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Practical Considerations for Early Relapsed/Refractory Multiple Myeloma in the Canadian Landscape in 2025

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Background

Multiple-class drug combinations have long been integral to the management of multiple myeloma (MM). This has led to significant advances in myeloma survival with agents such as lenalidomide and daratumumab moving to frontline therapy. Therefore, relapse therapy requires rational sequencing strategies to prioritize effective regimens with each treatment line without compromising access to subsequent lines.

At first relapse, most transplant-eligible patients would have undergone RVd (lenalidomide, bortezomib, dexamethasone) induction with subsequent consolidative high-dose therapy with autologous stem cell rescue and Len (lenalidomide) maintenance. For transplant-ineligible patients, frontline therapy with DRd (daratumumab, lenalidomide, dexamethasone) has become the standard of care until myeloma progression or drug intolerance. With the increasing adoption of quadruple therapy in frontline treatment, a significant proportion of patients will soon be multi-class exposed or refractory at early relapse, including exposure to daratumumab, lenalidomide, and bortezomib.

This shift necessitates careful consideration of treatment sequences based on available regimens, which include previous treatment responses, cytogenetic and molecular risk profiles (e.g., high-risk versus standard-risk disease), disease kinetics at relapse, and the potential benefit of therapies with novel mechanisms of action. Achieving and maintaining sustained minimal residual disease (MRD) negativity is also critical, as patients in this category consistently experience better outcomes, regardless of cytogenetic risk or line of therapy.[1]

The provisional algorithm from Canada's Drug Agency (CDA) sets out the currently funded and available combinations for Canadian patients with relapsed MM.[2] Patients should be treated with agents that their disease is sensitive to at the time of relapse. Most patients will be lenalidomide-refractory by the time of the second line, and by the third line, most patients will be either exposed or refractory to both an immunomodulatory drug (IMiD) and proteasome inhibitor (PI; bortezomib or carfilzomib), as well as an anti-CD38 monoclonal antibody (mAb; daratumumab or isatuximab), resulting in the need to use agents with alternative mechanisms of actions. Complicating sequencing decisions is the paucity of data supporting many of these combinations following treatment with an anti-CD38 monoclonal antibody as these are being moved into earlier lines of therapy.

The differentiation of these considerations allows for rational sequencing strategies tailored to the patient. This review will focus on patients with early relapsed/refractory MM (RRMM; 1-3 prior lines), who are relapsing on lenalidomide and daratumumab and those who are relapsing on lenalidomide but not exposed to daratumumab, with particular focus on recently available therapies, such as SVd (selinexor, bortezomib, dexamethasone), IsaKd (isatuximab, carfilzomib, dexamethasone) and IsaPd (isatuximab, pomalidomide, dexamethasone).

A Quick Primer on Daratumumab-based Combinations in Early RRMM

Daratumumab is currently available in combination with either lenalidomide or bortezomib in the relapsed setting (POLLUX, CASTOR).[3,4] The phase III POLLUX trial randomized patients to lenalidomide and dexamethasone with or without daratumumab (DRd vs. Rd). The results showed a median progression-free survival (PFS) of 45 months and median overall survival (OS) of 67.7 months DRd vs. a median PFS of 17.5 months and 51.8 months OS for Rd alone. The rates of MRD negativity were higher for the triplet combination (21 vs. 6.4%). However, OS was similar for patients who achieved MRD negativity, regardless of the therapy they received.[3] Despite the impressive results of the POLLUX trial, most patients will be ineligible for this combination as many patients received lenalidomide with or without daratumumab at frontline treatment.

As for the Phase III CASTOR trial, the median PFS was once again longer in the daratumumab arm at 16.7 months vs. 7.1 months (HR: 0.22). Similarly, patients who received daratumumab had higher rates of MRD negativity (14 vs. 2%).[4] Unfortunately, in the subgroup of patients who are lenalidomide-refractory at the last line of treatment, the median PFS was 9.3 months vs. 4.4 months, with MRD negativity rates of only 8.9% in the DVd arm compared to 0% in the Vd arm. Even in patients who were lenalidomide-exposed but not refractory, the median PFS was 9.5 months vs. 6.1 months, and MRD rates were 7.9% and 1.7%, respectively.[5] Real-world retrospective data from the Canadian Myeloma Research Group and German Munster Myeloma databases show a slight improvement in reported PFS for patients (n=23) receiving DVd, which is reported at a median of 12.9 months.[6]

Lenalidomide and Daratumumab-Refractory Patients

For patients in whom disease progresses on both lenalidomide and daratumumab (i.e. frontline DRd), primary treatment considerations based on the CADTH funding algorithm include the use of PI-based regimens, such as SVd, Kd (carfilzomib, dexamethasone) or PVd (pomalidomide, bortezomib, dexamethasone).[2] Access to Pom (pomalidomide) remains limited to double-class refractory disease (progressed on Len and PI), often in the third line or later **(Table 1)**.

