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VIRTUAL EXPERTS KNOWLEDGE SHARE

MULTIPLE MYELOMA: IS IT TIME TO RETHINK HOW WE SEQUENCE TREATMENTS?

13th JANUARY 2026

This promotional meeting is organised by Menarini Stemline UK and is intended for UK healthcare professionals with an interest in multiple myeloma.
This meeting will contain product-related information.
Prescribing Information and Adverse Event reporting information are available at the end of the slide deck and available on request.

MAT-GB-SEL-00724 | December 2025

WELCOME & INTRODUCTIONS

Prof. Karthik Ramasamy

Hematologist

Oxford University Hospitals NHS Trust, UK

INTRODUCING THE SCIENTIFIC COMMITTEE

Prof. Karthik Ramasamy
Hematologist
Oxford University Hospitals NHS Trust, UK

Dr Joshua Richter
Hematologist
Icahn School of Medicine at Mount Sinai, USA

Dr Faisal Basheer
Hematologist
Cambridge University Hospitals NHS Trust, UK

Dr Andrew Charlton
Hematologist
Newcastle Upon Tyne Hospitals NHS Trust, UK

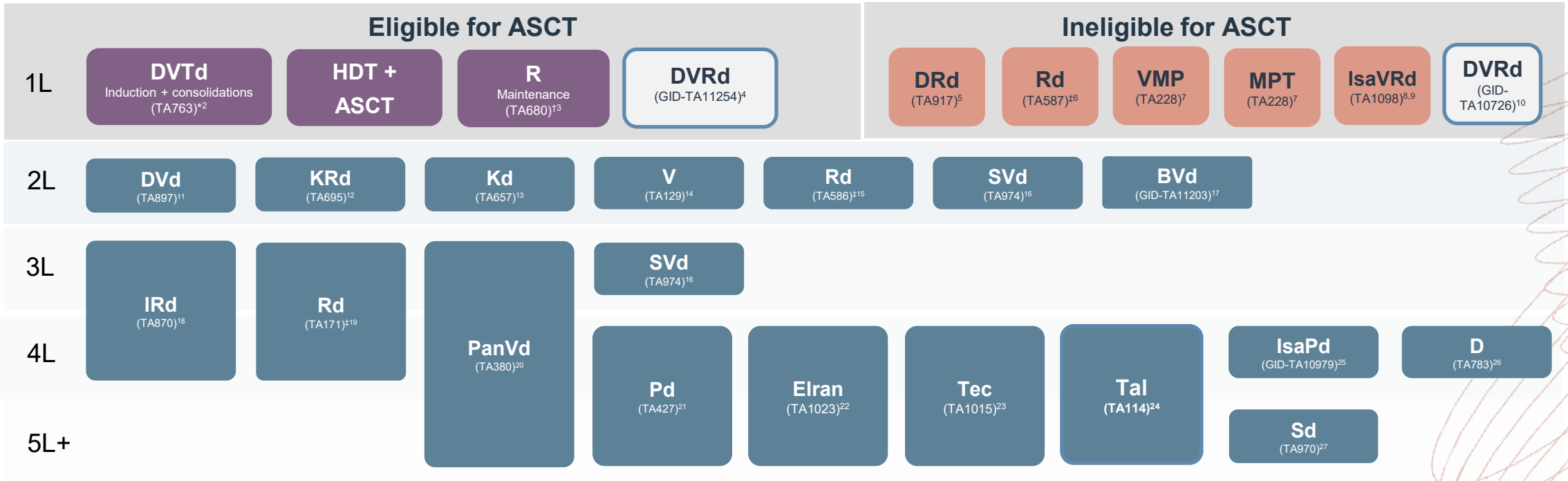
ACKNOWLEDGEMENT AND DISCLOSURES

This programme has been sponsored by Menarini Stemline and is intended for healthcare professionals practising in the UK

Expert disclosures:

- **Prof. Karthik Ramasamy** has received financial support/sponsorship for - Advisory boards: AbbVie, Adaptive Biotech, Amgen, Bristol-Myers Squibb (Celgene), GSK, Johnson & Johnson, Karyopharm, Menarini Stemline, Oncopeptides, Pfizer, Recordati, Sanofi, Takeda; Research support: Amgen, Bristol-Myers Squibb (Celgene),GSK, Johnson & Johnson, Sanofi, Takeda; Speaker fees: Adaptive Biotech, Bristol-Myers Squibb (Celgene), GSK, Johnson & Johnson, Menarini Stemline, Oncopeptides, Recordati, Sanofi, Takeda; Travel: Johnson & Johnson, Takeda
- **Dr Joshua Richter** has received financial support/sponsorship for - Consultancy fees/advisory board: AbbVie, Bristol Myers Squibb, FORUS Therapeutics, Genentech, Janssen, Karyopharm Therapeutics, Menarini Stemline, Pfizer, Regeneron, Sanofi, Takeda; Speaker fees: Adaptive Biotechnologies, Bristol Myers Squibb, Janssen, Menarini Stemline, Sanofi
- **Dr Faisal Basheer** has received financial support/sponsorship for - Honoraria: J&J, Jazz Pharmaceuticals; Speaker fees: Sanofi, Pfizer, Menarini Stemline, Daiichi-Sankyo; Sponsorships: AbbVie, Pfizer; Advisory: BMS, J&J
- **Dr Andrew Charlton** has received financial support/sponsorship for - Advisory Board: Sanofi, Takeda; Consultancy: Menarini Stemline, BMS; Speaker's Fees: JNJ, Takeda, Sanofi, Menarini Stemline, Pfizer; Conference Support: JNJ, Takeda, Amgen, BMS, Menarini Stemline

CURRENT UK TREATMENT LANDSCAPE



Please note that this recommended treatment pathway is current as of December 2025. IsaPd is approved for use under the Cancer Drugs Fund.[24,27] BVd is available on the Cancer Drugs Fund and awaiting final NICE guidance.[17,28] DVRd guidance is in development by NICE and expected publication date is March 2026.[4,10]
* Induction before high-dose chemotherapy and ASCT;[2] † Maintenance treatment after ASCT;[3] ‡ 1L: Thalidomide is contraindicated (including for pre-existing conditions that it may aggravate) or the person cannot tolerate thalidomide; 2L: After treatment with bortezomib[6,15]

1/2/3/4/5L, first-/second-/third-/fourth-/fifth-line; ASCT, autologous stem cell transplant; BVd, belantamab mafodotin, bortezomib, dexamethasone; D, daratumumab; DRd, daratumumab, lenalidomide, dexamethasone; DVd, darantumumab, bortezomib, dexamethasone; DVRd, daratumumab, bortezomib, lenalidomide, dexamethasone; DVTd, daratumumab, bortezomib, thalidomide, dexamethasone; E, elranatamab; GID, guidance in development; IRd, ixazomib, lenalidomide, dexamethasone; IsaPd, isatuximab, pomalidomide, dexamethasone; IsaVRd, isatuximab, bortezomib, lenalidomide, dexamethasone; Kd, carfilzomib, dexamethasone; KRd, carfilzomib, lenalidomide, dexamethasone; MoA, mechanism of action; MM, multiple myeloma; MPT, melphalan, prednisone, thalidomide; NICE, National Institute for Health and Care Excellence; Pd, pomalidomide, dexamethasone; PanVd, panobinostat, bortezomib, dexamethasone; R, lenalidomide; Rd, lenalidomide, dexamethasone; Sd, selinexor, dexamethasone; SVd, selinexor, bortezomib, dexamethasone; TA, technology appraisal; Tal, talquetamab; TE, transplant eligible; Tec, teclistamab; TNE, transplant non-eligible; V, bortezomib; VMP, bortezomib, melphalan, prednisone.

1. NICE. NG35; 2. NICE. TA763; 3. NICE. TA680; 4. NICE. GID-TA11254. 5. NICE; TA917; 6. NICE. TA587; 7. NICE. TA228; 8. NICE. TA1098; 9. Myeloma UK. First quadruplet treatment for transplant-ineligible patients approved in England and Wales. Available at: https://www.myeloma.org.uk/news/first-quadruplet-treatment-for-transplant-ineligible-patients-approved-in-england-and-wales/; 10. NICE. GID-TA10726;
11. NICE. TA897; 12. NICE. TA695; 13. NICE. TA657; 14. NICE. TA129; 15. NICE. TA586; 16. NICE. TA974; 17. NICE. GID-TA11203; 18. NICE. TA870; 19. NICE. TA171; 20. NICE. TA380; 21. NICE. TA427;
22. NICE. TA1023; 23. NICE. TA1015; 24. NICE. TA114; 25. NICE. GID-TA10979; 26. NICE. TA783; 27. NICE. TA970; 28. National Cancer Drugs Fund List. Version 1. 379. 26th November 2025. Available at: https://www.england.nhs.uk/wp-content/uploads/2017/04/national-cdf-list-ver1.379.pdf. Accessed December 2025

MEETING OBJECTIVES

- Establish the current challenges in treating multiple myeloma, and explain how these challenges are driven by the genetic heterogeneity of the disease
- Understand how the evolving treatment landscape limits available treatment options with proven efficacy in the relapsed/refractory setting, especially for lenalidomide-refractory patients
- MoA — Establish the need for therapies with novel mechanisms of action in relapsed refractory multiple myeloma
- Explore the evolution of the UK multiple myeloma pathway and how real-world clinical dilemmas shape decisions across lines of treatment
- Discuss the role of selinexor within multiple myeloma treatment landscape for multiple myeloma through interactive case studies

AGENDA

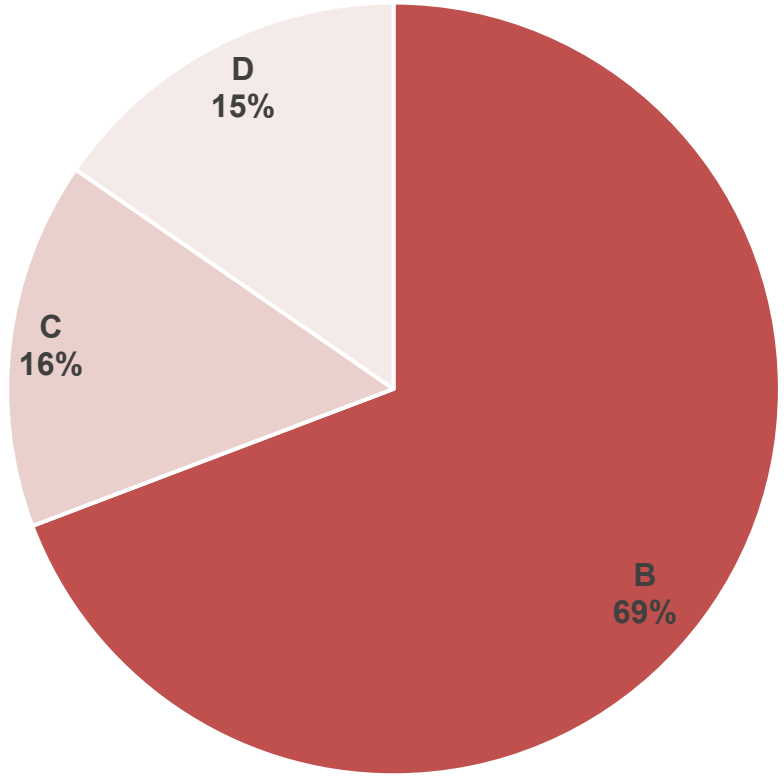
MULTIPLE MYELOMA: IS IT TIME TO RETHINK HOW WE SEQUENCE TREATMENTS?

Timings	Topic	Facilitator
18:05	**Myeloma bench to bedside: considerations at each line of therapy**	Joshua Richter
18:20	**Every move matters: rethinking sequencing strategies in modern myeloma**	Karthik Ramasamy
18:35	**Clinical studies to clinical reality: patient case studies** 1. Andrew Charlton, chaired by Joshua Richter 2. Faisal Basheer, chaired by Karthik Ramasamy	All
19:25	**Summary & close**	Karthik Ramasamy

POLLING QUESTION 1

WHAT FACTOR IS MOST IMPORTANT WHEN SELECTING THERAPY FOR RELAPSED MULTIPLE MYELOMA THERAPY?

A. Age
B. Prior refractoriness
C. Treatment sequencing
D. Comorbidities



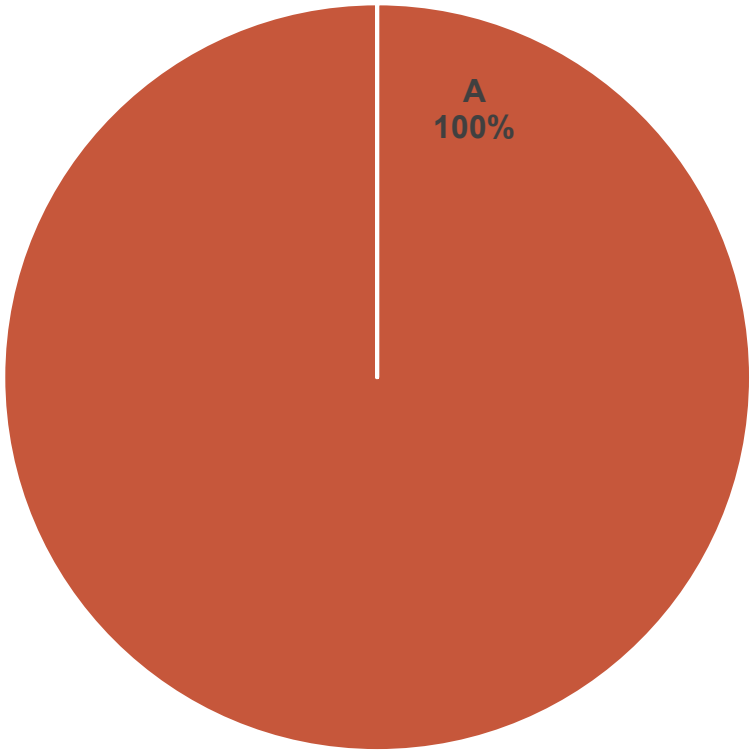
POLLING QUESTION 2

HOW IMPORTANT IS TREATMENT SEQUENCING WHEN SELECTING THERAPY FOR RELAPSED MULTIPLE MYELOMA?

A. Very important

B. Occasionally important

C. Not important



MYELOMA BENCH TO BEDSIDE:
CONSIDERATIONS AT EACH LINE OF THERAPY

Dr Joshua Richter

Hematologist

Icahn School of Medicine at Mount Sinai, US

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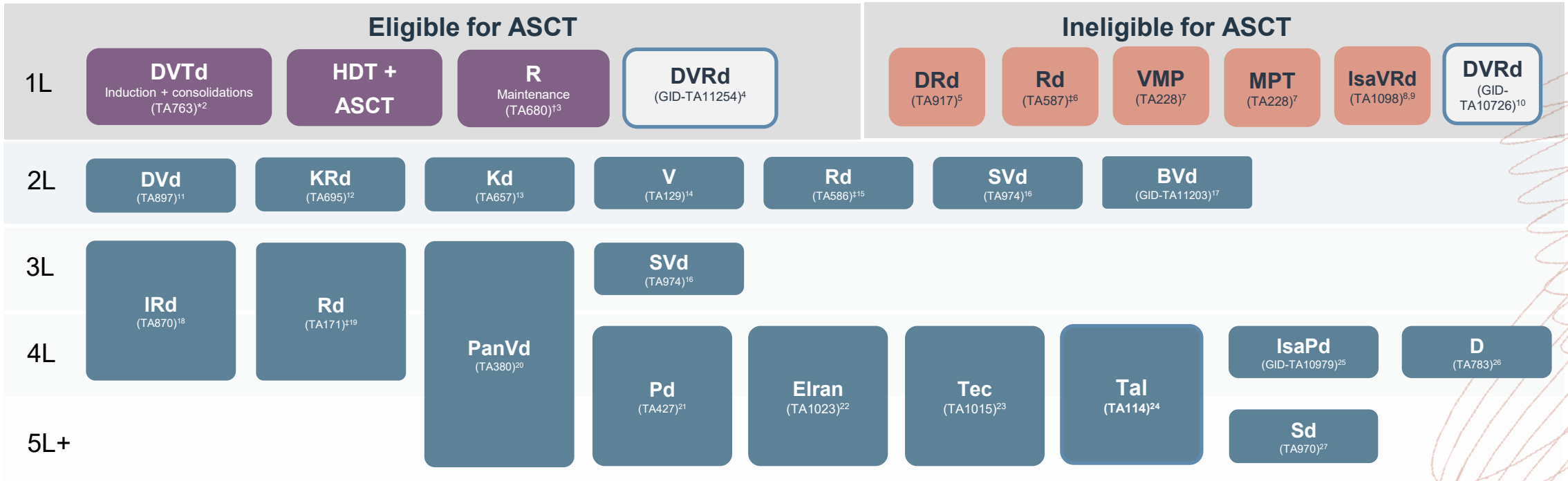
NEW TREATMENT OPTIONS MEANS NEW TREATMENT CHALLENGES



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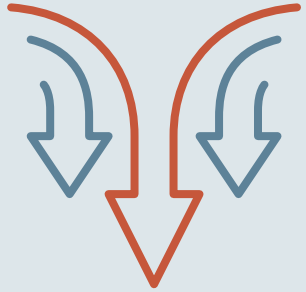
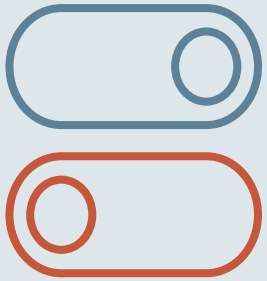
THERE ARE LIMITED TREATMENT CLASSES FOR PATIENTS WITH RRMM[1-3]

Most patients treated for MM experience **numerous relapses**, with each remission being of **shorter duration**[4,5]



With each successive relapse, treatment options become **more limited** as patients become **refractory**[1–3,6,7]



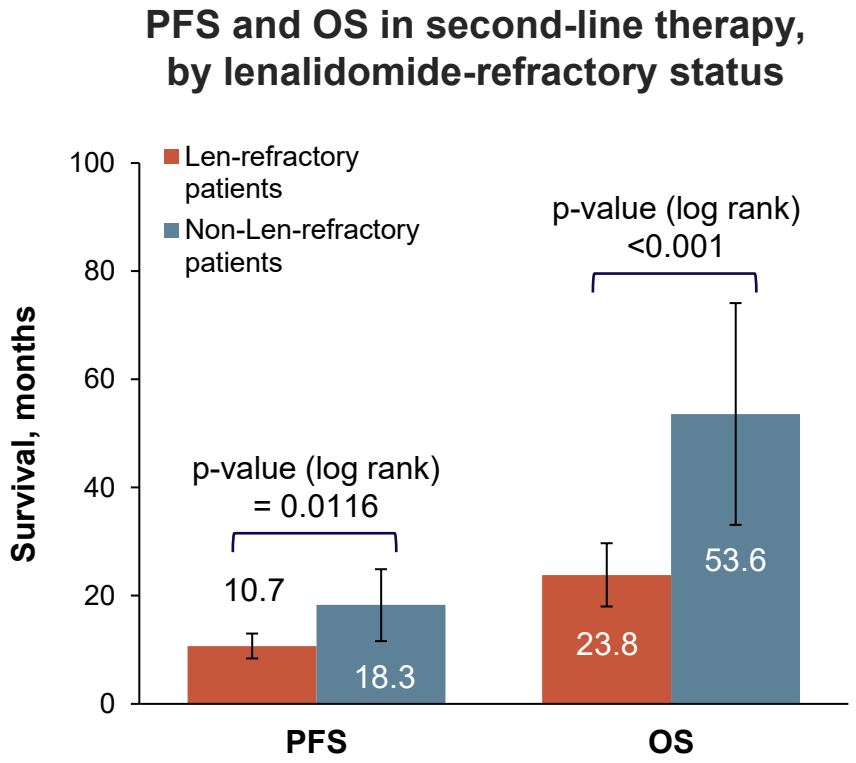
For relapsed disease, strategies include **switching** to a different class of therapy with a **distinct MoA**[1–7]

MoA, mechanism/mode of action; MM, multiple myeloma; RRMM, relapsed/refractory multiple myeloma

References: 1. Mikhael J. Clin Lymphoma Myeloma Leuk. 2020;20(1):1-7; 2. Sellin M, et al. Transl Oncol. 2022;22:101448; 3. Oriol A, et al. Expert Rev Anticancer Ther. 2020;20(1):31-44; 4. van de Donk NWCJ, et al. Lancet. 2021;397(10272):410-27; 5. Theodoropoulos N, et al. Target Oncol. 2020;15(6):697-708; 6. Kumar S, et al. Blood Cancer J. 2022;12(6):98; 7. Dimopoulos MA, et al. Ann Oncol. 2021;32(3):309-22

DISMAL OUTCOMES FOR PATIENTS RELAPSING AFTER FIRST LINE LENALIDOMIDE REGIMENS

GREEK EXPERIENCE[1]



GERMAN MYRIAM REGISTRY[2]

Response (from start of 2L, non SCT)	Relapsed (n=89)	Refractory (n=155)
ORR, n (%)	27 (30.3)	44 (28.4)
CR, n (%)	4 (4.5)	3 (1.9)
VGPR, n (%)	12 (13.5)	10 (6.5)

Survival (from start of 2L, non SCT)	Relapsed (n=89)	Refractory (n=155)
mPFS (95% CI), mos	11.9 (6.0-25.1)	8.6 (4.8–10.4)
mOS (95% CI), mos	NR	20.9 (15.1-37.9)
2-yr OS (95% CI), %	63 (47-74)	–

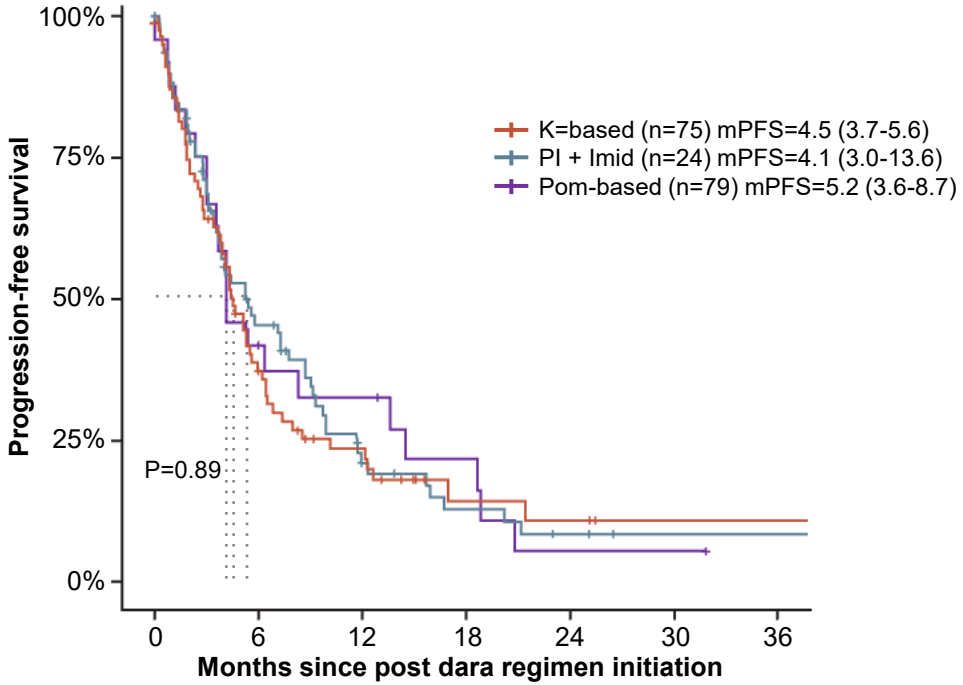
CI, confidence interval; CR, complete response; L, line; Len, lenalidomide; (m)PFS, (median) progression-free survival; (m)OS, (median) overall survival; mos, months; NR, not reached; ORR, overall response rate; SCT, stem cell transplant; VGPR, very good partial response

1. Kastritis E, et al. Clin Lymphoma Myeloma Leuk. 2024;24(7):468-77; 2. Reiser M, et al. Abstract P909, EHA 2024 (poster presentation) presented at EHA 2024

