Nuove Molecole in Arrivo

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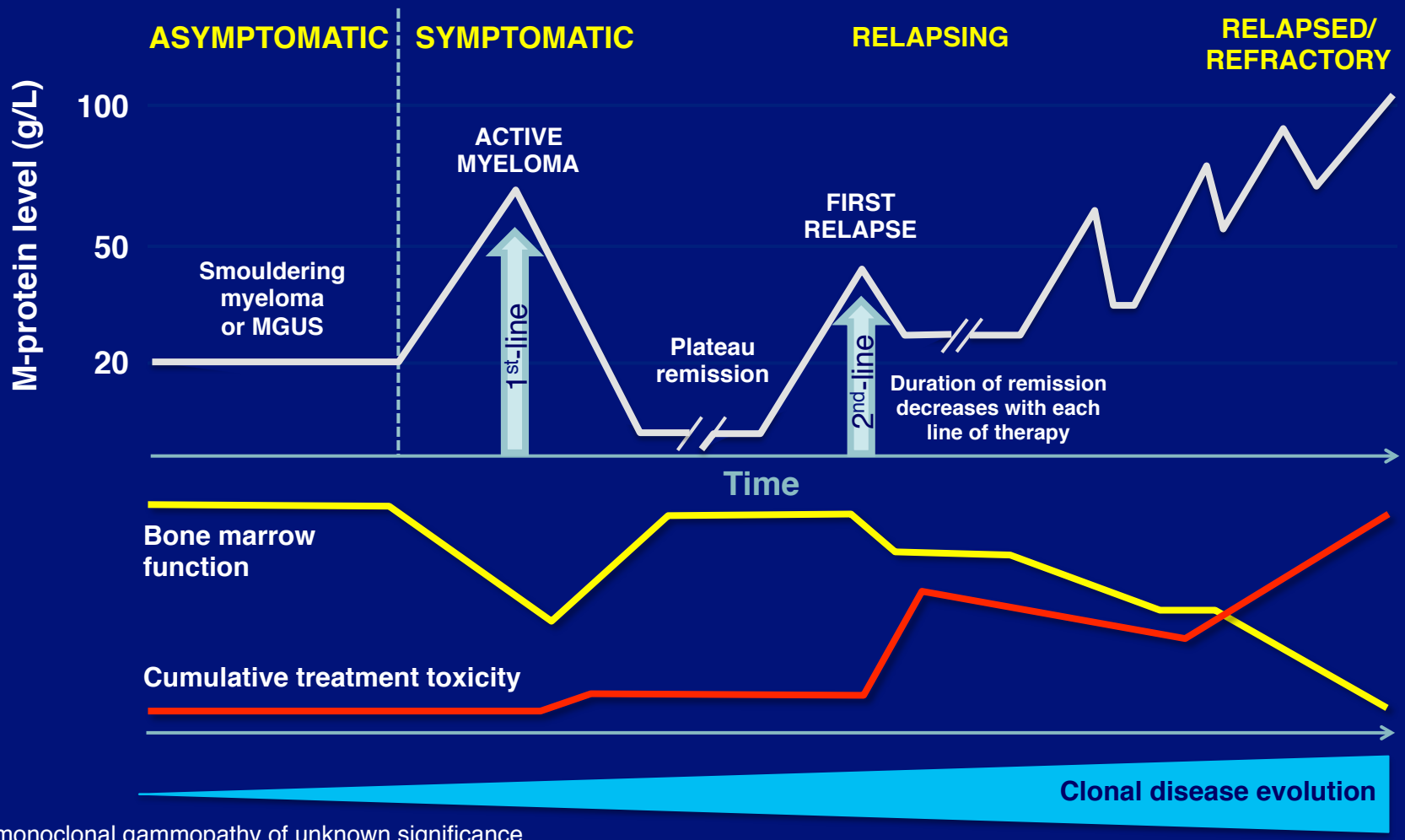
ttern of remission and relapse defines natural course of multiple myeloma

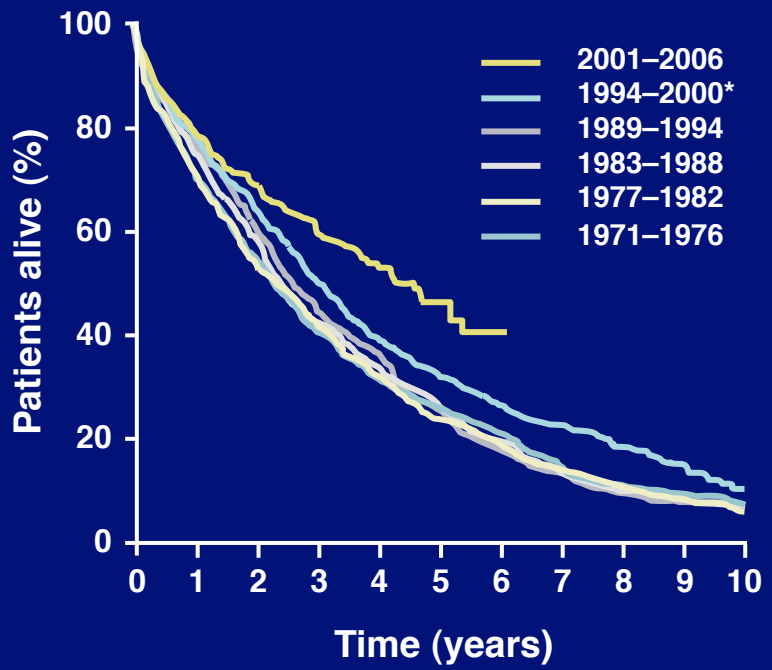


MGUS, monoclonal gammopathy of unknown significance.

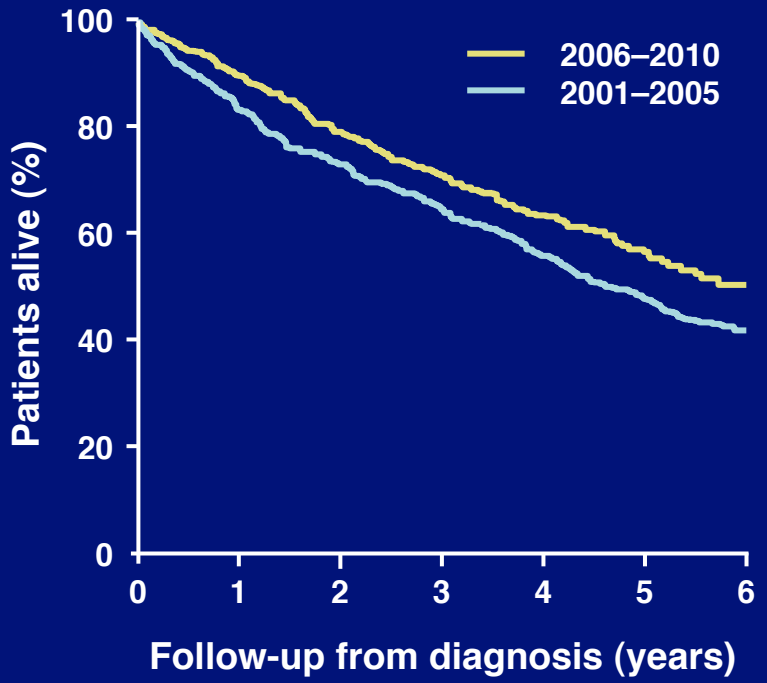
Figure adapted from Durie BGM. Concise review of the disease and treatment options; Edition 2016. http://myeloma.org/pdfs/ConciseReview.pdf [Accessed July 2016]; Chung DJ, et al. Cancer Immunol Res 2016;4:61-71; Boland E, et al. J Pain Symptom Manage 2013;46:671-80; Bolli N, et al. Nat Commun 2014;5:2997.

rtality remains high although novel agents have resulted in improved survival

OS from diagnosis between 1971 and 2006 (N=2,981)[1]



OS from diagnosis between 2001 and 2010 (N=1,038)[2]



mprovement during this time period thought to be due to high-dose therapy and supportive care.

There is still a need for more efficient treatments offering higher response and better outcomes

OS, overall survival.

[1] Adapted from Kumar SK, et al. Blood 2008;111:2516–20; [2] Kumar SK, et al. Leukemia 2014;28:1122–8.

Main randomized trials in relapsed refractory MM patient

Regimen	ORR, %	CR, %	TTP/PFS, mo	OS
Bortezomib vs Dexamethasone[1]	38 vs 18	6 vs 1	6.2 vs 3.5	80% vs 66% @ 1 year
Bortezomib+Doxil vs Bortezomib[2]	44 vs 41	4 vs 2	9.3 vs 6.5	76% vs 65% @ 15 mo
Lenalidomide-dexamethasone vs Dexamethasone[3,4]	61/60.2 vs 19./24	14.1/15.9 vs 0.6/3.4	11.1/11.3 vs 4.7/4.7	29.6/NR vs 20.2/20.6 mo
Pomalidomide – dexamethasone vs Dexamethasone[5]	31 vs 10	1 vs 0	4 vs 1.9	12.7 vs 8.1 mo

1.Richardson PG, et al. N Engl J Med. 2005; 352:2487-2498 2.Orlowski RZ, et al J Clin Oncol. 2007: 38
r DM, et al N Engl J Med. 2007; 357: 2133-2142 4. Dimopoulous M, et al. N Engl J med,. 2007; 357: 2123-2132, 5. San Miguel et al, Lancet Oncol 2013; 14(11)

Treatment options for relapsed refractory MM patients

Transplant Eligible Patients

Bortezomib-based Induction

↓

Autologous Transplant

Transplant Inelegible Patients

VMP/MPT

FIRST RELAPSE

Second Transplant

Lenalidomide-dexamethasone

Bortezomib-dexamethasone/Doxil

SECOND RELAPSE

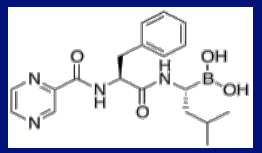
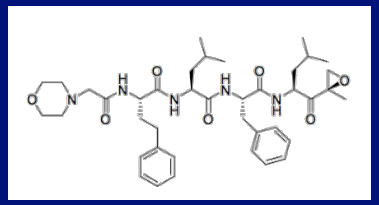
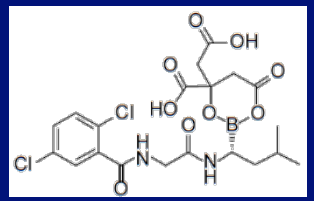
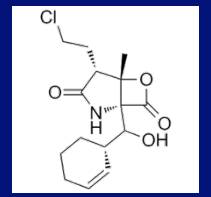
Lenalidomide-dexamethasone

Bortezomib-dexamethasone/Doxil

Pomalidomide-Dexamethasone*

*at second or subsequent relapse in pts pr
treated with both lenalidomide and bortezo

Treatment landscape: Proteasome inhibitors

	Bortezomib	Carfilzomib	Ixazomib	Marizomib
Structure & chemical class	 Boronate[3]	 Epoxyketone[3]	 Boronate[3]	 Lactam/β-lactone[3]
Type of Inhibition	Reversible[4]	**Irreversible**[4]	Reversible[4]	**Irreversible**[4]
Mechanism of Action	•Inhibits preferentially **β5**, but also **β1** and **β2**[2] •Formation of tetrahedral intermediate with side-chain hydroxyl groups (with proteasome and other classes of proteases)[6]	•Inhibits preferentially **β5**, but also **β1** and **β2**[2] •Formation of covalent adduct with N-terminal threonine active site (exclusively within the proteasome)[6]	•Inhibits preferentially **β5**, but also **β1** and **β2**[2]	•Inhibits **all three** proteolytic activities, with **IC50 values** in the **nM range**[5]
Route of Administration	Intravenous, subcutaneous[4]	Intravenous[3]	Oral[4]	Intravenous[4]

Proteasome inhibitors vary by chemical class, mechanism of action, type of inhibition[1-6]

[1] Mujtaba and Dou. Discov Med 2011;12(67):471-80; [2] Muz et al., Drug Des Devel Ther 2016;10:217-26; [3] Wang. Oncolog
Park) 2011; 25 Suppl 2:19-24; [4] Kurtin and Bilotti. J Adv Pract Oncol 2013;4(5):307-21; [5]
Curr Cancer Drug Targets 2011;11(3):254-84; [6] Arastu-Kapur et al. Clin Cancer Res 2011;1

Treatment landscape: Monoclonal antibodies

Target	Antibody	Mechanism of action	Activity as single agent	Activity/under evaluation in combo
CS1 (SLAMF7)	**Elotuzumab (Humanized IgG1k)**	ADCC Enhance NK activity Interference with cell interaction	-	+ VD + Rd
CD38	**Daratumumab (Fully human IgG1k)**	ADCC CDC ADCP Direct induction of apopotosis Modulation CD38 function	+	+ V-based + Rd + Pd
	Isatuximab (SAR650984; chimeric IgG1k)		+	+ VCD + Rd
	MOR202 (fully human IgG1λ)		+	

MM: multiple myeloma; ADCC: antibody depandent cell-mediated cytotoxicity; ADCP: antibody depedent cell-mediated phagocytosis; CDC; complement dependent cytotoxicity; VD: bortezomib-dexamethasone; Rd: lenalidomide;dexamethasone; Pd: pomalidomide-dexamethasone; VCD: bortezomib-cyclophosphamide-dexamethasone; V: bortezomib

Treatment options for relapsed refractory MM patients

Transplant Eligible Patients

Bortezomib-based Induction

↓

Autologous Transplant

Transplant Inelegible Patients

VMP/MPT

FIRST RELAPSE

Second Transplant

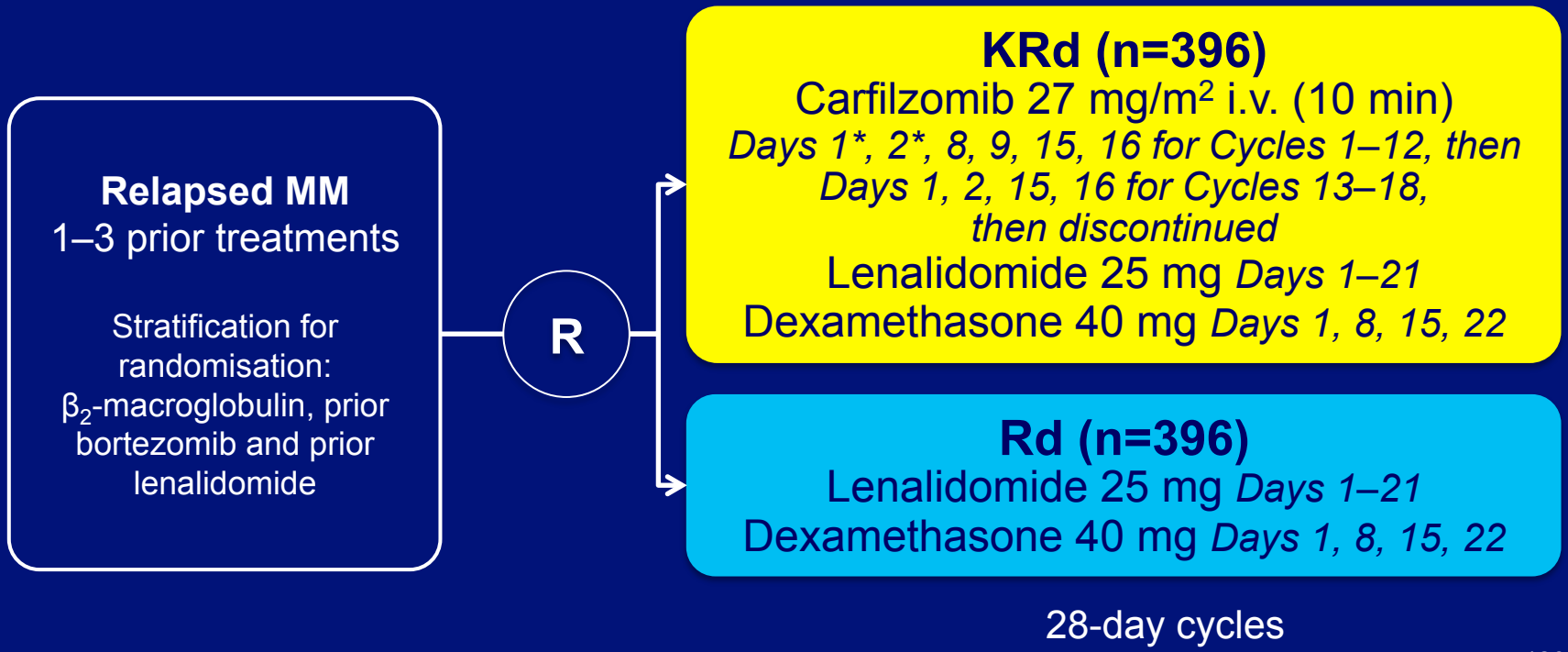
- Lenalidomide-dexamethasone
- Bortezomib-dexamethasone/Doxil

SECOND RELAPSE

- Lenalidomide-dexamethasone
- Bortezomib-dexamethasone/Doxil
- Pomalidomide-Dexamethasone*

*at second or subsequent relapse in pts previ
treated with both lenalidomide and bortezomib

