NEW TREATMENT STRATEGIES FOR MULTIPLE MYELOMA

THE GIMEMA EXPERIENCE

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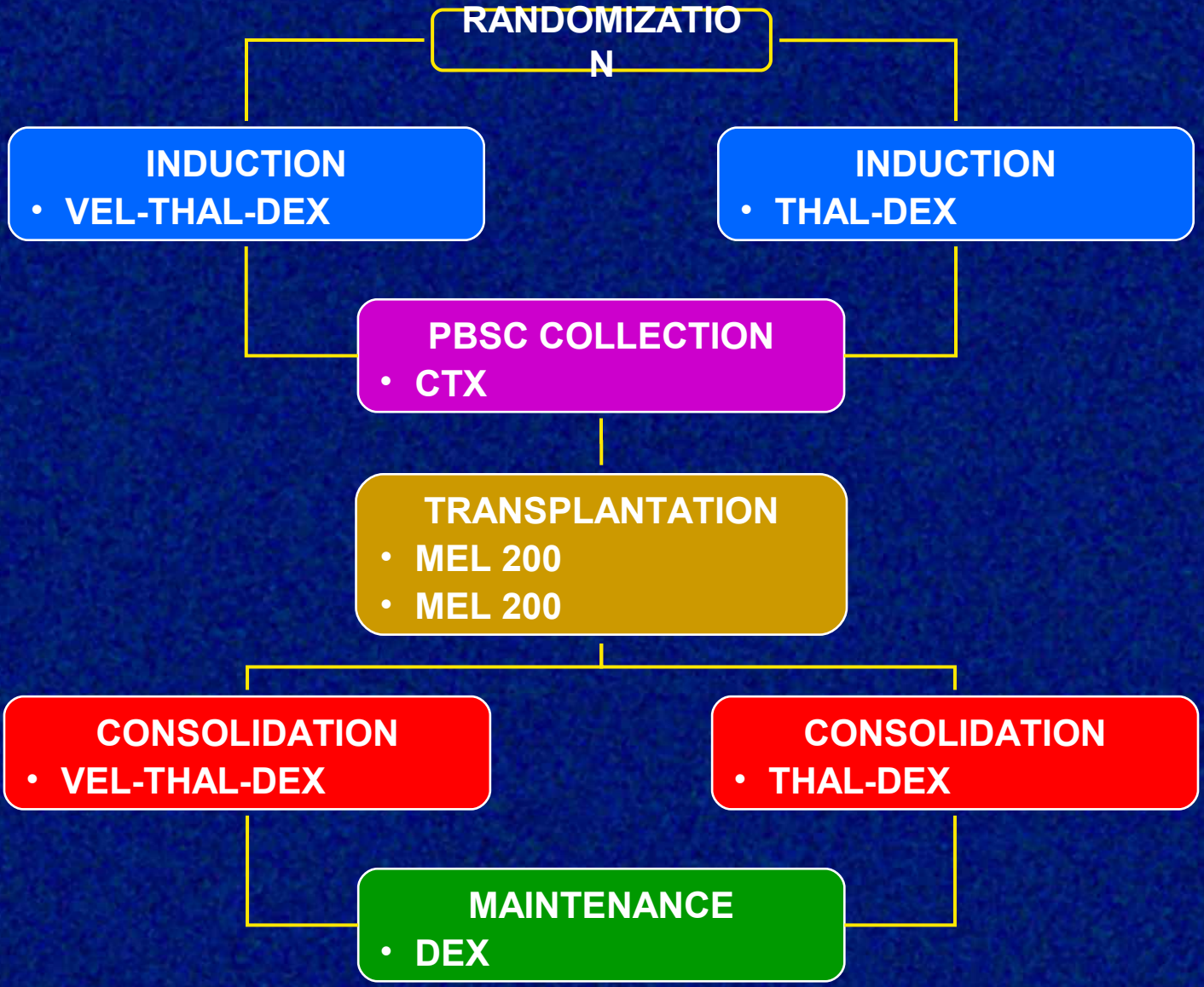
TD vs VTD

MEL200

in newly diagnosed patients

ranomized trial

Protocol GIMEMA 26866138-MMY-3006
VTD vs TD incorporated into double ASCT for MM



RESPONSE TO PRIMARY THERAPY

	% of patients		
RESPONSE	VTD (n=129)	TD (n=127)	P value
CR+nCR	36	9	<0.001
≥ VGPR	60	27	<0.001
< PR	7	20	0.003
Progression	0	5.5	0.008

EBMT criteria (with added nCR and VGPR categories)

RESPONSE TO FIRST ASCT (MEL 200 mg/m^2)

	% of patients		
RESPONSE	VTD (n=74)	TD (n=79)	P value
CR+nCR	57	28	<0.001
CR	45	19	<0.001
≥ VGPR	77	54	0.003

EBMT criteria (with added nCR and VGPR categories)

PBSC HARVEST (CTX 4 g/m^2)

	VTD (n=112)	TD (n=108)	P value
CD34+ cells (x10^6/kg)	9.2 (0-29)	10.6 (0-37)	N.S.
≥4.0 (% pts)	94	93	N.S.
N° apheresis	1 (0-5)	2 (0-4)	N.S.

Median values (range)

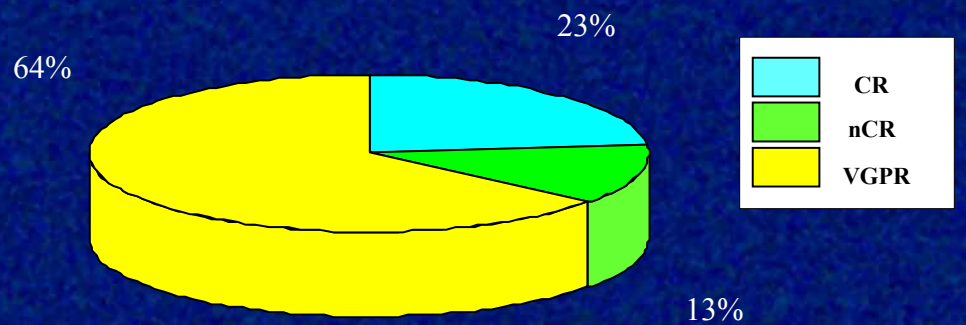
VTD as consolidation for

patients in ≥ VGPR after ASCT

Increases

CLINICAL IMPACT OF VTD CONSOLIDATION

Response at study entry
(evaluable 39 pts.)



STATUS CHANGES DURING CONSOLIDATION:

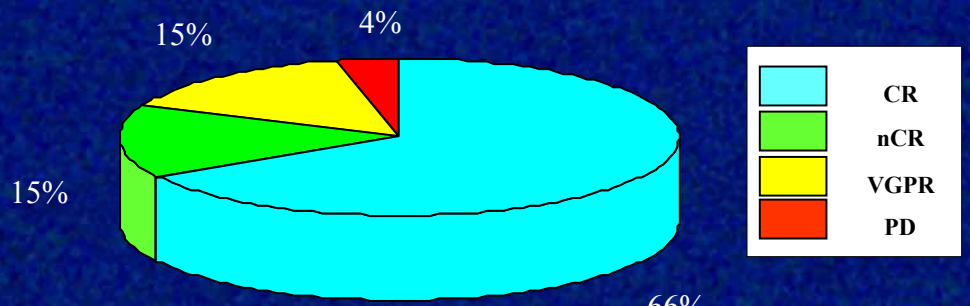
11 VGPR → CR

3 VGPR → nCR

4 nCR → CR

1PR → PD

Response after VTD consolidation
(evaluable 27 pts.)

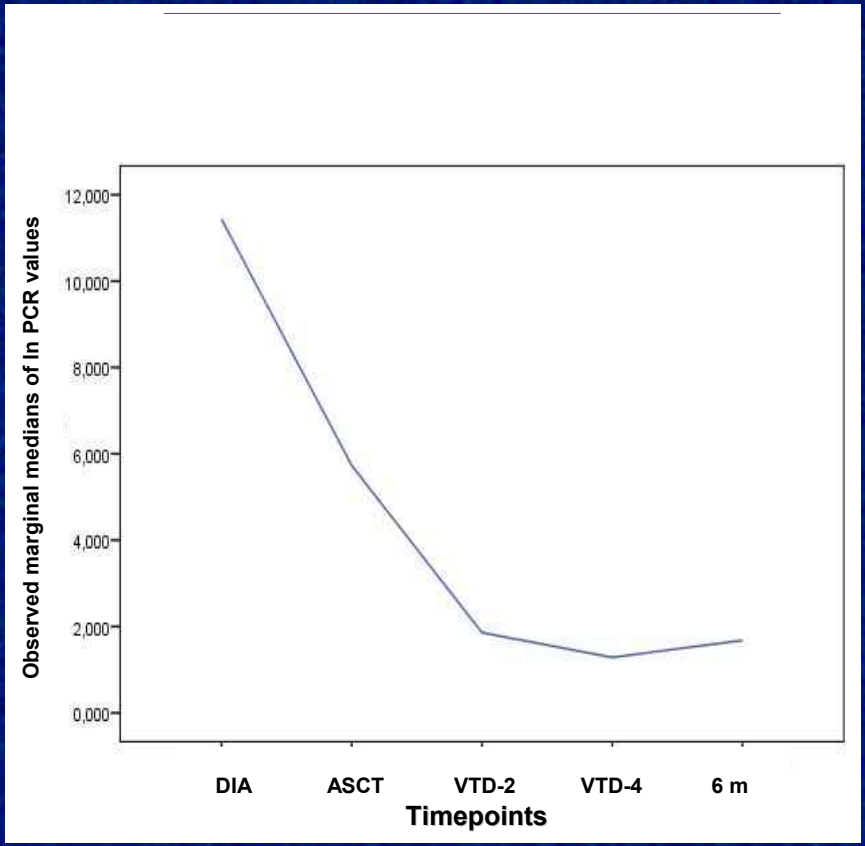


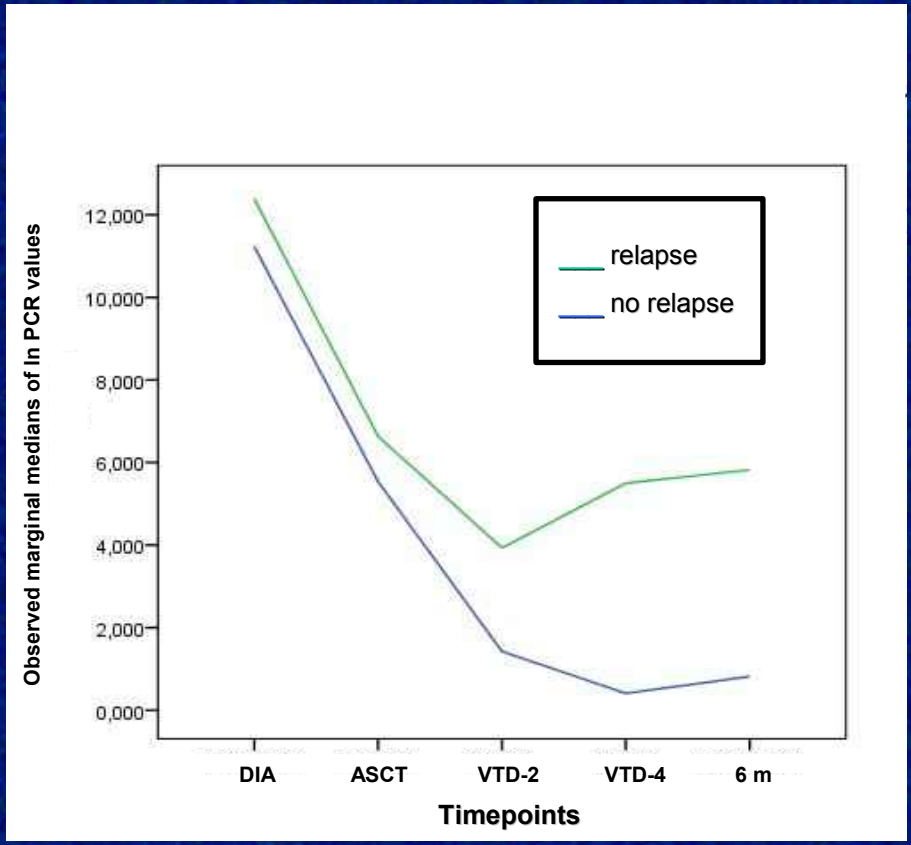
MOLECULAR RESULTS

Treatment phase	evaluable pts	PCR-neg pts
After ASCT	40	2(5%) (one transient)
After VTD 2 courses	33	5(15%) (one transient)
After VTD 4 courses	29	6(21%) (all true MR)

- median follow-up from enrollment: 24 months
- 6 patients achieved a true molecular remission (at least two pcr-negative samples)
- Seven relapses among PCR+ pts vs no relapses among MR pts (at 24,18(x3), 12 and 6 months from enrollment)
- No molecular relapses among patients with true “MR”

