

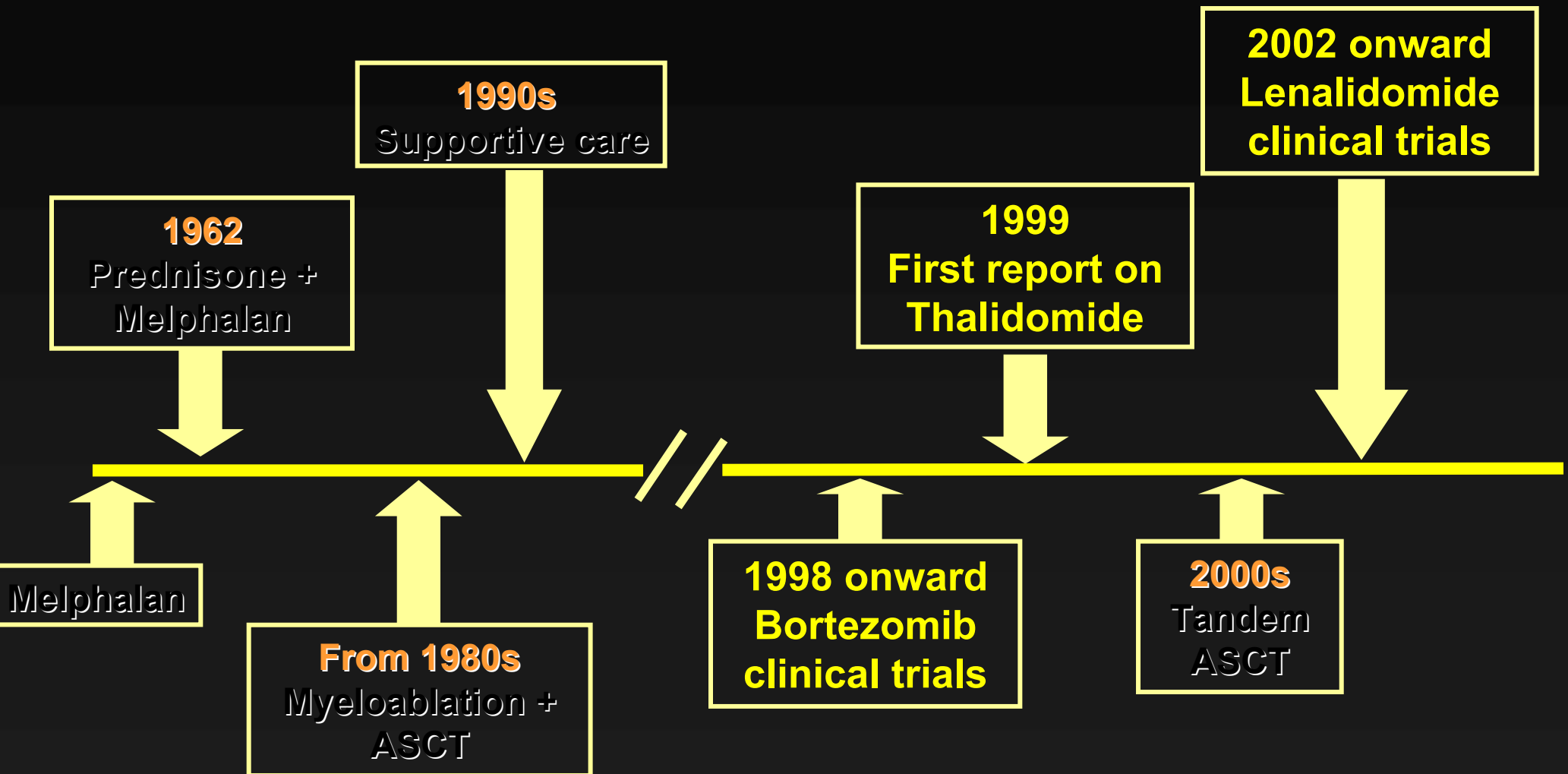
NEW DEVELOPMENTS IN  
**MULTIPLE MYELOMA**

MADRID, SPAIN  
MAY 16 – MAY 17, 2008

**What is best for the young patient  
with newly diagnosed disease?**

*María-Victoria Mateos  
University Hospital of Salamanca  
Salamanca, Spain*

# Progress in the treatment of MM over the past 40 years



# Front-line therapy – standard of care

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- High-dose melphalan with ASCT is considered the standard of care for patients aged  $\leq 65$  years
- **VAD** has been a standard induction regimen prior to ASCT
  - CR rate with VAD typically only  $\sim 10\%$
- CR is associated with 

