COR2ED

THE HEART OF MEDICAL EDUCATION

PART 3

MULTIPLE MYELOMA: CURRENT BEST PRACTICES IN THE TREATMENT OF EARLY RRMM – AN EXPERT VIEW

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September 2024

MM, multiple myeloma; RR, relapse/refractory

DEVELOPED BY LYMPHOMA & MYELOMA CONNECT

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

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EDUCATIONAL OBJECTIVES

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

APPROACH TO RELAPSED MM
DRUG CLASSES, CAR-T AND TRIPLET COMBINATIONS

MM, multiple myeloma

AN APPROACH TO RELAPSED MM

NOT A SIMPLE ALGORITHM OF TREATMENT #1, THEN #2, THEN #3…

Categories

- 1-3 prior lines AND ≥4 prior lines
- Optimize the use of the 4 major classes of drugs in early relapse (recent incorporation of CAR-T):
  - proteasome inhibitors
  - immunomodulatory agents
  - monoclonal antibodies
  - XPO1 inhibitors

Principles

1. Depth of response matters…*likely incorporate MRD soon*
2. High risk vs. standard risk…*more aggressive treatment in high-risk*
3. Balance efficacy and toxicity…*initially and constantly assess*
4. Overcome drug resistance…*change mechanism of action when possible*

Expert view

MM, multiple myeloma; MRD, minimal residual disease; XPO1, exportin-1

DRUGS APPROVED FOR THE TREATMENT OF RRMM

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

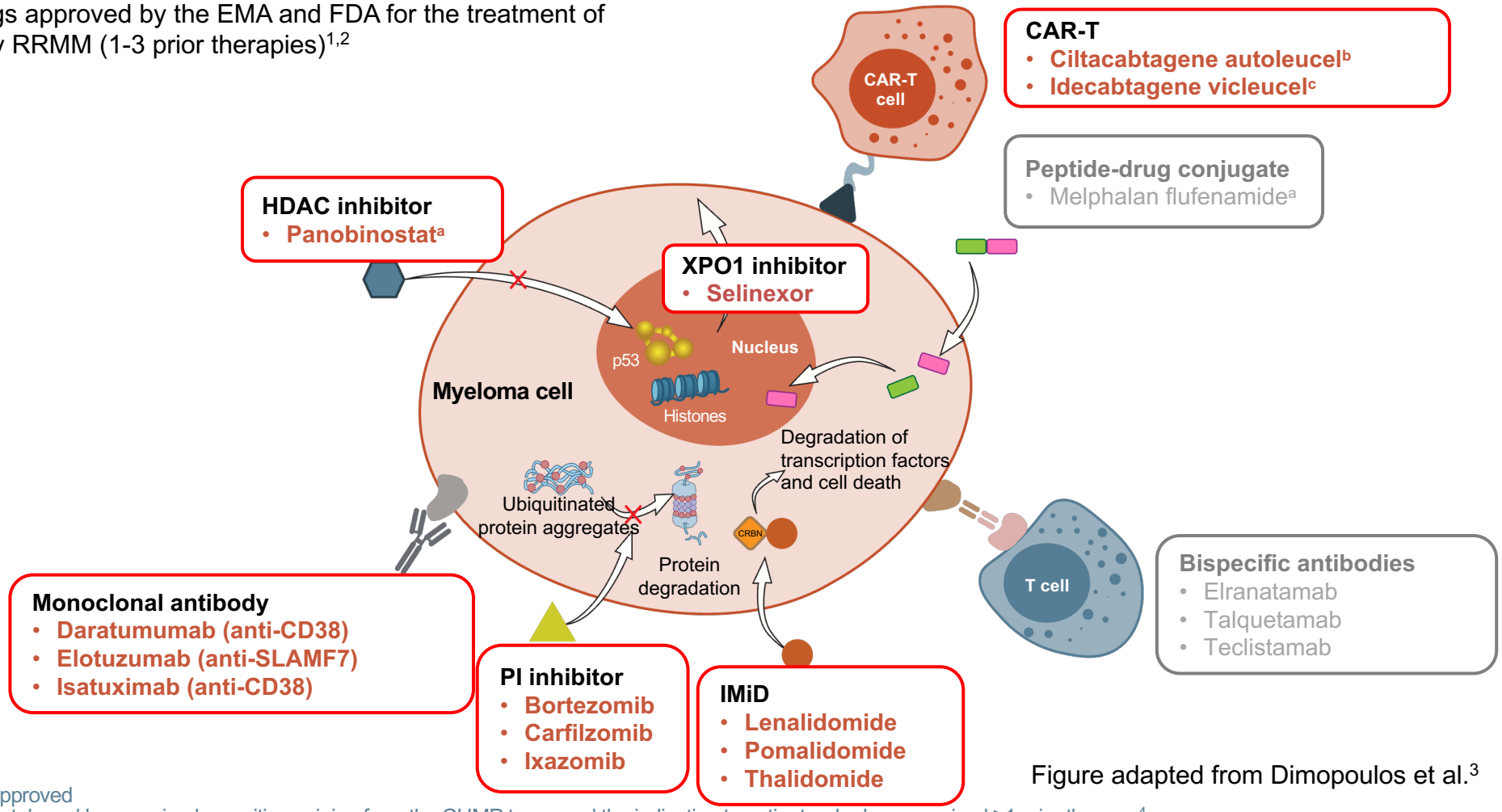


Figure adapted from Dimopoulos et al.[3]

