Treatment of relapsed/refractory Myeloma

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Treatment of relapsed/refractory myeloma

Backbone of treatment

- **thalidomide**
- **bortezomib**
- **lenalidomide**

Treatment of relapsed/refractory myeloma

- Single agents versus combinations?
- Duration of treatment: fixed cycles or until maximum response?
- Maintenance?

Treatment of relapsed/refractory myeloma

- Since no therapy is curative, all options need to be considered
- No definitive data exist on the optimum treatment sequence or regimen
- Factors to consider
  - prior therapy and response
  - disease manifestations and organ function
  - age, performance status, and comorbidities
  - adverse events due to prior therapies and ease of administration
  - Possible predictive factors, ie poor risk cytogenetics

Definition of relapsed/refractory myeloma

Relapsing myeloma: Clinically active disease after one or more prior therapies but not refractory to the most recent treatment

Anderson et al Leukemia 2008;22:231

Definition of relapsed/refractory myeloma

Refractory myeloma: Includes patients who never achieved minor response or better

- Non-responding, non-progressing: no significant change in myeloma protein and no evidence of clinical progression
- Primary refractory, progressive: symptomatic and/or myeloma protein progression

Anderson et al Leukemia 2008;22:231

Definition of relapsed/refractory myeloma

Relapsed-and-refractory myeloma:

Relapse of disease in patients who must have achieved minor response or better and then progress during treatment or within 2 months after completion of treatment

Anderson et al Leukemia 2008;22:231

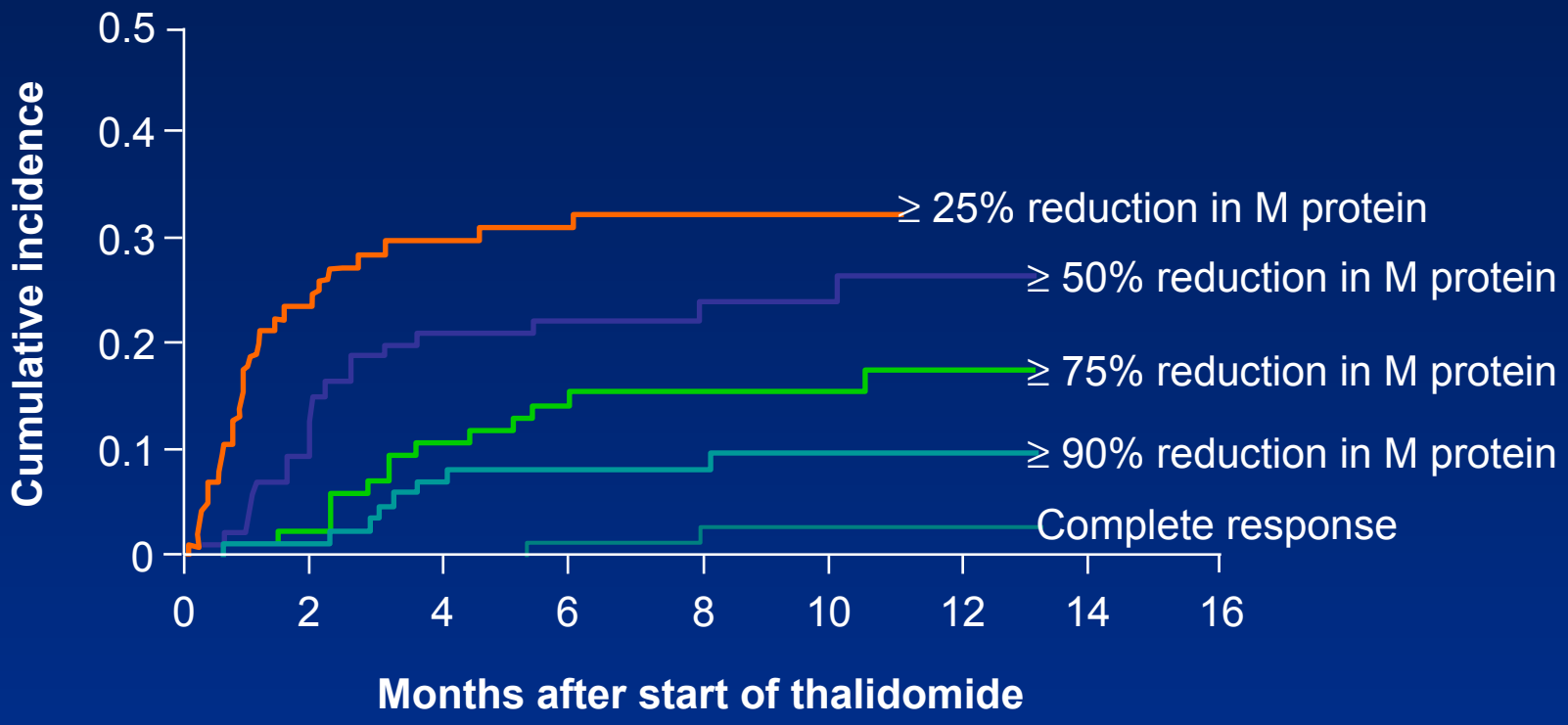
When to start next treatment in relapsed/refractory myeloma

1. Development of new soft tissue plasmacytomas or bone lesions on skeletal survey, CT or MRI
2. Definite increase (ie at least 50% increase and at least 1 cm) of existing plasmacytomas or bone lesions
3. Hypercalcemia (11.5 mg/dl)
4. Decrease in hemoglobin of >2g/dl or to less than 10 gm/dL
5. Rise in serum creatinine by 2 mg/dl or more
6. Hyperviscosity

Consider treatment if a significant monoclonal protein relapse, defined as doubling in two consecutive measurements separated by ≤ 2 months

Anderson et al Leukemia 2008;22:231

Single-agent thalidomide as salvage therapy in MM



Singhal S, et al. N Engl J Med. 1999;341:1565-71.

Thalidomide + dexamethasone combination studies in relapsed/refractory MM

Study	Thal dose, mg/day	Dex dose*	M protein decrease, n/n (%)		
			75–100%	50–75%	25–50%
Palumbo et al. 2001	100	40 mg/day	14/77 (18)	18/77 (23)	19/77 (25)
Dimopoulos et al. 2001	200–400	20 mg/m^2	13/44 (30)	11/44 (25)	1/44 (2)
Alexanian et al. 2002	100–300	20 mg/m^2	12/21 (57)	1/21 (5)	–
Anagnostopoulos et al. 2003 (D resistant)	200–600	20 mg/m^2	22/47 (47)	–	–
Tosi et al. 2004	200	40 mg/day	5/12 (42)	2/12 (17)	2/12 (17)
Hatjiharissi et al. 2004	200	20 mg/m^2	1/25 (4)	17/25 (68)	–
Palumbo et al. 2004	100	40 mg/day	29/120 (24)	33/120 (28)	–
Schütt et al. 2005‡	200–400	20 mg/m^2	5/22 (23)	8/22 (36)	–

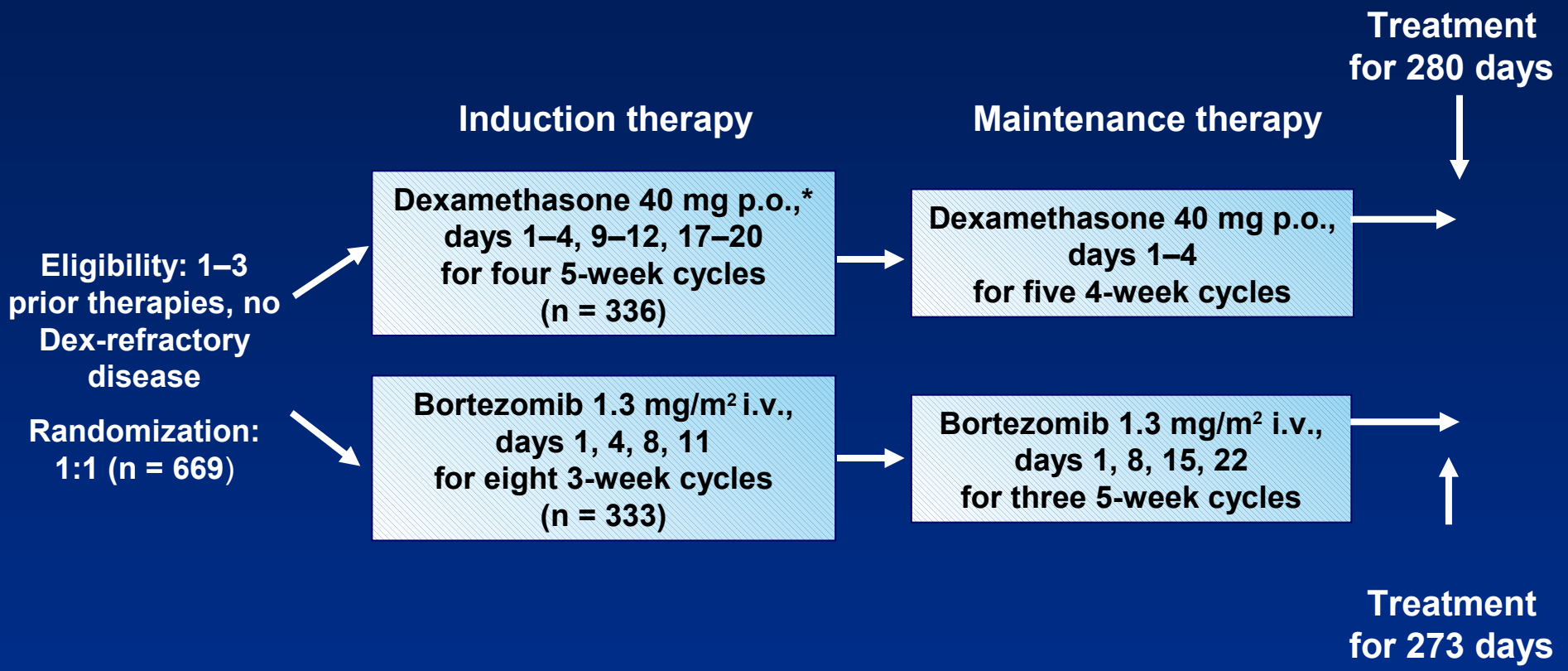
* Pulsed dosing, varies by study.

‡ Outcome parameters are different from others.

Alexanian R, et al. Ann Oncol. 2002;13:1116. Anagnostopoulos A, et al. Br J Haematol. 2003;121:768. Dimopoulos MA, et al. Ann Oncol. 2001;12:991. Hatjiharissi E, et al. Hematol Oncol. 2004;22:159. Palumbo A, et al. Haematologica. 2001;86:399. Palumbo A, et al. Hematol J. 2004;5:318. Schütt P, et al. Ann Hematol. 2005;84:594. Tosi P, et al. Eur J Haematol. 2004;73:98.

Bortezomib vs high-dose dexamethasone in relapsed MM

APEX international phase III study



* Patients with progressive disease on Dex were eligible to cross over to bortezomib in a companion study.

Richardson PG, et al. N Engl J Med. 2005;352:2487-98.

Updated results from the APEX trial

Response	Bortezomib[1] (n = 315)	Dexamethasone[1] (n = 312)	Bortezomib[2] at 14 months follow-up (n = 315)
ORR, %	38	18	43
CR	13% 6	0.6	16% 9
nCR	7	1	7
PR	32	17	34
Median TTP, months	6.2	3.5	6.2
Median TTR, months	1.4	1.4	1.4
Median response duration, months	8.0	5.6	7.8

Survival*	Bortezomib	Dexamethasone‡	p value
Median OS, months	29.8	23.7	0.027
1-Year survival rate, %	80	67	0.002

*Median follow-up 22 months; death rate 44%.
‡More than 62% of patients on dexamethasone crossed over to bortezomib.

TTR = time to response.

1. Richardson PG, et al. N Engl J Med. 2005;352:2487-98.
2. Richardson PG, et al. Blood. 2007;110:3557-60.

Pegylated liposomal doxorubicin + bortezomib vs bortezomib alone in previously treated MM

MMY-3001: a randomized, phase III, international, multi-centre study

Inclusion criteria (N = 646)

- PD after response to ≥ 1 prior therapy or refractory to initial treatment
- ECOG performance status 0 or 1
- Platelet count ≥ 75,000/mm^3
- Haemoglobin ≥ 8.0 g/dl
- Absolute neutrophil count ≥ 1,000/mm^3
- Creatinine clearance rate ≥ 30 ml/min
- Bortezomib-naive
- No progression on prior anthracyclines

Bortezomib 1.3 mg/m^2, days 1, 4, 8, and 11 (n = 322)

Bortezomib 1.3 mg/m^2, days 1, 4, 8, and 11 Doxorubicin 30 mg/m^2, day 4 (n = 324)

21-Day cycle → For 8 cycles or until PD or adverse event

Primary end-point: TTP

Secondary end-points: OS, PFS, CR + PR, safety

ECOG = Eastern Cooperative Oncology Group;
PFS = progression-free survival.