prolonged survival
very low levels of residual disease
good QoL

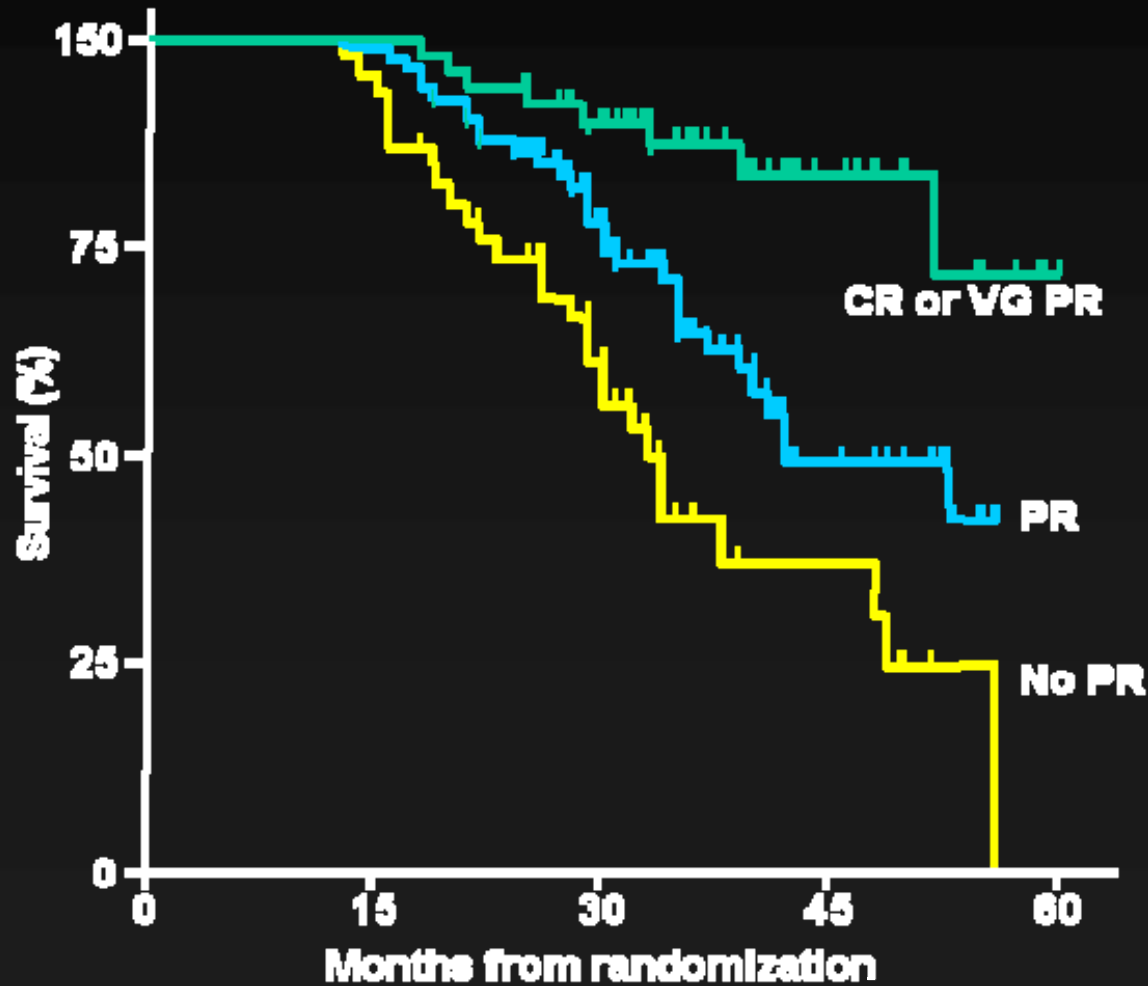
**Important aim of treatment: achievement of CR**

