

NEW DEVELOPMENTS IN

MULTIPLE MYELOMA

MADRID, SPAIN

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The Role and Timing of Autologous SCT for Multiple Myeloma in 2008

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ASCT vs Conventional CT

Results of Randomized Studies

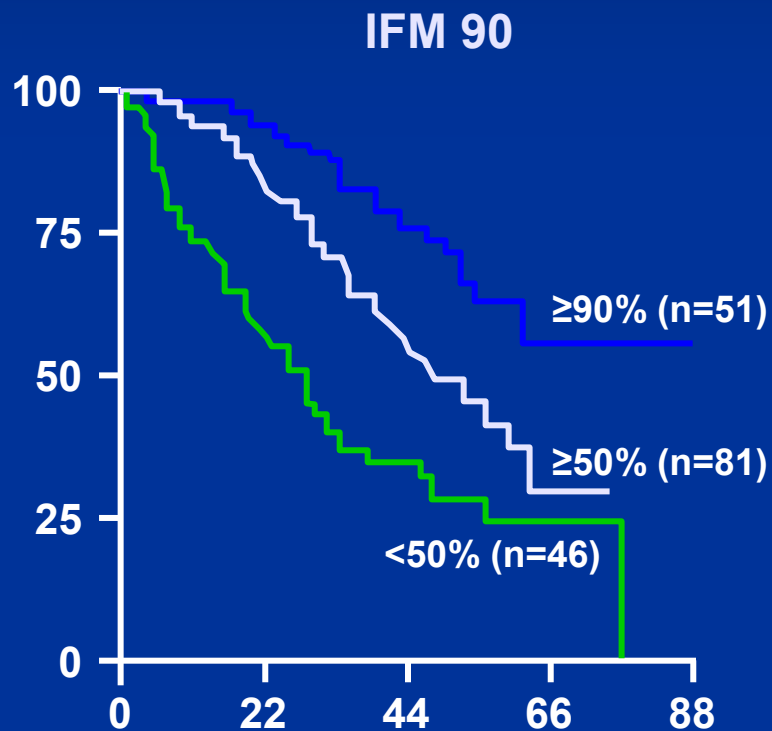
Author	N of pts	Age	CR rate	EFS	OS
Attal 1996	200	≤65	38% vs 14% ***	7-yr EFS 16% vs 8%	7-yr OS 43% vs 27%
Fermand 1998**	185	≤ 55	19% vs 5%	39 m vs 13m	65m vs 64m
Child 2003	401	≤ 65	44% vs 8%	32m vs 20m	54m vs 42m
Palumbo 2004	195	<70	25% vs 6%	28m vs 15m	58m+ vs 42m
Fermand 2005	190	55-65	42% vs 20% ***	25m vs 19m	48m vs 47m
Blade 2005*	164	<65	30% vs 11%	42 m vs 33m	61m vs 66m
Barlogie 2006 *	516	≤ 70	11% vs 11%	7-yr PFS 17% vs 16%	7-yr OS 37% vs 42%

•Randomized after induction Chemo

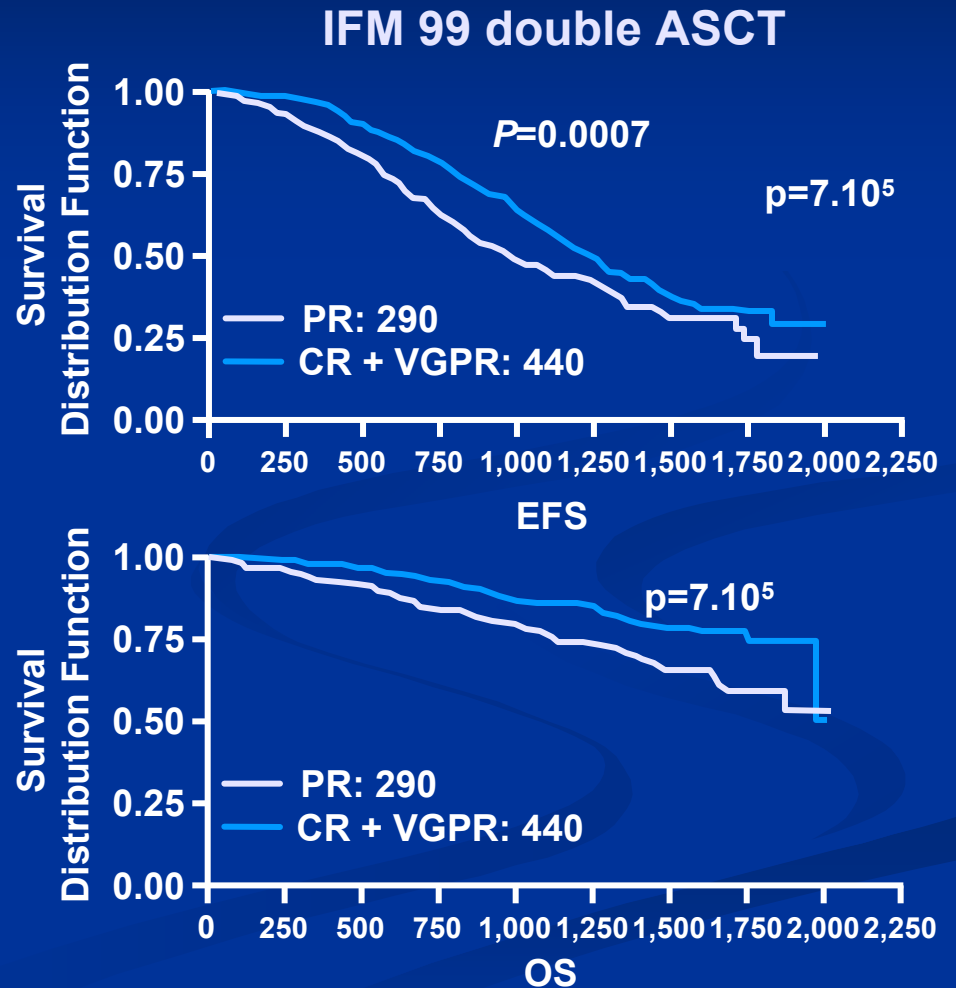
** early vs late ASCT

*** CR + VGPR

Impact of CR + VGPR on outcome



Attal NEJM 96



Haroussesau ASH 2006

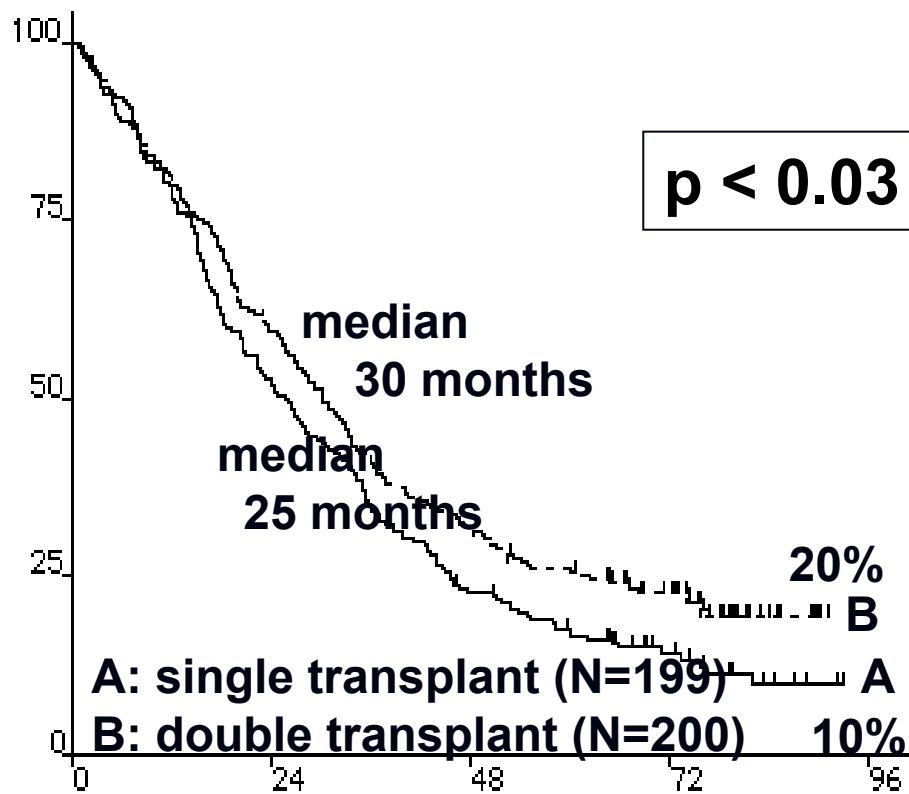
Conventional Chemotherapy vs ASCT Randomized Studies

