Novel Agents and Regimens for Relapsed and Refractory Multiple Myeloma

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2010 Guidelines

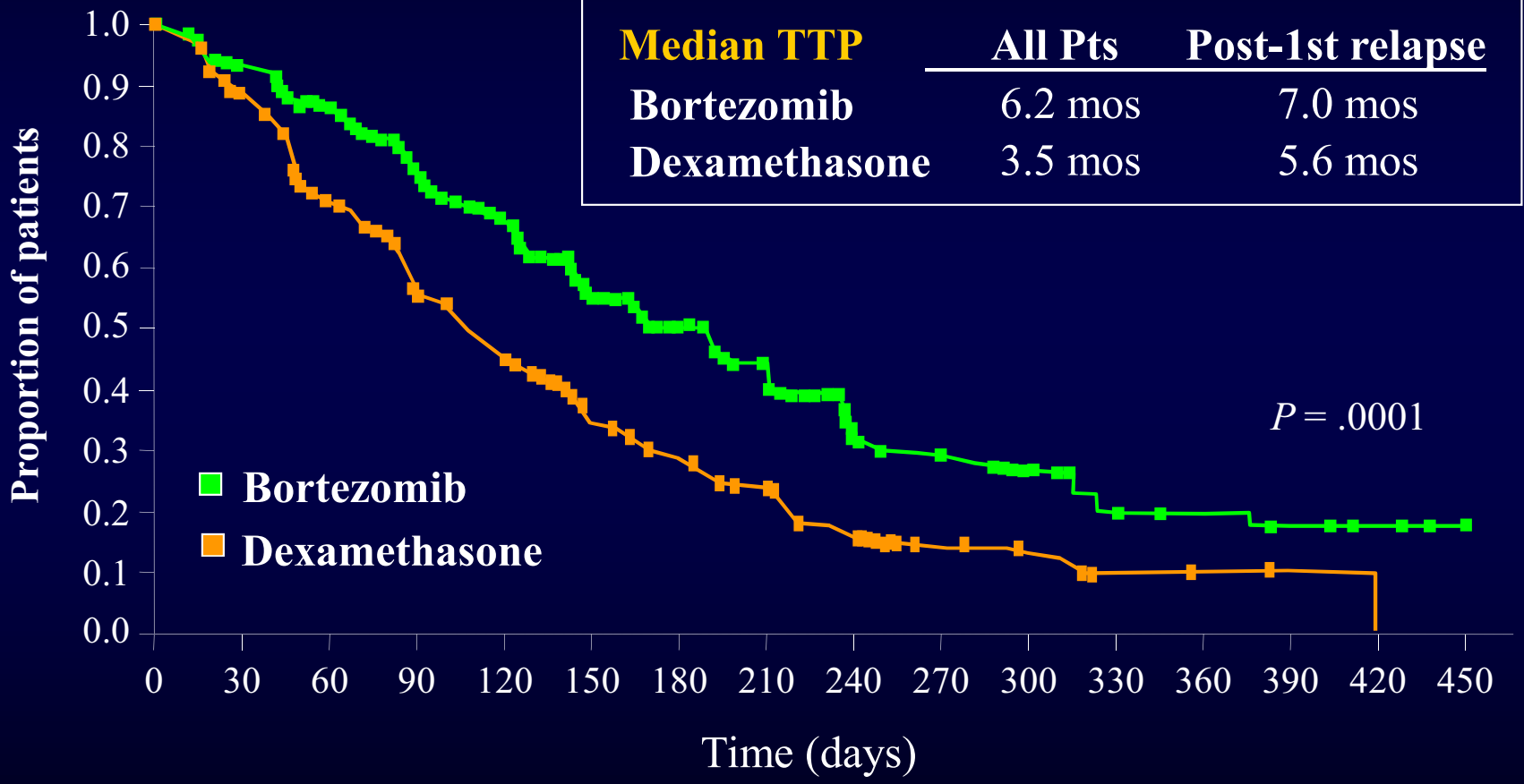
- Repeat primary therapy (if relapse occurs at > 6 mos)
- Bortezomib (cat. 1)
- Bortezomib/liposomal doxorubicin (1)
- Lenalidomide/dex (1)
- Bendamustine (2B)
- Bortezomib/dex
- Lenalidomide
- High-dose cyclophosphamide, or Cy-VAD
- Thalidomide, or thalidomide/dex
- Dex, or DCEP, or DT-PACE

NCCN Practice Guidelines. Multiple Myeloma. V.1.2011.

Bortezomib vs. Dex

78% improvement in median time-to-progression

Median TTP	All Pts	Post-1st relapse
Bortezomib	6.2 mos	7.0 mos
Dexamethasone	3.5 mos	5.6 mos



Richardson, PG et al. *N Engl J Med*. 2005;352:2487-2498.

Bortezomib/PLD vs. Bortezomib

Median progression-free survival

Bortezomib	PLD + Bortezomib
6.5 months	9.3 months

Statistical analysis:
HR (95% CI) 1.82 (1.41-2.35)
***P* = .000004**

Orlowski, RZ et al. J. Clin. Oncol. 25:3892-3901, 2007.

