Relapsed/Refractory Multiple Myeloma: Things we talk about in the MDT And things we hope we can talk about soon

Dr Jaimal Kothari
Consultant Haematologist
Oxford University Hospitals

@DrJamKothari

Topics to Cover Today

1. Optimal therapy at first relapse
2. Who should get a second transplant ?
3. The role of clarithromycin as an adjunct to Lenalidomide/IMID based therapy (after ASH 2019)
4. Belantamab Mafadotin
5. Venetoclax

1st Relapse

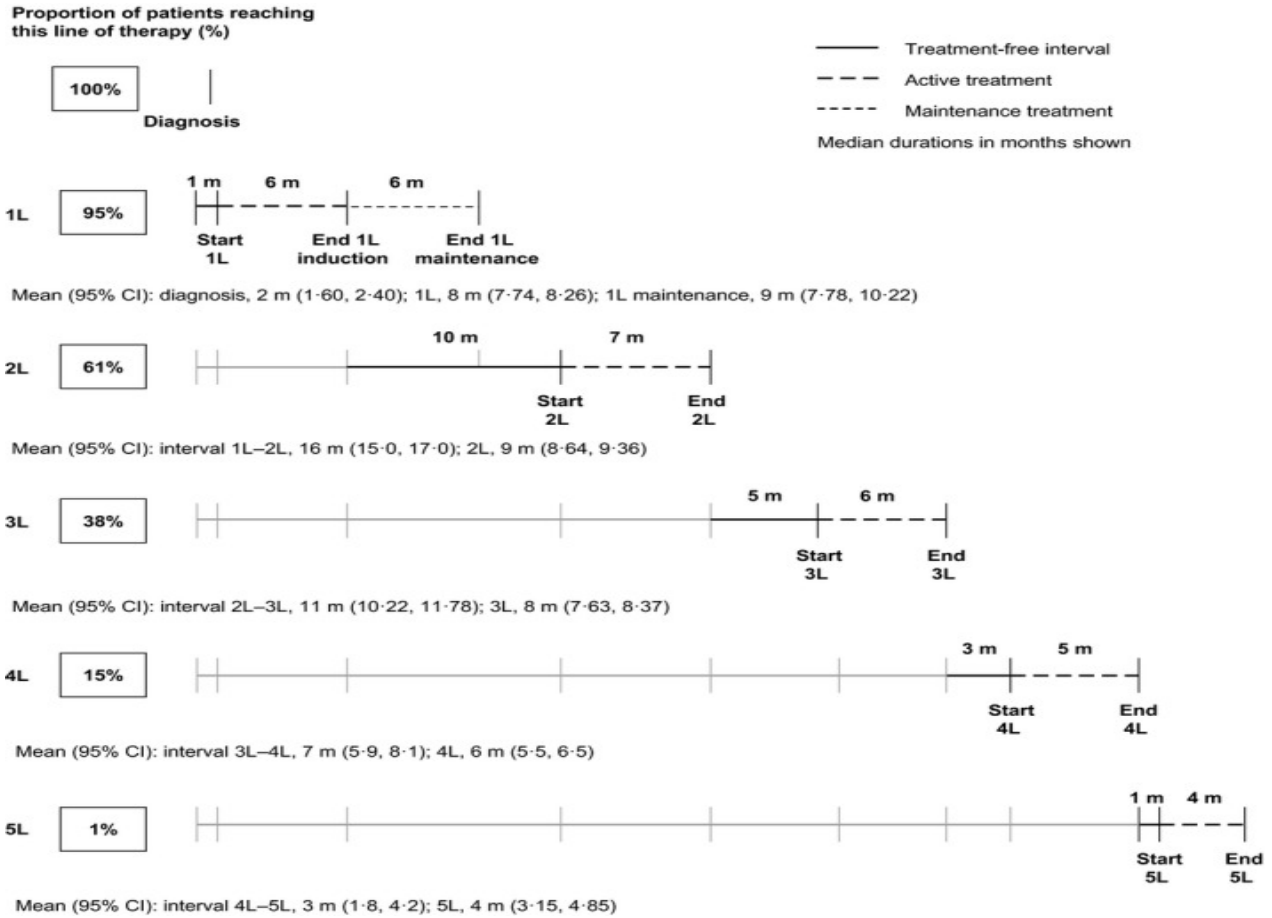
OPTIONS:

- Len/Dex (RD)
- Daratumumab, Bortezomib + Dexamethasone (DVD)
- Carfilzomib + Dexamethasone (for Velcade naive) (KD)

So, why shouldn't EVERYBODY get DVD ?

Should I save some of my better therapies for later ?

Real life chart review of 5000 patients across 7 European Countries



Yong et al, Br J Haematol. 2016 Oct; 175(2): 252–264.

Things to Consider….

- If you use Len/Dex at 2nd line, can't use it as a triplet in 3rd line (IRD), which has better PFS, better in high risk patients than RD (PFS)
- If patient is Velcade refractory , don't expect great results from DVD – (But is it still the best option ??)
- KD may be more of an option for some patients getting RD as first line therapy. BUT aren't triplets ALWAYS better than doublets ?!
- How does one fit in a second transplant with the continuous 2nd line therapies that you treat until progression

How

Is

- RD ,

Better

- RD,

OR, in 3 years

Is

- DVD
- OR k later)

OR

- DVD until progression

The Answer is *NO-ONE* knows

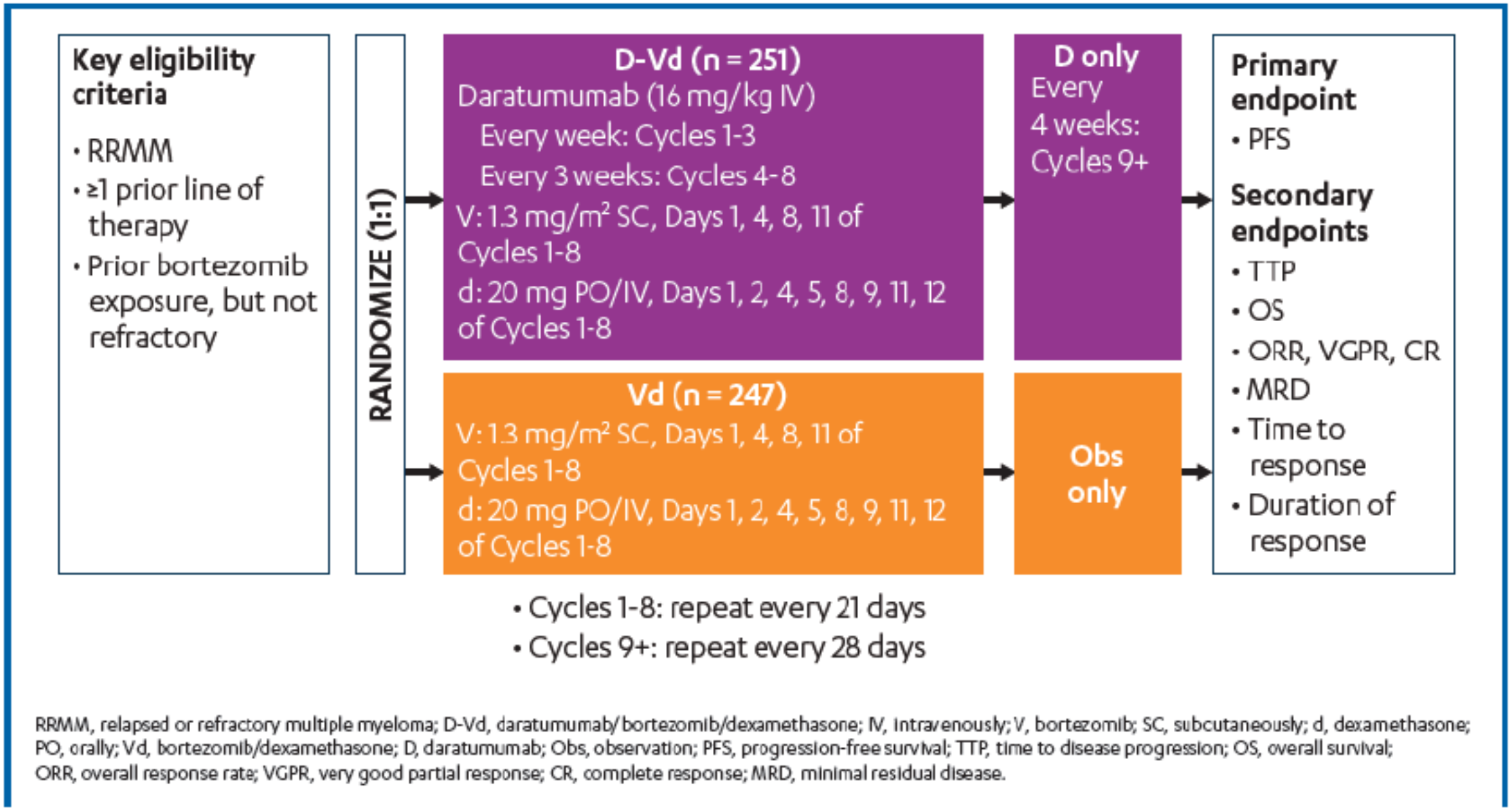
Very difficult to extrapolate survival data in this type of setting

Endless Cross-Trial Comparisons often confuse the matter

Key points to consider in the R/R Setting :

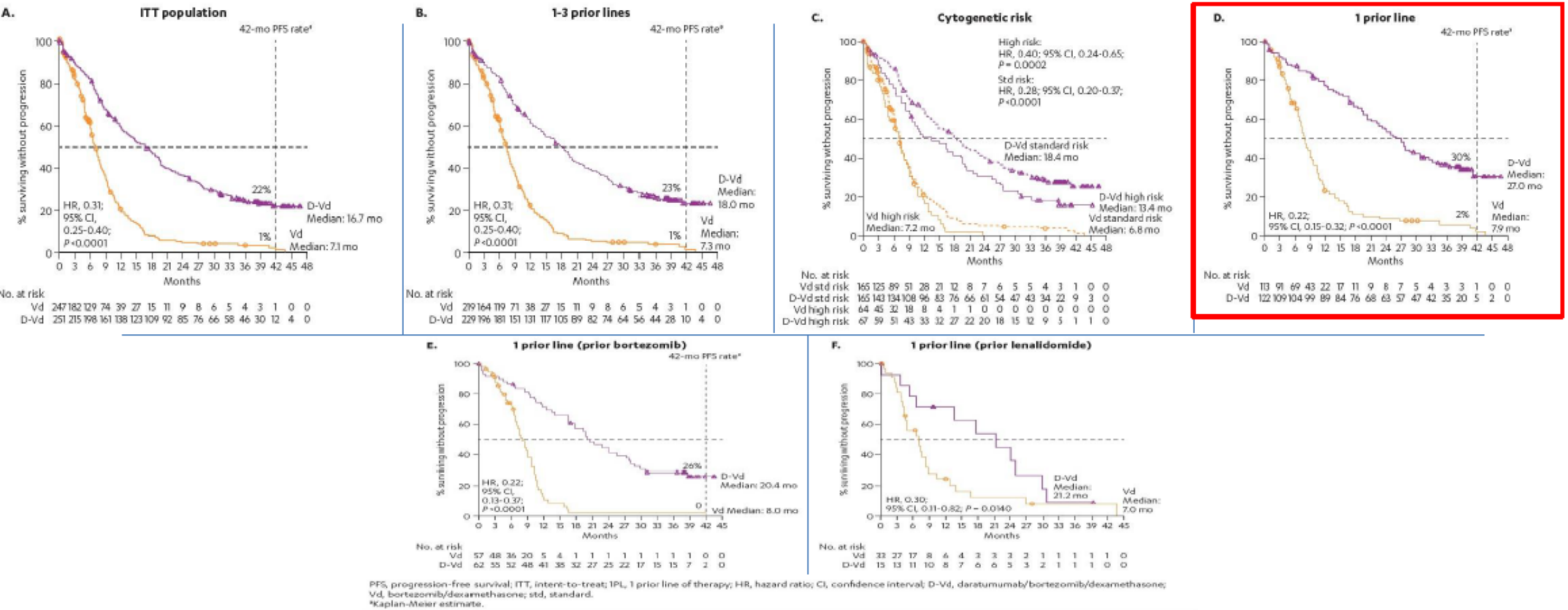
- **Standard/low risk patients continue to do well, and will respond to many options**
- **Aiming for MRD negativity appears to still have value in the R/R setting**
- **High-risk patients often go from one therapy to the next quickly**
- **-Have to consider the burden of endless continuous therapies, until death**
- **Need to clearly understand what the NHS/CDF pathway allows, and have good relationships with your pharmacists**

CASTOR Study Design



RRMM, relapsed or refractory multiple myeloma; D-Vd, daratumumab/bortezomib/dexamethasone; IV, intravenously; V, bortezomib; SC, subcutaneously; d, dexamethasone; PO, orally; Vd, bortezomib/dexamethasone; D, daratumumab; Obs, observation; PFS, progression-free survival; TTP, time to disease progression; OS, overall survival; ORR, overall response rate; VGPR, very good partial response; CR, complete response; MRD, minimal residual disease.

Daratumumab-Vd Maintained Significant PFS and ORR Benefit



PFS, progression-free survival; ITT, intent-to-treat; 1PL, 1 prior line of therapy; HR, hazard ratio; CI, confidence interval; D-Vd, daratumumab/bortezomib/dexamethasone; Vd, bortezomib/dexamethasone; std, standard.
*Kaplan-Meier estimate.

Table 2. Response and MRD-negative Rates Overall and in Patients With 1PL

Response,[a] n (%)	ITT/Response-evaluable			1PL		
	D-Vd (n = 240)	Vd (n = 234)	*P* value	D-Vd (n = 119)	Vd (n = 109)	*P* value
ORR	203 (85)	148 (63)	<0.0001	109 (92)	81 (74)	0.0007
≥CR	72 (30)	23 (10)	<0.0001	51 (43)	16 (15)	<0.0001
sCR	23 (10)	6 (3)		17 (14)	5 (5)	
CR	49 (20)	17 (7)		34 (29)	11 (10)	
≥VGPR	151 (63)	68 (29)	<0.0001	91 (77)	46 (42)	<0.0001
VGPR	79 (33)	45 (19)		40 (34)	30 (28)	
PR	52 (22)	80 (34)		18 (15)	35 (32)	
MRD negativity (10^{-5})[b]	(n = 251)	(n = 247)		(n = 122)	(n = 113)	
n (%)	35 (14)	4 (2)	<0.000001	24 (20)	3 (3)	0.000025
Sustained MRD negativity (10^{-5}), n (%)[c]	8 (3)	0		7 (6)	0	

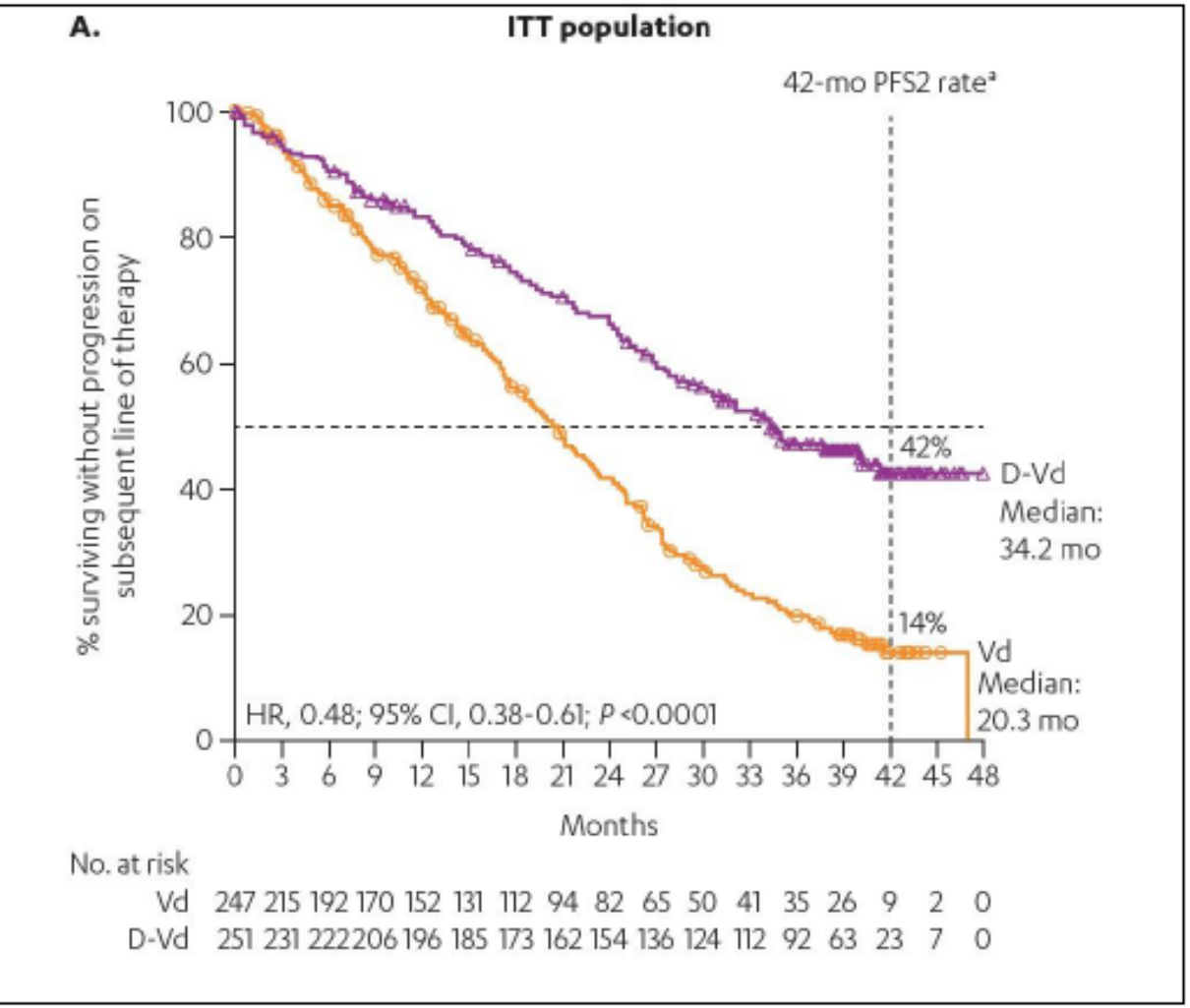
MRD, minimal residual disease; 1PL, 1 prior line of therapy; ITT, intent-to-treat; D-Vd, daratumumab/bortezomib/dexamethasone; Vd, bortezomib/dexamethasone; ORR, overall response rate; CR, complete response; sCR, stringent complete response; VGPR, very good partial response; PR, partial response; MRD, minimal residual disease.

