The Management of Patients With Relapsed/Refractory Disease: Single-Agent or Combination Therapy?

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MMRF
Multiple Myeloma Research Foundation

Clinical Considerations for Relapsed/Refractory Disease

- Disease characteristics / prior therapy
  - Aggressiveness of relapse
  - Relapsed or relapsed and refractory disease
  - "High risk disease"
  - Prior therapies (eg SCT, prior IMiD, bortezomib-based therapy)
- Toxicity considerations
  - Peripheral neuropathy
  - Thrombotic risk
  - Myelosuppression
  - Impact of prior therapies (eg SCT, other cumulative toxicity)

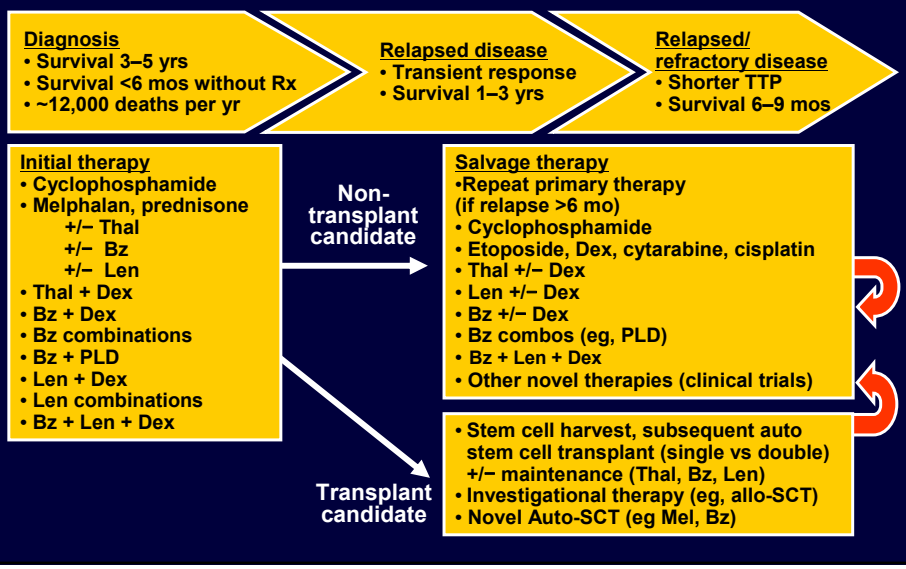
Special Populations in Relapsed/Refractory MM
Clinical Features Associated With Poor Prognosis

- Refractory to prior treatment (relapsed and refractory)
- Age >65 yr: majority of patients with MM are older (median age at diagnosis ~70 yr)
- Increased β_2m, decreased serum albumin, low platelet count
- Cytogenetic abnormalities: eg, chromosome 13 del, t(4;14), del 17, p53
- Renal dysfunction
  - Up to 50% of patients with MM have renal dysfunction
  - Between 20%–30% of patients have concomitant renal failure
- Extensive bone disease
- Extramedullary MM

Unmet need for new agents to treat these patients

Barlogie B et al. *Blood*. 2004;103:20.
Bladé J et al. *Arch Intern Med*. 1998;158:1889.
Facon T et al. *Blood*. 2001;97:1566.
Fonseca R et al. *Cancer Res*. 2004;64:1546.
Kumar SK et al. *Mayo Clin Proc*. 2004;79:867.
Kyle R. *Stem Cells*. 1995;13(suppl 2):56.
Kyle R et al. *Mayo Clin Proc*. 2003;78:21.
Richardson PG et al. *J Natl Compr Canc Netw*. 2007;5:149.

Multiple Myeloma: Current Treatment (USA)
Adapted From NCCN Practice Guidelines (2008)

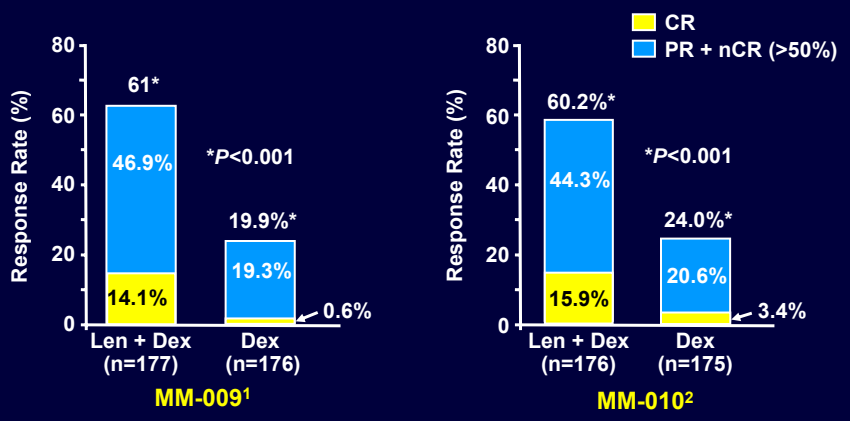


Lenalidomide: Development Summary in Relapsed/Refractory MM

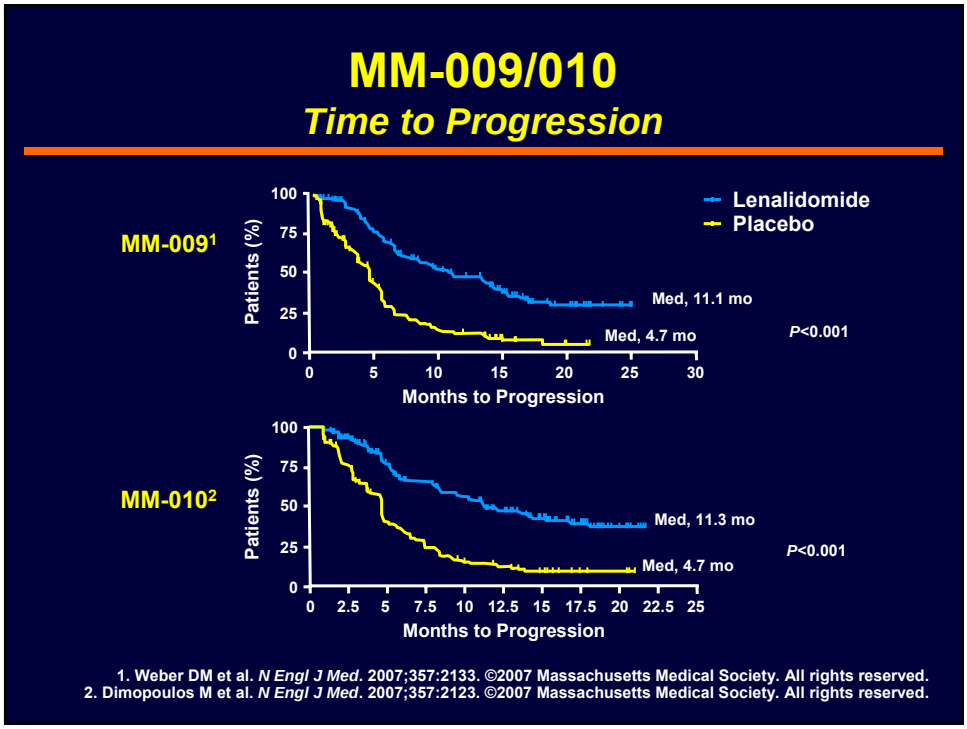
- Preclinical (2000): targets MM (caspase 8-mediated apoptosis) and microenvironment *in vitro*, *in vivo*
- Phase 1 trial (2001): MTD 25 mg PO; no somnolence, constipation, neuropathy; 71% MR or better (n=24)
- Phase 2 trial (2003): 25% CR + PR + MR (n=102), incl. 4% CR (EBMT criteria); addition of low dose dex in SD/PD feasible with response seen
- Phase 2 trial (2004): Lenalidomide monotherapy in relapsed and refractory MM, 225 pts, 30 sites; 27% CR + PR + MR (EBMT criteria)
- Phase 3 trials (2005): Lenalidomide/Dex vs Dex/placebo in relapsed MM, 705 pts, 97 sites
- FDA approval 2006

