

# Die Rolle der Kortikosteroide und deren Alternativen



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## Activity of DEX in MM

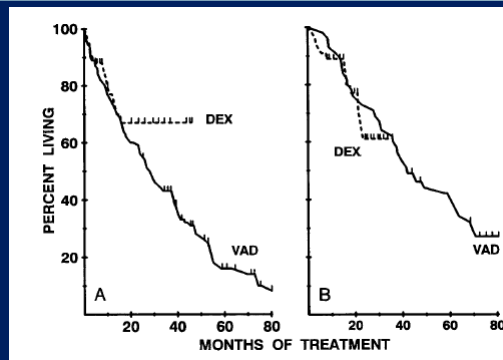
- Dexamethasone (DEX) inhibits mRNA expression of interleukin-6 in myeloma cells
- DEX induces plasma cell apoptosis by blocking the IL-6 support network

## DEX for previously untreated patients with MM

	Tumor Mass	
	Low	Intermediate/High
Response rate to VAD	69%	50%
Response rate to DEX	51%	37%

$P = .08$  (for both comparisons)

Survival:



Alexanian et al., Blood 1992;80:887

## Efficacy of combinations in relapsed/refractory MM

Regimen	Phase	n	CR + PR	CR + nCR	Reference
Bortezomib + dex	1/2	32	67%	29% (CR only)	Solano et al. <i>Haematologica</i> 2006;91 (abstract 1210)
Bortezomib + dex	3b	624	54%	35%	Mikhael et al. <i>Blood</i> 2006;108 (abstract 3530)
Thalidomide + dex	2	77	41%	18%	Palumbo et al. <i>Haematologica</i> 2001;86:399-403
Lenalidomide + dex (MM-010, MM-009)	3	176	59%	15% (CR only)	Dimopoulos et al. <i>Blood</i> 2005;106 (Abstract 6)
		170	59%	13% (CR only)	

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

- **Patients** (n=445) (median age: 65 years)
- **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%
1-year OS	87%	96%
18 month OS	80%	91%

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

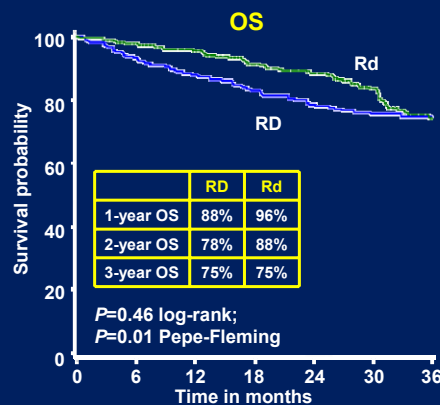
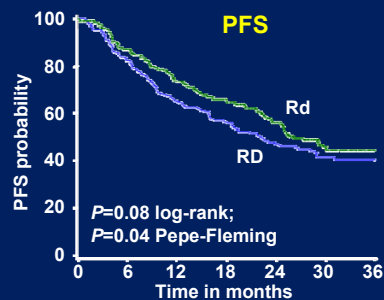
- **No significant difference in response duration, TTP and PFS between two arms**

Rajkumar *et al.* (abstract 74)

