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Current management of relapsed&refractory multiple myeloma

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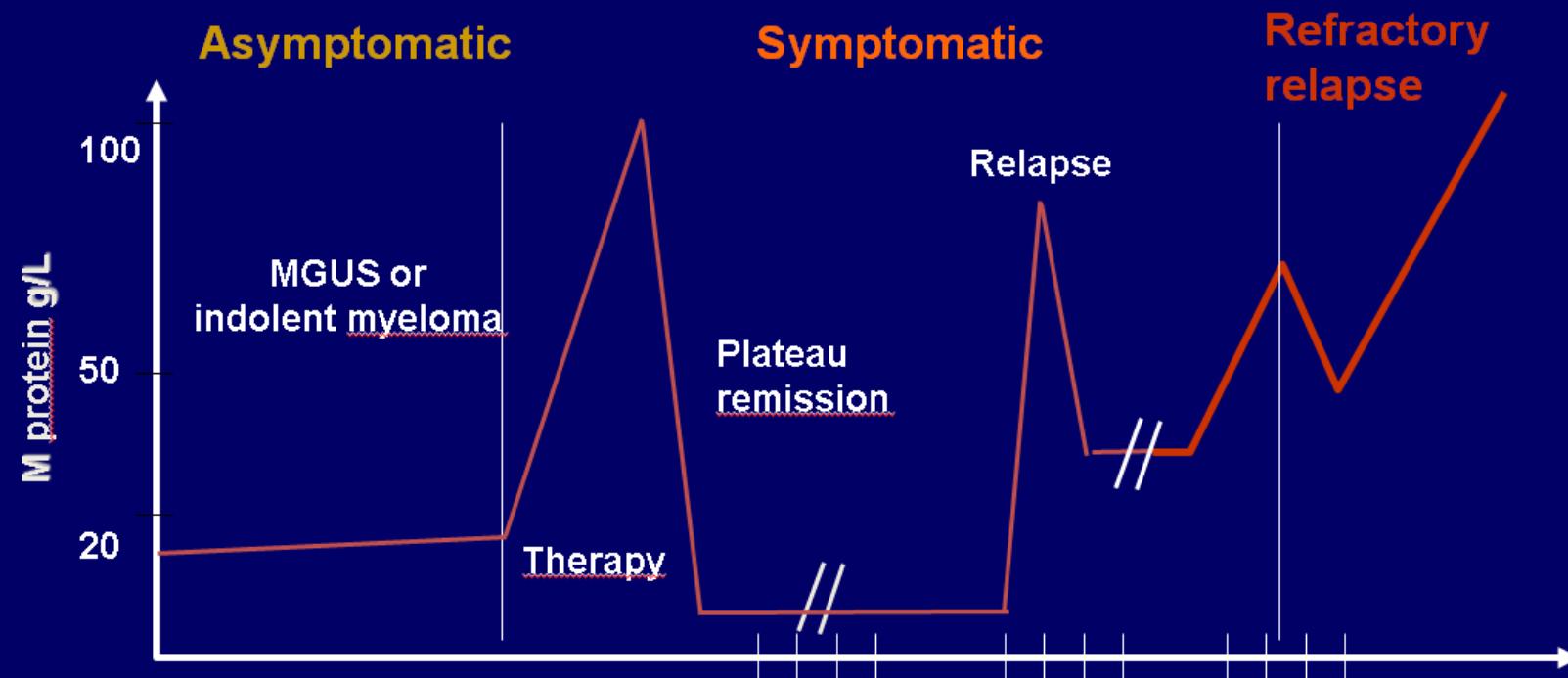
Tallinn, 19th October 2017

Disclosures Michel Delforge

- consultancy: Amgen, BMS, Celgene, Janssen, Takeda
- research grants (institution): Celgene, Janssen

An inconvenient truth about myeloma

The vast majority of patients will relapse



When to start treatment: biochemical versus clinical relapse

Progressive disease^a

To be used for calculation of time to progression and progression-free survival end points for all patients including those in CR (includes primary progressive disease and disease progression on or off therapy)

Progressive Disease: requires any one or more of the following:

Increase of $\geq 25\%$ from baseline in

Serum M-component and/or (the absolute increase must be $\geq 0.5 \text{ g/dl}$)^b

Urine M-component and/or (the absolute increase must be $\geq 200 \text{ mg/24h}$)

Only in patients without measurable serum and urine M-protein levels: the difference between involved and uninvolved FLC levels. The absolute increase must be $> 10 \text{ mg/dl}$.

Bone marrow plasma cell percentage: the absolute % must be $\geq 10\%$ ^c

Definite development of new bone lesions or soft tissue plasmacytomas or definite increase in the size of existing bone lesions or soft tissue plasmacytomas

Development of hypercalcemia (corrected serum calcium $> 11.5 \text{ mg/dl}$ or 2.65 mmol/l) that can be attributed solely to the plasma cell proliferative disorder

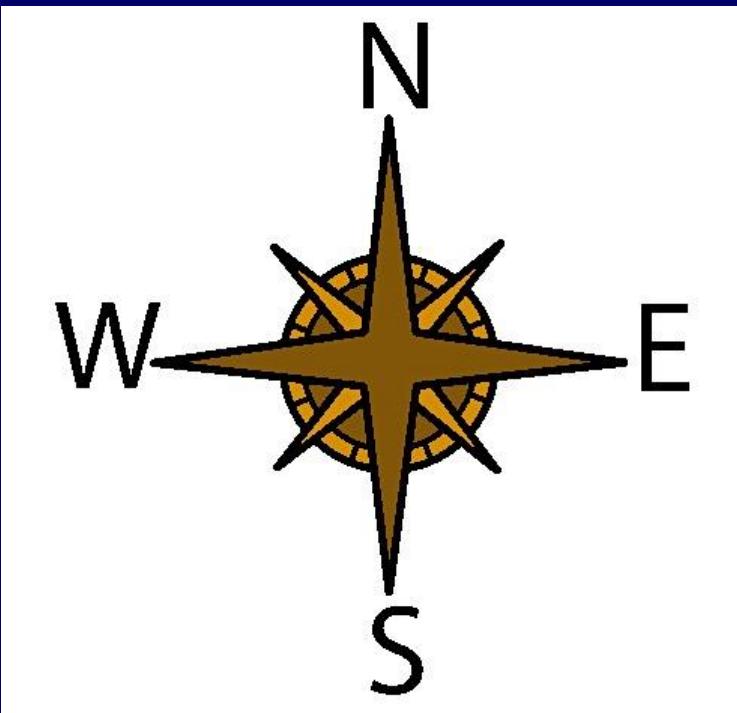
International Myeloma Working Group Uniform Response Criteria
Leukemia 2006;20:1467

for a biochemical
progression/relapse without
symptoms a careful ‘watch and
wait’ approach is justified

Therapeutic choice for MM relapse requires an ‘holistic’ approach

Disease-related Factors

*Type of relapse, cytogenetic risk,
extramedullary disease*



Efficacy and toxicity of
previous treatments

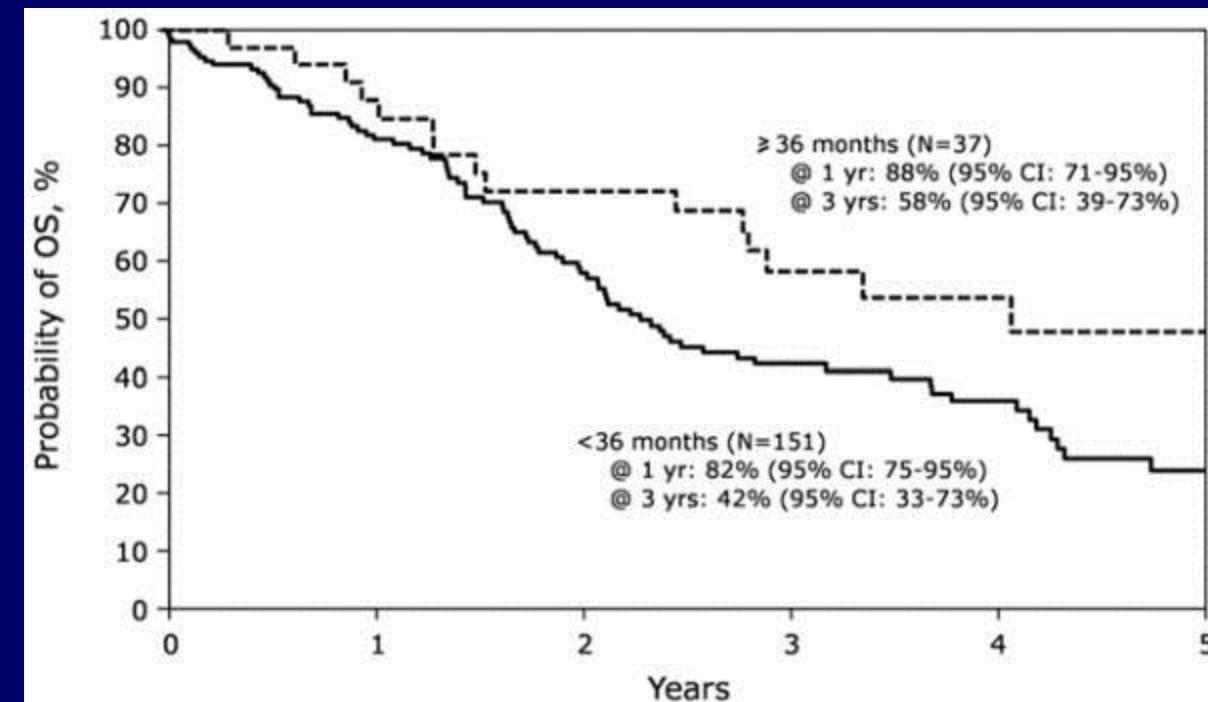
Patient-related factors
(Age, transplant eligibility,
comorbidities, frailty)

Available therapeutic options

What is the role of a second autograft ?

Report From the Center for International Blood and Marrow Transplant Research

- n=187
- Median time between ASCT I & II: 32 months (in 69% > 24 months)
- Median follow up after ASCT II: 47 months



- Second ASCT at relapse is feasible
- Best outcome observed in later relapses (>36 months from ASCT I)

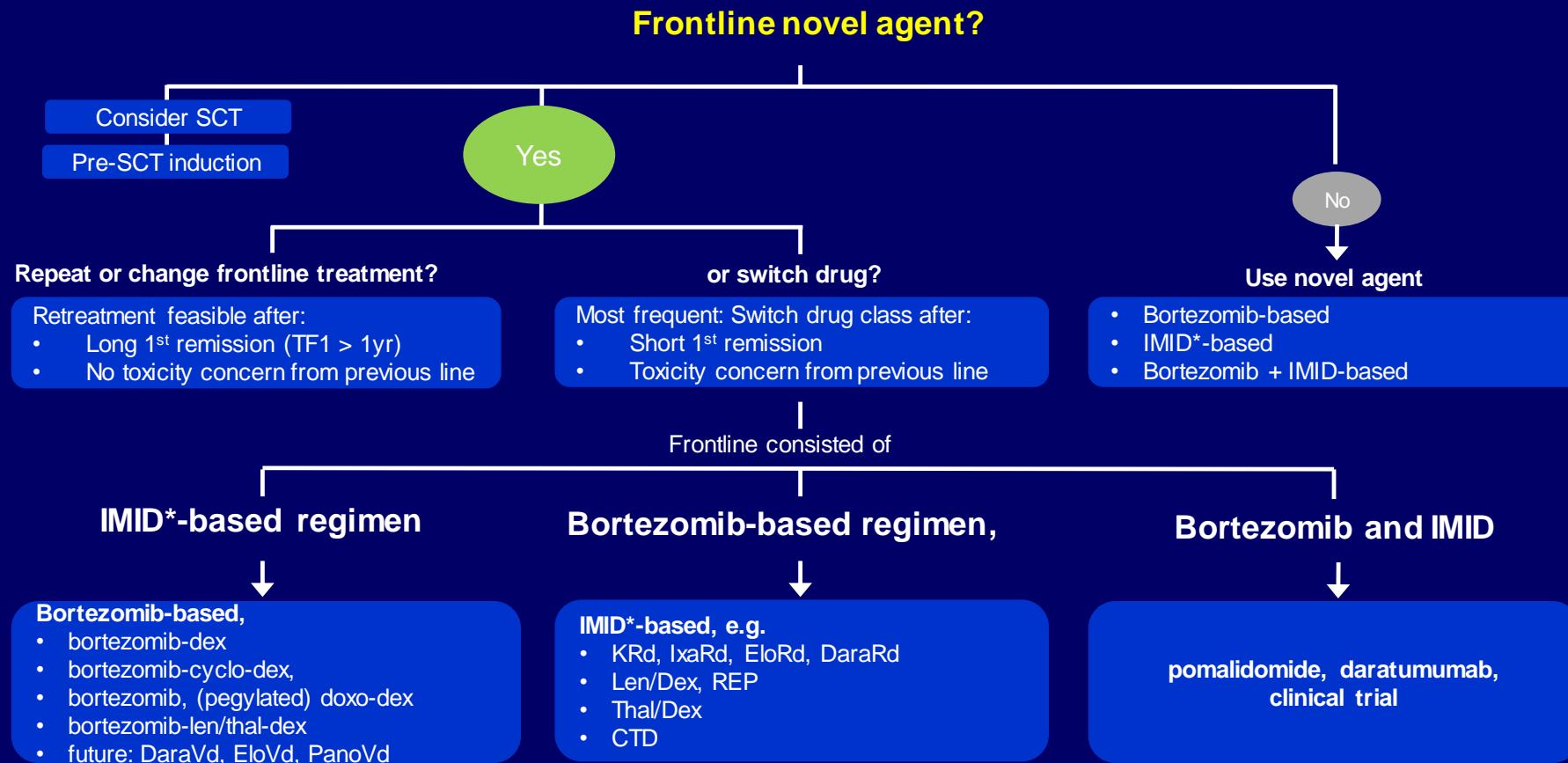
Is there still a role for allogeneic transplantation ?

Reduced intensity-conditioned allogeneic stem cell transplantation for multiple myeloma relapsing or progressing after autologous transplantation: a study by the European Group for Blood and Marrow Transplantation

Outcomes and prognostic factors of reduced intensity-conditioned allo-SCT (RIC allo-SCT) for multiple myeloma (MM) relapsing or progressing after prior autologous (auto)-SCT are not well defined. We performed an analysis of 413 MM patients who received a related or unrelated RIC allo-SCT for the treatment of relapse/progression after prior auto-SCT. Median age at RIC allo-SCT was 54.1 years, and 44.6% of patients had undergone two or more prior auto-SCTs. Median OS and PFS from the time of RIC allo-SCT for the entire population were 24.7 and 9.6 months, respectively. Cumulative non-relapse mortality (NRM) at 1 year was 21.5%. In multivariate analysis, CMV seronegativity of both patient and donor was associated with significantly better PFS, OS and

RIC should be reserved for young and (ultra) high-risk myeloma patients at first sensitive relapse

Relapsed multiple myeloma: classical treatment algorithm for first relapse



adapted from Sonneveld P and Broiji A. Haematologica 2016. 101(4): 396-406

Overview of proteasome inhibitors

Drug	Class	Proteasomal target			reversibility	Route of administration	Frequency of dosing
		caspase	trypsin	chymotrypsin			
Bortezomib ¹ (PS-341)	boronic acid	X		X	reversible	IV/SC	days 1,4,8,11/21d
Ixazomib ² (MLN-9708)	boronic acid	X		X	reversible	oral	once per week
Carfilzomib ³ (PR-171)	epoxyketone			X	irreversible	IV	days 1,2,8,9,15,16/28d
Oprozomib ⁴ (ONX-0912)	epoxyketone			X	irreversible	oral	daily
Marizomib ⁵ (NPI-0052)	salinospore	X	X	X	irreversible	IV	days 1,4,8,11/21d

1. Richardson et al. New Engl J Med 2003;344:8:26
2. Kumar et al. Lancet Oncol 2014;15:1503
3. Siegel et al. Blood 2012;120:2817
4. Chauhan et al. Blood 2012;116:4904
5. Richardson et al. Blood 2016;127:2693

Bortezomib + dex versus bortezomib as second line-treatment: Retrospective matched-pairs analysis

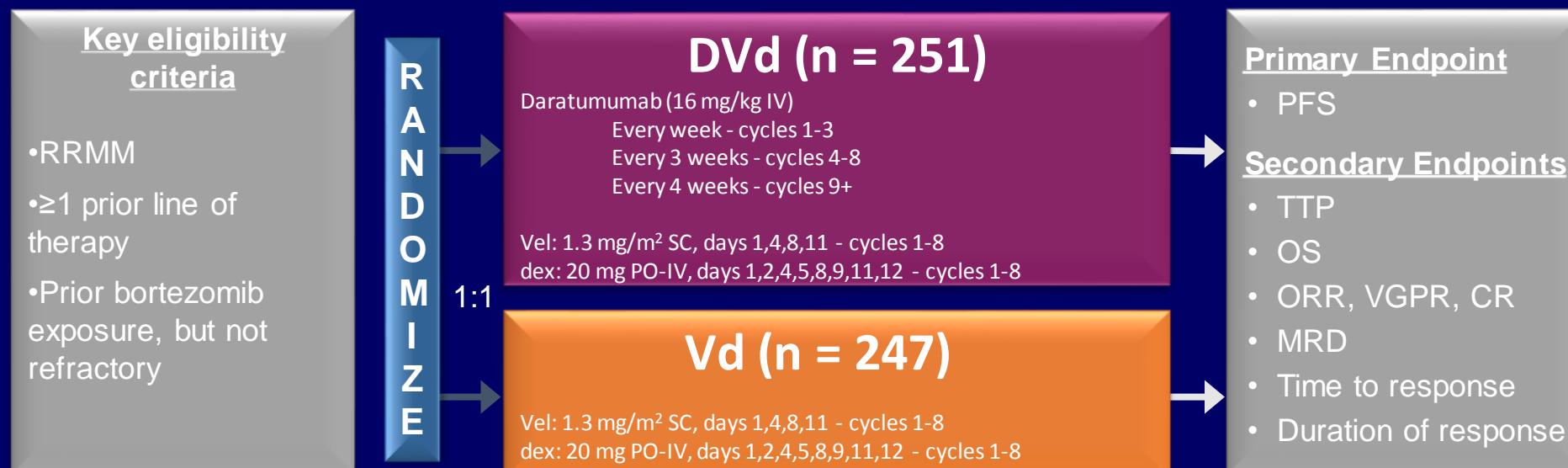
- Patients (n=218)
 - Patient-level data from 3 studies
 - Patients treated with bortezomib-dex in phase 2 MMY-2045 study¹
 - Patients randomized to single-agent bortezomib in
 - phase 3 APEX (bortezomib vs high-dose dex)²
 - phase 3 DOXIL-MMY-3001 (bortezomib +/- Doxil)³

	bortezomib+dexa	bortezomib	p-value
TTP	13.6 mo	7.0 mo	0.003
PFS	11.9 mo	6.4 mo	0.051
Overall response	75%	62.2%	< 0.001