Harousseau. *Ann Oncol* 2002;13:49–54

Attal et al. *N Engl J Med* 1996;335:91–7

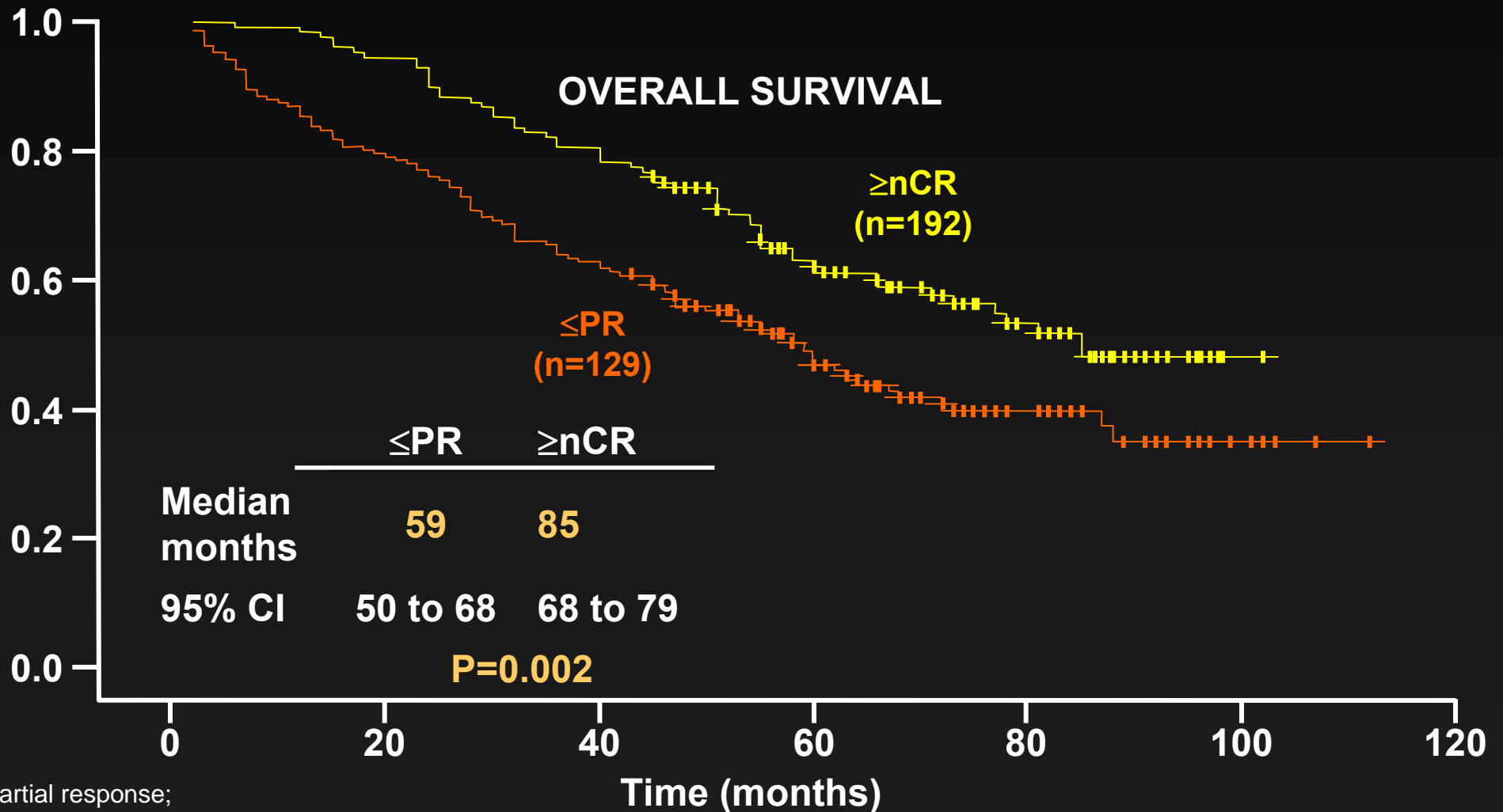
Ludwig et al. IMW 2007 (abstract PO-1103)

# IFM90: Quality of response and survival with conventional chemotherapy or ASCT



# Prognostic impact of $\geq nCR$ attainment

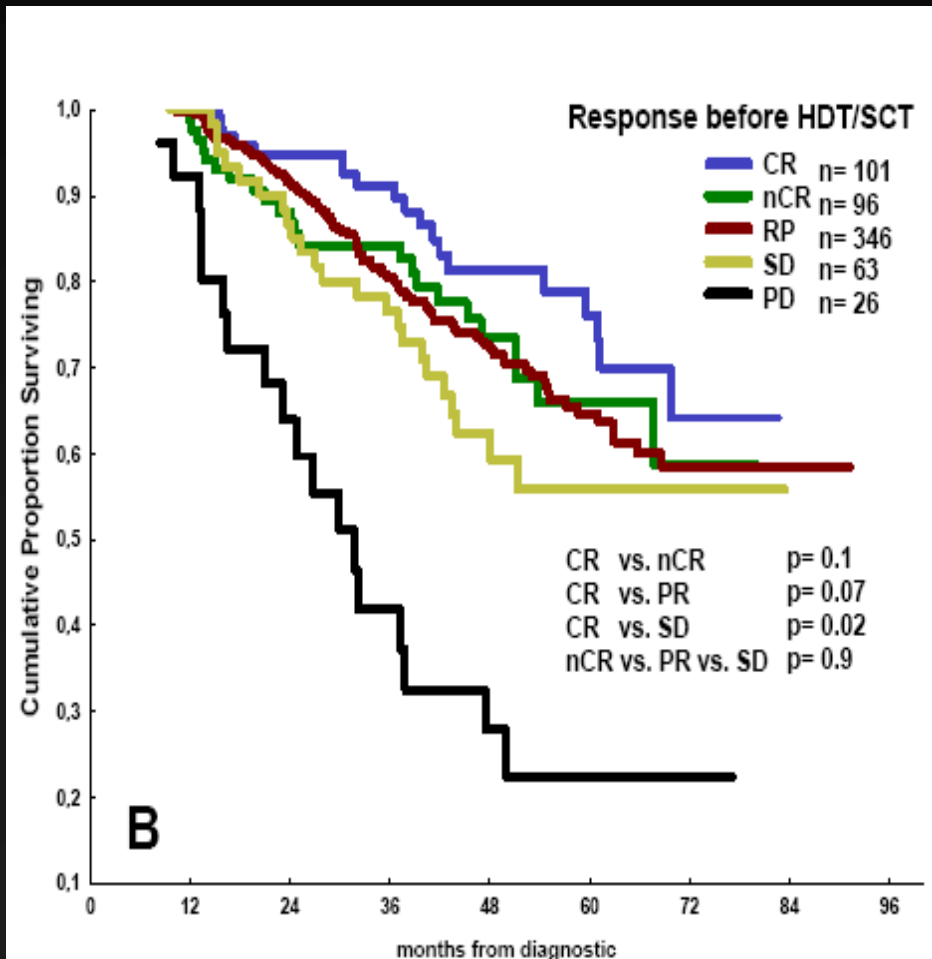
## Bologna 96 clinical study: single vs double ASCT



