TREATMENT OF MULTIPLE MYELOMA CURRENT STATUS AND FUTURE DIRECTIONS

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TREATMENT OF MM

CONVENTIONAL CHEMOTHERAPY

Gold Standard : MP

- Melphalan + Prednisolone (per os 1 4-day course every 4 to 6 weeks)
- Introduced in the early sixties
- No significant improvement with the addition of other agents
- < 50% PR, very rare CR

→ Standard > 65 years unfit for ASCT

High-dose dexamethasone (VAD)

- More rapidly active but more toxic (infections)
- Less toxic for stem cells

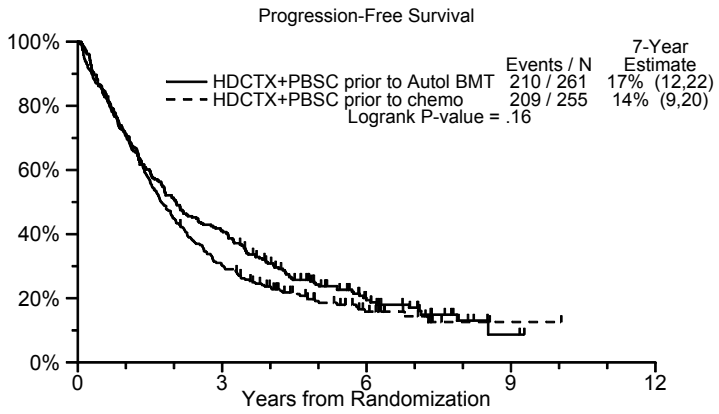
→ Standard ≤ 65 years as induction prior to ASCT

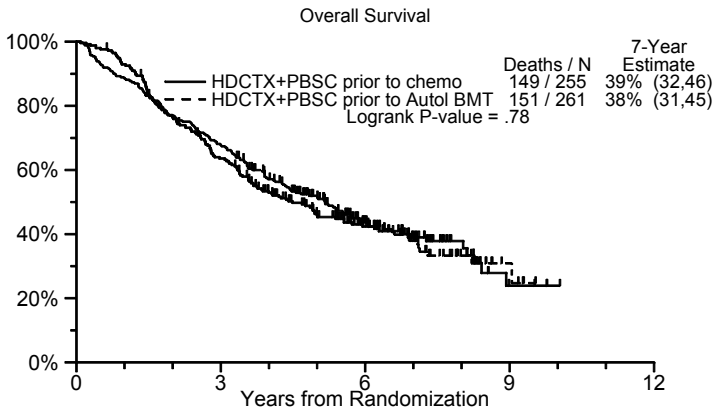
CONVENTIONAL CHEMOTHERAPY (CC) vs ASCT RANDOMIZED STUDIES

	No. of pts	Age	CR rate	Median EFS	Median OS
IFM90 *(N Engl J Med 96)*	200	≤ 65	5 vs 22**	18 vs 28**	44 vs 57**
MRC7 *(N Engl J Med 03)*	401	≤ 65	8 vs 44**	19 vs 31**	42 vs 54**
Italian MMSG *(Blood 04)*	194	50-70	6 vs 25**	16 vs 28**	42 vs 58+**

* 2 courses of IDM (100mg/m²)
** Significant

SWOG 9321


Progression-Free Survival
Events / N
7-Year Estimate
HDCTX+PBSC prior to Autol BMT 210 / 261 17% (12,22)
HDCTX+PBSC prior to chemo 209 / 255 14% (9,20)
Logrank P-value = .16
100%
80%
60%
40%
20%
0%
0
3
6
9
12
Years from Randomization

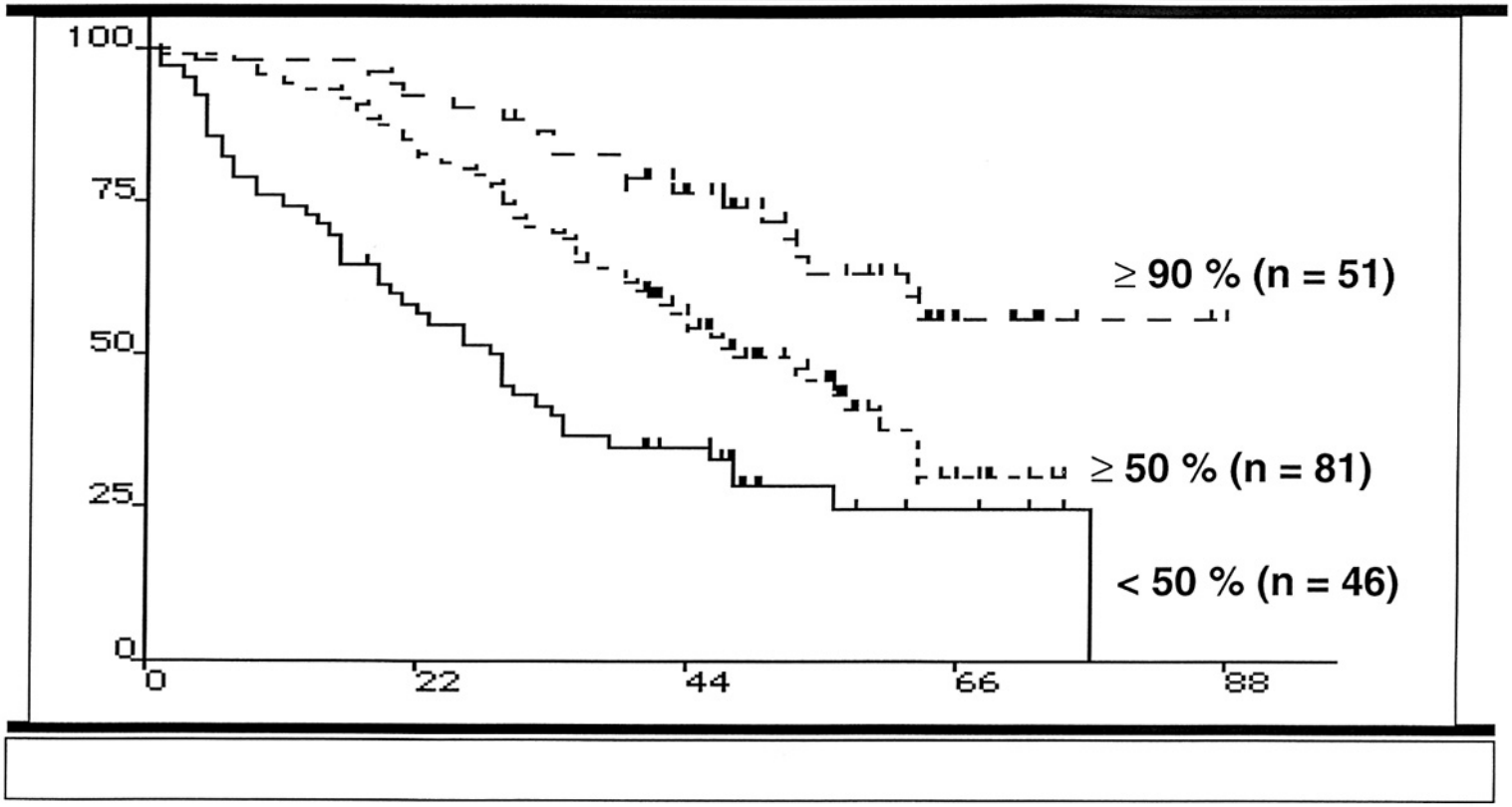

Overall Survival
Deaths / N
7-Year Estimate
HDCTX+PBSC prior to chemo 149 / 255 39% (32,46)
HDCTX+PBSC prior to Autol BMT 151 / 261 38% (31,45)
Logrank P-value = .78
100%
80%
60%
40%
20%
0%
0
3
6
9
12
Years from Randomization

Comparison of IFM 90 and US Intergroup trials
Chemotherapy better in US study

		IFM 90 N = 200	S9321 N = 516
AUTO	CR rate (%)	22*	17
	7-yr EFS (%)	16	17
	7-yr OS (%)	43	37
CHEMO	CR rate (%)	5	15
	7-yr EFS (%)	8	16
	7-yr OS (%)	27	42

* Assessed by electrophoresis only

IFM 90 : Survival according to response



Randomized studies comparing ASCT and CC Conclusions

- **OS improvement is related to CR rate increase**
- **ASCT is superior to most standard CC regimens but when results of CC are improved, the benefit of ASCT is no more significant**
- **The comparison of ASCT with standard CC is no longer an issue since results of ASCT have improved in the past 10 years**

CC vs ASCT

- ASCT is the standard of care in younger patients (up to 65 years of age)

- OS improvement is related to CR achievement

- ASCT is superior to CC when it increases CR rate

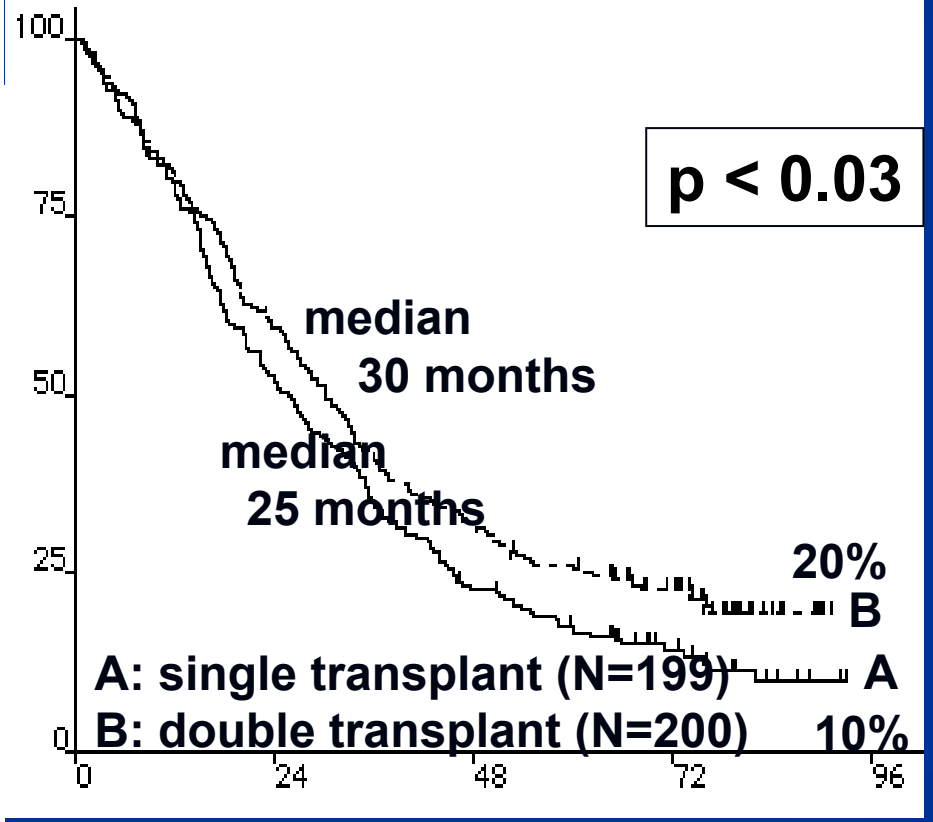
- HDM is superior to conventional doses of Melphalan and is the best way to administer alkylating agents

Improvement of ASCT results in the past 10 years IFM Experience

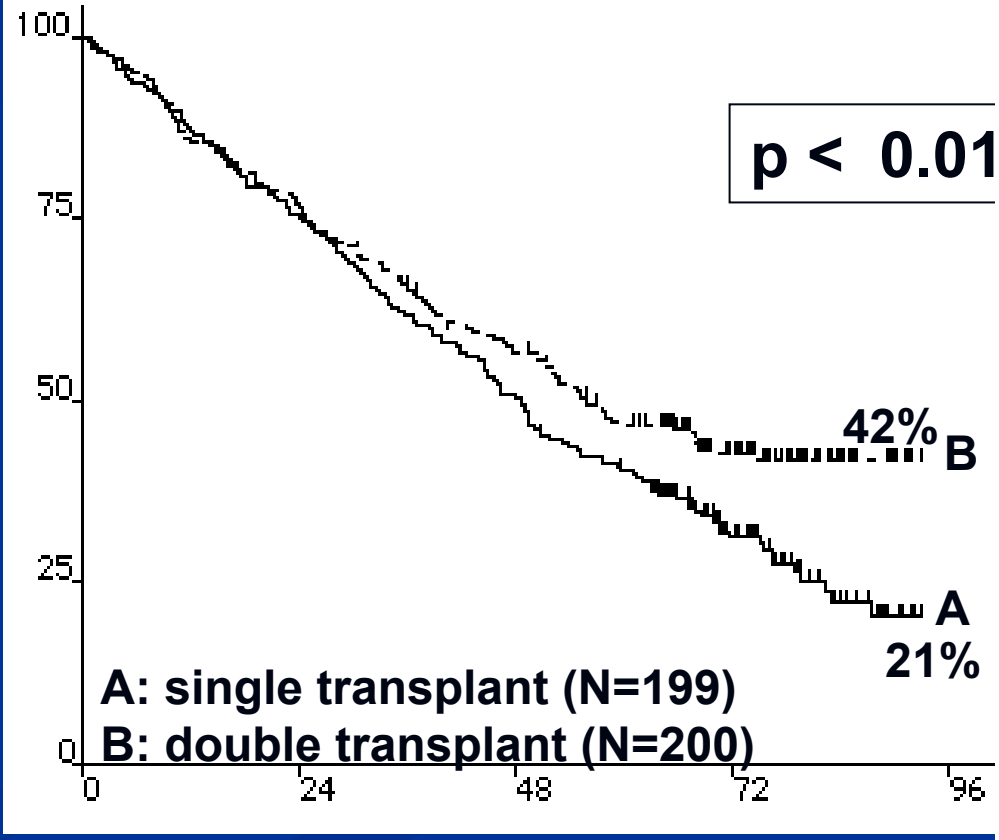
	IFM 90 N = 200 single ASCT	IFM99 N = 1064 Double ASCT
CR + VGPR	38 %	54.5%
Med EFS	28 M	36 M
5-yr OS	52 %	62 %
Med OS	57 M	NR at 66 M

IFM 94

EFS



Overall

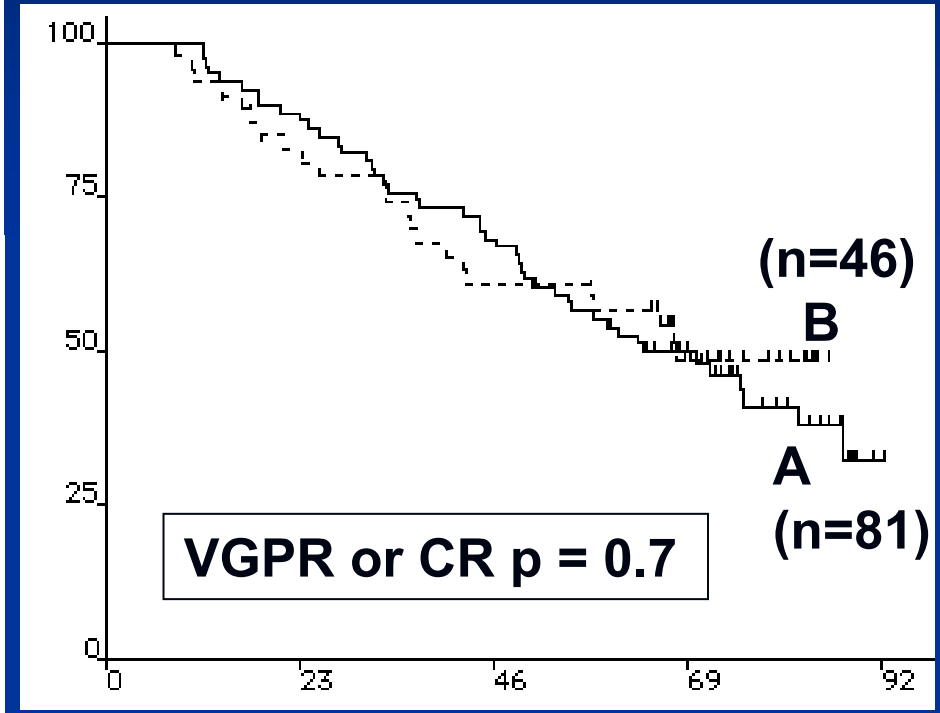


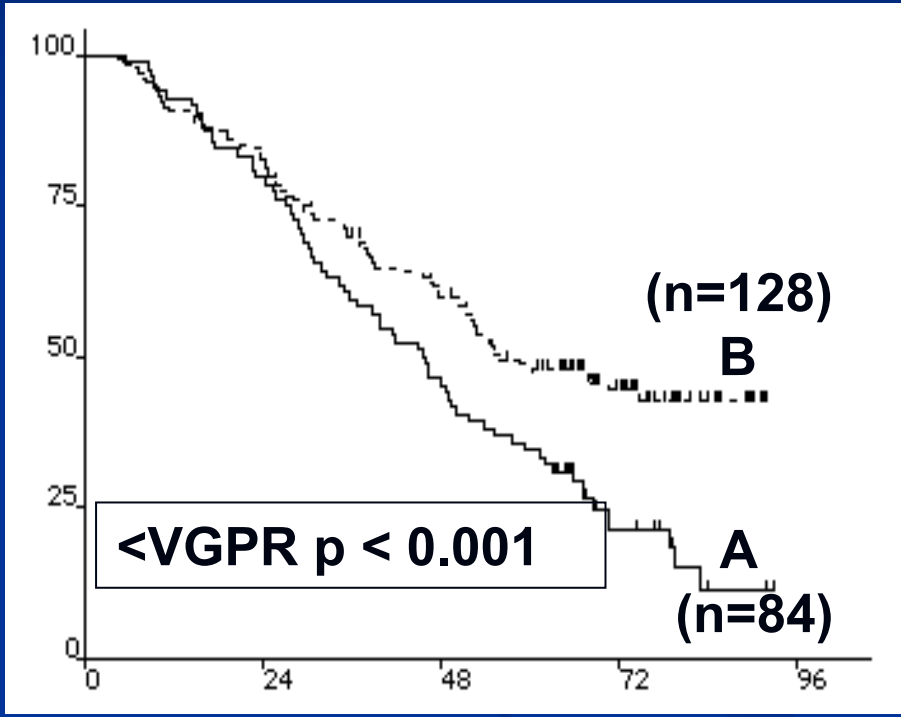
SINGLE vs DOUBLE ASCT RANDOMIZED STUDIES

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

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

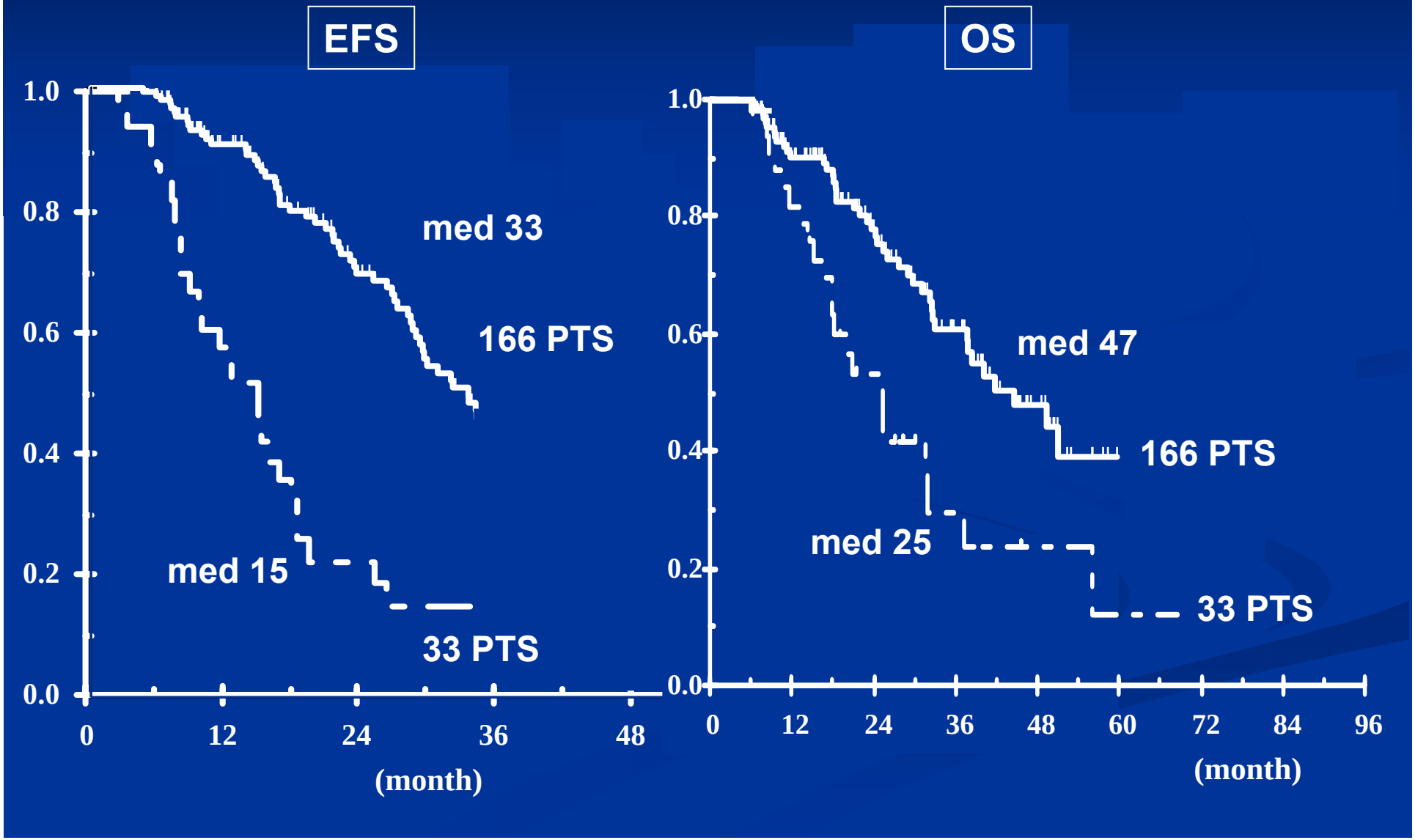
JSM





DOUBLE ASCT WITH MORE INTENSIVE 2ND HDT IMPROVES THE OUTCOME OF POOR-RISK MM

Historical Comparison in pts with high B2 and del 13



ROLE OF CONSOLIDATION IN TT2
Barlogie Blood 2006

TT2 without Thalidomide (n=345) vs TT1 (n=231)

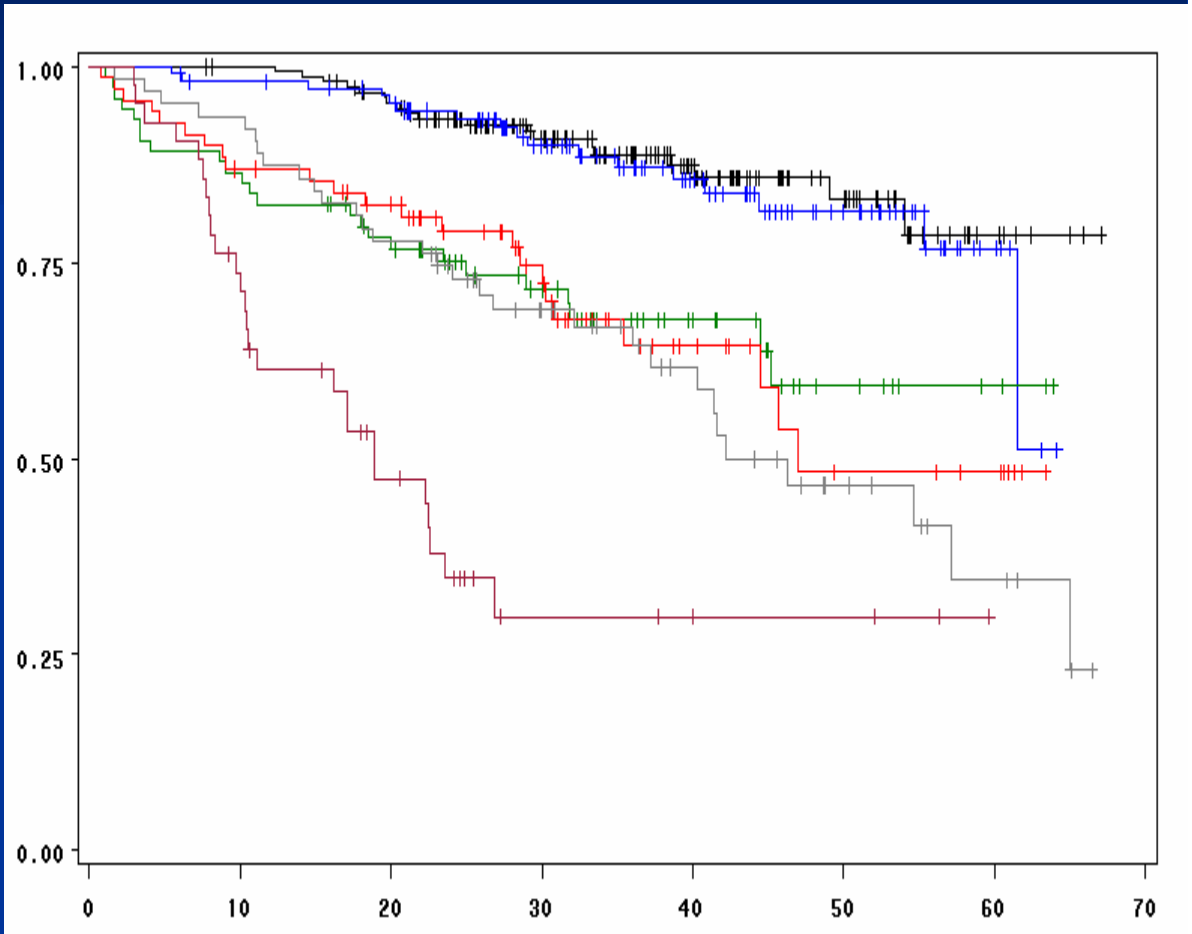
- Identical CR rate (43%vs 41%)
- Superior 5-yr EFS:43%vs 28% (p<.001)
- trend for improved SV :62%vs 57%
- TT2>TT1 in pts without cytogenetic abnormalities (2/3)

- Role of consolidation with DCEP ?

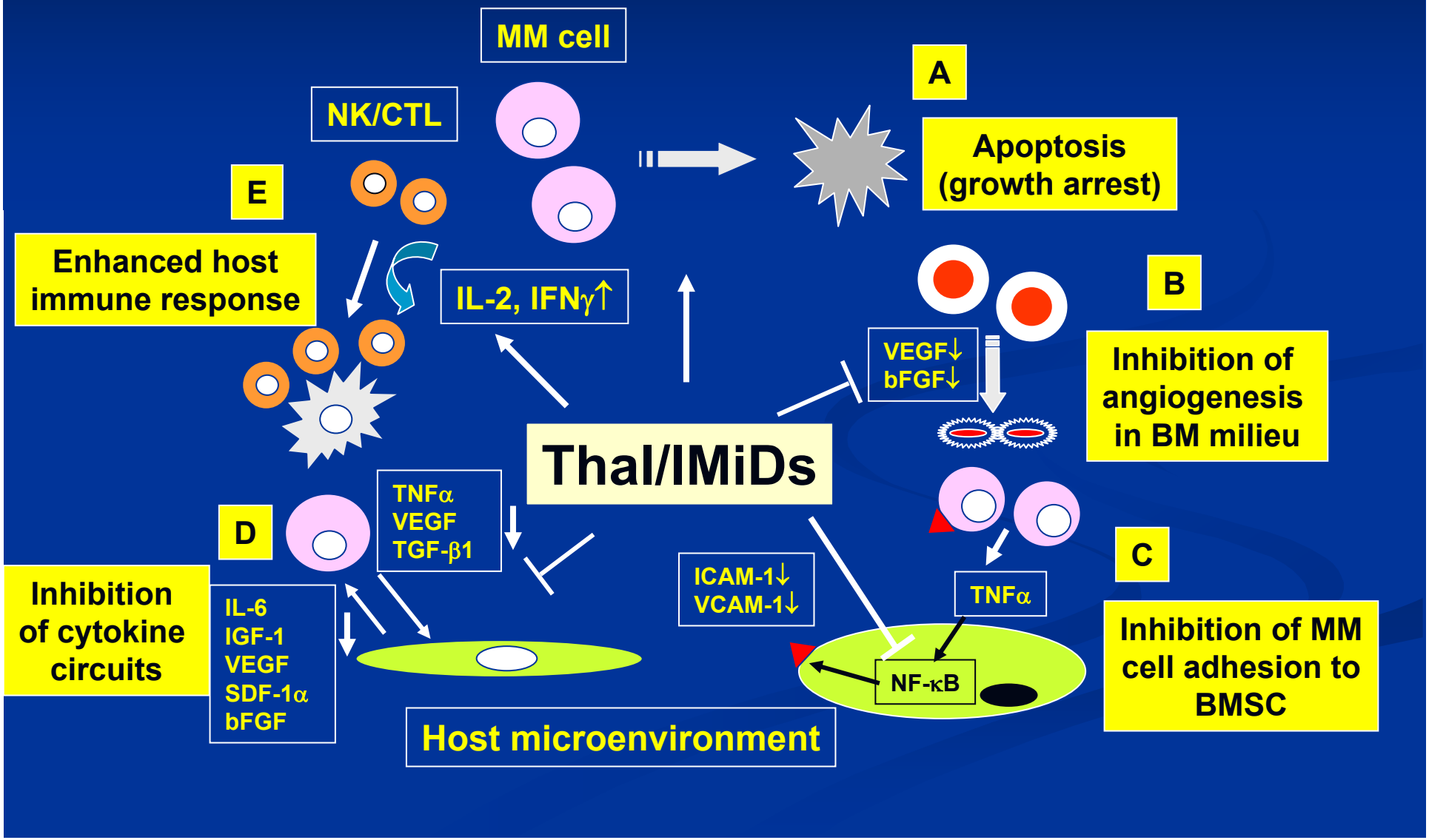
Cytogenetic + β2m model

OS

No t(4;14), no del(17p), β2m<4, no del(13)	155 pts
No t(4;14), no del(17p), β2m<4, del(13)+	110 pts
No t(4;14), no del(17p), β2m>4, no del(13)	74 pts
No t(4;14), no del(17p), β2m>4, del(13)+	69 pts
t(4;14) or del(17p)>60%, β2m<4	63 pts
t(4;14) or del(17p)>60%, β2m>4	42 pts



Targeting the Myeloma Cell in Its BM Microenvironment



THALIDOMIDE ALONE IN RELAPSED MM RESULTS

- Reduction in paraprotein of ≥ 25% : 40-80%
- Partial remission in 10-50% of patients and CR possible in some heavily pretreated pts
- Optimal daily dose (IFM study 100 vs 400): 400 more toxic and no SV benefit if Dex added if no response at 3 m
- Early onset of response and maximal response within 2-4 months

THALIDOMIDE + DEXAMETHASONE

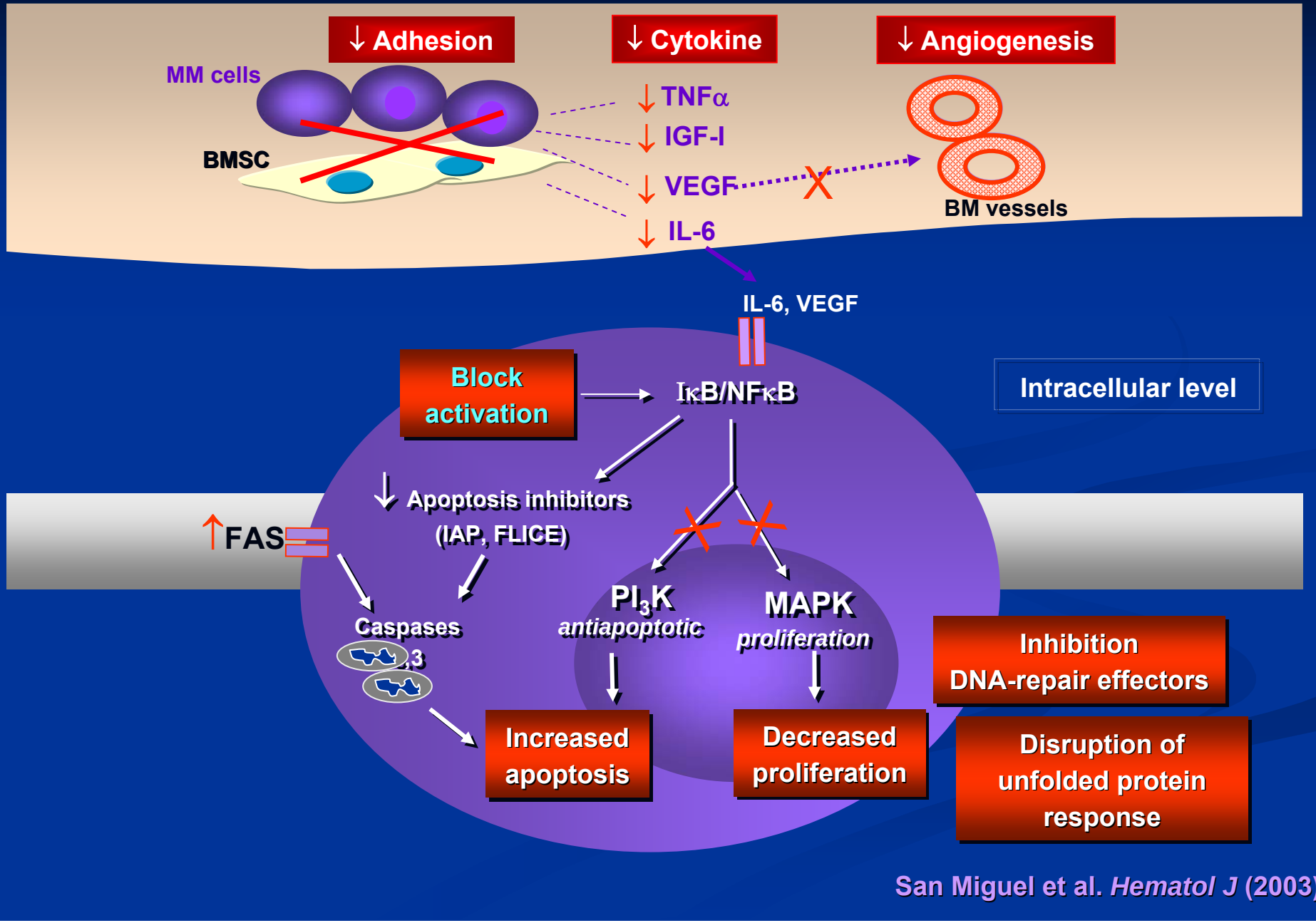
- Synergy in preclinical studies

- Lower doses of Thalidomide
  → better tolerance of Thal but more infectious complications and risk od DVT

- More effective ?
  - 65-80% response rate in relapsed / refractory MM
  - As first salvage therapy improves the outcome as compared to CC :median PFS 17m vs 11 (p=.002) SV at 3 yr 60% vs 26% (p=.001) *(Palumbo 2004)*