[a] No longer FDA-approved
[b] Ciltacabtagene autoleucel has received a positive opinion from the CHMP to expand the indication to patients who have received ≥1 prior therapy.[4]
[c] Idecabtagene vicleucel is approved for the treatment of patients who have received ≥2 prior therapies

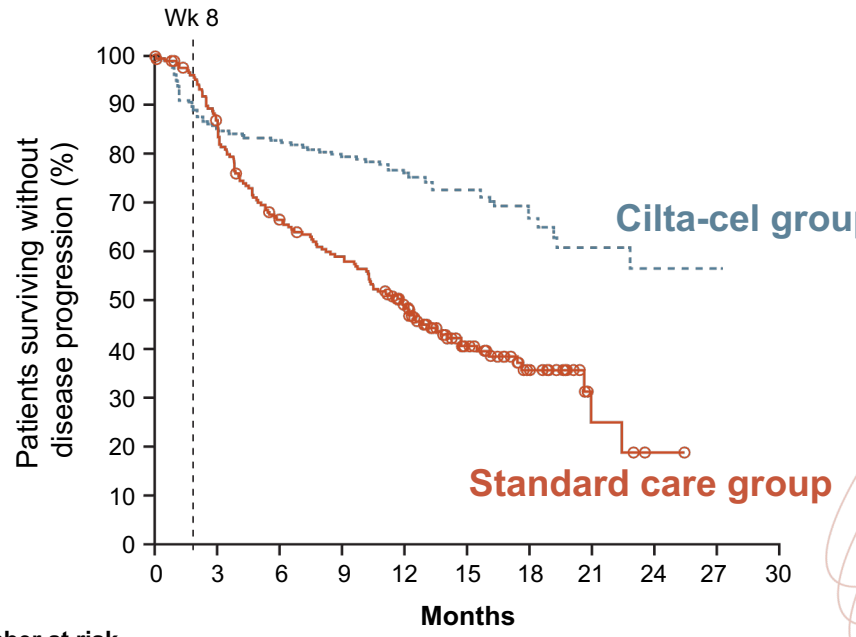
CAR T, chimeric antigen receptor T cell; CD38, cluster of differentiation 38; CHMP, Committee for Medicinal Products for Human Use; EMA, European Medicines Agency; HDAC, histone deacetylase; IMiD, immunomodulatory drug; p53, tumour protein 53; PI, proteasome inhibitor; RRMM, relapsed/refractory multiple myeloma; SLAMF7, signalling lymphocyte activation molecule family 7; XPO1, exportin 1

1. Summary of Product Characteristics available from: https://www.ema.europa.eu/en/medicines. Last accessed 4 April 2024; 2. US Product Information available from: https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm. Last accessed 12 June 2024; 3. Dimopoulos M-A, et al. Clin Lymphoma Myeloma Leuk. 2022;22:460-473;
4. https://www.ema.europa.eu/en/medicines/human/variation/carvykti. Last accessed 12 June 2024

CARTITUDE-4: CILTA-CEL
RECENTLY APPROVED IN ALL RELAPSED MM

- 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
- Overall, CAR-T–specific adverse events were manageable with appropriate supportive care
- 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 pomalidomide, bortezomib and dexamethasone

CAR T, chimeric antigen receptor T cell; CI, confidence interval; cilta-cel, ciltacabtagene autoleucel; HR, hazard ratio; MM, multiple myeloma; ORR, overall response rate; Wk, week

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

PATIENT OUTCOMES IN REAL-WORLD PRACTICE

ONLY FEW PATIENTS WITH MM REACH LATER LINES OF THERAPY

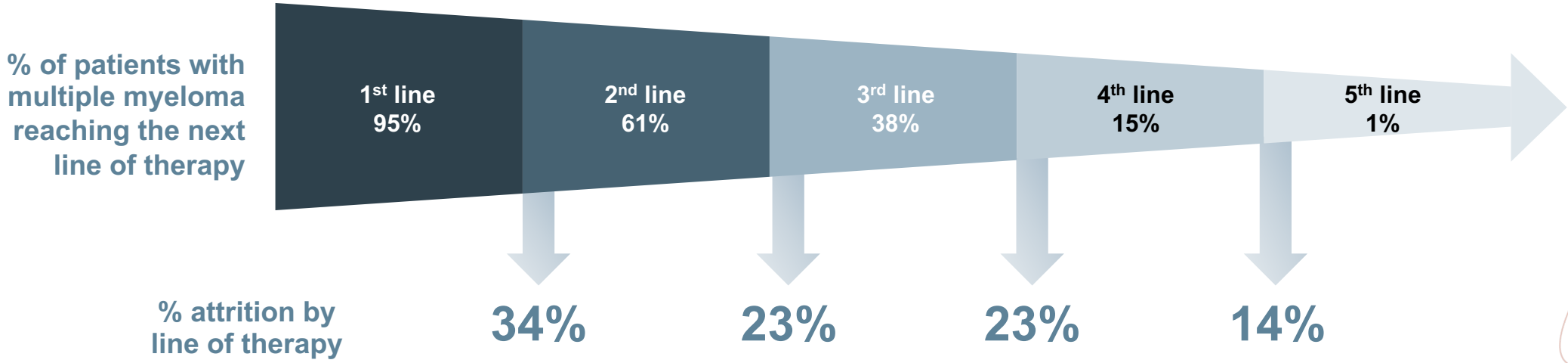


Figure adapted from Yong et al.

