Is personalized therapy ready for primetime ?

Shaji Kumar, M.D.
Professor of Medicine
Mayo Clinic

Scottsdale, Arizona

Rochester, Minnesota

Jacksonville, Florida

Press 1 if you have back pain with your myeloma

Press 2 if you are anemic with your myeloma

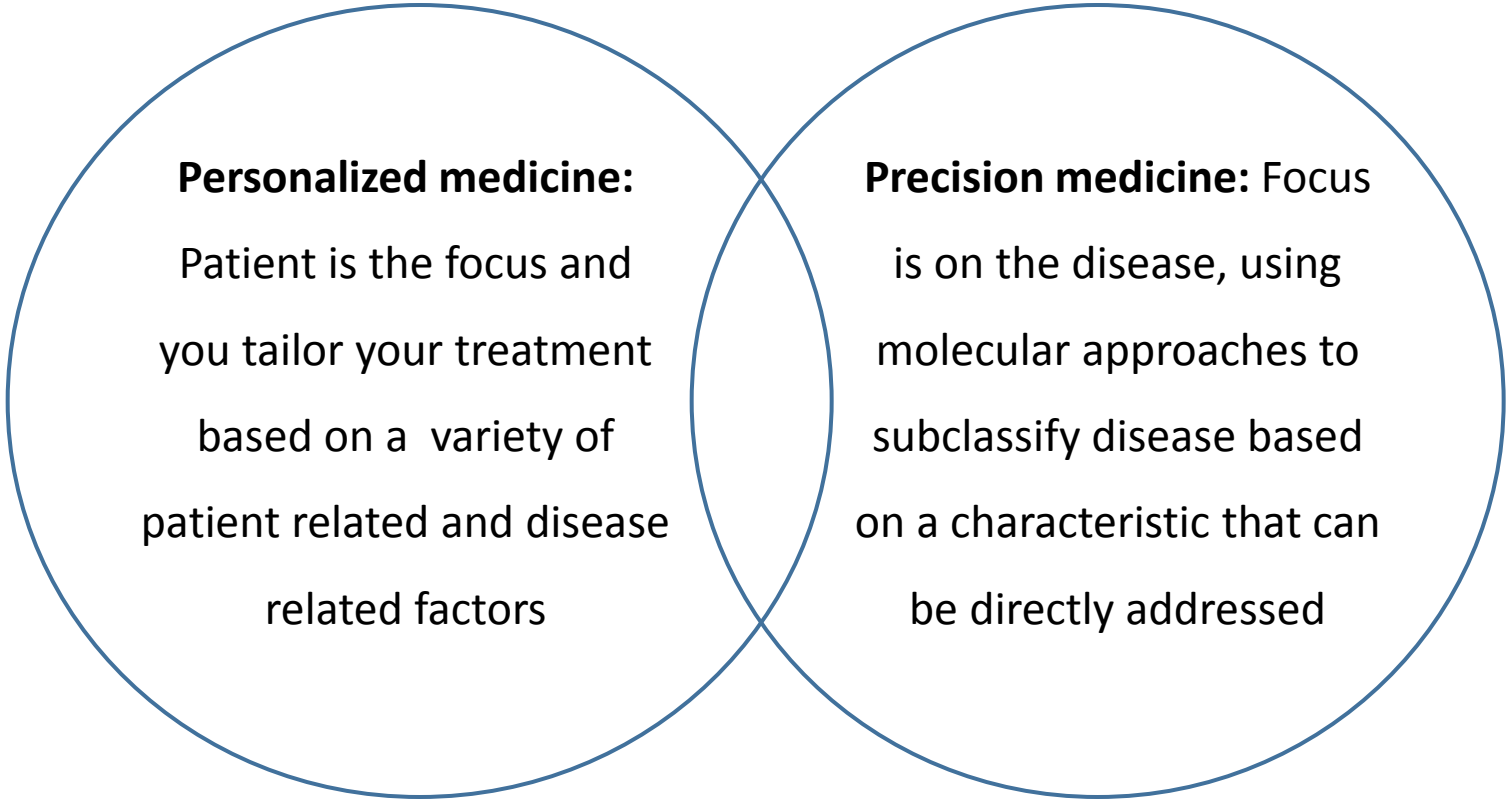
Press 3 if you cannot sleep because of dexamethasone

Press 4 if your fingers and toes are numb

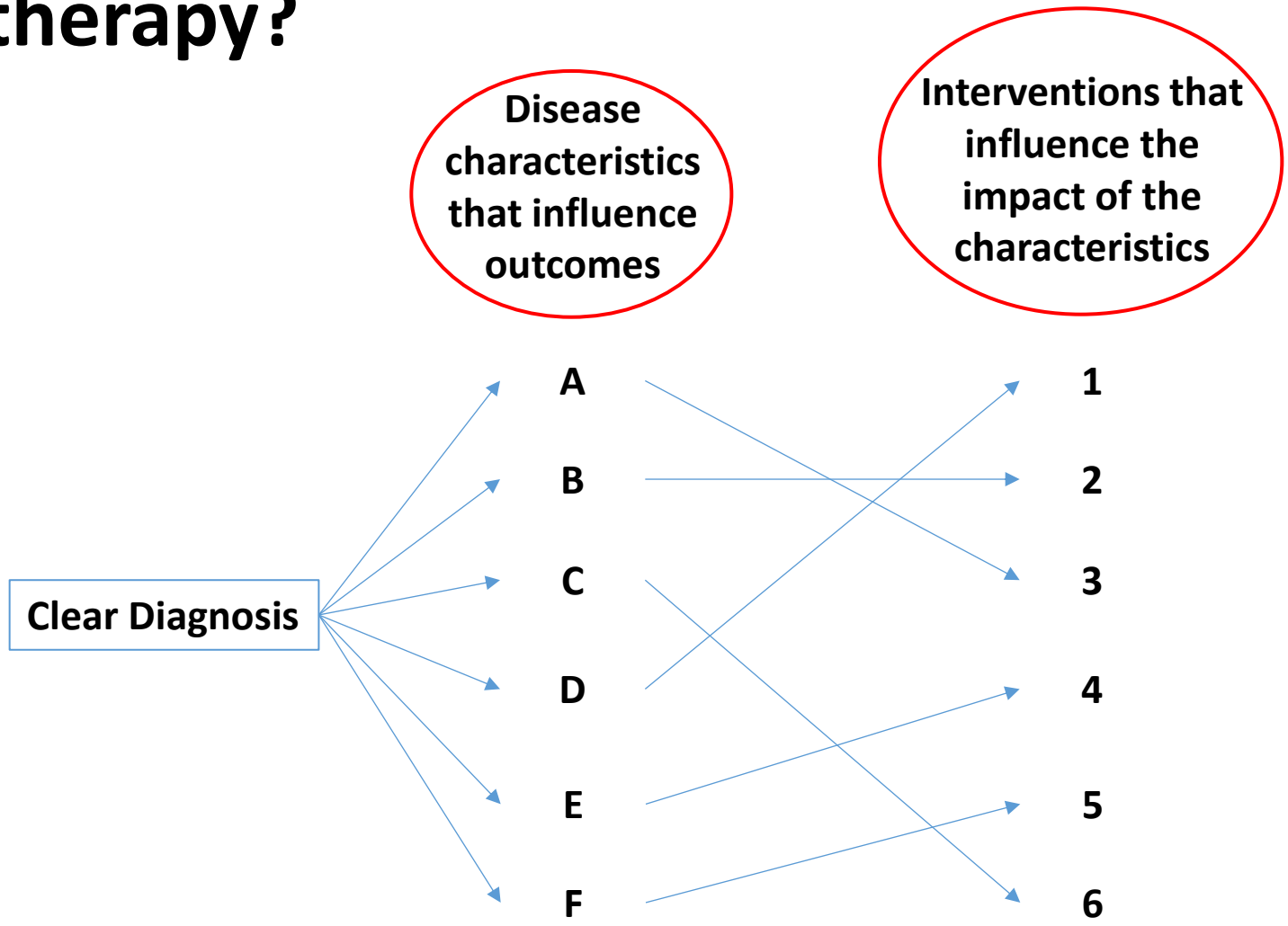
Personalized medicine

- As physicians, we always adapt the therapy to the patient, taking into account a multitude of factors
  - Disease characteristics
  - Patient wishes
  - Logistics etc….
- ***Customizing*** *therapy to individual patient**, based on specific*** ***characteristics,*** *leading to the* ***optimal outcom***e

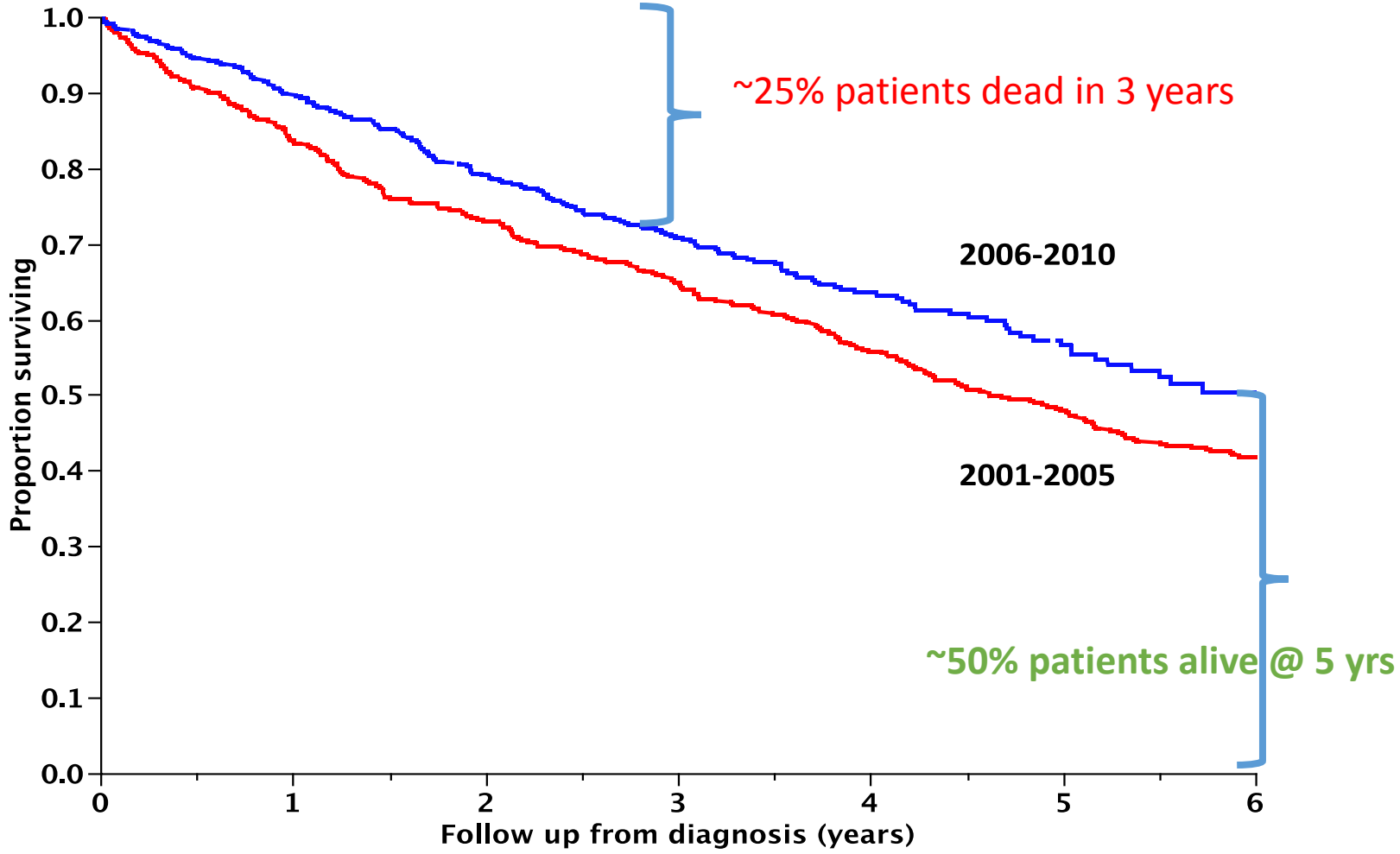
Personalized Medicine OR Precision Medicine?