Data from Orlowski RZ, et al. J Clin Oncol. 2007;25:3892-901.

Bortezomib ± pegylated liposomal doxorubicin in previously treated MM: response

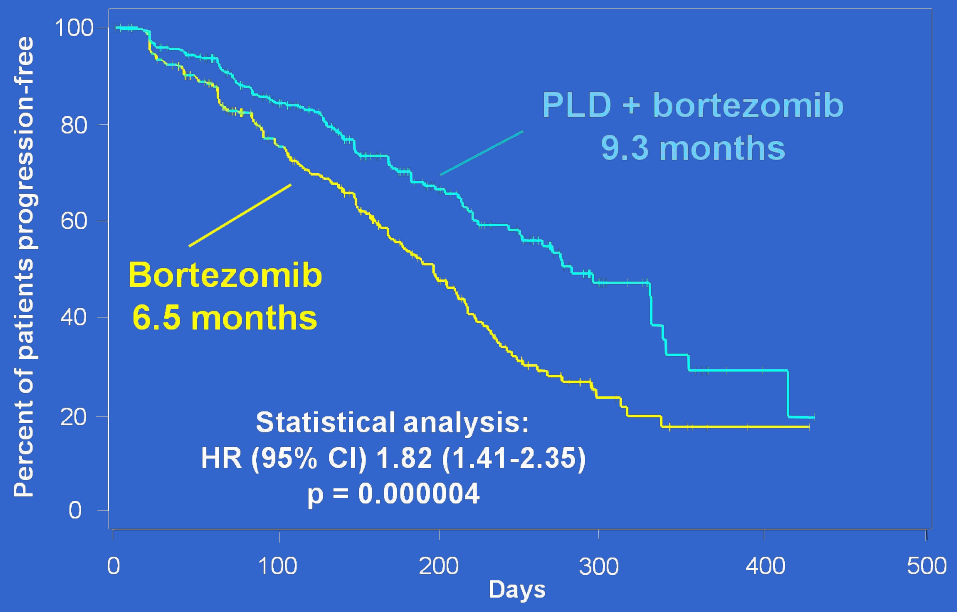
Response	Bortezomib alone (n = 322)	Bortezomib + doxorubicin (n = 324)	p value
CR, %	2	4	
nCR, %	8	9	
CR + VGPR, %	19	27	0.0157
PR, %	39	40	
CR + PR, %	41	44	0.43
Median duration of CR + PR (95% CI), days	213 (180–254)	311 (309–394)	0.0008

CI = confidence interval;
VGPR = very good partial response.

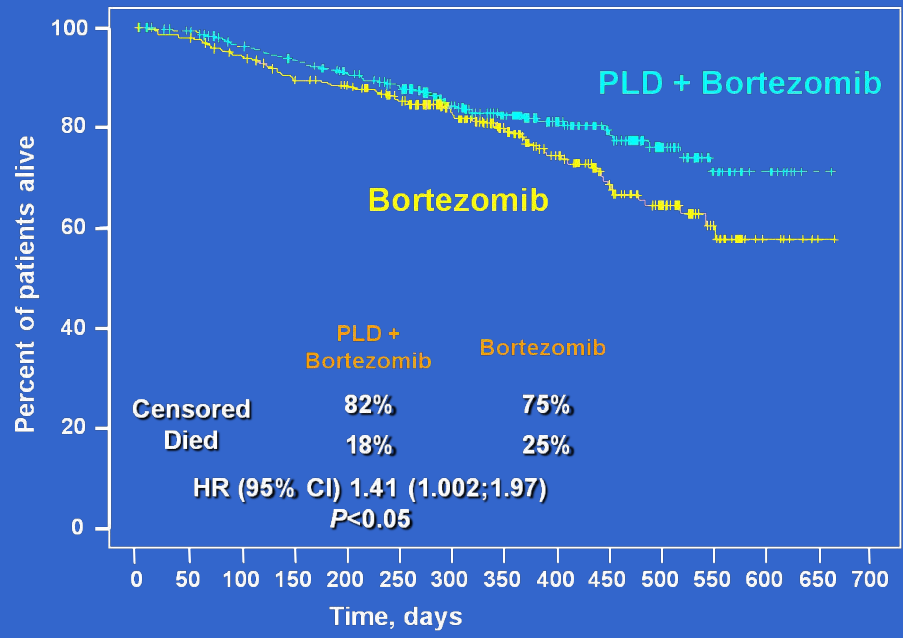
Data from Orlowski RZ, et al. J Clin Oncol. 2007;25:3892-901.

Phase III: Bortezomib + DOXIL® vs bortezomib

Time to progression



Overall survival



DOXIL: approved in United States in combination with bortezomib in patients who have not previously received bortezomib and have received at least one prior therapy

CAELYX: EMEA is recommending adoption of new indication: in combination with bortezomib for the treatment of progressive MM in patients who have received ≥1 prior therapy and who have already undergone, or are unsuitable for, bone marrow transplant

http://www.emea.europa.eu

PLD, pegylated liposomal doxorubicin

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

Combinations of Bortezomib with chemotherapy in Rel/Ref MM

Combination	N	ORR	CR	
Bortezomib intermediate-dose dex and continuous low-dose oral cyclophosphamide	50	82%	16%	Kropff et al. Br J Haematol 2007;138:330–337
Bortezomib, Bendamustine Prednisone	46	61%	15%	Poenisch *et al.* ASH 2007 (abstract 2723)
Bortezomib, Melphalan, Dexamethasone	32	78%	≥VGPR 40%	Popat et al. EHA 2008 (Abstract 918)
Bortezomib Plus Oral Cyclophosphamide and Prednisone	19*	89%	53%	Reece et al J Clin Oncol 2008; 26:4777-4783
Bortezomib , Dexamethasone, Bendamustine	50	84%	NR	Fenk *et al.* *Leuk Lymphoma* 2007; 48:2345–51

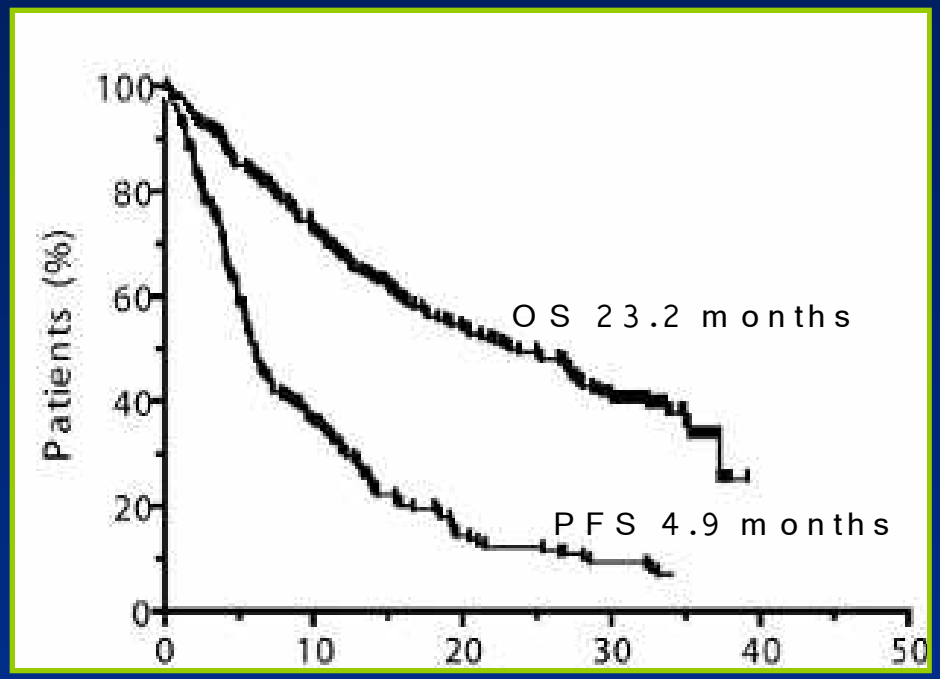
* At MTD

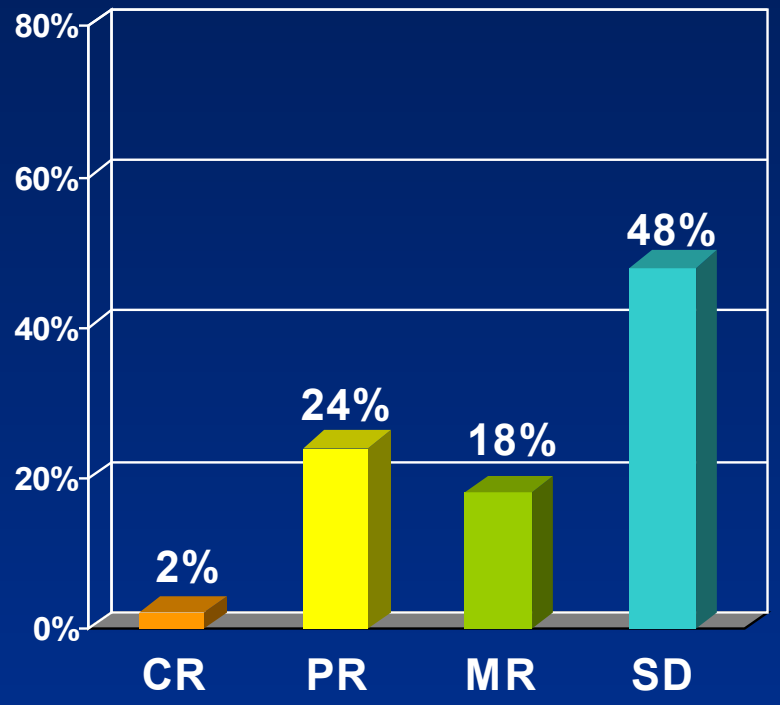
Combinations of bortezomib with thalidomide in Rel / Ref MM

Combination	N	ORR (≥PR)	CR	
Bortezomib, doxil, thalidomide (VDT)	23	65%	23%	Chanan-khan et al ASH 2006
Bortezomib, Thalidomide Dexamethasone	85	55%	16% ≥ nCR	Zangari et al ASH 2005
Bortezomib, Melphalan, Thalidomide and prednisone (VMPT)	30	66%	17% , VGPR 27%	Palumbo et al Blood 2007
Bortezomib, Melphalan, Dexamethasone and intermittent Thalidomide (VMDT)	62	66%	13%, VGPR 27%	Terpos et al Leukemia 2008

Lenalidomide single agent in Relapsed & Refractory MM

N=222 patients with relapsed & refractory MM





Richardson et al Blood 2009

Lenalidomide + Dexamethasone in relapsed/refractory MM (MM-009 and MM-010 phase III trials)

North American MM-009 (48 centres USA, Canada)
International MM-010 (50 centres Europe, Australia, Israel)

