

Relapse after Autotransplantation for Myeloma

- Defining the problem
- Identifying Opportunity

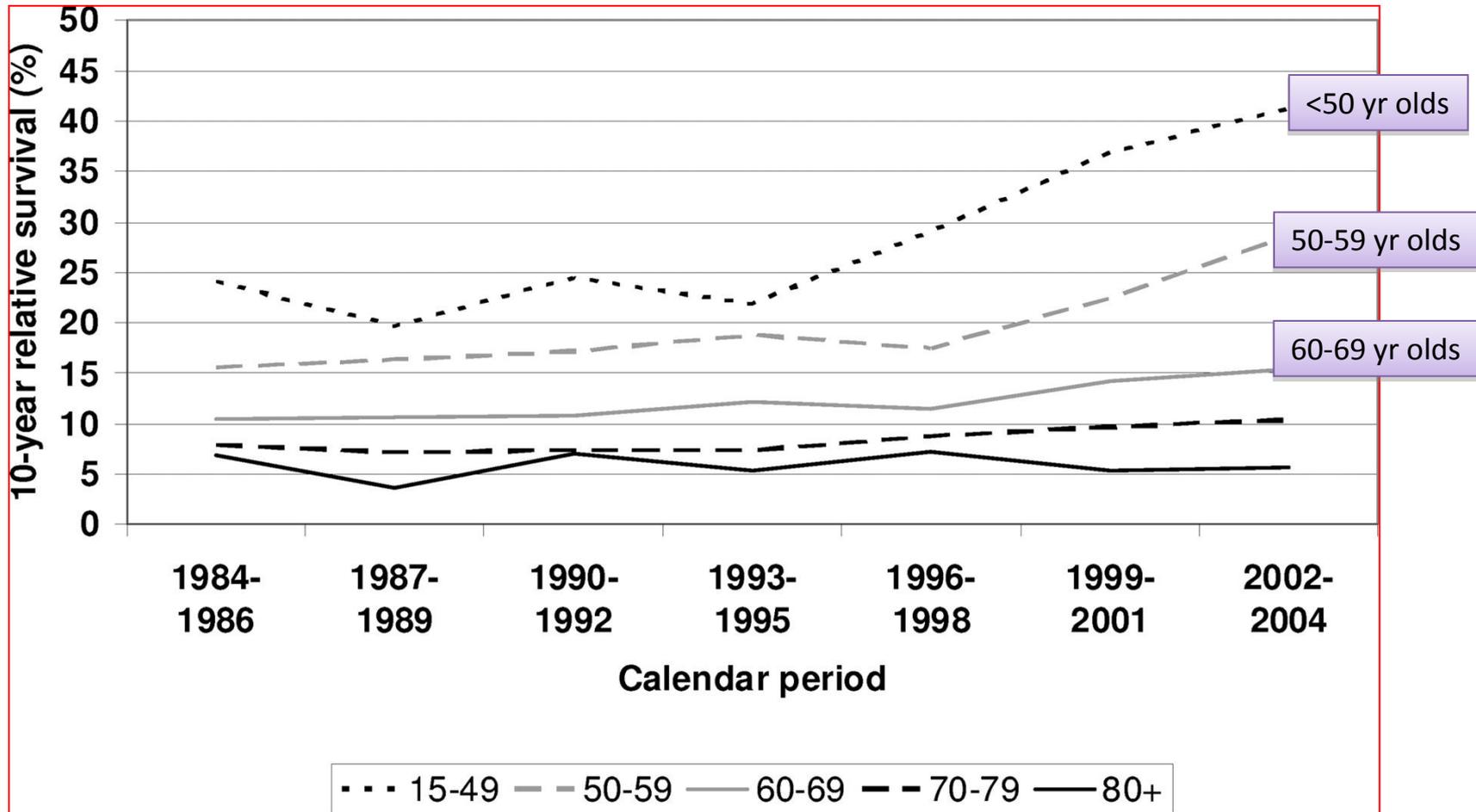
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Topics

- Epidemiology of Relapse
- Post Relapse Survival
- Biology of Relapse
- Who does not relapse? Why?

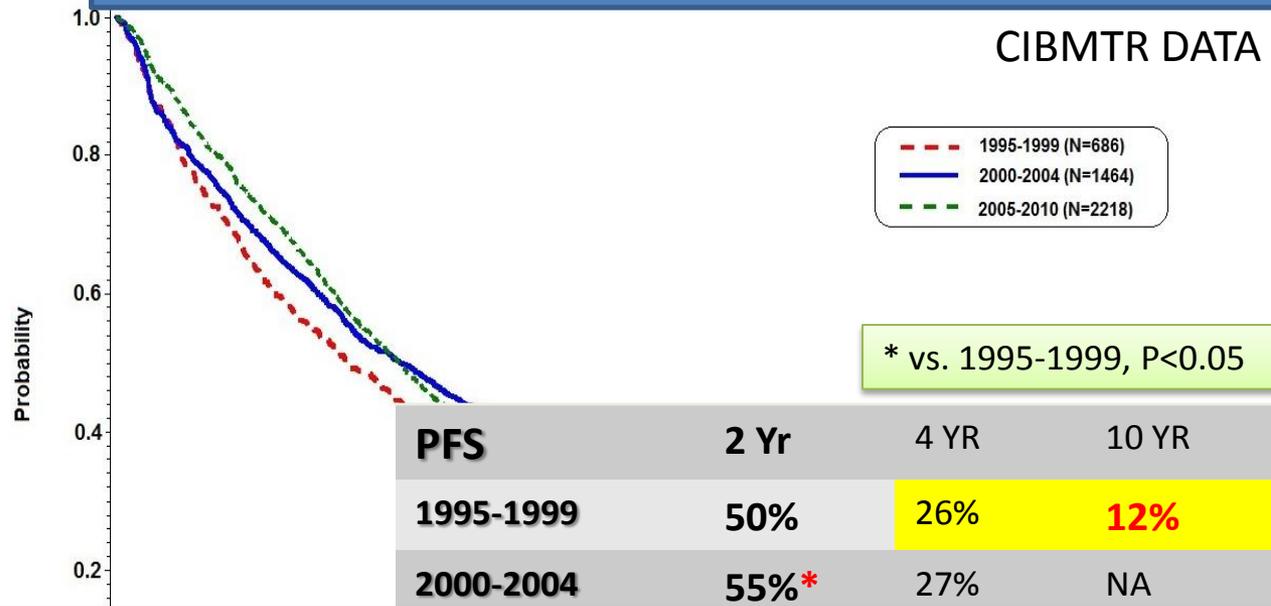
- Preventing and Treating Relapse – the clinical opportunities

MYELOMA SURVIVAL Has Improved Over Time



Current 10 yr survivor fraction – May be 50% for younger patients?

Progression after Upfront Auto-HCT



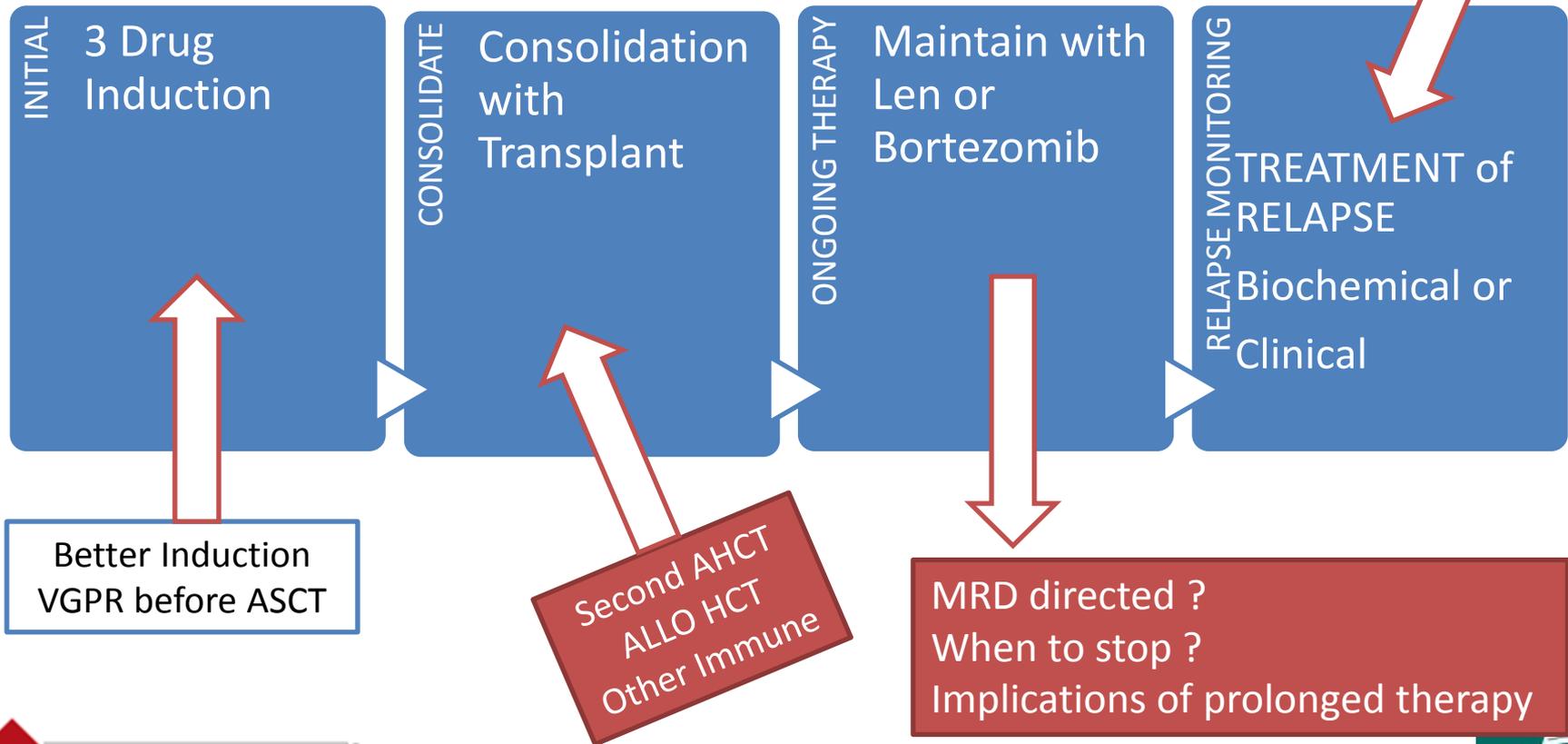
The best median PFS with modern induction and maintenance – is about 46 mo

