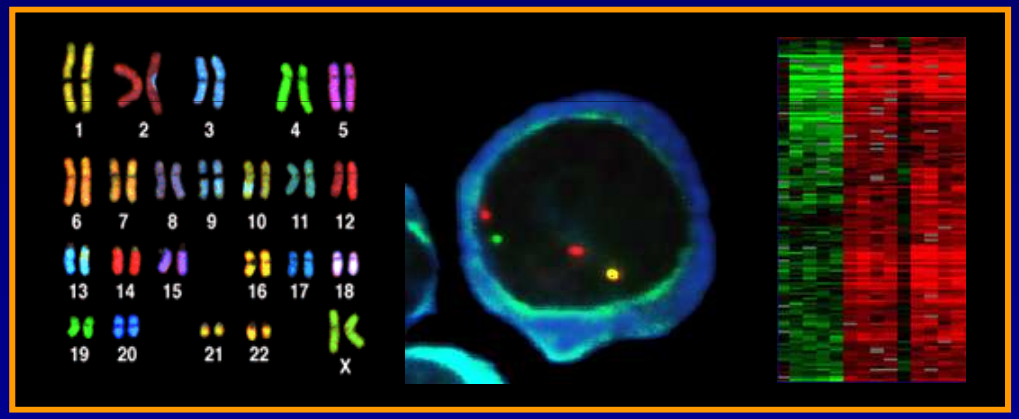
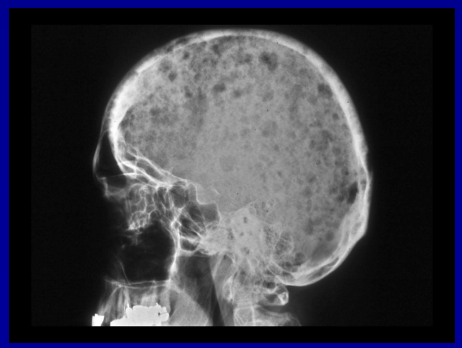
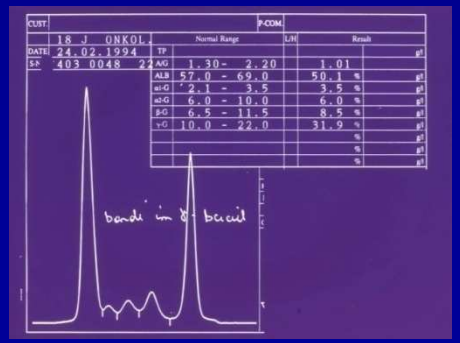
MULTIPLE MYELOMA
…not just one disease!

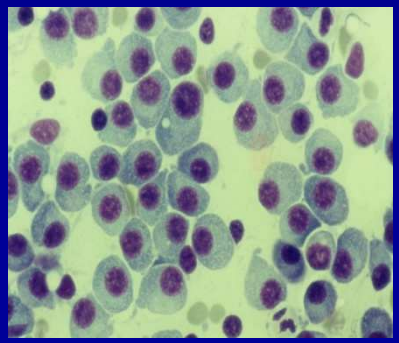
- Risk stratification
- Individualization of treatment

3 decades





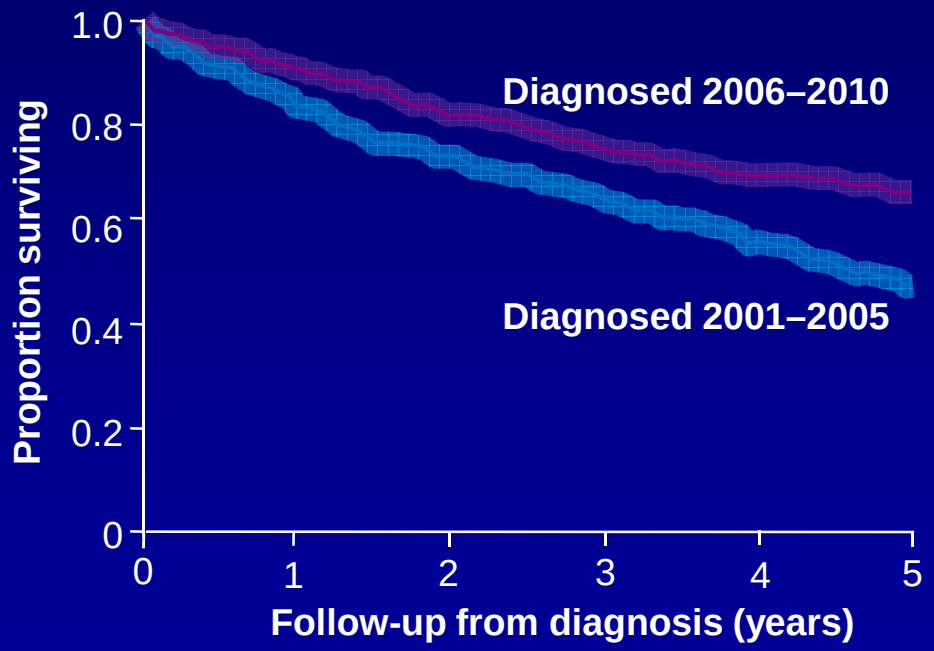




Drach J, ASH 2012

Continued Improvement in Survival Since the Introduction of Novel Agents

- 1,056 pts grouped into 2001–2005 and 2006–2010 cohorts
- Survival improved over time, particularly in pts aged > 65 years (p = 0.001)



Survival	2001–2005	2006–2010	p
Median OS, years	4.6	NR	0.001
1-year survival, %	83	90	
5-year estimated OS, %			
Overall	48	66	
> 65 years	31	56	0.001
< 65 years	63	73	NS

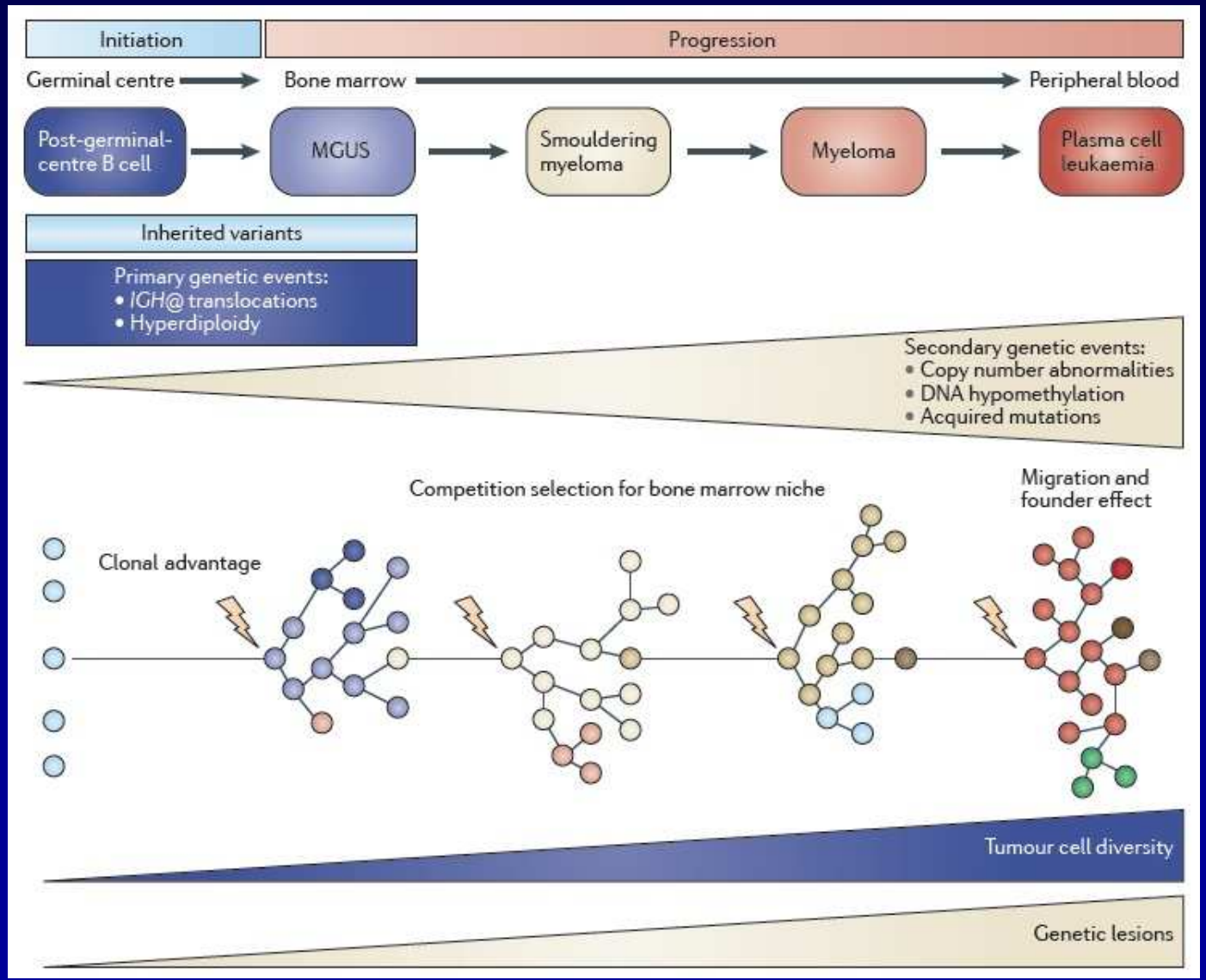
Kumar SK, et al. Blood. 2012;120:[abstract 3972]. Updated data presented at ASH 2012.

Progress and Challenges in the Treatment of MM; 2013

- **Progress**
  - Better Understanding of Disease Biology
  - Sustantial improvements in outcome due to availability of Novel Therapies
    - Potential for MM to become a chronic disease in most pts, and in some, a functional cure?
  - Management of adverse events and comorbidities of intensive therapy vs. novel agents (e.g. limiting the impact of genotoxic injury)

