Highlights from
IMS 20th meeting 2023

F. Patriarca- Udine

Strategie terapeutiche nel paziente “difficile-da-trattare” :
con ricaduta precoce dopo la terapia di prima linea

30-31 gennaio 2024
BOLOGNA, Royal Hotel Carlton

Functional high-risk MM

&

pts who relapse within 12 and 18 months after optimal initial therapy

pts with no apparent or no necessarily high features at diagnosis

F. Gay , ASH 2023

Frequency of functional high risk MM

Study	**Jimenez-Zepeda et al.** Princess Margaret Cancer Center (PM)	**Kumar et al.** CIBMTR database	**Spencer et al.** Australian and New Zealand MRDR	**Kastritis et al.** Department of Clinical Therapeutics, (Athens, Greece)	**D'Agostino et al.** CoMMpass dataset	**Bygrave et al.** NCRI Myeloma XI	**Soekojo et al.** CoMMpass dataset	**Yan et al.** National Longitudinal Cohort of Hematological Diseases (China)
Total N°of pts	184	3256	1320	297	926	1349	512	629
Type of treatment	 ASCT: 100%	 ASCT: 100%	N/A	 ASCT: 53%	 ASCT: 100%	CTd vs. CRd (induction) If ≤VGPR prior ASCT: VTd ASCT: 100%	 ASCT: N/A	PIs and/or IMiDs: 100% ASCT: 100%
Definition	PD *within 12 months* from transplant	PD *within 24 months* from transplant	PD *within 12 months* from diagnosis	PD *within 12 months* from transplant	PD *within 18 months* from diagnosis	PD *within 12 months* from transplant	PD *within 12 months* from diagnosis without HRCA	PD *within 18 months* from diagnosis
Early relapse (%)	**14%**	**38%**	**9%**	**14%**	**21%**	**13%**	**11%**	**18%**

ASCT, autologous stem cell transplantation; PD, progressive disease; PIs, protheosome inhibitors; IMiDs, immunomodulatory drugs; MDRD, Myeloma and Related Diseases Registry; Center for International Blood and Marrow Transplant Research (CIBMTR); HRCA, high risk cytogenetic abnormalities

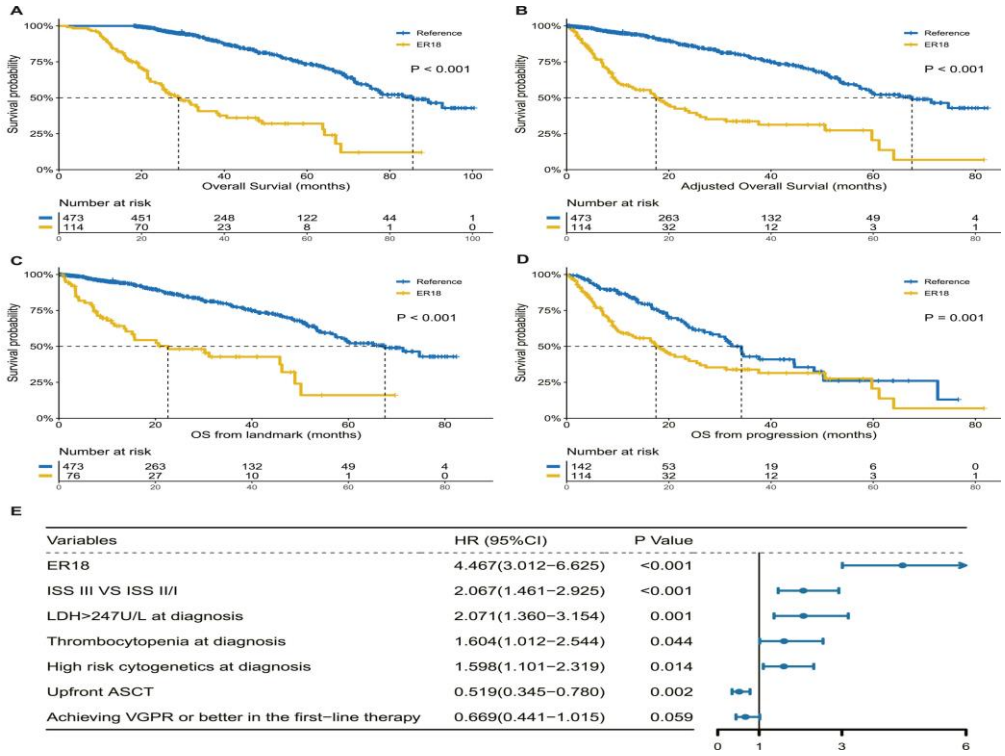
PIs-based IMiDs-based Pis+IMiDs-based Other (not including anti-CD38)

American Society *of* Hematology

Jimenez-Zepeda VH, et al., Bone Marrow Transplant. 2015; Kumar SK, Leukemia. 2018; (Spencer A, et al. Blood. 2019; Kastritis E, et al. Clin Lymphoma, Myeloma Leuk. 2020; (D'Agostino M, et al. Clin Cancer Res. 2020; (Bygrave C, et al., . Br J Haematol. 2021; (Soekojo et al., Blood Cancer J. 2022 (Yan et al., Cancer 2023

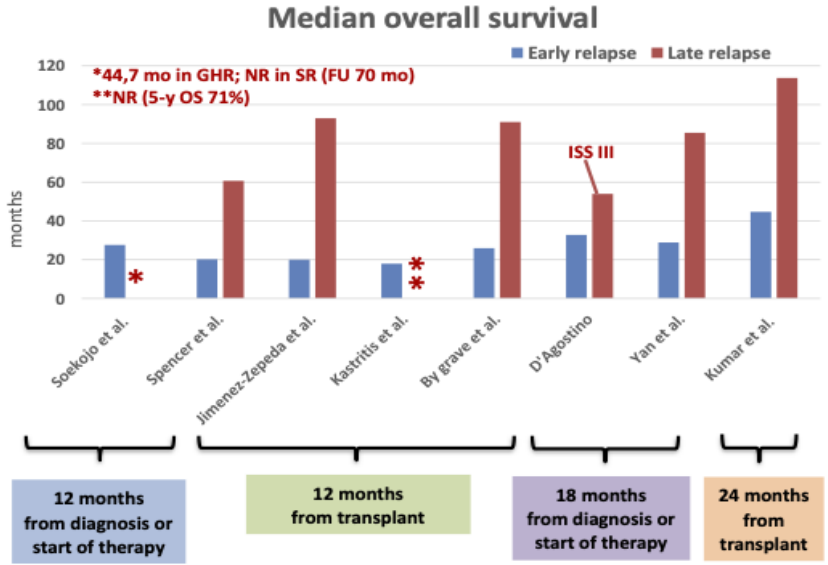
F. Gay , ASH 2023

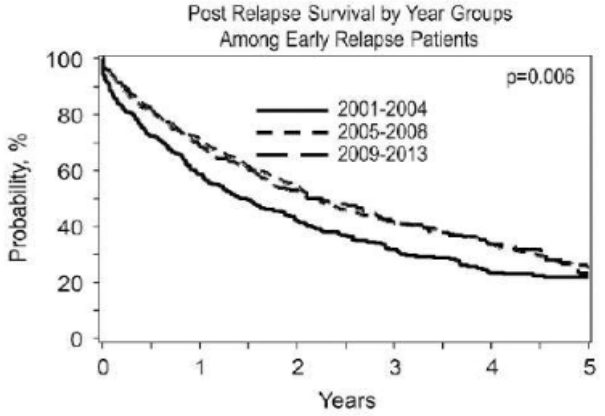
Dynamic definition of HR MM is a more powerful prognostic factor than static definition



