International Myeloma Society

18th International Myeloma Workshop

SEPTEMBER 8-11, VIENNA AUSTRIA

Approach to First Relapse

Meletios (Thanos) Dimopoulos, MD
Professor of Hematology/Oncology
Rector of the National and Kapodistrian University of Athens (NKUA)
Plasma Cell Dyscrasias Unit, Department of Clinical Therapeutics,
NKUA, School of Medicine, Athens, Greece

Disclosures

Name of Company	Advisory Board	Honoraria
Amgen	X	X
Janssen	X	X
Celgene/Genesis	X	X
Sanofi		X
Takeda	X	X
BMS	X	X
GSK	X	X

Factors to Consider When Selecting Treatment at First Relapse

Disease-Related Factors[1,2]

- **Type and risk status of disease**
- **Presence of refractory disease**
- Aggressiveness of current relapse

Treatment-Related Factors[1,2]

- **Type of prior Txs and prior response**
- **Prior Tx-related toxicity**
- Bone marrow reserve
- Expected efficacy and toxicity of proposed Tx
- Expectations of the patient

Patient-Related Factors[1,2,3]

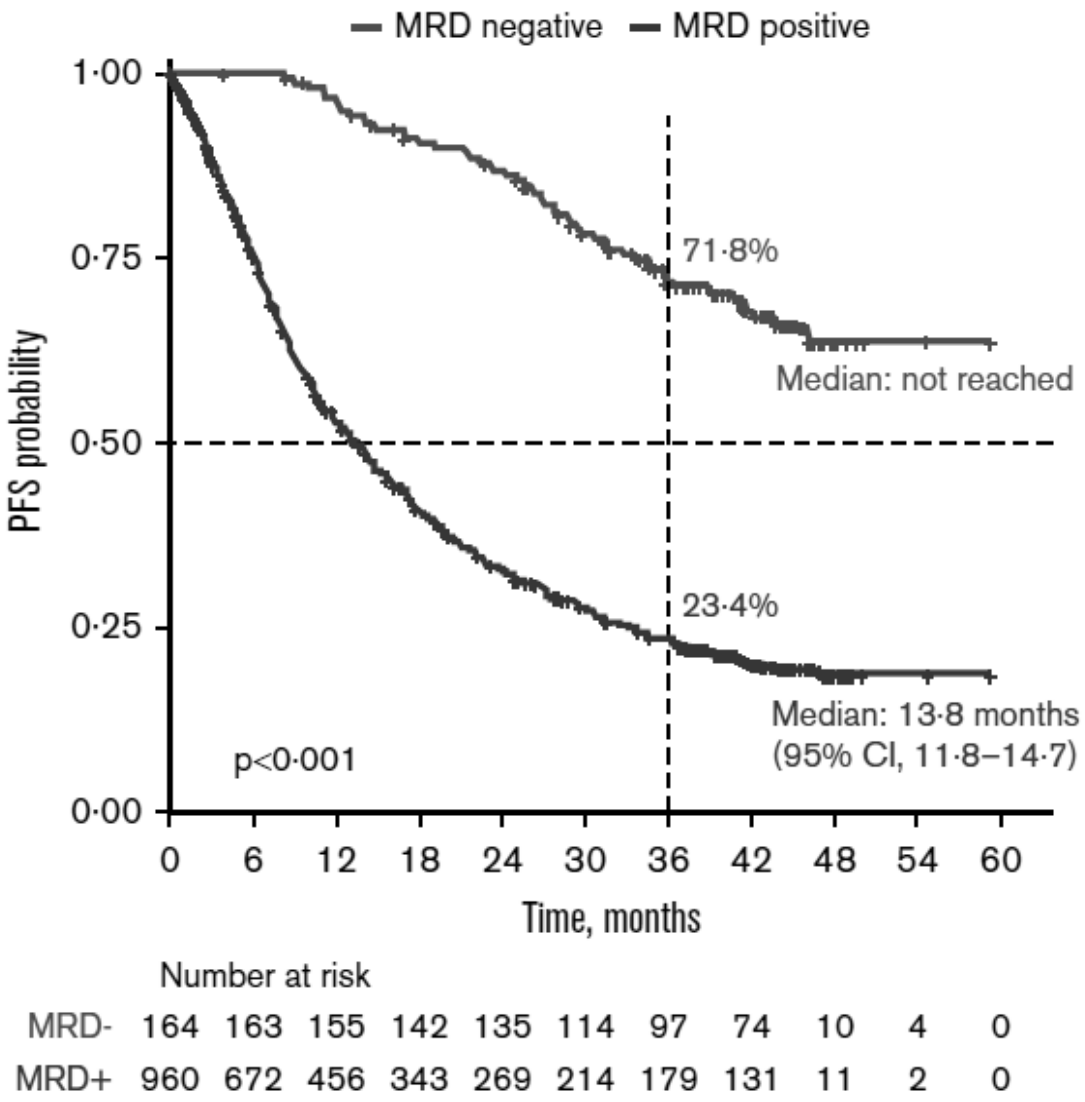
- **Age, frailty, and performance status**
- Comorbidities
- Renal insufficiency/hepatic impairment

