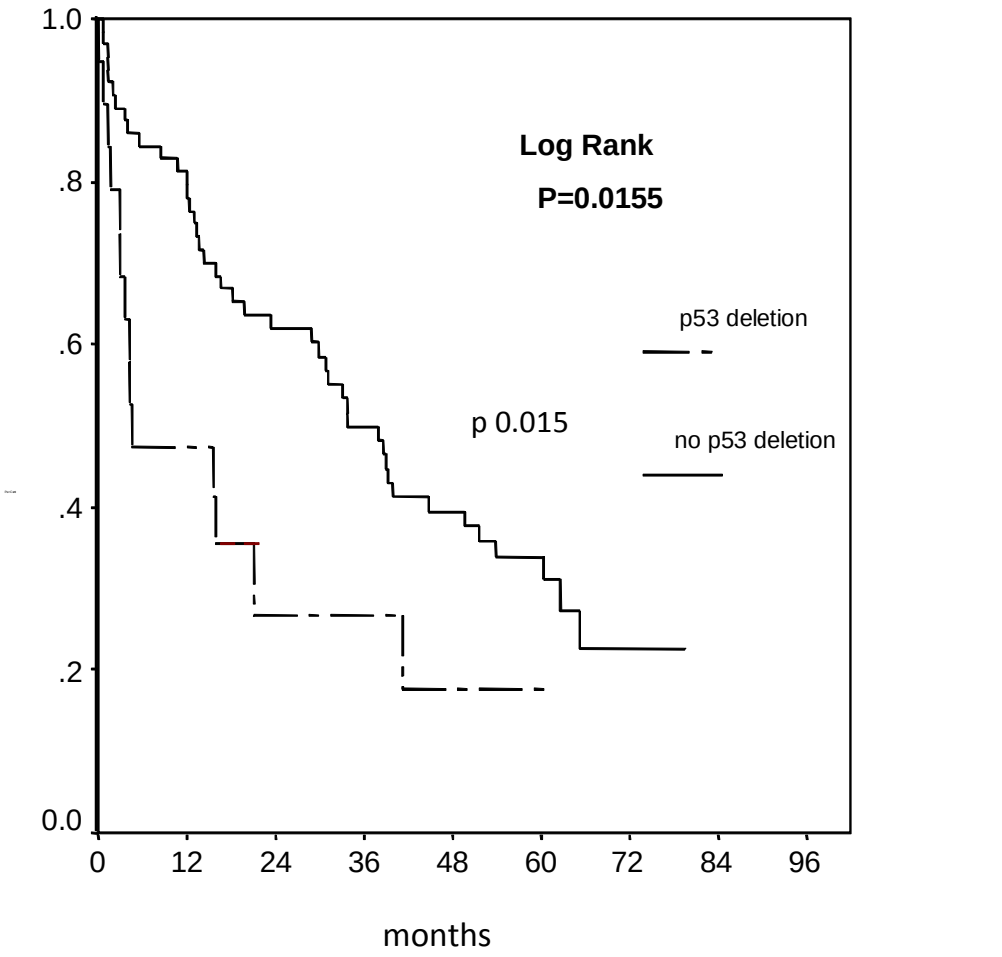
p53 in Relapsed MM

OS for relapse/refractory MM patients with or without p53 deletion was 4.2 months vs 37.8 months, p <0.01