Inclusion criteria

- ≤ 3 prior therapies
- No Dex resistance
- Normal hepatic and renal function

Len 25 mg days 1–21
Placebo days 22–28
Dex 40 mg days 1–4, 9–12, 17–20

× 4 courses

Placebo days 1–28
Dex 40 mg days 1–4, 9–12, 17–20

Continue until PD

Same, except Dex days 1–4

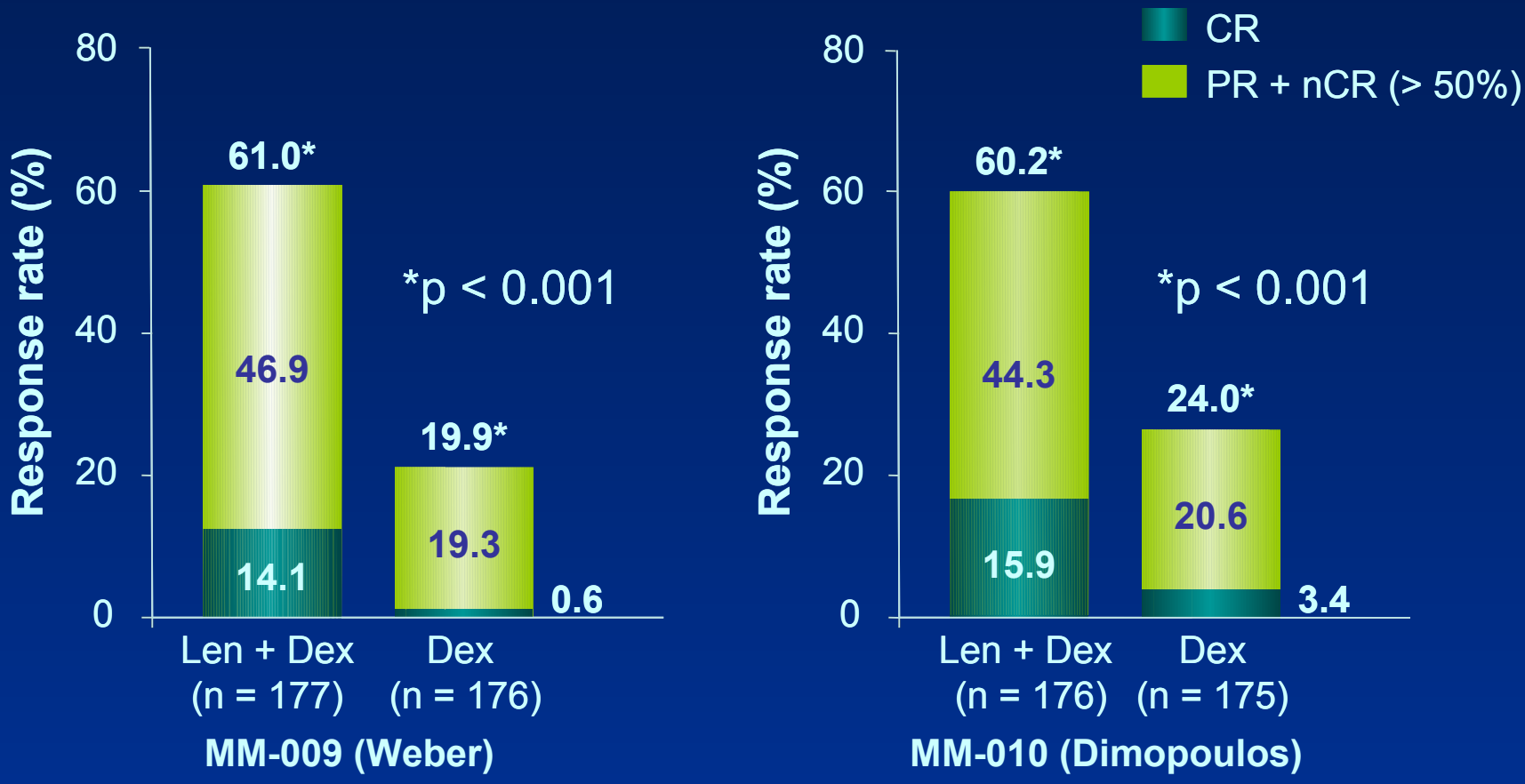
Primary end-point: TTP (by Bladé criteria)
Secondary end-points: OS, RR, safety, 1st skeletal-related event, PS

Additional stratification by β_2M concentration (≤ 2.5 mg/ml vs > 2.5 mg/ml), prior transplant (0 vs ≥ 1), and prior MM treatment regimens (< 1 vs ≥ 1)

Dimopoulos M, et al. N Engl J Med. 2007;357:2123-32.
Weber DM, et al. N Engl J Med. 2007;357:2133-42.

MM-009 and MM-010: response rates

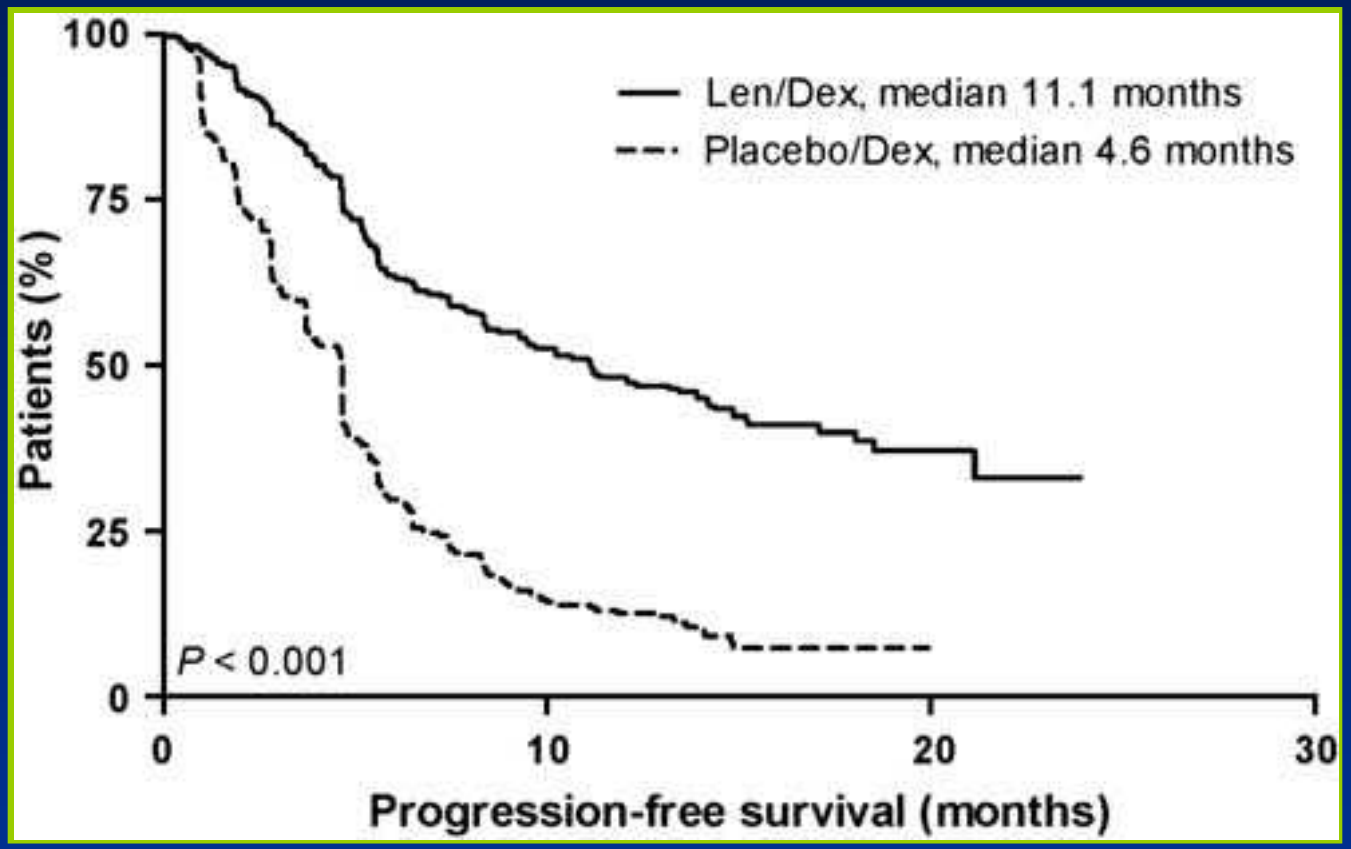
EBMT response data



Dimopoulos M, et al. N Engl J Med. 2007;357:2123-32.
Weber DM, et al. N Engl J Med. 2007;357:2133-42.

Long term follow up of MM-009 & MM-010 phase III trials

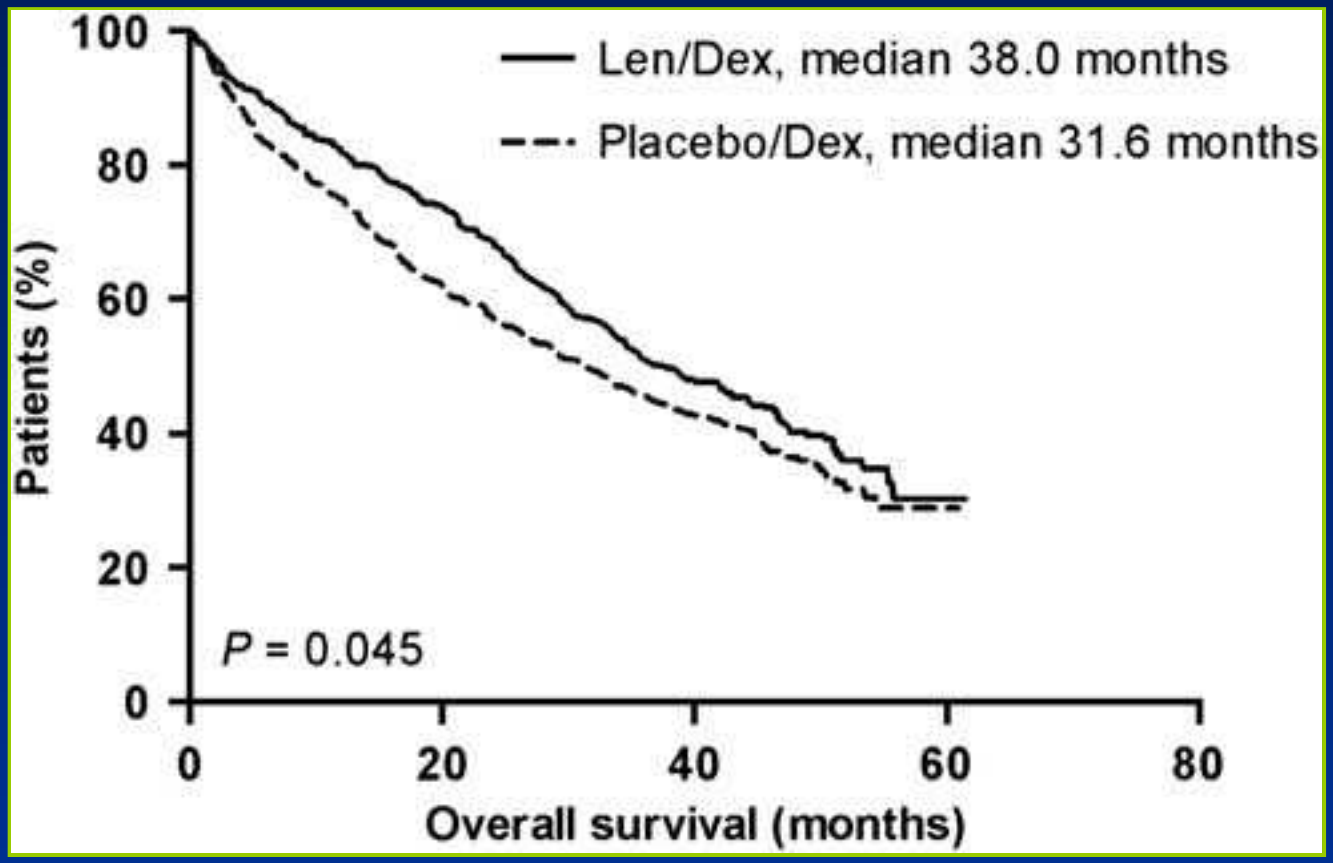
Progression Free survival



Dimopoulos et al Leukemia 2009

Long term follow up of MM009 & MM010 phase III trials

Overall survival



Dimopoulos et al Leukemia 2009

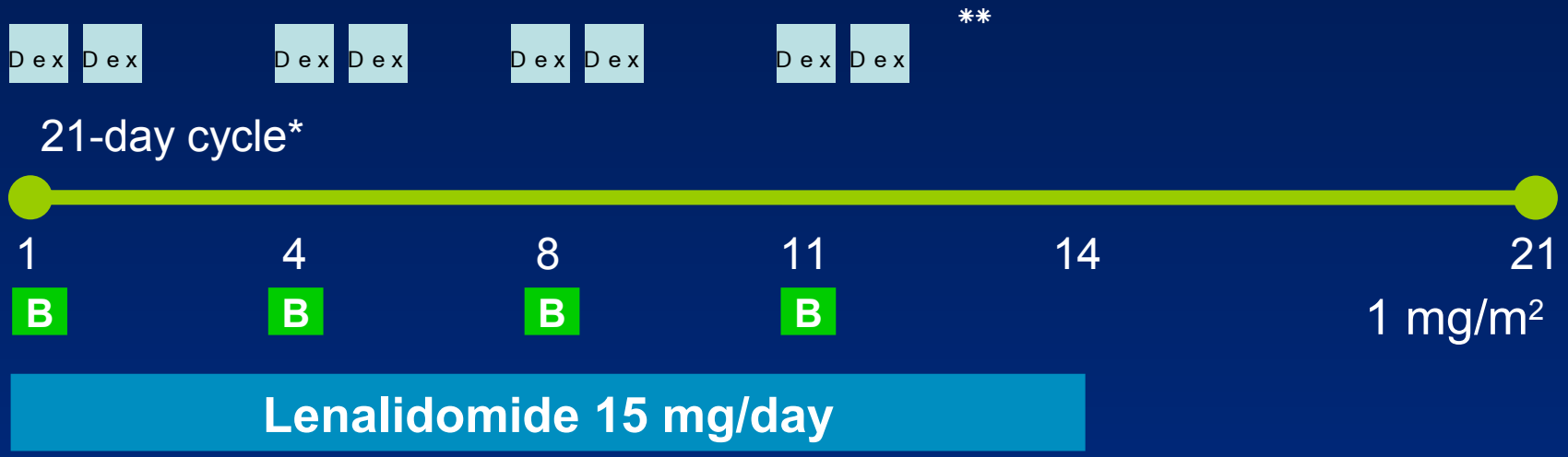
Combinations of Lenalidomide with chemotherapy

