

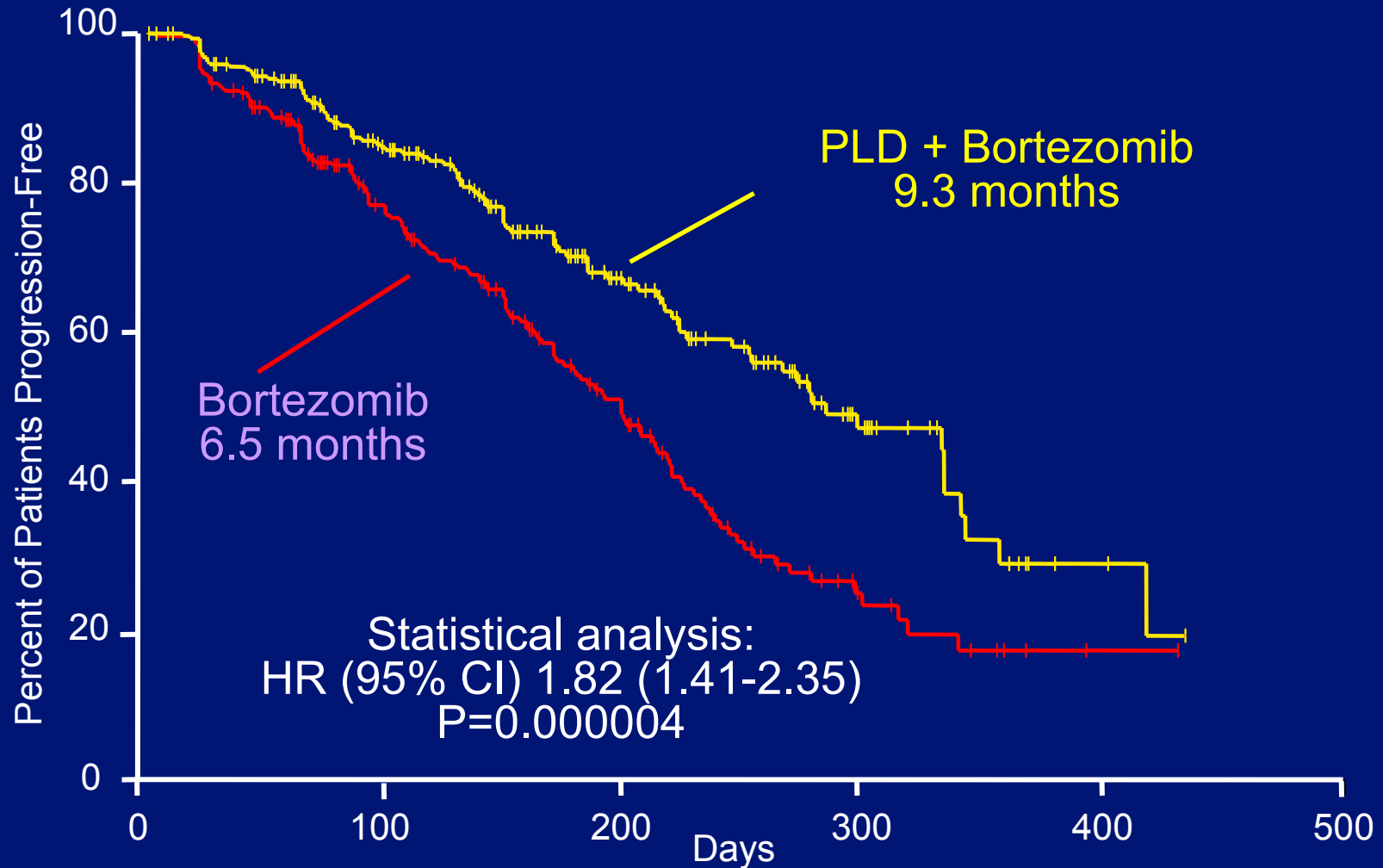
# **New combinations for MM**

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# Phase III: Bortezomib + pegylated liposomal doxorubicin vs bortezomib: Time to progression



APEX: TTP was 6.2 months

**2 or 3 drug combination?**

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# Summary of bortezomib induction regimens

	Harousseau VD vs VAD (n=223 vs 219)	Cavo VTD vs TD (n=199 vs 200) (abstract 158)	Sonneveld PAD vs VAD (n=75 vs 75) (abstract 653)		Knop VCD (n=100) (abstract 2776)
<b>Results post-induction</b>					
CR + nCR	15% vs 7%	33% vs 12%	5% vs 1%		n/a
≥VGPR	39% vs 16%	61% vs 30%	42% vs 15%		50%
CR + PR	82% vs 65%	92% vs 78.5%	83% vs 59%		79%
<b>Results post-ASCT</b>					
CR + nCR	40% vs 22%	54% vs 29%	23% vs 9%		n/a
≥VGPR	61% vs 44%	75% vs 53%	80% vs 50%		n/a
CR + PR	n/a	n/a	93% vs 80%		n/a