- Currently used as frontline therapy

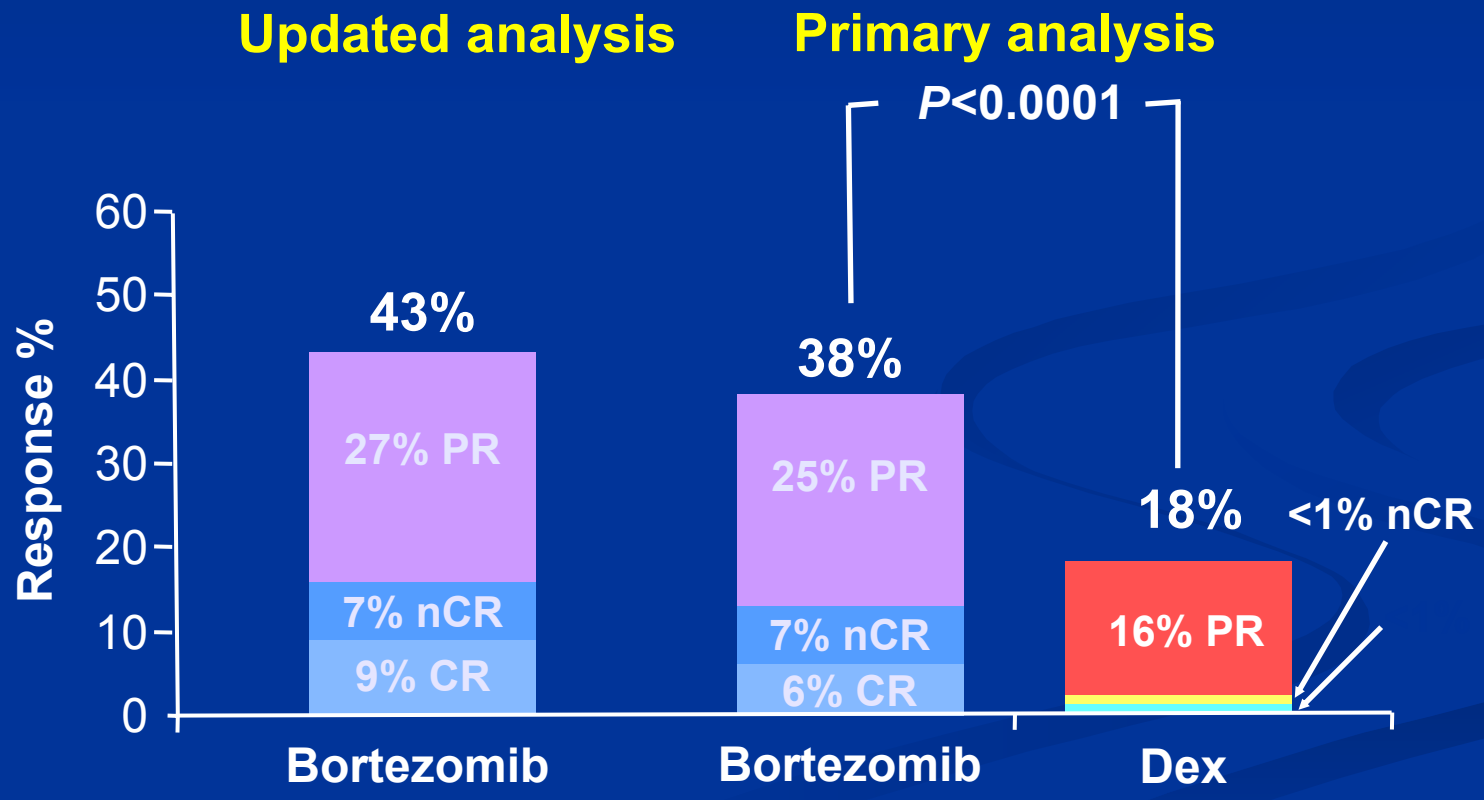
Bortezomib (VELCADE™)



San Miguel et al. *Hematol J* (2003)

Updated APEX efficacy data
Response rates

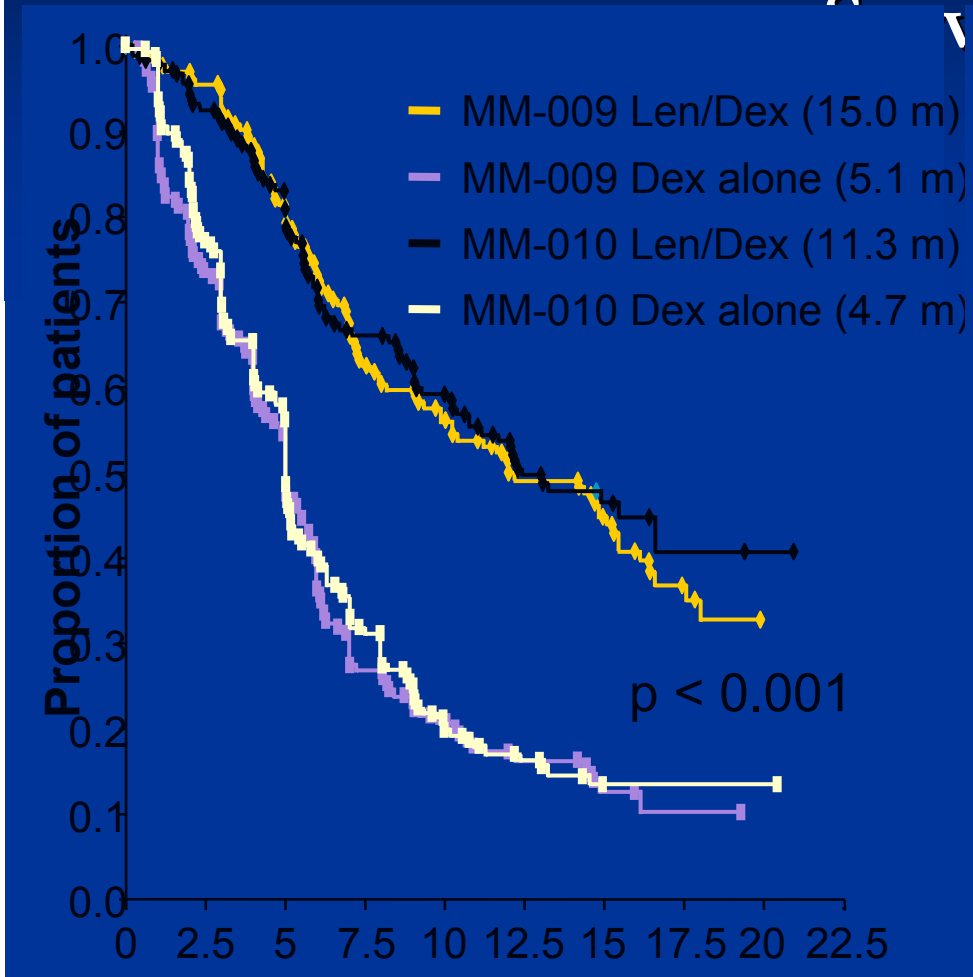
ORR with bortezomib improved from 38% to 43%



Lenalidomide + Dex Vs Dexamethasone (MM-009/010)

JSM

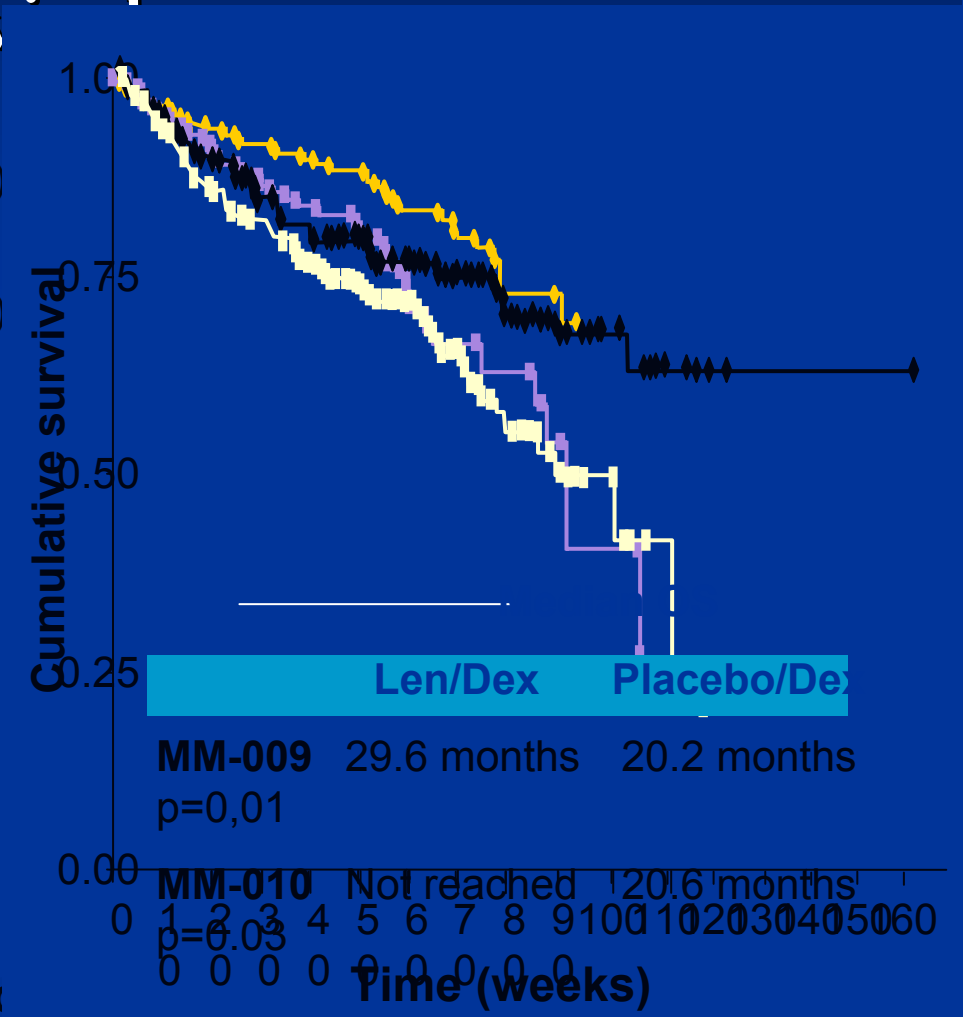
Time to Progression



Cut-off date: June 2005.

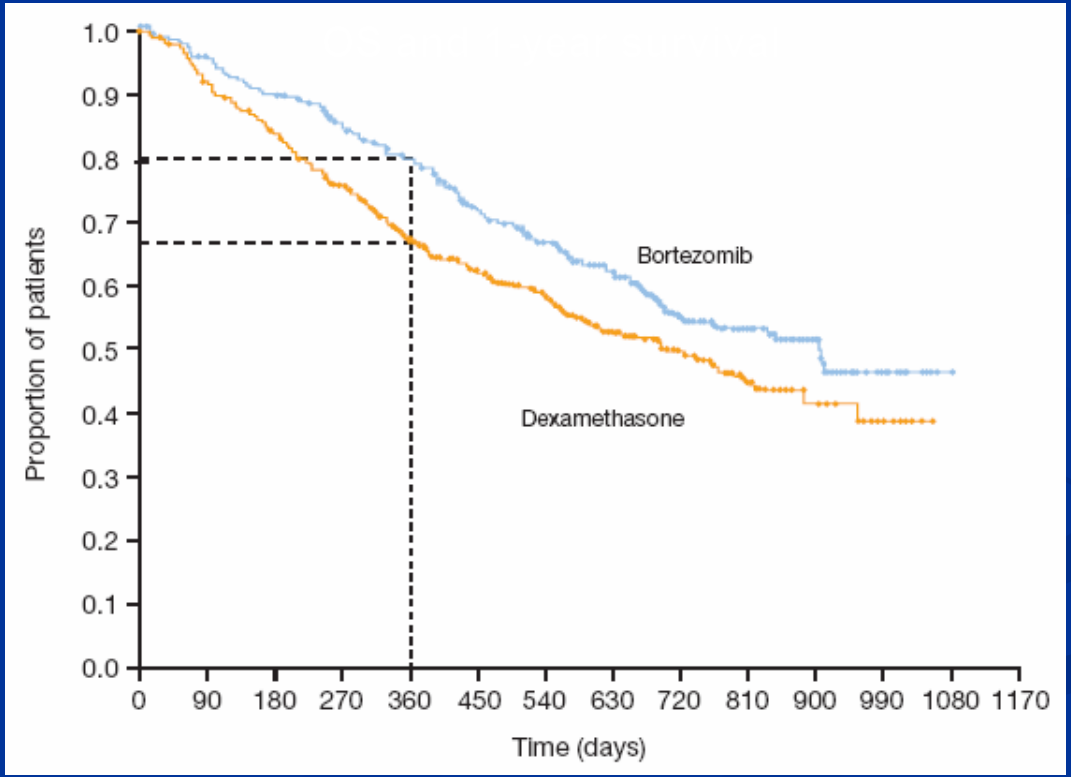
progression (months)

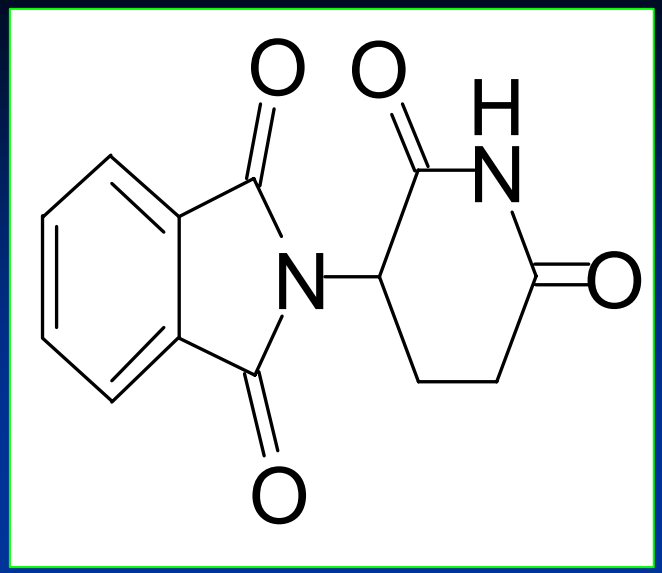
Overall



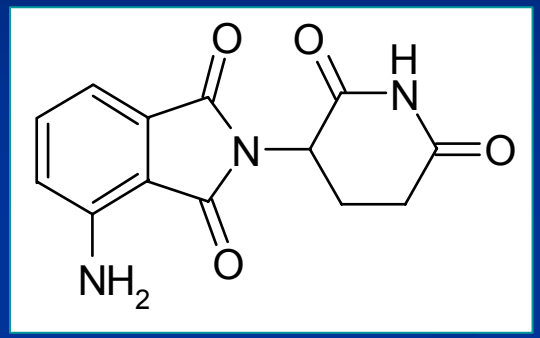
Updated APEX survival data

- Superior survival for bortezomib
  - Median OS: bortezomib 29.8 months vs 23.7 months for high-dose Dex (*P*=0.0272)
  - 1-year survival rate: 80% vs 67% (*P*=0.0002)

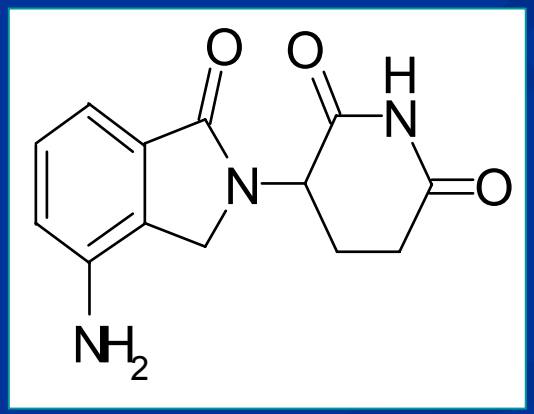




Thalidomide

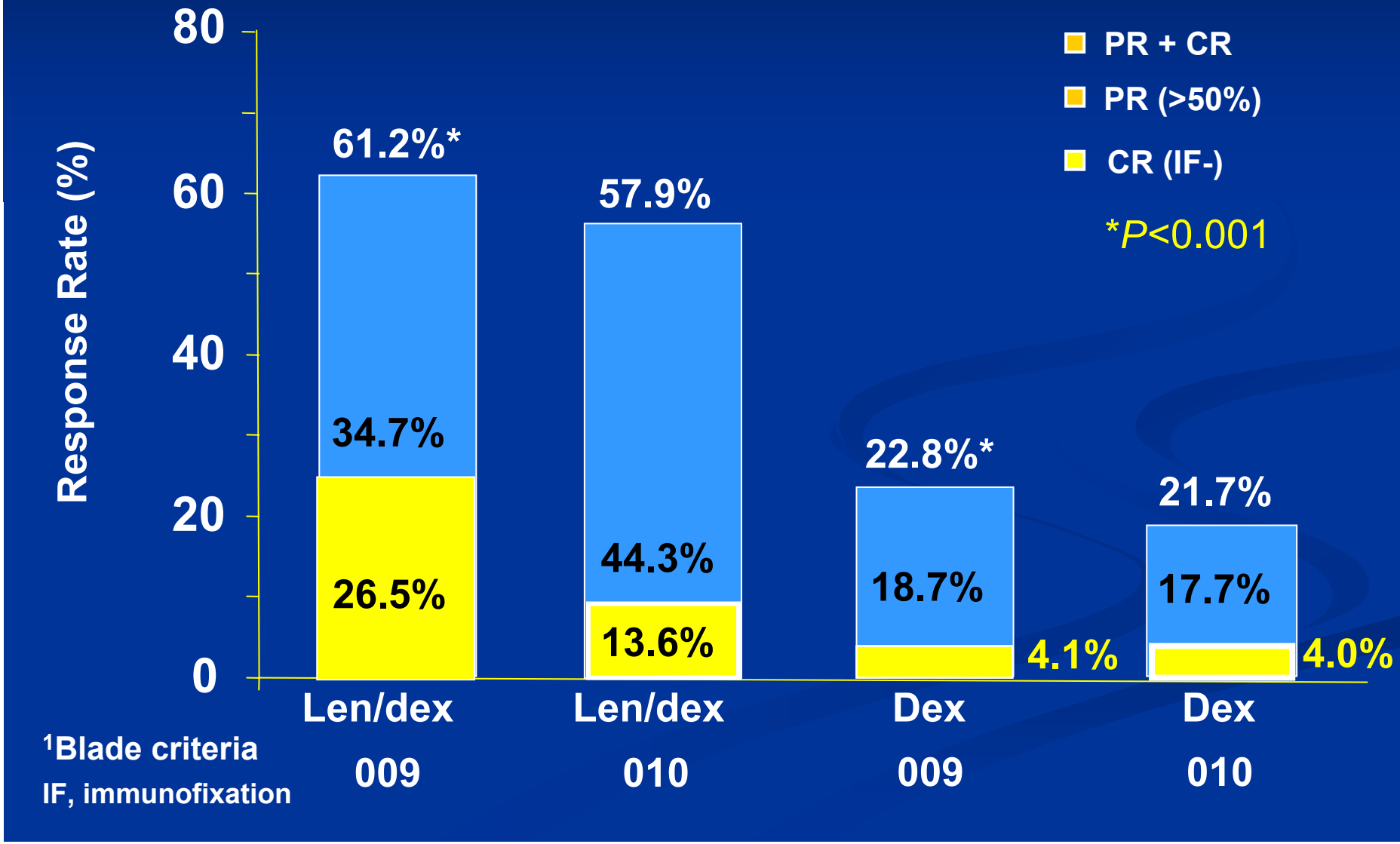


Actimid™ (CC- 4047)



Revlimid™ (Lenalidomide)
(CC-5013)

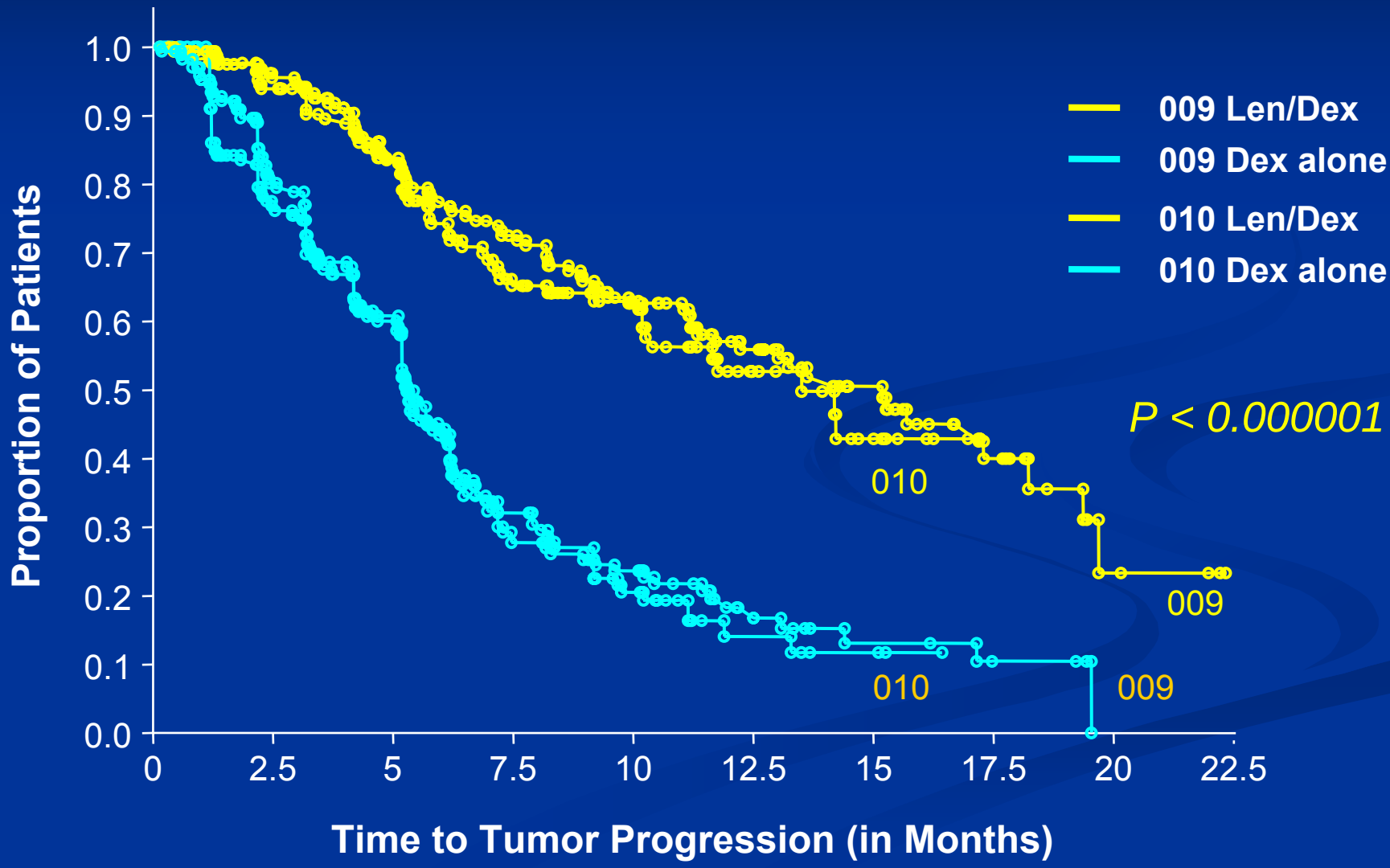
MM-009/010: Response[1]



[1]Blade criteria

IF, immunofixation

MM- 009/010 Time to Progression



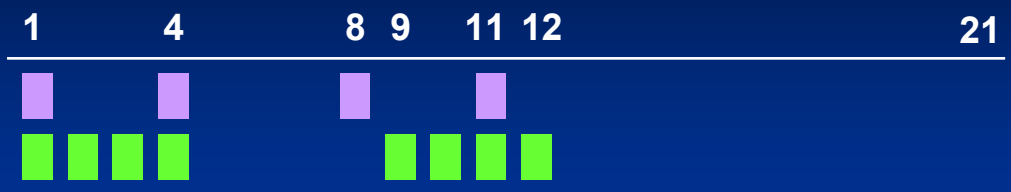
The future role of transplantation in multiple myeloma

Thal-based regimens prior to ASCT

	Randomized trial[1]		Historical comparison[2]	
	Dex n=100	Thal/Dex n=99	VAD n=100	Thal/Dex n=100
Response rate (%)	41	63	52	76
CR + nCR (%)	0	4	13	13
DVT (%)	3	17	2	15
Early death	11	7	6	6

BORTEZOMIB + DEX IN NEWLY DIAGNOSED MM

4 x 21-day cycles



	After bortezomib + dex n = 48	After SCT n = 42
RR after 4 cycles	75%	92%
CR	21%	19%
VGPR	10%	33%
PR	35%	33%
MR	8%	7%

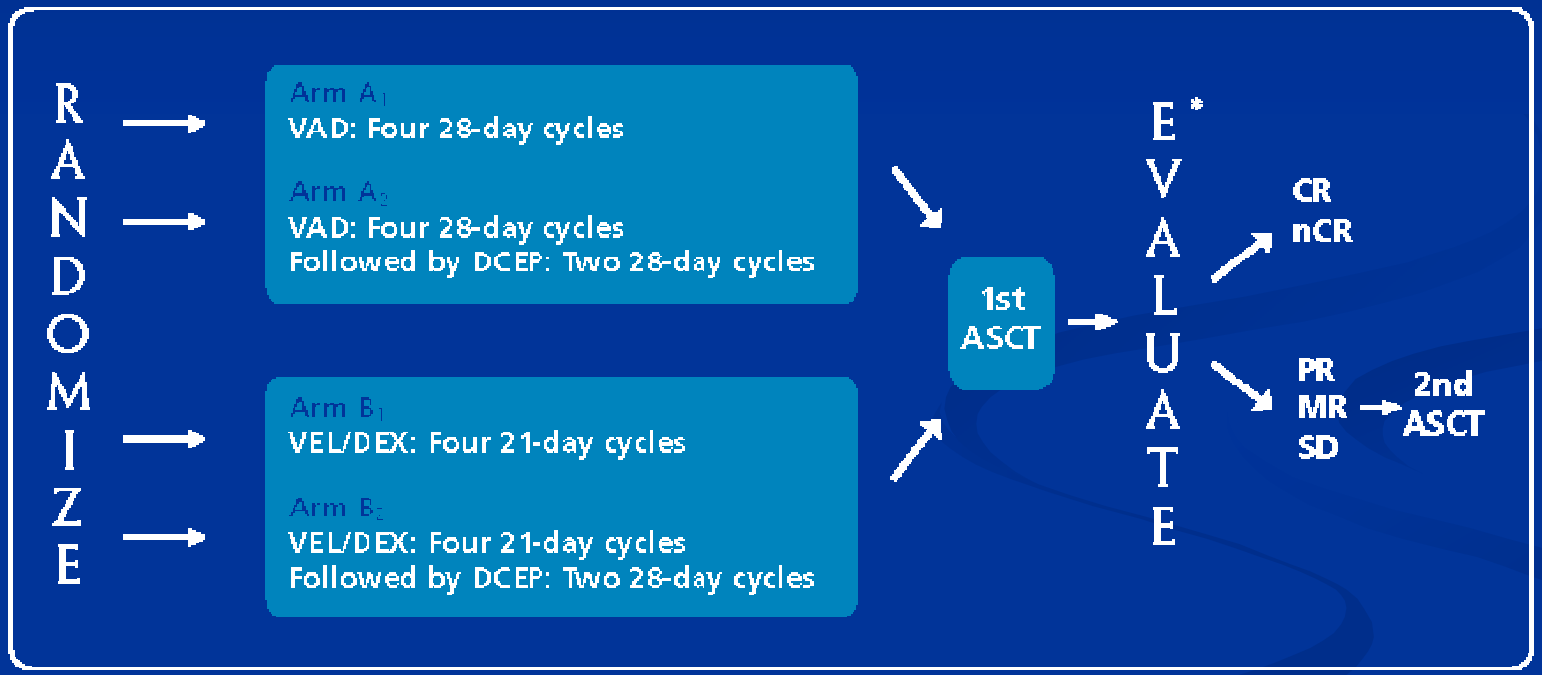
- Stem cell collection in 45 patients (median 2 collections required [range 1–4])
- Well tolerated: AEs mainly grade 1/2 (1 grade 4 GI)
  PN: 6% grade 3 and 8% grade 2
- Results form basis for IFM Phase III trial of bortezomib + dex vs VAD

Harousseau *et al*. *Haematologica* 2005;90(Suppl 1):148 (Abstract P0.724), Presented at IMW, Sydney, 2005

IFM 2005-01

IFM 2005-01
STUDY SCHEMA

Accrual Goal = 480



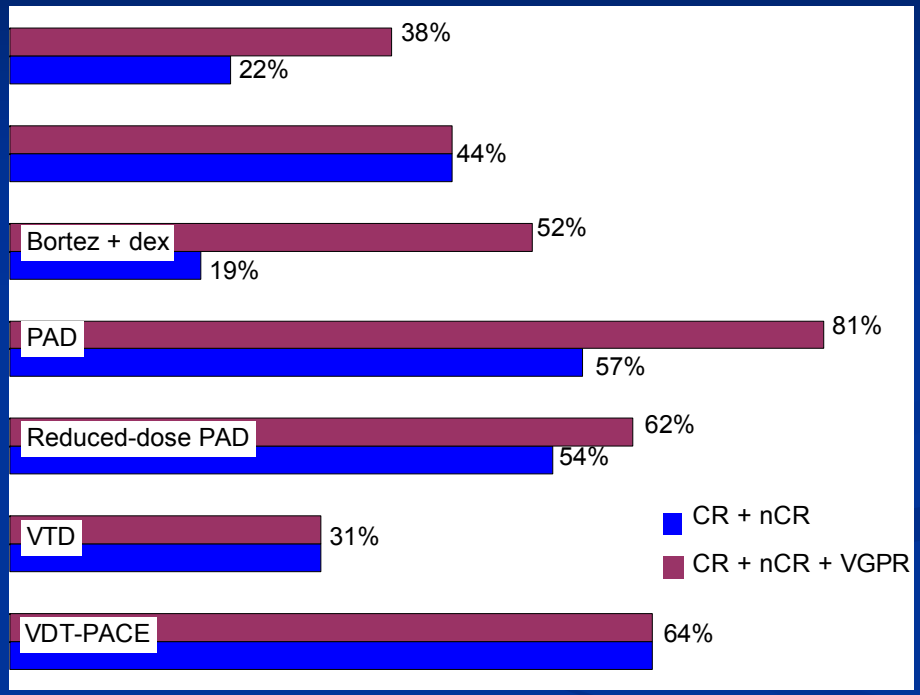
* Evaluation based on modified Blood and Marrow Transplantation (EBMT) criteria.[1]

† Not a complete list of inclusion and exclusion criteria. Before making a decision regarding trial enrollment, please consult the complete list in the trial summary.

CONVENTIONAL SCT vs BORTEZOMIB INDUCTION REGIMEN

Conventional SCT
Attal 1996, Morgan 2003

Bortezomib induction regimen



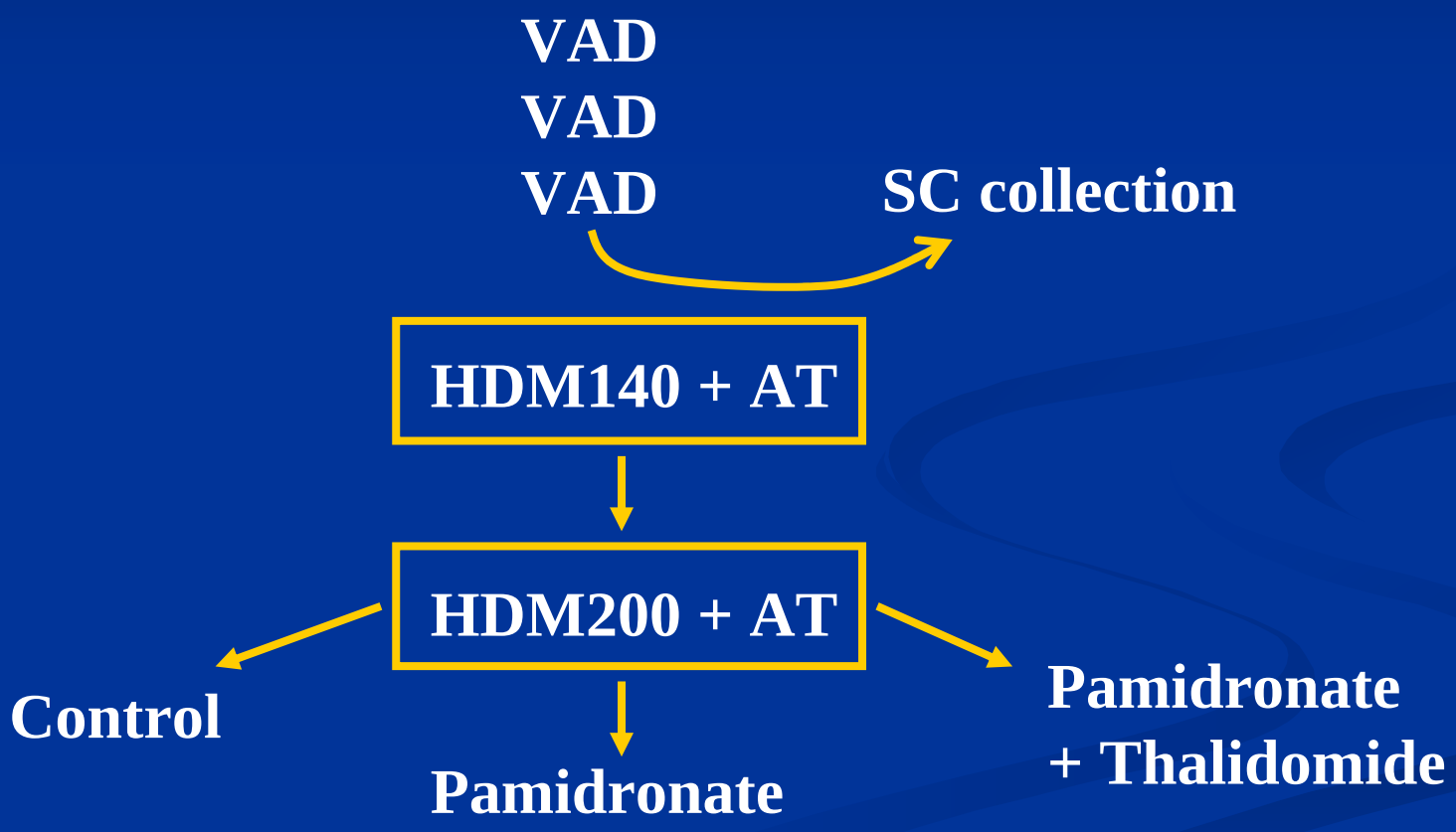
Integrating bortezomib into induction regimen may result in superior CR rates compared with conventional induction regimen

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)

IFM 99-02 - M. ATTAL Blood 2006

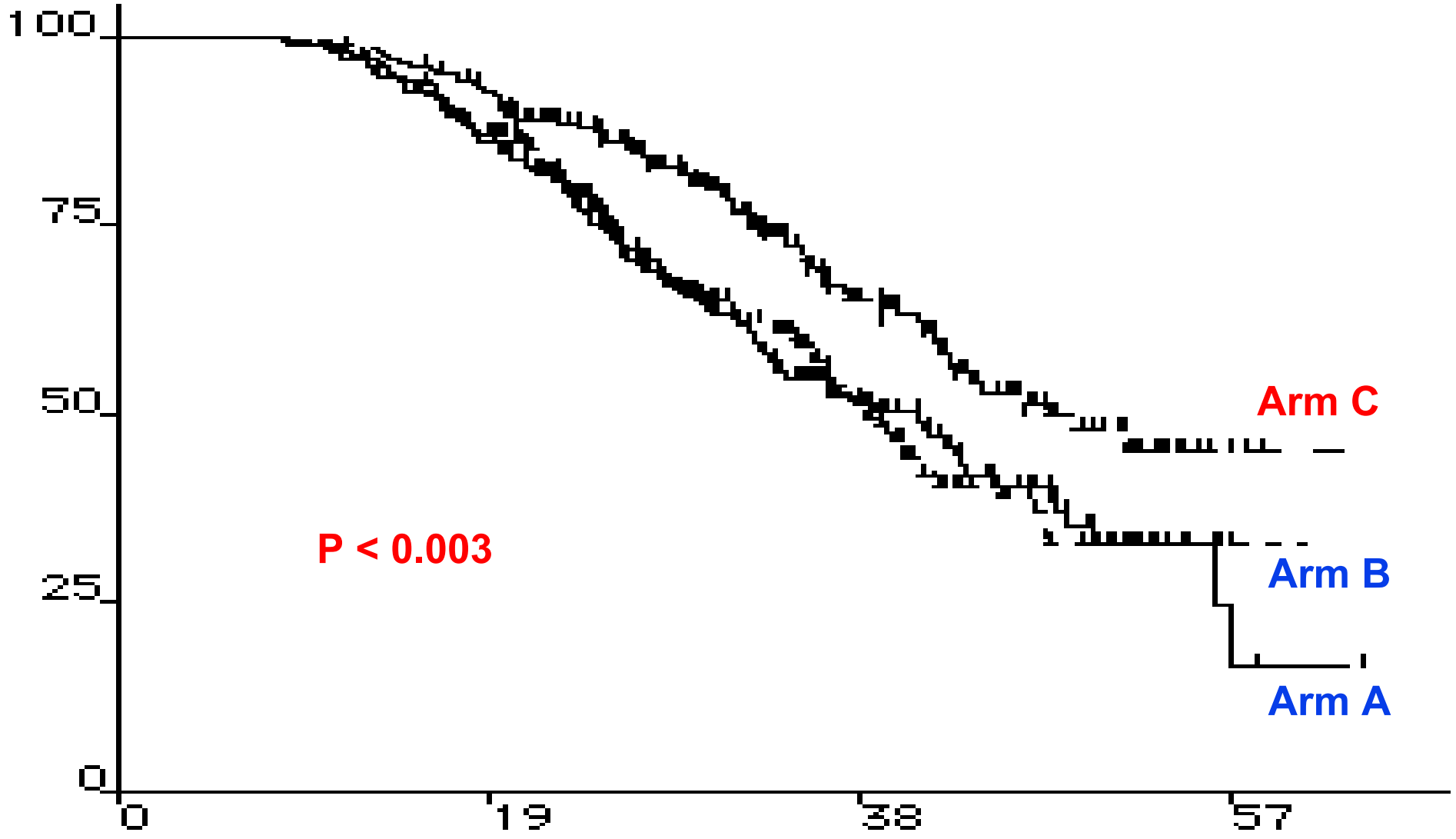
Pts ≦ 65 y ; 0/1 adverse prognostic factors (Δ13, β2m)