Randomised, open-label, multicentre, phase 3 trial: KRd vs Rd

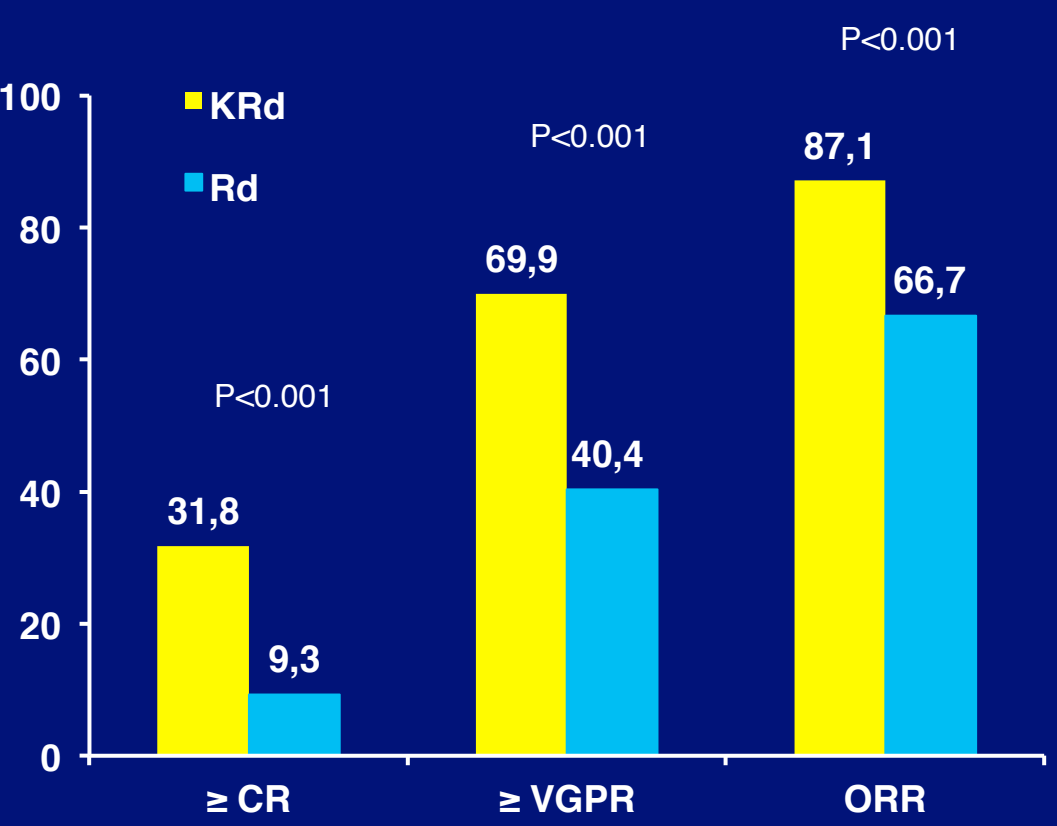


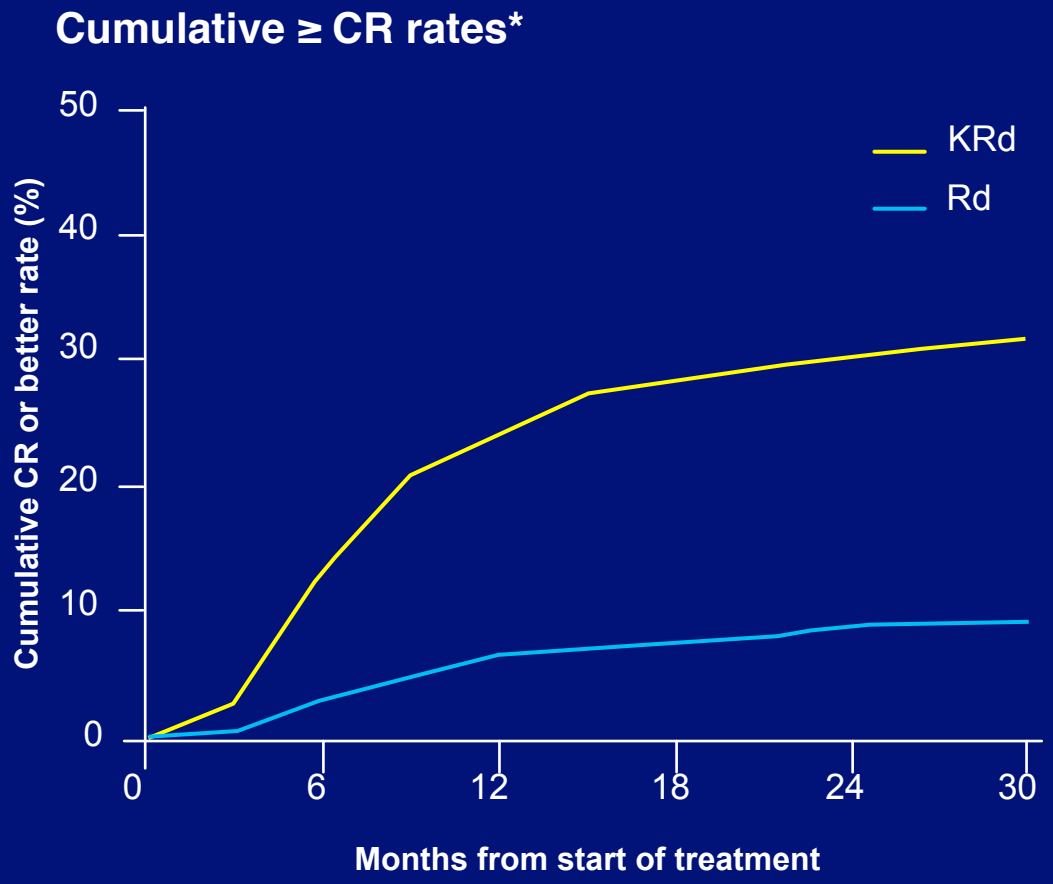
- N=792
- 1–3 prior treatments
- Excluded: Progressive disease while on bortezomib/lenalidomide*
- Primary endpoint: PFS
- Secondary endpoints: OS, ORR, DOR, HRQoL, safety

*20 mg/m2 on Days 1, 2, C

*PD after the first 3 months of therapy/ at any time if it was the last line of treatment; DOR, duration of response; HRQoL, health-related quality of life; i.v., intravenous; KRd, carfilz
omide and weekly dexamethasone; MM, multiple myeloma; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; R, randomisation; Rd, lenalidomide an
dexamethasone.Stewart AK, et al. N Engl J Med 2015;372

Response rates: KRd vs Rd

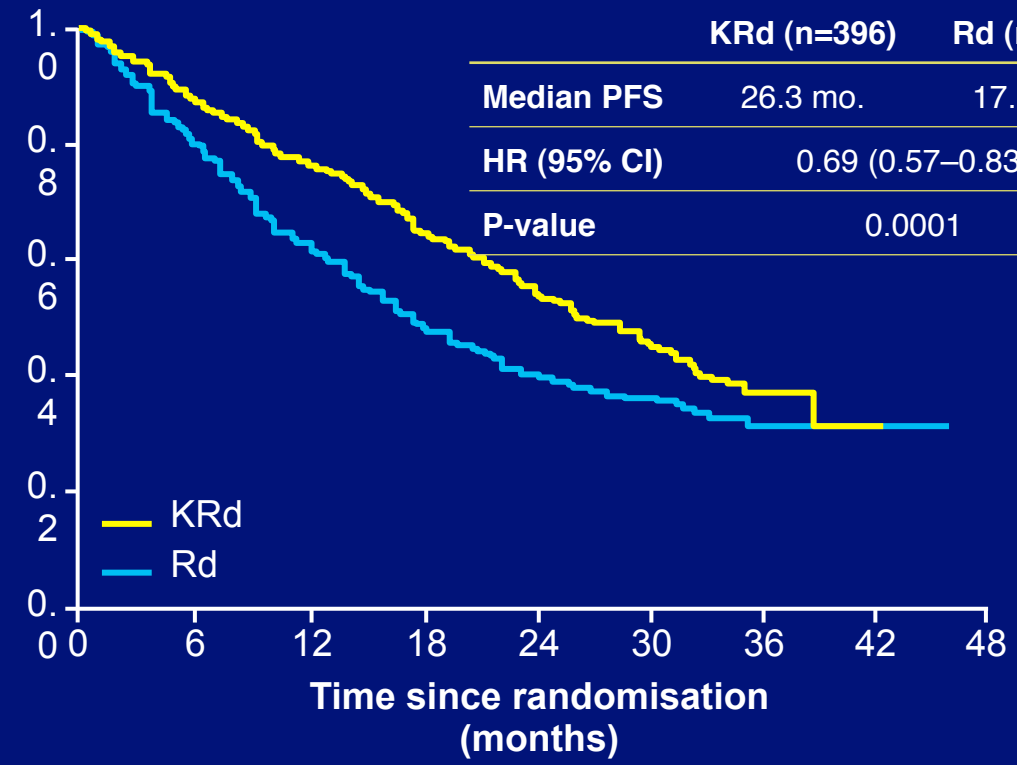




CR, complete response; KRd, carfilzomib with lenalidomide and weekly dexamethasone; ORR, overall response rate; Rd, lenalidomide and weekly dexamethasone; VGPR, very good partial response.

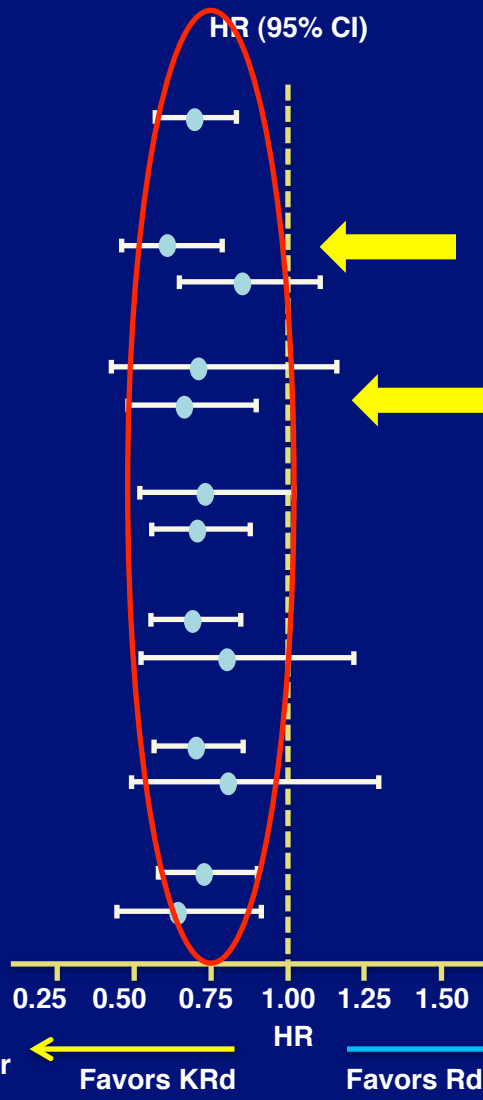
Stewart AK, et al. N Engl J Med 2015;372:142–52.

Progression free survival: KRd vs Rd



	KRd (n=396)	Rd (n=396)
Median PFS	26.3 mo.	17.6 mo.
HR (95% CI)	0.69 (0.57–0.83)	
P-value	0.0001	

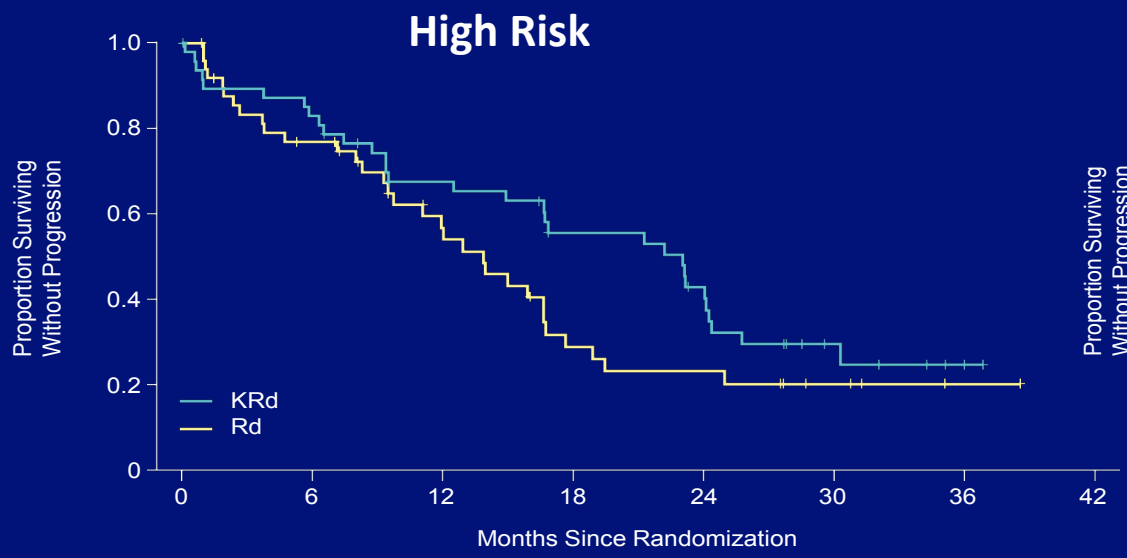
	KRd (n)	Rd (n)
Intent-to-treat group		
Overall	396	396
Subgroup		
Age, years		
18–64	211	188
≥65	185	208
Risk group by FISH		
High-risk	48	52
Standard-risk	147	170
Prior treatment with bortezomib		
No	135	136
Yes	261	260
Prior treatment with lenalidomide		
No	317	318
Yes	79	78
Non-responsive to bortezomib in any prior regimen		
No	336	338
Yes	60	

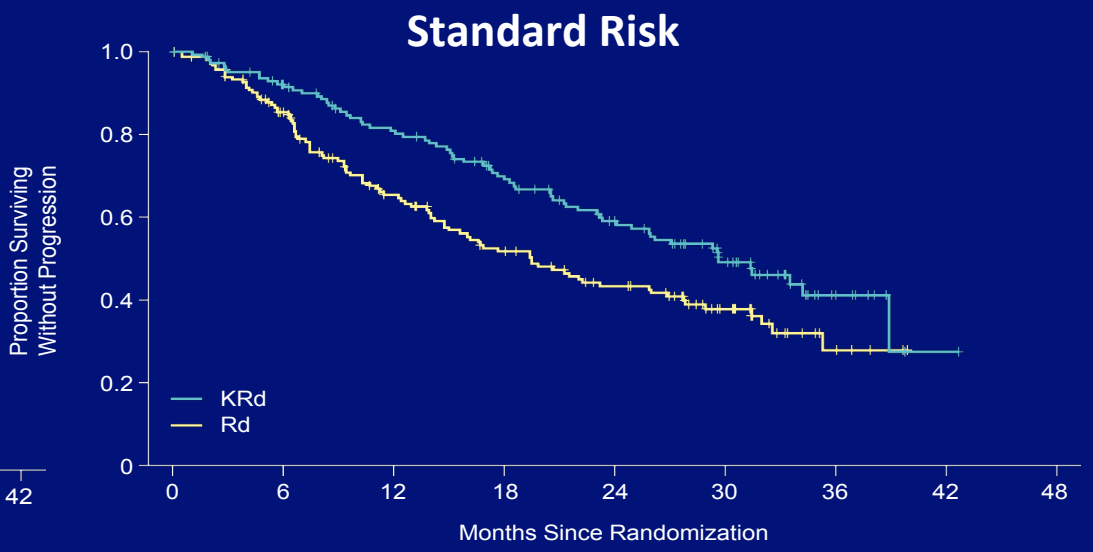


o was discontinued after cycle 18, which corresponds to 16.5 months since randomisation.

nfidence interval; HR, hazard ratio; KRd, carfilzomib with lenalidomide and weekly dexamethasone; CI, confidence interval; FISH, fluorescence in situ hybridisation; azard ratio; IMiD, immunomodulatory drugs; KRd, carfilzomib with lenalidomide and weekly dexamethasone; Rd, lenalidomide and weekly dexamethasone.PFS, progression-free s nalidomide and weekly dexamethasone.Stewart AK, et al. N Engl J Med 2015;372:142–52.

Phase III ASPIRE: PFS Subgroup analysis based on cytogenetic status





	KRd (n=48)	Rd (n=52)
PFS, median months	23.1	13.9
Hazard ratio (95% CI)	0.70 (0.43–1.16)	

	KRd (n=147)	Rd (n=170)
PFS, median months	29.6	19.5
Hazard ratio (95% CI)	0.66 (0.48–0.90)	

- In the high-risk group, treatment with KRd resulted in a median PFS of nearly 2 years, which was a 9-month improvement vs Rd (HR, 0.70)
- Treatment with KRd also led to a 10-month improvement in median PFS vs Rd in patients with standard-risk cytogenetics (HR, 0.66)

Avet Loiseau H, ASH 2015 Abst 731

Safety: KRd vs Rd

gory	KRd (n=392)	Rd (n=389)
an treatment duration, ks	88.0	57.0
AE, % ade ≥3 treatment- nergent AE	96.9 83.7	97.2 80.7
tment discontinuations, % D E	69.9 39.8 15.3	77.9 50.1 17.7
ous AE, %	59.7	53.7
hs within 30 days of last , % D es	7.7 0.5 6.9	8.5 1.3 6.9

Adverse event of interest, %	KRd (n=392)		Rd (n=389)	
	All Grade	Grade ≥3	All Grade	Gra ≥
Dyspnoea	19.4	2.8	14.9	1
Peripheral neuropathy†	17.1	2.6	17.0	3
Hypertension	14.3	4.3	6.9	1
Acute renal failure†	8.4	3.3	7.2	3
Cardiac failure†	6.4	3.8	4.1	1
Deep vein thrombosis	6.6	1.8	3.9	1
Ischaemic heart disease†	5.9	3.3	4.6	2
Pulmonary embolism	3.6	3.1	2.3	2
Second primary malignancy†	2.8	2.3	3.3	2

AE, adverse event; KRd, carfilzomib with lenalidomide and weekly dexamethasone; Rd, lenalidomide and weekly dexamethasone.
Stewart AK, et al. N Engl J Med 2015;372:142–52.