In every new line of therapy, ~15-35% of patients are lost

MM, multiple myeloma

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

EARLY RELAPSE

In real practice, most patients at first relapse will have one of the following:

- Daratumumab + pomalidomide + dexamethasone (APOLLO)
- Isatuximab + pomalidomide + dexamethasone (ICARIA)

- Daratumumab + carfilzomib + dexamethasone (CANDOR)
- Isatuximab + carfilzomib + dexamethasone (IKEMA)

- Selinexor + bortezomib + dexamethasone (BOSTON)

ANTI-CD38 TRIPLET REGIMENS

IMPROVED PFS IN PATIENTS WITH MM

DKd

CANDOR[1]

DKd vs. Kd after ≥ PR to 1-3 prior lines

mPFS 29 vs. 15 mo

HR 0.59

	PFS HR
Len-refractory	0.46
≥2 prior LOT	0.55
High risk	0.49

DKd was associated with a favourable benefit-risk profile

Isa-Kd

IKEMA[2]

Isa-Kd vs. Kd after 1-3 prior lines,

mPFS 36 vs. 19 mo

HR 0.53

	PFS HR
Len-refractory[c]	0.60
≥1 prior LOT[c]	0.48
High risk[d]	0.72

The safety profile was manageable and as expected

DPd

APOLLO[3]

Dara-Pd vs. Pd after ≥1 prior line with len and PI

mPFS 12 vs. 7 mo

HR 0.63

z	PFS HR
Len-refractory	0.66
2-3 prior LOT	0.66
High risk	0.85

No new safety concerns were identified with the daratumumab combination

Isa-Pd

ICARIA-MM[4]

Isa-Pd vs. Pd after ≥2 prior lines with len and PI

mPFS 12 vs. 6 mo

HR 0.60

	PFS HR
Len-refractory	0.59
≥3 prior LOT	0.59
High risk	0.66

The addition of isatuximab to pomalidomide and dexamethasone was well tolerated

CD38, cluster of differentiation 38; d, dexamethasone; D, daratumumab; HR, hazard ratio; Isa, isatuximab; len, lenalidomide; K, carfilzomib; LOT, line of therapy; MM, multiple myeloma; mo, months; (m)PFS, (median) progression-free survival; P, pomalidomide; PI, proteasome inhibitor; PR, partial response

1. Usmani SZ, et al. Lancet. Oncol. 2022;23:65-76; 2. Moreau P, et al. Lancet. 2021;397:2361-2371; 3. Dimopoulos MA, et al. Lancet Oncol. 2021;22:801-812; 4. Attal M, et al. Lancet. 2019;394:2096-2107

NCCN GUIDELINES
EARLY RELAPSE

NCCN GUIDELINES
EARLY RELAPSE

Therapy for previously treated multiple myeloma Relapsed/refractory disease after 1-3 prior therapies	
Preferred regimens *Order of regimens does not indicate comparative efficacy*	
Bortezomib-refractory	Lenalidomide-refractory
• 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 therapy 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 therapy including lenalidomide and a PI* • Isatuximab-irfc/pomalidomide/dexamethasone (category 1) After two prior therapies including an IMiD and a PI with disease progression on/within 60 days of completion of last therapy • Ixazomib/pomalidomide/dexamethasone

IMiD, immunomodulatory drug; PI, proteasome inhibitor

Kumar SK, et al. Multiple Myeloma, Version 2.2024, NCCN Clinical Practice Guidelines in Oncology. J Natl Compr Canc Netw. 2023;21(12):1281-301

NCCN GUIDELINES
EARLY RELAPSE

Therapy for previously treated multiple myeloma Relapsed/refractory disease after 1-3 prior therapies	
Other recommended regimens	
• Carfilzomib (twice weekly)/dexamethasone (category 1) • Elotuzumab/lenalidomide/dexamethasone (category 1) • Bortezomib/cyclophosphamide/dexamethasone (category 1) • 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 with 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 an IMiD and a PI 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 • Dexamethasone/thalidomide/cisplatin/doxorubicin/cyclophosphamide/etoposide ± bortezomib After at least three prior therapies including a PI and an IMiD or are double-refractory to a PI and an IMiD • Daratumumab

IMiD, immunomodulatory drug; MM, multiple myeloma; PI, proteasome inhibitor.

Kumar SK, et al. Multiple Myeloma, Version 2.2024, NCCN Clinical Practice Guidelines in Oncology. J Natl Compr Canc Netw. 2023;21(12):1281-301