What do we need for personalized therapy?



Myeloma is not one disease

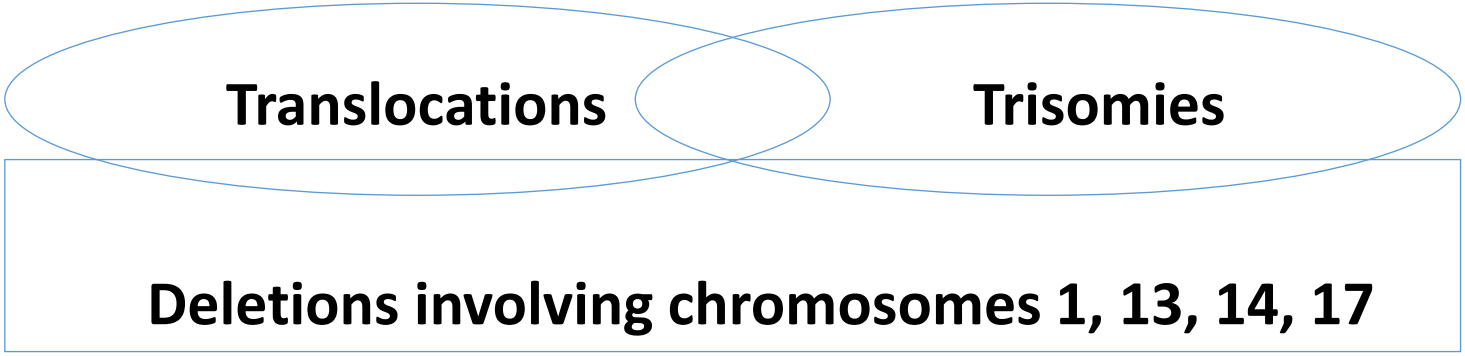


Kumar SK, et al. Leukemia. 2014;28:1122-1128.

What makes them different?

- ***Tumor clone***:
  - Genetic abnormalities
  - Proliferation, circulating cells etc.
- ***Host***:
  - Age, performance status
- ***Host and tumor***:
  - International staging system (ISS)
  - Immune parameters
- ***Variety of other "prognostic factors" have been described***

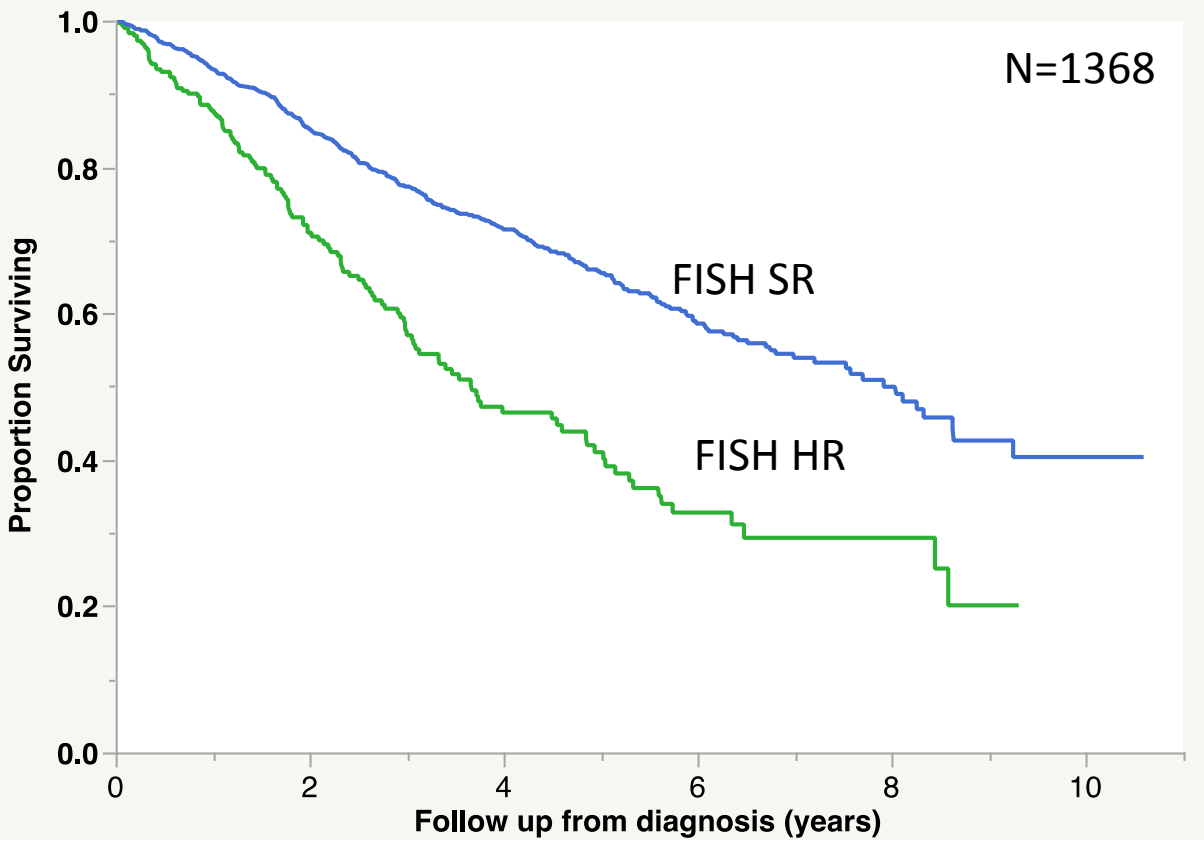
Genetic abnormalities in myeloma



FISH abnormality	Frequency (%)
Trisomy(ies) without IgH abnormality	*201 (42%)*
IgH abnormality without trisomy(ies)	*146 (30%)*
IgH abnormality with trisomy(ies)	*74 (15%)*
Monosomy 14 in absence of IgH translocations or trisomy(ies)	*22 (4.5%)*
Other cytogenetic abnormalities	*26 (5.5%)*
Normal	*15 (3%)*

Kumar S, et al. Blood. 2012;119:2100-2105.

Impact of FISH high risk abnormalities



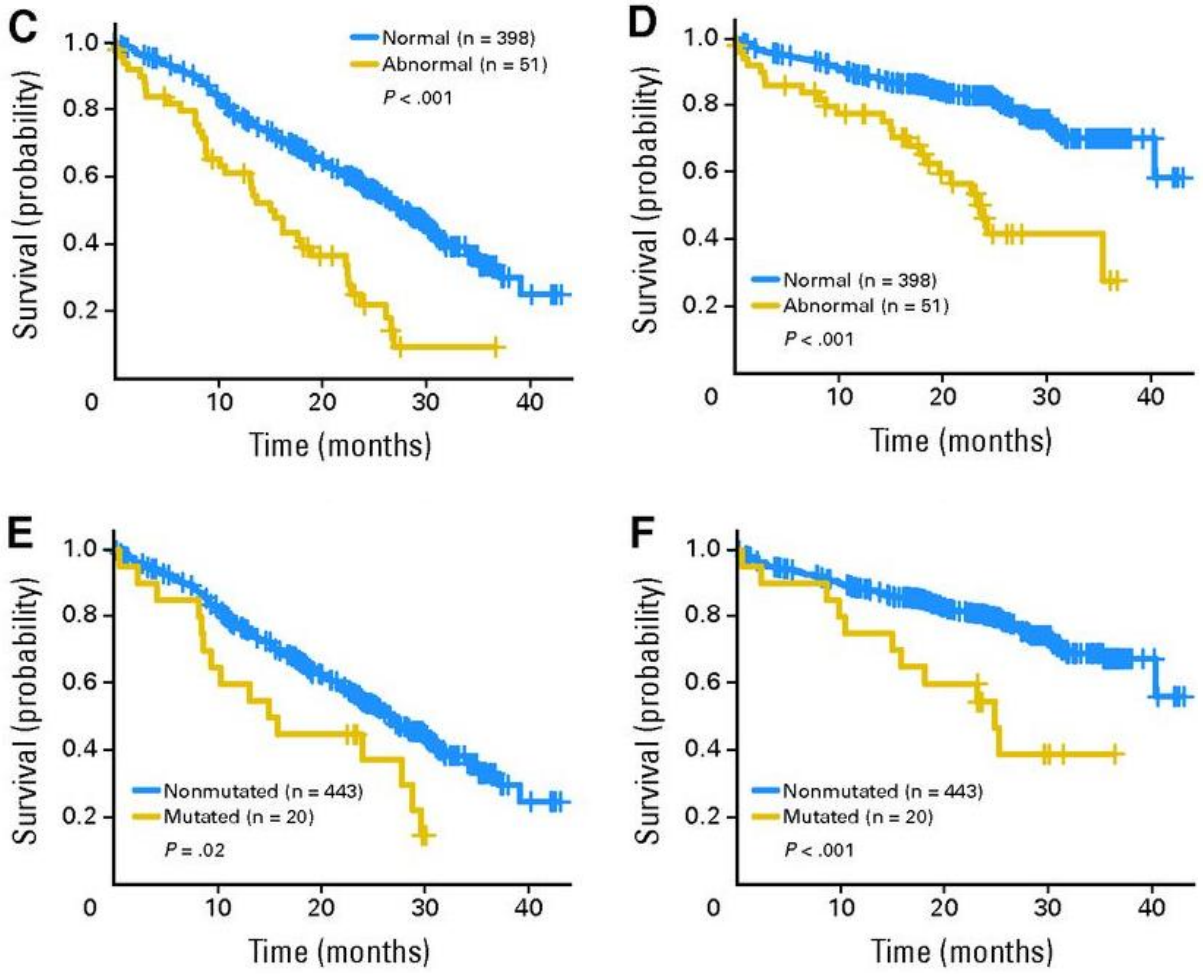
Kumar et al, unpublished

Mutations and outcomes

PFS **OS**

P53 mutations

ATM/ATR mutations



Walker et al, JCO August 17, 2015

Increasing number of tools

The old

- Alkylators
- Anthracyclines
- Corticosteroids

And the new….