Combination	N	ORR / ≥VGPR	
Lenalidomide, PL Doxorubicn, Vincristine Dexamethasone	50*	75%** / 29% (CR+nCR)	Baz et al Ann Oncol 2006
Lenalidomide, adriamycin, and dexamethasone	47*	77% / 74%	Knop et al Blood 2009
Lenalidomide. Cyclophosphamide Dexamethasone	31	81% / 36%	Schey et al ASH 2008
Lenalidomide. Cyclophosphamide PO Dexamethasone	13	77% / 8%	Reece et al ASH 2008

*Phase II, at MTD

**Modified Southwest Oncology Group responses

Phase II trial of Len with bortezomib and Dex in relapsed/refractory MM: trial design

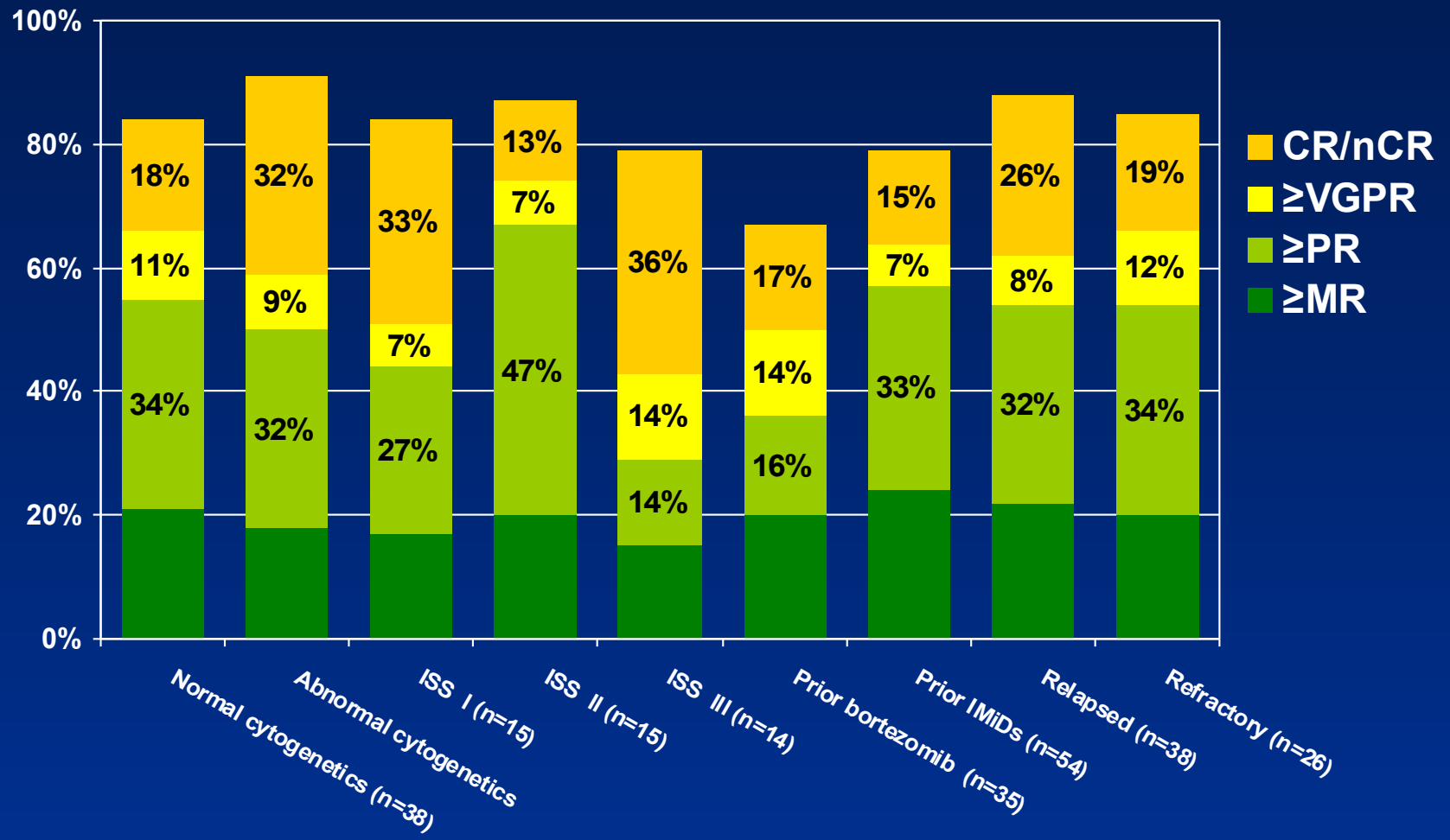


*Patients received antithromobotic and antiviral prophylaxis.

** Dex 40 mg cycles 1–4, 20 mg cycles 5–8

Anderson KC et al ASCO 2009

Lenalidomide, bortezomib, and dexamethasone in rel/ref MM



Anderson KC et al ASCO 2009

Lenalidomide, Melphalan, Prednisone and Thalidomide (RMPT)

Lenalidomide 10 mg/day on days 1–21,
Melphalan 0.18 mg/kg on days 1–4,
prednisone at 2 mg/kg on days 1–4.
Thalidomide 50 mg/day or 100 mg/day days 1–28.
Aspirin 100 mg/day
} every 28 days X 6 courses.
Maintenance Lenalidomide alone at 10 mg/day on days 1–21.

N= 44 patients with rel or ref MM

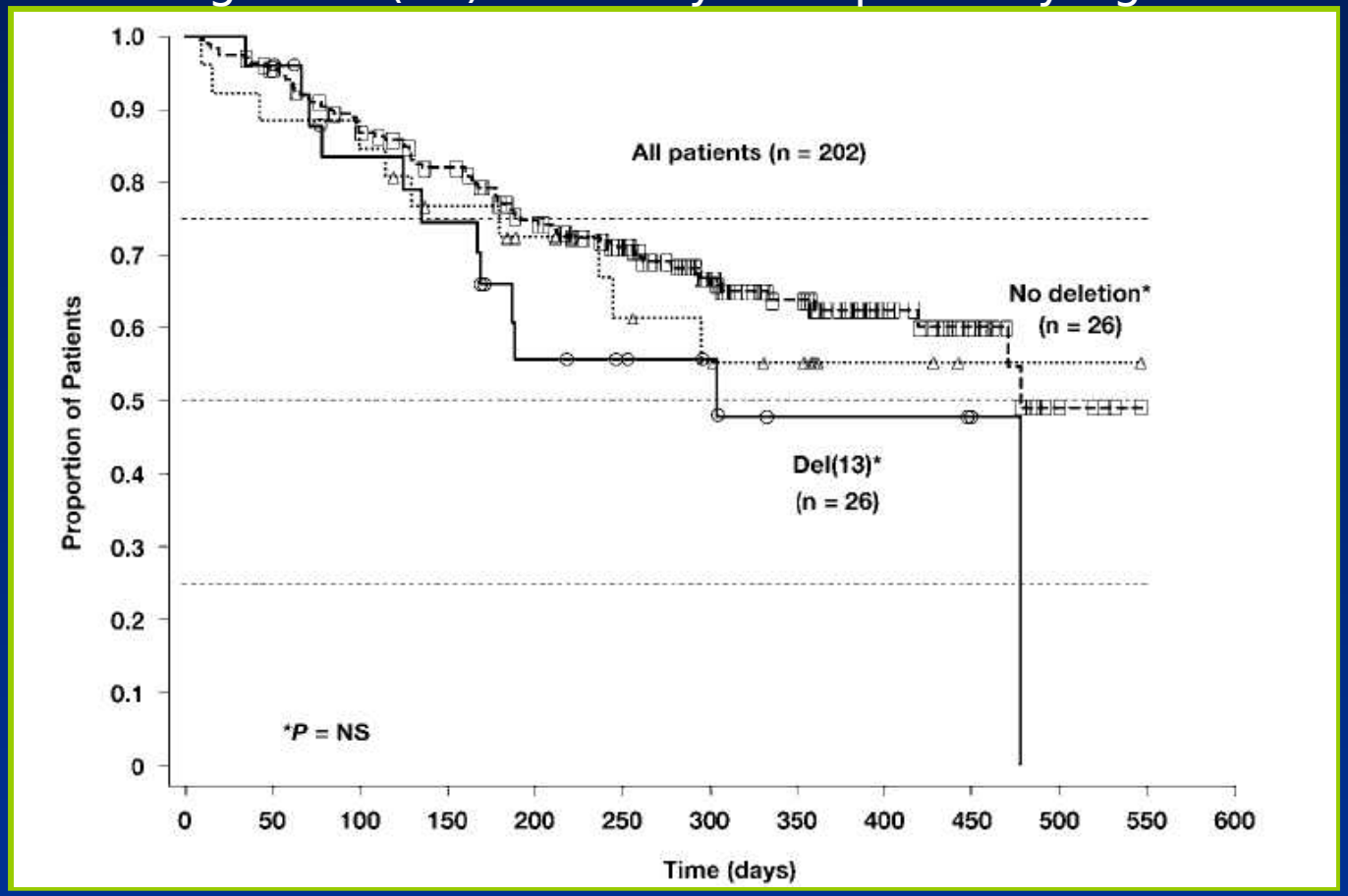
59% received RMPT as 2nd line,41% as 3rd line.
23% prior thalidomide, 20% prior bortezomib
≥(PR) in 76% , VGPR in 30%
Thalidomide 100 mg, ≥PR rate 93.3% (VGPR 46.7%)
Thalidomide 50 mg ≥PR 64.7%
The 1-year- PFS was 48.6% and the 1-year OS 90%.

Palumbo et al ASH 2008

Impact of cytogenetics

Impact of del13 (metaphase cytogenetics) in patients with Rel / Ref MM treated with Bortezomib

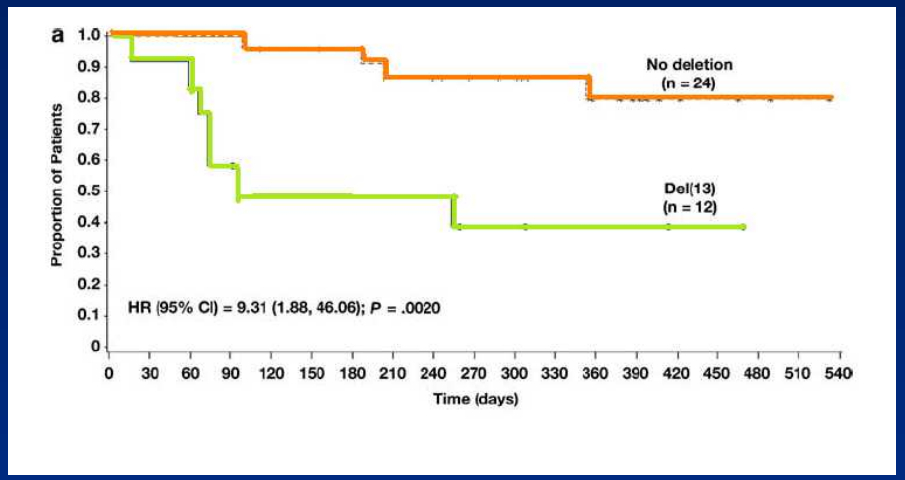
OS in all 202 patients, and matched-pairs patients in the SUMMIT trial according to del(13) status by metaphase cytogenetics.