## Phase III ECOG trial: lenalidomide + high-dose dex (RD) vs lenalidomide + low-dose dex (Rd)

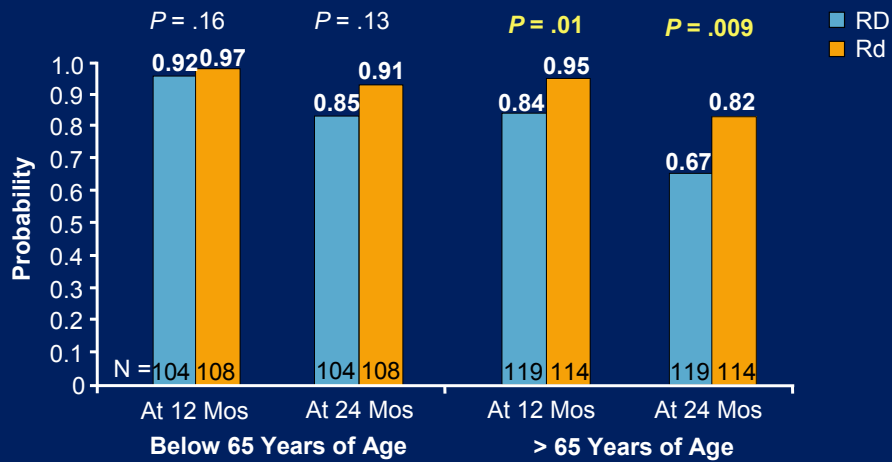
### Primary study results

	RD (n=214)	Rd (n=207)
ORR @ 4 cycles, %	79	69
≥VGPR within 4 cycles, %	42	24
DVT/PE (grade 3/4), %	26	12



Rajkumar *et al.* ASH 2008 Joint ASH/ASCO symposium

## ECOG (E4A03): Survival by Age



Rajkumar SV, et al. ASH 2007. Abstract 74.

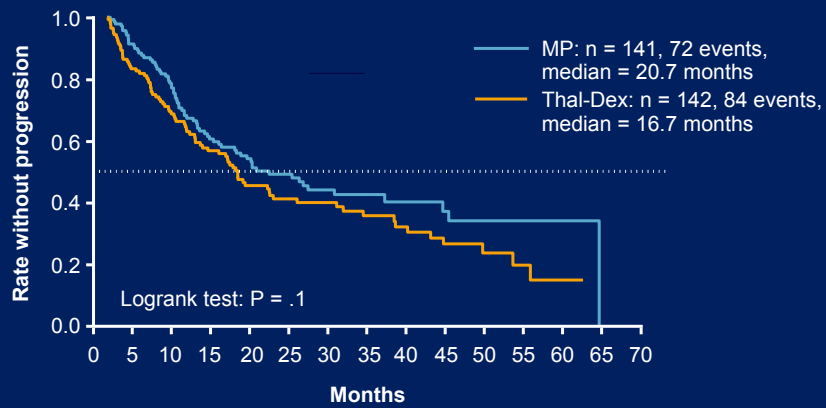
## Thal-Dex vs MP (CEMSG Study): Response

- Higher RR with Thal-Dex
- More rapid response
  - Time to response: 6 vs 10 wks ( $P < .0001$ )
  - Time to best response: 16 vs 23 wks ( $P < .0002$ )

Parameter, %	TD (n = 145)	MP (n = 143)
CR	15	7
nCR	15	7
VGPR	18	15
PR	21	21
MR	12	21
SD	4	18
PD	15	10

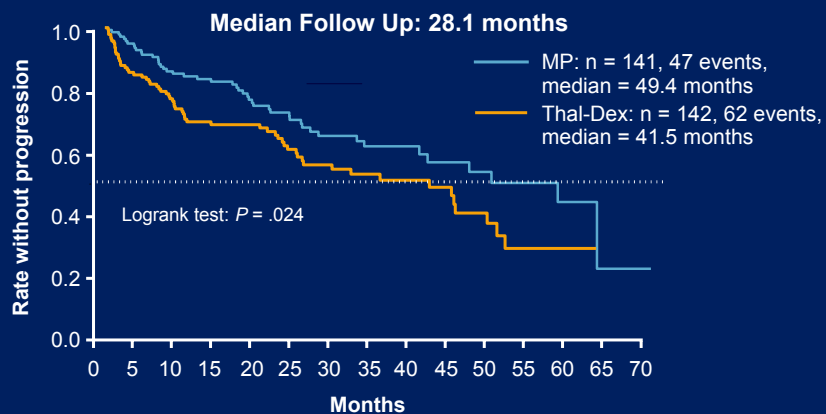
Ludwig H, et al. ASH 2007. Abstract 529.

## Thal-Dex vs MP (CEMSG Study): Progression-Free Survival



Ludwig H, et al. ASH 2007. Abstract 529.

## Thal-Dex vs MP (CEMSG Study): Overall Survival



Ludwig H, et al. ASH 2007. Abstract 529.