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Bortezomib Combination Data

Regimen	Phase	n	CR + PR	CR + nCR	Reference
Bortezomib	3	333	43 %	16 %	Richardson PG, *et al.* *Blood* 2007;110:3557–3560
+ Dex (after cycle 2 for PD or after cycle 4 for SD)	3b expanded access program	638	51 %	33 % (CR + VGPR)	Mikhael JR, et al. *Br J Haematol* 2009;144:169–175
+ Liposomal doxorubicin	3	324	52 %	17 %	Harousseau JL, *et al.* *ASCO* 2007. Abstract 8002.
+ doxorubicin + dexamethasone **(PAD)**	2	64	67 %	25 % (CR + VGPR)	Palumbo A, *et al.* *Ann Oncol* 2008;19:1160–1165
+ intermediate-dose dex + cyclophosphamide **(VCD)**	2	54	82 %	16 %	Kropff M, *et al.* *Br J Haematol* 2007;138:330-337
+ melphalan + prednisone + thalidomide **(VMPT)**	1/2	30	67 %	43 % (includes VGPR)	Palumbo A, *et al.* Blood 2007;109: 2767–2772

Lenalidomide/Dex vs. Dex

Survival benefit retained despite 47% cross-over

- **Median OS**
  - **Len/Dex: 38 months**
  - **Placebo/Dex: 31.6 months**
  - ***P* = .045**

Dimopoulos, MA et al. Leukemia 23:2147-2152, 2009.

Other Lenalidomide Combinations

Lenalidomide	Phase	n	CR + PR	CR + nCR	Reference
+ melphalan + prednisone + thalidomide (MPTR)	2	44	75 %	34 % (VGPR + CR)	Palumbo A, Leukemia. 2010;24:1037-1042.
+ bortezomib + dexamethasone (VRD)	2	64	69%	26 %	Anderson KC, et al. ASCO 2009. Abstract 8536.
+ cyclophosphamide + prednisone (RCP)	1/2	15	87 % (including MR)	NA	Reece DE, *et al.* ASH 2008. Abstract 1723.
+ doxorubicin + dex (RAD)	1/2	69	73 %	15 % (CR only)	Knop S, et al. Blood 2009;113:4137-4143.

Upcoming Promising Approaches

- Novel single agents
  - Carfilzomib
  - Pomalidomide
- New combination regimens
  - Bortezomib + siltuximab / vorinostat / panobinostat / tanespimycin / perifosine
  - Bortezomib/PLD + vorinostat
  - Carfilzomib + len/dex
  - Lenalidomide/dex + vorinostat / α-CS-1 / thalidomide

2009 ASH Abstract 303

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PX-171-004, An Ongoing Open-Label, Phase II Study of Single-Agent Carfilzomib (CFZ) in Patients with Relapsed or Refractory Myeloma (MM); Updated Results From the Bortezomib-Treated Cohort

Siegel D, Wang L, Orlowski RZ, Kaufman JL, Stewart AK, Kukreti V, Alsina M, Jakubowiak AJ, Jagannath S, McDonagh KT, Belch A, Bahlis NJ, Shustik C, Le MH, Kunkel L, Bennett MK, Kauffman M, Vij R, and The Multiple Myeloma Research Consortium (MMRC)

Prior Therapies & Refractory Status

Median Number of Prior Therapies	3
Prior Treatments	**N (%)**
Bortezomib	35 (100)
Lenalidomide *OR* Thalidomide	27 (77)
Lenalidomide *AND* Thalidomide	10 (29)
Corticosteroid	34 (97)
Alkylator	31 (89)
Anthracycline	11 (31)
Stem Cell Transplant	28 (80)
	N (%)
Refractory to Last Therapy	14 (40)

Siegel D, et al. ASH 2009. Abstract 303.

Patient Characteristics

Prior Therapies

	Cohort 1 20 mg/m²		Cohort 2 20/27 mg/m²
	BTZ-treated (N=36)	BTZ-naive (N=59)	BTZ-naive (N=60)
Median no. of prior therapies (range)	3	2	2
Prior treatments, %			
Bortezomib	100	0	3
Thalidomide (Thal)	69	68	53
Lenalidomide (Len)	**39**	**46**	**68**
Len and Thal	31	20	32
Corticosteroid	97	98	95
Alkylating agent	89	81	83
Anthracycline	31	24	25
Stem cell transplant	81	78	68
Refractory to last therapy,* %	**42**	**49**	**40**

*Most patients received a combination regimen as their last therapy

Vij R, et al. ASCO 2010. Abstract 8000.

Responses

	N (%)
CR	1 (3)
VGPR	1 (3)
PR	4 (12)
MR	4 (12)
SD	13 (39)

≥PR : 18%

≥MR : 30%

≥SD : 70%

ORR (≥ PR) = 18%

CBR (≥ MR) = 30%

Disease Control in 70%

Siegel D, et al. ASH 2009. Abstract 303.

Outcomes

Single-agent Anti-tumor Activity

BTZ-treated Cohort

Response rate	Cohort 1 20 mg/m^2 (N=34)*
CR	0%
VGPR	9%
PR	12%
MR	12%
SD	35%
PD	32%

ORR 21% (CR, VGPR, PR)

CBR 33% (CR, VGPR, PR, MR)

