Primary Refractory or Multiply-Relapsed Multiple Myeloma: What Are our Options?

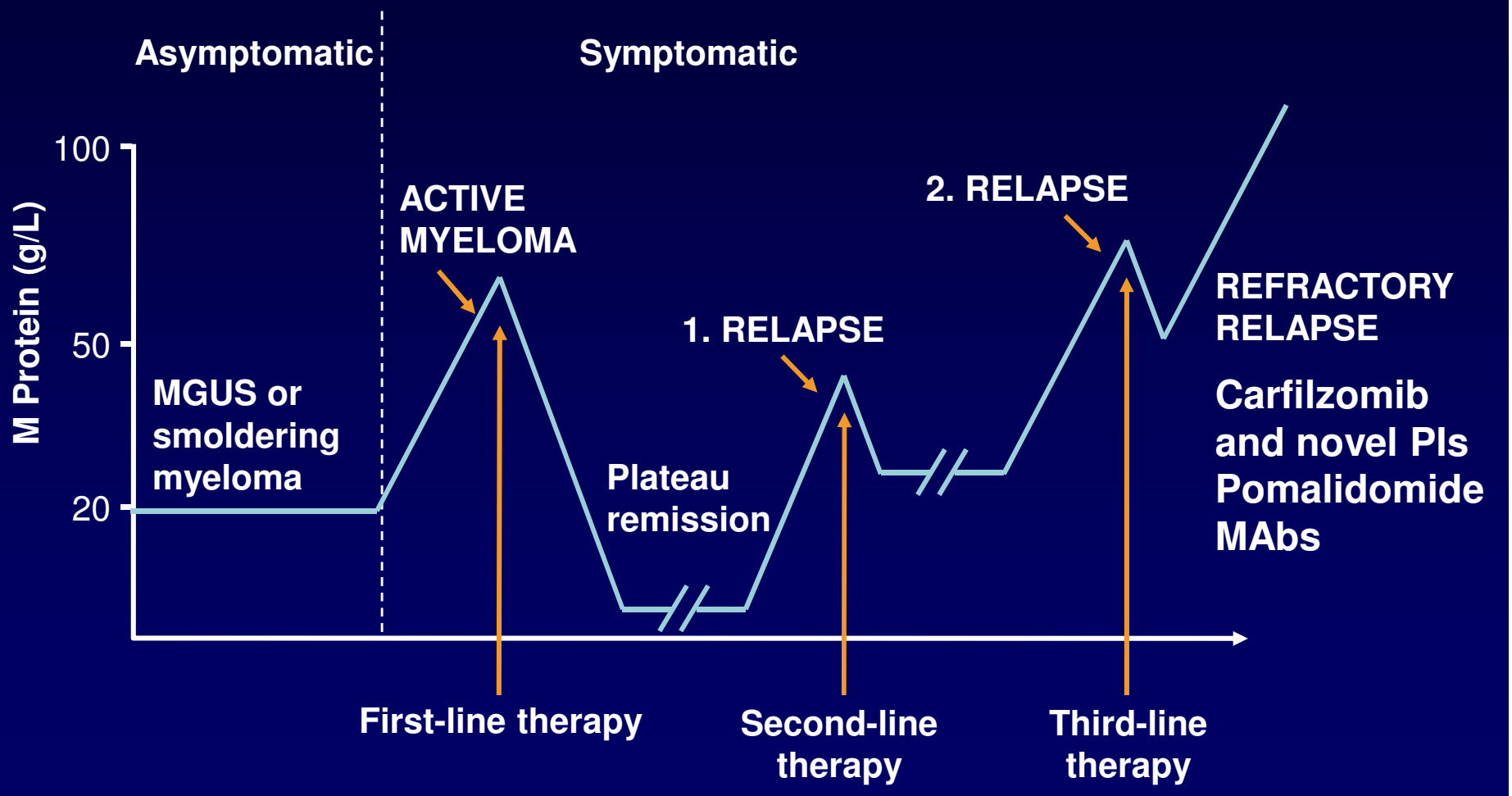
Evangelos Terpos, MD, PhD
Department of Clinical Therapeutics
University of Athens School of Medicine, Athens, Greece

prIME oncology

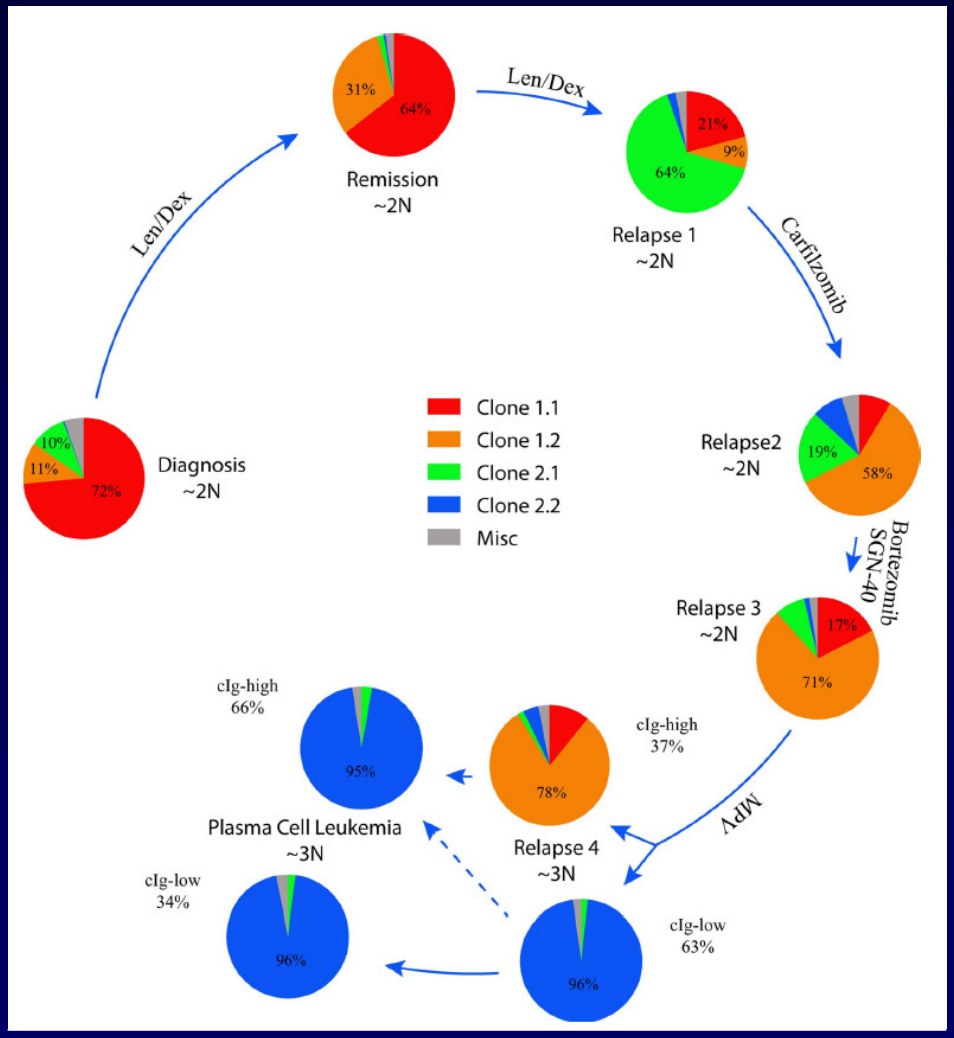
Disclosures

Contracted research from: Onyx

Natural History of Multiple Myeloma



Different Clones Emerging Over Time



Is risk stratification a myth?

- Different clones emerge over time
- Depends on previous therapy
- Combinations better than single agents
- No molecularly targeted therapy
- Ultimate refractoriness to all agents

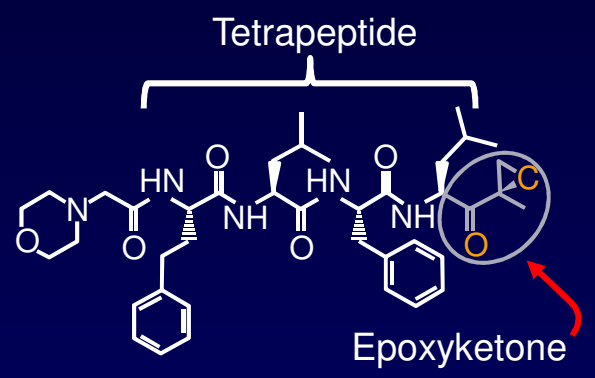
Keats JJ, et al. *Blood.* 2012;120(5):1067-1076.

Unmet Clinical Needs for RR MM

- Multiple myeloma refractory to both lenalidomide-based and bortezomib- based regimens
- Plasmacytoma relapses
- High-risk features, ie, del17p
- Important for treatments to target tumor growth and concomitant immunosuppression while being easy to administer and well tolerated for long-term use

Carfilzomib: A Novel Proteasome (Chymotryptic) Inhibitor

- Novel chemical class with highly selective and irreversible proteasome binding[1]
- Improved antitumor activity with consecutive-day dosing[1]
- No neurotoxicity in animals[2]
- Durable responses in relapsed and relapsed/refractory MM without neuropathy[3]
- Carfilzomib/lenalidomide/DEX vs lenalidomide/DEX phase III trial for new drug approval[4]



1. Demo SD, et al. *Cancer Res.* 2007;67(13):6383-6391. 2. Kirk, et al. *Blood.* 2008;112(110):2765. 3. Siegel DS, et al. Blood. 2010;116(21). Abstract 985. 4. US National Institutes of Health. ClincialTrials.gov Web site. Available at: http://clinicaltrials.gov/ct2/show/NCT01080391. Accessed March 25, 2013.

Carfilzomib

Trial	N*	Population	Previous Lines, n	ORR, %	MR/SD, %	Median TTP, mos
003-A0[1]	39	Relapsed/ refractory	>2	18	8/41	6.2
003-A1[2]	266	Relapsed/ refractory	≥2	24	13/31	7.8
004 (BTZ exposed)[3]	35	Relapsed/ refractory	1-3	21	12/35	8.1
004 (BTZ naïve)[4]		Relapsed/ refractory	1-3			
• 20 mg/m^2	59			42	17/22	8.3
• 20/27 mg/m^2	67			52	12/15	NR
006 (combo with LEN/DEX)[5]	50	Relapsed/ refractory	1-3	78	2/8	–

- Neuropathy from phase II experience: 9.6% grades 1/2 and 1.4% grade 3

1. Jagannath S, et al. *J Clin Oncol.* 2009;27(15S): Abstract 8504. 2. Siegel DS, et al. *Blood.* 2012;120(14):2817-2825. 3. Vij R, et al. *J Clin Oncol.* 2010;28(15S): Abstract 8000. 4. Vij R, et al. Blood. 2012;119(24):5661-5670. 5. Wang M, et al. *J Clin Oncol.* 2011;29(uppl): Abstract 8025.