Overall survival and p53 deletions/mutations in relapse MM patients



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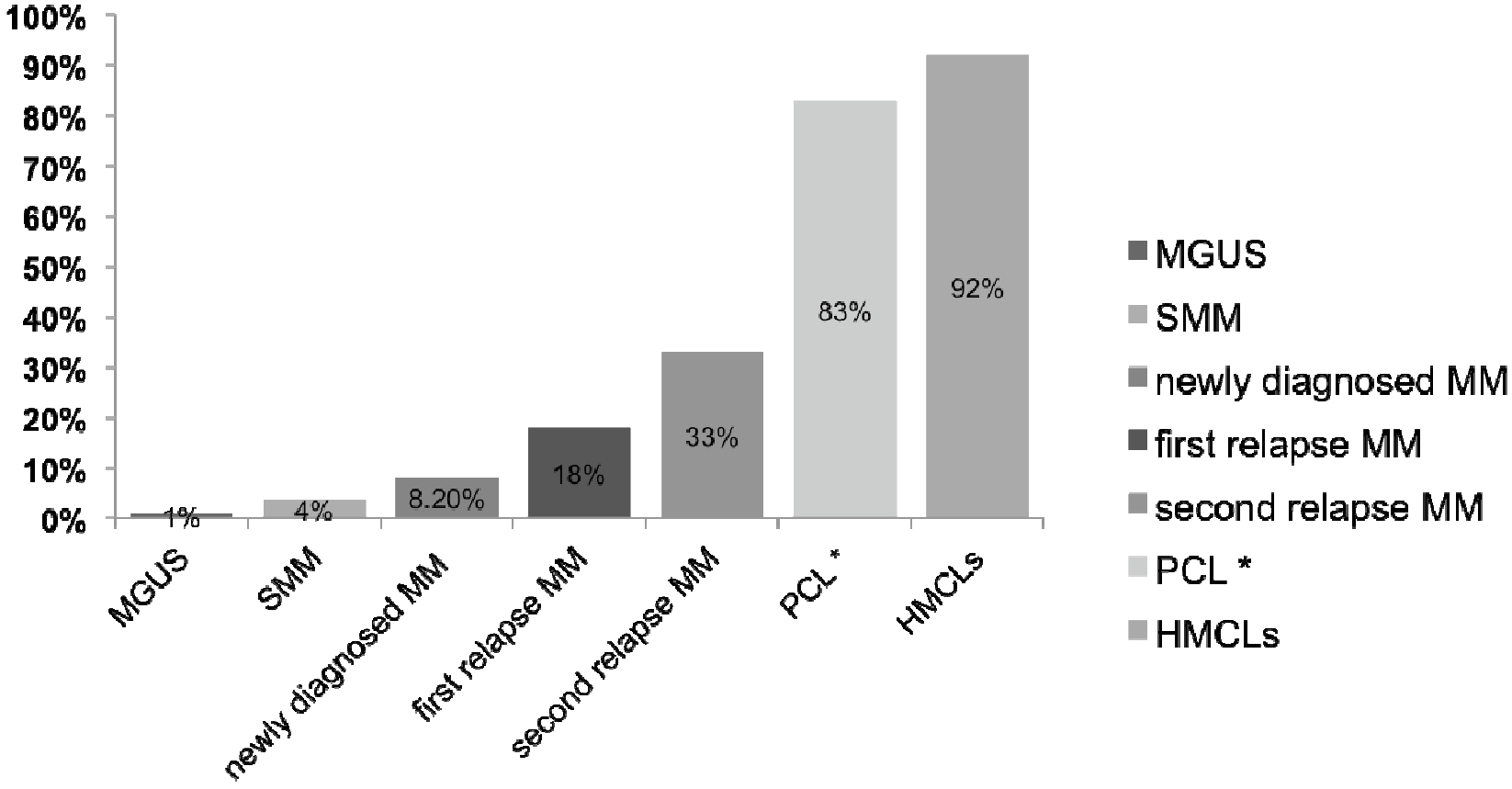
P53 deletion/mutation



Studied 8 patients with 17p deletions at RR 7 did not have deletion at diagnosis

FISH (MGUS n=184, SMM n=116, relapsed MM n=62 and PCL n=26)
aCGH (newly diagnosed MM n=224, relapsed MM n=158 and HMCLs n=48)
p 53 mutational status was evaluated in relapsed MM (n=84) and HMCLs (n=48)

*Tiedemann et al. Leukemia. 2008; 22, 1044-1052
Fonseca. Manuscript in preparation