1. Dimopoulos et al. Haematologica 2013;98:1264-72
2. Richardson et al. NEJM 2005;352:2487-98
3. Orlowski et al. JCO 2007;25:3892-901

Bortezomib plus daratumumab (CASTOR): study design

Multicenter, randomized, open-label, active-controlled phase 3 study



- Cycles 1-8: repeat every 21 days
- Cycles 9+: repeat every 28 days

Statistical analyses

- 295 PFS events: 85% power for 4.3 month PFS improvement
- Interim analysis: ~177 PFS events

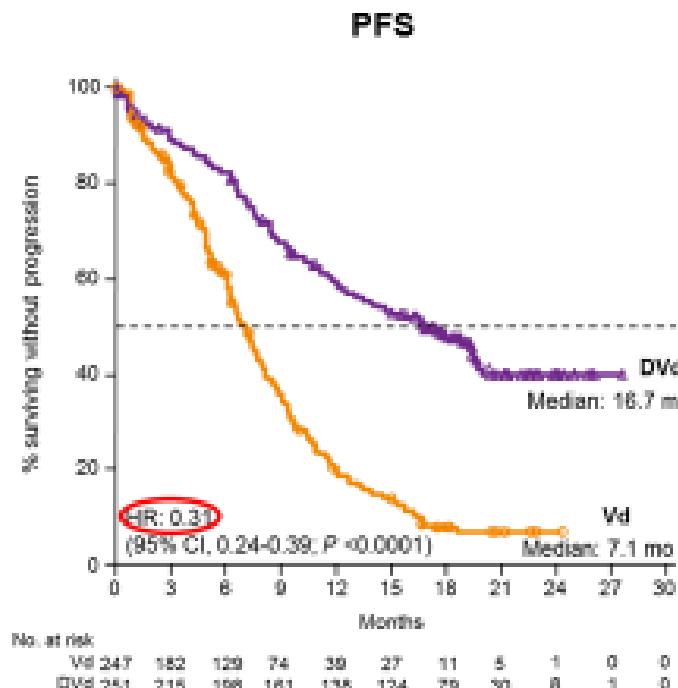
Daratumumab IV administered in 1000 mL to 500 mL; gradual escalation from 50 mL to 200 mL/hour permitted

RRMM, relapsed or refractory multiple myeloma; DVd, daratumumab/bortezomib/dexamethasone; IV, intravenous; Vel, bortezomib; SC, subcutaneous; dex, dexamethasone; PO, oral; Vd, bortezomib/dexamethasone; PFS, progression-free survival; TTP, time to progression; ORR, overall response rate; VGPR, very good partial response; CR, complete response; MRD, minimal residual disease.

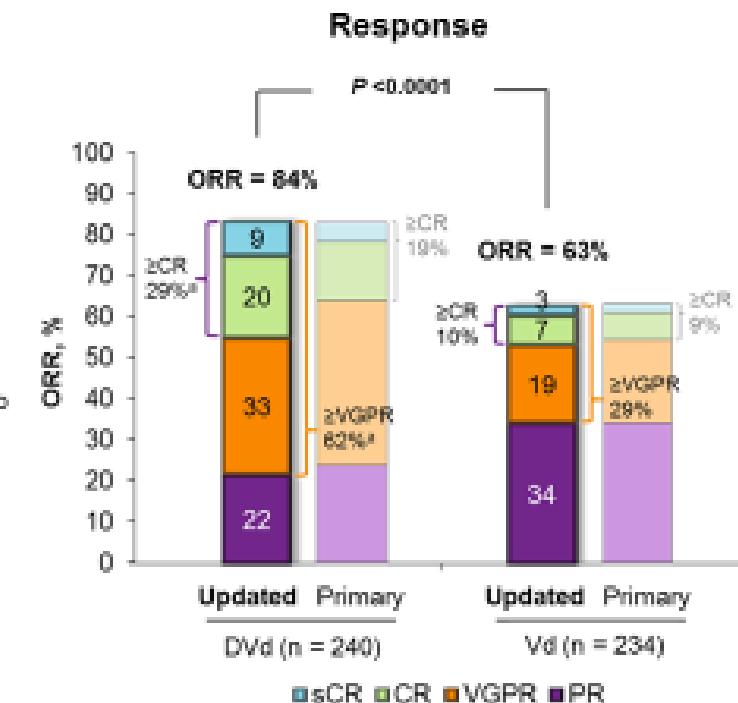
CASTOR: Dara-Vd (DVd) vs Vd

updated progression-free survival

CASTOR update: ITT



- Median follow-up: 19.4 months



69% reduction in risk of progression for DVd vs Vd
9.6-month improvement in median PFS for DVd vs Vd
Responses continue to deepen

CI, confidence interval; HR, hazard ratio; PR, partial response; sCR, stringent

complete response; VGPR, very good partial response.

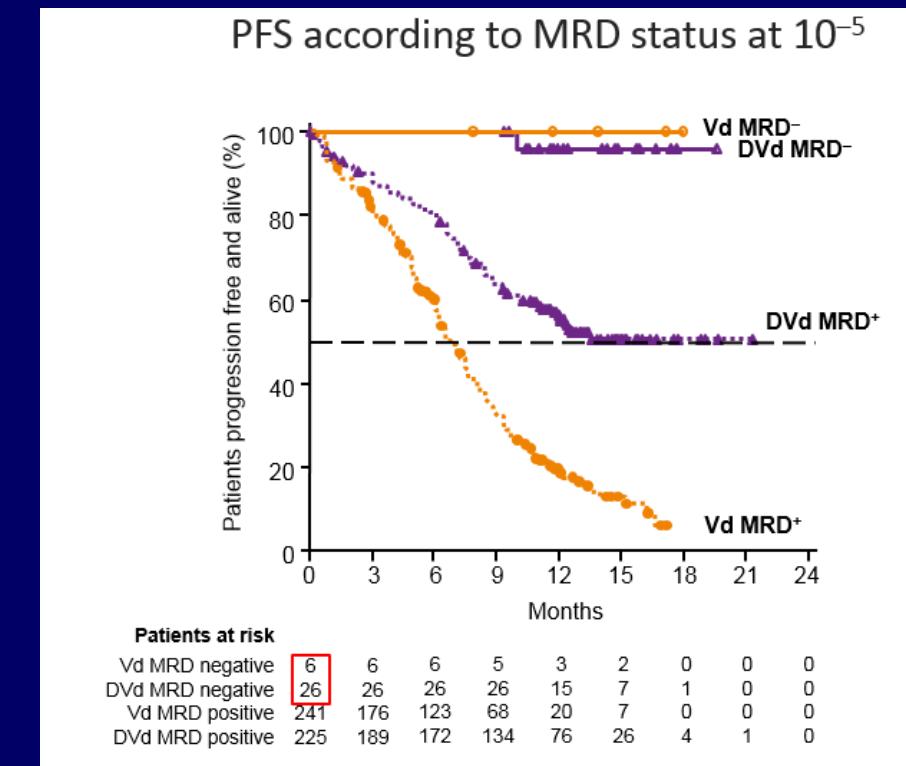
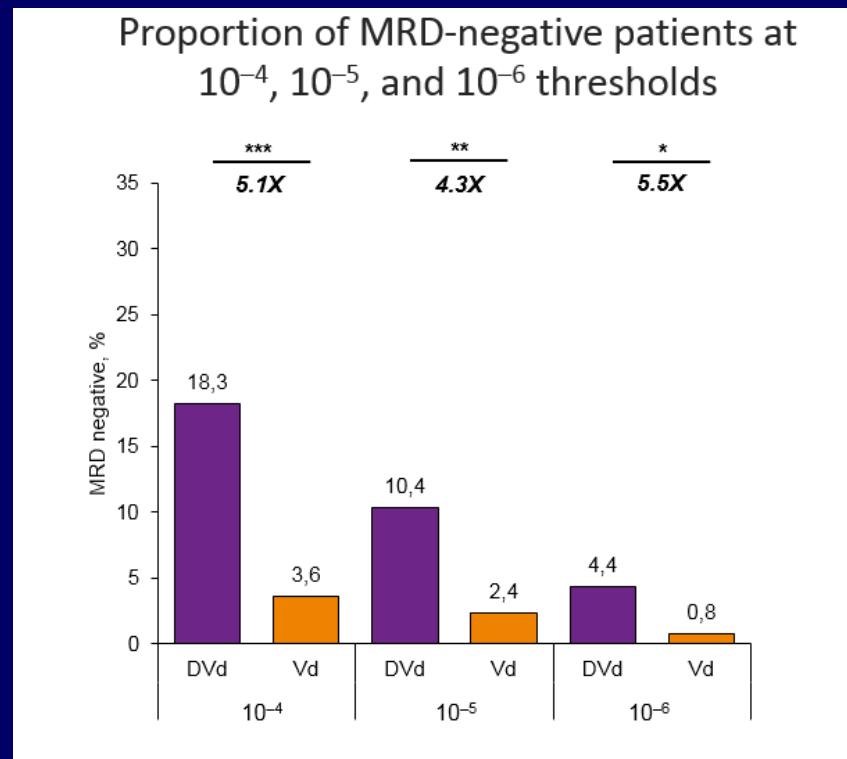
1. Palumbo A, et al. N Engl J Med 2016; 375(8):754-765.

$P < 0.0001$ for DVd vs Vd.

NB: Primary analysis based on median follow-up of 7.4 months¹

Weisel K, et al. Presented at EHA 2017 (Abstract S459), oral presentation.

CASTOR: Dara-Vd (DVd) vs Vd MRD status

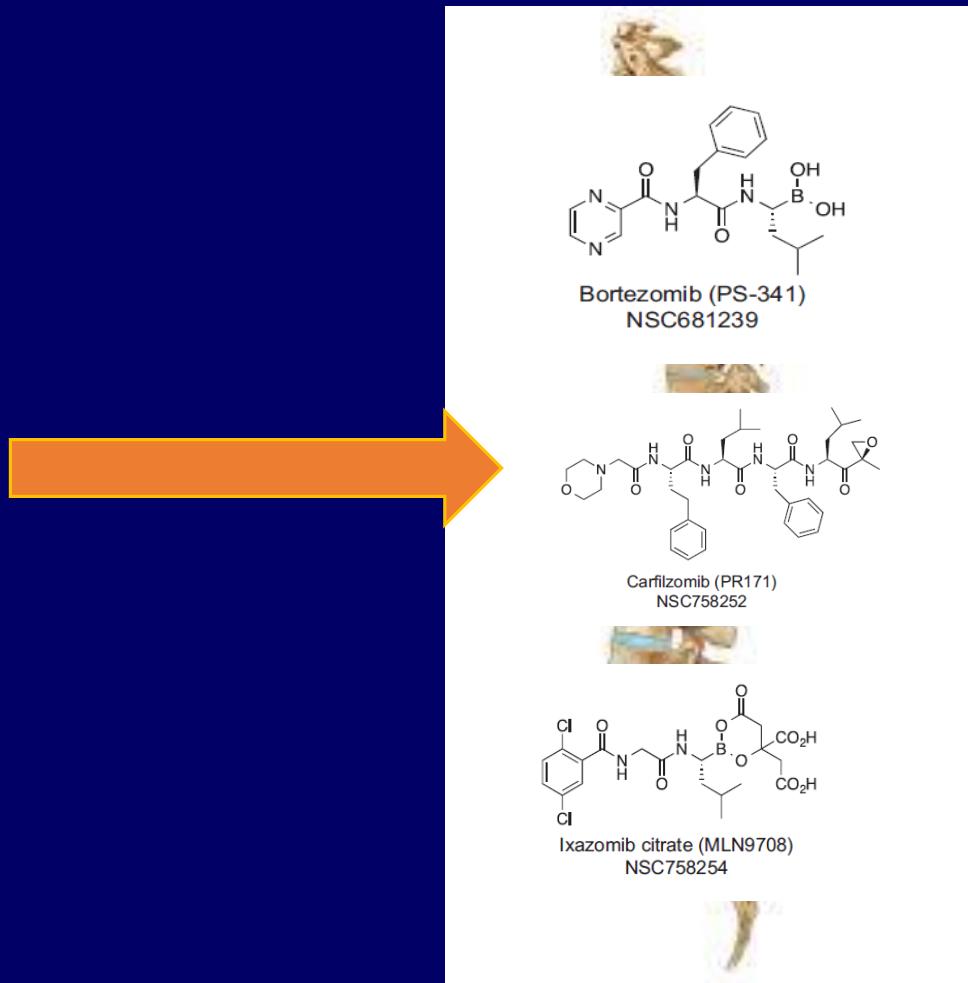


- Daratumumab in combination with standard of care significantly improved MRD-negative rates at all thresholds
- Lower risk of progression in MRD-negative patients
- PFS benefit in MRD-positive patients who received daratumumab-containing regimens versus standard of care

P values calculated using likelihood-ratio chi-square test
*** $P < 0.0001$; ** $P < 0.005$; * $P < 0.05$

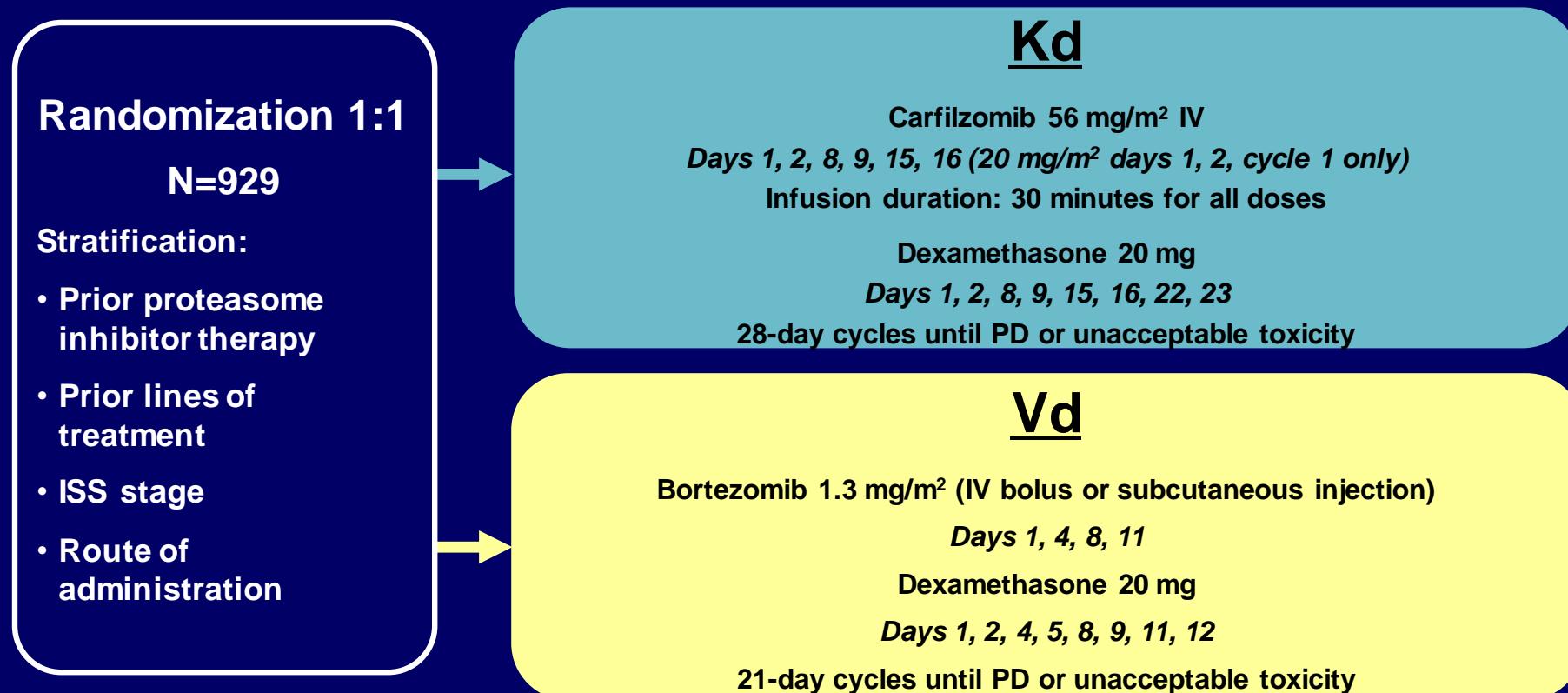
Avet-Loiseau H, et al. Presented at ASH 2016 (Abstract 246), oral presentation
Spencer et al. Presented at IMW 2017 (Abstract PS-151), poster presentation

Building further on the proteasome inhibitor backbone



ENDEAVOR: Carfilzomib-dex vs Bortezomib-dex

Study Design



ISS, International Staging System; IV, intravenous; Kd, carfilzomib and dexamethasone; PD, progressive disease; Vd, bortezomib and dexamethasone; V, bortezomib.