Yan W et al, Cancer 2023

Outcome of *functional high risk (FHR)* MM





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Only a proportion of HRF MM showed HR features at diagnosis

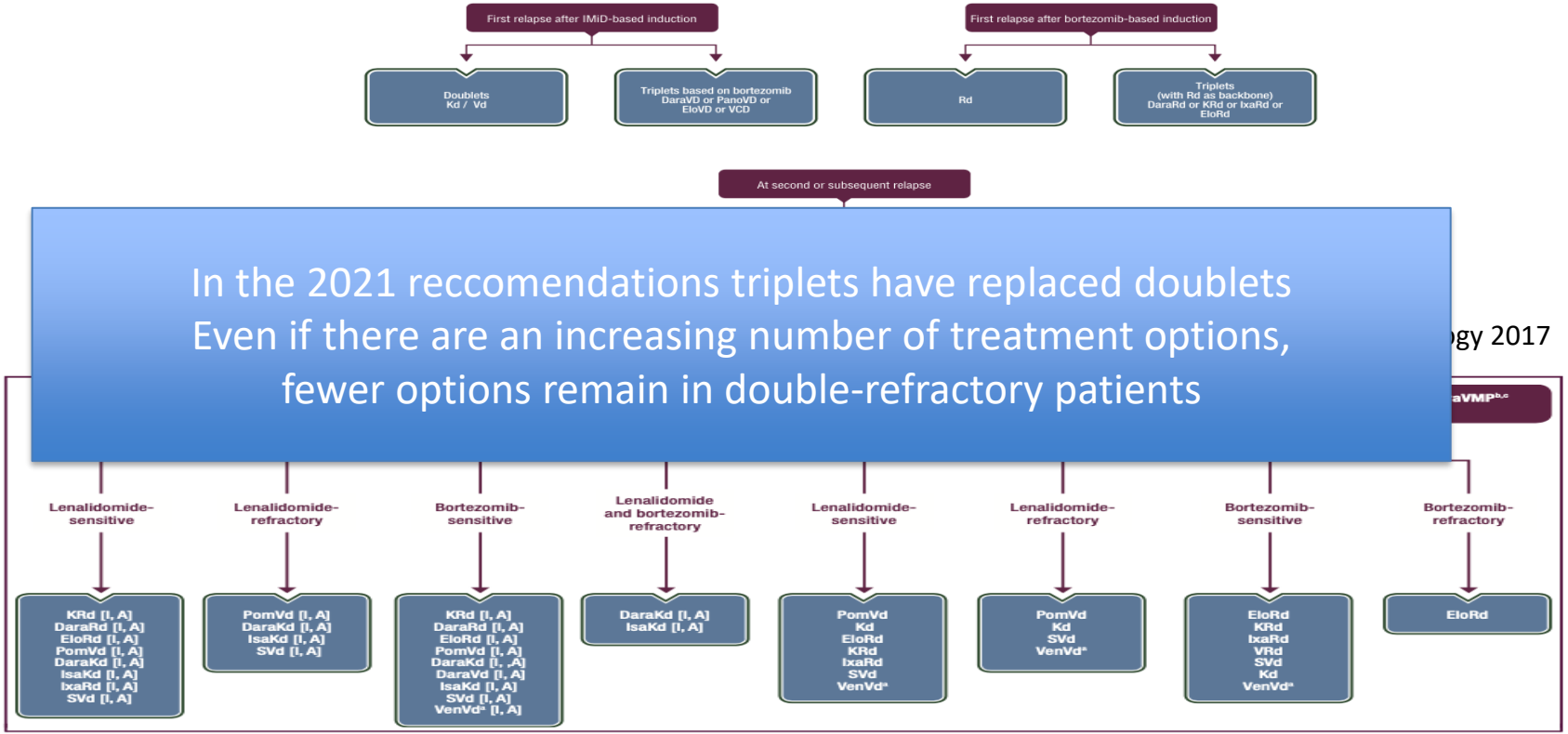
	Soekojo 2022	Bygrave 2021	Yan 2023
n° FHR MM	61	174	114
ISS I-II-III	28%-33%-39%	22%-42%-27%	28%-37%-45%
R-ISS I-II-III	21%-70%-8%	-	13%-67%-19%
Cyto SR-HR-UHR		28%-36%-36%	
Mol HR signature	UAMS 26%, IFM 18%		

Only a proportion of HRF MM showed suboptimal response to induction

Bygrave 2021: CR+ VGPR 64.4% in ER vs 72.4% in nER
Yan 2023 : CR+ VGPR 51.8% in ER vs 90.2% in nER