Phase 3 study of weekly oral ixazomib plus lenalidomide-dexamethasone

Global, double-blind, randomized, placebo-controlled study design

-3 prior lines
xcluded
efractory to PIs
nd Len Based

N=722

Randomization

1:1

Ixazomib + Lenalidomide + Dexamethasone
Ixazomib: 4 mg on days 1, 8, and 15
Lenalidomide: 25 mg* on days 1-21
Dexamethasone: 40 mg on days 1, 8, 15, 22

Repeat every 28 days until progression, or unacceptable toxicity

Placebo + Lenalidomide + Dexamethasone
Placebo: on days 1, 8, and 15
Lenalidomide: 25 mg* on days 1-21
Dexamethasone: 40 mg on days 1, 8, 15, 22

Stratification:
- Prior therapy: 1 vs 2 or 3
- ISS: I or II vs III
- PI exposure: yes vs no

Primary endpoint:
- PFS

Key secondary endpoints:
- OS
- OS in patients with del(17p)

Response and progression (IMWG 2011 criteria[1]) assessed by an independent review committee (IRC) blinded to both treatment and investigator assessment

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

1. Rajkumar S, et al. Blood 2011;117:4691–5.

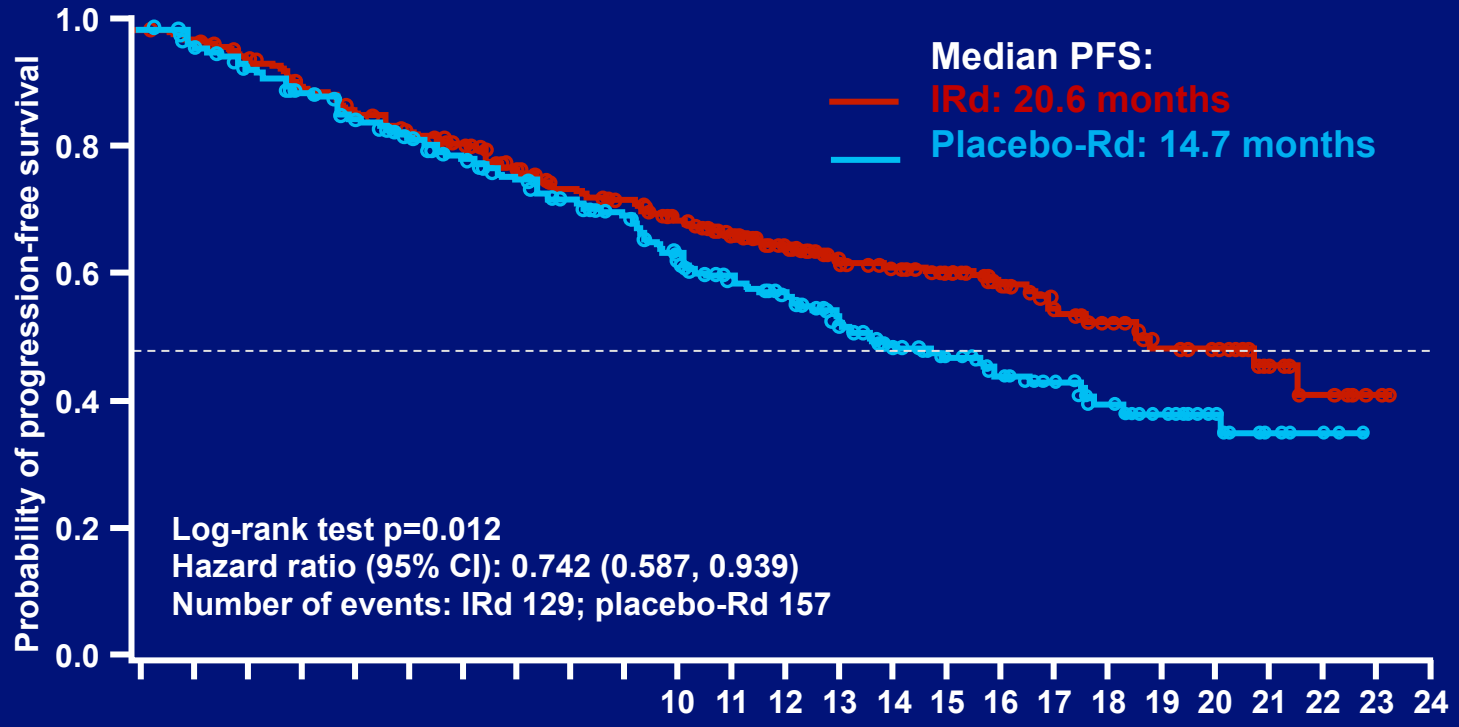
Moreau P, ASH 2015 Abst 727

Improved response rates, durable responses, and improved time to progression (TTP) with IRd

Response rates	IRd (N=360)	Placebo-Rd (N=362)	p-value
Confirmed ORR (≥PR), %	78.3	71.5	p=0.035
CR+VGPR, %	48.1	39.0	p=0.014
Response categories			
CR, %	11.7	6.6	p=0.019
PR, %	66.7	64.9	–
VGPR, %	36.4	32.3	–
Median time to response, mos	1.1	1.9	–
Median duration of response, mos	20.5	15.0	–
Median TTP, mos	21.4	15.7	HR 0.712 P=0.007

Moreau P, ASH 2015 Abst 727

Final PFS analysis



Number of patients at risk:																								
IRd	360	345	332	315	298	283	270	248	233	224	206	182	145	119	111	95	72	58	44	34	26	14	9	1	0
Placebo-Rd	362	340	325	308	288	274	254	237	218	208	188	157	130	101	85	71	58	46	31	22	15	5	3	0	0

Median follow-up: ~15 months

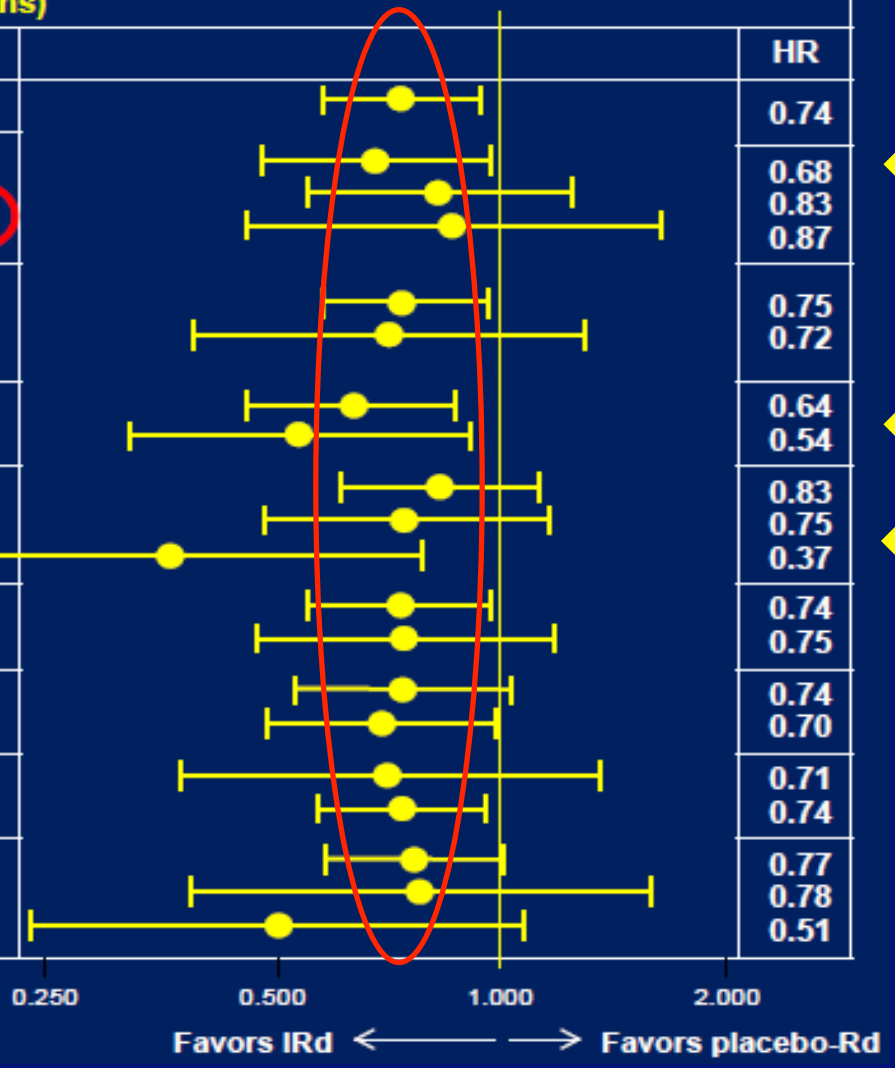
A significant, 35% improvement in PFS with IRd vs placebo-Rd

Interim OS analysis @ 23 months of FU: 81 and 90 deaths in ixazomib and placebo, respectively

Moreau P, ASH 2015 Abst 727

Ird vs Rd: Subgroup analysis

		N		Median PFS (months)		
Variable	Subgroup	Placebo-Rd	IRd	Placebo-Rd	IRd	HR
All patients	ALL	362	360	14.7	20.6	0.74
Age (yrs)	≤65	176	168	14.1	20.6	0.68
	>65-75	125	145	17.6	17.5	0.83
	>75	61	47	13.1	18.5	0.87
ISS stage (stratification factor)	I or II	318	314	15.7	21.4	0.75
	III	44	46	10.1	18.4	0.72
Cytogenetic risk	Standard-risk	216	199	15.6	20.6	0.64
	High-risk	62	75	9.7	21.4	0.54
Number of prior therapies	1	217	224	15.9	20.6	0.83
	2	111	97	14.1	17.5	0.75
	3	34	39	10.2	NE	0.37
Proteasome inhibitor	Exposed	253	250	13.6	18.4	0.74
	Naive	109	110	15.7	NE	0.75
Prior IMiD therapy	Exposed	204	193	17.5	NE	0.74
	Naïve	158	167	13.6	20.6	0.70
Refractory to last prior therapy	Yes	55	59	NE	NE	0.71
	No	307	301	14.1	20.6	0.74
Relapsed or refractory	Relapsed	280	276	15.6	18.7	0.77
	Refractory	40	42	13.0	NE	0.78
	Ref & rel	42	41	13.1	NE	0.51



Moreau P, NEJM 2016

AEs after median follow-up of 23 months: increased rates with IRd driven by low-grade events

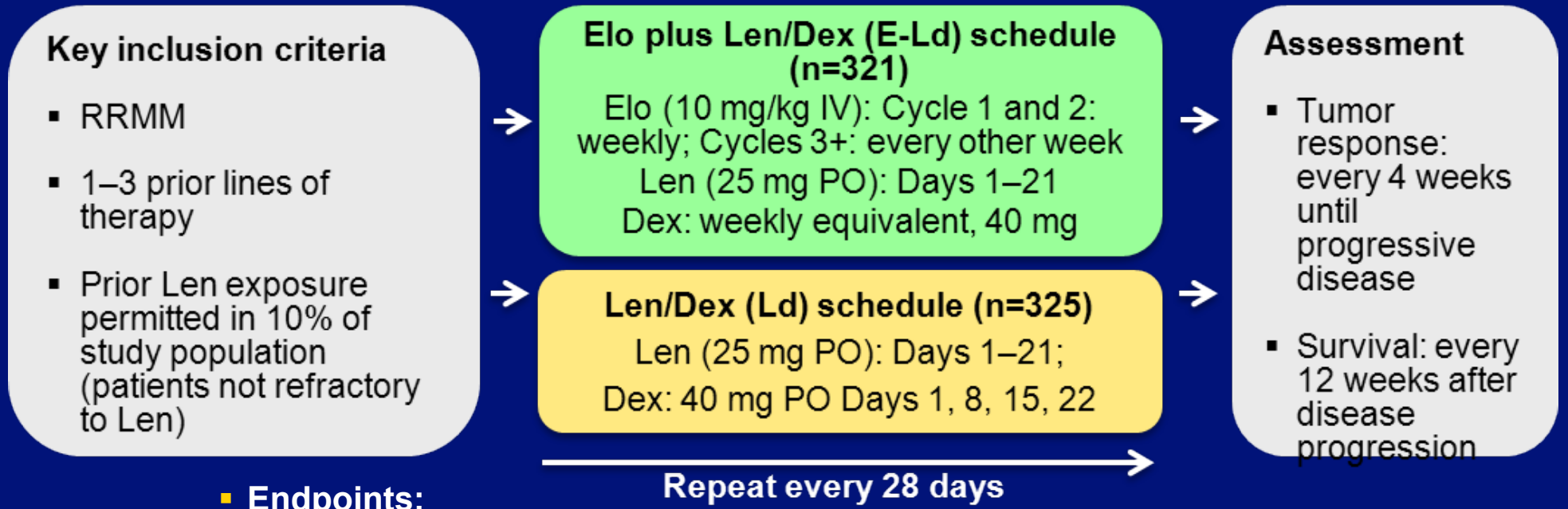
	IRd (N=361), %			Placebo-Rd (N=359), %		
Preferred terms	All-grade	Grade 3	Grade 4	All-grade	Grade 3	Grade 4
AEs overlapping with lenalidomide						
Diarrhea	45	6	0	39	3	0
Constipation	35	<1	0	26	<1	0
Nausea	29	2	0	22	0	0
Vomiting	23	1	0	12	<1	0
Rash*	36	5	0	23	2	0
Back pain	24	<1	0	17	3	0
Upper respiratory tract infection	23	<1	0	19	0	0
Thrombocytopenia	31	12	7	16	5	4
AEs with proteasome inhibitors						
Peripheral neuropathy*	27	2	0	22	2	0
Peripheral edema	28	1	0	20	1	0
AEs with lenalidomide						
Thromboembolism*	8	2	<1	11	3	<1
Neutropenia*	33	18	5	31	18	6

*Represents multiple MedDRA preferred terms.

Moreau P, ASH 2015 Abst 727

ELOQUENT-2: Elotuzumab-Ld vs Ld

- Open-label, international, randomized, multicenter, phase 3 trial (168 global sites)

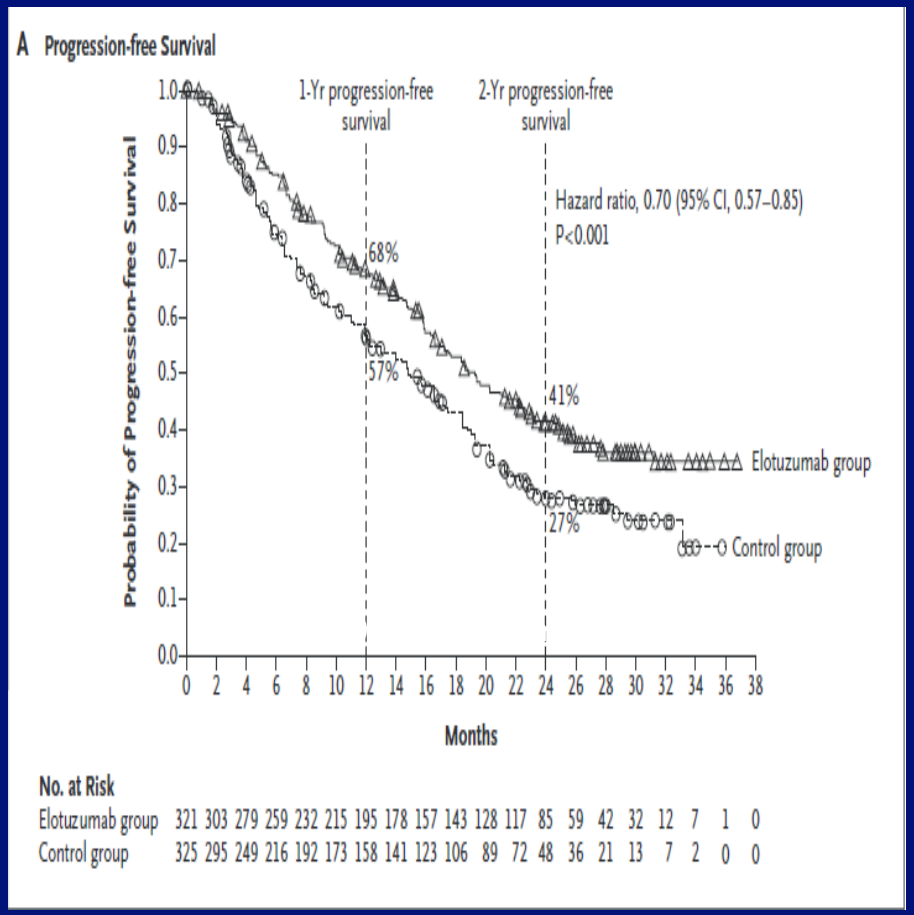


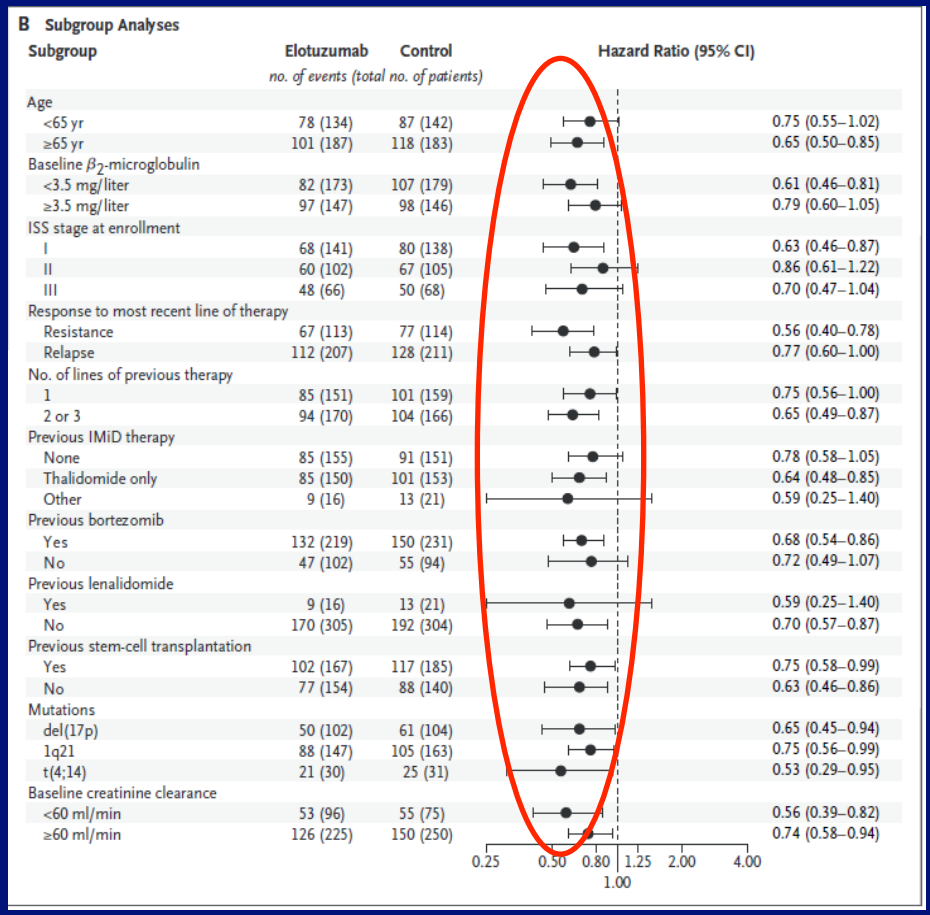
- **Endpoints:**
  - **Co-primary: PFS and ORR**
  - **Other: overall survival (data not yet mature), duration of response, quality of life, safety**
- **All patients received premedication to mitigate infusion reactions prior to elotuzumab administration**
- **Elotuzumab IV infusion administered ~ 2–3 hours**

Lonial S et al N Engl J Med, 2015: 1-11

ELOQUENT-2: Elotuzumab-Ld vs Ld

Progression-free survival





lenalidomide-dexamethasone

Major benefit in pts with 1 prior line of therapy and > median time from diagnosis*