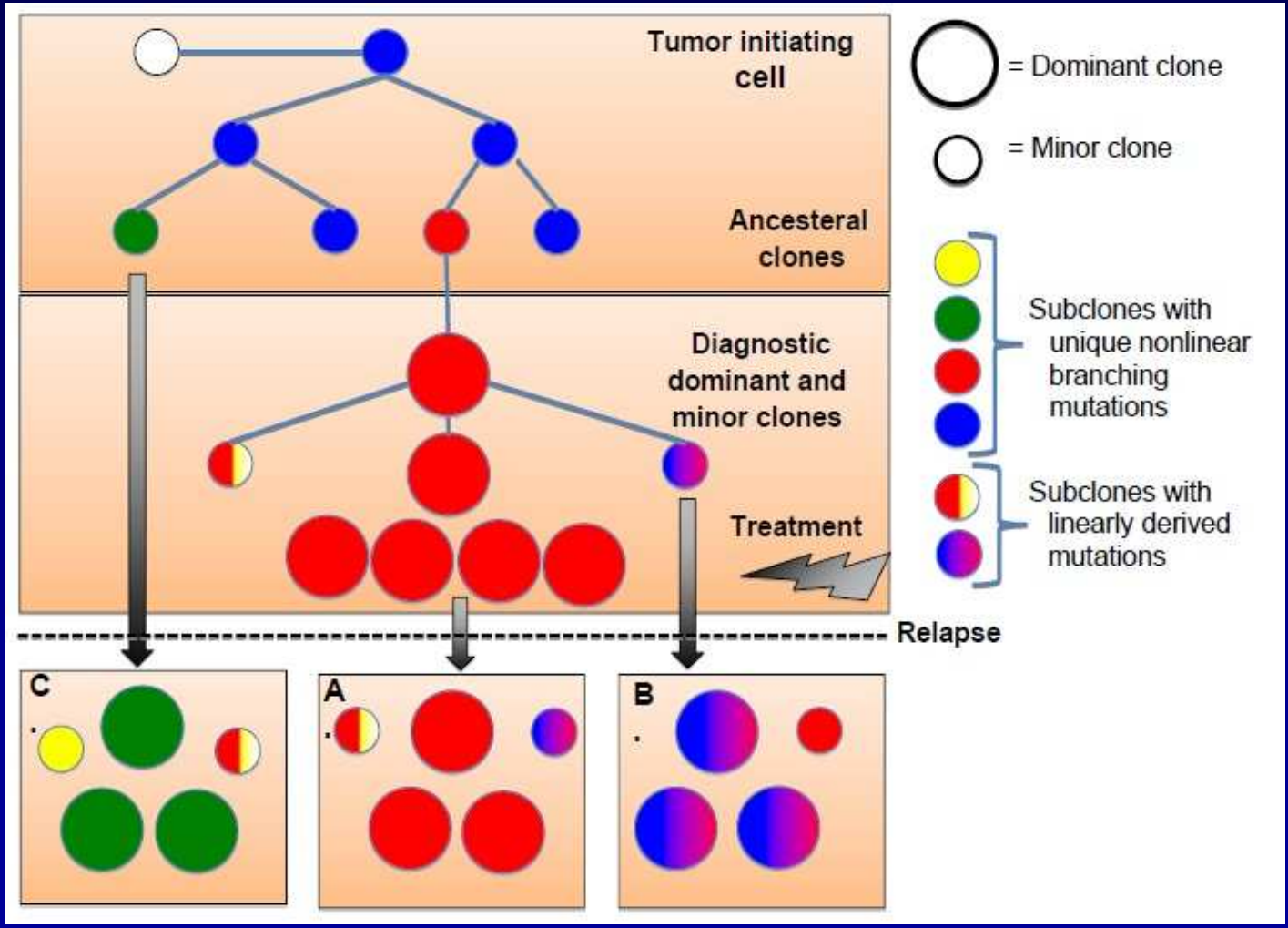
- **Challenges**
  - MM remains incurable in majority of pts
  - Increasing symptom burden due to disease and cumulative effects of treatments
  - Managing balance of disease control and quality of life
  - Does SCT benefit every eligible pt and what is its contribution to OS ?

Initiation and Progression of MM



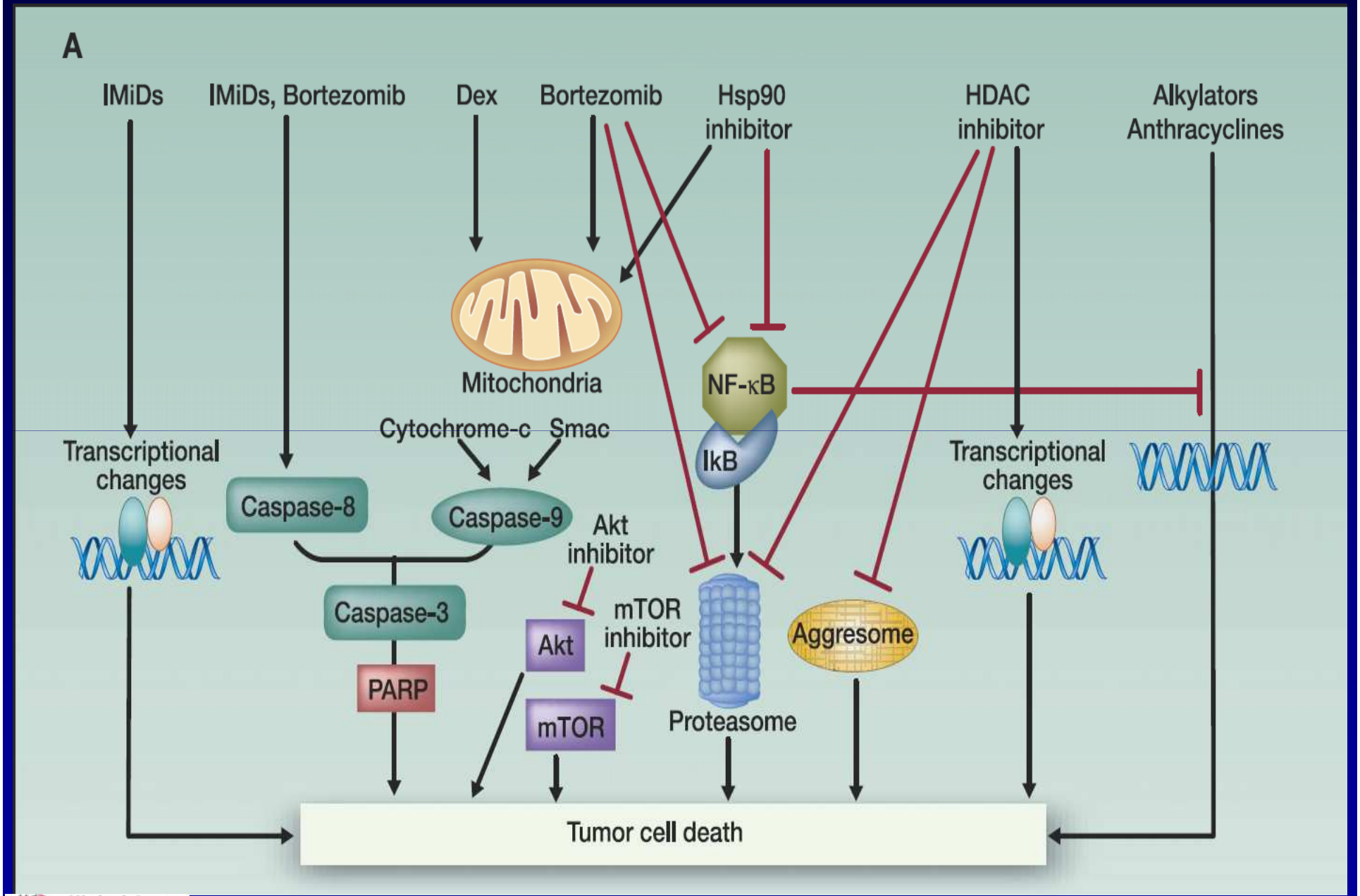
Morgan et al. Nat Rev Cancer 2012;12:335-348

Clonal Architecture at Diagnosis and Relapse: Clonal Tides Instead of Linear Evolution



Bahlis et al. Blood 2012;120:1077-1086

Rational Combination Strategies in MM, Plus MoAbs (Elo,Dara)



Clinical Cancer Research

Adapted from Lonial S, Mitsiades CS, Richardson PG. Clin Cancer Res 2011;17:1264-1277

Best Response to RVD in newly diagnosed MM (Phase I/II)

Response, n (%)	All pts (N=66)	Phase II (N=35)
CR	19 (29)	13 (37)
nCR	7 (11)	7 (20)
VGPR	18 (27)	6 (17)
PR	22 (33)	9 (26)
CR+nCR	26 (39)	20 (57)
(90% CI)	(29, 50)	(42, 71)
CR+nCR+VGPR	44 (67)	26 (74)
(90% CI)	(56, 76)	(59, 86)
At least PR	66 (100)	35 (100)
(90% CI)	(96, 100)	(92, 100)

- Response improvement seen in 42/56 pts (75%) from C4–8 and 20/38 pts (53%) beyond C8
- Median (range time to best overall response) was 2.1(0.6,20) mos

Richardson et al, *Blood* 2010

RVD: Impact of Baseline Characteristics and Cytogenetic Abnormalities

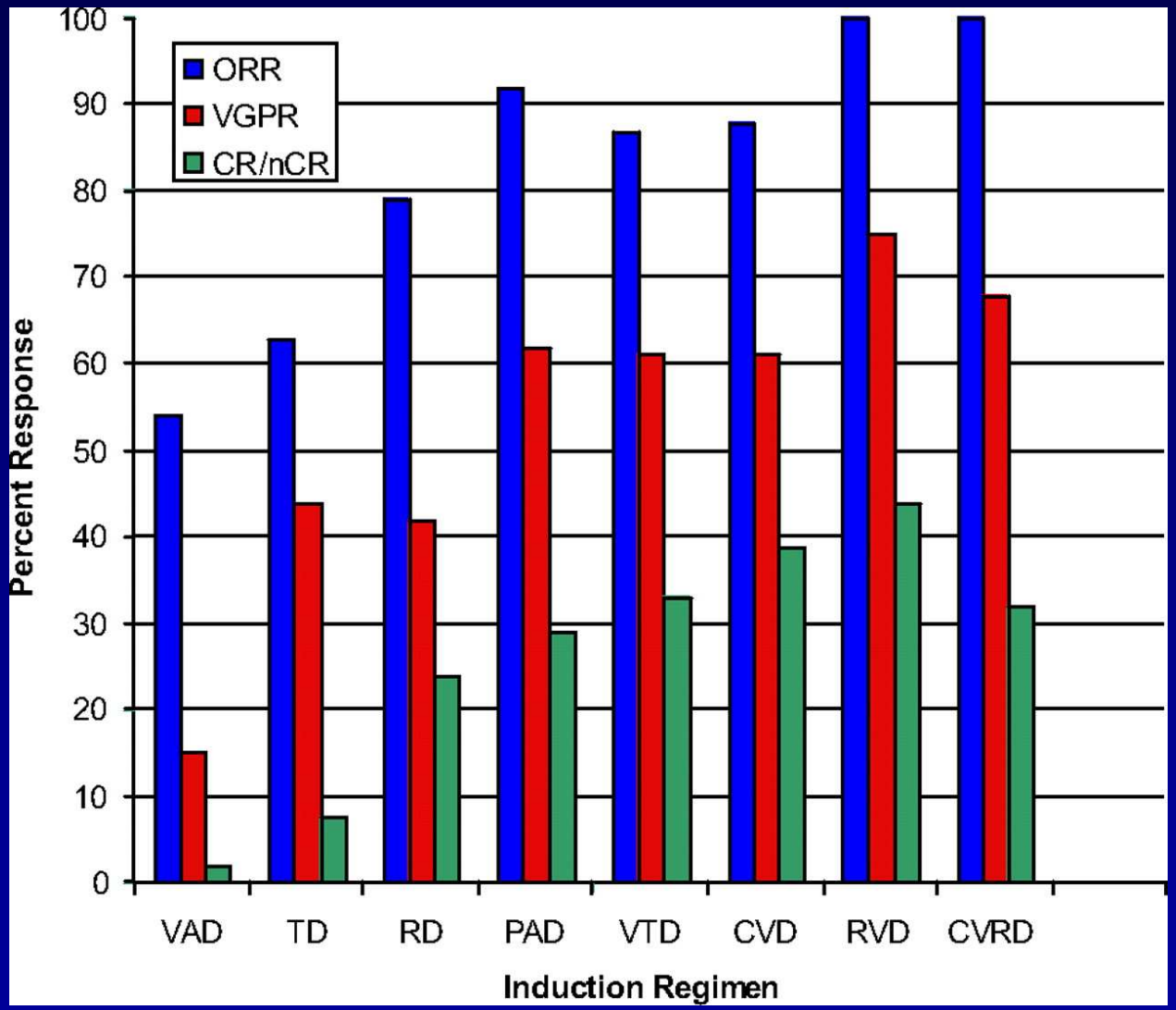
		N	≥VGPR, %	24-mo PFS*, %
ISS stage	I	29	72	85
	II/III	37	62	54
β_2-microglobulin, mg/L	<3.5	44	73	75
	≥3.5	22	55	48
Albumin, g/dL	<3.5	24	71	57
	≥3.5	42	64	74
Abnormal metaphase cytogenetics	Yes	6	83	40
	No	60	65	71
Del 13/13q by FISH	Yes	24	75	67
	No	27	59	65
Del 17p by FISH	Yes	5	60	33
	No	45	67	68
t(4;14) by FISH	Yes	2	100	100
	No	39	62	58
t(11;14) by FISH	Yes	11	64	58
	No	40	70	66
Del 17p and/or t(4;14) by FISH	Yes	6	67	50
	No	44	66	68

