

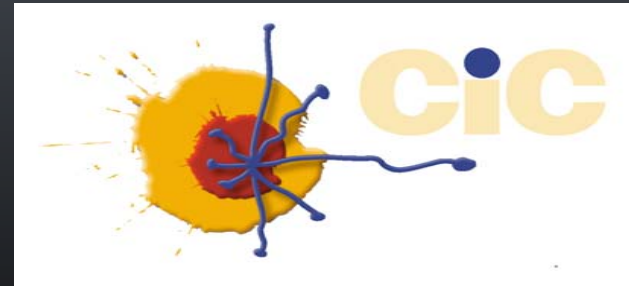
Treatment Options for Young Patients Newly diagnosed with Multiple Myeloma

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Talidomide

Thalidomide combinations in the Up-front setting

Regimen	Patients, n	Response, % (\geq PR)	Reference
Thal-Dex vs Dex	103 vs 104	63 vs 41	<i>Rajkumar, JCO 2006</i>
Thal-Dx vs Dex¹	235 vs 235	63 vs 46	<i>Rajkumar ASH 2006</i>
Thal-Dex vs VAD	100 vs 100	76 vs 52	<i>Cavo, Blood 2005</i>
TAD vs VAD	200 vs 200	80 vs 63	<i>Goldschmith, ASH 2005</i>
T+VA²D vs VA²D	115 vs 115	81 vs 66	<i>Zervas, ASH2006</i>

¹ TTP : 22 vs 6,5 months ² Doxil

**Adequate stem cell collection*

Thal/Dex vs. Placebo/Dex in Newly Diagnosed MM

An International, Multicentre, Double-Blind Trial
470 Patients (median age 65 years)

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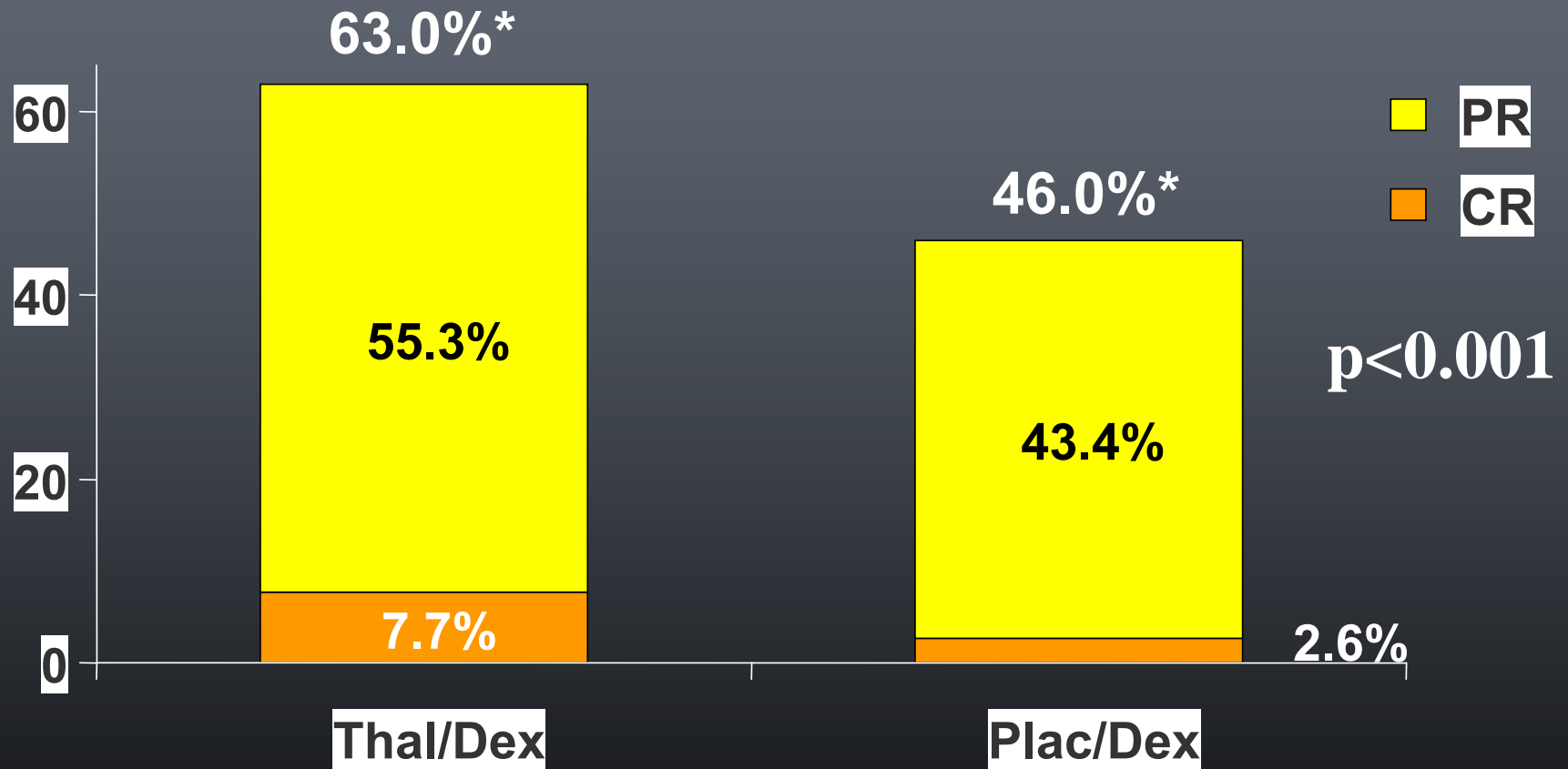
Thal/Dex

*Thal (escalated from 50 mg/d to 100 mg/d through cycle 1 & to 200 mg/d to start cycle 2);
Dex (40 mg on days 1-4, 9-12, and 17-20 for first four cycles; then on days 1-4 monthly after)*