Lonial S et al N Engl J Med, 2015: 1-11; *Post hoc analysis EHA

ELOQUENT-2: Elotuzumab-Ld vs Ld

Safety

Event	Elotuzumab Group (N=318)		Control Group (N=317)	
	Any Grade	Grade 3 to 4	Any Grade	Grade 3 to 4
Common hematologic toxic effect — no. (%)†				
Lymphocytopenia	316 (99)	244 (77)	311 (98)	154 (49)
Anemia	306 (96)	60 (19)	301 (95)	67 (21)
Thrombocytopenia	266 (84)	61 (19)	246 (78)	64 (20)
Neutropenia	260 (82)	107 (34)	281 (89)	138 (44)
Common nonhematologic adverse event — no. (%)				
General disorder				
Fatigue	149 (47)	27 (8)	123 (39)	26 (8)
Pyrexia	119 (37)	8 (3)	78 (25)	9 (3)
Peripheral edema	82 (26)	4 (1)	70 (22)	1 (<1)
Nasopharyngitis	78 (25)	0	61 (19)	0
Gastrointestinal disorder				
Diarrhea	149 (47)	16 (5)	114 (36)	13 (4)
Constipation	113 (36)	4 (1)	86 (27)	1 (<1)
Musculoskeletal or connective-tissue disorder				
Muscle spasms	95 (30)	1 (<1)	84 (26)	3 (1)
Back pain	90 (28)	16 (5)	89 (28)	14 (4)
Other disorder				
Cough	100 (31)	1 (<1)	57 (18)	0
Insomnia	73 (23)	6 (2)	82 (26)	8 (3)

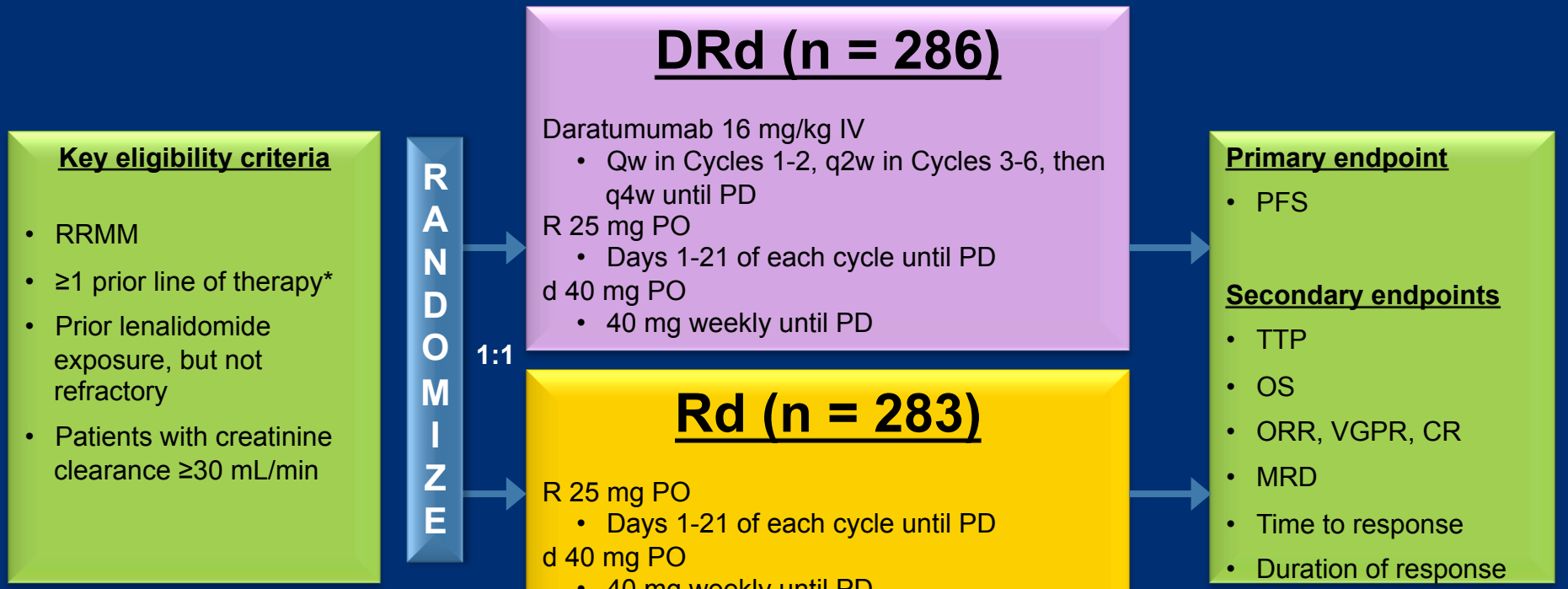
- **No Grade 4–5 infusion reactions**
- **33 patients (10%) infusion reaction , 29/33 grade 1-2**
- **2 (1%) discontinued because of an infusion reaction**

enalidomide-dexamethasone

Lonial S et al N Engl J Med, 2015: 1-11

POLLUX: Study Design

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



Stratification factors

- No. prior lines of therapy
- ISS stage at study entry
- Prior lenalidomide

Cycles: 28 days

Statistical analyses

- 295 PFS events: 85% power for 7.7 month PFS improvement
- Interim analysis: ~177 PFS events

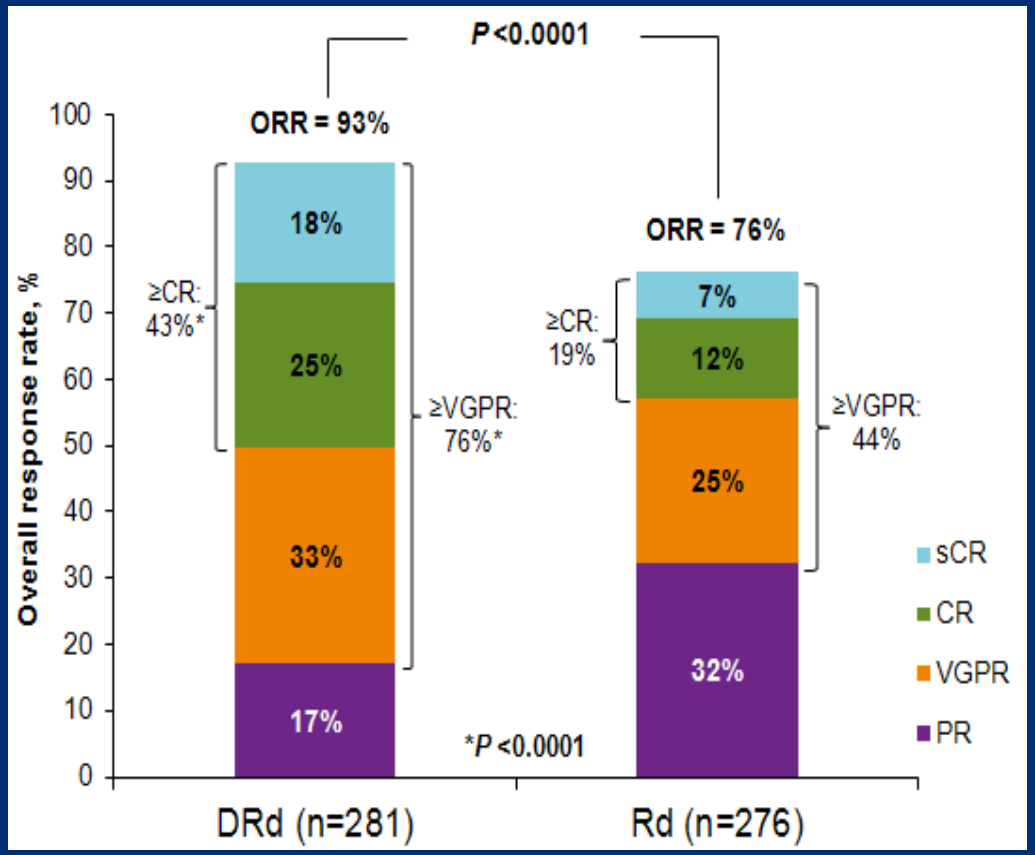
Pre-medication for the DRd treatment group consisted of dexamethasone 20 mg[a], paracetamol, and an antihistamine

[a]On 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.* around 90% of pts 1-3 prior lines

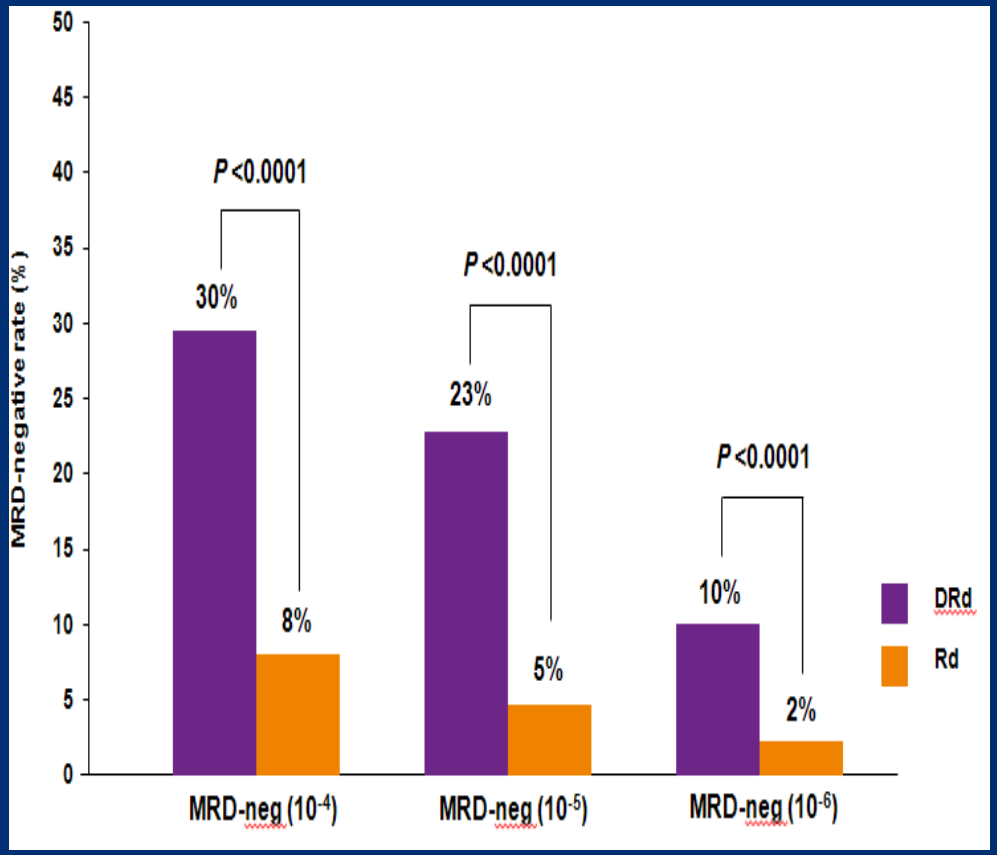
Dimopoulus et al.

POLLUX: Study Design

Overall response rate



MRD negative rate



- Median duration of response: Not reached for DRd vs 17.4 months for Rd
- Median time to response: 1.0 month for DRd vs 1.3 months for Rd

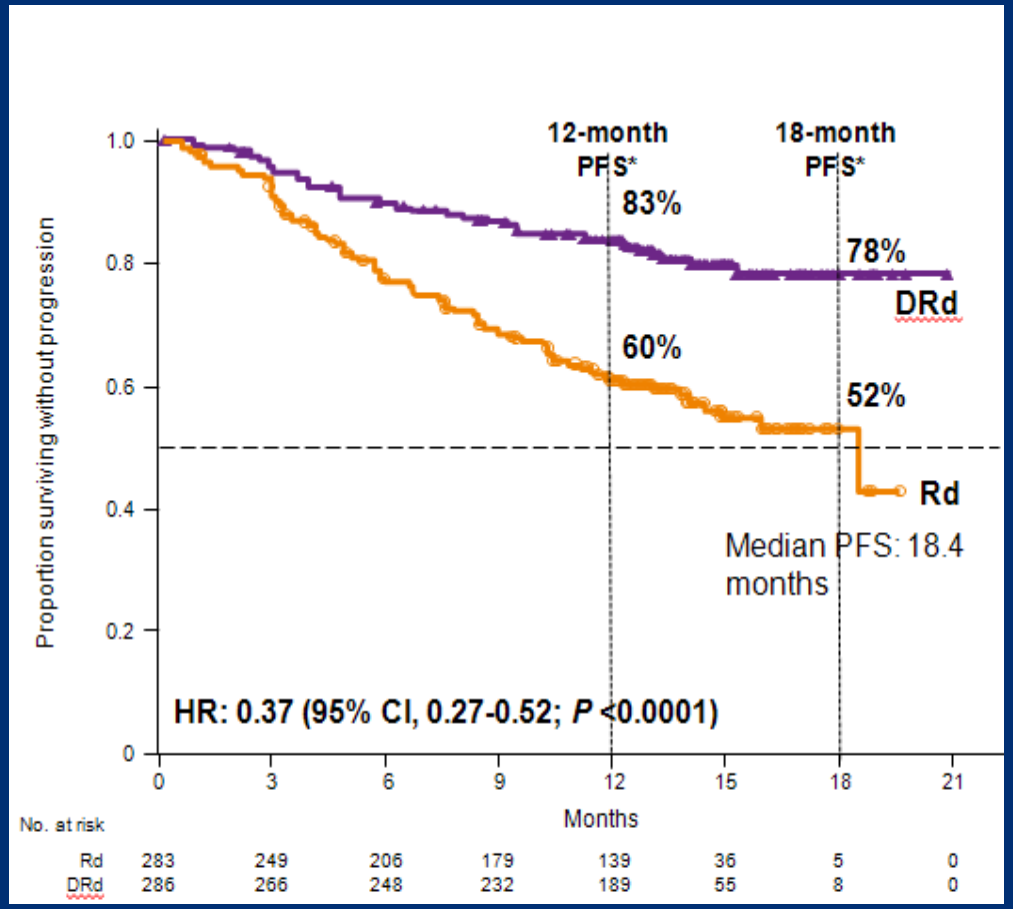
Significantly higher MRD-negative rates for DRd vs Rd

Daratumumab lenalidomide dexamethasone; Rd: lenalidomide dexamethasone

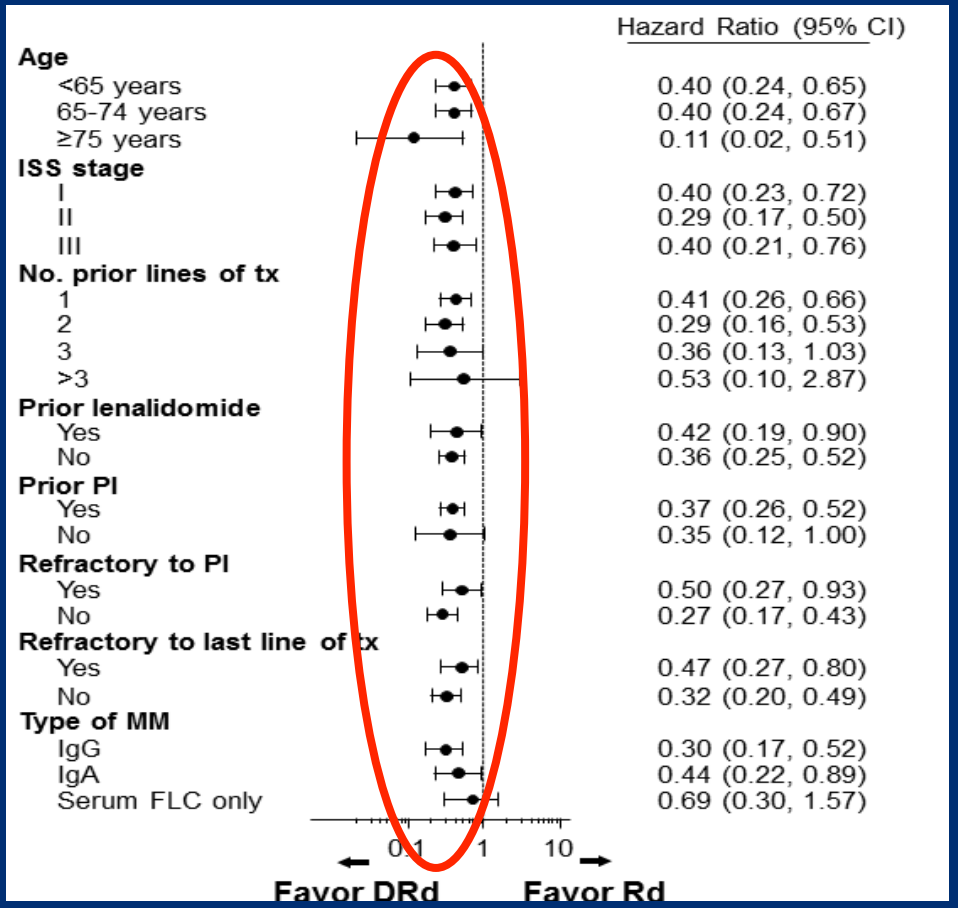
Dimopoulus et al.

POLLUX: Study Design

Progression-free Survival (PFS)



PFS: Subgroup analysis



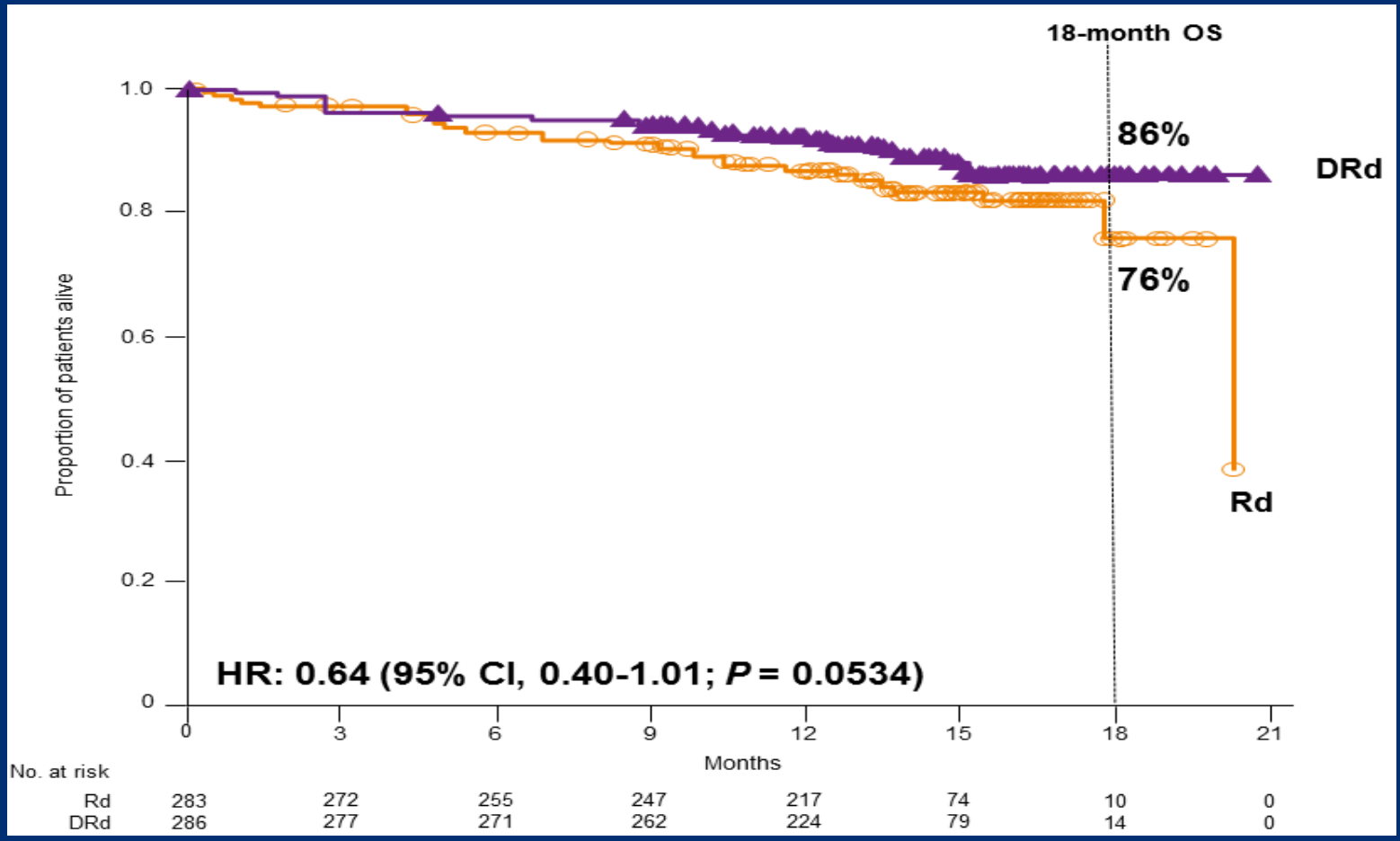
63% reduction in the risk of disease progression or death for DRd vs Rd

Higher efficacy was observed for DRd versus Rd across all subgroups

Daratumumab lenalidomide dexamethasone; Rd: lenalidomide dexamethasone

Dimopoulus et al.