- **ASCT: CR + VGPR increase in 6/7 studies**
- **EFS : ASCT is superior to CC when CR + VGPR rate is improved (5/6 studies)**
- **OS depends on salvage Tt. However OS is improved with either early or late ASCT (5 years median OS vs 3-4 years with CC)**
- **If the results of CC are improved, the benefit of ASCT is probably no more significant**
- **Comparisons CC/ASCT are now irrelevant since results of both approaches have improved !!!**

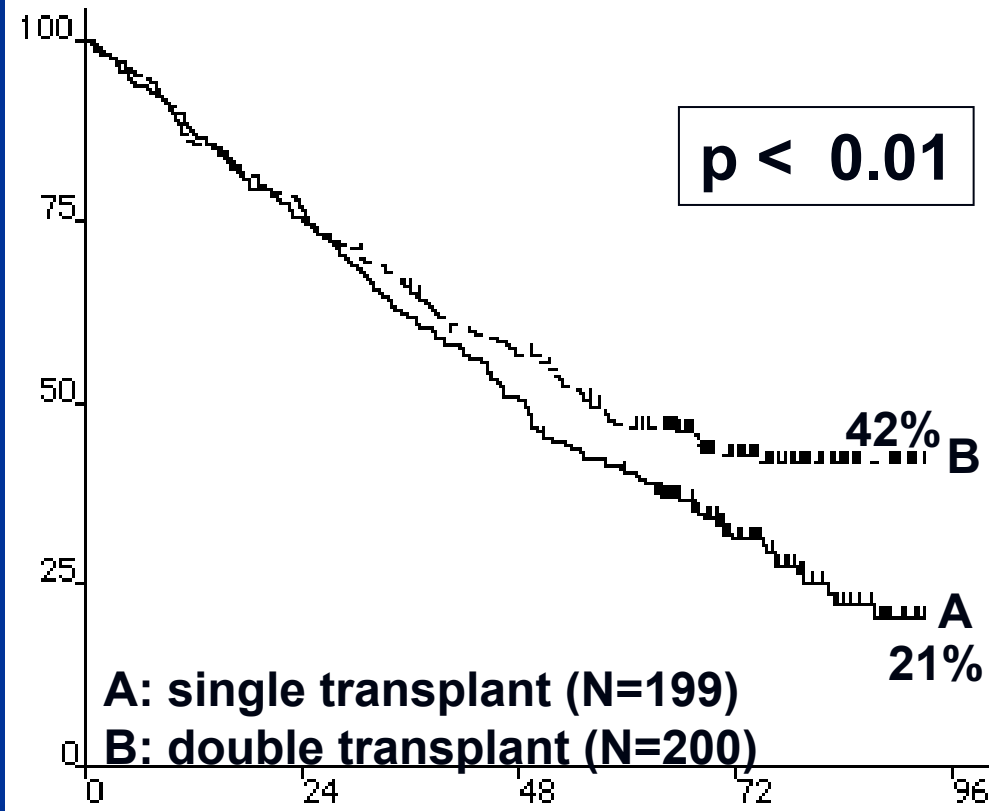
**IS IT POSSIBLE TO
FURTHER IMPROVE ASCT
RESULTS ?**

IFM 94

EFS



Overall Survival



Single versus double ASCT results of published randomized

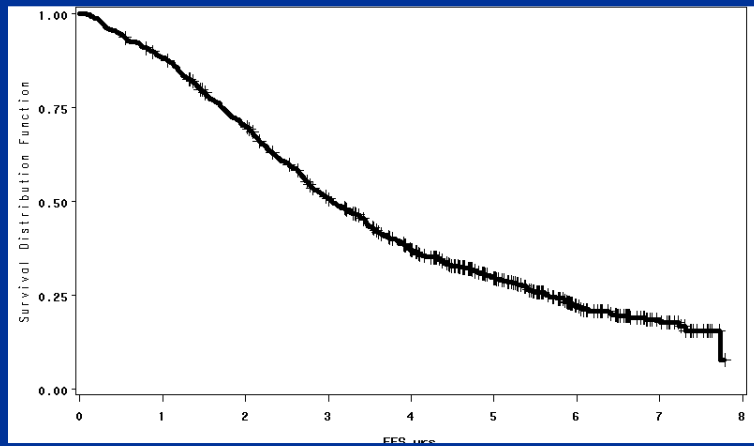
	Number of patients	EFS	OS
IFM 94 Attal NEJM 03	399	7-yr = 10% vs 20% (p < 0.03)	7-yr 21% vs 42% (p < 0.01)
Bologna 96 Cavo et al JCO 07	321	Med 23 m vs 35 m (p < 0.001)	7 -yr 43% vs 46% (p = 0.90)
Hovon 24 Sonneveld Haematol 07	304	Med 21 m vs 22 m 6-yr 15% vs 7% (p = 0.013)	Med 50 m vs 55 (p = 0.51)