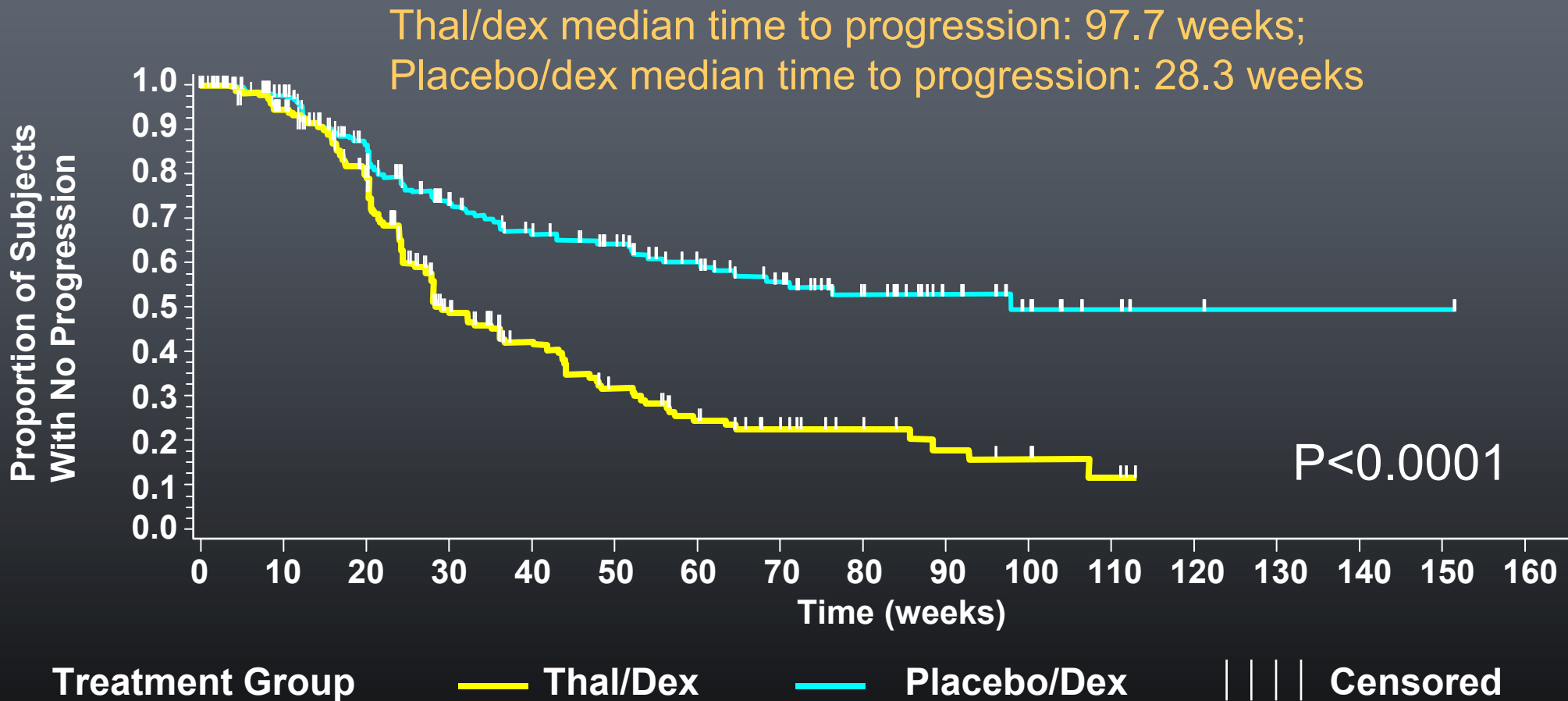
Placebo/Dex

Treatment in both arms continued until MM progression or undue toxicity

Thal/Dex vs. Placebo/Dex in Newly Diagnosed MM: Response Rates



Thal/Dex vs. Placebo/Dex in Newly Diagnosed MM: Time to Progression



Thal/Dex vs. Placebo/Dex in Newly Diagnosed MM

Major Grade 3/4 Toxicities

	Thal/Dex N = 234	Placebo/Dex N = 232
DVT/PE	43 (18.4%)	8 (3.4%)
Pneumonia	26 (11.1%)	18 (7.8%)
Hyperglycemia	14 (6.0%)	12 (5.2%)
Bradycardia	4 (1.7%)	0 (0%)
Myocardial ischemia	6 (2.6%)	2 (0.9%)
Stroke/ischemia	7 (3.0%)	3 (1.3%)
Any grade 4 event	71 (30.3%)	53 (22.8%)

Thalidomide+VAD (Doxil) vs VAD (Doxil) (n=232)

	VAD x 4	Thal-VAD x 4
➤PR %	66	81
Constipation	10	57
PN	14	46
Dizziness	0	54
Skin Rash	0	13

❖ Thal 200 mg daily

Zervas (Greek Myeloma study Group). ASH 2006. Abstrac 3536

Results of the Hovon/GMMG study: TAD vs VAD followed by ASCT

	Response Rate \geq PR (CR)	
	VAD (n=200)	TAD (n=200)

After 3 Cycles

63% (3%)

80% (7%)¹

After Trx

88% (13%)

91% (9%)

1 p>0.001

Thal (200mg-400) (Adria 9 mg/n² x 4 d)

Goldschmidt (ASH 2005, Abs 424)

Dex / Thal vs VAD as Pre-Transplant treatment in 204 MM patients

	Thal / Dex	VAD	p
. Response (VGPR)			
- Before Trx	35 %	13 %	0.002
- After Trx	44 %	42 %	0.8
. DVT	23 %	7 %	0.004
. PN	17 %	13 %	0.4
. Hospitalization(days)	8	20	0.001

Talidomide + Dexamenthasone & Double ASCT in 142 MM patients

➤ CR: 54% after ASCT (vs 33% in patients with double ASCT without Thal/Dx)

	-13q & t(4;14)	-13q alone	t(4;14)alone	None
. % VGPR to Tal/Dx	12 %	41 %	50%	
. % VGPR to ASCT	68 %	80%	80%	
. OS (3 y)	92 %			88%
. EFS (3y)	70%			77%

