Stem cell Transplantation in Multiple Myeloma in 2009

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–Nantes Atlantique–

AUTOLOGOUS STEM-CELL TRANSPLANTATION

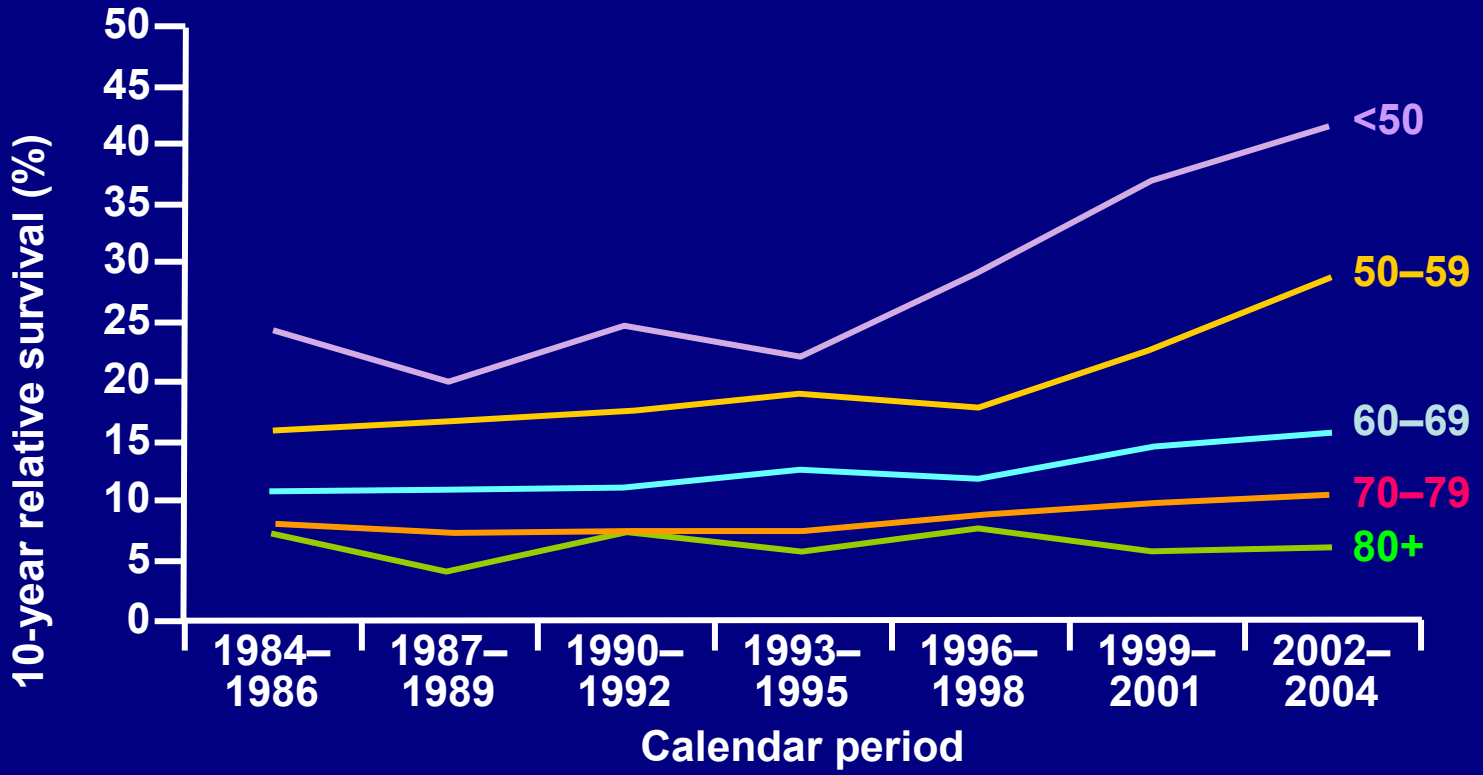
RESULTS ACHIEVED WITH ASCT

	ASCT	CC
CR	15-25%	< 10%
VGPR	40-50%	< 20%
Median PFS	25-35 months	15-20 months
Median OS	55-60 months*	42-60 months

Until now ASCT has been the standard of care for patients up to 65 years without major organ dysfunction

Improvements in survival according to the age

Period estimates of 10-yr survival by major age groups in defined calendar periods



Brenner et al. Blood 2008;111:2521–26

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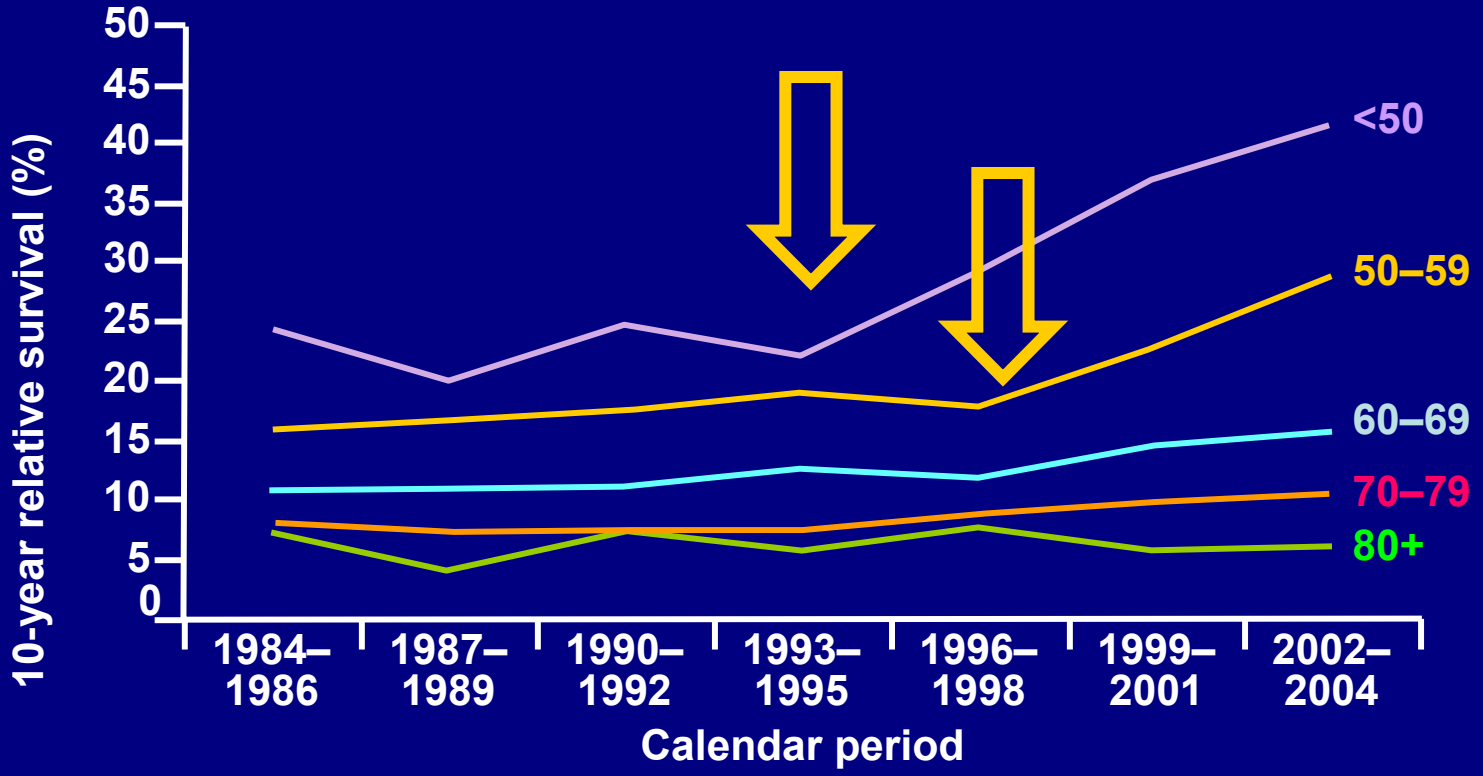

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What have we learned in the past 20 years ?

Preparative regimen : Mel 200 mg/m2

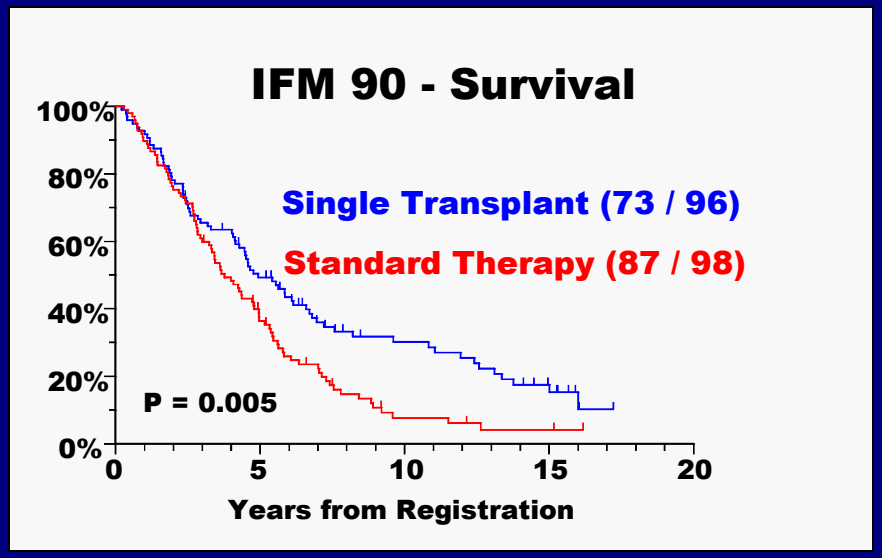
ASCT > CC (7 randomized trials)

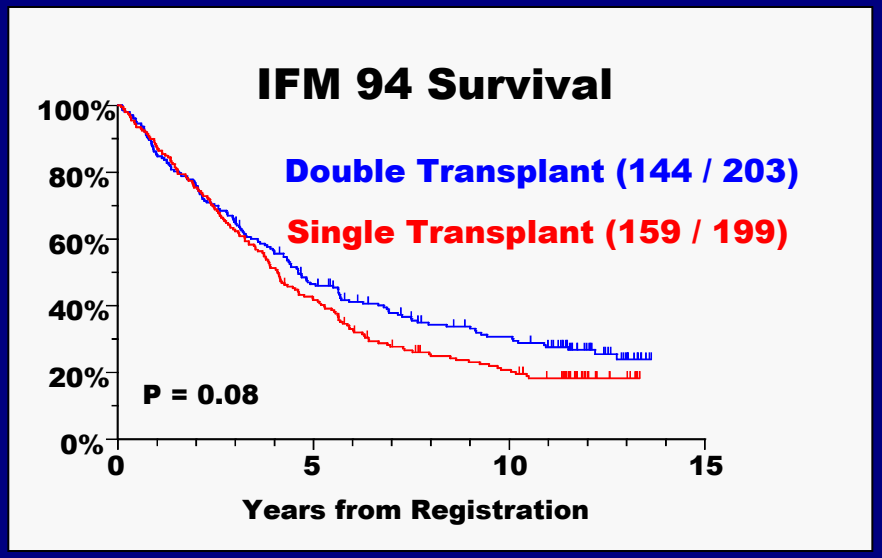
Double vs single ASCT PFS

Impact of ASCT on OS in younger patients

Impact of CR achievement

LONG-TERM FOLLOW-UP OF IFM 90 and 94





With longer follow-up results remain stable
Survival significantly longer in the transplant arm compared to the conventional chemotherapy arm
Trend in favor of double vs single ASCT

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

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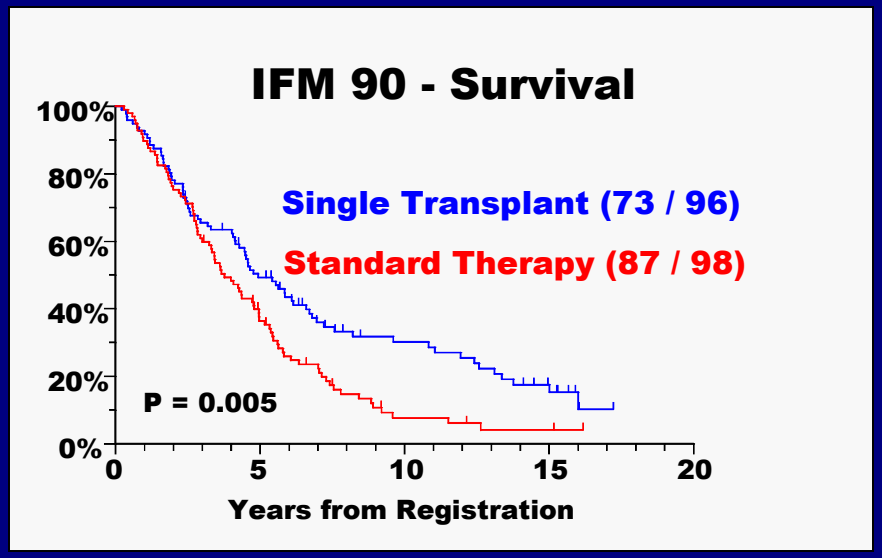
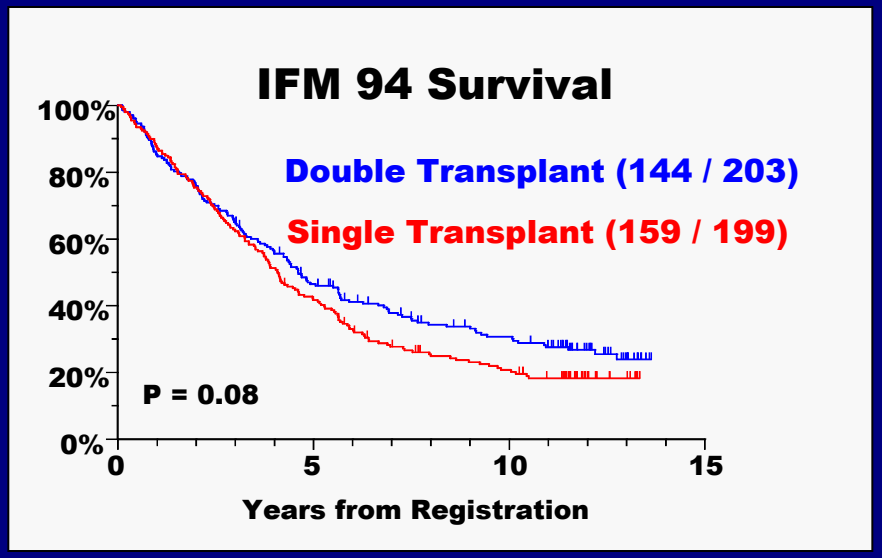
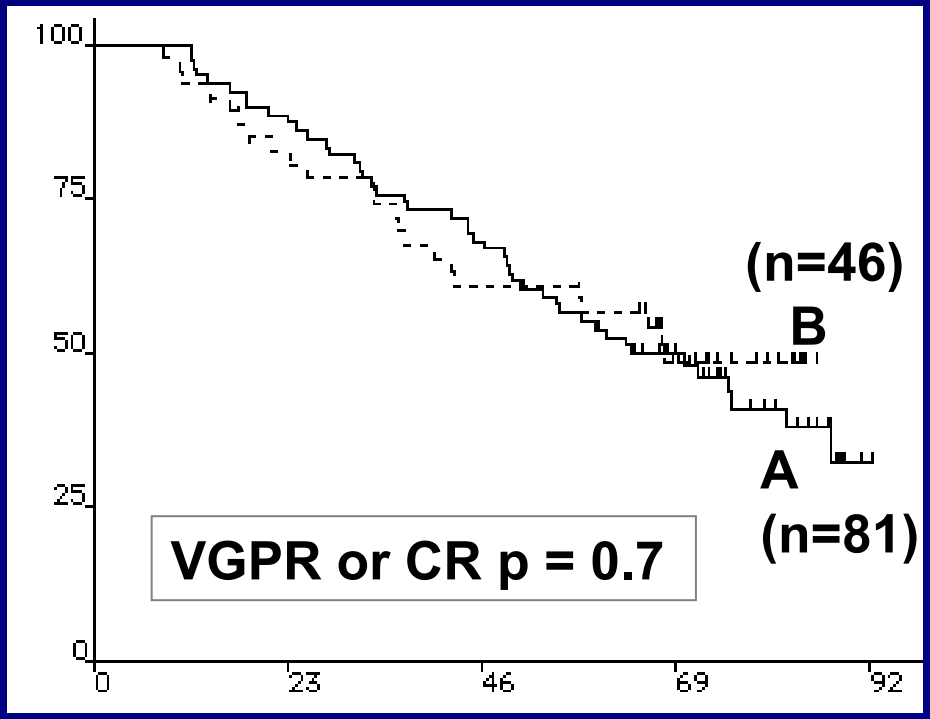
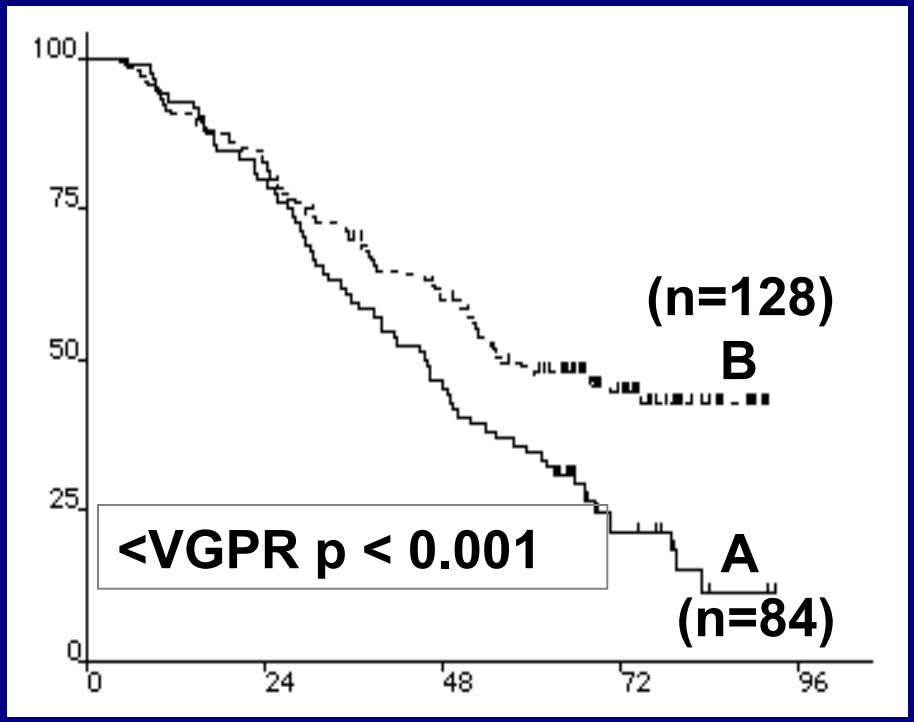




With longer follow-up results remain stable
Survival significantly longer in the transplant arm compared to the conventional chemotherapy arm
Trend in favor of double vs single ASCT