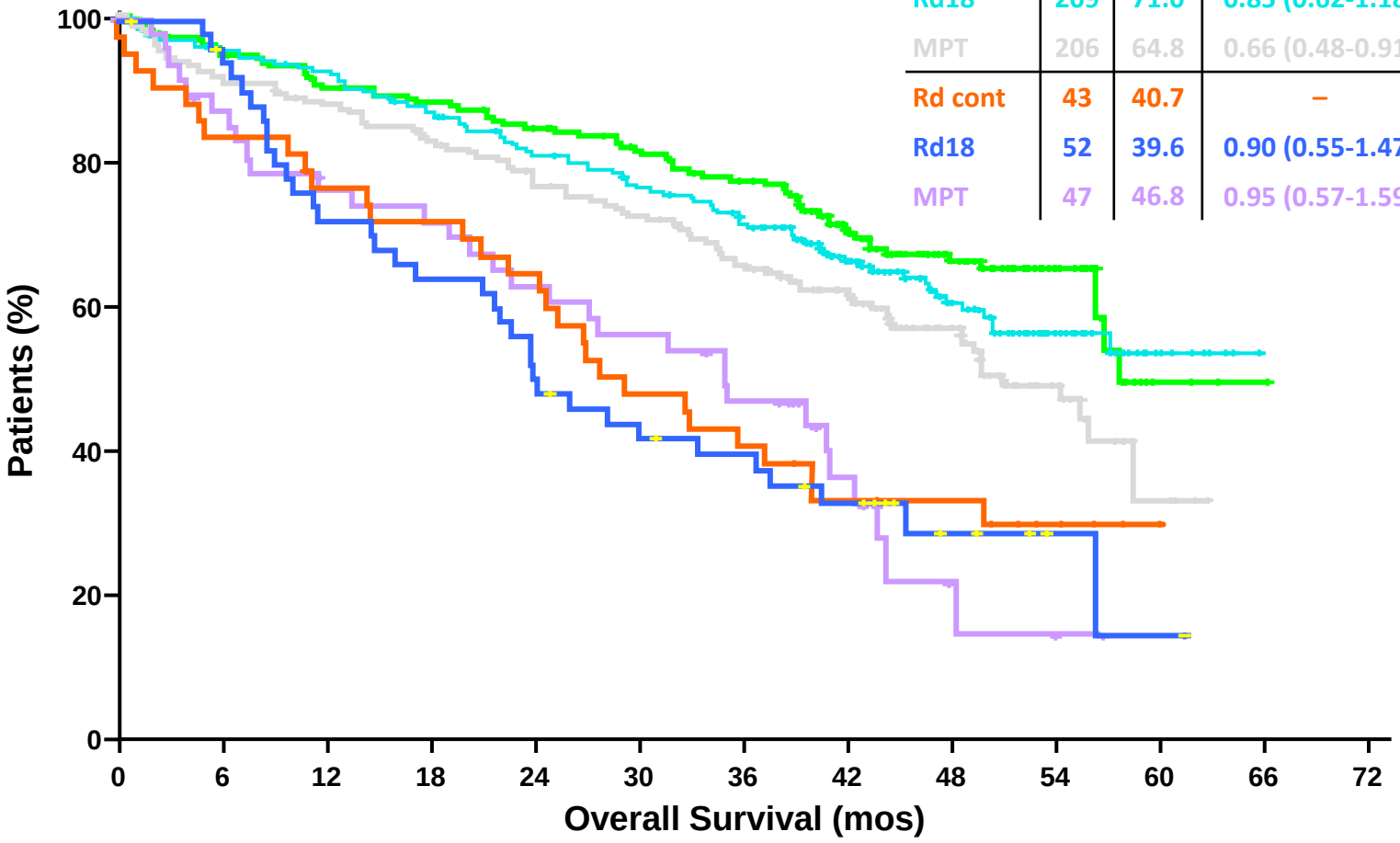
- Proteasome inhibitors
- IMiDs
- HDAC inhibitors
- Monoclonal antibodies

Tailoring the intervention

- Use of a specific ***drug*** or drug class
- Use of multidrug ***combinations***
  - E.g., PI + IMiD
- Varying the ***duration*** of therapy
  - Continuous vs. fixed
- Targeting a particular level of ***response***
  - E.g. CR or MRD negativity

What does not help high risk

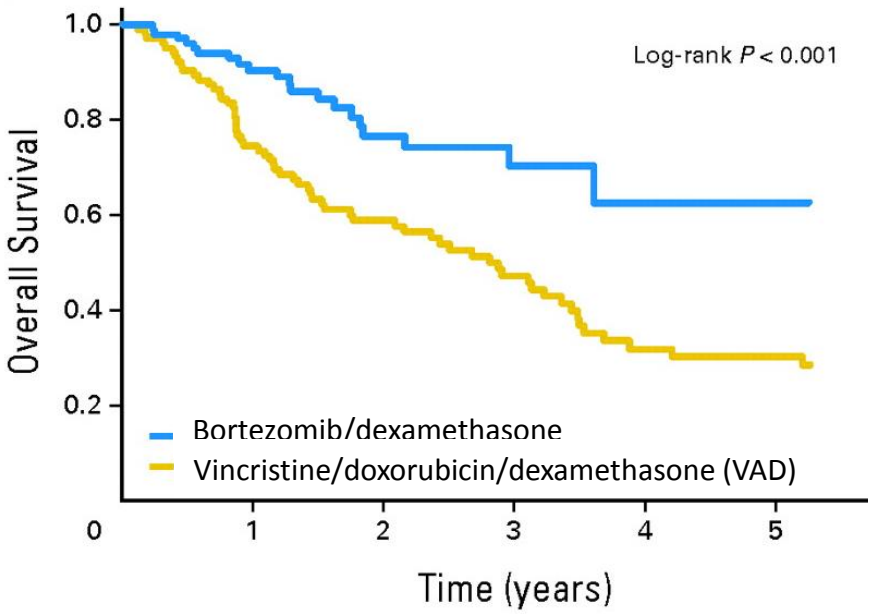
	n	3-yr, %	HR (95% CI) (Rd cont vs)	*P* Value (Rd cont vs)
Rd cont	205	77.1	–	–
Rd18	209	71.0	0.85 (0.62-1.18)	.337
MPT	206	64.8	0.66 (0.48-0.91)	.009
Rd cont	43	40.7	–	–
Rd18	52	39.6	0.90 (0.55-1.47)	.676
MPT	47	46.8	0.95 (0.57-1.59)	.859



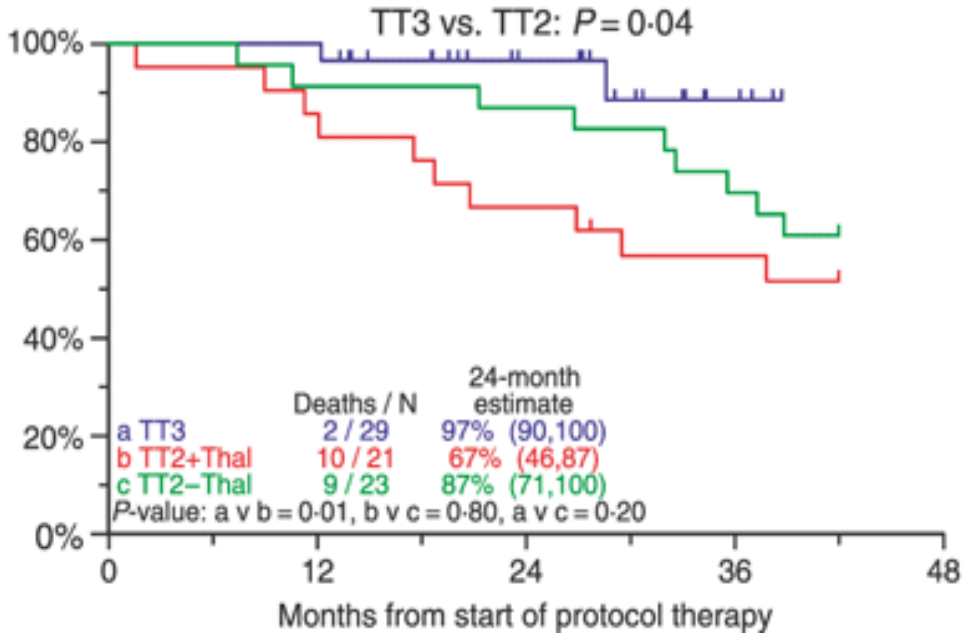
Avet-Loiseau et al, ASH 2015

Bortezomib and t(4;14): OS Analysis

OS in pts with t(4;14) with induction



OS by GEP-defined FGFR3/MMSET subgroup



Avet-Loiseau H, et al. J Clin Oncol. 2010;28:4630-4634. Pineda-Roman, et al. Br J Haematol. 2008;140:625-634.