Lenalidomide

Lenalidomide Combinations in the Up-front setting

Author	Treatment schedule	Patients	Response Rate (%)	Reference
Rajkumar	Lenalidomide-Dex	34	91 (6CR)	Blood 2006; 106: 4050
Niesvizky	Clarithromycin-Lenalidomide-Dex	42	86 (25CR +11nCR)	Blood 2005;106:642

Lenalidomide + Dexamethasone for newly diagnosed MM

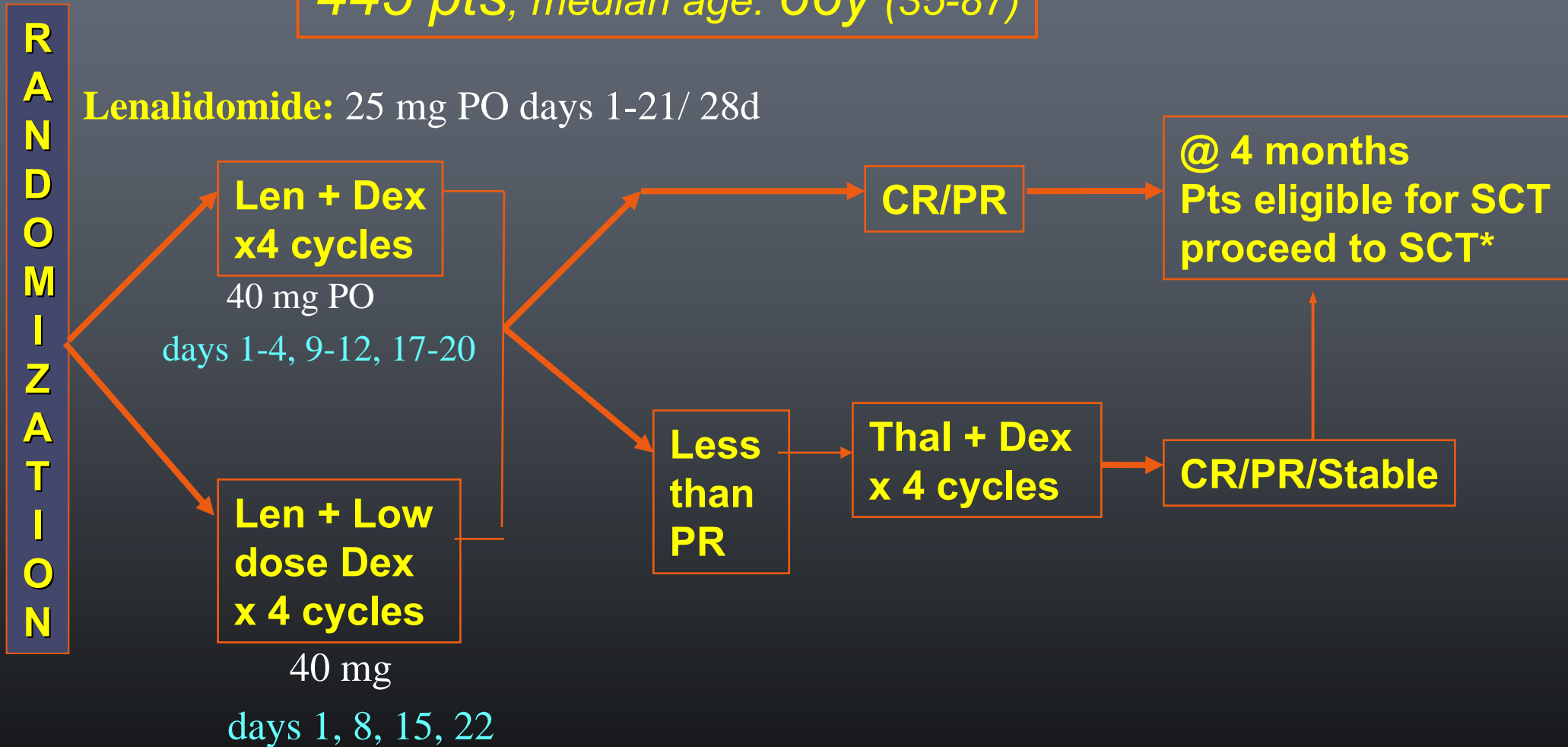
- Lenalidomide : 25 mg days 1-21; 28-day cycle
 - Dex : 40 mg days 1-4, 9-12 y 17-20
 - ASA daily for DVT prophylaxis
- CR/PR/SD
at 4 cycles
- 34 patients
 - **ORR 91%** (18% CR, 38% VGPR, 35% PR).
15 pts: adequate collection of PBSC (>3,0 x10⁶/Kg)
PFS and OS at 2 y: 74 and 91%
- SCT planned;
off treatment
- No SCT; remain
on treatment at
MD's discretion

G3-4 hematologic toxicities : 33%; Neutropenia (4 pts)

G3-4 Non-hematologic toxicities: **55% pts**; Fatigue (4 pt), Pneumonia (2 pt), DVT (1 pt)

Lenalidomide plus high-dose Dex vs low-dose Dex in newly diagnosed MM: (ECOG study)

445 pts; median age: 66y (35-87)



➤ All patients receive some form of DVT prophylaxis (ASA or LMWH)

Lenalidomide plus high-dose Dex vs low-dose Dex in newly diagnosed MM: (ECOG study)

Serious adverse events occurring during first 4 months of therapy

Toxicity	High (N=223)	Low (N=222)	P value
Hemoglobin (Grade ≥ 3)	1.8%	1.8%	>0.9
Neutrophils (Grade ≥ 3)	2.7%	3.2%	0.787
Platelets (Grade ≥ 3)	1.8%	1.4%	>0.9

Lenalidomide plus high-dose Dex vs low-dose Dex in newly diagnosed MM: (ECOG study)

Toxicity	High (N=223)	Low(N =222)	P value
Infection/Pneumonia (Grade ≥ 3)	16.1%	9.0%	0.031
Fatigue (Grade ≥ 3)	11.7%	4.1%	0.004
Hyperglycemia (Grade ≥ 3)	5.8%	2.3%	0.090
Neuropathy (Grade ≥ 3)	0.4%	1.4%	0.372

Lenalidomide plus high-dose Dex vs low-dose Dex in newly diagnosed MM: (ECOG study)

