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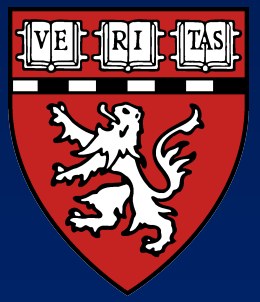

Novel combination therapies for the treatment of relapsed/refractory Multiple Myeloma: Current Phase I/II combinations

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Integration of Novel Therapy Into Myeloma Management

Bortezomib, Lenalidomide, Thalidomide, Doxil

Treatment of Relapsed/Refractory MM (single agent/combinations)

Induction/First-line Therapy

Transplant/Maintenance

New Drug Approvals in Multiple Myeloma

Six FDA/EMEA Drug Approvals
in Last Five Years

Median survival prolonged from 3-7 years (especially in younger patients)

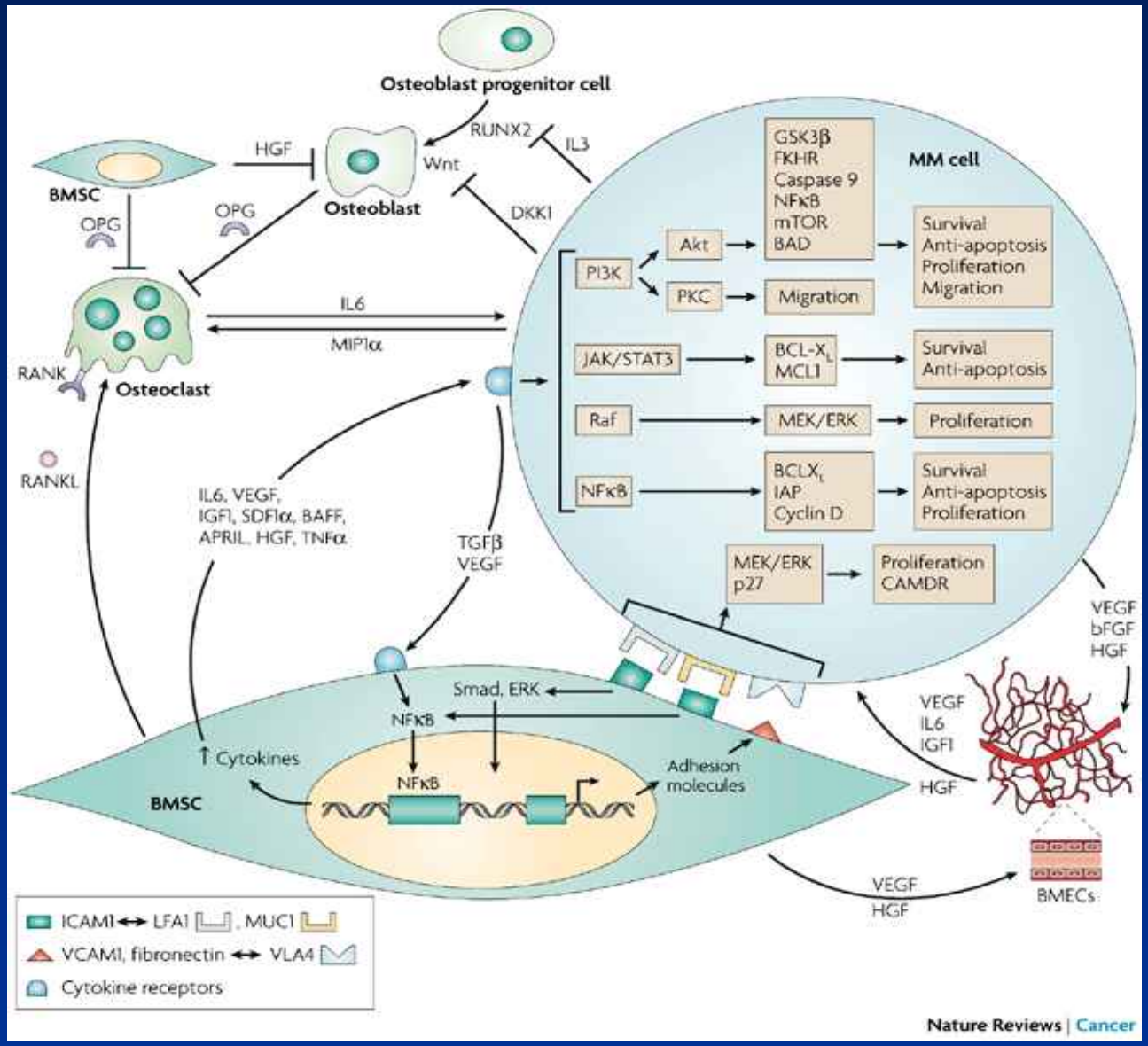
Three additional drug combinations in phase III clinical trial for new drug approval

Rationally Based Combination Therapies

- Bortezomib and Hsp 90 inhibitor
- Bortezomib and doxil
- Bortezomib and NPI-0052
- Bortezomib and perifosine
- Bortezomib and LBH 589
- Bortezomib and Smac peptides
- Bortezomib and Bcl 2 inhibitor
- Bortezomib and p38 MAPK inhibitor
- Bortezomib and HuLuc63
- Lenalidomide and mTOR inhibitor
- Lenalidomide and Anti-CD40 antibody
- Lenalidomide and doxil
- Lenalidomide and HuLuc63
- Lenalidomide and LBH 589
- Lenalidomide and perifosine
- Lenalidomdide and Bevacizumab
- Lenalidomide and Vaccine