## 'Steroid-free' regimens in MM

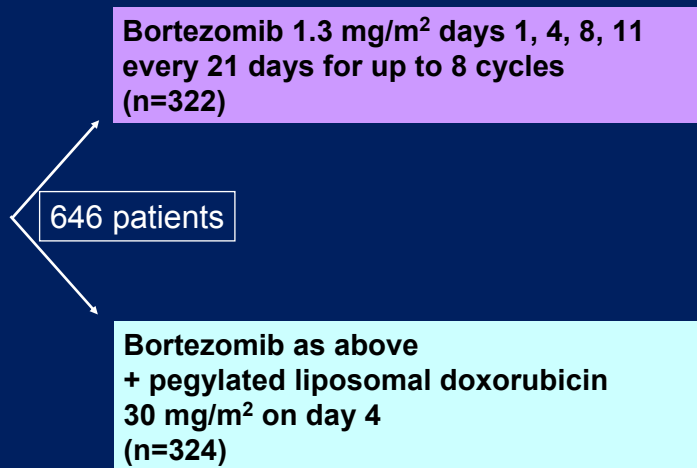
### Available data

## Efficacy of single agents in relapsed/refractory MM

Regimen	Phase	n	CR + PR	CR + nCR	Reference
Bortezomib (APEX)	III	331	43%	16%	Richardson <i>et al.</i> <i>Blood</i> 2005;106 (Abstract 2547)
Thalidomide	II	712	28.2%	1.6%	Prince <i>et al.</i> <i>Leuk Lymphoma</i> 2007;48:46–55
		1629	29.4%	1.6%	Glasmacher <i>et al.</i> <i>Br J Haematol</i> 2006;132:584–593
Lenalidomide	II	222	26%	Not stated	Hussein <i>et al.</i> ASCO 2008 (Abstract 8524)
		102	17%	4%	Richardson <i>et al.</i> <i>Blood</i> 2006;108:3458–3464

## Phase III: bortezomib + DOXIL<sup>®</sup> vs bortezomib for relapsed/refractory MM Study design

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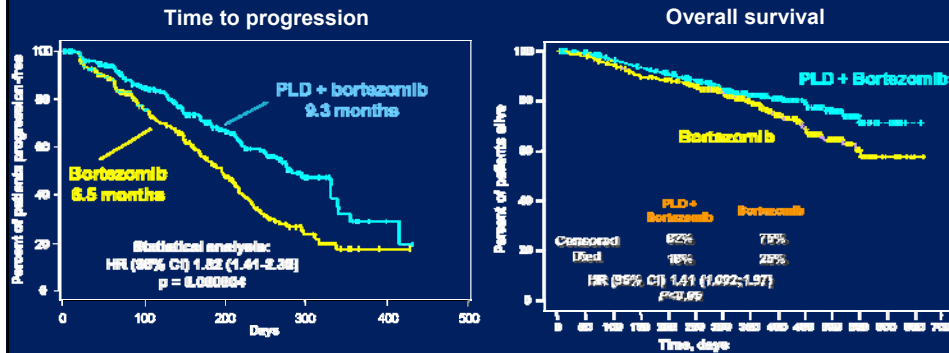
Orlowski et al. *J Clin Oncol* 2007;25: 3892-3901

## Updated Response Rates

	Bortezomib (N=310)	PLD + Bortezomib (N=303)	P value
Total (CR + nCR + PR)	44%	52%	0.050
CR + nCR	13%	17%	
PR	31%	35%	
CR + VGPR*	20%	30%	0.007

