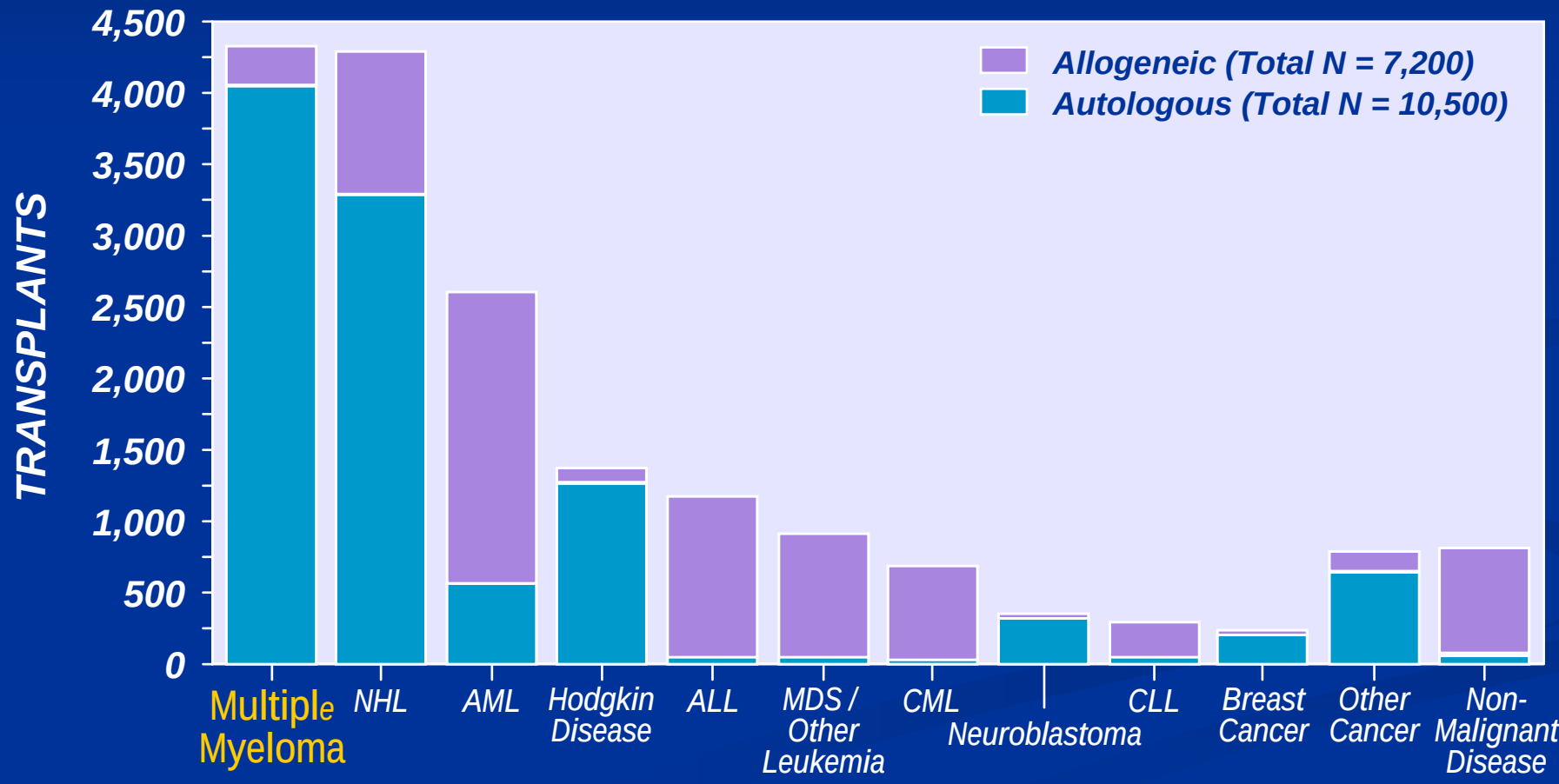
INDICATIONS FOR BLOOD AND MARROW TRANSPLANTATION IN NORTH AMERICA 2003



High dose therapy in MM

1 - HDT versus CC ?

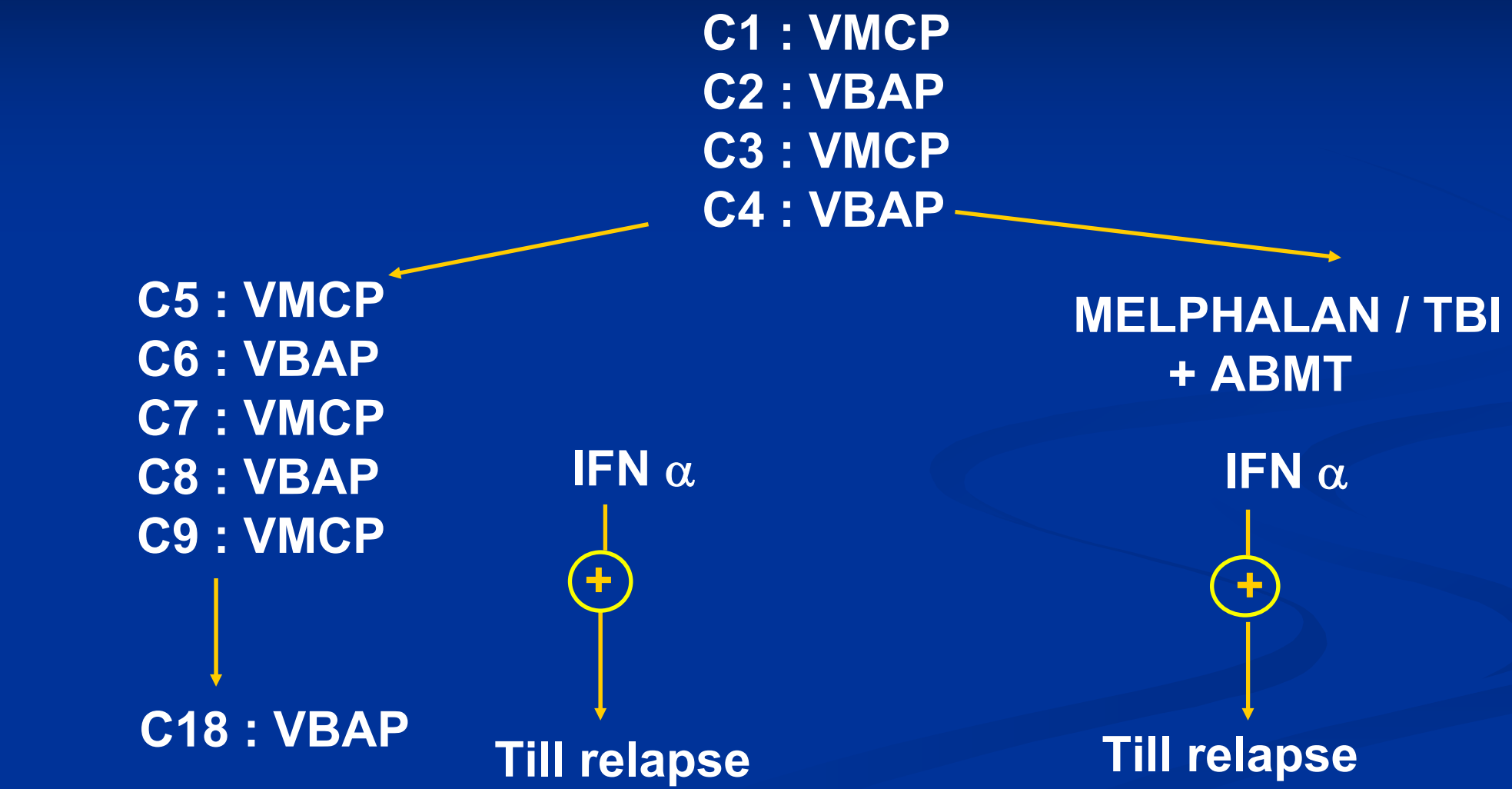
2 - Which preparative regimen ?

3 - Double transplantation ?

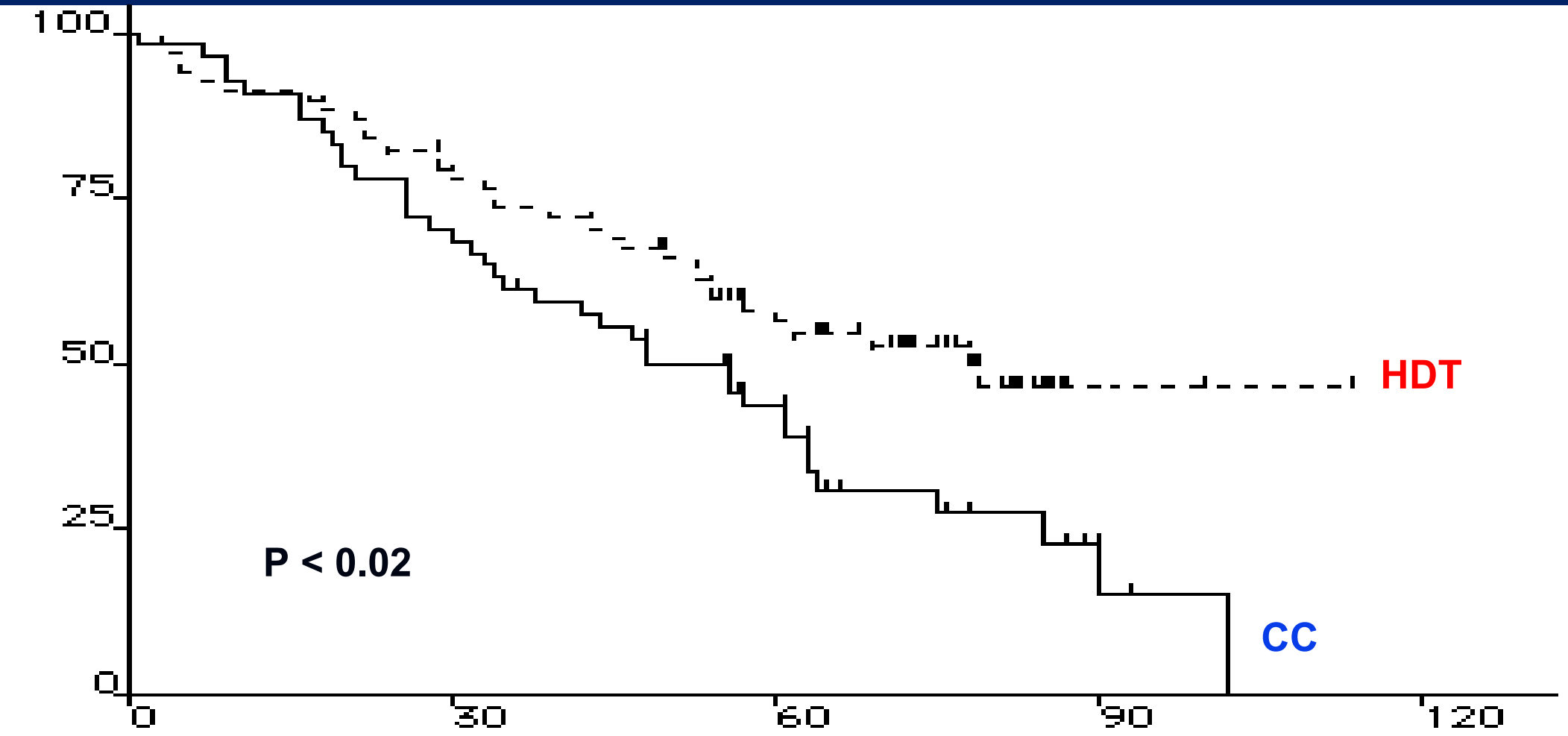
4 - HDT and new drugs?