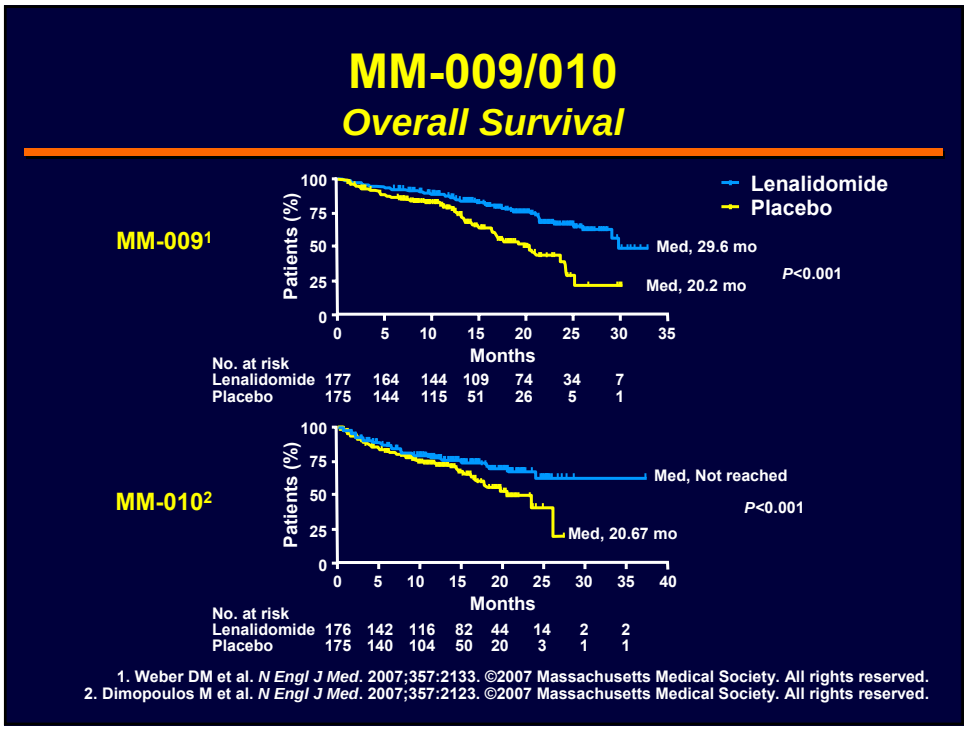
Hideshima T et al. *Blood*. 2000;96:2943.
Richardson PG et al. *Blood*. 2002;100:3063.
Richardson PG et al. *Blood*. 2006;108:3458.
Richardson PG et al. *Blood*. 2005;106:449a. Abstract 1565.
Weber DM et al. *N Engl J Med*. 2007;357:2133.
Dimopoulos M et al. *N Engl J Med*. 2007;357:2123.

Phase 3 Trials of Len + Dex in Relapsed/Refractory MM (MM-009/010)
Response Rates

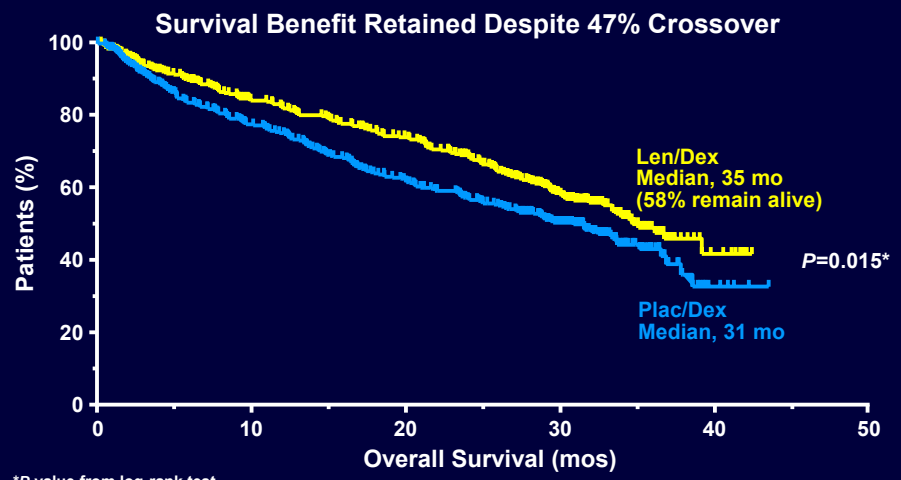


1. Weber DM et al. *N Engl J Med*. 2007;357:2133.
2. Dimopoulos M et al. *N Engl J Med*. 2007;357:2123.


MM-009/010
Time to Progression
MM-009[1]
Patients (%)
100
75
50
25
0
0 5 10 15 20 25 30
Months to Progression
Lenalidomide
Placebo
Med, 11.1 mo
Med, 4.7 mo
P<0.001
MM-010[2]
Patients (%)
100
75
50
25
0
0 2.5 5 7.5 10 12.5 15 17.5 20 22.5 25
Months to Progression
Med, 11.3 mo
Med, 4.7 mo
P<0.001
1. Weber DM et al. N Engl J Med. 2007;357:2133. ©2007 Massachusetts Medical Society. All rights reserved.
2. Dimopoulos M et al. N Engl J Med. 2007;357:2123. ©2007 Massachusetts Medical Society. All rights reserved.


