

The Combination of Pegylated Liposomal Doxorubicin and Bortezomib Significantly Improves Time to Progression and Overall Survival of Patients with Relapsed / Refractory Multiple Myeloma Compared with Bortezomib Alone : Updated Results from a Randomized Phase III Study

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for the DOXIL-MMY-3001 study investigators

Disclosures for All Authors

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Scientific Advisory Board	None

Pre-clinical Rationale

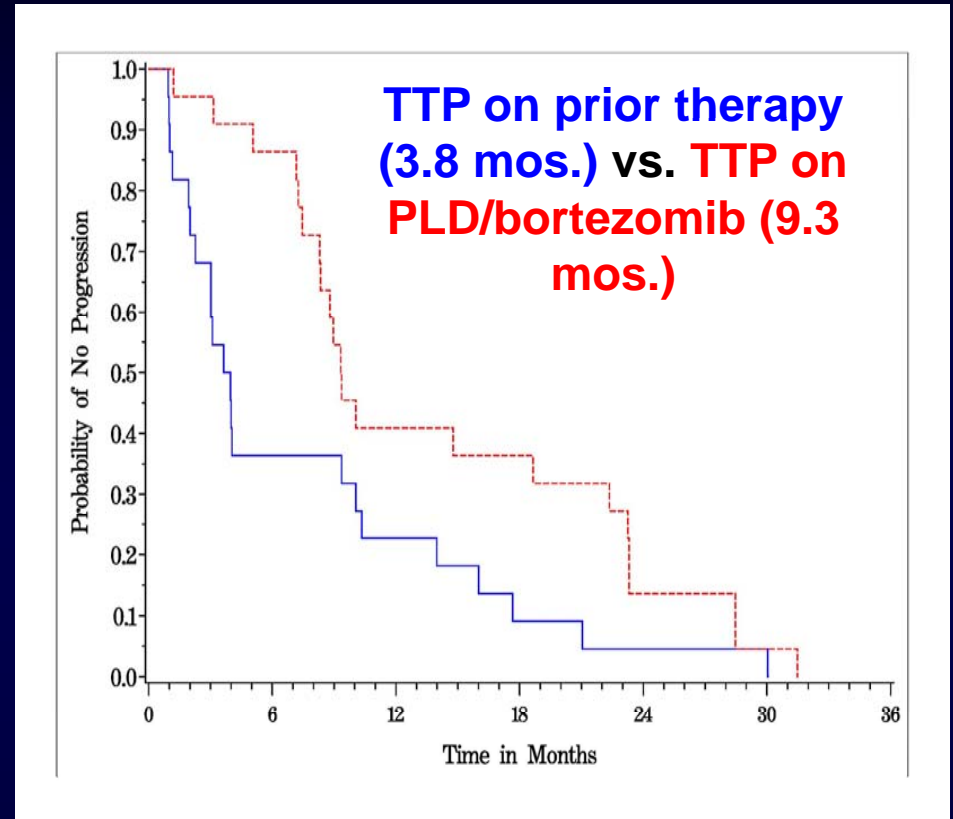
- Interactions occur through multiple pathways to enhance anti-tumor efficacy
 - Bortezomib abrogates anthracycline resistance
 - NF- κ B^{1,2}, Bcl-2, P-glycoprotein, DNA damage repair³
 - Anthracyclines abrogate bortezomib resistance
 - Suppression of stress response protein MKP-1⁴

• Additive or synergistic effects are seen in both *in vitro*^{1,2,3} and *in vivo*⁴ model systems

¹Ma, MH et al. Clin. Cancer Res. 9:1136, 2003. ²Mitsiades, N et al. Blood 101:2377, 2003. ³Hideshima, T et al. Blood 101:1530, 2003. ⁴Small, GW et al. Mol. Pharmacol. 66:1478, 2004.

