Canada's Drug and Health Technology Agency

CADTH Reimbursement Recommendation

# Optimal Pharmacotherapy for Transplant-Ineligible Multiple Myeloma

Therapeutic Review

# CADTH FMEC Recommendations

**The CADTH Formulary Management Expert Committee (FMEC) concluded that evidence included in the CADTH systematic review and network meta-analysis (NMA) supports the use of first-line daratumumab in patients with multiple myeloma who are ineligible for transplant.** FMEC noted that, in newly diagnosed patients, daratumumab-containing regimens such as daratumumab/bortezomib/melphalan/prednisone and daratumumab/lenalidomide/dexamethasone showed statistically significant difference in progression-free survival when compared to the base comparator with lenalidomide/dexamethasone. In relapsed or refractory multiple myeloma, daratumumab/lenalidomide/dexamethasone also showed statistically significant difference in progression-free survival compared to lenalidomide/dexamethasone. However, based on results from the economic analysis using publicly available prices, a reduction in the price of daratumumab is required for this treatment to be considered cost-effective at conventional willingness to pay thresholds, in the first-line setting relative to being used as a treatment in the second-line setting.

**FMEC recommends the choice between the use of carfilzomib/dexamethasone or pomalidomide/bortezomib/dexamethasone in the second- or third-line setting be left at the physician's discretion for patients with relapsed or refractory multiple myeloma who received a daratumumab-containing regimen in the first-line setting**. FMEC also noted that a difference in efficacy between the two regimens was not determined; however, pomalidomide/bortezomib/dexamethasone is less costly and has an oral formulation, and thus may be preferred. Another important consideration would be the side effect profile of each drug regimen.

# Therapeutic Landscape

## What Is Multiple Myeloma?

Multiple myeloma is an incurable plasma cell neoplasm, characterized by an uncontrolled growth of plasma cells in the bone marrow. The preferred first-line therapy for newly diagnosed multiple myeloma is high dose chemotherapy followed by autologous stem cell transplantation. For patients who are not eligible for this procedure due to health risks or other reasons a number of multi-drug regimens can be offered to these patients. It is estimated over 50% of patients may not be eligible for transplant.

## Why Did CADTH Conduct This Review?

Publicly funded drug plans requested this therapeutic review to determine in what sequences drugs for transplant-ineligible multiple myeloma should be reimbursed to maximize clinical and cost-effectiveness while considering patient safety, characteristics, experience, and preferences.

### Person with Lived Experience

A person with lived experience presented her journey living with multiple myeloma after being diagnosed in 2020 at the age of 77. As an avid traveler, she began noticing her energy levels and strength were declining, and her family physician noted a decline in kidney functions, leading to further testing and a diagnosis. She began treatment with Revlimid, dexamethasone and monthly infusion of zoledronic acid. She reported symptoms such as anemia, neuropathy, diarrhea, bone pain, fatigue, cramps, and concerns of infections. She emphasized the need for treatment protocols to consider patient circumstances when looking at treatment options, highlighting that Dexamethasone had unbearable side effects for her treatment specifically. Although she hasn't reached remission, her treatment has kept her proteins stable for 44 months now. She emphasized that for patients, convenience in the treatment method is important, such as an oral form. Lastly, she expressed that reducing side effects such as brain fog, stomach issues, shaking and energy levels are critical for patients.

# Stakeholder Feedback

## What Did We Hear From Patients?

CADTH received input on project scope from Myeloma Canada. Patients want treatments that balance efficacy, safety and quality of life, are least invasive, and are financially accessible.

## What Did We Hear From Clinicians?

CADTH consulted clinical experts who provided inputs on the project scope and feedback to the clinical and health economic reports. It was noted that while they welcomed the project, they also expressed caution given the complexity of the disease, the heterogeneity of multiple myeloma patients and the constantly evolving treatment landscape. Clinicians have also highlighted that newer therapies are available such as CAR-T therapies and selinexor since the initiation of this review.

## What Did We Hear From the Pharmaceutical Industry?

CADTH has received inputs and feedback from multiple manufacturers. They have provided inputs on the project scope and feedback to the clinical and health economic reports. The industry feedback described the strengths and limitations of the NMA and the context around the current treatment landscape.

## What Did We Hear From Public Drug Programs?

CADTH was requested by (and received support from) Public drug plans to initiate this therapeutic review on multiple myeloma, specifically on the transplant-ineligible patient population.

**Refer to Stakeholder Input section of the CADTH report**

# Deliberative Summary

FMEC addressed the following questions based on the results of the clinical and economic analyses, patients' input, and clinicians' input as well as provisional funding algorithms on the management of multiple myeloma.

Of note, the NMA only included drugs that were identified in the project scope published in May 2021; therefore, any new therapy since that date (e.g., CAR-T therapies, selinexor) was not included in the analysis of this review.