*Response-evaluable population

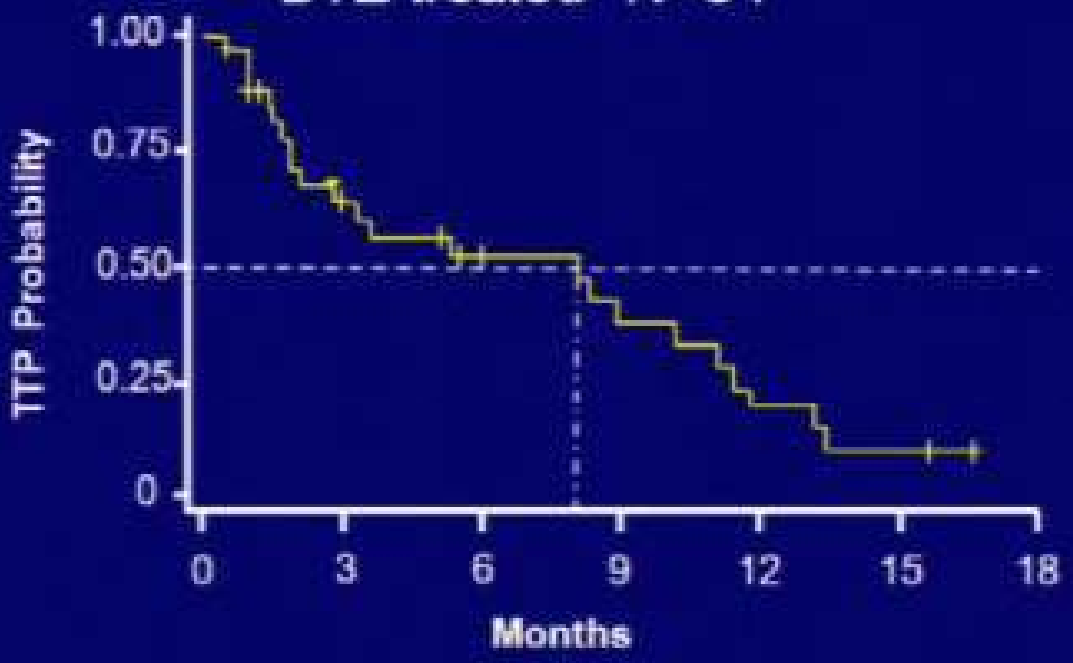
Vij R, et al. ASCO 2010. Abstract 8000.

Time to Progression

	BTZ-treated (N=33)
Median Time to Progression	5.3 months
Median follow up	11.5 months

Siegel D, et al. ASH 2009. Abstract 303.

Time to Progression



Median TTP, mos (95% CI)	8.1 (2.8–11.1)
Median DOR, mos (95% CI)	
≥MR	8.5 (7.3–NE)
≥PR	11.5 (7.2–15.2)

*Response-evaluable population; NE=not estimable

Vij R, et al. ASCO 2010. Abstract 8000.

Adverse Events

Adverse Event*,1	Overall n (%)	≥ Grade 3 n (%)
Fatigue	22 (63)	1 (3)
Nausea	19 (54)	1 (3)
Vomiting	14 (40)	1 (3)
Dyspnea	13 (37)	2 (6)
Diarrhea	12 (34)	0 (0)
Increased Creatinine	12 (34)	1 (3)
Upper Respiratory Infection	12 (34)	2 (6)

Siegel D, et al. ASH 2009. Abstract 303.

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Adverse Events*

Reported in ≥20% or ≥Grade 3 in ≥5% (Safety Population)

Adverse Event* (N=155)	All Grades (%)	≥ Grade 3 (%)
Pneumonia	11	11
Anemia	32	9.7
Neutropenia	25	9.7
Thrombocytopenia	25	9.0
Fatigue	54	5.2
Dyspnea	34	3.9
Upper respiratory infection	28	1.9
Vomiting	25	1.9
Diarrhea	28	1.3
Headache	28	1.3
Peripheral edema	21	1.3
Nausea	45	0.6
Pyrexia	27	0.6
Increased creatinine	20	0.6
Cough	27	0

*Includes both related and non-related AEs

Vij R, et al. ASCO 2010. Abstract 8000.

Neuropathy

- Prior history of drug- or disease-related neuropathy: 83%
- Active grade 1/2 neuropathy at baseline: 69%
- Neuropathy adverse events noted on study
  - Grade 1/2 (n = 3): 8.6%
  - Grade 3 (n = 1): 2.9%
  - Grade 4: 0%
- No discontinuations or dose reductions for peripheral neuropathy

Siegel D, et al. ASH 2009. Abstract 303.

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Treatment-Emergent Neuropathy Was Infrequent and Not Treatment Limiting

	Cohort 1 20 mg/m²		Cohort 2 20/27 mg/m²
	BTZ-treated (N=36)	BTZ-naïve (N=59)	BTZ-naïve (N=60)
Active Grade 1/2 peripheral neuropathy at baseline,* %	50	42	43
Treatment-emergent neuropathy, %			
Grade 1/2	16.7	11.9	15
Grade 3	2.8	1.7	0
Grade 4	0	0	0
Treatment discontinuations due to peripheral neuropathy, %	2.8%	0	0

*Grade based on physical assessment at screening (NCI-CTC scale)

Vij R, et al. ASCO 2010. Abstract 8000.

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2009 ASH Abstract 301

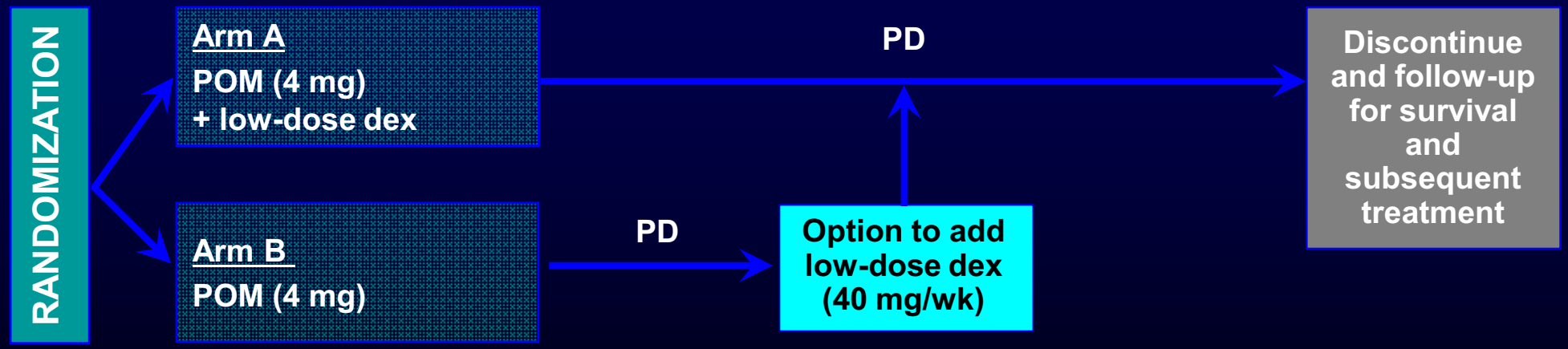
A Phase 1/2 Multi-Center, Randomized, Open Label Dose Escalation Study to Determine the Maximum Tolerated Dose, Safety, and Efficacy of Pomalidomide Alone or in Combination with Low-Dose Dexamethasone in Patients with Relapsed and Refractory Multiple Myeloma Who Have Received Prior Treatment That Includes Lenalidomide and Bortezomib