Recent Studies	Agent	Median TTP/PFS
CALGB 100104	Lenalidomide	46 mo
IFM Attal et al	Lenalidomide	41 mo
HOVON-GMMG	Bortezomib	35 mo
MRC IX	Thalidomide	30 mo

“The Modern Triple Sequence”

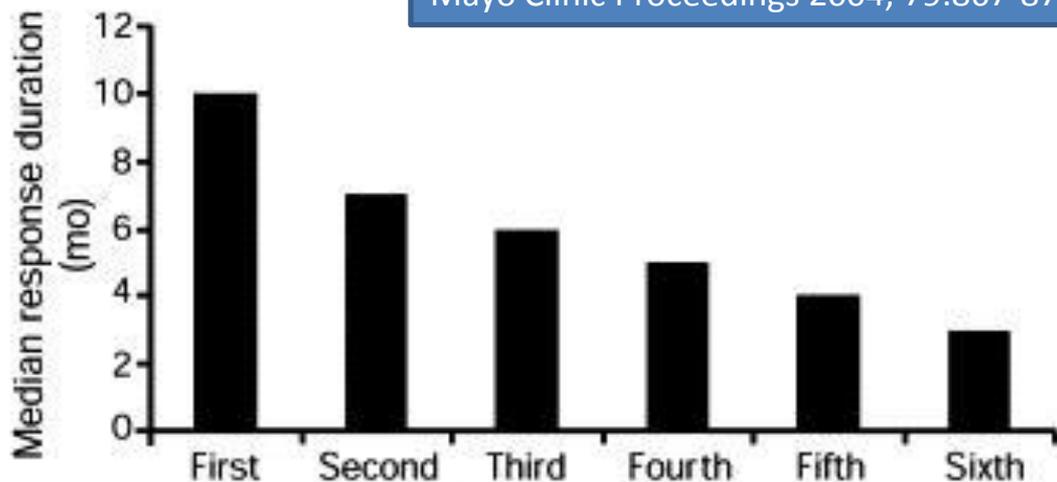
Induction AutoHCT and Maintenance

- Randomized trials – Achievement of VGPR/CR or better
- Emerging data – PCR or Multicolor Flow based remissions



Treatment and Survival after first relapse in MM

Mayo Clinic Proceedings 2004; 79:867-874

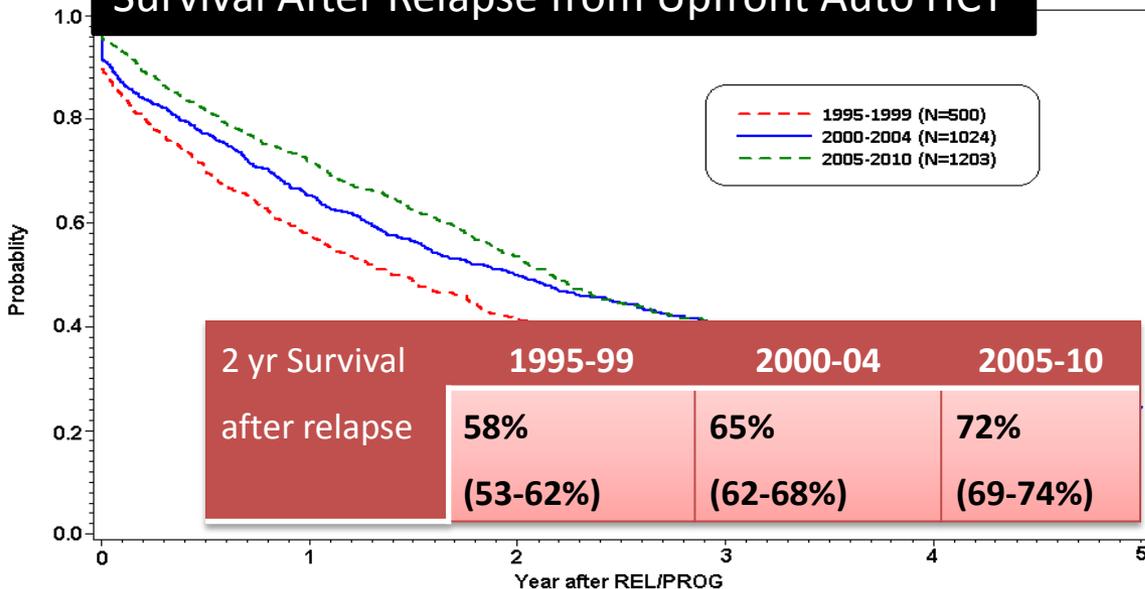


Median OS to salvage therapy -1.5 years (b/w 1985-98)

- IMWG International survey ASCO 2012, Durie et al
- Median PFS and OS after relapse #1: 13 mo and 35 mo

Salvage Regimen	Response Rate
1	58%
2	45%
3	30%
4	15%

Survival After Relapse from Upfront Auto HCT



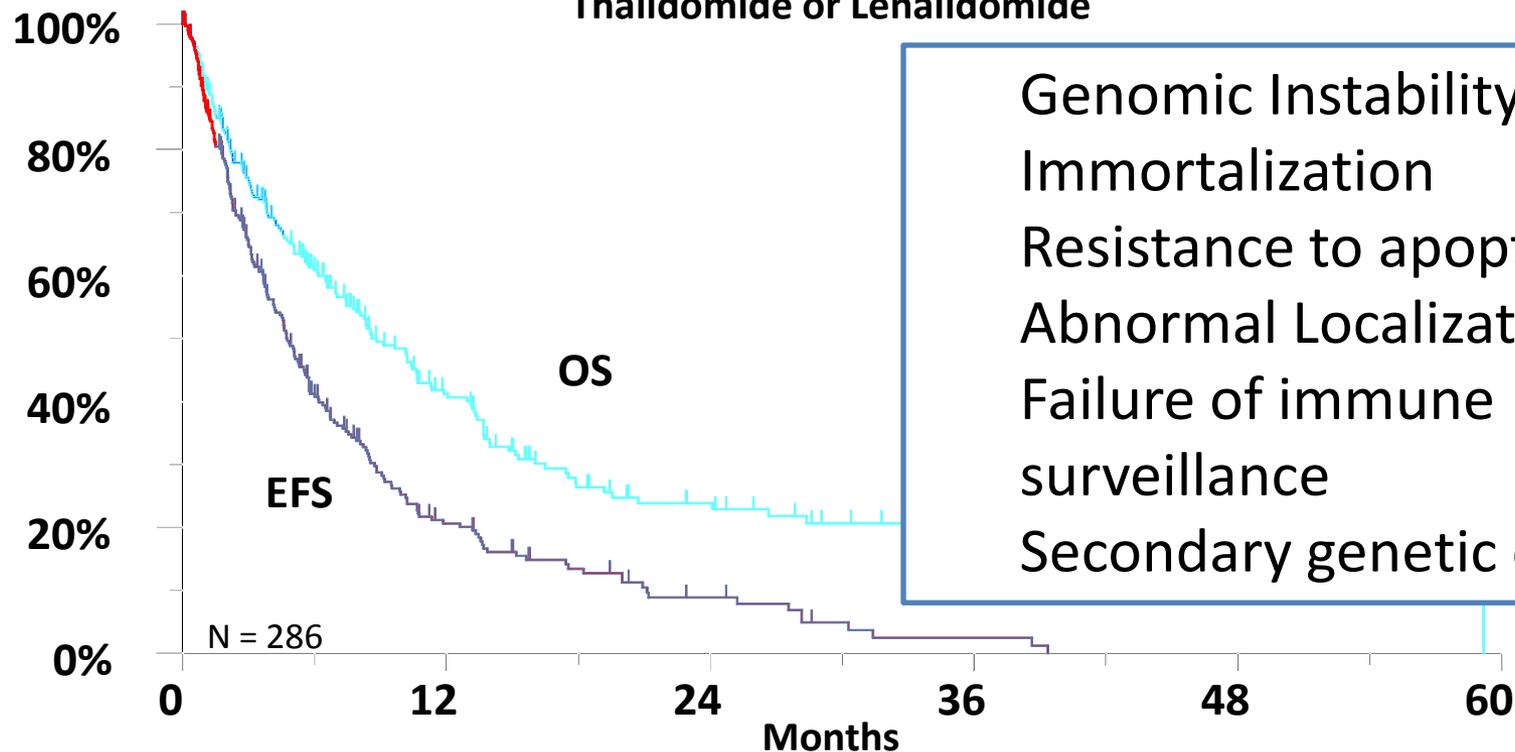
Dual (IMiD and Proteasome Inhibitor) Refractory