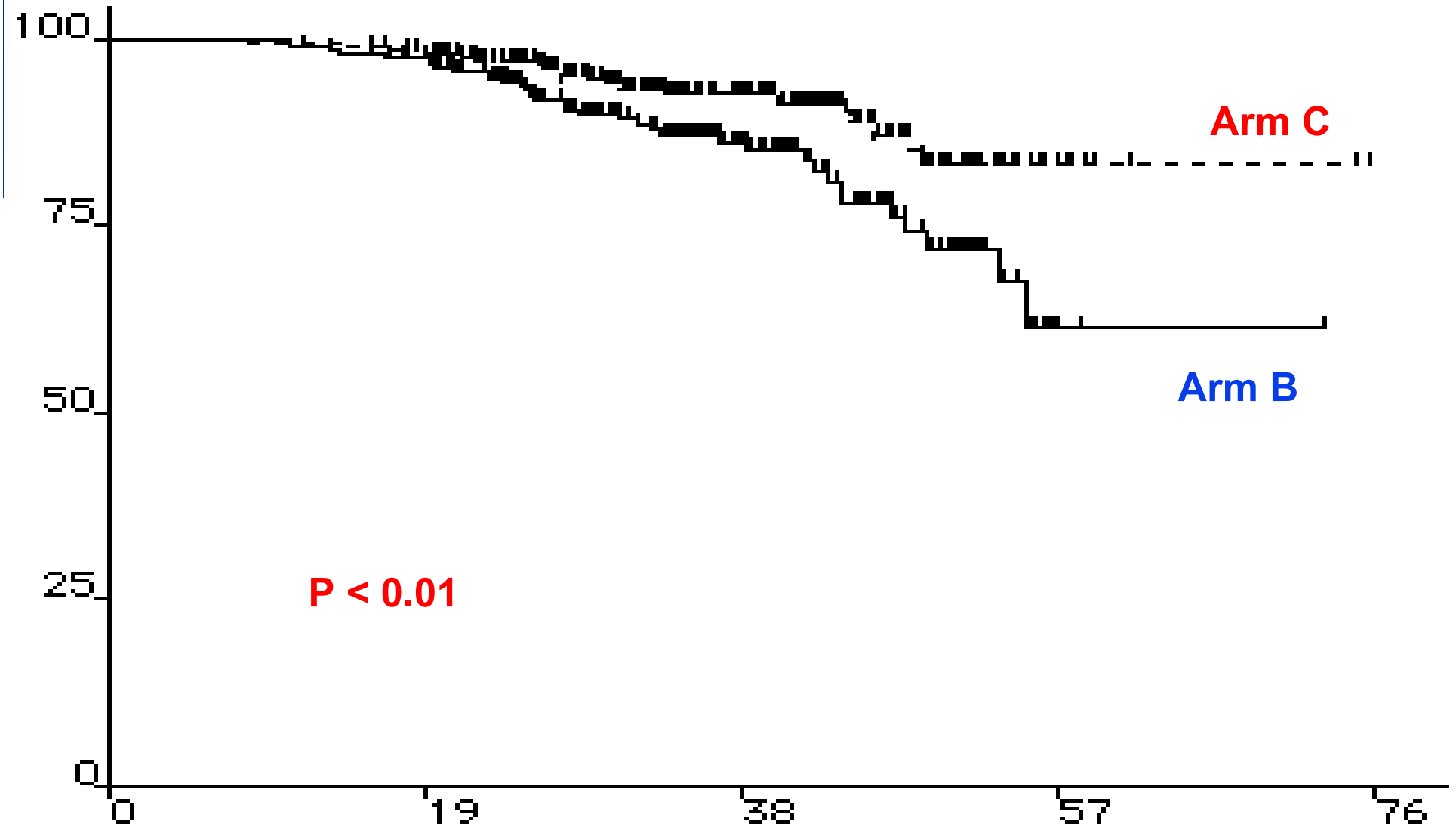
IFM 99 02: Response Rate ≥ 90%.

	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

IFM 99 02 : EFS from Diagnosis



IFM 99 02 : Overall Survival according to Thal (Arm B versus Arm C).



TOTAL THERAPY II

ROLE OF THALIDOMIDE *(Barlogie NEJM 2006)*

- 668 pts randomized to recieve or not Thal during inductionTX,consolidation and maintenance

- CR 62% vs 43% (p<0.001)

- 5-year EFS 56% vs 44% (p=0.01)

- No difference in OS due to shorter SV after relapse 1.1 yr vs 2.7 yr (p=0.001)

- 30% DVT and 27 % PN

JLH

Differences between the thalidomide arms of IFM 99/02 and Total Therapy 2

	TT2	IFM 99/02
Duration of Treatment	From the beginning until disease progression or side effedts	After doubleASCT until disease progression or side-effects
DVT	30% (Thal + chemo)	2%(Thal alone)
PN > 2	27% (longer duration ?)	7%
SV after Relapse	< control arm (selection of resistant clones ?)	identical to control arm

- Optimal dose and duration of Thalidomide treatment ?

- Other agents are current evaluated (Bortezomib, Lenalidomide)

Update on recent developments for elderly patients with newly diagnosed multiple myeloma

IFM 99-06
Newly diagnosed MM 65-75 years

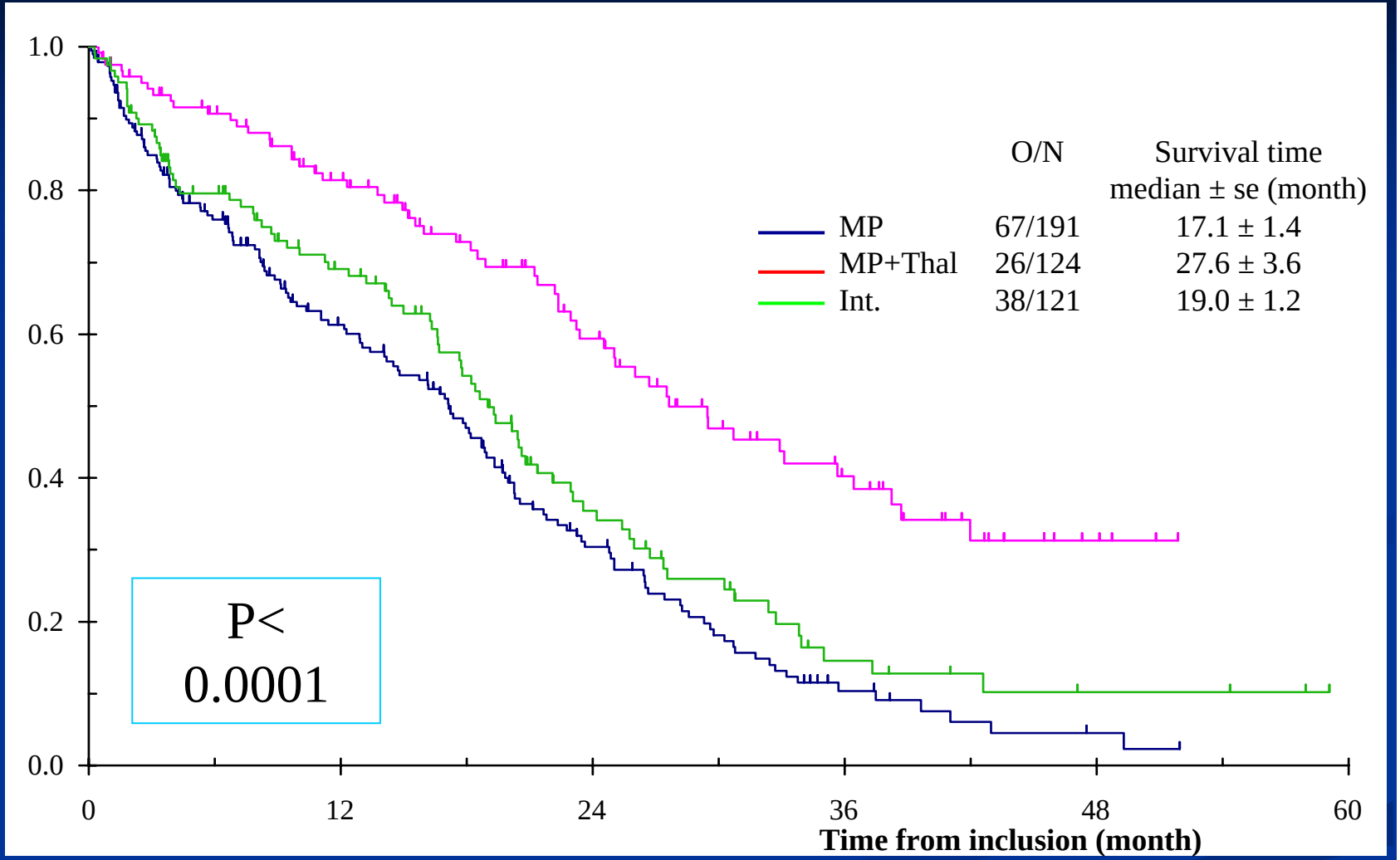
JSM

Arm A	Arm B	Arm C
MP 1 ↓ MP 2 ↓ MP 3 ⇣ MP 12	Arm A + **Thalidomide** ≤ 400 mg/d	VAD 1 ↓ VAD 2 ↓ Cyclophosphamide 3g/m^2 + G-CSF + PBSC harvest ↓ MEL 100 mg/m^2 + PBSC + G-CSF ↓ MEL 100 mg/m^2 + PBSC + G-CSF
	Clodronate for all pts	

Response to treatment in the IFM 99-06 trial
Second interim analysis

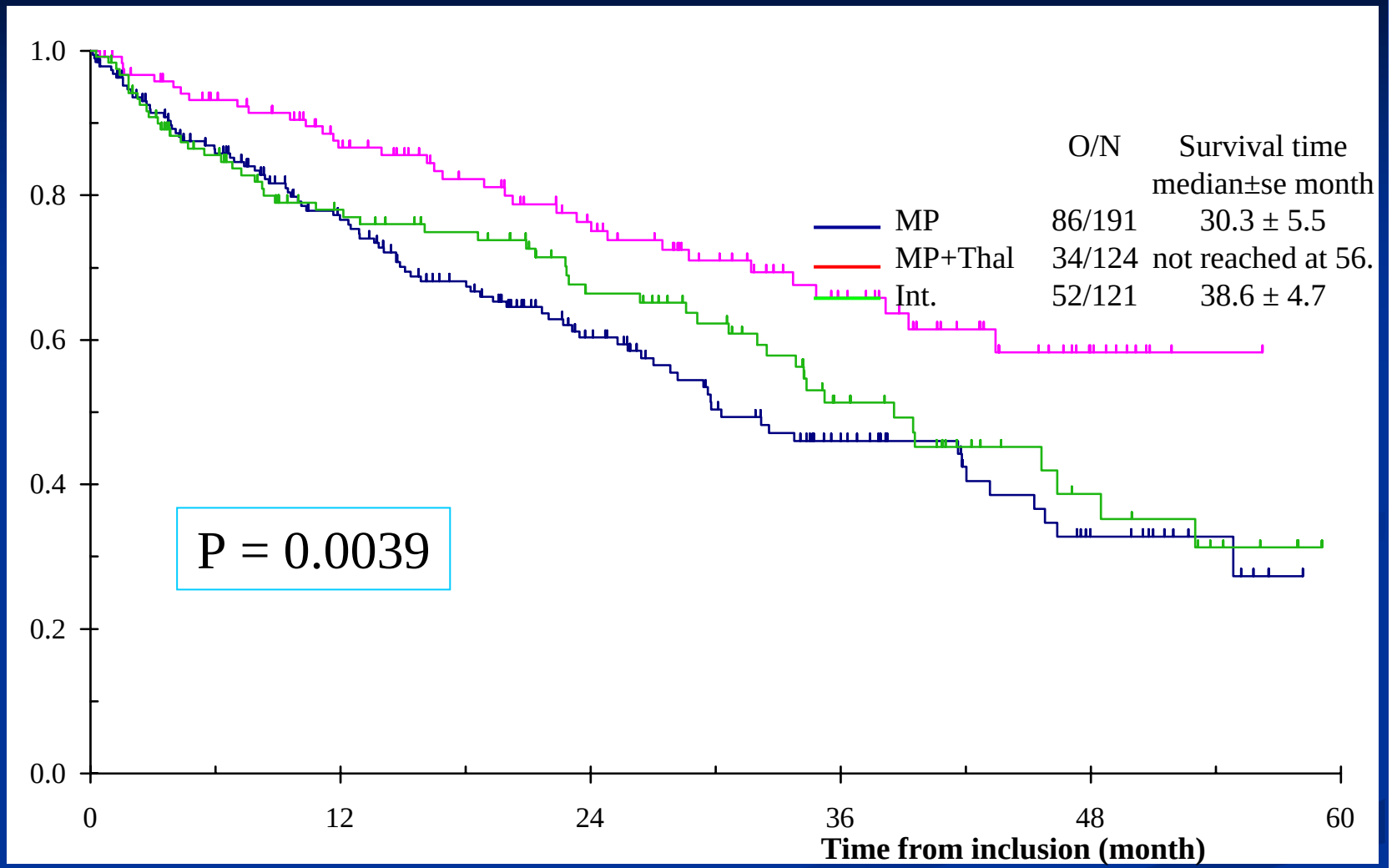
Category of response	% of patients (at 12 months)		
	MP	MP-T	MEL100
Complete response	3	14	18
≥ 90%	8	51	39
≥ 50%	34	84	71

PROGRESSION-FREE SURVIVAL ACCORDING TO TREATMENT



# 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.

OVERALL SURVIVAL ACCORDING TO TREATMENT



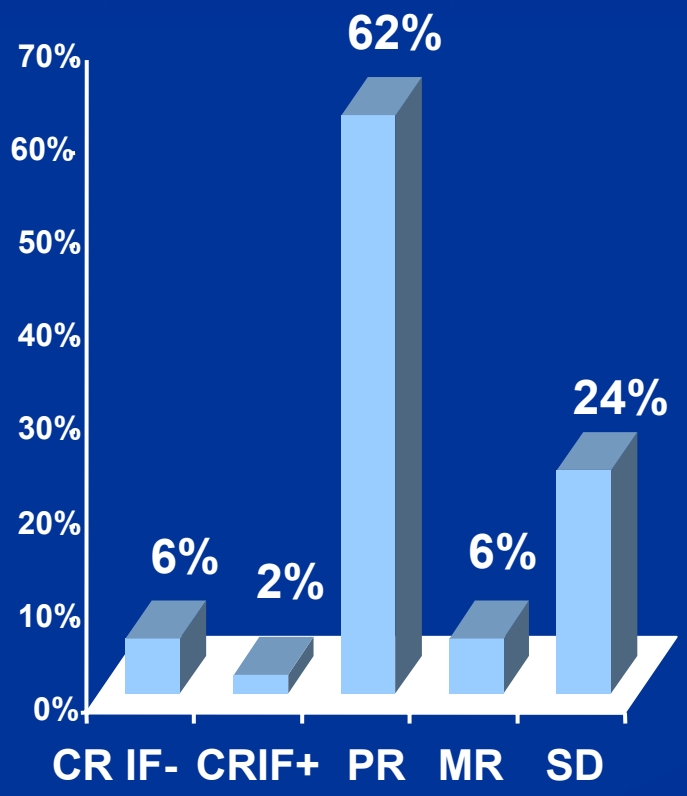
# at risk											
	191	150	120	97	69	49	34	22	13	6	MP
	124	105	88	73	61	47	35	22	9	1	MP+Thal
	121	95	77	68	52	44	28	17	11	6	Int.

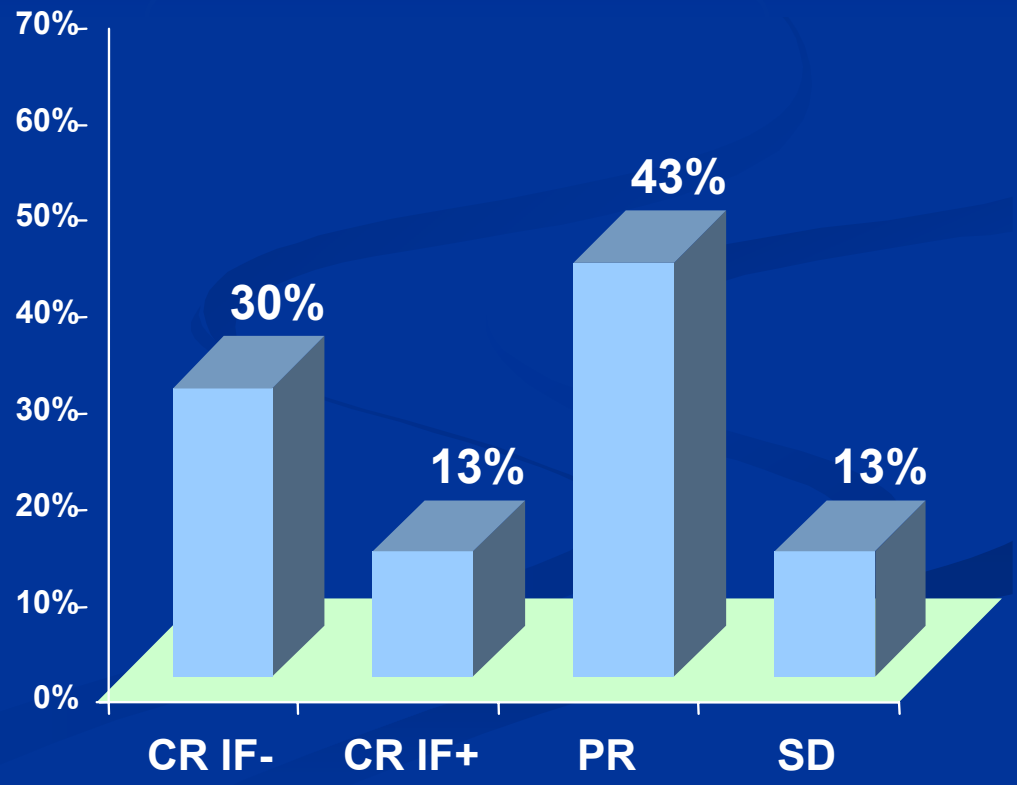
MP vs MPT in older patients

	Palumbo et al (1)		Facon et al(2)	
	MP N=126	MPT N=129	MPT N=191	MPT N=124
Response rate (%)	47	76	81	40
CR rate (%)	2	16	15	2
PFS (median)	13.6	29.2	29.5	17
3-yr OS	64	80	65	48

(1) Lancet 2006
(2) ASCO 2006

MPV response rates (n=53)
Analysis of best response achieved





MPT vs ASCT

	No. of pts	EFS	OS
IFM 90 (Single ASCT)	100	Med 28 m	Med 57 m
IFM 99 06 (MPT)	124	Med 28 m	NR at 56 m
IFM 99 02-04 *(Double ASCT Thal in some pts)*	1064	Med 36m	NR at 66 m
TT 2 Thal arm *(Double ASCT)*	334	5-yr 56 %	5-yr 62 %

NOVEL AGENTS IN PLACE OF ASCT ?

Combination Therapy with novel agents (MPT, MPV, MPR, VTD…) will probably :

- yield CR rates comparable to those achieved with single ASCT
- be superior to CC (MP)
- improve the outcome of older patients who are not candidate to ASCT
- NOT replace ASCT in younger patients since ASCT results have already improved

ALLOGENEIC SC TRANSPLANTATION WHAT WE KNOW

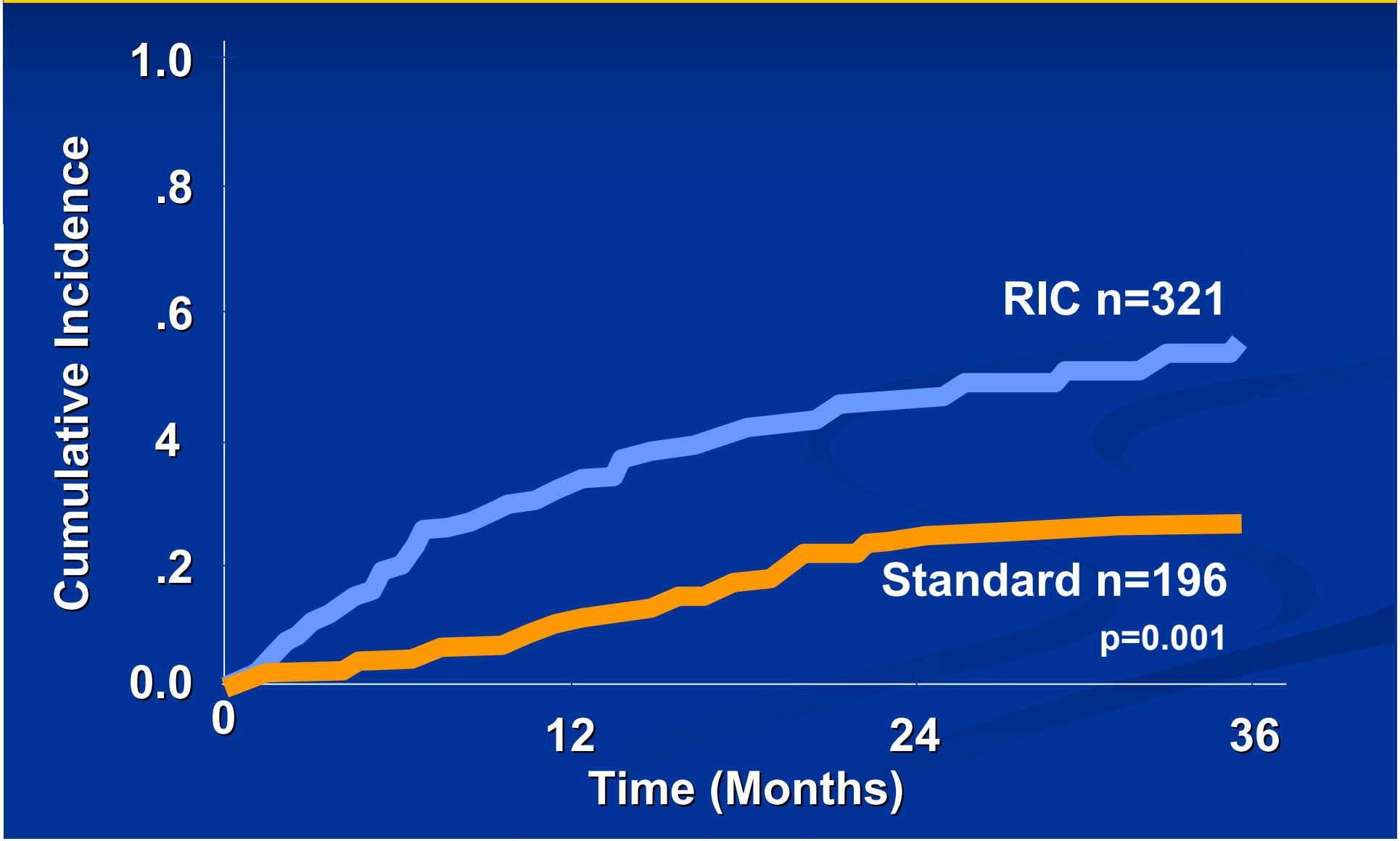
- High transplant-related mortality
- Short-term retrospective comparisons are in favor of autologous SCT

BUT

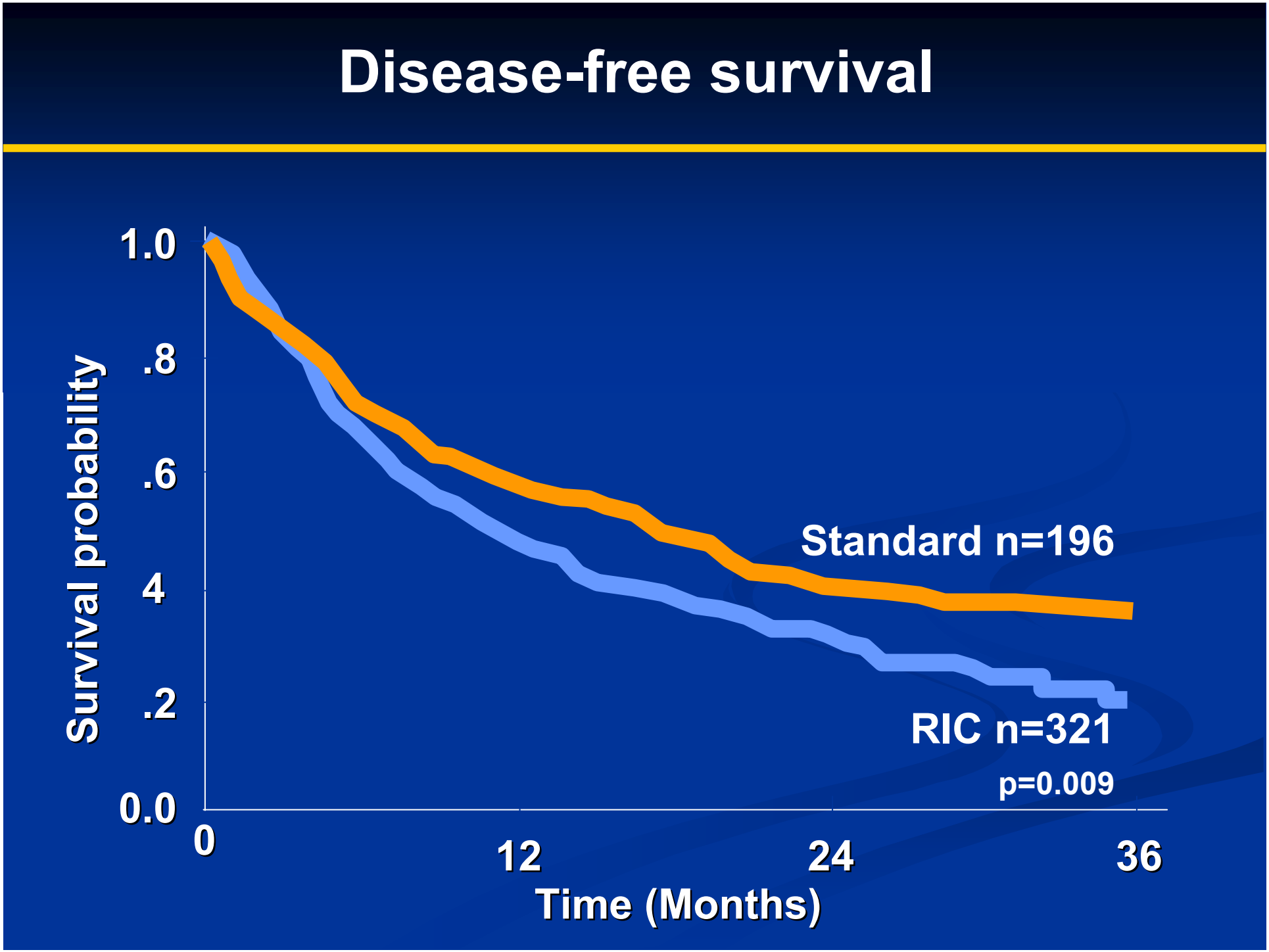
- Durable CR (including molecular remissions) : the only curative treatment ?
- Remissions with DLI : GVM effect
- Better results if better supportive care and earlier transplantation (Gahrton 2001)

Transplant related mortality: EBMT retrospective study

Relapse: EBMT retrospective study



Disease-free survival

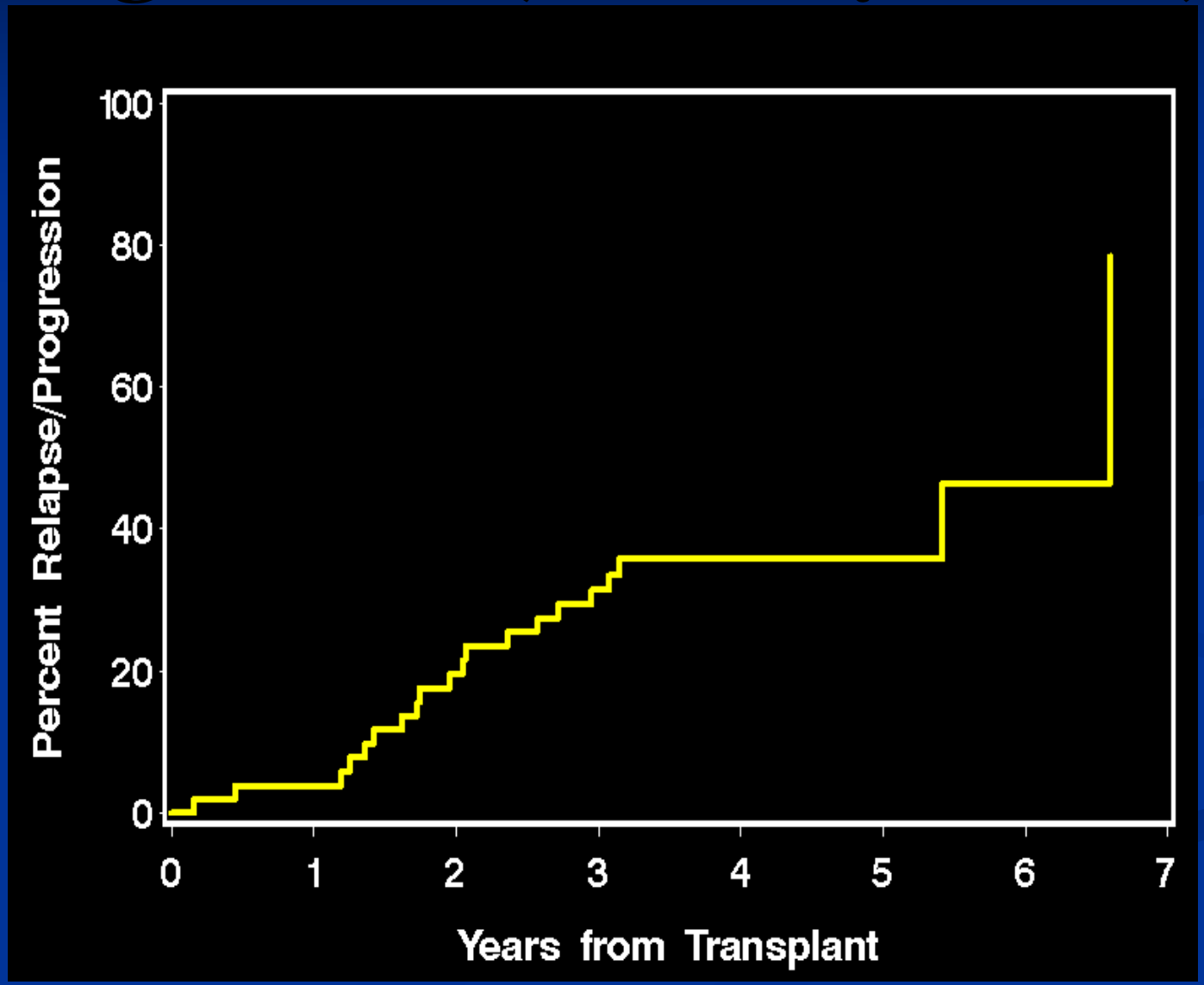


Auto-allo tandem transplantation

	Maloney	*Kröger*	*Carella*	*Bruno*	*Seok*
Acute GvHD II – IV	38.5 %	32 %	44 %	36 %	33 %
Acute GvHD III – IV	8 %	6 %	18 %	11 %	8 %
Chronic GvHD	64 %	28 %	37 %	31 %	50 %
Complete remission	52 %	55 %	62 %	58 %	83 %
Median follow-up (months)	18	16	30	9	14
Estimated overall survival	78 % (2 yrs)	70 % (3 yrs)	62 % (3 yrs)	n. d.	100 % (2 yrs)
Estimated progression-free survival	55 % (2 yrs)	54 % (3 yrs)	56 % (3 yrs)	n. d.	100 % (2 yrs)
Treatment-related mortality at day 100 at one year	0 % 17 %	6 % 11 %	0 % 6 %	2 % 16 %	0 % 0 %

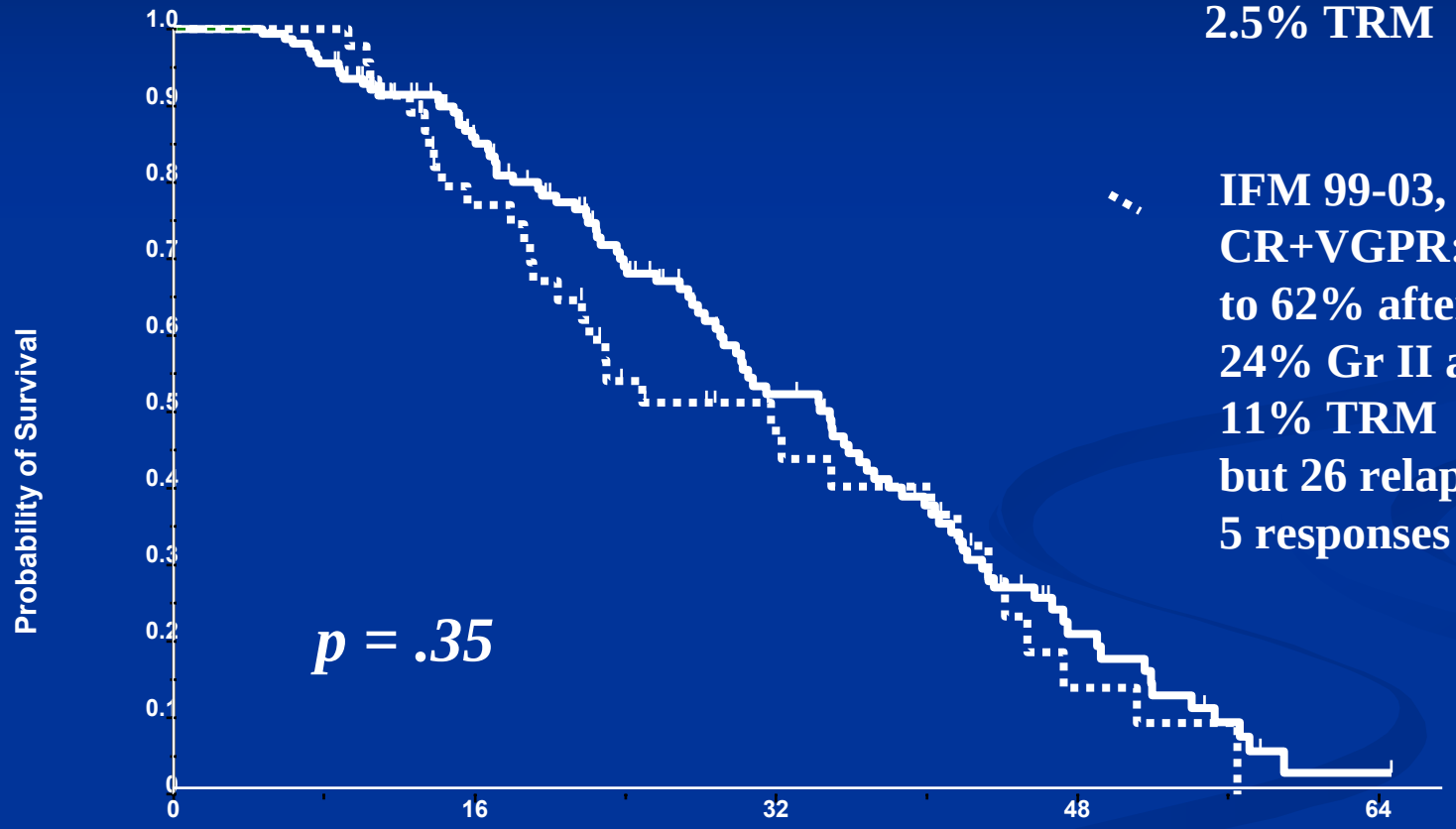

M. Attal
(94/95-02)
T. Facon
(99-06)
H. Avet-Loiseau
(FISH)
P. Moreau
(95/99-06)
F. Garban
(99-03)
SORTIE

Cumulative Incidence of Progression (Maloney 11/05)