ENDEAVOR:

Key Eligibility Criteria

Inclusion:

- Relapsed MM
- 1–3 prior treatments
- ECOG PS 0–2
- PR or better to at least 1 prior regimen
- Prior treatment with V or K was allowed if:
 - ≥PR to prior treatment
 - ≥6 month PI treatment-free interval
 - Was not removed owing to toxicity

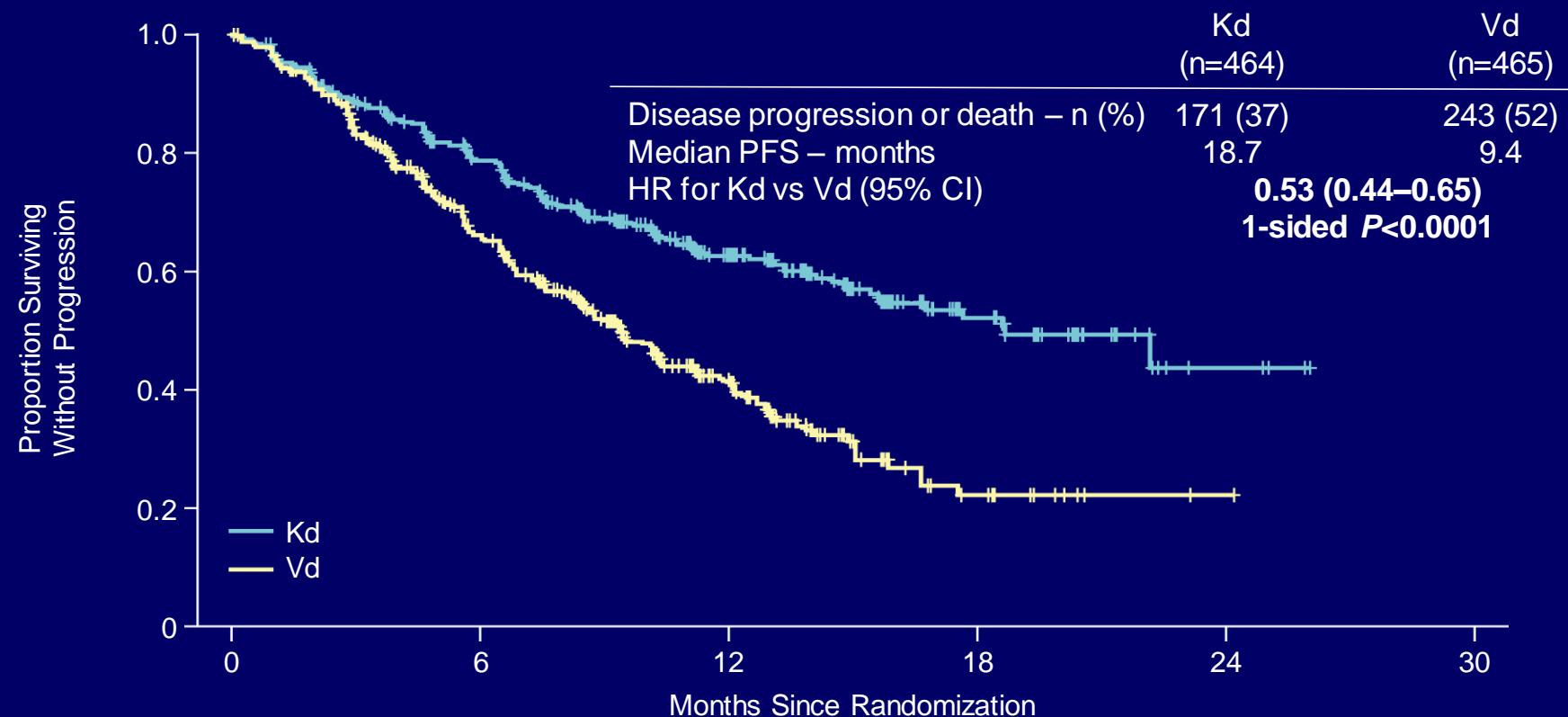
Exclusion:

- Grade 3 or 4 PN (or grade 2 with pain) within 14 days prior to randomization
- Myocardial infarction within 4 months prior to randomization
- New York Heart Association class III or IV heart failure
- LVEF <40%
- Creatinine clearance <15 mL/min

ECOG PS, Eastern Cooperative Oncology Group performance status; K, carfilzomib; LVEF, left ventricular ejection fraction; MM, multiple myeloma; PN, peripheral neuropathy; V, bortezomib.

ENDEAVOR: Progression-Free Survival

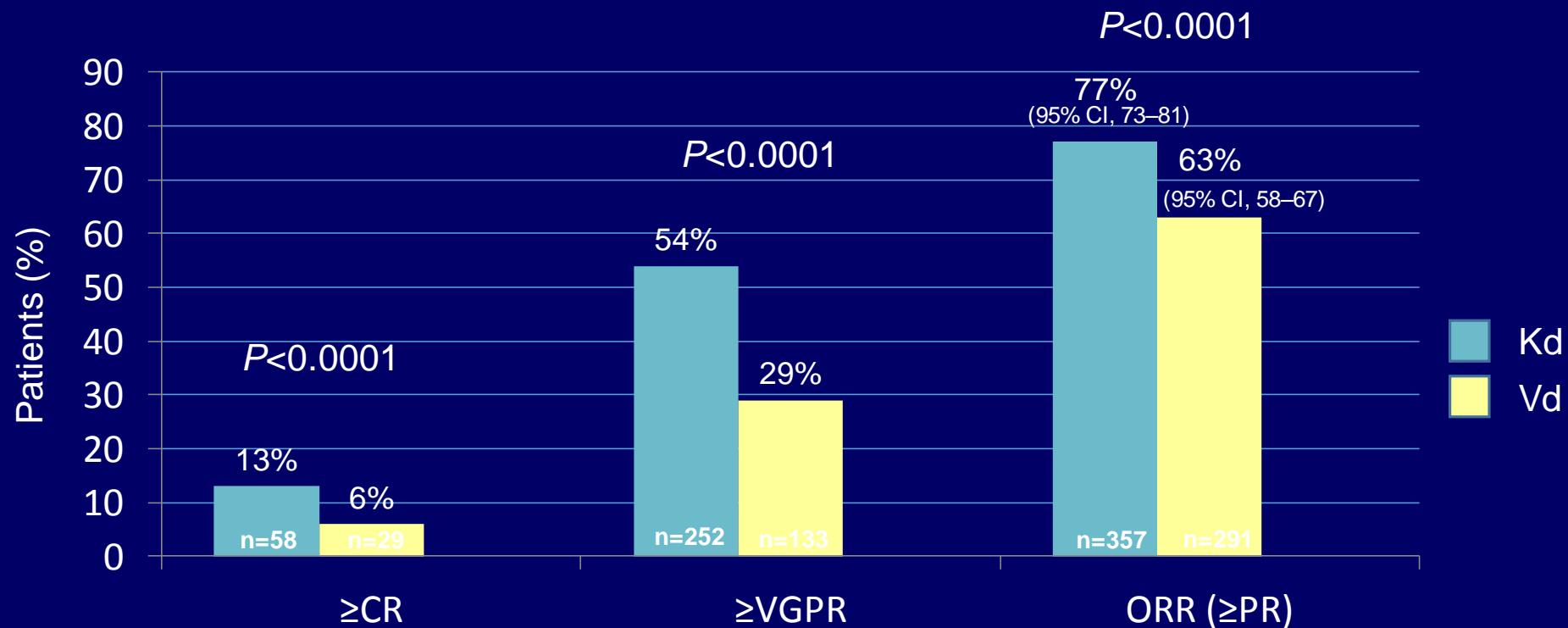
Intent-to-Treat Population (N=929)



- Median follow-up: 11.2 months

CI, confidence interval; HR, hazard ratio; ITT, intent-to-treat; Kd, carfilzomib and dexamethasone; PFS, progression-free survival; Vd, bortezomib and dexamethasone.

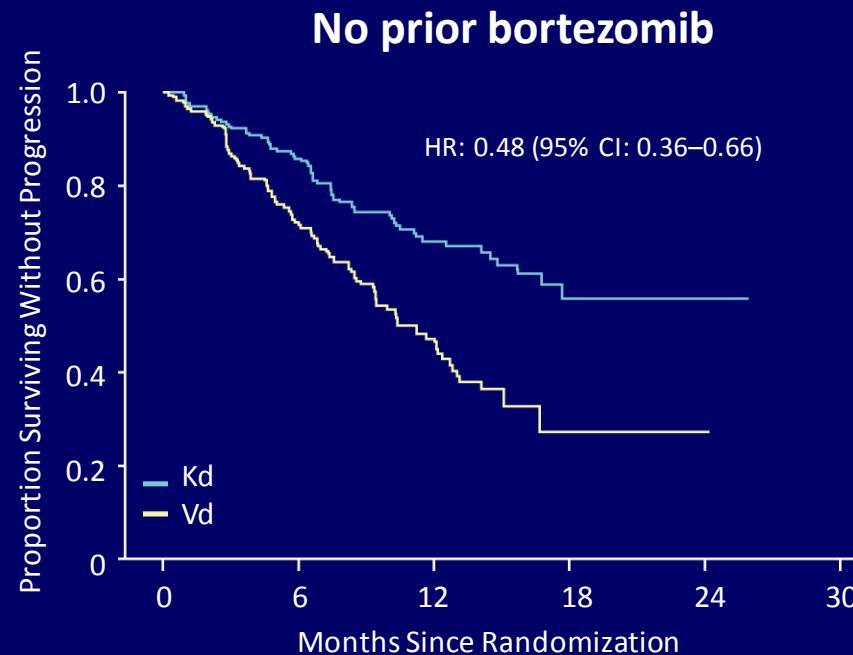
ENDEAVOR: response rates



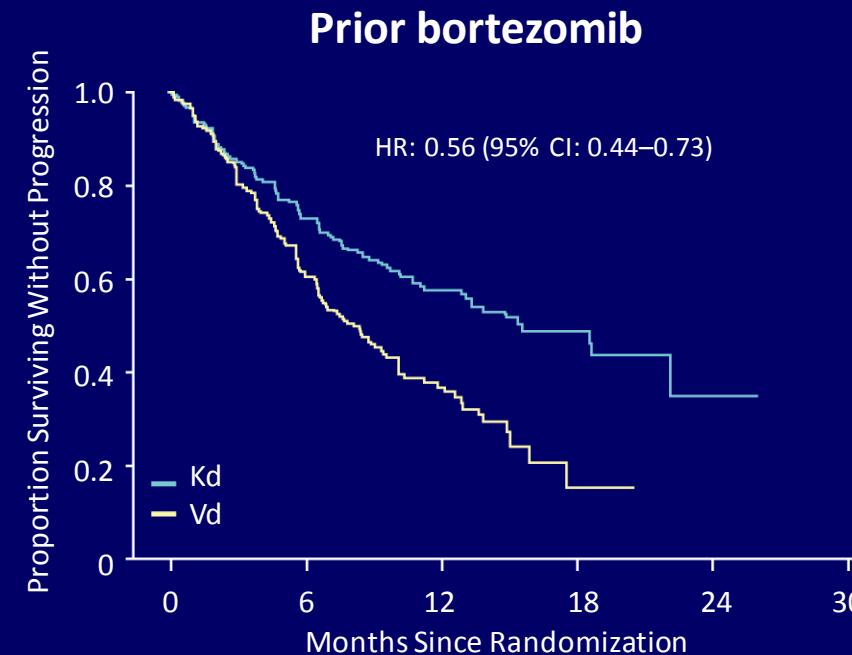
- Median DOR: **21.3 months (95% CI, 21.3–NE)** for Kd vs **10.4 months (95% CI, 9.3–13.8)** for Vd

CI, confidence interval; CR, complete response; DOR, duration of response; ORR, overall response rate; Kd, carfilzomib and dexamethasone; NE, not estimable; PR, partial response; Vd, bortezomib and dexamethasone; VGPR, very good partial response.

ENDEAVOR: Progression-Free Survival and Overall Response Rates by Prior Bortezomib Exposure



	Kd (n=214)	Vd (n=213)
Median PFS, mo	NE	11.2
ORR, % (95% CI)	84 (78–88)	65 (59–72)

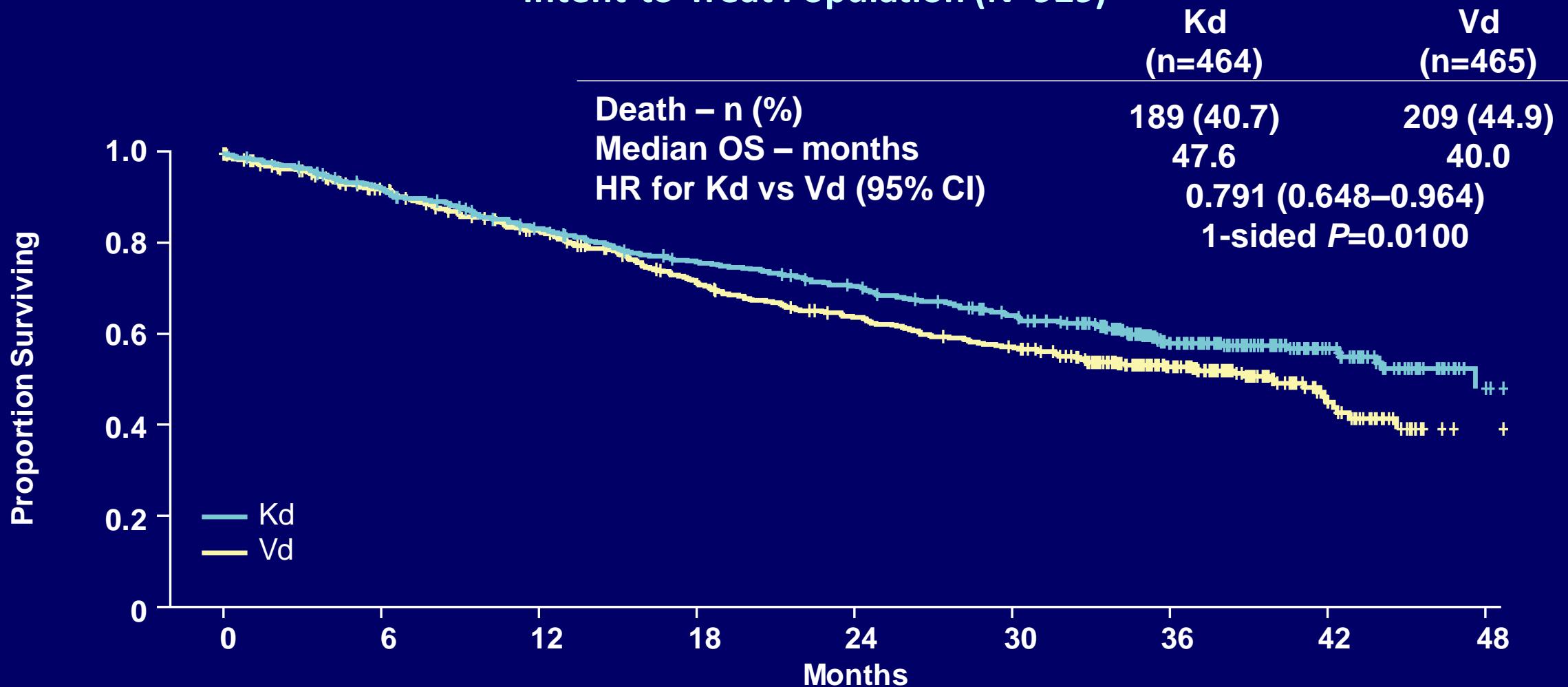


	Kd (n=250)	Vd (n=252)
Median PFS, mo	15.6	8.1
ORR, % (95% CI)	71 (65–77)	60 (54–66)

CI, confidence interval; HR, hazard ratio; Kd, carfilzomib and dexamethasone; NE, not estimable; ORR, overall response rate; PFS, progression-free survival; Vd, bortezomib and dexamethasone.

ENDEAVOR: update on overall survival

Intent-to-Treat Population (N=929)



Number at risk:

Kd	464	423	373	335	308	270	162	66	10
Vd	465	402	351	293	256	228	140	39	5

ENDEAVOR

non-hematologic AEs Occurring in ≥20% of Patients (n=919)

AE, %	Kd (n=463)		Vd (n=456)	
	All grade	Grade ≥3	All grade	Grade ≥3
Nonhematologic AEs (preferred term)				
Diarrhea	31	4	38	8
Fatigue	29	5	29	7
Dyspnea	29	5	13	2.2
Pyrexia	28	2.4	14	0.7
Constipation	15	0.4	27	2.0
Peripheral neuropathy	9	1.3	27	5
Cardiac failure*	8	5	3	1.8
Ischemic heart disease*	3	1.7	2.0	1.5
Hypertension	25	9	9	3
Peripheral edema	22	0.9	17	0.7
Asthenia	20	4	16	3

*Grouped term.

AE, adverse event; Kd, carfilzomib and dexamethasone; Vd, bortezomib and dexamethasone.

