

Role and timing of Autologous SCT

Jean-Luc Harousseau



Inter groupe Francophone du Myélome



Role of Transplantation in the current treatment of Multiple Myeloma

- **Rescue Treatment**

 - Primary Refractory**

 - Relapsed Patients**

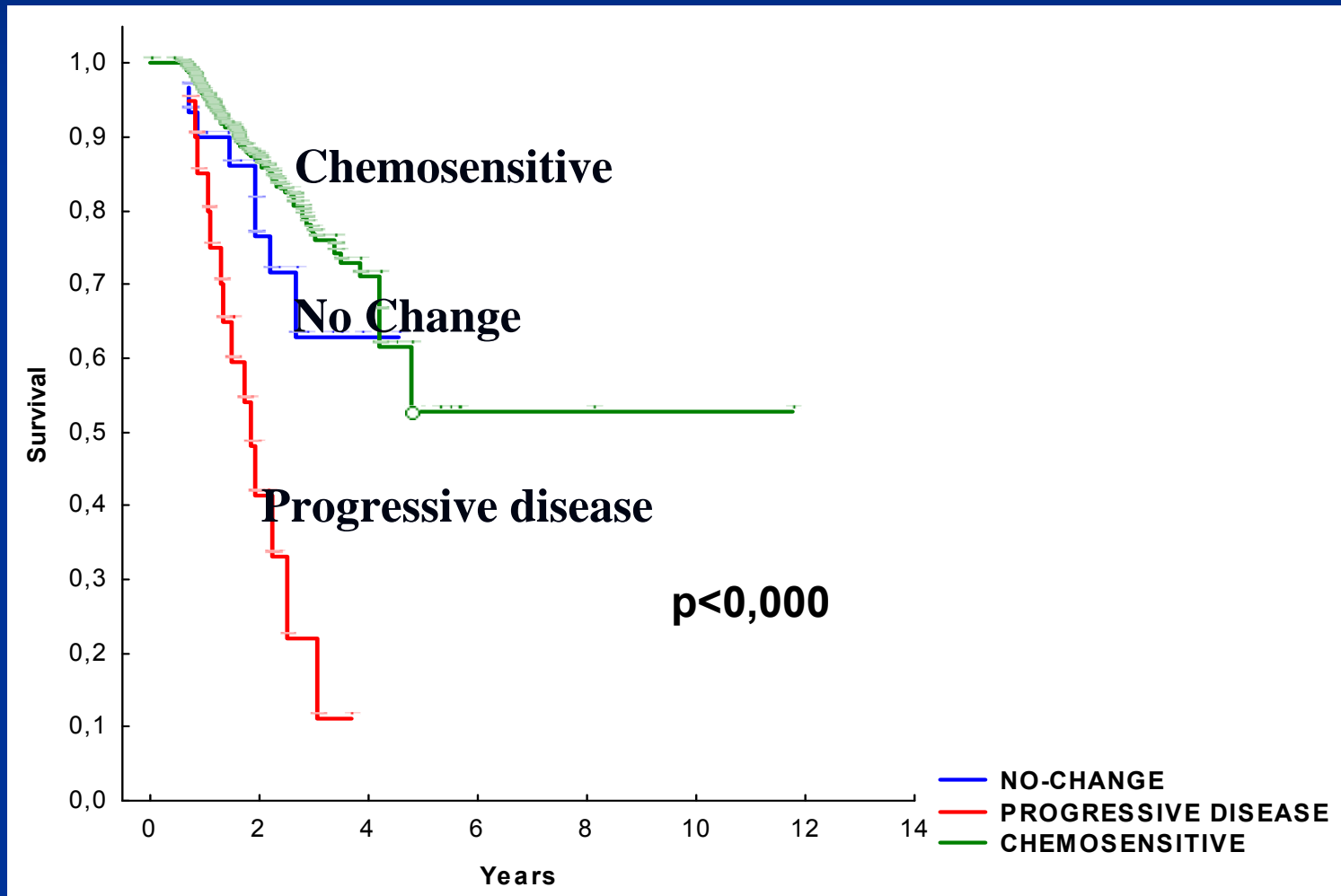
- **Up-front treatment**

ASCT for primary refractory MM

- « Myeloablative regimens supported by ASCT appeared useful primarily in patients with primary resistant disease during the 1st year of therapy » (Alexanian Blood 1994)
- Results of ASCT better in primary refractory MM than in resistant relapses (Vesole Blood 1996)
- Median OS from ASCT in primary refractory MM: 30-39 months (Vesole Blood 1996, Rajkumar BMT 1999)
- Lack of response to initial induction therapy does not appear to preclude a good response to ASCT (Kumar BMT 2004)

Overall Survival

No-change vs Progressive Disease vs Chemosensitive patients



Role of Transplantation in the current treatment of Multiple Myeloma

- **Rescue Treatment**

 - Primary Refractory

 - Relapsed Patients

- **Up-front treatment**

ASCT for relapsed MM

- Useful rescue treatment: no difference in OS between upfront and rescue ASCT (Fermand Blood 1998)
- Stem cell collection often difficult in previously treated pts
Early collection/ late ASCT (Gertz BMT 2000)
- With the possibility of using new agents sequentially after relapse, it will become difficult to show the benefit of ASCT as rescue Tt (identical SV after relapse)
- In the US Intergroup study median SV after rescue ASCT was only slightly better than salvage chemo 30 m vs23 m p=0.13) (Barlogie Blood 2006)
The survival benefit of any Tt will be better
shown UPFRONT

Role of Transplantation in the current treatment of Multiple Myeloma

- **Rescue Treatment**
- **Up-front treatment**

CURRENT ISSUES

- 1) Are novel agents going to replace ASCT ?
- 2) Are novel agents going to improve ASCT ?

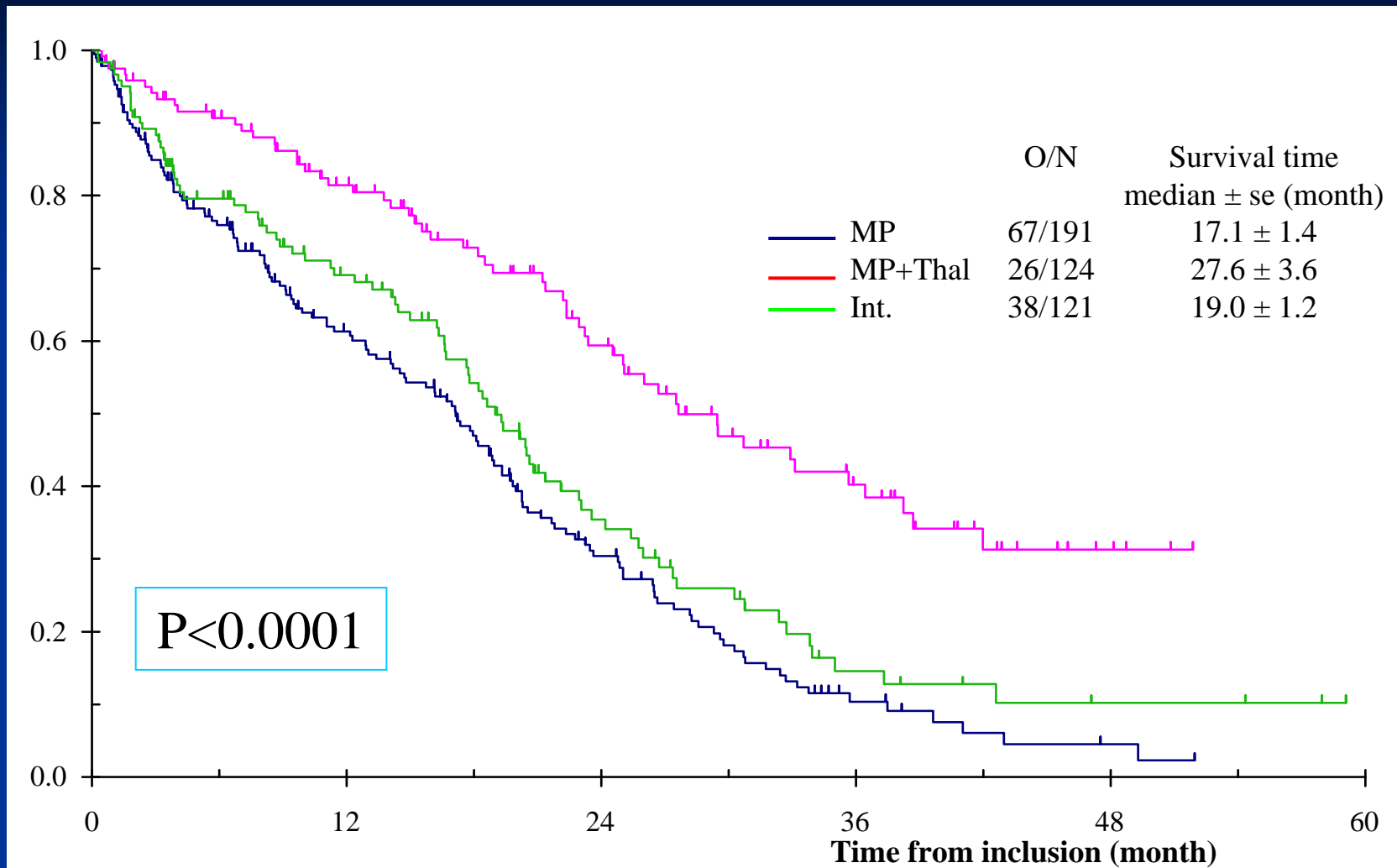
CONVENTIONAL CHEMOTHERAPY vs ASCT RANDOMIZED TRIALS

	CT	CR rate (%)	EFS (%)	SV (%)
IFM 90 (NEJM 96)	VMCP/VBAP	5 vs 22	7 yr 8 vs 16	7 yr 27 vs 43
MRC 7 (NEJM 03)	ABCM	8 vs 44	Med 19 vs 31	Med 42 vs 54
US Intergroup trial (JCO 06)	VAD + VBMCP	15 vs 17	7 yr 16 vs 17	42 vs 37

CONVENTIONAL CHEMOTHERAPY vs ASCT RANDOMIZED STUDIES

- EFS and OS improvement with ASCT are related to CR + VGPR increase
- ASCT is superior to CC when CR + VGPR rate is improved
- If the results of CC are improved, the benefit of ASCT is probably no more significant