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

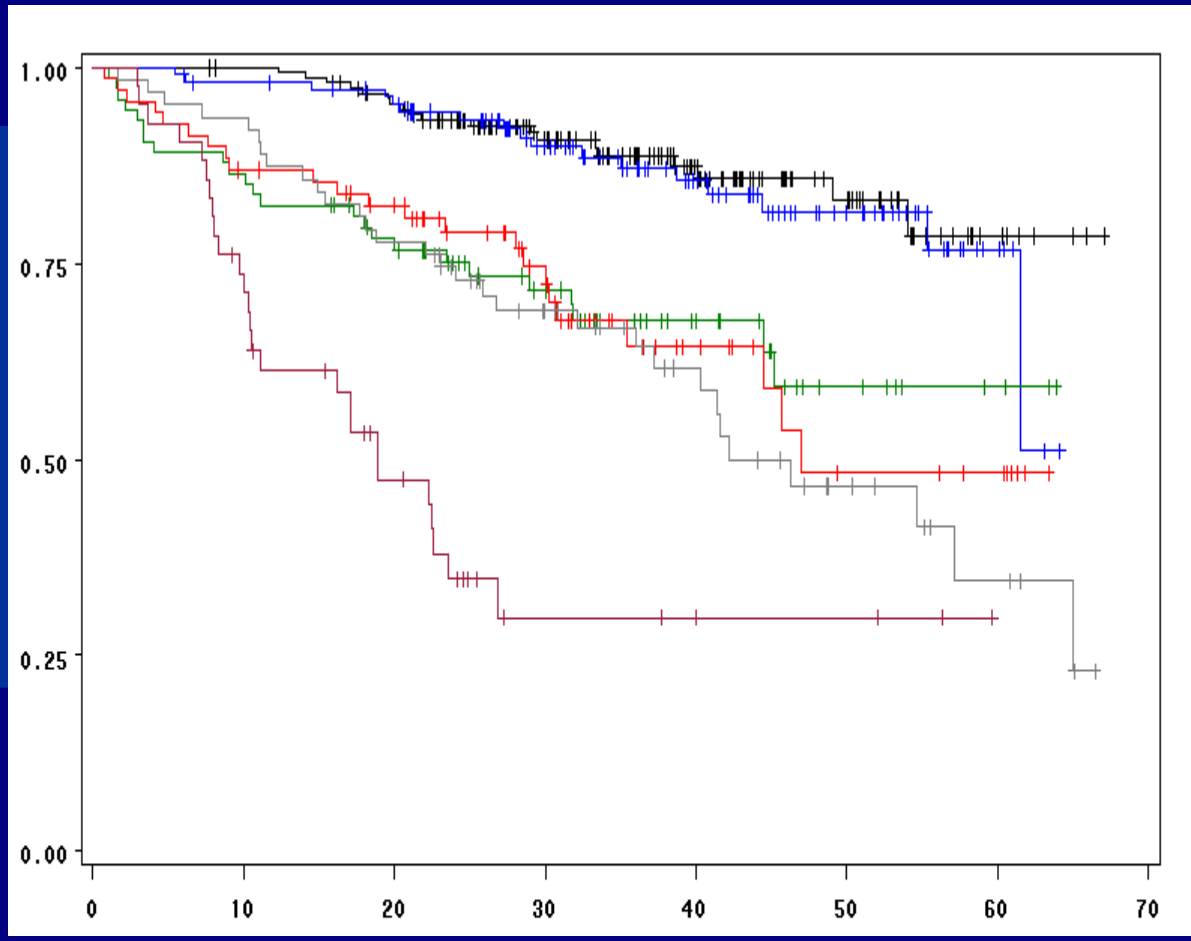




Cytogenetic + b2m model
H Avet Loiseau Blood 2007

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



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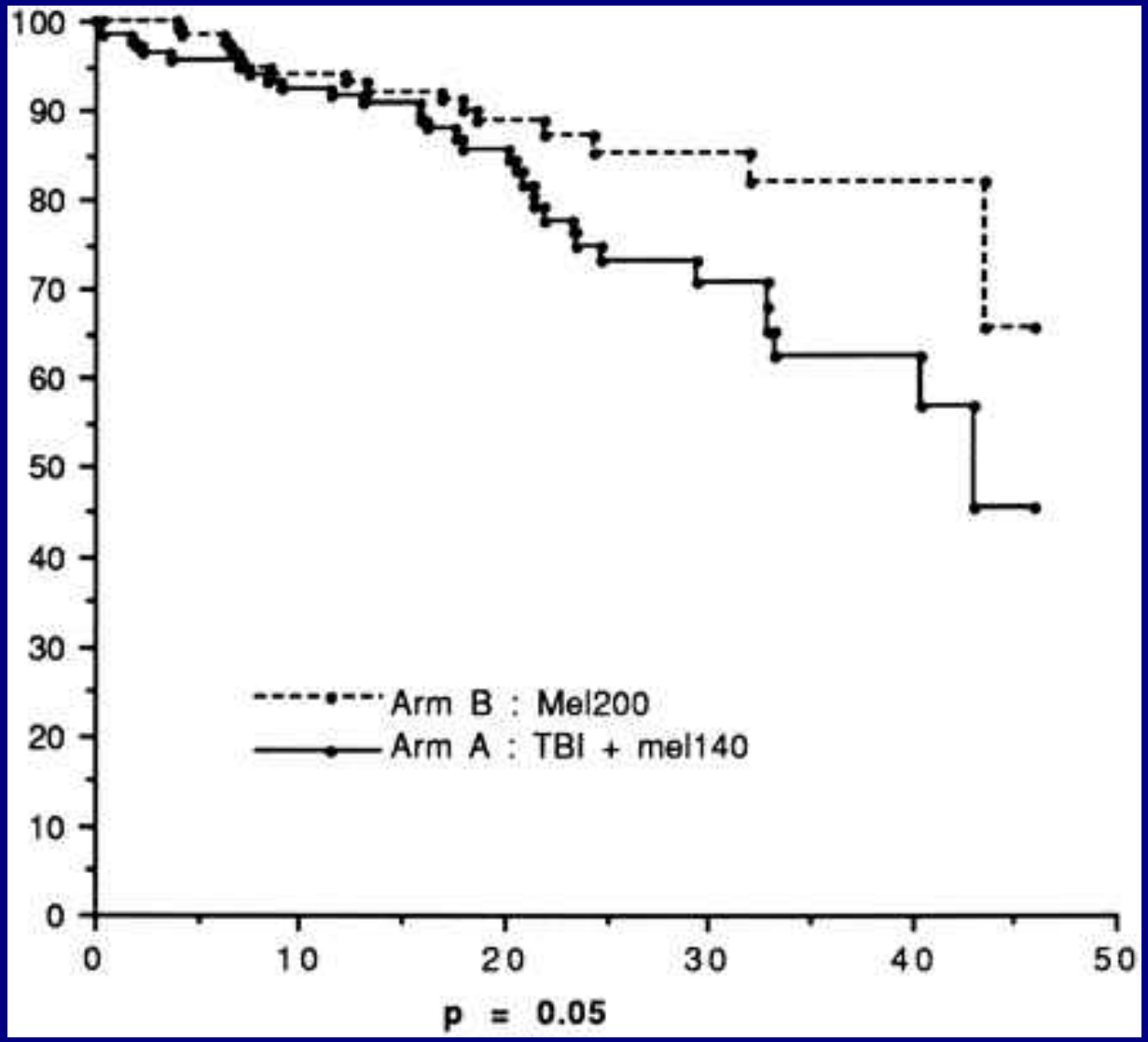
Impact of ASCT on OS in youger patients

IFM95-02 trial



Moreau et al, Blood 2002

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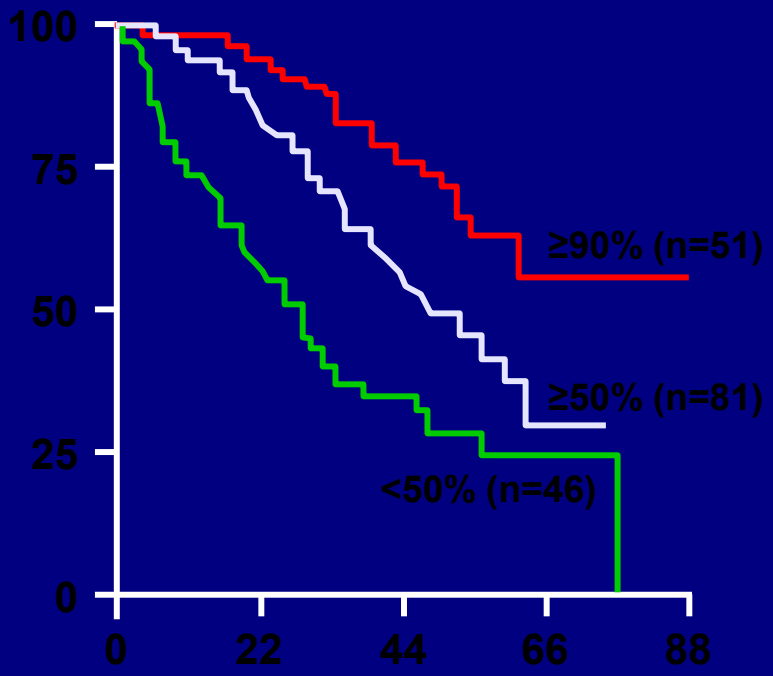
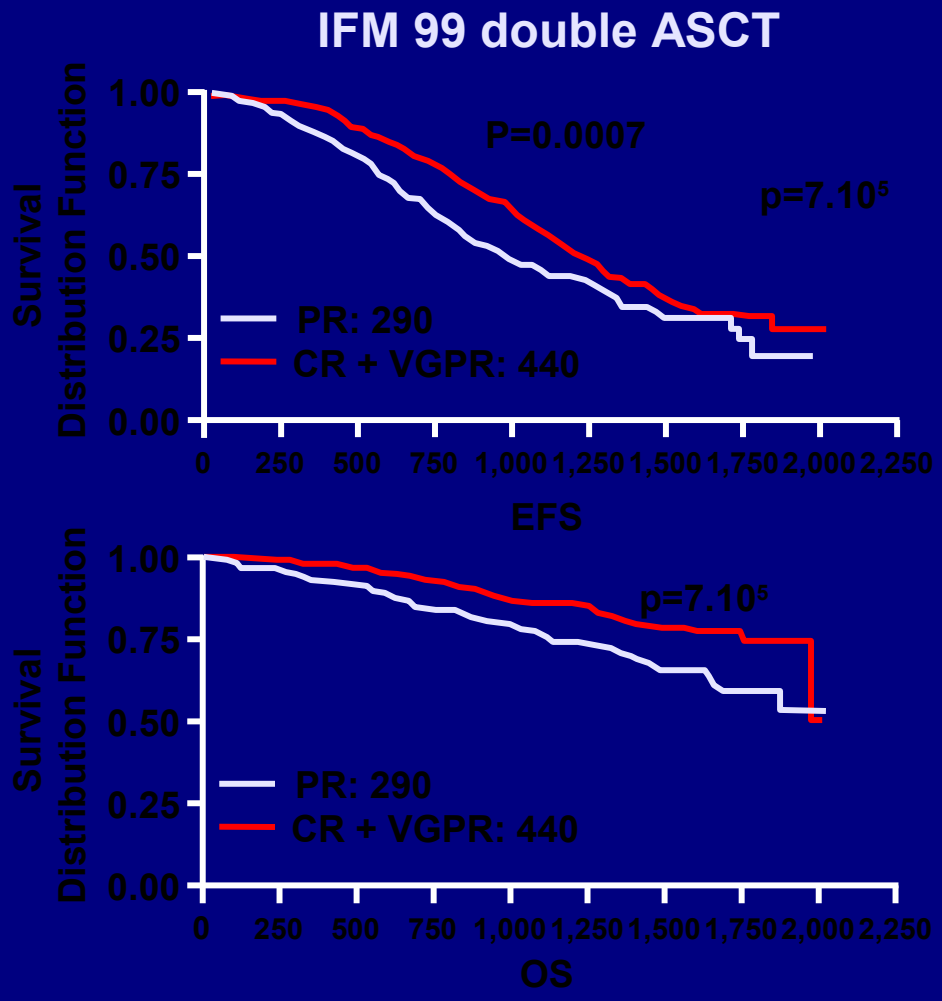
Recent improvements

- Induction therapy

Impact of CR + VGPR on outcome



Attal M NEJM 96



Harousseau JL JCO in press

Thal-Dex prior to ASCT

	TD vs D	TD vs VAD	TD vs VAD
Author	Rajkumar JCO 2006	Cavo Blood 2005	Macro ASH 2006
N° of pts	201	200	204
Response Prior to ASCT	RR: 69% vs 51%	RR: 76% vs 52% RR	VGPR 35% vs 17
DVT	17% vs 3%	15% vs 2%	23% vs 7.5%

Thal-Dex prior to ASCT

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

Len-Dex prior to ASCT

-No randomized study comparing induction with Len-Dex to other regimens

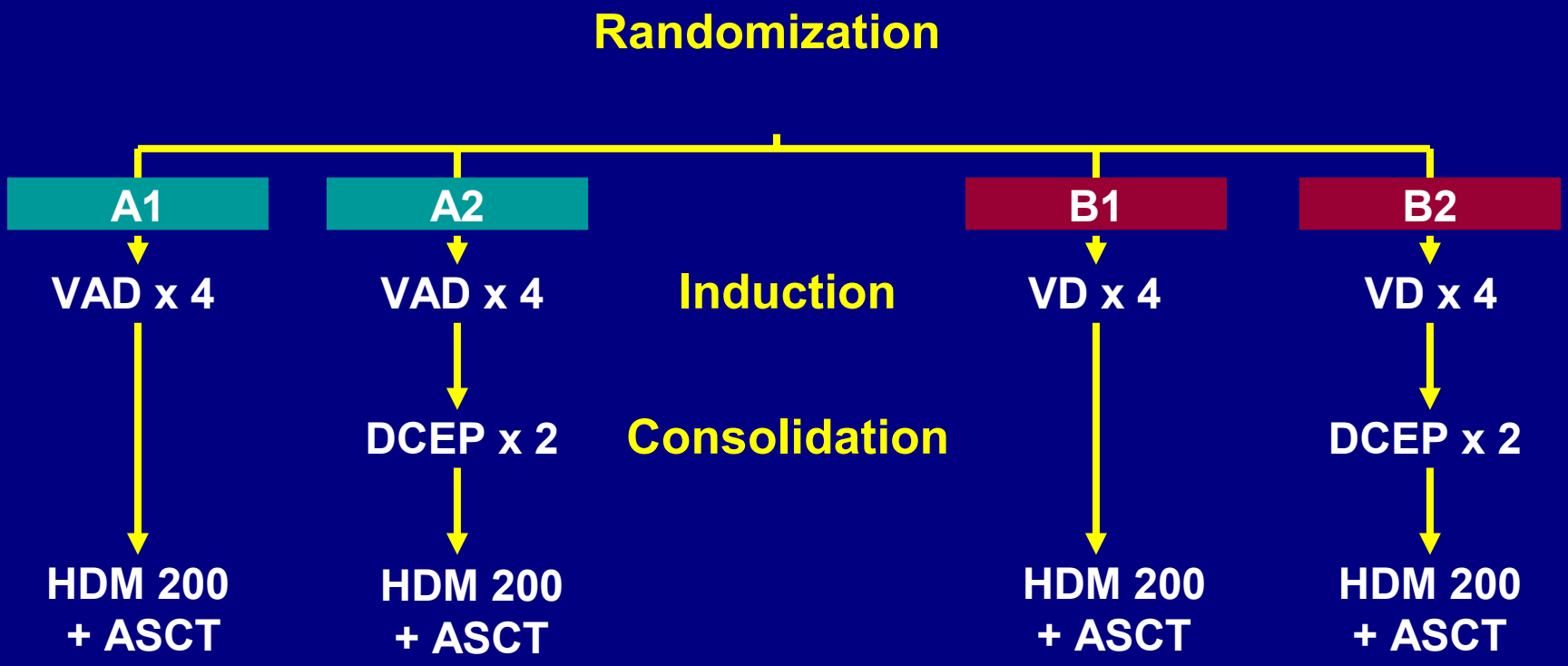
- In available studies on Len-Dex, patients who were candidates for ASCT and who received 4 cycles prior to ASCT were mixed with patients who received long-term treatment

-Response rate after 4 cycles was the primary end-point of the ECOG E4A03 trial

	Len-Dex	Len-dex
PR rate	80%	67%
VGPR rate:	44%	26%

Vel-Dex prior to ASCT
IFM 2005-01 TRIAL

Study Design



Second ASCT if <VGPR

IFM 2005-01
Response To Induction (4 cycles)

	VAD N=210	Vel-Dex N=214	P value
CR	1%	6%	0.0109
CR+nCR	7%	15%	0.0035
≥ VGPR	16%	39%	< 0.0001
≥ PR	65%	82%	<.0001
MR+SD	28%	13%	
PD	4%	5%	
Death	3%	0.5%	

Response by IRC assessment

Harousseau ASH 2008

Response to First ASCT
Intent-to-treat analysis

	VAD N=213	Vel-Dex N=212	P value
CR	9%	17%	0.016
CR + nCR	19%	37%	<0.0001
≥ VGPR	38%	57%	0.0003
≥ PR	79%	84%	NS
MR/SD/PD	4%	3%	
No ASCT	17%	13%	

