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Navigating Sequencing in Relapsed/ Refractory Multiple Myeloma: Canadian Experts Discuss the Evidence and the Evolving Options

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Dr. Peter Anglin's clinical focus remains in haematologic and lymphoid malignancies. He is currently Physician Lead for the Stronach Regional Cancer Centre in Newmarket, Ontario. He has also developed an interest in health systems delivery, process redesign in the ambulatory setting, and optimizing drug access for oncology patients. He continues to serve in an advisory capacity to a number of pharmaceutical and health-related organizations. He remains the medical director of CarePath, a cancer navigation and support service supporting Cancer Care Ontario and Ontario cancer patients.

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Paola Neri is an Associate Professor of Medicine, attending physician in the Hematology division at University of Calgary and member of the Arnie Charbonneau Cancer Institute. Since January 2019, she has been the Scientific Director of the Cancer Translational Research Core, a clinically accredited laboratory located at the Arthur Child Comprehensive Cancer Center in Calgary. Dr. Neri received her medical degree at Magna Græcia University, Catanzaro, Italy in 2000. She completed her specialty in Medical Oncology at Magna Græcia University, Catanzaro, Italy in 2005 and received a PhD in Molecular Oncology and Experimental Immunology in 2011. From 2003-2006 she was Research Associate at Dana-Farber Cancer Institute, Harvard Medical School, Boston, USA under the mentorship of Dr. Kenneth Anderson. In June 2008, she joined the University of Calgary. The main focus of her research is the study of multiple myeloma (MM) with a particular interest in genomic studies with the goal of identifying mechanisms of drug resistance and discovering novel therapeutic targets for this incurable disease. Dr. Neri is well published in the field and received national and international grants from several agencies including International Myeloma Society, Leukemia and Lymphoma Society, Multiple Myeloma Research Foundation and Canadian Institute of Health Research (CIHR). In 2019 she received the Engineered Air Chair (research funds) in Cancer Research from University of Calgary. In 2021 she was selected by the International Myeloma Society to receive the Ken Anderson Young Investigator Award for her important translational work in multiple myeloma. In 2025 she has received the Global Impact in Myeloma Research Award from the Canadian Myeloma Research Group (CMRG). She is currently member of the American Society of Hematology, co-chair of Charbonneau Research & Innovation Committee in Calgary and member of Blood Editorial Board, very active both in preclinical and clinical trial research in Myeloma.

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Relapsed and refractory (R/R) multiple myeloma presents increasingly complex therapeutic decisions. Clinicians must not only weigh efficacy and tolerability but consider how today's treatment decisions will affect future options. In a roundtable discussion, myeloma experts discuss practical approaches to sequencing therapies across diverse patient scenarios.

Dr. Anglin: I'll start with providing a very brief background on early R/R myeloma in Canada. In the transplant-eligible sphere, most frontline patients received lenalidomide, bortezomib, and dexamethasone (RVd), followed by transplant and lenalidomide maintenance therapy. Quadruplet therapies are now being incorporated into frontline therapy, but it will be some time before we start to routinely see patients relapsing after a quadruplet regimen.

In the transplant-ineligible group, we're starting to see patients relapsing after daratumumab, lenalidomide, and dexamethasone (DRd), which has been available in the Canadian setting now for about 3 years.