## Table 1: Why Did FMEC Make These Recommendations?

| Questions or considerations | Discussion Points |
|---|---|
| **Is there sufficient evidence to support the prioritization of daratumumab-containing regimens in the first- and/or second-line setting based on clinical and cost-effectiveness?** | • For patients with newly diagnosed multiple myeloma who are not eligible for transplant, FMEC recommends prioritizing a regimen that contains daratumumab as first-line treatment. FMEC discussed the publicly available price of daratumumab, and jurisdictions may need to consider negotiating further price reductions to improve the cost-effectiveness of a daratumumab-containing regimen in the first line of treatment.<br>• Based on the economic analysis, FMEC noted that sequences which utilised daratumumab-based regimens in the first line generated the highest number of quality adjusted life years (between 5.3 to 5.7) but also the highest costs (between $800,000 and $1,000,000) based on publicly available prices. Depending on what these sequences were compared to, the incremental cost-effectiveness ratio consistently exceeded ~$450,000 per QALY gained. A price reduction is therefore required for daratumumab to be considered cost effective, at conventional willingness to pay thresholds, if used in the first line setting. The degree of price reduction will depend on currently negotiated prices for all treatment regimens used to treat transplant ineligible multiple myeloma.<br>• FMEC noted that the results of the network meta-analysis demonstrated that daratumumab/lenalidomide/dexamethasone and daratumumab/bortezomib/melphalan/prednisone regimens have shown statistically superior progression-free survival estimates when compared to lenalidomide/dexamethasone in the first line setting. |

| Questions or considerations | Discussion Points |
|---|---|
| | • FMEC clinical experts suggested that daratumumab/bortezomib/melphalan/prednisone is no longer clinically relevant in Canada due to increased toxicity with melphalan.<br>• The results of the network meta-analysis were similar to the MAIA clinical trial and the FACON NMA and correlate with clinical experts' opinions as well as international guidelines.<br>• Given patient harms were unable to be evaluated in the network meta-analysis, FMEC acknowledged that clinicians need to consider the safety profiles of individual treatment when choosing an optimal first-line or second-line regimen for patients.<br>• The results of qualitative reviews have highlighted the impact of treatments of multiple myeloma on the quality of life. The chosen regimen should align with patients' preferences and optimize their experiences with the treatment journey.<br>• FMEC's guest specialists identified that treatment options for transplant-ineligible patients would be offered to patients who decline to undergo a transplant as also heard from the patient with lived experience. |
| **Is there sufficient evidence to support the prioritization of lenalidomide-containing regimens in the first- and/or second-line setting in patients who are less fit and cannot take daratumumab, based on clinical and cost-effectiveness?** | • FMEC was unable to issue any recommendation for this question:<br>1) the proportion of patients with newly diagnosed multiple myeloma who are not eligible for transplant nor suitable for a daratumumab-containing regimen due to frailty is small, and it only represents less than 5% of this population according to FMEC clinical experts; and<br>2) there is a lack of certainty in the clinical evidence for lenalidomide in the first- and second-line setting. |
| **Is there sufficient evidence to support the prioritization of carfilzomib-containing regimens and pomalidomide-containing regimens** | • The clinical efficacy between pomalidomide/bortezomib/dexamethasone and carfilzomib/dexamethasone is comparable based on the results from the NMA. FMEC noted that generic versions of pomalidomide were available at the time of the analysis, but prices from Ontario were used and do not reflect prices paid by other jurisdictions. Based on these lower prices paid across Canada, this reduces the cost of |

| Questions or considerations | Discussion Points |
|---|---|
| **based on clinical and cost-effectiveness?** | pomalidomide-based regimens in the economic analysis to be less costly than carfilzomib-based regimens. FMEC recommended a note be added to the Economic Report to this effect.<br>• For patients with relapsed or refractory multiple myeloma who received a daratumumab-containing regimen in the first-line setting, FMEC recommended the choice between pomalidomide/bortezomib/dexamethasone and carfilzomib/dexamethasone in the second- or third-line setting be left at the physician's discretion.<br>• FMEC discussed that if using a pomalidomide-based regimen in second line, the preferred regimen is pomalidomide/bortezomib/dexamethasone based on the NMA.<br>• Of note, selinexor was not considered by FMEC in the second-line setting as it was not available at the time of the review nor included at the time of the initiation of the review. |
| **Is there sufficient evidence to support the prioritization of isatuximab-containing regimens, based on clinical and cost effectiveness?** | • FMEC was unable to issue any recommendation for this question.<br>• Isatuximab is only relevant at this time for patients who previously received lenalidomide/dexamethasone +/-bortezomib up to 5 years ago and who now relapse. Isatuximab is not used in patients who have already received a daratumumab-containing regimen as both drugs have a similar mechanism of action. |

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# Feedback on Draft Recommendations

<to be updated after the stakeholder feedback period>

# FMEC Information

**Members of the Committee**: Dr. Alun Edwards, Ms. Valerie McDonald, Dr. Jim Silvius, Dr. Marianne Taylor, Dr. Maureen Trudeau, Dr. Dominika Wranik, Dr. Emily Reynen (Chair), Dr. Irwindeep Sandhu (guest specialist), and Dr. Darrell White (guest specialist).

**Meeting dates**: October 17, 2023 and November 30, 2023

**Conflicts of interest**: None

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