n/a: not available

# 3 drug combinations

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# Therapeutic Algorithm

## Level of Evidence 1b ( $\geq 1$ Randomized Trial)

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Diagnosis

> 65 years

MPT

>

MP

5 randomized trials

MPV

>

MP

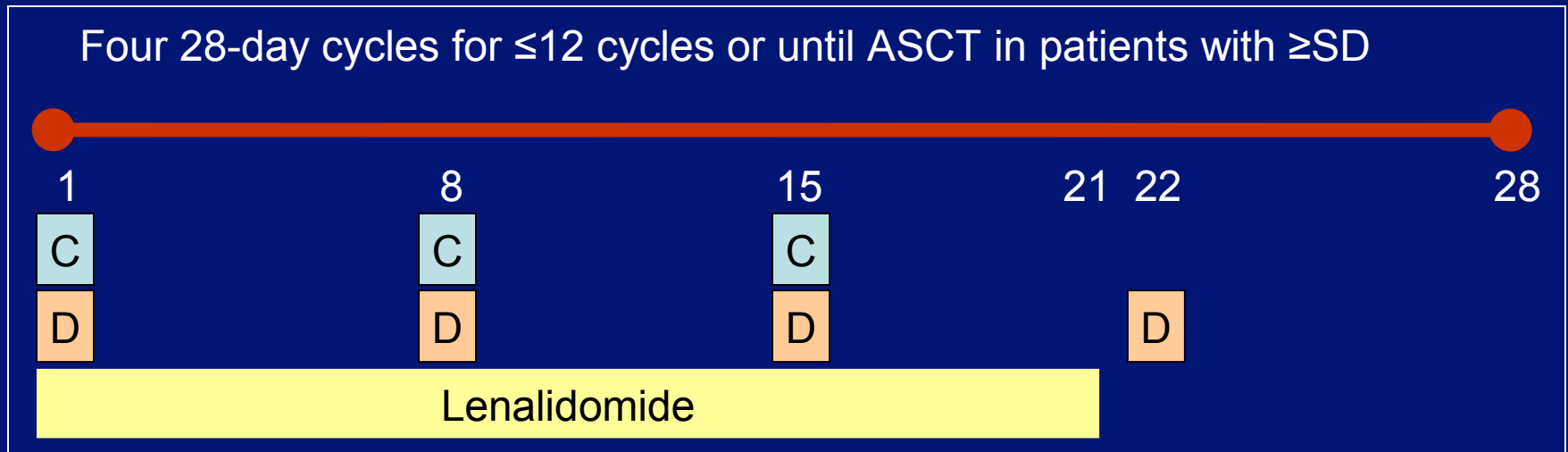
1 randomized trial

MPR

MP

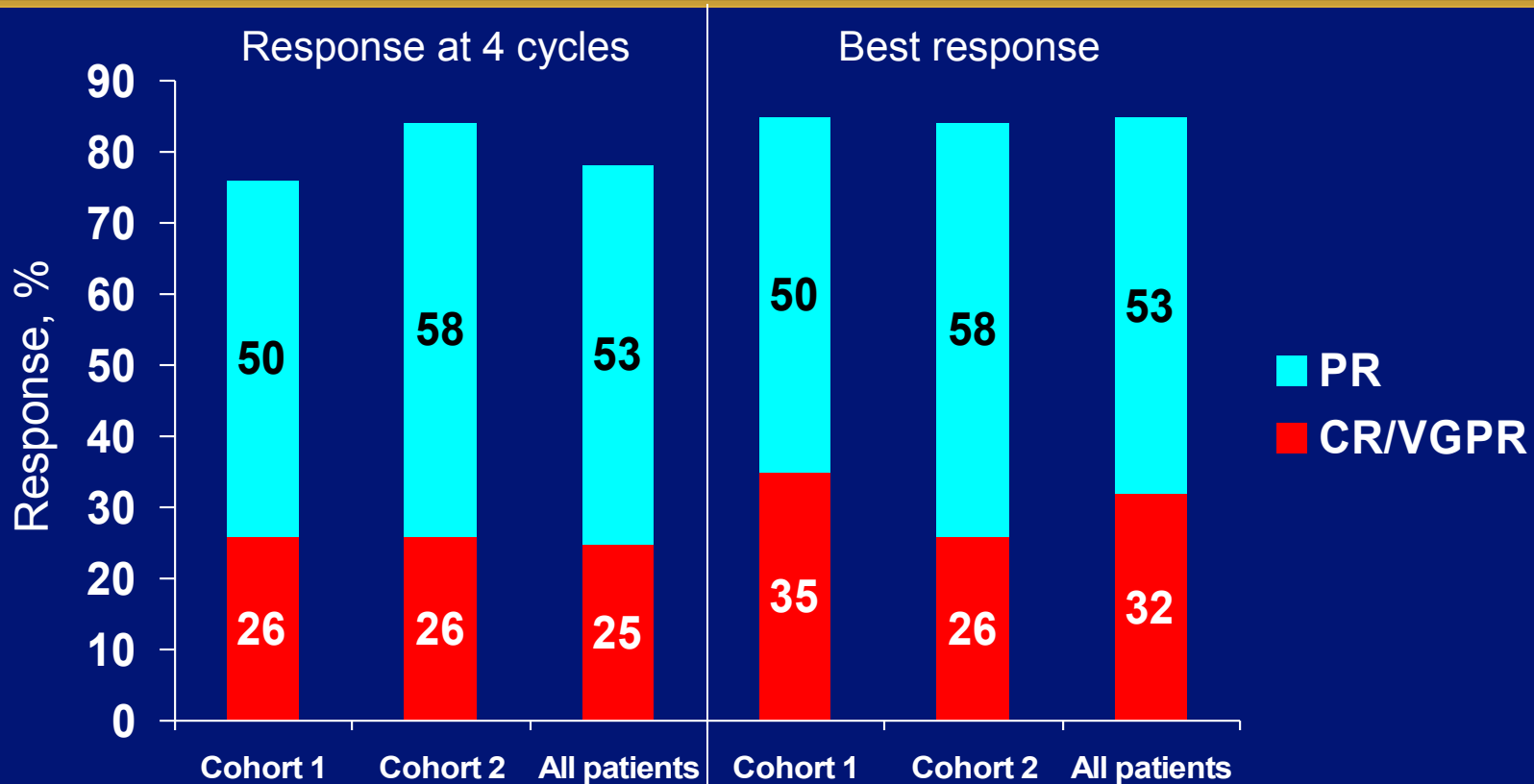
under evaluation

# Cyclophosphamide, Lenalidomide, Dexamethasone CRd trial in Newly Diagnosed MM



- Cohort 1 (n=34), accrued from June 2006 to July 2007
  - Lenalidomide 25 mg/d, days 1–21; Dex, 40 mg/d, days 1, 8, 15, 22; cyclophosphamide, 300 mg/m<sup>2</sup> days 1, 8, 15
- Cohort 2 (n=19), accrued due to need for cyclophosphamide dose reduction in cohort 1
  - Treatment as per cohort 1, except cyclophosphamide 300 mg (fixed dose) days 1, 8, 15
- ASA or full anticoagulation for all patients

# Cyclophosphamide, Lenalidomide, Dexamethasone, CRd trial: Response



- 34 patients went to stem cell collection
- 8 patients failed first attempt (3 salvaged with AMD3100, 1 salvaged with CTX, 4 did not reattempt/failed)
- Median collection  $7.0 \times 10^6$  CD34 cells/kg
- 11 patients have since gone to ASCT