[a]Response-evaluable population.

[b]ITT population.

[c]Sustained MRD negativity for ≥12 months.

PFS 2


A.
ITT population
42-mo PFS2 rate[a]
% surviving without progression on subsequent line of therapy
100
80
60
40
20
0
42%
D-Vd
Median:
34.2 mo
14%
Vd
Median:
20.3 mo
HR, 0.48; 95% CI, 0.38-0.61; P <0.0001
0 3 6 9 12 15 18 21 24 27 30 33 36 39 42 45 48
Months
No. at risk
Vd 247 215 192 170 152 131 112 94 82 65 50 41 35 26 9 2 0
D-Vd 251 231 222 206 196 185 173 162 154 136 124 112 92 63 23 7 0

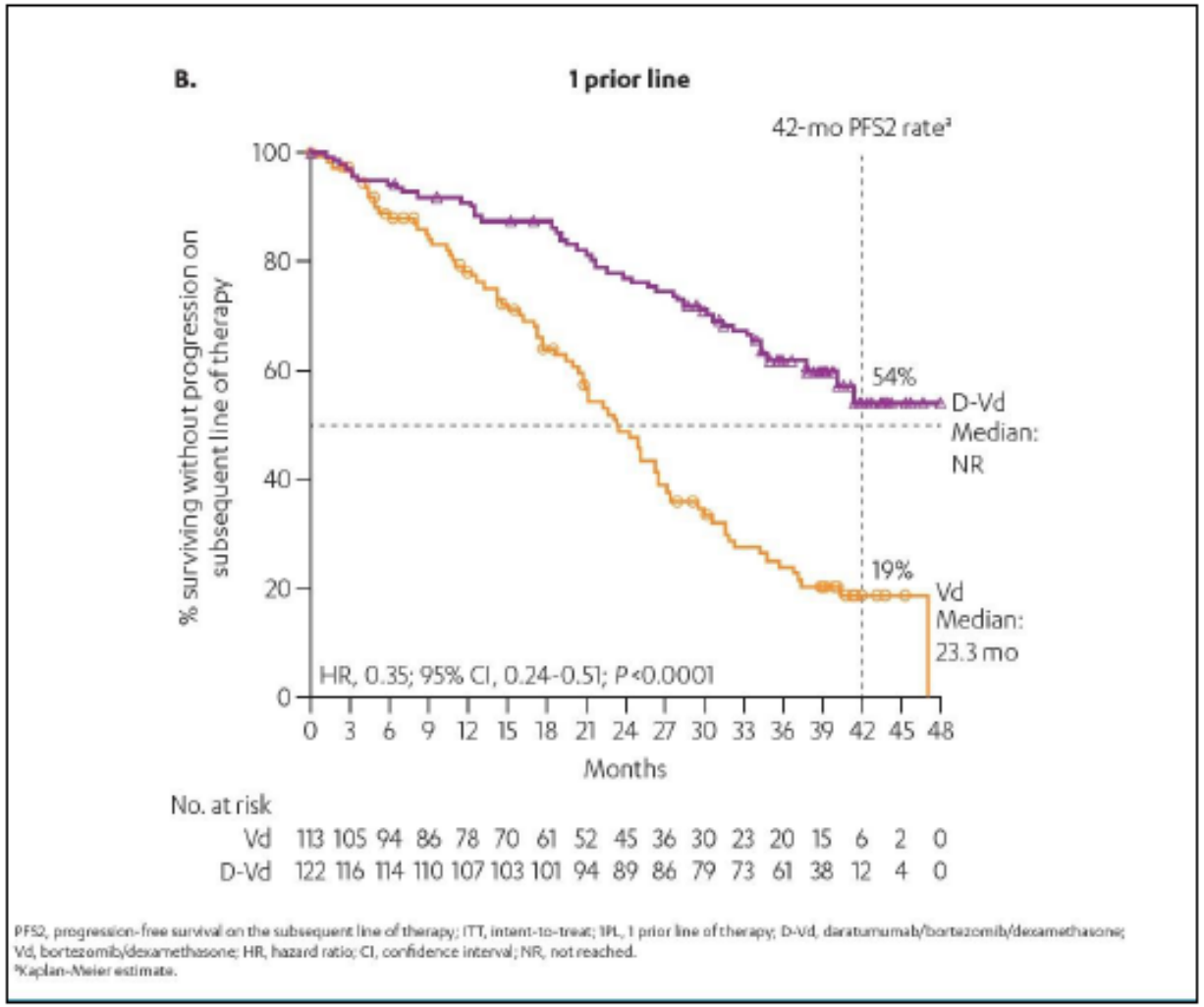

B.
1 prior line
42-mo PFS2 rate[a]
% surviving without progression on subsequent line of therapy
100
80
60
40
20
0
54%
D-Vd
Median:
NR
19%
Vd
Median:
23.3 mo
HR, 0.35; 95% CI, 0.24-0.51; P <0.0001
0 3 6 9 12 15 18 21 24 27 30 33 36 39 42 45 48
Months
No. at risk
Vd 113 105 94 86 78 70 61 52 45 36 30 23 20 15 6 2 0
D-Vd 122 116 114 110 107 103 101 94 89 86 79 73 61 38 12 4 0
PFS2, progression-free survival on the subsequent line of therapy; ITT, intent-to-treat; 1PL, 1 prior line of therapy; D-Vd, daratumumab/bortezomib/dexamethasone; Vd, bortezomib/dexamethasone; HR, hazard ratio; CI, confidence interval; NR, not reached.
[a]Kaplan-Meier estimate.

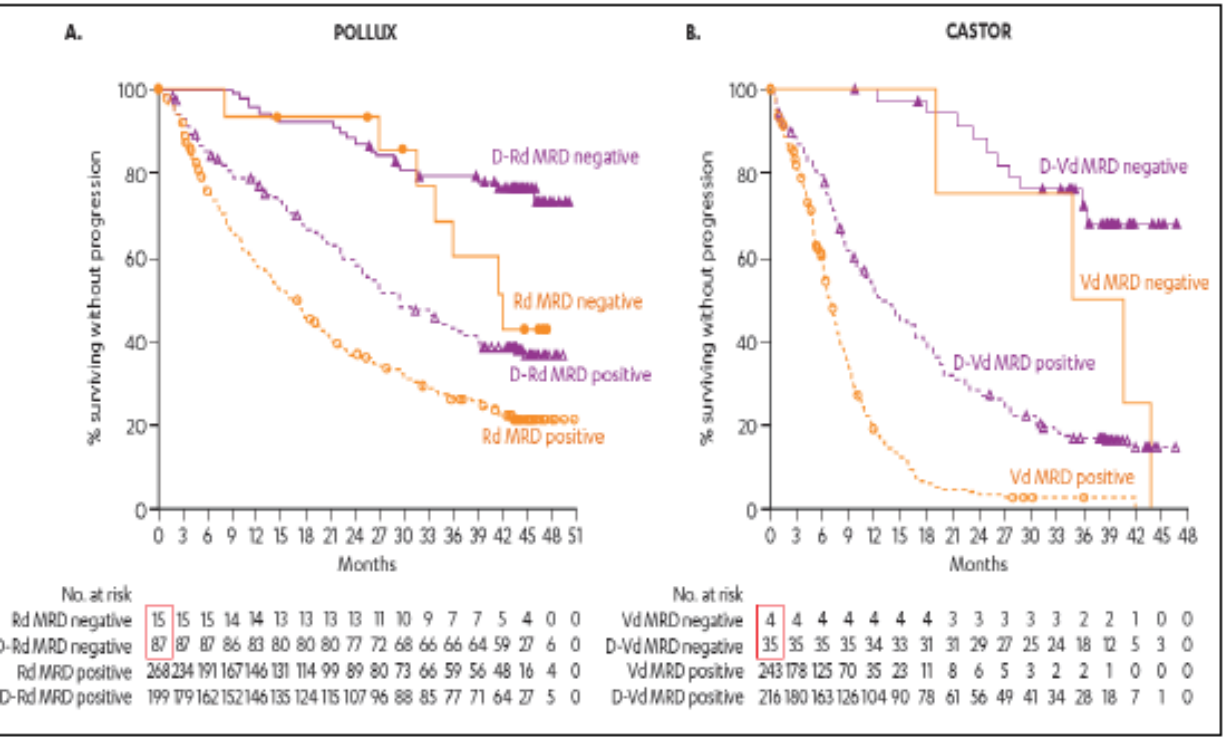
Table 3. Most Common (≥20% of Patients) and Grade 3/4 (≥5% of Patients) TEAEs

TEAE, n (%)	All grades		Grade 3/4	
	D-Vd (n = 243)	Vd (n = 237)	D-Vd (n = 243)	Vd (n = 237)
Hematologic				
Thrombocytopenia	145 (60)	105 (44)	112 (46)	78 (33)
Anemia	71 (29)	75 (32)	38 (16)	38 (16)
Neutropenia	48 (20)	23 (10)	33 (14)	11 (5)
Lymphopenia	32 (13)	9 (4)	24 (10)	6 (3)
Nonhematologic				
Peripheral sensory neuropathy	121 (50)	90 (38)	11 (5)	16 (7)
Upper respiratory tract infection	85 (35)	43 (18)	6 (3)	1 (0.4)
Diarrhea	86 (35)	53 (22)	9 (4)	3 (1)
Cough	71 (29)	30 (13)	0	0
Constipation	54 (22)	38 (16)	0	2 (0.8)
Fatigue	55 (23)	58 (25)	12 (5)	8 (3)
Back pain	53 (22)	24 (10)	6 (3)	3 (1)
Pneumonia	38 (16)	31 (13)	25 (10)	24 (10)
Hypertension	24 (10)	8 (3)	16 (7)	2 (0.8)

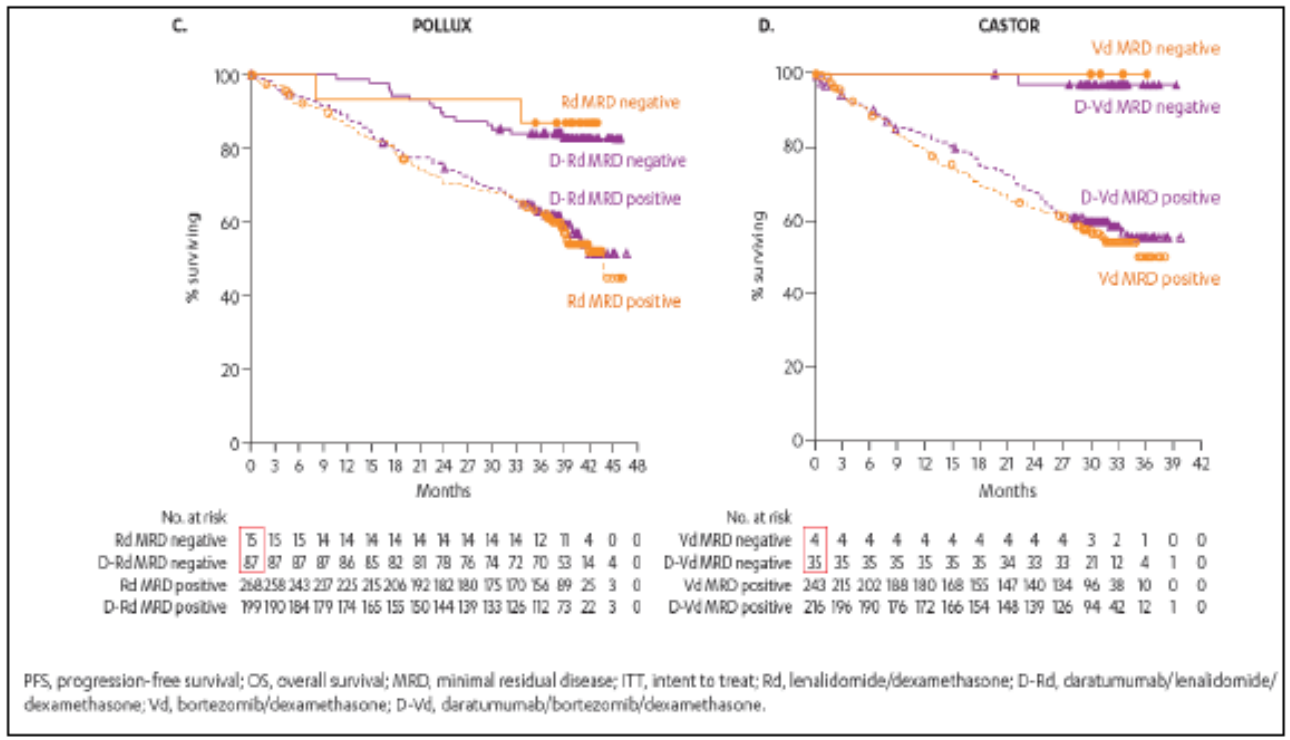
TEAE, treatment-emergent adverse event; D-Vd, daratumumab/bortezomib/dexamethasone; Vd, bortezomib/dexamethasone.

MRD Negativity Leads to Prolonged PFS and OS

PFS



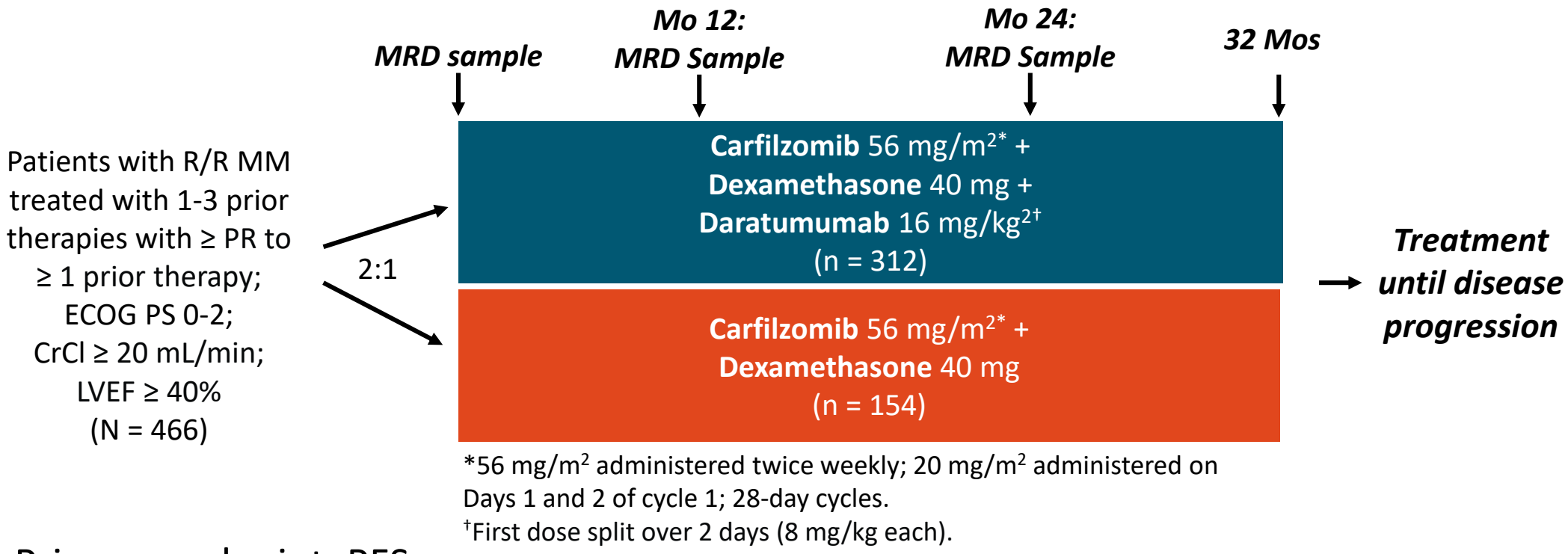
OS



PFS, progression-free survival; OS, overall survival; MRD, minimal residual disease; ITT, intent to treat; Rd, lenalidomide/dexamethasone; D-Rd, daratumumab/lenalidomide/dexamethasone; Vd, bortezomib/dexamethasone; D-Vd, daratumumab/bortezomib/dexamethasone.