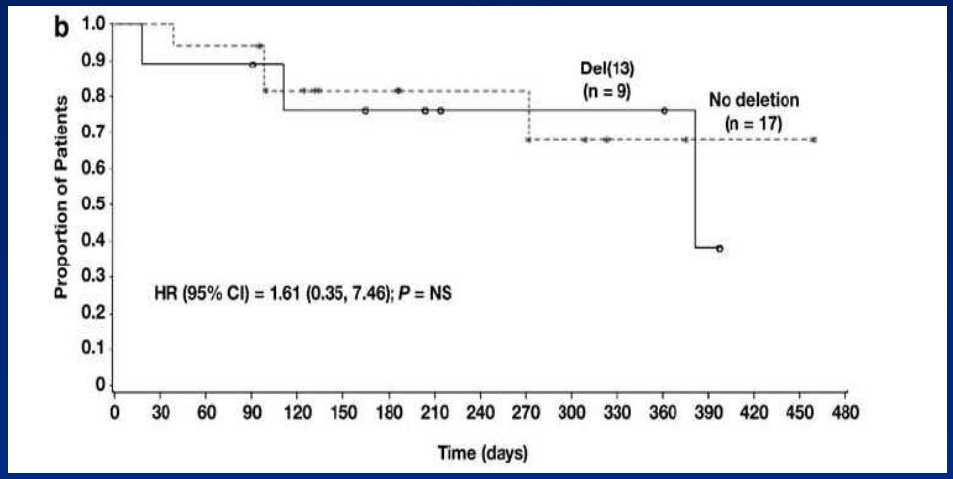


Jagannath et al Leukemia 2007

Impact of del13 (metaphase cytogenetics) in patients with Rel / Ref MM treated with Bortezomib

APEX trial: OS in matched-pairs patients in the according to del(13) status by metaphase cytogenetics (a) in dexamethasone-treated patients; (b) in bortezomib-treated patients.





Jagannath et al Leukemia 2007

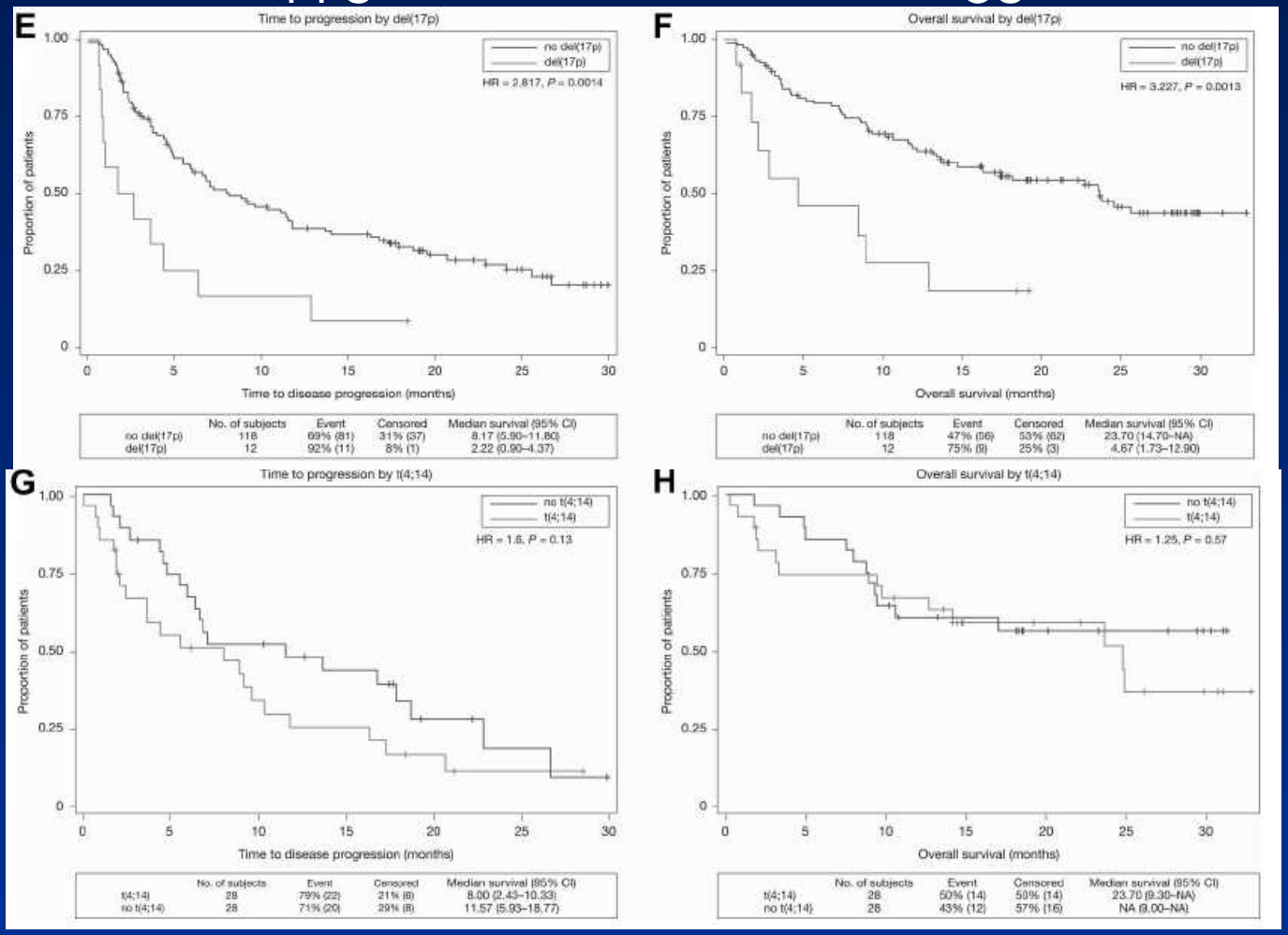
Bortezomib: Impact of cytogentic abnormalities (FISH)

Cytogenetic Abnormality	N of evaluable cases	Response if CA present	Response if CA negative	P-value
Del13q	39	10/13 (77%)	13/26 (50%)	0.15
t(4;14)	40	4/6 (67%)	19/34 (56%)	0.68
t(11;14)	40	2/6 (33%)	21/34 (62%)	0.17
Amp CKS1B	36	8/12 (67%)	13/24 (57%)	0.72

Chang et al Leukemia Research 2007

Len/Dex in patients with rel/ ref MM
Impact of del17p

PFS OS

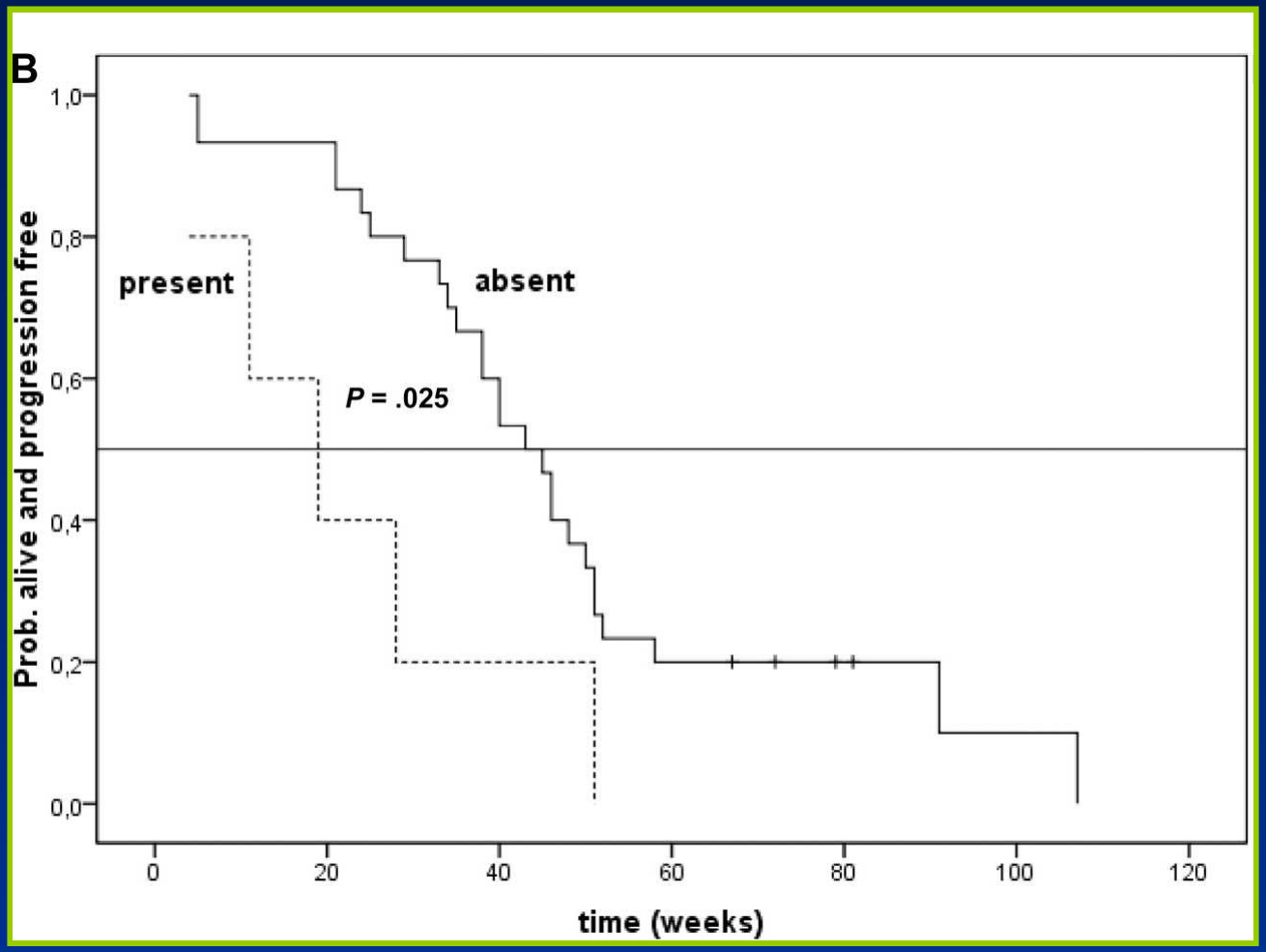


del17p

t(4;14)

Reece et al Blood 2009

Lenalidomide Doxorubicin Dexamethasone Impact of del17p

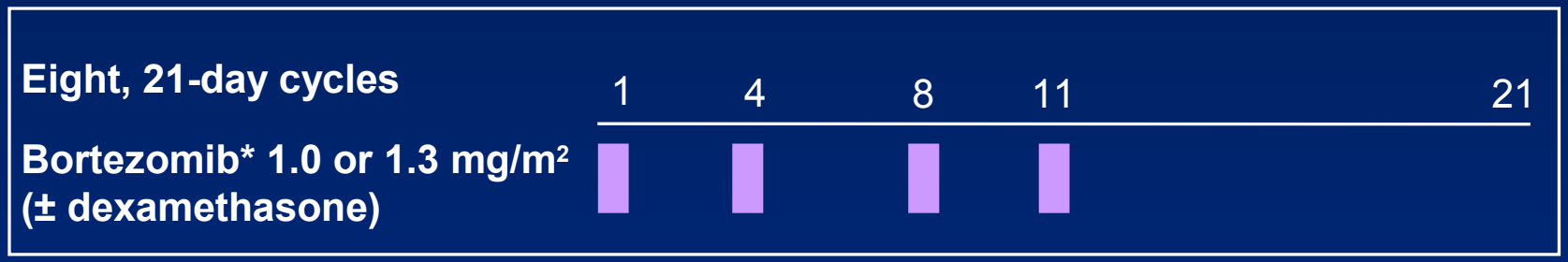


Knop et al Blood 2009

Impact of prior treatments

MMY-2036 RETRIEVE Phase II study: bortezomib retreatment after initial response

Patients who responded to prior bortezomib treatment and relapsed after ≥6 months



Study objectives	Sample size: n=128
Primary	Best response rate
Secondary	Safety, best confirmed M-protein response, DOR, TTP