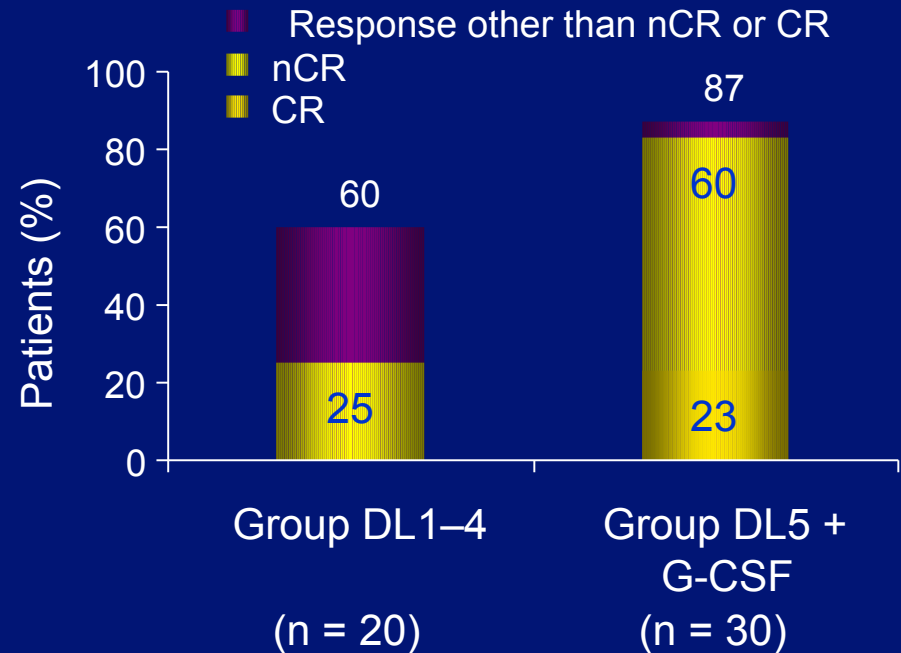
Kumar S et al. *Blood*. 2008;112:40 [abstract 91]; updated results presented at: 50th ASH Annual Meeting; December 6–9, 2008; San Francisco, CA



# Lenalidomide; Doxorubicin, Dexamethasone, RAD trial: safety and efficacy in relapsed MM patients

Grade 3 or 4 adverse event	%*
Neutropenia	44
Thrombocytopenia	32
Peripheral neuropathy	0
VTE	7.5

\* Reported in 69 patients.

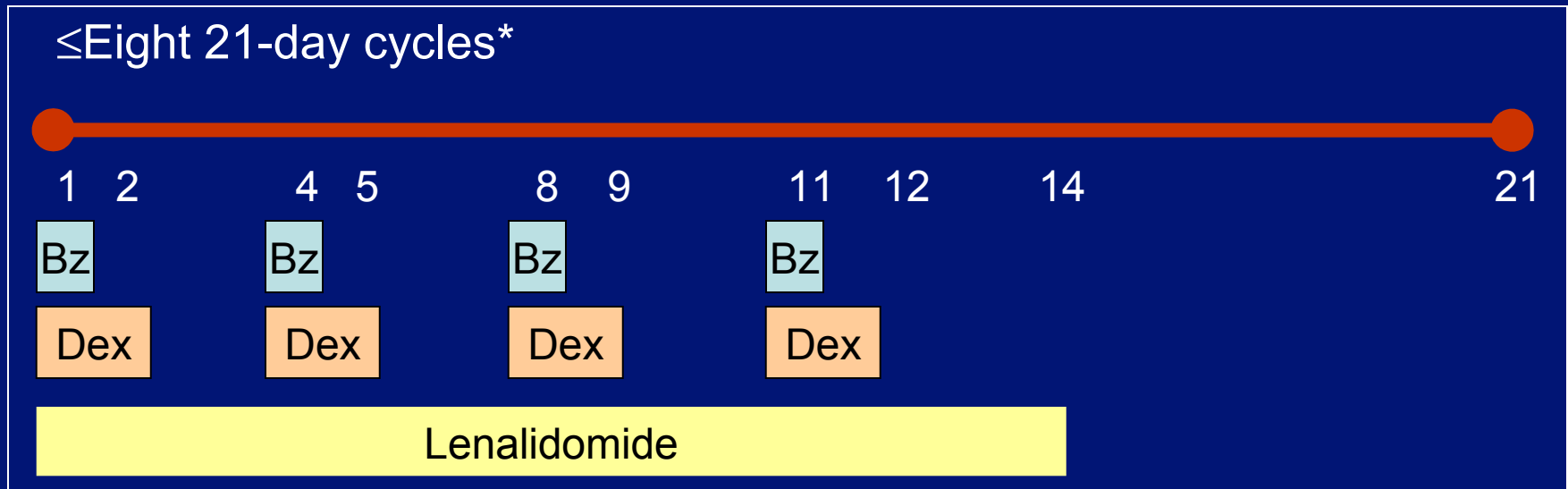


Cytogenetic abnormality	Patients, n/evaluatable (%)	≥ PR, n
del(13q)	17/37 (46)	12
t(4;14)	4/25 (16)	3 (PD: 1)
del(17p)	6/31 (19)	2 (SD + PD: 2)

# Bortezomib, Cyclophosphamide, Dexamethasone, VCD combinations in the relapsed/refractory setting

Bortezomib	Phase	n	CR + PR	CR + nCR	EFS, PFS, OS	Reference
+ cyclophosphamide + intermediate-dose dex	2	54	82%	16%	EFS: 12 months OS: not reached @ 15 months	Kropff <i>et al.</i> <i>Br J Haematol</i> 2007;138:330-7
+ cyclophosphamide + dex	1/2	16	75%	31%	PFS: 7 months	Davies <i>et al.</i> <i>Haematologica</i> 2007; 92: 1149-1150
+ cyclophosphamide + prednisone	1/2	37 (19 at dose reported)	95%	50%	1-year PFS 56% 1-year OS 89%	Reece <i>et al.</i> <i>JCO</i> 2008;26: 4777-4783

# Bortezomib, Lenalidomide, and Dexamethasone RVD trial in Newly Diagnosed MM



\*Dex, 40 mg/d, days 1, 2, 4, 5, 8, 9, 11, 12; 20 mg/d, cycles 5–8, amended to 20 mg/10 mg cycles 1–4/5–8 based on safety data