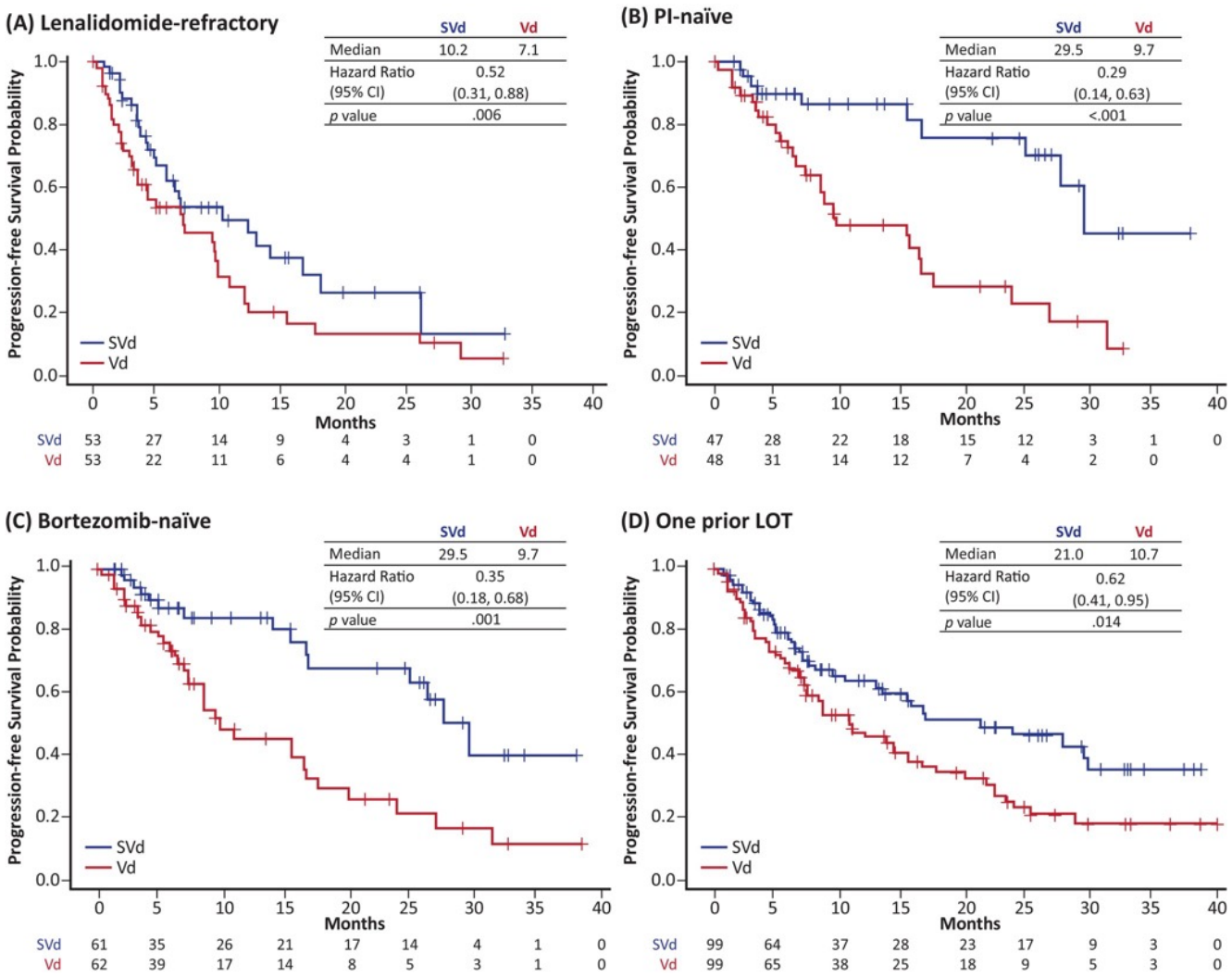
Against this backdrop, we have the arrival of the B-cell maturation antigen (BCMA)-targeted bispecific therapies, teclistamab and elranatamab; the novel combination, selinexor, bortezomib, and dexamethasone (XVd); as well as the antibody-drug conjugate, belantamab mafodotin.

Now that we've set the stage, let's discuss a case. For a 74-year-old patient relapsing after 4 years of DRd, who is therefore lenalidomide- and CD38 antibody-refractory, what would your next step be?

Dr. Neri: Carfilzomib could be an option, but the cardiotoxicity associated with this therapy could be a concern, given the age of the patient. Pomalidomide and dexamethasone (Pd) or pomalidomide, cyclophosphamide, and dexamethasone (PCd) are available now in Alberta, but these combinations are associated with limited progression-free survival (PFS) of approximately 5 to 10 months, which is not acceptable in the second-line setting. Based on these treatment considerations, I prefer XVd. In the BOSTON trial, the median PFS in the XVd arm was almost 14 months, and in the subgroup with only one prior therapy, the median PFS was 21 months.

If they're funded, belantamab mafodotin, pomalidomide, and dexamethasone (BPd) and belantamab mafodotin, bortezomib, and dexamethasone (BVd) could also be considered.

Dr. Anglin: **How would you decide between XVd, a belantamab mafodotin combination, or carfilzomib and dexamethasone (Kd) for the older patient in the second-line multiple myeloma setting?**



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. Progression-free survival with (A) lenalidomide-refractory, (B) PI-naïve, (C) bortezomib-naïve, and (D) one prior LOT subgroups; *used with permission from European J of Haematology, Volume: 113, Issue: 2, Pages: 242-252, First published: 01 May 2024, DOI: (10.1111/ejh.14223*

Abbreviations: CI: confidence interval; **LOT:** line of therapy; **P:** proteasome inhibitor; **SVd:** selinexor + bortezomib + dexamethasone; **Vd:** bortezomib + dexamethasone. p values are 1-sided.