MINIMAL RESIDUAL DISEASE - QUANTITATIVE PCR





VTD: progression-free survival of patients PCR negative or positive

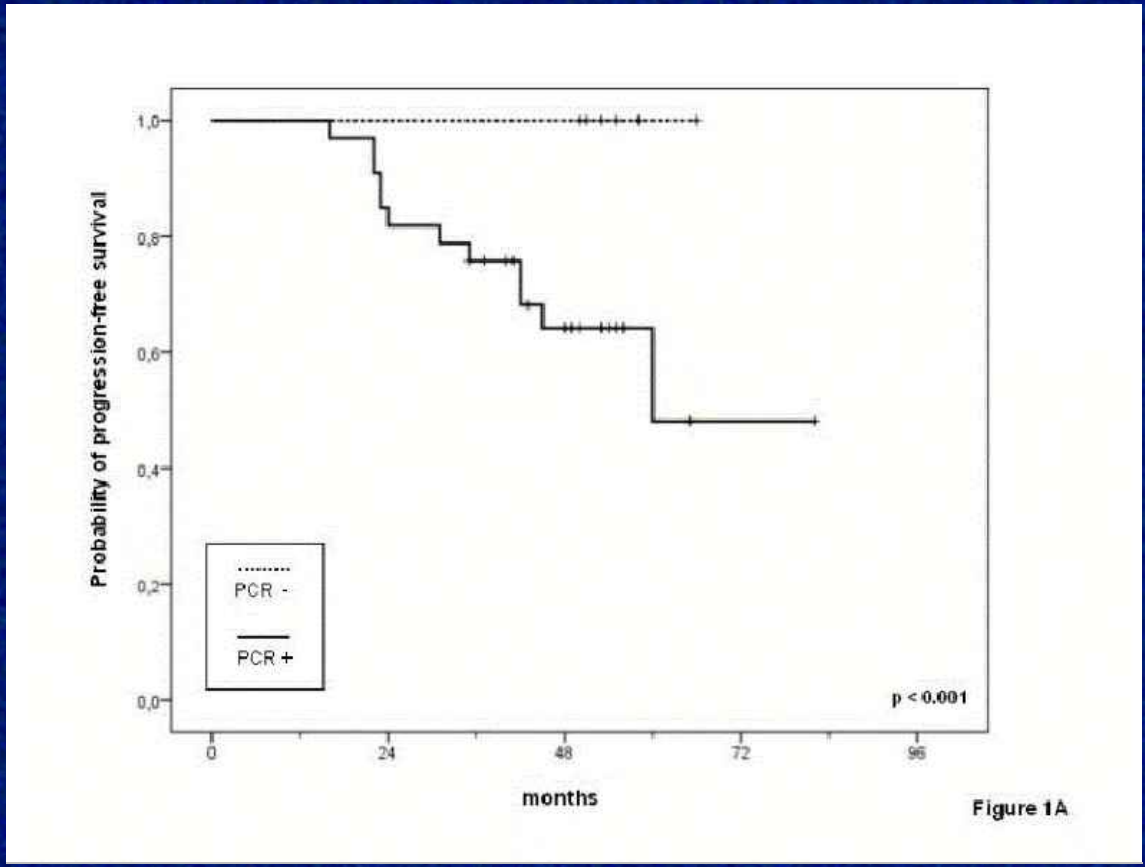
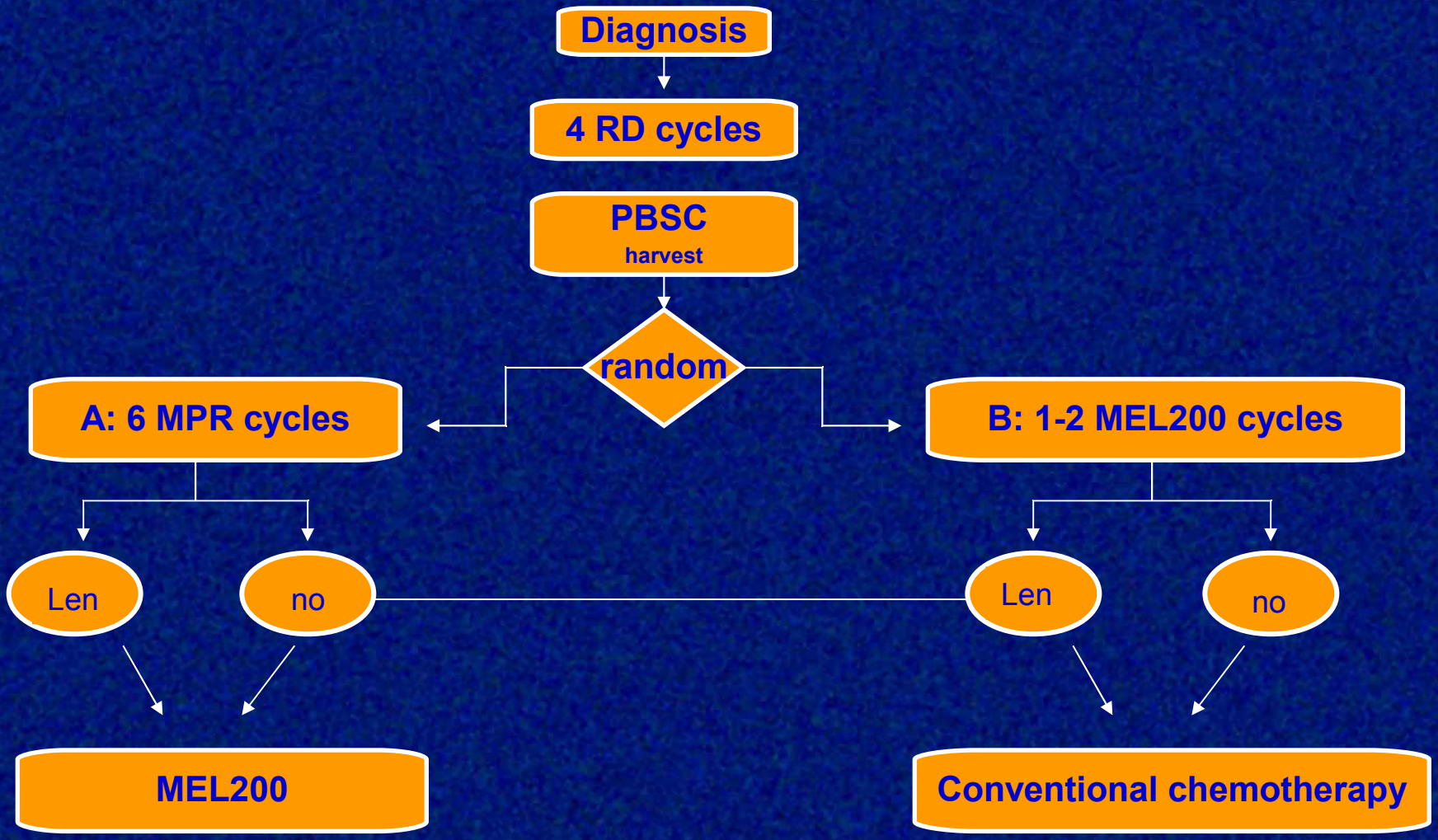


