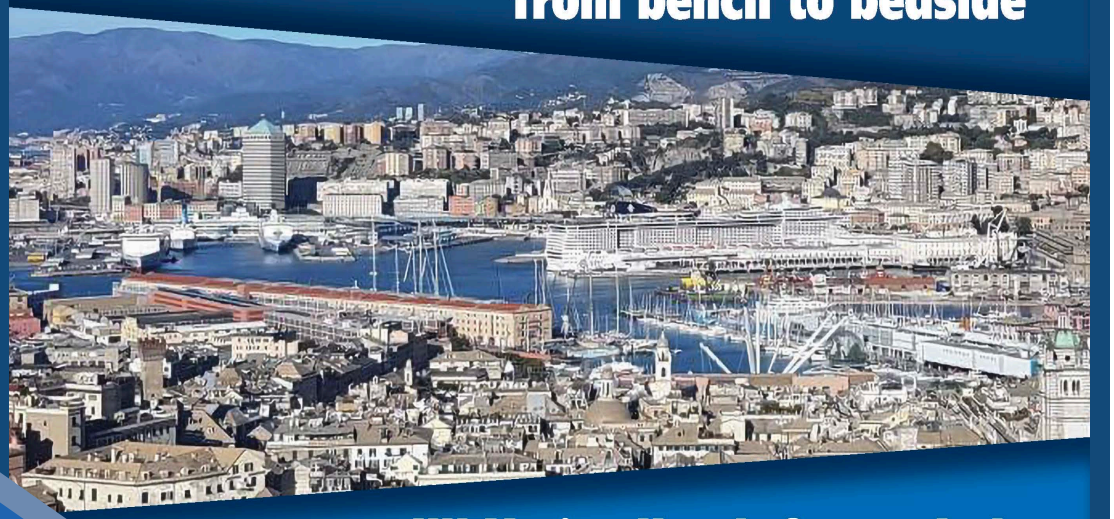
2023 Multiple Myeloma updates:
from bench to bedside



NH Marina Hotel, Genoa, Italy
20-21 November 2023

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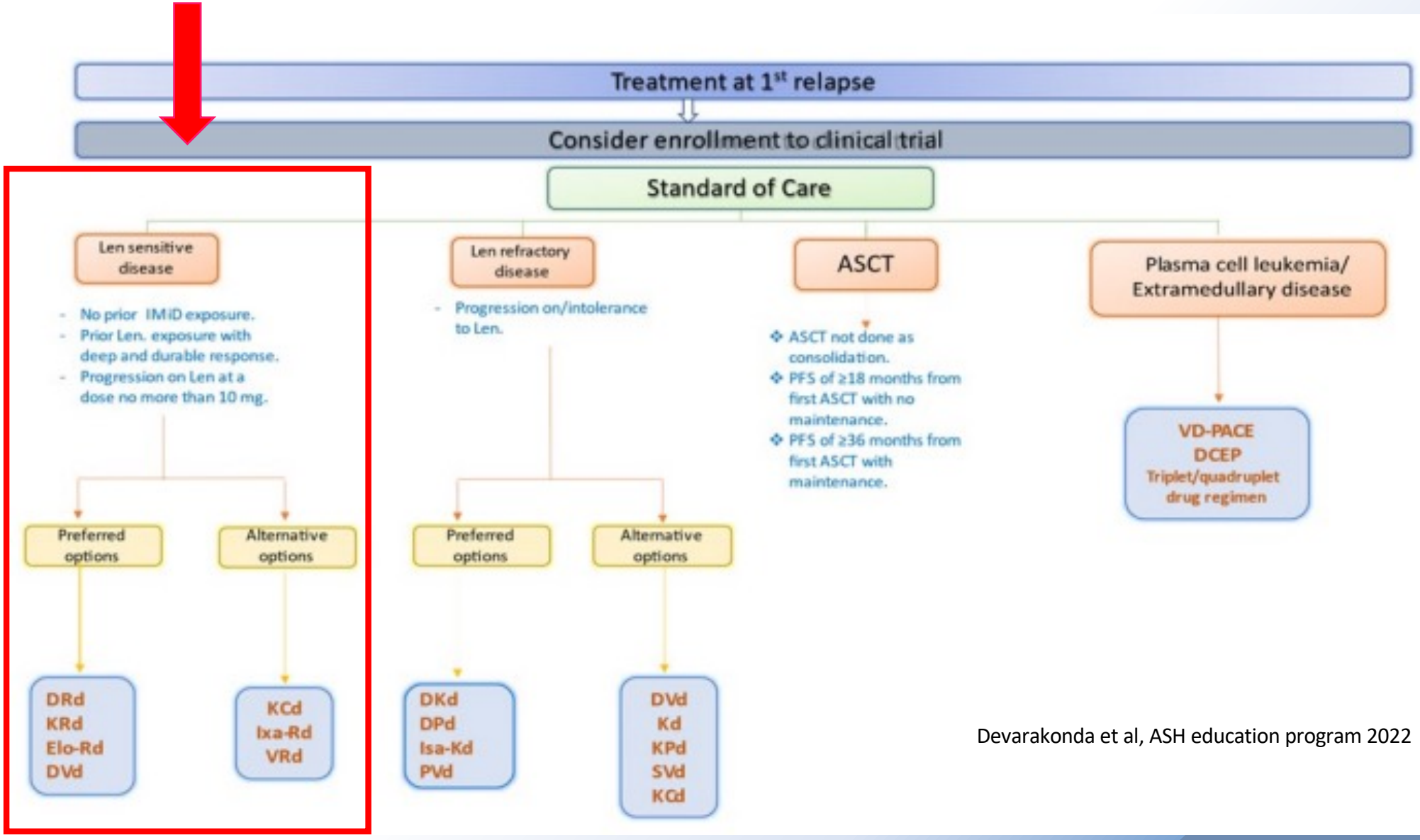
Pavia

Lenalidomide-based triplet regimens in first relapsed Multiple Myeloma patients:real-world evidence

Silvia Mangiacavalli MD
COI Disclosure

Company name	Research support	Employee	Consultant	Stockholder	Speakers bureau	Advisory board	Other
AMGEN					x	x	
BMS					x	x	
GSK					x	x	
JANSSEN					x	x	
SANOFI					x	x	
TAKEDA					x	x	

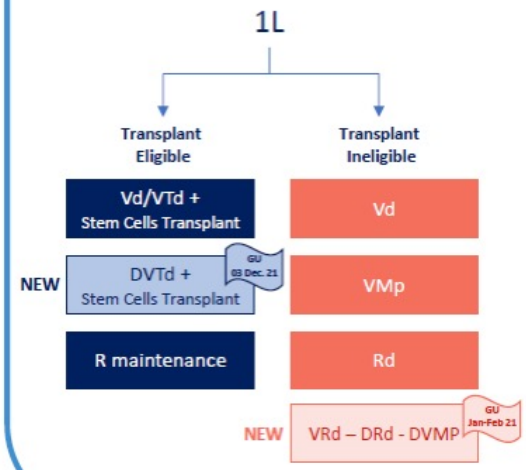
Treatment algorithm for Myeloma at first relapse
Focus on Rd-based triplets



Devarakonda et al, ASH education program 2022

Treatment algorithm for Myeloma at first relapse

Today reimbursed treatments in 1L



Median time to relapse from Dara combo regimens

Gazzette Ufficiali/mPFS Principali Trattamenti Approvati in Italia

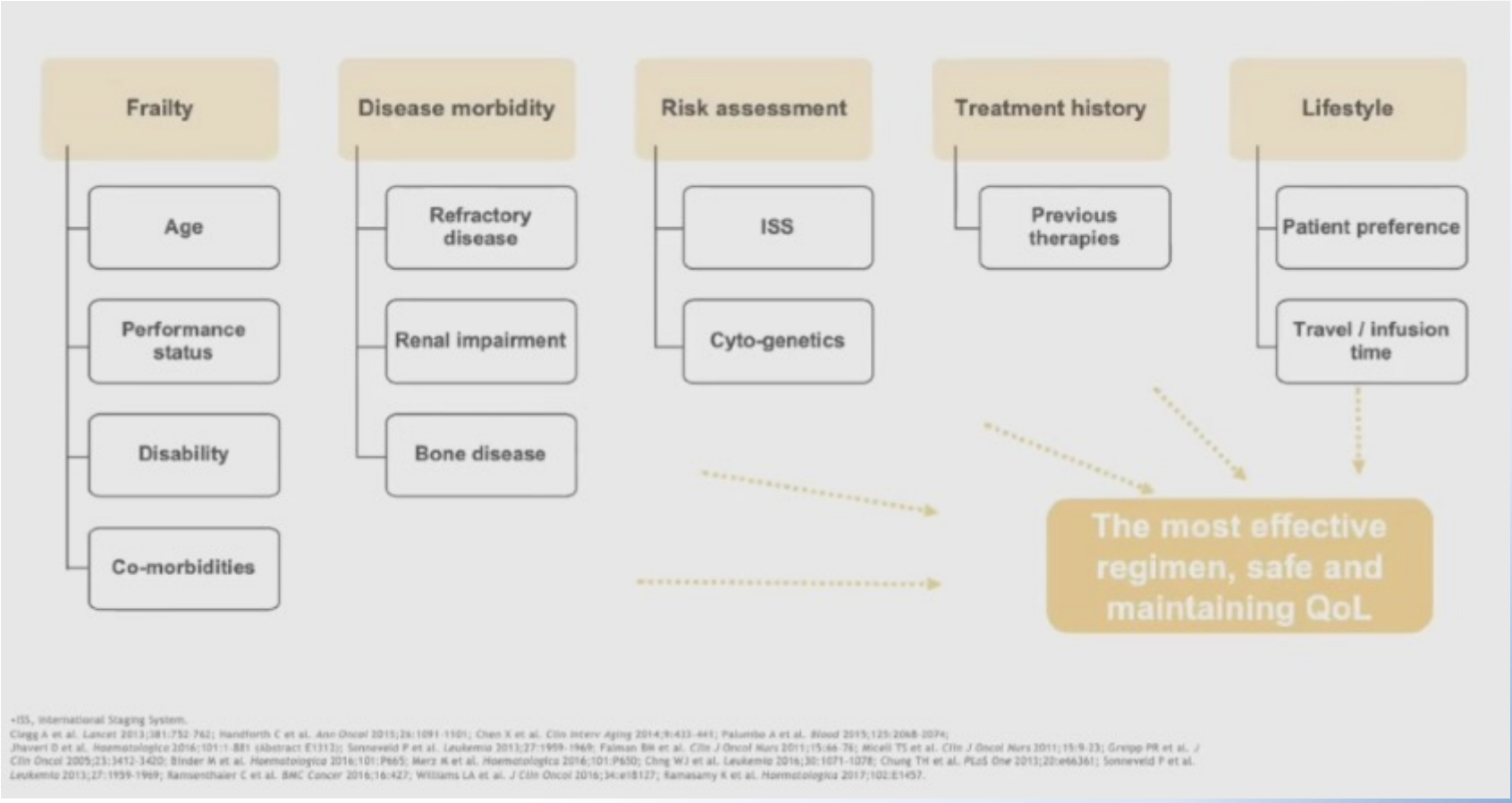
1L	GU + 3 mesi	mPFS ITT	Timing mediano recidive
VRd	Feb→Mag 2021 [1]	43 [4]	> 2024
DVMP	Gen→Apr 2021 [2]	36,4 [5]	> 2024
DRd	Gen→Apr 2021 [2]	NR [6]	> 2024
Len maint	Mag→Ago 2018 [3]	46,3 [7] (IFM)	Giu 2022

