COR2ED

THE HEART OF MEDICAL EDUCATION

PART 1

MULTIPLE MYELOMA: UNMET MEDICAL NEEDS IN EARLY RELAPSE

Dr Elena Zamagni,
University of Bologna, Italy

September 2024

DEVELOPED BY LYMPHOMA & MYELOMA CONNECT

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

LYMPHOMA & MYELOMA connect®
POWERED BY COR2ED

Acknowledgement and disclosures

This LYMPHOMA & MYELOMA CONNECT programme is supported through an independent educational grant from Menarini Stemline Oncology. The programme is therefore independent, the content is not influenced by the supporter and is under the sole responsibility of the experts.

Please note: The views expressed within this programme are the personal opinions of the experts. They do not necessarily represent the views of the experts' institutions, or the rest of the LYMPHOMA & MYELOMA CONNECT group.

Expert disclaimer:

- **Dr Elena Zamagni** has received financial support/sponsorship for research support, consultation, or speaker fees from the following companies: Janssen, BMS, Amgen, Pfizer, GSK and Sanofi

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

MULTIPLE MYELOMA
CURRENT TREATMENT LANDSCAPE AND CHALLENGES

Current **ESMO treatment guidelines** recommend frontline regimens including **anti-CD38 mAbs** and **proteasome inhibitors** and/or **immunomodulators agents** for NDMM[1]

However, with earlier use of triplet combinations in first-line, patients are now becoming **triple- or penta-exposed** and even **penta-refractory** after very few lines of therapy[1,2]

These include treatments containing the immunomodulator **lenalidomide** and the anti-CD38 mAb **daratumumab**[1]

CD38, cluster of differentiation 38; ESMO, European Society for Medical Oncology; mAb, monoclonal antibody; NDMM, newly diagnosed multiple myeloma