PX-171-003A1: Phase II Trial of Carfilzomib in Relapsed/Refractory MM

Study population (N = 266)

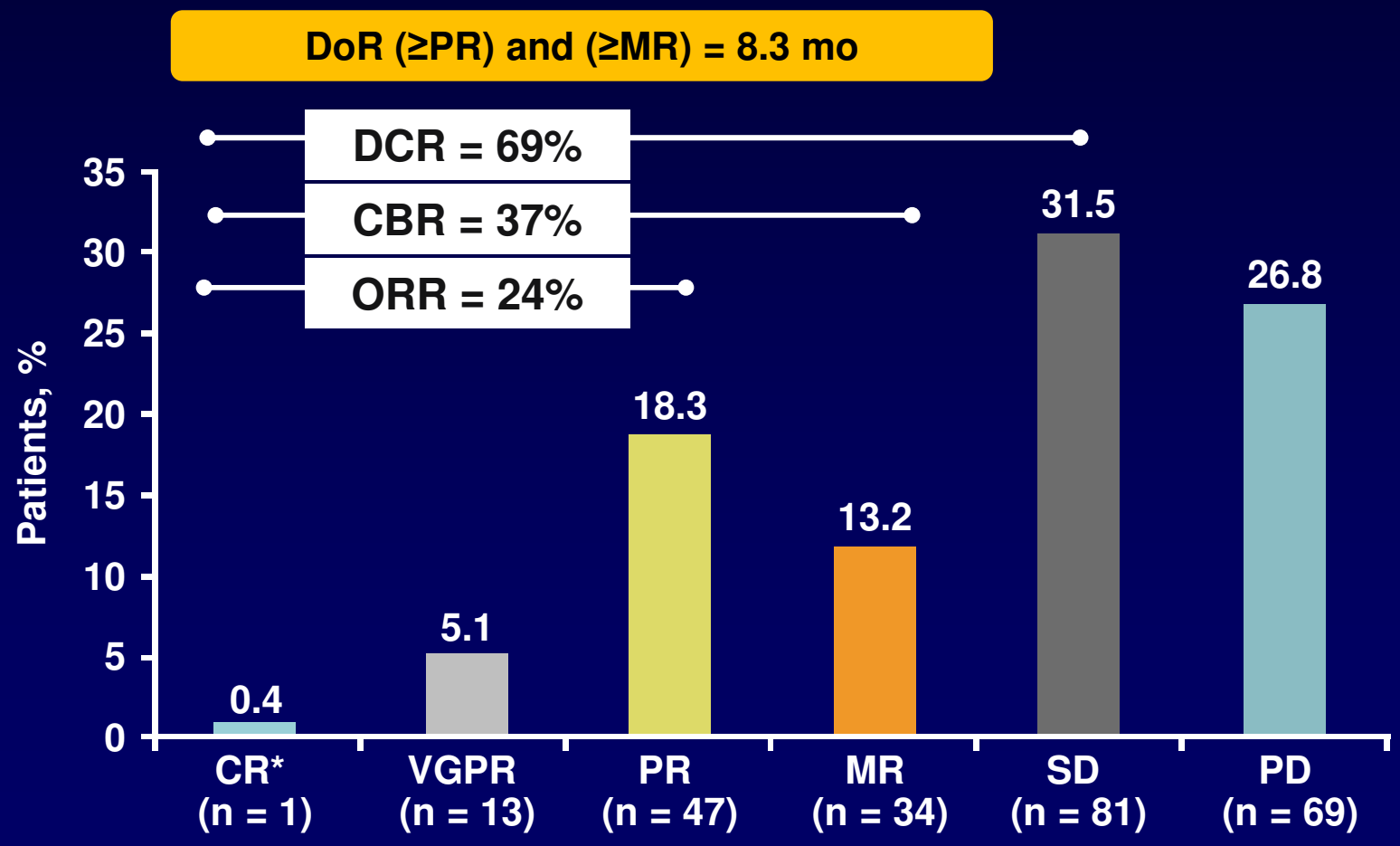
- Progression during treatment or within 60 days of completion of the treatment, or SD as a best response = refractory to last regimen
- Received all 4 classes of approved therapies: bortezomib, IMiDs lenalidomide, or thalidomide, alkylating agent, anthracycline
- Neuropathy: grade 1 or 2 without pain

- Cycle 1: 20 mg/m^2 IV
- Cycles 2-12: 27 mg/m^2 IV

- Primary endpoint: ORR (CR + VGPR + PR [IMWG criteria])
- Secondary endpoints: CBR (ORR + MR [EBMT criteria]), DOR, PFS, TTP, OS, safety

Siegel DS, et al. *Blood.* 2008;112(11). Abstract 864.

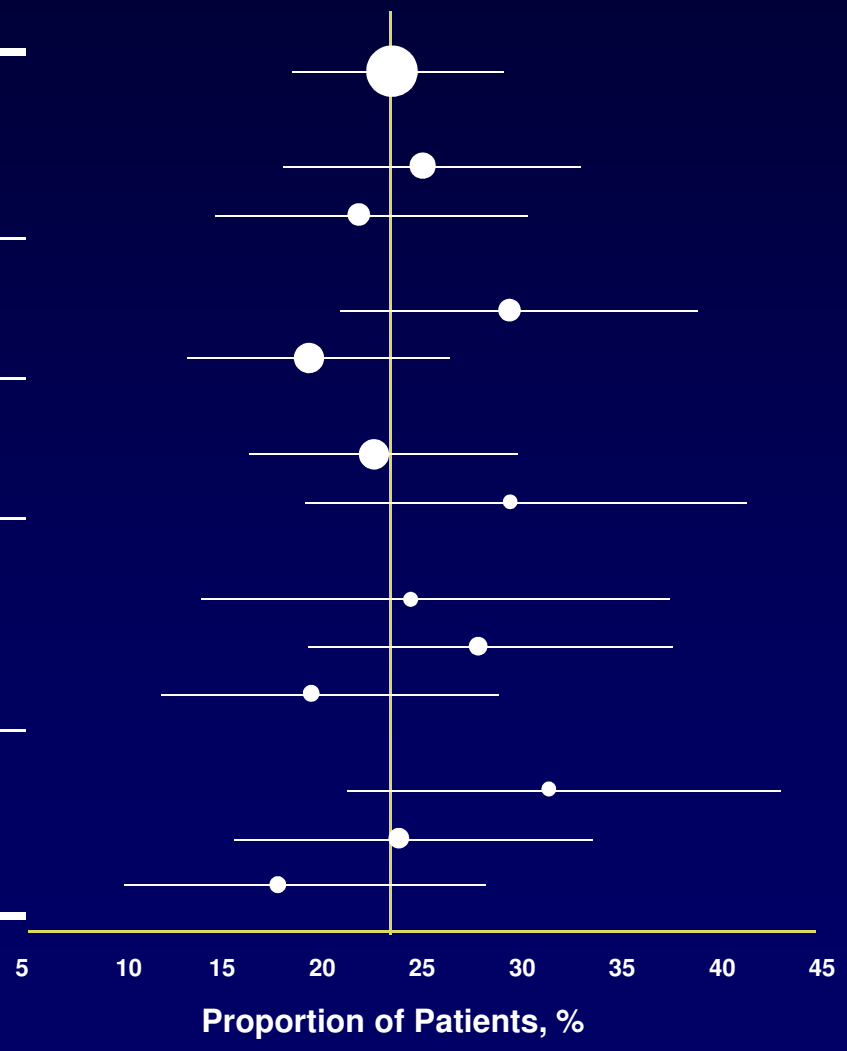
Responses (Response-Evaluable Population, N = 257)



Siegel DS, et al. *Blood.* 2012;120(14):2817-2825.

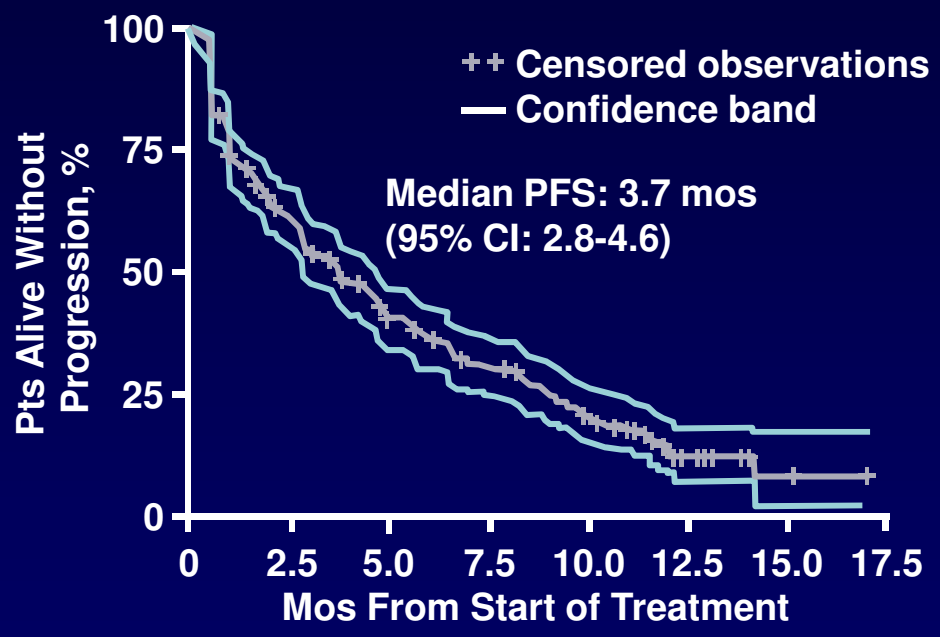
Responses According to Demographic and Baseline Disease Characteristics

Characteristic	n	ORR	95% CI
All patients	257	23.7	18.7-29.4
Age			
<65 years	139	25.2	18.2-33.2
>65 years	118	22.0	14.9-30.6
Gender			
Female	108	29.6	21.2-39.2
Male	149	19.5	13.4-26.7
Cytogenetics or FISH			
Normal/favorable	158	22.8	16.5-30.1
Unfavorable	71	29.6	19.3-41.6
Baseline CrCl (mL/min)			
30 to <50	57	24.6	14.1-37.8
50 to <80	100	28.0	19.5-37.9
≥80	92	19.6	12.0-29.1
ISS stage			
I	76	31.6	21.4-43.3
II	96	24.0	15.8-33.7
III	78	17.9	10.2-28.3