1.https://www.gazzettaufficiale.it/eli/gu/2021/02/20/43/sg/pdf; 2.https://www.gazzettaufficiale.it/eli/gu/2021/01/14/10/sg/pdf; 3.https://www.gazzettaufficiale.it/eli/gu/2018/05/24/119/sg/pdf

4.Durie BGM et al, Lancet. 2017; 389:519–527; 5.Mateos MV et al, Lancet. 2020; 395:132–141; 6.Facon T et al, N Engl J Med. 2019; 380:2104–2115; 7Attal M et al, N Engl J Med. 2012; 366:1782–1791 – RCP Revlimid

➢ **1L patients currently treated with new therapeutic options will relapse from these newly approved regimens not before Jun 2024, most of them after 2025**

Many factors impact on treatment choice at relapse



•ISS, International Staging System.

Clegg A et al. *Lancet* 2013;381:752-762; Handforth C et al. *Ann Oncol* 2015;26:1091-1101; Chen X et al. *Clin Interv Aging* 2014;9:433-441; Palumbo A et al. *Blood* 2015;125:2068-2074; Jhaveri D et al. *Haematologica* 2016;101:1-881 (Abstract E1312); Sonneveld P et al. *Leukemia* 2013;27:1959-1969; Faiman BM et al. *Clin J Oncol Nurs* 2011;15:66-76; Micell TS et al. *Clin J Oncol Nurs* 2011;15:9-23; Greipp PR et al. *J Clin Oncol* 2005;23:3412-3420; Binder M et al. *Haematologica* 2016;101:P665; Merz M et al. *Haematologica* 2016;101:P630; Ching WJ et al. *Leukemia* 2016;30:1071-1078; Chung TH et al. *PLoS One* 2013;20:e66361; Sonneveld P et al. *Leukemia* 2013;27:1959-1969; Kansenthaler C et al. *BMC Cancer* 2016;16:427; Williams LA et al. *J Clin Oncol* 2016;34:e18127; Ramasamy K et al. *Haematologica* 2017;102:E1457.

Treatment algorithm for Myeloma at 1^ relapse

IMiDs based combinations

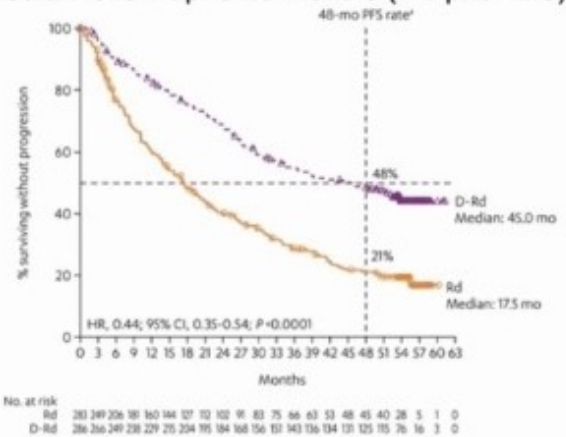
DaraRd
PFS: 44.5 m, HR: 0.44
CR 56%

KRd
PFS: 26.3 m, HR: 0.69
CR 32%

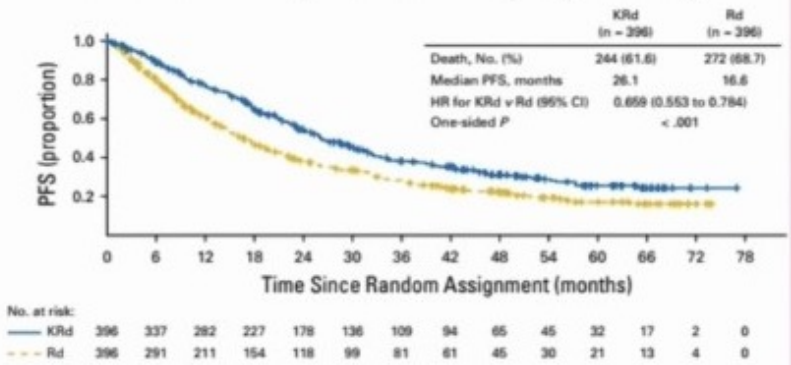
EloRd
PFS: 19.4 m, HR: 0.71
CR 5%

IxaRd
PFS: 20.6 m, HR: 0.74
CR 12%

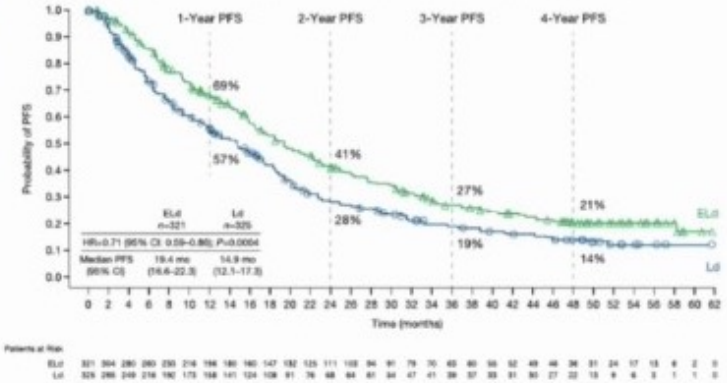
POLLUX: DRd > Rd (response, PFS, PFS2)
Median follow-up: 54.8 months (≥ 1 prior line)



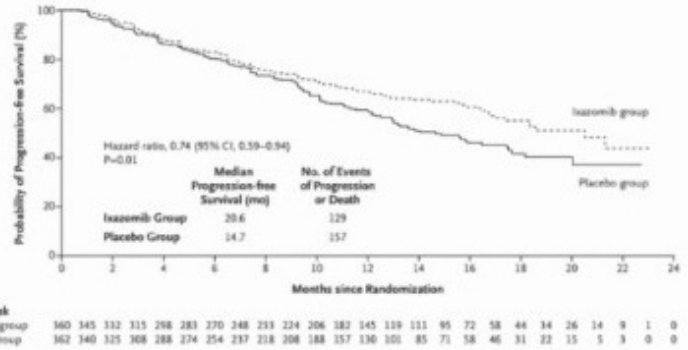
ASPIRE: KRd > Rd (response, PFS, OS)
Median follow-up: 48.8 months (1-3 prior lines)



ELOQUENT-2: Elo-Rd > Rd (response, PFS, OS)
Median follow-up: 46 months (1-3 prior lines)