Richardson R, Siegel D, Baz R, Kelley SL, Munshi NC, Sullivan D, McBride L, Doss D, Larkins G, Jacques C, Donaldson A, and Anderson KC

Study Design

Phase 1 (MTD)

Phase 2 (Open Label)



Richardson P, et al. ASH 2009. Abstract 301.

Safety Profile

Adverse event, n	POM Dose 2 mg (n = 6)	3 mg (n = 8)	4 mg (n = 8)	5 mg (n = 10)
Neutropenia[a]	8	8	7	9
Thrombocytopenia[a]	2	6	0	0
Anemia[a]	2	7	2	0
VTE	1 (G2)	0	0	1 (G3)
Treatment-emergent SAEs	7	7	4	4
Deaths[b]	2	1	1	0
POM dose reduction	0	1	0	9

SAEs, severe adverse events; VTE, venous thromboembolism.

a. Grade 3/4; b. Includes deaths occurring at least 28d after last treatment (both due to rapid PD).

Richardson P, et al. ASH 2009. Abstract 301.

Best Responses

POM Dose (± Dex)	Best Response[a][1]
2 mg (n = 6)	1 PR, 1 SD, 1 PD, 3 NE
3 mg (n = 8)	1 CR, 1 MR, 5 SD, 1 NE
4 mg (n = 8)	2 PR, 3 MR, 1 SD, 2 NE
5 mg (n = 10)	3 PR, 2 MR, 3 SD, 1 PD, 1 NE

CR, complete response; MR, minimal response; NE, not evaluable; PD, progressive disease; PR, partial response; SD, stable disease. a. As measured using modified EBMT criteria[2,3] every 28d.

- 7/25 evaluable pts (28%) ≥ PR; 13/25 pts (52%) ≥ MR[4]
- 15 pts received dex in addition to POM for either lack of response or PD; 8/15 pts (53%) improved response after dex added, with durability of response also improved from 13.5 to 16.9 wks[1]

1. Richardson P, et al. ASH 2009. Abstract 301. 2. Bladé J, et al. Br J Haematol. 1998;102:1115-1123. 3. Richardson PG, et al. N Engl J Med. 2003;348:2609-2617. 4. Anderson KC, et al. Leukemia. 2008;22:231-239.

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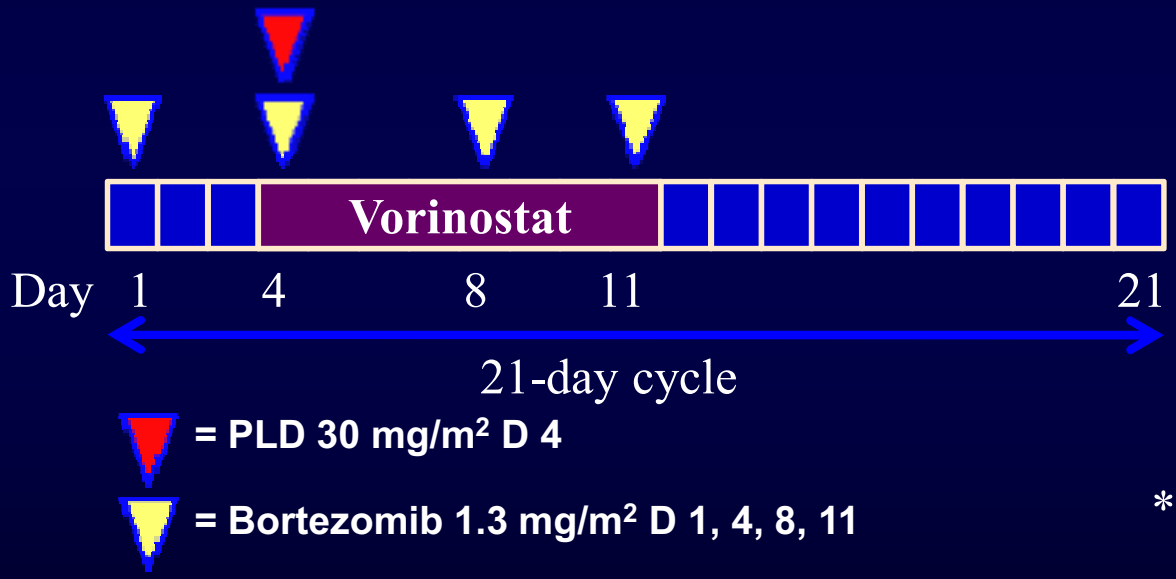
2009 ASH Abstract 306

Vorinostat in Combination with Pegylated Liposomal Doxorubicin and Bortezomib for Patients with Relapsed/Refractory Multiple Myeloma: Results of a Phase I Study

Voorhees PM , Gasparetto C, Richards KL, Garcia R, Strader JS, Ferraro M, MacLean J, Winans D, Moore DT, Dodd A, Foster MC, Gabriel DA, Shea TC, Serody J, van Deventer HW, Rizvi S, Orlowski RZ, and Hurd DD

Study Design

- Multi-center phase I trial targeting relapsed and/or refractory myeloma



Dose Level	Vorinostat* D 4-11†
1	200 mg
2	300 mg
3	400 mg

* Vorinostat dosed 2 hours prior to PLD

Voorhees PM, et al. ASH 2009. Abstract 306.

