CADTH

CADTH Reimbursement Review

Provisional Funding Algorithm

Indication: Multiple myeloma

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CADTH

About CADTH: CADTH is an independent, not-for-profit organization responsible for providing Canada's health care decision-makers with objective evidence to help make informed decisions about the optimal use of drugs, medical devices, diagnostics, and procedures in our health care system.

Funding: CADTH receives funding from Canada's federal, provincial, and territorial governments, with the exception of Quebec.

Key Messages

- The lenalidomide-bortezomib-dexamethasone regimen should be considered as an option for induction therapy in patients with multiple myeloma who are eligible for transplant.
- The carfilzomib-lenalidomide-dexamethasone regimen can be given before or after a regimen that contains an anti-CD38 monoclonal antibody.
- If covered by public drug programs, regimens that contain isatuximab would be second-line options, particularly for patients who are eligible for transplant.
- Regimens that contain pomalidomide-dexamethasone and those that contain carfilzomib-dexamethasone should be available, one after the other and in any order, to patients after they fail a regimen that contains an anti-CD38 monoclonal antibody.
- The pomalidomide-dexamethasone and pomalidomide-cyclophosphamide-dexamethasone regimens should be considered options after a patient has failed first-line lenalidomide-bortezomib-dexamethasone.

Background

The provisional funding algorithm process is used to provide advice when the drug programs have indicated that there is a need to establish an appropriate place in therapy for the drug under review relative to alternative treatments that are currently reimbursed by the drug programs, including the impact on the appropriate sequencing of treatments for the purposes of reimbursement. The creation of a new provisional funding algorithm or update of an existing provisional funding algorithm is typically initiated following the issuance of a new pan-Canadian Oncology Drug Review Expert Review Committee (pERC) recommendation when there are potential implications regarding the funding sequence of drugs within a therapeutic area. CADTH will only initiate work on a provisional funding algorithm at the request of the CADTH Provincial Advisory Group (PAG).

The following item are considered by the expert panels when advising the jurisdictions on the provisional algorithm for the relevant indication:

- unmet therapeutic need for patients (particularly those in understudied populations)
- evidence supporting a particular sequence of therapies (if available)
- clinical experience and opinion that support a particular sequence of therapies
- clinical practice guidelines
- variability across jurisdictions regarding the reimbursement status of existing treatment options
- affordability and sustainability of the health care system
- implementation considerations at the jurisdictional level.

Note that provisional funding algorithms are not treatment algorithms; they are neither meant to detail the full clinical management of each patient nor the provision of each drug regimen. The diagrams may not contain a comprehensive list of all available treatments, and some drugs may not be funded in certain jurisdictions. Most drugs are subject to explicit funding criteria, which may also vary between jurisdictions. Readers are invited to refer to the cited sources of information on the CADTH website for more details.

Provisional funding algorithms delineate treatment sequences available to patients who were never treated for the condition of interest (i.e., incident population). Time-limited

funding of new options for previously or currently treated patients (i.e., prevalent population) is not detailed in the algorithm.

Provisional funding algorithms may contain drugs that are under consideration for funding. Algorithms will not be dynamically updated by CADTH following changes to drug funding status. Revisions and updates will occur only upon request by jurisdictions.

Cancer drug programs from federal and provincial jurisdictions requested supplemental implementation advice along with a CADTH provisional funding algorithm on multiple myeloma. Refer to Appendix 1 for a list all past CADTH advice and recommendations relevant for this therapeutic area.

Implementation Issues

At the request of the participating drug programs, CADTH convened a panel of clinical experts in Canada to provide advice for addressing the outstanding implementation issues as follows:

1. use of lenalidomide-bortezomib-dexamethasone (RVd) as induction therapy in patients who are eligible for transplant
2. sequencing of novel therapies in the relapsed or refractory setting, considering evidence and affordability of options
3. sequencing and selection of carfilzomib or pomalidomide combined with dexamethasone after failure of an anti-CD38–containing regimen, considering evidence and affordability
4. use of pomalidomide-dexamethasone (Pd) after failure of first-line lenalidomide-bortezomib combination therapy.