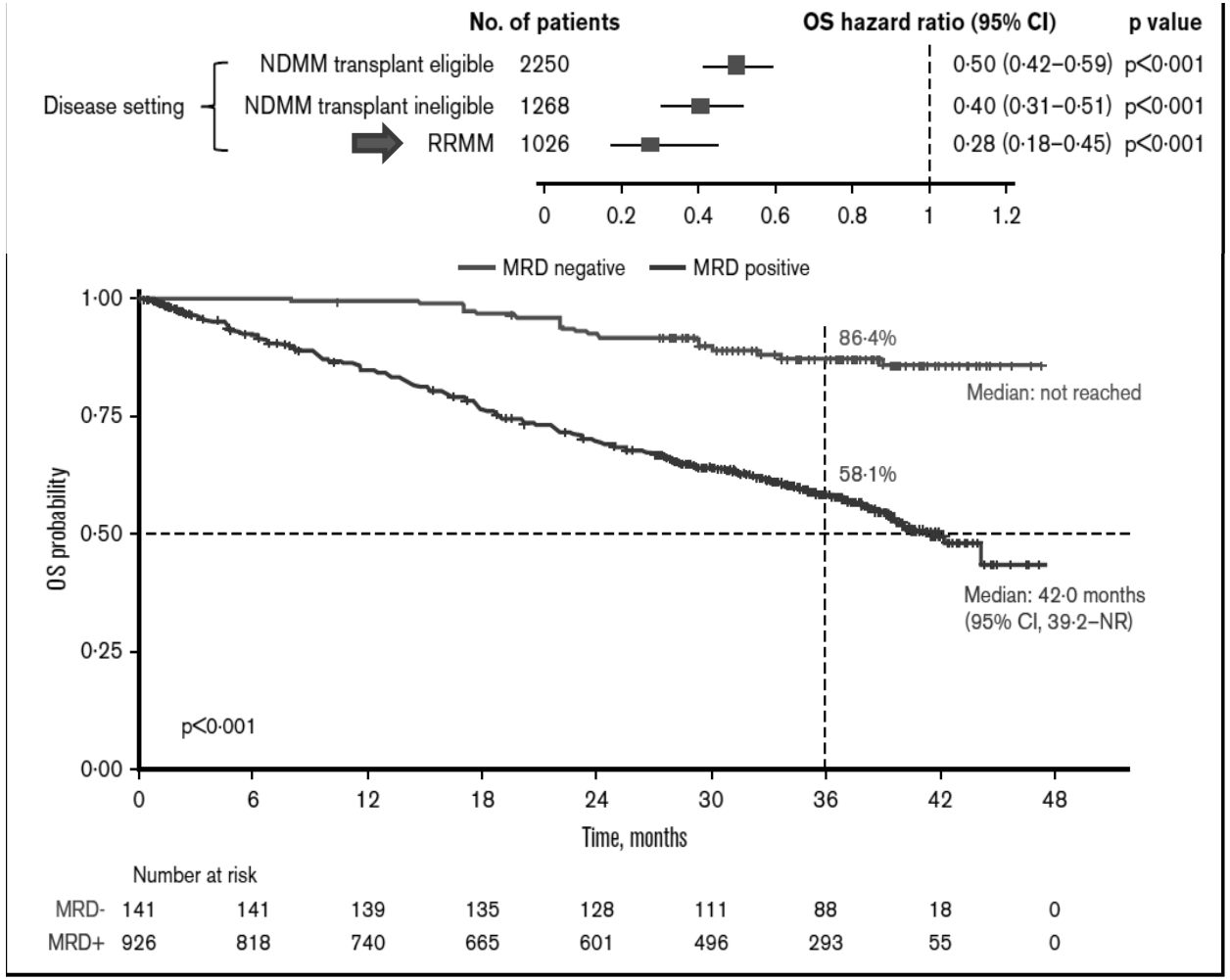
Goals of Treatment

- **Maximize response (MRD negativity) and maintain disease control**[4,5]
- Delay or prevent disease progression
- Balance efficacy with tolerability and QoL[4,5]
- **Prolong PFS and OS**[5]

1. Sonnevald, et al. *Haematologica* 2016;101:396-406. 2. Nooka, et al. *Blood*. 2015;125:3085-3099.
3. Laubach, et al. *Leukemia.* 2016;30:1005-1017. 4. Mohty B, et al. *Leukemia* 2012;26:73-85.
5. Pratt G, et al. *Br J Haematol*. 2014;167:131-133.

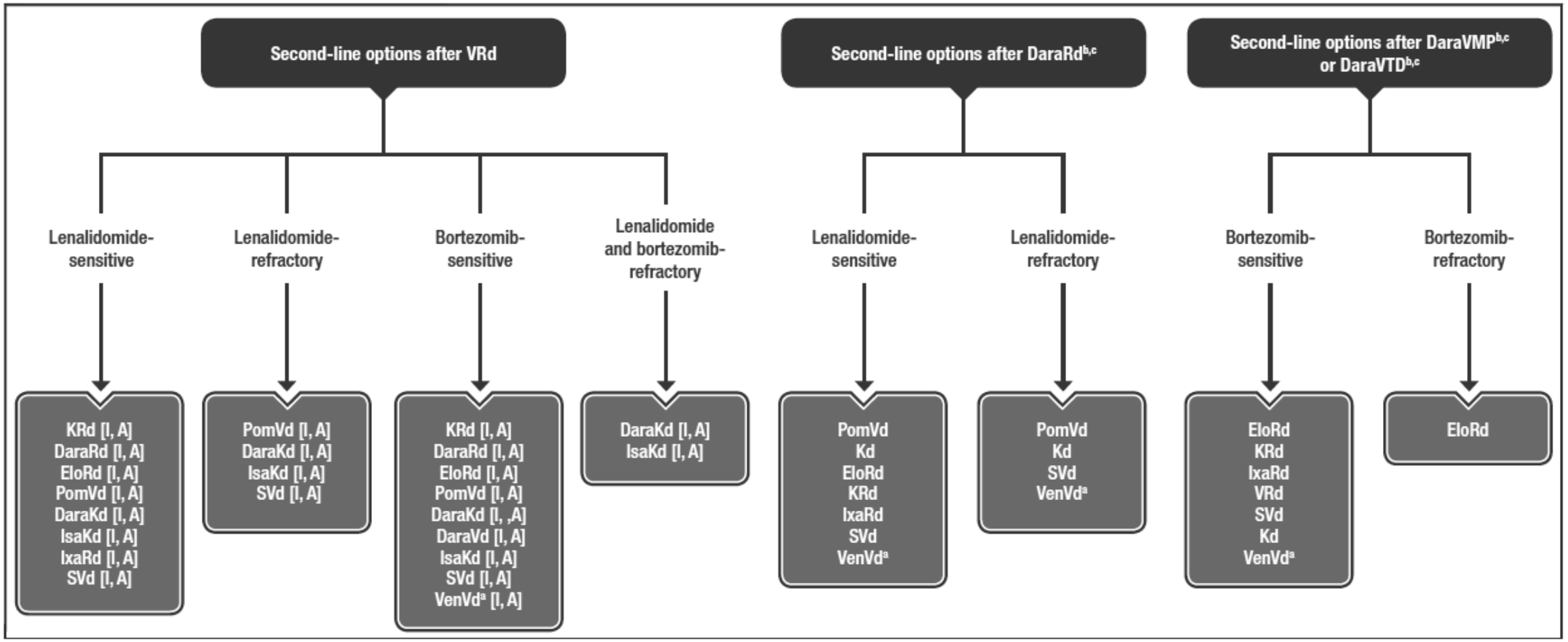
MRD negativity Increases PFS and OS in RRMM patients





Munshi NS, et al. Blood Adv. 2020 Dec 8;4(23):5988-5999.