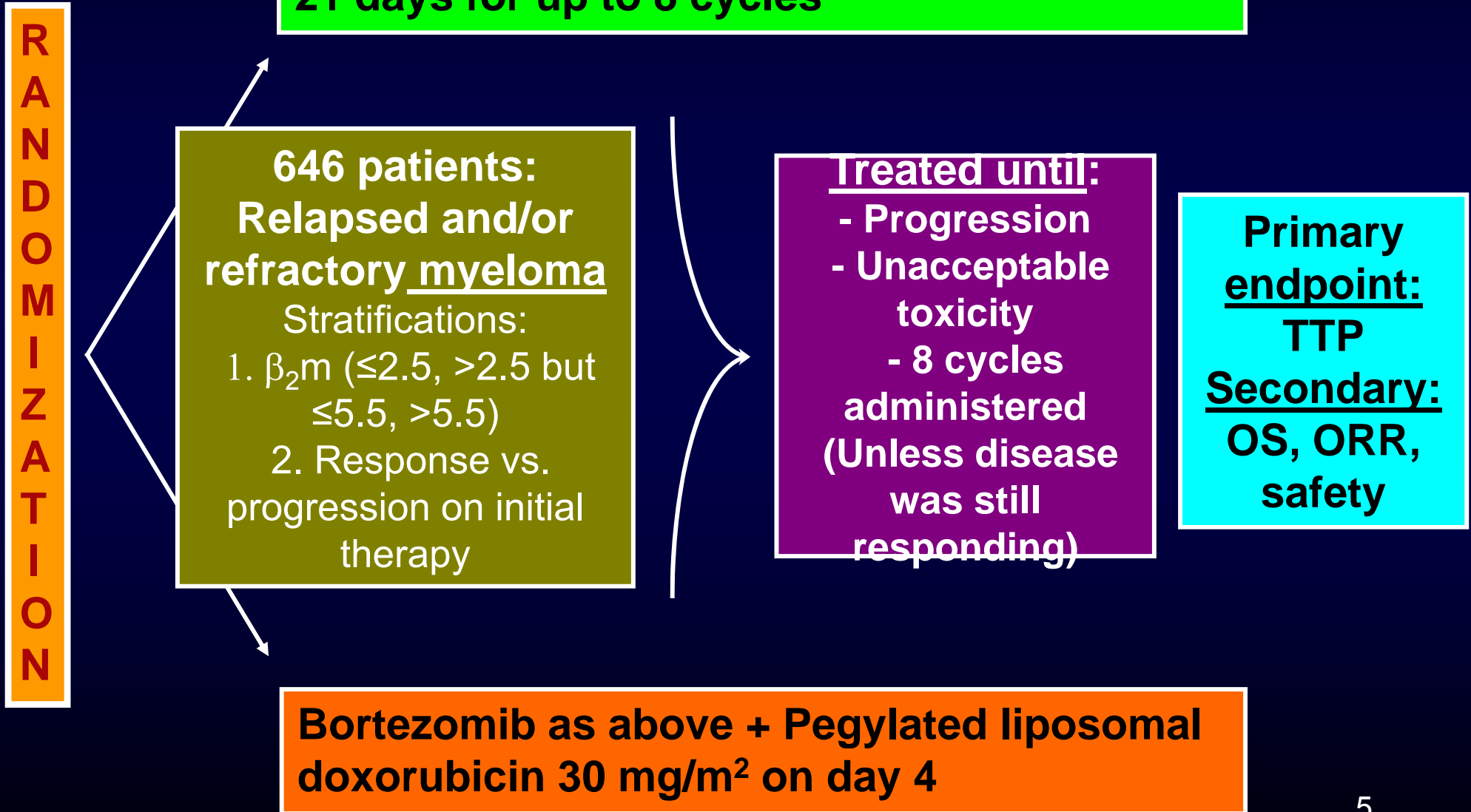
Clinical Rationale

- PLD + bortezomib was well tolerated in phase I¹
 - Bortezomib @ 1.3 mg.m² days 1, 4, 8, 11 q 21 days
 - PLD @ 30 mg/m² day 4
- Enhanced response rate
- Favorable long-term outcome measures²



¹Ortved, RZ et al. Blood 105:3058, 2005. ²Biehn, SE et al. Ann. Hematol. In press and available online, 2006.

