COR2ED

THE HEART OF MEDICAL EDUCATION

VIRTUAL EXPERTS KNOWLEDGE SHARE

OPTIMISING THE MANAGEMENT OF MULTIPLE MYELOMA IN THE EARLY RELAPSED/REFRACTORY SETTING

Thursday 30th May 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 disclaimers:

Assoc. Prof. Karthik Ramasamy, has received financial support/sponsorship for research support, consultation, or speaker fees from the following companies: AbbVie, Adaptive Biotechnologies, Amgen, Celgene (BMS), EUSA Pharma, GSK, Janssen, Karyopharm, Oncopeptides, Pfizer, Sanofi, Takeda, Menarini Stemline and Takedax

Prof. Aurore Perrot, has received financial support/sponsorship for research support, consultation, or speaker fees from the following companies: Abbvie, Amgen, BMS, GSK, Janssen, Menarini Stemline, Pfizer, Sanofi and Takeda

Prof. Hermann Einsele, has received financial support/sponsorship for research support, consultation, or speaker fees from the following companies: BMS/Celgene, Janssen, Amgen, Takeda, Sanofi, GSK, Novartis and Roche

Assoc. Prof. Joshua Richter, has received financial support/sponsorship for research support, consultation, or speaker fees from the following companies: Janssen, BMS, Pfizer, Karyopharm, Sanofi, Takeda, Genentech, Abbvie, Regeneron, Forus, Menarini, Adaptive Technologies

MEETING OBJECTIVES

To educate learners on 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
- Knowing the safety profiles of novel drugs and understanding the best strategies to prevent or manage side effects

AGENDA

OPTIMISING THE MANAGEMENT OF MULTIPLE MYELOMA IN THE EARLY RELAPSED/REFRACTORY SETTING

Timings	Topic	Facilitator
5 mins	Welcome, introductions and scene setting: Challenge of optimising treatment for early RRMM in the era of multiple novel therapies	Karthik Ramasamy
15 mins	Current treatments for early RRMM*: Linking mechanism of action and efficacy	Aurore Perrot
15 mins	Best practices in combining and sequencing therapies for optimal outcomes	Hermann Einsele
15 mins	Insights from clinical practice on how to manage tolerability and safety	Joshua Richter
20 mins	Patient case study presentation and discussion	All
15 mins	Q&A discussion	Facilitated by Joshua Richter
5 mins	Summary & a look to the future	Joshua Richter

RRMM, Relapsed refractory multiple myeloma

*After 1-3 prior lines of therapy

INTRODUCING THE SCIENTIFIC COMMITTEE

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

Prof. Aurore Perrot
Hematologist
University of Toulouse, France

Prof. Hermann Einsele
Hematologist-Oncologist
University of Würzburg, Germany

Assoc. Prof. Joshua Richter
Hematologist-Oncologist
Icahn School of Medicine at Mount Sinai, USA

CHALLENGE OF OPTIMISING TREATMENT FOR EARLY RRMM IN THE ERA OF MULTIPLE NOVEL THERAPIES

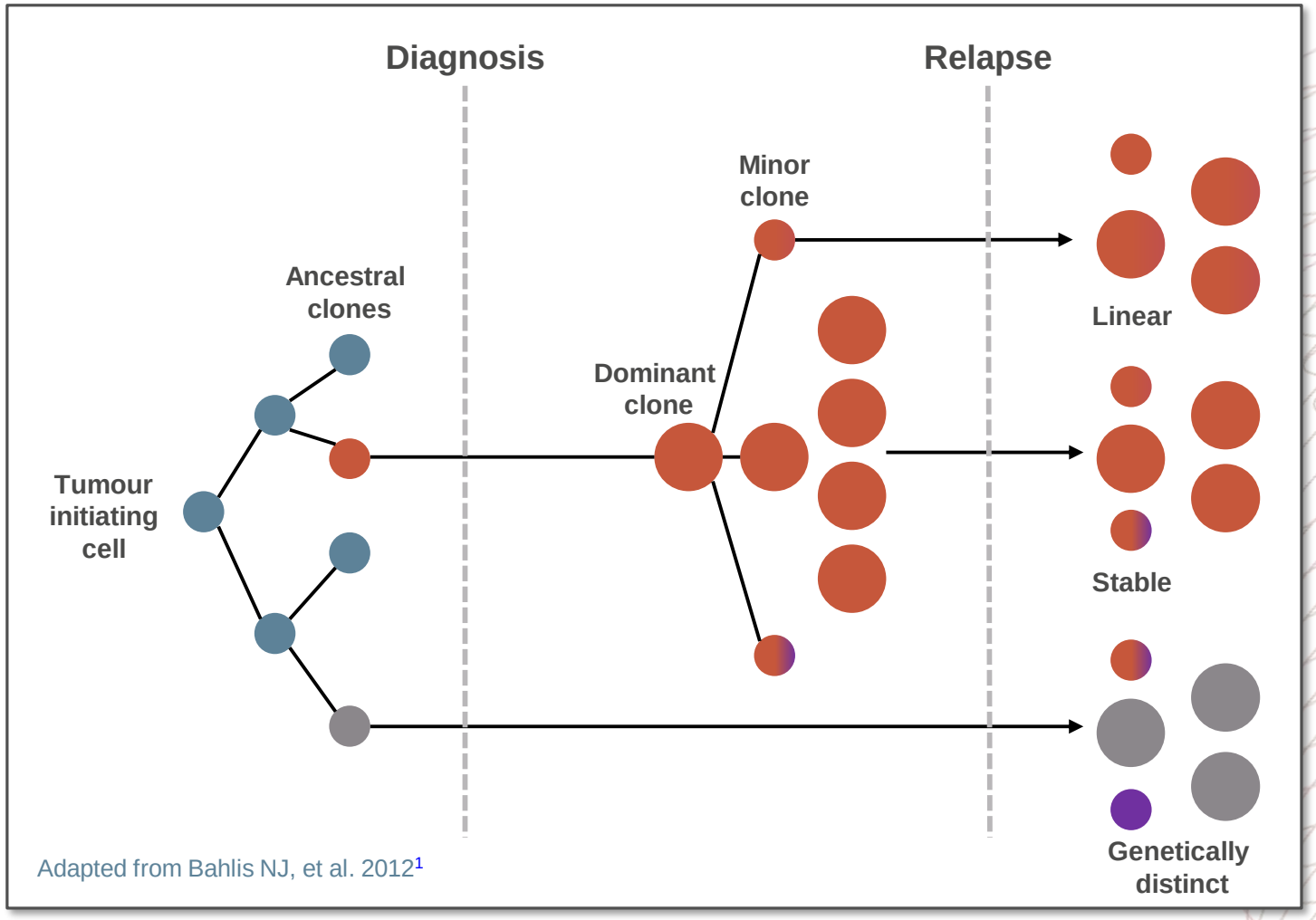
Assoc. Prof. Karthik Ramasamy

Hematologist-Oncologist

Oxford University Hospitals NHS Trust, UK

DEVELOPMENT OF MULTIPLE, GENETICALLY DISTINCT SUBCLONES IN MULTIPLE MYELOMA

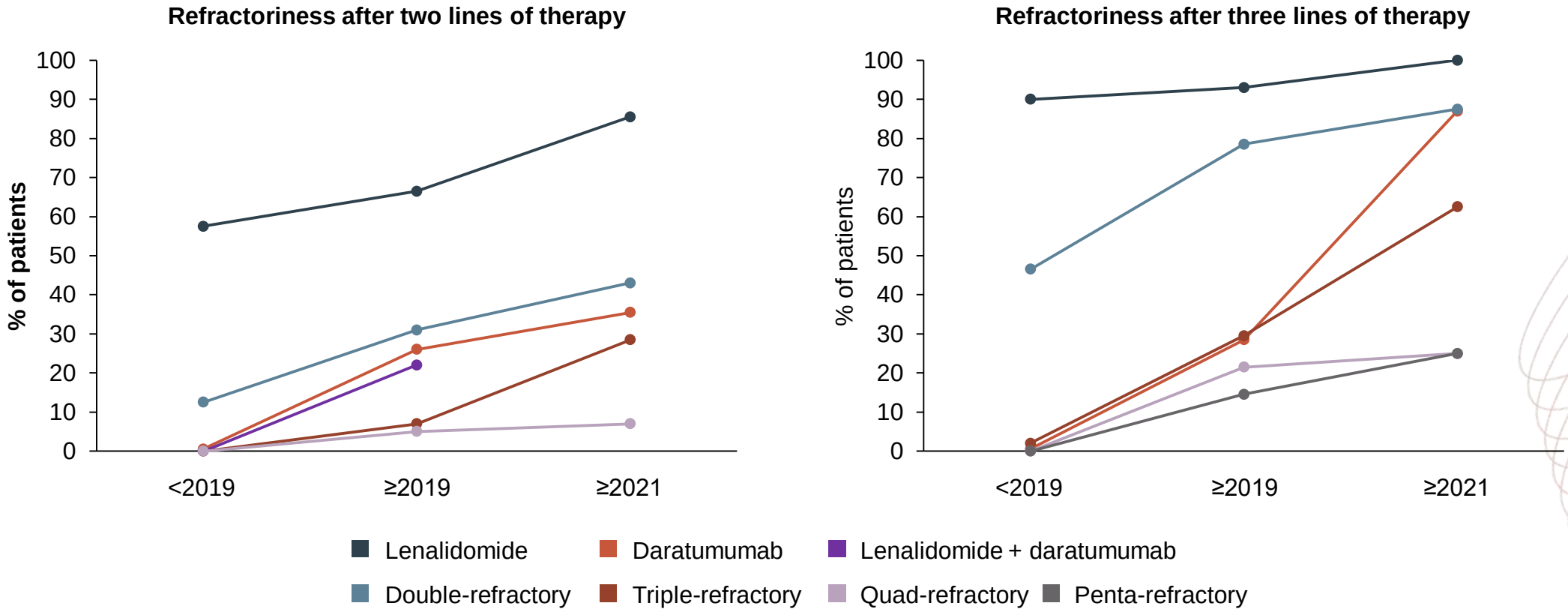
- Subclones develop over time due to selective pressures from the microenvironment and treatment[1,2]
- Clonal evolution can lead to **disease progression** and **treatment resistance**[3]



1. Bahlis NJ. Blood. 2012;120:927-928; 2. Bolli N, et al. Nat Commun. 2014;5:2997; 3. Brioli N, et al. Br J Haematol. 2014;165:441-454

PREVALENCE OF EARLY REFRACTORINESS IS GROWING

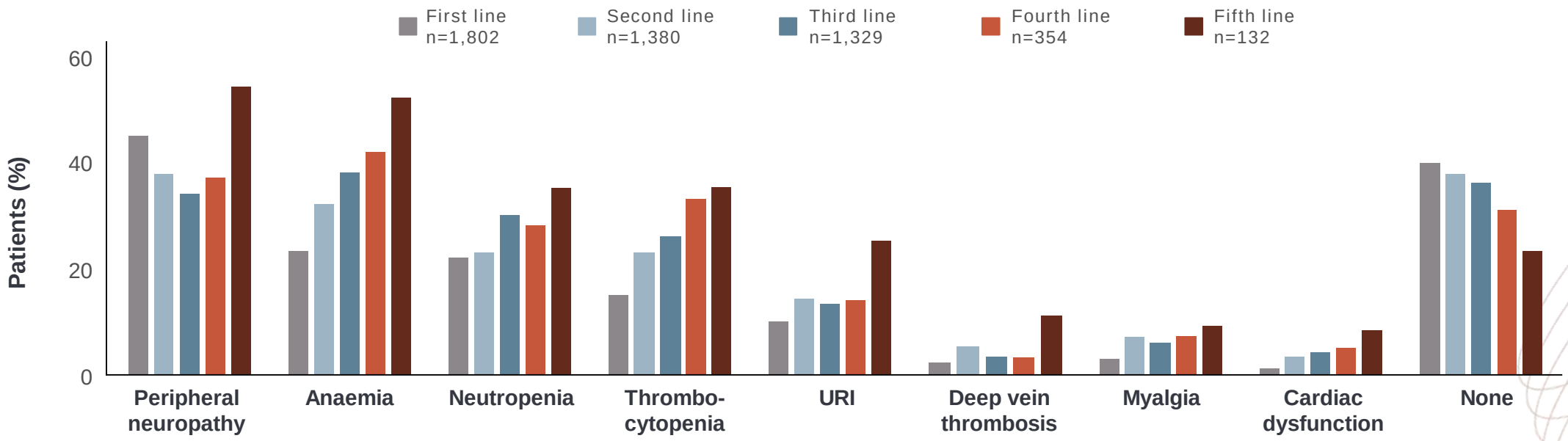
REAL-WORLD ASSESSMENT OF REFRACTORINESS PATTERNS IN 413 PATIENTS TREATED IN AN ITALIAN HAEMATOLOGICAL TERTIARY CARE CENTRE



Morè S, et al. Br J Haematol. 2023; 201:432-442

CHALLENGES IN SELECTING TREATMENTS AT RELAPSE: ADVERSE EVENTS BY LINE OF THERAPY

PATIENT CHART REVIEW[a]: ALL-GRADE COMORBIDITIES AND TOXICITIES BY MOST RECENTLY COMPLETED LINE OF THERAPY



The proportion of patients with toxicities or comorbidities tended to increase with line of therapy. Both are more likely to affect planned treatment in later vs earlier lines

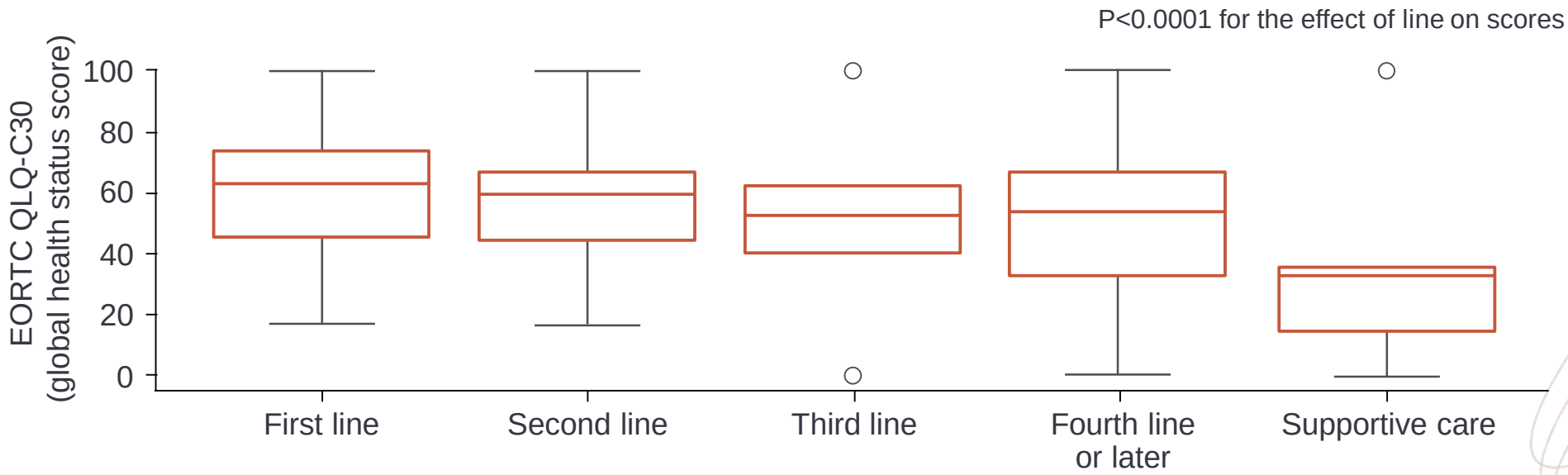
[a] Retrospective and cross-sectional review of 4,997 patient charts (1L: n=1,802; 2L: n=1,380; ≥3L: n=1,815) in Belgium, Germany, Italy, Spain, Switzerland, and UK

1L, first line; 2L, second line; 3L, third line; URI, upper respiratory infection

Yong K, et al. Br J Haematol. 2016;175:252-264

HEALTH-RELATED QUALITY OF LIFE DECREASED SIGNIFICANTLY WITH TREATMENT LINE

Mean EORTC QLQ-C30 global health status scores decreased from **63.0 at first line** to **59.7 at second line, 52.6 at third line, 53.6 at fourth line or later,** and **32.8 for patients receiving supportive care**



	Difference between second and first line	Difference between third and second line	Difference between fourth line or later and third line	Difference between supportive care and fourth line or later
Mean difference in global health status score	-3.3	-7.1	1.0	-20.8

Observation, cross-sectional, multicentre study conducted in France. Data presented are means, first quartiles, third quartiles, and minimums and maximums. Open circles denote extreme values. Higher scores for EORTC QLQ-C30 Global Health Status score indicate higher quality of life

EORTC, European Organisation for Research and Treatment of Cancer; QLQ-C30, Core Quality of Life questionnaire

Despiégel N, et al. Clin Lymphoma Myeloma Leuk. 2019;19:e13-e28

MULTIPLE DRUG CLASSES ARE APPROVED FOR THE TREATMENT OF RRMM

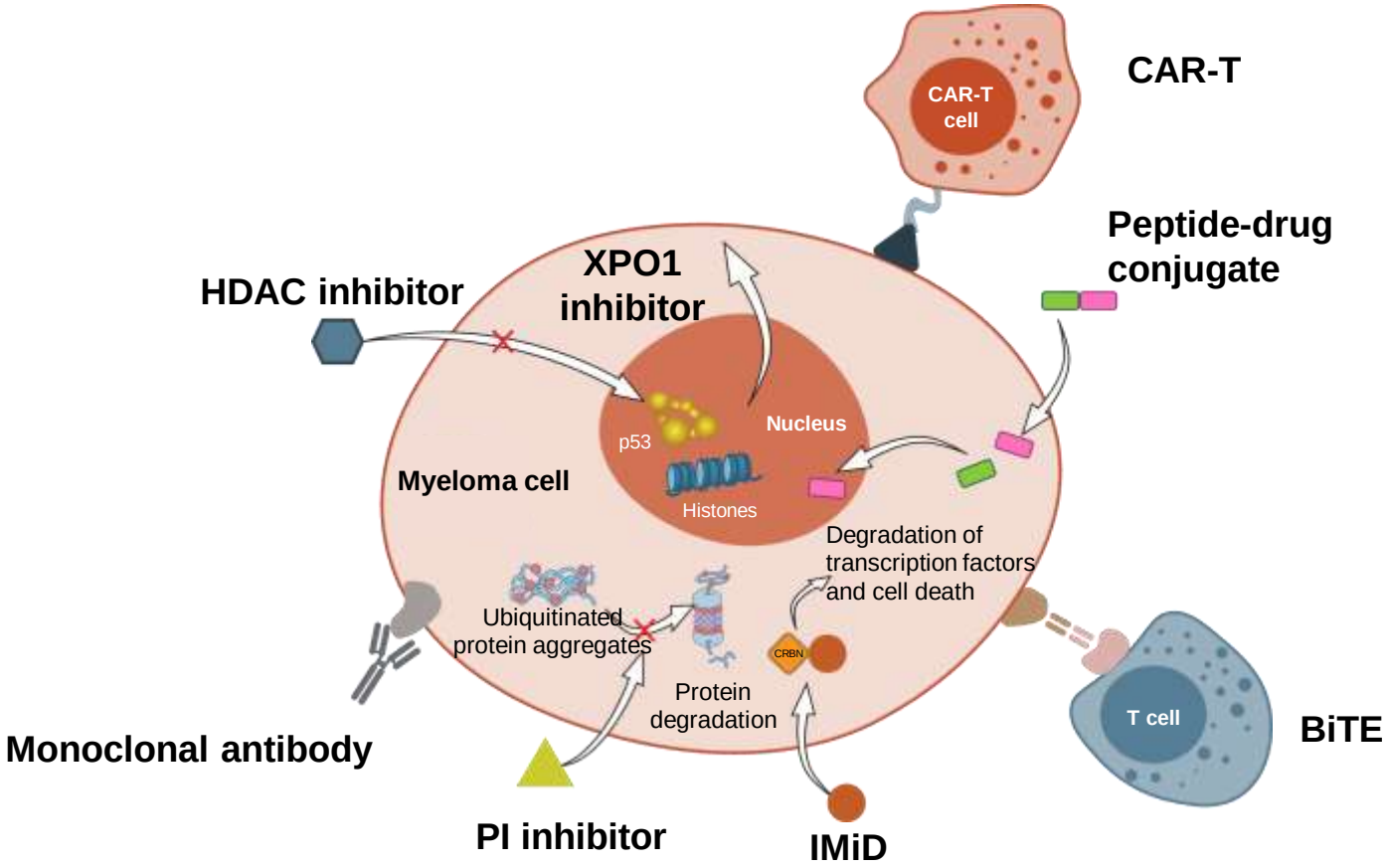


Figure adapted from Dimopoulos et al.

BiTE, bispecific T-cell engager; CAR T, chimeric antigen receptor T cell; HDAC, histone deacetylase; IMiD, immunomodulatory drug; PI, proteasome inhibitor; RRMM, relapsed/refractory multiple myeloma; SLAMF7, signalling lymphocyte activation molecule family 7; XPO1, exportin 1

Dimopoulos M-A, et al. Clin Lymphoma Myeloma Leuk. 2022;22:460-473.

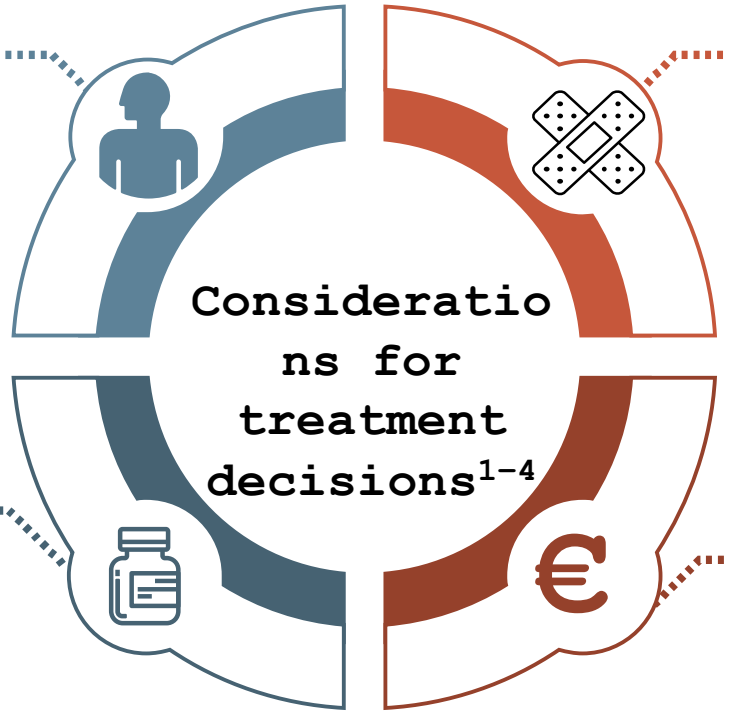
CONSIDERATIONS FOR TREATMENT DECISIONS

Patient

- Age
- Comorbidities
- Performance status
- Bone marrow reserve
- Preference

Therapy

- Response to prior therapy
- Toxicity of prior therapy
- Time from prior therapy
- Clinical trials available



Disease

- Duration of prior remission
- Disease burden
- End-organ function
- Standard vs high risk disease

Socio-economic

- Support system
- Treatment centre accessibility

RRMM, relapsed/refractory multiple myeloma

1. Nijhof IS, et al. Drugs 2018;78:19-37; 2. Orlowski RZ, et al. Clin Cancer Res. 2016;22:5443-5452; 3. Baz R, et al. Support Care Cancer. 2015;23:2789-2797; 4. Goodwin JA, et al. Cancer Nurs. 2013;36:301-308

CASE STUDY: PATIENT PROFILE

- Age 71 years, retired
- ECOG PS: 1
- PMH: Hypertension, paroxysmal atrial fibrillation
- Presented with bone pain and fatigue

- Diagnosis: June 2021
- IgG kappa multiple myeloma
- Hb:117 g/L, normal renal function
- Vertebral collapse
- MM FISH – 1p deletion
- R-ISS I standard risk

Educational case study

ECOG, Eastern Cooperative Oncology Group; FISH, fluorescence in situ hybridisation; Hb: haemoglobin; IgG: immunoglobulin; MM, multiple myeloma; PMH, previous medical history;
PS, performance status; R-ISS, revised International Staging System

CASE STUDY: TREATMENT

June 2021

Front-line treatment: Dara VTd – VGPR grade 1 neuropathy

November 2021

HDM ASCT – complete remission. Dara VTd consolidation

March 2022

Lenalidomide maintenance

March 2024

Biochemical progression on lenalidomide: Further treatment?