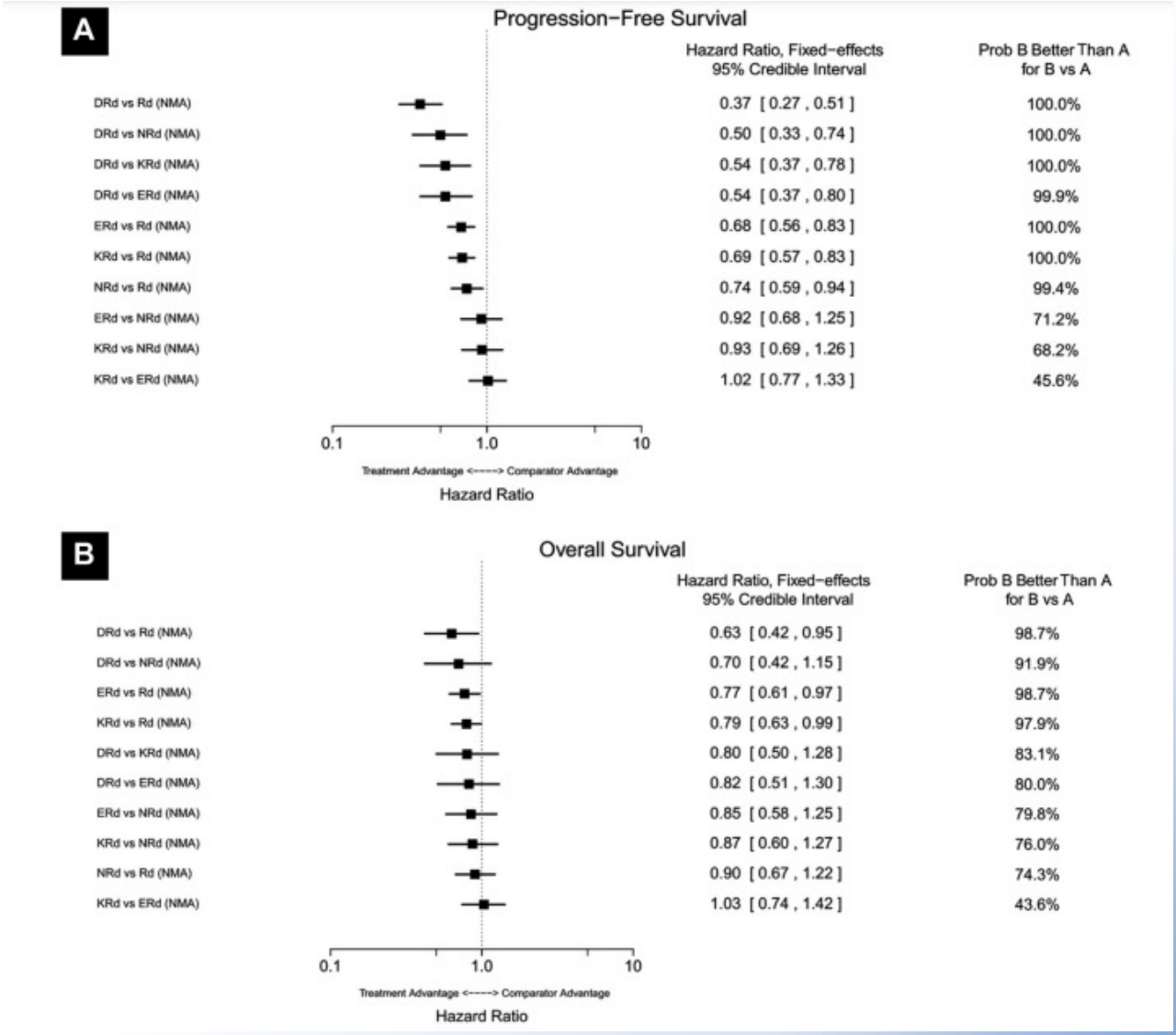
TOURMALINE-MM1: Ixa-Rd > Rd (response, PFS)
Median follow-up: 14.7 months (1-3 prior lines)



CR, complete response; Dara, daratumumab; d, dexamethasone; Elo, elotuzumab; IMiD, immunomodulatory drug; Ixa, ixazomib; K, carfilzomib; OS, overall survival; PFS, progression-free survival; R, lenalidomide

Bahlis N et al. Leukemia 2020; 34(7):1875-1884; Kaufman J et al. ASH 2019;abstract 1866 (poster presentation); Dimopoulos M et al. N Eng J Med 2016; 375:1319-1331; Lonial S et al. N Eng J Med 2015; 373:621-631; Dimopoulos M et al. Cancer 2018; 124(20):4032-4043; Siegel D et al J Clin Oncol 2018; 36(8):728-734; Stewart K et al. N Eng J Med 2015; 372:142-152 Moreau P et al. N Eng J Med 2016; 374:1621-1634

Network meta-analysis comparing Rd based triplets



Dimopoulos et al, Clinical Lymphoma Myeloma, 2018

Efficacy and outcome of Rd triplets at 1^ relapse in RCT

Table 2. Results of phase 3 randomized studies which evaluated regimens for patient with 1 to 3 prior lines of therapy

	Dara-Rd	Rd	K-Rd	Rd	Elo-Rd	Rd	Ixa-Rd	Rd	Kd	Vd	Dara-Vd	Vd	Dara-Kd	Kd	Isa-Kd	Kd	SVd	Vd	Ven-Vd	Vd
Median of prior lines of therapy in the study (range)	1 (1-11)		2 (1-3)		2 (1-4)		1 (1-3)		2 (1-3)		2 (1-10)		2 (1-3)		1 (1-3)		1 (1-3)		2 (1-3)	
Exclusion per prior therapy	Lenalidomide-resistant		Lenalidomide-resistant and bortezomib-resistant if at last line		Lenalidomide-resistant		Lenalidomide- or bortezomib-resistant		Bortezomib-resistant		Bortezomib-resistant		previous resistance to carfilzomib, or refractory to anti-CD38		previous treatment with carfilzomib, or refractory to anti-CD38		Bortezomib-resistant		Bortezomib-resistant	
ITT population	283	286	396	396	321	325	360	362	464	465	251	247	312	154	179	123	195	207	194	97
PFS	46	17.5	26.3	17.6	19.4	14.9	20.6	14.7	18.7	9.4	16.7	7.1	NE	15.8	NE	19.1	13.9	9.4	22.4	11.5
HR (95% CI)	0.42 (0.33-0.52)		0.69 (0.57-0.83)		0.71 (0.59-0.86)		0.74 (0.59-0.94)		0.53 (0.44-0.65)		0.31 (0.25-0.39)		0.63 (0.46-0.85)		0.53 (0.32-0.89)		0.70 (0.53-0.93)		0.63 (0.44-0.90)	
1 prior line	149	146	184	157	151	159	212	213	231	229	247	251	144	70	80	55	99	99	91	44
PFS	53.3	19.6	29.6	17.6	NA	NA	20.6	16.6	22.2	10.1	27	7.9					NA	NA	22.4	11.4
HR	0.42 (0.30-0.57)		0.713 (0.532-0.957		0.77 (0.59-1.01)		0.882 (0.65-1.197)		0.447 (0.330-0.606)		0.22 (0.15-0.32)		0.68 (0.40-1.14)		0.589 (0.309-1.123)		0.63 (0.41-0.96)		0.75 (0.45-1.26)	
2-3 prior lines	123	118	212	239	170	166	148	149	232	233	106	107	179	87	99	68	96	108	103	53
PFS	NA	NA	25.8	16.7	NA	NA	NE	12.9	14.9	8.4	NA	NA	NA	NA	NA	NA	NA	NA	NE	14
HR (95% CI)	2 prior lines: 0.39 (0.26-0.58)		0.720 (0.561-0.923)		0.68 (0.53-0.87)		0.58 (0.401-0.838)		0.604 (0.466-0.783)		2 prior lines: 0.46 (0.30-0.72)		0.61 (0.42-0.88)		0.479 (0.294-0.778)		2 prior lines: 0.65 (0.40-1.07)		0.54 (0.33-0.88)	
	3 prior lines: 0.48 (0.25-0.94)										3 prior lines: 0.60 (0.33-1.07)									

The results according to the number of prior lines of therapy are also reported where available.
NA, not available; NE, not estimable/not reached.

Katritis et al, Blood 2022

Median PFS, months	D-Vd	Vd	HR (95% CI); *P* value	D-Rd	Rd	HR (95% CI); *P* value
Early relapse	15.4	9.0	0.51 (0.26-1.00); *P* = 0.0488	36.9	11.7	0.41 (0.26-0.65); *P* = 0.0002
Late relapse	27.7	7.9	0.20 (0.14-0.29); *P* <0.0001	69.3	29.7	0.53 (0.37-0.77); *P* = 0.0007

Spencer et al, ASCO 2022

K-Rd real life

Characteristics	Patients (no. = 197)
Sex—no. of pts (%)	
Male	114 (58)
Female	83 (42)
Age (median—yr [IQR])	63 [56–69]
Distribution—no. of pts (%)	
<75 years	191 (97)
≥75 years	6 (3)
ISS stage—no. of pts (%)[a]	
I	85 (53)
II	28 (18)
III	46 (29)
Cytogenetic risk—no. of pts (%)[b]	
Standard risk	55 (73)
High risk	20 (27)
del(17p)	12 (14)
t(4;14)	14 (18)
t(14;16)	3 (4)
Creatinine clearance <60 ml/min—no. of pts (%)	37 (19)
60–30 ml/min	31 (16)
<30 ml/min	6 (3)
Extramedullary disease—no. of pts (%)	17 (9)
Previous lines of treatment (median—no. [range])	2 [1–8]
1 previous line—no. of pts (%)	86 (44)
2 previous lines—no. of pts (%)	47 (24)
≥3 previous lines—no. of pts (%)	64 (32)
Previous therapies—no. of pts (%)	
Bortezomib	189 (96)
Lenalidomide	89 (45)
ASCT	122 (62)
Disease refractory to bortezomib—no. of pts (%)	
No	162 (82)
Yes	35 (18)
Disease refractory to lenalidomide—no. of pts (%)	
No	153 (78)
Yes	44 (22)

TABLE 4 Multivariate analysis of variables favorably affecting survival outcomes

PFS	HR	95% CI	*p*-value
Response ≥ VGPR	0.163	0.060–0.440	<0.001
No. of prior lines of therapy ≤2	0.410	0.179–0.935	0.034
Standard risk CA[a]	0.425	0.189–0.955	0.038
OS	**HR**	**95% CI**	***p*-value**
Response ≥ VGPR	0.072	0.010–0.514	0.009
Del(17p) negativity	0.098	0.017–0.570	0.010
ISS stage I	0.170	0.030–0.968	0.046

Abbrevations: CA, cytogenetic abnormalities; no, number; VGPR, very good partial response.
[a]Standard risk defined as the absence of t(4;14) and t(14;16) and del (17p).