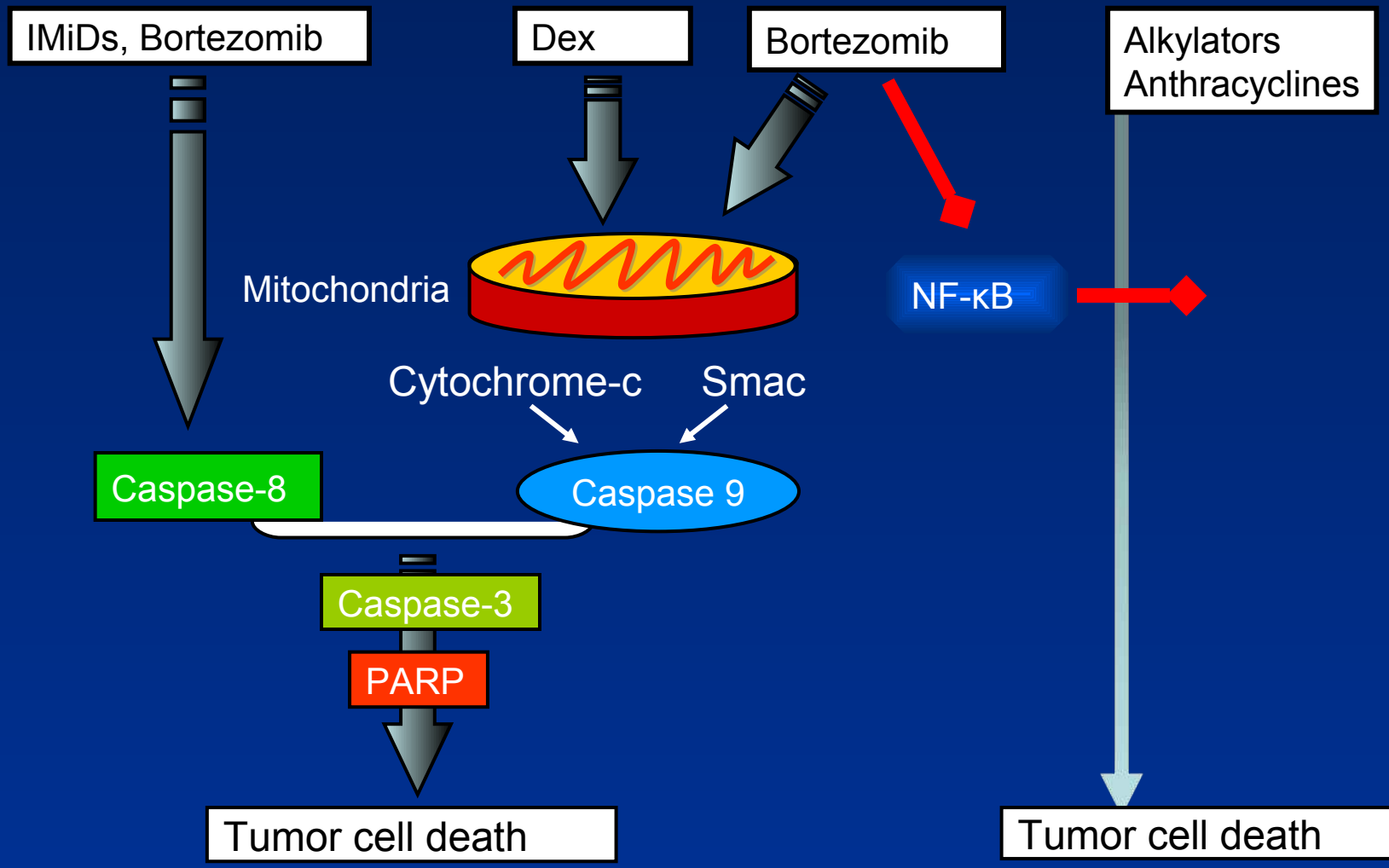
Lenalidomide and Bortezomib

Pathogenesis of Multiple Myeloma



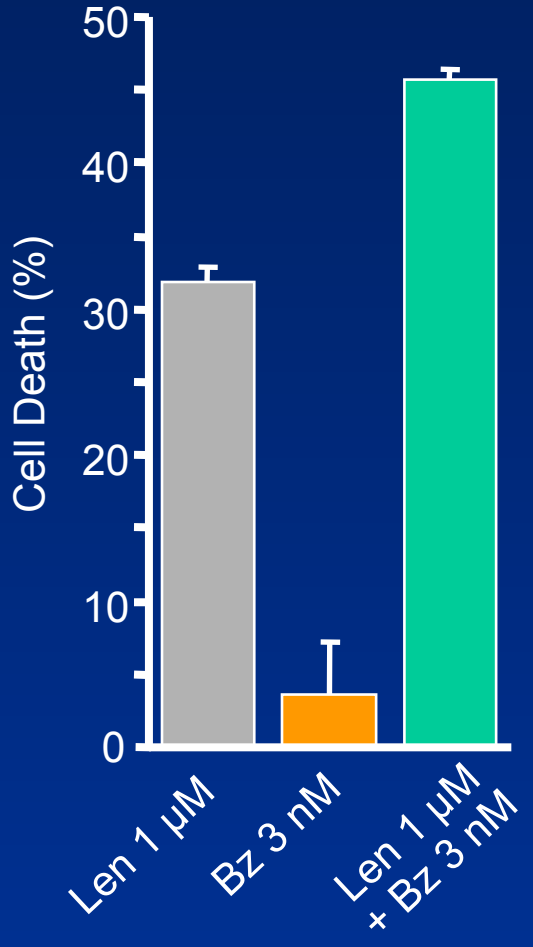
Hideshima T, et al. Nature Reviews Cancer 7, 585-598 (August 2007)

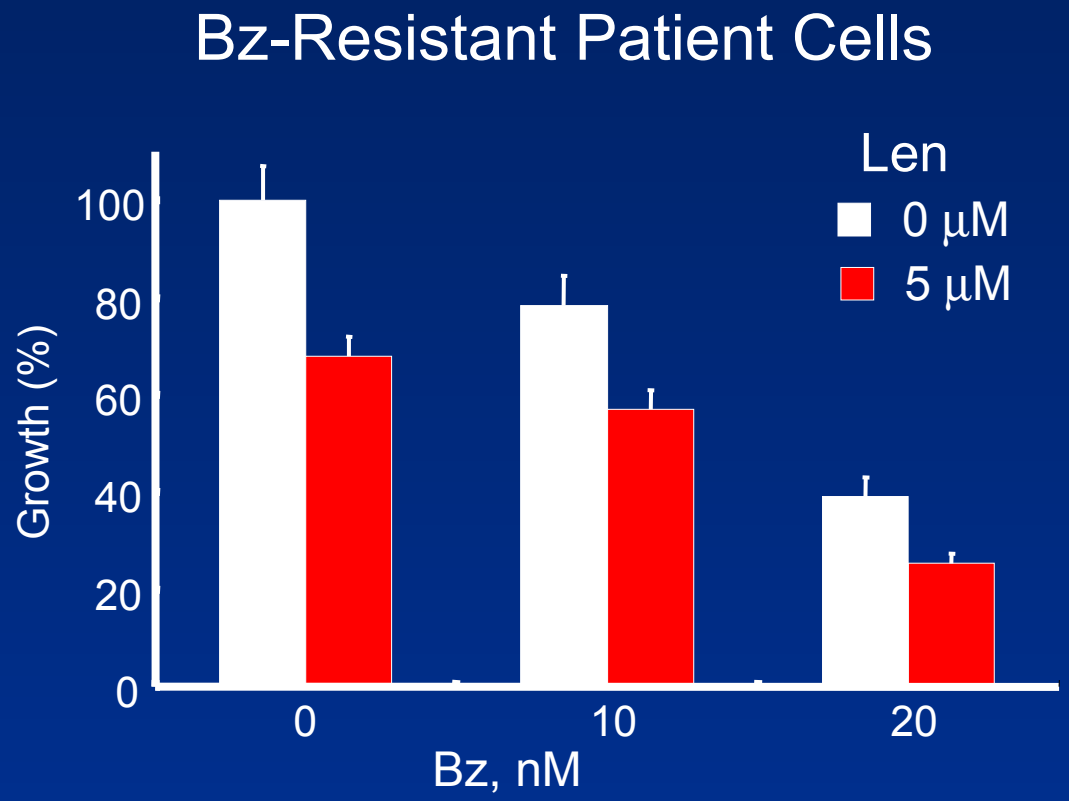
Rationale for Combination Therapy in Multiple Myeloma



From Richardson PG , Mitsiades CS, Hideshima T, Anderson KC: *Expert Review of AntiCancer Therapy*. 2008;8:1053.