1. Dimopoulos MA, et al. Ann Oncol. 2021;32:309-322; 2. Morè S, et al. Cancers (Basel) 2023;15(8):2203.

EHA-ESMO MM GUIDELINES – TRANSPLANT-INELIGIBLE PATIENTS

THE TREATMENT PARADIGM IN MM HAS CHANGED

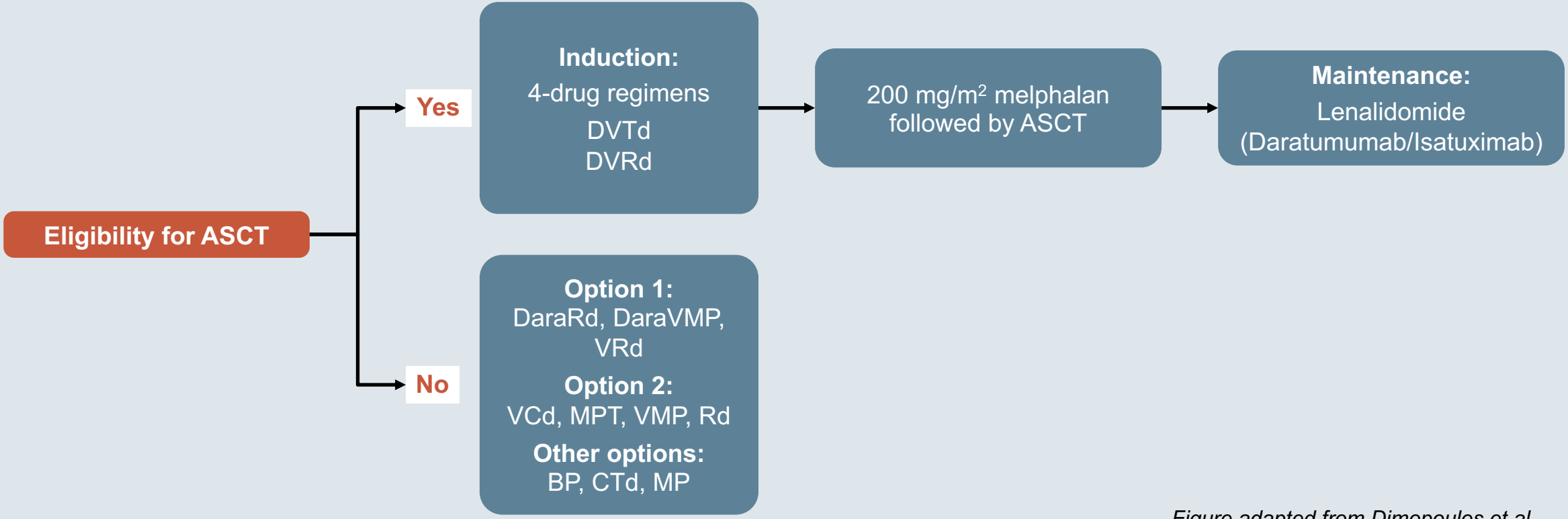


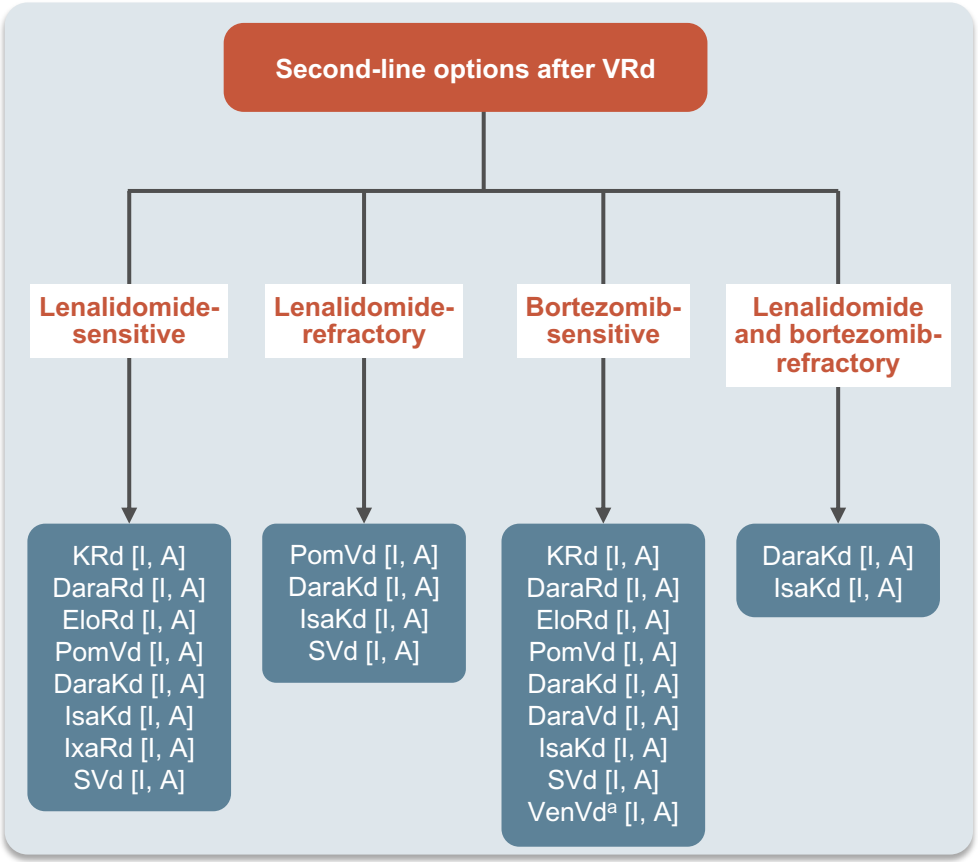
Figure adapted from Dimopoulos et al.

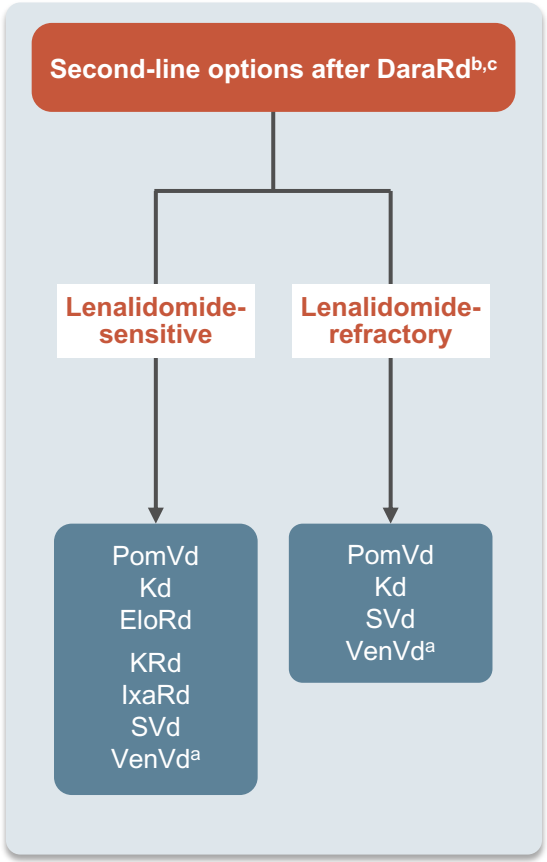
Anti-CD38 mAbs, IMiDs or PIs are used as early as 1L

1L, first-line; ASCT, autologous stem cell transplantation; B, bendamustine; C, cyclophosphamide; CD38, cluster of differentiation 38; d, dexamethasone; D, daratumumab; EHA, European Hematology Association; ESMO, European Society for Medical Oncology; IMiD, immunomodulatory drug; M, melphalan; MM, multiple myeloma; P, prednisone; PI, proteasome inhibitor; R, lenalidomide; T, thalidomide; V, bortezomib

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

MULTIPLE MYELOMA:
EHA-ESMO GUIDELINES FOR INITIAL RELAPSE





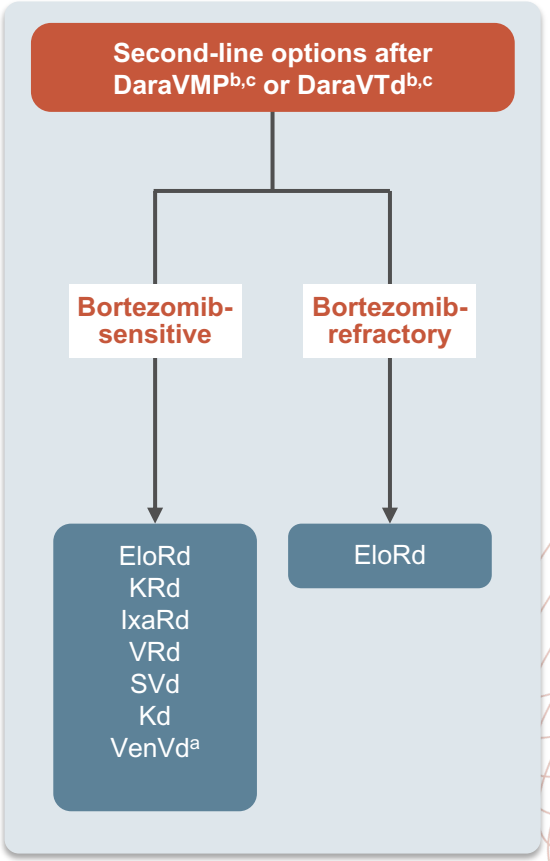


Figure adapted from Dimopoulos et al.