XPO1 INHIBITOR
MoA, EFFICACY AND SAFETY, GUIDANCE ON USE

MoA, mechanism of action; XPO1, exportin-1

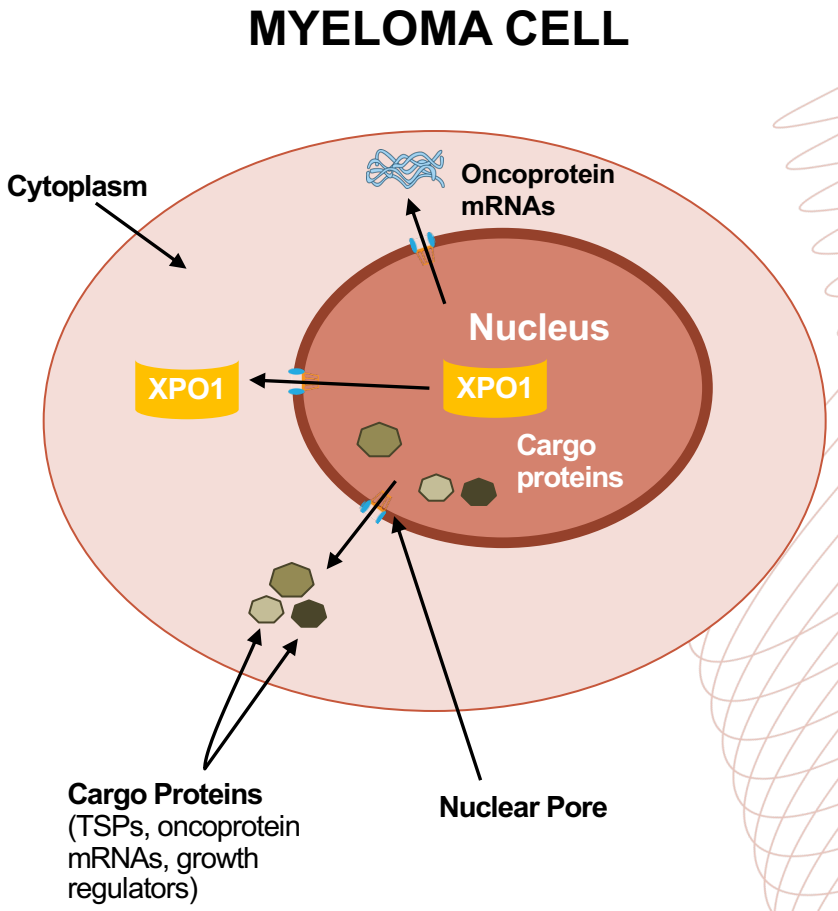
SELINEXOR IS A FIRST IN CLASS ORAL XPO1 INHIBITOR
MECHANISM OF ACTION

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; mRNA, messenger RNA; TSP, tumour suppressor protein; XPO1, exportin 1

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

SELINEXOR IS A FIRST IN CLASS ORAL XPO1 INHIBITOR

APPROVALS, DOSING, TRIALS, OUTCOMES AND SAFETY

	Sd[1]	SVd[2]	SPd[3]	SDd[4]	SKd[5,6]	SDVd[7]
FDA approval	≥4 prior treatments and refractory to 2 PI, 2 IMiD, and anti-CD38 mAb	≥1 prior therapy	N/A	N/A	N/A	N/A
Selinexor dosing[a]	80 mg BIW	100 mg QW	60 mg QW; SPd (P: 4 mg QD)	100 mg QW; SDd (D: 16 mg/kg)	80 mg QW; SKd (K: 56 mg/m^2)	100 mg Q4W (pt 1) 60 mg Q5W (pt 2)
Clinical trial	STORM trial (N=122) Phase 2b, single-arm	BOSTON trial (N=402) Phase 3	STOMP trial (N=65) Phase 1b/2	STOMP trial (N=34/30[b]) Phase 1/2b	STOMP trial (N=32) Phase 1b/2	SELIBORDARA (N=57) Phase 2
Comparator	N/A (median seven treatment lines)	SVd vs. Vd (V: 1.3 mg/m^2)	N/A (2+ lines of treatment)	N/A (≥3 lines of treatment)	N/A (1+ line of treatment)	N/A (≥3 lines of treatment [pt 1]; ≥1 lines of treatment [pt 2])
Outcomes (months)	mPFS = 3.7 mOS = 8.6	mPFS = 13.9 vs. 9.5	mPFS= 12.2	mPFS = 12.5	mPFS = 15/23.7$^{\text{triple-ref}}$	mPFS = 7.2 (pt 1); 25.1 (pt 2) mOS = 28.5 (pt 1); NR (pt 2)
Side effects	Thrombocytopenia, nausea, fatigue, anemia, neutropenia occurred across all trials					
Pearls[1,5]	Optimize hydration, caloric intake, blood counts, and concomitant medications, and give with antiemetics					

Safety: Side effects were consistent among studies. No new risks were identified for the combination therapies

[a] Dexamethasone 20 mg in STORM and 40 mg in BOSTON and STOMP trials; [b] CD38 mAb naïve

BIW, twice weekly; CD38, cluster of differentiation 38; d, dexamethasone; D, daratumumab; FDA, Food and Drug Administration; IMiD, immunomodulatory drug; N/A, not applicable; K, carfilzomib; mOS, median overall survival; mPFS, median progression-free survival; P, pomalidomide; PI, proteasome inhibitor; QD, daily; QW, weekly; S, selinexor; triple-ref, refractory to three drug classes; V, bortezomib; XPO1, exportin 1

