Recognizing and Responding to Resistance in Relapsed Multiple Myeloma

Philippe Moreau, MD
University Hospital Hôtel-Dieu
Nantes, France

Criteria That Will Influence the Choice of Therapy in the Relapse Setting

- ***Patient***
  - Age, performance status
  - Comorbidities
- ***Cytogenetic profile***
  - t(4;14), del 17p
- ***Socioeconomic factors***
  - Accessible health care
  - Cost
- ***Disease presentation at relapse***
  - Paraprotein relapse / agressive
  - On therapy / off therapy
  - Duration of first response
  - Renal impairment
  - Cytopenia
- ***Prior therapies***
  - Refractoriness to IMiDs, PI,…
  - Treatment-related toxicity (peripheral neuropathy, hematologic…)

Criteria That Will Influence the Choice of Therapy in the Relapse Setting

- ***Patient***
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  - Patient's choice
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AVAILABILITY OF DRUGS / CLINICAL TRIALS

The NEW ENGLAND JOURNAL of MEDICINE

N ENGL J MED 352;24 WWW.NEJM.ORG JUNE 16, 2005

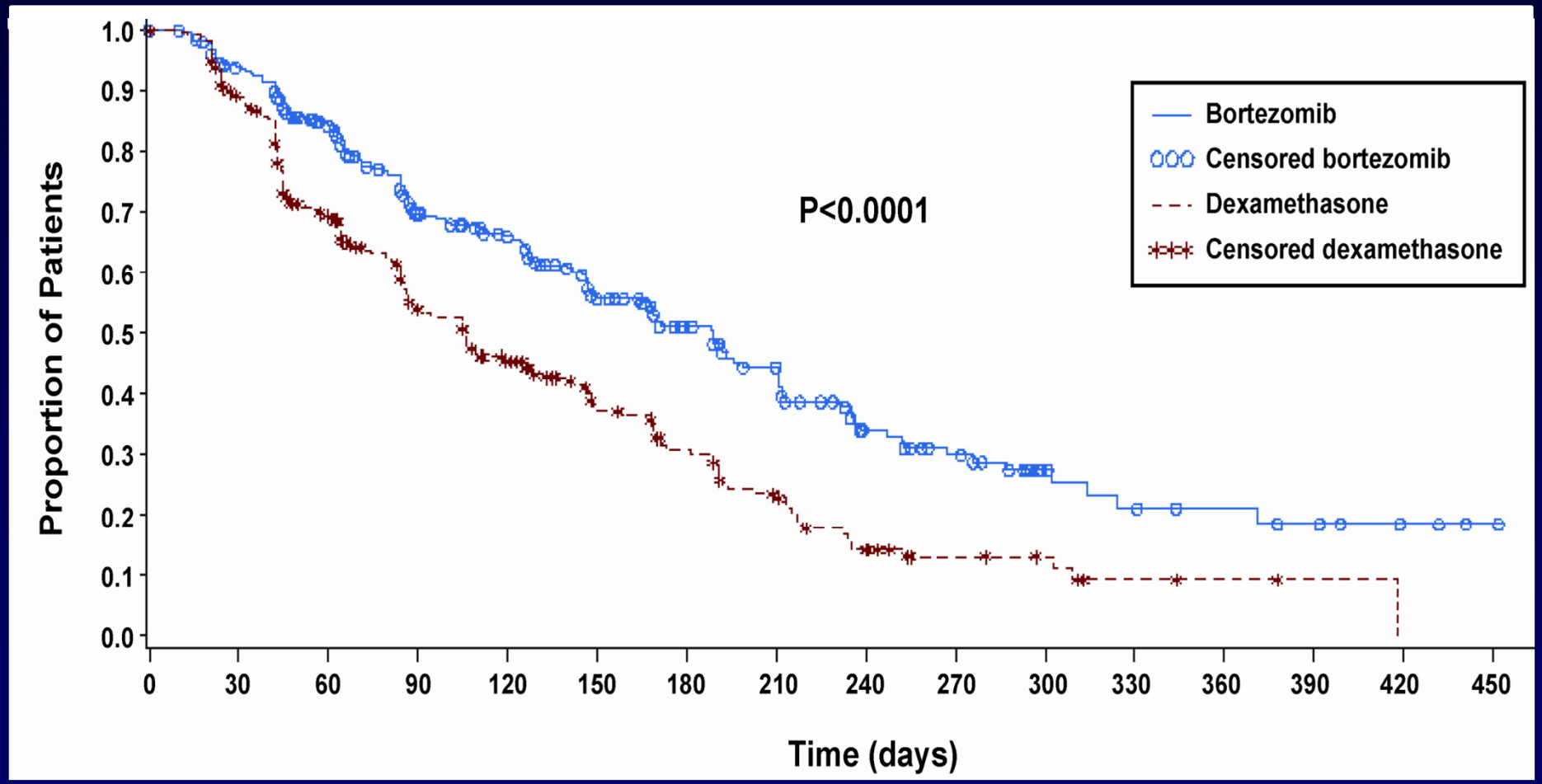
ORIGINAL ARTICLE

Bortezomib or High-Dose Dexamethasone for Relapsed Multiple Myeloma

Paul G. Richardson, M.D., Pieter Sonneveld, M.D., Michael W. Schuster, M.D., David Irwin, M.D., Edward A. Stadtmauer, M.D., Thierry Facon, M.D., Jean-Luc Harousseau, M.D., Dina Ben-Yehuda, M.D., Sagar Lonial, M.D., Hartmut Goldschmidt, M.D., Donna Reece, M.D., Jesus F. San-Miguel, M.D., Joan Bladé, M.D., Mario Boccadoro, M.D., Jamie Cavenagh, M.D., William S. Dalton, M.D., Anthony L. Boral, M.D., Ph.D., Dixie L. Esseltine, M.D., Jane B. Porter, M.S., David Schenkein, M.D., and Kenneth C. Anderson, M.D., for the Assessment of Proteasome Inhibition for Extending Remissions (APEX) Investigators*

Time to Progression (n = 669)

78% improvement in median TTP with bortezomib



Median TTP: bortezomib 6.2 months; dexamethasone 3.5 months

Richardson PG, et al. *N Engl J Med.* 2005;352(24):2487-2498.

MM-009 and MM-010

North American MM-009 (48 centers USA/Canada)
International MM-010 (51 centers Europe/Australia/Israel)

Lenalidomide 25 mg days 1–21
Placebo days 22–28
Dex 40 mg, days 1–4, 9–12, 17–20

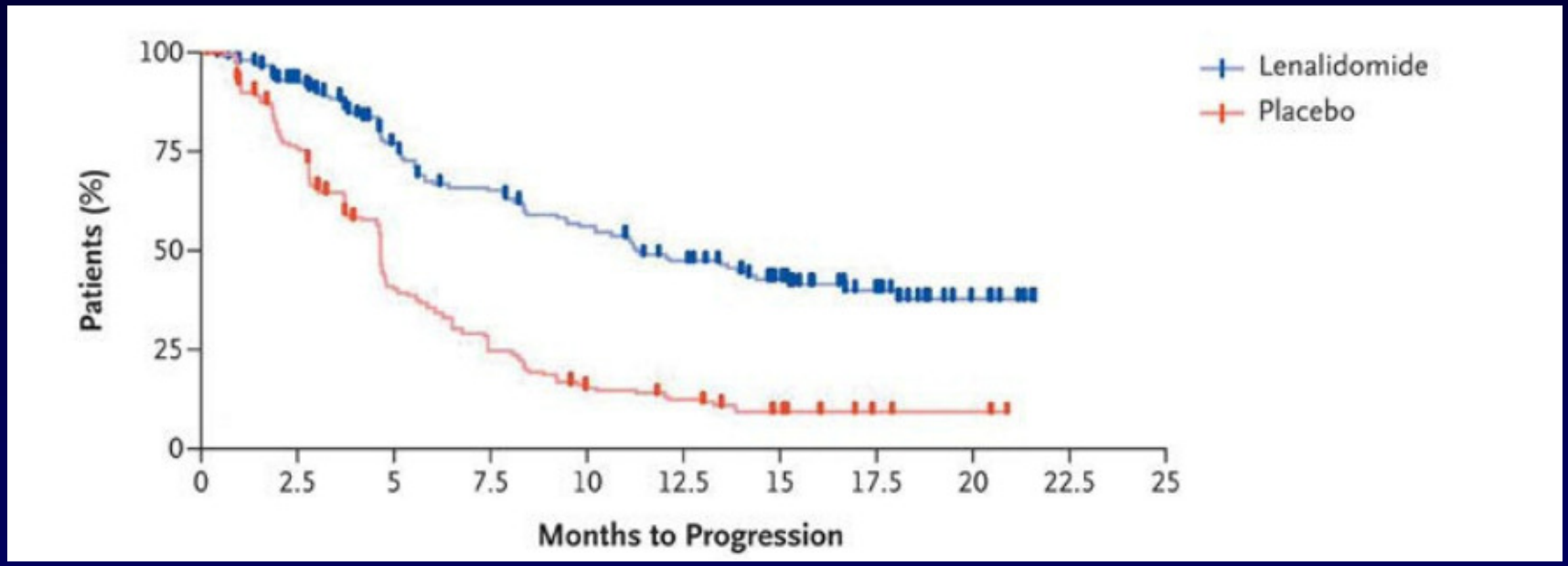
× 4 cycles → Until progression

Placebo days 1–28
Dex 40 mg, days 1–4, 9–12, 17–20

Primary end-point : TTP

Dimopoulos M, et al. *N Engl J Med.* 2007;357(21):2123-2132. Weber DM, et al. *N Engl J Med.* 2007;357(21):2133-2142.

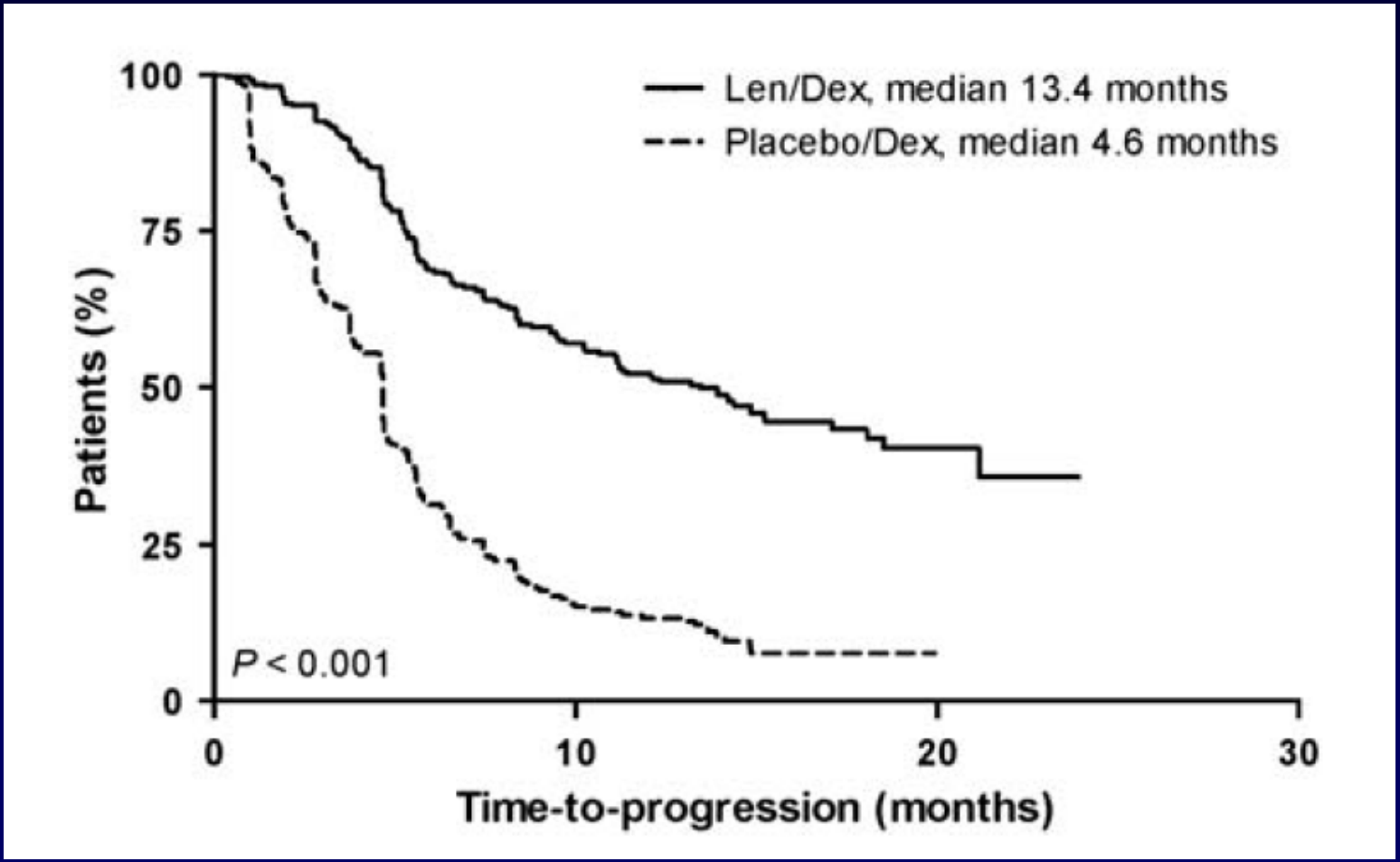
Time to Disease Progression for Intention-to-Treat Population



Lenalidomide group: 11.3 months
Placebo group: 4.7 months
} ***P*<.001**

Dimopoulos M, et al. *N Engl J Med.* 2007;357(21):2123-2132.

