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From bench to bedside: combination regimens in the present and future management of multiple myeloma

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Integration of Novel Therapy Into Myeloma Management

Bortezomib, Lenalidomide, Thalidomide, Doxil

Target MM in the BM microenvironment to overcome conventional drug resistance in vitro and in vivo

Effective in Relapsed/Refractory, Induction, Consolidation and Maintenance

Six FDA approvals and median survival prolonged from 3-4 to 6-7 years, maintenance adds at least 2-3 more years

Chromosomes and Prognosis in Multiple Myeloma

Nonhyperdiploid worse prognosis than hyperdiplo

t(11;14), hyperdiplody -standard risk

t(4;14), del(17p), del(13q14)-high risk

For novel treatments

Bortezomib, but not lenalidomide, can at least partially overcome t(4;14), del(13q14)-

del(17p) p53 remains high risk

Bortezomib and Lenalidomide Therapy

- Lenalidomide induces caspase 8 mediated apoptosis of MM cells in BM in vitro and in vivo; Dex (caspase 9) enhances response
- Synergistic MM cell toxicity of lenalidomide (caspase 8) with Bortezomib (caspase 9>8) in vitro and in vivo (dual apoptotic signaling)
- Phase I-II trials show that majority (58%) of patients refractory to either agent alone respond to the combination
- Phase I-II trials show 100% response with 74% CR/VGPR and 52% CR/nCR when used as initial therapy

Richardson et al JCO and Blood, 2010

Upfront Revlimid Velcade Dexamethasone

Best Resp, n (%)	All pts (N=66)	Phase II (N=35)
CR	19 (29)	13 (37)
nCR	7 (11)	7 (20)
VGPR	18 (27)	6 (17)
PR	22 (33)	9 (26)
CR+nCR	26 (39)	20 (57)
(90% CI)	(29, 50)	(42, 71)
CR+nCR+VGPR	44 (67)	26 (74)
(90% CI)	(56, 76)	(59, 86)
At least PR	66 (100)	35 (100)
(90% CI)	(96, 100)	(92, 100)

- Response improvement seen in 42/56 pts (75%) from C4–8 and 20/38 pts (53%) beyond C8
- Median (range time to best overall response) was 2.1(0.6,20) mos

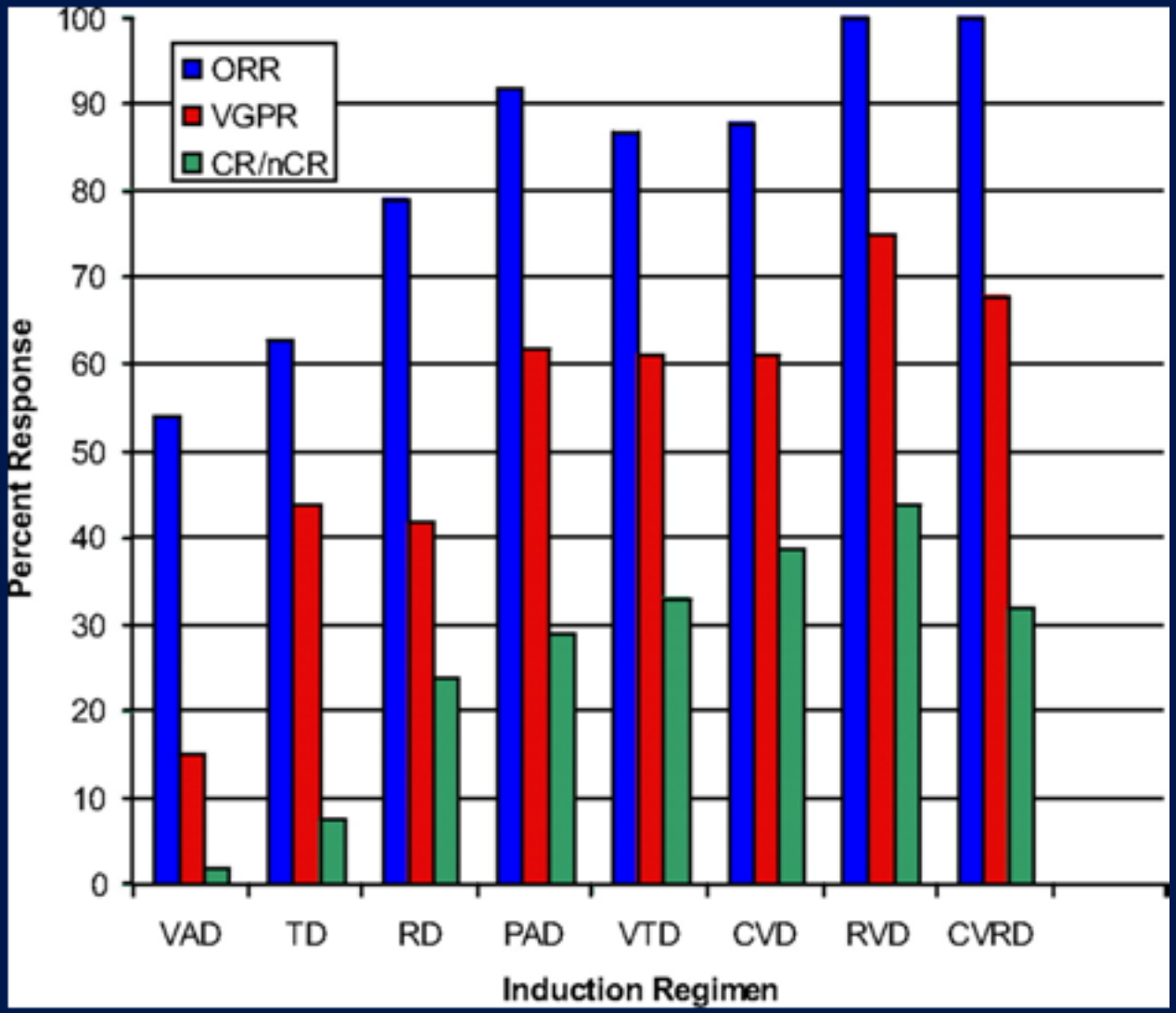
Richardson et al, Blood 2010

EVOLUTION STUDY: MRD negativity across arms

Response by algorithm (overall population), n (%)	VDCR (n = 42)	VDR (n = 42)	VDC (n = 32)	VDC-mod (n = 17)	TOTAL
CR	10 (24)	10 (24)	7 (22)	8 (47)	35
MRD sampling					
Patients ≥CR providing MRD sample, n (%)	10 of 10 (100)	7 of 10 (70)	4 of 7 (57)	7 of 8 (88)	28
Patients ≥CR MRD –ve, n (%)	5 of 10 (50)	6 of 7 (85)	0 of 4 (0)	2 of 7 (29)	13 of 28 (46)

Kumar et al, ASH 2010 abstr 621

Combinations in the Upfront Treatment of MM

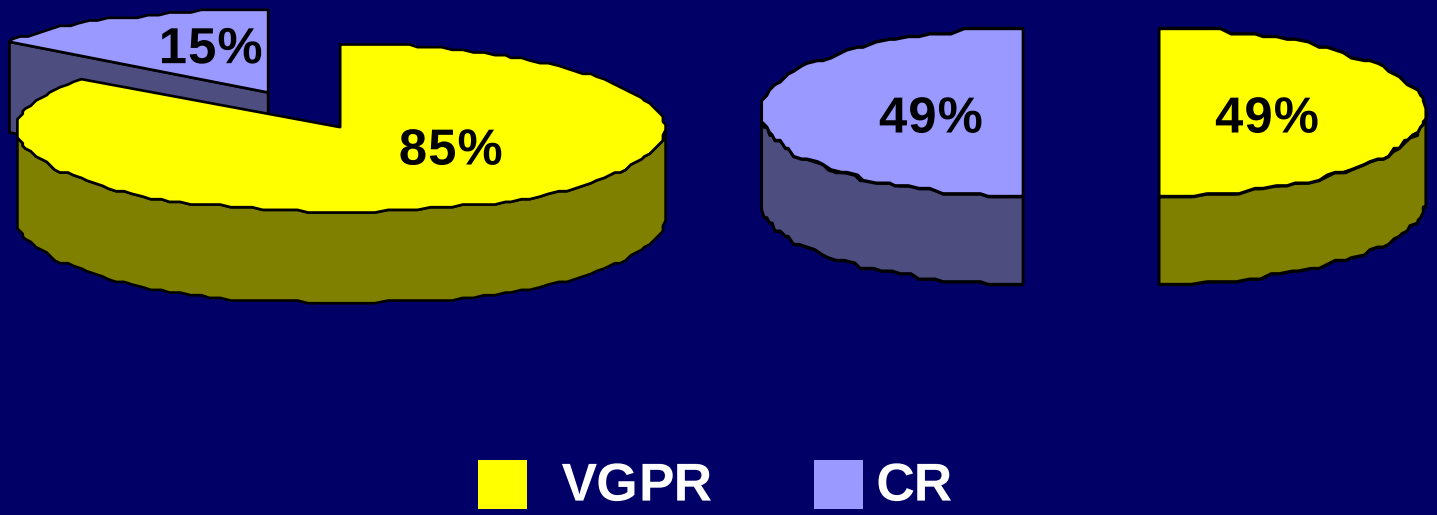


Stewart AK, Richardson PG, San Miguel JF *Blood* 2009

Clinical Impact of VTD Consolidation in VGPR Patients After ASCT

Responses after ASCT
VGPR 85%
CR 15%

Responses after VTD
VGPR 49%
CR 49%



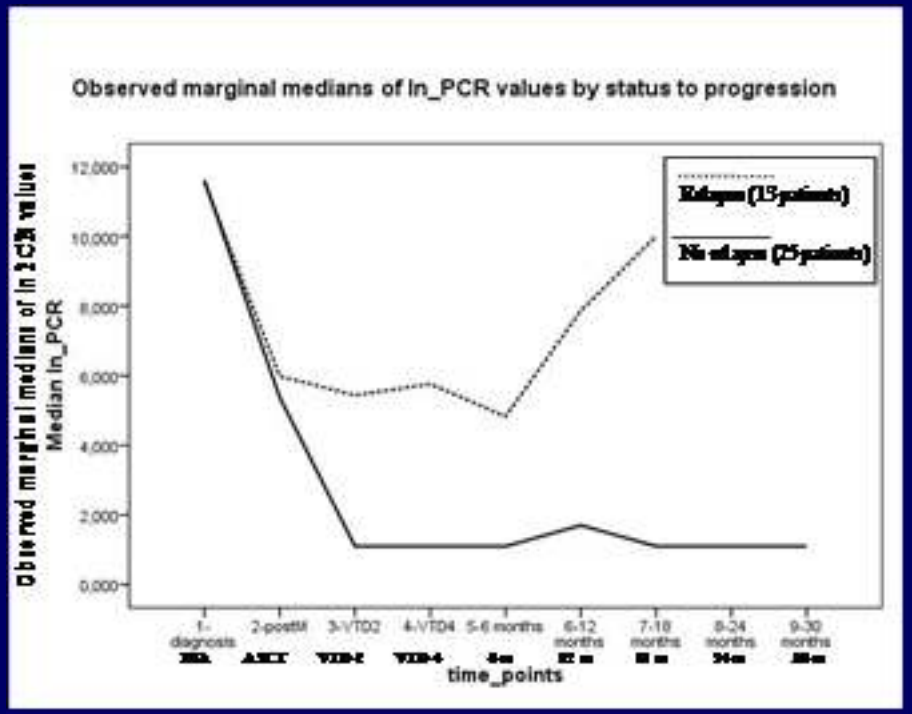
Ladetto M, et al. J Clin Oncol. 2010;28:2077-2084.