Figure 1A

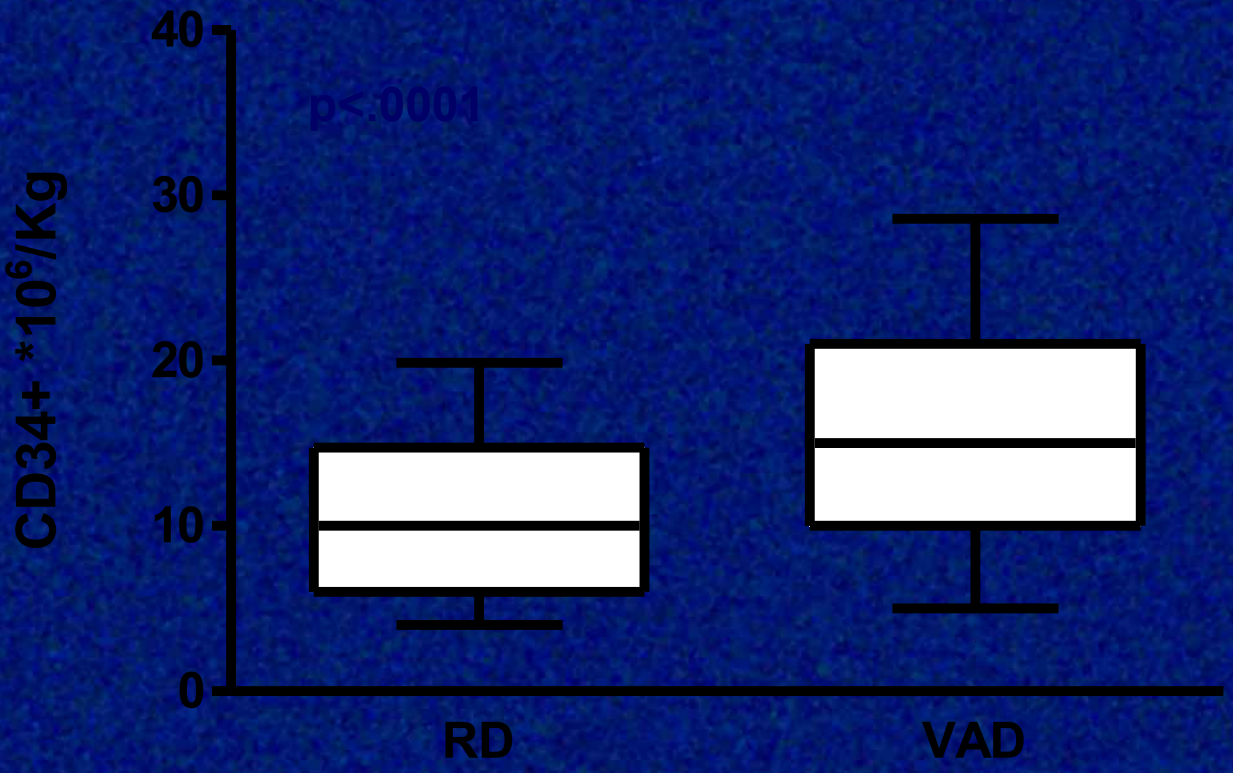
RD as Induction before ASCT

Mobilization Data

MPR vs MEL200 study design

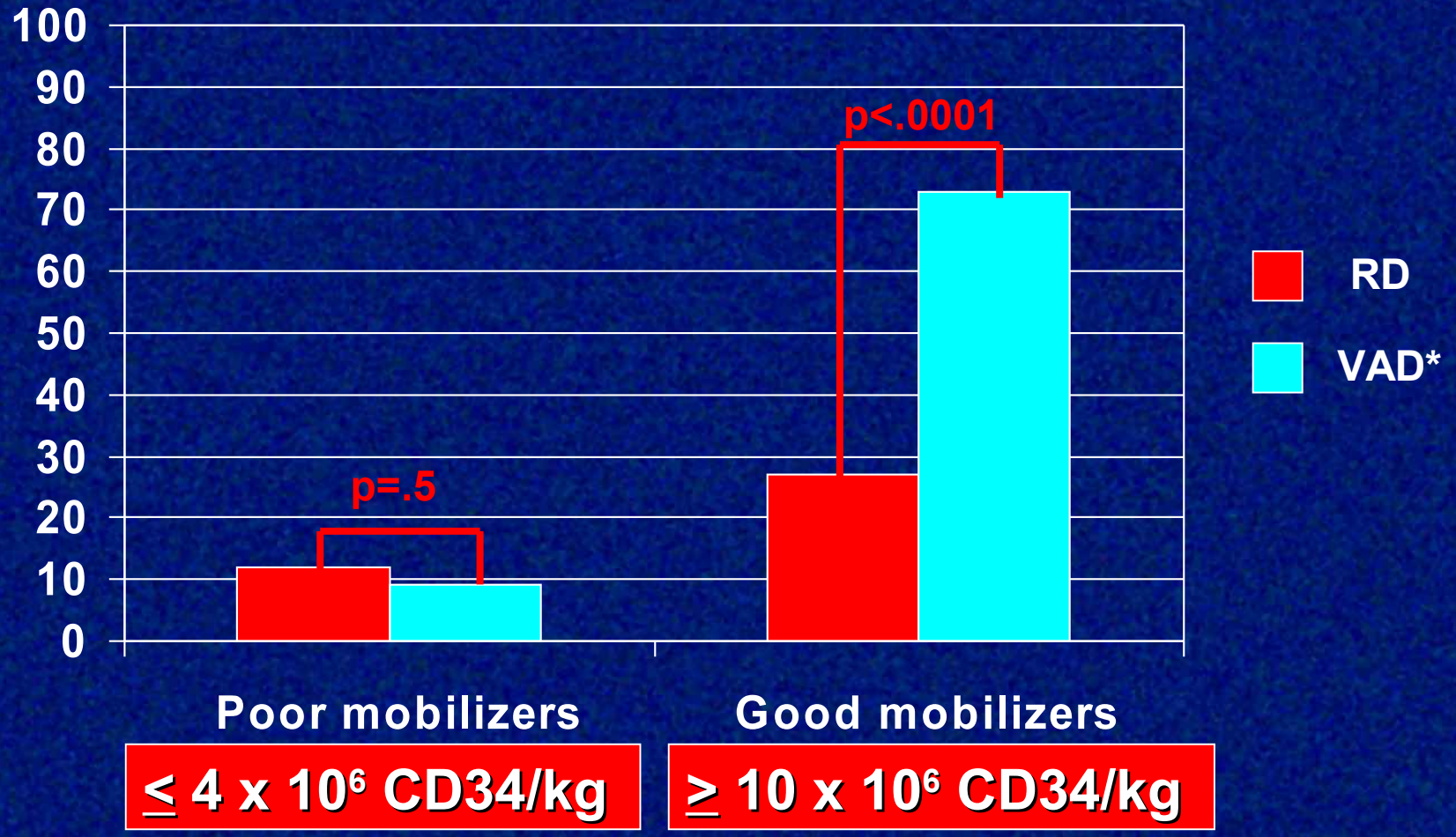


MOBILIZATION DATA: CD34+ YIELD



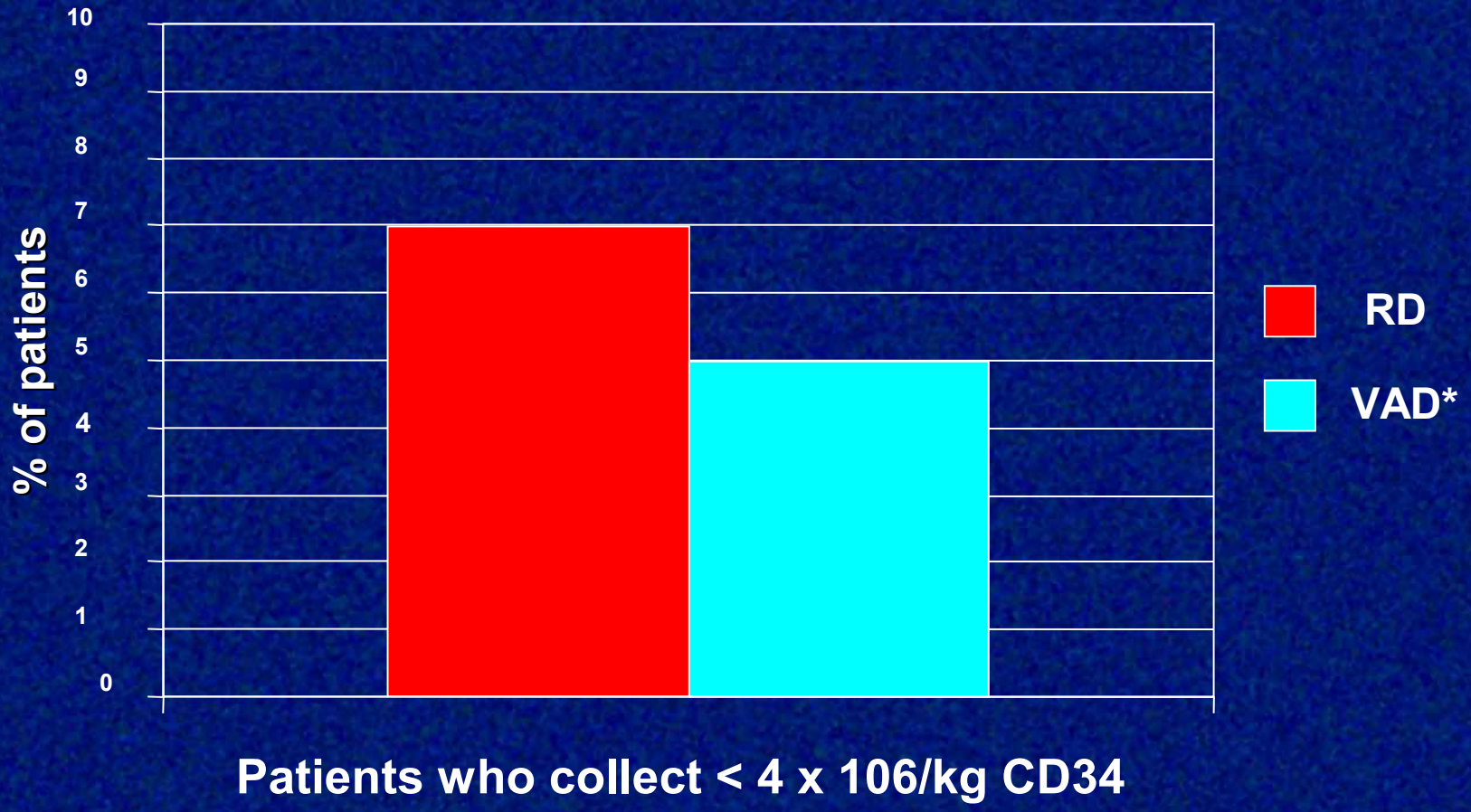
10 x 10^6 CD34/kg 15 x 10^6 CD34/kg

MOBILIZATION DATA



*historical comparison

MOBILIZATION DATA



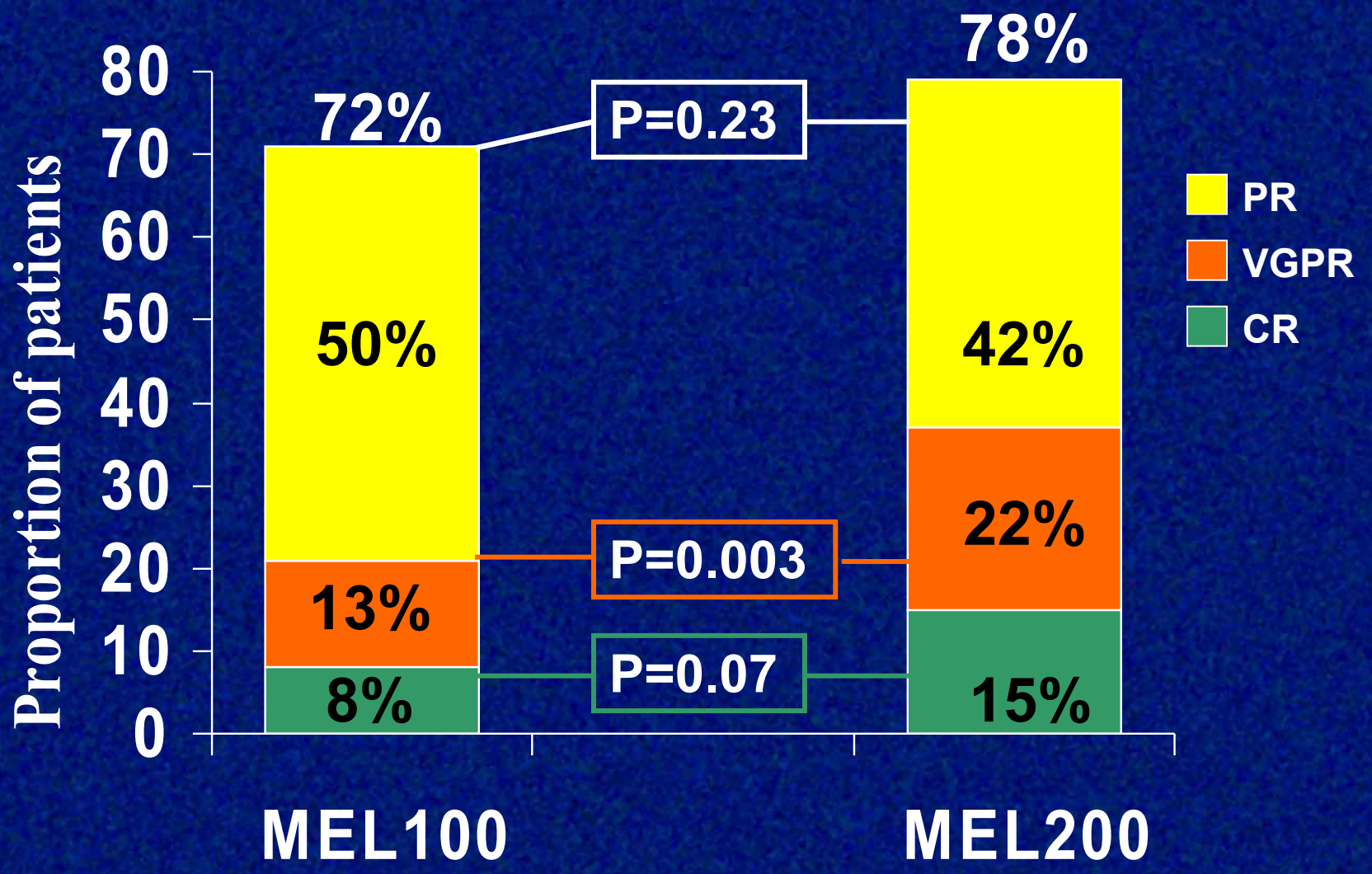
*historical comparison

MEL100 vs MEL200

in newly diagnosed patients

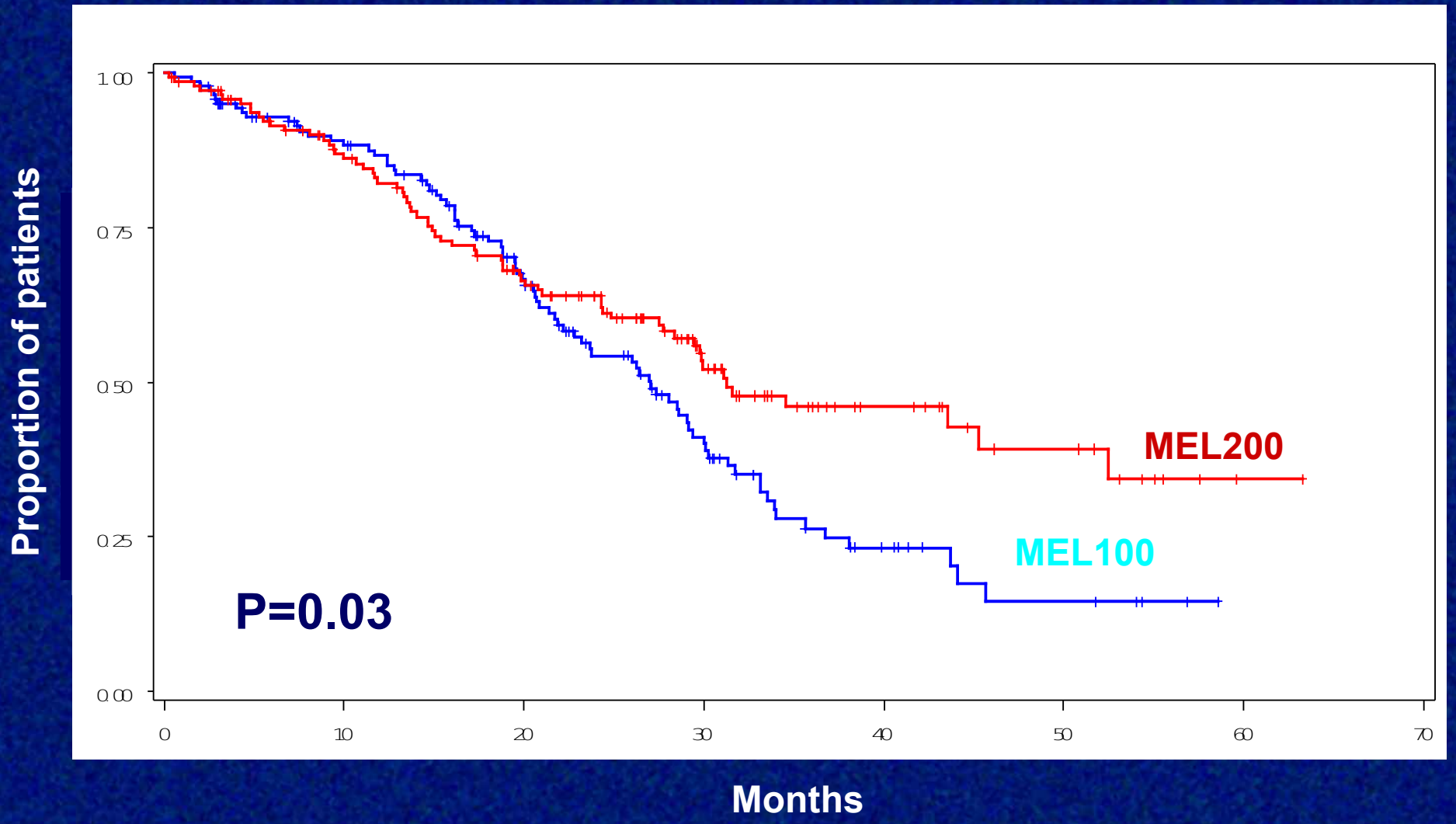
ranomized trial

Response Rate

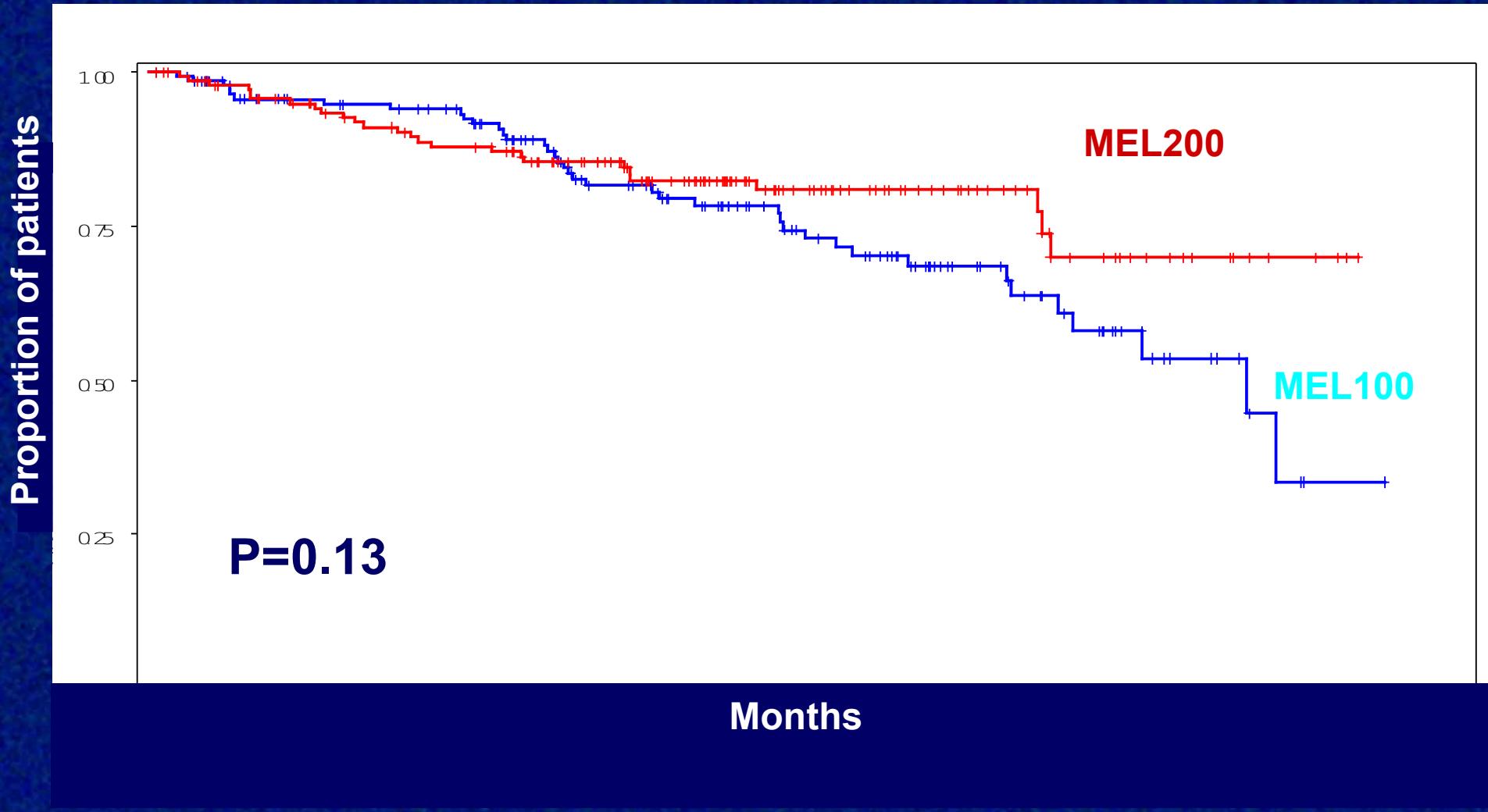


PR (>50%), VGPR (IF+ or >90%), CR (IF-)

Event-free Survival
(median follow-up 30.5 months)

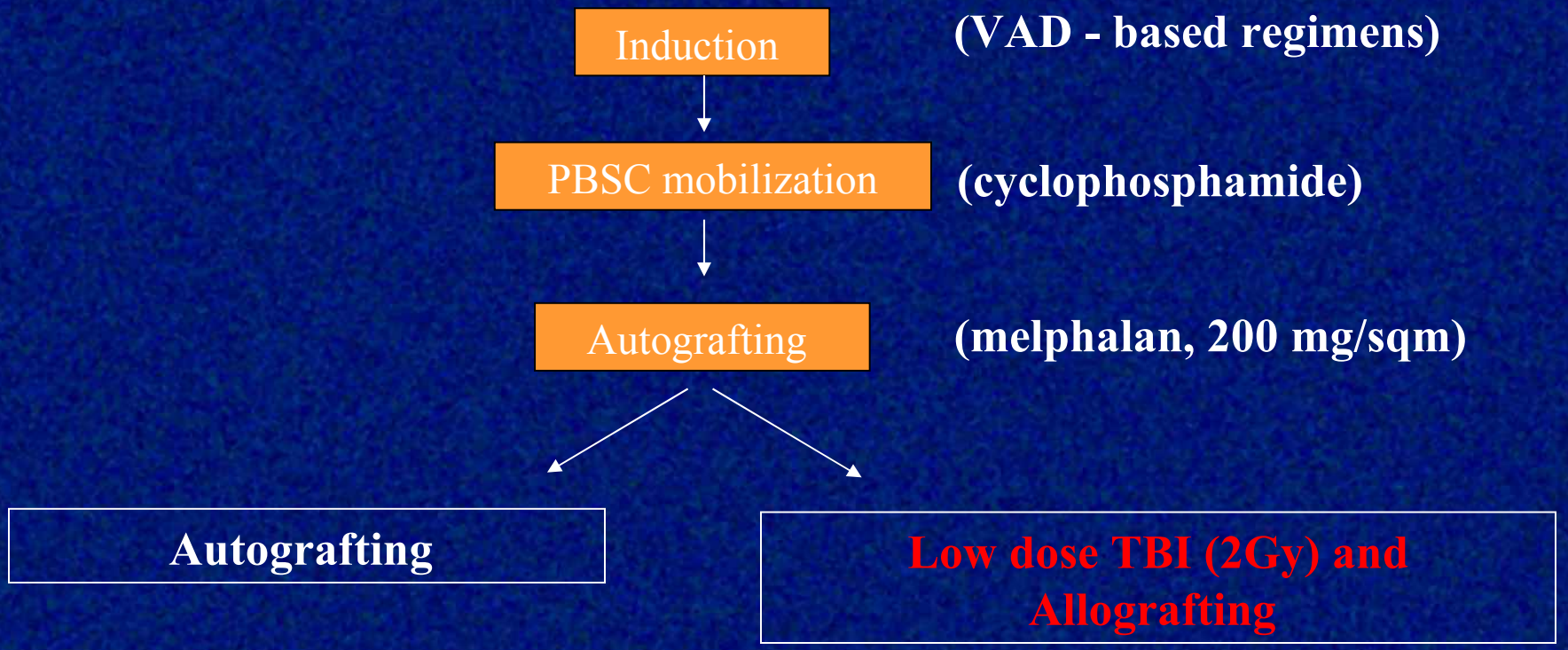


Overall Survival



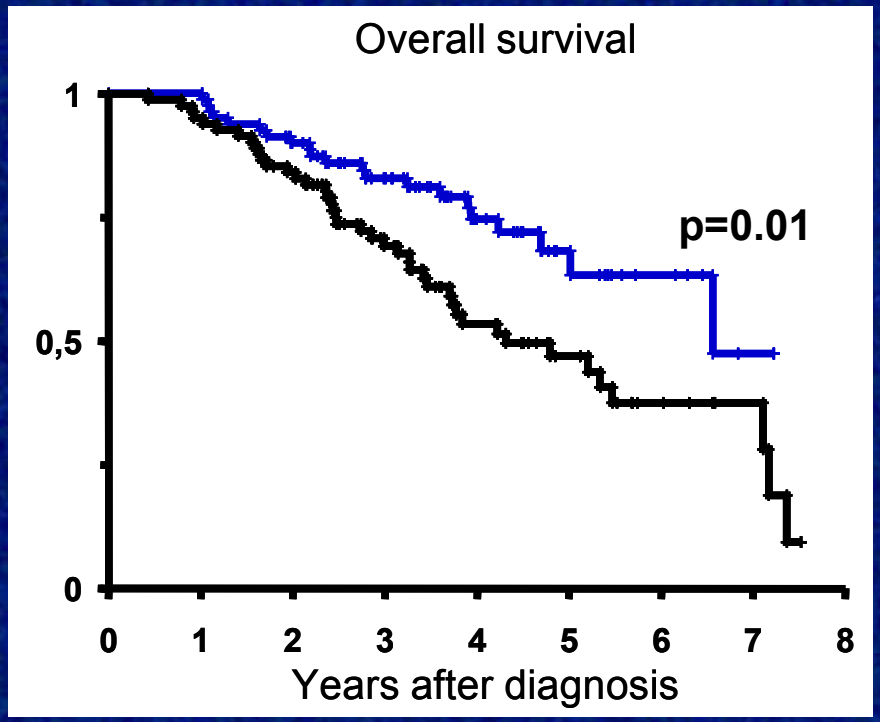
ASCT vs mini ALLO

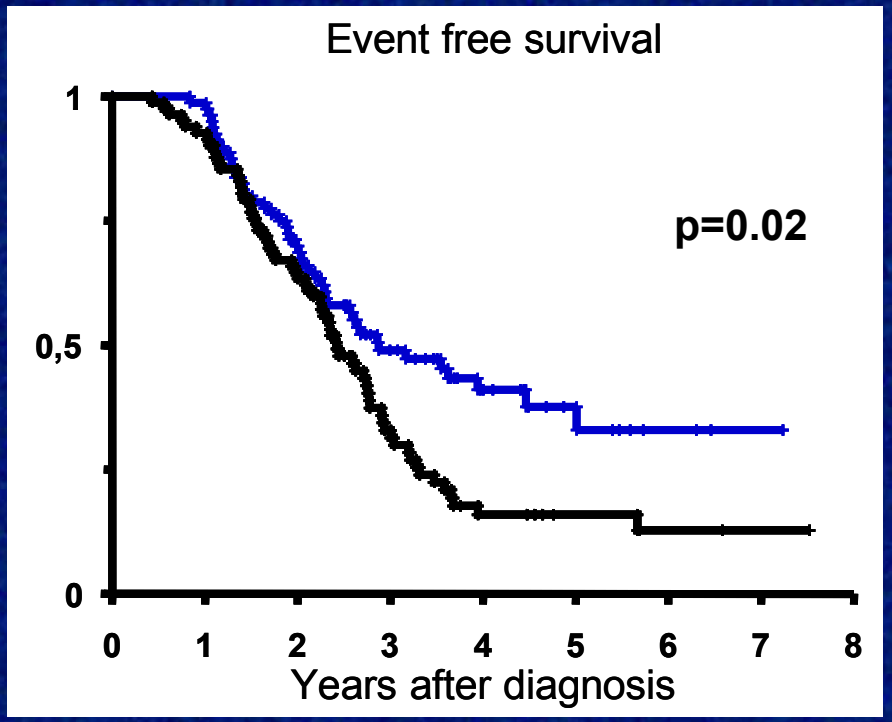
Treatment Assignment *



*Based on presence/absence of an HLA matched sibling

Outcome according to presence of HLA-identical siblings (n=162), Median follow up from diagnosis: 45 months, range 21-90