Ixazomib

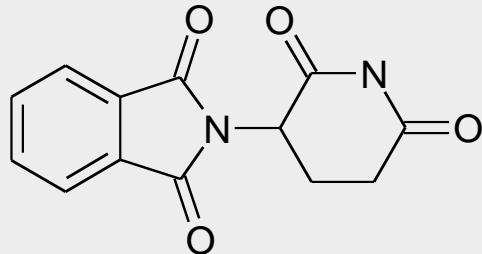
optimal dosing: 4 mg/w vs 5.5 mg/w

	Arm B (4 mg) (N = 35)	Arm C (5.5 mg) (N = 35)
ORR	31% (95% CI, 17-49)	54% (95% CI, 37-71)
No. of responders	11	19
sCR	0	1
CR	1	0
VGPR	7	10
PR	3	8
MR	5	1
Median OS*	NA	NA
% alive at 6 mo	100	100

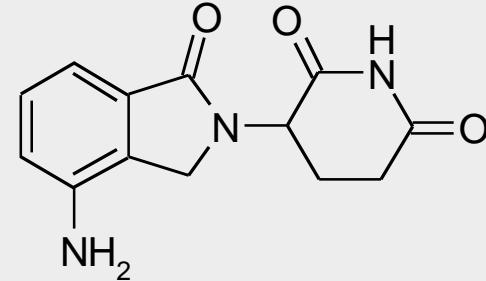
	Arm B (4 mg)	Arm C (5.5 mg)
Ixazomib		
Number of cycles	347	341
Median cycle total dose (range)	12 (2-12)	16.5 (4-16.5)
Number of patients with dose reductions, N (%)	6 (17)	15 (43)
Total number of dose reductions	7	21
Dexamethasone		

Kumar et al. Blood 2016;128:2415

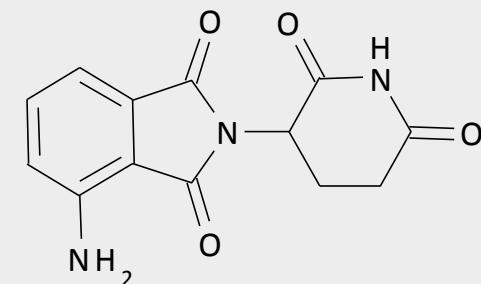
Molecular structure of thalidomide, lenalidomide and pomalidomide



Thalidomide
100-200 mg/d



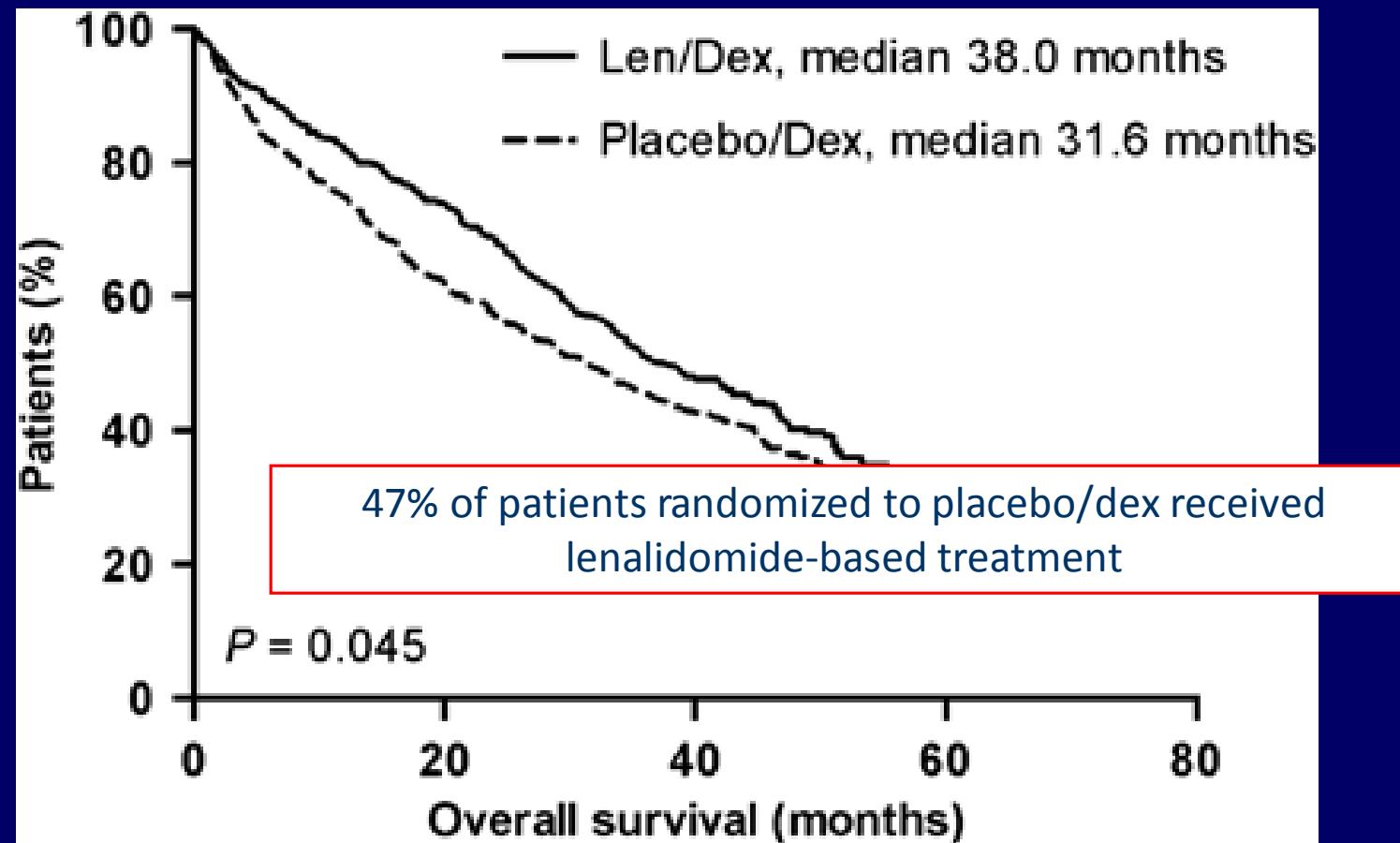
Lenalidomide
5-25 mg/d



Pomalidomide
1-4 mg/d

Structurally similar, but functionally different both qualitatively and quantitatively

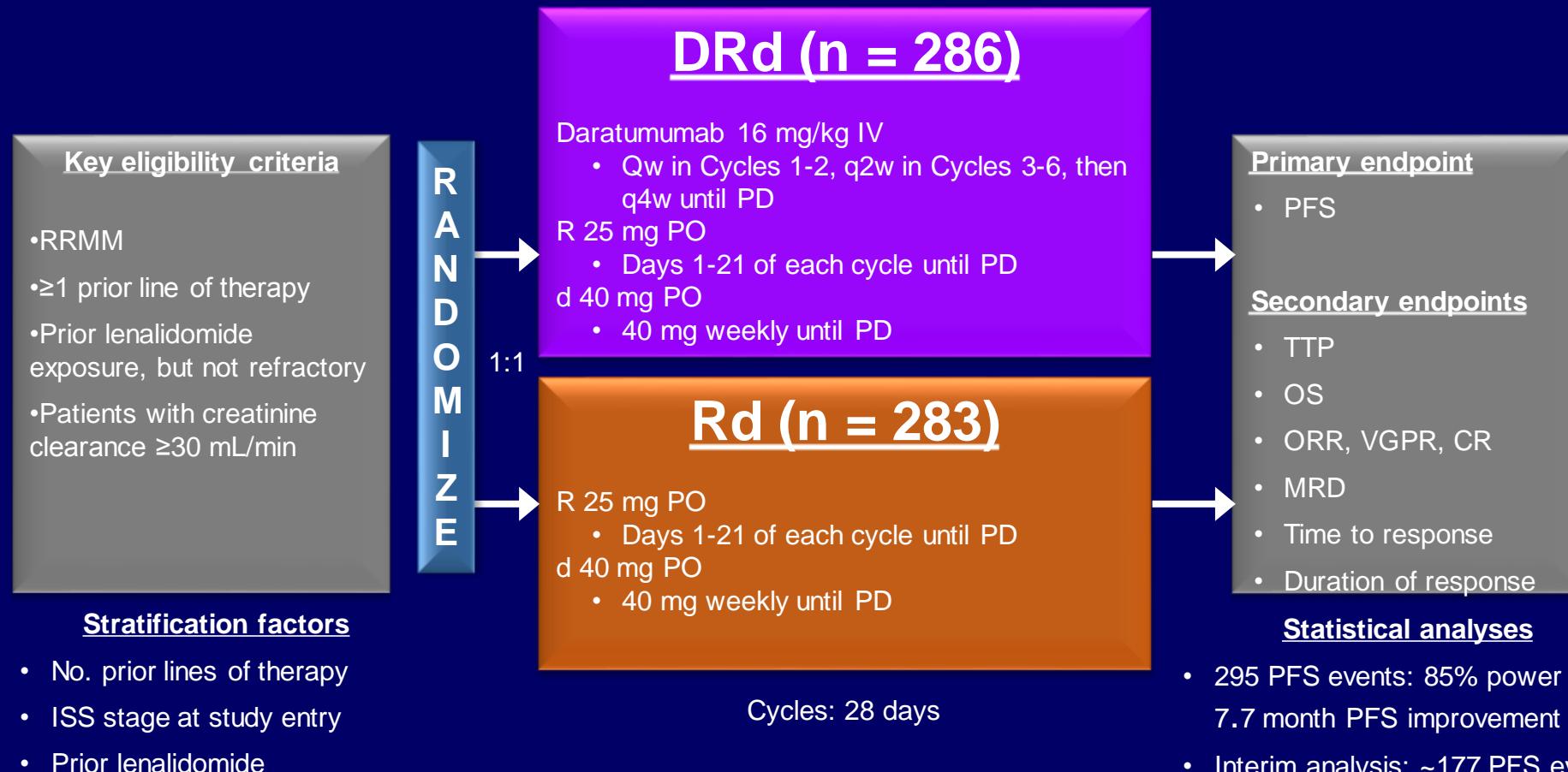
Lenalidomide+dexa vs dexa: overall survival



The Kaplan-Meier estimate of overall survival for the intent-to-treat population. The estimate of overall survival for the intent-to-treat population of the lenalidomide plus dexamethasone and dexamethasone-placebo groups. Len/Dex denotes lenalidomide plus dexamethasone; Placebo/Dex denotes dexamethasone-placebo. Survival curves were compared using log-rank test stratified by study ($P=0.045$).

POLLUX: Study Design

Multicenter, randomized (1:1), open-label, active-controlled phase 3 study

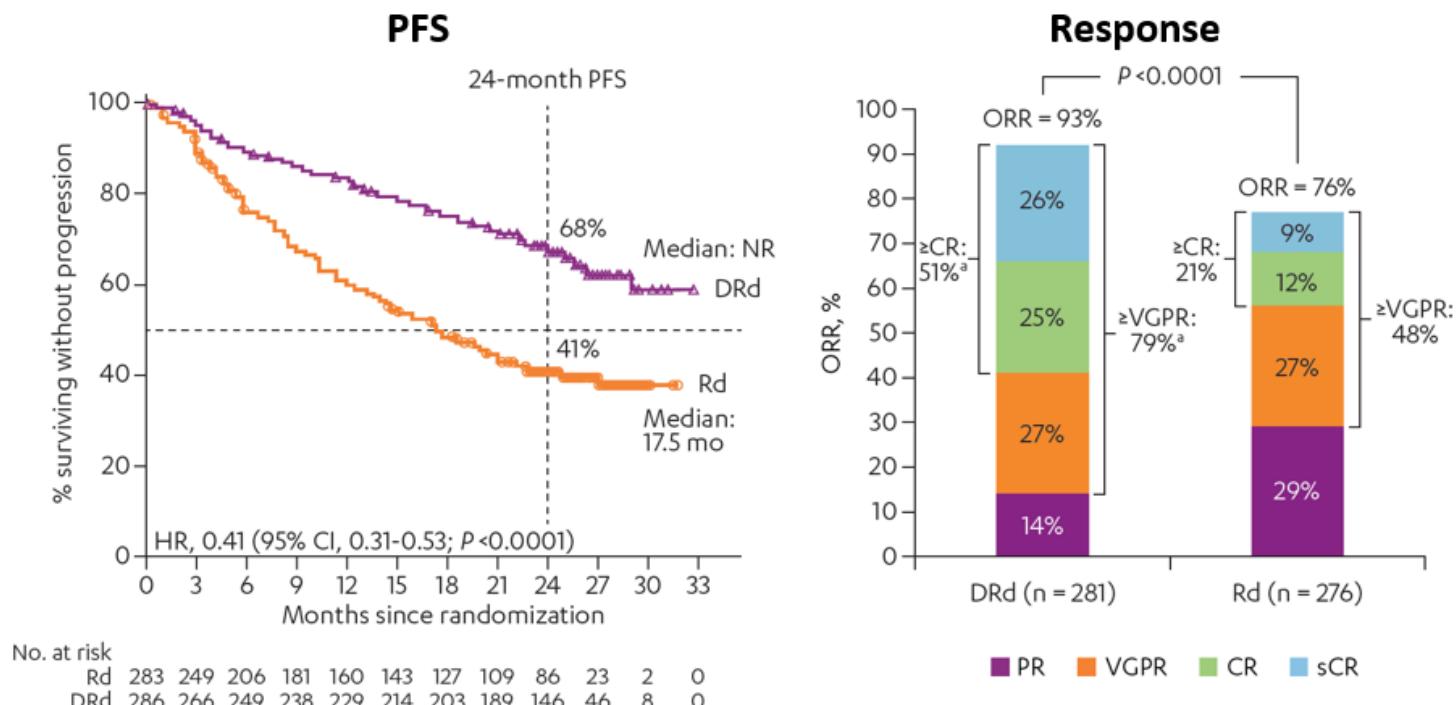


Pre-medication for the DRd treatment group consisted of dexamethasone 20 mg^a, paracetamol, and an antihistamine

^aOn daratumumab dosing days, dexamethasone was administered 20 mg premed on Day 1 and 20 mg on Day 2; RRMM, relapsed or refractory multiple myeloma; ISS, international staging system; R, lenalidomide; DRd, daratumumab/lenalidomide/dexamethasone; IV, intravenous; qw, once weekly; q2w, every 2 weeks; q4w, every 4 weeks; PD, progressive disease; PO, oral; d, dexamethasone; Rd, lenalidomide/dexamethasone; TTP, time to progression; MRD, minimal-residual disease.

DRd vs RD: Updated progression-free survival

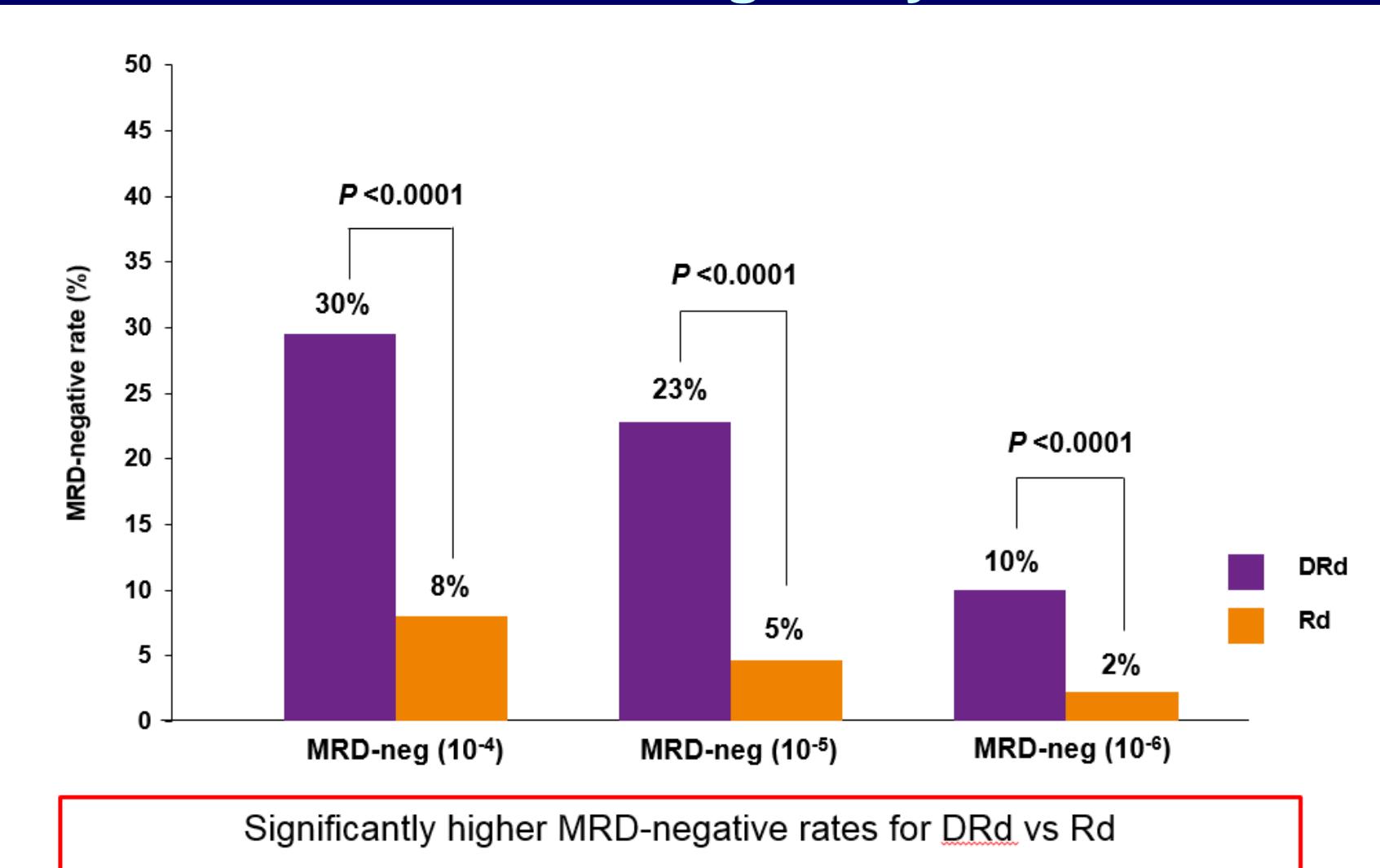
POLLUX update



- Median follow-up of 25.4 months

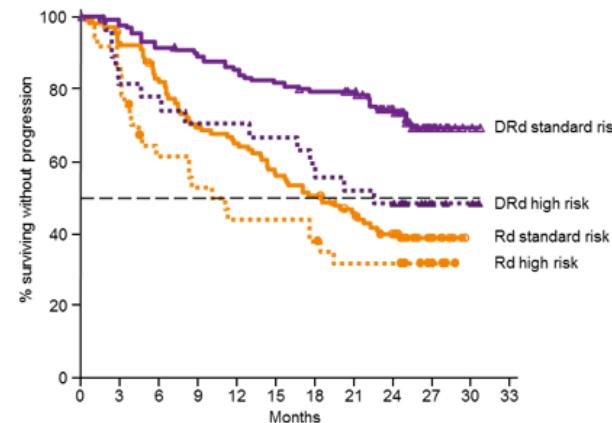
**DRd-treated patients had a 59% reduction in the risk of progression or death vs Rd
Deep responses continue in the DRd group with longer follow-up**

DRd vs RD: MRD negativity

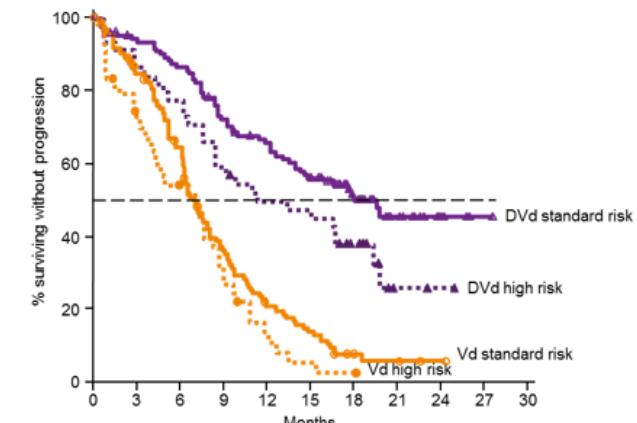


PFS with DRd and DVd according to cytogenetic risk

POLLUX



CASTOR



High risk	DRd n = 28	Rd n = 37
mPFS, mo	22.6	10.2
HR (95% CI)	0.53 (0.25-1.13)	
P value	0.0921	

Standard risk	DRd n = 133	Rd n = 113
mPFS, mo	NR	18.5
HR (95% CI)	0.30 (0.20-0.47)	
P value	<0.0001	

Standard risk	DVd n = 123	Vd n = 135
mPFS, mo	19.6	7.0
HR (95% CI)	0.26 (0.18-0.37)	
P value	<0.0001	

High risk	DVd n = 44	Vd n = 51
mPFS, mo	11.2	7.2
HR (95% CI)	0.45 (0.25-0.80)	
P value	0.0053	

Adding DARA to Rd or Vd prolongs PFS regardless of cytogenetic risk

mPFS, median PFS; NR, not reached.