Educational case study

ASCT, autologous stem cell transplant; Dara, daratumumab; HDM, high-dose melphalan; VTd, bortezomib, thalidomide, dexamethasone; VGPR, very good partial response

POLLING QUESTION

WHAT TREATMENT WOULD YOU CHOOSE AT 2ND LINE

A. Daratumumab, bortezomib, dexamethasone

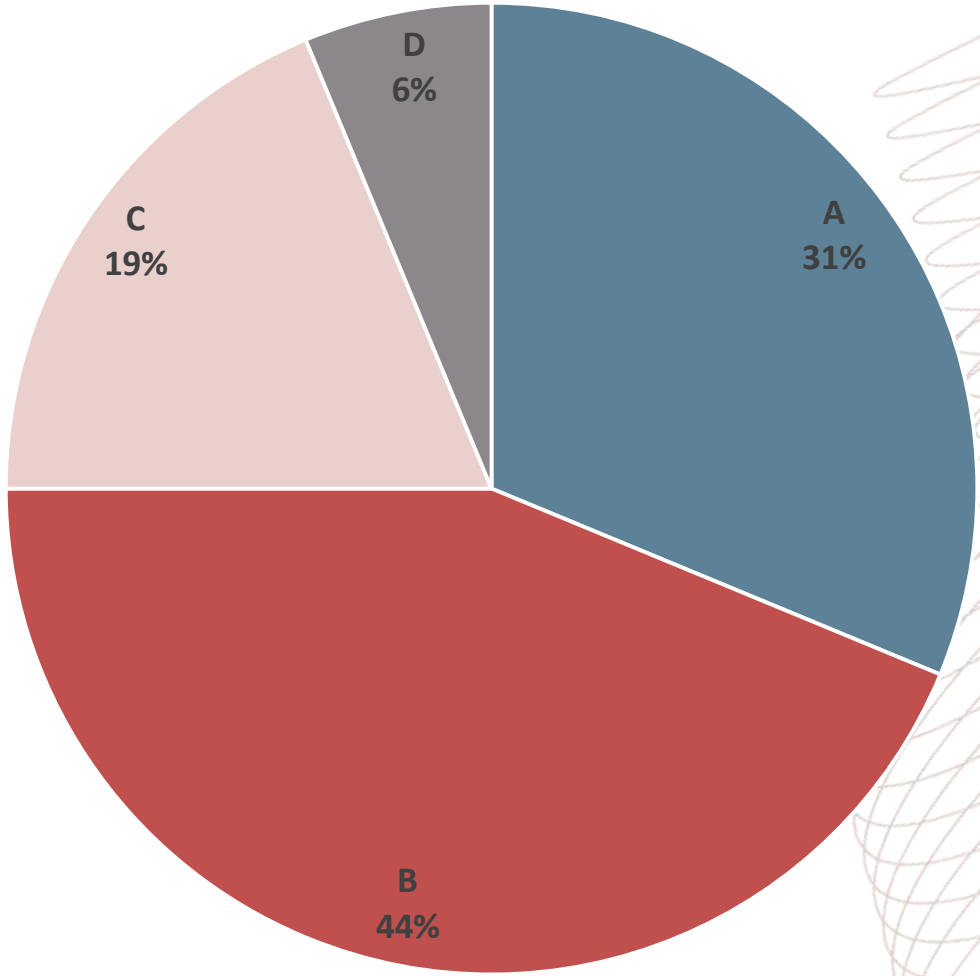
B. Daratumumab/isatuximab, carfilzomib, dexamethasone

C. Daratumumab, pomalidomide, dexamethasone

D. Selinexor, bortezomib, dexamethasone

E. Pomalidomide, bortezomib, dexamethasone

F. Carfilzomib, dexamethasone



CURRENT TREATMENTS FOR EARLY RRMM: LINKING MECHANISM OF ACTION AND EFFICACY

Prof. Aurore Perrot

Hematologist
University of Toulouse, France

DRUGS APPROVED FOR THE TREATMENT OF RRMM

Drugs approved by the EMA for the treatment of early RRMM (1-3 prior therapies)[2]

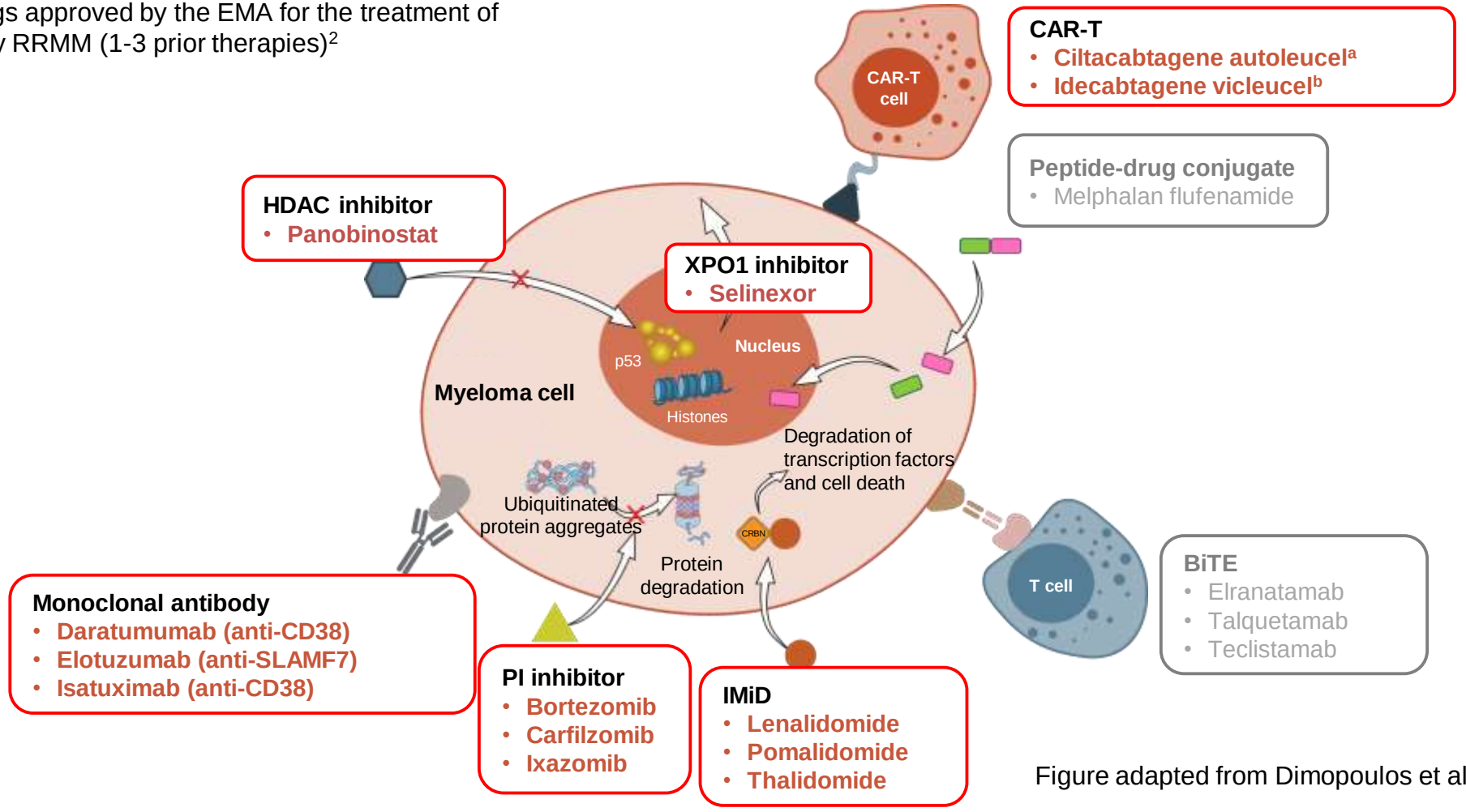


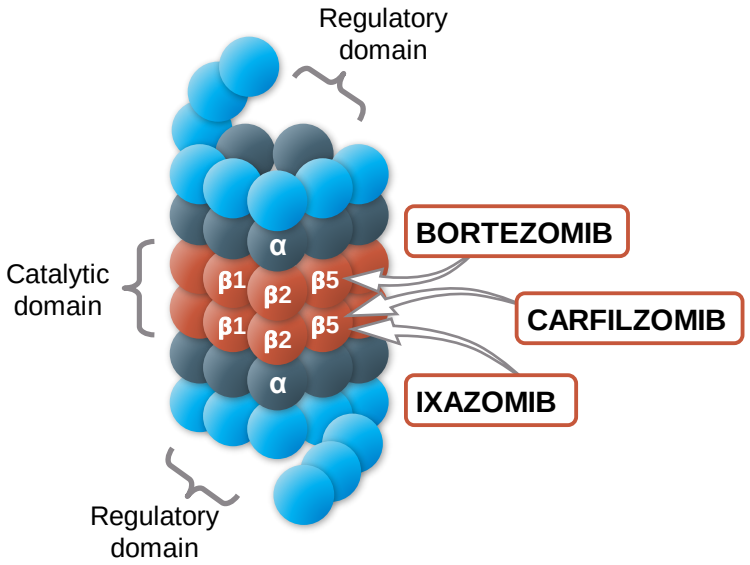
Figure adapted from Dimopoulos et al.[1]

[a] Ciltacabtagene autoleucel has received a positive opinion from the CHMP to expand the indication to patients who have received ≥1 prior therapy.[3b] Idecabtagene vicleucel is approved for the treatment of patients who have received ≥2 prior therapies

BiTE, bispecific T-cell engager; CAR T, chimeric antigen receptor T cell; CHMP, Committee for Medicinal Products for Human Use; EMA, European Medicines Agency; HDAC, histone deacetylase; IMiD, immunomodulatory drug; PI, proteasome inhibitor; RRMM, relapsed/refractory multiple myeloma; SLAMF7, signalling lymphocyte activation molecule family 7; XPO1, exportin 1

1. Dimopoulos M-A, et al. Clin Lymphoma Myeloma Leuk. 2022;22:460-473; 2. Summary of Product Characteristics are available from: https://www.ema.europa.eu/en/medicines. Last accessed 4 April 2024. 3. https://www.ema.europa.eu/en/medicines/human/variation/carvykti

PIs DISRUPT THE UNFOLDED PROTEIN RESPONSE PATHWAY AND INDUCE APOPTOSIS



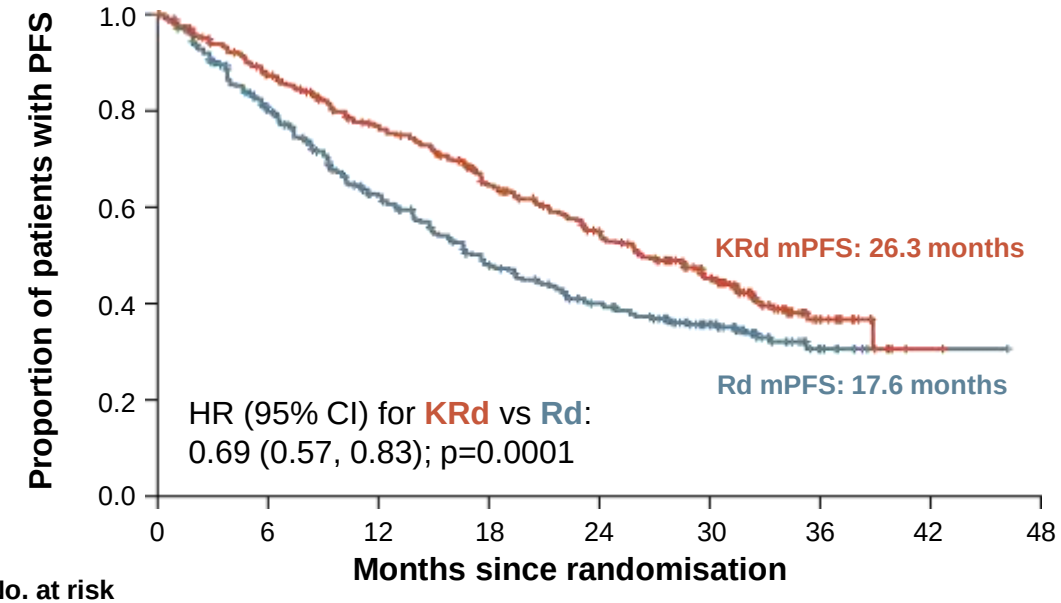
1. **Ubiquitin depletion**
2. **↑ER stress due to ↑misfolded proteins**
3. **NFκB downregulation**
4. **Activation of pro-apoptotic pathways**

ER, endoplasmic reticulum; NFκB, nuclear factor kappa B; PI, proteasome inhibitor

Kegyes D, et al. Blood Rev. 2023;61:101100

CARFILZOMIB AND IXAZOMIB INCREASED PFS IN PATIENTS WITH RRMM AND 1-3 PRIOR TREATMENTS

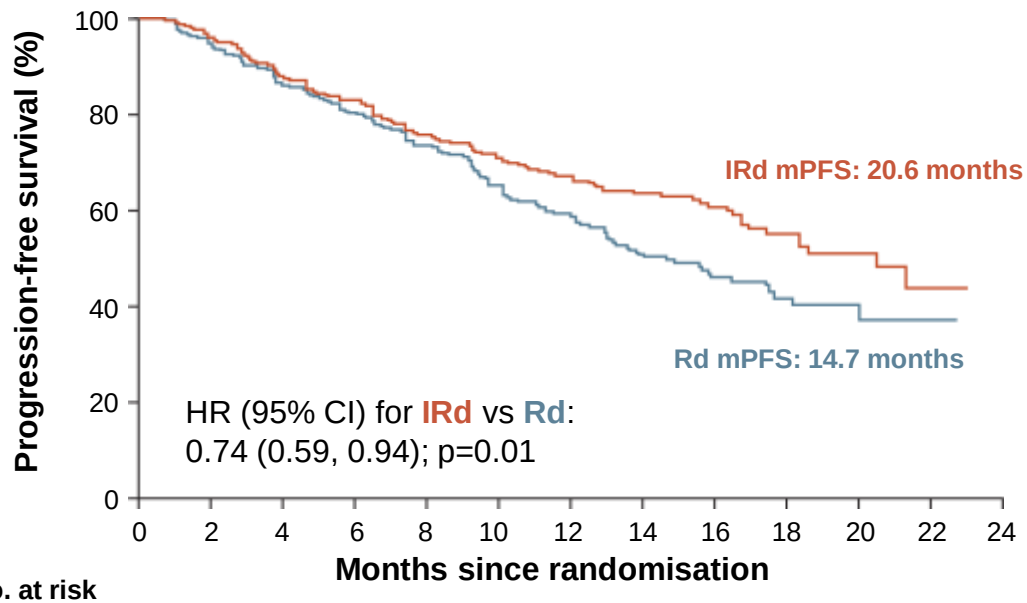
ASPIRE: Carfilzomib[1]



No. at risk

KRd:	396	332	279	222	179	112	24	1
Rd:	396	287	206	151	117	72	18	1

TOURMALINE-MM1: Ixazomib[2]



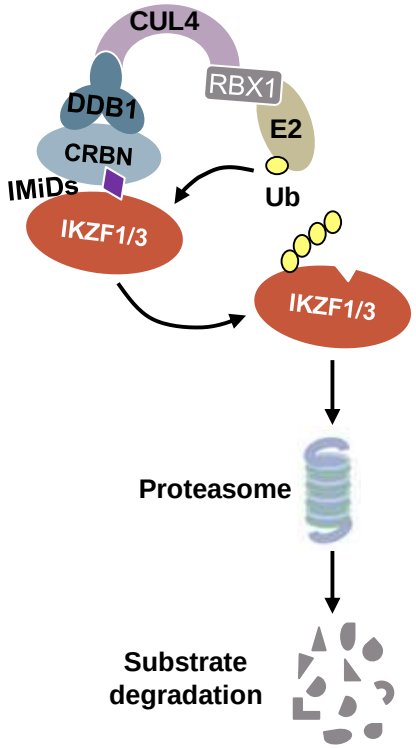
No. at risk

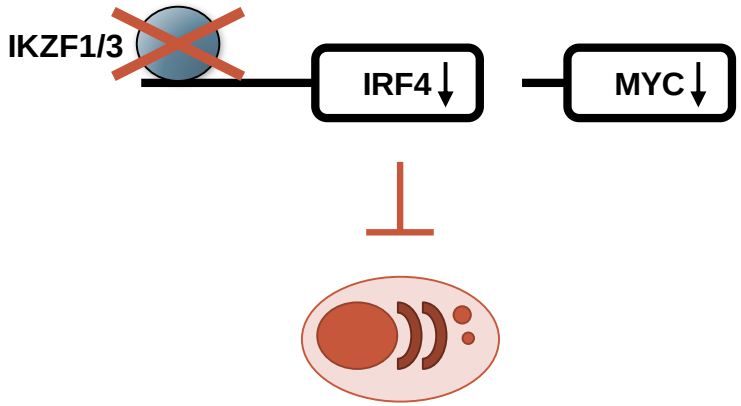
IRd:	360	332	298	270	233	206	145	111	72	44	26	9	0
Rd:	362	325	288	254	218	188	130	85	58	31	15	3	0

CI, confidence interval; d, dexamethasone; HR, hazard ratio; I, ixazomib; K, carfilzomib; (m)PFS; (median) progression-free survival; R, lenalidomide; RRMM, relapsed/refractory multiple myeloma

1. Stewart AK, et al. New Engl J Med. 2015;372:142-152; 2. Moreau P, et al. New Engl J Med. 2016;374:1621-1634

IMiDs BIND TO CRBN AND EXERT PLEIOTROPIC EFFECTS





Adapted from Wang S, et al. (2021)[1] and Krönke J, et al. (2014)[2]

IMiDs hijack the **CRL4 E3 ligase via CBRN** to ubiquitinate and degrade the lymphoid transcription factors, **IKZF1 and IKZF3**

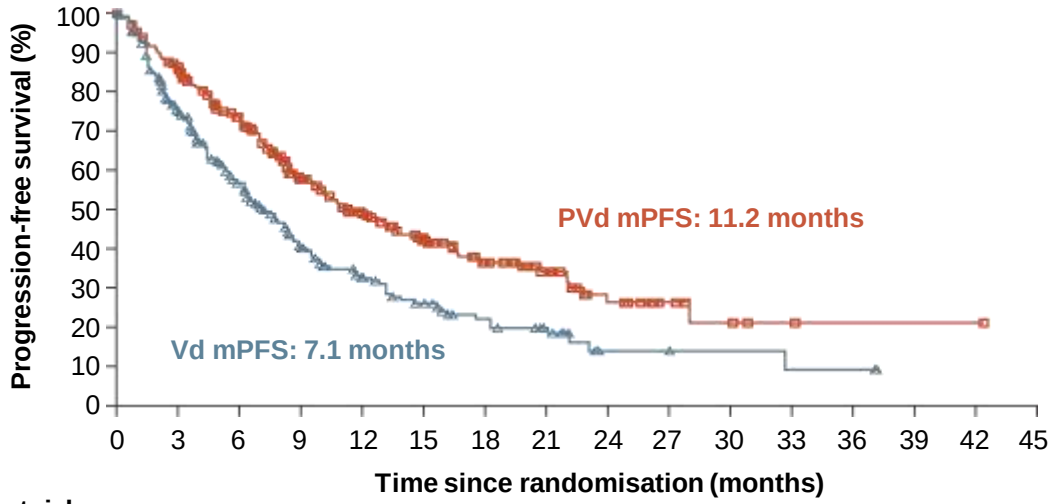
This results in the **downregulation of IRF4 and MYC** and the **inhibition of MM cell proliferation**

CRBN, cereblon; CRL4, Cullin–RING ubiquitin ligase complex 4; CUL4, cullin-4; DDB1, DNA damage-binding protein 1; E2, ubiquitin-conjugating enzymes; IKZF1 and 3, IKAROS family zinc finger 1 and 3; IMiD, immunomodulatory drug; IRF4, interferon regulatory factor 4; RBX1, small RING protein; Ub, ubiquitin

1. Wang S, et al. Biomarker Res. 2021;9:43; 2. Krönke J, et al. Oncoimmunology. 2014;3(7):e941742

OPTIMISMM: POMALIDOMIDE INCREASED PFS IN PATIENTS WITH RRMM PREVIOUSLY TREATED WITH LENALIDOMIDE

ITT population

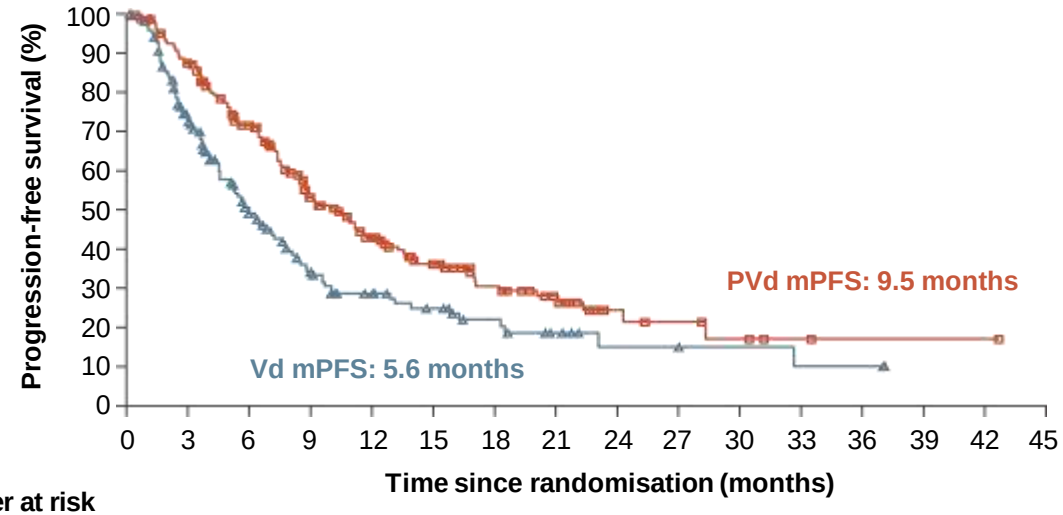


Number at risk

PVd	281	233	182	128	94	67	47	28	13	7	4	2	1	1	1	0
Vd	278	176	112	66	42	30	20	14	4	4	3	2	2	0	0	0

HR (95% CI) for PVd vs Vd:
0.61 (0.49, 0.77); p<0.0001

Lenalidomide-refractory patients



Number at risk

PVd	200	162	119	77	54	37	25	16	7	6	4	2	1	1	1	0
Vd	191	113	63	37	25	19	13	8	4	4	3	2	2	0	0	0

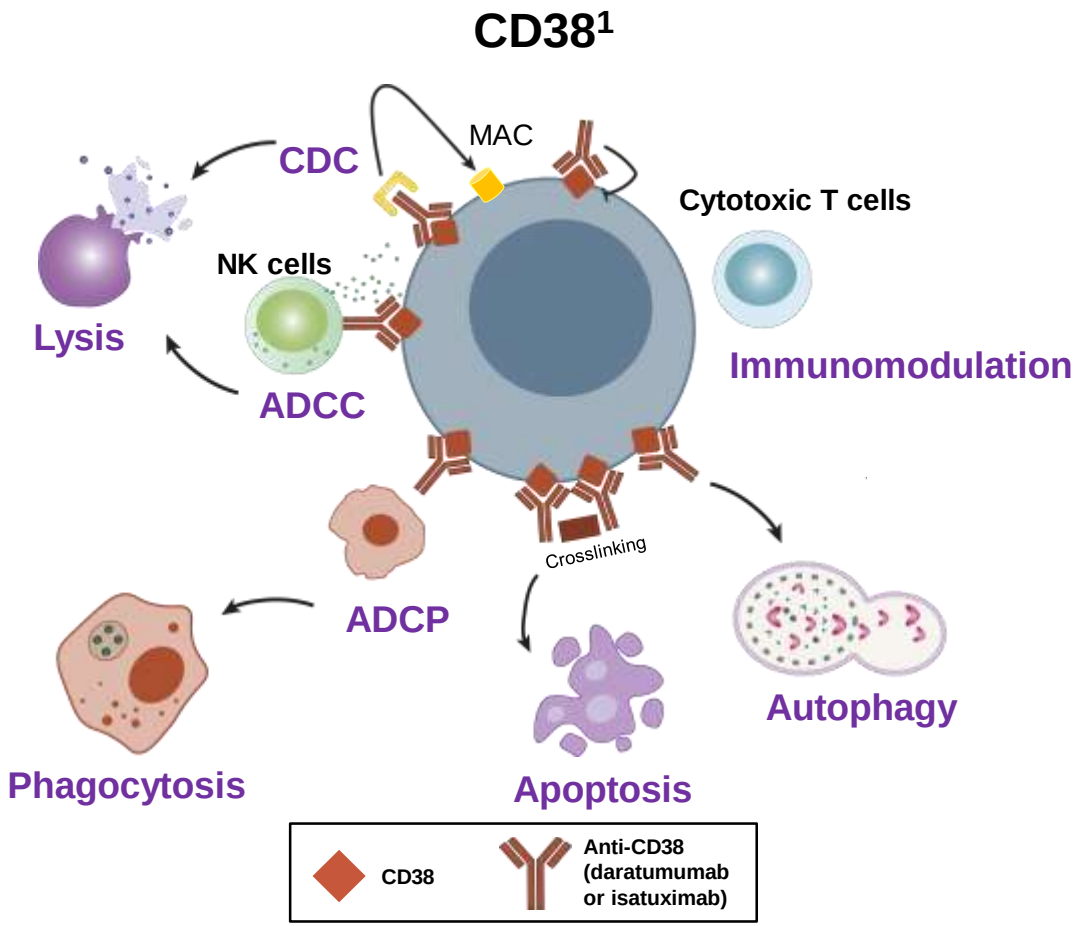
HR (95% CI) for PVd vs Vd:
0.65 (0.50, 0.84); p=0.0008

All patients had received 1-3 prior therapies including lenalidomide

CI, confidence interval; d, dexamethasone; HR, hazard ratio; ITT, intent to treat; (m)PFS, (median) progression-free survival; P, pomalidomide; RRMM, relapsed/refractory multiple myeloma; V, bortezomib

Richardson PG, et al. Lancet Oncol. 2019;20:781-794

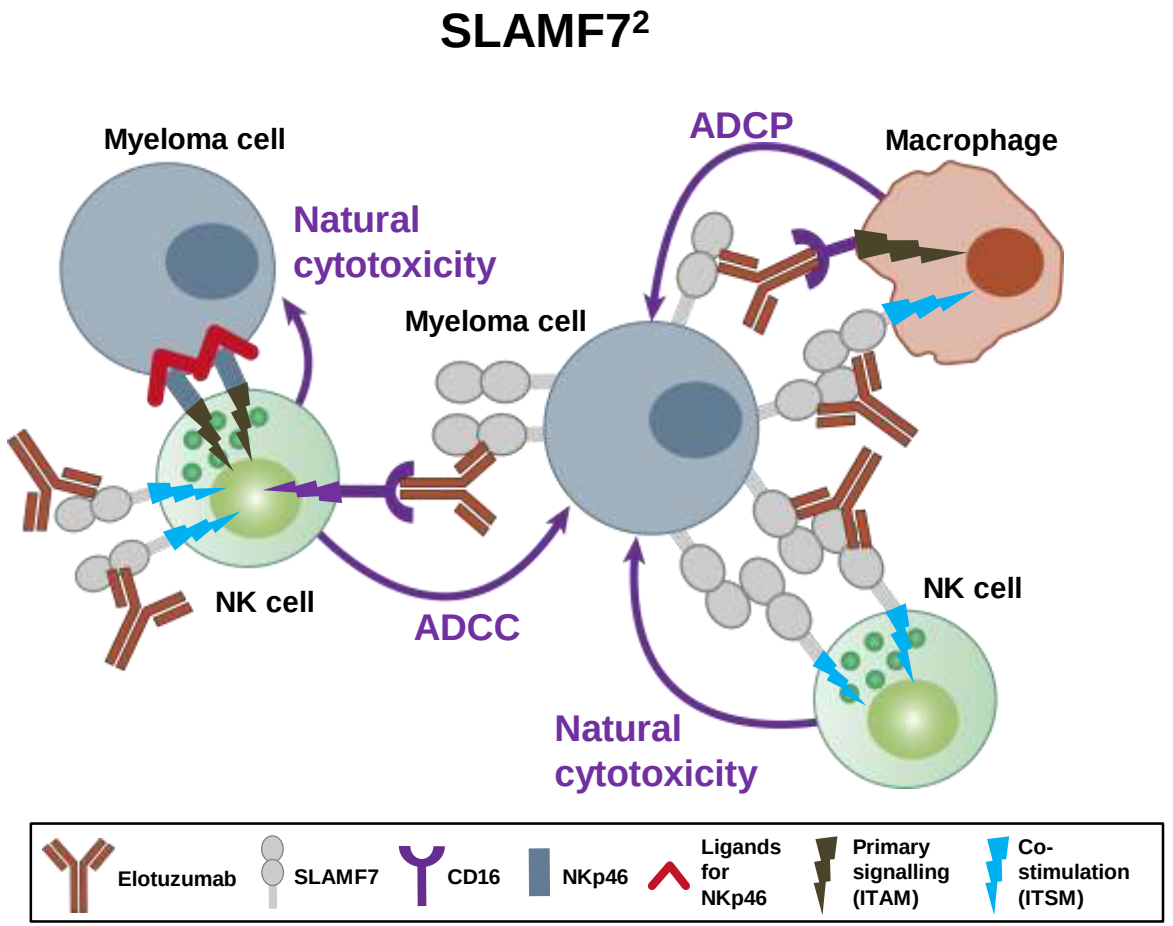
mAbs TARGETING CD38 AND SLAMF7 INDUCE MYELOMA CELL DEATH VIA CYTOTOXIC AND PHAGOCYTIC PATHWAYS



ADCC, antibody-dependent cell-mediated cytotoxicity; ADCP, antibody-dependent cellular phagocytosis; CDC, complement-dependent cytotoxicity; ITAM, immunoreceptor tyrosine-based activation motifs; ITSM, immunoreceptor tyrosine-based switch motifs; mAb, monoclonal antibody; MAC, membrane attack complex; NK, natural killer; SLAMF7, signalling lymphocyte activation molecule family member 7