IFM 9906 PFS T.FACON ASCO 06



# at risk	191	132	96	69	39	22	9	4	2	0	MP
	124	102	82	63	47	31	22	11	4	0	MP+Thal
	121	88	69	50	27	18	8	5	3	3	Int.

NOVEL AGENTS AS PRIMARY TREATMENT

	Author	N	Age	CR	CR+VGPR	CR+PR	EFS
MPT	Facon ASCO 2006	125	65-75	16%	50%	81%	Med 28 m
MPT	Palumbo Lancet 2006	129	60-85	15.5%	36%	76%	54% at 2 y
MPV	Mateos Blood 2006	60	> 65	32%	43%	89%	82% at 16 m
MPR	Palumbo ASH 2006	54	Med 71	24%	48%	81%	87% at 16 m
RD	Lacy ASH 2006	34	Med 64	18%	56%	91%	59% at 2 y

NOVEL AGENTS VERSUS ASCT

	MP *	MPT ①	Single ASCT ②
	<i>OLDER PATIENTS</i>		<i>YOUNGER PATIENTS</i>
CR rate	2 %	15-16 %	16-44 %
CR + VGPR rate	8-12 %	35-50 %	40-45 %
EFS	med 17m	med 28 m	med 28-30 m

① Palumbo Lancet 2006 / Facon ASCO 2006

② Attal NEJM 1996, Child NEJM 2003, Attal NEJM 2003,
Barlogie JCO 2006

CONCLUSIONS

1) Although they have been used in older patients, combinations using MP + novel agents yield

- CR
- CR + VGPR
- EFS

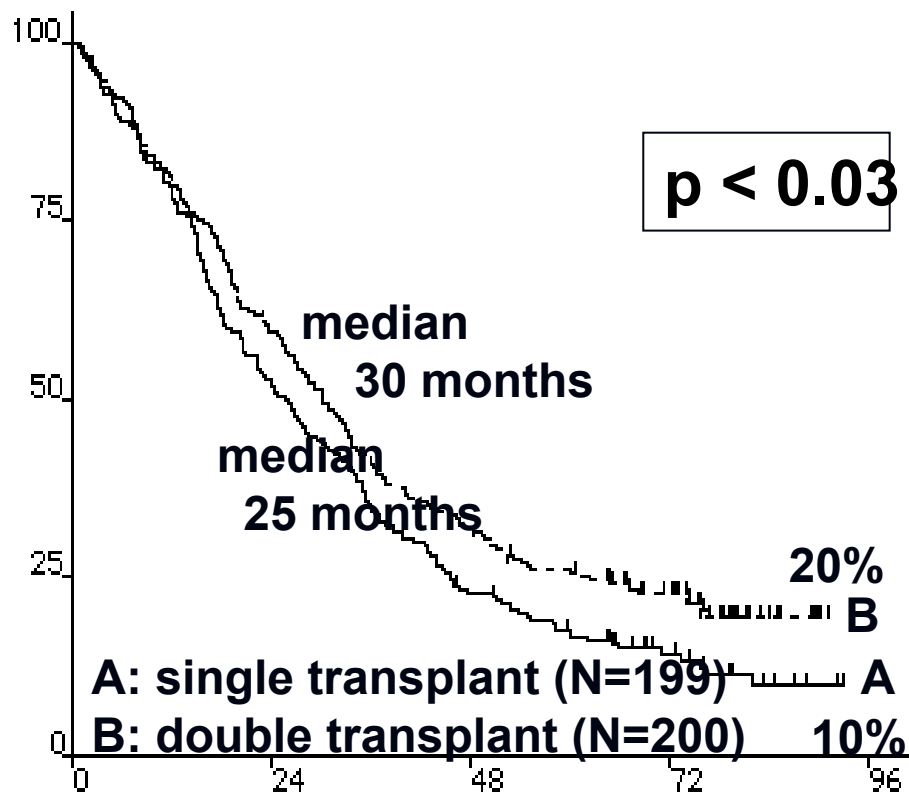
That are comparable to those achieved in younger patients with single ASCT

2) Other criteria (morbidity, QOL, cost) should also be considered

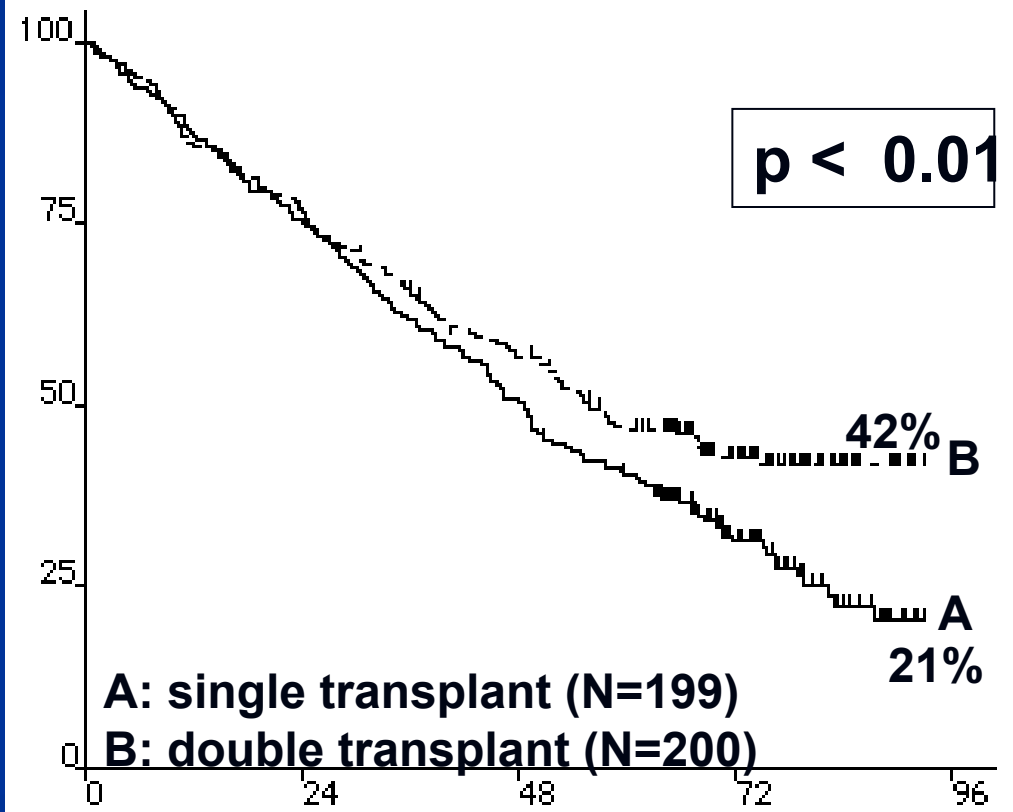
3) However results of HDT + ASCT have already improved by the use of novel agents

