Nuove indicazioni e nuove terapie nel mieloma multiplo

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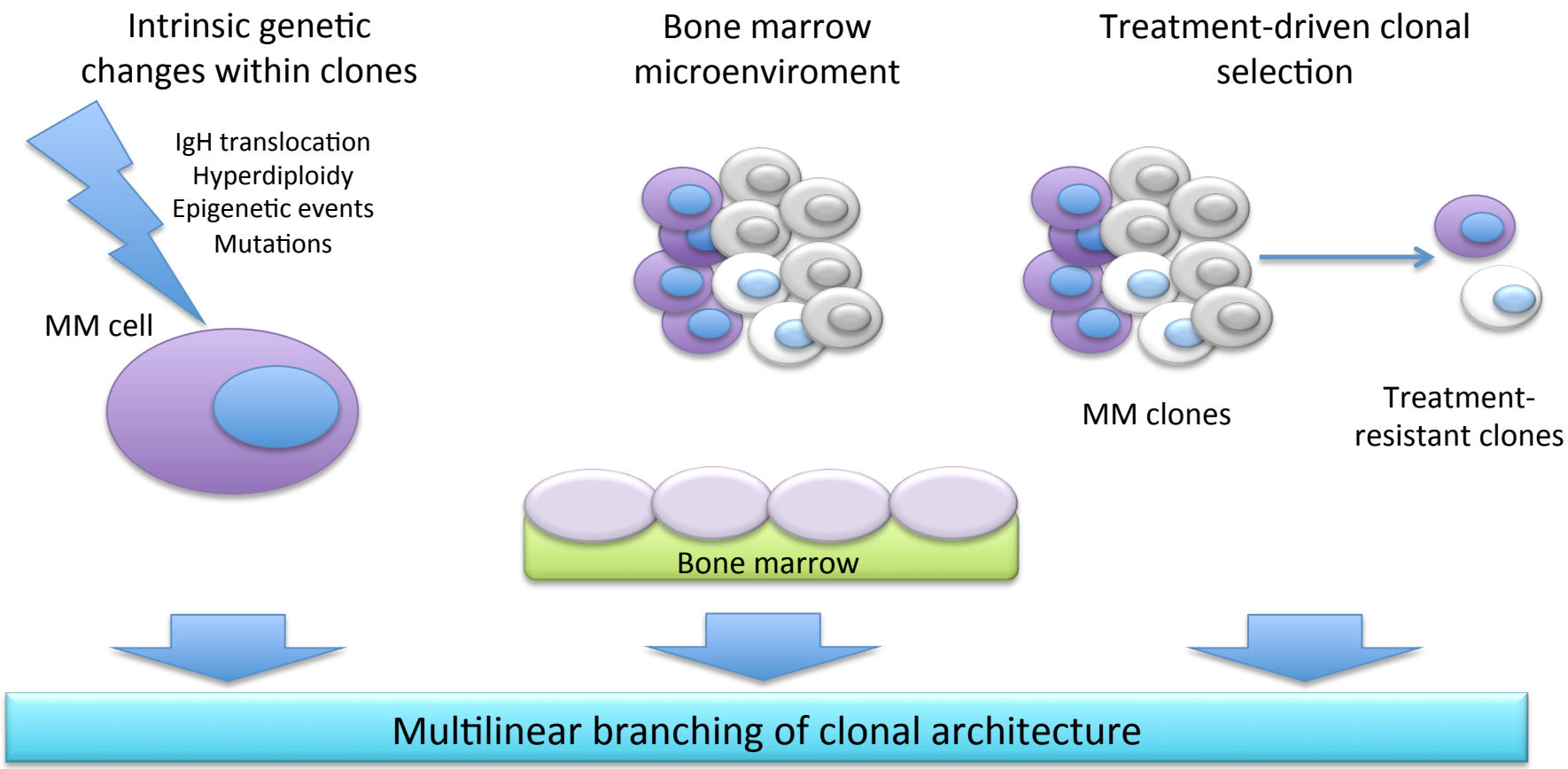
Multiple factors contribute to the clonal evolution and treatment resistance in MM

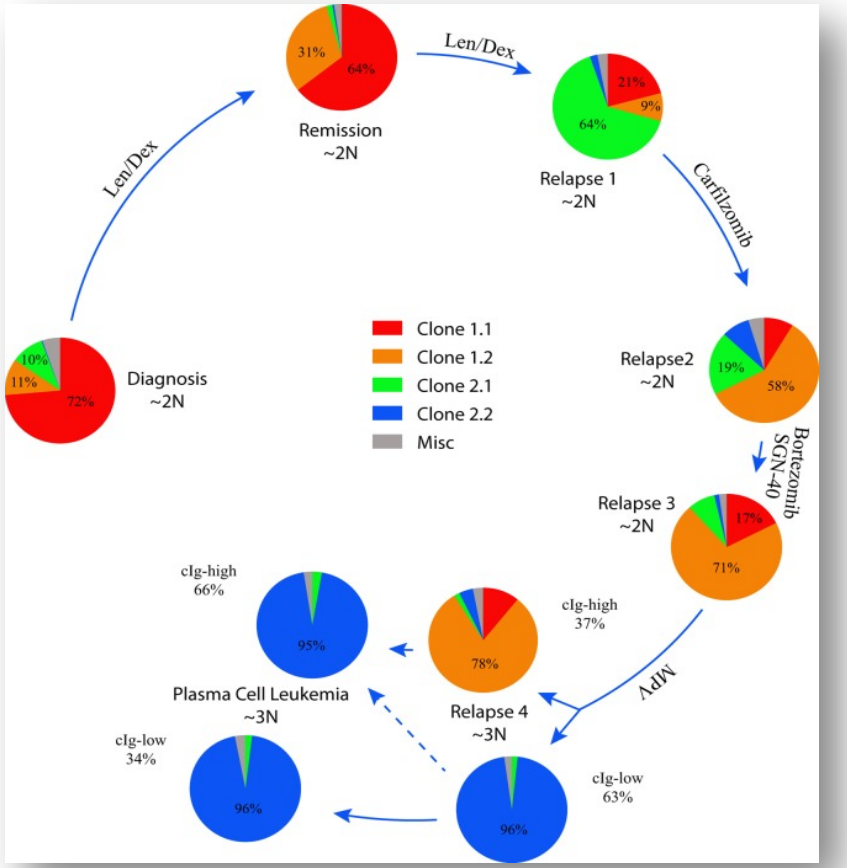


Morgan GJ et al. Nat Rev Cancer 2012;12:335-348

Why do we fail?: genomic clompexity

War of the clones

- 5 unique clones at diagnosis
- Variable chemotherapy response
- Minor drug resistant clone may become lethal



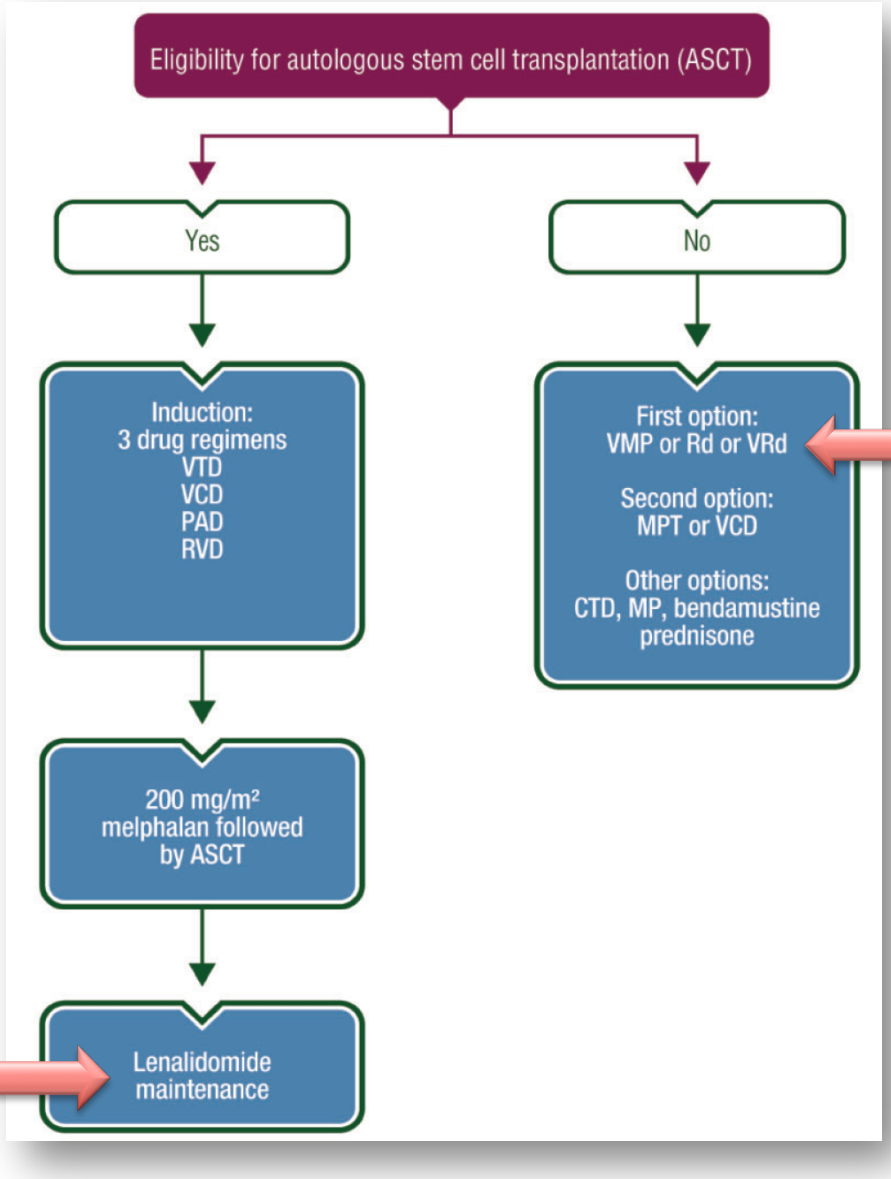
Keats JJ et al. Blood 2012;120(5):1067-1076

Implications of biology for treatment

- Multiple clones with variable drug sensitivity
  - Combination chemotherapy a necessity
- Resuscitation of drug-sensitive clones
  - Once resistant, not always resistant
  - Continuous suppressive therapy logical
- Minor drug-resistant clones lethal
  - Complete response is required

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

Front line treatment
ESMO guidelines 2017



VRd vs Rd improved PFS and OS and had an acceptable risk–benefit profile, in a phase 3 trial. Nevertheless, this triplet combination is not yet approved by the EMA

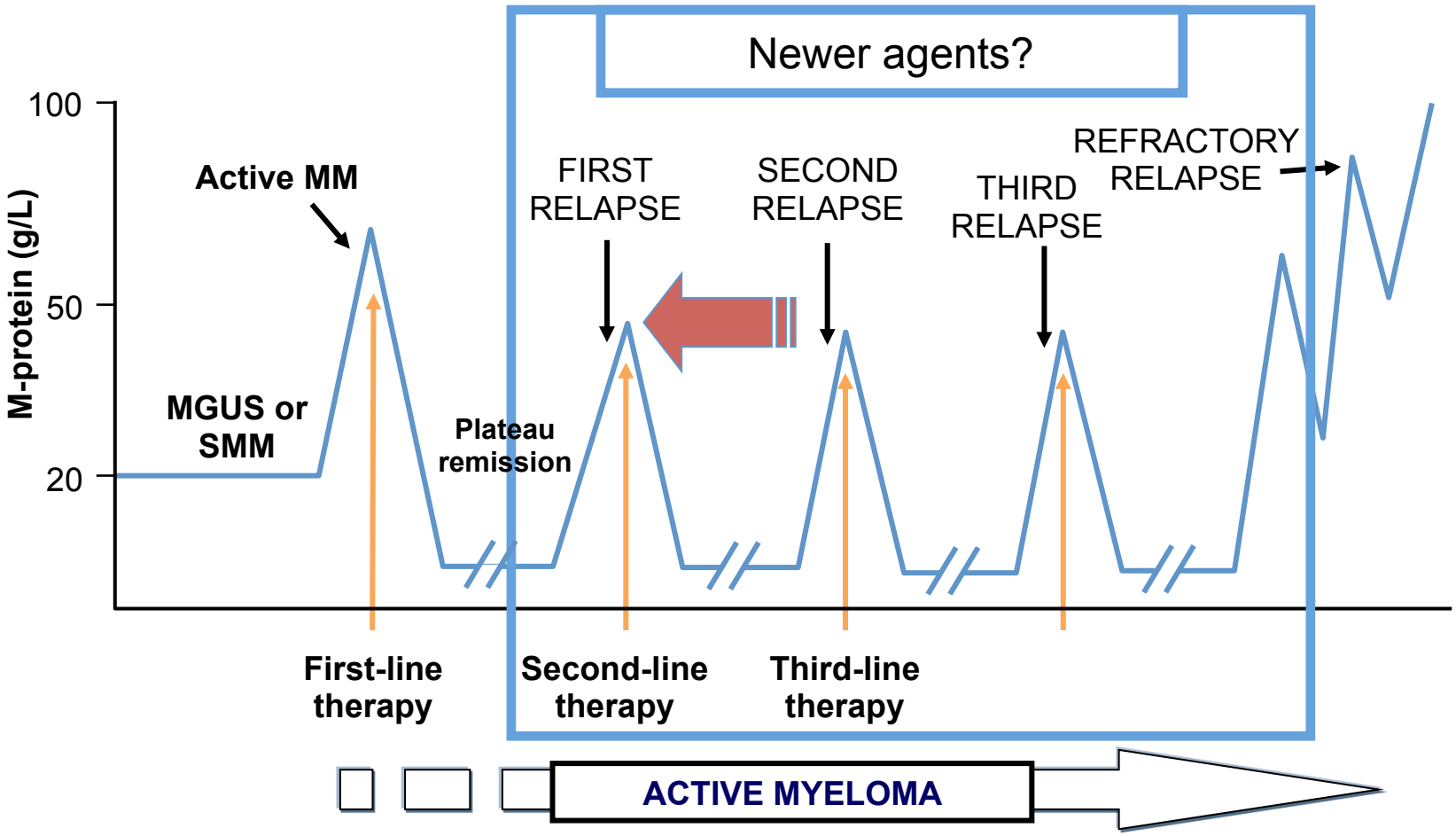
Durie BGM et al. Lancet 2016

In Feb 2017, the EMA approved lena as monotherapy for the maintenance treatment of pts with newly diagnosed MM who have undergone ASCT

Attal M et al, ASCO 2016

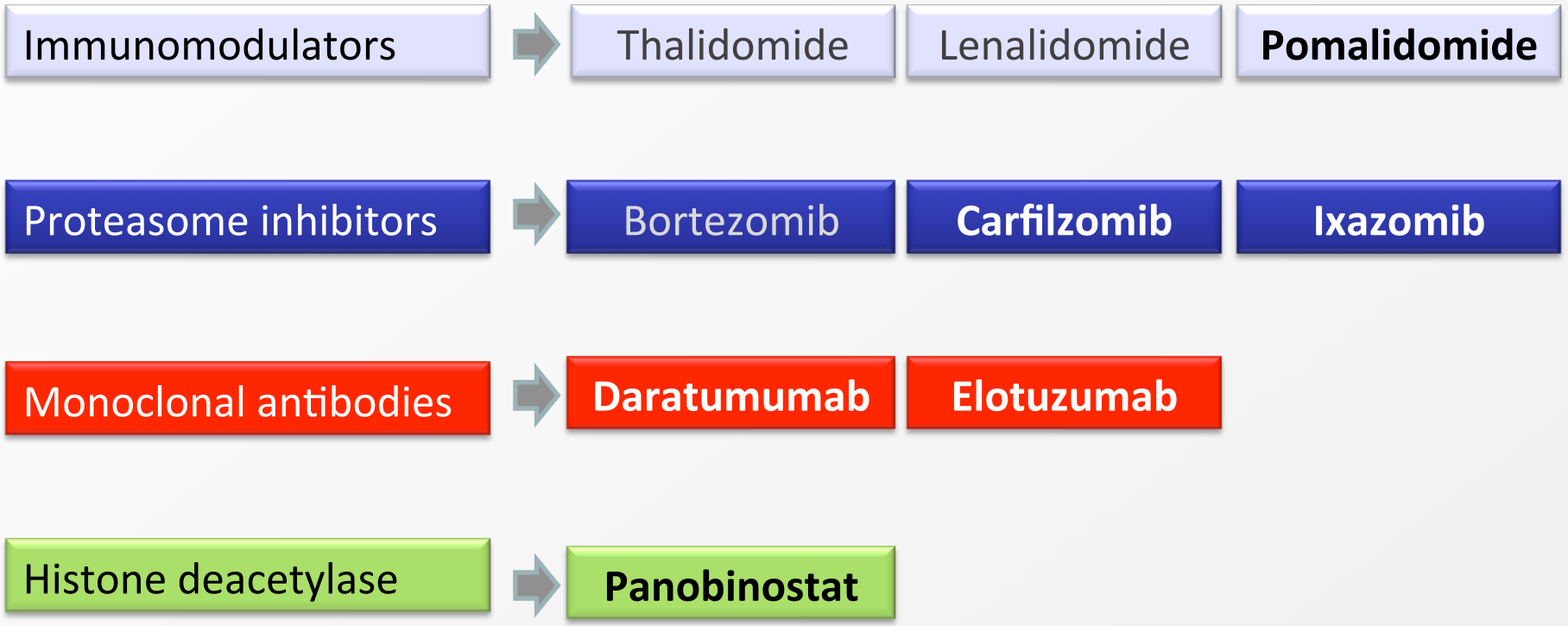
Moreau P et al. Ann Oncol. 2017

Relapsed/Refractory Multiple Myeloma: Changing the Paradigm



•MGUS, monoclonal gammopathy of unknown significance; MM, multiple myeloma; SMM, smoldering multiple myeloma.
•Figure adapted from Durie BGM. Concise review of the disease and treatment options. Multiple myeloma; 2011/2012. Available at: http://myeloma.org/pdfs/CR2011-Eng_b1.pdf.