Due to the early use of anti-CD38 monoclonal antibodies and lenalidomide, most patients will be refractory to these agents at early myeloma relapse. Selinexor is a first-in-class reversible nuclear export protein exportin 1 (XPO1) inhibitor. XPO-1 has been found to be upregulated in various cancer types, and increased XPO-1 expression in MM has been correlated with worse prognosis.[7] By blocking XPO1, tumour suppressor proteins accumulate, resulting in apoptosis and cell cycle arrest. Selinexor has activity as a single agent as well as in combination with many anti-myeloma therapeutics.[8] Due to its novel mechanism of action and ability to block tumour suppressor genes from exiting the myeloma cell, both clinical and preclinical data show efficacy in high-risk patients.[9,10]

SVd was approved by Health Canada in 2022 and is recently provincially funded in most Canadian provinces. The BOSTON trial, a randomized Phase III study, evaluated SVd vs. Vd (bortezomib, dexamethasone) in patients who had received one to three prior lines of therapy. The trial demonstrated a PFS benefit of SVd over Vd across all subgroups, particularly in PI-naive patients, who exhibited a median PFS of 29.5 months compared to 9.7 months in the Vd arm (hazard ratio (HR) 0.29; 95% confidence interval (CI): 0.14-0.63; $p < 0.001$)[11]. Notably, in patients who had received only one prior line of therapy, the median PFS was 21 months for SVd vs. 10.7 months for Vd (HR 0.62; 95% CI: 0.41-0.95; $p = 0.028$), indicating that SVd is a highly effective option, especially in PI-naive patients at first relapse. Patients who were Len refractory in 1-3 prior lines continued to derive benefit from the triplet combination compared to Vd with a median PFS of 10.2 months vs. 7.1 months (HR 0.52; 95% CI: 0.31-0.88).[12] Seventeen patients in the BOSTON trial received prior daratumumab, 11 in the SVd arm and 6 in the Vd arm. While the numbers are small, an exploratory analysis was performed, which showed a mPFS of 12.2 months vs. 5.6 months between the two groups, respectively. While the small numbers limit generalizability, it does support the use of SVd after daratumumab.[13]

Treatment with SVd, however, requires close monitoring for adverse events, especially during the initial cycles in which treatment intolerances predominate. A significant proportion (65%) of patients in the BOSTON trial required dose adjustments of selinexor with a median dose of 71.4 mg per week (protocol dose 100 mg/week).

Patients who had dose adjustments exhibited a median PFS of 16.6 months compared to 9.2 months in those who did not, suggesting that appropriate dose modifications can enhance treatment durability and patient outcomes through cumulative dose exposure. The overall response rate (ORR) was also higher in patients who received dose adjustments (81.7%) vs. those who did not (66.7%).[14] These findings underscore the importance of supportive care and proactive management of adverse events to prevent early discontinuation and maximize clinical benefit. Current recommendations suggest using at least two prophylactic antiemetics, including a 5-HT3 antagonist like ondansetron, combined with another antiemetic, such as olanzapine and/or aprepitant, to effectively mitigate nausea, a common side effect.[15] Additional supportive care involves fluid hydration to manage hyponatremia and the judicious use of growth factors to address cytopenias.[16]

Practical Considerations for SVd

SVd should be considered after the first relapse from DRd or Len maintenance, especially when the patient is bortezomib-naïve. Using SVd before a carfilzomib-based regimen in the treatment sequence is strategic, as bortezomib is unlikely to produce durable responses if administered after carfilzomib progression.[17,18] Individual provincial formularies may also limit the use of SVd if a patient is deemed refractory to a PI. Furthermore, transcriptomic data combined with *ex vivo* drug sensitivity studies indicate that resistance to daratumumab may be linked to increased sensitivity to selinexor, suggesting potential added synergy with selinexor following daratumumab relapse.[19]

In clinical practice, starting selinexor at a lower dose (e.g., 60-80 mg weekly) with dose adjustments as needed, combined with close monitoring and supportive care, helps minimize early treatment discontinuation due to intolerance. Aggressive antiemetic management should include at least dual prophylactic agents, particularly at the start of treatment. Administer 8 mg ondansetron 30 to 60 minutes before each selinexor dose, continuing every 8 hours for 2 days, along with low-dose olanzapine (2.5 mg–5.0 mg qhs) or aprepitant (125 mg PO on day 1, followed by 80 mg for 2 days each week).[20] Tapering after the first 6-8 weeks can be considered as nausea rates typically improve with each subsequent cycle.[16] Alternatively, a once-weekly oral dose of Akynzeo (netupitant 300 mg + palonosetron 0.5 mg) can also be considered, with or without low-dose olanzapine. Note that dexamethasone dose reduction may be required when using Neurokin-1 (NK1) receptor agonists.[21,22]

Lenalidomide-Refractory but Anti-CD38 Monoclonal Antibody-Sensitive Relapse

IsaKd is a compelling option in disease refractory to Len and/or bortezomib but not yet progressing on an anti-CD 38 mAb, as evidenced by the IKEMA trial **(Table 1)**. This Phase III trial randomized patients with 1-3 prior lines of therapy to IsaKd vs. Kd. The trial demonstrated a significantly longer median PFS for IsaKd (35.7 months) compared to Kd (19.2 months; HR 0.58; 95.4% CI: 0.42-0.79), with particular benefit observed in patients who had not received an anti-CD38 mAb in the frontline setting.[23] Notably, patients continued to derive durable responses even after more than one prior line of therapy, with a median PFS of 38.[24] months for those who had received one prior line of treatment, and 29.21 months for those with two or more treatment lines.[24] The improvement in PFS2 (47.2 months for IsaKd vs. 35.6 months for Kd; HR 0.68; 95% CI: 0.50-0.94) further supports the early use of isatuximab in combination with carfilzomib in relapsed/refractory settings in the non-anti-CD38 mAb-refractory patient group.[25]

Practical Considerations for IsaKd

To reduce the treatment burden associated with twice-weekly carfilzomib, a once-weekly schedule (70 mg/m^2 on Days 1, 8, and 15) has been explored in a Phase II trial, demonstrating high efficacy with an ORR of 87.55% and no new safety concerns.[26] This regimen may provide a more convenient option for patients; however, careful patient selection and cardiac optimization are crucial to managing the potential cardiotoxicity associated with carfilzomib.