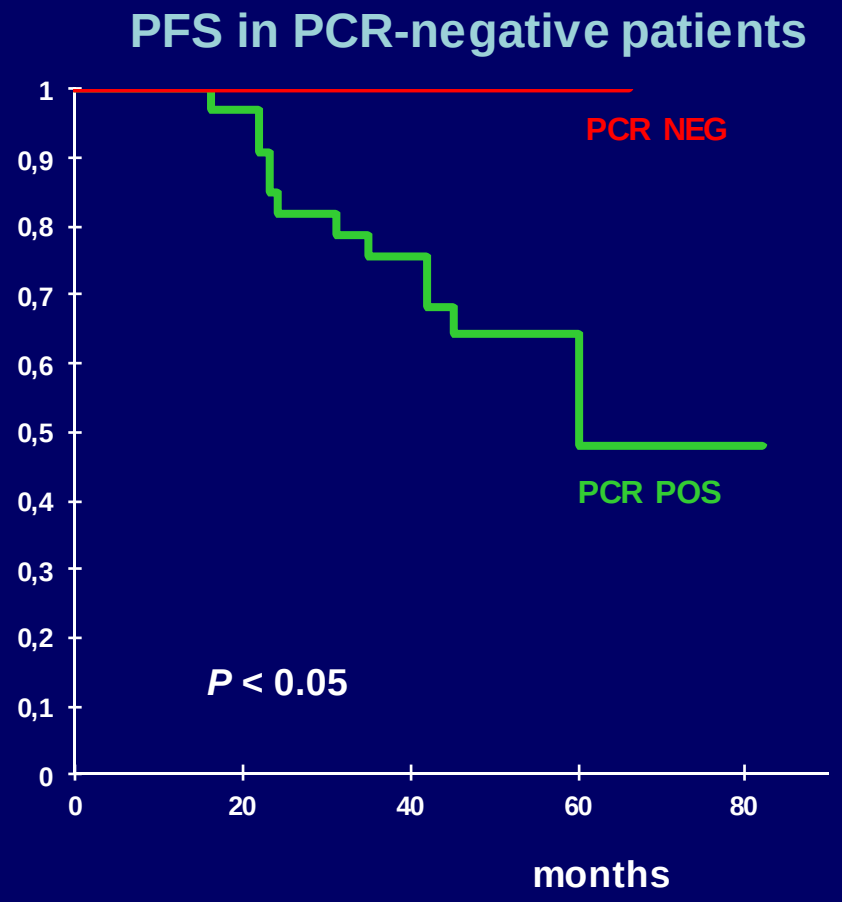
Complete Response are all the same?

Response Criteria	Tumor gene copy number
Diagnosis	25,000 – 500,000
PR	5,000 – 100,000
VGPR	1,500 – 20,000
Immunofixation-negative CR	1,000 – 10,000
Immunophenotypic CR*	10 – 100
Molecular CR^	5 – 20

**Paiva et al Blood 2009: 114;4369-72; ^Ladetto et al. J Clin Oncol . 2010;28(12):2077-84*

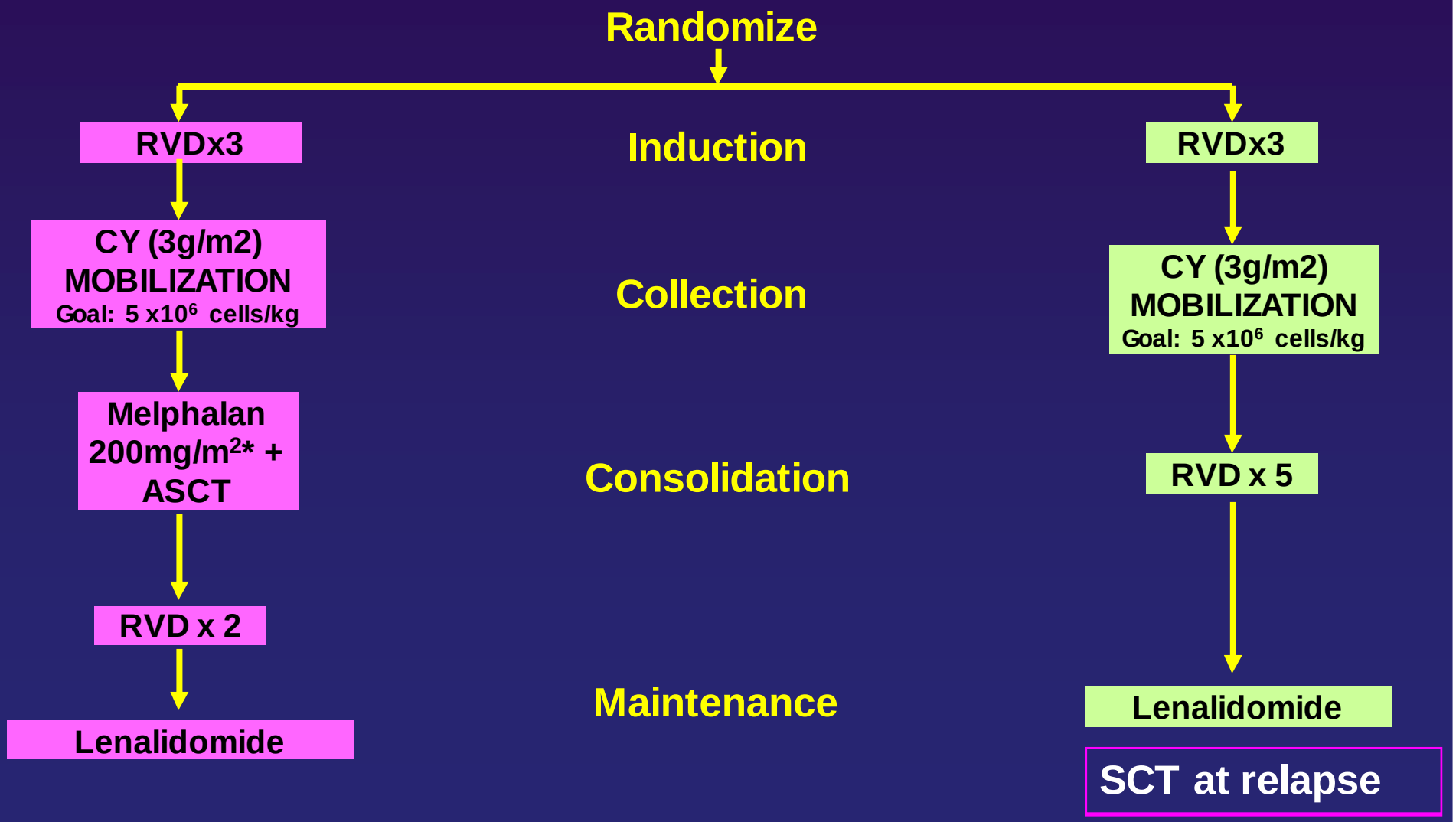
Clinical Impact of Minimal Residual Disease





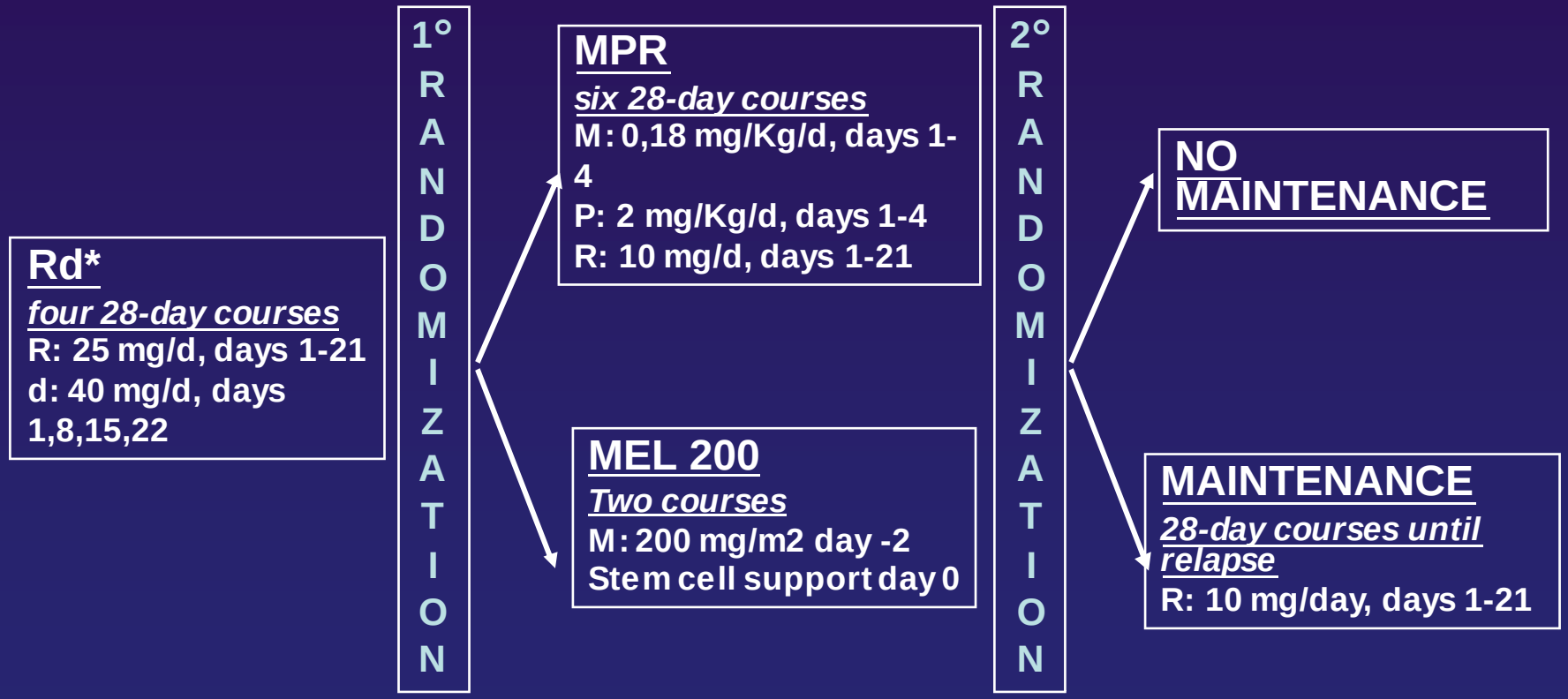
Ladetto M, et al. ASH 2009. Abstract 960.

IFM/DFCI 2009 Phase 3 Study
Newly Diagnosed MM (SCT candidates)



MPR versus Mel 200mg/m^2 x 2

- 402 patients (younger than 65 years) randomized from 62 centers
- Patients: Symptomatic disease, organ damage, measurable disease



*Thromboprophylaxis randomization: aspirin vs low molecular weight heparin

R, lenalidomide; M, melphalan; d, dexamethasone; P, prednisone

Palumbo A, et al. Blood. 2010; 116:[abstract 3573]. Updated data presented at ASH 2010.

Results

	MPR	MEL200	P value
CR	20%	25%	0.49
≥ VGPR	60%	58%	0.38
PFS at 12 months	91%	91%	0.77
OS at 12 months	97%	98%	0.27

Palumbo A, et al. Blood. 2010; 116:[abstract 3573]. Updated data presented at ASH 2010.