EFS and OS are poor in dual refractory disease

Median EFS
5 months

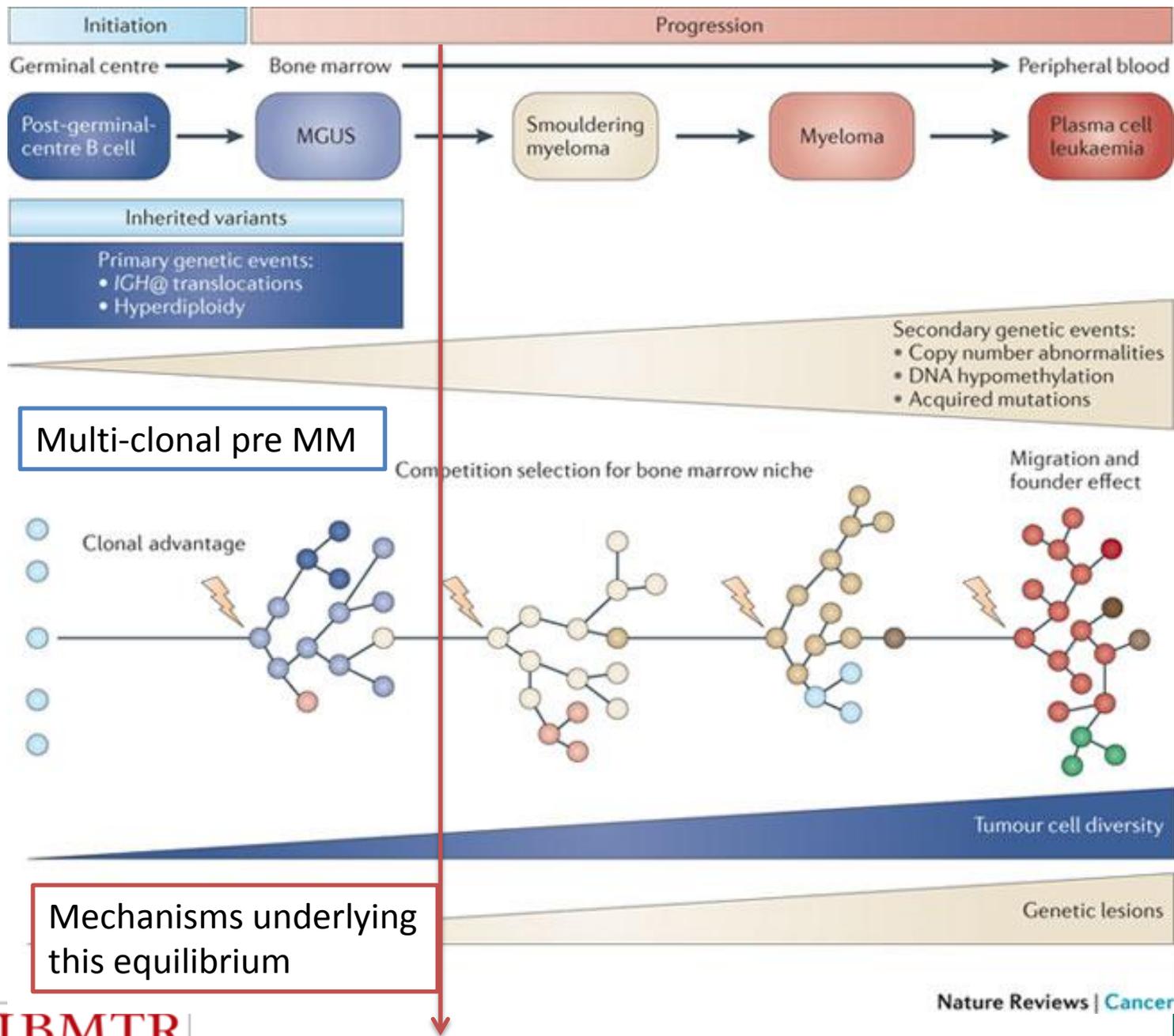
Median OS
9 months

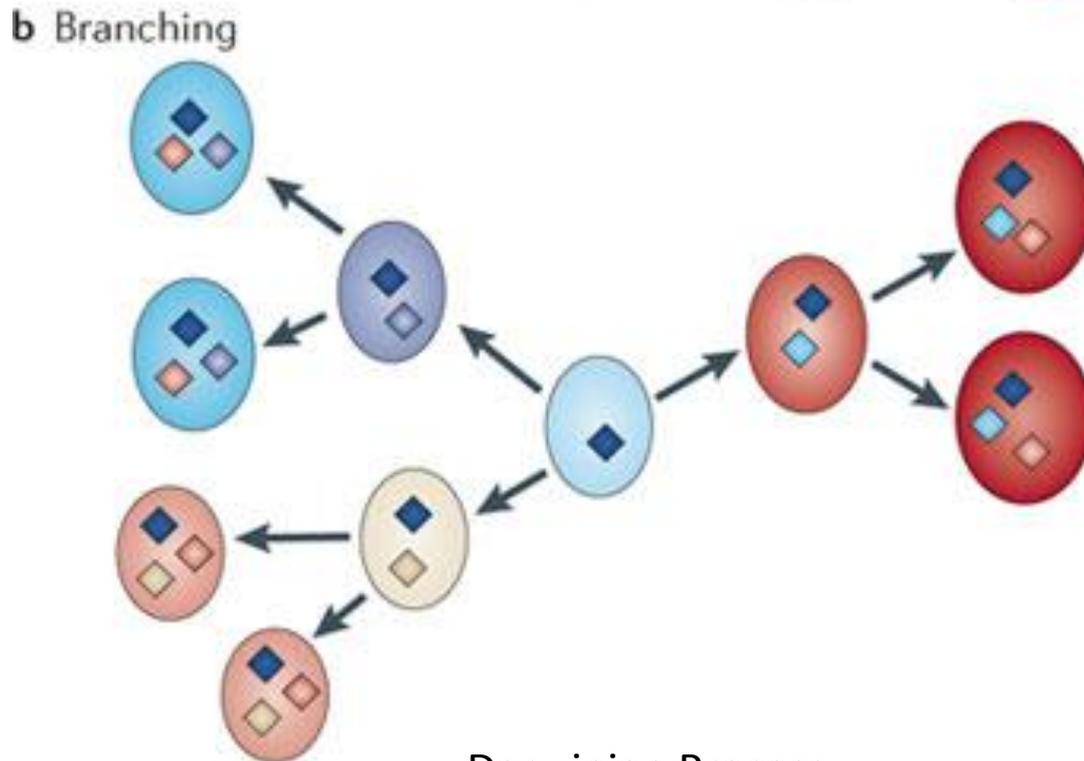
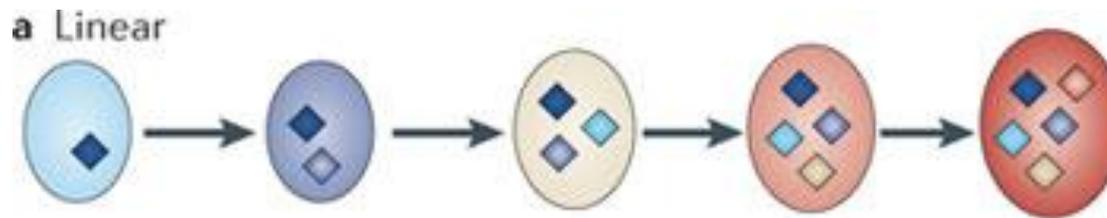
EFS and OS in Patients Relapsing and Refractory to Bortezomib and Thalidomide or Lenalidomide



Genomic Instability
Immortalization
Resistance to apoptosis
Abnormal Localization
Failure of immune surveillance
Secondary genetic changes