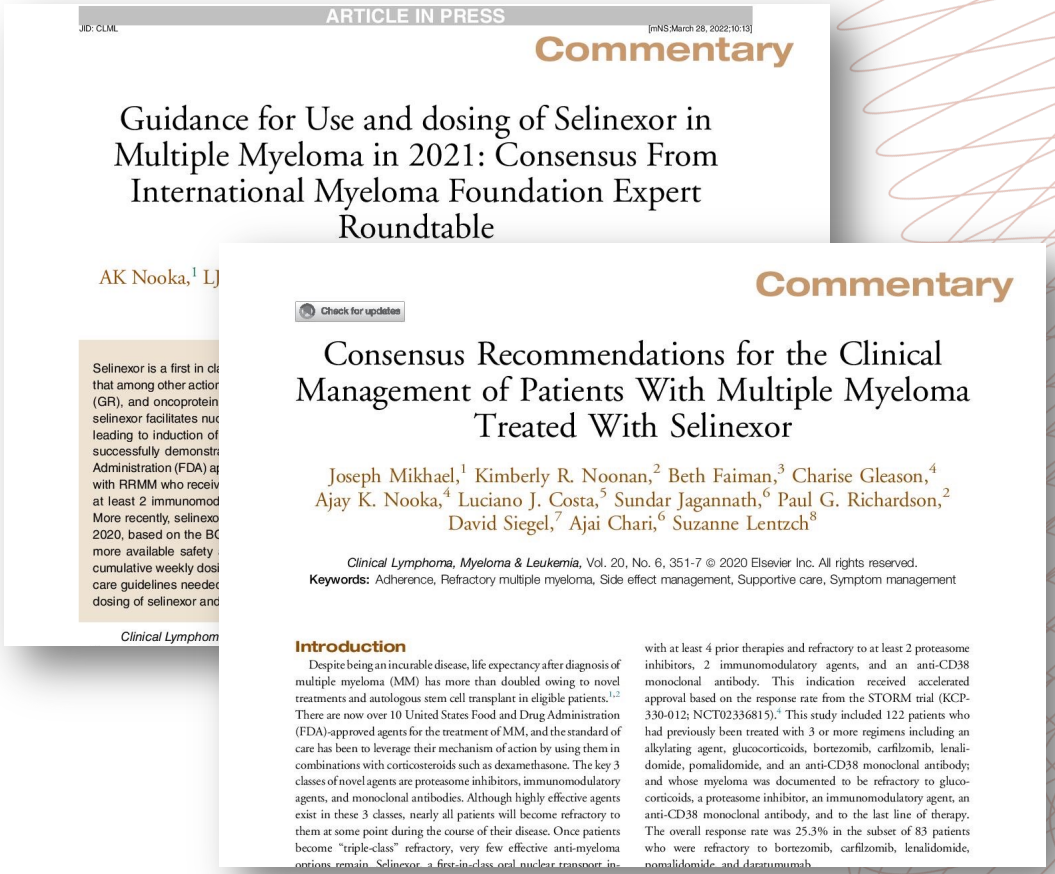
1. Chari A, et al. N Engl J Med. 2019;381:727-738; 2. Grosicki S, et al. Lancet. 2020;396:1563-73; 3. Chen CI, et al. Blood. 2020;136 (supplement 1):18-19 (Presented at ASH 2020); 4. Gasparetto C, et al. EJHaem. 2020;2:56-65; 5. Gasparetto C, et al. Br J Cancer. 2022;126:718-725; 6. Schiller GJ, et al. Blood. 2022;140 (supplement 1):10050-10053; 6. 7. González-Calle V, et al. Haematologica. 2024. Epub ahead of print. PMID: 38356463

SELINEXOR IS A FIRST IN CLASS ORAL XPO1 INHIBITOR
GUIDANCE AND EXPERT RECOMMENDATIONS

Selinexor has to be **administered carefully**, especially in the **first month**

Expert recommendations – Dr Mikhael

- **PREVENT** anorexia and nausea with two antiemetic agents (classic 5-HT3 antagonist AND olanzapine)
- **HYDRATE** weekly for the first weeks
- **MONITOR** food intake and possibly weight if meals missed
- **EDUCATE** patients about the potential side effects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Commentary

Guidance for Use and dosing of Selinexor in Multiple Myeloma in 2021: Consensus From International Myeloma Foundation Expert Roundtable

Commentary

Check for updates

Consensus Recommendations for the Clinical Management of Patients With Multiple Myeloma Treated With Selinexor

Joseph Mikhael,[1] Kimberly R. Noonan,[2] Beth Faiman,[3] Charise Gleason,[4] Ajay K. Nooka,[4] Luciano J. Costa,[5] Sundar Jagannath,[6] Paul G. Richardson,[2] David Siegel,[7] Ajai Chari,[6] Suzanne Lentzch[8]

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Keywords: Adherence, Refractory multiple myeloma, Side effect management, Supportive care, Symptom management