Clinical Practice Guidelines

Annals of Oncology



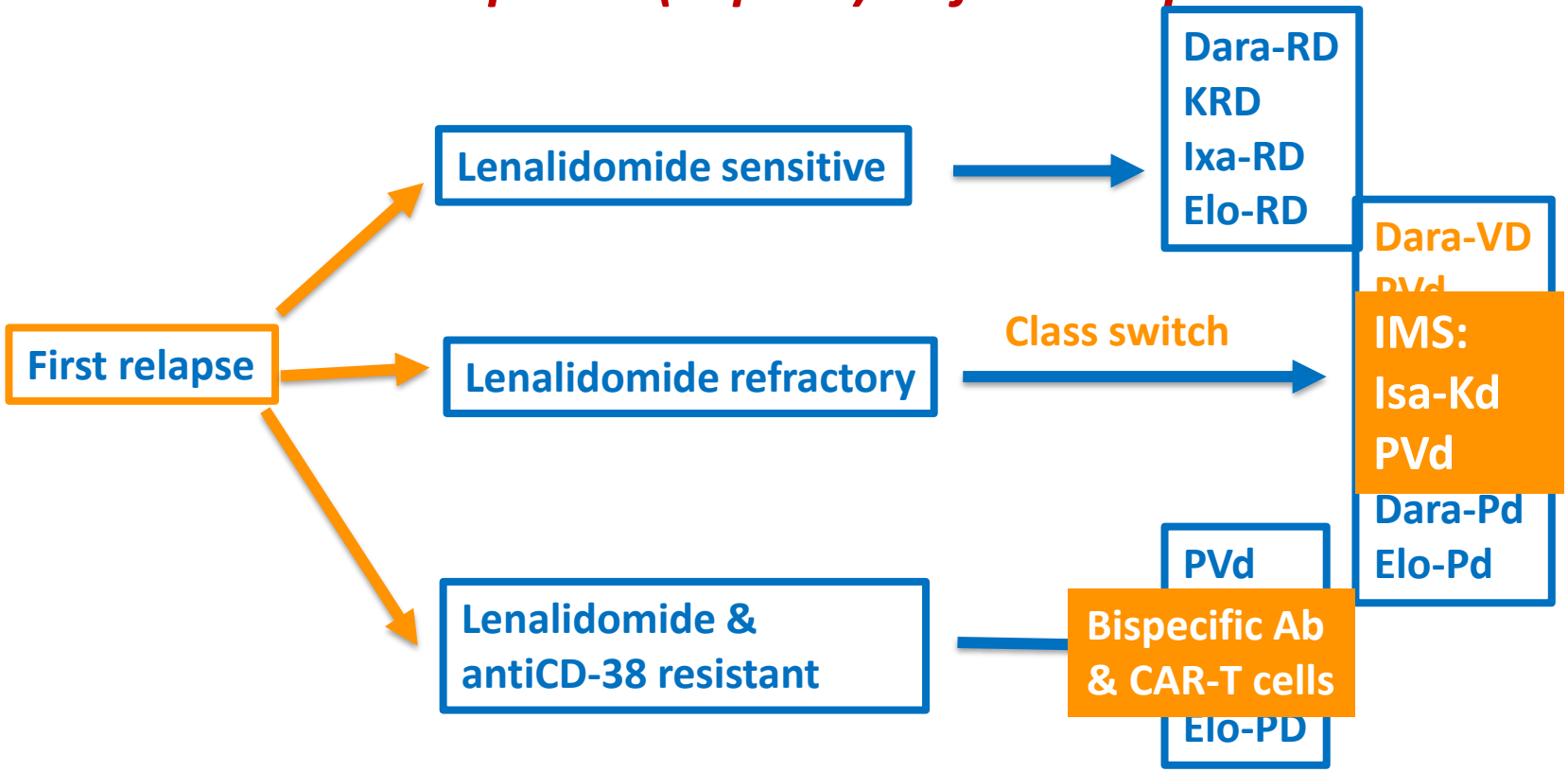
In the 2021 reccomendations triplets have replaced doublets
Even if there are an increasing number of treatment options, fewer options remain in double-refractory patients

ogy 2017

Figure 2. Second-line options for MM patients who received VRd and Dara-based front-line therapies.

Dimopoulos et al, Annals of Oncology 2021

Treatment options (triplets) at first relapse

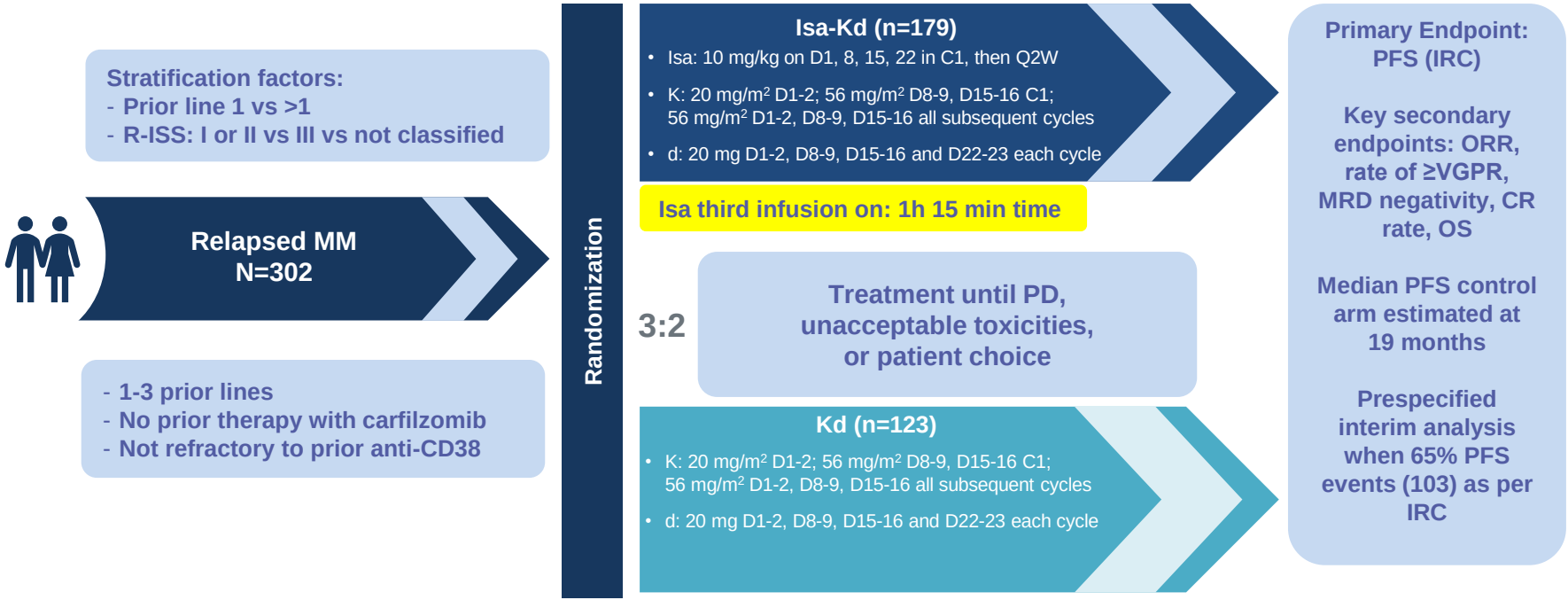


Opzioni di seconda linea a “confronto”