Biology of Relapse

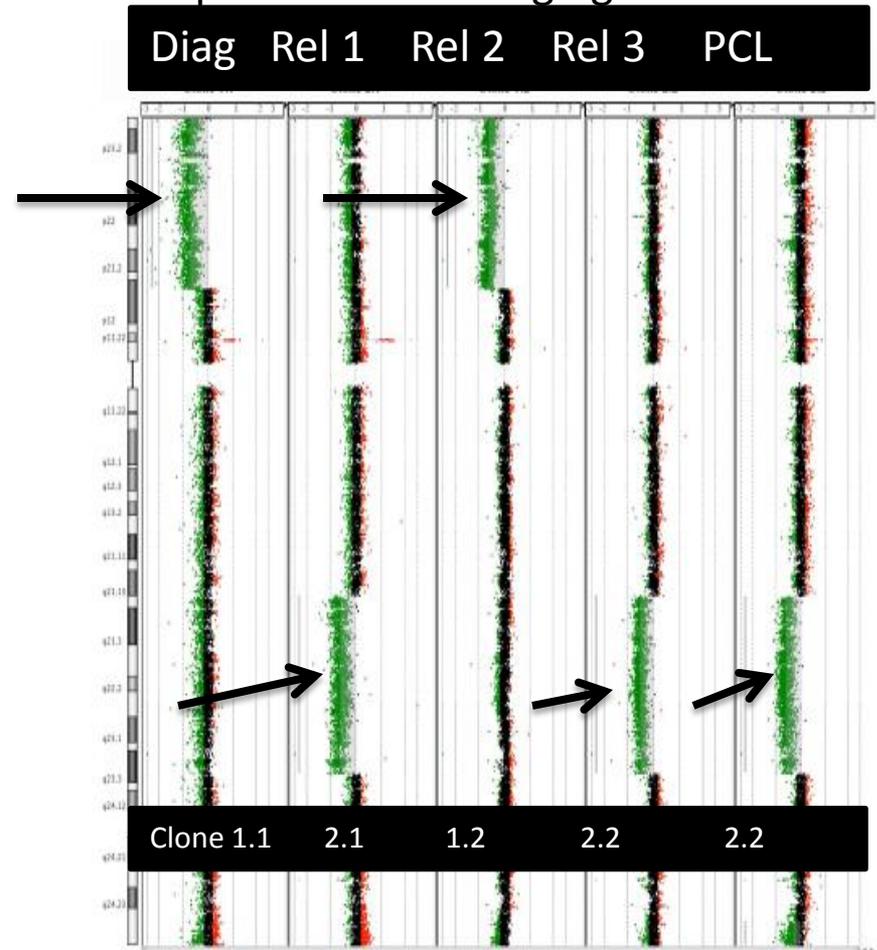




Darwinian Process

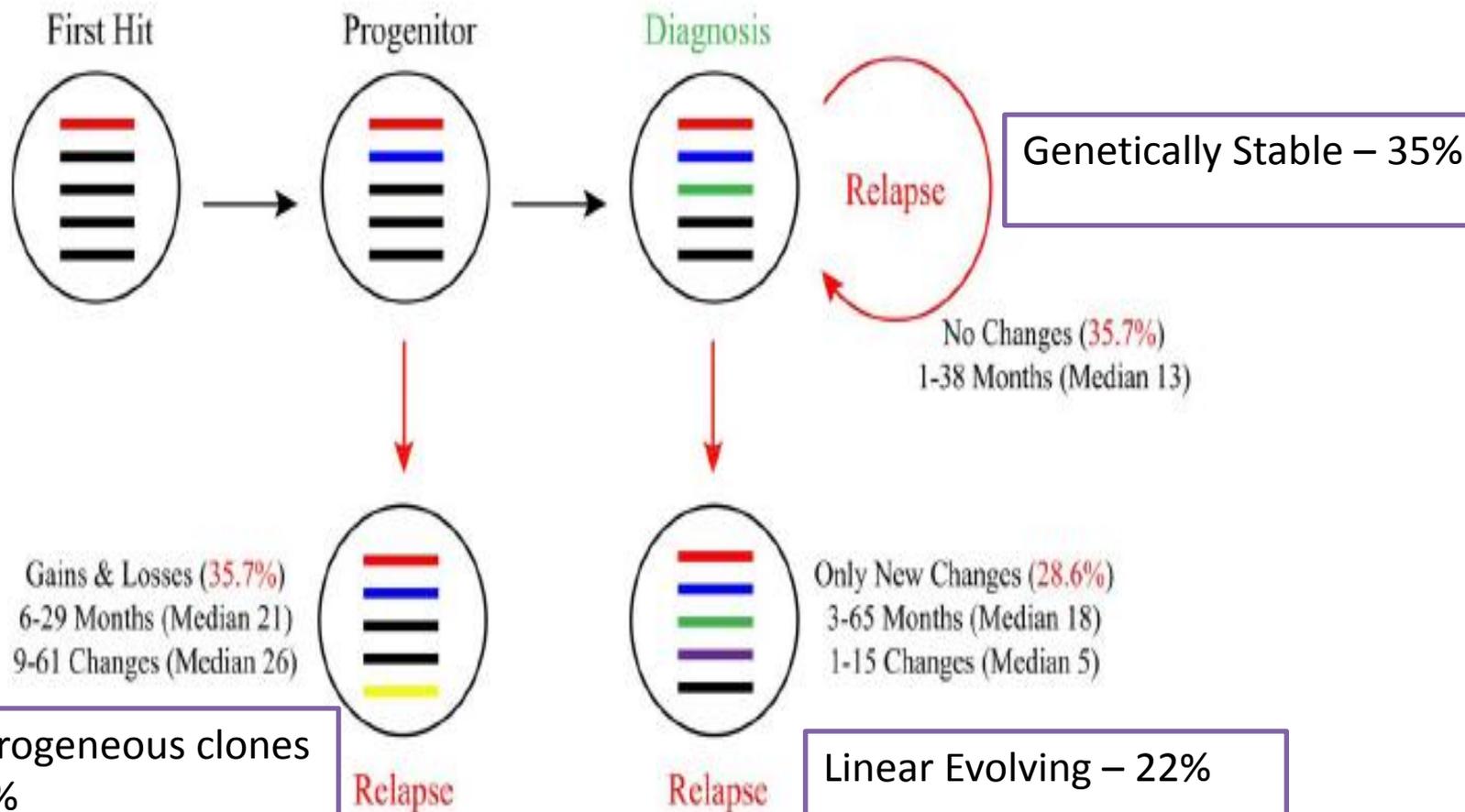
Correlating Clinical and Biologic Data

- Clinical Features of Relapse
 - diminishing responses, shortening durations of responses and emerging resistance and refractoriness
- Underlying Biology?
- Recent CGH studies –
- Darwinian Competition
- Clonal tides

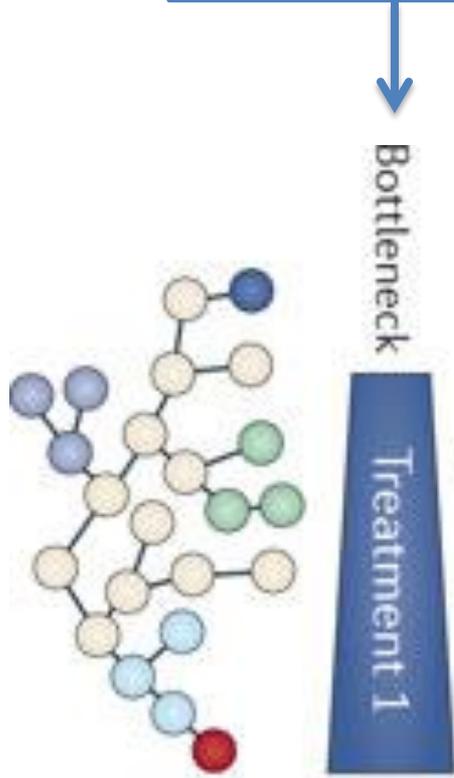


- Competition between sub clones over time in the same patient

Clonal Evolution of MM relapse



Rapid debulking (AHCT)



Bottleneck

Treatment 1

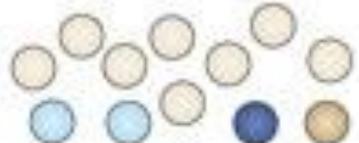
Maintenance.....