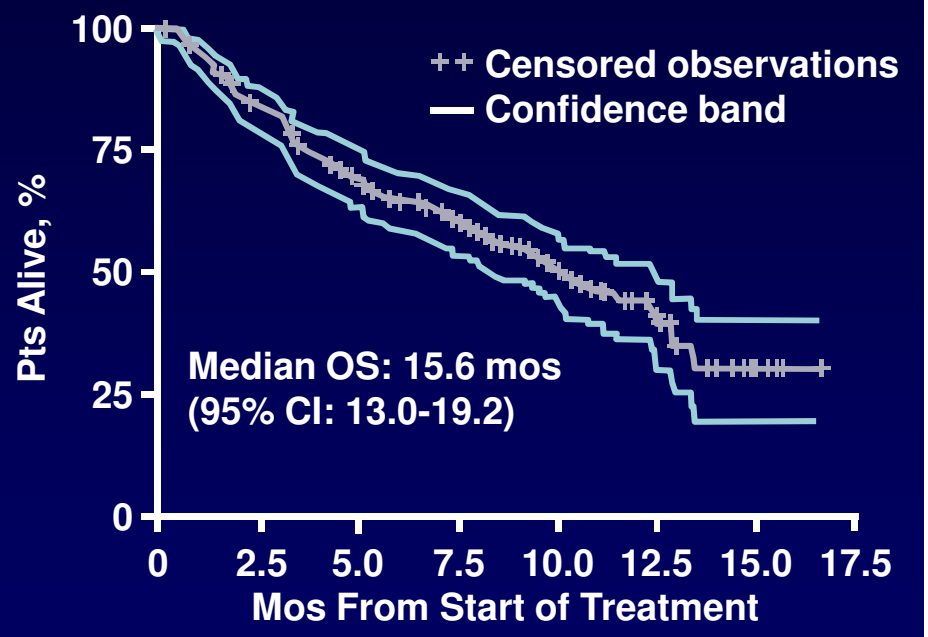


Siegel DS, et al. *Blood.* 2012;120(14):2817-2825.

Relapsed/Refractory MM: Single-Agent Carfilzomib (PX171-003 A1)



Median PFS: 3.7 mos



Median OS: 15.6 mos

Siegel DS, et al. *Blood.* 2012;120(14):2817-2825.

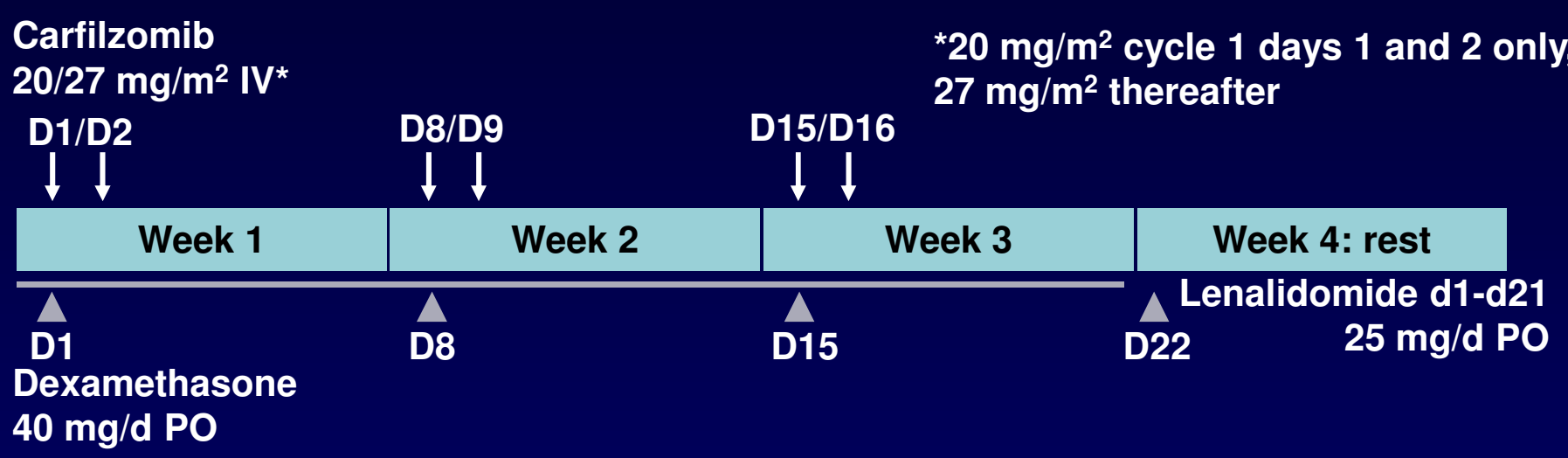
Single-Agent Carfilzomib: Safety

Hematologic AEs, %	Patients (N = 266)	
	All Grades	Grade 3/4
Anemia	46	24
Thrombocytopenia	39	29
Lymphopenia	23	20
Neutropenia	18	11
Febrile neutropenia	0.8	0.8

Nonhematologic AEs, %	Patients (N = 266)	
	All Grades	Grade 3/4
Fatigue	49	7.9
Nausea	45	1.9
Dyspnea	34	3.4
↑ serum creatinine	25	2.6
PN	12.4	1.1
Hypophospatemia	12	6.0
Pneumonia	12	9.4
Hyponatremia	11.7	8.3

Siegel DS, et al. *Blood.* 2012;120(14):2817-2825.

PX-171-006: Phase II Trial of Carfilzomib Plus Len/Dex in R/R MM



Response (N = 51)	n (%)
CR/nCR	12 (24)
VGPR	9 (18)
PR	19 (37)
MR	1 (2)
SD	3 (6)
ORR	40 (78)

Wang M, et al. *J Clin Oncol.* 2011;29(suppl): Abstract 8025.

Phase III ASPIRE Trial

Randomized 1:1

N = 700

Stratification:
- Prior bortezomib
- Prior lenalidomide
- β2-microglobulin levels

CRd

- Carfilzomib 27 mg/m^2 IV day 1, 2, 8, 9, 15, and 16 (20 mg/m^2 on days 1 and 2 of cycle one only)
- Lenalidomide 25 mg days 1-21
- Dexamethasone 40 mg once weekly

Cycle = 28 days

Rd

- Lenalidomide 25 mg days 1-21
- Dexamethasone 40 mg once weekly

Cycle = 28 days

Primary endpoint: progression-free survival

US National Institutes of Health. ClinicalTrials.gov Web site. Available at: http://clinicaltrials.gov/show/NCT01080391. Accessed March 25, 2013.

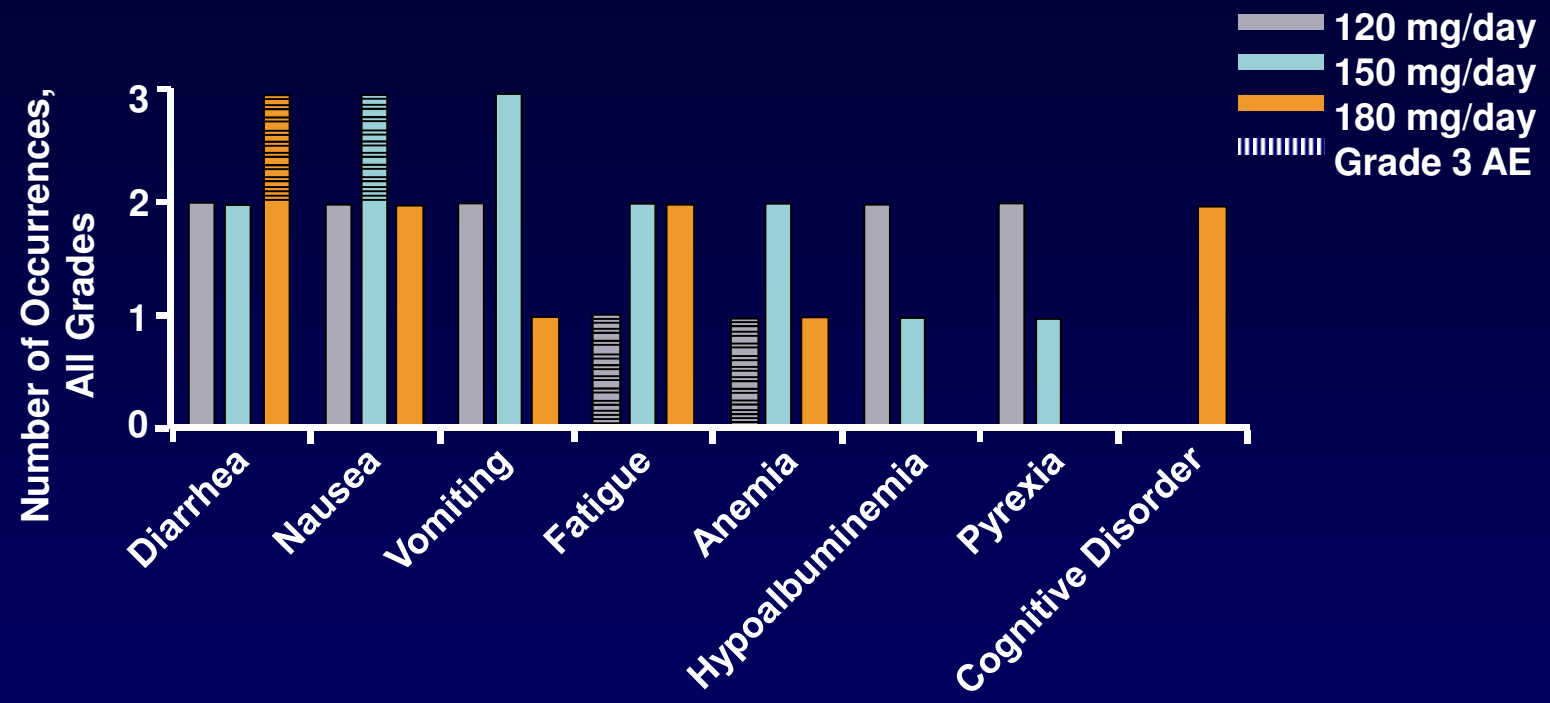
Phase Ib: Oprozomib (ONX 0912)

- Oprozomib (ONX 0912) is orally available, irreversible, next-generation proteasome inhibitor[1]
- MTD identified in patients with solid tumors as once-daily dose of 150 mg[2]
  - DLTs included grade 3 hypophosphatemia, nausea, dehydration
  - Prompted exploration of split-dose schedule with the drug administered twice daily
- Current study assessed safety, tolerability, and pharmacokinetics/pharmacodynamics of split-dose oprozomib schedule in patients with hematologic malignancies (myeloma and CLL)[1]

1. Savona MR, et al. *Blood.* 2012;120(21): Abstract 203. 2. Papadopoulos KP, et al. *J Clin Oncol.* 2011;29(suppl): Abstract 3075.