**p-values>0.15 for baseline characteristics p>0.3 according to cytogenetics

Richardson et al, *Blood* 2010

NOTE: No difference is detected in PFS according to cytogenetic abnormalities (all log rank p-values >0.3). Significant difference in PFS by ISS (I vs II/III, p=0.02). Other baseline comparisons include (DSS:p=0.44; B2M:p=0.14;albumin:p=0.14)

Combinations in the Upfront Treatment of MM



Stewart AK, Richardson PG, San Miguel JF *Blood* 2009

Novel Agent-based Induction Therapies

	Thalidomide-based	Lenalidomide-based	Bortezomib-based	Bortezomib + IMiD-based	New agents
2-drug combinations	TD	RD Rd	VD		
3-drug combinations	TAD CTD	RAD RCD BiRD	PAD VCD	VTD RVD	*CfzTD CfzRd **RId
4-drug combinations				VTDC RVDC RVDD	***R2V2

* Cfz: carfilzomib; ***R2V2: RVD + vori; **RId: lenalidomide, ixazomib (mln 9708), dex

Phase 1/2 Study of Carfilzomib, Lenalidomide, and Dexamethasone (CRd)

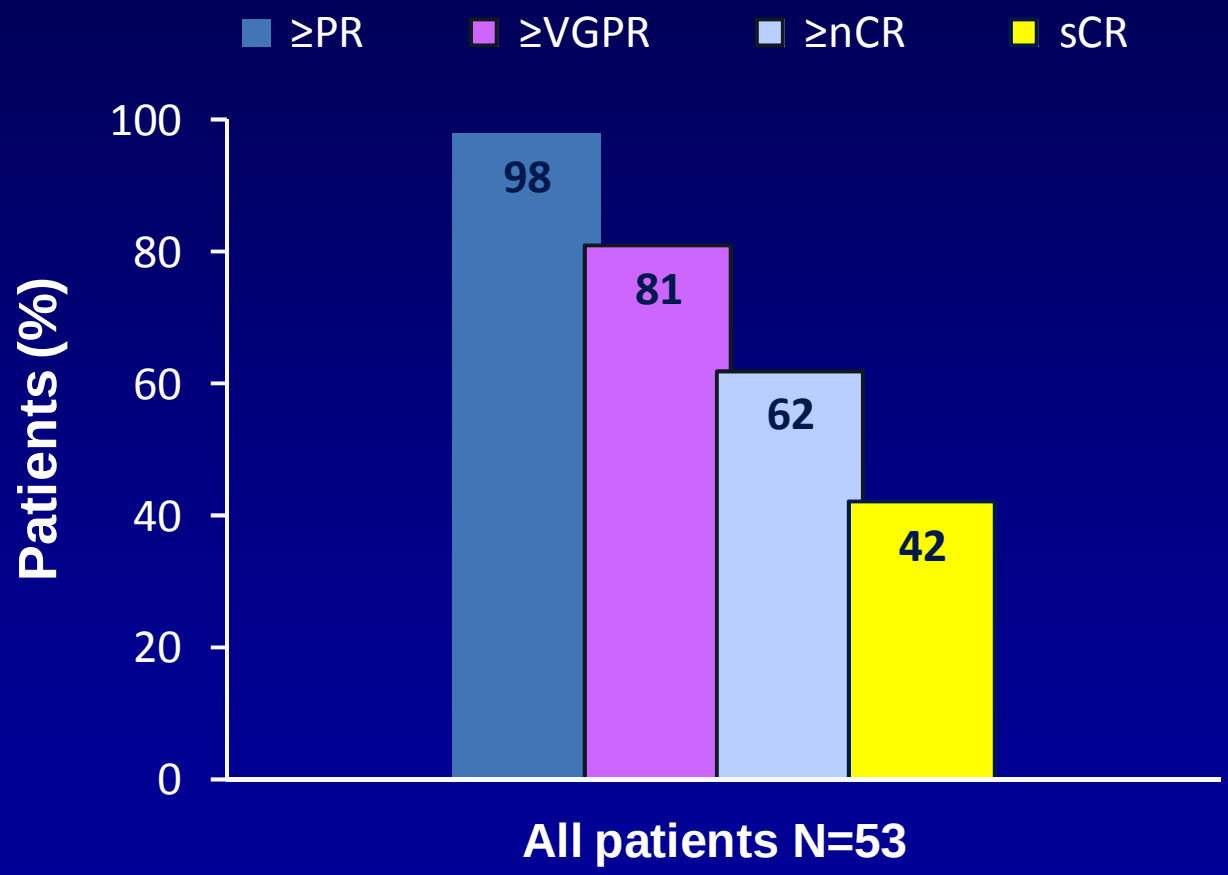
		ISS Stage		Cytogenetics		Carfilzomib Dosage		
Response, %	Overall (n=49)	I (n=20)	II/III (n=29)	Normal or Favorable (n=33)	Unfavorable (n=16)	20 mg/m^2	27 mg/m^2	36 mg/m^2
ORR	94	90	97	91	100	100	100	88
VGPR	65	65	66	61	75	100	100	47
sCR, nCR, or CR	53	50	55	52	56	75	85	38

- Generally well tolerated and manageable side effects
- Grade 3/4 adverse events in ≥10% of pts
  - Hematologic: anemia, neutropenia, thrombocytopenia
  - Non-hematologic: hyperglycemia, dyspnea, deep vein thrombosis/ pulmonary embolism

Jakubowiak AJ et al. *Blood* 2012.

CRd: Best Response

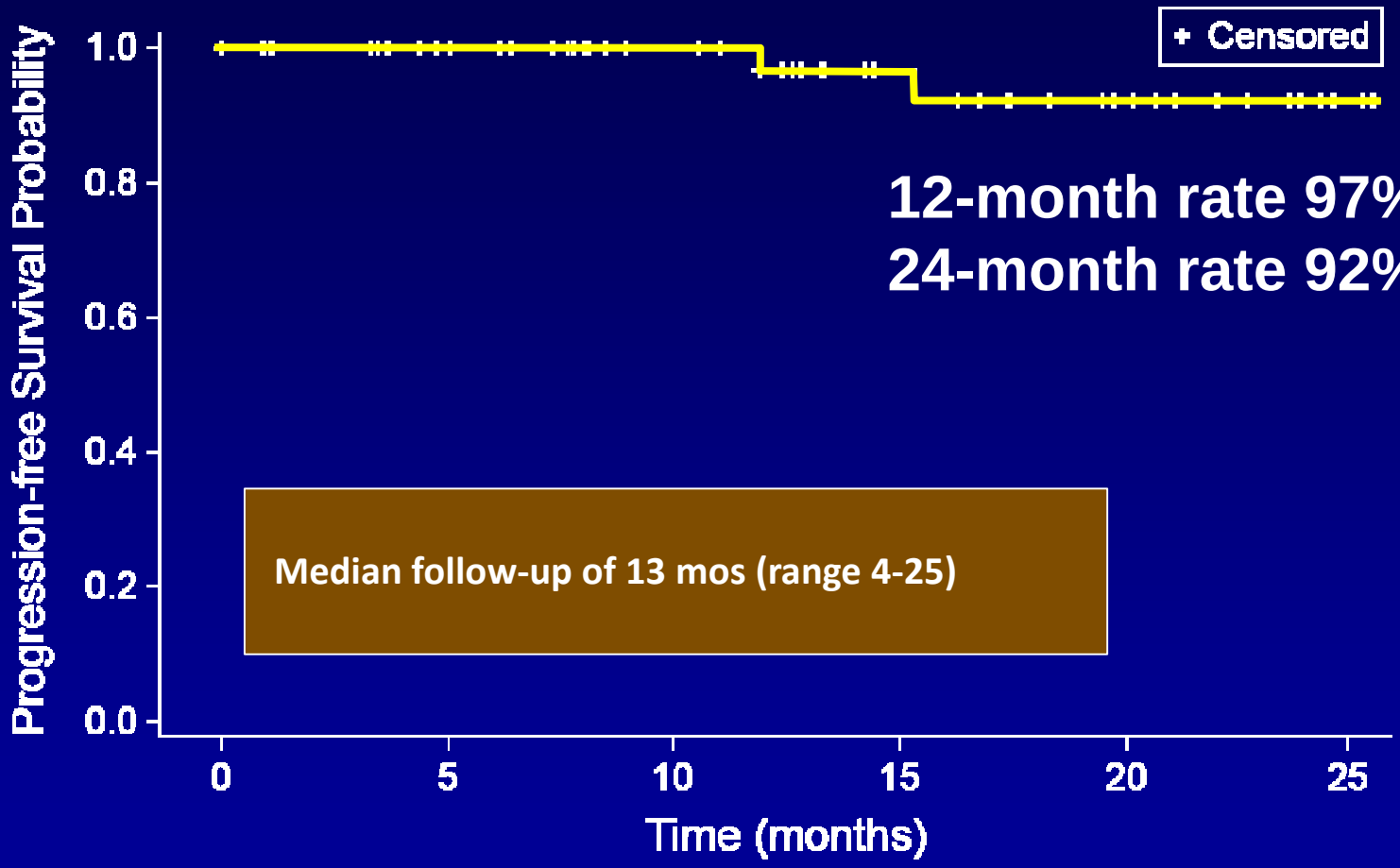
Median 12 cycles (range 1–25)