Rationale: Preclinical Combination of Lenalidomide (Len) + Bortezomib (Bz)





Mitsiades et al. Blood. 2002; Hideshima et al. 2003

Lenalidomide plus bortezomib: study design

Phase I multicenter dose-escalation study

Relapse and/or refractory MM (N=38)

Bortezomib 1.0 or 1.3 mg/m^2 on days 1, 4, 8, 11

Lenalidomide 5, 10, 15, or 20 mg on days 1-14 of 21-day cycle

Dexamethasone (40 mg on day and day after each lenalidomide dose) in patients with PD

NCI CTCAE for toxicity assessment

DLT G ≥3 non-hematological toxicity, G4 neutropenia for ≥5 days and/or neutropenic fever, or platelets <10,000/mm3 on >1 occasion despite transfusion

Response assessed by modified EBMT criteria

PD, progressive disease;
DLT, dose-limiting toxicity; G, grade

Richardson PG, et al. *Blood.* 2006;108:abstract 405.

Lenalidomide plus bortezomib: baseline characteristics

Baseline characteristics, n=28	
Relapse MM, n	12
Relapse/refractory MM, n	26
Male, %	65.8
Median age (range), years	60 (37-79)
Prior therapies, median (range)	5 (1-13)

Richardson PG, et al. *Blood.* 2006;108:abstract 405.

Lenalidomide plus bortezomib: efficacy outcomes

Efficacy outcomes	
ORR (95% CI), %	58 (46-75)
CR, %	6
Median DoR, months	6
Therapy ≥1 yr, %	30
Objective response, n/N (%)*	10/14 (71)

*in patients receiving dexamethasone

ORR, overall response rate; CR, complete response; DoR, duration of response

Richardson PG, et al. *Blood.* 2006;108:abstract 405.

Lenalidomide plus bortezomib: safety outcomes

Safety outcomes	
G3 hyponatremia	bor 1.3 mg/m^2 + len 10 mg
HZV reactivation, G4 neutropenia	bor 1.3 mg/m^2 + len 15 mg
Maximum tolerated dose	bor 1.0 mg/m^2 + len 15 mg
Dose reductions	bort=5, len=6, both=5
Discontinuations	1 with dexamethasone

Bort, bortezomib; len, lenalidomide; MTD, maximumm tolerated dose; dex, dexamethasone

Richardson PG, et al. *Blood.* 2006;108:abstract 405.

Lenalidomide plus bortezomib: response rates

Len	Bort 1.0 mg/m^2	Bort 1.3 mg/m^2
5 mg	2 PR, 1 MR	1 CR, 2 PR
10 mg	1nCR, 2 PR	2 Pr, 2 MR, 1 SD, 1 PD
15 mg	2 PR, 4 MR, 7 SD, 1 PD	2 PR, 5 SD

Lenalidomide plus bortezomib with/without dexamethasone is well tolerated and very active with durable responses in heavily pre-treated patients with relapsed and/or refractory MM

PR, partial response; MR minimal response;
PR, complete response; nCR, near complete response;
SD, stable disease; PD, progressive disease

Richardson PG, et al. *Blood.* 2006;108:abstract 405.

Lenalidomide plus bortezomib plus dexamethasone: baseline demographics

Baseline characteristics	
Relapse MM, n	24
Relapse/refractory MM, n	17
Male, %	66
IgG MM, %	63
Durie-Salmon stage III, %	59
Median age, years	67
Prior therapies, median	2
Subtypes of prior therapies, %	
Lenalidomide	2
Bortezomib	68
Dexamethasone	90
Thalidomide	78
SCT	32
Cycles of treatment, median	7

SCT,
stem cell transplant

Anderson KC et al. J Clin Oncol 2008;26:abs 8545.

Lenalidomide plus bortezomib plus dexamethasone: efficacy outcomes

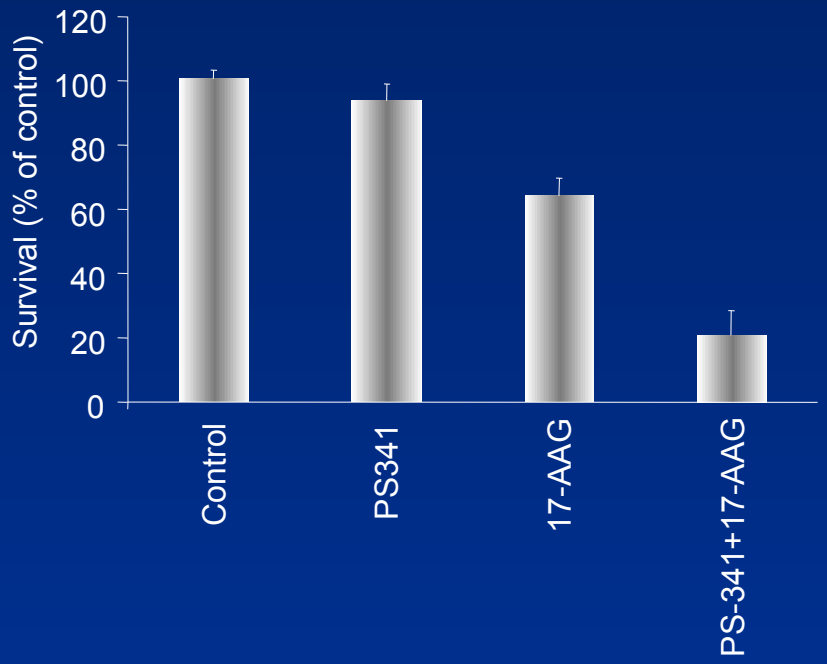
Efficacy outcomes	
ORR (95% CI), %	73 (55.6-85.1)
≥PR, %	55
VGPR/nCR/CR, %	36
Median DoR (95% CI), weeks	39 (13.5-63)
Median TTP, PFS and OS	not yet reached