[a] Patients with t(11;14)

[b] Patients who progress while on monthly daratumumab are considered as daratumumab-refractory

[c] All recommendations for patients who receive front-line therapy with daratumumab-based therapies are based on panel consensus as there are no trials evaluating regimens in second-line therapy that include patients who are refractory or exposed to daratumumab

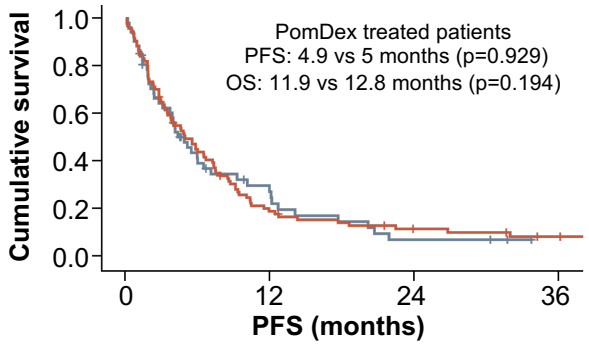
d, dexamethasone; Dara, daratumumab; EHA, European Hematology Association; Elo, elotuzumab; ESMO, European Society for Medical Oncology; Isa, isatuximab; Ixa, ixazomib; K, carfilzomib; M, melphalan; P, prednisone; Pom, pomalidomide; R, lenalidomide; S, selinexor; T, thalidomide; V, bortezomib; Ven, venetoclax

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

NDMM (TRANSPLANT-ELIGIBLE) PATIENT JOURNEY:
FIRST RELAPSE LENALIDOMIDE REFRACTORINESS

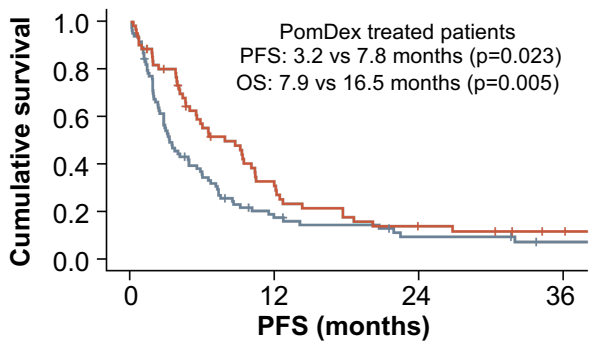
IMWG definition of refractoriness:
Progression during treatment or within 2 months of treatment discontinuation

PFS according to last LEN dose (5–15 mg vs 25 mg)



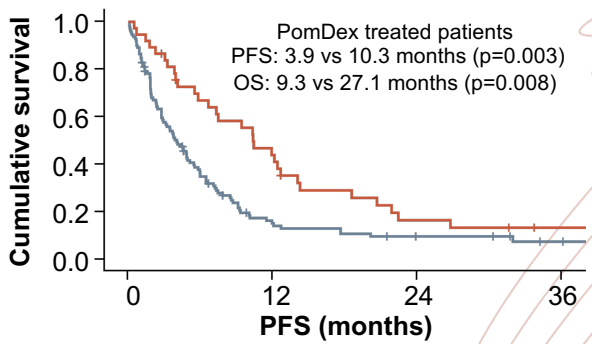
LEN last dose 5-15 mg	52	11	3	
LEN last dose 25 mg	95	17	8	4

PFS according to duration on LEN therapy <12 vs ≥12 months



LEN duration <12 mo	86	12	5	2
LEN duration >12 mo	61	16	6	2

PFS according to IMiD free interval (<18 months vs ≥18 months)



IMiD free interval <18 mo	110	13	6	2
IMiD free interval >18 mo	37	15	5	2

- How is lenalidomide resistance defined? What are the mechanisms?
- What is the impact of lenalidomide dose?
- Is the duration of prior lenalidomide exposure significant?
- Are newer IMiDs (CELMoDs) able to overcome lenalidomide resistance more effectively?

CELMoD, cereblon E3 ligase modulatory drug; Dex, dexamethasone; IMiD, immunomodulatory drug; IMWG, International Myeloma Working Group; NDMM, newly diagnosed multiple myeloma; LEN, lenalidomide; mo, months; OS, overall survival; PFS, progression-free survival; Pom, pomalidomide

Kastritis E, et al. Blood Adv. 2019;3:4095-4103

EHA-ESMO MM GUIDELINES

SECOND-LINE OPTIONS AFTER FRONT-LINE DARATUMUMAB

There are limited second-line options for difficult-to-treat MM patients who are:

- Anti-CD38-mAb-exposed/refractory
- Lenalidomide-refractory
- PI-naïve

Second-line options recommended by ESMO suggest switching target may be beneficial