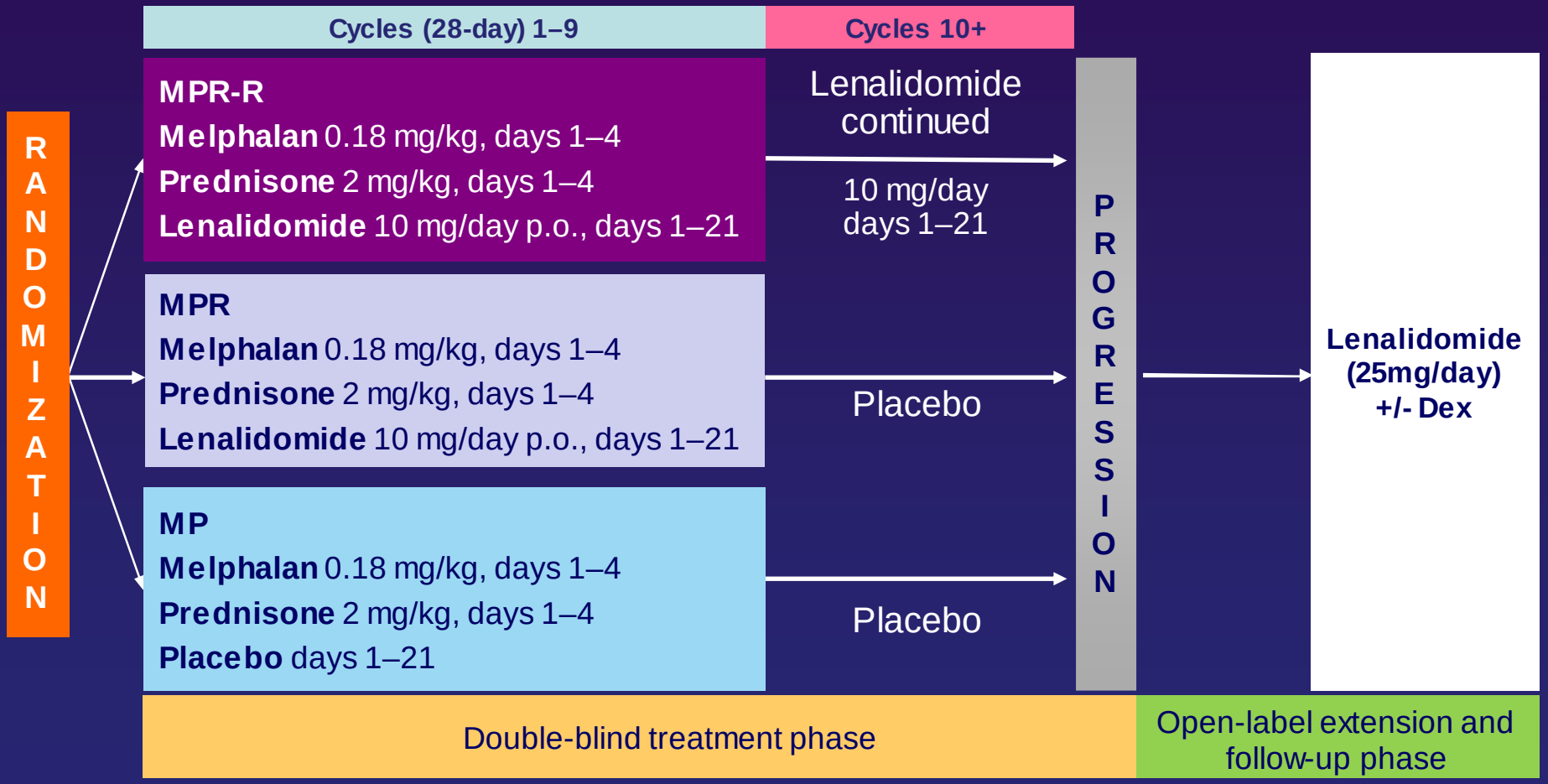
Newly Diagnosed SCT Ineligible Patients

	MPT[1] N = 129	VMP[2] N = 337	MPR[3] N = 153	MPR-R[3] N = 152	VTP[5] N = 130
CR	16%	30%	11%	16%	28%
≥ VGPR	29%	Not reported	33%	32%	≥nCR 36%
≥ PR	69%	71%	68%	77%	81%
PFS	21.8 mos	21.7 mos	14 mos[4]	31 mos[4]	31 mos
Median follow-up	38.4 mos	36.7 mos	25 mos[4]	25 mos[4]	32 mos

[1]Palumbo A, et al. *Blood.* 2008;112:3107-3114. [2]Mateos MV, et al. J Clin Oncol. 2010;28:2259-66.
[3] Palumbo A, et al. European Hematology Association 15th Congress. 2010. Abstract 566.
[4]Palumbo A, et al. Blood. 2010;116:[abstract 622]. Updated data presented at ASH 2010.
[5] Mateos MV, et al. Lancet Oncology. 2010;11:934-41.

Phase III study schema

51 centres in Europe, Australia, and Israel (N = 459)



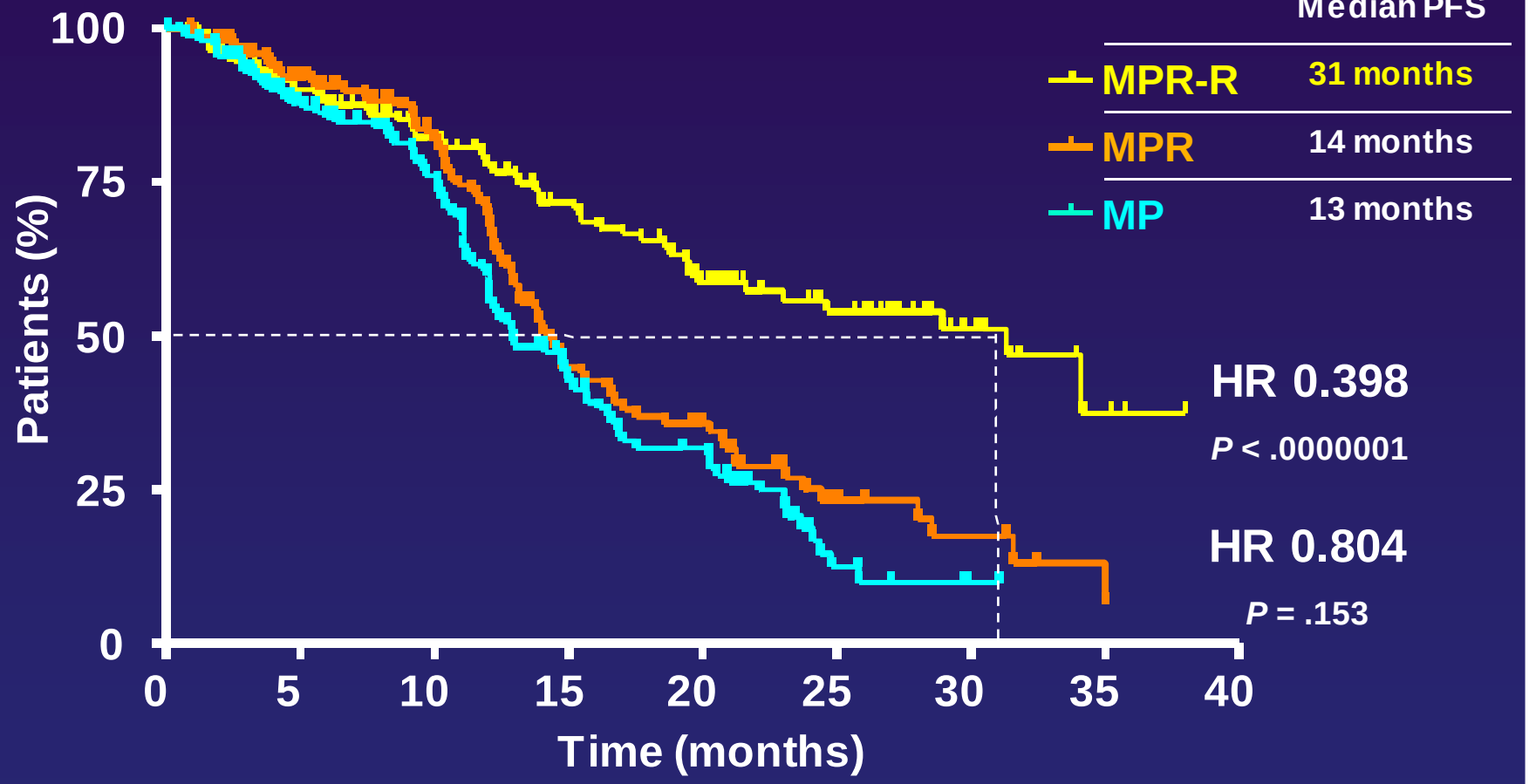
Stratification by age (≤ 75 vs > 75 years) and ISS stage (1, 2, or 3)

Palumbo A, et al. Blood. 2010; 116:[abstract 622]. Updated data presented at ASH 2010.

Progression-free survival*

All Patients

60% Reduced Risk of Progression



Median follow-up 25 months

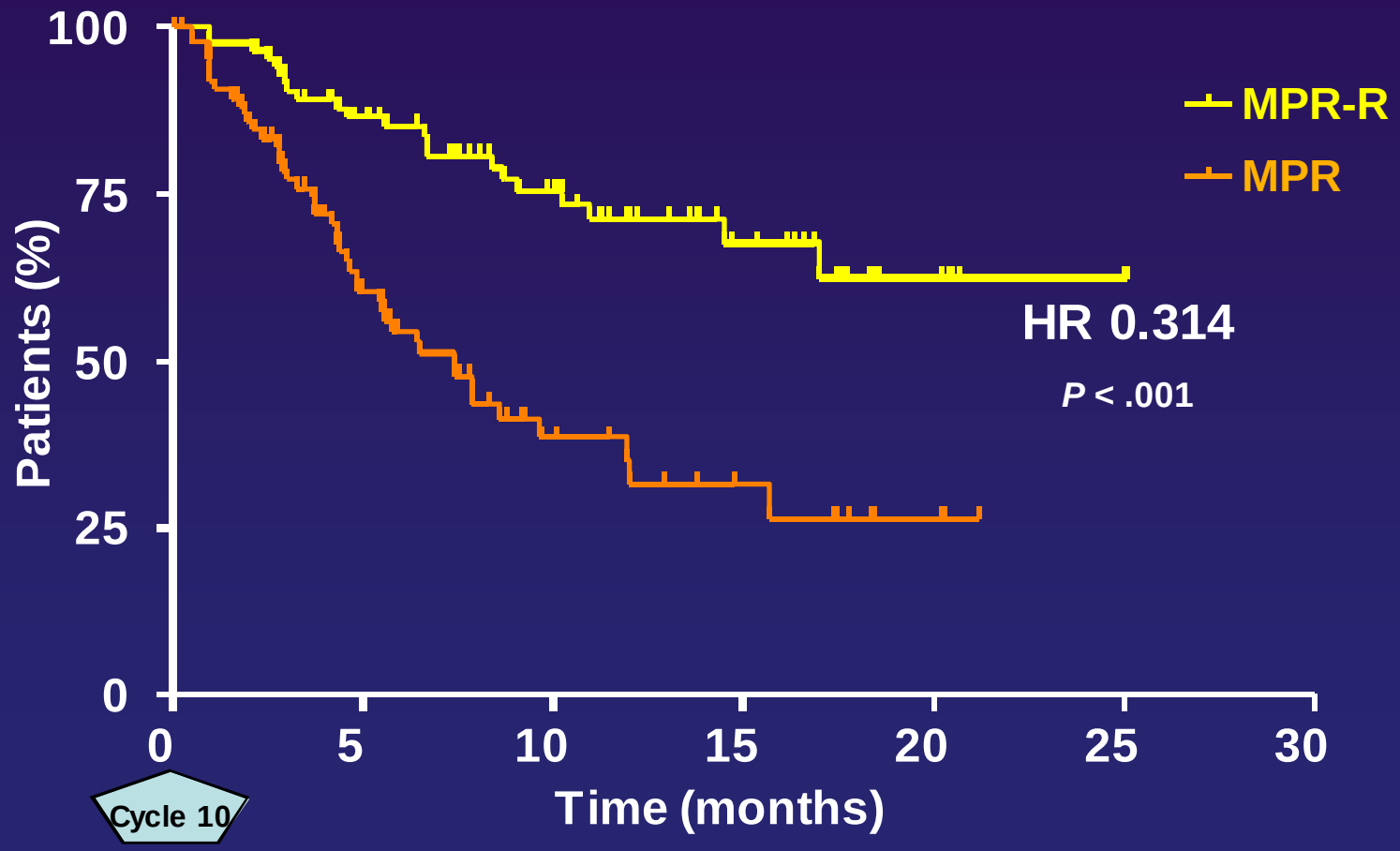
*Analysis based on data up to May 2010

Palumbo A, et al. Blood. 2010; 116:[abstract 622]. Updated data presented at ASH 2010.

