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Advancing the Management of Relapsed/Refractory MM Current Status

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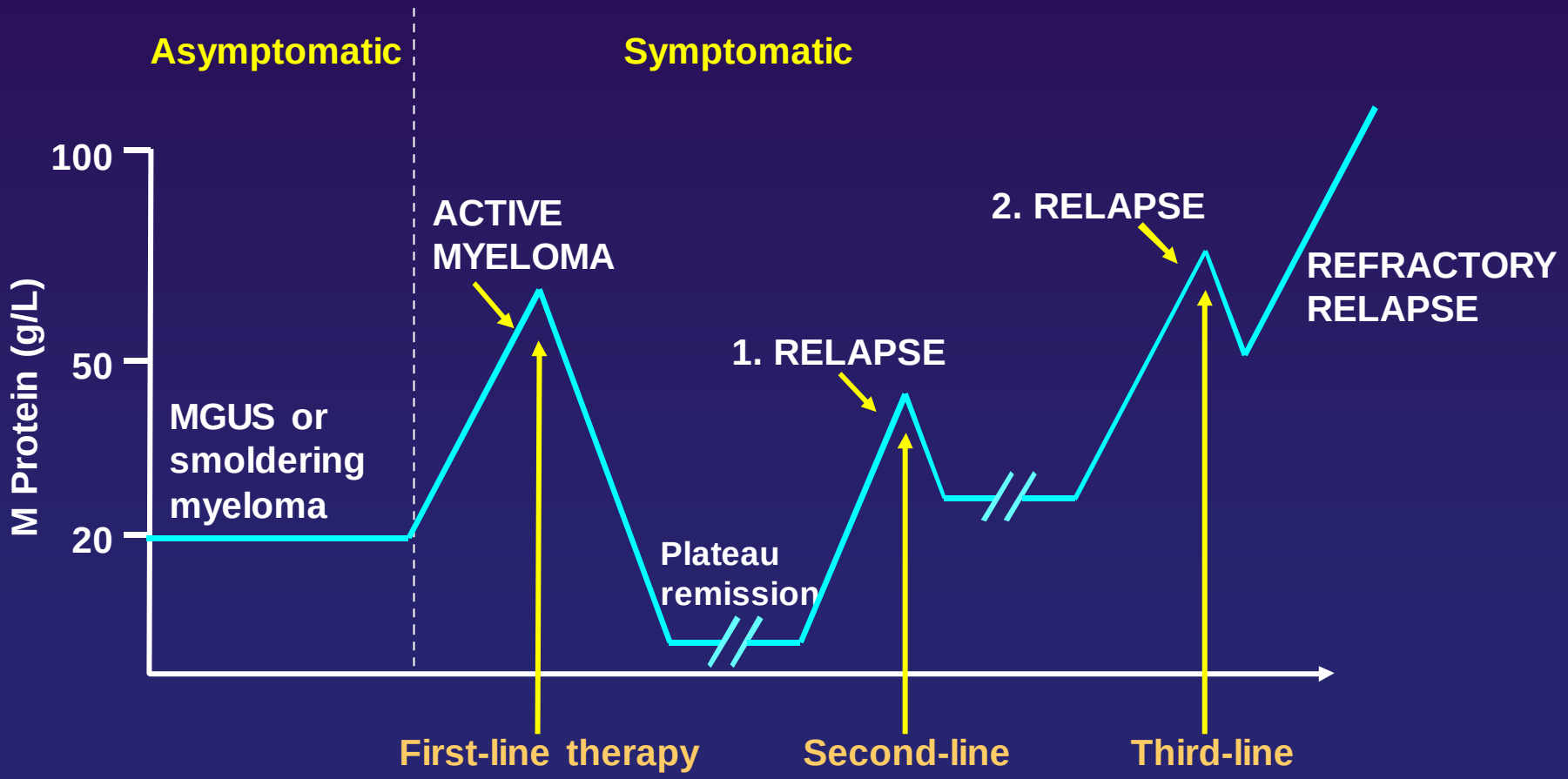
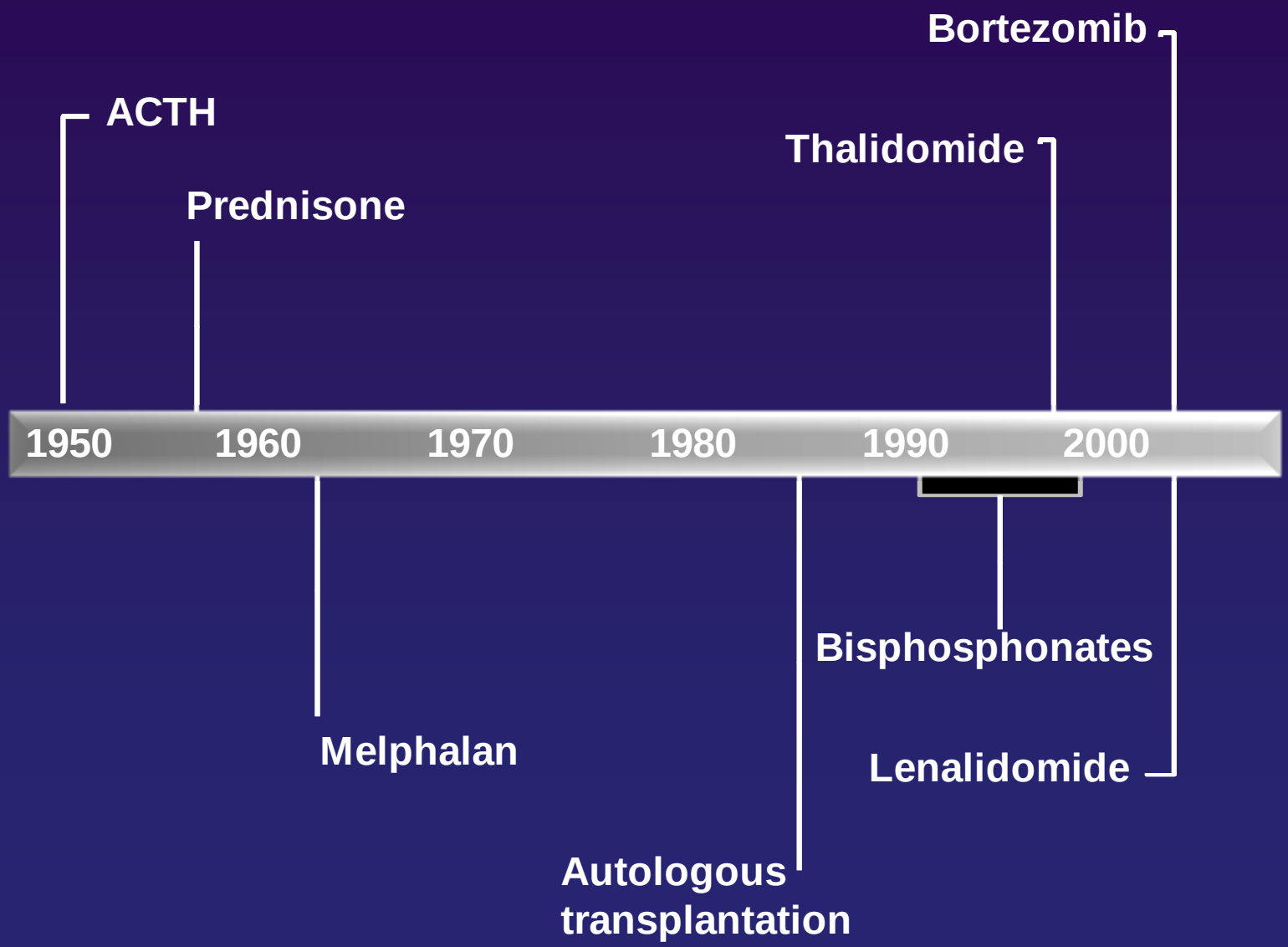
Natural history of multiple myeloma



MM Therapy Milestones



Adapted from Kyle RA, Rajkumar SV. *Blood*. 2008;111:2962-2972.

Multiple Myeloma: Current Treatment (USA)
Adapted from NCCN Practice Guidelines (2010)

Initial Therapy

- Cyclophosphamide
- Melphalan, prednisone + thalidomide, + bortezomib, + lenalidomide
- Thalidomide + dex
- Bortezomib + dex
- Bortezomib combos
- Bortezomib + liposomal doxorubicin
- Bortezomib +

Non-Transplant Candidate

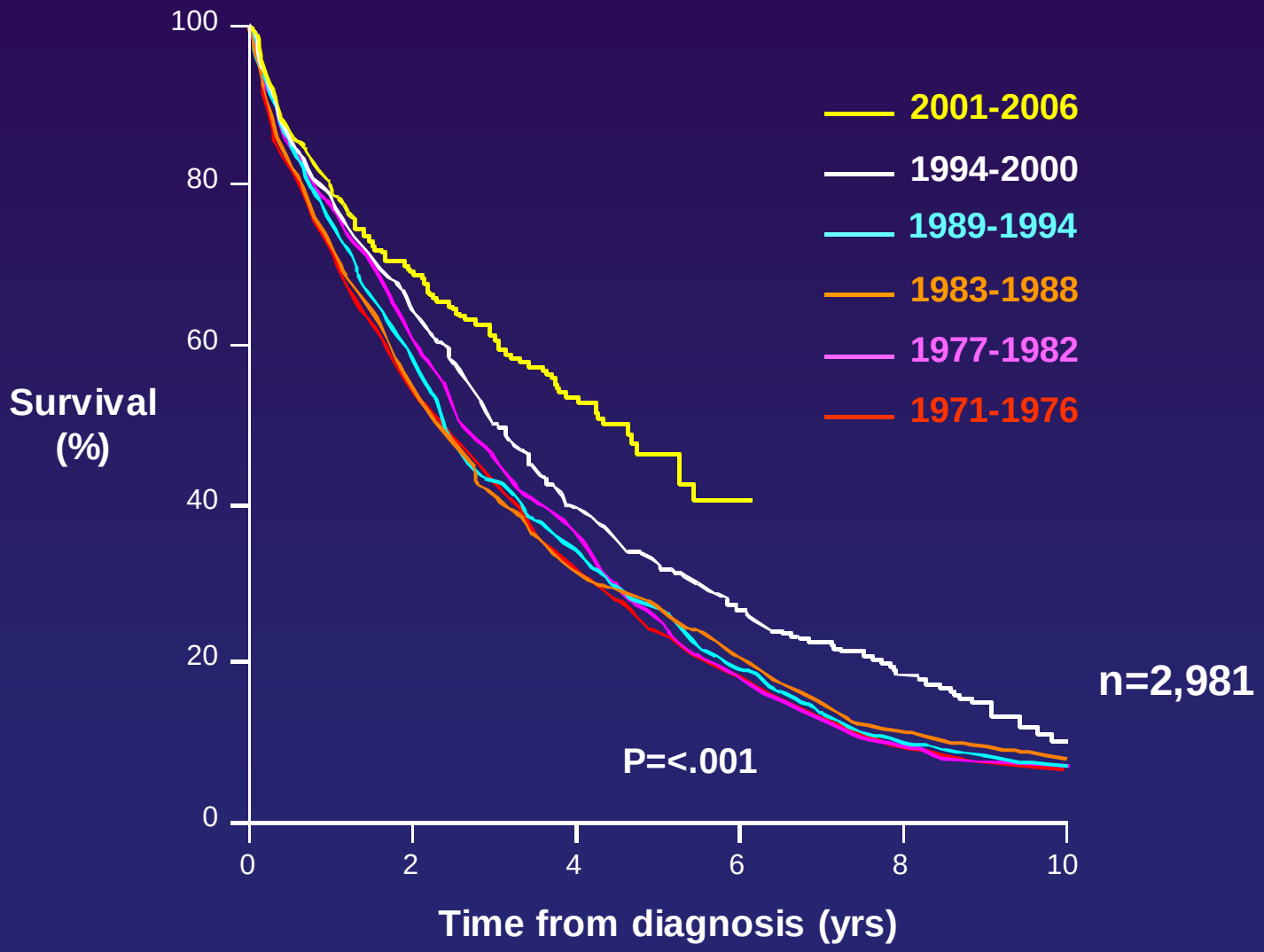
SCT Candidate

Salvage Therapy:

- Repeat primary therapy (if relapse > 6 mos)
- Cyclophosphamide
- Etoposide, dex, cytarabine, cisplatin
- Thalidomide +/- dex
- Lenalidomide +/- dex
- Bortezomib +/- dex; bendamustine
- Bortezomib combos (eg liposomal doxorubicin)
- Other novel therapies (clinical trials)

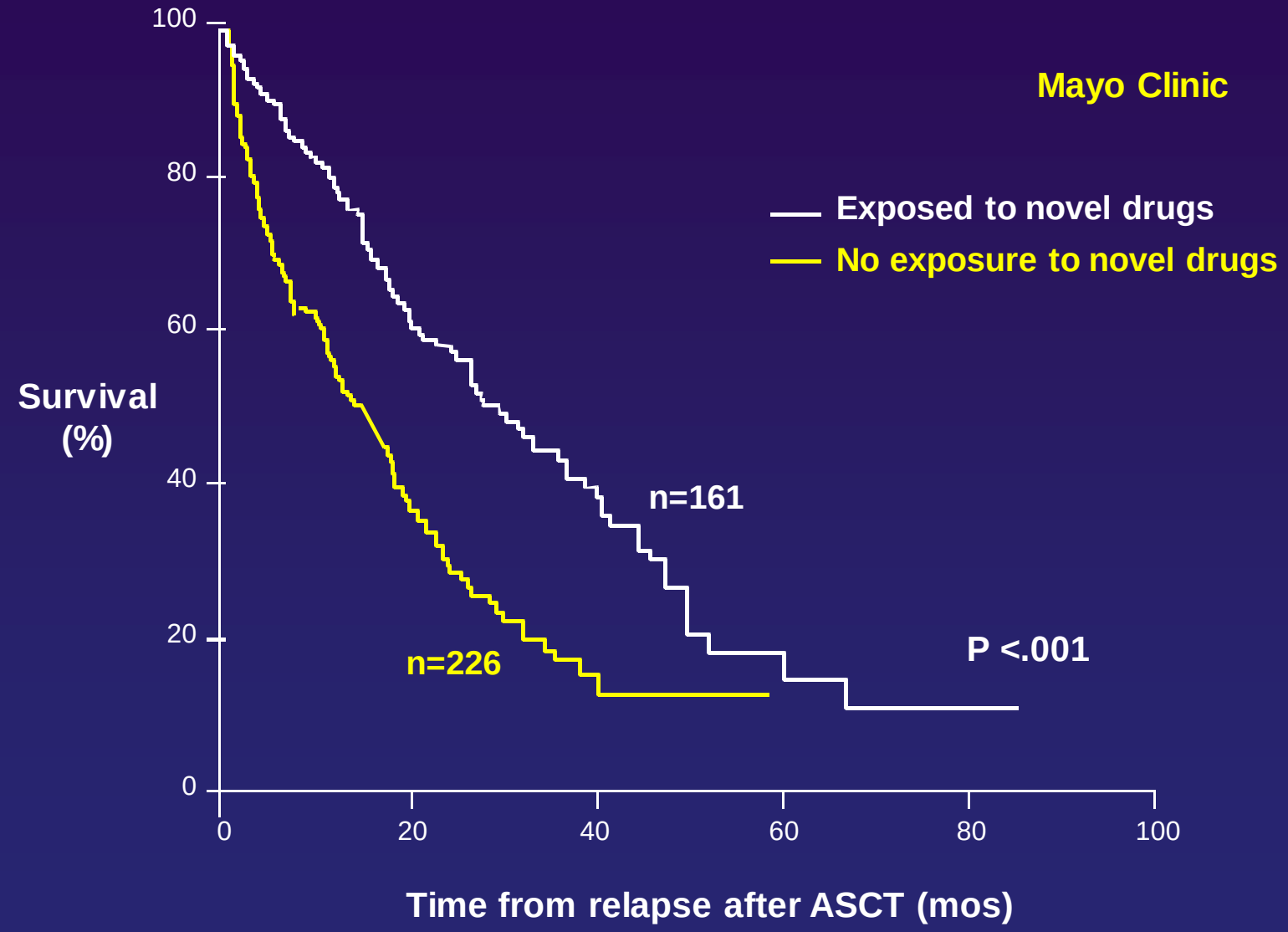
- Stem cell harvest, subsequent auto SCT (single vs double) +/- maintenance (thalidomide, bortezomib, lenalidomide)
- Investigational therapy (eg, allo-