ORR, overall response rate; PR, partial response; VGPR, very good partial response; nCR, near complete response; CR, complete response; DoR, duration of response; TTP, time to progression; PFS, progression free survival; OS, overall survival

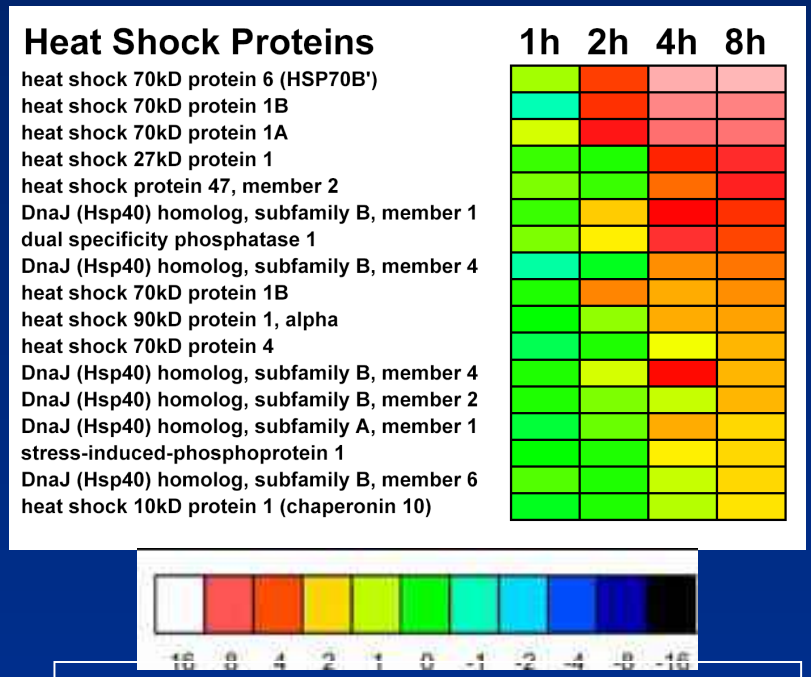
Anderson KC et al. J Clin Oncol 2008;26:abs 8545.

Tanespimycin + Bortezomib
Synergistic Anti-myeloma Activity

In vitro cytotoxicity model using myeloma cell lines: *synergy*



Induction of Hsp70 seen at 2 hrs; Hsp90 transcription increase occurring ~4-8 hrs following tanespimycin/BZ



Transcription / Translation Regulation
Signal Intensity

Mitsiades CS et al. Blood 2006 Feb 1;107(3)

Bortezomib plus tanespimycin: study design

Dose escalation and dose confirmation with two different formulations of tanespimycin

Days 1, 4, 8, 11 of every 21-day cycles

Dose escalating phase (n=36):
Tanespimycin 100-340 mg/m^2 as 1-hour infusion plus bortezomib 0.7-1.3 mg/m^2

Dose confirmation phase (n=27):
Cremophor (n=13) vs suspension formulation without steroid premedication (n=14)

Richardson PG et al. Blood 2007;110:abstract 1165.

Bortezomib plus tanespimycin: safety outcomes

No G3 neurotoxicity with any dose		
Recommended dose	Tanespimycin 340 mg/m^2	Bortezomib 1.3 mg/m^2

No difference in toxicity between 2 formulations		
G3/4 thrombocytopenia with tanespimycin formulations	Cremophor 15%	Suspension 12%

Diarrhea	Dizziness	Nausea	AST	Vomiting	Fatigue	ALT	Peripheral oedema
39%	27%	23%	23%	23%	19%	19%	19%

ALT, alanine aminotransferase; AST, aspartate aminotransferase

Richardson PG et al. Blood 2007;110:abstract 1165.

Bortezomib plus tanespimycin: response rates

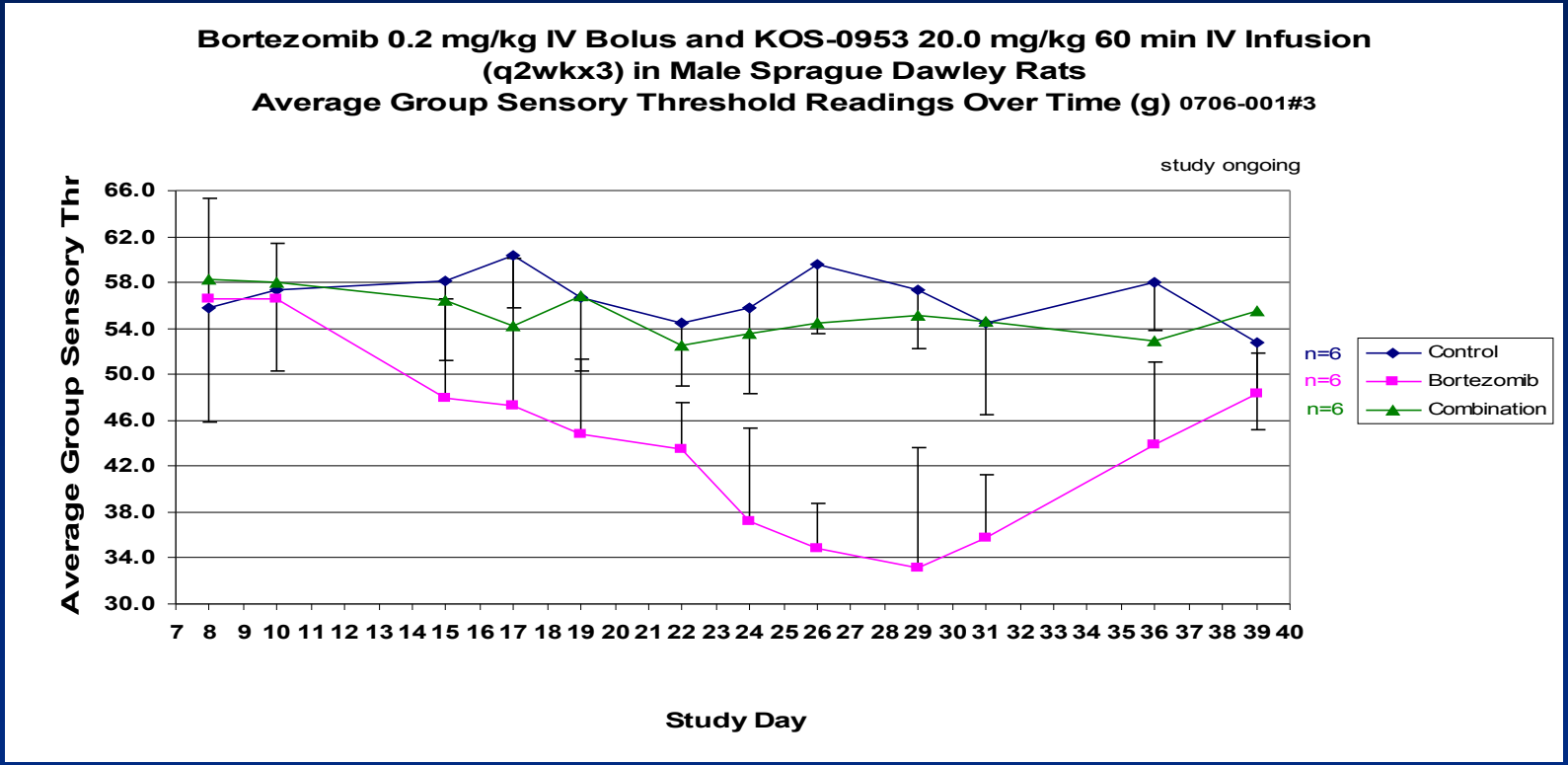
Bortezomib refractory	3 DR
Bortezomib-naïve, Cremophor formulation, n	
CR	2
PR	2
MR	4
Bortezomib-naïve, suspension formulation, n	
CR	1
PR	2
MR	1