5 - Allogeneic transplant ?

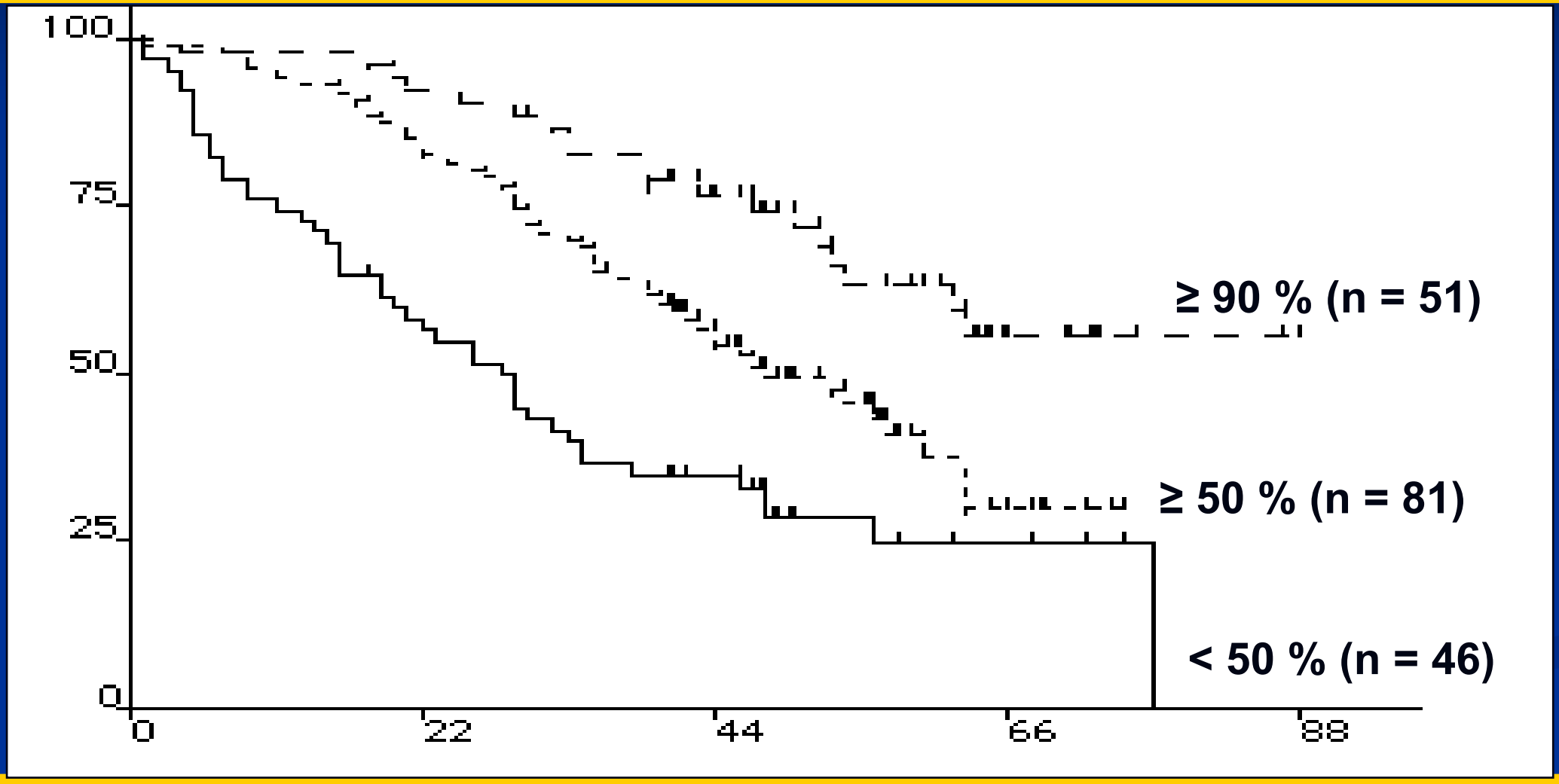
IFM 90 : General outline



IFM 90 : Survival ≤ 60 years



IFM 90 : Survival according to response



CC vs ASCT
RANDOMIZED STUDIES

	Nb of pts	Age	CC	HDT	SCT	Maintenance
IFM90 *(NEJM 96)*	200	≤ 65 Med 57	VMCP/VBAP	HDM14O + TBI 8G	BM	IFN
MRC7 *(NEJM 03)*	401	≤ 65 Med 55	ABCM	HDM200	PBSC	IFN
Italian MMSG (Turin 2004)	195	55-70 Med 62	MP	HDM100x2 + PBSC	PBSC	IFN + Dex
MAG91 *(ASH 99)*	190	55-65 Med 61	VMCP	HDM140 + Bu 16	PBSC	-
PETHEMA* (ASH 03)	164	≤ 65 Med 56	VBMCP/VBAD*	HDM140 + TBI 12G*	PBSC	IFN + Dex
US INTERGROUP (ASH 2003)	510		VAD/VBMCP	Mel + TBI 12G	PBSC	IFN vs 0

* In patients responding to initial CT

CC VS ASCT:

CR RATE

	CR defin	CC	ASCT	p. Value
IFM90	< 0 EP	5	22	< 0.001
MRC7	< 0 If	8	44	< 0.001
IMMSG	< 0 EP	7	26	<0.0001
PETHEMA	< 0 EP	11	30	0.002
USIG	< 0 If	15	17	NS

CC VS ASCT:

EFS

	Med F-up	CC	ASCT	p. Value
IFM90	7 y	18	28	0.01
MRC7	42 m	19	31	< 0.001
IMMSG	3 y	16	28	0.0036
MAG91	8.4 y	19	25	0.05
PETHEMA	44 m	34	42	NS
USIG	-	21	25	0.05

CC versus HDT: Overall Survival

	HD regimen	CC	HDT	p. Value
IFM90	Mel+TBI 8Gy	44	57	0.03
MRC7	Mel	42	54	< 0.001
IMMSG	Mel	43	58+	0.0008
MAG91	Mel+BU	45	42	NS
PETHEMA	Mel+TBI 12Gy	67	65	NS
USIG	Mel +TBI 12Gy	53	58	NS

Mel Without TBI should be the preparative regimen!!!