Consultation Process and Objectives

The implementation advice panel comprised 5 specialists in Canada with expertise in the diagnosis and management of patients with multiple myeloma, representatives from public drug programs, and a panel chair. The objective of the panel was to provide advice to the participating drug programs regarding the implementation issues noted in the Background section. A consensus-based approach was used, and input from stakeholders was solicited using questionnaires. Stakeholders, including patient and clinician groups and pharmaceutical manufacturers, and public drug programs were invited to provide input in advance of the meeting.

The advice presented in this report has been developed based on the experience and expertise of the implementation advice panel members and, as such, represents experience-informed opinion; it is not necessarily based on evidence.

Advice on Funding Algorithm

Summary of Implementation Advice

Implementation advice regarding the optimal sequencing of treatments is summarized in Table 1. For each implementation issue, a summary of the relevant panel discussion is provided for additional context.

Table 1: Summary of Advice for Addressing Implementation Issues

Issue	Advice	Rationale
Use of RVd as induction therapy in patients who are eligible for transplant	The panel advises that RVd should be considered as an option for induction therapy in patients with multiple myeloma who are eligible for a transplant.	There is evidence suggesting superior efficacy to CyBord, which was the regimen that had previously been most commonly used in this setting.
Sequencing of novel therapies in the relapsed or refractory setting, considering evidence and affordability of options	The panel advises that KRd can be sequenced before or after an anti-CD38–based regimen. The panel advises that isatuximab-containing regimens would be important second-line options, particularly for patient who are eligible for transplant, contingent on them being funded by public payers.	Although KRd is no longer a common option given the advent of the combination of daratumumab and lenalidomide, there is no evidence or other rationale to suggest that it would not be effective in this setting. Because patients who have received a transplant and are resistant to both lenalidomide and bortezomib would be prevalent in the second-line setting, isatuximab combined with an alternative proteasome inhibitor or immunomodulator would be the best option for these patients who have not been treated with an anti-CD38–based regimen.
Sequencing and selection of carfilzomib or pomalidomide combined with dexamethasone after failure of an anti-CD38–containing regimen, considering evidence and affordability	The panel advises that both Pd and Kd backbones should be available as sequential treatment options after failure of an anti-CD38–containing regimen.	There is some evidence to suggest that sequencing of Pd and Kd, in any order, provides a clinical benefit to patients. Additionally, the fact that pomalidomide and carfilzomib possess different mechanisms of action suggests that failure on one does not predict subsequent failure on the other.
Use of pomalidomide-dexamethasone after failure of first-line lenalidomide-bortezomib combination therapy	The panel advises that Pd or PCd are valid options after failure of first-line RVd.	Pd is no longer considered standard of care in this space. Instead, cyclophosphamide is added to Pd (PCd). There is evidence to suggest efficacy of PCd in this setting, and this evidence can be generalized to Pd.

CyBord = cyclophosphamide-bortezomib-dexamethasone; Kd = carfilzomib-dexamethasone; KRd = carfilzomib-lenalidomide-dexamethasone; PCd = pomalidomide-cyclophosphamide-dexamethasone; Pd = pomalidomide-dexamethasone; RVd = lenalidomide-bortezomib-dexamethasone.

In addition to the previously outlined advice, the panel indicated that because an improvement in cost-effectiveness was a condition for reimbursement in each of the recommendations related to the drugs in scope, implementation of any advice herein should be contingent upon ensuring that the relevant treatments are affordable to public payers.

Panel Discussion

Use of RVd as Induction Therapy in Patients Who Are Eligible for Transplant

There was consensus among the panellists that there is evidence to support the use of RVd as induction therapy in patients who are eligible transplant. CADTH has produced a Rapid Health Technology Review on RVd for patients who are eligible for transplant, finding that response, relapse, progression-free survival (PFS), and overall survival broadly favoured

RVd over bortezomib-cyclophosphamide-dexamethasone (CyBord).[1] Some public drug programs allow a switch from CyBord to RVd if there is a lack of response. It was noted that RVd is now the international standard of care in this setting, although the panellists also indicated that some clinicians may still wish to use CyBord as first line, as it is easier to use for patients with poor renal function or low blood counts. A panellist also noted that it can be difficult to tease out the impact of induction therapy, in isolation, because success of autologous stem cell transplant is determined by 3 elements: induction, transplant, and maintenance. All 3 components contribute to the depth of response and this correlates with the length of benefit.