Based on available data, it is challenging to determine whether pursuing IsaKd and foregoing SVd (thereby losing access to bortezomib if PI refractory) would result in better long-term outcomes than administering SVd before IsaKd. However, it is crucial to consider the treatment options available throughout a patient's treatment course and to prioritize maintaining multiple effective options to achieve durable long-term remission while also keeping in mind the potential for future effective regimens.

Study/Regimen	n/Prior Lines	Median Age, Years (Range)	Len Exposed (%)	Len Refractory (%)	Anti-CD38 Exposed (%)	Bort Exposed (%)	Bort Refractory (%)	mPFS (mo) in Study Population	mPFS (mo) in Len Refractory*	Notes*
BOSTON – SVd[11,12] S 100 mg qw, V 1.3 mg/m²qw, Dex (35-day/cycle)	195 (1-3 PL)	66 (59-72)	39%	27%	6%	69%	None	13.93 (HR 0.70; 95% CI: 0.53-0.93; p = 0.0075)	10.2 (HR 0.52; 95% CI, 0.31–0.88; p = .006) vs Vd arm	1 PL: mPFS 21 mo; PI-naive: 29.5 mo
BOSTON – Vd[11,12] V 1.3 mg/m² 2x/w (24w), then qw, Dex (21days/cycle for cycles 1-8, 35 days/cycle for cycles 9+)	207 (1-3 PL)	67 (61-74)	37%	26%	3%	70%	None	9.46 (HR 0.70; 95% CI: 0.53-0.93; p = 0.0075)	7.1	1 PL: mPFS 10.7 mo; PI-naive: 9.7 mo
IKEMA – IsaKd[18,20] Isa 10mg/kg IV qw cycle 1, then q2w cycle 2+, K 20 mg/m² IV D1,2, then 56 mg/m² IV thereafter on D 1, 2, 8, 9, 15, 16, 22, 23, Dex (28-days/cycle)	179 (1-3 PL)	65 (IQR 55-70)	40%	31.8%	1%	92.7%	31%	35.7 (HR 0.58; 95.4% CI: 0.42-0.79)	HR 0.586 (95% CI: 0.353-0.972)	TEAE event rate per patient-year: 1.08
IKEMA – Kd[18,20] K 20 mg/m² IV D1,2, then 56 mg/m² IV thereafter on D 1, 2, 8, 9, 15, 16, 22, 23, Dex (28-days/cycle)	123 (1-3 PL)	63 (IQR 57-70)	48%	34.1%	-	85.4%	36%	19.2 (HR 0.58; 95.4% CI: 0.42-0.79)	-	TEAE event rate per patient-year: 0.97
ICARIA-MM – IsaPd[22,23] Isa 10 mg/kg IV qw cycle 1, then q2w cycle 2+, P 4 mg D1-21, Dex (28 days/cycle)	154 (2+ PL)	68 (60-74)	100%	94%	None	100%	77%	11.5 (HR 0.596; 95% CI: 0.44-0.81; p = 0.001)	-	Almost all Len exposed/refractory
ICARIA-MM – Pd[22,23] P 4 mg D1-21, Dex (28 days/cycle)	153 (2+ PL)	66 (59-71)	100%	92%	None	100%	75%	6.5 (HR 0.596; 95% CI: 0.44-0.81; p = 0.001)	-	Almost all Len exposed/refractory
OPTIMISMM – PVd[24,25] P 4 mg D1-14, V 1.3 mg/m² D 1, 8, 11 (cycle 1-8), then D 1, 8, Dex (21 days/cycle)	281 (1-3 PL)	67 (60-73)	100%	71%	None	72%	9%	11.2 (HR 0.61; 95% CI: 0.49-0.77; p < 0.0001)	9.53 (HR 0.65; 95% CI: 0.40-0.84; p = 0.0008)	17.84 mo in 1 PL and len refractory (HR 0.55; 95% CI: 0.33-0.94; p = 0.0267)
OPTIMISMM – Vd[24,25] V 1.3 mg/m² D1,8,11 (cycle 1-8), then D 1, 8, Dex (21 days/cycle)	278 (1-3 PL)	68 (59-73)	100%	69%	None	73%	12%	7.1 (HR 0.61; 95% CI: 0.49-0.77; p < 0.0001)	5.59 (HR 0.65; 95% CI: 0.40-0.84; p = 0.0008)	9.49 mo in 1 PL and len refractory (HR 0.55; 95% CI: 0.33-0.94; p = 0.0267)