IFM 99-06
Newly diagnosed MM 65-75 years

Arm A

MP 1

↓

MP 2

↓

MP 3

⇣

MP 12

Arm B

Arm A

+

Thalidomide

≤ 400 mg/d

Arm C

VAD 1

↓

VAD 2

↓

Cyclophosphamide 3g/m^2
+ G-CSF
+ PBSC harvest

↓

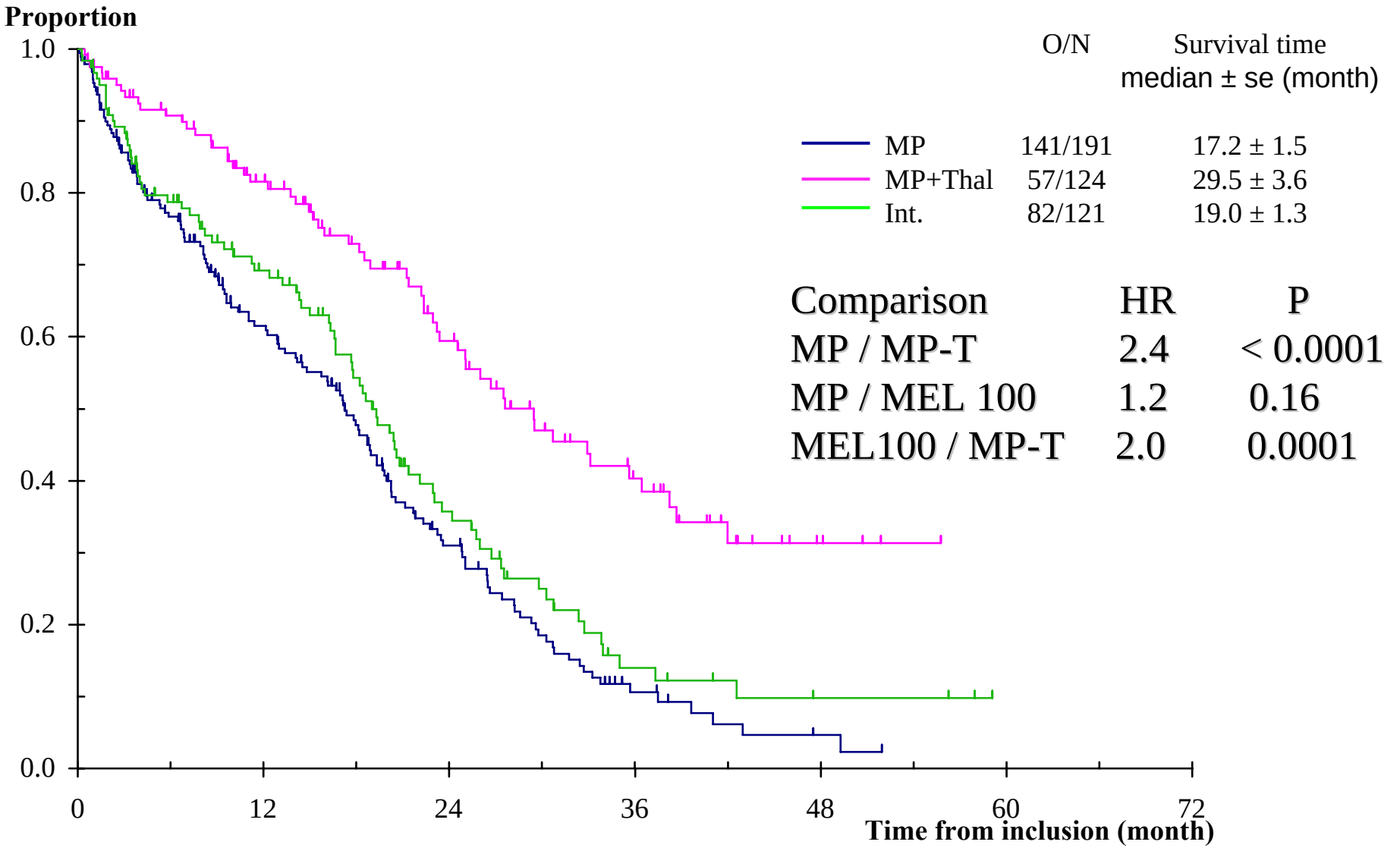
MEL 100 mg/m^2
+ PBSC + G-CSF

↓

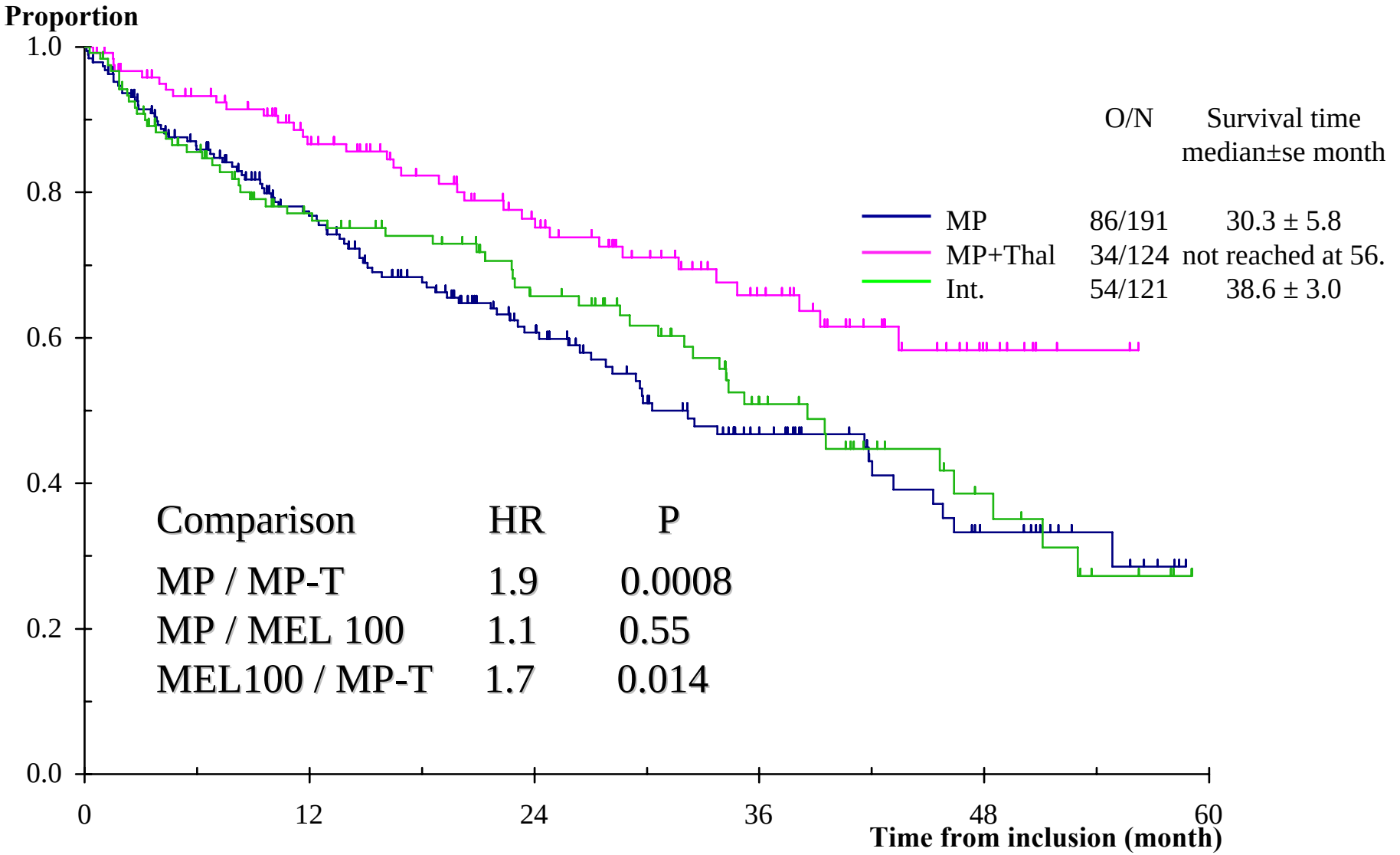
MEL 100 mg/m^2
+ PBSC + G-CSF

Clodronate for all pts

PROGRESSION-FREE SURVIVAL ACCORDING TO TREATMENT



OVERALL SURVIVAL ACCORDING TO TREATMENT



Autologous SCT: Current status in young and elderly patients

- **In young patients (< 65 years), ASCT:**
  - **Is the Standard of care**
  - **Survival benefit is related to CR achievement**
  - **TBI (12G) or BU 16 should be avoid**
- **In elderly patients (> 65 years), ASCT:**
  - **Is not recommended**

High dose therapy in MM

1 - HDT versus CC ?

2 - Which preparative regimen ?

3 - Double transplantation ?

4 - HDT and new drugs?

5 - Allogeneic transplant ?

IFM 95 : Design

VAD x 3

Stem cell collection

Randomisation

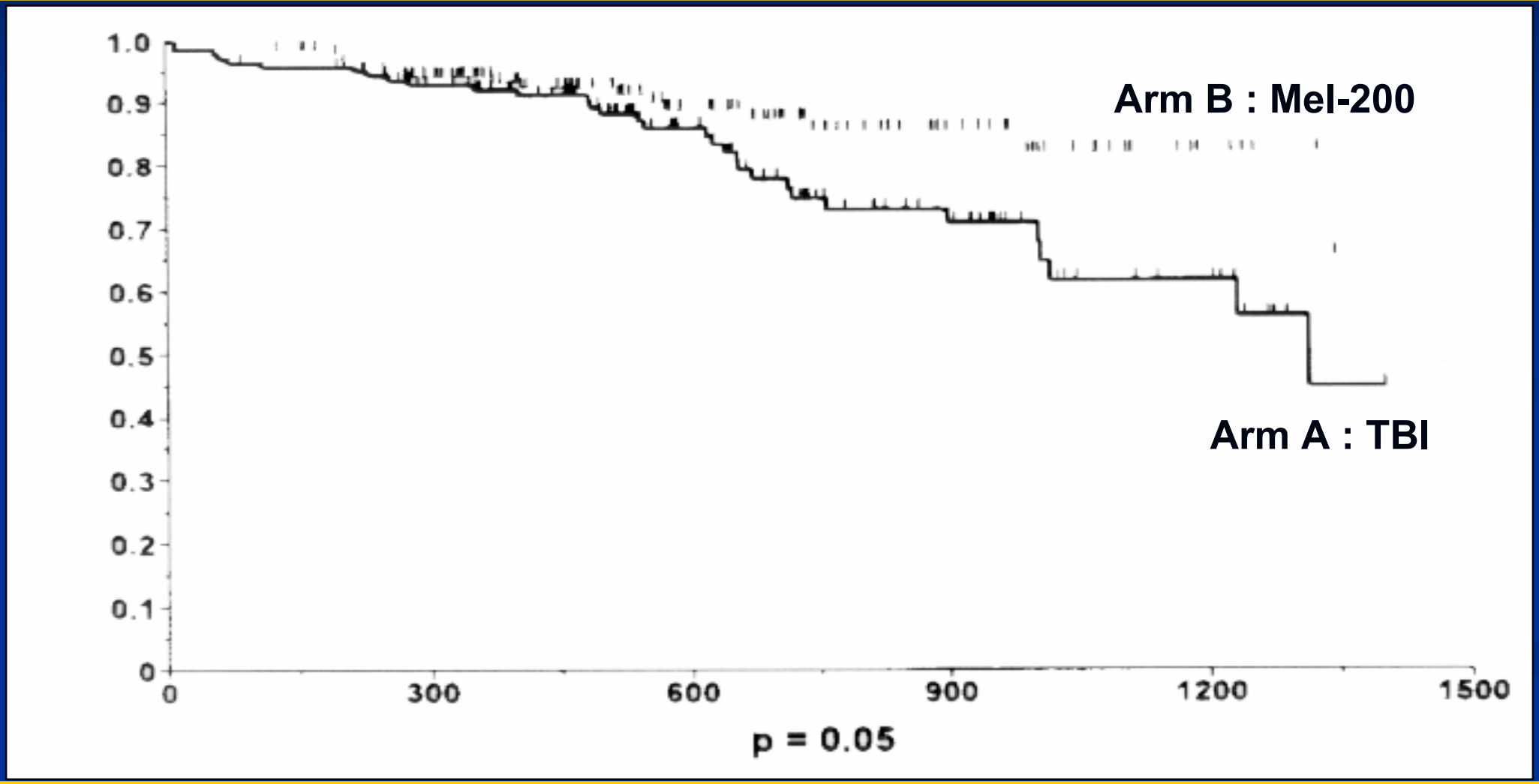
ARM A =
MEL-140 + TBI
+ PBSC

ARM B =
MEL-200
+ PBSC

IFM 95 : T.R. Toxicity

	Arm A	Arm B	p.
ANC < 500	10 d	8 d	<0.001
Plat < 25 000	7 d	5 d	<0.001
Nb of plat T.S.	2	1	0.001
Grade 3/4 toxicities (%)			
- mucositis	51	30	0.01
- cardiac	4	1	
- pulmonary	6	1	
- renal	4	2	
T.R.M. (%)	4	0	0.07

IFM 95 : SURVIVAL



IFM 95 : CONCLUSIONS

1 - Mel-200 improves T.R. toxicities.

2 - Mel-200 improves OS but not EFS

(better survival after relapse)

C Mel-200 is the recommended preparative regimen !

High dose therapy in MM

1 - HDT versus CC ?

2 - Which preparative regimen ?

3 - Double transplantation ?

4 - HDT and new drugs?

5 - Allogeneic transplant ?