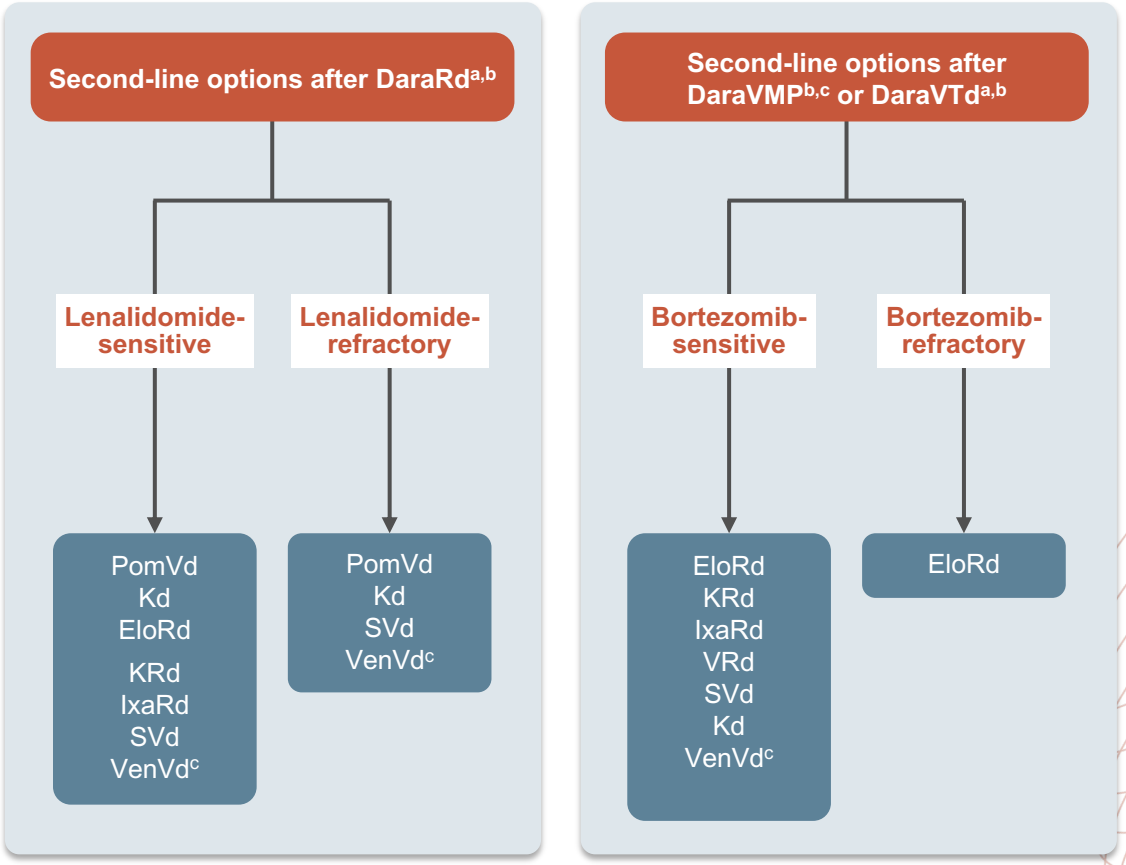


Figure adapted from Dimopoulos et al.

[a] Patients who progress while on monthly daratumumab are considered as daratumumab-refractory

[b] All recommendations for patients who receive front-line therapy with daratumumab-based therapies are based on panel consensus as there are no trials evaluating regimens in second-line therapy that include patients who are refractory or exposed to daratumumab

[c] Patients with t(11;14)

CD38, cluster of differentiation 38; d, dexamethasone; Dara, daratumumab; EHA, European Hematology Association; Elo, elotuzumab; ESMO, European Society for Medical Oncology; Ixa, ixazomib; K, carfilzomib; M, melphalan; mAb, monoclonal antibody; MM, multiple myeloma; P, prednisone; PI, proteasome inhibitor; Pom, pomalidomide; R, lenalidomide; S, selinexor; T, thalidomide; V, bortezomib; Ven, venetoclax

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

RECHALLENGED WITH ANTI-CD38 mAbs
OUTCOMES ARE SUBOPTIMAL IN THESE PATIENTS

In the EMMY cohort analysis,[a] **173 patients** who initiated a second LOT with **anti-CD38-based combinations** after a first exposure to daratumumab or isatuximab were identified and described[1]

- Of these, **127 (73%) were anti-CD38 refractory**

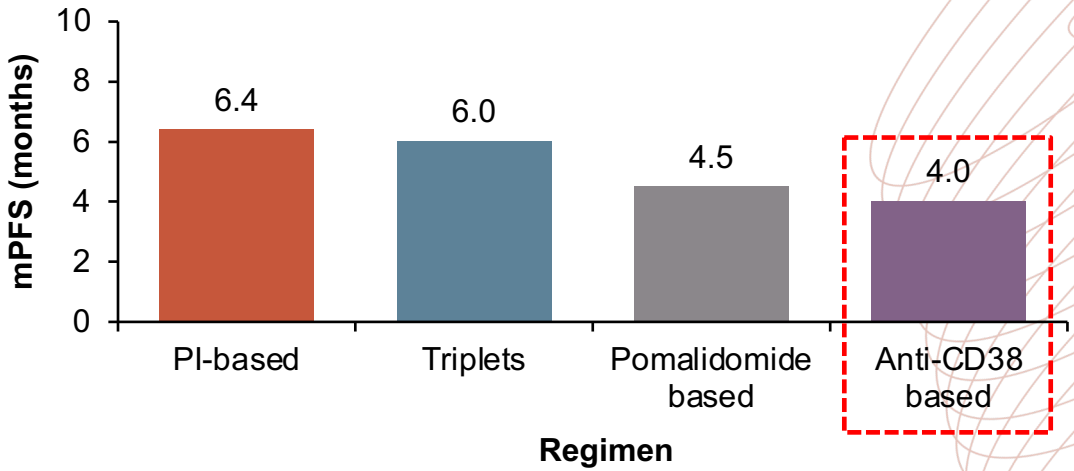
Median PFS and OS[1]

Patient group	Median PFS (95% CI), months	Median OS (95% CI), months
All CD38-retreated (n=173)	4.7 (3.8–6.5)	16.5 (13.9–21.6)
Anti-CD38 non-refractory	7.2 (3.4–NR)	N/A
Anti-CD38 refractory	4.6 (3.7–6.0)	N/A
Anti-CD38-Rd (n=35)	3.8 (1.8–7.2)	25.1

A single-centre analysis described **183 patients** with RRMM who progressed during therapy with a daratumumab- or isatuximab-based regimen**, then received further therapy**[2]

- Patients received anti-CD38 therapy after a median of two prior LOTs (range, 1–10)

Median PFS in post anti-CD38 treatment line by regimen[2, b]



[a] The EMMY cohort is a non-interventional, prospective dynamic cohort study conducted by IFM group;
[b] Only regimens received by ≥20% of ITT patient population.