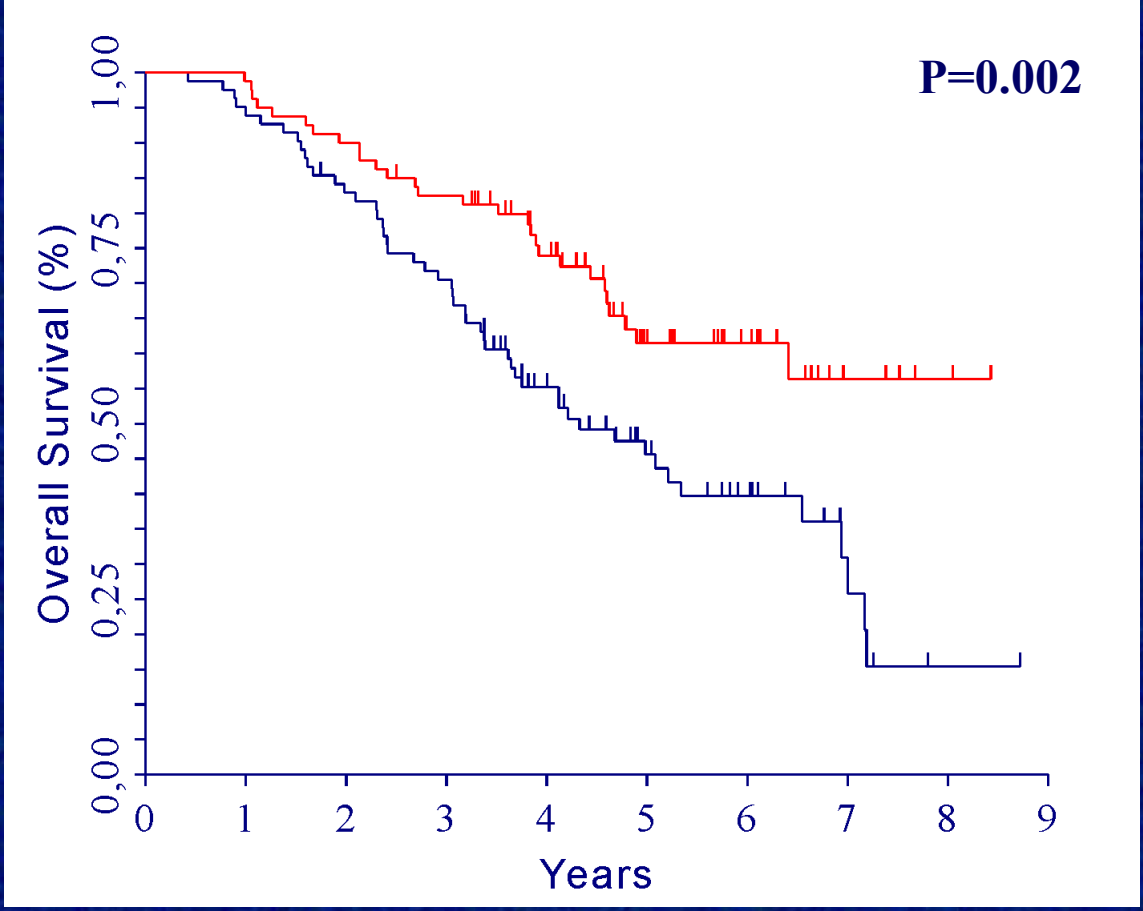




HLA-Id sibling:
YES n=80
NO

B. Bruno et al NEJM 2007

Overall Survival
80 patients with HLA-identical sibling and 82 patients without



Median Overall Survival

HLA-id sibling:
median not reached
No HLA-id sibling:
52 months

HR: 0.49
95% CI: 0.31-0.78; P=0.003

PAD – MEL100

in Newly Diagnosed Patients

Randomized Trial

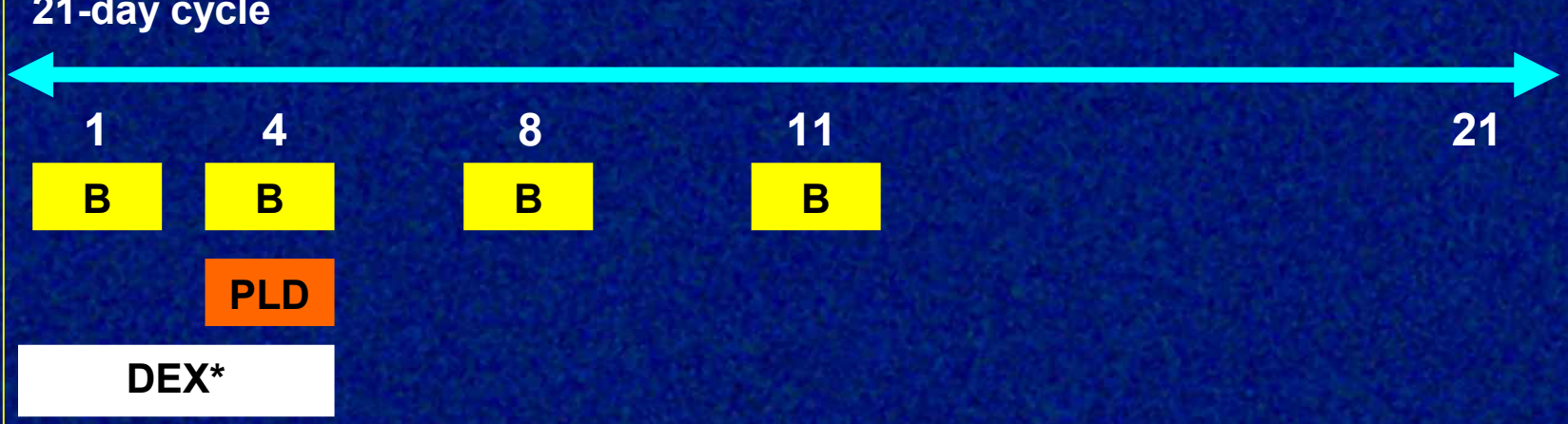
Treatment Schedule

INDUCTION

PAD-MEL100-LP-L

PAD = Bortezomib+Pegylated Doxorubicin+Dexamethasone; MEL100 = Melphalan100 mg/m^2;
LP = Lenalidomide + Prednisone; L= Lenalidomide

PAD



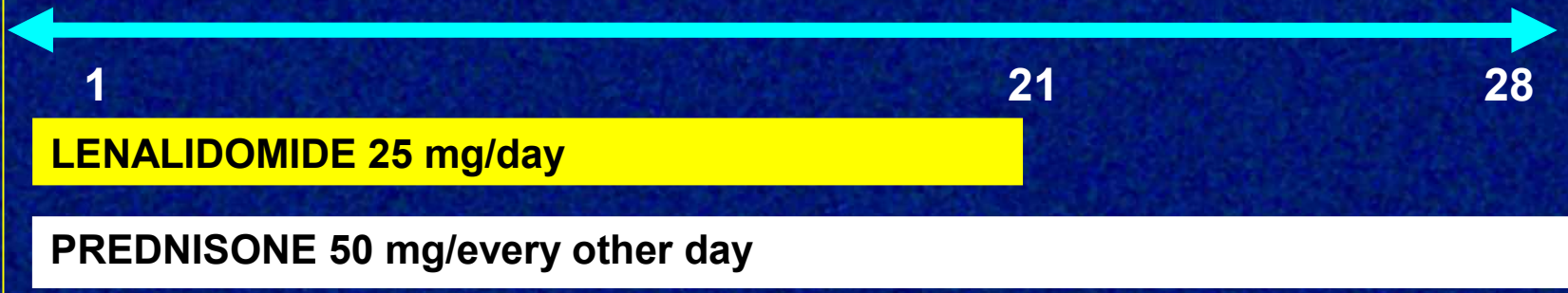
B = Bortezomib 1.3 mg/sqm; PLD = Pegylated Doxorubicin 30 mg/m^2; DEX = Dexamethasone 40 mg/day
*DEX days 1-4, 8-11, 15-18 on cycle 1