IFM 94

EFS



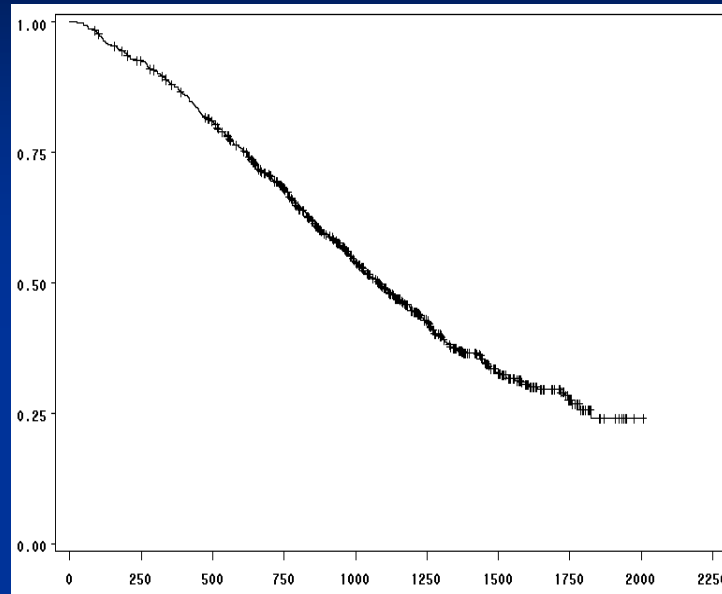
OS



OVERALL RESULTS

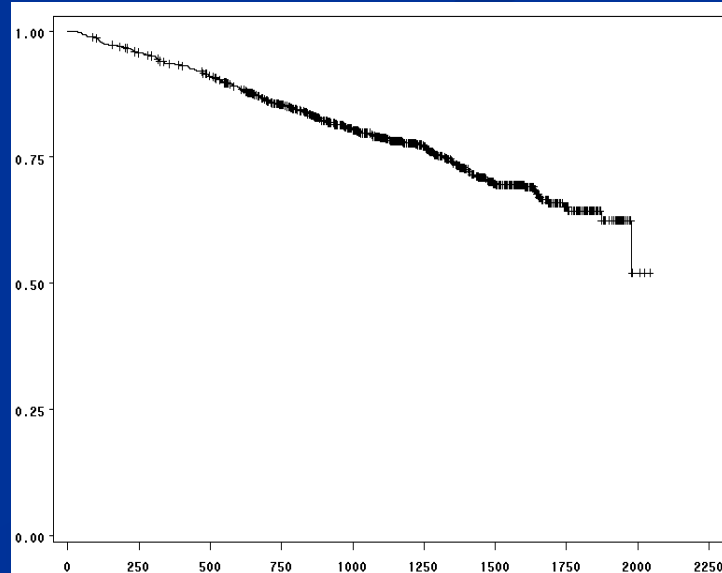
N = 1064 median follow-up 41 months

EFS



Median
35 months

OS



Median not
Reached at 5.5 years



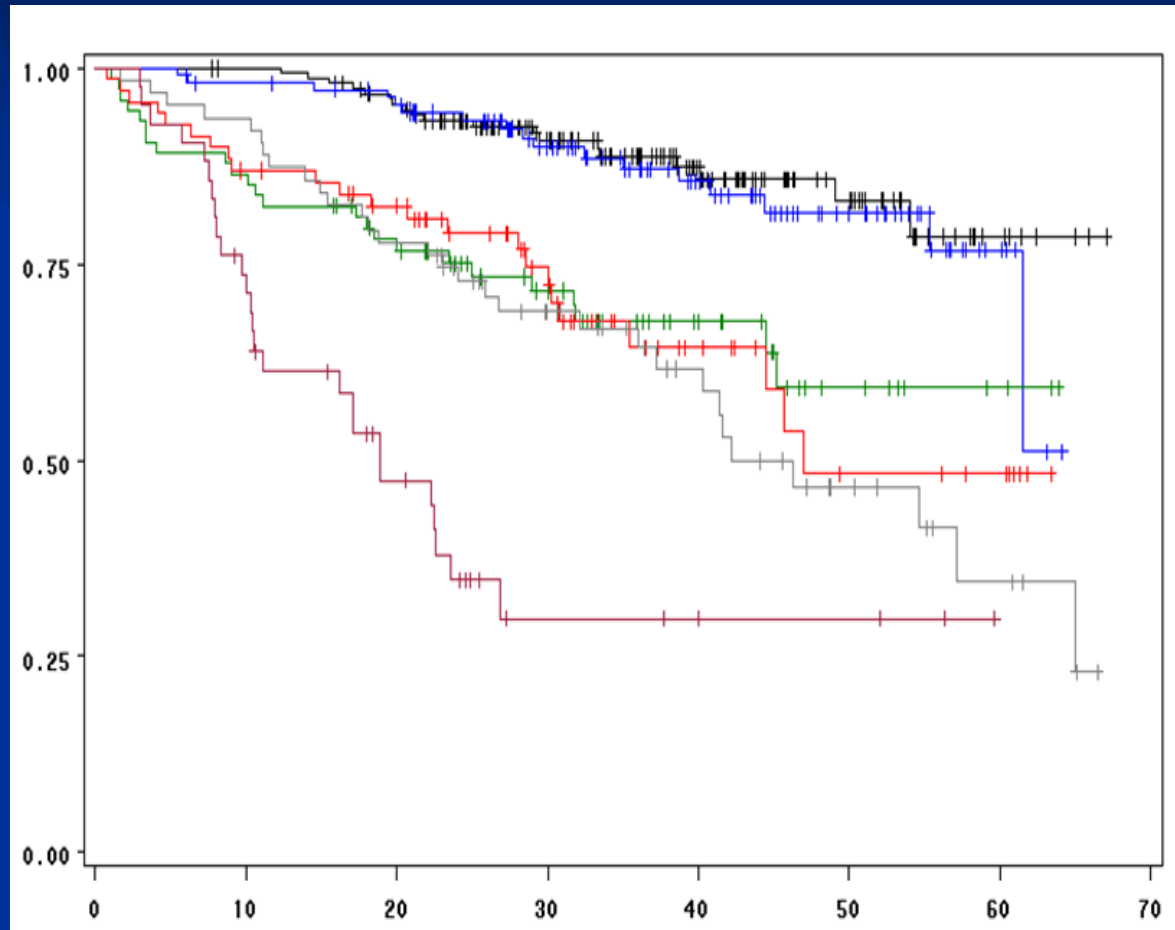
CURRENT ISSUES

- 1) Are novel agents going to replace ASCT ?
- 2) Are novel agents going to improve ASCT ?

Cytogenetic + $\beta 2m$ model

OS

No t(4;14), no del(17p), $\beta 2m < 4$, <u>no del(13)</u>	155 pts
No t(4;14), no del(17p), $\beta 2m < 4$, <u>del(13)+</u>	110 pts
No t(4;14), no del(17p), <u>$\beta 2m > 4$</u> , no del(13)	74 pts
No t(4;14), no del(17p), <u>$\beta 2m > 4$</u> , <u>del(13)+</u>	69 pts
t(4;14) <u>or</u> del(17p) > 60%, <u>$\beta 2m < 4$</u>	63 pts
t(4;14) <u>or</u> del(17p) > 60%, <u>$\beta 2m > 4$</u>	42 pts



THE ROLE OF NOVEL AGENTS IN THE CONTEXT OF HIGH-DOSE THERAPY

1. Induction Treatment

2. Preparative Regimen

3. Maintenance/consolidation

Thal-Based Regimens prior to ASCT

	TD vs D	TD vs VAD	TD vs VAD	TAD vs VAD
Author	Rajkumar JCO 2006	Cavo Blood 2005	Macro ASH 2006	Soldschmidt ASH 2005
N° of pts	201	200	204	406
Response Prior to ASCT	RR: 69M vs 51% No ≠ce in CR rate	RR: 76% vs 52% No ≠ce in CR rate	RR VGPR 35% vs 17%	RR 73% vs 60% No ≠ce in CR rate
Response After ASCT	-	-	VGPR 44% vs 42%	CR 19% vs 13%
DVT	17% vs 3%	15% vs 2%	23% vs 7.5%	8% vs 4% *

* LMWH prophylaxis

Response to induction therapy (preliminary analysis, N=161)

VAD (A1+A2)
N=82

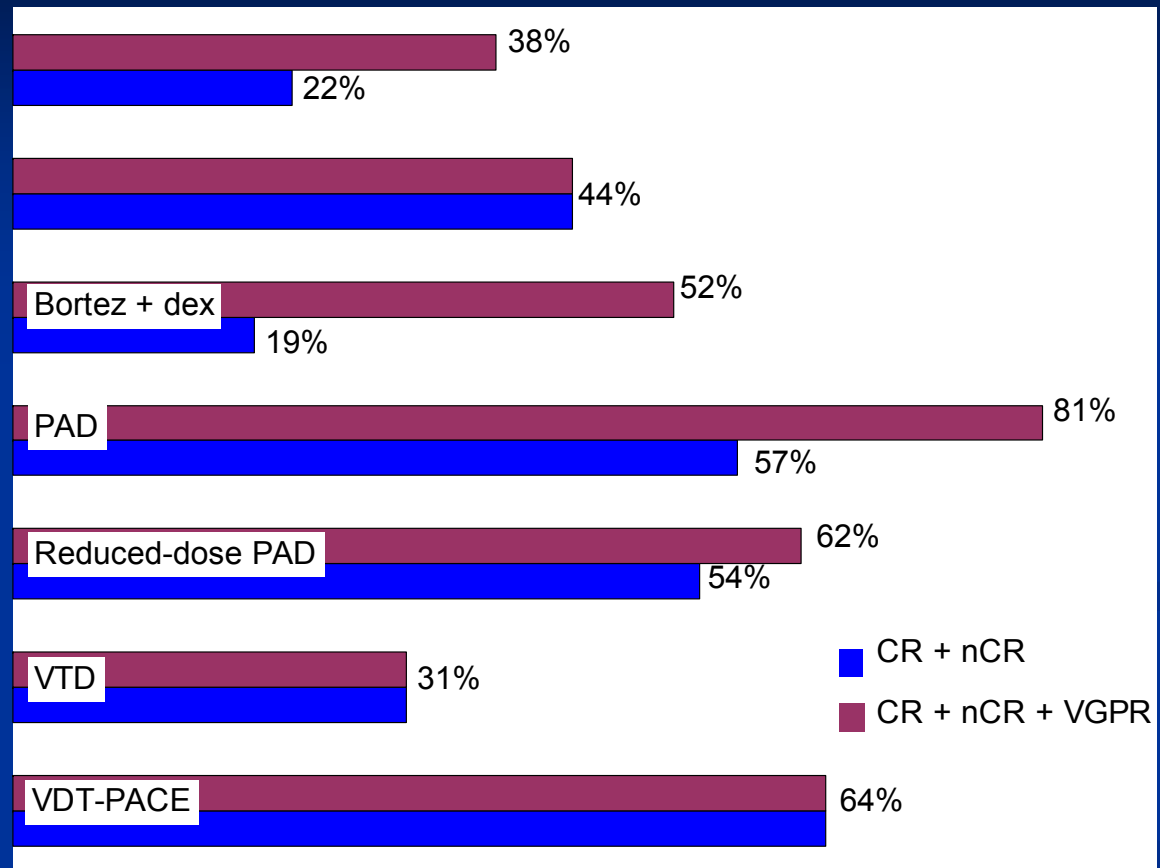
Vel/Dex
(B1+B2) N=79

CR/nCR	9%	20%
if B2M>3	9%	20%
if del(13)	11%	25%
CR+VGPR	26%	43%
CR+PR	67%	82%

CONVENTIONAL SCT vs BORTEZOMIB INDUCTION REGIMEN

Conventional SCT
Attal 1996, Child 2003

Bortezomib induction regimen



Integrating bortezomib into induction regimen may result in superior CR rates compared with conventional induction regimen

Harousseau *et al. Haematologica* 2005;90(Suppl 1):148 (Abstract P0.724)

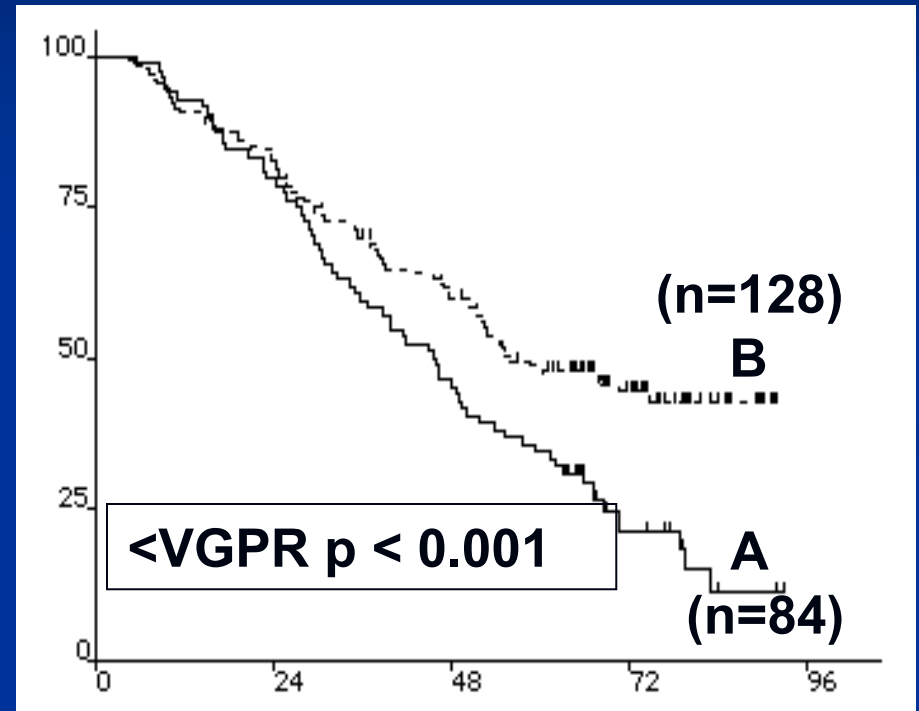
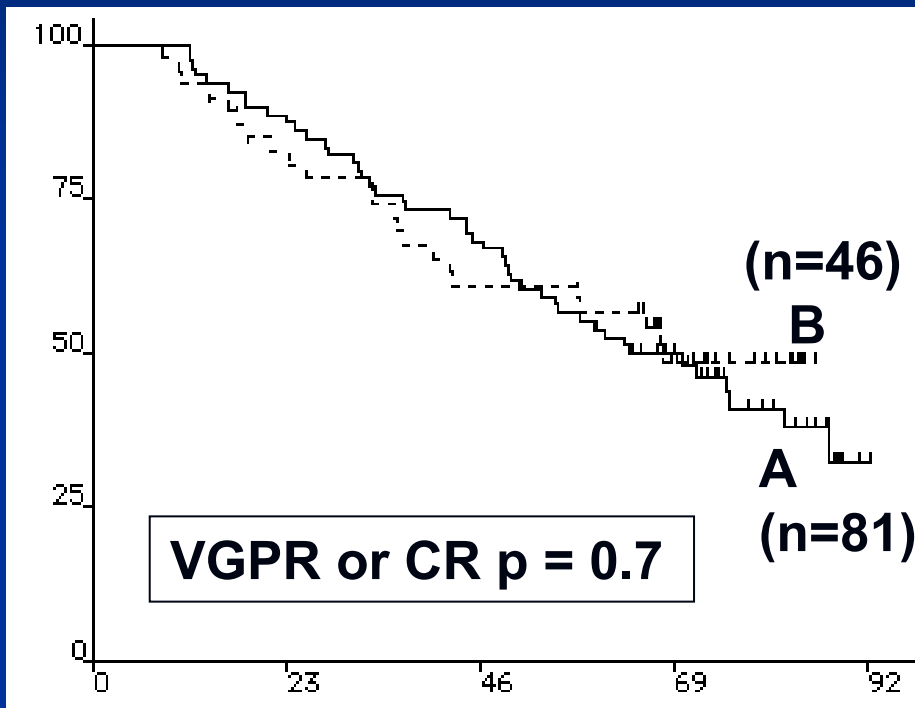
Popat *et al. Blood* 2005;106 (Abstract 2554)