Landmark analysis

69% Reduced Risk of Progression

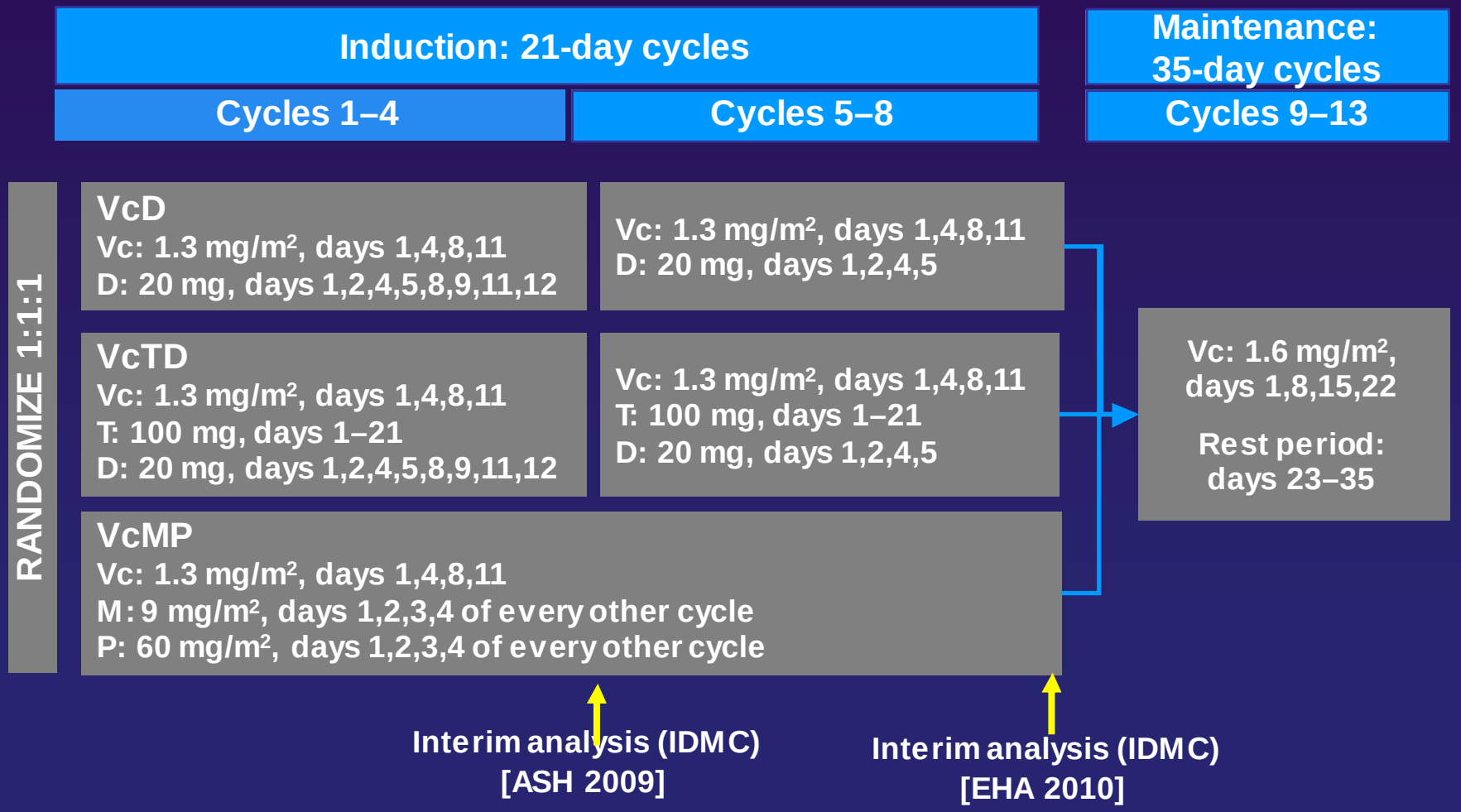
MPR | **Lenalidomide Continuous Therapy**



Palumbo A, et al. Blood. 2010; 116:[abstract 622]. Updated data presented at ASH 2010.

Weekly Bortezomib Maintenance Therapy After Bortezomib-Based Induction Regimens in Elderly Newly Diagnosed Multiple Myeloma Patients

Niesvizky et al ASH 2010 abstr 619

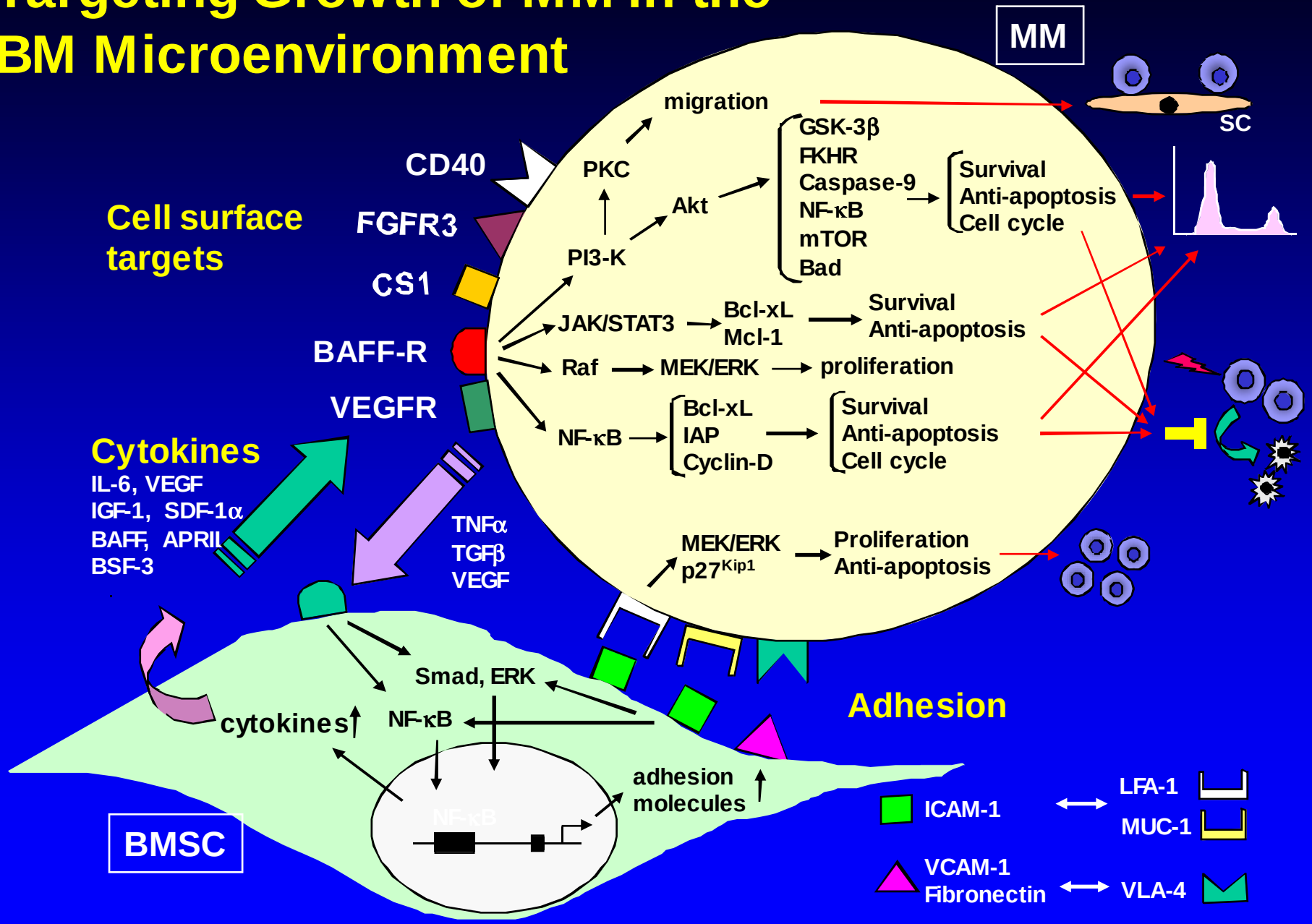


Summary

- All three regimens (VcD, VcTD, VcMP) were active in elderly patients with newly diagnosed MM
- Maintenance with single-agent Vc post induction was well tolerated
- Vc maintenance resulted in increased ≥VGPR rates in all three arms
- PFS appeared similar between the treatment arms in the ITT population

Niesvizky et al ASH 2010 abstr 619

Targeting Growth of MM in the BM Microenvironment



Hideshima T and Anderson KC. Nat Rev Cancer 2002, 2:927-37. Hideshima T et al. Blood. 2004;104:607-18.

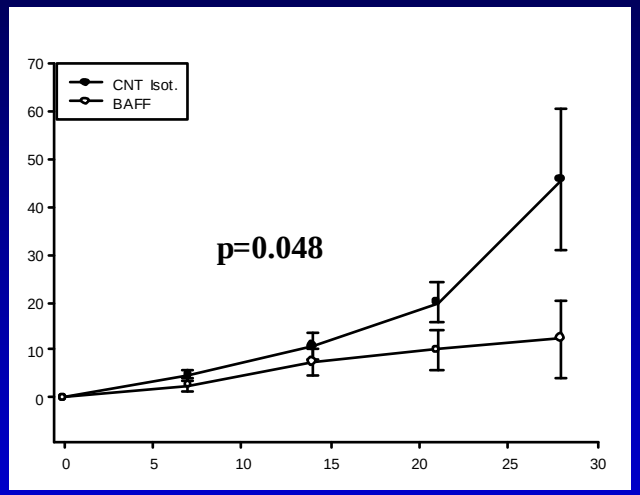
Elotuzumab/Len/Dex in Relapsed MM

- Elotuzumab targets CS-1 on MM cells; clinical trial achieved SD but no responses
- Preclinical studies show len and elotuzumab trigger synergistic MM cytotoxicity
- Phase 1: 82%, Phase 2: 81% ORR, 37% VGPR/CR
- Well tolerated 14% neutropenia,13%thrombocytopenia
- 10 mg/kg elotuzumab is recommended Phase 3 dose
- Phase 3 Randomized Trial of Lenalidomide/Dexamethasone With or Without Elotuzumab in Relapsed or Refractory MM in 2011

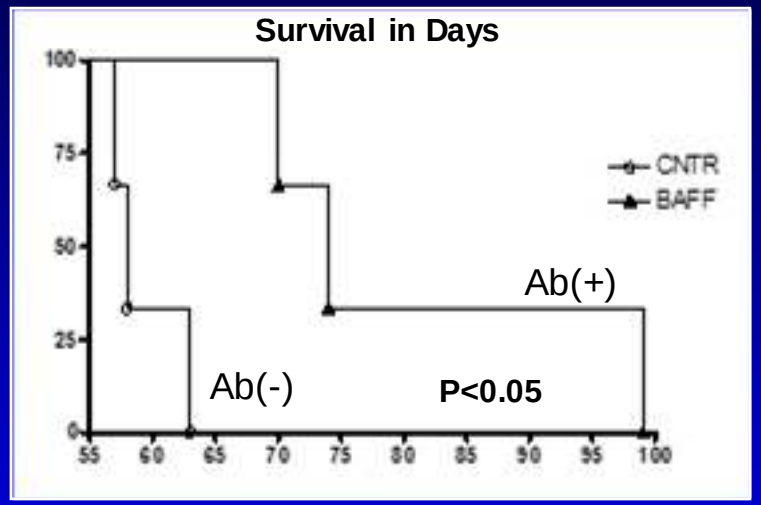
Richardson PG, et al. Blood. 2010:116;[abstract 986]. Lonial S et al. Blood. 2010:116;[abstract 1936]

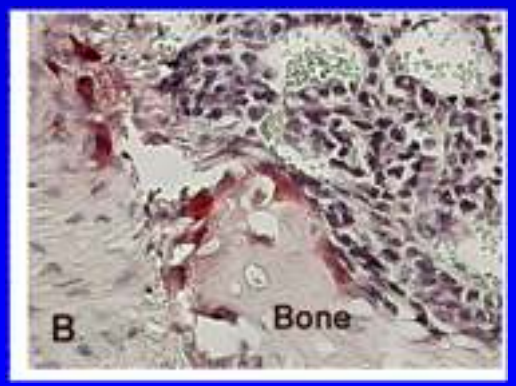
Anti-BAFF MAb Inhibits Osteoclasts and Prolongs Survival in SCID-Hu Model of MM