TABLE 2 Adverse events (all grades and grade ≥ 3)

	No. of patients (%)	
Adverse event	All grades	≥ grade 3
Hematological		
Anemia	131 (66)	14 (7)
Thrombocytopenia	124 (63)	36 (18)
Neutropenia	98 (50)	41 (21)
Non hematological		
Thrombotic events	22 (11)	7 (4)
Gastrointestinal toxicities	33 (17)	3 (1)
Elevated liver function tests	26 (13)	5 (2)
Infections	72 (36)	21 (11)
Skin rash	19 (10)	5 (3)
Of specific interest (cardio-vascular)		
Hypertension	31 (16)	12 (6)
Arrhythmia	12 (6)	1 (0.5)
Heart failure	7 (3)	2 (1)

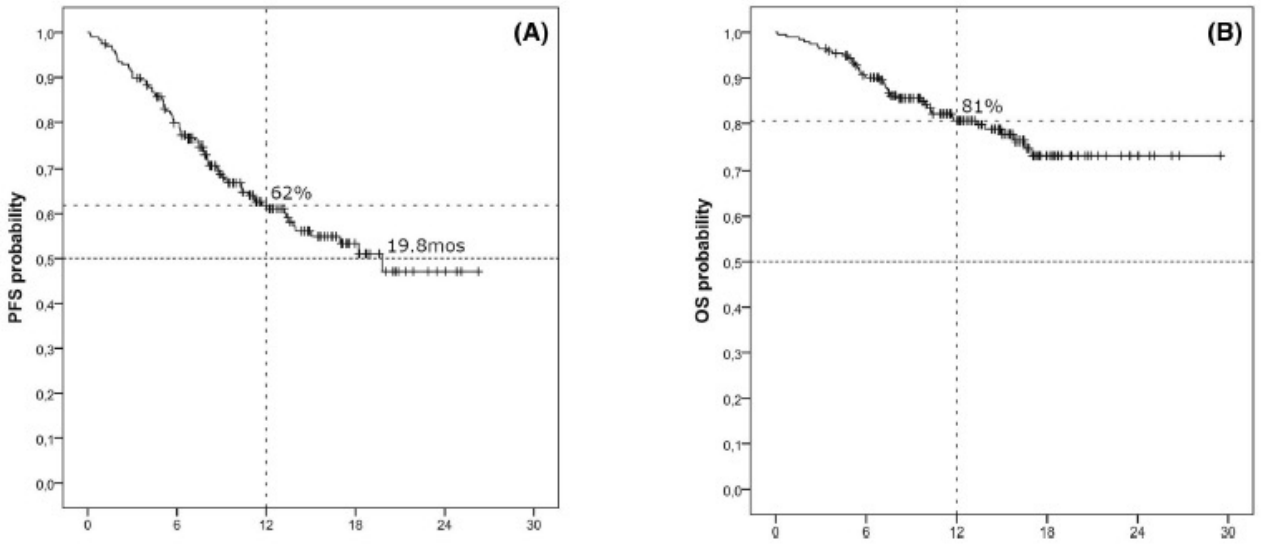


FIGURE 1 Kaplan-Meyer curves of progression free survival (PFS) (A) and overall survival (OS) (B) of the whole series of 197 relapsed and refractory multiple myeloma (RRMM) patients treated with carfilzomib–lenalidomide–dexamethasone (KRd) in a real-life setting

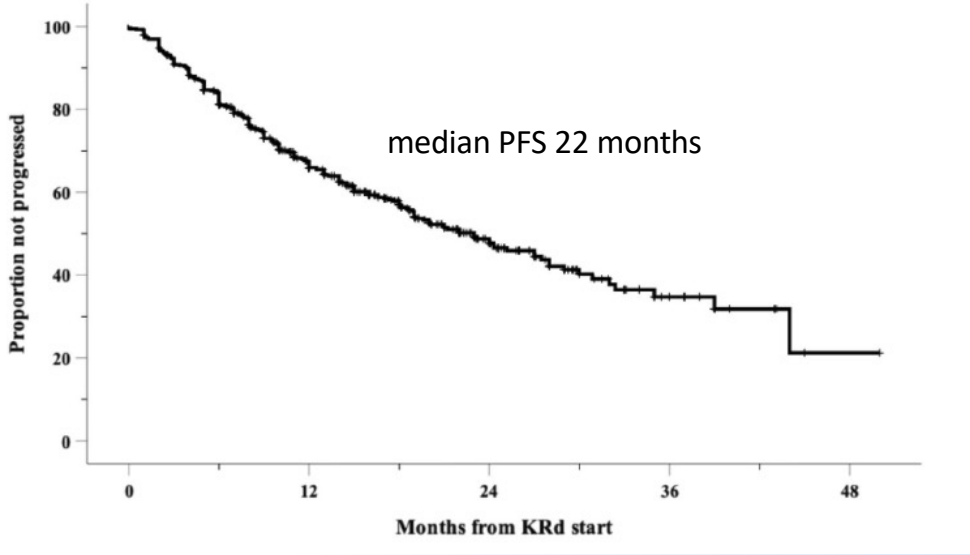
Rocchi et al, Hematol Oncol 2021

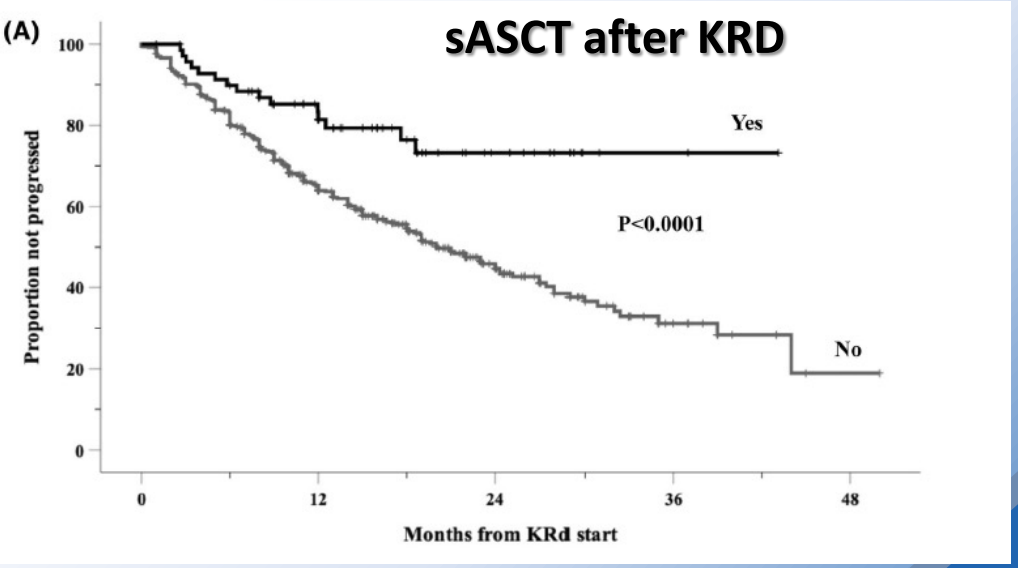
K-Rd real life

TABLE 1 Clinical features of 600 relapse and refractory multiple myeloma (RRMM) patients treated with carfilzomib, lenalidomide, and dexamethasone (KRd) as salvage regimen in a real-life approach. Data were collected at the time of therapy start

Median age (range) yrs	64 (33–85)
Gender	
Male, n (%)	295 (49.2)
Female n (%)	305 (50.8)
Serum isotype	
IgG n (%)	333 (55.5)
IgA n (%)	141 (23.5)
IgM n (%)	1 (0.2)
IgD n (%)	8 (1.3)
Non-secretory n (%)	4 (0.7)
Micromolecular n (%)	113 (18.8)
Creatinine clearance	
≥30 ml/min	551 (91.8)
<30 ml/min	49 (8.2)
ISS (n = 559, 93.1%)	
I n (%)	219 (39.2)
II n (%)	159 (28.4)
III n (%)	181 (32.4)
FISH analysis available (n = 231, 38.5%)	
Standard risk n (%)	174 (75.3)
High risk n (%)	57 (24.7)
LDH (n = 478, 79.6%)	
Normal n (%)	207 (43.3)
Elevated n (%)	271 (56.7)
Previous lines of treatment (median – n [range])	2 (1–11)
1 line	297 (49.5)
2 lines	132 (22)
3 lines	80 (13.3)
≥4 lines	91 (15.2)
Previous exposure to lenalidomide n (%)	218 (36.3)
Previous ASCT (autologous stem cell transplant) n (%)	
Yes	267 (44.5)
No	333 (55.5)

Abbreviation: ISS, International staging system.





Martino et al, Hematol Oncol 2022

K-Rd real life

TABLE 3 Univariate and multivariate analyses of PFS

	N	Univariate			Multivariate model 1		Multivariate model 2	
		PFS @ 24 months	HR (%95 CI)	p value	HR (%95 CI)	p value	HR (%95 CI)	p value
Age, (years)								
<65	313	52.7	1.34	**0.019**	1.22	0.13	1.16	0.45
≥65	287	42.4	(1.05–1.72)		(0.95–1.58)		(0.79–1,72)	
Gender								
Female	295	52.7	1.28	**0.046**	1.35	**0.022**	1.35	0.14
Male	305	41.6	(1.01–1.64)		(1.04–1.74)		(0.9–2.0)	
ISS (N = 559)								
I-II	378	51.2	1.73	**<0.0001**	1.71	**<0.0001**	1.77	**0.005**
III	181	35.7	(1.34–2.23)		(1.32–2.22)		(1.18–2.65)	
Creatinine clearance								
≥30 ml/min	551	48.4	1.46	0.061	-	-	-	
<30 ml/min	49	40.1	(0.98–2.18)					
LDH (N = 478)								
Normal	207	42	0.82	**0.11**	-	-	-	-
Elevated	271	46.4	(0.62–1.05)					
Lines of therapy								
1	297	51.7	1.35	**0.018**	1.28	0.06	1.28	0.26
>1	303	43.7	(1.05–1.72)		(0.99–1.66)		(0.83–1.99)	
Previous ASCT								
No	267	50.2	1.15		-	-	-	-
Yes	333	44.5	(0.9–1.47)	0.27				
Previous lenalidomide								
No	382	53.9	1.53	**0.001**	1.46	**0.004**	1.43	0.12
Yes	218	38.4	(1.2–1.96)		(1.13–1.89)		(0.91–2.25)	
FISH risk (N = 231)								
Standard	174	51.9	2.45	**<0.0001**	-	-	2.46	**<0.0001**
High	57	25.9	(1.62–3.69)				(1.6–3.76)	

Abbreviations: CI, confidence interval; ISS, International Staging System; PRS, progression-free survival.