Oakervee *et al. Br J Haematol* 2005;129:755–62

Badros *et al. Blood* 2005;106 (Abstract 2747)

Wang *et al. Blood* 2005;106 (Abstract 784)

The only factor predicting the impact of the 2nd ASCT is the result of the first



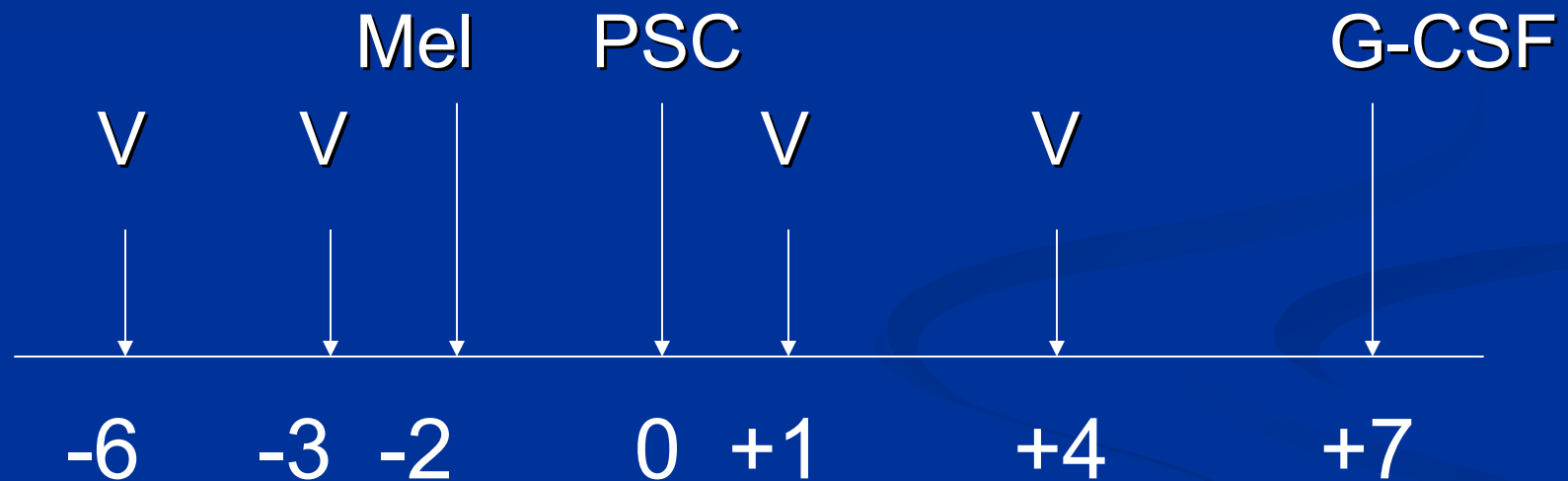
THE ROLE OF NOVEL AGENTS IN THE CONTEXT OF HIGH-DOSE THERAPY (CONT'D)

1. Induction Treatment

2. Preparative Regimen

3. Maintenance/consolidation

The Vel-Mel regimen



V = Velcade 1mg/m²/d

Mel = Melphalan 200mg/m²

The Vel-Mel Regimen: Results

- 25 pts (18 frontline)
- PN < 500/mm³ = 7 d (5-10)
- Plat < 20000/mm³ = 1.5 d (0-7)
- Severe Mucositis = 20%
- Response Rate:
 - ✓ CR = 31%
 - ✓ VGPR = 46%
 - ✓ CR / VGPR = 77%