Oprozomib Dose Escalation

- Split-dose MTD not reached

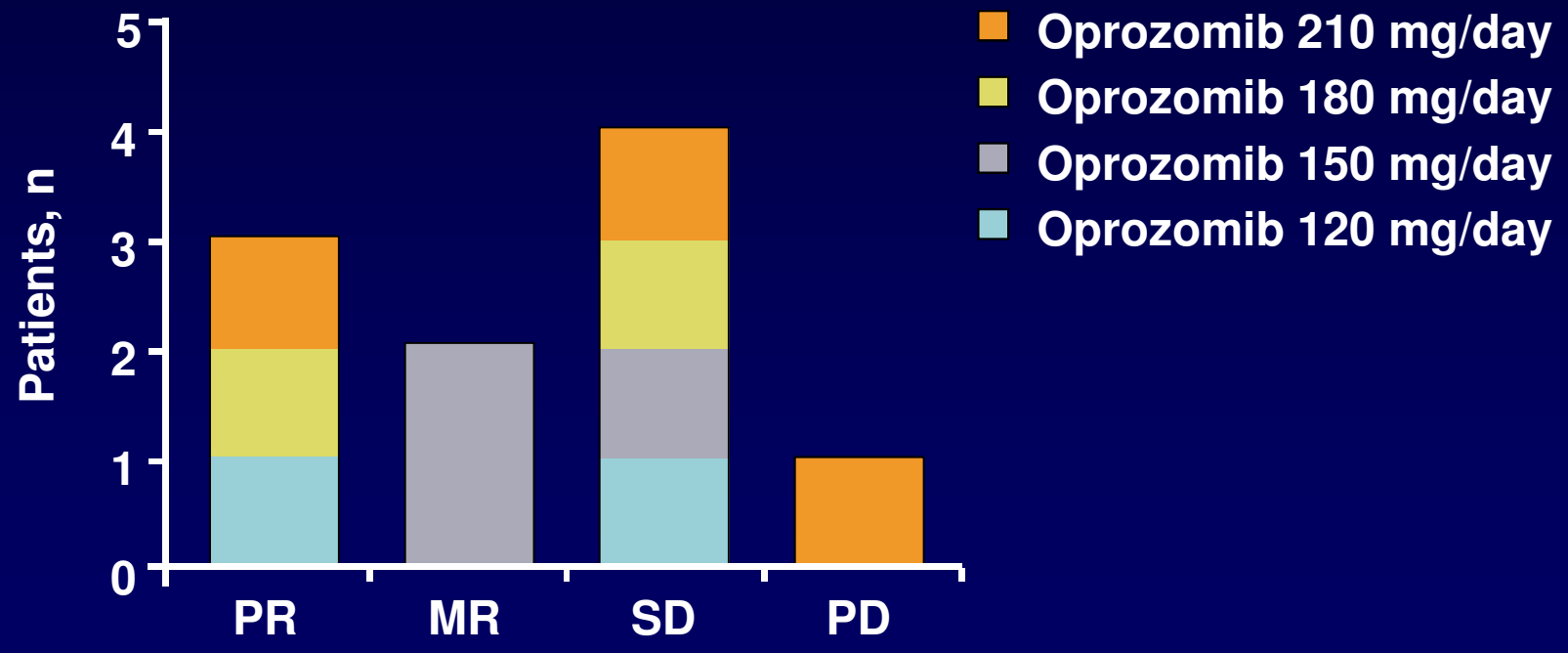


Malignancy of Patient, n	120 mg/day (n = 3)	150 mg/day (n = 3)	180 mg/day (n = 3)
Myeloma	2	3	2
CLL	1	0	1

Savona MR, et al. *Blood.* 2012;120(21): Abstract 203.

Oprozomib Efficacy

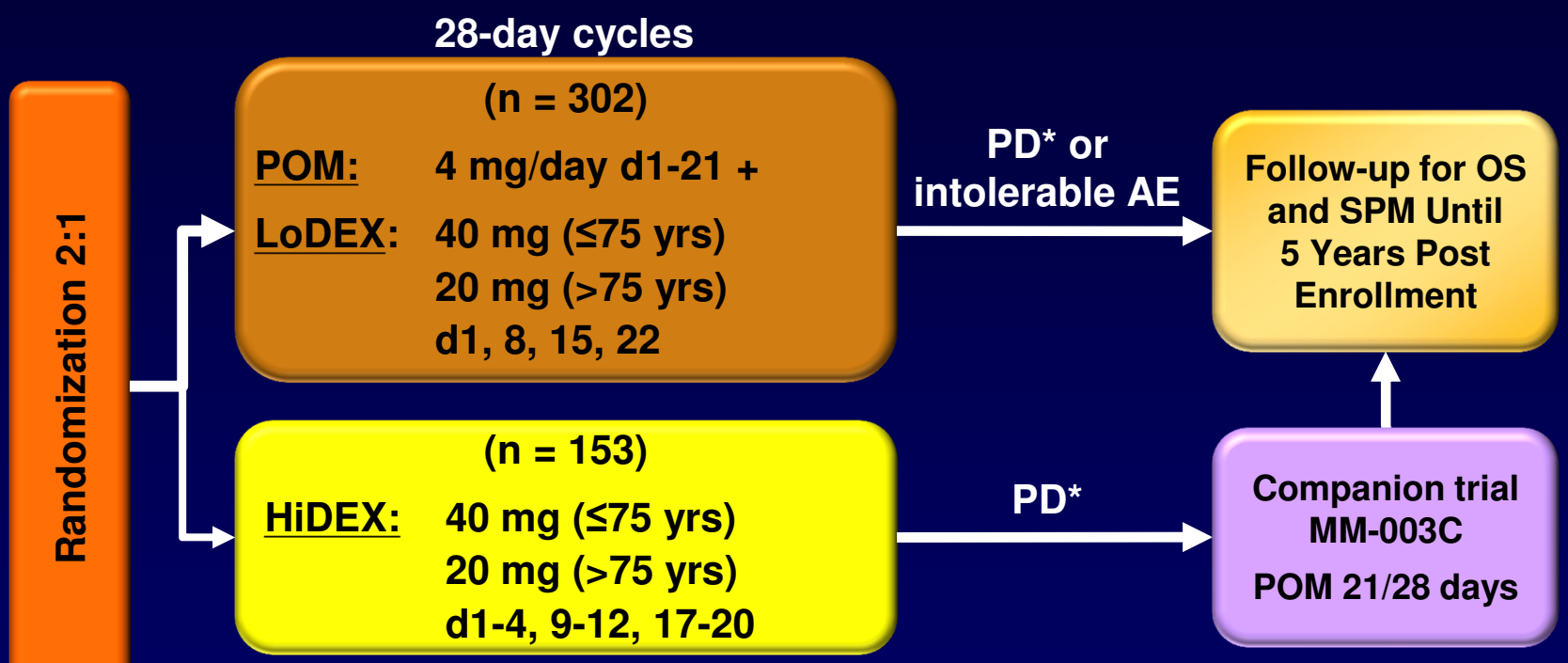
- Proteasome inhibition is dose dependent
  - >80% inhibition with oporozomib 210 mg/day



Savona MR, et al. *Blood.* 2012;120(21): Abstract 203.

MM-003 Design: Pomalidomide + LoDEX vs HiDEX

Refractory MM Pts Who Have Failed BORT and LEN



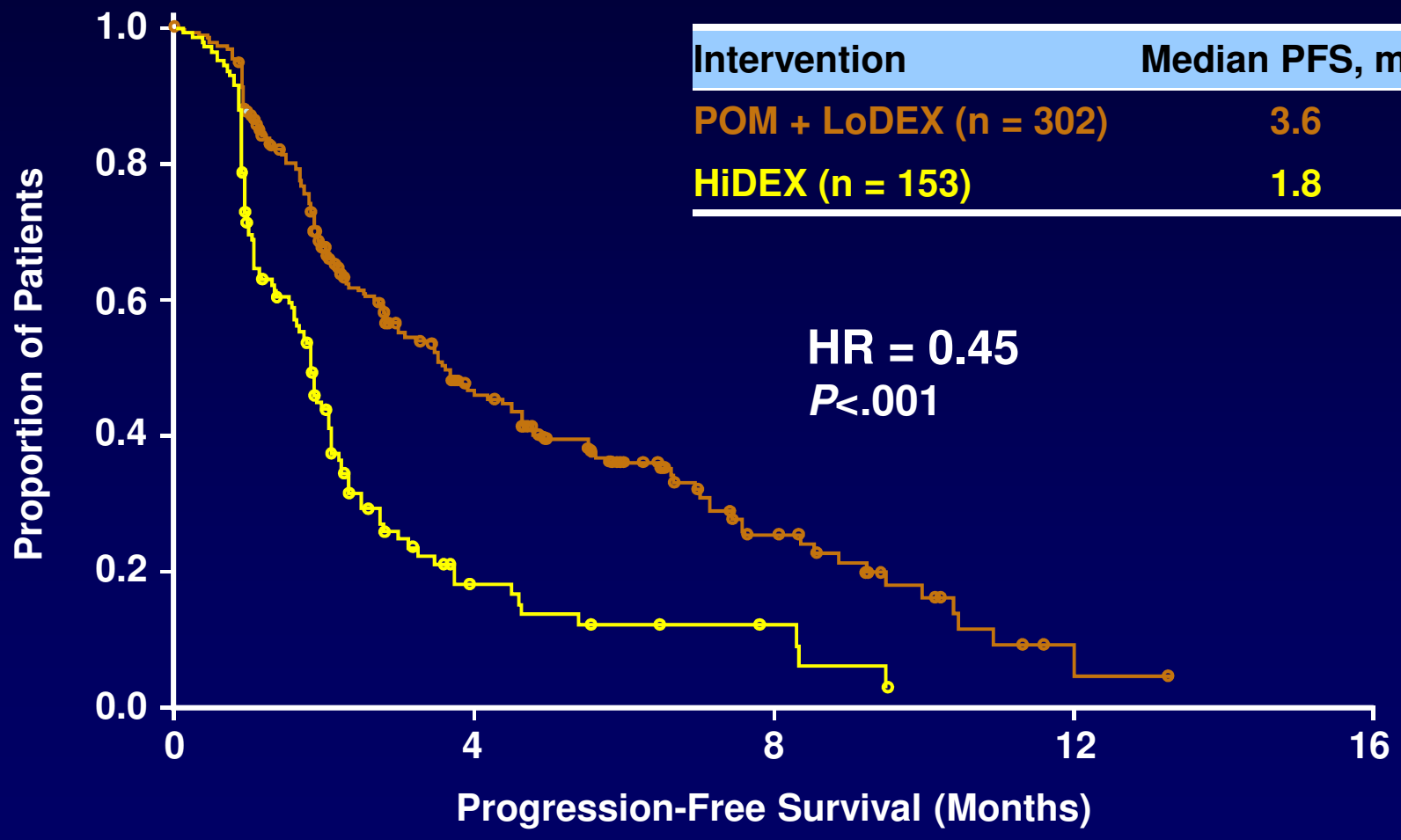
Thromboprophylaxis was indicated for those receiving POM or with DVT history

Stratification

- Age (≤75 vs >75 yrs)
- Number of prior Tx (2 vs >2)
- Disease population

Dimopoulos MA, et al. *Blood.* 2012;120(21): Abstract LBA-6.