Sequencing of Novel Therapies in the Relapsed or Refractory Setting, Considering Evidence and Affordability of Options

To address this implementation issue, the panellists discussed the effectiveness of sequencing of novel triplet therapies containing at least 2 of the following: a proteasome inhibitor (PI), an immunomodulator, and an anti-CD38 antibody, all combined with dexamethasone. The panel discussed the use of carfilzomib-lenalidomide-dexamethasone (KRd) in patients who have received prior anti-CD38 regimens and the effectiveness of an anti-CD38 regimen in patients who have received KRd.

There was agreement among the panellists that there is a lack of evidence to inform the use of KRd in patients who have received prior daratumumab- or isatuximab-containing regimens. The panellists noted that this is likely because the approval and use of KRd predated the approval of anti-CD38 monoclonal antibodies, and therefore most of the studies involving KRd had already been completed. Despite the lack of evidence, panellists believed that KRd should still be an option, and noted that there is no biological rationale to suggest that KRd would not be efficacious in a patient previously treated with an anti-CD38 monoclonal antibody. Results from the BOSTON trial were mentioned, which demonstrated efficacy for bortezomib-selinexor-dexamethasone combination in patients who had been treated with daratumumab, and may provide some evidence, albeit limited, that a regimen containing a PI can be efficacious in patients who had previously received daratumumab.[2] The panellists noted that the decision regarding whether to use KRd in this setting would likely depend on refractoriness to prior lenalidomide and thus ineligibility to KRd. It was further noted that because most patients receive lenalidomide as part of their initial therapy, they will be progressing on lenalidomide; hence, KRd is becoming less relevant to practice. There was agreement among the panellists that KRd is not used frequently in Canada.

KRd was the first triplet regimen that contained carfilzomib, and fulfilled a need at one time, but has been largely replaced by other regimens. The other regimens that contain carfilzomib are relevant, according to the panel. The panellists noted that carfilzomib-dexamethasone (Kd) has been shown in a phase III trial to be a more effective regimen than bortezomib-dexamethasone and that it has acceptable toxicity.[3] It was noted that carfilzomib-cyclophosphamide-dexamethasone may also be used in this setting, and is likely a common regimen in Canada.

There was consensus among the panellists that there is evidence supporting the effectiveness of daratumumab or isatuximab-containing regimens in patients who have received KRd. The panellists agreed that limiting a patient to 1 triplet therapy, as is implemented in some jurisdictions, would not make clinical sense and may compromise patient care. It was noted that virtually all previous doublets have been shown to be inferior in outcome when compared to a triplet drug regimen.

The panel discussed the role of anti-CD38 antibodies in the relapsed or refractory setting. According to the panellists, the priority is to integrate anti-CD38 monoclonal antibodies as soon as possible into patient care. Patients who failed first-line daratumumab-lenalidomide-dexamethasone (DRd) will be refractory to both an anti-CD38 and lenalidomide, so clinicians will want a PI in their subsequent regimen or pomalidomide, and then will flip the backbone therapy in the third line. Patients who are eligible for transplant will typically progress on lenalidomide maintenance and would require access to an anti-CD38–containing regimen as well as a PI or pomalidomide in the second line, and then flip the backbone therapy in third-line treatment. The only currently available anti-CD38–containing regimen for these patients is daratumumab-bortezomib-dexamethasone (DVd). However, a panellist noted that the median PFS with DVd in the lenalidomide-refractory group has been disappointing (7.9 months). As a result, carfilzomib combined with an anti-CD38 (such as isatuximab) would be a valid alternative in these patients, if they can tolerate the regimen. They noted that the use of isatuximab-carfilzomib-dexamethasone could potentially double the PFS benefit in patients who are refractory to lenalidomide, compared with a doublet regimen. The panellists noted that until weekly carfilzomib is funded, some will not want the more frequent carfilzomib and may stay with bortezomib. The panellists added that patients who are eligible for transplant should have as many funded options for pharmacological intervention as patients who are not eligible for transplant. This would be consistent with the traditional strategy in multiple myeloma, to treat patients who are younger and more fit more aggressively than patients who are older.