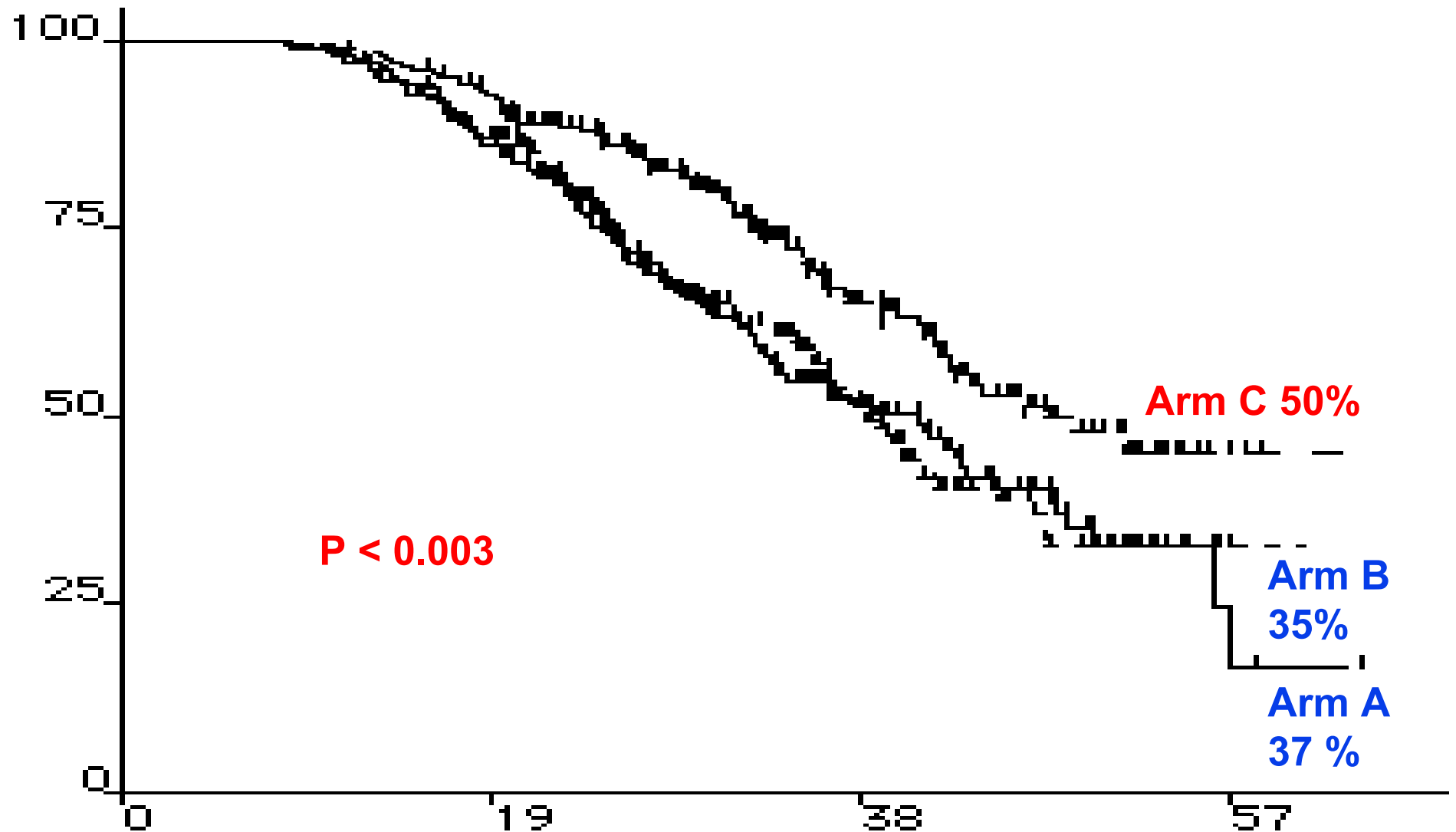
THE ROLE OF NOVEL AGENTS IN THE CONTEXT TO HIGH-DOSE THERAPY

1. Induction Treatment

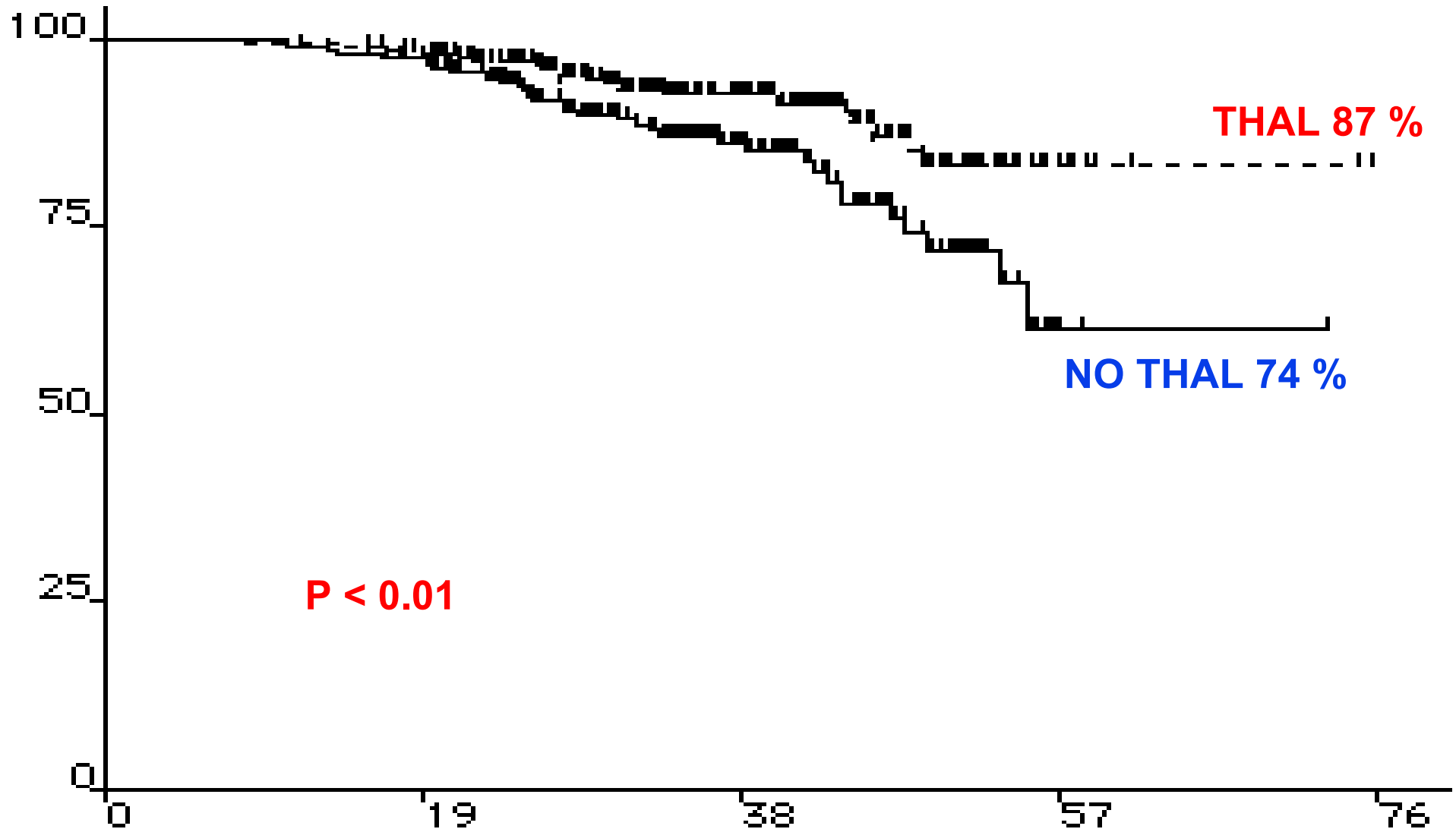
2. Preparative Regimen

3. Maintenance/consolidation

IFM 99 02 : 4-yr EFS from Diagnosis



IFM 99 02 : 4-yr OS according to Thal (Pam vs Pam/Thal)



IFM 99 02: Response Rate $\geq 90\%$.

	Arm A	Arm B	Arm C	p
▪ After VAD	15%	15%	16%	NS
▪ At Random	45%	47%	50%	NS
▪ After Random	55%	57%	68%	0.03

OTHER STUDIES ON POST ASCT MAINTENANCE WITH THALIDOMIDE

Abdelkefi (ASH 2006)

	Double ASCT N= 69	p	Single ASCT + Thal maintenance (6M)
VGPR	51%	0.04	67%
2-year PFS	70%	0.08	84%

Spencer (ASH 2006)

	12M-Thal + P/2 N=114	p	P/2 N= 129
1yr CR + Ncr	24%	< 0.01	15%
2 yr PFS	66%	0.0005	40%
2 yr OS	91%	0.02	80%

CONCLUSIONS I

**Combinations including novel agents
(Thalidomide, Bortezomib, Lenalidomide)**

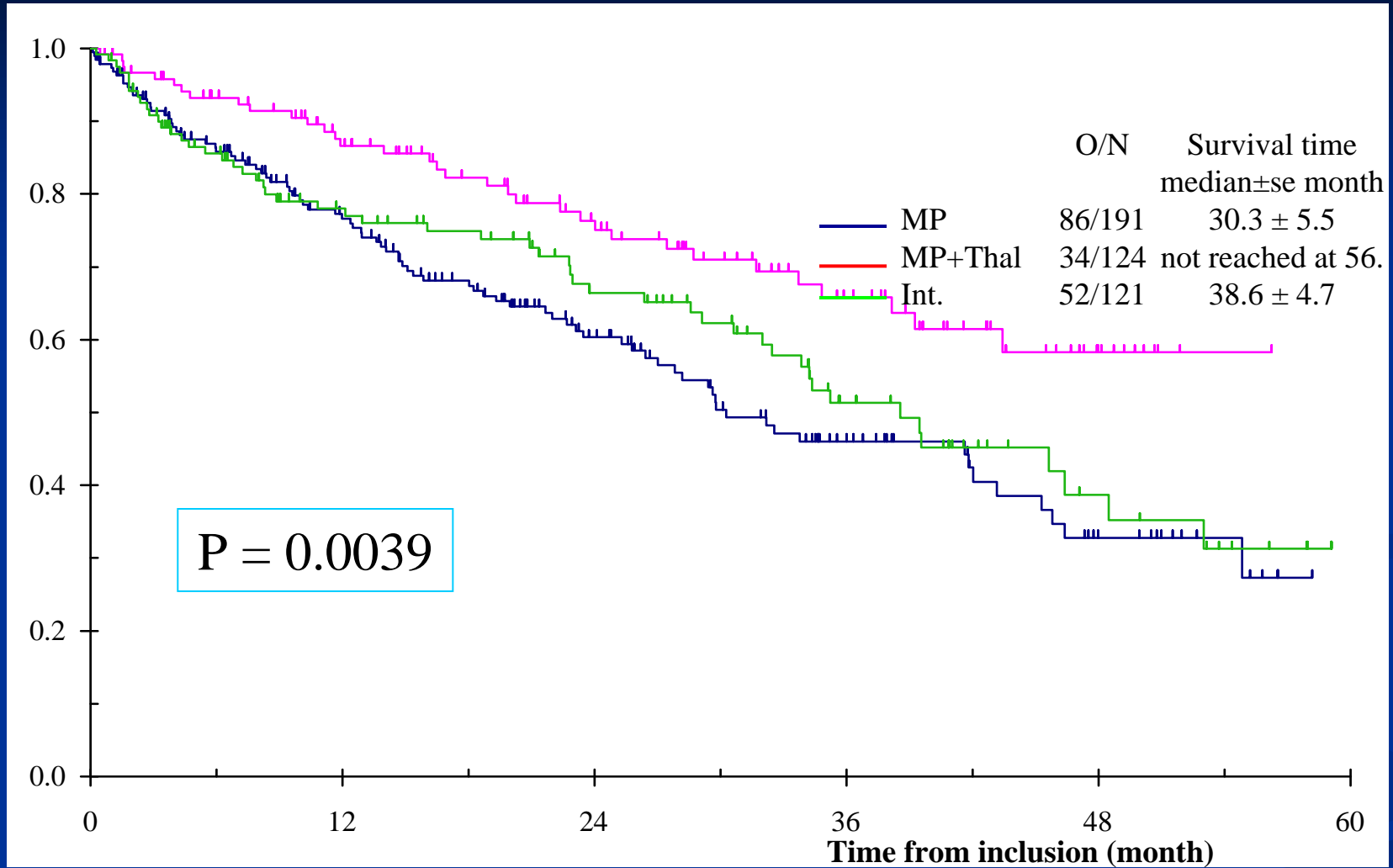
- **are superior to conventional chemotherapy**
- **yield CR and PFS rates that are comparable to historical results achieved with ASCT**
- **raise some concerns about safety and cost**

CONCLUSIONS II

However, results of ASCT have improved with further dose-intensification and the introduction of Thalidomide as post ASCT maintenance

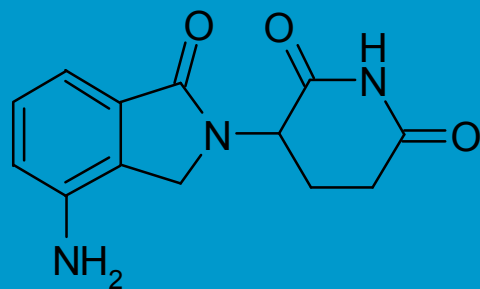
- Ongoing trials are evaluating the impact of Bortezomib and Lenalidomide in the ASCT paradigm specially for poor-risk patients
- In the near future, it might be necessary to compare the BEST strategy including ASCT with the BEST strategy without ASCT