1. Gozzetti A, et al. Hum Vaccin Immunother. 2022;18:2052658; 2. Campbell KS, et al. Front Immunol. 2018;9:2551

mAbs TARGETING CD38 AND SLAMF7 INDUCE MYELOMA CELL DEATH VIA CYTOTOXIC AND PHAGOCYTIC PATHWAYS

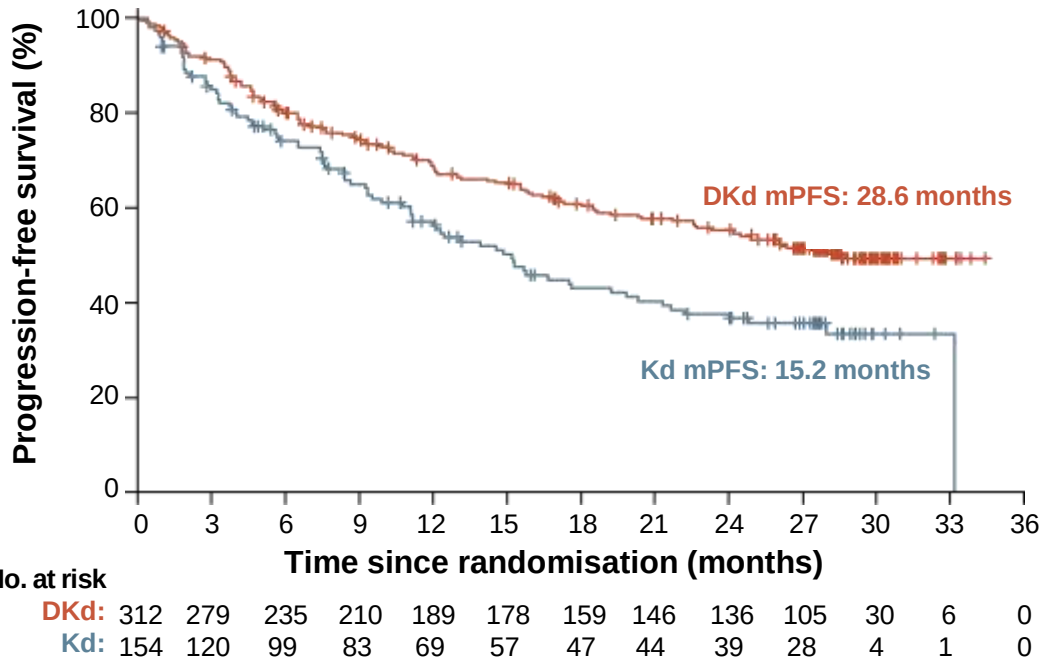


ADCC, antibody-dependent cell-mediated cytotoxicity; ADCP, antibody-dependent cellular phagocytosis; CDC, complement-dependent cytotoxicity; ITAM, immunoreceptor tyrosine-based activation motifs; ITSM, immunoreceptor tyrosine-based switch motifs; mAb, monoclonal antibody; MAC, membrane attack complex; NK, natural killer; SLAMF7, signalling lymphocyte activation molecule family member 7

1. Gozzetti A, et al. Hum Vaccin Immunother. 2022;18:2052658; 2. Campbell KS, et al. Front Immunol. 2018;9:2551

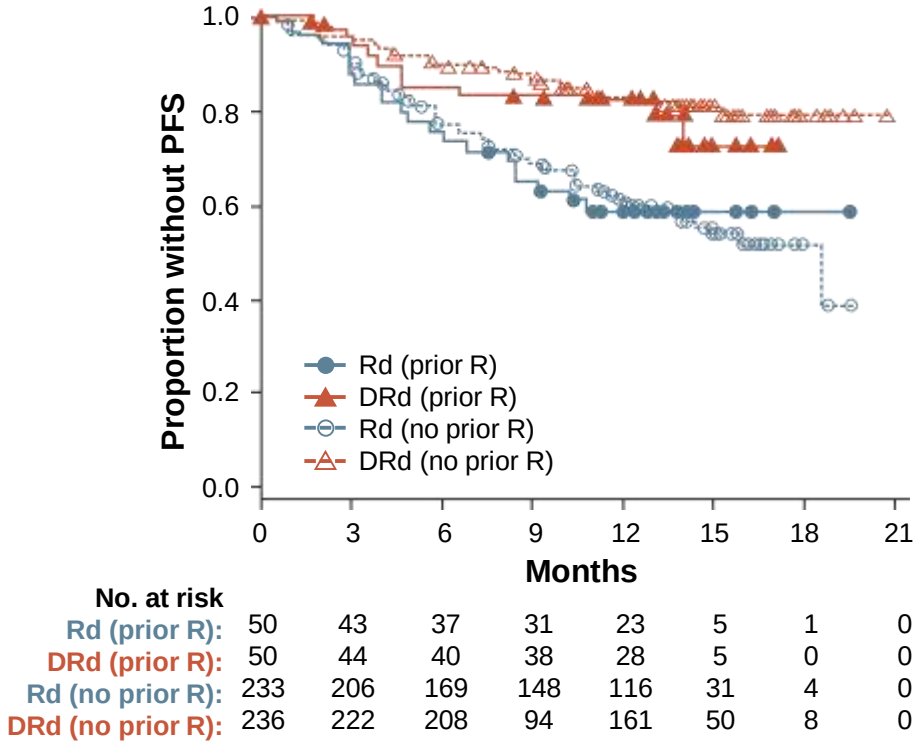
PFS BENEFIT WITH DARATUMUMAB IN PATIENTS WITH RRMM AND 1-3 PRIOR TREATMENTS

CANDOR[1]



HR (95% CI) for **DKd** vs **Kd**:
0.59 (0.45, 0.78); p<0.0001

POLLUX[2]

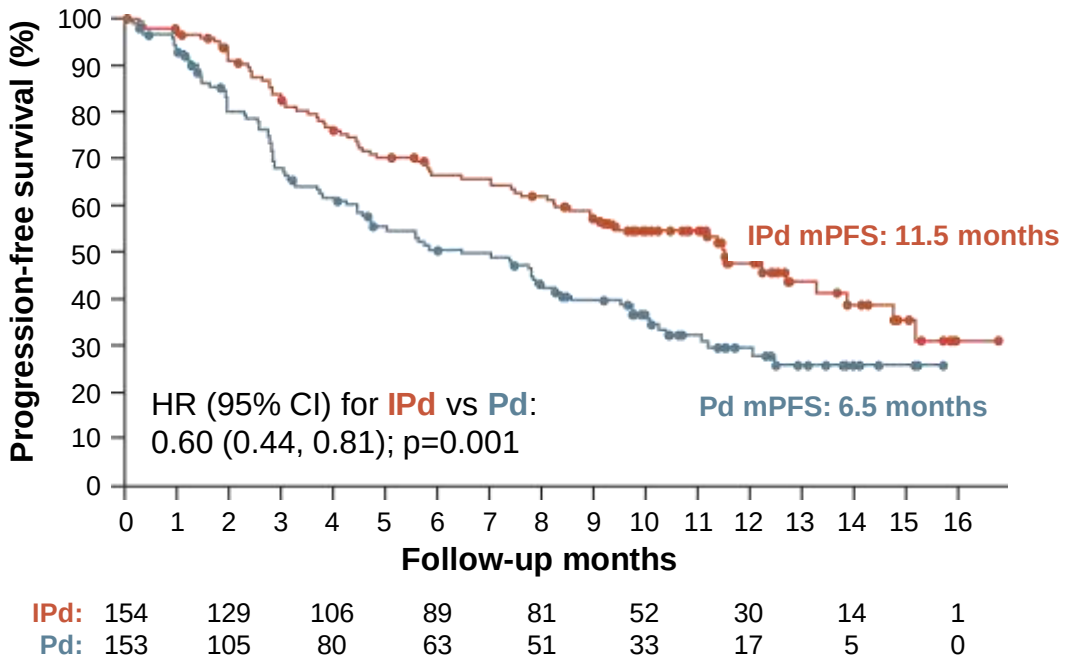


HR (95% CI) for **DRd** vs **Rd**:
No prior lenalidomide: 0.36 (0.25, 0.52); p<0.001
Prior lenalidomide: 0.42 (0.19, 0.90); p=0.02

CI, confidence interval; d, dexamethasone; D, daratumumab; HR, hazard ratio; K, carfilzomib; (m)PFS, (median) progression-free survival; R, lenalidomide; RRMM, relapsed/refractory multiple myeloma

1. Usmani SZ, et al. Lancet Oncol. 2022;23:65-76; 2. Dimopoulos MA, et al. New Engl J Med. 2016;375:1319-1331

ADDITION OF ISATUXIMAB TO Pd IMPROVED PFS IN PATIENTS WITH RRMM

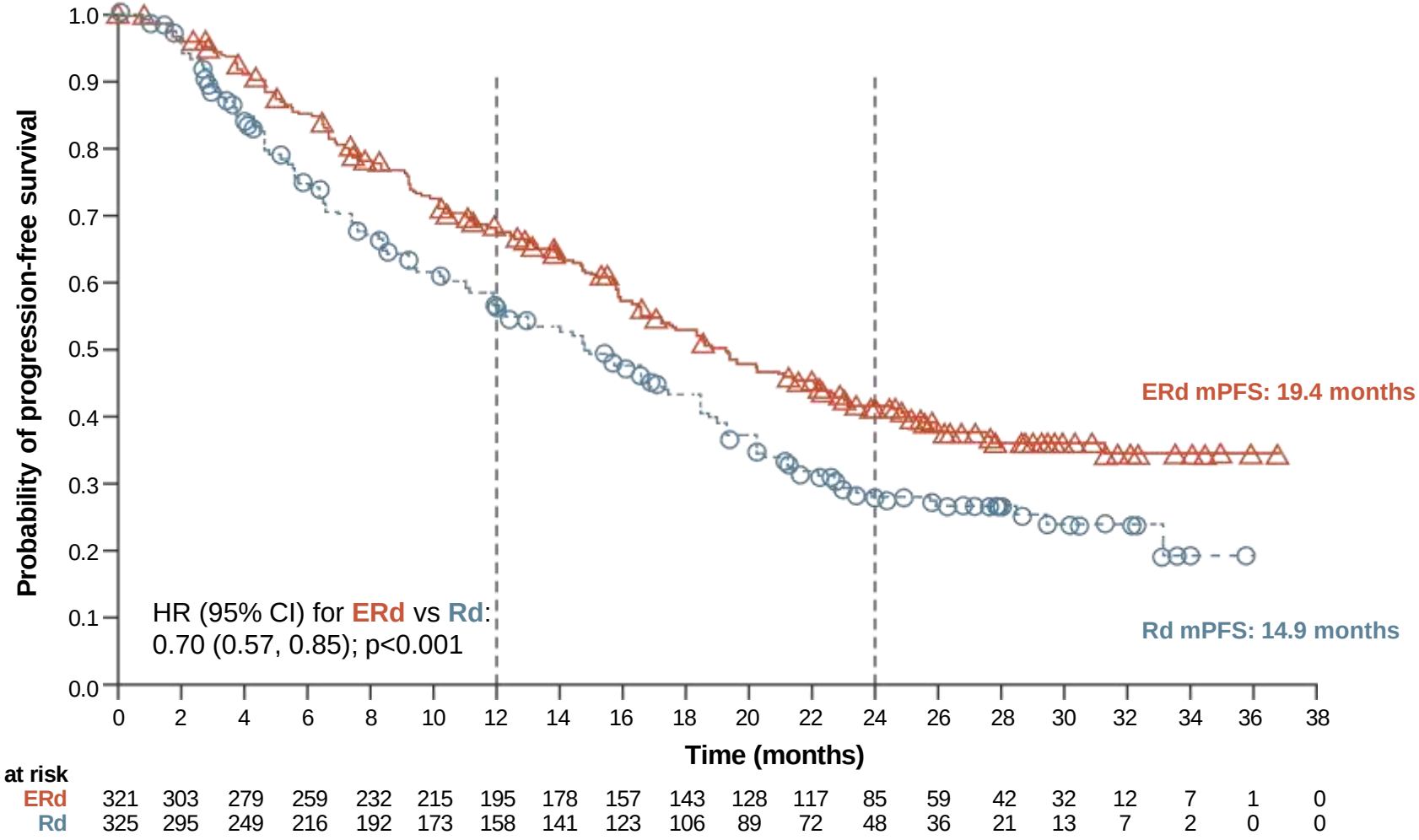


- ICARIA enrolled patients who had previously received treatment with lenalidomide and a PI
- 93% of patients were refractory to lenalidomide, and 71% were refractory to both lenalidomide and a PI
- A PFS benefit was observed with isatuximab in patients with refractoriness to lenalidomide and/or a PI

CI, confidence interval; d, dexamethasone; HR, hazard ratio; I, isatuximab; (m)PFS, (median) progression-free survival; P, pomalidomide; PI, proteasome inhibitor; RRMM, relapsed/refractory multiple myeloma

Attal M, et al. Lancet. 2019;394:2096-2107

PFS BENEFIT WITH ELOTUZUMAB IN PATIENTS WITH RRMM AND 1-3 PRIOR TREATMENTS IN ELOQUENT-2



CI, confidence interval; d, dexamethasone; E, elotuzumab; HR, hazard ratio (m)PFS, (median) progression-free survival; R, lenalidomide; RRMM, relapsed/refractory multiple myeloma

Lonial S, et al. New Engl J Med. 2015;373:621-631

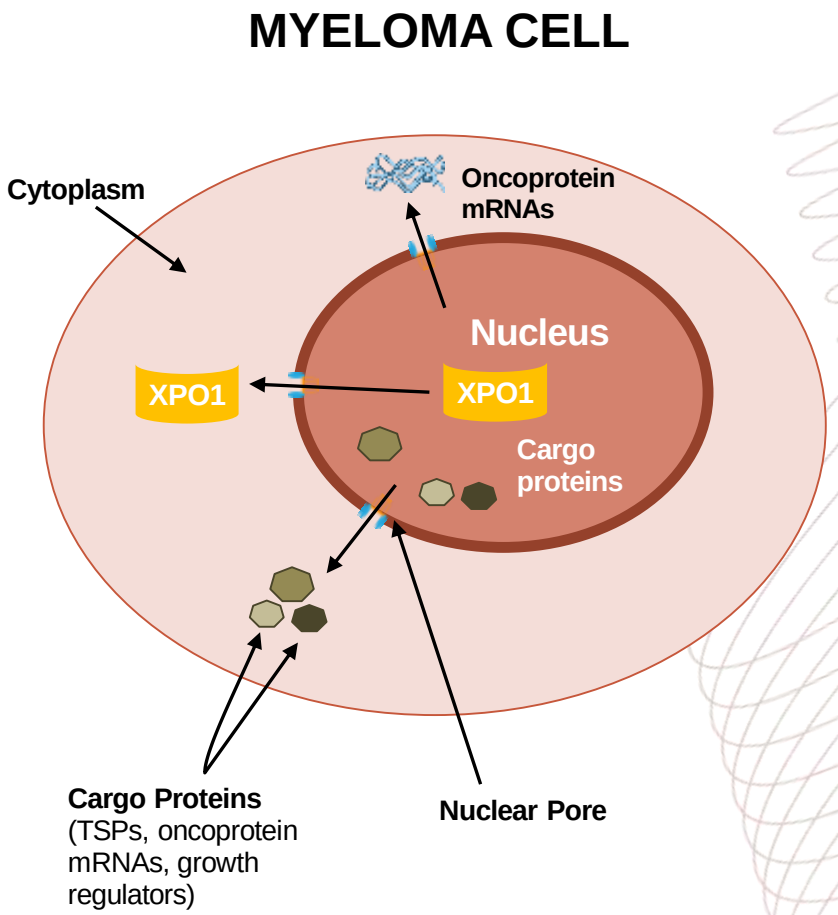
SELINEXOR IS A FIRST IN CLASS ORAL XPO1 INHIBITOR WITH A UNIQUE MECHANISM OF ACTION

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



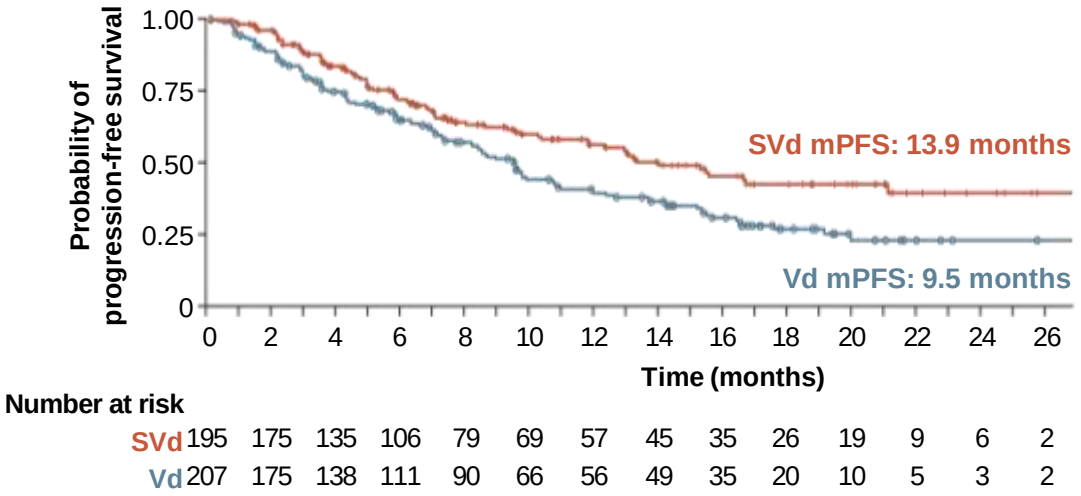
MM, multiple myeloma; TSP, tumour suppressor protein; XPO1, exportin 1

Mo CC, et al. EJHaem. 2023;4:792-810

A STATISTICALLY SIGNIFICANT IMPROVEMENT IN mPFS WITH SVd VS Vd INCLUDING IN PI-NAÏVE PATIENTS

BOSTON investigated SVd vs Vd in patients with RRMM treated with 1-3 prior therapies

ITT population[1]



HR (95% CI) for SVd vs Vd:
0.70 (0.53, 0.93); p=0.0075

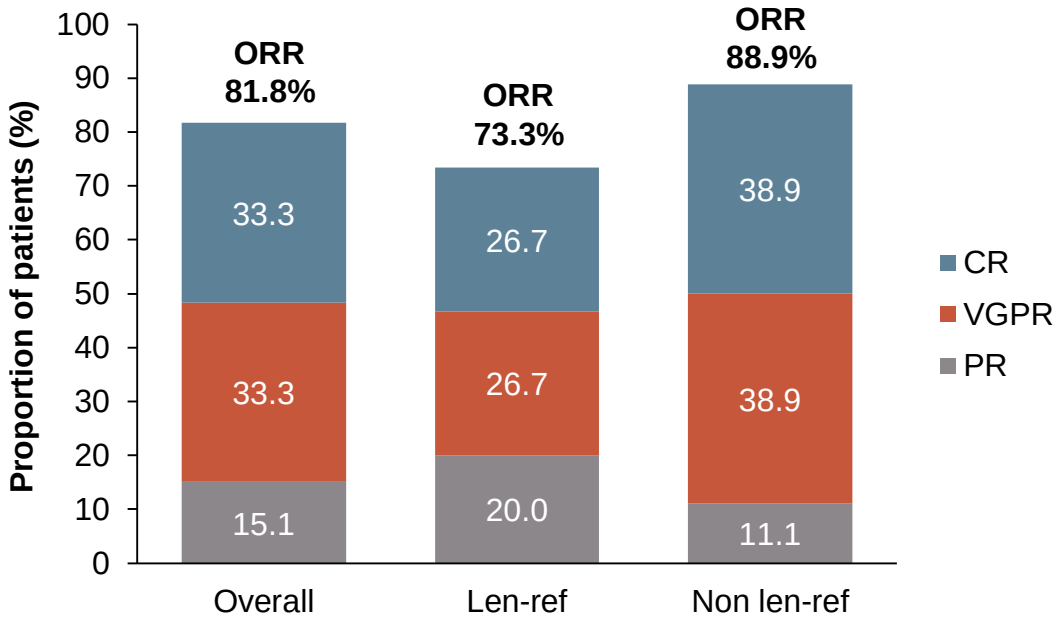
Subgroup analyses[2]

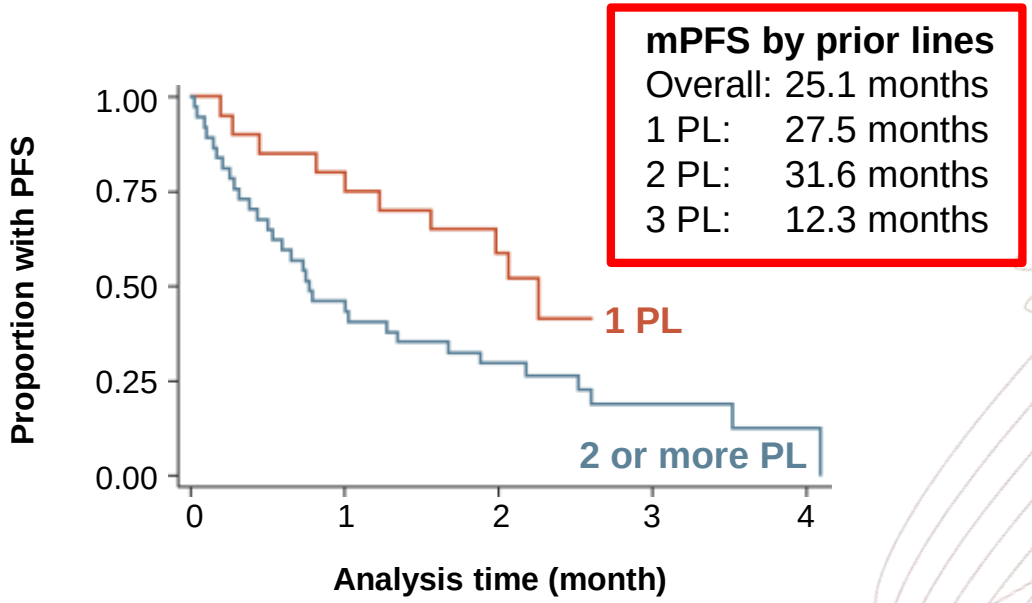
	1 prior LOT		PI-naïve		Bortezomib-naïve	
	SVd (n=99)	Vd (n=99)	SVd (n=47)	Vd (n=48)	SVd (n=61)	Vd (n=62)
Median PFS, mo (95% CI)	**21.0** (13.2-NR)	**10.7** (7.3-16.4)	**29.5** (27.5-NR)	**9.7** (8.4-23.7)	**29.5** (24.8-NR)	**9.7** (8.4-17.5)
HR (95% CI); two-sided p-value	**0.62** (0.41-0.95); 0.028		**0.29** (0.14-0.63); <0.001		**0.35** (0.18-0.68); 0.002	

CI, confidence interval; d, dexamethasone; HR, hazard ratio; ITT, intent to treat; LOT, line of therapy; mPFS, median progression-free survival; NR, not reached; PI, proteasome inhibitor; RRMM, relapsed/refractory multiple myeloma; S, selinexor; V, bortezomib

1. Grosicki S, et al. Lancet. 2020;396:1563-1573; 2. Mateos M-V, et al. Hemasphere. 2023;7(Suppl):e7454106

EFFICACY AND SAFETY OF QUADRUPLET THERAPY WITH S-DVd IN THE PHASE 2 GEM-SELIBORDARA TRIAL





Most common grade ≥3 AEs[a]: Thrombocytopenia (39.4%), infection (30.3%), neutropenia (21.2%), asthenia/fatigue (18.2%), nausea/vomiting (9.1%), anaemia (6.1%)

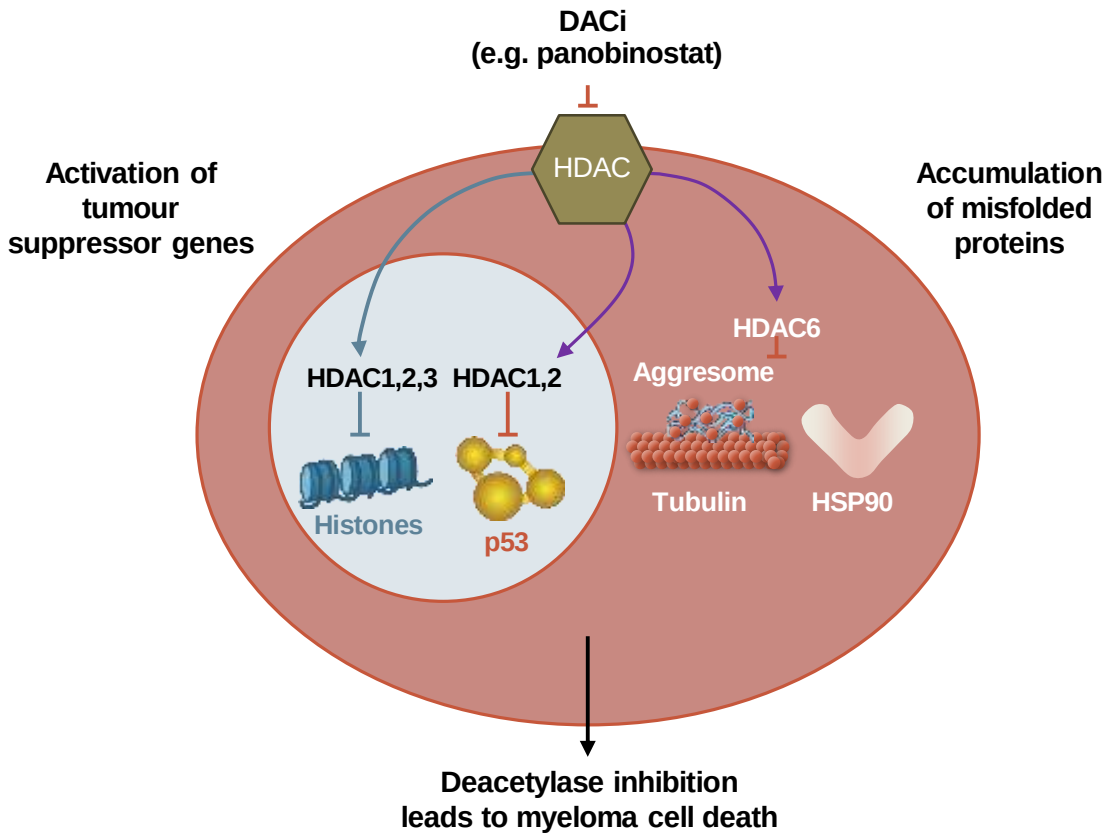
The study comprised two parts: Part 1 included 24 patients with ≥3 prior therapies, and Part 2 included 33 patients with ≥1 prior therapies. Data are presented here for Part 2

[a] Affecting ≥5% of patients

AE, adverse event; CR, complete response; d, dexamethasone; D, daratumumab; len-ref, lenalidomide-refractory; mPFS, median progression-free survival; ORR, overall response rate; PL, prior line; PR, partial response; S, selinexor; V, bortezomib; VGPR, very good partial response

González-Calle V, et al. Haematologica. 2024; Online ahead of print (doi: 10.3324/haematol.2023.284089)