*ITT/biomarker-risk-evaluable analysis set: patients in the ITT population with both RNA and DNA results available.

San Miguel J, et al. Presented at EHA 2017 (Abstract S101), oral presentation.

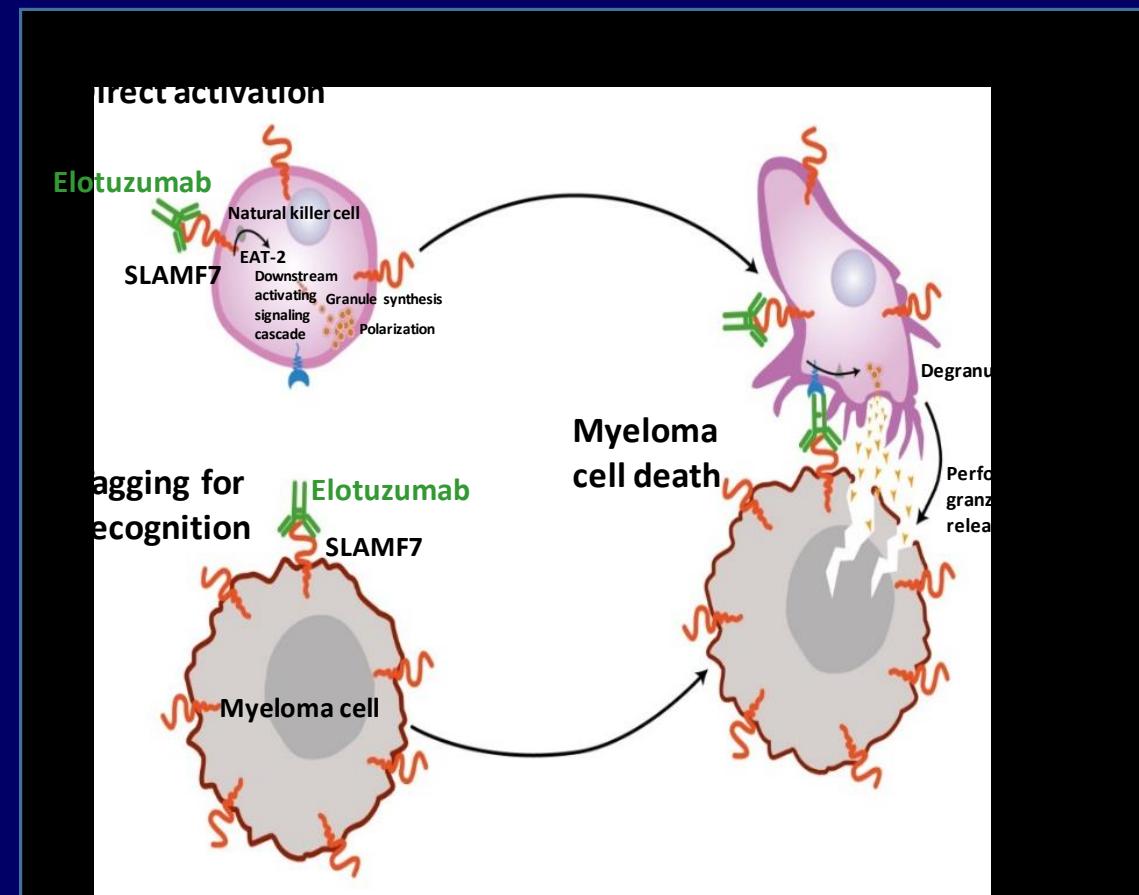
DRd and DVd: overview of adverse events

	65-74 years		≥75 years	
	DRd (n = 123)	Rd (n = 108)	DRd (n = 29)	Rd (n = 35)
TEAE (≥10%): POLLUX				
Patients with grade 3/4 TEAE, n (%)	103 (84)	86 (80)	24 (83)	27 (77)
Hematologic TEAE, n (%)				
Neutropenia	67 (55)	40 (37)	13 (45)	11 (31)
Anemia	20 (16)	23 (21)	1 (3)	7 (20)
Thrombocytopenia	19 (15)	16 (15)	2 (7)	5 (14)
Nonhematologic TEAE, n (%)				
Hypokalemia	4 (3)	5 (5)	4 (14)	1 (3)
Pneumonia	15 (12)	7 (7)	3 (10)	4 (11)
TEAE (≥10%): CASTOR				
Patients with grade 3/4 TEAE, n (%)	76 (81)	60 (70)	18 (90)	26 (74)
Hematologic TEAE, n (%)				
Thrombocytopenia	49 (52)	28 (33)	9 (45)	13 (37)
Anemia	14 (15)	15 (17)	2 (10)	4 (11)
Lymphopenia	12 (13)	5 (6)	1 (5)	0
Neutropenia	14 (15)	3 (4)	0	1 (3)
Nonhematologic TEAE, n (%)				
Pneumonia	11 (12)	5 (6)	3 (15)	6 (17)
Fatigue	6 (6)	1 (1)	3 (15)	4 (11)
Peripheral sensory neuropathy	3 (3)	9 (11)	2 (10)	2 (6)
Bronchitis	3 (3)	3 (4)	2 (10)	0
Diarrhea	2 (2)	1 (1)	2 (10)	0

	65-74 years		≥75 years	
	DRd (n = 123)	Grade 3/4	DRd (n = 29)	Grade 3/4
IRR (>5%): POLLUX				
Patients with IRR, n (%)	61 (50)	6 (5)	12 (41)	4 (14)
IRR, n (%)				
Dyspnea	13 (11)	1 (1)	4 (14)	1 (3)
Chills	8 (7)	0	3 (10)	1 (3)
Feeling cold	2 (2)	0	2 (7)	1 (3)
Wheezing	2 (2)	1 (1)	2 (7)	1 (3)
Vomiting	7 (6)	1 (1)	2 (7)	0
Bronchospasm	7 (6)	0	0	0
Cough	7 (6)	0	0	0
Nausea	7 (6)	0	0	0
IRR (>5%): CASTOR				
Patients with IRR, n (%)	43 (46)	8 (9)	13 (65)	2 (10)
IRR, n (%)				
Bronchospasm	11 (12)	1 (1)	4 (20)	1 (5)
Throat irritation	2 (2)	0	4 (20)	0
Cough	8 (9)	0	3 (15)	0
Dyspnea	10 (11)	4 (4)	3 (15)	0
Chills	3 (3)	0	2 (10)	0
Nausea	6 (6)	0	0	0
Hypertension	6 (6)	5 (5)	0	0

Elotuzumab: SLAMF7-targeted mAb therapy

- Humanized mAb targeted against SLAMF7; highly expressed on myeloma and NK cells but not on normal tissues¹
- Dual mechanism of action:
 - Direct activation:
Binding to SLAMF7 directly activates NK cells, but not myeloma cells^{2,3}
 - Tagging for recognition:
Activation of NK cells via CD16 → killing of myeloma cells via ADCC²



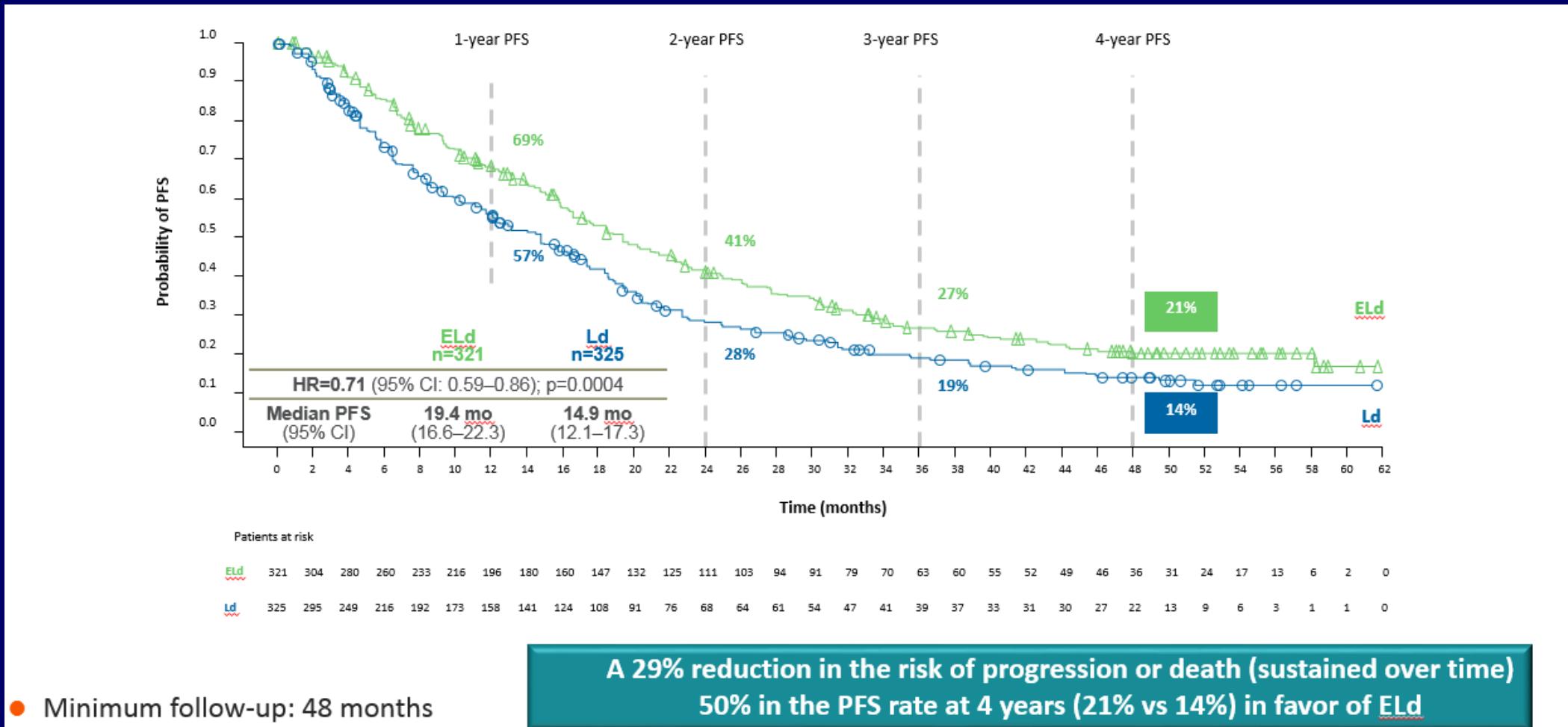
SLAMF7 = Signaling Lymphocyte Activation Molecule-F7

1. Hsi ED et al. *Clin Cancer Res* 2008;14:2775–84; 2. Collins SM et al. *Cancer Immunol Immunother* 2013;62:1841–9;

3. Guo H et al. *Mol Cell Biol* 2015;35:41–51

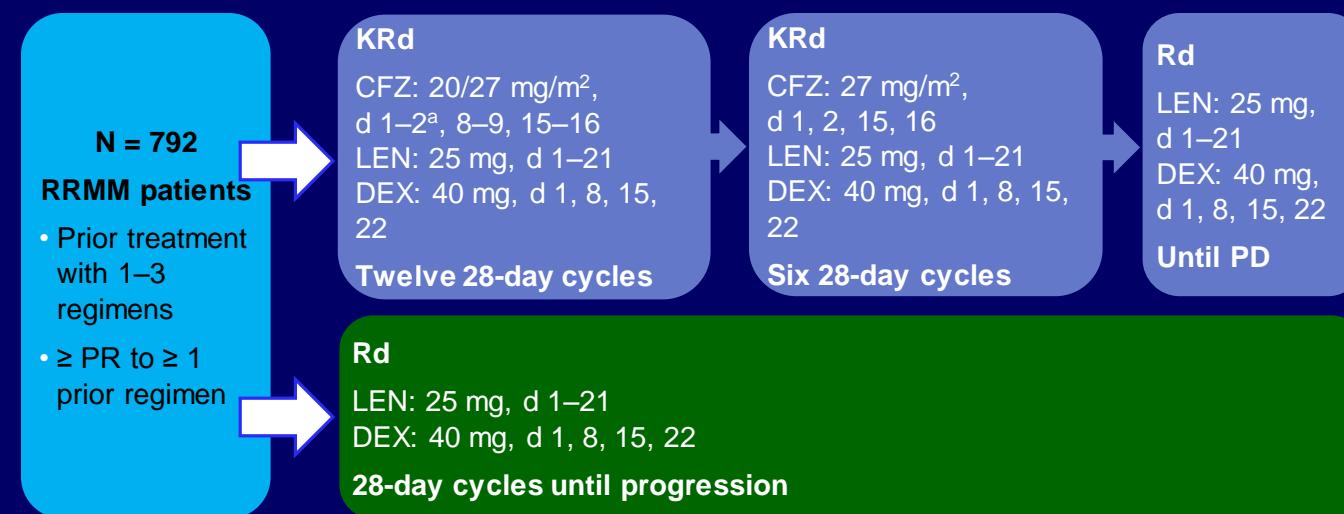
EloRd vs Rd

4 y-progression free survival



ASPIRE: Carfilzomib-Lenalidomide-Dexamethasone (KRd) vs Lenalidomide-Dexamethasone (Rd)

- Phase 3, open-label, randomized, multicentre study

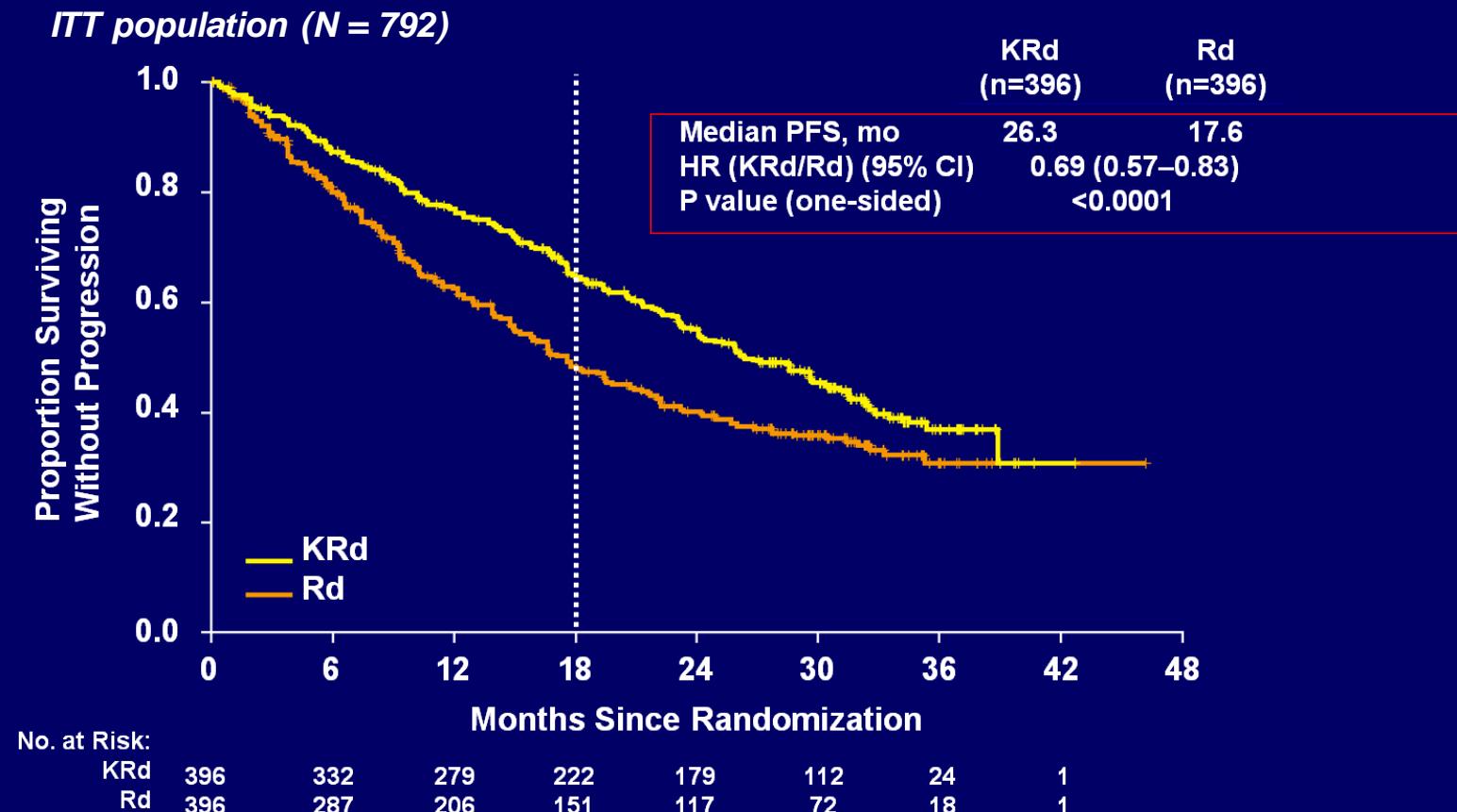


- Patients received antiviral and antithrombotic prophylaxis
- Primary endpoint: PFS
- Secondary endpoints: OS, ORR, DoR, HRQoL, safety

^aCarfilzomib is administered at 20 mg/m² on Days 1 and 2 of cycle 1, 27 mg/m² thereafter.