IFM 9906 OS T.FACON ASCO 2006

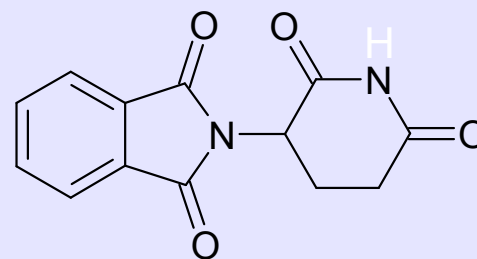


# at risk	0	12	24	36	48	60
MP	191	150	120	97	69	49
MP+Thal	124	105	88	73	61	47
Int.	121	95	77	68	52	44

Molecular and preclinical profiles: lenalidomide versus thalidomide



Lenalidomide

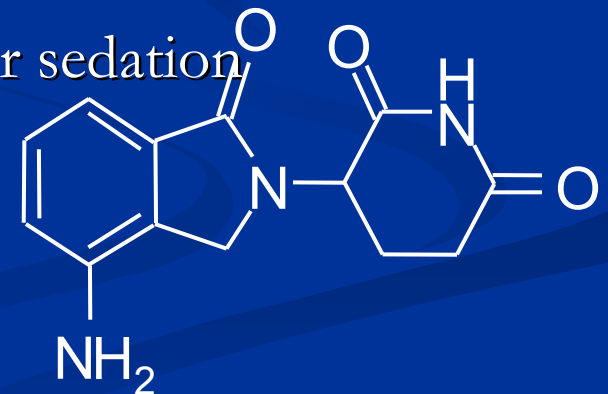


Thalidomide

**Structurally similar, but functionally different:
qualitatively and quantitatively**

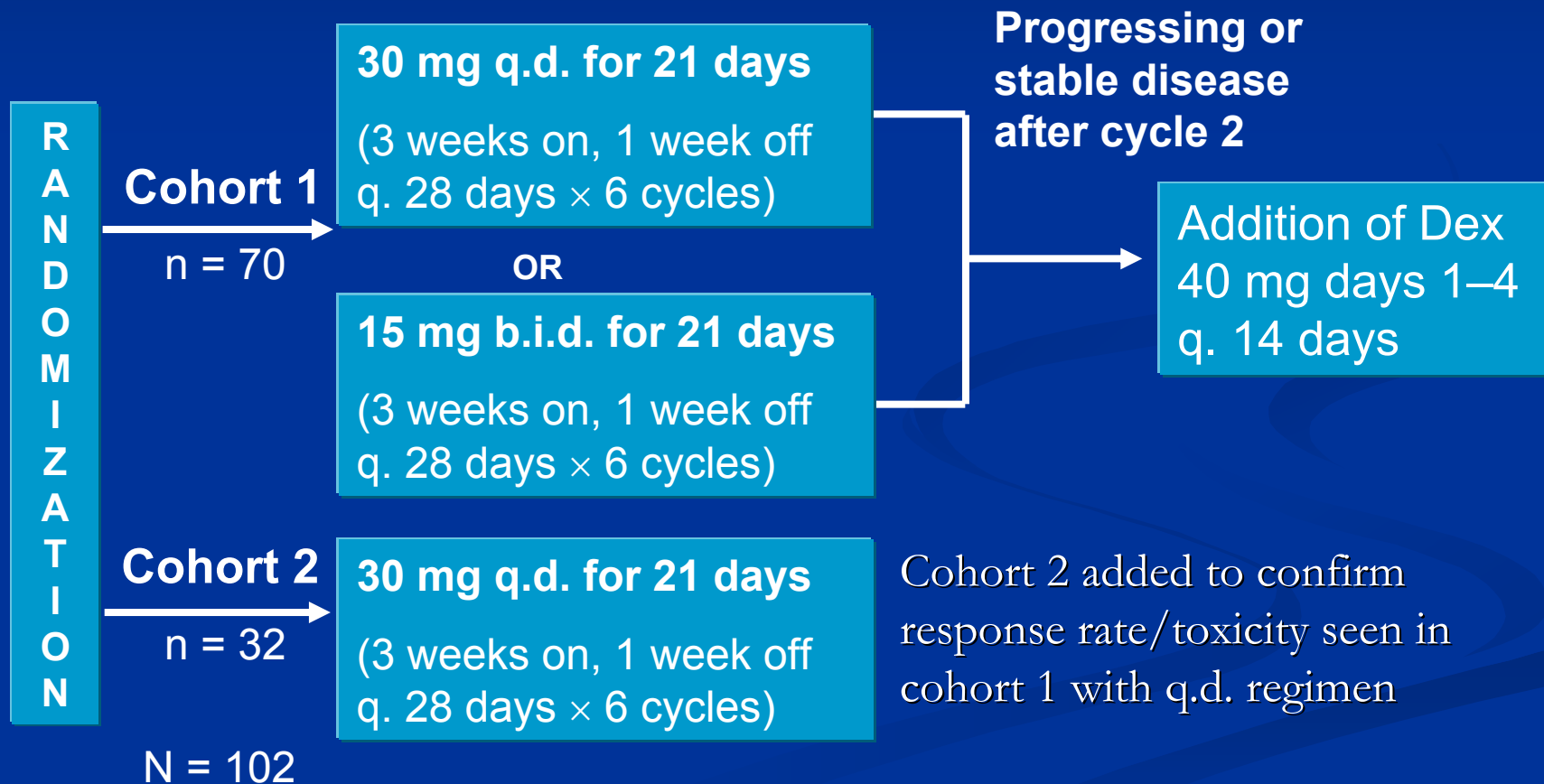
Lenalidomide

- More “potent” immunomodulator than thalidomide
 - more potent inhibitor of TNF- α
 - increased stimulation of T-cell proliferation
 - augmented stimulation of production of IL-2 and IFN- γ
- Different side-effect profile from that of thalidomide
 - greater myelosuppression
 - no significant constipation, neuropathy, or sedation
- Not teratogenic in animal models (including New Zealand white rabbit)
 - embryotoxic at 100 \times human dose

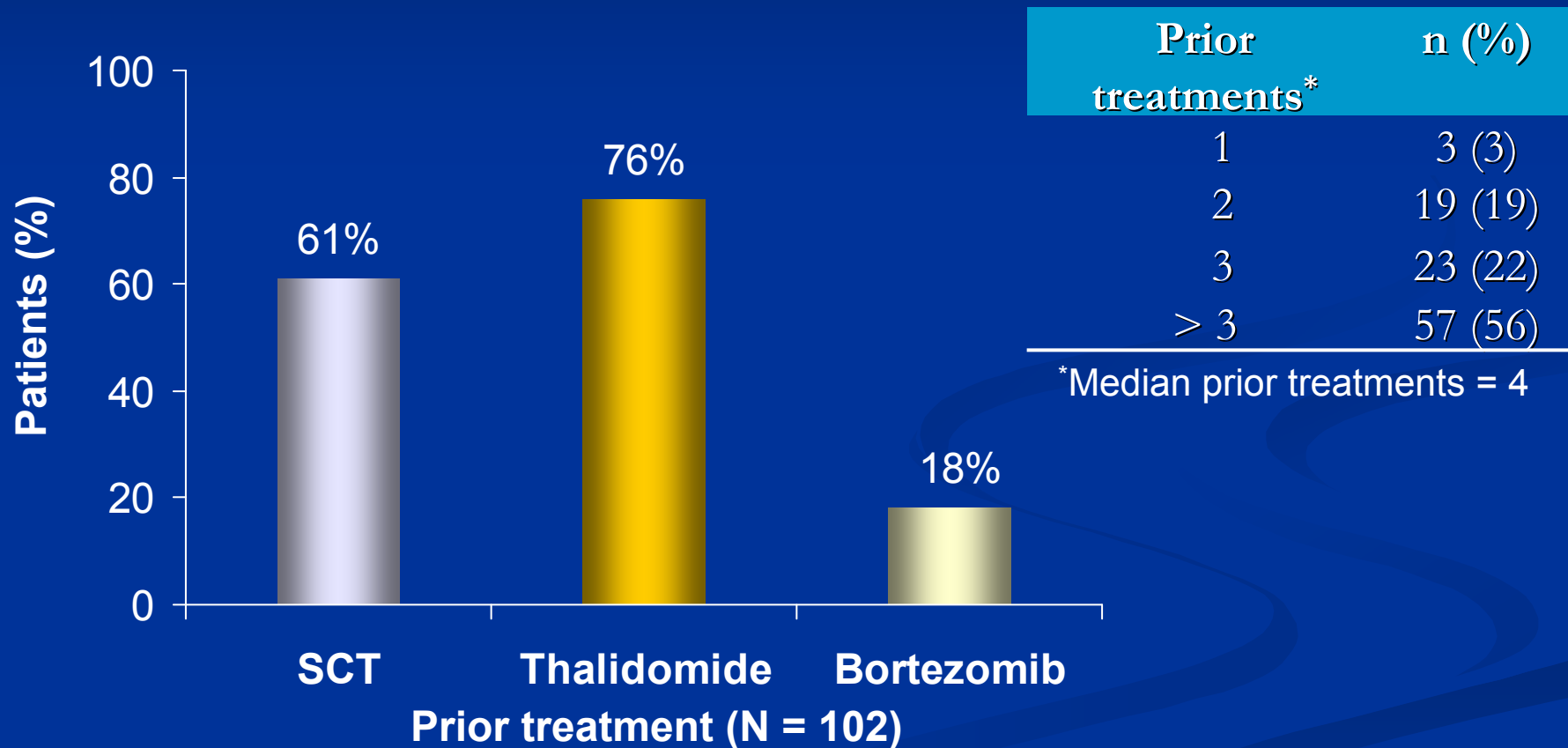


Phase II trial of lenalidomide with or without dexamethasone in relapsed/refractory MM

Treatment scheme



Phase II trial of lenalidomide with or without dexamethasone in relapsed/refractory MM



Phase II trial of lenalidomide with or without dexamethasone in relapsed/refractory MM

Responses

	Total N	CR n (%)	PR n (%)	MR n (%)	SD n (%)	PD n (%)
Lenalidomide 15 mg b.i.d.	35	0 (0)	5 (14)	5 (14)	14 (40)	8 (23)
Lenalidomide 30 mg q.d.	67	4 (6)	8 (12)	4 (6)	29 (43)	12 (18)
Combined	102	4 (4)	13 (13)	9 (9)	43 (42)	19 (19)

CR = complete (100% paraprotein) response.

PR = partial (50%–99% paraprotein) response.

MR = minor (25%–49% paraprotein) response.

SD = stable disease (< 25% paraprotein reduction).

PD = progression of disease.

Phase II trial of lenalidomide with or without dexamethasone in relapsed/refractory MM

Adverse events*

	15 mg b.i.d.	30 mg q.d.
	n (%)	n (%)
Neutropenia	24 (69)	41 (61)
Leucopenia	12 (34)	25 (37)
Lymphopenia	14 (40)	25 (37)
Thrombocytopenia	15 (43)	21 (31)
Anaemia	5 (14)	11 (16)

*Grade 3 or 4 with frequency > 10% in all 102 patients.

Two phase III trials of Len/Dex in relapsed/refractory MM: MM-009 and MM-010

North American MM-009 (48 centres USA/Canada): Weber
International MM-010 (51 centres Europe/Australia/Israel): Dimopoulos