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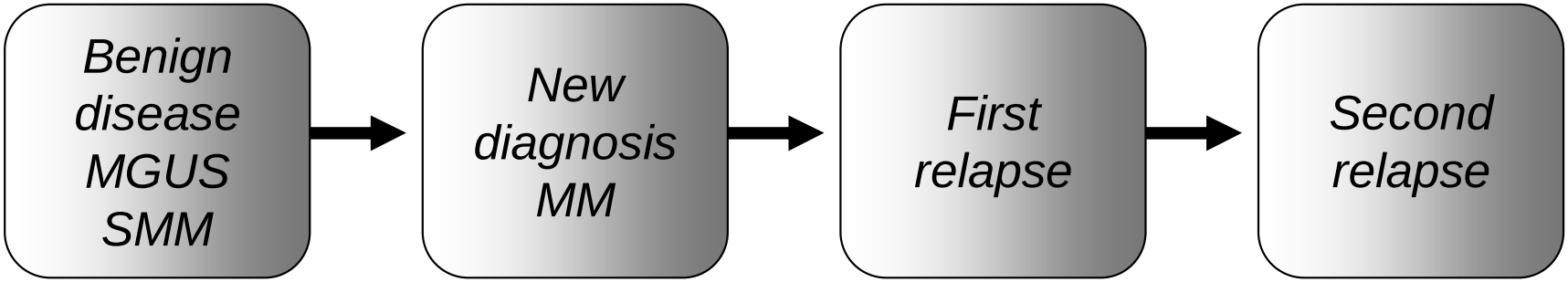
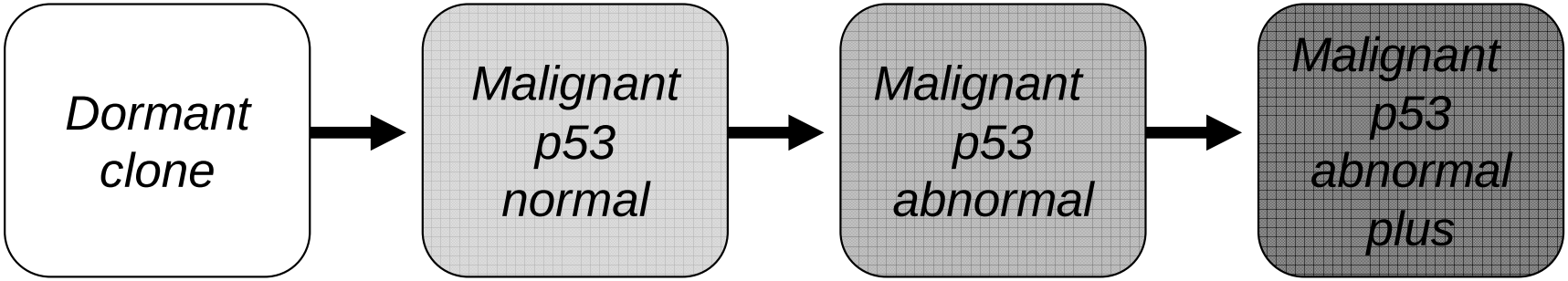
Staging of MM

Clinical staging



Molecular staging



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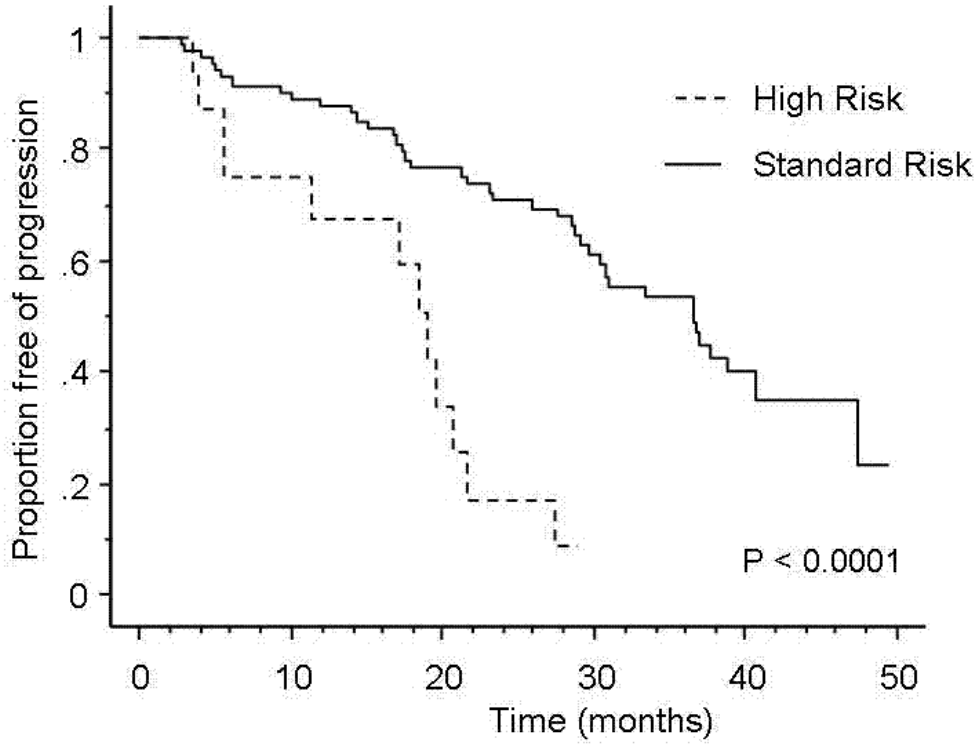
High Risk MM and Lenalidomide