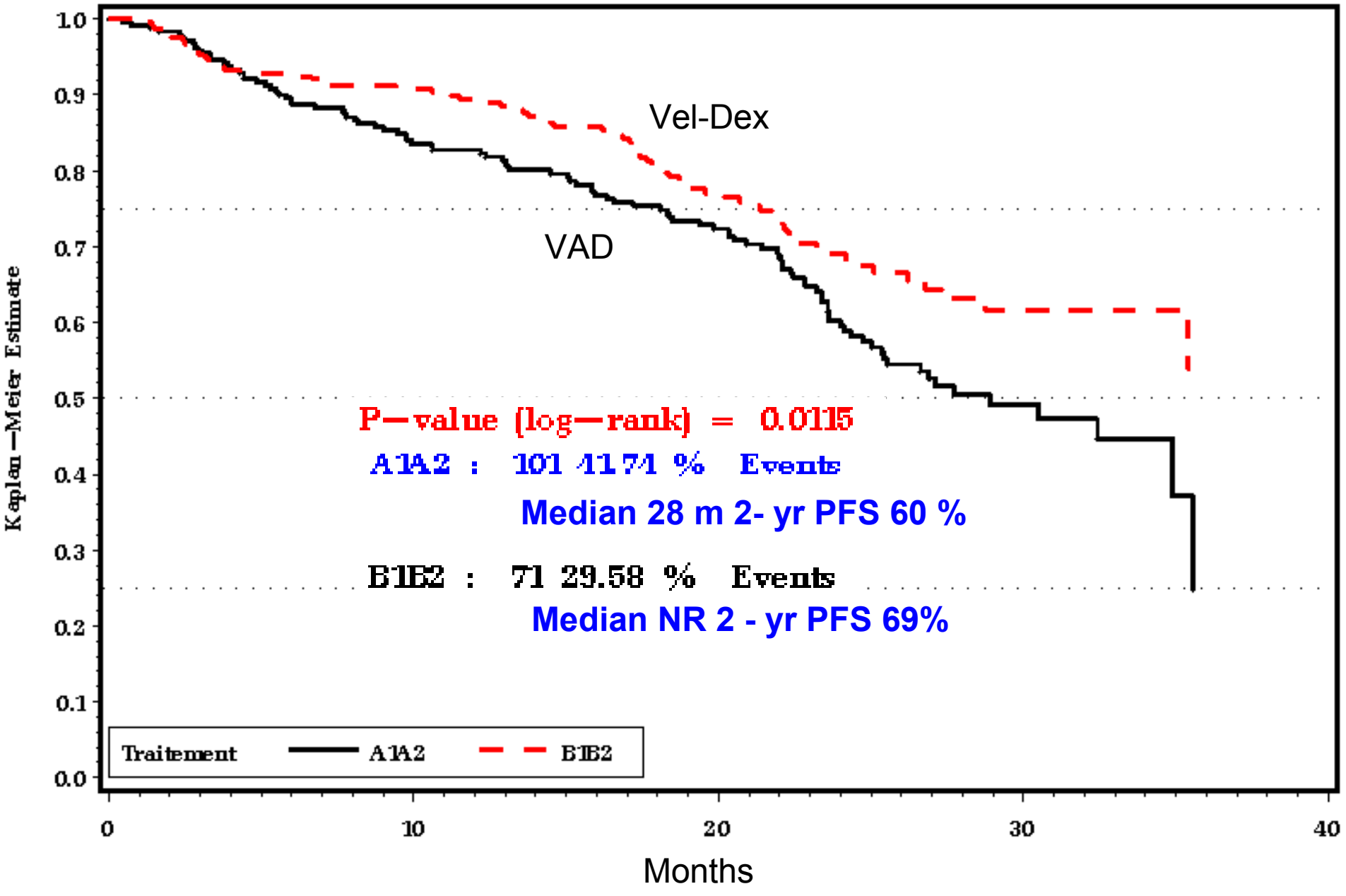
Two-drug regimens: response before and after ASCT

	TD vs VAD[1]	VD vs VAD[2]
N° of pts	204	424
pre-ASCT ≥VGPR (%)	35 vs 13 P = 0.002	39 vs 16 P<0.0001
post-ASCT ≥VGPR (%)	44 vs 42 P=NS	57 vs 38 P=0.0003

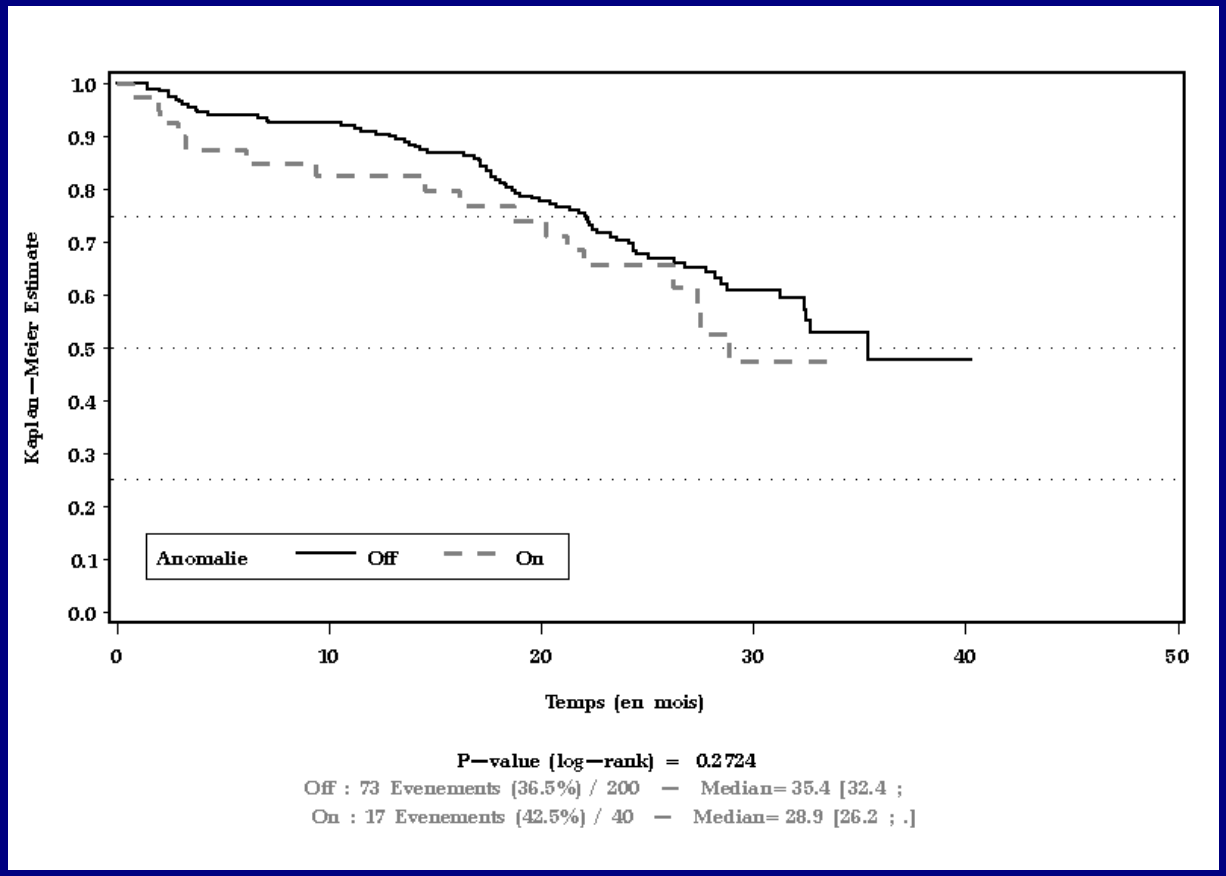
VD is clearly superior to VAD while TD is not
VD appears to be superior to TD.
No information on post-ASCT rate with RD/Rd

1 Macro et al ASH 2006 (abs. 57) 2 Harousseau ASH 2008

PFS (2 yr median f-up)



IFM 2005-01
Impact of t(4;14) and del(17p) on PFS in patients treated with Vel/dex



Three-Drug combinations prior to ASCT

	TAD vs VAD Lokhorst IMW 09	TCD vs VAD Morgan ASH 07	PAD vs VAD Sonneveld ASH 08	VTD vs VAD Cavo ASH 08
Nb of pts	402	251	300	460
Pre ASCT RR	72 vs 54	87 vs 75	83 vs 75	94 vs 79
≥ VGPR	32 vs 15	39 vs 27	42 vs 15	62 vs 29

Three-Drug combinations prior to ASCT

	TAD vs VAD 1	TCD vs VAD 2	PAD vs VAD 3	VTD vs VAD 4
Nb of patients	402	251	300	460
Pre ASCT				
RR	72 vs 54	87 vs 75	83 vs 75	94 vs 79
≥ VGPR	32 vs 15	39 vs 27	42 vs 15	62 vs 29
Post ASCT				
CR	16 vs 11	51 vs 40	15 vs 9	43 vs 23
≥ VGPR	49 vs 32	67 vs 43	59 vs 47	76 vs 58

1 Lokhorst (Hovon/GMMSG)IMW 2009

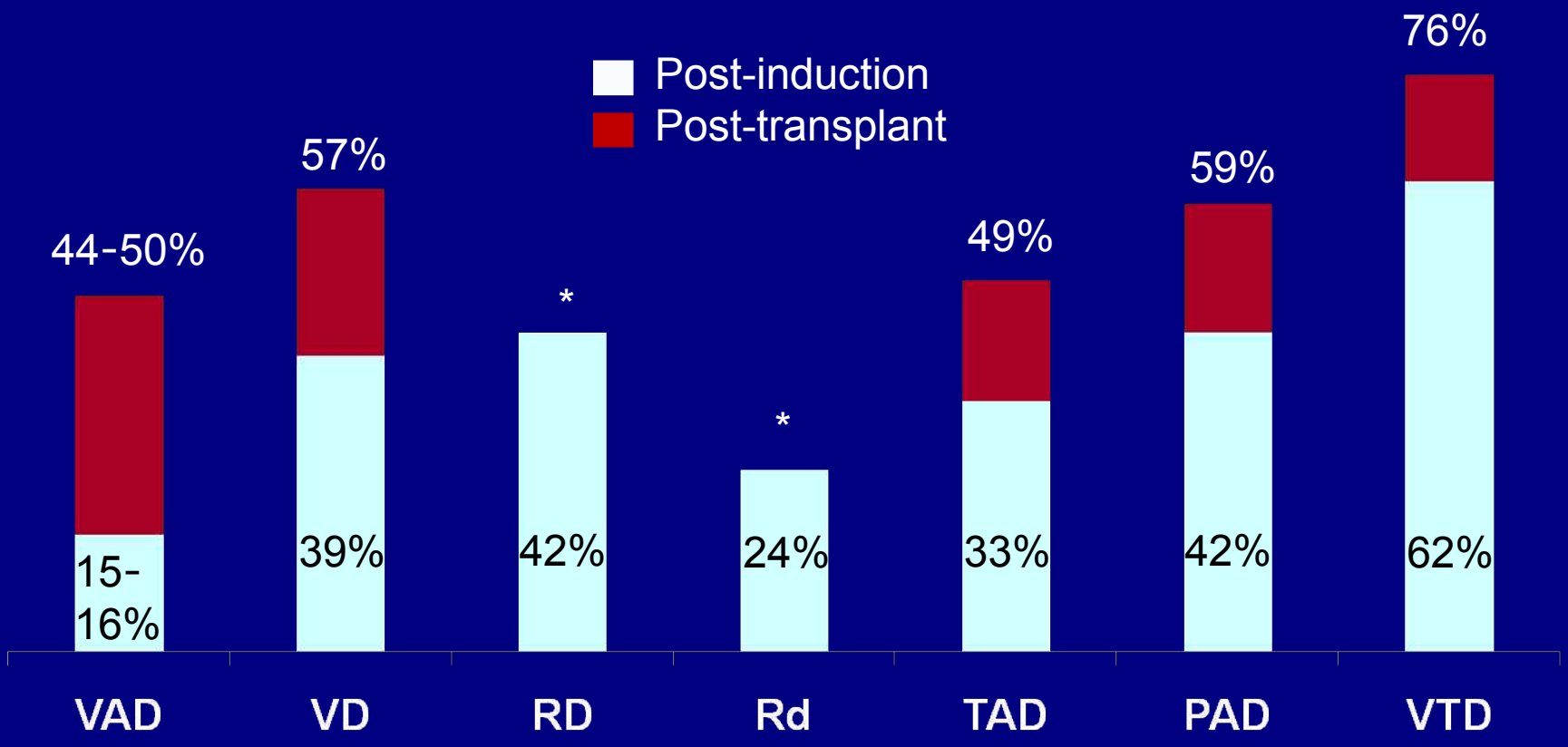
2 Morgan (MRC) ASH 2007

3 Sonneveld(Hovon/GMMSG ASH 2008

4 Cavo (GIMEMA) ASH 2008

Summary of novel agent induction trials (randomized studies)

≥ VGPR rates post-induction and post-transplant

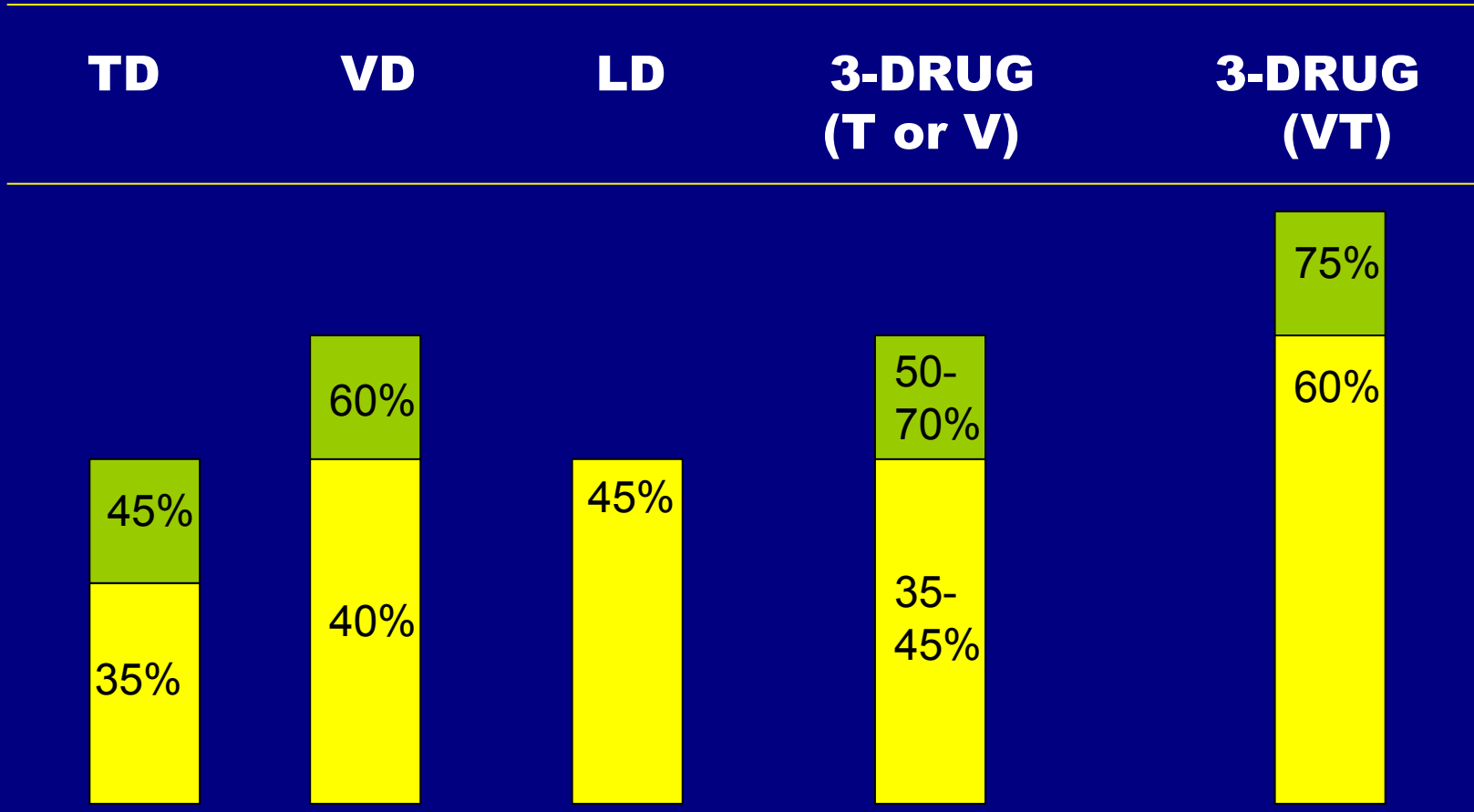


*Post-transplant data not available

Harousseau et al. ASH/ASCO symposium during ASH 2008
Rajkumar et al. ASCO 2008 (Abstract 8504);
ASH/ASCO symposium during ASH 2008

Lokhorst et al. Haematologica 2008;93:124–7
Sonneveld et al. ASH 2008 (abstract 653); IMW (abstract 152)
Cavo et al. ASH 2008 (abstract 158); IMW 2009 (abstract 451)

Induction treatment VGPR rate



CONCLUSION

Bortezomib-based combinations appears to be superior to thalidomide-based combinations (VD>TD,PAD>TAD)

Preliminary results with VD induction show that a higher initial tumor burden reduction may translate into a longer PFS

Bortezomib might overcome poor prognosis related to t(4;14)

VTD appears to yield the best results

Incidence of PN in Bortezomib induction trials

Study		Grade 2	Grade 3/4
IFM	Vel-Dex	18%	7%
	VAD	8%	2%
GIMEMA	VTD	n/a	9%
	TD	n/a	2%
HOVON-65/GMMG-HD4	PAD	13% (Grade 2)	16%
	VAD	17% (Grade 2)	6%
PETHEMA/GEM	TD	n/a	n/a
	VTD	n/a	16%

VD vs VTD
IFM 2007-02

stratification according to b2m and del13
4 cycles
Evaluation at 2 cycles and 4 cycles

VD (IFM 2005/01)

Vel 1.3mg/m2 J1,4,8,11
Dex 40mg J1-4,9-12
Cycles 1- 2
J 1-4 cycles 3-4

VTD

Vel 1mg/m2 J1,4,8,11
Thal 100mg/j
Dex idem
Increase to V 1.3 and T 200
if < RP at 2cycles

enoxaparin 40000 U

Primary objectice CR rate 202 patients included

Recent improvements

Induction therapy

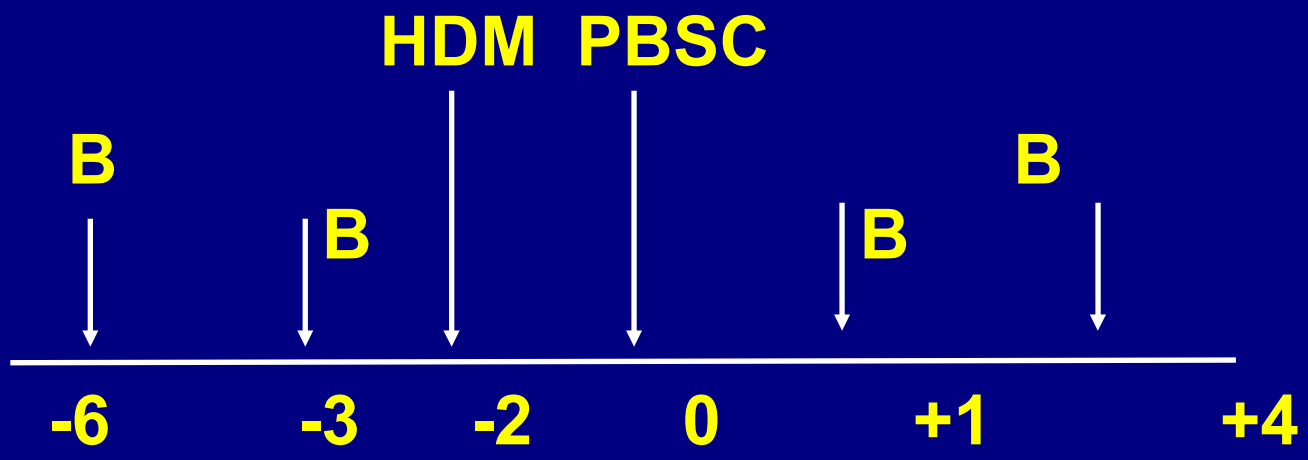
Preparative regimen

VEL-MEL STUDY DESIGN

Open-label, multicenter, phase II study in de 54 de novo MM pts < 65 yrs

Primary endpoint: CR + VGPR rates at 3 mo post HDT

Secondary endpoint: safety profile



B= Bortezomib 1mg / m²

HDM= Melphalan 200 mg / m²

RESPONSE to VEL-Mel +ASCT

	All pts n=53	VAD n=28	Bor-Dex n=18	≥ 2 lines n=7
CR	18 (34%)	36%	39%	14%
≥ VGPR	37 (70%)	68%	72%	71%
≥ PR	50 (94%)	93%	100%	86%
SD	2 (4%)	7%	0	0
PD	1 (2%)	0	0	14%