PANOBINOSTAT AND PIs ACT SYNERGISTICALLY TO INHIBIT REMOVAL OF MISFOLDED PROTEINS



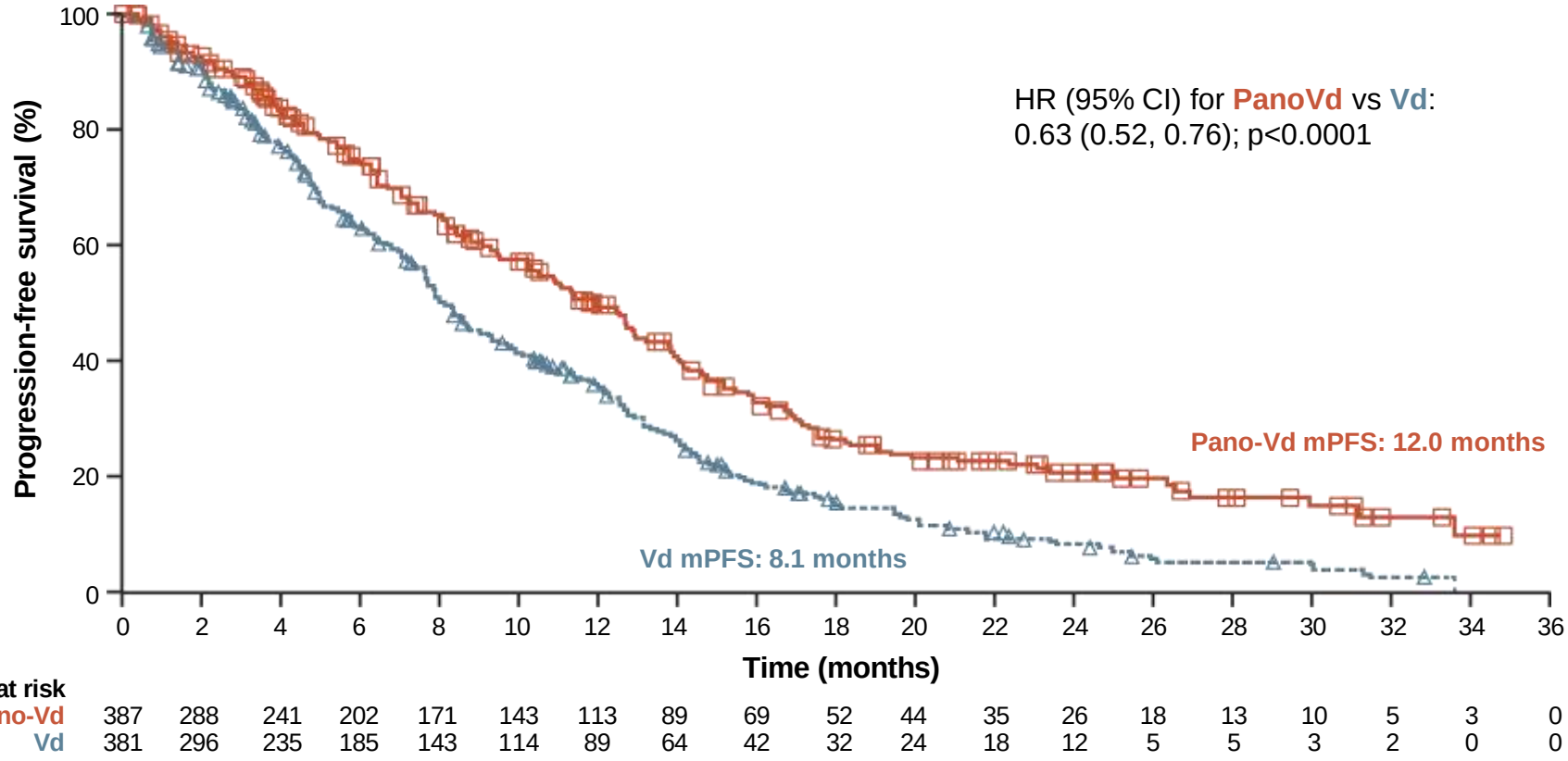
- Overexpression of HDACs is a marker of poor prognosis in patients with MM
- HDACs mediate epigenetic silencing of tumour suppressor genes in MM cells and removal of misfolded proteins by the aggresome
- Dual targeting of the proteasome and aggresome pathways through PIs and DACi may be effective in patients with RRMM

DACi, deacetylase inhibitors; HDAC, histone deacetylase; HSP90, heat-shock protein 90; PI, proteasome inhibitor; (RR)MM, (relapsed/refractory) multiple myeloma

Cornell RF and Kassim AA. Bone Marrow Transplant. 2016;51:479-491

ADDITION OF PANOBINOSTAT TO BORTEZOMIB AND DEXAMETHASONE IMPROVED PFS IN PATIENTS WITH RRMM

The PANORAMA1 phase 3 trial investigated Pano-Vd vs Vd in patients who had received 1-3 previous treatment regimens



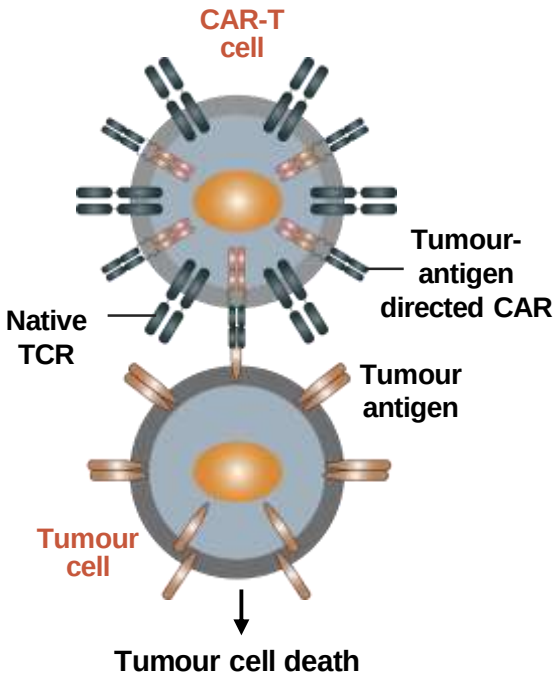
Number at risk																		
Pano-Vd	387	288	241	202	171	143	113	89	69	52	44	35	26	18	13	10	5	3	0
Vd	381	296	235	185	143	114	89	64	42	32	24	18	12	5	5	3	2	0	0

CI, confidence interval; d, dexamethasone; HR, hazard ratio; (m)PFS, (median) progression-free survival; pano, panobinostat; RRMM, relapsed/refractory multiple myeloma; V, bortezomib

San-Miguel JF, et al. Lancet Oncol. 2014;15:1195-1206

EMERGING EVIDENCE SUPPORTS THE USE OF CAR-T THERAPIES IN PATIENTS WITH EARLY RRMM

Mechanism of action[1]



	KarMMa-1[2] (n=140)	KarMMa-3[3] (n=254)	CARTITUDE-1[5] (n=113)	CARTITUDE-4[7] (n=208)
Treatment	ide-cel		cilta-cel	
Patient population	≥3 prior lines of therapy[a]	2-4 prior lines of therapy	≥3 prior lines of therapy[a,b]	1-3 prior lines of therapy[d]
ORR	73%	71%	97%	85%
mPFS, months	8.8	13.8	34.9[6]	NR[e]
mOS, months	19.4	41.4[4]	NR[6,c]	NR[e]

[a] Including a PI, IMiD and an anti-CD38 antibody. [b] Or were double-refractory to a PI and IMiD. [c] mOS was not reached after a median follow-up of 33.4 months. [d] All patients had lenalidomide resistance and had received a PI and IMiD. [e] mOS and mPFS were not reached after a median follow-up of 15.9 months

CAR-T, chimeric antigen receptor T-cell; cilta-cel, ciltacabtagene autoleucel; ide-cel, idecabtagene vicleucel; IMiD, immunomodulatory agent; mOS, median overall survival; mPFS, median progression-free survival; NR, not reported; ORR, overall response rate; PI, proteasome inhibitor; RRMM, relapsed/refractory multiple myeloma; TCR, T-cell receptor

1. Cornell RF and Kassim AA. Bone Marrow Transplant. 2016;51:479-491. 2. Munshi NC, et al. New Engl J Med. 2021;384:705-716; 3. Rodriguez Otero P, et al. Blood. 2023;142 (suppl 1):1028; 4. BMS Press Release. Available from: https://shorturl.at/dhBE7 (last accessed: April 2024); 5. Berdeja JG, et al. Lancet. 2021;398:314-324; 6. Munshi N, et al. Hemasphere. 2023;7(Suppl):e6102468; 7. San-Miguel J, et al. New Engl J Med. 2023;389:335-347

CONCLUSIONS

- PIs, IMiDs and mAbs form the backbone of treatment for MM based on their proven efficacy
- However, most patients ultimately become resistant to these agents and require a switch to treatment with a different MoA
- Selinexor is the first selective nuclear export inhibitor approved for the treatment of RRMM and has demonstrated efficacy in patients with early relapse (1-3 prior therapies)
- CAR-T therapies are efficacious and are approved in heavily pretreated patients and have recently been approved in patients with early relapse

CAR-T, chimeric antigen receptor T-cell; IMiD, immunomodulatory drug; mAbs, monoclonal antibodies; MoA, mechanism of action; PI, proteasome inhibitor; (RR)MM, (relapsed/refractory) multiple myeloma

BEST PRACTICES IN COMBINING AND SEQUENCING THERAPIES FOR OPTIMAL OUTCOMES

Prof. Hermann Einsele

Hematologist-Oncologist

University of Würzburg, Germany

ROLE OF DARATUMUMAB AND LENALIDOMIDE IN 1L TREATMENT

LENALIDOMIDE AND DARATUMUMAB-BASED REGIMENS HAVE BECOME PART OF THE SoC FOR 1L TREATMENT OF NDMM

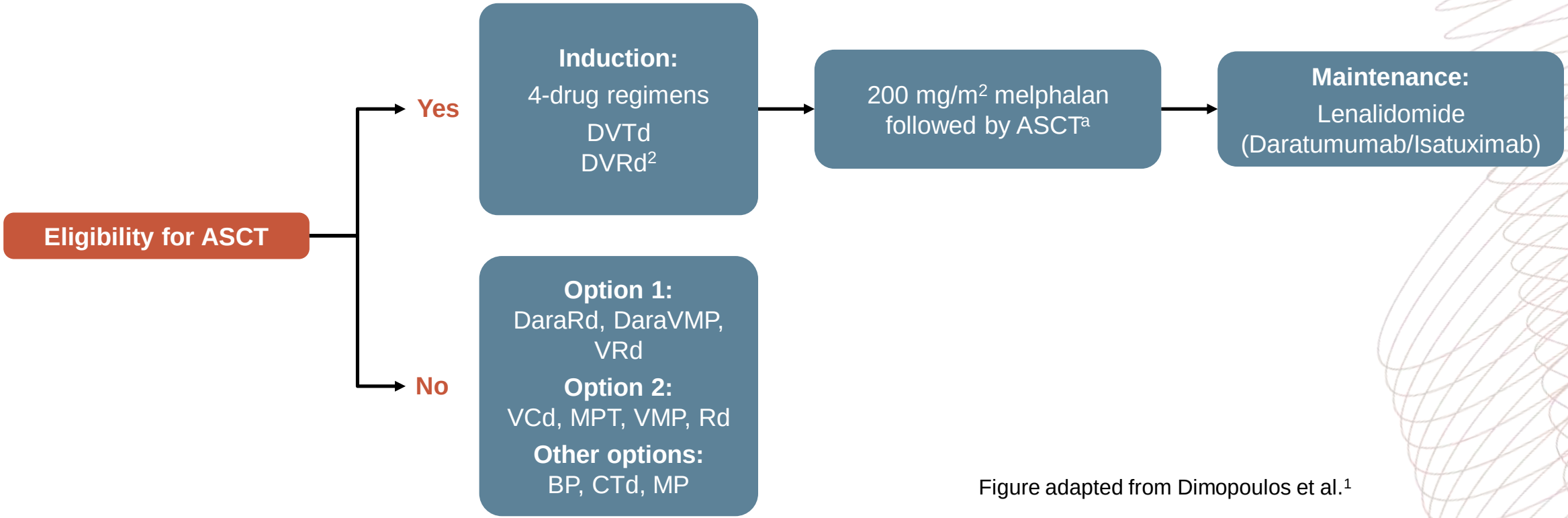


Figure adapted from Dimopoulos et al.[1]

[a] Tandem for high-risk disease or suboptimal response consolidation.

1L, first line; ASCT, autologous stem cell transplantation; B, bendamustine; C, cyclophosphamide; d, dexamethasone; D, daratumumab; M, melphalan; NDMM, newly diagnosed multiple myeloma; P, prednisone; R, lenalidomide; SoC, standard of care; T, thalidomide; V; bortezomib

1. Dimopoulos MA, et al. Ann Oncol. 2021;32:309-322; 2. Sonneveld P, et al. New Engl J Med 2024;390:301-313;

IMPACT OF ADMINISTRATION OF LENALIDOMIDE AND DARATUMUMAB-BASED REGIMENS AT 1L

Administration of lenalidomide and daratumumab-based regimens at 1L could lead to:

A growing population of **PI-naïve** patients at 2L[1]	An increasing need for more effective options in patients with MM **refractory to lenalidomide**[1,2]	A growing population of patients with MM **refractory to anti-CD38-based therapies** in earlier lines of treatment[3]

1L, first line; 2L, second line; d, dexamethasone; D, daratumumab; (ND)MM, (newly diagnosed) multiple myeloma; PI, proteasome inhibitor; R, lenalidomide

1. Dimopoulos MA, et al. Ann Oncol. 2021;32:309-322; 2. de Arriba de la Fuente F, et al. Cancers (Basel) 2022;15:155; 3. Kastritis E, et al. Hemasphere 2023;7:e975

MEDIAN PFS IS SUBOPTIMAL IN LENALIDOMIDE-EXPOSED OR REFRACTORY PATIENTS

	CANDOR[1]		CASTOR[2]		IKEMA[3]		ENDEAVOR[4]		POLLUX[5]		ELOQUENT-2[6,7]		OPTIMISMM[8a]		APOLLO[9a]		EMNO2[10a]	BOSTON[11,12]	
	DKd	Kd	DVd	Vd	IKd	Kd	Kd	Vd	DRd	Rd	ERd	Rd	PVd	Vd	DPd	Pd	KPd	SVd	Vd
mPFS, months																			
ITT	28.6	15.2	16.7	7.1	NC	19.2	18.7	9.4	44.5	17.5	19.4	14.9	11.2	7.1	12.4	6.9	19.1	13.9	9.5
Lena-exposed	25.9	11.1	-	-	NC	16.1	12.9	7.3	38.8	18.6	24.9	7.4	11.2	7.1	12.4	6.9	19.1	-	-
Lena-refractory	28.1	11.1	7.8	4.9	NC	15.7	8.6	6.6	-	-	-	-	9.5	5.6	9.9	6.5	-	10.2	7.1

In IKEMA, the MRD negativity rate was 33.5% in the ITT population and 29.8% in the lenalidomide-refractory population[13]

[a] All patients in OPTIMISMM, APOLLO and EMNO2 were previously exposed to lenalidomide

d, dexamethasone; D, daratumumab; E, elotuzumab; I, isatuximab; ITT, intention to treat; K, carfilzomib; Lena, lenalidomide; mPFS, median progression-free survival; MRD, minimal residual disease; NC, not calculated; P, pomalidomide; R, lenalidomide; S, selinexor; V, bortezomib

1. Usmani S, et al. Lancet Oncol. 2022;23:65-76; 2. Mateos M-V, et al. Clin Lymphoma, Myeloma Leuk. 2020;20:509-518;
3. Moreau P, et al. Lancet. 2021;397:2361-2371; 4. Moreau P, et al. Leukemia. 2017;31:115-122; 5. Bahlis N, et al. Leukemia. 2020;34:1875-1884;
6. Lonial S, et al. N Engl J Med. 2015:373:621-631; 7. Lonial S, et al. J Clin Oncol. 2016;34(suppl 15):8037; 8. Richardson P, et al. Lancet Oncol. 2019;20:781-794;
9. Dimopoulos MA, et al. Lancet Oncol. 2021;22:801-812; 10. Sonneveld P, et al. Hemasphere. 2022;6:e786; 11. Grosicki S, et al. Lancet 2020;396:1563-73; 12. Lelou X, et al. J Clin Oncol 2021;39(15_suppl):8024; 13. Martin T et al. Blood Cancer J 2023;13:72.

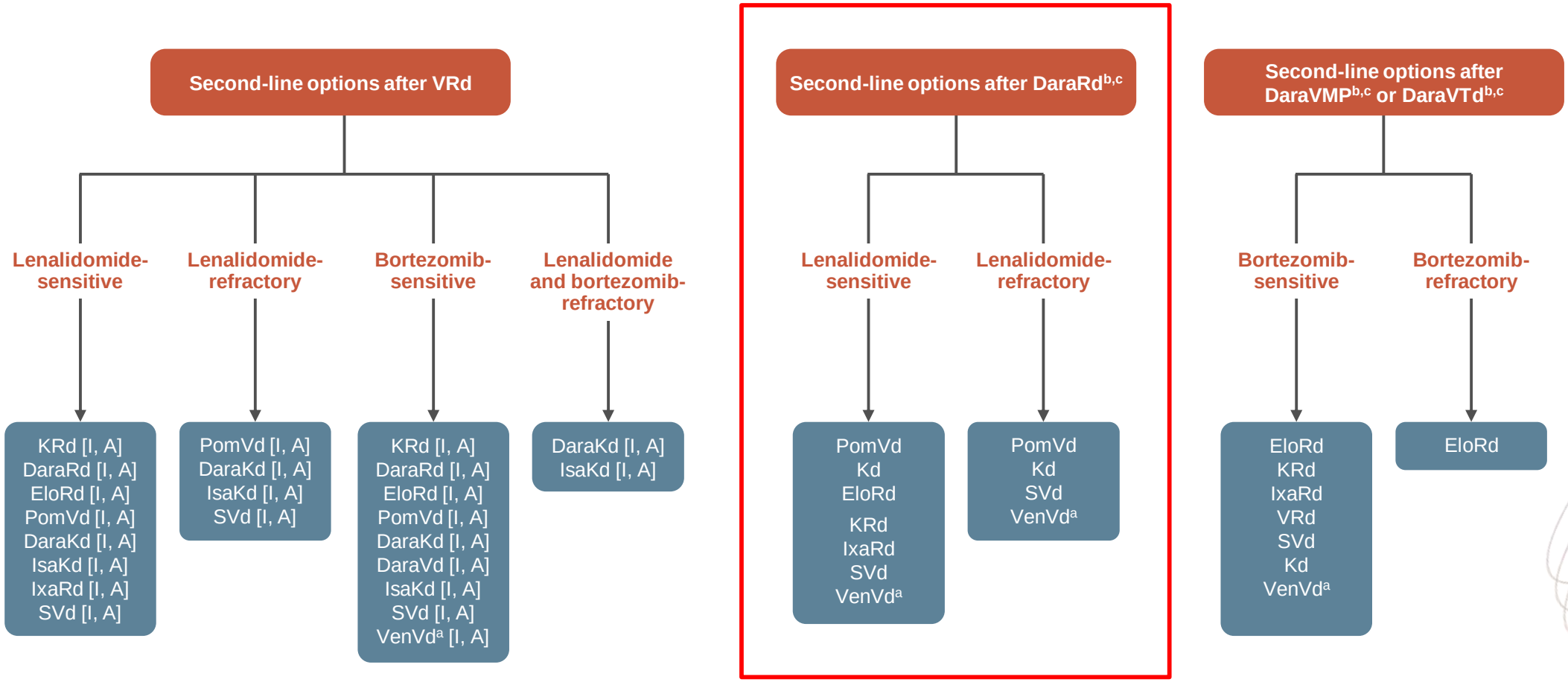
OUTCOMES ARE POOR FOR PATIENTS PREVIOUSLY EXPOSED TO CD38 MONOCLONAL ANTIBODIES (TRIPLE CLASS EXPOSED)

Study	Treatment history	mOS, months	Response to subsequent treatment	
			mPFS, months	ORR, %
MAMMOTH[1a]	Double refractory	11.2	3.4	38
	Triple or quad-refractory	9.2		29
	Penta-refractory	5.6		30
LocoMMotion[2b]	Triple class exposed	12.4	4.6	30
Connect MM registry[3c]	1-3 prior lines	16.8	5.6	28
	≥4 prior lines	10.0	3.0	

[a] All patients are refractory to a CD38 mAb plus PIs and/or IMiDs; [b] Received ≥1 PI, IMiD and CD38 mAb; [c] Including lenalidomide and a CD38 mAb
IMiD, immunomodulatory drug; mAb, monoclonal antibody; MM, multiple myeloma; mOS, median overall survival; mPFS, median progression-free survival; ORR, overall response rate; PI, proteasome inhibitor

1. Gandhi UH, et al. Leukemia. 2019;33:2266-2275; 2. Mateos M-V, et al. Leukemia. 2022;36:1371-1376; 3. Abonour R, et al. Hemasphere. 2023;7(Suppl):e52503e2

ESMO GUIDELINES: SECOND-LINE TREATMENT OPTIONS



[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; Elo, elotuzumab; Isa, isatuximab; Ixa, ixazomib; K, carfilzomib; M, melphalan; P, prednisone; Pom, pomalidomide; R, lenalidomide; S, selinexor; V, bortezomib; Ven, venetoclax

Dimopoulos MA, et al. Ann Oncol. 2021;32(3):309-322

SVd IS THE ONLY APPROVED TRIPLET THERAPY ALLOWING DOUBLE CLASS SWITCH IN DRd-EXPOSED PATIENTS

	ESMO treatment recommendations after DRd (based on panel consensus)[a,b]			Class switch
	Triplet/doublet combination			
Lenalidomide-sensitive	–	Carfilzomib	Dexamethasone	Single
	Pomalidomide	Bortezomib	Dexamethasone	Single
	Lenalidomide	Carfilzomib	Dexamethasone	Single
	Lenalidomide	Elotuzumab	Dexamethasone	Single
	Lenalidomide	Isatuximab	Dexamethasone	None
	Selinexor	Bortezomib	Dexamethasone	**Double**
Lenalidomide-refractory	–	Carfilzomib	Dexamethasone	Single
	Pomalidomide	Bortezomib	Dexamethasone	Single
	Selinexor	Bortezomib	Dexamethasone	**Double**

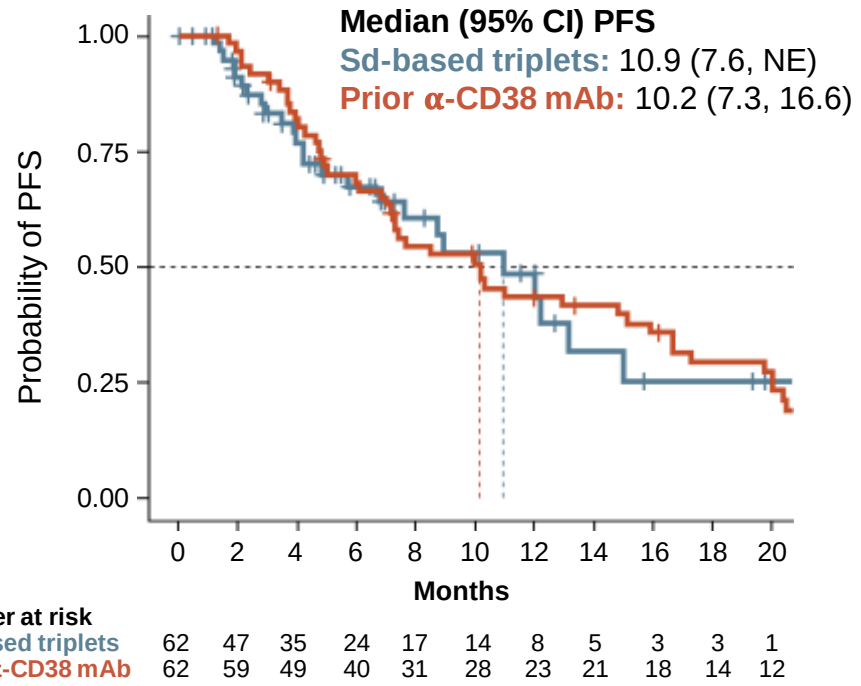
[a] Venetoclax-based combinations are an option for patients with t(11;14)
[b] Patients who progress while on monthly daratumumab are considered as daratumumab-refractory

d, dexamethasone; D, daratumumab; R, lenalidomide; S, selinexor; V, bortezomib

Table created from information in Dimopoulos MA, et al. Ann Oncol. 2021;32(3):309-322

SELINEXOR-BASED TRIPLETS IN PATIENTS PREVIOUSLY TREATED WITH CD38 mAb

Sd-based triplets vs prior α-CD38 mAb



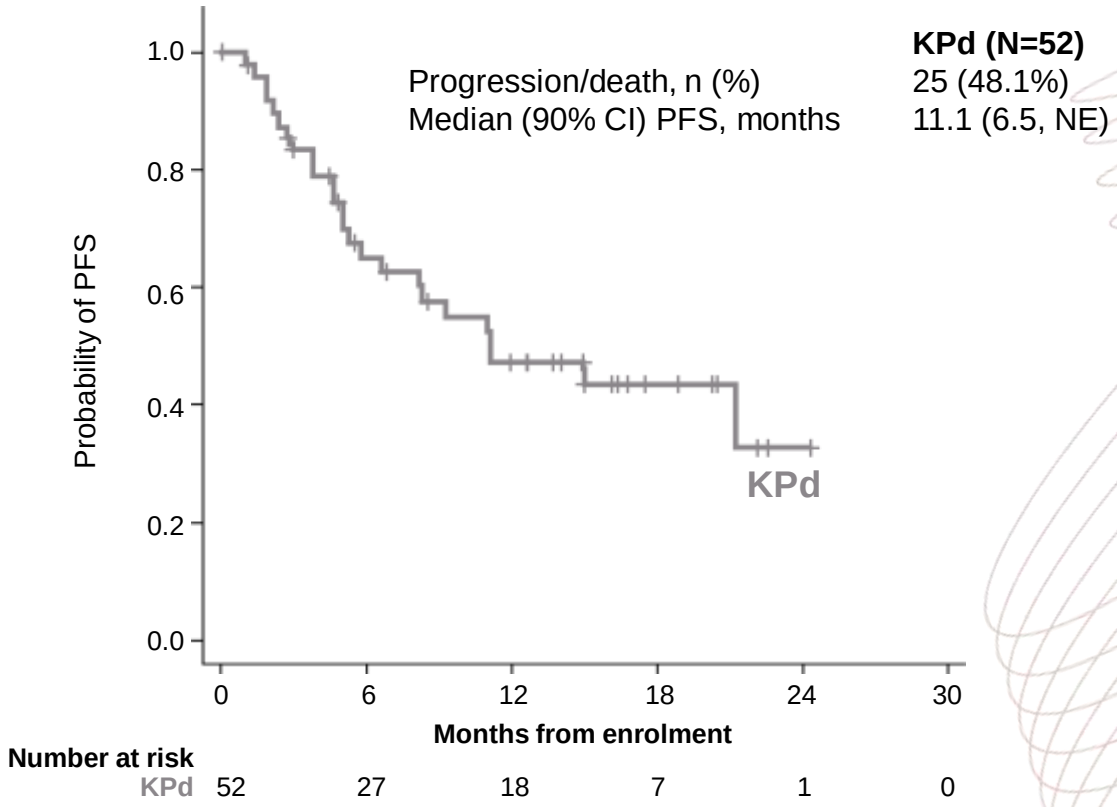
- Efficacy and safety of SPd, SVd and SKd was analysed in a subset of patients (n=62) from STOMP and BOSTON previously treated with a CD38 mAb
  - 74% refractory to lenalidomide; 85% refractory to daratumumab
- ORR and mPFS were comparable between the selinexor-based treatment and prior CD38 mAb treatment:
  - ORR: 58.1% vs 63.8%
  - mPFS: 10.9 vs 10.2 months
  - mOS: 20.4 months with a selinexor-based triplet
- Adverse events were generally manageable with standard supportive care and dose modifications
- A Phase 3 RCT is ongoing to compare SPd vs EloPd in patients previously treated with an IMiD, PI and CD38 mAb (NCT05028348)

d, dexamethasone; Elo, elotuzumab; IMiD, immunomodulatory drug; K, carfilzomib; mAb, monoclonal antibody; mOS, median overall survival; (m)PFS, (median) progression-free survival; NE, not evaluable; ORR, overall response rate; P, pomalidomide; PI, proteasome inhibitor; RCT, randomised controlled trial; S, selinexor; V, bortezomib