There was no difference by disease stage and cytogenetics

Jakubowiak AJ, et al. *ASCO* 2012

CRd: Progression-free Survival

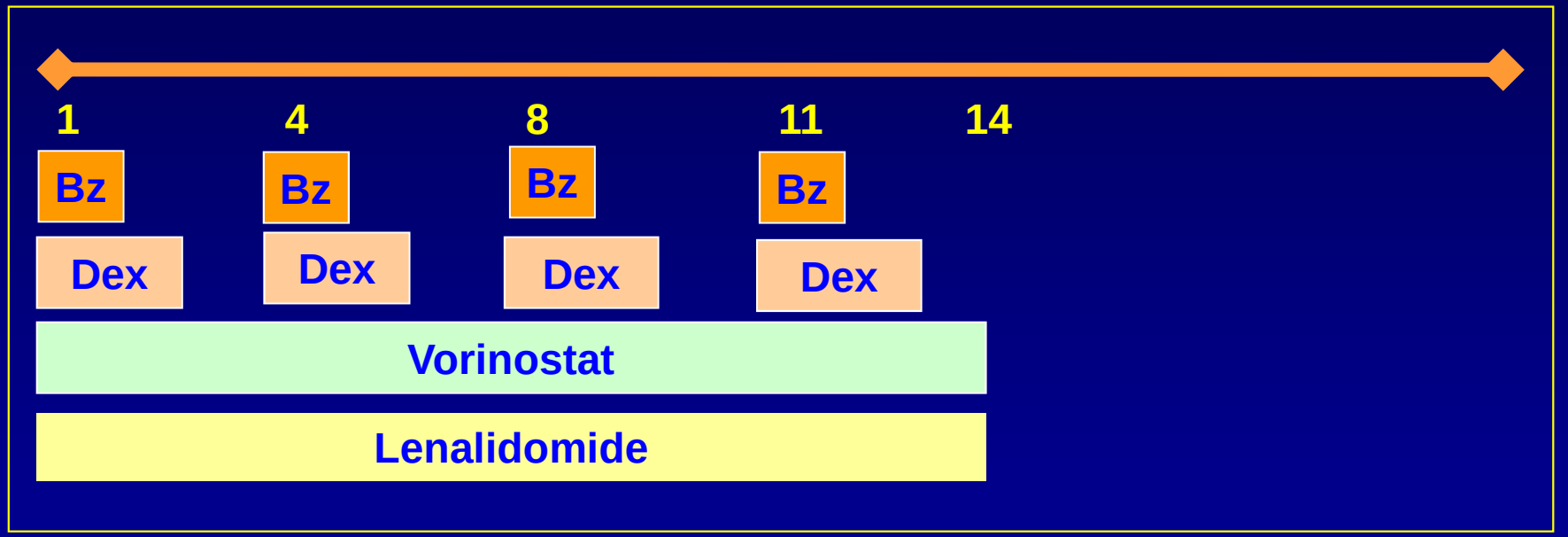


All pts with sCR have maintained response for median 9 months (range 1–20)

Jakubowiak AJ, et al. ASCO. 2012

RVD + Vori: "R2V2" Treatment Schedule

- Dose escalation of Vorinostat
- Up to eight 21-day cycles

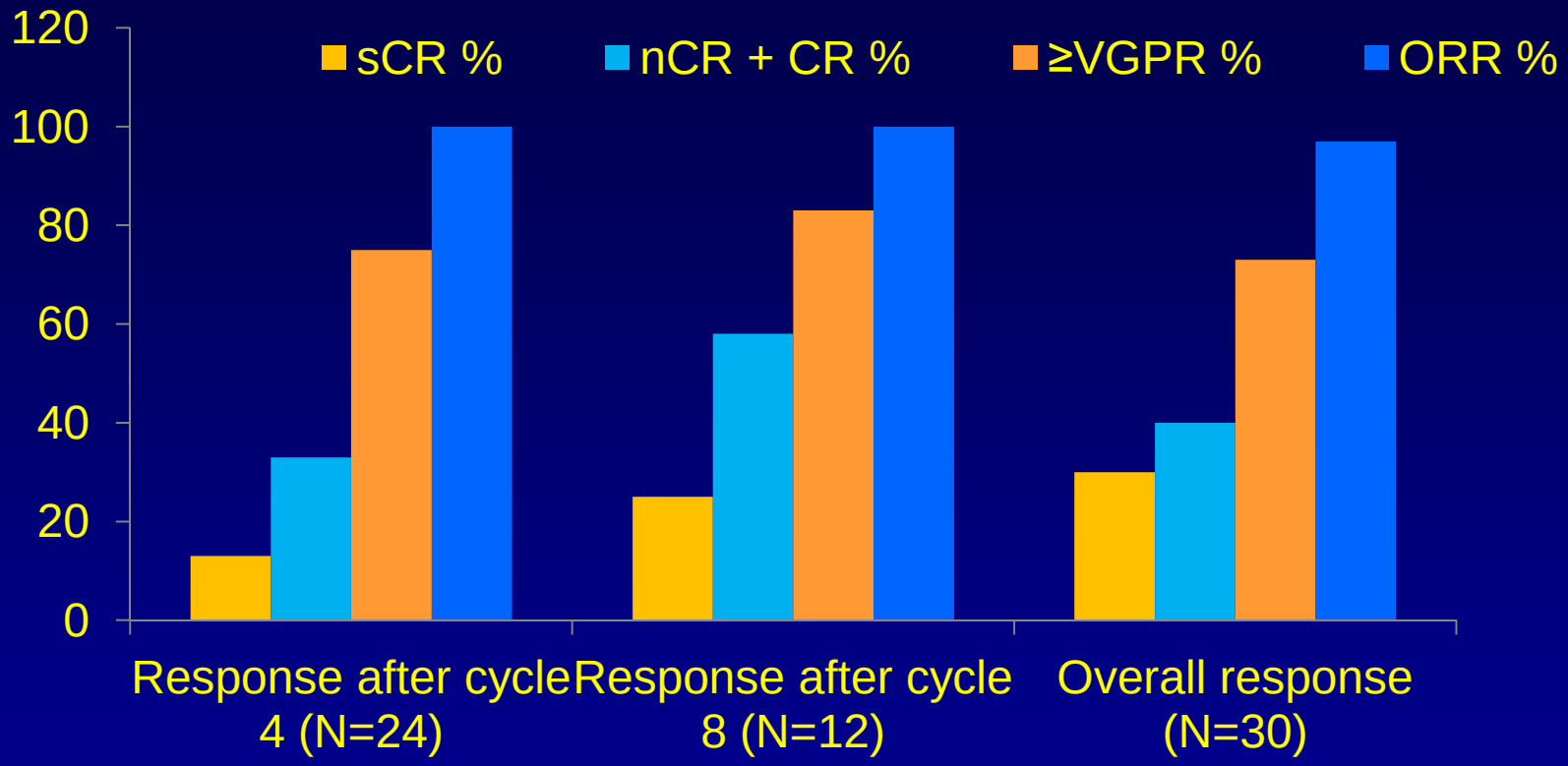


*Dex, 20 mg/day Days 1, 2, 4, 5, 8, 9, 11 and 12; 10 mg, cycles 5–8

- Pts ≥PR may proceed to ASCT after ≥4 cycles
- Maintenance therapy permitted after C8 in pts ≥SD using lenalidomide and/or bortezomib (investigator's choice)
- Risk-directed anti-thrombotic therapy with daily aspirin (81 or 325 mg) or LMWH or Coumadin (with target INR 2-3)
- Antiviral therapy as prophylaxis against Herpes Zoster required

Kaufman et al, ASH 2012

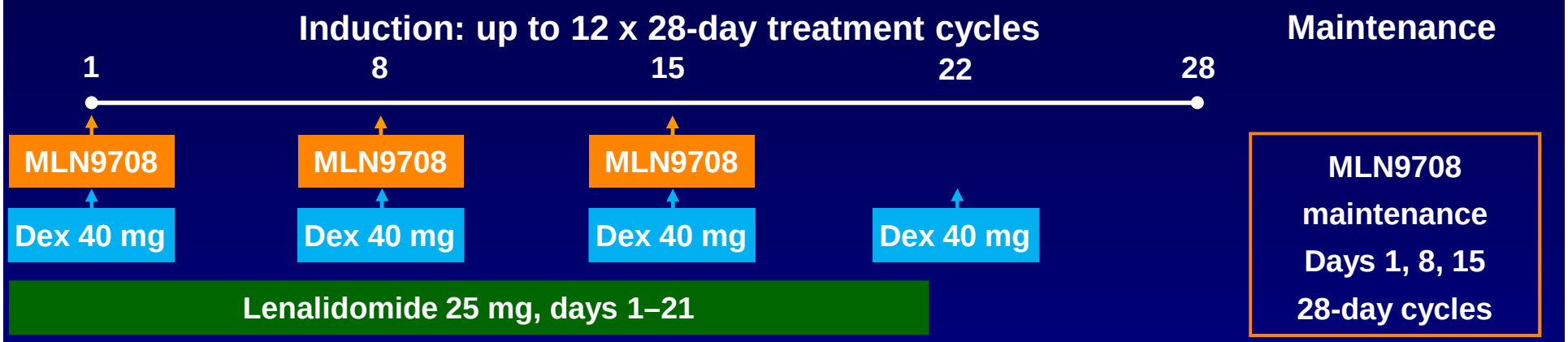
R2V2: Response to Treatment



	4 cycles	8 cycles	Overall Response
sCR %	13	25	30
nCR or CR %	33	58	40
VGPR %	75	83	73
ORR %	100	100	97

Kaufman et al, ASH 2012

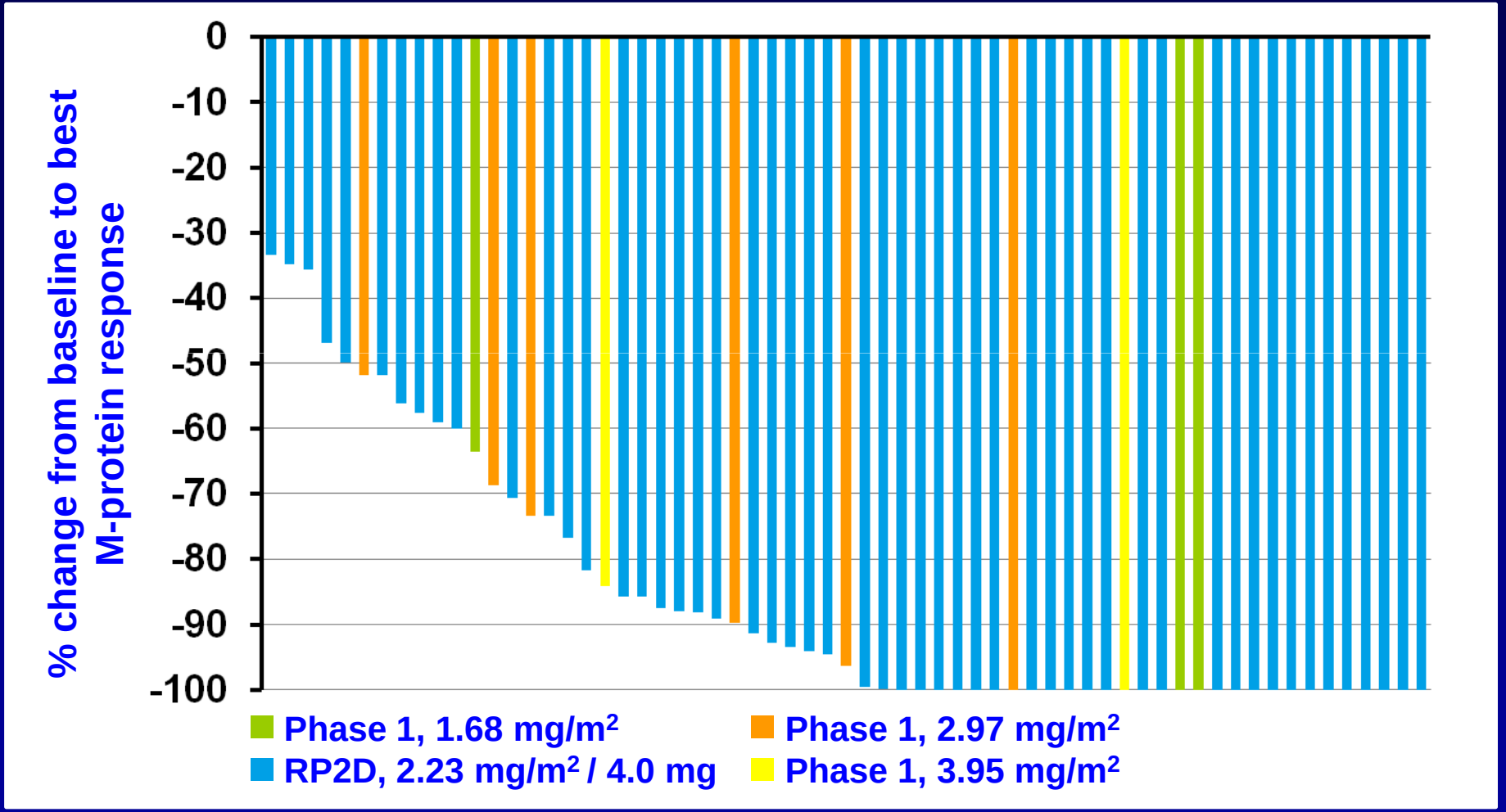
Ixazomib (MLN9708), lenalidomide and dexamethasone ("RId") : Study design