Overall Survival



18-month overall survival: 86% in DRd versus 76% in Rd

Daratumumab lenalidomide dexamethasone; Rd: lenalidomide dexamethasone

Dimopoulus M et al.

Adverse Events (AEs)

Infusion-related Reactions (IRRs)

IRRs ≥2%	Safety Analysis Set (n = 283)	
	All grades (%)	Grade 3 (%)
Patients with IRRs	48	5
Cough	9	0
Dyspnea	9	0.7
Vomiting	6	0.4
Nausea	5	0
Chills	5	0.4
Bronchospasm	5	0.4
Pruritus	3	0.4
Throat irritation	3	0
Headache	3	0
Nasal congestion	3	0
Wheezing	2	0.7
Laryngeal edema	2	0.4
Rhinorrhea	2	0
Pyrexia	2	0

- No grade 4 or 5 IRRs were reported
- 92% of all IRRs occurred during the first infusion
- 1 patient discontinued daratumumab due to an IRR

Most common AEs

	DRd (n = 283)		Rd (n = 281)	
Hemat AEs	All-grade (%) ≥25%	Grade 3/4 (%) ≥5%	All-grade (%) ≥25%	Grade 3/4 (%) ≥5%
Neutropenia	59	52	43	37
Febrile neutropenia	6	6	3	3
Anemia	31	12	35	20
Thrombocytopenia	27	13	27	14
Lymphopenia	6	5	5	4
Non-hemat AEs				
Diarrhea	43	5	25	3
Fatigue	35	6	28	3
Upper resp. tract infection	32	1	21	1
Constipation	29	1	25	0.7
Cough	29	0	13	0
Muscle spasms	26	0.7	19	2
Pneumonia	14	8	13	8

Infections and infestations:

- Grade 3 or 4: 28% patients in DRd vs 23% patients in Rd
- The most common grade 3 or 4 infections/infestations AE was pneumonia (8% vs 8%)

aratumumab lenalidomide dexamethasone; Rd: lenalidomide ethasone

Dimopoulus et al.

Strategies at relapse…
How to make the right choice?

Patient Characteristics

Age
Comorbidities (cardiovascular, pulmonary functions)
Compliance

Efficacy of Previous therapy

1-3 prior lines
Lenalidomide naive (sensitive)
Bortezomib naive/sensitive/ refractory

Safety of Previous therapy

Toxicities
Neuropathy
DVT/PE
Cardiac toxicity

Type of relapse

Aggressiveness

Treatment options for relapsed refractory MM patients

Transplant Eligible Patients

Bortezomib-based Induction

↓

Autologous Transplant

Transplant Inelegible Patients

VMP/MPT

FIRST RELAPSE

Second Transplant

- Lenalidomide-dexamethasone
- Bortezomib-dexamethasone/Doxil

SECOND RELAPSE

- Lenalidomide-dexamethasone
- Bortezomib-dexamethasone/Doxil
- Pomalidomide-Dexamethasone*

*at second or subsequent relapse in pts previ
treated with both lenalidomide and bortezomib

Treatment options for relapsed refractory MM patients

Transplant Eligible Patients

Bortezomib-based Induction

↓

Autologous Transplant

Transplant Inelegible Patients

VMP/MPT

FIRST RELAPSE

Second Transplant

KRd; ERd; DRd, IRd

Bortezomib-dexamethasone/Doxil

SECOND RELAPSE

KRd; Erd; DRd, IRd

Bortezomib-dexamethasone/Doxil

Pomalidomide-Dexamethasone*

*at second or subsequent relapse in pts pre
treated with both lenalidomide and bortezor

Treatment options for relapsed refractory MM patients

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Bortezomib-dexamethasone/Doxil

Pomalidomide-Dexamethasone*

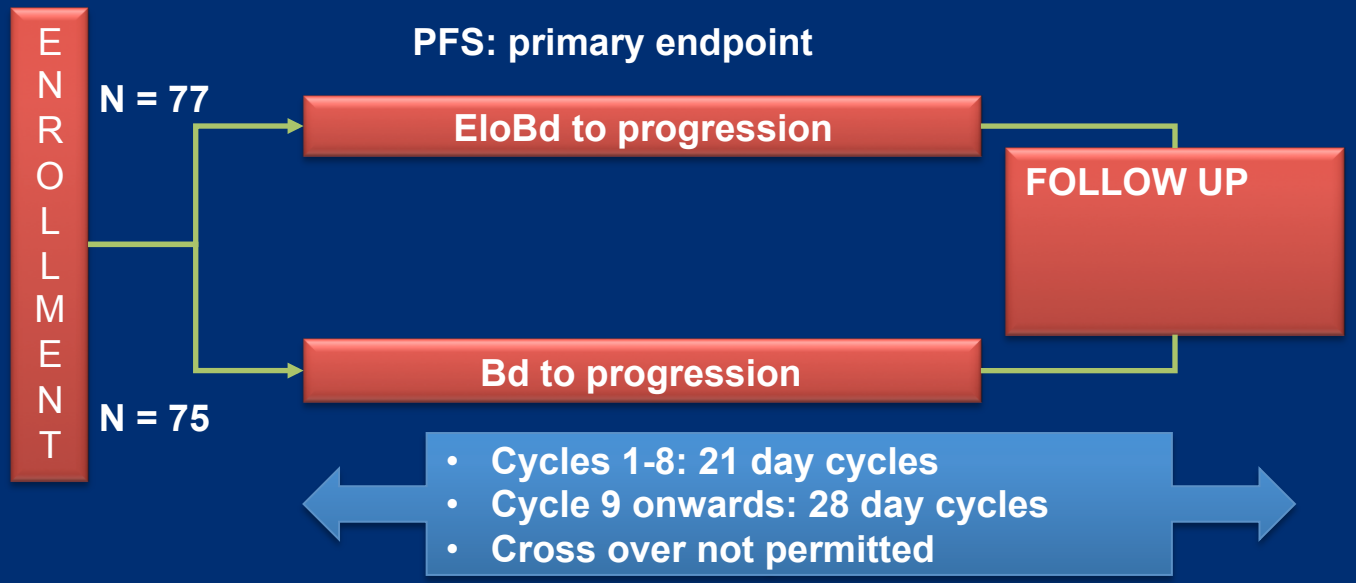
*at second or subsequent relapse in pts pre
treated with both lenalidomide and bortezor

CA204-009: A randomized, open-label, phase 2 study of tezomib and dexamethasone with or without elotuzumal patients with RRMM

- **Investigational arm (EloBd): elotuzumab 10 mg/kg IV + bortezomib 1.3 mg/m^2 IV* + (dexamethasone 20 mg po, *or* 8 mg IV and 8 mg po)**
- **Control arm (Bd): bortezomib 1.3 mg/m^2 IV + dexamethasone 20 mg po**

Key inclusion criteria

- RRMM
- 1–3 prior therapies
- ECOG PS ≤2
- Prior proteasome inhibitor (PI) treatment permitted if not refractory to PI



Sample Size/Power:

- N = 152. 80% power to detect a HR of 0.69 with 103 progression events
- 2-sided 0.30 significance level specified to test for difference in PFS between arms (p≤0.3 was considered significant

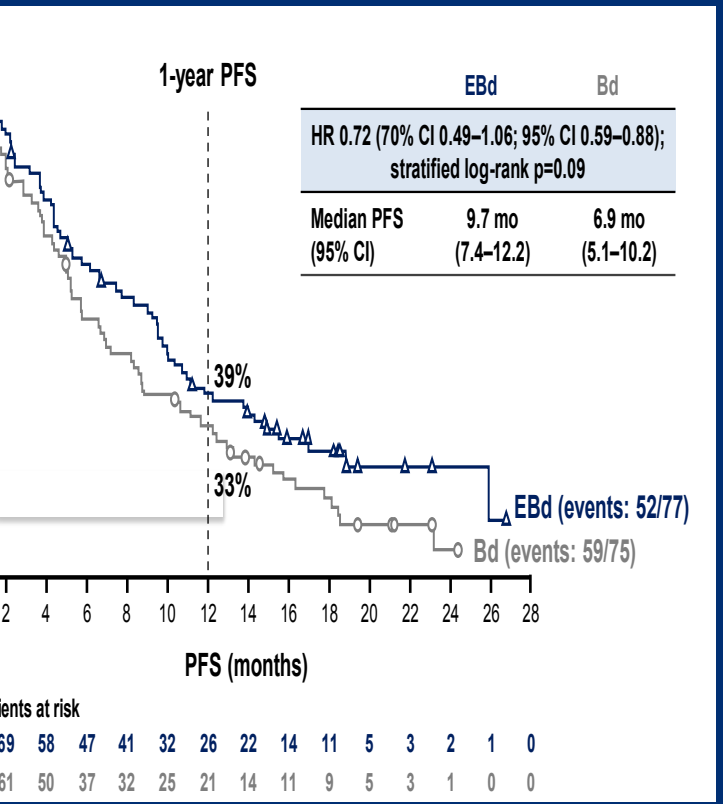
Accrual from Nov 2011
Interim analysis: June 2014

*Bortezomib to be administered SC following regulatory approval

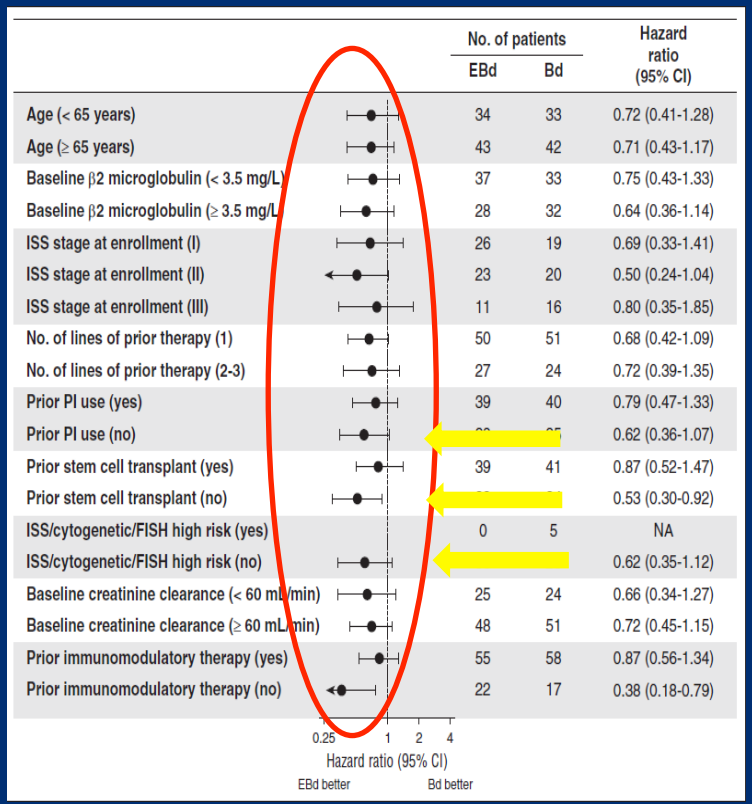
Jakubowiak A et al. EHA 2015

CA204-009: A randomized, open-label, phase 2 study of tezomib and dexamethasone with or without elotuzumal patients with RRMM

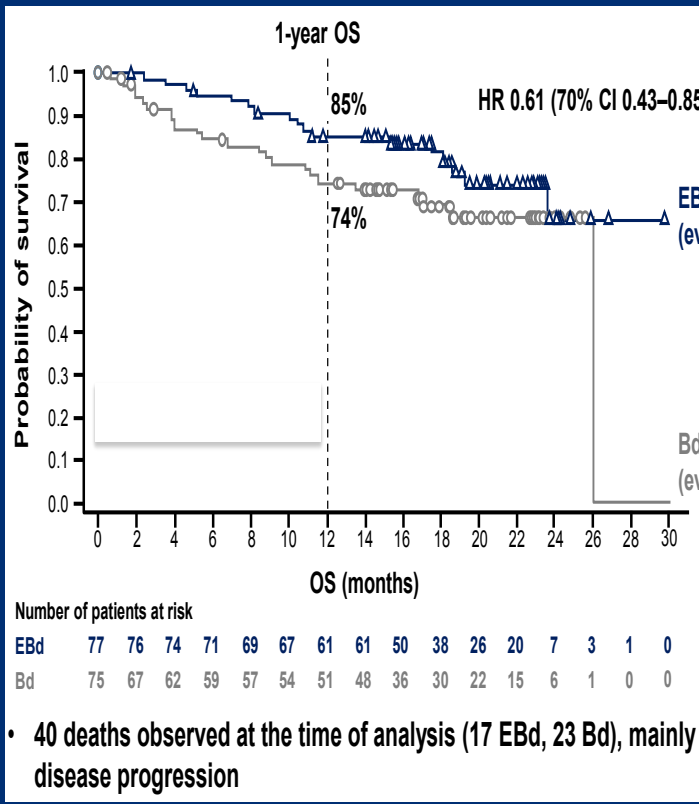
PFS



PFS subgroup analysis



OS



- 40 deaths observed at the time of analysis (17 EBd, 23 Bd), mainly disease progression

Elotuzumab-bortezomib-dexamethasone; Bd: bortezomib dexamethasone; PFS: progression-free survival, OS: overall survival

Jakubowiak A ,et al. EHA 2015 a
Jakubowiak A, et al. Blood. 2016;127(23):2

A204-009: A randomized, open-label, phase 2 study of bortezomi dexamethasone with or without elotuzumab in patients with RR

Safety

Events, n (%)	EBd (n=75)		Bd (n=75)	
	Any grade	Grade 3–4	Any grade	Grade 3–4
All adverse events	75 (100)	51 (68)	72 (96)	45 (60)
Infections and infestations	49 (65)	13 (17)	40 (53)	10 (13)
Diarrhea	32 (43)	6 (8)	25 (33)	3 (4)
Constipation	29 (39)	1 (1)	22 (29)	0
Cough	29 (39)	1 (1)	17 (23)	0
Anemia	28 (37)	5 (7)	21 (28)	5 (7)
Peripheral neuropathy	26 (35)	6 (8)	25 (33)	7 (9)
Pyrexia	25 (33)	0	20 (27)	3 (4)
Peripheral edema	22 (29)	3 (4)	18 (24)	0
Insomnia	22 (29)	0	14 (19)	1 (1)
Asthenia	20 (27)	3 (4)	21 (28)	2 (3)
Fatigue	20 (27)	3 (4)	19 (25)	1 (1)
Paresthesia	20 (27)	0	14 (19)	4 (5)
Nausea	19 (25)	1 (1)	16 (21)	1 (1)
Thrombocytopenia	12 (16)	7 (9)	20 (27)	13 (17)

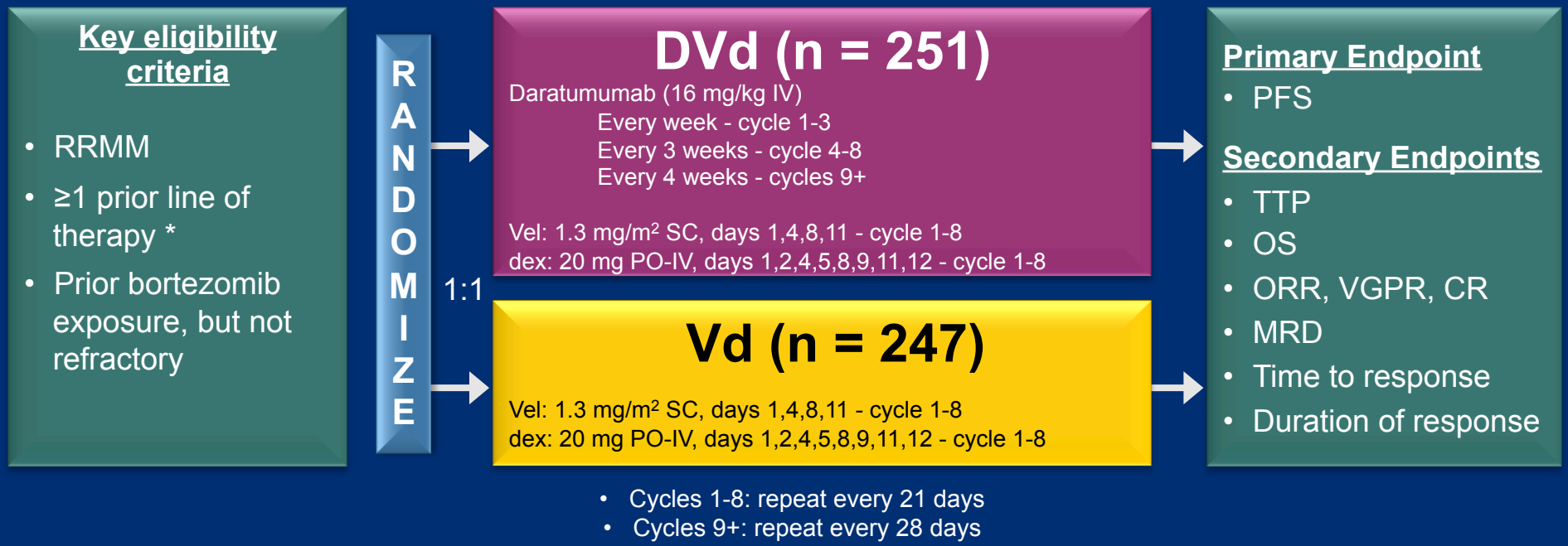
- No Grade 3–5 infusion reactions (7% grade 1-2)
- No patient discontinued because of an infusion reaction