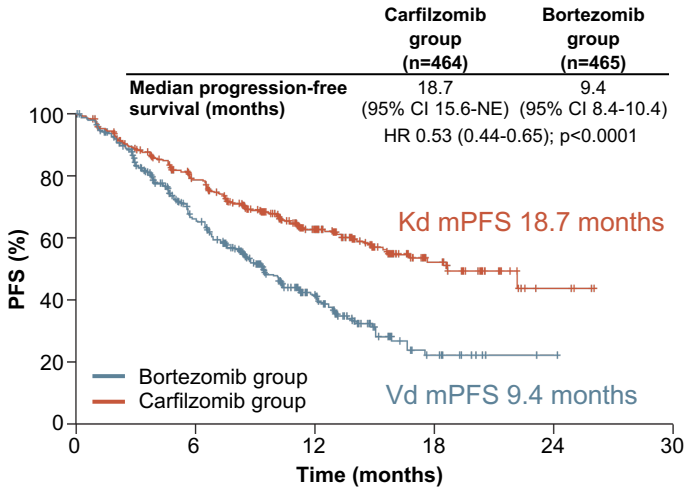
CD38, cluster of differentiation 38; CI, confidence interval; IFM, Intergroupe Francophone du Myélome; ITT, intention to treat; LOT, line of therapy; mAb, monoclonal antibody; (m)PFS, (median) progression-free survival; N/A, not applicable; NR, not reached; OS, overall survival; PI, proteasome inhibitor; Rd, lenalidomide-dexamethasone; RRMM, relapsed/refractory multiple myeloma

1. Hulin C, et al. Blood. 2022;140 (supplement 1):7133-7135. Presented at the ASH Annual Meeting 2022 (Abstract #3174);
2. Kastritis E, et al. Blood. 2022;140 (supplement 1):7324-7325. Presented at the ASH Annual Meeting 2022 (Abstract #3256)

RELAPSE TREATMENT AFTER DRd

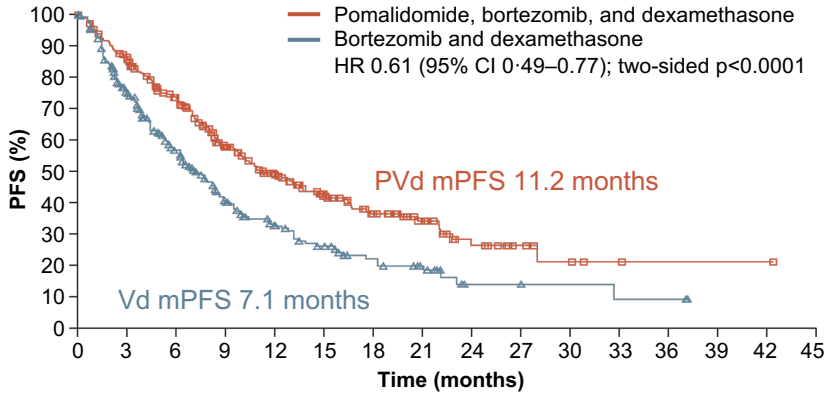
ENDEAVOR[1]

1–3 prior lines of therapy



OPTIMISMM[2]

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



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

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;

1. Dimopoulos MA, et al. Lancet Oncol. 2016.17:27-38; 2. Richardson PG, et al. Lancet Oncol. 2019;20:781-794;

EHA-ESMO MM GUIDELINES
SUBSEQUENT RELAPSE

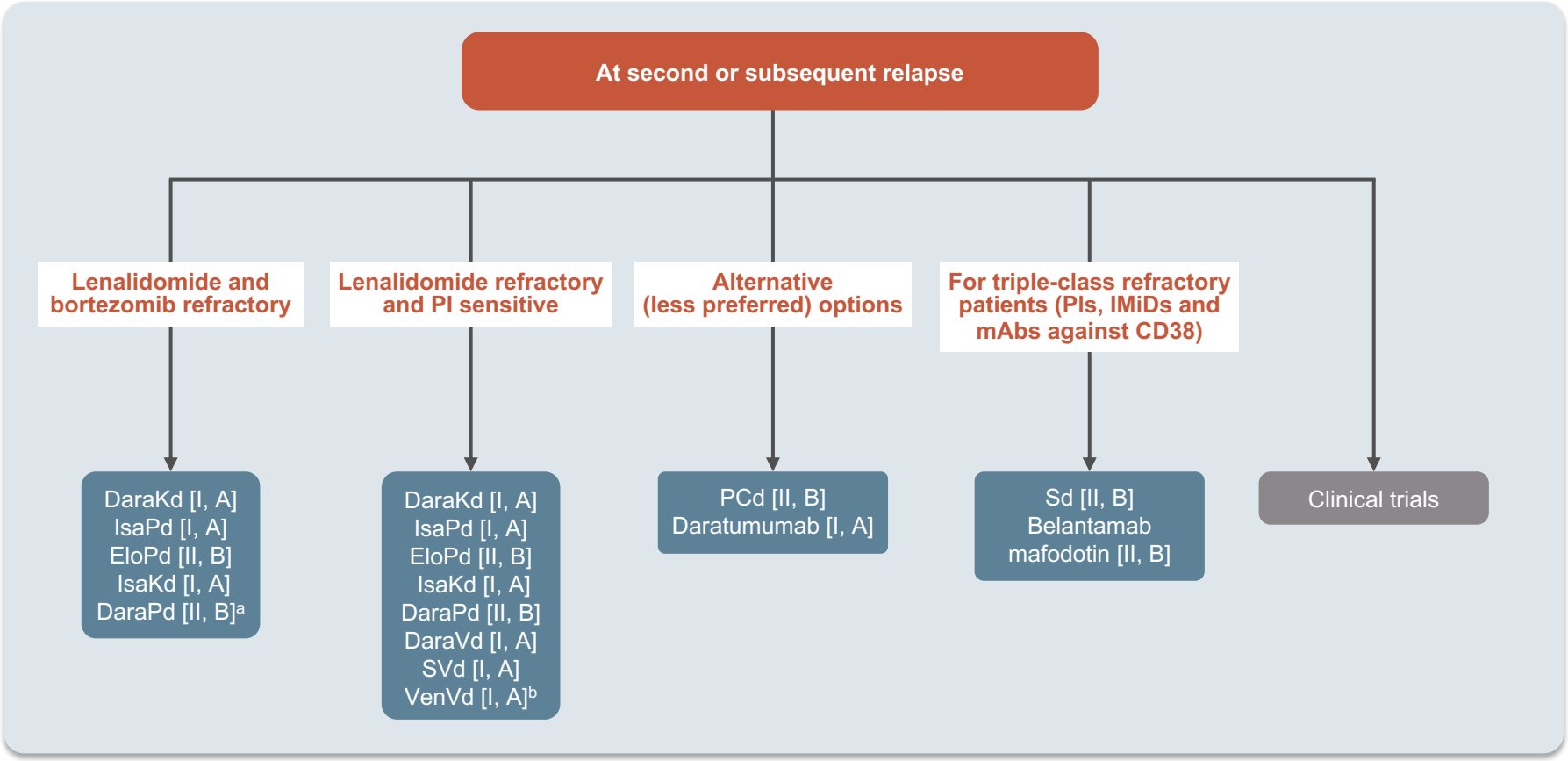


Figure adapted from Dimopoulos et al.