IMWG criteria

M Roussel ASH 2008

MATCHED CASE-CONTROL STUDY: Response to Mel 200 or Vel-Mel

	Control (Mel 200) n= 115	Pilot Vel-Mel n= 46
CR	20 (18%)	19 (42%)
≥VGPR	62 (54%)	32 (70%)
≥PR	113 (98%)	44 (96%)
SD	2 (2%)	2 (4%)

Matched according to induction Tt (VAD od Vel/Dex), response to Induction and age

M Roussel ASH 2008

Recent improvements

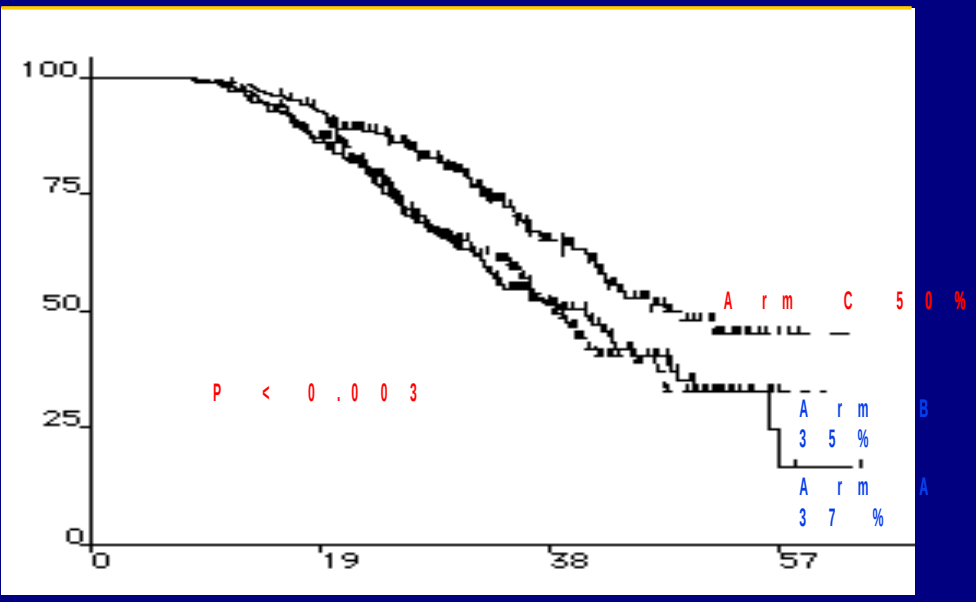
Induction therapy

Preparative regimen

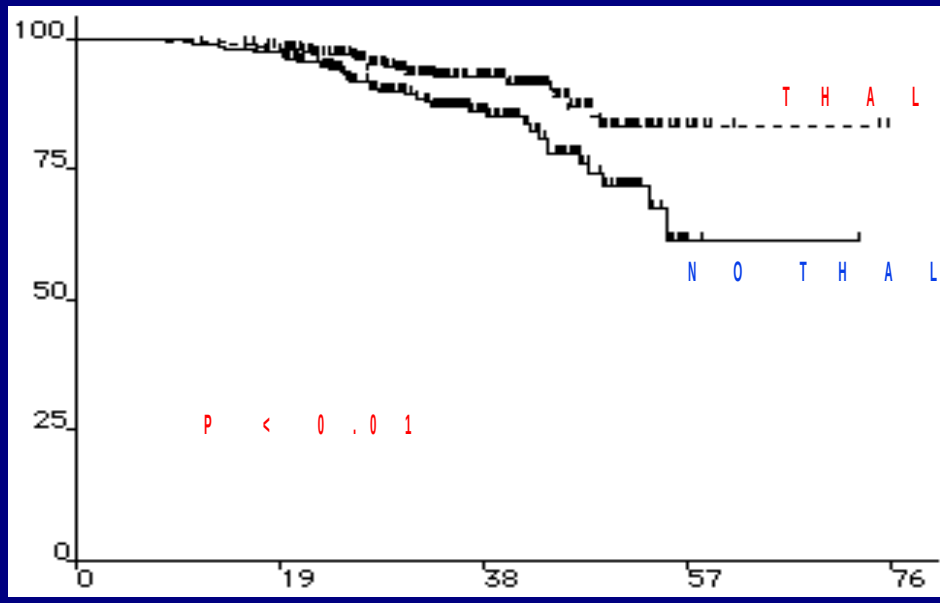
Post- ASCT treatment

Role of Thalidomide as Post ASCT maintenance Tt

4-yr EFS

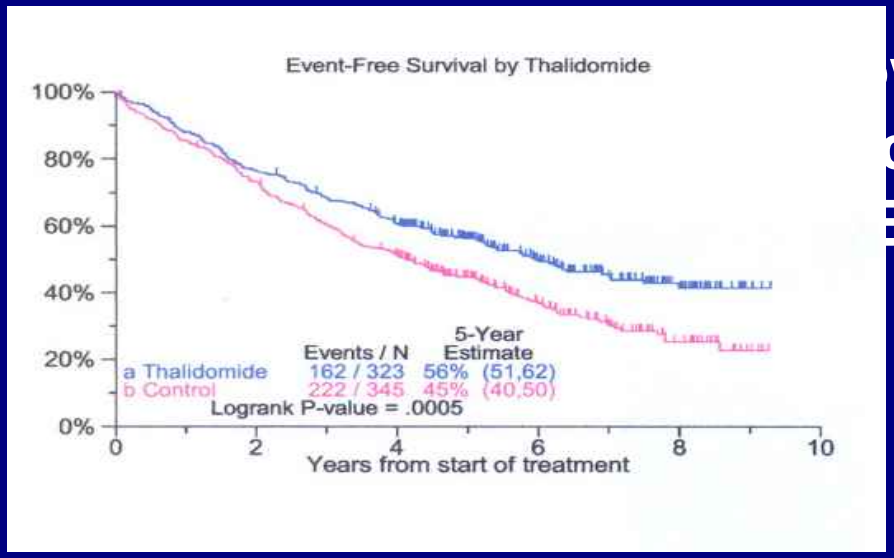


4-yr OS

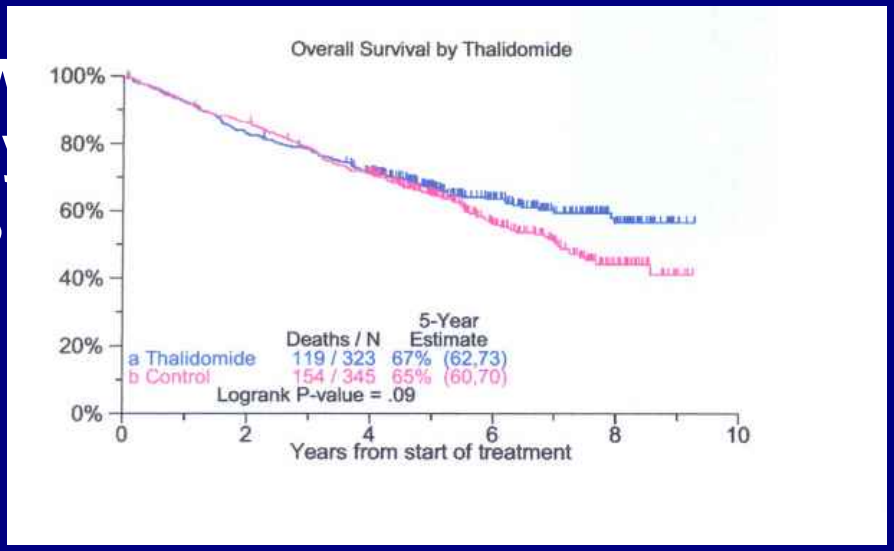


TOTAL THERAPY 2
IMPACT OF THALIDOMIDE

EFS

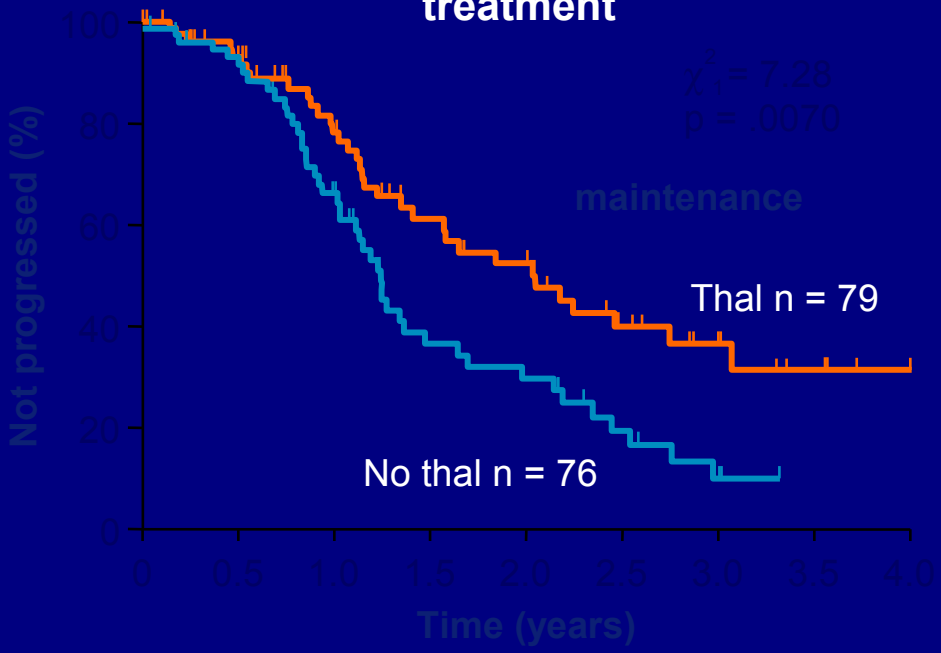


OS

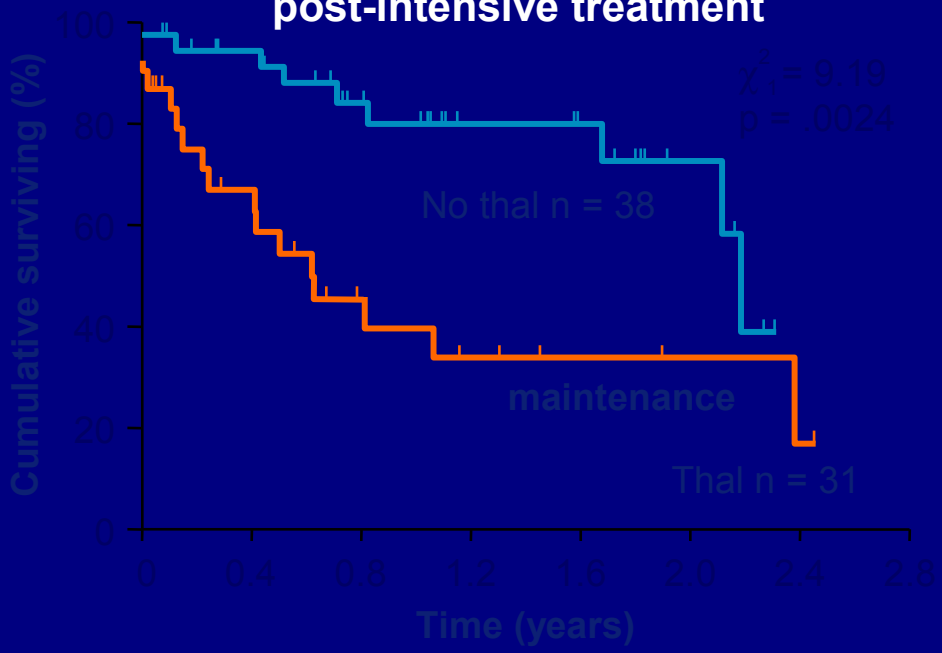


Impact of maintenance on survival after relapse in the intensive arm

PFS for PRs post-intensive treatment



Survival after relapse for PRs post-intensive treatment



- The cause for rapid death following relapse for thalidomide maintenance cases is uncertain:
  - selection of resistant clones
  - lack of effective treatment for relapse

Morgan GJ, et al. Blood. 2008;112:[abstract 656], updated data presented at ASH 2008.

Thalidomide Maintenance Studies

Author	Reference	Induction	ASCT	Thal Administration	Design
Barlogie	NEJM 06 Blood 08	50% Thal	Double	Starting dose 400mg/D Until relapse	Initial randomisation Thal vs no Thal
Attal	Blood 06	No Thal	Double	Starting dose 400mg/D Until relapse	After ASCT No treatment vs Thal+Pamidronate
Spencer	JCO 09	No Thal	Single	200 mg/D 1 year	After ASCT
Morgan	ASH 08	50% Thal	Single	100 mg/D Until relapse	After ASCT
Lokhorst	IMW 09	50% Thal	Double	200 mg/D Until relapse	Initial randomisation TAD → Thal VAD → IFN

Thalidomide Maintenance Studies
-
Positive Results

	Response (CR or CR + VGPR)	PFS	OS
Barlogie	YES	YES	YES in patients with Cytogenetic abnormalities
Attal	YES	YES	NO
Spencer	YES	YES	YES
Morgan	YES	YES	NO
Lokhorst	YES	YES	NO

Maintenance Thalidomide

1) Thalidomide maintenance increases the CR/VGPR and PFS rates
2) But no firm conclusion as regards OS
   Long follow-up is needed before showing OS data
   (more possibilities of salvage at relapse)
3) Thalidomide could improve OS only in subgroups of patients (<VGPR or poor-risk cytogenetics)
4) Optimal duration of post-ASCT is unknown (long-term treatment is associated with more toxicity)
5) Results of trials with Velcade or revlimid are awaited

VTD consolidation

- **Aim**
  - Assess impact of VTD consolidation on residual MM cells in patients achieving ≥VGPR after ASCT by qualitative and quantitative PCR
- **Treatment**
  - VTD started within 6 months from ASCT (for 4 cycles)
    - Bortezomib 1.6 mg/m^2 once weekly (days 1, 8, 15, 22)
    - Thalidomide 50 mg/day (increments of 50 mg every 7 days up to 200 mg)
    - Dex 20 mg/day, days 1-4, 8-11, 15-18
- **Results (n=40)**
  - Six patients converted to MR
  - No clinical relapse observed in MR patients at median follow-up of 26 months

Ladetto et al. ASH 2008 (abstract 3683)

Recent improvements

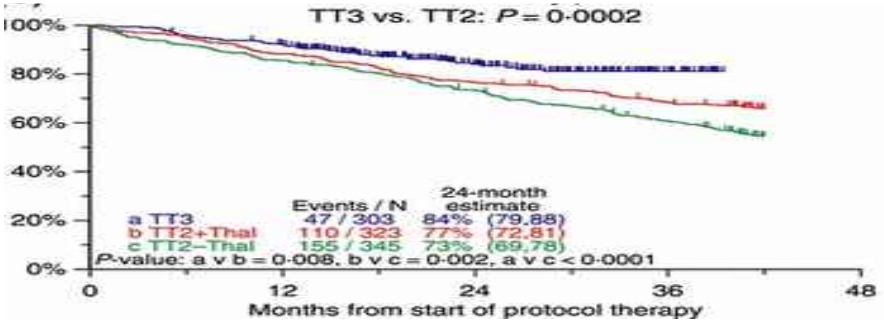
Induction therapy

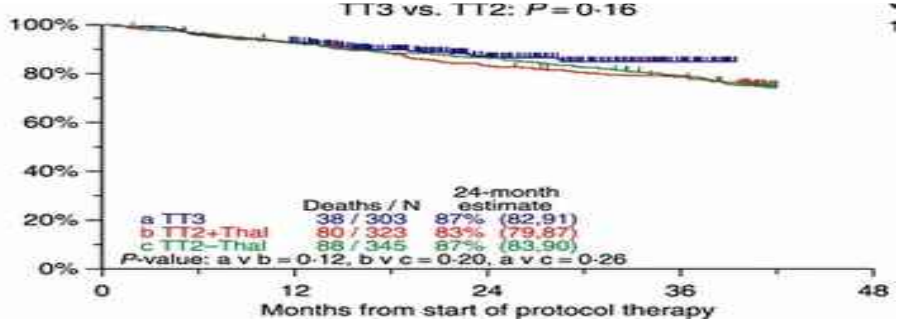
Preparative regimen

Post- ASCT treatment

Novel agents pre and post

T T 3 vs TT 2
Impact of bortezomib
Pineda-Roman (BJH 2008)





PAD induction + reduced-intensity ASCT + lenalidomide consolidation/maintenance

- Patients (n=102) (65-75 years

Palumbo et al. ASH 2008 (abstract 159)b

- Treatment

Induction (four 21-day PAD cycles)

Intensification
Tandem Melphalan 100 mg/m² (MEL100) + ASCT

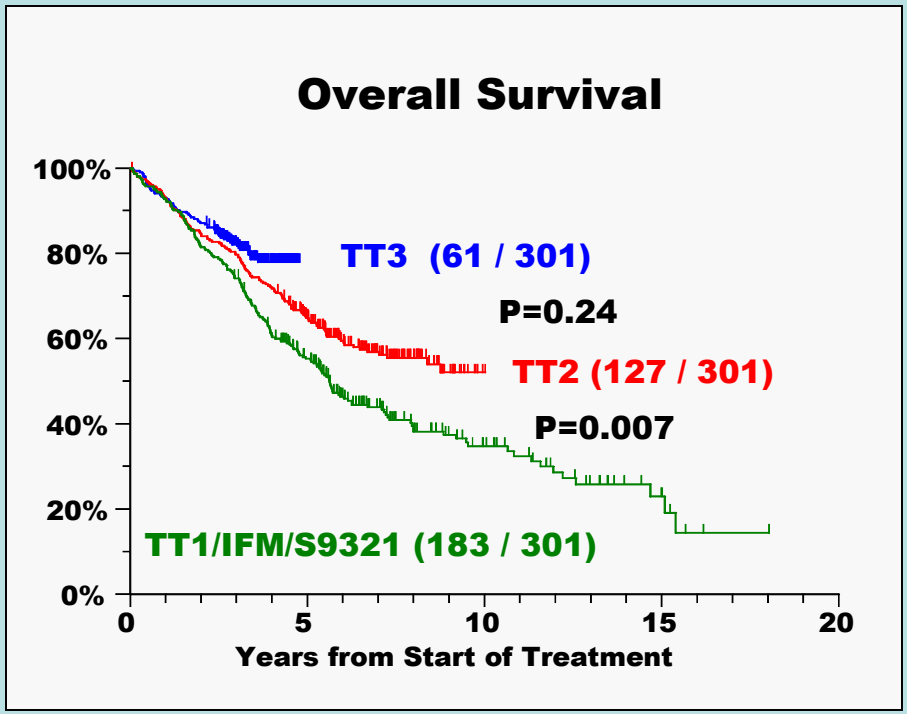
Consolidation (four 28-day LP cycles)
(Lenalidomide 25 mg days 1-21 + Prednisone 50 mg every other day)