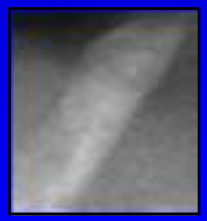
Control

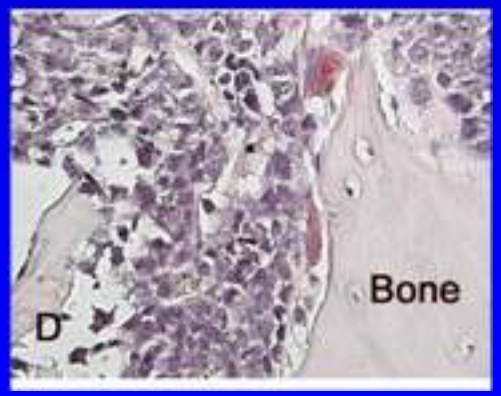


Anti-BAFF Ab-Treated







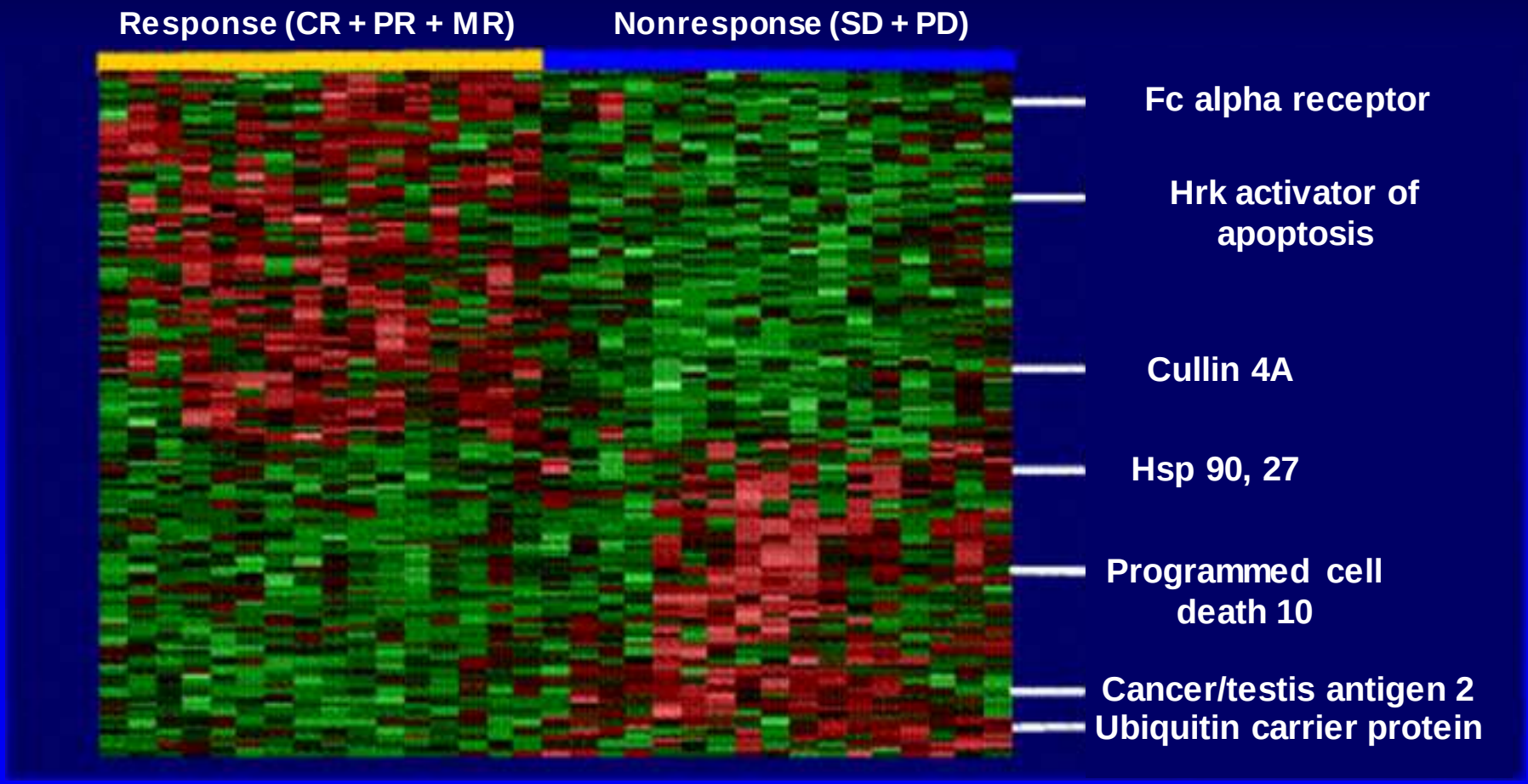


Clinical Trial Ongoing

Neri P, et al. Clin Can Res 2007; 13: 5903.

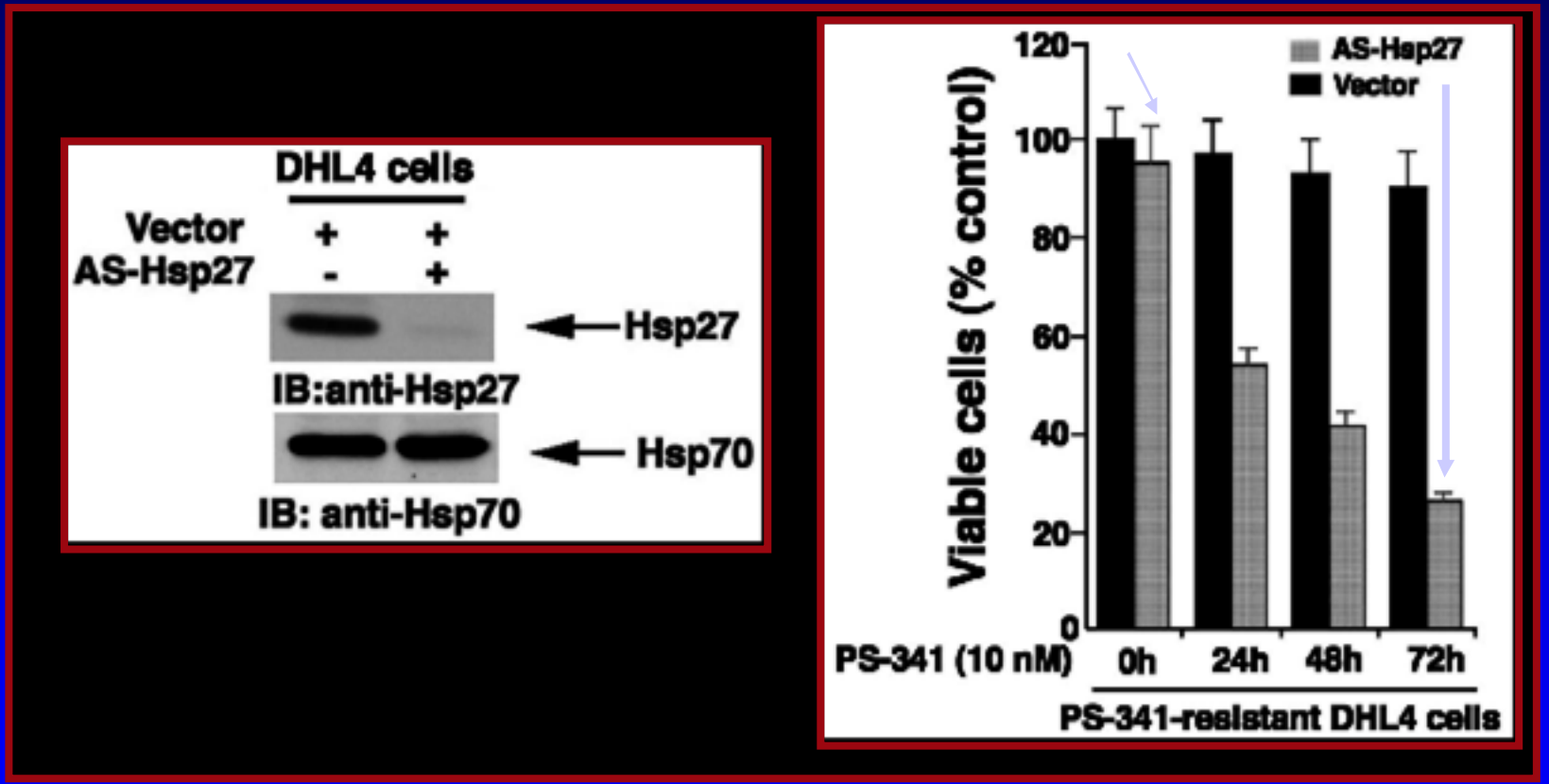
Development of Personalized Medicine

Genes Correlated With Response (Bortezomib)



Richardson et al. N Engl J Med. 2003; 348:2609-2617

Anti-Sense-Hsp27 Restores Sensitivity in Bortezomib-Resistant DHL4 cells



Chauhan et al., Cancer Research 2003 , 3, 6174-6177.

p38MAPK Inhibitor Enhances Bortezomib-Induced Cytotoxicity

Clinical Trial of p38MAPK Inhibitor and Bortezomib

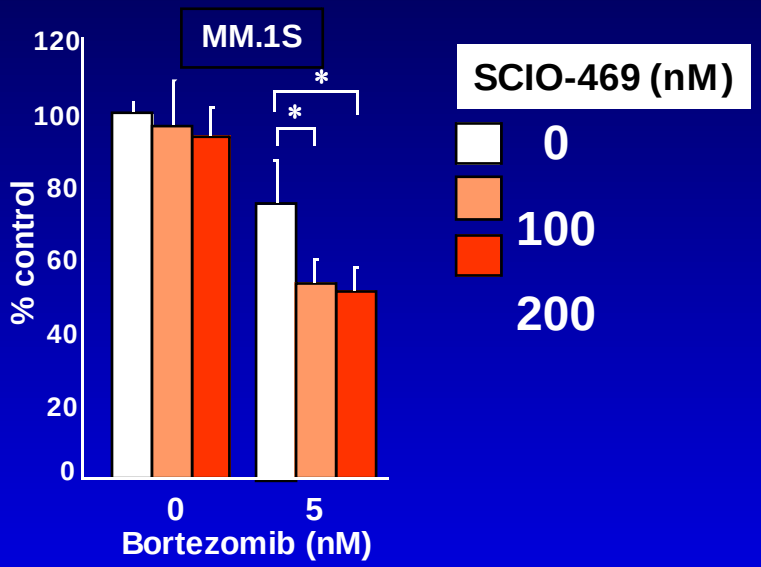
p38 MAPK ⊣ **p38MAPK inhibitors**

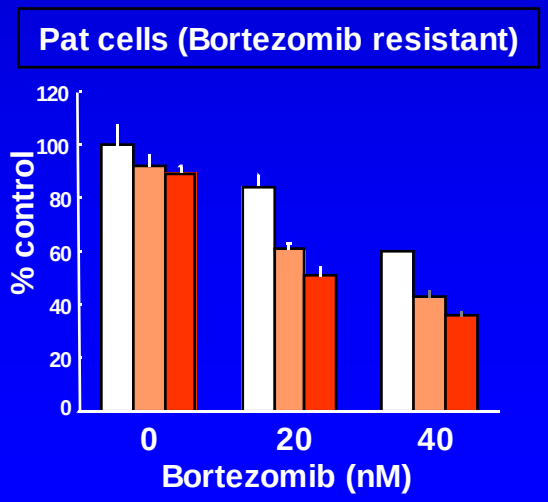
↓

MAP kinase-activated protein kinase-2 (MAPKAPK-2)

↓

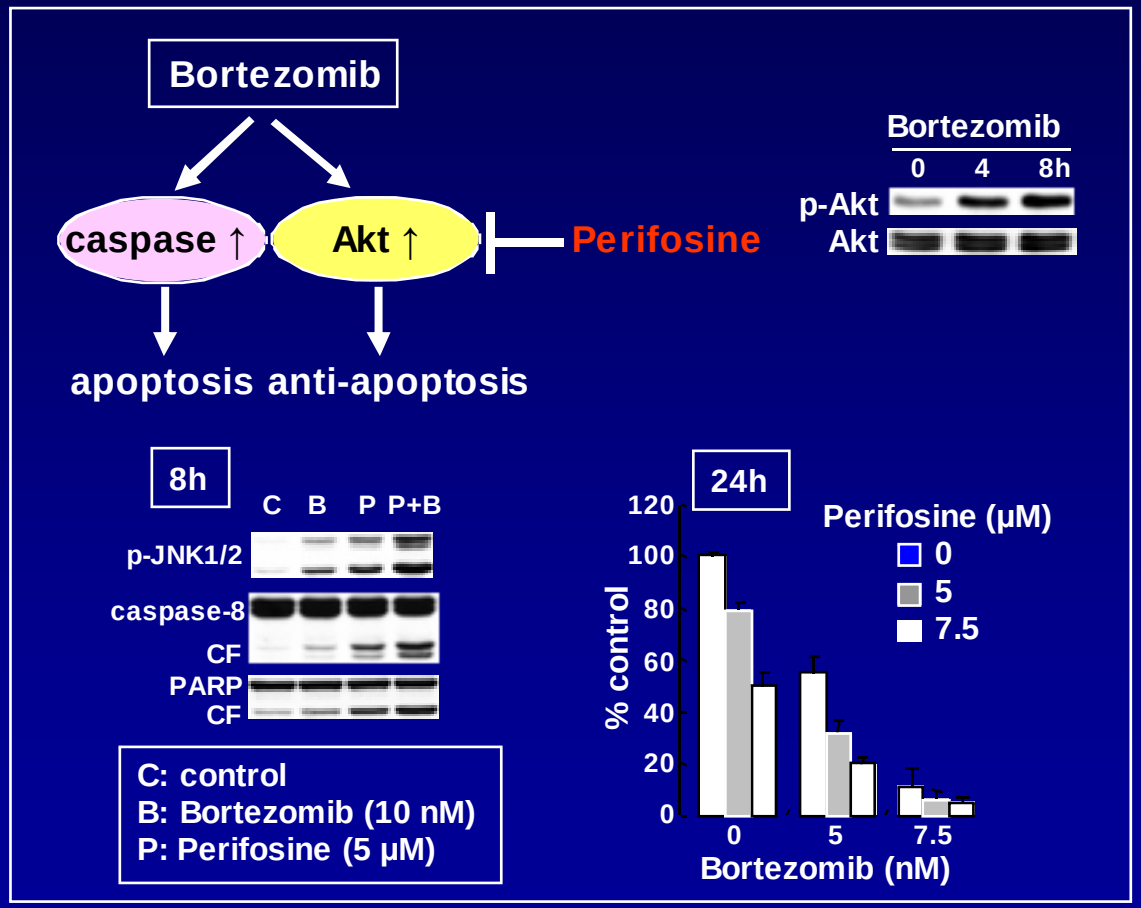
Hsp27 ↓





Hideshima et al, Oncogene 2004, 23:8766-8776

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, mo (range)	Median OS, mo
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