Elotuzumab-bortezomib-dexamethasone; Bd: bortezomib dexamethasone

Jakubowiak A ,et al. EHA 201
Jakubowiak A, et al. Blood. 2016;127(23

CASTOR: Study Design

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

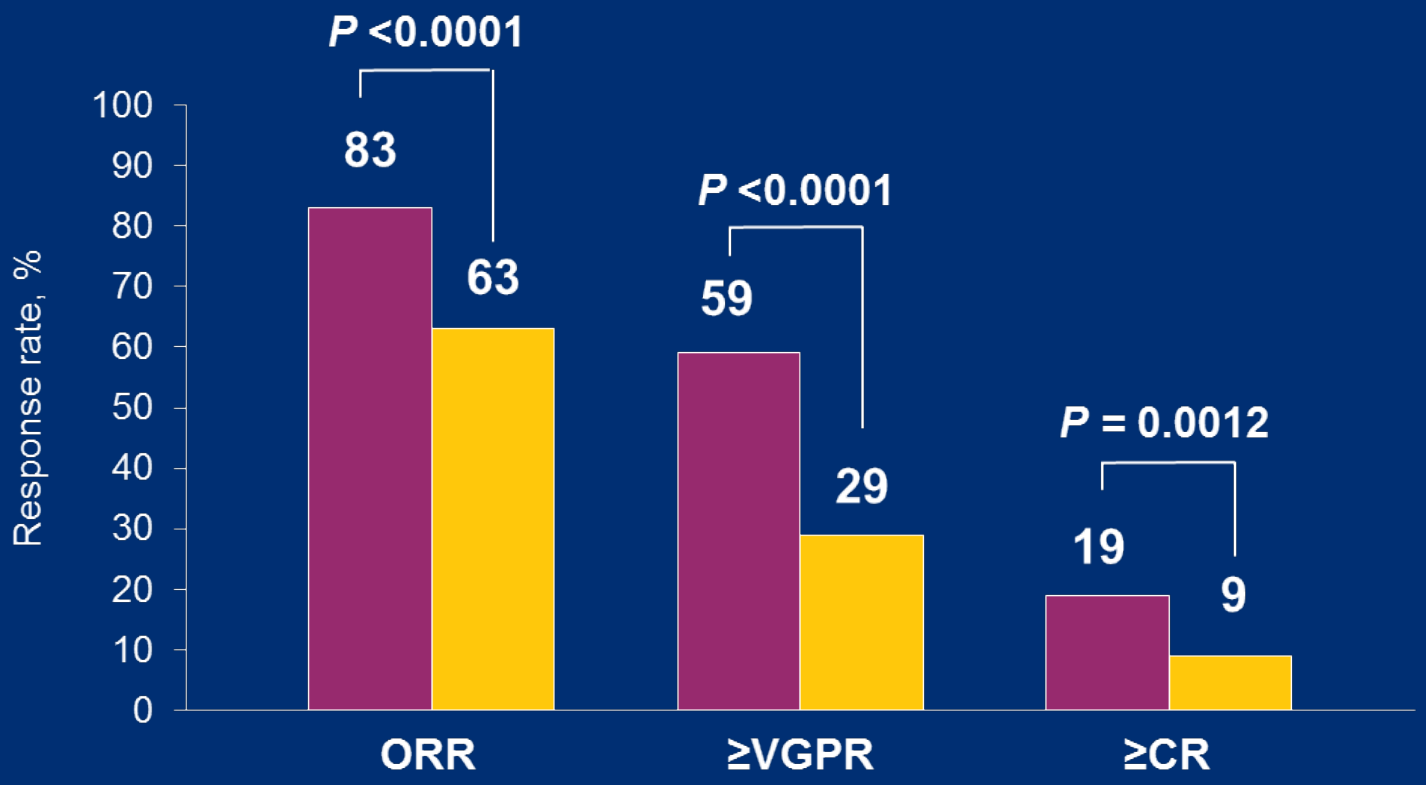


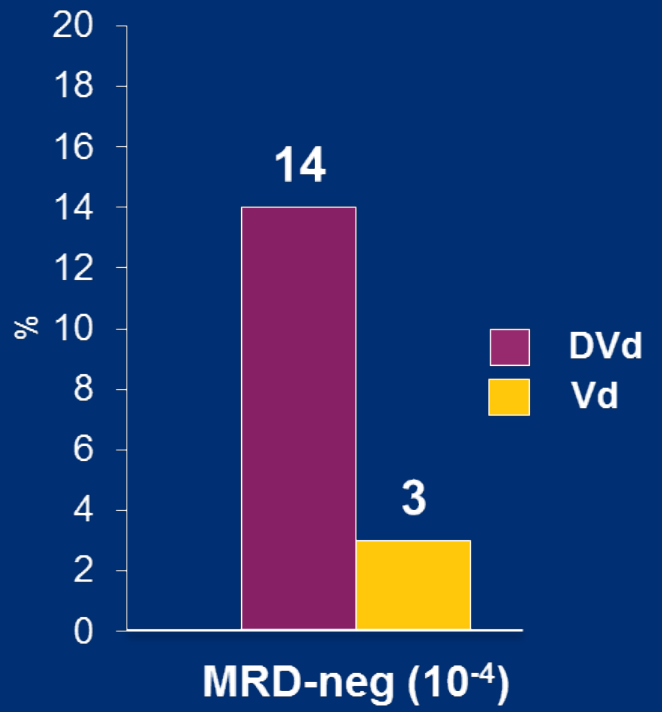
Daratumumab IV administered in 1000 mL to 500 mL; gradual escalation from 50 mL to 200 mL/min permitted

*90% 1-3 prior line of therapy; 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.

Palumbo A et al. EH

Overall Response Rate[a]



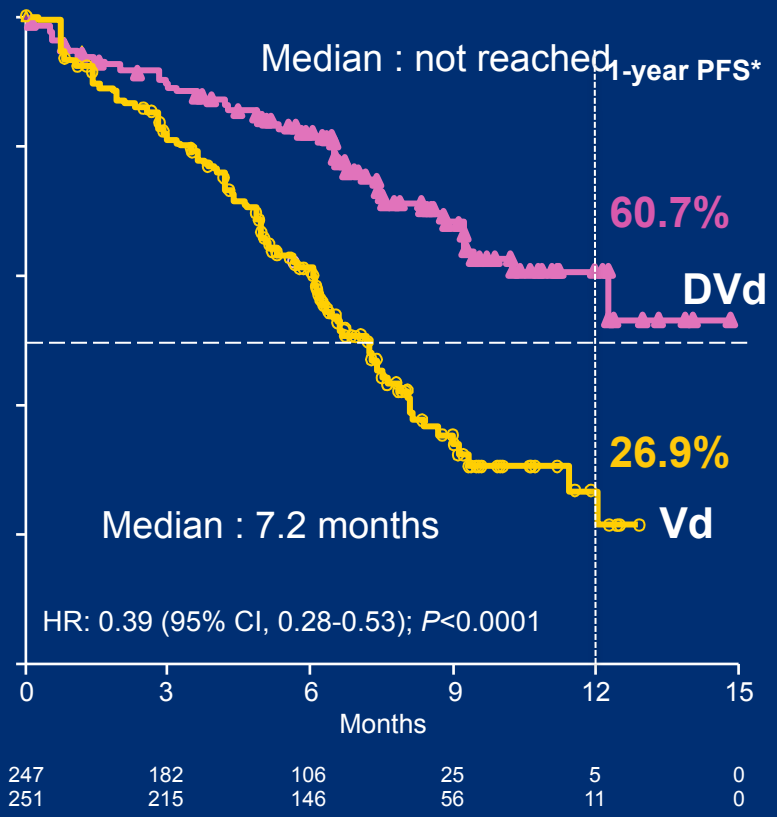


nse-evaluable population; ORR, overall response rate; VGPR, very good partial response; CR, complete se; MRD, minimal residual disease; DVd, daratumumab-bortezomib-dexamethasone; Vd, bortezomib-ethasone.

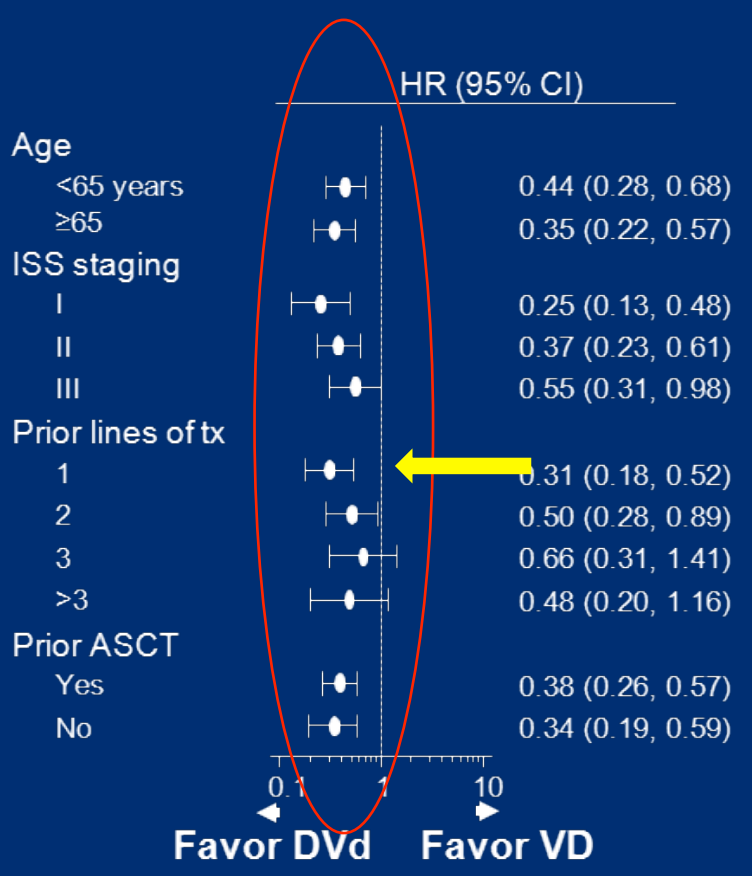
Palumbo A et al. EH

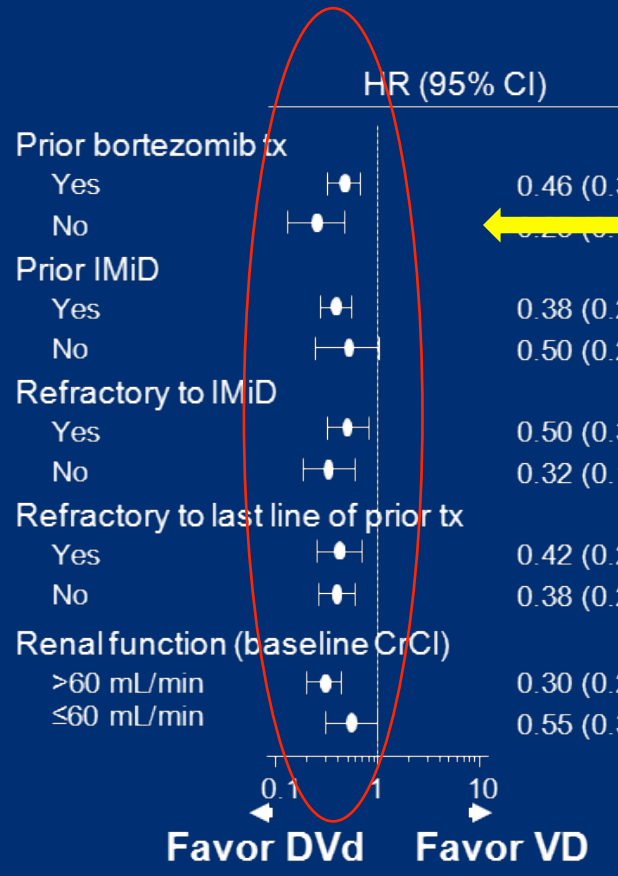
CASTOR: Study Design

ogression-free Survival (PFS)



PFS: subgroup analysis





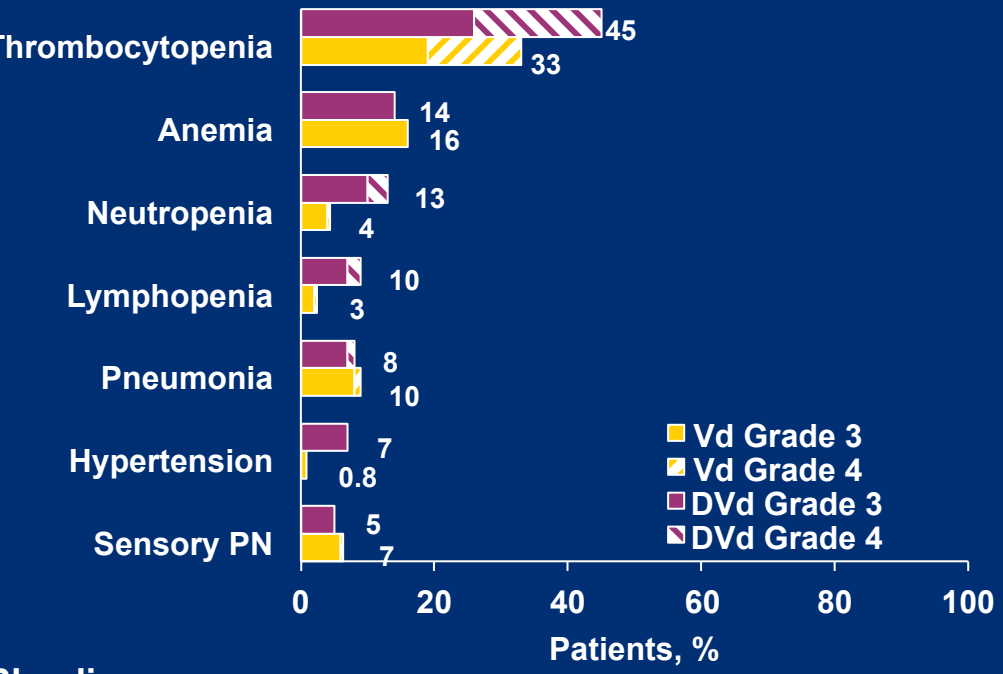
61% reduction in the risk of disease progression or death for DVd vs Vd

daratumumab bortezomib dexamethasone; Vd: bortezomib dexamethasone

Palumbo A et al. EH

Adverse events

ost Common (>5%) Grade 3-4 TEAE



Bleeding:
All grades: 7% in DVd vs 4% in Vd; Grade 3-4: 3 pts in DVd vs 2 pts in Vd

nfections:
Grade 3-4 AEs: 21% in DVd vs 19% in Vd; Serious AEs: 20% in DVd vs 18% in Vd

Discontinued for sensory peripheral neuropathy:
All grades: 0.4% in DVd vs 3% in Vd

Discontinued for TEAE:
7% in DVd vs 9% in Vd

aratumumab bortezomib dexamethasone; Vd: bortezomib dexamethasone

Infusion-related Reactions (IRRs)

	Safety Analysis Set (n =
	All grades	Grade
Patients with IRRs, %	45	9
Most common (>5%) IRRs		
Dyspnea	11	2
Bronchospasm	9	3
Cough	7	0

- No grade 4 or 5 IRRs observed
- 98% of patients with IRRs experienced the event on the first infusion
- 2 patients discontinued due to IRRs
  - Bronchospasm in the first patient
  - Bronchospasm, laryngeal edema, and skin rash in the second patient

Preinfusion: dexamethasone 20 mg, paracetamol 650-1000 mg, diphenhydramine 25-50 mg
Stop infusion immediately for mild symptoms; once resolved, resume at half the infusion rate

Palumbo A et al. EHA

Strategies at relapse…
How to make the right choice?