MM-003: Progression-Free Survival
ITT Population



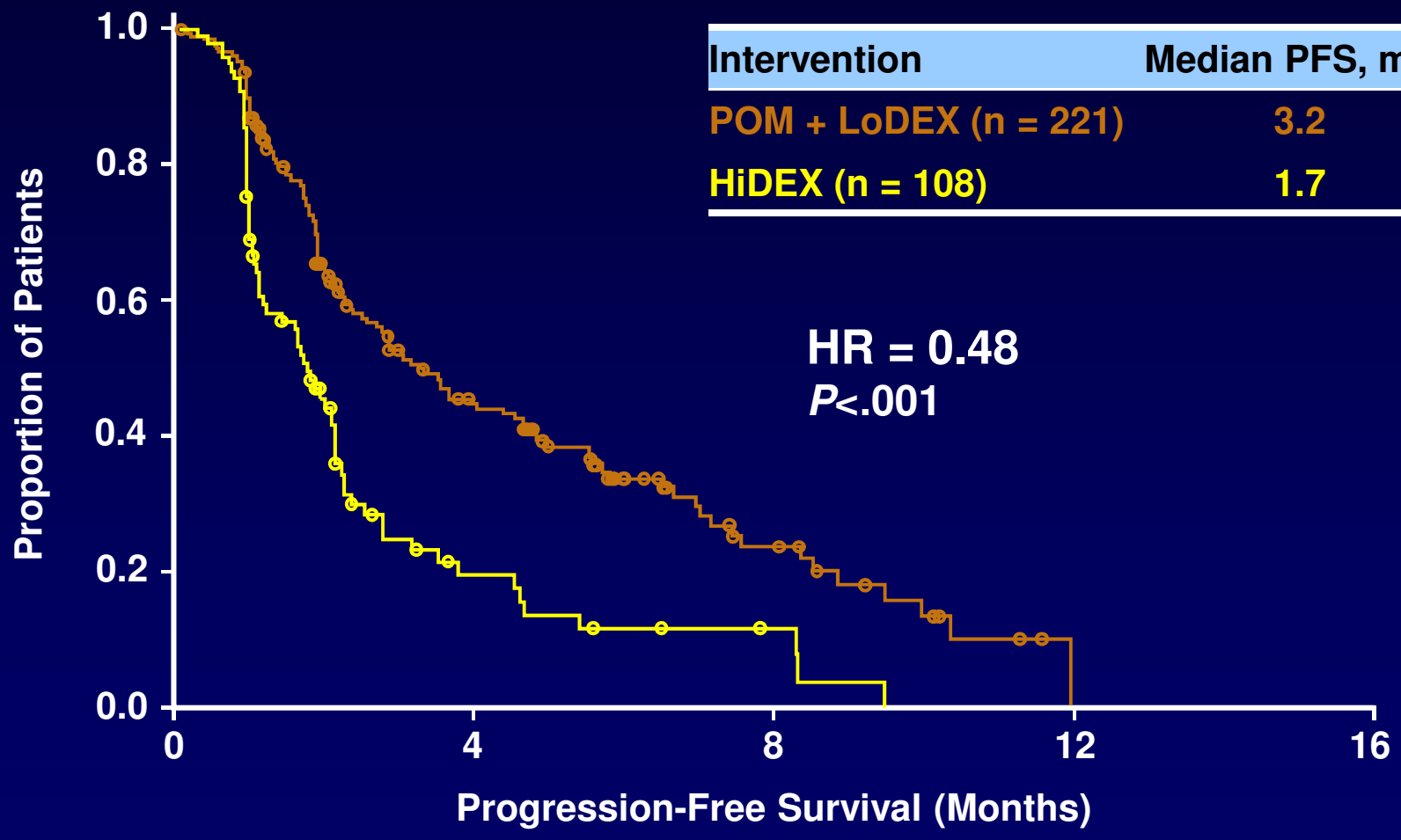
Intervention	Median PFS, mos
POM + LoDEX (n = 302)	3.6
HiDEX (n = 153)	1.8

HR = 0.45
***P*<.001**

Dimopoulos MA, et al. *Blood.* 2012;120(21): Abstract LBA-6.

MM-003: Progression-Free Survival

Patients Refractory to Both LEN and BORT

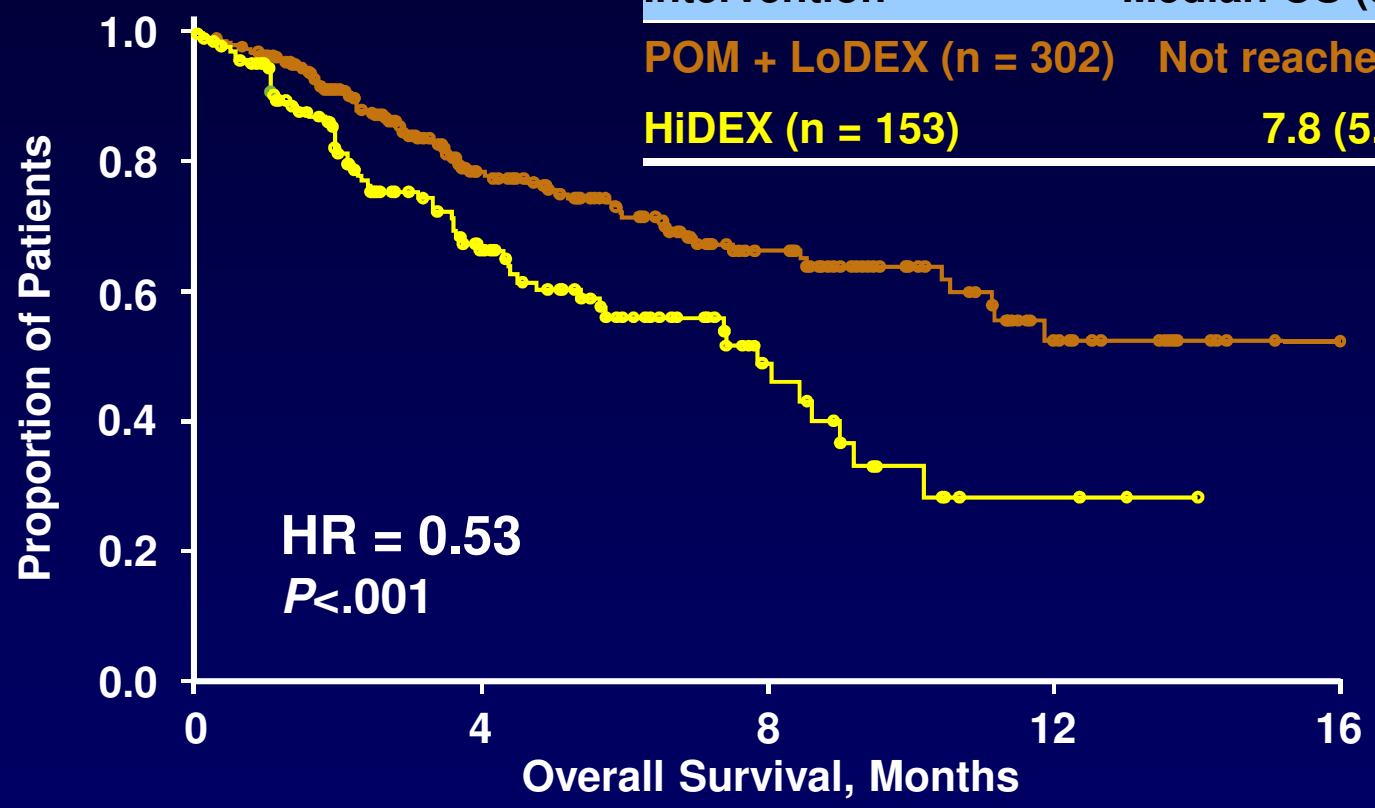


Intervention	Median PFS, mos
POM + LoDEX (n = 221)	3.2
HiDEX (n = 108)	1.7

HR = 0.48
P<.001

Dimopoulos MA, et al. *Blood.* 2012;120(21): Abstract LBA-6.