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

Richardson P, et al. ASH 2009 abstract 1869

PI3K/AKT/mTOR Inhibitors in MM

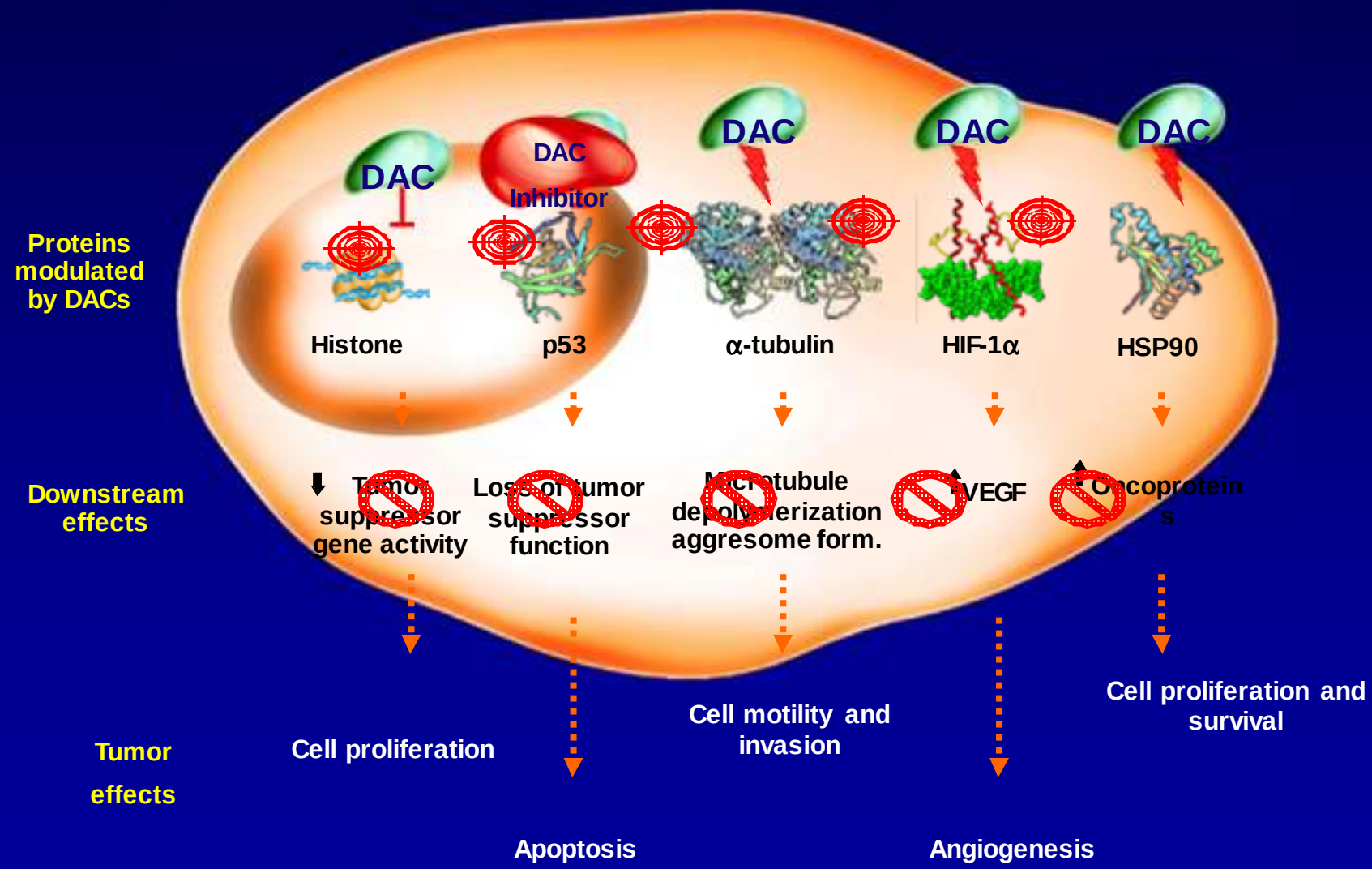
≥ *MR*	Target	+/- Dex	Bort + Dex	Len +/- Dex
Perifosine	AKT	*38%*	*38%* [2]	*70%*[3]
Everolimus	mTORC1	7%[4]		*63%*[5]
Temsirolimus	mTORC1	*37%*[6]	*47%* [7]	*24%*[8]

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 2010. Abstract 990; 8. Hofmeister CC et al. ASH 2009. Abstract 2884.

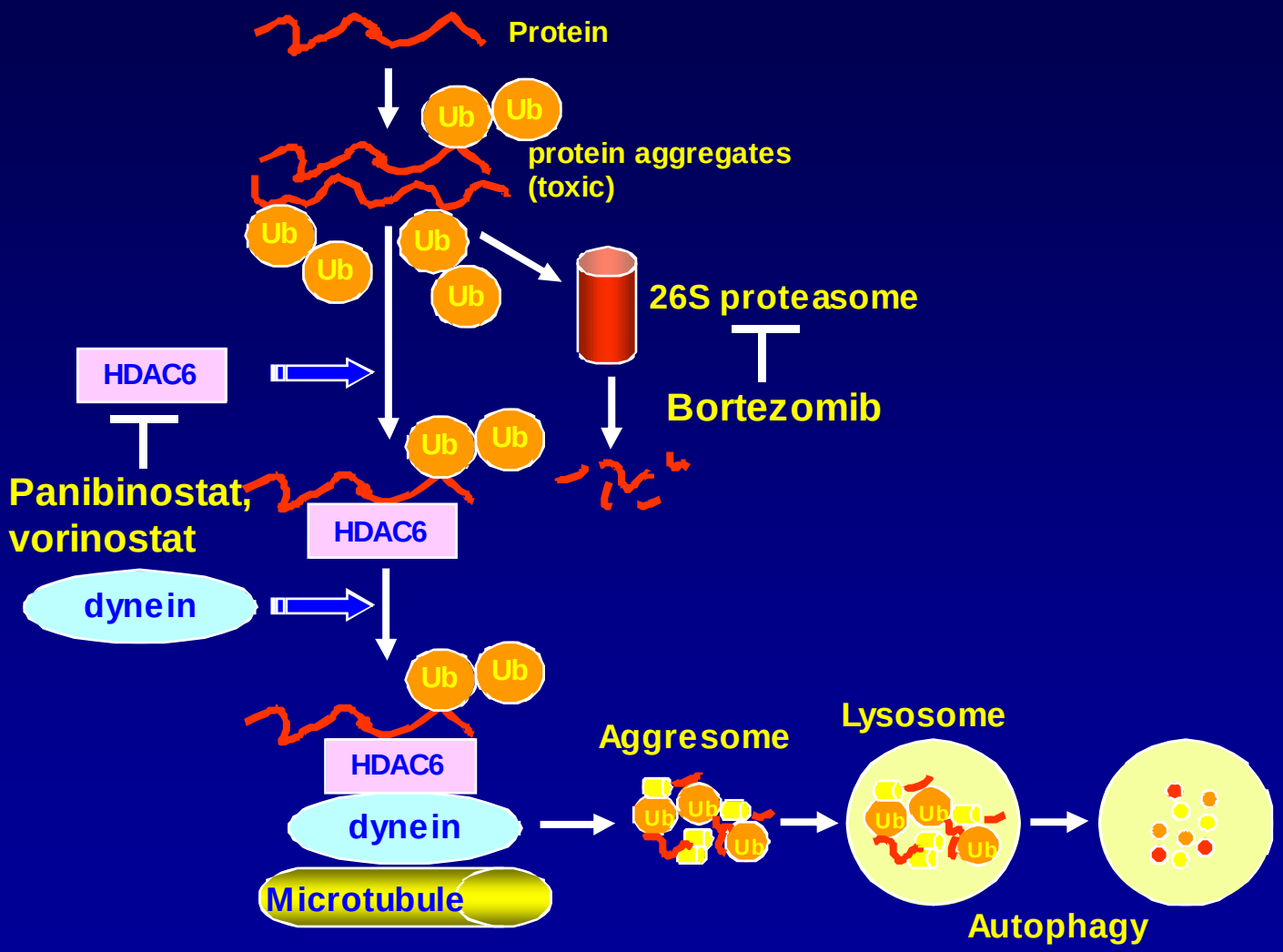
EVALUATION OF CDKIs IN MM

CDKI ID/ code number	Reported CDK activity	Other kinase activity	Phase of development	References
I. Selective CDKs activity				
PD 0332991	CDK4,6/cyclin D	—	Phase I/II in combination with bortezomib and dexamethason in R/R MM	Baughn L et al. *Cancer. Res.* 2006
II. Multi-CDKs activity				
Seliciclib	CDK2/cyclin A ,E CDK7/cyclin H CDK9/cyclinT1	—	Preclinical testing	Raje N et al. *Blood.* 2005.
P276-00	CDK1/cyclin B CDK4/cyclin D CDK9/cyclinT1	—	Phase I multicenter study in R/R MM (India)	Raje N et al. *Leukemia.* 2009.
III. Multi-CDKs and additional targeted kinase activity				
AT-7519	CDK1/cyclin B CDK2/cyclin A, E CDK4,6/cyclin D CDK7,9/cyclin H, T	GSK-3β	Phase I/II alone and in combination with bortezomib	Santo L et al. *Oncogene* . 2010