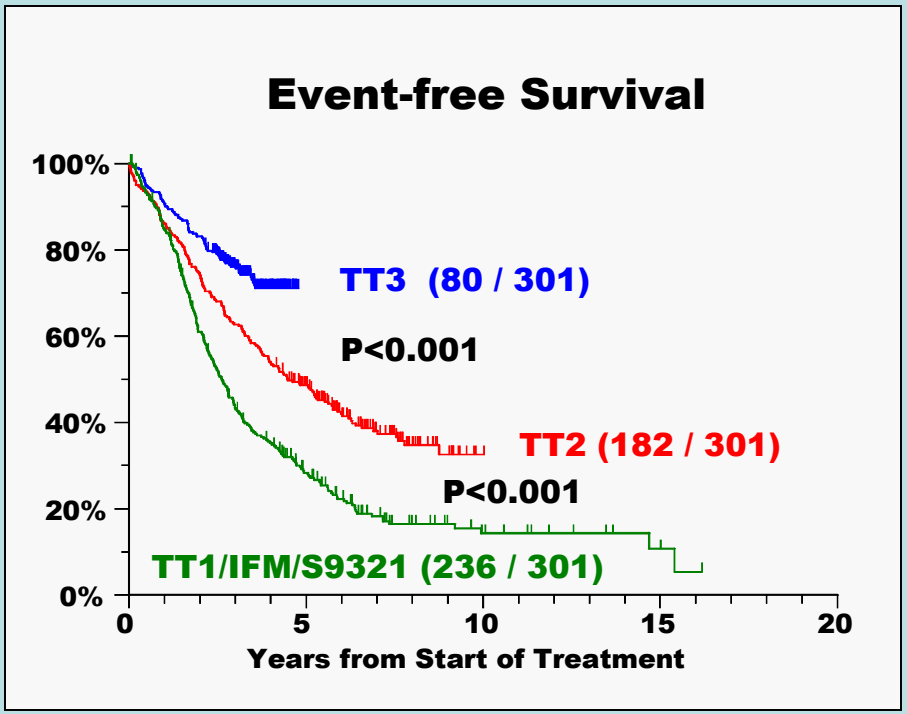
Maintenance
Lenalidomide (10 mg days 1-21 every 28 days

	After PAD	After tandem MEL100 + ASCT	After LP Consolidation
CR	13%	41%	53%
≥ VGPR	59%	88%	88%
≥ PR	94%	Not available	100%

LONG-TERM FOLLOW-UP OF IFM, S9321 & TT

Pair-mate Analyses (Albumin, B2M, LDH, Hemoglobin)

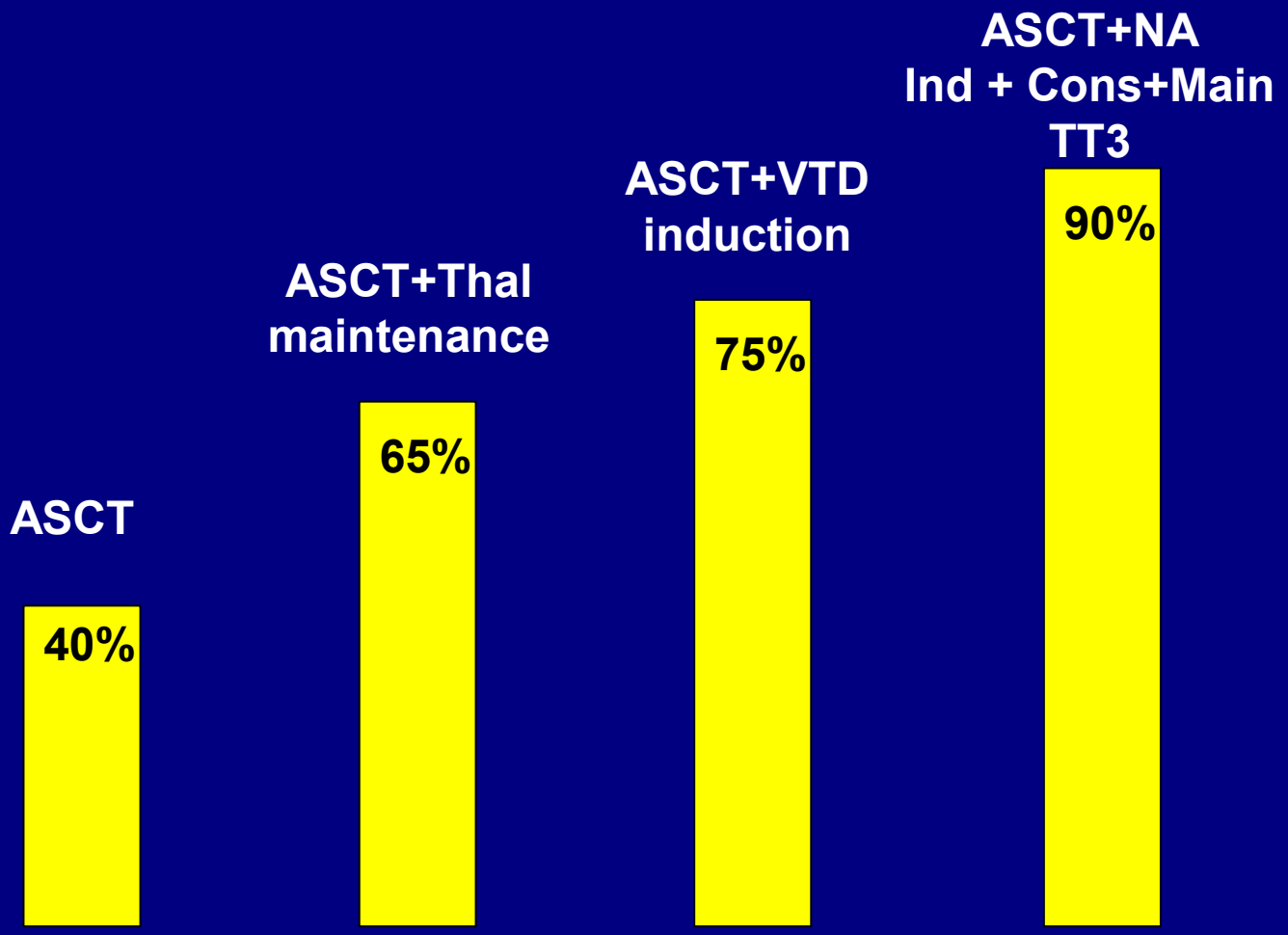




NOTE THE PROGRESSIVELY SUPERIOR OUTCOMES OBSERVED WITH TT3 > TT2 > TT1 AND OTHER TRIALS

In TT3 novel agents were administered at all steps Induction,consolidation and maintenance

Novel agents plus ASCT
CR + TBRP rate



Recent improvements

Induction therapy

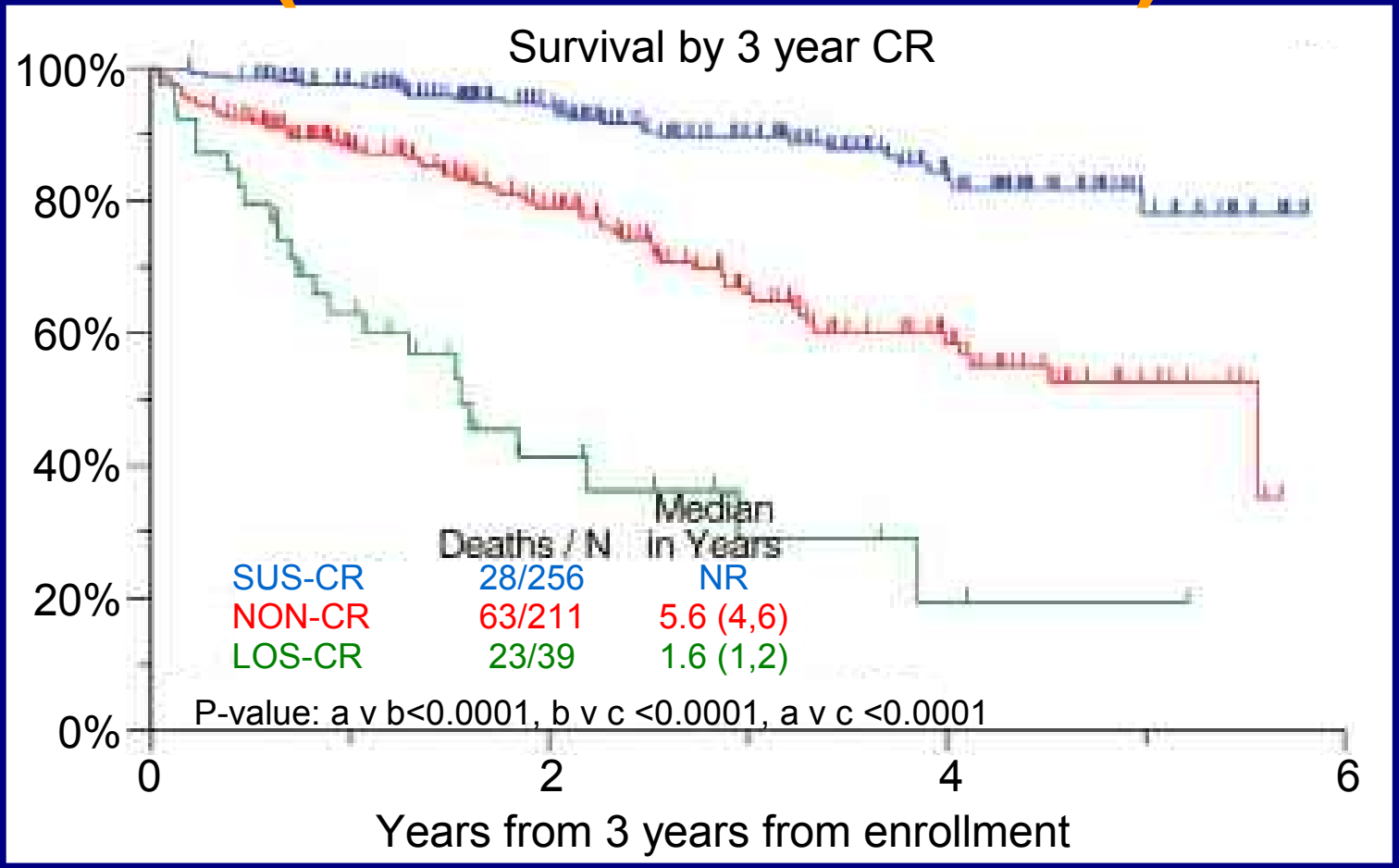
Preparative regimen

Post- ASCT treatment

Novel agents pre and post

Impact of CR level and duration

Importance of achieving durable complete response (Results from TT2)

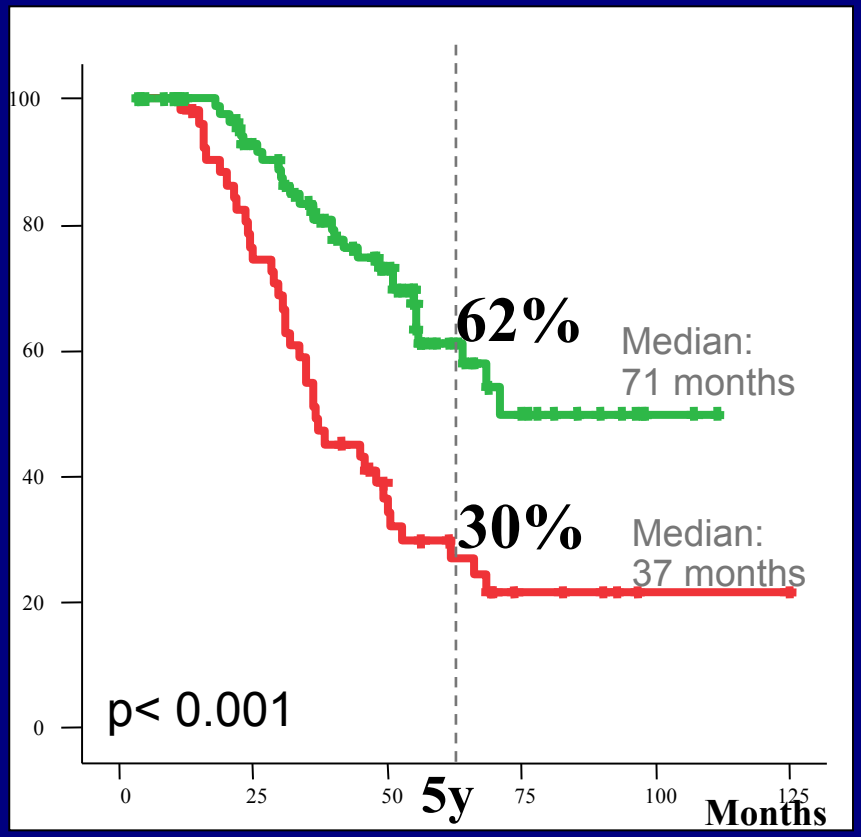


SUS-CR: achieved and sustained CR status
NON-CR: never achieved CR status
LOS-CR: attained and lost CR status

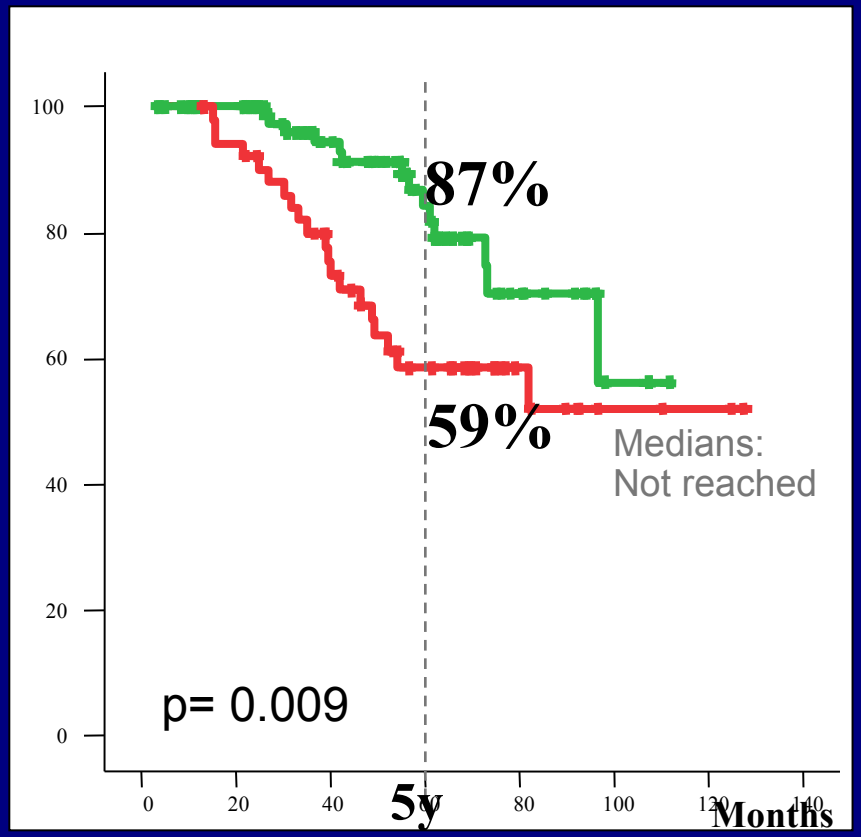
Barlogie et al. Cancer 2008;113:355–359

Impact on Survival of MRD by Immnunophenotyping in BM obtained 3 months after ASCT in CR patients

PFS



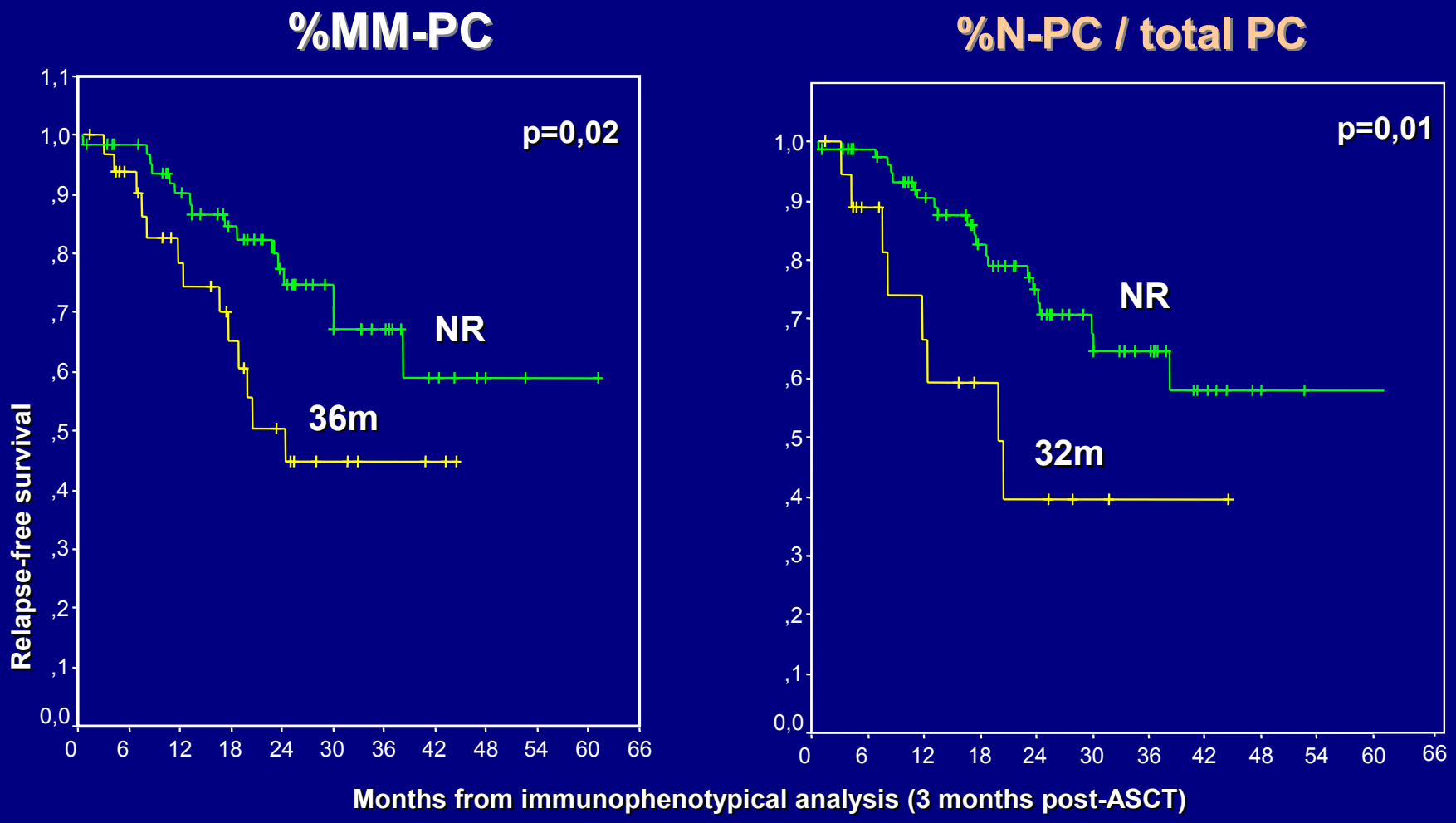
OS



MRD negative (n=94)
MRD positive (n=53)

