COR2ED

THE HEART OF MEDICAL EDUCATION

PART 2

MULTIPLE MYELOMA: THE RELEVANCE OF ADDING A NEW MoA IN THE TREATMENT OF RRMM – AN EXPERT VIEW

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MoA, mechanism of action; MM, multiple myeloma; RR, relapse/refractory

DEVELOPED BY COR2ED

This programme is developed by LYMPHOMA & MYELOMA CONNECT, an international group of experts working in the field of hematological malignancies

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EDUCATIONAL OBJECTIVES

- Know how to incorporate the **latest scientific and clinical insights on the treatment of MM** into clinical practice, focusing on the relapsed/refractory setting
- Knowing the **MoA** and how this translates into the **efficacy** profile of novel drugs
- **Learning from best practices** on treatment **sequencing**, treatment **combinations** and **dosing** in MM
- Knowing the **safety** profiles of novel drugs and what the best strategies are to prevent or act on side effects

FIRST LINE TREATMENT

- Usually contains
  - Bortezomib
  - Corticosteroids
  - Lenalidomide
- Today may contain
  - Daratumumab

Dimopoulos MA, et al. Ann Oncol. 2021;32:309–322;

MULTIPLE MYELOMA

PREMISE 1: AT DIAGNOSIS THE DISEASE IS ALREADY COMPLEX WITH MULTIPLE (SUB)CLONES AND GENOME ABERRATIONS[1,2]
PREMISE 2: GENOMIC ABERRATIONS CORRELATE TO DRUG SENSITIVITY/RESISTANCE[3,4]
PREMISE 3: AT RELAPSE THE CANCER GENOME HAS CHANGED[5,6]

Summary of proteasome subunit mutations from different myeloma cohorts

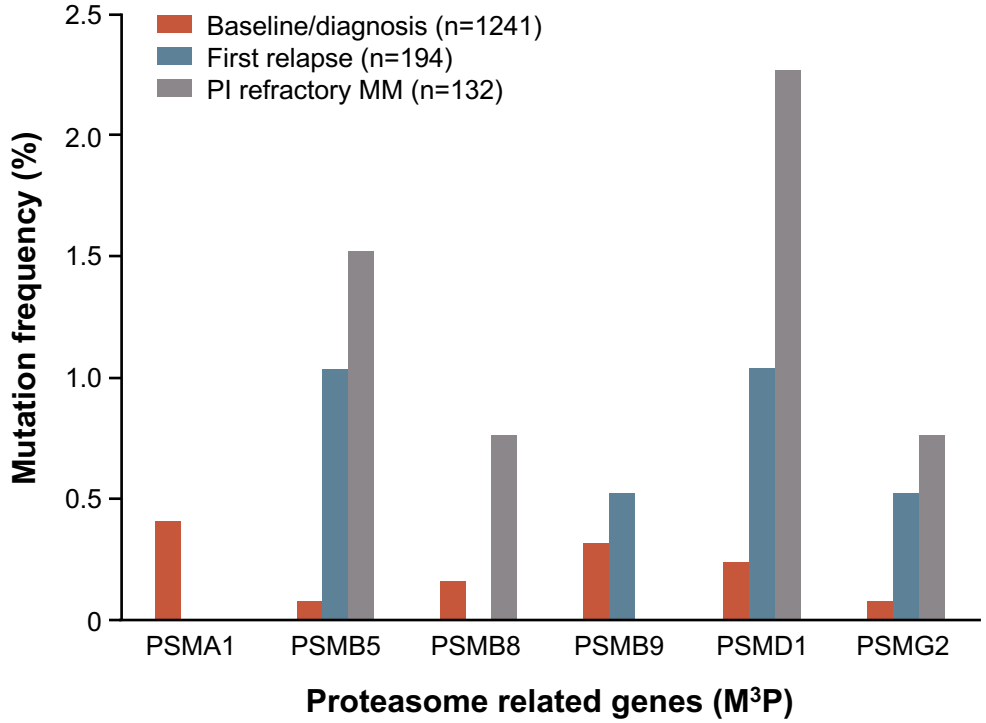
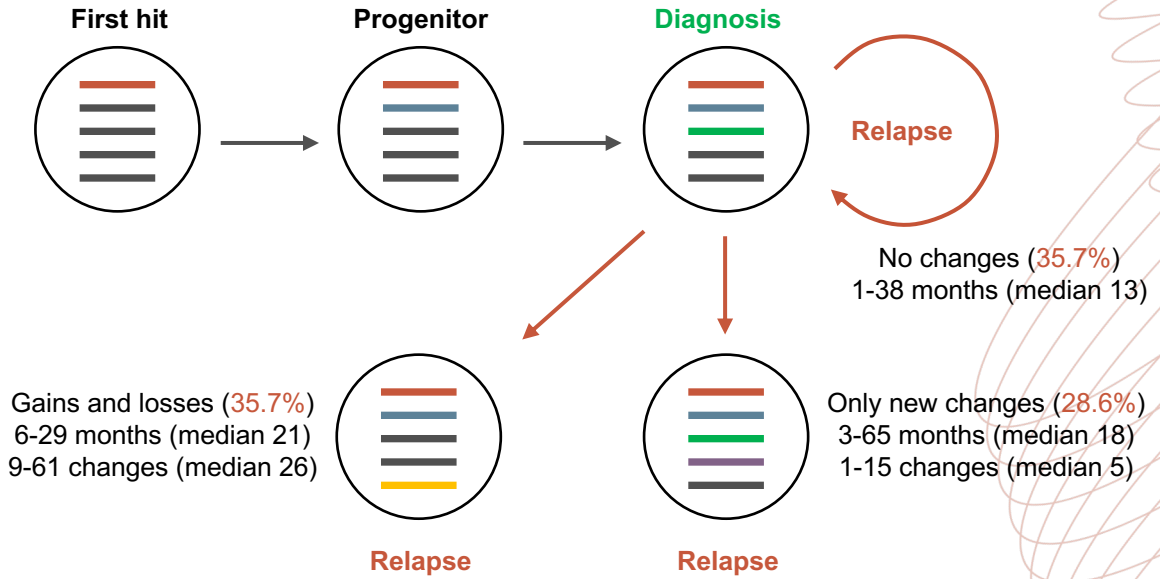


Figure adapted from Barrio et al.[5]

Summarized findings from 28 patients with a sequential sample pair



Coloured bars represent theoretical CNAs perceived to exist at a particular point in the evolution of the tumour

Figure adapted from Keats et al.[6]

M³P, multiple myeloma mutational panel; MM, multiple myeloma; PI, proteasome inhibitor; PSMA1, proteasome 20S subunit alpha 1; PSMB5/8/9, proteasome 20S subunit beta 5/8/9; PSMD1, proteasome 26S subunit, non-ATPase 1; PSMG2, proteasome assembly chaperone 2

1. Walker BA, et al. Blood. 2018;132:587-597; 2. Lohr JG, et al. Cancer Cell. 2014;25:91-101; 3. Marcotte R, et al. Cell. 2016;164:293-309; 4. Barrio S, et al. Leukemia. 2019;33:447-456; 5. Barrio S, et al. Leukemia. 2019;33:447-456 . 6. Keats JJ, et al. Blood. 2012;120:1067–1076