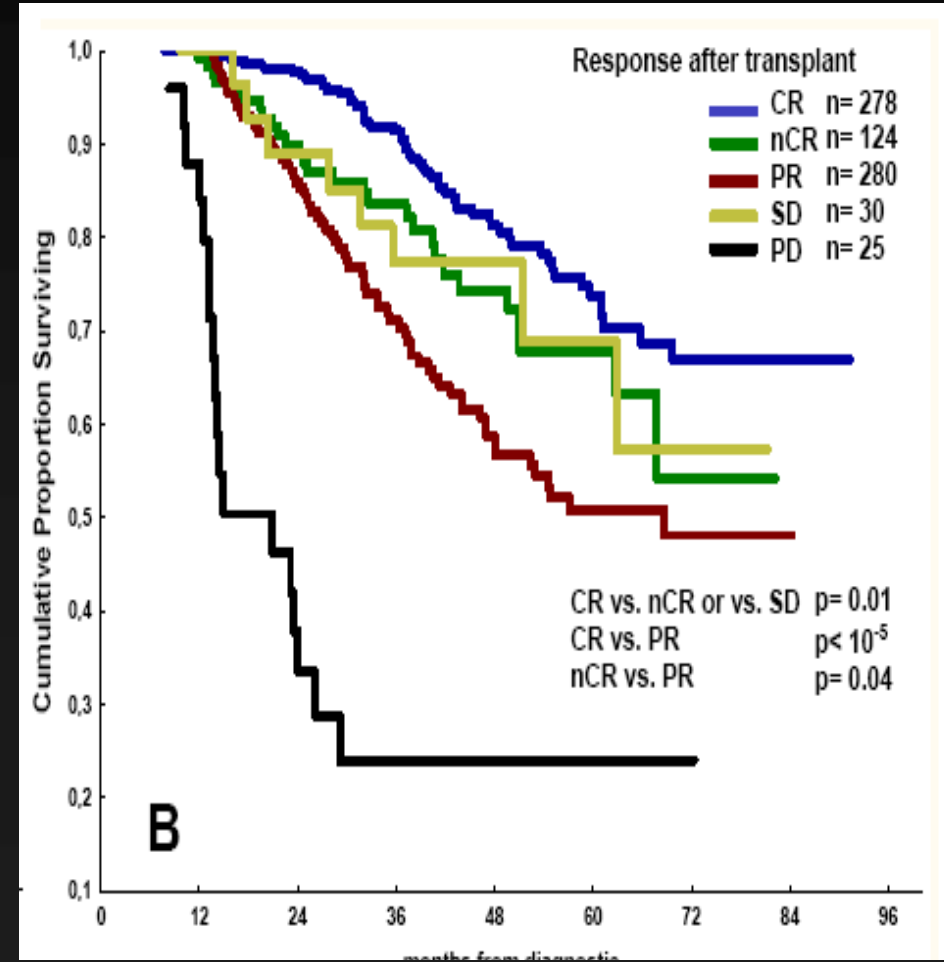
PR, partial response;  
nCR, number of complete responses

# Prognostic impact of CR obtained before and after ASCT: GEM2000 clinical study: single ASCT

OS



OS



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**What is the role of novel agents as induction therapy?**

**Does ASCT improve the efficacy of novel agents-based induction regimens?**

# Thalidomide combinations in the up-front setting

Regimen	Patients, n	Response, % (CR + nCR)	Reference
Thal-Dex vs Dex	103 vs 104	63 vs 41	Rajkumar. <i>JCO</i> 2006
Thal-Dex vs Dex <sup>1</sup>	235 vs 235	63 vs 46 (7.7) vs (2.6)	Rajkumar. <i>JCO</i> 2008
Thal-Dex vs VAD	100 vs 100	76 vs 52 (10) vs (8)	Cavo. <i>Blood</i> 2005
Thal-Dex vs VAD	102 vs 102	65 vs 47 (35) vs (13)*	Macro. <i>ASH</i> 2006
TAD vs VAD	200 vs 200	72 vs 54 (4) vs (2)	Lokhorst. <i>Hematol</i> 2008
T+VA <sup>2</sup> D vs VA <sup>2</sup> D	115 vs 115	81 vs 66 (38) vs (19)*	Zervas. <i>Annals of Oncol</i> 2007
CTD vs CVAD	124 vs 127	87 vs 75 (19) vs (9)	Morgan G. <i>ASH</i> 2007