MM-009/010
Overall Survival
MM-009[1]
Patients (%)
100
75
50
25
0
0 5 10 15 20 25 30 35
Months
Lenalidomide
Placebo
Med, 29.6 mo
Med, 20.2 mo
P<0.001
No. at risk
Lenalidomide 177 164 144 109 74 34 7
Placebo 175 144 115 51 26 5 1
MM-010[2]
Patients (%)
100
75
50
25
0
0 5 10 15 20 25 30 35 40
Months
Med, Not reached
Med, 20.67 mo
P<0.001
No. at risk
Lenalidomide 176 142 116 82 44 14 2 2
Placebo 175 140 104 50 20 3 1 1
1. Weber DM et al. N Engl J Med. 2007;357:2133. ©2007 Massachusetts Medical Society. All rights reserved.
2. Dimopoulos M et al. N Engl J Med. 2007;357:2123. ©2007 Massachusetts Medical Society. All rights reserved.

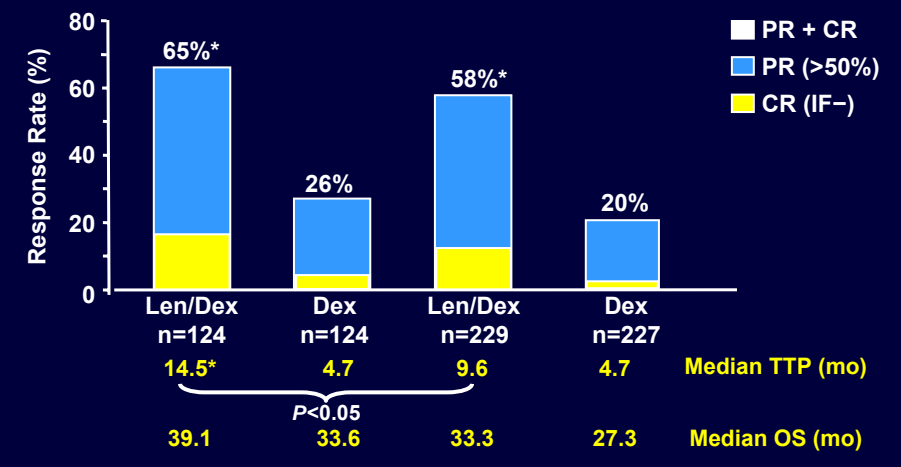
Pooled Analysis of MM-009 and MM-010 Data: Updated OS



*P value from log-rank test.
(patients analyzed for extended follow-up remained in original groups despite crossover)

Weber D et al. *Blood*. 2007;110:128a. Abstract 412.

Pooled Analysis of MM-009 and MM-010 Data
Response, TTP, and OS According to Number of Prior Therapies



*EBMT criteria.

Weber D et al. *Blood*. 2007;110:128a. Abstract 412.

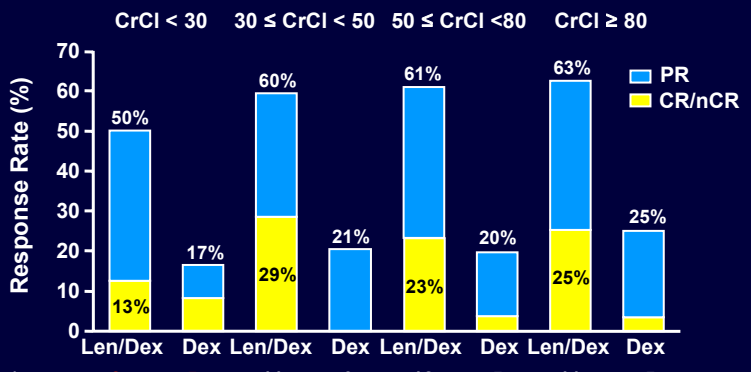
Pooled Analysis of MM-009 and MM-010 Data
Impact of Prior Thalidomide Therapy

Thal Naïve vs Thal Exposed
Median time from diagnosis: 2.8 yr vs 4.0 yr (*P*<0.05)
Median lines of prior therapy: 2 vs 3 (*P*<0.05)

	n	ORR (≥PR) (%)	Median TTP (mo)
Thal naïve	226	65	13.8
Prior Thal	127	54	8.3
Progressed (CR/PR)	54	43	7.0
SD	31	45	7.0
Refractory (PD)	20	50	7.1

Weber D et al. *Blood*. 2007;110:128a. Abstract 412.

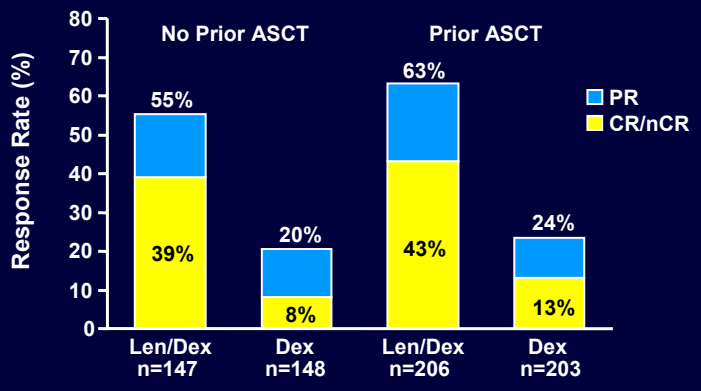
Pooled Analysis of MM-009 and MM-010 Data
Impact of Creatinine Clearance



Median TTP (mo)	8	5	11	3	12	5	11	5
Neutropenia (%)	38	8	43	6	39	2	31	4
Thrombocytopenia (%)	38	0	19	18	16	5	7	6
Infection (%)	56	33	31	18	20	15	22	15

Weber D et al. *Blood*. 2007;110:128a. Abstract 412.

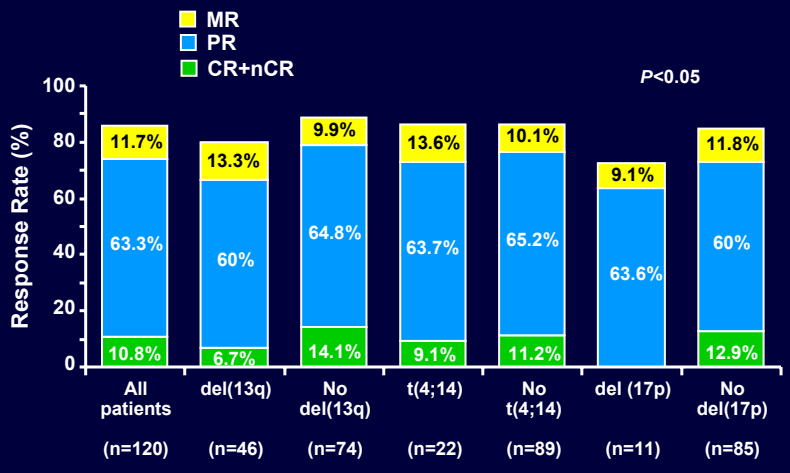
Pooled Analysis of MM-009 and MM-010 Data
Impact of Prior Autologous Stem Cell Transplant



	Len/Dex n=147	Dex n=148	Len/Dex n=206	Dex n=203	
Median TTP (mo)	13.2	4.7	10.9	4.7	*P*=0.44
Neutropenia (%)	28.6	2.0	40.3	4.4	
Thrombocytopenia (%)	18.4	8.8	14.6	7.4	

Weber D et al. *Blood*. 2007;110:128a. Abstract 412.