CFZ, carfilzomib; DEX, dexamethasone; LEN, Lenalidomide; KRd, carfilzomib, Lenalidomide, low-dose dexamethasone.

ASPIRE Trial: KRd vs Rd median progression-free Survival

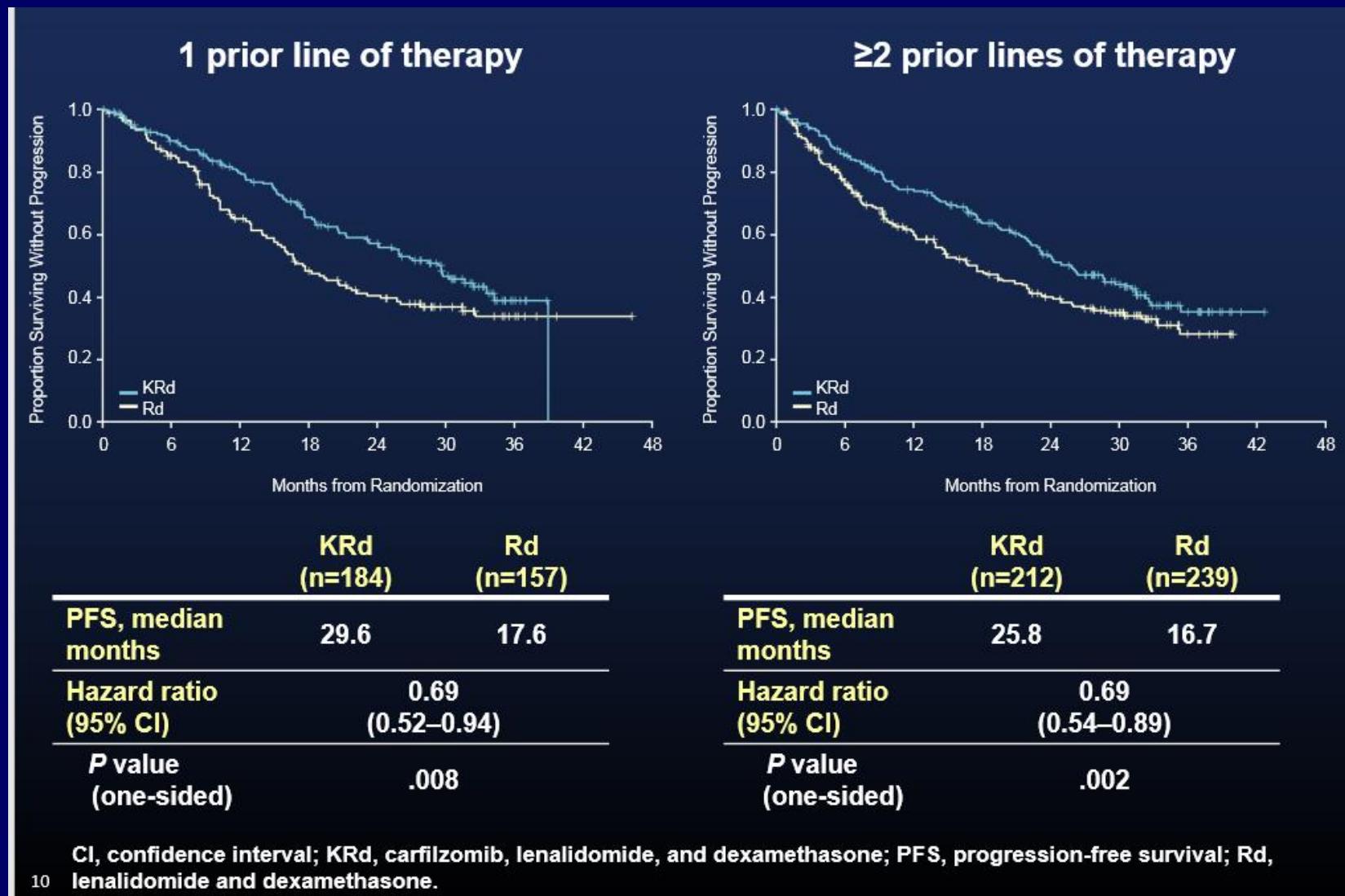


HR, hazard ratio; ITT, intention-to-treat; KRd, carfilzomib, lenalidomide, low-dose dexamethasone; PFS, progression-free survival; Rd, lenalidomide, low-dose dexamethasone.

Stewart AK, et al. N Engl J Med. 2015;372:142-52.

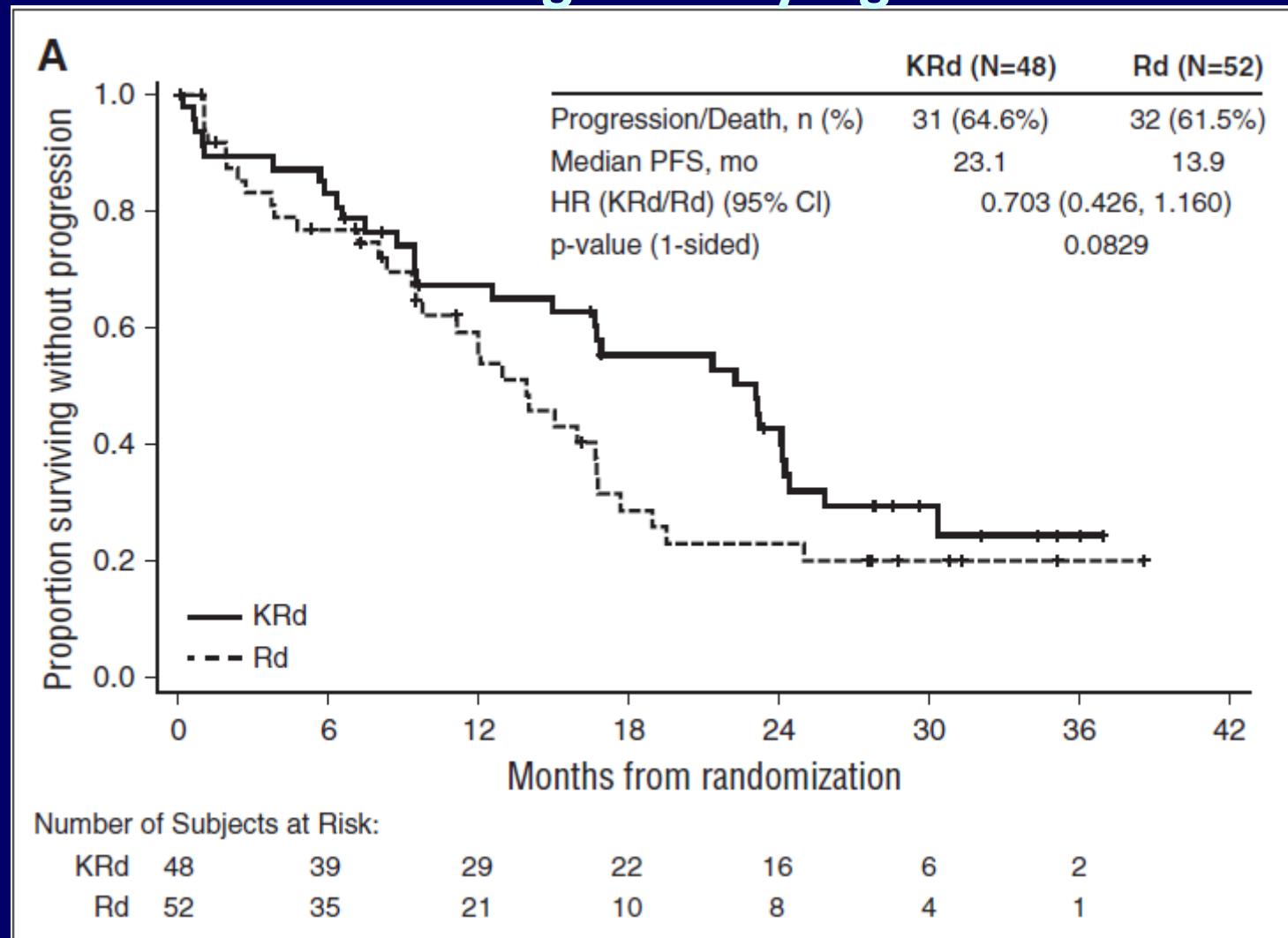
ASPIRE Trial: KRd vs Rd

Progression-free Survival according to previous lines of therapy



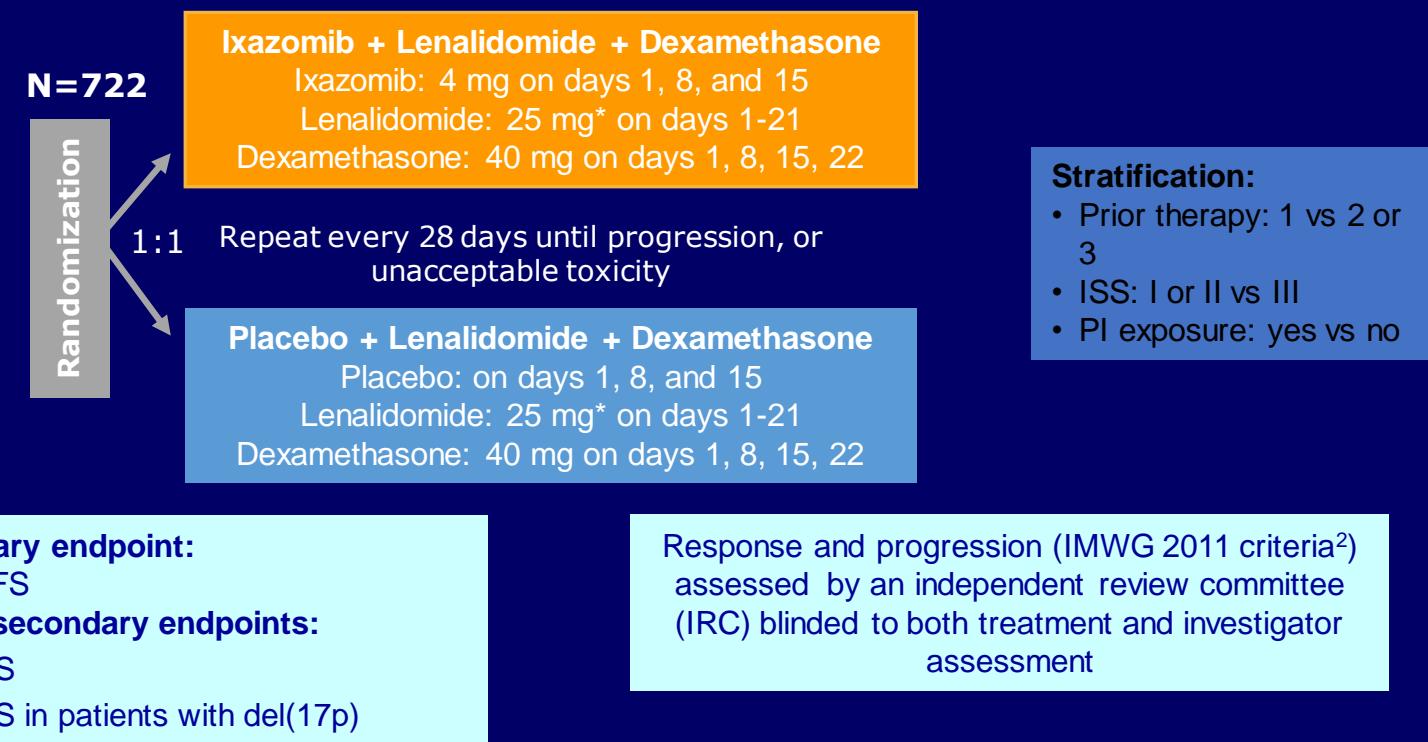
ASPIRE Trial: KRd vs Rd

outcome for high-risk cytogenetics



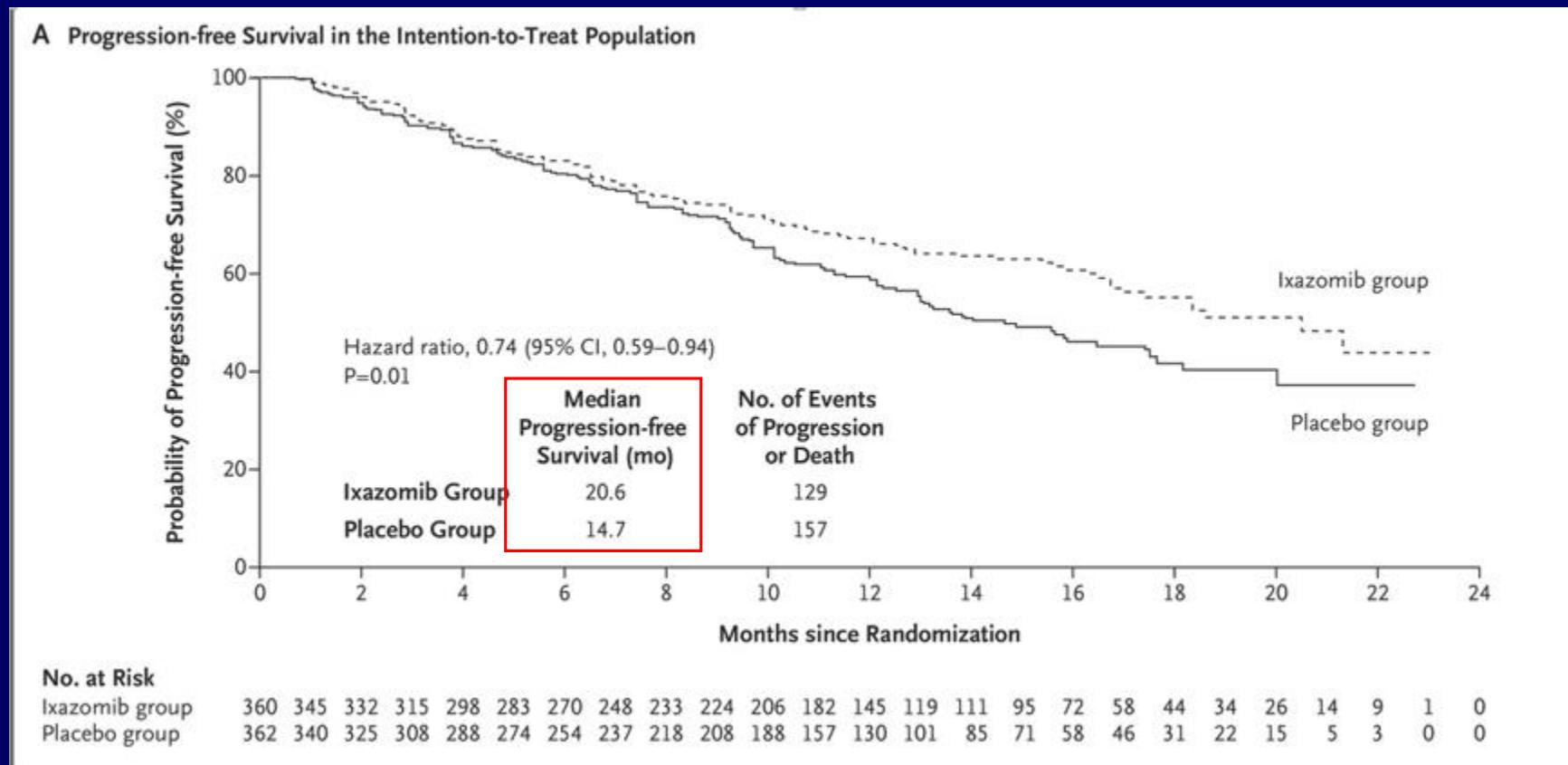
TOURMALINE MM1:

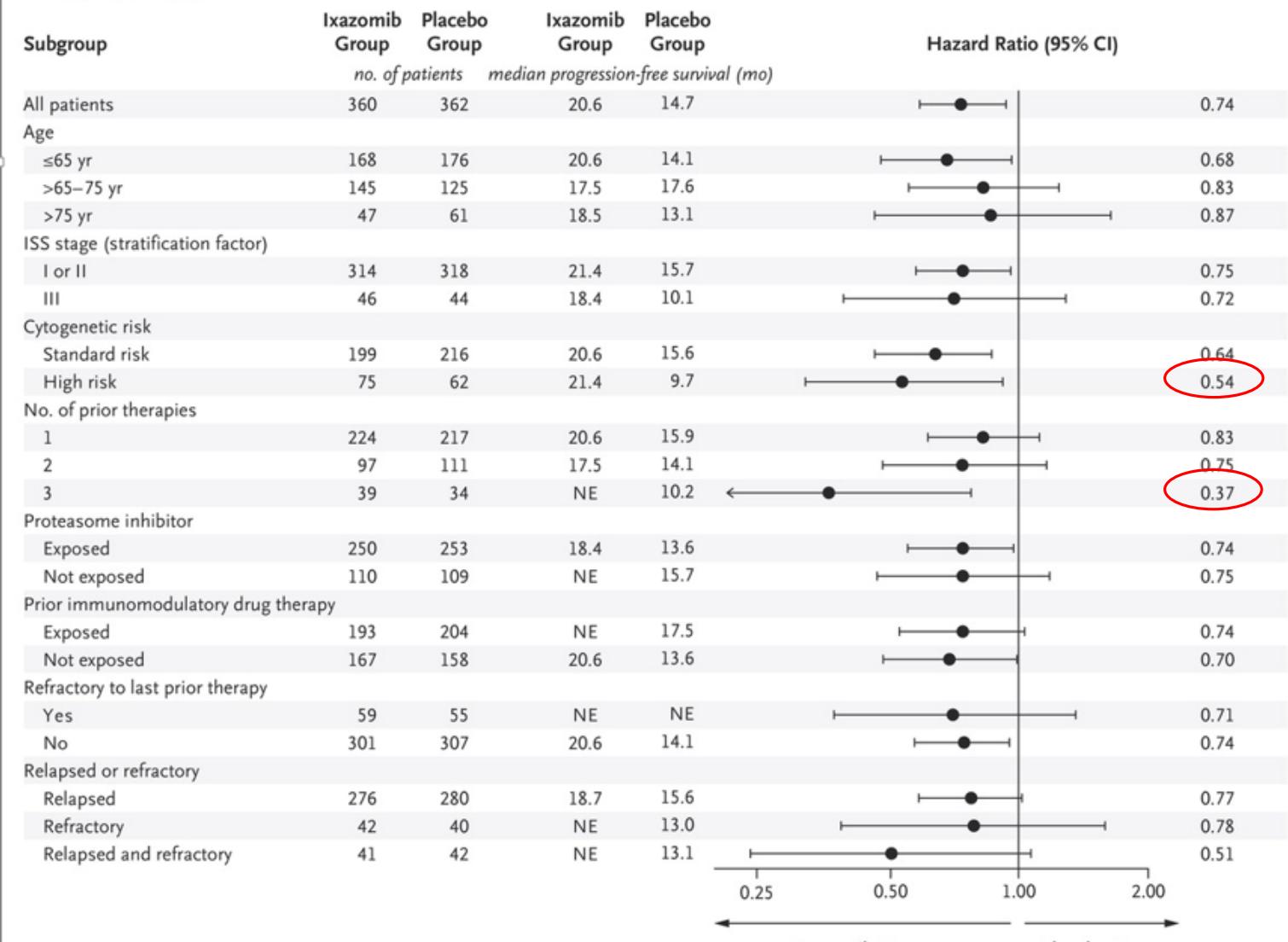
Ixazomib-Lenalidomide-Dexamethasone (IxRaD) vs Lenalidomide-Dexamethasone (Rd)



*10 mg for patients with creatinine clearance ≤60 or ≤50 mL/min, depending on local label/practice

TOURMALINE MM1: Progression-free survival



B Subgroup Analysis

TOURMALINE MM1: Safety

Table 4. Common Adverse Events and Other Adverse Events of Clinical Importance in the Safety Population at the 23-Month Analysis.^a

Adverse Event	Ixazomib Group (N=361)			Placebo Group (N=359)		
	Any Grade	Grade 3	Grade 4	Any Grade	Grade 3	Grade 4
<i>number of patients (percent)</i>						
Common hematologic adverse events of any cause[†]						
Neutropenia‡	118 (33)	64 (18)	17 (5)	111 (31)	63 (18)	22 (6)
Thrombocytopenia‡	112 (31)	43 (12)	26 (7)	57 (16)	19 (5)	13 (4)
Anemia	103 (29)	34 (9)	0	98 (27)	48 (13)	0
Common nonhematologic adverse events of any cause[†]						
Diarrhea	164 (45)	23 (6)	0	139 (39)	9 (3)	0
Rash§						
Standardized MedDRA query	131 (36)	18 (5)	0	82 (23)	6 (2)	0
High-level term	72 (20)	9 (2)	0	45 (13)	6 (2)	0
Other adverse events of clinical interest						
Arrhythmias¶	56 (16)	17 (5)	3 (<1)	53 (15)	10 (3)	1 (<1)
Thromboembolism¶	29 (8)	9 (2)	2 (<1)	38 (11)	11 (3)	1 (<1)
Liver impairment‡	26 (7)	7 (2)	0	21 (6)	4 (1)	0
Hypertension						
Any	22 (6)	11 (3)	0	18 (5)	4 (1)	0
Hypertensive crisis	1 (<1)	0	0	0	0	0
Hypotension¶	22 (6)	4 (1)	0	21 (6)	1 (<1)	0
Heart failure¶	16 (4)	7 (2)	2 (<1)	14 (4)	4 (1)	2 (<1)

Network meta-analysis of treatment outcomes in RRMM

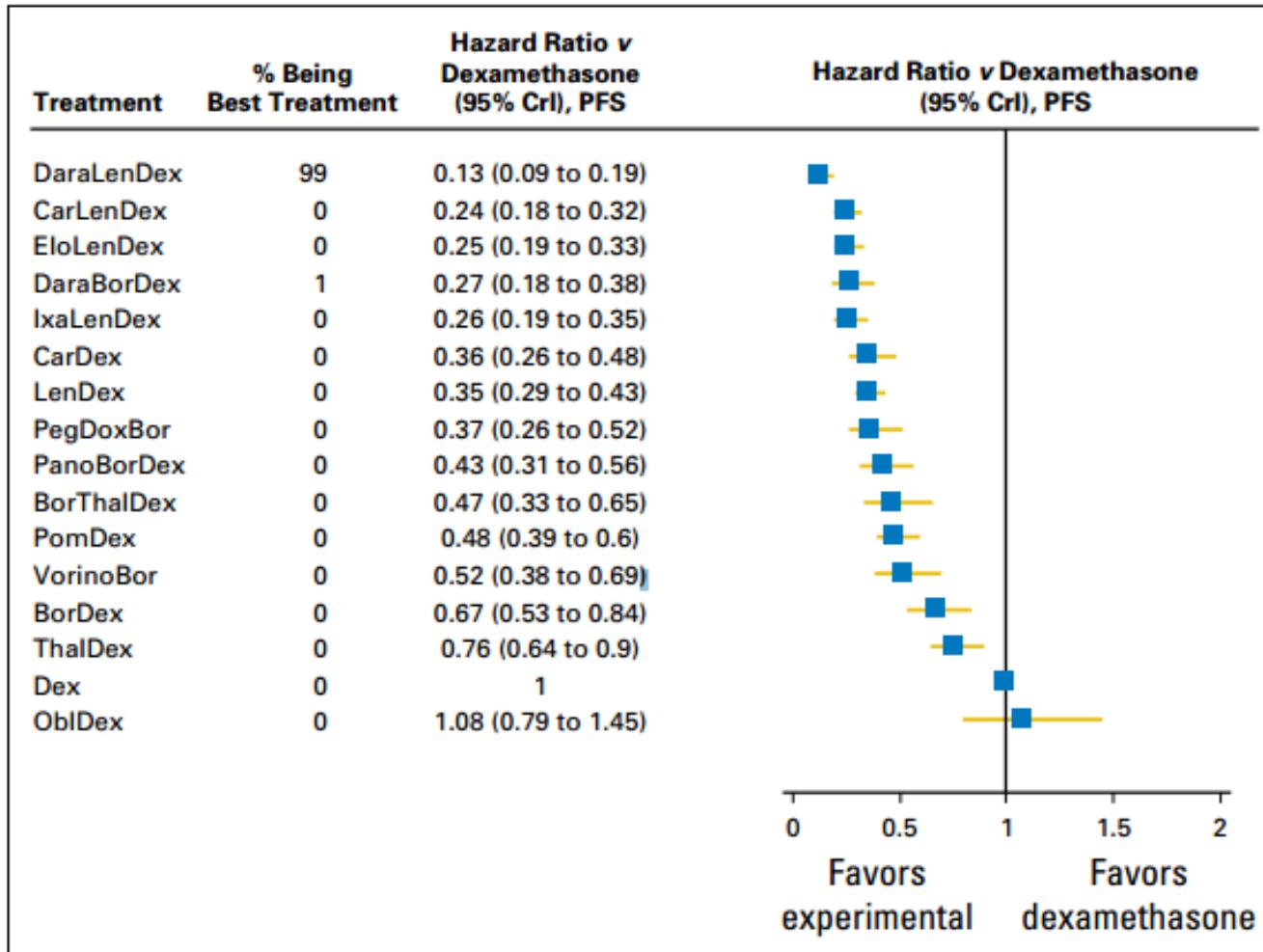


Fig 4. Forest plot of network meta-analysis results. Bor, bortezomib; Car, carfilzomib; Crl, credible interval; Dara, daratumumab; Dex, dexamethasone; Elo, elotuzumab; Ixa, ixazomib; Len, lenalidomide; Obl, oblimersen; Pano, panobinostat; PegDox, pegylated liposomal doxorubicin; PFS, progression-free survival; Pom, pomalidomide; Thal, thalidomide; Vorino, vorinostat.

Current and future options for patients with first-relapse MM

bortezomib-based triplet induction

autograft (one or two)

consolidation -/+ maintenance

proteasome-inhibitor based

Rd (cont.)

Rd (18)

VMP

Second
ASCT/Allo-RIC

Rd-based

Retreatment with VD

Kd
PFS: 18.7 months¹
(HR: 0.53; p<0.0001)

Dara+ VD
PFS: Not reached⁷
(HR: 0.39; p<0.001)

Elo + VD
PFS: 9.7 months⁸
(HR: 0.72; p=0.09)

KRd
PFS: 26.3 months²
(HR: 0.69; p<0.0001)

DRd
Median PFS not reached⁴
(HR: 0.37; p<0.001)

IRd
PFS: 20.6 months⁵
(HR: 0.74; p=0.012)

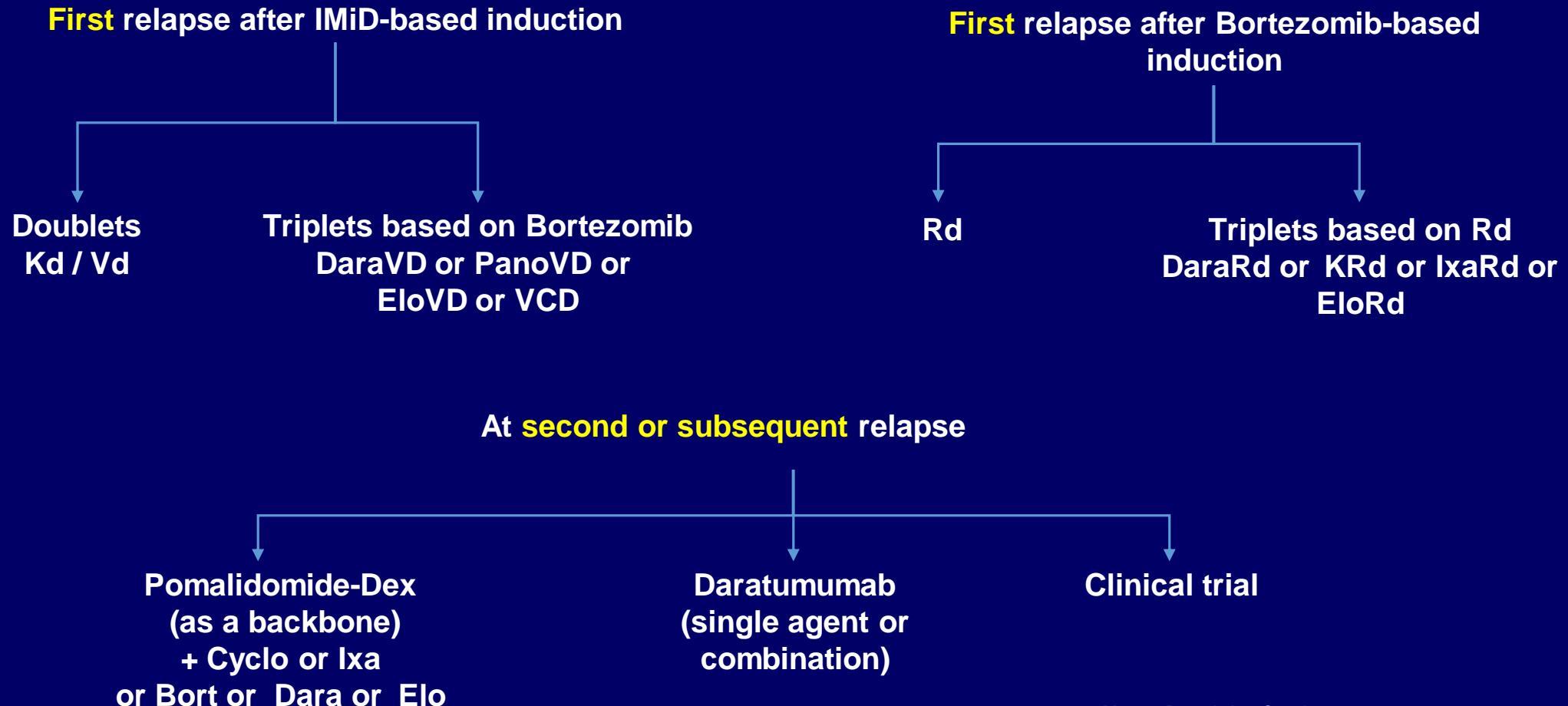
ERd
PFS: 19.4 months³
(HR: 0.70; p<0.001)

1. Dimopoulos MA, et al. Lancet Oncol. 2016; 17: 27-38 ; 2. Stewart AK, et al. N Engl J Med 2015;372:142-52; 3. Lonial S, et al. N Engl J Med 2015; 373(7):621-31;

4. Dimopoulos MA, et al. N Engl J Med 2016;375:1319-1331; 5. Moreau P et al. N Engl J Med 2016;374(17):1621-34; 6. San Miguel JF, et al. Lancet Oncol. 2014;15(11):1195-1206;

7. Palumbo, A et al. N Engl J Med 2016;375:754-66; 8. Jakubowiak A et al. Blood 2016: 127(23):2833-40

Relapsed MM: ESMO guidelines 2017



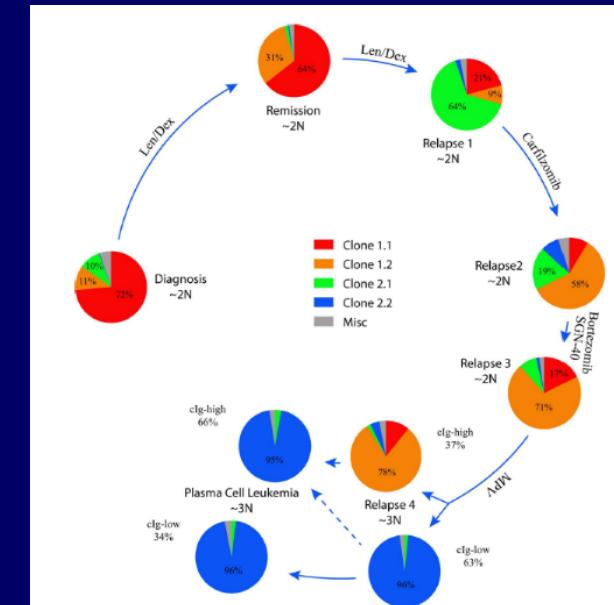
Moreau P, et al. Ann Oncol 2017;00:1–11, 2017.

Moreau P, et al. Ann Oncol 2017;00:1–11

A doublet or triplet at relapse ?