[a] Only phase 1b data are published for DaraPd. Publication of phase 3 data are expected in 2021. [b] For patients with t(11;14) or high BCL-2 levels

BCL-2, B-cell lymphoma 2; CD38, cluster of differentiation 38; Dara, daratumumab; EHA, European Haematology Association; Elo, elotuzumab; ESMO, European Society for Medical Oncology; IMiD, immunomodulatory drug; Isa, isatuximab; Kd, carfilzomib-dexamethasone; mAb, monoclonal antibody; MM, multiple myeloma; PCd, pomalidomide-cyclophosphamide-dexamethasone; Pd, pomalidomide-dexamethasone; PI, proteasome inhibitor; S, selinexor; Sd, Selinexor-dexamethasone; Vd, bortezomib-dexamethasone; Ven, venetoclax

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

THIRD-LINE TREATMENT POMA-BASED:
Elo-Pd, Isa-Pd, Dara-Pd – STUDY RESULTS

	Eloquent-3 Elo-Pd arm	ICARIA Isa-Pd arm	APOLLO Dara-Pd arm
Median prior lines of therapy	3	3	2
Prior lenalidomide, %	98	100	100
Lenalidomide refractory, %	90	94	79
PI refractory, %	78	77	47
Double refractory (lena + PI), %	68	72	42
Median PFS, months	**10.3**	**11.5**	**12.4**
HR for PFS	0.54 (p=0.0078)	0.60 (p=0.001)	0.63 (p=0.0018)
Median PFS in len-refractory patients, months	**10.3**	**11.4 (HR 0.59)**	**9.9 (HR 0.66)**
Median PFS in double-refractory patients, months	10.2 (HR 0.56)	11.2 (HR 0.58)	7.7 (HR 0.74)
HR for PFS in high-risk FISH	0.52	0.66	0.85
ORR, %	53	63	69
CR rate, %	5	9 (MRD neg 5%)	25 (MRD neg 9%)
Haematologic toxicity (gr 3–4), % • **Neutropaenia** • **Thrombocytopaenia**	 13 8	 85 31	 68 17
Non-hematological (gr 3–4), % • **IRR (all grades)** • **Infections** • **Pneumonia**	 3 13 5	 38 (3% gr 3–4) Not available 16	 5 28 13
Treatment discontinuation due to Aes, %	18 vs 24	7 vs 13	2 vs 3

AE, adverse event; CR, complete response; Dara-Pd, daratumumab, pomalidomide and dexamethasone; Elo-Pd, elotuzumab, pomalidomide and dexamethasone; FISH, fluorescent in-situ hybridisation; gr, grade; HR, hazard ratio; IRR, infusion-related reaction; Isa-Pd, isatuximab, pomalidomide and dexamethasone; lena, lenalidomide; MRD, minimal residual disease; ORR, overall response rate; PFS, progression-free survival; PI proteosome inhibitor; Poma, pomalidomide

Dimopoulos MA, et al. N Engl J Med. 2018;379:1811-1822; Attal M, et al. Lancet. 2019;394:2096-2107; Dimopoulos MA, et al. Lancet Oncol. 2021;22:801-812

CURRENT UNMET NEEDS IN EARLY R/R SETTING

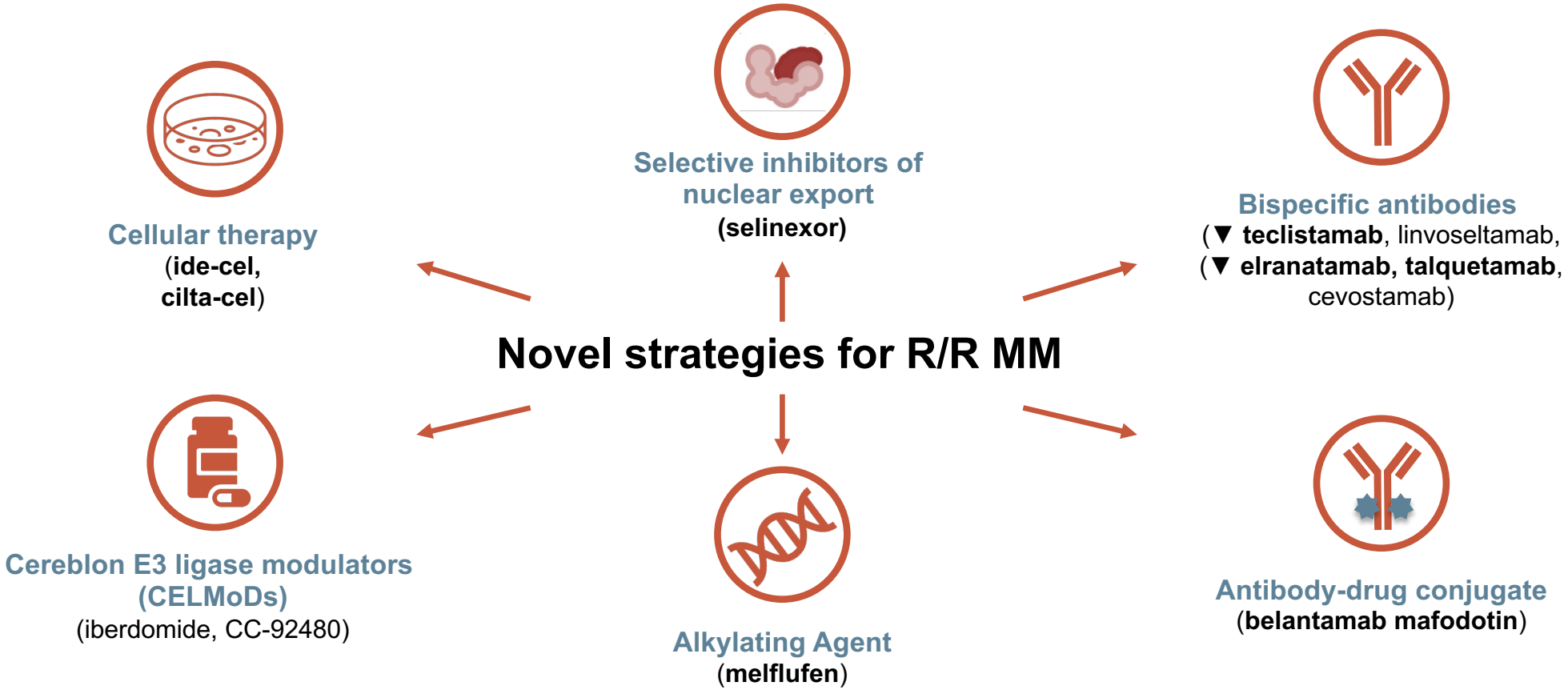
- Limited effective treatment options for **early relapsed double-** and **triple-refractory patients**[1]
- Due to patient attrition at each LoT, a substantial proportion of patients do not progress to third-line treatment[2]
- Limited effective treatment options for **transplant-ineligible patients relapsing during** or **after Dara-Rd**, including disappointing results with Dara re-treatment[3,4]
- **Lack of clear standard of care** on the **use**, **combination** and **sequencing** of the growing number of **MM treatment options**, complicated by the heterogeneity of this population[5,6]
- Issues with **access** (approval and cost) to **novel immunotherapies** in many countries[7]