Lenalidomide/Dexamethasone in Previously Treated MM With Poor-Risk Cytogenetics:MM-016



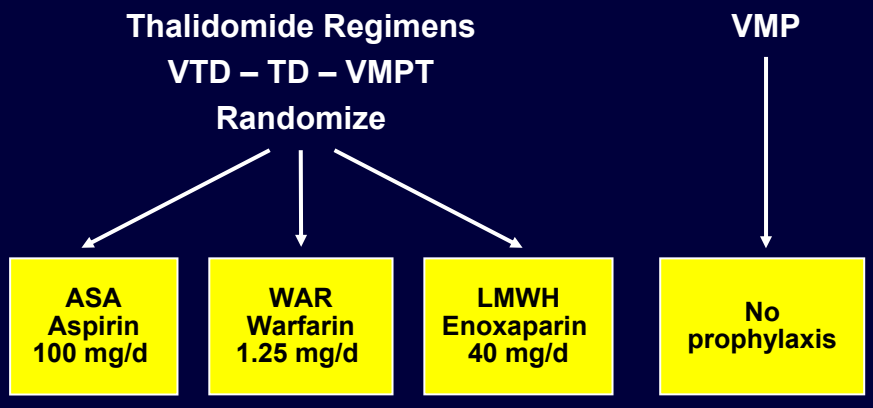
Bahlis NJ et al. *Blood*. 2007;110:1052a. Abstract 3597.

Appropriate Prophylaxis: VTE Risk Factors

- Central venous line
- Concomitant chemotherapy (eg, alkylators)
- Doxorubicin use
- Erythropoietin use
- High-dose dexamethasone use
- High tumor mass
- Immobilization / orthopedic procedure
- Ongoing infection / inflammation
- Older age
- Previous VTE
- Thrombophilia
- Family history

Palumbo A et al. *Leukemia*. 2008;22:414.

LMWH vs Warfarin vs ASA in Newly Diagnosed MM Treated with Thalidomide-Containing Regimens*

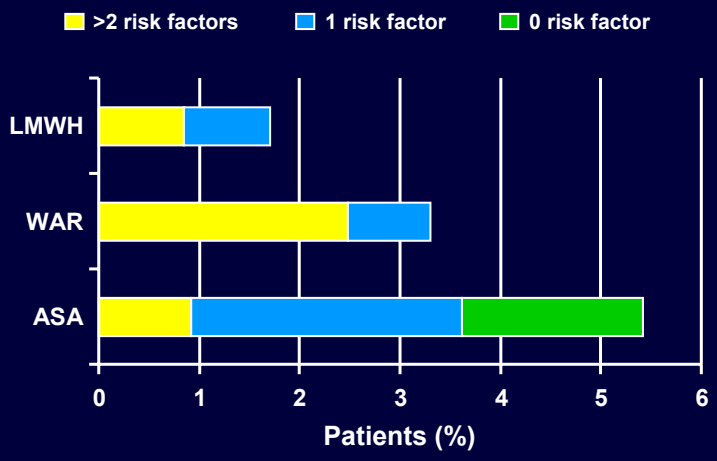


- VTD-TD (<65 yr): 9 wk before ASCT
- VMPT (>65 yr): 6 mo

*A prospective randomized GIMENA phase 3 trial.

Palumbo A et al. *Blood*. 2007;110: Abstract 310.

LMWH vs Warfarin vs ASA Prophylaxis for Thalidomide-Containing Regimens
VTE According to Risk Factors



Palumbo A et al. *Blood*. 2007;110: Abstract 310.

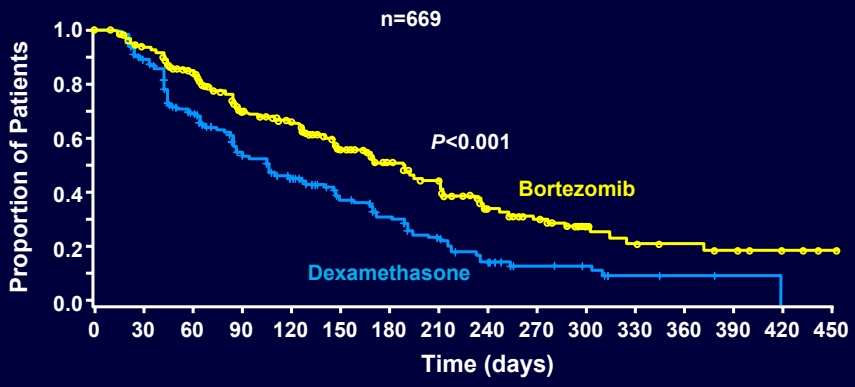
Bortezomib: Bench to Bedside in Relapsed/Refractory Myeloma

- 2000: preclinical studies, Bz targets MM (caspase 9-mediated apoptosis, NF-κB inhibition) and microenvironment *in vitro*, *in vivo:* phase 1 trials
- 2001: phase 2 trials, 256 pts (SUMMIT + CREST)
- SUMMIT Study: Bz monotherapy ~ 35% CR + PR + MR, incl 10% CR/nCR (EBMT criteria); 202 pts
- 2002–2003: APEX phase 3 study, Bz monotherapy vs HD dex; 669 pts
- Accelerated approval (FDA) 2003
- EMEA approval 2004
- Approval (FDA) 2005

Hideshima T et al. *Clin Cancer Res.* 2001;61:3071.
LeBlanc R et al. *Cancer Res.* 2002;62:4996.
Orlowski RZ et al. *J Clin Oncol.* 2002;20:4420.
Richardson PG et al. *N Engl J Med.* 2003;348:2609.
Jagannath S et al. *Br J Haematol.* 2004;127:165.
Richardson PG et al. *N Engl J Med.* 2005;352:2487.