Study/Regimen	n/Prior Lines	Median Age, Years (Range)	Len Exposed (%)	Len Refractory (%)	Anti-CD38 Exposed (%)	Bort Exposed (%)	Bort Refractory (%)	mPFS (mo) in Study Population	mPFS (mo) in Len Refractory*	Notes*
CASTOR – DVd[4,5] D 16 mg/kg IV qw cycles 1-3, D1 cycles 4-8 (21days/cycle), then D1 cycle 9+ (28 days/cycle), V 1.3 mg/m² D1,8,11 (cycles 1-8), Dex	251 (≥1 PL)	64 (30-88)	36%	24%	None	65%	None	16.7 (HR 0.31; 95% CI: 0.25-0.40; p < 0.0001)	7.8 (HR 0.44; 95% CI: 0.28-0.68; p = 0.0002)	21.2 mo in 1 PL len exposed/refractory (HR 0.30; 95% CI: 0.11-0.82; p = 0.014)
CASTOR – Vd[4,5] V 1.3 mg/m² D1,8,11 (cycles 1-8), Dex (21 days/cycle)	247 (≥1 PL)	64 (33-85)	49%	33%	None	66%	None	7.1 (HR 0.31; 95% CI: 0.25-0.40; p < 0.0001)	4.9 (HR 0.44; 95% CI: 0.28-0.68; p = 0.0002)	7 mo in 1 PL len exposed/refractory (HR 0.30; 95% CI: 0.11-0.82; p = 0.014)
ENDEAVOR – Kd[26-28] K 20 mg/m² IV D1,2 cycle 1, then 56 mg/m² IV D 8, 9, 15, 16, 22, 23, Dex (28 days/cycle)	464 (1-3 PL)	65 (35-89)	38%	-	None	54%	3.2%	18.7 (HR 0.53; 95% CI: 0.44-0.65; p < 0.0001)	8.6	15.6 mo in 1 PL and len exposed
ENDEAVOR – Vd[26-28] V 1.3 mg/m² D 1, 4, 8, 11, Dex (21 days/cycle)	465 (1-3 PL)	65 (30-88)	38%	-	None	54%	4%	9.4 (HR 0.53; 95% CI: 0.44-0.65; p < 0.0001)	6.6	15.6 mo in 1 PL and len exposed

* Subgroup analyses were exploratory and not included in the study objectives. Therefore, they do not control for type 1 errors. Analyses of subgroups are often not powered or adjusted for multiplicity to assess efficacy outcomes across these subgroups.
Dex, Dexamethasone given as either 40mg q weekly if age <75 years and 20mg q weekly if age ≥ 75 years

Table 1: Key Approved Phase III Clinical Trials and Outcomes in the Management of Post-Lenalidomide Relapsed/Refractory Multiple Myeloma with 1-3 Prior Lines of Therapy; *Courtesy of C.W. Phua, MD, FRCPC, Sylvia McCulloch, MD, MSc, FRCPC*

Abbreviations: Anti-CD38: anti-CD38 monoclonal antibody; **Bort:** bortezomib; **CI:** confidence interval; **D:** day, **Dex:** dexamethasone; **DVd:** daratumumab, bortezomib, dexamethasone; **HR:** hazard ratio; **IMiDs: i**mmunomodulatory drugs; **IQR:** interquartile range; **Isa:** isatuximab; **IsaKd:** isatuximab, carfilzomib, dexamethasone; **IsaPd:** isatuximab, pomalidomide, dexamethasone; **Kd:** carfilzomib, dexamethasone; **len:** lenalidomide; **mPFS:** median progression-free survival; **mo:** months; **PI:** proteasome inhibitor; **PL:** prior lines; **Pd:** pomalidomide, dexamethasone; **PVd:** pomalidomide, bortezomib, dexamethasone; **qw:** every week; **SVd:** selinexor, bortezomib, dexamethasone; **TEAE:** treatment-emergent adverse events; **Vd:** bortezomib, dexamethasone; **w:** weekly.

Study/Regimen	n	Median Age (Years)	Prior Lines	Triple Class Refractory (%)	Dara Ref (%)	mPFS (Months)	mOS (Months)	Notes
DREAMM-7[34]; BVd (B 2.5mg/kg IV q3w, V 1.3mg/m^2 D1,4, 8, 11 cycles 1-8) vs. DVd	243 (BVd); 251 (DVd)	65 (34-86) BVd; 64 (32-89) DVd	≥1 PL (not refractory to or intolerant of bortezomib or daratumumab)	None	Dara exposed 1% BVd and 2% DVd	36.6 vs. 13.4 (HR 0.41; 95% CI 0.31-0.53); p<0.00001	@ 18 months OS 84% vs. 73% (HR 0.57 95% CI 0.4-0.8); p=0.00049	Previous PI: 90% BVd, 86% DVd Previous IMiD: 81% BVd, 86% DVd
DREAMM-8[35]; BPd (B 2.5 mg/kg IV cycle 1, then 1.9 mg/kg IV q4w cycle 2+, P 4 mg D1-21 (28 days/ cycle) vs. PVd (21 days/cycle)	155 (BPd); 80 (PVd)	67 (40-82) BPd; 68 (34-86) PVd	≥1 PL that included lenalidomide	81% BPd and 76% PVd (Len refractory)	22% BPd and 25% PVd to anti-CD38 mAb	NR vs. 12.7 (HR 0.52; 95% CI 0.37-0.73); p<0.001	Data not yet mature	Ocular events are managed with dose delays, and every 8 weeks dosing
CARTITUDE-4[36]; Cilta-cel 0.75 × 10^6 CAR-T cells/kg vs. SOC (PVd/DPd)	208 (Cilta-cel); 211 (SOC)	61.5 (27-78) Cilta-cel; 61 (35-80) SOC	1-3 PL including PI and lenalidomide (lenalidomide refractory)	14.4% (Cilta-cel) and 15.6% (SOC)	23.1% (Cilta-cel) and 21.3% (SOC)	NR vs. 11.8 months (HR:0.26 (95% CI 0.18-0.38); p<0.0001	Data not yet mature	US FDA-approved after 1 or more PL including an IMiD, PI and refractory to Lenalidomide
KarMMa-3[37]; Ide-cel 150-450 x 10^6 CAR-T cells vs. SOC with the option for crossover after confirmed PD	254 (Ide-cel); 132 (SOC)	63 (30-81) Ide-cel; 63 (42-83) SOC	2-4 PL (IMiD, PI and daratumumab)	65% (Ide-cel) and 67% (SOC)	95% (Ide-cel) and 93% (SOC)	13.8 months vs. 4.4 months (HR 0.49 95% CI, 0.38-0.63)	Data not yet mature	US FDA-approved after 2 or more lines of therapy