CANDOR: Study Design

- Multicenter, randomized phase III study



*56 mg/m^2 administered twice weekly; 20 mg/m^2 administered on Days 1 and 2 of cycle 1; 28-day cycles.
†First dose split over 2 days (8 mg/kg each).

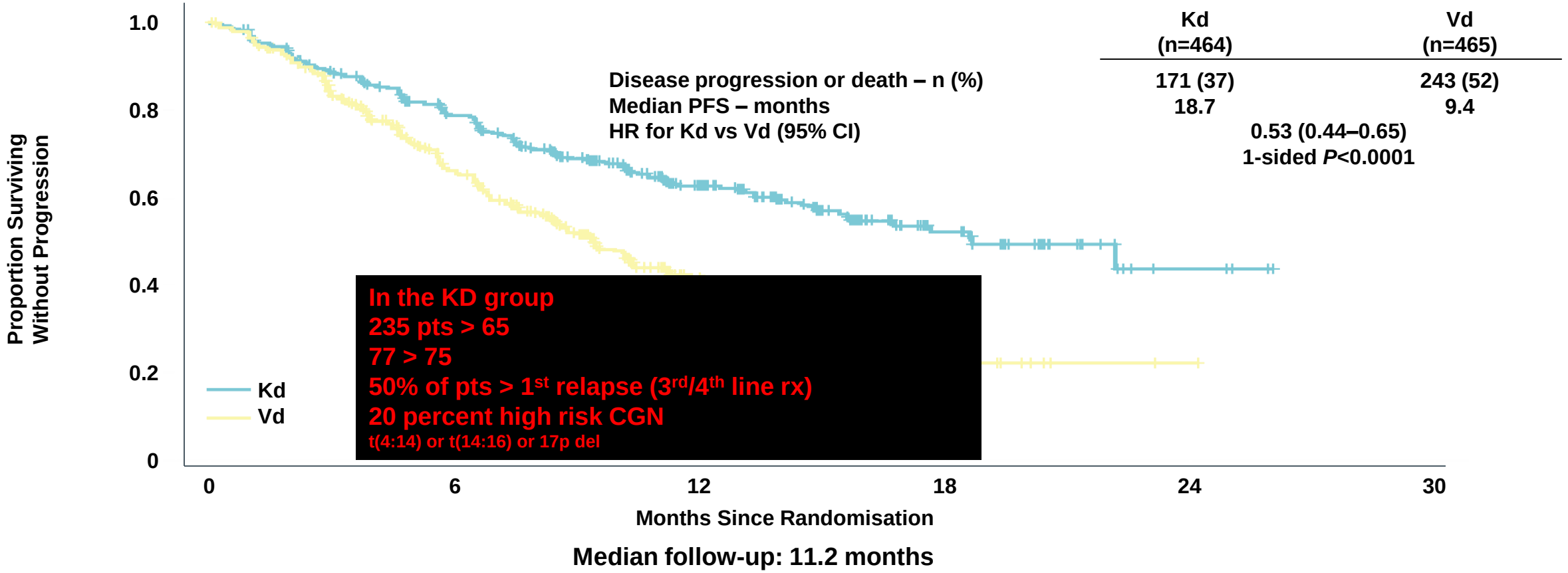
- Primary endpoint: PFS
- Key secondary endpoints: ORR, MRD, and OS

Usmani. ASH 2019. Abstr LBA6.

The ENDEAVOR TRIAL

Primary End Point: Progression-Free Survival

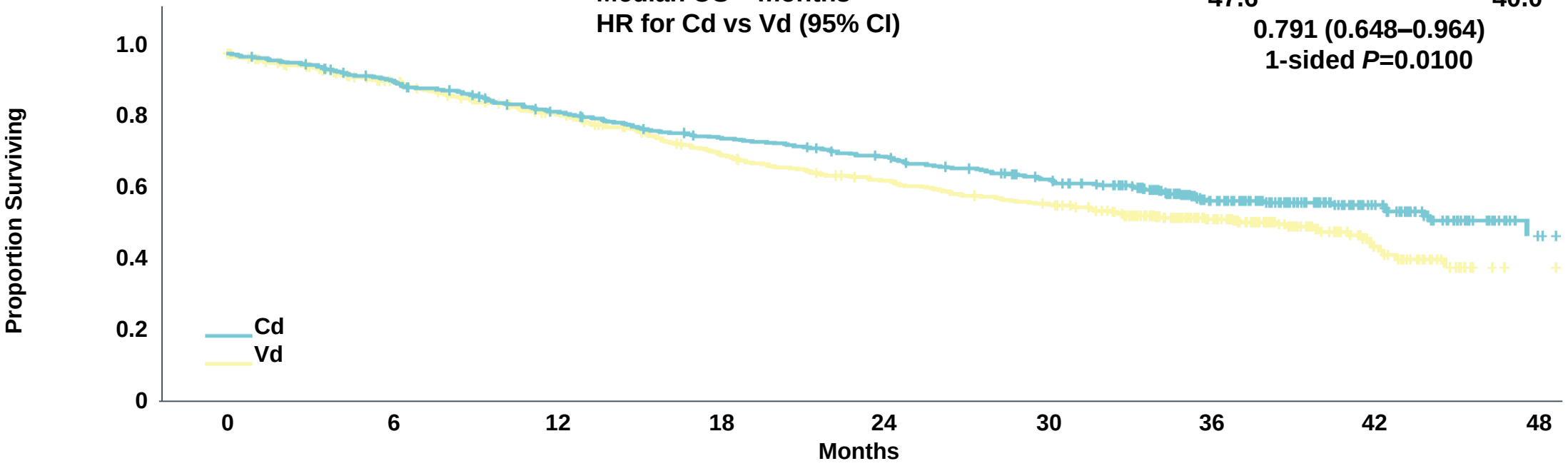
Intent-to-Treat Population (N=929)



Median follow-up: 11.2 months

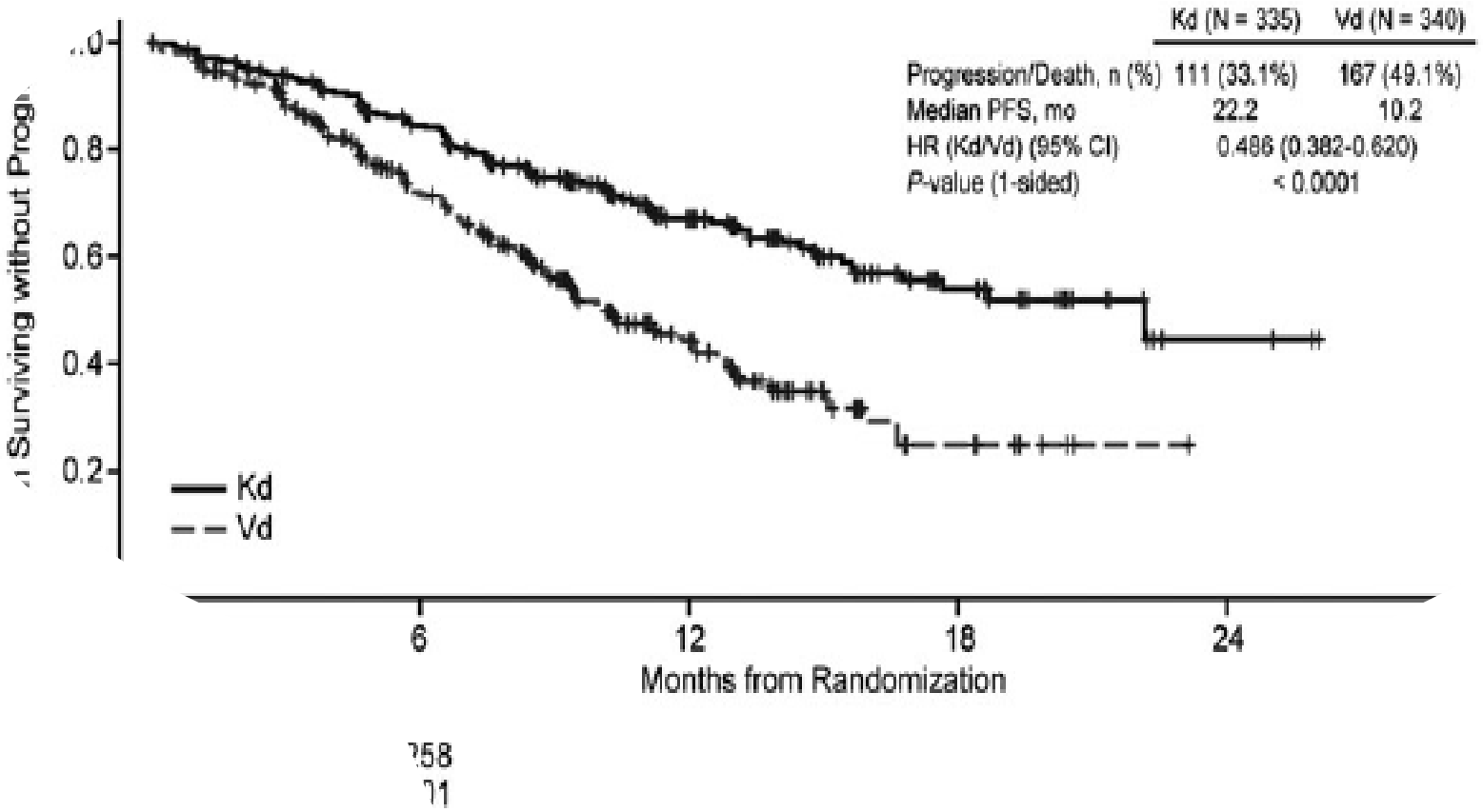
Secondary endpoint: Overall Survival

	Kd (n=464)	Vd (n=465)
Death – n (%)	189 (40.7)	209 (44.9)
Median OS – months	47.6	40.0
HR for Cd vs Vd (95% CI)	0.791 (0.648–0.964)	
	1-sided *P*=0.0100	



Number at risk:									
Cd	464	423	373	335	308	270	162	66	10
Vd	465	402	351	293	256	228	140	39	5

Patients Relapsing >12 months from previous therapy



KD PFS 22.2 months

Mateos et al, Haematological Oncology, 2018 (36)

CANDOR: Baseline Characteristics

Characteristics	KdD (n = 312)	Kd (n = 154)
Median age, yrs (range)	64 (29-84)	65 (35-84)
▪ ≤ 64, n (%)	163 (52.2)	77 (50.0)
▪ 65-74, n (%)	121 (38.8)	55 (35.7)
▪ ≥ 75, n (%)	28 (9.0)	22 (14.3)
ECOG PS, n (%)		
▪ 0/1	295 (94.6)	147 (95.5)
▪ 2	15 (4.8)	7 (4.5)
ISS stage, n (%)		
▪ I	147 (47.1)	79 (51.3)
▪ II	103 (33.0)	48 (31.2)
▪ III	61 (19.6)	27 (17.5)
Cytogenic risk category by FISH, n (%)		
▪ High*	48 (15.4)	26 (16.9)
▪ Standard†	104 (33.3)	52 (33.8)
▪ Unknown	160 (51.3)	76 (49.4)

Characteristics	KdD (n = 312)	Kd (n = 154)
Number of prior therapies, n (%)		
▪ 1	144 (46.2)	70 (45.5)
▪ ≥ 2	168 (53.8)	83 (53.9)
Prior therapies, n (%)		
▪ Bortezomib	287 (92.0)	134 (87.0)
▪ Lenalidomide	123 (39.4)	74 (48.1)
Refractory to prior bortezomib, n (%)	88 (28.2)	47 (30.5)
Refractory to prior lenalidomide, n (%)	99 (31.7)	55 (35.7)

*Comprising genetic subtypes t(4;14), t(14;16), or del(17p).
†Comprising all other subtypes.

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CANDOR: PFS

- Prolonged PFS with KdD vs Kd (median: NR vs 15.8 mos; HR: 0.63; 95% CI: 0.46-0.85; *P* =.0014)

Subgroup		HR* KdD vs Kd (95% CI)
ISS stage	▪ 1 or 2 ▪ 3	0.61 (0.43-0.85) 0.71 (0.37-1.36)
Age at baseline	▪ ≤ 64 ▪ 65-74 ▪ ≥ 75	0.57 (0.38-0.86) 0.72 (0.43-1.20) 0.97 (0.39-2.43)
Region	▪ North America ▪ Europe ▪ Asia Pacific	0.04 (0.01-0.34) 0.86 (0.60-1.23) 0.49 (0.25-0.93)
Baseline ECOG PS	▪ 0-1 ▪ 2	0.69 (0.51-0.94) 0.31 (0.08-1.19)
Baseline CrCl, mL/min	▪ ≥ 15 to < 50 ▪ ≥ 50 to < 80 ▪ ≥ 80	0.46 (0.21-1.02) 0.78 (0.45-1.33) 0.67 (0.44-1.02)

*HR < 1 favors KdD.

Subgroup		HR* KdD vs Kd (95% CI)
Cytogenic risk group	▪ High ▪ Standard ▪ Unknown	0.58 (0.30-1.12) 0.55 (0.31-0.97) 0.72 (0.47-1.11)
Number of prior therapies, n (%)	▪ 1 ▪ ≥ 2	0.70 (0.42-1.17) 0.63 (0.44-0.92)
Prior lenalidomide exposure	▪ No ▪ Yes	0.87 (0.56-1.35) 0.52 (0.34-0.80)
Refractory to lenalidomide	▪ No ▪ Yes	0.85 (0.57-1.27) 0.45 (0.28-0.74)
Prior proteasome inhibitor exposure	▪ No ▪ Yes	0.93 (0.29-3.02) 0.64 (0.47-0.88)
Refractory to bortezomib	▪ No ▪ Yes	0.59 (0.40-0.85) 0.83 (0.49-1.41)

*HR < 1 favors KdD.

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CANDOR: Response Rates

- Median time to first response was 1 mo in the KdD and Kd arms

Responses, %	KdD (n = 312)	Kd (n = 154)
ORR	84.3*	74.7*
VGPR or better	69.2	48.7
CR or better	28.5	10.4
MRD negative at 12 mos (10^{-5} threshold)	17.6	3.9
MRD-negative CR at 12 mos (10^{-5} threshold)	12.5†	1.3†
Best MRD-negative CR (10^{-5} threshold)	13.8	3.2

*P = .0040
†P < .0001

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Slide credit: clinicaloptions.com

CANDOR: Overall Safety

AEs, n (%)	KdD (n = 308)	Kd (n = 153)
Treatment-emergent AEs		
▪ All grade	306 (99.4)	147 (96.1)
▪ Grade ≥ 3	253 (82.1)	113 (73.9)
▪ Serious	173 (56.2)	70 (45.8)
▪ Led to treatment discontinuation	69 (22.4)	38 (24.8)
▪ Led to dose reduction	113 (38.6)	53 (34.6)
Treatment-emergent fatal AEs	30 (9.7)	8 (5.2)
▪ Infections	14 (4.5)	4 (2.6)
▪ Cardiac disorders	4 (1.3)	0
▪ Neoplasms	4 (1.3)	2 (1.3)
▪ General disorders and administration site disorders	3 (1.0)	1 (0.7)
▪ Respiratory, thoracic, and mediastinal disorders	2 (0.6)	1 (0.7)
▪ Injury, poisoning, and procedural complications	1 (0.3)	0
▪ Metabolism and nutrition disorders	1 (0.3)	0
▪ Nervous system disorders	1 (0.3)	0
Treatment-related fatal AEs	5 (1.6)*	0

*1 case each of pneumonia, sepsis with development of *Clostridium difficile* enterocolitis, septic shock (with pneumocystis pneumonia), acinetobacter infection, and cardio-respiratory arrest.

Usmani. ASH 2019. Abstr LBA6.