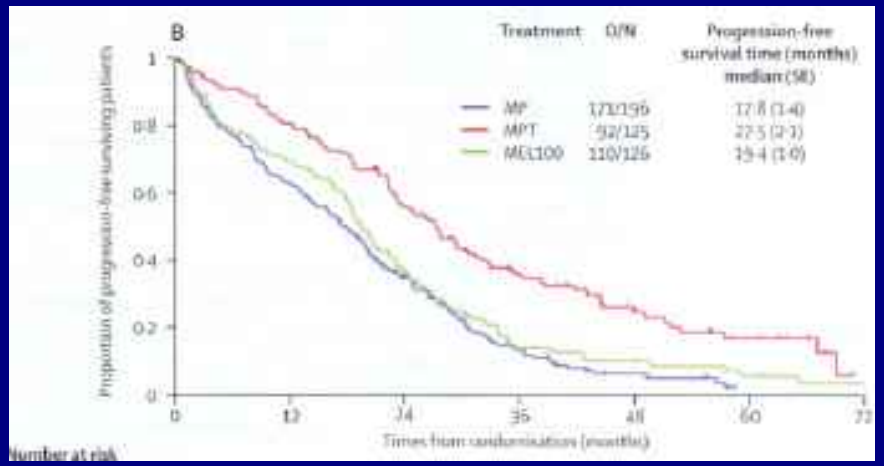
Paiva et al; Blood. 2008; 112: 4017-23

RFS: Impact of immunophenotyping at 3 months post-ASCT in 99 CR (IF-) patients

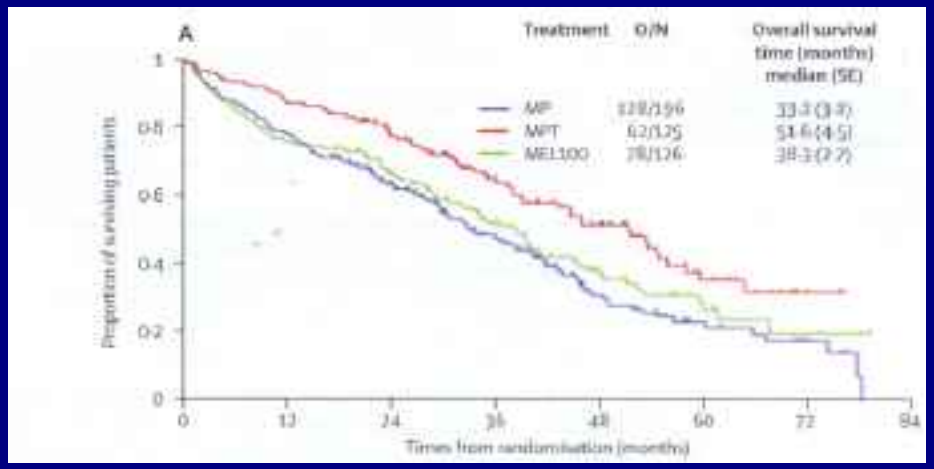


MP-Thal vs MP vs MEL100
T. Facon Lancet 2007

PFS



OS



	MP N=196	IDM N=126	MPT N=125
Best response at 12 mos			
CR	2%	18%	13%
CR+VGPR	7%	43%	47%
Median PFS	18 m	19m	28 m
Median OS	52 m	38m	33 m

MP vs MPT : PFS and OS

	GIMEMA Blood 08	IFM 99-06 Lancet 07	IFM 01-01 JCO 09	NMSG EHA 08	HOVON ASH 08
PFS (med,mo.)					
MP	14.5	18	19	18	10
MPT	22	27.5	24	20	13
P	.0004	<.0001	.001	NS	<.001
OS (med,mo.)					
MP	47	33	27.5	33	30
MPT	45	51.5	45	29	37
P	NS	.0006	.03	NS	NS

In 45 studies, MPT was superior to MP in terms of PFS
In 2/5 studies, MPT was superior to MP in terms of OS.

Response to treatment
High CR rate with VMP

	VMP, N=337		MP, N=331		
	EBMT[1]	Uniform[2†]	EBMT[1]	Uniform[2†]	p-value
ORR (≥PR)	71%	74%	35%	39%	$<10^{-6}$
CR	30%	33%	4%	4%	$<10^{-6}$
VGPR	NA	8%	NA	4%	
PR	40%	33%	31%	31%	
MR	9%	NA	22%	NA	
SD	18%	23%	40%	58%	

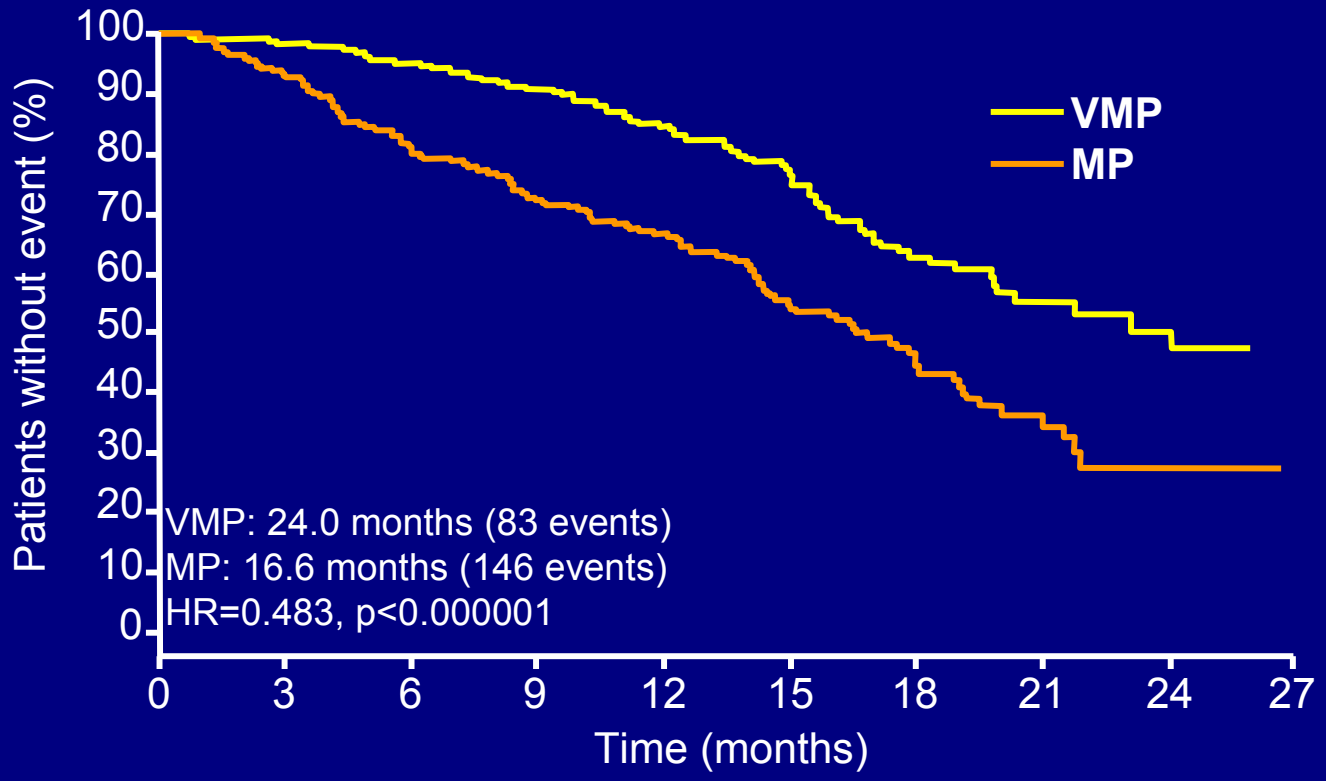
*CT or Urine

†Post-hoc analysis by International Uniform Response Criteria[2]

1. Bladé et al. Br J Haematol 1998;102:1115-23
2. Durie et al. Leukemia 2006;20:1467-73

San Miguel et al. N Engl J Med 2008;359:906–17

Time to progression:
52% reduced risk of progression with VMP



Number of patients at risk:

VMP:	344	295	272	245	185	111	65	31	17
MP:	338	296	241	206	152	86	53	22	5

San Miguel et al. N Engl J Med. 2008; 359:906-17; EHA 2008;110:Abstract 473.

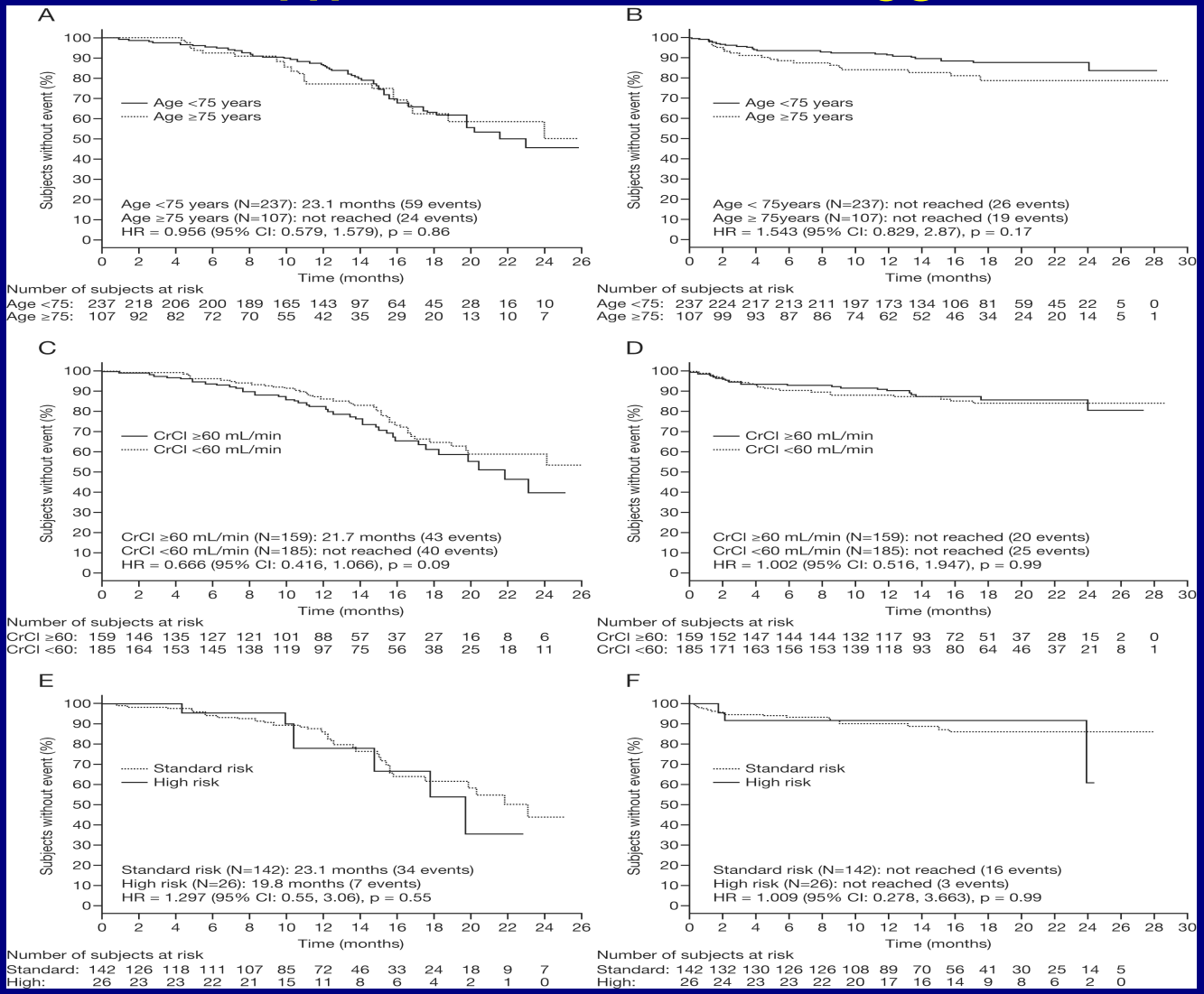
Efficacy in patients with poor prognostic characteristics

TTP OS

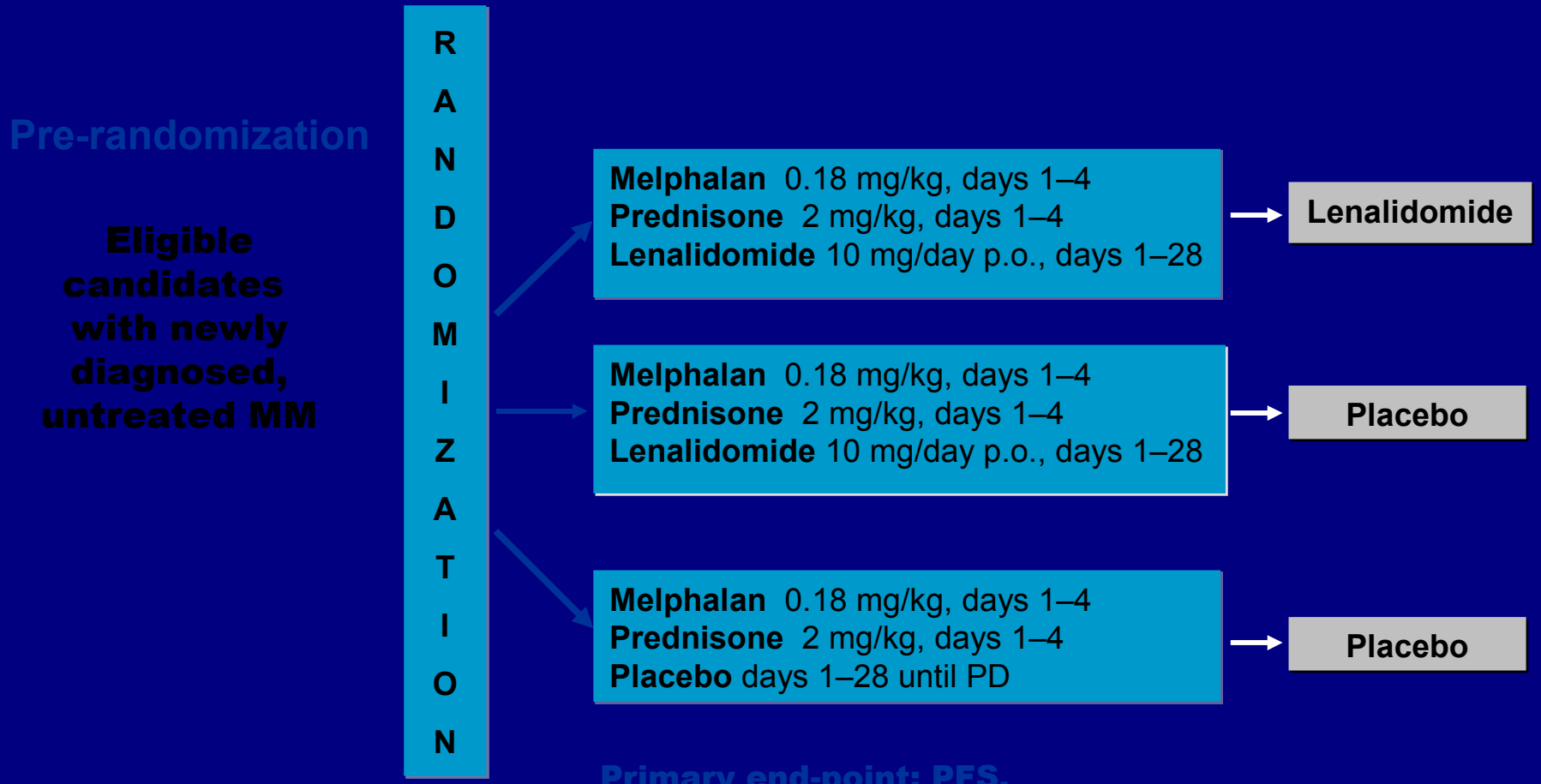
Age ≥75 vs <75 years

CrCl <60 vs ≥60 mL/min

High-risk (t(4;14), t(14;16), del 17p) vs standard-risk cytogenetics by FISH



EMN/Celgene study in patients > 65 years



EMN = European Myeloma Network.

Palumbo A, et al. Haematologica. 2006;91:181 [abstract 0491].
Palumbo A, et al. J Clin Oncol. 2006;24: [abstract 7518].