Current novel therapies for RRMM by the drug's mechanism of action



Treatment options for R/R MM

Transplant Eligible Patients

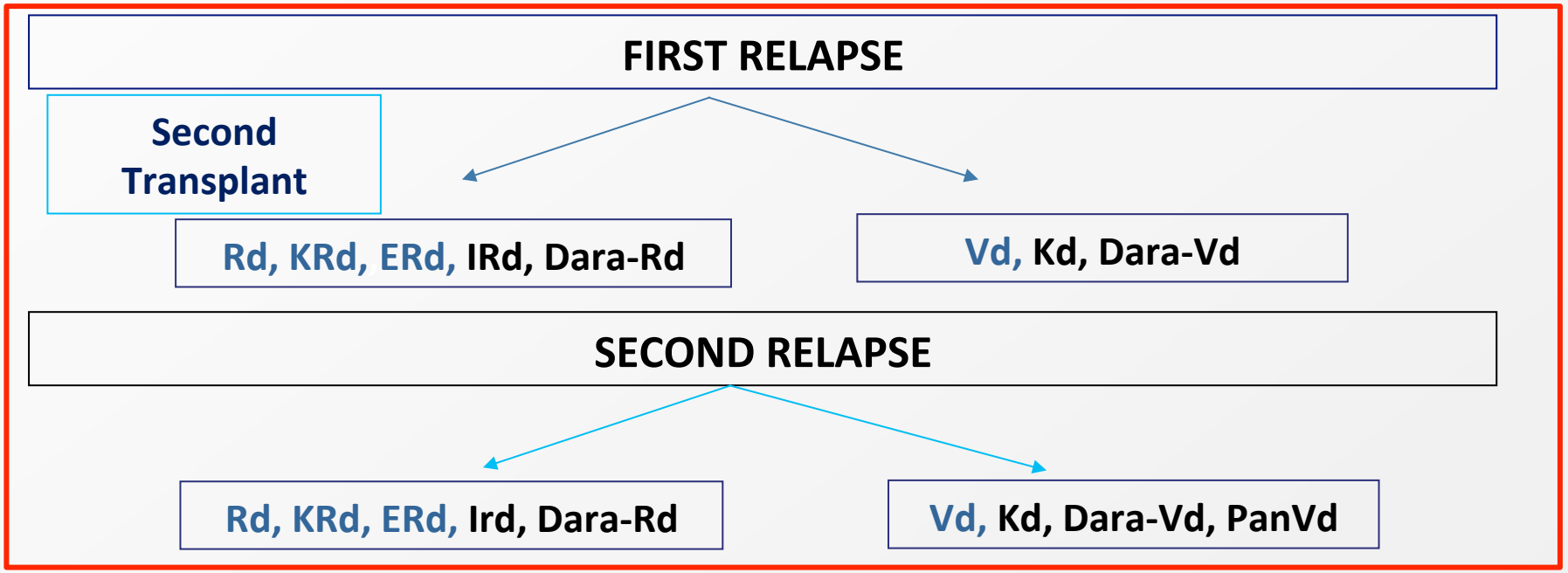
Bortezomib-based Induction

↓

Autologous Transplant

Transplant Inelegible Patients

VMP, Rd (MPT)



Pomalidomide-Dexamethasone

Daratumumab Single Agent

Clinical trials
(MoAbs, check-point inhibitors, venetoclax, selinexor, anti BCMA…)

Key clinical considerations at relapse

Patient

- Age
- Co-morbidities
- Support network
- Performance status
- QoL
- Bone marrow reserve
- Oral vs IV

Prior treatment

- ASCT
- PI-based
- IMiD-based
- Alkylators
- Maintenance

Disease and molecular ass

- Extramedullary disease
- Aggress… of relap…
- Clinical vs biochemical relapse
- Focal lesions
- Cytogenetic risk status
- Speed paraprotein increase

esponse and tolerability

- esponse to prior therapy
- PFS
- Side effects
- TFI

Plethora of new randomized studies to help guide treatment decisions

Control Arm	Comparator Arm	Trial
Bortezomib-Dexamethasone	**Carfilzomib-dexamethasone** **Panobinostat-bortezomib-dexamethasone** **Daratumumab-bortezomib-dexamethasone**	ENDEAVOR PANORAMA1 CASTOR
Lenalidomide-Dexamethasone	**Carfilzomib-lenalidomide-dexamethasone** **Ixazomib-lenalidomide-dexamethasone** **Elotuzumab-lenalidomide-dexamethasone** **Daratumumab-lenalidomide-dexamethasone**	ASPIRE TOURMALINE1 ELOQUENT2 POLLUX

Options of therapy for RRMM patients

Induction Bortezomib-based combination

↓

ASCT (melphalan 200)

↓

Nothing/Consolidation/Maintenance

Induction Bortezomib-based combo

Lenalidomide-dex

Second ASCT/Allo-RIC

1st relapse

IMiD's-based combinations

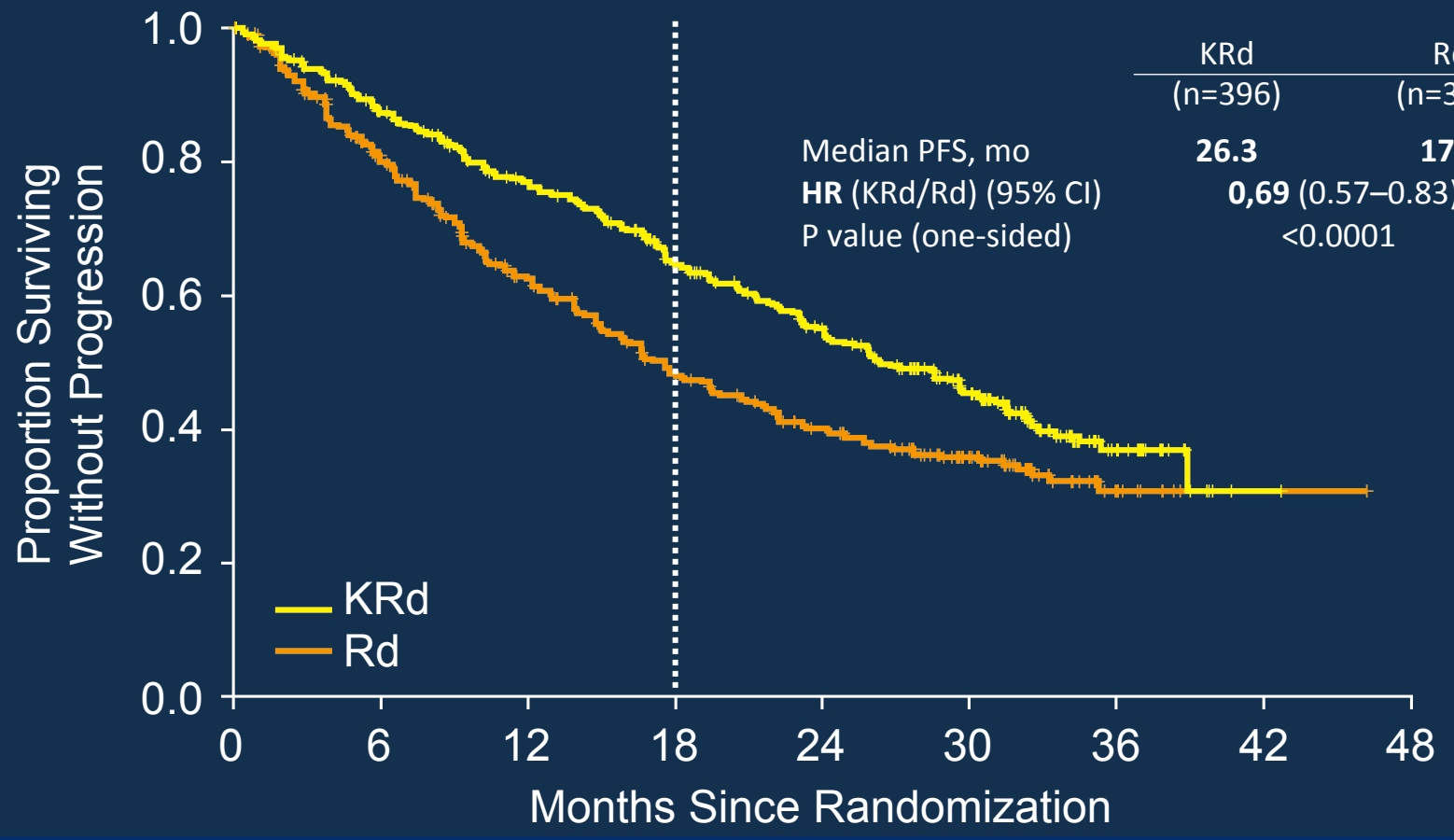
- Carfilzomib plus Rd
- Elotuzumab plus Rd
- Daratumumab plus Rd
- Ixazomib plus Rd

1. Stewart AK, et al. N Engl J Med 2015;372:142-52; 2. Lonial S, et al. N Engl J Med 2015; 373(7):621–31;
3. Dimopoulos et al. N Engl J Med 2016; 375:1319-31 4. Moreau P et al. N Engl J Med 2016;374(17):1621-34.

ASPIRE: KRd vs Rd (N=792)

ORR: 87% vs 66%

≥CR rate: 32% vs 9%



	KRd (n=396)	Rd (n=396)
Median PFS, mo	**26.3**	**17.6**
HR (KRd/Rd) (95% CI)	**0,69** (0.57–0.83)	
P value (one-sided)	<0.0001	

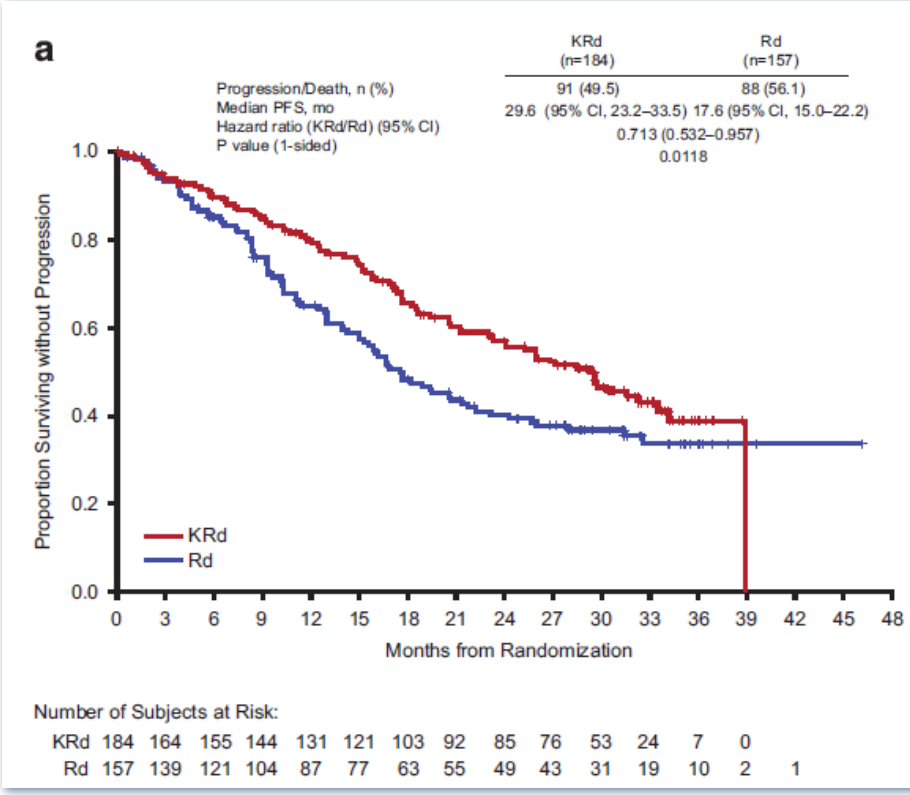
Median follow-up was 32.3 months for KRd and 31.5 months for Rd

KRd-treated pts had a 31% reduction in the risk of disease progression or death in comparison with Rd

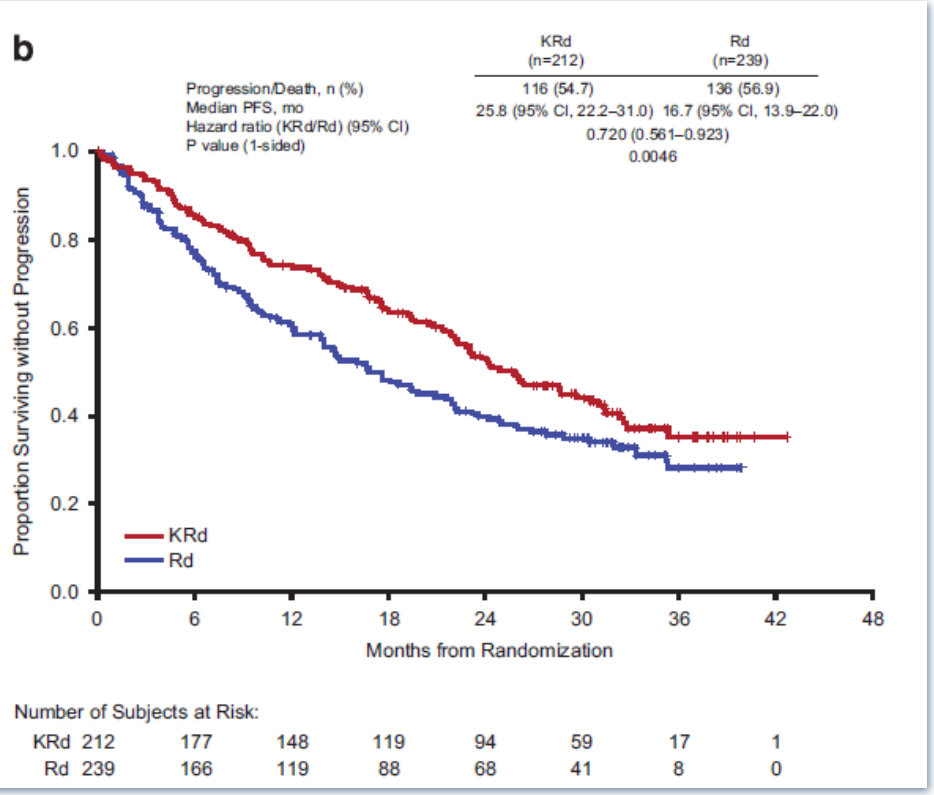
Stewart K et al, NEJM 2015

Primary Endpoint: PFS by previous treatment

1 previous line of tp



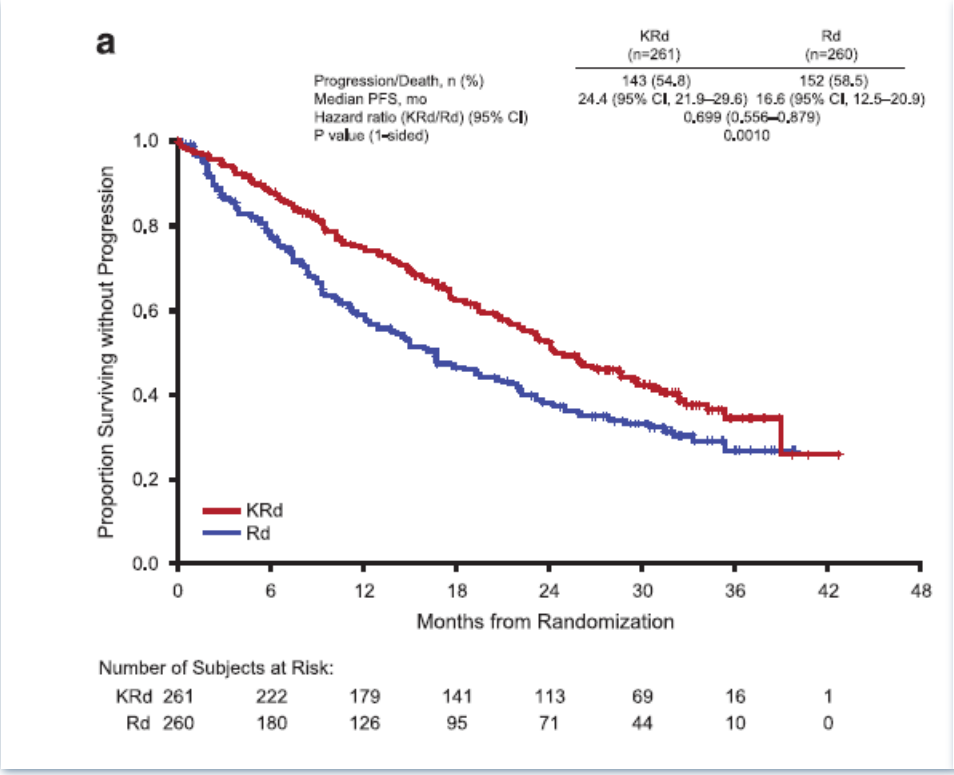
≥2 previous lines of tp



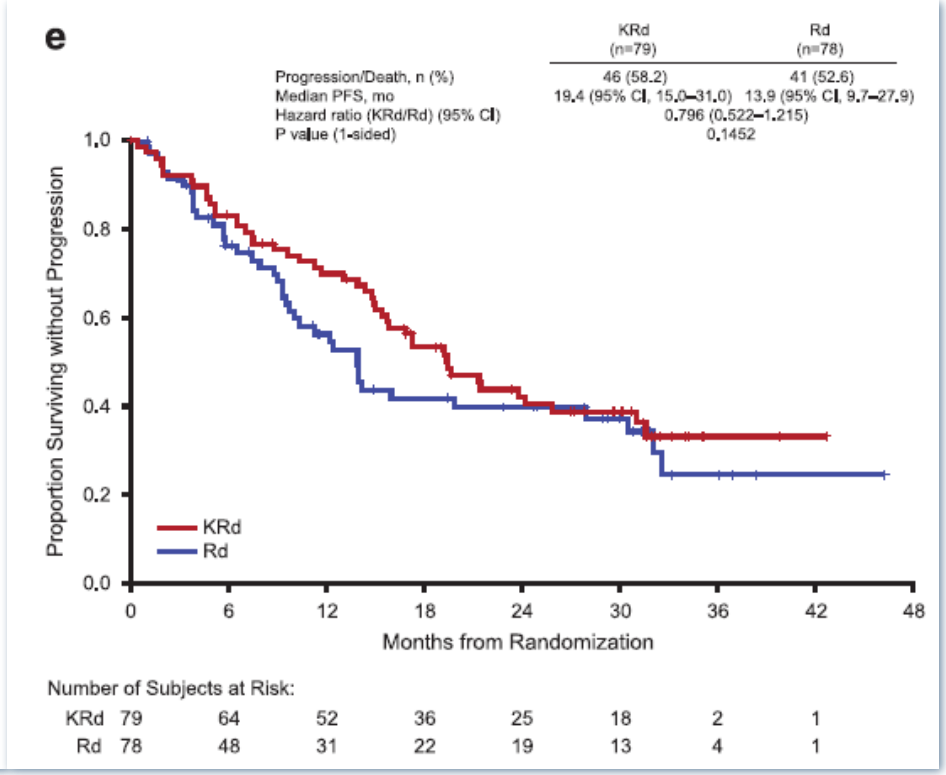
Dimopoulos MA, Blood Cancer Journal 2017

Primary Endpoint: PFS by previous treatment

Previous Btz exposure



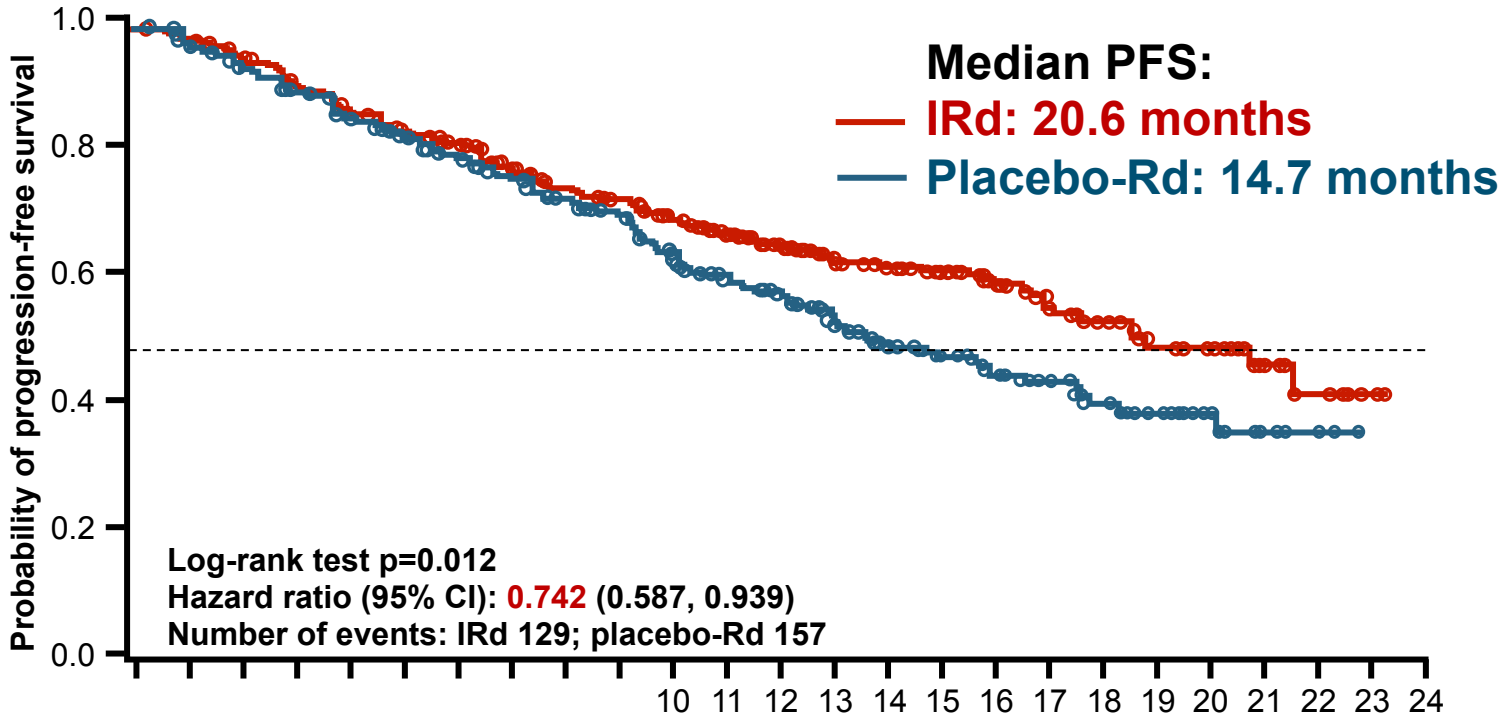
Previous Len exposure



Dimopoulos MA, Blood Cancer Journal 2017

TOURMALINE-MM1: IRd vs Placebo-Rd

ORR: 78% vs 72%
≥CR rate: 12% vs 7%



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

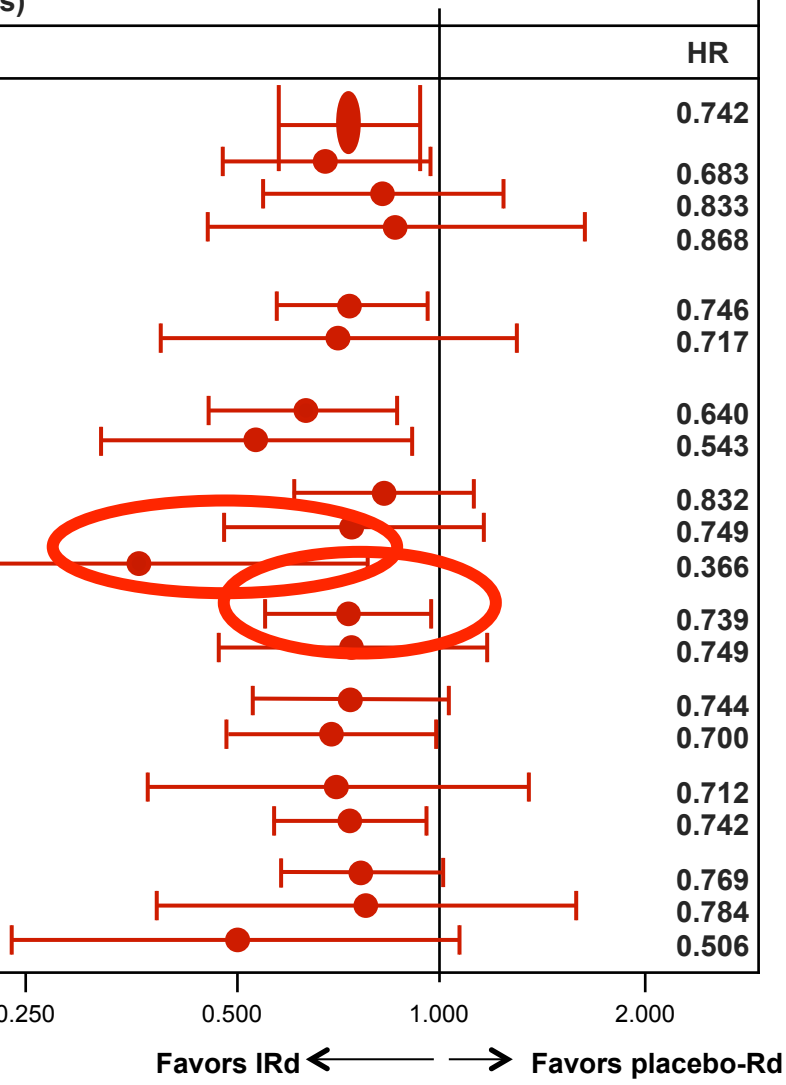
- Median follow-up: 14.8 months in the IRd group and 14.6 months in the placebo-Rd group