TABLE 5 Adverse events (AEs) (all grades and grade ≥3)

	N of patients (%)	
Adverse event	All grades	≥ Grade 3
Hematological		
Anemia	296 (49,3)	55 (9,2)
Neutropenia	256 (42,7)	80 (13,3)
Thrombocytopenia	255 (42,5)	65 (10,8)
Non hematological		
Cardiovascular toxicity/thrombotic events	210 (35)	61 (10.1)
Gastrointestinal toxicity	99 (16,5)	13 (2,2)
Liver toxicity	35 (5,8)	7 (1,2)
Infections/FUO	185 (30.8)	42 (7)
Skin toxicity	30 (5)	6 (1)

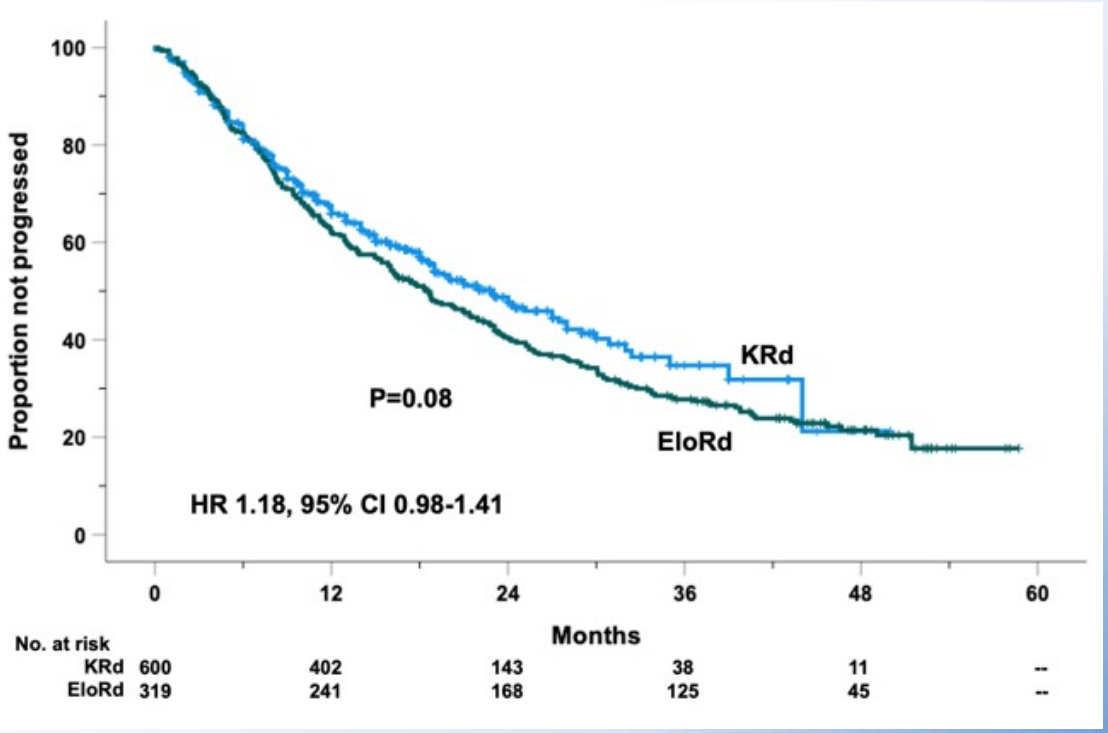
Martino et al, Hematol Oncol 2022

Risk score for outcome using Rd-based triplets

TABLE 1 | Clinical features of 919 relapsed/refractory multiple myeloma (RRMM) patients treated with carfilzomib, lenalidomide, and dexamethasone (KRd) or elotuzumab, lenalidomide, and dexamethasone (EloRd) as salvage regimens in a real-life setting.

Age	
Median, years	67
Range	33–91
Gender	
Male, *n* (%)	459 (49.9)
Female, *n* (%)	460 (50.1)
International Stage System (ISS)	
I, *n* (%)	318 (39.1)
II, *n* (%)	259 (31.8)
III, *n* (%)	237 (29.1)
Missing, *n*	105
FISH analysis	
Standard risk, *n* (%)	229 (77.1)
High risk, *n* (%)	68 (22.9)
Missing, *n*	622
LDH	
Normal, *n* (%)	379 (48.2)
Abnormal, *n* (%)	407 (51.8)
Missing, *n*	133
Number of lines of previous therapy	
1 line	495 (53.9)
2 lines	205 (22.3)
3 lines	102 (11.1)
>3 lines	117 (12.7)
Previous exposure to lenalidomide	
No, *n* (%)	615 (66.9)
Yes, *n* (%)	304 (33.1)
Previous ASCT (autologous stem cell transplant)	
No, *n* (%)	529 (57.6)
Yes, *n* (%)	340 (42.4)
Disease status at KRd/EloRd start	
Relapse, *n* (%)	670 (72.9)
Refractory, *n* (%)	249 (27.1)

- median PFS was 20.3 months (95% CI 18.2–22.4)

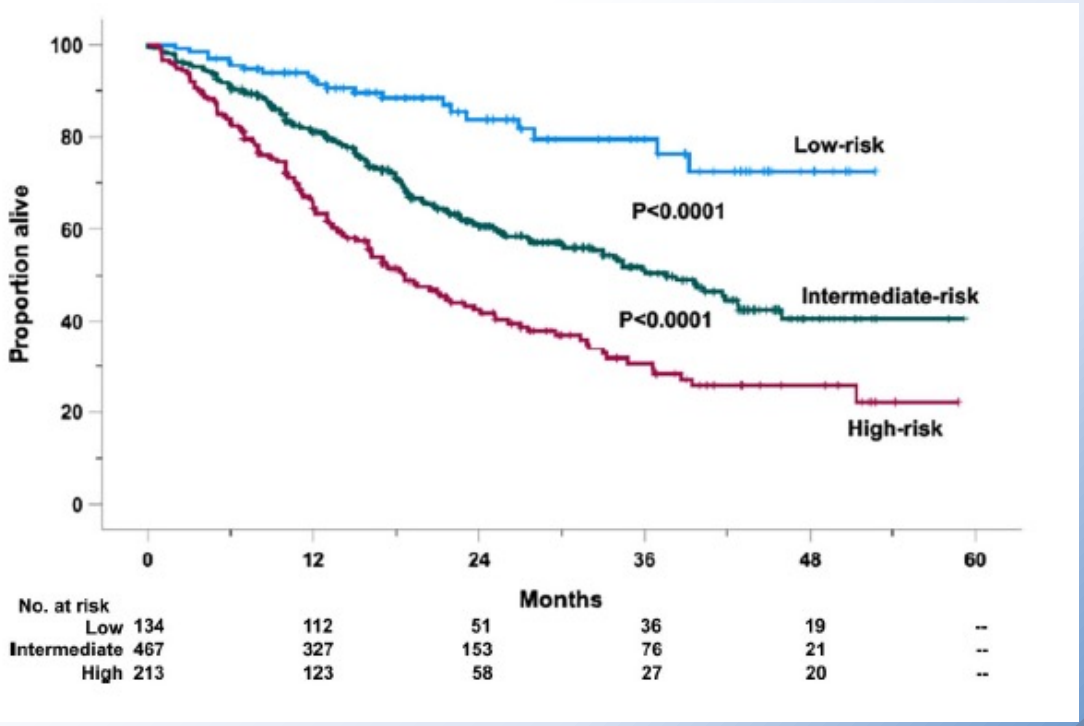


Morabito et al,Front Oncol 2022

Risk score for outcome using Rd-based triplets

Table S1. Regression coefficients (b), percentage weights (%), and the overall survival risk score calculation derived from the 5-factor multivariate model. This analysis was carried out in 814 relapsed/refractory multiple myeloma (RRMM) cases treated with KRd (n=559 cases) or EloRd (n=255), in which all the variables were available.

Variables	Regression coefficients (b)	Score calculation	Risk scores (%)
Interval diagnosis-therapy, >3.5 years	0.383	0.383/2.154 = 0.178	≤ 3.5 = 0 > 3.5 = 17.8
Prior exposure to lenalidomide	0.264	0.264/2.154 = 0.123	No = 0 Yes = 12.3
International Stage System (ISS), III	0.274	0.274/2.154 = 0.127	I-II = 0 III = 12.7
Age, > 65.5 years	0.547	0.547/2.154 = 0.254	≤ 65.5 = 0 > 65.5 = 25.4
Number of previous lines of therapies	0.686	0.686/2.154 = 0.318	≤ 3 = 0 > 3 = 31.8
	***Total=2.154**		