Dr. Richter: I joke that we need to treat myeloma like a chess game. It's not only the next move that matters. We need to consider how that next move will impact subsequent moves. We know that patients who received DRd tend to be somewhat older and frailer. If I am not anticipating the patient will proceed to CAR T-cell therapy in the future, I will be more likely to choose a BCMA-targeted therapy early on.

Age and prior therapies have the greatest impact on our treatment decisions in R/R multiple myeloma. Interestingly, researchers at Moffitt looked at predictors of response to selinexor, and they found that refractoriness to anti-CD38 antibodies did not influence progression-free survival outcomes; in fact, those who were anti-CD38 refractory had numerically better outcomes. In addition, at the 2023 American Society of Hematology (ASH) meeting, Dr. Maria-Victoria Mateos shared that the median PFS in the subset of patients in the XVd arm of the BOSTON trial who were proteasome inhibitor-naive was almost 30 months. This shows we've come a long way in the treatment of R/R multiple myeloma.

Dr. Anglin: In the Canadian environment, belantamab mafodotin combinations are available compassionately, although they are not funded. Meanwhile, bispecific therapies are being used in the fourth line and beyond, while CAR T-cell therapy may be a future option. How do you think about sequencing BCMA agents?

Dr. White: That's a difficult question. There is a lack of data, outside of sub-analyses, to help us determine the best sequencing for our patients. It is not clear to what extent anti-BCMA therapy affects the efficacy of future BCMA-targeted therapies. Additionally, in Canada, we must think about what will be funded. Currently, in Canada, patients refractory to BCMA-targeted therapy would not be eligible to access teclistamab. Given the unknowns, XVd in the second-line setting warrants serious consideration, as it doesn't preclude us from accessing BCMA-targeted bispecific therapies in the future.

Dr. Neri: I agree. Currently, we don't have the data to determine whether patients exposed to belantamab mafodotin remain sensitive to BCMA-targeted therapy, and this makes it challenging to use this new therapy.

Dr. Anglin: How do patient comorbidities and social factors affect your decision making?

Dr. Richter: These factors significantly impact my decision making. We don't want to exacerbate any known comorbid health issue with the therapy we choose, because we want to make sure that we're preserving not just quantity of life, but also quality of life. If patients already have neuropathy, we may want to avoid bortezomib. If they have cardiac issues, carfilzomib is not ideal.

We should also consider the frequency of visits required with various treatment options, and how long patients are spending at the clinic. Obviously IV therapy means more time in the chair, compared to subcutaneous therapy. These are especially important considerations when we know patients will be continuing therapy for the long-term.