CHANGING + ADDING DRUG CLASS

Clonal dynamics in a patient with high-risk MM

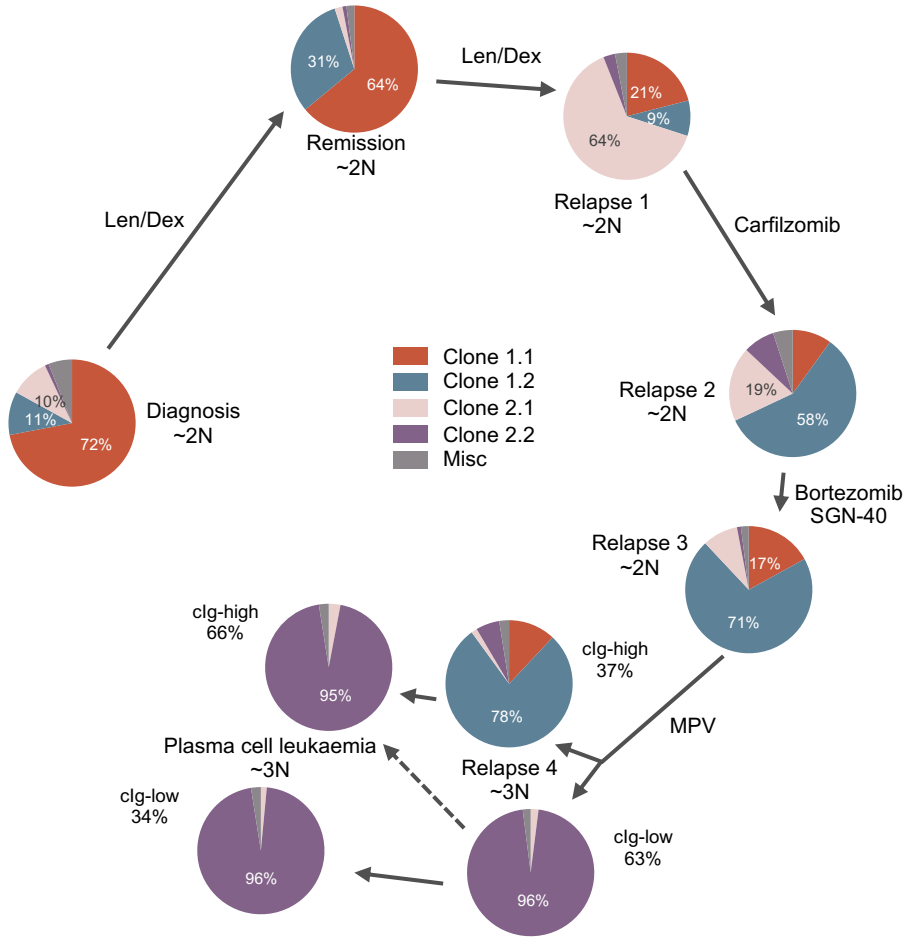


Figure adapted from Keats et al.[1]

Considerations at relapse[1]

Therapy	Patient	Disease characteristics
Prior drug class	Age / frailty / performance status	Early / late relapse
Prior efficacy	Patient preferences	Biochemical / symptomatic relapse
Duration of treatment	Comorbidities	Tumour burden
Previous toxicities	Bone marrow reserve	Cytogenetics
Refractoriness	Quality of life	Aggressiveness
Expected toxicities	End organ function	M-protein level

dex, dexamethasone; Len, lenalidomide; MM, multiple myeloma

1. Keats JJ, et al. Blood. 2012;120:1067-1076; 2. expert view

STRATEGY ADVICE 1

- Treat biochemical relapse/progression
- Switch to or add new MoA
- Treat continuously, if tolerated

STRATEGY ADVICE 2
HOW TO CHOOSE A REGIMEN?

- If two regimens are “equally effective”

MoA

- Aim for completely new MoAs, if not ➔
- What gives the biggest change in MoA from the last treatment?
- Aim for drugs that the patient has not received

(Think ahead)? Consider the next lines

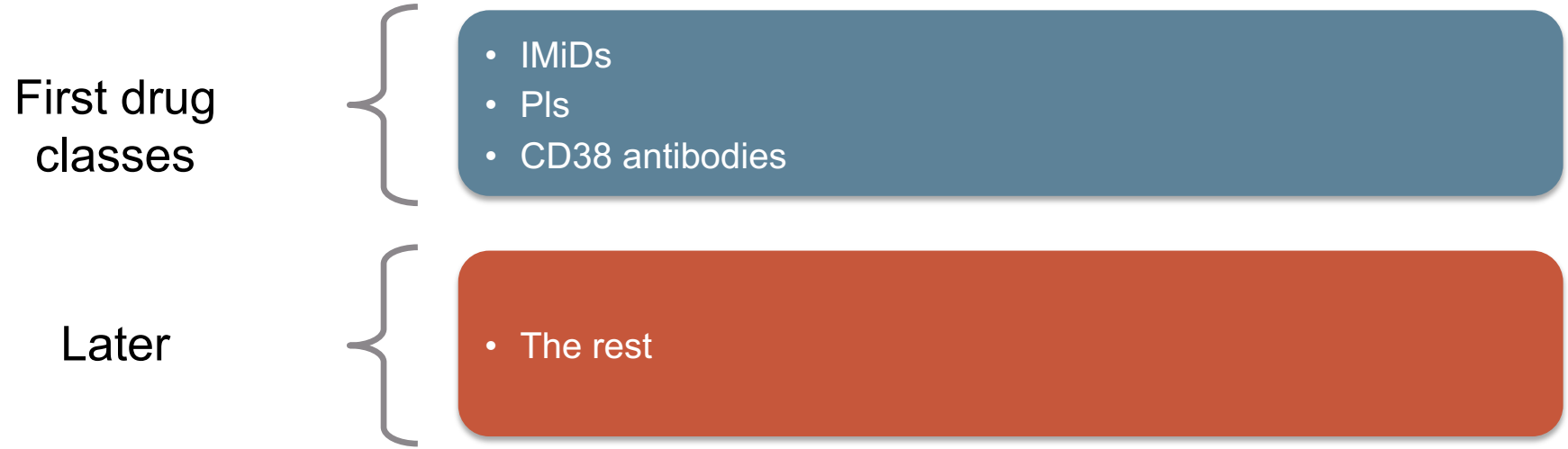
- Drugs with limited combinations
- Studies

Expert view

MoA, mechanism of action;

STRATEGY ADVICE 2
HOW TO CHOOSE A REGIMEN?

- What drug groups should the patient receive first?