Time to Disease Progression for Intention-to-Treat Population

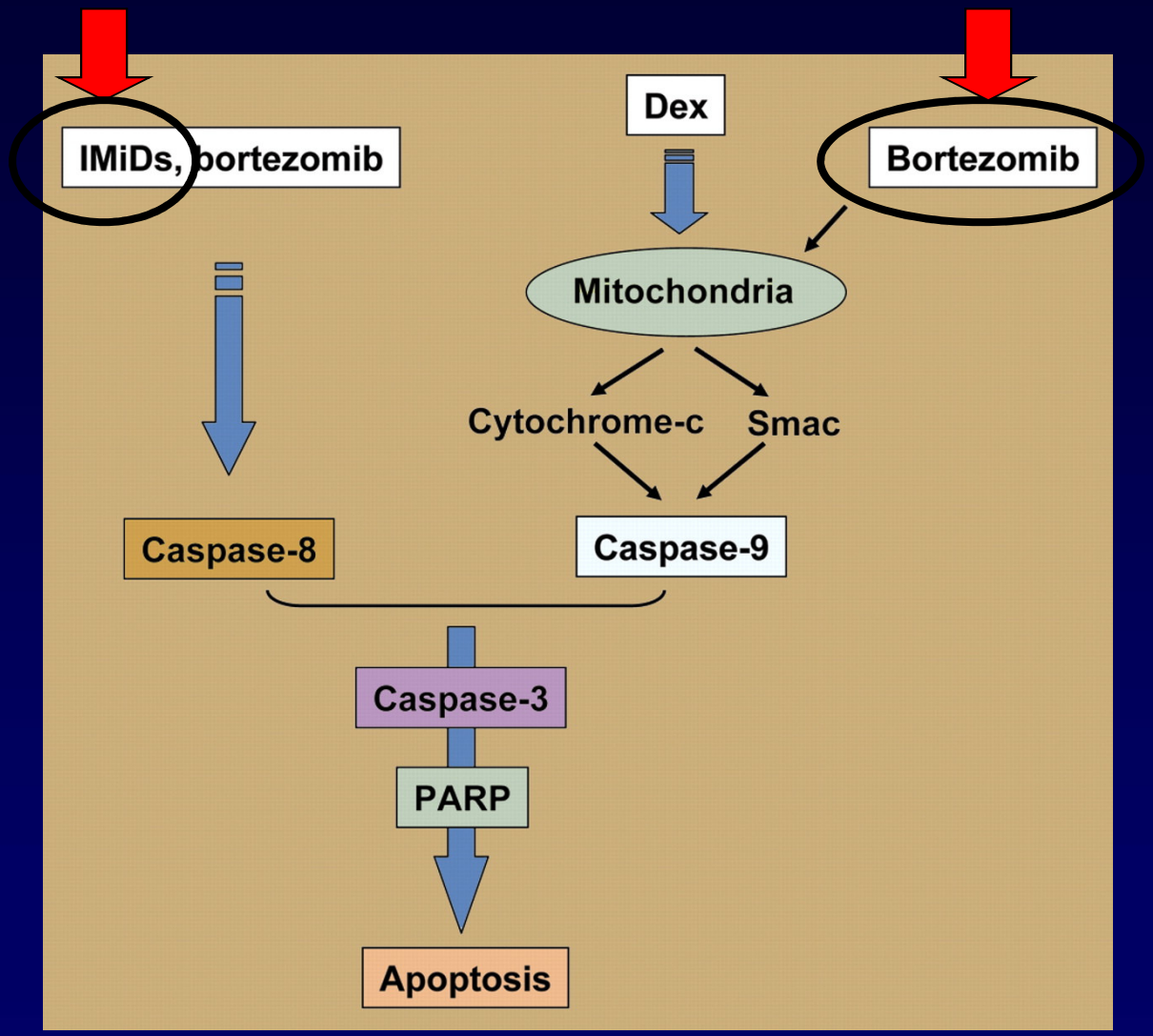


Updated results MM009-MM010. Median follow-up, 48 months

Dimopoulos MA, et al. *Leukemia.* 2009;23(11):2147-2152.

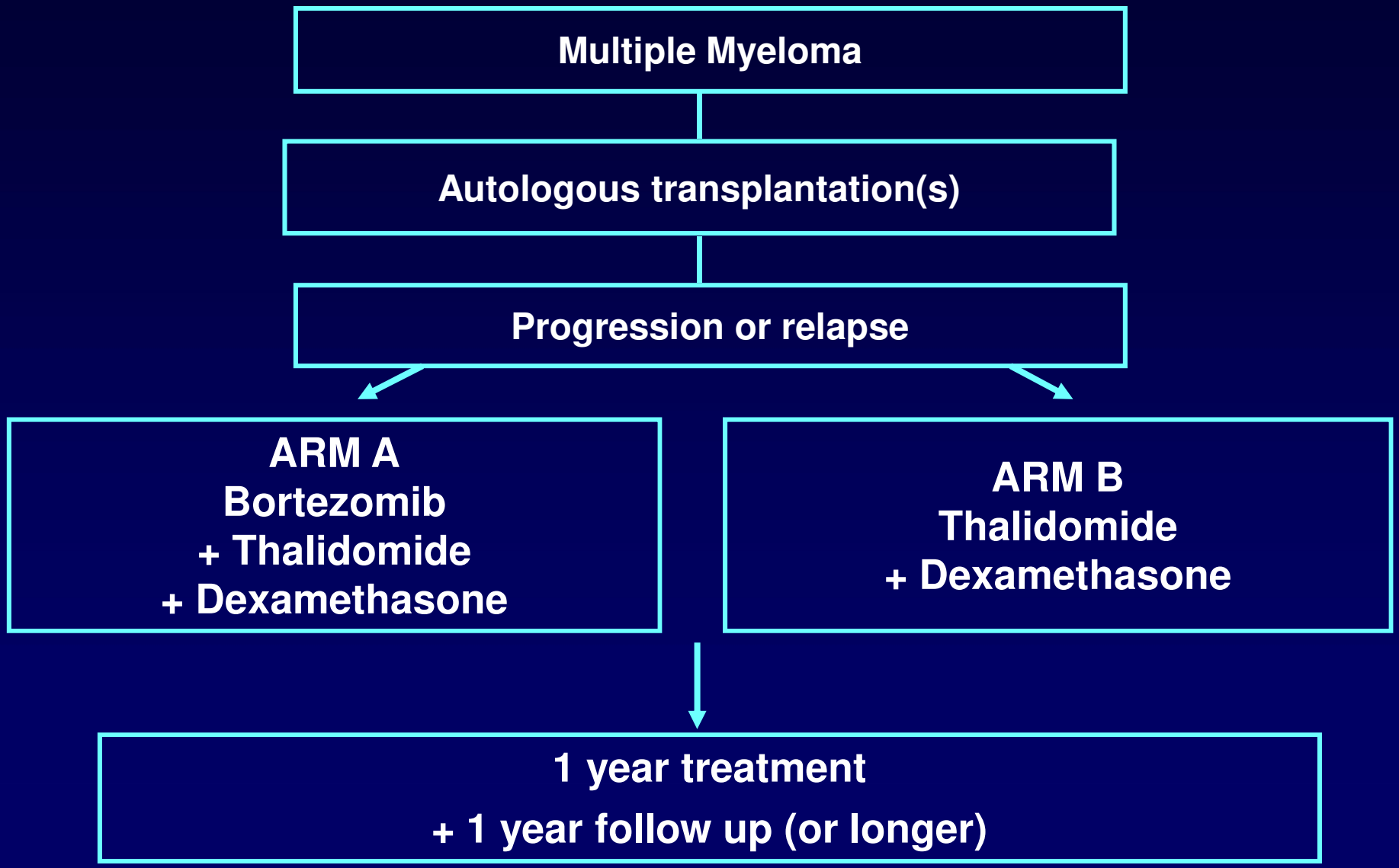
blood
JOURNAL OF THE AMERICAN SOCIETY OF HEMATOLOGY

Toward a new therapeutic backbone in myeloma

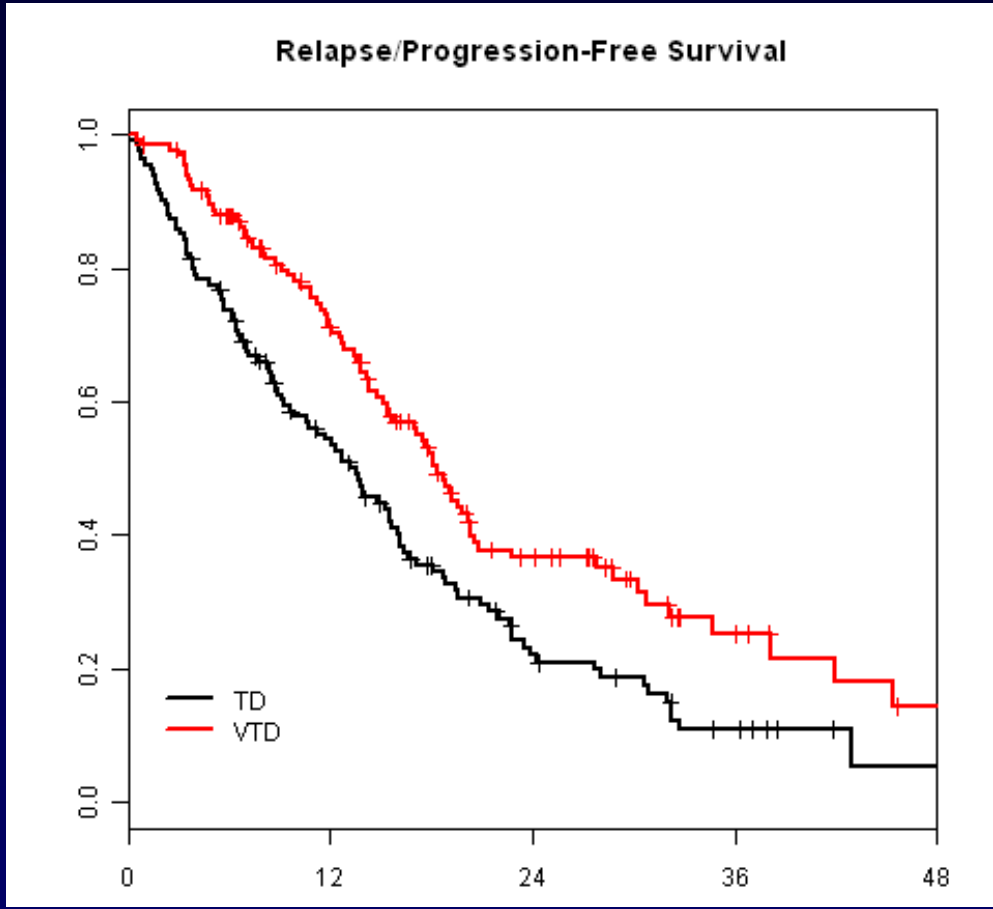


Richardson, P. *Blood* 2007;109(7):2672-2673.