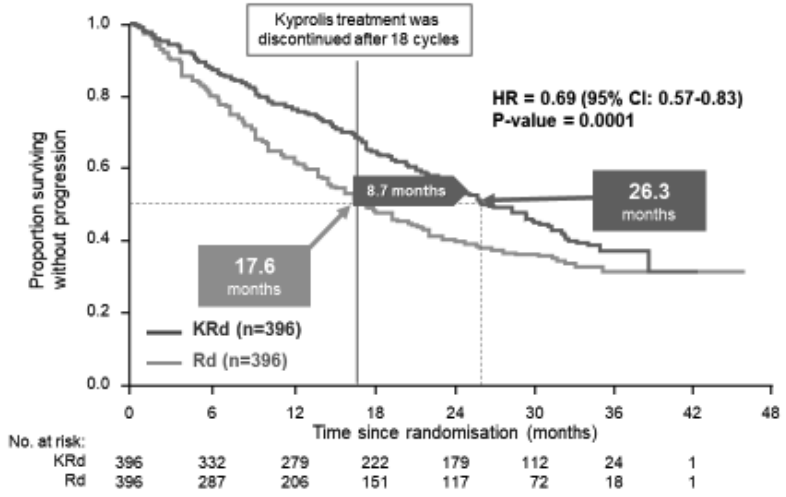
ESMO 2021 recommendations for first relapse



Dimopoulos MA, et al. Ann Oncol 2021;32(3):309-322/Hemasphere 2021;5(2):e528.

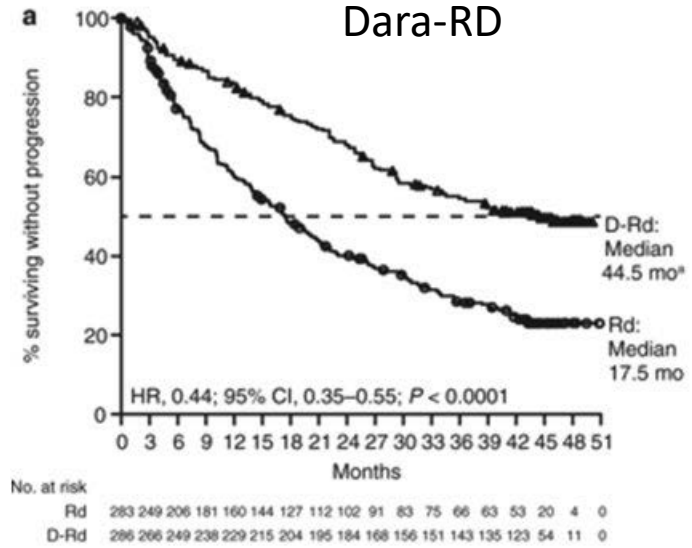
For lenalidomide naïve or sensitive patients

KRD



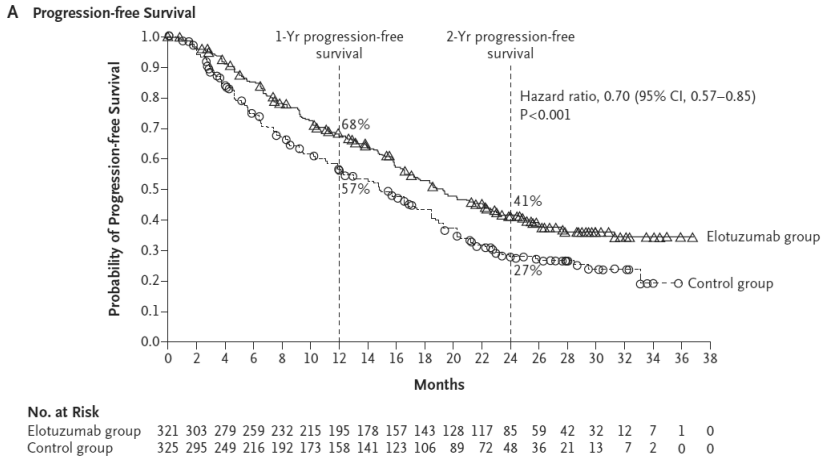
Stewart AK, et al. N Engl J Med 2015;372:142-52.

Dara-RD



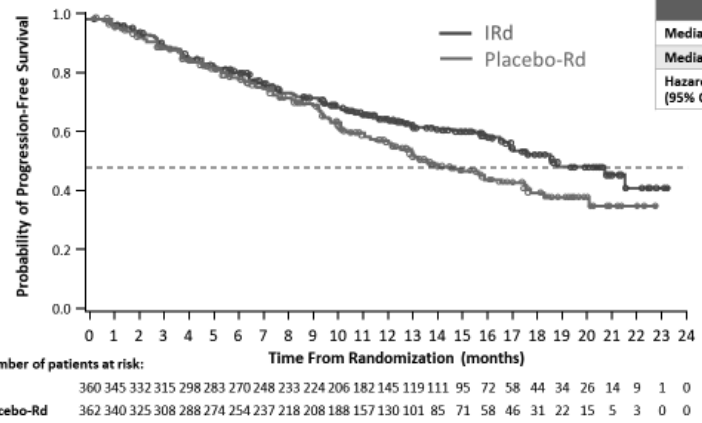
Bahlis NJ, et al. Leukemia 2020;34:1875-1884.