Slide credit: clinicaloptions.com

CANDOR: Common Treatment-Emergent AEs

Treatment-Emergency AE,* n (%)	KdD (n = 308)		Kd (n = 153)	
	All Grades	Grade ≥ 3	All Grades	Grade ≥ 3
Hematologic				
▪ Thrombocytopenia	115 (37.3)	75 (24.4)	45 (29.4)	25 (16.3)
▪ Anemia	101 (32.8)	51 (16.6)	48 (31.4)	22 (14.4)
▪ Neutropenia	43 (14.0)	26 (8.4)	15 (9.8)	9 (5.9)
▪ Lymphocytopenia	27 (8.84)	21 (6.8)	12 (7.8)	11 (7.2)
Nonhematologic				
▪ Diarrhea	97 (31.5)	12 (3.9)	22 (14.4)	1 (0.7)
▪ Hypertension	94 (30.5)	54 (17.5)	42 (27.5)	20 (13.1)
▪ Upper respiratory tract infection	90 (29.2)	8 (2.6)	35 (22.9)	2 (1.3)
▪ Fatigue	75 (24.4)	24 (7.8)	28 (18.3)	7 (4.6)
▪ Dyspnea	61 (19.8)	12 (3.9)	34 (22.2)	4 (2.6)
▪ Pneumonia	55 (17.9)	41 (13.3)	19 (12.4)	13 (8.5)

*AEs included for all grades occurred in ≥2 0% of patients; AEs included in grade ≥ 3 occurred in ≥ 5% of patients.

Usmani. ASH 2019. Abstr LBA6.

CANDOR: AEs of Interest

Treatment-Emergent AEs, n (%)	KdD (n = 308)		Kd (n = 153)	
	All Grades	Grade ≥ 3	All Grades	Grade ≥ 3
Acute renal failure	18 (5.8)	9 (2.9)	12 (7.8)	10 (6.5)
Cardiac failure*	23 (7.5)	12 (3.9)	16 (10.5)	13 (8.5)
Ischemic heart disease	13 (4.2)	9 (2.9)	5 (3.3)	4 (2.6)
Respiratory tract infection	225 (73.1)	89 (28.9)	84 (54.9)	24 (15.7)
Peripheral neuropathy	53 (17.2)	3 (1.0)	13 (8.5)	0
Hypertension	98 (31.8)	55 (17.9)	44 (28.8)	21 (13.7)
IRR (on same day as any carfilzomib infusion)	126 (40.9)	38 (12.3)	43 (28.1)	8 (5.2)
Daratumumab-related infusion infection	56 (18.2)	7 (2.3)	0	0
Viral infection	63 (20.5)	19 (6.2)	22 (14.4)	3 (2.0)

*Rate of cardiac failure event leading to carfilzomib discontinuation similar between arms (3.9% and 4.6%).

Usmani. ASH 2019. Abstr LBA6.

Slide credit: clinicaloptions.com

CANDOR: Investigator Conclusions

- Significant PFS benefit for patients with R/R MM treated with KdD vs Kd
  - 37% reduction in risk of progression or death
  - Benefit maintained across all prespecified clinically important subgroups
- Deeper responses observed in patients treated with KdD vs Kd
  - MRD-negative CR rate at 12 mos nearly 10-fold higher with KdD vs Kd
- Safety profile consistent with that observed with each individual agent, except for more fatal treatment-emergent AEs with KdD vs Kd possibly due to greater therapy exposure, age, and frailty
  - Infections most common reason for fatal events
- The investigators concluded that KdD should be considered as a treatment option for patients with R/R MM

Usmani. ASH 2019. Abstr LBA6.

KD versus DVD (in the velcade naive patient)

- KD may be an option if significant residual neuropathy from 1st line therapy
- Potential hypersensitivity to Daratumumab
- On balance, do NOT use KD to ‘save’ Daratumumab as a single agent in 4th line.
- No trial comparison, but helpful information from CANDOR trial on MRD negativity in patients treated with KD
- Remember cardiac toxicity/hypertension with Carfilzomib (consider once weekly dosing)

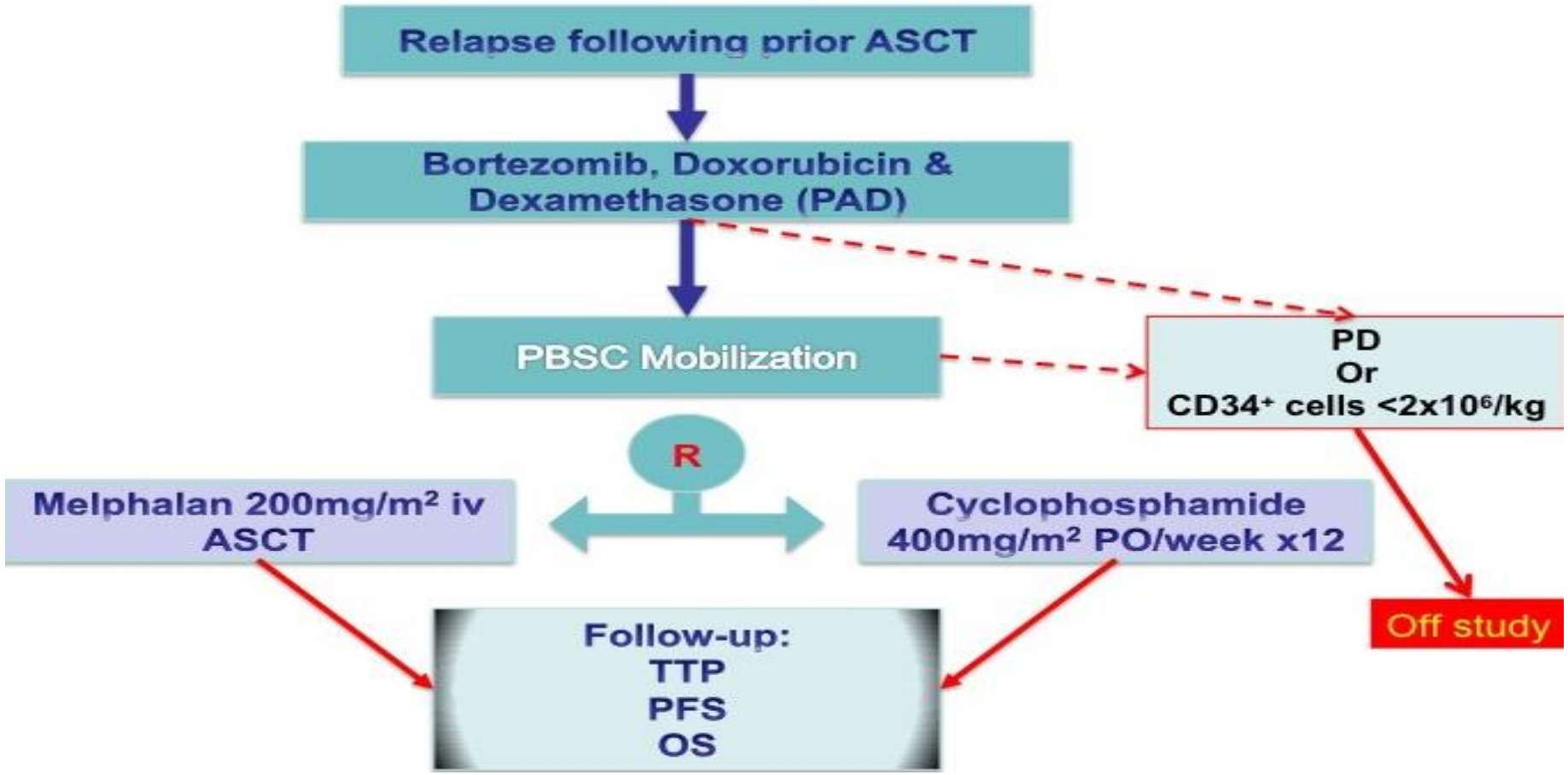
So who should get a second transplant at relapse?

- Only one randomised study, with a now meaningless comparator
- A lot of registry data suggests that the patients that benefit MOST:

- do not have high-risk cytogenetics at relapse
- ISS I/II
- have at *least* a year remission from first transplant
- have maintenance post transplant
- are younger

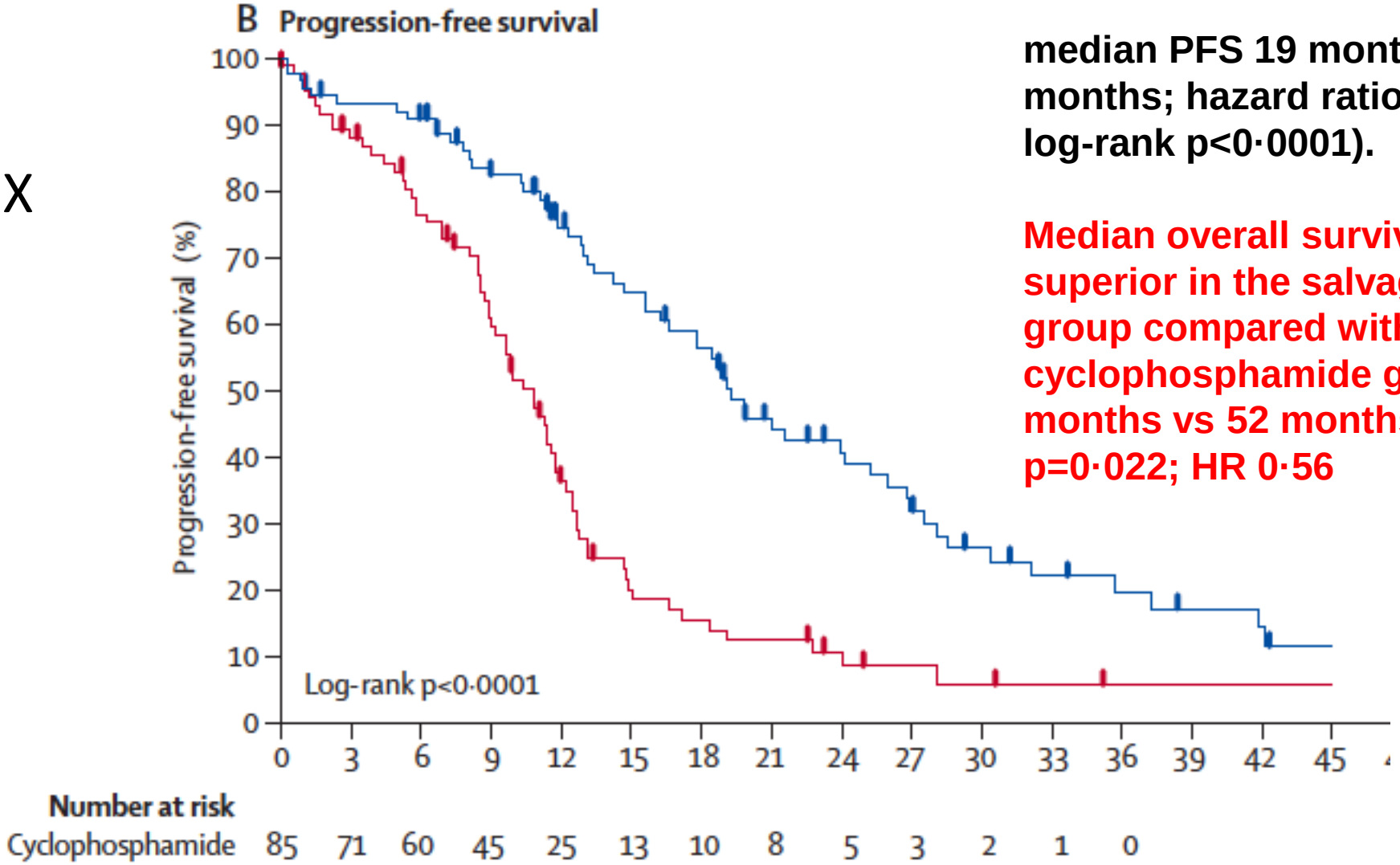
- Myeloma XII study will not help answer the question

Myeloma X Study Schema



Myeloma X

Trial



median PFS 19 months vs 11 months; hazard ratio [HR] 0·45 log-rank p<0·0001).

Median overall survival was superior in the salvage ASCT group compared with weekly cyclophosphamide group (67 months vs 52 months; log-rank p=0·022; HR 0·56

BUT look how the PFS compares…

Study	No.	ORR (%)	Median PFS (months)	Median OS (months)	TRM (%)
Shah et al. [111]	44	90	12.3	31.7	2
Jimenez-Zepaeda et al. [110]	81	97	16.4	53	3
Olin et al. [116]	41	55	8.5	20.7	7
Fenk et al. [114]	55	75	14	52	5
Alvares et al. [120]	83	—	15.6	34.8	—
Burzynski et al. [115]	25	64	12	19	8
Mehta et al. [133]	42	81	12.5	32	10
Eliece et al. [117]	26	69	14.8	38.1	0
Gonsalves et al. [107]	98	86	10.3	33	4
Yhim et al. [119]	48	—	18	55.5	—
Lemieux et al. [108]	81	93	18	48	0
Michaelis et al. [109]	187	—	3-year PFS: 13%	3-year OS: 46%	2

TRM treatment-related mortality, *ORR* overall response rate, *PFS* progression-free survival, *OS* overall survival

So, in 2020, with the following patient…

- 65 years old, ISS 1, diagnosed 2016, treated with RCD on Myeloma XI, no maintenance. Now relapsed. 3.5 year remission from Mel 200.

  Repeat cytogenetics – no high risk features

OPTIONS

- Myeloma XII Study (ITD followed by Transplant +/- Ixa Maintenance)
- DVD until progression
- DVD until best response , then Mel 200 (+/- Dara maintenance)

Salvage Autologous Transplant and Lenalidomide Maintenance Versus Continuous Lenalidomide/Dexamethasone for Relapsed Multiple Myeloma: Results of the Randomized GMMG Phase III Multicenter Trial Relapse

"The ReLAPse Trial"

- Arm A – Rd, (Len 25, dex 40 weekly), then Mel 200 and Len 10mg until BD. (139pts)
- Arm B – Rd (as above) until PD. (138 pts)
- 95% of patients had only 1 prior line (1-3 allowed)
- *With a median f/u of 3 years – no difference in PFS – 20.7 vs 18.8 months*

Baertsch et al, ASH 2018

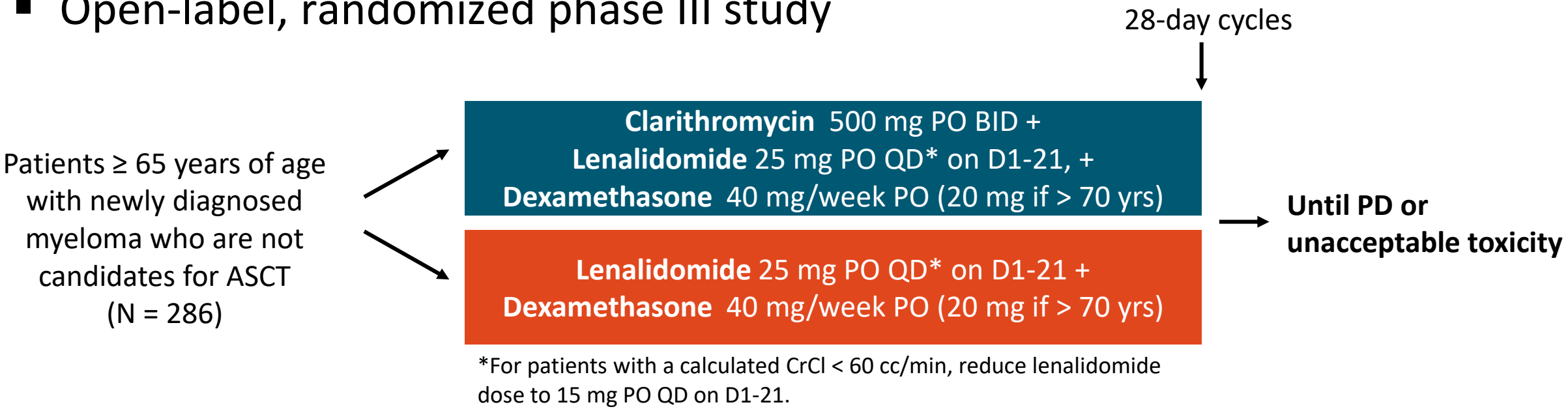
Lenalidomide, Dexamethasone, and Clarithromycin in Myeloma: Background

- For patients with transplant-ineligible myeloma, continuous Rd is a standard of care[1]; it is also used as a backbone for various other combinations
- Clarithromycin: antibiotic, immunomodulator, antineoplastic drug; optimizes effect of glucocorticoids[2]
- Phase II study of clarithromycin/lenalidomide/dexamethasone (BiRd) produced high ORR and CR rates (90.3% vs 38.9%, respectively) in patients with newly diagnosed symptomatic myeloma[2]
  - Superior PFS and responses vs Rd in matched-pair case-control analysis[3]
- Phase III GEM-CLARIDEX trial comparing efficacy of Rd vs clarithromycin + Rd in patients with newly diagnosed myeloma who are not candidates for ASCT[4]

1. Facon. Blood. 2018;131:301. 2. Niesvizky. Blood. 2008;111:1101. 3. Gay. Am J Hematol. 2010;85:664. 4. Puig. ASH 2019. Abstract 694.