Study Schema



Progression-Free Survival

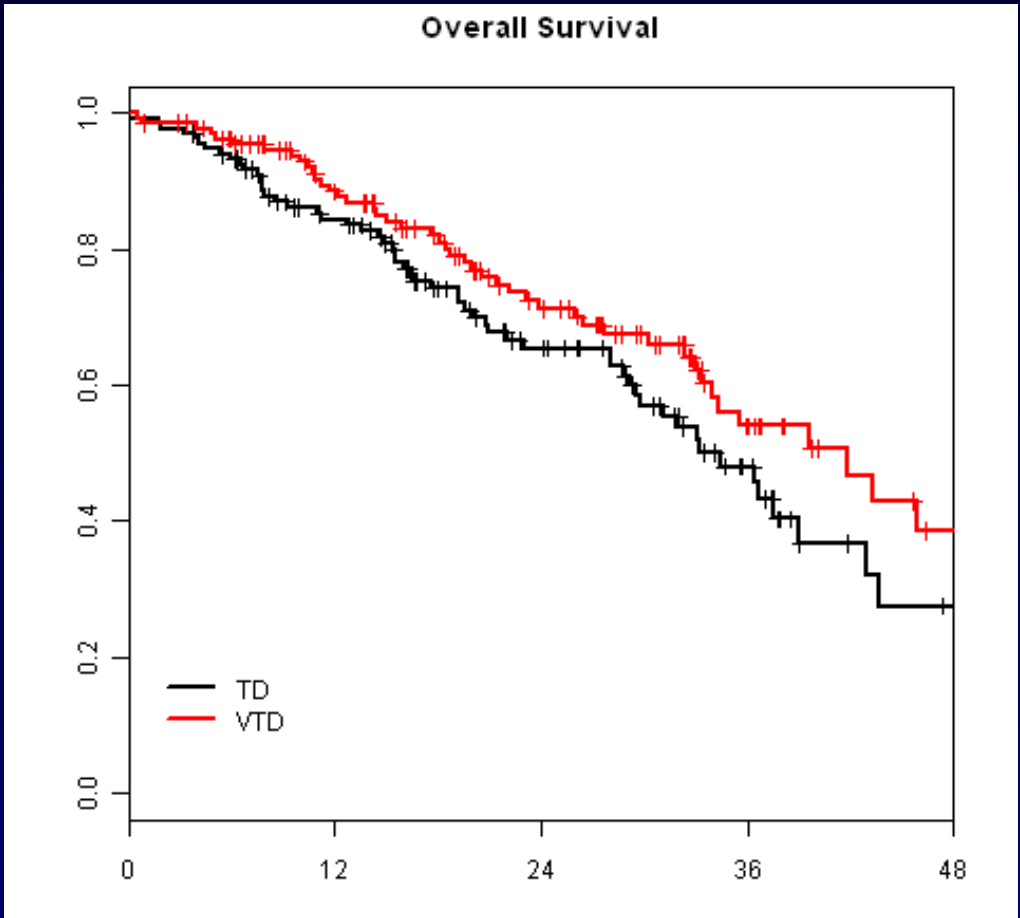


P **= .0007, HR = 0.6**

No. of patients at risk:				
VTD (N = 135)	84	31	10	3
TD (N = 134)	63	20	7	1

Garderet L, et al. *J Clin Oncol.* 2012;30(20):2475-2482.

Overall Survival



P **= .09**

At 2 years
VTD: 71%
TD: 65%

No. of patients at risk:				
VTD (N = 135)	101	62	23	8
TD (N = 134)	99	55	21	5

Garderet L, et al. *J Clin Oncol.* 2012;30(20):2475-2482.

VOLUME 27 · NUMBER 34 · DECEMBER 1 2009

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Multicenter, Phase I, Dose-Escalation Trial of Lenalidomide Plus Bortezomib for Relapsed and Relapsed/Refractory Multiple Myeloma

Paul G. Richardson, Edie Weller, Sundar Jagannath, David E. Avigan, Melissa Alsina, Robert L. Schlossman, Amitabha Mazumder, Nikhil C. Munshi, Irene M. Ghobrial, Deborah Doss, Diane L. Warren, Laura E. Lunde, Mary McKenney, Carol Delaney, Constantine S. Mitsiades, Teru Hideshima, William Dalton, Robert Knight, Dixie-Lee Esseltine, and Kenneth C. Anderson

Best Response to Lenalidomide Plus Bortezomib Combination Therapy

Treatment Dose			Patients by Response Type											
			CR		nCR		PR		MR		SD		PD	
Cohort	Lenalidomide, mg	Bortezomib, mg/m^2	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
1	5	1.0	0		0		2		0		1		0	
2	5	1.3	1		0		1		1		0		0	
3	10	1.0	0		1		2		0		0		0	
4	10	1.3	0		0		2		2		1		1	
5	15	1.0	0		0		1		4		7		2	
6	15	1.3	0		1		3		1		2		0	
Total			1	2	2	6	11	31	8	22	11	31	3	8

38 patients, median 5 lines of therapy
87% thal, 55% bortezomib, 89% dex, 61% ASCT
61% response

Richardson PG, et al. *J Clin Oncol.* 2009;27(34):5713-5719.

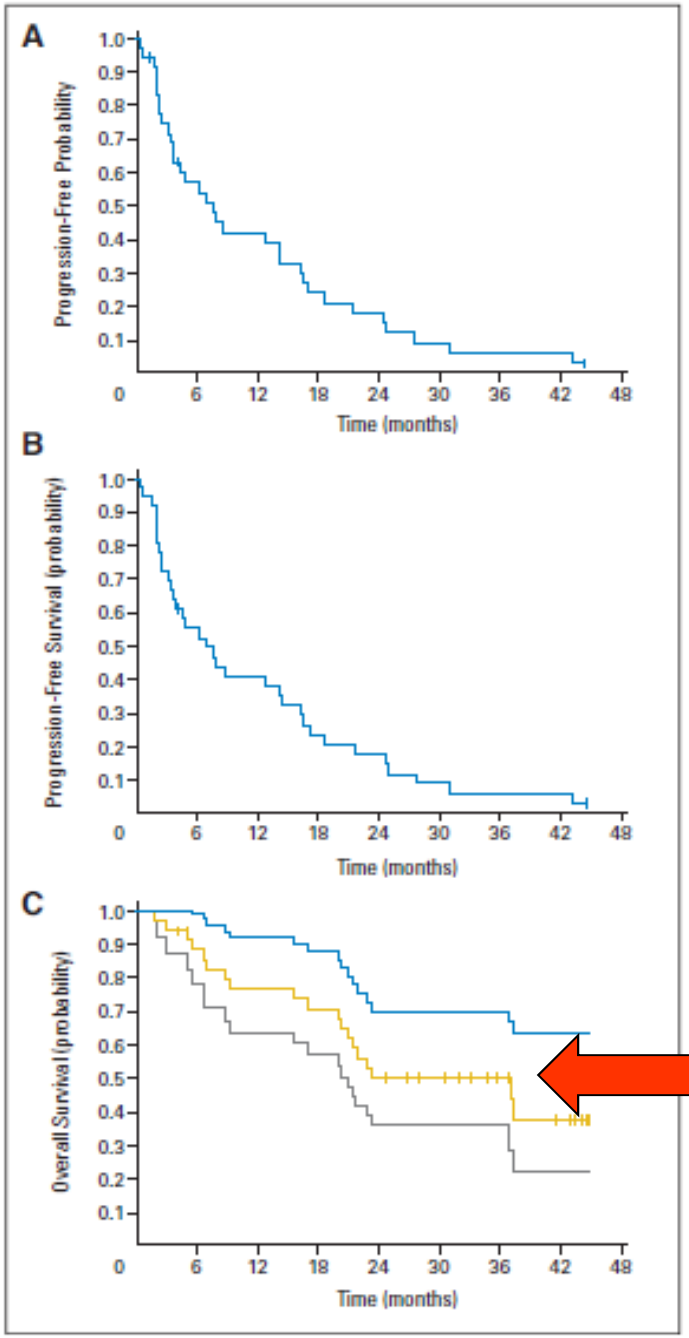


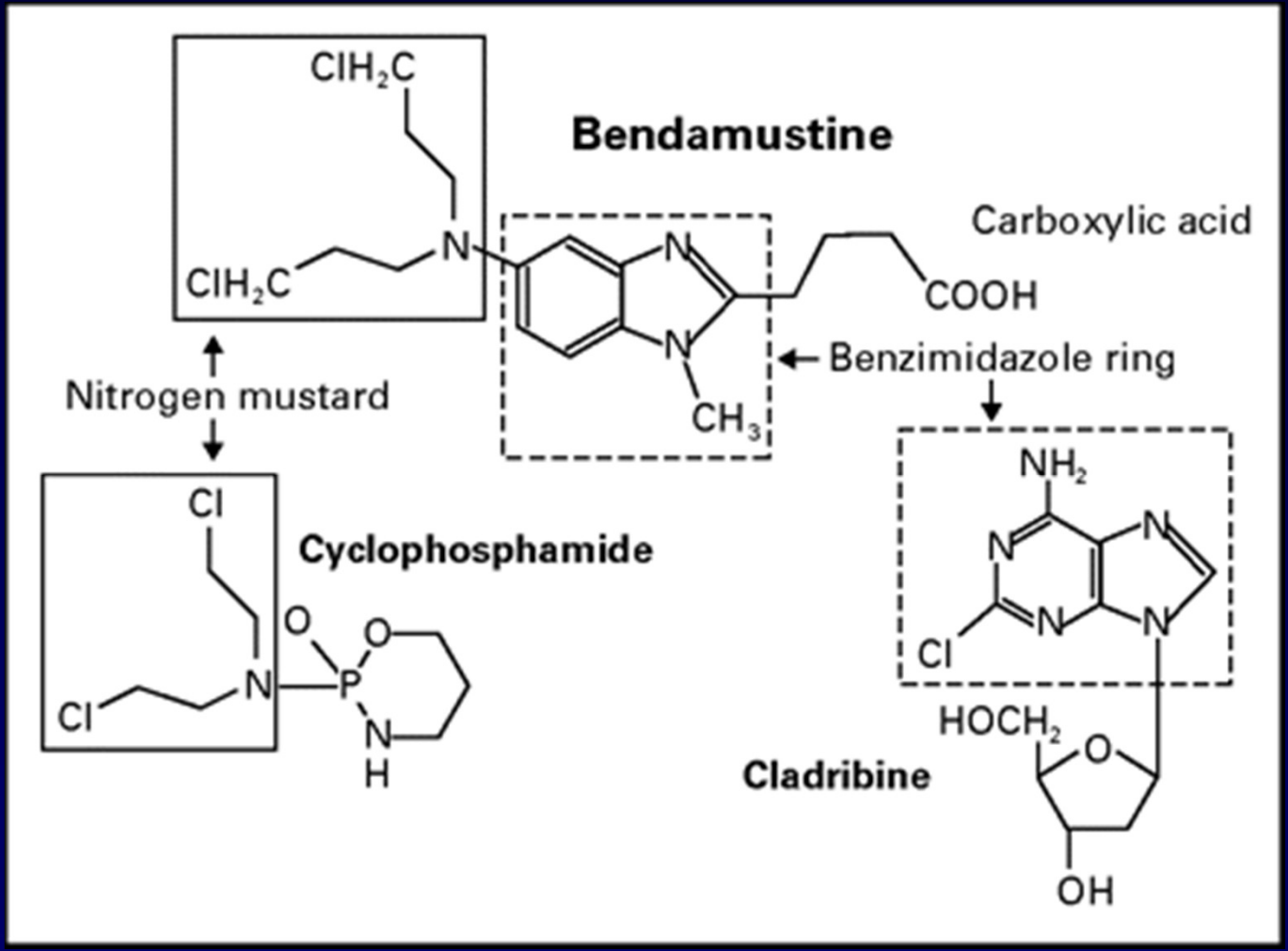
Fig 2. Kaplan-Meier estimates (in months) and 95% CIs of (A) time to progression, (B) progression-free survival, and (C) overall survival in 36 patients.

Median survival 37 months

Richardson PG, et al. *J Clin Oncol.* 2009;27(34):5713-5719.

- Bendamustine
- Carfilzomib / MLN9708
- Pomalidomide
- Elotuzumab / daratumumab
- HDAC inhibitors …

Chemical Structure of Bendamustine, Cyclophosphamide, and Cladribine



Cl, chlorine; H, hydrogen; N, nitrogen; O, oxygen; P, phosphorous

Cheson BD, et al. *J Clin Oncol.* 2009;27(9):1492-1450.

Bendamustine in relapsed and refractory patients— Report of 110 patients enrolled in the French compassionate-use program

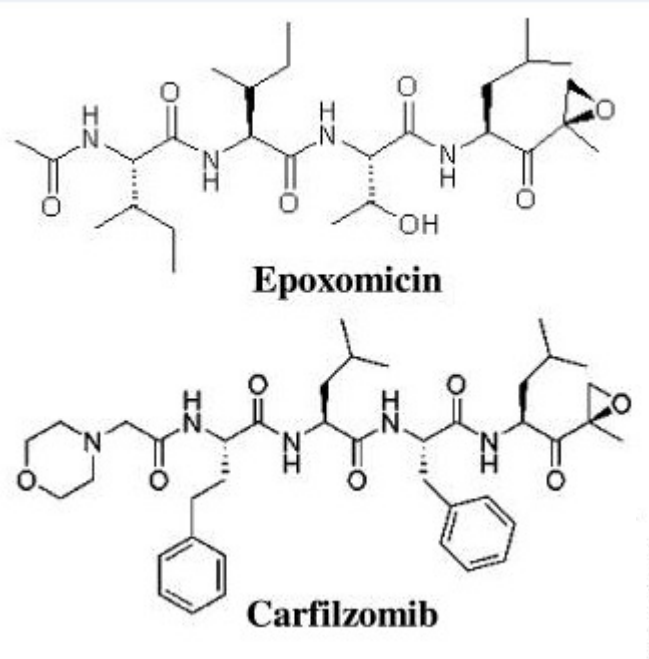
Damaj G, Moreau P, et al. *Leuk Lymphoma*. 2012;53(4):632-634.