*Depending on prior dose of bortezomib
DOR, duration of response

Petrucci et al. ASH 2008 (Abstract 3690)

Phase 2 RETRIEVE study: Results

- **Patients (n=130)**
  - **Response to previous bortezomib: 27% CR, 73% PR**
  - **Median treatment-free interval since previous bortezomib: 14.3 months**
- **Results**

Single best response to bortezomib retreatment by serum or urine M-protein analysis (N=124)

	Serum	Urine
Evaluable patients	105	62
CR + PR	61%	60%
CR	10%	34%
PR	50%	26%
CR + PR + MR	83%	79%
MR	22%	19%
No change	12%	16%
PD	5%	5%

Petrucci et al. ASH 2008 (Abstract 3690)

Bortezomib + vorinostat for patients with MM who previously received bortezomib

- Patients (n=13) previously treated with bortezomib (not within 3 months prior to study enrollment)
- Treatment (3+3 design for ≤8 cycles; cycles repeated every 21 days)
  - Vorinostat 200 mg bid or 400 mg
  - Bortezomib dose escalation: 0.7−1.3 mg/m^2
  - Dexamethasone 20 mg (for disease progression)

- Results
  - Best response: PR (n=5), MR (n=1), SD (n=7)
  - Drug-related AEs in 11/13 patients
    - 90% AEs mild to moderate, 5 patients with serious AEs (7 events)
    - Grade 4 thrombocytopenia (n=1), Grade 3 drug-related AEs (n=8)
    - Most common toxicities (any grade): fatigue, nausea, diarrhea
    - Eleven patients discontinued treatment: 6 due to PD, 5 due to AEs

In patients who have relapsed while on, or were refractory to, previous bortezomib therapy, the combination of bortezomib and vorinostat (+/- dex) shows activity with acceptable tolerability

Weber et al. ASH 2008 (Abstract 3711)

Phase 1/2: Bortezomib + Perifosine in patients who previously received bortezomib

- Patients (n=84)
  - median age 63 years
  - 83% had relapsed/refractory MM (median 5 lines of prior treatment)
    - 69% bortezomib-refractory disease
    - Prior therapy: Bortezomib (100%), dex (98%), thalidomide (74%), lenalidomide (75%) and SCT (57%)
- Treatment:
  - Perifosine 50 mg qd
  - Bortezomib 1.3 mg/m^2 (d 1, 4, 8, 11) in 21-d cycles
  - Dex 20mg (on day of and after each Bortezomib dose) added in patients with PD

Richardson et al. ASH 2008 (Abstract 870)

Phase 1/2: Bortezomib + Perifosine in patients who previously received bortezomib

		CR/nCR	PR	MR	ORR	SD	PD
All Patients: Best response	n=72	4%	17%	17%	38%	40%	22%
Median TTP (all patients)	6.3 months						
Median TTP in patients with ≥ MR	8.8 months						

- **Median time to response: 5 cycles (range: 2-8)**
- **81% previously treated with bortezomib plus dexamethasone**

Richardson et al. ASH 2008 (Abstract 870)

Phase 1/2: Bortezomib + Perifosine in patients who previously received bortezomib

		CR/nCR	PR	MR	ORR	SD
Bortezomib refractory: Best response	n=52	2%	12%	17%	31%	44%
Median TTP (all patients)	6.2 months					
Median TTP for patients with ≥ MR	9.4 months					

- **Median time to response: 6 cycles (range: 2-8)**
- **83% bortezomib/dexamethasone refractory**
- **Combination well tolerated; most common grade 3/4 toxicities: cytopenias, pneumonia, renal dysfunction, joint pain**
  - **No therapy-related mortality**
  - **Low treatment-emergent neuropathy (16%)**
  - **Manageable gastrointestinal toxicity, hyponatremia, hyperglycemia**
  - **Infrequent dose reductions**
  - **Expected toxicity profile**

Richardson et al. ASH 2008 (Abstract 870)

Effects of prior thalidomide exposure on response, TTP and OS with Len/Dex

	No prior exposure to thalidomide		*P*	Prior exposure to thalidomide		*P*
	Len/Dex (n=226)	Dex (n=204)		Len/Dex (n=127)	Dex (n=147)	
CR	19%	2.5%	-	7.9%	1.4%	-
VGPR	19.5%	4.4%	-	13.4%	0.7%	-
PR	26.1%	20.6%	-	32.3%	12.2%	-
ORR	64.6%	27.5%	<0.001	53.5%	14.3%	<0.001
DOR (median)	16.2 months	7.9 months	0.003	13.4 months	5.1 months	0.004
TTP (median)	13.9 months	4.7 months	<0.001	8.4 months	4.6 months	<0.001
PFS (median)	13.2 months	4.7 months	<0.001	8.4 months	4. 6 months	<0.001
OS (median)	36.1 months	32 months	0.04	33.3 months	28.7 months	ns

For patients treated with Len/Dex, TTP and PFS were significantly longer in patients without prior exposure to thalidomide (TTP: *P*=0.004, PFS: *P*=0.02)

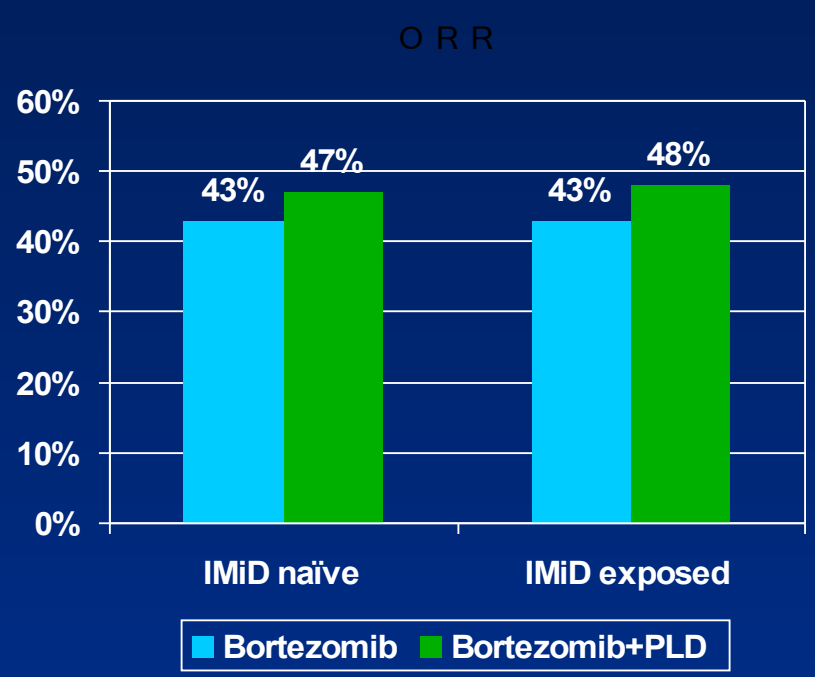
Wang et al. Blood 2008; 112:4445-4451

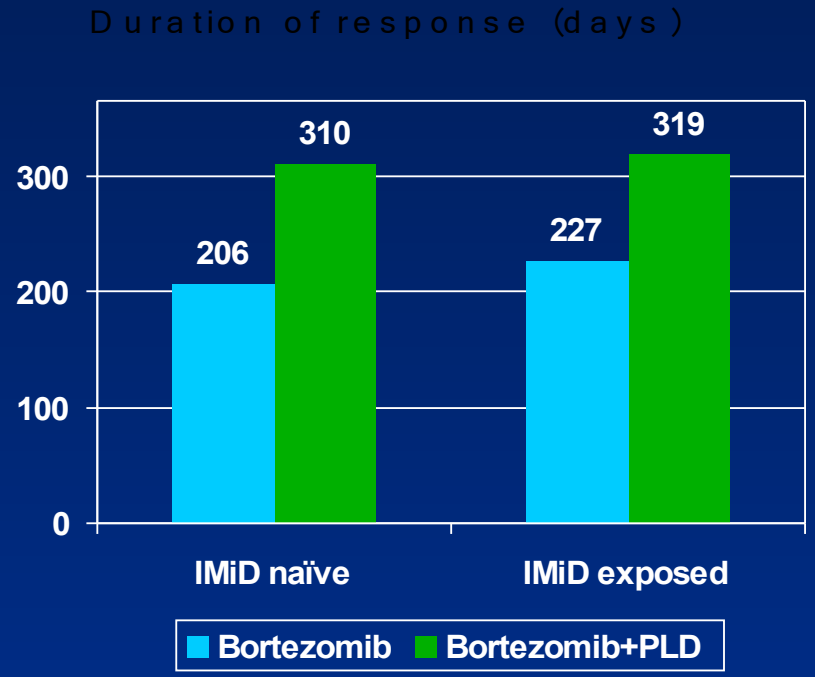
Len + Dex outcome according to prior Thal resistance

	Best response ≥SD, who never progressed on thalidomide (n = 54)	Thalidomide-relapsed patients with best response ≥SD, who progressed on thalidomide (n = 31)	Progressed on thalidomide and never responded to prior thalidomide treatment (n = 20)
OR rate, %	64.8	41.9	50.0
CR+VGPR	24.1	19.3	25
Median response duration (95% CI),weeks	58.1 (30.4 - NE)	38.1(22.9-NE)	NE (26.1- NE)
Responders only	**n = 35**	**n = 13**	**n = 10**
Median TTP (95% CI), months	9.3 (5.6 to 18.0)	7.8(5.6 - 12.1)	7.2 (6.0 - NE)
Median PFS (95% CI), months	9.3 (5.6 to 18.0)	7.8(5.2 - 11.1)	7.0 (4.9 - 16.9)
Median OS (95% CI), months	NR (33.3, NE)	25.7(19.5, NR)	29.3 (21.2- 36.7)

Wang M, et al. Blood. 2008

Bortezomib +/- Pegylated liposomal Doxorubicin
Impact or prior IMiD treatment

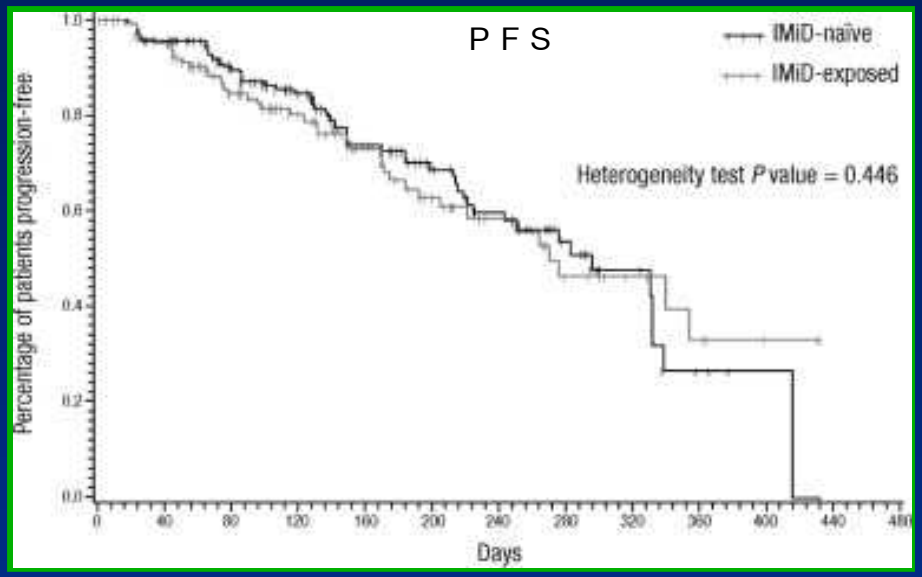




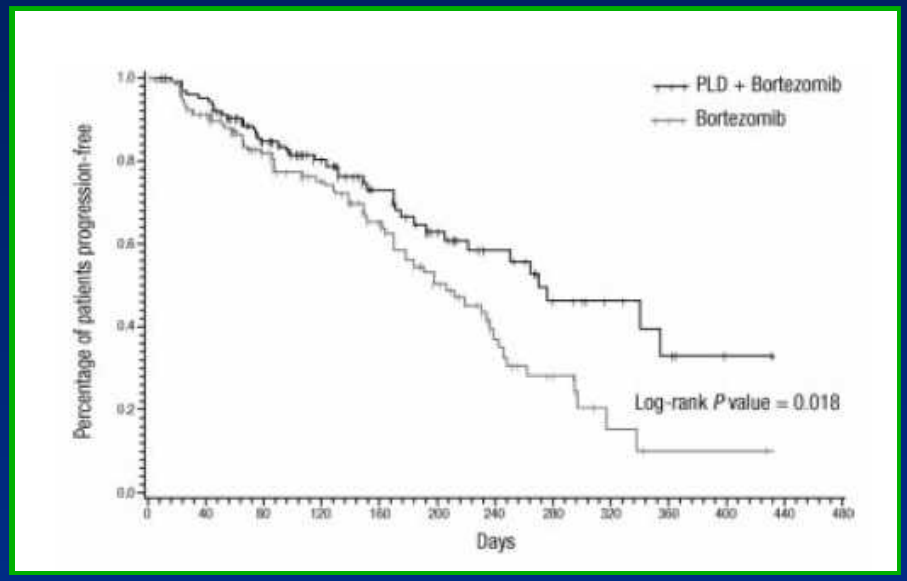
Sonneveld et al Cancer 2008

Bortezomib +/- Pegylated liposomal Doxorubicin
Impact or prior IMiD treatment

Bortezomib + PL Doxorubicin: Impact of prior IMiD treatment on PFS



Bortezomib + PL Doxorubicin vs bortezomib alone in IMiD pretreated patients on PFS