Toxicity	High (N=223)	Low (N=222)	pvalue
DVT/PE (Grade ≥ 3)	18.4%	6.3%	<0.001
Atrial fibrillation/flutter (Grade ≥ 3)	3.1%	0.0%	0.015
Cardiac ischemia (Grade ≥ 3)	1.8%	0.5%	0.372

Lenalidomide plus high-dose Dex vs low-dose Dex in newly diagnosed MM: (ECOG study)

Outcome	High (N=223)	Low (N=222)	
Survival at 1 year	86%	96%	
Deaths	35	10	

Bortezomib

Bortezomib combinations in the Up-front setting

Pilot studies

Treatment schedule	Patients	Response Rate ≥ PR (%)	Reference
Bortezomib-Dex	48	88 (8 CR + 10nCR)	Jagannath, <i>ASH 2006</i>
Bortezomib-Dex	48	66 (21 CR)	Harousseau, <i>Hematologica 2006</i>
Bortezomib-Dex (alt)	40	60 (13 CR)	Rosiñol, <i>ASH 2006 (3086)</i>
Bortezomib ¹ -Adria-Dex	20	89 (11 CR + 5nCR)	Popat, <i>ASH 2005</i>
Bortezomib ² -Adria-Dex	21	95 (24 CR)	Oakervee, <i>BJH 2005; 129:755-62</i>
Bortezomib-Doxil	63*	79 (28)	Orlowski, <i>ASH 2006 (797)</i>
Bortezomib-Doxil-Dex	36	89 (32 CR)	Jakubowiak, <i>ASH 2006 (3093)</i>
Bortezomib-Thal	28	88 (22 CR)	Borello, <i>ASH 2006 (3528)</i>
Bortezomib-Thal-Dex	38	92 (18 CR)	Wang, <i>ASH 2005</i>

* 29 evaluables

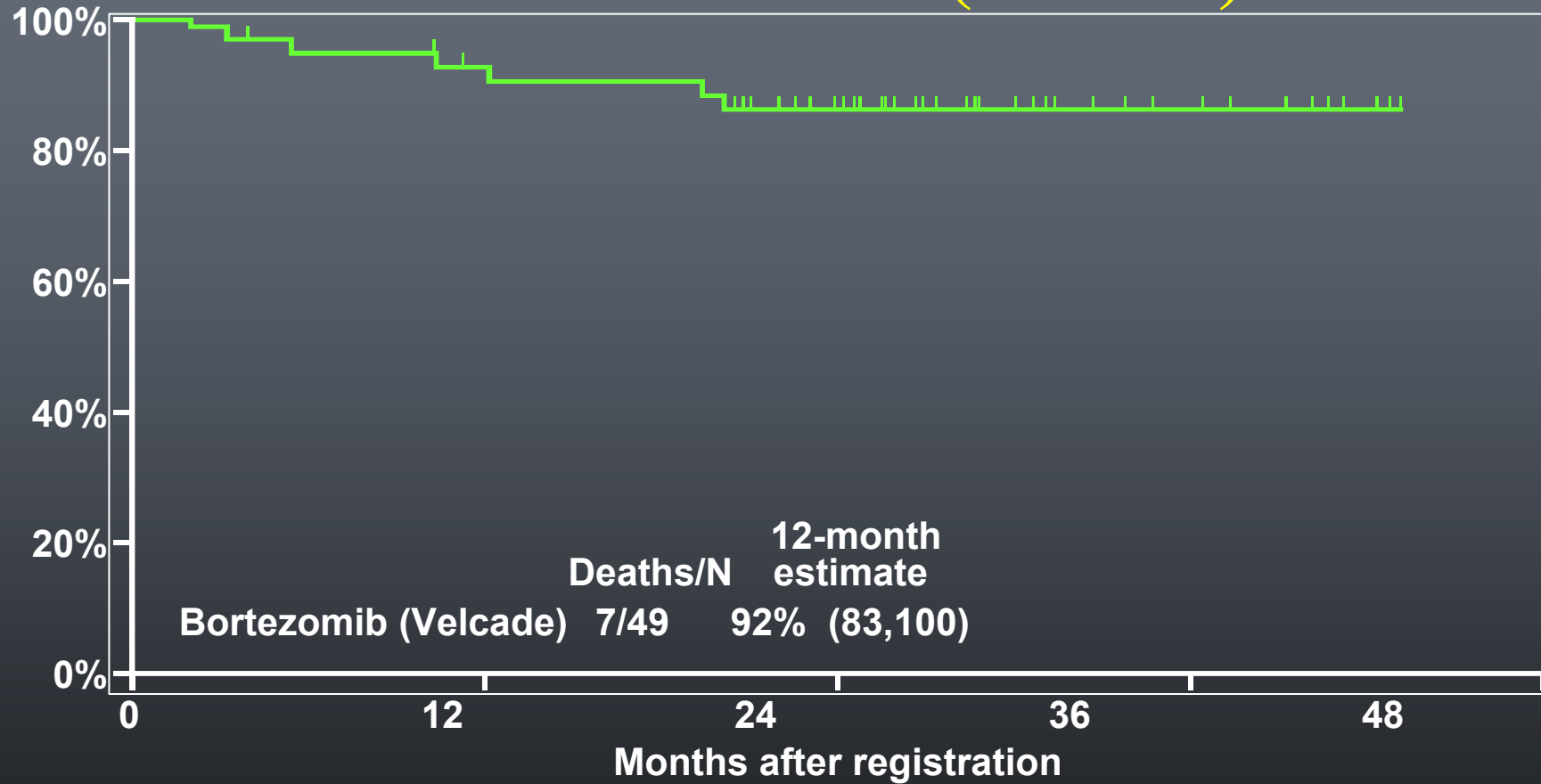
Bortezomib+ Dexamethasone: *Improvement In Response With addition of Dexamethasone*

- 36 patients (74%) received dexamethasone
 - 17 (47%) from cycle 3, 18 (50%) from cycle 5, and 1 (3%) from cycle 6
- 25 of 36 (69%) patients who received dexamethasone had an improved response