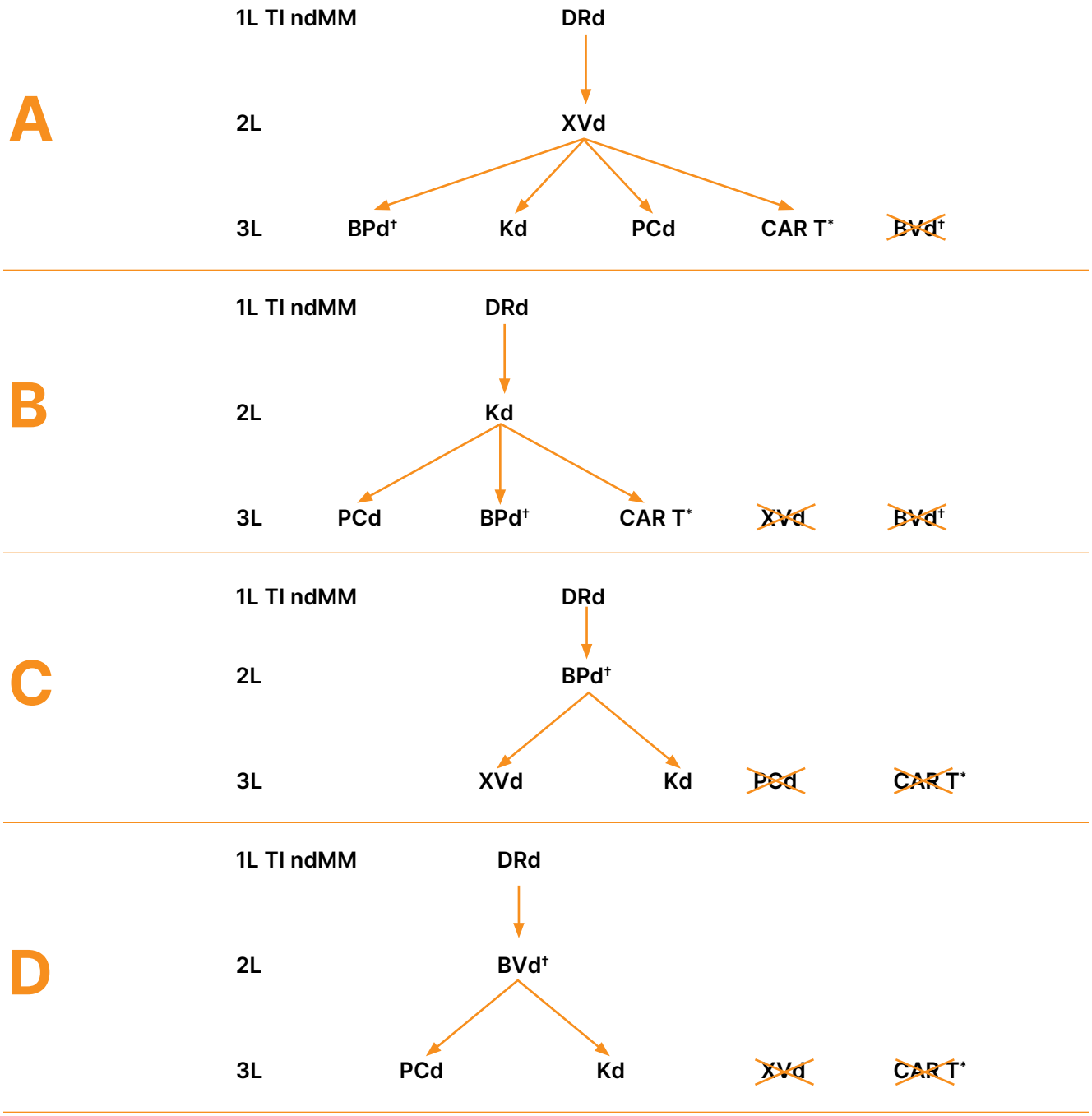
Dr. Anglin: I want to discuss transplant-ineligible patients entering the third-line setting, who received finite bortezomib-based therapy, such as CyBorD, followed by DRd. We're certainly still seeing these patients in our clinic. These patients are usually bortezomib-sensitive, and resistant to lenalidomide and anti-CD38 therapy. What's your treatment approach for these third-line patients?

Dr. White: For patients who are bortezomib-exposed, but not resistant, traditionally, we would reuse bortezomib, as a fixed-course therapy. In addition, the BOSTON trial demonstrated that, among patients previously treated with bortezomib, responses to XVd remained superior to the control arm, and the PFS was reasonable, at between ~11.5 and 13 months. As long as the patient hasn't experienced limiting or severe peripheral neuropathy, and as long as they're not refractory to bortezomib, XVd remains a good option for these patients.

Dr. Anglin: In transplant-eligible patients, by the time they enter the third line, patients have typically received RVd induction, transplant, and lenalidomide maintenance, followed by isatuximab, carfilzomib, and dexamethasone (IsaKd). (Occasionally, bortezomib-based therapy has been used in the frontline for high-risk patients). In the Canadian setting, the IKEMA trial demonstrated a median PFS of 18 months for IsaKd among the subgroup of R/R MM patients who had received more than one prior line of therapy. How would you approach these transplant-eligible patients relapsing after second-line therapy?

Dr. Neri: A very important factor here is whether patients have high-risk disease. In the BOSTON trial, XVd demonstrated impressive efficacy in high-risk patients. I saw this in one of my own high-risk patients, who progressed after a T-cell therapy and is doing very well on XVd.

We also want to consider age and frailty. Patients may be relapsing 4 or 5 years after transplant. XVd is an option for older and frailer patients at this stage, and we'll soon have access to BVd or BPd for these patients as well.