- Phase 1: oral MLN9708 dose-escalation
  - Standard 3+3 schema, 33% dose increments, based on cycle 1 dose-limiting toxicities (DLTs)
- Phase 2: oral MLN9708 at the RP2D from phase 1
- Stem cell collection allowed after 3 cycles, with autologous stem cell transplantation (ASCT) deferred until after 6 cycles
- MLN9708 maintenance continued until progression or unacceptable toxicity
- Mandatory thromboprophylaxis with aspirin or low-molecular-weight heparin

Kumar S. et al, *ASH* 2012

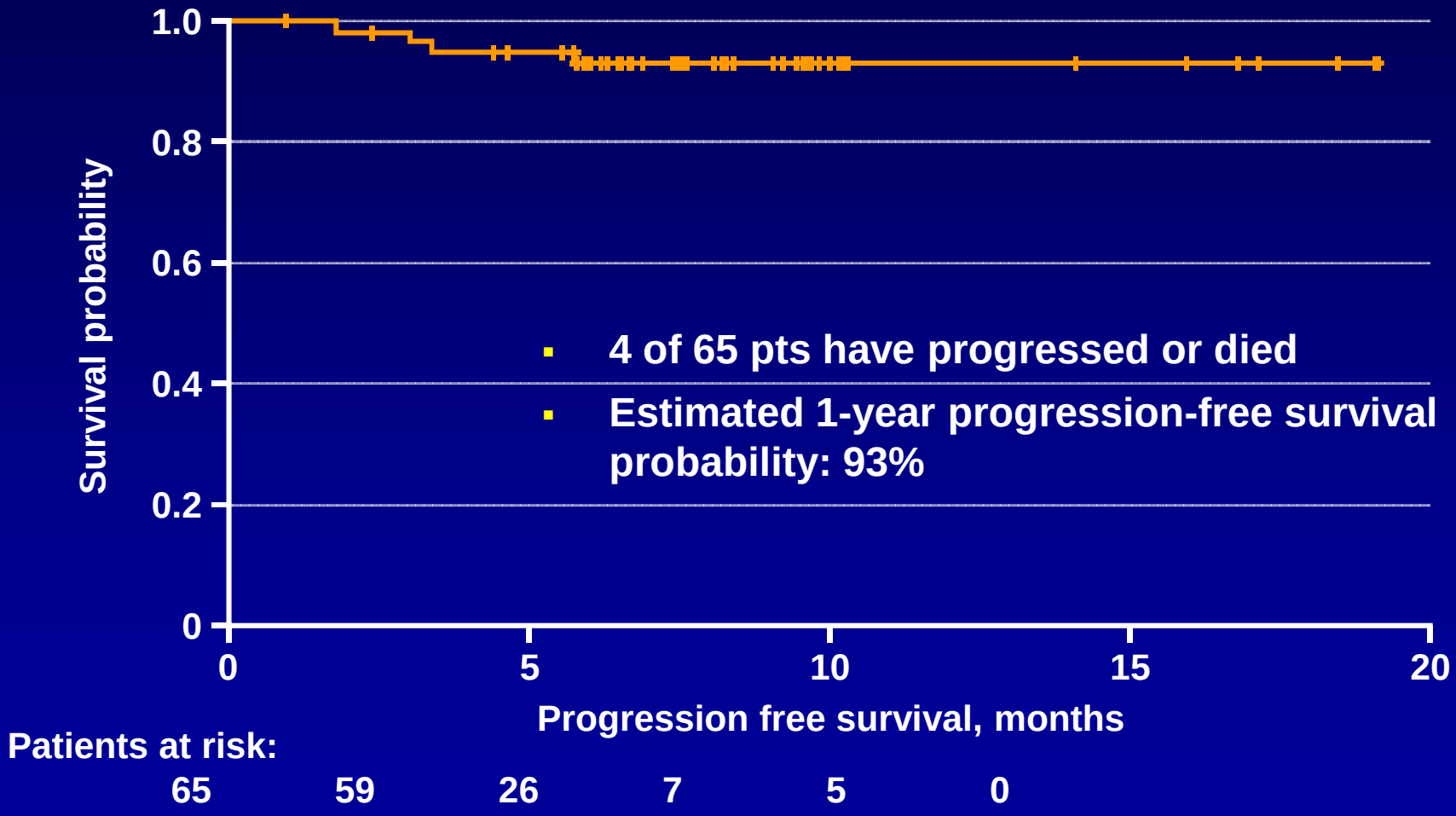
Best percent change in M-protein from baseline in response-evaluable patients



- 48% of pts achieved 100% reduction in M-protein
- Reductions were seen at multiple dose levels

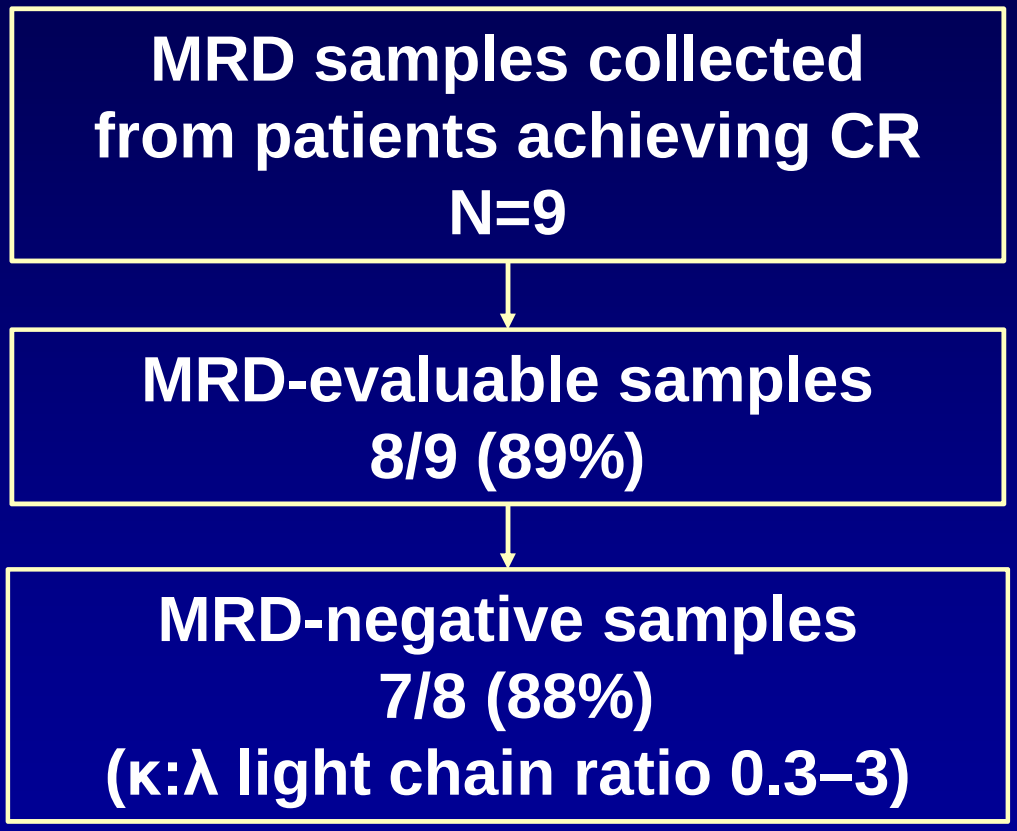
Kumar S. et al, *ASH* 2012

Progression-free survival



Kumar S. et al, *ASH* 2012

MRD evaluation



Kumar S. et al, *ASH* 2012

What is the Role of Transplantation in MM in the Era of Novel Agents?

Could ASCT be Delayed for Some Pts, and if so who?

Benefit of early transplantation in ECOG trial

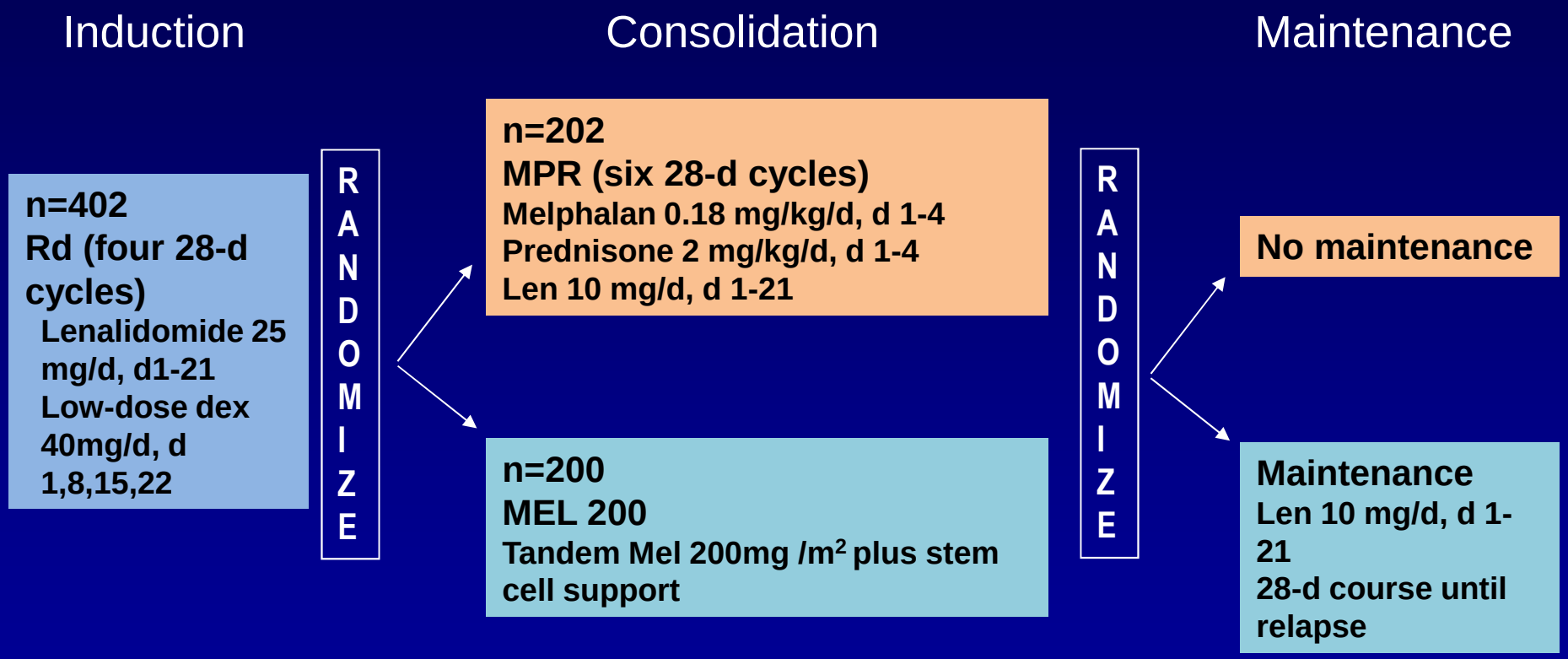
Post-hoc retrospective analysis

- Patients < 65 years, who successfully completed first four cycles of therapy

- Results
  - OS at 3-years
    - Early ASCT: 94%
    - Continued protocol therapy (RD or Rd): 78%
  - However, not a randomized comparison….