Treatment Schedule

CONSOLIDATION AND MAINTENANCE

LP: CONSOLIDATION

28-day cycle

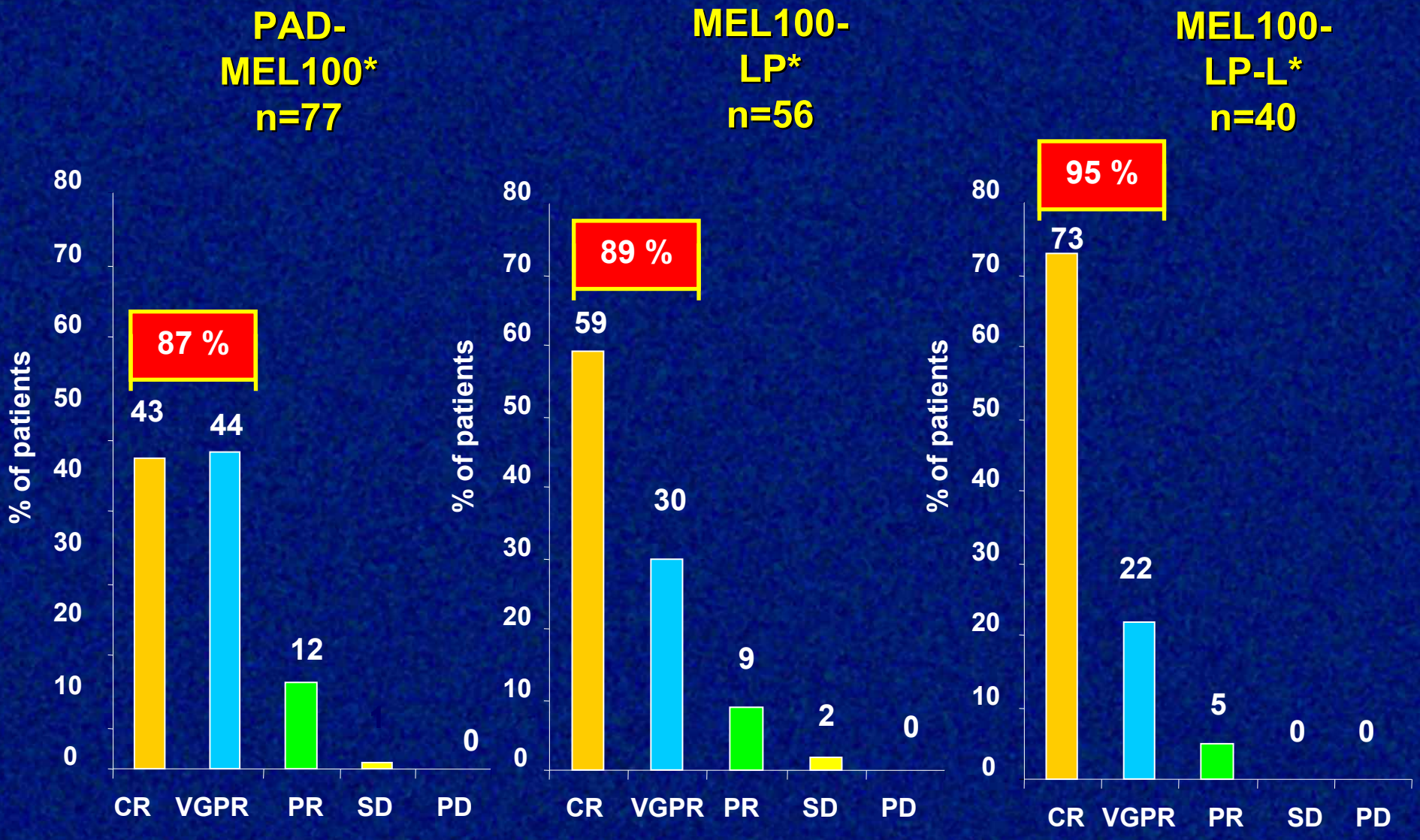


L: MAINTENANCE

28-day cycle

Response Rate

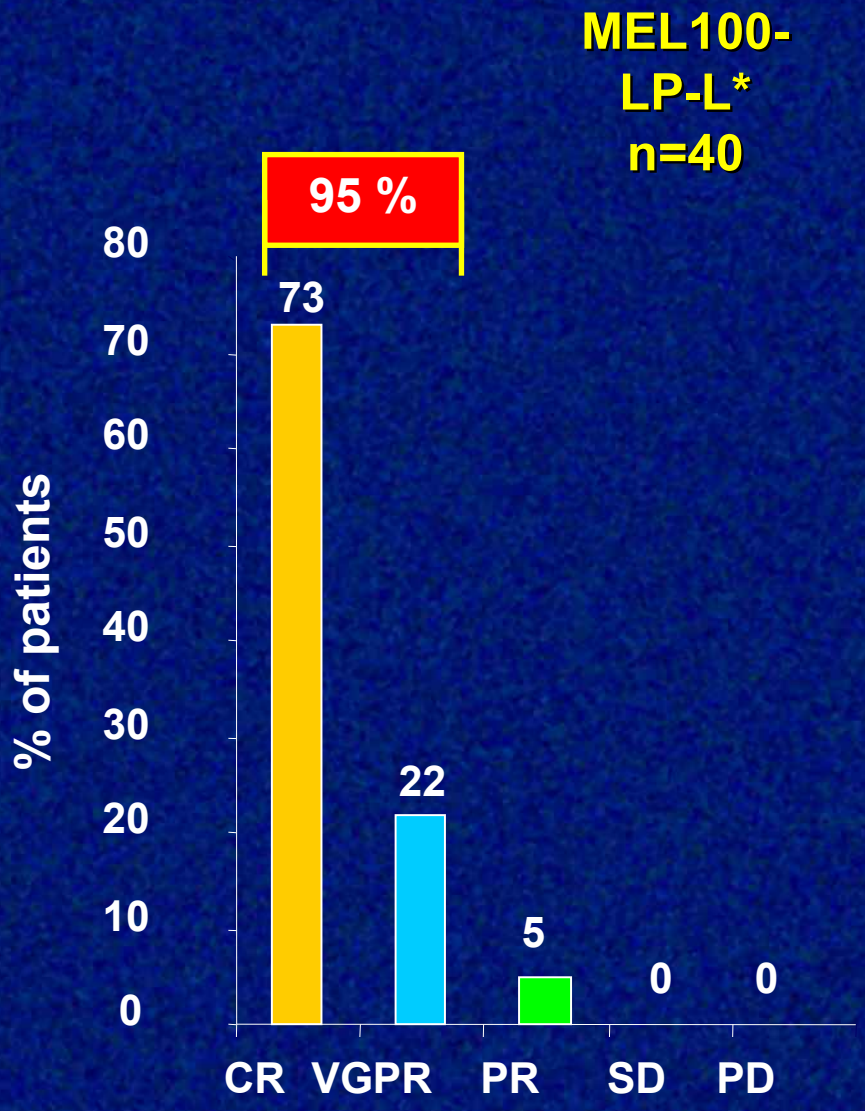
PAD-MEL100 vs MEL100-LP vs MEL100-LP-L

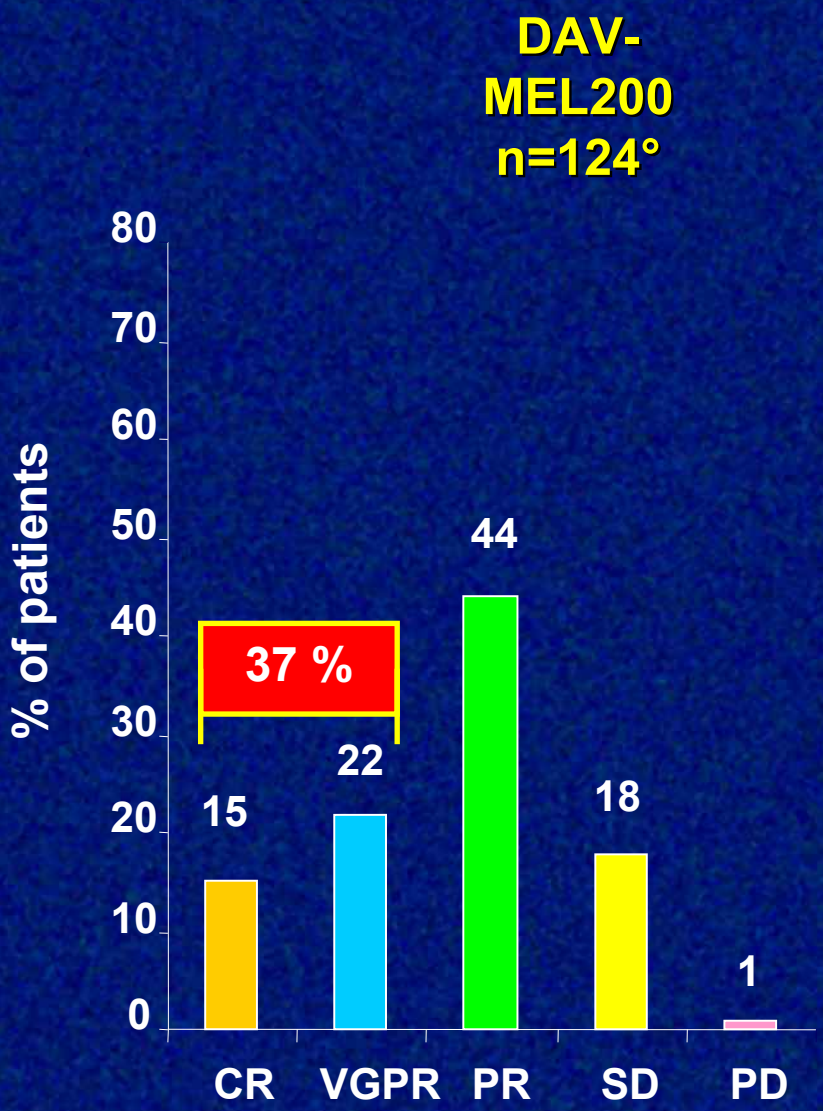


*Per protocol

Response Rate

PAD-MEL100 vs DAV-MEL200

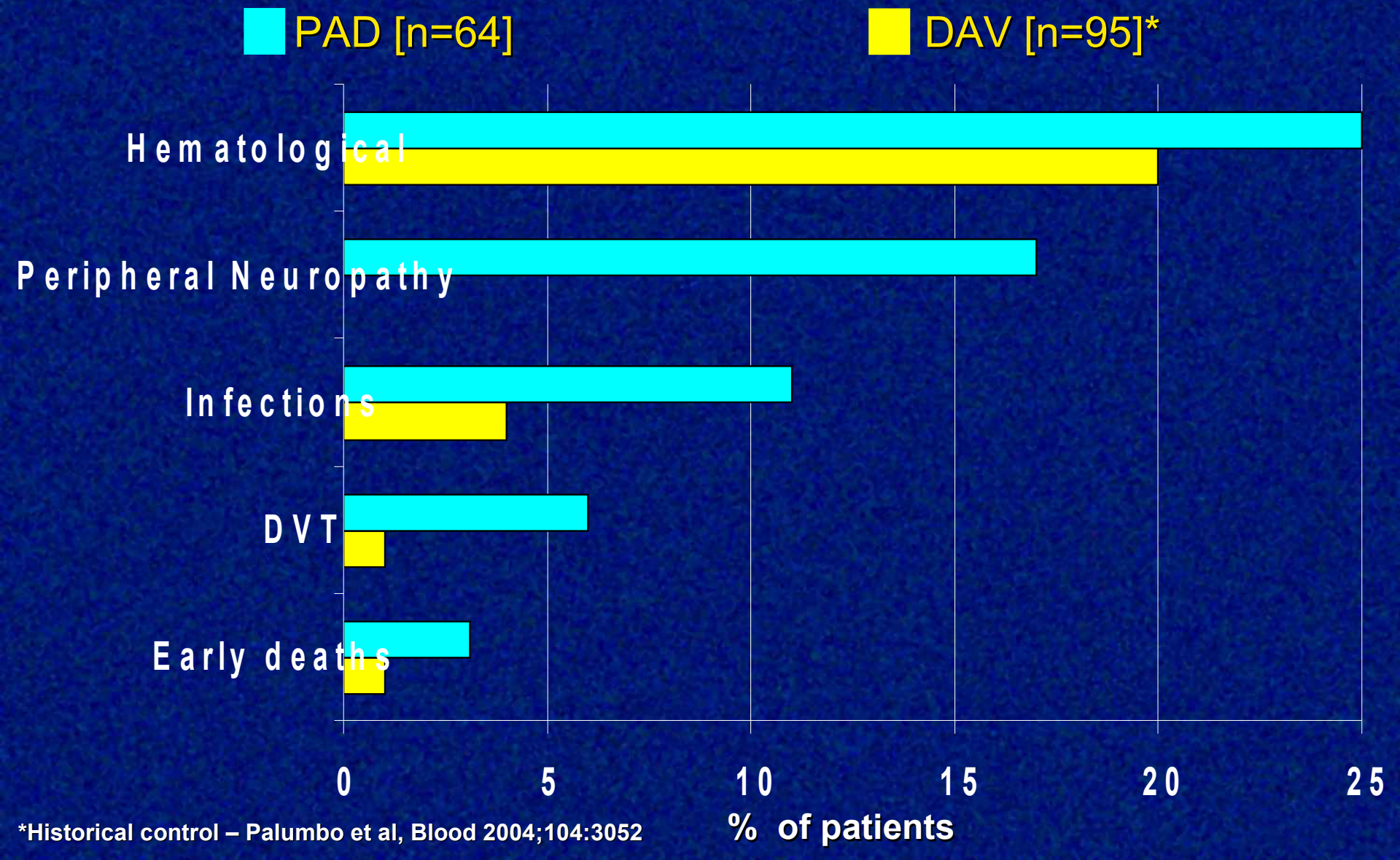




*Per protocol

°Historical control – Palumbo et al. Blood 2007;108 [abs727]

PAD vs DAV: Grade 3–4 Adverse Events



*Historical control – Palumbo et al, Blood 2004;104:3052

MP vs MPT

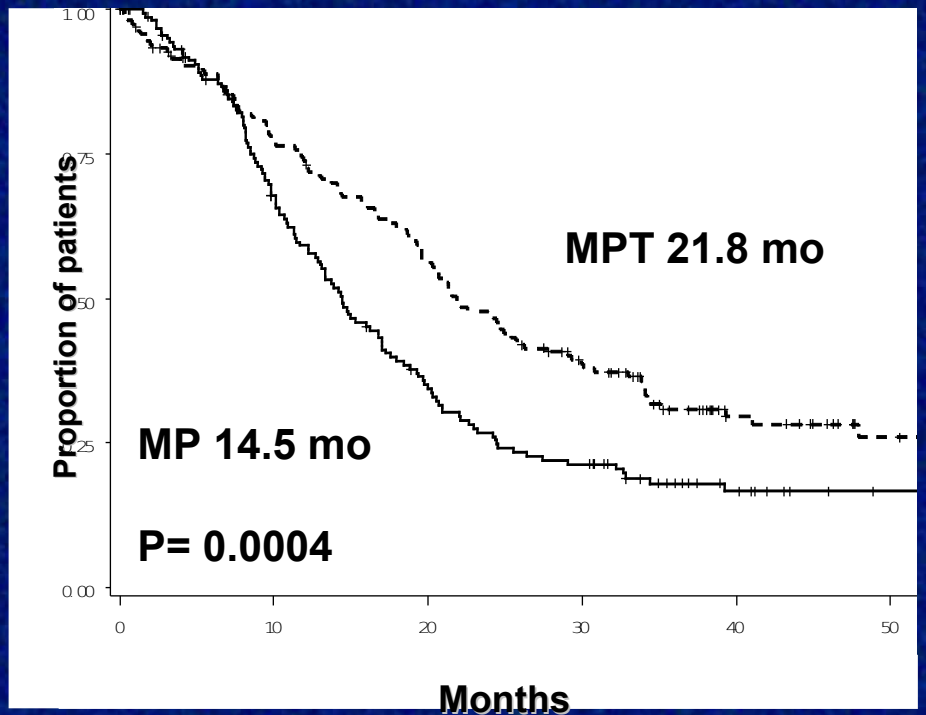
Update Analysis

MP vs MPT in Newly Diagnosed Elderly MM

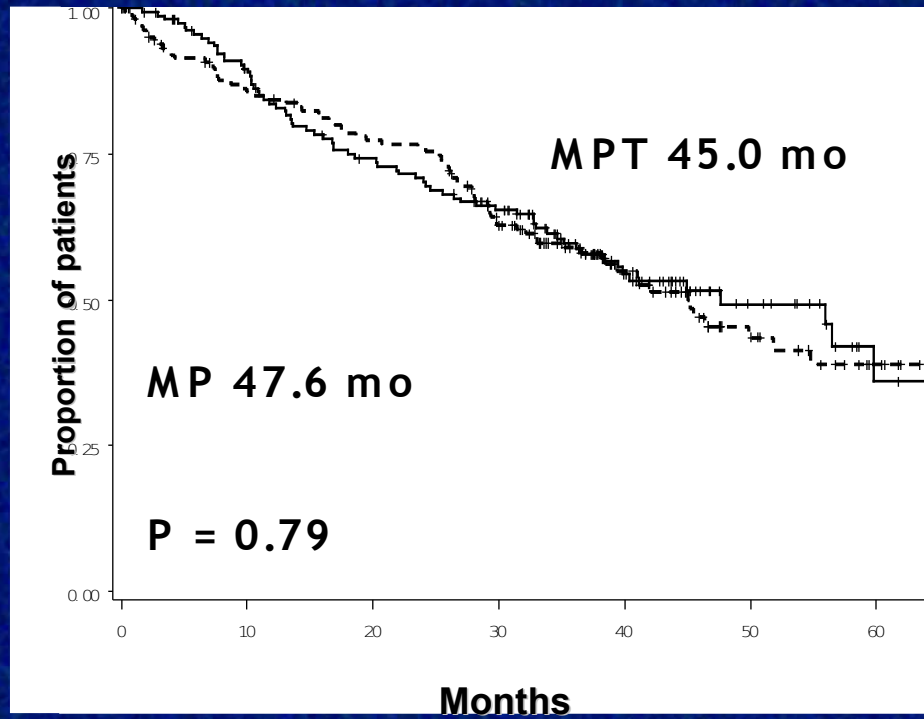
Age: ≥ 65 years

Melphalan, 4 mg^2 (7 days/28 days)
Prednisone, 40 mg^2 (7 days/28 days) — 6 cycles
Thalidomide, 100 mg/day continuously