	R-Free Regimens			mAbs anti-CD38 not reimbursed			R-based Regimens	
EFFICACY DATA	CASTOR[1-2] DVd (251)	ENDEAVOR[3-4] Kd (464)	OPTIMISMM[5,6] PVd (281)	APOLLO[7] DscPd (151)	CANDOR[8-10] DKd (312)	IKEMA[11,12] IsaKd (179)	POLLUX[13-15] DRd (286)	ASPIRE[16,17] KRd (396)
No of median prior lines	2	2	2	2	2	2	1	2
Len-refractory %	**24**	**24**	**71**	**79**	**32**	**32**	**0**	**7**
≥ CR (%)	**30**	**13**	**16**	**25**	**29**	**44**	**57**	**32**
NGS MRD neg[10-5] ITT (%)	15	NA	NA	9	23	33,5	32,5	ND
mPFS ITT (▲ mos) HR	**17 (▲ 9.6) 0.31**	**19 (▲ 9.3) 0.53**	**11 (▲ 4.1) 0.61**	**12,4 (▲ 5.5) 0.63**	**29 (▲ 13.4) 0.59**	**35,7 (▲ 16.5) 0.58**	**44,5 (▲ 27) 0.44**	**26 (▲ 8.7) 0.69**
mPFS 1PLoT (▲ mos) HR	27 (▲ 19) 0.22	22 (▲ 12.1) 0.45	21 (▲ 9.1) 0.54	14,1 (▲ 1.5) 0.7	NR (▲ NR) 0.66	NR (▲ NR) 0.59	53 (▲ 34) 0.42	30 (▲ 12) 0.71
mPFS Len-refr (▲ mos) HR	**8 (▲ 2.9) 0.44**	**9 (▲2.0) 0.36**	**9.5 (▲ 3.9) 0.65**	9.9 (▲ 3.4) 0.66	**28 (▲ 17) 0.46**	**NR (▲ NR) 0.59**	**ND**	**ND**
mPFS in early relapse	**15 HR 0.51**	**NE**	**NE**	**NE**	**NE HR 0.6**	**25 HR 0.58**	**37 HR 0.41**	**21**

IKEMA

Study design: Isa-Kd vs Kd in relapsed multiple myeloma



Sample size calculation: ~300 patients and 159 PFS events to detect 41% risk reduction in hazard rate for PFS with 90% power and one-sided 0.025 significance level

IKEMA study: NCT03275285
C, cycle; CR, complete response; D, day; d, dexamethasone; IRC, Independent Review Committee; Isa, isatuximab; K, carfilzomib; MM, multiple myeloma; MRD, minimal residual disease; ms, months; ORR, overall response rate; OS, overall survival; PFS, progression free survival; Q2W, once every 2 weeks; R-ISS, revised international staging system; VGPR, very good partial response

Moreau et al. Lancet 2021 S0140-6736(21)00592-4

FINAL PFS ANALYSIS

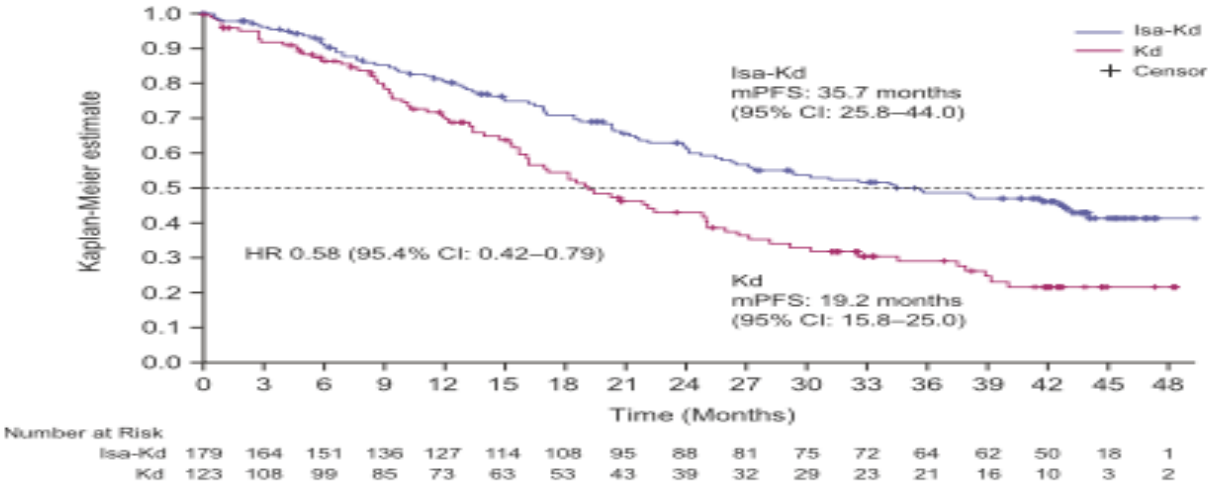


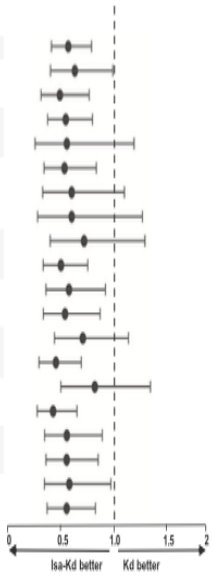
Fig. 2 Updated PFS with Isa-Kd vs Kd (ITT population). CI confidence interval, d dexamethasone, HR hazard ratio, Isa isatuximab, ITT intent to treat, K carfilzomib, mPFS median progression-free survival.

Median follow-up 43.9 months

Martin T et al, Blood Cancer J 2023

T. Martin et al.

Subgroup		Isa-Kd Events/total	Kd Events/total	Hazard ratio (95% CI)
All patients		86/179	77/123	0.576 (0.418–0.792)
Age	<65 years	43/88	38/66	0.637 (0.410–0.990)
	≥65 years	43/91	39/57	0.497 (0.321–0.771)
Baseline eGFR (MDRD)	≥60 mL/min/1.73 m²	55/122	60/93	0.553 (0.382–0.801)
	<60 mL/min/1.73 m²	23/43	10/18	0.562 (0.266–1.189)
ISS staging at study entry	I	39/89	43/71	0.541 (0.350–0.837)
	II	34/63	17/31	0.608 (0.336–1.099)
	III	13/26	16/20	0.607 (0.290–1.268)
High-risk cytogenetic status	Yes	26/42	21/31	0.724 (0.406–1.290)
	No	50/114	48/77	0.508 (0.341–0.758)
1q21+	Yes	39/75	35/52	0.582 (0.368–0.923)
	No	39/84	33/55	0.546 (0.342–0.873)
Number of prior lines of therapy (IRT)	1	41/80	31/55	0.712 (0.445–1.138)
	>1	45/99	46/68	0.460 (0.302–0.698)
Prior PI treatment[a]	Yes	43/81	26/47	0.824 (0.506–1.343)
	No	43/98	51/76	0.434 (0.286–0.657)
Prior IMiD treatment[a]	Yes	37/81	37/62	0.562 (0.355–0.892)
	No	49/98	40/61	0.560 (0.367–0.854)
Refractory to lenalidomide	Yes	31/57	30/42	0.586 (0.353–0.972)
	No	55/122	47/81	0.560 (0.378–0.829)