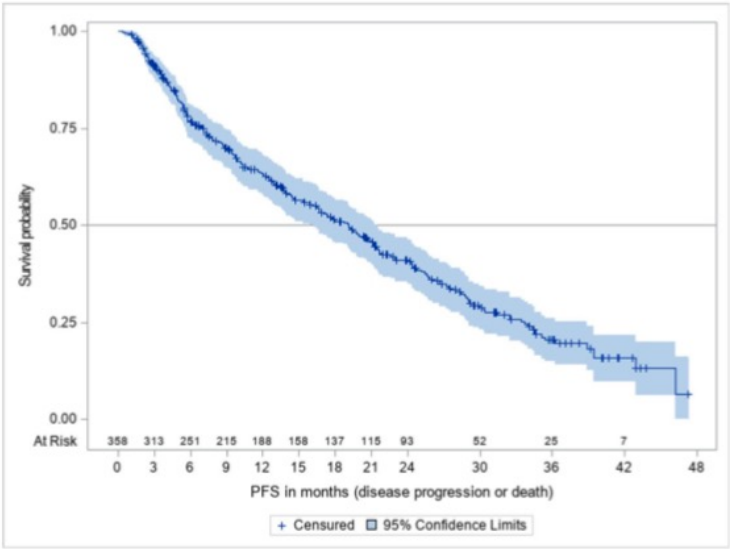


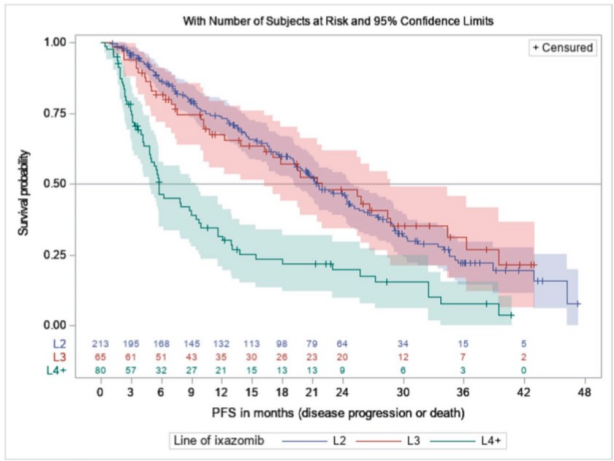
Morabito et al,Front Oncol 2022

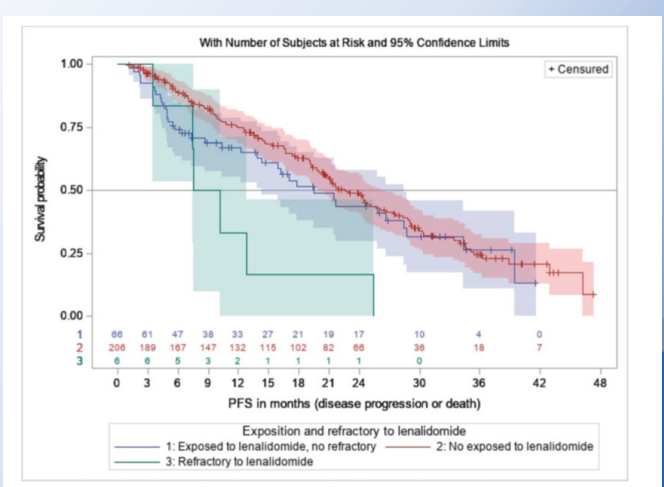
Ixa-Rd real life REMIX study

Table 1 Patient demographics and disease characteristics

	All patients ($N=376$)
Median age at IXA-Rd start (in years) (IQR)	71 (65.0–77.5)
≥75, *n* (%)	133 (35.4)
≥80, *n* (%)	69 (18.4)
Male Sex, *n* (%)	185 (49.2)
Charlson index total score, *n* (%)	
0	246 (65.4)
1–2	100 (26.6)
3–4	21 (5.6)
≥5	9 (2.4)
ECOG at IXA-Rd start, *n* (%)	$n=209$
0	69 (33.0)
1	102 (48.8)
≥2	38 (18.2)
Simplified frailty scale at IXA-Rd start, *n* (%)	$n=283$
Frail	138 (48.8)
Non frail	145 (51.2)
M Protein type,(*n* (%)	
IgG	211 (56.1)
IgA	81 (21.5)
None	58 (15.4)
Other	9 (2.4)
Data not available	20 (5.3)
Light chain type, *n* (%)	
Kappa	257 (68.4)
Lambda	112 (29.8)
Data not available	7 (1.9)
Cytogenetic features at IXA-Rd start, *n* (%)	
Standard-risk cytogenetic abnormalities	167 (44.4)
High-risk cytogenetic abnormalities	45 (12.0)
Data not available	164 (43.6)
Median time since diagnosis (in years)	4.0
Line of treatment at IXA-Rd start, *n* (%)	
L2	227 (60.4)
L3	68 (18.1)
L4+	81 (21.5)
Creatinine clearance (ml/min) at IXA-Rd start, *n* (%)	$n=304$
>50	238 (78.3)
30–50	43 (14.1)
≤30	23 (7.6)







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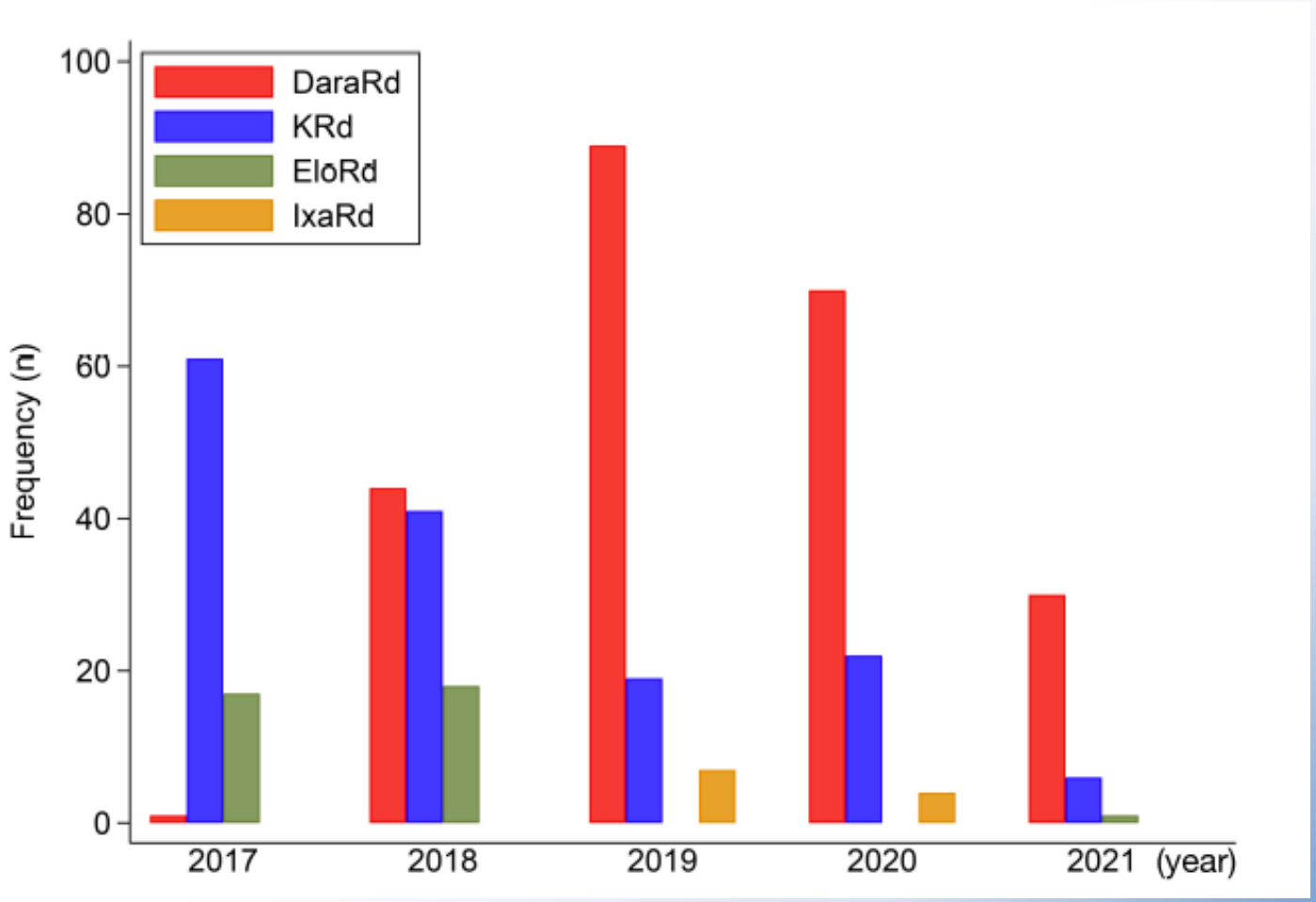
Rd-based triplets in 1^ relapse
Pattern of use overtime



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Rd-based triplets in 1^ relapse propensity score matched analysis of real life data

	Original cohorts			Pseudo-population (IPTW analysis)	
Type of treatment at relapse	**KRd (N=99)**	**DaraRd (N=217)**	***P* value**	**KRd**	**DaraRd**
Myeloma-defining events at diagnosis					
Any CRAB criteria, N (%)	94 (94.9)	202 (93.1)	0.598	-	-
HyperCalcemia	22 (22.2)	34 (15.7)	0.204	16.2%	15.2%
Renal failure	24 (24.2)	61 (28.2)	0.496	27.2%	27.7%
Anemia	55 (55.6)	121 (56.0)	>0.90	51.2%	52.3%
Bone lesions	81 (81.8)	158 (73.2)	0.118	83.0%	83.3%
Only SLiM[a] CRAB criteria, N (%)	5 (5.1)	15 (6.9)	0.458	-	-
ISS, N (%)					
Stage II and III	59 (63.4)	129 (64.5)	0.896	61.4%	63.8%
First-line, N (%)					
ASCT in first-line	71 (71.7)	118 (54.4)	0.004	67%	64%
PI-based therapy	96 (97.0)	207 (95.4)	0.761	97.5%	97.5%
Good quality response during first-line, N (%)					
≥VGPR	69 (69.7)	146 (68.5)	0.896	69.6%	69.3%
Time from diagnosis and relapse in years, mean (SD)	2.9 (2.2)	3.4 (2.7)	0.107	2.8 (2.1)	2.9 (2.1)
Median age at second-line start in years, mean (SD)	64 (8)	69 (9)	<0.001	66 (8)	66 (10)
Cytogenetic proflie at relapse, N (%)					
Missing	28 (28)	80 (39)			
Evaluable	71 (72)	137 (61)			
Standard	41 (42)	79 (35)	>0.90	57.2%	60.4%
High risk[b]	30 (30)	58 (26)		42.8%	39.6%

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Rd-based triplets in 1^ relapse propensity score matched analysis of real life data

	Original cohorts		IPTW analysis
Best overall response[a], N (%)	**DaraRd (N=211)**	**KRd (N=98)**	**OR, (95% CI), *P* value**
CR or better sCR CR	47 (22.2) 8 (3.7) 39 (18.5)	26 (26.6) 8 (8.2) 18 (18.4)	1.2, (0.8-1.9), *P*=0.360
VGPR or better VGPR PR	133 (63) 86 (40.8) 60 (28.4)	64 (64.4) 38 (37.8) 22 (22.5)	0.9, (0.6-1.3), *P*=0.582
ORR[b]	193 (91.5)	85 (86.7)	0.9, (0.5-1.6), *P*=0.685
SD and PD	18 (8.6)	13 (13.2)	-

Table 3. Non-hematological adverse events (all grades and grade ≥3) in DaraRd and KRd cohorts.