Expert view
MoA, mechanism of action;

RELAPSE TREATMENT

OVERALL RESPONSE RATE BASED ON PRIOR TREATMENT HISTORY

Changing and adding drug class

In patients previously treated with bortezomib, randomized to DRd, the biggest increase in overall response rate is seen

	# of patients in group		Overall response rate, n (%)[a]		
Subgroup	**D-Rd**	**Rd**	**D-Rd**	**Rd**	**p value[b]**
ITT	281	276	261 (92.9)	211 (76.4)	<0.0001
Prior lines of therapy					
1	147	142	137 (93.2)	114 (80.3)	0.0003
2 to 3	120	115	114 (95.0)	85 (73.9)	<0.0001
1 to 3	267	257	251 (94.0)	199 (77.4)	<0.0001
Prior therapy					
Bortezomib	237	232	218 (92.0)	175 (75.4)	<0.0001
Lenalidomide	50	47	42 (84.0)	32 (64.0)	0.0233
Thalidomide	119	123	109 (91.6)	87 (70.7)	<0.0001
Refractory to bortezomib	57	56	50 (87.7)	38 (67.9)	0.0113

Changing drug class

Retreatment

Adding drug class

Data are based on computerised algorithm

[a] Response-evaluable population; [b] p value was generated using the Cochran-Mantel-Haenszel χ^2 test; (D-)Rd, (daratumumab), lenalidomide, dexamethasone; ITT, intent-to-treat

Dimopoulos MA, et al. Haematologica. 2018;103:2088-2096

OPTIONS FOR SECOND LINE TREATMENT

PI  IMiD  CD38 ab 

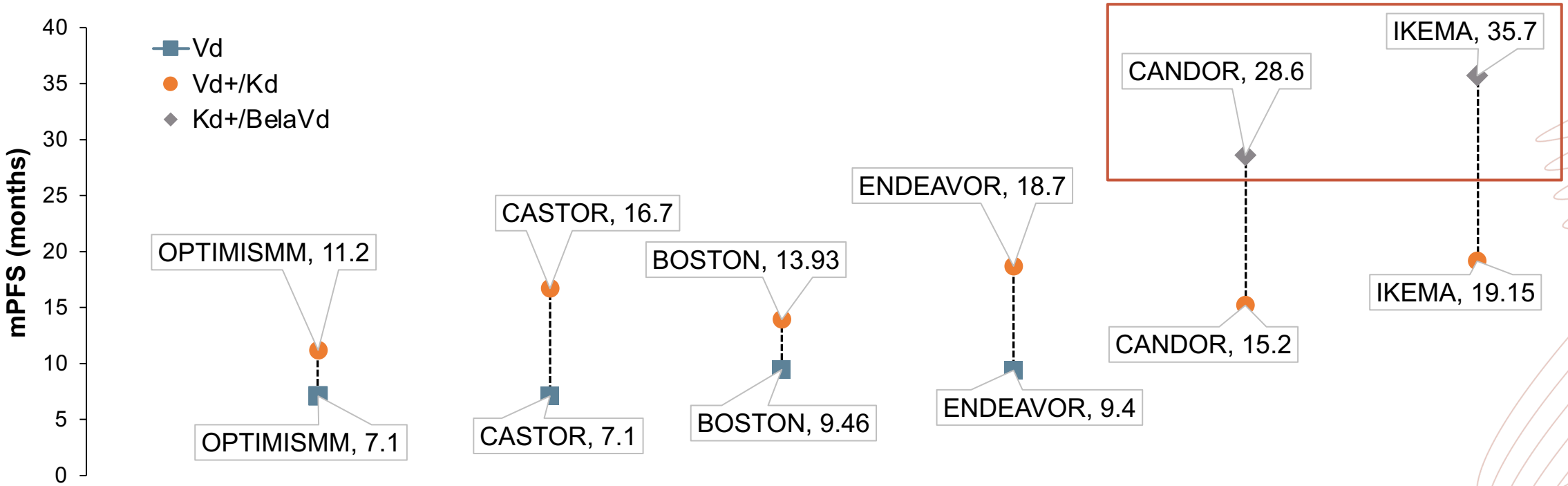
- **After (V)Rd/Rd/ASCT-Len** → Proteasome inhibitor-based treatment + CD38 ab
- **After D-VMP** → IMiD-based treatment
- **After DRd** → Proteasome inhibitor-based treatment

Expert view

ASCT, autologous stem cell transplant; CD38 ab, cluster of differentiation 38 antibody; D, daratumumab; IMiD, immunomodulatory drug; Len, lenalidomide; PI, proteasome inhibitor; Rd, lenalidomide plus dexamethasone; V, bortezomib; VMP, bortezomib, melphalan, and prednisone

PROTEASOME INHIBITOR-BASED SECOND-LINE TREATMENT

mPFS OF DIFFERENT TRIALS AFTER Rd – or ASCT-Len



%	OPTIMISMM[1]		CASTOR[2]		BOSTON[3]		ENDEAVOR[4]		CANDOR[5]		IKEMA[6,7]	
	PVd (n=281)	Vd (n=278)	DVd (n=251)	Vd (n=247)	SVd (n=195)	Vd (n=247)	Kd (n=464)	Vd (n=465)	DKd (n=312)	Kd (n=154)	Isa-Kd (n=179)	Kd (n=123)
Prior lines of therapy												
1	40	41	49	46	51	48	50	50	46	46	44	45
Prior therapies												
Bortezomib	72	73	65	66	69	70	54	54	92	87	93	85
Lenalidomide	100	100	36	49	40	37	38	38	39	48	40	48

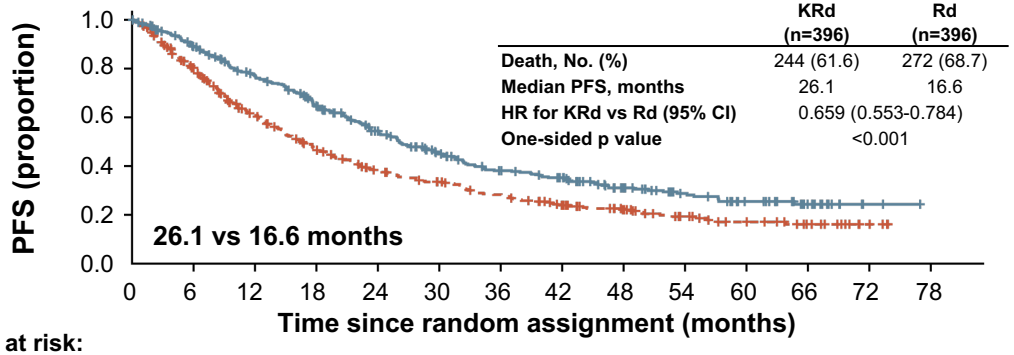
Head-to-head studies have not been conducted. Cross-trial comparisons are not appropriate.

ASCT, autologous stem cell transplant; DKd, daratumumab, carfilzomib, dexamethasone; DVd, daratumumab, bortezomib, dexamethasone; Isa-Kd, isatuximab, carfilzomib, dexamethasone; Kd, carfilzomib, dexamethasone; Len, lenalidomide; mPFS, median progression-free survival; NR, not reached; PVd, pomalidomide, bortezomib, dexamethasone; Rd, lenalidomide, dexamethasone; SVd, selinexor, bortezomib, dexamethasone; Vd, bortezomib, dexamethasone;

1. Richardson PG, et al. Lancet Oncol. 2019;20:781-794 (OPTIMISMM); 2. Mateos M-V, et al. 2020;20:509-518 (CASTOR); 3. Grosicki S, et al. Lancet. 2020;396:1563-1573 (BOSTON); 4. Dimopoulos MA, et al. Lancet Oncol. 2016.17:27-38 (ENDEAVOR); 5. Usmani SZ, et al. Lancet. Oncol. 2022;23:65-76 (CANDOR); 6. Moreau P, et al. Lancet. 2021;397:2361-2371 (IKEMA); 7. Martin T, et al. Blood Cancer J. 2023;13:72 (IKEMA)