Improved Survival in Multiple Myeloma



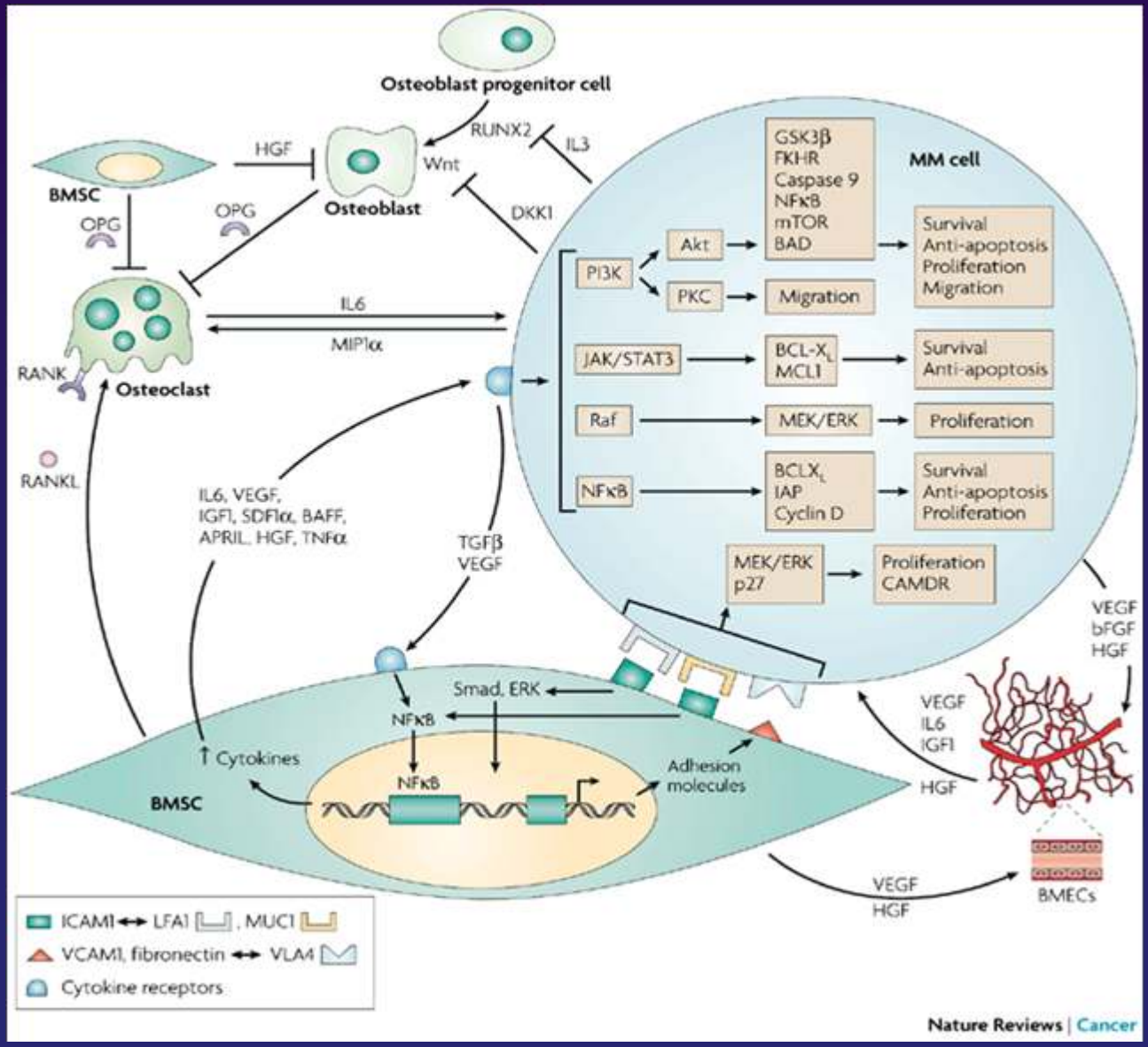
Kumar S K et al, *Blood*, 2008

Overall Survival from Relapse



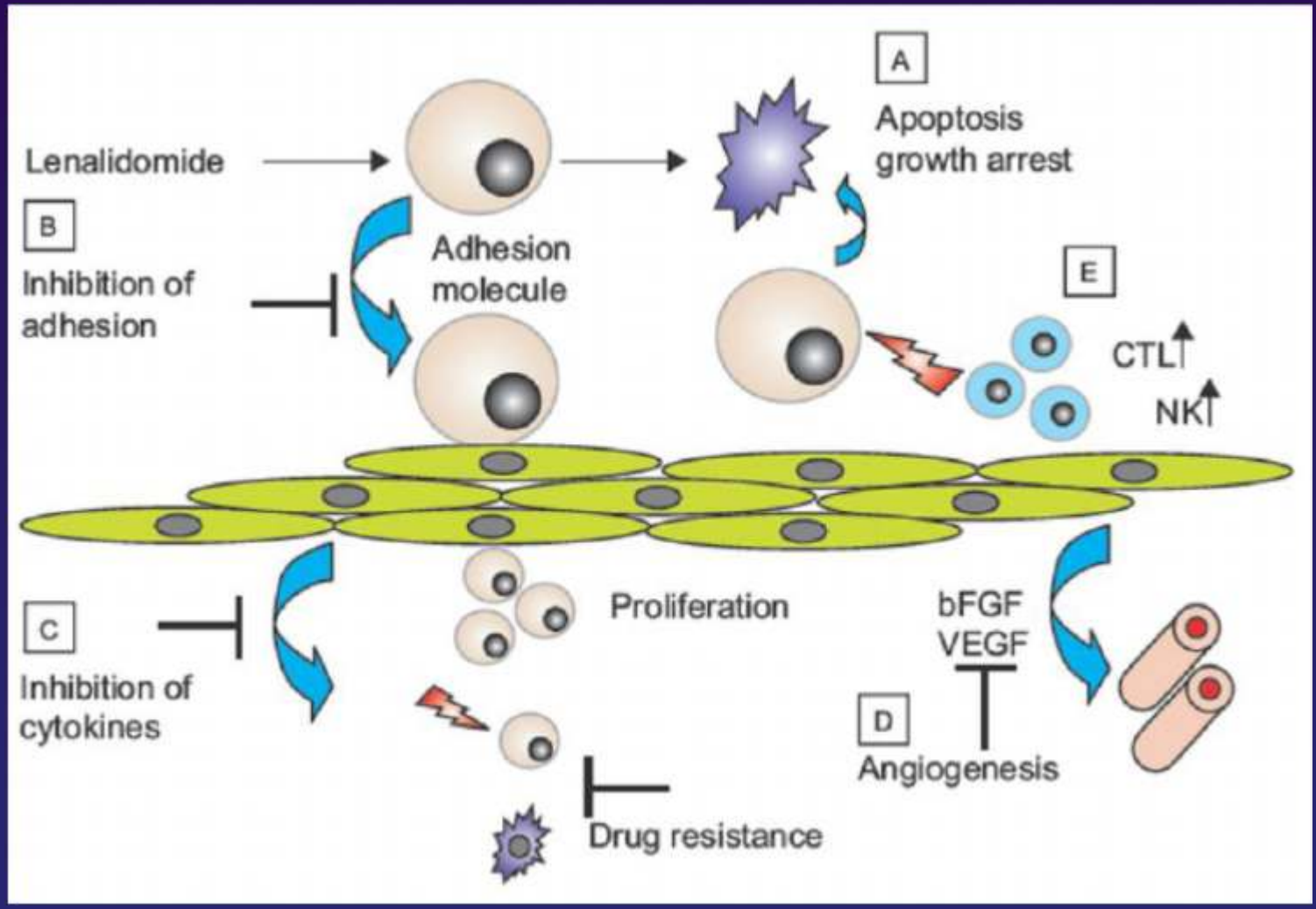
Kumar S K et al, *Blood*, 2008

Pathogenesis of Multiple Myeloma



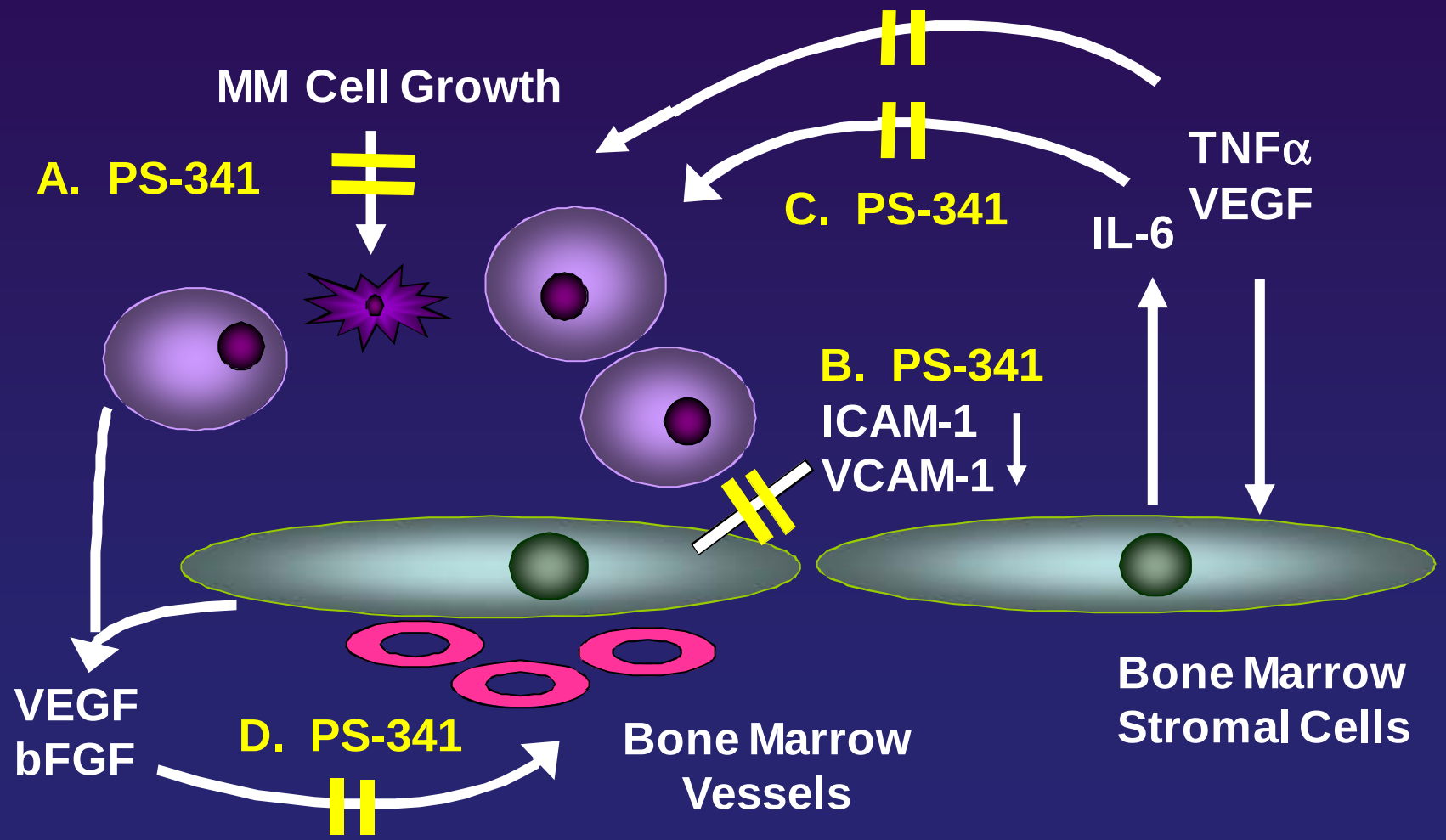
Hideshima T, et al. *Nature Reviews Cancer* 7, 585-598 (August 2007)

Lenalidomide (IMiDs): Mechanism of Action



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

Bortezomib (PS-341) Targets MM Cells in the BM Microenvironment



Hideshima et al. *Cancer Res* 2001; 61: 3071
Hideshima et al. *Oncogene* 2001; 20: 4519
Mitsiades et al. *Blood* 2002; 99: 4079
Hideshima et al. *J Biol Chem* 2002; 277: 16639

Integration of Novel Therapy Into Myeloma Management

>> Induction/First-line Therapy

>>Transplant/Consolidation/Maintenance

>> Treatment of Relapsed/Refractory MM
(single agent/combinations/new drugs/clinical trials)

Definitions for Relapsed/Refractory Myeloma

- Relapsing myeloma: Clinically active disease after one or more prior therapies but not refractory to the most recent treatment
- Refractory myeloma: Includes pts who never achieved minimal response (MR) 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
- Relapsed-and-refractory myeloma: Relapse of disease in pts who must have achieved MR or better and then progress during treatment or within 2 mos (60d) after completion of treatment

Anderson KC et al. *Leukemia.* 2008;22:231.

When to Start Treatment in Relapsed/Refractory Myeloma?

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

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

Anderson KC et al. *Leukemia.* 2008;22:231.

Clinical Considerations for Relapsed/Refractory MM: Key Points

- Disease control (vs cure): DOR/PFS as important as depth of response
- Efficacy of salvage therapy ~ a function of activity and tolerability plus continuity of treatment
- Disease characteristics at relapse and response to prior therapy
  - Aggressiveness of relapse
  - Relapsed or relapsed/refractory MM
  - “High-risk disease”
  - Prior therapies
  - Participation in clinical trials a priority
- Toxicity considerations
  - Peripheral neuropathy
  - Thrombotic risk
  - Myelosuppression
  - Impact of prior treatment

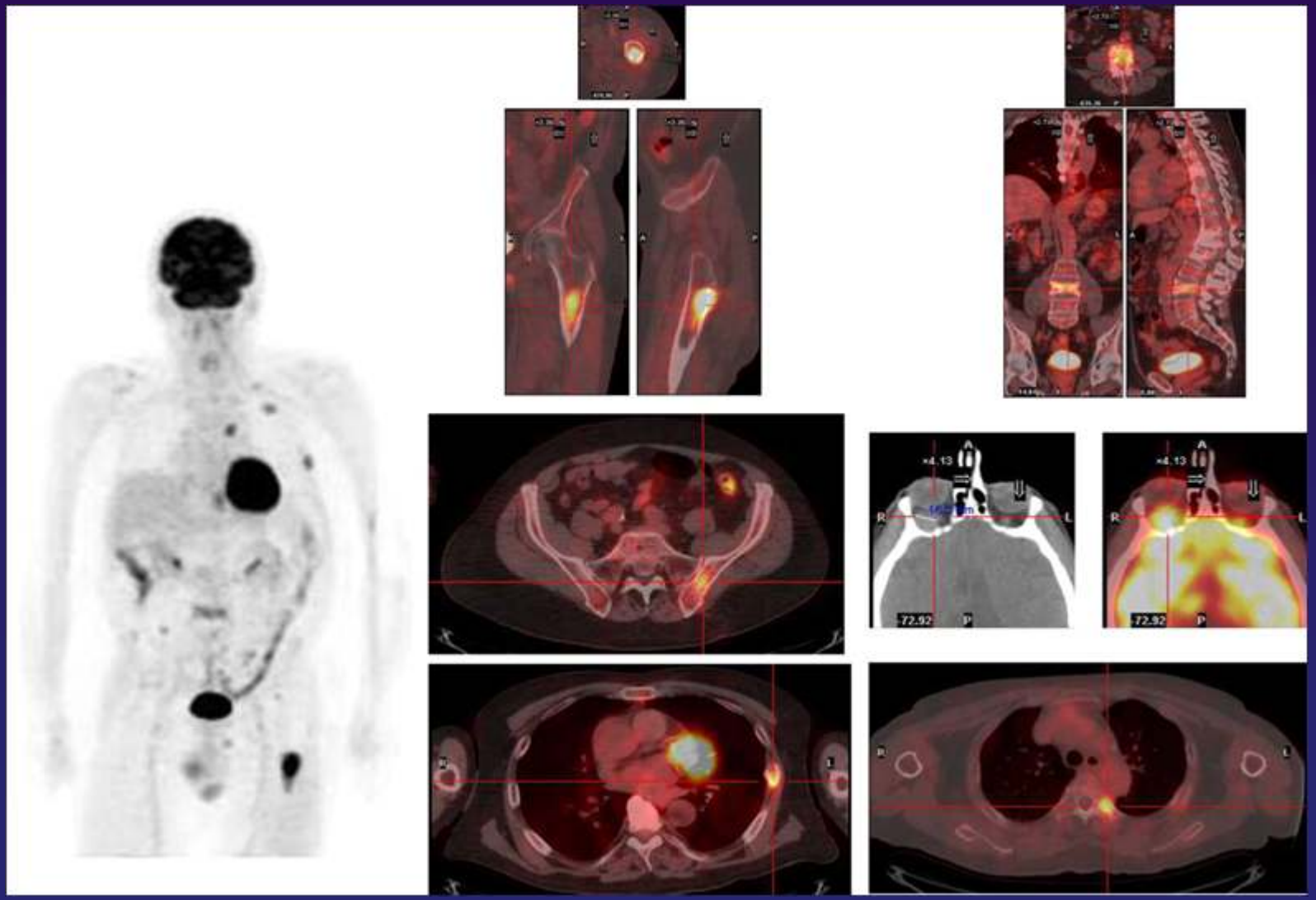
Special Populations in Relapsed/Refractory MM
Features Associated With Poor Prognosis

- Refractory to prior treatment (relapsed and refractory)
- Age >65 yr: majority of pts with MM are older (median age at diagnosis ~70 yr)
- Increased β2m, decreased serum albumin, low platelet count
- Cytogenetic abnormalities: chromosome 13 del, t(4;14), t(14,16), del 17p13
- Renal dysfunction
  - Up to 50% of pts with MM have renal dysfunction
  - 20%–30% of pts have concomitant renal failure
- Extensive bone disease
- Extramedullary MM
- Extent of disease is now being better defined with improved imaging techniques (eg MRI, PET/CT)
- Emerging Role of GEP, Array CGH, Proteomics

Unmet need for new agents to treat these pts.