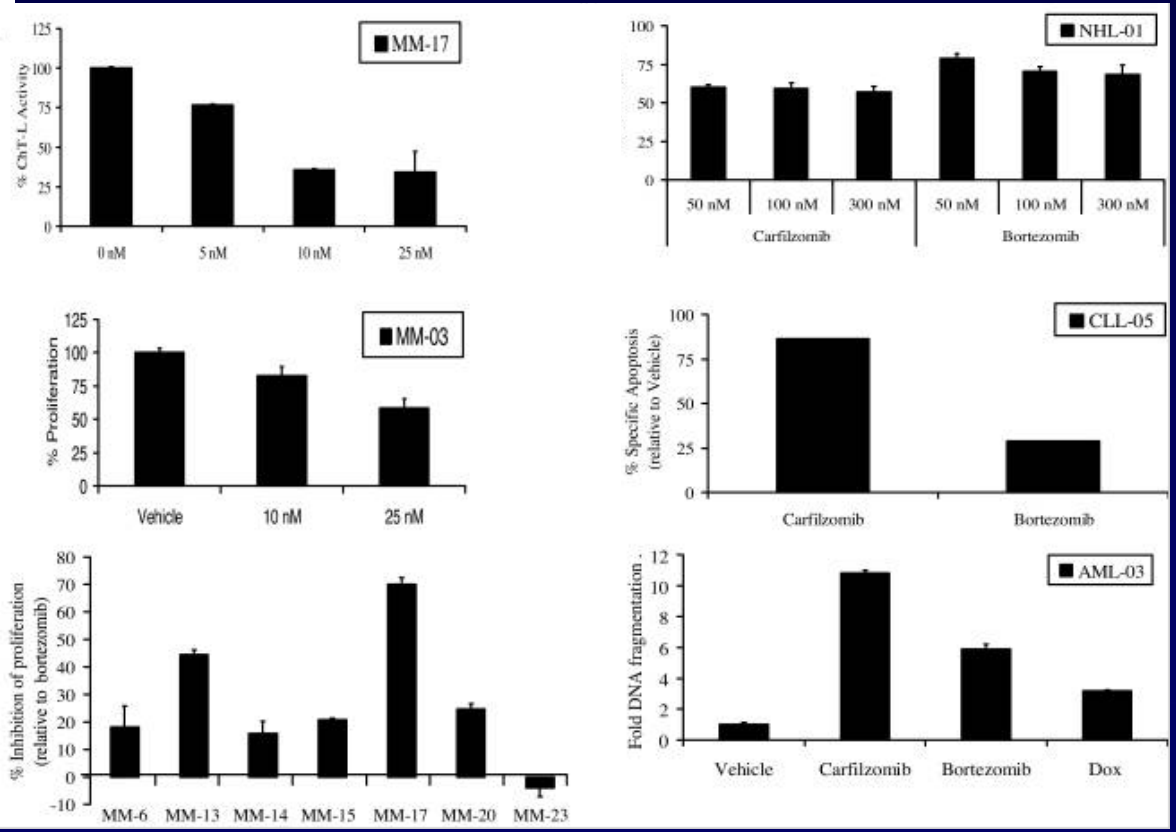
Bendamustine in Relapsed /Refractory Patients
French Compassionate-use Program (n=110)

Previous line of treatment, median (range)	4 (1-9)
Any alkylating agents, n (%)	110 (100%)
Any steroids, n (%)	110 (100%)
Bortezomib, n (%)	110 (100%)
Lenalidomide based, n (%)	93 (85%)
Thalidomide based, n (%)	57 (52%)
Previous autologous SCT (n)	66
Single / Tandem	30 / 36
Response to the last treatment before bendamustine (n)	
PR	8
SD / PD	11 / 71
Missing data	20
Response to bendamustine	110 patients (%)
ORR	33 (30)
CR	2 (2)
PR	31 (28)
SD	22 (20)
PD	55 (50)

The median PFS and OS time for the entire cohort were 9.3 and 12.4 months, respectively.

Carfilzomib





Kuhn DJ, et al. *Blood*. 2007;110(9):3281-3290.

blood

2012 120: 2817-2825
Prepublished online July 25, 2012;
doi:10.1182/blood-2012-05-425934

A phase 2 study of single-agent carfilzomib (PX-171-003-A1) in patients with relapsed and refractory multiple myeloma

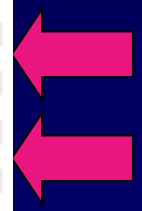
David S. Siegel, Thomas Martin, Michael Wang, Ravi Vij, Andrzej J. Jakubowiak, Sagar Lonial, Suzanne Trudel, Vishal Kukreti, Nizar Bahlis, Melissa Alsina, Asher Chanan-Khan, Francis Buadi, Frederic J. Reu, George Somlo, Jeffrey Zonder, Kevin Song, A. Keith Stewart, Edward Stadtmauer, Lori Kunkel, Sandra Wear, Alvin F. Wong, Robert Z. Orlowski and Sundar Jagannath

- **Progressive disease required at study entry**
- **Relapsed from ≥2 prior lines of therapy**
  Must include BTZ
  Must include THAL or LEN
- **Refractory to last regimen**

Table 1. Baseline demographics and clinical characteristics (N = 266)

Characteristic	Value
Median age, y (range)	63 (37-87)
Male, n (%)	155 (58)
Ethnicity, n (%)	
Black	53 (20)
Asian/Pacific Islander	6 (2)
White	190 (71)
Hispanic	10 (4)
Other	7 (3)
Median time from diagnosis, y (range)	5.4 (0.5-22.3)
Ig class heavy chain, n (%)	
IgG	193 (73)
IgA	45 (17)
IgD	2 (1)
Light chain only or not specified	26 (10)
International Staging System stage, n (%)	
I	76 (29)
II	102 (38)
III	81 (31)
ECOG performance status, n (%)	
0	69 (26)
1	162 (61)
2	35 (13)
Cytogenetic/FISH prognostic markers, n (%)	
Normal/favorable	159 (60)
Unfavorable	75 (28)
Unknown/not done	32 (12)
PN, n (%)*	
0	60 (23)
1	178 (67)
2	28 (11)
Median creatinine clearance, mL/min (range)	70 (16-203)
Median serum β2-microglobulin, mg/L (range)†	4.3 (0.4-20.5)
Prior lines of therapy, median (range)	5 (1-20)
≥ 4, n (%)	217 (82)
Refractory to last regimen	
Progressive disease on therapy	198 (74)
Progressive disease within 60 d	38 (14)
≤ 25% response	16 (6)
Prior agents, median (range)	13 (3-45)
Bortezomib, n (%)‡	265 (99.6)
In most recent prior regimen, n (%)	132 (50)
Immunomodulatory agent, n (%)	266 (100)
Lenalidomide, n (%)	249 (94)
Thalidomide, n (%)	199 (75)
Pomalidomide, n (%)	9 (3)
Corticosteroid, n (%)	261 (98)
Alkylating agent, n (%)	246 (92)
Stem cell transplant, n (%)	198 (74)
Anthracycline, n (%)	171 (64)

*Based on physical assessment at screening (NCI-CTC scale).
†n = 259.
‡One patient who had not received prior bortezomib was enrolled. The deviation from the inclusion criteria was discovered after the patient had initiated treatment.



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

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

Best Overall Responses (n = 257)

	All patients (n = 257)	Patients with unfavorable cytogenetic/ FISH markers (n = 71)
Response category, n (%)		
Complete response	1 (0.4)	0 (0)
Very good partial response	13 (5.1)	3 (4.2)
Partial response	47 (18.3)	18 (25.4)
Minimal response	34 (13.2)	3 (4.2)
Stable disease	81 (31.5)	28 (39.4)
Progressive disease	69 (26.8)	15 (21.1)
Not evaluable	12 (4.7)	4 (5.6)
Overall response, n (%)	61 (23.7)	21 (29.6)
95% CI	18.7-29.4	19.3-41.6
Clinical benefit rate, n (%)	95 (37.0)	24 (33.8)
95% CI	31.1-43.2	23.0-46.0
PFS, median (95% CI), mo	3.7 (2.8-4.6)	3.6 (2.3-4.6)
Median duration of response, mo (95% CI)†	7.8 (5.6-9.2)	6.9 (3.7-8.5)
Mean treatment duration, mo (range)‡	3.0 (0.03-16.9)	3.6 (0-11.1)

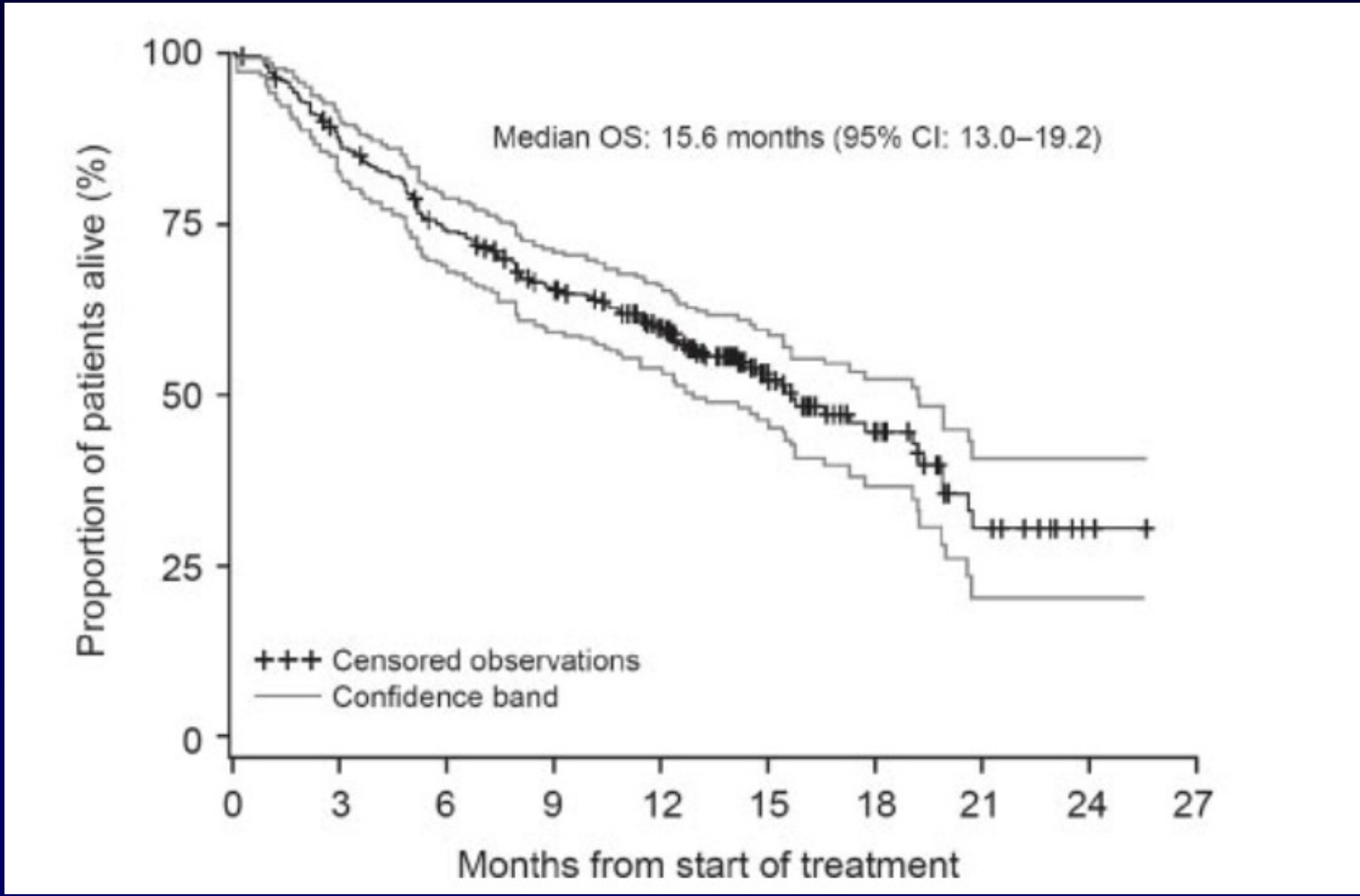
*Response-evaluable population.

†Calculated for patients with partial response or better.

‡Before the opening of the extension study (PX-171-010), individual protocol exceptions were granted for 7 patients to continue receiving treatment beyond 12 cycles.