SECOND LINE AFTER D-VMP: IMiD-BASED

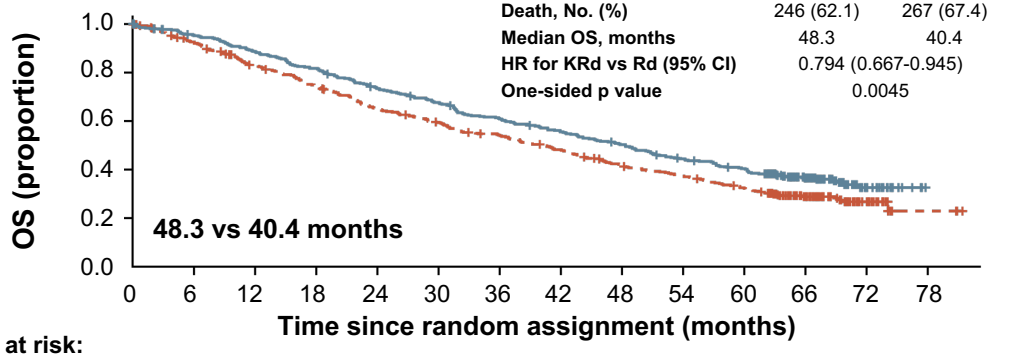
KRd vs Rd[1]



	KRd (n=396)	Rd (n=396)
Death, No. (%)	244 (61.6)	272 (68.7)
Median PFS, months	26.1	16.6
HR for KRd vs Rd (95% CI)	0.659 (0.553-0.784)	
One-sided p value	<0.001	

No. at risk:

KRd	396	337	282	227	178	136	109	94	65	45	32	17	2	0
Rd	396	291	211	154	118	99	81	61	45	30	21	13	4	0

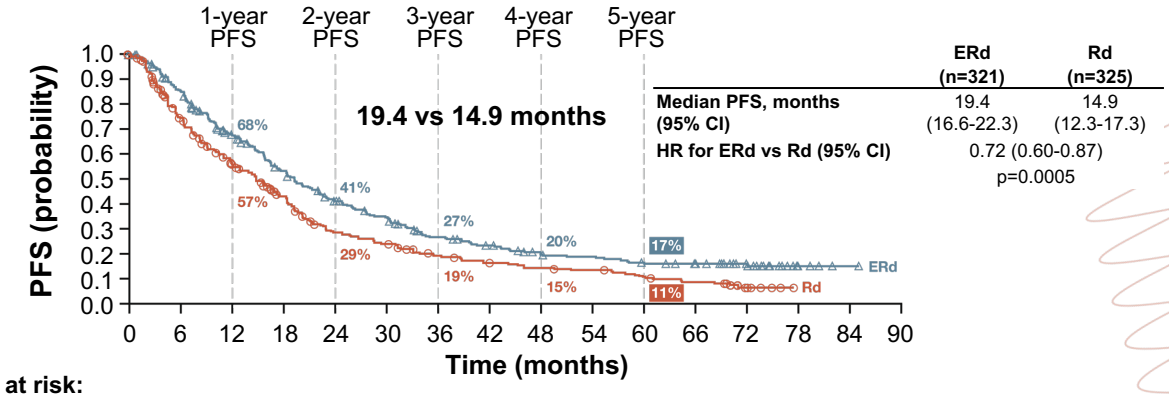


	KRd (n=396)	Rd (n=396)
Death, No. (%)	246 (62.1)	267 (67.4)
Median OS, months	48.3	40.4
HR for KRd vs Rd (95% CI)	0.794 (0.667-0.945)	
One-sided p value	0.0045	

No. at risk:

KRd	396	369	343	316	282	259	232	211	190	166	149	88	22	0
Rd	396	356	313	281	243	220	199	176	149	133	113	69	20	3

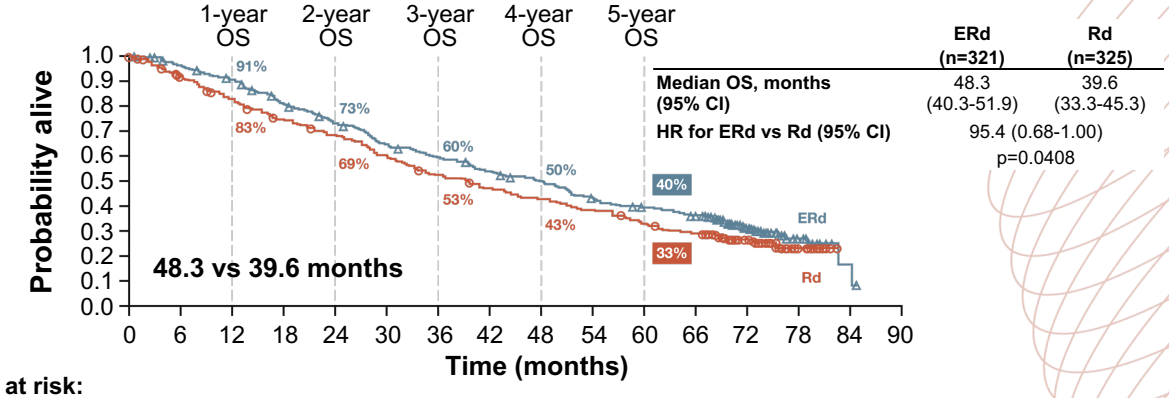
EloRd vs Rd[2]



	ERd (n=321)	Rd (n=325)
Median PFS, months (95% CI)	19.4 (16.6-22.3)	14.9 (12.3-17.3)
HR for ERd vs Rd (95% CI)	0.72 (0.60-0.87)	
	p=0.0005	

No. at risk:

KRd	321	261	196	149	113	92	67	56	44	41	34	31	18	4	1	0
Rd	325	217	159	109	69	58	42	35	30	27	21	16	6	0	0	0



	ERd (n=321)	Rd (n=325)
Median OS, months (95% CI)	48.3 (40.3-51.9)	39.6 (33.3-45.3)
HR for ERd vs Rd (95% CI)	95.4 (0.68-1.00)	
	p=0.0408	

No. at risk:

KRd	321	303	283	250	224	197	181	163	149	129	115	105	57	15	2	0
Rd	325	287	255	228	208	184	159	142	128	116	98	86	47	9	0	0

Head-to-head studies have not been conducted. Cross-trial comparisons are not appropriate.

D-VMP, daratumumab, bortezomib, melphalan, prednisone; EloRd, elotuzumab, lenalidomide, dexamethasone; HR, hazard ratio; IMiD, immunomodulatory drug; KRd, carfilzomib, lenalidomide, dexamethasone; OS, overall survival; PFS, progression-free survival; Rd, lenalidomide, dexamethasone

1. Siegel DS, et al. J Clin Oncol. 2018;36:728-34; 2. Dimopoulos M, et al. Blood Cancer J. 2020;10:91

SECOND LINE AFTER D-VMP: IMiD-BASED
KRd OR ELoRd

- Why not DPd ➔ Already daratumumab-refractory
- Why not IxaRd ➔ No OS benefit
- Why not PVd ➔ Re-use of bortezomib; studied in lenalidomide-exposed

- KRd or EloRd?
- For KRd:
  - KRd best PFS HR (0.66 vs 0.72 for EloRd)[1,2]
  - EloRd may not be as good directly after daratumumab
- EloRd:
  - EloRd best tolerated
  - Patient already exposed to PI

Expert view

DPd, daratumumab, pomalidomide; D-VMP, daratumumab, bortezomib, melphalan, prednisone; EloRd, elotuzumab, lenalidomide, dexamethasone; HR, hazard ratio; IMiD, immunomodulatory drug; IxaRd, ixazomib, lenalidomide, dexamethasone; KRd, carfilzomib, lenalidomide, dexamethasone; OS, overall survival; PI, proteasome inhibitor; PFS, progression-free survival; PVd, pomalidomide, bortezomib, dexamethasone

1. Siegel DS, et al. J Clin Oncol. 2018;36:728-34; 2. Dimopoulos M, et al. Blood Cancer J. 2020;10:91

RELAPSE TREATMENT AFTER DRd?