Siegel et al. Blood 2010; 116(21); Abstract 38; oral presentation at ASH 2010

Phase 3: MPR versus Tandem ASCT



Primary end point: PFS

Palumbo et al. ASH 2011 (Abstract 3069)

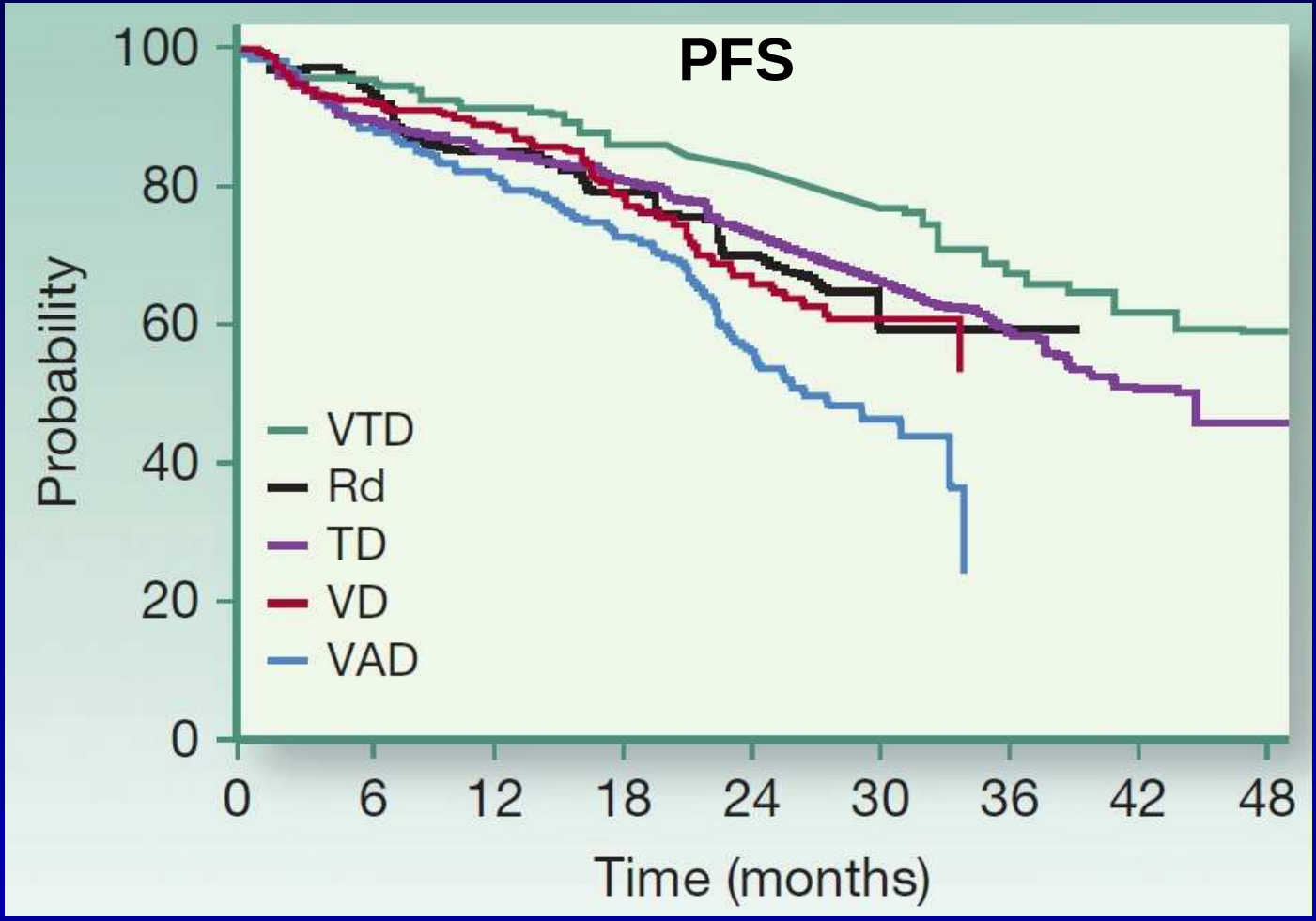
Phase 3: MPR versus Tandem ASCT

- Pts (n=402) with newly diagnosed MM
- Treatment
  - Len / low-dose dex induction
  - Randomization: MPR vs tandem ASCT
  - Randomization: Maintenance Len until PD vs no maintenance
- Median follow up 26 mos

	MPR (n=202)	MEL 200 (n=200)	p
CR	20%	25%	0.49
≥VGPR	60%	58%	0.24
2-yr PFS	54%	73%	<0.001
2-yr OS	87%	90%	0.19
Gr 3/4 neutropenia	55%	89%	<0.001
Gr 3/4 infections	0%	17%	<0.001
Gr 3/4 GI toxicity	0%	21%	<0.001
DVT	2.44%	1.13%	0.43
Second tumors	0.5%	1.5%	0.12

Palumbo et al. ASH 2011 (Abstract 3069)

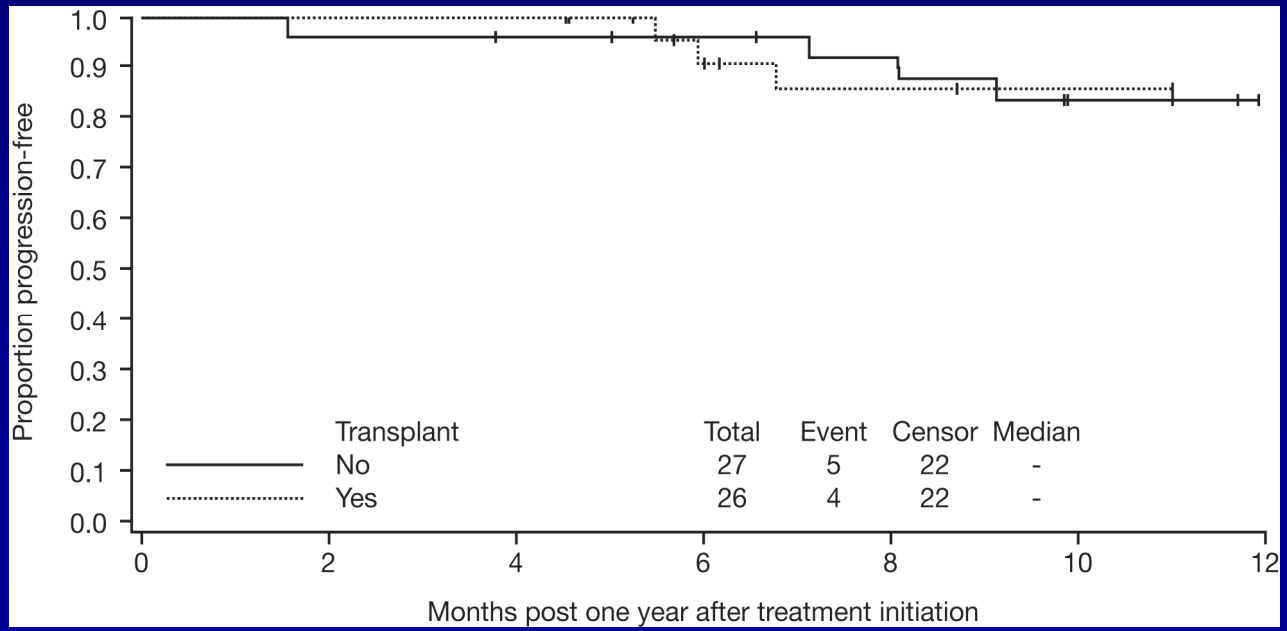
Impact of Upfront New Drug-containing Regimens in the Setting of High-dose Therapy



Palumbo et al. *Clin Cancer Res* 2011; 17(6): 1253-1263

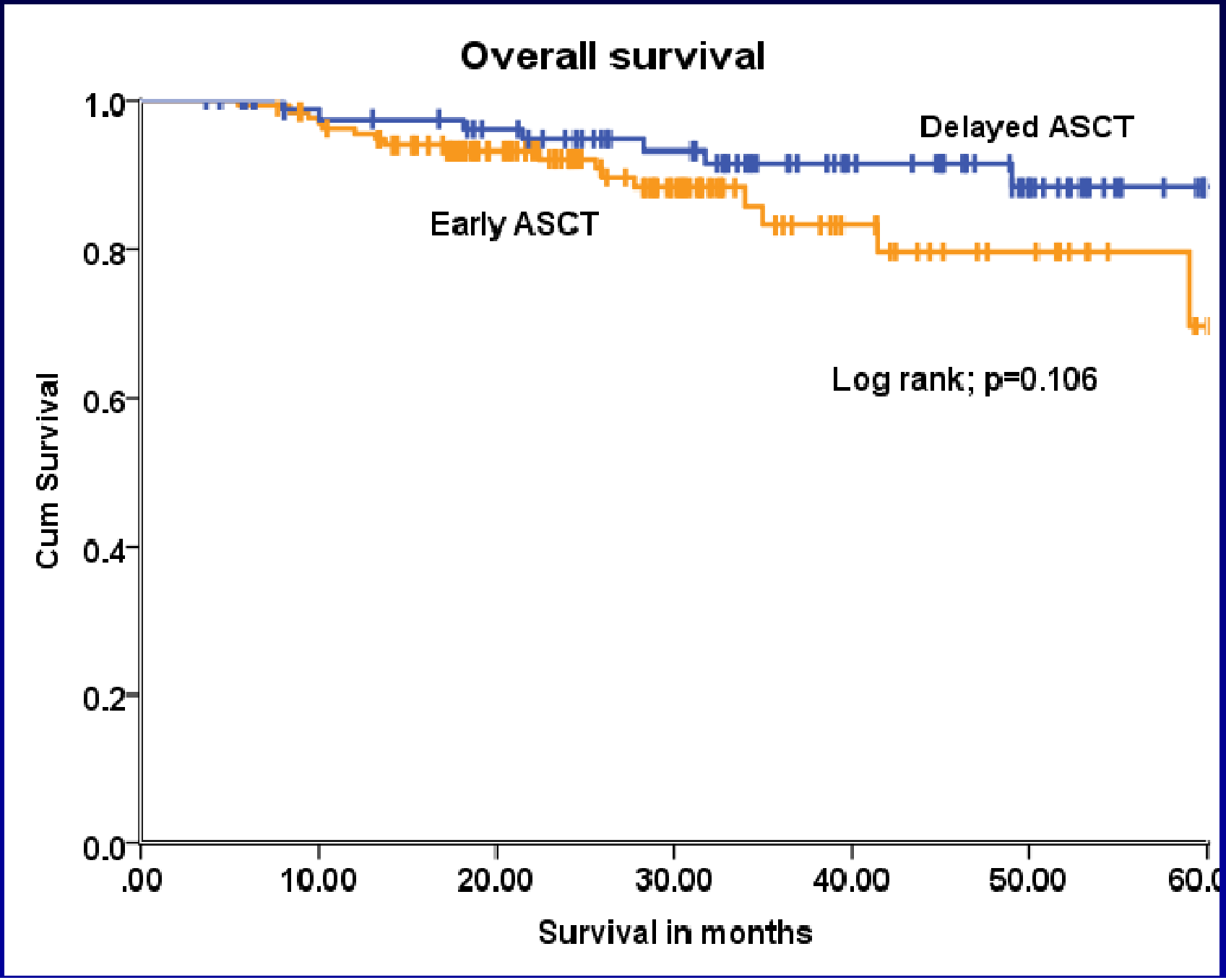
RVD Phase I/II: PFS by ASCT Status from 1-yr Landmark