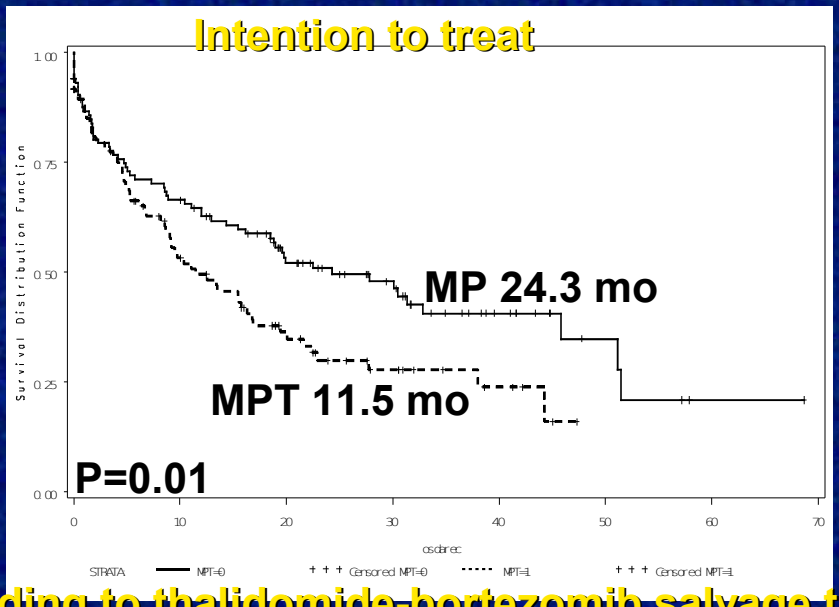
Progression-free survival



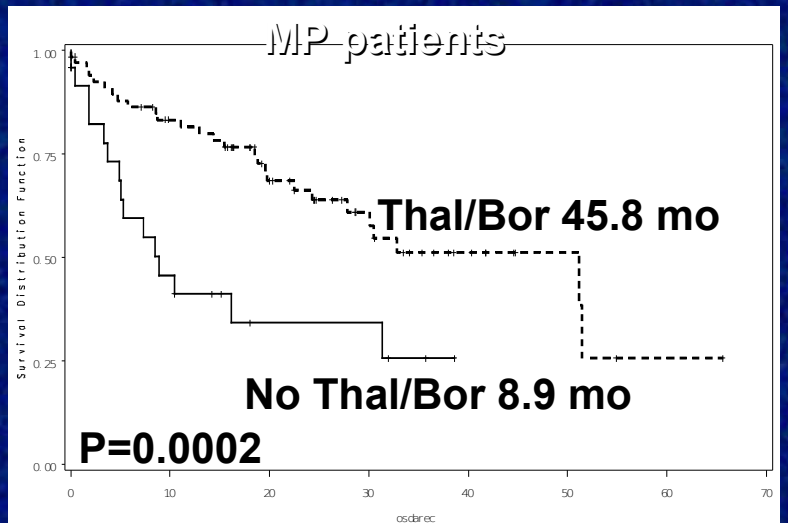
Overall survival

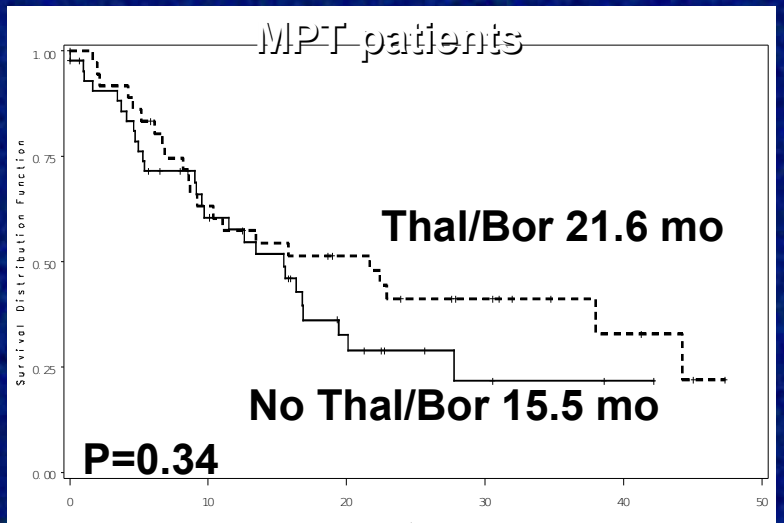


MP vs MPT
Survival from relapse

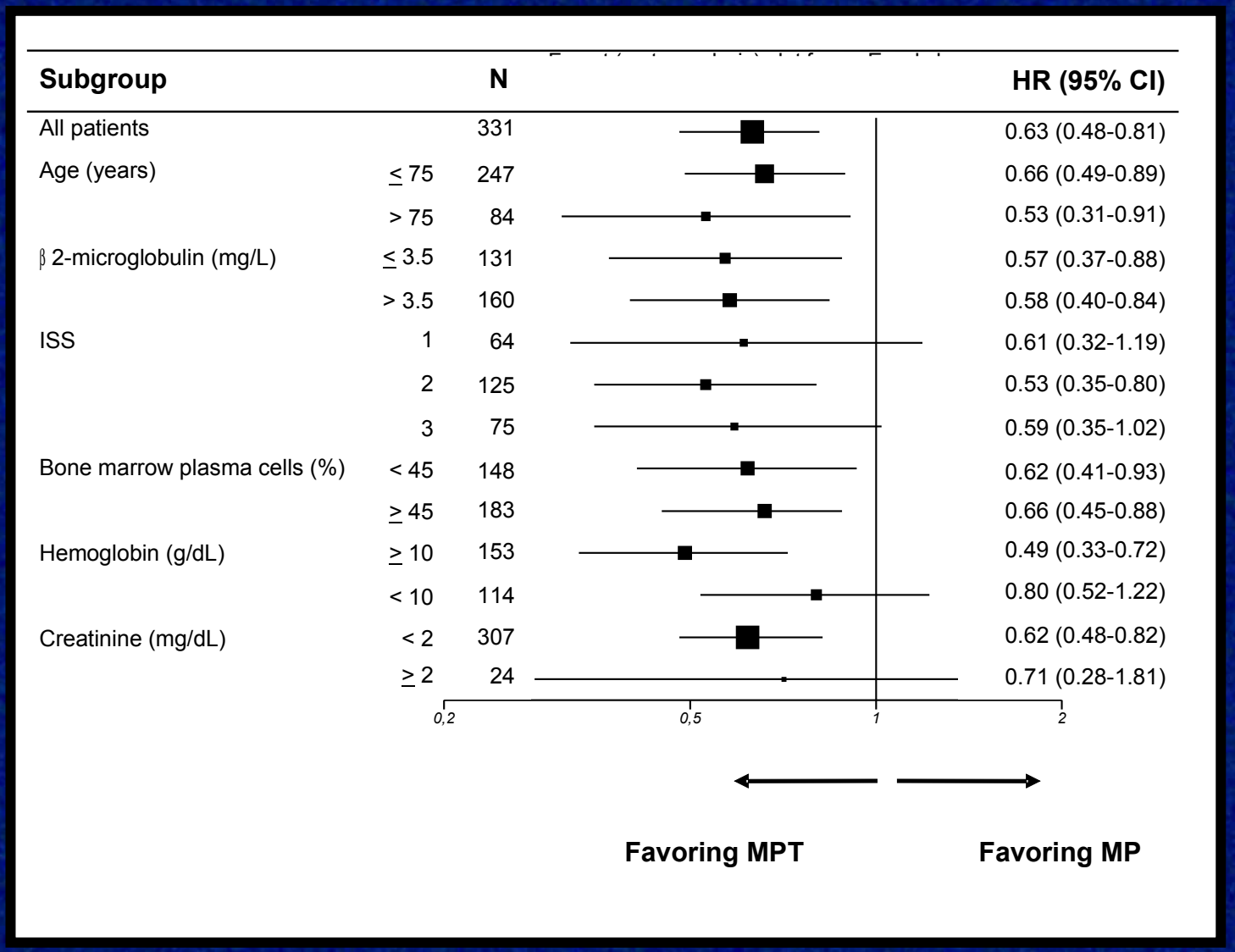


According to thalidomide-bortezomib salvage therapy





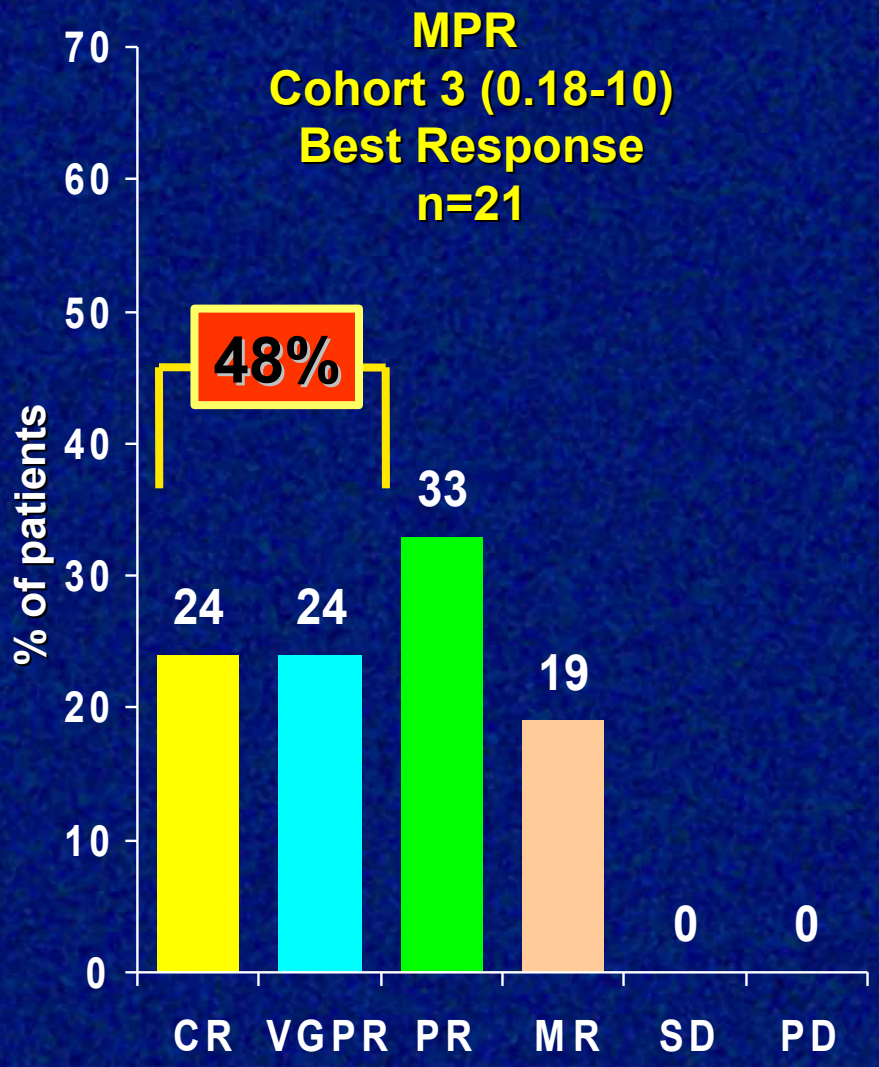
MP vs MPT
Subgroup analysis on PFS

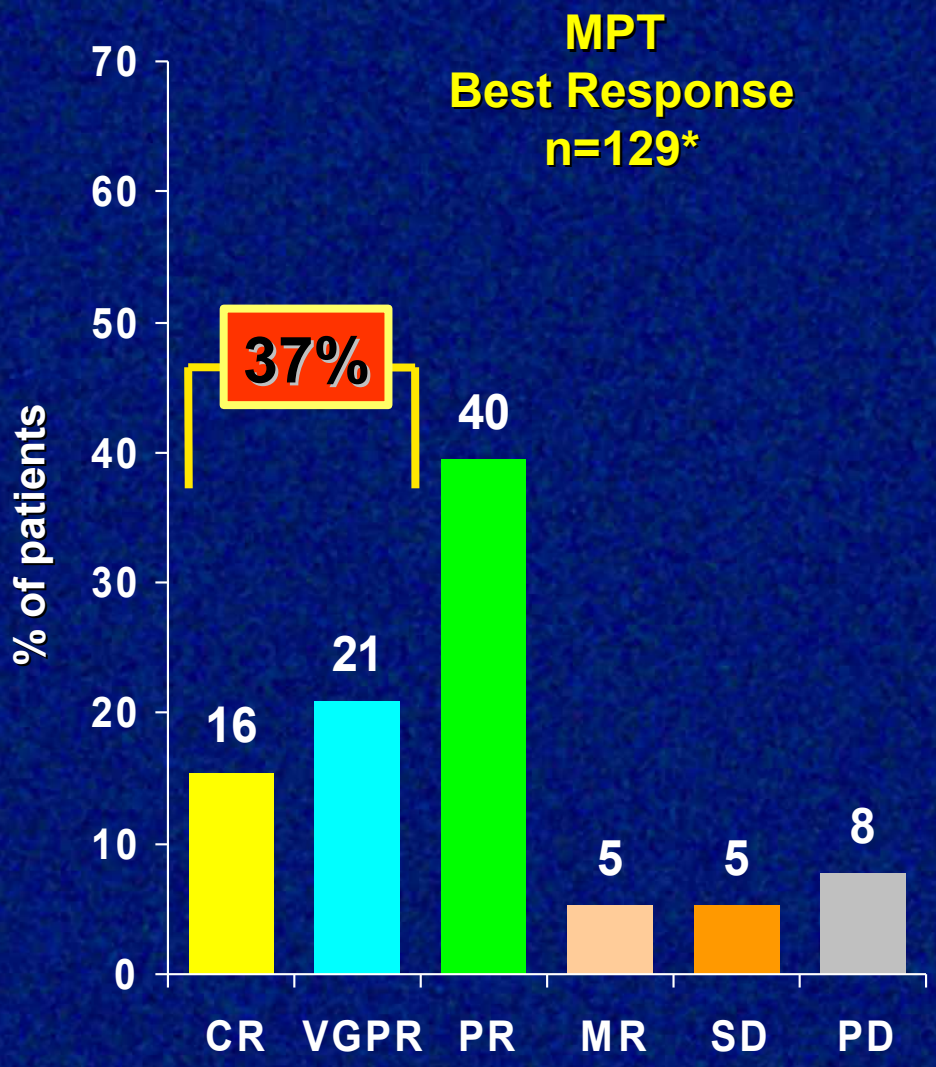


MPR

in Newly Diagnosed Patients

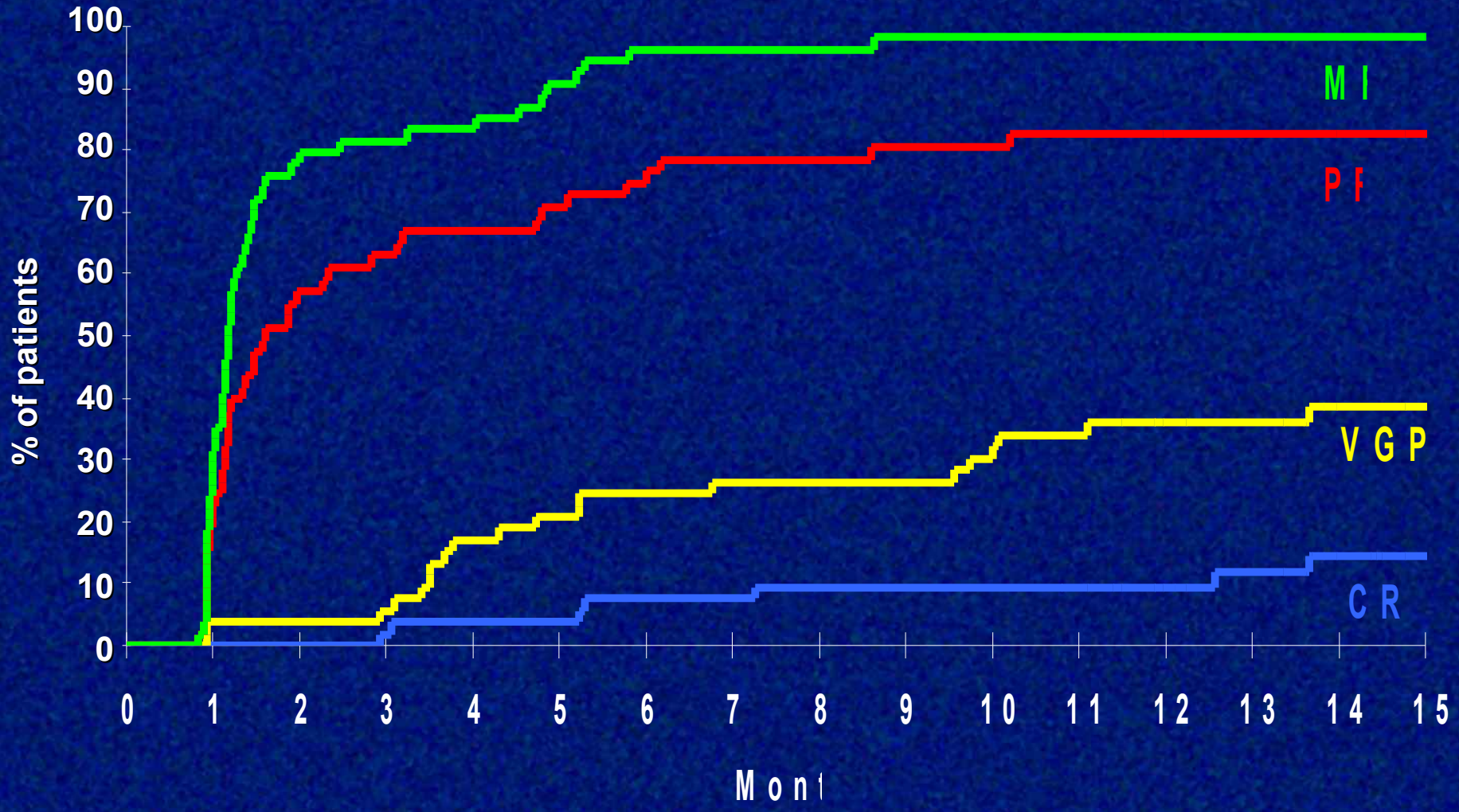
Response
MPR vs MPT



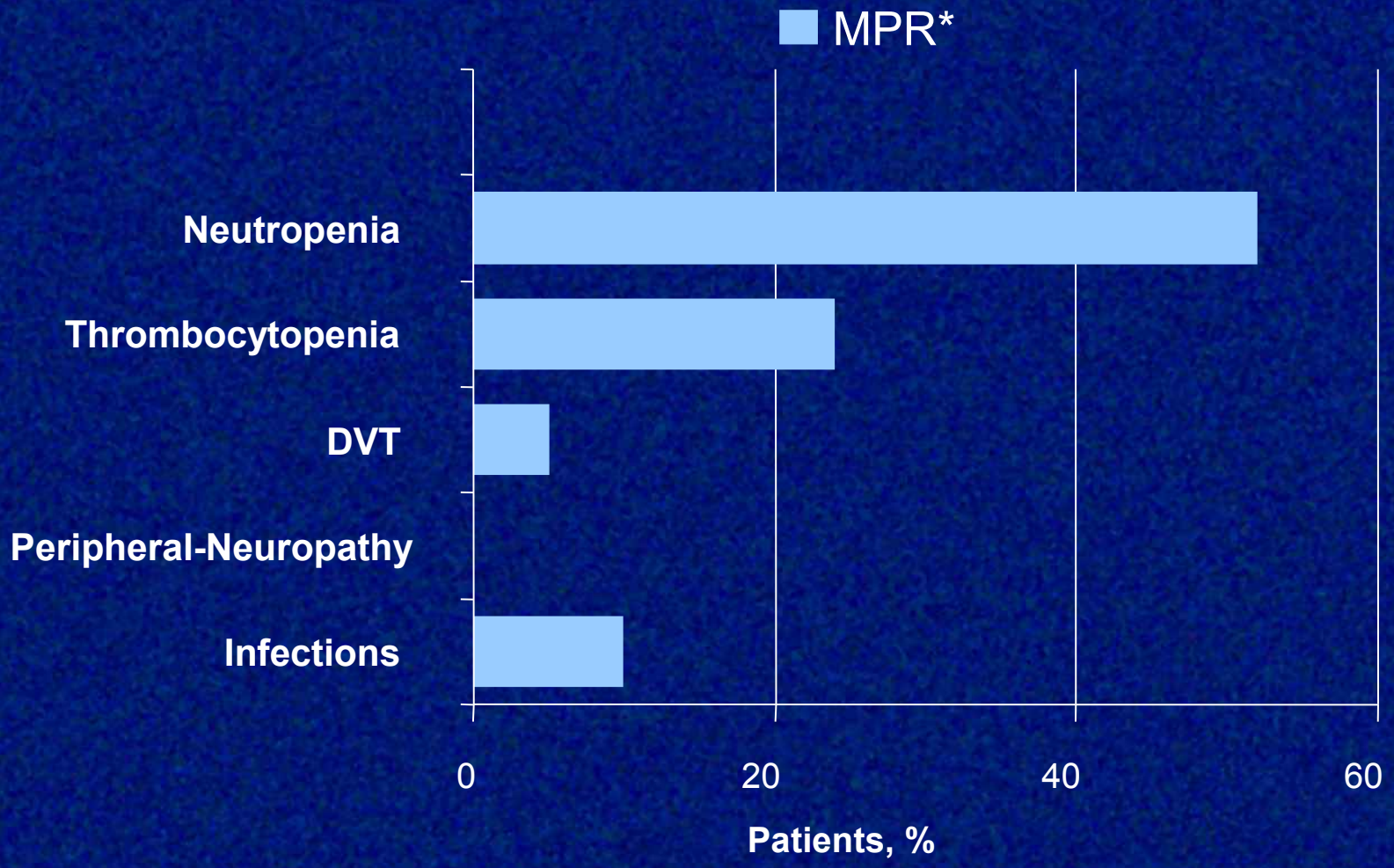


*Historical control – Palumbo et al, Lancet 2006
5.4% of response not available

Time to response



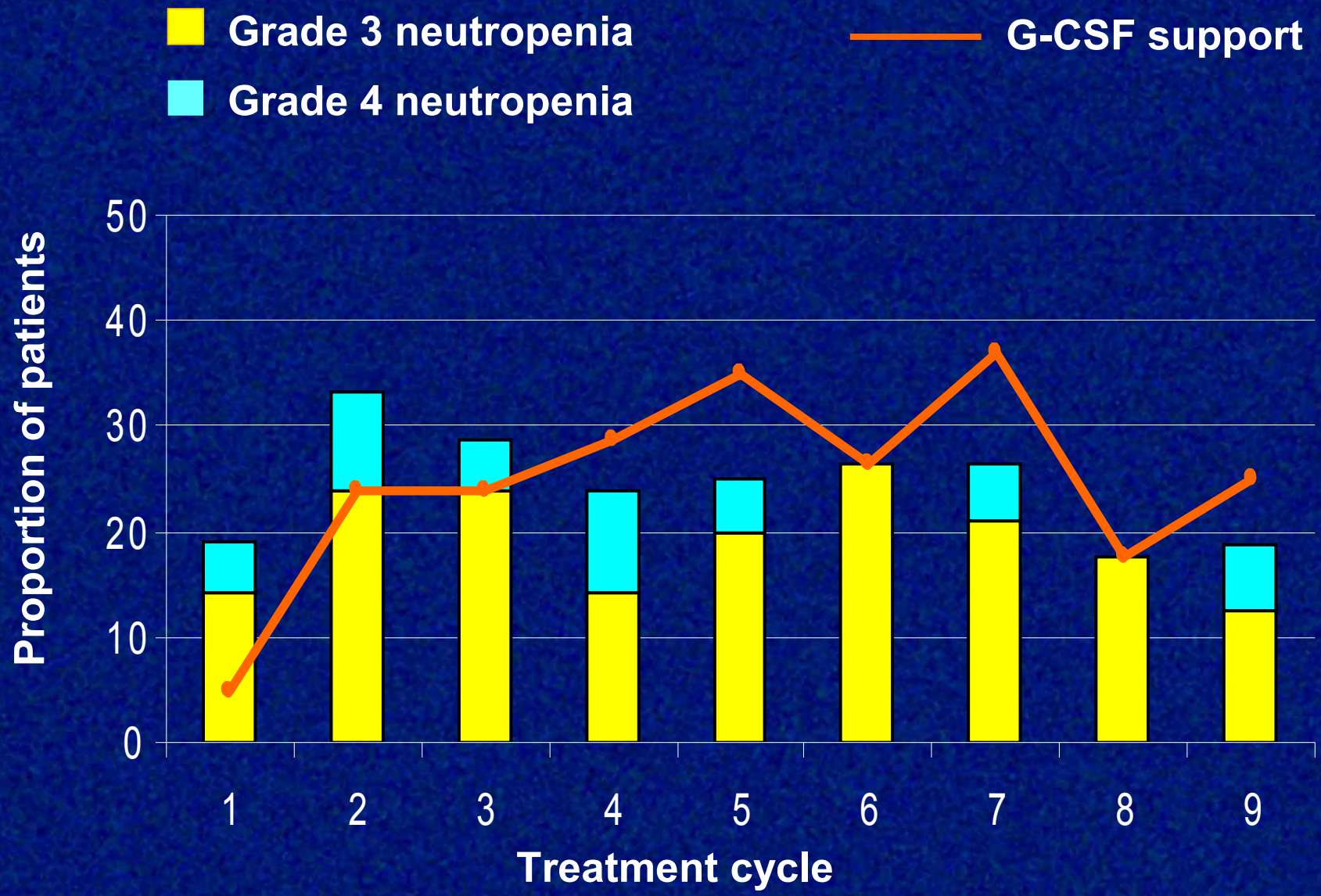
MPR: Grade 3/4 AEs