Introduction

Despite being an incurable disease, life expectancy after diagnosis of multiple myeloma (MM) has more than doubled owing to novel treatments and autologous stem cell transplant in eligible patients.[1,2] There are now over 10 United States Food and Drug Administration (FDA)-approved agents for the treatment of MM, and the standard of care has been to leverage their mechanism of action by using them in combinations with corticosteroids such as dexamethasone. The key 3 classes of novel agents are proteasome inhibitors, immunomodulatory agents, and monoclonal antibodies. Although highly effective agents exist in these 3 classes, nearly all patients will become refractory to them at some point during the course of their disease. Once patients become "triple-class" refractory, very few effective anti-myeloma options remain. Selinexor, a first-in-class oral nuclear transport in-

with at least 4 prior therapies and refractory to at least 2 proteasome inhibitors, 2 immunomodulatory agents, and an anti-CD38 monoclonal antibody. This indication received accelerated approval based on the response rate from the STORM trial (KCP-330-012; NCT02336815).[4] This study included 122 patients who had previously been treated with 3 or more regimens including an alkylating agent, glucocorticoids, bortezomib, carfilzomib, lenalidomide, pomalidomide, and an anti-CD38 monoclonal antibody; and whose myeloma was documented to be refractory to glucocorticoids, a proteasome inhibitor, an immunomodulatory agent, an anti-CD38 monoclonal antibody, and to the last line of therapy. The overall response rate was 25.3% in the subset of 83 patients who were refractory to bortezomib, carfilzomib, lenalidomide, pomalidomide, and daratumumab

Expert view

5-HT3, 5-hydroxytryptamine type 3 (receptor); XPO1, exportin 1

Nooka AK, et al. Clin Lymphoma Myeloma Leuk. 2022;22:e526-e531; Mikhael J, et al. Lymphoma Myeloma Leuk. 2020;20:351-357

SELINEXOR IS A FIRST IN CLASS ORAL XPO1 INHIBITOR
GUIDANCE AND EXPERT EXPERIENCE

Selinexor has to be **administered carefully**, especially in the **first month**

Expert experience – Dr Mikhael

1. Starting dose is 100 mg per US PI, but in my practice, **I start with a lower dose**
2. I tell every patient the **worst month** is the **first month**
3. I dose the **5-HT3 antagonist** continuously the day prior, the day of and the day after each dose of selinexor for the first month
4. I dose the **olanzapine (usually 2.5 mg)** the night prior, the night of and the night after each dose of selinexor for the first month
5. **Dose de-escalation** of the **antiemetics** can then occur – most patients do not need them in the long-term
6. I arrange for an evaluation if they **miss more than two meals** in a row in the first month
7. I dose **weekly dexamethasone** on the **same day** as **selinexor**
8. I **engage the patient's care partner** to be aware of the potential side effects


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Commentary

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AK Nooka,[1] LJ

Commentary

Check for updates

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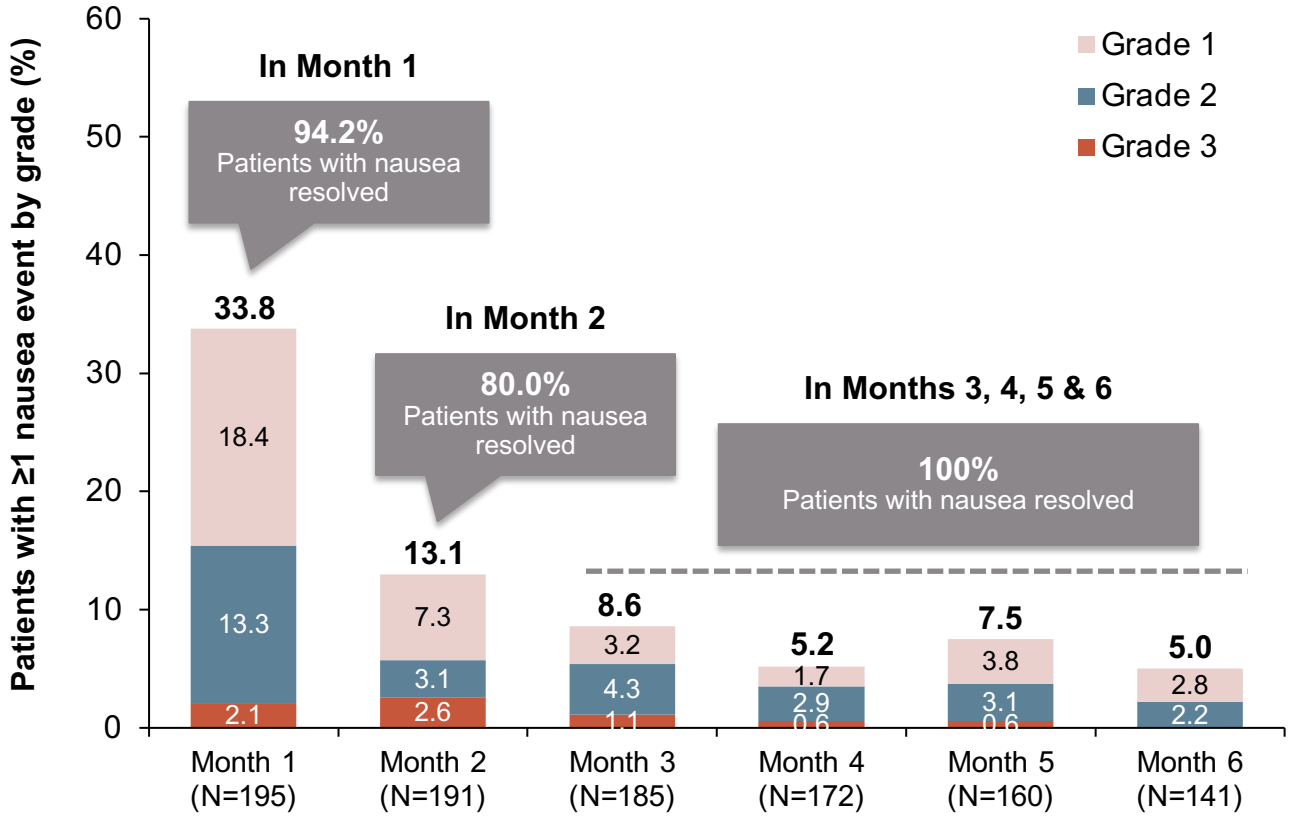
Expert view