IFM 94 : General outline

VAD 1
VAD 2
VAD 3

Autologous Stem Cell Collection

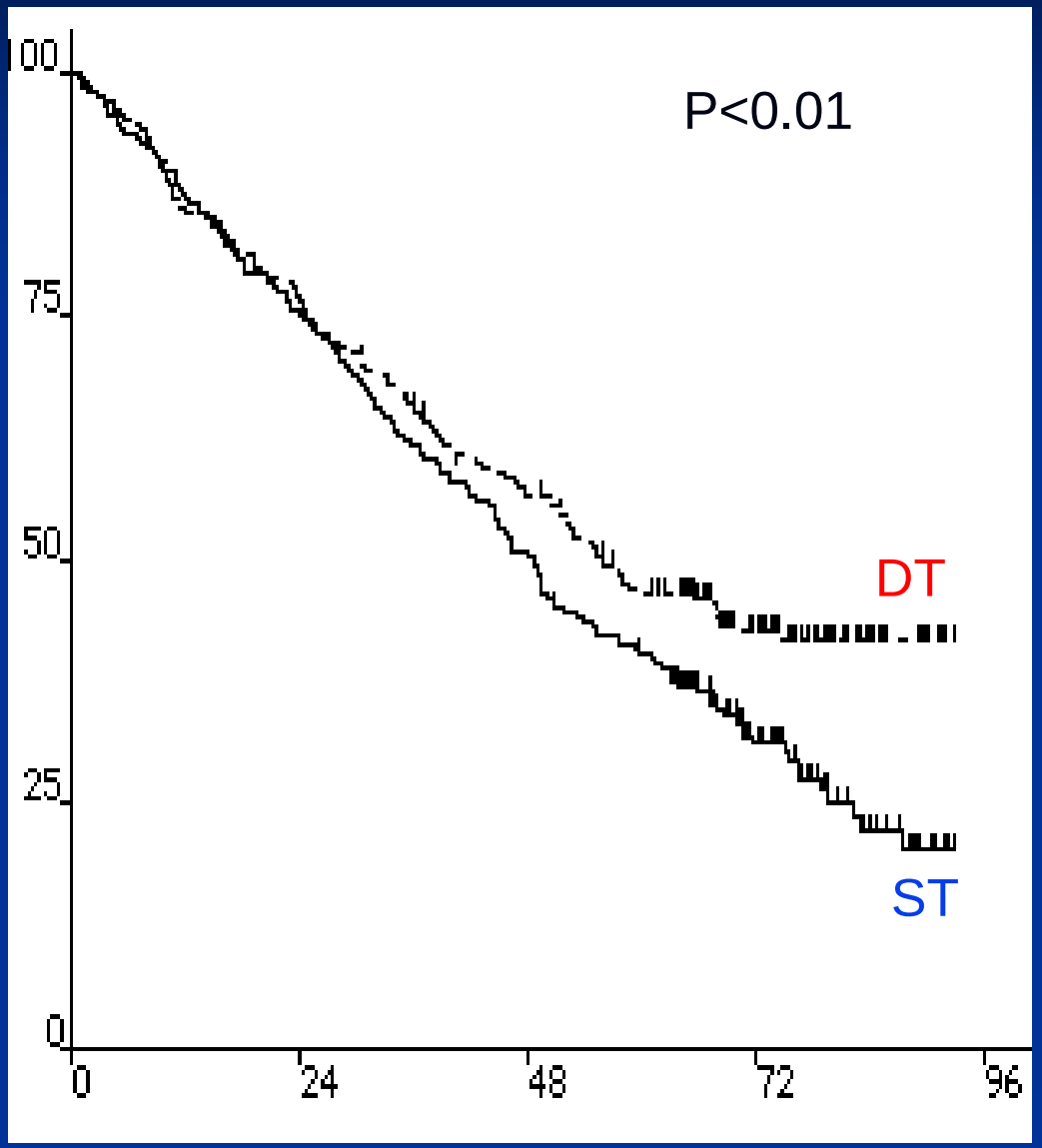
HDM (140)
Autologous Graft

HDM (140) + TBI
Autologous Graft

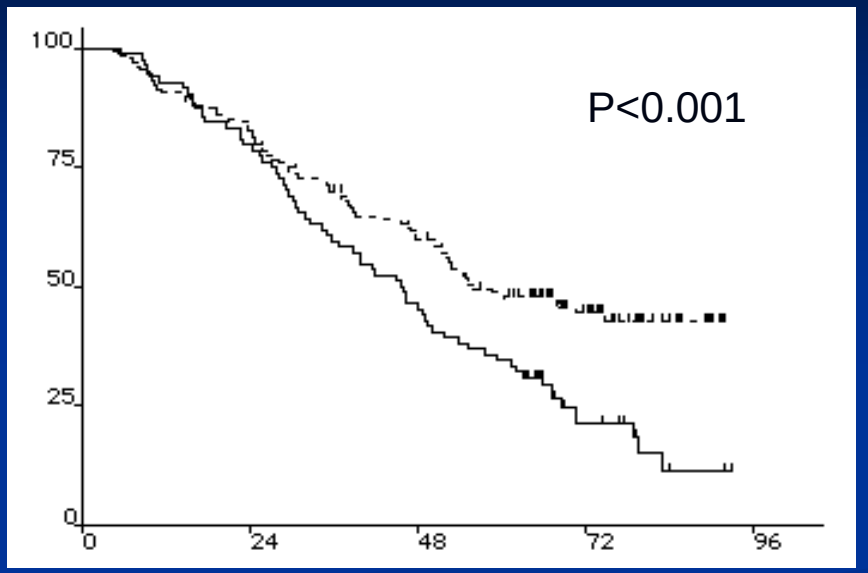
HDM (140) + TBI
Autologous Graft

IFM 94 : Overall Survival

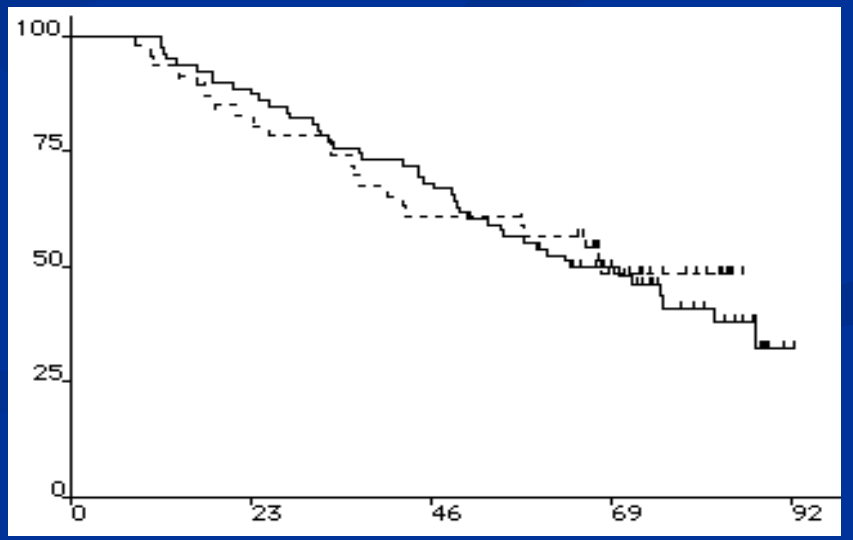
ALL PATIENTS



OS if response to 1st graft < 90%



OS if response to 1st graft ≥ 90 %



SINGLE VS DOUBLE ASCT RANDOMIZED STUDIES

	Single	Double	Δ
**IFM 94*	HDM140 +TBI	HDM 280 + TBI	HDM 140
*MAG95	Multidrug +TBI	HDM 280 + TBI	/
*Bologna	HDM 200	HDM 320 + BU	HDM 120 + BU
**GMMG*	HDM 200	HDM 400	HDM 200
*Hovon	HDM70x2	HDM140+CY+TBI	CY + TBI

SINGLE VS DOUBLE ASCT:

MEDIAN EFS

	Med F-up	Single	Double	p. value
IFM 94	75 m	25	30	0.03
MAG 95	53 m	31	33	NS
Bologna	3 y	21.5	31	0.02
GMMG	26 m	23	NR	0.03
Hovon	56 m	20	22	0.016

SINGLE VS DOUBLE ASCT

MEDIAN OS

	Med F-up	Single	Double	p. value
IFM94	75 m	48	58	0.01
MAG95	53 m	49	73	0.04
Bologna	40 m	56	60	NS / 0.01
GMMG	?	?	?	?
Hovon	56 m	55	50	NS

SINGLE vs DOUBLE ASCT

- Current results are in favor of double ASCT
  (OS in 3/5 studies, EFS in 4/5 studies)

- Long follow-up is needed before drawing definite conclusions (IFM 94, MAG, Hovon)

-However, 7-year EFS is only 20% in the DT arm
Maintenance Therapy: Thal?

High dose therapy in MM

1 - HDT versus CC ?

2 - Which preparative regimen ?

3 - Double transplantation ?

4 - HDT and new drugs?

5 - Allogeneic transplant ?

Optimizing Stem Cell Transplantation (SCT)

- **The role of new drugs:**
  - **In the induction regimen**
  - **In the conditioning regimen**
  - **In the maintenance regimen**

ASCT: the Induction Regimen.

The goals of the Induction Regimen

- **Rapid reduction of tumor mass:**

  Dexamethasone based (DEX or VAD) !

- **Adequate stem cell collection:**

  No Alkylating agents !

Q : Could New Drugs improve DEX or VAD ?

ASCT and New Drugs: induction

Author	Regimen	N	RR	CR/VGPR	p
Cavo	VAD	100	52%	14%	0.001
	Dex-Thal	100	76%	19%	
Rajkumar	Dex	104	41%		0.002
	Dex-Thal	103	63%		
Goldschmidt	VAD	200	63%	CR= 3%	0.001
	TAD	200	80%	CR=7%	
Harousseau	Dex-Vel	48	67%	31%	
Rajkumar	Dex-Rev	34	91%	38%	

ASCT and New Drugs: Induction

- New Drugs + DEX > DEX alone or VAD:
  - ✓ 20 - 38% of CR or VGPR (vs 10%).
  - ✓ Adequate stem cell collection.