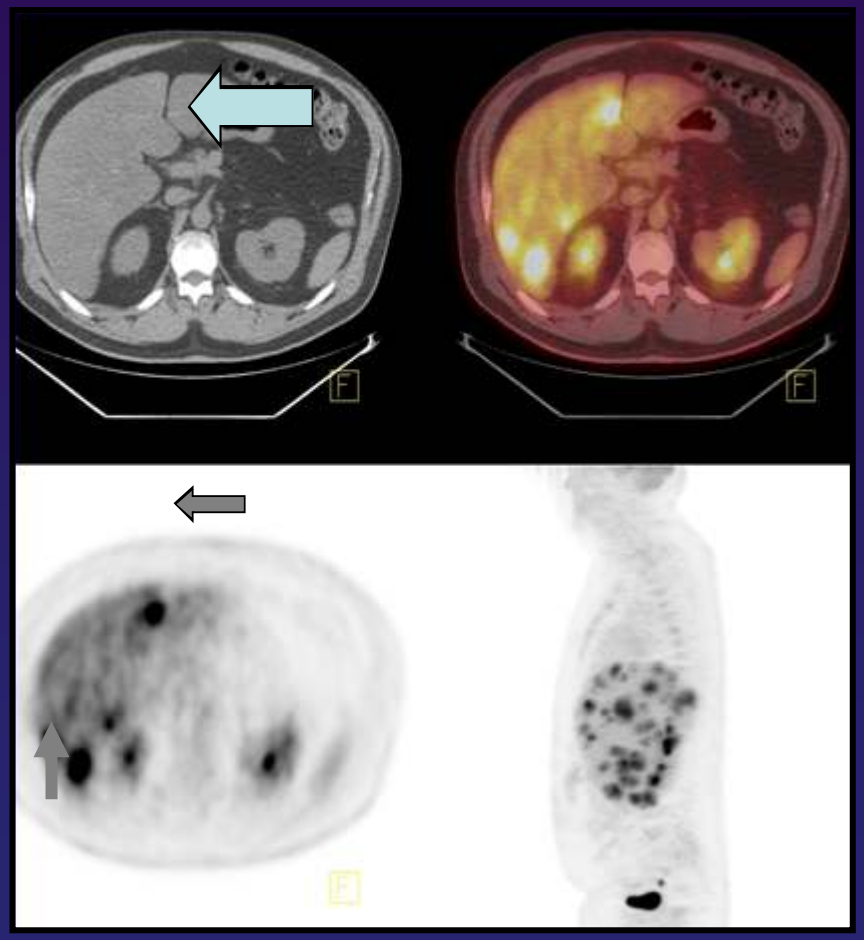
Barlogie B et al. *Blood*. 2004;103:20.
Bladé J et al. *Arch Intern Med*. 1998;158:1889.
Facon T et al. *Blood*. 2001;97:1566.
Fonseca R et al. *Cancer Res*. 2004;64:1546.
Kumar SK et al. *Mayo Clin Proc*. 2004;79:867.
Kyle R. *Stem Cells*. 1995;13(suppl 2):56.
Kyle R et al. *Mayo Clin Proc*. 2003;78:21.

PET/CT IMAGING in MM



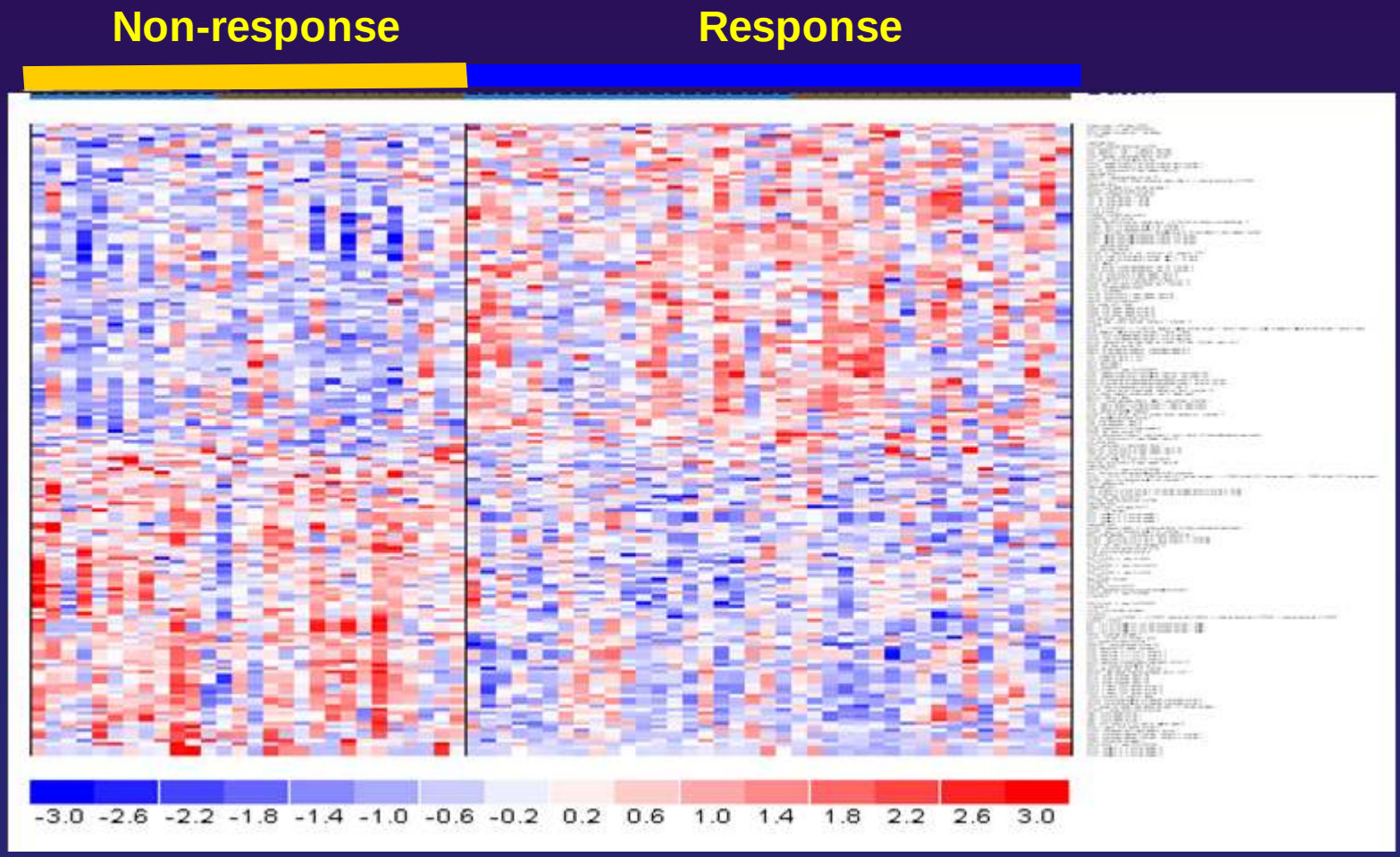
Stewart AK, Richardson PG, San Miguel JF *Blood* 2009

PET/CT in Extramedullary MM



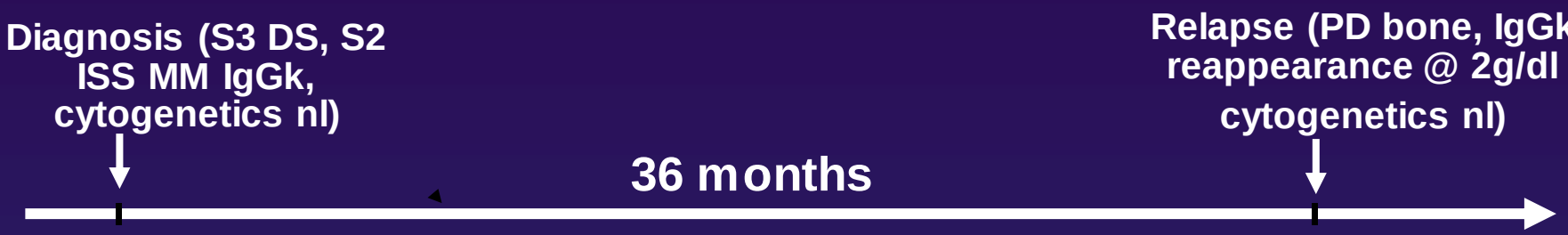
Axial fused FDG PET/CT and rotatating MIP images reveals multifocal hepatic plasmacytomas with moderately intense FDG accumulation.

Gene Microarray Predicts Clinical Response to Combination of Bortezomib and Dexamethsone



Munshi N et al. *Blood.* 2008;112: Abstract 2746.

Pt Case – Induction/Consolidation and Maintenance Regimen



Initial Therapy + ASCT

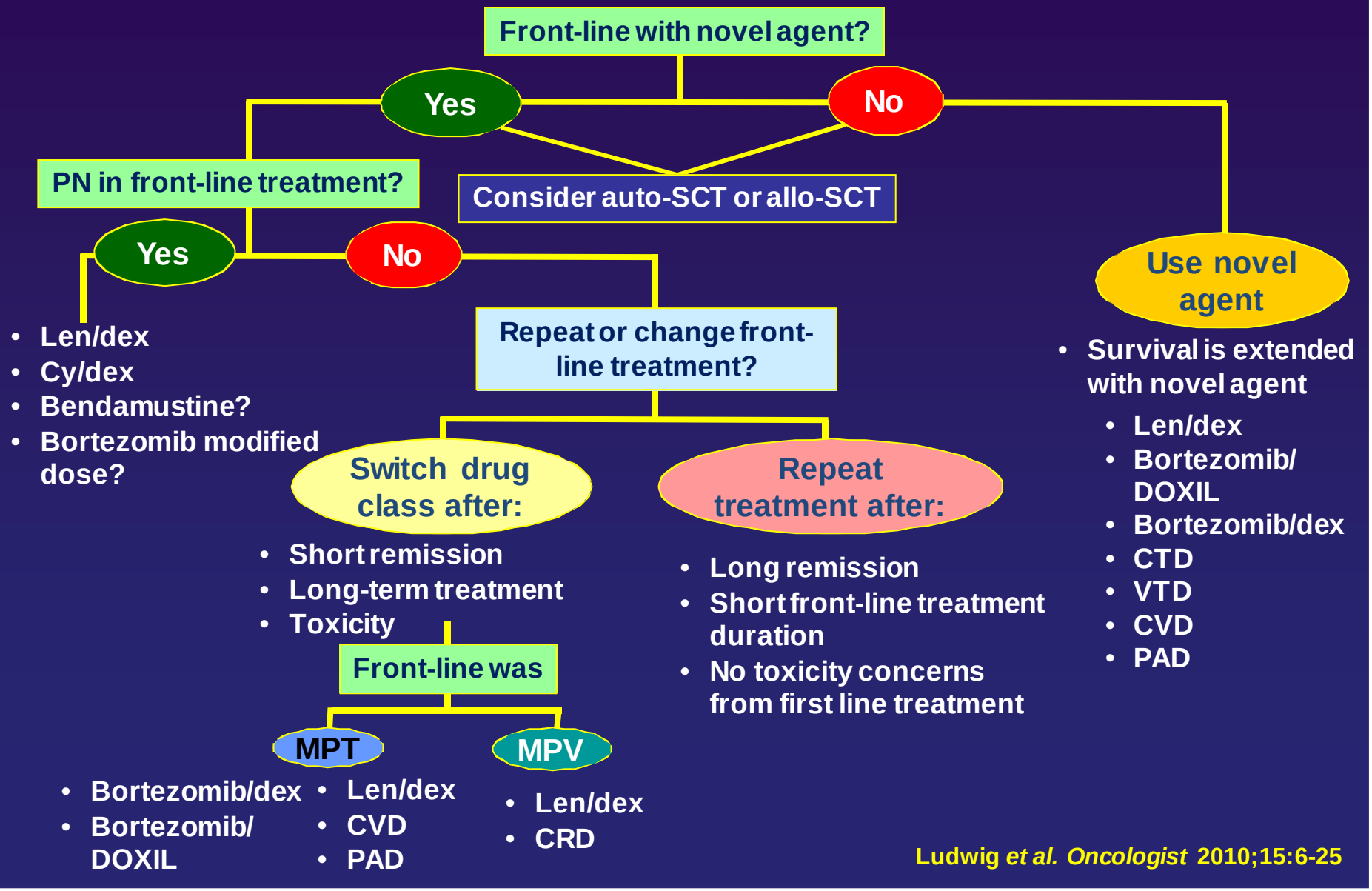
- IV bisphosphonate (zoledronic acid)
- Vertebral Kyphoplasty
- 6 cycles: Bz-Thal-Dex (VTD)
- Best response: CR
- Side effects
  - Facial edema, wt gain, anxiety and insomnia >> steroid dose reduction
  - Mild constipation
  - Paresthesia, numbness in extremities >> Bz and Thal dose reduction (for presumed BiPN/TiPN)
- ASCT (Mel 200 mg/m^2): stem cell mobilization with HD Cytoxan + GCSF
- Post-ASCT response: cont'd CR

Post-ASCT Therapy

- Thal maintenance (100 mg/d)
- Cont'd bisphosphonate
- Response: cont'd CR
- Side effects
  - Mild fatigue, constipation
  - Re-emergent PN (TiPN)

Now with PD; What Next?

Treatment at Relapse



Ludwig *et al. Oncologist* 2010;15:6-25

Treatment of Relapsed/Refractory Myeloma

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

Clinical Factors When Choosing Therapy for Relapsed Disease

- Comorbid conditions
- Previous therapy
- Time from previous therapy
- Mode of drug administration
- Risk profile
- Potential role of second ASCT or allo-SCT

Laubach JP et al. *Leukemia*. 2009; Sep 10. [Epub ahead of print].
Blade J, Rosinol L. *Haematologica*. 2009;94:163.

Relapse Following ASCT

Is there a role for a second ASCT?

Or

Is there a potential for benefit from an allo-SCT utilizing RIC, after successful salvage, if an HLA-identical sibling donor has been established as part of a clinical trial?

SCT as Salvage

- **Autologous[1,2]**
  - **4-yr OS for early vs late: 66% vs 61%**
  - **Median OS for early vs late: 23 mos vs 30 mos**
  - **Pro: Improved chance of response?**
  - **Con: Additional compromise and deterioration because of toxicity**
- **Allogeneic[3,4,5]**
  - **Pro: Potentially curative (at least up front?); RIC regimens increase number of pts considered for this option**
  - **Con: High rate of GVHD, treatment-related mortality; sibling donor availability, no difference seen in PFS between Auto-SCT in recent CTN study**

1. Fermand JP et al. *Blood*. 1998;92:3131.
2. Barlogie B et al. *J Clin Oncol*. 2006;24:929.
3. Bruno B et al. *N Engl J Med*. 2007;356:1110.
4. Moreau P et al. *Blood*. 2008;112:3914.
5. Krishnan A et al, ASH 2010.

Efficacy of Single Agents in Relapsed/Refractory MM

Regimen	Phase	n	CR	PR	Median OS (mos)
Thalidomide[1,2]	2	712	1.6%	26%	–
		1,629	1.6%	27.8%	14
Lenalidomide[3] 30 mg	2	222	2%	24%	23.2
Bortezomib[4] (APEX)	3	331	9%	34%	29.8

Still room for improvement → combination therapy

1. Prince HM et al. *Leuk Lymphoma* 2007;48:46.
2. Glasmacher A et al. *Br J Haematol.* 2006;132:584.
3. Richardson PG et al. *Blood*. 2009;114:772.
4. Richardson PG et al. *Blood.* 2007;110:3557.

Combinations in Relapsed/Refractory MM

Regimen	Phase	n	CR + PR	CR + nCR
Thal (200–400 mg) + dex (20 mg)[1]	2	44	55% (PR only)	0%
Thal (100 mg) + dex (40 mg)*[2]	2	77	41%	18%
Bortezomib ± dex (20 mg)†[3]	2	638	51%	11% (CR)
Bortezomib (1 mg/m^2, 3 mg/m^2) + dex (20 mg)[4]	2	54	38%	11%
Bortezomib + PLD[5]	3	324	44%	13%
Lenalidomide + dex (40 mg)[6,7] (MM-010, MM-009)	3	176	60%	24%
		170	61%	24%

*Response rate measured by M-protein reduction
† Expanded-access program where pts had received ≥ 2 prior therapies

1. Dimopoulos MA et al. *Ann Oncol.* 2001;12:991.
2. Palumbo A et al. *Haematologica.* 2001;86:399.
3. Mikhael JR et al. *Br J Haematol.* 2009;144:169.
4. Jagannath S et al. *Br J Haematol.* 2004;127:165.
5. Orlowski RZ et al. *J Clin Oncol.* 2007;25:3892.
6. Weber DM et al. *N Engl J Med.* 2007;357:2133.
7. Dimopoulos M et al. *N Engl J Med.* 2007;357:2123.

Lenalidomide-Based Regimens

- Significant response and survival benefit with len/dex vs dex/placebo[1]
  - ORR: 60.6% vs 21.9% *P*<0.001
  - CRR: 15% vs 2% *P*<0.001
  - mTTP: 13.4 mos vs 4.6 mos *P*<0.001
  - mDOR: 15.8 mos vs 7 mos *P*<0.001
  - mOS: 38 mos vs 31.6 mos *P*=0.045
- Pts with moderate-severe renal insufficiency respond equally well to Len/Dex[2-6]
- Superior efficacy regardless of prior SCT[7], thalidomide[8], or poor risk cytogenetics[9]
- *In vitro* inhibitory effect on osteoclast differentiation[10]

1. Dimopoulos MA et al. *Leukemia*. 2009;Jul 23. [Epub].
2. Weber DM et al. *N Engl J Med*. 2007;357:2133.
3. Dimopoulos M et al. *N Engl J Med*. 2007;357:2123.
4. Lonial S et al. Haematologica. 2007;92: Abstract PO-663.
5. Weber DM et al. *J Clin Oncol*. 2008;26: Abstract 8542.
6. Zangari M et al. EHA 2008; Abstract 638.
7. Weber D et al. *Blood*. 2007;110:128a. Abstract 412.
8. Wang D et al. *Blood*. 2008;112:4445.
9. Bahlis NJ et al. *Blood*. 2007;110:1052a. Abstract 3597.
10. Breitkreutz I et al. *Blood*. 2006;108. Abstract 3485.