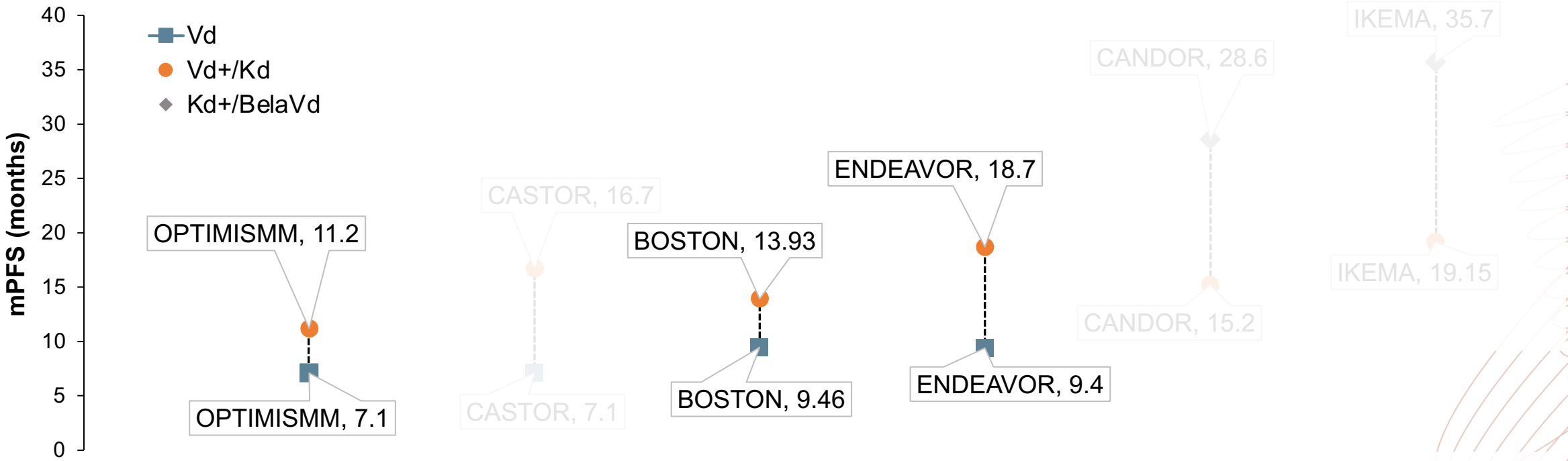
- No CD38 options
- No lenalidomide options
- Adamant to include a PI
- As always, triplets are preferred
- What options are there?
  - PVd
  - SVd
  - Kd?

Expert view

CD38, cluster of differentiation 38; DRd, daratumumab, lenalidomed, dexamethasone; Kd, carfizomib, dexamethasone; PI, proteasome inhibitor; PVd, pomalidomide, bortezomib, dexamethasone; SVd, Selinexor bortezomib, dexamethasone;

PROTEASOME INHIBITOR-BASED SECOND-LINE TREATMENT

mPFS OF DIFFERENT TRIALS AFTER Rd – or ASCT-Len



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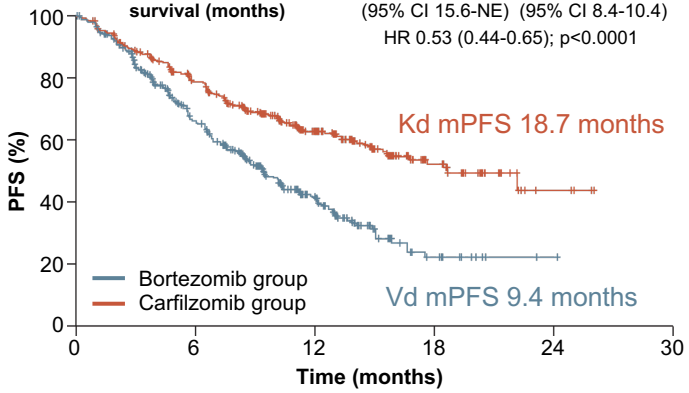
RELAPSE TREATMENT AFTER DRd

ENDEAVOR[1]

1–3 prior lines of therapy

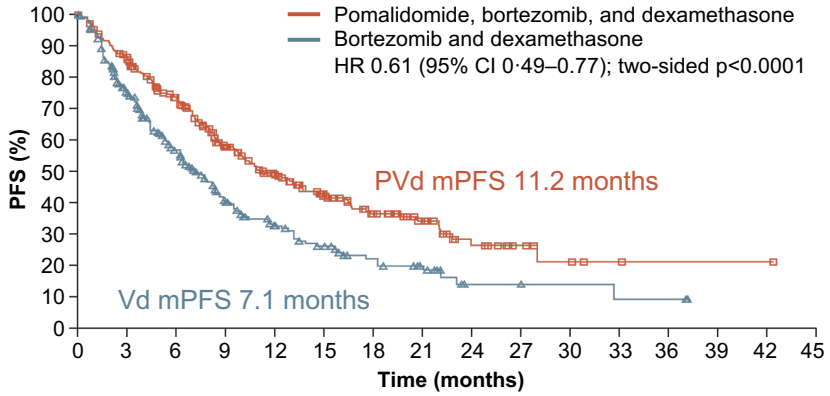
	Carfilzomib group (n=464)	Bortezomib group (n=465)
Median progression-free survival (months)	18.7 (95% CI 15.6-NE)	9.4 (95% CI 8.4-10.4)

HR 0.53 (0.44-0.65); p<0.0001



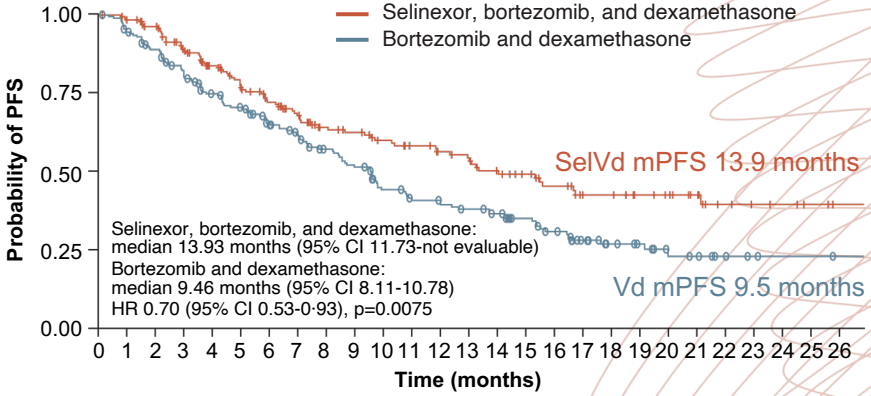
OPTIMISMM[2]

1–3 prior lines of therapy, received **prior treatment** with a **lenalidomide-containing regimen** for ≥2 consecutive cycles, not bortezomib refractory



BOSTON[3]

1–3 prior lines of therapy



Kd[1]

- Doublet
- PI
- One different MoA

Acceptable safety and tolerability profile of carfilzomib

PVd[2]