Schiller GJ, et al. Clin Lymphoma Myeloma Leuk. 2023;23:e286-e296.e4

KPd FOR LENALIDOMIDE REFRACTORY PATIENTS

- SELECT phase 2 study enrolled 52 patients with early RRMM
  - 100% were lenalidomide-refractory
  - 75% were lenalidomide and daratumumab-refractory
- All patients were treated with KPd
  - ORR: 58% (primary endpoint not met)
  - mPFS: 11.1 months
  - mOS: 18.8 months
- Adverse events were consistent with the known safety profile of these agents



CI, confidence interval; d, dexamethasone; K, carfilzomib; mOS, median overall survival; m(PFS), (median) progression-free survival; NE, not evaluable; ORR, overall response rate; P, pomalidomide; RRMM, relapsed/refractory multiple myeloma

Perrot A, et al. Leuk Lymphoma. 2024; Online ahead of print (doi: 10.1080/10428194.2024.2322030)

CURRENT TREATMENT OPTIONS FOR TRIPLE CLASS REFRACTORY PATIENTS

- **XPO1 inhibitor:** Selinexor[1]
- **Peptide-drug conjugate:** Melflufen[2]

Non-T-cell-directed therapies

- **CAR-T therapy**
  - Idecabtagene vicleucel[3]
  - Ciltacabtagene autoleucel[4]
- **Bispecific antibodies**
  - Teclistamab[5]
  - Talquetamab[6]
  - Elranatamab[7]

T-cell-directed therapies

CAR-T, chimeric antigen receptor T-cell; IMiD, immunomodulatory drug; mAb, monoclonal antibody; PI, proteasome inhibitor; SmPC, Summary of Product Characteristics; XPO1, exportin 1

1. Nexpovio® (selinexor). SmPC (August 2023). Stemline Therapeutics B.V.; 2. Pepaxti® (melphalan flufenamide). SmPC (March 2024). Oncopeptides AB (publ); 3. Abecma® (idecabtagene vicleucel). SmPC (July 2023). Bristol-Myers Squibb Pharma EEIG; 4. Carvykti® (ciltacabtagene autoleucel). SmPC (December 2023). Janssen-Cilag International NV; 5. Tecvayli® (teclistamab) SmPC (February 2024). Janssen-Cilag International NV; 6. Talvey® (talquetamab). SmPC (March 2024). Janssen-Cilag International NV; 7. Elrexfio® (elranatamab). SmPC (January 2024). Pfizer Europe MA EEIG. All available from https://www.ema.europa.eu/en/medicines. Last accessed 21 March 2024

CAR-T THERAPY AND BISPECIFIC ANTIBODIES: CHALLENGES

- Both **CAR-T therapy** and **bispecific antibodies** have **significantly improved outcomes** for patients with ≥3 prior lines of therapy[1-5]
- Both are associated with challenges:

CAR-T THERAPY	BISPECIFIC ANTIBODIES
• Complex logistics and high cost can be a barrier to widespread use[6] • Risk of adverse reactions including CRS, infections, ICANS and secondary cancers[7,8] • CAR-T cell exhaustion can lead to relapse[9]	• Require ongoing treatment[10] • Risk of adverse reactions including CRS, infections and ICANS[7] • Continuous exposure to a bispecific can lead to T-cell exhaustion and treatment resistance[11]

Timing and sequencing strategies for **optimal efficacy and safety** remain unclear

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

1. Berdeja JG, et al. Lancet. 2021;398:314-324; 2. Munshi NC, et al. New Engl J Med. 2021;384:705-716; 3. Moreau P, et al. New Engl J Med. 2022;387:495-505; 4. Chari A, et al. New Engl J Med. 2022;387:2232-2244; 5. Lesokhin AM, et al. Nat Med. 2023;29:2259-2267; 6. Gajra A, et al. Pharmaceut Med. 2022;36:163-171; 7. Khanam R, et al. J Clin Med. 2023;12:5539; 8. Verdun N and Marks P. New Engl J Med. 2024;390:584-586; 9. Zhu X, et al. Front Cell Dev Biol. 2022;10:1034257; 10. Lancman G, et al. Blood Cancer Discov. 2021;2:423-433; 11. Philipp N, et al. Blood. 2022;140:1104-1118

CAN TREATMENT SEQUENCING MAXIMISE THE POTENTIAL OF T-CELL DIRECTED THERAPIES?

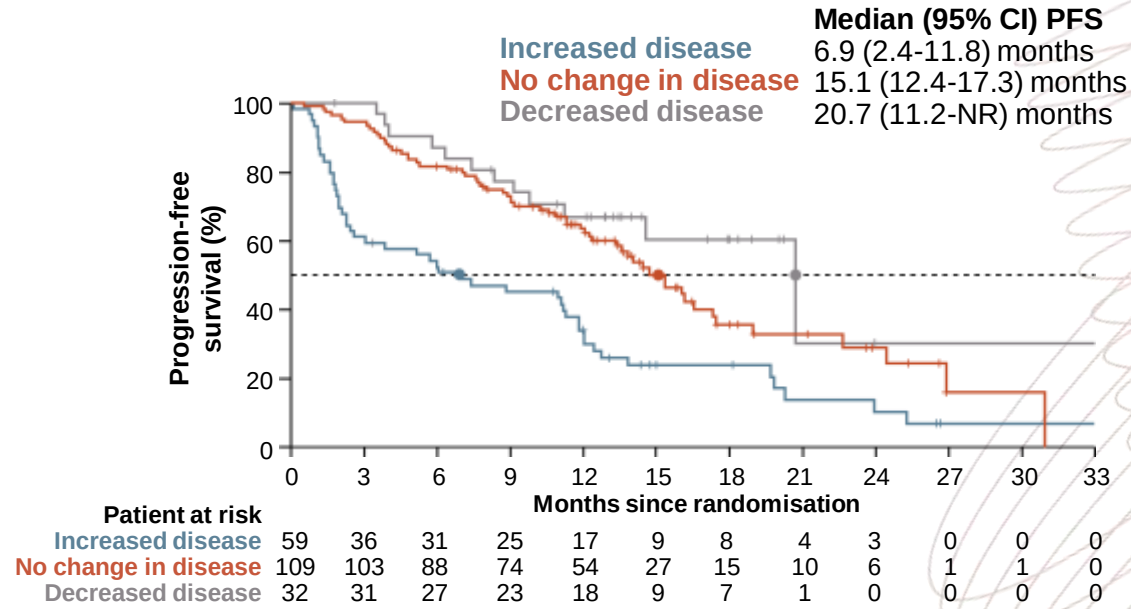
- Use of bridging therapies
- Earlier use of BCMA-TT
- Optimal sequencing of BCMA-TT
- Use of T-cell sparing agents

BCMA-TT, B-cell maturation antigen targeted therapies

IMPACT OF BRIDGING THERAPY ON DISEASE BURDEN, EFFICACY AND SAFETY

- In the KarMMA-3 phase 3 trial, 213 patients received bridging therapy[a] prior to ida-cel infusion
- **Change in disease burden after bridging:** 28% increased, 51% no change, 15% decreased
- Patients with **decreased or no change in disease burden** achieved a **numerically longer PFS** and **higher ORRs** with ida-cel vs those with increased disease burden
- The **decreased disease burden** group had the lowest incidence of high-grade CRS and iiNT events

PFS by change in disease burden during bridging therapy



Patients with increased disease burden were more likely to have triple class refractory disease:

Less pretreatment prior to CAR-T therapy may result in more effective and safer bridging options

[a] Either DPd, DVd, IRd, Kd or EloPd

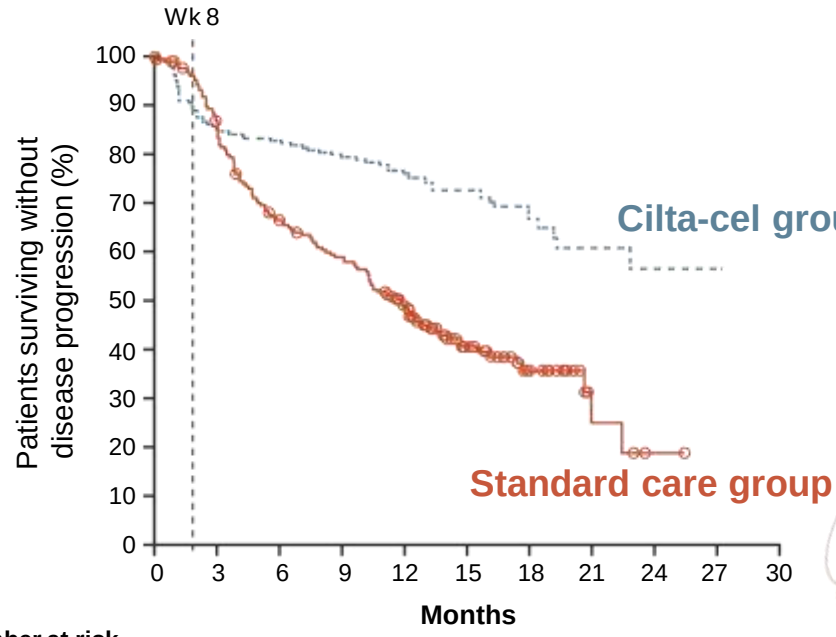
CAR-T, chimeric antigen receptor T-cell; CI, confidence interval; CRS, cytokine release syndrome; d, dexamethasone; D, daratumumab; Elo, elotuzumab; I; ixazomib; ida-cel, idecabtagene vicleucel; iiNT, investigator-identified neurotoxicity; K, carfilzomib; NR, not reached; ORR, overall response rate; P, pomalidomide; PFS, progression-free survival; R, lenalidomide; V, bortezomib

Einsele, H, et al. Presented at the 2023 International Myeloma Society Annual Meeting. 27-30 September 2023; Athens, Greece. Abstract P008

CARTITUDE-4: CILTA-CEL IN EARLIER TREATMENT LINES

- Patients who had received 1-3 lines of therapy were randomised to cilta-cel (n=208) or standard care (n=211[a])
- All patients were refractory to lenalidomide; 14.4% of cilta-cel group and 15.6% of standard care group were triple class refractory
- Cilta-cel resulted in a significantly lower risk of disease progression or death than standard care (HR, 0.26; 95% CI, 0.18 to 0.38; p<0.001)
- ORRs were 84.6% in the cilta-cel group vs 67.3% in the standard care group
- Cilta-cel may have a better side effect profile when used earlier in treatment

Progression-free survival



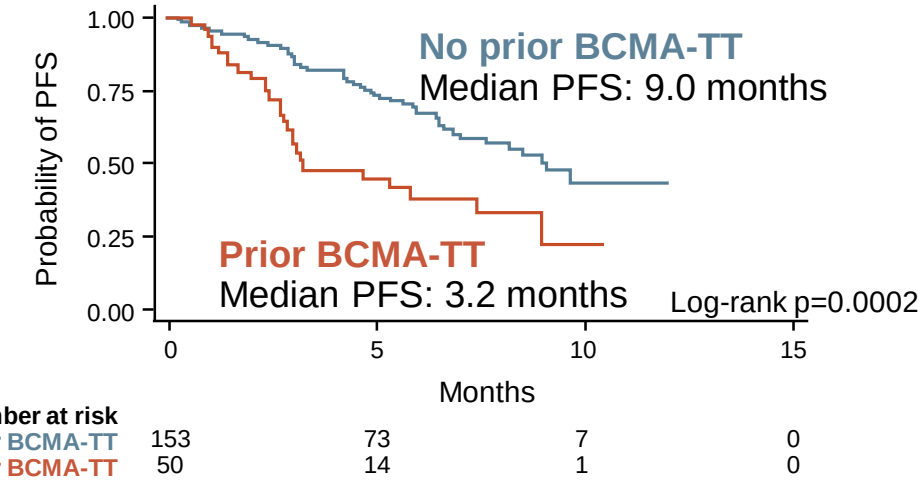
Number at risk											
Cilta-cel group	208	177	172	166	146	94	45	22	9	1	0
Standard-care group	211	176	133	116	88	46	20	4	1	0	0

[a] 87% received daratumumab, pomalidomide and dexamethasone and 13% received daratumumab, bortezomib and dexamethasone
cilta-cel, ciltacabtagene autoleucel; CI, confidence interval; HR, hazard ratio; ORR, overall response rate

San-Miguel J, et al. New Engl J Med. 2023;389:335-347

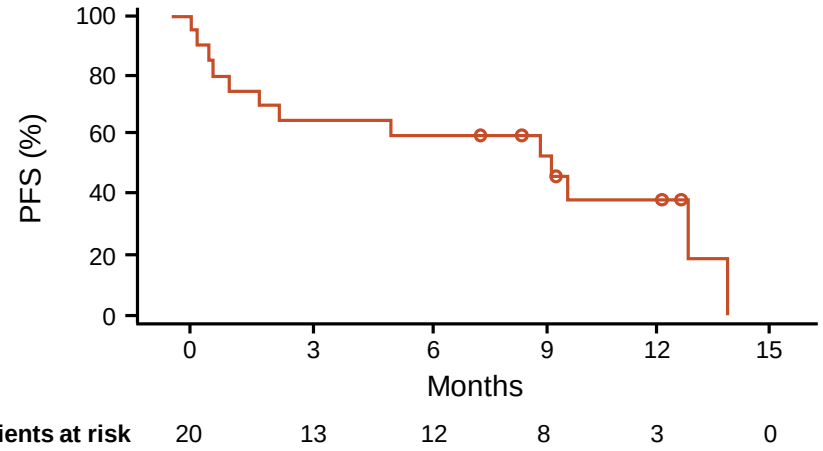
CAR-T THERAPY: RESPONSES MAY BE SUBOPTIMAL IN PATIENTS PREVIOUSLY EXPOSED TO A BCMA-TT

Real-world experience[1]



- Patients with prior BCMA-TT experience[a] (n=50) or no prior BCMA-TT experience (n=153) were treated with ida-cel
- Prior BMCA-TT cohort had a lower ORR (74% vs 88% and lower mPFS (3.2 vs 9.0 months) than the cohort without prior BMCA-TT

CARTITUDE-2 cohort C[2]



- Cohort C is evaluating cilta-cel in 20 patients with heavily pretreated RRMM, previously exposed to BCMA-TT[b]
- ORR and mPFS were lower than in CARTITUDE-1[3] where patients had no prior BCMA-TT experience (60.0% vs 98% and 9.1 vs 34.9 months)

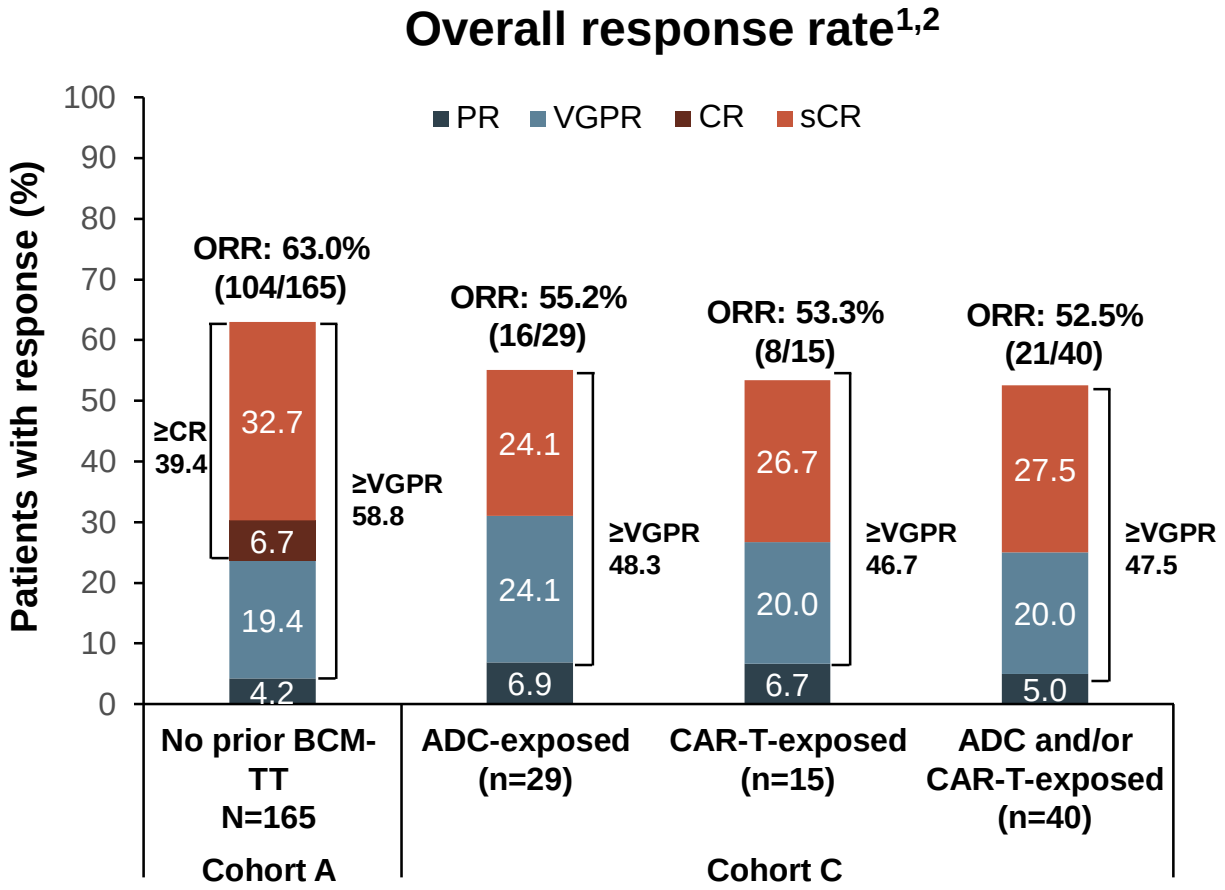
[a] 38 antibody-drug conjugate, seven bispecific, five CAR-T

[b] 13 antibody-drug conjugate, seven bispecific

BCMA-TT, B-cell maturation antigen-targeted therapy; CAR-T, chimeric antigen receptor T-cell; cilta-cel, ciltacabtagene autoleucel; ida-cel, idecabtagene vicleucel; (m)PFS, (median) progression-free survival; ORR, overall response rate; RRMM, relapsed/refractory multiple myeloma

1. Ferreri CJ, et al. Blood Cancer J. 2023;13:117; 2. Cohen AD, et al. Blood. 2023;141:219-230; 3. Lin Y, et al. J Clin Oncol. 2023;41(16_Suppl):8009

BISPECIFICS: SIMILAR RESPONSE IN PATIENTS WITH OR WITHOUT PRIOR EXPOSURE TO A BCMA-TT



- The MajesTEC-1 phase 1/2 study enrolled 165 patients who were BCMA-TT naïve (cohort A) and 40 patients with prior BCMA-TT exposure (cohort C)[a]
- ORR was similar between cohorts A and C (63.0 vs 52.5%)
- ORR was also similar between patients exposed to ADCs or CAR-T therapy (55.2% vs 53.3%)

[a] 29 ADC, 15 CAR-T

ADC, antibody-drug conjugate; BCMA-TT, B-cell maturation antigen targeted therapy; CAR-T, chimeric antigen receptor T cell; CR, complete response; ORR, overall response; PR, partial response; sCR, stringent complete response; VGPR, very good partial response

1. Moreau P, et al. N Engl J Med. 2022;387:495-505; 2. Touzeau C, et al. Hemasphere. 2022;6:85-86 (presented during the European Hematology Association 2022 Congress; Oral abstract #S184); 3. https://multiplemyelomahub.com/medical-information/teclistamab-for-relapsedrefractory-multiple-myeloma-updated-phase-iii-majestec-1-results. Last accessed April 2024

USE OF T-CELL SPARING AGENTS TO IMPROVE T-CELL FITNESS

- T-cell exhaustion can limit the effectiveness of T-cell-directed therapies such as CAR-T therapies and bispecific antibodies
- Multiple factors can contribute to T-cell exhaustion including age, disease burden and prior cancer treatments
- Use of T-cell-sparing rather than T-cell-depleting agents prior to T-cell-directed therapies has the potential to improve treatment responses

T-cell-sparing	T-cell-depleting
XPO1 inhibitors	PIs
IMiDs	Alkylating agents
E3 ligase modulators	IgG1 antibody therapies
Checkpoint inhibitors	

CAR-T, chimeric antigen receptor T-cell; IgG, immunoglobulin G; IMiD, immunomodulatory drug; PI, proteasome inhibitor, XPO1, exportin 1

Binder AF, et al. Front Immunol 2023;14:1275329

CONCLUSIONS

- Increasing numbers of patients with MM are lenalidomide and/or daratumumab-refractory at early relapse; the prognosis for these patients is poor
- Class switch is recommended to improve outcomes for these patients
  - Double class switch can be achieved if patients switch from DRd to SVd
- Once patients are refractory to an IMiD, PI and CD38 mAb (triple class refractory), treatment options include an XPO1 inhibitor, ADC or T-cell-directed therapy
- T-cell-directed therapies have improved the prognosis for triple class refractory patients, but there are still challenges to be overcome
- Optimisation of treatment sequencing with T-cell sparing treatments, such as IMiDs and XPO1 inhibitors, after early relapse may maximise the potential of T-cell-directed therapies

ADC, antibody-drug conjugate; d, dexamethasone; D, daratumumab; IMiD, immunomodulatory drug; mAb, monoclonal antibody; MM, multiple myeloma; PI, proteasome inhibitor; R, lenalidomide; S, selinexor; V, bortezomib; XPO1, exportin 1

MANY THANKS FOR YOUR KIND ATTENTION!

Uniklinikum Würzburg

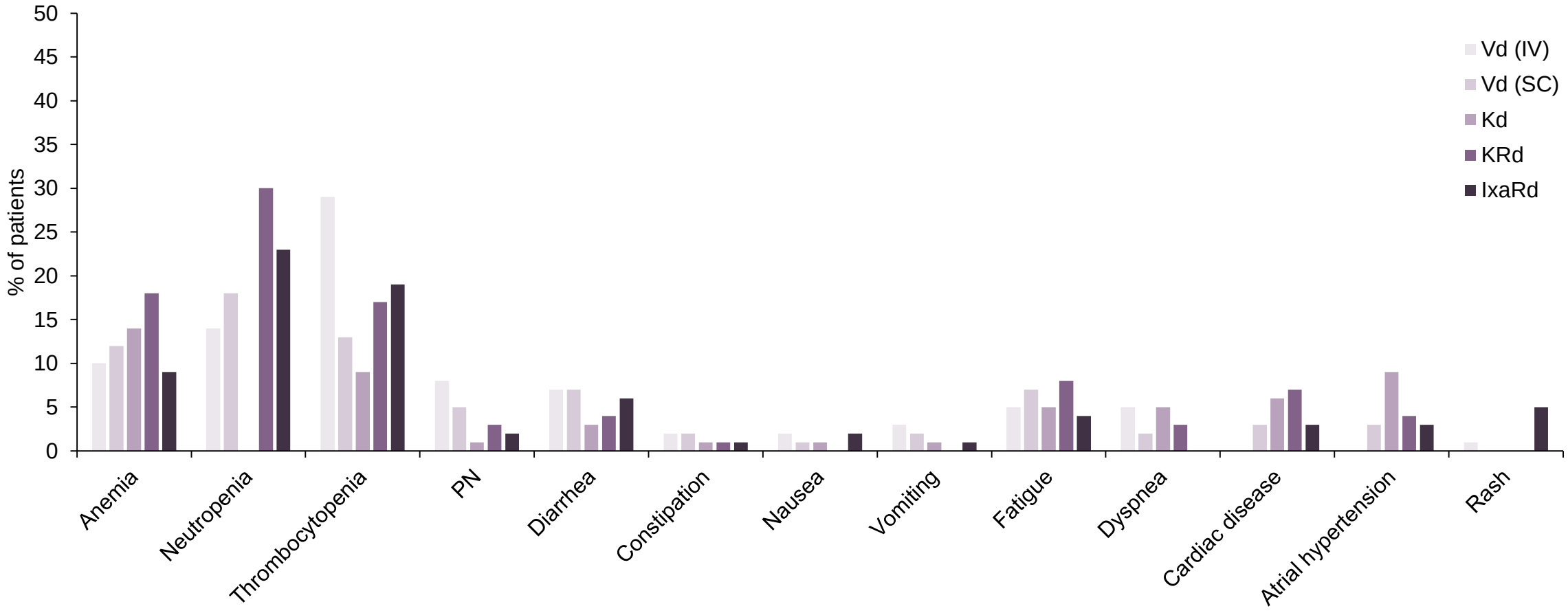
INSIGHTS FROM CLINICAL PRACTICE ON HOW TO MANAGE TOLERABILITY AND SAFETY

Assoc. Prof. Joshua Richter

Haematologist-Oncologist

Icahn School of Medicine at Mount Sinai, USA

PROTEASOME INHIBITORS: MOST COMMON GRADE ≥3 SIDE EFFECTS REPORTED IN PIVOTAL TRIALS

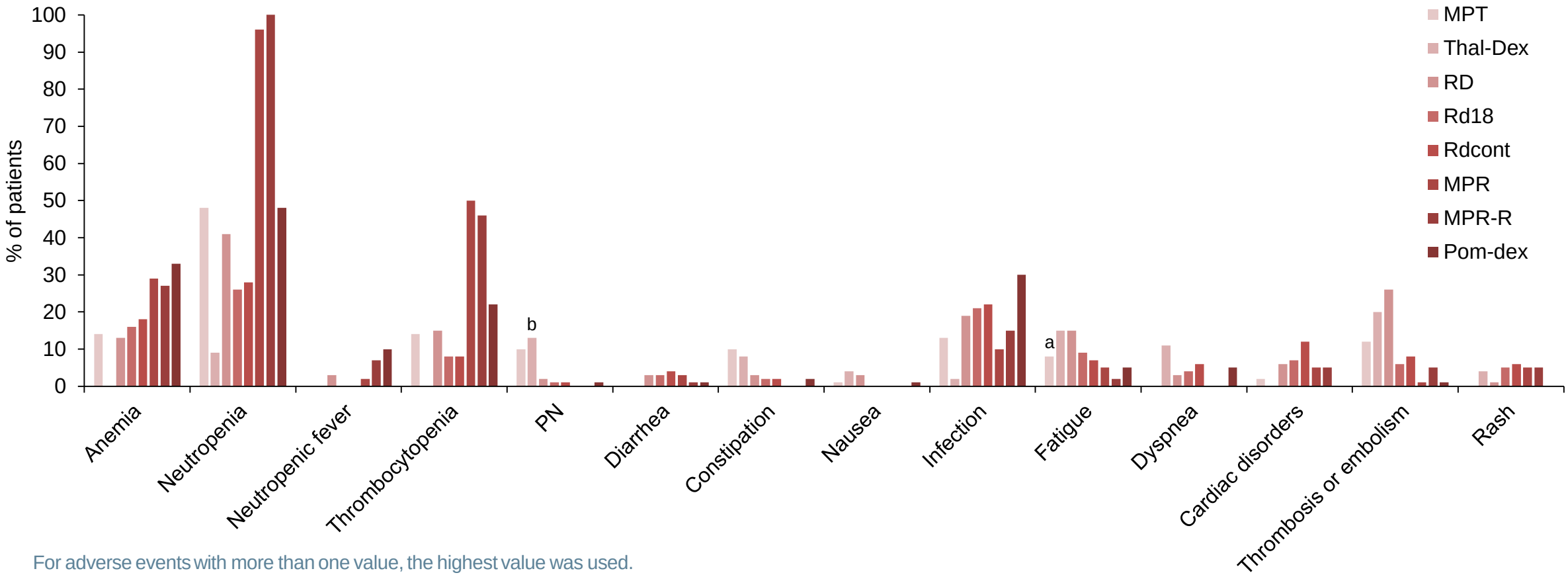


For adverse events with more than one value, the highest value was used. 21% of patients in one of the Vd (SC) studies received bortezomib IV. Cardiac disease included cardiac failure and ischemic heart disease

IV, intravenous; IxaRd, ixazomib plus lenalidomide plus dexamethasone; Kd, dexamethasone; KRd, carfilzomib plus lenalidomide plus dexamethasone; KRd, carfilzomib plus lenalidomide plus dexamethasone; PN, peripheral neuropathy; SC, subcutaneous; Vd, bortezomib plus dexamethasone

Delforge M and Ludwig H. Blood. 2017;129:2359-2367

IMIDs: MOST COMMON GRADE ≥3 SIDE EFFECTS REPORTED IN PIVOTAL TRIALS



For adverse events with more than one value, the highest value was used.