Lenalidomide-Based Regimens
Frequently Observed Toxicities

- Myelosuppression, specifically neutropenia, and thrombocytopenia
- VTE when used in combination with dexamethasone
  - Importance of thromboprophylaxis
  - Pts who develop a thrombo-embolic episode do not experience shorter OS or TTP[1-5]
- Rash
- Fatigue, myalgia
- Diarrhea

1. Weber DM et al. *N Engl J Med*. 2007;357:2133.
2. Dimopoulos M et al. *N Engl J Med*. 2007;357:2123.
3. Lonial S et al. Haematologica. 2007;92: Abstract PO-663.
4. Weber DM et al. *J Clin Oncol*. 2008;26: Abstract 8542.
5. Zangari M et al. EHA 2008; Abstract 638.

Bortezomib-Based Regimens

- 78% improvement in median TTP with Bz (6.2 mos) vs HD Dex (3.5 mos), *P*<0.001[1]
- Progression-free and OS prolonged when Bz combined with PLD [2]
- Pts with poor prognostic factors, high-risk disease benefit most [3,4]
- Responses in pts with renal failure requiring dialysis [4]
- Bone anabolic effect [5,6]

1. Richardson PG et al. *N Engl J Med.* 2005;352:2487.
2. Orlowski RZ et al. *J Clin Oncol.* 2007;25:3892.
3. Richardson PG et al. *Br J Haematol.* 2007;137:429.
4. Chanan-Khan AA et al. *Blood.* 2007;109:2604.
5. Pennisi A et al. *Am J Hematol.* 2009;84:6.
6. Terpos et al. *Br J Haematol* 2006;135:688–92.

Bortezomib-Based Regimens
Frequently Observed Toxicities

- Peripheral neuropathy
- Thrombocytopenia
- Gastrointestinal dysfunction
- Fatigue
- Rash

Richardson PG et al. *J Clin Oncol*. 2006;24:3113.
Badros A et al. *Cancer*. 2007;110:1042.
Lonial S et al. *Blood*. 2005;106:3777.

Peripheral Neuropathy Management

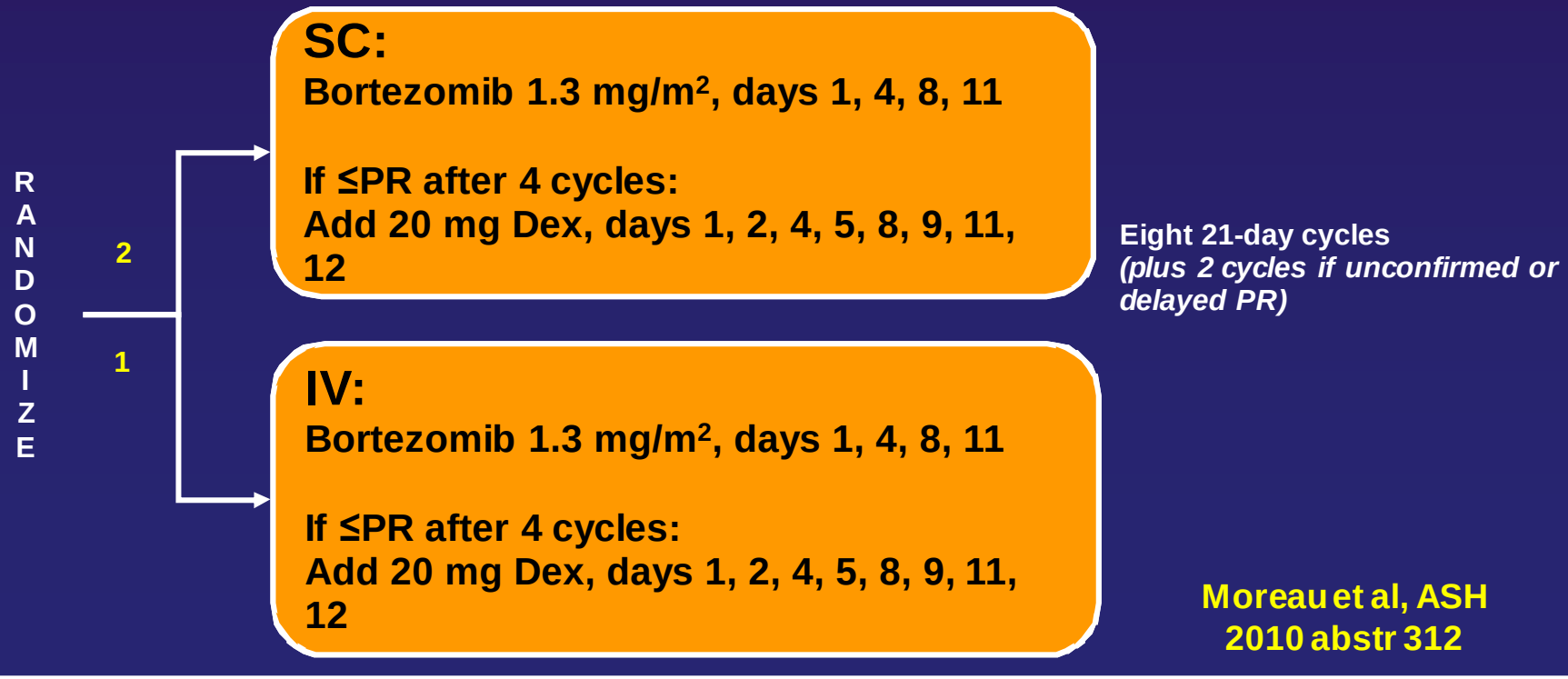
- Baseline assessment and monitoring at each visit is crucial
- Pt education on signs and symptoms of peripheral neuropathy (PNY) and importance of reporting symptoms
- Dose reduction and schedule change essential

- Symptom control/PN prevention
  - Vitamins/minerals (B complex, folic acid, vit E, magnesium, potassium)
  - Amino acids (acetyl carnitine, alpha-lipoic acid)
  - Avoid supplements on day of bortezomib administration
  - Miscellaneous (topical creams, tonic water for cramps)
  - FDA-approved agents for the treatment of diabetic neuropathy (duloxetine, pregabalin)
  - Other agents (doxepin)

Richardson PG et al. *J Clin Oncol*. 2006;24:3113.
Colson K et al. *Clin J Oncol Nurs*. 2004;8:473.
Perone G et al. *Leukemia*. 2009
Richardson et al, *British Journal of Hematology*. 2009

Intravenous versus Subcutaneous Bortezomib; A Phase III Trial (ASH 2010)

- Non-inferiority design
  - 60% retention of the IV treatment effect by ORR after 4 cycles of treatment
  - 2:1 randomization SC vs IV (N=222)
  - Stratification : ISS stage, number of prior lines of therapy (1 vs >1)
- 53 centers in 10 countries (Europe, Asia, and South America)



Moreau et al, ASH 2010 abstr 312

Primary Endpoint: Response After 4 Cycles (Single-Agent Bortezomib)

Moreau et al, ASH 2010 abstr 312

Response rate, %	Bortezomib IV (N=73)	Bortezomib SC (N=145)	Relative risk (95% CI)
ORR (CR + PR)	42	42	0.99 (0.71, 1.37)
CR	8	6	
CR + nCR	14	12	
PR	34	36	
nCR	5	6	
VGPR	3	4	
≥VGPR (CR + nCR + VGPR)	16	17	

Data shown for the response-evaluable population

Peripheral Neuropathy (PN)

	Bortezomib IV (N=74)	Bortezomib SC (N=148)	P-value *
Any PN event, %	53	38	0.04
Grade ≥2, %	41	24	0.01
Grade ≥3, %	16	6	0.03
Risk factors for PN, %			
Grade 1 PN at baseline	28	23	
Diabetes at baseline	11	13	
Exposure to prior neurotoxic agents	85	86	

*P-values are based on 2-sided Fisher's exact test

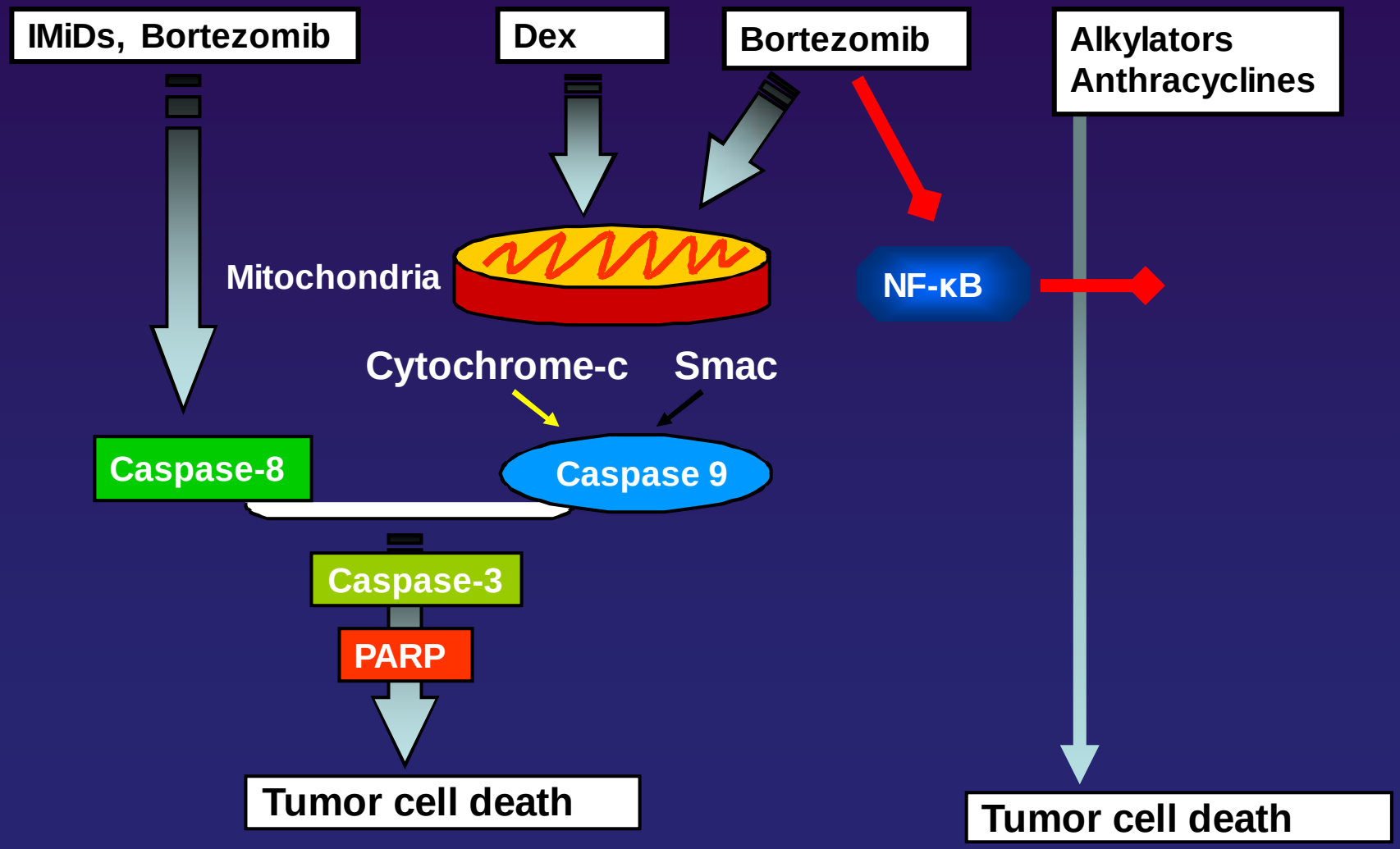
Moreau et al, ASH 2010

Conclusions

- The efficacy of bortezomib was similar by SC and IV administration in patients with relapsed MM
  - similar PK (systemic exposure) and PD (proteasome inhibition) profiles
- SC administration has an improved safety profile
  - significantly fewer all-grade, grade ≥2, and grade ≥3 PN events
- SC administration had acceptable local tolerability

Moreau et al, ASH 2010

Rationale for Combination Therapy in Multiple Myeloma



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

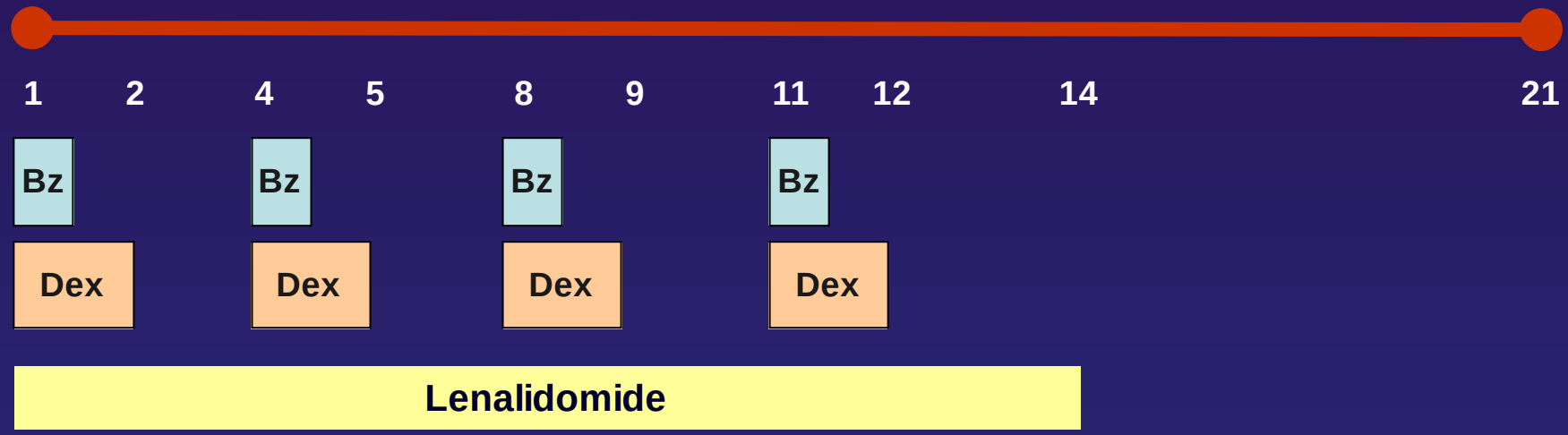
Triple and Quadruple Lenalidomide- and Bortezomib-Based Combinations

Regimen	N [evaluable]	Responses	Toxicities
VMPT[1]	30	• 7% PD • 27% SD • 23% PR • 43% CR/VGPR	• PNY
VCD[2]	35	• 71% PR	• G3-4 myelosuppression 7 pts
VMD[3]	53	• 23% CR/nCR • 34% CR/nCR (at MTD)	• G3-4 TCP, infections, neutropenia, PNY
RVD[4]	62	• 84% ≥MR • 68% ≥PR • 21% nCR/CR	• G1/2 myelosuppression; DVT 2 pts • G3 PNY 1 pt
RCD[5]	21	• 14% VGPR • 5% CR	• Neutropenia, DVT 3 pts
PAD[6]	64	• 25% VGPR • 67% ≥PR	• G3-4 TCP, neutropenia, infections, anemia, GI disturbances, PNY

1. Palumbo A et al. *Blood*. 2007;109:2767.
2. Delasalle K et al. *Haematologica*. 2007;92: Abstract PO-616.
3. Popat R et al. *Br J Haematol*. 2009;144:887.
4. Richardson et al. *Blood*. 2010;27: Abs 8536.
5. Morgan GJ et al. *Br J Haematol*. 2007;137:268.
6. Palumbo A et al. *Ann Oncol*. 2008;19:1160.

Phase 1 Trial of Lenalidomide with Bortezomib +/- Dex (RVD) in relapsed/refractory MM: study design

Up to 8 21 day cycles* ; MTD Len 15 mgs, Bz 1.0 mgs/m2; ORR 60 %; OS 37 mos



*Dex added if PD on RV; 40 mg/day D 1, 2, 4, 5, 8, 9, 11 and 12; 20 mg, cycles 5–8; Amended to 20mg/10mg cycles 1-4/5-8 based on safety data

Richardson PG et al. *J Clin Oncol*. 2009;27:5713.