26% reduction in the risk of progression of death

Moreau P et al. NEJM 2016

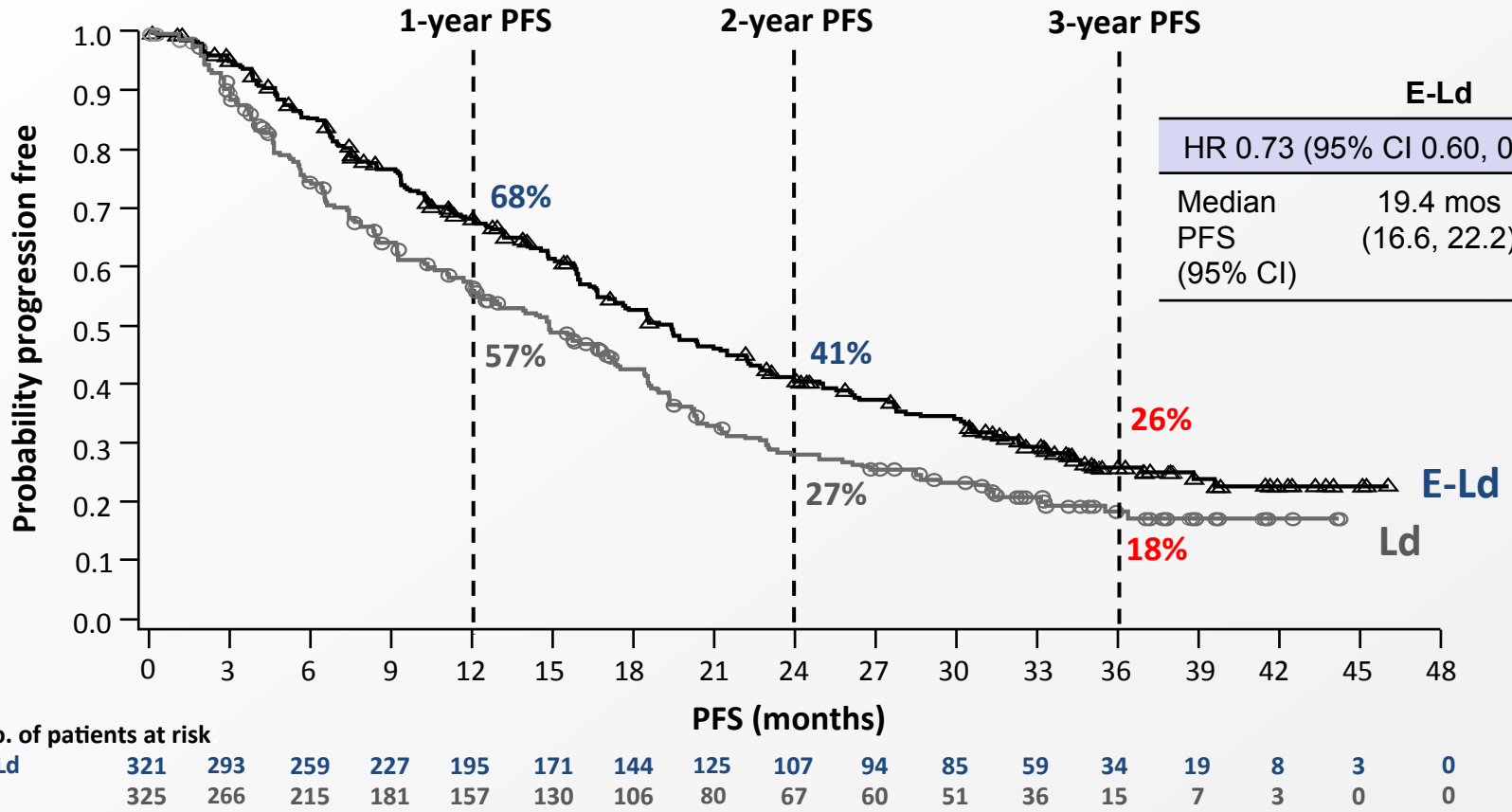
Consistent PFS benefit across pre-specified patient subgroups

		N		Median PFS (months)		
Variable	Subgroup	Placebo-Rd	IRd	Placebo-Rd	IRd	HR
All patients	ALL	360	362	14.7	20.6	0.742
Age (yrs)	≤65	176	168	14.1	20.6	0.683
	>65-75	125	145	17.6	17.5	0.833
	>75	61	47	13.1	18.5	0.868
ISS stage (stratification factor)	I or II	318	314	15.7	21.4	0.746
	III	44	46	10.1	18.4	0.717
Cytogenetic risk	Standard-risk	216	199	15.6	20.6	0.640
	High-risk	62	75	9.7	21.4	0.543
Number of prior therapies	1	217	224	15.9	20.6	0.832
	2	111	97	14.1	17.5	0.749
	3	34	39	10.2	NE	0.366
Proteasome inhibitor	Exposed	253	250	13.6	18.4	0.739
	Naive	109	110	15.7	NE	0.749
Prior IMiD therapy	Exposed	204	193	17.5	NE	0.744
	Naïve	158	167	13.6	20.6	0.700
Refractory to last prior therapy	Yes	55	59	NE	NE	0.712
	No	307	301	14.1	20.6	0.742
Relapsed or refractory	Relapsed	280	276	15.6	18.7	0.769
	Refractory	40	42	13.0	NE	0.784
	Ref & rel	42	41	13.1	NE	0.506



ELOQUENT-2: Elo-Ld vs Ld

ORR:	79%	vs	66%
≥CR rate:	5%	vs	9%



	E-Ld	Ld
HR 0.73 (95% CI 0.60, 0.89); p=0.0014		
Median PFS (95% CI)	19.4 mos (16.6, 22.2)	14.9 mos (12.1, 17.2)

No. of patients at risk

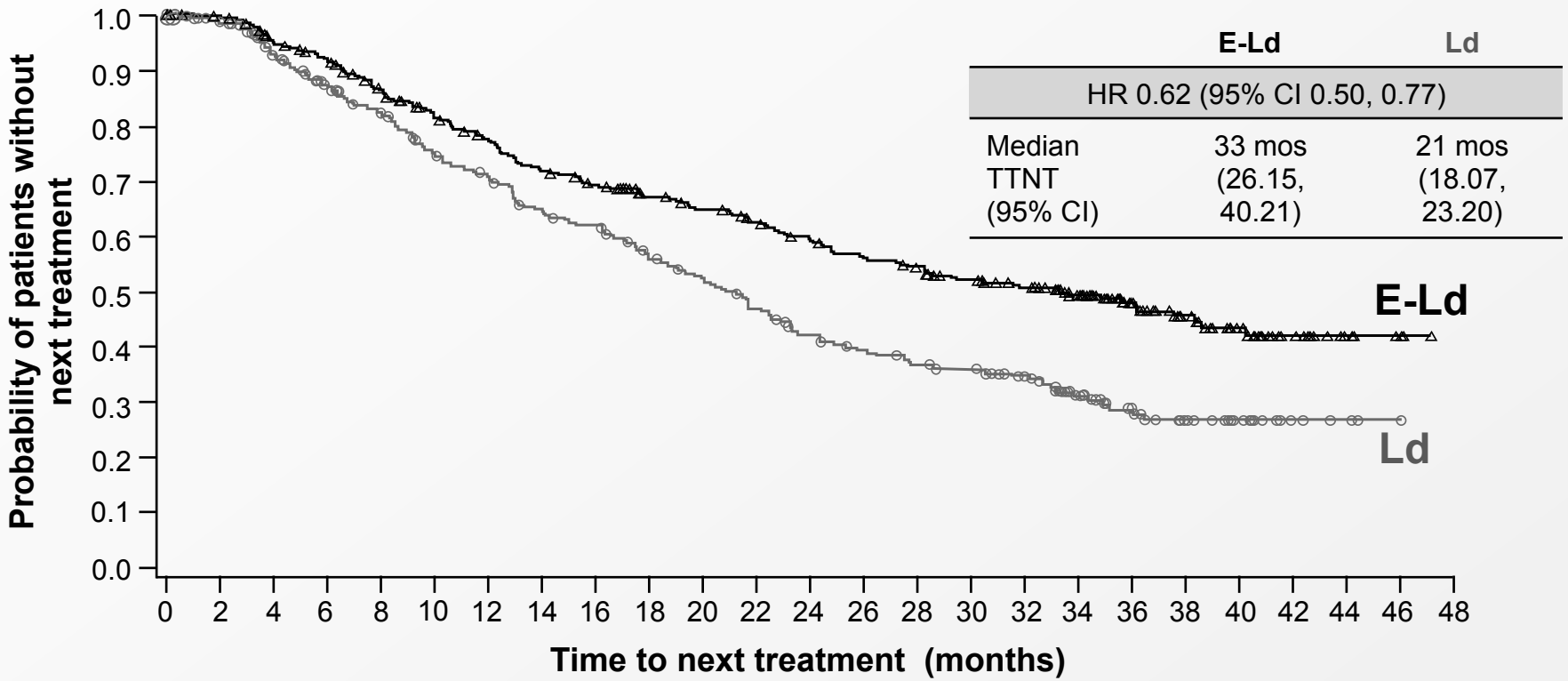
E-Ld	321	293	259	227	195	171	144	125	107	94	85	59	34	19	8	3	0
Ld	325	266	215	181	157	130	106	80	67	60	51	36	15	7	3	0	0

PFS benefit with Elo-Rd was maintained over time (vs Rd):
Overall 27% reduction in the risk of disease progression or death

Lonial S et al, NEJM 2015
Dimopoulos MA, et al ASH 2015

ELOQUENT-2: EloRd vs Rd

Time to Next Treatment



	E-Ld	Ld
HR 0.62 (95% CI 0.50, 0.77)		
Median TTNT (95% CI)	33 mos (26.15, 40.21)	21 mos (18.07, 23.20)

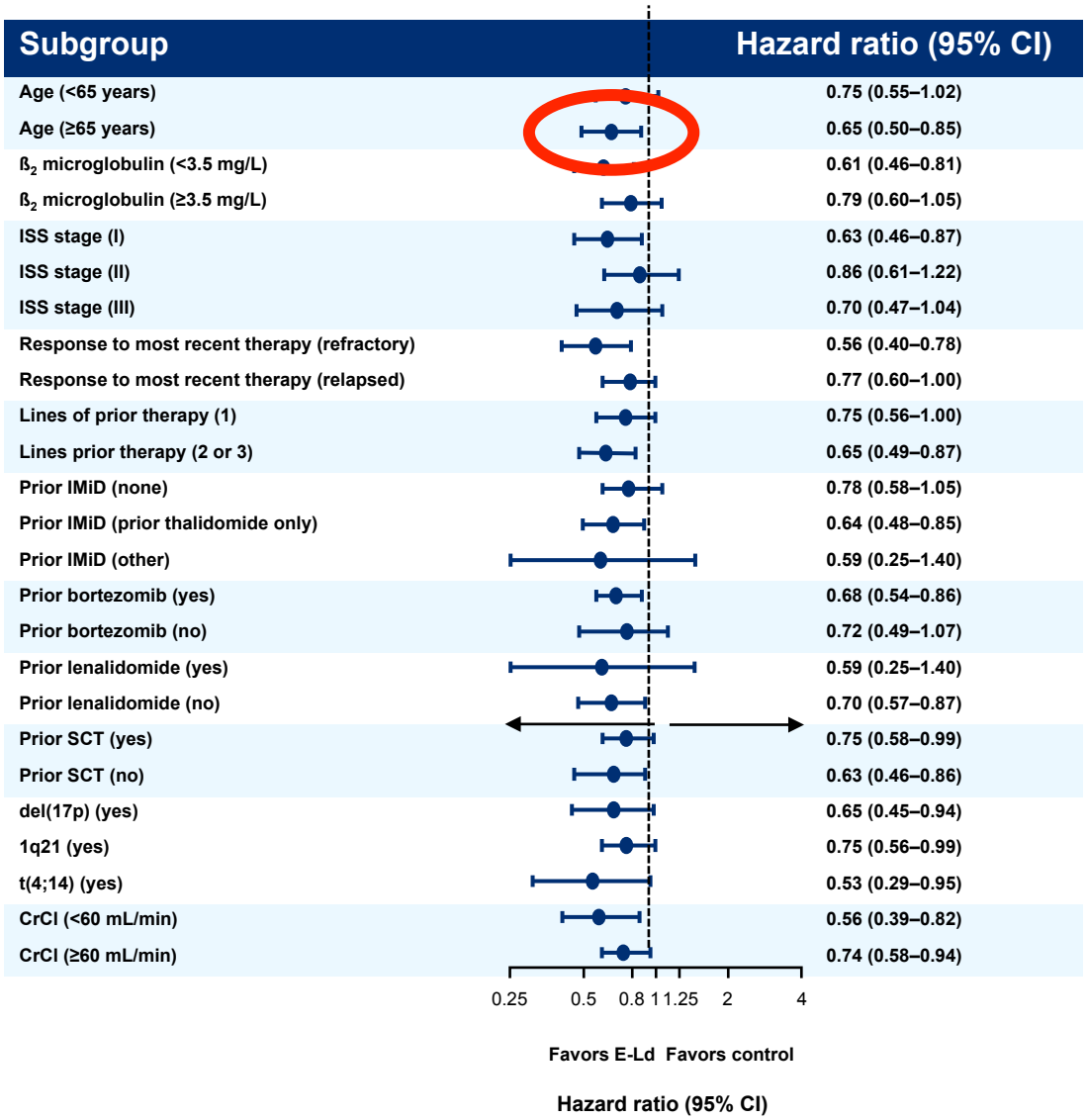
No. of patients at risk

E-Ld	321	315	294	282	259	239	225	208	198	182	174	165	153	144	138	126	118	94	65	46	32	14	6	3	0
Ld	325	305	276	251	232	206	193	174	166	148	135	120	105	96	89	85	76	46	30	20	13	5	3	1	0

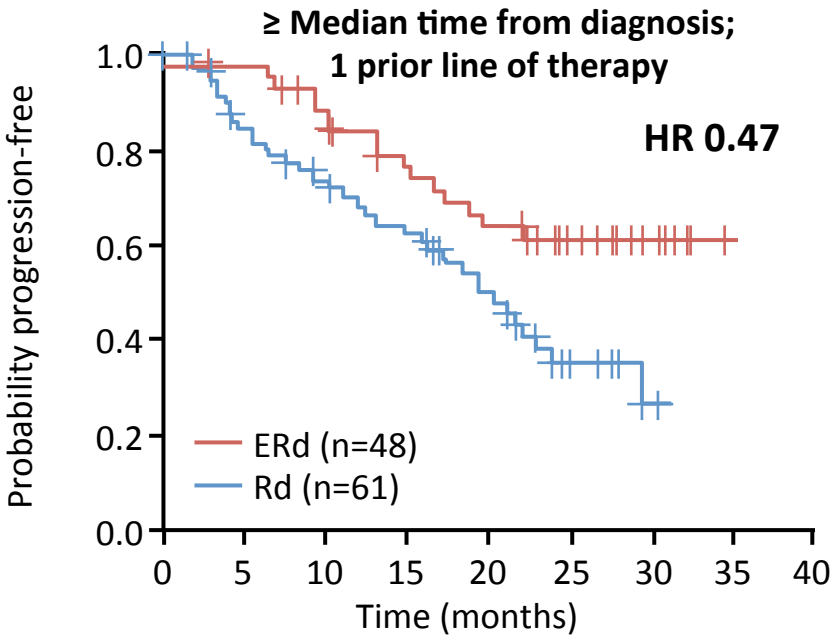
E-Ld-treated patients had a median delay of 1 year in the time to next treatment vs Ld-treated patients