Outcomes by cytogenetic risk group

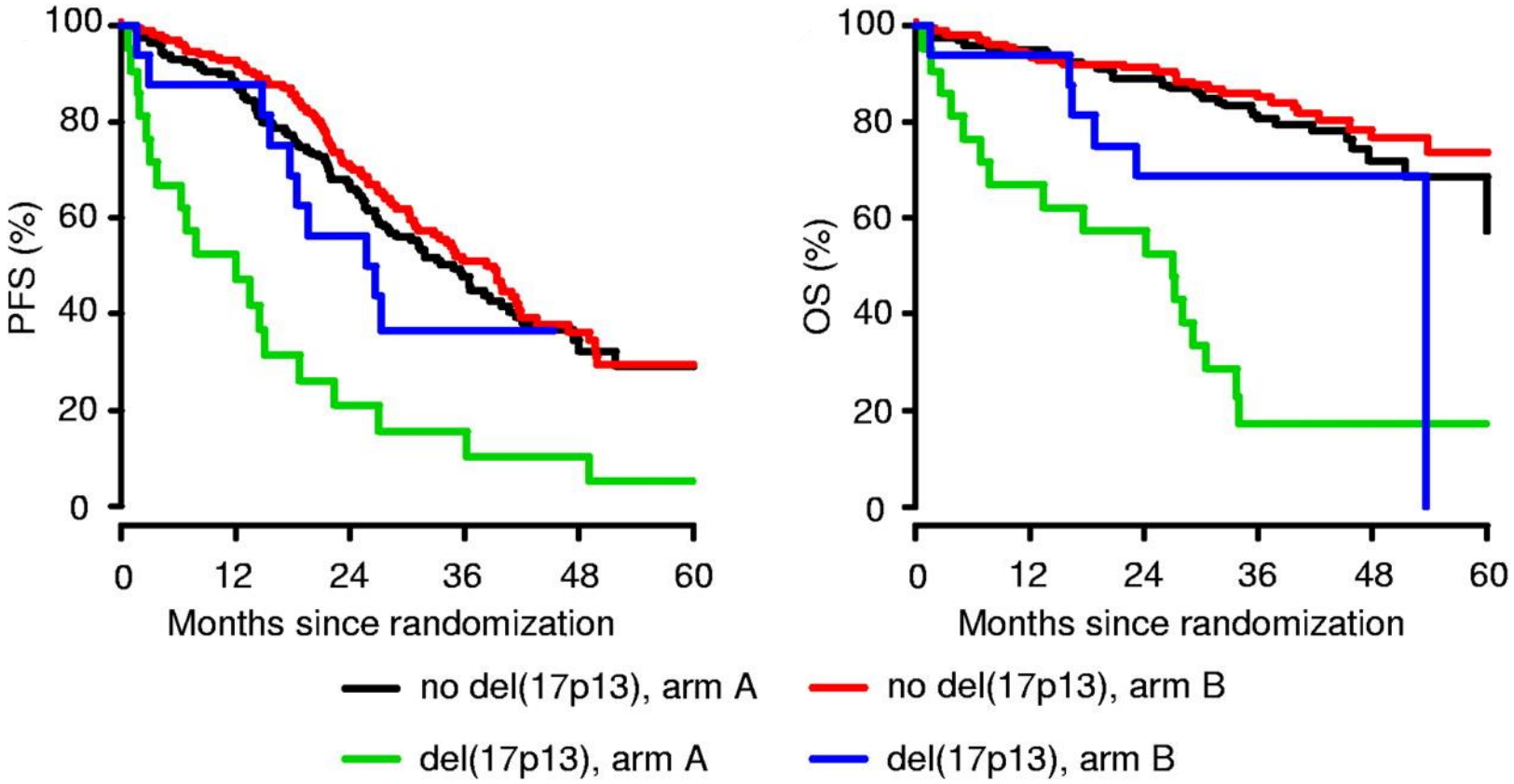
	ORR, %		≥VGPR, %		≥CR, %		Median PFS, months		
	IRd	Placebo-Rd	IRd	Placebo-Rd	IRd	Placebo-Rd	IRd	Placebo-Rd	HR
All patients	78.3*	71.5	48.1*	39	11.7*	6.6	20.6	14.7	0.742*
Standard-risk patients	80	73	51	44	12	7	20.6	15.6	0.640*
All high-risk patients	79*	60	45*	21	12*	2	21.4	9.7	0.543
Patients with del(17p)[†]	72	48	39	15	11*	0	21.4	9.7	0.596
Patients with t(4;14) alone	89	76	53	28	14	4	18.5	12.0	0.645

*p<0.05 for comparison between regimens. [†]Alone or in combination with t(4;14 or t(14;16).
Data not included on patients with t(14:16) alone due to small numbers (n=7).

- In the IRd arm, median PFS in high-risk patients was similar to that in the overall patient population and in patients with standard-risk cytogenetics

Moreau et al. ASH 2015

Bortezomib and del(17p)

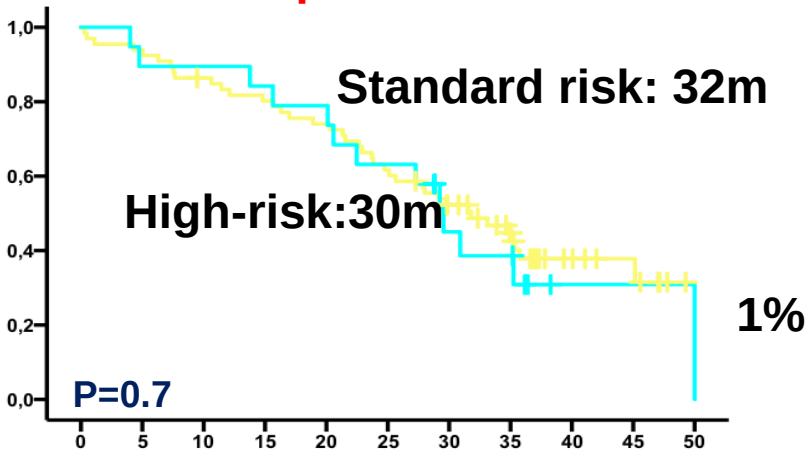


HOVON-65/GMMG-HD4: VAD induction, tandem SCT, and thalidomide maintenance vs PAD induction, tandem SCT, and bortezomib maintenance

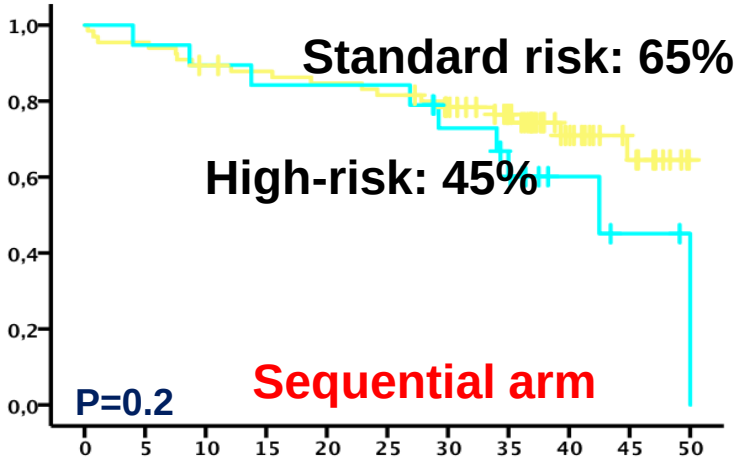
Neben K, et al. Blood. 2012;119:940-948.