100 patients treated with Len/Dex 3/04 -> 11/07

16 w/Hi Risk features:

del 13 CC, t(4;14),t(14;16) FISH, PCLI ≥ 3%

	VGPR	PR	OS	PFS
All			nr	31mo
STD	45%	89%		37
HI	38%	81%		19



Kapoor et al. ASH 2008, abstract #95

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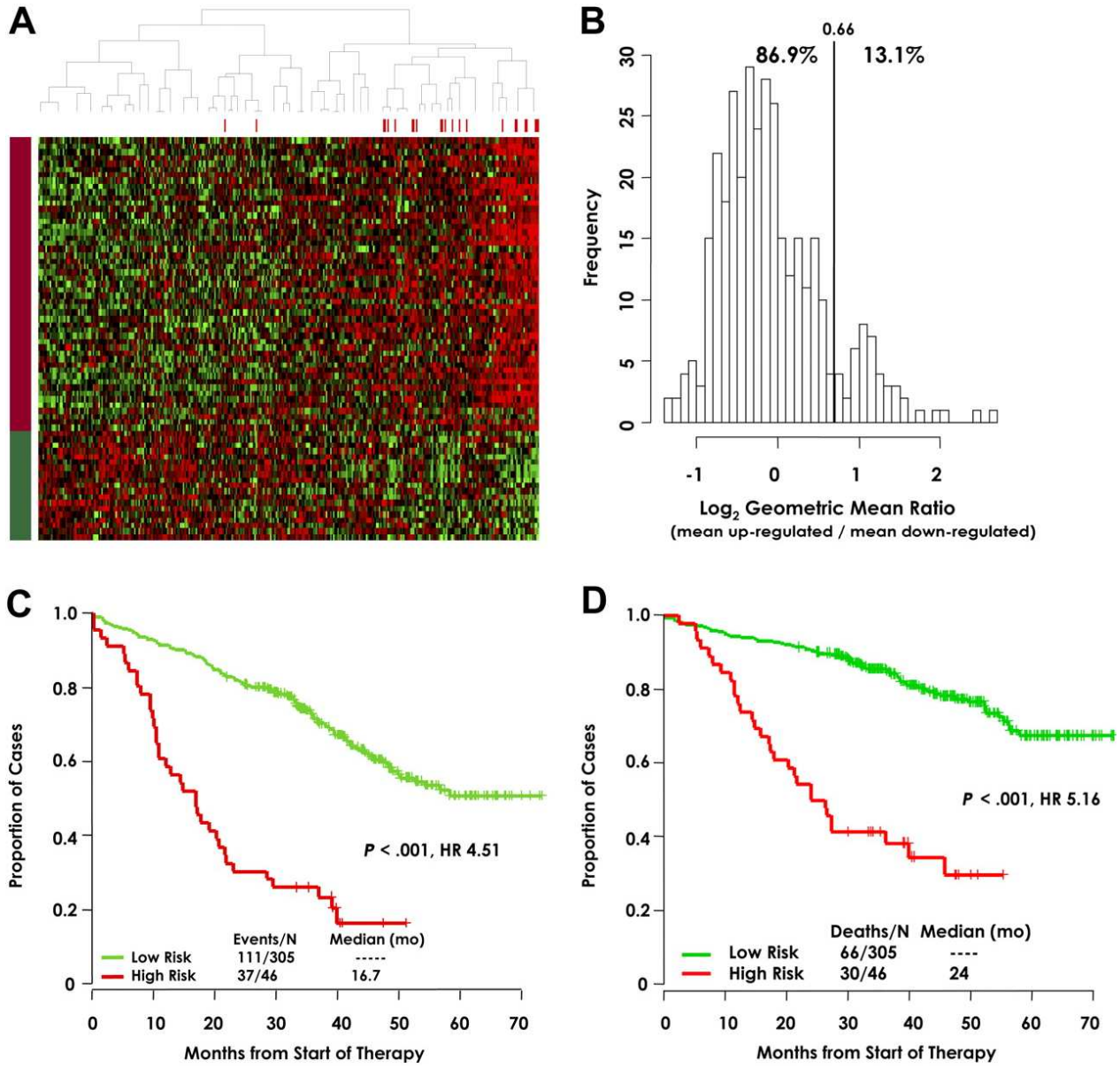
GEP signatures