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

Overall Survival



Overall survival in response-evaluable patients (n = 257) treated with single-agent carfilzomib

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

blood

2012 119: 5661-5670
Prepublished online May 3, 2012;
doi:10.1182/blood-2012-03-414359

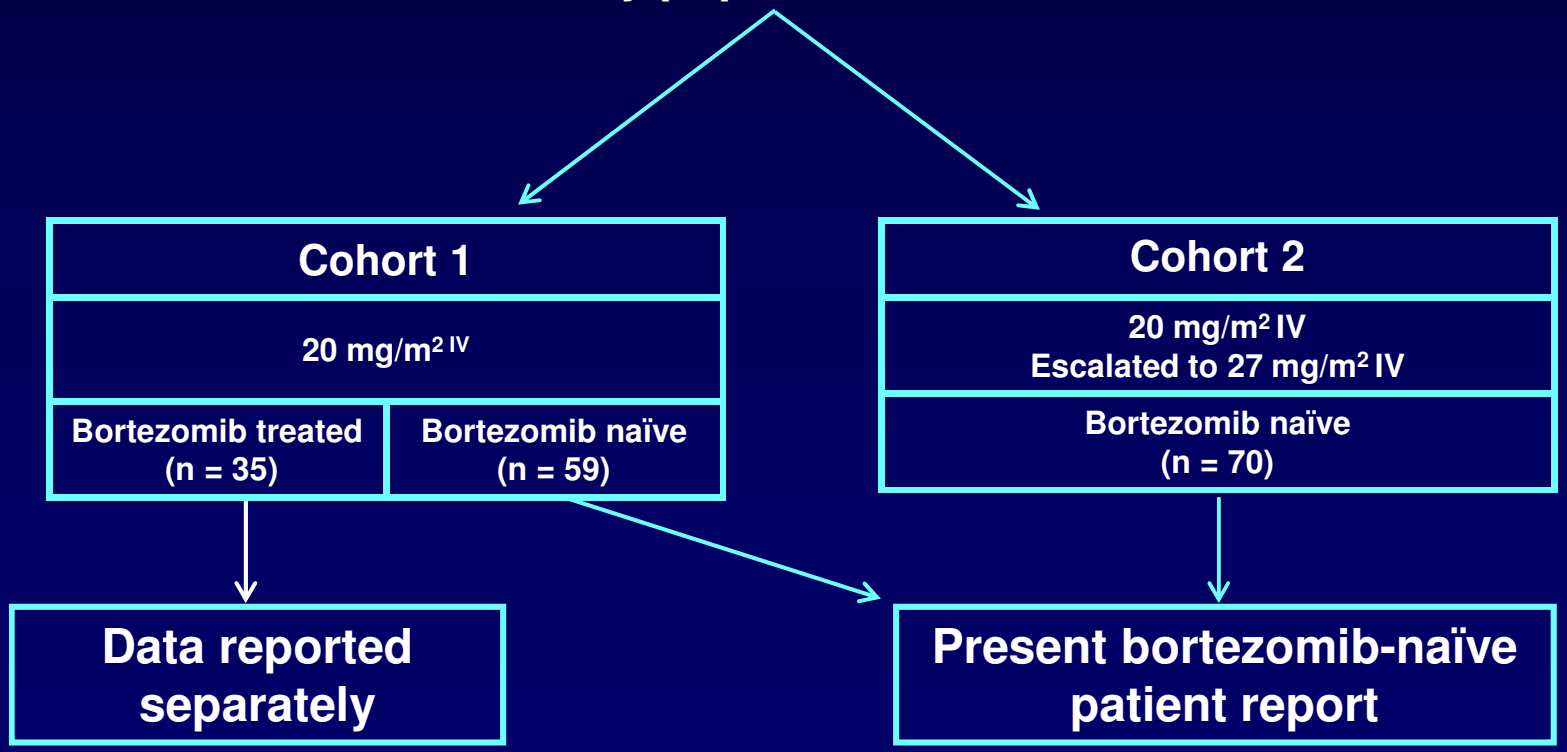
An open-label, single-arm, phase 2 (PX-171-004) study of single-agent carfilzomib in bortezomib-naive patients with relapsed and/or refractory multiple myeloma

Ravi Vij, Michael Wang, Jonathan L. Kaufman, Sagar Lonial, Andrzej J. Jakubowiak, A. Keith Stewart, Vishal Kukreti, Sundar Jagannath, Kevin T. McDonagh, Melissa Alsina, Nizar J. Bahlis, Frederic J. Reu, Nashat Y. Gabrail, Andrew Belch, Jeffrey V. Matous, Peter Lee, Peter Rosen, Michael Sebag, David H. Vesole, Lori A. Kunkel, Sandra M. Wear, Alvin F. Wong, Robert Z. Orlowski and David S. Siegel

PX-171-004 Study Schema

- Measurable multiple myeloma
- ECOG performance status 0-2
- Responsive to ≥1 line of prior therapy
- Relapsed and/or refractory following 1-3 prior treatment regimens

PX-171-004 (NCT00530816)
Study population = 164



Vij R, et al. *Blood.* 2012;119(24):5661-5670.

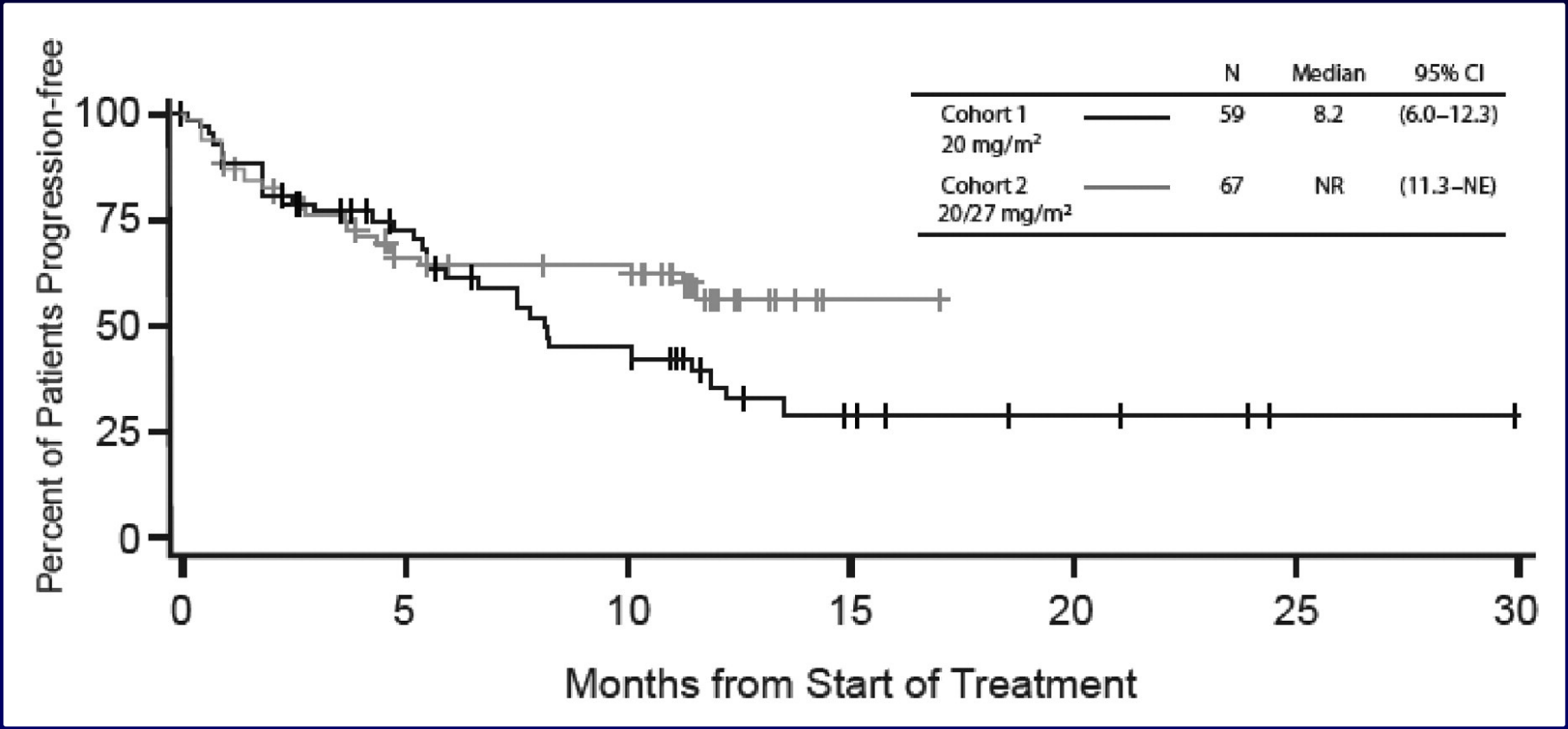
Response Rate After 6 Cycles of Treatment in Response-Evaluable Poulation (N = 126)

	Cohort 1 20 mg/m^2 N = 59	Cohort 2 20/27 mg/m^2 N = 67	Total N = 126
Best response, n (%)			
CR	2 (3.4)	1 (1.5)	3 (2.4)
VGPR	8 (13.6)	18 (26.9)	26 (20.6)
PR	15 (25.4)	16 (23.9)	31 (24.6)
MR	10 (16.9)	8 (11.9)	18 (14.3)
SD	13 (22.0)	10 (14.9)	23 (18.3)
PD	7 (11.9)	11 (16.4)	18 (14.3)
ORR (CR + VGPR + PR)	25 (42.4)	35 (52.2)	60 (47.6)
95% CI*	29.6 – 55.9	39.7 – 64.6	38.7 – 56.7
CBR (ORR + MR)	35 (59.3)	43 (64.2)	78 (61.9)
95% CI*	45.7 – 71.9	51.5 – 75.5	52.8 – 70.4

*Exact 95% CI for ORR and CBR rate.

Vij R, et al. *Blood.* 2012;119(24):5661-5670.

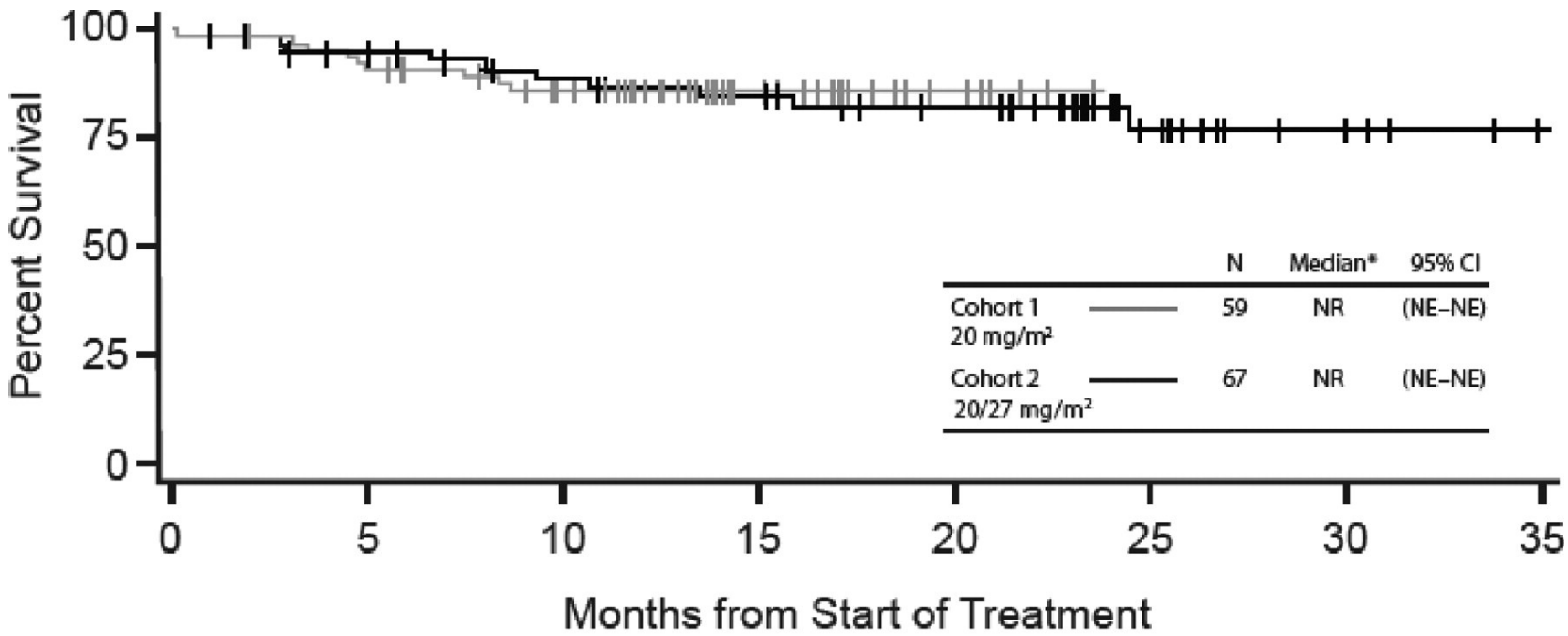
Progression-Free Survival for Cohorts 1 and 2



NR, not reached; NE, not estimable

Vij R, et al. *Blood.* 2012;119(24):5661-5670.