		Response to bortezomib				Total
		SD	MR	PR	nCR	
Response to bortezomib + dexamethasone	MR	4				4
	PR	5	7			12
	VGPR		3	3		6
	nCR			1		1
	CR	1			1	2
	Total	10	10	4	1	

Bortezomib+ Dexamethasone OS

In All Patients (N = 49)



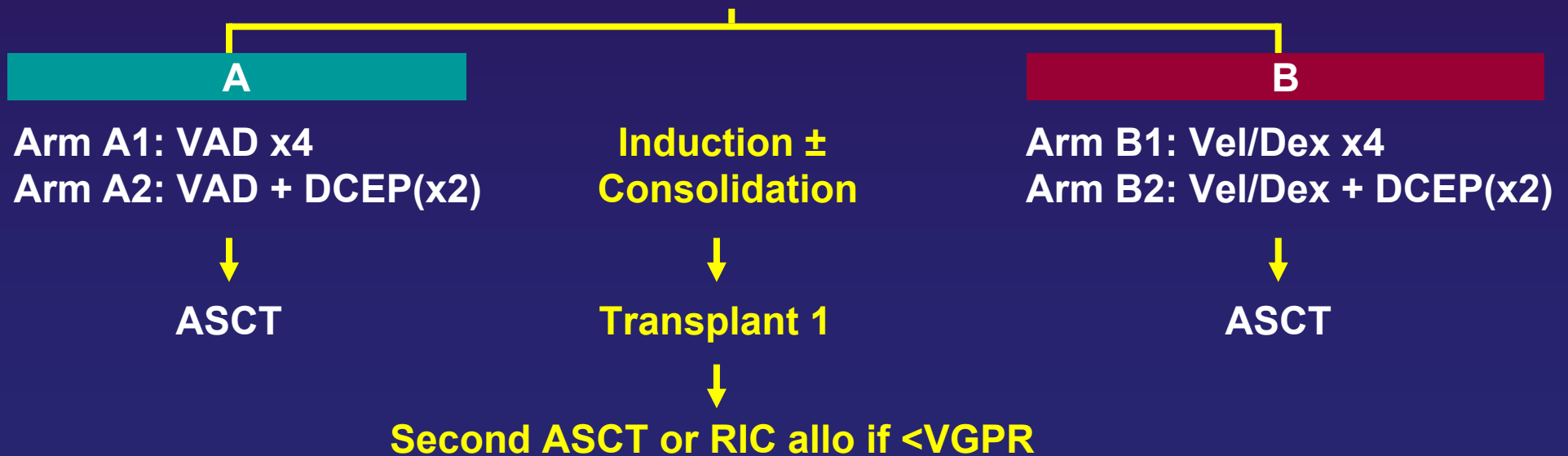
- Median follow-up 26.7 months
- Estimated 1- and 2-year survival rates: 92% and 85%

Vel/Dex vs. VAD Induction in Newly Diagnosed MM: Preliminary Analysis of IFM 2005-01 Trial

- ▶ Patients: 480 pts, Preliminary analysis on first 165 pts.
- ▶ Treatment Scheme

Randomization

Stratification for $\beta 2$ microglobulin and Ch 13 abnormalities



Velcade-Dex vs VAD as pre-Transplant induction regimen

	By Induction		By Consolidacion	
	Vel-Dex x 4*	VAD x 4*	No DCEP	DCEP
	79 pts	82 pts		
➤ PR	82%	67%	79%	89%
CR/nCR	20%	9%	11%	28%

❖ Results including \pm DCEP in both arms

- Patients No requiring 2nd Trx: 78% vs 55%

- Responses to Vel Dex were also higher in patientes with high B2M (CR:20% vs 9%) & Del 13 (CR : 25% vs 11%).

Vel/Dex vs. VAD Induction in Newly Diagnosed MM: Preliminary Analysis of IFM 2005-01 Trial

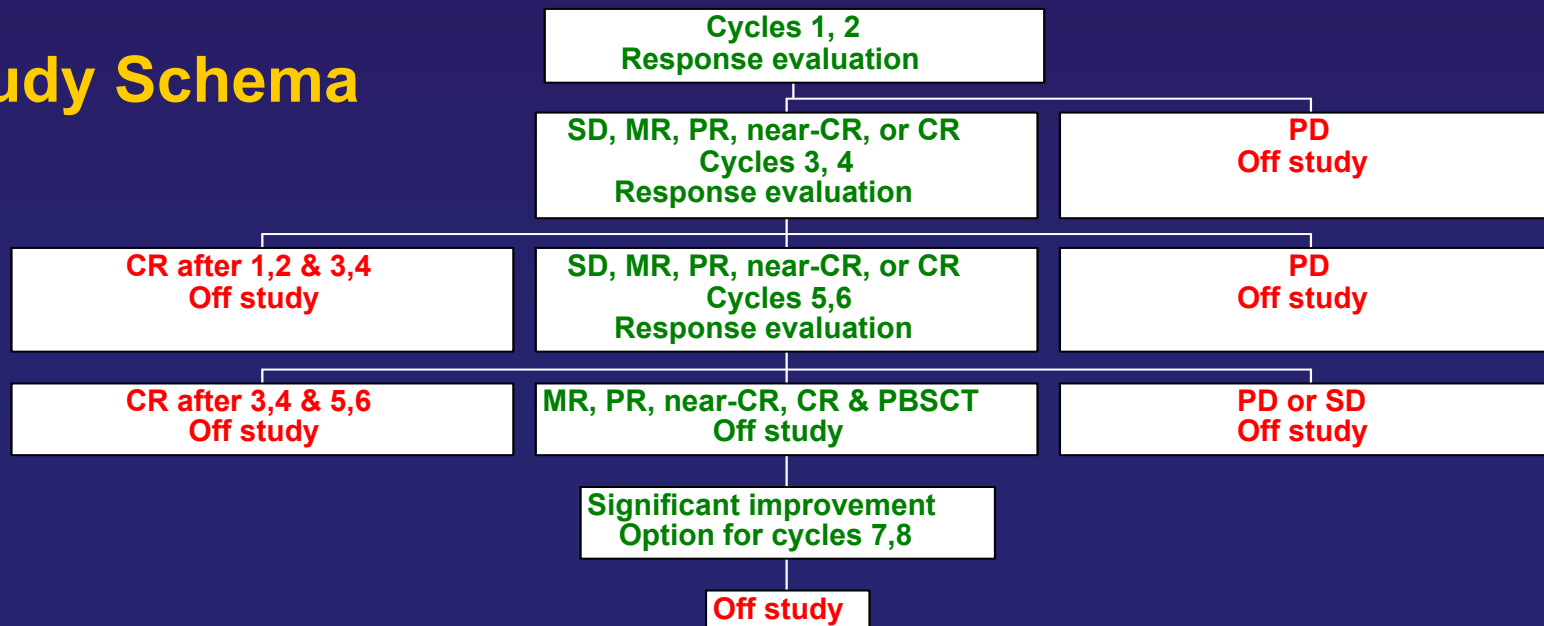
► **Safety:** Notable toxicities during induction