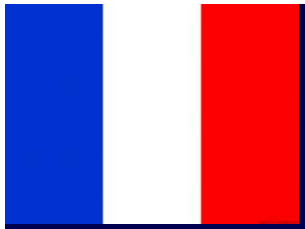
- Risk of progression decreased markedly after 12 mos
- Post-hoc landmark analysis from 1-yr post-treatment initiation in 53 pts who had not progressed at 1-yr follow-up
  - No difference detected (log-rank p=0.84) in PFS by whether pts received ASCT or not (pts not censored at time of ASCT)

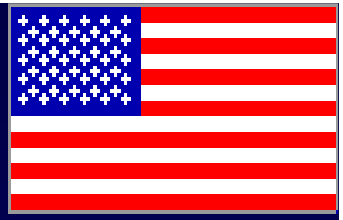


Richardson et al, *Blood* 2010

RVD Induction followed by early versus late ASCT (Lonial et al, ASH 2012)







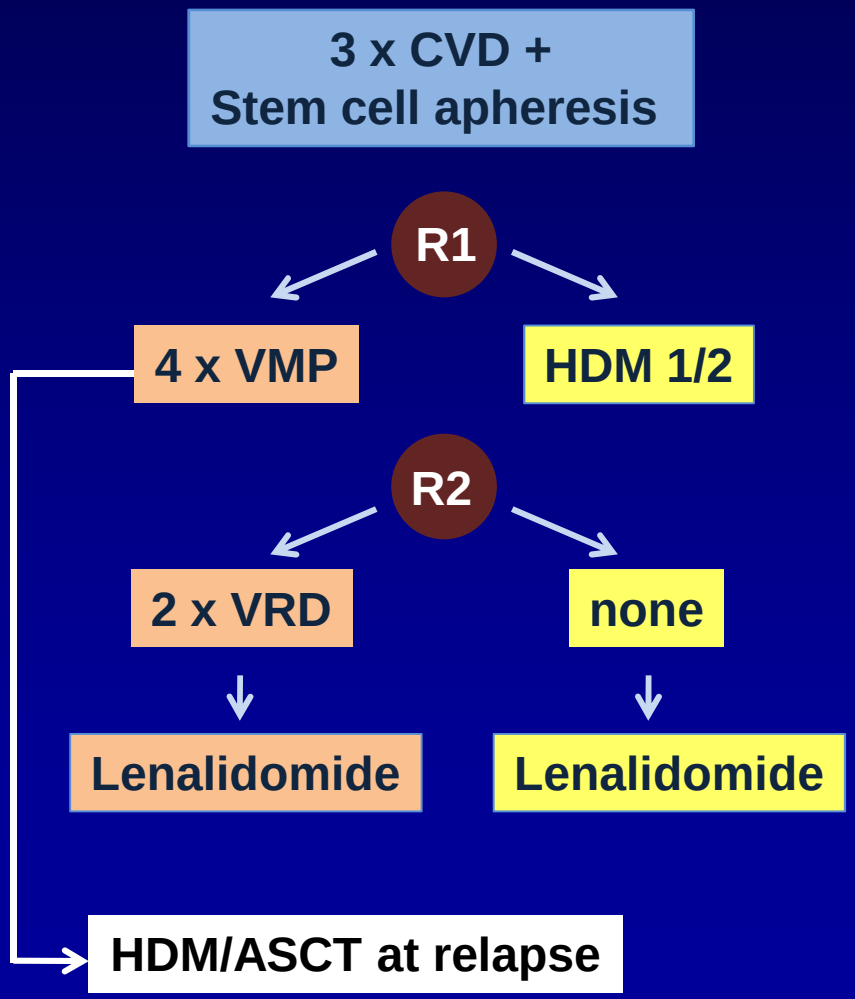
IFM/DFCI 2009 Phase 3 Study

Newly Diagnosed MM (SCT candidates; n= 1660)

Randomize

RVDx3	Induction	RVDx3
CY (3g/m2) MOBILIZATION Goal: 5 x10^6 cells/kg	Collection	CY (3g/m2) MOBILIZATION Goal: 5 x10^6 cells/kg
Melphalan 200mg/m^2* + ASCT	Consolidation	RVD x 5
RVD x 2	Maintenance	Lenalidomide
Lenalidomide		SCT at relapse

Novel Agents Alone versus Intensive Therapy + Novel Agents: European Intergroup Trial



Registration
Induction

Stem cell mobilization in all pts

Consolidation

Maintenance
until relapse

http://www.clinicaltrials.gov/ct2/show/NCT01208766?term=Sonneveld&rank=2

Bortezomib- based Retreatment and Selected Newer Salvage Strategies in MM

Bz – based Combos	ORR (%)	TTP (months)	OS (months)
All pts	39	7.5	16.6
Bortezomib-exposed:			
Relapsed (vs refractory)	57	8.5	19.7
Prior therapies:			
≤4	43	8.2	13.3
>4	29	7.1	20.0
Unknown	45	5.6	–
Newer Salvage Combos			
RD + Elo (1703)	90%	36	
Pom Vel Dex	80%	N/A	
Carfilzomib Pom Dex	65%	N/A	

Knopf et al. ASH 2012 (Abstract 1863)
Richardson et al. ASH 2012, IMW 2013
Shah et al, ASH 2012

Chromosomes and Prognosis in Multiple Myeloma

For conventional and high dose therapy (SCT):

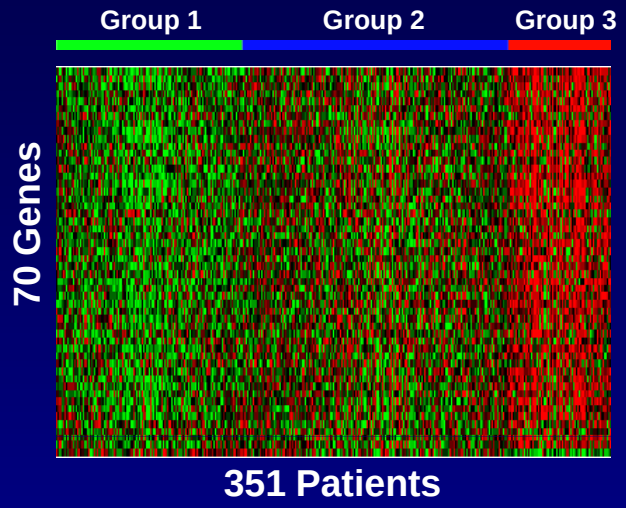
Nonhyperdiploid worse prognosis than hyperdiploid
t(11;14), hyperdiploidy - standard risk
t(4;14), del(17p), del(13q14)- high risk

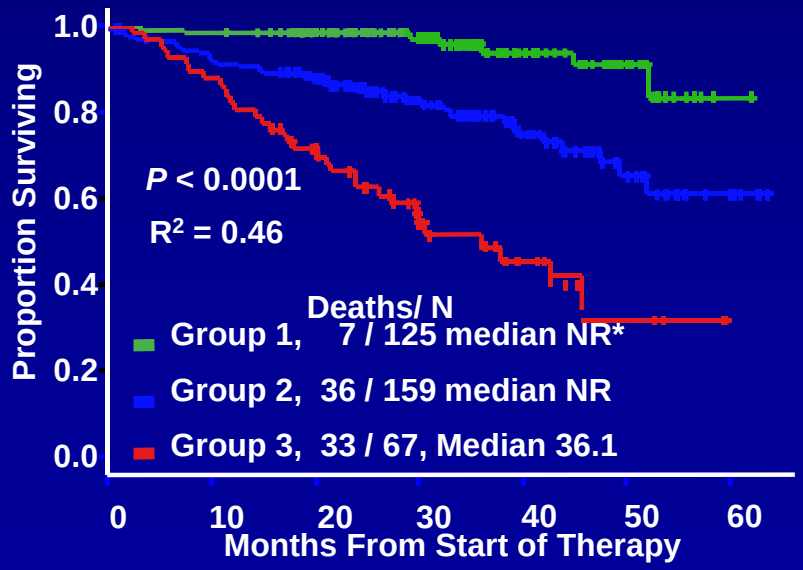
For novel treatments
Bortezomib, but not lenalidomide, can at least partially overcome t(4;14), del(13q14)-

del(17p) p53 remains high risk

Gene Expression Profiling Predicts Outcome

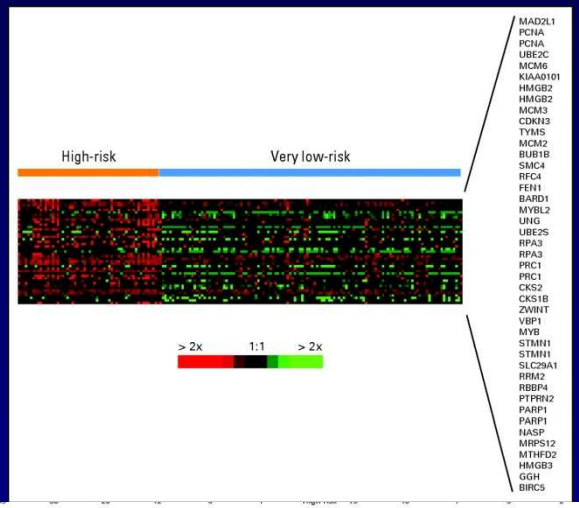
70-gene model

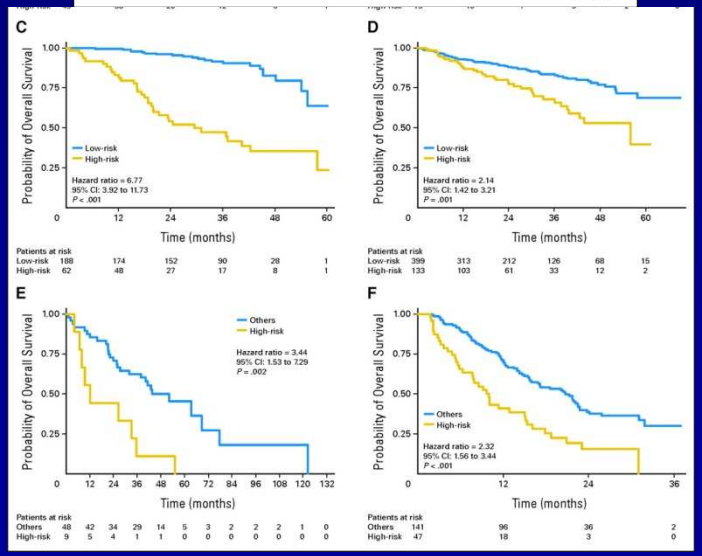




Shaughnessy JD et al. *Blood*. 2007;109:2276-2284.