Overall Survival for Cohorts 1 and 2



NR, not reached; NE, not estimable

Vij R, et al. *Blood.* 2012;119(24):5661-5670.

FOCUS Phase III

Randomized

Relapsed / refractory MM

Progression on last therapy

Prior exposure to IMids, bortezomib

Carfilzomib vs Best Supportive Care

ENDEAVOR Phase III

Randomized

Relapsed / refractory MM (1-3 prior lines of therapy)

Bortezomib-dex vs carfilzomib (56mg/m^2)-dex

Until progression

Phase III ASPIRE Trial

Randomized 1:1

N = 700

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

CRd

- Carfilzomib 27 mg/m2 IV day 1, 2, 8, 9, 15, and 16 (20 mg/m2 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

MLN9708 Oral Single-Agent, Relapse

	N	Phase	Findings	ORR	
MLN9708 Weekly (Kumar Abs 816)	32	Phase I, dose escalation (D1, 8, 15; cycle 28 days up to 12 cycles)	Median 6 lines ttt (97% BTZ, 91% LEN) 56% refractory MTD 2.97 mg/m²	18 evaluable pts 1 VGPR, 1 PR, 8 SD	MTD defined Rash Tolerance OK Efficacy in heavily pretreated
MLN9708 Bi-weekly (Richardson Abs 301)	56	Phase I, dose escalation (26 pts), Expansion cohort (30 pts) (D1, 4, 8, 11 21-day cycles, up to 12 cycles)	Median 6 lines ttt (100% BTZ) 52% refractory MTD: 2 mg/m² No periph neuropathy	46 evaluable pts 6 ≥ PR (1 CR, 5 PR) 1 minim resp	MTD defined Rash Tolerance OK Efficacy in heavily pretreated

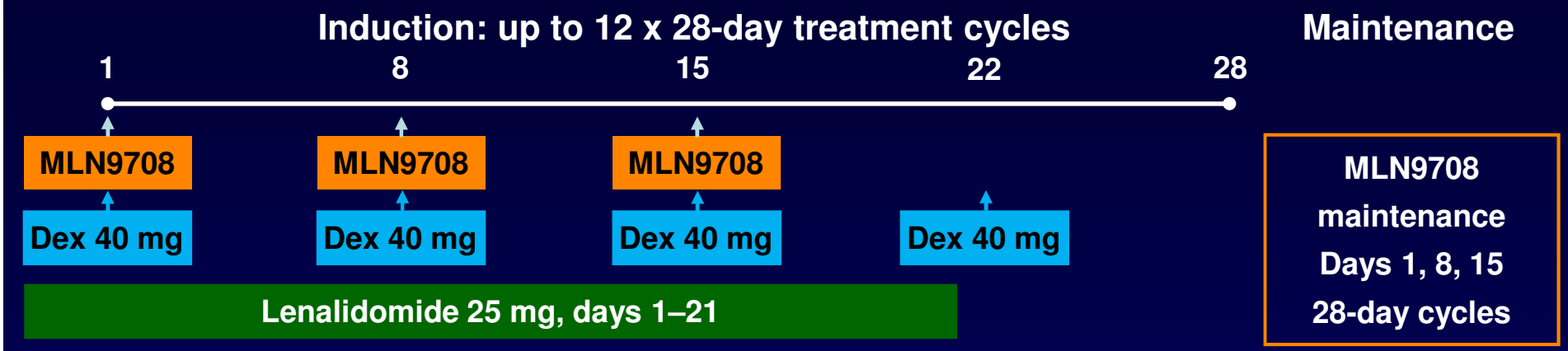
Kumar S, et al. *Blood.* 2011;118: Abstract 816; Richardson PG, et al. *Blood.* 2011;118: Abstract 301.

Phase 1/2 Study of Weekly MLN9708, an Investigational Oral Proteasome Inhibitor, in Combination With Lenalidomide and Dexamethasone in Patients With Previously Untreated Multiple Myeloma

Kumar SK, Berdeja JG, Niesvizky R, Lonial S, Hamadani M, Stewart AK, Roy V, Hari P, Vescio R, Berg D, Lin J, Di Bacco A, Estevam J, Gupta N, Hui A-M, Richardson PG

Kumar S, et al. *Blood.* 2012;120: Abstract 332.

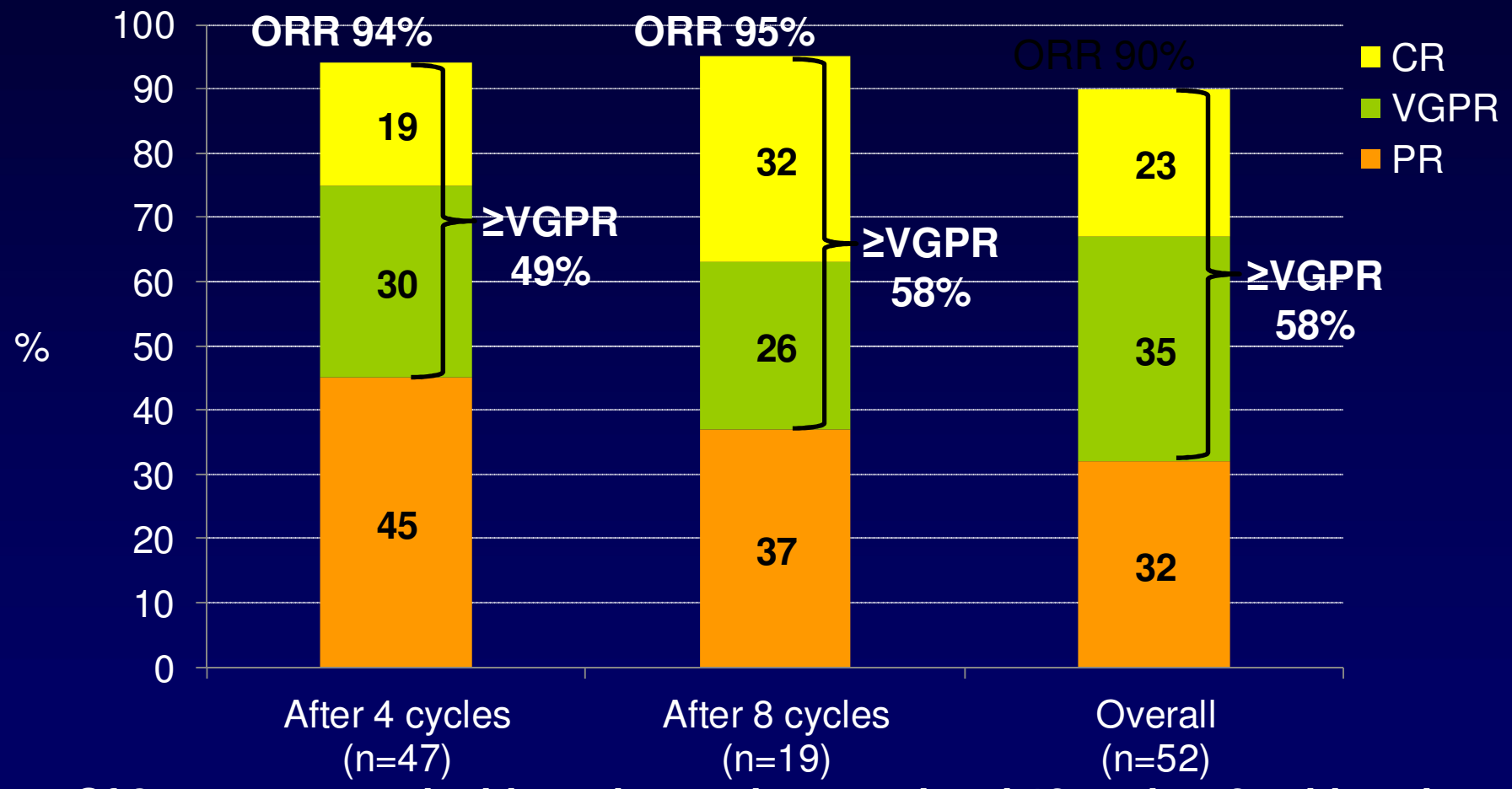
Study Design



- Phase I: oral MLN9708 dose escalation
  - Standard 3 + 3 schema, 33% dose increments, based on cycle 1 dose-limiting toxicities (DLTs)
- Phase II: oral MLN9708 at the RP2D from phase I
- Stem cell collection allowed after 3 cycles, with autologous stem cell transplantation (ASCT) deferred until after 6 cycles
- MLN9708 maintenance continued until progression or unacceptable toxicity
- Mandatory thromboprophylaxis with aspirin or low-molecular-weight heparin

Kumar S, et al. *Blood.* 2012;120: Abstract 332.

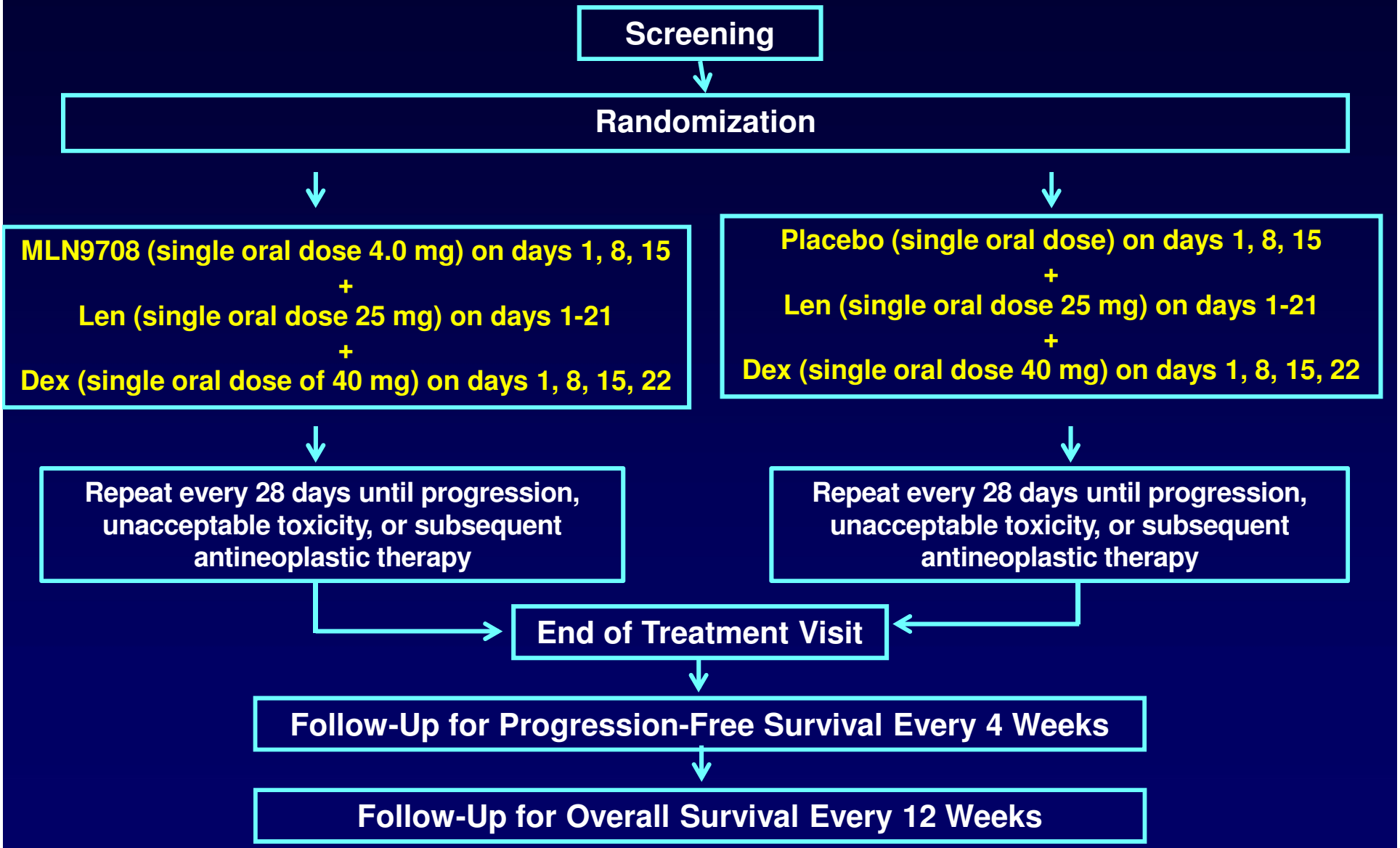
Preliminary Response Data Over Course of Treatment – Patients Treated at RP2D (2.23 mg/m^2 / 4.0 mg)



- **Of 3 response-evaluable patients who completed 12 cycles, 2 achieved CR and 1 VGPR**

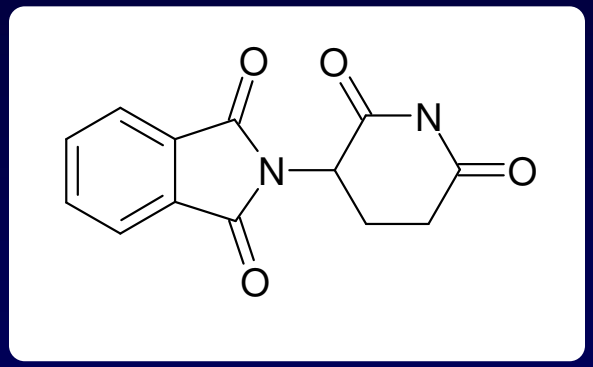
Kumar S, et al. *Blood.* 2012;120: Abstract 332.