	VAD (A1+A2) N=81	Vel/Dex (B1+B2) N=81
Overall:		
Gr ≥ 3 AE, n (%)	29 (36%)	24 (30%)
Gr ≥ 4 AE, n (%)	8 (10%)	7 (9%)
SAE, n (%)	14 (17%)	12 (15%)
Death, n (%)	1 (1%)	1 (1%)
By Event:		
Neutropenia (Gr 3/4)	7%	4%
Fever/infection (all grades)	17%	14%
Mucositis (Gr 3/4)	10%	1%
Neurologic toxicity (including PN, paraesthesias, and dysaesthesias)	Gr 1/2: 7% Gr 3/4: 0	Gr 1/2: 23% Gr 3/4: 4%
Thrombosis (all grades)	4%	2%

Bortezomib / PLD as Induction Therapy for Symptomatic MM: CALGB Study 10301

- ▶ **Patients:** 63 with symptomatic MM
 - Preliminary response available for 57 pts, final response for 29 pts
 - Toxicity data available for 57 pts
- ▶ **Dose and Schedule:** Up to eight 21-day cycles
 - Bortezomib 1.3 mg/m² days 1, 4, 8, 11
 - PLD 30 mg/m² day 4

▶ Study Schema



Bortezomib / PLD as Induction Therapy for Symptomatic MM: CALGB Study 10301

- ▶ **Patients & Schedule:** 63; Up to eight 21-day cycles
 - Bortezomib 1.3 mg/m² days 1, 4, 8, 11
 - PLD 30 mg/m² day 4

Response	Preliminary n = 57 evaluable	Final n = 29 evaluable
Treatment received	≥ 2 cycles	Completed study
CR / nCR	9 (16%)	8 (28%)
PR	24 (42%)	15 (52%)
ORR (CR + PR)	58%	79%

- PFS, OS not yet reached with a median of 10 mos follow-up
- SC collection: data available on 6 pts; mobilization successful, post-SCT recovery data not yet available

Bortezomib and Dex Induction in Younger MM pts: PETHEMA Phase II Trial

► Dose and Schedule: Alternating bortezomib and Dex

- Bortezomib at 1.3 mg/m² on days 1, 4, 8 and 11 (cycles 1, 3, 5)
- Dexamethasone 40 mg PO on days 1-4, 9-12 and 17-20 (cycles 2, 4 and 6)
- Stem cell collection with G-CSF alone and high dose-therapy intensification (HDT) with Melphalan-200
- Responses evaluated by the EBMT criteria but a VGPR category was included

Alternating Bortezomib & Dexamethasone as induction regimen prior to ASCT

- 40 patients
- ORR 76% (15% CR, 19%, 27% PR, 15% mR).
- In patients who achieve at least PR the reduction in MC was similar for Bortezomib and Dexamethasone .
- Mobilization : in all patients. CD34 ($4.8 \cdot 10^6$ with one apheresis).
- No G3 neuropathy (only 1 G2 and 9 G1).

Novel drugs as induction therapy before ASCT

% Complete Responses & nCR

Pre-ASCT

Post-ASCT (1st)

Reference

Vel-Dex	21%	33%	Harousseau, <i>Hematol</i> 2006
Vel-Dex (alt)	13%	40%	Rosiñol, <i>ASH</i> 2006 (3086)
Vel-Dox-Dex	32%	54%	Jakubowiak, <i>ASH</i> 2006 (3093)
PAD	16%	54%	Popat, <i>ASH</i> 2005
V-T-D	19%	31%	Wang, <i>ASH</i> 2005
V-DTPACE	16%	80%	Barlogie, <i>ASH</i> 2005

No problems with stem cell collection or engraftment

ASCT: Response Rate in Randomized studies

	N	% CR	
		Post-ASCT (1 st)	Post-ASCT (2 nd)
IFM-960	200	38%*	-
MRC-037	407	44%	-
<u>PETHEMA-94</u>	216	30%	-
<u>US INTERGROUP</u>	516	11%	-
<u>IFM-94</u>	399	37%*	50%*
<u>HOVON-24</u>	303	13%	28%
<u>BOLONIA 96</u>	228	33%	48%

* It includes VGPR

Treatment Options for Young Patients

Newly diagnosed with Multiple Myeloma

Maintenance Treatment

Total Therapy +/- Thalidomide : “Arkansas study”

	Thalidomide arm	No Thalidom. arm	
CR	63%	43%	0.001
EFs 5y	56%	44%	0.001
OS 5y	65%	65%	0.0
OS after Relapse	1.1 y	2.7 y	

- Thal was discontinued in 60% within 4 years.
- 83% of patients in the Control group received Thal. as salvage therapy
- Shorter survival in >65 y

Role of Novel drugs in Maintenance treatment:

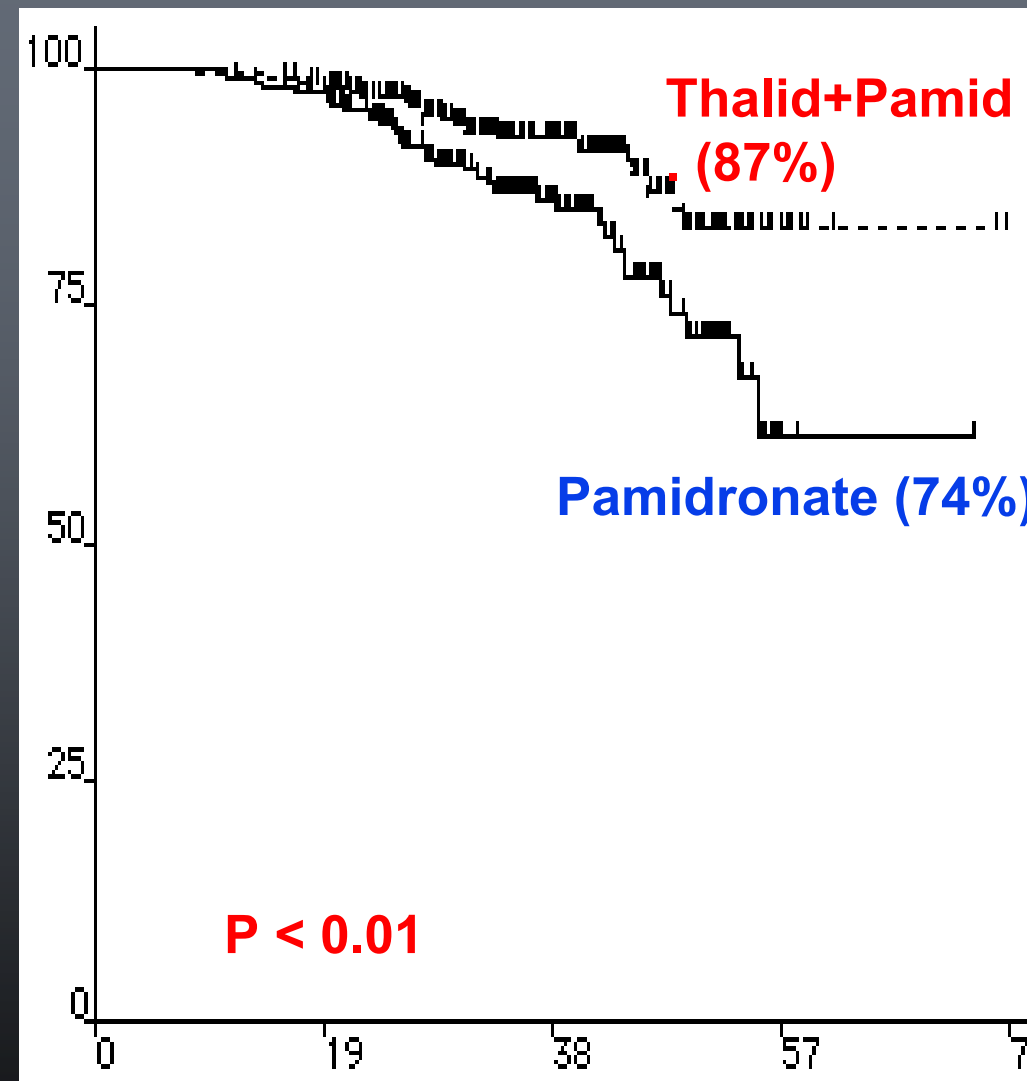
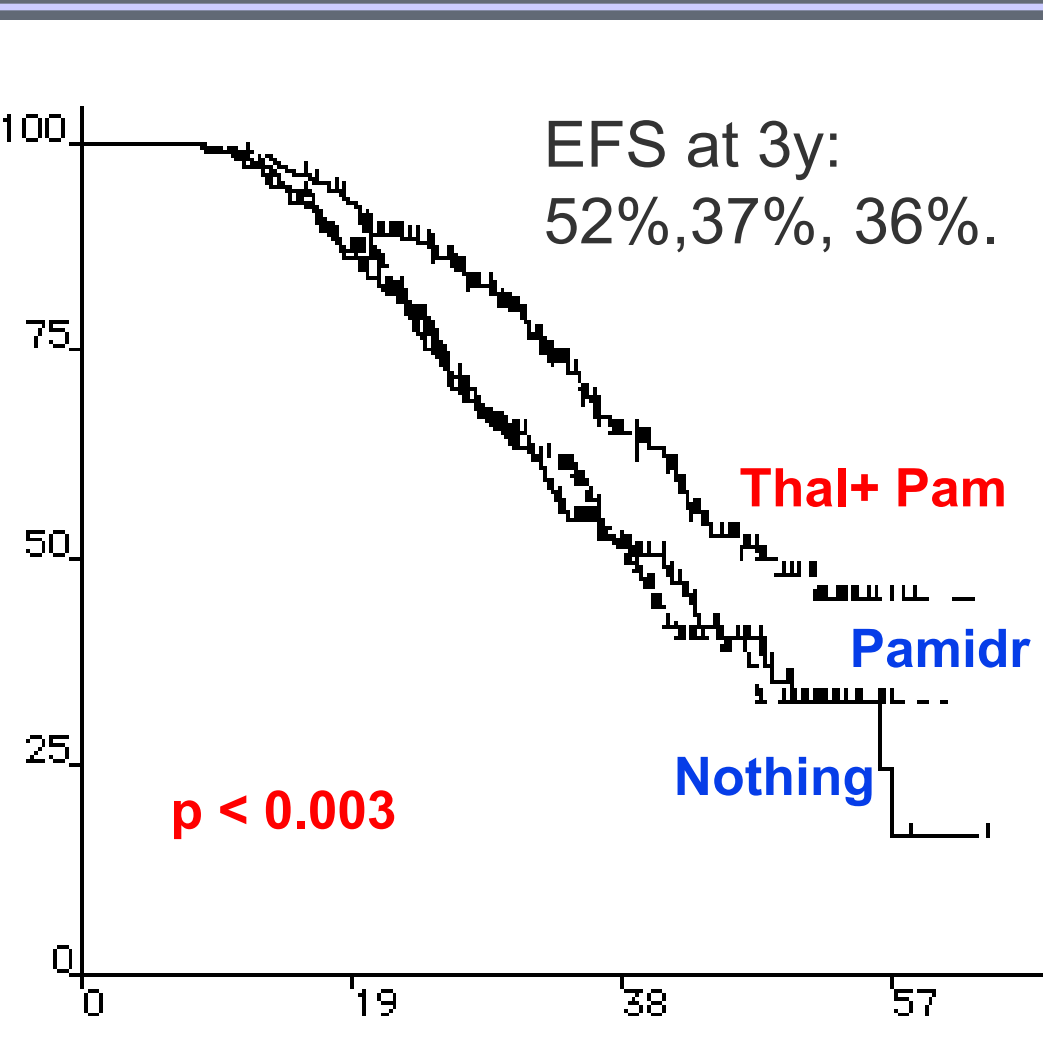
IFM 99 02 : Study Design (Inclusion: 0 or 1 Factor del 13 ; β 2m)