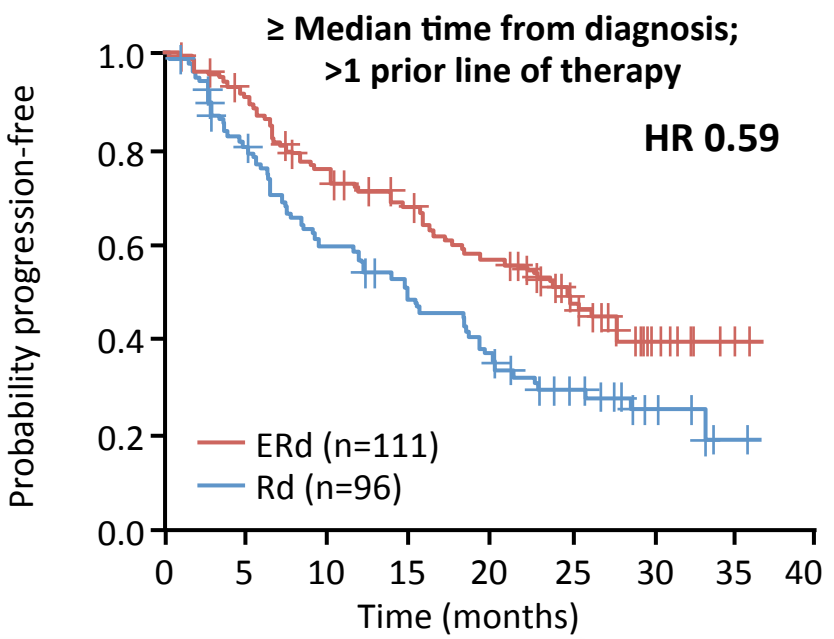
Lonial S et al, NEJM 2015

Progression-Free Survival in Predefined Subgroups

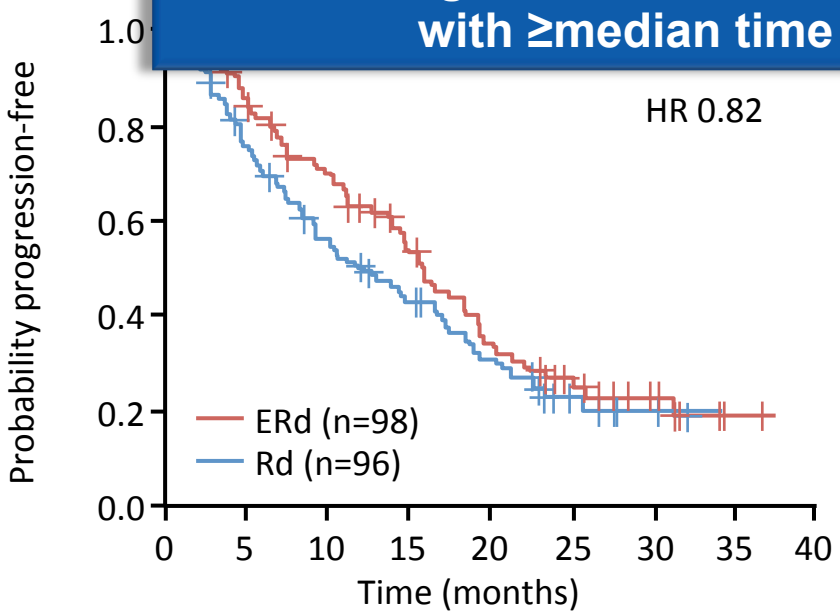


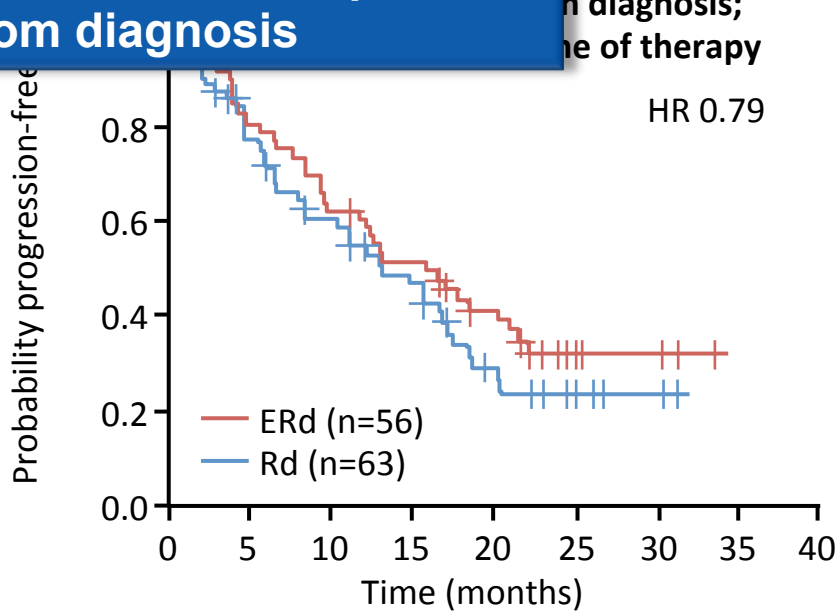
Patients With ≥ Median Time From Diagnosis (3.5 yrs)



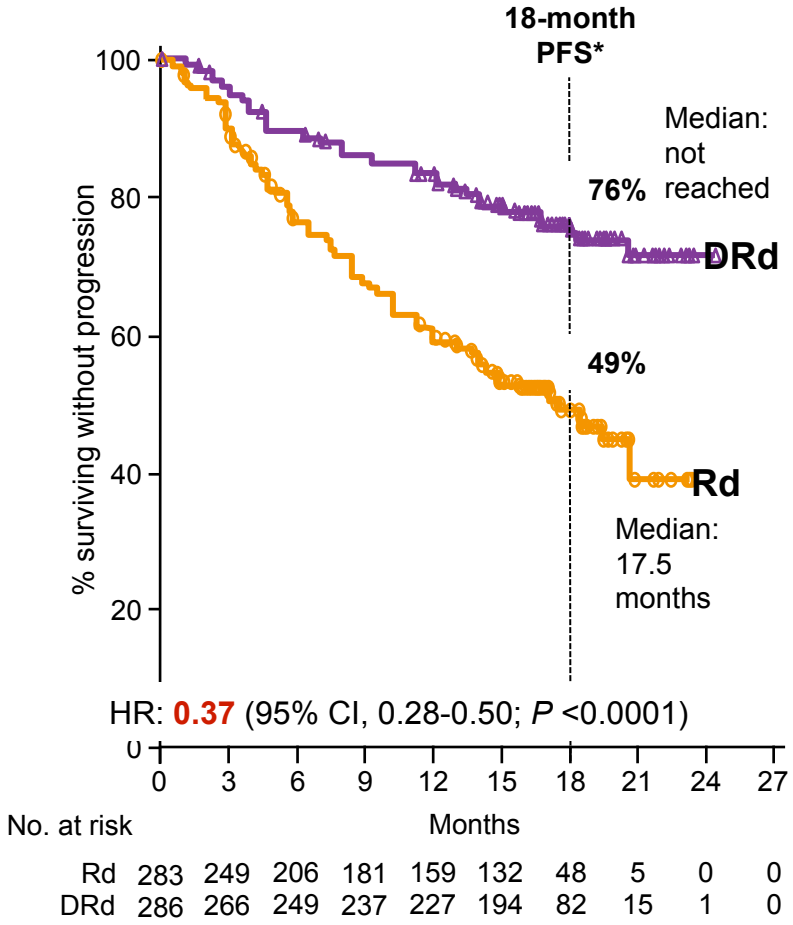


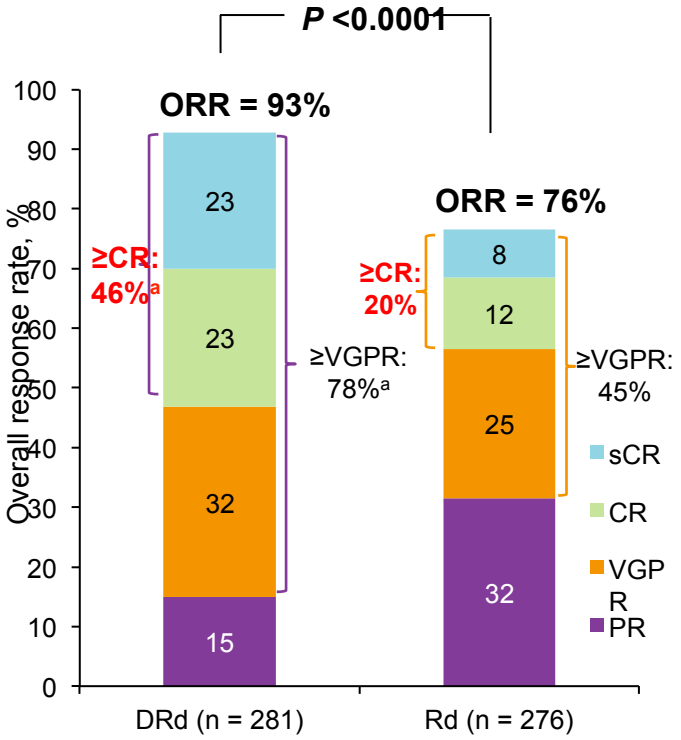
Greater magnitude of benefit was observed in patients with ≥median time from diagnosis





POLLUX: DaraRd vs Rd



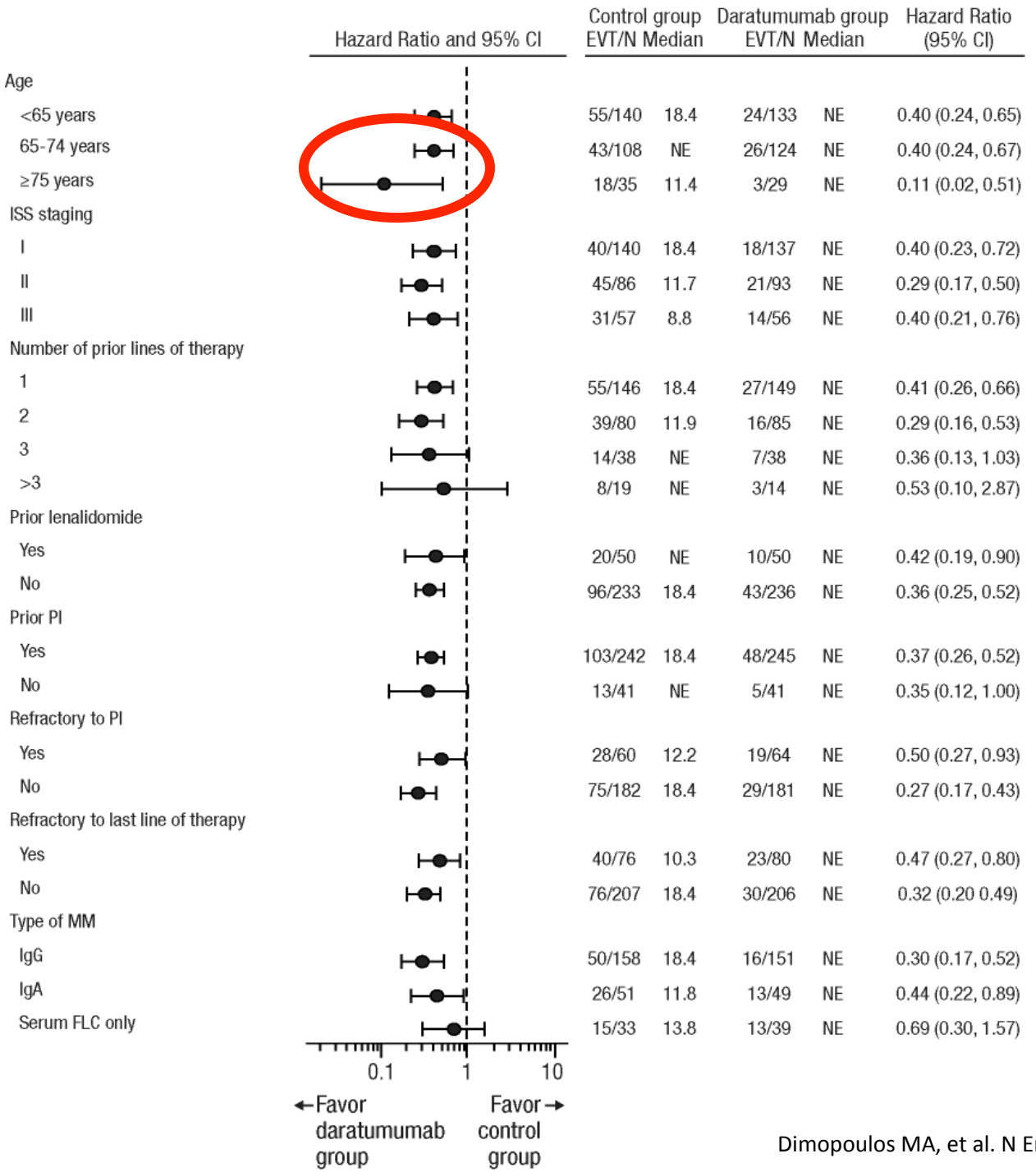


Median follow-up: 17.3 (range, 0-24.5) months

DRd-treated patients had a 63% reduction in the risk of disease progression or death in comparison with Rd Responses continue to deepen in the DRd group with longer follow-up

Note: PFS: ITT population; ORR: response-evaluable population.
*Kaplan-Meier estimate;
[a]*P* <0.0001 for DRd vs Rd.

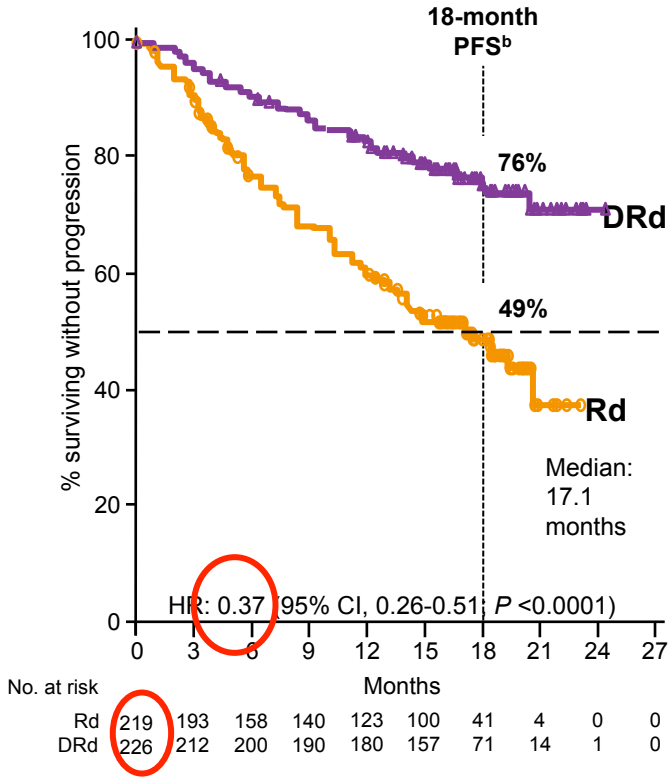
Usmani SZ, et al. Presented at ASH 2016 (Abstract 1151), oral presentation.



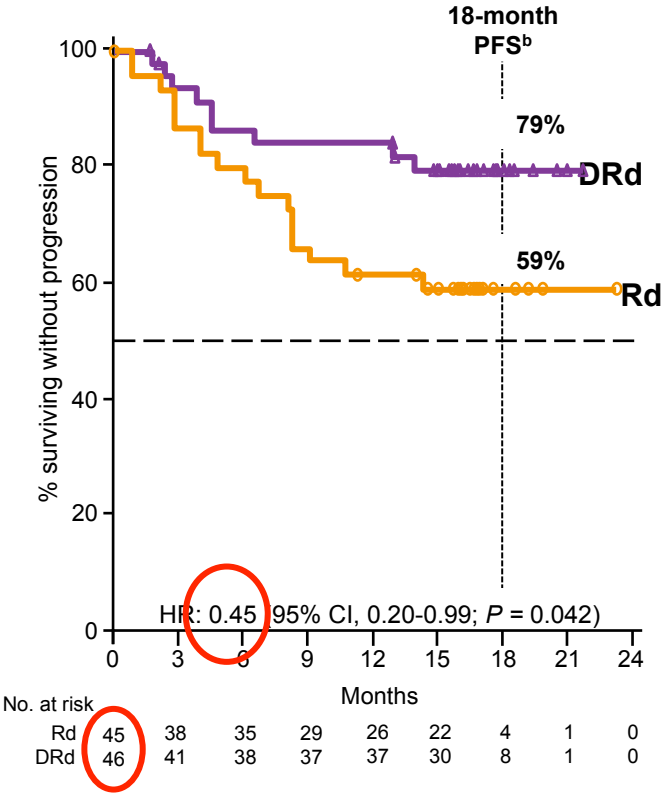
Dimopoulos MA, et al. N Engl J Med 2016;375:1319-1331.

POLLUX: DaraRd vs Rd

Lenalidomide-naïve[a]



Lenalidomide-exposed[a]



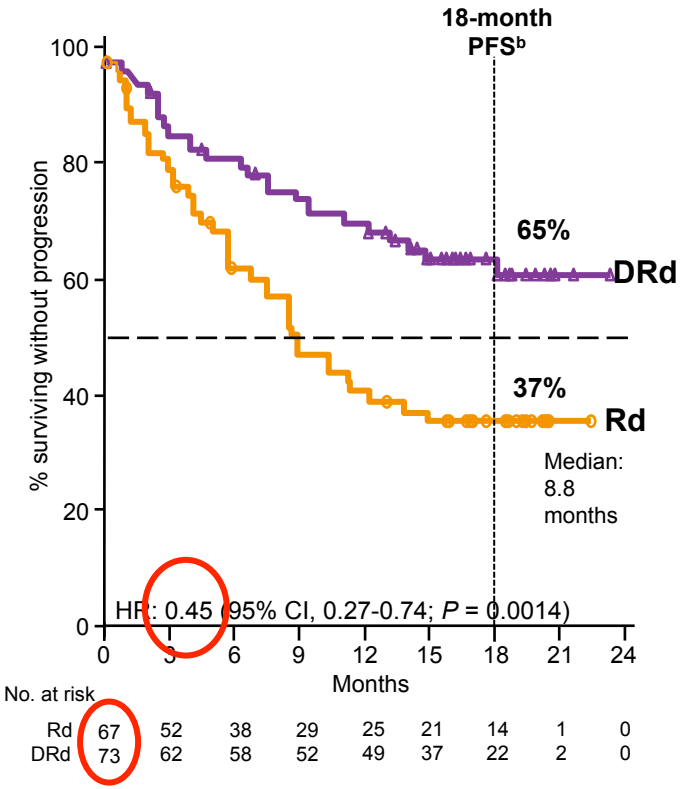
DRd maintains treatment benefit in lenalidomide-naïve and exposed patients

[a]in 1 to 3 prior lines
[b]Kaplan-Meier estimate.

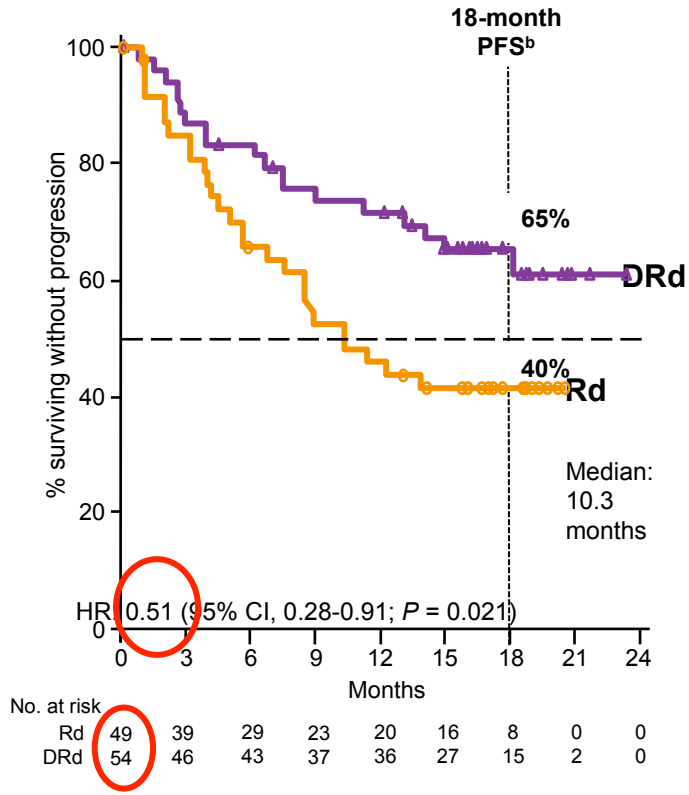
Moreau P, et al. Presented at ASH 2016 (Abstract 489), oral presentation

POLLUX: DaraRd vs Rd

Refractory to Last Line of Therapy[a] (28% of patients in both arms)



Bortezomib-refractory[a]



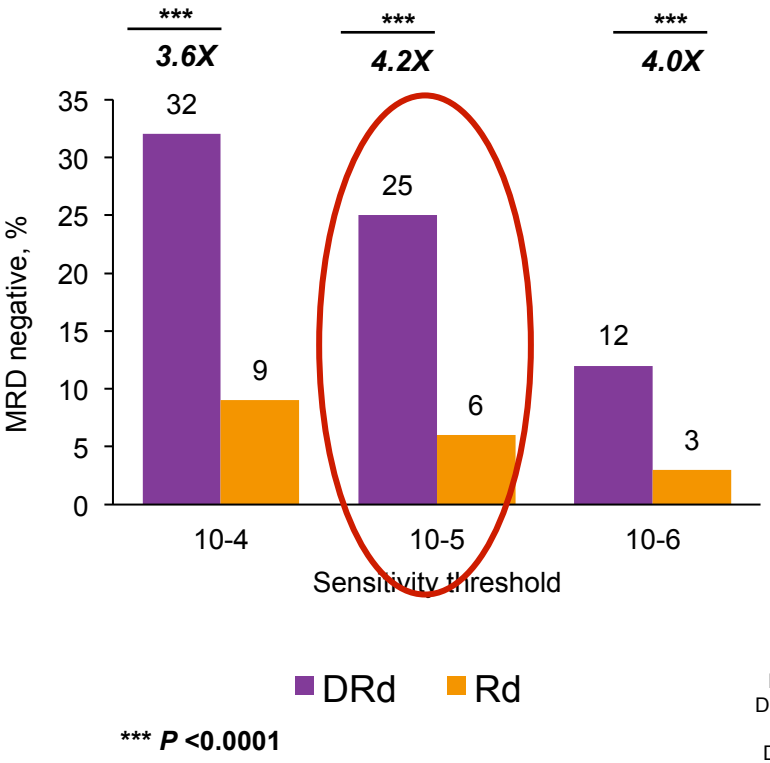
DRd treatment benefit observed in patients refractory to last line of therapy, including bortezomib-refractory patients

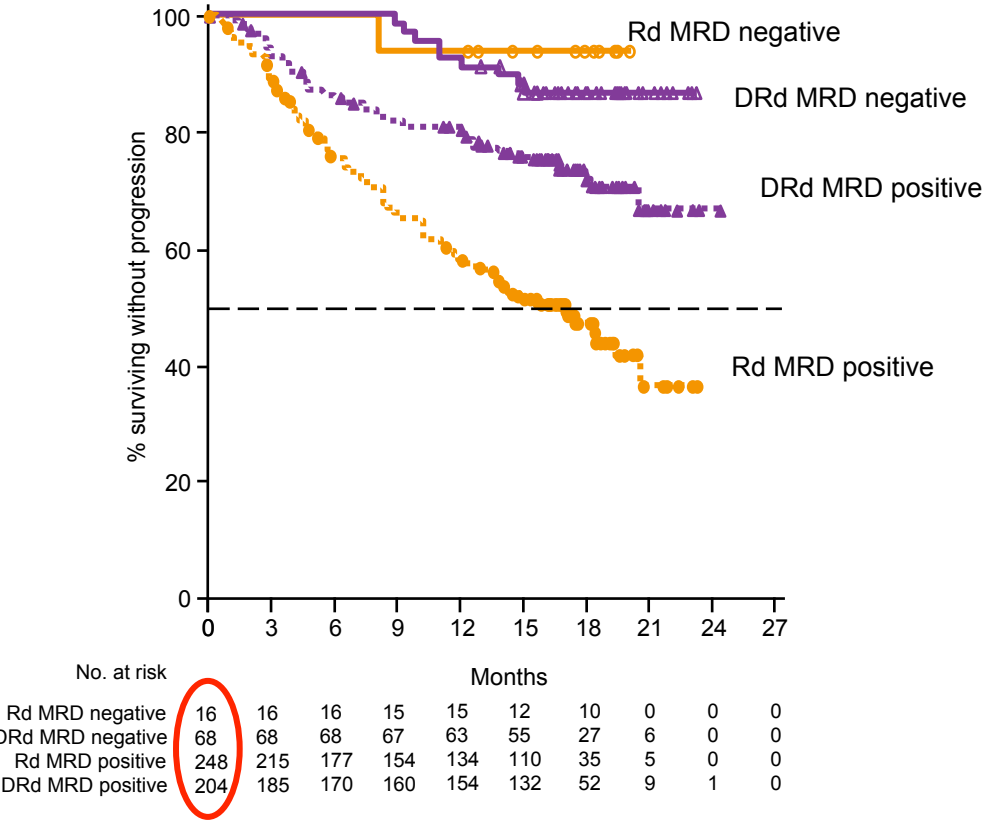
[a]in 1 to 3 prior lines
[b]Kaplan-Meier estimate.