RELAPSE AFTER DARATUMUMAB REGIMEN

DISMAL OUTCOMES FOR PATIENTS

PFS of patients in subsequent therapy following daratumumab-containing regimens, based on regimen types



Median prior lines of treatment: 2-3

Previous treatment with DVd	N	Median PFS	95% CI
Carfilzomib-based therapy	12	4.3	1.8-6.2
Pomalidomide-based therapy	47	7.3	4.1-9.7
IMiD + PI based on carfilzomib and/or pomalidomide	4	4.5	0-NRY

Previous treatment with DRd	N	Median PFS	95% CI
Carfilzomib-based therapy	41	2.8	1.9-4.6
Pomalidomide-based therapy	24	3.4	1.3-5.2
IMiD + PI based on carfilzomib and/or pomalidomide	9	3.6	0.9-NRY

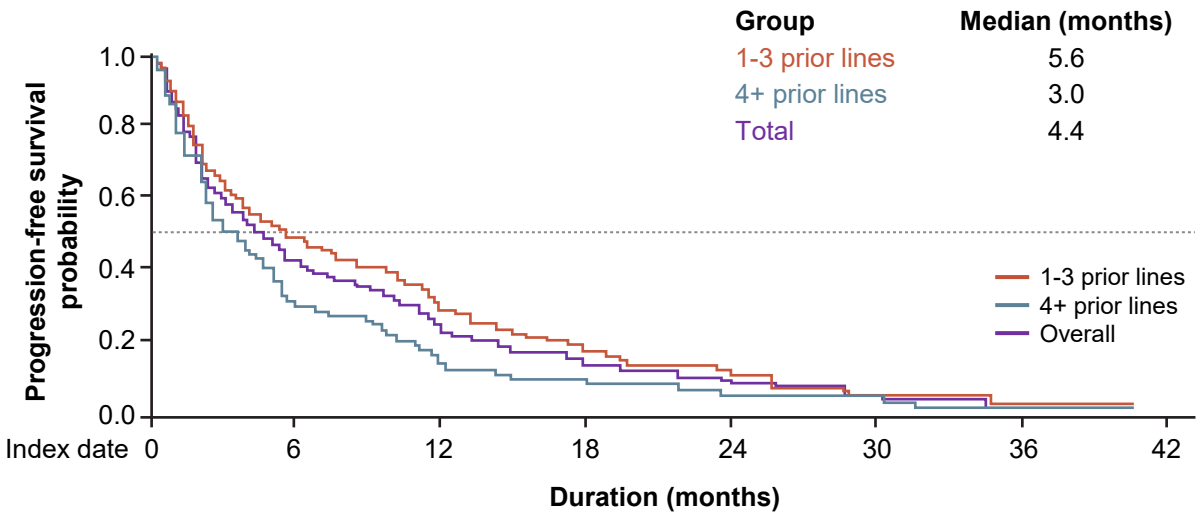
"…the poor outcome of MM patients when standard regimens based on carfilzomib and/or pomalidomide are utilised directly after daratumumab-based therapy given in the relapsed setting. Novel therapies, including immune therapies, are urgently needed to improve the outcomes of these daratumumab-exposed patients"

CI, confidence interval; DRd, daratumumab/lenalidomide/dexamethasone; DVd, daratumumab/bortezomib/dexamethasone; IMiD, immunomodulatory drug; K, carfilzomib; MM, multiple myeloma; (m)PFS, (median) progression-free survival; NRY, not reached yet; PFS, progression-free survival; PI, protease inhibitor; pom, pomalidomide

LeBlanc R, et al. Eur J Haematol. 2023;111(5)815-23

PATIENTS PREVIOUSLY TREATED WITH LENALIDOMIDE AND ANTI-CD38 HAD A POOR OVERALL RESPONSE AND POOR SURVIVAL OUTCOMES[1,2]

KM PLOT OF PROGRESSION-FREE SURVIVAL[1]



Adapted from Abonour R, et al

- ORR from the index treatment line was 28.4%, with
  - median PFS of 4.4 months and
  - median OS of 14.2 months
- Patients with fewer prior lines of treatment had improved survival vs patients with a higher number of prior lines[1,2]

A large, US, multicenter, prospective observational cohort of 3011 patients with NDMM who were previously treated with lenalidomide and an anti-CD38 mAb in the same or different lines, and had started a subsequent line of treatment (index date)[1]

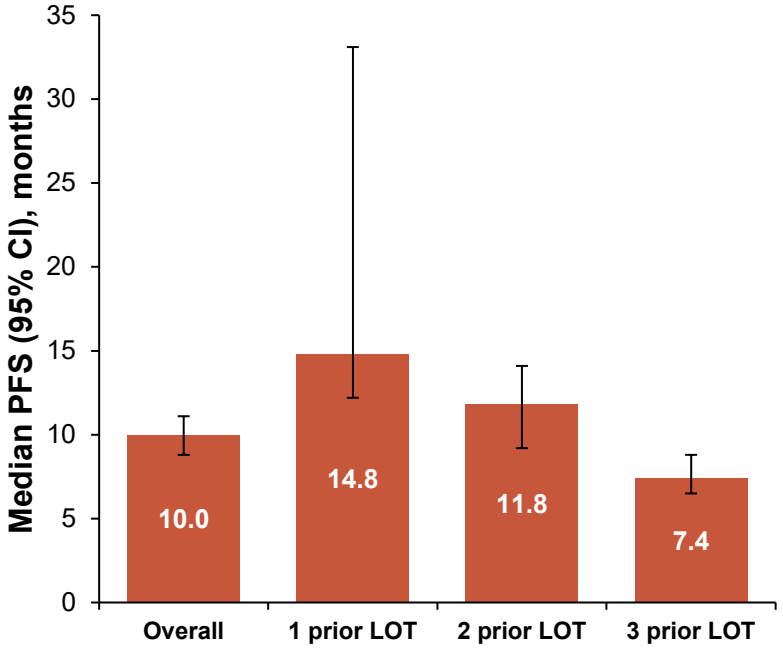
This result highlights the need for more effective treatment options in patients with prior exposure to lenalidomide and an anti-CD38 mAb[2]

NDMM; newly diagnosed multiple myeloma; mAB, monoclonal antibody; OS, overall survival; PFS, progression-free survival

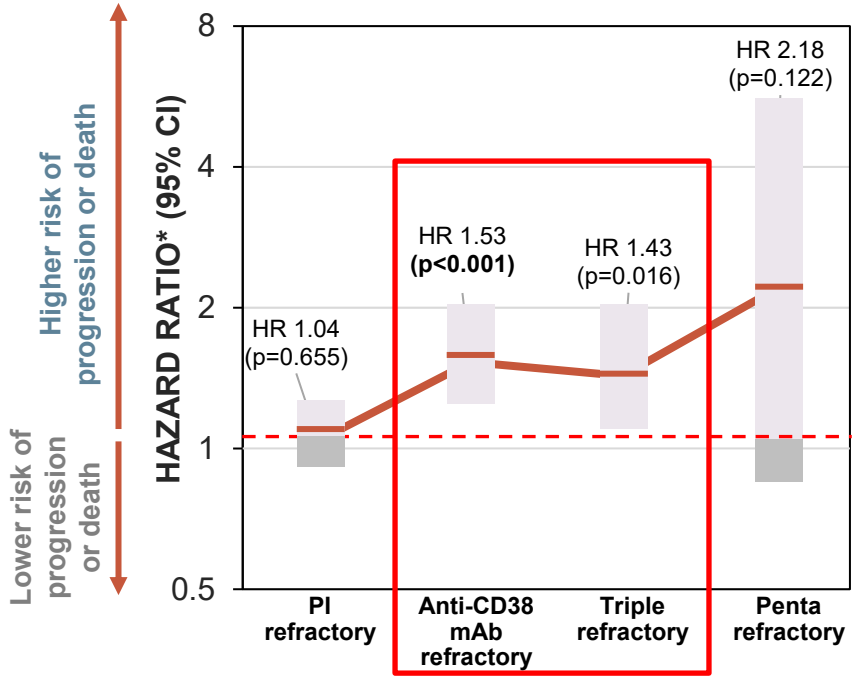
1. Abonour R, et al. HemaSphere. 7: e52503e2. https://doi.org/10.1097/01.HS9.0000970564.52503.e2 (EHA 2023 Hybrid Congress); 2. Ramasamy K, et al. Clin Lymphoma Myeloma Leuk. 2025; 25(5):337-348.e2

POOR PFS IN LENALIDOMIDE-REFRACTORY AND TRIPLE-CLASS REFRACTORY PATIENTS

PFS by number of prior LOT after first index treatment in lenalidomide-refractory patients



Prognostic factors for PFS: Refractory state



- PFS for **anti-CD38-mAb-refractory** MM is at least as **poor** as with **triple-refractory** MM
- **Same outcomes** were observed for **OS**

There is a need for novel and effective treatment options for use as early as 2L therapy for lenalidomide-refractory MM

Analysis of individual patient-level data from daratumumab clinical trials: APOLLO, CASTOR, CANDOR, EQUULEUS, ALCYONE, MAIA, GRIFFIN, POLLUX, and CASSIOPEIA. *Reference for each factor was the absences of the refractory state

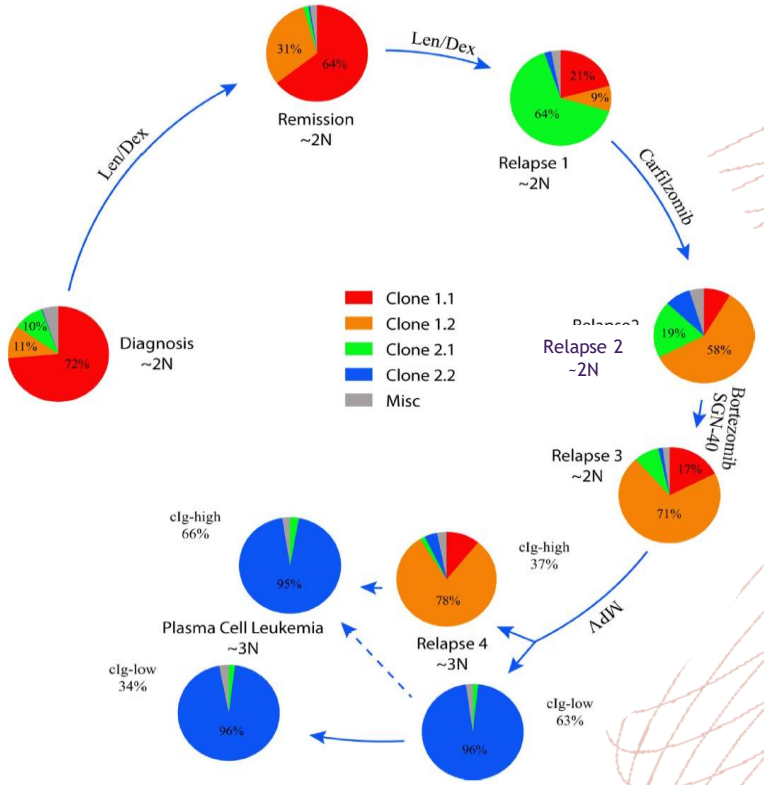
2L, second-line; CI, confidence interval; HR, hazard ratio; L, line; LOT, line-of-therapy; mAb, monoclonal antibody; MM, multiple myeloma; OS, overall survival; PFS, progression-free survival; PI, proteasome inhibitor

Yong K, et al. Eur J Cancer. 2025;215:115157

TREATMENT DRIVES EXPANSION OF RESISTANCE IN MM, CREATING CHALLENGES UPON PROGRESSION

- Tumours can follow several evolutionary paths over a patient's disease course[1]
- In the example on the right, two different dominant clones coexisted, and their relative abundance appeared to be modulated by the therapy received[1]
- Combination therapies are important to target all coexisting disease subclones, especially in cytogenetically high-risk patients[1]

Retreatment of a patient with a regimen on which they have previously progressed should be avoided due to potential drug resistance[1]



Example of clonal dynamics in a patient with high-risk MM*[1]

Used with permission of Elsevier Science & Technology Journals, from Keats JJ, et al. 2012; permission conveyed through Copyright Clearance Center, Inc.[1]

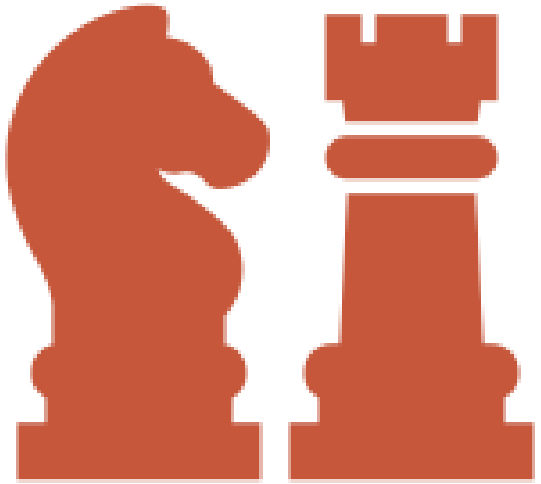
* Summarised results of 8 different FISH assays indicate the relative abundance of each clone defined by aCGH at the 5 time points studied. Pie charts showing the relative proportions of each indicated clone are ordered clockwise starting on the left in longitudinal order. Arrow length is proportional to the time interval. High-risk MM was cytogenetically defined high-risk disease [(t(4;14), t(14;16), t(14;20), del(17p)][1]

aCGH, array-based comparative genomic hybridisation; cIg, cytoplasmic immunoglobulin; Dex, dexamethasone; FISH, fluorescence in situ hybridisation; Len, lenalidomide; Misc, miscellaneous; MM, multiple myeloma; MOA, mechanism/mode of action; RRMM, relapsed/refractory MM

1. Keats JJ, et al. Blood. 2012;120(5):1067-76

SEQUENCING CONSIDERATIONS

THE STRATEGY GAME



- Patients are exposed to **multiple therapies** earlier in the treatment pathway leading to **refractoriness**
- **Clonal evolution** due to treatment selective pressure means new treatments with **new MoAs are needed**
- As new MoAs become available, how do we **optimise treatment sequence**?

MoA, mechanism of action

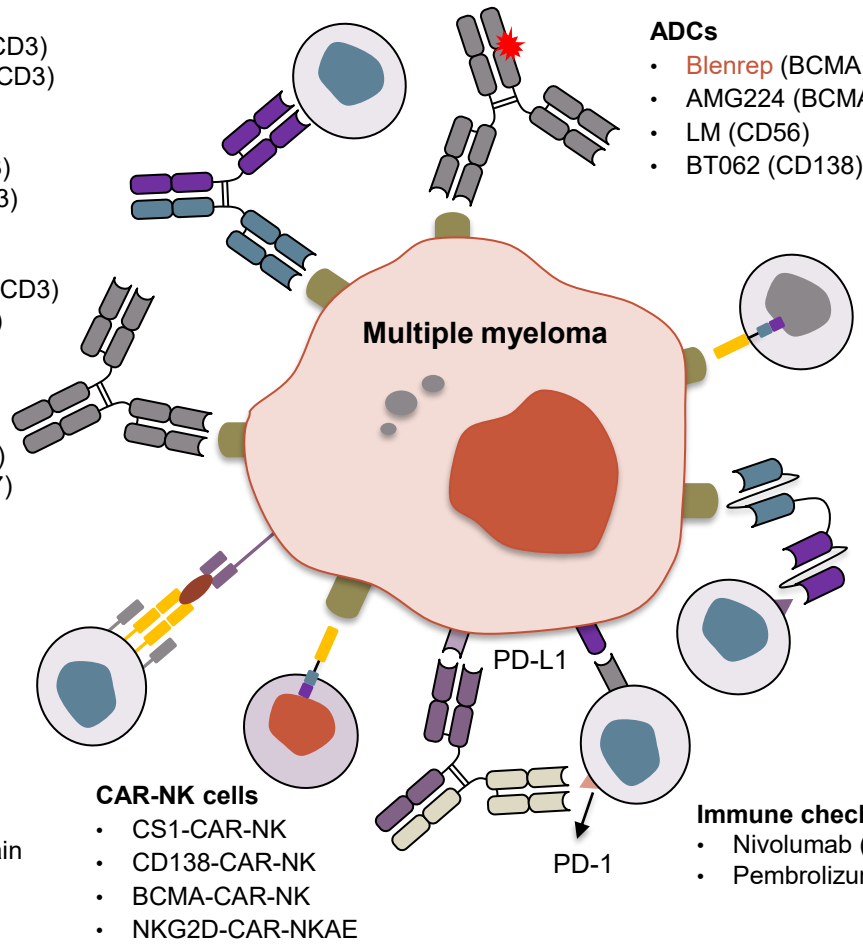
IMMUNOTHERAPIES IN MULTIPLE MYELOMA

NUMEROUS NOVEL TARGETED IMMUNOTHERAPIES HAVE BEEN EXPLORED

BsAbs
- Teclistamab (BCMA/CD3)
- Elranatamab (BCMA/CD3)
- Linvoseltamab (BCMA/CD3)
- F182112 (BCMA/CD3)
- Etenamig (BCMA/CD3)
- Talquetamab (GPRC5D/CD3)
- Cevostamab (FcRH5/CD3)
- AMG424 (CD38/CD3)

mAbs
- Daratumumab (CD38)
- Elotuzumab (SLAMF7)
- Isatuximab (CD38)
- Mezagitamab (CD38)

TCR-T cells
- PRAME
- SSX2
- MAGEA4
- Survivin
- NY-ESO-1
- Immunoglobulin J chain



ADCs
- Blenrep (BCMA)
- AMG224 (BCMA)
- LM (CD56)
- BT062 (CD138)

CAR-T cells
- Abecma (BCMA)
- Carvykti (BMCA)
- CT103A (BCMA)
- CT053 (BCMA)
- FHVH33 (BCMA)
- Orva-cel (BCMA)
- ALLO-715 (BCMA)
- GC012F (BCMA/CD19)
- MCARH109 (GPRC5D)
- OriCAR-017 (GPRC5D)
- Arlo-cel (GPRC5D)

CAR-NK cells
- CS1-CAR-NK
- CD138-CAR-NK
- BCMA-CAR-NK
- NKG2D-CAR-NKAE

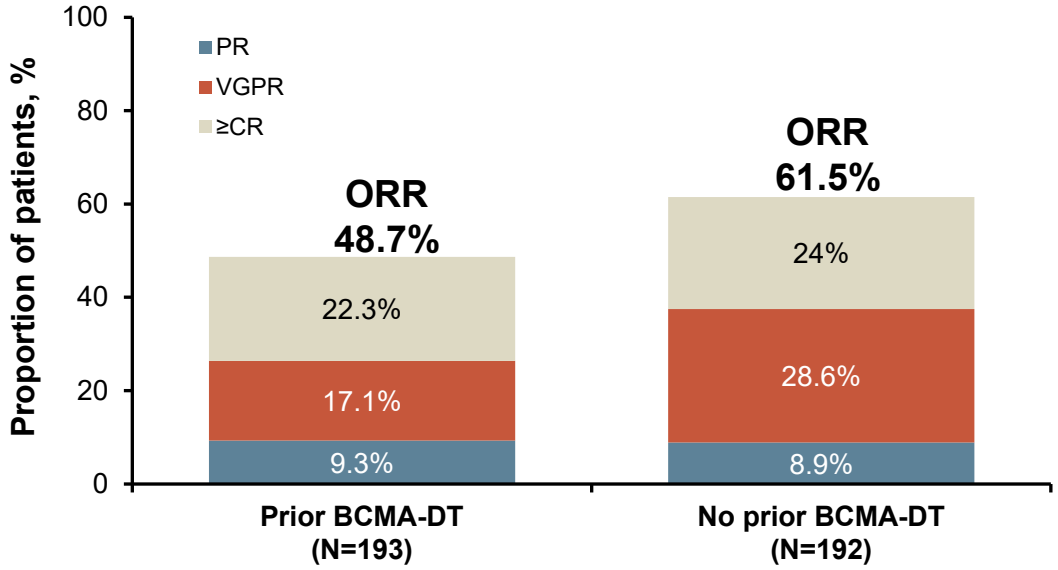
Immune checkpoint inhibitors
- Nivolumab (PD1)
- Pembrolizumab (PD1)

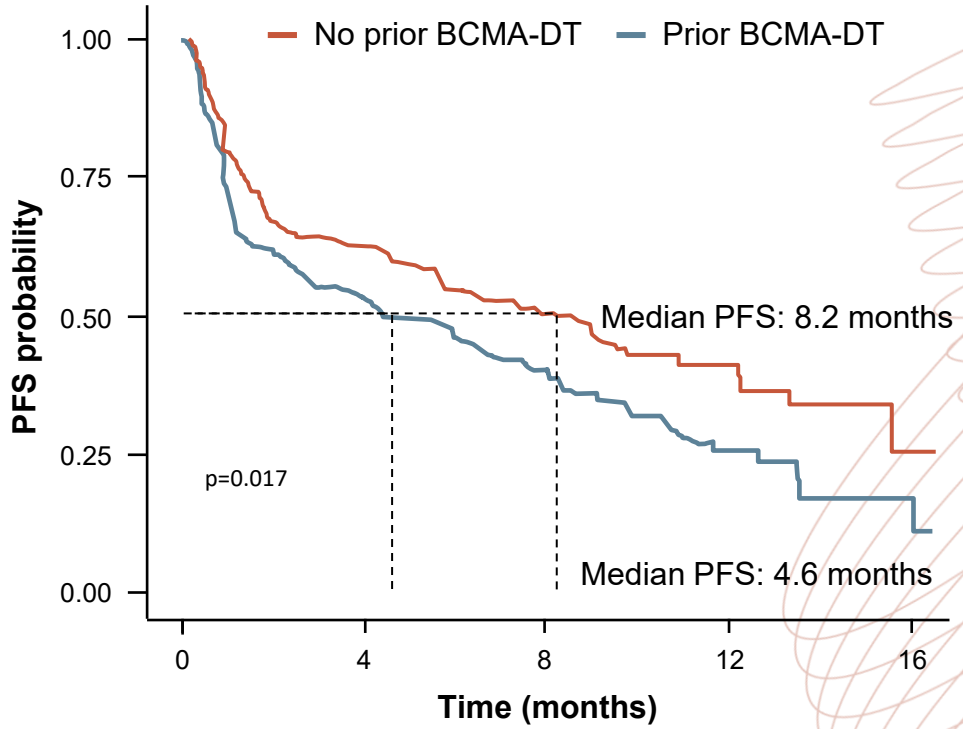
mAbs: monoclonal antibodies; ADCs: antibody-drug conjugates; BsAbs: bispecific antibodies; BiTEs: bispecific T-cell engagers; ICIs: immune checkpoint inhibitors; CAR-T: chimeric antigen receptor T; BCMA: B cell maturation antigen; GPRC5D: G protein-coupled receptor, class C, group 5, member D; FcRH5: Fc receptor-homolog 5; SLAMF7: SLAM Family Member 7; NKG2D: Natural-killer group 2, member D; PD-1: programmed cell death protein 1; PD-L1: programmed death-ligand 1