Effect of DAC on Histone and Non-histone Proteins



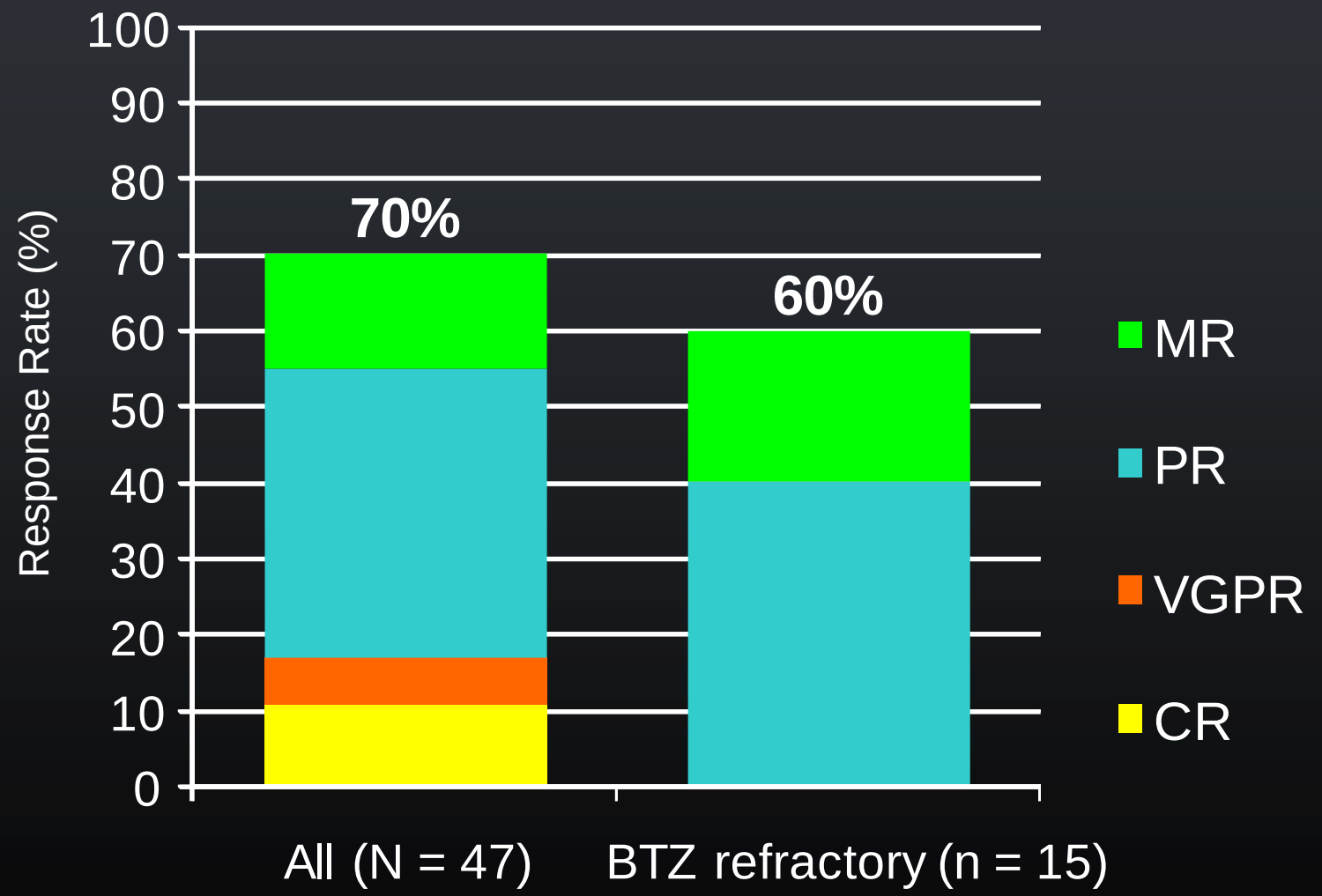
Blockade of Ubiquinated Protein Catabolism



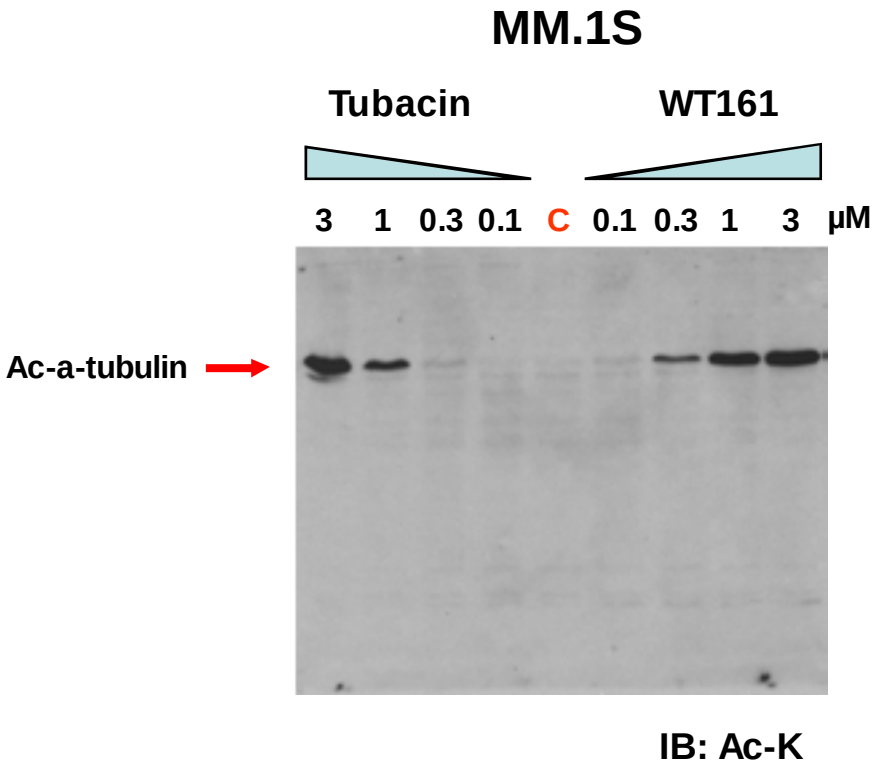
Hideshima et al, Clin Cancer Res;2005; 11: 8530
Catley et al, Blood 2006; 108: 3441-9.

Panobinostat + Bortezomib to Inhibit Aggresome and Proteasome in Relapsed Refractory MM

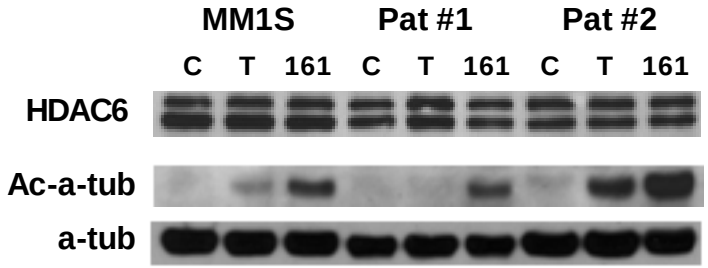
San Miguel et al, ASCO 2010

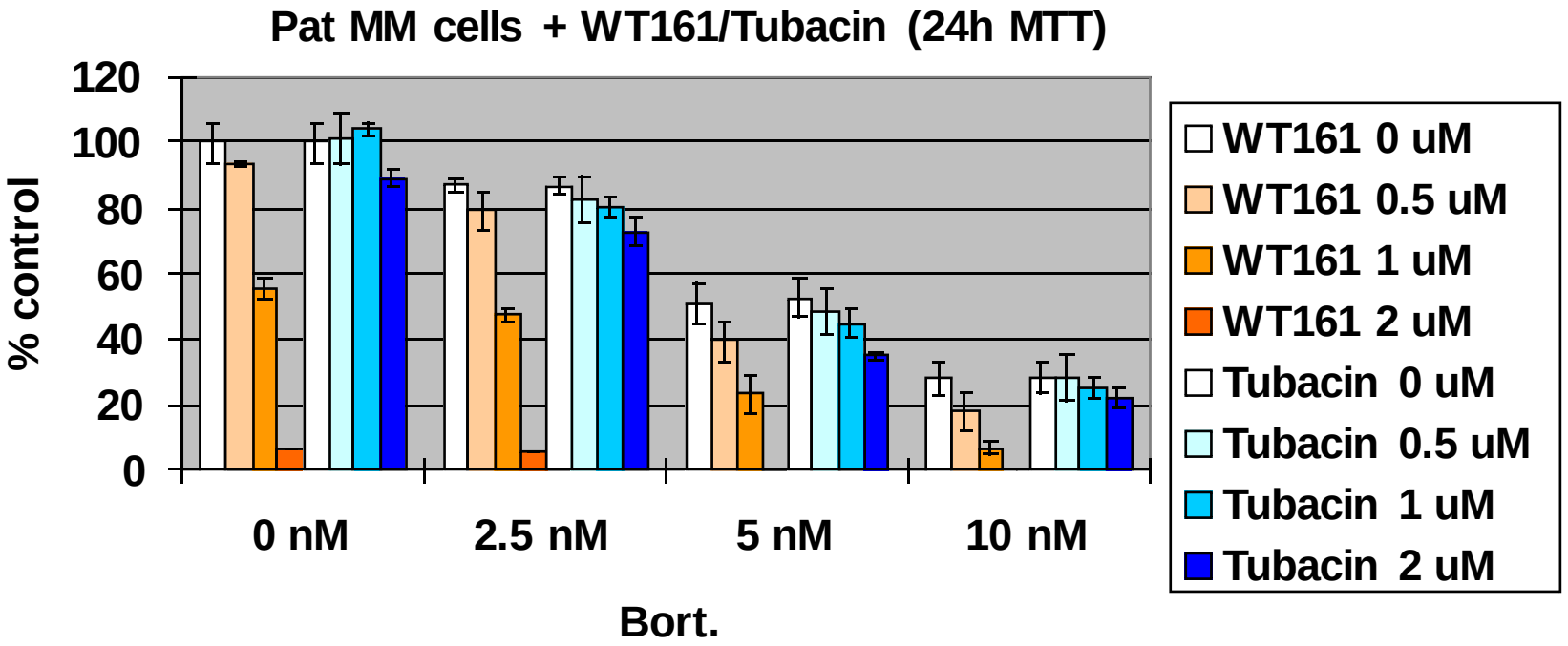


WT161 is More Potent HDAC6 Inhibitor Than Tubacin



HDAC 6 Selective Inhibitor WT161 Enhances Bortezomib-Induced Cytotoxicity in Patient MM Cells





Hideshima et al, 2011

Bench to Bedside Translation of HDAC 6 Selective Inhibitor ACY 1215

Orally bioavailable, highly potent, selective inhibitor of HDAC 6 synthesized in fall 2009

Synergistic MM cytotoxicity with Bortezomib in vitro and in vivo

Favorable PK/PD, toxicity profile

Highly favorable FDA regulatory process from pre-IND through IND allowance

Phase Ia/Ib/II clinical trial of ACY1215, alone and with Bortezomib, beginning spring 2011

Lenalidomide-Based Novel Combination Therapies: Additional Phase 1/MTD Studies – *Relapsed/Refractory Multiple Myeloma*

Combination[a]	ORR, %	CR/nCR, %	≥ VGPR, %	MTD
CRd (n = 48)[1]	67	6	34	• Not reached • Maximum carfilzomib dose: 27 mg/m^2 • Lenalidomide: 10-25 mg days 1-21 • Dexamethasone: 40 mg weekly
VLD (n/N = 30/31)[2]	53	NR	20	• Not reached • Maximum vorinostat dose: 400 mg • Lenalidomide: 10-25 mg days 1-21 • Dexamethasone: 40 mg weekly
R + RAD001 (n/N = 20/20)[3]	25	5	NR	• MTD reached: • RAD001 5 mg/day, days 1-21 • Lenalidomide 5 mg/day, days 1-21
Perofosine + Rd (n/N = 30/32)[4]	50	13	23	• MTD reached: • Perifosine: 100 mg daily • Lenalidomide: 25 mg, days 1-21 • Dexamethasone: 40 mg weekly (cycles 1-4); 20 mg weekly (cycles 5+)

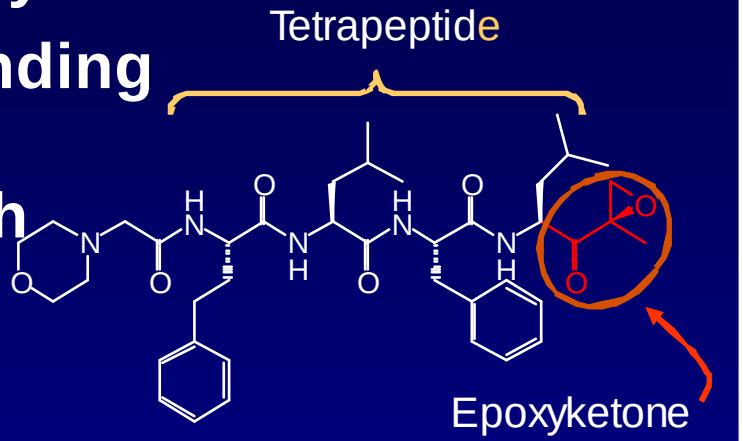
[a] Data are current as of the 2010 American Society of Hematology meeting; studies are ongoing.

CR, complete response; CRd, carfilzomib, lenalidomide, low-dose dexamethasone; MTD, maximum tolerated dose; nCR, near complete response; NR, not reported; ORR, overall response rate; R, lenalidomide; Rd, lenalidomide, low-dose dexamethasone; VGPR, very good partial response; VLD, vorinostat, lenalidomide, dexamethasone.