Dara, daratumumab; LoT, line of therapy; MM, multiple myeloma; Rd, lenalidomide and dexamethasone; R/R, relapsed/refractory

1. Kastritis E, et al. Blood 2022;139(19):2904–2917; 2. Fonseca R, et al. BMC Cancer 2020;20:1087; 3. Dimopoulos MA, et al. Ann Oncol 2021;32(3):309–322; 4. Kastritis E et al. Abstract #3256. ASH Annual Meeting 2022; 5. Mateos MV, et al. Leukemia 2022;36:1371–1376; 6. Ntanasis-Stathopoulos I, et al. Clin Lymphoma Myeloma Leuk 2021;21(6):379–385. 7. Bhatt P, et al. Curr Oncol 2023;30(2):2322–2347; 8. Mateos MV, et al. Blood 2020:136(1):22–23; 9. Zamanillo I, et al. Blood 2024;143(20):2029–2036.

ADDRESSING THE UNMET NEEDS IN EARLY RRMM

SELINEXOR IS APPROVED FROM SECOND LINE ONWARDS



▼ This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions.

MM, multiple myeloma; RR, relapsed/refractory

Hernández-Rivas JÁ, et al. Biomark Res. 2022:10(1)

SELINEXOR IS A FIRST IN CLASS ORAL XPO1 INHIBITOR

MECHANISM OF ACTION[1]

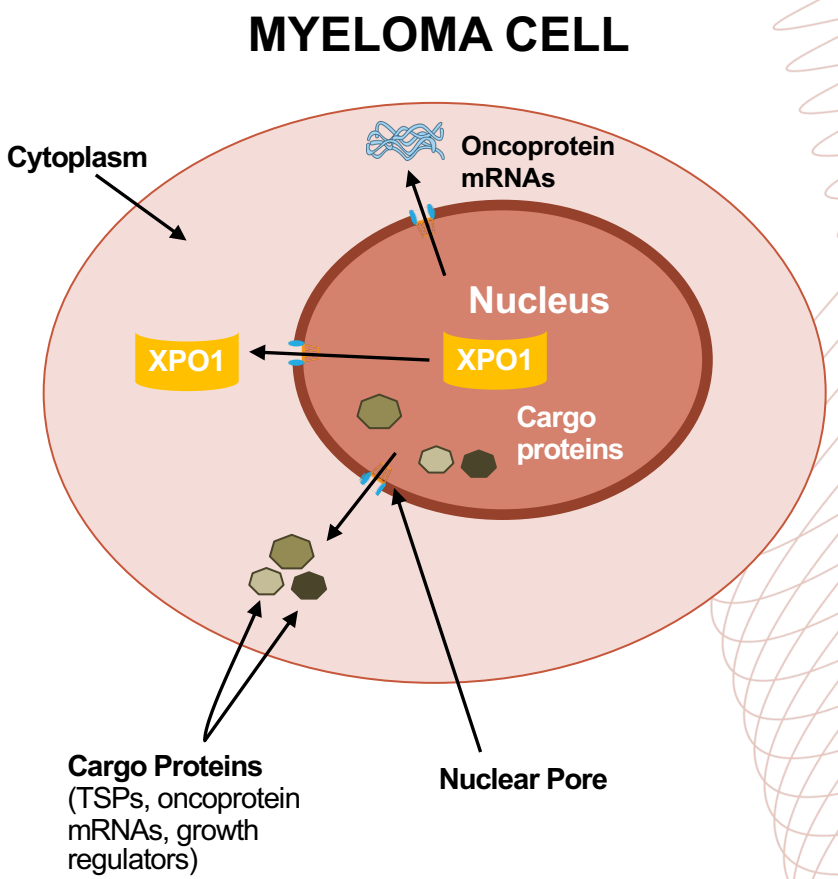
ESMO recommendations for daratumumab-pretreated patients include regimens containing **selinexor in combination with bortezomib and dexamethasone**, as well as carfilzomib and pomalidomide-based regimens[2]

XPO1:

- XPO1 is a **nuclear export protein** that transports nuclear proteins to the cytoplasm via nuclear pore complexes
- XPO1 is **overexpressed in many tumour types**, including MM
- It exports TSPs to the cytoplasm, where they are unable to function and elevates cytosolic levels of pro-survival proteins
- This results in **dysregulation of growth signalling** and **increased anti-apoptotic signalling**

Selinexor:

- Blocks XPO1 so that it **cannot carry cargo** out of the nucleus
- **TSPs accumulate in the nucleus**, causing **cell cycle arrest** and **apoptosis**
- Traps oncoprotein mRNA in the nucleus, so they cannot be translated



ESMO, European Society for Medical Oncology; MM, multiple myeloma; mRNA, messenger RNA; TSP, tumour suppressor protein; XPO1, exportin 1

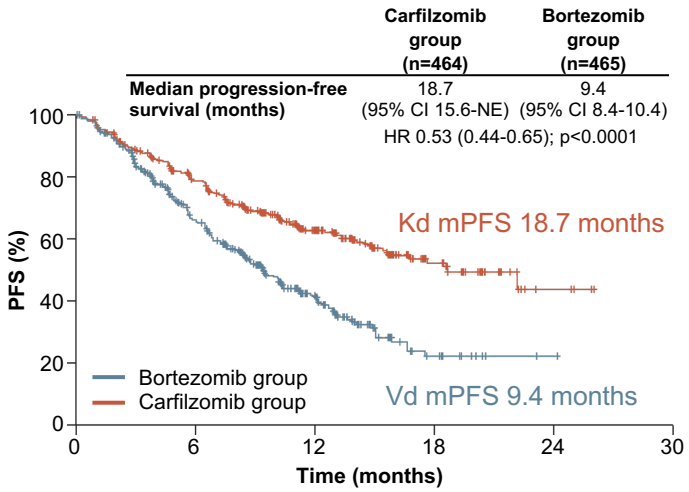
1. Mo CC, et al. EJHaem. 2023;4:792-810; 2. Dimopoulos MA, et al. Ann Oncol. 2021;32:309-322

RELAPSE TREATMENT AFTER DRd

HOW DOES SVD FIT WITH OTHER TREATMENTS?

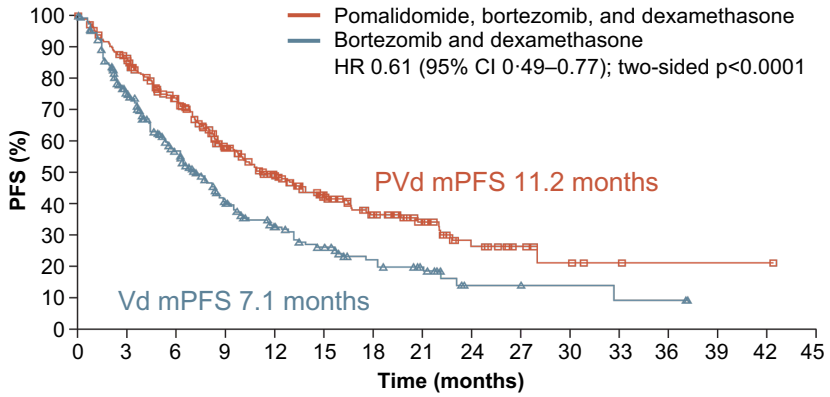
ENDEAVOR[1]

1–3 prior lines of therapy



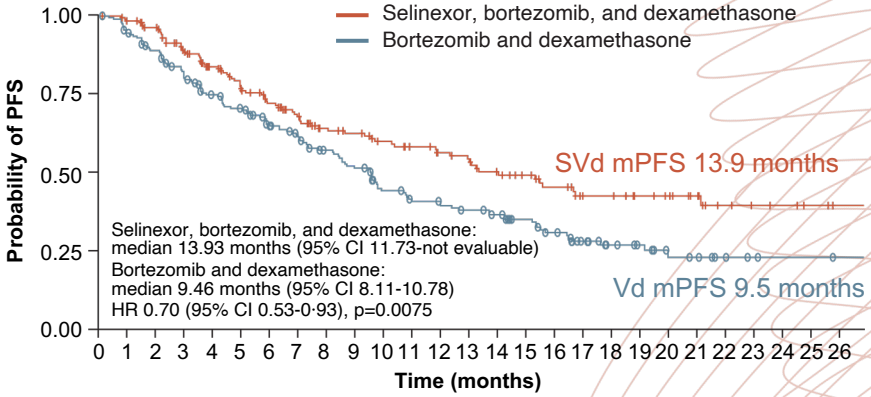
OPTIMISMM[2]

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; SVd, 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

KEY CLINICAL TAKEAWAYS

- Current guidelines recommend **lenalidomide-based treatment in the frontline setting**
- **Non-transplant eligible patients may become anti-CD38 refractory** after one prior line of therapy
- Although therapeutic advances in MM have improved outcomes, this has generated a **wide range of patient profiles at early relapse**, many with substantial **unmet needs**
- There is a need for **new targets/new drugs** with different **mechanism of action**
- **SVd** may be a suitable treatment option for early relapsed patients previously treated with lenalidomide and daratumumab, as it offers a **double MoA switch**

CD38, cluster of differentiation 38; MM, multiple myeloma

FIND OUT MORE ABOUT RRMM IN PARTS 2 AND 3

PART 2: THE RELEVANCE OF ADDING A NEW MoA IN TREATING RRMM – AN EXPERT VIEW

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

MM, multiple myeloma; RR, relapsed/refractory;

COR2ED
THE HEART OF MEDICAL EDUCATION

For more information visit

LYMPHOMA & MYELOMA connect®
POWERED BY COR2ED

Connect on LinkedIn @LYMPHOMA & MYELOMA CONNECT

Watch on YouTube @COR2ED

Email info@cor2ed.com

Visit us at https://cor2ed.com/

Follow us on Twitter @lym_mm_connect

Heading to the heart of Independent Medical Education since 2012