APEX
Time to Progression

78% Improvement in Median TTP With Bz

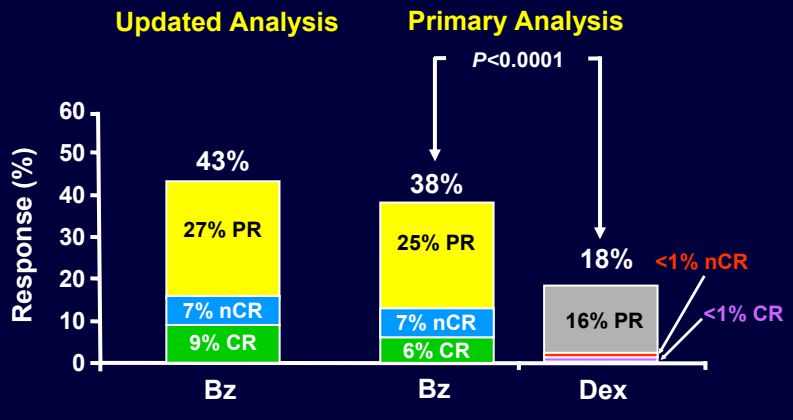


Median TTP: Bz, 6.2 mo
Dex, 3.5 mo

Richardson PG et al. *N Engl J Med*. 2005;352:2487.

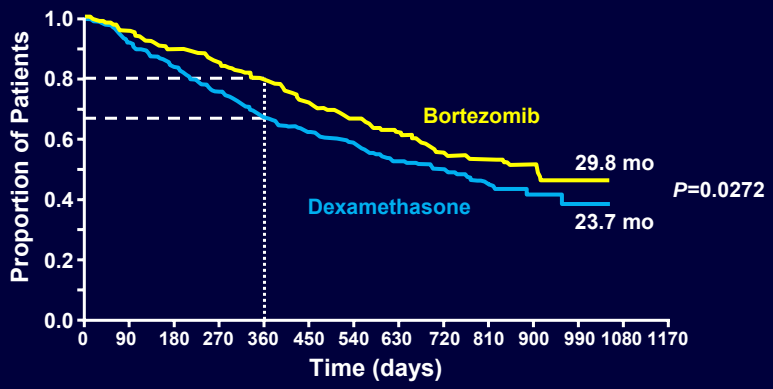
Updated APEX Efficacy Data
Response Rates

ORR With Bz Improved From 38% to 43%



Richardson PG et al. *Blood*. 2007;110:3557.

Updated APEX Results
OS



- Superior survival despite >62% of HD dexamethasone patients crossing over to bortezomib
  - 1-yr survival rate: 80% vs 67%; *P*=0.0002

Richardson PG et al. *Blood.* 2007;110:3557.

Bortezomib: Dose Modification Guidelines

Toxicity	Action
Any grade 3 non-hematologic or grade 4 hematologic	• Stop bortezomib until symptoms resolved • Reinitiate at 25% reduced dose
Thrombocytopenia*	
Grade 4	• Reduce dose to 1.0 mg/m^2

*Consider supportive care measures including platelet transfusion or G-CSF

Peripheral Neuropathy Management

Toxicity	Action
Grade 1 (paresthesias or loss of reflexes) without pain or loss of function	• None
Grade 1 with pain or grade 2 (interferes with function but not with activities of daily living [ADL])	• Reduce dose to 1.0 mg/m^2
Grade 2 with pain or grade 3 (interferes with ADL)	• Withhold treatment until toxicity resolves, then reinitiate at a dose of 0.7 mg/m^2 once weekly
Grade 4 (permanent sensory loss that interferes with function)	• Discontinue treatment

Richardson PG et al. *J Clin Oncol*. 2006;24:3113.

Prognostic Factors Associated With Response Rate in SUMMIT

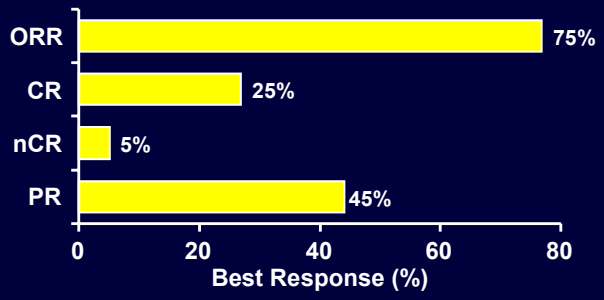
- No significant difference in response rate by
  - Number or type of prior therapy
  - Karnofsky performance status (KPS)
  - β_2m level
  - Presence of chromosome 13 deletion
  - High CR rate in light-chain disease
- Lower RR* (multivariate analysis)
  - >50% BMPC
  - Age >65 yr (but age not a factor for TTP, OS)

*$P<0.05$.

Richardson PG et al. *Blood*. 2005;106:2977.

Bortezomib in MM Patients With Renal Failure Requiring Dialysis

- Retrospective analysis of 24 patients treated with
  - Single-agent Bz
  - Bz combinations (+ Dex + Thal/Dex + Thal/doxorubicin)
- Number of therapies prior to Bz: median, 2 (range, 0–6)
  - 1 patient newly diagnosed



Chanan-Khan AA et al. *Blood*. 2007;109:2604.

Myeloma-Related Bone Disease

- Bortezomib
  - Large number of preclinical and clinical studies[1–7]
    - Inhibitory effect on bone resorption (osteoclasts)
    - Stimulatory effect on bone formation (osteoblasts)
  - Effect on bone is direct and not only due to antimyeloma activity
  - Bone anabolic effect unique to bortezomib
- Lenalidomide
  - *In vitro* inhibitory effect on osteoclast differentiation[8]
- Thalidomide
  - Inhibition of bone resorption[9,10]
  - No effect on osteoblasts[4]

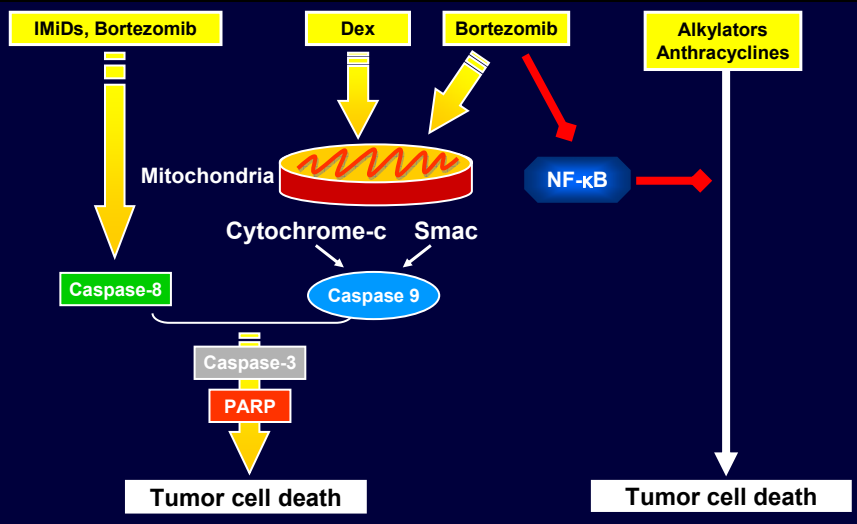
1. Boissy P et al. *Blood.* 2006;108:1000a. Abstract 3508.
2. Pennisi A et al. *Blood.* 2006;108:154a. Abstract 509.
3. Giuliani N et al. *Blood*. 2007;110:334.
4. Heider U et al. *Eur J Haematol*. 2006;77:233.
5. Zangari MZ et al. EHA. 2007. Abstract 695.
6. Terpos E et al. *Br J Haematol.* 2006;135:688.
7. Terpos E et al. *IMW* 2007. Abstract PO-320.
8. Breitkreutz I et al. *Blood.* 2006;108. Abstract 3485.
9. Terpos E et al. *Leukemia.* 2005;19:1969.
10. Tosi P et al. *Eur J Haematol.* 2006;76:399.