Lu Q, et al. Mol Biomed. 2024;5:10.1186/s43556-024-00188-w

OUTCOMES OF BISPECIFIC ANTIBODIES AFTER PRIOR BCMA-DT

EFFICACY OUTCOMES WITH TECLISTAMAB





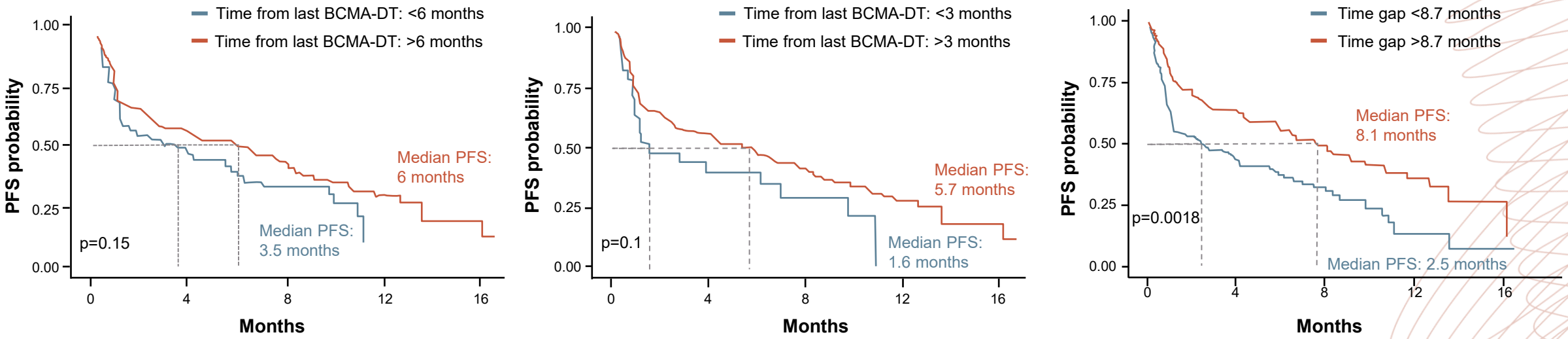
- The prior BCMA-DT cohort had **worse ORR** (p=0.012) **and ≥VGPR** (p=0.009), **but similar ≥CR rates** (p=0.78) compared with those without prior BCMA-DT
- In MVA there was a strong signal for worse ORR in the prior BCMA-DT cohort; however, prior BCMA-DT was not independently associated with the likelihood of achieving response (HR 0.64, 95% CI: 0.41-1.01; p=0.057)

Teclistamab efficacy is strongly affected by prior exposure to BCMA-DT

BCMA, B-cell maturation antigen; CR, complete response; DoR, duration of response; DT: directed therapy; HR, hazard ratio; MVA: multivariate analysis; ORR, overall response rate; PFS, progression-free survival; PR, partial response; VGPR, very good partial response

Dima D, et al. Abstract #897, ASH 2024 (oral presentation)

OUTCOMES OF BISPECIFIC ANTIBODIES AFTER PRIOR BCMA-DT PFS OUTCOMES WITH TECLISTAMAB STRATIFIED BY TIMING OF PRIOR BCMA-DT



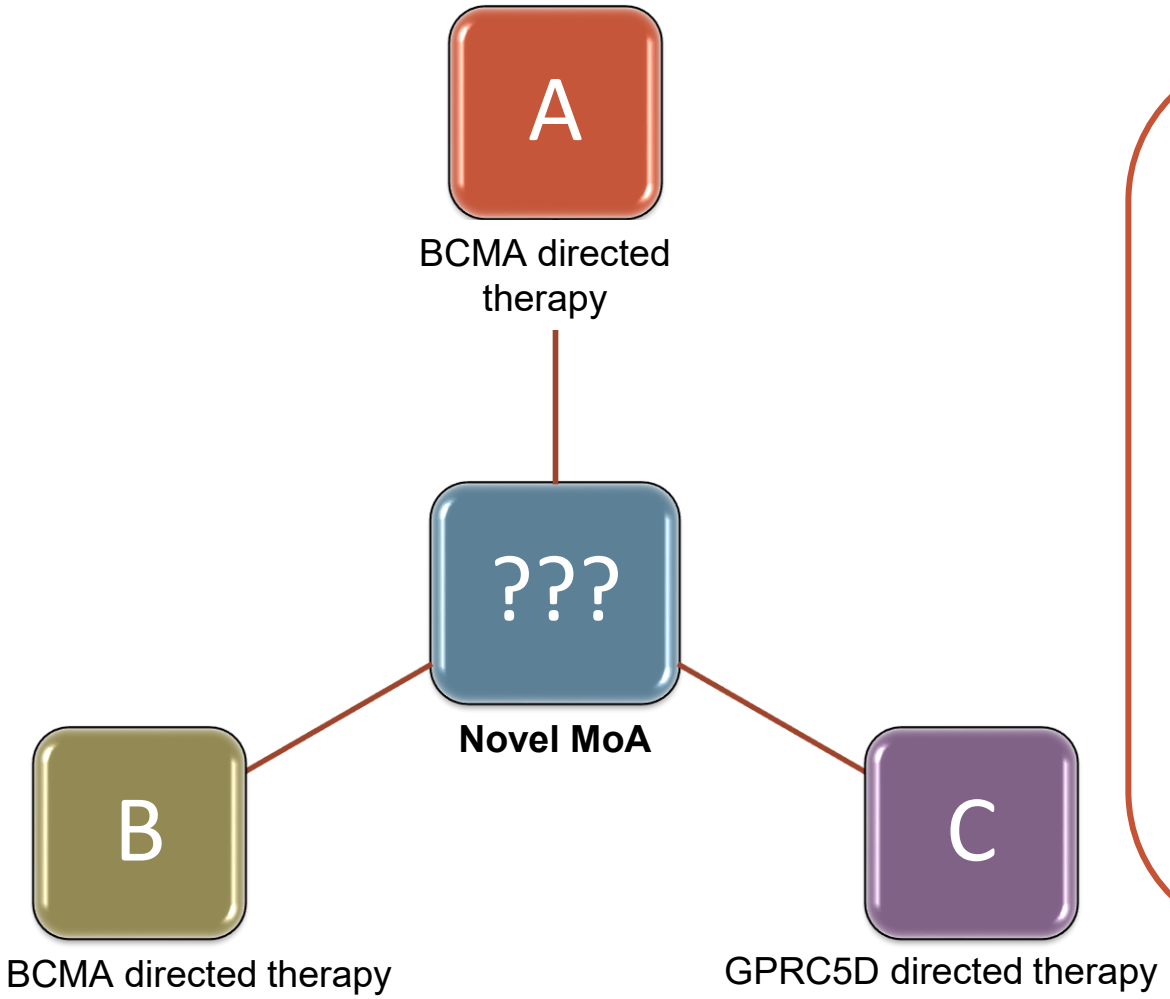
The analysis showed that the **optimal cut-off for time** from the last **BCMA-DT exposure to teclistamab initiation** was **8.7 months**

Patients with >8.7 months between last exposure to prior BCMA-DT and teclistamab initiation had a **superior median PFS with teclistamab** (8.1 months, 95% CI: 4.6-11.7) vs patients with <8.7 months from last prior BCMA-DT exposure (2.5 months, 95% CI: 1.1-5.7), p=0.001

BCMA, B-cell maturation antigen; CI, confidence interval; DT, directed therapy; PFS, progression-free survival

Dima D, et al. Abstract #897, ASH 2024 (oral presentation)

SEQUENCING CONSIDERATIONS



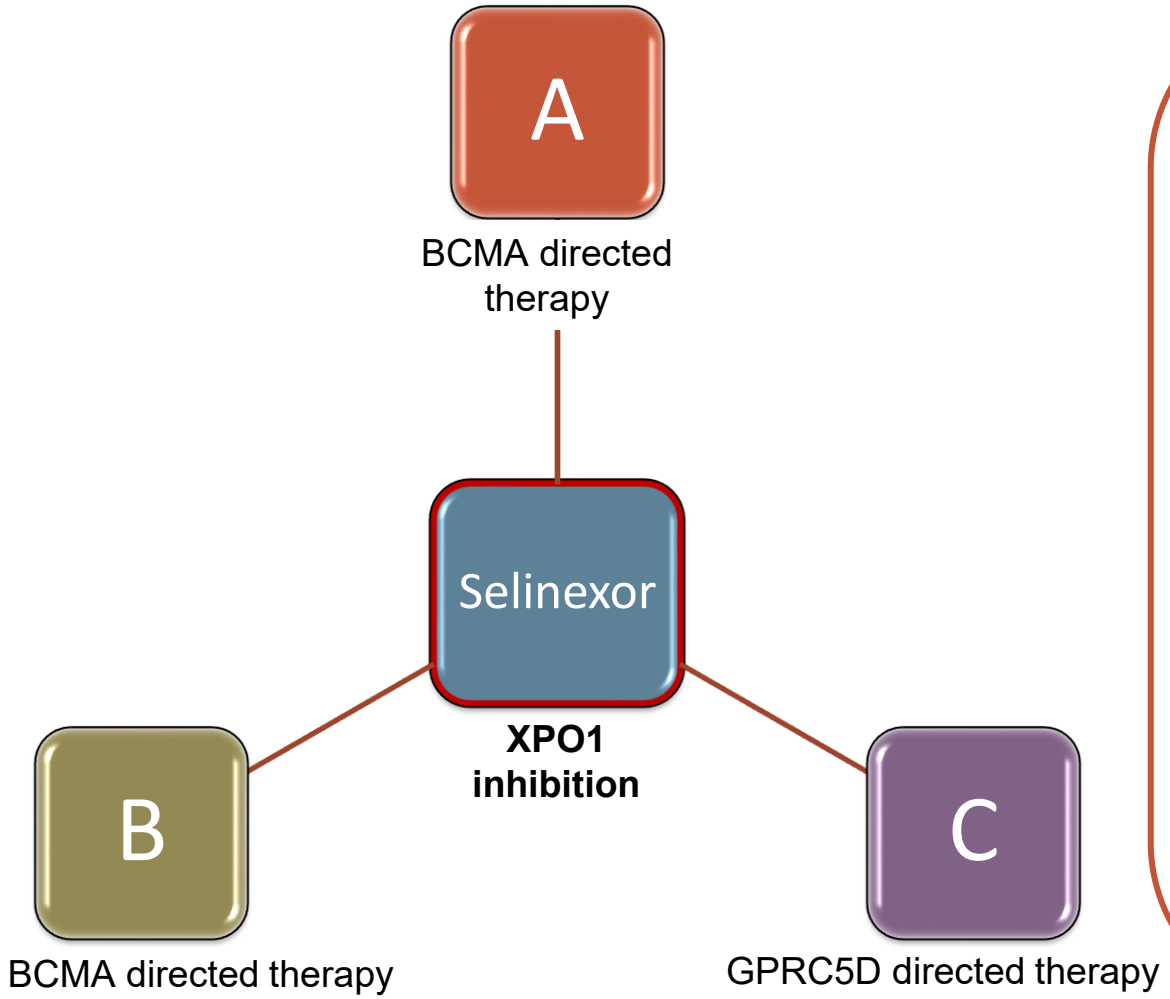
Many new therapies are emerging for MM, but challenges still remain…

- Patients relapse or become refractory to PIs, IMiDs and anti-CD38 mAbs in very early relapse
- Availability of T-cell directed therapies but how do we optimise treatment sequencing
- There is a need for a treatment between T-cell directed therapies:
  - to promote T-cell fitness and reduce T-cell exhaustion
  - enhance the results of later T-cell directed therapy

BCMA, B-cell maturation antigen; CD, cluster of differentiation; GPRC5D, G-protein-coupled receptor, class C group 5, member D; IMiDs, immunomodulatory drugs; mAbs, monoclonal antibodies; MM, multiple myeloma; MoA, mechanism of action

Davis LN, et al. Cancers 2021;13:1686

SEQUENCING CONSIDERATIONS



Many new therapies are emerging for MM, but challenges still remain…

- Patients relapse or become refractory to PIs, IMiDs and anti-CD38 mAbs in very early relapse
- Many patients may not be eligible for ASCT
- Considering patient-related factors will support **treatment sequencing decisions to impact survival outcomes**
- **Need for a treatment between T-cell direct therapies:**
  - **to promote T-cell fitness and reduce T-cell exhaustion**
  - **Enhancing the results of later T-cell** directed therapy

ASCT, autologous stem cell transplant; BCMA, B-cell maturation antigen; CD, cluster of differentiation; GPRC5D, G-protein-coupled receptor, class C group 5, member D; IMiDs, immunomodulatory drugs; mAbs, monoclonal antibodies; MM, multiple myeloma; MoA, mechanism of action; XPO1, exportin-1

Davis LN, et al. Cancers 2021;13:1686

HOW DO WE NAVIGATE THE FUTURE OF MM TREATMENT?

Bench side

- New MoAs/combinations earlier in the treatment pathway impact choices
- Treatment between immunotherapies that don't impact T-cells/ microenvironment
- Using the best treatment to give longest PFS

Bedside

- Treatment history
- Patient characteristics
- Patient expectations and desires

MM, multiple myeloma; MoA, mechanism of action; PFS, progression-free survival

EVERY MOVE MATTERS:
RETHINKING SEQUENCING STRATEGIES IN MODERN MYELOMA

Prof. Karthik Ramasamy

Hematologist

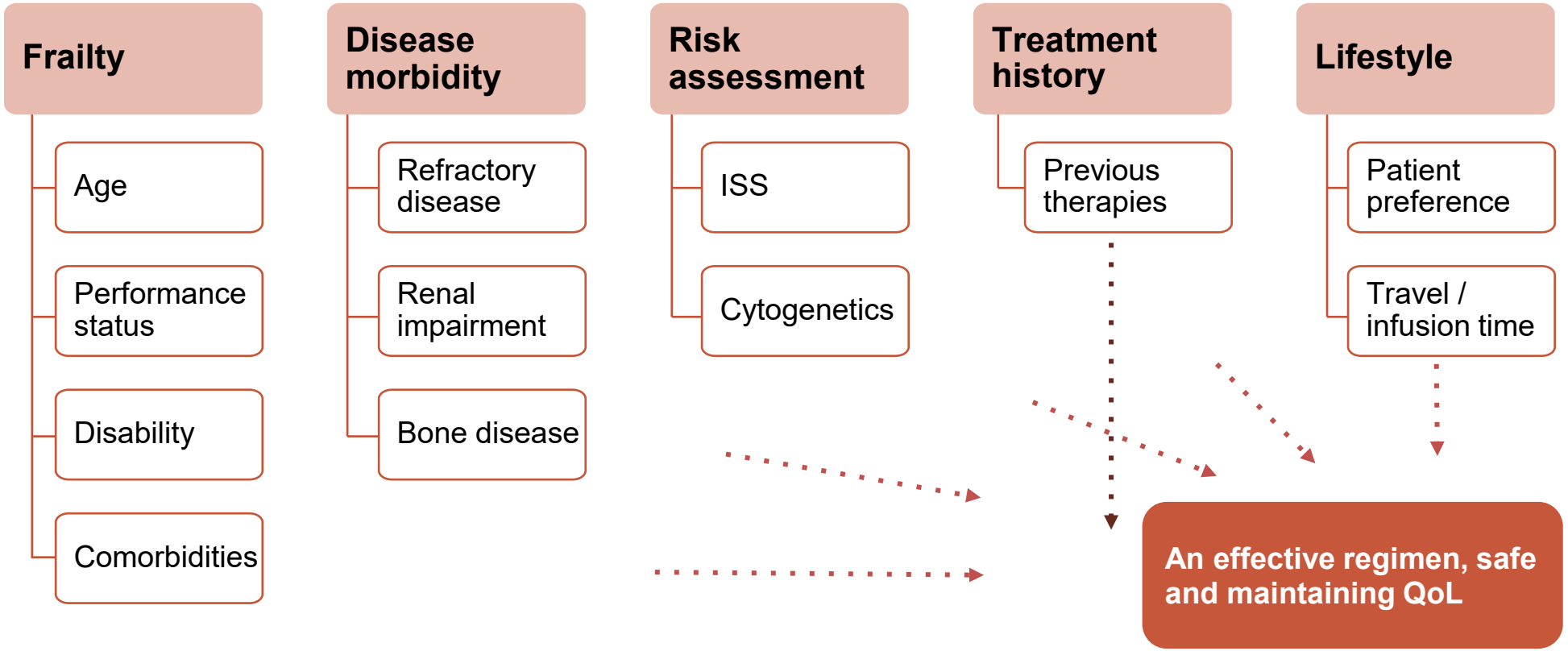
Oxford University Hospitals NHS Trust, UK

OVERVIEW

- Why is sequencing the new challenge in MM?
- Principles of sequencing
  - PI sensitivity & Len-refractory
  - Retaining immune fitness
  - New MoA
- Incorporation in clinical practice

Len, lenalidomide; MM, multiple myeloma; MoA, mechanism of action; PI, proteasome inhibitor

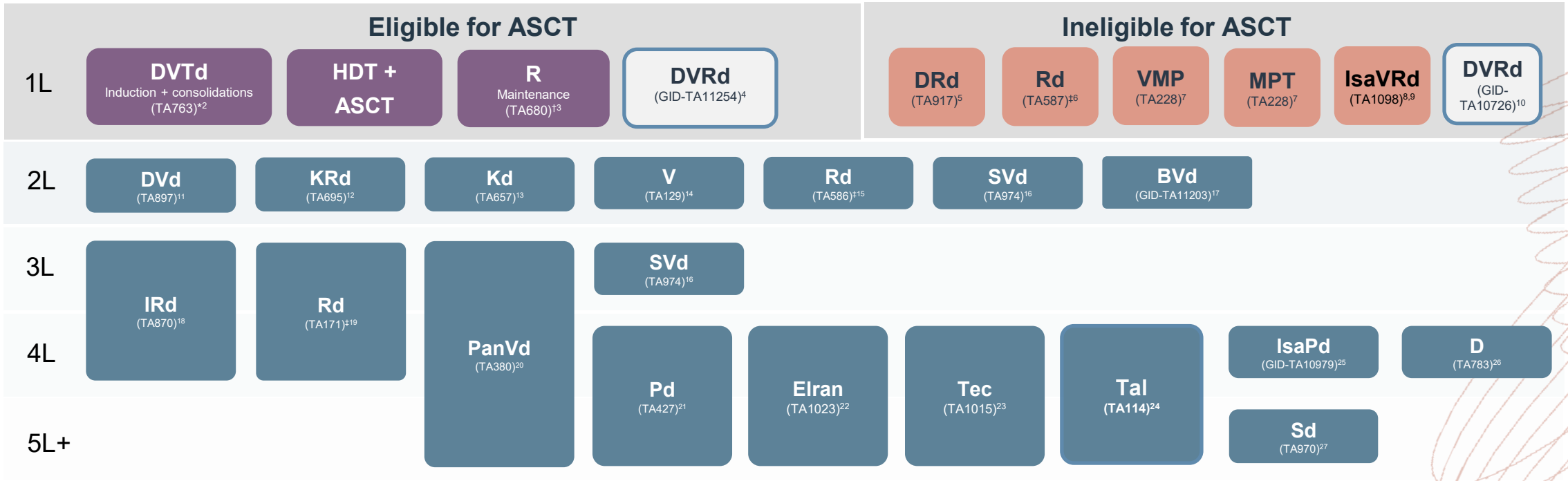
DISEASE AND PATIENT-BASED FACTORS INFLUENCING TREATMENT DECISION-MAKING AT THE RELAPSE SETTING



Treatment history is a crucial factor

ISS, International Staging System; QoL, quality of life.
Information based on speaker's expert opinion

THE FUTURE TREATMENT PATHWAY FOR MM MAY INCLUDE ADDITIONAL QUADRUPLETS AT FIRST LINE FOR TE AND TNE PATIENTS [1-27]



Please note that this recommended treatment pathway is current as of December 2025. IsaPd is approved for use under the Cancer Drugs Fund.[24,27] BVd is available on the Cancer Drugs Fund and awaiting final NICE guidance.[17,28] DVRd guidance is in development by NICE and expected publication date is March 2026.[4,10]
* Induction before high-dose chemotherapy and ASCT;[2] † Maintenance treatment after ASCT;[3] ‡ 1L: Thalidomide is contraindicated (including for pre-existing conditions that it may aggravate) or the person cannot tolerate thalidomide; 2L: After treatment with bortezomib[6,15]

1/2/3/4/5L, first-/second-/third-/fourth-/fifth-line; ASCT, autologous stem cell transplant; BVd, belantamab mafodotin, bortezomib, dexamethasone; D, daratumumab; DRd, daratumumab, lenalidomide, dexamethasone; DVd, darantumumab, bortezomib, dexamethasone; DVRd, daratumumab, bortezomib, lenalidomide, dexamethasone; DVTd, daratumumab, bortezomib, thalidomide, dexamethasone; E, elranatamab; GID, guidance in development; IRd, ixazomib, lenalidomide, dexamethasone; IsaPd, isatuximab, pomalidomide, dexamethasone; IsaVRd, isatuximab, bortezomib, lenalidomide, dexamethasone; Kd, carfilzomib, dexamethasone; KRd, carfilzomib, lenalidomide, dexamethasone; MoA, mechanism of action; MM, multiple myeloma; MPT, melphalan, prednisone, thalidomide; NICE, National Institute for Health and Care Excellence; Pd, pomalidomide, dexamethasone; PanVd, panobinostat, bortezomib, dexamethasone; R, lenalidomide; Rd, lenalidomide, dexamethasone; Sd, selinexor, dexamethasone; SVd, selinexor, bortezomib, dexamethasone; TA, technology appraisal; Tal, talquetamab; TE, transplant eligible; Tec, teclistamab; TNE, transplant non-eligible; V, bortezomib; VMP, bortezomib, melphalan, prednisone.