- Triplet
- PI
- One different MoA

Adverse events accorded with the individual profiles of pomalidomide, bortezomib, and dexamethasone

SelVd[3]

- Triplet
- PI
- **Two different MoAs**

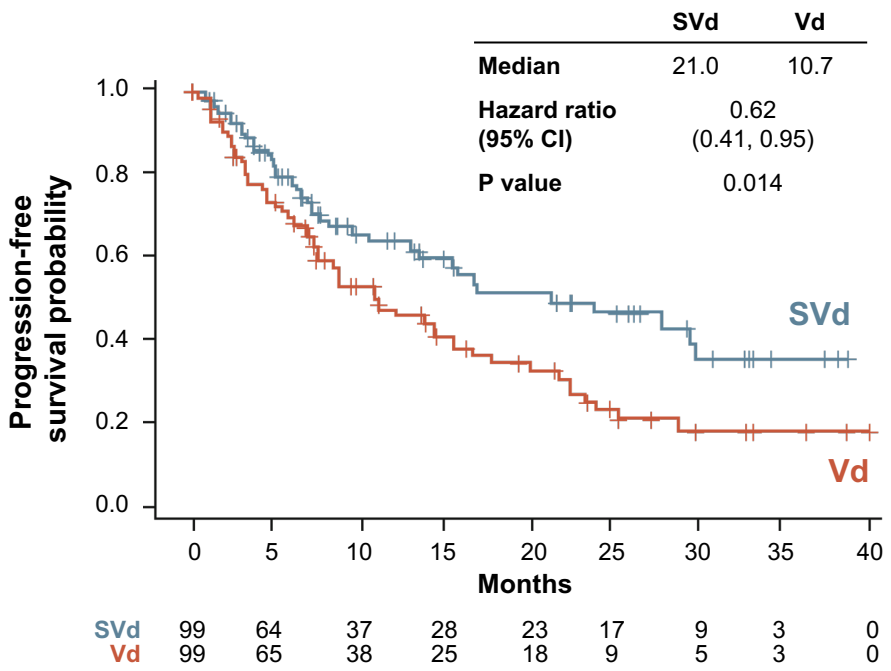
Safety results were consistent with the individual adverse event profiles of selinexor, bortezomib, and dexamethasone

CI, confidence interval; DRd, daratumumab, lenalidomide and dexamethasone; HR, hazard ratio; Kd, carfilzomib and dexamethasone; MoA, mechanism of action; (m)PFS, (median) progression-free survival; NE, not estimable; PI, proteasome inhibitor; PVd, pomalidomide, bortezomib, and dexamethasone; SelVd, selinexor, bortezomib, and dexamethasone; Vd, bortezomib and dexamethasone.

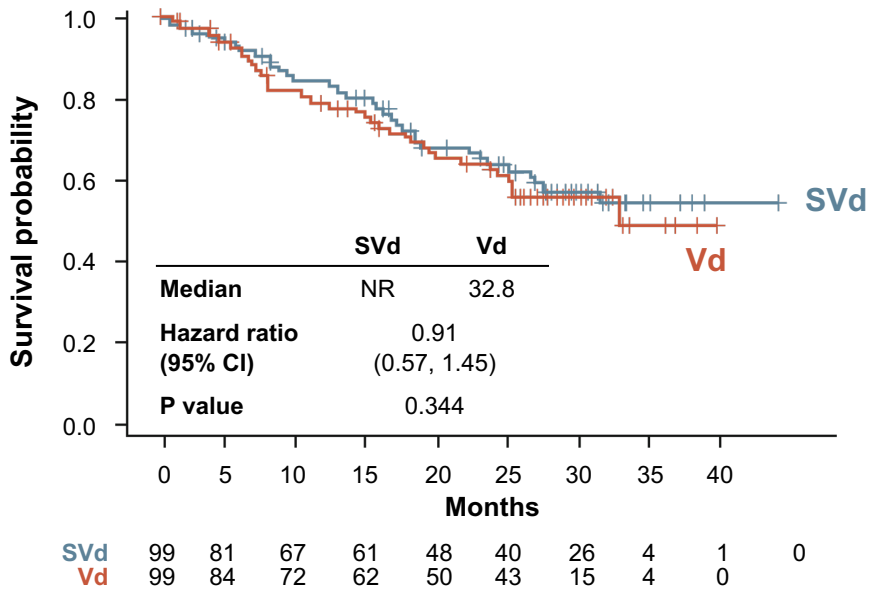
1. Dimopoulos MA, et al. Lancet Oncol. 2016.17:27-38; 2. Richardson PG, et al. Lancet Oncol. 2019;20:781-794; 3. Grosicki S, et al. Lancet. 2020;396:1563-1573

BOSTON SUBGROUP ANALYSIS OF PATIENTS WITH ONE PRIOR LINE OF THERAPY: SIGNIFICANT IMPROVEMENT IN PFS WITH SVd VS Vd

PFS



OS



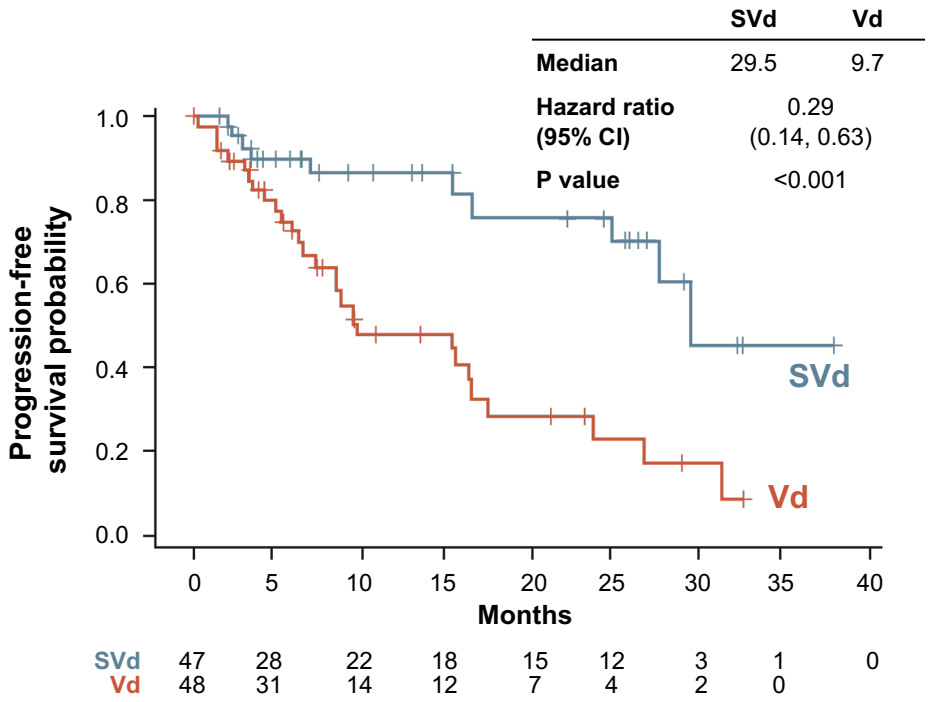
- Higher ORR with SVd vs Vd (80.8% vs 66.7%; OR 2.40; p=0.005)
- Higher ≥ VGPR with SVd vs Vd (52.5% vs 29.3%; OR 2.65; p<0.001)