*Melphalan 0.18 mg/kg,days 1–4; Prednisone 2 mg/kg,days 1–4; Lenalidomide 10 mg/day,days 1–21

Palumbo A. et al. *J Clin Oncol*. 2007;25(28):4459-4465.

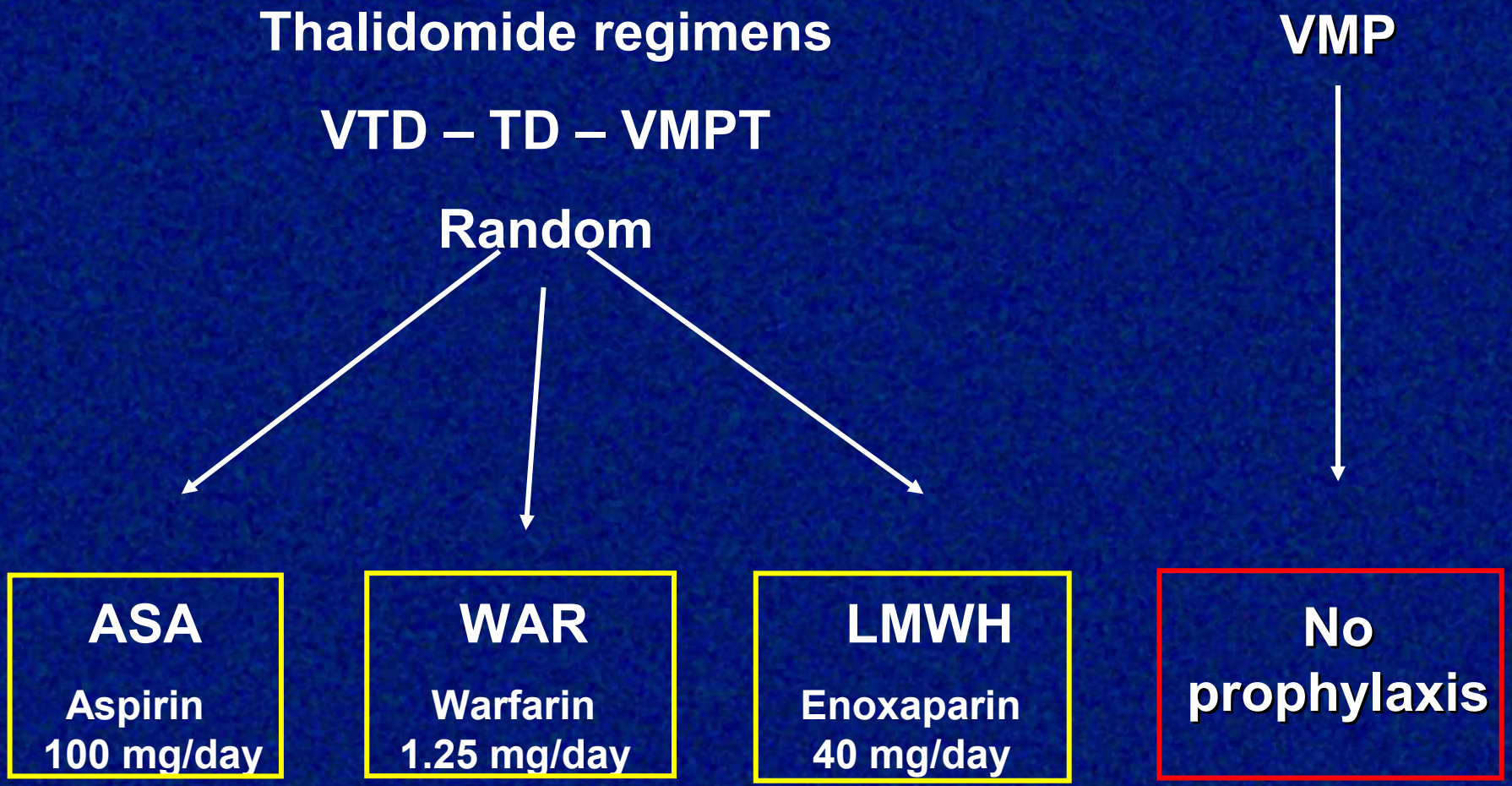
MPR: Neutropenia



Enoxaparin vs Aspirin vs LMWH

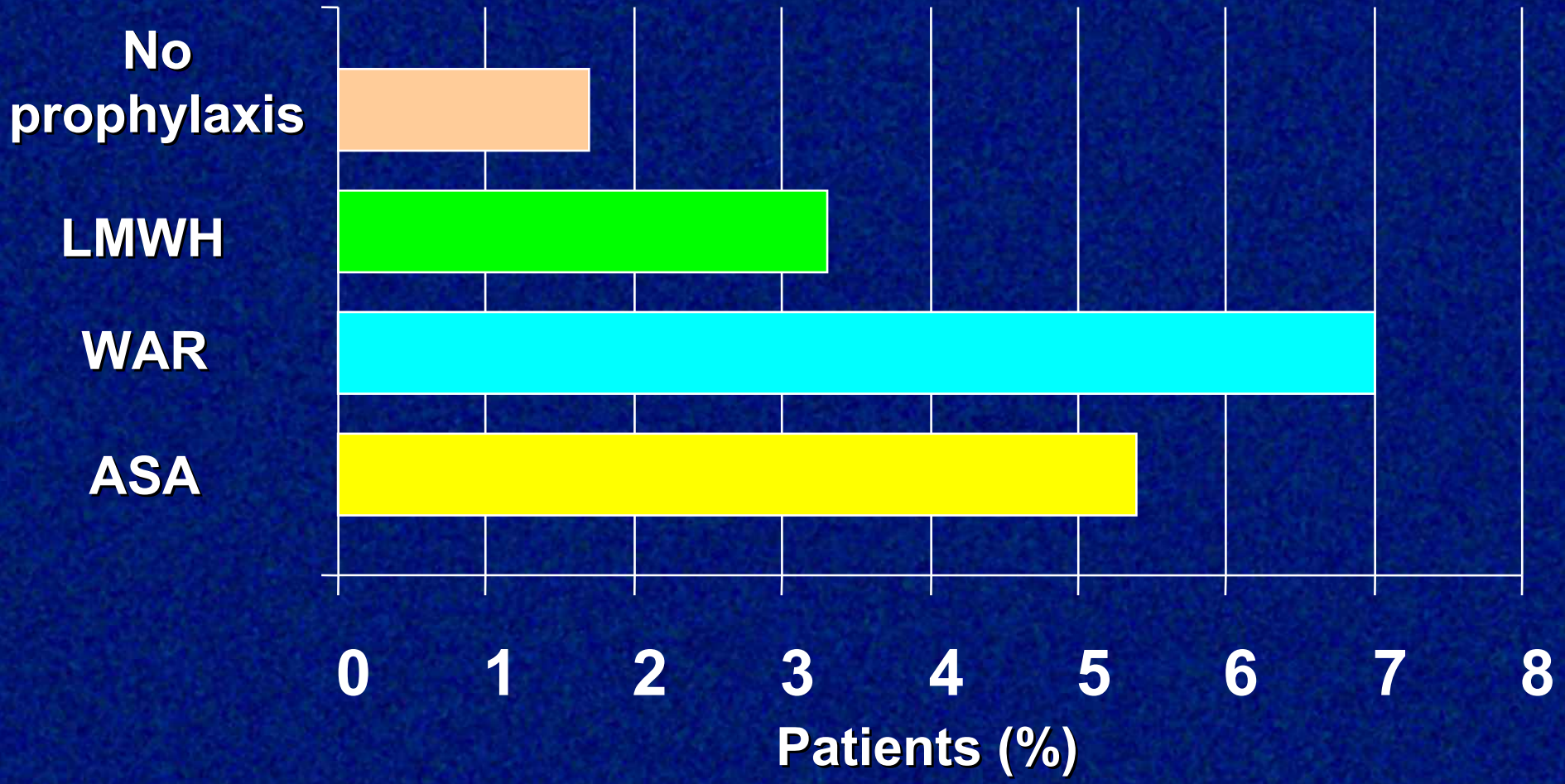
In MM Treated with Thalidomide

Study design 2

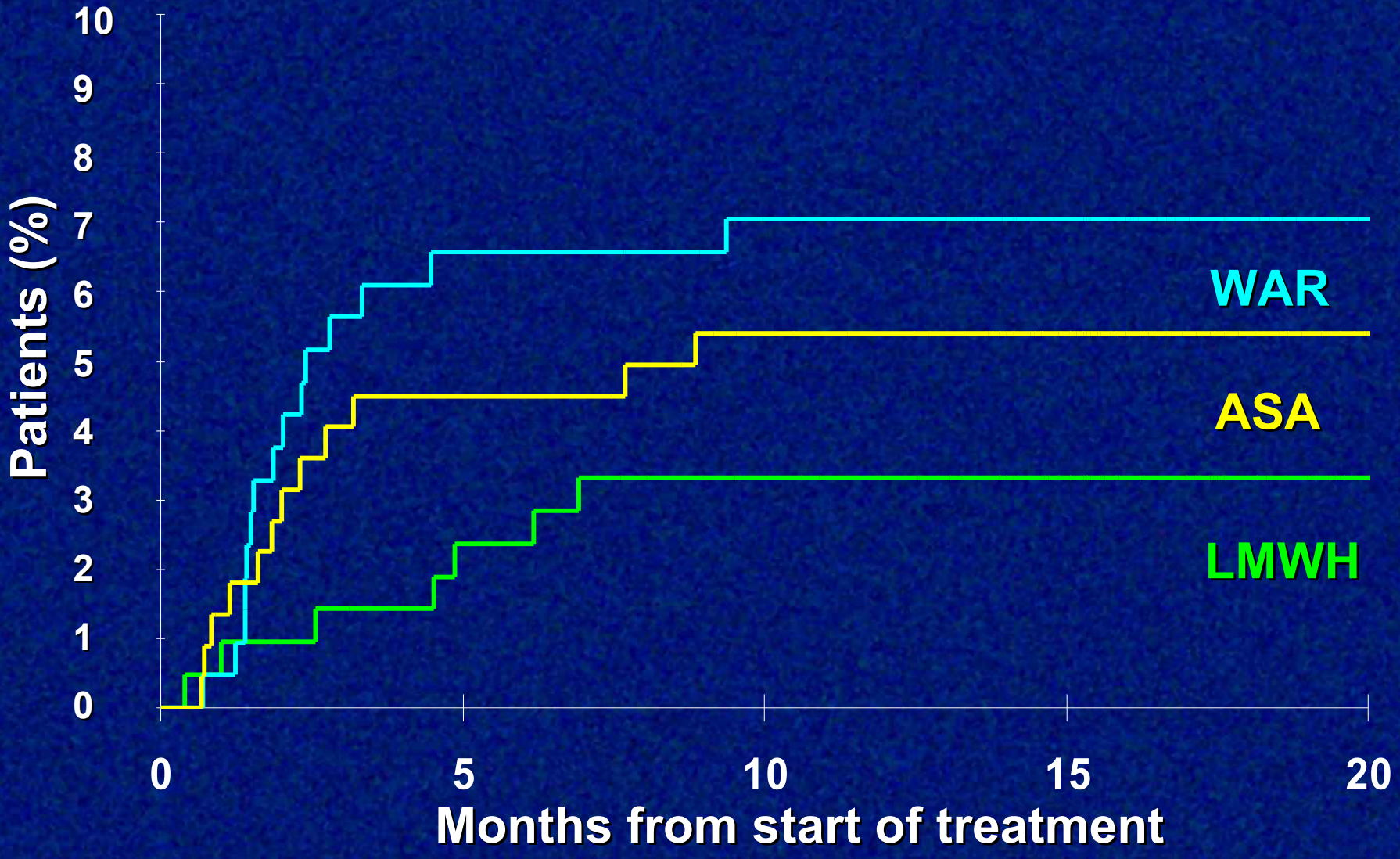


- VTD-TD: 9 weeks before ASCT
- VMPT: 6 months

Grade 3-4 Thromboembolic Events



Time to Onset of Thromboembolic Events



Combined Thrombosis, Bleeding and c-v Events

Combined toxicity	ASA (N=223)	WAR (N=214)	LMWH (N=211)	VMP (N=229)
All thrombosis	5.4%	7.0%	3.3%	1.7%
Total bleeding	4.5%	2.3%	1.9%	3.1%
Cardio-vascular	0,9%	0%	3,1%	1,3%
Total	10.8%	9.3%	8.3%	6.1%