Elo-RD



Lonial S and Dimopoulos MA, et al. N Engl J Med 2015;373:621-31

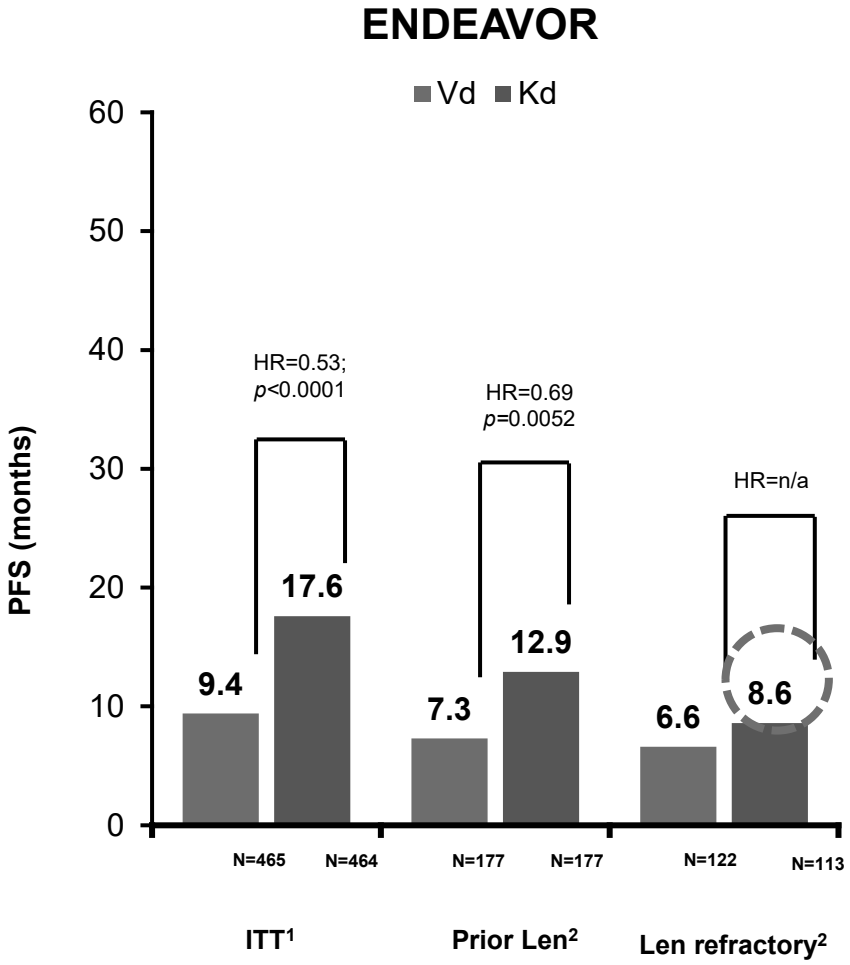
Ixa-RD



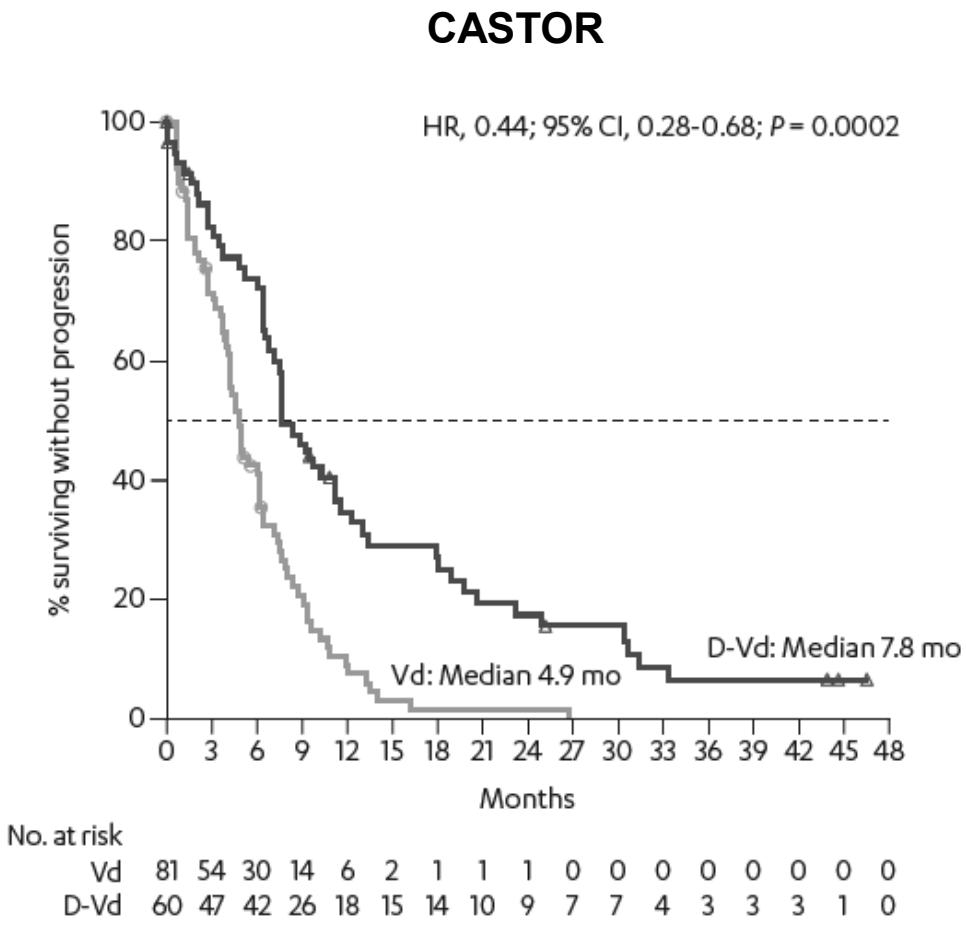
	IRd (n = 360)	Rd (n = 360)
Median follow-up, months	~ 15	
Median PFS, months	20.6	14.7
Hazard ratio (95% CI)	0.74 (0.59–0.94) Log-rank test P = 0.01	

Moreau P, et al. N Engl J Med. 2016;374:1621-1634.