5-HT3, 5-hydroxytryptamine type 3 (receptor); US PI, United States Product Information; XPO1, exportin 1

Nooka AK, et al. Clin Lymphoma Myeloma Leuk. 2022;22:e526-e531; Mikhael J, et al. Lymphoma Myeloma Leuk. 2020;20:351-357

SVd TREATMENT-RELATED NAUSEA IN BOSTON WAS TRANSIENT WITH DECREASING INCIDENCE AFTER THE FIRST MONTH OF THERAPY

Percentage of Patients Experiencing Nausea Events per Month in the SVd Arm of BOSTON



In the SVd arm, nausea events were observed in 50% of patients (% Grade 3).

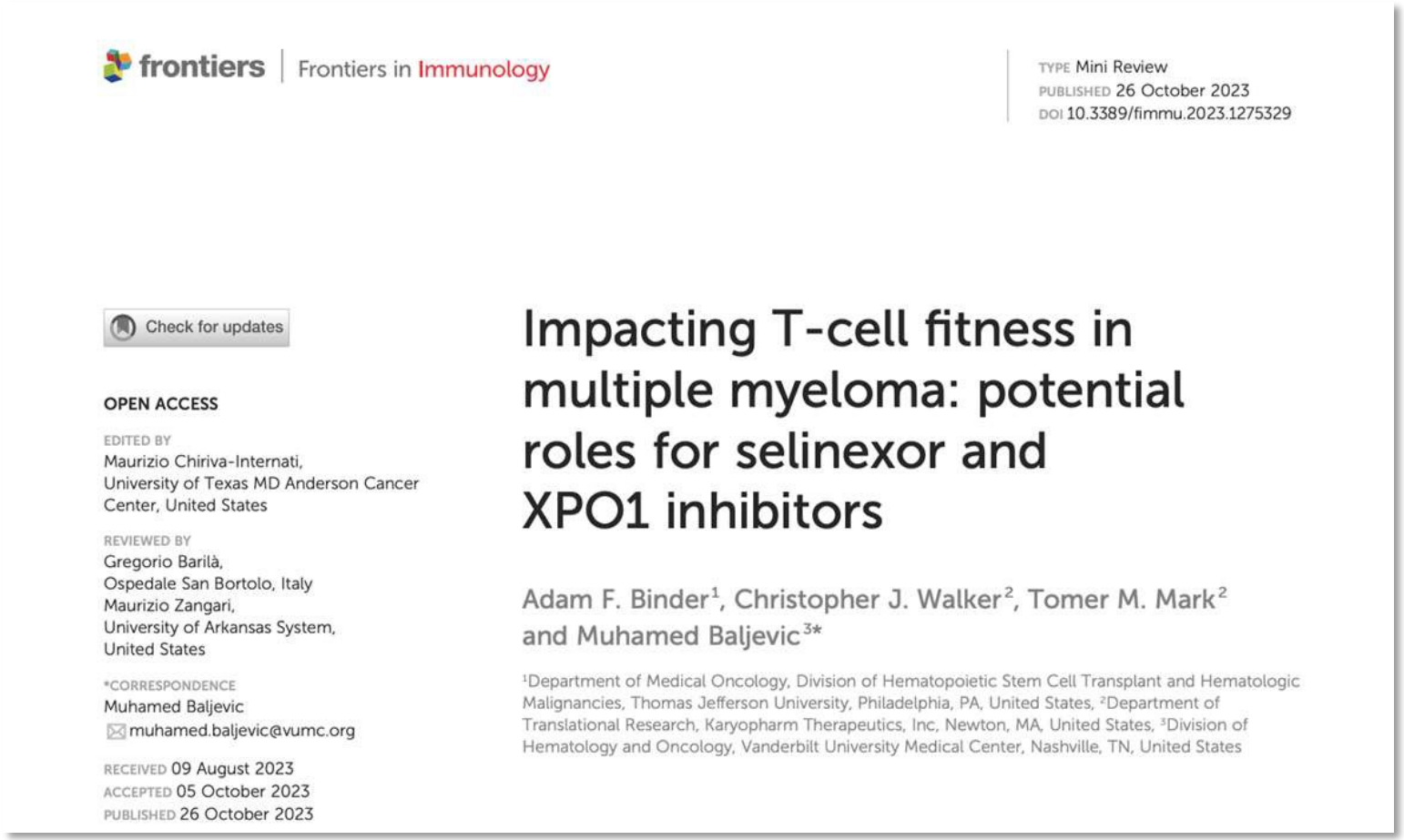
The SVd trial protocol required a prophylactic 5-HT3 antagonist to address nausea but allowed for other interventions as required.

SVd, selinexor, bortezomib, dexamethasone

Nooka AK, et al. Clin Lymphoma Myeloma Leuk. 2022;7:e526-e531

HOW DOES SELINEXOR FIT INTO OUR USE OF CAR-T?