\* According to the IMWG 2006 criteria

## Phase III: Bortezomib + DOXIL<sup>®</sup> vs bortezomib



PLD, pegylated liposomal doxorubicin

Orlowski et al. *J Clin Oncol* 2007;25:3892-3901

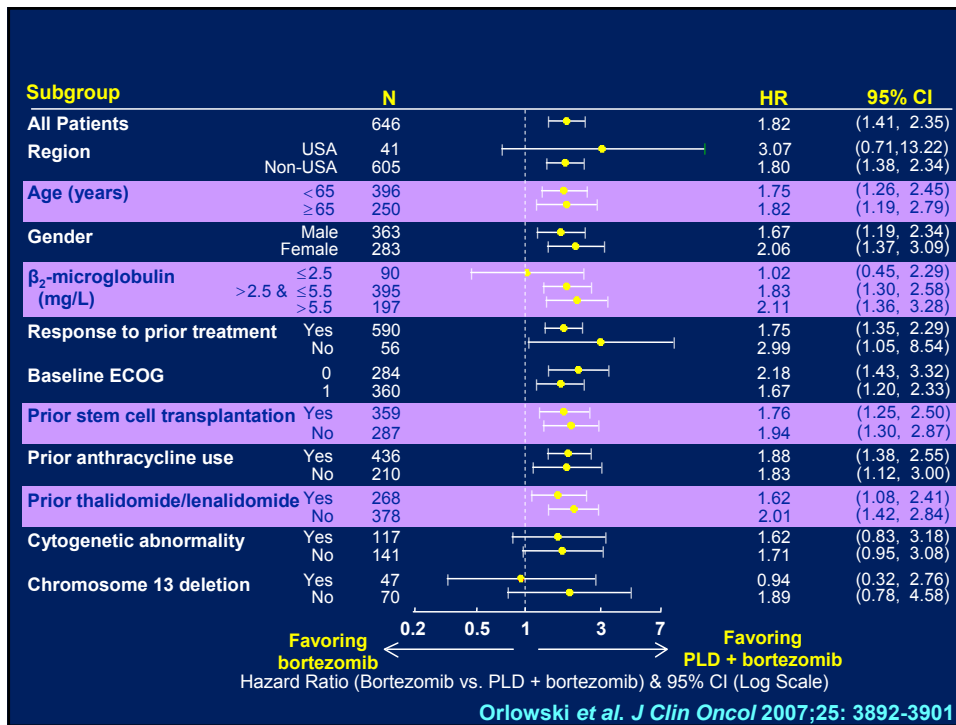
## Phase 3: bortezomib + DOXIL<sup>®</sup> vs bortezomib for relapsed/refractory MM

Grade 3/4 adverse events (%)	Bortezomib (n=318)	Bortezomib + DOXIL (n=318)
Thrombocytopenia	15	22
Neutropenia	14	30
Anemia	9	9
Peripheral neuropathy	9	4
Hand-foot syndrome	0	5

### Conclusion

- Bortezomib + DOXIL significantly improves TTP over bortezomib alone
- Toxicities were manageable and acceptable

Orlowski et al. *J Clin Oncol* 2007;25: 3892-3901



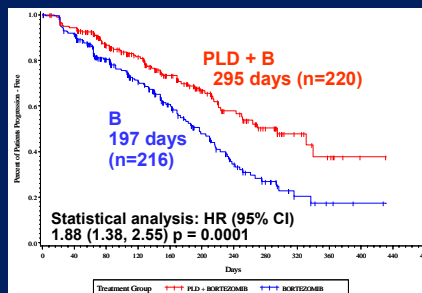
## Prolonged TTP with Bortezomib + PLD

### Anthracycline Exposed vs Naive

	PLD + B (vs. B) Anthracycline exposed	PLD + B (vs. B) Anthracycline naive
Median TTP (days)	295 (vs 197)	282 (vs 197)
HR (95% CI)	1.88 (1.38, 2.55) p=0.0001	1.83 (1.12, 2.30) p=0.015
Heterogeneity test*	P = 0.716	

Grade 3/4 AE(%)	PLD + B	
	Exposed (n=215)	Naive (n=103)
PN	4	6
Neutropenia	30	28
Febrile neutropenia	3	4
Bleeding/hemorrhage	4	4
Mucositis/stomatitis	2	3
Hand foot syndrome	6	2
Thromboembolic	0	1
Alopecia	0	0
Symptomatic cardiac	-	-