Refractoriness to Lenalidomide - ENDEAVOR & CASTOR: PFS

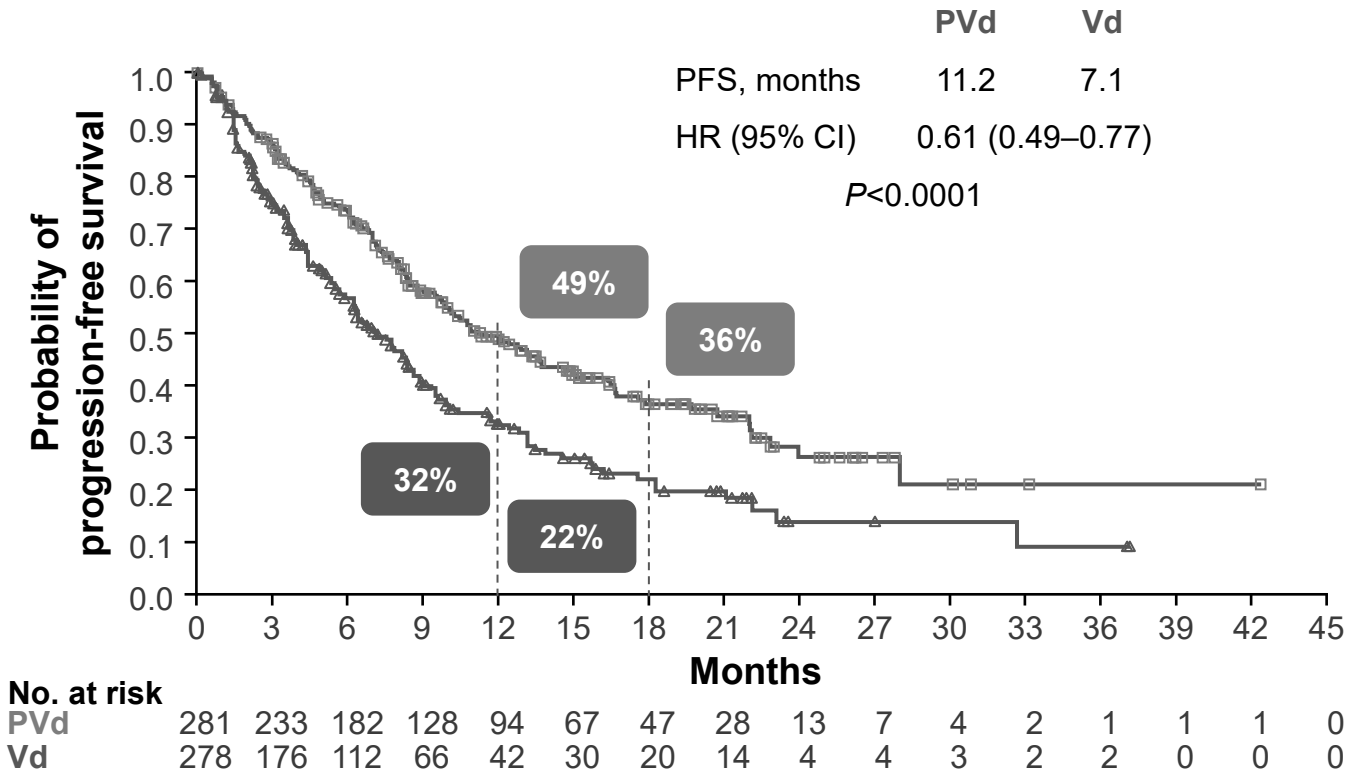


Adapted by Moreau P, et al. Leukemia. 2017;31:115-22



Spencer A, et al. Haematologica. 2018;103:2079-2087

Optimismm: PomVd offers PFS advantage over Vd



PFS by LEN-refractoriness

	PVd	Vd
LEN-refractory*		
n/N	120/200	118/191
Median PFS, months	9.53	5.59
HR (95% CI) *P*-value	0.65 (0.50–0.84) <0.001	
LEN-nonrefractory		
n/N	34/81	44/87
Median PFS, months	22.01	11.63
HR (95% CI) *P*-value	0.48 (0.30–0.75) 0.001	

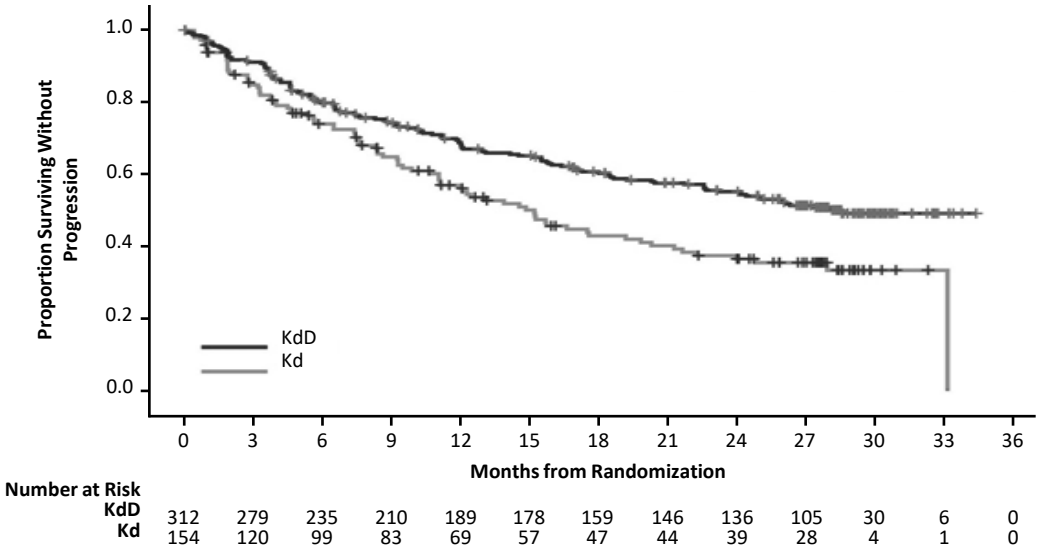
Richardson PG, et al. Lancet Oncol 2019;20:781–94.

Summary of Studies for anti-CD38 naïve – lenalidomide refractory patients: PI combinations with MoAbs

	CASTOR		CANDOR		IKEMA	
	D-Vd	Vd	Kd	Kd-D (N=99)	Kd	Isa-Kd (N=57)
mFU, months[c]	40.0		16.9		20.7	
mPFS, months	**7.8**	**4.9**	**15.2**	**28.6**	**19.15**	**NR**
PFS HR (95% CI) p-value	**0.44 (0.28-0.68) p=0.0002**		**0.59 (0.45-0.78)**		**0.531 (0.318-0.889)**	
ORR, %	77	49	75	84	82.9	86.6
≥VGPR	45	10	49	69	56.1	72.6
≥CR	16	4	10	29	27.6	39.7
MRD-neg rate, %	8	0	4	18	13	29.6