- **Patients achieving  $\geq$ PR may proceed to ASCT after  $\geq$ 4 cycles**
- **Maintenance therapy permitted in patients achieving  $\geq$ SD using weekly (days 1 and 8) schedule of Bort, and Dex on days 1, 2, 8, and 9**
- **Antithrombotic therapy with daily ASA (81 or 325 mg)**
- **Antiviral therapy as prophylaxis against herpes zoster**

Richardson P et al. *Blood*. 2008;112:41 [abstract 92]; updated results presented at: 50th ASH Annual Meeting; December 6–9, 2008; San Francisco, CA

# Bortezomib, Lenalidomide, and Dexamethasone in Newly Diagnosed MM: Response Data

- Responses assessed by EBMT<sup>1</sup> criteria and Uniform Criteria (UC)<sup>2</sup> (modified to include nCR)<sup>3</sup>

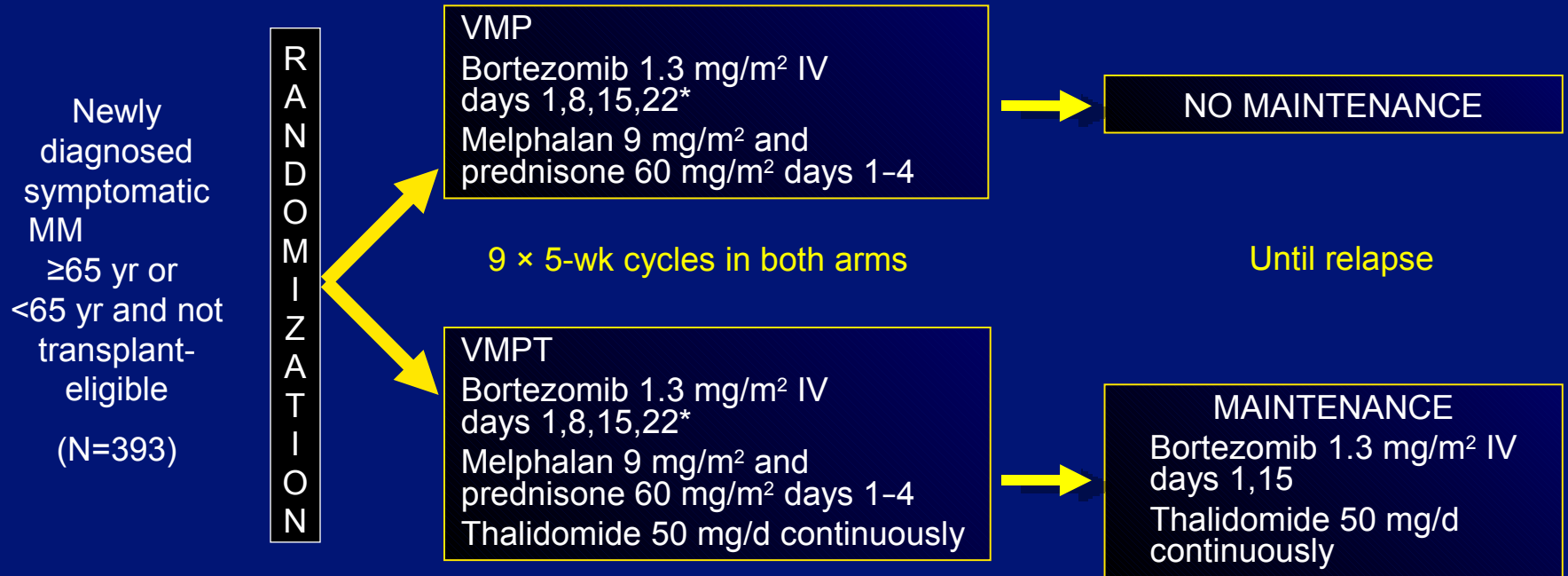
EBMT/UC Response (N=65 Evaluable as of Nov 2008)	n (%)
CR	17 (26)
nCR	12 (18)
VGPR	20 (30)
PR	36 (55)
≥VGPR	<b>48 (74)</b>
≥PR	65 (100)

1. Bladé J et al. *Br J Haematol.* 1998;102:1115; 2. Durie BGM et al. *Leukemia.* 2006;20:1467 [published corrections in *Leukemia.* 2006;20:2220, *Leukemia.* 2007;21:1134]; 3. Richardson P et al. *Blood.* 2008;112:41 [abstract 92]; updated results presented at: 50th ASH Annual Meeting; December 6–9, 2008; San Francisco, CA