Shaughnessy et al, Blood2007, 109(6), 2276-2284

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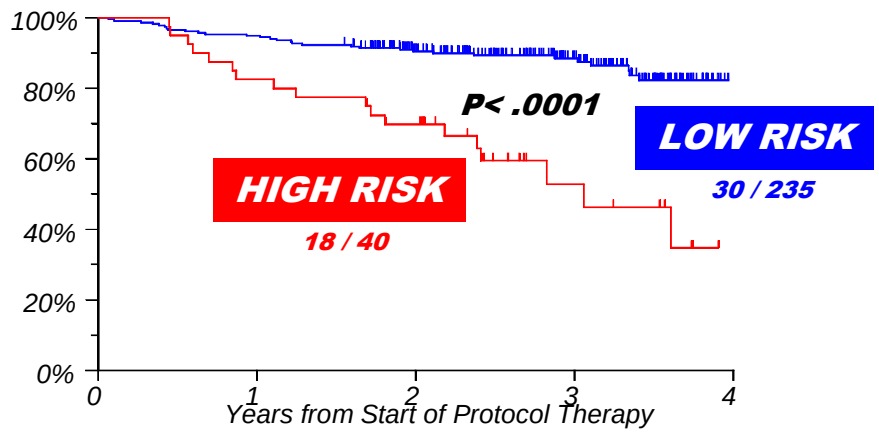
UAMS: Total Therapy 4 and 5

OVERALL SURVIVAL

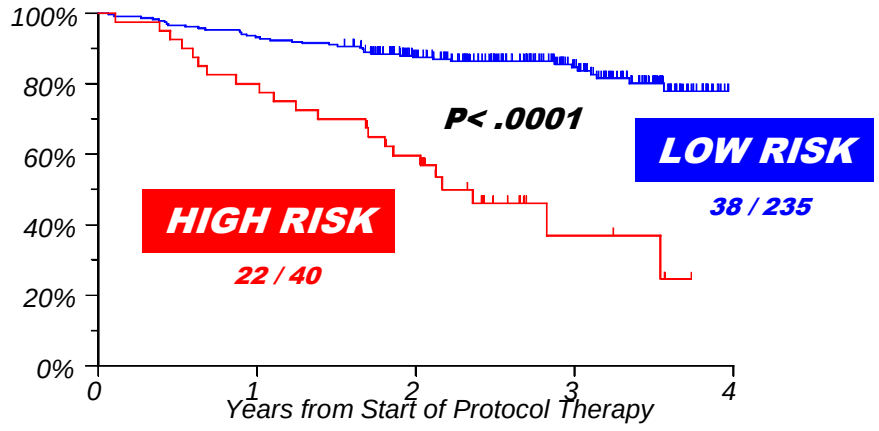


NEW PROTOCOLS:

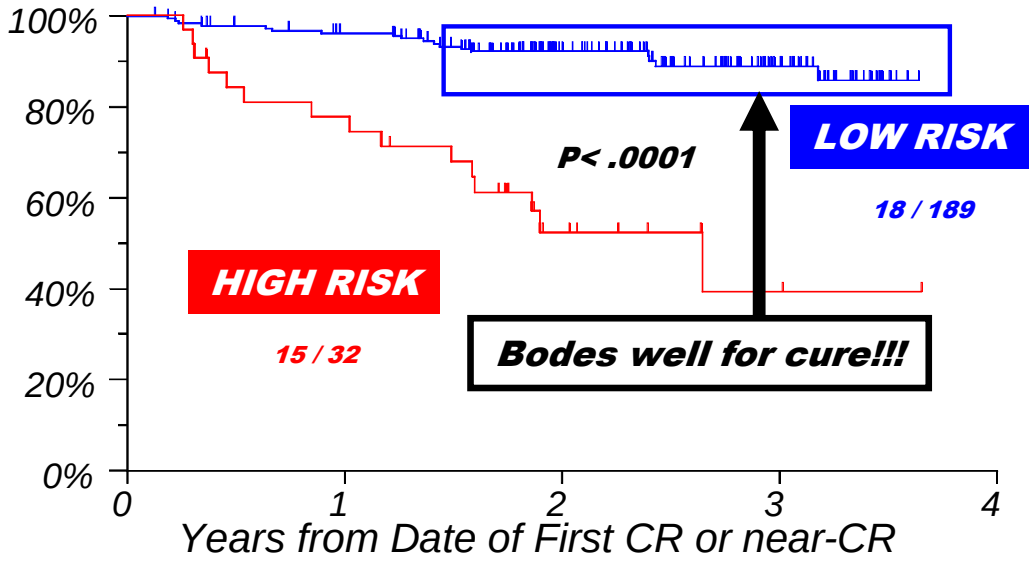
Low risk: TT4 (reduce toxicities)
Randomize TT3 v TT3-lite

High risk: TT5 (sustain CR)
MEL80-VTD- PACE
R-VD / M-VD maintenance

EVENT-FREE SURVIVAL



CR DURATION



Courtesy of Dr Barlogie

ARTICLE

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Initial genome sequencing and analysis of multiple myeloma

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Multiple myeloma is an incurable malignancy of plasma cells, and its pathogenesis is poorly understood. Here we report the massively parallel sequencing of 38 tumour genomes and their comparison to matched normal DNAs. Several new and unexpected oncogenic mechanisms were suggested by the pattern of somatic mutation across the data set. These include the mutation of genes involved in protein translation (seen in nearly half of the patients), genes involved in histone methylation, and genes involved in blood coagulation. In addition, a broader than anticipated role of NF-κB signalling was indicated by mutations in 11 members of the NF-κB pathway. Of potential immediate clinical relevance, activating mutations of the kinase BRAF were observed in 4% of patients, suggesting the evaluation of BRAF inhibitors in multiple myeloma clinical trials. These results indicate that cancer genome sequencing of large collections of samples will yield new insights into cancer not anticipated by existing knowledge.