NR: not reported

CANDOR: Better PFS with KdD vs Kd

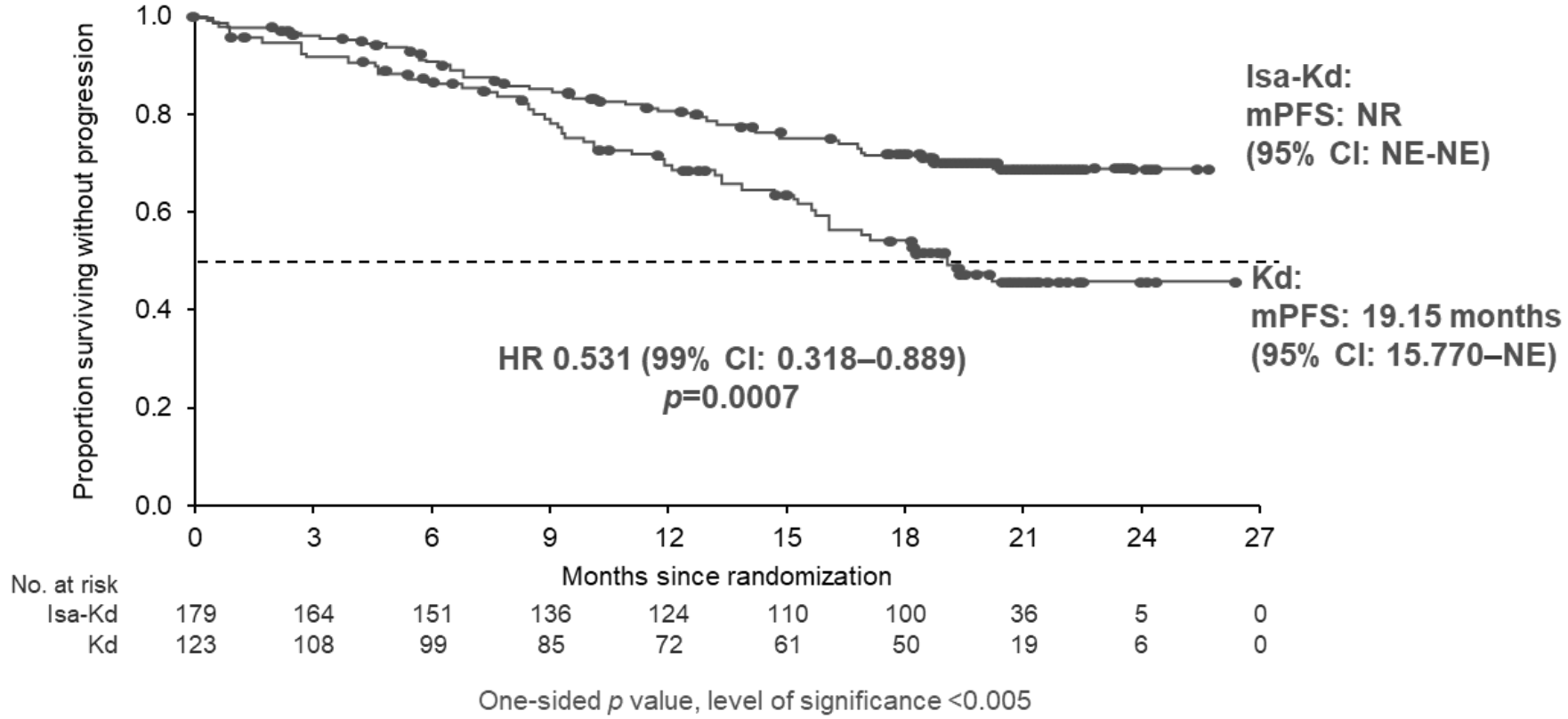


	KdD (n = 312)	Kd (n = 154)
Median treatment duration, months	18.3	9.3
Median PFS follow-up, months	27.8	27.0
Median PFS by ORCA, months	**28.6**	**15.2**
HR (KdD/Kd) (95% CI)	**0.59 (0.45–0.78)**	

Subgroup	KdD (n = 312) Events/ Patients	KdD (n = 312) Median PFS, months	Kd (n = 154) Events/ Patients	Kd (n = 154) Median PFS, months	Hazard ratio for KdD vs Kd (95% CI)
Number of prior lines of therapy					
1	52/133	**NE**	30/67	**21.3**	0.66 (0.42, 1.04)
≥2	88/179	**24.2**	55/87	**12.5**	0.55 (0.39, 0.78)
Refractory to PI*					
No	86/212	**NE**	50/99	**16.6**	0.58 (0.40, 0.82)
Yes	54/100	**13.1**	35/55	**8.7**	0.65 (0.42, 1.00)
Prior lenalidomide exposure					
No	83/189	**NE**	38/80	**21.3**	0.64 (0.43, 0.95)
Yes	57/123	**25.9**	47/74	**11.1**	0.49 (0.33, 0.74)
Refractory to lenalidomide					
No	94/213	**28.6**	50/99	**19.9**	0.63 (0.44, 0.90)
Yes	46/99	**28.1**	35/55	**11.1**	0.46 (0.28, 0.73)

Dimopoulos et al., ASH 2020: Abstract 2325 (poster presentation)

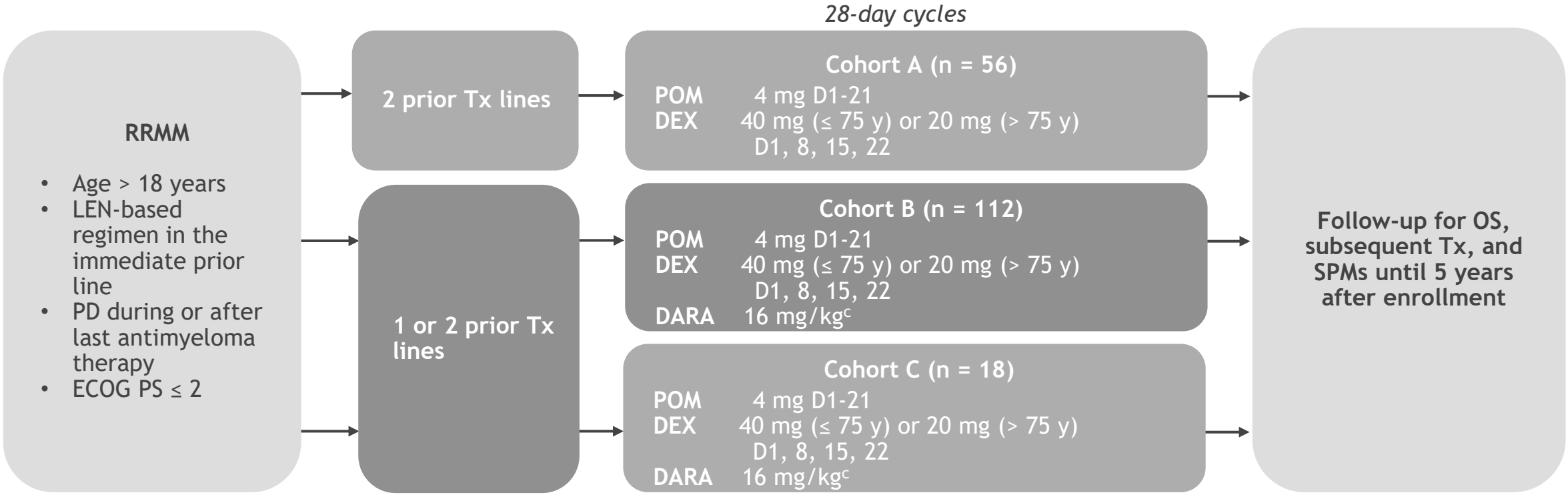
IKEMA: IsaKd vs Kd - Interim PFS analysis