DOXIL-MMY-3001 Study Design



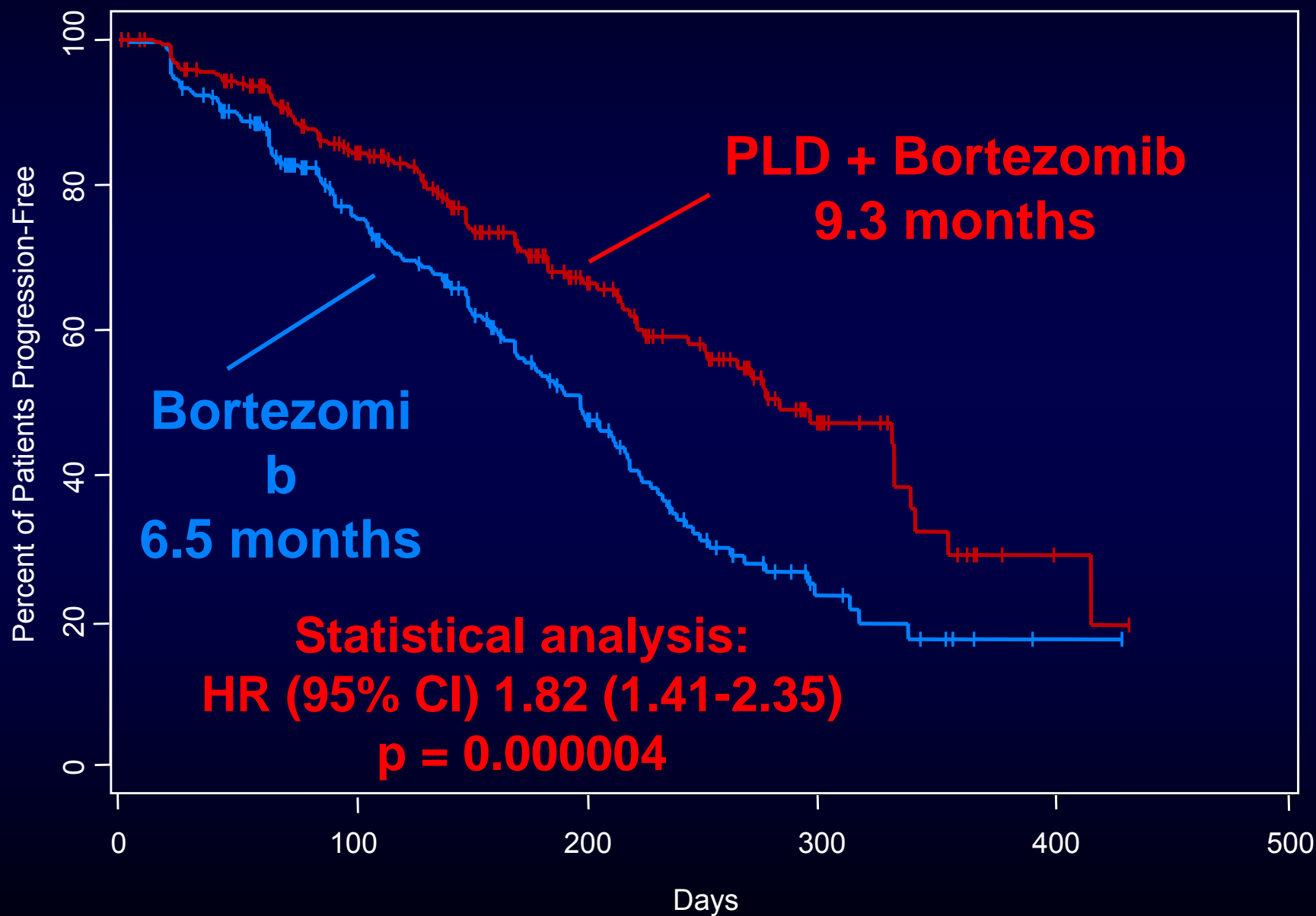
Baseline Characteristics

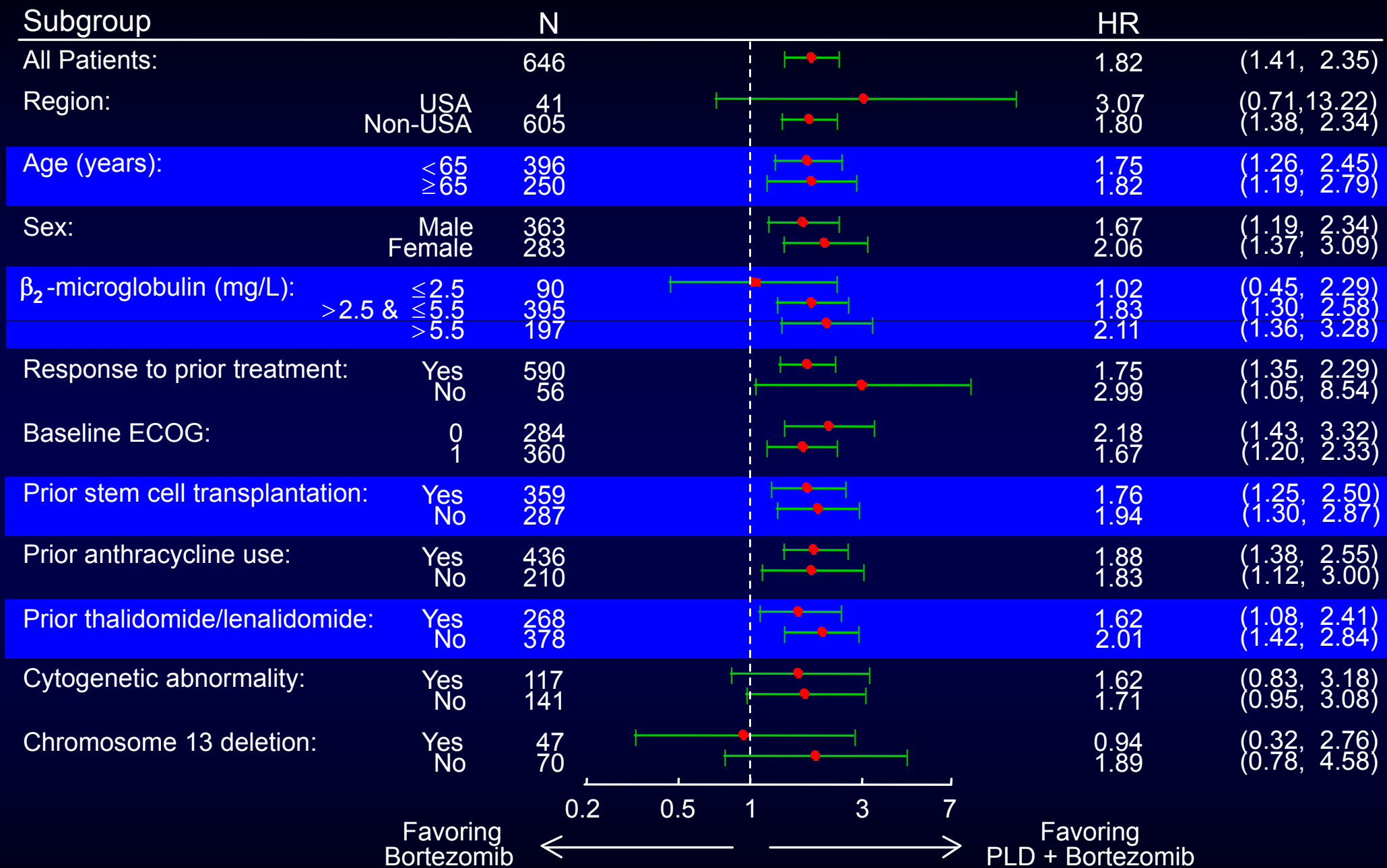
		Bortezomib N = 322	PLD + Bortezomib N = 324
Median age		62 yrs.	61 yrs.
Gender	Male / Female	54% / 46%	58% / 42%
Race	White	94%	90%
MM Type	IgG, IgA/D/M, L-chain	62%, 25%, 12%	57%, 29%, 12%
Time since diagnosis	Median	37.5 mos.	35.2 mos.
β_2-m (mg/L)	≤ 2.5	14%	14%
	$>2.5 - \leq 5.5$	55%	56%
	>5.5	31%	30%
Response to initial therapy	Responded, then progressed	92%	91%
	Primary refractory	8%	9%
Cytogenetic abnormality	Yes	19%	17%
	Not done	58%	58%