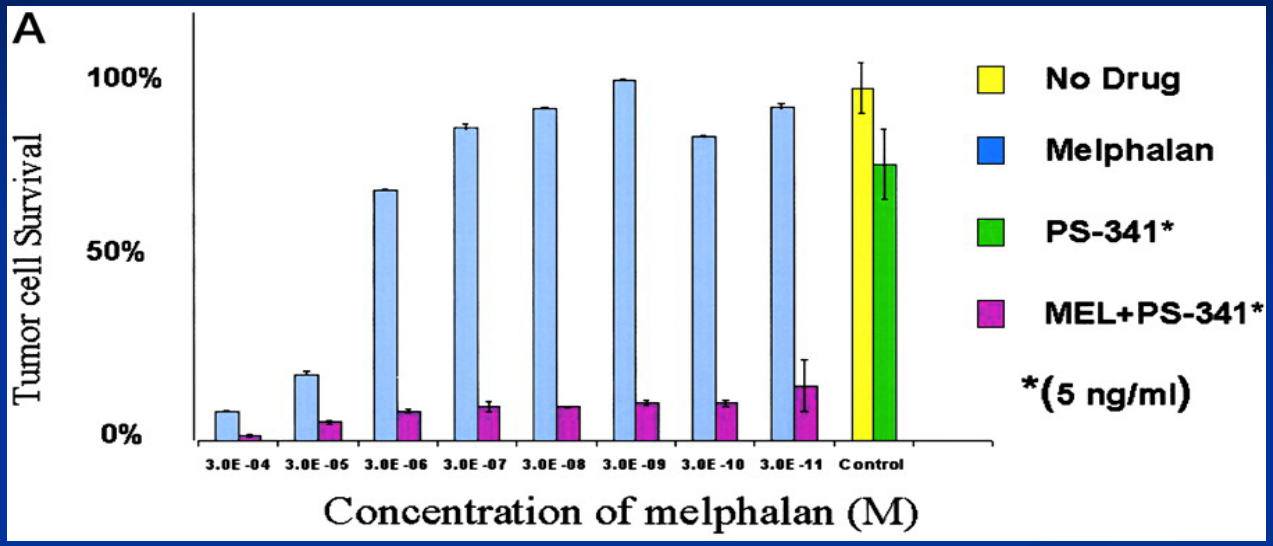
Optimizing Stem Cell Transplantation (SCT)

- **The role of new drugs:**
  - **In the induction regimen**
  - **In the conditioning regimen**
  - **In the maintenance regimen**

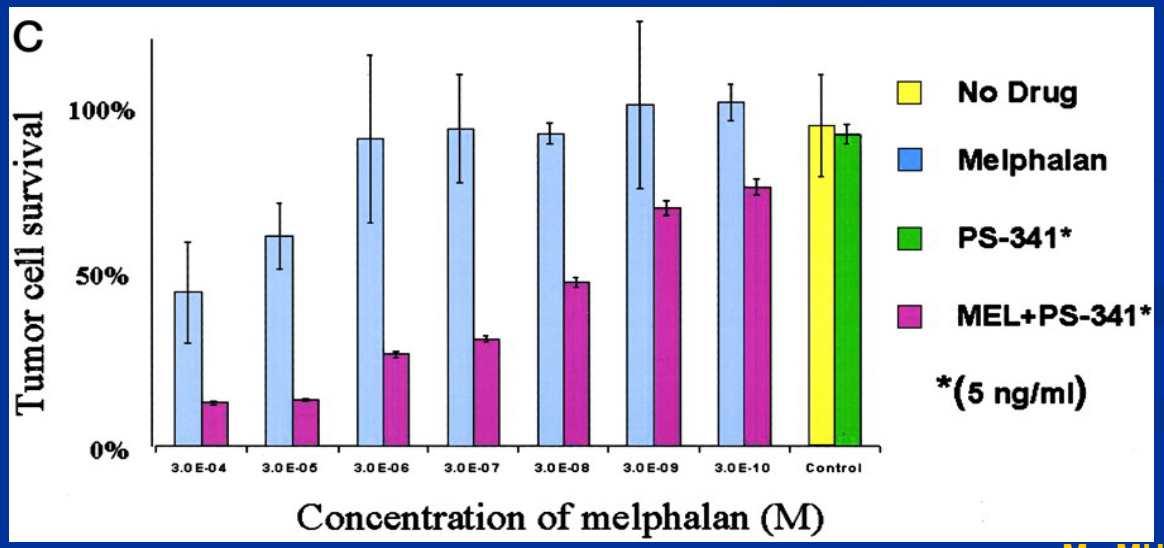
HDT and New Drugs: the HD Regimen

- The Standard HD regimen:
  - ✓ Mel 200mg / m^2
- The addition of Velcade was logical:
  - ✓ Synergistic effects
  - ✓ No shared toxicities

Cell lines and fresh MM cells : synergistic Effect between melphalan and bortezomib



MM cells lines



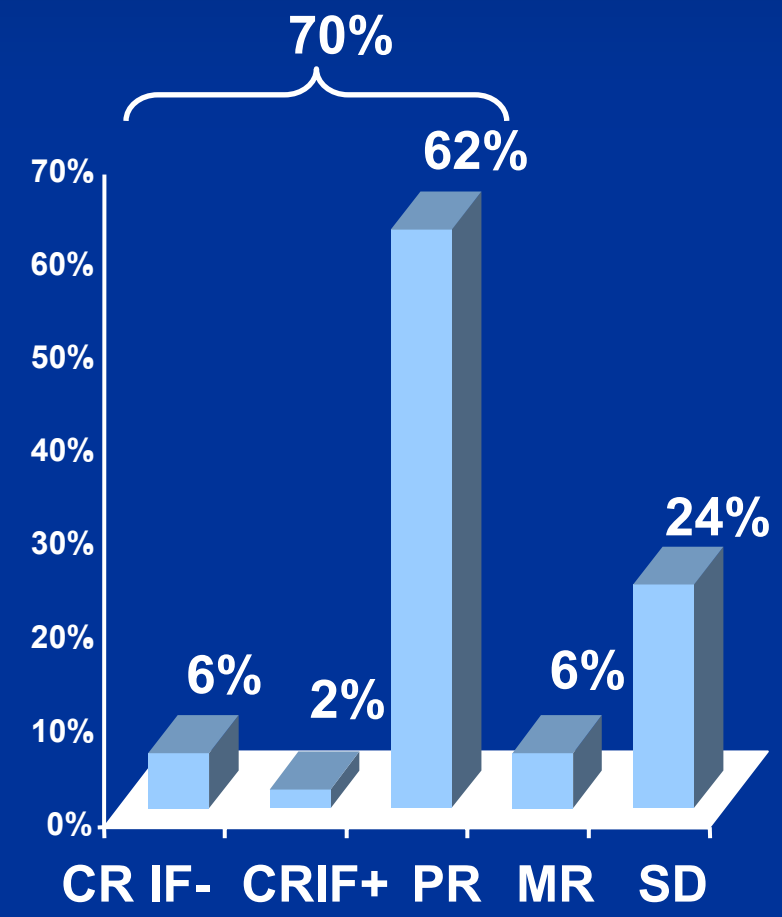
Fresh MM BMMCs

Ma MH *Clinic Cancer Res* 2003 9:1136–44

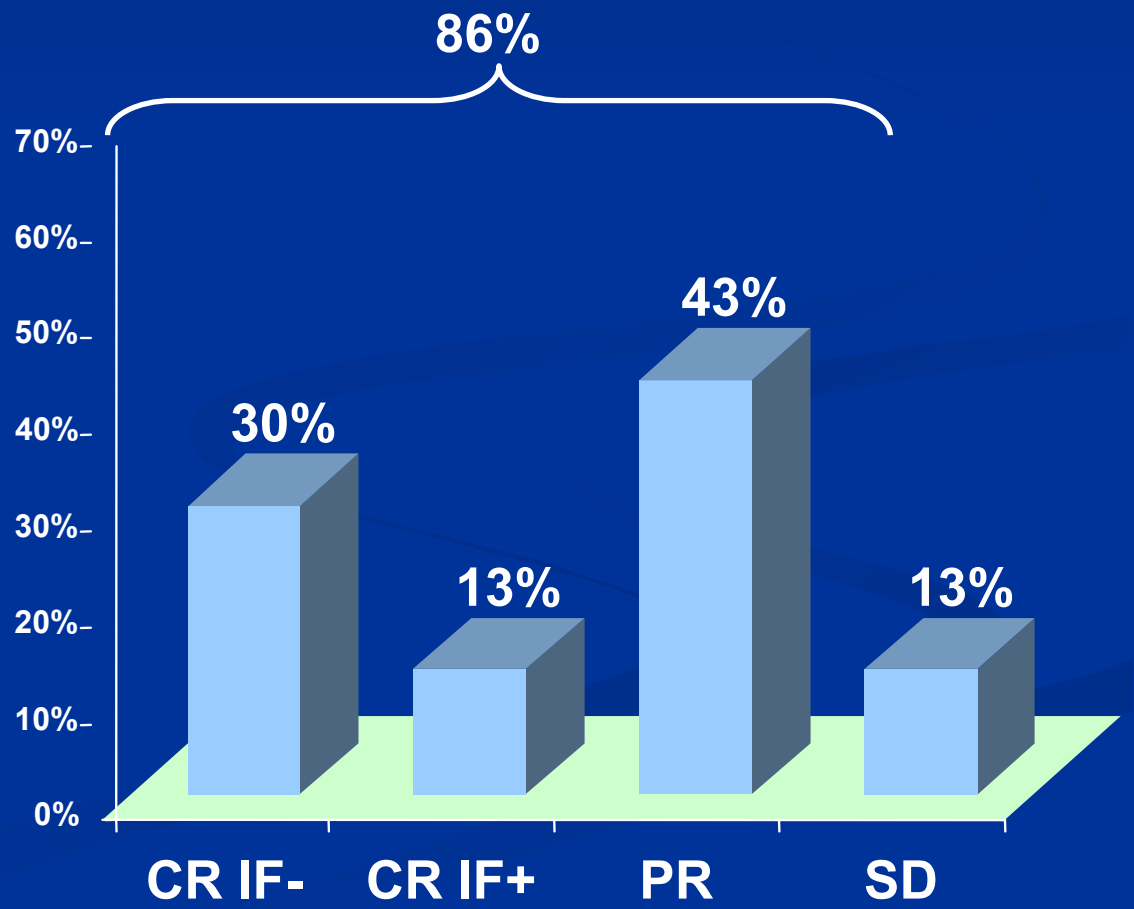
V-MP: Response rates (n=53)