[a] Listed as a combined event of somnolence/fatigue/dizziness in the original publication

[b] 6% sensory and 7% motor peripheral neuropathy

IMID, immunomodulatory drug; MPR, melphalan plus prednisone plus lenalidomide for 9 cycles; MPR-R, MPR followed by lenalidomide maintenance; MPT, melphalan plus prednisone plus thalidomide; NR, not reported; PN, peripheral neuropathy; Pom-dex, pomalidomide plus weekly dexamethasone; RD, lenalidomide plus high-dose dexamethasone; Rd18, lenalidomide plus weekly dexamethasone for 18 cycles; Rdcont, lenalidomide plus weekly dexamethasone until progression; Thal-Dex, thalidomide plus high-dose dexamethasone

Delforge M and Ludwig H. Blood. 2017;129:2359-2367

CD38 mAb: MOST COMMON GRADE ≥3 SIDE EFFECTS REPORTED IN PIVOTAL TRIALS

Grade 3 or 4 AEs, [a] n (%)	CASTOR[1] DVd (N=243)	POLLUX[2] DRd (N=283)	IKEMA[3] IKd (N=177)
Common hematologic AEs			
Thrombocytopenia	110 (45)	36 (13)	53 (30)
Anaemia	35 (14)	35 (12)	39 (22)
Neutropenia	31 (13)	147 (52)	34 (19)
Lymphopenia	23 (10)	15 (5)	NR
Febrile neutropenia	NR	16 (6)	NR
Common non-hematologic AEs			
Pneumonia	20 (8)	22 (8)	37 (21)
Hypertension	16 (7)	NR	36 (20)
Peripheral sensory neuropathy	11 (5)	NR	NR
Fatigue	11 (5)	18 (6)	6 (3)
Diarrhea	9 (4)	15 (5)	5 (3)
Dyspnea	9 (4)	9 (3)	9 (5)
Insomnia	0	1 (0.4)	9 (5)

[a] Grade 3-4 AEs (preferred term) reported in ≥5% of safety population.

AE, adverse event; d, dexamethasone; D, daratumumab; I, isatuximab; mAb, monoclonal antibody; NR, not reported; R, lenalidomide; V, bortezomib

1. Palumbo A, et al. New Engl J Med. 2016;375:754-766; 2. Dimopoulos M, et al. New Engl J Med. 2016;375:1319-1931; 3. Moreau P, et al. Lancet. 2021;397:2361-2371

PREVENTION AND MANAGEMENT OF SIDE EFFECTS ASSOCIATED WITH IMiDs, PIs AND mAbs

Types of side effect	Prevention	Management
Infections		
Herpes Zoster	Antiviral prophylaxis with aciclovir or derivative	Aciclovir, valaciclovir, famciclovir, penciclovir at therapeutic doses
Influenza	Vaccination	Oseltamivir, zanamivir
Bacterial infections	Vaccination against pneumococci, *H influenzae*. Antibacterial prophylaxis only in patients with high-risk infections	B-Lactam antibiotics, macrolides, fluoroquinolones
Gastrointestinal disorders		
Nausea/emesis	Domperidone, alizapride, metoclopramide in case of severe nausea: 5-HT3 antagonists, neurokinin-1 antagonists w/o 5-HT3 antagonists	Alizapride, metoclopramide in case of severe nausea/emesis: 5-HT3 antagonists, neurokinin-1 antagonists w/o 5-HT3 antagonists, dexamethasone
Constipation	Fibre-rich diet, adequate fluid intake, physical exercise, macrogol	Osmotic laxatives, stimulant laxatives; in case of opioid-induced bowel atony: naltrexone or naloxone, distigmin, pyridostigmin
Diarrhoea	Normal diet	Loperamide, diphenoxylate + atropine, probiotics; in case of severe symptoms: long-acting somatostatin; in case of bile acid malabsorption, cholesevelam
Neuromusculoskeletal disorders and pain		
Peripheral neuropathy	Regular and careful monitoring of symptoms of PN	Dose reduction, regimen modification or discontinuation of neurotoxic drugs; in case of painful PN: gabapentin, pregabalin, amitriptyline, duloxetine, venlafaxine, opioids; lidocaine patches/cream, acupuncture, TENS
Orthostatic dysregulation, hypotonia	Regular and careful monitoring of symptoms, adequate fluid intake, physical exercise	Dose reduction and/or discontinuation of neurotoxic drugs or blood pressure–lowering drugs; midodrine, mineralocorticoids, physical exercise

5-HT3, 5-hydroxytryptamine receptor subtype 3; IMiD, immunomodulatory agent; mAb, monoclonal antibody; PI, proteasome inhibitor; PN, peripheral neuropathy; TENS, transcutaneous electrical nerve stimulation; w/o, without

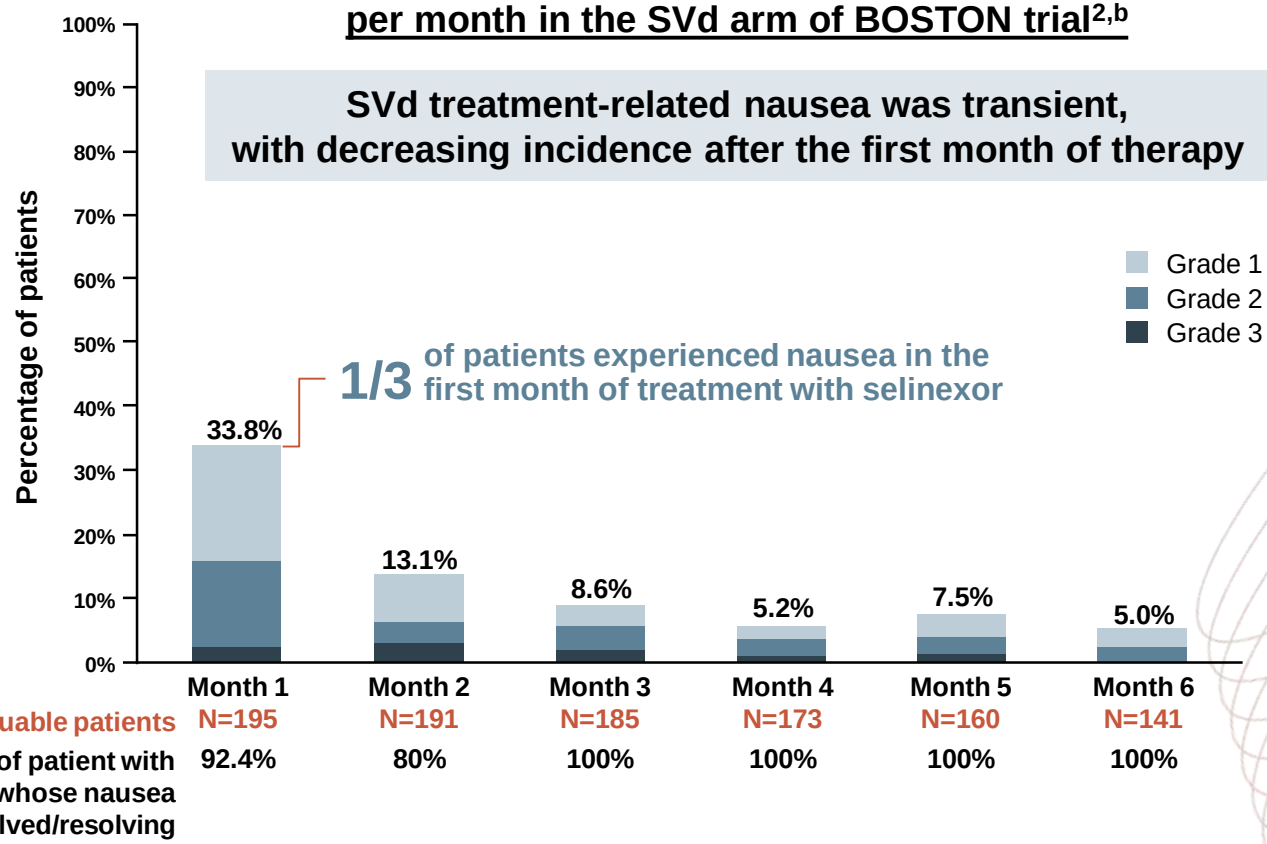
Adapted from Delforge M and Ludwig H. Blood. 2017;129:2359-2367

SELINEXOR: MOST COMMON GRADE ≥3 SIDE EFFECTS REPORTED IN BOSTON STUDY

Grade 3-4 AEs, [a] n (%)[1]	SVd (N=195)
Hematological AEs	
Thrombocytopenia	77 (39)
Anaemia	31 (16)
Neutropenia	17 (9)
Non-hematological AEs	
Fatigue	26 (13)
Pneumonia	24 (12)
Cataract	17 (9)
Nausea	15 (8)
Asthenia	16 (8)
Diarrhea	12 (6)
Peripheral neuropathy	9 (5)

Percentage of patients experiencing nausea events per month in the SVd arm of BOSTON trial[2,b]

SVd treatment-related nausea was transient, with decreasing incidence after the first month of therapy



[a] Grade 3-4 AEs (preferred term) reported in ≥5% of safety population

[b] Patients in the BOSTON trial were administered 5-HT3 receptor antagonists and other anti-nausea agents prior to and during treatment with selinexor

5-HT3, 5-hydroxytryptamine (receptor) subtype 3; AE, adverse event; d, dexamethasone S, selinexor; V, bortezomib

1. Grosicki S, et al. Lancet. 2020;396:1563-1573; 2. Nooka AK, et al. Clin Lymphoma Myeloma Leuk. 2022;22:e526-e531

SELINEXOR: USE OF PROPHYLACTIC ANTIEMETICS

A 5-HT3 RECEPTOR ANTAGONIST AND/OR OTHER ANTINAUSEA AGENTS SHOULD BE PROVIDED PRIOR TO AND DURING TREATMENT WITH SELINEXOR[1]

Selinexor supportive care guidelines[2]

Adverse event	Management	Dose
Thrombocytopenia	Platelet transfusions	Per institutional guidelines
	TPO agonist: Romiplostim	5-10 µg/kg SC QW
	TPO agonist: Eltrombopag	100-50 mg PO QD
Nausea and vomiting	**5-HT3 antagonist:** Ondansetron	8 mg PO or equivalent Q8H before selinexor and for 2 days following.
	Olanzapine	2.5-5.0 mg PO QHS starting C1D1
	NK1R antagonist: Rolapitant	180 mg PO within 2 hours prior to each dose
	NK1R antagonist: Aprepitant	125 mg PO d1, 80 mg PO d2, 3
Weight loss/ anorexia	Olanzapine[a]	2.5-5.0 mg (low dose) PO QHS
	Megestrol acetate[a]	400 mg PO QD
Fatigue	Methylphenidate	5-10 mg PO QAM
	Dexamethasone	Supportive dose care

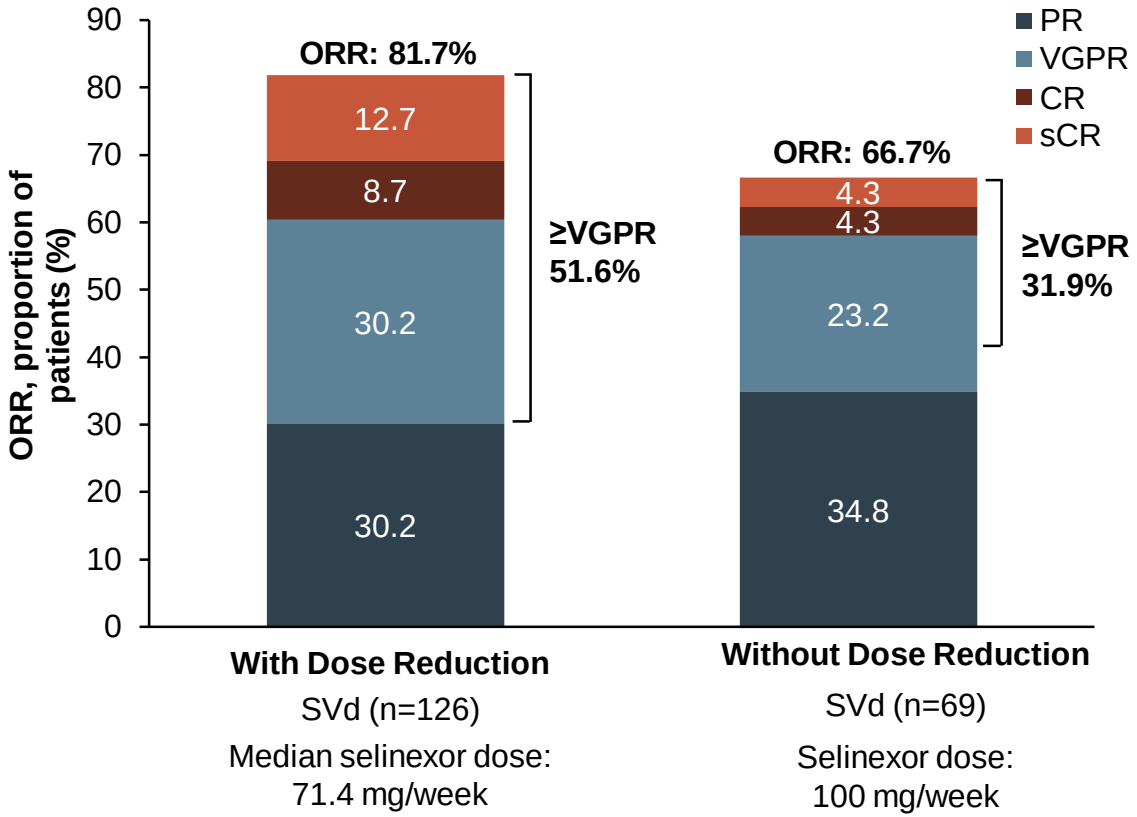
[a] Continue until weight is within 5 pounds of goal weight.

5-HT3, 5-hydroxytryptamine (receptor subtype 3); C1D1, cycle 1 day 1; d, day; NK1R, neurokinin 1 receptor antagonist; PO, by mouth; Q8H, once every 8 hours; QAM, every morning; QD, once daily; QHS, every night at bedtime; QW, once per week; SC, subcutaneous

1. Nexpovio (selinexor), Summary of Product Characteristics (August 2023). Stemline Therapeutics B.V.; 2. Mo C, et al. Exp Rev Hematol. 2021;14:697-706

SELINEXOR DOSE WAS REDUCED WITHOUT COMPROMISING EFFICACY IN BOSTON

mPFS: 16.6 months with selinexor dose reduction vs 9.2 months without selinexor dose reduction



Dosage-adjusted incidence[a] of AEs of clinical interest in ≥25% of patients in the SVd arm

Treatment-emergent adverse event	On or before first dose reduction in selinexor (N=195)	After first dose reduction in selinexor (N=126)
Thrombocytopenia	62.5	47.6
Anaemia	17.9	10.3
Nausea	31.6	7.3
Fatigue	28.1	9.9
Decreased appetite	21.5	6.4
Vomiting	14.4	3.8
Diarrhoea	12.9	5.2
Weight decrease	9.0	5.9
Peripheral neuropathy	7.9	5.2

A Dosage-adjusted incidence is defined as the average number of events per 100 patients during a 4-week treatment period. AE, adverse event; CR, complete response; mPFS, median progression free survival; ORR, overall response rate; PR, partial response; sCR, stringent complete response; SVd, selinexor + bortezomib + dexamethasone; VGPR, very good partial response

Jagannath S, et al. Clin Lymphoma Myeloma Leuk. 2023;23:917-923.e3

CAR-T THERAPIES: MOST COMMON GRADE ≥3 SIDE EFFECTS REPORTED IN PIVOTAL TRIALS

Grade 3 or 4 AEs,[a] n (%)	KarMMa[1] Ide-cel (N=128)	CARTITUDE-1[2] Cilta-cel (N=97)
Any AE	**127 (99)**	**91 (94)**
Hematologic event		
Neutropenia	114 (89)	92 (95)
Anaemia	77 (60)	66 (68)
Thrombocytopenia	67 (52)	58 (60)
Leukopenia	50 (39)	59 (61)
Lymphopenia	34 (27)	48 (50)
Febrile neutropenia	20 (16)	NR
Other		
Hypophosphatemia	20 (16)	7 (7)
Hypocalcemia	10 (8)	3 (3)
Cytokine release syndrome	7 (5)[b]	4 (4)
Hyponatremia	7 (5)	4 (4)
Neurotoxic effect	4 (3)[c]	9 (9)[d]
Fatigue	2 (2)	5 (5)
Aspartate aminotransferase increased	2 (2)	5 (5)

[a] Grade 3-4AEs (preferred term) reported in ≥5% of participants. [b] The clustered term includes the preferred term. Included is one patient who had progression to a grade 5 event. [c] KarMMa: Investigator-identified neurotoxicity was the preferred term. [d] CARTITUDE-1: ICANS reported in 16 (17%) patients, with grade 3–4 events in 2 (2%); other neurotoxicities (events not reported as ICANS [i.e., onset after a period of recovery from cytokine release syndrome and ICANS]) were reported in 12 (12%) patients, eight (8%) with grade 3–4; note that ICANS and other neurotoxicities are not mutually exclusive as eight (8%) of 97 patients had both ICANS and other neurotoxicity of any grade

AE, adverse event; CAR-T, chimeric antigen receptor T-cell; Cilta-cel, ciltacabtagene autoleucel; ICANS; immune effector cell–associated neurotoxicity syndrome; Ide-cel, idecabtagene vicleucel; NR, not reported

1. Munshi N, et al. New Engl J Med. 2021;384:705-716; 2. Berdeja J, et al. Lancet. 2021;398:314-324

BISPECIFIC ANTIBODIES: MOST COMMON GRADE ≥3 SIDE EFFECTS REPORTED IN PIVOTAL TRIALS

Grade 3 or 4 AEs,[a] n (%)	MagenetisMM-3[1] Elranatamab (N=123)	MonumenTAL-1[2] SC talquetamab 405 µg weekly (N=30)	MonumenTAL-1[2] SC talquetamab 800 µg every 2 wk (N=44)	MonumenTAL-1[2] IV Talquetamab All doses (N=102)	MajestTEC-1[3] Teclistamab (N=165)
Any AE	**87 (71)**	**26 (87)**	**38 (86)**	**92 (90)**	**156 (95)**
Hematologic event					
Anaemia	46 (37)	9 (30)	10 (23)	34 (33)	61 (37)
Neutropenia	60 (49)	18 (60)	14 (32)	27 (26)	106 (64)
Thrombocytopenia	29 (24)	7 (23)	5 (11)	13 (13)	35 (21)
Lymphopenia	31 (25)	12 (40)	17 (39)	48 (47)	54 (33)
Leukopenia	NR	9 (30)	6 (14)	16 (16)	12 (7)
Non-hematologic event					
Hypophosphatemia	NR	5 (17)	3 (7)	14 (14)	NR
Rash-related event[b]	NR	0	7 (16)	1 (1)	NR
COVID-19 related	19 (15)	NR	NR	NR	20 (12)
Pneumonia	NR	NR	NR	NR	21 (13)
Hypokalemia	13 (11)	NR	NR	NR	NR
Increased alanine aminotransferase	NR	1 (3)	3 (7)	2 (2)	NR
Increased aspartate aminotransferase	NR	0	3 (7)	2 (2)	NR
Increased γ-glutamyltransferase	NR	1 (3)	3 (7)	3 (3)	NR
Cytokine release syndrome[c]	0	1 (3)	0	5 (5)	1 (1)

[a] Grade 3-4 AEs (preferred term) reported in ≥5% of participants. [b] Included contact dermatitis, dermatitis, erythematous rash, generalized exfoliative dermatitis, maculopapular rash, and rash. [c] In MajesTEC-1, events associated with cytokine release syndrome were graded according to the criteria of the American Society for Transplantation and Cellular Therapy

AE, adverse event; IV, intravenous; NR, not reported; SC, subcutaneous; wk, weeks

1. Lesokhin A, et al. Nat Med. 2023;29:2259-2267; 2. Chari A, et al. New Engl J Med. 2022;387:2232-2244; 3. Moreau P, et al. New Engl J Med. 2022;387:495-505

INFECTION PREVENTION STRATEGIES FOR T-CELL REDIRECTION THERAPIES (1/2)

Intervention	Indication/duration	
	CAR-T	BsAb
Bacterial		
Levofloxacin (or cefdinir or augmentin if allergy/intolerance to fluoroquinolone)	Start when ANC <500 or per physician discretion and continue until neutrophil recovery	Start with onset of therapy and administer during the first month
Immunoglobulin replacement	Day +30 through 1 year. After 1 year continue until serum IgG >400 mg/dL[a]	From second month of therapy until end of therapy or serum IgG >400 mg/dL[a] (whichever is longer)
Pneumococcus conjugated vaccine (PCV)	Revaccination can begin 3–6 months after therapy. CDC recommends 1 dose of PCV20 or 1 dose of PCV15 followed by 1 dose of PPSV23 at least 1 year later	Update vaccination status prior to starting BsAb
Herpes Simplex Virus/Varicella Zoster Virus		
Acyclovir or valacyclovir	Universal and indefinite prophylaxis, irrespective of vaccination status	
Cytomegalovirus (CMV)		
Pharmacological prophylaxis not recommended	Routine monitoring not recommended. Monitoring of viral load and CMV-directed therapy recommended in patients with suspected CMV-related disease or otherwise unexplained fever and/or cytopenias or in high-risk patients	
COVID-19		
Immunisation	Follow health authorities' recommendations for immunosuppressed patients. Revaccination 3-6 months after CAR-T therapy	

[a] Discount monoclonal component that may be responsible for IgG elevation

ANC, absolute neutrophil count; BsAb, bispecific antibody; CAR-T, chimeric antigen receptor T cell; CDC, Centers for Disease Control and Prevention; CMV, cytomegalovirus; COVID-19, coronavirus Disease 2019; PCV(15/20), pneumococcus conjugated vaccine(, 15/20-valent); PPSV23, pneumococcal polysaccharide vaccine, 23-valent

Mohan M, et al. Br J Haematol. 2023;203:736-746

INFECTION PREVENTION STRATEGIES FOR T-CELL REDIRECTION THERAPIES (2/2)

Intervention	Indication/duration	
	CAR-T	**BsAb**
Influenza		
Immunisation	Seasonal	
Hepatitis B virus		
Entecavir or tenofovir	Carriers of HBV (HBs Ag-positive) or patients with a previous history of HBV infection (HBs Ag-negative, anti-HBc Ab-IgG positive)	
Yeast and mould		
Fluconazole	Start when ANC <500 and continue until neutrophil recovery, consider ongoing prophylaxis with anti-mould azole in high-risk patients[a]	
Pneumocystis jirovecii		
Trimethoprim/sulfamethoxazole or dapsone or atovaquone suspension or pentamidine	Start on Day +30 through 6 months, or until CD4 ≥200/mm^3 (whichever is longer)	Start with therapy and continue for its duration or until CD4 ≥200/µL (whichever is longer)

[a] High-risk candidates such as recipients of >1 dose of tocilizumab, use of second line agents such as anakinra or siltuximab for management of CRS and ICANS, prolonged and or high dose steroid use (requiring >3 days of ≥10 mg dexamethasone per day with a 7-day period or receiving ≥doses of methylprednisolone ≥1 g per day) should be considered for a more intensive azole based anti-mould prophylaxis

ANC, absolute neutrophil count; BsAb, bispecific antibody; CAR-T, chimeric antigen receptor T cell; HBc Ab, hepatitis B core antibody; HBs Ag, hepatitis B surface antigen; HBV, hepatitis B virus

Mohan M, et al. Br J Haematol. 2023;203:736-746

CARDIAC MONITORING

Baseline evaluation (prior to initiation or any change in MM treatment regimen)

- Age
- Comorbidities and CV risk factors (smoking, HTN, DM, CHF, CAD, valvular HD, renal insufficiency, among others)
- CGA for elderly patients

- ECG for all patients
- TTE advised for all patients (required for high-risk patients)
- Biomarkers (troponin and NT-proBNP among others)

Risk stratify patients according to these factors and specific treatment for risk of CV toxicity
Optimise pre-existing conditions

Low-risk (consider cardiology referral)	High-risk (cardiology/cardio-oncology referral is recommended) Consider dose reduction as needed