Lenalidomide and Bortezomib as "Backbone Agents" in MM

- Phase 1/2 study in newly-diagnosed pts
- Combination with low-dose Dex ("Dex sparing")
- Platform for maintenance, especially as well tolerated
- Low rate of DVT, significant PN
- Combination with conventional and other novel therapies in relapsed/refractory disease (eg, MoAbs; "next-generation" small molecule inhibitors)

Additional Combination Therapies Investigating New Agents with Bz and Len

- **Bortezomib +**
  - Hsp 90 inhibitor
  - NPI-0052
  - Perifosine
  - LBH 589
  - Smac peptides
  - Bcl-2 inhibitor
  - p38 MAPK inhibitor
  - HuLuc63 MoAb (Elo)
  - GCS100
  - SAHA
  - Plitidepsin
- **Lenalidomide +**
  - Carfilzomib
  - mTOR inhibitor
  - Anti-CD40 MoAb
  - PL doxorubicin
  - HuLuc63 MoAb (Elo)
  - LBH 589
  - Perifosine
  - Bevacizumab
  - Vaccines
  - NPI-0052
  - SAHA
  - Plitidepsin

FUTURE DIRECTIONS IN RELPASED/ REFRACTORY MM:

Next Generation Novel Agents

Novel Anti-MM Drugs in Clinical Trials

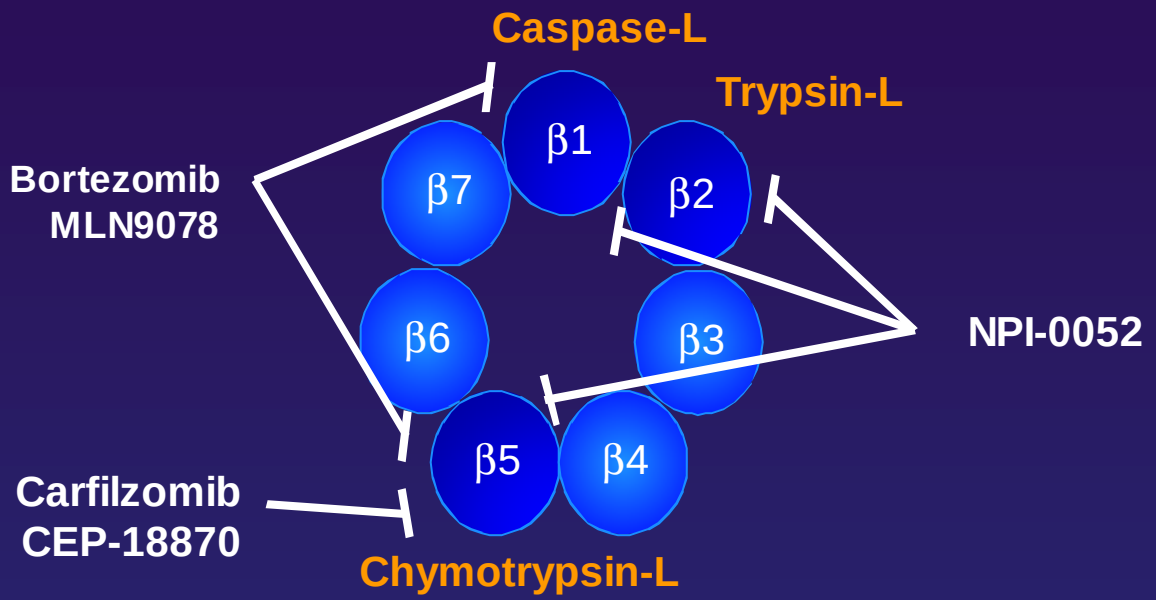
- Second generation proteasome inhibitors
- Third generation immunomodulatory agents (IMIDs)
- Histone deacetylase inhibitors
- AKT/mTOR inhibitors
- Monoclonal antibodies
- DNA-damaging agents

Proteasome Inhibitors: MoA

β-subunit ring of the proteasome

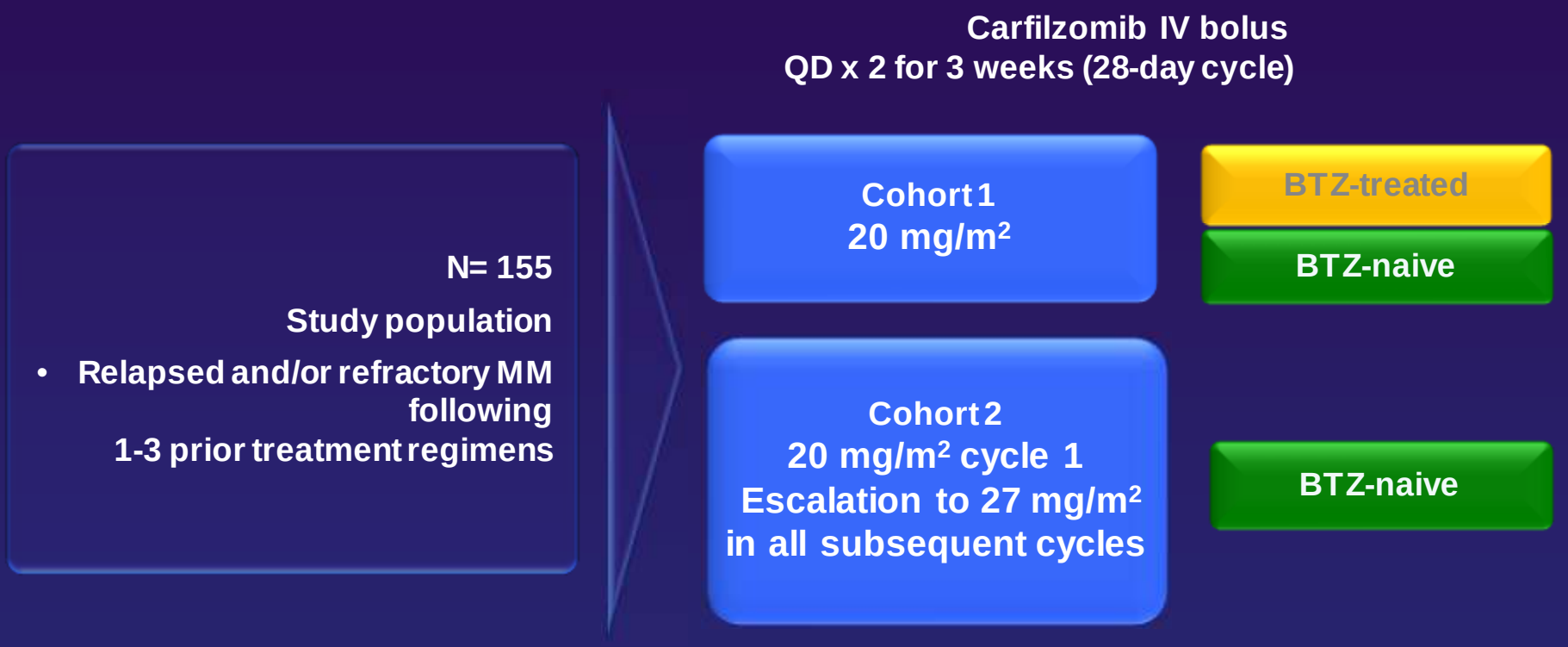
Catalytic site

Three distinct N-terminal threonine protease active sites



	Type	Catalytic inhibition			Reversibility	PO/IV	Dosing (days/cycle)
		Chymotryp.	Casp.	Tryp.			
Bortezomib	Boronate	X	X		Reversible	IV	1, 4, 8, 11
Carfilzomib	Epoxyketone	X			Irreversible	IV	1-2, 8-9, 15-16
NPI-0052	Salinospora	X	X	X	Irreversible	IV	1, 8, 15
CEP-18870	Boronate	X			Reversible	IV/PO	1, 8, 15

Single-Agent Carfilzomib: PX-171-004 Study Design



Primary endpoint: Overall response rate (CR+PR) (IMWG criteria)
Secondary endpoints: Duration of response, PFS, TTP, OS, safety

Vij R et al. J Clin Oncol. 2010;XX: Abstract 8000.

Single-Agent Carfilzomib: PX-171-004 Trial

Response Rate	BTZ-naive pts[a] Cohort 1 20 mg/m^2 (N = 53)[a]	BTZ-naive pts[a] Cohort 2 20/27 mg/m^2 (N = 53)[a]	BTZ-treated pts[a] Cohort 1 20 mg/m^2 (N = 34)[a]
CR	2%	0%	0%
VGPR	13%	17%	9%
PR	30%	38%	12%
ORR	45%	55%	21%
MR	13%	8%	12%
SD	30%	26%	35%
PD	9%	11%	32%

Bortezomib (APEX) ≥ *PR 43%*

Vij R et al. J Clin Oncol. 2010 abs.

Single-Agent Carfilzomib in PX-171-004: Adverse Events (PNY)

	Cohort 1 20 mg/m^2		Cohort 2 20/27 mg/m^2
	BTZ-treated (N=36)	BTZ-naive (N=59)	BTZ-naive (N=60)
Active grade 1/2 peripheral neuropathy (PNY) at baseline,[a] %	50	42	43
Treatment-emergent neuropathy, %			
Grade 1/2	17	12	15
Grade 3	3	2	0
Grade 4	0	0	0
Treatment discontinuations due to PNY, %	3%	0	0

- Overall, no marked↑ in PNY with carfilzomib treatment seen

Vij R et al. J Clin Oncol. 2010 abs.

[a]Grade based on physical assessment at screening (NCI-CTC scale).

003 Study Design

Primary endpoint: ORR

– IMWG response criteria (IRC assessed)

Secondary endpoints

– CBR (ORR+ MR), DOR, OS, PFS, TTP, safety

1. Jagannath S, et al. ASH 2009 *J Clin Oncol*. 2009; 27: Abstract 8504.

Siegel D, *et al*. Presented at: 52nd ASH Annual Meeting, December 7th, 2010; Orlando, FL.

Responses Rates in Subsets of Interest

	ORR	CBR	DOR for ORR
PD on or within 60 days of last Rx (n=227)	**24%**	**34%**	**8.3 mo**
# of prior bortezomib lines of therapy			
1 (n=122)	**30%**	**40%**	**8.3 mo**
≥2 (n=135)	**19%**	**29%**	**6.9 mo**
Bortezomib-refractory in last line			
n=116 (45%)	**19%**	**31%**	**8.4 mo**
Bortezomib-refractory in any prior line			
n=184 (72%)	**17%**	**28%**	**7.8 mo**

Siegel D, *et al*. Presented at: 52nd ASH Annual Meeting, December 7th, 2010; Orlando, FL.

Treatment-emergent Adverse Events* (N=266)

	Any Grade, %	Grade 3/4, %
Hematologic (≥15%)		
Anemia	44	22
Thrombocytopenia	38	27
Lymphopenia	23	18
Neutropenia	17	10
Non-hematologic (≥25%)		
Fatigue	46	7.1
Nausea	41	1.5
Dyspnea	31	3.0
Diarrhea	29	0
Pyrexia	29	1.1
Upper respiratory tract infection	26	4.1
Headache	25	1.9
Other AEs of interest		
Febrile neutropenia	0.8	0.8
Peripheral neuropathy†	12	0.8
Tumor lysis syndrome	0.4	0

*Any cause

† includes: neuropathy, peripheral neuropathy, peripheral sensory neuropathy, and peripheral motor neuropathy

Siegel D, *et al*. Presented at: 52nd ASH Annual Meeting, December 7th, 2010; Orlando, FL.

Third Generation Immunomodulatory Agents ~ Pomalidomide

- Lenalidomide + Dex[1,2] ≥ *PR: 60%* (15% CR) TTP: 11.2 mos
- Pomalidomide + Dex[3] ≥ *PR 63%* (5% CR) PFS: 11.6 mos
- N = 60 pts with relapsed MM after 1-3 previous lines of treatment (62% previous IMID) - pts with Len/Bz refractory [4]

  → *46% ORR* (9% VGPR, 23% PR, 14% MR)

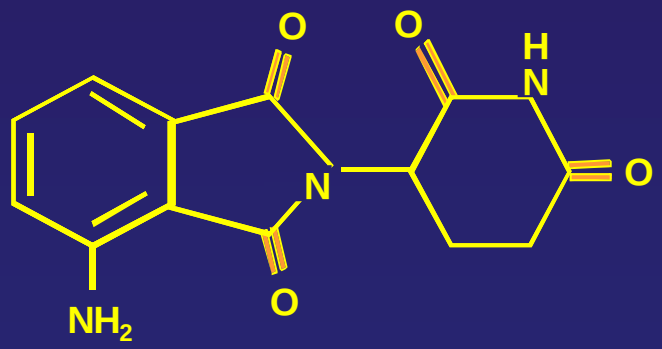
- Pom +/- dex (MM-002) Phase 1; PR 28% MR 52%

  (relapsed/refractory; median 6 lines of prior therapy) [5]

1. Weber DM et al. *N Engl J Med.* 2007;357:2133.
2. Dimopoulos M et al. *N Engl J Med.* 2007;357:2123.
3. Lacy MQ et al. *J Clin Oncol.* 2009;27:5008.
4. Lacy M et al. *J Clin Oncol.* 2010;XX: Abstract 8002.
5. Richardson et al, *ASH* 2010

Background

- Pomalidomide (POM) is a distinct immunomodulatory agent that has demonstrated direct anti-myeloma effects in lenalidomide-refractory patients with significant antiproliferative activity in vitro[1-2]
- POM has a different clinical efficacy and safety profile, with MTD of 2mg daily for 28 days of a 28-day cycle in a phase 1 study in relapsed MM[3-4]



Pomalidomide

1. Hideshima et al. Blood. 2000;96(9):2943-50. 2. Mitsiades N, et al. Blood. 2002;99:4525-4530.
3. Schey et al. J Clin Oncol. 2004;22:3269-3276. 4. Streetly et al. Br J Haematol. 2008;141:41-51.

Rationale

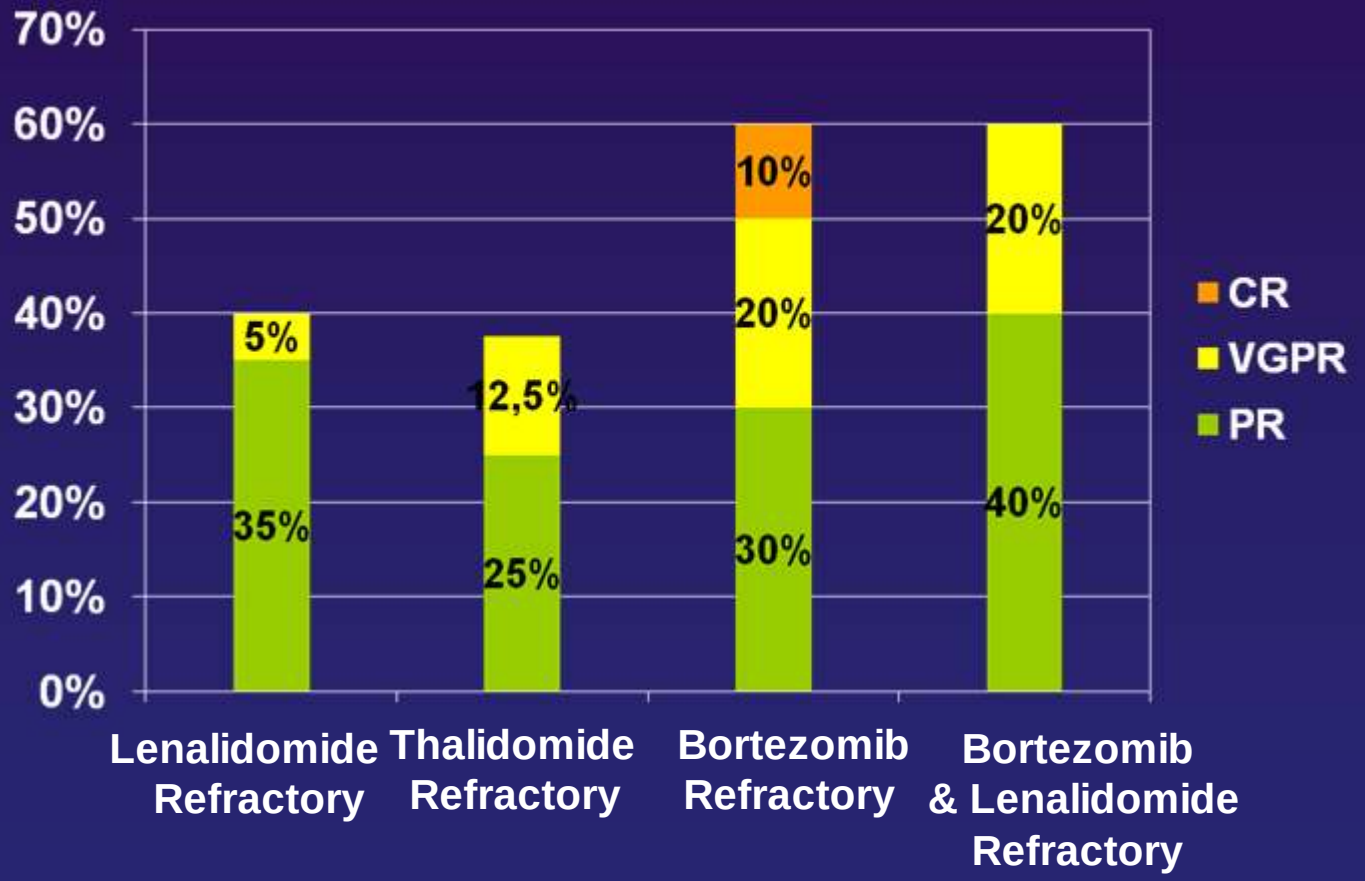
- POM: clinical efficacy in heavily pretreated pts following lenalidomide (LEN) treatment at a dose of 2 mg given continuously with dex

Phase 2 IIT study: POM 2 mg + low-dose dexamethasone (dex)[1-3]			
	ORR	PFS	OS
1-3 prior therapies[1]	63%	11.6 mos	94% at 6 mos
Refractory to LEN[2]	32%	4.8 mos	13.9 mos
Refractory to LEN & Bz[3]	26%	8 mos	86% at 6 mos

- MM002 evaluated POM 21 of 28 days ± low-dose dex to explore higher dose (2 – 5 mg)[4]
  - Relapsed and refractory MM
  - Received both LEN & bortezomib (Bz): refractory to last therapy
- MM002: Final Phase 1 and preliminary Phase 2 data are presented

1. Lacy et al. J Clin Oncol. 2009;27:5008-5014. 2. Lacy et al. Leukemia. 2010;Sept 9:Epub ahead of print. 3. Lacy et al. ASCO 2010 Presentation (Abstract 8002). 4. Richardson P, et al. Blood. 2009;114:126-127[abstract 301].

Pomalidomide with Dexamethasone in pts with MM refractory to other Novel Agents



Lacy MQ et al. *J Clin Oncol.* 2009;27:5008.