CI, confidence intervals; NR, not reached; OR, odds ratio; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; SVd, selinexor, bortezomib, dexamethasone; Vd, bortezomib, dexamethasone; VGPR, very good partial response

Mateos MV, et al. Eur J Haematol. 2024;1-11

BOSTON SUBGROUP ANALYSIS OF PATIENTS WITH PI NAÏVE MM: SIGNIFICANT IMPROVEMENT IN PFS WITH SVd VS Vd

PFS



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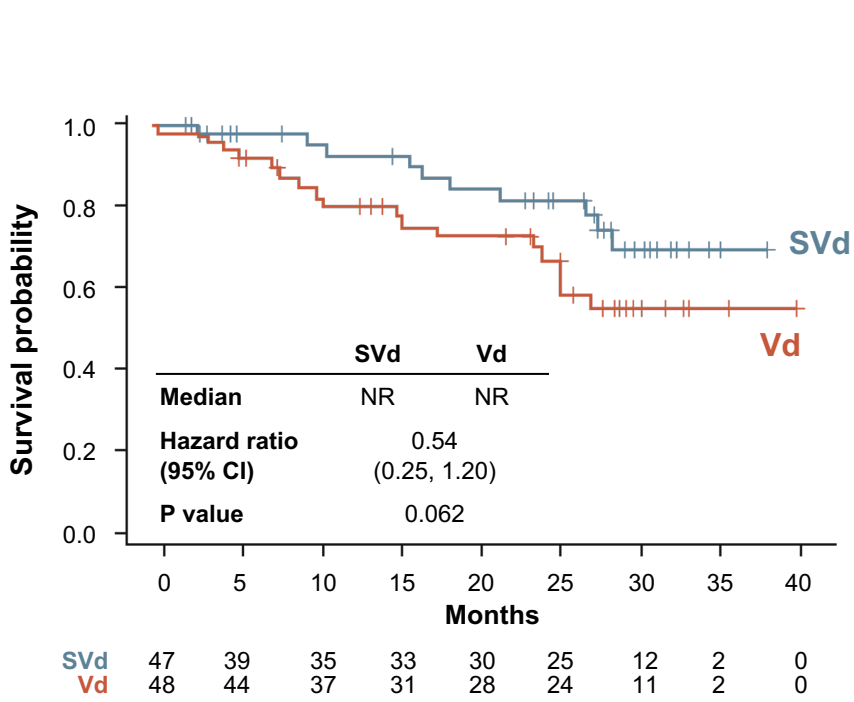


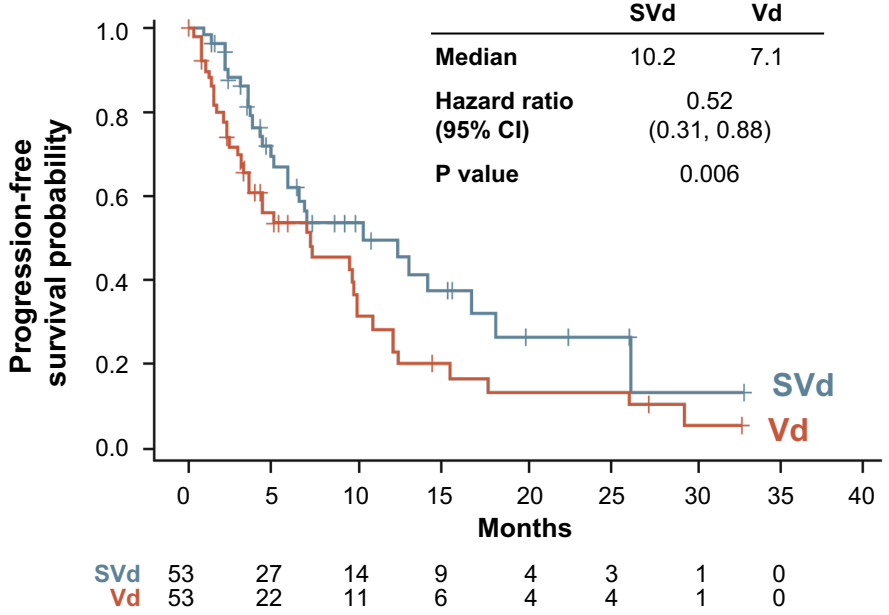
- Higher ORR with SVd vs Vd (67.9% vs 47.2%; OR 2.59 [95% CI, 1.17–5.77]; p=0.009)
- Higher ≥ VGPR with SVd vs Vd (35.8% vs 24.5%; OR 1.74 [95% CI, 0.72–4.21]; p=0.109)

CI, confidence intervals; MM, multiple myeloma; NR, not reached; OR, odds ratio; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; PI, proteasome inhibitor; SVd, selinexor, bortezomib, dexamethasone; Vd, bortezomib, dexamethasone; VGPR, very good partial response

Mateos MV, et al. Eur J Haematol. 2024;1-11

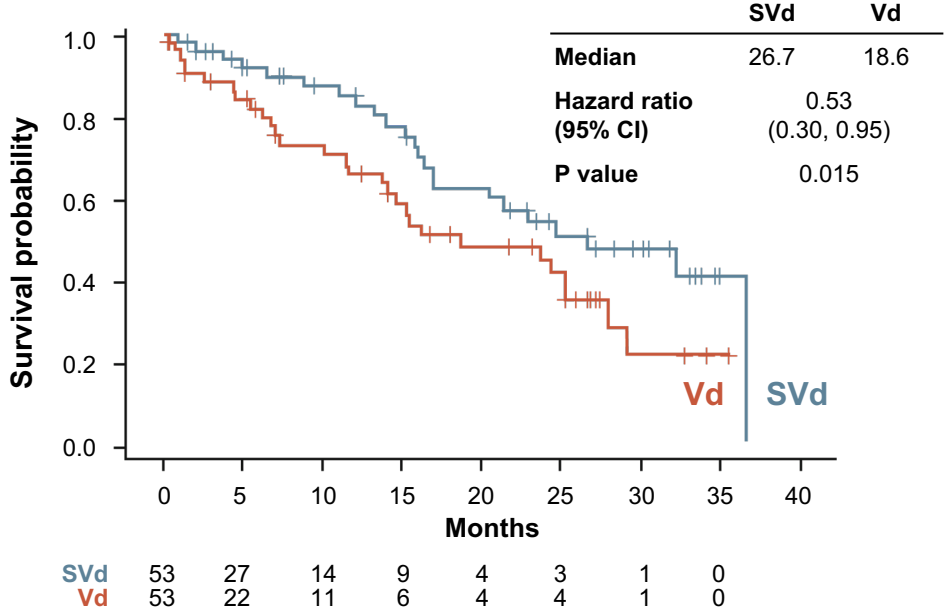
BOSTON SUBGROUP ANALYSIS OF PATIENTS WITH LENALIDOMIDE-REFRACTORY MM: SIGNIFICANT IMPROVEMENT IN PFS AND OS WITH SVd VS Vd

PFS



	SVd	Vd
Median	10.2	7.1
Hazard ratio (95% CI)	0.52 (0.31, 0.88)	
P value	0.006	

OS



	SVd	Vd
Median	26.7	18.6
Hazard ratio (95% CI)	0.53 (0.30, 0.95)	
P value	0.015	

- Higher ORR with SVd vs Vd (76.6% vs 70.8%; OR 1.30 [95% CI, 0.51–3.33]; p=0.290)
- Higher ≥ VGPR with SVd vs Vd (53.2% vs 41.7%; OR 1.54 [95% CI, 0.68–3.48]; p=0.154)