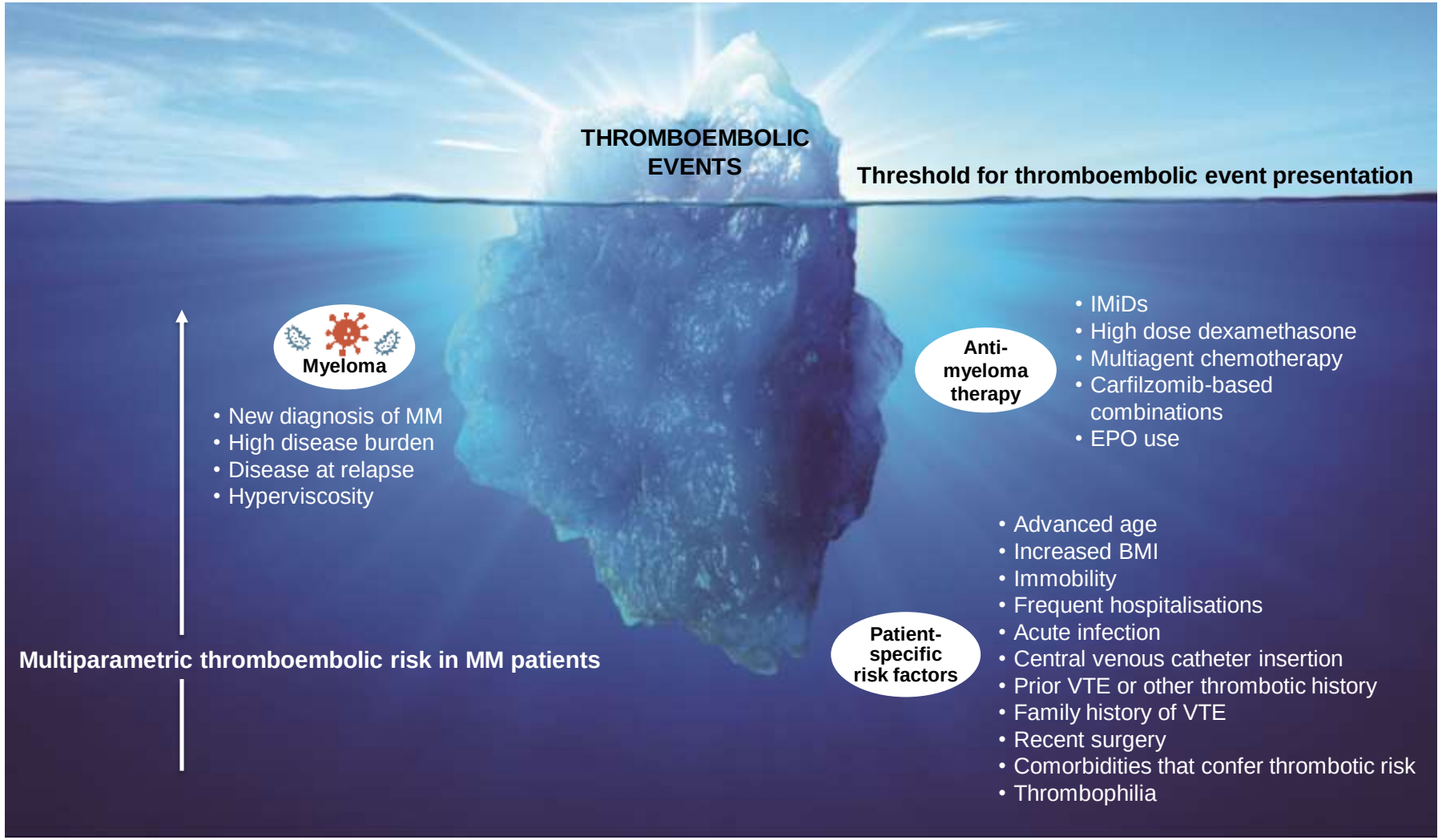
Monitoring during treatment
For all agents monitor fluid balance/weight, check for new symptoms (dyspnoea, oedema, chest pain among others), frequent evaluation of concurrent medications
Monitor blood pressure prior to every new treatment cycle

Carfilzomib: electrolytes/ECG, troponin/BNP prior to each cycle; TTE at least every 3 months and prior to reinitiation in case of interruption (required in case symptomatic HF or decrease by 10% or more in EF (to <50%-55%))	Bortezomib/lenalidomide/thalidomide: ECG, troponin and BNP every 3-6 cycles and consider TTE at least once per year and as clinically indicated • Novel therapies including bispecific agents/CAR-T: ECG, troponin/BNP and TTE as clinically indicated

BNP, brain natriuretic peptide; CAD, coronary artery disease; CAR-T, chimeric antigen receptor T-cell therapy; CGA, comprehensive geriatric assessment; CHF, congestive heart failure; CV, cardiovascular; DM, diabetes mellitus; ECG, electrocardiogram; EF, ejection fraction; HD, heart disease; HF, heart failure; HTN, hypertension; MM, multiple myeloma; NT-proBNP, N-terminal pro-B-type natriuretic peptide; TTE, transthoracic echocardiogram

El-Cheikh J, et al. Blood Cancer J. 2023;13:83

RISK ASSESSMENT FOR THROMBOSIS



BMI, body mass index; EPO, recombinant erythropoietin; IMiD, immunomodulatory agent; MM, multiple myeloma; VTE, venous thromboembolism

Fotiou D, et al. Cancers (Basel). 2022;14:6216

THROMBOSIS: RISK ASSESSMENT AND MANAGEMENT

Newly diagnosed or RRMM patient

Perform a thorough VTE assessment
Use IMWG, IMPEDE-VTE or SAVED risk scores

Constant re-evaluation of thrombotic risk throughout disease course

No risk	Low risk	High risk	Very high risk
• 0 points by IMWG • 0 points by IMPEDE-VTE	• 1 point by IMWG • ≤3 by IMPEDE-VTE • <2 by SAVED	• >1 by IMWG • 4-7 and ≥8 by IMPEDE-VTE • ≥3 by SAVED	*Not currently defined based on available RAMs and guidelines*
No thromboprophylaxis	Aspirin 81-325 mg (100 mg preferred)	LMWH (enoxaparin 40 mg or equivalent) or DOAC* (rivaroxaban/apixaban) Prophylactic dose or therapeutic dose warfarin	*Therapeutic dose LMWH or DOAC or warfarin* *No data or guidelines to currently support this practice*

- Bleeding risk, renal function, platelet count, concomitant medication and patient choice taken into consideration
- Continue thromboprophylaxis for at least 6 months and consider downgrading if the disease is in remission or upgrading based on changes in thrombotic risk

[a] DOAC preferred. DOAC, direct oral anticoagulant; IWMG, International Myeloma Working Group; LMWH, low molecular weight heparin; RAM, risk assessment model; RRMM, relapsed/refractory multiple myeloma; VTE, venous thromboembolism

Adapted from Fotiou D, et al. Cancers (Basel). 2022;14:6216

FRAILTY ASSESSMENT

IMWG FRAILTY SCORE

- **Age**
- **Comorbidities:**
  - CCI
- **Patient-reported functional status**
  - Katz Index of Independence in Activities of Daily Living
  - Lawton Instrumental Activities of Daily Living

Fit = score 0

Intermediate fit = score 1

Frail = score ≥2

INCL. PROGNOSTIC FEATURES

R-MCI SCORE

- **Age**
- **Comorbidities**
  - Renal function
  - Pulmonary function
- **Frailty evaluation**
- **Karnofsky performance status**
- **Cytogenetics**

Fit	Intermediate fit	Frail
score ≤3	score 4-6	score >6

MRP score

- **Age**
- **WHO performance status**
- **ISS stage**
- **Circulating CRP levels**

Low risk	Medium risk	High risk

INCL. OBJECTIVE PARAMETERS

MAYO CLINIC SCORE

- **Age**
- **ECOG performance status**
- **Circulating NT-proBNP levels**

Stage I	Stage II	Stage III	Stage IV
score 0	score 1	score 2	score 3

EVALUATION OF SARCOPENIA

- **Muscle mass:** CT 3rd lumbar vertebra area
- **Muscle function:** grip strength
- **Physical performance:** gait speed, etc.

SENESCENCE BIOMARKERS

SIMPLIFIED ASSESSMENTS

SIMPLIFIED FRAILTY SCORE

- **Age**
- **Comorbidities**
  - CCI
- **ECOG performance status**

None-frail	Frail
score 0-1	score ≥2

QUALITY-OF-LIFE QUESTIONNAIRE

- **Patient-reported functional status**
  - EORTC QoL questionnaire C30

CCI, Charlson Comorbidity Index; CRP, C-reactive protein; CT, computed tomography; ECOG, Eastern Cooperative Oncology Group; EORTC QoL, European Organisation for Research and Treatment of Cancer quality of life; IMWG, International Myeloma Working Group; ISS, International Staging System for Multiple Myeloma; MRP, UK Myeloma Research Alliance Risk Profile; NT-proBNP, N-terminal pro-B-type natriuretic peptide; R-MCI, Revised Myeloma Comorbidity Index; WHO, World Health Organization

Adapted from Bonello F, et al. Cancers (Basel). 2020;12:3106

DOSE MODIFICATIONS FOR FRAIL PATIENTS

Drug	Fit	Intermediate	Frail
PIs			
Bortezomib	1.3 or 1.5 mg/m^2	1 mg/m^2	0.7 or 1 mg/m^2
Carfilzomib	27, 36, 56 or 70 mg/m^2	20 or 27 mg/m^2	15 mg/m^2
Ixazomib	4 mg	3 mg	2.3 mg
IMIDs			
Lenalidomide	25 mg	15 mg	10 mg
Pomalidomide	4 mg	3 mg	2 mg
Thalidomide	100 or 200 mg	50 or 100 mg	50 mg
Alkylating agents			
Cyclophosphamide	300 mg/m^2	150 or 225 mg/m^2	75 or 150 mg/m^2
Bendamustine	90 or 100 mg/m^2	70, 75 or 80 mg/m^2	25, 50 or 60 mg/m^2
Melphalan	0.25 mg/kg	0.18 mg/kg	0.13 mg/kg
Antibodies			
Daratumumab	16 mg/kg	No adjustment	No adjustment
Elotuzumab	10 mg/kg	No adjustment	No adjustment
XPO1 inhibitors[2]			
Selinexor (in SVd regimen)	100 mg/week	80-100 mg/week	60-80 mg/week
Histone deacetylase inhibitor	20 mg	15 mg	10 mg
Panobinostat			

d, dexamethasone; IMID, immunomodulatory drug; PI, proteasome inhibitor; S, selinexor; V, bortezomib; XPO1 exportin 1

Table adapted from Leng S, et al. Hematology Am Soc Hematol Educ Program. 2019;2019:125-136

DOSE MODIFICATION FOR PATIENTS WITH RENAL DYSFUNCTION

Agents	Mechanism of action	CrCl	Dose adjustment
Ixazomib	PI	• ≥30 mL/min • <30 mL/min[a]	• 4 mg on Day 1, 8 and 15 • 3 mg on Day 1, 8 and 15
Lenalidomide	IMiD	• >60 mL/min • 30-59 mL/min • 15-29 mL/min • <15 mL/min[a]	• 25 mg daily • 10-15 mg daily • 10 mg daily or 15 mg every other day • 5 mg daily
Pomalidomide	IMiD	• ≥45 mL/min • <45 mL/min	• No dose adjustment • Further studies needed for safety/efficacy
Melphalan	Alkylating agent	• >60mL/min • 15-59 mL/min • <15 mL/min[a]	• No dose adjustment • 25% reduction • 50% reduction

No dose adjustment required for bortezomib, carfilzomib, dexamethasone, cyclophosphamide, thalidomide, doxorubicin, selinexor, daratumumab, elotuzumab, and panobinostat in patients with renal impairment

[a] Or ESRD on HD

CrCl, creatinine clearance; ESRD, end-stage renal disease; HD, haemodialysis; IL-6, interleukin-6; IMiD, immunomodulatory agent; mAb, monoclonal antibody; PI, proteasome inhibitor

George LL, et al. Clin Lymphoma Myeloma Leuk. 2021;21:812-822

CONCLUSIONS

- PIs, IMiDs and mAbs are the mainstay of treatment for RRMM but are associated with a range of both hematological and non-hematological side effects
- Prevention and management of side effects is critical to improve safety and tolerability and long-term adherence to treatments
- Selinexor is associated with nausea during initial treatment, but this is often transient and can be minimised through dose reduction and the use of anti-emetics
- Infection prevention strategies are important for the safe use of T-cell directed therapies
- Cardiac monitoring, venous thromboembolism risk assessment and dose adjustments for frailty and renal dysfunction also need to be considered as part of the holistic management of patients with MM

IMiD, immunomodulatory agent; mAb, monoclonal antibody; MM, multiple myeloma; PI, proteasome inhibitor; RRMM, relapsed/refractory multiple myeloma

PATIENT CASE STUDY PRESENTATIONS & DISCUSSION

CASE STUDY 1: PATIENT PROFILE

- Age 78 years
- ECOG PS: 1
- PMH: Hypertension, mild obesity, T2DM
- Presented with hip pain and fatigue

- Diagnosis: November 2021
- IgG lambda multiple myeloma
- Hb:103 g/L, mild renal impairment
- Lesions in left hip
- MM FISH – No high-risk chromosomal abnormality
- R-ISS I standard risk

Educational case study

ECOG, Eastern Cooperative Oncology Group; FISH, fluorescence in situ hybridisation; Hb, haemoglobin; IgG: immunoglobulin; MM, multiple myeloma; PMH, previous medical history; PS, performance status; R-ISS, revised International Staging System; T2DM, type 2 diabetes mellitus

CASE STUDY 1: TREATMENT

November 2021

- Front-line treatment: DaraRd – complete remission

November 2023

- Patient reported increasing bone pain and multiple new lesions were detected

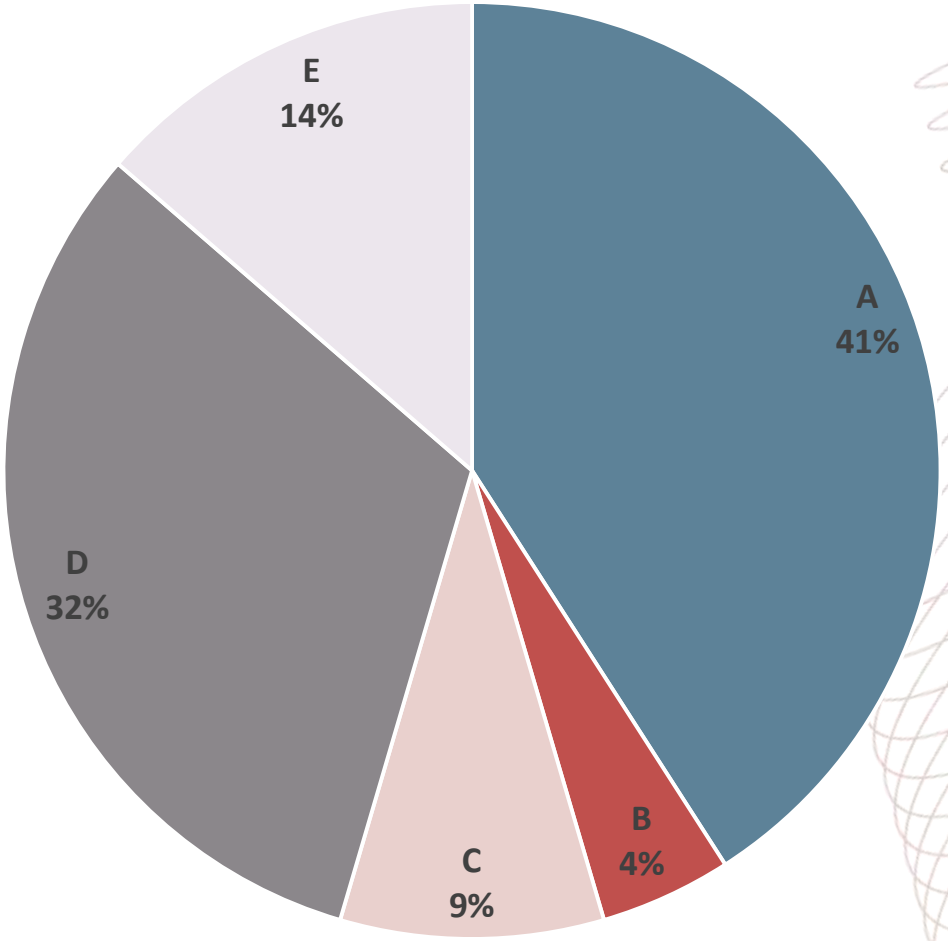
Educational case study

DaraRd, daratumumab, lenalidomide, dexamethasone.

CASE STUDY 1: POLLING QUESTION

IN YOUR COUNTRY WHAT TREATMENT WOULD BE OFFERED AT 2ND LINE?

A. Pomalidomide, bortezomib, dexamethasone
B. Carfilzomib, dexamethasone
C. Elotuzumab, lenalidomide, dexamethasone
D. Selinexor, bortezomib, dexamethasone
E. Other



CASE STUDY 1: TREATMENT

November 2021

- Front-line treatment: DaraRd – complete remission

November 2023

- Patient reported increasing bone pain and multiple new lesions were detected

December 2023

- Second-line treatment: SVd
  - Patient developed Grade 2 nausea after the first dose despite prophylactic Akynzeo (NK_1 receptor antagonist/5-HT_3 receptor antagonist)
  - Selinexor dose was reduced from 100 to 80 mg per week and the patient was prescribed olanzapine
  - Nausea resolved and patient continued with the lower dose of selinexor

February 2024

- Patient achieved a VGPR and is continuing to receive SVd
  - Anti-nausea drugs were successfully tapered off

Educational case study

DaraRd, daratumumab, lenalidomide, dexamethasone; VGPR, very good partial response; SVd, selinexor, bortezomib, dexamethasone

CASE STUDY 2: PATIENT PROFILE

- Age 59 years
- ECOG PS: 0
- PMH: None of note
- Presented with back pain

- Diagnosis: March 2021
- IgG kappa multiple myeloma
- Hb:112 g/L, normal renal function
- Small vertebral lesions
- MM FISH – t(4;14), gain 1q21
- R-ISS II intermediate risk

Educational case study

ECOG, Eastern Cooperative Oncology Group; FISH, fluorescence in situ hybridisation; Hb, haemoglobin; IgG: immunoglobulin; MM, multiple myeloma; PMH, previous medical history; PS, performance status; R-ISS, revised International Staging System

CASE STUDY 2: TREATMENT

March 2021

- Front-line treatment: VRd followed by ASCT and lenalidomide maintenance

January-July 2023

- 1st relapse: DaraKd; 2nd relapse: IsaPd

October 2023

- 3rd relapse: Ide-cel
  - Day 2: Patient developed grade 1 CRS
  - Day 5: Persistent fever treated with tocilizumab
  - Day 6: Patient developed hesitant speech and reported headache
  - Day 7: Patient experienced seizures and was diagnosed with grade 3 ICANS (ICE score 2)

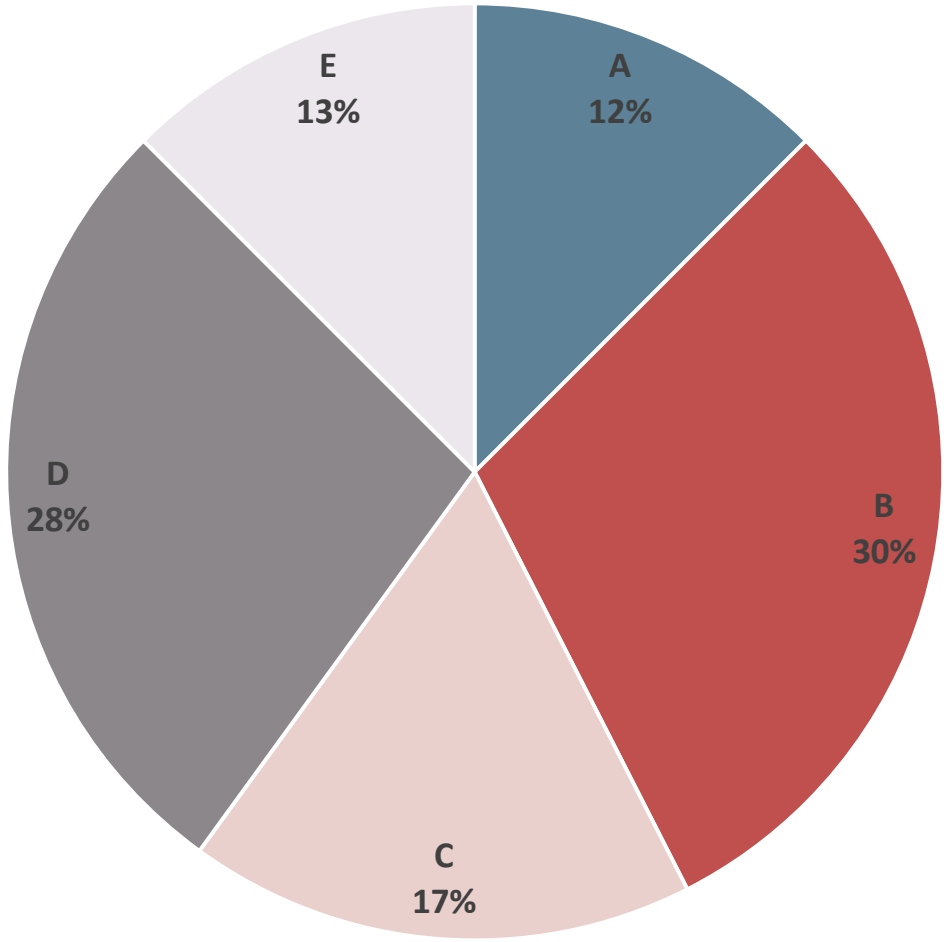
Educational case study

ASCT, autologous stem cell transplant; CRS, cytokine release syndrome; DaraKd, daratumumab, carfilzomib, dexamethasone; ICANS, immune effector cell-associated neurotoxicity syndrome; ICE, immune effector cell-associated encephalopathy; ide-cel, idecabtagene vicleucel; IsaPd, isatuximab, pomalidomide, dexamethasone; VRd, bortezomib, lenalidomide, dexamethasone

CASE STUDY 2: POLLING QUESTION

HOW WOULD YOU TREAT THIS PATIENT (SELECT ALL THAT APPLY)?

A. Supportive care only
B. Dexamethasone
C. Methylprednisolone
D. Tocilizumab
E. Anakinra



CASE STUDY 2: TREATMENT

- Front-line treatment: VRd followed by ASCT and lenalidomide maintenance
- 1st relapse: DaraKd; 2nd relapse: IsaPd
- 3rd relapse: Ide-cel
  - Day 2: Patient developed grade 1 CRS
  - Day 5: Persistent fever treated with tocilizumab
  - Day 6: Patient developed hesitant speech and reported headache
  - Day 7: Patient experienced seizures and was diagnosed with grade 3 ICANS (ICE score 2)
  - Treatment: Patient was transferred to the ICU and treated with dexamethasone, tocilizumab, lorazepam and levetiracetam
  - Day 10: ICANS resolved
- Patient achieved a CR

Educational case study

ASCT, autologous stem cell transplant; CRS, cytokine release syndrome; DaraKd, daratumumab, carfilzomib, dexamethasone; ICANS, immune effector cell-associated neurotoxicity syndrome; ICE, immune effector cell-associated encephalopathy; ICU, intensive care unit; ide-cel, idecabtagene vicleucel; IsaPd, isatuximab, pomalidomide, dexamethasone; VRd, bortezomib, lenalidomide, dexamethasone

Q&A DISCUSSION

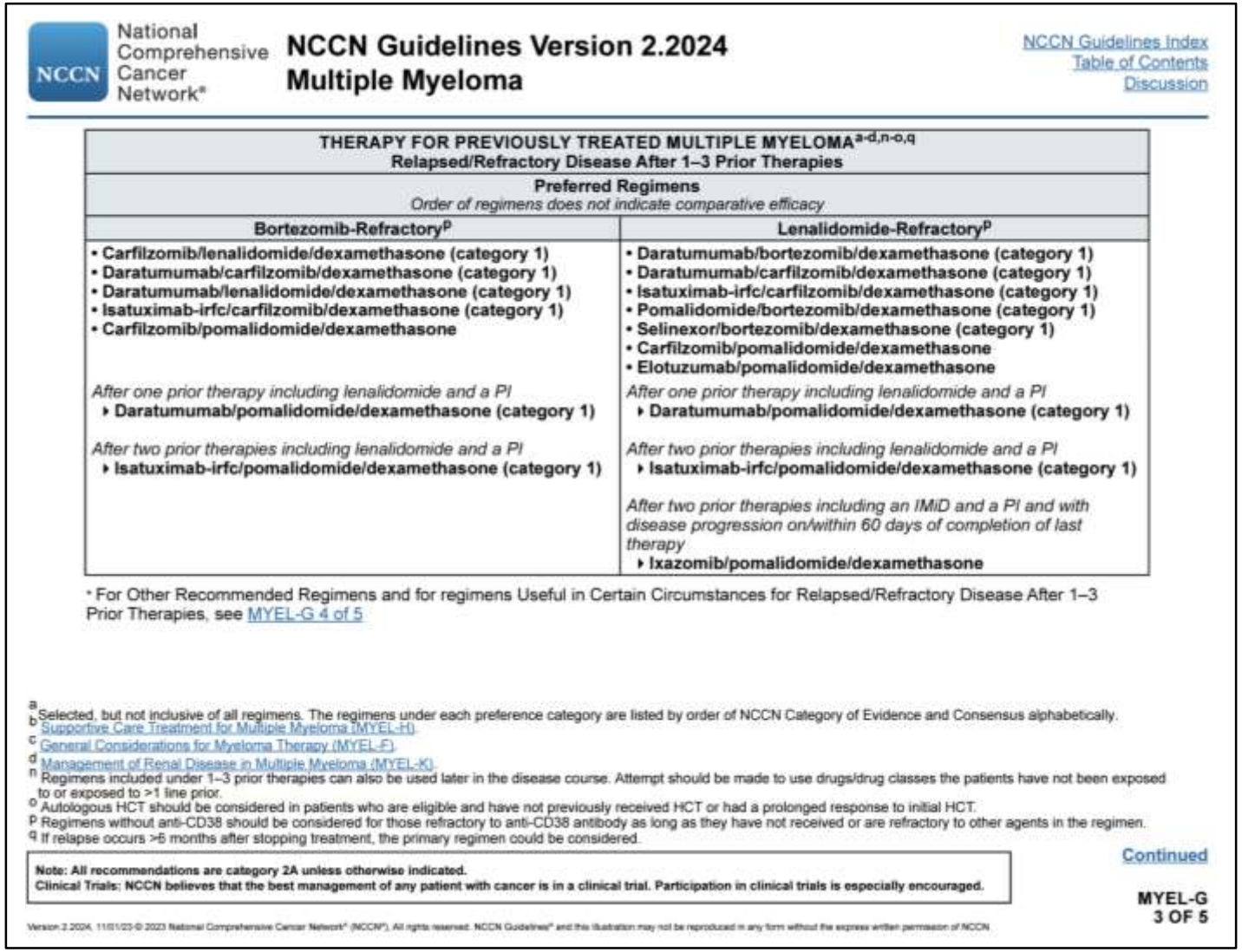
SUMMARY AND LOOK TO THE FUTURE

Assoc. Prof. Joshua Richter

Hematologist-Oncologist

Icahn School of Medicine at Mount Sinai, USA

NCCN GUIDELINES FOR EARLY RRMM



National Comprehensive Cancer Network®

NCCN Guidelines Version 2.2024
Multiple Myeloma

NCCN Guidelines Index
Table of Contents
Discussion

THERAPY FOR PREVIOUSLY TREATED MULTIPLE MYELOMA[a-d,n-o,q]
Relapsed/Refractory Disease After 1–3 Prior Therapies

Preferred Regimens
Order of regimens does not indicate comparative efficacy

Bortezomib-Refractory[p]	Lenalidomide-Refractory[p]
• **Carfilzomib/lenalidomide/dexamethasone (category 1)** • **Daratumumab/carfilzomib/dexamethasone (category 1)** • **Daratumumab/lenalidomide/dexamethasone (category 1)** • **Isatuximab-irfc/carfilzomib/dexamethasone (category 1)** • **Carfilzomib/pomalidomide/dexamethasone** *After one prior therapy including lenalidomide and a PI* ‣ **Daratumumab/pomalidomide/dexamethasone (category 1)** *After two prior therapies including lenalidomide and a PI* ‣ **Isatuximab-irfc/pomalidomide/dexamethasone (category 1)**	• **Daratumumab/bortezomib/dexamethasone (category 1)** • **Daratumumab/carfilzomib/dexamethasone (category 1)** • **Isatuximab-irfc/carfilzomib/dexamethasone (category 1)** • **Pomalidomide/bortezomib/dexamethasone (category 1)** • **Selinexor/bortezomib/dexamethasone (category 1)** • **Carfilzomib/pomalidomide/dexamethasone** • **Elotuzumab/pomalidomide/dexamethasone** *After one prior therapy including lenalidomide and a PI* ‣ **Daratumumab/pomalidomide/dexamethasone (category 1)** *After two prior therapies including lenalidomide and a PI* ‣ **Isatuximab-irfc/pomalidomide/dexamethasone (category 1)** *After two prior therapies including an IMiD and a PI and with disease progression on/within 60 days of completion of last therapy* ‣ **Ixazomib/pomalidomide/dexamethasone**