<sup>1</sup> TTP : 22 vs 6,5 months

<sup>2</sup> Doxil

\* ≥ VGPR

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

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

*No problems with stem cell collection*

# Phase 3 HOVON-50/GMMG-HD3 trial: TAD vs VAD

	TAD (n=201)	VAD (n=201)	P
<b>Results post induction</b>			
CR	4%	2%	
≥ VGPR	33%	15%	< 0.001
CR + PR	<b>72%</b>	<b>54%</b>	< 0.001
<b>Results post ASCT</b>			
CR	16%	11%	0.19
≥ VGPR	49%	32%	< 0.001
CR + PR	<b>79%</b>	<b>76%</b>	0.55

**Grade 3–4 events:** VAD 33%, TAD 41% ( $p = 0.13$ )

**Grade 3–4 neurology:** VAD 7%, TAD 12% ( $p = 0.09$ )

**VTEs:** VAD 4%, TAD 8% ( $p = 0.08$ )

*No problems with stem cell collection*

# Phase 3 UK trial: CTD vs CVAD

	CTD (n=124)	CVAD (n=127)	P
<b>Results post induction</b>			
CR	19,4%	9,4%	0,03
≥ VGPR	38,8%	26,7%	
CR + PR	87,1%	74,8%	0.01
<b>Results post ASCT</b>			
CR	51,3%	39,6%	0,08
≥ VGPR	67%	53%	
CR + PR	87,9%	76%	0.8

*No problems with stem cell collection*

# Lenalidomide + Dex compared with Dex alone in newly-diagnosed MM (SWOG trial)

- **Patients** (n=198)
- **Treatment**
  - Len/Dex: Len 25 mg/d (28 of 35 days for 3 induction cycles, then 21 of 28 days as maintenance thereafter)
  - Dex (40 mg days 1–4, 9–12, 17–20 induction, then days 1–4, 15–18 maintenance)
- **Results**

	Len/Dex (n=100)	Dex (n=98)
CR + PR	85%	51%
CR	22%	4%
1-year PFS	77%	55%
1-year OS	93%	91%

*Early stop due to the benefit of Len-Dex..... "crossover"*

## Adverse events

- **20 VTEs** with Len/Dex (14 on ASA prophylaxis)
- **12** with Dex (all on ASA; 5 after crossover to Len/Dex)

# Phase 3: Lenalidomide + high-dose dex (RD) vs lenalidomide + low-dose dex (Rd)

ECOG trial

- **Patients (n=445)** (median age: 65 years)
- **Primary endpoint:** RR at 4 months, not designed to evaluate long-term outcomes
- **Treatment**
  - RD: lenalidomide 25 mg/day days 1–21 every 28 days  
dex 40 mg days 1–4, 9–12, 17–20 every 28 days
  - Rd: same lenalidomide dose; dex 40 mg days 1, 8, 15, 22 every 28 days

## Results

	RD (n=223)	Rd (n=222)
<b>Best response</b>		
CR + VGPR	52%	42%
≥ PR	82%	71%
<b>1-year OS</b>	87%	96%
<b>18 month OS</b>	80%	91%

%	RD (n=223)	Rd (n=222)
<b>Neutropenia</b>	10	19
<b>DVT/PE</b>	25	9
<b>Infections</b>	16	6
<b>Any ≥ Gr 3 non-hem AE</b>	49	32
<b>Any ≥ Gr 4 AE</b>	20	9
<b>Early death</b>	5	0.5

- No significant difference in response duration, TTP and PFS between two arms
- Successful CD34+ collection in 97% of cases

# BiRD: Clarithromycin + Lenalidomide + dex in MM with poor prognostic features

- **Patients (n=72)**
- **Treatment**
  - Clarithromycin 500 mg bid
  - Len/Dex: Len 25 mg/d (21 of 28 days)
  - Dex (40 mg days 1–4, 7, 14 and 21 at cycle 1, then days 1, 7, 14 and 21)
- **Results**

	BiRD (n=72)
CR + PR	90,3%
sCR	30,6%
CR	8,3%
VGPR	34,7%
2-year OS	97,2%

## Adverse events

- **11 VTEs (15,3%) (all on ASA prophylaxis)**
- **≥G3 neutropenia: 19,4%, thrombocytopenia: 22,2%**

# Lenalidomide-based combinations in the Up-front setting

Author	Treatment schedule	Patients	Response Rate (%)	Reference
Kumar S	<b>Len-Cy-Dex</b>	33	79%	ASH 2007; 190a
Richardson P	<b>Len-Bz-Dex</b>	33	89% (35CR+nCR+VGPR)	ASH 2007; 187a