Moreau P, et al. Presented at ASH 2016 (Abstract 489), oral presentation

POLLUX: DaraRd vs Rd

MRD-negative Rate (10^{-5}) by Prior Treatment Status





MRD-negative patients achieve prolonged PFS

Moreau P, et al. Presented at ASH 2016 (Abstract 489), oral presentation

Options of therapy for RRMM patients

Induction Bortezomib-based combination

↓

ASCT (melphalan 200)

↓

Nothing/Consolidation/Maintenance

Induction Bortezomib-based combo

Lenalidomide-dex

Second ASCT/ Allo-RIC

1st relapse

IMiDs-based combinations

Carfilzomib plus Rd
PFS: 26.3m, HR: 0.69[1]

Elotuzumab plus Rd
PFS: 19.4m, HR: 0.73[2]

Daratumumab plus Rd
PFS: NR (76%@18m), HR: 0.37[3]

Ixazomib plus Rd
PFS: 20.6m, HR: 0.74[4]

1. Stewart AK, et al. N Engl J Med 2015;372:142-52; 2. Dimopoulos MA et al. presented at ASH 2015 (Abstract 28), oral presentation;
3. Usmani SZ, et al. Presented at ASH 2016 (Abstract 1151), oral presentation; 4. Moreau P et al. N Engl J Med 2016;374(17):1621-34.

Options of therapy for RRMM patients

Induction Bortezomib-based combination

↓

ASCT (melphalan 200)

↓

Nothing/Consolidation/Maintenance

Induction Bortezomib-based combo

Lenalidomide-dex

Second ASCT/ Allo-RIC

1st relapse

PIs-based combinations

- Kd
- VD + Daratumumab

IMiDs-based combinations

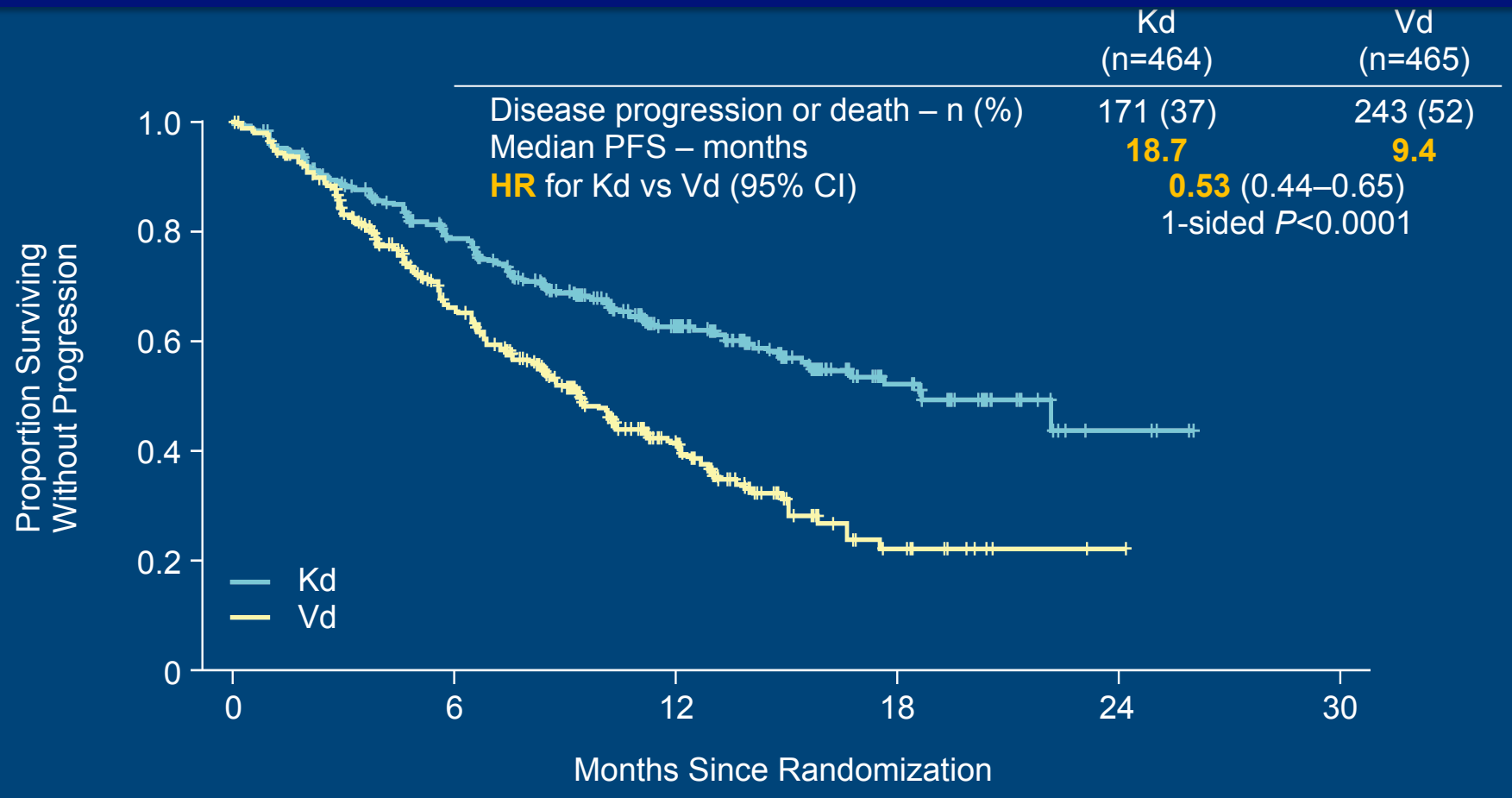
- Carfilzomib plus Rd
  PFS: 26.3m, HR: 0.69[1]
- Elotuzumab plus Rd
  PFS: 19.4m, HR: 0.73[2]
- Daratumumab plus Rd
  PFS: NR, HR: 0.37[3]
- Ixazomib plus Rd
  PFS: 20.6m, HR: 0.74[4]

1. Stewart AK, et al. N Engl J Med 2015;372:142-52; 2. Dimopoulos MA et al. presented at ASH 2015 (Abstract 28), oral presentation;
3. Usmani SZ, et al. Presented at ASH 2016 (Abstract 1151), oral presentation; 4. Moreau P et al. N Engl J Med 2016;374(17):1621-34.

ENDEAVOR: Kd at double dose (56 mg/sm) vs Vd (N=929)

ORR: 77% vs 63%

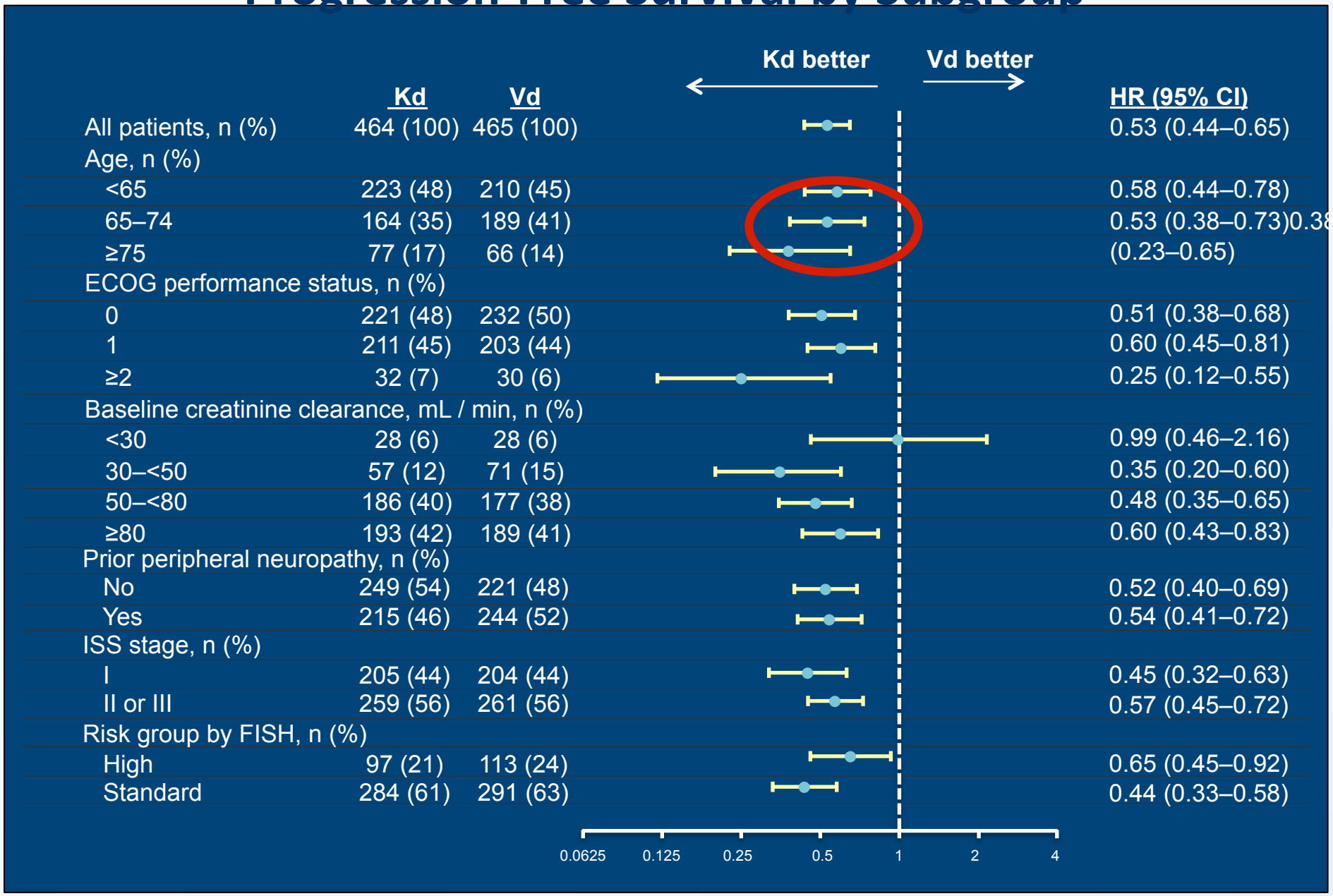
≥CR rate: 13% vs 6%



- **Median follow-up: 11.9 in the carfilzomib group vs 11.1 in the bortezomib group**

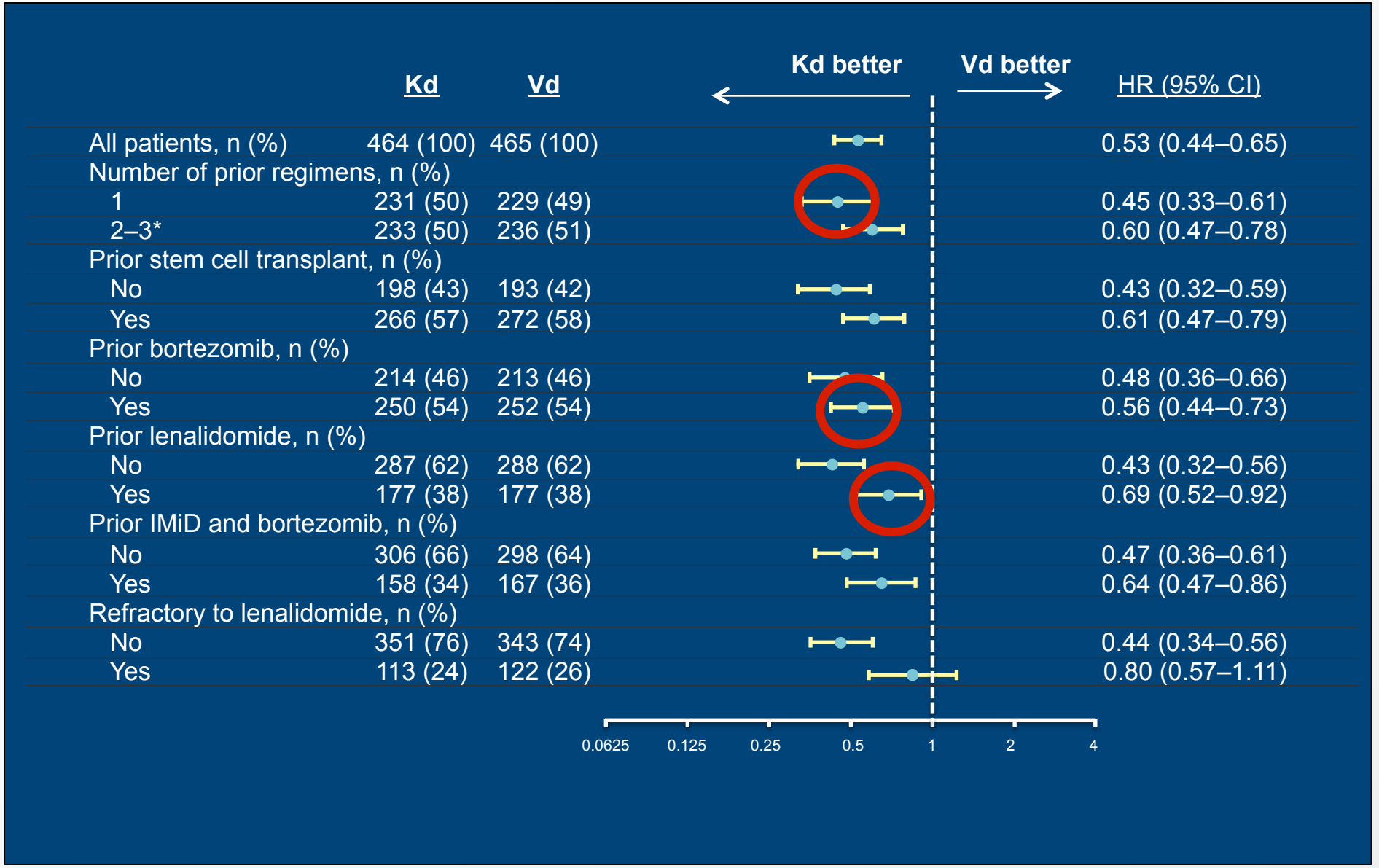
Dimopoulos D et al, Lancet Oncology 2016

Progression-Free Survival by Subgroup



Dimopoulos D et al, Lancet Oncology 2016

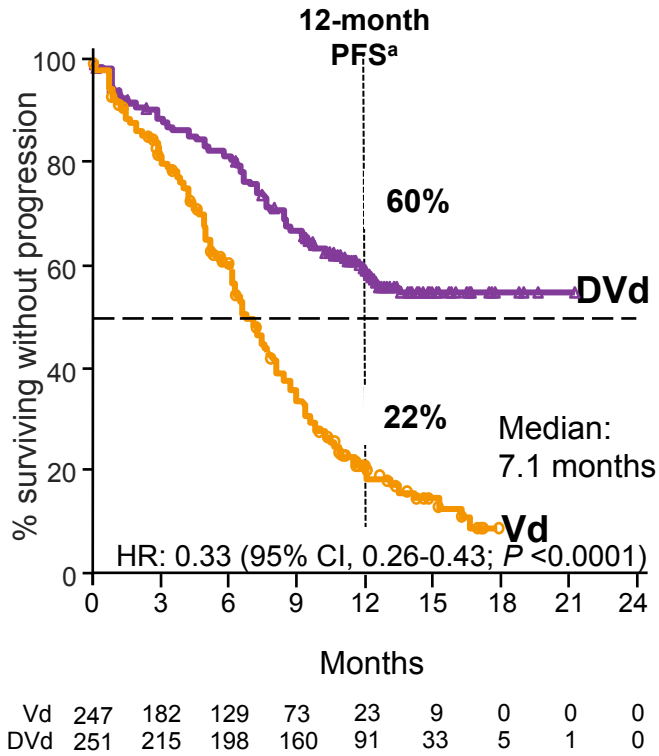
Progression-Free Survival by Subgroup (continued)

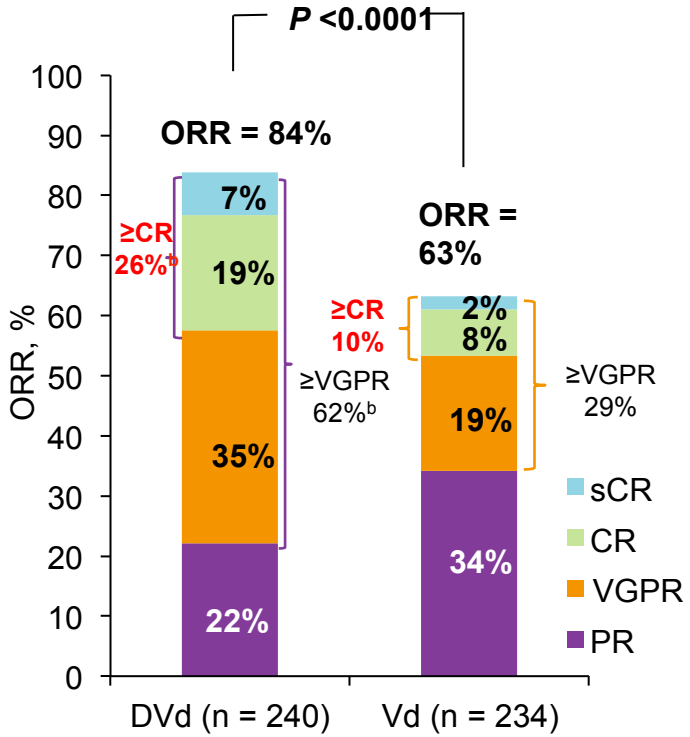


	Kd	Vd	HR (95% CI)
All patients, n (%)	464 (100)	465 (100)	0.53 (0.44–0.65)
Number of prior regimens, n (%)			
1	231 (50)	229 (49)	0.45 (0.33–0.61)
2–3*	233 (50)	236 (51)	0.60 (0.47–0.78)
Prior stem cell transplant, n (%)			
No	198 (43)	193 (42)	0.43 (0.32–0.59)
Yes	266 (57)	272 (58)	0.61 (0.47–0.79)
Prior bortezomib, n (%)			
No	214 (46)	213 (46)	0.48 (0.36–0.66)
Yes	250 (54)	252 (54)	0.56 (0.44–0.73)
Prior lenalidomide, n (%)			
No	287 (62)	288 (62)	0.43 (0.32–0.56)
Yes	177 (38)	177 (38)	0.69 (0.52–0.92)
Prior IMiD and bortezomib, n (%)			
No	306 (66)	298 (64)	0.47 (0.36–0.61)
Yes	158 (34)	167 (36)	0.64 (0.47–0.86)
Refractory to lenalidomide, n (%)			
No	351 (76)	343 (74)	0.44 (0.34–0.56)
Yes	113 (24)	122 (26)	0.80 (0.57–1.11)