Extramedullary Disease

- Extramedullary disease usually associated with poor prognosis[1]
- Response to chemotherapy generally poor[1]
- Resistance to chemotherapy frequent[1]
- Thalidomide may be less effective[1-3]
- Bortezomib is active[4]
- Lenalidomide also active, especially in combination[5]

1. Damaj G et al. *Eur J Haematol*. 2004;73:402.
2. Bladé J et al. *Br J Haematol*. 2001;113:422.
3. Rosiñol L et al. *Haematologica*. 2004;89:832.
4. Laura R et al. *Eur J Haematol*. 2006;76:405.
5. Richardson PG et al. *Blood*. 2006;108:124a. Abstract 405.

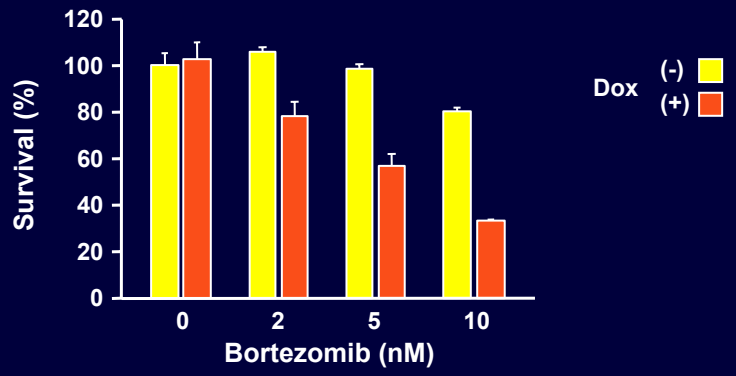
Rationale for Combination Therapy in Multiple Myeloma



From Richardson PG *et al. Expert Review of Anticancer Therapy*. 2008;8:1053.

Preclinical Rationale for Combination Therapy in Clinical Trials

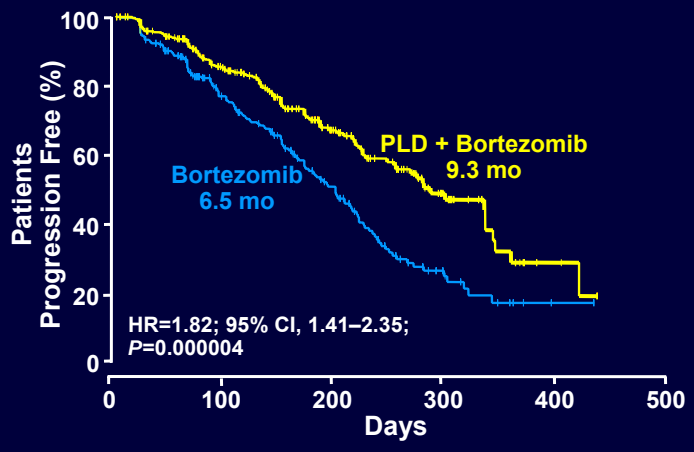
Low-dose bortezomib enhances and restores sensitivity to DNA damaging chemotherapy (doxorubicin)



Mitsiades N et al. *Blood*. 2002;101:2377.

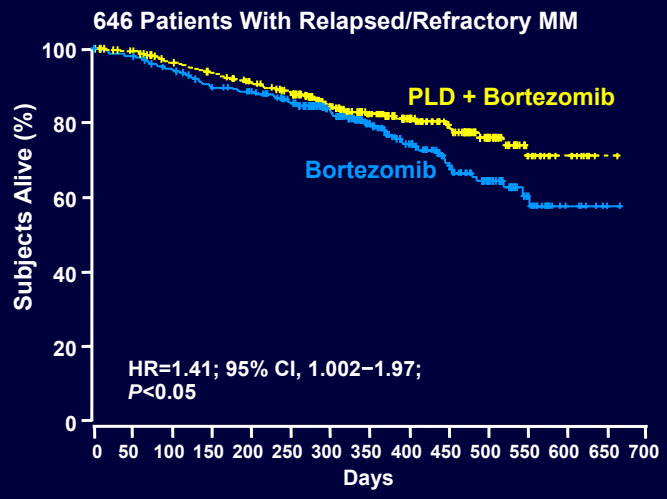
Bortezomib + Liposomal Doxorubicin vs Bortezomib Alone: TTP

646 Patients With Relapsed/Refractory MM



Orlowski RZ et al. *J Clin Oncol*. 2007;25:3892. Reprinted with permission.

Bortezomib + Liposomal Doxorubicin vs Bortezomib Alone: OS



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

Bortezomib + Liposomal Doxorubicin vs Bortezomib Alone: Subanalyses

- TTP is superior for bortezomib + liposomal doxorubicin over bortezomib alone regardless of
  - Extent of prior therapy and anthracycline exposure[1]
  - ISS stage and time since initial diagnosis[2]
- In early-relapse group (relapse within 12 months after ASCT), 12-month survival rate is significantly better with bortezomib + liposomal doxorubicin than with bortezomib alone[3]
- Normalization of light chain κ/λ ratio is associated with prolonged TTP and higher response rates[4]

1. Blade J et al. *Blood.* 2007;110:127a. Abstract 410.
2. Sutherland HJ et al. *Blood.* 2007;110:805a. Abstract 2740.
3. Kumar S et al. *Blood.* 2007;110:802a. Abstract 2730.
4. Orlowski RZ et al. *Blood.* 2007;110:803a. Abstract 2735.