Patient Characteristics

Age
Comorbidities (cardiovascular, pulmonary functions)
Compliance

Efficacy of Previous therapy

1-3 prior lines
Bortezomib naive/sensitive

Safety of Previous therapy

Toxicities
Neuropathy
DVT/PE
Cardiac toxicity

Type of relapse

Aggressiveness

Treatment options for relapsed refractory MM patients

Transplant Eligible Patients

Bortezomib-based Induction

↓

Autologous Transplant

Transplant Inelegible Patients

VMP/MPT/(Rd)

FIRST RELAPSE

Second Transplant

Lenalidomide-dexamethasone

Bortezomib-dexamethasone/Doxil

SECOND RELAPSE

Lenalidomide-dexamethasone

Bortezomib-dexamethasone/Doxil

Pomalidomide-Dexamethasone*

*at second or subsequent relapse in pts pre
treated with both lenalidomide and bortezor

Treatment options for relapsed refractory MM patients

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Autologous Transplant

Transplant Inelegible Patients

VMP/MPT/(Rd)

FIRST RELAPSE

Second Transplant

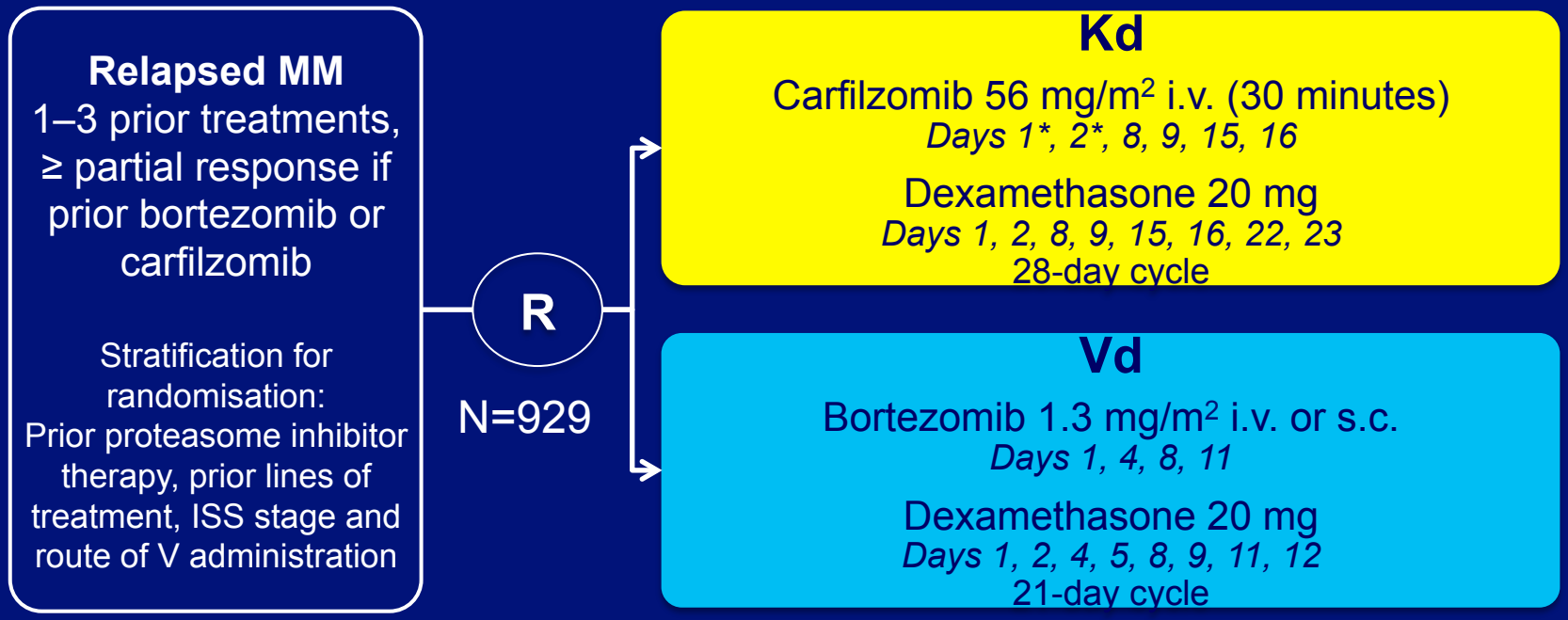
- Lenalidomide-dexamethasone
- DVd;EVd

SECOND RELAPSE

- Lenalidomide-dexamethasone
- DVd;EVd
- Pomalidomide-Dexamethasone*

*at second or subsequent relapse in pts previ
treated with both lenalidomide and bortezomi

Randomised, open-label, multicentre, phase 3 trial: Kd vs Vd



1–3 prior treatments

*20 mg/m^2 on Days 1, 2, Cycle

ECOG PS 0–2

Prior treatment with bortezomib or carfilzomib was allowed if: ≥ partial response to prior treatment ≥6 month PI treatment-free interval

- **Not discontinued due to toxicity**

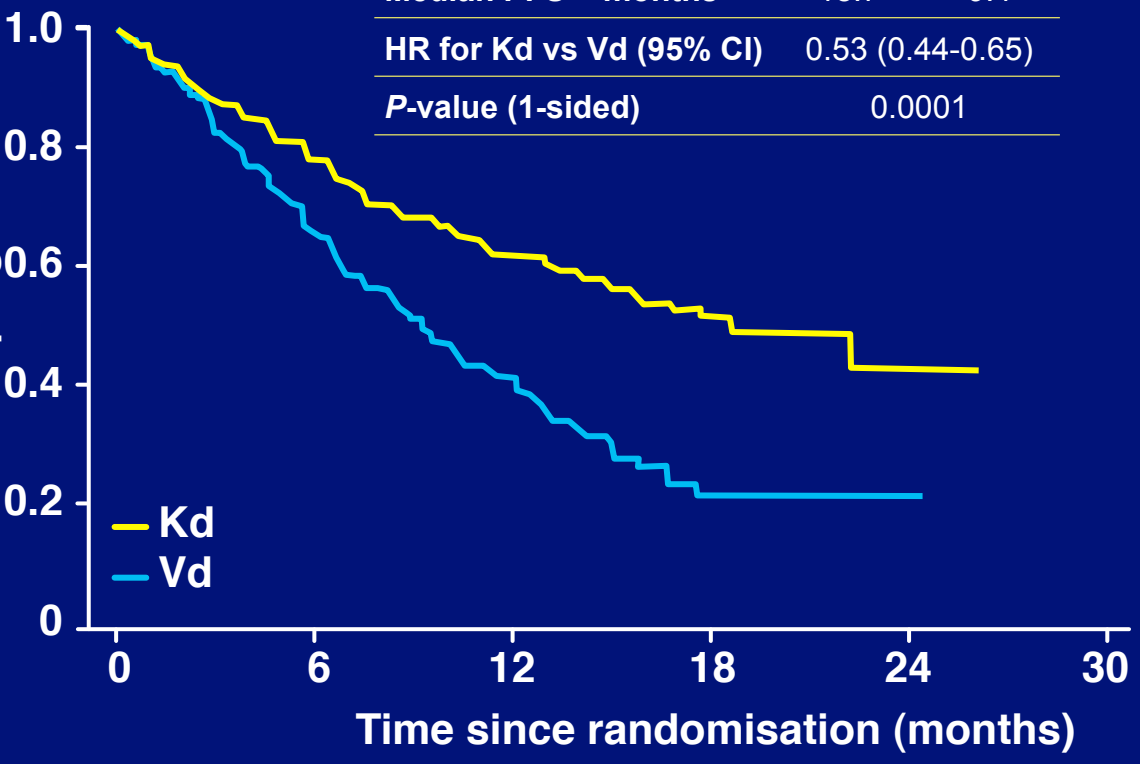
Primary endpoint: PFS

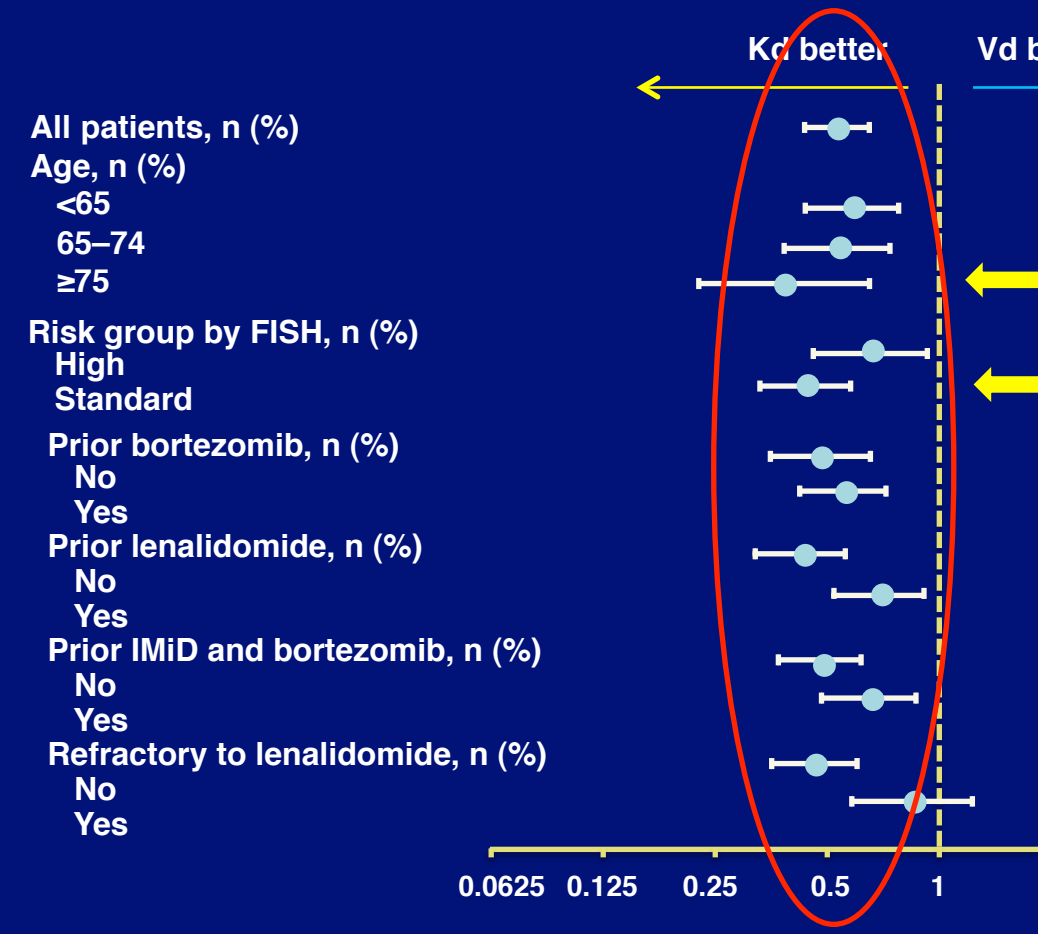
Secondary endpoints: OS, ORR, DOR, grade ≥2 peripheral neuropathy rate, safety

DOR, duration of response; ISS, International Staging System; i.v., intravenous; Kd, carfilzomib with dexar
MM, multiple myeloma; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; R, randomisation; s.c., subcutaneous; Vd, bortezomib with dexar
Dimopoulos MA, et al. Lancet Oncol 2016;17:27-38; clinicaltrials.gov/ct2/show/NCT01568866 [Accessed

Progression-free survival

	Kd (n=464)	Vd (n=465)
Disease progression or death - n (%)	171 (37)	243 (52)
Median PFS - months	18.7	9.4
HR for Kd vs Vd (95% CI)	0.53 (0.44-0.65)	
P-value (1-sided)	0.0001	





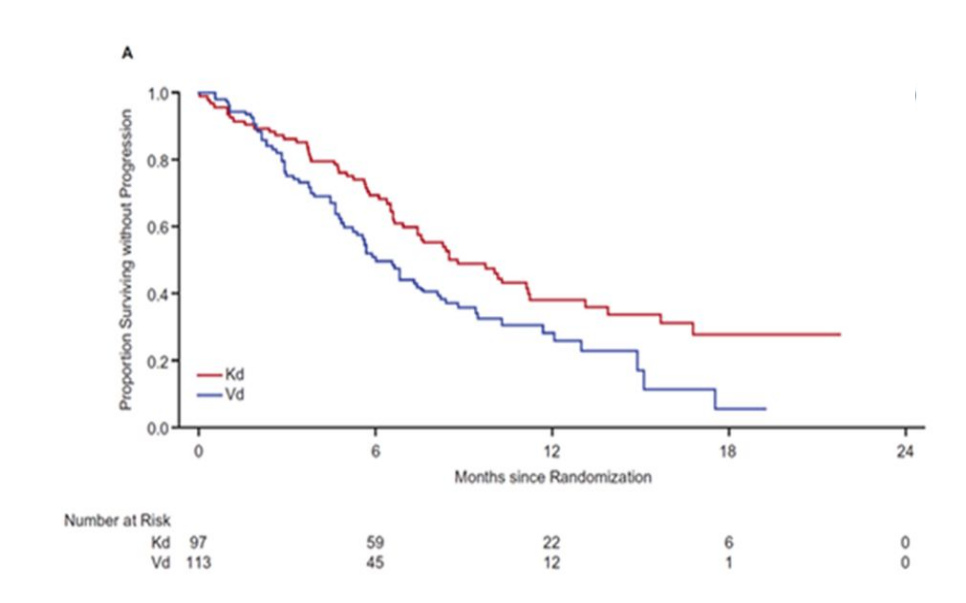
- **Median follow-up: 11.2 months**

CI, confidence interval; HR, hazard ratio; Kd, carfilzomib with dexamethasone; PFS, progression-free survival; Vd, bortezomib with dexamethasone.

Dimopoulos MA, et al. Lancet Oncol 2016;17:27-38.

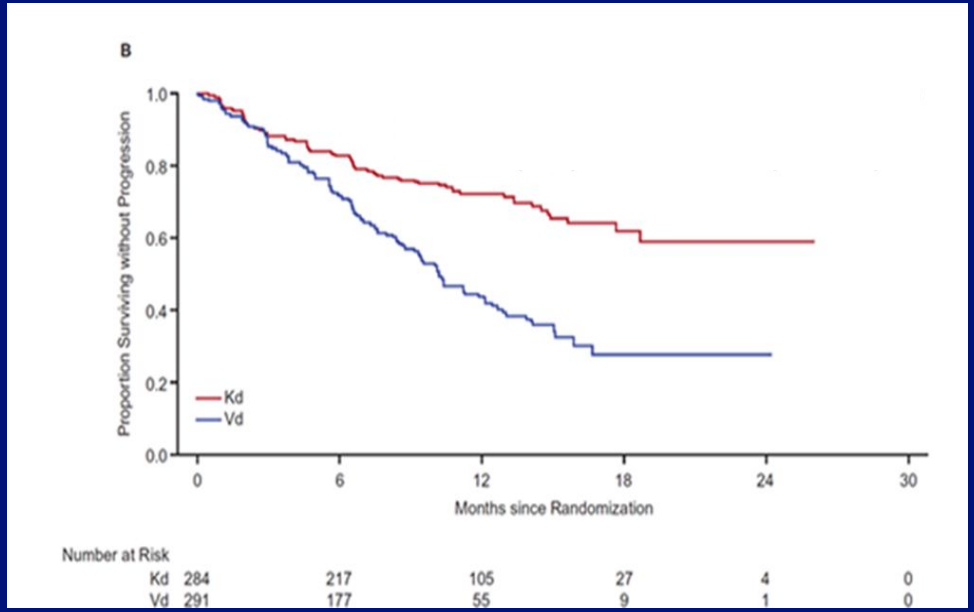
Phase III ENDEAVOR trial: Subgroup analysis in HR patients – PFS data

High-risk group



	Kd (n=97)	Vd (n=113)
PD or death, n (%)	56 (57.7)	71 (62.8)
Median PFS, mo	8.8	6.0
HR fro KD vs VD (95% CI)	0.66 (0.45 – 0.92)	

Standard-risk group



	Kd (n=97)	Vd (n=113)
PD or death, n (%)	81 (28.5)	142 (48.8)
Median PFS, mo	NE	10.2
HR fro KD vs VD (95% CI)	0.439 (0.33 – 0.578)	

Chng WJ, ASH 2015 Abst 30

Safety

	Kd (n=463)	Vd* (n=456)
dian treatment duration, eks	40	27
, %		
Any grade AE	98	98
Grade ≥3 AE	73	67
Serious AE	48	36
se reduction due to an AE,	23	48
atment discontinuations, %		
Discontinuation due to disease progression	25	36
Discontinuation due to AE	14	16
-study deaths, %		
Deaths due to disease progression	0.9	0.9
Deaths due to AEs	4	3

patients in the Vd group, 79% received subcutaneous bortezomib throughout their treatment.
opulation: Patients that received at least one dose of study treatment.

dverse event; Kd, carfilzomib with dexamethasone; Vd, bortezomib with dexamethasone.
oulos MA, et al. Lancet Oncol 2016;17:27-38.

AE, %	Kd (n=463)		Vd* (n=456	
	All grade	Grade ≥3	All grade	Gra ≥3
Acute renal failure†	8	4	5	3
Cardiac failure†	8	5	3	1.8
Ischaemic heart disease†	3	1.7	2.0	1.5
Deep vein thrombosis	4	0.9	0.9	0.4
Pulmonary embolism	3	1.7	0.9	0.9
Pulmonary hypertension†	1.3	0.6	0.2	0.2

*Among patients in the Vd group, 79% received subcutaneous bortezomib throughout their treatment.
† Grouped term.

Strategies at relapse…
How to make the right choice?

Patient Characteristics

Age
Comorbidities (cardiovascular, pulmonary functions)
Compliance

Efficacy of Previous therapy

1-3 prior lines
Bortezomib naive/sensitive

Safety of Previous therapy

Toxicities
Neuropathy
DVT/PE
Cardiac toxicity

Type of relapse

Aggressiveness

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Bortezomib-based Induction

↓

Autologous Transplant

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Second Transplant

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- DVd;EVd

SECOND RELAPSE

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- DVd;EVd
- Pomalidomide-Dexamethasone*

*at second or subsequent relapse in pts previ
treated with both lenalidomide and bortezomi

Treatment options for relapsed refractory MM patients

Transplant Eligible Patients

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↓

Autologous Transplant

Transplant Inelegible Patients

VMP/MPT

FIRST RELAPSE

Second Transplant

- Lenalidomide-dexamethasone
- DVd;Evd; Kd

SECOND RELAPSE

- Lenalidomide-dexamethasone
- Kd
- DVd;Evd,Kd
- Pomalidomide-Dexamethasone*

*at second or subsequent relapse in pts previ
treated with both lenalidomide and bortezomi