* For Other Recommended Regimens and for regimens Useful in Certain Circumstances for Relapsed/Refractory Disease After 1–3 Prior Therapies, see MYEL-G 4 of 5

[a] Selected, but not inclusive of all regimens. The regimens under each preference category are listed by order of NCCN Category of Evidence and Consensus alphabetically.
[b] Supportive Care Treatment for Multiple Myeloma (MYEL-H).
[c] General Considerations for Myeloma Therapy (MYEL-F).
[d] Management of Renal Disease in Multiple Myeloma (MYEL-K).
[n] Regimens included under 1–3 prior therapies can also be used later in the disease course. Attempt should be made to use drugs/drug classes the patients have not been exposed to or exposed to >1 line prior.
[o] Autologous HCT should be considered in patients who are eligible and have not previously received HCT or had a prolonged response to initial HCT.
[p] Regimens without anti-CD38 should be considered for those refractory to anti-CD38 antibody as long as they have not received or are refractory to other agents in the regimen.
[q] If relapse occurs >6 months after stopping treatment, the primary regimen could be considered.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

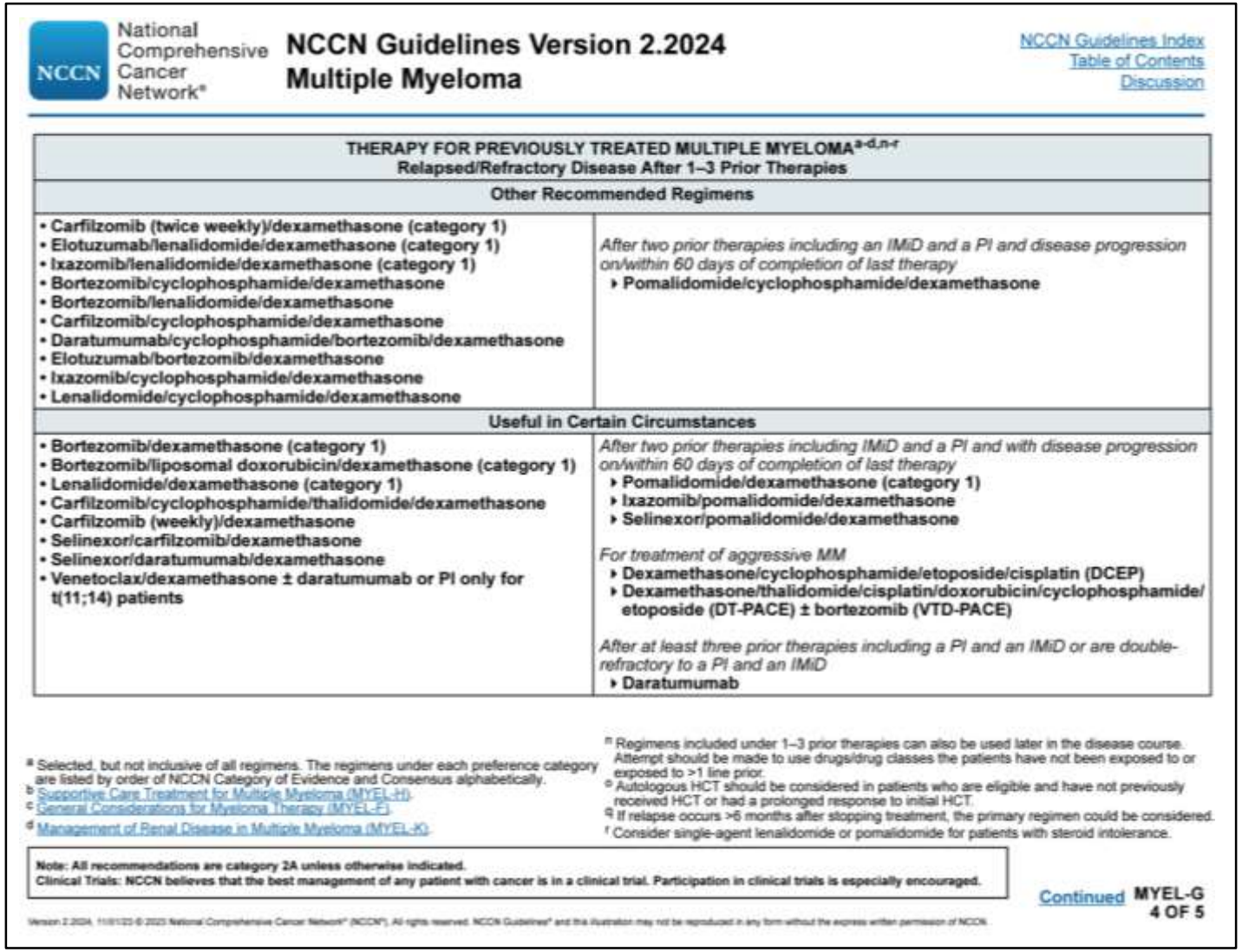
Continued

MYEL-G
3 OF 5

HCT, haematopoietic stem cell transplantation; IMiD, immunomodulatory drug; MM, multiple myeloma; PI, proteasome inhibitor

Kumar SK, et al. J Natl Compr Cancer Netw. 2023;21:1281-1301

NCCN GUIDELINES FOR EARLY MM



National Comprehensive Cancer Network®

NCCN Guidelines Version 2.2024
Multiple Myeloma

NCCN Guidelines Index
Table of Contents
Discussion

THERAPY FOR PREVIOUSLY TREATED MULTIPLE MYELOMA[a-d,n-r]
Relapsed/Refractory Disease After 1–3 Prior Therapies

Other Recommended Regimens

- **Carfilzomib (twice weekly)/dexamethasone (category 1)**
- **Elotuzumab/lenalidomide/dexamethasone (category 1)**
- **Ixazomib/lenalidomide/dexamethasone (category 1)**
- **Bortezomib/cyclophosphamide/dexamethasone**
- **Bortezomib/lenalidomide/dexamethasone**
- **Carfilzomib/cyclophosphamide/dexamethasone**
- **Daratumumab/cyclophosphamide/bortezomib/dexamethasone**
- **Elotuzumab/bortezomib/dexamethasone**
- **Ixazomib/cyclophosphamide/dexamethasone**
- **Lenalidomide/cyclophosphamide/dexamethasone**

After two prior therapies including an IMiD and a PI and disease progression on/within 60 days of completion of last therapy
- **Pomalidomide/cyclophosphamide/dexamethasone**

Useful in Certain Circumstances

- **Bortezomib/dexamethasone (category 1)**
- **Bortezomib/liposomal doxorubicin/dexamethasone (category 1)**
- **Lenalidomide/dexamethasone (category 1)**
- **Carfilzomib/cyclophosphamide/thalidomide/dexamethasone**
- **Carfilzomib (weekly)/dexamethasone**
- **Selinexor/carfilzomib/dexamethasone**
- **Selinexor/daratumumab/dexamethasone**
- **Venetoclax/dexamethasone ± daratumumab or PI only for t(11;14) patients**

After two prior therapies including IMiD and a PI and with disease progression on/within 60 days of completion of last therapy
- **Pomalidomide/dexamethasone (category 1)**
- **Ixazomib/pomalidomide/dexamethasone**
- **Selinexor/pomalidomide/dexamethasone**

For treatment of aggressive MM
- **Dexamethasone/cyclophosphamide/etoposide/cisplatin (DCEP)**
- **Dexamethasone/thalidomide/cisplatin/doxorubicin/cyclophosphamide/etoposide (DT-PACE) ± bortezomib (VTD-PACE)**

After at least three prior therapies including a PI and an IMiD or are double-refractory to a PI and an IMiD
- **Daratumumab**

[a] Selected, but not inclusive of all regimens. The regimens under each preference category are listed by order of NCCN Category of Evidence and Consensus alphabetically.
[b] Supportive Care Treatment for Multiple Myeloma (MYEL-H).
[c] General Considerations for Myeloma Therapy (MYEL-F).
[d] Management of Renal Disease in Multiple Myeloma (MYEL-K).
[n] Regimens included under 1–3 prior therapies can also be used later in the disease course. Attempt should be made to use drugs/drug classes the patients have not been exposed to or exposed to >1 line prior.
[o] Autologous HCT should be considered in patients who are eligible and have not previously received HCT or had a prolonged response to initial HCT.
[q] If relapse occurs >6 months after stopping treatment, the primary regimen could be considered.
[r] Consider single-agent lenalidomide or pomalidomide for patients with steroid intolerance.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

Continued MYEL-G 4 OF 5

HCT, haematopoietic stem cell transplantation; IMiD, immunomodulatory drug; MM, multiple myeloma; PI, proteasome inhibitor

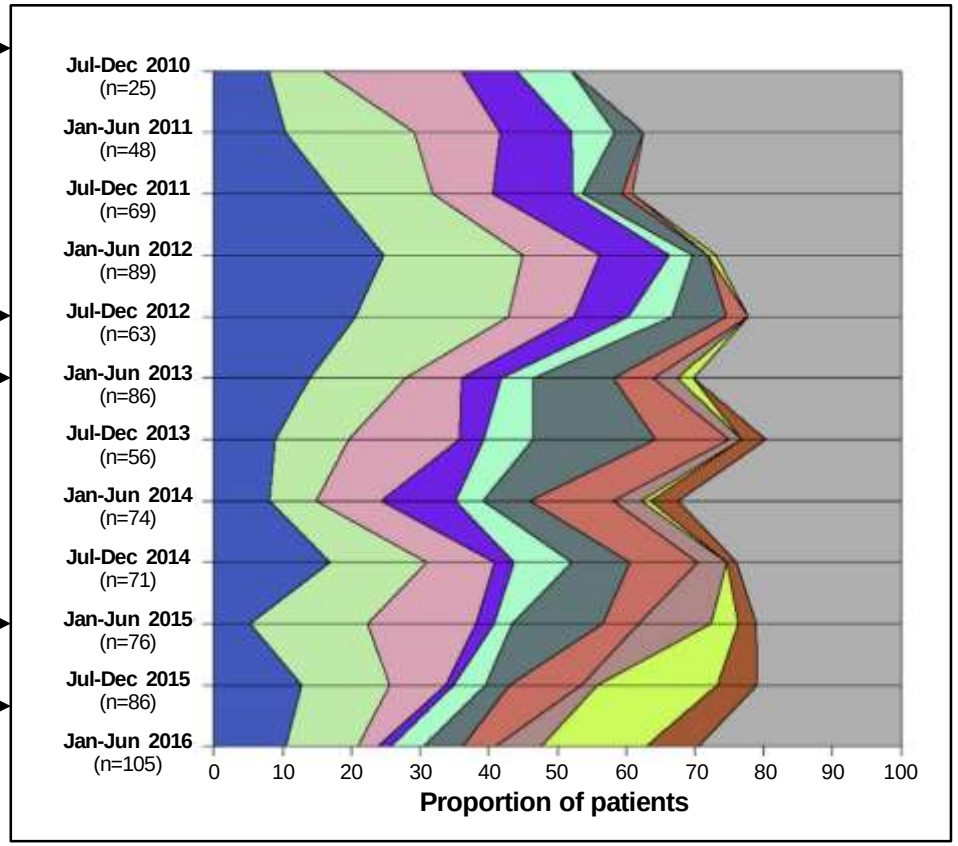
Kumar SK, et al. J Natl Compr Cancer Netw. 2023;21:1281-1301

SECOND LINE TREATMENT PATTERNS IN THE CONNECT MM REGISTRY FROM 2010 TO 2016

Prior to 2010
Bortezomib
Thalidomide
Lenalidomide
Doxorubicin

Jul 2012:
Carfilzomib
Feb 2013:
Pomalidomide

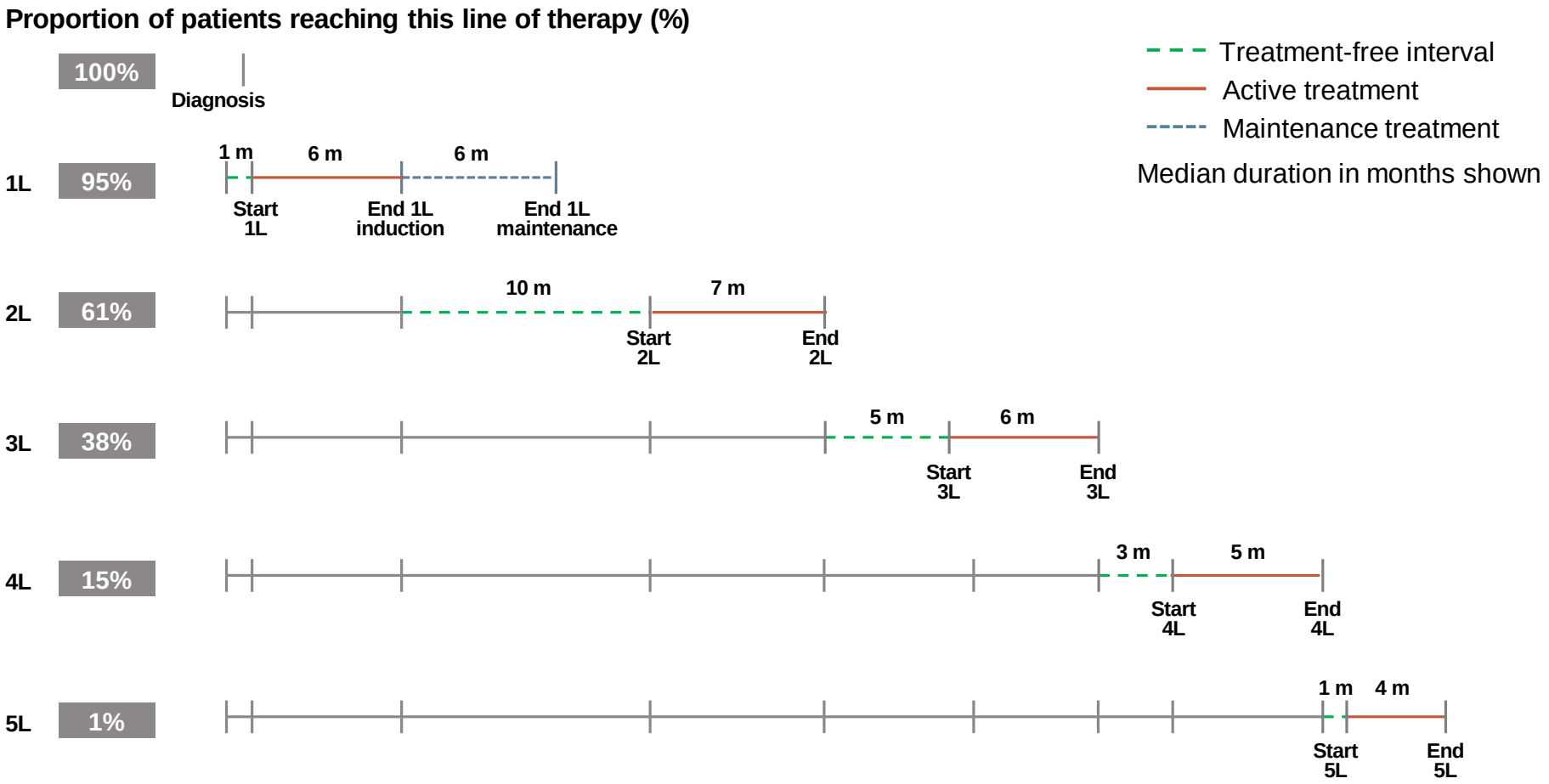
Feb 2015:
Panobinostat
Nov 2015
Daratumumab
Ixazomib
Elotuzumab



Cy, cyclophosphamide; d, dexamethasone; K, carfilzomib; MM, multiple myeloma; P, pomalidomide; R, lenalidomide; V, bortezomib

Jagannath S, et al. Clin Lymphoma Myeloma Leuk. 2018;18:480-485.e3

TREATMENT DURATION AND TREATMENT-FREE INTERVALS IN REAL-WORLD PRACTICE

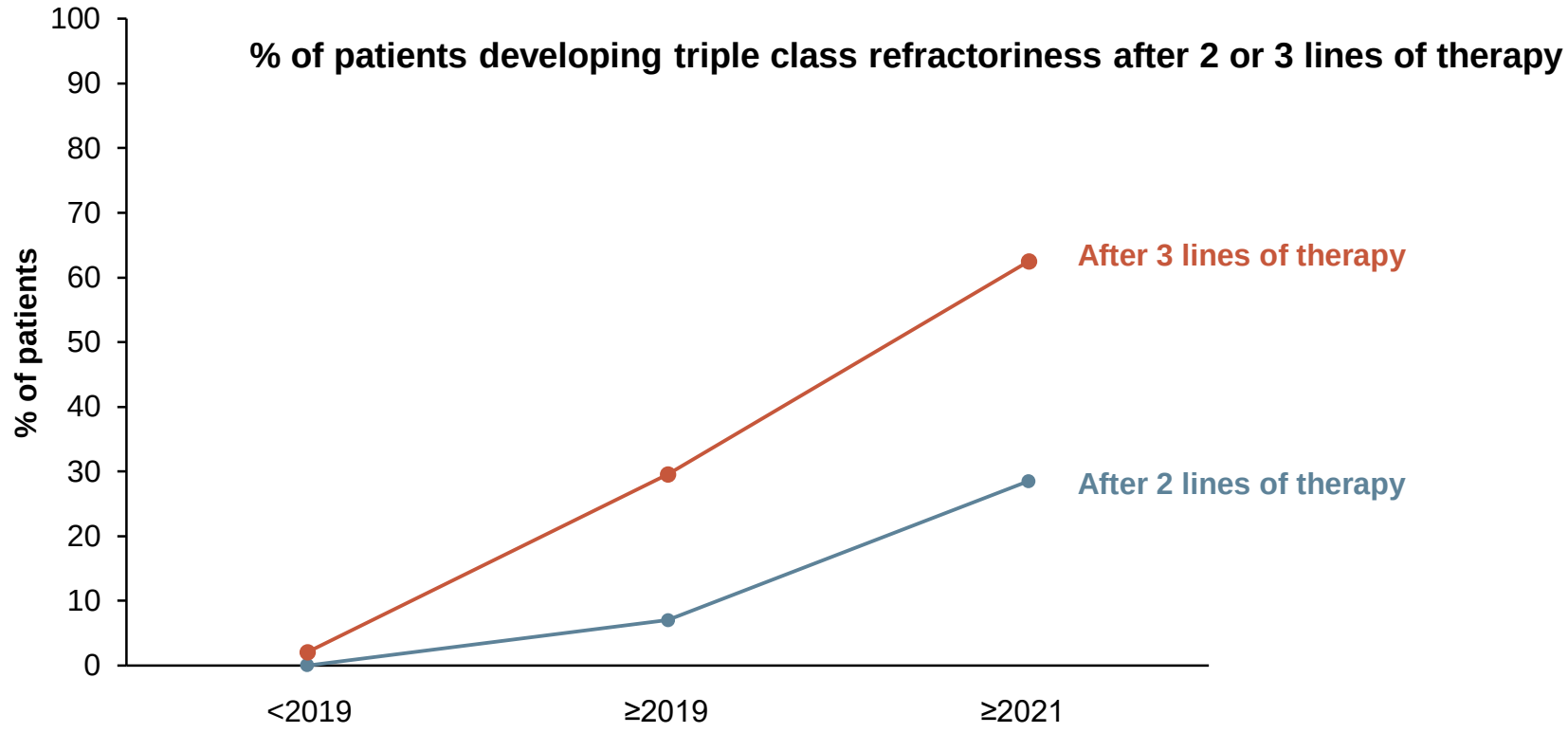


Data from 4997 patient charts in Belgium, France, Germany, Italy, Spain, Switzerland, and the UK. The proportion of patients who had received each line are from a cross-sectional review; data on durations of treatment and treatment-free intervals are from a retrospective review.
1L-5L, first line-fifth line treatment; m, month

Yong K, et al. Br J Haematol. 2016;175:252-264

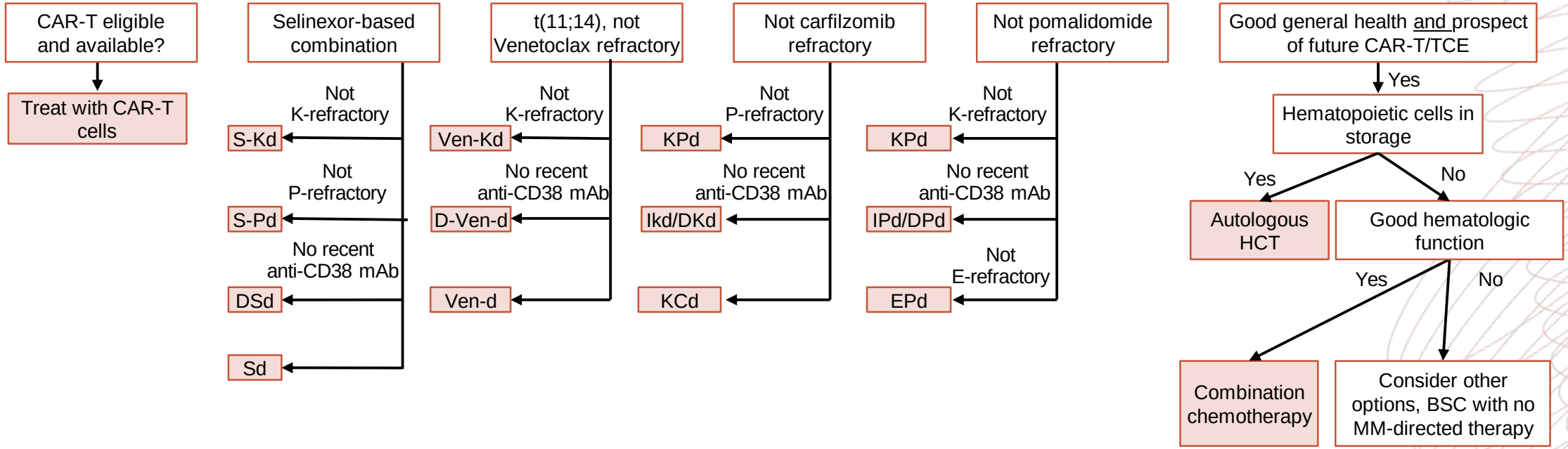
PREVALENCE OF TRIPLE CLASS REFRACTORINESS IS GROWING

REAL-WORLD ASSESSMENT OF REFRACTORINESS PATTERNS IN 413 PATIENTS TREATED IN AN ITALIAN HAEMATOLOGICAL TERTIARY CARE CENTRE



Morè S, et al. Br J Haematol. 2023; 201:432-442

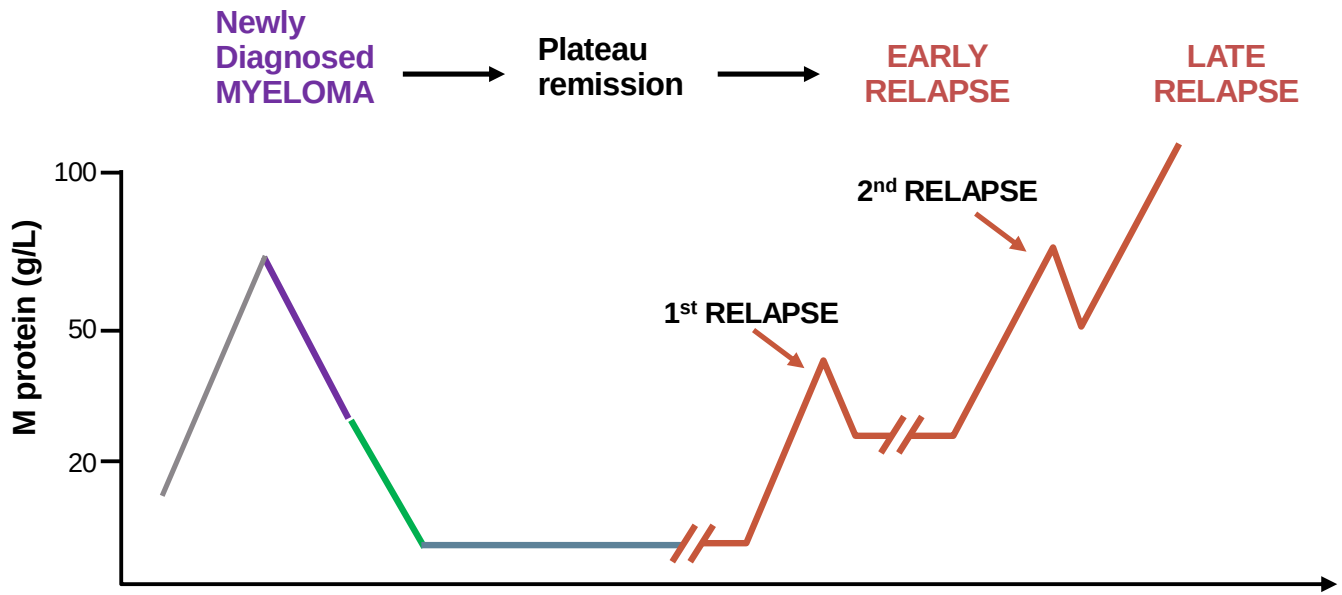
SUGGESTED APPROACH TO THE TREATMENT OF TRIPLE CLASS REFRACTORY EARLY RRMM



BSC, best supportive care; C, cyclophosphamide; CAR-T, chimeric antigen receptor T cell (therapy); d, dexamethasone; D, daratumumab; E, elotuzumab; HCT, hematopoietic cell transplantation; I, isatuximab; K, carfilzomib; mAb, monoclonal antibody; MM, multiple myeloma; P, pomalidomide; S, selinexor; TCE, T-cell engager; Ven, venetoclax

Adapted from Costa LJ, et al. Br J Haematol. 2022;198:244-256

PREDICTION: HOW WILL WE TREAT RRMM IN 5 YEARS' TIME?



Induction
QUAD: No transplant

Consolidation
MRD+: CAR T (TE) vs. Bispecific (TI)

Maintenance
MRD-: Maintenance: Lenalidomide/mAb vs. Bispecific

Early relapse (1-3 prior lines)
XPO1 inhibitor
Novel CAR T (Different Ag)
Novel Ab: ADC-combination vs. bi-/trivalent Ab

Late relapse
Third party cellular therapy (NK + T cell)
CRISPR gene editing strategies
Bispecific combinations

ADC, antibody-drug conjugate; Ag, antigen; CAR T, chimeric antigen receptor T cell; CRISPR, clustered regularly interspaced short palindromic repeats; (m)Ab, (monoclonal) antibody; M protein, monoclonal protein (or M spike); MRD, minimal residual disease; NK, natural killer; QUAD, quadruplet; RRMM, relapsed/refractory multiple myeloma; TE, transplant eligible; TI, transplant ineligible; XPO1, exportin 1

Slide adapted from presentation at ASCO 2020 (Tom Martin).

KEY CLINICAL TAKEAWAYS

- Myeloma is a continually evolving field with modern day induction regimens yielding near 100% response rates in the front-line setting with typically durable remissions
- This has been achieved through triplets and quadruplets comprised of the 3 classic MOAs: IMiD, PI, mAb
- In the relapsed/refractory space it is important to embrace novel MOAs/targets to optimally manage recurrent disease: XPO1, BCMA, GPRC5d
- T-cell health is an important long-term consideration for patients to maximise efficacy of T-cell redirection therapy
- Treatments that are T-cell-sparing, such as XPO1 inhibitors and IMiDs, have the potential to preserve T-cell health

BCMA, B-cell maturation antigen; GPRC5D, G protein–coupled receptor class C group 5 member D; IMiD, immunomodulatory drug; mAb, monoclonal antibody; MOA, mechanism of action; PI, proteasome inhibitor; XPO1, exportin 1

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