Table 2: Selected Phase 3 Trials in Early Relapsed/Refractory Multiple Myeloma; *Courtesy of C.W. Phua, MD, FRCPC, Sylvia McCulloch, MD, MSc, FRCPC*

Abbreviations: BVd: belantamab mafodotin, bortezomib, dexamethasone; **BPd:** belantamab mafodotin, pomalidomide, dexamethasone; **CAR:** chimeric antigen receptor; **CI:** confidence interval; **Cilta-cel:** ciltacabtagene autoleucel; **Dara Ref:** daratumumab refractory; **DVd:** daratumumab, bortezomib, dexamethasone; **HR:** hazard ratio; **Ide-cel:** idecabtagene vicleucel; **IMiD: i**mmunomodulatory drugs, **Len Ref:** lenalidomide refractory; **mOS:** median overall survival; **mPFS:** median progression-free survival; **NR:** not reached; **PD:** progressive disease; **PI:** proteasome inhibitor; **PL:** prior lines; **PVd:** pomalidomide, bortezomib, dexamethasone; **SOC:** standard of care; **US FDA:** United States Food and Drug Administration.

In patients who do not receive isatuximab with carfilzomib, an alternative option is IsaPd (isatuximab, pomalidomide, dexamethasone), as demonstrated in the ICARIA-MM trial. This combination is considered after at least two prior lines of therapy, including lenalidomide and a PI **(Table 1)**. The trial showed that IsaPd had a median PFS of 11.53 months compared to 6.47 months with Pd alone (HR 0.596; 95% CI: 0.436-0.814; p = 0.001).[27] Updated data also indicate statistically significant improvements in OS, with IsaPd achieving 24.6 months vs. 17.7 months with Pd (HR 0.776; 95% CI: 0.594-1.015; p = 0.0319). Additionally, median PFS2 was

also longer with IsaPd, at 17.5 months vs.12.9 months with Pd (HR 0.735; 95% CI: 0.569-0.950; p = 0.0091).[28]

Practical Considerations for IsaPd

IsaPd is well tolerated and may be prioritized for patients who are not candidates for carfilzomib, particularly in the elderly population, where carfilzomib can be challenging to administer. For these patients, a more tolerable bortezomib-based regimen such as SVd can be used in the second line, with IsaPd reserved for the third line. In some provinces IsaPd is available to patients who progressed on upfront RVd.

Real-world Data on Post-anti-CD38 Monoclonal Antibody Relapse

The initial trials leading to the funding and approval of carfilzomib with dexamethasone (ENDEAVOR) and pomalidomide with dexamethasone were performed prior to the widespread use of daratumumab.[31,34] The Canadian Myeloma Research Group has since analyzed the effectiveness of these regimens in the post-daratumumab setting using real-world Canadian datasets. Their analysis showed that patients who received carfilzomib-based therapy post-daratumumab had a median PFS of 4.5 months and OS of 14.5 mo. For the group who received pomalidomide-based therapy, the PFS was 5.2, and the OS was 21.7 months. In the group that received both an IMiD and PI combined with either carfilzomib and/or pomalidomide, the median PFS and OS were 4.1 months and 14.5 months, respectively.[35] These results, while not meeting our hopes, underscore the need for including novel agents that target new pathways in earlier lines of therapy. This highlights a significant gap in our currently funded regimens. It is our hope that these newer and more effective regimens, which have shown efficacy in treating this difficult-to-manage patient population, will soon be accessible.

Evolving Therapeutic Strategies for Emerging Challenges in Early RRMM

The landscape of MM therapy is rapidly evolving, with novel agents targeting new pathways and employing unique mechanisms of action. These therapies hold significant promise for improving patient outcomes, especially as more patients are exposed to anti-CD38 mAb in frontline settings. Recent data from the PERSEUS and IMROZ trials have highlighted the benefits of incorporating anti-CD38 mAb into four-drug regimens for newly diagnosed MM, benefiting both transplant-eligible and transplant-ineligible patients. In the PERSEUS trial, the combination of DaraRVd demonstrated a 48-month PFS rate of 84.3% compared to 67.7% with RVd alone (HR 0.42; 95% CI: 0.30-0.59; P < 0.0001) in transplant-eligible newly-diagnosed patients.[36] Similarly, the IMROZ trial showed that IsaRVd achieved a 60-month PFS rate of 63.2% vs. 45.2% with RVd alone (HR 0.596; 98.5% CI: 0.406-0.876; P = 0.0005) in transplant-ineligible patients.[37]