### Time to Progression (Anthracycline Exposed)



## Effects of prior thalidomide on response and TTP with bortezomib + PLD

Bortezomib + PLD		
	Thalidomide naïve	Thalidomide exposed
n	194	130
ORR (%)	47	48
TTP (days)	295	270
<ul style="list-style-type: none"> <li>↗ Comparable response and TTP with bortezomib + PLD in patients with and without prior thalidomide</li> <li>↗ No evidence of cross-resistance to prior thalidomide</li> </ul>		

PLD, pegylated liposomal doxorubicin

Sonneveld *et al. Cancer* 2008;112:1529–37

## Bortezomib + PLD

Bortezomib	Phase	n	CR + PR	CR + nCR	Abstract
+ DOXIL <sup>®</sup>	3	324	52%	17%	Harousseau <i>et al. JCO</i> 2007; 25(18S): Abstract 8002 (Oral Presentation)
+ DOXIL + thalidomide	2	23	65%	23%	Chana-Khan <i>et al. ASH</i> 2006; Abstract # 3539

DOXIL<sup>®</sup>, pegylated liposomal doxorubicin

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## Bortezomib and Pegylated Liposomal Doxorubicin (PLD) as Induction Therapy for Adult Patients with Symptomatic Multiple Myeloma: Cancer and Leukemia Group B Study 10301.

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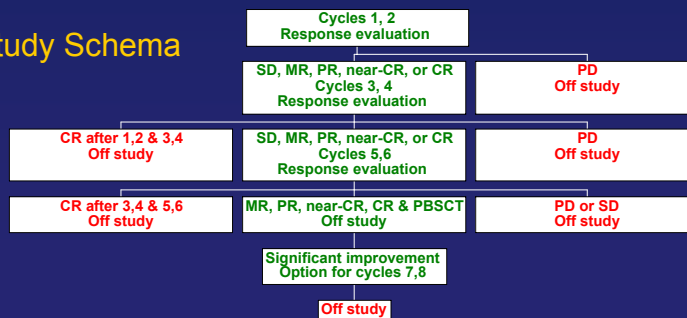
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## Bortezomib / PLD as Induction Therapy for Symptomatic MM: CALGB Study 10301

- ▶ **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/m<sup>2</sup> days 1, 4, 8, 11
  - PLD 30 mg/m<sup>2</sup> day 4

### ▶ Study Schema



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Orlowski et al. ASH 2006, abstract #797

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

### ► Response

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%)
<b>ORR (CR + PR)</b>	<b>58%</b>	<b>79%</b>

- 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

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Orlowski et al. ASH 2006. abstract #797

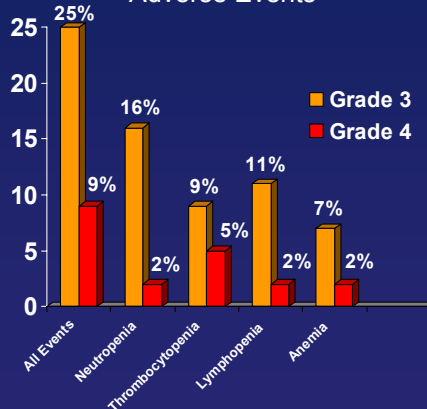
## Bortezomib / PLD as Induction Therapy for Symptomatic MM: CALGB Study 10301

### ► Toxicity:

#### Grade 3/4 Non-Hematologic Adverse Events:

- Grade 3 reported in 58% and Grade 4 in 9%
- Most common included:
  - fatigue (16%)
  - sensory neuropathy (13%)
  - hand-foot syndrome (9%)
  - syncope (9%)

#### Grade 3/4 Hematologic Adverse Events



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Orlowski et al. ASH 2006. abstract #797

## Kortikoid-freie Regime Indikationen

- Hohes Patientenalter und schlechter Allgemeinzustand aufgrund von Komorbiditäten
- Schwer kontrollierbarer Diabetes
- Schwer kontrollierbare arterielle Hypertonie
- Kortison-Empfindlichkeit aufgrund der Persönlichkeitsstruktur (Induktion von Unruhe, psychischer Irritationen bis zu Halluzinationen und Psychosen)
- Gastrointestinale Ulzera in der Anamnese