MM-003: Overall Survival
ITT Population



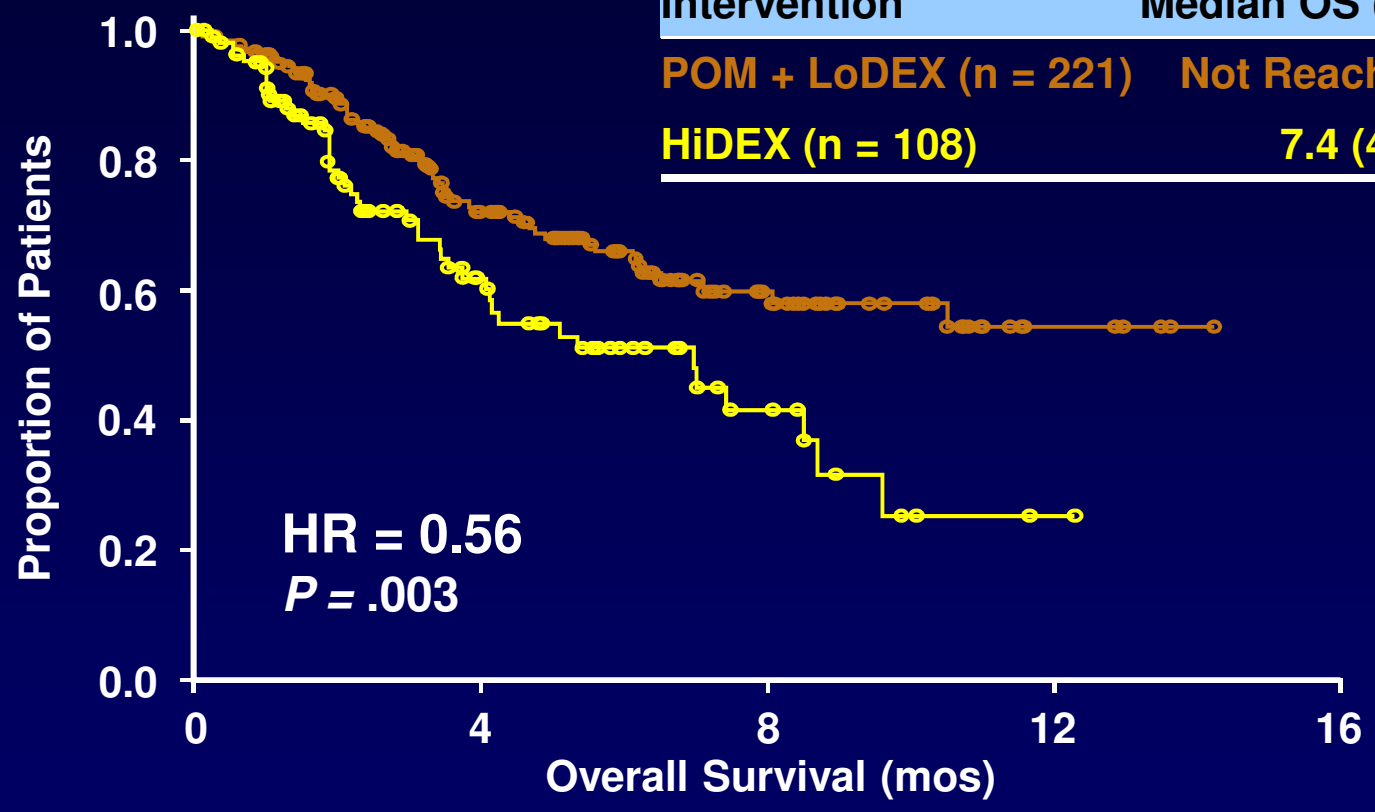
Intervention	Median OS (95% CI), mos
POM + LoDEX (n = 302)	Not reached (11.1-NE)
HiDEX (n = 153)	7.8 (5.4-9.2)

- **29% of pts received POM after progression on HiDEX**

Dimopoulos MA, et al. *Blood.* 2012;120(21): Abstract LBA-6.

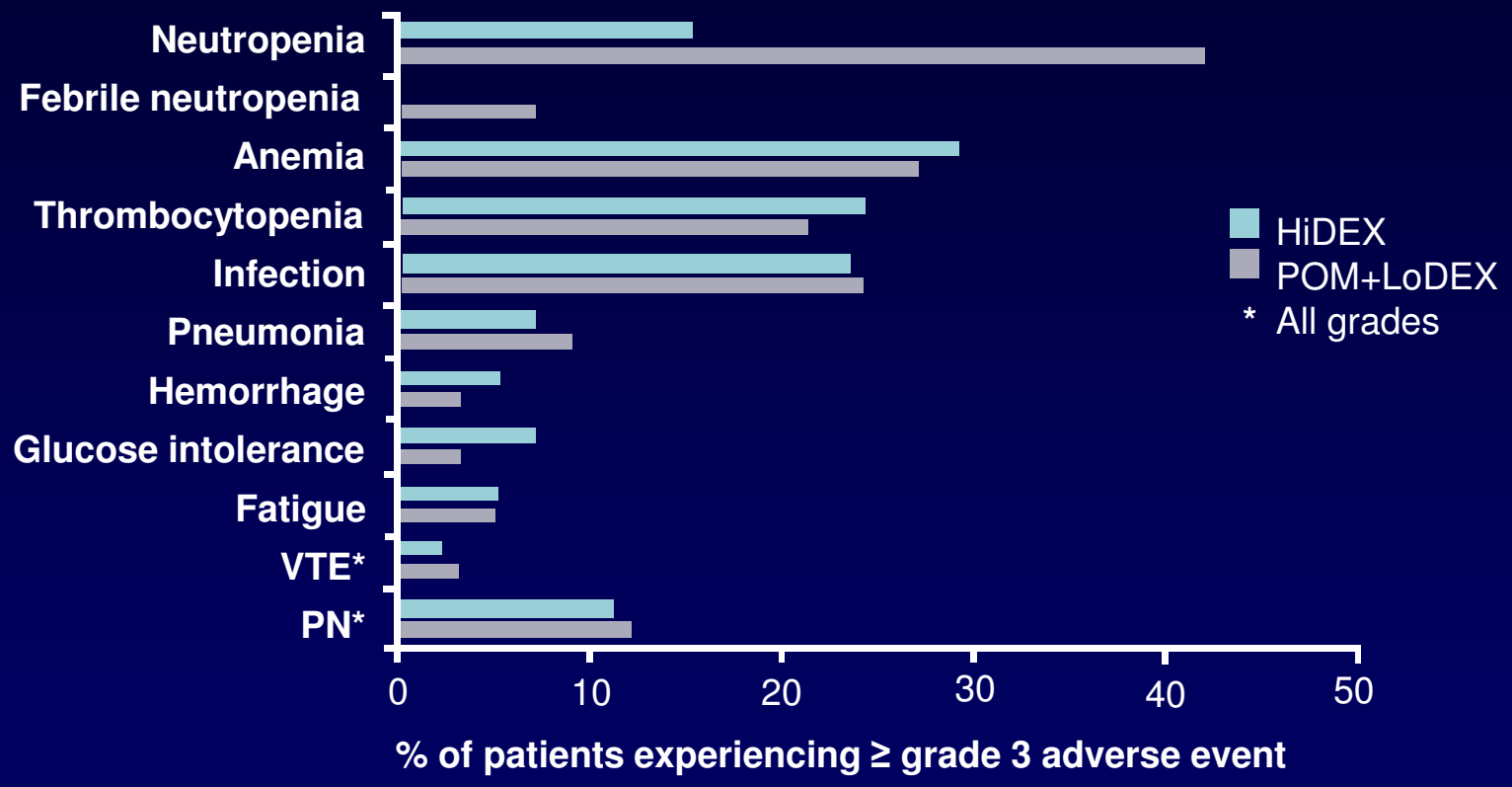
MM-003: Overall Survival
Patients Refractory to Both LEN and BORT

Intervention	Median OS (95% CI), mos
POM + LoDEX (n = 221)	Not Reached (8.5-NE)
HiDEX (n = 108)	7.4 (4.3-9.2)



Dimopoulos MA, et al. *Blood.* 2012;120(21): Abstract LBA-6.

MM-003: Adverse Events



7% of POM + LoDEX and 6% of HiDEX patients discontinued due to AEs

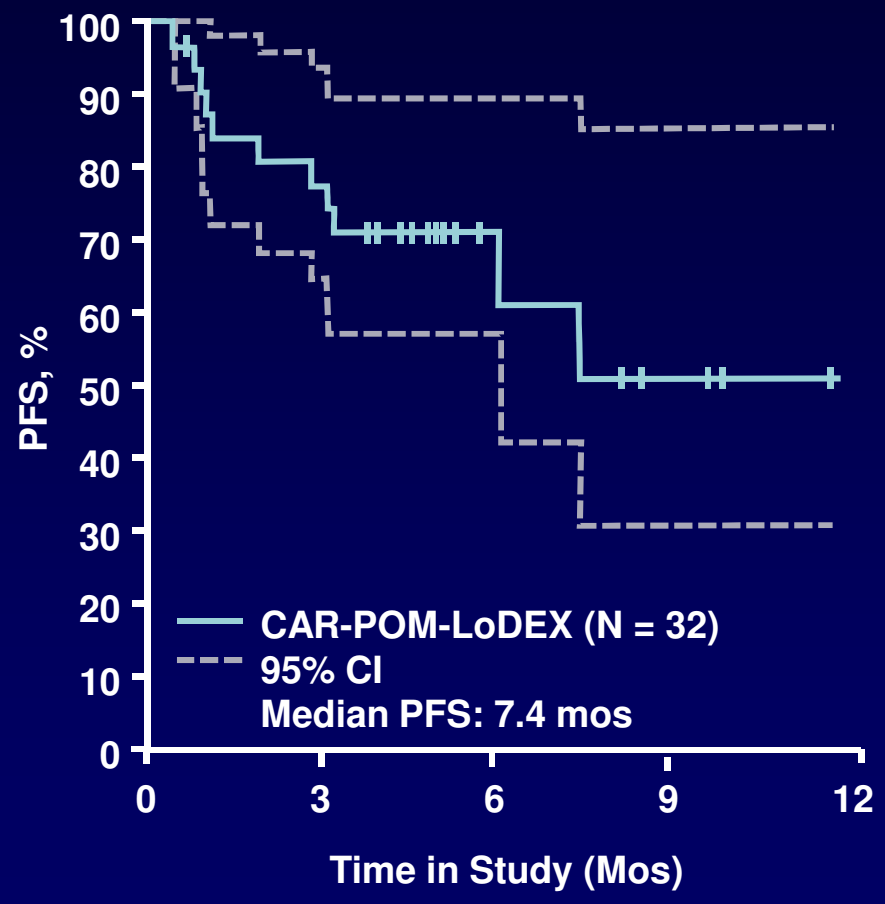
Dimopoulos MA, et al. *Blood.* 2012;120(21): Abstract LBA-6.

Carfilzomib/Pomalidomide/LoDEX

- Carfilzomib has single-agent activity in relapsed/refractory MM
- Pomalidomide is a third-generation IMiD
- RVD and early data of carfilzomib + lenalidomide/dexamethasone demonstrate utility of proteasome + IMiD combination
- Current phase I/II study determined MTD of carfilzomib in combination with pomalidomide and dexamethasone
  - Carfilzomib administered at 20 mg/m^2 loading dose, followed by 27, 36, 45, or 54 mg/m^2 study dose
- Patients were heavily pretreated (median: 6 previous regimens; range: 1-15)
- MTD established as starting dose: 20/27 mg/m^2 for phase II segment

Shah JJ, et al. *Blood.* 2012;120(21): Abstract 74.