N=52

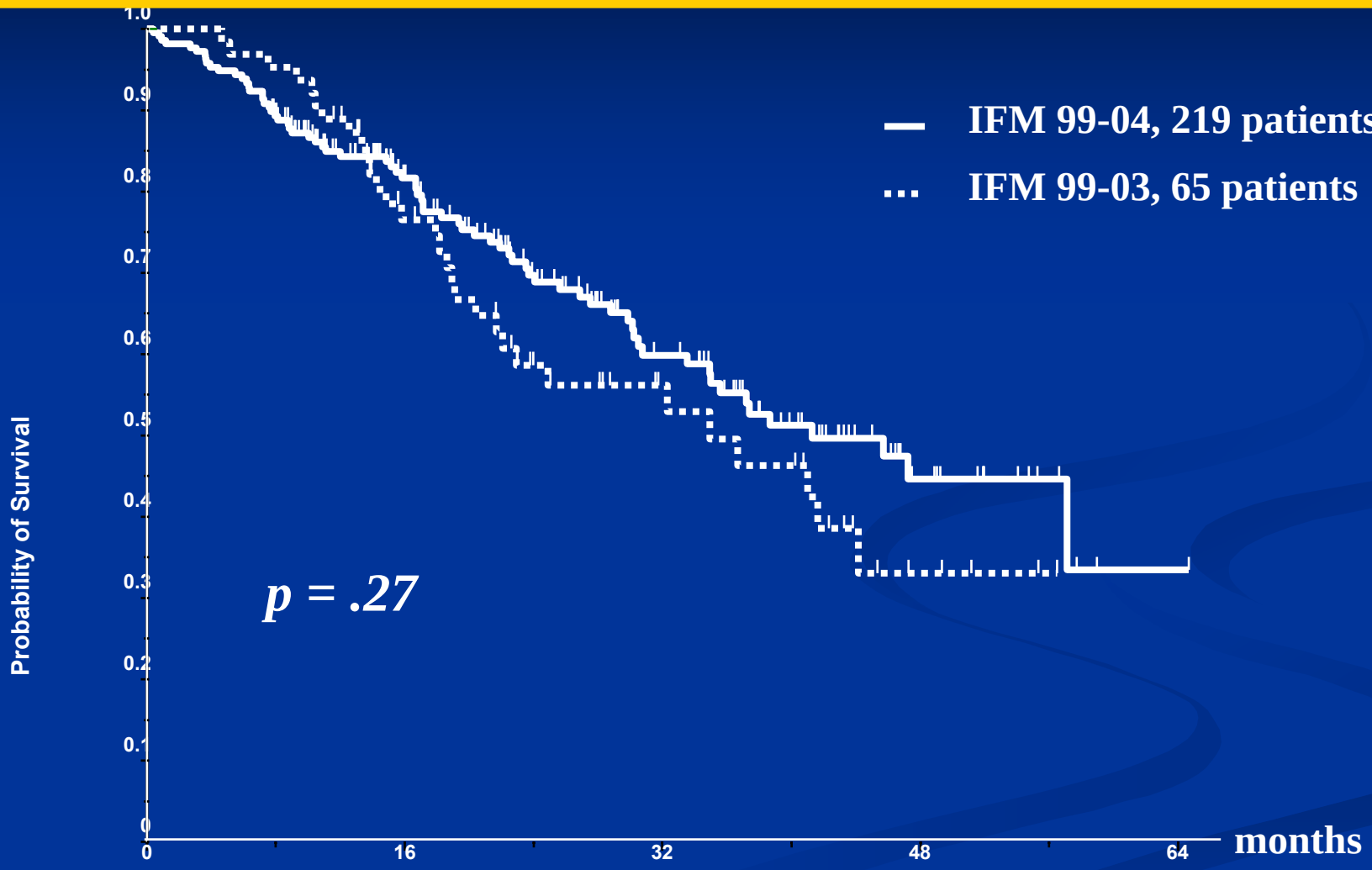
EVENT-FREE SURVIVAL PROTOCOL COMPLETED



IFM 99-04, 166 patients
2.5% TRM

IFM 99-03, 46 patients
CR+VGPR:from 47%
to 62% after RIC
24% Gr II aGVH
11% TRM
but 26 relapses 17 DLI
5 responses in early rel

OVERALL SURVIVAL IFM99-03 VS 99-04



IS THERE A ROLE OF ALLO IN MM ?

- **NOT IN GOOD RISK MM**

  = Results of current treatments do not justify the risk of 10-15% 1-year TRM and 30-40 % CGVHD

  = specially with the introduction of novel agents which already challenge Autologous SCT !

- In most studies f-up is still short but relapse appears to be a major concern
- In poor risk MM

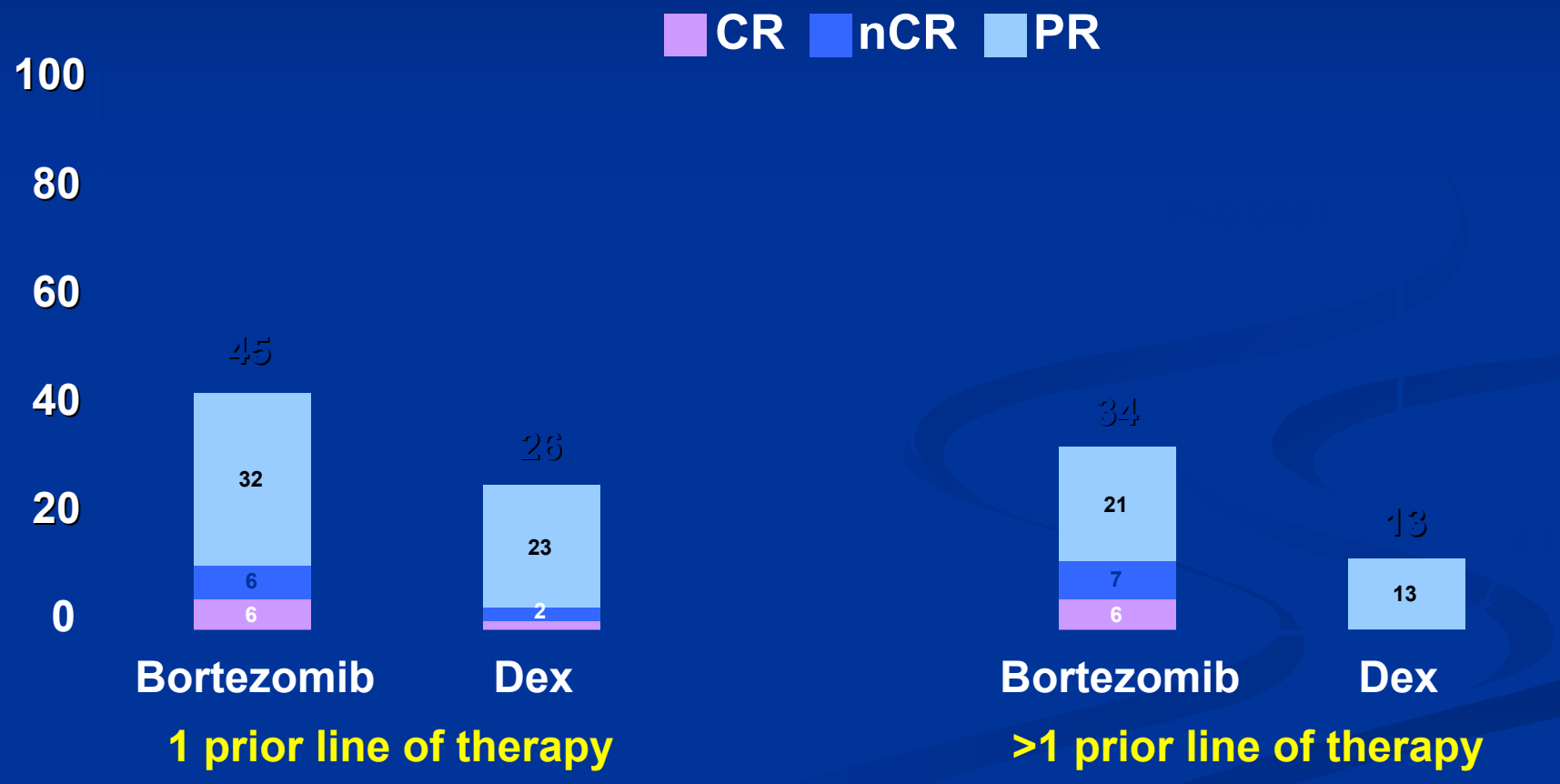
  = Auto/RIC ALLO not > tandem Auto

  = High relapse rate

ONLY IN CLINICAL TRIALS

Bortezomib in the treatment of relapsed MM

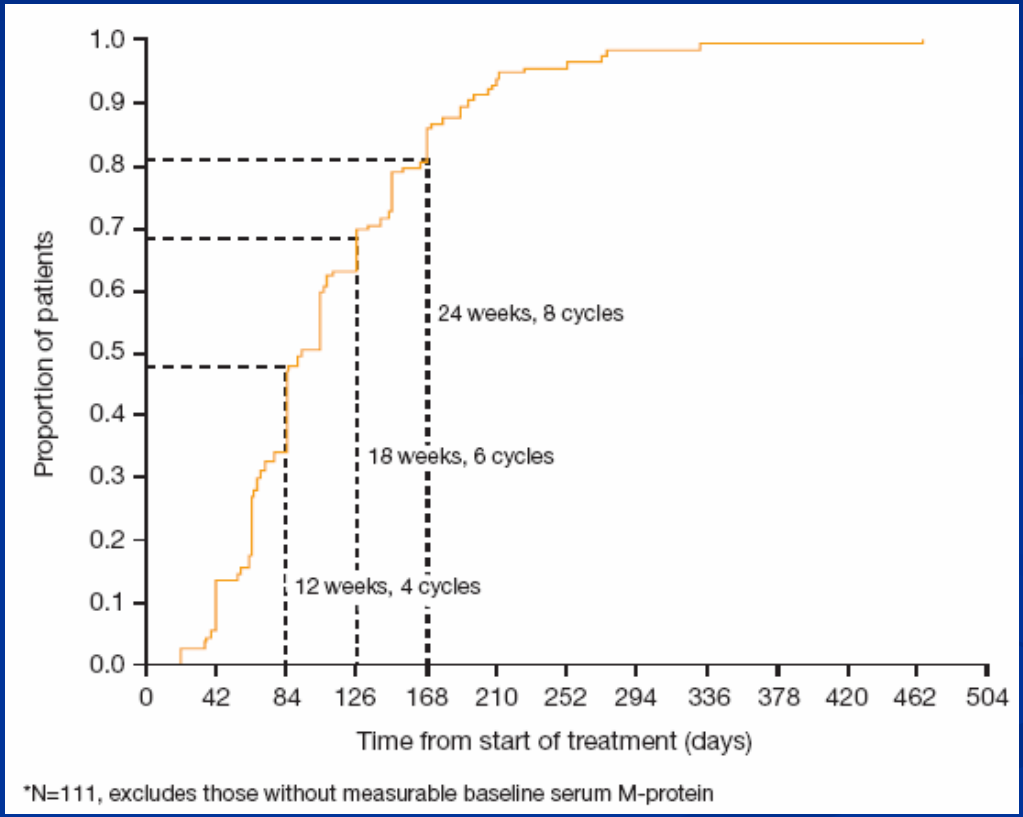
Higher response rates with second-line treatment compared with later therapy



Sonneveld *et al. Haematologica* 2005;90(Suppl 1):146 (Abstract PO.721); Poster at IMW 2005

Best response achieved after longer duration of bortezomib therapy

Time to maximal serum M-protein reduction in patients responding to bortezomib



Approximately 20% of patients responding to bortezomib achieved maximal M-protein reduction in cycle 8 or later

Bortezomib dose modification for the management of PN

Severity of PN signs/symptoms	Modification of dose and regimen
Grade 1 (paresthesia and/or loss of reflexes without pain or loss of function)	No action
Grade 1 with pain or grade 2 (interfering with function but not with ADL)	Reduce bortezomib to 1.0 mg/m^2
Grade 2 with pain or grade 3 (interfering with ADL)	Withhold bortezomib until toxicity resolves then reinitiate at 0.7 mg/m^2 and administer once per week
Grade 4 (permanent sensory loss interfering with function)	Discontinue bortezomib

Relapsed or Refractory

Bortezomib Combination Regimens in Relapsed Multiple Myeloma

Study	Regimen	Evaluable Patients (n)	CR/nCR	PR	OR
Berenson (ASH 2005)	Bortezomib + Arsenic Trioxide + Ascorbic Acid	21	10%	10%	19%
Reece (ASH 2005)	Bortezomib + Cyclophosphamide + Prednisone	20	15%	30%	45%
Popat (ASH 2005)	Bortezomib + Low-dose Melphalan + Dexamethasone	21	5%	48%	52%
Palumbo (ASH 2005)	Bortezomib + Melphalan + Prednisone + Thalidomide	29	28%	41%	69%
Kropff (ASH 2005)	Bortezomib + Dexamethasone + Cyclophosphamide	50	12%	70%	82%
Terpos (ASH 2005)	Bortezomib + Melphalan + Dexamethasone + Thalidomide	36	42%	17%	58%

Relapsed or Refractory

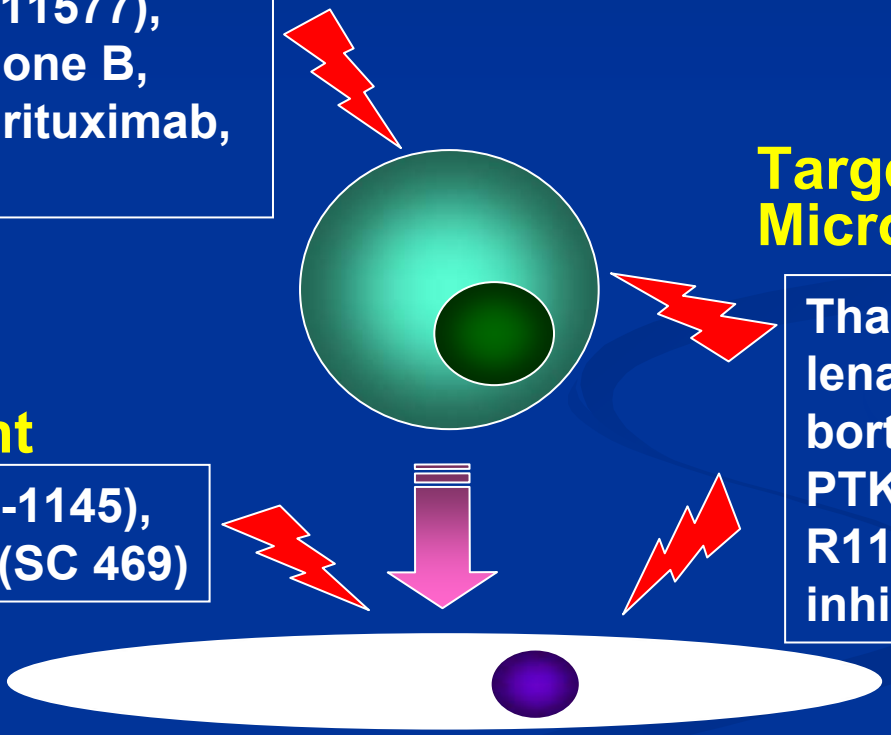
Bortezomib Combination Regimens in Relapsed Multiple Myeloma

Study	Regimen	Evaluable Patients (n)	CR/nCR	PR	OR
Orlowski (Blood 2005)	Bortezomib + Doxil®	22	36%	36%	73%
Berenson (JCO 2006)	Bortezomib + Melphalan	34	15%	32%	47%
Zangari (ASH 2005)	Bortezomib + Thalidomide +/- Dexamethasone	85	16%	39%	55%
Chanan-Khan (IMW 2005)	Bortezomib + Doxil + Thalidomide	16	25%	38%	63%
Hollmig (ASH 2004)	Bortezomib + Doxorubicin + Thalidomide + Dexamethasone	16	25%	38%	63%
Richardson (ASH 2005)	Bortezomib + Lenalidomide	21	10%	43%	52%

Novel Therapies Targeting the Myeloma Cell in Its BM Microenvironment

Targeting MM Cell

17AAG, TRAIL, SAHA, IGF1R Inhibitors, FTI (eg, R11577), telomestatin, epothilone B, oblimersen sodium, rituximab, CD40 MoAb



Targeting MM Cell BM Microenvironment

Thalidomide, lenalidomide, bortezomib, AS_2O_3, PTK787, FTI (e.g., R11577), 2ME2, LPAAT inhibitors

Targeting BM Microenvironment

IKK inhibitors (eg, PS-1145), P38-MAPK inhibitors (SC 469)

Combinations With Bortezomib

- Phase I-II
  - Liposomal doxorubicin[1]
  - Low-dose melphalan[2]
  - Thalidomide ± Dex[3]
- New trials
  - Lenalidomide
  - Dexamethasone + low-dose po cyclophosphamide
  - Dexamethasone + liposomal doxorubicin
  - As_2O_3
  - 17- AAG (KOS 953)
  - Scios 469 (P38 MAPK inhibition)
  - FTI inhibitors

1. Orlowski RZ, et al. ASH 2003; Abstract 1639.
2. Yang et al. ASH 2003; Abstract 826.
3. Zangari et al. ASH 2003; Abstract 830.

Gene Microarray Identifies Molecular Mechanism of Bortezomib Anti-MM Activity and Potential Pathways of Resistance

➢Caspase cascade

↑ pro-caspases -9, -7 and –5
↑ Fas (Apo-1, CD95)
↑ DR5 Apo2L/TRAIL receptor
↑ Fas (transmembrane)
↓ soluble (decoy) Fas (alt. Splicing)
↓ Toso (negative Fas regulator)
↓ Caspase inhibitors

➢IGF signaling

IGF-1
↓ IGF-1R
↓ insulin receptor substrate-1 (IRS-1)

➢IκB

IκB kinase-alpha, ↑ IκB kinase-gamma

Ubiquitin/Ptoteasome pathway

↑ Ubiquitin
↑ p40.5, p44.5, p55, p58
↑ HsN3, HsC7-I, HsC10-II
↑ p112, p97,
↑ Nin1p, HC5, HC8,
↑ POH1, X, Y, Z,

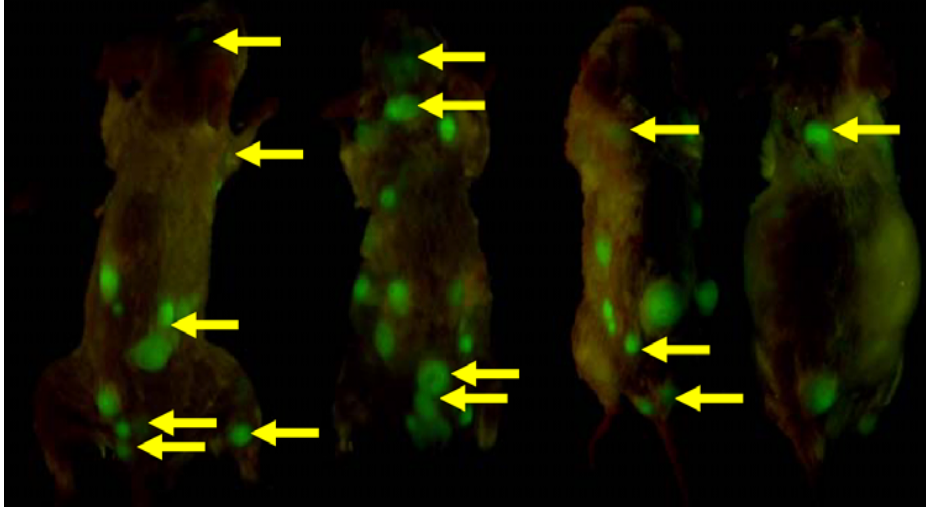
Molecular Chaperones

↑ hsp90
↑ hsp70
↑ hsp40
↑ hsp28
↑ hsp32 (heme oxygenase-1)
↑ heat shock protein apg-1
↑ mitochondrial hsp75

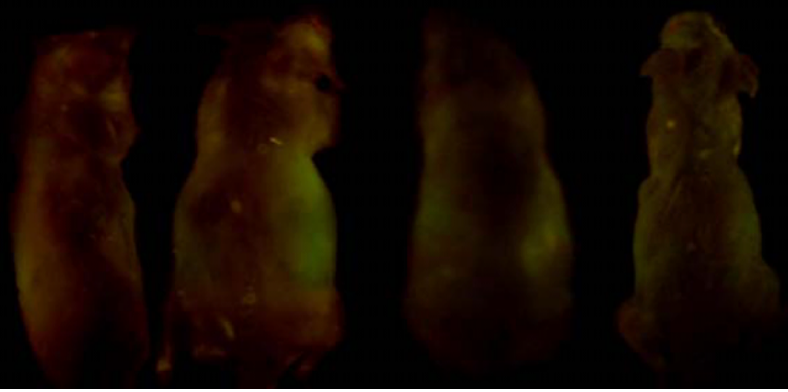
Mitsiades et al. Proc Natl Acad Sci (USA) 2002; 99: 14374

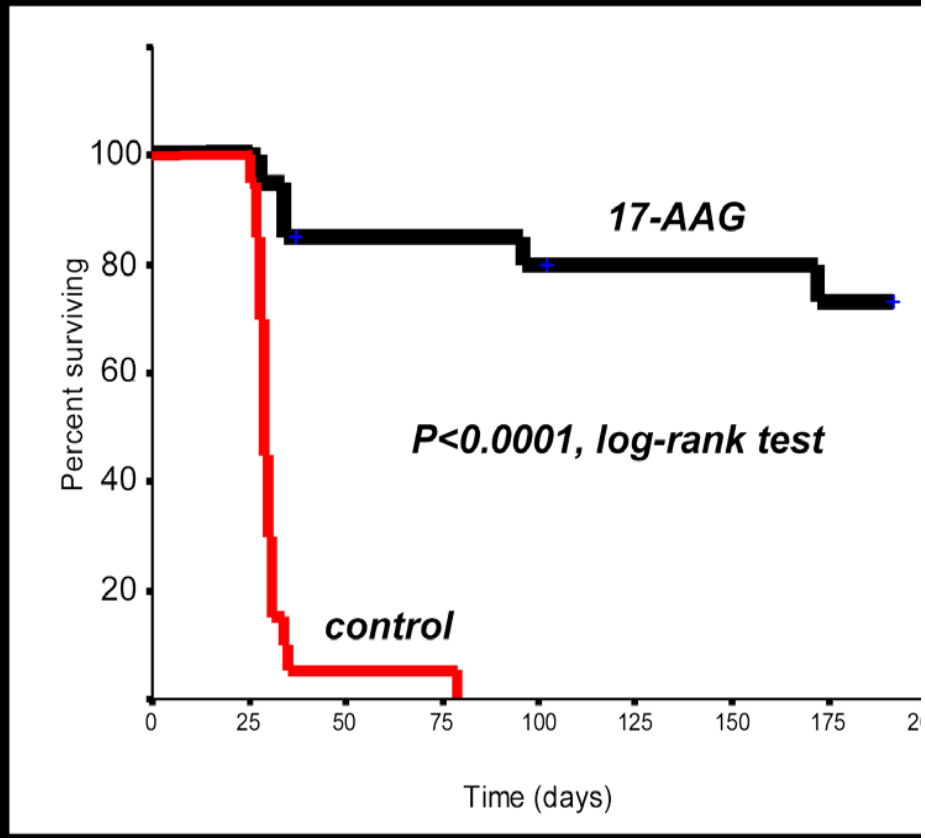
The Hsp90 Inhibitor 17-AAG Prolongs Survival in a SCID/NOD Mouse Model of Diffuse Multiple Myeloma

Control cohort

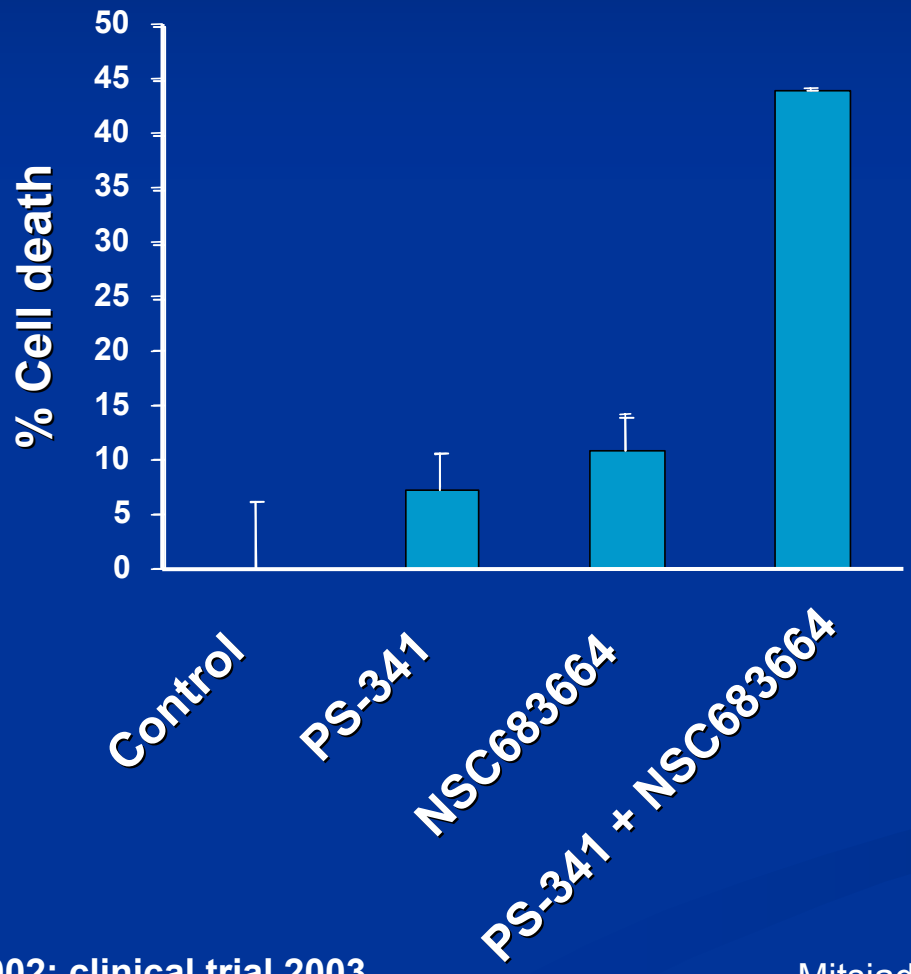


17-AAG-treated cohort





Bortezomib + Hsp-90 inhibitor augments MM cell death*

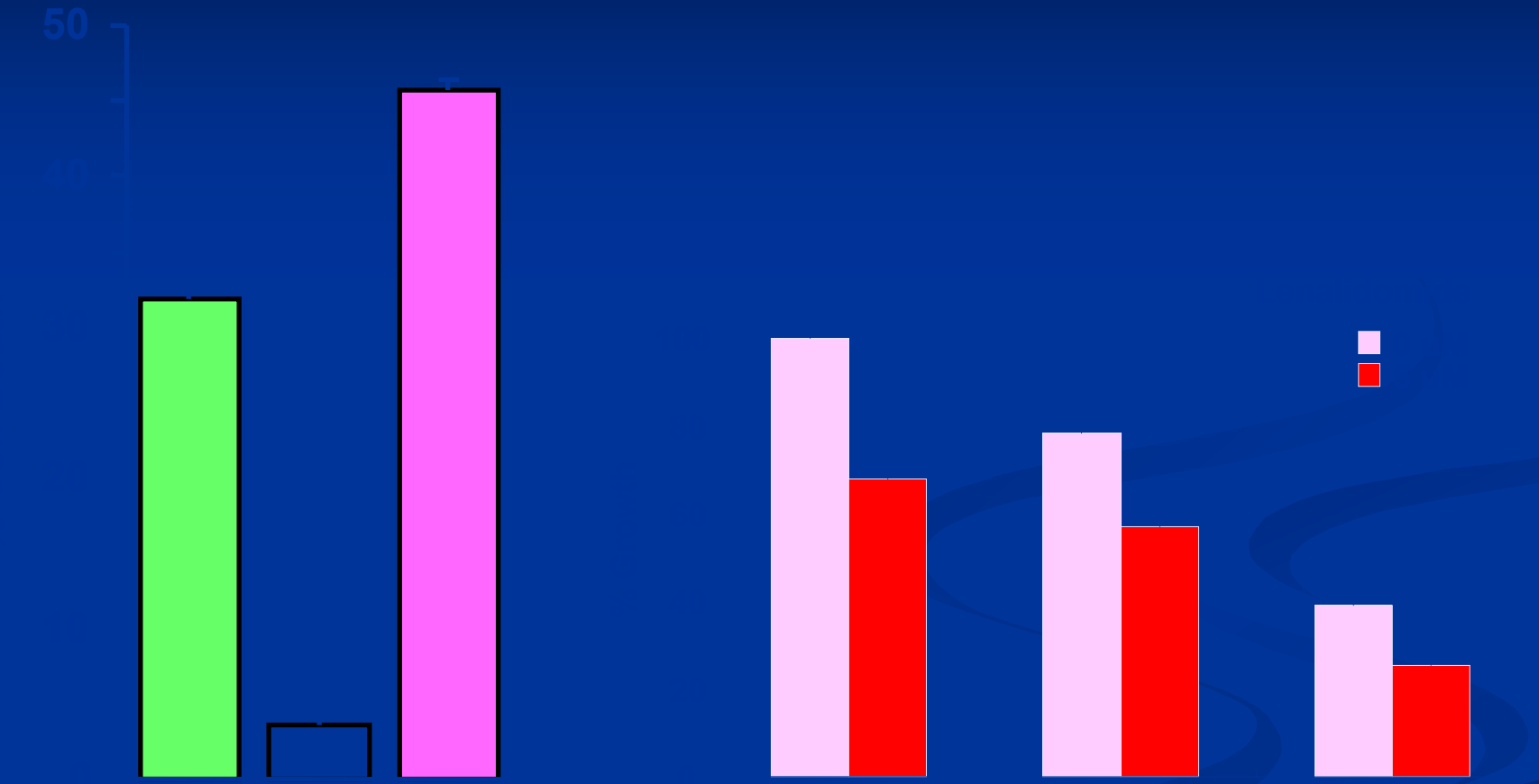


Bortezomib combined with an Hsp-90 inhibitor is much more cytotoxic than either agent alone

***2002: clinical trial 2003**

Mitsiades *et al. Proc Natl Acad Sci USA* 2002;99:14374–9

Combination of Bortezomib + Lenalidomide



Mitsiades N, et al. *Blood*. 2002;101:2377.

THALIDOMIDE IN COMBINATION IN NEWLY DIAGNOSED PATIENTS

with conventional chemotherapy

-TCD
-DVd T
-MP T

with novel agents (bortezomib)

-TVD ,TT3
-MPVT

Bortezomib-associated PN is reversible in the majority of patients (APEX)

- **Incidence of PN (37% 124/331)**
  - 10% grade 1
  - 18% grade 2
  - 8% grade 3
  - <1% grade 4
- **64% (58/91) of patients with ≥grade 2 PN experienced improvement or resolution**
  - 55% (50/91) had complete resolution (return to baseline)
  - 9% (8/91) experienced improvement by at least 1 CTC grade
  - Median time to improvement/resolution:
    110 days from diagnosis

THALIDOMIDE ALONE
TOXICITY IS RELATED TO THE DAILY DOSE

Incidence of grade ≤ 2 adverse effects *(Singhal 1999)*

	200 mg N = 83	400 mg N = 72	600 mg N = 57	800 mg N = 46
Constipation	35	44	44	59
Weakness/Fatigue	29	31	39	48
Somnolence	34	43	40	43
Tingling/Numbness	12	14	19	28
Dizziness	17	25	23	28
Rash	16	18	21	26
Mood changes	16	24	23	22
Incoordination	16	17	14	22
Tremor	10	13	19	22

PERIPHERAL NEUROPATHY

- Clinical symptoms : mostly sensitive neuropathy
  - . Numbness, paresthesia
  - . Pain in the hands or arms, feet or legs
- Electrophysiologic studies
  - . Mostly axonal damage
- Incidence
  - . 28% overall *(Glasmacher 2005)*
  - . Up to 75% in patients with prolonged treatments *(Tosi 2004)*
  - . Role of previous Tx and previous neuropathy
- Prognosis
  - . Grade > II 6% overall (27.5% in patients treated > 1yr)
  - . Can be irreversible if Tx not promptly withdrawn

DEEP VEIN THROMBOSIS

- Clinical manifestations
  - At the site of CVL or at distant sites
  - Including pulmonary embolism

- Date of onset : median time 42 D

- Incidence (FDA report + clinical studies)

Thal alone	Thal + Dex	Thal + Chemo
< 5%	10 – 15%	up to 30%

Bortezomib in Relapsed MM

- **Phase II SUMMIT, CREST**
  - Basis for initial approval for treatment of relapsed/refractory MM in 2003 (USA) and 2004 (Europe)
- **Phase III APEX**
  - Sub-analysis confirmed significant efficacy in patients who had received only 1 prior line of therapy compared with those who had received more than one line of prior therapy
  - 2005: bortezomib approved for treatment of patients with MM who have received at least 1 prior therapy (USA and Europe)

APEX: Peripheral Neuropathy (PN)

- 69% of 310 pts on Bortezomib reported symptoms of PN at baseline (FACT/GOG-Ntx score >0)
- PN reported in:
  - Bortezomib 36% (≥ Grade 3 = 8%)
  - Dex 9% (≥ Grade 3 < 1%)
- Baseline FACT/GOG-Ntx score directly correlated with development of ≥ Grade 3 PN
- PN ≥ Grade 2 improved or resolved in 51% of pts
  - Median time to improvement or resolution from first onset = 107 d (~ 3.5 mos)

Lenalidomide Phase 1 Trial in Relapsed Multiple Myeloma

Results

- Dose-limiting toxicities of myelosuppression in all patients treated with 50-mg dose after day 28
- MTD 25 mg in this patient population
- No somnolence, constipation, or neuropathy at any dose
- Stable disease or response in 79% of patients
  - 71%: ≥25% decrease in M protein
  - 8%: stable disease

MTD, maximal tolerated dose

Richardson PG et al. *Blood*. 2002;100:3063.