Phase III GEM-CLARIDEX: Clarithromycin + Rd vs Rd in Newly Diagnosed, ASCT-Ineligible Patients With Myeloma

- Open-label, randomized phase III study



- Primary endpoint: PFS
- Secondary endpoints: ORR, DOR, TTP, OS, safety, MRD (NGS), PFS2, QoL

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GEM-CLARIDEX: Baseline Characteristics

Characteristic	Clarithromycin + Rd (n = 143)	Rd (n = 143)
Median age, yrs (range)	76 (65-91)	75 (65-93)
▪ ≥ 75 yrs, %	54.5	59.0
ECOG PS, %		
▪ 0	25	31
▪ 1	51	46
▪ 2	23	20
CrCl, %		
▪ < 60 mL/min	6	7
▪ ≥ 60 mL/min	94	93

Characteristic	Clarithromycin + Rd (n = 143)	Rd (n = 143)
M-protein, %		
▪ IgG	52	59
▪ IgA	33	26
▪ Other	0	3
▪ Bence Jones	15	12
Risk*, %		
▪ Standard	75	79
▪ High	18	17

*Presence of del(17p), t(4;14), t(14;16).

Puig. ASH 2019. Abstract 694.

GEM-CLARIDEX: Patient Disposition

Disposition Event	Clarithromycin + Rd (n = 143)	Rd (n = 143)
Median tx duration, months	7.4	8.6
Median cycles, no. (range)	8 (1-41)	10 (1-40)
Any AE, n (%)	143 (100)	143 (100)
Grade ≥ 3 TEAE, n (%)	117 (81.8)	118 (82.5)
Treatment discontinuations, n (%)	91 (63.2)	66 (46.2)
▪ Disease progression	26 (28.6)	31 (47.0)
▪ Unacceptable AE	16 (17.6)	12 (18.2)
▪ AE-related death	21 (23.1)	8 (12.1)
▪ Other	28 (24.2)	15 (22.7)

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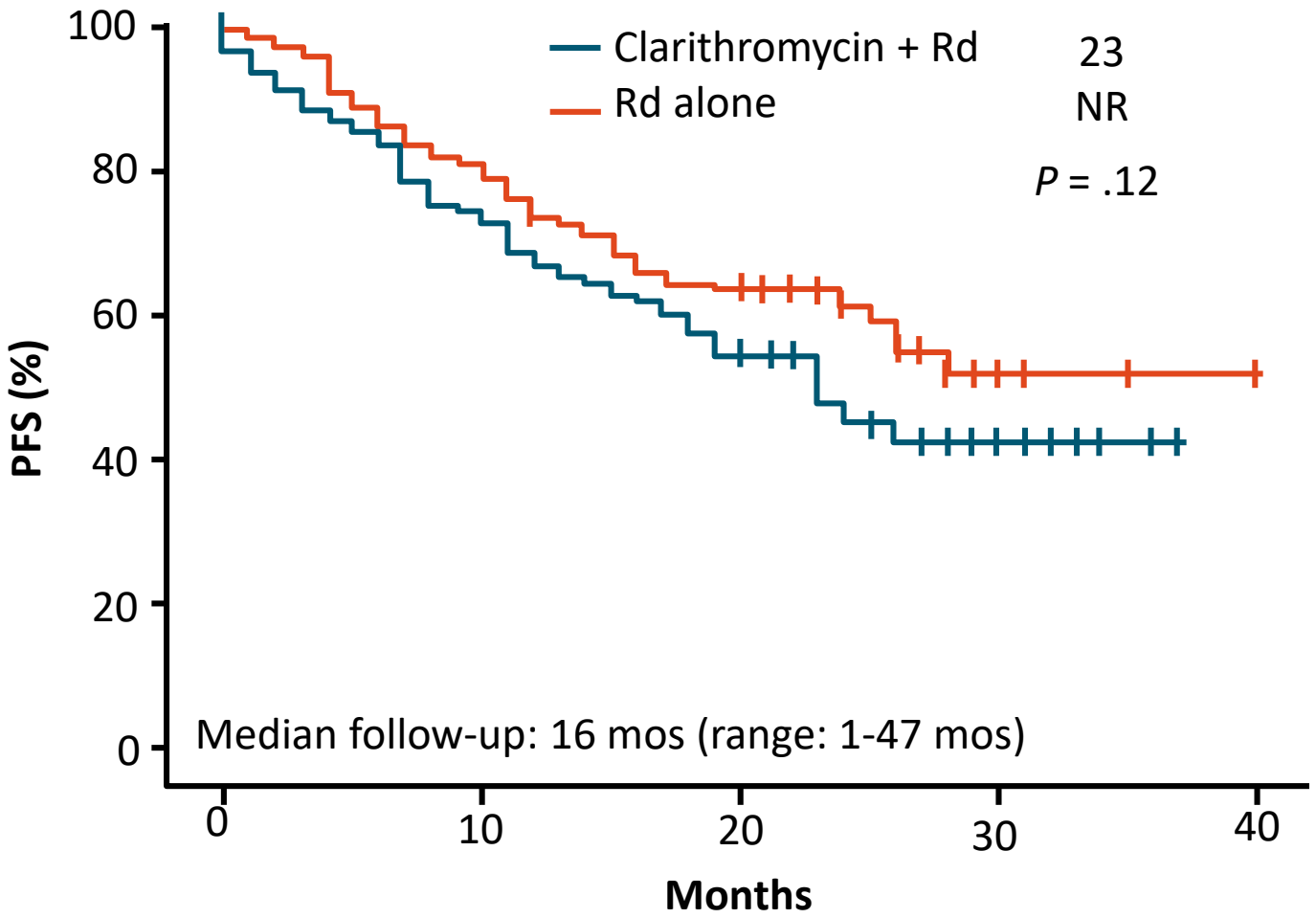
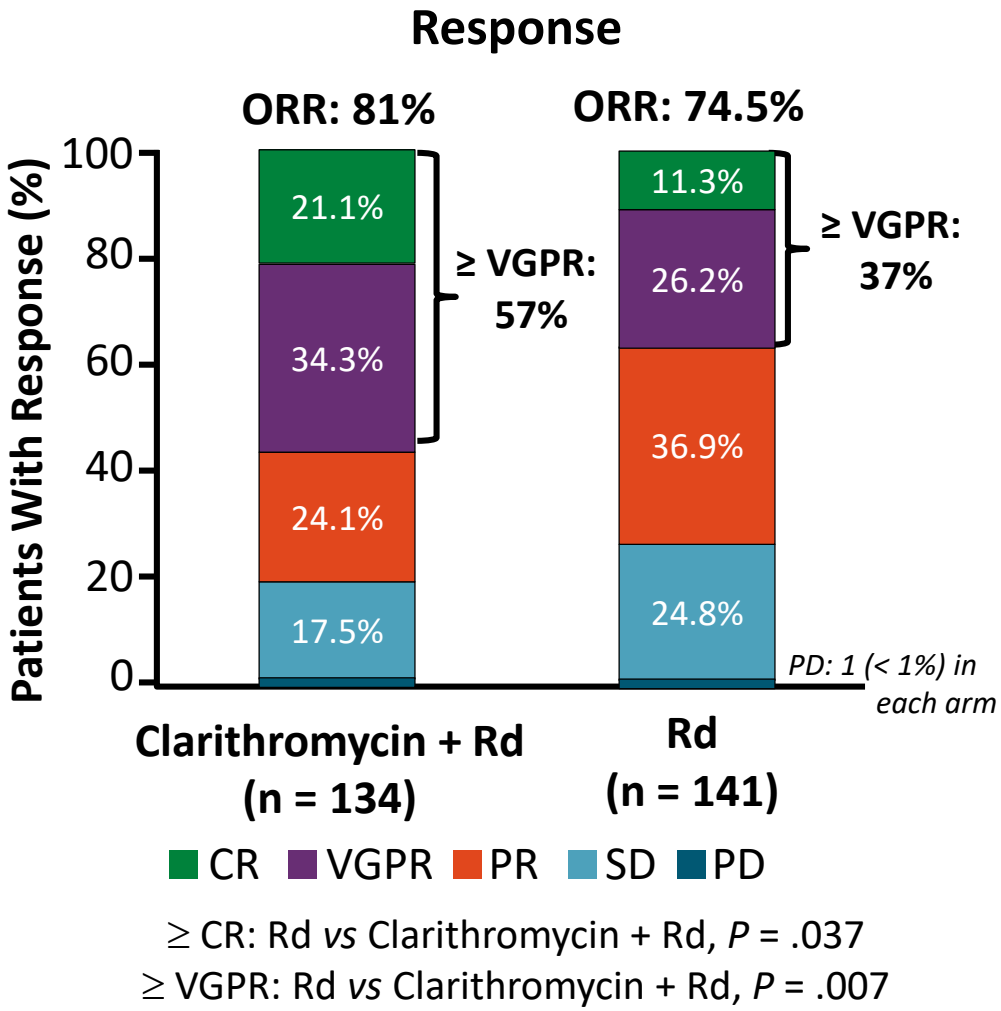
GEM-CLARIDEX: PFS (Primary Endpoint) and Response





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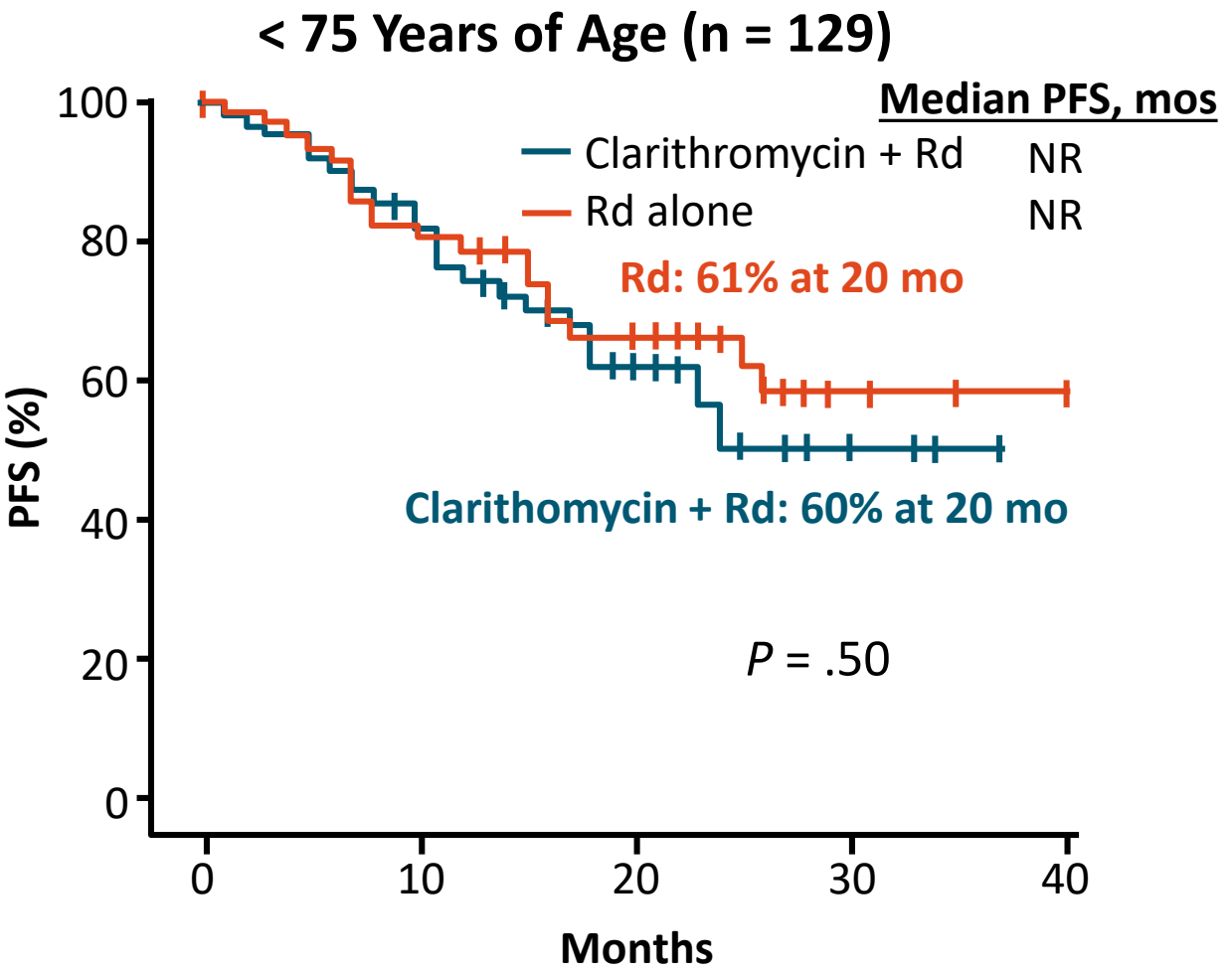
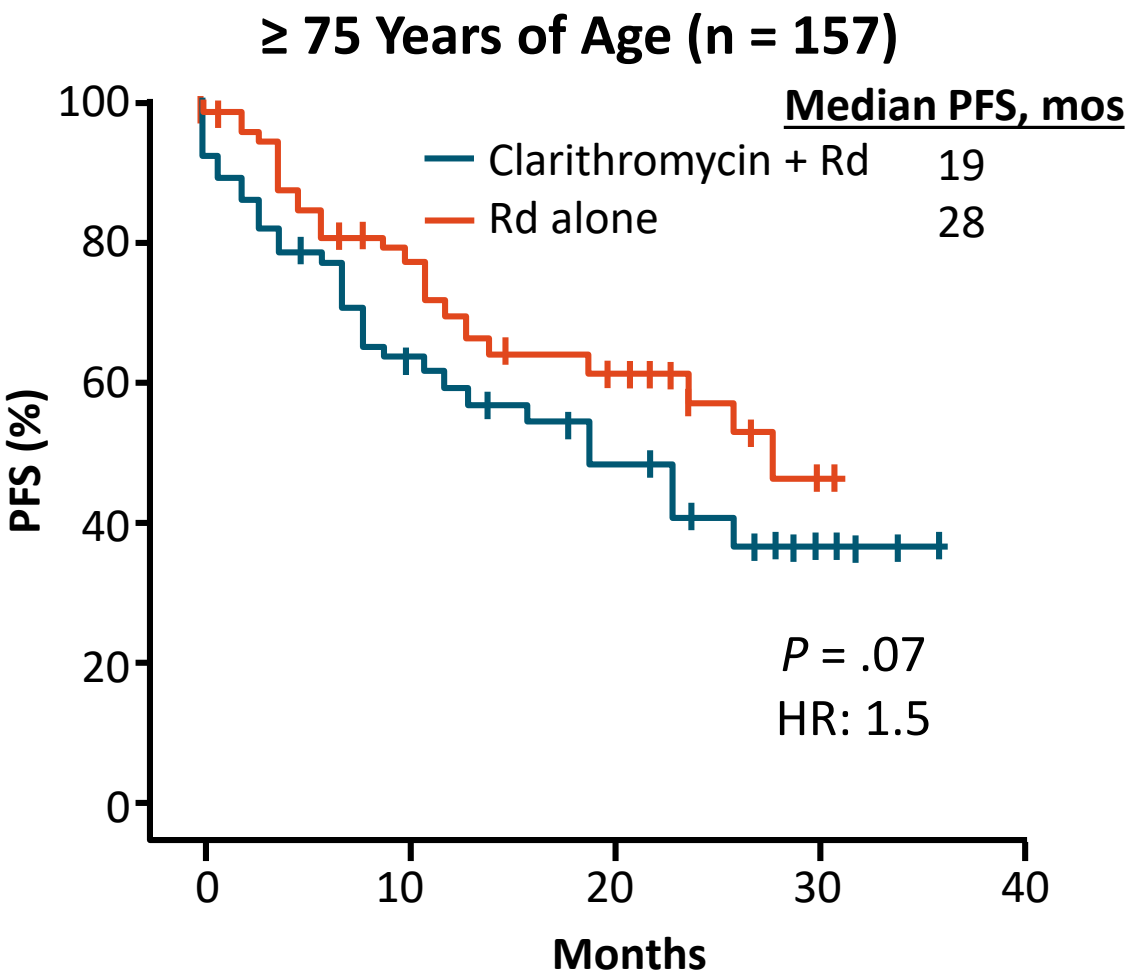
GEM-CLARIDEX: PFS by Age





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GEM-CLARIDEX: Common Adverse Events

Adverse Event, n (%)		Clarithromycin + Rd		Rd		
		Any Grade	Grade 3/4	Any Grade	Grade 3/4	
Hematologic	Neutropenia	30 (20.8)	15 (10.4)	46 (31.9)	24 (16.7)	
	Thrombocytopenia	20 (13.9)	7 (4.9)	20 (13.9)	4 (2.8)	
	Anemia	21 (14.6)	3 (2.1)	25 (17.4)	10 (6.9)	*P* = .04
Nonhematologic	Asthenia	32 (22.2)	13 (9)	32 (22.2)	2 (1.4)	
	Diarrhea	19 (13.2)	4 (2.8)	21 (14.6)	5 (3.5)	
	Skin rash	15 (10.4)	4 (2.8)	20 (13.9)	4 (2.8)	
	Pneumonia	14 (9.8)	14 (9.8)	11 (7.6)	8 (5.6)	
	Other infections	28 (19.4)	10 (6.9)	22 (15.3)	8 (5.6)	
	Steroid-related AEs*	32 (22.2)	14 (9.7)	24 (16.7)	3 (2.1)	

*Includes tremors (22%), anxiety (12%), insomnia (18%), diabetes, infections.