Prior Therapies

		Bortezomib (N = 322)	PLD + Bortezomib (N = 324)
# of prior therapies	1 line	34%	34%
	≥ 2 lines	66%	66%
Corticosteroid		99%	99%
Alkylating agents		90%	92%
Anthracyclines		67%	68%
Thalidomide/lenalidomide		43%	40%
Stem cell transplant		54%	57%

Time to Progression





Hazard Ratio (Bortezomib vs. PLD + Bortezomib) & 95% CI (Log Scale)

Summary of IA Results

- Patients treated with PLD + bortezomib combination had 45% reduction in developing disease progression
- Median TTP improved from 6.5 months to 9.3 months with the combination therapy
- OS data was not mature, no statistically significant difference between the two groups
- The Safety profile of the combination consistent with known toxicities of PLD and bortezomib as single agents
- These results were the basis of the recently granted
FDA approval for the combination Doxil/Velcade in relapsed MM

Updated Drug Exposure Data

		Bortezomib (N = 318)	PLD + Bortezomib (N = 318)
Mean # of Cycles	Mean + SD	6.0 + 2.8	5.8 + 2.9
Mean bortezomib dose (mg/m ²)	Mean ± SD	1.23 ± 0.1	1.21 ± 0.1
Mean PLD dose (mg/m ²)	Mean ± SD	N/A	28.9 ± 2.2