IFM 99 trials

Double ASCT

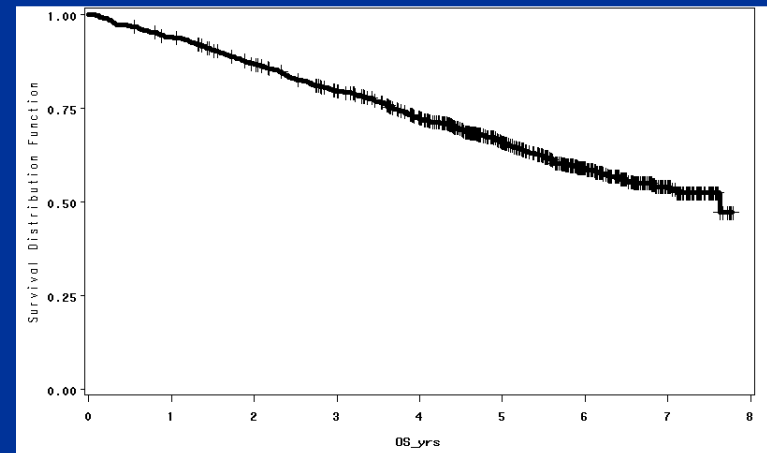
EFS

Median 3y

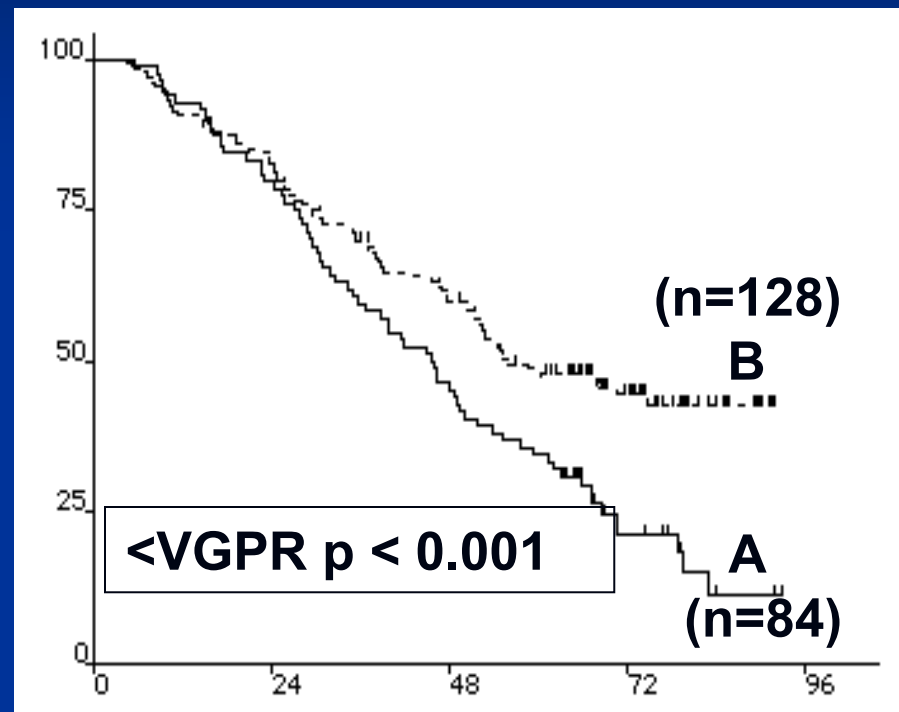
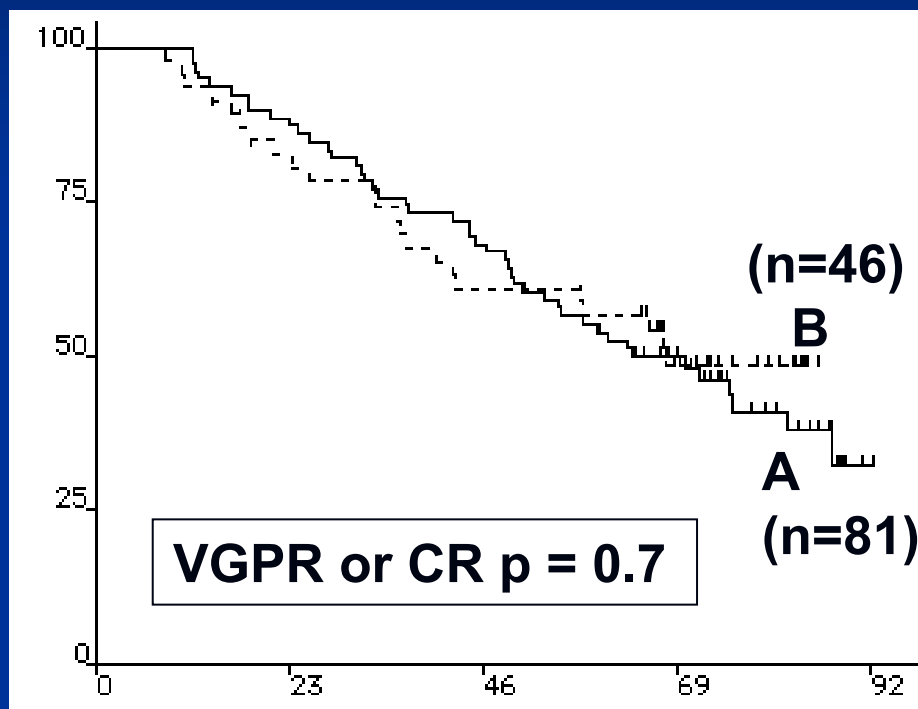