Treatment options for relapsed refractory MM patients

Transplant Eligible Patients

Bortezomib-based Induction

↓

Autologous Transplant

Transplant Inelegible Patients

VMP/MPT

FIRST RELAPSE

Second Transplant

Rd, KRD, ERd,IRD

Vd, EVd; Kd

SECOND RELAPSE

Rd,KRD,Erd,IRD

Kd

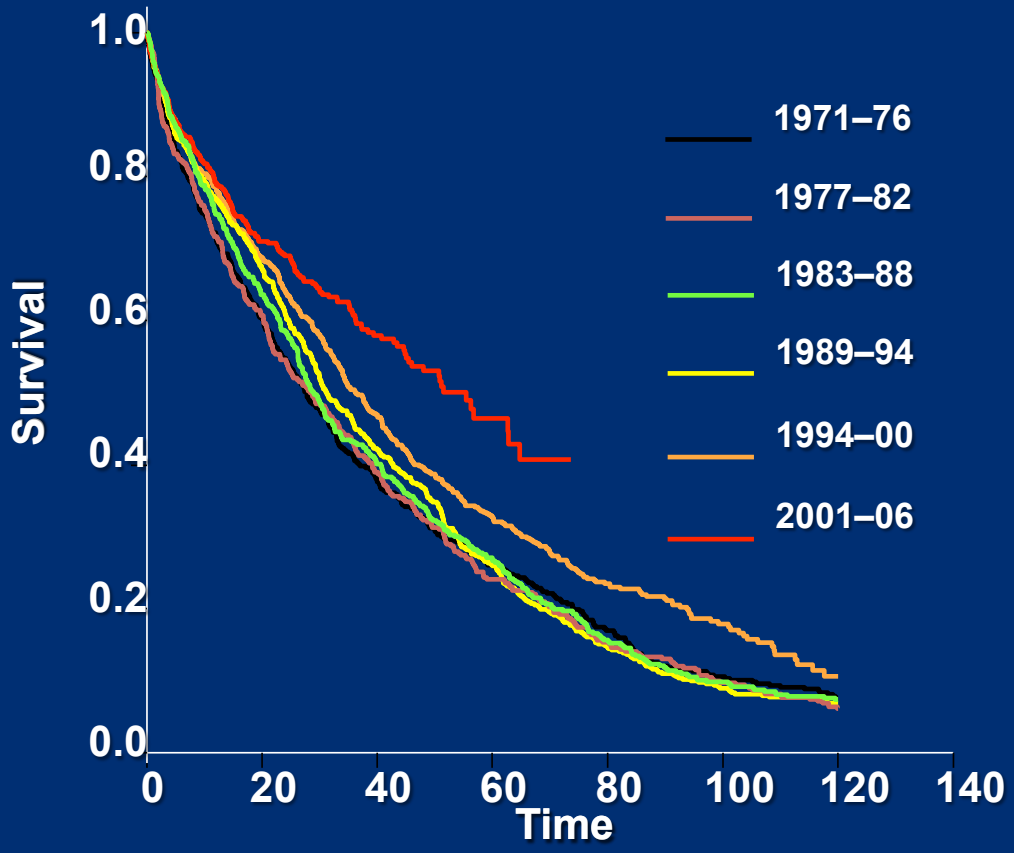
Vd,Evd,Kd

Pomalidomide-Dexamethasone*

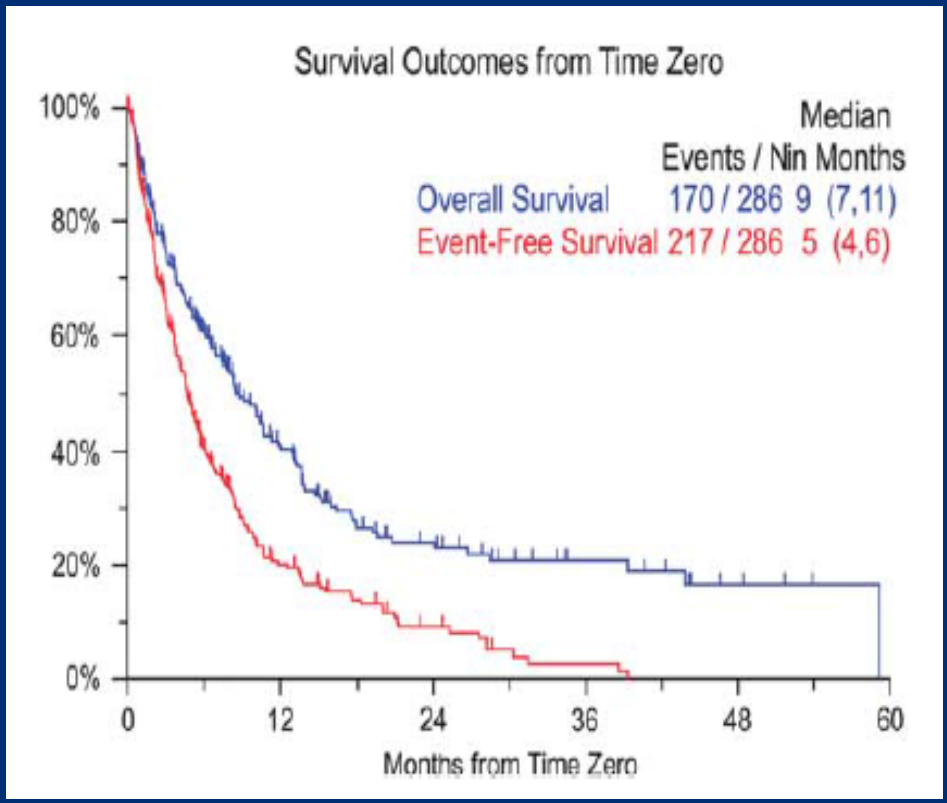
*at second or subsequent relapse in pts previ
treated with both lenalidomide and bortezomi

Unmet medical need

Impact of IMIDs and PIs



Survival in pts refractory to IMIDs and PIs

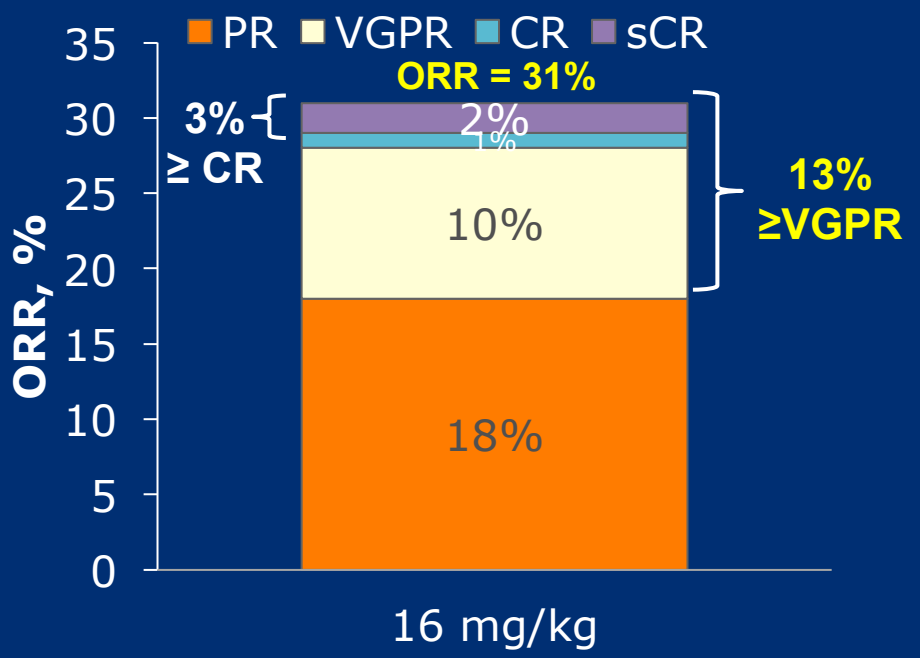


IMIDs: immunomodulatory agents; PIs: proteasome inhibitors

Kumar SK, et al. Blood. 2008;11
Kumar SK, et al. Leukemia. 2012

EN501 and SIRIUS (MMY2002) Combined Analysis: Effica in Combined Analysis

	16 mg/kg (N = 148)	
	n (%)	95% CI
ORR (sCR+CR+VGPR+PR)	**46 (31)**	**23.7-39.2**
Best response		
sCR	3 (2)	0.4-5.8
CR	2 (1)	0.2-4.8
VGPR	14 (10)	5.3-15.4
PR	27 (18)	12.4-25.4
MR	9 (6)	2.8-11.2
SD	68 (46)	37.7-54.3
PD	18 (12)	7.4-18.5
NE	7 (5)	1.9-9.5
VGPR or better (sCR+CR +VGPR)	**19 (13)**	**7.9-19.3**
CR or better (sCR+CR)	**5 (3)**	**1.1-7.7**

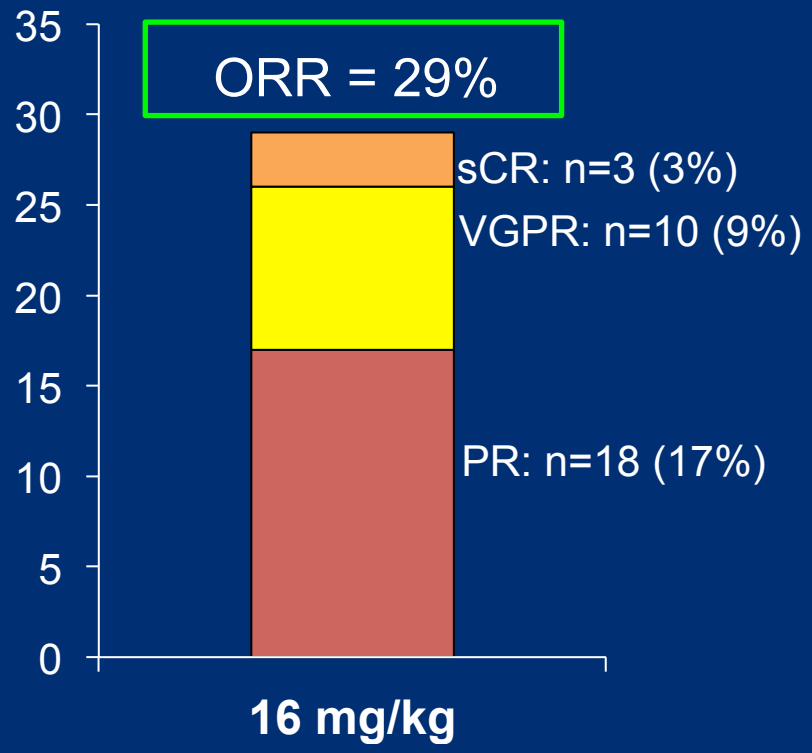


- ORR = 31%
- ORR was consistent in subgroups including age, number of prior lines of therapy, refractory status, or renal function

Usmani S, et al. Oral presentation: 57th American Society of Hematology (ASH) Annual Meeting & E December 5-8, 2015; Orlando, FL. Abstract 29.

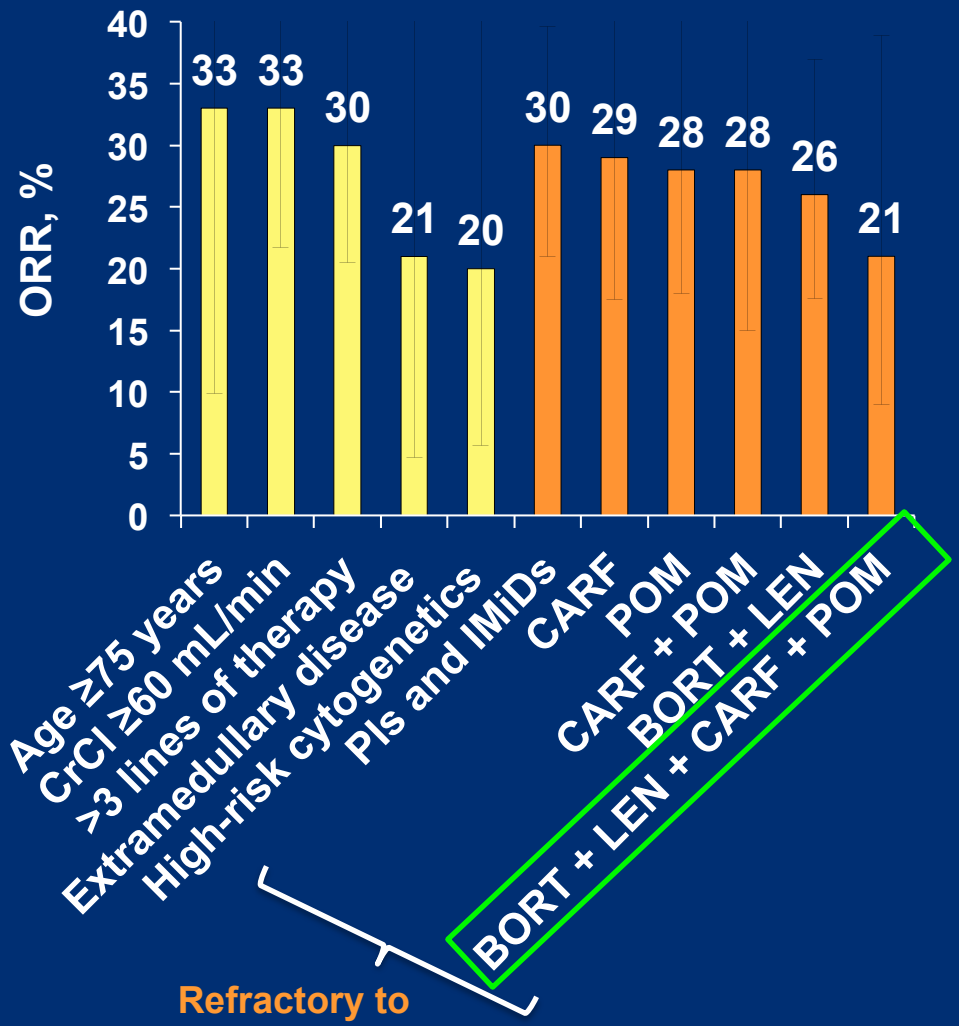
Sirius Trial: overall response rate

All patients



- ≥ VGPR 12%, ≥ MR 34%
- Median time to response: 1 month
- Median duration of response: 7.4 months

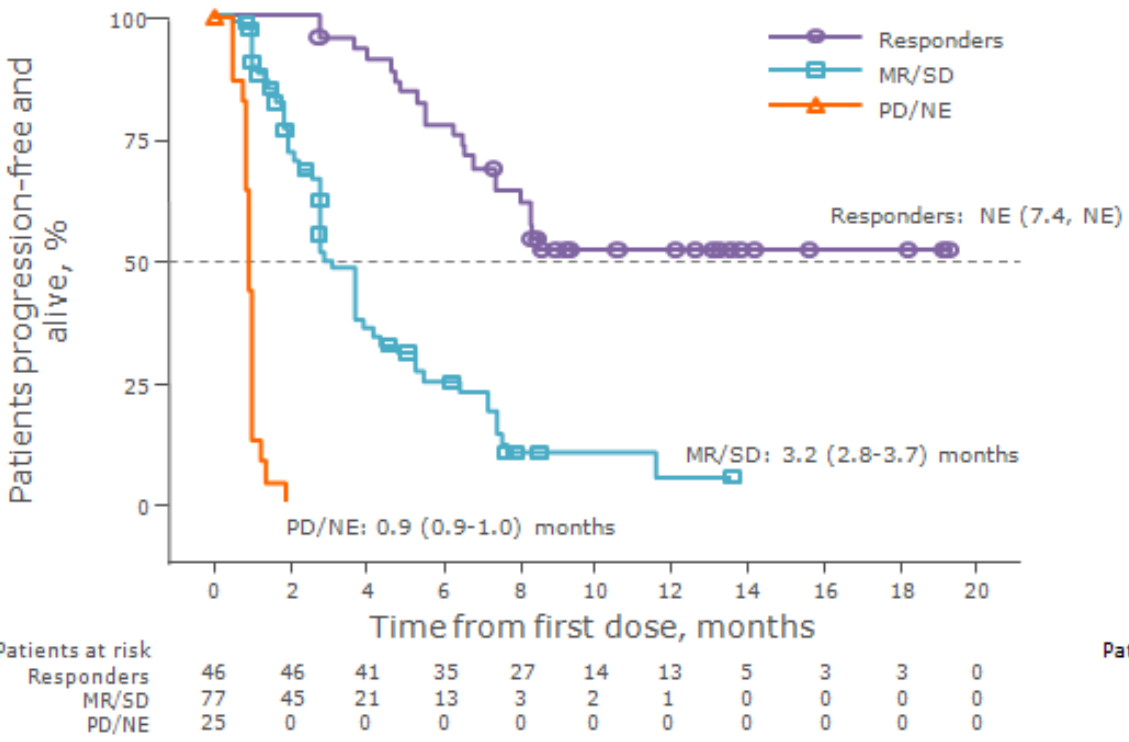
By patients subgroup



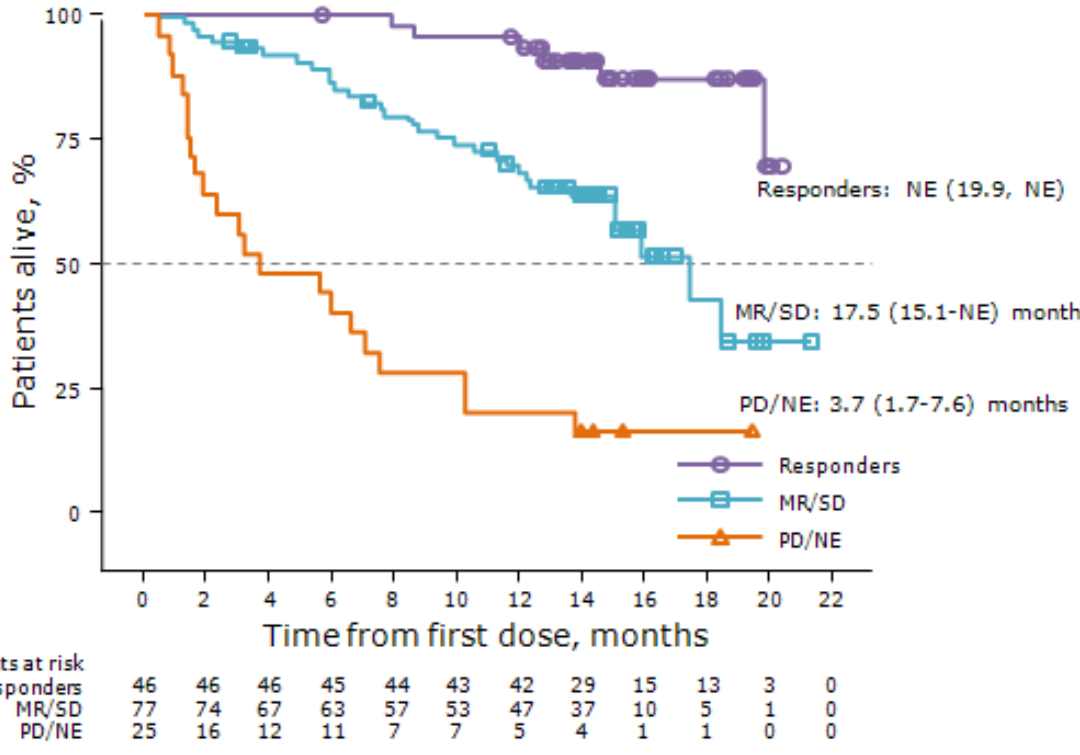
Lonial et al. ASCO 2015 (Abstract LBA8512); oral pr

GEN501 and SIRIUS (MMY2002) Combined Analysi

Progression-free Survival



Overall Survival



- **For the combined analysis, median OS = 19.9 (95% CI, 15.1-NE) months**
- **1-year overall survival rate = 69% (95% CI, 60.4-75.6)**

Usmani S, et al. Oral presentation: 57th American Society of Hematology (ASH) Annual Meeting & Exposition; December 5-8, 2015; Orlando, FL. Abs

GEN501 and SIRIUS (MMY2002) Combined Analysis: Summary of Clinical Safety

TEAE, n (%)	Any grade N = 148	Grade ≥3 N = 148
Fatigue	61 (41)	3 (2)
Nausea	42 (28)	0
Anemia	41 (28)	26 (18)
Back pain	36 (24)	3 (2)
Cough	33 (22)	0
Neutropenia	30 (20)	15 (10)
Thrombocytopenia	30 (20)	21 (14)
Upper respiratory tract infection	30 (20)	1 (<1)

- AEs were consistent with the individual GEN501 and SIRIUS studies; no new safety signals were identified
- 48% of patients had IRRs
  - 46%, 4%, and 3% occurred during the first, second, and subsequent infusions, respectively

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Treatment options for relapsed refractory MM patients

Transplant Eligible Patients

Bortezomib-based Induction

↓

Autologous Transplant

Transplant Inelegible Patients

VMP/MPT

FIRST RELAPSE

Second Transplant

Rd, KRD, ERd,IRD

Vd, Evd; Kd

SECOND RELAPSE

Rd,KRD,Erd,IRD

Kd

Vd,Evd,Kd

Pomalidomide-Dexamethasone*

↓

Daratumumab Single Agent

*at second or subsequent relapse in pts previ
treated with both lenalidomide and bortezomi

Thanks