1. Wang M, et al. *Haematologica*. 2010;95(s2):157. [abstract 388].
2. Richardson PG, et al. *Blood*. 2010;116(21):813. [abstract 1951].
3. Mahindra AK, et al. *Blood*. 2010;116(21):1258. [abstract 3051].
4. Jakubowiak AJ, et al. *Blood*. 2010;116(21):1264. [abstract 3064].

Carfilzomib: A Novel Proteasome (Chymotryptic) Inhibitor

- Novel chemical class with highly selective and irreversible proteasome binding
- Improved antitumor activity with consecutive day dosing
- No neurotoxicity in animals
- Durable responses in relapsed and relapsed refractory MM w/o neuropathy
- Carfilzomib lenalidomide Dex versus lenalidomide Dex phase III trial for new drug approval



[1]Demo et al. (2007), Cancer Research, 67:6383 [2]Kirk et al, (2008) Blood, 112: 2765 Siegel et al ASH 2010

Upfront Carfilzomib Rd

Best Resp, %	(N=27)
sCR/CR/nCR	**55**
sCR	22
CR/nCR	33
≥VGPR	**70**
≥PR	**96**

***As of data cutoff date: 12 November 2010,**

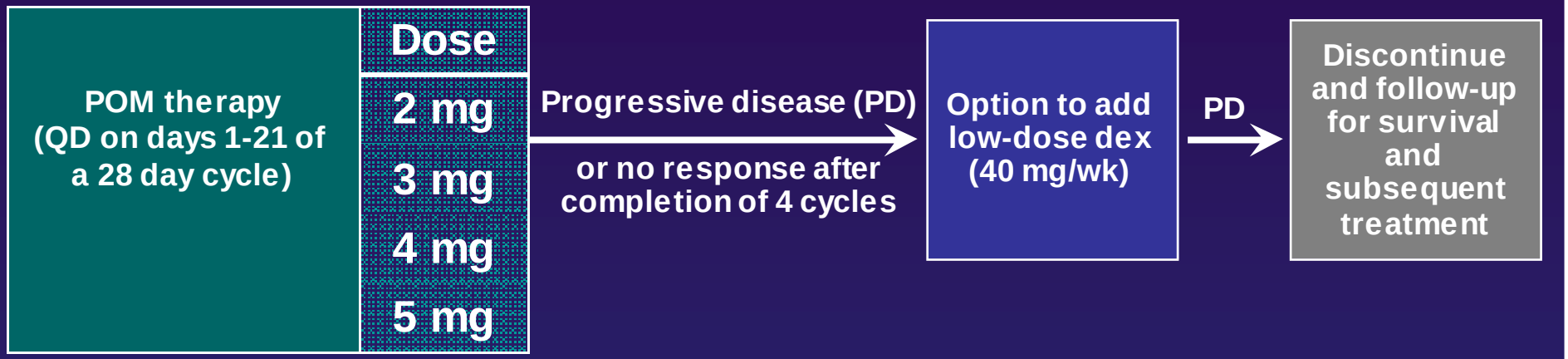
4 patients not evaluable for response

(2 did not complete 1 cycle, 2 response not yet confirmed)

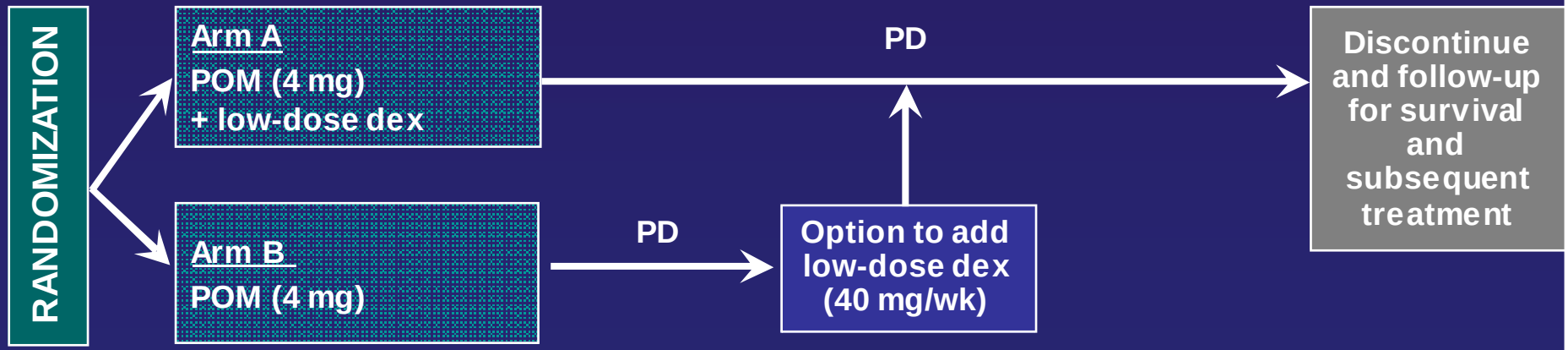
Jakubowiak et al, ASH 2010 abstr 862

MM-002 Study Schema
POM ± Low-Dose Dex in Relapsed and Refractory MM

Phase 1 (MTD)



Phase 2 (Open Label)



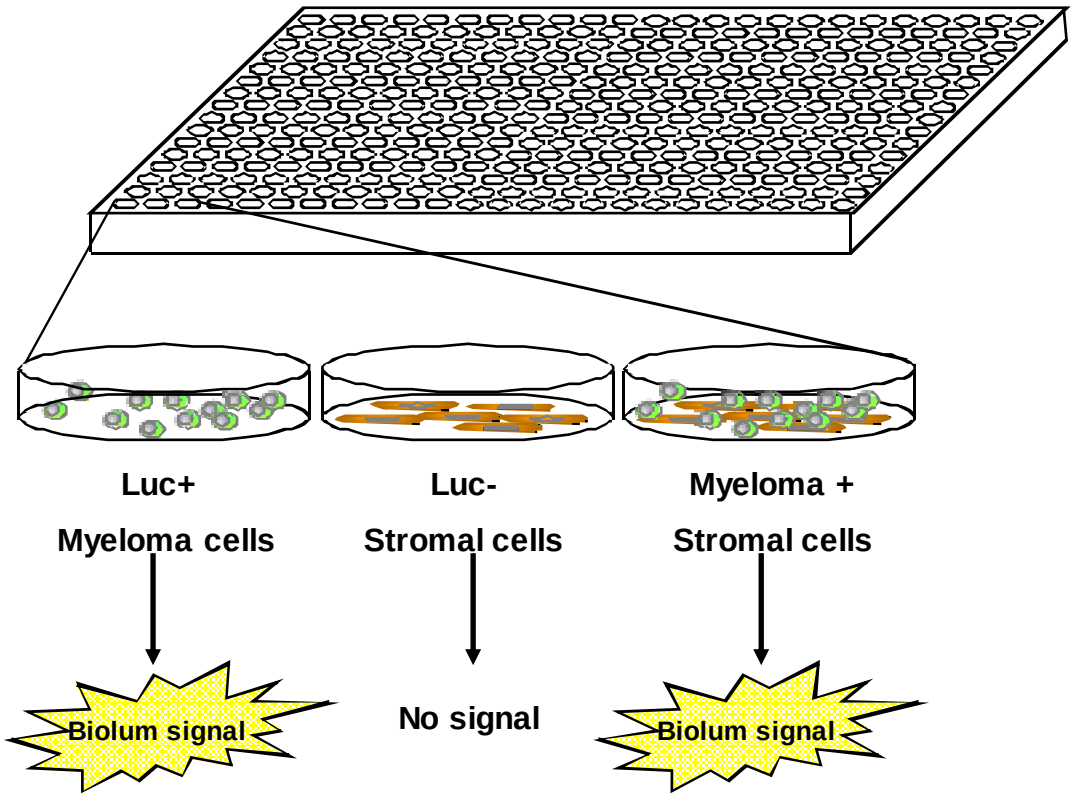
Richardson et al, ASH 2010 abstr 864

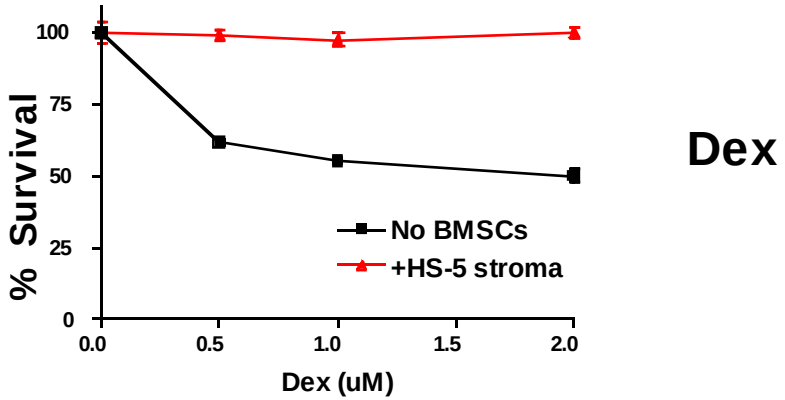
Pomalidomide ± Low-Dose Dex in Relapsed and Refractory MM

- Manageable toxicity profile in heavily pretreated pts
  - MTD: 4 mg days 1-21 of 28-day cycle
  - Most common hematologic G 3/4 AE: myelosuppression
- Low incidence of G 3/4 PN and DVT
- Responses in heavily pretreated relapsed and refractory pts
  - Median lines of prior therapy: 6 in Phase 1; 5 in Phase 2
  - Phase 1:
    - ≥PR: 25%; ≥MR: 50%
    - Median DOR: 20.1 wks
    - Median PFS: 20.1 wks
    - Median OS: 79.6 wks
  - Phase 2:
    - ≥PR 25%; ≥MR 38%
    - Median DOR not reached

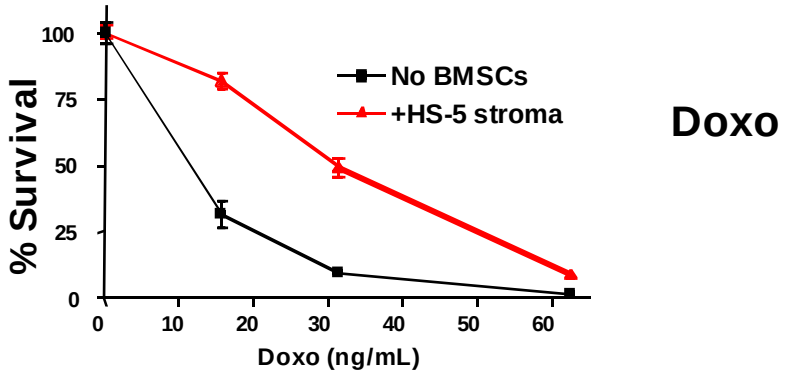
Richardson et al, ASH 2010 abstract 864

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

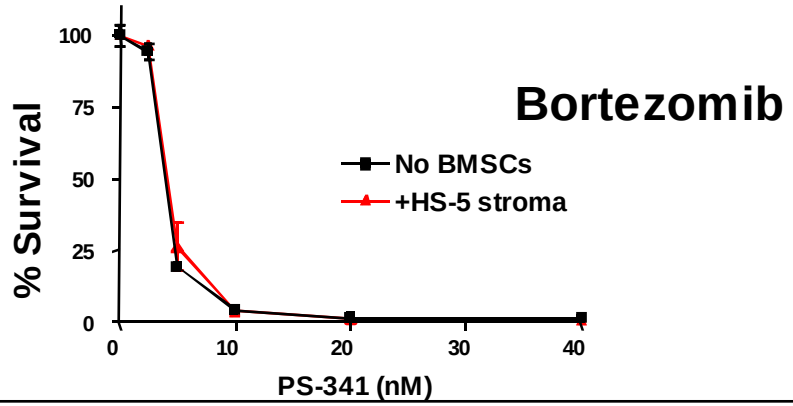




Dex



Doxo



Bortezomib

McMillin et al. Nat Med 2010; 16: 483.

Conclusions and Future Directions

1. Combination novel therapy represents a new treatment paradigm in MM targeting the tumor cell in its microenvironment which has markedly improved OR, CR, EFS and OS.

2. Next generation proteasome inhibitors and immunomodulatory agents show great promise.

3. Rationally-designed combination therapies (IMiDs, proteasome inhibitors, HDAC inhibitors, and MoAbs) will achieve durable CR in the majority of patients.

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