Sequential vs. alternating VMP/ Rd

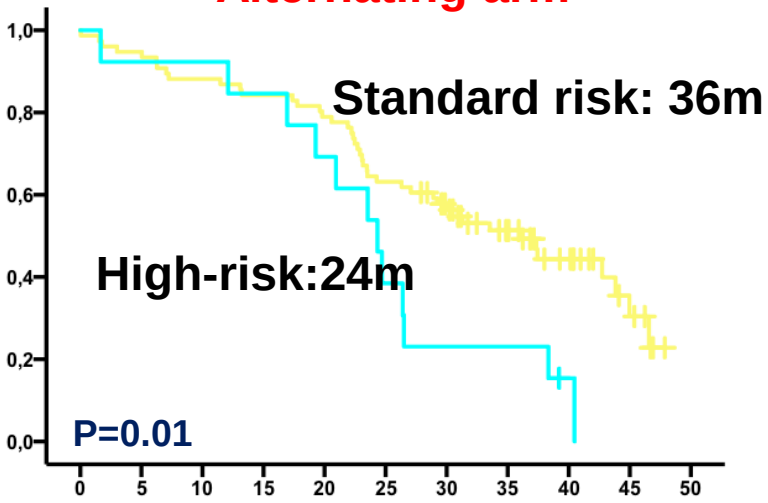
Sequential arm

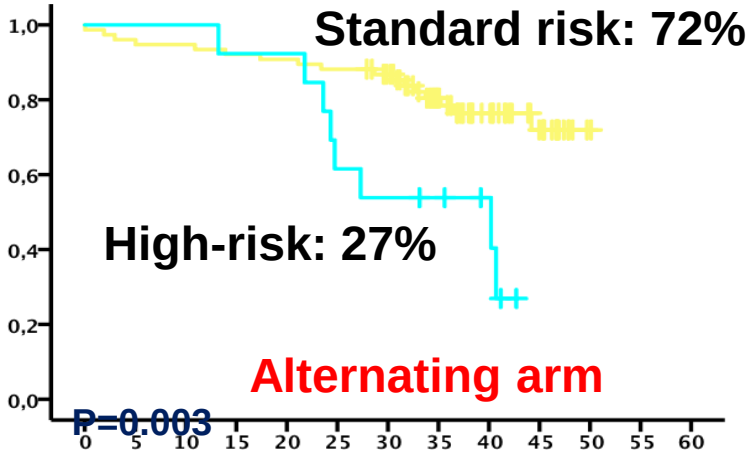


4years-OS



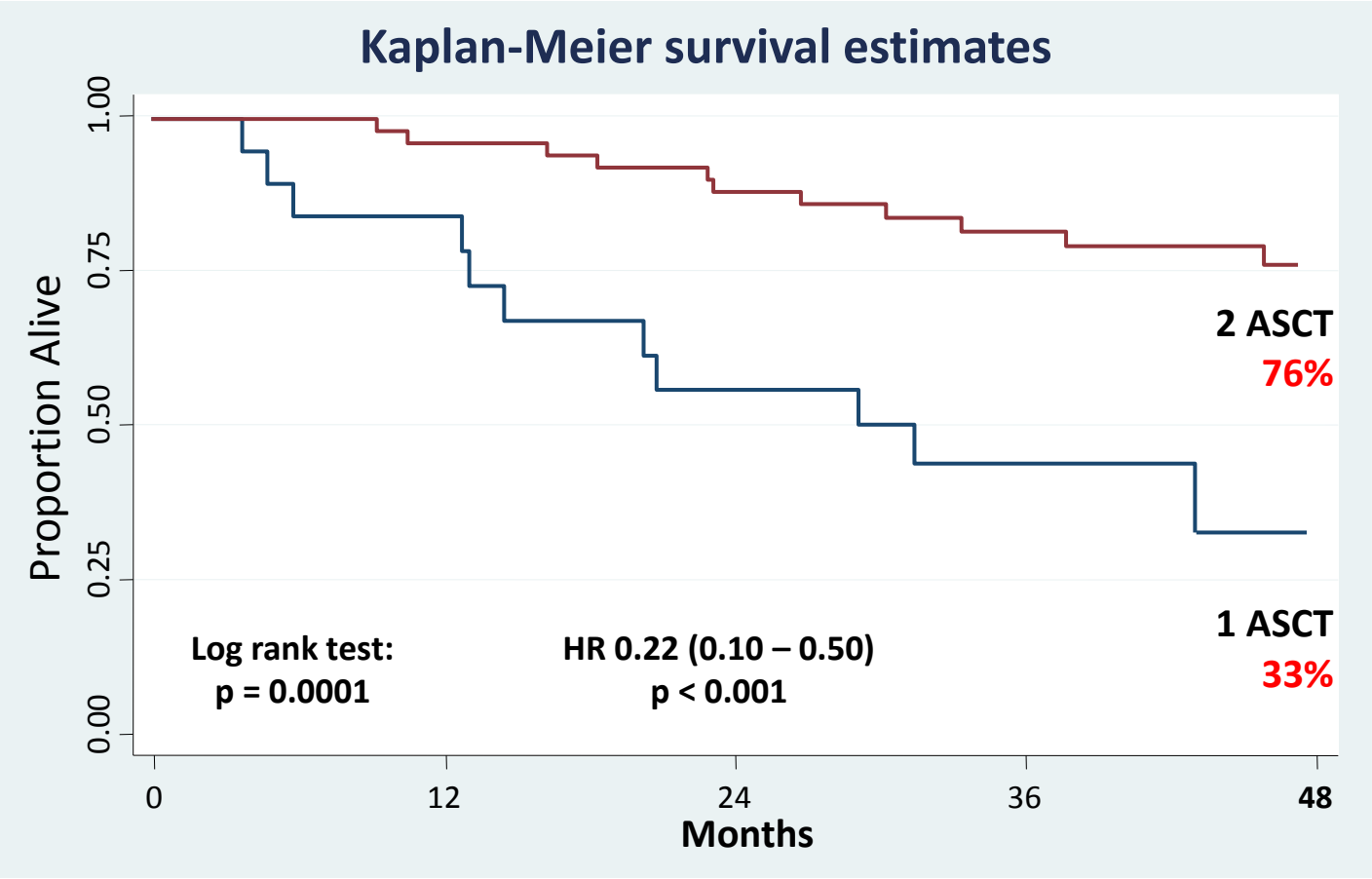
Alternating arm





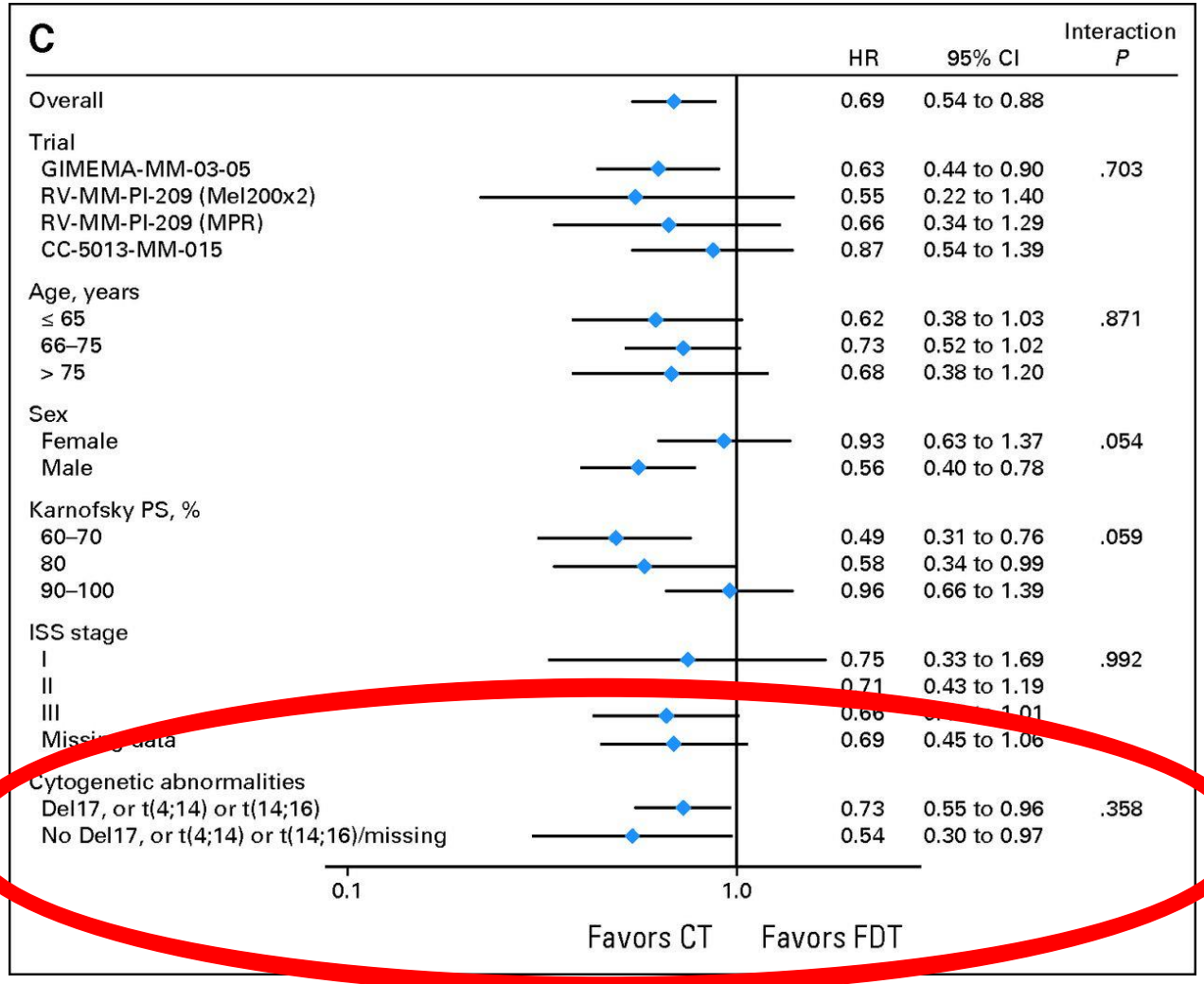
Mateos MV et al. ASH 2015

Tandem ASCT : del(17p) ± t(4;14)



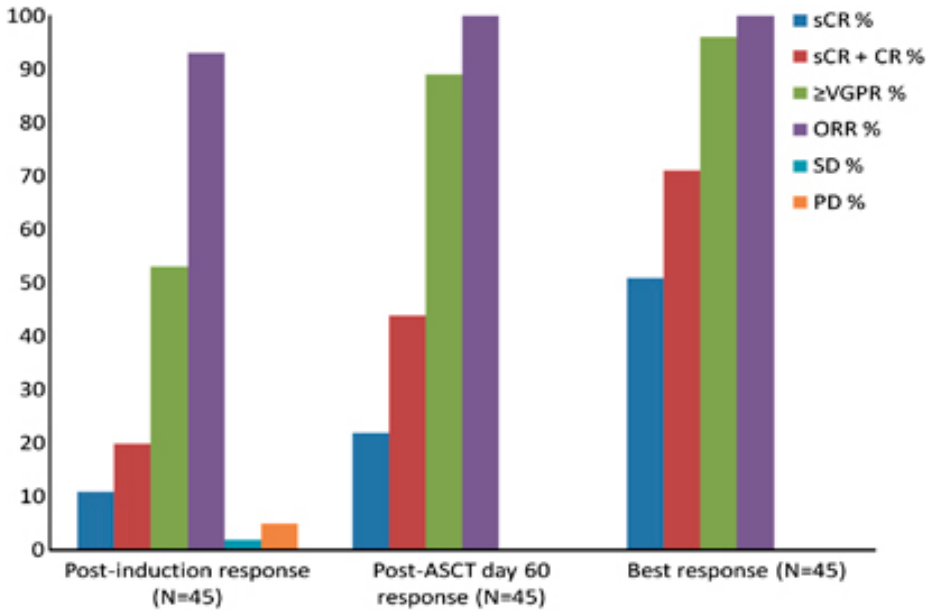
Cavo M, et al. ASH 2013. Abstract 767.