As these effective combinations move to front-line therapy, most patients are likely to become triple-class refractory at early relapse, further complicating treatment selection. Consequently, a broad range of distinct treatment options, optimized sequencing, and efficacy in later-line settings is crucial. Two Phase III studies on belantamab mafodotin have recently been published, showing impressive results, which are anticipated to undergo review for US Food and Drug Administration (FDA) approval following its market withdrawal after the DREAMM-3 study failed to demonstrate a statistically significant PFS benefit **(Table 2)**.[38-40] Belantamab mafodotin is associated with unique ocular side effects, necessitating eye exams, but it is quite manageable with appropriate dose reductions and adjustments to treatment frequency. Additionally, two Phase III clinical updates on B-cell maturation antigen (BCMA) chimeric antigen receptor (CAR) T-cell therapies in early RRMM have demonstrated potent activity **(Table 2)**.[41,42] These therapies are effective in improving responses in triple-class refractory patients with early RRMM. It is imperative that we prioritize efforts to ensure these advanced treatments are available to our patients in a timely manner.

Conclusion

A range of treatment options is crucial, given the highly heterogeneous nature of MM, which presents with a variable and often unpredictable disease course. The complexity of MM, both at diagnosis and relapse, is driven by increasing genomic events and clonal evolution, leading to numerous mechanisms of therapy resistance. We are now confronted with the specific need for efficacious treatments in triple-class refractory patients in early RRMM. Despite these challenges, the advancements in treatment have been

tremendous, and the landscape is poised to change significantly in the upcoming years.

While the current review considered the available options as somewhat static, it is important to recognize that new approvals are on the horizon, driven by ongoing advancements in MM care. These emerging treatments, often accessible through clinical trials, offer opportunities to target myeloma cells using unique mechanisms of action. Promising results have been observed with deep treatment responses from CelMods (Cereblon E3 ligase modulators) and agents targeting not only BCMA but G Protein-Coupled Receptor, Family C, Group 5, Member D (GPRC5D) and Fc Receptor-Like 5 (FCRL5) as well. These novel therapies are likely to reshape our treatment approaches in MM, moving us closer to the common goals of achieving durable remission and, potentially, a cure.

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References:

1. Munshi NC, Avet-Loiseau H, Anderson KC, Neri P, Paiva B, Samur M, et al. A large meta-analysis establishes the role of MRD negativity in long-term survival outcomes in patients with multiple myeloma. Blood Adv. 2020;4(23):5988-99.
2. Canada's Drug Agency- L'Agence des medicaments du Canada. CADTH Reimbursement Review - Porvisional Funding Algorithm. Indication: Multiple myeloma. 2024 August.
3. Dimopoulos MA, Oriol A, Nahi H, San-Miguel J, Bahlis NJ, Usmani SZ, et al. Overall Survival With Daratumumab, Lenalidomide, and Dexamethasone in Previously Treated Multiple Myeloma (POLLUX): A Randomized, Open-Label, Phase III Trial. J Clin Oncol. 2023;41(8):1590-9.
4. Mateos MV, Sonneveld P, Hungria V, Nooka AK, Estell JA, Barreto W, et al. Daratumumab, Bortezomib, and Dexamethasone Versus Bortezomib and Dexamethasone in Patients With Previously Treated Multiple Myeloma: Three-year Follow-up of CASTOR. Clin Lymphoma Myeloma Leuk. 2020;20(8):509-18.
5. Spencer A, Lentzsch S, Weisel K, Avet-Loiseau H, Mark TM, Spicka I, et al. Daratumumab plus bortezomib and dexamethasone versus bortezomib and dexamethasone in relapsed or refractory multiple myeloma: updated analysis of CASTOR. Haematologica. 2018;103(12):2079-87.
6. Mian H, Eisfeld C, Venner CP, Masih-Khan E, Kardjadj M, Jimenez-Zepeda VH, et al. Efficacy of Daratumumab-Containing Regimens Among Patients With Multiple Myeloma Progressing on Lenalidomide Maintenance: Retrospective Analysis. Front Oncol. 2022;12:826342.
7. Schmidt J, Braggio E, Kortuem KM, Egan JB, Zhu YX, Xin CS, et al. Genome-wide studies in multiple myeloma identify XPO1/CRM1 as a critical target validated using the selective nuclear export inhibitor KPT-276. Leukemia. 2013;27(12):2357-65.
8. Schiller GJ, Lipe BC, Bahlis NJ, Tuchman SA, Bensinger WI, Sutherland HJ, at al. Selinexor-Based Triplet Regimens in Patients With Multiple Myeloma Previously Treated With Anti-CD38 Monoclonal Antibodies. Clin Lymphoma Myeloma Leuk. 2023 Sep;23(9):e286-e296.e4.
9. Richard S, Chari A, Delimpasi S, Simonova M, Spicka I, Pour L, et al. Selinexor, bortezomib, and dexamethasone versus bortezomib and dexamethasone in previously treated multiple myeloma: Outcomes by cytogenetic risk. Am J Hematol. 2021;96(9):1120-30.
10. Tai YT, Landesman Y, Acharya C, Calle Y, Zhong MY, Cea M, et al. CRM1 inhibition induces tumor cell cytotoxicity and impairs osteoclastogenesis in multiple myeloma: molecular mechanisms and therapeutic implications. Leukemia. 2014;28(1):155-65.
11. Grosicki S, Simonova M, Spicka I, Pour L, Kriachok I, Gavriatopoulou M, et al. Once-per-week selinexor, bortezomib, and dexamethasone versus twice-per-week bortezomib and dexamethasone in patients with multiple myeloma (BOSTON): a randomised, open-label, phase 3 trial. Lancet. 2020;396(10262):1563–1573.
12. Mateos MV, Engelhardt M, Leleu X, Mesa MG, Cavo M, Dimopoulos M, et al. Impact of prior treatment on selinexor, bortezomib, dexamethasone outcomes in patients with relapsed/refractory multiple myeloma: Extended follow-up subgroup analysis of the BOSTON trial. Eur J Haematol. 2024;113(2):242-52.
13. Mateos MV, Engelhardt M, Leleu X, Mesa MG, Auner HW, Cavo M, et al. P917: Selinexor, Bortezomib, and Dexamethasone in Patients With Previously Treated Multiple Myeloma: Updated Results of Boston Trial by Prior Therapies. Hemasphere. 2023;7(S3):e7454106.
14. Jagannath S, Delimpasi S, Grosicki S, Van Domelen DR, Bentur OS, Spicka I, et al. Association of Selinexor Dose Reductions With Clinical Outcomes in the BOSTON Study. Clin Lymphoma Myeloma Leuk. 2023;23(12):917-23 e3.
15. FORUS Therapeutics Inc. Product monograph XPOVIO 2022 [Available from: https://pdf.hres.ca/dpd_pm/00066090.PDF].
16. Nooka AK, Costa LJ, Gasparetto CJ, Richardson PG, Siegel DS, Chari A, et al. Guidance for Use and dosing of Selinexor in Multiple Myeloma in 2021: Consensus From International Myeloma Foundation Expert Roundtable. Clin Lymphoma Myeloma Leuk. 2022;22(7):e526-e31.
17. Mateos M, Gavriatopoulou M, Facon T, Auner HW, Leleu X, Hajek R, et al. Effect of Prior Treatment with Proteasome Inhibitors on the Efficacy and Safety of Once-Weekly Selinexor, Bortezomib, and Dexamethasone in Comparison with Twice-Weekly Bortezomib and Dexamethasone in Relapsed or Refractory Multiple Myeloma: Subgroup Analysis from the Boston Study. Blood. 2020;136(Supplement 1):48-50.
18. Kuhn DJ, Chen Q, Voorhees PM, Strader JS, Shenk KD, Sun CM, et al. Potent activity of carfilzomib, a novel,