Rationale for 'triplet':

- overcoming drug resistance by combining drugs with different mode of action
- improve long-term outcome without increase in toxicity
- easy mode of administration



Triplet

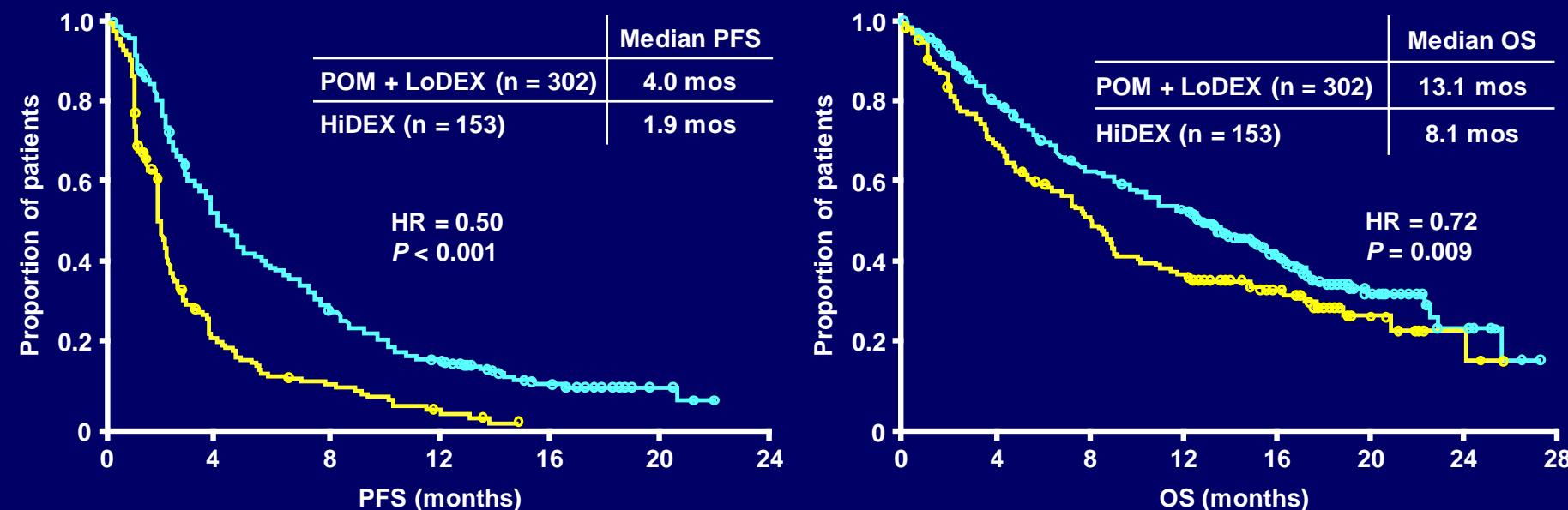
- High-risk
- Aggressive relapse
- Fit patient



Doublet

- Standard risk
- Non-aggressive relapse
- Frail (elderly) patient

Pomalidomide in bortezomib and lenalidomide refractory/intolerant patients progression-free and overall survival



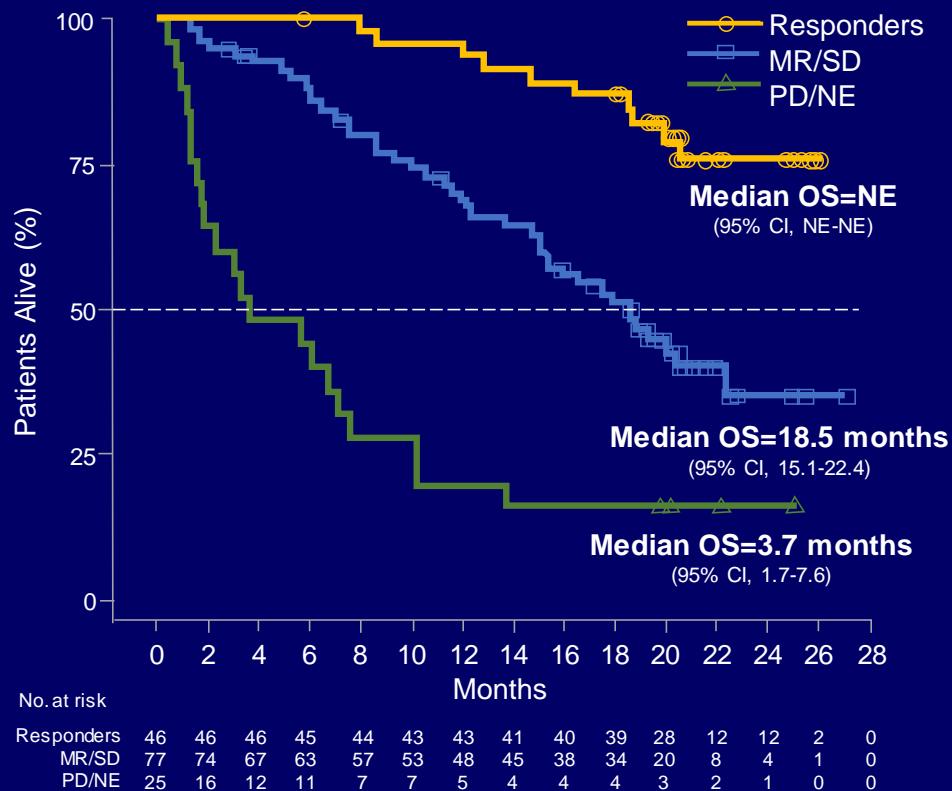
- Compared with HiDEX, POM + LoDEX significantly improved PFS (4.0 vs 1.9 months; $P < 0.001$) and OS (13.1 vs 8.1 months; $P = 0.009$)
- 85 patients (56%) in the HiDEX arm received subsequent POM

PFS based on IMWG criteria. Data cut-off 1 September 2013. Intent-to-treat population.

HiDEX, high-dose dexamethasone; ITT, intent-to-treat; IMWG, International Myeloma Working Group; LoDEX, low-dose dexamethasone; OS, overall survival; PFS, progression-free survival; POM, pomalidomide.

Daratumumab: single-agent activity

- Daratumumab single agent
- Patients received a median of 5 prior lines of therapy
 - 86.5% of patients were double refractory to a proteasome inhibitor (PI) and immunomodulatory drug (IMiD)³
- Combined overall response rate (ORR): 31%³
- Median overall survival (OS): 20.1 months³
 - 2-year OS was ~75% in responders
 - Median OS was 18.5 months in MR/SD patients



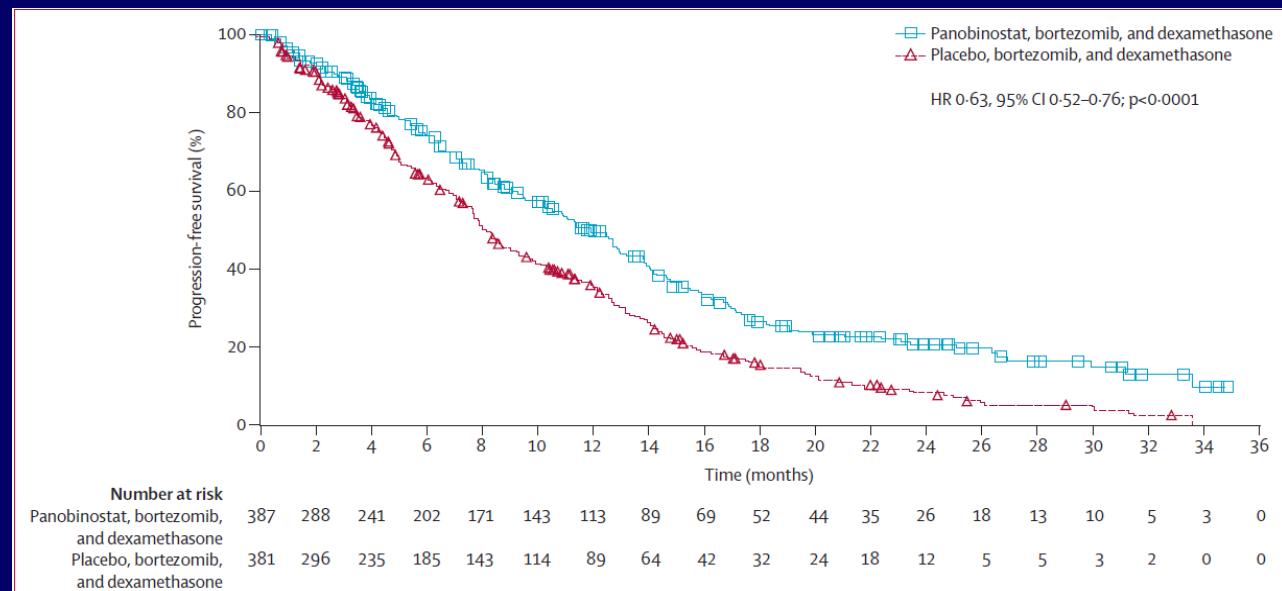
MR, minimal response; SD, stable disease; PD, progressive disease; OS, overall survival; CI, confidence interval; NE, not evaluable.

1. Lokhorst HM, et al. N Engl J Med. 2015;373:1207-19;
2. Lonial S, et al. Lancet. 2016;387:1551-60;
3. Usmani SZ, et al. Blood. 2016;128:37.

Bortezomib plus panobinostat

Panobinostat plus bortezomib and dexamethasone versus placebo plus bortezomib and dexamethasone in patients with relapsed or relapsed and refractory multiple myeloma: a multicentre, randomised, double-blind phase 3 trial

Jesús F San-Miguel, Vânia T M Hungria, Sung-Soo Yoon, Meral Beksac, Meletios Athanasios Dimopoulos, Ashraf Elghandour, Wiesław Wiktor Jedrzejczak, Andreas Günther, Thanyaphong Na Nakorn, Noppadol Siritanaratkul, Paolo Corradini, Suporn Chuncharunee, Je-Jung Lee, Robert L Schlossman, Tatiana Shelekhova, Kwee Yong, Daryl Tan, Tontanai Numbenjapon, Jamie D Cavenagh, Jian Hou, Richard LeBlanc, Hareth Nahi, Lugui Qiu, Hans Salvender, Stefano Pulini, Philippe Moreau, Krzysztof Warzocha, Darrell White, Joan Bladé, WenMing Chen, Javier de la Rubia, Peter Gimsing, Sagar Lonial, Jonathan L Kaufman, Enrique M Ocio, Ljupco Veskovski, Sang Kyun Sohn, Ming-Chung Wang, Jae Hoon Lee, Hermann Einsele, Monika Sopala, Claudia Corrado, Bourras-Rezki Bengoudifa, Florence Binlich, Paul G Richardson



Venetoclax in combination with bortezomib-dexa

Phase I/II study

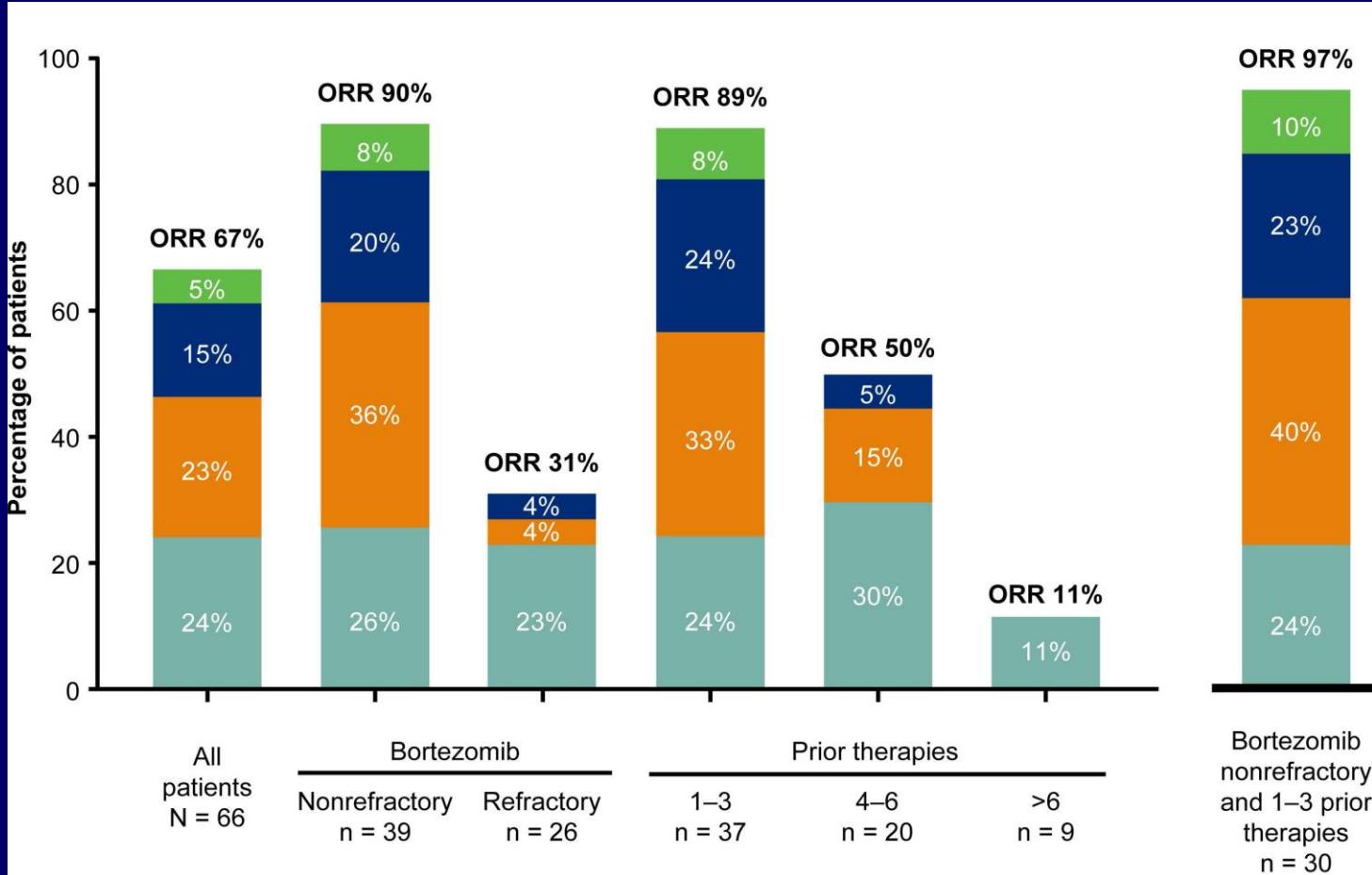
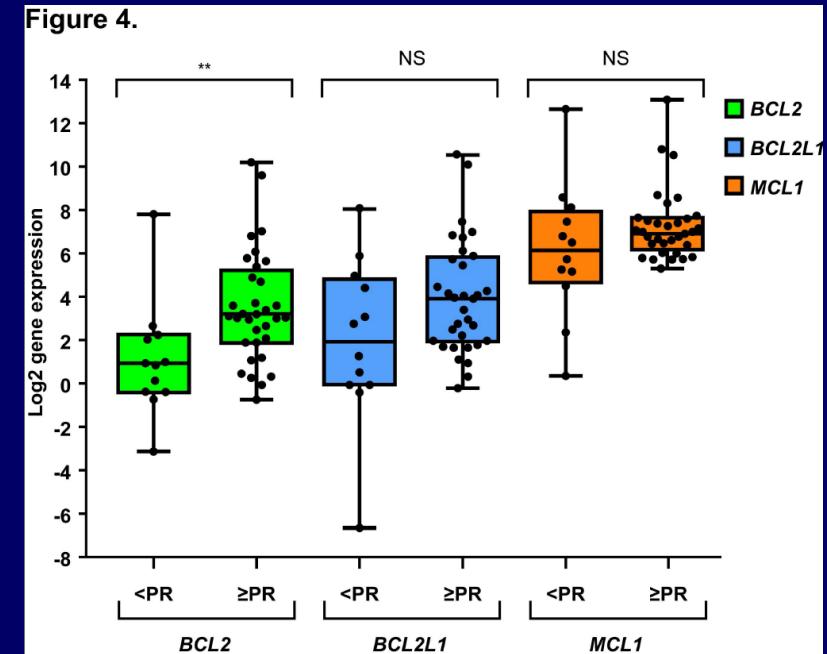
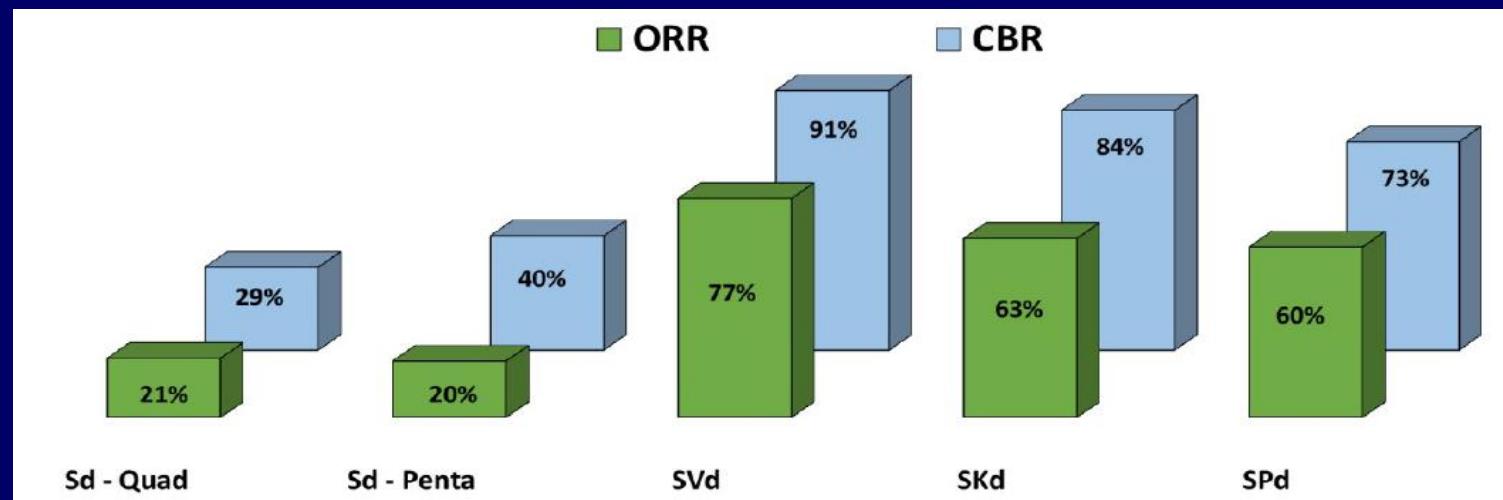


Figure 4.



Selinexor in refractory MM improved efficacy in combination

Patient Characteristics	Sd – Quad Patients	Sd – Penta Patients	SVd Patients	SKd Patients	SPd Patients
Patients Enrolled	48	31	33	22	20
Median Age (range)	62 (41 – 78)	68 (34 – 78)	63 (43 – 74)	64 (55 – 74)	61 (43 – 83)
Median Priors (range)	7 (3 – 16)	7 (5 – 17)	4 (1 – 11)	4 (2 – 10)	5 (2 – 9)



ORR = complete response + very good partial response
CBR = ORR + minor response

Lonial S, et al. Presented at IMW 2017 (Abstract OP-022), oral presentation

Conclusions

- The treatment paradigm of relapsed MM is rapidly changing
- IMIDs and PI's remain the backbone of MM treatment at relapse
- new treatment options create more complexity in therapeutic decision making
- however, with several options available, the treatment can be better tailored according to disease-, patient- related characteristics and previous treatment
- optimal prevention and management of adverse events can further improve the quality of life and improve compliance