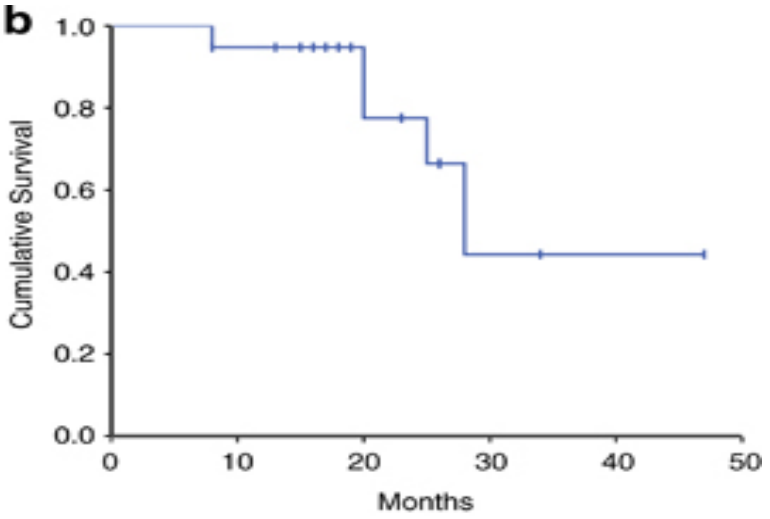
Effect of treatment duration

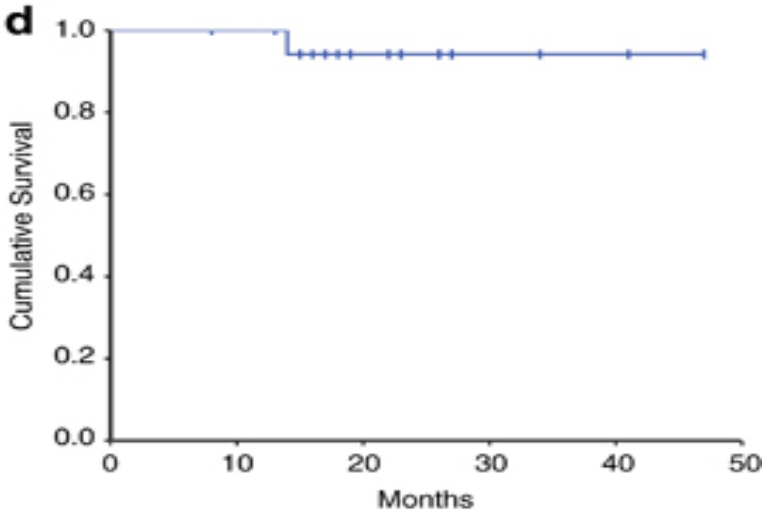


Antonio Palumbo et al. JCO doi:10.1200/JCO.2014.60.2466

VRD consolidation and maintenance

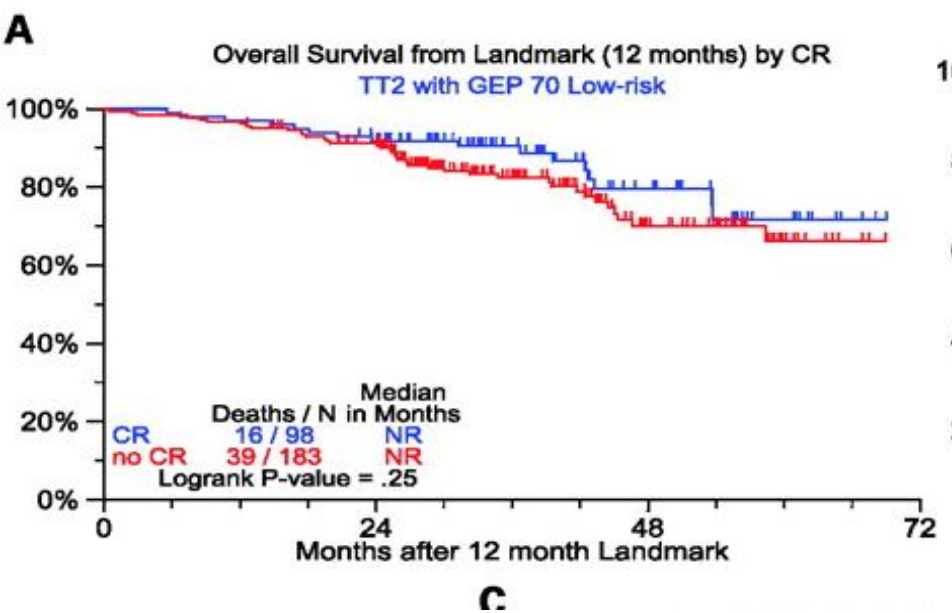


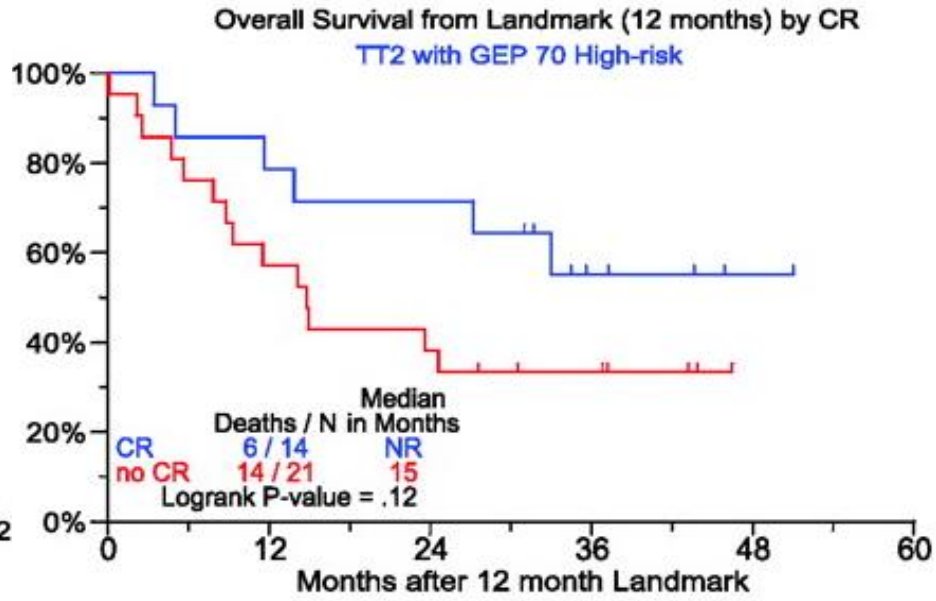




Nooka et al., Leukemia (2014) 28, 690–693

CR is particularly important for HR MM





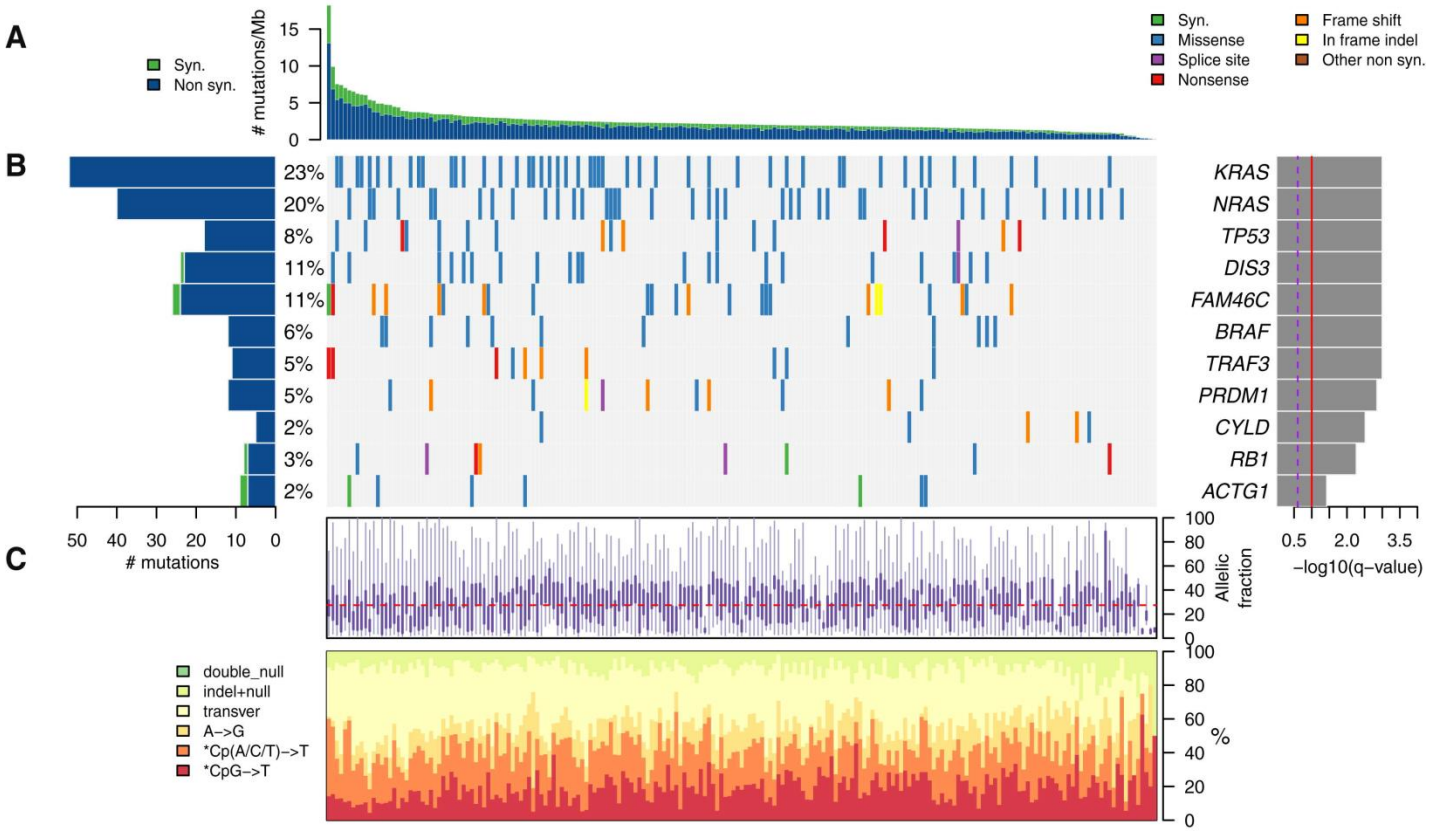
Leukemia (2011) 25, 1195–1197

Venetoclax and t(11;14

n (%)[a]	Evaluable patients with t(11;14) (n=17)	Evaluable patients without t(11;14)[b] (n=26)	All evaluable patients (n=43)
Objective response rate (CR+ VGPR + PR)	4 (24)	1 (4)	5 (12)
Complete response (CR)	2 (12)	0	2 (5)
Very good PR (VGPR)	2 (12)	1 (4)[c]	3 (7)
Partial response (PR)	0	0	0
Minimal response	1 (6)	0	1 (2)
Stable disease (SD)	5 (29)	12 (46)	17 (40)