Dimopoulos D et al, Lancet Oncology 2016

CASTOR: DaraVd vs Vd





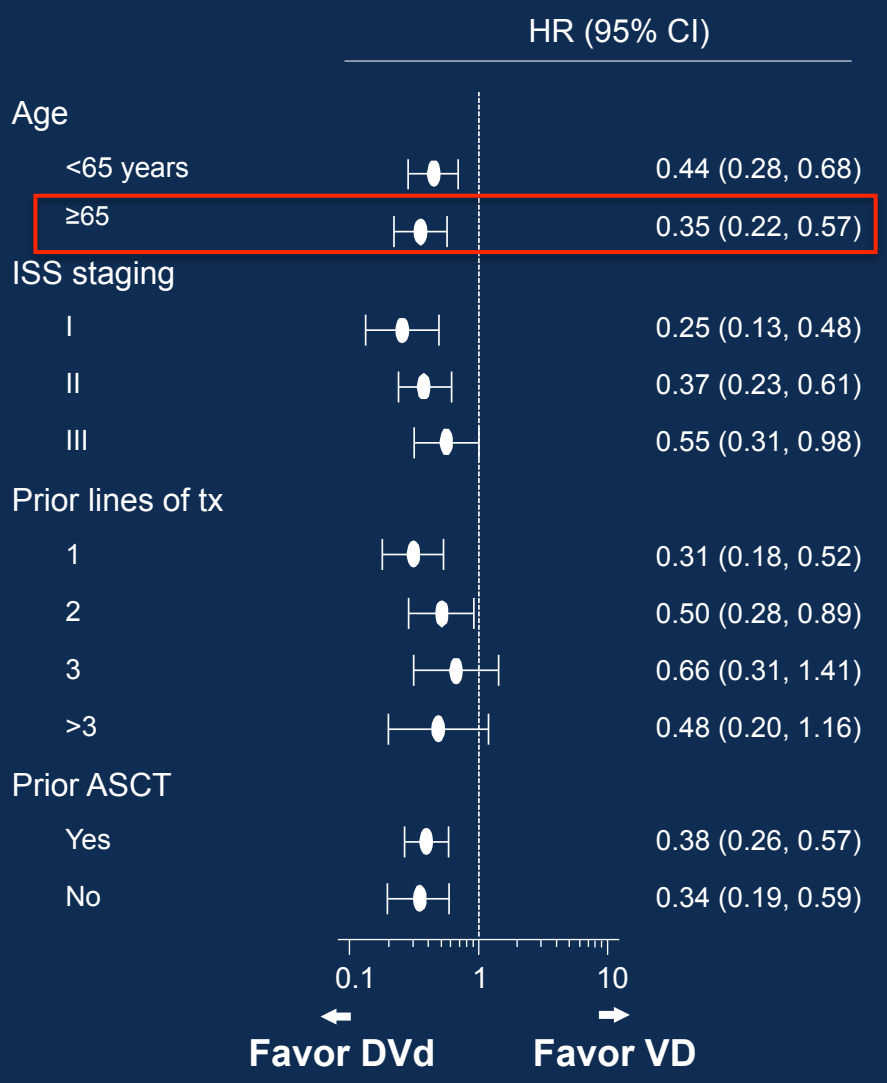
- Median (range) follow-up: 13.0 (0-21.3) months
- An additional 7% of patients receiving DVd achieved ≥CR with

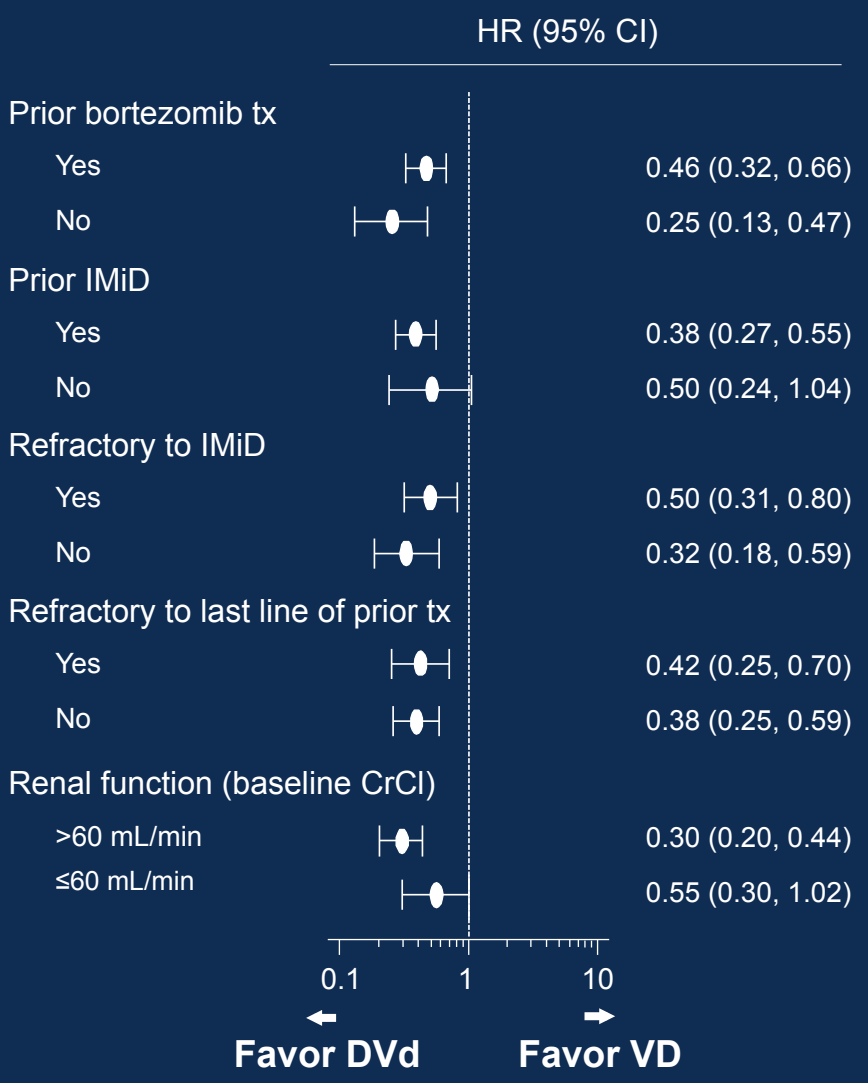
DVd-treated patients had a 67% reduction in the risk of disease progression or death in comparison with Vd Responses continue to deepen in the DVd group with longer follow-up

ITT, intent-to-treat.
Note: PFS = ITT population; ORR = response-evaluable population.
[a]Kaplan-Meier estimate.
[b]*P* <0.0001 for DVd versus Vd.

Mateos M, et al. Presented at ASH 2016 (Abstract 1150), oral presentation;

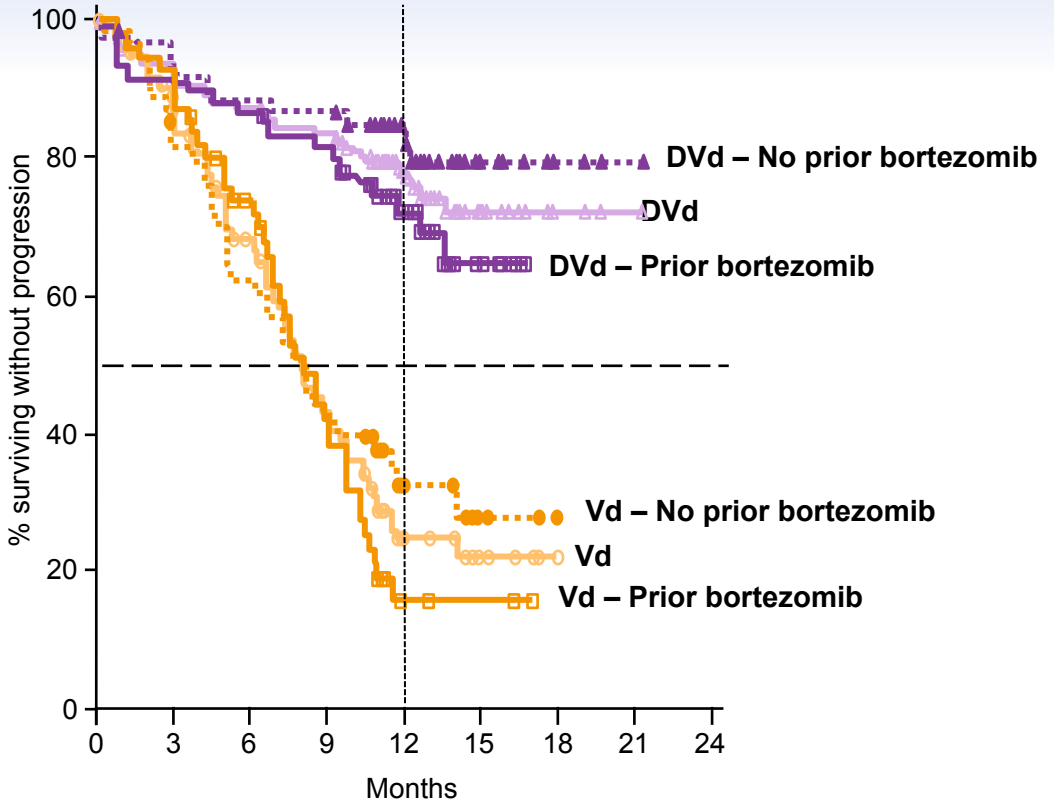
PFS: Subgroup Analysis





Tx, treatment; CrCl, creatinine clearance.

PFS by Prior Bortezomib Exposure: 1 Prior Line Population

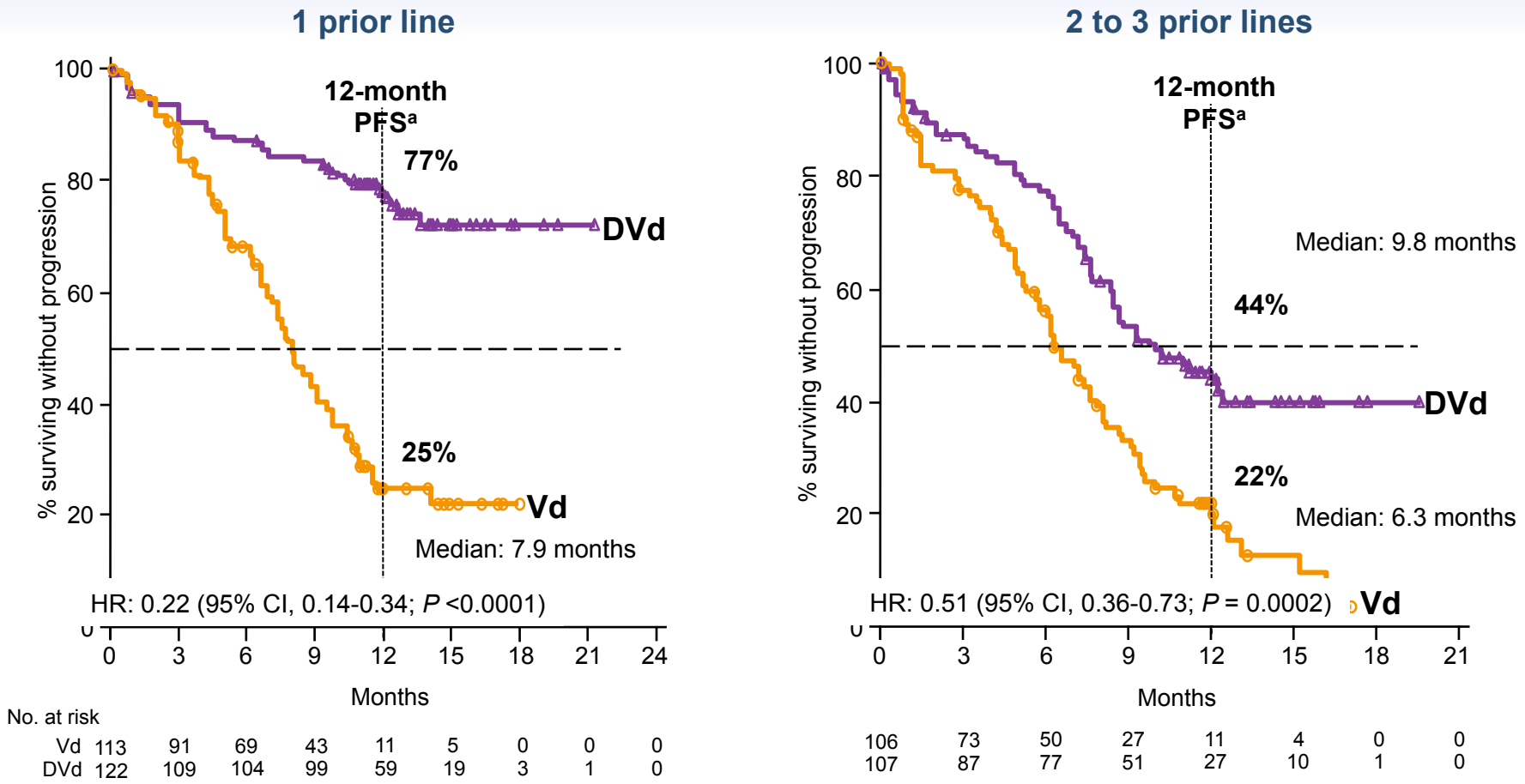


No. at risk									
Vd	113	91	69	43	11	5	0	0	0
DVd	122	109	104	99	59	19	3	1	0
Vd – No prior bortezomib	56	43	33	23	8	3	0	0	0
DVd - No prior bortezomib	60	54	52	51	30	10	3	1	0
Vd – Prior bortezomib	57	48	36	20	3	2	0	0	0
DVd - Prior bortezomib	62	55	52	48	29	9	0	0	0

DVd provides treatment benefit regardless of prior bortezomib exposure

Mateos M, et al. Presented at ASH 2016 (Abstract 1150), oral presentation;

PFS: Prior Lines of Treatment

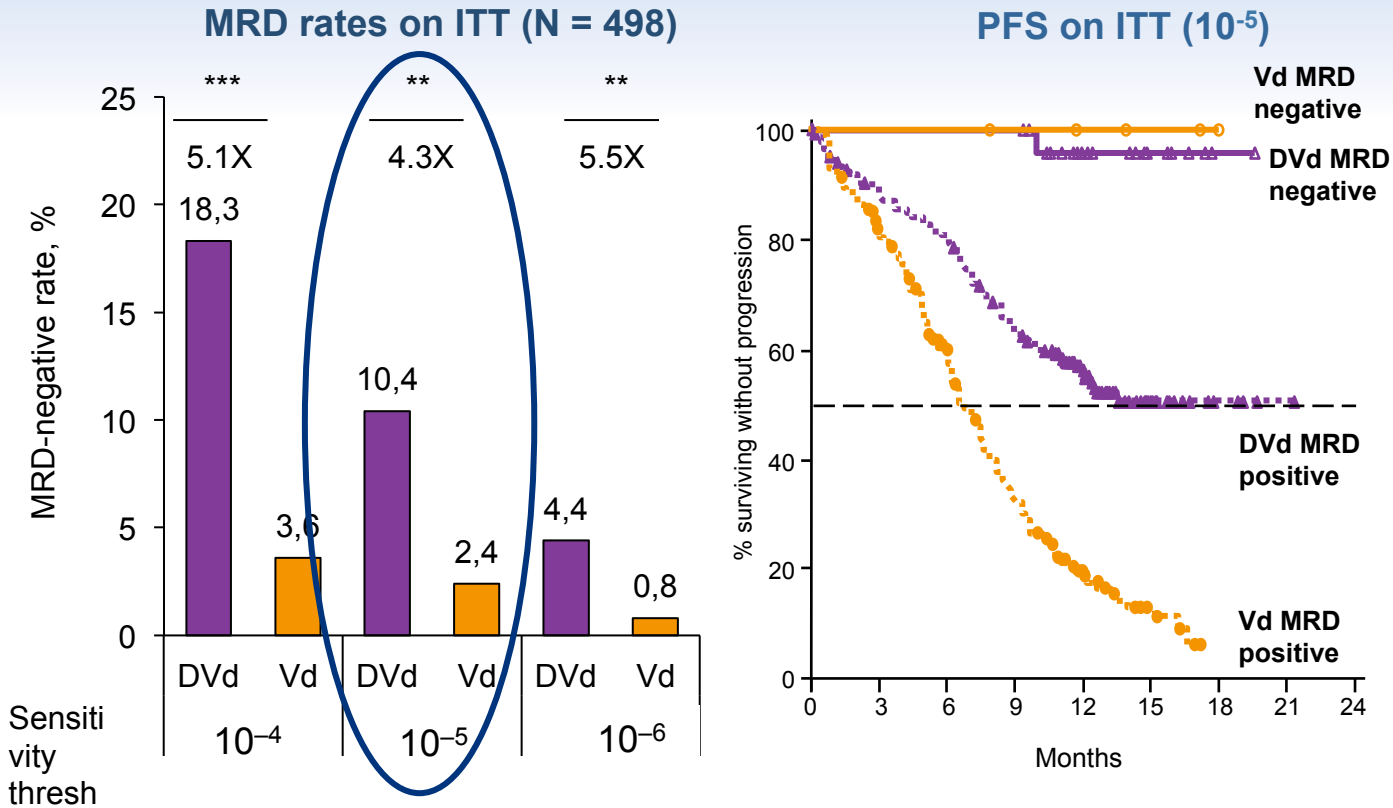


DVd is superior to Vd regardless of prior lines of therapy, with greatest benefit observed in 1 prior line

[a]Kaplan-Meier estimate.

Mateos M, et al. Presented at ASH 2016 (Abstract 1150), oral presentation;

MRD rates and PFS



- MRD was evaluated by ClonoSEQ-NGS-based assay in a central lab at three sensitivity thresholds, for patients with suspected CR and also for patients who maintain CR at C9 and C15

- MRD-negative rates for DVd were ≥3-fold higher across all thresholds
- MRD negativity is associated with better outcomes

***P <0.0001; **P <0.01; NS, not significant.
P values calculated using likelihood-ratio chi-square test.
MRD-negativity rate = proportion of pti with negative MRD test results at any time during treatment.

Mateos M, et al. Presented at ASH 2016 (Abstract 1150), oral presentation;

Options of therapy for RRMM patients

Induction Bortezomib-based combination

↓

ASCT (melphalan 200)

↓

Nothing/Consolidation/Maintenance

Induction Bortezomib-based combo

Lenalidomide-dex

1st relapse

PIs based combinations		IMiDs based combinations	
Kd PFS: 18.7 months, HR: 0.53[1]	**VD + Daratumumab** PFS: NR (60%@12m) HR:0.33[7]	**Carfilzomib plus Rd** PFS: 26.3m, HR: 0.69[2]	**Elotuzumab plus Rd** PFS: 19.4m, HR: 0.73[3]
Panobinostat-bz/cz PFS: 12 months, HR: 0.63[6]	**Elo-Bd** PFS: 9.7m, HR: 0.72[8]	**Daratumumab plus Rd** PFS: NR (76%@18m), HR: 0.37[4]	**Ixazomib plus Rd** PFS: 20.6m, HR: 0.74[5]

1. Dimopoulos MA, et al. Lancet Oncology 2016; 17: 27-38 ; 2. Stewart AK, et al. N Engl J Med 2015;372:142-52; 3. Dimopoulos MA et al. presented at ASH 2015 (Abstract 28), oral presentation; 4. Usmani SZ, et al. Presented at ASH 2016 (Abstract 1151), oral presentation; 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. Mateos M, et al. Presented at ASH 2016 (Abstract 1150), oral presentation; 8. Jakubowiak A et al. Blood 2016: 127(23):2833-40

Adverse events

	COMBINATION	GRADE 3 / 4 (%)
ASPIRE	Rd + Carfilzomib	**HYPERTENSION (4)** **CARDIAC FAILURE (4)** ACUTE RENAL FAILURE (3)
ELOQUENT	Rd + Elotuzumab	**INFUSION REACTION (1)**
TOURMALINE	Rd + Ixazomib	RASH (5)
POLLUX	Rd + Daratumumab	**INFUSION REACTION (5)**
PANORAMA	Vd + Panobinostat	DIARRHEA (25) FATIGUE (24) VOMITING (7)
ENDEAVOR	Kd	**HYPERTENSION (9)** **DYSPNEA (5)** **CARDIAC FAILURE (5)**
POLLUX	Vd + Daratumumab	**INFUSION REACTION (9)** HYPERTENSION (7)

How are we going to proceed in the clinical practice?