**3 or 4 drug combinations?**

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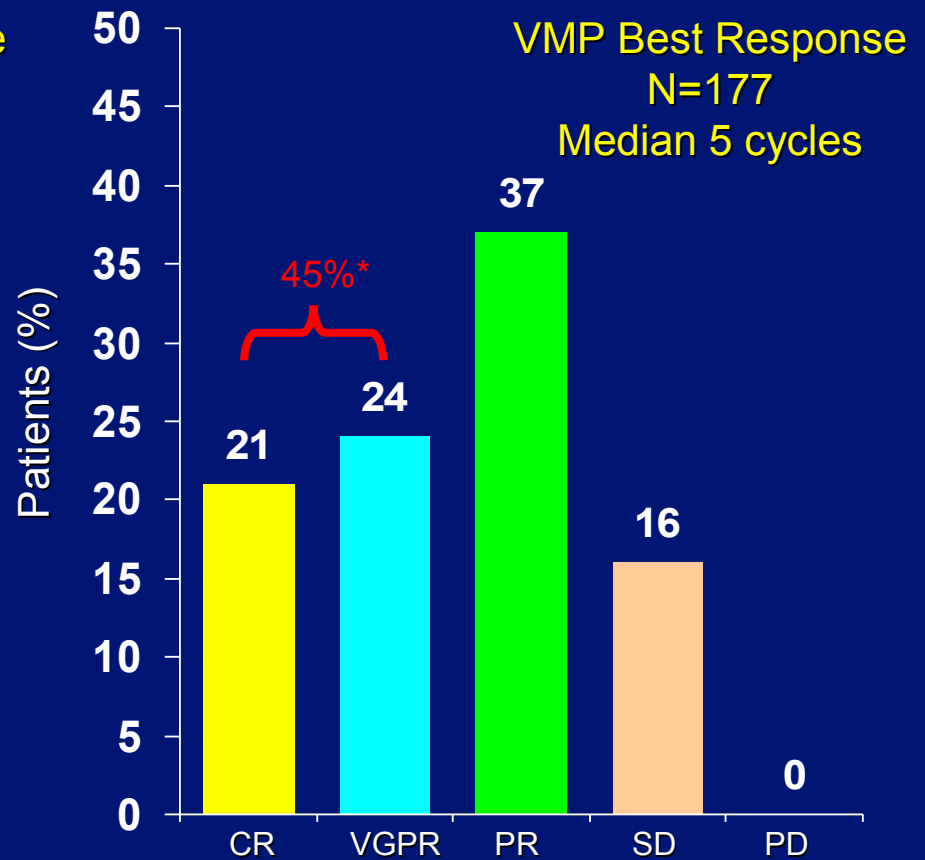
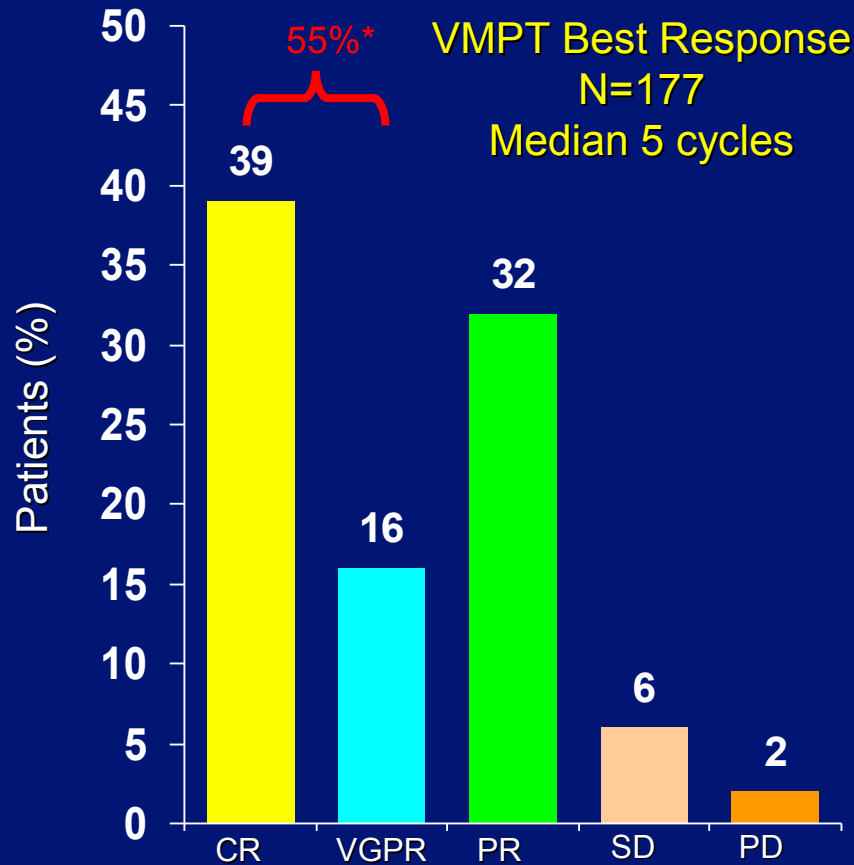
# Phase III Study of Bortezomib, Melphalan, Prednisone (VMP) ± Thalidomide (VMPT) in Newly Diagnosed MM



\*61 VMP patients and 70 VMPT patients were treated with biweekly infusions of bortezomib

Palumbo A et al. *Blood*. 2008;112:243 [abstract 652]; updated results presented at:  
 50th ASH Annual Meeting; December 6–9, 2008; San Francisco, CA

# VMPT vs VMP in Newly Diagnosed MM: Efficacy



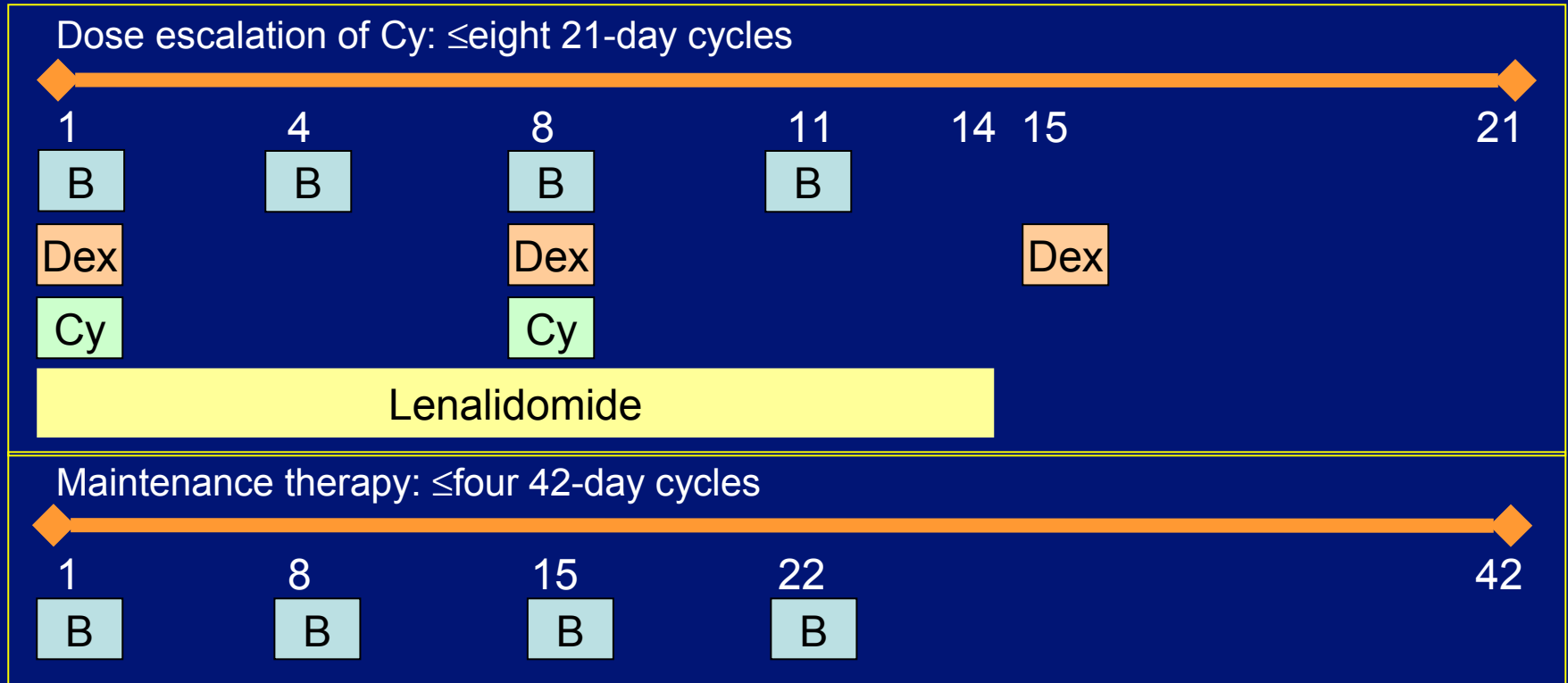
	VMPT	VMP	P Value
Time to next therapy @ 36 mo, %	80	78	.56
PFS @ 36 mo, %	74	70	.28
OS @ 36 mo, %	88	87	.75