Response Rate

- ORR 78% (7/8); 1 non-responder in cohort 1

Dose Level (# evaluable pts)	Response
1 (N=3)	2 PRs, 1 PD†
2 (N=3)	1 CR, 1 VGPR‡, 1 PR
3 (N=2)	2 VGPRs‡

† Disease refractory to prior bortezomib-based therapy and VAD

‡ 2 VGPRs with unmeasurable disease by SFix and UFix awaiting bone marrow confirmation of response depth

Voorhees PM, et al. ASH 2009. Abstract 306.

2008 ASH Abstract 867

Preliminary Results of CNTO 328 (Siltuximab), An Anti-Interleukin-6 Monoclonal Antibody, in Combination with Bortezomib in the Treatment of Relapsed or Refractory Multiple Myeloma

Rossi J-F, Manges RF, Sutherland HJ, Jagannath S, Voorhees P, Sonneveld P, Delforge M, Pegourie B, Alegre A, de la Rubia J, La Police D, Bandekar R, Xie H, and Orlowski RZ

C0328T06 Study Design

RANDOMIZATION

290 patients with relapsed and/or refractory myeloma

INDUCTION: Bortezomib @ 1.3 mg/m^2 on days 1, 4, 8, 11, 22, 25, 29, 32 every 42 days for up to 4 cycles

Maintenance phase after induction dexamethasone added at progression

INDUCTION: Bortezomib as above + CNTO 328 @ 6 mg/kg on days 1, 15, and 29 for up to 4 cycles

Primary endpoint: PFS
Secondary: OS, ORR, safety, PK, PD

Rossi JF, et al. ASH 2008. Abstract 867.

Responses

- Responses by EBMT criteria seen in 57%
  - CR or PR: 12 pts (3 with CR, 9 with PR)
- Median TTP 8.7 months
  - Range 1.2-22.4
- Randomized comparison of bortezomib versus CNTO 328 + bortezomib underway
  - Accrual completed

Rossi JF, et al. ASH 2008. Abstract 867.

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2009 ASH Abstract 304

Phase Ib Multicenter Dose Escalation Study of Carfilzomib Plus Lenalidomide and Low Dose Dexamethasone (CRd) in Relapsed and Refractory Multiple Myeloma (MM)

Ruben Niesvizky R, Wang L, Orlowski RZ, William Bensinger W, Alsina M, Gabrail N, Gutierrez A, Kunkel L, Kauffman M and The Multiple Myeloma Research Consortium (MMRC)[8]

Study Design

- Multicenter phase Ib study
- Patients with 1-3 prior lines of therapy and relapsed multiple myeloma
- Cycles q 28 days

	Days of Administration (dose escalation cohorts)		
Agent	Cycles 1-4	Cycles 5-8	Cycles 9-16
CFZ	1, 2, 8, 9, 15, 16	1, 2, 8, 9, 15, 16	1, 2, 15, 16
Len	1-21	1-21	1-21
Dex 40mg	1, 8, 15, 22	1	1

Niesvizky R, et al. ASH 2009. Abstract 304.

Prior Therapies

Prior Therapies	Median (range)
Number	2 (1-3)
	%
Bortezomib	72
Immunomodulatory Agents	87.5
Lenalidomide	62.5
Thalidomide	44
Corticosteroid	97
Alkylating Agents	78
Anthracycline	28
Stem Cell Transplant	78
Refractory: immediate prior therapy	47

Niesvizky R, et al. ASH 2009. Abstract 304.