OS

Median NR at 7 y



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



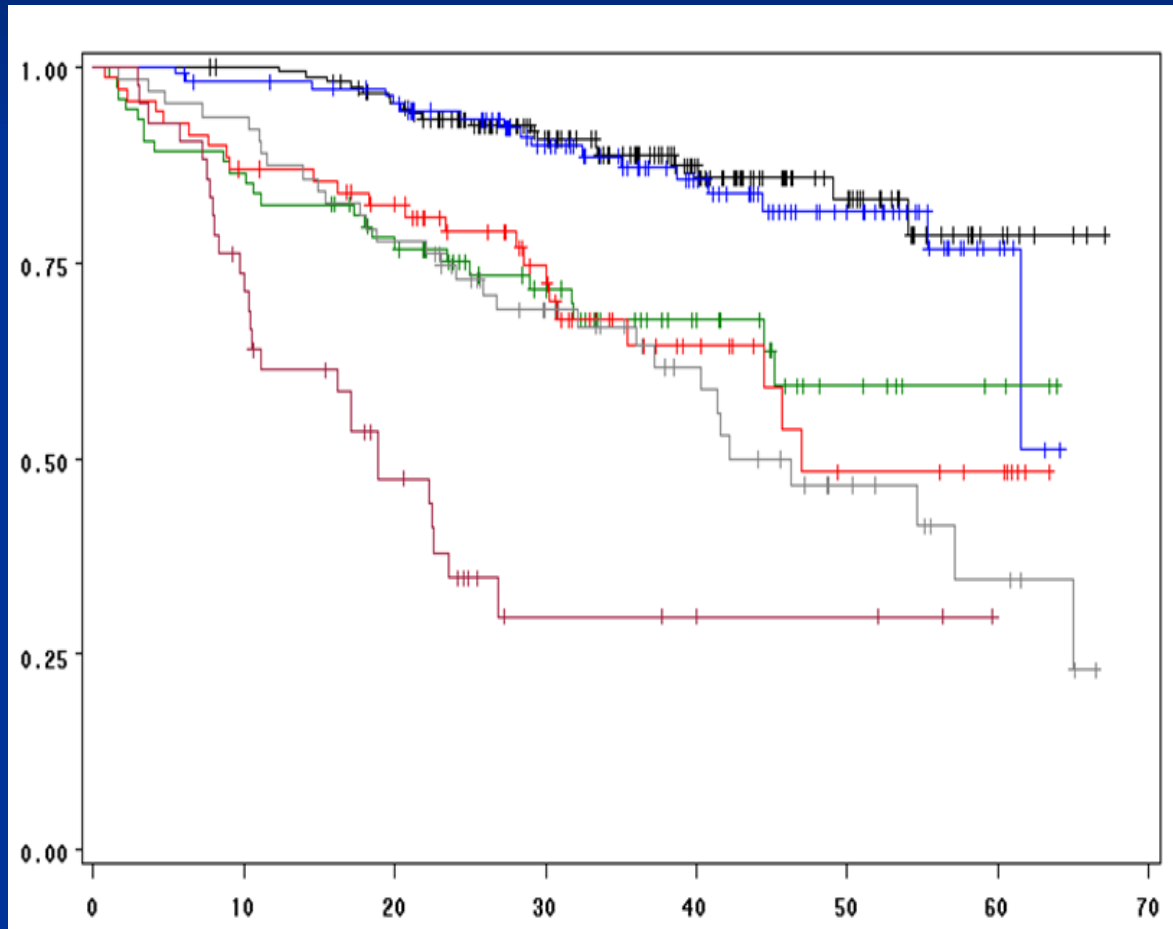
Attal NEJM 2003

Cytogenetic + b2m model

H Avet Loiseau Blood 2007

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



NOVEL AGENTS IN COMBINATION WITH ASCT

MAINTENANCE

IFM 99 02 : Study Design

**Inclusion: Δ 13 ; β 2m
(0 or 1 Factor)**

- **VAD x 3**
- **Mel-140 + PBSC**
- **Mel 200 + PBSC**

Randomization

No maintenance

Pamidronate

Pami + Thali

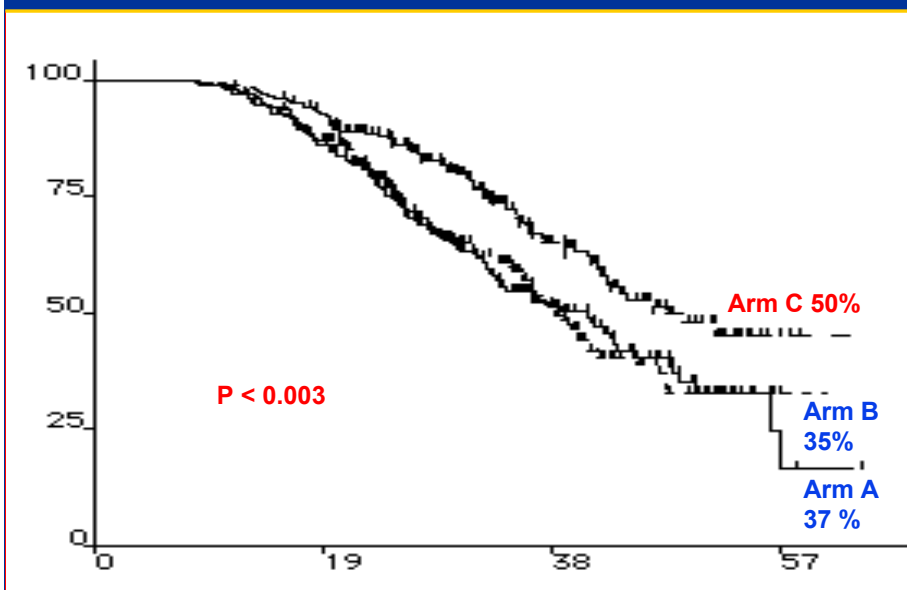
IFM 99 02 (Attal M Blood 2006)

Response Rate $\geq 90\%$

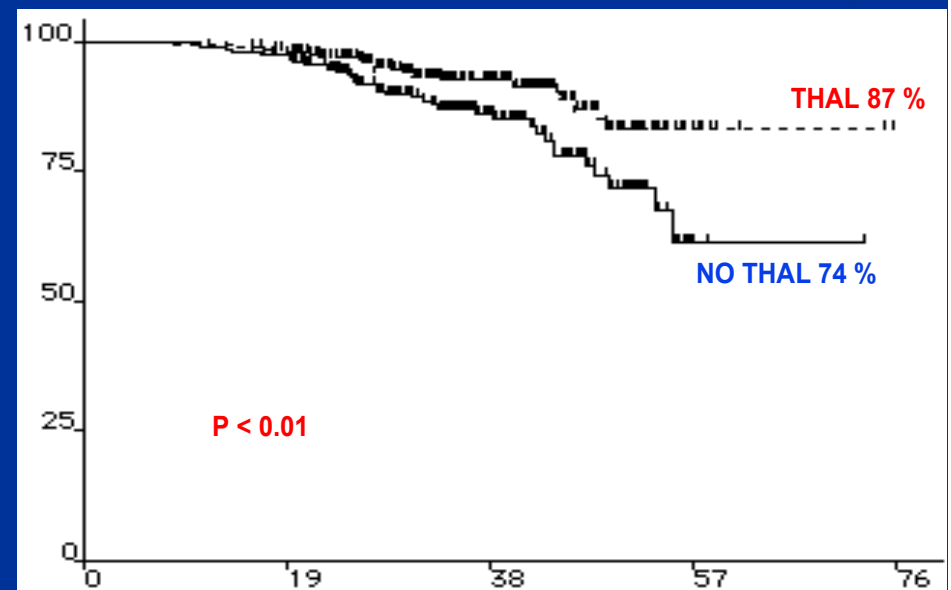
	No tt n=200	Pam n=196	Pam/Th an=201	p
▪ After VAD	15%	15%	16%	NS
▪ At Random	47%	47%	50%	NS
▪ After Random	55%	57%	67%	0.001

Role of Thalidomide as Post ASCT maintenance Tt

4-yr EFS



4-yr OS



Attal Blood 2006

Other Studies on Post-ASCT With Thalidomide

	N	Dose	CR Rate	PFS	OS
Barlogie <i>N Engl J Med</i> 2006	668	400 until prog or AE	62% vs 43%	5-yr PFS 56% vs 44%	NS
Abdelkefi Blood 2007†	140	100 6 m	67% vs 51%	3-yr PFS 85% vs 57%	3-y OS 85% vs 65%
Spencer IMMW 2007‡	243	200 12 m	24% vs 15%	2-yr PFS 63% vs 36%	2-yr OS 91% vs 80%

† Single ASCT + thalidomide vs double ASCT

‡ Thal/PDN vs PDN

OPTIMAL SCHEDULE ?

	Dose	Duration	Discontinuation	Grade ^{3/4} PN
Barlogie (NEJM 2006)	Start 400 mg/D	From onset → relapse	30% *	27%
Attal (Blood 2006)	Start 400 mg/D med 200mg/D	From ASCT → relapse med duration 15 months	39%	7%
Abdelkefi (Blood 2007)	100 mg/D	6 months	9%	4%
Spencer (IMW 2007)	200mg/D	12 months	31%	10%

* within 2 years

INDUCTION TREATMENT PRIOR TO ASCT

Thal-Dex prior to ASCT

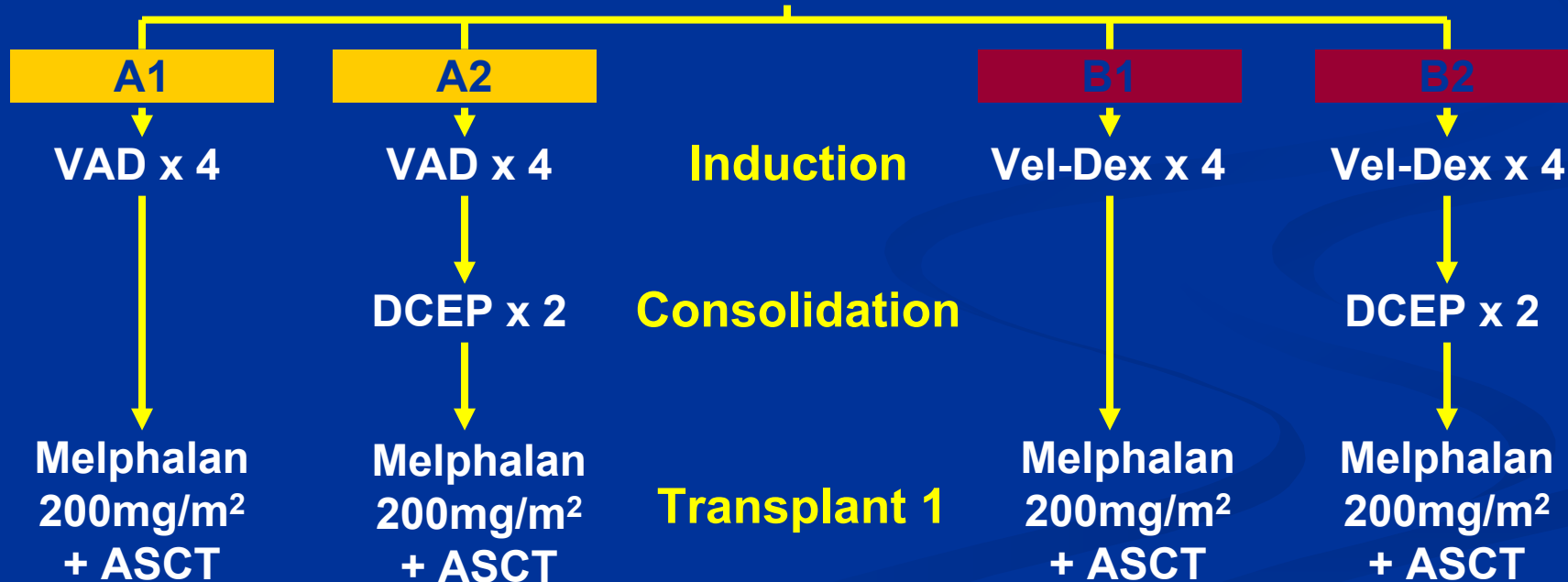
	TD vs D	TD vs VAD	TD vs VAD
Author	Raikumar <i>J Clin Oncol</i> 2006	Cavo <i>Blood</i> 2005	Macro <i>ASH</i> 2006
Pts (N)	201	200	204
RR prior to ASCT	69% vs 51% No \neqce in CR rate	76% vs 52% No \neqce in CR rate	VGPR 35% vs 17%
RR after ASCT	–	–	VGPR 44% vs 42%
DVT	17% vs 3%	15% vs 2%	23% vs 7.5%