Phase 2 Study Bortezomib-Doxorubicin-Dexamethasone
Recovery of Renal Function

Patients

- 37 pts with MM-induced acute renal failure
  - 17 pts with de novo MM; 20 with progressive disease

Treatment

- 21-day cycle: bortezomib 1.0 mg/m^2, days 1, 4 ,8 ,11; doxorubicin 9 mg/m^2, days 1, 4, 8, 11 (until safety analysis), then 9 mg/m^2, days 1, 4; dex 40 mg, days 1, 4, 8, 11

Results

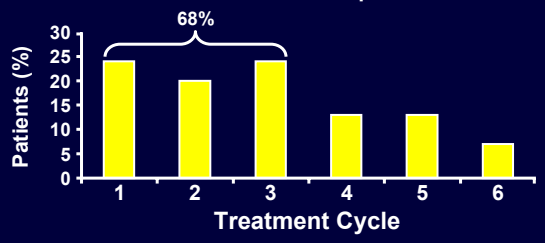
Tumor Response	Evaluable Patients (n=22)	Glomerular Filtration Rate (GFR) (mL/min)	
		Baseline	Best Response
CR/nCR	12	18.2 (13–45)	62.5 (20–134)
PR	4	25 (15–44)	81 (16–114)
MR	3	17 (10–45)	35 (33–45)
NC/PD	3	13 (4–15)	18 (11–25)
CR + PR	16 (73%)	GFR > 75 mL/min: 9 (56%)	

Ludwig H et al. *Blood.* 2007;110:1054a. Abstract 3603.

VMPT for Relapsed/Refractory MM

Response	All Patients (n=30)	VMPT 2nd-Line (n=14)	VMPT 3rd-Line (n=16)
CR or VGPR, n (%)	13 (43)	8 (57)	5 (31)
PR, n (%)	7 (23)	3 (21)	4 (25)
SD, n (%)	8 (27)	3 (21)	5 (31)
PD, n (%)	2 (7)	0	2 (13)

Time to Best Response



VMPT, bortezomib, melphalan, prednisone, thalidomide

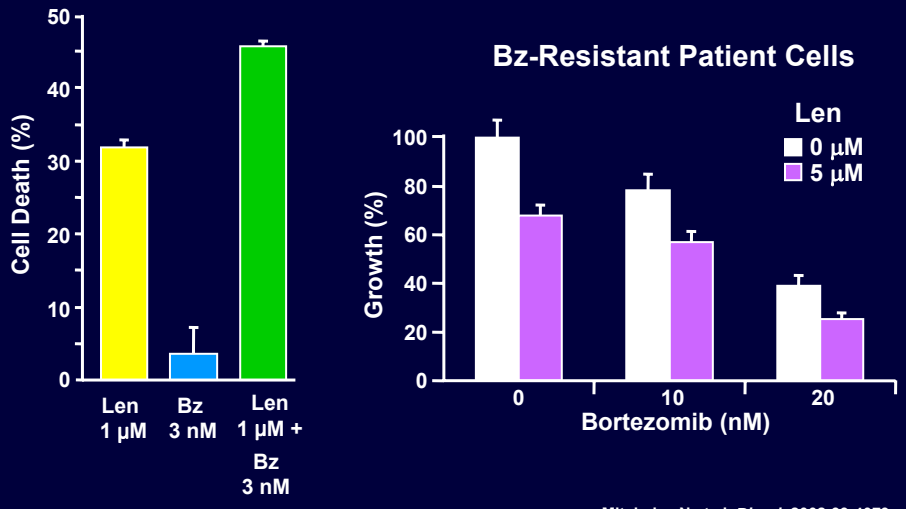
Palumbo A et al. *Blood.* 2007;109:2767.

Other Rationally Based Combination Therapies

- Bortezomib + Hsp 90 inhibitor
- Bortezomib + NPI-0052
- Bortezomib + perifosine
- Bortezomib + LBH 589
- Bortezomib + Smac peptides
- Bortezomib + bcl-2 inhibitor
- Bortezomib + p38 MAPK inhibitor
- Bortezomib + HuLuc63
- Lenalidomide + mTOR inhibitor
- Lenalidomide + anti-CD40 antibody
- Lenalidomide + PLD
- Lenalidomide + HuLuc63
- Lenalidomide + LBH 589
- Lenalidomide + perifosine
- Lenalidomdide + bevacizumab
- Lenalidomide + vaccines

Bortezomib and Lenalidomide

Rationale: Preclinical Combination of Lenalidomide + Bortezomib

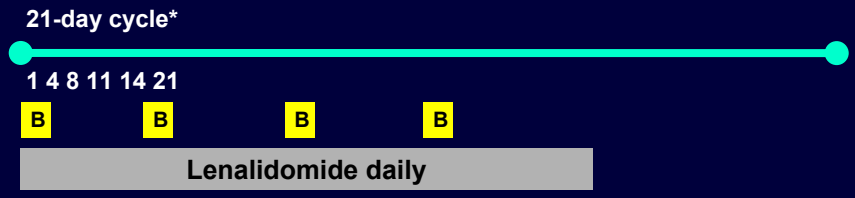


Mitsiades N et al. *Blood.* 2002;99:4079.

Phase 1 Trial of Lenalidomide and Bortezomib (Rev/Vel) in Relapsed/Refractory MM

Bortezomib (mg/m^2) IV	Lenalidomide, mg/day			
	5	10	15	20
1.0	Cohort 1	Cohort 3	Cohort 5	Cohort 7
1.3	Cohort 2	Cohort 4	Cohort 6	Cohort 8

8 cohorts of 3–6 pts, with additional 10 enrolled at MTD



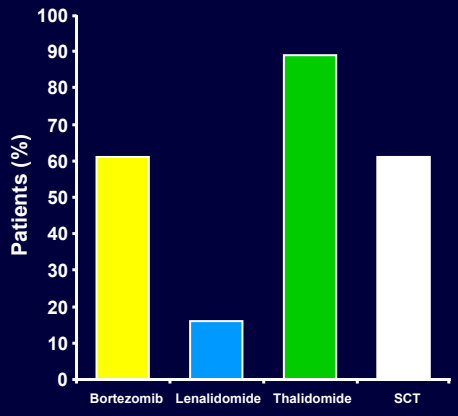
*For a maximum of 8 cycles; Dex added (20 mg, days of and day following bortezomib) for ps with PD: extension phase for pts in response

Richardson PG et al. *Blood*. 2006;108:124a. Abstract 405.

Lenalidomide + Bortezomib (Rev/Vel) in Relapsed/Refractory MM: Baseline Characteristics

Characteristic	(n=38)
Median age, yr (range)	60 (37–79)
Male, n (%)	25 (66)
Myeloma type, %	
IgG	68
IgA	24
Durie-Salmon stage III at diagnosis, %	42
Disease status, n (%)	
Relapsed	12 (32)
Relapsed and refractory	26 (68)
Median prior therapies, n (range)	5 (1–13)

Prior therapies, n=38



Richardson PG et al. *Blood*. 2006;108:124a. Abstract 405.