Carfilzomib/Pomalidomide/LoDEX: Outcomes



Outcome	CAR-POM-LoDEX (N = 32)
Response rates (n = 30), %	
• ORR	50
– ≥VGPR	13
– PR	37
• Minor response	17
• SD	23
• PD	10
Median PFS, mos	7.4
1-yr OS, %	90

- Serious adverse events of note
  - Grade 3 pneumonia: n = 3
  - Pulmonary emboli: n = 1
  - Congestive heart failure: n = 1
  - No grade 3/4 peripheral neuropathy

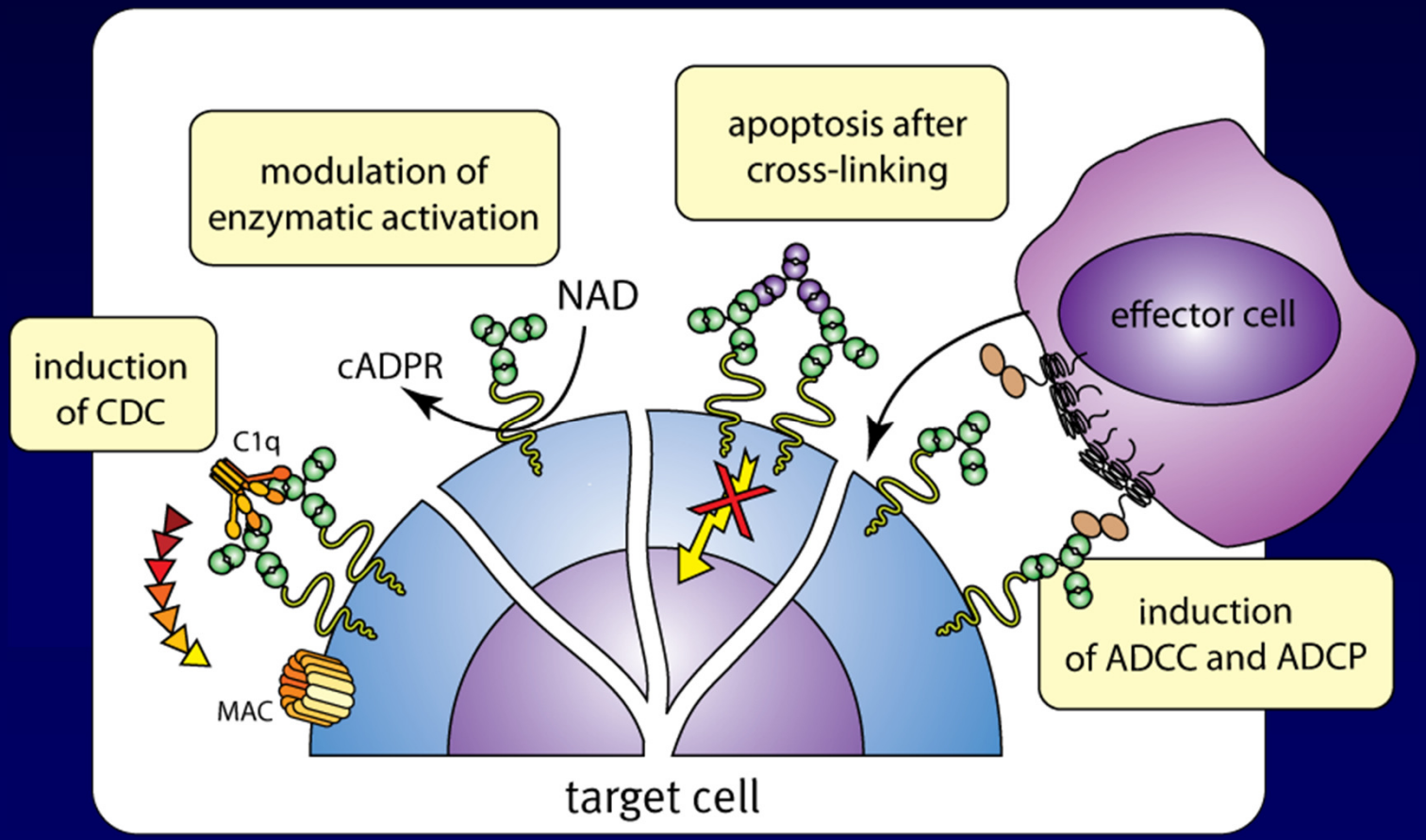
Shah JJ, et al. *Blood.* 2012;120(21): Abstract 74.

Monoclonal Antibodies in RR MM

Author	Regimen	Target	N	Phase	Preliminary Data
Jagannath et al[1]	BT062	Syndecan-1, CD138	32	I	Acceptable toxicity profile
Fanale et al[2]	Lucatumumab	CD40	164	I	MTD for MM: 4.5 mg/kg/wk
Mahadevan et al[3]	Samalizumab	CD200	3	I/II	MTD not yet established
Raje et al[4]	Tabalumab	BAFF	48	I	CR 4%, VGPR 8%, PR 33% TTP 4.9 mos, DOR 7.3 mos
Rossi et al[5]	BTZ + siltuximab	IL6	21	I/II	ORR: 57% TTP: 8.7 mos
Jakubowiak et al[6]	BTZ + elotuzumab	CS1	28	I	ORR: 48% TTP: 9.4 mos
Lonial et al[7]	Elotuzumab + LEN + DEX	CS1	73	II	ORR: 82%
Plesner et al[8]	Daratumumab	CD38	32	I/II	At doses 4 mg/kg and above, 8 of the 12 patients had at least an MR

1. Jagannath S, et al. *Blood.* 2011;118(21): Abstract 305. 2. Fanale M, et al. 2011;118(21): Abstract 3702. 3. Mahadevan D, et al. *Blood.* 2010;116(21): Abstract 2465. 4. Raje N, et al. *Blood.* 2012;120(21): Abstract 447. 5. Rossi JF, et al. *Blood.* 2008;112(11): Abstract 867. 6. Jakubowiak AJ, et al. *J Clin Oncol.* 2010;28(15s suppl): Abstract 8003. 7. Lonial S, et al. *Blood.* 2011;118(21): Abstract 303. 8. Plesner T, et al. *Blood.* 2012;120(21): Abstract 73.

Daratumumab: A human CD38 mAb with broad-spectrum killing activity



de Weers M, et al. *J Immunol.* 2011;186(3):1840-1848.

Daratumumab - Trial Design

Part 1

Dose-escalation cohorts

Open label, weekly i.v. infusion, 8 weeks

Dose-escalation: 3+3 scheme*

0.005→0.05→0.1→0.5→1.0 →2.0→4.0→8.0→16.0 →24.0 mg/kg

Part 2

Expansion cohort

Open label, single arm, weekly for 8 weeks followed by

i.v. infusions every other week up to week 24

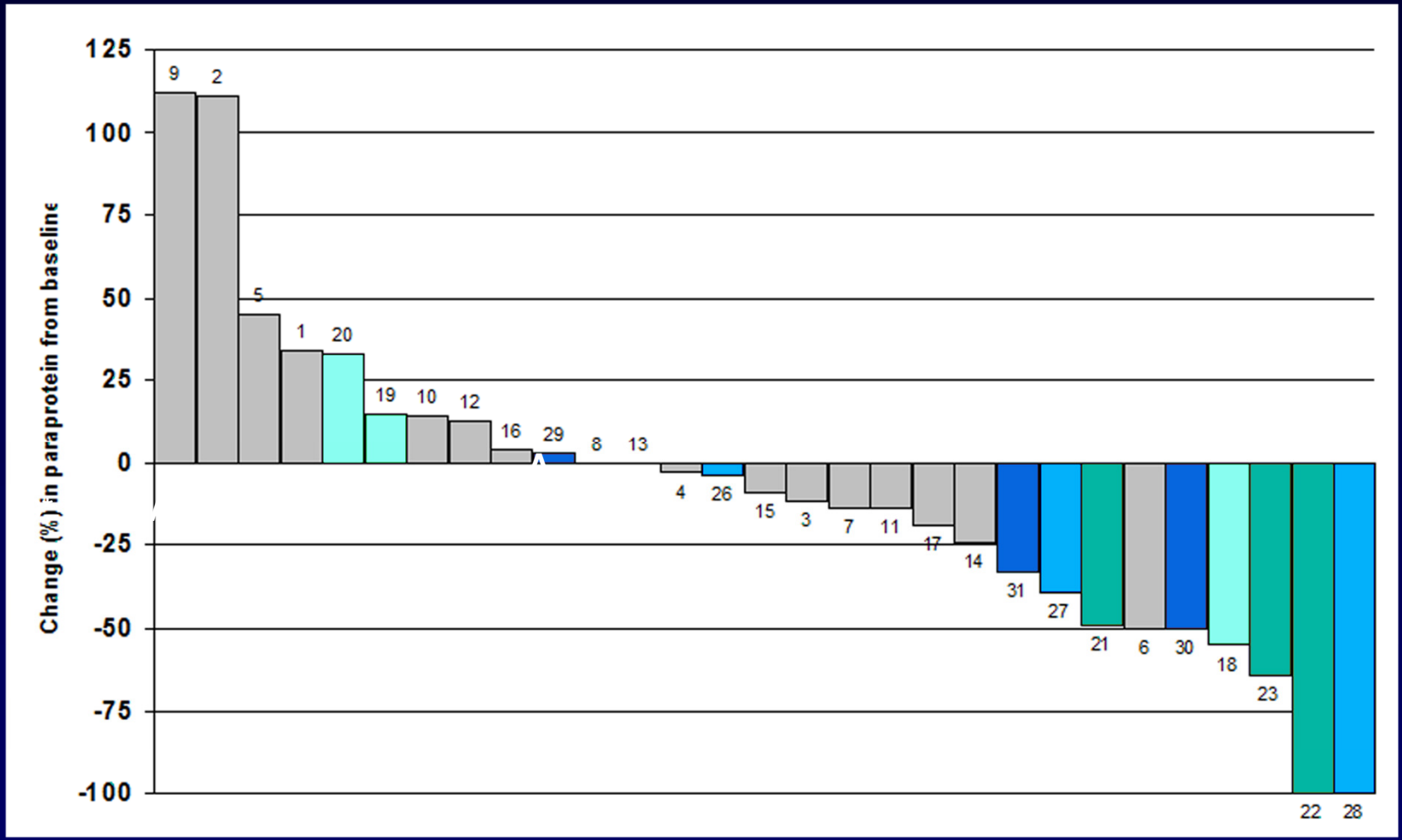
dose to be decided

16 patients

*: - start with pre-dose at 10% of the full dose, max 10 mg
- three week wait after first full dose
- governed by independent data monitoring committee

Plesner T, et al. *Blood.* 2012;120(21): Abstract 73.