Vel/Dex IFM 2005-02 (ASH 2007)

Primary analysis: post-induction response in VAD (A1+A2) vs Vel-Dex (B1+B2)

Randomization

stratified by β_2 -microglobulin level ($>3\text{mg/L}$ vs $\leq 3\text{mg/L}$) and presence of chromosome 13 abnormalities (by FISH analysis)



Second ASCT or RIC allo if <VGPR

Response to Induction Intention-to-Treat (ITT) Analysis

	VAD (A1+A2) N=242	Vel-Dex (B1+B2) N=240	P value
CR	2.9%	9.6%	0.0023
CR+nCR	8.3%	21.3%	< 0.0001
≥ VGPR	18.6%	46.7%	< 0.0001
≥ PR	62.8%	80.0%	< 0.0001
MR+SD	23.6%	10%	
PD	3.3%	4.2%	
Death	2.9%	0.8%	
NE	7.4 %	3.8 %	

Response by Investigator Assessment

Harousseau *et al.* ASH 2007 (abstract 450)

Post-ASCT Response ITT Analysis

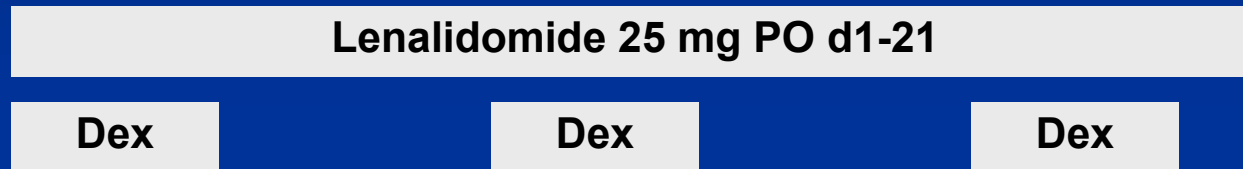
	VAD (A1+A2) N=242	Vel-Dex (B1+B2) N=240	
CR + nCR	23.6%	35.0%	0.0056
≥ VGPR	41.7%	61.7%	
≥ PR	72.7%	80.4%	
MR/SD/PD	2.9%	2.5%	
NE	24%	17%	

Harousseau *et al.* ASH 2007 (abstract 450)

Treatment Schedule

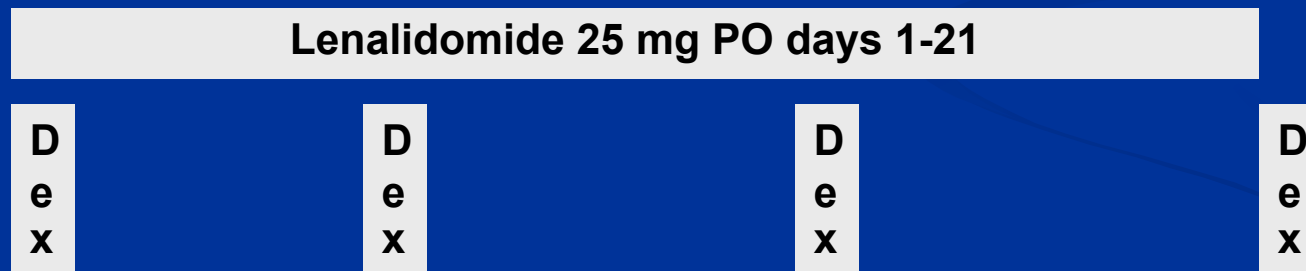


RD



Total Dex
dose per
Cycle =
480 mg

Rd



Total Dex
dose per
Cycle =
160 mg

Response within 4 cycles

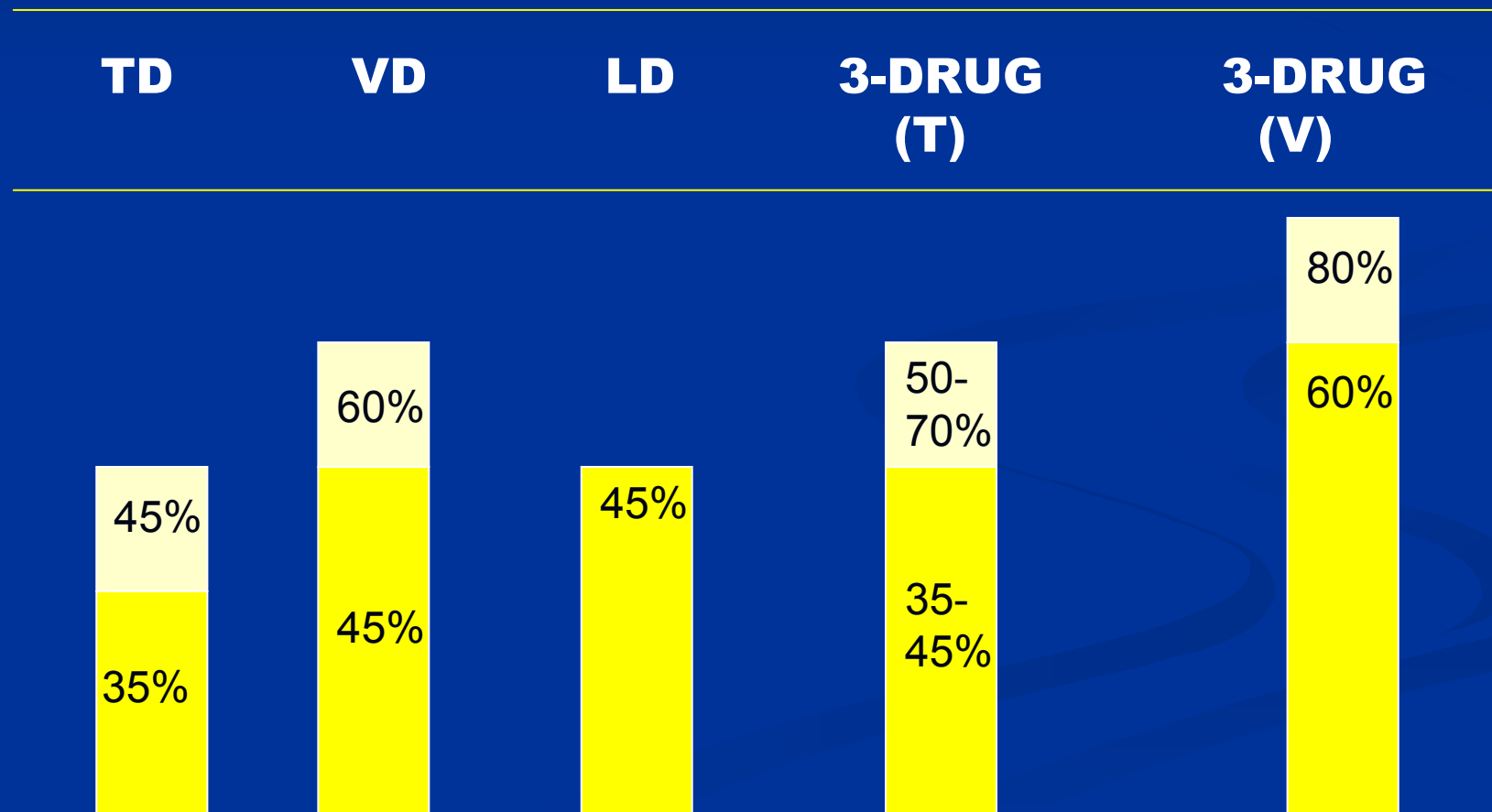
Rajkumar ASH 2007

	Arm A N=196	Arm B N=190	Total N=386	Fisher's Exact p-value 2-sided
➤PR	82%	70%	76%	0.007
CR+VGPR	44%	26%	35%	<0.001