Blood Cancer Journal 2023

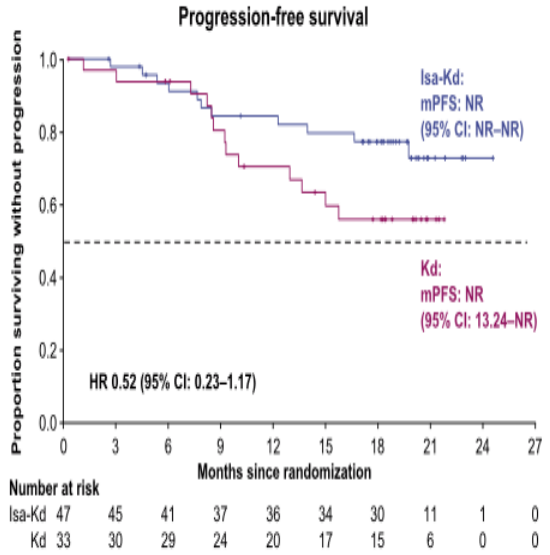


Figure 4. Progression-free survival among patients who received a transplant as their 1 prior line of therapy.

TCTJ 2023

Early relapse was defined as relapse that occurred <12 months from initiation of the most recent line of therapy for patients with 2 prior lines of therapy, <18 months for patients with 1 prior line of therapy, or <12 months following frontline ASCT

Table 1. Key patient demographics and baseline characteristics in IKEMA early relapse and late relapse patients (ITT population).

	Early Relapse		Late Relapse	
	Isa-Kd (n=61)	Kd (n=46)	Isa-Kd (n=104)	Kd (n=72)
ISS stage at study entry				
Stage I	19 (31.1)	25 (54.3)	63 (60.6)	44 (61.1)
Stage II	28 (45.9)	12 (26.1)	31 (29.8)	18 (25.0)
Stage III	14 (23.0)	9 (19.6)	9 (8.7)	9 (12.5)
Unknown	0	0	1 (1.0)	1 (1.4)
Cytogenetics at study entry[b,c]				
High risk	21 (34.4)	16 (34.8)	19 (18.3)	13 (18.1)
Standard risk	33 (54.1)	28 (60.9)	71 (68.3)	48 (66.7)
Missing	7 (11.5)	2 (4.3)	14 (13.5)	11 (15.3)

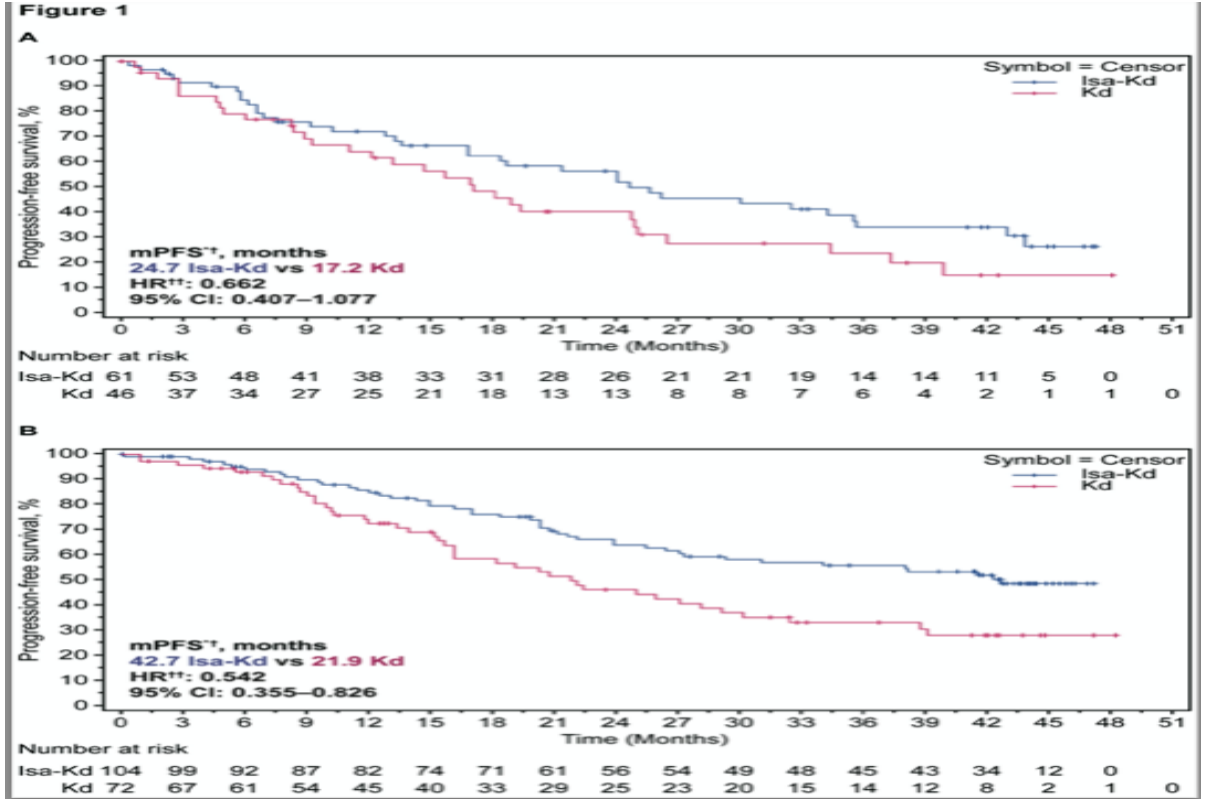
Facon T. Haematologica 2023, ASH 2023

	Early relapse		Late relapse	
	Isa-Kd (n=61)	Kd (n=46)	Isa-Kd (n=104)	Kd (n=72)
Prior lines of therapy, median (min–max)	2.0 (1–4)	2.0 (1–4)	1.0 (1–4)	2.0 (1–4)
1, n (%)	20 (32.8)	19 (41.3)	58 (55.8)	35 (48.6)
2, n (%)	24 (39.3)	12 (26.1)	34 (32.7)	22 (30.6)
3, n (%)	16 (26.2)	14 (30.4)	11 (10.6)	14 (19.4)
>3, n (%)	1 (1.6)	1 (2.2)	1 (1.0)	1 (1.4)
Prior ASCT	30 (49.2)	14 (30.4)	81 (77.9)	53 (73.6)
Refractory status, n (%)				
Relapsed and refractory	54 (88.5)	41 (89.1)	55 (52.9)	49 (68.1)
Refractory to IMiD agent	33 (54.1)	27 (58.7)	34 (32.7)	27 (37.5)
Refractory to PI	34 (55.7)	24 (52.2)	15 (14.4)	17 (23.6)
Refractory to IMiD agent and PI	21 (34.4)	14 (30.4)	8 (7.7)	11 (15.3)
Refractory to last regimen	49 (80.3)	39 (84.8)	32 (30.8)	29 (40.3)