irreversible inhibitor of the ubiquitin-proteasome pathway, against preclinical models of multiple myeloma. Blood. 2007;110(9):3281-90.
19. Sudalagunta PR , Renatino-Canevarolo R , Meads MB, Coelho Siqueira Silva MD, Cubitt C, De Avila G, et al. Rationale for Selinexor Treatment in Daratumumab-Refractory MM Patients Identified by Paired Ex Vivo Drug Sensitivity and RNA-seq. Presented at: The 63rd American Society of Hematology Annual Meeting & Exposition; December 11-14, 2021; Atlanta, GA. 2021.
20. Gavriatopoulou M, Chari A, Chen C, Bahlis N, Vogl DT, Jakubowiak A, et al. Integrated safety profile of selinexor in multiple myeloma: experience from 437 patients enrolled in clinical trials. Leukemia. 2020;34(9):2430-40.
21. Purdue Pharma. Product monograph: Akynzeo 2017 [Available from: https://pdf.hres.ca/dpd_pm/00041433.PDF].
22. Merck Canada Inc. Product monograph: Emend 2014 [Available from: https://www.merck.ca/en/wp-content/uploads/sites/20/2021/04/EMEND-PM_E.pdf].
23. Moreau P, Dimopoulos MA, Mikhael J, Yong K, Capra M, Facon T, et al. Isatuximab, carfilzomib, and dexamethasone in relapsed multiple myeloma (IKEMA): a multicentre, open-label, randomised phase 3 trial. Lancet. 2021;397(10292):2361-71.
24. Capra M, Martin T, Moreau P, Martinez G, Oriol A, Koh Y, et al. Isatuximab Plus Carfilzomib and Dexamethasone in Relapsed Multiple Myeloma: Ikema Subgroup Analysis By Number of Prior Lines of Treatment. Blood. 2022;140(Supplement 1):7138-40.
25. Martin T, Dimopoulos MA, Mikhael J, Yong K, Capra M, Facon T, et al. Isatuximab, carfilzomib, and dexamethasone in patients with relapsed multiple myeloma: updated results from IKEMA, a randomized Phase 3 study. Blood Cancer J. 2023;13(1):72.
26. Vesole DH, Berdeja J, Matous J, Trudel S, Schade H, Munster P, et al. P902: Isatuximab, weekly carfilzomib and dexamethasone as salvage therapy for RRMM; interim results from a phase 2 trial. HemaSphere. 2023;7(S3):e5189693..
27. Attal M, Richardson PG, Rajkumar SV, San-Miguel J, Beksac M, Spicka I, et al. Isatuximab plus pomalidomide and low-dose dexamethasone versus pomalidomide and low-dose dexamethasone in patients with relapsed and refractory multiple myeloma (ICARIA-MM): a randomised, multicentre, open-label, phase 3 study. Lancet. 2019;394(10214):2096-107.
28. Richardson PG, Perrot A, San-Miguel J, Beksac M, Spicka I, Leleu X, et al. Isatuximab plus pomalidomide and low-dose dexamethasone versus pomalidomide and low-dose dexamethasone in patients with relapsed and refractory multiple myeloma (ICARIA-MM): follow-up analysis of a randomised, phase 3 study. Lancet Oncol. 2022;23(3):416-27.
29. Richardson PG, Oriol A, Beksac M, Liberati AM, Galli M, Schjesvold F, et al. Pomalidomide, bortezomib, and dexamethasone for patients with relapsed or refractory multiple myeloma previously treated with lenalidomide (OPTIMISMM): a randomised, open-label, phase 3 trial. Lancet Oncol. 2019 Jun;20(6):781-794.
30. Dimopoulos M, Weisel K, Moreau P, et al. Pomalidomide, bortezomib, and dexamethasone for multiple myeloma previously treated with lenalidomide (OPTIMISMM): outcomes by prior treatment at first relapse. Leukemia. 2021;35:1722-1731.