Sequencing and Selection of Carfilzomib or Pomalidomide Combined With Dexamethasone After Failure of an Anti-CD38 Regimen, Considering Evidence and Affordability

The panellists noted that there is evidence for the sequencing of carfilzomib and pomalidomide, including a recent article published by the Canadian Myeloma Research Group (CMRG), which focuses on patients with relapsed multiple myeloma, using a Canadian database.[4] Although few patients were refractory to daratumumab in the study (due to limitations of availability of daratumumab), the overall results suggested that there is evidence that responses remain consistent whether patients received a pomalidomide-containing regimen followed by a carfilzomib-containing regimen (median PFS of 5.4 months) or vice versa (median PFS of 4.9 months). The panellists were also clear that given the 2 distinct mechanisms of action of these drugs, there is no pharmacological rationale to suggest that they should not be sequenced.

The panellists noted that public drug programs limit choices post-daratumumab to either carfilzomib or pomalidomide backbones, rather than allowing access to both. Panellists indicated that with the coming funding of daratumumab triplets in the first-line setting, this would effectively reduce the number of available lines of novel drug therapy down to 2, and this would be a step backwards in the treatment of multiple myeloma, where 3 lines of therapy have been the standard for many years. The panel emphasized that losing a line of treatment is very distressing to clinicians and patients. In terms of affordability concerns, one should keep in mind that survival has doubled in multiple myeloma in the past 2 decades. Patients living longer will be treated longer, and this will naturally be more costly. The panellists also pointed out that reducing the number of available lines of therapy from 3 to 2 is currently not a transparent nor evidence-based decision. The panel readily acknowledged that the price of oncology drugs, in general, has skyrocketed in the past decade.

There was also discussion among the panellists about how the loss of a line of therapy raises the issue of inequities within the Canadian health care system. Patients who have the

financial means to pay out of pocket or those with good private insurance will have access to further lines of therapy, while those who cannot will be limited to 2 lines, as the only options after these 2 drugs would be bortezomib and then palliation. Additionally, this limitation on the number of lines of therapy may create a rural-urban divide, as patients who live near major centres will likely have better access to clinical trials, also giving them access to further lines of therapy, while those who live in rural areas will not be as readily able to access clinical trials. The panellists were unanimous in stating that these types of inequities should be considered and addressed. They also expressed concern with regards to clinical trial access in general, given that most clinical trials now require exposure to 3 prior lines of therapy.

Pd Use After Failure of First-Line RVd

There was consensus among the panellists that there is no evidence to support use of Pd after failure of RVd; however, it was also felt that lack of evidence does not necessarily suggest that the regimen is not effective in this setting. The panel noted that the evidence will likely never be available. The panel emphasized that real-world evidence, such as initiatives led by the CMRG, can be valuable in answering some of these questions. The panel indicated that most evidence on Pd comprise patients who have had sequential lenalidomide and bortezomib, as suggested by the Health Canada-approved indication. However, the panel noted that from a biological standpoint, there would be no difference in experiencing lenalidomide and bortezomib sequentially or in combination.

The panellists noted that most specialists do not use Pd anymore, but would instead add cyclophosphamide to the regimen (creating the PCd regimen) and cited evidence to support this approach. In a randomized study, 70 patients who were refractory to lenalidomide received either PCd or Pd, and the objective response rate was 65% versus 39%, respectively (P = 0.035) and the PFS was 9.5 months versus 4.4 months (P = 0.106), respectively.[5] The panel felt that this evidence is sufficient to support use of either Pd or PCd after first-line RVd.