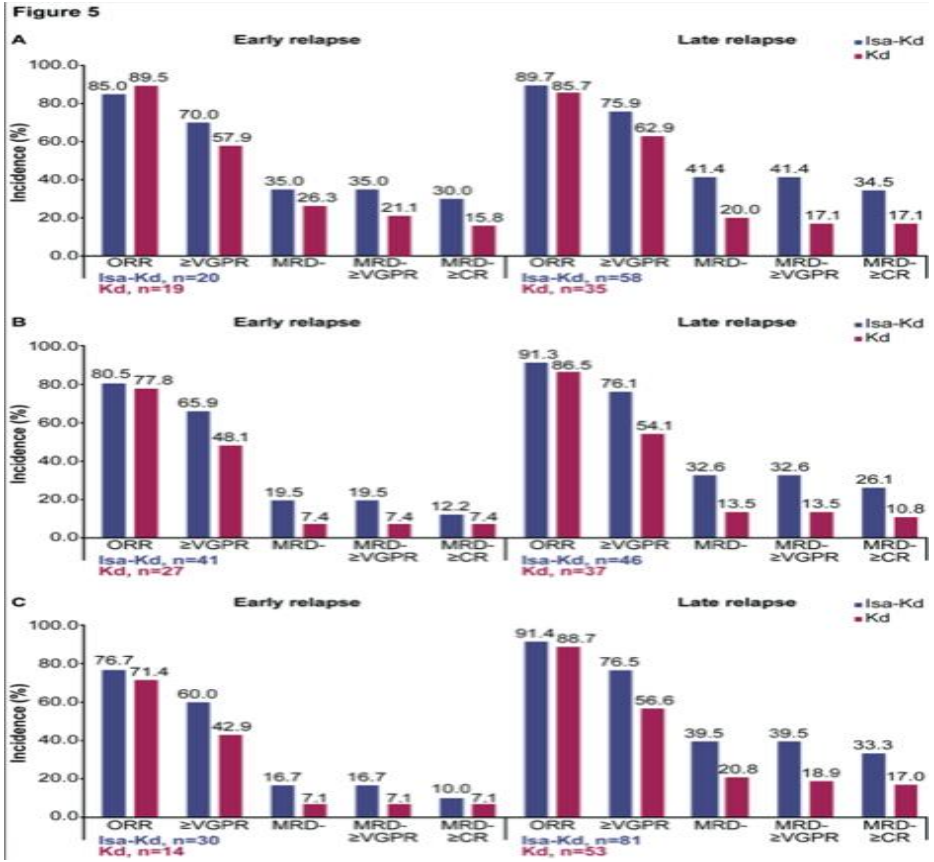
Facon T. Haematologica 2023, ASH 2023

Early relapse

Late relapse



Facon T. Haematologica 2023



Depth of response after
(A) 1 prior LOT,

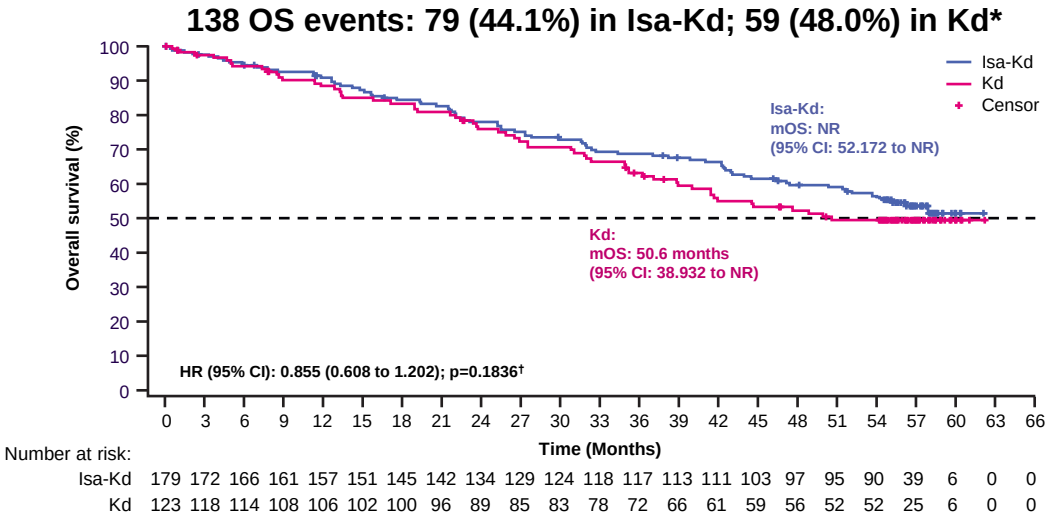
(B) 2 prior LOT

(C) prior ASCT.

Facon T. Haematologica 2023

OS analysis: *the longest OS in a phase 3 study of a len-free regimen in the RR setting*

- Extrapolating the current observed trend for an additional 12 months of follow-up, the mOS estimate for Isa-Kd arm is **63 months** (95% CI: 59–69)
- This corresponds to an estimated 1-year difference in mOS

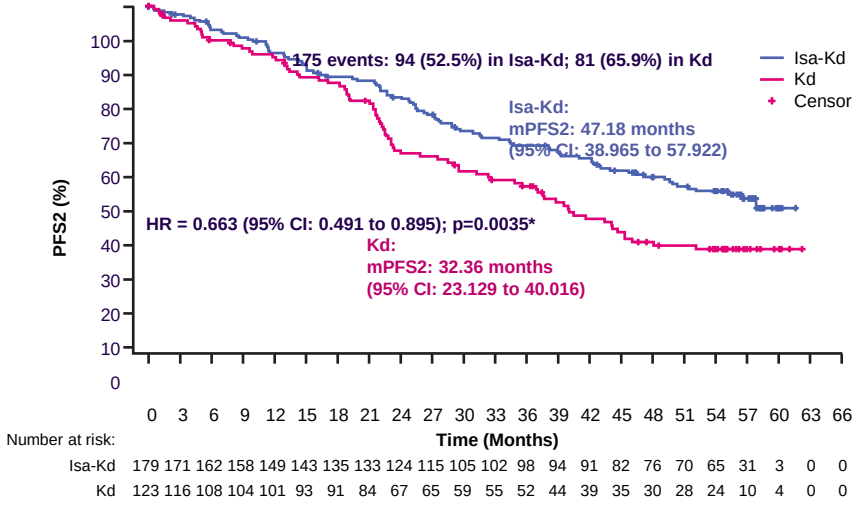


- **After a median follow-up of 56.6 months, mOS was not reached in the Isa-Kd arm**
- **The extrapolated mOS estimate of 63 months for Isa-Kd corresponds to an estimated 1-year difference in mOS versus Kd**