Sonneveld et al Cancer 2008

Renal Impairement

Thalidomide in patients with renal impairment/failure

Thalidomide

- Small amount cleared by kidneys[1]
- Pharmacokinetics are similar in patients with renal failure[2]
- Can be used in renal failure[3]
  - n=20; CR + PR 45%
  - Toxicity profile similar to patients with normal renal function
  - Recovery of normal renal function in most responsive patients
- May cause severe hyperkalemia in some patients with renal failure[4]

1. Izzedine et al. Nephrol Dial Transplant 2005;20:2011–2012
2. Eriksson et al. J Pharm Pharmacol 2003;55:1701–1706
3. Tosi et al. Eur J Haematol 2004;73:98–103
4. Harris et al. Br J Haematol 2003;122:160–161

Lenalidomide in patients with renal impairment/failure

- Primarily excreted by kidneys
- Patients with creatinine levels >2.5 mg/dL excluded from Phase 3 trials
- Subanalysis of phase 3 Len/dex trials[1]
  - Significantly reduced survival in patients with severe renal impairment

	No RI CrCl >80 mL/min (n=158)	Mild RI CrCl 50≧ – <80 mL/min (n=125)	Moderate RI CrCl 30≧–<50 mL/min (n=42)	Severe RI CrCl <30 mL/min (n=16)
ORR	64%	64%	62%	50%
OS	Not reached	34.7 months	30.4 months	18.6 months*
Lenalidomide dose reductions for AEs	17%	34%	40%	38%

*P<0.01 vs no RI

- Increased toxicity in patients with high creatinine levels[1,2]
  - Particularly ≥Grade 3 thrombocytopenia
- Dose reduction in patients with impaired renal function is mandatory[3,4]

1. Weber et al. ASCO 2008 (Abstract 8542)
2. Reece et al. Blood 2006;108 (abstract 3548)
3. Revlimid SmPC June 2007
4. Chen et al. J Clin Pharmacol 2007;47:1466–1475

Len + Dex in patients with a creatinine clearance above or below 50 ml/min

Retrospective subgroup analysis of patients with impaired renal function enrolled in MM-009 and MM-010

- no significant differences in RR, TTP, or OS between patients treated with Len + Dex with a creatinine clearance (CLCr) above or below 50 ml/min
- in 16 patients treated with Len + Dex who had a CrCl of < 30 ml/min, median TTP and OS were shorter than for those with a CLCr > 30 ml/min

Renal function, CL_{Cr} (ml/min)	Grade 3 and 4 thrombocytopenia, %	p value
< 50	13.8	
≥ 50	4.6	< 0.01
< 30	18.8	
≥ 30	5.5	< 0.05

There were no differences for grade 3 and 4 neutropenia at either cut-off.

Weber D, et al. Blood. 2006;108 [abstract 3547].

Recommended dose adjustments at the start of lenalidomide therapy in patients with impaired renal function

	Renal function (CL_{Cr})	Lenalidomide dose adjustment
Mild renal impairment	($CL_{Cr} \geq 50$ ml/min)	25 mg once daily*
Moderate renal impairment	($30 \leq CL_{Cr} < 50$ml/min)	10 mg once daily
Severe renal impairment	($CL_{Cr} < 30$ ml/min, not requiring dialysis)	15 mg every other day
End-stage renal disease	($CL_{Cr} < 30$ ml/min, requiring dialysis)	5 mg daily (following dialysis)

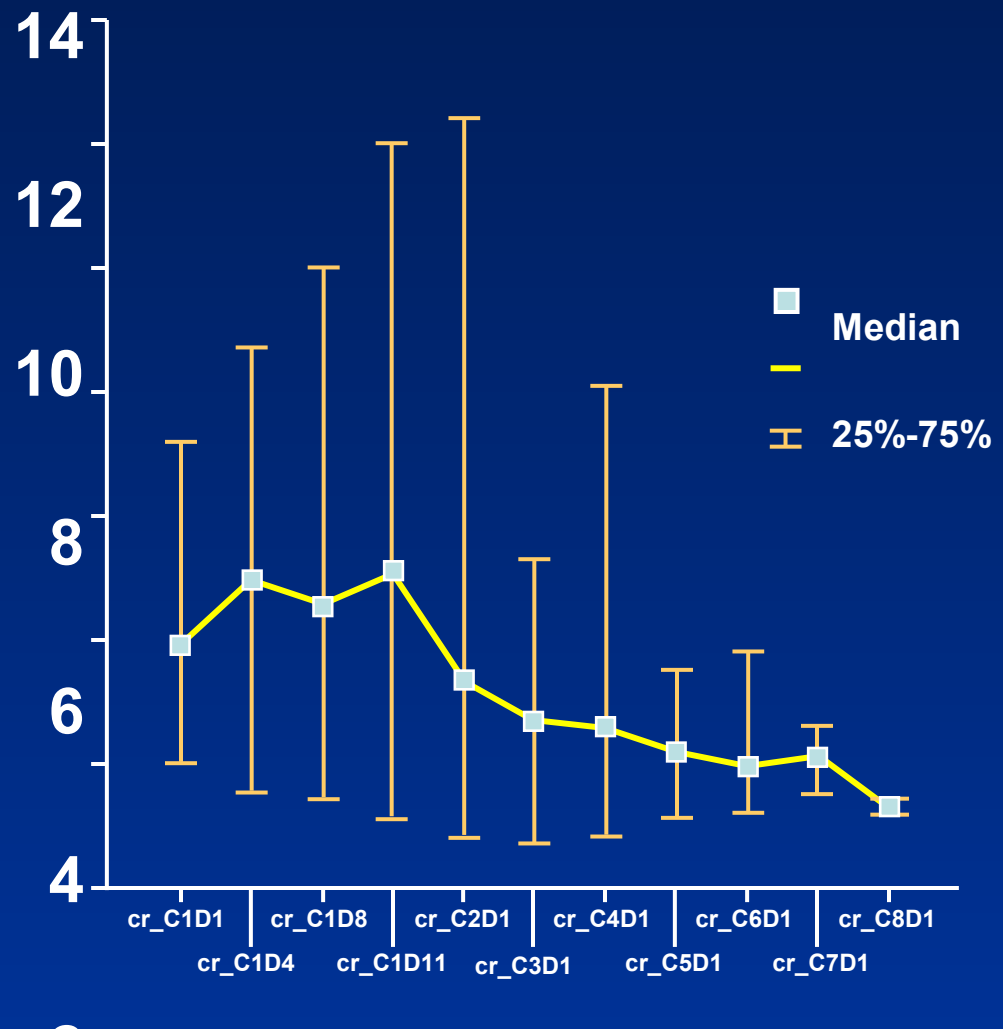
* Full dose

Revlimid SmPC 2009

Studies of bortezomib in MM patients with renal impairment/failure

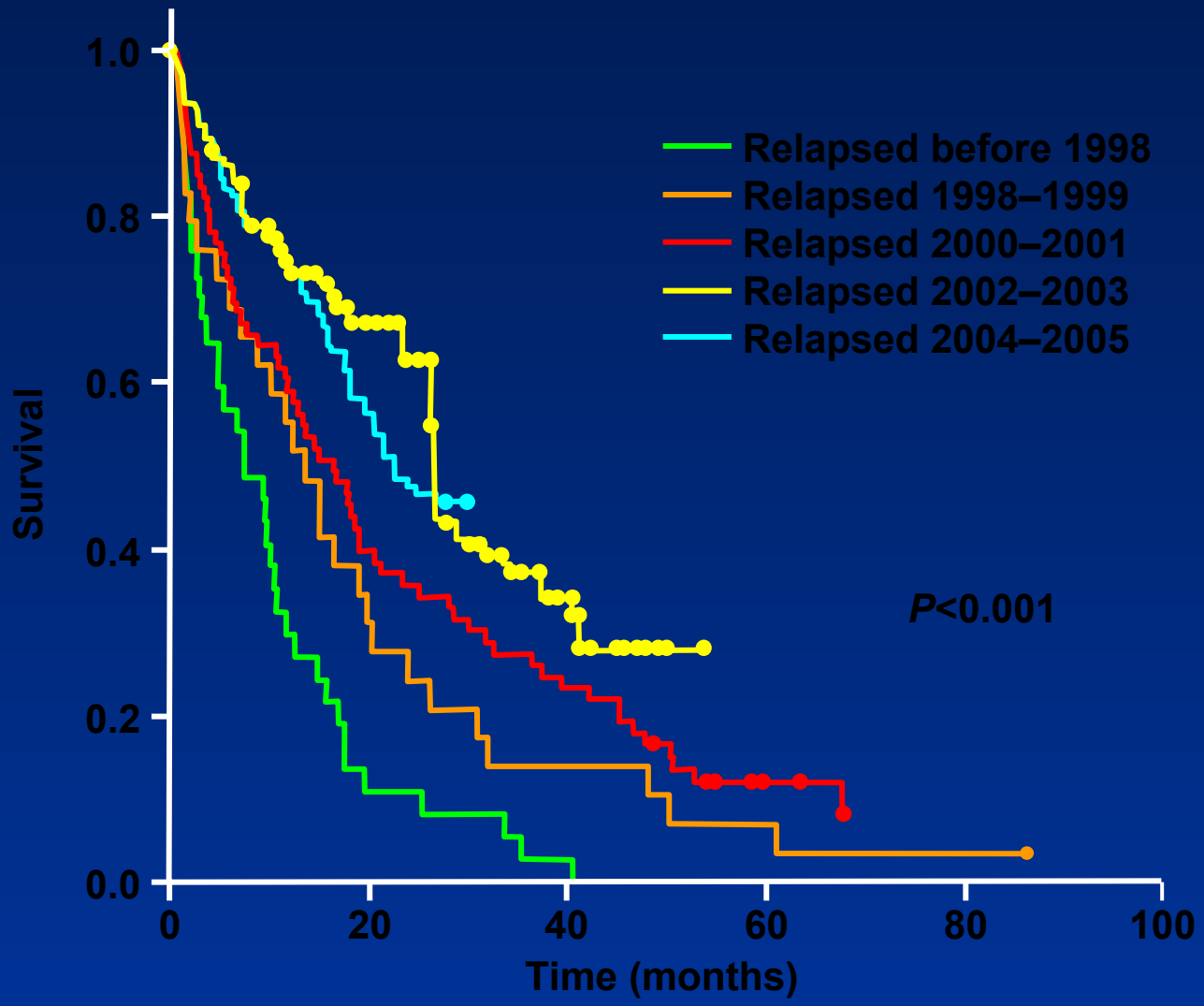
Study details	Patients with renal impairment (n)	Dialysis pts (n)	Outcome
Jagannath *et al. Cancer* 2005;103:1195–2000 (SUMMIT, CREST subanalysis)	151		• Bortezomib effective • Manageable toxicities
San Miguel *et al.* Leukemia 2008 (APEX subanalysis)	62		• Efficacy, safety, TTP, OS not substantially affected in moderate-to- severe renal impairment
Chanan-Khan *et al. Blood* 2007; 109:2604–2606		24	• High response rate • Manageable AEs
Mulkerin *et al. Blood* 2007;110:(Abstract 3477)	34	9	• Bortezomib clearance independent of renal function
Ailawadhi *et al. Blood* 2007;110:(Abstract 1477)	54	3	• No significant association between renal function and response to treatment
Ludwig *et al. Haematologica* 2007;92:1411–1414	3	5	• Reversal of renal failure in 5 out of 8 patients
Ludwig *et al. Blood* 2007;110:(Abstract 3603)	37	9	• Reversal of acute renal failure in 41% of patients
Dimopoulos et al *et al. CLM 2009*	46	9	• Renal response in 59% of patients within a median of 11 days. 2/9 patients became dialysis-independent.