Competition for bone marrow niche

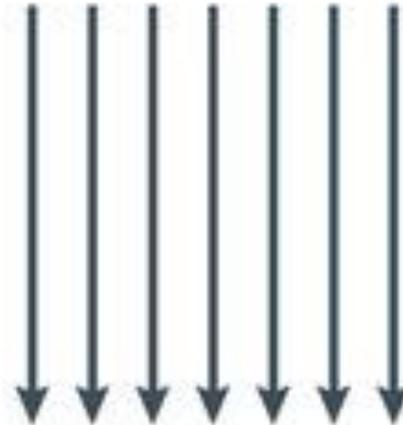
Late relapse: better prognosis



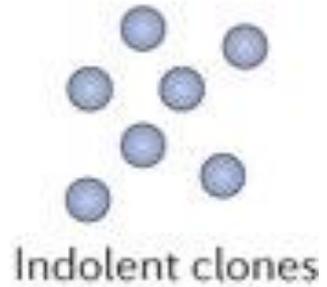
Early relapse: worse prognosis



Post-treatment therapy

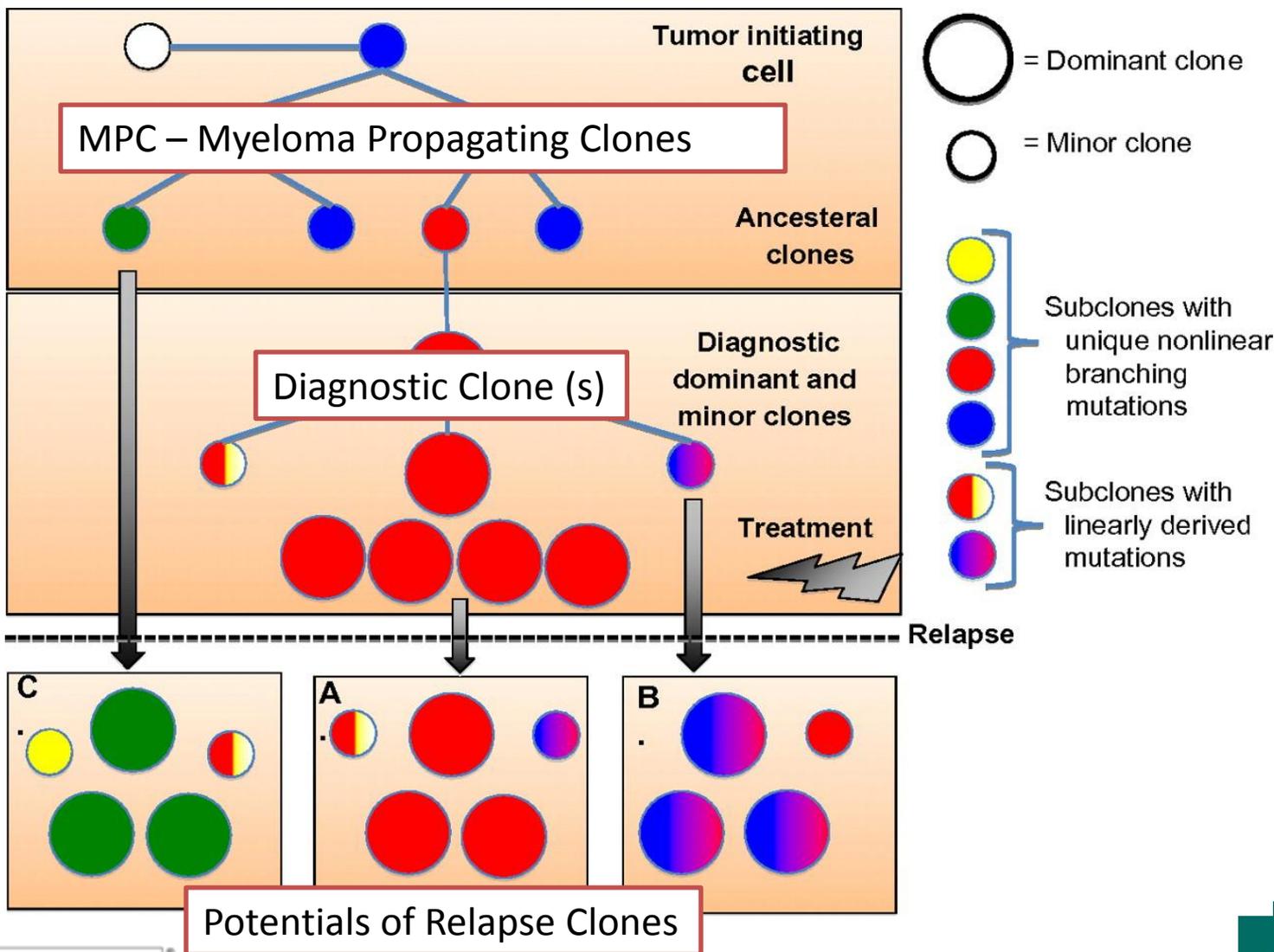


STASIS or Punctuated Equilibrium



Nature Reviews | Cancer

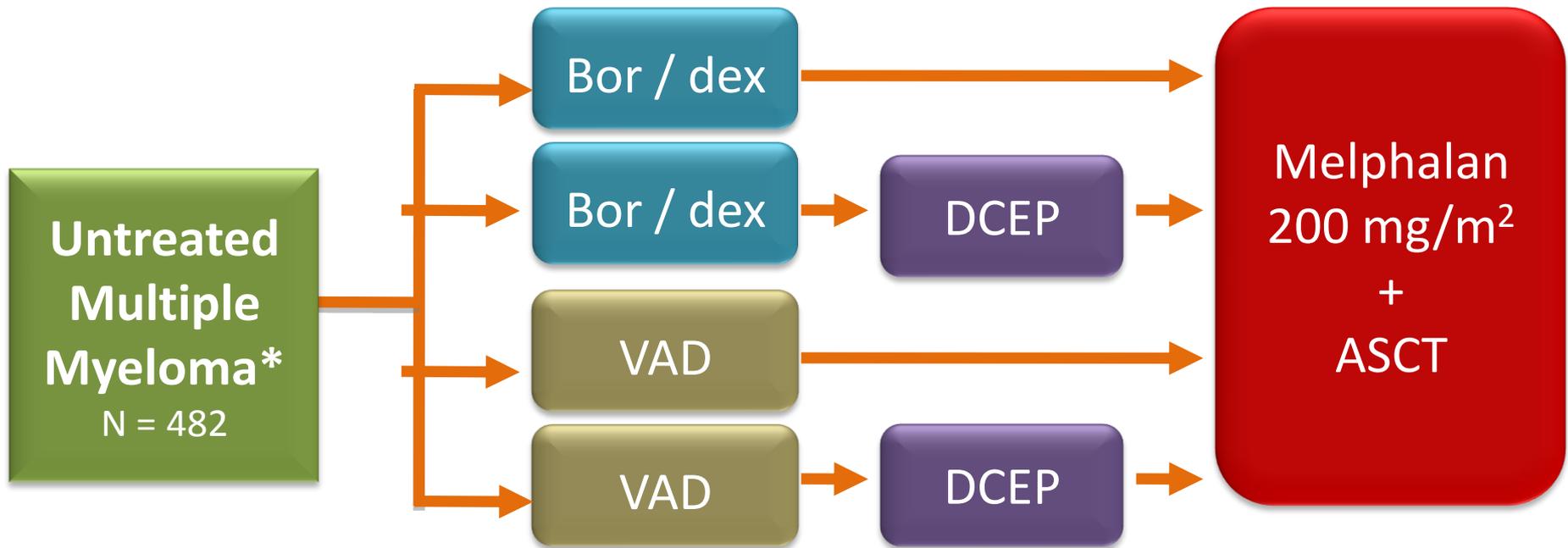
Clonal architecture in MM at diagnosis and relapse



Does treatment impact the biology of Relapse?

- Comparison of paired diagnosis and relapse DNA samples by SNP array
- 2 distinct patterns of sub-clonal evolution in MM
 - Linear pattern (2/3)
 - **Nonlinear pattern (1/3) –**
 - **dominant subclone eliminated by therapy but minor subclone survived and expanded at relapse.**
 - **in Bortezomib treated patients and those with CR/VGPR**
 - Bortezomib-based treatment:
 - eliminate the ‘driver’ mutation but lead to persistent sub-clones that are a reservoir for relapse.

Clinical Evidence?



*Patients were stratified by β_2 -microglobulin and albumin levels.

IFM2005 / 01, VD vs. VAD, Phase III

Should Biology inform treatment?

“Molecular Mayhem at relapse “

- Pathways known
 - ERK, NFκB, PI3K
- Some of them have specific directed MM therapy in trials
- **Disruption of protein degradation pathway is our most advanced targeted therapy at this time**
- Molecular classification
- Or Molecular Diagnosis?

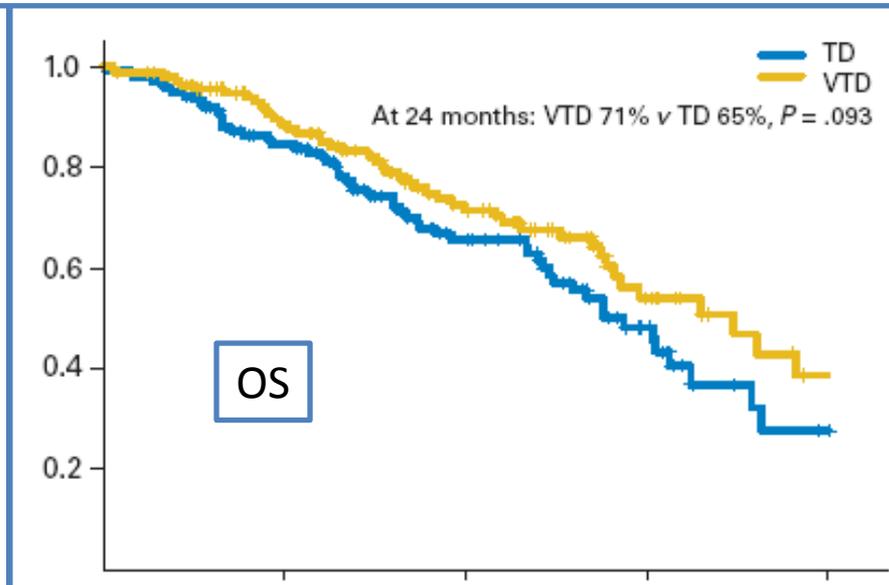
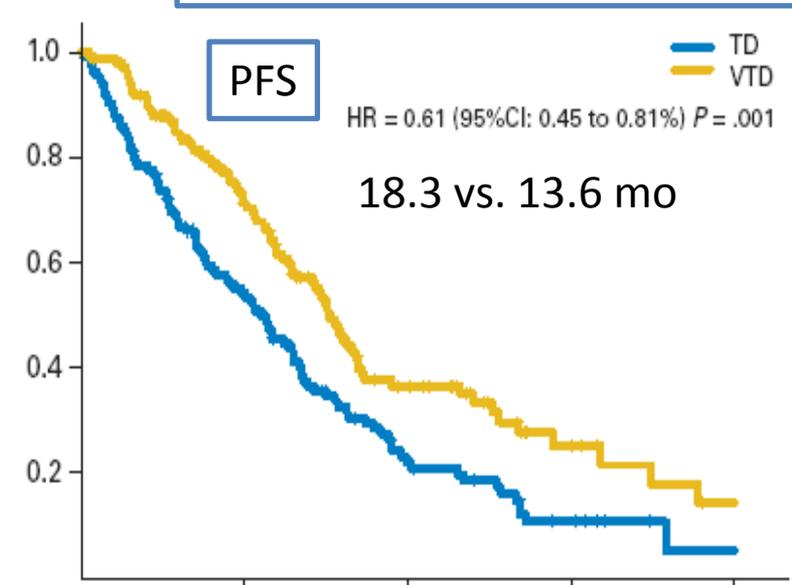
QUESTIONS:

- Continuous treatment → selection of aggressive clones when multiple sub-clones are present?
- Treatment Implications for maintenance?
- Retreatment with previously tried agents is warranted as a previous clone re-emerges
- Combination chemotherapy for multi-clonal aggressive relapse
- Avoiding genotoxic therapy to avoid exerting selection pressure in the background of clonal heterogeneity