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Mortality

Causes of death, n (%)

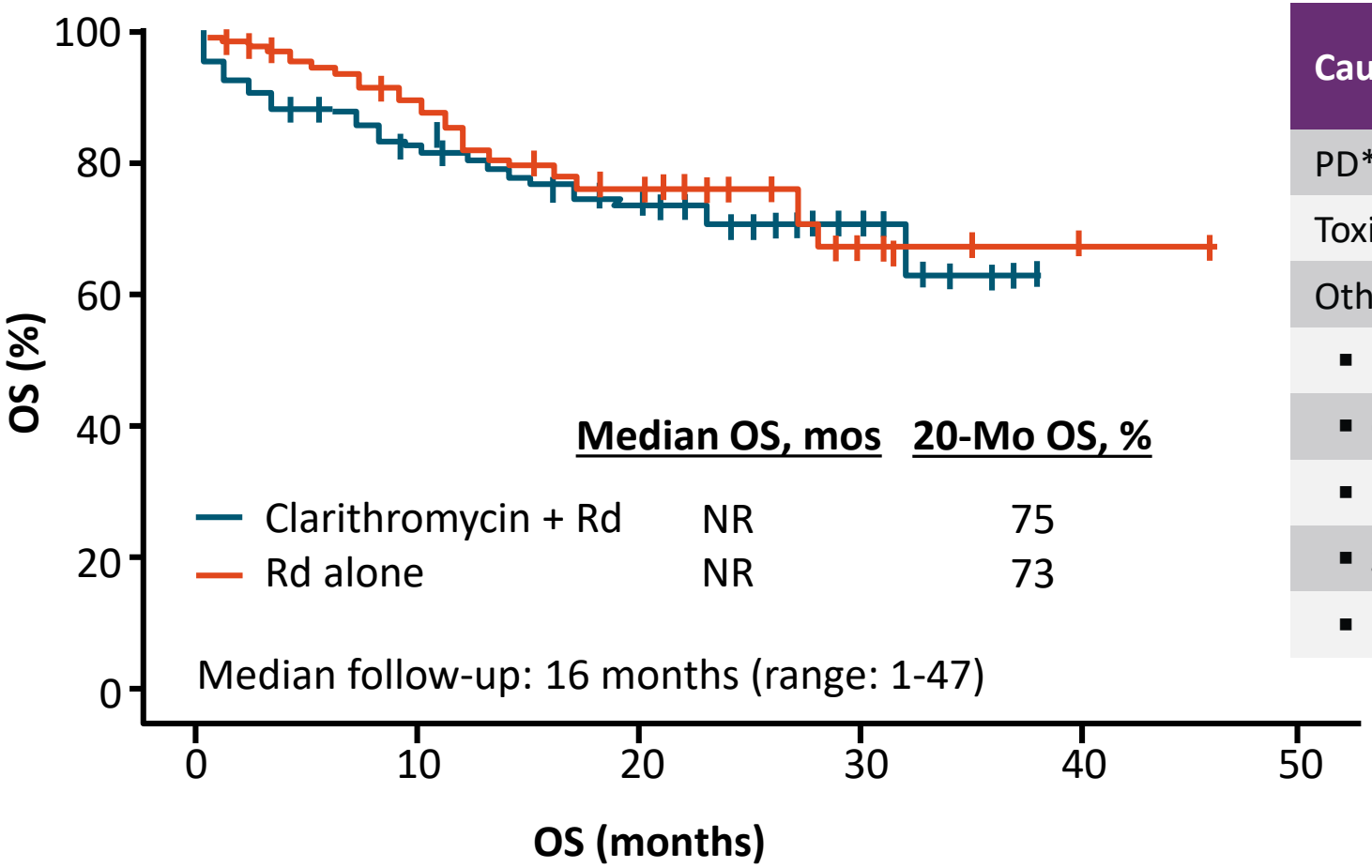
	Overall (n=62)	Rd (n=29)	CRd (n=33)	p
Progressive disease	17 (27.5)	**14 (48.3)**	**3 (9.1)**	**0.001**
Toxicity	6 (9.7)	0 (0)	6 (18.2)	
Other	39 (62.9)	15 (51.7)	24 (72.7)	0.116
- Infections	18 (29)	**6 (20.6)**	**12 (36.4)[3]**	**0.022**
- Cardiovascular events	5 (8.1)	2 (6.9)	3 (9.1)	0.752
- Unknown	12 (19.3)	6 (20.7)	5 (15.1)	0.741
- SPM	3 (4.8)	1 (3.4)[1]	2 (6.1)[2]	0.669
- Miscellaneous	2 (3.2)	0 (0)	2 (6.1)	-

[1] 1 case of MDS, [2] 1 case of colon cancer and 1 case of pancreatic adenocarcinoma

[3] 11 of them in pts ≥75 yo

GEM-CLARIDEX: Overall Survival and Mortality

Overall Survival



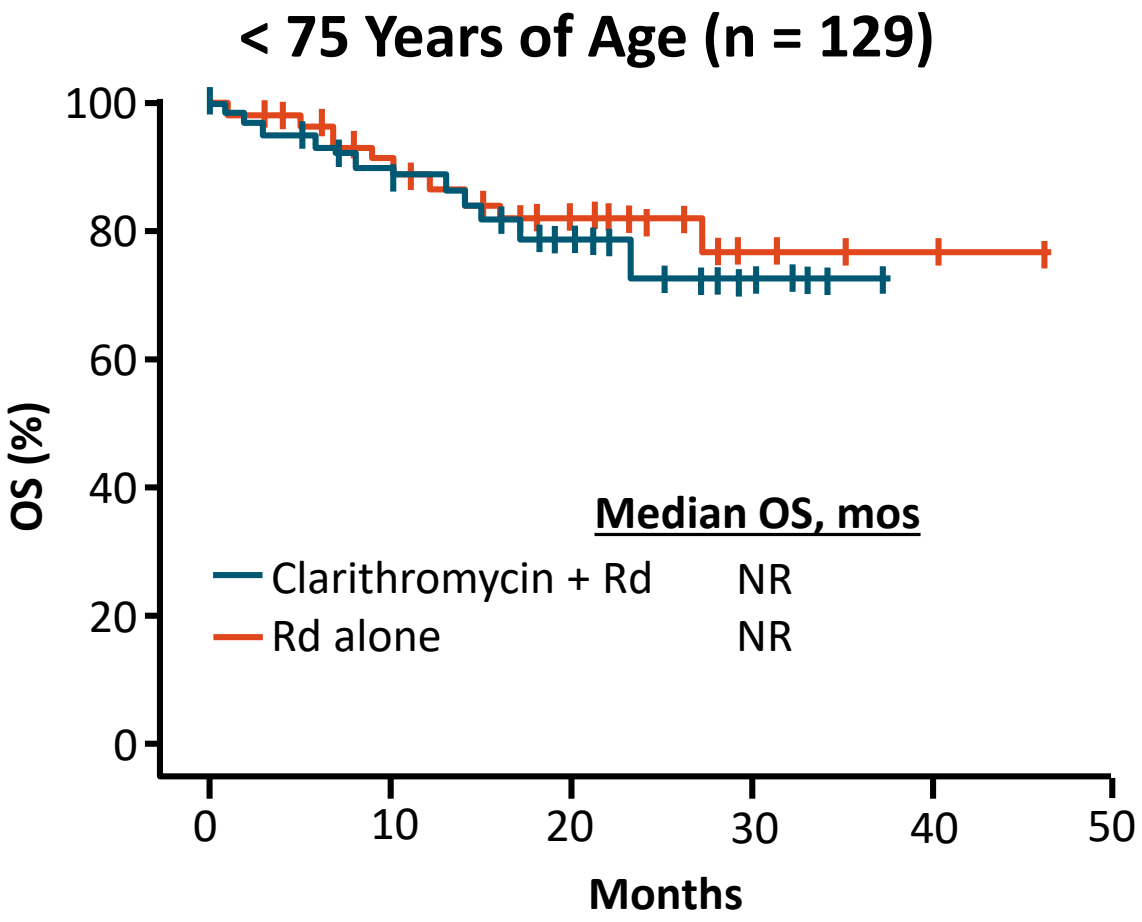
Mortality

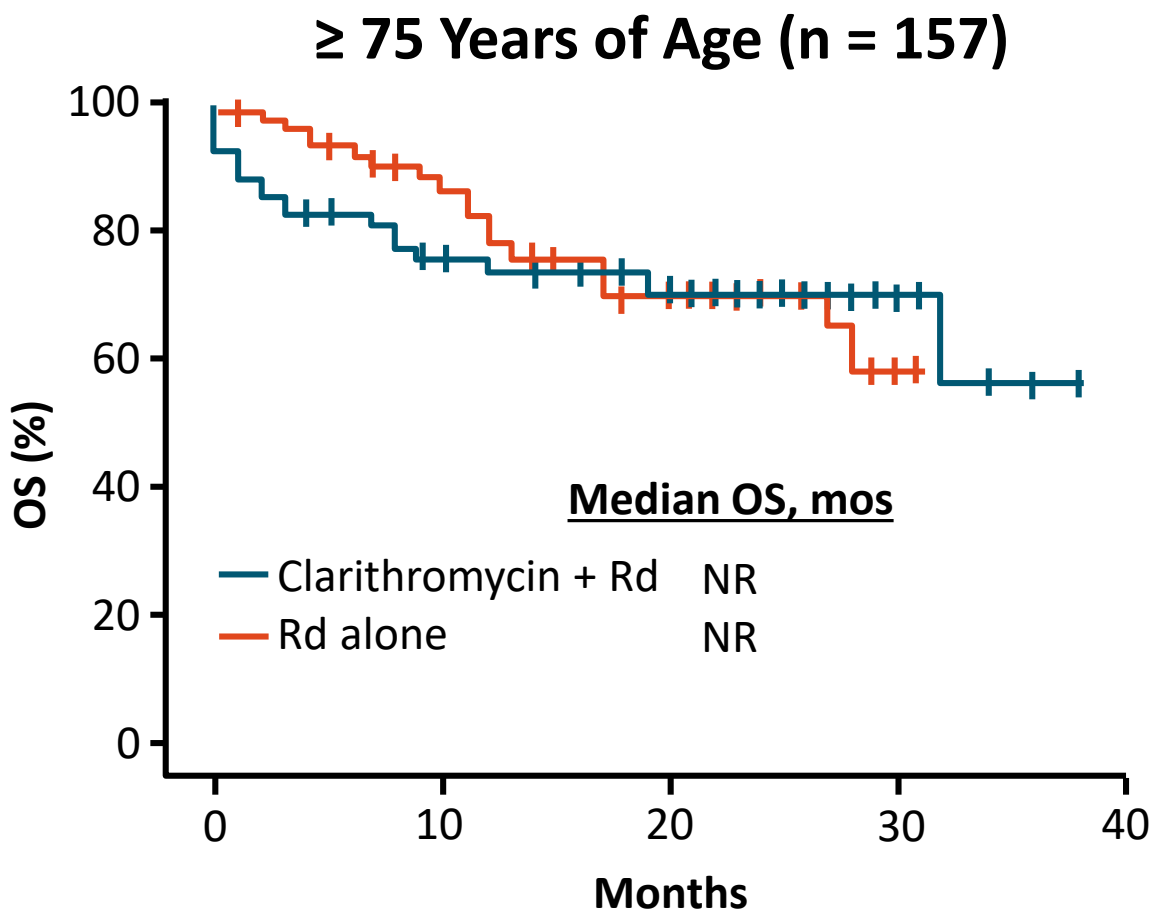
Cause, n (%)	Overall (n = 62)	Clarithromycin + Rd (n = 33)	Rd (n = 29)
PD*	17 (27.5)	3 (9.1)	14 (48.3)
Toxicity	6 (9.7)	6 (18.2)	0
Other*	39 (62.9)	24 (72.7)	15 (51.7)
▪ Infections	18 (29.0)	12 (36.4)	6 (20.6)
▪ CV events	5 (8.1)	3 (9.1)	2 (6.9)
▪ Unknown	12 (19.3)	5 (15.1)	6 (20.7)
▪ SPM	3 (4.8)	2 (6.1)	1 (3.4)
▪ Misc	2 (3.2)	2 (6.1)	0

*P = .001

Puig. ASH 2019. Abstract 694.

GEM-CLARIDEX: Overall Survival by Age





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GEM-CLARIDEX: Investigator Conclusions

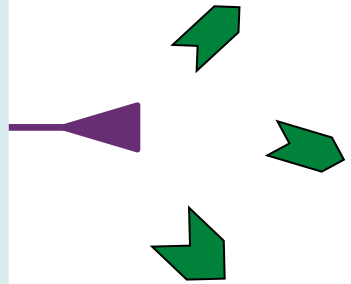
- In this phase III trial, no significant PFS improvement was reported with addition of clarithromycin to Rd in newly diagnosed, transplant-ineligible patients with myeloma
  - Addition of clarithromycin significantly increased response rates
  - However, addition of clarithromycin significantly increased incidence of deaths from toxicity, mostly from infections and in patients ≥ 75 years of age
  - Increased steroid AUC induced by clarithromycin was partially responsible for both increased response rates and increased infections on experimental arm

Gerds. ASH 2019. Abstr 557.

BCMA-Targeted Therapies

Antibody–Drug Conjugates
Belantamab mafodotin
MEDI2228
CC-99712

BCMA



Bispecific T-Cell Engagers
AMG 420
AMG 701
CC-93269
REGN5458
JNJ-64007957
PF-06863135

CAR T-Cell Therapies
Idecabtagene vicleucel
LCAR-B38M
P-BCMA-101
bb21217
ALLO-715

Myeloma cell

Belantamab Mafodotin: BCMA-Targeted ADC

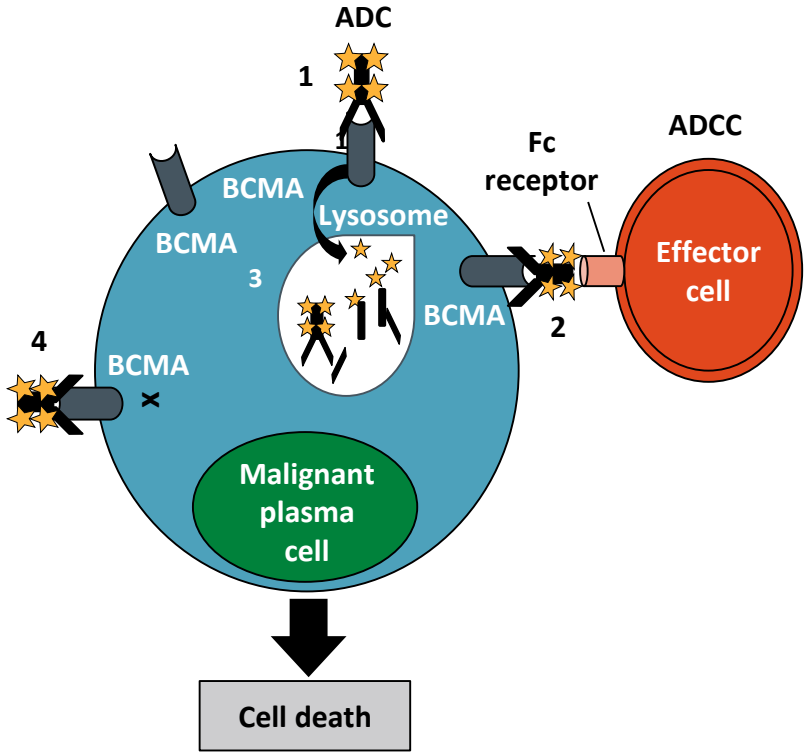
- **Belantamab mafodotin (GSK2857916)**: Humanized, afucosylated, IgG1 **BCMA-targeted ADC** that neutralizes soluble BCMA
  - Preclinical studies demonstrate selective, potent activity

Belantamab Mafodotin

Cytotoxic agent	**–MMAF (non–cell-permeable, highly potent auristatin)**
Afucosylation	**–Enhanced ADCC**
Linker	**–Stable in circulation**

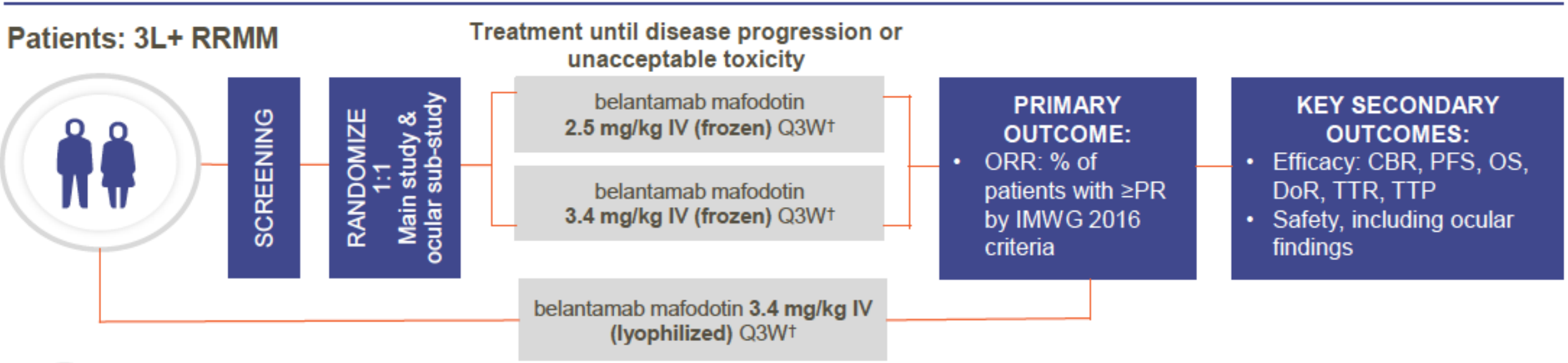
Four mechanisms of action:

1. **ADC**
2. **ADCC**
3. **Immunogenic cell death**
4. **BCMA receptor signaling inhibition**



Tai. Blood. 2014;123:3128. Trudel. Lancet Oncol. 2018;19:1641. Trudel. Blood Cancer J. 2019;9:37.