3-drug INDUCTION TREATMENT RESULTS OF RANDOMIZED STUDIES

	TAD vs VAD	TCD vs CVAD	VTD vs TD
	Lokhorst Haematologica 2008	Morgan ASH 2007	Cavo ASH 2007
Number of patients	402	251	256
Post Induction			
CR+VGPR	33% vs 15%	38% vs 26%	60% vs 27%
Post ASCT			
CR+VGPR	49% vs 32%	67% vs 43%	77% vs 42%

Induction treatment VGPR rate



Combination of novel agents in the ASCT paradigm

Total Therapy 3 (Barlogie ASCO 2007)

- **Complex protocol with 2 cycles of V-DTPACE as induction, double ASCT, V-DTPACE consolidation, maintenance with VTD**
- **2-yr CR + n-CR 80%**
2-yr EFS 84% 2-yr OS 87%
- **TT 3 appears to overcome poor prognosis related to t(4;14) and is superior to TT2 in poor risk MM**

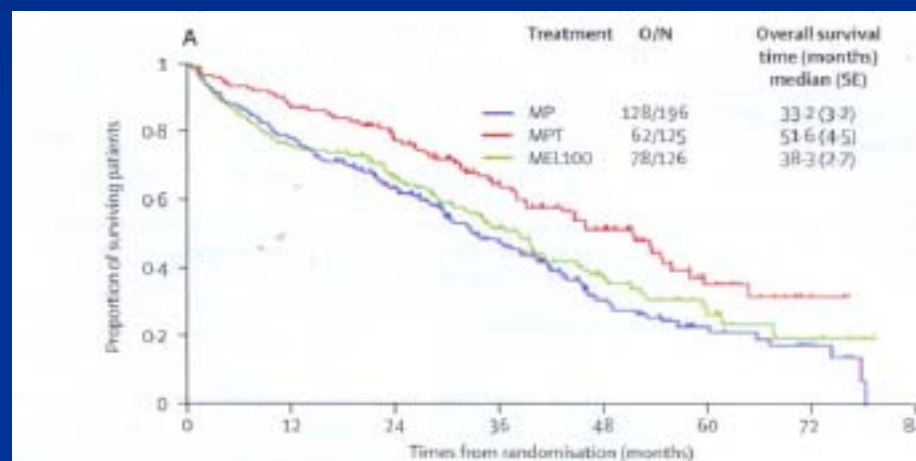
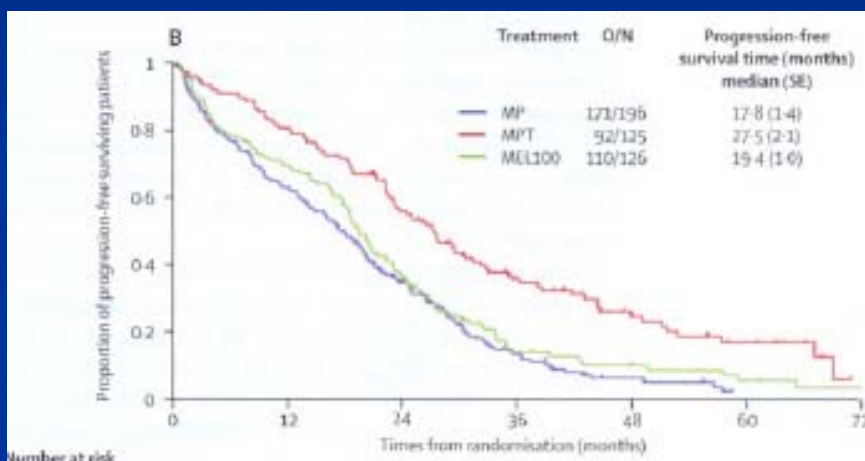
**NOVELS AGENTS
INSTEAD OF ASCT**

MP-Thal vs MP vs MEL100

T. Facon Lancet 2007

PFS

OS



MP
N=196

MPT
N=125

Best response at 12 months

CR

2%

13%

CR+VGPR

7%

47%

Median PFS

18 m

28 m

Median OS

52 m

33 m

VISTA TRIAL

VMP vs MP

(J. San Miguel ASH 2007)

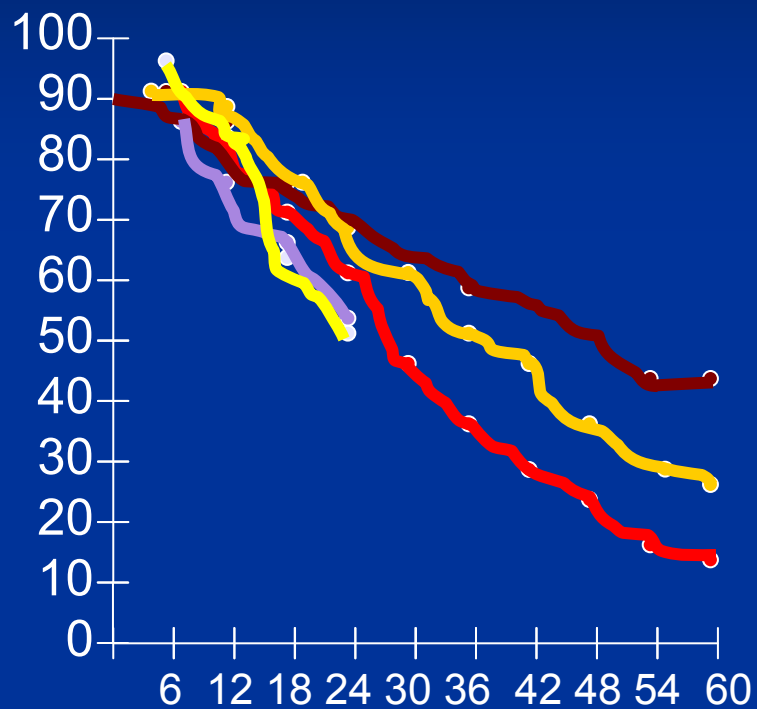
	MP	MPT
	N = 335	n= 336
CR	15%	35%
CR+VGPR	10%	45%
Median PFS	17 m	24 m
2-year OS	70%	83%