MM- 009/010 Grade 3/4 Hematologic Toxicity

	MM-009		MM-010	
	Len/De x N = 170	Dex N =171	Len/De x N = 176	Dex N =175
Neutropenia, %	30.0	3.5	17.6	1.1
Febrile Neutropenia	2.9	0	1.1	0
Thrombocytopenia	10.6	6.4	9.7	5.7
Anemia	10.6	3.5	4.5	4.0

MM- 009/010 Grade 3/4 Other Adverse Events

	MM-009		MM-010	
	Len/Dex N = 170	Dex N =171	Len/Dex N = 176	Dex N =175
DVT/PE, %	15.3	3.5	8.5	4.5
Atrial Fibrillation	4.7	0	0.6	1.7
CHF	2.4	0	0.6	0
Constipation	1.8	0	1.7	0.6
Diarrhea	2.4	0	2.4	1.2
Fatigue	5.9	4.7	6.8	3.4
Neuropathy	2.9	1.2	1.1	0.6

AUTOLOGOUS STEM CELL TRANSPLANTATION

1. Is ASCT still superior to CC ?
2. Are tandem ASCT superior to single ASCT ?
3. What is the best induction TT prior to ASCT ?
4. What is the role of consolidation/maintenance ?
5. Will novel agents replace ASCT ?

AUTOLOGOUS STEM CELL TRANSPLANTATION

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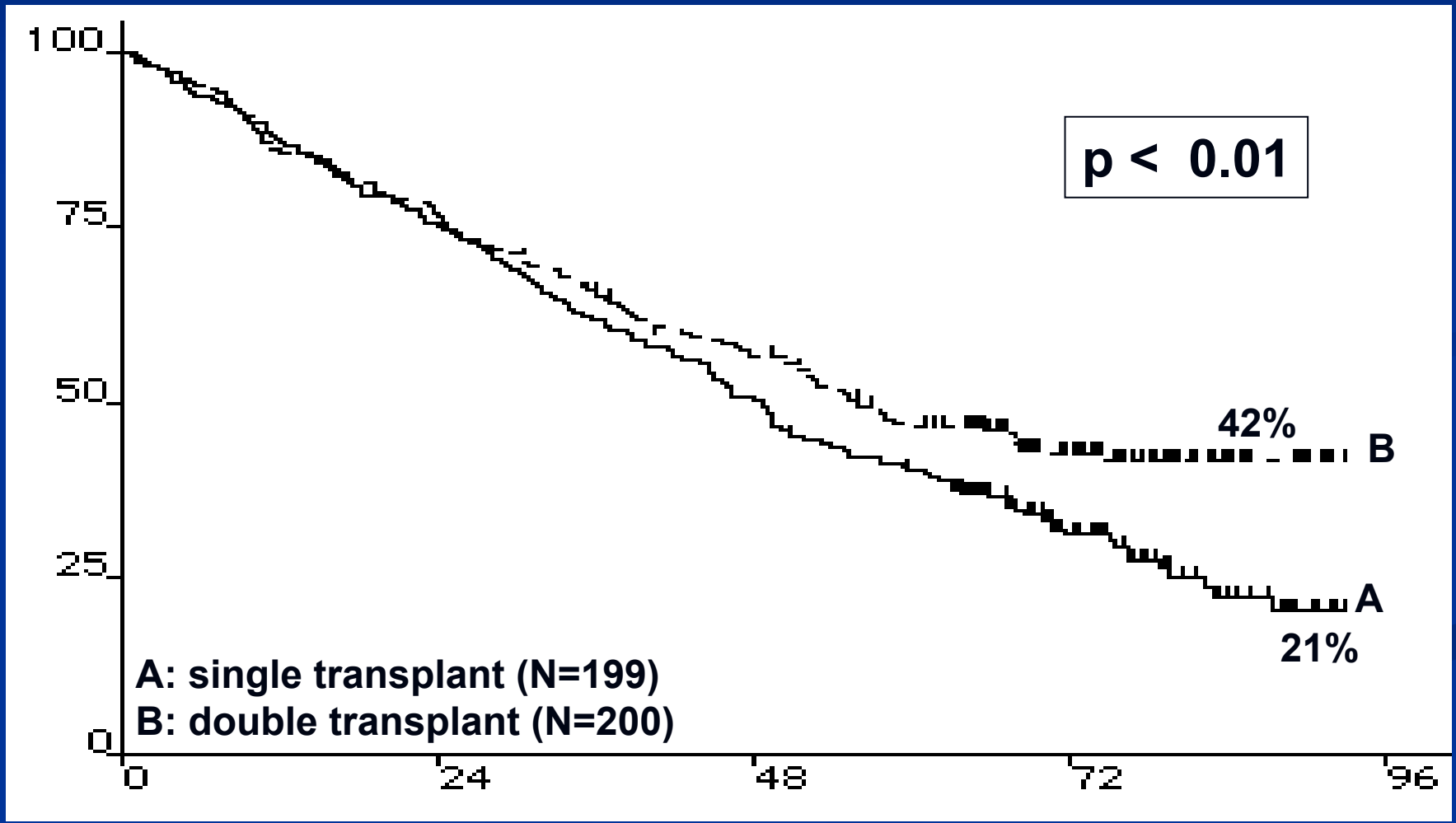
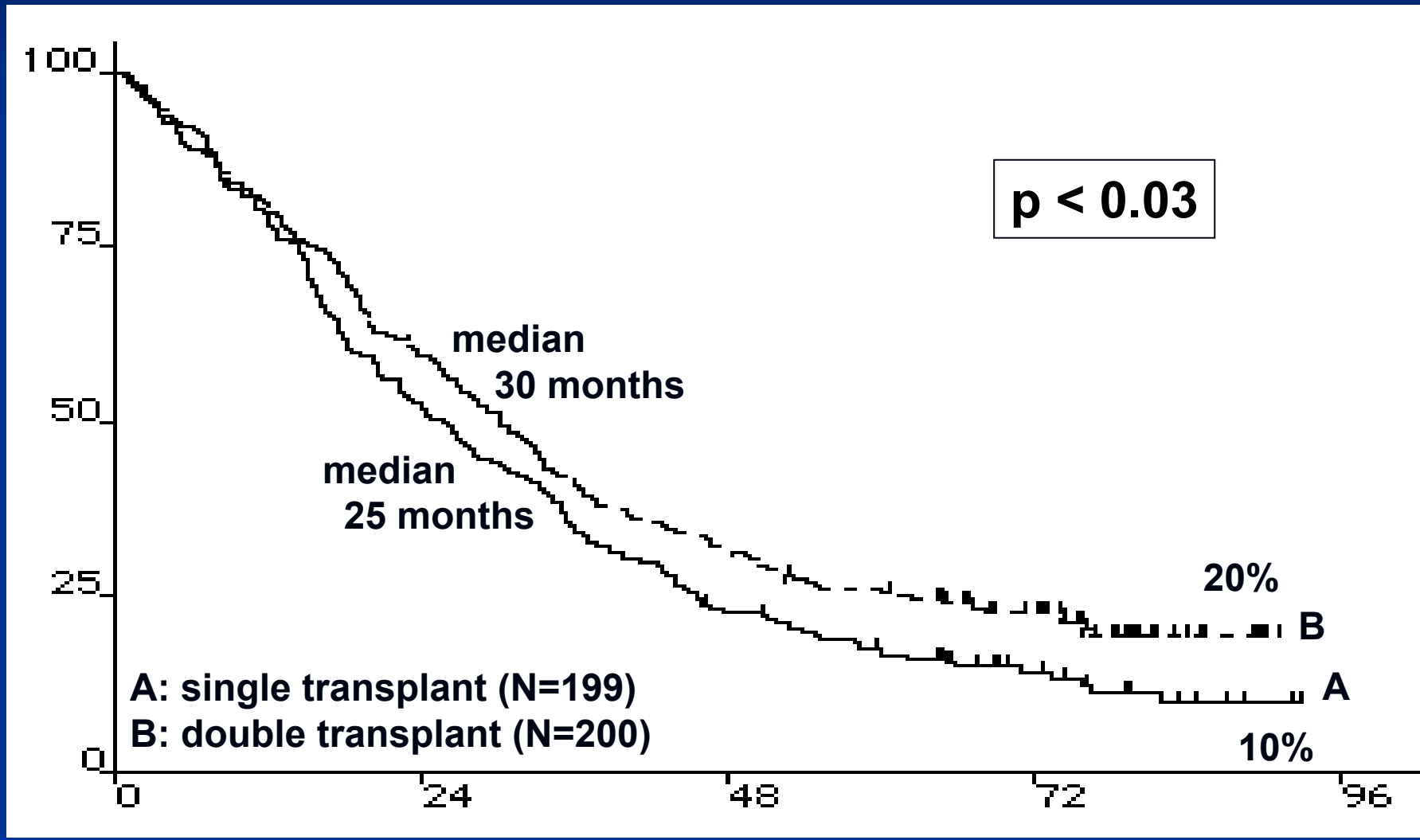
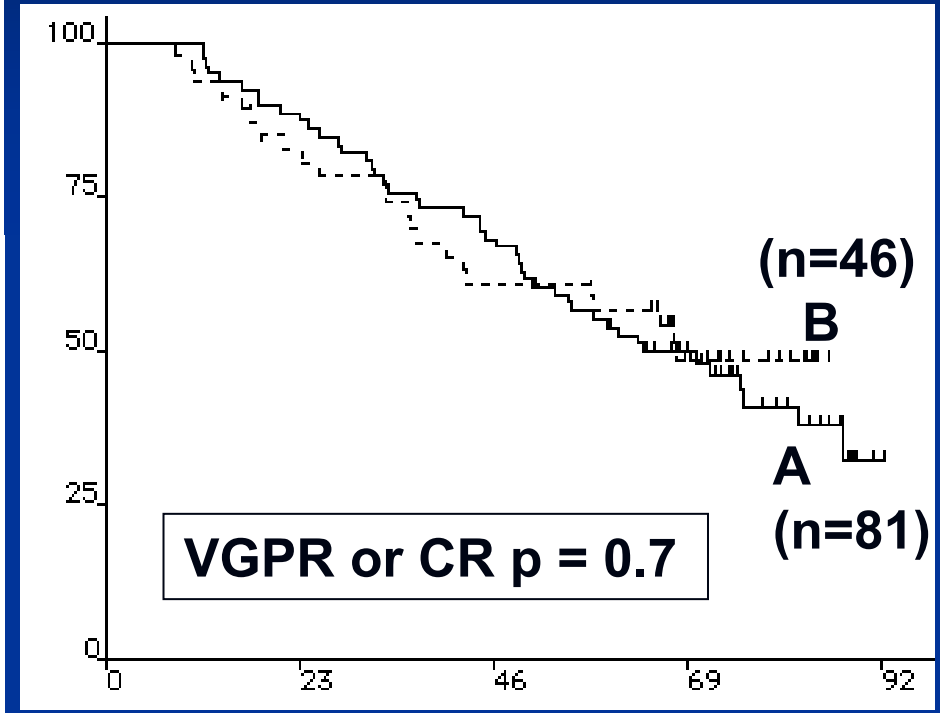
IFM 94 : OVERALL SURVIVAL

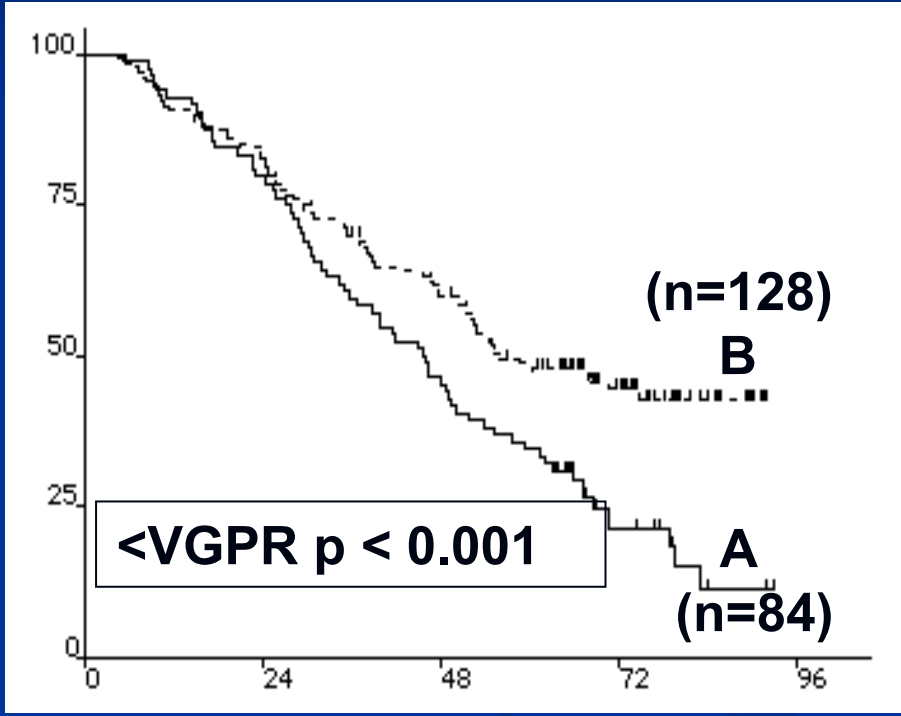


IFM 94 : EFS


100
75
50
25
0
0
24
48
72
96
p < 0.03
median
30 months
median
25 months
20%
B
A
10%
A: single transplant (N=199)
B: double transplant (N=200)

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





AUTOLOGOUS STEM CELL TRANSPLANTATION

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INDUCTION TREATMENT CONCLUSION

1) Bortezomib-containing regimens appear to increase the CR rate prior to ASCT

2) However we still don't know whether a higher CR rate prior to ASCT

-will result in a higher overall CR rate (Barlogie 06,Goldschmidt ASH 05)

-will improve OS

AUTOLOGOUS STEM CELL TRANSPLANTATION

1. Is ASCT still superior to CC ?
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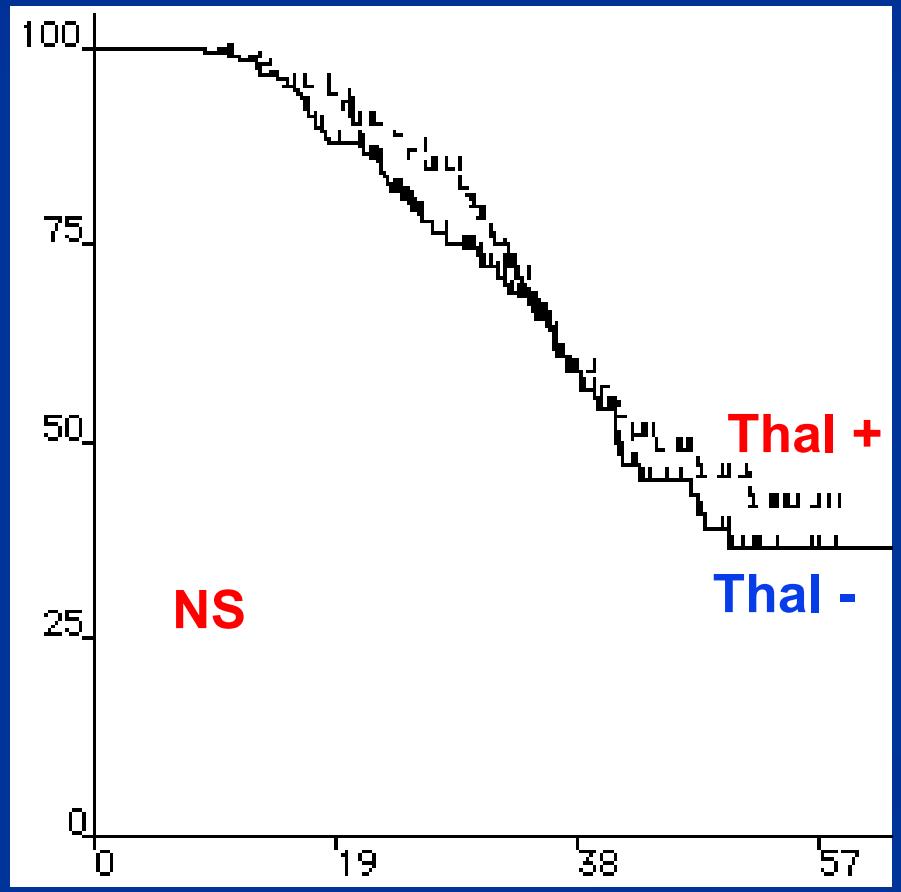
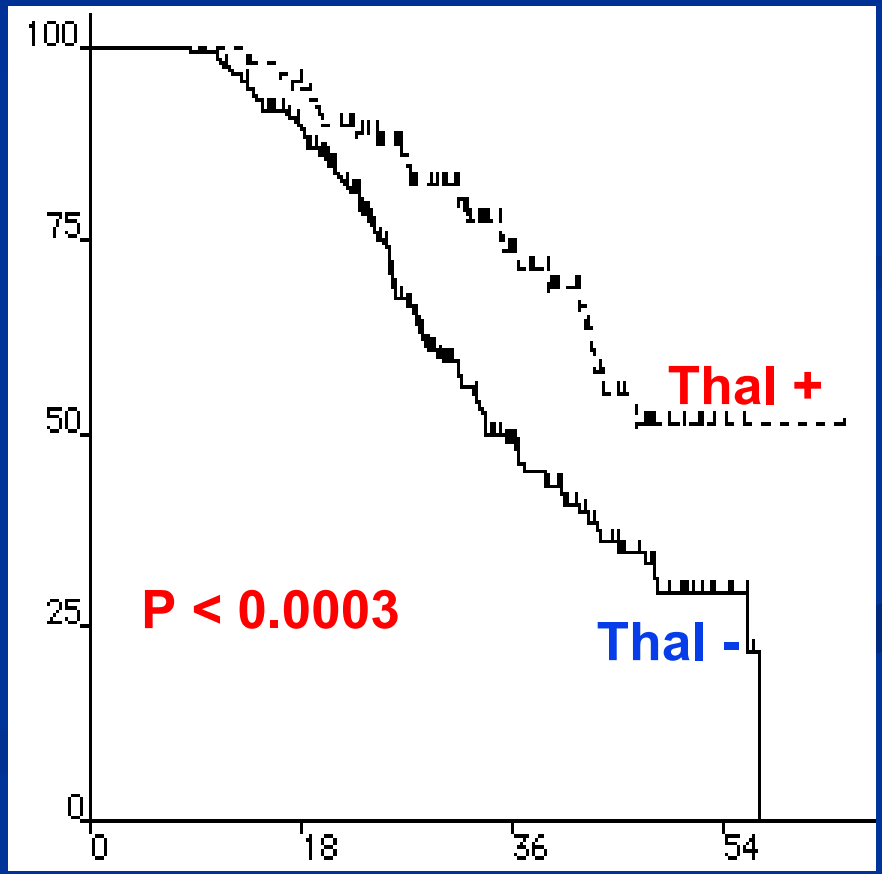
IFM 99 02 : EFS According to Response at Random

Response at Random ≥ 90%



Response at Random < 90%



IFM 99 02 : The Thalidomide Arm.

- The most common toxicities were: neuropathy (68%), fatigue (34%), constipation (20%), neutropenia (7%), and cardiac (4%).
- The incidence of DVT was not increased in the Thal arm (4%).
- 39% of patients had to discontinue Thal for drug-related AE.
- Neuropathy was the main reason for discontinuation.
- Median duration of Thal : 15 m (1-51).
- Mean dosage of Thal : 200 mg / d (50-400).

AUTOLOGOUS STEM CELL TRANSPLANTATION

1. Is ASCT still superior to CC ?
2. Are tandem ASCT superior to single ASCT ?
3. What is the best induction TT prior to ASCT ?
4. What is the role of consolidation/maintenance ?
5. Will novel agents replace ASCT ?

COMPARISON OF IFM 90 / IFM 94 AND IFM99 TRIALS

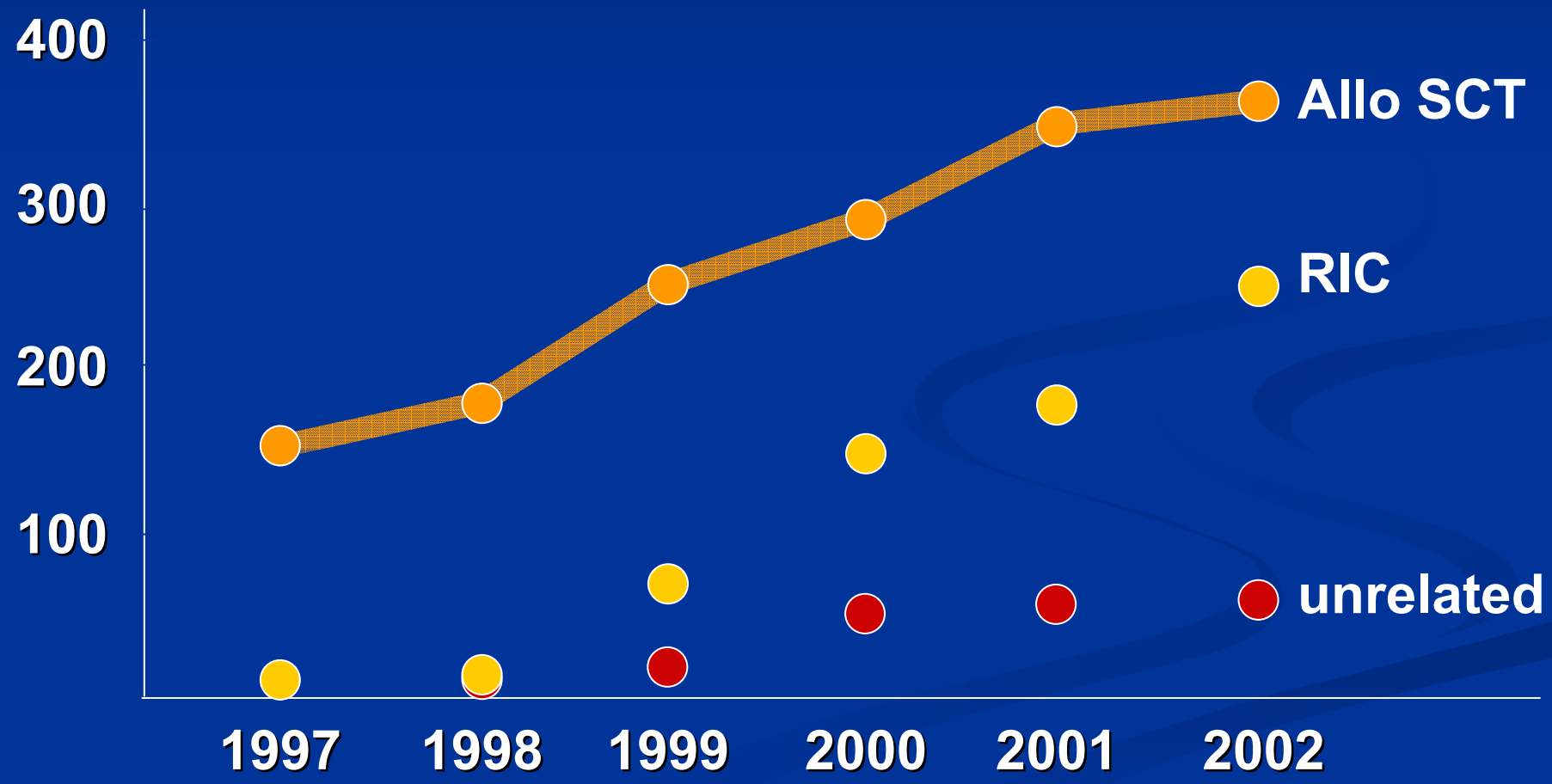
	IFM90 N = 200		IFM94* N = 399		IFM99 N = 1064
	CT	Auto	Single	Double	Double
Med EFS	18	27	25	30	35
5y SV	12%	52%	38%	46%	62%

* patients < 60 years

C0NCLUSIONS

- Novel agents already improve OS when used in relapsed MM
- Novel agents are changing the standard of care in older patients
- Novel agents improve the results of ASCT and are even challenging ASCT in younger patients
- Patients without unfavorable prognostic factors already obtain prolonged EFS but patients with high B2M and unfavorable cytogenetics need other approaches

Allogeneic SCT for Multiple Myeloma in Europe (EBMT)



DE NOVO MM, < 65 years, β2M > 3mg/l AND D13

VAD x 4

Stem cell collection

ASCT n°1 : HDM 200

HLA-sibling donor available
Mini-allo

Bu 4 Fluda 25X5
ATG 2.5/KG X5

IFM9903 trial N=65

No donor available
ASCT n°2

HDM 220 +/- anti-IL6

IFM9904 trial N=219

TOTAL THERAPY II

Comparison with TT1 ***(Barlogie, ASCO 2005)***

- **668 pts compared to 231 pts treated with TT1**
- **CR and near CR 66% vs 43% ($p < 0.001$)**
- **4-yr EFS and OS:62% and 69%**
- **TT2>TT1 in pts without cytogenetic abnormalities (2/3)**
- **benefit even in the non Thal arm**

DE NOVO MM, < 65 years, β2M > 3mg/l AND D13

VAD x 4

Stem cell collection

ASCT n°1 : HDM 200

HLA-sibling donor available
Mini-allo

Bu 4 Fluda 25X5
ATG 2.5/KG X5

IFM9903 trial N=65

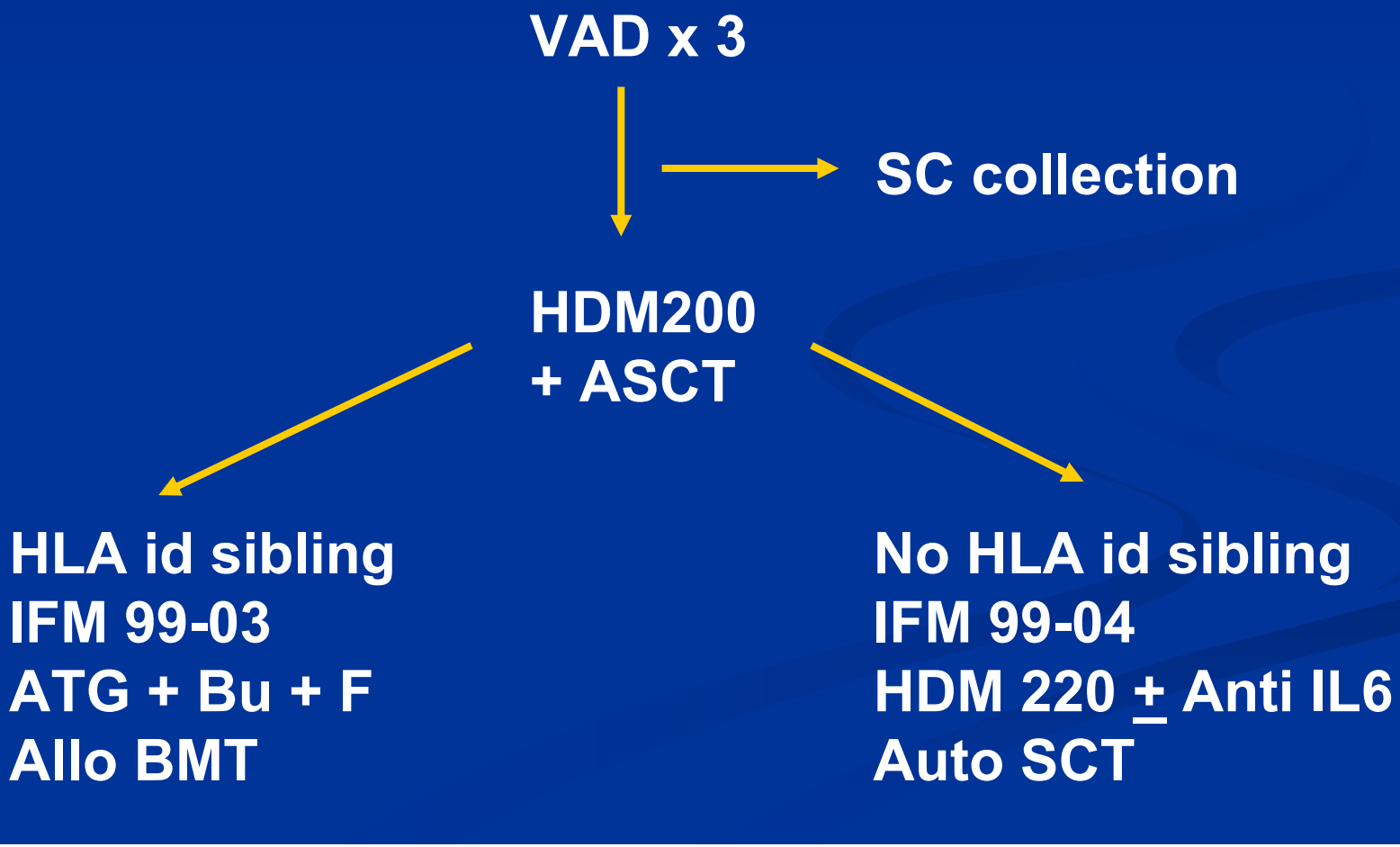
No donor available
ASCT n°2

HDM 220 +/- anti-IL6

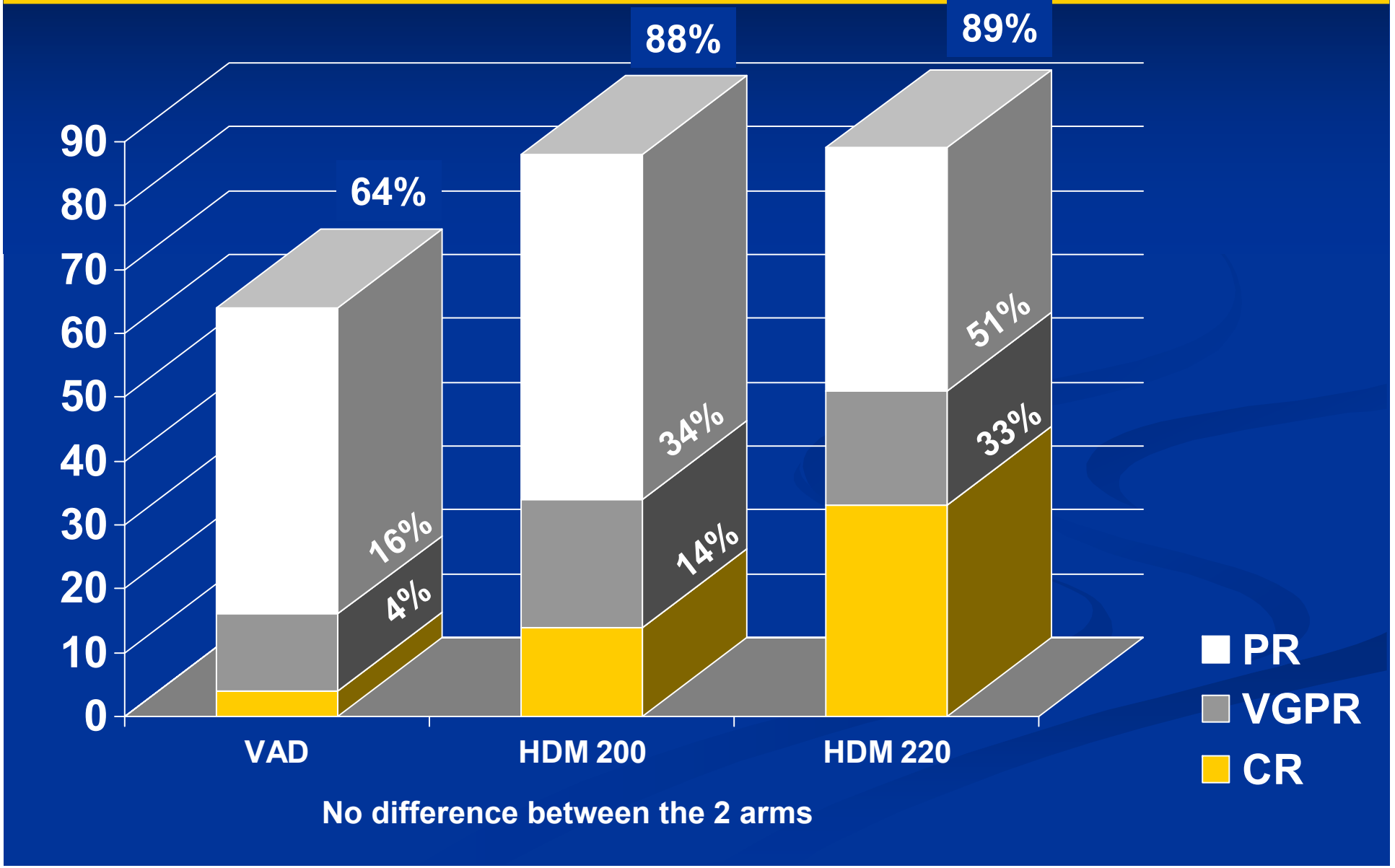
IFM9904 trial N=219

IFM 99-03 / 99-04

- ≤ 65 years
- β2 mic > 3 mg/l + Δ13 (FISH)