# Lenalidomide in stem cell transplantation

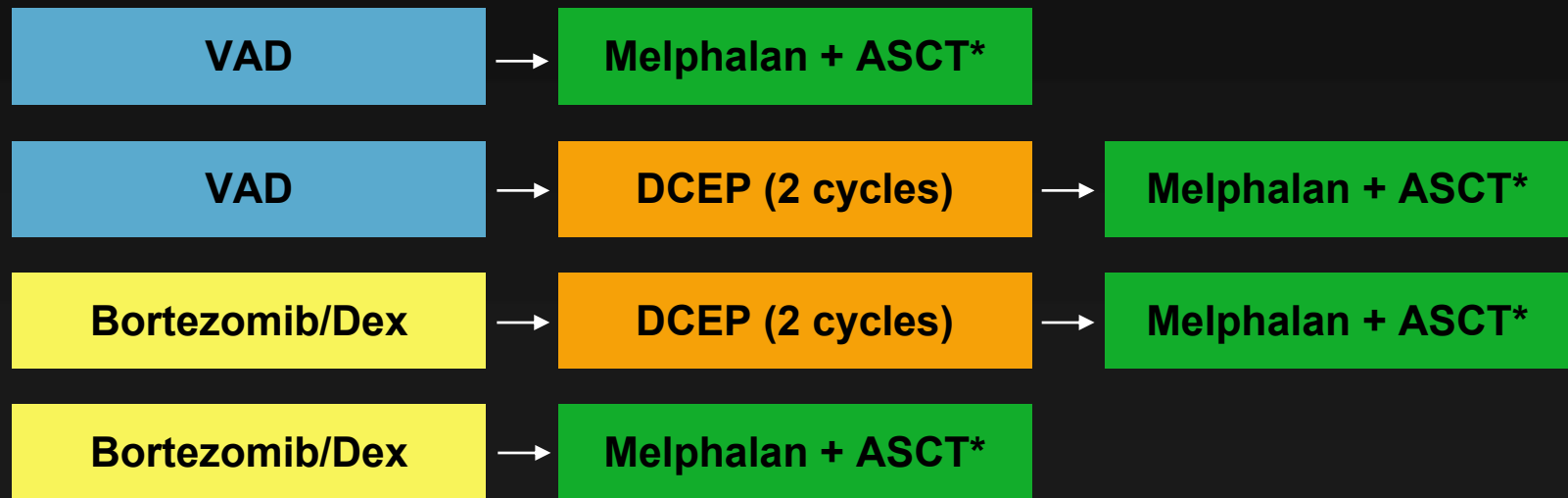
- Patients treated with Len induction therapy have lower stem cell yields with growth factor mobilization
- Lower yields may become clinically important when attempting to obtain stem cells from elderly patients, those with prior radiation therapy or with higher bone marrow plasma cell infiltration

***Recommendation: To collect PBSC after no more than 4-6 cycles of Len using Cyclophosphamide as mobilizing agent***

# Bortezomib-Dex vs VAD as induction treatment prior to ASCT in newly diagnosed MM (IFM 2005/01)

*Four 21-day cycles;  
stem cell collection  
between cycles 3, 4  
after G-CSF*

Patients with  
newly  
diagnosed,  
symptomatic  
MM ≤ 65 years  
of age  
(N = 480)



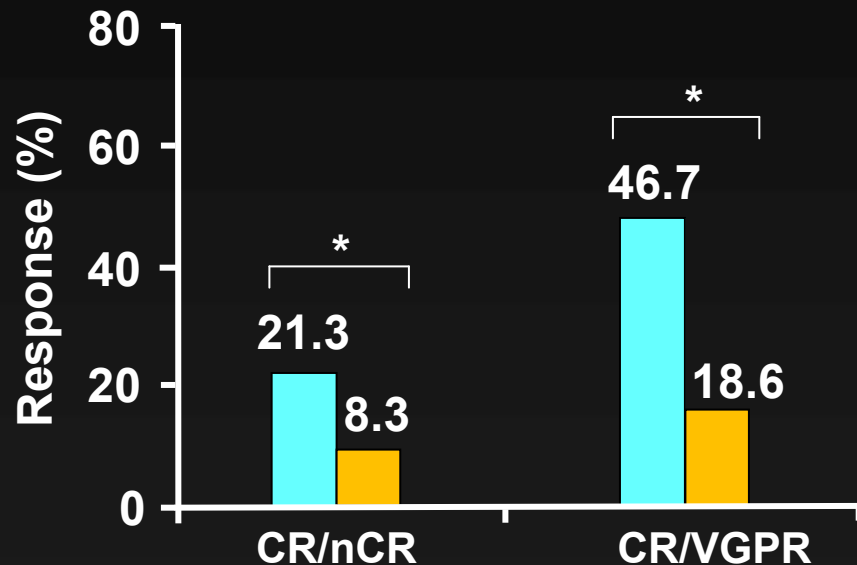
Stratification by cytogenetics,  $\beta$ 2-microglobulin level  
Primary analysis: Post induction response

\* Second ASCT or reduced-intensity conditioning allogeneic transplantation if < VGPR