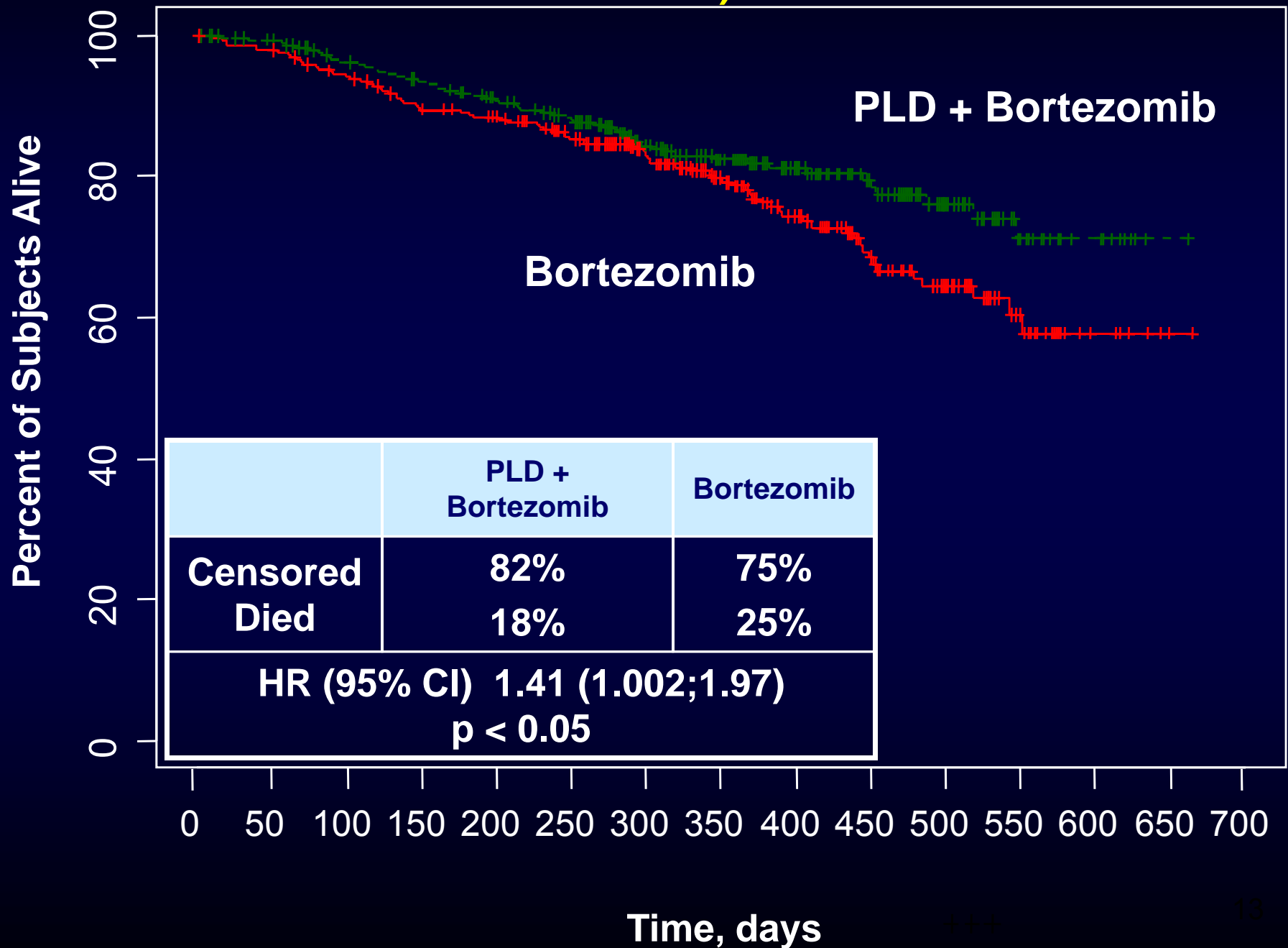
- Addition of PLD did not significantly compromise the ability to administer bortezomib
- Both groups received a median of 6 cycles of therapy, compare with 5 cycles reported at interim analysis

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

Updated Overall Survival (med f-up 14 m)



Updated Overview of AEs

	Bortezomib % (% IA)*	PLD + Bortezomib % (% IA)*
Any AEs	97 (97)	99 (98)
Related AEs	88 (86)	97 (94)
Serious AEs	33 (31)	38 (36)
Related SAEs	16 (15)	22 (22)
AEs with outcome death	4 (3)	4 (4)
AEs leading to PLD discontinuation	N/A	41 (36)
AEs leading to Btz discontinuation	29 (24)	36 (30)

* IA: Interim Analysis Results as reported previously

Updated Overview of AEs

	Bortezomib % (% IA)*	PLD + Bortezomib % (% IA)*
Any AEs	97 (97)	99 (98)
Related AEs	88 (86)	97 (94)
Serious AEs	33 (31)	38 (36)
Related SAEs	16 (15)	22 (22)
Grade ≥ 3	69 (64)	84 (80)
Related Grade ≥ 3	56 (52)	73 (68)
AEs leading to bortezomib discontinuation	29 (24)	36 (30)
AEs leading to PLD discontinuation	N/A	41 (36)
AE with outcome death	4 (3)	4 (4)

* IA: Interim Analysis Results as reported previously

Updated Most Common AE (>15%)