\* $P < .001$

Palumbo A et al. *Blood*. 2008;112:243 [abstract 652]; updated results presented at: 50th ASH Annual Meeting; December 6–9, 2008; San Francisco, CA

# Bortezomib, Dexamethasone, Cyclophosphamide, Lenalidomide (VDCR) in Newly Diagnosed MM

## Phase I EVOLUTION Trial



Bort 1.3 mg/m<sup>2</sup> IV; Dex 40 mg po; Len 15 mg po; Cy dose-escalating 100–500 mg/m<sup>2</sup> po

- Prophylactic antibiotics, acyclovir, and anticoagulants as required
- Eligible patients could undergo ASCT after 4 cycles

Kumar S et al. *Blood*. 2008;112:41 [abstract 93]; updated results presented at: 50th ASH Annual Meeting; December 6–9, 2008; San Francisco, CA



# VDCR in Newly Diagnosed MM: Response rate

Dose Level	Cy Dose, mg/m <sup>2</sup>	Enrolled	Treated	Patients Undergoing ASCT	Remain on Treatment	Best Unconfirmed Response, N=25		
						CR (sCR)	VGPR (nCR)	PR
1	100	3	3	3	0	2 (2)	1	-
2	200	4	4*	1	0	1 (1)	-	3
3	300	4	4*	1	0	2 (1)	2 (1)	-
4	400	8	7†	4	1	2	3	2
5	500	7	7*	N/A‡	5	2 (1)	2	3
<b>Total</b>		26	25	9	6	<b>9 (5)</b>	<b>8 (1)</b>	<b>8</b>

Recommended dose of Cy was 500 mg/m<sup>2</sup>

CR 36%

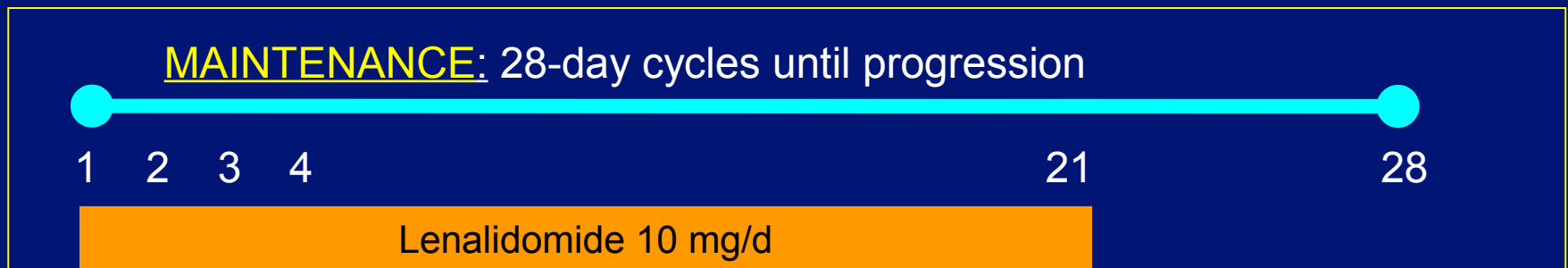
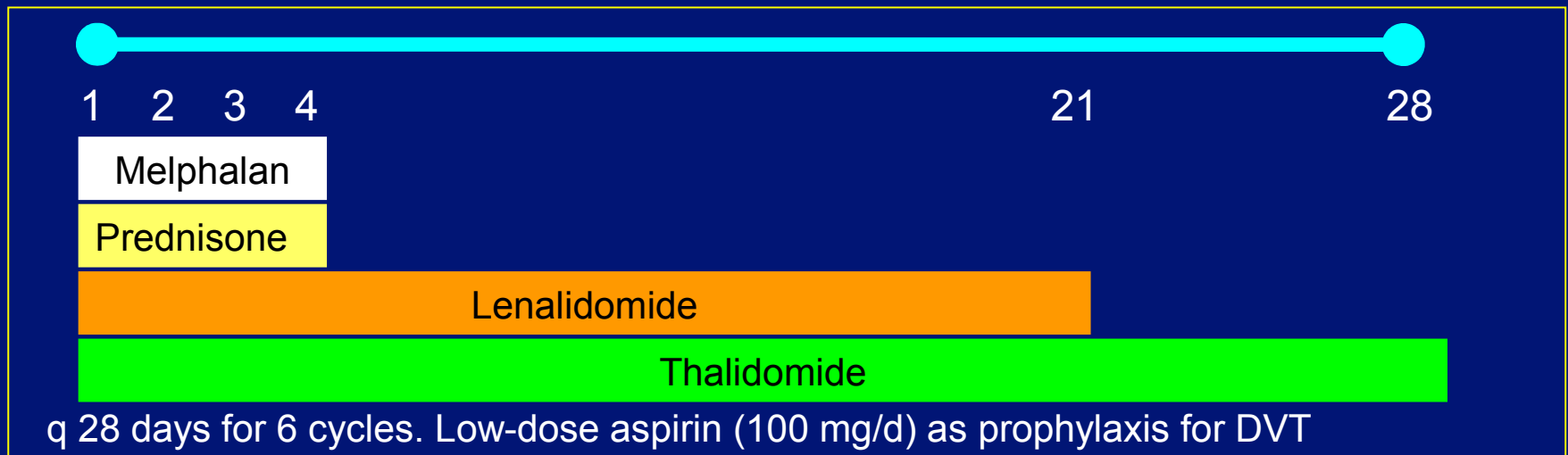
> VGPR 68%