Current Treatment of Relapse

RELAPSED MYELOMA --RECENT STUDIES

VTD vs. TD combination in first relapse after Auto HCT

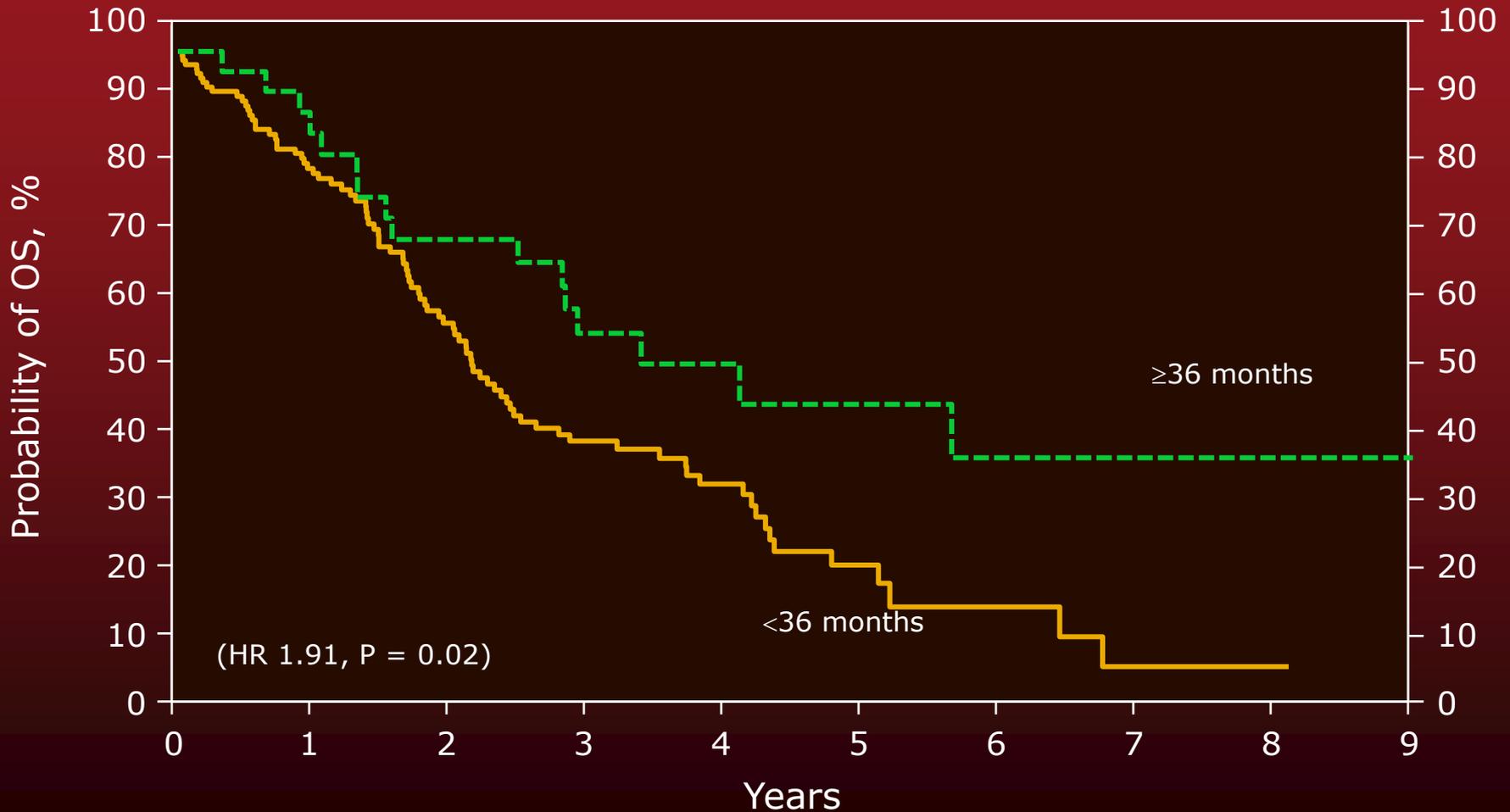


Other agents in Relapsed Disease		ORR, %	TTP/PFS, Mos	Median OS, Mos
Len + dex	MM-009 ^[1]	61	11	35 ^[5]
Len + dex	MM-010 ^[2]	60	11	
Bortezomib	APEX ^[3]	43	6	30
Vdox	MMY-3001 ^[4]	44	9	NE

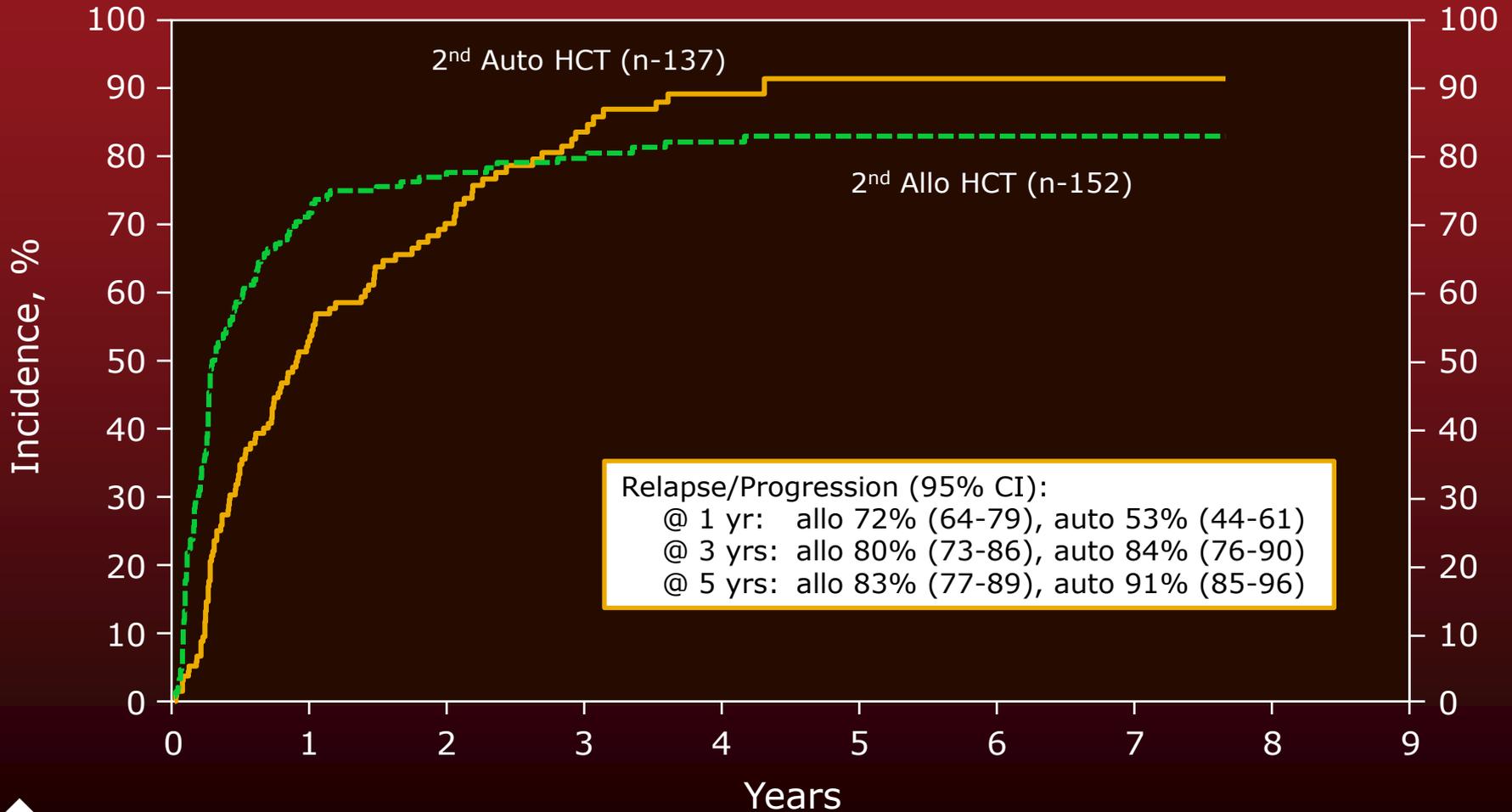
Garderet L et al. JCO 2012;30:2475-2482 Weber DM, et al. N Engl J Med. 2007;357:2133-2142. 2. Dimopoulos M, et al. N Engl J Med. 2007;357:2123-2132. 3. Richardson PG, et al. Blood. 2007;110:3557-3560. 4. Orłowski RZ, et al. J Clin Oncol. 2007;25:3892-3901. 5. Weber D, et al. Blood. 2007;110:Abstract 412.

Salvage second AutoHCT at Relapse

(stratified by Time from first Auto HCT to Relapse)



Salvage Second Allo or Auto HCT

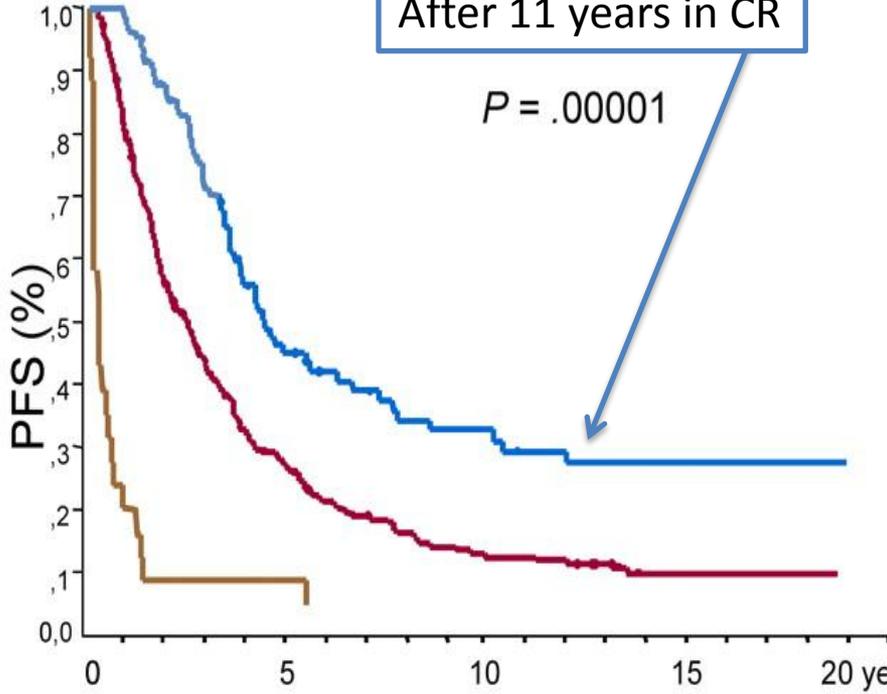


Who does not Relapse?