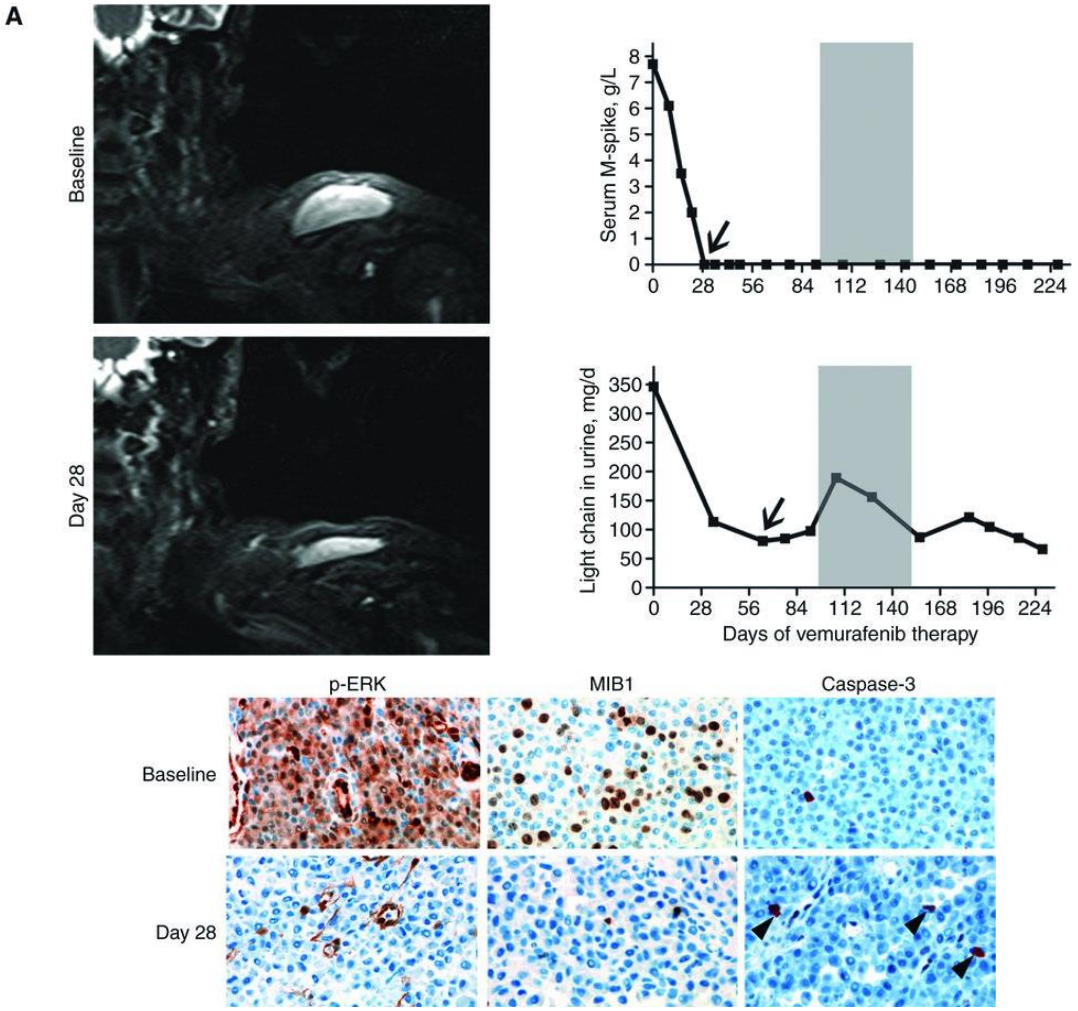
Kumar et al, ASH 2015

Evolving genome of MM



Lohr et al

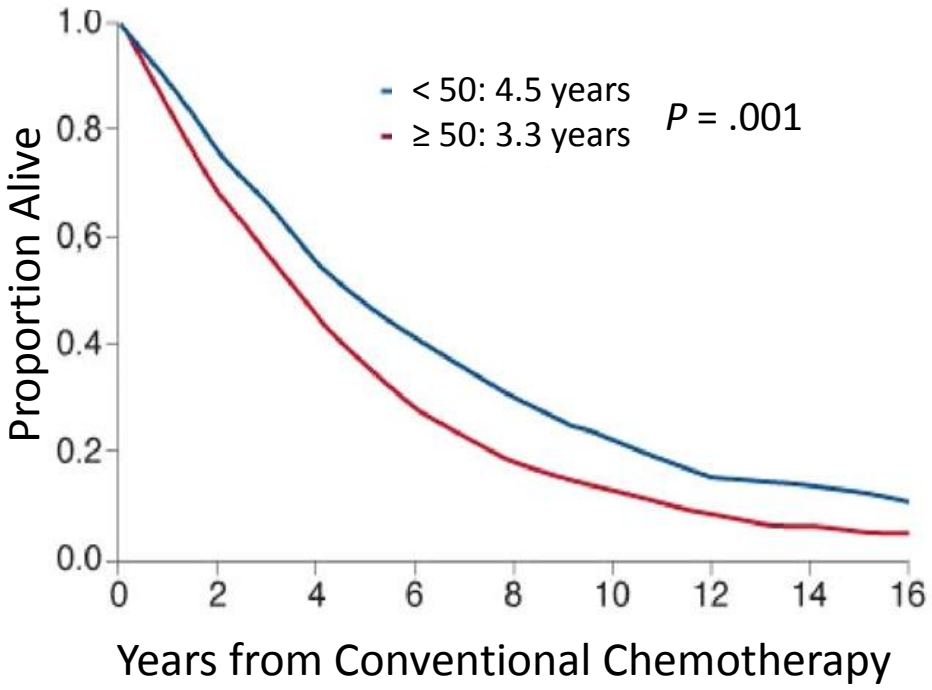
Digging deeper….targeting therapy



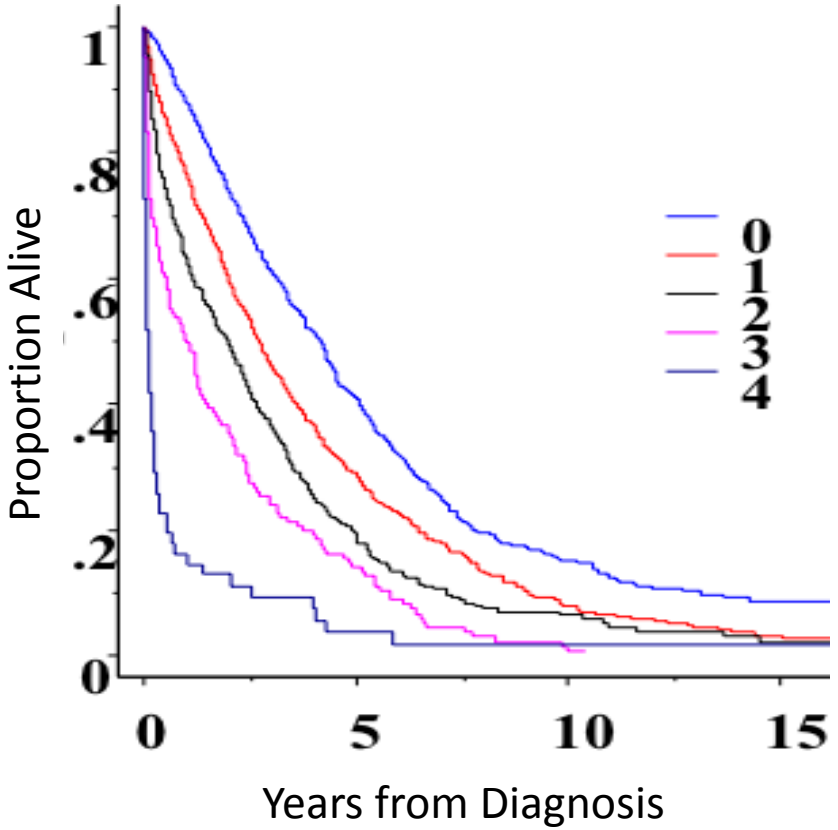
Andrulis et al, Cancer Discovery August 2013 3; 862

Age and Performance Status

Impact of age



Impact of ECOG performance stage



Ludwig H, et al. Blood. 2008;111:4039-4047. Kumar et al, unpublished data.

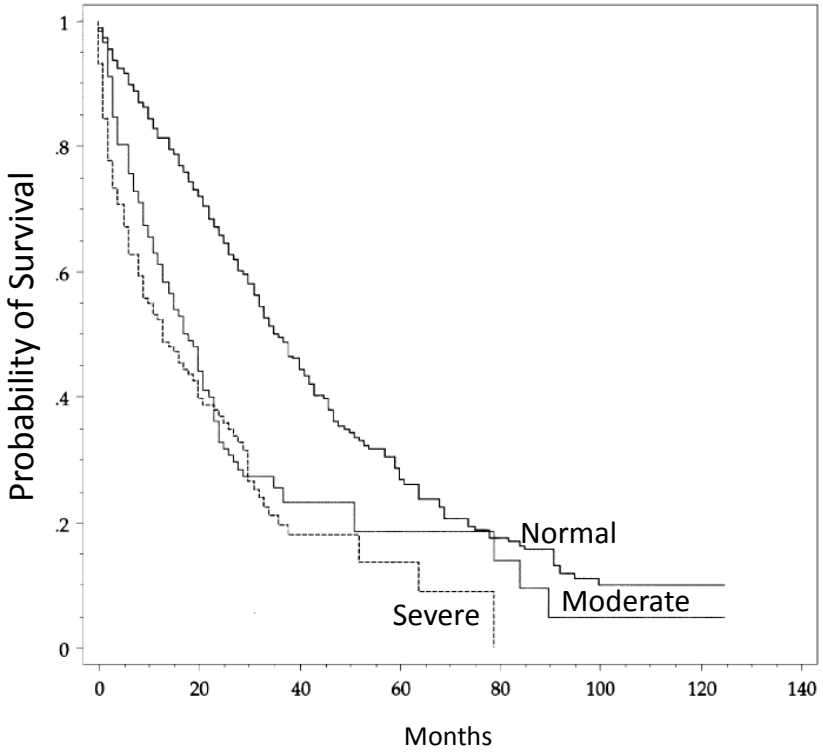
Risk factors		
• Age over 75 years • Mild, moderate or severe frailty: patients needing help for household tasks and personal care* • Comorbidities: cardiac dysfunction pulmonary dysfunction hepatic dysfunction renal dysfunction		
GO-GO	***MODERATE-GO***	***SLOW-GO***
No risk factors ↓ DOSE LEVEL 0	At least one risk factor ↓ DOSE LEVEL –1	At least one risk factor plus occurrence of grade 3-4 non-hematologic AE ↓ DOSE LEVEL –2

Agent	DOSE LEVEL 0	DOSE LEVEL –1	DOSE LEVEL –2
Dexamethasone	40 mg/d d 1,8,15,22 / 4 wks	20 mg/d d 1,8,15,22 / 4 wks	10 mg/d d 1,8,15,22 / 4 wks
Melphalan	0.25 mg/kg or 9 mg/m^2 d 1-4 / 4-6 wks	0.18 mg/kg or 7.5 mg/m^2 d 1-4 / 4-6 wks	0.13 mg/kg or 5 mg/m^2 d 1-4 / 4-6 wks
Thalidomide	100 mg/d	50 mg/d	50 mg qod
Lenalidomide	25 mg/d d 1-21 / 4 wks	15 mg/d d 1-21 / 4 wks	10 mg/d d 1-21 / 4 wks
Bortezomib	1.3 mg/m^2 twice weekly d 1,4,8,11 / 3 wks	1.3 mg/m^2 once weekly d 1,8,15,22 / 5 wks	1.0 mg/m^2 once weekly d 1,8,15,22 / 5 wks
Prednisone	60 mg/m^2 d 1-4 or 50 mg qod	30 mg/m^2 d 1-4 or 25 mg qod	15 mg/m^2 d 1-4 or 12.5 mg qod
Cyclophosphamide	100 mg/d d1-21/ 4 wks or 300 mg/m^2/d d 1,8,15 / 4 wks	50 mg/d d 1-21 / 4 wks or 150 mg/m^2/d D 1,8,15 / 4 wks	50 mg qod d 1-21 / 4 wks or 75 mg/m^2/d d 1,8,15 / 4 wks

Palumbo A, et al. Blood. 2011;118:4519-4529.