Analysis of the best response so far achieved

1st cycle V-MP



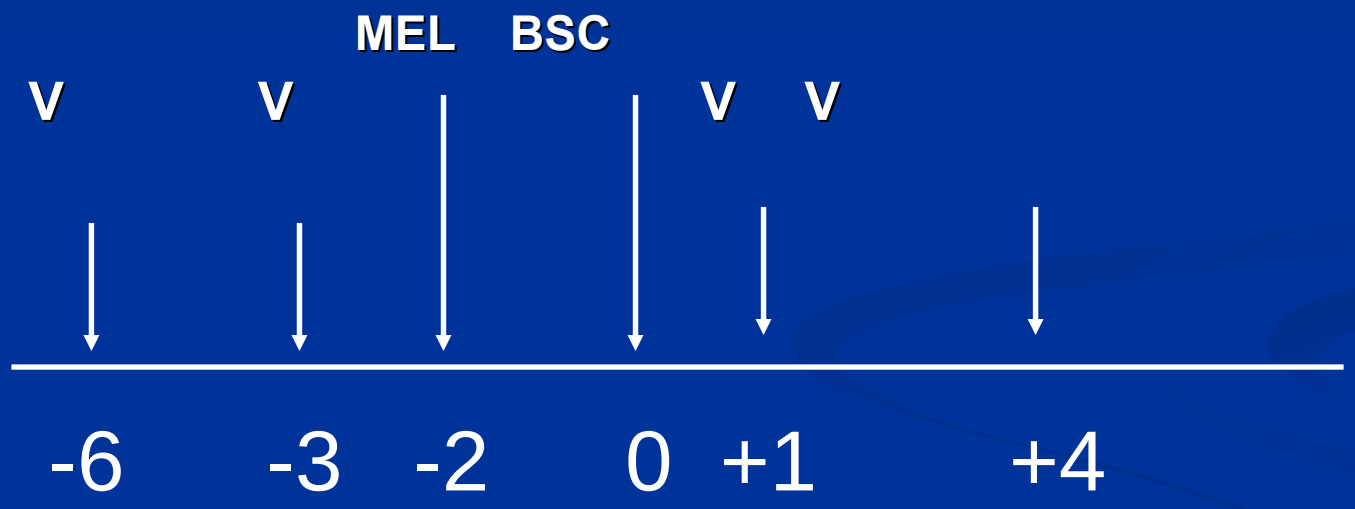
Best response: *median 5 cycles (2-9)*



V-MP: TOXICITY according to Cycles (n=60)

	GRADE ≥ 3	
	1st-2 cycles	≥3 cycles
NAUSEA	2%	0%
VOMITING	2%	0%
DIARRHEA	8%	2%
CONSTIPATION	6%	2%
ANOREXIA	2%	0%
ASTENIA	4%	2%
INFECTION	12%	4%
PN	8%	6%
THROMBOCYTOPENIA	33%	17%
NEUTROPENIA	33%	24%
ANEMIA	8%	2%

The VEL-MEL Regimen



V= Velcade 1mg / m^2

MEL= Melphalan 200 mg / m^2

The Vel-Mel Regimen: Patients

- N = 25
- Median Age = 56 y (39-67)
- Status of disease:
  - ✓ Response < 50% to VAD = 18
  - ✓ Response < 90% to HDM = 7

The VEL-MEL Regimen

- PN < 500/mm^3 = 7 d (5-10)
- Plat < 20000/mm^3 = 1.5 d (0-7)
- Severe Mucositis = 20%
- Response Rate:
  - ✓ CR = 31% !!
  - ✓ VGPR = 46%
  - ✓ CR + VGPR = 77% !!!!

Optimizing Stem Cell Transplantation (SCT)

- **The role of new drugs:**
  - **In the induction regimen**
  - **In the conditioning regimen**
  - **In the maintenance regimen**

ASCT and New Drugs: Maintenance

- Maintenance after ASCT is a logical issue : Residual Disease .
- The effective Maintenance therapy is unknown:
  - ✓Chemotherapy failed to demonstrate any benefit.
  - ✓Maintenance interferon showed a modest increase in PFS without any, or with minimal, survival benefit.
  - ✓Corticosteroid were found to prolong the duration of response, however the impact on survival was controversial.
- Thus, Thalidomide was an attractive candidate:
  - ✓Oral agent
  - ✓Active among patients who had failed high dose therapy,
  - ✓With doses as low as 50 mg,
  - ✓Without myelosuppressive toxicity.

IFM 99 02 : Study Design

Inclusion: Δ 13 ; ß2m
(0 or 1 Factor)