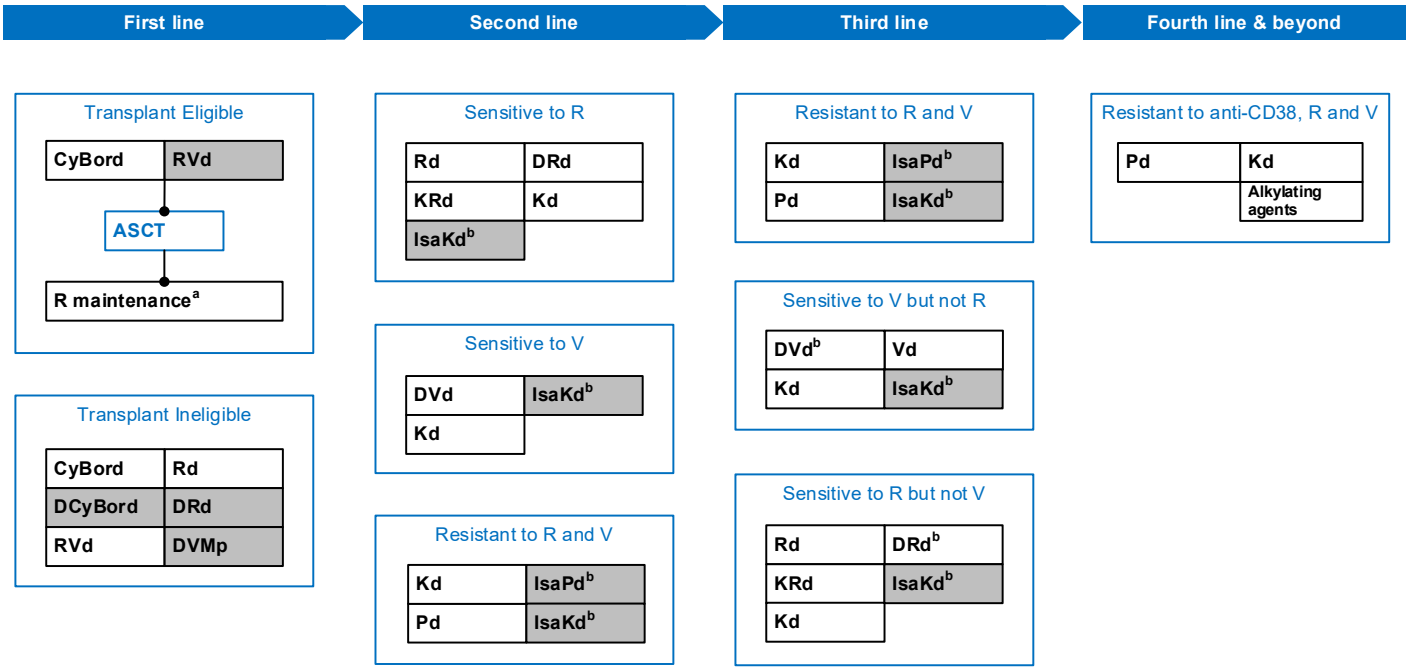
It was noted that in some jurisdictions, there are limitations placed on using cyclophosphamide with these novel regimens. The panellists strongly felt that such limitations restrict the ability to use older, very effective, and much less expensive drugs and should be reconsidered.

Other Remarks

The panellists emphasized that given the continual introduction of new therapies, it will be imperative to have a mechanism for continually updating any algorithm that is generated. As mentioned in the Background section of this report, updates to algorithms may be requested by jurisdictions when new therapies become available.

Provisional Funding Algorithm

Figure 1: Provisional Funding Algorithm Diagram for Multiple Myeloma



ASCT = autologous stem cell transplant; CyBord = cyclophosphamide-bortezomib-dexamethasone; DCyBord = daratumumab-cyclophosphamide-bortezomib-dexamethasone DRd = daratumumab-lenalidomide-dexamethasone; DVd = daratumumab-bortezomib-dexamethasone; DVMp = daratumumab-bortezomib-melphalan-prednisone; IsaKd = isatuximab-carfilzomib-dexamethasone; IsaPd = isatuximab-pomalidomide-dexamethasone; Kd = carfilzomib-dexamethasone; KRd = carfilzomib-lenalidomide-dexamethasone; Pd = pomalidomide-dexamethasone; R = lenalidomide; Rd = lenalidomide-dexamethasone; RVd = lenalidomide-bortezomib-dexamethasone; V = bortezomib; Vd = bortezomib-dexamethasone.

Notes: Patients with drug resistance cannot be re-treated with the same drug(s).

Cyclophosphamide may be added to Kd, Pd, and Rd.

White boxes indicate that the therapy is funded across most jurisdictions. Grey boxes indicate that the therapy is under review for funding (pCPA or province or cancer agency).

[a] Maintenance optional.

[b] If not resistant to an anti-CD38 biologic.

Figure 1 depicts the provisional funding algorithm proposed by the panel. Note that this diagram is a summary representation of the drug funding options for the condition of interest. It is not a treatment algorithm; it is neither meant to detail the full clinical management of each patient nor the provision of each drug regimen. The diagram may not contain a comprehensive list of all available treatments, and some drugs may not be funded in certain provinces. All drugs are subject to explicit funding criteria, which may also vary between provinces. Readers are invited to refer to the individual drug entries on the CADTH website for more details.