Maximal Change in Paraprotein

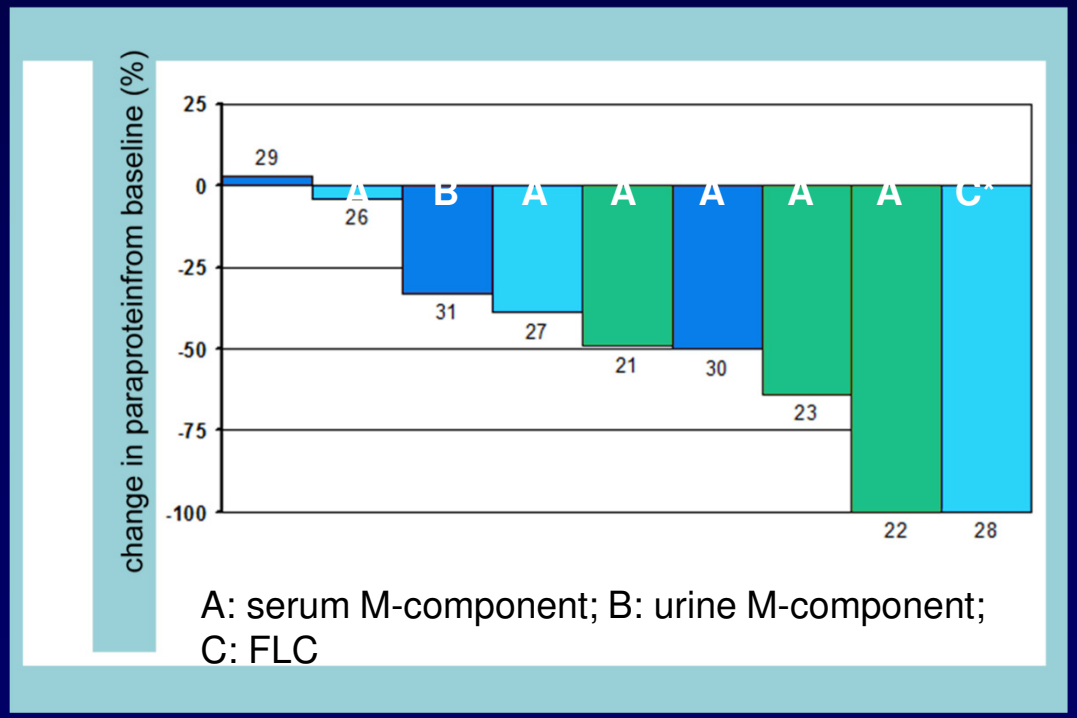


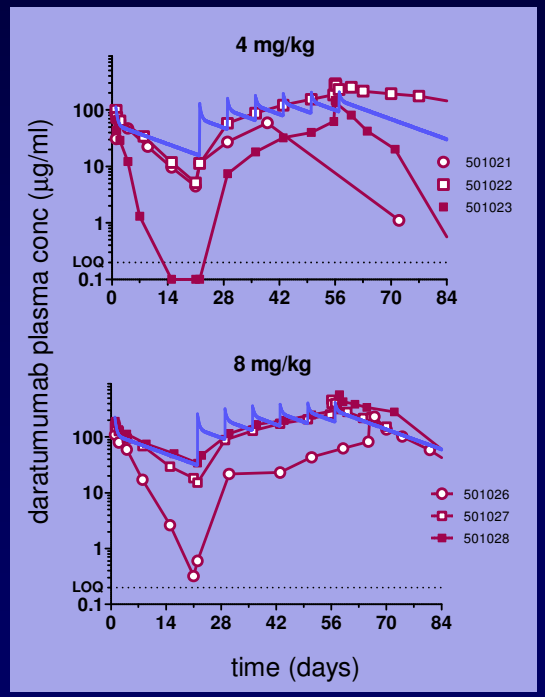
≤1 mg/kg | 2 mg/kg | 4 mg/kg | 8 mg/kg | 16 mg/kg

Lokhorst et al. EHA 2012;Abstract 1143

Correlation Between Exposure and Decline in Paraprotein

- At doses ≥ 4 mg/kg, daratumumab trough levels were consistent ≥ 10 µg/ml and observed PK values approximately estimated PK values
- In 9 patients dosed with daratumumab ≥ 4 mg/kg, 6 clinical responses were observed - 4 PR and 2 MR





4 mg/kg | 8 mg/kg | 16 mg/kg

Lokhorst et al. EHA 2012;Abstract 1143

Daratumumab Results

- Safety
  - 26% of patients experienced infusion reactions
  - Temporary dose-dependent decrease in peripheral blood NK cells
  - No significant platelet or hemoglobin changes
  - Serious adverse events observed across cohorts
    - 0.1 mg/kg (grade 2 cytokine release syndrome; grade 3 anemia; grade 4 thrombocytopenia), 1 mg/kg (grade 3 AST), 2 mg/kg (grade 3 bronchospasm), 24 mg/kg (grade 2 bronchospasm)
- Response rate
  - Dose-dependent reduction in paraprotein
  - High AUC correlates with prolonged PFS
  - 67% ≥MR in patients receiving ≥4 mg/kg
  - Response accompanied by bone marrow clearance of myeloma cells

Plesner T, et al. *Blood.* 2012;120(21): Abstract 73.

What Is the Role for Transplantation at Relapse/ in Refractory Disease?

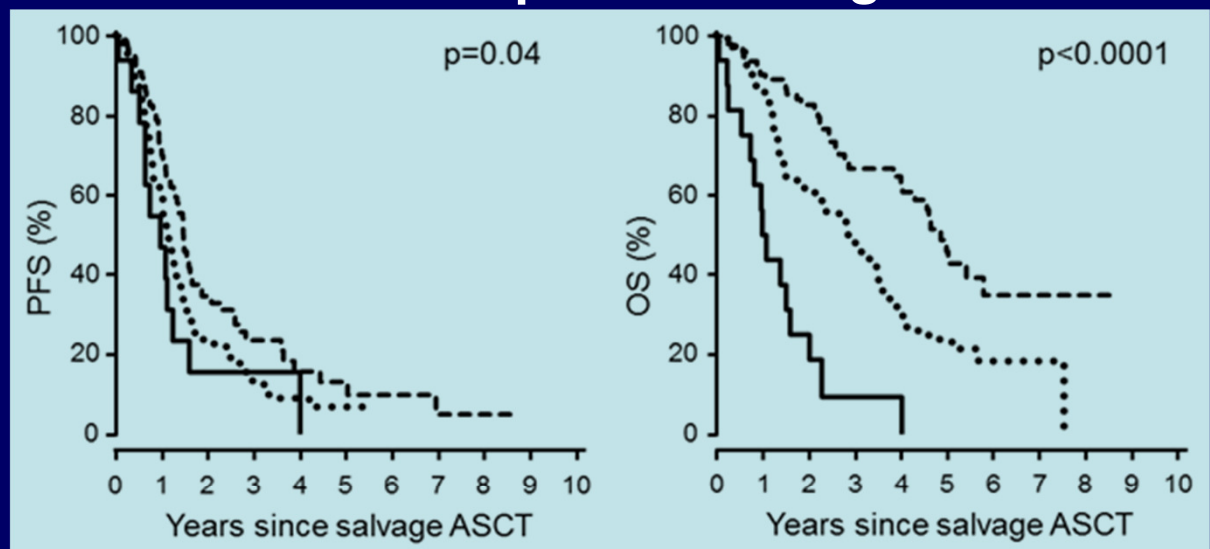
Autologous Retransplantation for Patients With Relapsed MM

- **Retrospective review**
  - Pts who received salvage ASCT after upfront ASCT (n = 200)
- **Results**
  - Median follow-up after salvage ASCT: 57.1 months
  - Median PFS: 15.2 months
  - Median OS: 42.3 months
  - ORR (≥PR) at day 100: 80.4%
  - Factors associated with improved PFS and OS after salvage ASCT:
    - Remission duration of >18 months after upfront ASCT
    - Bortezomib- or lenalidomide containing re-induction regimen
    - Response to reinduction
    - ISS stage I prior to salvage ASCT
    - Year of salvage ASCT (2005 or thereafter)

Neben K, et al. Blood. 2012;120(21): Abstract 3086.

Autologous Retransplantation for Patients With Relapsed MM

- Creation of risk stratification model based on remission duration after upfront ASCT and ISS prior to salvage ASCT



Line	Score	ISS	Duration of Remission after 1st ASCT	PFS		OS	
				HR	Median time	HR	Median time
- - -	Low risk (n=96)	I	>18 months	1	17.6 months	1	58.5 months
·····	Intermediate risk (n=74)	I II/III	≤ 18 months > 18 months	1.43	13.8 months	2.03	33.9 months
———	High risk (n=16)	II/III	≤ 18 months	1.94	11.7 months	6.83	13.5 months

Neben K, et al. Blood. 2012;120(21): Abstract 3086.

ASCT in Primary Refractory MM

- **Patients** (n = 80) with primary refractory MM (49 SD, 31 PD)
- Treatment
  - Tandem transplants (double ASCT or single ASCT + alloSCT)
- **Results**
  - No significant difference in ≥PR in pts with SD or PD

Measure	Pts With SD (n = 49)	Pts With PD (n = 31)	*P* Value
Stable condition or MR after transplant, %	38	7	.0017
Early progression after transplant, %	2	22	.0043
PFS from first transplant, yrs	2.3	0.6	.00004
OS from first transplant, yrs	6	1.1	.00002

- **Conclusion**
  - Pts with PD do not benefit from ASCT; pts with SD have outcome comparable to those with chemosensitive disease

Rosiñol L, et al. *Haematologica.* 2012;97(4):616-621.

Conclusions

- Carfilzomib and pomalidomide are effective in both bortezomib- and lenalidomide-refractory patients
- Combinations of these agents with standard chemotherapy or other novel antimyeloma agents produce encouraging results in double-refractory patients
- ASCT is an option for relapsed patients
- Novel monoclonal antibodies (eg, daratumumab, elotuzumab, tabalumab) in combination with PIs, IMiDs, or conventional chemotherapy may be the future for the salvage treatment of RR myeloma patients