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

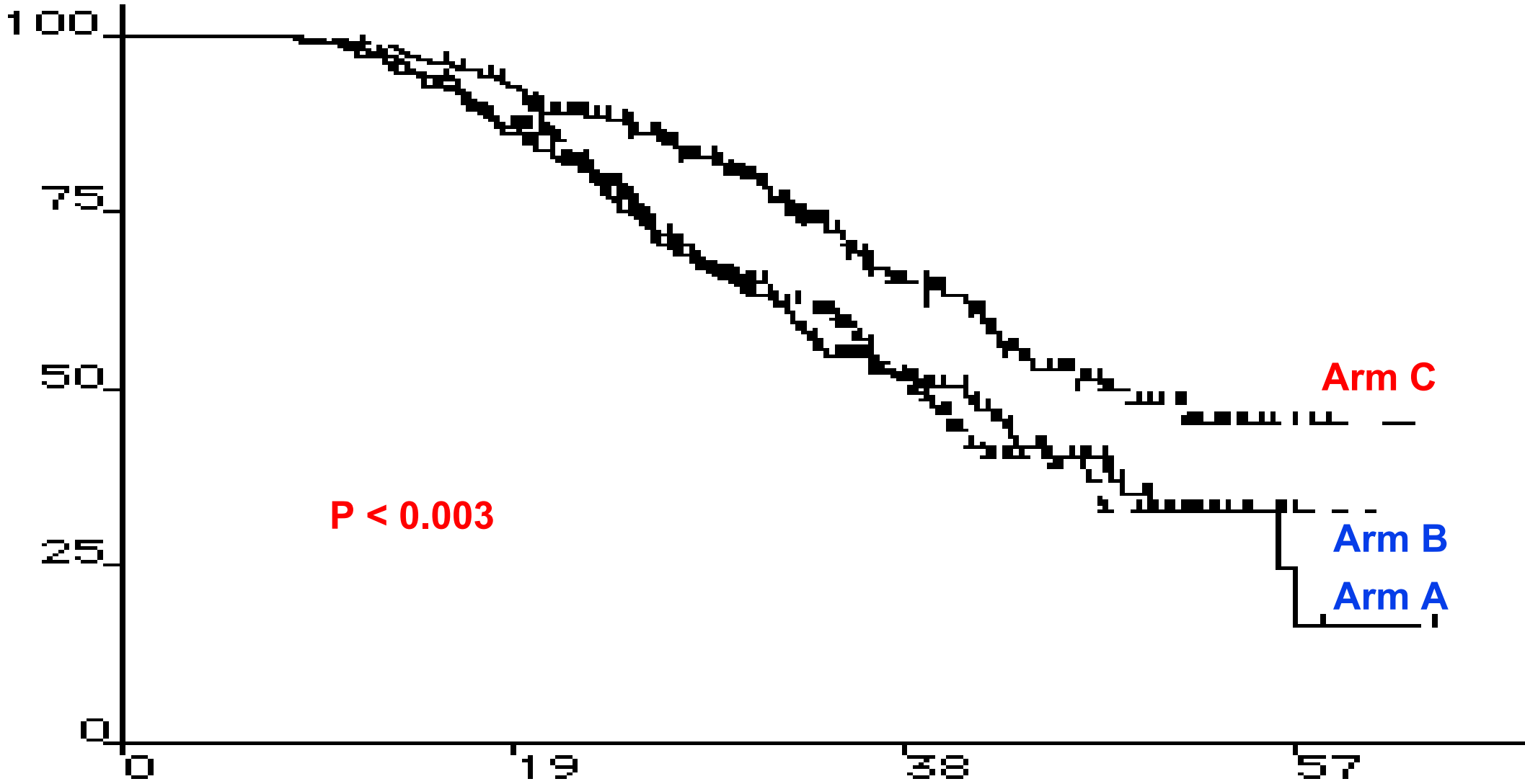
Randomization

No maintenance	Pamidronate	Pamidronate + Thal

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

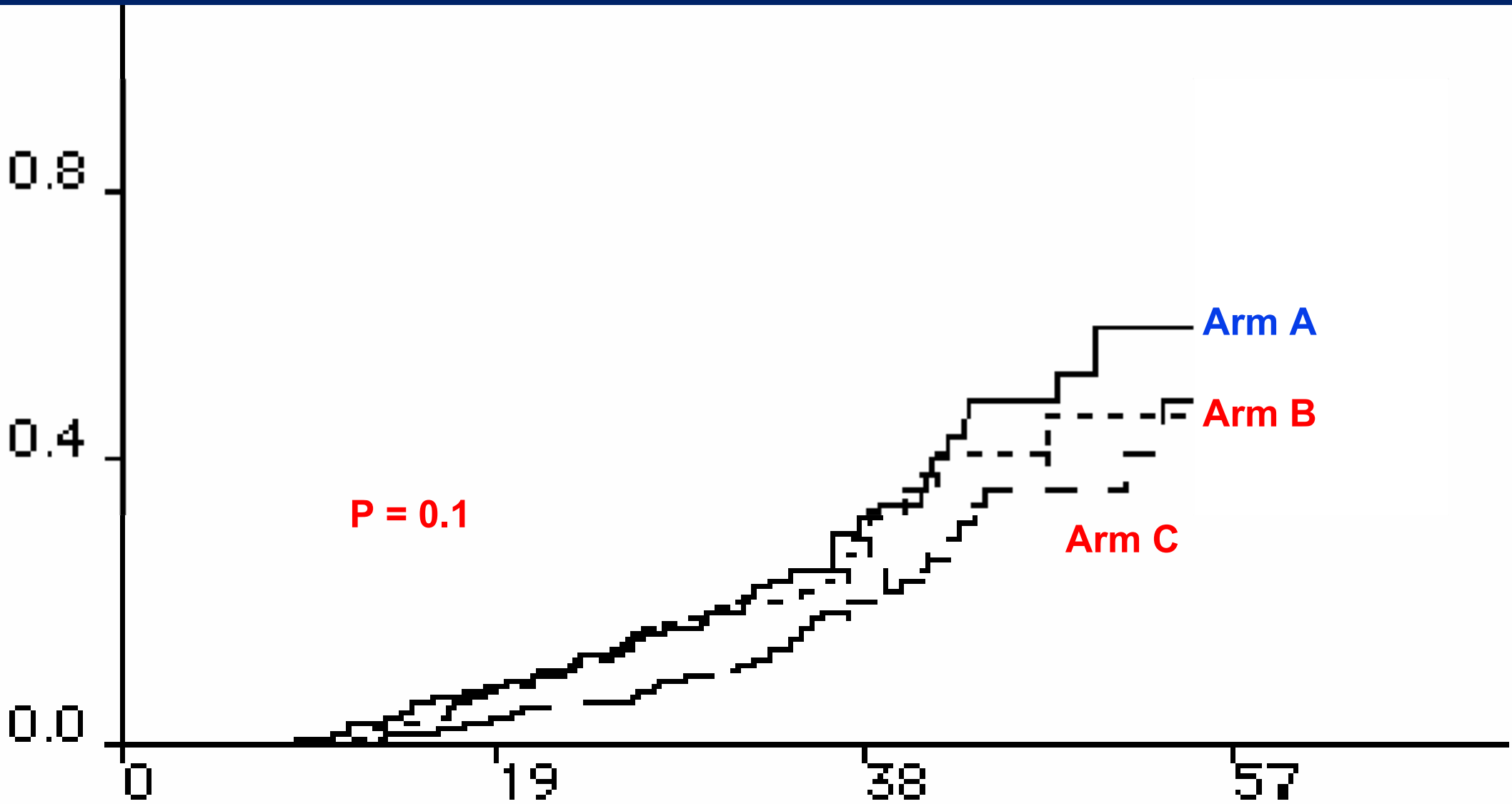
IFM 99 02 : EFS from Diagnosis



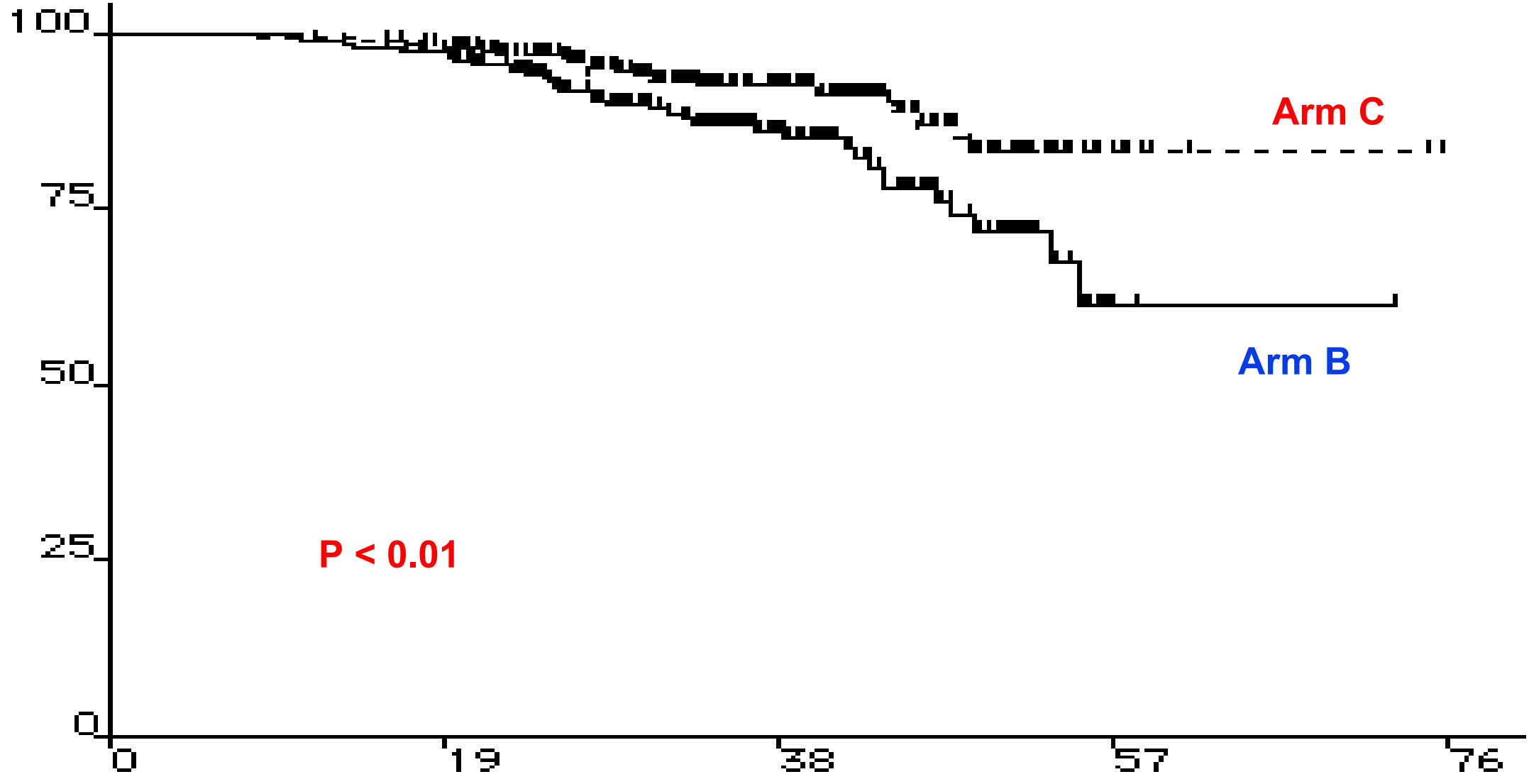
IFM 99 02 : Risk of Bone Events.

	Arm A	Arm B	Arm C	p
▪ Bone Events	24%	20%	18%	NS
▪ 4-year risk of Bone Events	53%	46%	35%	0.1

IFM 99 02 : Risk of Bone Events

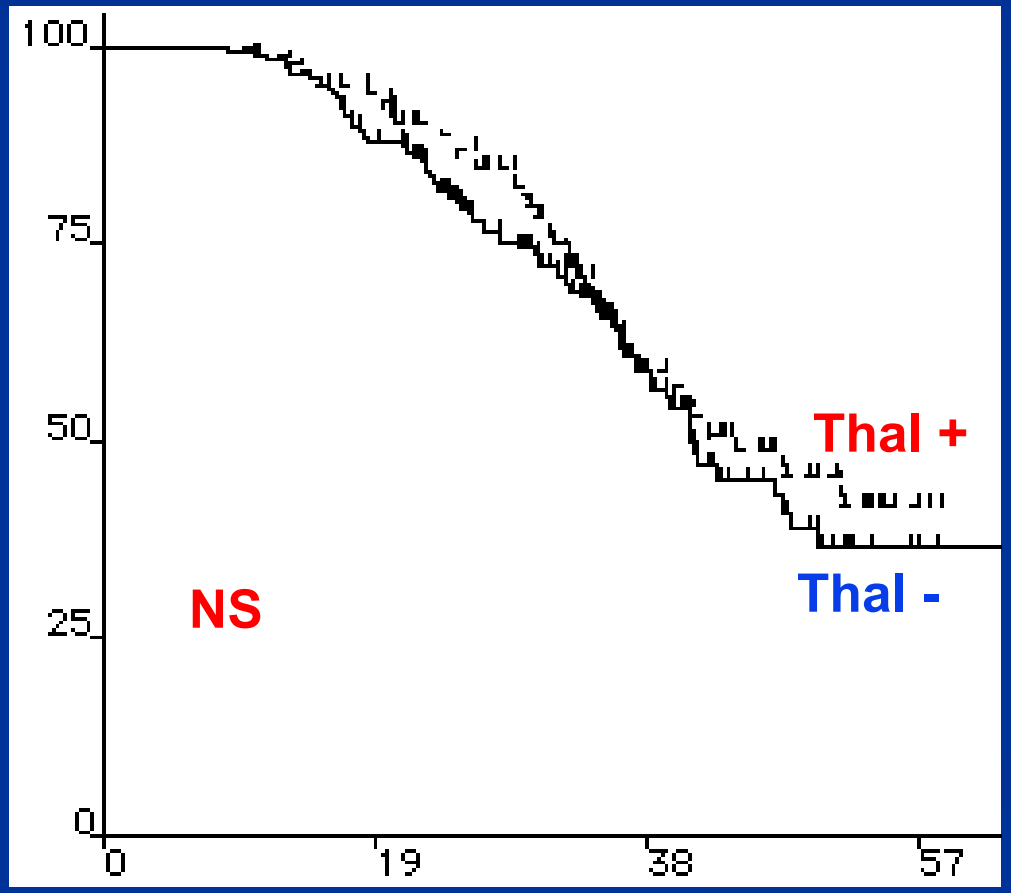


IFM 99 02 : Overall Survival according to Thal (Arm B versus Arm C).

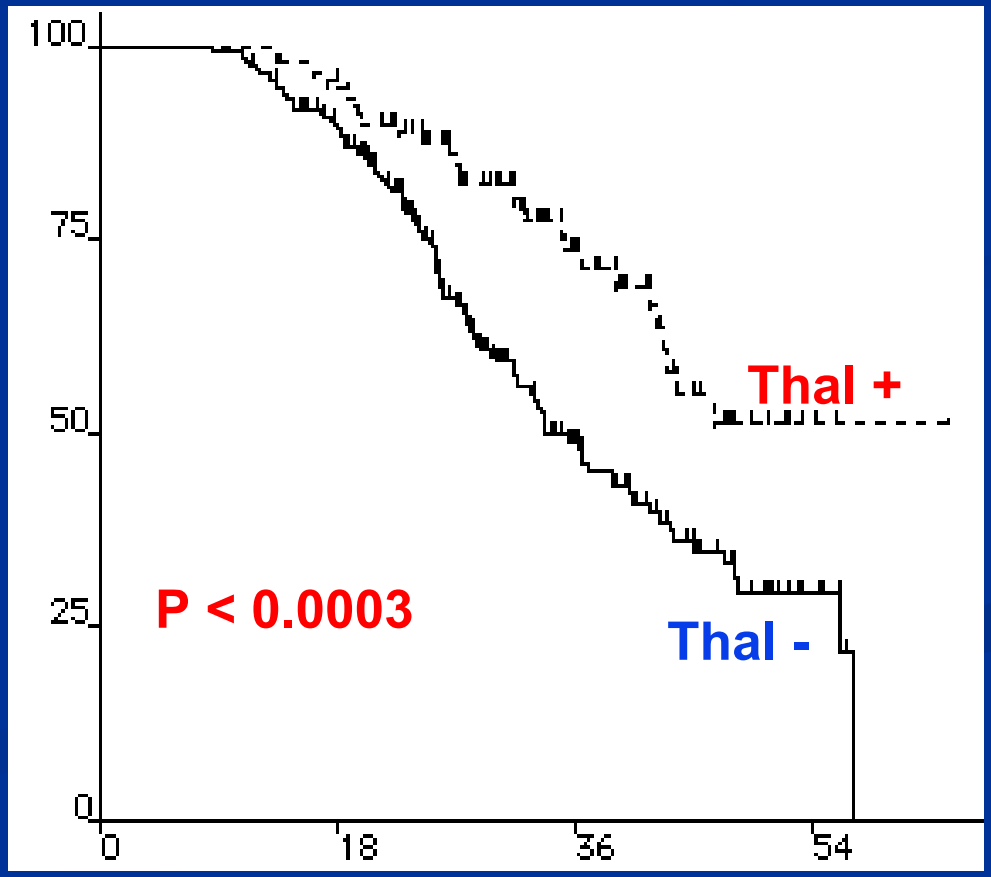


IFM 99 02 : EFS According to Response at Random

Response at Random ≥ 90%



Response at Random < 90%



IFM 99 02: Conclusions

- **Thalidomide improves**:
  Response rate, EFS, and OS when given after ASCT.