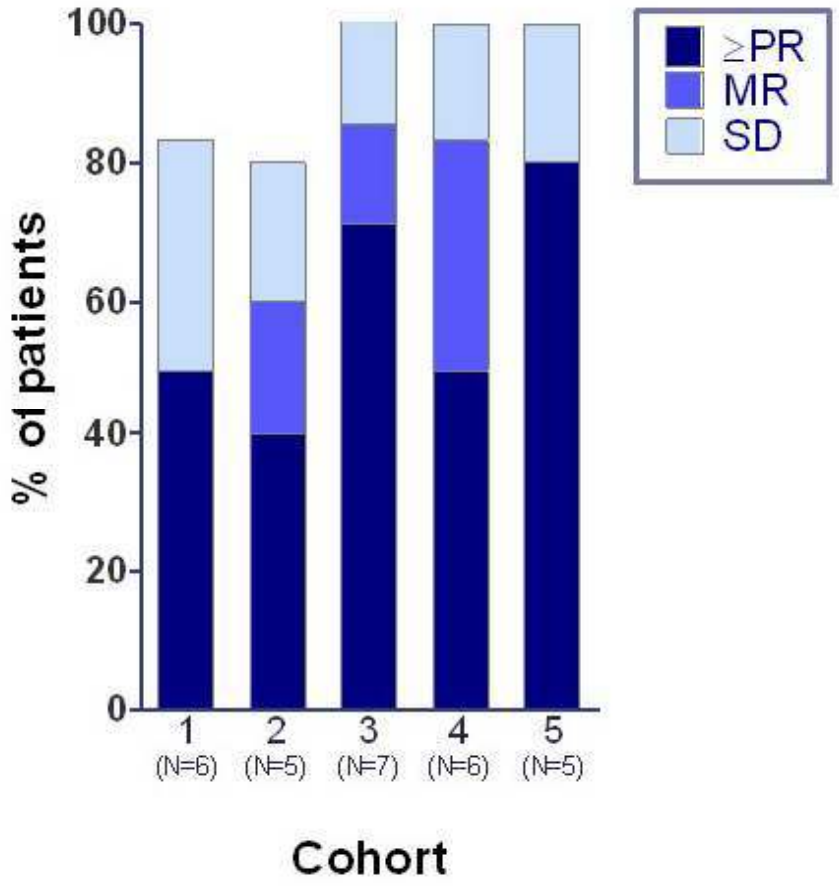
Adverse Events

Adverse Events	n (%)	
	All Grades ≥ 20%	Grade 3 / 4 ≥ 5%
Fatigue	12 (44)	-
Diarrhea	9 (33)	-
Neutropenia	9 (33)	6 (22)
Anemia	7 (26)	4 (15)
Back Pain	7 (26)	-
Cough	7 (26)	-
Dyspnea	7 (26)	-
Thrombocytopenia	6 (22)	6 (22)
Arthralgia	6 (22)	-
Rash	6 (22)	-
U Respiratory Infection	6 (22)	-
Hyperglycemia	5 (18)	3 (11)

- No DLTs or grade 5 toxicities through first 5 cohorts (N = 27)
- No fatigue ≥ grade 3 or thrombotic events

Niesvizky R, et al. ASH 2009. Abstract 304.

Activity



CRd: Cohorts 1-5
CFZ: 15 to 20 mg/m^2
LEN: 10 to 25 mg

Response	N (%)
CR/nCR	6 (21)
VGPR	5 (17)
PR	6 (21)
MR	4 (14)
SD	6 (21)

≥PR : 59%

≥MR : 72%

≥SD : 93%

- All responses seen at <MTD; 29/32 pts evaluable
- Cohort 6 will use carfilzomib at 27 mg/m^2 in cycle 2

Niesvizky R, et al. ASH 2009. Abstract 304.

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2009 ASH Abstract 305

Combined Vorinostat, Lenalidomide and Dexamethasone Therapy in Patients with Relapsed or Refractory Multiple Myeloma: A Phase I Study

Siegel D, Weber DM, Mitsiades CS, Dimopoulos MA, Harousseau J-L, Rizvi S, Howe J, Reiser D, Byrne C, Anderson KC, and Richardson P

Study Design

Multicenter, open-label, non-randomized, Phase I, dose-escalation study in patients with relapsed / refractory MM

Dose level	Dosing regimen		
	Vorinostat (mg qd) 7 days on, 7 days off (Days 1-7 and Days 15-21) in each 28-day cycle	Lenalidomide (mg qd) x 21 days (Days 1-21) in each 28-day cycle	Dexamethasone (mg qd) (Days 1, 8, 15, and 22) in each 28-day cycle
1	300	10	40
2	400	10	40
3	400	15	40
4	400	20	40
5	400	25	40

Siegel D, et al. ASH 2009. Abstract 305.

Study Dosing

Study Design

- Patients were sequentially enrolled into 1 of 5 escalating dose levels of vorinostat in combination with lenalidomide using a standard 3 + 3 design for ≤8 cycles
- At the MTD, the cohort was to be expanded to a total of 16 patients (6 + 10).

Table 1. Dose-Escalation Scheme

	Dosing Regimen (in each 28-day cycle)		
Dose Level	Vorinostat, mg QD (days 1–7, 15–21)	Lenalidomide, mg QD (days 1–21)	Dexamethasone, mg QD (days 1, 8, 15, 22)
1	300	10	40
2	400	10	40
3	400	15	40
4	400	20	40
5	400	25	40

QD=once daily

Richardson PG, et al. ASCO 2010. Abstract 8031.

Response in Evaluable Patients

Best overall single response rate (CR+PR): 46% (13/28)

Siegel D, et al. ASH 2009. Abstract 305.

Response in Evaluable Patients

Best overall single response rate (CR+PR): 53% (16/30)

Richardson PG, et al. ASCO 2010. Abstract 8031.

Response if Prior Lenalidomide

Response rate (non-refractory; CR+PR): 50% (3/6)
Response rate (refractory*; CR+PR): 17% (1/6)
Response rate (refractory*; CR+PR+MR+SD): 50% (3/6)

*Lenalidomide refractory: no response to prior lenalidomide-containing regimens or progression on or ≤ 60 days of receiving lenalidomide-containing regimen, or relapsed, refractory, intolerant, and/or ineligible for other therapies, including bortezomib.

Siegel D, et al. ASH 2009. Abstract 305.

Response if Prior Lenalidomide

MR or better in nonrefractory patients: 57.1% (4/7)
MR or better in refractory* patients: 33.3% (2/6)

*Defined as no response on or progression within 60 days of receiving lenalidomide-containing regimen, or relapsed, refractory, intolerant, and/or ineligible for other therapies, including bortezomib.

Richardson PG, et al. ASCO 2010. Abstract 8031.