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 (MM) Who Have Received Prior Treatment That Includes Lenalidomide and Bortezomib; ASH 2010

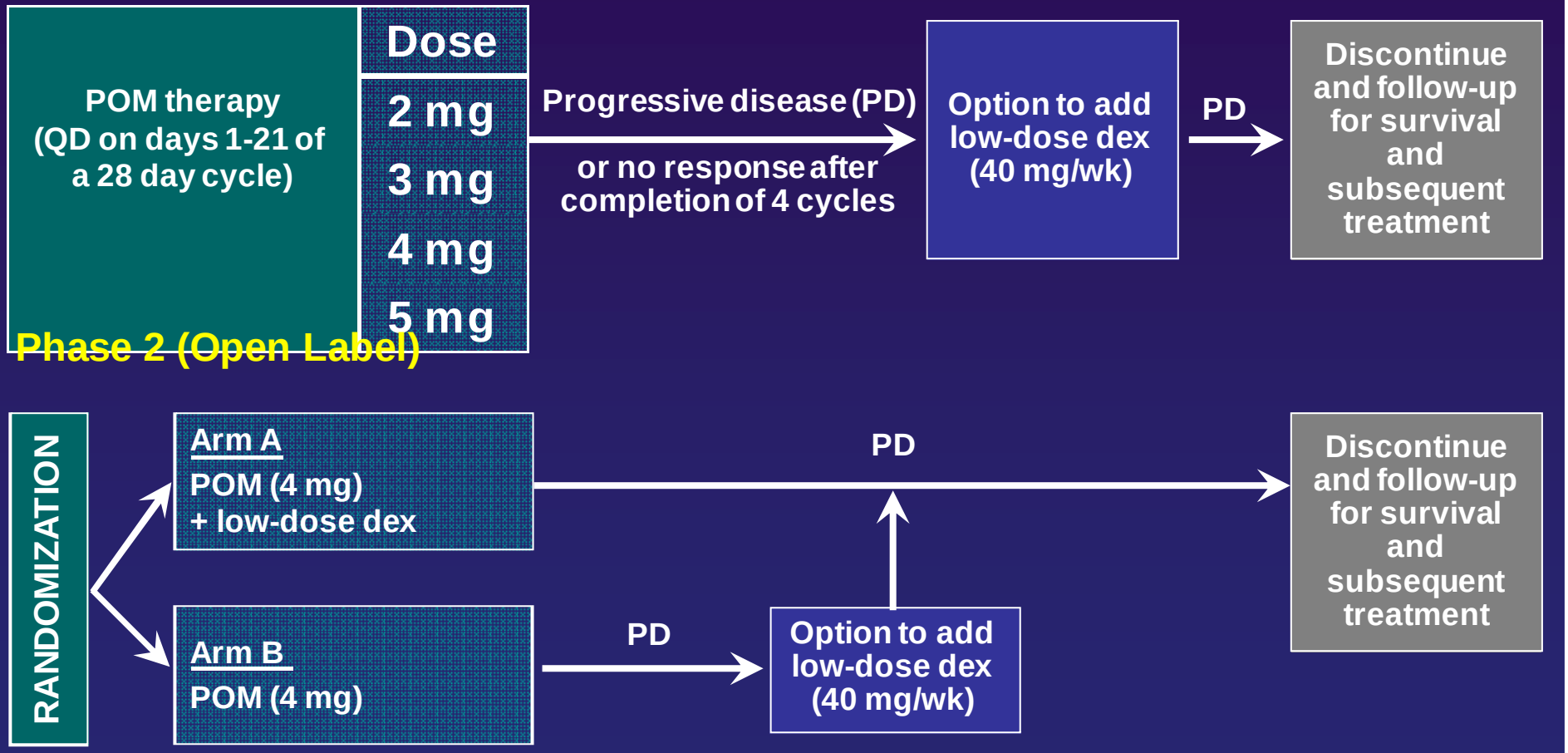
Paul Richardson[1], David Siegel[2], Rachid Baz[3], Susan L Kelley[4], Nikhil C Munshi[1], Daniel Sullivan[3], Melissa Alsina[3], Deborah Doss[1], Laura McBride[2], Gail Larkins[5], Maria Lizza[5], Xin Yu[5], Mohamad Zaki[5], Christian Jacques[5], Kenneth C Anderson[1]

[1]Dana-Farber Cancer Institute, Boston, MA; [2]Hackensack University Medical Center, Hackensack, NJ; [3]H. Lee Moffitt Cancer Center and Research Institute, Tampa, FL; [4]Multiple Myeloma Research Consortium, Norwalk, CT; [5]Celgene Corporation, Summit, NJ

MM-002 Study Schema

POM ± Low-Dose Dex in Relapsed and Refractory MM

Phase 1 (MTD)



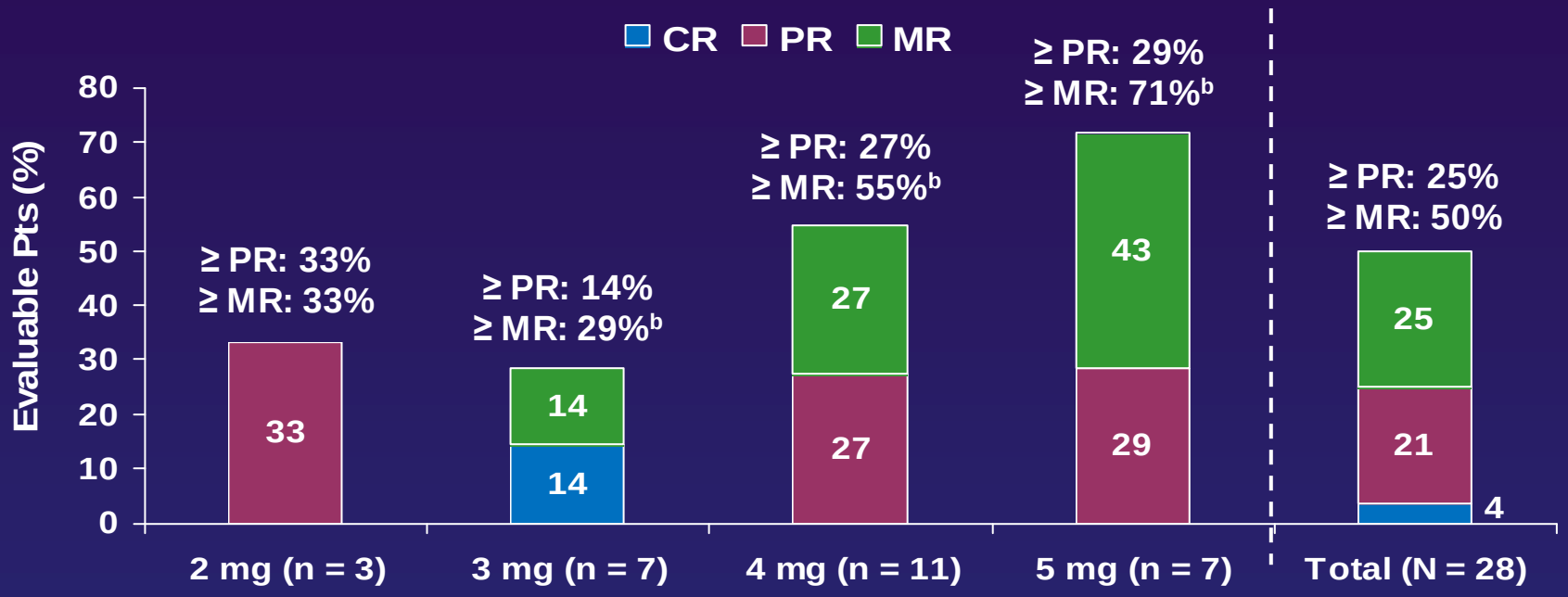
Concomitant Medications: anti-coagulants, G-CSF use after Cycle 1, erythroid growth factors, bisphosphonates, transfusions with platelet, RBCs as clinically indicated .

MM-002: Phase 1

POM ± Low-Dose Dex in Relapsed and Refractory MM

Best Response & Clinical Outcome

(Evaluable Pts[a] [n=28])



- Best response (≥ PR) to POM alone: 18%
- Median time to best response[c]: 16.1 wks
- Median DOR: 20.1 wks (assessed for responders only)
- Median PFS: 20.1 wks (95% CI: 12.0, 36.0)
- Median OS: 79.6 wks (95% CI: 61.9, NE)

a. Includes eligible, treated and evaluable for efficacy assessment; b. Discrepancies in totals due to rounding
c. Response rates based on EBMT criteria; includes pts on POM alone (n=9), pts who had dex added for SD (n=7), and pts who had dex added for PD (n=12)

MM-002: Conclusions

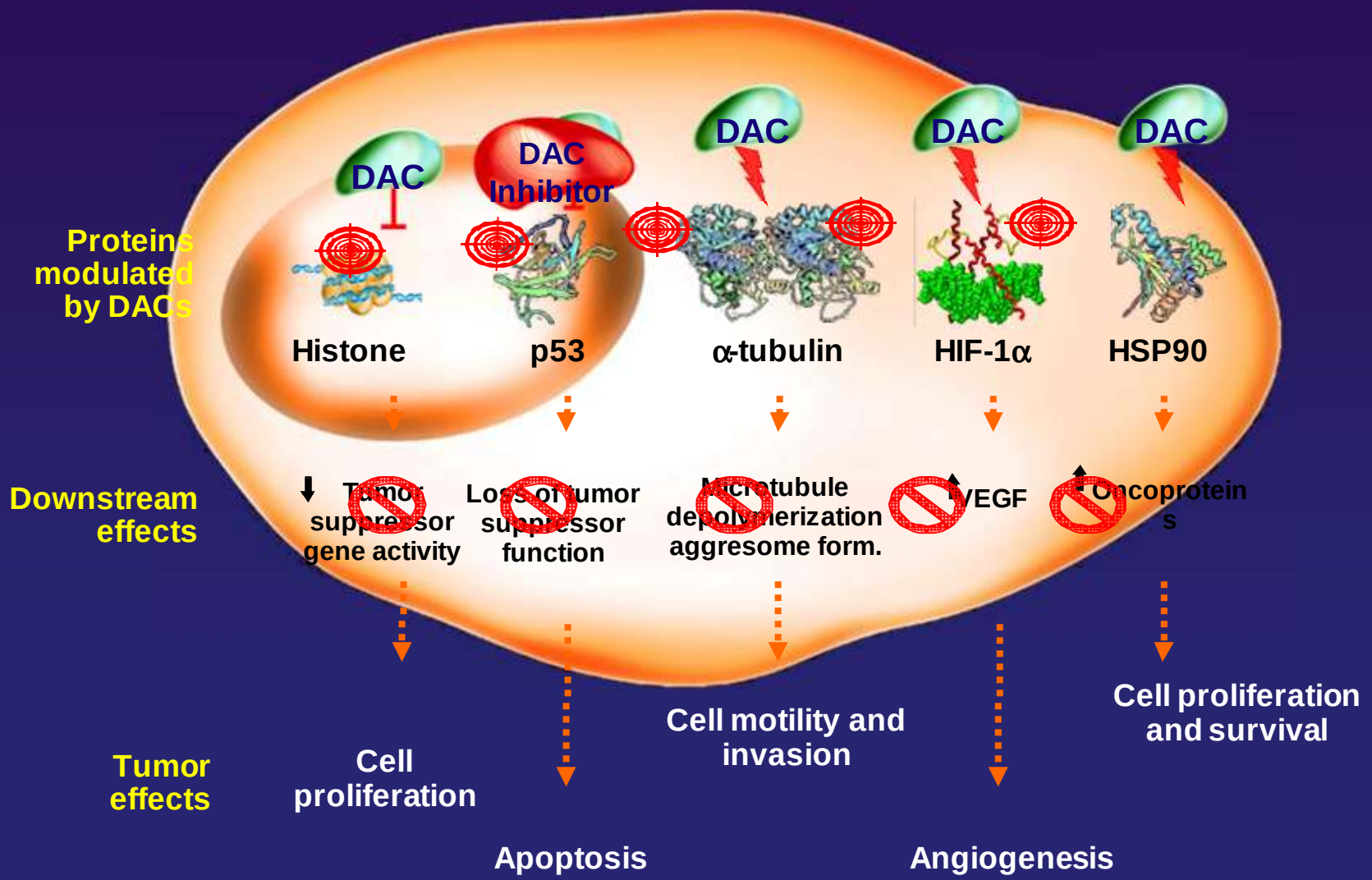
POM ± Low-Dose Dex in Relapsed and Refractory MM

- Manageable toxicity profile in heavily pretreated pts status-post LEN & Bz therapy
  - MTD: 4 mg days 1-21 of a 28-day cycle
  - Most common hematologic G 3/4 AE: myelosuppression
- Very low incidence of G 3/4 PN and DVT
- Clinically meaningful responses in heavily pretreated relapsed and refractory pts who have received prior LEN & Bz
  - Median lines of prior therapy: 6 in Phase 1; 5 in Phase 2
  - Phase 1 (evaluable pts):
    - ≥PR: 25%; ≥MR: 50%
    - Median DOR: 20.1 wks
    - Median PFS: 20.1 wks
    - Median OS: 79.6 wks
  - Phase 2 (aggregated data):
    - ≥PR 25%; ≥MR 38%
    - Median DOR not reached

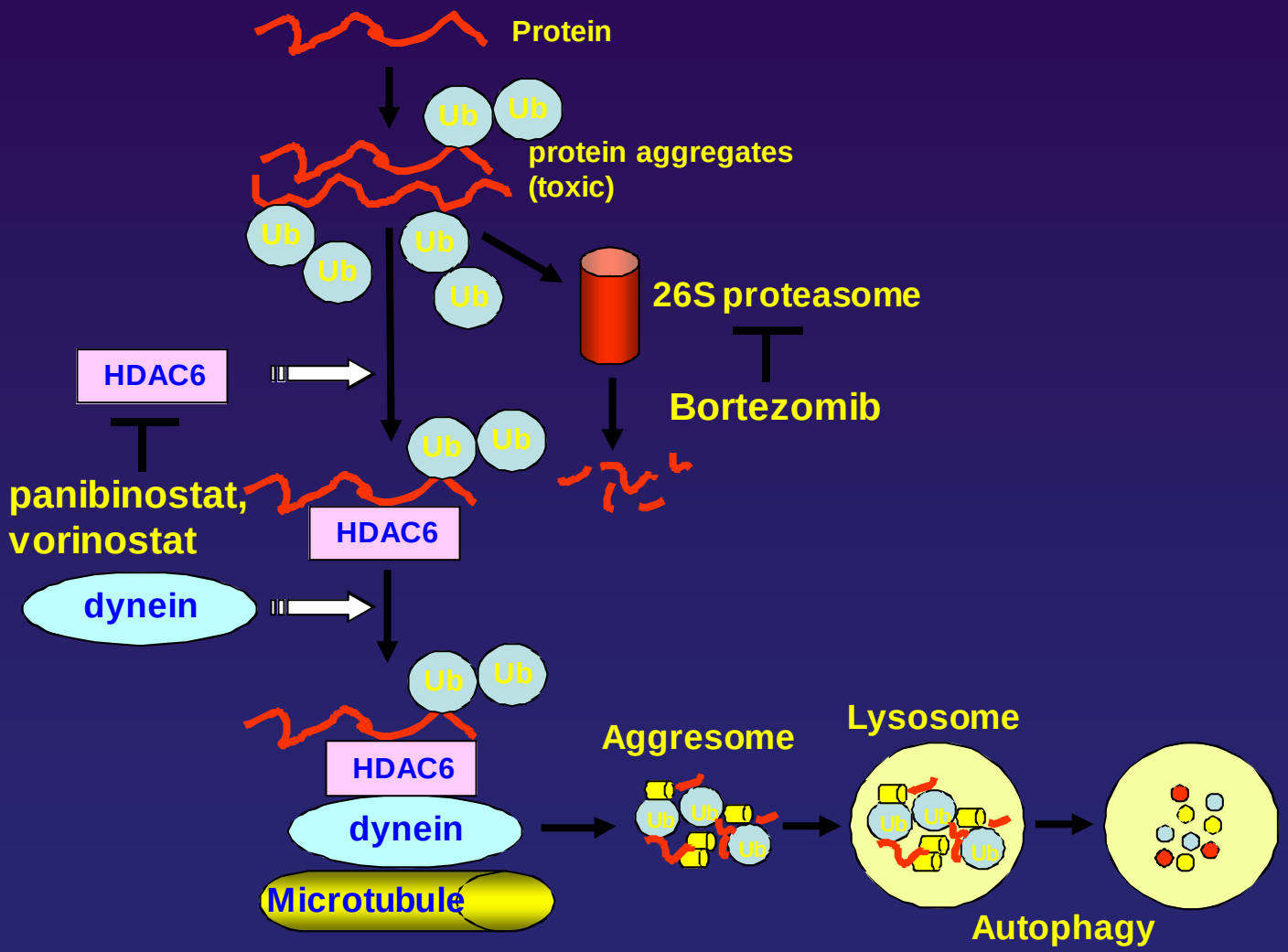
Future Directions

- Final analysis of Phase 2 (N=221)
- Analysis of GEP/surrogates
- Additional studies in relapsed and refractory MM
- Further dose exploration in less heavily pre-treated patients
- Novel combinations (e.g. POM/Bz/dex, second-generation proteasome inhibitors, alkylating agents, clarithromycin/dex, other small molecules, MoABs)

Effect of DAC on Histone and Non-histone Proteins



Blockade of Ubiquinated Protein Catabolism



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

Histone-Deacetylase Inhibitors in MM

- Single agent[1,2,3,4] → ≥ *MR 0-10 %*
- + Bort +/- Dex[5,6,7,8,9] → ≥ *MR 42-95%*