This algorithm reflects current provisional funding recommendations and/or individual product reimbursement recommendations, and the typical approach of treating until disease progression or unacceptable toxicity if specified in respective product monographs. Discontinuation for intolerance may alter subsequent options (e.g., belantamab mafodotin stopped for intolerance would not preclude access to teclistamab). Cilta-cel has been removed from the latest provisional funding algorithm due to pCPA negotiations concluding without an agreement. It is included above as it reflects a potential future multiple myeloma therapy valued by physicians and patients; *adapted from Canadian Journal of Health Technologies, January 2026, Volume 6, Issue 1.*

* Cilta-cel: currently not funded, pCPA negotiations concluded without an agreement.

† BPd/BVd: currently not funded, under consideration for negotiation with pCPA.

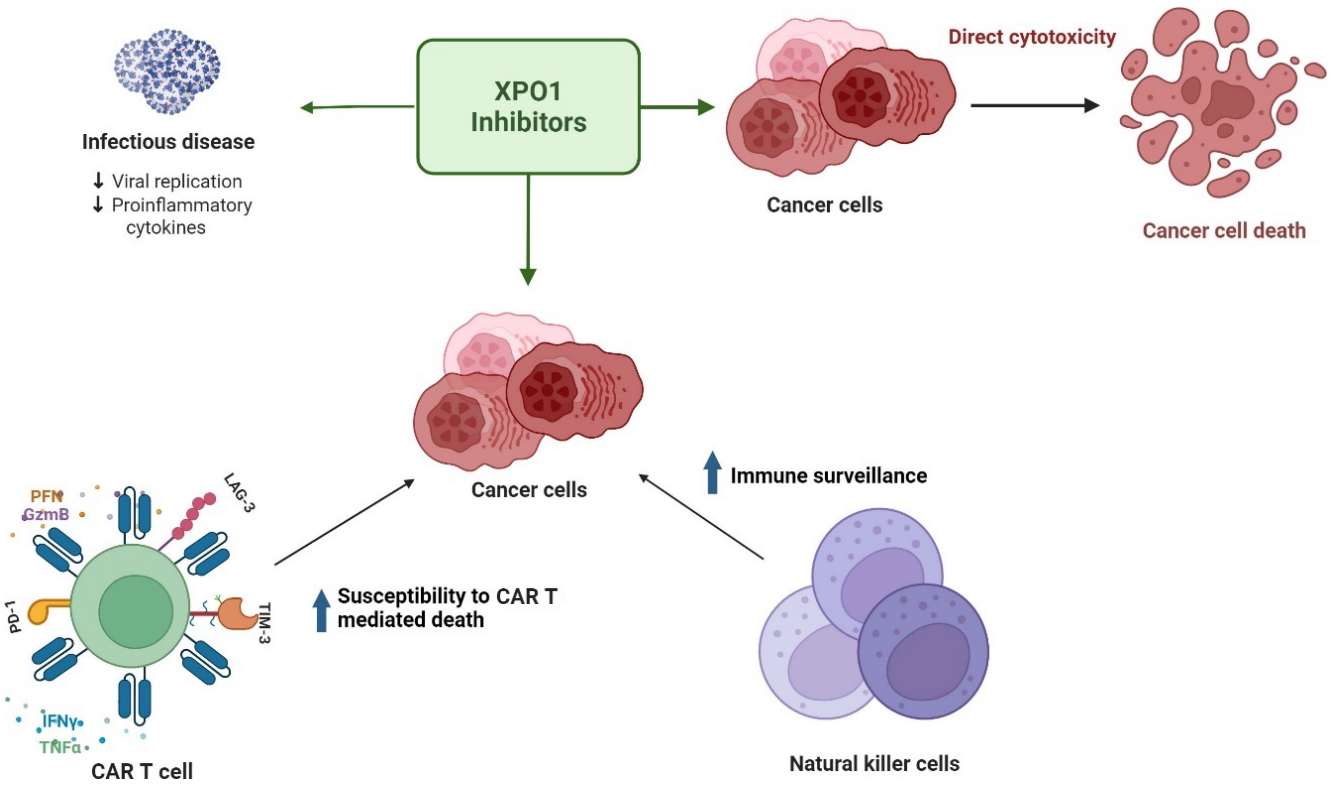
Abbreviations: TI: transplant ineligible; **ndMM:** newly diagnosed multiple myeloma; **1L:** first line; **2L:** second line; **3L:** third line; **B:** belantamab mafodotin; **C:** cyclophosphamide; **D:** daratumumab; **d:** dexamethasone; **K:** carfilzomib; **P:** pomalidomide; **V:** bortezomib; **X:** XPOVIO®

Dr. Anglin: For transplant-eligible patients who are now receiving quadruplet therapy, what are your thoughts on the next line of therapy?