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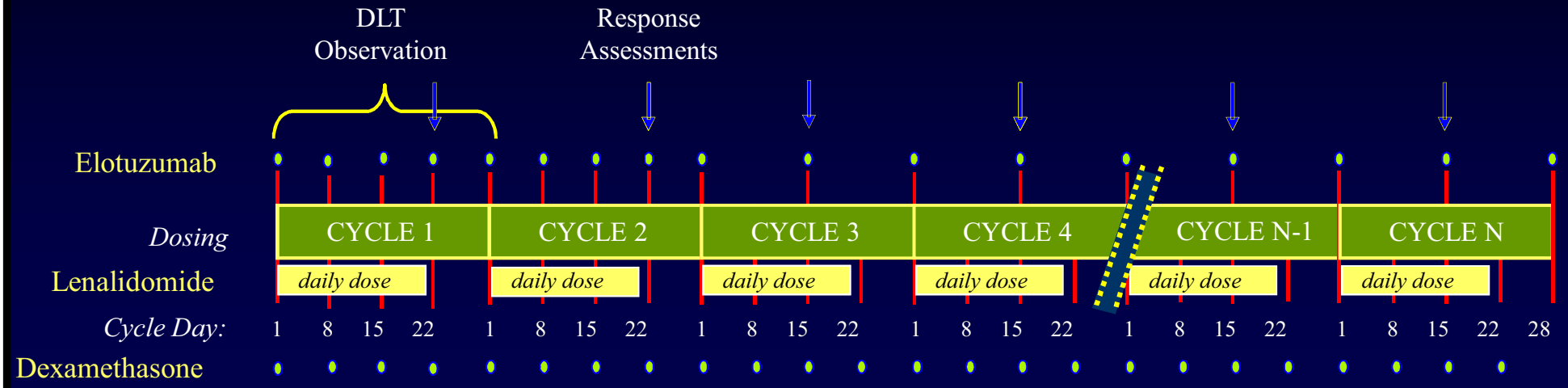
2009 ASH Abstract 432

Phase 1/2 Study of Elotuzumab in Combination with Lenalidomide and Low Dose Dexamethasone in Relapsed or Refractory Multiple Myeloma: Interim Results

Lonial S, Vij R, Harousseau J-L, Facon T, Kaufman J, Mazumder A, Moreau P, Leleu X, Fry J, Singhal A, and Jagannath S

Elotuzumab, Lenalidomide, Low-Dose Dexamethasone in Rel/Refr MM: Phase 1/2



- Phase Ib: 3+3 dose escalation evaluating 5, 10, and 20 mg/kg elotuzumab + 25 mg len and low dose dex
  - First 5 patients were limited to 6 cycles; remaining 23 patients are being treated until disease progression or unacceptable toxicity
- Phase II: randomizing (1:1) approx. 60 pts to elotuzumab 10 vs 20 mg/kg

Lonial S, et al. ASCO 2010. Abstract 8020.

Response Rate

	Total Patients (%)	Patients w/o Prior Lenalidomide
Total treated population (≥1 dose)	28	22
ORR (≥PR; IMWG criteria)	23 (82%)	21 (95%)
VGPR	5 (18%)	5 (23%)

Lonial S, et al. ASH 2009. Abstract 432.

Response Rate: Phase Ib

Best Confirmed Response (IMWG Criteria)

	Total Patients (%)		Lenalidomide-Naïve Patients (%)	
Total ITT population	28		22	
ORR (≥ PR)	23	(82)	21	(95)
CR	1	(4)	1	(5)
VGPR	7	(25)	6	(27)

Lonial S, et al. ASCO 2010. Abstract 8020.

Lenalidomide/Thalidomide/Dex

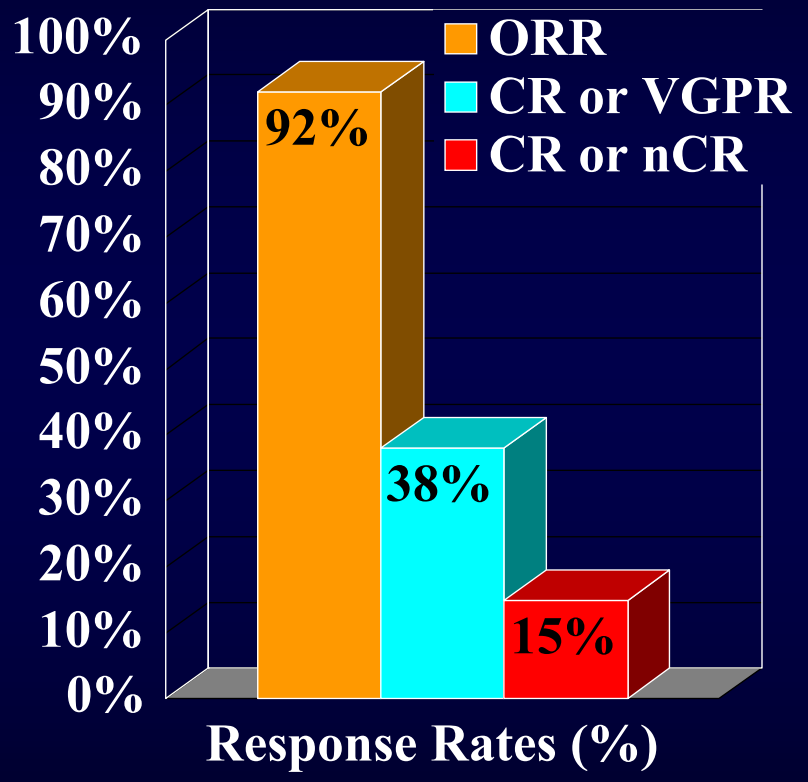
	Lenalidomide (Days 1-21)	Thalidomide (Days 1-28)	Dexamethasone (c1, 2: Days 1-4, 9-12, 17-20; c3+: Days 1-4)
Dose level 1	15 mg	100 mg	40 mg
Dose level 2	25 mg	100 mg	40 mg
Dose level 3	25 mg	200 mg	40 mg

Cohort	Patients enrolled	DLT
1	3	0
2	6	Steroid-induced
3	9	1: G3 Rash; 1: G3 Hypertension

Shah, JJ et al. ASH 2010. Abstract 1948.