Moreau et al, IMS 2023

PFS2 (time from randomization to PD on subsequent therapy)

Sustained isatuximab benefit through the subsequent lines



ITT population	PFS2 HR (95% CI)
At final PFS analysis Median follow-up: 43.96 months	0.683 (0.496–0.941)
At OS analysis Median follow-up: 56.6 months	0.663 (0.491–0.895)

Subsequent treatments

	Isa-Kd%	Kd%
Imids	85	81
PI	47	41
anti-CD38	29	63
belantamab	16	3
Anti-BCMA bispecific	7	4
CAR-T	2	5
SCT	13	17

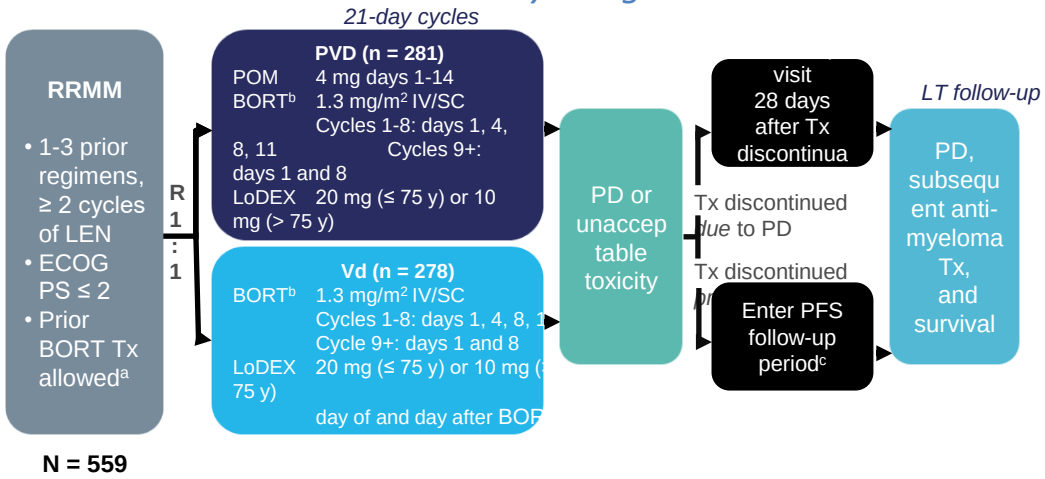
Moreau et al, IMS 2023

%	Interim PFS analysis: M follow-up 20.7 mo		Final PFS analysis: M follow-up 43.9 mo		OS analysis: M follow-up 56.6 m	
	Isa-Kd	Kd	Isa-Kd	Kd	Isa-Kd	Kd
Any TEAE	97.2	95.9	98.9	97.5	98.9	97.5
Grade≥3 TEAE	76.8	67.2	83.6	73.0	84.2	73.0
Grade 5 TEAE	3.4	3.3	5.6	4.9	6.8	4.9
Any TEAE leading stop	8.5	13.9	12.0	18	13.6	18.0
Cardiac Disorders All grades (≥3)					7.9 (4.0)	8.2 (4.1)
Cardiac failure All grades (≥3)					4.5 (2.3)	6.6 (3.3)
PE all grades (≥3)					1 (0.6)	1 (0.8)

Moreau et al, IMS 2023

Optimismm: PVD versus VD in RRMM

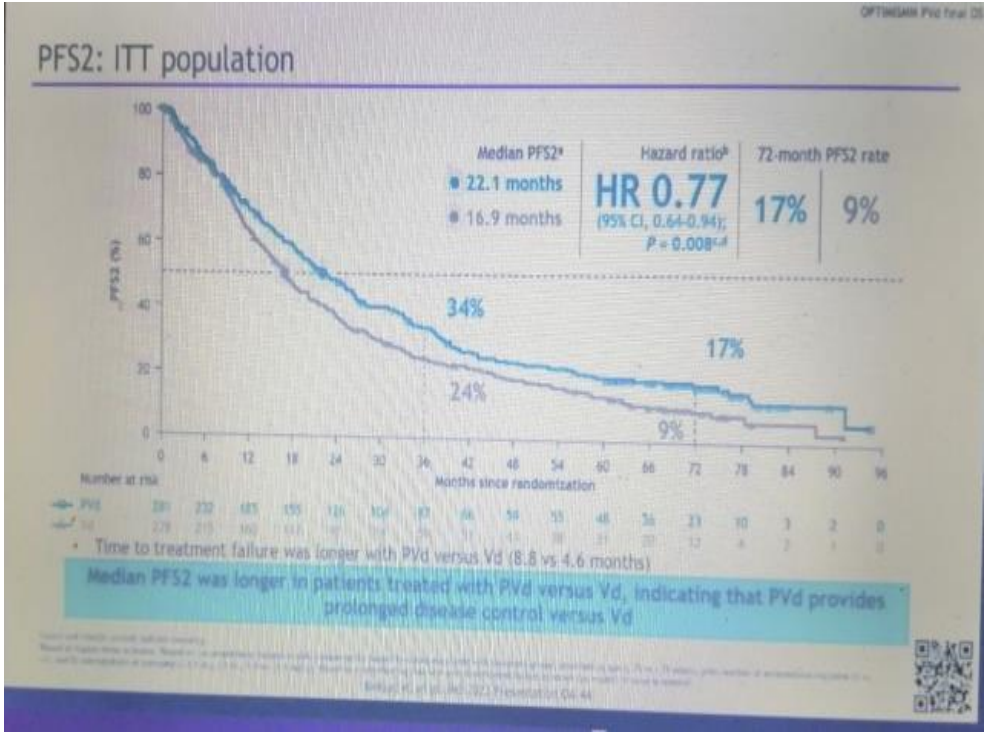
Study design



N = 559

- **NCT01734928**
- **Stratification**
  - Age (≤ 75 vs > 75 years)
  - No. of prior anti-myeloma regimens (1 vs > 1)
  - β_2-microglobulin levels at screening (< 3.5 vs ≥ 3.5 mg/L to ≤ 5.5 vs > 5.5 mg/L)

Richardson PG, et al. *Lancet Oncol.* 2019;