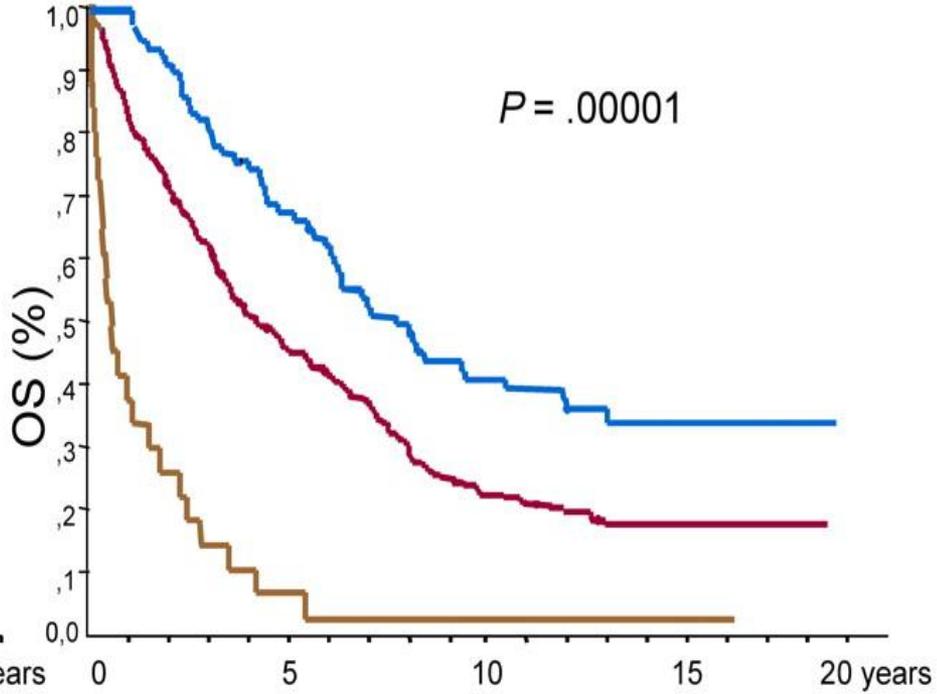
LONG TERM CR – some never relapse

No further relapse
After 11 years in CR

$P = .00001$



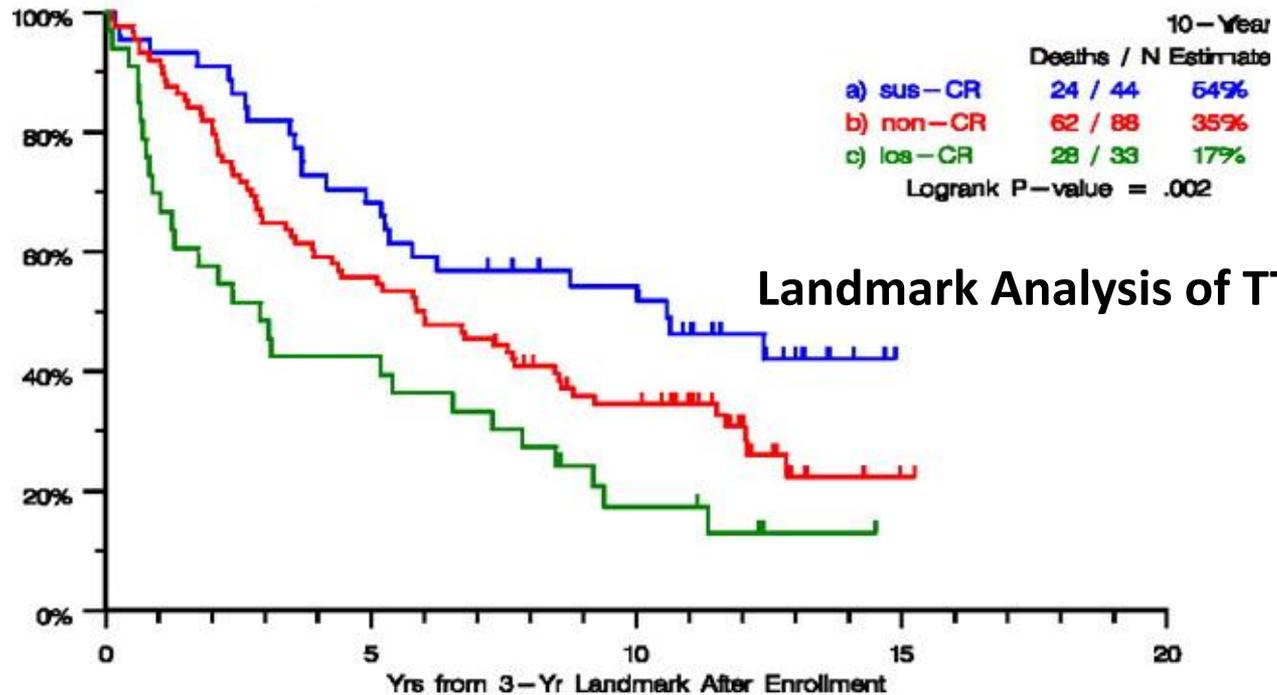
$P = .00001$



years from transplantation

CR (n=84) — nCR (n=66) + VGPR (n=54) + PR (n=114) — SD (n=12) + PD (n=14) —

SUSTAINED CR vs. NO CR vs. Unsustained CR



Long survival without CR – patients with prior MGUS /SMM
 Importance of immune reconstitution
 Flow Analysis of plasma cell immune paresis

Hoering A et al. Blood 2009;114:1299-1305

Long term survival → freedom from PROGRESSION not RELAPSE

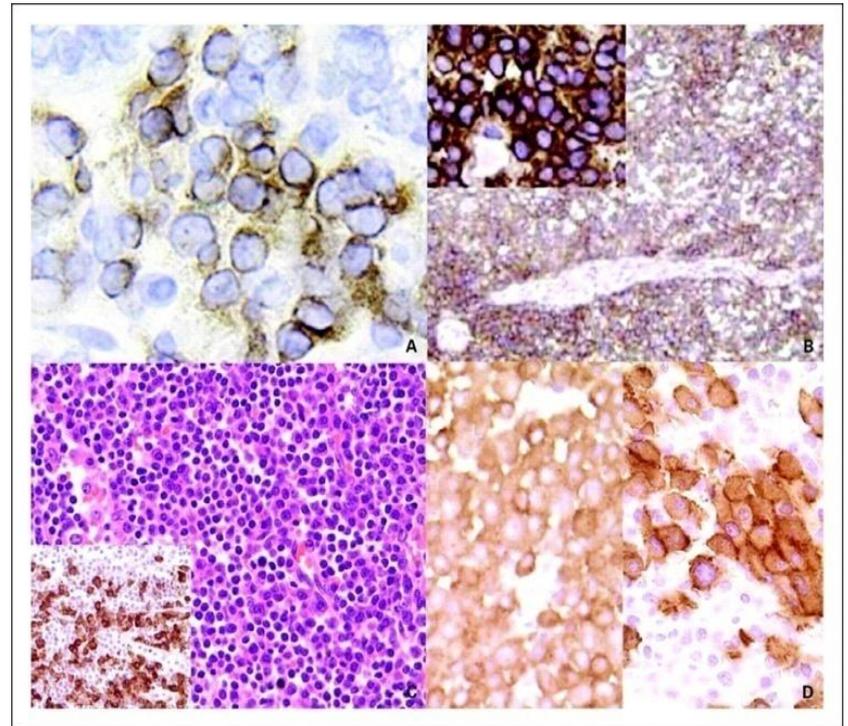
- Genomic/genetic classification of myeloma – clones one can live with vs. those that need to be eradicated
- Immune Mechanisms that underlie MGUS like states (post treatment) – clonal equilibrium
- Avoid: emergence of resistant clones or prevent factors that promote genomic instability

Those at highest risk of early Relapse

New Agents and Relapsed MM

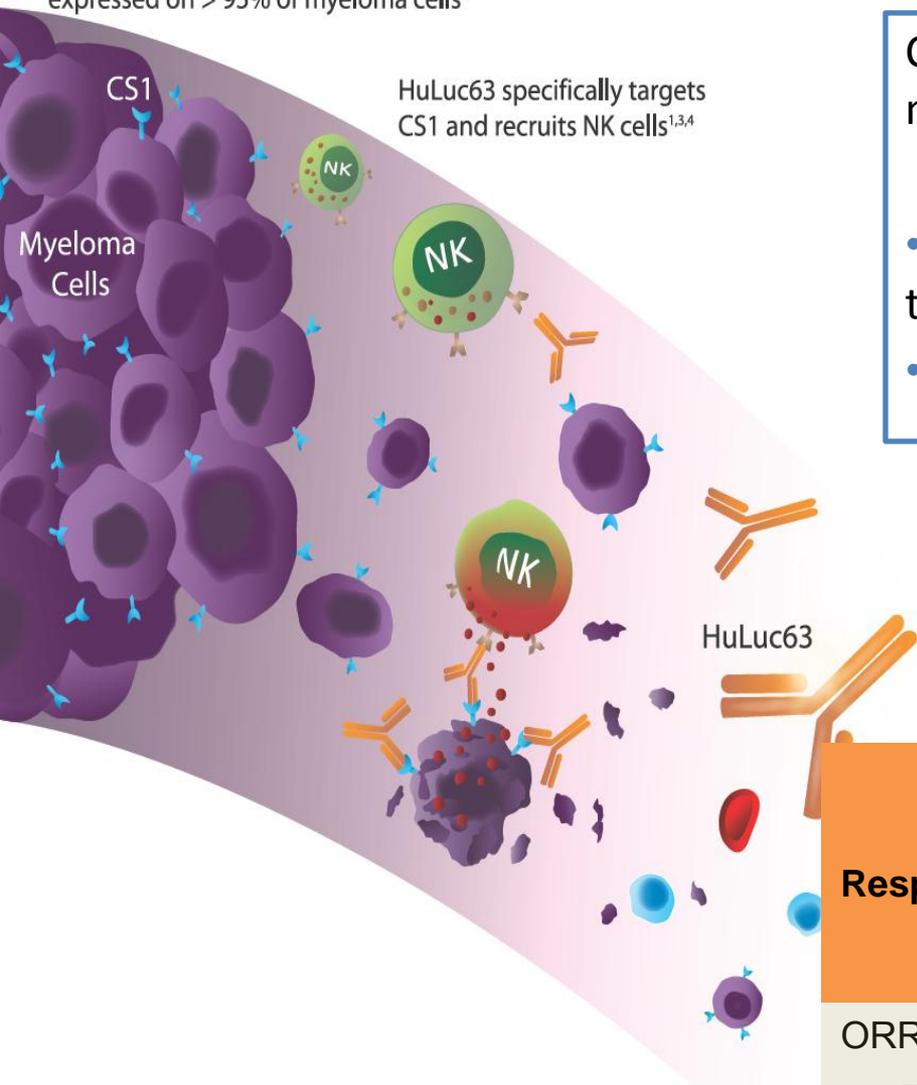
Elotuzumab

- Humanized IgG₁ mAb targeting human CS1, a cell-surface glycoprotein^[1,2]
- CS1 highly expressed on > 95% of MM cells^[1-3]
 - Lower expression on NK cells
 - Little to no expression on normal tissues