- The interim PFS analysis showed overwhelming efficacy of Isa-Kd compared with Kd, with a hazard ratio of 0.531
- At the time of analysis, overall survival data were immature

Moreau P, et al. Lancet. 2021 Jun 19;397(10292):2361-2371

DaraPomDex is another option for second line therapy in len refractory patients: MM-014 trial



- **Primary endpoint:** ORR by mIMWG criteria
- **Secondary endpoints:** PFS, OS, DOR, TTR, TTP, safety
- **Key exploratory endpoints for cohort B:** pharmacodynamic and mechanistic biomarkers of POM+DEX+DARA; QOL by EQ-5D

Data cutoff date: March 24, 2020

Median follow-up: 28.4 months

NCT01946477

Siegel DS, et al. ASH 2020. Abstract 2314.

MM-014-Cohort B: Baseline patient and disease characteristics

Characteristic	ITT Population (N = 112)
Age, median (range), years	66.5 (39.0–83.0)
> 65 years, n (%)	62 (55.4)
Male, n (%)	76 (67.9)
Time since diagnosis, median (range), years	3.4 (0.5–11.6)
ECOG PS, n (%)	
0	44 (39.3)
1	67 (59.8)
2	1 (0.9)
R-ISS stage (calculated), n (%)	
I	30 (26.8)
II	53 (47.3)
III	8 (7.1)

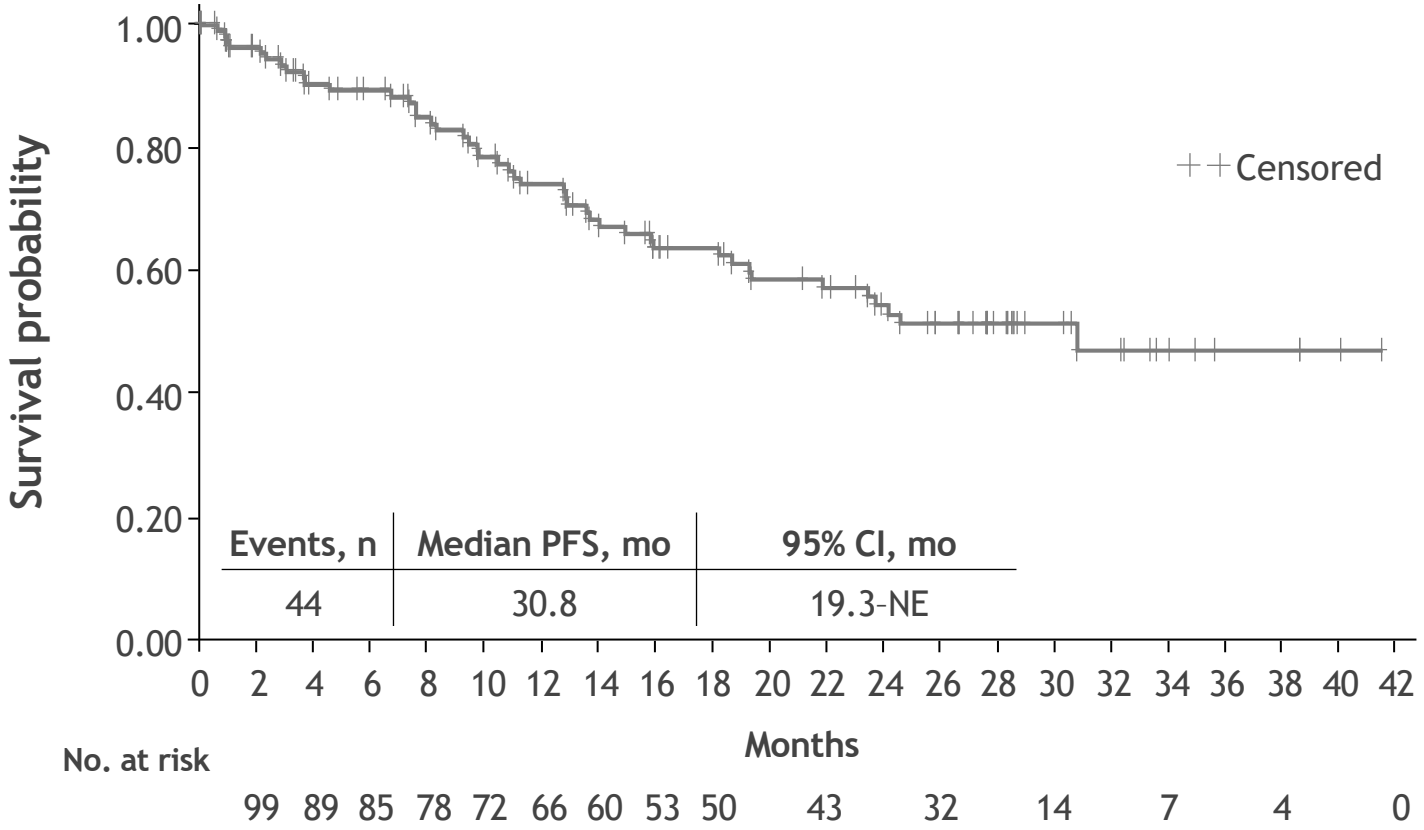
Prior treatment	ITT population (N = 112)
No. of prior LOT, median (range)	1 (1–2)
One prior LOT, n (%)	70 (62.5)
Two prior LOT, n (%)	42 (37.5)
Prior therapies, n (%)	
LEN	112 (100)
BORT	87 (77.7)
SCT	78 (69.6)
CFZ	11 (9.8)
IXA	4 (3.6)
Refractory to LEN, n (%)	84 (75.0)
Duration of most recent prior LEN-containing regimen, median (range), months	23.9 (0.4–116.8)
Most recent prior LEN dose, n (%)	
25 mg	35 (31.3)
20 mg	4 (3.6)
15 mg	18 (16.1)
≤ 10 mg	54 (48.2)
Missing	1 (0.9)