Ongoing Phase 3 trial of Bortezomib plus tanespimycin versus Bortezomib in relapsed myeloma

DR, durable response.

Richardson PG et al. Blood 2007;110:abstract 1165.

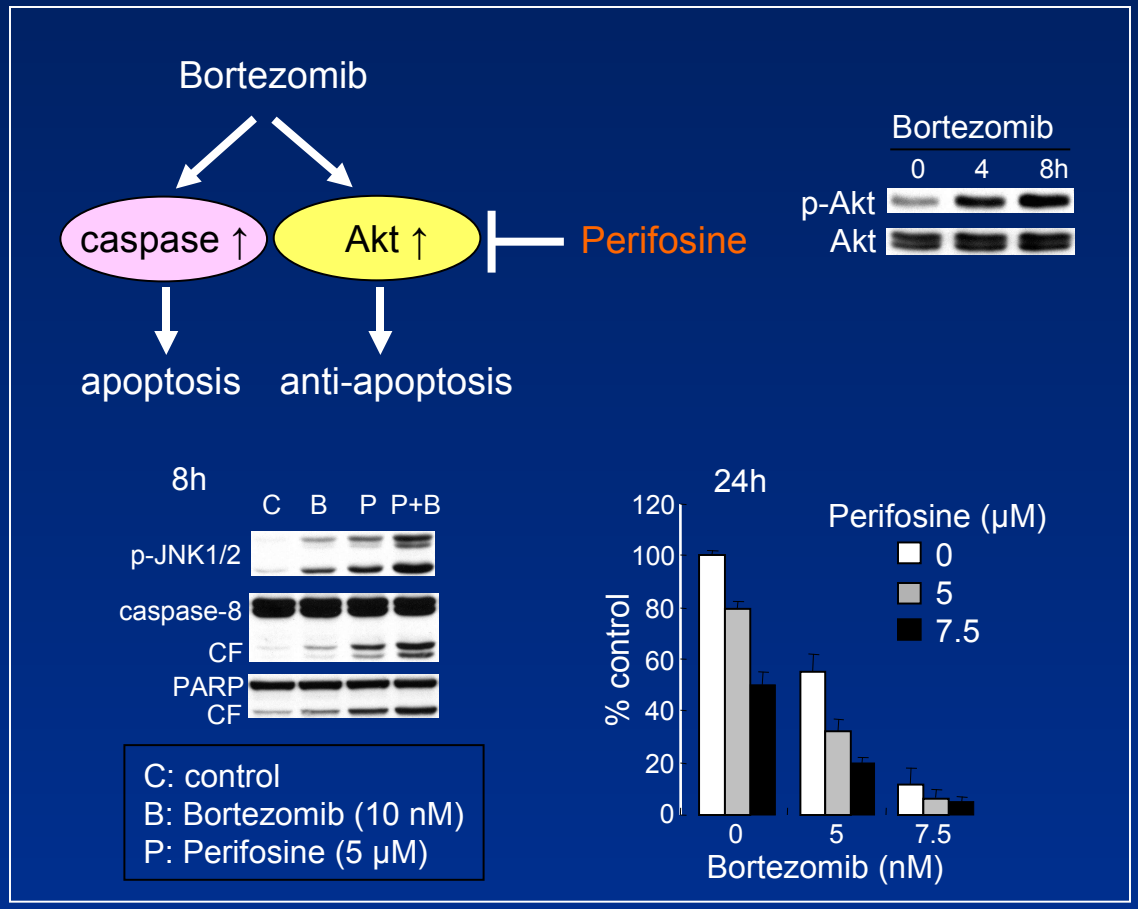
Rodent Model of Neuropathy



- 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 to bortezomib alone, indicating a neuroprotective effect of tanespimycin

Richardson et al, ASH 2007

Akt Inhibitor Perifosine Enhances Bortezomib-Induced Cytotoxicity in MM Cells



Hideshima et al. Blood 2006; 107: 4053-52

Bortezomib plus perifosine: study design

Phase I/II study

Relapse or relapse/refractory MM previously treated with bortezomib (N=18)

Perifosine 50 mg or 100 mg daily

Bortezomib 1.0 or 1.3 mg/m^2 on days 1, 4, 8, 11 in 21-day cycles

Dexamethasone 20 mg on days of/after each bortezomib dose in patients with PD

NCI CTCAE v3.0 used for toxicity assessment

DLT any G non-hematologic toxicity, G4 neutropenia for ≥5 days and/or neutropenic fever or platelets <10,000/mm^3 on >1 occasion despite transfusion

Response assessed by modified EBMT and Uniform criteria

Richardson P et al. Blood 2007;110:abstract 1170

Bortezomib plus perifosine: baseline characteristics

Baseline characteristics	
Relapse/refractory MM, n	14
Male, %	61
Median age (range), years	64 (42-87)
Prior therapies, median (range)	5 (2-7)
Subtypes of prior therapies, %	
Bortezomib	100
Dexamethasone	89
Thalidomide	67
Lenalidomide	33
SCT	56

SCT, stem cell transplant

Richardson P et al. Blood 2007;110:abstract 1170

Bortezomib plus perifosine: safety

Safety outcomes	
Grade 3/4 AEs, %	
Fatigue	6
Thrombocytopenia	25
Anaemia	13
Dose reductions, n	
Perifosine	1
Bortezomib	3

Bortezomib plus perifosine: efficacy

Response (n=15)*	N (%)	Duration (weeks)
PR (peri+bor)	2 (13)	24, 13+
MR (peri+bor)	1 (7)	10+
MR (peri+bor+dex)	2** (13)	38+, 18+
SD (peri+bor)	3 (20)	18+, 16+, 13+
SD (peri+bor+dex)	3 (20)	38, 22+, 12+