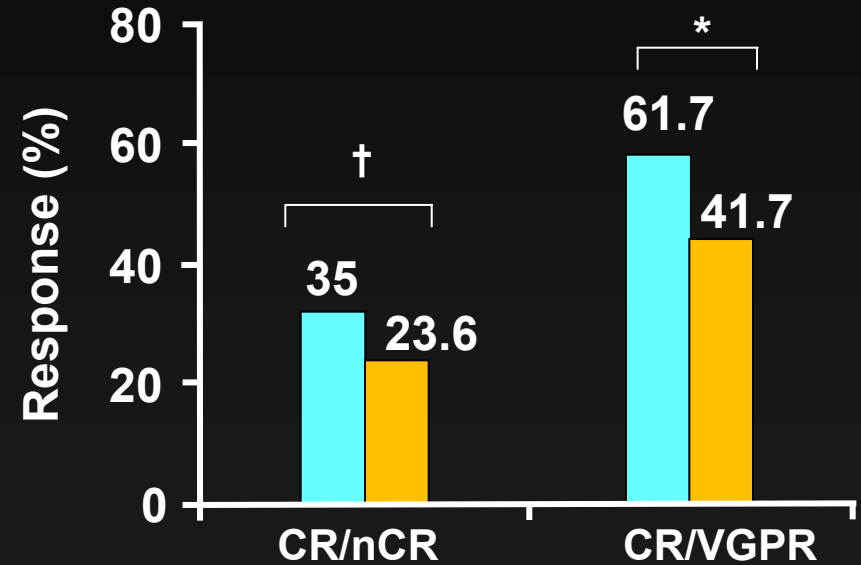
# Bortezomib-Dex vs VAD

## Response rates

### Post induction



### Post ASCT



■ Bortezomib-dex > PR 80%  
■ VAD

*No problems with stem cell collection*

\* $P < 0.0001$ ; † $P = 0.0056$

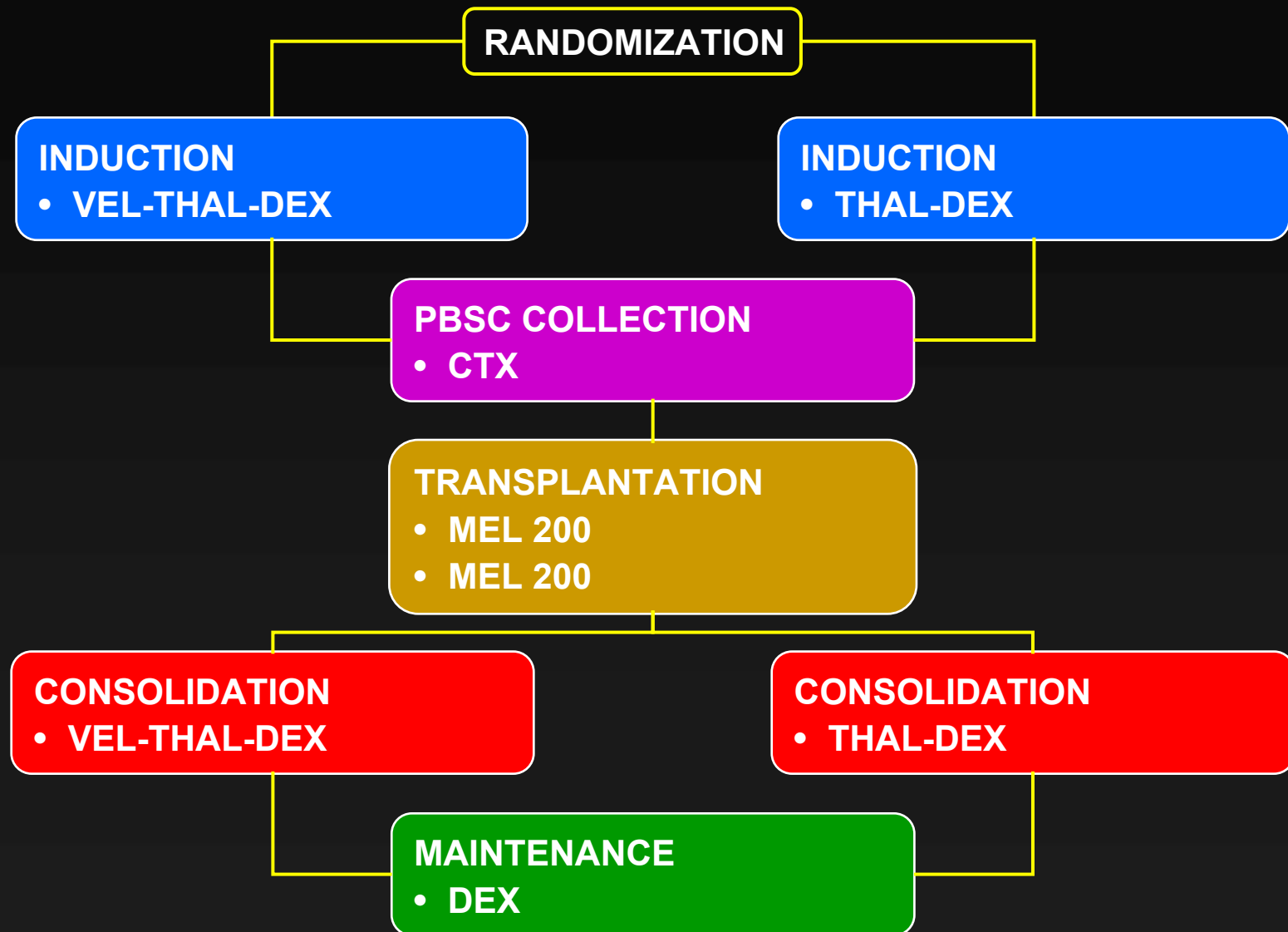
Harousseau *et al.* ASH 2007 (Abstract 450)