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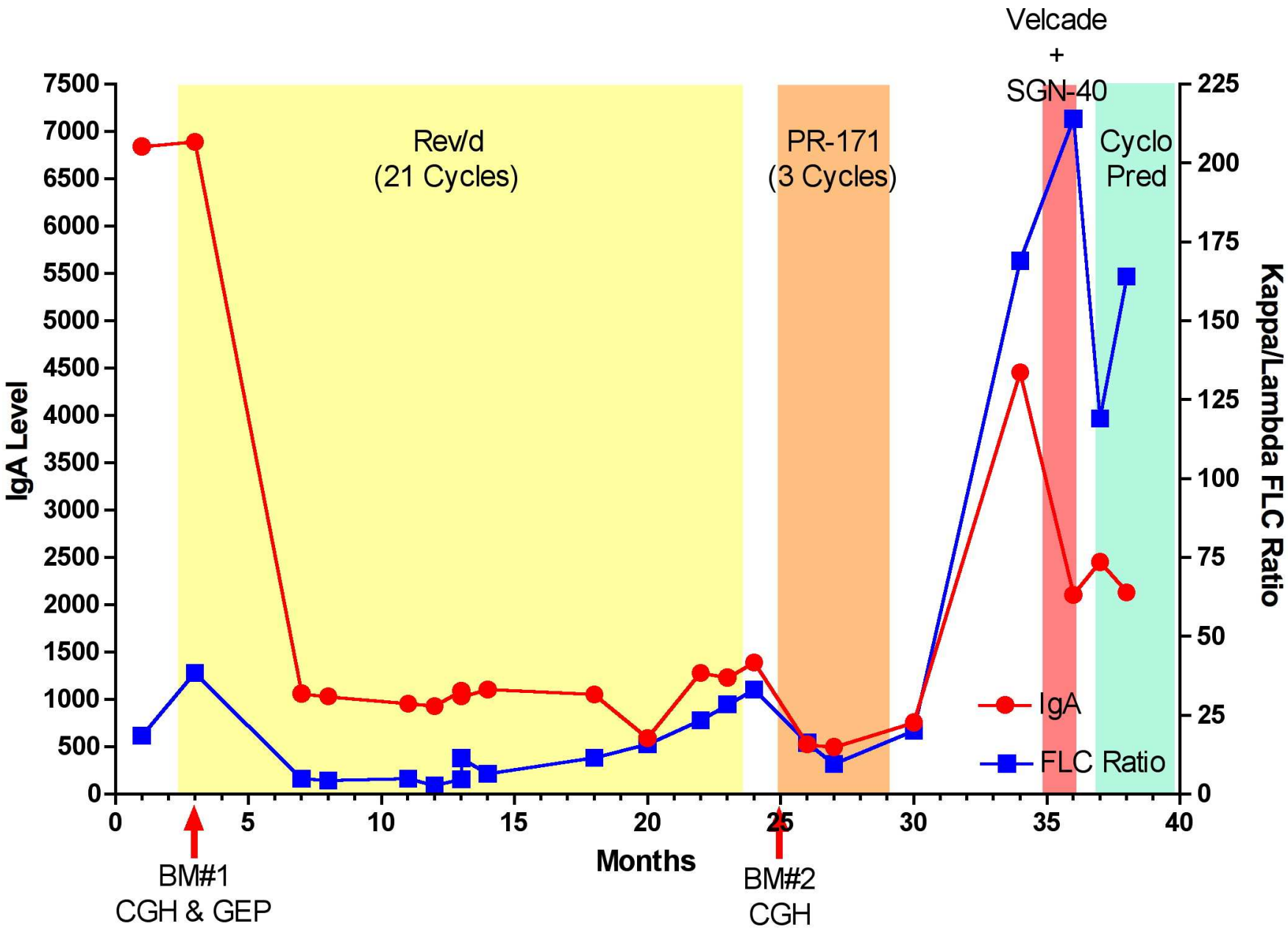
Clinical Course - Case Report