ECOG/E4A03 Adverse events

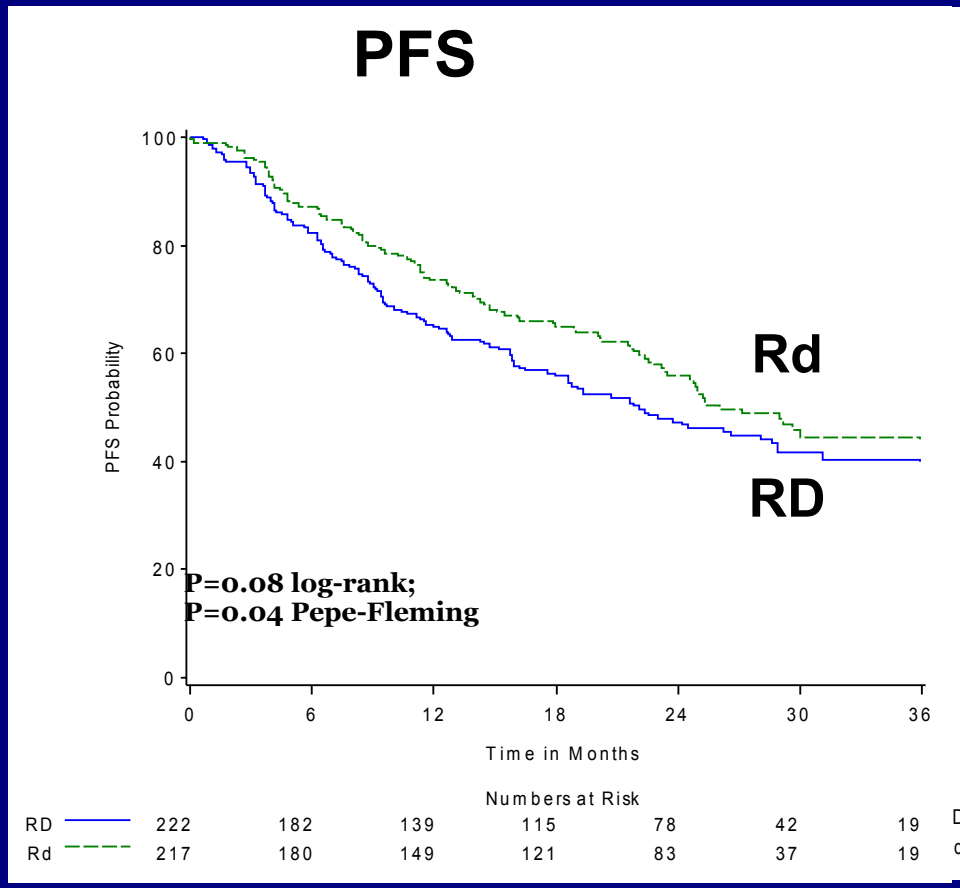
Type (≥ Grade 3)	Rd (N=223)	Rd (N=220)	P
DVT/PE	25%	11%	<0.001
Infection/Pneumonia	16%	8%	0.019
Cardiac ischemia	3%	0.5%	0.068
Any non Hem toxicity (Grade ≥ 3)	66%	46%	<0.001
Toxicity of any type (Grade ≥ 4)	27%	17%	0.022
Early deaths (< 4 mo. All pts)	5%	0.5%	0.003

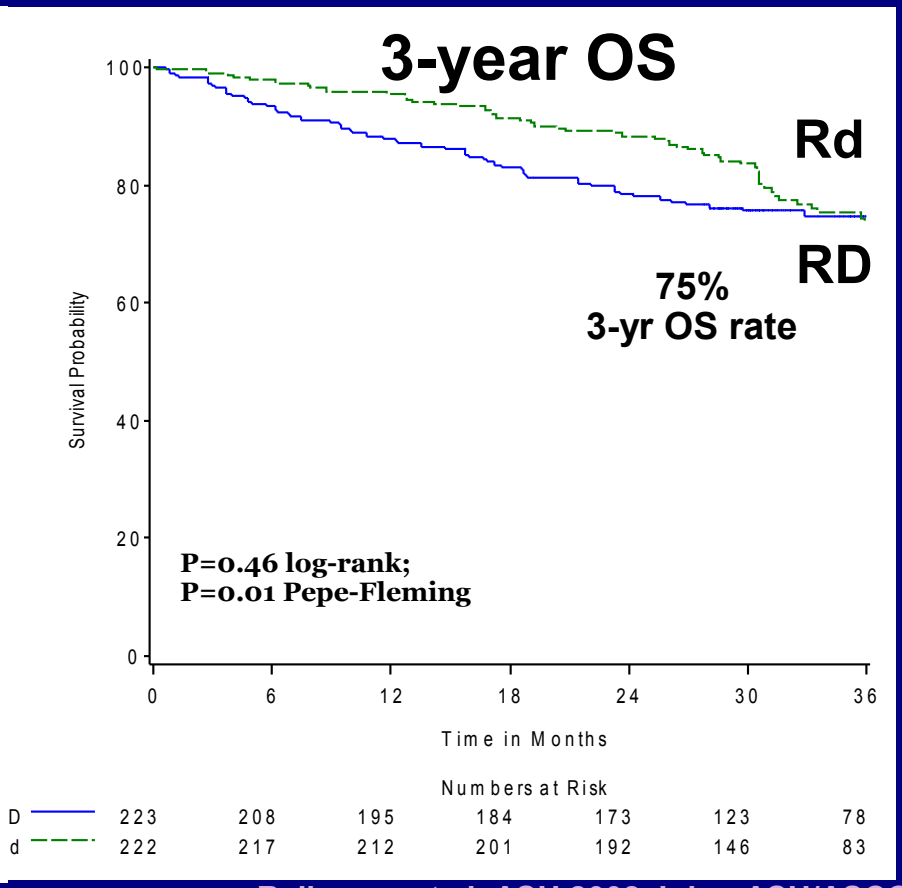
Rajkumar et al. JCO 2008;26:455s

Phase III ECOG trial: RD vs Rd

After 4 induction cycles

	RD	Rd
≥VGPR	51% (17%)	40% (14%)
≥PR	81%	70%

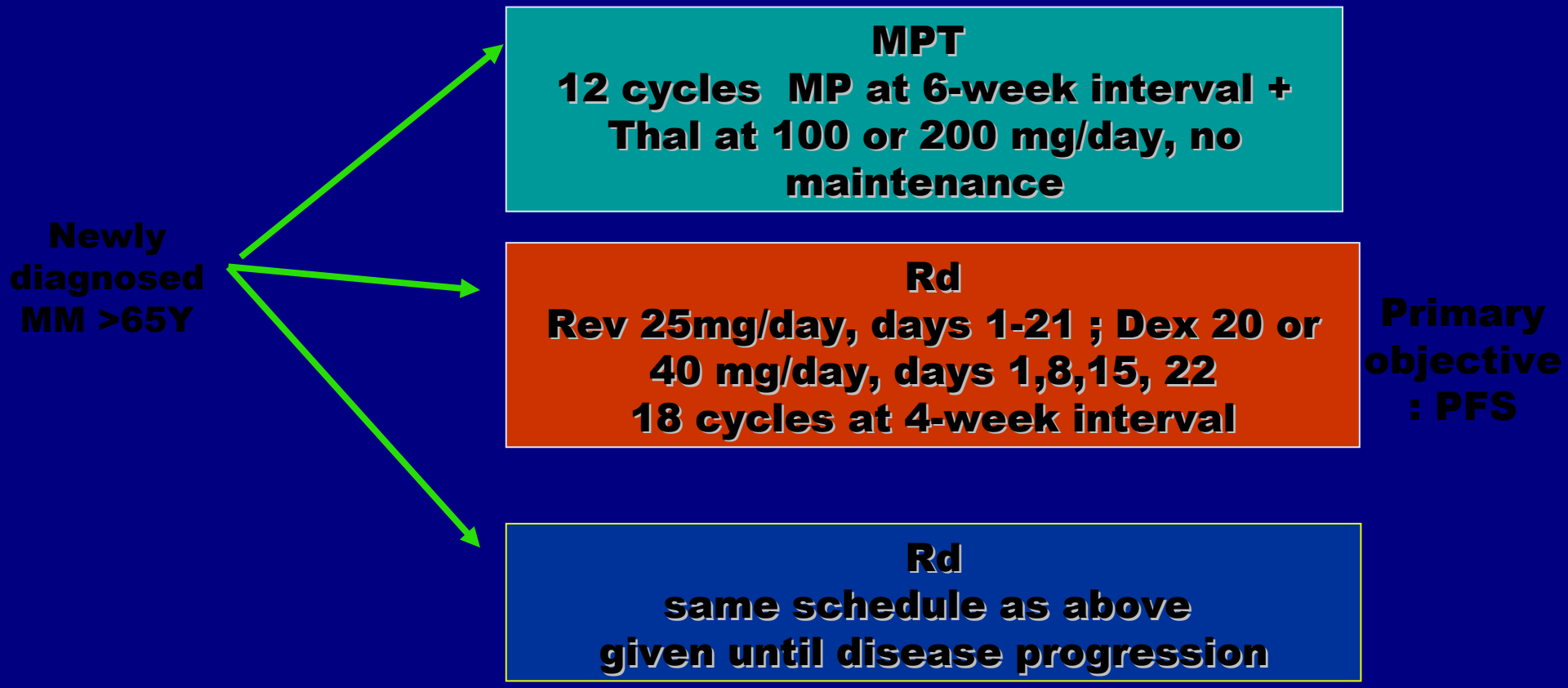




Rajkumar et al. ASH 2008 Joing ASH/ASCO symposium

MPT vs Revlimid-low dose Dexamethasone in Newly Diagnosed Myeloma Patients, Aged > 65 Years

CC5013-MM-020, IFM 2007-01, FIRST study



Lenalidomide/dexamethasone AS PRIMARY TREATMENT

Follow-up is still short
In available studies patients can proceed to ASCT

Reference	Treatment	N	CR/VGPR rate	PFS
Lacy Mayo clin Proc 07	LD	34	56%	2-yr 59%
Rajkumar	LD	196	52%	med 19m
ASH 07	Ld	190	42%	med 21m
Niesvizky Blood 08	BiRD no ASCT	52	70%	2-yr 75%

RVD Efficacy
P. Richardson ASCO 08

- Best response (EBMT/UC)* in 66 evaluable pts as of May 2008:
  - 17 CR (26%)
  - 7 nCR (11%)
  - 23 VGPR (35%)
  - 18 PR (27%)
  - 1 MR (2%)
- Overall response rate, (ORR;CR/nCR+PR) 98% (95% CI: 87.4–99.9%)
  - CR/nCR+VGPR: 71%
  - CR/nCR: 36%

*ubject to confirmation

CONCLUSION

- Dramatic improvement of ASCT results is achieved with the addition of novel agents
- However a number of questions remain to be addressed (induction ,role of consolidation/maintenance)
- With prolonged treatment with novel agents (MPT,MPV,Rd,RVD) it is now possible to achieve up to 30% CR and up to 70% VGPR without ASCT
- In published trials median PFS are comparable to those achieved in the past with ASCT (24-28 months)
- Therefore trials comparing Novel agents + ASCT upfront vs Novel agents + ASCT at relapse are warranted

IFM 2009/ DFCI Trial

ALLOGENEIC STEM CELL TRANSPLANTATION

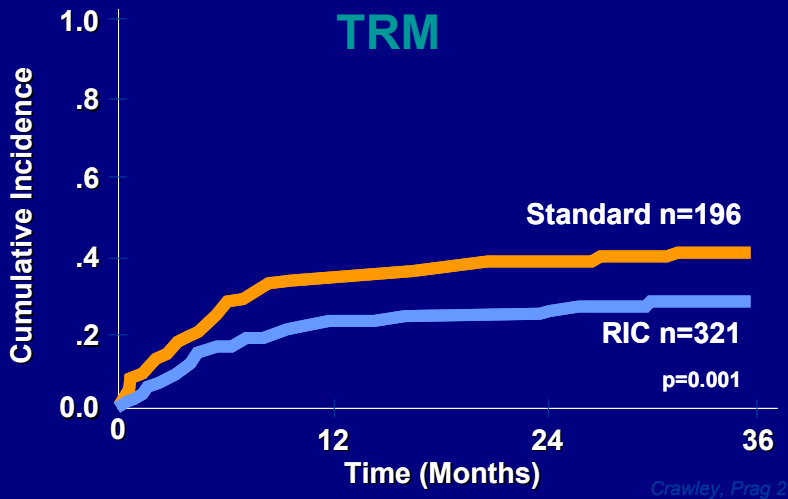
ALLOGENEIC SCT IN FRONTLINE THERAPY MYELOABLATIVE REGIMEN

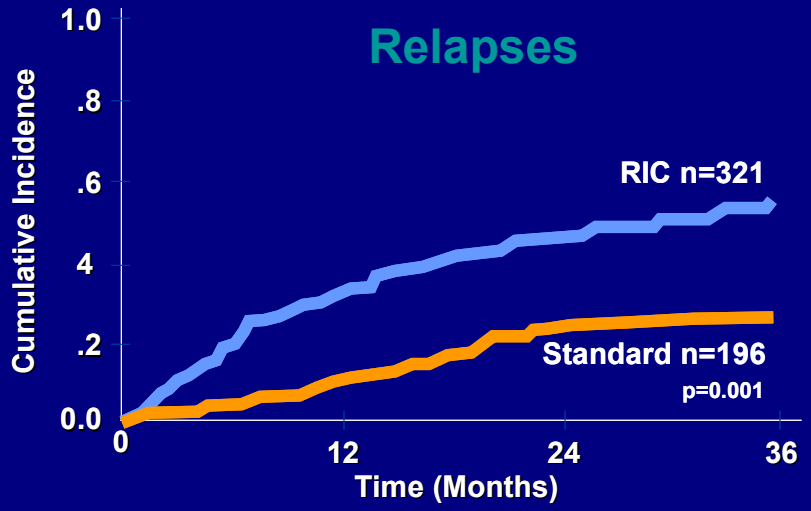
	N	TRM	EFS
HOVON JCO 2003	53	34%	Med 18m
US INTERGROUP JCO 2006	36	53%	22% or 7y
SFGM P. Moreau	116	43%	Med 21m

Myeloablative regimens are almost abandonned in MM

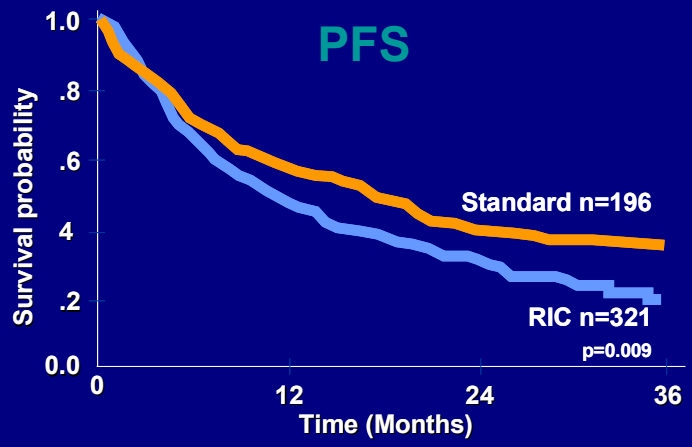
RIC vs myeloablative EBMT retrospective analysis

(Crawley, Blood 2006)