# Toxicities during induction

	VAD n = 239	Vel-Dex n = 238
Any AE, n (%)	204 (85.4%)	209 (87.8%)
Grade ≥ 3, n (%)	97 (40.6%)	91 (38.2%)
Grade ≥ 4, n (%)	34 (14.2%)	25 (10.5%)
SAE, n (%)	74 (31%)	60 (25.2%)
AE leading to study drug discontinuation, n (%)	10 (4.2%)	16 (6.7%)
AE leading to death, n (%)	7 (2.9%)	2 (0.8%)
Fatigue (all grades)	16.7%	21.4%
Rash (all grades)	5.4%	10.1%
GI symptoms (all grades)	25.9%	22.3%
Peripheral Neuropathy	22.6%	35.3%
Grade 1	14.6%	17.2%
Grade 2	6.7%	11.8%
Grade 3–4	1.3%	6.3%

# Protocol GIMEMA 26866138-MMY-3006

## VTD vs TD incorporated into double ASCT for MM



# Bortezomib-Thalidomide-Dex (VTD) vs Bortezomib-Dex (TD)

	VTD (%)	TD (%)	
<b>Responses after induction (n = 256)</b>			<b>P</b>
CR/nCR	36	9	< 0.001
≥ VGPR	60	27	< 0.001
< PR	7	20	0.003
Progression	0	5,5	0.008
<b>Responses after ASCT (n = 153)</b>			<b>P</b>
CR	45	19	< 0.001
CR/nCR	57	28	< 0.001
≥ VGPR	77	54	0.003

# VTD vs TD

	VTD (%)	TD (%)	
	Toxicity Gr 3–4 (%)		P
PN	7	2	0.03
Rash	6.5	1	0.01
TVP	3	6.5	0.01
Discontinued	3	6	
	CD34+ x10 <sup>6</sup> /kg		P
Total	9.2	10	NS
> 4 (%)	94	93	NS
Apheresis	1 (0–5)	2 (0–4)	

> 91% of patients received > 90% of bortezomib dose

# Bortezomib combinations for newly diagnosed MM – ASH 2007

Bortezomib regimen	Phase	n	CR + PR	CR + nCR	Abstract*
+ DOXIL, dex	2 (elderly pts)	65	Pre-SCT:97% Post-SCT: 100%	Pres-SCT:12% Post-SCT: 30% (CR only)	Palumbo <i>et al.</i> (abstract 448)
+ lenalidomide, dex	1/2	33	89% VGPR 35%	n/a	Richardson <i>et al.</i> (abstract 187)
+ cyclophosphamide, dex + VTD	2	25	100% ≥VGPR 54%	31%	Jagannath <i>et al.</i> (abstract 188)
+ cyclophosphamide, dex	2	33	≥VGPR 100%	66%	Reeder <i>et al.</i> (abstract 3601)
+ cyclophosphamide, dex	1/2 (dose finding)	30	77%	10% (CR only)	Kropff <i>et al.</i> (abstract 3599)
+ ascorbic acid, melphalan	2	35	39%	16% (CR only)	Berenson <i>et al.</i> (abstract 3602)
+ DOXIL, thal	2	31	65%	12% (CR only)	Chanan-Khan <i>et al.</i> (abstract 3614)

\*Abstracts from *Blood* 2007;110

# Conclusions on induction options for young patients with newly diagnosed MM

- **VAD is DEAD**
- **Thal-Dex** new gold standard... *Suboptimal?*
- Higher response rates (> 80%, particularly CR rates) could be obtained by **adding adriamycin or cyclophosphamide**
- ASCT seems to add to the RR over and above those obtained by Thal-containing regimens
- **Vel-Dex or VTD** are superior to VAD or TD, and CR increases after ASCT
- **Len-based combinations** are very effective in newly diagnosed MM pts, but further analysis are needed to know the role of ASCT

# Young newly diagnosed MM patients

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**Induction** (Vel, Thal or Len-based combinations)



**ASCT\*** (Me1 200)      *\*Does ASCT benefit all pts?*



**Maintenance/Consolidation** (Thal/Vel/Len +/- Predn)\* (1y)