1. NICE. NG35; 2. NICE. TA763; 3. NICE. TA680; 4. NICE. GID-TA11254. 5. NICE; TA917; 6. NICE. TA587; 7. NICE. TA228; 8. NICE. GID-TA10912; 9. Myeloma UK. First quadruplet treatment for transplant-ineligible patients approved in England and Wales. Available at: https://www.myeloma.org.uk/news/first-quadruplet-treatment-for-transplant-ineligible-patients-approved-in-england-and-wales/; 10. NICE. GID-TA10726;
11. NICE. TA897; 12. NICE. TA695; 13. NICE. TA657; 14. NICE. TA129; 15. NICE. TA586; 16. NICE. TA974; 17. NICE. GID-TA11203; 18. NICE. TA870; 19. NICE. TA171; 20. NICE. TA380; 21. NICE. TA427;
22. NICE. TA1023; 23. NICE. TA1015; 24. NICE. GID-TA10969; 25. NICE. GID-TA10979; 26. NICE. TA783; 27. NICE. TA970; 28. National Cancer Drugs Fund List. Version 1. 379. 26th November 2025. Available at: https://www.england.nhs.uk/wp-content/uploads/2017/04/national-cdf-list-ver1.379.pdf. Accessed December 2025

EHA-EMN 2025 GUIDELINES

At second or subsequent relapse

At 3rd and 4th line for eligible patients according to prior lines of therapy (mainly PI + lenalidomide exposed/refractory)

Cilta-cel [I, A]
Ide-cel [I, A]
BelaPd [I, A]
DaraPd [I, A]
IsaPd [I, A]
EloPd [I, A]
BelaVd [I, A]

If not given before
DaraKd [I, A]
IsaKd [I, A]
DaraVd [I, A]
Kd [I, A]
SVd [I, A]

For triple-class refractory/exposed patients (PIs, IMiDs, and mAbs against CD38)

BCMA-targeted therapy:
CAR-T: Cilta-cel [I, A]
Ide-cel [I, A]
for patients at 3rd and 4th line; then [II, B] for patients after 4th line

BsAbs: Teclistamab [II, B]
Elranatamab [II, B]
Linvoseltamab [II, B]

ADC: BelaPd [I, A]

GPRC5D-targeted therapy:
BsAb: Talquetamab [II, B]

Other regimens:
Melflufen [I, B]
Sd [II, B]

For four-class refractory/exposed patients (PIs, IMiDs, mAbs against CD38 and CAR-T or ADC previously)

GPRC5D-targeted therapy
Talquetamab [II, B]

BCMA-targeted therapy:
BsAbs: Teclistamab [II, B]
Elranatamab [II, B]
Linvoseltamab [II, B]

Other regimens:
Melflufen [I, B]
Sd [II, B]

Clinical trials

T-cell redirecting therapies are becoming the **SoC** in these patients and there is an **unmet need before, between, and after treatment** with BCMA- and GPRC5D-targeted therapies

ADC, antibody-drug conjugate; BCMA, B-cell maturation antigen; Bela, belantamab mafodotin; BsAb, bispecific monoclonal antibody; CAR-T, chimeric antigen receptor T cell; cilta-cel, ciltacabtagene autoleucel; D, dexamethasone; Dara, daratumumab; EHA, European Hematology Association; Elo, elotuzumab; EMN, European Myeloma Network; GPRC5D, G-protein-coupled receptor class C group 5 member D; ide-cel, idecabtagene vicleucel; IMiD, immunomodulatory drug; Isa, isatuximab; Ixa, ixazomib; K, carfilzomib; Kd, carfilzomib/dexamethasone; L, line; Pd, pomalidomide/dexamethasone; PI, proteasome inhibitor; R, lenalidomide; Rd, lenalidomide/dexamethasone; S, selinexor; SoC, standard of care; Vd, bortezomib/dexamethasone

Dimopoulos MA, Terpos E, et al. Nat Rev Clin Oncol. 2025:1-21

TREATMENT LANDSCAPE IN MULTIPLE MYELOMA

1st line

ASCT eligible

- Anti-CD38 + PI + IMiD + dex
- ASCT
- Len / dara-len

ASCT ineligible

- Dara-len-dex
- Dara-VMP / RVd
- Anti-CD38 + PI + IMiD + dex

2nd line

Based on sensitivity/refractoriness to daratumumab and lenalidomide

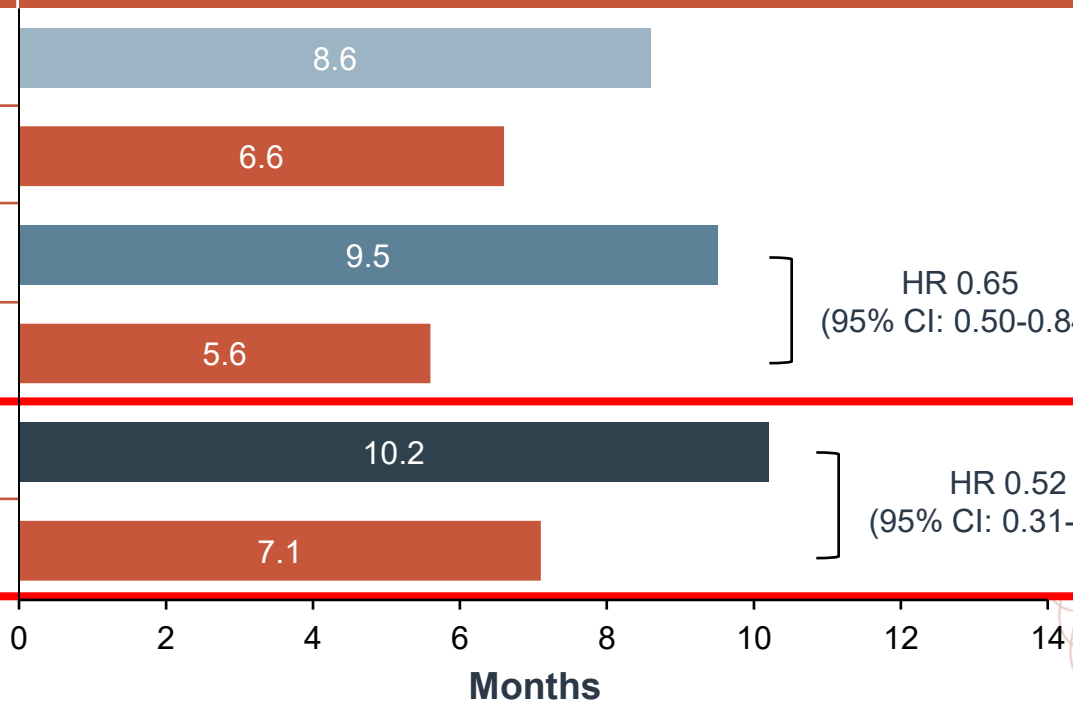
ASCT, autologous stem cell transplant; dara, daratumumab; dex, dexamethasone; IMiD, immunomodulatory drug; len, lenalidomide; PI, proteasome inhibitor; RVd, lenalidomide/bortezomib/dexamethasone; VMP, bortezomib/melphalan/prednisolone

Expert input; Dimopoulos MA, et al. Ann Oncol. 2022;32(3):309-22

PI NAÏVE OR PI NON REFRACTORY PATIENTS

PFS IN LENALIDOMIDE-REFRACTORY PATIENTS

Study	Regimen	Arm	mPFS in lenalidomide-refractory patients
ENDEAVOR[1] 1-3 prior lines of therapy	**Kd**[1]: Doublet, PI, one new MoA	Kd	8.6
		Vd	6.6
OPTIMISMM[2*] 1-3 prior lines of therapy, received prior treatment with a lenalidomide-containing regimen for ≥2 consecutive cycles, not bortezomib refractory	**PVd**[2]: Triplet, PI, one new MoA	PVd	9.5
		Vd	5.6
BOSTON[3†] 1-3 prior lines of therapy	**SVd**[3]: Triplet, PI, two new MoAs	SVd	10.2
		Vd	7.1



Data presented side by side for illustration purposes only – this is not a head-to-head comparison of these studies

* Median follow-up was 15.9 months; † Median follow-up was 28.2 months (SVd) and 27.1 months (Vd)

CI, confidence interval; HR, hazard ratio; Kd, carfilzomib/dexamethasone; MoA, mechanism of action; (m)PFS, (median) progression-free survival; (m)OS, (median) overall survival; PI, proteasome inhibitor; PVd, pomalidomide/bortezomib/dexamethasone; SVd, selinexor/bortezomib/dexamethasone; Vd, bortezomib/dexamethasone

1. Moreau P, et al. Leukemia. 2017;31:115-22. 2. Richardson PG, et al. Lancet Oncol. 2019;20:781-94; 3. Mateos MV, et al. Eur J Haematol. 2024;113:242-52

PI NAÏVE OR PI NON REFRACTORY PATIENTS

OS IN LENALIDOMIDE-REFRACTORY PATIENTS

Study	Regimen	Arm	mOS in lenalidomide-refractory patients
ENDEAVOR[1] 1-3 prior lines of therapy	**Kd**[1]: Doublet, PI, one new MoA	Kd Vd	**There was no significant difference in mOS** with Kd vs. Vd in **lenalidomide-refractory** patients[4‡]: **Kd, 29.2 months vs.** Vd, 21.4 months; **HR 0.86** (95% CI: 0.62-1.18)
OPTIMISMM[2*] 1-3 prior lines of therapy, received prior treatment with a lenalidomide-containing regimen for ≥2 consecutive cycles, not bortezomib refractory	**PVd**[2]: Triplet, PI, one new MoA	PVd Vd	**There was no significant difference in mOS** with PVd vs. Vd in **lenalidomide-refractory** patients[5§]: **Kd, 29.8 months vs.** Vd, 24.2 months; **HR 0.89** (95% CI: 0.71-1.12)
BOSTON[3†] 1-3 prior lines of therapy	**SVd**[3]: Triplet, PI, two new MoAs	SVd Vd	**Lenalidomide-refractory** patients had significantly **longer mOS** with SVd vs. Vd[3†]: **SVd, 26.7 months vs.** Vd, 18.6 months; **HR 0.53** (95% CI: 0.30-0.95)

Data presented side by side for illustration purposes only – this is not a head-to-head comparison of these studies

* Median follow-up was 15.9 months; † Median follow-up was 28.2 months (SVd) and 27.1 months (Vd)

CI, confidence interval; HR, hazard ratio; Kd, carfilzomib/dexamethasone; MoA, mechanism of action; (m)PFS, (median) progression-free survival; (m)OS, (median) overall survival; PI, proteasome inhibitor; PVd, pomalidomide/bortezomib/dexamethasone; SVd, selinexor/bortezomib/dexamethasone; Vd, bortezomib/dexamethasone

1. Moreau P, et al. Leukemia. 2017;31:115-22. 2. Richardson PG, et al. Lancet Oncol. 2019;20:781-94; 3. Mateos MV, et al. Eur J Haematol. 2024;113:242-52

RETAINING IMMUNE FITNESS

KEY CONSIDERATIONS FOR CHOICE OF RELAPSE TREATMENT

Patient & treatment related

- **Prior regimen** used
- Patient **age** and **frailness**
- **Comorbidities**

Therapy-management related

- Therapy **waiting time**
- **ICANS/CRS** management for CAR-T and bispecific antibodies
- **GI** side effects
- **Infection rates** and other specific toxicities

Target related

- **T-cell fitness & T-cell exhaustion**
- **Target modification/loss**

CAR-T, chimeric antigen receptor T cell; CRS, cytokine release syndrome; GI, gastrointestinal; ICANS, immune effector cell-associated neurotoxicity syndrome

Devarakonda S, et al. Hematology Am Soc Hematol Educ Program. 2022;2022(1):560-8; Nathwani N, et al. Am Soc Clin Oncol Educ Book. 2021;41:358-75; Binder AF, et al. Front Immunol. 2023:14:1275329; Zhou X, et al. Haematologica. 2023;108:958-68

T-CELL DIFFERENTIATION/EXHAUSTION IN RESPONSE TO ACUTE AND CHRONIC STIMULI

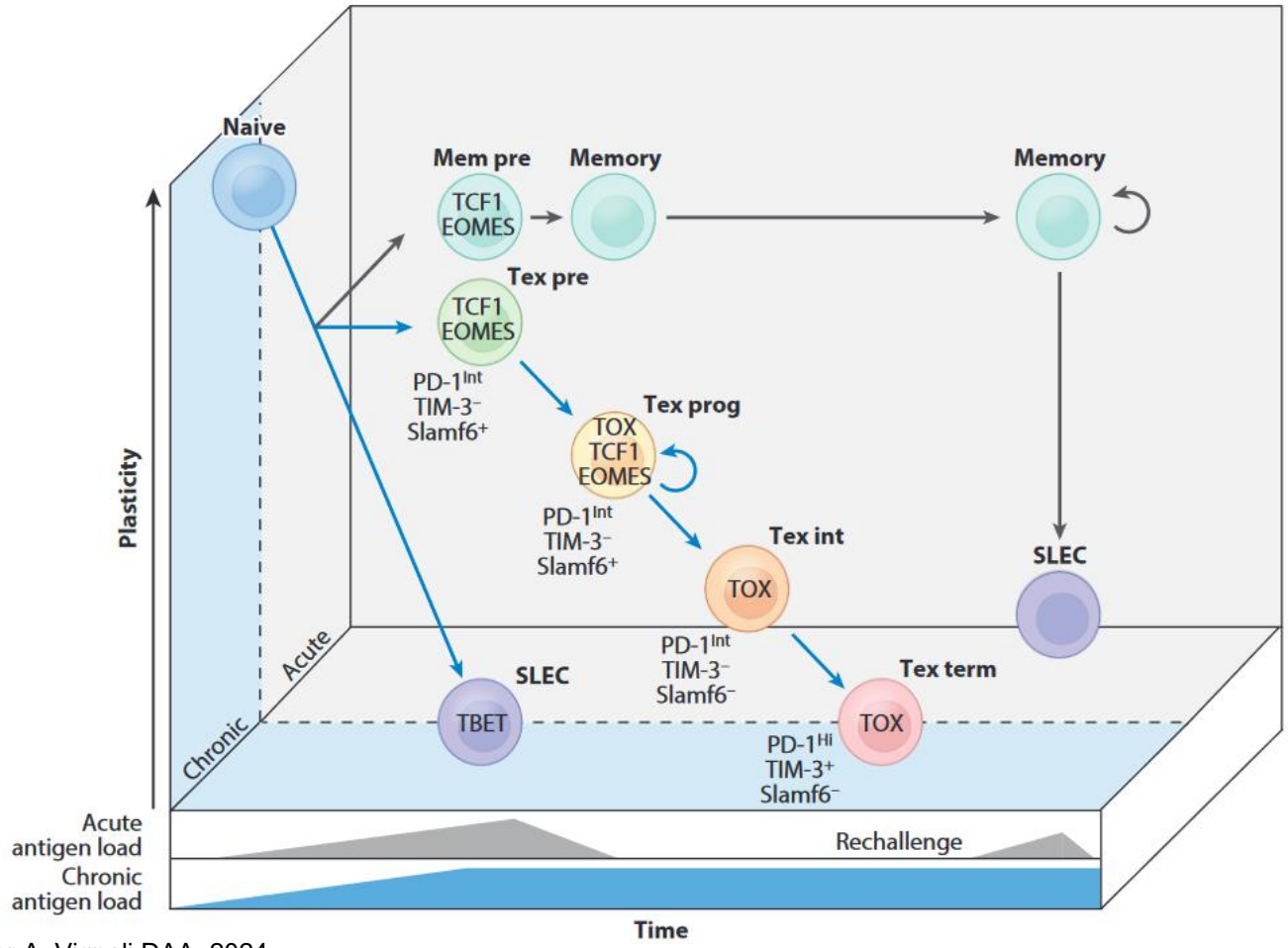


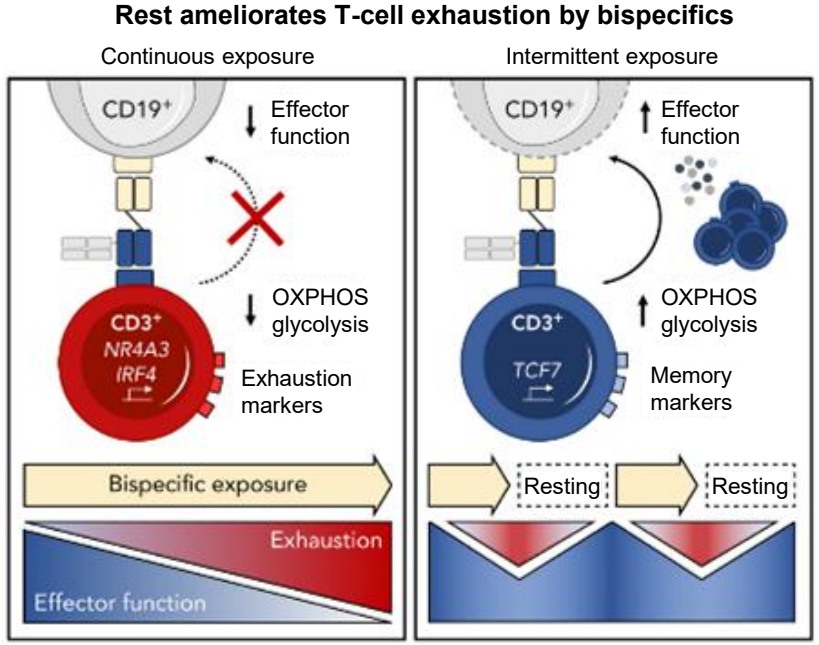
Figure reproduced from Baessler A, Vignali DAA. 2024

Int, intermediate; mem pre, memory precursor; pre, precursor; prog, progenitor; SLECs, short-lived effector cells; TCF1, T cell factor 1; Term, terminally; Tex, exhausted T cell; TOX, thymocyte selection–associated HMG box protein

Baessler A, Vignali DAA. Annu Rev Immunol. 2024;42:179-206

TREATMENT-FREE INTERVALS MAY COUNTERACT T-CELL EXHAUSTION

- Most bispecific antibody therapies have been developed with **continuous therapy schedules**, which can be detrimental to T-cell fitness[1]
- Accumulating data suggest that **treatment-free intervals** can be beneficial in functional and transcriptional T-cell rejuvenation[1]

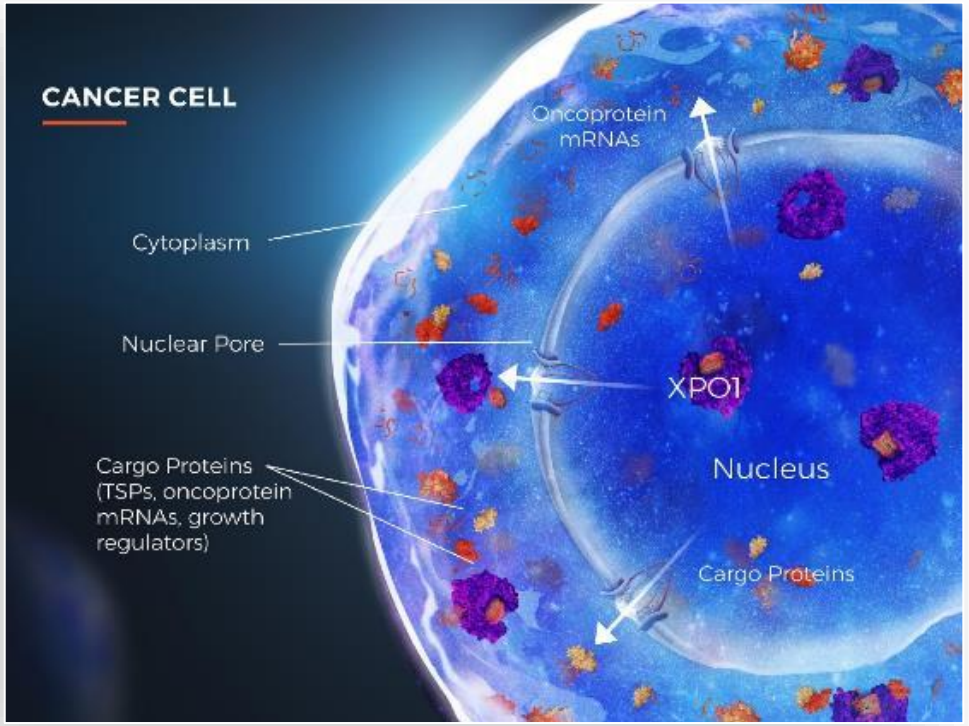


- Continuous exposure to a CD19xCD3 bispecific molecule induces T-cell exhaustion[2]
- Treatment-free intervals transcriptionally reprogram and functionally reinvigorate T cells[2]

1. Binder AF, et al. Front Immunol. 2023:14:1275329; 2. Philipp N, et al. Blood. 2022:140(10):1104-18

SELINEXOR:

A FIRST-IN-CLASS ORAL EXPORTIN 1 (XPO1) INHIBITOR[1]



XPO1 overexpression:

Inactivates tumour suppressor proteins[2]

- TSPs need to be localised in the nucleus to initiate apoptosis thereby suppressing tumour growth[3,4]
- Overexpression of XPO1 results in their functional inactivation of TSPs[2]

Enhances proto-oncogene translation[5]

- XPO1 overexpression increases nuclear export, and subsequent translation and protein synthesis of multiple eIF4E-bound oncogenic mRNAs

Disrupts growth regulation[2,3]

- Increased XPO1 expression promotes sustained cellular proliferation through increased cytoplasmic localisation and expression of master growth regulators

Selinexor is indicated i) in combination with bortezomib and dexamethasone for the treatment of adult patients with MM who have received ≥1 prior therapy ii) in combination with dexamethasone for the treatment of MM in adult patients who have received ≥4 prior therapies and whose disease is refractory to ≥2 proteasome inhibitors, two immunomodulatory agents and an anti-CD38 monoclonal antibody, and who have demonstrated disease progression on the last therapy

eIF4E, eukaryotic translation initiation factor 4E; TSP, tumour suppressor protein; XPO1, exportin-1

1. Peterson TJ, et al. Ann Pharmacother. 2020;54(6):577-82; 2. Sun Q, et al. Signal Transduct Target Ther. 2016;1:16010; 3. Tai Y-T, et al. Leukemia. 2014;28(1):155-65; 4. O'Hagan HM, et al. Oncogene. 2004;23(32):5505-12; 5. Culjkovic-Kraljacic B, et al. Cell Rep. 2012;2(2):207-15

GENE CLUSTERS CORRELATED WITH EX VIVO SENSITIVITY/ RESISTANCE TO SELINEXOR SHOWED PATTERNS OPPOSING THOSE OF DARATUMUMAB

MM transcriptomic profile overlayed with gene clusters correlated with treatment sensitivity and resistance

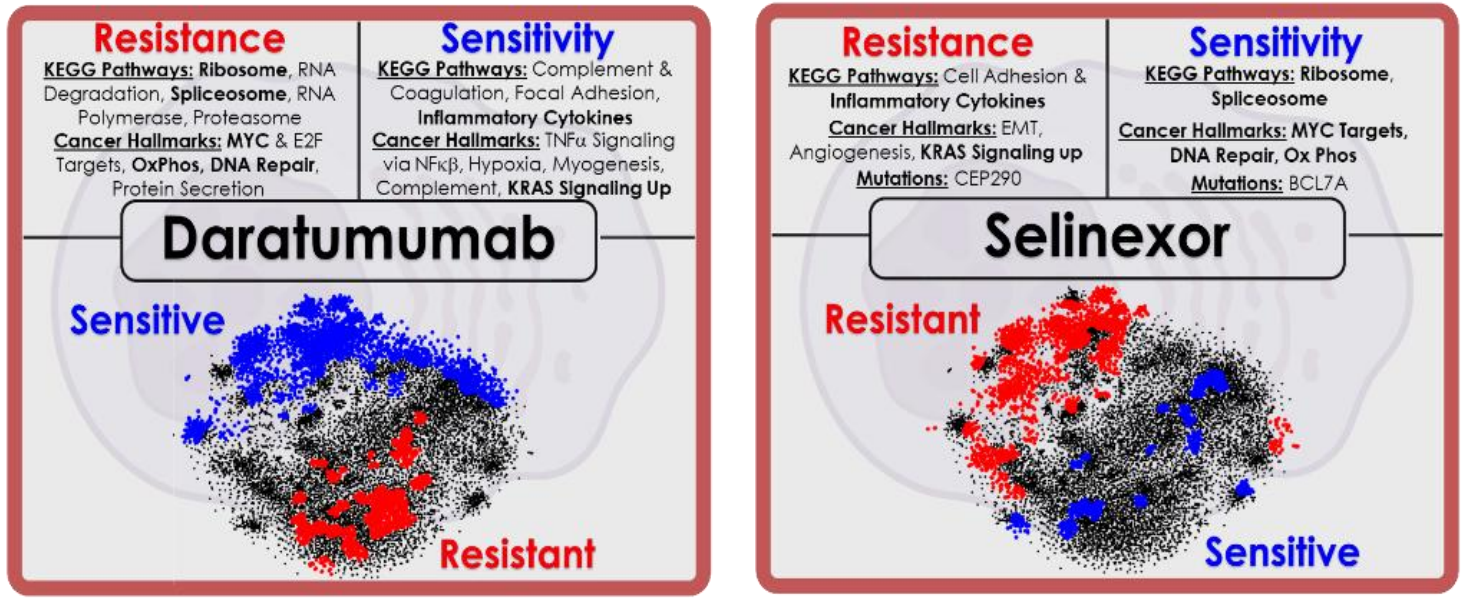


Figure reproduced from Sudalagunta PR, et al. 2025

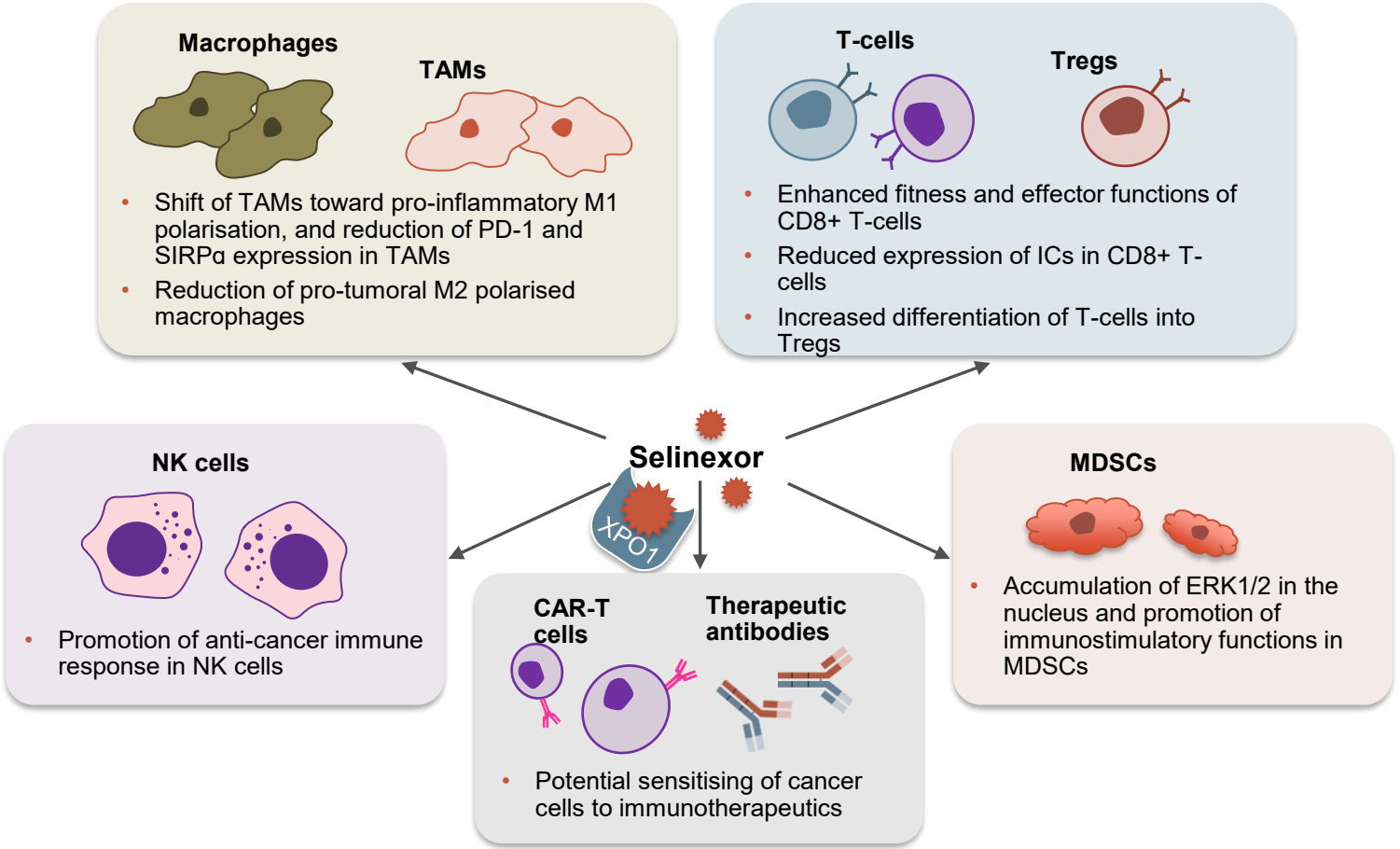
Genes associated with **resistance** to **daratumumab** were found to be associated with **sensitivity** to **selinexor** and vice versa