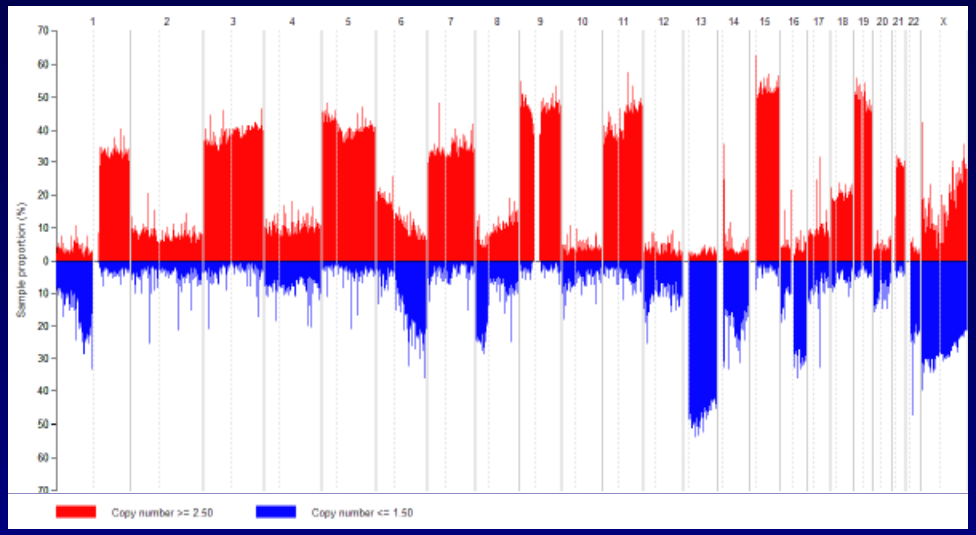
15-gene model

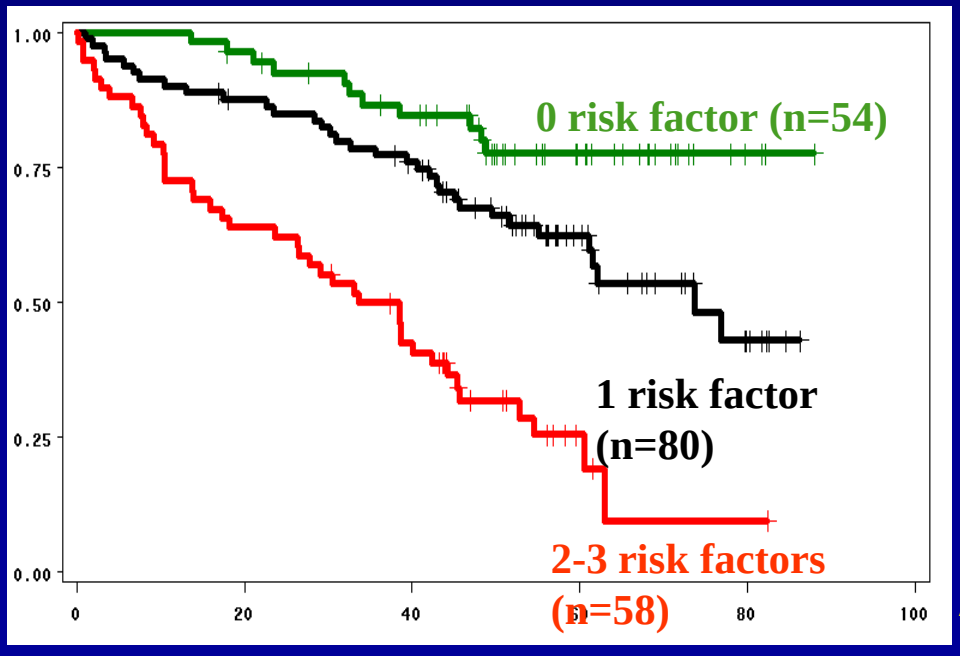




Decaux O et al. JCO 2008;26:4798-4805

SNP Array-Based MM Prognostic Model





Copy number analyses reveal novel prognostic classification

Identifies regions of clinical importance especially amp 5q del12p

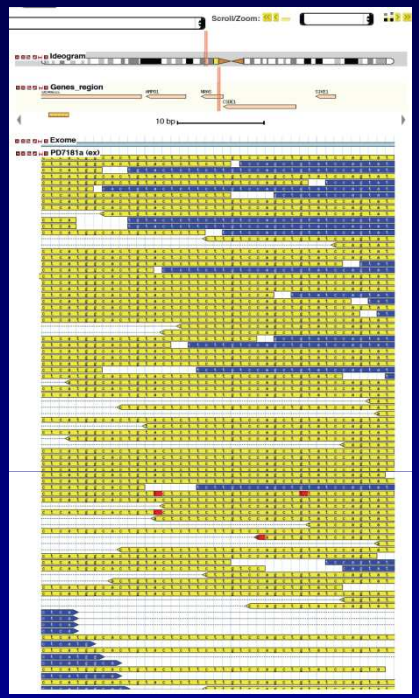
SNParrays highlight few regions with bi-allelic deletions

SNP analysis may lead to an individual therapeutic approach.

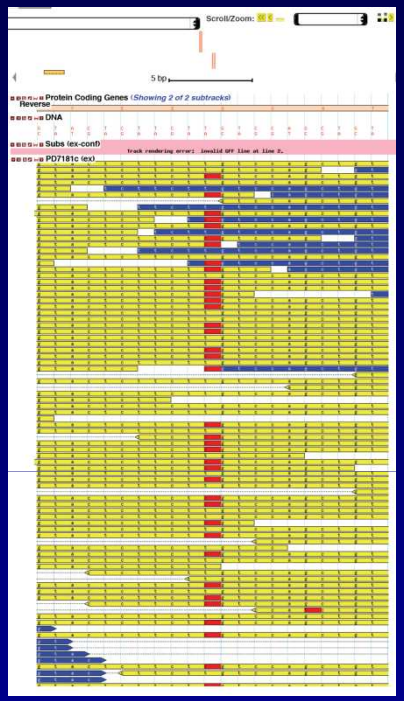
Avet-Loiseau et al J Clin Oncol 2009; 27: 4585-90.

Whole Genome Sequencing Identifies Acquisition of New Changes in MM: 71 Patient Study

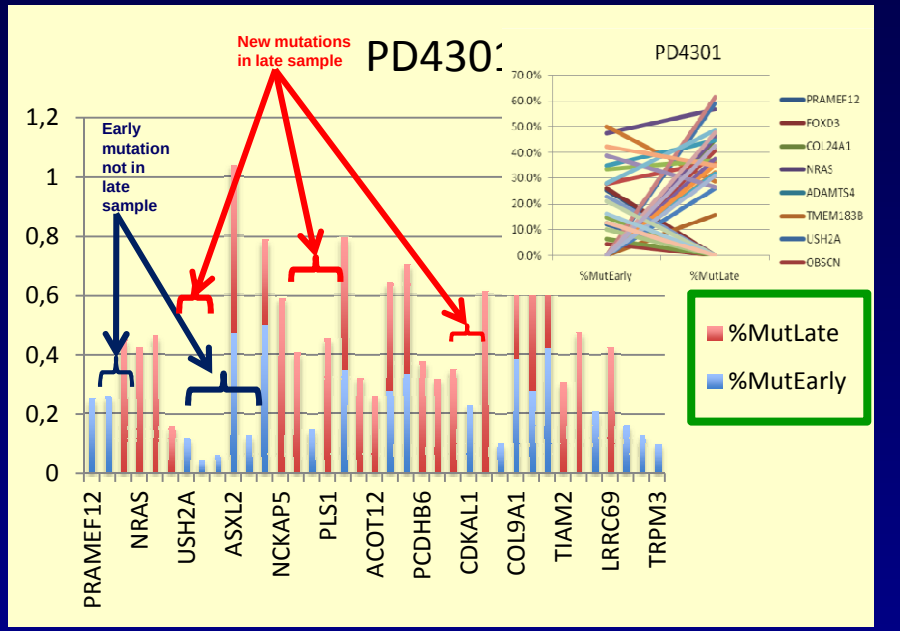
(Munshi NC et al, ASH 2012 Abs. 276)

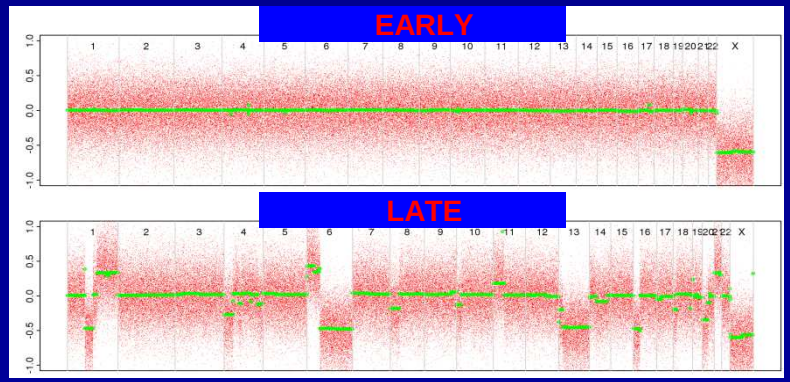


Early Tumor

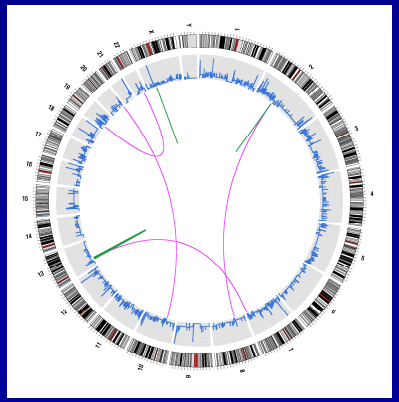


Late Tumor

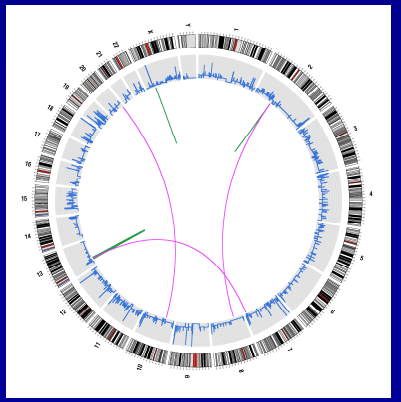




Early Tumor



Late Tumor



Induction/Consolidation/Maintenance +/- SCT: Questions / Considerations

- Novel agent containing induction/consolidation regimens improve the depth of response
- Administration of consolidation and /or maintenance therapy results in an improvement in overall outcome, i.e. PFS, OS in various settings
- What then is the impact of prolonged therapy (with or without SCT) regarding tolerability, quality of life, treatment at relapse?
- Is SCT therefore needed in all eligible pts: are there features which can define who needs what when (eg ISS1 vs ISS II/III; Cytogenetics, FISH; GEP; MRD)?

In the Era of Targeted Therapy….

- Improved classification of MM
- Identification of targets in the myeloma cell and the BM microenvironment
- Development of novel agents targeting essential biological pathways (PIs, IMiDs, other small molecule inhibitors; MoAbs)
- Development of rationally-based combination therapies and effective salvage treatment
- Concepts to treat MRD (maintenance, vaccines)
- Development of individualized treatment thru GEP, other tools as better predictors of outcome
- Now and in the future - early SCT is not required in every transplant - eligible pt…

  e.g. ISS 1 (vs ISS 2/3); cytogenetic profile ; +/- extra-medullary disease; response characteristics during induction; MRD status
- Participation in Randomized Trials is key….
- One Size therefore does not fit all!