Primary mechanism of action: NK cell-mediated ADCC against myeloma cells^[1,2]

CS1, a cell surface glycoprotein, is expressed on > 95% of myeloma cells^{1,2}



CS1 is highly and uniformly expressed on multiple myeloma and normal plasma cells and

– Restricted expression on NK cells

- Elotuzumab binds to the CS1 receptor of the target cell resulting in target cell death
- MOA observed to be mainly NK-mediated ADCC

ELOTUZUMAB + LENALIDOMIDE

Response	Elotuzumab 20 mg/kg (n = 37)	Total (N = 73)
ORR (≥ PR), n (%)	27 (73)	60 (82)
<ul style="list-style-type: none"> ▪ Pts with ≥ 2 previous therapies 	13 (65)	30 (75)

HuLuc63-recruited NK cells eliminate myeloma cells through ADCC^{1,2,3,4}

Carfilzomib

Trial	N*	Population	Previous Lines, n	ORR, %	MR/SD%	Median TTP, Mos
003-A0 ^[1]	39	Relapsed/ refractory	> 2	18	8/41	6.2
003-A1 ^[2]	257	Relapsed/ refractory	≥ 2	24	12/--	--
004 (Bz exposed) ^[3]	35	Relapsed/ refractory	1-3	21	12/35	8.1
004 (Bz naive) ^[4] 20 mg/m ²	59	Relapsed/ refractory	1-3	42	17/22	8.3
20/27 mg/m ²	67	Relapsed/ refractory		52	12/15	NR
006 (combo with len/dex) ^[5]	50	Relapsed/ refractory	1-3	78	2/8	--

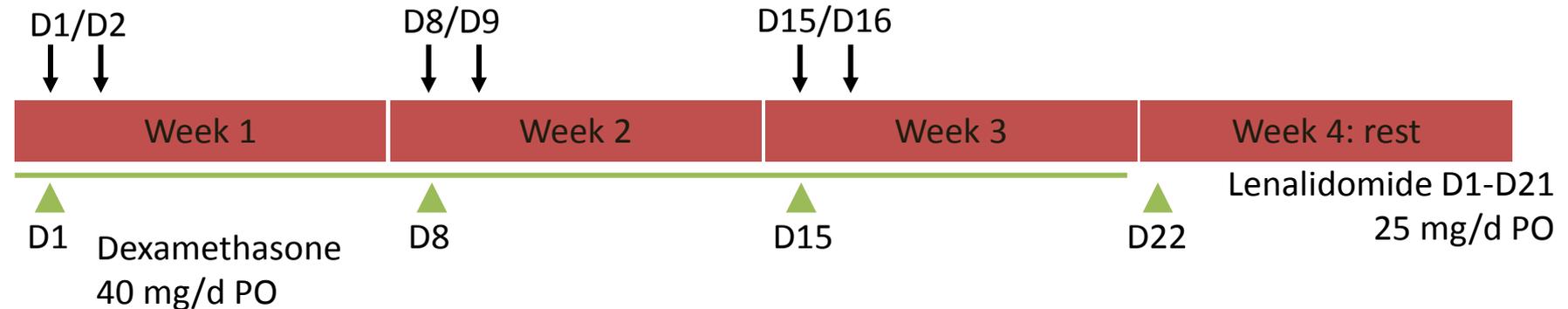
*Evaluable for response.

*Neuropathy from phase II experience
9.6% grades 1/2 and 1.4% grade 3*

PX-171-006: Phase II Carfilzomib Plus Len/Dex in Relapsed/Refractory MM

Carfilzomib
20/27 mg/m² IV*

*20 mg/m² cycle 1 days 1 and 2 only,
27 mg/m² thereafter



Response (N = 51)	n (%)
CR/nCR	12 (24)
VGPR	9 (18)
PR	19 (37)
MR	1 (2)
SD	3 (6)
ORR	40 (78)

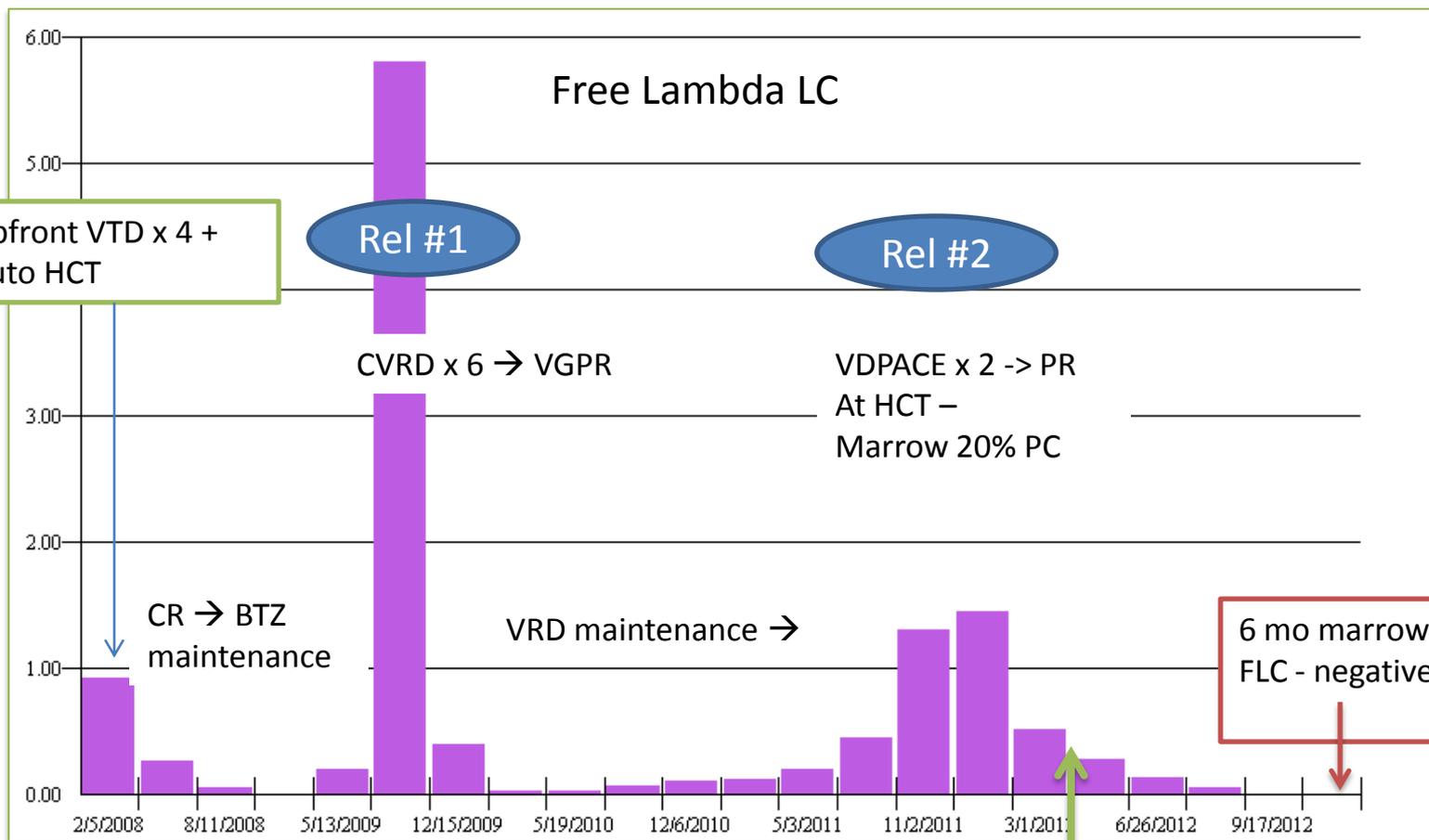
Pomalidomide

- IFM 2009-02
- Median follow-up: 11.3 months (similar in the 2 arms)

Outcome	Arm A: 21/28 days (n = 43)	Arm B: 28/28 days (n = 41)	Total
ORR (\geq PR), %	35.0	34.0	34.5
▪ CR, n	1	2	3
▪ VGPR, n	1	1	2
▪ PR, n	13	11	24
Median time to first response, mos	2.7	1.1	1.8
Median duration of response, mos	10.5	7.2	8.1
▪ \geq 1 yr in responders, %	47.5	36.0	37.5

NK based strategy vs. MM? - An Anecdote

Thakar M et al



Priorities in the setting of MM relapse

PREVENTION OF RELAPSE AFTER AUTO HCT

- Genetics of relapse clones after modern triple phase sequence – design ancillary protocols to current trials
- Achieve the 2 Mechanisms of long term OS :
 - sus-CR or a “secondary” MGUS like state
 - Avoid a los-CR
- Cellular therapies to reverse MM specific immune paresis
- IMiDs / Elotuzumab and PD-1-PDL axis
- **Clinical priority :**
 - High risk patients
 - Allogeneic strategies revival

Clinical Priorities

RELAPSE AFTER AUTO HCT – NEED FOR BETTER TREATMENT

- **Target First Relapse after AutoHCT**
 - Treat as a priority event and design unique trials
 - Re-induce with combination and debulk vs. sequential therapies
 - **Novel conditioning trials for AutoHCT**
 - Allo HCT and maintenance
 - **Genomics of relapse – same clone vs. subclone vs. new clone. How do we distinguish and choose therapy?**

THANK YOU