Median serum creatinine by cycles after treatment with bortezomib-based regimens



Roussou *et al*. Leukemia & Lymphoma 2008

Impact of novel agents on outcome in relapsed/refractory disease (n=387)



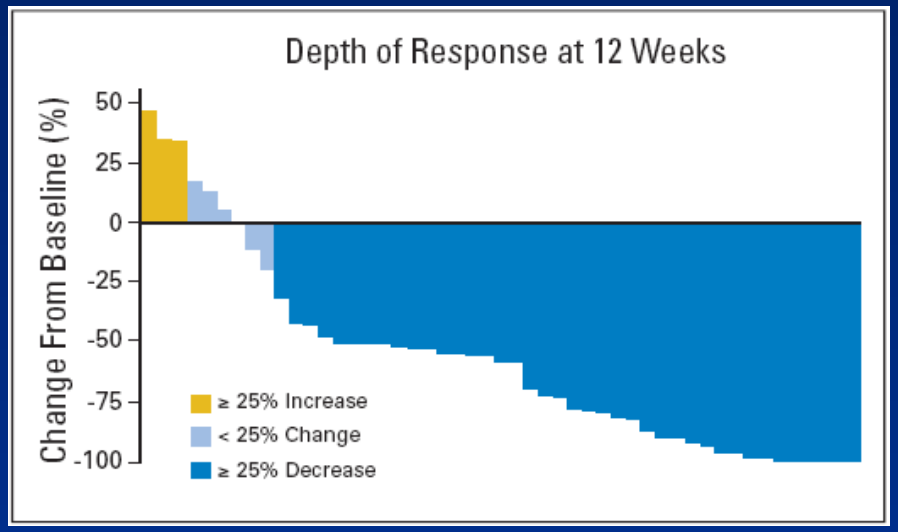
Kumar *et al.* Blood 2008

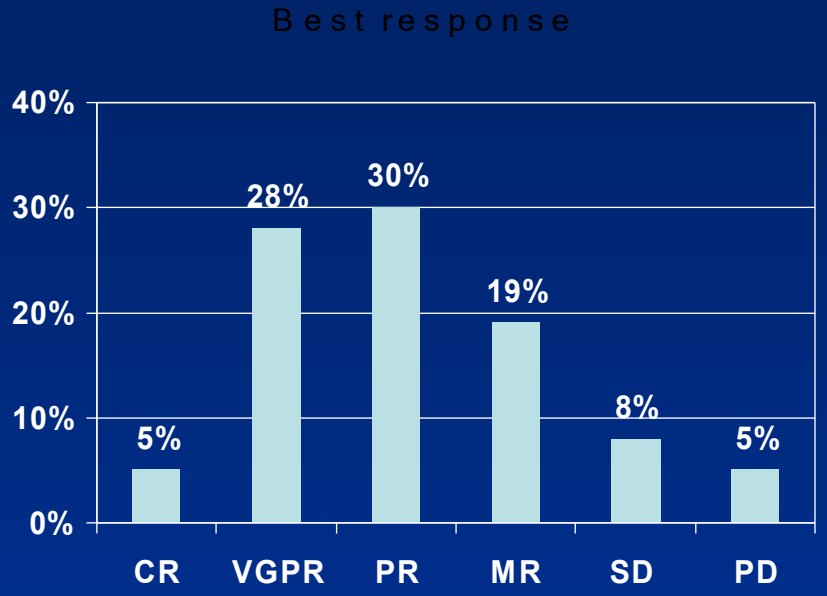
Pomalidomide with Dexamethasone in Rel/Ref MM

N=60 patients

62% had previous IMiD therapy (35% prior lenalidomide, 47% prior thalidomide)

33% had prior bortezomib





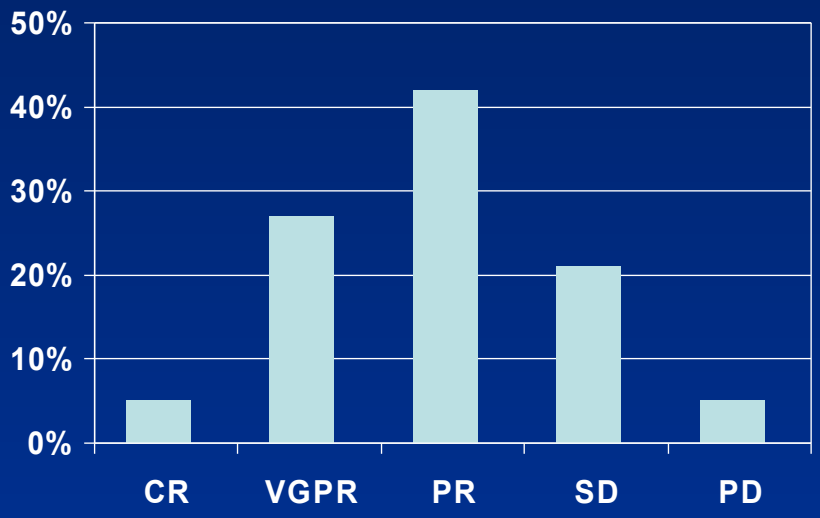
Lacy M et al J Clin Oncol 2009 (In press)

Pomalidomide with Dexamethasone in Rel/Ref MM with high risk features

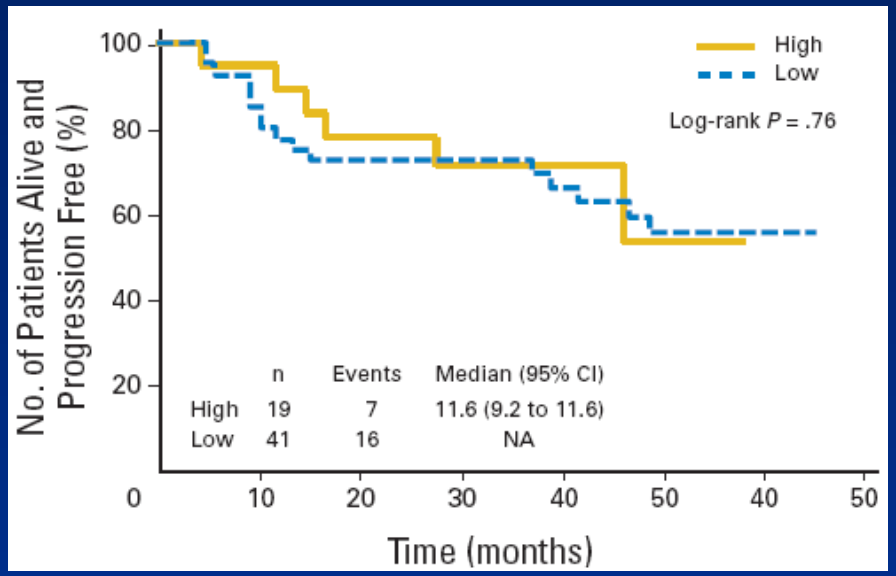
High risk : PCLI 3% ; deletion 17p, t(4;14), or t(14;16) by FISH; or deletion 13 by conventional cytogenetics .

N=19 patients with high risk features

Best response

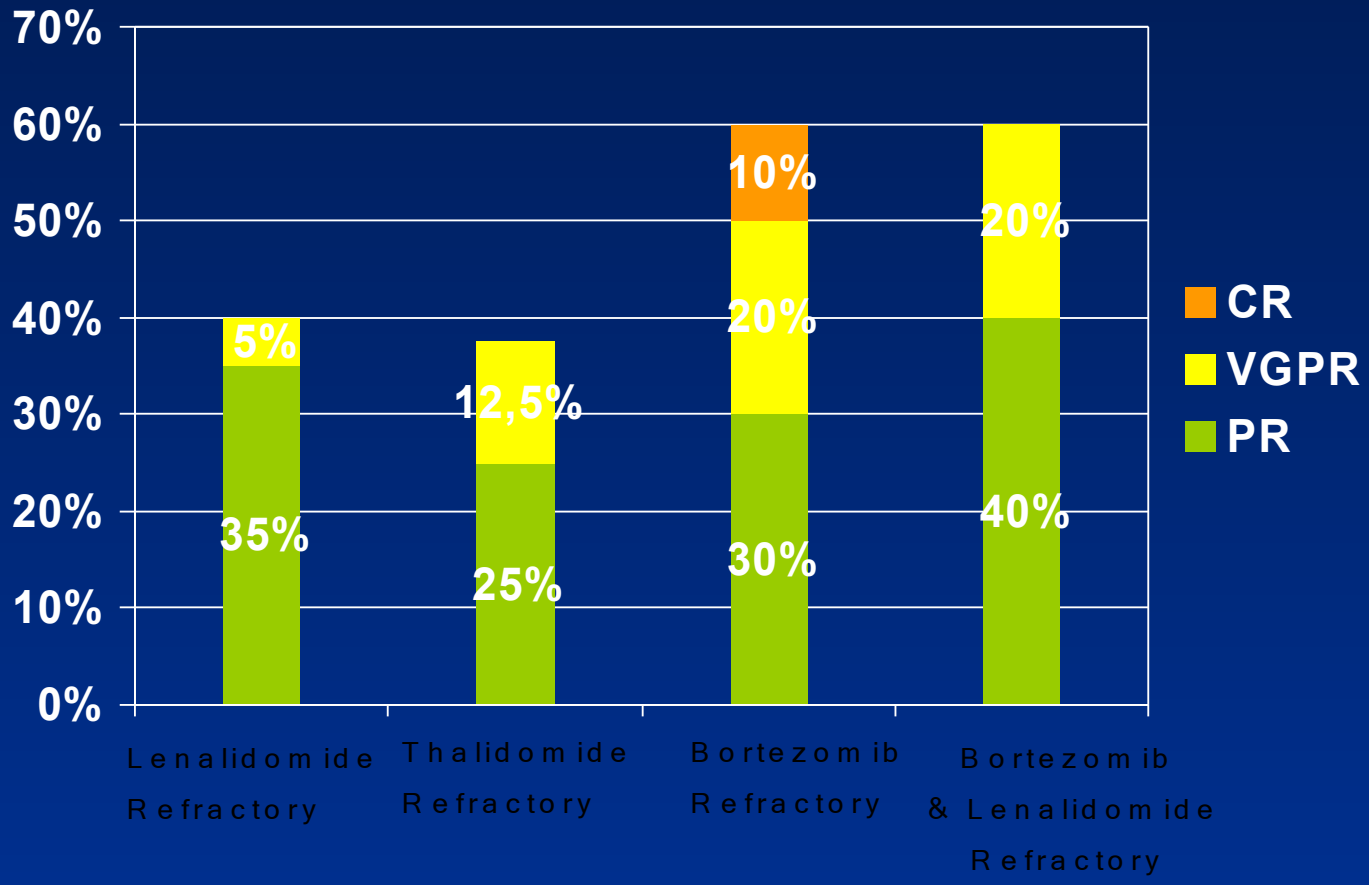


Progression-free survival based on presence or absence of high-risk features



Lacy M et al J Clin Oncol 2009 (In press)

Pomalidomide with Dexamethasone in patients with MM refractory to novel agents



Lacy M et al J Clin Oncol 2009 (In press)

Conclusions

- Novel agents in patients with Rel / Ref MM have increased progression free and overall survival
- Some patients may enjoy a long disease-free survival
- Retreatment with agents such as bortezomib is feasible and may be associated with significant responses
- Lenalidomide can be administered for protracted periods in responding patients
- Pomalidone-low dose dexa is emerging as a new active regimen for heavily pretreated patients
- Combinations of novel agents may increase quality and duration of responses

Conclusions

- Bortezomib-based regimens may be the treatment of choice in patients with renal impairment
- Lenalidomide and bortezomib may overcome the impact of prior thalidomide treatment
- Refractoriness to thalidomide may be associated with shorter PFS after treatment with Lenalidomide
- Novel agents may overcome the impact of some poor cytogenetic features
- Patients with del17p have poor outcome even with novel agents – novel treatments are needed for these patients

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