BCL7A, BAF chromatin remodeling complex subunit BCL7A; CEP290, centrosomal protein 290; KEGG, kyoto encyclopedia of genes and genomes; NFκβ, nuclear factor kappa B; MM, multiple myeloma; MYC, MYC proto-oncogene; RNA, ribonucleic acid; TNFα, tumor necrosis factor alpha

Sudalagunta PR, et al. Cancer Res. 2025;85(2):378-98

SELINEXOR INFLUENCES MULTIPLE IMMUNE CELLS PATHWAYS

Schematic illustration of influence of selinexor on immune cells and immunotherapy



Selinexor potentially **sensitises cancer cells** to **CAR-T cells** and therapeutic **antibodies**[a]

Selinexor is suggested to **impact macrophages** and **tumour-associated macrophages** (TAMs), **myeloid-derived suppressor cells** (MDSCs), **natural killer** (NK) **cells**, and T-cells in the **tumour microenvironment**

[a] Selinexor SmPC does not specify guidance on its use in sequence with CAR-T cells

CAR-T, chimeric antigen receptor T-cell; ERK1/2, extracellular-signal regulated kinases 1/2; IC, immune checkpoint; MDSC, myeloid-derived suppressor cell; NK, natural killer; PD-1, programmed death 1; SIRPα, signal regulatory protein alpha; TAM, tumour-associated macrophage; Treg, regulatory T-cell

Tasbihi K, Bruns H. Cells. 2025;14(6):430

XPO1 INHIBITORS HAVE POTENTIAL TO PROMOTE T-CELL FITNESS AND REDUCE T-CELL EXHAUSTION

- **XPO1 inhibitors:**[1]
  - Have direct **cytotoxic effects** on tumour cells
  - **Decrease inflammation** in infectious disease
  - May facilitate a **favourable immune microenvironment** for effector T-cells to combat T-cell exhaustion

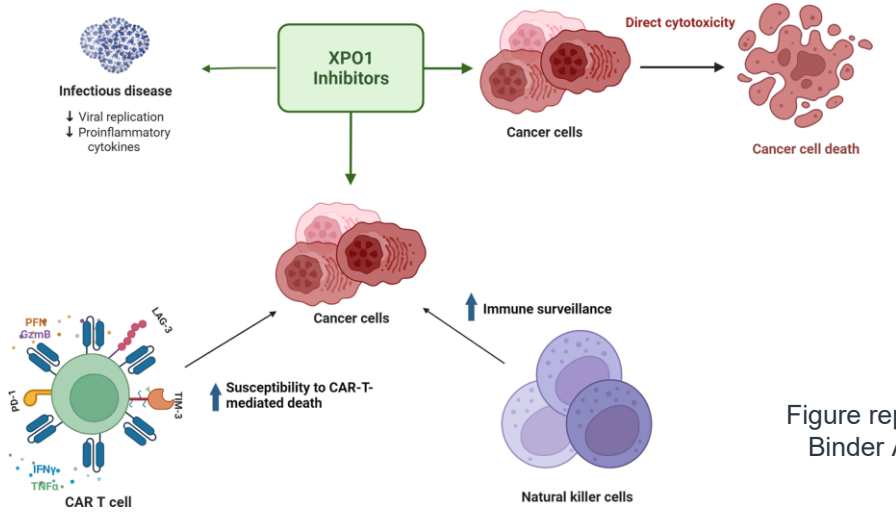


Figure reproduced from Binder AF, *et al*. 2023

"In addition to direct cytotoxicity against malignant cells, ***XPO1 inhibitors may modulate the immune microenvironment to promote T-cell fitness*** *and* ***reduce markers of T-cell exhaustion***[2]*"*

INTERNATIONAL MYELOMA WORKING GROUP RECOMMENDATION[2]

Use a therapy with a different mechanism of action or immunotherapy targeting a different antigen for patients progressing while receiving, or shortly after receiving, BCMA-targeting T-cell engagers (TCE)

"The ***XPO1 inhibitors*** *selinexor and eltanexor* ***reduced T-cell exhaustion*** *in cell lines and animal models, suggesting their potential role in revitalising these key effector cells*[1]*"*

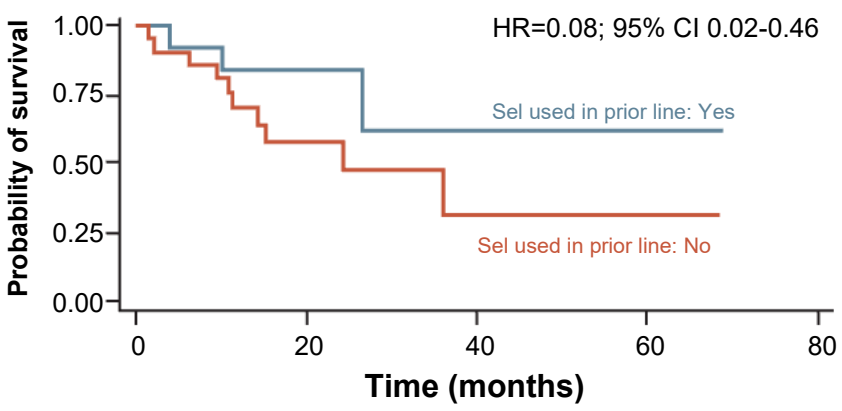
CAR-T, chimeric antigen receptor T-cell; XPO1, exportin 1; BCMA, B-cell maturation antigen; TCE, T-cell engagers

1. Binder AF, et al. Front Immunol. 2023:14:1275329; 2. Costa, LJ, et al. Leukemia. 2025;39(3):543-54

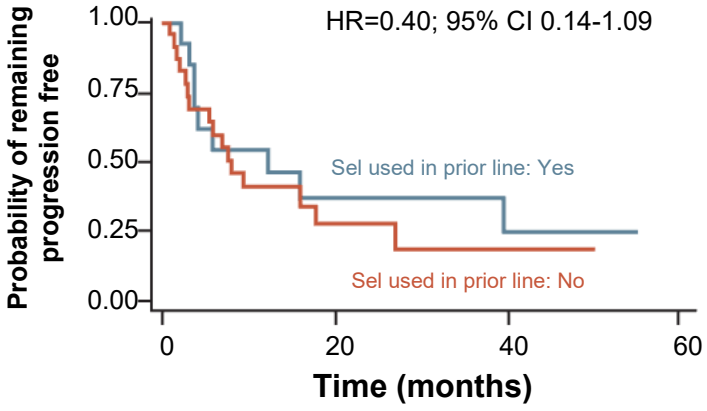
SEQUENCING SELINEXOR AND BCMA-DIRECTED THERAPY

- In a retrospective cohort study, the impact of prior treatment with a selinexor-containing regimen on CAR-T outcomes was evaluated in patients with R/R MM
- The BCMA-directed CAR-T products administered included ide-cel (60%), cilta-cel (35.6%), and CC-98633/BMS-986354 (4.4%)
- At a median follow-up of 68 months, **median DoR was 8.1 months** (IQR 2.6-39), **median PFS was 8.1 months** (IQR 3.1-39.5), and **median OS was 35.9 months** (IQR 14.2-NR)

OS if selinexor was used in the immediate prior LOT before CAR-T therapy



PFS if selinexor was used in the immediate prior LOT before CAR-T therapy



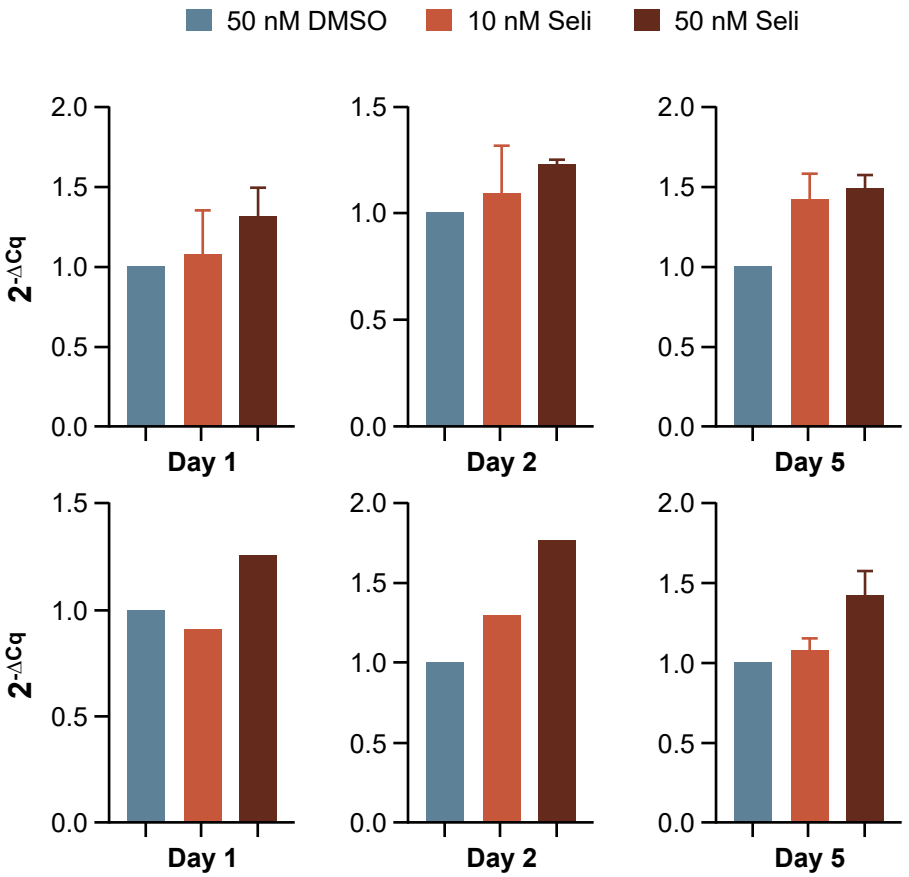
Patients who received selinexor in the **therapy line immediately preceding CAR-T** demonstrated **longer PFS and OS** compared to those exposed in earlier lines

Prior selinexor exposure did not compromise the efficacy or safety of anti-BCMA CAR-T in R/R MM, with **encouraging PFS and OS observed post-CAR-T in patients previously treated with selinexor**

CAR, chimeric antigen receptor; CI, confidence interval; DoR, duration of response; HR, hazard ratio; IQR, interquartile range; LOT, line of therapy; MM, multiple myeloma; NR, not reached; OS, overall survival; PFS, progression-free survival; R/R, relapsed/refractory; BCMA, B-cell maturation antigen

Costa BA, et al. J Clin Med 2025;14:1316

UPREGULATION OF BCMA BY SELINEXOR IN MM CELL LINES



BCMA gene expression increased by selinexor treatment in OPM-2 cell line (top) and AMO1 cell line (bottom)

Figure reproduced from Vebruggen C, et al. 2025

- Selinexor treatment leads to a time- and dose-dependent upregulation of BCMA expression at both the protein and transcript levels
- Cell viability was not impacted by the chosen selinexor concentrations
- Selinexor may enhance target antigen availability on the cell surface, potentially improving the efficacy of BCMA-directed immunotherapies
- This needs to be investigated further in patient samples

BCMA, B-cell maturation antigen; DSMO; diamethyl sulfoxide; MM, multiple myeloma; Seli, Selinexor

Verbruggen C, et al. Blood 2025; 146 (Supplement 1): 6102 (ASH Annual Meeting 2025, poster)

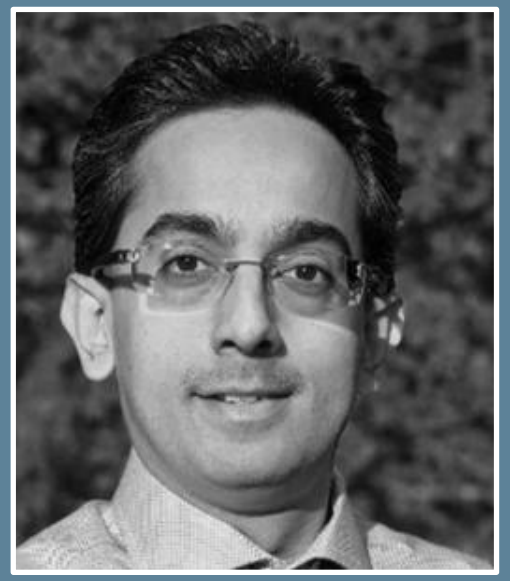
INCORPORATION INTO CLINICAL PRACTICE

- Recognition that patients **remain PI sensitive**[1]
- SVd may be a suitable treatment option for early relapsed patients previously treated with lenalidomide and daratumumab, as it **offers a double MoA switch**[2]
- Continuous use of targeted immunotherapies has potential to **exhaust T cells/induce target loss** and **increase infections**[3,4]
- Incorporate new MoA such as XPO1 inhibition to **induce disease response** and **regain immune fitness**[3,5-7]

MoA, mechanism of action; PI, proteasome inhibitor; SVd, selinexor bortezomib dexamethasone; XPO1, exportin 1

1. Ramasamy K, clinical experience; 2. Schiller GJ, et al. Clin Lymphoma Myeloma Leuk 2023.23(9):e286–e296.e4 3. Binder AF, et al. Front Immunol. 2023:14:1275329; 4. Philipp N, et al. Blood. 2022:140(10):1104-18;
5. Peterson TJ, et al. Ann Pharmacother. 2020;54(6):577-82; 6. Tasbihi K, Bruns H. Cells. 2025;14(6):430;
7. Costa, LJ, et al. Leukemia. 2025;39(3):543-54

CLINICAL STUDIES TO CLINICAL REALITY
PATIENT CASE STUDIES



Dr Faisal Basheer

Hematologist
Cambridge University Hospitals
NHS Trust, UK

Dr Andrew Charlton

Hematologist
Newcastle Upon Tyne Hospitals
NHS Trust, UK

THERAPEUTIC INDICATIONS

NEXPOVIO▼ (SELINEXOR) IS INDICATED:[1]

in combination with **bortezomib and dexamethasone** for the treatment of adult patients with multiple myeloma who have received **at least one prior therapy**

in combination with **dexamethasone** for the treatment of multiple myeloma in adult patients who have received at least **four prior therapies** and whose disease is **refractory to at least two proteasome inhibitors, two immunomodulatory agents and an anti-CD38 monoclonal antibody**, and who have demonstrated **disease progression on the last therapy**

CD38, cluster of differentiation 38

1. NEXPOVIO® (selinexor) Summary of Product Characteristics. Menarini Stemline UK. 2024

PATIENT CASE 1

PATIENT PROFILE

- 66-year-old retired civil servant
- Previously fit and well
- Presented to GP with 5-6 months of decline, multiple chest infections requiring antibiotics
- Latterly developed lower back pain
- Referred to hematology due to finding of an IgG PP on serum EP

Diagnosis: Mid 2017

Further investigations showed:

- IgG kappa PP 30g/L
- B2M 1.9, Cr 58, Ca^{2+} 2.3, Hb 109 g/L, K 51, L 5.6
- WB-DWMRI: no bony lesions, OA of spine
- BMB: 10% PCs, CD138+ / MUM1+ / CD56+ / k-restricted
- No high-risk genetics
- **Classified: Smouldering myeloma**
- **Management: Active monitoring**

Educational case study

B2M, beta-2 macroglobulin; BMB, bone marrow biopsies; Ca2+, calcium; CD, cluster of differentiation; EP, electrophoresis; GP, general practitioner; Hb, hemoglobin; IgG, immunoglobulin G; K, kappa; L, lambda; K:L, kappa-lambda ratio; OA, osteoarthritis; PC, plasma cells; PP, paraprotein; WB-DWMRI, whole body-diffusion weighted MRI

PATIENT CASE 1: TREATMENT

AFTER 6 MONTHS OF MONITORING (START OF 2018):

- Paraprotein had risen to 49 g/L (from 30 g/L)
- **MDT:** No clear clinical progression but decision to treat
- **Management:** 5 x VTD to a PR (12g/L)

L1

Bortezomib, thalidomide, dexamethasone (VTD)

Received 5 cycles of VTD to a PR (12g/L)

- Complications:
  - Peripheral sensory neuropathy resulting in dose reductions of bortezomib and thalidomide

Educational case study

MDT, multidisciplinary team; PR, partial response; VTD, Bortezomib, Thalidomide, Dexamethasone

PATIENT CASE 1: TREATMENT

L1

Bortezomib, thalidomide, dexamethasone (VTD)

HDT-ASCT

Melphalan and ASCT

- Day 100 BMB – 2% PCs
- PP remained at 11g/L

MAINTENANCE

Lenalidomide maintenance

Received 51 cycles

Mid 2022:

- Biochemical relapse around 4 years post-ASCT (PP 21g/L)

Educational case study

ASCT, autologous stem cell transplantation; BMB, bone marrow biopsies; HDT, high dose therapy; PC, plasma cells; PP, paraprotein; PR, partial response

PATIENT CASE 1: POLLING QUESTION 1

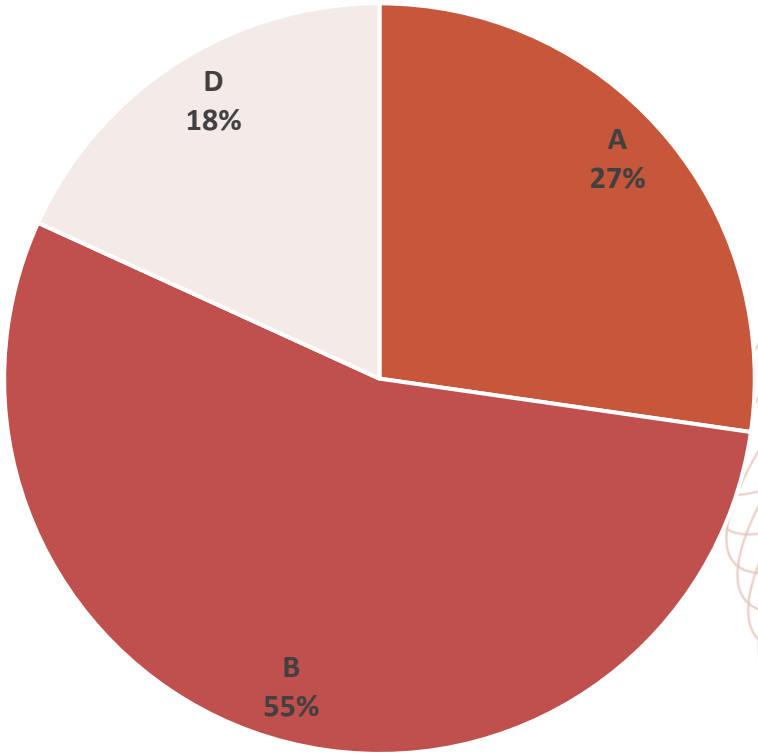
WHICH OF THE FOLLOWING TREATMENT OPTIONS, AVAILABLE AT THE TIME, WOULD YOU HAVE CHOSEN?

A. Kd

B. DVd

C. Vd

D. Clinical trial (Myeloma XII – ITD and 2nd ASCT)



Educational case study

ASCT, autologous stem cell transplant; DVd, daratumumab, bortezomib, dexamethasone; ITD, ixazomib, thalidomide and dexamethasone; Kd, carfilzomib and dexamethasone; Vd, bortezomib and dexamethasone

PATIENT CASE 1: TREATMENT

L1 — **Bortezomib, thalidomide, dexamethasone (VTD)**

HDT-ASCT — **Melphalan and ASCT**

MAINTENANCE — **Lenalidomide maintenance**

L2 — **Carfilzomib and dexamethasone (Kd)**

- 2 years of therapy
- VGPR at best
- PP fell to 2g/L

Mid 2024:

- **Relapse with PP rise to 14 g/L**

Patient rationale:

- Patient elected for Kd due to concerns about having bortezomib again due to previous peripheral neuropathy

Educational case study

ASCT, autologous stem cell transplantation; HDT, high dose therapy; PP, paraprotein; VGPR, very good partial response

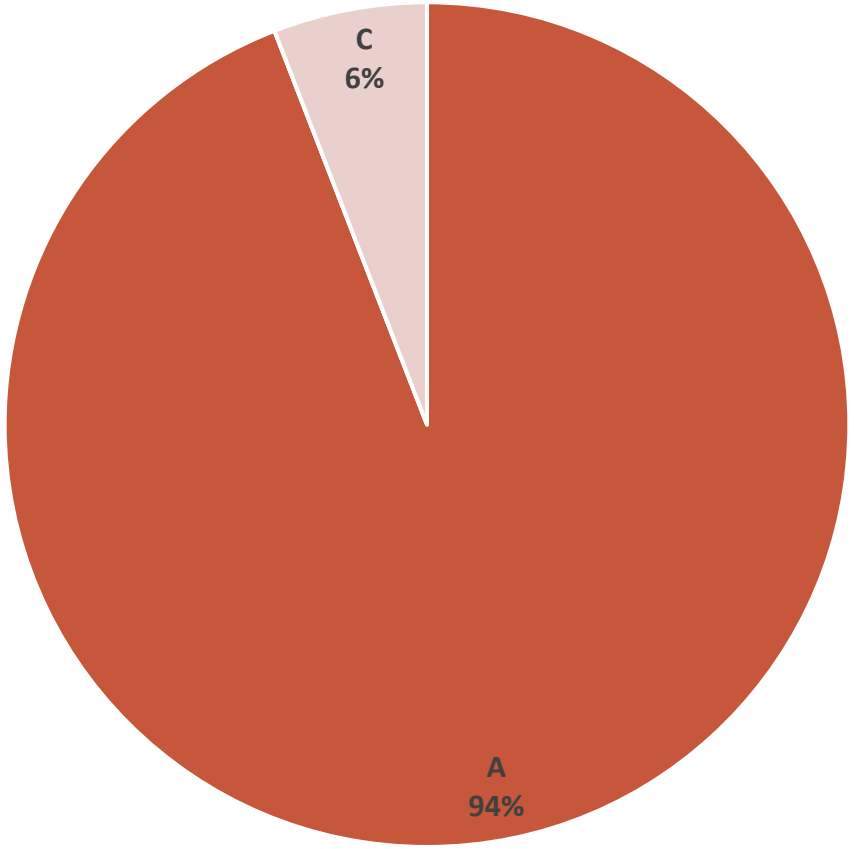
PATIENT CASE 1: POLLING QUESTION 2

WHICH 3L OPTIONS WOULD YOU CONSIDER NEXT?