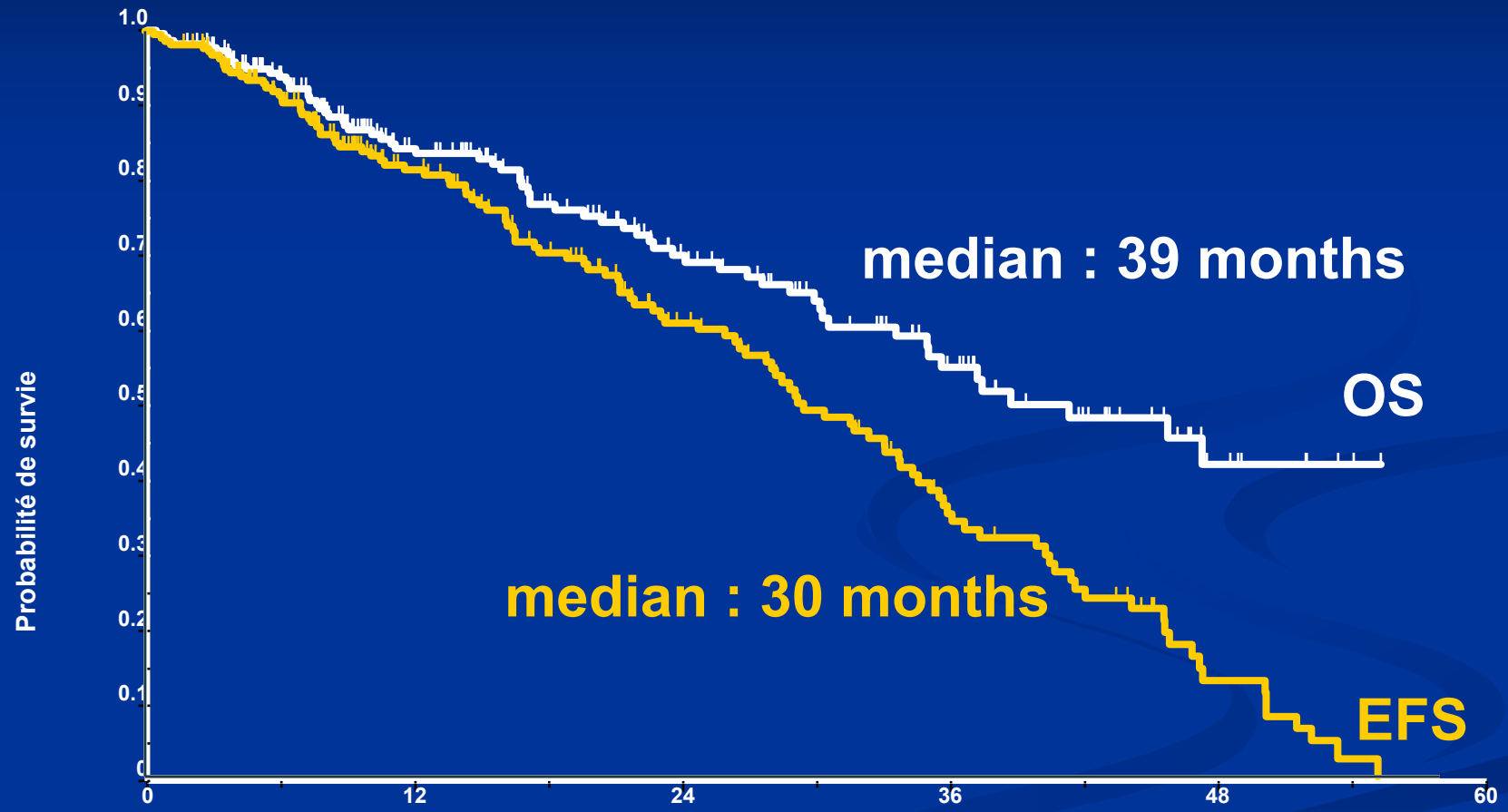


IFM 99-04 P MOREAU BLOOD 2006
RESPONSE RATE



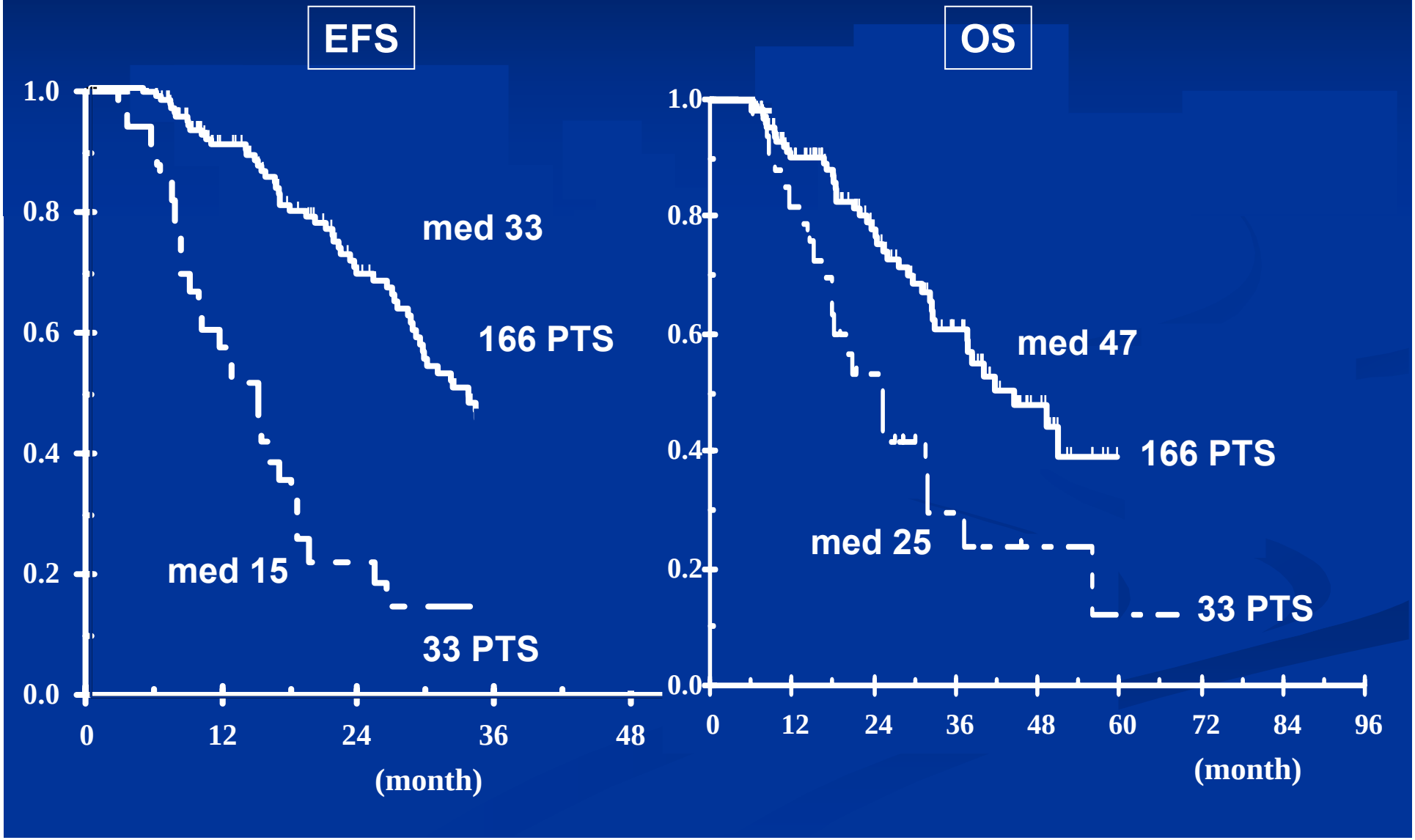
No difference between the 2 arms

IFM 99-04

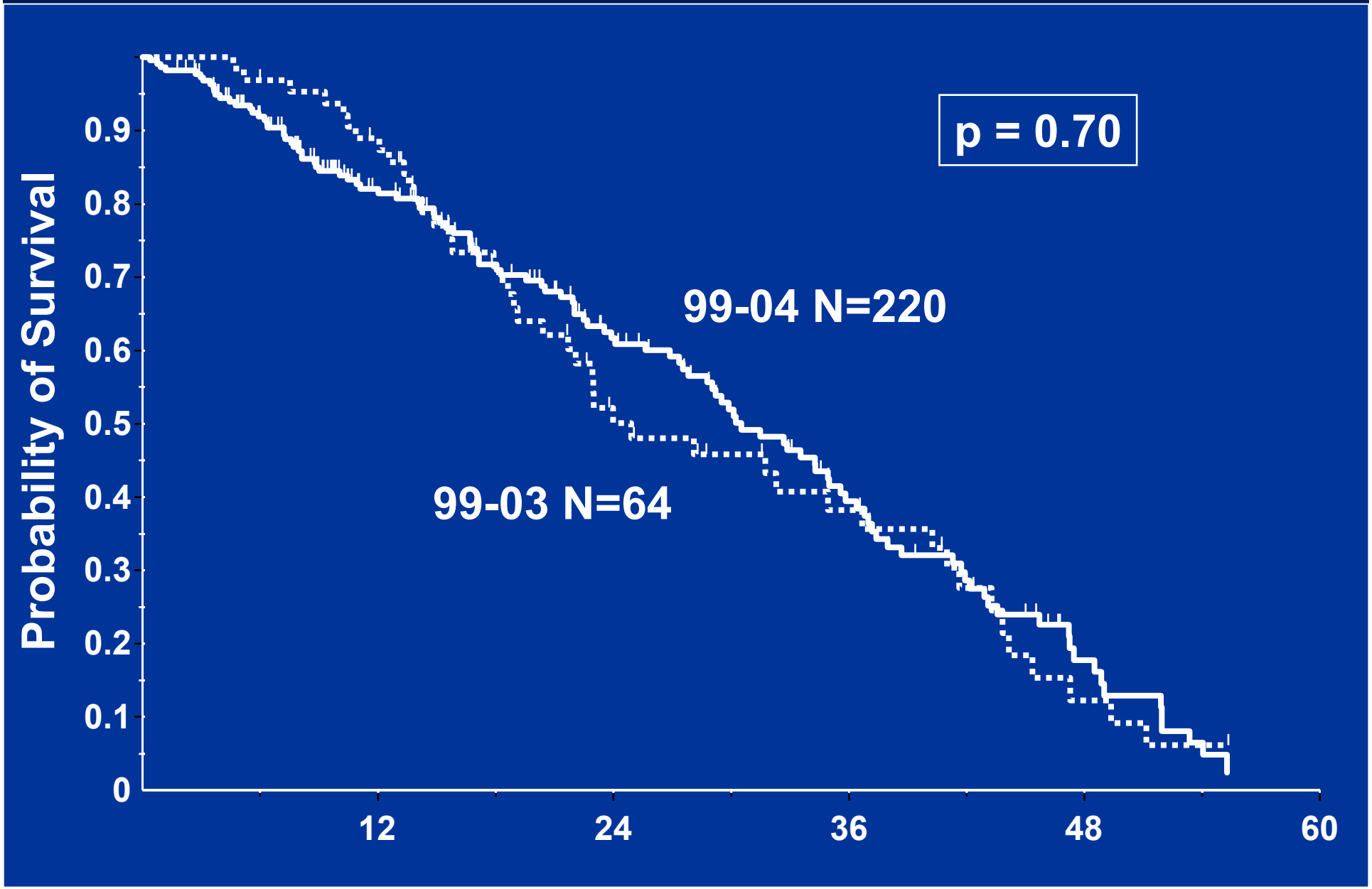

Probabilité de survie
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
0
12
24
36
48
60
median : 39 months
OS
median : 30 months
EFS

DOUBLE ASCT WITH MORE INTENSIVE 2ND HDT IMPROVES THE OUTCOME OF POOR-RISK MM

Historical Comparison



EFS intent-to-treat: IFM 99-03 VS 99-04



HOW TO IMPROVE ASCT

- Double ASCT
- Further increase of dose-intensity
- Integrating novel agents in the ASCT paradigm

IFM 2005-01

Patients with newly diagnosed MM ≤ 65 y.o.

R

	A1	A2	B1	B2
INDUCTION	VAD VAD VAD VAD*	Vel/Dex Vel/Dex Vel/Dex Vel/Dex*	VAD VAD VAD VAD*	Vel/Dex Vel/Dex Vel/Dex Vel/Dex*
	1st ASCT	1st ASCT		
CONSOL.			DCEP DCEP	DCEP DCEP
			1st ASCT	1st ASCT

2nd ASCT if < CR within 3 months

*** SC collection**

IS THERE A ROLE FOR ALLO IN MM ?

- Probably not in good risk patients = results of current treatments do not justify the risk, (specially with the introduction of novel agents)
- In poor risk MM results do not appear to be > Tandem Auto ⟶ evaluate other preparative regimens and GVH prophylaxis
- Follow-up is still short but relapse appears to be a major concern with miniallo
- Role of Novel Agents in reducing the risk of relapse post-RIC allo SCT?

IFM 2005

Induction trial (IFM 2005-01)

VAD **Dex/Vel** **VAD DCEP** **Dex/Vel DCEP**

Autologous Transplantation

Mel 200 + CSP

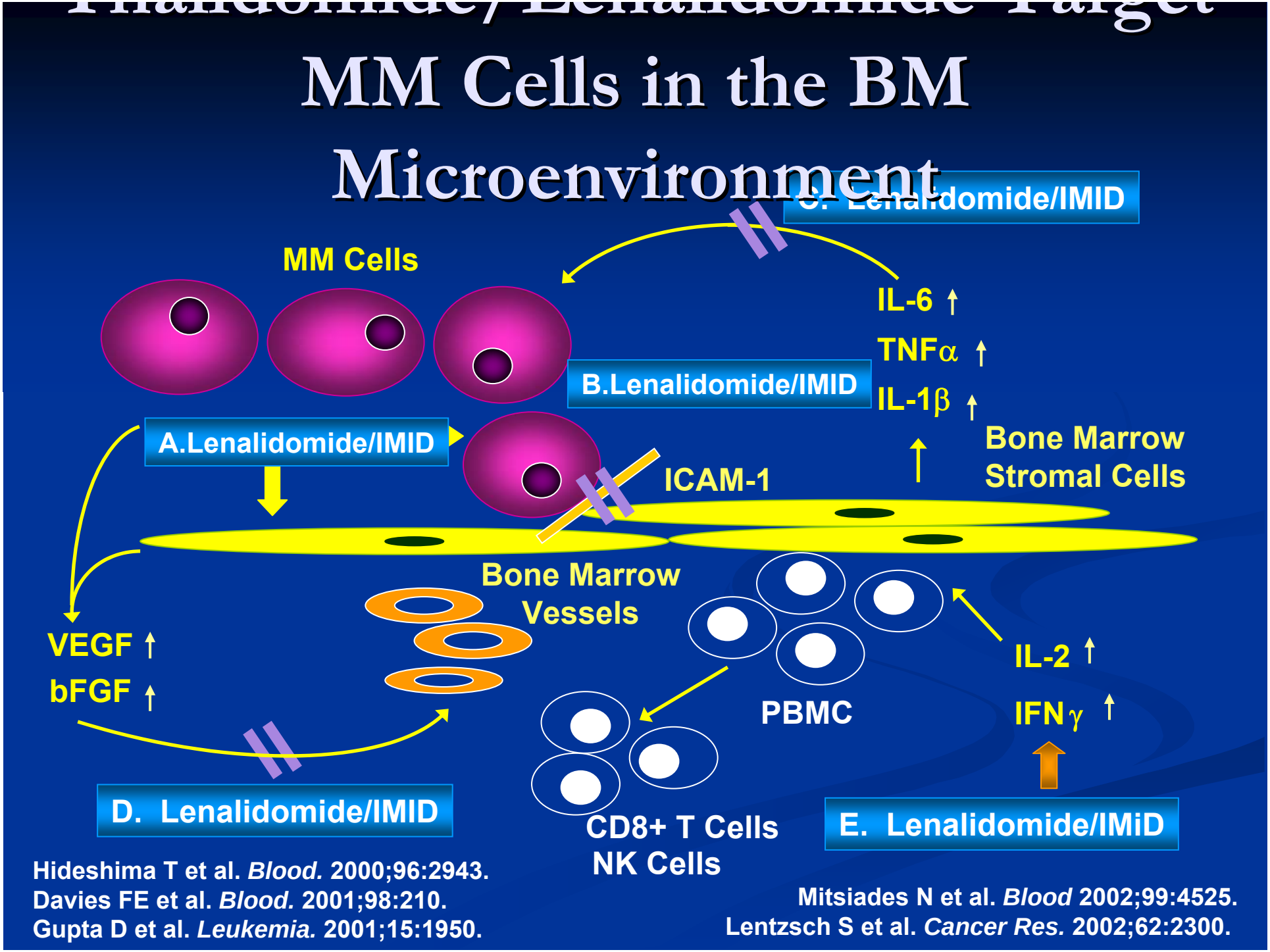
If response within 3 months < 90% : Second ASCT
Or RIC Allo if HLA id donor and 1 adverse pc factor

Patients with <90% response after 2 ASCT :3months of THAL

Maintenance trial (IFM 2005-02)

Revlimid VS Placebo

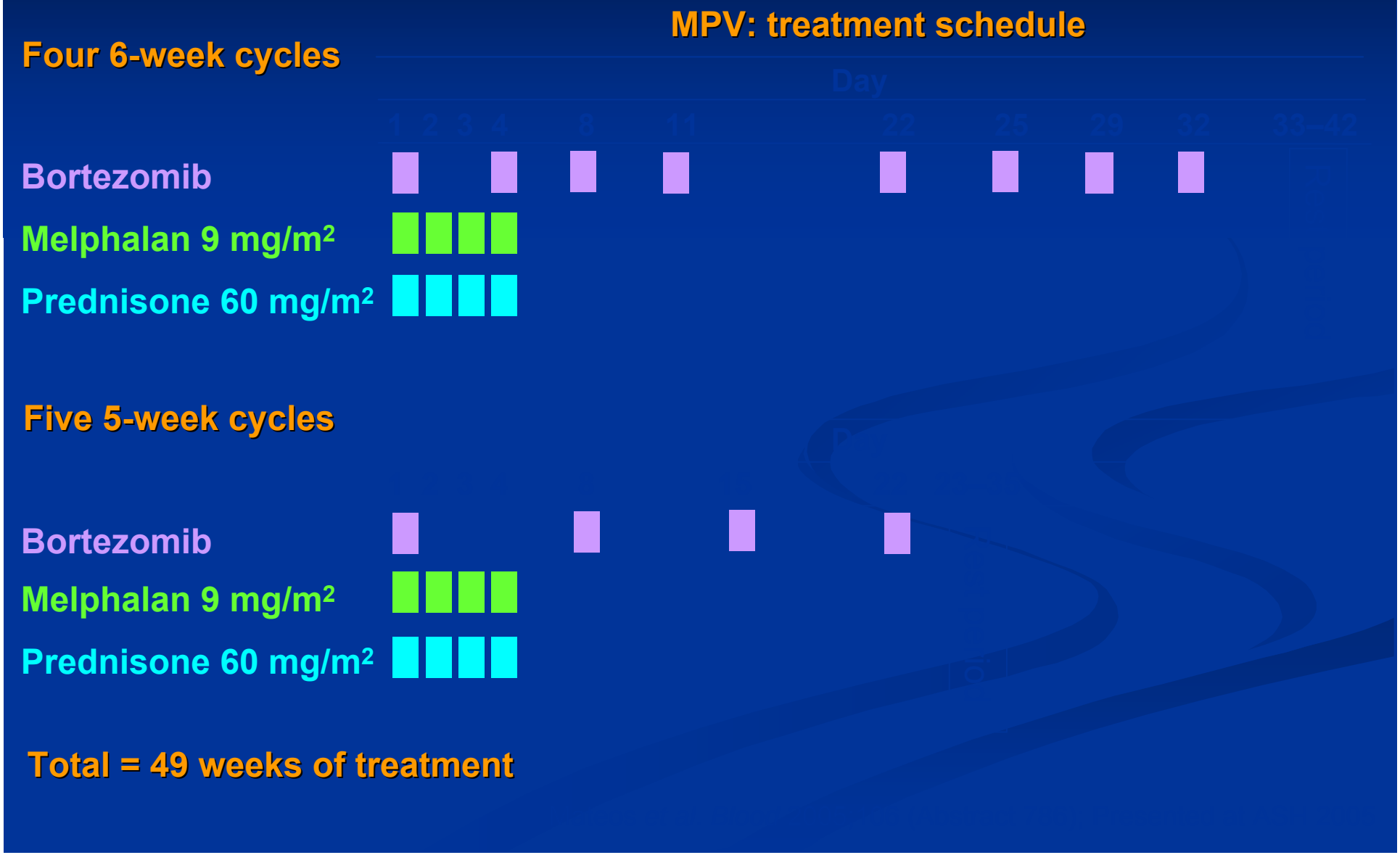
Thalidomide/Lenalidomide Target MM Cells in the BM Microenvironment



Hideshima T et al. *Blood.* 2000;96:2943.
Davies FE et al. *Blood.* 2001;98:210.
Gupta D et al. *Leukemia.* 2001;15:1950.

Mitsiades N et al. *Blood* 2002;99:4525.
Lentzsch S et al. *Cancer Res.* 2002;62:2300.

MPV: treatment schedule



TRAITEMENT DU MYELOME MULTIPLE

Un pronostic redoutable

- Maladie peu sensible aux chimiothérapies
  - Alkylants (Melphalan)
  - Corticoïdes (Dexaméthasone)
- Pronostic constamment fatal
  - Médiane survie longtemps estimée à 3 ans

Une maladie douloureuse et invalidante

- Atteinte osseuse
- Anémie

→ Progrès récents
- nouvelles stratégies
- nouveaux traitements

LES MODALITES THERAPEUTIQUES

- Alkylants (Melphalan)
- Corticoïdes (Dexaméthasone hautes doses)
- Interféron
- Traitement intensif + greffe
- Thalidomide
- Velcade®
- Autres traitements en développement (analogues Thalidomide)

INTERFERON
L'ESPOIR DECU

- N'est plus utilisé en combinaison avec la chimio

- En entretien après chimio conventionnelle (méta-analyse de 12 essais randomisés)
  - 6 mois prolongation de SV sans progression
  - 7 mois prolongation de SV globale

  Mais { effets secondaires
  coût

- En entretien après autogreffe ?

AUTOLOGOUS S/C TRANSPLANTATION

1. Stem cell collection

- Collect enough SC to perform 2 ASCT
- In newly diagnosed patients this objective is easily reached with G-CSF alone (10μg/kg) or with Cyclophosphamide + G-CSF (5μg/kg)

2. Conditioning regimen

IFM 95 : HDM 200 at least as effective and better tolerated compared to HDM140 + TBI

3. Source of SC

No evidence that CD34+ selected PBSC are superior to unselected PBSC (3 randomized trials)

LE TRAITEMENT INTENSIF

Rôle de l'IFM

- Essai IFM 90 (patients ≤ 65 A)
  - Autogreffe > chimio conventionnelle (tx réponse, SSE, SV globale)
  - Impact de la RC sur la survie

- Confirmation 7 ans plus tard par l'essai anglais

CC vs ASCT

FACTS

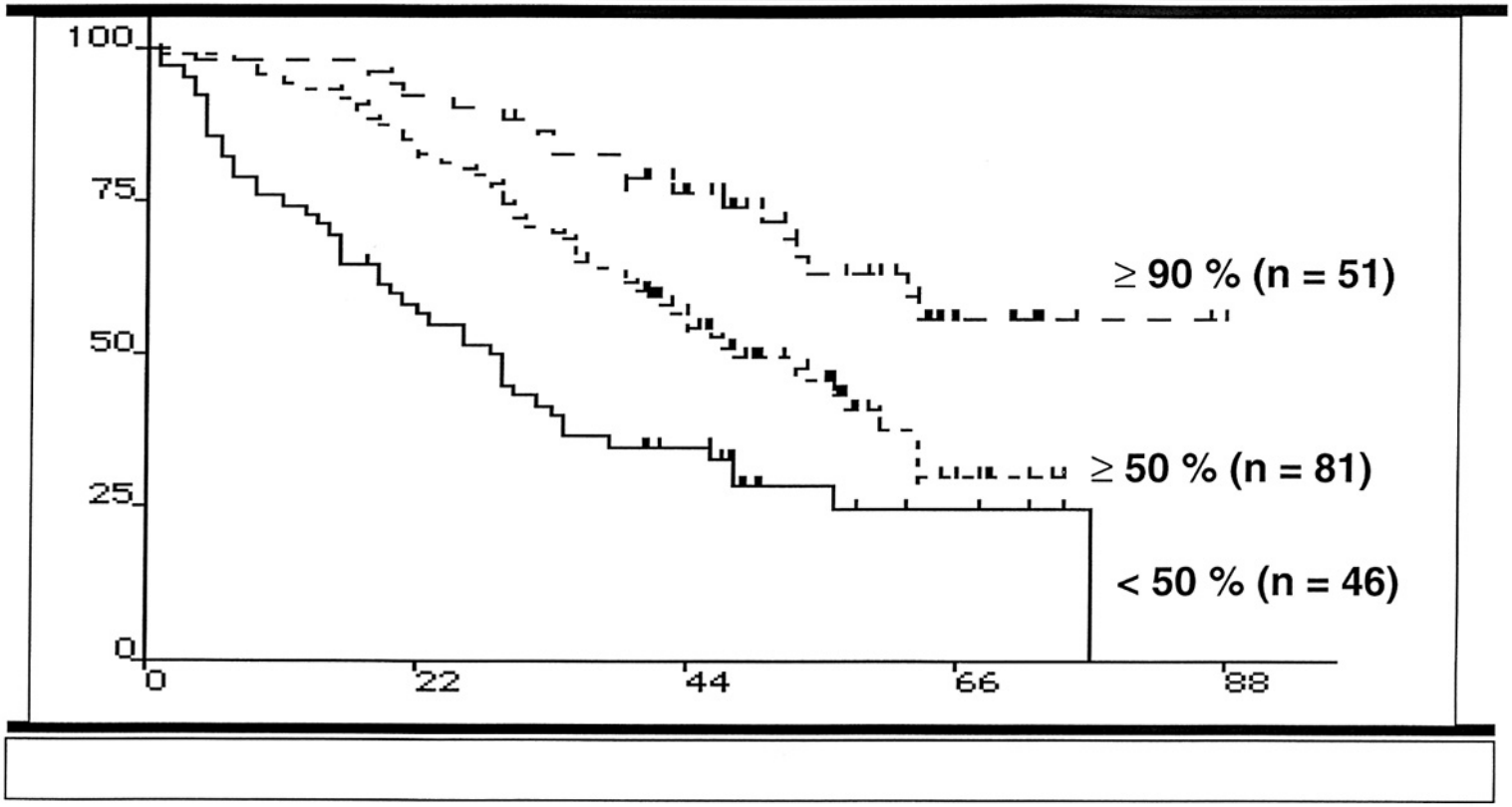
- Standard of care in patients up to the age of 65
- Should not be restricted to patients responding to initial CT (Pethema)
- Survival benefit is related to CR achievement

CC vs ASCT
RANDOMIZED STUDIES

	Nb of pts	Age	CR rate	Median EFS	Median OS
IFM90 *(NEJM 96)*	200	≤ 65	5 vs 22**	18 vs 28**	44 vs 57**
MRC7 *(NEJM 03)*	401	≤ 65	8 vs 44**	19 vs 31**	42 vs 54**
Italian MMSG *(Blood 04)*	194	50-70	6 vs 25**	16 vs 28**	42 vs 58+**
MAG 91 *(ASH 99)*	190	55-65	-	19 vs 25**	45 vs 42
PETHEMA* *(ASH 03)*	164	≤ 65	11 vs 30**	34 vs 42	67 vs 65
US Intergroup *(ASH 04)*	516	-	15 vs 17	21 vs 25	53 vs 62

* only in patients responding to initial CC
** significant

IFM 90 : Survival according to response



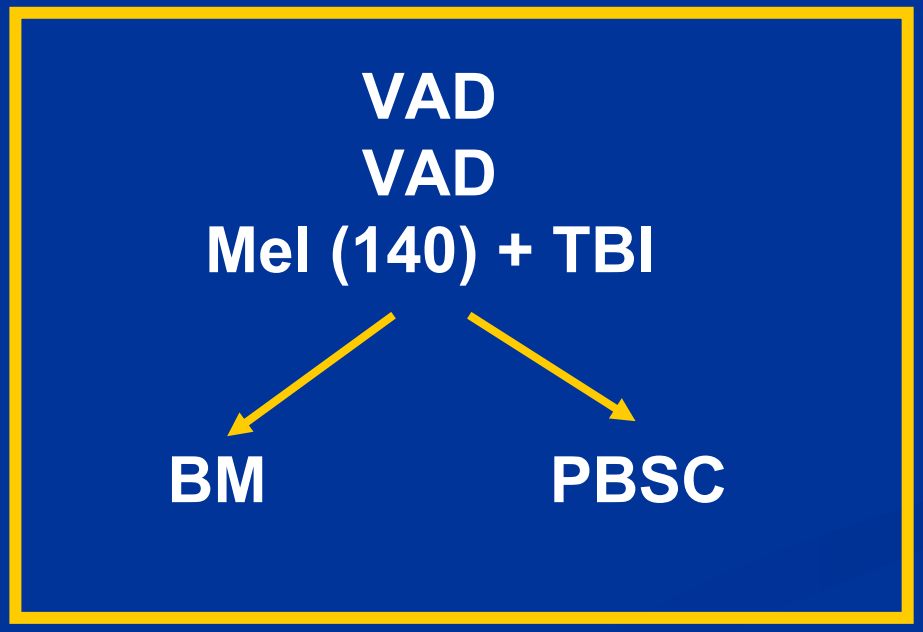
IFM 94

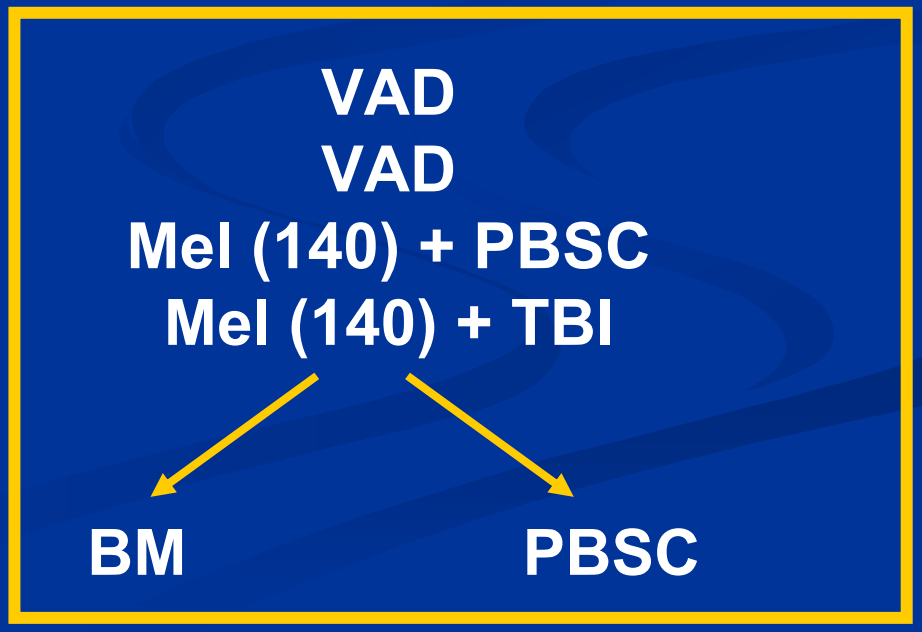
Newly diagnosed patients ≤ 60 years

First randomisation : single versus double

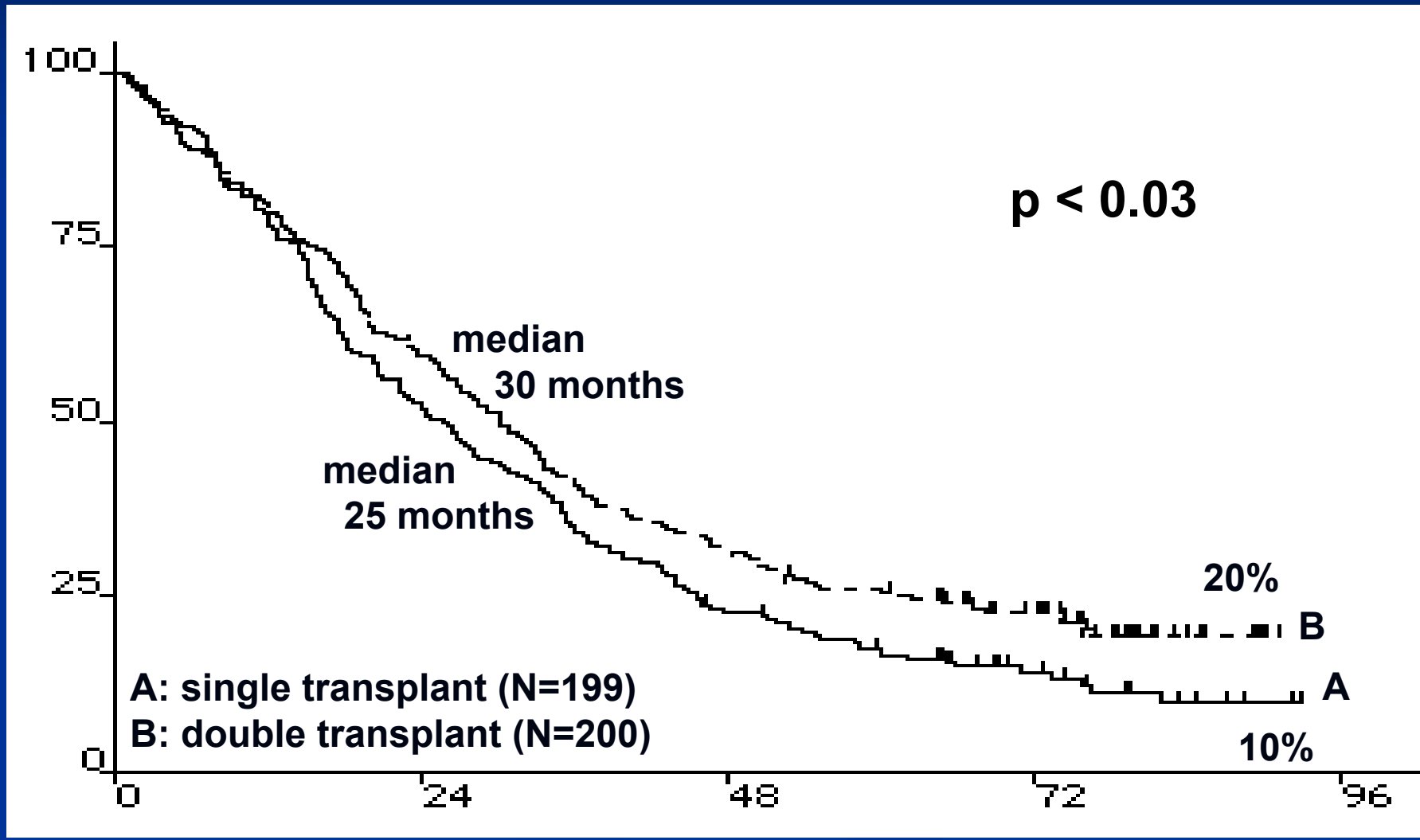
VAD
VAD
VAD

Second randomisation : BM versus PBSC

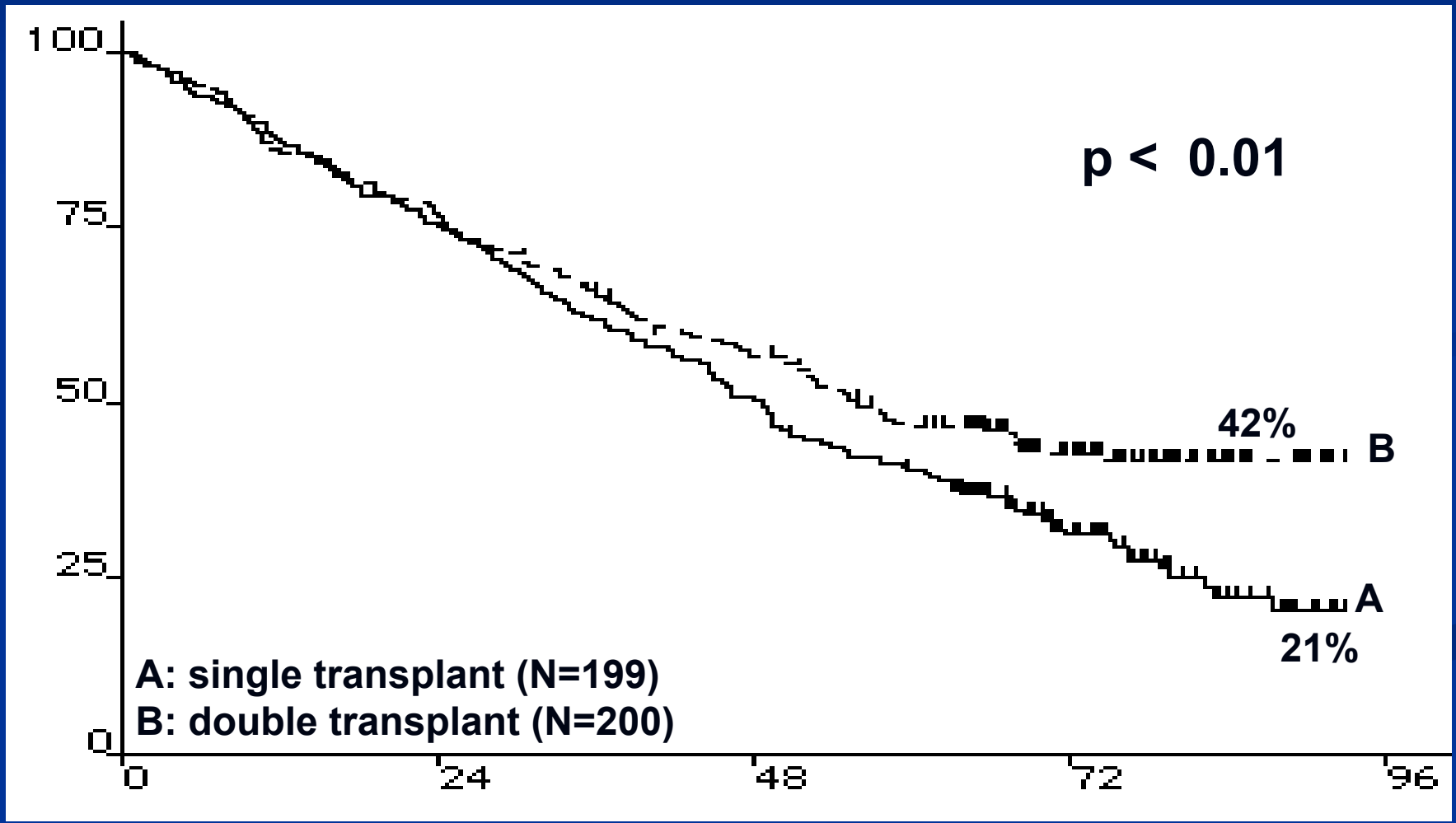




IFM 94 : EFS


100
75
50
25
0
0
24
48
72
96
p < 0.03
median
30 months
median
25 months
20%
B
A
10%
A: single transplant (N=199)
B: double transplant (N=200)