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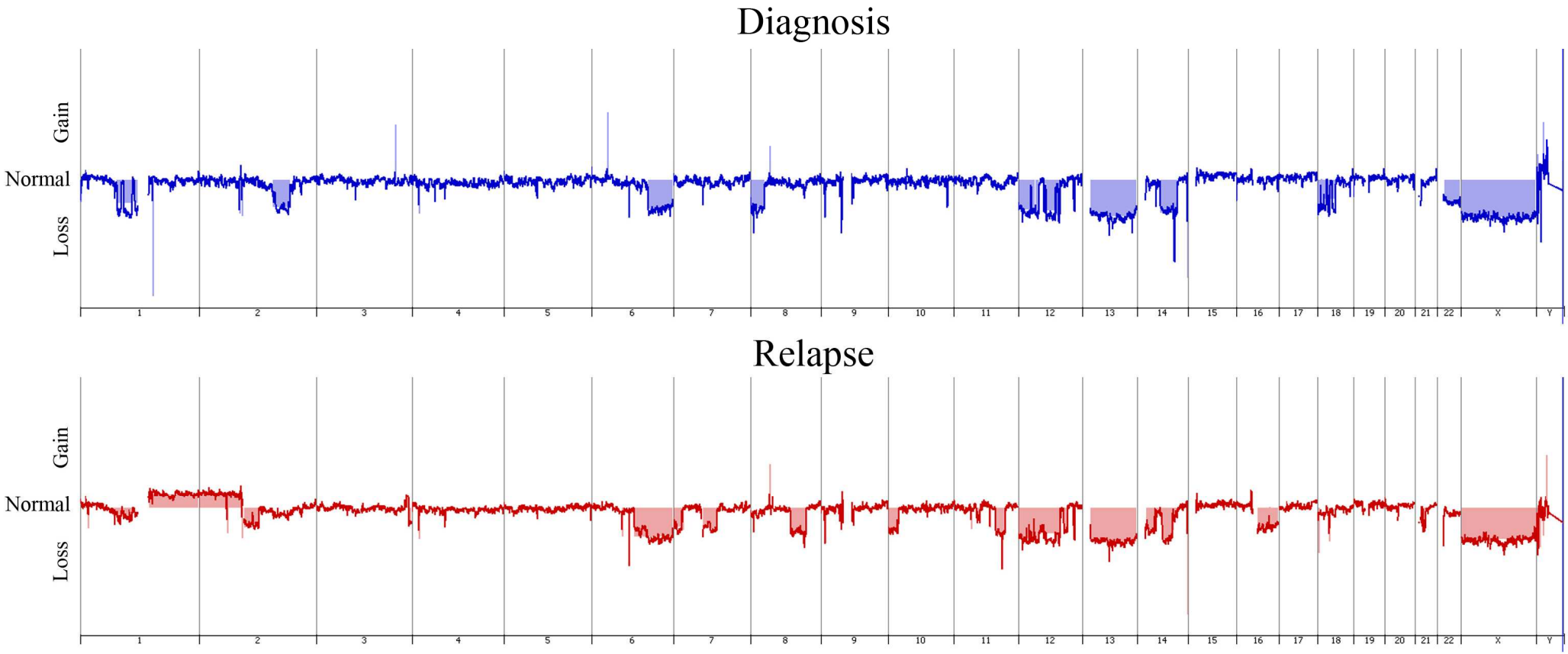
Whole Genome Comparison of Diagnostic and Relapse Samples



A significant number of differences were detected (The most of any pair studied to date). However, it is possible to sort out the driver events, diagnostic passenger events, and events unique to the relapse sample that may mediate Rev/d resistance

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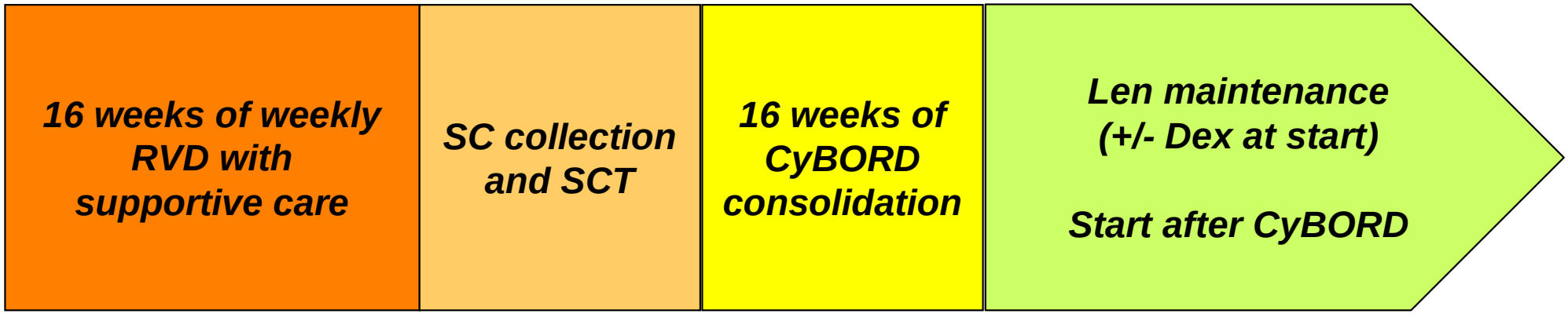
Standard Risk MM SCT

Minimize gap between Rx end and SCT

Bisphosphonate per Mayo; RNE responsibility

High Risk MM SCT

Minimize gap between Rx end and SCT



Bisphosphonate per Mayo; RNE responsibility

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In AZ everything is possible!

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Rhett Ketterling

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Esteban Braggio

Travis Henry

Samar Issa

Angela Mayo

Jacy Spong

NUS

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