A. SVd

B. PanoVd

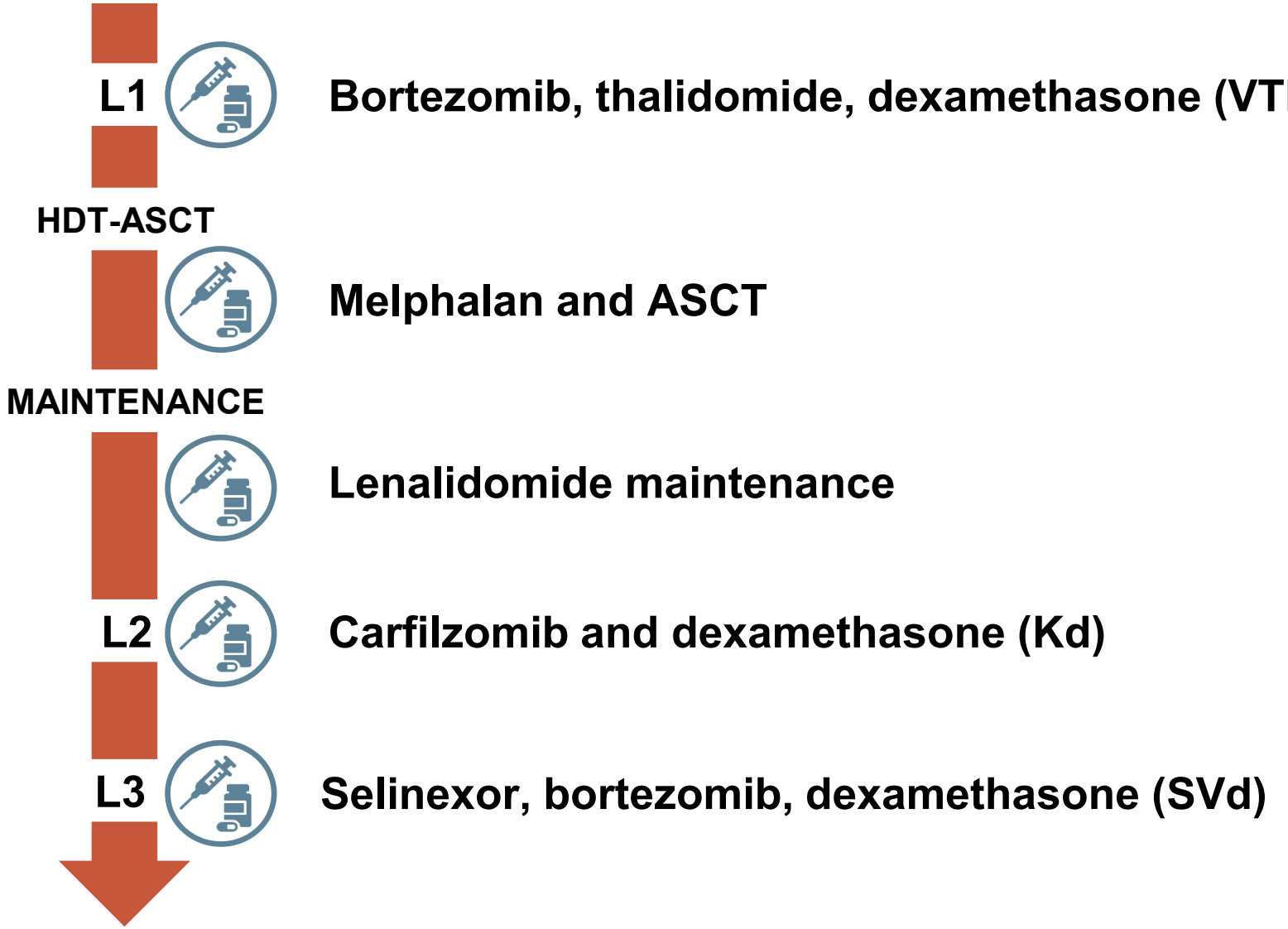
C. CTD or other Cyclophosphamide-based



Educational case study

CTD, cyclophosphamide, thalidomide and dexamethasone; PanoVd, Panobinostat; bortezomib and dexamethasone; SVd, Selinexor, bortezomib and dexamethasone

PATIENT CASE 1: TREATMENT



Patient rationale:

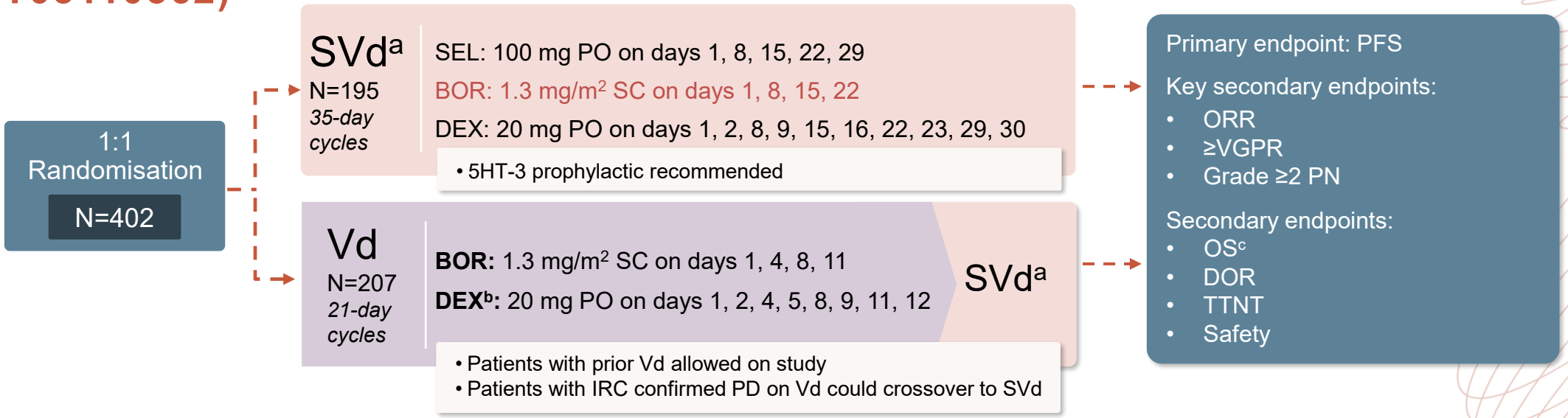
- Patient keen for SVd
- PN now less concerning but started with bortezomib dose reduction (1mg/m^2)

Educational case study

ASCT, autologous stem cell transplantation; HDT, high dose therapy; PN, peripheral neuropathy

BOSTON: A PHASE 3, GLOBAL, RANDOMISED, OPEN-LABEL, CONTROLLED STUDY IN PATIENTS WITH MULTIPLE MYELOMA WHO HAD RECEIVED 1-3 PRIOR THERAPIES[1]

STUDY DESIGN – PHASE 3, MULTICENTRE, RANDOMISED, OPEN-LABEL STUDY (NCT03110562)[1]



- Median age was 67 years (IQR 59-73) and 81 (20%) patients were aged ≥75 years or older[1]
- Median number of previous regimens was two (1-2), 75 (19%) patients had received three previous lines of therapy, and 139 (35%) patients had undergone SCT[1]

[a] SVd (Selinexor, bortezomib, dexamethasone) approved by EMA; not reimbursed in France;[2,3] [b] DEX dosing presented is for cycles 1-8; for cycles ≥9 DEX was given as 20 mg on days 1, 2, 8, 9, 15, 16, 22, 23, 29, and 30 of each 35-day cycle;[1] [c] OS is not yet reached[1]

BOR, bortezomib; DEX, dexamethasone; DOR, duration of response; IQR, interquartile range; IRC, independent review committee; OS, overall survival; PD, progressive disease; PFS, progression free survival; PN, peripheral neuropathy; PO, taken orally; SC, subcutaneous; SCT, stem cell transplant; SEL, selinexor; SVd, selinexor/bortezomib/dexamethasone; TTNT, time to next treatment; Vd, bortezomib/dexamethasone; VGPR, very good partial response

1. Grosicki S, et al. Lancet. 2020;396(10262):1563-73; 2. European Medicines Agency. Nexpovio. 2023. Available at: https://www.ema.europa.eu/en/medicines/human/EPAR/nexpovio.European (Accessed: January 2026); 3. Haute Autorité de Santé. Nexpovio 20mg. 2023. Available at: https://www.has-sante.fr/upload/docs/application/pdf/2023-08/nexpovio_19042023_summary_ct20195_en.pdf (Accessed: January 2026).

PATIENT DEMOGRAPHICS IN THE BOSTON TRIAL[1]

	SVd (n=195)	Vd (n=207)
Age, years		
Median (IQR)	66 (59-72)	67 (61-74)
18-50	15 (8%)	11 (5%)
51-64	71 (36%)	64 (31%)
65-74	75 (38%)	85 (41%)
>75	34 (17%)	47 (23%)
Sex		
Male	115 (59%)	115 (56%)
Female	80 (41%)	92 (44%)
ECOG performance status[a]		
0	69 (35%)	77 (37%)
1	106 (54%)	114 (55%)
2	20 (10%)	16 (8%)

	SVd (n=195)	Vd (n=207)
Cytogenetic abnormalities[b]		
del(17p)	21 (11%)	16 (8%)
t(14;16)	7 (4%)	11 (5%)
t(4:14)	22 (11%)	28 (14%)
1q21 amplification	80 (41%)	71 (34%)
Any of the above	97 (50%)	95 (46%)
Not assessed	15 (8%)	24 (12%)
R-ISS disease stage at screening		
1-2	173 (89%)	177 (86%)
3	12 (6%)	16 (8%)
Unknown	10 (5%)	14 (7%)
Time since initial diagnosis, years		
	3.8 (2.5-5.4)	3.6 (2.1-5.6)

	SVd (n=195)	Vd (n=207)
Number of previous lines of therapy		
One	99 (51%)	99 (48%)
Two	65 (33%)	64 (31%)
Three	31 (16%)	44 (21%)
Previous stem-cell transplantation		
	76 (39%)	63 (30%)
Previous therapy		
Bortezomib	134 (69%)	145 (70%)
Carfilzomib	20 (10%)	21 (10%)
Ixazomib	6 (3%)	3 (1%)
Daratumumab	11 (6%)	6 (3%)
Lenalidomide	77 (39%)	77 (37%)
Pomalidomide	11 (6%)	7 (3%)

[a] Scores range from 0 to 5, with higher scores reflecting greater disability;
[b] Fluorescence in-situ hybridisation was carried out at central laboratories and used to assess cytogenetic risk status

ECOG, Eastern Cooperative Oncology Group; IQR, interquartile range; R-ISS, revised international staging system; SVd, selinexor-bortezomib-dexamethasone; Vd, bortezomib-dexamethasone

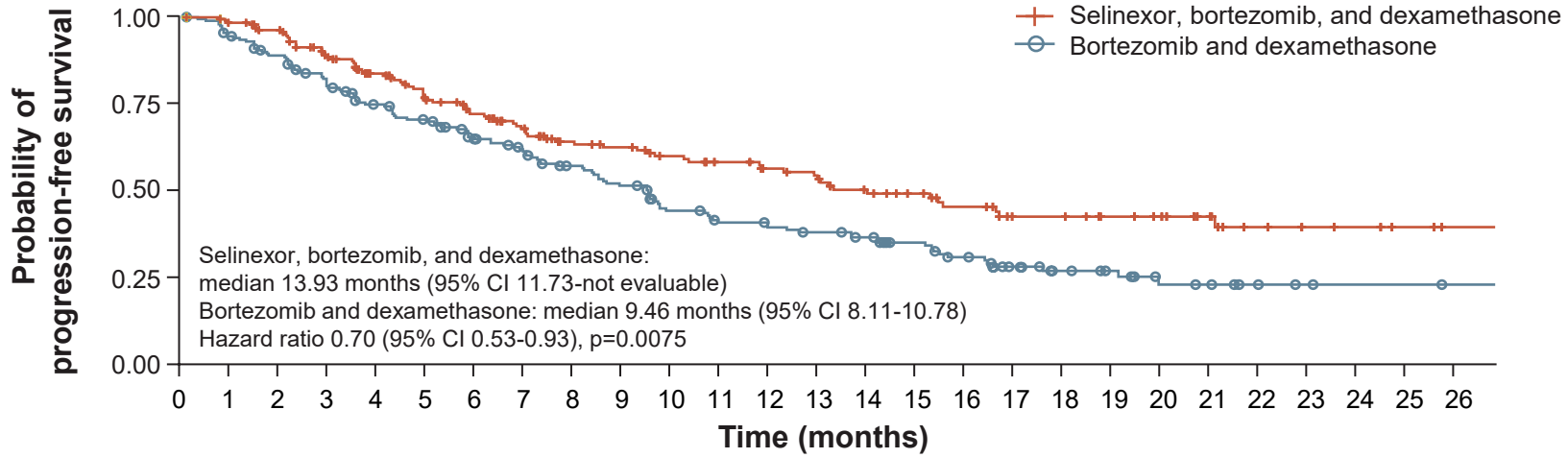
1. Grosicki S, et al. Lancet. 2020; 14; 396(10262): 1563-73

BOSTON

STATISTICALLY SIGNIFICANT INCREASE IN mPFS WITH SVd[a] vs. Vd[1]

	SVd arm (N=195)	Vd arm (N=207)
Median PFS (95% CI), months[b]	13.93 (11.73-NE)	9.46 (8.11-10.78)
HR 0.70 (95% CI: 0.53-0.93); one-sided p=0.0075		

Kaplan-Meier estimates of progression-free survival among patients in the ITT population[1]



Number at risk (number censored)																											
Selinexor, bortezomib, and dexamethasone	195	187	175	152	135	117	106	89	79	76	69	64	57	51	45	41	35	27	26	22	19	14	9	7	6	4	2
	(0)	(5)	(12)	(21)	(31)	(37)	(42)	(50)	(57)	(59)	(63)	(66)	(71)	(73)	(76)	(80)	(83)	(89)	(90)	(94)	(97)	(102)	(106)	(108)	(109)	(111)	(113)
Bortezomib and dexamethasone	207	187	175	152	138	127	111	100	90	81	66	59	56	53	49	42	35	26	20	16	10	8	5	4	3	3	2
	(0)	(8)	(10)	(15)	(20)	(22)	(29)	(32)	(37)	(37)	(41)	(43)	(44)	(45)	(47)	(52)	(55)	(60)	(65)	(69)	(73)	(75)	(78)	(79)	(80)	(80)	(81)

These data represent:

1. An increase of 4.47 months in median PFS[1]
2. A 30% reduction in the risk of disease progression[1]

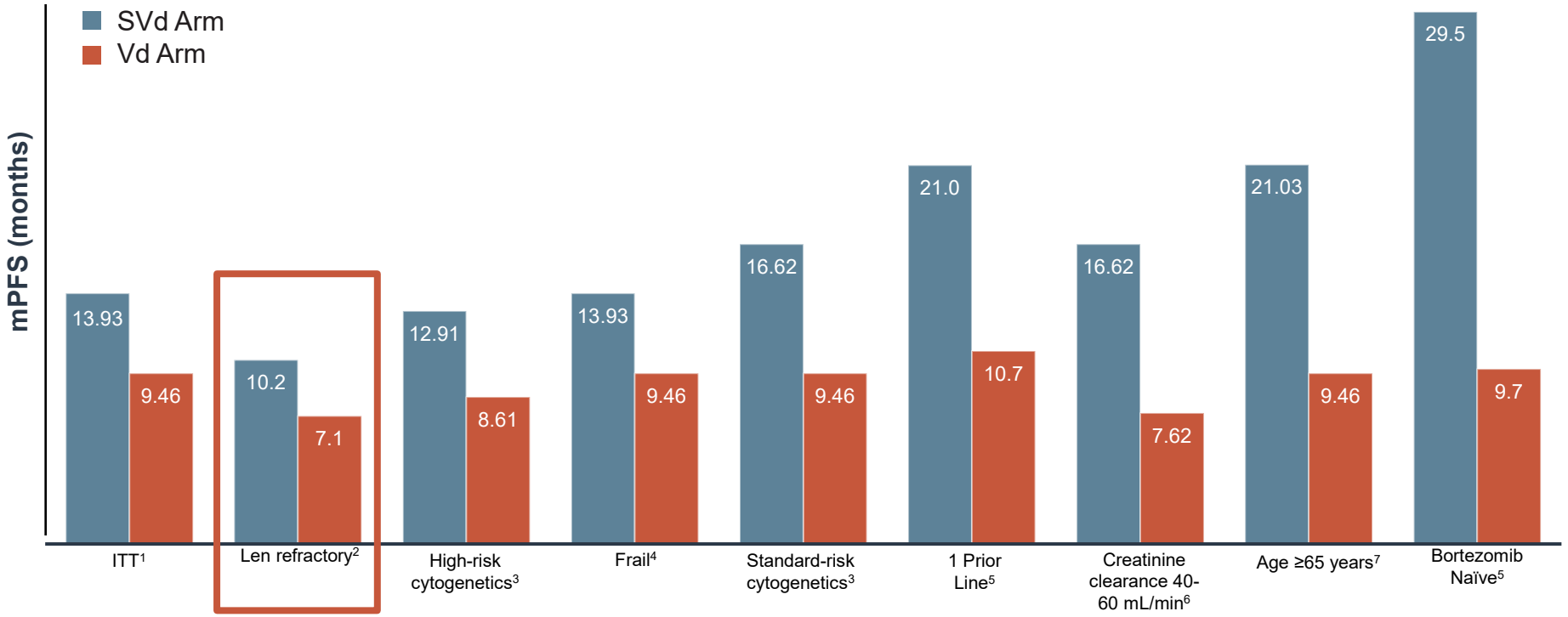
[a] SVd (Selinexor, bortezomib, dexamethasone) approved by EMA;[2] [b] The study was ongoing at the time of publication; the analysis was performed after a median follow-up period of 13.2 months for the SVd arm and 16.5 months for the Vd arm (data cutoff: 18 February 2020)[1]

CI, confidence interval; HR, hazard ratio; ITT, intention-to-treat; NE, not evaluable; PFS, progression free survival; SVd, Selinexor/bortezomib/dexamethasone; Vd, bortezomib/dexamethasone

1. Grosicki S, et al. Lancet. 2020;396(10262):1563-73; 2. European Medicines Agency. Nexpovio. 2023. Available at: https://www.ema.europa.eu/en/medicines/human/EPAR/nexpovio.European. (Accessed: January 2026).

CONSISTENT PFS BENEFIT ACROSS SUBGROUPS[1-6]

Subgroups reflect a range of MM patient characteristics



Limitations of subgroup analyses:

These subgroup analyses were exploratory in nature, not included in the study objectives, and do not control for type 1 error.

These subgroup analyses were not powered or adjusted for multiplicity to assess PFS across these prespecified subgroups.

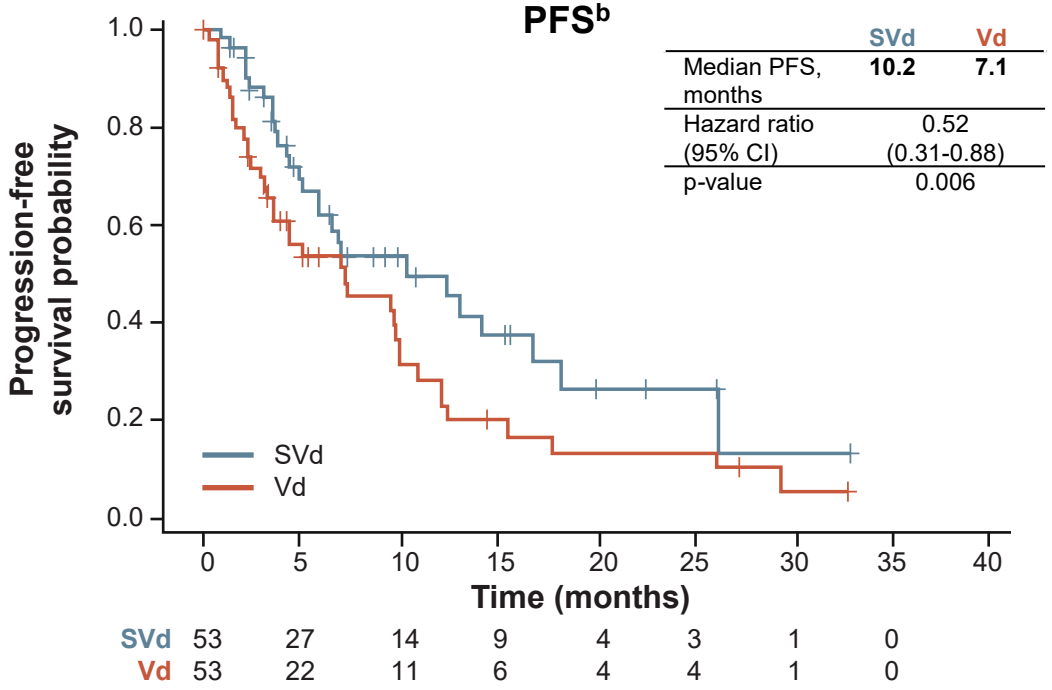
ITT, intent-to-treat; Len/len, lenalidomide; mPFS, median progression-free survival; PFS, progression-free survival; PI, proteosome inhibitor; SVd, selinexor-bortezomib-dexamethasone; Vd, bortezomib, dexamethasone.

1. Grosicki S, et al. Lancet. 2020;14;396(10262):1563-73; 2. Mateos MV, et al. Presented at EHA Hybrid Congress 2023 June 8-11, 2023. Poster # P886; 3. Richard S, et al. Am J Hematol. 2021; 96(9): 1120-30. 4. Auner HW, et al. Am J Hematol. 2021;96(6):708-18; 5. Mateos MV, et al. Presented at EHA Hybrid Congress 2023 June 8-11, 2023. Poster # P917; 6. Delimpasi S, et al. Am J Hematol. 2022; 97(3): E83-E86; 7. Auner HW, et al. Am J Hematol. 2021;96:708–718 (supplementary material).