\*1 patient not evaluable for DLT per protocol †1 patient excluded (did not receive study treatment due to a heart problem);  
1 other patient not evaluable for DLT per protocol ‡Patients have not undergone sufficient cycles (4)

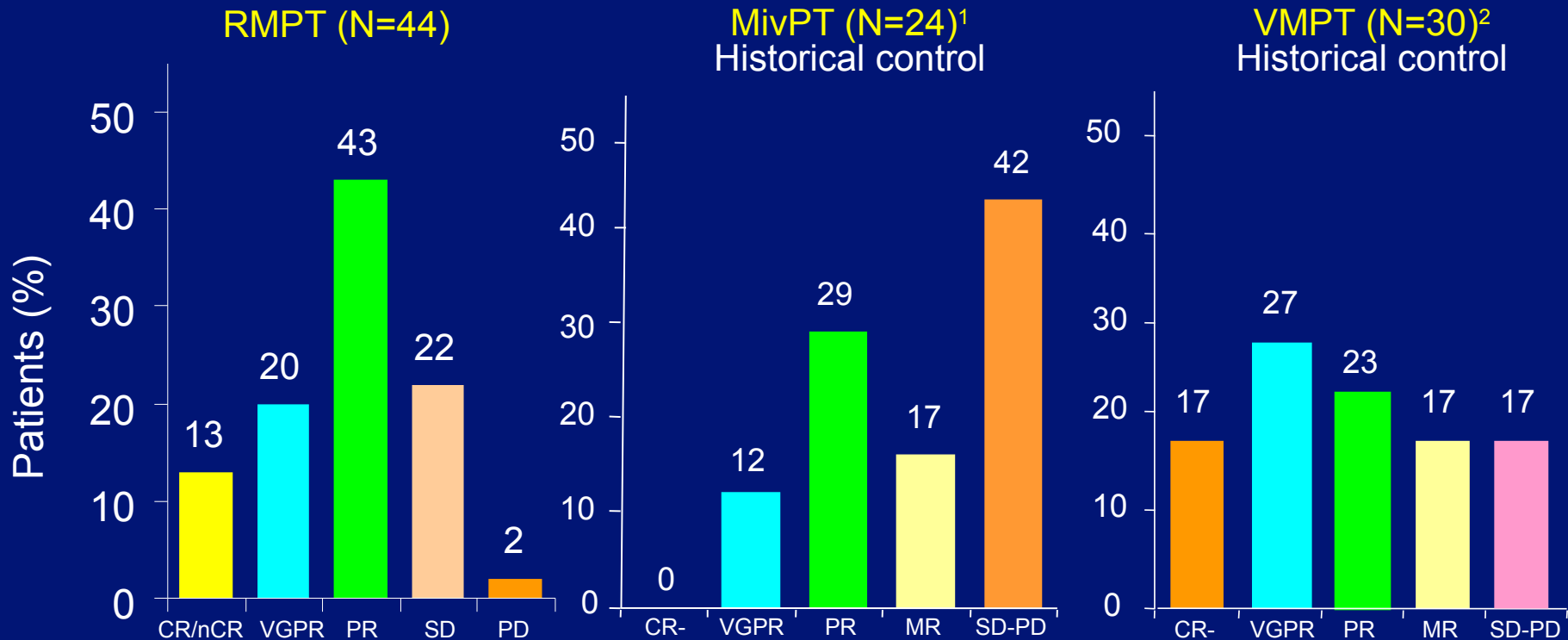
Kumar S et al. *Blood*. 2008;112:41 [abstract 93]; updated results presented at:  
50th ASH Annual Meeting; December 6–9, 2008; San Francisco, CA

# Phase II Trial of Lenalidomide, Melphalan, Prednisone, and Thalidomide (RMPT) in Relapsed/Refractory MM

Cohort	Melphalan (mg/kg) po	Prednisone (mg/kg) po	Lenalidomide (mg/d) po	Thalidomide (mg/d) po
1 (n=22)	0.18	2	10	50
2 (n=22)	0.18	2	10	100