Perifosine in combination with bortezomib (with/without dexamethasone) was well tolerated and active in mostly relapsed/refractory MM patients

*Dexamethasone added to 6 patients
**patients refractory to prior bort+dex
SD, stable disease defined as <25% reduction in M-protein

Richardson P et al. Blood 2007;110:abstract 1170

Perifosine Bortezomib Dexamethasone (n =72)

Richardson et al, ASH 2008 Abstr 870

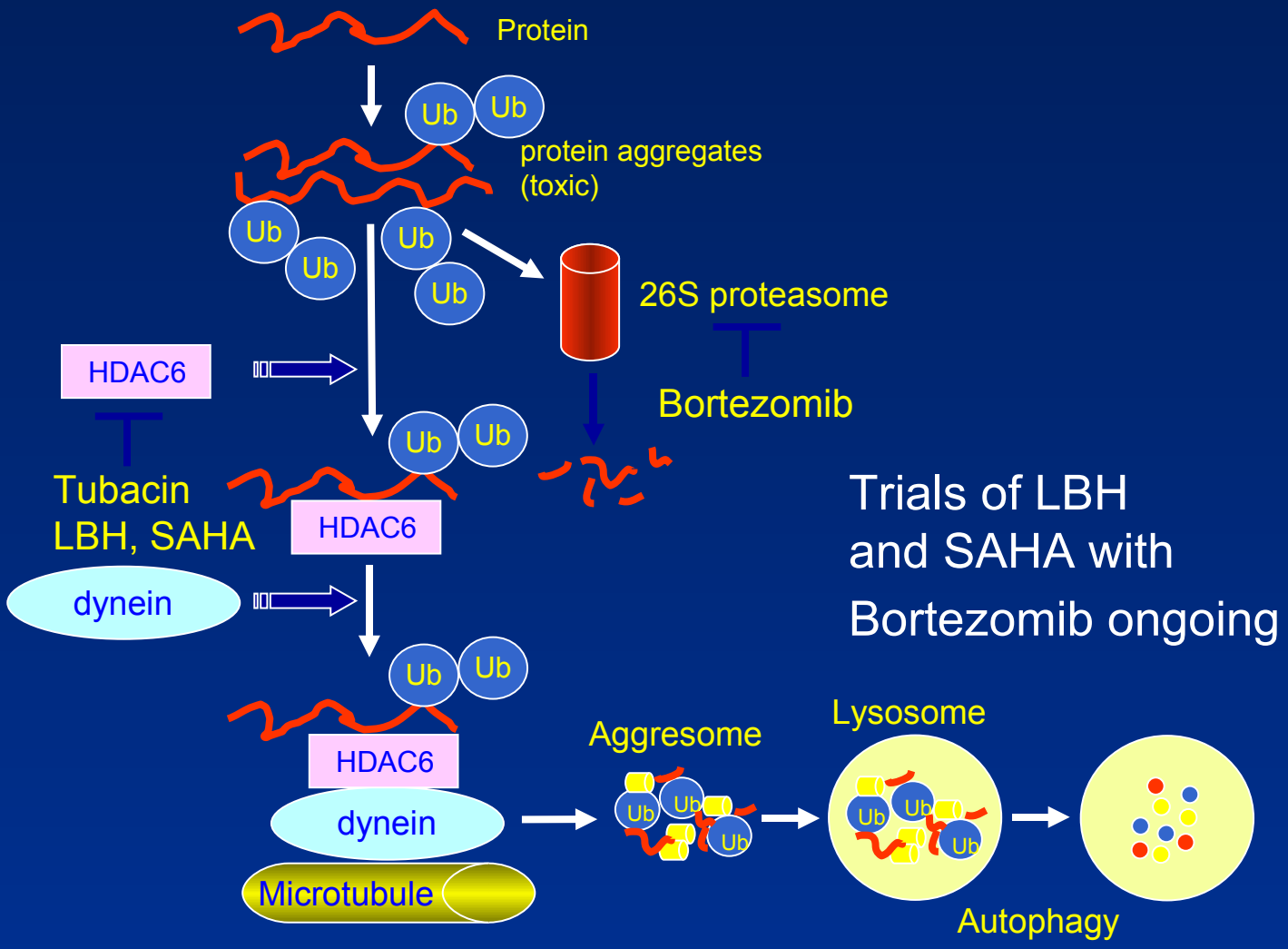
Median 5 prior lines of treatment

- Median # of prior Bz lines of treatment: 2
- Overall Response Rate: 38%
- Median TTP: 6.3 mos
- Bortezomib Refractory Pts (n = 52)
- Overall Response Rate: 31%
- Median TTP: 6.2 mos
- Toxicities manageable

Clinical trial of Bortezomib and perifosine versus Bortezomib in relapsed MM ongoing for FDA approval

Richardson et al, ASH 2008 Abstr 87

Blockade of Ubiquinated Protein Catabolism



Trials of LBH and SAHA with Bortezomib ongoing

Hideshima et al, Clin Cancer Res;2005; 11: 8530
Catley et al, Blood 2006; 108: 3441-9.

Bortezomib plus vorinostat A: study design

Phase I

Relapsed/refractory MM

Maximum tolerated dose, pharmacokinetics, pharmacodynamics

Bortezomib 1.3 mg/m^2 on days 1, 4, 8 and 11 of a 21-day cycle

Vorinostat 100-400 mg days 4-11

Badros AZ et al., J Clin Oncol 2008;26: abstract 8548

Bortezomib plus vorinostat A: baseline characteristics

Baseline characteristics, n=23	
Median age (range), years	54 (39-78)
Median time from diagnosis to study (range), years	5.3 (1.5-9)
IgG, n	11
IgA, n	4
Light chain, n	8
Complex karotype, n	14
Prior therapies, median (range)	7 (3-13)
Prior therapies, n	
Thalidomide	23
Lenalidomide	17
SCT	20

Badros AZ et al., J Clin Oncol 2008;26: abstract 8548

Bortezomib plus vorinostat A: safety

Safety	
Maximum tolerated dose	bortezomib 1.3 mg/m^2 + vorinostat 400 mg
Grade 3/4 AEs, n	
Requiring transfusion	13
Growth factors	6
Fatigue	11
Diarrhea	5
Atrial fibrillation	1
Shingles	1
Pneumonia	2

Badros AZ et al., J Clin Oncol 2008;26: abstract 8548

Bortezomib plus vorinostat A: response rates

Prior bortezomib	ORR	N=	VGPR	PR	SD	PD
Naïve	42%	4	1	2	1	
Prior treatment		10	1	2	5	1
Refractory		9		3	4	1