BOSTON SUBGROUP ANALYSIS OF PATIENTS WITH LENALIDOMIDE-REFRACTORY MM[1]

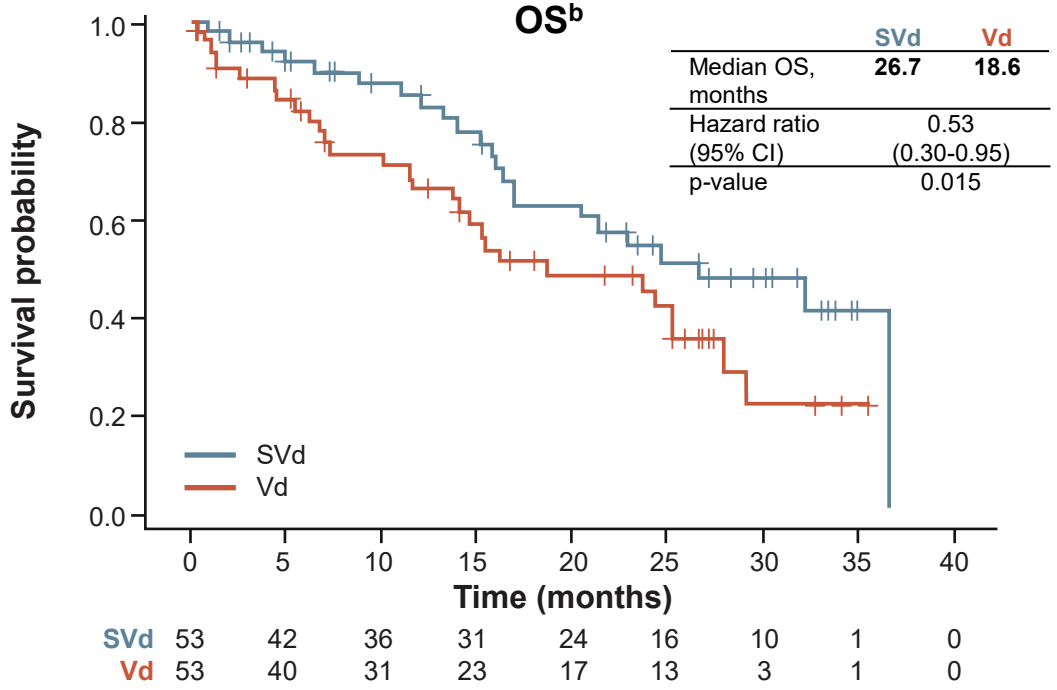
STATISTICALLY SIGNIFICANT IMPROVEMENT IN PFS AND OS WITH SVd[a] vs. Vd[1]

PFS[b]



	SVd	Vd
Median PFS, months	**10.2**	**7.1**
Hazard ratio (95% CI)	0.52 (0.31-0.88)	
p-value	0.006	

OS[b]



	SVd	Vd
Median OS, months	**26.7**	**18.6**
Hazard ratio (95% CI)	0.53 (0.30-0.95)	
p-value	0.015	

- Higher ORR with SVd vs. Vd (67.9% vs. 47.2%; OR 2.59 [95% CI: 1.17-5.77]; p=0.009)[1]
- Higher ≥VGPR with SVd vs. Vd (35.8% vs. 24.5%; OR 1.74 [95% CI: 0.72-4.21]; p=0.109)[1]

[a] SVd (Selinexor, bortezomib, dexamethasone) approved by EMA;[2] [b] These subgroup analyses were exploratory in nature, not included in the study objectives and do not control for type 1 error. The analyses were not powered or adjusted for multiplicity to assess efficacy outcomes across these subgroups[1]

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

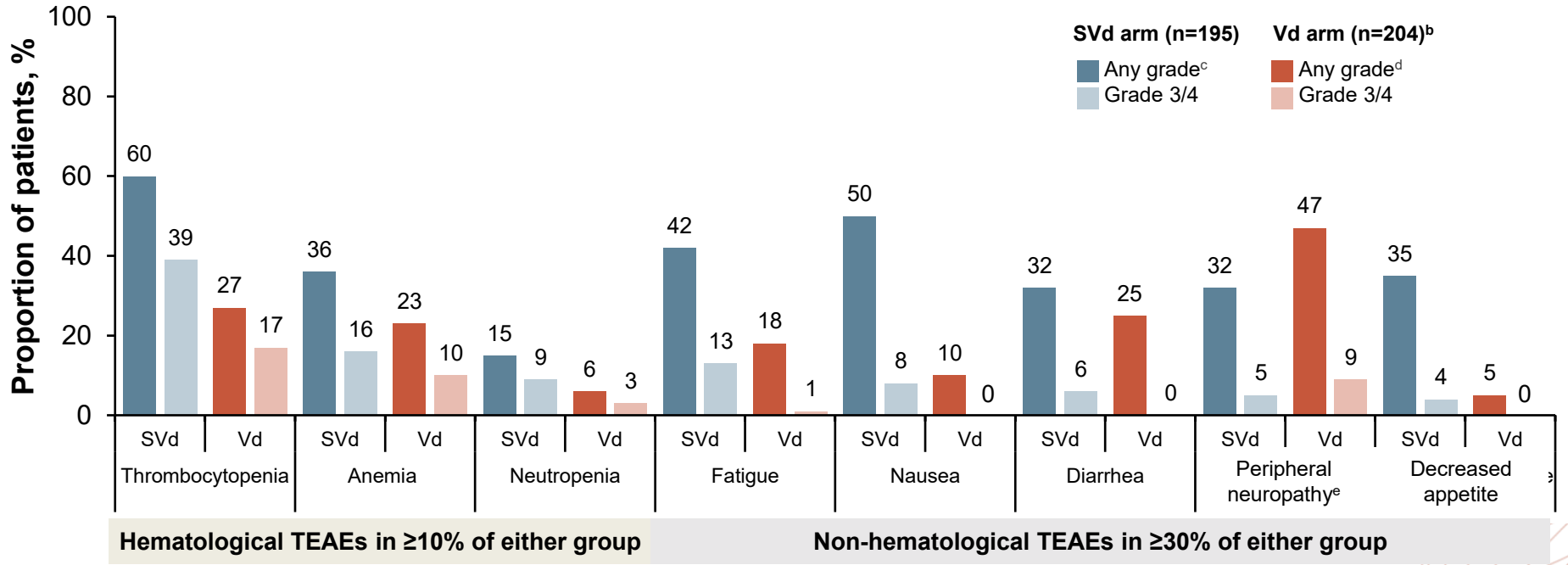
1. Mateos MV, et al. Eur J Haematol 2024;113(2):242-52; 2. European Medicines Agency. Nexpovio. 2023. Available at: https://www.ema.europa.eu/en/medicines/human/EPAR/nexpovio.European. (Accessed: January 2026).

BOSTON

SVd SAFETY[a]

The most common any grade AEs were GI AEs, thrombocytopenia and anemia, the most common Grade 3/4 AEs were thrombocytopenia, fatigue, anemia and pneumonia[1]

Appropriate AE management, including **dose modifications** and **supportive measures**, is important to maintain treatment adherence and optimise outcomes[1]



[a] SVd (Selinexor, bortezomib, dexamethasone) approved by EMA;[2] [b] Three patients from this group who did not receive any doses of study drug were excluded from the safety population; [c] Includes four Grade 5 events: three (2%) cases of pneumonia and one (1%) case of bronchitis; [d] Includes four Grade 5 events: three (1%) cases of pneumonia and one (<1%) case of anemia; [e] Includes high-level MedDRA term "peripheral neuropathies NEC"[1]

AE, adverse event; GI, gastrointestinal; MedDRA, medical dictionary for regulatory activities; SVd, selinexor/bortezomib/dexamethasone; TEAE, treatment-emergent adverse event; Vd, bortezomib/dexamethasone

1. Grosicki S, et al. Lancet. 2020;396(10262):1563-73; 2. European Medicines Agency. Nexpovio. 2023. Available at: https://www.ema.europa.eu/en/medicines/human/EPAR/nexpovio.European (Accessed: January 2026).

PATIENT CASE 1: TREATMENT

3RD LINE: SELINEXOR, BORTEZOMIB, DEXAMETHASONE (SVd)

- **Cycle 1**
  - Bortezomib dose reduction (1mg/m^2)
  - Selinexor starting dose of 100mg
  - Anti-emetics: metoclopramide, ondansetron (for 3-4 days after each dose) and olanzapine 2.5 mg nocte
- **Cycle 4:**
  - VGPR attained (PP unmeasurably low)
  - Dexamethasone to 10mg for proximal myopathy
  - Selinexor to 80mg for G3 thrombocytopenia
- **Cycle 5:**
  - Bortezomib to 0.7mg/m^2 for PN
- **Cycle 7:**
  - CR obtained

Educational case study

CR, complete response; DXM, dexamethasone; G, grade; PN, peripheral neuropathy; PP, paraprotein; SVd, Selinexor, bortezomib and dexamethasone; VGPR, very good partial response

PATIENT CASE 1: TREATMENT

3RD LINE: SELINEXOR, BORTEZOMIB, DEXAMETHASONE (SVd)

- **Cycle 10:**
  - Stopped DXM due to toxicity

- **Mid/late 2025**
  - Maintained CR to 14 cycles of SVd (15 months)
  - Elected to come off therapy for lifestyle reasons
  - Remains in CR

Educational case study

CR, complete response; DXM, dexamethasone; SVd, Selinexor, bortezomib and dexamethasone

PATIENT CASE 1: DISCUSSION POINTS

- Efficacy in the Len-refractory patient
- Importance of patient preferences
- Manageable toxicity profile with dose reductions, even with pre-existing toxicities
- Important to monitor steroid toxicity as with all Dex-containing regimens
- Working within commissioning limitations (e.g. 3 lines containing PIs)

Educational case study

Dex, dexamethasone; Len, Lenalidomide; PIs, proteasome inhibitors

PATIENT CASE 2

PATIENT PROFILE

- 79 year-old male
- Receiving oral medications for:
- Hypertension
- Type II diabetes mellitus

Diagnosis: Mid 2021

- IgG kappa myeloma diagnosed
  Paraprotein 16 g/l, Kappa 68, K:L 6.8
- BM trephine: 20% plasma cells,
  Congo red stain negative
- ISS 1, FISH not available
- CTSS: no lytic lesions
- No SLiM-CRAB features
- **Classified: Smouldering myeloma**
- **Management: Monitoring**

Educational case study

CTSS, clinical trials support service; IgG, immunoglobulin G; ISS, Multiple Myeloma International Staging System; K:L, kappa-lambda ratio; SLiM-CRAB, diagnostic criteria from the International Myeloma Working Group

PATIENT CASE 2: TREATMENT

EARLY 2022

- **Progression**
  - IgG paraprotein 24 g/l (from 16 g/l), Kappa 200, K:L 8.6
  - Anemia: Hb 90 g/l (from 110g/l)
  - BM trephine: 50% plasma cells, Congo red stain negative
  - CTSS: no lytic lesions
- Active myeloma
- **MDT:** consider VCD or lenalidomide/dexamethasone
- **Management:** lenalidomide/dexamethasone

Patient rationale:
- Own reading about VCd and Rd
- Preference Rd as oral

Educational case study

BM, bone marrow; CTSS, clinical trials support service; Hb, hemoglobin; IgG, immunoglobulin G; K:L, kappa-lambda ratio; MDT, multidisciplinary team; Rd, lenalidomide and dexamethasone; VCd, Bortezomib with dexamethasone and cyclophosphamide

PATIENT CASE 2: TREATMENT

L1

Lenalidomide and dexamethasone

- Best response: PR after 6 cycles
- Improvement in anemia
- Complications:
  - DVT despite VTE prophylaxis
  - Mild cytopenia requiring dose adjustment

Early 2023:

- **Progression (on 1L len/dex):**
  - Paraprotein 18 g/l (from nadir 9 g/l)
  - Hb 76 g/l
  - BM Trephine: 80% plasma cells
  - CTSS: small bone lesions in sternum, ribs, spine and pelvis
- MDT: Consider DVd
- Management: Commenced DVd

Patient rationale:

- Local outreach able to deliver (less travel)
- Keen to try monoclonal Ab based treatment

Educational case study

Ab, antibody; BM, bone marrow; CTSS, clinical trials support service; DVd, daratumumab, velcade, dexamethasone; DVT, deep vein thrombosis; Hb, hemoglobin; MDT, multidisciplinary team; PR, partial response; VTE, venous thromboembolism

PATIENT CASE 2: TREATMENT

L1 **Lenalidomide and dexamethasone**

Refractory to:
- Len/dex

L2 **Daratumumab, bortezomib, dexamethasone (DVd)**
- Best response: VGPR after 6 cycles
- Improvement in anemia
- Complications: none
- Completed 26 cycles in total (8 combination + 18 daratumumab maintenance)

Late 2024:
- **Second progression (on 2L DVd):**
  - Paraprotein 10 g/l (from nadir <2 g/l)
  - Asymptomatic progression, no cytopenia
  - CTSS: no new lesions

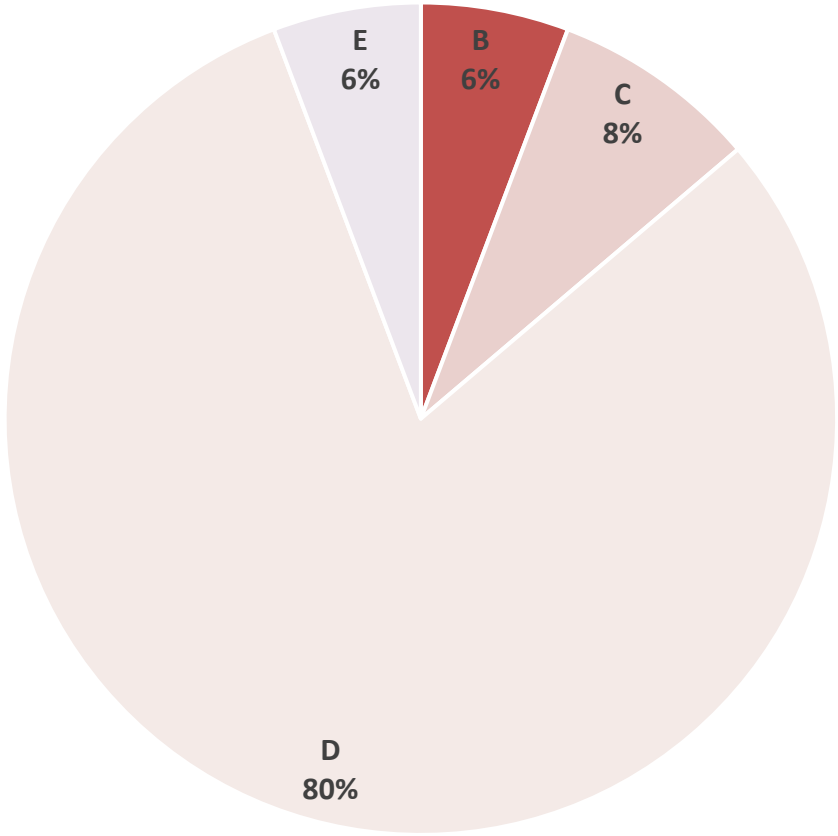
Educational case study

CTSS, clinical trials support service; DVd, daratumumab, velcade, dexamethasone; VGPR, very good partial response

PATIENT CASE 2: POLLING QUESTION 1

WHICH 3L OPTIONS WOULD YOU CONSIDER NEXT?

A. Clinical trial
B. CTDa
C. PanoVD
D. SVd
E. Steroid pulse then move to 4L
F. Other



Educational case study

CTDa, cyclophosphamide, thalidomide and dexamethasone; PanoVD, Panobinostat, bortezomib and dexamethasone; SVd, Selinexor, bortezomib and dexamethasone

PATIENT CASE 2: TREATMENT

LATE 2024

- **Second progression** (on 2L DVd):
  - Age 82 years, Frailty – PS 1-2, walking with stick
  - Co-morbidities: Hypertension and poorly controlled diabetes
  - Only minimal peripheral neuropathy

- **MDT:** Consider selinexor, bortezomib, dexamethasone (SVd) or clinical trial
- **Management:** SVd commenced

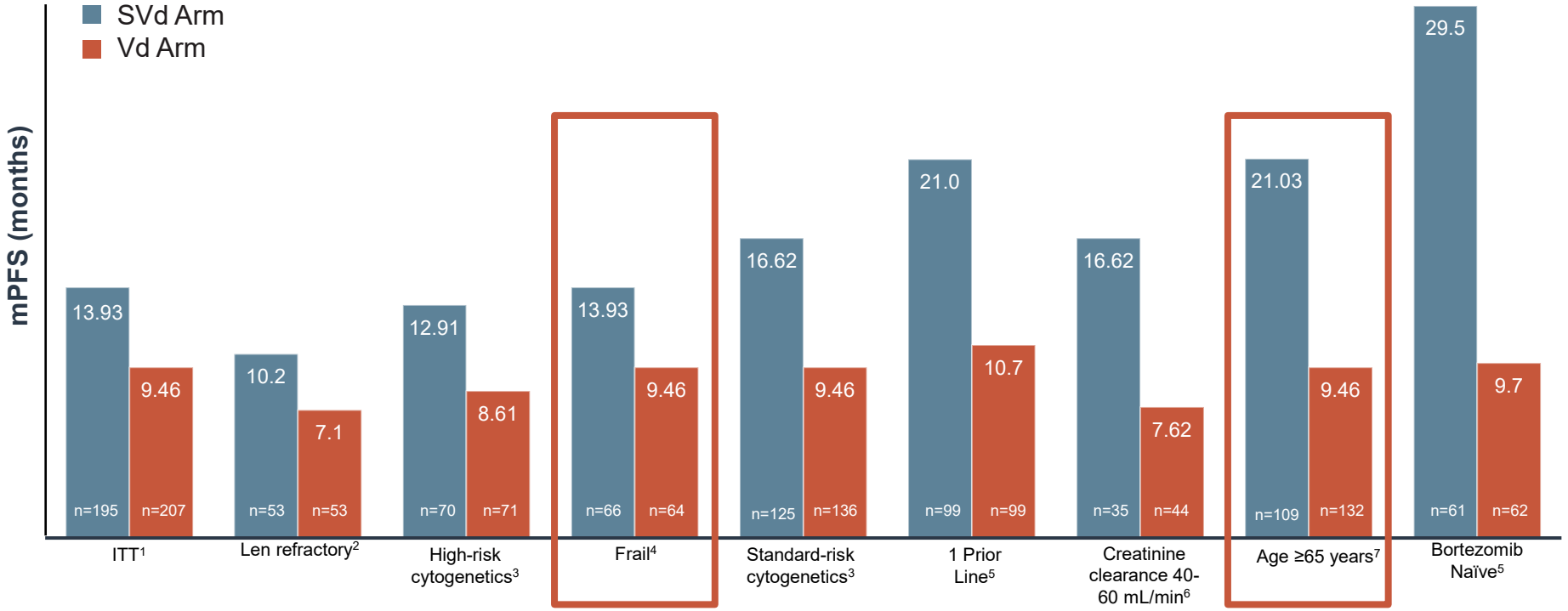
Patient rationale:
- Interested in recently NICE approved therapy / mature trial data
- Tolerated bortezomib well
- Local outreach able to deliver (less travel compared to trial medication at tertiary centre)

Educational case study

BM, bone marrow; CTSS, clinical trials support service; Hb, hemoglobin; IgG, immunoglobulin G; K:L, kappa-lambda ratio; MDT, multidisciplinary team; Rd, lenalidomide and dexamethasone; VCD, Bortezomib with dexamethasone and cyclophosphamide

BOSTON: CONSISTENT PFS BENEFIT ACROSS SUBGROUPS[1-6]

Subgroups reflect a range of MM patient characteristics



Limitations of subgroup analyses:

These subgroup analyses were exploratory in nature, not included in the study objectives, and do not control for type 1 error.

These subgroup analyses were not powered or adjusted for multiplicity to assess PFS across these prespecified subgroups.

ITT, intent-to-treat; Len/len, lenalidomide; mPFS, median progression-free survival; PFS, progression-free survival; PI, proteosome inhibitor; SVd, selinexor-bortezomib-dexamethasone; Vd, bortezomib, dexamethasone.

1. Grosicki S, et al. Lancet. 2020;14;396(10262):1563-73; 2. Mateos MV, et al. Presented at EHA Hybrid Congress 2023 June 8-11, 2023. Poster # P886; 3. Richard S, et al. Am J Hematol. 2021; 96(9): 1120-30. 4. Auner HW, et al. Am J Hematol. 2021;96(6):708-18; 5. Mateos MV, et al. Presented at EHA Hybrid Congress 2023 June 8-11, 2023. Poster # P917; 6. Delimpasi S, et al. Am J Hematol. 2022; 97(3): E83-E86; 7. Auner HW, et al. Am J Hematol. 2021;96:708–718 (supplementary material).

CASE STUDY 2: TREATMENT

L1 

Lenalidomide and dexamethasone (Len/dex)

L2 

Daratumumab, bortezomib, dexamethasone (DVd)

- Best response: VGPR after 6 cycles
- Improvement in anemia
- Complications: none
- Completed 26 cycles in total (8 combination + 18 daratumumab maintenance)

L3 

Selinexor, bortezomib and dexamethasone (SVd)

- Community diabetic team input
- Best response: VGPR after 1 cycle (PP <2 g/l from 10 g/l)

Refractory to:

- Len/dex
- DVd

Educational case study

DVd, daratumumab, bortezomib, dexamethasone; PP, paraprotein; SVd, Selinexor, bortezomib and dexamethasone; VGPR, very good partial response

PATIENT CASE 2: TREATMENT

3RD LINE: SELINEXOR, BORTEZOMIB, DEXAMETHASONE (SVd)

Best response: VGPR after 1 cycle (PP <2 g/l from 10 g/l)

Cycle 1 (35 days)		
Selinexor	100 mg OW	D1, 8, 15, 22 and 29
Bortezomib	1.3 mg/m^2 OW	D1, 8, 15 and 22
Dexamethasone	10 mg OW	D1, 8, 15, 22 and 29

Complications	Treatment
Grade I diarrhea and fatigue, irritability with steroid	PRN loperamide
Minimal nausea	1L antiemetic: Regular domperidone, PRN ondansetron 2L antiemetic: olanzapine (not required)
No cytopenia, no hyponatremia	

Educational case study

D, day; OW, once a week; PP, paraprotein; PRN, as needed; VGPR, very good partial response

PATIENT CASE 2: TREATMENT

3RD LINE: SELINEXOR, BORTEZOMIB, DEXAMETHASONE (SVd)

Best response: VGPR after 1 cycle (PP <2 g/l from 10 g/l)

Cycle 2-3 (35 days)		
Selinexor	80 mg OW	D1, 8, 15, 22 and 29
Bortezomib	1.3 mg/m^2 OW	D1, 8, 15 and 22
Dexamethasone	4 mg OW	D1, 8, 15, 22 and 29

Complications
Grade I diarrhea and fatigue
No cytopenia, no hyponatremia
No neuropathy, minimal nausea

Current response:

Remains in VGPR (PP <2 g/l) after 10 cycles

Educational case study

D, day; OW, once a week; PP, paraprotein; PRN, as needed; VGPR, very good partial response

SELINEXOR[1]

TOXICITIES AND MANAGEMENT

Most frequent toxicities[2]

- Thrombocytopenia
- Nausea
- Fatigue
- Anemia

Prophylactic use of antiemetics[4]

- **A 5-HT_3 receptor antagonist and other antinausea agents should be provided prior to and during treatment with selinexor[4]**

Dose reductions

Selinexor-related AEs may be managed by dose reductions: BOSTON study[2]

- **Overall dose modifications were more common in the SVd[a] arm vs the Vd arm, 89% vs 76%, respectively[2]**
- **In the SVd[a] arm, 65% of patients had a selinexor dose reduction during treatment[3]**
- **Median dose of selinexor was 71.4 mg/wk[3]**

The **following selinexor dose reduction** recommendations are suggested for patients who experience an adverse reaction[b] while taking **SVd**[4,a]

Dose reduction	SVd dose
Recommended starting dose	100 mg once weekly
First dose reduction	80 mg once weekly
Second dose reduction	60 mg once weekly
Third dose reduction	40 mg once weekly
Discontinue if symptoms do not resolve	

[a] SVd (Selinexor, bortezomib, dexamethasone) approved by EMA;[5] [b] Side effects related to selinexor are largely dosage and schedule dependent and may be mitigated with prophylactic antiemetics and standard monitoring with dose adjustments as needed[4]

The supportive care guidance provided herein are prepared by FORUS Therapeutics Inc. and should not be relied upon as being complete or mandating any particular course of medical care. All treatment decisions are solely at the discretion of the treating physician or healthcare professional. Prophylactic antithrombotic, antimicrobial, or antiemetic agents are not required for treatment with selinexor but may be indicated in specific patients and/or when other anticancer drugs are administered

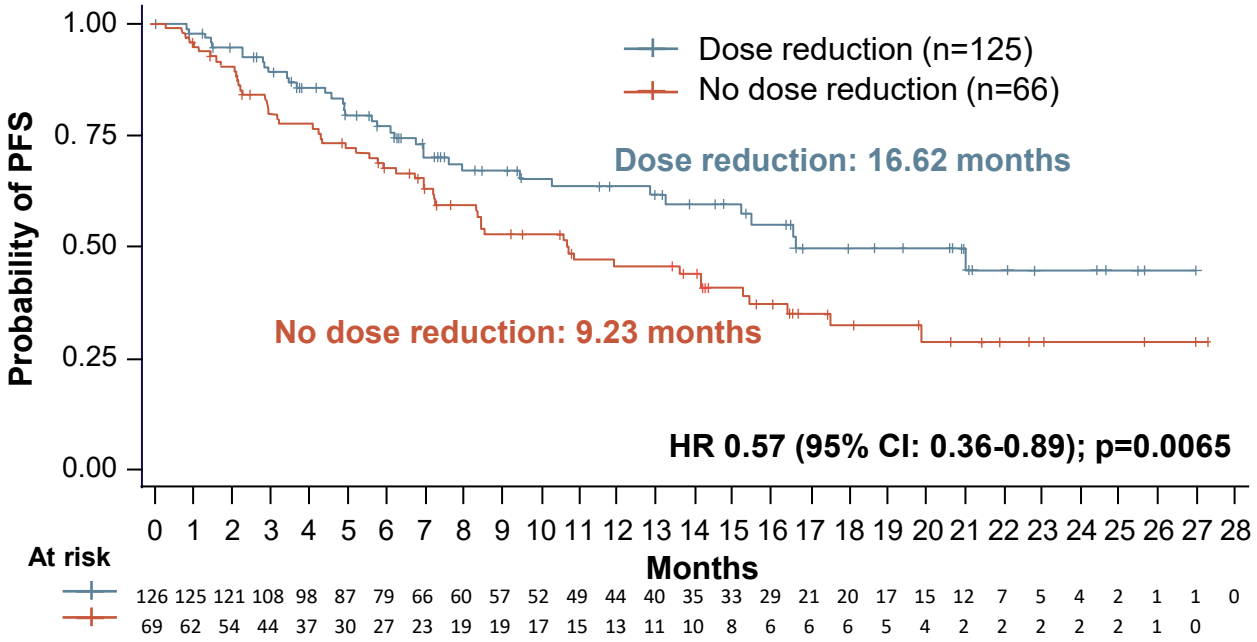
AE, adverse event; PO, by mouth; qam, every morning; qhs, every night; SVd, selinexor/bortezomib/dexamethasone; Vd, bortezomib/dexamethasone

1. Selinexor. Product monograph. FORUS Therapeutics Inc. May 2022; 2. Grosicki S, et al. Lancet. 2020;396:1563-73; 3. Jagannath S, et al. Clin Lymphoma Myeloma Leuk. 2023;23(12); 4. Nexpovio (selinexor) Summary of Product Characteristics. Available at: https://www.ema.europa.eu/en/documents/product-information/nexpovioepar-product-information_en.pdf; 5. European Medicines Agency. Nexpovio. 2023. Available at: https://www.ema.europa.eu/en/medicines/human/EPAR/nexpovio.European (Accessed: January 2026).