# Phase II Trial of RMPT in Relapsed/Refractory MM: Response vs MivPT and VMPT



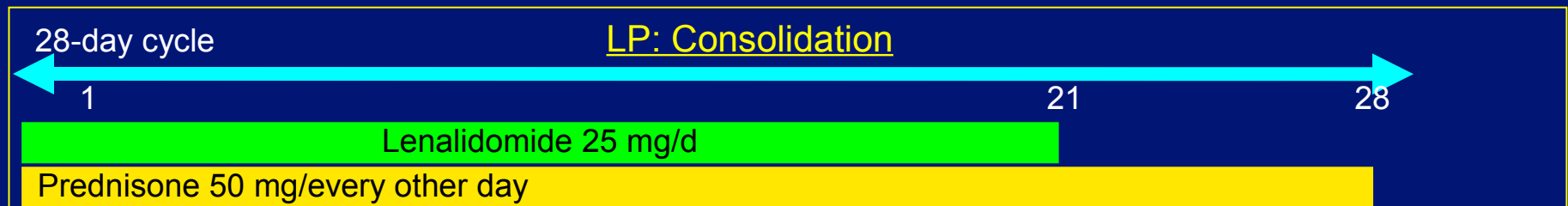
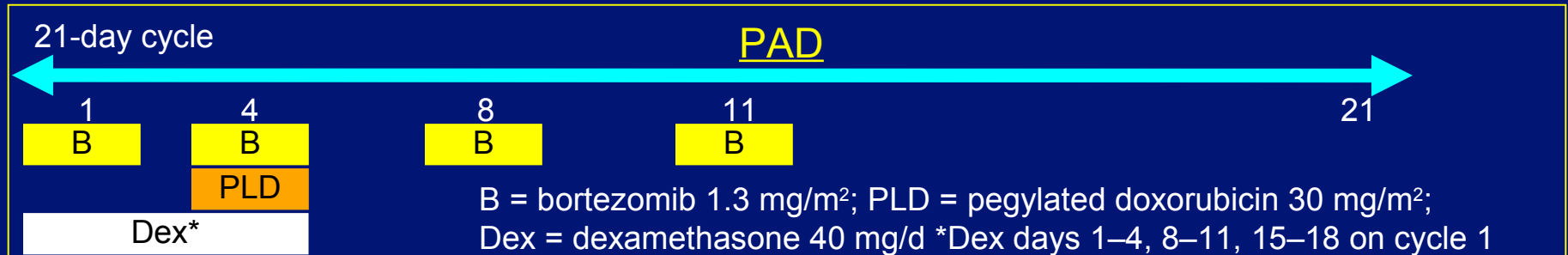
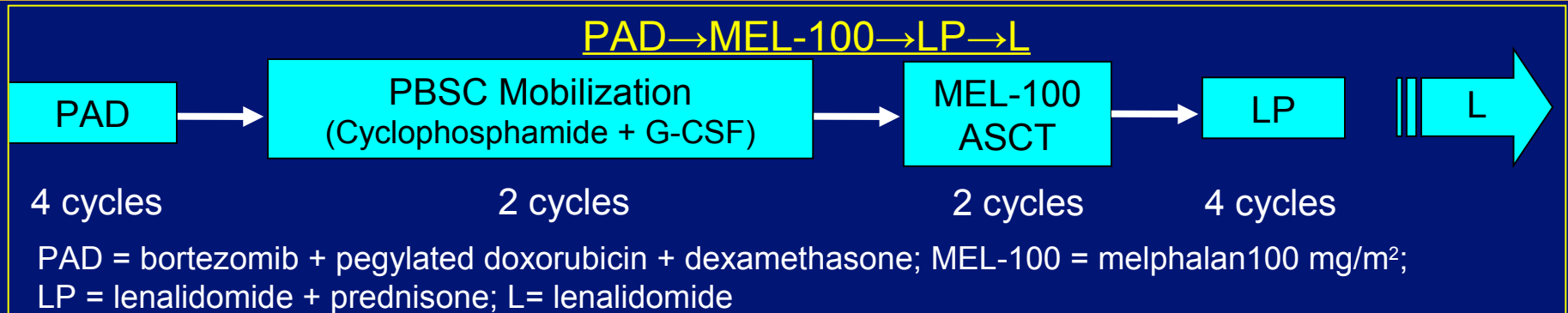
	MivPT <sup>1</sup> , %	VMPT <sup>2</sup> , %	RMPT, %
CR	0	17	13
≥VGPR	12	44	33
PFS @ 1 yr	20	65	55
OS @ 1 yr	60	76	66

1. Palumbo A et al. *Eur J Haematol*. 2006;76:273; 2. Palumbo A et al. *Blood*. 2007;109:2767  
 Palumbo A et al. *Blood*. 2008;112:321 [abstract 868]; updated results presented at: 50th ASH Annual Meeting; December 6–9, 2008; San Francisco, CA

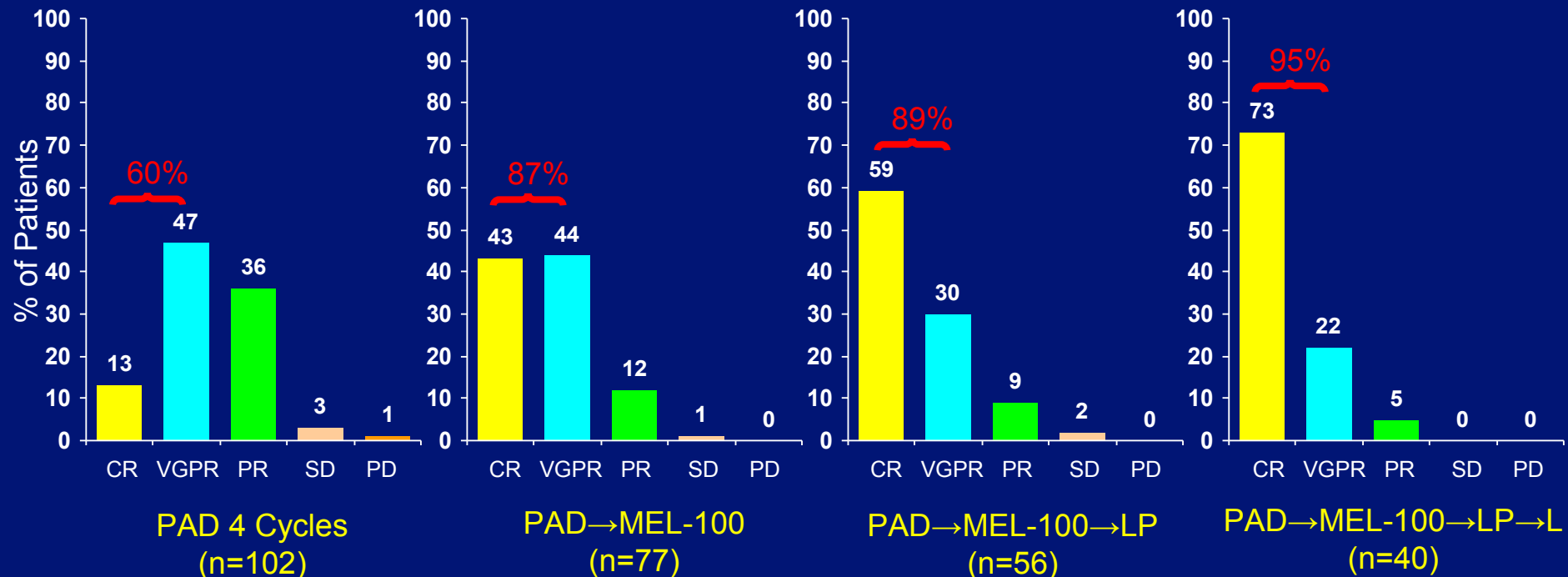
# Sequential approach

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# PAD Induction, MEL-100, Len/Prednisone Consolidation, and Len Maintenance in Elderly Patients With Newly Diagnosed MM



# PAD vs PAD→MEL-100 vs PAD→MEL-100→LP vs PAD→MEL-100→LP→L: Response Rate\*



\*Per protocol

Palumbo A et al. *Blood*. 2008;112:65 [abstract 159]; updated results presented at: 50th ASH Annual Meeting; December 6–9, 2008; San Francisco, CA

# Preliminary Conclusions

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- 3 drug combos seem superior to 2 drug combo
- Unclear which is the best 3 drug combo
- VMPT double the CR rate of VMP
- Randomized studies are needed