Lenalidomide + Bortezomib (Rev/Vel) in Relapsed/Refractory MM: Preliminary Results

Cohort	Dose Bort (mg/m^2)/ Len (mg)	No. of Cycles	EBMT Response (n=36 evaluable)					
			CR	nCR	PR	MR	SD	PD
1	1.0/5	20–22			2	1		
2	1.3/5	16–20	1		2			
3	1.0/10	12–18		1	2			
4	1.3/10	3–12			2	2	1	1
5	1.0/15	3–8			2	4	7	1
6	1.3/15	1–2			2		5	

58%

- Toxicities
  - Grade 3/4 neutropenia; grade 3/4 thrombocytopenia
  - No significant PN, fatigue (≥ grade 3)
  - No thrombotic events
  - 2 DLTs: hyponatremia (cohort 4); herpes zoster infection (cohort 6)

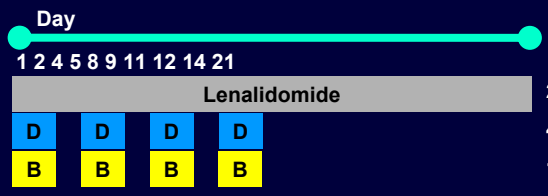
Richardson PG et al. *Blood*. 2006;108:124a. Abstract 405.

Lenalidomide and Bortezomib as "Backbone Agents" in MM

- Phase 2 studies in relapsed and relapsed/ refractory MM
- Phase 1/2 study in newly diagnosed patients
- Combination with low-dose Dex ("Dex sparing")
- Combination with conventional and other novel therapies (eg, monoclonal antibodies; "next generation" small molecule inhibitors)

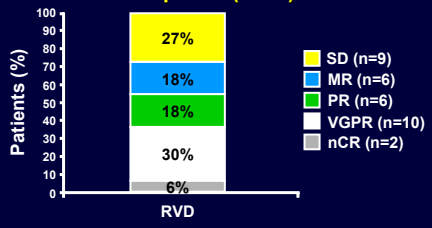
RVD in Relapsed/Refractory MM

*Preliminary Phase 2 Study Results**



ASA (81 or 325 mg/day) as DVT prophylaxis; herpes zoster prophylaxis
Continued cycles until SCT, disease progression, or toxicity

Clinical Response (n=41)



Most Frequent Grade 3/4 Toxicities (n=41)

Thrombocytopenia	22%
Fatigue	5%
Diarrhea	2%
PN	2%
Rash	2%

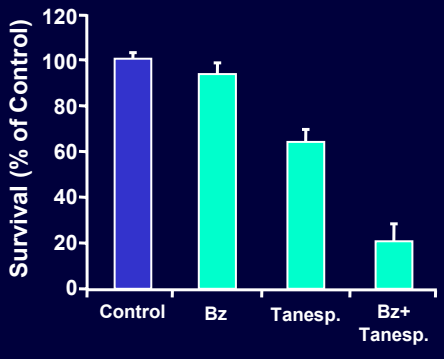
* 41 pts enrolled; median treatment duration, 7 cycles (range, 1–20)

Richardson PG et al. *Blood*. 2007;110:124a. Abstract 405.

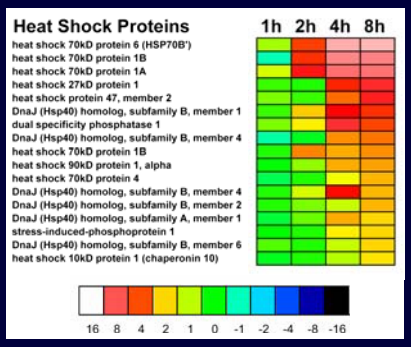
Tanespimycin + Bortezomib

Synergistic Anti-MM Activity

In vitro **cytotoxicity model using MM cell lines suggests synergy**



Induction of Hsp70 seen at 2 hr; Hsp90 transcription increase ~4–8 hr following tanespimycin + BZ



Transcription / Translation Regulation Signal Intensity

Mitsiades CS et al. *Blood.* 2006;107:1092.

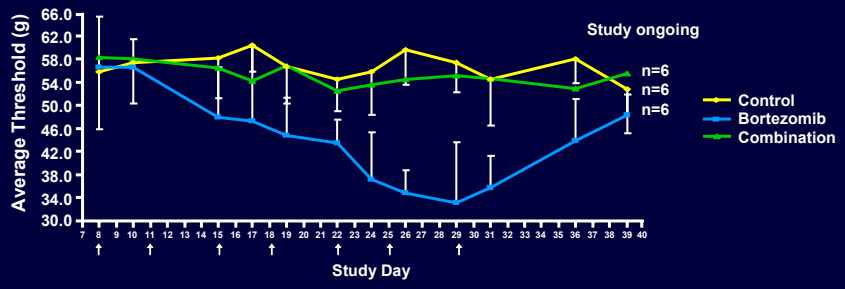
Tanespimycin + BZ and PNY

- 57 pts received bortezomib (1.3 mg/m^2) + tanespimycin (150–340 mg/m^2)
- Median relative dose intensity
  - Bortezomib: 95% (range, 59%–105%)
  - 28 pts received ≥3 cycles of the combination
- No pt with G3 or greater PNY
  - In the 228 pts treated with 1.3 mg/m^2 bortezomib in the SUMMIT and CREST phase II trials, 13% developed G3 treatment-emergent PNY

Richardson PG et al. *Blood*. 2007;110:353a. Abstract 1165.

Rodent Model of Neuropathy

Average Group Sensory Threshold Readings Over Time



- Rats were treated with saline (control), bortezomib (0.2 mg/kg), or bortezomib (0.2 mg/kg) plus tanespimycin (20 mg/kg). Sensory thresholds were measured using a von Frey anesthesiometer
- Combination of tanespimycin with bortezomib demonstrated a lack of neurotoxicity compared with bortezomib alone, indicating a neuroprotective effect of tanespimycin

Richardson PG et al. *Blood*. 2007;110:353a. Abstract 1165.

Summary: Single Agent or Combination?

- New approaches for relapsed and relapsed/refractory disease
  - Bortezomib ± Dex
  - Len + Dex
  - Other novel "doublet" combinations
  - Optimal sequencing, drug resistance, side effect management impact decision making
- Special features of relapsed/refractory disease favor combinations of 2-3 or more agents
- Multiple lines of therapy can be used and drugs can be revisited in combination
- The importance of steroid-sparing regimens / role of lower doses of dexamethasone (eg, impact on bone disease)