BOSTON

SELINEXOR DOSE REDUCTION WAS ASSOCIATED WITH IMPROVED EFFICACY[1]

PFS by dose reduction in patients in the SVd[a] arm[2]



ORR by dose reduction of selinexor in the SVd[a] arm[2]

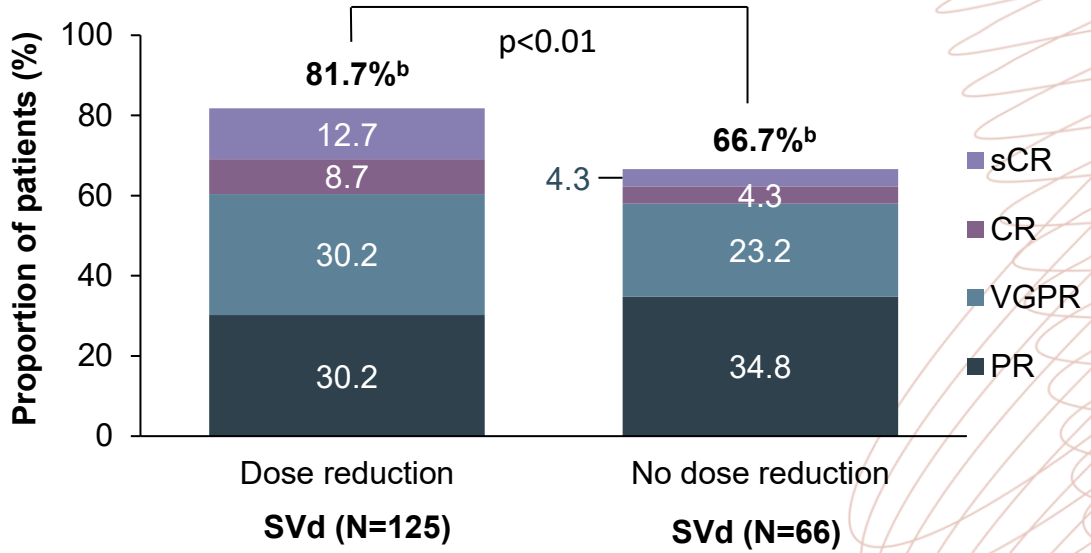


Figure adapted from Jagannath S, et al. 2021.[1]

- These subgroup analyses were exploratory in nature, not included in the study objectives, and do not control for type 1 error
- The analyses were not powered or adjusted for multiplicity to assess efficacy outcomes across these subgroups

[a] SVd (Selinexor, bortezomib, dexamethasone) approved by EMA;[3] [b] ORR is the proportion of patients who have a PR or better, before IRC-confirmed PD or initiating a new multiple myeloma treatment or crossover.[1]

CR, complete response; HR, hazard ratio; IRC, independent review committee; mPFS, median progression-free survival; ORR, overall response rate; PR, progressive response; PD, progressive disease; PFS, progression-free survival; sCR, stringent complete response; SVd, selinexor/bortezomib/dexamethasone; VGPR, very good partial response

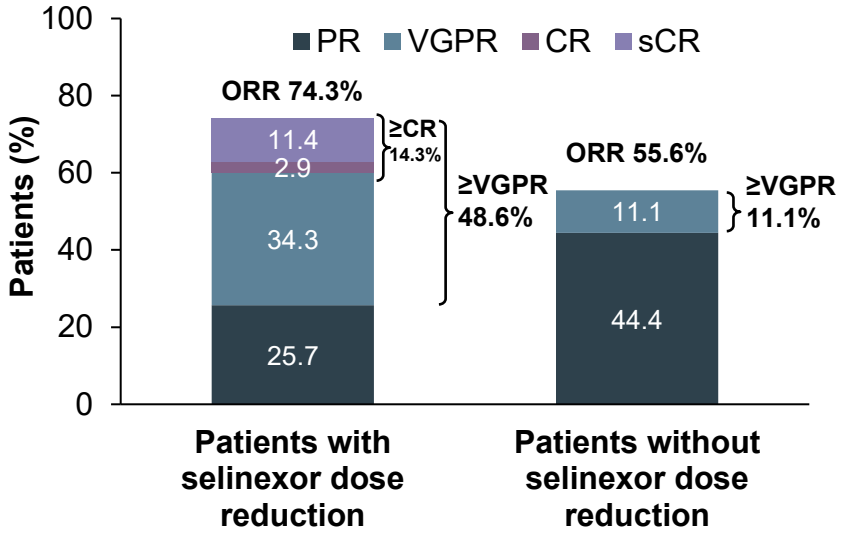
1. Jagannath S, et al. Clin Lymphoma Myeloma Leuk. 2023;23(12):917-23.e3; 2. Jagannath S, et al. Abstract #3793; poster presented at ASH 2021; 3. European Medicines Agency. Nexpovio. 2023. Available at: https://www.ema.europa.eu/en/medicines/human/EPAR/nexpovio.European (Accessed: January 2026).

BOSTON

IMPACT OF SELINEXOR DOSE REDUCTIONS IN LEN-REFRACTORY MM[1]

BOSTON SVd[a] arm: 53 LEN-refractory patients (35 had selinexor dose reductions and 18 did not)[1]

Response to SVd[a] in LEN-refractory patients by dose reduction group[1]



Parameter	Patients with Sel dose reductions (N=35)[1]	Patients without Sel dose reductions (N=18)[1]
Median time to best response (PR or better) (range), mo[1]	2.7 (0.7-11.7)	1.4 (0.7-2.1)
Median DoR (95% CI), mo[1]	15.3 (12.2-NE)	4.2 (4.2-NE)
Median TTNT (95% CI), mo[1]	14.8 (13.4-26.7)	4.8 (4.2-NE)
Median PFS (95% CI), mo[1]	13.9 (6.9-NE)	5.1 (3.5-NE)
Median OS, mo[2]	26.7	24.6
HR (95% CI)[2]	0.91 (0.37-2.28)	

- **Global health status QoL** scores showed greater **improvement** in patients with dose reductions vs. patients without[1]
- In patients with dose reductions, a **lower proportion** experienced **any-grade TRAEs** after the first dose reduction (except thrombocytopenia)[1]

In **LEN-refractory patients**, **selinexor dose reductions** were associated with **increased PFS, decrease in any-grade TRAE rate and** were consistent with the analysis of selinexor dose reductions for the ITT population[1]

[a] SVd (Selinexor, bortezomib, dexamethasone) approved by EMA[3]

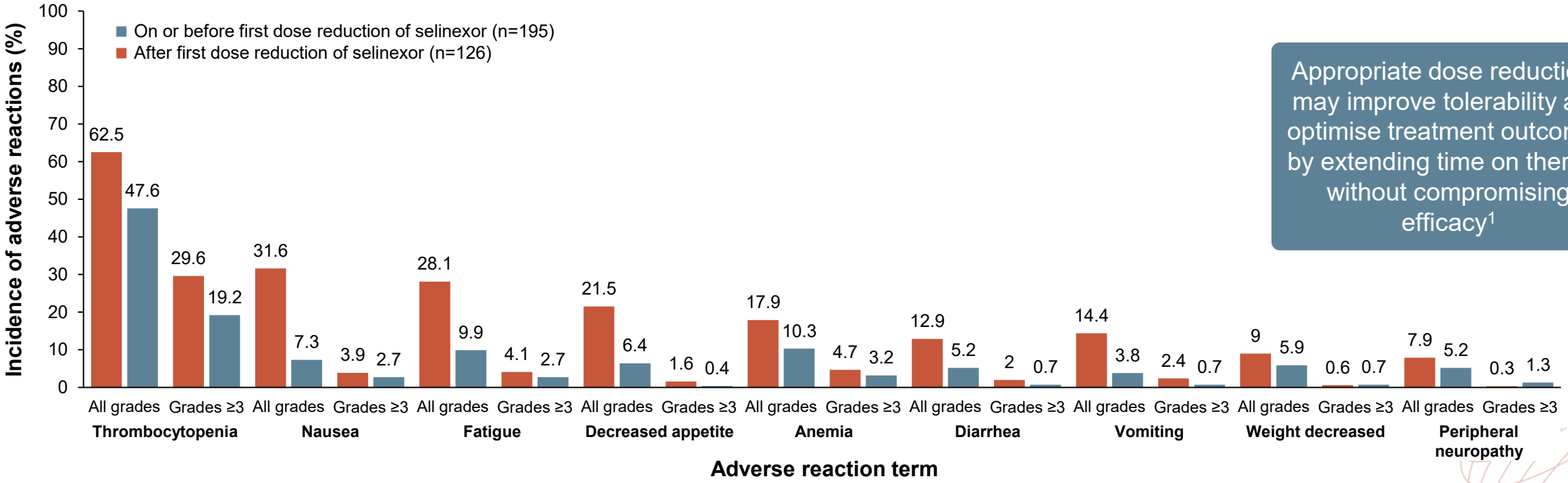
CI, confidence interval; CR, complete response; DoR, duration of response; HR, hazard ratio; ITT, intention-to-treat; LEN, lenalidomide; MM, multiple myeloma; mo, months; NE, not estimable; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; sCR, stringent complete response; SVd, selinexor/bortezomib/dexamethasone; TRAE, treatment-related adverse events; TTNT, time to next treatment; VGPR, very good partial response

1. Delimpasi S, et al. Poster presentation at EHA; 2025; Milan, Italy (Abstract no. PF743); 2. Delimpasi S, et al. Poster PF743. Presented at EHA; 2025; Milan, Italy; 3. European Medicines Agency. Nexpovio. 2023. Available at: https://www.ema.europa.eu/en/medicines/human/EPAR/nexpovio.European (Accessed: January 2026).

BOSTON

DOSE REDUCTIONS OF SELINEXOR MAY IMPROVE TOLERABILITY AND OPTIMISE TREATMENT OUTCOMES[1]

Duration-adjusted[a] incidence of AEs of clinical interest[1]



Appropriate dose reductions may improve tolerability and optimise treatment outcomes by extending time on therapy without compromising efficacy[1]

Figure adapted from Jagannath S, et al. 2021.[1]

Overall, 21% (n=41) of patients treated with selinexor + Vd and 16% (n=32) of patients treated with Vd alone discontinued treatment due to treatment-emergent adverse reactions[2]

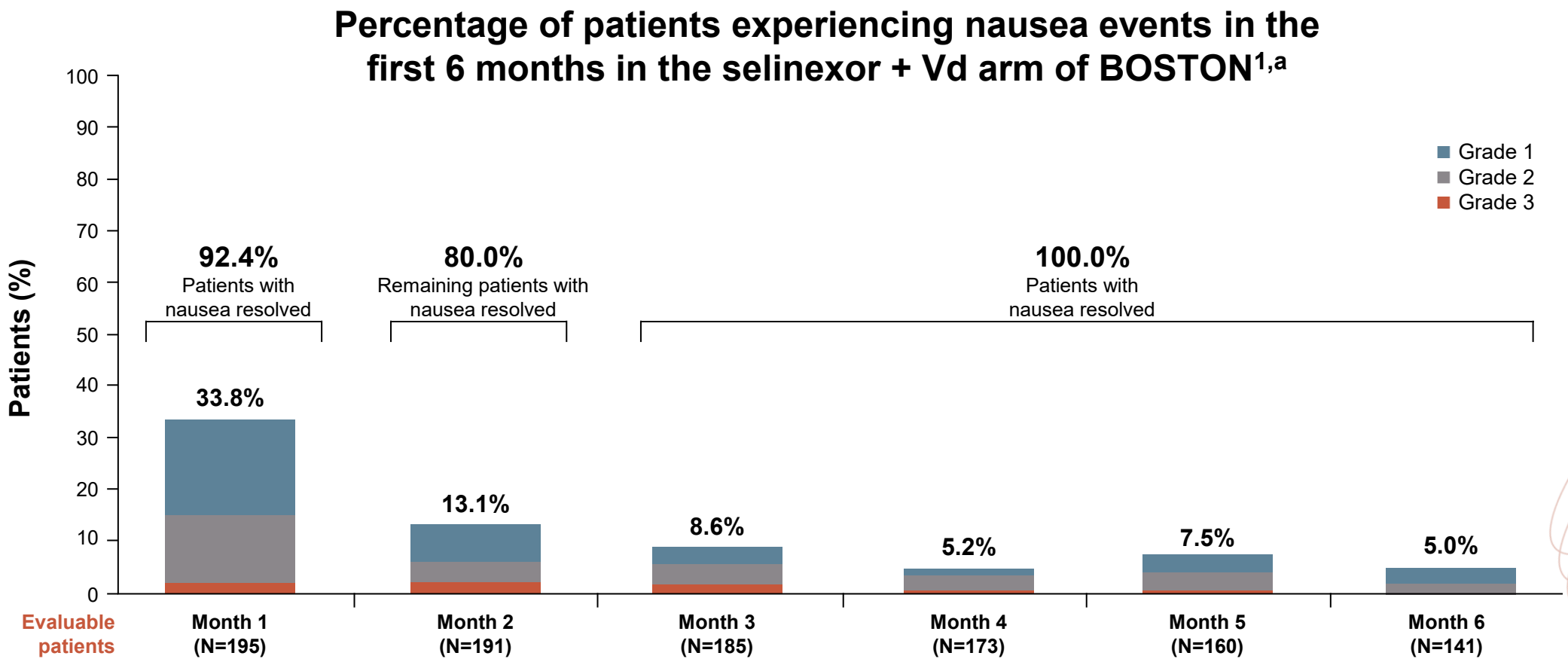
These subgroup analyses were exploratory in nature, not included in the study objectives and did not control for type 1 error.

[a] Duration-adjusted incidence of adverse events is defined as the average number of events per 100 patients during a 4-week cycle[1]

AE, adverse event; Vd, bortezomib, dexamethasone

1. Jagannath S, et al. Clin Lymphoma Myeloma Leuk. 2023;23(12):917-23.e3; 2. Grosicki S, et al. Lancet. 2020;14;396(10262):1563-73

GI AEs



The BOSTON protocol required a prophylactic 5-HT3 antagonist to manage nausea but allowed for other interventions as required[1]

[a] SVd (Selinexor, bortezomib, dexamethasone) approved by EMA[2]

AE, adverse event; BP, best practice; GI, gastrointestinal; IQR, interquartile range; MM, multiple myeloma; NR, not reached; R/R, relapsed refractory; TTF, time to treatment failure; Vd, bortezomib/dexamethasone

1. Nooka AK, et al. Clin Lymphoma Myeloma Leuk. 2022;22(7):e526-e531; 2. European Medicines Agency. Nexpovio. 2023. Available at: https://www.ema.europa.eu/en/medicines/human/EPAR/nexpovio.European (Accessed: January 2026).

3RD LINE: SELINEXOR, BORTEZOMIB, DEXAMETHASONE

PATIENT SPECIFIC CONSIDERATIONS

- Optimise co-morbidities pre-treatment
- Supportive management and additional FBC monitoring if pre-existing cytopenia
- Monitor electrolytes
- Monitor for neuropathy as bortezomib continued until progression

- **Nausea:** combination anticipatory anti-emetics, local practice varies - olanzapine, aprepitant
- **Diarrhea:** loperamide effective
- **Dosing:** once maximal response/plateau achieved, titrate dosing to minimise toxicity aiming for longevity on regimen

FBC, full blood count

REFLECTIONS ON CLINICAL REALITY

- **SVd is a highly effective option in relapsed/refractory multiple myeloma (RRMM)[1]**
- **Patients previously exposed to bortezomib**
  - Prior induction regimens may include VRD, Dara-VRd, or DVD (CASTOR trial)[2]
  - Bortezomib re-treatment is feasible (RETRIEVE trial)[3]
  - SVd builds on this backbone by adding a novel mechanism of action[4]
  - Particularly relevant for patients progressing on lenalidomide maintenance post-transplant[4]
- **Lenalidomide-refractory patients**
  - SVd as a treatment choice in patients who underperform on IMiD-based therapy (functional high-risk)[5]
- **Optimising outcomes with selinexor**
  - Dose modification and proactive prophylaxis are essential for tolerability and sustained benefit[6]

Dara-VRD, daratumumab-VRD; DRd, daratumumab, lenalidomide, dexamethasone; DVd, daratumumab, bortezomib, dexamethasone; IMId, immunomodulatory drugs; MOA, mechanism of action; PFS, progression-free survival; PI, Proteasome inhibitor; RRMM, relapsed/refractory multiple myeloma; SVd, Selinexor, bortezomib and dexamethasone; Vd, bortezomib and dexamethasone; VRd, bortezomib, lenalidomide and dexamethasone

1. Grosicki S, et al. Lancet. 2020;14;396(10262):1563-73; 2. Sonneveld P, et al. Journal of Clinical Oncology 2023; 41: 1600-1609; 3. Petrucci MT, et al. Br J Haematol 2013; 160: 649-659; 4. NICE Guidance. 2024. TA974. Selinexor with bortezomib and dexamethasone for previously treated multiple myeloma. Available at: https://www.nice.org.uk/guidance/ta974/documents/html-content-10 (Accessed: January 2026); 5. Leleu X, et al. J Clin Oncol. 2021;39(suppl 15):Abstr. 8024; 6. Nexpovio (selinexor) Summary of Product Characteristics. Available at: https://www.ema.europa.eu/en/documents/product-information/nexpovioepar-product-information_en.pdf;

KEY CLINICAL TAKEAWAYS AND CLOSE

Prof. Karthik Ramasamy
Hematologist
Oxford University Hospitals NHS Trust, UK

KEY CLINICAL TAKEAWAYS

IS IT TIME TO RETHINK HOW WE SEQUENCE TREATMENT IN MULTIPLE MYELOMA?

- Multiple myeloma evolves as a **multi-clonal disease leading to resistance and refractoriness** to multiple agents over time, creating a persistent unmet clinical need
- Despite therapeutic advances, **there is a need for new drugs with different modes of action** e.g . XPO1 inhibition
- Careful consideration is required in how to sequence novel emerging T-cell engaging therapies optimally with existing treatments to **maximise long-term outcomes**
  - Pre-clinical data has shown that **selinexor has the potential to promote T-cell fitness and reduce T-cell exhaustion**
- In the real-world setting, **selinexor can be effective and its toxicities manageable,** even in poor-prognosis settings such as lenalidomide-refractory disease:
  - Median PFS with SVd vs Vd in Len-refractory multiple myeloma patients was **10.2 months vs 7.1 months** respectively
  - Median OS with SVd vs Vd in Len-refractory multiple myeloma patients was **26.7 months vs 18.6 months** respectively

OS, overall survival; PFS, progression-free survival; SVd, Selinexor, bortezomib and dexamethasone; Vd, bortezomib and dexamethasone; XPO1, Exportin 1 protein

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Bodenackerstrasse 17
4103 Bottmingen
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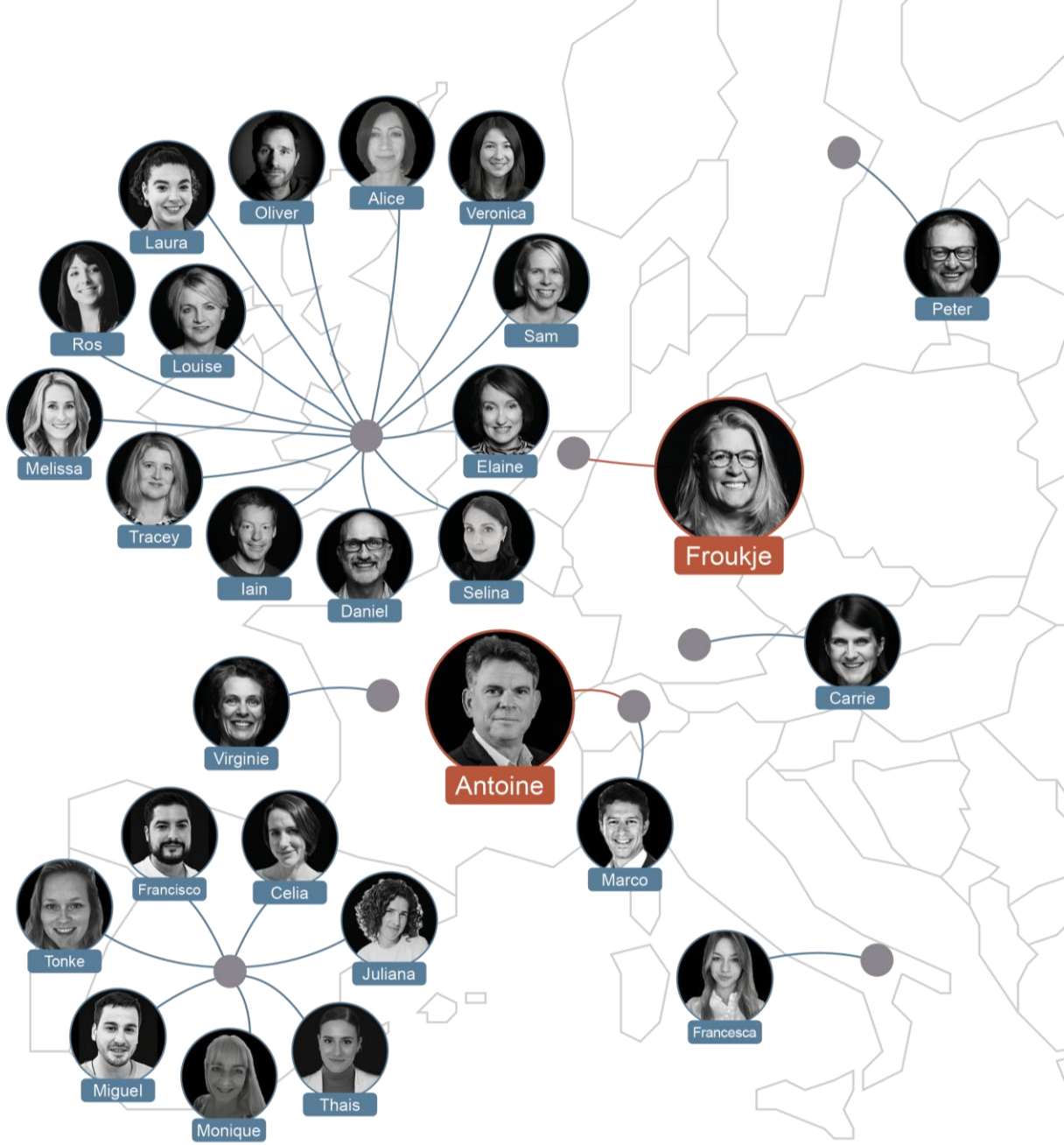

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