BORT, bortezomib; CFZ, carfilzomib; ITT, intention to treat; IXA, ixazomib; LOT, line(s) of treatment; PS, performance status; R-ISS, Revised International Staging System; SCT, stem cell transplant.

Siegel DS, et al. ASH 2020. Abstract 2314.

MM-014-Cohort B: PFS

- Median PFS was 30.8 months (95% CI, 19.3 months to NE)
  - LEN-refractory disease: median PFS, 23.7 months (95% CI, 14.0 months to NE)
  - LEN-relapsed disease: median PFS, NE (95% CI, 18.2 months to NE)



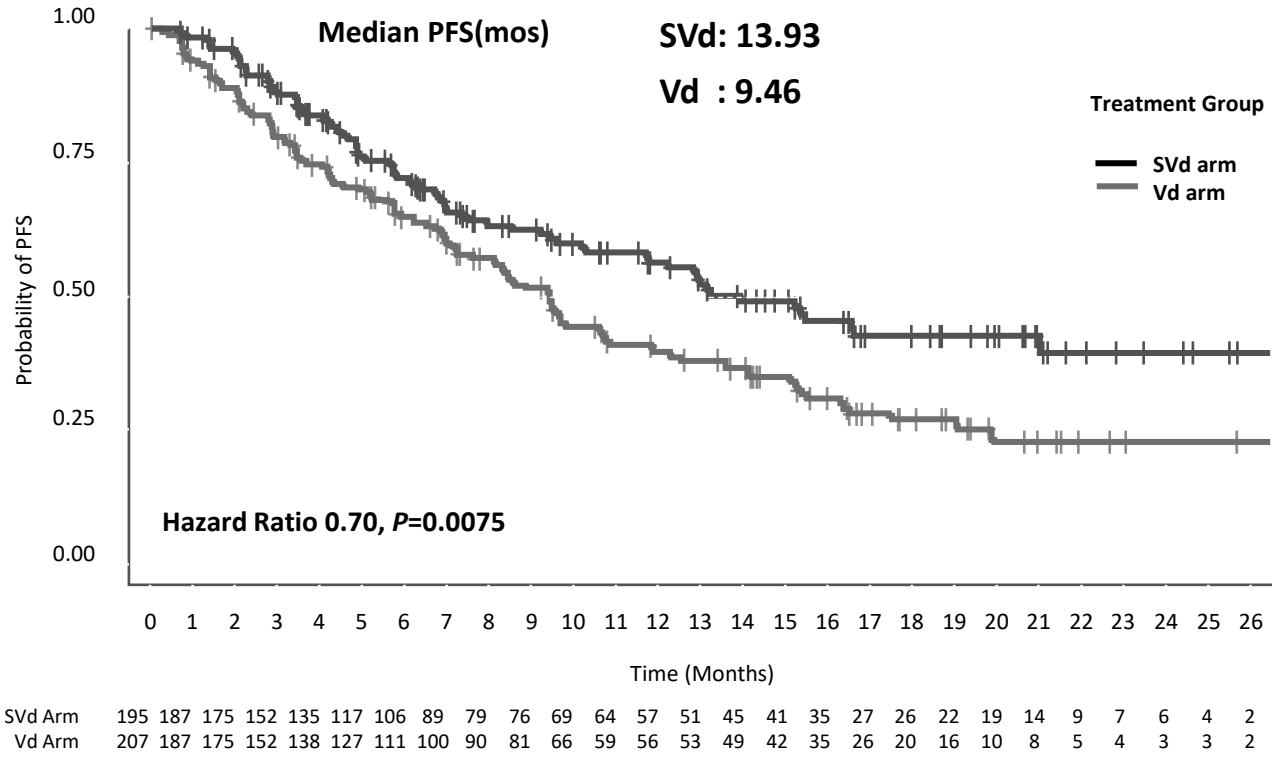
[a]OS data not yet mature at the time of this analysis.
ITT, intention to treat; LEN, lenalidomide; NE, not estimable; OS, overall survival; PFS, progression-free survival.

Siegel DS, et al. ASH 2020. Abstract 2314.

Possible (but weaker) treatment option for Anti-CD38 AND lenalidomide pretreated/refractory patients: Sel-VD

BOSTON Trial: Selinexor-Vd vs Vd

Median 1 prior line; Prior Daratumumab:5.5%; Prior lenalidomide: 39.5%



Intention-to-treat (ITT) population N=402, Data cut-off February 18, 2020
*HR=Hazard Ratio 95% CI=0.53–0.93 one-sided *P* value

Meletios A. Dimopoulos ASCO 2020

Summary/Conclusions

- **Patients who had received a bortezomib-based therapy upfront without lenalidomide or daratumumab should receive an Rd-based regimen**, i.e. KRd, Dara-Rd, IRd or EloRd [I, A]. Dara-Rd provides the best PFS for these patients, while only KRd and EloRd showed an OS benefit over Rd to date.
- **Patients who are refractory to lenalidomide upfront could receive either PomVD, DaraKd, IsaKd or Dara-Vd [I, A].** DaraPomDex is another effective regimen but data from phase 3 studies at second line are limited.
- SelVd is another option for patients who have failed lenalidomide and are sensitive to PIs [I, A], if available.
- Second-line ASCT can be performed in patients who received primary therapy that included an ASCT followed by lenalidomide maintenance and had an initial remission duration of ≥36 months (panel consensus).

Dimopoulos MA, et al. Ann Oncol 2021;32(3):309-322/Hemasphere 2021;5(2):e528.

THANK YOU