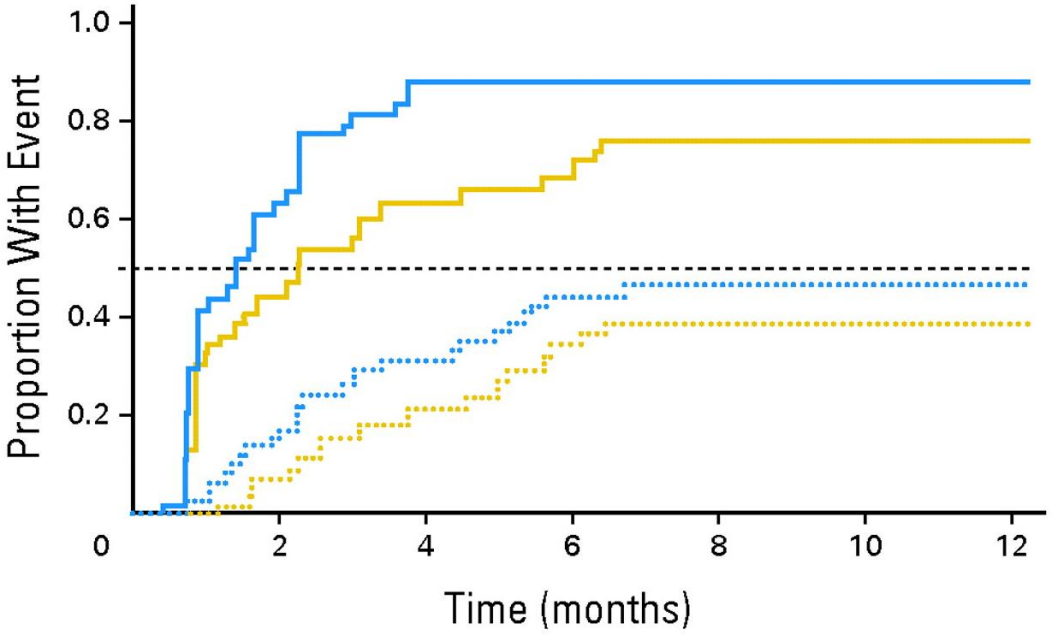
Renal Failure and Bortezomib

OS by Renal Impairment at Diagnosis



Normal renal function: p-creatinine < 130 µmol/L
Moderate renal function: p-creatinine 130 -200 µmol/L
Severe renal function: p-creatinine > 200 µmol/L

Cumulative Incidence of
Myeloma Response and Renal Response

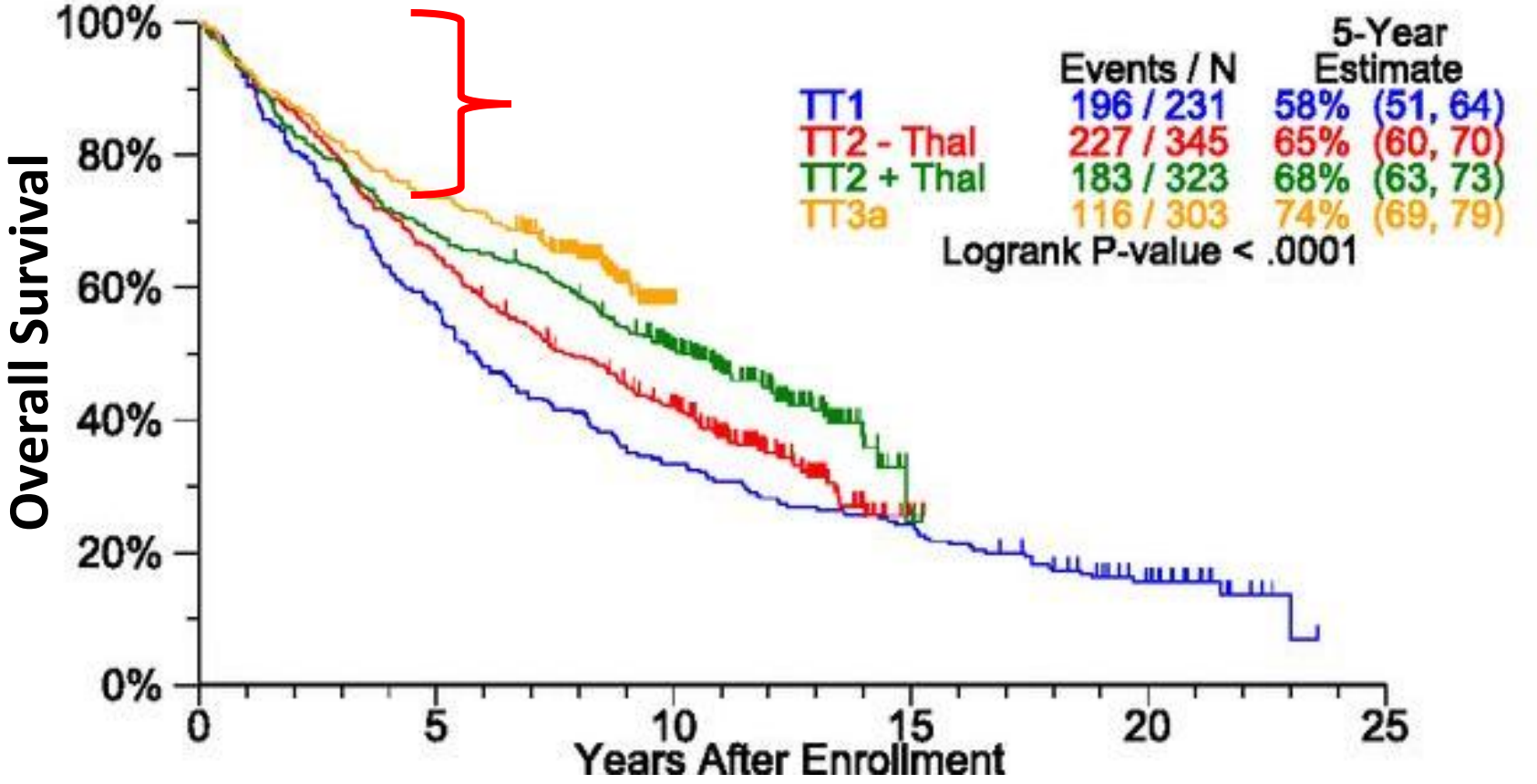


Any MM response (CR-MR); n = 58; median 1.4 mo
CR/nCR MM; n = 58; median NA

Any renal response (CR-MR); n = 58; median 2.2 mo
CR/ renal; n = 58; median NA

Knudsen LM, et al. Eur J Haematol. 2000:65:175-181. Ludwig, et al. J Clin Oncol. 2010;28:4635-4641.

Just give the most intense Rx to all….



Barlogie B, et al. Blood. 2014;124:3043-3051.

Exceptional response

- Patients receiving Rd as initial therapy and TTP>72m
- Identified 33 exceptional responders; 25 primary Rd, 8 Rd induction followed by autologous transplantation.
- Fifteen (45%) had known clonal plasma cell disorder prior to the diagnosis of MM.
- Trisomies were present in 19 (79%), none had high risk cytogenetic features at baseline.
- 25 patients (76%) had a CR, while 8 (24%) achieved the exceptional response state without ever achieving a CR.

Vu et al, BCJ, September 2015,

Toxicity

"I stopped taking the medicine because I prefer the original disease to the side effects."

Cost

"Surely, you must have some way to pay for your prescription, Mr. Fromberg!"

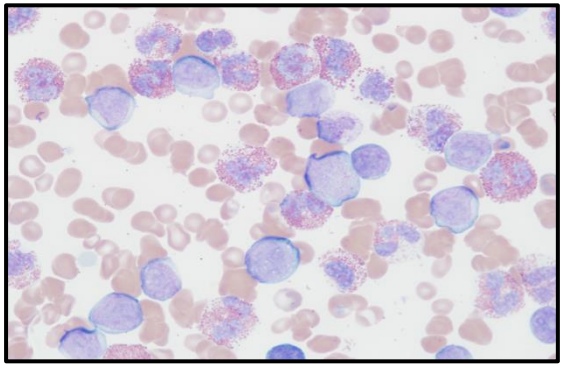
FLT3 ITD
1. Sorafenib
2. Midostaurin
3. Quizartinib
4. Gilteritinib
5. Crenolanib
6. FLX-925

IDH1/2
1. AG-120- IDH1
2. AG-221- IDH2
3. AG-881- pan IDH inhibitor

EZH2
1. Tazemetostat
2. E7438

MLL PTD/ fusions
1. DOT1L-EPZ-5676

_Tp53_
1. *WEE1* inhibitor-AZD1775



Genomic targets for AML

KRAS/NRAS
1. Trametinib
2. Binimetinib

DNMT3A & TET2
1. 5-AZA
2. Decitabine
3. SGI-110

ASXL1, SUZ12, EED (PRC2)- Epigenetic modifiers
1. LSD1 inhibitors
2. BET inhibitors
3. UTX/JMJD3 inhibitors

Kit-D816V
Dasatinib

So, we have the tools…..

- We know myeloma is a heterogeneous disease
- We can predict the disease behavior, i.e., risk
- We know that specific approaches can modify the risk, at least for some
- Then,…..

Why not?

The future is here!