RTD : Efficacy

- Based on studies of the mechanisms of resistance to lenalidomide
- Phase I portion completed
- Predictable side-effects
- Evidence of anti-myeloma efficacy



Shah JJ, et al. ASH 2010. Abstract 1948.

Targeting Kinesin Spindle Protein

- Inhibiting KSP stops myeloma cell division, causing apoptosis
- Phase I ARRY520: well tolerated
  - No neuropathy signal
  - Cytopenias and GI effects
- In phase I, two patients with PRs, several with MRs and SD
- Phase II portion started

Shah, JJ et al. ASH 2010. Abstract 1959.

Novel Agents and Regimens for Relapsed and Refractory Multiple Myeloma : Summary

Robert Z. Orlowski, M.D., Ph.D.

Director, Myeloma Section

Associate Professor of Lymphoma/Myeloma, and Experimental Therapeutics; Division of Cancer Medicine

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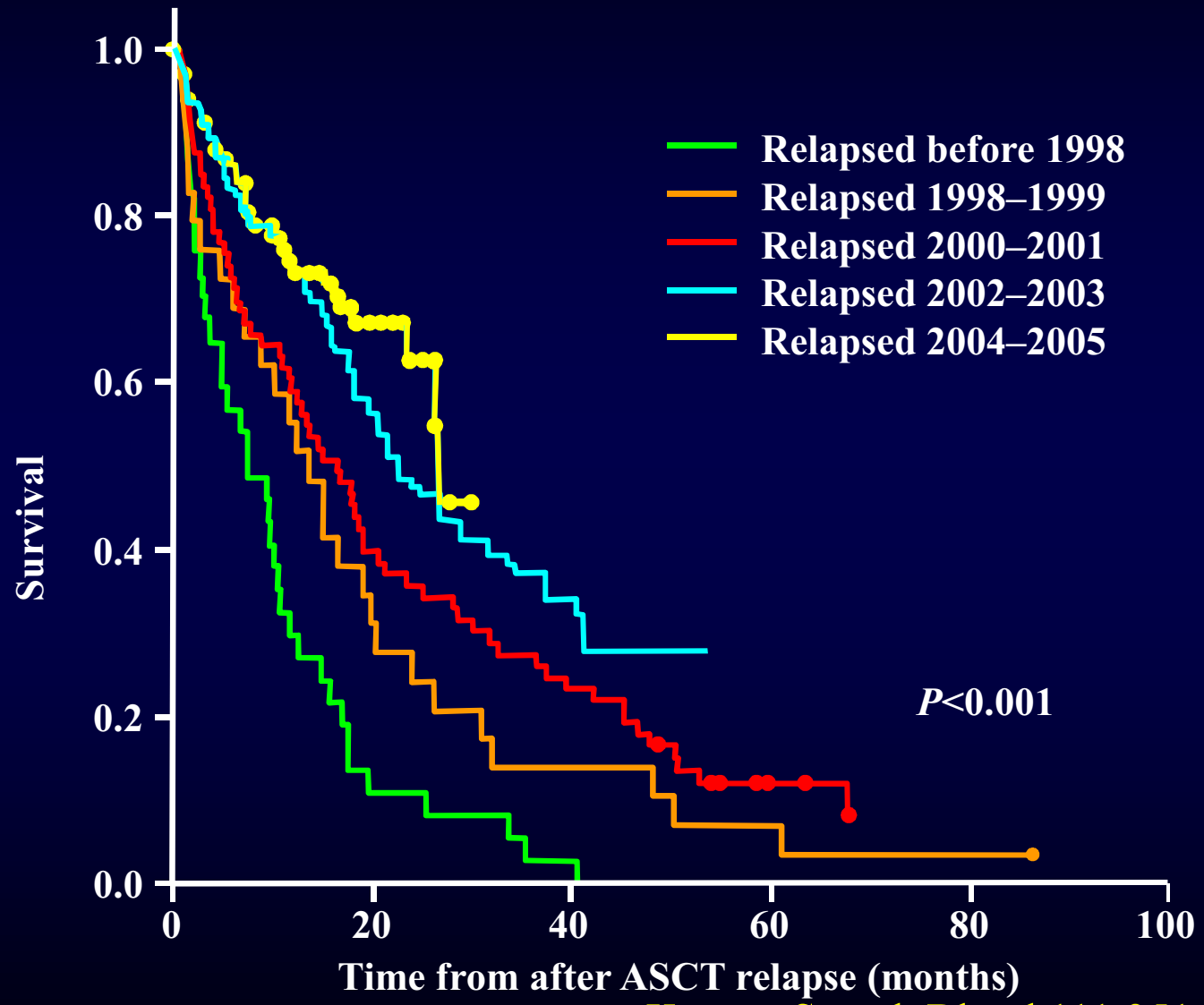
Relapsed/Refractory Therapy

- RDex and VDox are the standards of care in this setting
  - How well do they work with prior R and V?
- Novel single agents, such as carfilzomib and pomalidomide
  - Combine well with other agents
- New combinations, such as with siltuximab, elotuzumab, vorinostat

Other Options

- "Novel-er" agents on the way as well
  - ARRY520
- Add old agents that are new again to prior active regimens
  - Cyclophosphamide
- Mix and match agents that had been used in different combinations
  - If had RD, VD ⇒ RVD
  - If had RD, TD ⇒ RTD

Impact of Novel Agents at Relapse



Kumar, S et al. Blood 111:2516-2520, 2008.