NOVEL AGENTS AS PRIMARY TREATMENT

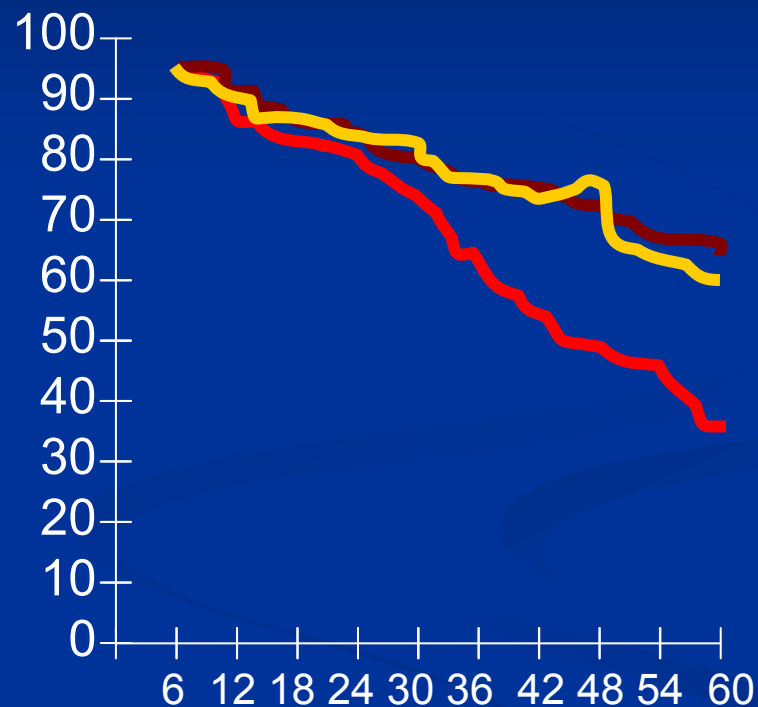
	MPT T. Facon (Lancet 2007)	MPT A. Palumbo (Lancet 2006)	MPV J. San Miguel (ASH 2007)	Single ASCT No maintenance
CR	13%	16%	35%	20-40%
CR+VGPR	47%	36%	45%	20-50%
Median PFS	28 m	54% at 2 y	24 m	25-35 m

Novel Agents vs Double ASCT

PFS



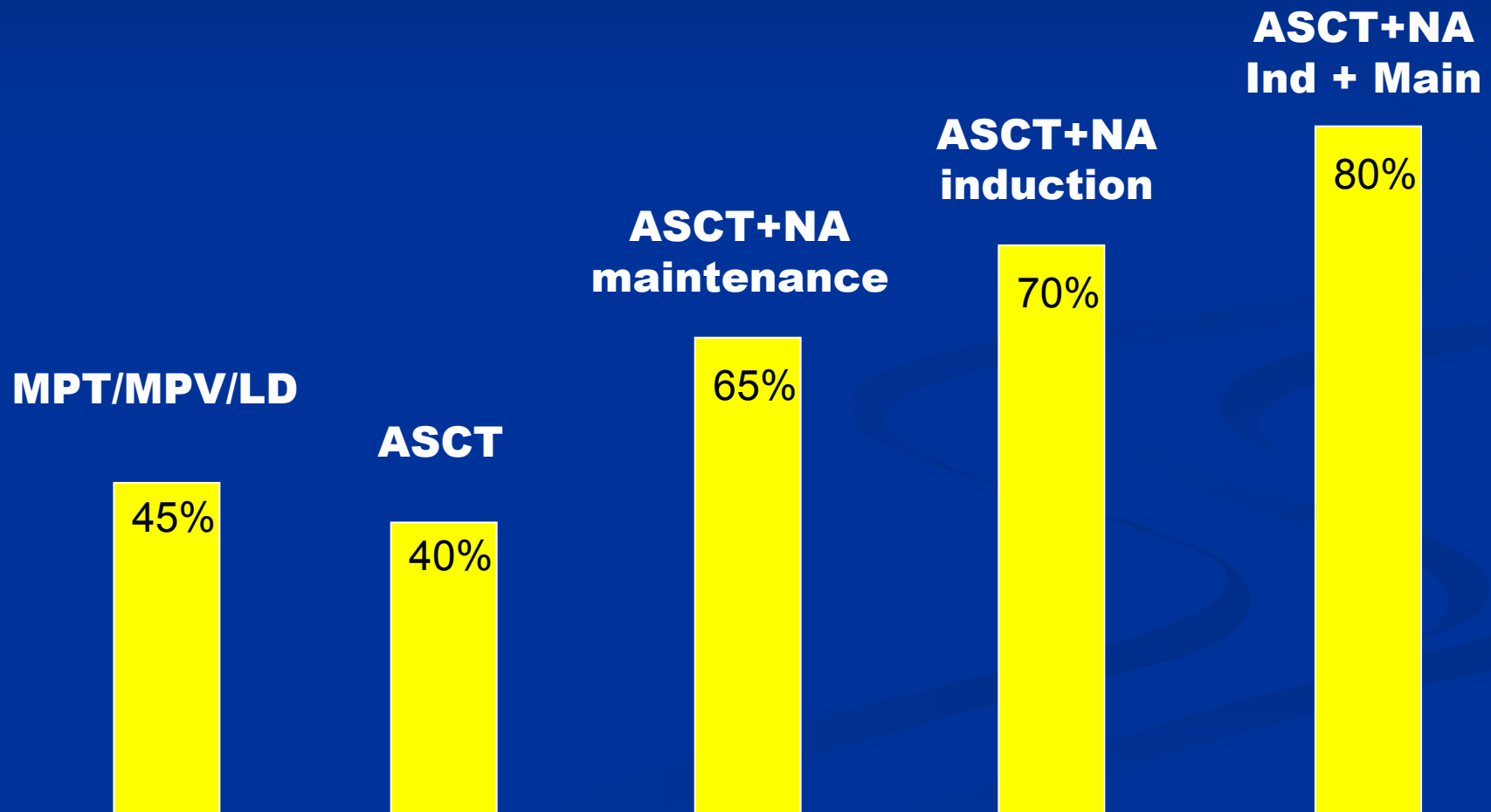
OS



- MPT Facon**
- Barlogie TT2 without Thal**
- MPT Palumbo**
- MPV**
- IFM 99**

- MPT Facon**
- TT2**
- IFM 99**

Novel agents with and without ASCT VGPR rates



Novel Agents with or without ASCT

	MPT / MPV	ASCT + NA maintenance	NA Induction + ASCT	Induction ASCT + maint
CR + VGPR	35 – 45 %	> 60 %	60 – 80 %	80%
PFS	Med ≈ 28 m	Single ASCT 85% at 3 yr Double ASCT 50-65 % at 4 yr	NA	85 % at 2yr ?

CONCLUSION

- 1) Prolonged treatment with novel agents yields CR/VGPR rates (35-45%) and PFS rates (up to 50 % at 2 yr) that are comparable to those achieved with single ASCT without maintenance**
- 2) The addition of novel agents to HDT yields much higher CR/VGPR rates (60-80%) and much longer PFS (up to 80% at 2y)**
- 3) The only acceptable comparison is therefore NA + ASCT upfront vs NA +ASCT at relapse**