IFM 94 : OVERALL SURVIVAL



SINGLE vs DOUBLE ASCT RANDOMIZED STUDIES

	Nb of pts	Age	Results
IFM 94 *(NEJM 03)*	399	< 61	EFS and OS ↗
MAG 95 *(Turin 04)*	227	< 56	No difference
Bologna *(Turin 04)*	220	< 61	EFS ↗
GMMG *(Turin 04)*	261	< 66	EFS ↗
Hovon *(Turin 04)*	303	< 66	CR and EFS ↗

T-CELL DEPLETED SCT FOR FIRST-LINE TREATMENT

Lokhorst (J C Oncol 2003;21:1728-33)

- 53 patients with an HLA identical sibling

- Median age 48 y (31-56)

- Variable T-cell depletion (1-7 x 10^5/kg) + cyclosporine

- Induction treatment

VAD alone	5
1 IDM	26
2 IDM	22

T-CELL DEPLETED SCT FOR FIRST-LINE TREATMENT RESULTS

- A GVHD ≥ 2 — 24/53 (43%)
- C GVHD — 43% (30% extensive)
- 100 day TRM — 34%
- 89% response rate
  19% CR rate
- median PFS 17 Mo
  median OS 25 Mo
  only 3 pts in continuing CR

NON MYELOABLATIVE CONDITIONING REGIMEN

Objective

- To ensure engraftment and reduce TRM with immunosuppressive treatment while harnessing GVM effect
- Different approaches (Purine analogs, low-dose TBI, ATG) *(Slavin 1998, Giralt 1997, Storb 1998)*
- DFS and OS are related to disease status at Tx (high relapse rate in advanced patients)

→ AUTO SCT followed by mini-allo

AUTOLOGOUS SCT FOLLOWED BY MINI-ALLO

Author	N	Med Age	Rel/Ref	Auto	Mini Allo	Immuno Suppression
Maloney *Blood 2003*	54	52	48%	HDM200	LD TBI	MM + CYA
Badros *Blood 2002*	31*	56	55%	30 Prior ASCT	HDM100 or M/F/LD TBI	CYA + MPDN
Kroger *Turin 2004*	47**	52	None	HDM200	M/F/ATG	CYA + MTX

* 6 unrelated

** 23 unrelated donors
All front-line

AUTOLOGOUS SCT FOLLOWED BY MINI-ALLO

Author	N	Chimer	CR	AGVH ➢ II	100 d TRM	M F-up	cGVH	Results
Maloney Blood 2003	54 *	100%	52%	36.5%	2%	18m	46%	2-yr OS 78% 2-yr PFS 55%
Badros *Blood 2002*	31**	89%	61%	58%	10%	6 m	36%	1 yr EFS 86%
Kroger *Turin 2004*	47	100%	55%	32%	6%	15 m	32%	3-yr OS 70% 3-yr EFS 54%***

* 1 DLI ** 18 DLI *** Unrelated:66% vs related 47%

THALIDOMIDE
RENAISSANCE D'UN VIEUX TRAITEMENT

- Sédatif retiré de la pharmacopée en 1962 pour ses effets tératogènes

- Toujours utilisé dans certaines formes de lèpre et certains troubles dysimmunitaires

- Considéré comme antiangiogénique

→ **Nouvelle arme dans le MM**

THALIDOMIDE

Thalidomide alone

- Pionnering work by the Little Rock group in heavily pretreated patients
- Initial results confirmed by a number of Phase II studies (in relapsed / refractory patients)
  - 30-80% responses
  - rapid responses
  - toxicity:optimal dosage ?
  - with the usual dosage (400mg/D) side effects are manageable but long-term toxicity is a concern (peripheral neuropathy) in many patients

THALIDOMIDE + DEXAMETHASONE

- Synergy in preclinical studies
- Lower doses of Thalidomide
  → better tolerance
- More effective ?
  - 65-80% response rate in relapsed / refractory MM
  - As first salvage therapy improves the outcome as compared to CC :median PFS 17m vs 11 (p=.002) SV at 3 yr 60% vs 26% (p=.001) (Palumbo 2004)
- Currently used as frontline therapy

THALIDOMIDE + CHEMOTHERAPY

- Thalidomide : no hematological toxicity
- Synergy in preclinical studies
- Effective in relapsed/refractory patients (TCD, DT - PACE) but high incidence of DVT
- Currently tested as frontline therapy

BORTEZOMIB IN MM

Richardson (SUMMIT 025 Phase II trial)

- Velcade 1.3mg/m² IV on days 1, 4, 8 and 11
  21 D cycles (max 8 cycles)

- 202 pts heavily pretreated
  - median number of prior regimens : 6
  - 64% prior stem cell transplant
  - 83% prior Thal TX

- 91% refractory to the last prior TX

SUMMIT RESULTS

- 35% overall response (CR + PR + MR)
- 10% CR
- Response independent of prior therapy
- Median SV 16 months
- Median TTP 7 months
- 74 pts with SD/PD received PS341 + Dex

→ 24% improved response

SUMMIT RESULTS
TOXICITY

	All grades (0%)	Grade 3/4 (%)
Nausea	55	6
Diarrhea	44	8
Fatigue	41	12
Thrombocytopenia	40	31
Neuropathy	31	12

VELCADE
APEX TRIAL

- Multicenter international Phase III randomized trial
- 669 pts enrolled at 94 centers
- Relapsed or refractory MM (after 1-3 lines Tt)
- Velcade vs Dexamethasone
- Companion study : Velcade for patients progressing with Dex
- Primary end point : time to progression

APEX TRIAL RESULTS

- Median time to progression significantly improved 6.2 m vs 3.5 m ($p < 0.0001$)
- CR + PR : 38% vs 18% ($p < 0.0001$)
- CR : 6% vs 1% ($p = 0.0001$)
- OS and 1-year significantly improved

VELCADE IN MM
ONGOING AND FUTURE STUDIES

- In combination with
  - Dexamethasone
  - Chemo - MP
    - Doxil
  - Thalidomide

- In frontline therapy
  - Older patients
  - Prior to SCT

ACTIMID

Phase I *(J Clin Oncol 2004)*

- 24 relapsed / refractory pts
- oral, dose-escalation (1, 2, 5, 10mg / D)
- 67% RR, 54% PR, 17% CR
- MTD : 2 mg/d
- dose limiting toxicity : neutropenia
- 3 DVT

SUMMARY
YOUNGER PATIENTS (<65yo)

Standard of care

- **Induction : Dex based regimen**
- **Collection of SC : enough SC to perform 2 ASCT**
- **Consolidation : double ASCT**

YOUNGER PATIENTS (< 65 yo)
QUESTIONS TO BE ADDRESSED

- **Stratification according to initial prognostic factors**
- **Double ASCT for all pts or only for selected pts (less than 90% response after initial CT ?)**
- **Induction : how to improve the CR rate prior to ASCT**
  - **add Thal**
  - **other novel agents**
- **Maintenance therapy**
- **Place of allogeneic SCT**

PROGNOSTIC FACTORS IN NEWLY DIAGNOSED PATIENTS

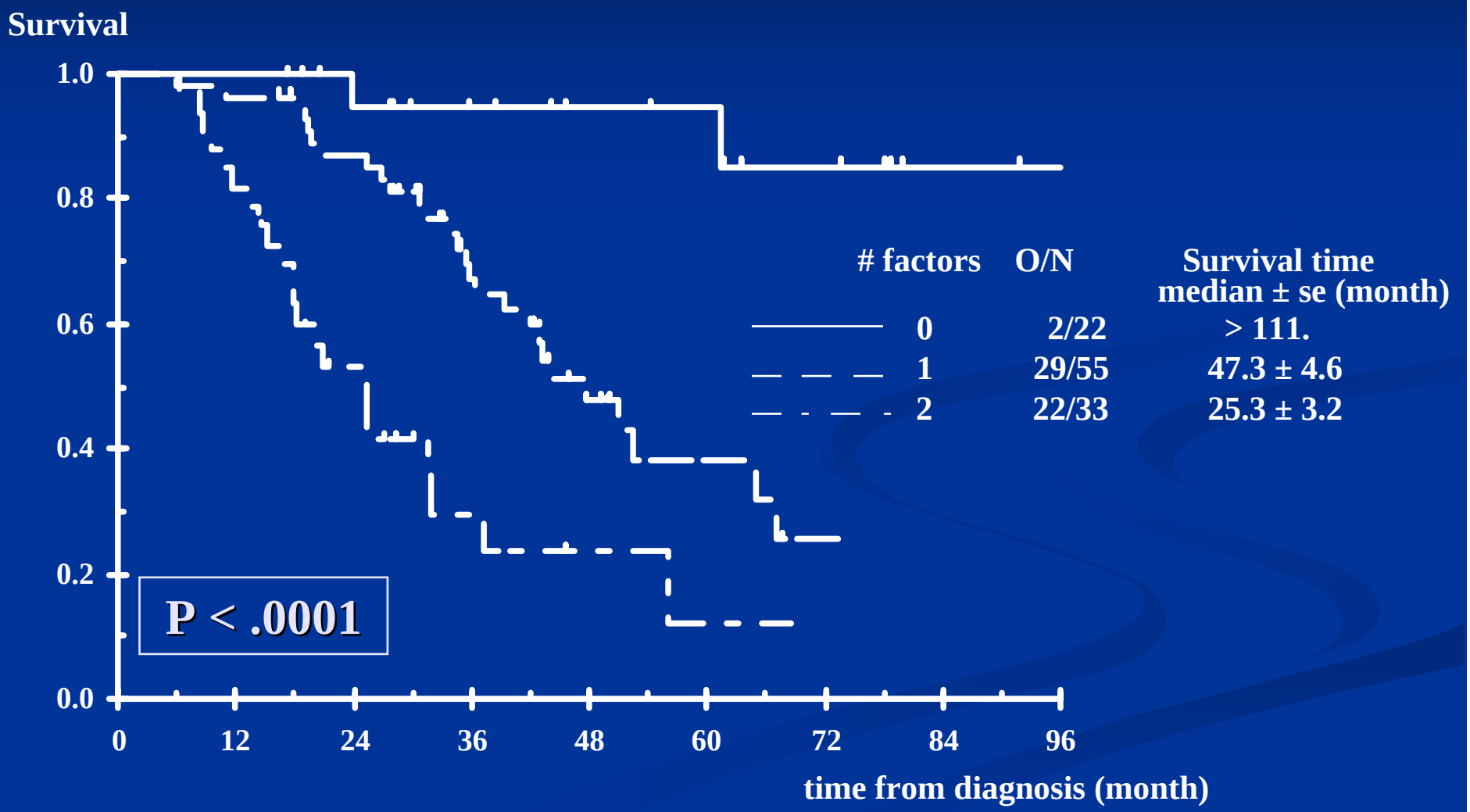
Initial characteristics

- IgA
- CRP, Albumin
- β2 M, LDH
- cytogenetics ++

Treatment related

- response to initial CT
- achievement of CR

Overall survival according to the number of unfavorable prognostic factors (β2m ≥ 2.5 mg/L, Δ13)



YOUNGER PATIENTS (< 65 yo) QUESTIONS TO BE ADDRESSED

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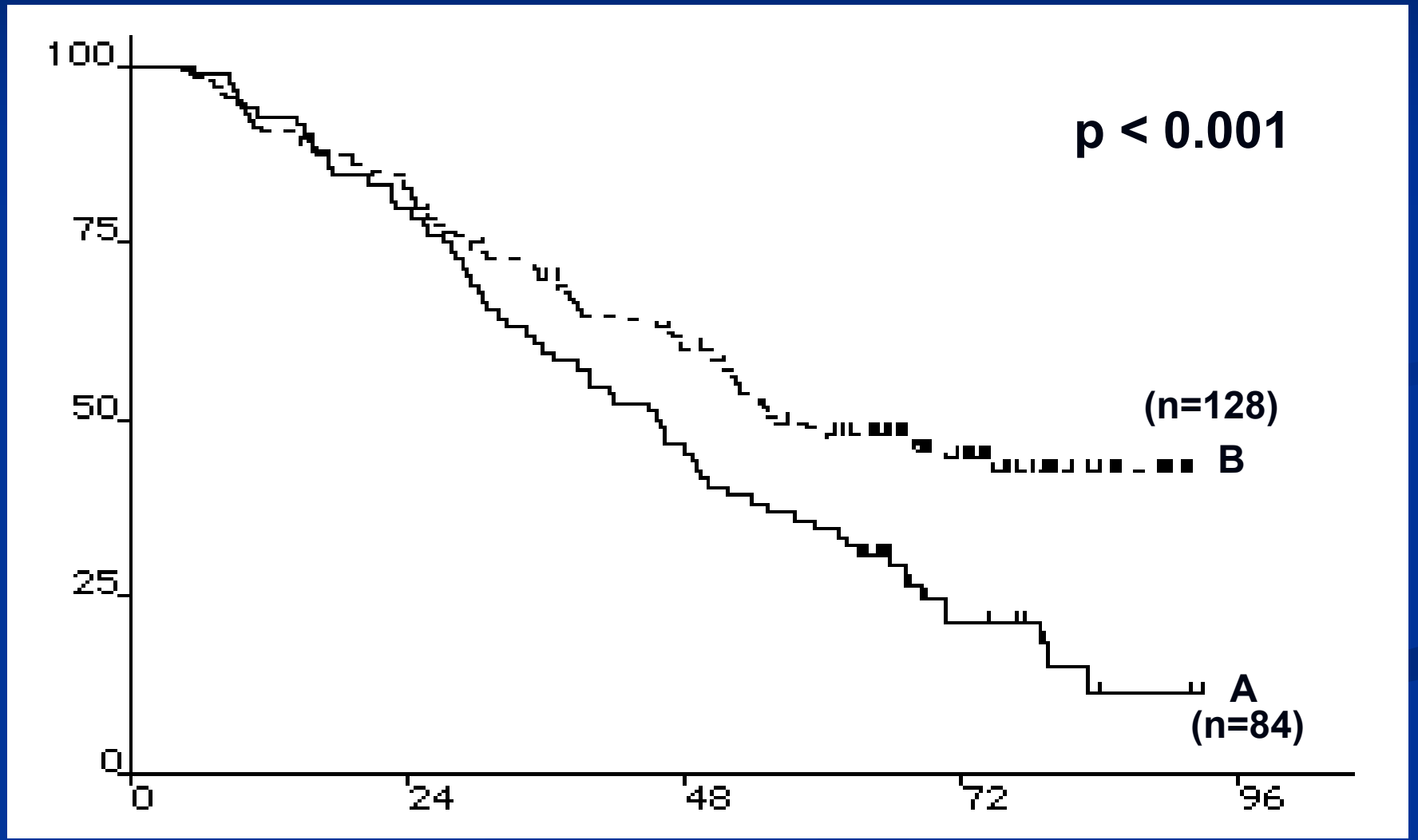
- Double ASCT for all pts or only for selected pts (less than 90% response after initial CT ?)
- Induction : how to improve the CR rate prior to ASCT
  - add Thal
  - other novel agents
- Maintenance therapy
- Place of allogeneic SCT

IFM 94 :
OS IF RESPONSE TO 1st GRAFT < 90%



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  - add Thal
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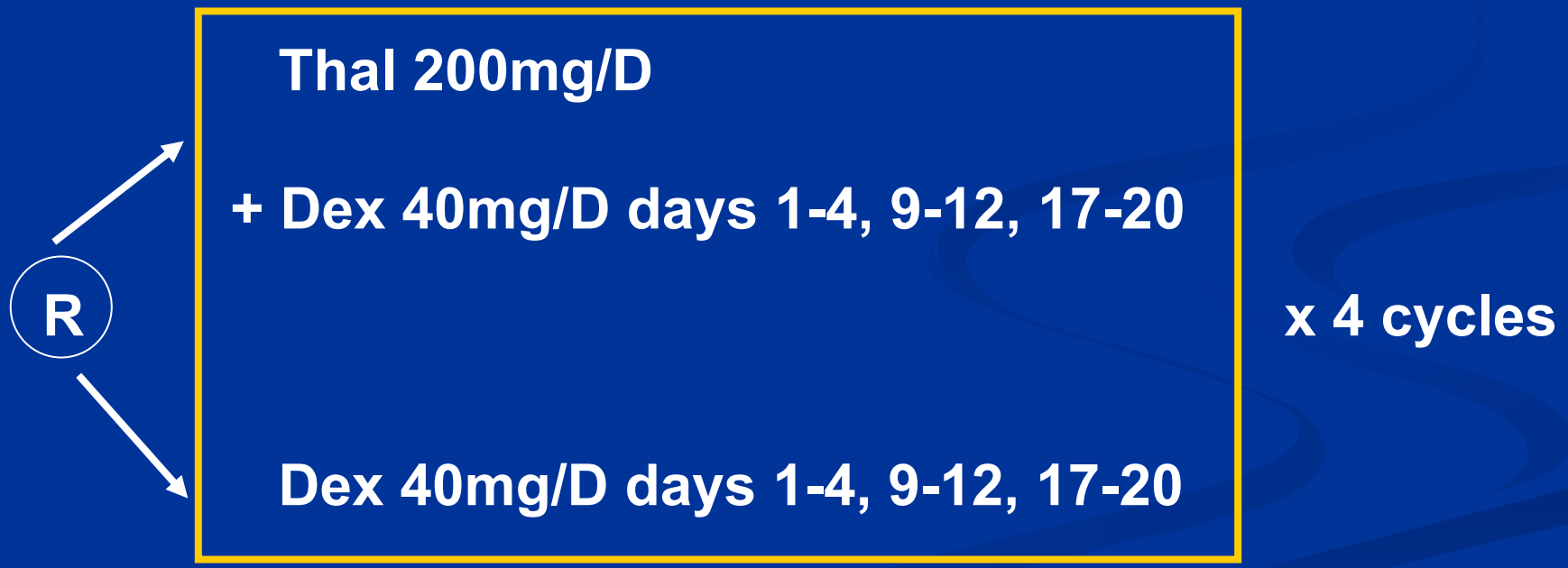
- Maintenance therapy
- Place of allogeneic SCT

THAL/DEX FOR NEWLY DIAGNOSED MM RANDOMIZED PHASE III ECOG TRIAL

Rajkumar et al (ASCO 2004)



ECOG E1A00
PRELIMINARY RESULTS
EFFICACY

	THAL/DEX N=100	Dex N=101
Response rate	68%	46%
Med-time to response	1.1 m	1.1 m
CR	3%	0%
Sucessful harvest	91%	100%

ECOG E1A00
PRELIMINARY RESULTS
TOXICITY

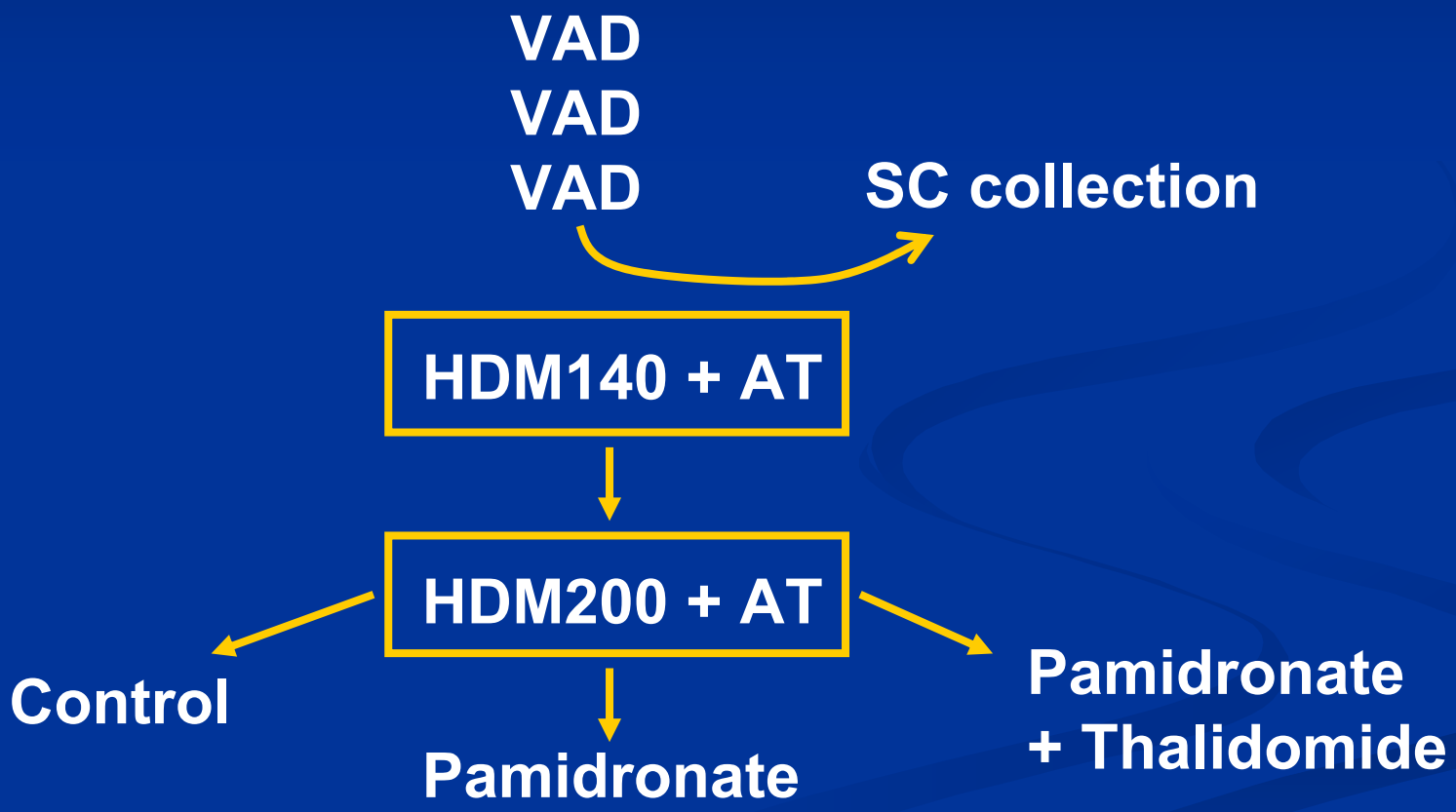
	THAL/DEX	Dex
Toxicity ≥ 4	33%	15%
DVT	16%	3%
Death within 4 months	7%	11%

YOUNGER PATIENTS (< 65 yo) QUESTIONS TO BE ADDRESSED

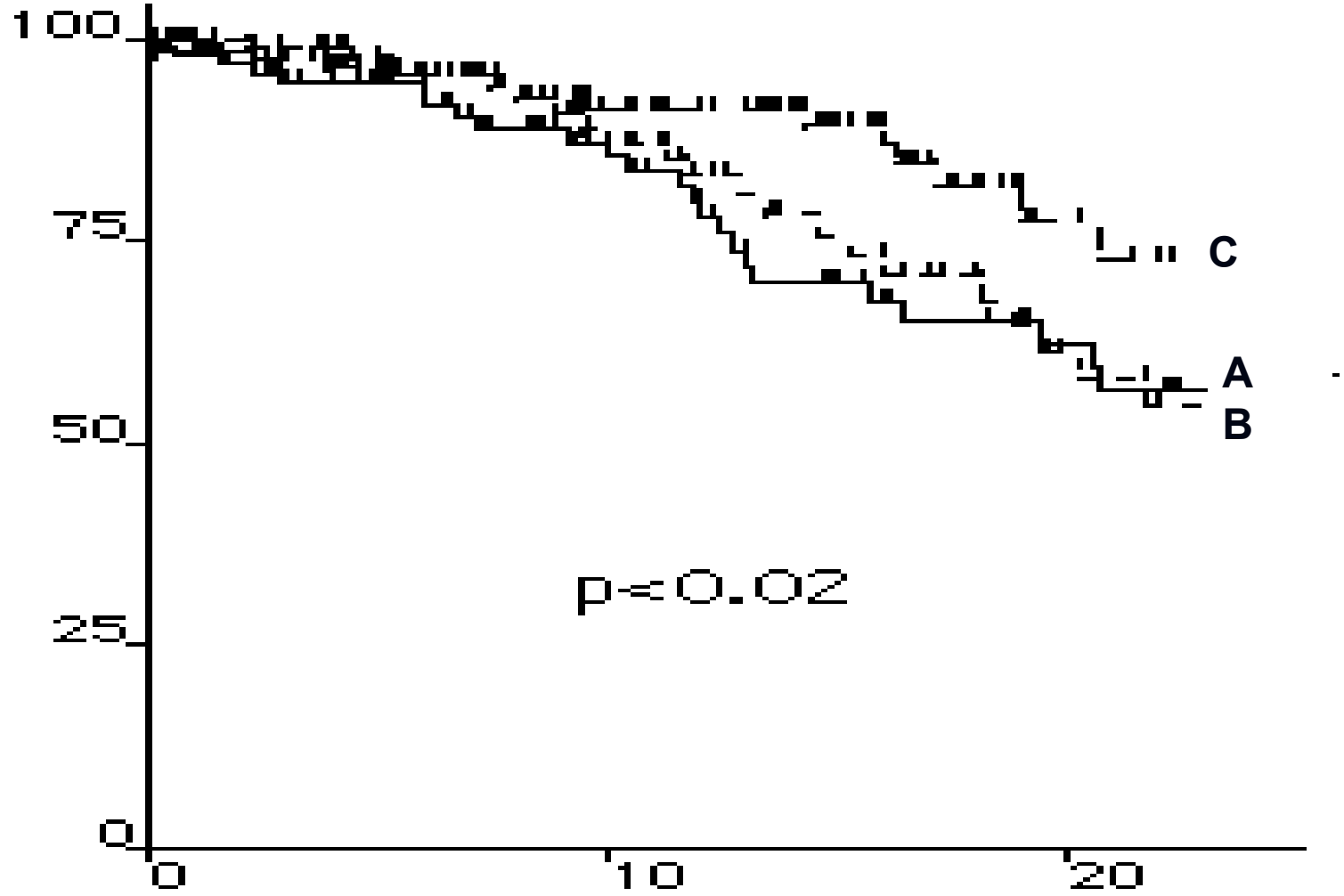
- Stratification according to initial prognostic factors
- Double ASCT for all pts or only for selected pts (less than 90% response after initial CT ?)
- Induction : how to improve the CR rate prior to ASCT
  - add Thal
  - other novel agents
- Maintenance therapy
- Place of allogeneic SCT

IFM 99-02

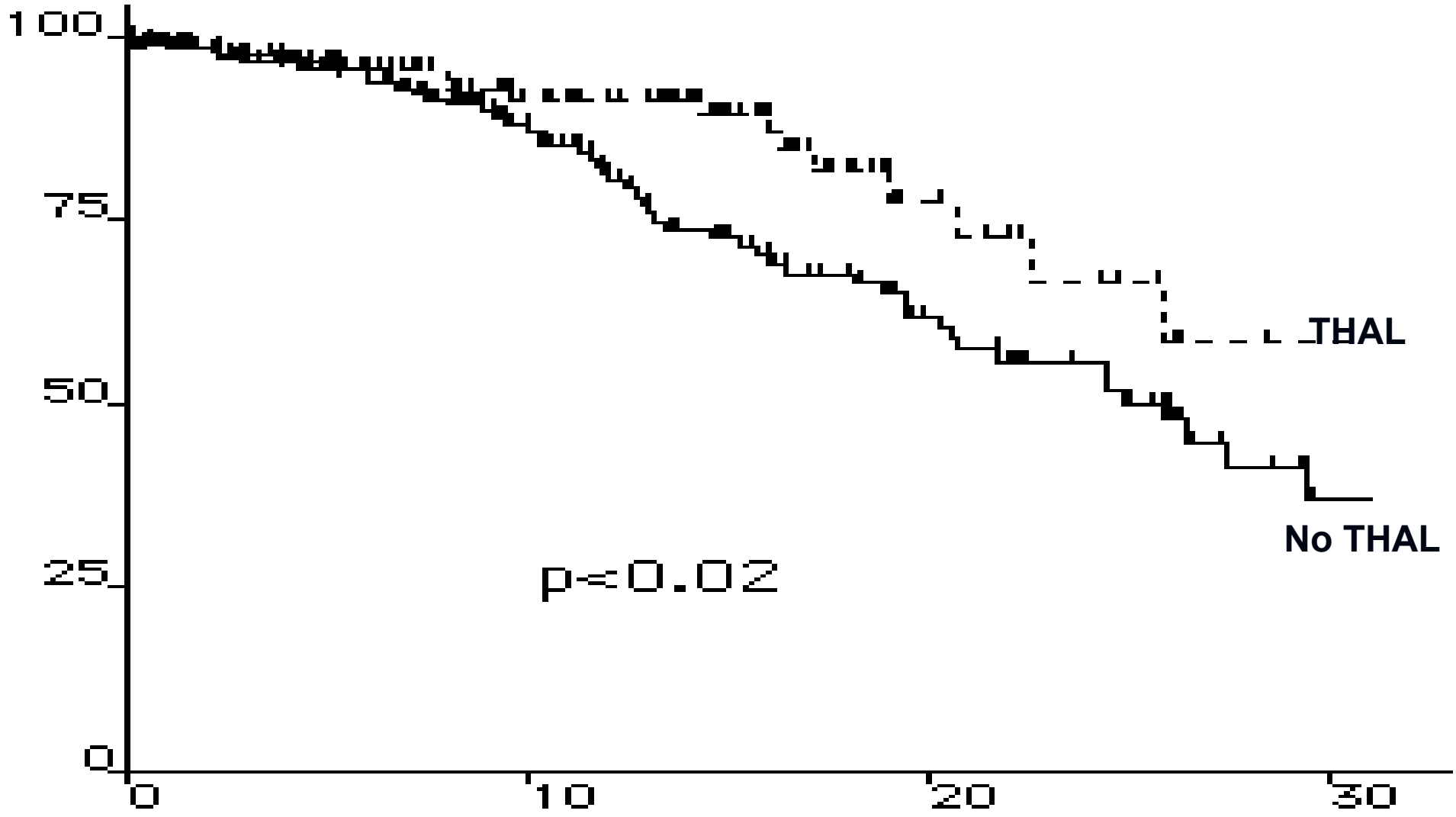
- Patients ≤ 65 years
- 0 or 1 adverse prognostic factors (chr 13, β2 M)



IFM 99 02 : EFS ACCORDING TO RANDOM



IFM 99 02 : EFS ACCORDING TO THAL



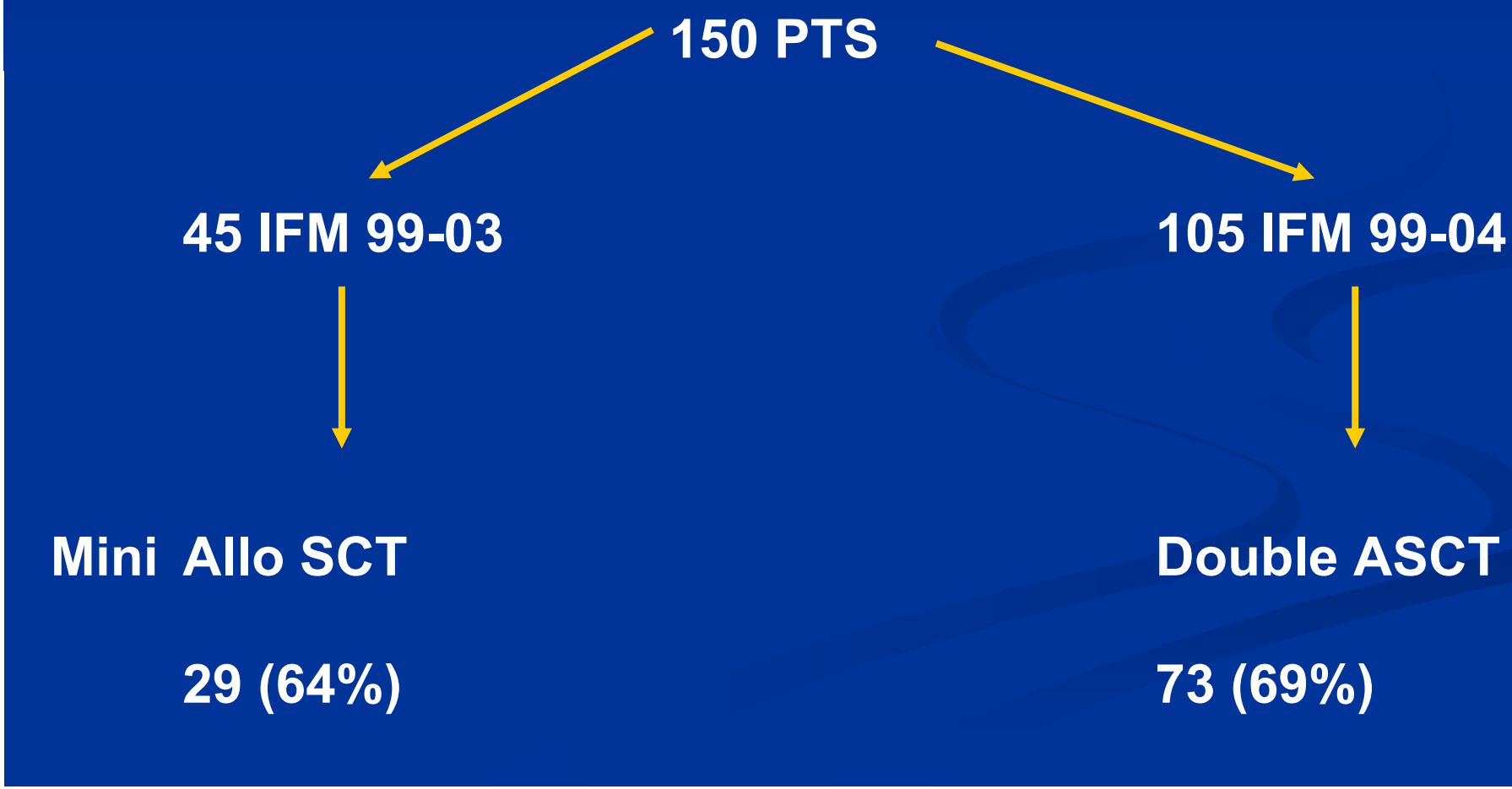
YOUNGER PATIENTS (< 65 yo)
QUESTIONS TO BE ADDRESSED

- Stratification according to initial prognostic factors
- Double ASCT for all pts or only for selected pts (less than 90% response after initial CT ?)
- Induction : how to improve the CR rate prior to ASCT
  - add Thal
  - other novel agents
- Maintenance therapy
- Place of allogeneic SCT