DREAMM-2



ELIGIBILITY CRITERIA:

- ✓ Measurable disease**
- ✓ ECOG PS 0–2
- ✓ ≥ 3 prior lines of therapy
- ✓ *Refractory to proteasome inhibitor, immunomodulatory agent, and refractory/intolerant to anti-CD38 mAb
- ✓ Patients with mild/moderate renal impairment and grade 2 cytopenias were permitted
- ✓ Prior BCMA-targeted therapy excluded
- ✓ Prior auto-SCT allowed, allo-SCT excluded

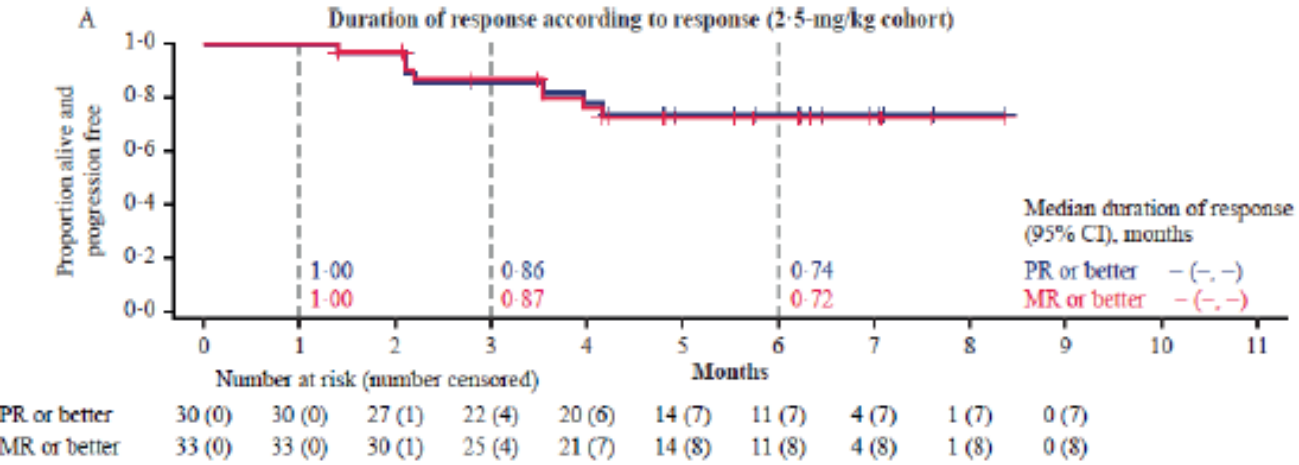
Characteristic	belantamab mafodotin 2.5 mg/kg (N=97)	belantamab mafodotin 3.4 mg/kg (N=99)
Age, median (IQR), years	65 (60–70)	67 (61–72)
Sex, n (%) Male Female	 51 (53) 46 (47)	 56 (57) 43 (43)
ISS stage at screening, n (%) I II III Unknown/ missing	 21 (22) 33 (34) 42 (43) 1 (1)	 18 (18) 51 (52) 30 (30) 0
Cytogenetics risk, n (%) High risk* Other	 41 (42) 56 (58)	 47 (47) 52 (52)
Number of prior lines of therapy, median (range)	7 (3–21)	6 (3–21)
Refractory to prior immunomodulatory agent, proteasome inhibitor and an anti-CD38 antibody, n (%)	97 (100)	99 (100)

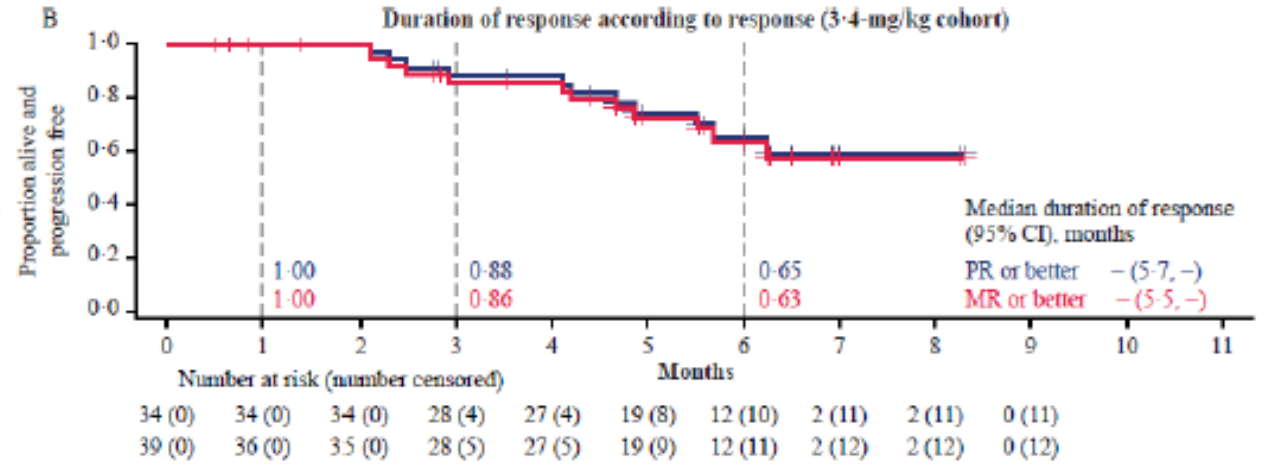
*High-risk cytogenetics defined as having any of the following cytogenetic features: t(4;14), t(14;16), 17p13del, or 1q21+.
IQR, interquartile range; ISS, International Staging System
Lonial S et al. Lancet Oncology, 2019, epub ahead of print

IRC-assessed response*	belantamab mafodotin 2.5 mg/kg (N=97)	belantamab mafodotin 3.4 mg/kg (N=99)
ORR†, n (%) (97.5% CI)	30 (31) (20.8–42.6)	34 (34) (23.9–46.0)
sCR, n (%)	2 (2)	3 (3)
CR, n (%)	1 (1)	0
VGPR, n (%)	15 (15)	17 (17)
PR, n (%)	12 (12)	14 (14)
CBR‡, n (%) (97.5% CI)	33 (34) (23.5–45.8)	39 (39) (28.5–51.1)

Intent-to-treat population. *As assessed using 2016 IMWG criteria (Kumar S et al. *Lancet Oncol* 2016; 17: e328–346.). †defined as PR or better. ‡defined as MR or better.
CBR, clinical benefit rate; CI, confidence interval; CR, complete response; IMWG, International Myeloma Working Group; IRC, independent review committee; MR, minimal response; ORR, overall response rate; PR, partial response; sCR, stringent complete response; VGPR, very good partial response.
Lonial S et al. Lancet Oncology, 2019, epub ahead of print

IRC-assessed outcome (median)	belantamab mafodotin 2.5 mg/kg (N=97)	belantamab mafodotin 3.4 mg/kg (N=99)
OS, months	NR‡	NR‡
PFS, months (95% CI)	2.9 (2.1–3.7)†	4.9 (2.3–6.2)†
DoR, months	NR‡	NR‡
Patients with DoR ≥4 months (% [95% CI])*	78 (57–89)	87 (69–95)





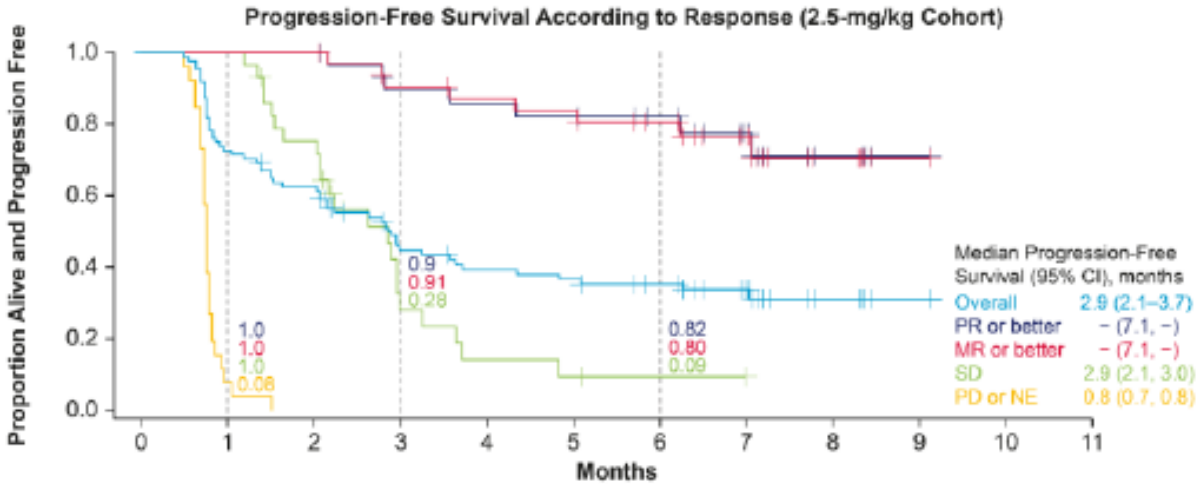
Follow up is ongoing to confirm durability

Intent-to-treat population. *As of data cut-off. †Not reached for patients with partial responses or better. ‡Not reached for responders in either cohort and median duration of follow-up was 6.3 and 6.9 months, respectively. CI, confidence interval; DoR, duration of response; IRC, independent-review committee; NR, not reached; OS, overall survival; PFS, progression-free survival

Lonial S et al. Lancet Oncology. 2019. epub ahead of print

mPFS was 2.9 and 4.9 mos in the 2.5-mg/kg and 3.4-mg/kg groups, not reached in patients with MR or better

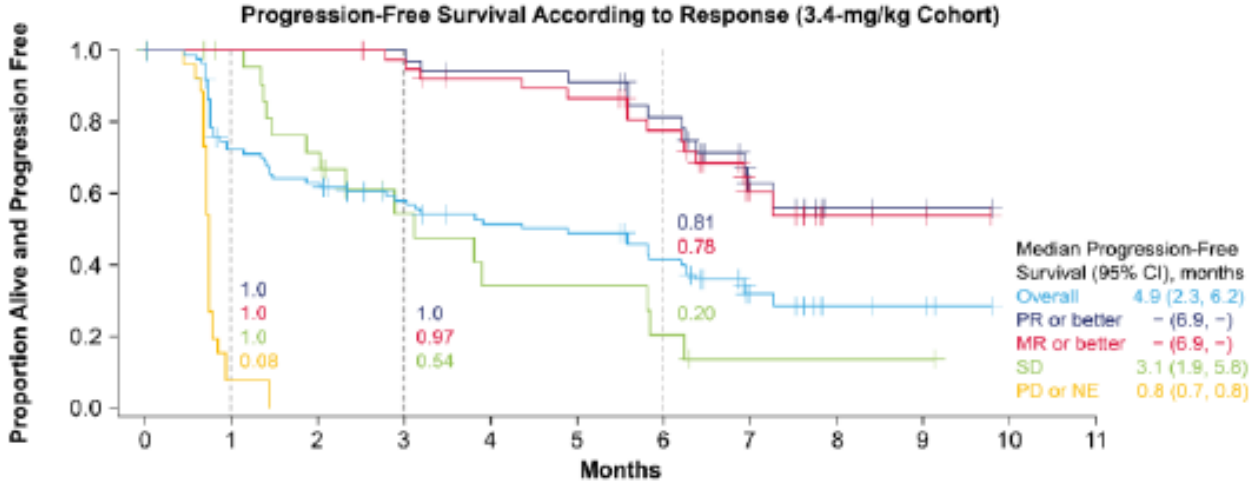
A. PFS survival by response (belantamab mafodotin 2.5-mg/kg)



Number at risk (number of events)

All patients	97 (0)	64 (24)	54 (33)	34 (47)	29 (51)	27 (53)	22 (54)	14 (55)	5 (56)	1 (56)	0 (56)
PR or better	30 (0)	30 (0)	30 (0)	25 (3)	23 (4)	22 (5)	19 (5)	13 (6)	4 (7)	1 (7)	0 (7)
MR or better	33 (0)	33 (0)	33 (0)	28 (3)	26 (4)	25 (5)	21 (6)	14 (7)	5 (8)	1 (8)	0 (8)
SD	30 (0)	29 (0)	21 (7)	6 (18)	3 (21)	2 (22)	1 (22)	0 (22)			
PD or NE	34 (0)	2 (24)	0 (26)								

B. PFS survival by response (belantamab mafodotin 3.4-mg/kg)



Number at risk (number of events)

All patients	99 (0)	62 (24)	54 (32)	45 (36)	38 (41)	36 (43)	29 (48)	10 (54)	4 (55)	3 (55)	0 (55)
PR or better	34 (0)	34 (0)	34 (0)	34 (0)	31 (2)	30 (3)	25 (6)	9 (11)	3 (12)	2 (12)	0 (12)
MR or better	39 (0)	39 (0)	39 (0)	37 (1)	33 (3)	31 (5)	26 (8)	9 (13)	3 (14)	2 (14)	0 (14)
SD	23 (0)	21 (0)	15 (6)	8 (9)	5 (12)	5 (12)	3 (14)	1 (15)	1 (15)	1 (15)	0 (15)
PD or NE	37 (0)	2 (24)	0 (26)								

Post-hoc analysis. Responses in intent-to-treat population as assessed by IRC according to 2016 IMWG criteria (Kumar S et al. *Lancet Oncol* 2016;17:e328–346).
IMWG, International Myeloma Working Group; IRC, independent review committee; MR, minimal response; NE, not evaluable; PD, progressive disease; PFS, progression-free survival; PR, partial response; SD, stable disease.

Safety overview

All AE's of interest and any AE's >20% in either cohort

Number of patients with event (safety population), n (%)*	Belantamab mafodotin 2.5 mg/kg (N=95)				Belantamab mafodotin 3.4 mg/kg (N=99)			
	Grade 1-2	Grade 3	Grade 4	Grade 5	Grade 1-2	Grade 3	Grade 4	Grade 5
Keratopathy or corneal epithelium changes†	41 (43)	26 (27)	0	0	53 (54)	20 (20)	1 (1)	0
Thrombocytopenia‡	14 (15)	8 (8)	11 (12)	0	24 (24)	11 (11)	22 (22)	1 (1)
Anemia	4 (4)	19 (20)	0	0	12 (12)	22 (22)	3 (3)	0
Nausea	23 (24)	0	0	0	31 (31)	1 (1)	0	0
Pyrexia	18 (19)	2 (2)	1 (1)	0	21 (21)	4 (4)	0	0
Blurred vision§	17 (18)	4 (4)	0	0	28 (28)	2 (2)	0	0
Infusion-related reactions¶	17 (18)	3 (3)	0	0	15 (15)	1 (1)	0	0
Increased aspartate aminotransferase	17 (18)	2 (2)	0	0	18 (18)	6 (6)	0	0
Fatigue	13 (14)	2 (2)	0	0	21 (21)	5 (5)	0	0
Dry eye**	12 (13)	1 (1)	0	0	23 (23)	0	0	0
Neutropenia††	4 (4)	5 (5)	4 (4)	0	12 (12)	12 (12)	3 (3)	0

Listed in order of decreasing frequency of Any Grade events in the 2·5-mg/kg cohort. *Events reported based on Common Terminology Criteria for Adverse Events criteria v4.03 in the safety population (including all patients who received at least one dose of trial treatment). †Keratopathy or corneal epithelium changes (considered an adverse event of special interest [AESI]) were observed by ophthalmic examination. ‡Thrombocytopenia (considered an AESI) includes preferred terms thrombocytopenia, decreased platelet count, and cerebral hemorrhage. § Blurred vision includes preferred terms vision blurred, diplopia, visual acuity reduced and visual impairment. ¶Infusion-related reactions (considered an AESI) includes preferred terms infusion-related reaction, pyrexia, chills, diarrhea, nausea, asthenia, hypertension, lethargy, tachycardia, vomiting, cough and hypotension occurring within 24 hours of infusion. **Dry eye includes preferred terms dry eye, ocular discomfort, eye pruritus and foreign body sensation in eye. ††Neutropenia includes neutropenia, febrile neutropenia and neutrophil count decreased. Lonial S et al. Lancet Oncology, 2019, epub ahead of print.