Inclusion criteria

- ≤ 3 prior therapies
- No Dex resistance
- Normal hepatic and renal function

Len 25 mg days 1–21
Placebo days 22–28
Dex 40 mg, days 1–4, 9–12, 17–20

× 4 courses



Continue
until PD

Placebo days 1–28
Dex 40 mg, days 1–4, 9–12, 17–20

Same, except
Dex days 1–4

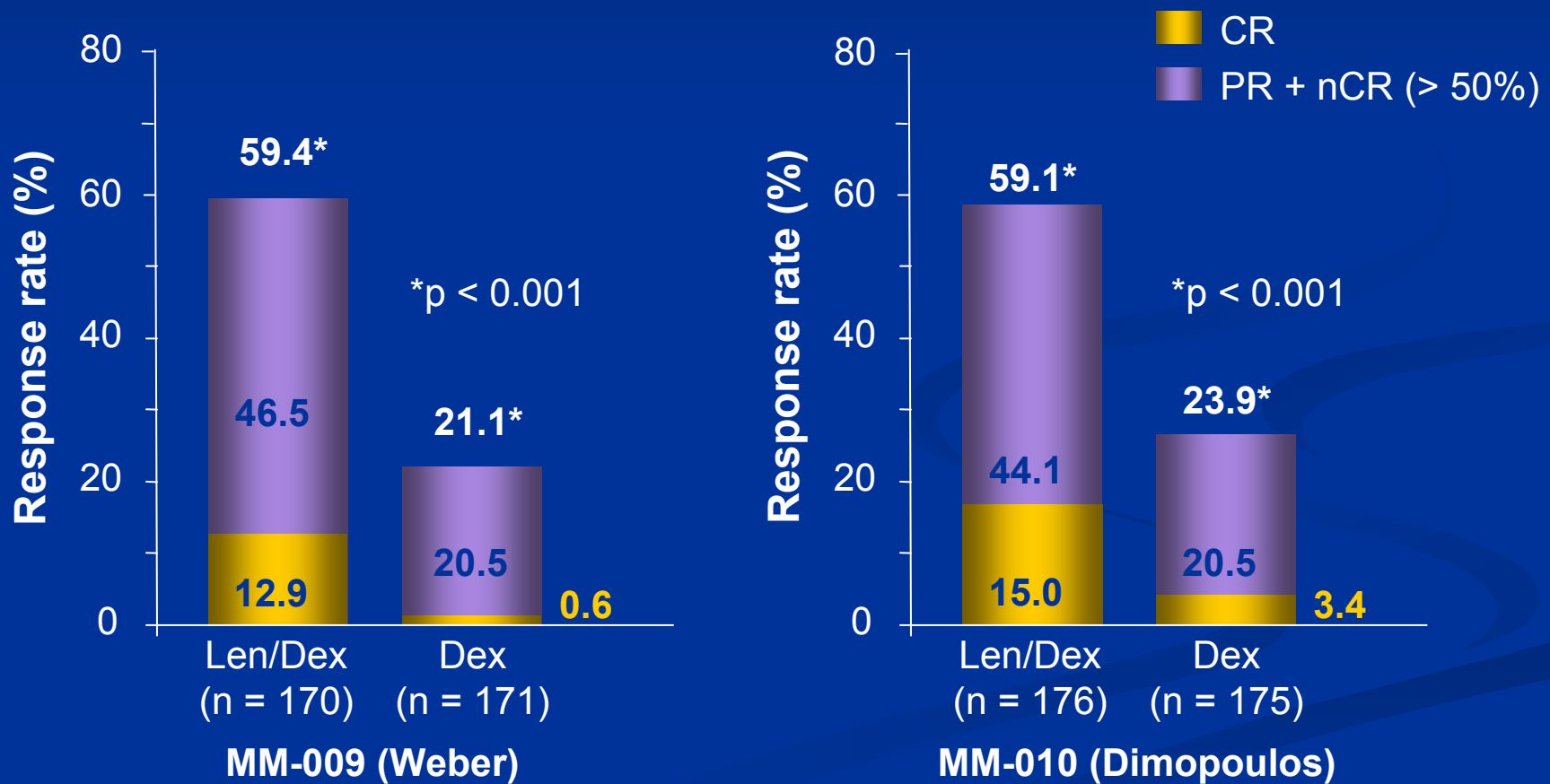
Primary end-point: TTP (by Bladé criteria)

Secondary end-points: OS, RR, safety, 1st skeletal-related event, PS

Additional stratification by β_2 M (≤ 2.5 mg/mL vs > 2.5 mg/mL), prior transplant (0 vs ≥ 1), and prior MM treatment regimens (1 versus > 1).

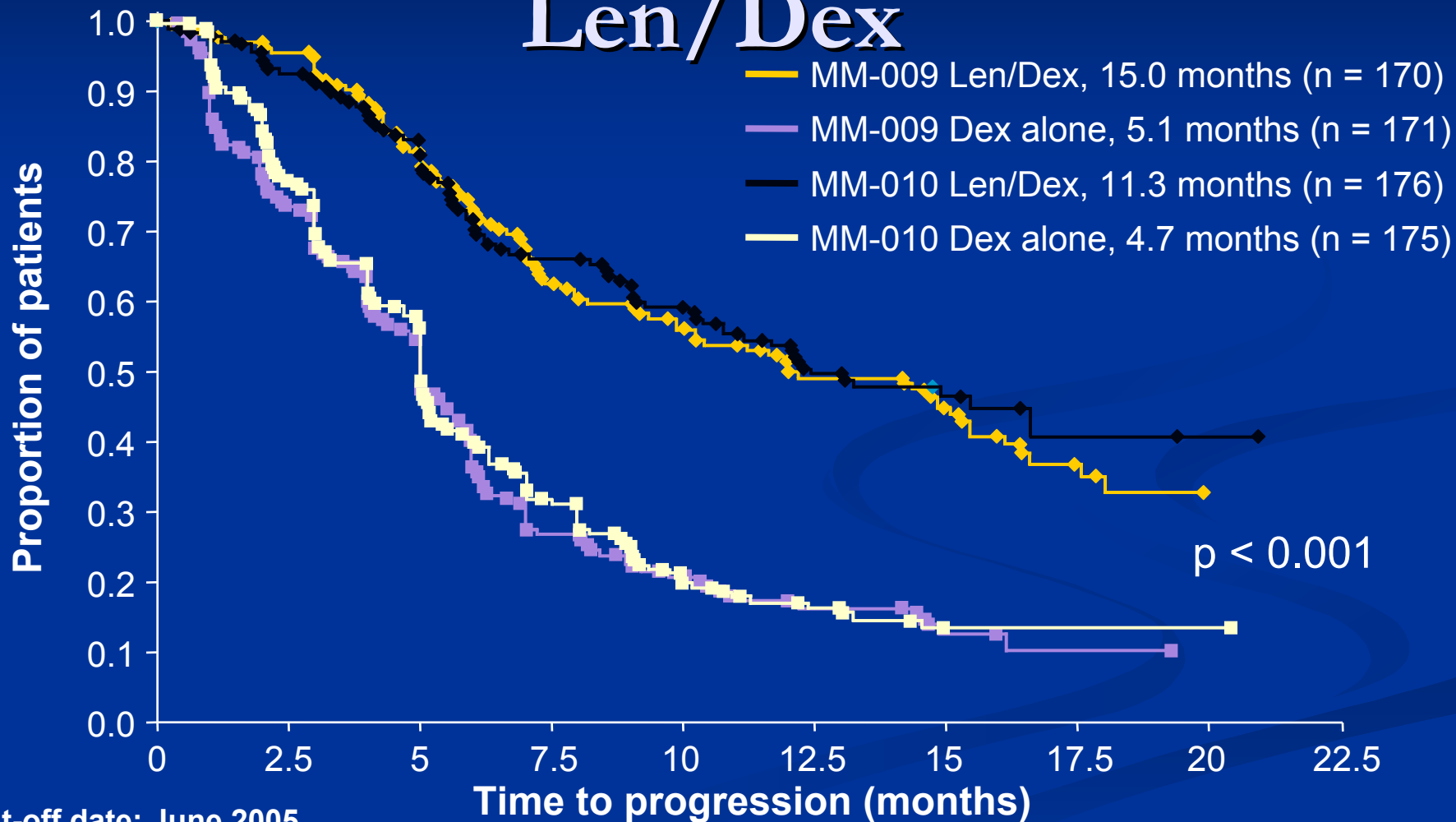
MM-009 and MM-010: higher response rates with Len/Dex

EBMT response data



Weber DM, et al. J Clin Oncol. 2006;24:[abstract 7521].
Dimopoulos M, et al. Blood. 2005;106:6a.

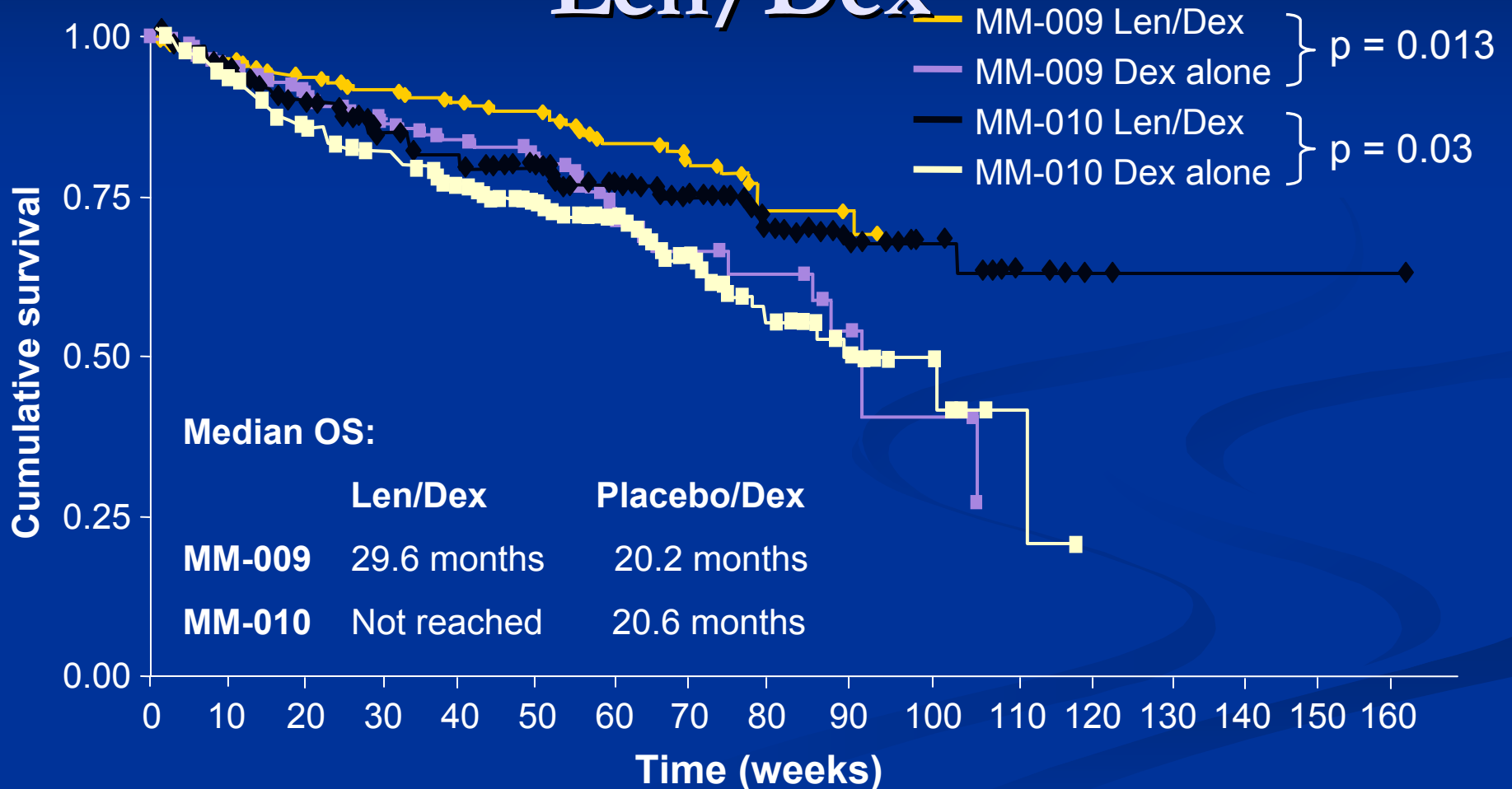
MM-009 and MM-010: longer time to progression with Len/Dex



Cut-off date: June 2005.