Dr. Richter: There are few head-to-head trials to guide us here. If asked to rank the efficacy of BCMA therapies, most myeloma treaters will put CAR T-cell therapy at the top, followed by bispecific therapy, and then belantamab mafodotin. For younger patients, the goal is to try to get them to a CAR T-cell therapy that will be available in the coming years, or a bispecific antibody. I wouldn't rush to give them a BCMA agent like belantamab mafodotin early on. Looking at the CARTITUDE-1 data, cilta-cel was given at the end of the road, so to speak, and, 5 years later, a third of these patients are not on treatment, and may, in fact, be cured. Therefore, I would rather give patients XVd or IsaKd in the second line, so that CAR T-cell or bispecific therapy will be available to them in the future.

Dr. Anglin: When do you think CAR T-cell therapy will be funded in multiple myeloma?

Dr. White: Realistically, I think it will be more than a year before we have access to CAR T-cell therapy for multiple myeloma patients in Canada. I hope we get access to cilta-cel in the second-line setting and beyond. If cilta-cel isn't funded, there are very good products coming down the line that may, in fact, be better in terms of safety.



XPO1 inhibitors have direct cytotoxic effects on tumor cells, decrease inflammation in infectious disease, and may facilitate a favorable immune microenvironment for effector T cells to combat T-cell exhaustion; *used with permission from Binder AF, Walker CJ, Mark TM and Baljevic M (2023) Impacting T-cell fitness in multiple myeloma: potential roles for selinexor and XPO1 inhibitors. Front. Immunol. 14:1275329. doi: 10.3389/fimmu.2023.1275329*

Dr. Anglin: We've talked about the expansive role of XVd in R/R MM. How do you manage the side effects of this therapy?

Dr. Richter: Many therapies have what I call distal toxicity. Take lenalidomide – patients feel fine at the start of therapy, but over time, their platelet counts drop, and we need to reduce the dose. Selinexor has what I think of as proximal toxicity. We need to focus on getting patients through those first three to four cycles, and then it's very well tolerated.

We typically give three antiemetics upfront: dexamethasone, a 5-HT3 receptor antagonist such as ondansetron, and an aprepitant-like drug. In my clinic, we like to prescribe rolapitant, due to the low risk of drug interactions. However, if patients have no access to it, I recommend Akynzeo, which is netupitant and palonosetron, along with dexamethasone.

Personally, I prescribe XVd on a 28-day cycle – once weekly for 3 weeks, followed by 1 week off treatment. While this dosing schedule wasn't assessed in the BOSTON trial or any other study, I think this dosing regimen is better-tolerated and this approach helps maintain adherence to therapy.

Dr. Anglin: Lastly, can you all reflect on a key takeaway point on therapeutic sequencing in R/R multiple myeloma?

Dr. White: I think XVd offers a novel mechanism of action. At the moment, in Canada, it's a combination that we aren't able to come back to, if we use Kd or BVd in the second-line. However, BPd and Kd are options in the third-line, post XVd. In this way, using XVd in the second line provides an opportunity to add one line of therapy to the treatment journey. It's an exciting time in myeloma care, one that calls upon us to look to the future and consider how the choices we make today will shape the options available for our patients in the future.

Dr. Richter: As myeloma doctors, it is very difficult to predict how patients will respond to therapy. Therefore, we want to give patients as many opportunities to get a home run as possible. That might occur with selinexor, or isatuximab, or a BCMA-based therapy. Especially within the constraints of the Canadian system, plotting out a course of events that exposes patients to as many mechanisms of action as possible gives patients the optimal number of opportunities to do well.

Dr. Neri: While this hasn't come up in the discussion, emerging research suggests T-cell fitness is preserved with XVd, and this is important. In the future, we may even use selinexor as a bridging therapy for CAR T-cell therapy. In addition, research presented at the most recent ASH meeting suggests that selinexor may increase BCMA expression on myeloma cells, which may enhance their susceptibility to BCMA-targeted therapies. When we combine this emerging research with the fact that XVd doesn't limit future treatment options, we have many different rationales to use selinexor in the second-line setting.

Rapidly evolving evidence is reshaping second- and later-line treatment strategies in Canada. Thoughtful sequencing that balances efficacy, safety, patient factors, and future access to therapies is essential to caring for patients, both today and tomorrow.

Financial Disclosures

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