	Bortezomib (N=318)		PLD+Bortezomib (N=318)	
	All % (%IA)	G3/4 % (%IA)	All % (%IA)	G3/4 % (%IA)
Nausea	40 (37)	1 (<1)	48 (46)	3 (2)
Diarrhea	39 (34)	5 (4)	46 (43)	7 (7)
Constipation	31 (28)	1 (1)	31 (28)	1 (1)
Vomiting	22 (19)	1 (1)	32 (31)	4 (4)
Thrombocytopenia	28 (25)	17 (15)	33 (30)	24 (22)
Neutropenia	22 (20)	16 (14)	36 (35)	32 (30)
Anemia	21 (20)	10 (9)	25 (23)	9 (9)
Fatigue	28 (26)	3 (2)	36 (31)	6 (5)
Pyrexia	22 (22)	1 (1)	31 (29)	1 (1)
Asthenia	18 (16)	4 (3)	22 (19)	6 (6)
Anorexia	14 (11)	<1 (0)	19 (18)	2 (2)
Headache	18 (16)	0 (0)	19 (18)	1 (1)
Neuralgia	20 (16)	5 (5)	17 (14)	3 (3)
Cough	12 (11)	0 (0)	18 (16)	0 (0)
Stomatitis	3 (3)	<1 (<1)	18 (18)	2 (2)
Hand foot syndrome	<1 (0)	0 (0)	19 (16)	6 (5)

Updated Selected AEs of Clinical Interest

	Bortezomib (N=318)		PLD+Bortezomib (N=318)	
	Total % (%IA)**	Grade 3/4 % (%IA)**	Total % (%IA)**	Grade 3/4 % (%IA)**
Peripheral Neuropathy *	45 (39)	11 (9)	42 (35)	7 (4)
Febrile Neutropenia	2 (2)	2 (2)	3 (3)	3 (3)
Bleeding/hemorrhage	10 (9)	1 (1)	14 (14)	4 (4)
Thromboembolic Events	1 (1)	1 (1)	1 (1)	1 (1)
Cardiac Events	7 (7)	3 (3)	11 (10)	3 (2)
Alopecia	1 (1)	0 (0)	2 (2)	0 (0)

*Include dictionary derived terms: neuropathy, neuropathy peripheral, peripheral motor neuropathy, peripheral sensory neuropathy, polyneuropathy

** Interim analysis results as reported previously

Conclusions I

- PLD + bortezomib significantly improved TTP and OS in previously treated MM compared with bortezomib monotherapy
- Benefits seen in clinically relevant groups
 - Prior IMiD use, post-transplant
 - Those with high risk features
 - Elevated β_2m , elderly, cytogenetic abnormalities
- Significant improvement in RR (CR+VGPR)

Conclusions II

- Safety and adverse event profile is predictable and manageable
- Increased risk of some adverse events
 - Neutropenia, thrombocytopenia, diarrhea, vomiting, asthenia, fatigue, hand foot syndrome
- No increase in other relevant events
 - Peripheral neuropathy, cardiac events
- Low incidence of thromboembolic events
 - No thromboprophylaxis necessary

Acknowledgements

- The patients who made this study possible
- Investigators, research nurses, and study coordinators at 154 sites in 18 countries
- Johnson & Johnson Pharmaceutical Research & Development

Back up Slides

Response Rates at IA

	Bortezomib (N = 310)	PLD + Bortezomib (N = 303)	p value
Total (CR + nCR + PR)	43%	48%	0.251
CR + nCR	11%	14%	
PR	32%	34%	