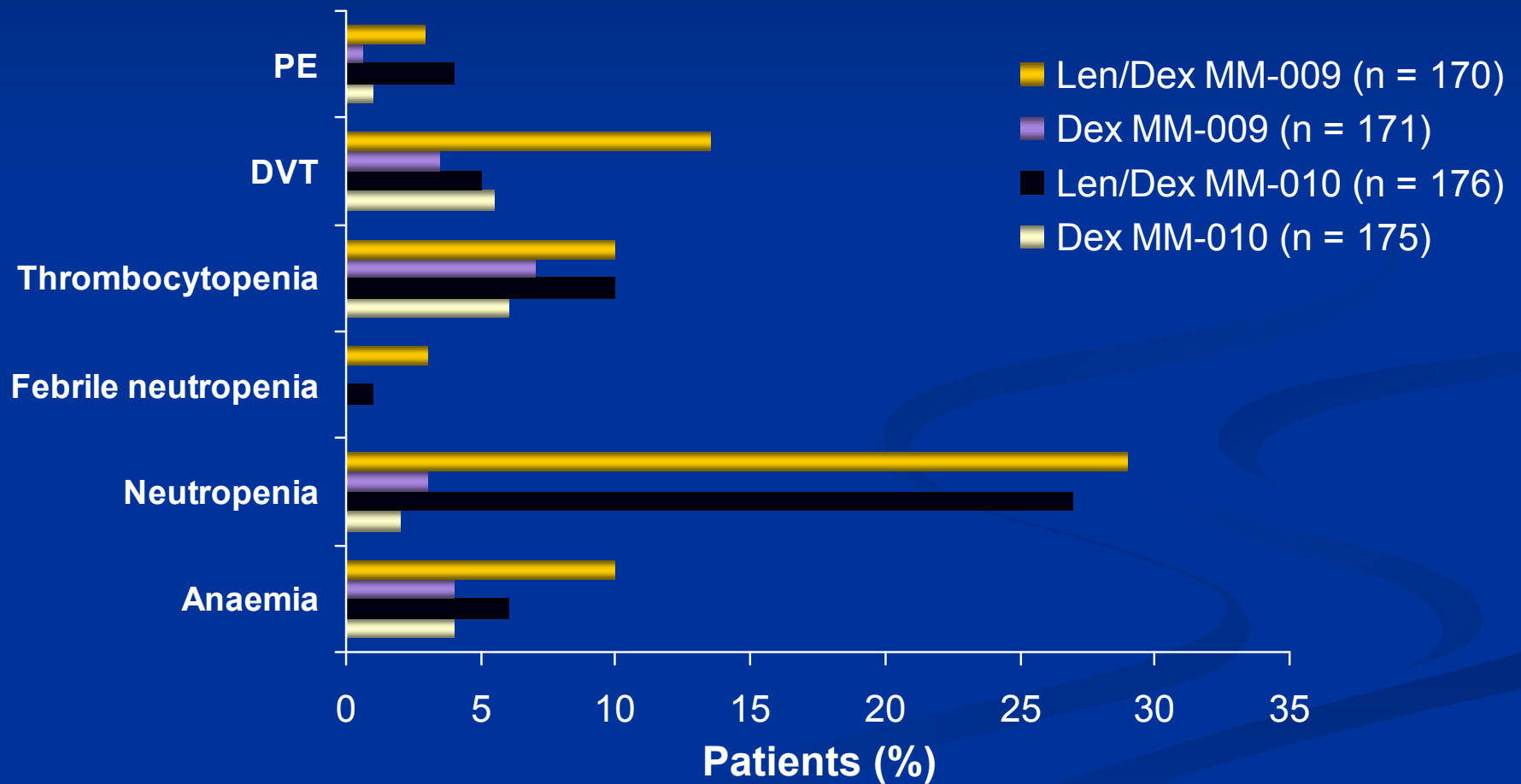
Weber D. Presented at ASCO Annual Meeting, 2005.
Dimopoulos M, et al. Presented at ASH Annual Meeting, 2005.

MM-009 and MM-010: increased overall survival with Len/Dex



Dimopoulos M, et al. Blood. 2005;106:6a.
Weber DM, et al. Presented at ASCO Annual Meeting, 2006.

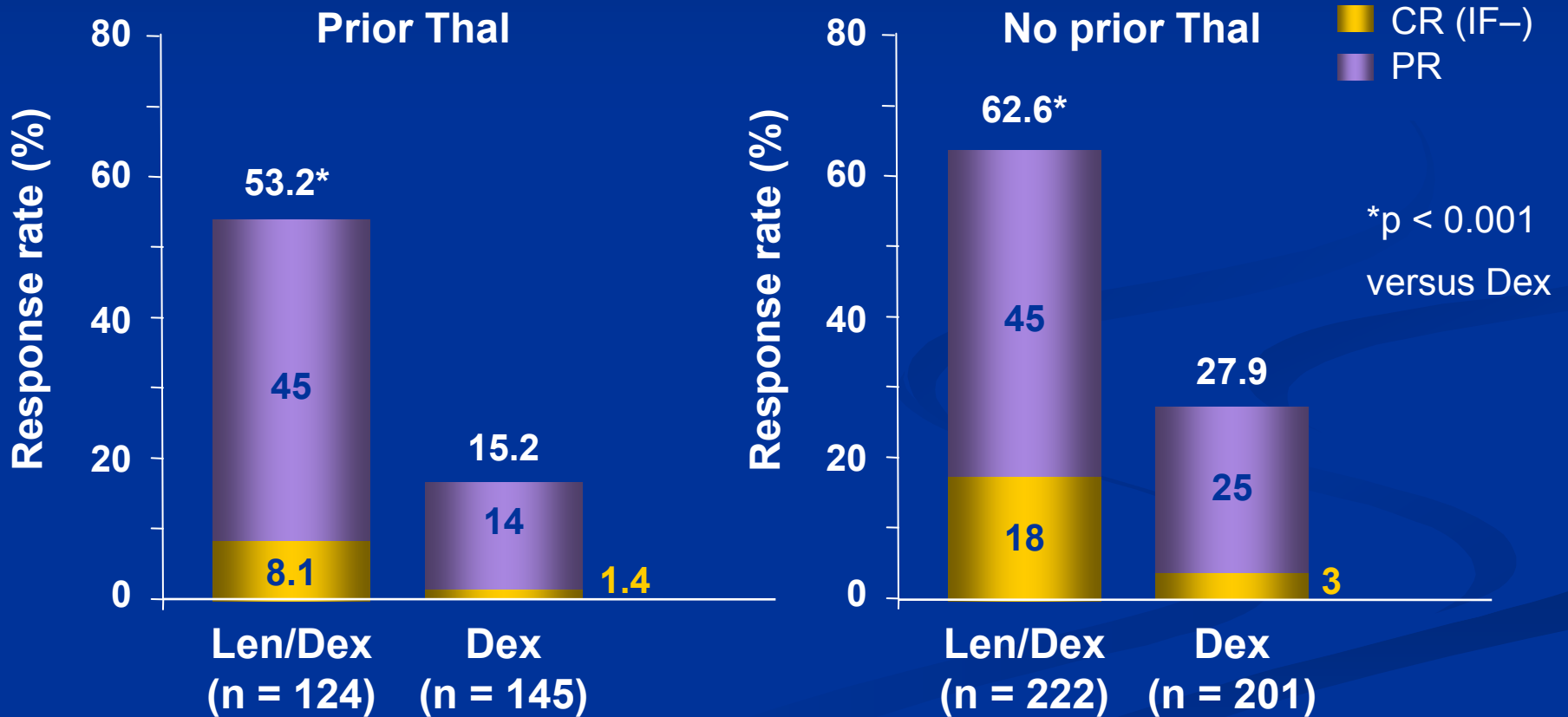
MM-009 and MM-010: grade 3/4 adverse events



Weber D. Presented at ASCO Annual Meeting, 2005.
Dimopoulos M, et al. Presented at ASH Annual Meeting, 2005.

Higher response rates with Len/Dex versus Dex regardless of prior thalidomide

- Subgroup analysis of MM-009 and MM-010



Lenalidomide dosing for patients with impaired renal function

Renal function (CL_{Cr})	Multiple myeloma	Myelodysplastic syndromes
Mild ($CL_{Cr} \geq 50$ mL/min)	25 mg qd (full dose)	10 mg qd (full dose)
Moderate ($30 \leq CL_{Cr} < 50$ mL/min)	10 mg qd *	5 mg qd
Severe ($CL_{Cr} < 30$ mL/min, <i>not</i> requiring dialysis)	15 mg q 48 hr	5 mg q 48 hr
ESRD ($CL_{Cr} < 30$ mL/min, requiring dialysis)	15 mg 3x a week following each dialysis	5 mg 3x a week following each dialysis

* Dose may be escalated to 15 mg qd after 2 cycles if patient is not responding to treatment

CL_{Cr} = creatinine clearance.
ESRD = end stage renal disease.

Data on file; Celgene Corp.

TOTAL THERAPY II

ROLE OF THALIDOMIDE (*Barlogie NEJM 2006*)

- 668 pts randomized to receive or not Thal during induction TX, consolidation and maintenance
- CR 62% vs 43% ($p < 0.001$)
- 5-year EFS 56% vs 44% ($p = 0.01$)
- No difference in OS (65%)
- due to shorter SV after relapse
1.1 yr vs 2.7 yr ($p = 0.001$)

CONCLUSIONS on the Role of Transplantation in Refractory/Relapse MM patients

- **All refractory / relapsed MM patients will receive rescue treatment with novel agents before transplant.**
- **The efficacy of Trx as rescue treatment should be re-evaluated in prospective trials including novel agents**

SINGLE vs DOUBLE ASCT RANDOMIZED STUDIES

	No. of pts	Age	Results
IFM 94 (<i>N Engl J Med</i> 03)	399	< 61	EFS and OS ↗
MAG 95 (<i>Sydney 05</i>)	227	< 56	OS ↗
Bologna (<i>Sydney 05</i>)	220	< 61	EFS ↗
GMMG (<i>Sydney 05</i>)	261	< 66	EFS ↗
Hovon (<i>Sydney 05</i>)	303	< 66	CR and EFS ↗