CI, confidence intervals; MM, multiple myeloma; OR, odds ratio; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; SVd, selinexor, bortezomib, dexamethasone; Vd, bortezomib, dexamethasone; VGPR, very good partial response

Mateos MV, et al. Eur J Haematol. 2024;1-11

BOSTON SUBGROUP ANALYSES:

AEs WERE GENERALLY MANAGEABLE AND SAFETY PROFILES WERE SIMILAR ACROSS THE SUBGROUPS

Grade 3-4 TRAEs occurring in >5% of lenalidomide-refractory patients

Preferred term, n (%)	Lenalidomide-refractory	
	SVd (n=53)	Vd (n=52)
Haematological		
Thrombocytopenia	24 (45)	16 (31)
Anaemia	4 (8)	2 (4)
Neutropenia	2 (4)	1 (2)
Non-haematological		
Fatigue	5 (9)	0
Nausea	5 (9)	0
Diarrhoea	6 (11)	0
Peripheral neuropathy	2 (4)	4 (8)
Asthenia	1 (2)	1 (2)
Cataract	7 (13)	1 (2)
Vomiting	4 (8)	0

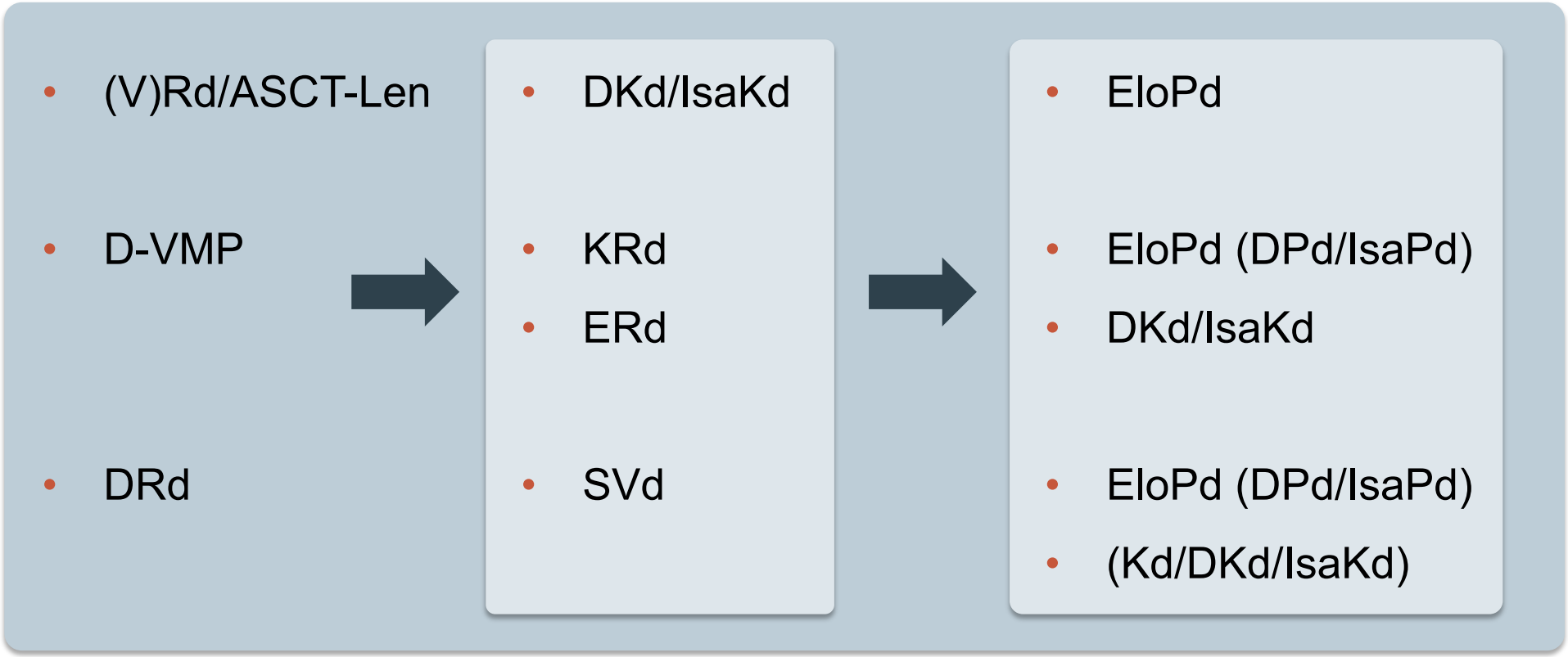
Grade 3-4 TRAEs occurring in >5% of patients with one prior LOT

Preferred term, n (%)	One prior LOT	
	SVd (n=99)	Vd (n=99)
Haematological		
Thrombocytopenia	37 (37)	16 (16)
Anaemia	5 (5)	2 (2)
Neutropenia	9 (9)	2 (2)
Non-haematological		
Fatigue	12 (12)	0
Nausea	8 (8)	0
Diarrhoea	3 (3)	0
Peripheral neuropathy	6 (6)	9 (9)
Asthenia	9 (9)	2 (2)
Cataract	8 (8)	0
Vomiting	5 (5)	0

AE, adverse event; LOT, line of therapy; SVd, selinexor, bortezomib, dexamethasone; TRAEs, treatment-related adverse events; Vd, bortezomib, dexamethasone

Mateos MV, et al. Eur J Haematol. 2024;1-11

CONCLUSIONS



Expert view

ASCT, autologous stem cell transplant; DKd, daratumumab, carfilzomib, dexamethasone; DPd, daratumumab, pomalidomide; DRd, daratumumab, lenalidomide, dexamethasome; D-VMP, daratumumab, bortezomib, melphalan, prednisone; EloPd, elotuzumab, pomalidomide; ERd, elotuzumab, lenalidomide, dexamethasone; IsaKd, isatuximab, carfilzomib, dexamethasone; IsaPd, isatuximab, pomalidomide; Kd, carfilzomib, dexamethasone; KRd, carfilzomib, lenalidomide, dexamethasone; Len, lenalidomide; Pd, pomalidomide; PVd, pomalidomide, bortezomib, and dexamethasone; Rd, lenalidomide, dexamethasone; SVd, selinexor, bortezomib, dexamethasone; V, bortezomib

KEY CLINICAL TAKEAWAYS

- Multiple myeloma is a **highly heterogeneous disease** from diagnosis
- The **heterogeneic clones** vary in their sensitivity to different treatments. Therefore, **combinations are preferable**
- Each new treatment should preferably include drugs with **novel mechanisms of action**, which is **more important** when multiple myeloma becomes **refractory** rather than just exposed

USE
- The best available treatment
- Regimens from controlled clinical trials

PREFER
- Treatments with OS benefit
- Changing (adding) MoA
- Triplets

TREAT
- At biochemical relapse
- Treatment approach should be continuous

Expert view

MoA, mechanisms of action; OS, overall survival

FIND OUT MORE ABOUT RRMM IN PARTS 1 AND 3

PART 1: UNMET MEDICAL NEEDS IN EARLY RELAPSE

PART 3: CURRENT BEST PRACTICES IN THE TREATMENT OF EARLY RRMM – AN EXPERT VIEW

MM, multiple myeloma; RR, relapsed/refractory;

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