Badros AZ et al., J Clin Oncol 2008;26: abstract 8548

Bortezomib plus vorinostat B: study design

Phase I, multicenter, open-label trial (N=34)

Bortezomib 0.7, 0.9, 1.1 or 1.3 mg/m^2 on days 1, 4, 8 and 11 of a 21-day cycle

Vorinostat 200 mg bid or 300-400 mg daily for 14 days

Cycles repeated every 21 days for ≤8 cycles or until PD or intolerable toxicity

Dexamethasone 20 mg (days 1-4 and 17-20) could be added to patients with PD

Weber D et al., Blood 2008;112:abstract 871

Bortezomib plus vorinostat B: safety

Safety outcomes	
Highest dose	bort 1.3 mg/m^2 + vorin 400 mg
Maximum tolerated dose	Not determined
Dose limiting toxicities	
G3 transient AST elevation	bort 0.9 mg/m^2 + vorin 400 mg
G4 thrombocytopenia	bort 1.3 mg/m^2 + vorin 400 mg
Drug-related AE, %	
Nausea	62
Diarrhea	59
Thrombocytopenia	50
Vomiting	50

Weber D et al., Blood 2008;112:abstract 871

Bortezomib plus vorinostat B: efficacy

Efficacy outcomes	
Overall, %	
PR	26
MR	21
SD	53
Prior bortezomib (n=13), %	
PR	39
MR	8
SD	54
Median (95% CI) DoR, days	89 (9-369)

The combination of bortezomib and vorinostat is active for treatment of MM, even among patients with prior exposure to bortezomib

Weber D et al., Blood 2008;112:abstract 871

Vorinostat-Bortezomib

Weber et al ASH 2008 Abstr 871

Effective for treatment of relapsed/refractory MM

Overall response (PR + CR) ~38-43%

≥ SD ~90%

Effective despite prior bortezomib therapy

Overall response ~29-35%

SD ~41-53%

Overall response refractory pts ≥ PR ~29-38%

SD refractory pts ~42-50%

Well Tolerated

Fatigue, Diarrhea, thrombocytopenia

Phase III trial of Bortezomib and SAHA versus Bortezomib in relapsed MM ongoing for FDA approval

Panobinostat-Bortezomib

Active for treatment of relapsed / refractory MM

- Overall response (PR + VGPR + CR) = 50%

Active despite prior bortezomib therapy

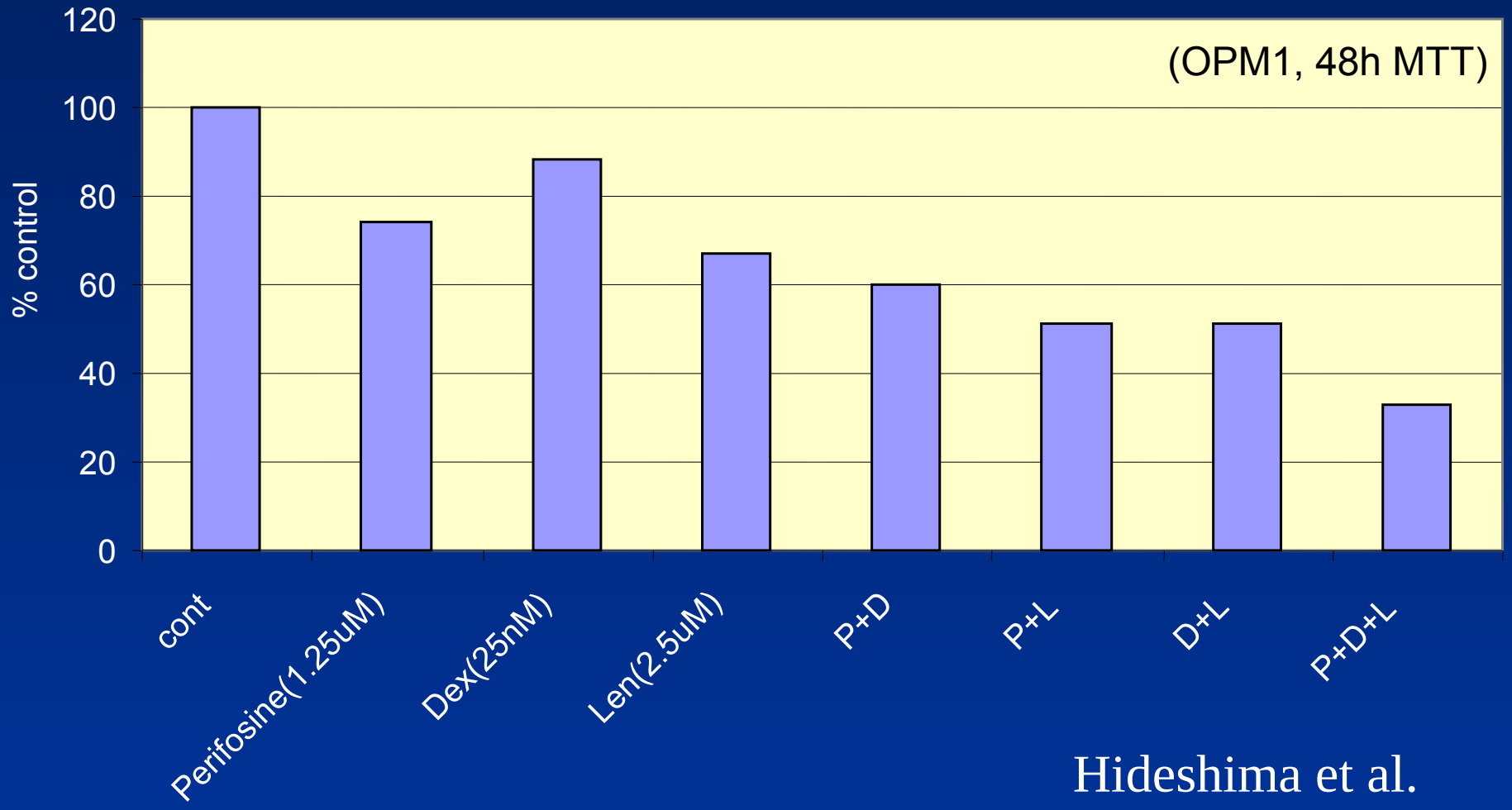
- 7 responses in patients with prior bortezomib
- 5 of these responders were refractory to their last bortezomib based therapy

Well tolerated

- Fatigue, Diarrhea, Thrombocytopenia

Szer et al, 2009

Perifosine Enhances MM Cell Cytotoxicity Induced by Lenalidomide + Dexamethasone



Hideshima et al.