EMERGING EVIDENCE THAT SELINEXOR DOES NOT IMPAIR T-CELL HEALTH



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Impacting T-cell fitness in multiple myeloma: potential roles for selinexor and XPO1 inhibitors

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CAR-T, chimeric antigen receptor T-cell;
Binder AF, et al. Front Immunol. 2023:14:1275329;

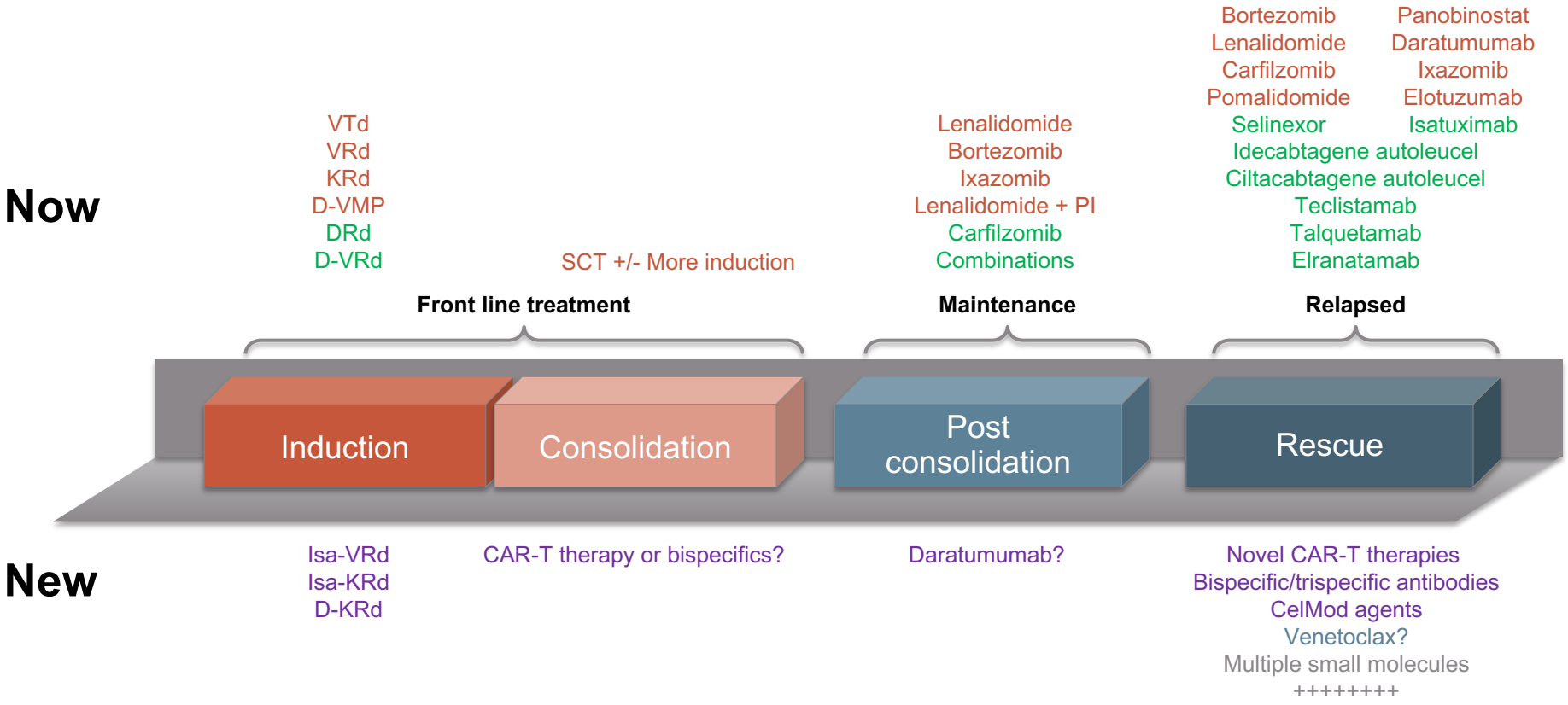
KEY CLINICAL TAKEAWAYS

- The **treatment landscape** for **early relapsed multiple myeloma** is expanding, including **CAR-T cell therapies** now available (prioritised for functional high-risk patients)
- **Early relapse** management involves **several drug classes**:
  - Immunomodulatory agents, proteasome inhibitors, monoclonal antibodies, XPO1 inhibitors
- **Selinexor** is a first-in-class **XPO1 inhibitor**. Side effects can be managed through **dose modifications** and with the use of **antiemetics**
- **General principles** of therapy selection include:
  - **Introducing** a new **mechanism of action**
  - Using a **triplet combination**
  - Selecting the **best combination** based on **patient, disease** and **treatment characteristics**

There is no “perfect” sequence

CAR-T, chimeric antigen receptor T cell; XPO1, exportin-1

THE EVOLUTION OF MYELOMA THERAPY



Expert view

CAR-T, chimeric antigen receptor T-cell; Cy, cyclophosphamide; d, daratumumab; d, dexamethasone; Isa, isatuximab; K, carfilzomib; M, melphalan; PI, proteasome inhibitor; R, lenalidomide; SCT, stem cell transplant; T, thalidomide; V, bortezomib

FIND OUT MORE ABOUT RRMM IN PARTS 1 AND 2

PART 1: UNMET MEDICAL NEEDS IN EARLY RELAPSE

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

MM, multiple myeloma; RR, relapsed/refractory;

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