	All Grades		≥ Grade 3	
	DaraRd (N=217)	**KRd (N=99)**	**DaraRd (N=217)**	**KRd (N=99)**
Adverse events, N (%)				
Infections	60 (27.7)	35 (35.4)	21 (9.7)	13 (13.1)
Gastrointestinal[a]	41 (18.9)	18 (18.2)	5 (2.3)	5 (5.1)
Fatigue	21 (9.7)	12 (12.1)	5 (2.3)	1 (1.0)
Deep vein thrombosis	9 (4.2)	10 (10.1)	4 (1.8)	4 (4.0)
Rash	9 (4.2)	7 (7.1)	3 (1.4)	1 (1.0)
Peripheral neuropathy	9 (4.2)	3 (3.0)	1 (0.5)	2 (2.0)
Hepatic[b]	2 (0.9)	4 (4.0)	0 (0.0)	1 (1.0)
Acute renal failure	2 (0.9)	3 (3.0)	0 (0.0)	2 (2.0)
Adverse event of specific interest, N (%)				
Cardiac[c]	4 (1.8)	12 (12.1)	1 (0.5)	7 (7.1)
Hypertension	5 (2.3)	8 (8.1)	1 (0.5)	5 (5.1)

DaraRd had overall lower incidence of all grade AE (IPTW analysis: OR=0.4, 95% CI: 0.3-0.6, P<0.001).

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Rd-based triplets in 1^ relapse propensity score matched analysis of real life data

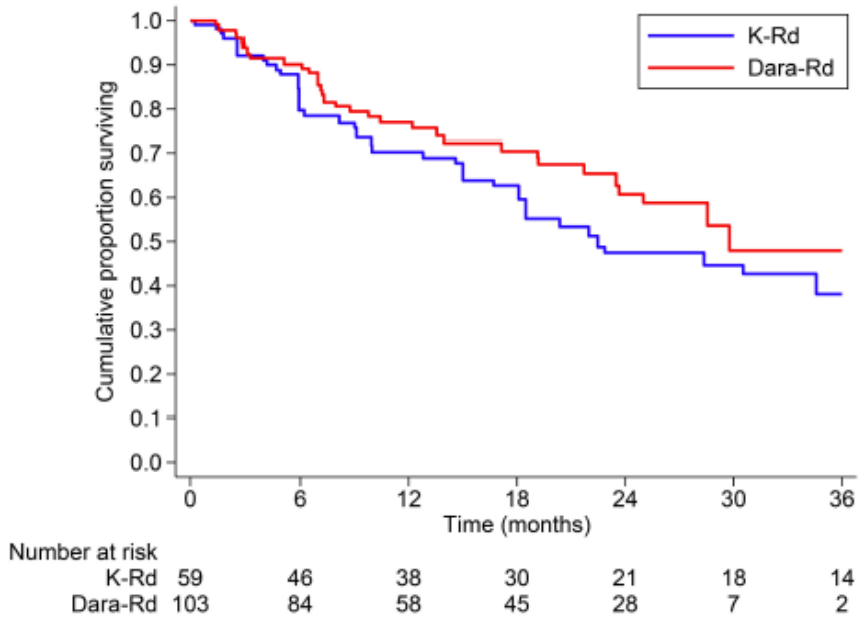

Figure 2. Progression-free survival of patients treated with DaraRd *versus* KRd after cohort matching. DaraRd: daratumumab-lenalidomide-dexamethasone; Krd: carfilzomib-lenalidomide-dexamethasone.

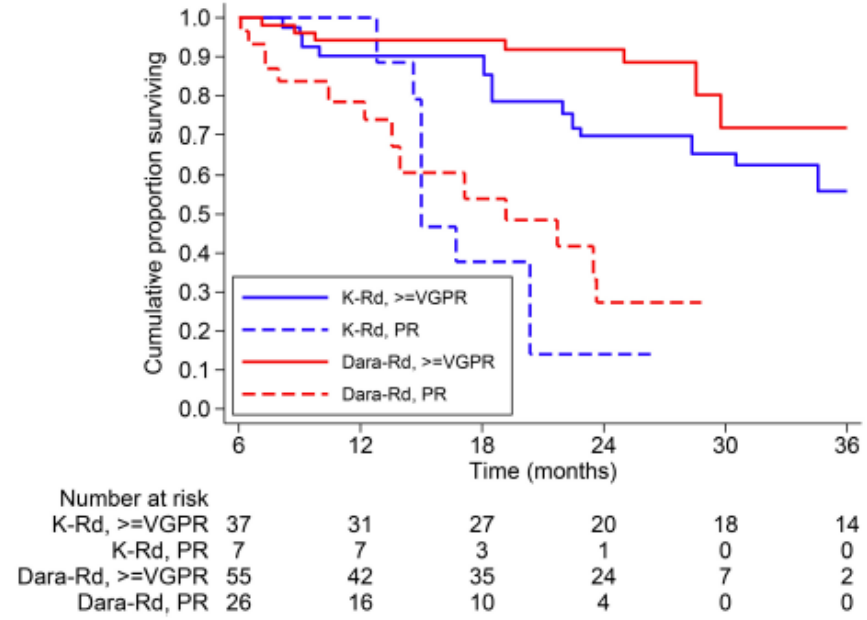

Figure 3. Six-month landmark analysis of progression-free survival after cohort matching according to therapy received (DaraRd *versus* KRd) and response achieved. DaraRd: daratumumab-lenalidomide-dexamethasone; Krd: carfilzomib-lenalidomide-dexamethasone.

Adjusted median PFS of DaraRd vs KRd = 29.8 months vs. 22.5 months (IPTW analysis: HR=0.7, 95% CI: 0.6-1.0, P=0.028)

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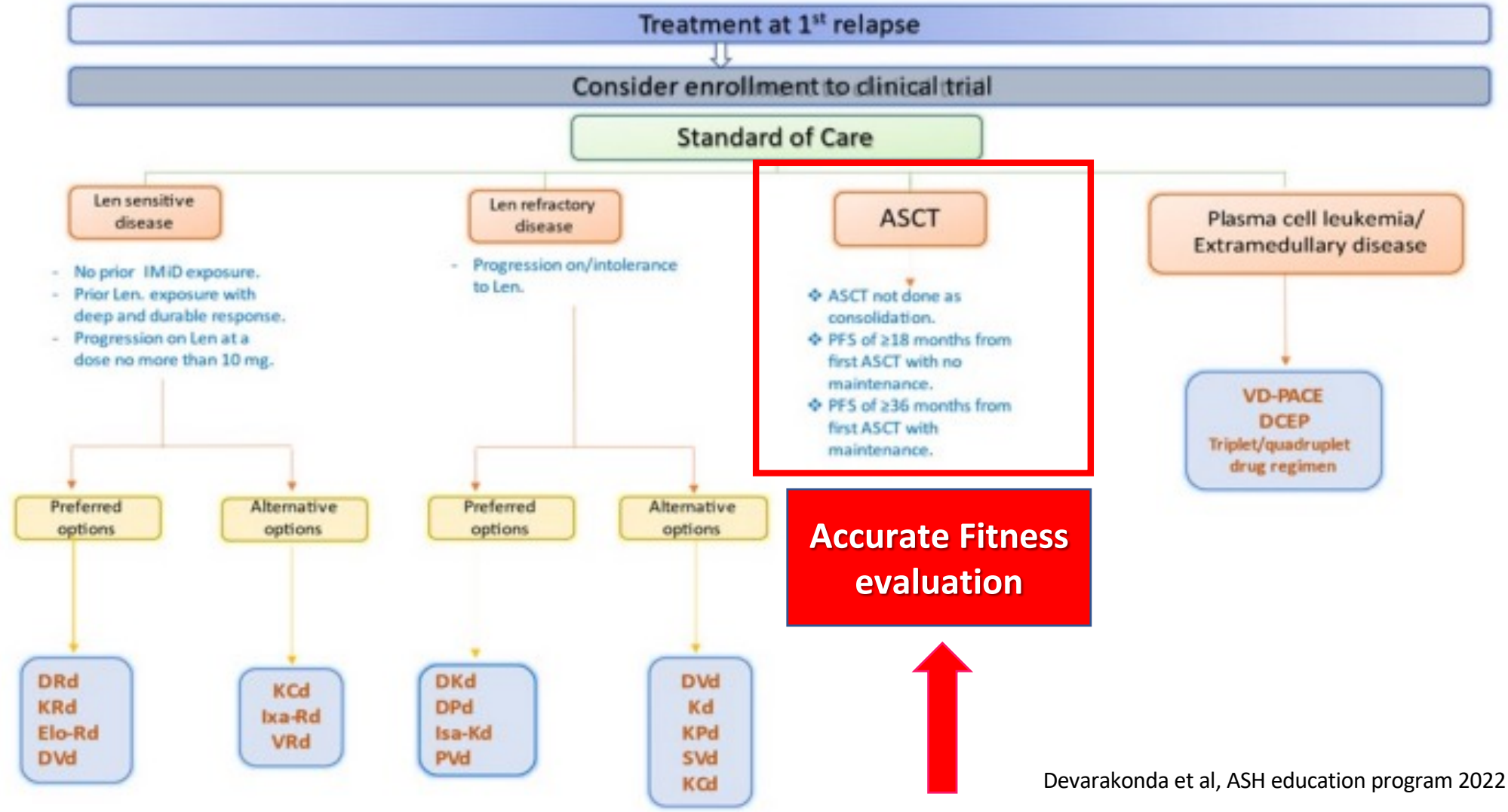
Treatment algorithm for Myeloma at first relapse
Focus on salvage ASCT



Devarakonda et al, ASH education program 2022

Rd-based triplets in 1^ relapse followed by sASCT
EBMT sASCT data after KRD

Table 1. Population description.