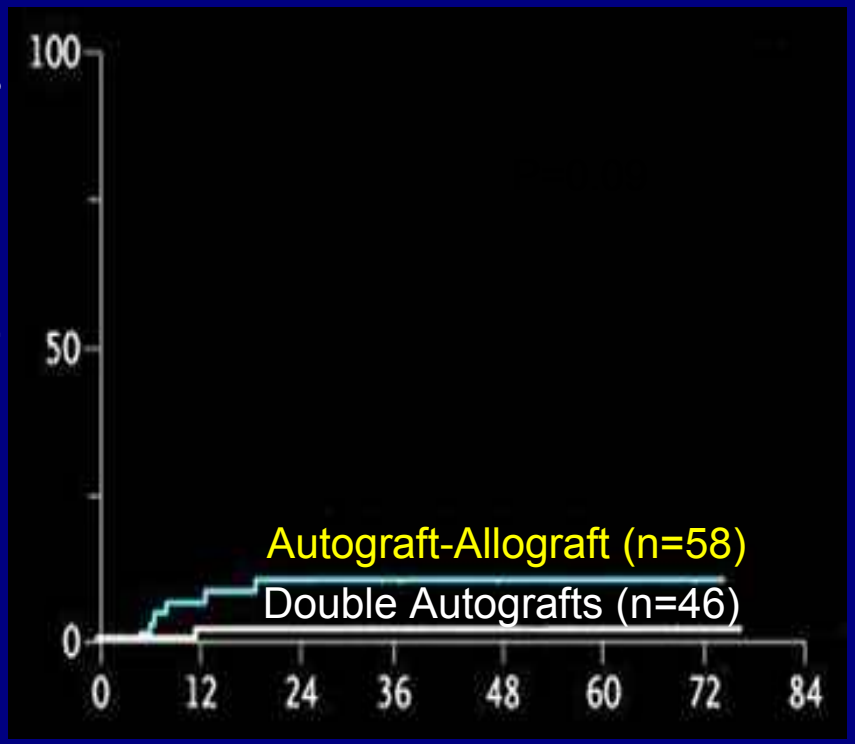
Crawley, Prag 2005

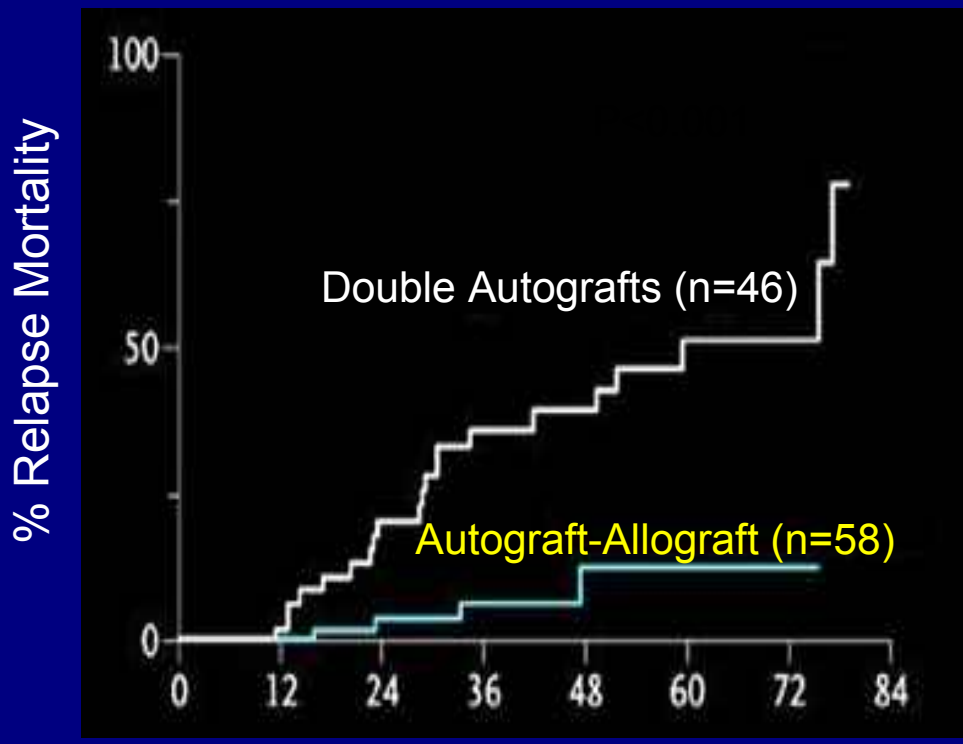


ORIGINAL ARTICLE

A Comparison of Allografting with Autografting for Newly Diagnosed Myeloma

N ENGL J MED 356;11 WWW.NEJM.ORG MARCH 15, 2007



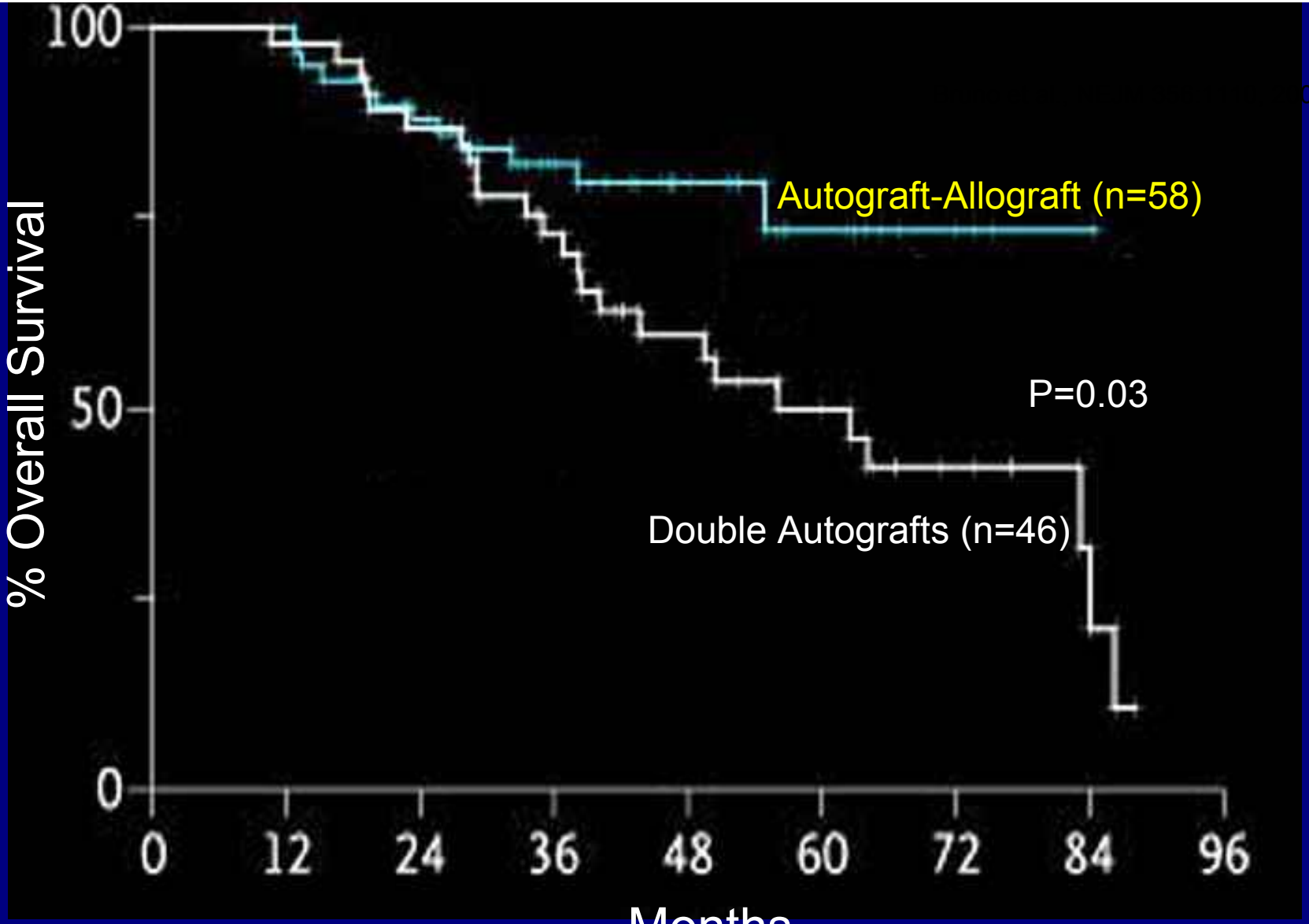


Months

Bruno et al., NEJM 356:1110, 2007.

CONCLUSIONS

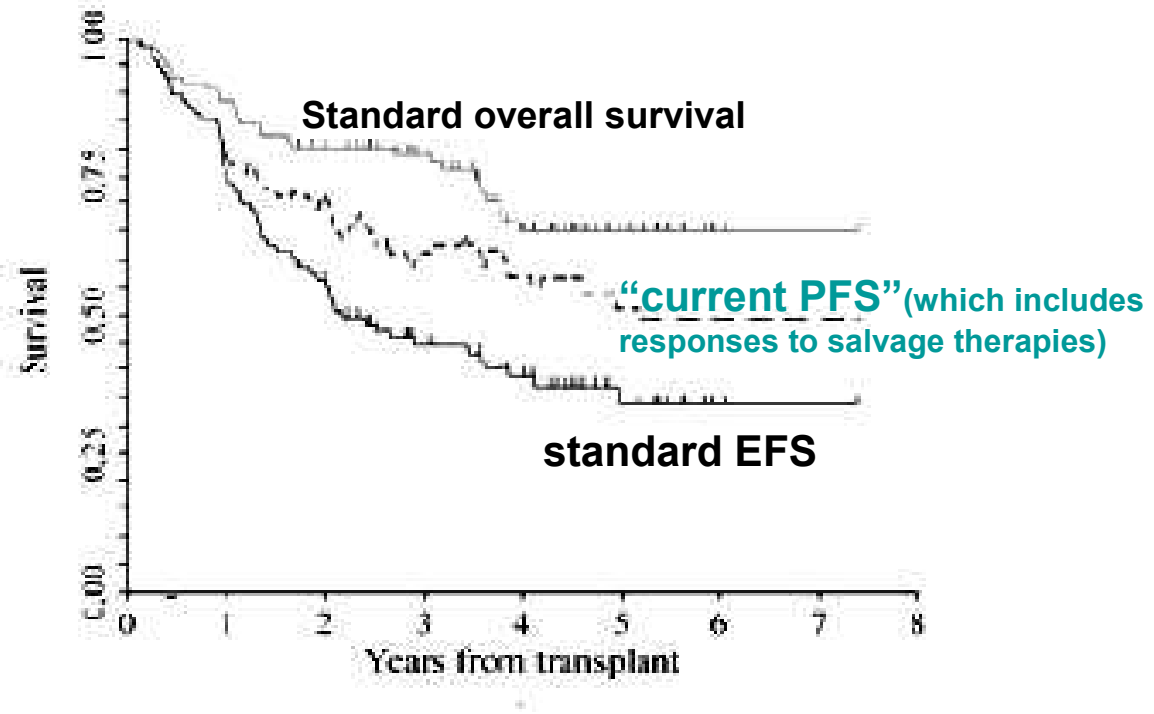
Among patients with newly diagnosed myeloma, survival in recipients of a hematopoietic stem-cell autograft followed by a stem-cell allograft from an HLA-identical sibling is superior to that in recipients of tandem stem-cell autografts. (ClinicalTrials.gov number, NCT00415987.)



Tandem Auto-RIC Allo

Updated results (med f-up 5 years)

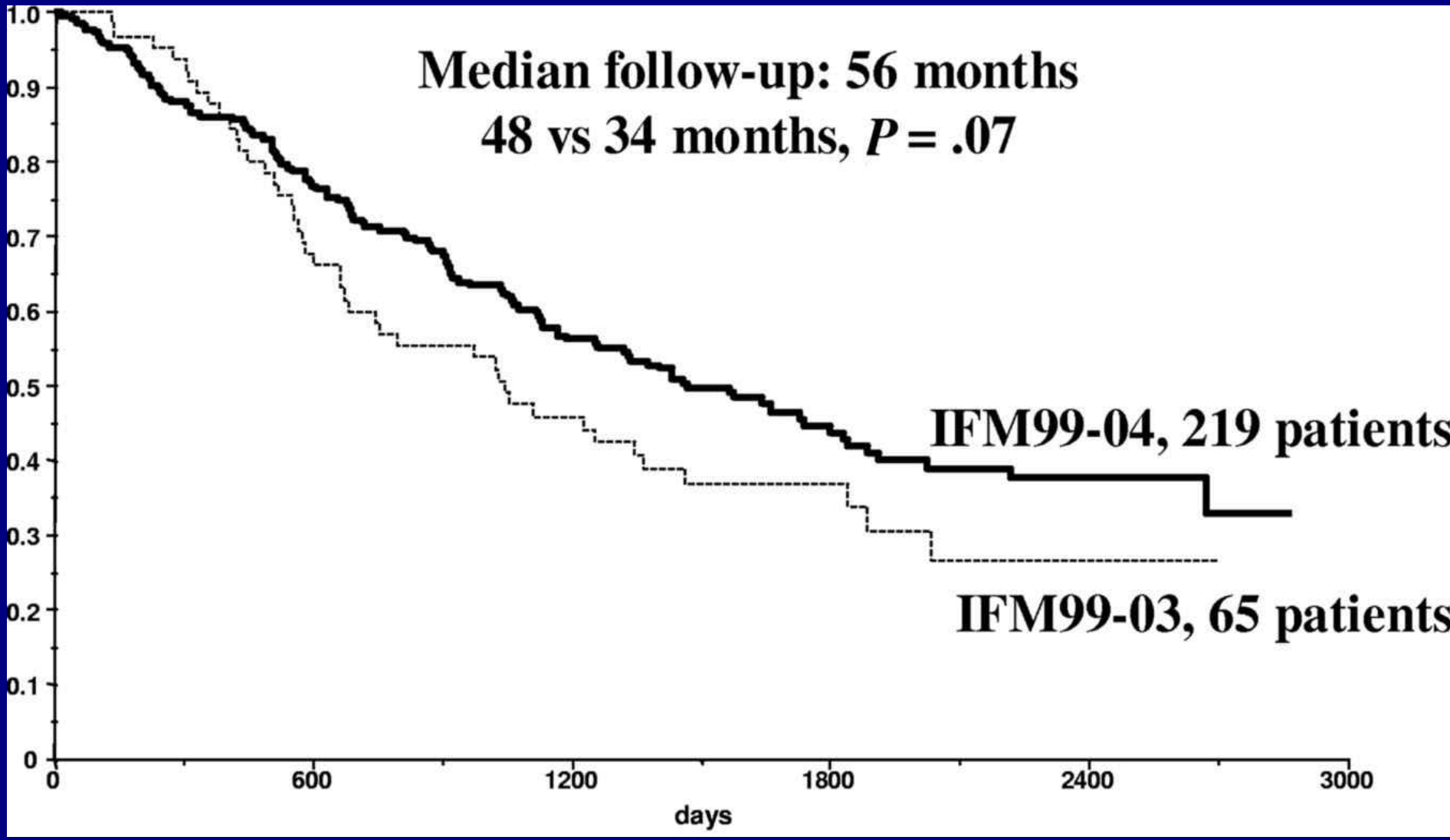
100 newly diagnosed patients



53% CR
38% Grade 2-4 aGVHD
50% cGVHD
11% TRM

Bruno et al., Blood 2009

IFM 99-03/04 Updated OS
P Moreau Blood 2008



2nd ASCT vs RIC-ALLO

	Selection Criteria	RIC	Results
IFM9903 Blood 09	Poor-risk	F/B/ATG	NS
B Bruno NEJM 07	NO	LD TBI	RIC better OS O.O3 EFS 0.07
ROSINOL Blood 08	<VGPR after ASCT1	F/M	NS

AUTO/RIC ALLO Conclusions

- TRM rate is still 10-15% at 2 years
- 30-50% C-GVHD (morbidity and late mortality)
- GVM and GVH are linked
  → Allogeneic dilemna

① → Patients selection
Not in good risk patients

② → Test strategy to reduce relapses without increasing GVHD
(DLI + / - novel agents after SCT)

③ → Frontline = only in clinical trials

DLI +/- novel agents for patients not in CR at 100 days

- 32 pts (age 35-68 med 50)
- 19 upfront 13 postASCT relapse
- Med number of DLI 2 (1-4)
- Thal 15 Vel 8 Len 2

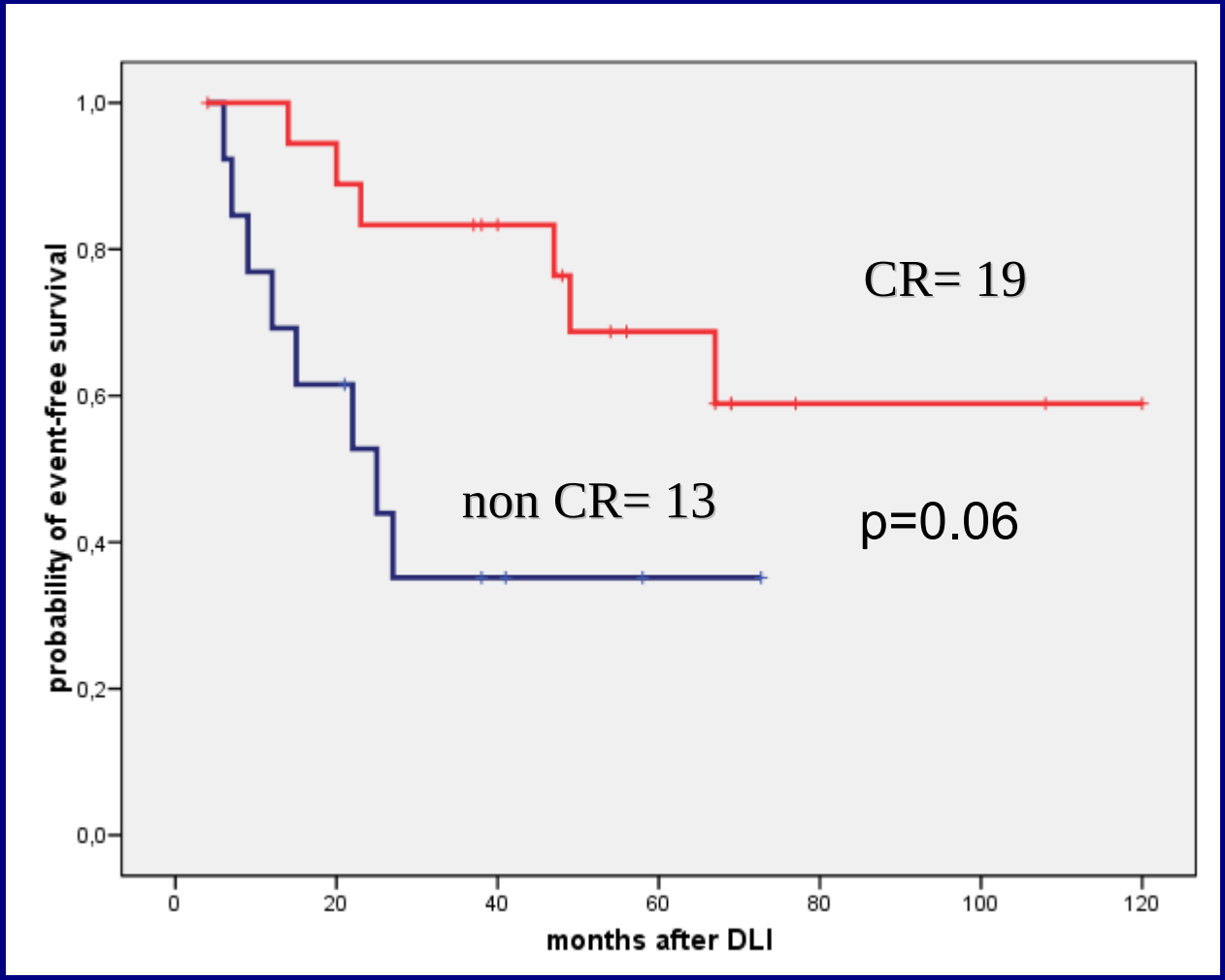
- 19 CR (59%)
- 6 VGPR (19%)

- Median f-up 56 months

N Kroger

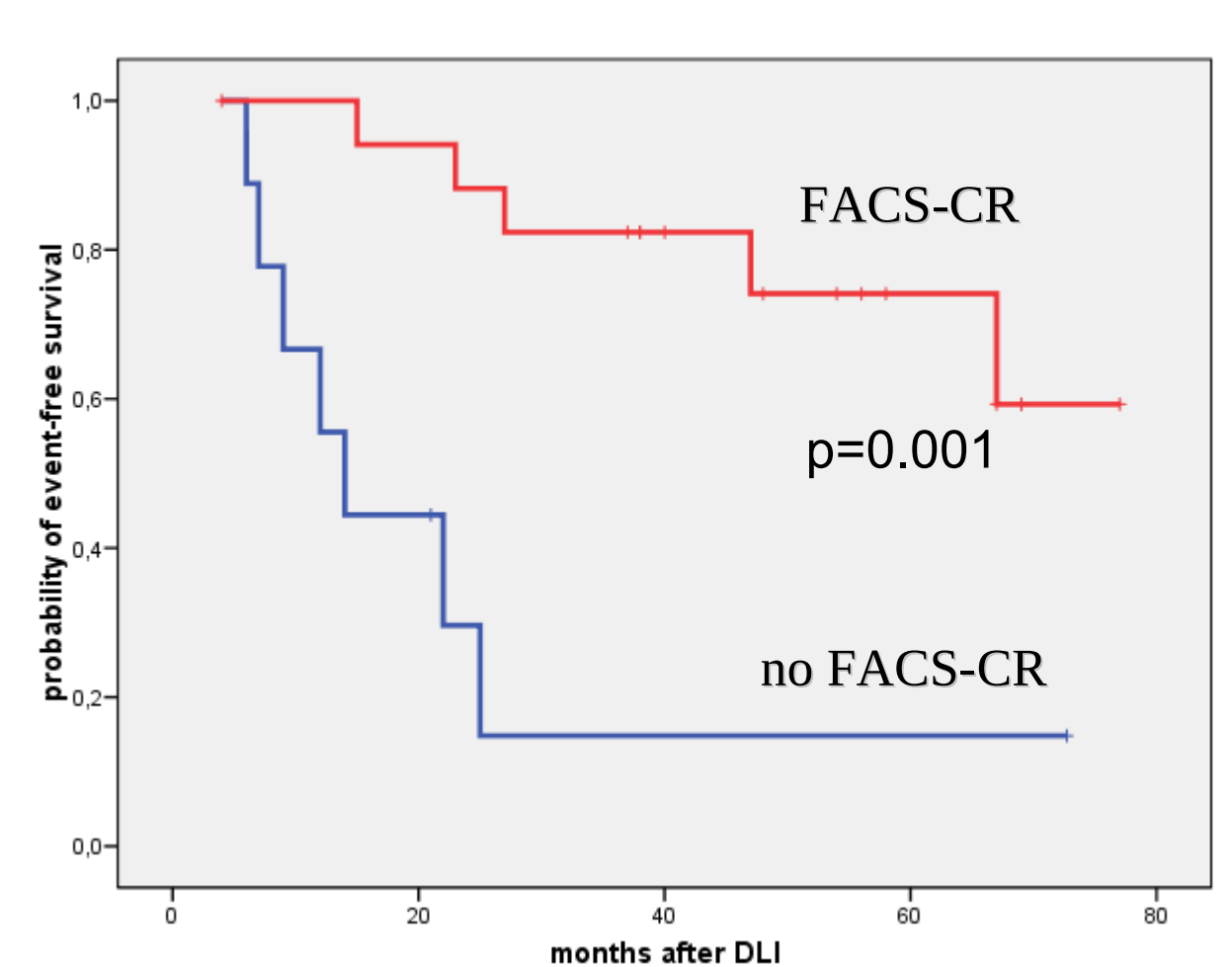
DLI +/- new agents after allo-SCT

According EBMT criteria



DLI +/- new agents after allo-SCT for patients with PR/VGPR

According Flow cytometry (sensitivty: 10^{-4})



THE IFM