- **This survival benefit**:
  - ✓ **Was not due to a maintenance effect** :
    Not observed among patients in CR after ASCT
  - ✓ **Was due to the reduction of the residual tumor mass**:
    Only observed among patients failing to achieve CR after ASCT

- Since thalidomide improves the survival by reducing the tumor mass (rather than by a maintenance effect) :

⇨ **Stopping thalidomide as soon as a very good partial response has been reached (2 or 3 months)** could be an effective strategy in order to reduce the side effects and to avoid thalidomide-resistance at time of relapse.

ASCT and New Drugs: Maintenance / Consolidation

- After ASCT, Thal was demonstrated to be an effective drug.
- However, Neuropathy was a major limiting factor (IFM 99: 68%).
- Revlimid was a logical alternative :
  - ✓Oral agent
  - ✓Effective at low dose
  - ✓At least as effective as Thal
  - ✓Without neurological toxicity
- SWOG, CALGB, IFM 2005 02 protocols.

IFM 2005-02 protocol

ASCT as part of 1st line TT

Randomization

Arm A

Arm B

Consolidation: Revlimid 25 mg/d, 2 months

Placebo till relapse

Revlimid 10 mg/d till relapse

ASCT and New Drugs : Conclusions.

- New drugs will improve:
  - ✓ The induction regimen: 30-40% of CR/VGPR.
  - ✓ The HD regimen: 70-80% of CR/VGPR.
  - ✓ The duration of response (Thal+, Rev?).
- Such a CR rate, efficiently maintained, could be associated with "cure" !!

High dose therapy in MM

1 - HDT versus CC ?

2 - Which preparative regimen ?

3 - Double transplantation ?

4 - HDT and new drugs?

5 - Allogeneic transplant ?

IFM 99 : Factors : Δ 13 ; $ß_2$>3mg/L

0 - 1 Factor

VAD x 3

Mel-140 + PBSC

Mel-200 + PBSC

IFM 99-02

- No maintenance
- Pamidronate
- Pamidronate + Thalidomide

2 Factors

VAD x 3

Mel-200 + PBSC

IFM 99-03

HLA id Sibling

Non-myeloablative

Allo-BMT

IFM 99-04

No HLA id Sibling

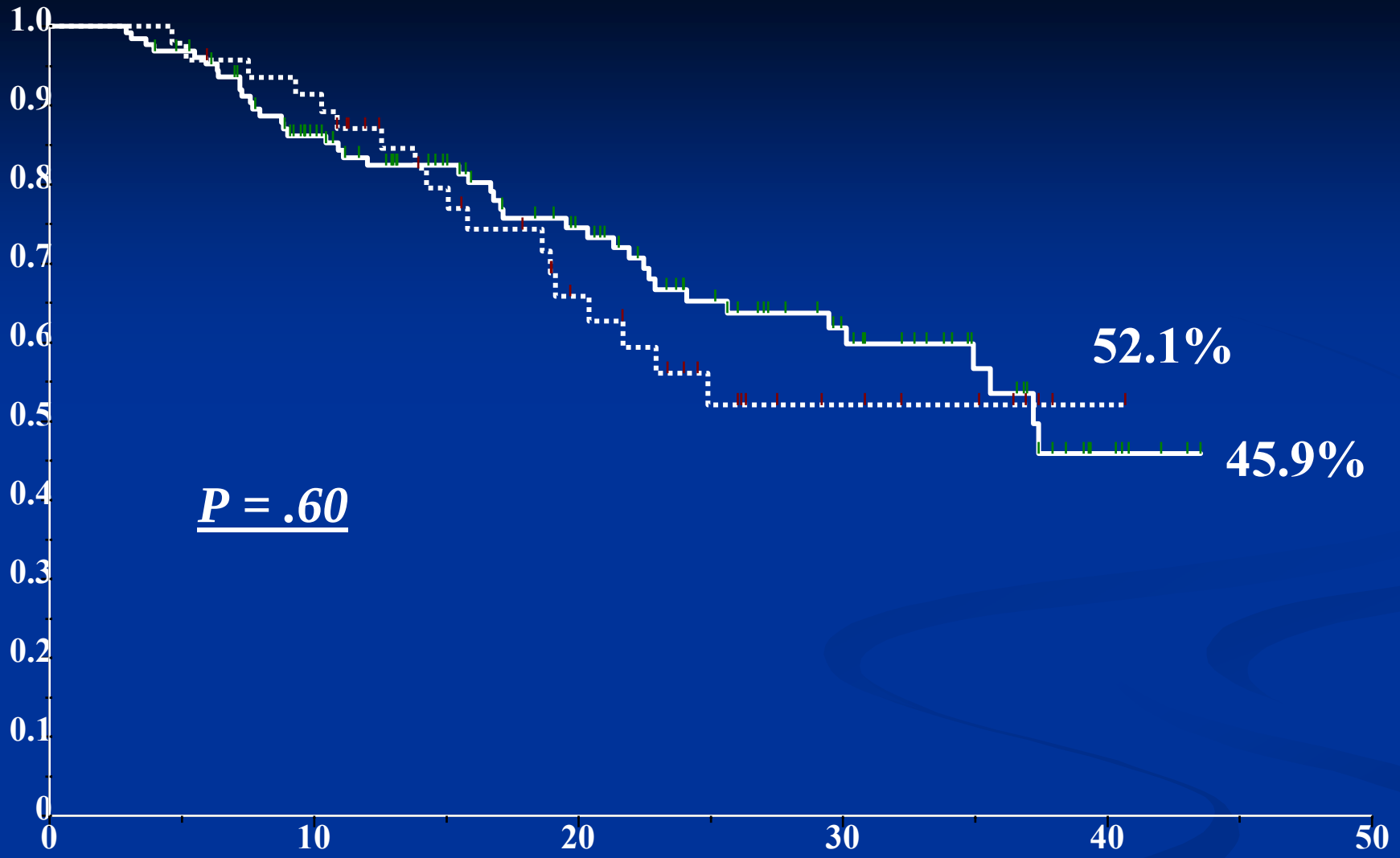
Mel-220 + PBSC

± anti IL6

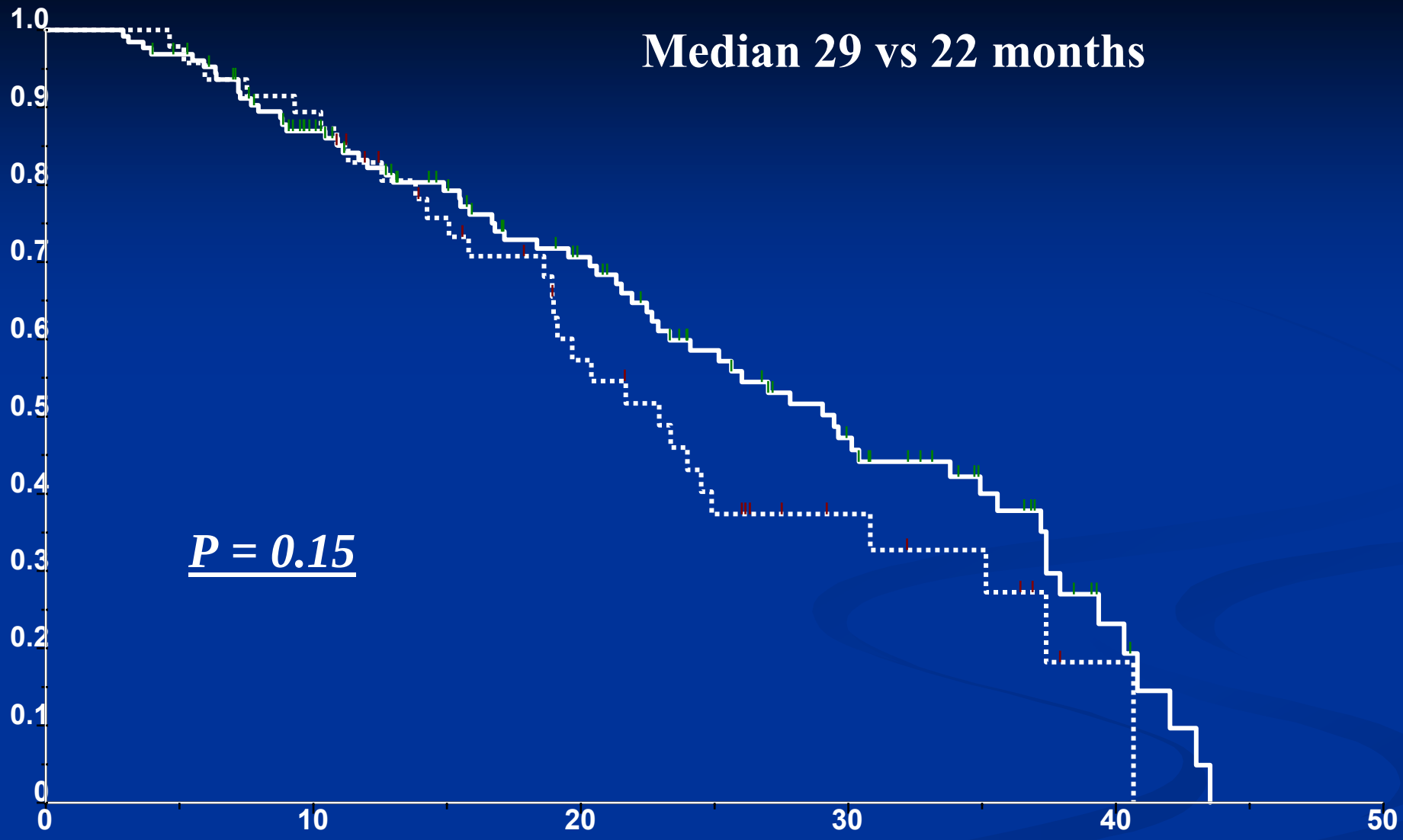
PBSC collection = IFM 99-01

➔ Cyclo (4g/m2) + G-CSF

➔ SCF + G-CSF



Intent-to-treat : Survival IFM9903 vs IFM9904



Intent-to-treat : EFS, IFM9903 vs IFM9904

Allogeneic SCT: The role of reduced intensity conditioning

- High and rapid relapse rate in the high risk population.

- Thus, 2 different strategies can be proposed:
  - ✓To limit its indication to low risk patients

    No ! : 6 year OS >82% after ASCT in the IFM 9902
  - ✓To further control the residual tumor mass after allogeneic SCT By using consolidation / maintenance protocols: Dex-Thal, Rev, Vel ?