Study Overview / Tourmaline

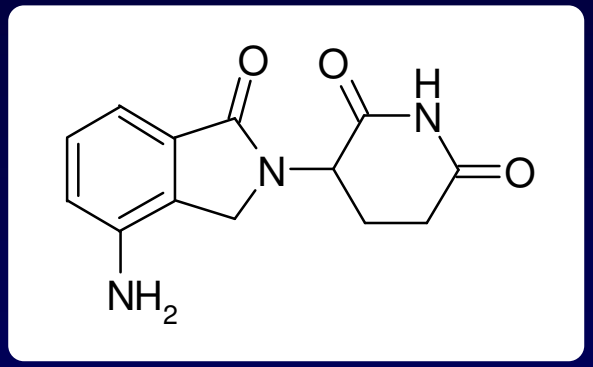


ISS, International Staging System

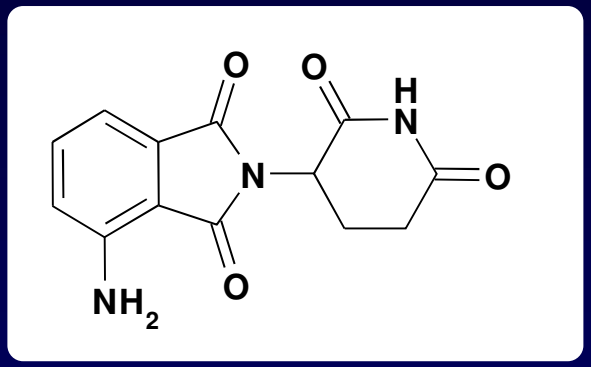
Molecular Structure of Thalidomide, Lenalidomide and Pomalidomide



Thalidomide
100-200 mg/d
Neuropathy
Constipation
Sedation
DVT



Lenalidomide
15-25 mg/d
Myelosuppression
Skin rash
DVT



Pomalidomide
1-4 mg/d

Structurally similar, but functionally different both qualitatively and quantitatively

Leukemia (2010) 24, 1934–1939

www.nature.com/leu

ORIGINAL ARTICLE

Pomalidomide (CC4047) plus low dose dexamethasone (Pom/dex) is active and well tolerated in lenalidomide refractory multiple myeloma (MM)

MQ Lacy[1], SR Hayman[1], MA Gertz[1], KD Short[1], A Dispenzieri[1], S Kumar[1], PR Greipp[1], JA Lust[1], SJ Russell[1], D Dingli[1], S Zeldenrust[1], R Fonseca[2], PL Bergsagel[2], V Roy[3], JR Mikhael[2], AK Stewart[2], K Laumann[4], JB Allred[4], SJ Mandrekar[4], SV Rajkumar[1] and F Buadi[1]

Confirmed response rate[a,b]	32% (95% CI: 19-53)
Confirmed response rate[a]	32% (95% CI: 17-51)
No. of responders[a]	11
VGPR	2
PR	9
MR	4
Best response	
VGPR	3 (9%)
PR	8 (23%)
MR	5 (15%)
SD	12 (35%)
PD	6 (18%)
Median time to response[a]	2.0 mo (range: 0.7 – 3.9)
Duration of response[a,c]	9.1 mo (95% CI: 6.5 – NA)
Overall survival[c]	13.9 mo (95% CI: NA)
Progression-free survival[c]	4.8 mo (95% CI: 2.7 – 10.1)

[a]Does not include MR per study; [b]Study design uses the first 32 patients; [c]Kaplan-Meier method

Lacy MQ, et al. *Leukemia.* 2010;24(11):1934-1939.

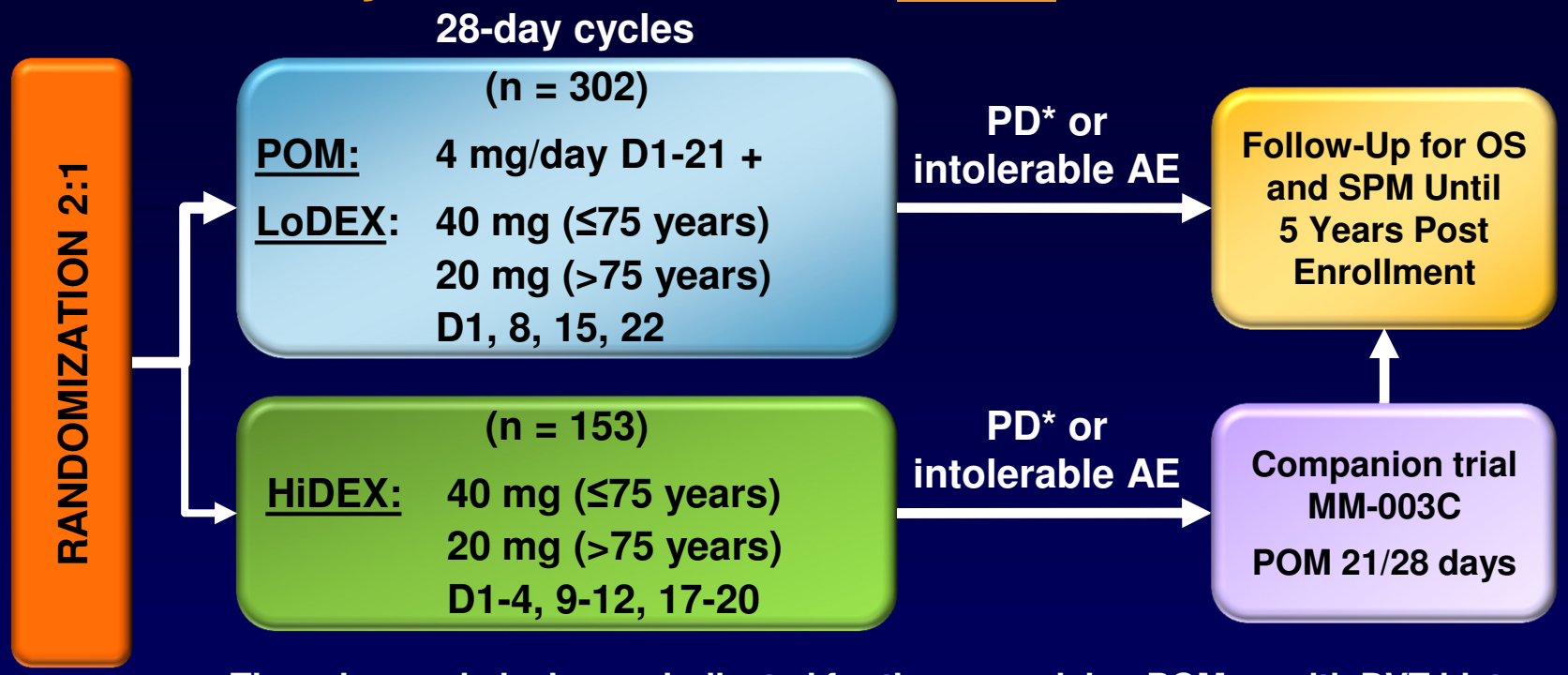
Pomalidomide in Combination With Low-Dose Dexamethasone Demonstrates a Significant Progression Free Survival and Overall Survival Advantage, in Relapsed/Refractory MM: A Phase 3, Multicenter, Randomized, Open-Label Study

Dimopoulos MA, Lacy MQ, Moreau P, Weisel KC, Song KW, Delforge M, Karlin L, Goldschmidt H, Banos A, Oriol A, Yu X, Sternas L, Jacques CJ, Zaki M, San Miguel JF

Dimopoulos MA, et al. *Blood.* 120: Abstract LBA6.

MM-003 Design: POM + 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 years vs >75 years)
- Number of prior Tx (2 vs >2)
- Disease status (refractory vs relapsed and refractory vs refractory and intolerant [BORT only])

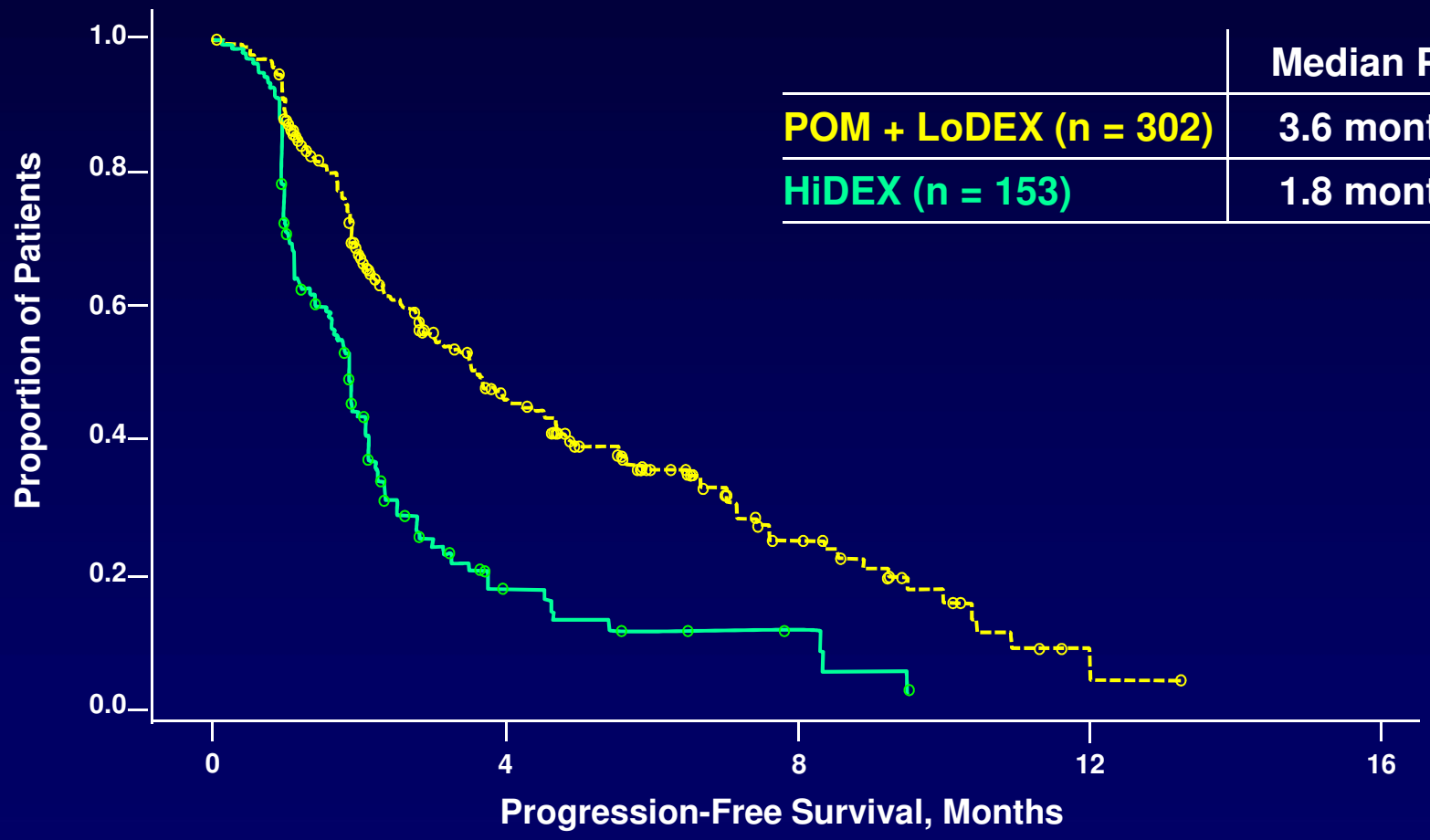
Progression of disease was independently adjudicated in real-time

AE, adverse event; DVT, deep vein thrombosis; HiDEX, high-dose dexamethasone; OS, overall survival; PD, progressive disease; POM, pomalidomide; RRMM, relapsed/refractory multiple myeloma; SPM, second primary malignancy; Tx, treatment