	PVd	Vd	p
Median OS (months)	35.6	31.6	0.571
72 mo- OS rate	26%	23%	

A trend toward improved median OS

Median PFS2 longer in PVd vs Vd

Beksac M et al, IMS 2023

% grade 3-4 AE	PVd	Vd
thrombocytopenia	28	25
neutropenia	**47**	9
Infections	**35**	19
Peripheral neuropathy	8	4
Invasive SPM	5	3
Hematological SPM	1	1
Solid SPM	4	2

Beksac M et l, IMS 2023

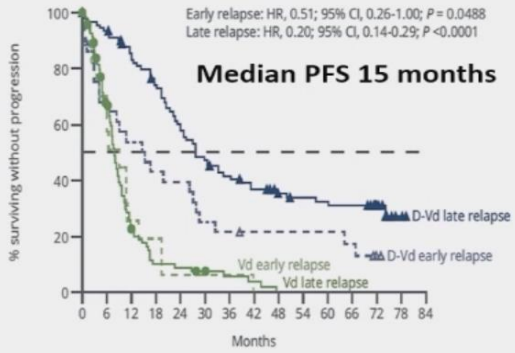
CONCLUSIONS

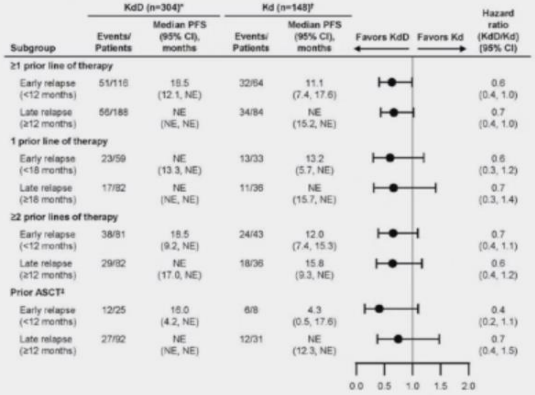
- Functional high-risk MM is still an unmet clinical need either because we cannot identify early pts at risk or because of lack of effective treatments.
- Switch drug class and maintain treatment intensity may have a role.
- At IMS meeting OS data were presented and they were not a measure of efficacy but gave an idea of sequencing and long term tolerability.
- Trials with bispecific antibodies and CAR-T are ongoing in this setting.

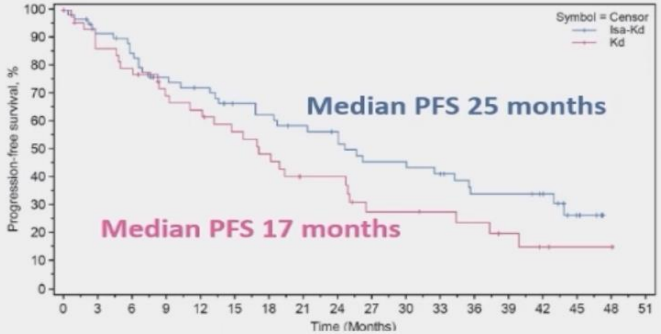
First relapse options: proteasome inhibitors backbone

CASTOR | **CANDOR** | **IKEMA**

EARLY RELAPSE







DVd
1 prior line: median 27 mo HR 0.22
Len ref: median 7.1 moHR 0.44
Early relapse: 15 months H R0.51

DKd
1 prior line: median NE HR 0.66
Len ref: median NE HR 0.63
Early relapse: median NE HR 0.6

IsaKd
1 prior line: median NA HR 0.71
Len ref: median NA HR 0.58
Early relapse: median 25 months HR 0.6

D, daratumumab; V, bortezomib; d, dexamethasone; K, carfilzomib; Isa, isatuximab; PFS, progression-free susrvival

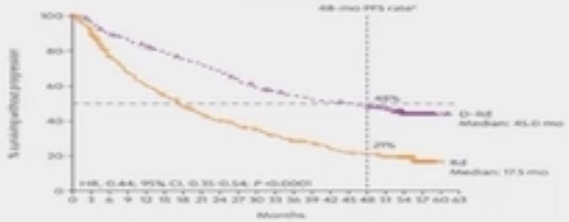
Mateos MV, et al. Clinical lymphoma Myeloma and Leukemia 2019; Usmani S, et al Lancet Oncol 2022; Martin T et al, BCJ 2023

First relapse options in lenalidomide naive patients

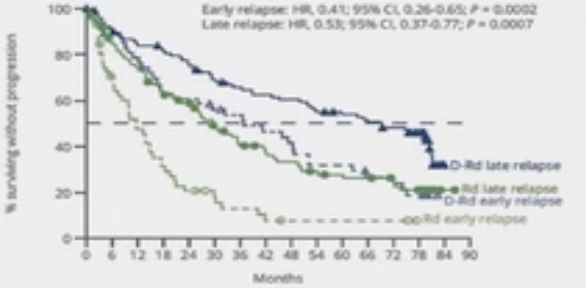
DaraRd
PFS: median 44.5 mo, HR: 0.44
1 prior line: median NR HR 0.42
Early relapse: median 37 mo, HR 0.41

KRd
PFS: median 26.3 m, HR: 0.69
1 prior line: median 29.6 HR 0.71
Early relapse: median 21 months

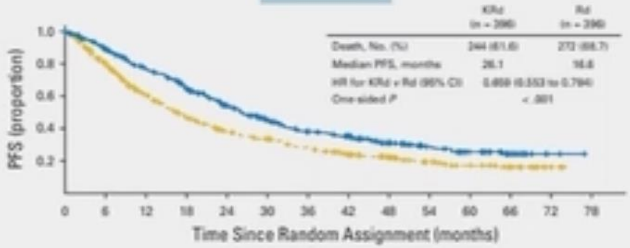
POLLUX

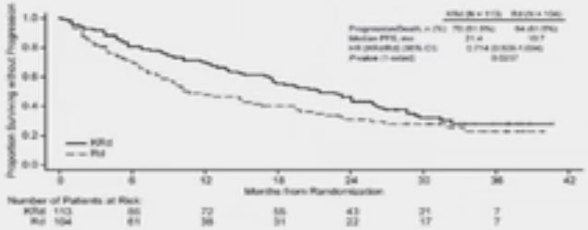


EARLY RELAPSE



ASPIRE





Dara/D, daratuumab; Elo, Elotuzuma; R, lenalidomide; t; PFS, progression-free survival

Bahlis Leukemia 2020; Kaufman ASH 2019; Dimopoulos NEJM 2016; Dimopoulus M et al BCJ 2017; Dimopoulos Cancer 2018; Siegel JCO 2018; Stewart NEJM 2015; Spencer et al., poster 8052 ASCO 2022; Mateos et al, Hematological Oncology. 2018