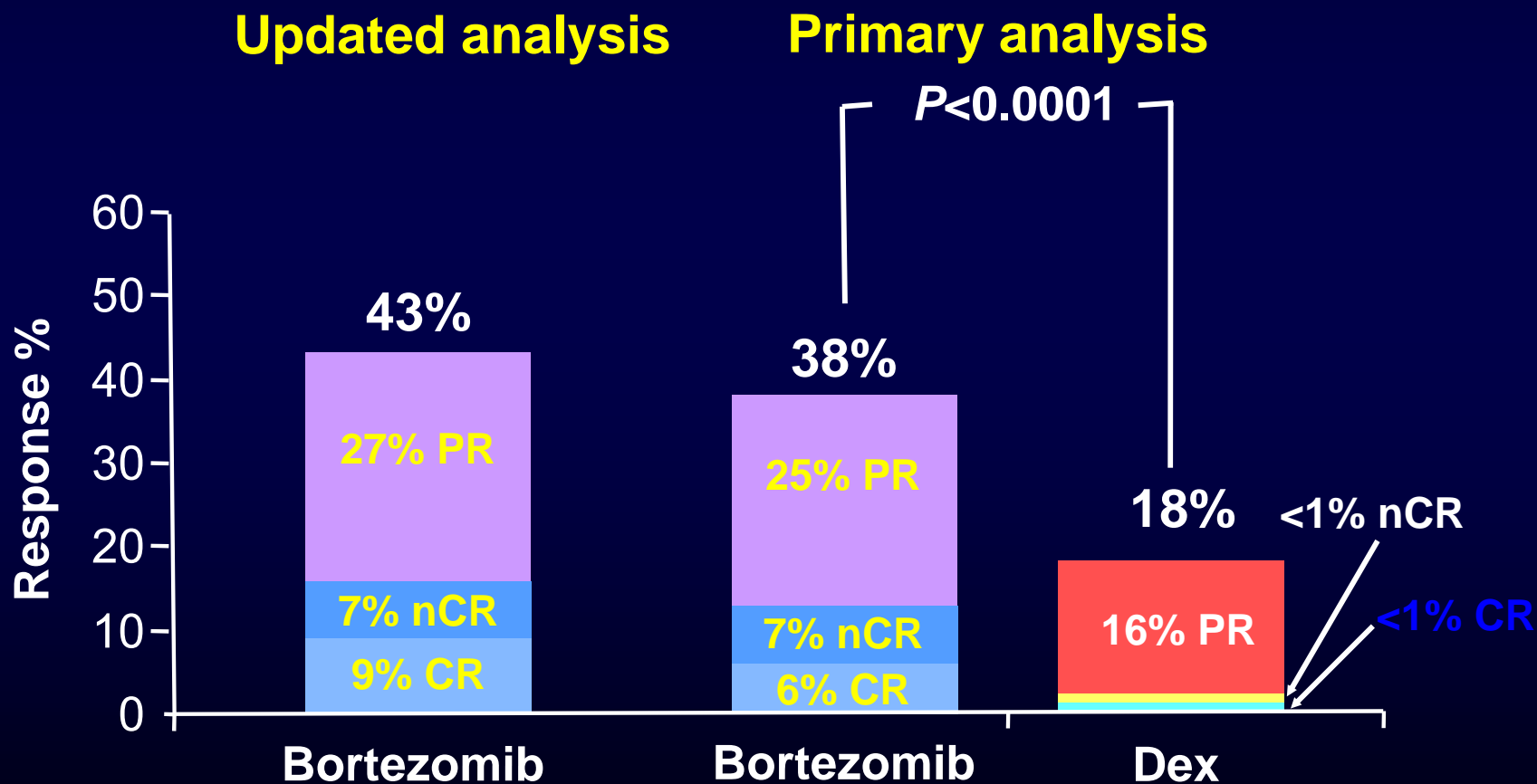
CR + VGPR*	20%	28%	0.0113
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* According to the IMWG 2006 criteria

Updated APEX efficacy data

Response rates

ORR with bortezomib improved from 38% to 43%



Updated APEX survival data

- Superior TTP 6.2m vs 3.5 m
- Superior survival despite cross-over
 - Median OS: bortezomib 29.8 months vs 23.7 months for high-dose Dex ($P=0.0272$)
 - 1-year survival rate: 80% vs 67% ($P=0.0002$)