- **Type of relapse: aggressive,…**
  - KRd/DaraRd for aggressive relapses with rapid control required

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  - IMiDs-based combos: DaraRd & EloRd……. 1st preference for elderly
  - PIs-based combos: DaraVd & Kd…….. 1st preference for elderly

Stewart AK, et al. N Engl J Med 2015;372:142-52; Dimopoulos MA et al. presented at ASH 2015 (Abstract 28), oral presentation; Moreau P et al. N Engl J Med 2016;374(17): 1621-34; Dimopoulos et al. Presented at EHA 2016 (Abstract LB2238), oral presentation; Palumbo A, et al. Poster presented at ASH 2015 (Abstract 1844), oral presentation; Palumbo, A. N Engl J Med 2016.375(8):754-766.

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- **Number and type of prior lines of therapy**

- KRd:	after PIs/PIs-sensitive;	after 1 and ≥2 lines
- IRd:	after PIs/PIs-sensitive;	after 2-3 prior lines; primary refractory
- DaraRd:	after PIs/regardless PIs-sensitivity;	after 1 and ≥ 2 lines
- EloRd:	after PIs/regardless PIs-sensitivity;	time from dx is > 3.5 yrs (regardless 1 vs ≥2)
- Kd:	after PIs/IMiDs (s/r);	after 1 or ≥2 prior lines
- DaraVd:	after PIs/IMiDs (s/r);	after 1 line

Dimopoulos MA, et al. Presented at EHA 2015 (Abstract S427); Moreau P et al. N Engl J Med 2016;374(17): 1621-34; Dimopoulos et al. Presented at EHA 2016 (Abstract LB2238), oral presentation; Mateos MV, personal communication; Moreau P et al. Leukemia 2017;31:115–122; Mateos M, et al. Presented at ASH 2016 (Abstract 1150), oral presentation; Nihof IS, et al. Blood 2016; 128(19):2297-2306.

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- **Number and type of prior lines of therapy**

- **Cytogenetic abnormalities:**
  - KRd/IRd: best option in patients with t(4;14) and del(17/17p)
  - DaraRd: improve but not overcome
  - EloRd: improve t(4;14)/overcome del(17/17p)
  - Kd: no good option for high risk CA
  - DaraVd: improve and almost overcome

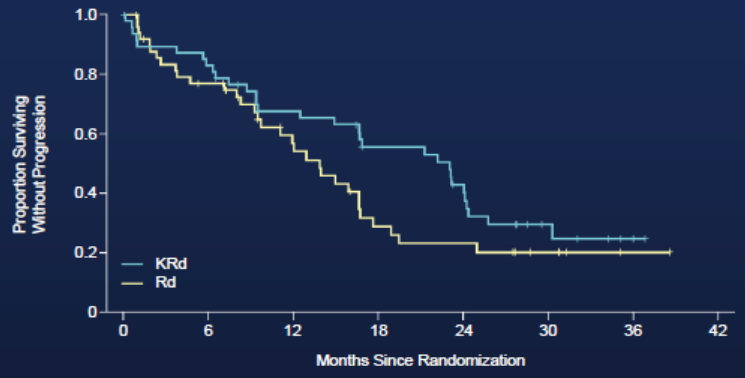
Avet Loiseau H et al. Blood 2016;128(9):1174–1180; Richardson P et al. ASCO 2016 (Abstract 8018); Usmani SZ, et al. Presented at ASH 2016 (Abstract 1151), oral presentation; Mateos MV, personal communication; Chng W-J, et al. Leukemia 2017 Feb 3. doi: 10.1038/leu.2016.390. [Epub ahead of print]; Mateos M, et al. Presented at ASH 2016 (Abstract 1150), oral presentation; Nihof IS, et al. Blood 2016; 128(19):2297-2306.

ASPIRE: KRd vs Rd

PFS by cytogenetic risk status at baseline

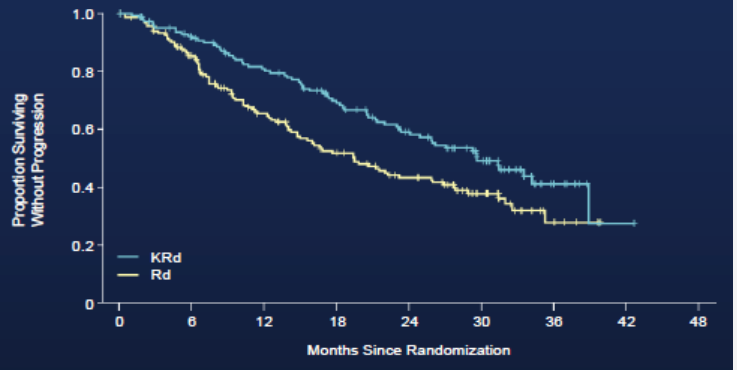
High risk defined by: t(4;14) or t(14;16) or with del(17p) in ≥60% of PCs

High Risk



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

Standard Risk



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

Table 4. Efficacy by specific cytogenetic abnormality at baseline (high-risk subgroup)

Cytogenetic abnormality	High-risk subgroup			
	t(4;14) Only		del(17p) Only in ≥60% of plasma cells	
	KRd (n = 30)	Rd (n = 25)	KRd (n = 13)	Rd (n = 13)
PFS, median mo	23.1	16.7	24.5	11.1
ORR, n (%)*	24 (80.0)	18 (72.0)	10 (76.9)	6 (46.2)

Avet-Loiseau H et al , Blood 2016

TOURMALINE-MM1: Outcomes by cytogenetic risk group

	ORR, %		≥VGPR, %		≥CR, %		Median PFS, months		
	IRd	Placebo-Rd	IRd	Placebo-Rd	IRd	Placebo-Rd	IRd	Placebo-Rd	HR
All patients	78.3*	71.5	48.1*	39	11.7*	6.6	20.6	14.7	0.742*
Standard-risk patients	80	73	51	44	12	7	20.6	15.6	0.640*
All high-risk patients	79*	60	45*	21	12*	2	21.4	9.7	0.543
Patients with del(17p)[†]	72	48	39	15	11*	0	21.4	9.7	0.596
Patients with t(4;14) alone	89	76	53	28	14	4	18.5	12.0	0.645

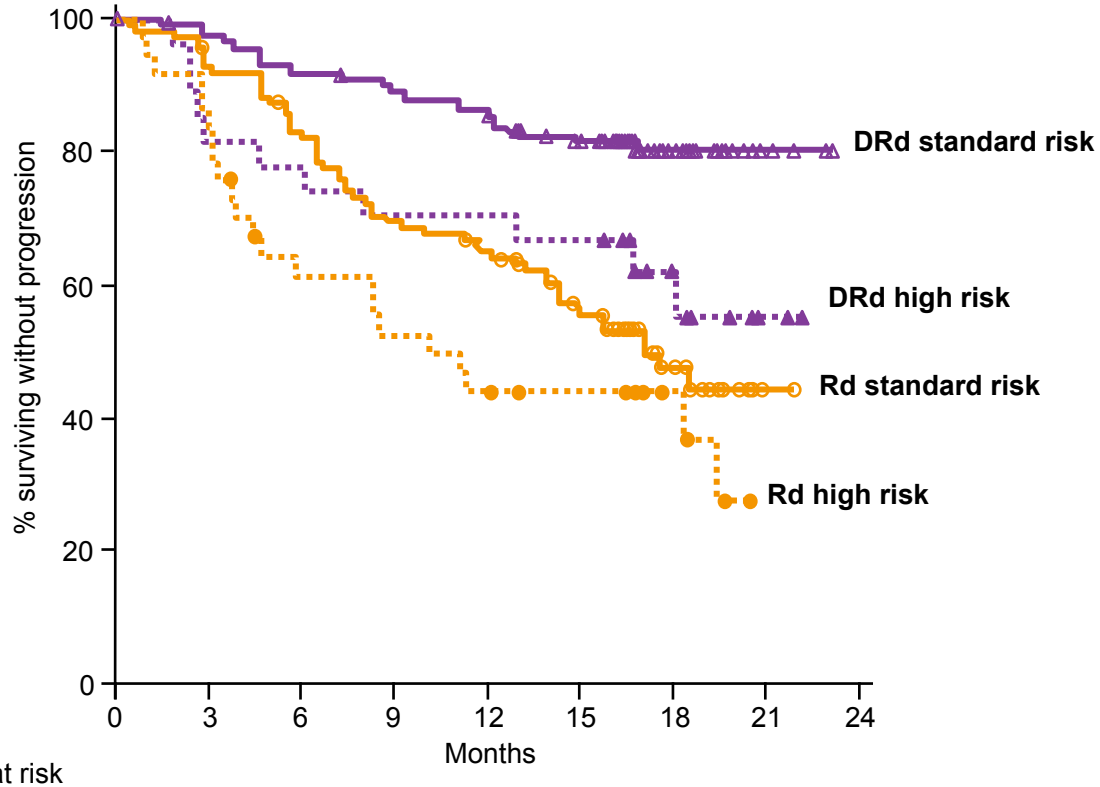
*$p<0.05$ for comparison between regimens. [†]Alone or in combination with t(4;14) or t(14;16).
Data not included on patients with t(14:16) alone due to small numbers (n=7).

- Median OS could not be estimated
- In the IRd arm, median PFS in high-risk patients was similar to that in the overall patient population and in patients with standard-risk cytogenetics

Moreau P et al, NEJM 2016

POLLUX: PFS by Cytogenetic Risk[a]

- **Comparable results in 1-3 prior line population**
- **ORR for DRd vs Rd:**
  - High risk: 85% vs 67% (*P* = 0.14)
  - Std risk: 95% vs 82% (*P* = 0.0020)



No. at risk

Rd std Risk	113	104	92	77	71	57	20	1	0
DRd std risk	133	128	120	116	111	98	41	4	0
Rd high risk	37	32	21	18	15	13	6	0	0
DRd high risk	28	22	21	19	19	18	9	2	0

High risk	**DRd** n = 28	**Rd** n = 37
Median PFS, mo	**NR**	**10.2**
HR (95% CI)	0.44 (0.19-1.03)	
P-value	0.0475	

Standard risk	**DRd** n = 133	**Rd** n = 113
Median PFS, mo	**NR**	**17.1**
HR (95% CI)	0.30 (0.18-0.49)	
P-value	<0.0001	

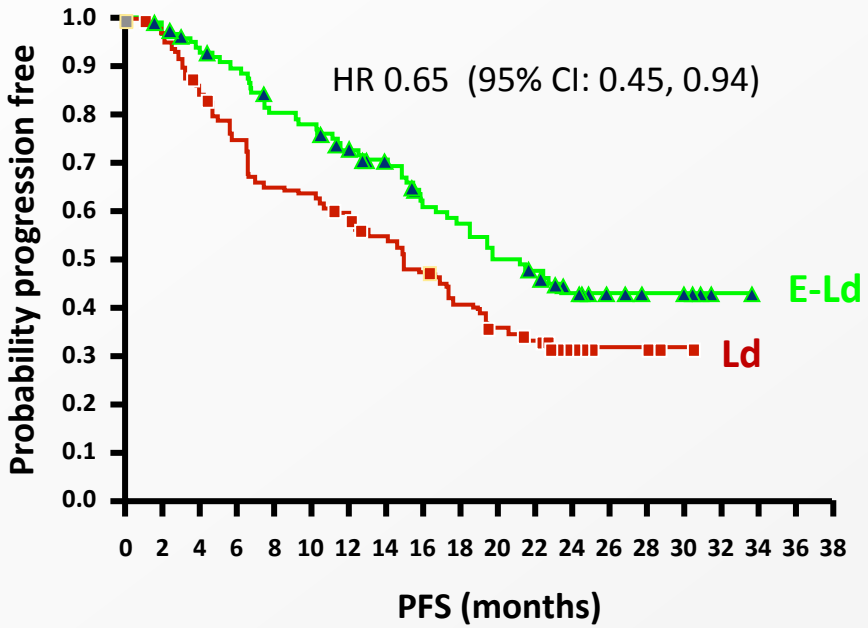
[a]Central next-generation sequencing. High risk patients had any of t(4;14), t(14;16), del17p. Standard risk had an absence of high risk abnormalities.

Usmani SZ, et al. Presented at ASH 2016 (Abstract 1151), oral presentation.

ELOQUENT-2: EloRd vs Rd

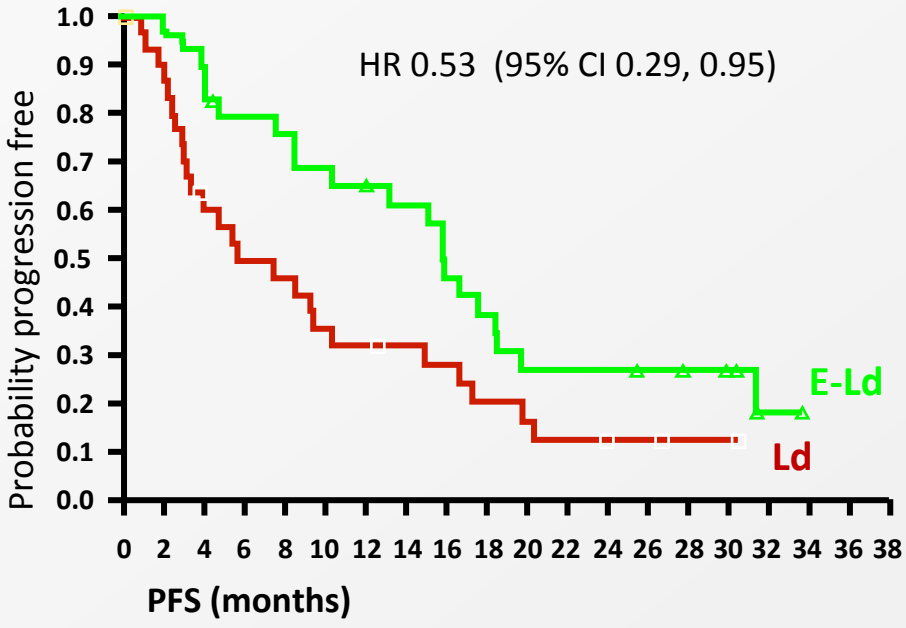
PFS according to del(17p) and t(4;14)

del(17p)+



E-Ld: median (95% CI): 21.19 (16.62, NE)
Ld: median (95% CI): 14.92 (10.61, 18.50)

t(4;14)+

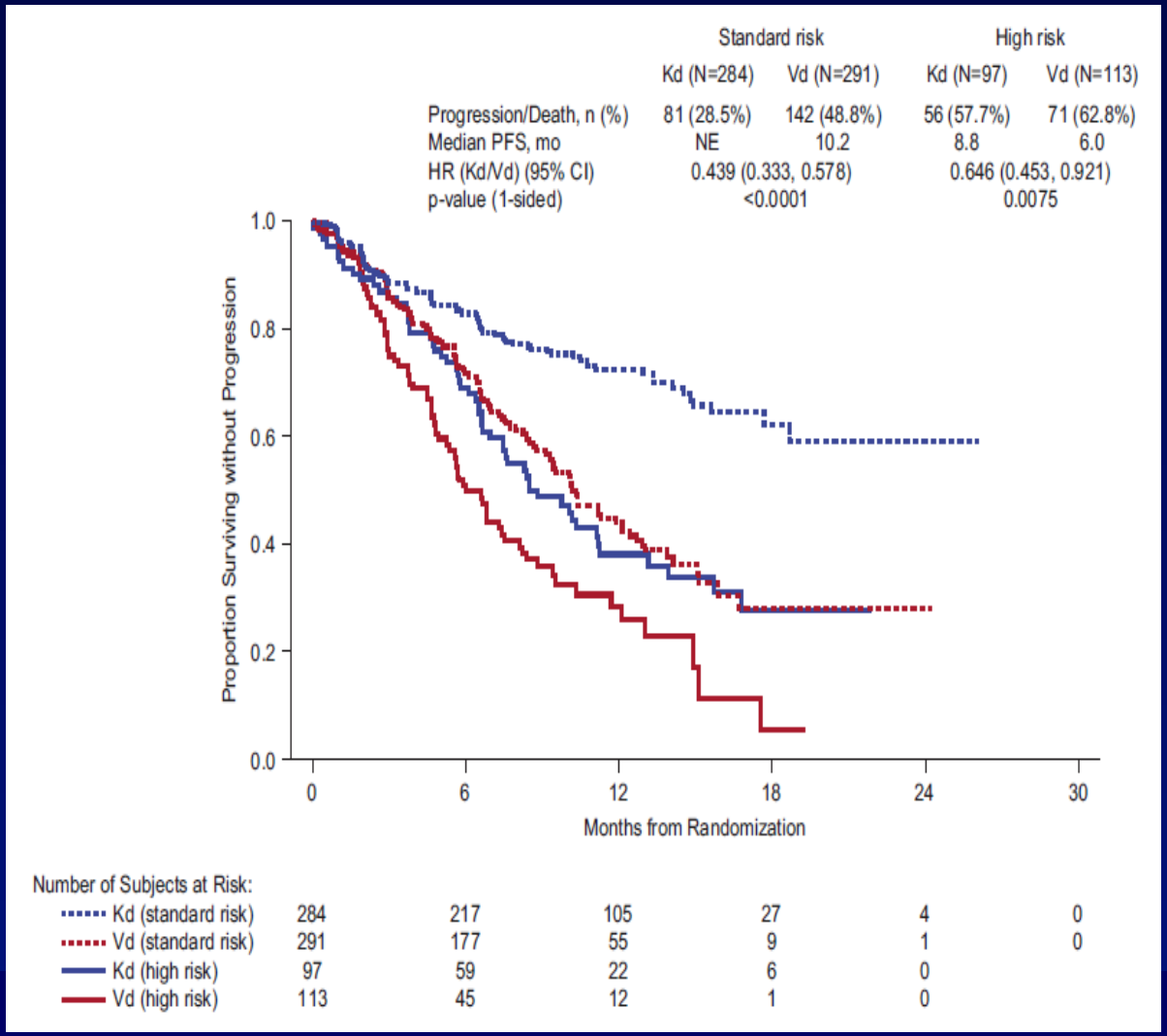


E-Ld: median (95% CI): 15.84 (8.41, 18.46)
Ld: median (95% CI): 5.55 (3.09, 10.25)

Elo-Rd del(17p) negativity: median (95% CI): 18.46 (15.84, 22.77)

Dimopoulos M et al, ASH 2015
Lonial S et al, NEJM 2015

Kd vs Vd: PFS by Cytogenetic Risk Status at Baseline



High risk

	Kd (n=97)	Vd (n=113)
PFS, median months (95% CI)	8.8 (6.9–11.3)	6.0 (4.9–8.1)
HR (95% CI)	0.646 (0.453–0.921)	
P-value	0.0075	

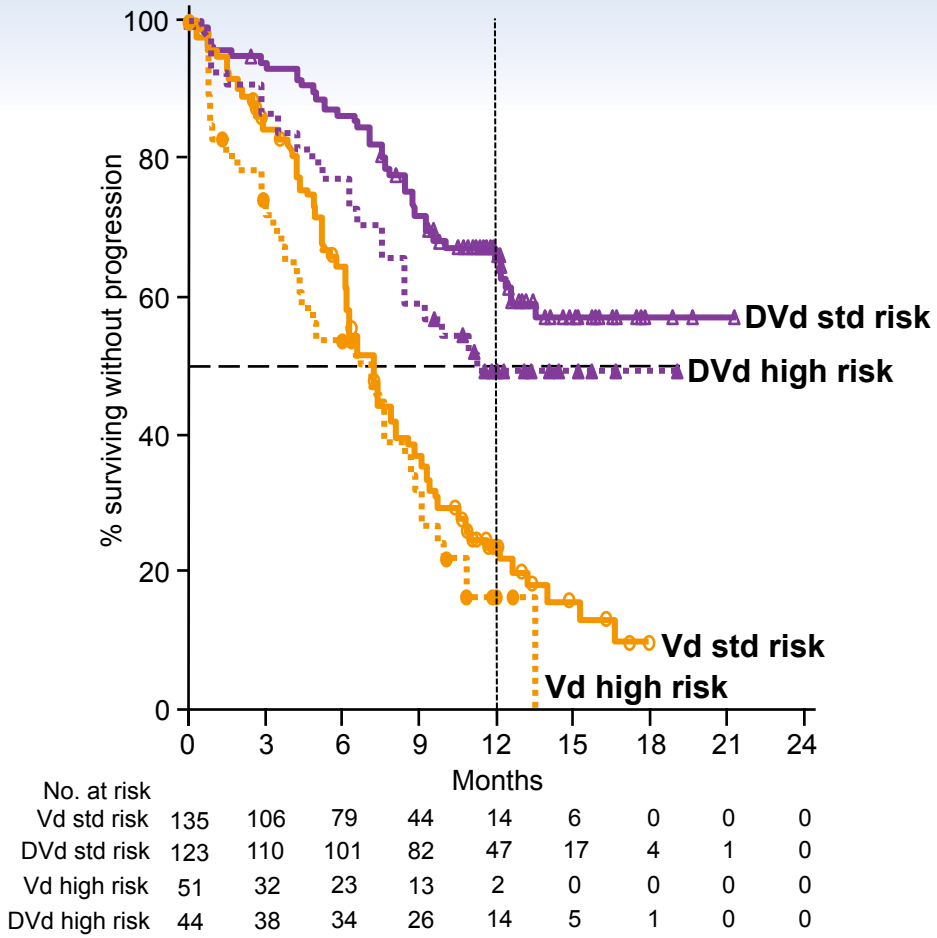
Standard risk

	Kd (n=284)	Vd (n=291)
PFS, median months (95% CI)	NE (18.7–NE)	10.2 (9.3–12.2)
HR (95% CI)	0.439 (0.333–0.578)	
P-value	<0.0001	

NE, not estimable

Chng W-J, et al. Leukemia 2017

CASTOR: PFS: Cytogenetic Risk in All Evaluable Patients[a]



High risk[b]	DVd n = 44	Vd n = 51
Median PFS, mo	**11.2**	**7.2**
HR (95% CI)	0.49 (0.27-0.89)	
P value	0.0167	
	n = 44	n = 47
ORR, %	**82**	**62**
P value	0.039	

Standard risk	DVd n = 123	Vd n = 135
Median PFS, mo	**NR**	**7.0**
HR (95% CI)	0.29 (0.20-0.43)	
P value	<0.0001	
	n = 118	n = 131
ORR, %	**85**	**64**
P value	0.0003	

- DVd improves outcomes regardless of cytogenetic risk

NR, not reached.