100 VERSUS 400 TOXICITY

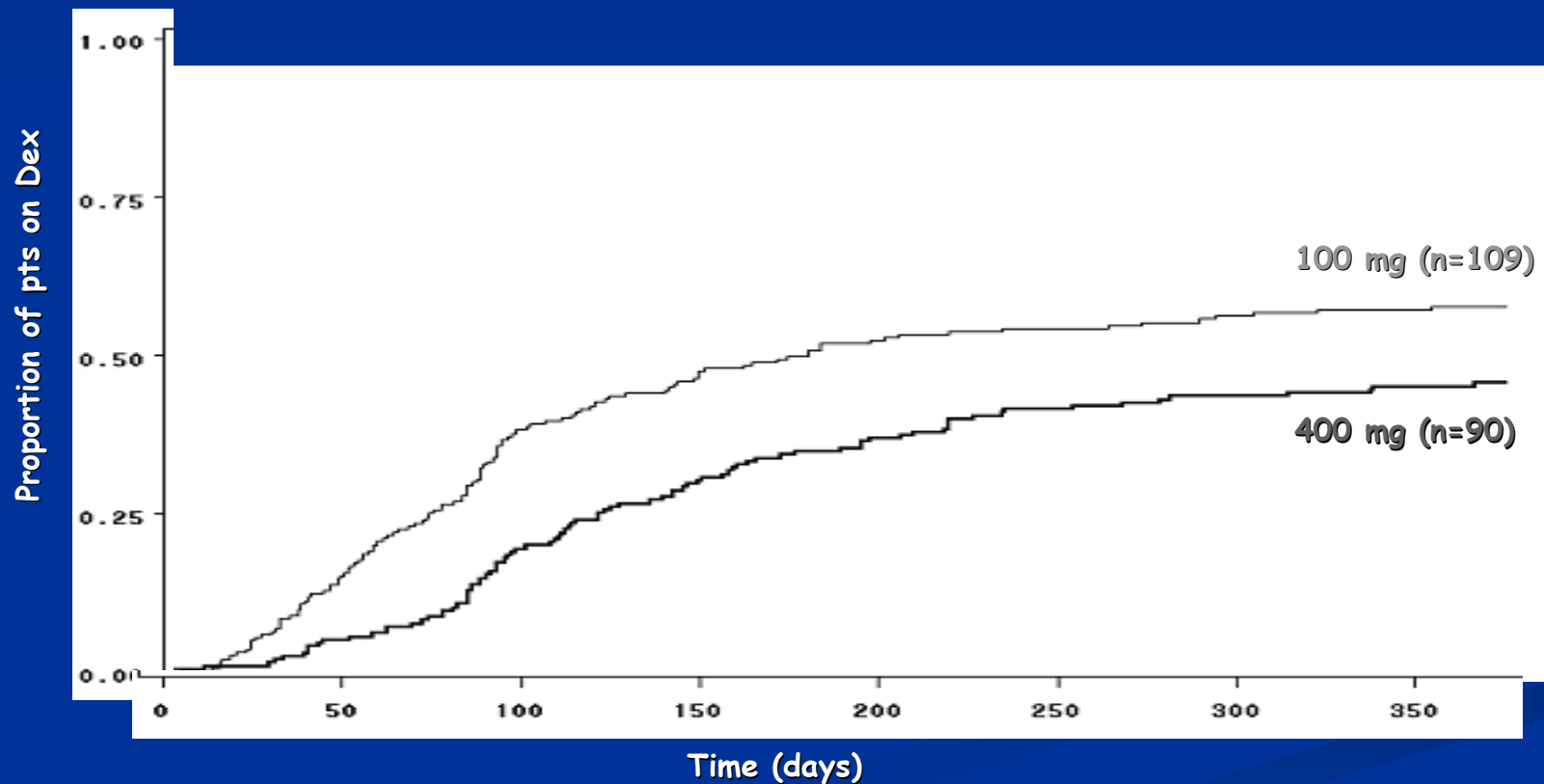
Percentage of grade ≥ 2 side effects

	400mg/D	100mg/D	p
Drowsiness	33	13	< 0.001
Constipation	40	28	0.01
P. Neuropathy	32	19	0.05
DVT	9	7	NS

Yakoub Agha (ASH 2005)

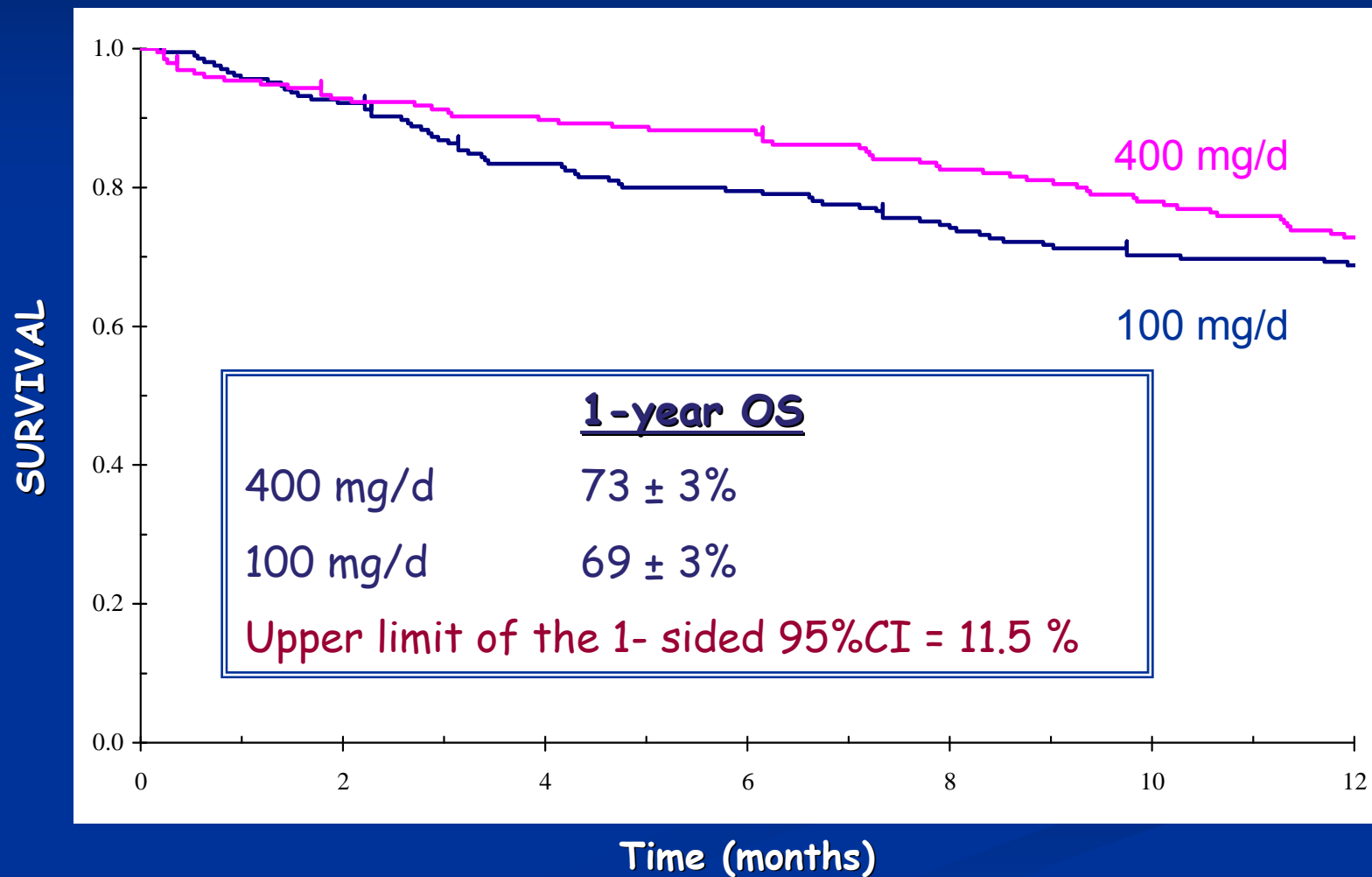
DEXAMETHASONE ADDITION IN THE 400 PATIENTS ACCORDING TO TREATMENT ARM

P= .002



Yakoub Agha (ASH 2005)

OVERALL SURVIVAL IN THE 400 PATIENTS ACCORDING TO TREATMENT ARM



Yakoub Agha (ASH 2005)

CONCLUSION

- THAL 100 mg/d \pm Dex is comparable in terms of survival with 400 mg/d \pm Dex in pts with RRMM.
- THAL 100 mg/d is better tolerated than 400 mg/d specific with less drowsiness, constipation, and peripheral neuropathy