  In prev ref to Bz[5,9] → 30-60% responses
- + Len + Dex[10,11] → ≥ *MR 63-69%*

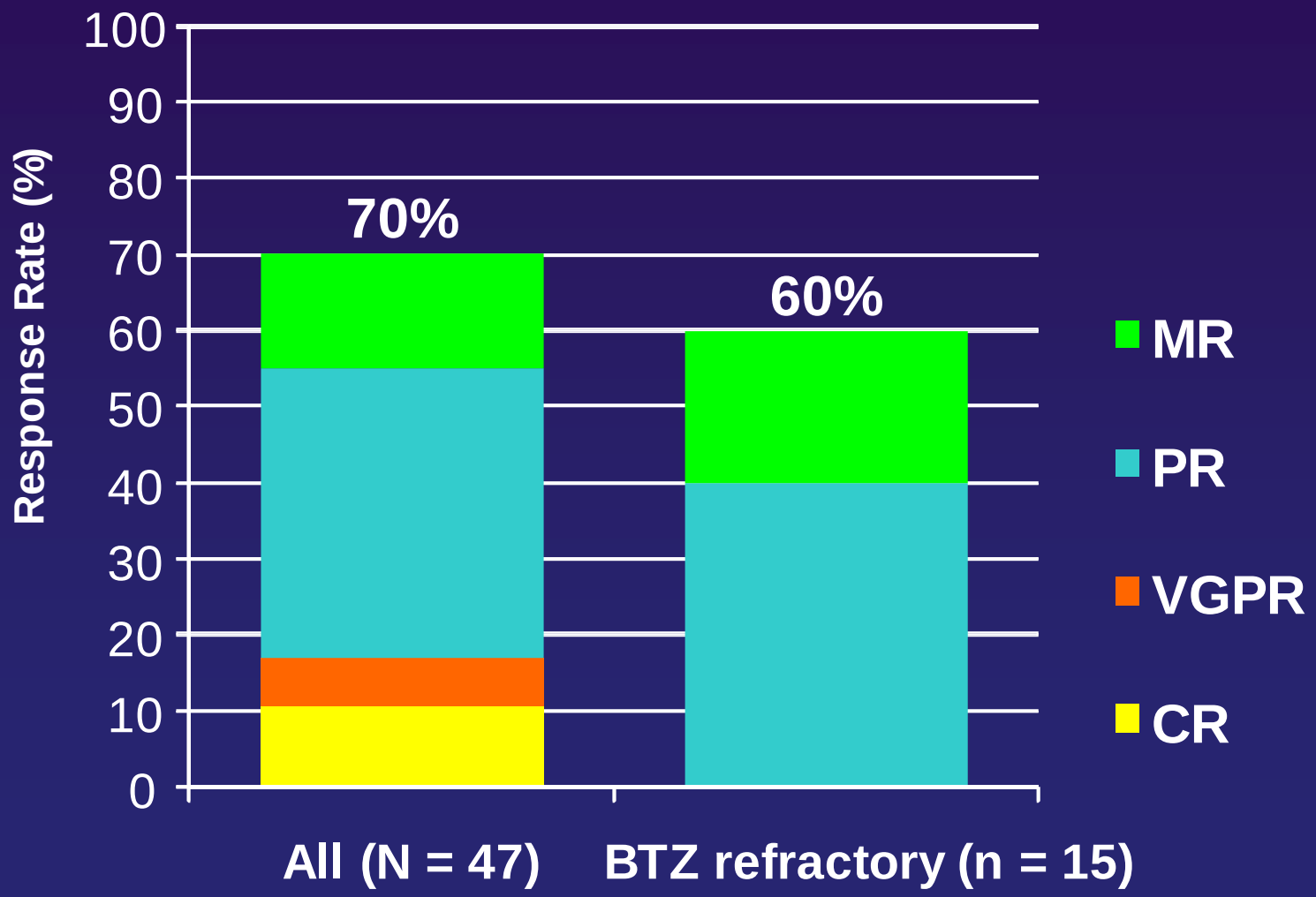
  In prev Len[11] →≥ MR 38% responses

Vorinostat[1,6,7,9,11]
Panobinostat[2,5,10]
ITF2357[3]
Romidepsin[4,8]

1. Richardson PG et al. *Leuk Lymphoma.* 2008;49:385.
2. Wolf JL et al. ASH 2008. Abstract 2774.
3. Galli M et al. ASH 2007. Abstract 1175.
4. Niesvizky R et al. ASH 2005. Abstract 2574.
5. San-Miguel JF et al. ASCO 2010. Abstract 8001.
6. Badros A et al. *Clin Cancer Res*. 2009;15:5250.
7. Weber DM et al. IMW 2009. Abstracts 242 and 248.
8. Harrison SJ et al. ASH 2008. Abstract 3698.
9. Mazunder A et al. IMW 2009. Abstract A306.
10. Mateos M et al. ASCO 2010. Abstract 8030.
11. Richardson PG et al. ASCO 2010. Abstract 8031.

Panobinostat + Bortezomib Efficacy

San Miguel et al, ASCO 2010



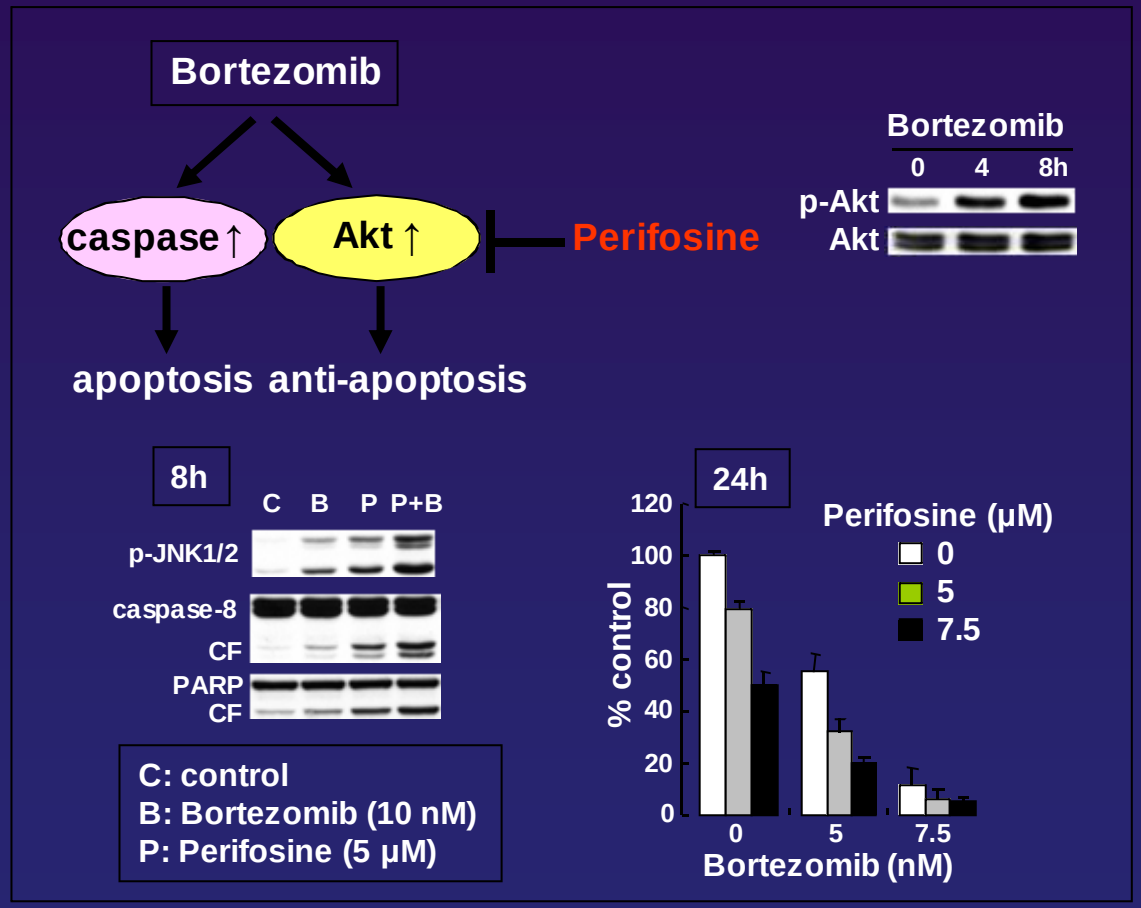
PI3K/AKT/mTOR Inhibitors in MM

≥ *MR*	Target	+/- Dex	Bort + Dex (n=73)*	Len +/- Dex
Perifosine	AKT	*38%*	*38%* [2**]	*70%*[3]
Everolimus	mTORC1	7%[4]		*63%*[5]
Temsirolimus	mTORC1	*37%*[6***]	*73%* [7]	*24%*[8]

* Median OS 23 mos **similar in Bz refractory *** TTP: 138 days

1. Richardson P et al. ASH 2007. Abstract 1164; 2. Richardson PG et al. IMW 2009. Abstract A349;
3. Jakubowiak AJ et al. IMW 2009. Abstract A347; 4. Guenther A et al. ASCO 2010. Abstract 8137;
5. Mahindra AK et al. ASCO 2010. Abstract 8032; 6. Farag SS et al. *Leuk Res.* 2009;33:1475;
7. Ghobrial IM et al. ASH 2009. Abstract 748; 8. Hofmeister CC et al. ASH 2009. Abstract 2884.

Akt Inhibitor Perifosine Enhances Bortezomib-Induced Cytotoxicity in MM Cells



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

Perifosine/Bortezomib ± Dexamethasone in Relapsed/Refractory Myeloma: Phase I/II

- Long-term follow-up results of phase I/II study (N = 73)

Patients	ORR, %	Median TTP, mos (range)	Median OS, mos
All	38	6.4 (5.3-7.1)	22.5
• Bort relapsed	55	8.8 (6.3-11.2)	25
• Bort refractory	32	5.7 (4.3-6.4)	16

- Grade 3/4 AEs in ≥ 5%: thrombocytopenia, neutropenia, anemia; otherwise well tolerated
- Phase III clinical trial of Bortezomib/dex and perifosine versus bortezomib/dex in relapsed MM ongoing for FDA approval

Richardson P, et al. ASH 2009

Elotuzumab In Combination with Lenalidomide and Dexamethasone In Patients with Relapsed Multiple Myeloma: Interim Results of a Phase 2 Study; ASH 2010

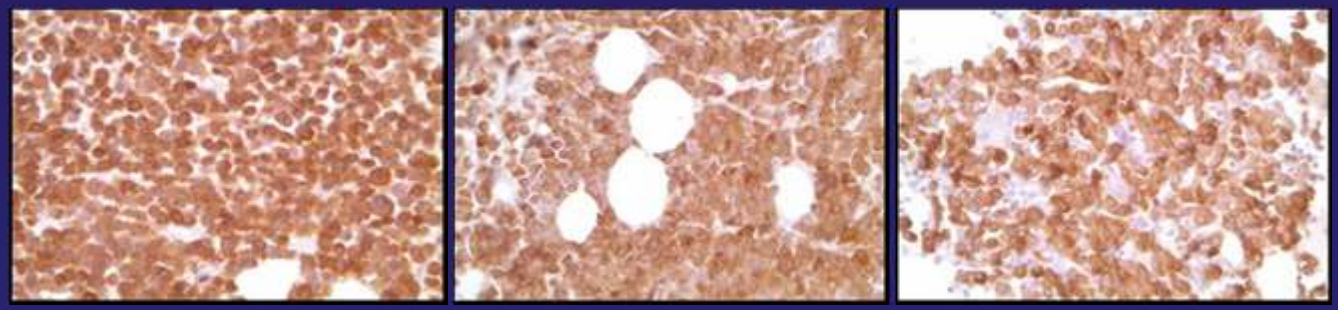
PG Richardson,[1,2] P Moreau,[3] AJ Jakubowiak,[2,4] T Facon,[5] S Jagannath,[2,6] R Vij,[2,7] DE Reece,[2,8] D White,[9] MS Raab,[10] L Benboubker,[11] J-F Rossi,[12] C Tsao,[13] T Parli,[13] D Berman,[14] AK Singhal,[13] S Lonial[2,15]

[1]Dana-Farber Cancer Institute, Boston, MA, USA; [2]Multiple Myeloma Research Consortium, Norwalk, CT, USA; [3]Hematology Department, University Hospital, Nantes, France; [4]University of Michigan Comprehensive Cancer Center, Ann Arbor, MI, USA; [5]Hôpital Claude Huriez, Service des Maladies du Sang, Lille, France; [6]Mount Sinai Medical Center, New York, NY, USA; [7]Washington University School of Medicine, St. Louis, MO, USA; [8]Princess Margaret Hospital, Toronto, Ontario, Canada; [9]Queen Elizabeth II Health Sciences Centre, Halifax, Nova Scotia, Canada; [10]Universitaetsklinikum Heidelberg, Heidelberg, Germany; [11]CHU Tours-Hôpital Bretonneau, Tours, France; [12]CHU de Montpellier-Hôpital Saint-Eloi, Montpellier, France; [13]Facet Biotech,* Redwood City, CA, USA; [14]Bristol-Myers Squibb, Princeton, NJ, USA; [15]The Winship Cancer Institute, Emory University School of Medicine, Atlanta, GA, USA

*Facet Biotech is now Abbott Biotherapeutics Corp.

Elotuzumab: Background

- Elotuzumab (HuLuc63) is a humanized monoclonal IgG1 antibody targeting human CS1, a cell surface glycoprotein[1,2]
- CS1 is highly and uniformly expressed on MM cells[1–3]
  - Restricted expression on NK cells
  - Little to no expression on normal tissues

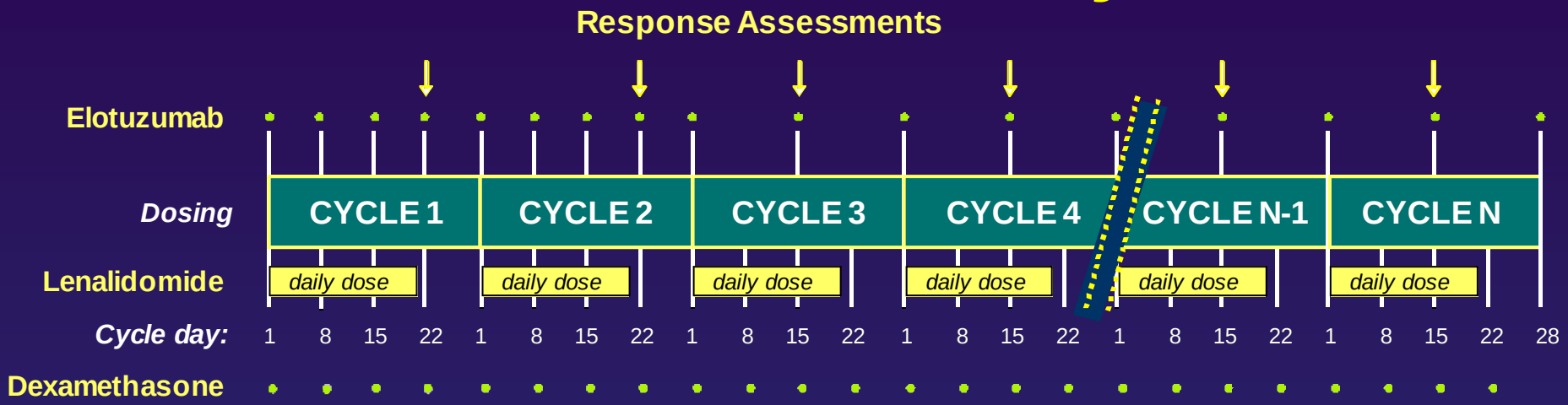


- In a MM xenograft mouse model, the antitumor activity of elotuzumab was enhanced by the addition of lenalidomide[4]

MM, multiple myeloma; NK, natural killer.

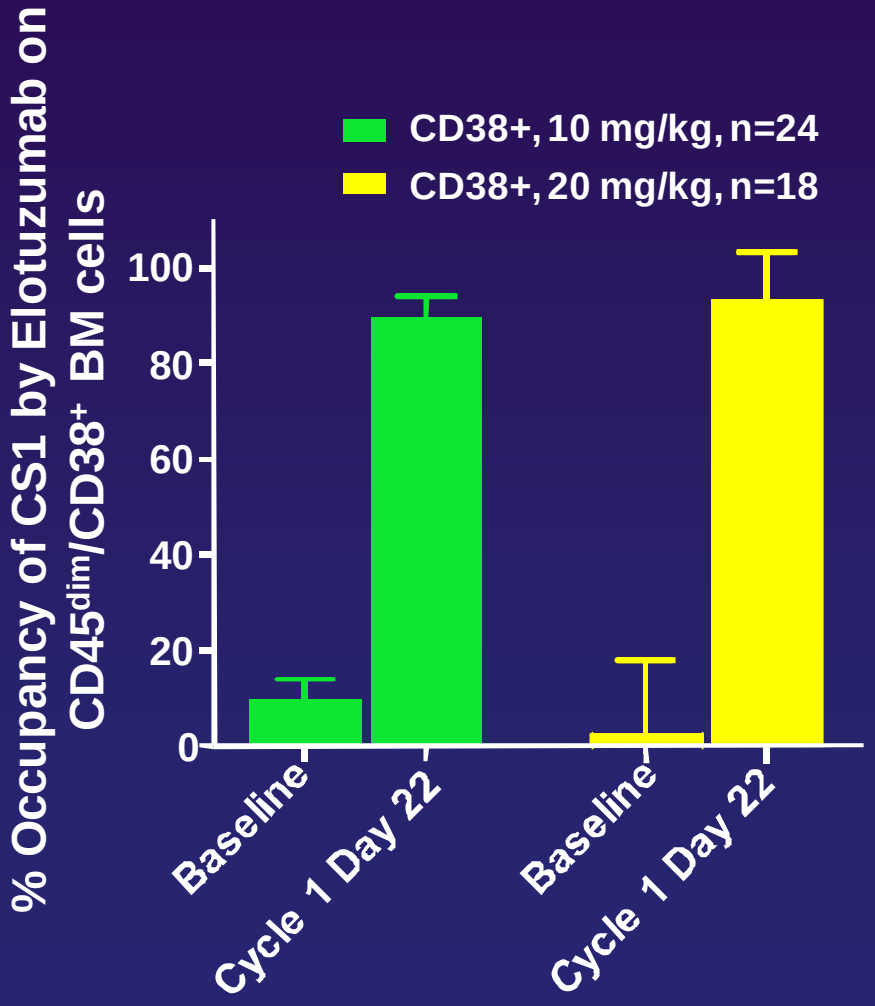
1. Hsi ED et al. *Clin Cancer Res*. 2008;14:2775-2784. 2. Tai YT et al. *Blood*. 2008;112:1329-1337.
3. van Rhee F et al. *Mol Cancer Ther*. 2009;8:2616-2624. 4. Lonial S et al. *Blood*. 2009;114:432.