[a]ITT/Biomarker risk–evaluable analysis set.

[b]Central next-generation sequencing. High-risk patients had any of t(4;14), t(14;16), or del17p. Standard-risk patients had an absence of high-risk abnormalities.

Mateos M, et al. Presented at ASH 2016 (Abstract 1150), oral presentation

Sub-groups analysis of PFS for Novel Combos

	POLLUX DRd	CASTOR DVd	ASPIRE KRd	ENDEAVOR Kd	ELOQUENT-2 ERd	TOURMALINE-MM1 IxaRd
HR overall population	**0.37**	**0.39**	**0.69**	0.53	0.73	0.74
Higher Age	**HR 0.11** (>75 yr)	**HR 0.35** (≥65 yr)	HR 0.87 (>65 yr)	**HR 0.38** (≥75 yr)	**HR 0.65** (≥65 yr)	HR 0.87 (>75 yr)
HR cyto	**HR 0.44**	**HR 0.49**	**HR 0.70**	**HR 0.65**	**HR 0.65**	**HR 0.54**
pos vs neg	@18 mos: 66% vs 85%	Med PFS 11.2 mos vs NR	Med PFS 23.1 vs 29.6 mos	Med PFS NR vs 6.0 mos	(del17p) PFS 21.2 vs 18.4	Med PFS 21 .4 vs 20.6 mos
Moderate RI	UK	**HR 0.55** (CrCl<60)	UK (93% crCl>50)	**HR 0.60** (crCl<50)	**HR 0.56** (CrCl<60)	UK
Refractory population	HR 0.47	HR 0.42	-	-	0.56	0.71
IMiDs refractory	-	HR 0.50 vs 0.32	-	HR 0.80 vs 0.44	-	-
Bort refractory	HR 0.50 vs 0.27	-	HR 0.79 vs 0.69	-	UK	-

1. Dimopoulos M, et al. NEJM 2016. 2. Palumbo A et al, NEJM 2016. 3. Stewart AK, et al. N Engl J Med. 2015;372:142-152. 4. Dimopoulos MA, et al. Lancet Oncol. 2016;17:27-38. 5. Lonial S, et al. N Engl J Med. 2015;373:621-631. 6. Moreau P, et al. N Engl J Med. 2016;374:1621-1634.

Novel combos

	POLLUX DRd vs Rd	CASTOR DVd vs Vd	ASPIRE KRd vs Rd	ENDEAVOR Kd vs Vd	ELOQUENT-2 ERd vs Rd	TOURMALINE-MM1 IRd vs Rd
N° Median lines	1 (1-11) 82% 1-2	2	2	2	2	59% 1-2
Prior Len (%)	18	71	20	38	5	12
Prior Bort (%)	86 (PI)	67	66	54	68	69
Refractory pop. (%)	28	30	UK	UK	35	12 (7% primary)
Bort-refractory (%)	20	-	15	-	22	NA
Len-refractory	-	30		24	-	-
HR cyto (%)	9	16 (del 17p) 8 (t 4;14)	12	21	31	21

1. Dimopoulos M, et al. NEJM 2016. 2. Palumbo A et al, NEJM 2016. 3. Stewart AK, et al. N Engl J Med. 2015;372:142-152. 4. Dimopoulos MA, et al. Lancet Oncol. 2016;17:27-38. 5. Lonial S, et al. N Engl J Med. 2015;373:621-631. 6. Moreau P, et al. N Engl J Med. 2016;374:1621-1634..

Daratumumab single agent
Update Regolatorio

✓ Nov 2015: FDA Approval

*"Darzalex is indicated for the treatment of patients with multiple myeloma who have received **at least three prior lines of therapy including a proteasome inhibitor (PI) and an immunomodulatory agent or who are double-refractory** to a PI and an immunomodulatory agent."*

http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm472875.htm

✓ Apr 2016: EMA Approval

*"Darzalex as **monotherapy** is indicated for the treatment of adult patients with **relapsed and refractory** multiple myeloma, whose **prior therapy included a proteasome inhibitor and an immunomodulatory** agent and who have demonstrated **disease progression on the last therapy**."*

DARATUMUMAB SINGLE AGENT

Daratumumab as a single agent[1,2]

Approved by FDA and EMA in relapsed/ refractory multiple myeloma

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]

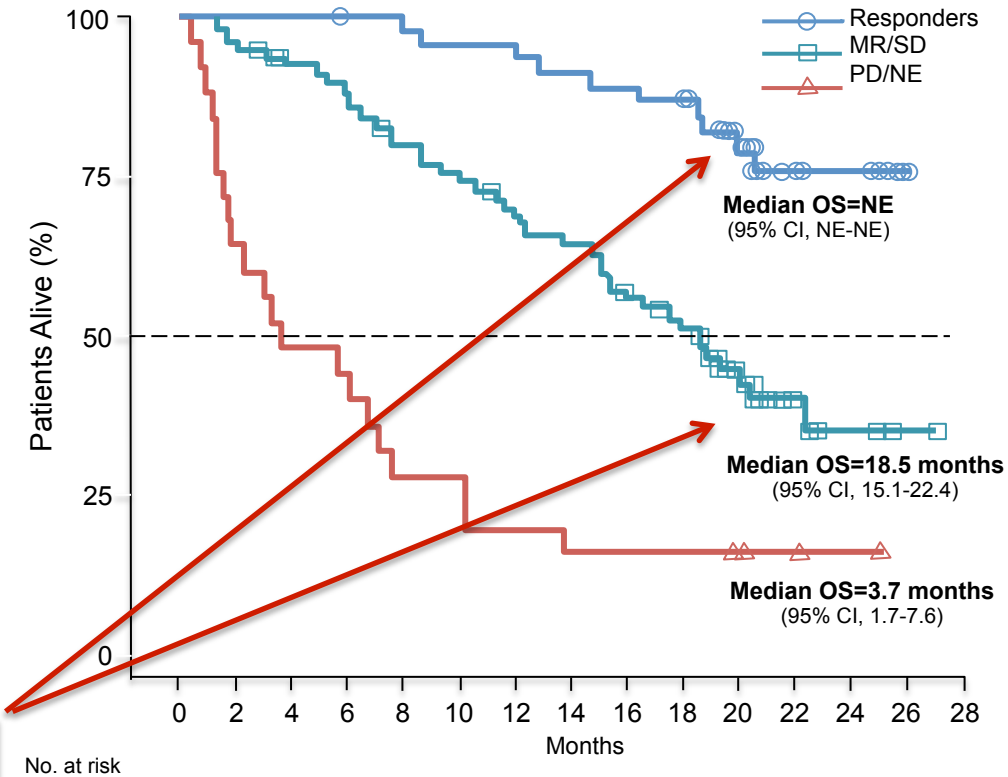
Combined overall response rate (ORR): 31%[3]

Median PFS of 4.0 months

Median overall survival (OS) of 20.1 months[3]

2-year OS was ~75% in responders

Median OS was 18.5 months in MR/ SD patients



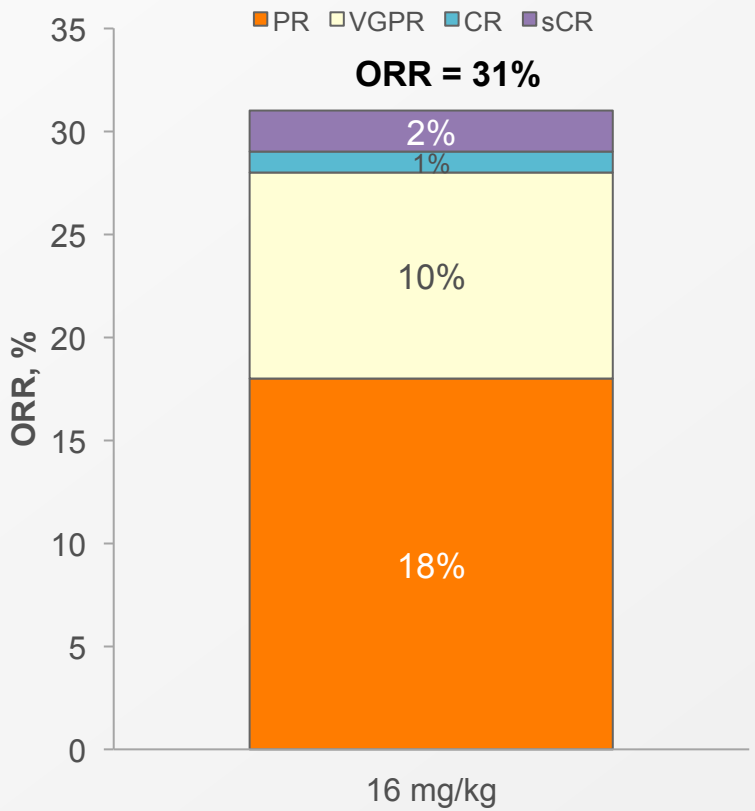
MR, minimal response; SD, stable disease; PD, progressive disease; OS, overall survival; CI, confidence interval; NE, not evaluable.

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(1):37-44.

Efficacy 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

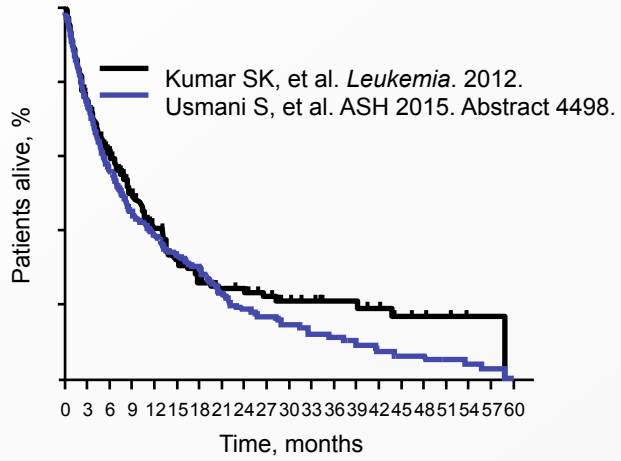
CBR 83%

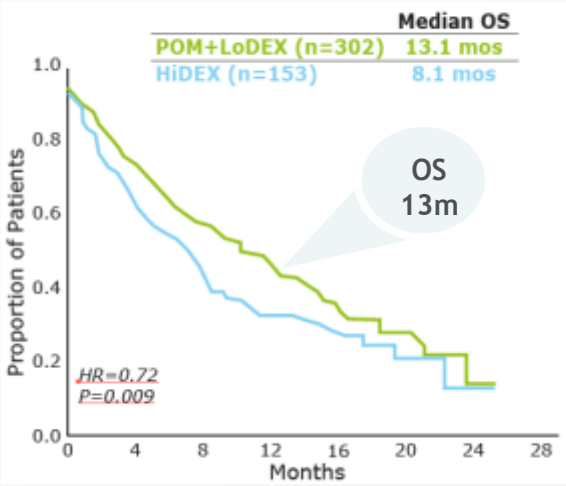


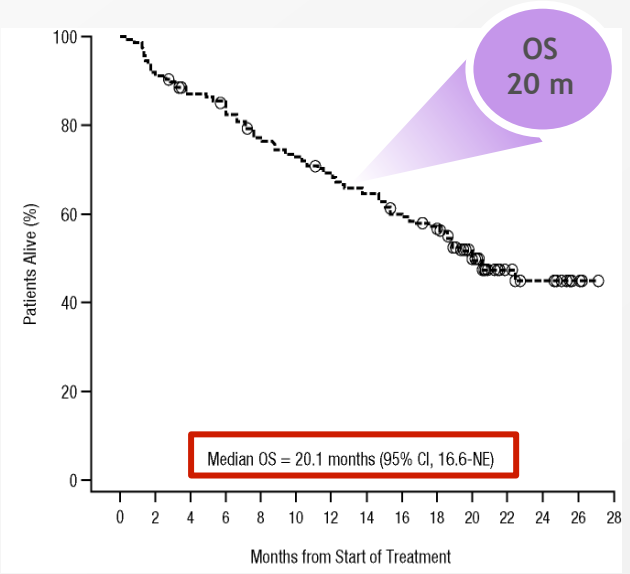
- **ORR = 31%**
- **CBR = 83% → OS benefit observed also in SD/MR pts**
- ORR was consistent in subgroups including age, number of prior lines of therapy, refractory status, or renal function

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

The Breakthrough (BT) population outcome







1. Kumar SK, et al. Leukemia. 2012;26(1):149-157.
2. Usmani S, et al. Presented at: 57th American Society of Hematology (ASH) Annual Meeting & Exposition; December 5-8, 2015; Orlando, FL. Abstract 4498.

mOS 5-9 months in patients relapsed or refractory MM after ≥3 prior lines of therapy, including IMID and PI

Pomalidomide: mOS 13,1months in patients relapsed or refractory MM after ≥2 prior lines of therapy, including IMID and PI

Daratumumab: mOS of 20 months in patients with relapsed or refractory, double refractory or relapsed after ≥3 L, including pomalidomide and carfilzomib

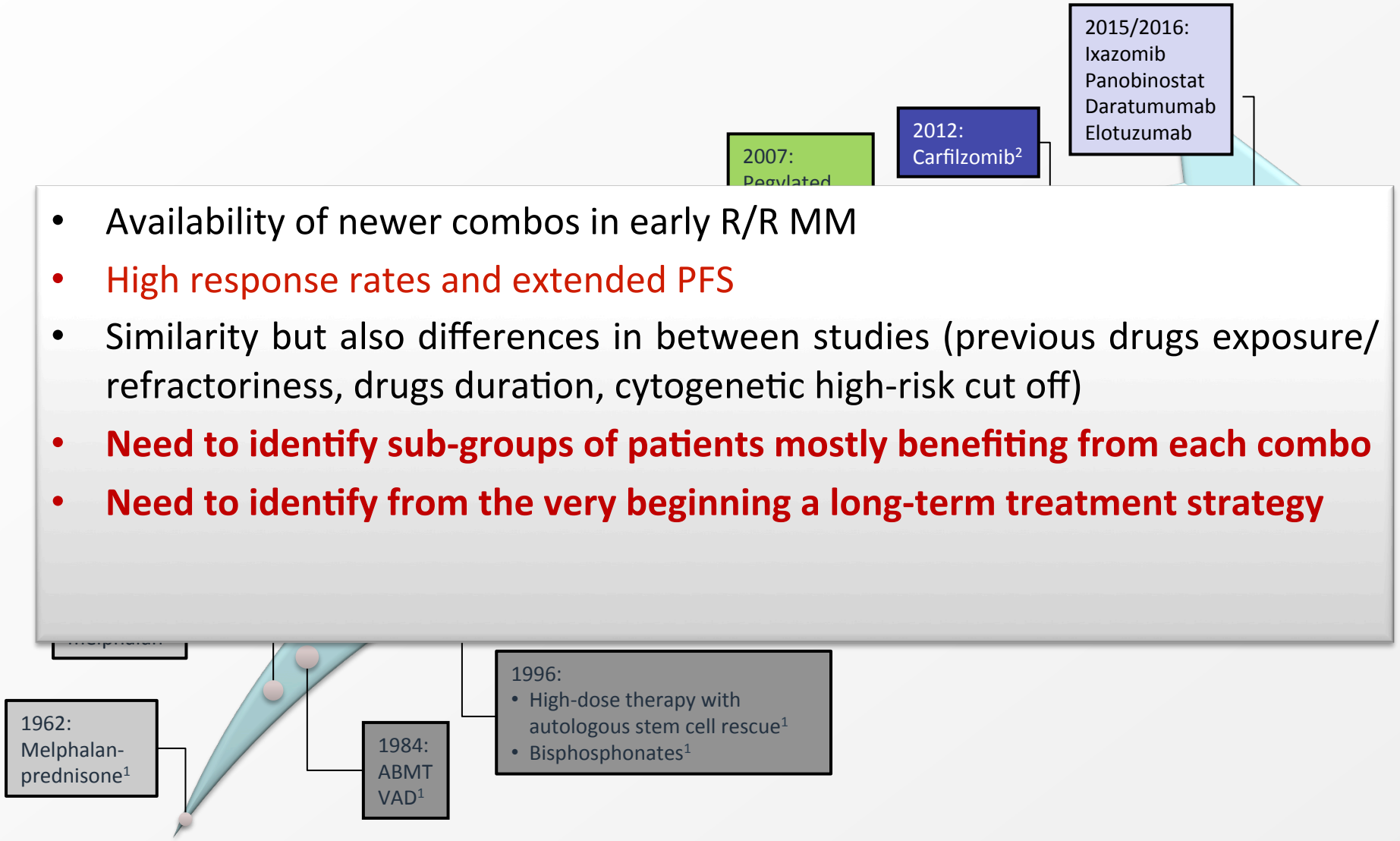
mAbs: clinical trial endponits

- New mechanism of action
- Need for new endpoints?

	Dara mono Overall	Dara mono ≥PR	Dara mono SD/MR	PomDex Overall
Median PFS	4.0	15 m (extimated)	3.2 m	4.0 m
Median OS	19.9	NR	17.5 m	13.1 m

	Elo-Rd	Rd
Median PFS	19.4 m	14.9 m
Median TTNT	33.0 m	21.0 m

Conclusions and future directions



- Availability of newer combos in early R/R MM
- High response rates and extended PFS
- Similarity but also differences in between studies (previous drugs exposure/ refractoriness, drugs duration, cytogenetic high-risk cut off)
- **Need to identify sub-groups of patients mostly benefiting from each combo**
- **Need to identify from the very beginning a long-term treatment strategy**

ABMT=autologous bone marrow transplant; VAD=vincristine/doxorubicin/dexamethasone.

1. Latif T et al. *Exp Hematol Oncol*. 2012;1:27. 2. Kyprolis [prescribing information]. Onyx Pharmaceuticals, Inc; South San Francisco, CA.
3. Pomalyst [prescribing information]. Celgene Corporation; Summit, NJ.