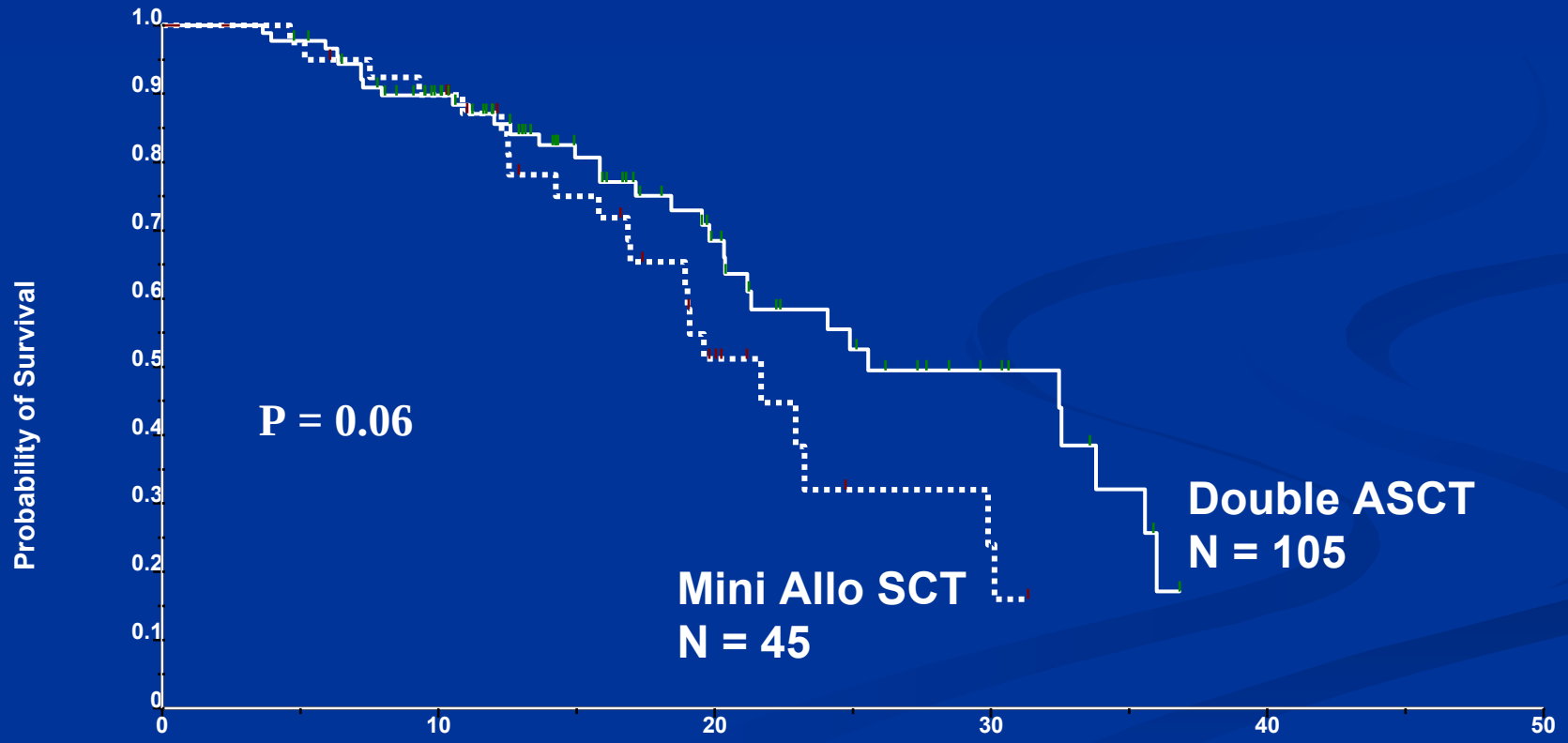
Transplant related mortality: EBMT retrospective study

IFM 99
03 / 04
PRELIMINARY RESULTS (1)

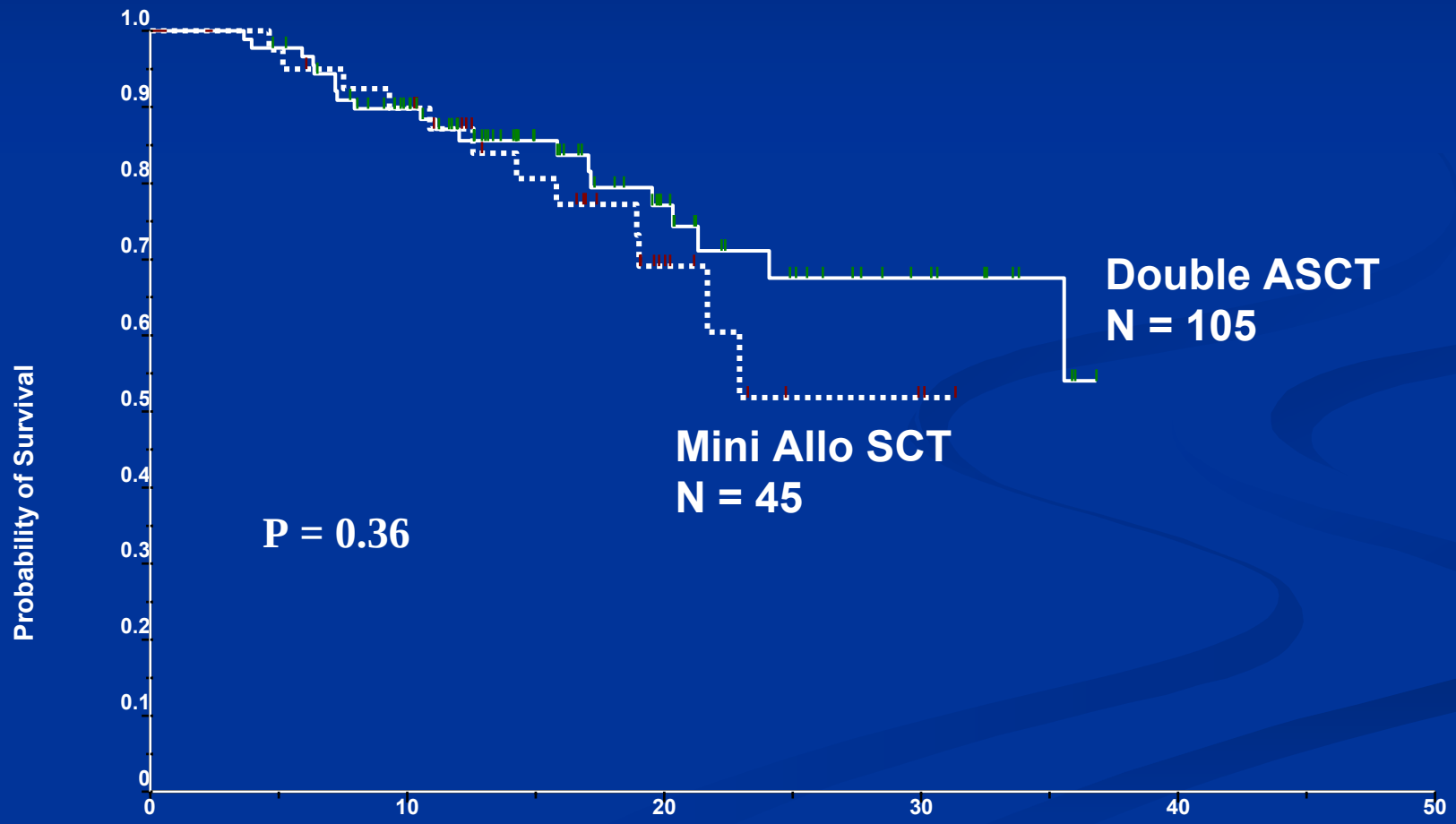
From 10/99 to 01/02



EFS
INTENT TO TREAT ANALYSIS



SURVIVAL
INTENT TO TREAT ANALYSIS



MINI ALLO-SCT
THE ROLE OF CHROMOSOME 13 DELETION

Kroger Blood 2004

	13q- N = 31	No 13q- N = 37	P value
2 yr SV	18%	67%	0.03
2 yr EFS	18%	42%	0.03
Cumulative incidence of relapse	77%	44%	< 0.001
1-yr TRM	18%	24%	0.4

PROGNOSTIC FACTORS
RISK GROUPS

IFM *(Facon 2001)*

β2 M + chr 13 abnormalities (FISH)

Nb adverse PF	0 (20%)	1 (50%)	2 (30%)
Median SV	111 m	47 m	25 m

ALLOGENEIC SCT

Main question : for all patients up to the age of 65 with an HLA identical sibling ?

YES

- Only in a prospective trial comparing double autologous SCT and autologous SCT + mini allo

NO

- Good prognosis (β2m < 3, no hypodiploidy, no chr13 abn) : no indication since a high incidence of prolonged EFS is achieved with double auto

- Poor prognosis (β2m > 3 and chr13 abno)
  → Phase II trial (Maxi BMT, MUD)

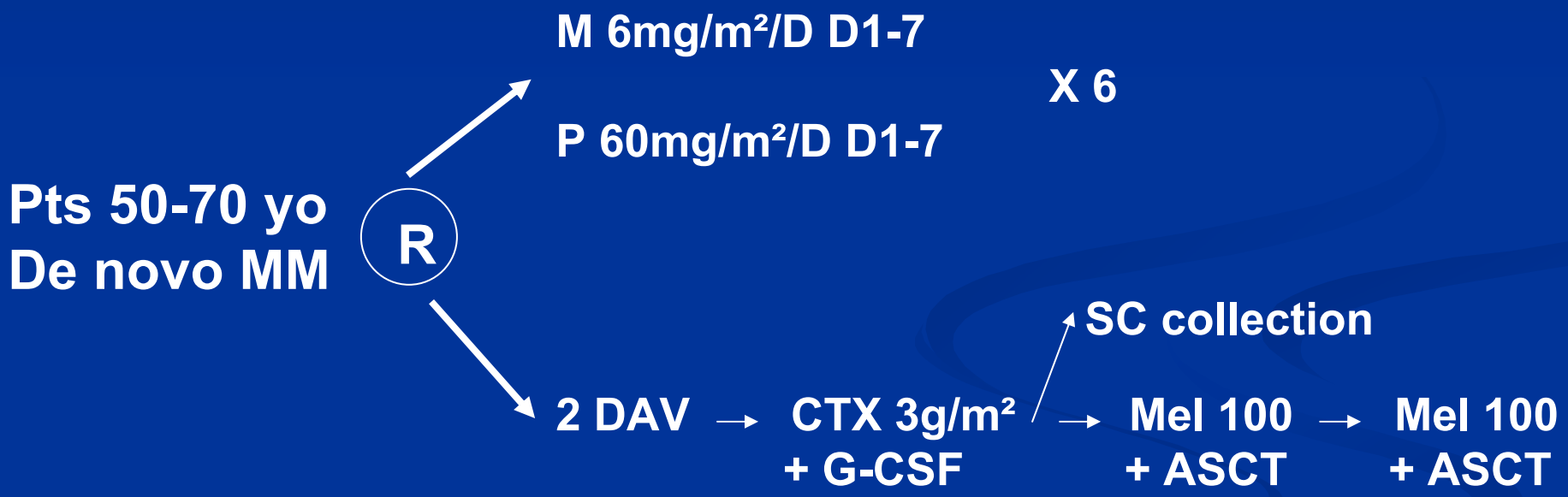
- Intermediate : clinical trial testing auto + mini allo

OLDER PATIENTS > 65 yo

- Results with MP are not satisfactory
- Other approaches are clearly needed
  - intermediate dose Melphalan + ASCT
  - Thal + MP
  - PS 341 + MP

OLDER PATIENTS
MEL 100 + ASCT

Palumbo et al (Blood 2004)



Maintenance therapy in both arms : αIFN 3M IU x 3/wk
+ Dex 40mg D1-4 every 2 months

INDUCTION with VAD

	No Pts	CR %	CR+ VGPR %
Palumbo	95	5	NA
Attal IFM 94	399	NA	12
Moreau	399	4	13
Lenhoff	274	4	NA
Barlogie	231	5	NA
Segeren	379	2	NA
Cavo	100	13	14

TREATMENT SCHEDULES

Melphalan 4 mg/m² 7 days/month for 6 courses

+

Prednisone 40 mg/m² 7 days/month for 6 courses

+

Thalidomide 100mg/d continuously until relapse

or

Melphalan 4 mg/m² 7 days/month for 6 courses

+

Prednisone 40 mg/m² 7 days/month for 6 courses

MP vs MP THAL RESPONSE RATES

	MPT N = 49	MP N = 44
CR + near CR	39%*	7%
Response rate (>50%)	79.5%	43%

** 24.5% CR (negative IF)*

ADVERSE EVENTS

WHO (grade)	MPT 1-2	MPT 3-4	MP 1-2	MP 3-4
Hematologic (%)	35	22	30	27
Constipation (%)	27	6	-	-
Neurologic (%)	31	8	-	-
Infection (%)	16	12	11	-
Thromboemb.(%)	18		-	
Early death (%)	4		2	

TRAITEMENTS DE SUPPORT

- Diphosphonates
  - Clodronate
  - Pamidronate
  - Zolédronate

- EPO

RELAPSED / REFRACTORY MM

- Therapeutic options
  - supportive care
  - repeat initial CT
  - use another CT regimen
  - ASCT
  - Thalidomide (+/- Dex)
  - other novel agents

ALLOGENEIC SC TRANSPLANTATION WHAT WE KNOW

- High transplant-related mortality
- Short-term retrospective comparisons are in favor of autologous SCT

BUT

- Durable CR (including molecular remissions) : the only curative treatment ?
- Remissions with DLI : GVM effect
- Better results if better supportive care and earlier transplantation (Gahrton 2001)

ALLOGENEIC SCT

- Possibly the only curative treatment of MM
- Balance between GVH and GVM
- High TRM
- Better results if performed upfront
- Encouraging preliminary results with autologous SCT followed by mini allo *(Maloney, Kroger)*
- However inferior results with mini allo in patients with poor risk disease (chr 13) *(Kroger, IFM 99)*

INTERFERON

- No longer used in combination with CT
- Maintenance therapy (meta-analysis of 12 randomized trials)
  - 6 months prolongation of PFS
  - 7 months prolongation of OS

THERAPEUTIC POSSIBILITIES

- Alkylating agents
- High-dose corticoids
- Interferon
- High-dose therapy
- Thalidomide
- Novel agents

IFM 94 TRIAL
RESPONSE RATE

	Single TX N = 199		Double TX N = 200
HDM 140			
Response	-		77
CR	-		15
CR + VGPR	-		26
HDM 140 + TBI			
Response	84		89
CR	34		35
VGPR + CR	42	p=0.15	50

PLACE de l'AUTOGREFFE

Rôle de l'IFM

- Essai IFM 90 (patients ≤ 65 A)
  - Autogreffe > chimio conventionnelle (tx réponse, SSE, SV globale)
  - Impact de la RC sur la survie

- Confirmation 7 ans plus tard par l'essai anglais

ALKYLATING AGENTS

- MP has been the standard regimen for decades
- 50% PR
  CR very rare
  Maximum responses may take several months
- No survival benefit for combination CT vs MP
- Should be avoided if ASCT is planned

→ Standard in elderly patients

HIGH-DOSE STEROIDS

- VAD (or VAMP) :
  - initially used in pts refractory to alkylating agents
  - 60-80% PR in newly diagnosed pts (10% CR)
  - rapid response
  - no damage to SC

- Dex is responsible for much of the efficacy of VAD (or VAMP)

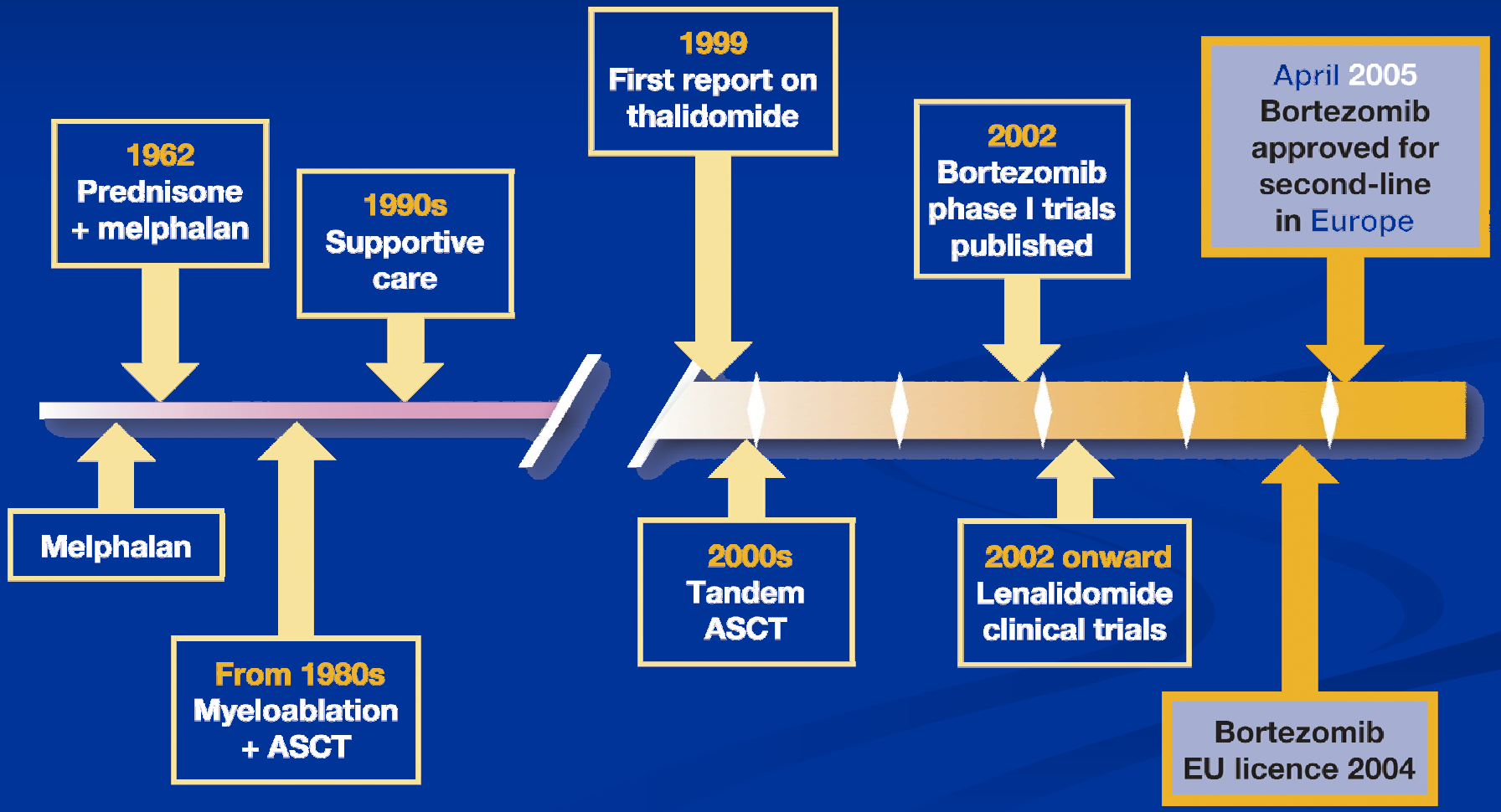
→ Standard induction TT in younger pts

IMiDs

- **Immunomodulating drugs**
  - inhibit NF-kB and activate Caspase-8
  - inhibit adhesion of MM cells to BM stromal cells
  - inhibit secretion of cytokines
  - inhibit angiogenesis
  - decrease MM cell proliferation

- 2 compounds are in clinical development (Revimid and Actimid)

Progress in the treatment of MM over the past 40 years



ALLOGENEIC SC TRANSPLANTATION

- Occurrence of GVHD is the major predictive factor for response after DLI in MM *(Lockhorst Blood 2002)*

→ Targets for GVH and GVM are the same ?

- With standard myeloablative regimens TRM remains too high even when used early

→ Select patients

→ Use strategy to reduce TRM while harnessing GVM

THALIDOMIDE ALONE IN RELAPSED MM RESULTS

- Reduction in paraprotein of ≥ 25% : 40-80%
- Partial remission in 10-50% of patients
- CR and VGPR possible even in heavily pretreated patients
- Early onset of response 4-12 weeks
- Maximal response within 2-4 months

Bortezomib-associated PN is reversible in the majority of patients (APEX)

- Incidence of PN (37% 124/331)
  - 10% grade 1
  - 18% grade 2
  - 8% grade 3
  - <1% grade 4

- 64% (58/91) of patients with ≥grade 2 PN experienced improvement or resolution
  - 55% (50/91) had complete resolution (return to baseline)
  - 9% (8/91) experienced improvement by at least 1 CTC grade
  - Median time to improvement/resolution:
    110 days from diagnosis

Reports of peripheral neuropathy

Bortezomib

Incidence

- Grade 1/2 29%
- Grade 3/4 8%

- Predominantly sensory
- Not all patients will develop PN
- Can be managed with dose modification
- Bortezomib-induced PN is reversible in majority of patients

Thalidomide

Incidence

- Grade 1/2 47%
- Grade 3/4 27%

- Mostly sensory neuropathy
- Cumulative toxicity: eventually all patients develop PN*
- Often limits dose and duration of treatment
- Thalidomide-associated PN can be irreversible

VISTA

International randomized, open-label, phase III trial in patients with previously untreated MM

Arm A: MPV

V 1.3 mg/m^2 days 1, 4, 8, 11, 22, 25, 29, 32 — 4 cycles

V 1.3 mg/m^2 days 1, 8, 22, 29 — 5 cycles

Arm B: MP

9 cycles

THALIDOMIDE IN COMBINATION WITH CHEMOTHERAPY IN PREVIOUSLY TREATED PATIENTS

		Nb of pts	Overall response
TCD	*Kropff 2001*	40	83%
	Dimopoulos 2004	53	60%
TCED	*Mochler 2001*	56	86%
MPT	*Palumbo 2006*	24	58%
MDT	*Srlkavic 2000*	21	81%
DT PACE	*Barlogie 2001*	135	54%
T DCEP	*Barlogie 2001*	38	36%

IFM 90 Trial

200 patients ≤ 65 y.o.

	CC N=100	HDT N=100	p. Value
Response rate (CR + VGPR)	38%	14%	<0.001
Median EFS	18 m	28 m	
7-year EFS	8%	16%	<0.01
Median OS	44 m	57 m	
7-year OS	25%	43%	<0.05

THALIDOMIDE IN COMBINATION WITH DEXAMETHASONE IN MM NEWLY DIAGNOSED PATIENTS

- **Active in indolent / smoldering MM**

Mayo Clinic	29 pts	34% PR
MDACC	28 pts	36% PR

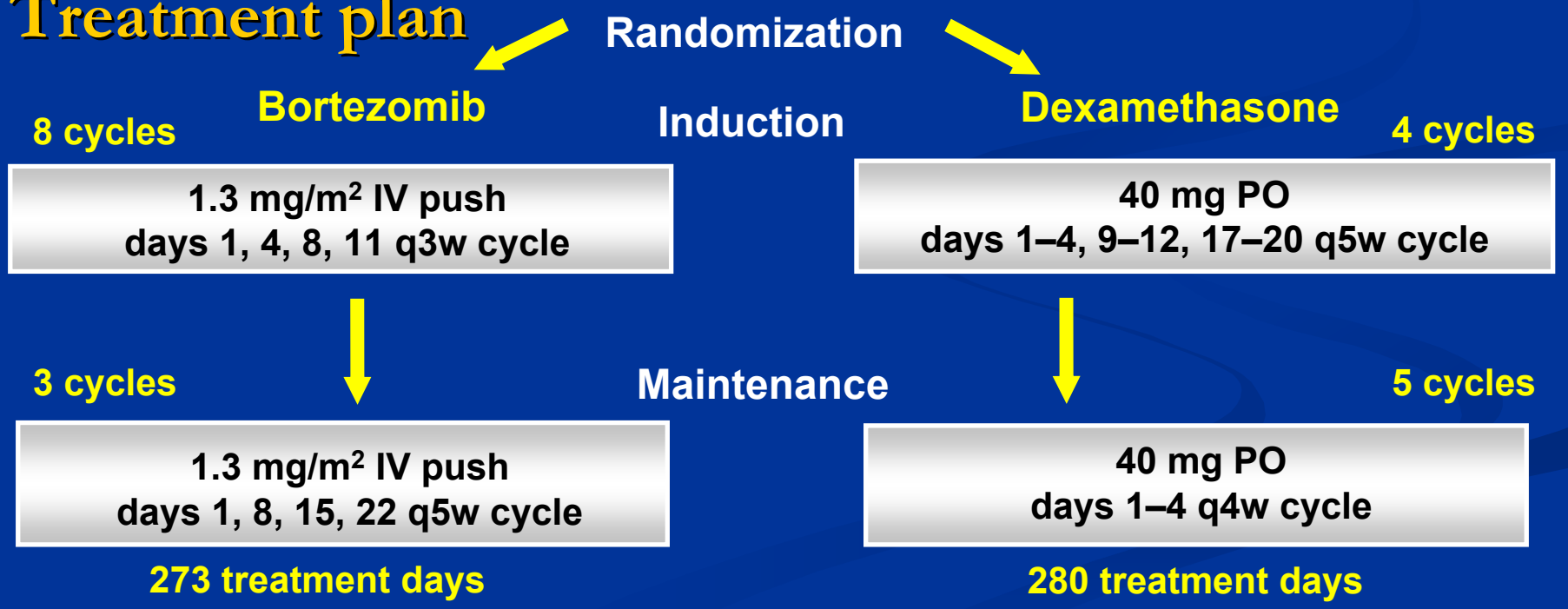
- **Active in previously untreated patients with symptomatic MM**

Mayo Clinic (JCO 2002)	50 pts	64% PR
MDACC (JCO 2003)	40 pts	72%PR

APEX: bortezomib vs dex

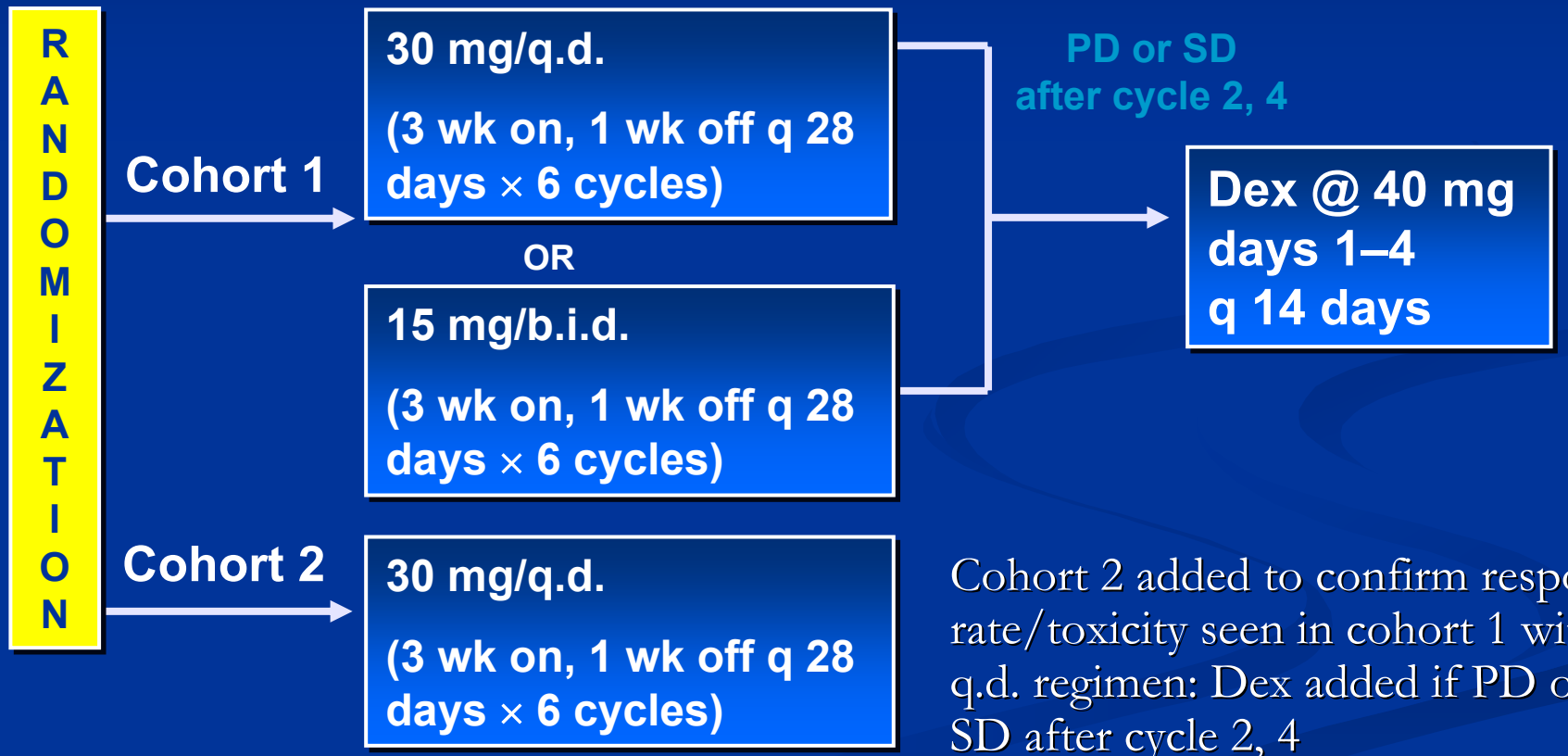
- International, randomized, open-label Phase III study in relapsed MM
  - 669 patients enrolled at 93 centers
  - 42% North America, 58% Europe/Israel

Treatment plan



Phase 2 Trial of Lenalidomide With or Without Dexamethasone in Relapsed/Refractory Myeloma

Treatment Scheme



Cohort 2 added to confirm response rate/toxicity seen in cohort 1 with q.d. regimen: Dex added if PD or SD after cycle 2, 4

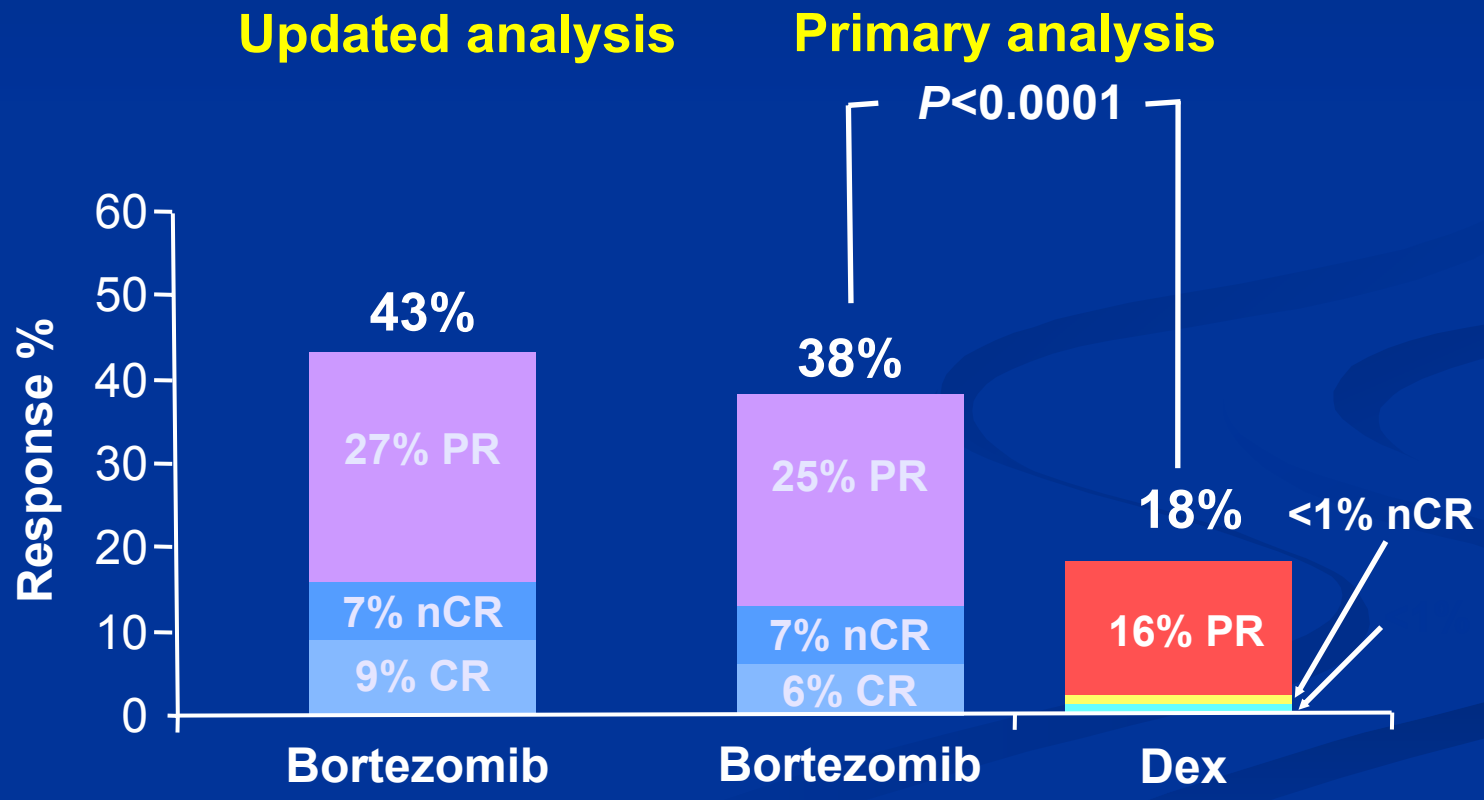
N=70

PD, progressive disease; SD, stable disease

Richardson PG et al. *Blood.* 2003;102:235a. Abstract 825.

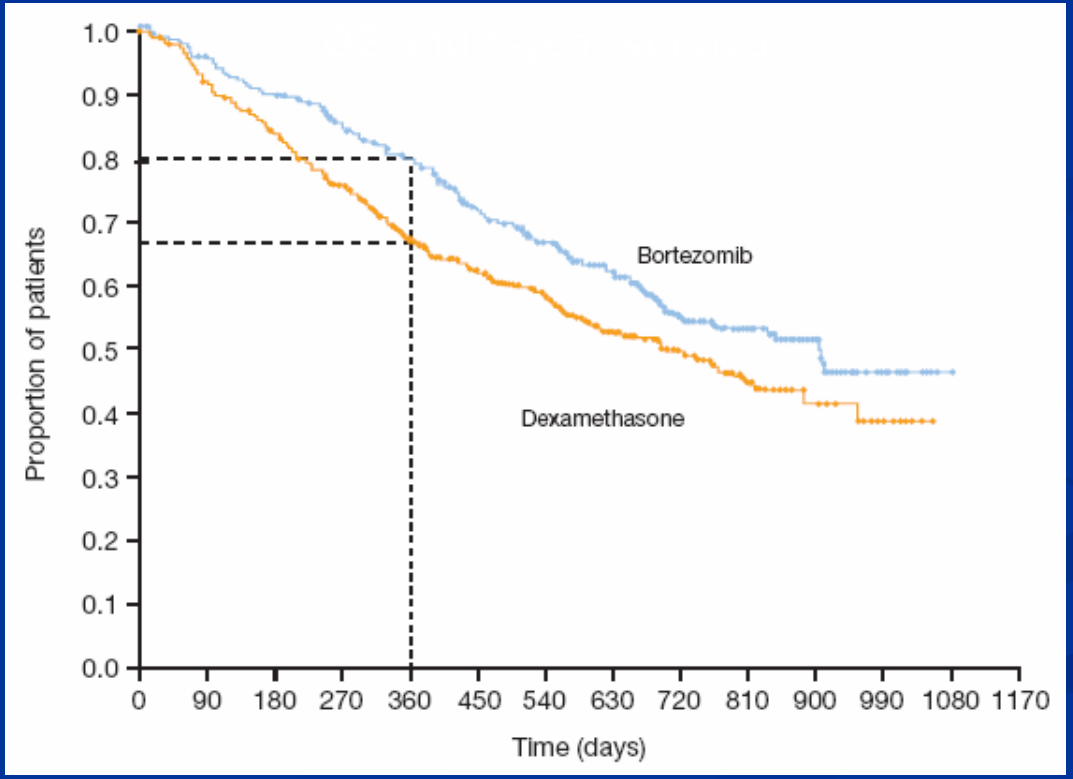
Updated APEX efficacy data
Response rates

ORR with bortezomib improved from 38% to 43%



Updated APEX survival data

- Superior survival for bortezomib
  - Median OS: bortezomib 29.8 months vs 23.7 months for high-dose Dex (*P*=0.0272)
  - 1-year survival rate: 80% vs 67% (*P*=0.0002)



TOTAL THERAPY II

4 phases of treatment (Barlogie NEJM 2006)

- intensive induction treatment (VAD, DCEP, CAD, DCEP) ± THAL throughout

- double ASCT (HDM 200)

- consolidation CT (DCEP / CAD)

- maintenance treatment (IFN + Dex)