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

Randomization

No maintenance	Pamidronate 90mg /m	Pamidr + Thalidom 100-400 mg/d
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IFM 99 02 : EFS & OS at 4 Years



RR after Randomization: 67%, 57%, 55%.
Skeletal Events : 18%, 21%, 24%

Attal et al Blood 2006

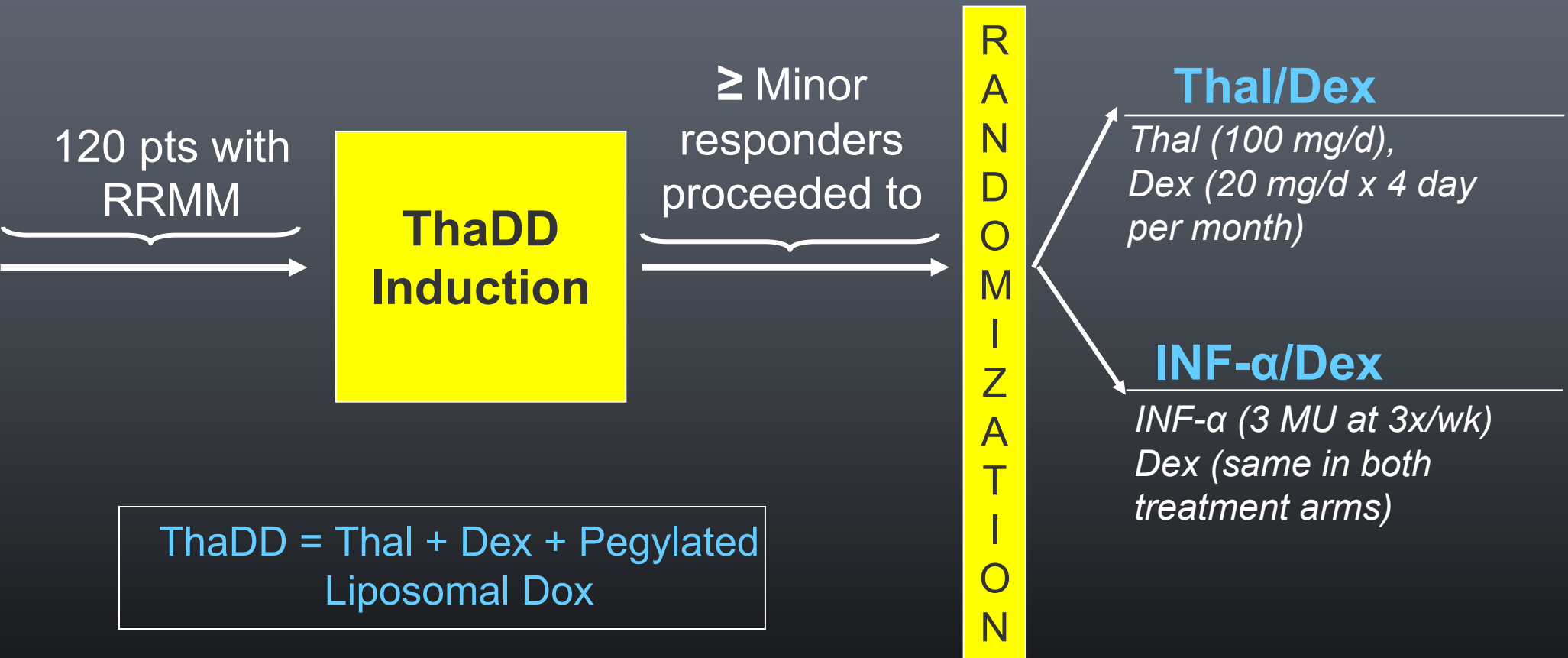
Maintenance treatment after ASCT¹: Thal/Prednisone vs Prednisone²

	Thal / Pred	Pred
. Patients	114	129
. PFS (2y)	66 %	40 %
. OS (2y)	91 %	80 %

1. After Mel 200
2. 6 weeks after Trx: Thal (200 mg x day x **12 months**); Predn (50mg alternate day until progression).
3. 64% of patients completed the 12 m of Thal at a median dose of 100 mg.
4. Once progression occurs similar survival in both arms
5. Neurological toxicities in Arm 1 but no differences in DVT

Maintenance with Thal/Dex vs. INF- α /Dex After ThaDD Induction

Study Design



Maintenance with Thal/Dex vs. INF- α /Dex After ThaDD Induction: Response

	Thal/Dex (n=36)	INF- α /Dex (n=38)	p value
TTP (median)	Not reached	21 mos	0.0139
OS (median)	35 mos	32 mos	0.0821

GEM 2000 Trial (1088 patients): 4+2 VBMCP/VBAD

A short course of Alkylating agents as induction Regimen prior to ASCT is an efficient regimen & doesn't preclude stem cell collection

- Efficient regimen.....RR: 79% (12% CR+ 12% nCR+ 55% PR)
& identify truly resistant patients (alkylating + high Dex)*
- Mobilization regimen : G-CSF (70%), cyclophosphamide + G-CSF (30%)
- 92% underwent the planned ASCT & only 3% do not proceed to ASCT due to low number of CD34 + cells
- Granulocyte & Platelet recovery by day + 11 & + 12.

CR after ASCT: 37%