Phase I MMRC Study of Three Drugs: Perifosine Dexamethasone and Lenalidomide

- Relapsed or Refractory MM (stage ≥ I): 4 - 54 patients
- 4 Week Cycle as follows:
  - Peri 50 mg + Dex 20 mg* + Len 15 mg** daily – 6 patients
  - Peri 50 mg + Dex 40 mg* + Len 15 mg** daily – 6 patients
  - Peri 100 mg + Dex 20 mg* + Len 15 mg** daily – 6 patients
  - Peri 100 mg + Dex 40 mg* + Len 15 mg** daily – 6 patients
  - Peri 50 mg + Dex 20 mg* + Len 25 mg** daily – 6 patients
  - Peri 50 mg + Dex 40 mg* + Len 25 mg** daily – 6 patients
  - Peri 100 mg + Dex 20 mg* + Len 25 mg** daily – 6 patients
  - Peri 100 mg + Dex 40 mg* + Len 25 mg** daily – 6 patients

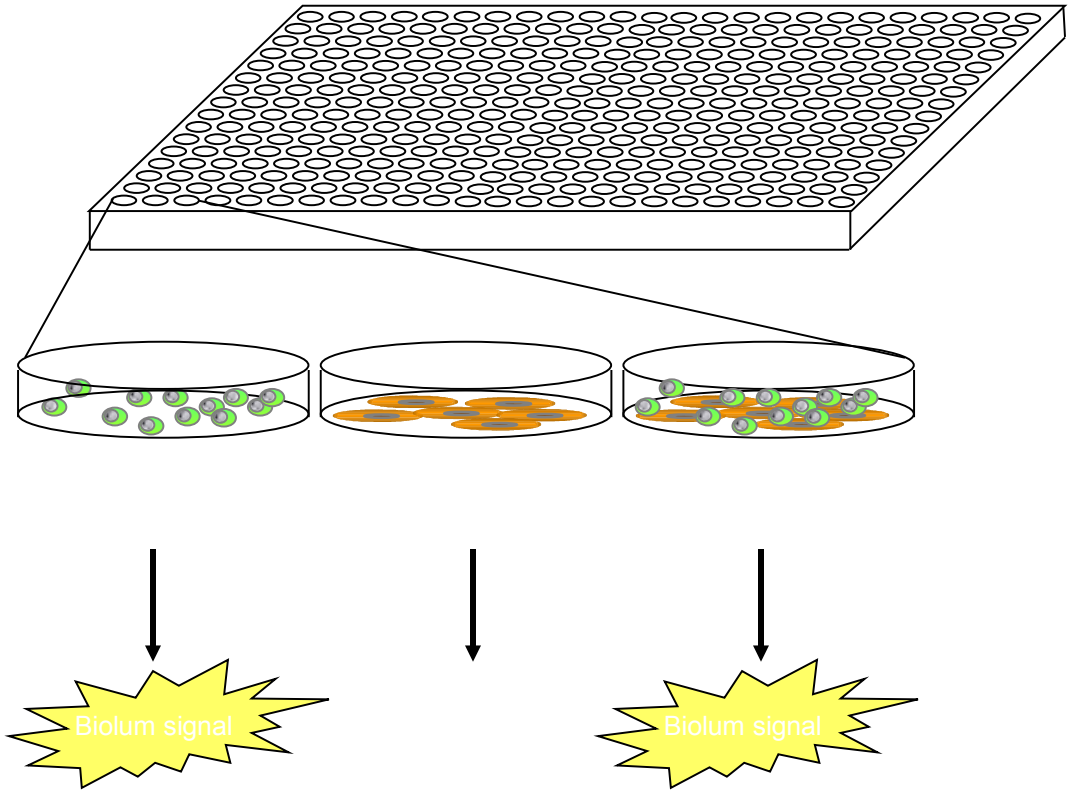
Phase I MMRC Study of Three Drugs: Perifosine Dexamethasone and Lenalidomide

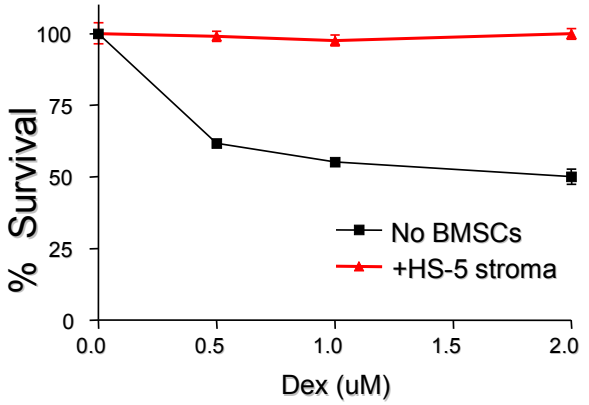
Relapsed Myeloma

Trial now completed within MMRC

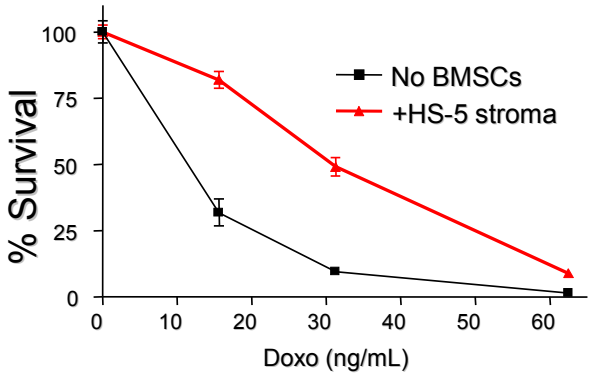
Well tolerated with responses in the majority of patients

High-Throughput Screening of MM with BMSCs to Define Optimal Combinations

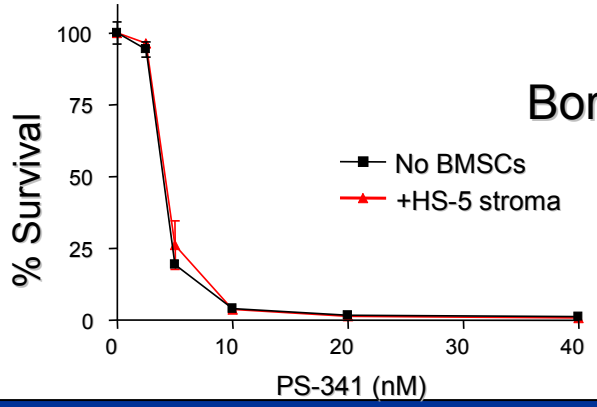




Dex



Doxo



Bortezomib

Conclusions and Future directions

- Best combinations are informed by preclinical rationale
- Novel combination therapies result in encouraging results, including high response rates and manageable toxicity
- Further studies are ongoing to further optimize the regimens and ensure that patients receive more effective and well-tolerated treatment

United Nations Against Myeloma:
Jerome Lipper and Lebow Bench to Bedside Research Team

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