31. Dimopoulos MA, Moreau P, Palumbo A, Joshua D, Pour L, Hájek R, et al. Carfilzomib and dexamethasone versus bortezomib and dexamethasone for patients with relapsed or refractory multiple myeloma (ENDEAVOR): a randomised, phase 3, open-label, multicentre study. Lancet Oncol. 2016 Jan;17(1):27-38.
32. Dimopoulos MA, Goldschmidt H, Niesvizky R, Joshua D, Chng WJ, Oriol A, et al. Carfilzomib or bortezomib in relapsed or refractory multiple myeloma (ENDEAVOR): an interim overall survival analysis of an open-label, randomised, phase 3 trial. Lancet Oncol. 2017;18(10):1327-37.
33. Moreau P, Joshua D, Chng WJ, Palumbo A, Goldschmidt H, Hájek R, et al. Impact of prior treatment on patients with relapsed multiple myeloma treated with carfilzomib and dexamethasone vs bortezomib and dexamethasone in the phase 3 ENDEAVOR study. Leukemia. 2017 Jan;31(1):115-122.
34. Miguel JS, Weisel K, Moreau P, Lacy M, Song K, Delforge M, et al. Pomalidomide plus low-dose dexamethasone versus high-dose dexamethasone alone for patients with relapsed and refractory multiple myeloma (MM-003): a randomised, open-label, phase 3 trial. Lancet Oncol. 2013;14(11):1055-66.
35. LeBlanc R, Mian H, Reece D, Su J, Masih-Khan E, Chu M, Jimenez-Zepeda V, Sebag M, Song K, Louzada M, Kotb R, Visram A, White D, Stakiw J, Reiman A, Aslam M, Bergstrom D, Kaedbey R, Gul E, Venner C. Outcome of carfilzomib/pomalidomide-based regimens after daratumumab-based treatment in relapsed multiple myeloma: A Canadian Myeloma Research Group Database analysis. Eur J Haematol. 2023 Nov;111(5):815-823. doi: 10.1111/ejh.14082. Epub 2023 Aug 13. PMID: 37574220.
36. Sonneveld P, Dimopoulos MA, Boccadoro M, Quach H, Ho PJ, Beksac M, et al. Daratumumab, Bortezomib, Lenalidomide, and Dexamethasone for Multiple Myeloma. N Engl J Med. 2024;390(4):301-13.
37. Facon T, Dimopoulos MA, Leleu XP, Beksac M, Pour L, Hajek R, et al. Isatuximab, Bortezomib, Lenalidomide, and Dexamethasone for Multiple Myeloma. N Engl J Med. 2024.
38. Dimopoulos MA, Hungria VTM, Radinoff A, Delimpasi S, Mikala G, Masszi T, et al. Efficacy and safety of single-agent belantamab mafodotin versus pomalidomide plus low-dose dexamethasone in patients with relapsed or refractory multiple myeloma (DREAMM-3): a phase 3, open-label, randomised study. Lancet Haematol. 2023;10(10):e801-e12.
39. Hungria V, Robak P, Hus M, Zherebtsova V, Ward C, Ho PJ, et al. Belantamab Mafodotin, Bortezomib, and Dexamethasone for Multiple Myeloma. N Engl J Med. 2024;391(5):393-407.
40. Dimopoulos MA, Beksac M, Pour L, Delimpasi S, Vorobyev V, Quach H, et al. Belantamab Mafodotin, Pomalidomide, and Dexamethasone in Multiple Myeloma. N Engl J Med. 2024;391(5):408-421.30.
41. San-Miguel J, Dhakal B, Yong K, Spencer A, Anguille S, Mateos MV, et al. Cilta-cel or Standard Care in Lenalidomide-Refractory Multiple Myeloma. N Engl J Med. 2023 Jul 27;389(4):335-347.
42. Rodriguez-Otero P, Ailawadhi S, Arnulf B, Patel K, Cavo M, Nooka AK, et al. Ide-cel or Standard Regimens in Relapsed and Refractory Multiple Myeloma. N Engl J Med. 2023 Mar 16;388(11):1002-1014

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