	Total ($n = 51$)
Age (years) – median (IQR)	61 (58–66)
≥ 60 years – *n*(%)	35 (68.6)
≥ 65 years – *n*(%)	19 (37.3)
Sex (male) – *n*(%)	35 (68.6)
Monoclonal component – *n*(%)	
IgG	29 (56.9)
IgA	12 (23.5)
Free light chain only	10 (19.6)
ISS disease stage – *n*(%)	
I	18 (42)
II	11 (26)
III	14 (32)
Missing	8
Cytogenetic profile risk – *n*(%)	
Standard risk	27 (71)
High risk	11 (29)
del(17p)	6 (16)
t(4;14)	5 (13)
Missing	13
Patients exposed to lenalidomide in 1st line of therapy – *n*(%)	7 (13.7)
Time between start of 1st and 2nd line of therapy (month) – median (IQR)	40.2 (30.9–53.4)
Time between 1st and 2nd ASCT (month) – median (IQR)	40.4 (31.7–55.1)
Time between start of 2nd line of therapy and 2nd ASCT (months) – median (IQR)	5.9 (4.8–8.1)
Number of cycles of KRd in induction – n (%)	
3 or 4	24 (50.0)
5 or 6	16 (33.3)
7 to 12	8 (16.7)
Missing	3

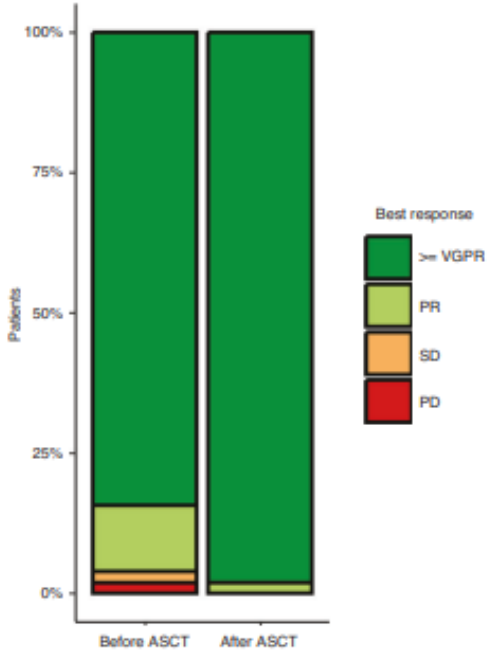
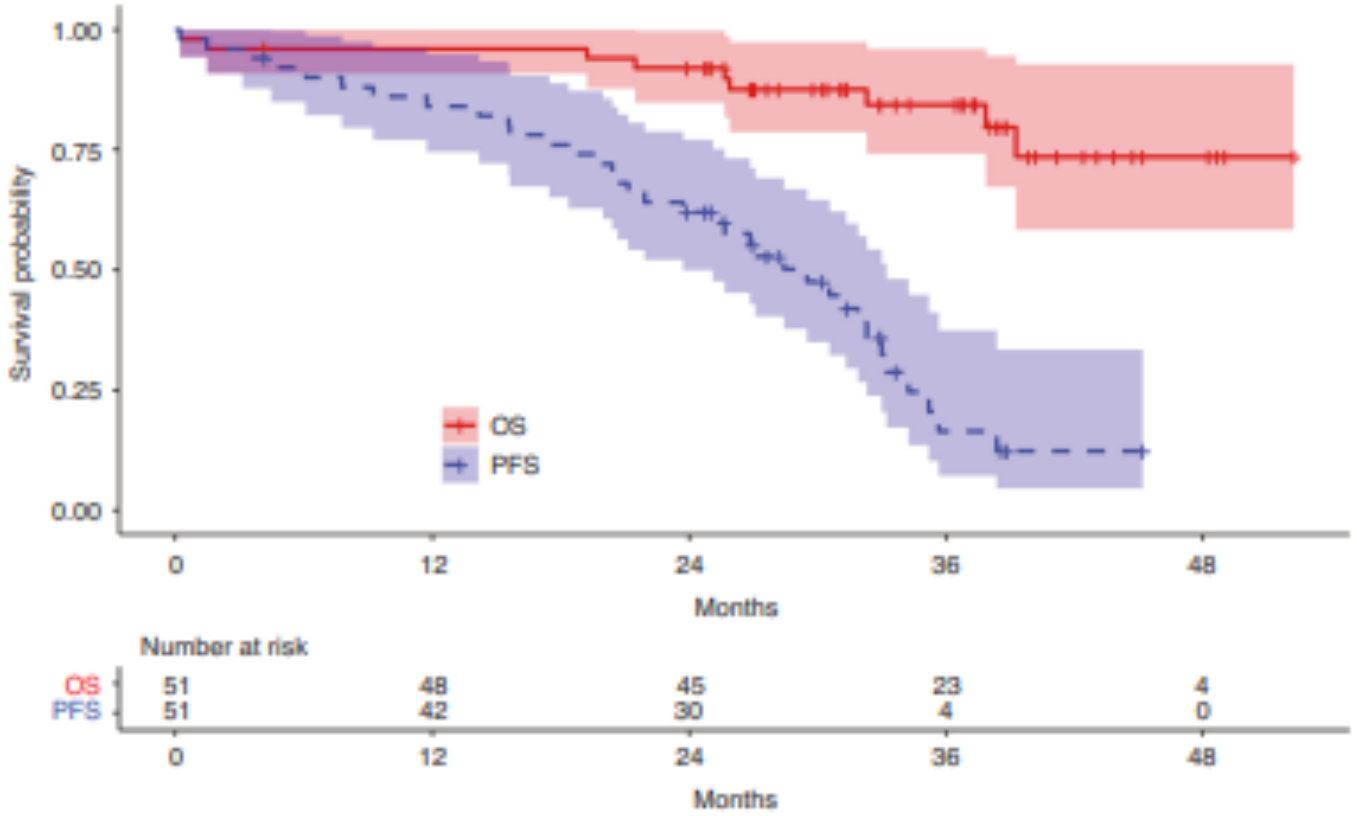


Fig. 1 Overall response rates. Best observed responses, before and after the second ASCT.

Tilmont et al, Bone Marrow Transplant 2023

Rd-based triplets in 1^ relapse followed by sASCT
EBMT sASCT data after KRD



- The median follow-up was 36.7 months (range 0.2 to 45.2 months)
- The median PFS was 29.5 months (IQR 18.4–34.2)
- the median OS was not reached

Rd-based triplets in 1^ relapse followed by sASCT
EBMT sASCT data after KRD

Table 2. Univariate analyses of co-factors influencing PFS.

	Median PFS (95% IC)	*p*-value
Age		0.63
< 65	27.1 months (21.9–35.2)	
> 65	30.6 months (21.2–NA)	
Score ISS III		0.95
I/II	31.9 months (23.7–38.4)	
III	27.1 months (21.2–NA)	
High-Risk cytogenetic profile		0.83
No	28.4 months (20.7–34.2)	
Yes	29.5 months (23.7–NA)	
VGPR / CR achieved after 1st ASCT		0.12
No	34.2 months (33.0–NA)	
Yes	27.1 months (21.9–32.3)	
Previous exposure to lenalidomide		0.55
No	28.4 months (23.7–33.0)	
Yes	35.7 months (20.4–NA)	
Number of KRd cycles administered		0.83
3–4	29.5 months (21.9–NA)	
5–6	30.6 months (25.1–NA)	
7–12	29.0 months (21.2–NA)	
Carfilzomib administration scheme		0.83
Bi-weekly	26.0 months (20.0–NA)	
Weekly	30.6 months (20.4–NA)	
VGPR / CR achieved before 2nd ASCT		**0.003**
No	**21.5 months (20.40–NA)**	
Yes	**31.3 months (26.8–35.7)**	
Time > 4 years between transplants		**0.027**
< 4 years	**28.4 months (20.0–33.2)**	
> 4 years	**30.6 months (25.10–NA)**	
Allogenic transplant before relapse		0.36
No	29.5 months (25.1–34.2)	
Yes	24.7 months (9.2–NA)	
Consolidation therapy given		0.45
No	27.1 months (21.9–33.0)	
Yes	35.2 months (21.2–NA)	
Maintenance therapy given		0.13
No	25.7 months (18.4–38.4)	
Yes	30.6 months (27.1–NA)	

Significant differences are placed in bold.

Tilmont et al, Bone Marrow Transplant 2023

Take Home Messages

- real-world data depict an evolving pattern in the daily management of lenalidomide-sensitive MM patients in first relapse, influenced by drug approval with a progressive increase in the use of DaraRd, even if PI based combo KRd/IxaRd regimen still retain an important role

- multicentric and retrospective data confirmed efficacy and comparable safety profile of Rd based triplets in the real-life setting of MM patients, in first relapse although there is some gap with respect to RCT

- previous exposure to lenalidomide, high-risk FISH, seems to decrease Rd-based triplets efficacy also in the real life setting

- salvage transplant is confirmed to be a valid strategy in the real word setting for fit patients with long lasting remission after 1^ line therapy whose efficacy could be enhanced by highly active Rd-based triplets induction (visit our P2226 at the next 2023 ASH meeting)

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