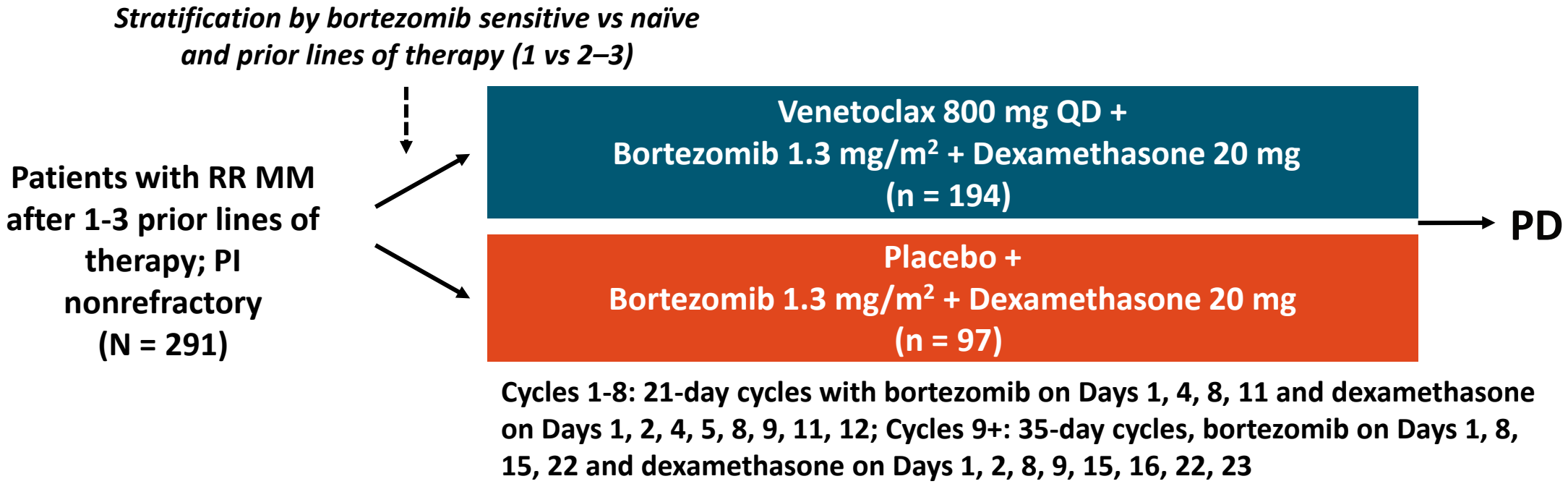
In Summary

- Some reasonable disease activity seen in a difficult to treat population (IMID/PI refractory, Dara intolerant/refractory)
- Response rate around 30%
- Eye toxicity is a significant issue
- Available on compassionate use in certain situations in some centres

- Large clinical development programme ensuing – inc VRD vs VRD+Bel. Unknown how combinations will affect toxicity

BELLINI Biomarker Subgroup Analysis: Study Design

- Double blind, randomized 2:1, placebo-controlled phase III trial



- Primary Endpoint: PFS (per IRC)
- Key Secondary Endpoints: ORR, ≥ VGPR, OS, QoL/PRO parameters

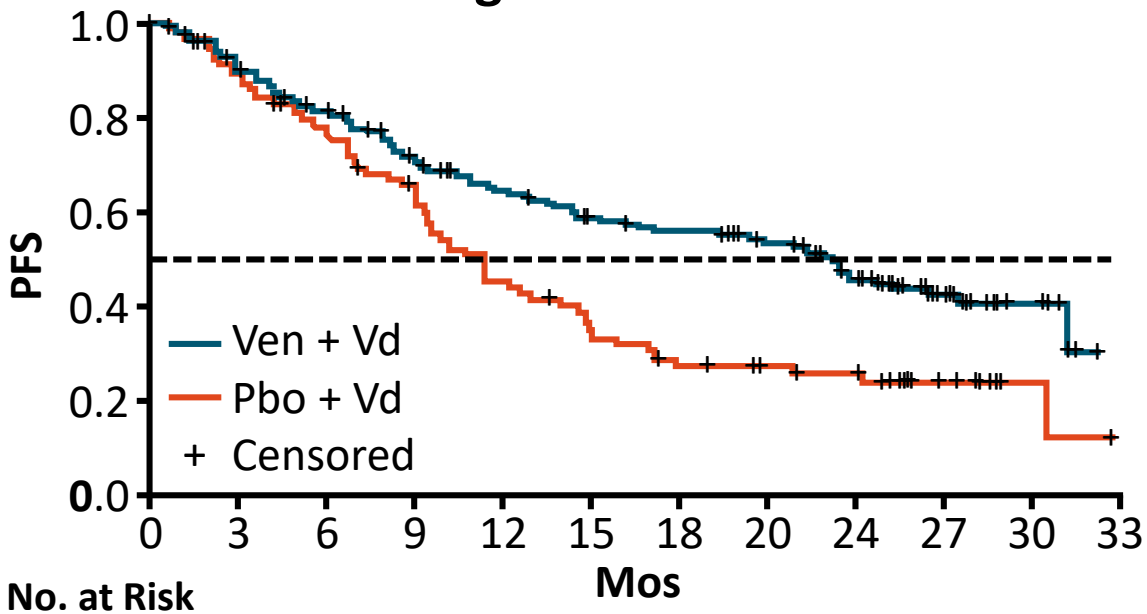
Harrison. ASH 2019. Abstr 142.

Table 1. BELLINI key data

	Ven-Bd	**Bd**
N	194	97
Deaths	41 (21.1%)	11 (11.3%)
ORR	159 (82%)	66 (68%)
≥ VGPR	59%	36%

BELLINI Biomarker Subgroup Analysis: PFS and OS in All Patients (ITT)

Investigator-Assessed PFS

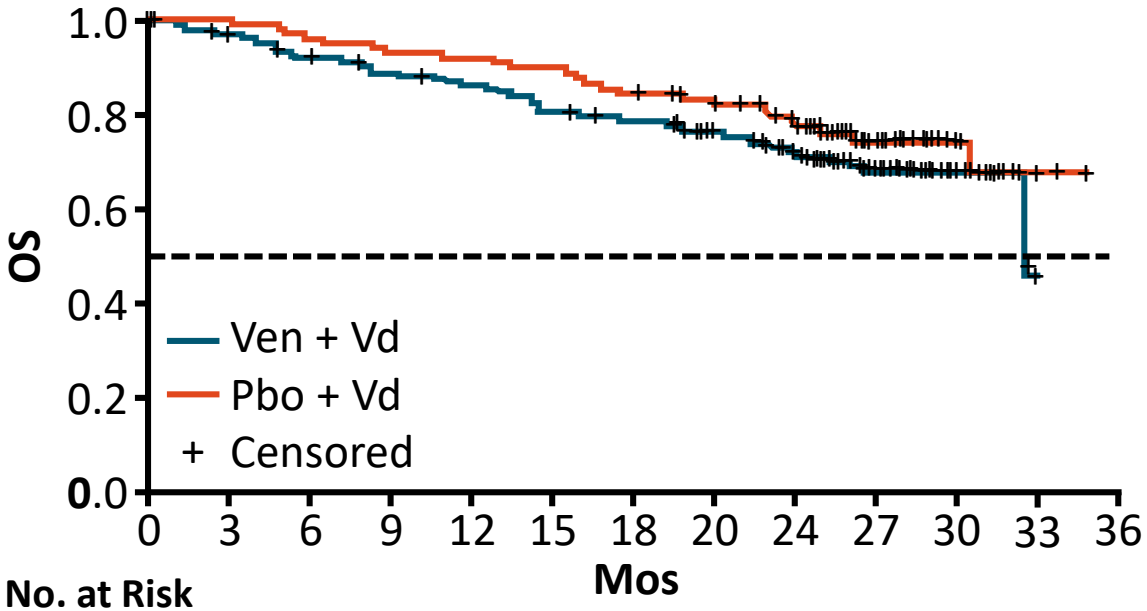


No. at Risk

194	163	140	118	101	89	84	75	58	27	9	0
97	83	69	57	39	30	22	19	17	8	2	0

Endpoint	Ven + Vd	Placebo + Vd
Median PFS, mos	23.2	11.4
HR (95% CI); *P* value	0.60 (0.44-0.83); .001	

OS



No. at Risk

194	186	174	165	159	150	144	133	118	62	18	0	
97	95	91	88	87	85	80	75	66	33	12	2	0

Endpoint	Ven + Vd	Placebo + Vd
Median OS, mos	32.5*	NR
HR (95% CI); *P* value	1.32 (0.82, 2.12); .256	

*estimated median may change with longer f/u due to number of censored pts

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BELLINI Biomarker Subgroup Analysis: Efficacy in Patients with t(11;14) Multiple Myeloma

Pts with t(11;14) PFS	Ven + Vd	Placebo + Vd
Median, mos	NR	9.3
HR (95% CI)	0.09 (0.02-0.44)	
P value	.003	
OS		
Median, mos	NR	NR
HR (95% CI)	0.68 (0.13-3.48)	
P value	.647	

Pts with t(11;14), %	Ven + Vd (n = 20)	Placebo + Vd (n = 15)	*P* value
ORR	95	47	.004
≥ VGPR	75	27	.013
≥ CR	55	7	.009
MRD			
▪ $< 10^{-4}$	45	0	.009
▪ $< 10^{-5}$	30	0	.06
▪ $< 10^{-6}$	25	0	.109

- Pts with t(11;14) achieved higher rates of response, including MRD negativity with venetoclax compared with placebo

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BELLINI Biomarker Subgroup Analysis: Efficacy in Patients with $BCL2^{high}$ Expression Excluding t(11;14)

Pts with *$BCL2^{high}$* and no t(11;14), %		
PFS	**Ven + Vd**	**Placebo + Vd**
Median, mos	NR	10.2
HR (95% CI)	0.41 (0.20-0.81)	
P value	.011	
OS		
Median, mos	NR	NR
HR (95% CI)	0.92 (0.35-2.44)	
P value	.866	

Pts with *$BCL2^{high}$* and no t(11;14), %	Ven + Vd (n = 51)	Placebo + Vd (n = 24)	*P* value
ORR	84	83	1.000
≥ VGPR	73	33	.003
≥ CR	35	0	.002
MRD			
▪ $< 10^{-4}$	28	4	.041
▪ $< 10^{-5}$	20	0	.049
▪ $< 10^{-6}$	6	0	.561

- Patients with $BCL2^{high}$ expression and negative for t(11;14) attained high rates of deeper responses with venetoclax compared with placebo

High BCL2 gene expression was determined by qPCR. MRD assessment performed by NGS on BM aspirate at time of CR/sCR and 6- and 12-mos post confirmation of CR/sCR

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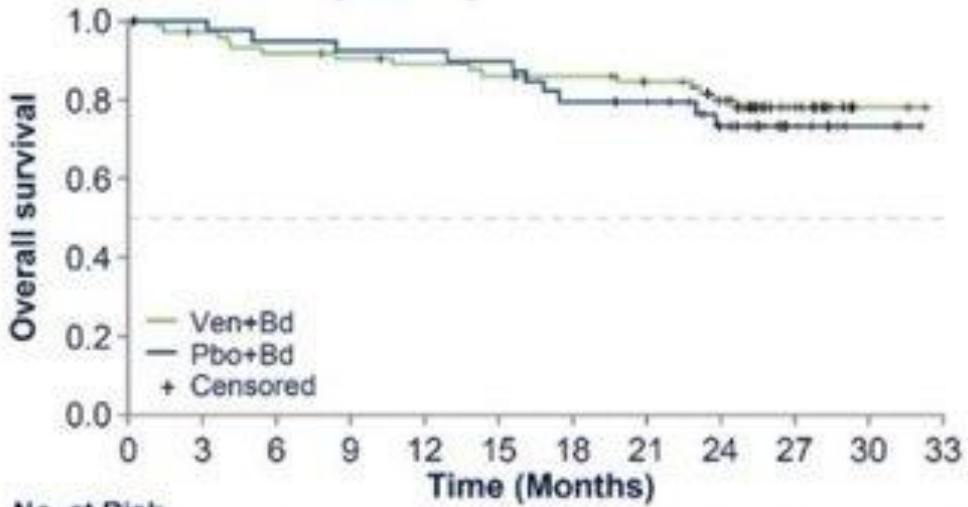
t(11;14) or *BCL2*^{high}

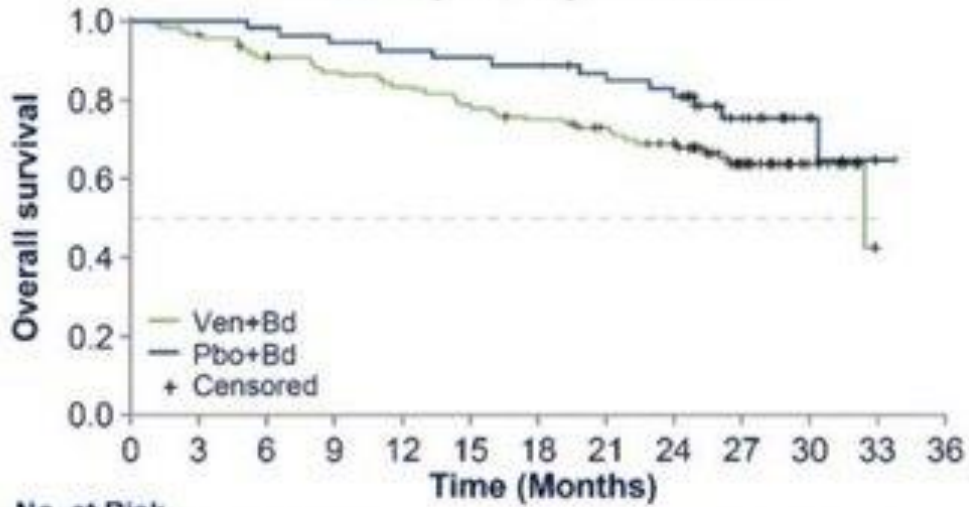


No. at Risk

74	70	66	64	62	60	59	56	48	22	2	0
40	39	37	36	36	35	31	29	21	9	3	0

OS	Ven+Bd	Pbo+Bd
Median, months	Not reached	Not reached
HR (95% CI)	0.92 (0.41, 2.08)	
P value	0.843	

Non-t(11;14) *BCL2*^{low}



No. at Risk

110	106	98	92	88	83	78	72	66	38	15	0	
54	53	52	50	49	48	47	44	41	22	8	1	0

OS	Ven+Bd	Pbo+Bd
Median, months	32.4	Not reached
HR (95% CI)	1.52 (0.81, 2.88)	
P value	0.194	

High *BCL2* gene expression was determined by qPCR.

BELLINI Biomarker Subgroup Analysis: Investigator Conclusions

- Addition of venetoclax to bortezomib/dexamethasone was efficacious in patients with R/R multiple myeloma harboring either t(11;14) or tumor cells with $BCL2^{high}$ expression
  - $BCL2^{high}$ gene expression associated with extended PFS and increased response rates in the venetoclax arm independent of t(11;14)
  - OS in pts with t(11;14) or $BCL2^{high}$ gene expression was similar in either arm
- In pts without t(11;14) and expressing low BCL2 levels, PFS not significantly improved with venetoclax, and OS favored placebo
- Additional biomarker-selected trials for patients with MM, including t(11;14) or $BCL2^{high}$ gene expression, are ongoing:
  - CANOVA: VenDex vs PomDex in RRMM,[NCT03539744] M15-538: VenKd vs Kd in RRMM,[NCT02899052] M15-654: VenDd vs VenDVd in RRMM[NCT03314181]

Harrison. ASH 2019. Abstr 142.

In Summary

- Increasing numbers of options is making decision making in this space more nuance
- Need to understand how to navigate CDF, and use 2nd transplant wisely
- High-risk patients are still doing badly
- BCMA is a target being exploited rapidly – CAR-T, Bispecific Antibodies, Antibody Drug Conjugates
- Venetoclax will have a role in the t(11;14) /bcl-2 high expressors population
- New IMIDs
- Other agents eg Selinexor