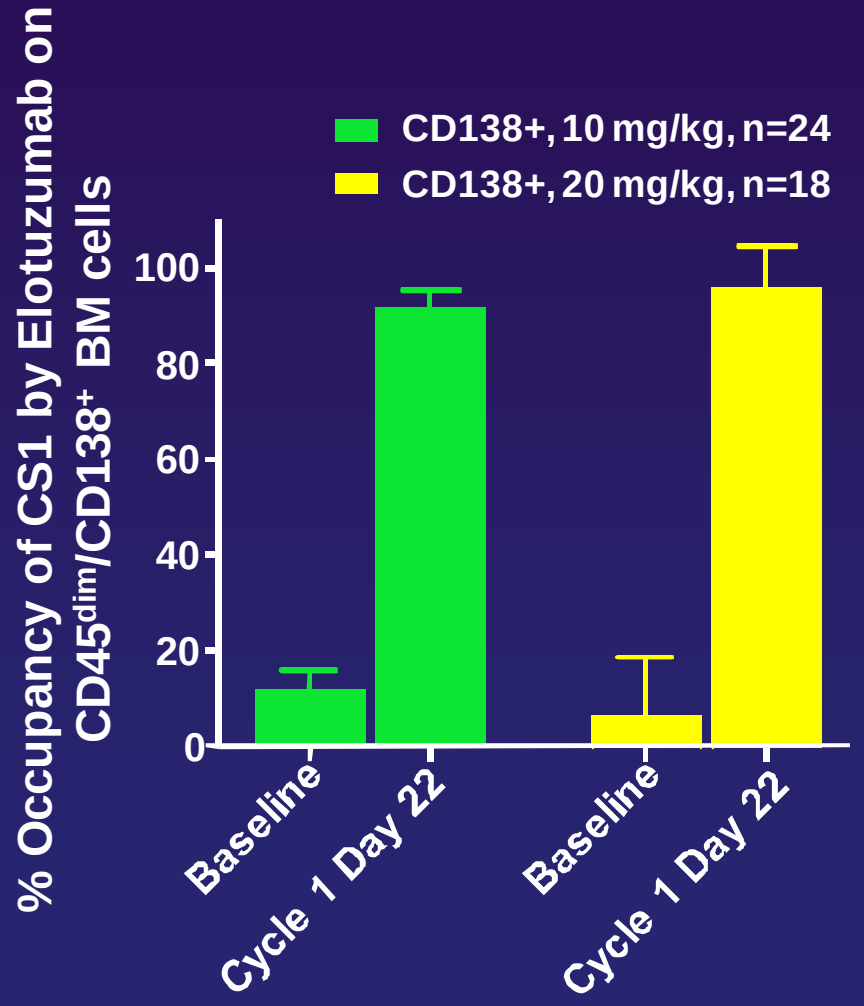
Randomized Phase 2 Study Schema



- Pts randomized to receive elotuzumab 10 or 20 mg/kg IV, in combination with lenalidomide 25 mg PO and low-dose dexamethasone 40 mg PO wkly (28-day cycles)
- Treatment continued until PD or unacceptable toxicity
- Premedication regimen (30–60 mins prior to elotuzumab infusion)
  - Methylprednisone 50 mg IV
  - Diphenhydramine 25–50 mg PO or IV (or equivalent)
  - Ranitidine 50 mg IV (or equivalent)
  - Acetaminophen 650–1000 mg PO

CS1 Saturation on CD38+ and CD138+ in Patient BM MM Cells





Conclusions

- Elotuzumab + len/dex was generally well tolerated
  - Gr 3/4 AEs >10%: neutropenia (14%), lymphopenia (14%), thrombocytopenia (13%)
  - Premedication regimen appears to mitigate the incidence and severity of infusion reactions
- High ORR in previously-treated MM pts
  - Phase 1: 82%[1,2]
  - Phase 2: 81% ORR, 37% VGPR/CR
- 10 mg/kg elotuzumab is recommended Phase 3 dose
  - High activity (90% ORR, 42% VGPR/CR), similar safety and CS1 saturation to 20 mg/kg
  - High ORR in β2M ≥3.5 mg/L, prior thalidomide and median ≥2 prior therapies
- Phase 3: Randomized, Open Label Trial of Lenalidomide/Dexamethasone With or Without Elotuzumab in Relapsed or Refractory MM anticipated to start early 2011 (NCT 01239797)

1. Lonial S et al. ASCO 2010; Abstract 8020 (Oral). 2. Lonial S et al. ASH 2010; Abstract 1936.

Bendamustine in MM

- **Newly diagnosed**
  - BP[1] vs MP → ORR: 75% vs 70%; CR: 32% vs 13%
  - TTP: 14 mos vs 10 mos
- **Relapsed/Refractory**
  - Single agent[2] → ORR: 55% (2CR, 7PR, 7mR); PFS: 6 mos
  - Benda-Thal-Pred[3] → ORR: 86% (14% CR, 18% VGPR, 50%PR)
  - Benda-Bortz-Dex[4] → ORR: 72% (25% VGPR, 47%PR)
  - Benda-Bort-Pred[5] → ORR: 75% (15% nCR,14% VGPR, 46% PR)
  - Benda-Len-Dex [6] → ORR: 67%

1. Ponisch W et al. *J Cancer Res Clin Oncol*. 2006;132:205.
2. Knop S et al. *Haematologica*. 2005,90:1287.
3. Ponisch W et al. *Br J Haematol*. 2008,143:191.
4. Hrusowsky V et al. *Blood*. 2007. Abstract 4851.
5. Ponisch W et al. ICML 2008.
6. Lentzsch S et al. ASH 2009. Abstract 1856.

Summary

- New approaches for relapsed and relapsed/refractory disease
  - Bz ± Dex, Len + Dex
  - Other 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
- Efficacy = activity + tolerability; duration of treatment key
- Steroid-sparing regimens, role of lower doses of dexamethasone (eg, effect on bone disease)

- **Participation in clinical trials a key priority**

Future Directions

1. Novel Therapy Combinations in MM: a new treatment paradigm targeting both the tumor cell and its microenvironment, which has already markedly improved OR, CR, EFS and OS.

2. Ongoing oncogenomic and proteomic studies are informing clinical protocol design and identifying novel therapeutic targets.

3. Future moleculary based, rationally designed combination therapies (eg IMiDs, proteasome inhibitors, HSP 90 inhibitors, HDAC inhibitors, AKT inhibition, and MoAbs +/- conventional therapy) will achieve durable CR in the majority of pts with the development of effective immune therapies.

4. Identification of new targets to inhibit growth of the MM cell in the BM microenvironment with improved classification and

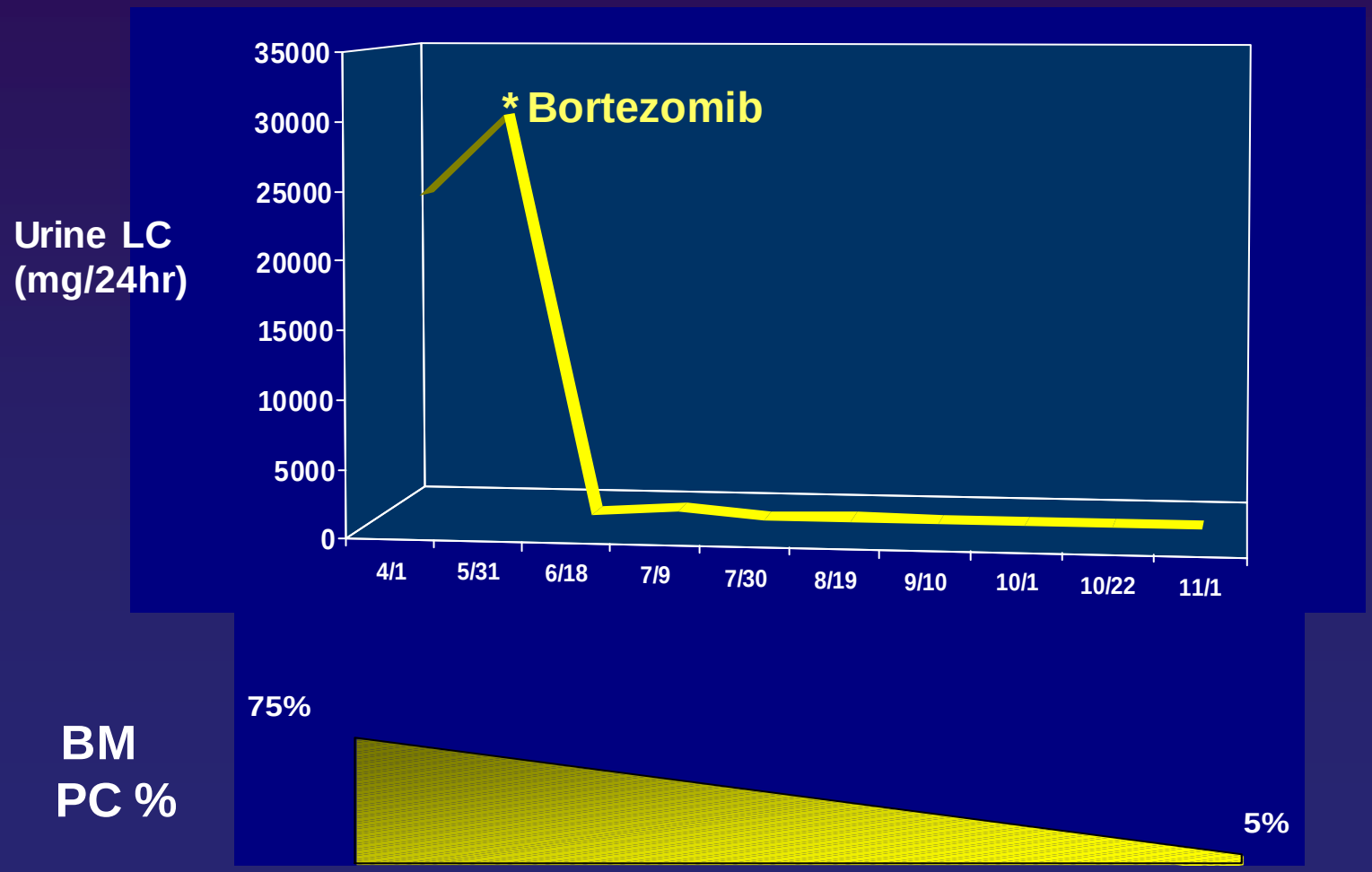
Future Directions (Continued)

- Tailored approach to therapy:
  - Identify groups of pts in whom multi-drug combinations are required versus pts in whom doublets/triplets as sequences (vs 4-5 agent combos) should be used
  - Use of GEP, Proteomics
  - Risk adaptation

The Impact of Novel Therapies in MM

- 66 yr old gentleman: S3a Kappa LC MM; Ch 13 del positive (diagnosed 1996, age 52 yrs)
- VAD ; Aredia ; Auto SCT x 2
- Thalidomide ; BLTD (1999- 2001)
- Allo SCT/DLI >> PD by D+100 (Dec 2001)
- Bortezomib monotherapy (2002)

CR to Bortezomib Monotherapy (040; dfci upn # 007: initials JB)



The Impact of Novel Therapies in MM (continued)

- Nov 2003: PD >> SAHA (Vorinostat)

  (single agent; phase I); stable disease

- April 2004: PD >> Lenalidomide (Len)

  (single agent; phase II ~ 014); VGPR

- December 2008: Early M protein increase; Bone Progression - ? "RevVel" next vs other bortezomib-based combination; Increased Len dosing and XRT - RevVel being kept in reserve together with other options

- January through Dec 2010; Continued Remission on Len

- " I am just glad to be above the divots"

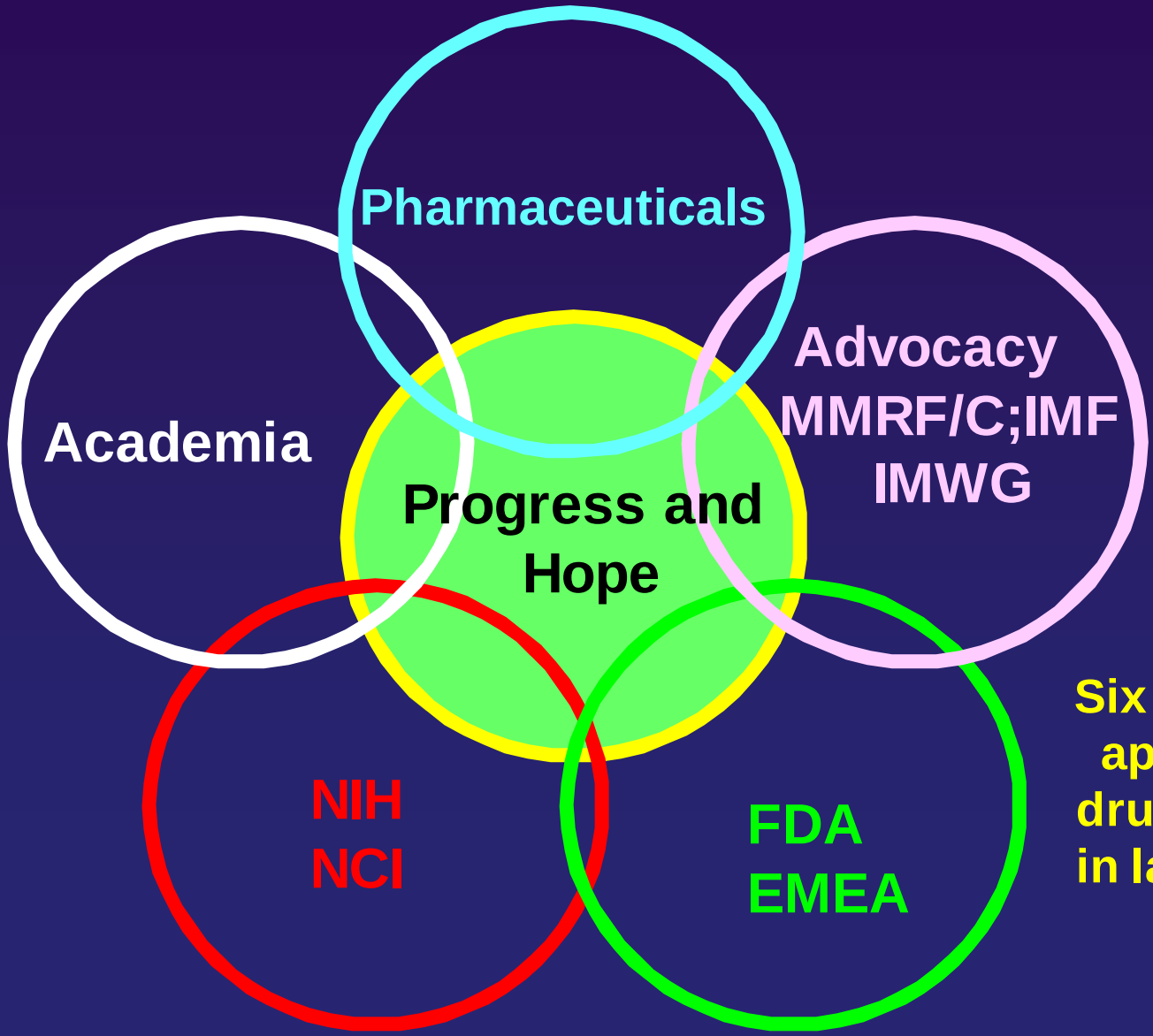
  JB, Newsweek 2006

The Impact of New Drug Development in MM…..

“If you guys didn’t work together and as hard as you do, I wouldn’t be here.”

JB, Pan Ohio Hope Ride for the ACS, 2010

Ongoing MM Collaborative Model for Rapid Translation from Bench to Bedside



Six new FDA approved drugs/combos in last 6 yrs

Clinical Investigators in MM - A Global Network: Leadership, including Anderson KC., Harousseau JL., San Miguel J., Dalton W., Kyle R.

APEX/ SUMMIT/CREST/ VISTA/ 009/010 Combination Studies Investigators: Sponsors incl. Millenium; Celgene; J & J; Novartis; BMS; Keryx; Merck; Study groups ~ IFM, EMN, ECOG, CALGB, Multiple Myeloma Research Consortium (MMRC) Advocacy/Support MMRF; IMF ; FDA; EMEA

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

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