VMPT

in Newly Diagnosed Patients

Treatment Schedule

- 511 patients (older than 65 years) randomized from 58 Italian centers
- Patients: Symptomatic multiple myeloma/end organ damage with measurable disease
  - ≥65 yrs or <65 yrs and not transplant-eligible; creatinine ≤ 2.5 mg/dL

RANDOMIZE

VMP
Cycles 1-9
Bortezomib 1.3 mg/m^2 IV: days 1,8,15,22*
Melphalan 9 mg/m^2 and prednisone 60 mg/m^2 days 1-4

→ **NO MAINTENANCE**

9 x 5-week cycles in both arms

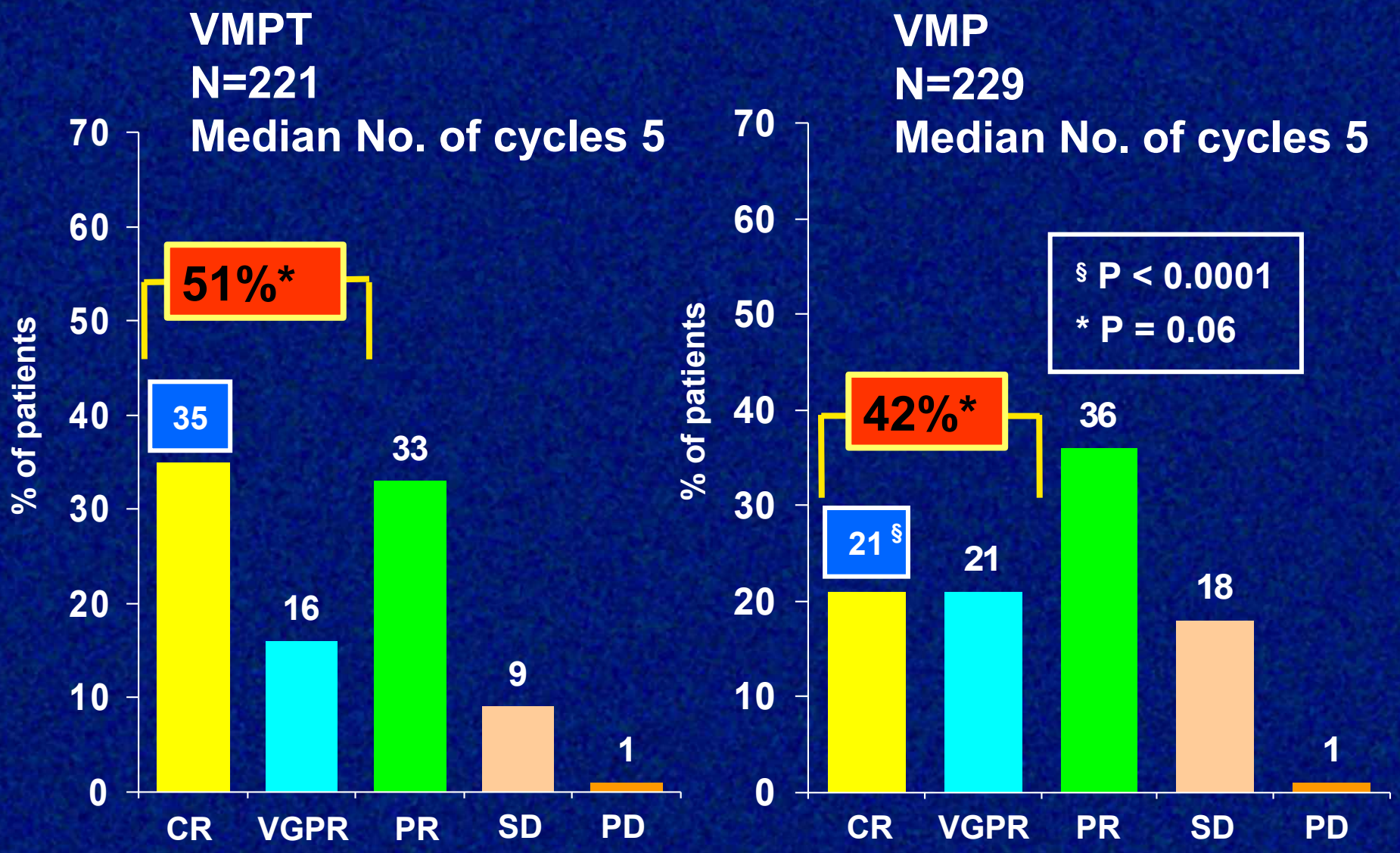
Until relapse

VMPT
Cycles 1-9
Bortezomib 1.3 mg/m^2 IV: days 1,8,15,22*
Melphalan 9 mg/m^2 and prednisone 60 mg/m^2 days 1-4
Thalidomide 50 mg/day continuously

→ **MAINTENANCE**
Bortezomib 1.3 mg/m^2 IV: days 1,15
Thalidomide 50 mg/day continuously

* 64 VMP patients and 71 VMPT patients were treated with twice-weekly infusions of Bortezomib

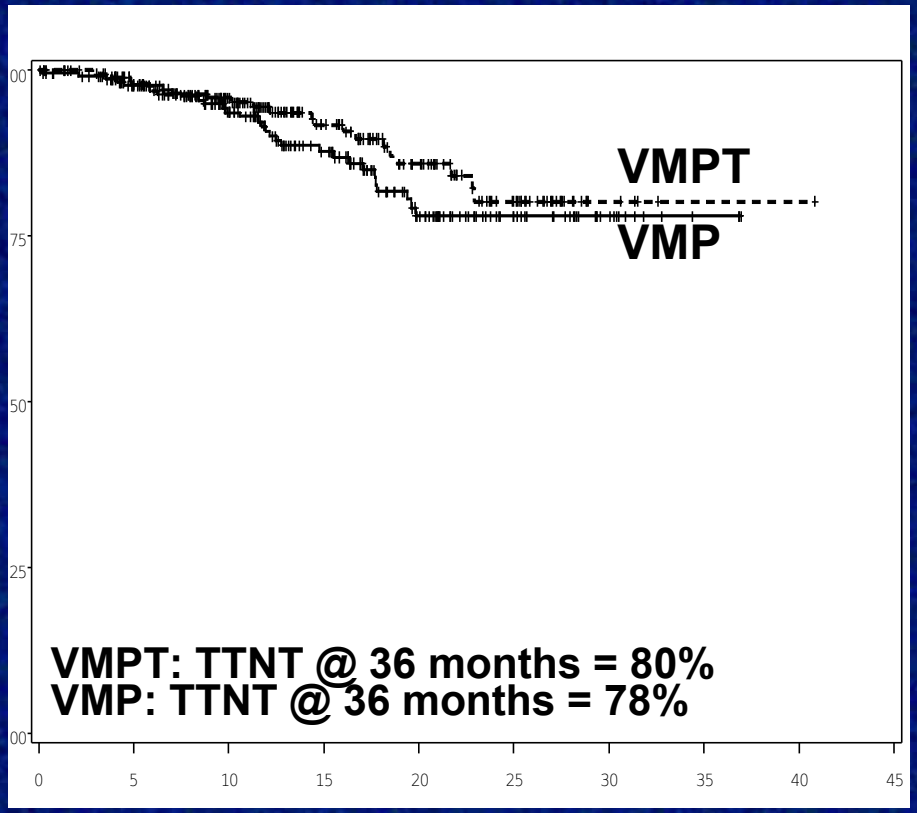
Best Response



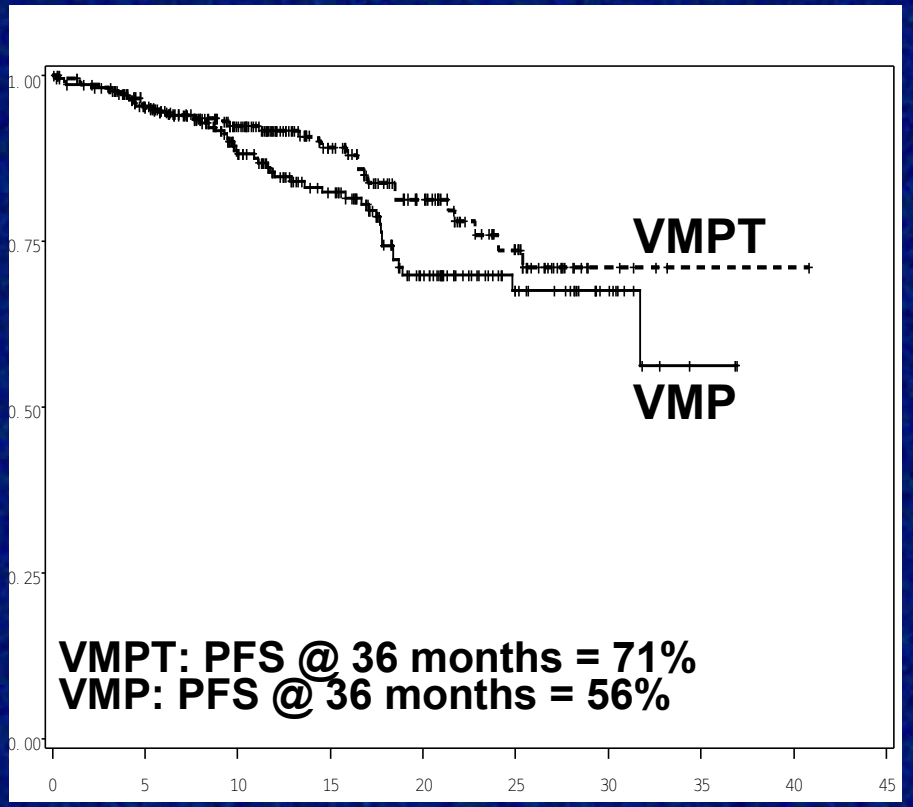
Time to next therapy
Progression free survival

Median follow-up 16.1 months

Time to next therapy



Progression free survival



Efficacy and Toxicity bortezomib infusion schedule

	VMPT		VMP	
	twice weekly (N=71)	weekly (N=150)	twice weekly (N=64)	weekly (N=165)
CR	38%	32%	27%	20%
Grade 3-4 Peripheral neuropathy	18%	2%	14%	2%
Dose reduction*	42%	11%	35%	13%
Discontinuation*	10%	3%	15%	4%

*Due to periferal neuropathy

25 VMPT and 19 VMP patients received both twice- and once-weekly

We Are Grateful to All Patients, Nurses and Physicians of the Participating Centers

1. ALESSANDRIA	Levis, Baraldi	**32. FOGGIA**	Monaco	**65. PISA**	Petrini/Benedetti
2. ANCONA	Leoni, Offidani	**33. FORLI'**	Amadori, Gentilini	**66. POTENZA**	Ricciuti, Vertone
3. AOSTA	Di Vito	**34. GALLARATE**	Ciambelli	**67. RAVENNA**	Zaccaria, Molinari
4. ASCOLI PICENO	Galieni, Bigazzi	**35. GENOVA**	Gobbi, Canepa	**68. REGGIO CAL.**	Nobile, Callea
5. ASTI	Scassa, Campa	**36. GENOVA**	Carella	**69. REGGIO EMILIA**	Gugliotta,Masini
6. AVELLINO	Cantore, Volpe	**37. LATINA**	Zapone	**70. RIMINI**	Pasquini, Fattori
7. AVIANO	Tirelli, Rupolo	**38. LECCE**	Pavone	**71. ROMA**	Annino, Bongarzoni
8. BARI	Dammacco, Lauta	**39. MATERA**	Ciancio	**72. ROMA**	Andriani
9. BARI	Liso	**40. MESSINA**	Brugiatelli, Mamone	**73. ROMA 1**	Foà, Petrucci
10. BERGAMO	Barbui, Galli	**41. MESSINA**	Musolino	**74. ROMA Cattolica**	Leone, De Stefano
11. BIELLA	Tonso	**42. MILANO**	Corradini, Montefusco	**75. ROMA R.Elena**	Petti, Pisani
12. BOLOGNA	Cavo, Tosi	**43. MILANO**	Morra	**76. ROMA S. Camillo**	Majolino, De Rosa
13. BOLZANO	Pescosta	**44. MILANO**	Bregni	**77. ROMA T. Vergata**	Amadori, Caravita
14. BRA	Vanni, Stefani	**45. MODENA**	Narni	**78. ROZZANO**	Santoro, Nozza
15. BRESCIA	Rossi, Crippa	**46. MONTEFIASC.**	Montanaro, Niscola	**79. S. G. ROTONDO**	Musto, Merla
16. CAGLIARI	Angelucci, Carubelli	**49. MONZA**	Pogliani, Rossini	**80. SASSARI**	Longinotti, Dore
17. CAGLIARI	Mantovani	**50. NAPOLI**	Rotoli,Catalano	**81. SIENA**	Lauria, Gozzetti
18. CAMPOBASSO	Storti	**51. NAPOLI**	Ferrara	**82. TARANTO**	Mazza, Casulli
19. CANDIOLO	Aglietta, Capaldi	**52. NOCERA INF.**	D'Arco, Califano	**83. TORINO 1**	Boccadoro
20. CATANIA	Giustolisi, Di Raimondo	**53. NOVARA**	Gaidano, Rossi	**84. TORINO 2**	Gallo, Pregno
21. CATANZARO	Piro	**54. NUORO**	Latte, Palmas	**85. TORINO MAURIZ.**	Poccardi, Gottardi
22. CATTOLICA	Pasquini	**55. ORBASSANO**	Saglio, Guglielmelli	**86. TORINO S. VITO**	Marinone, Ficara
23. CESENA	Guardigni	**56. PADOVA**	Semenzato, Zambello	**87. TORINO VALD.SE**	Bazzan, Rus
24. CHIOGGIA	Battista	**57. PALERMO**	Mirto, Cangialosi	**88. TREVISO**	Foscolo, Gherlinzoni
25. CIRIE'	Freilone, Beggiato	**58. PARMA**	Rizzoli, Giuliani	**89. TRIESTE**	De Sabbata
26. COSENZA	Morabito	**59. PAVIA**	Lazzarino, Corso	**90. UDINE**	Fanin, Patriarca
27. CREMONA	Passalacqua, Morandi	**60. PERUGIA**	Liberati, Nunzi	**91. VARESE**	Pinotti
28. CREMONA	Morandi	**61. PESARO**	Visani, Leopardi	**92. VENEZIA**	Chisesi
29. CUNEO	Gallamini, Grasso	**62. PESCARA**	Fioritoni, Spadano	**93. VERBANIA**	Montanara, Luraschi
30. FIRENZE	Bosi, Nozzoli	**63. PIACENZA**	Cavanna, Lazzaro	**94. VERONA**	Pizzolo, Meneghini
31. FOGGIA	Monaco, Ferrandina	**64. PINEROLO**	Griso	**95. VICENZA**	Rodeghiero, Elice