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

MM-003: Progression-Free Survival

ITT Population

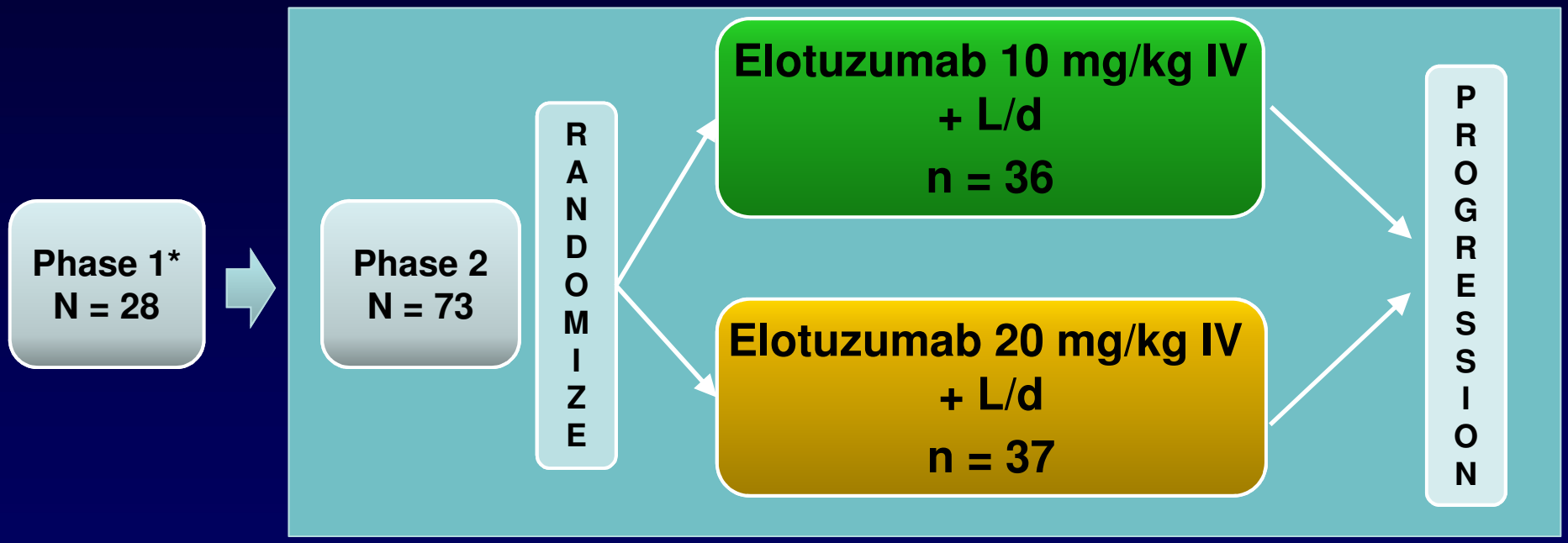


	Median PFS
POM + LoDEX (n = 302)	3.6 months
HiDEX (n = 153)	1.8 months

Based on adjudicated data; IMWG criteria

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

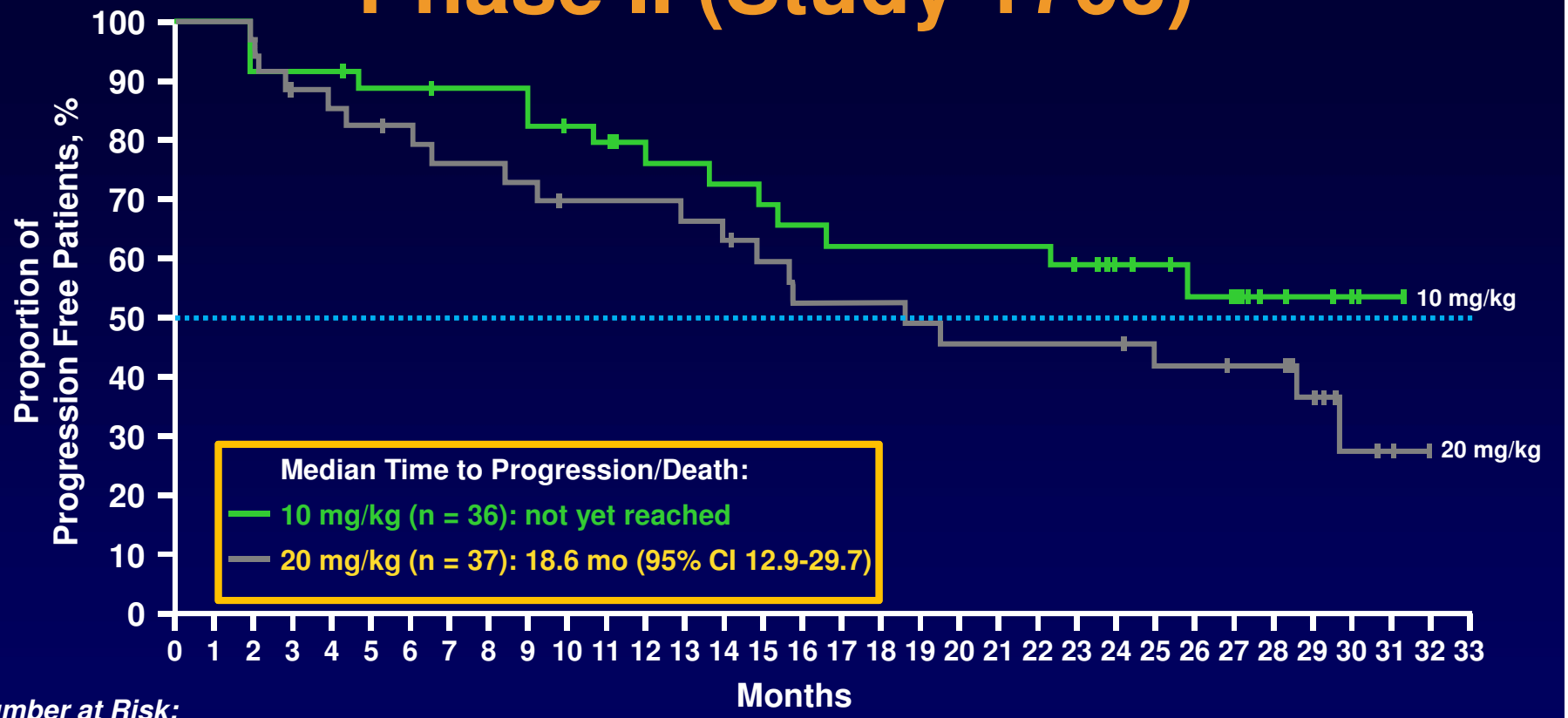
Elotuzumab + Lenalidomide/ Low-Dose Dex – Phase II



- Phase II: Patients (n = 73) with relapsed and/or refractory MM with 1-3 prior therapies were randomized to elotuzumab 10 or 20 mg/kg IV combined with
  - Lenalidomide 25 mg PO
  - Low-dose dexamethasone 40 mg PO

L/d = lenalidomide plus low dose dexamethasone
*Lonial S et al. *J Clin Oncol.* 2012;30(16):1953-1959.

Progression Free Survival Phase II (Study 1703)



Number at Risk:

36	*32*	*30*	*29*	*23*	*20*	*18*	*18*	*13*	*9*	*3*	*0*
37	*29*	*26*	*23*	*21*	*17*	*15*	*13*	*13*	*10*	*3*	*0*

At a median follow-up of 20.8 mo, median PFS has not been reached in the 10 mg/kg arm

– In the abstract, a preliminary median PFS of 26.9 mo was reported; however, no disease progression/death has been reported since then; continued maturation of the results has increased the number of patients at risk post the preliminary median PFS (in the denominator). Therefore, in this updated dataset the median has not been crossed

Lonial S, et al. *Blood.* 2011;118: Abstract 303; updated data.

ELOQUENT 2 Trial :

Len-dex vs Len-dex + elotuzumab
Primary endpoint : PFS

Pivotal phase III trial for approval of elotuzumab

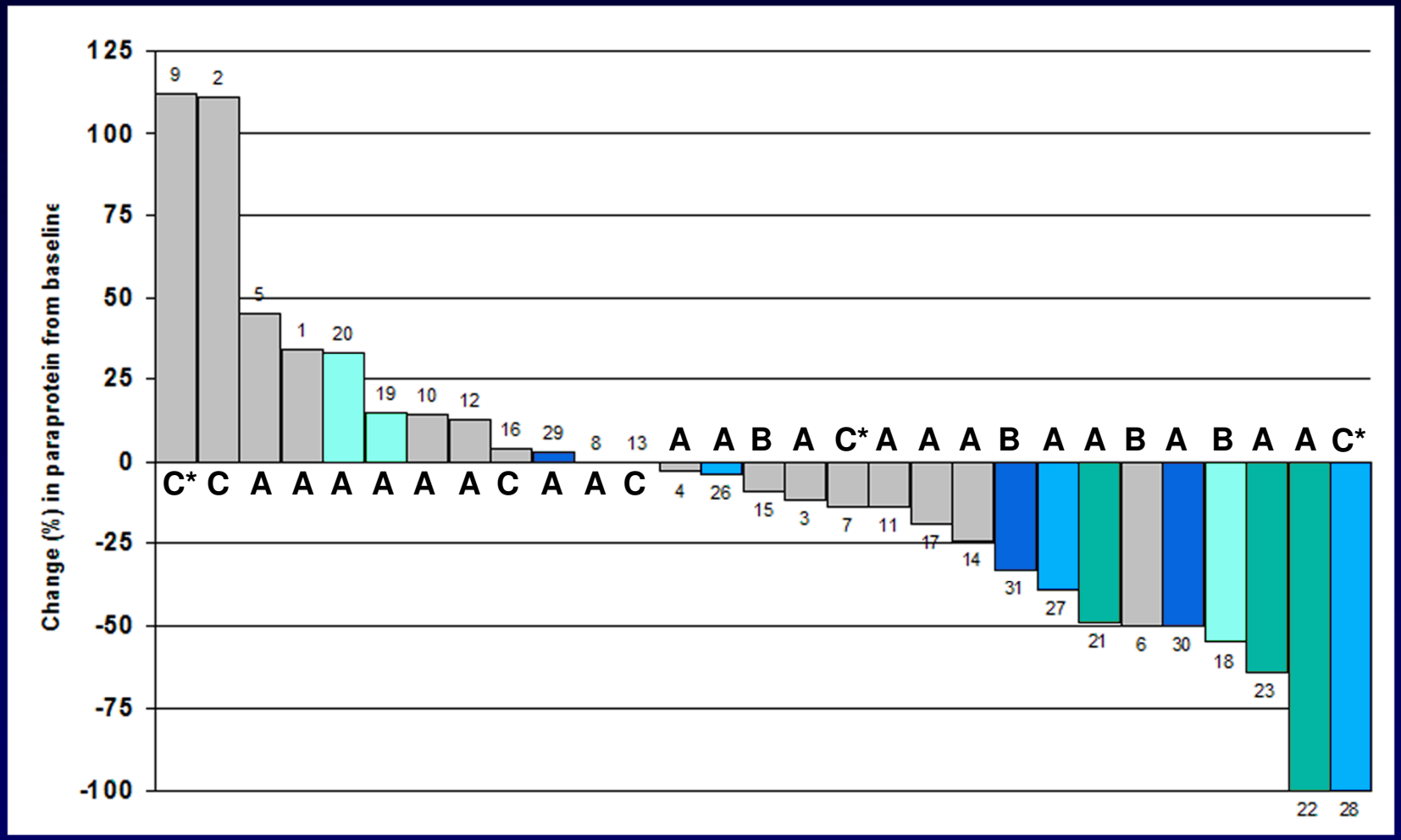
Daratumumab, a CD38 Monoclonal Antibody in Patients With Multiple Myeloma — Preliminary Efficacy and Pharmacokinetics Data From a Dose-Escalation Phase I/II Study

Lokhorst H, Gimsing P, Nahi H, Richardson P, Lisby S, Plesner T

Lokhorst H, et al. *Haematologica.* 2012;97(Suppl 1): Abstract 1143.

Maximal Change in Paraprotein

A: serum M-component → B: urine M-component → C: FLC



• Data at baseline below limits for measurable disease

Results are before database lock

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

PANORAMA 1

PANobinostat ORAl in Multiple myelomA

Pivotal Phase III Study: D2308

A multicenter, randomized, double-blind, placebo-controlled phase III study of panobinostat in combination with bortezomib and dexamethasone in patients with relapsed multiple myeloma

Conclusions

- Promising results using triplet combinations with novel agents: lenalidomide, bortezomib-based
- Other drugs: bendamustine, carfilzomib, pomalidomide, MoAb, HDAC inhibitors, oral PI…
  - High response rates; possibility of new strategies
- MM : « chronic disease », « maintenance »

!! Don't forget to enroll patients in clinical trials !!