First-Line Setting

Patients who are eligible for an autologous stem cell transplant can receive induction therapy with either CyBord or RVd (the latter being under consideration by jurisdictions). After transplant, maintenance with lenalidomide is available. Patients who are ineligible for transplant can be given CyBord or Rd (either with or without daratumumab, where available) or RVd. Daratumumab combined with bortezomib, melphalan, and prednisone is also an option is the transplant-ineligible setting.

Relapsed or Refractory

Treatment in the relapsed or refractory setting depends on response to prior therapies. Generally, patients with drug resistance cannot be treated again with the same drug, except for dexamethasone, which is found in all regimens. Depending on drug sensitivity, patients can be treated with Kd or Pd (combination with isatuximab is under jurisdictional review), KRd, lenalidomide-dexamethasone (Rd), DRd, or DVd. Subsequently, alternate regimens with a different PI or immunomodulator backbone can be offered in the third and fourth lines, depending on drug sensitivity. Cyclophosphamide may be added to some regimens, such as Pd, carfilzomib-dexamethasone, and Rd.

Appendix 1: Past CADTH Advice and Recommendations

Table 2: Relevant CADTH Recommendations

Generic name (brand name)	Date of recommendation	Recommendation and guidance on sequencing
Newly diagnosed		
Daratumumab (Darzalex) + lenalidomide (Revlimid) + dexamethasone	Mar 5, 2020	pERC conditionally recommends to reimburse daratumumab in combination with lenalidomide and dexamethasone (DRd) for patients with newly diagnosed MM who are not suitable for autologous stem cell transplant if the following conditions are met: • cost-effectiveness being improved to an acceptable level • feasibility of adoption (budget impact) being addressed pERC concluded that the optimal sequencing of therapies for patients with newly diagnosed MM who are not suitable for autologous stem cell transplant is unknown. Therefore, pERC was unable to make an evidence-informed recommendation on sequencing of treatments. pERC recognized that provinces will need to address this issue upon implementation of a reimbursement recommendation for DRd and noted that collaboration among provinces to develop a national, uniform approach to optimal sequencing would be of great value.
Lenalidomide (Revlimid) + bortezomib (Velcade) + Dexamethasone	June 19, 2019	pERC conditionally recommends to reimburse lenalidomide in combination with bortezomib and low dose dexamethasone in patients with newly diagnosed MM in whom stem cell transplantation is not intended if the following condition is met: • feasibility of adoption is addressed (budget impact) Reimbursement should be in patients with good performance status and treatment (with lenalidomide or low dose dexamethasone for the maintenance phase) should continue until unacceptable toxicity or disease progression. pERC concluded that the optimal sequencing of therapies for patients with newly diagnosed MM in whom stem cell transplantation is not intended is unknown. Therefore pERC was unable to make an evidence-based recommendation on sequencing of treatments. pERC recognizes that provinces will need to address this issue upon implementation of a reimbursement recommendation for VLd, and noted that collaboration among provinces to develop a national, uniform approach to optimal sequencing would be of great value.
Daratumumab (Darzalex) + bortezomib (Velcade) + melphalan + prednisone	August 29, 2019	pERC conditionally recommends to reimburse daratumumab in combination with bortezomib, melphalan, and prednisone (DVMP) for patients with newly diagnosed MM who are not suitable for ASCT if the following conditions are met: • cost-effectiveness being improved to an acceptable level • feasibility of adoption (budget impact) being addressed • treatment with daratumumab should continue until unacceptable toxicity or disease progression **Optimal sequencing of available therapies after progression on daratumumab in combination with bortezomib, melphalan, and prednisone:** pERC concluded that the optimal sequencing of therapies for patients with newly diagnosed MM who are not suitable for ASCT is unknown. Therefore pERC was unable to make an

Generic name (brand name)	Date of recommendation	Recommendation and guidance on sequencing
		evidence-based recommendation on sequencing of treatments. pERC recognizes that provinces will need to address this issue upon implementation of a reimbursement recommendation for daratumumab and noted that collaboration among provinces to develop and national, uniform approach to optimal sequencing would be of great value. **Daratumumab in combination with cyclophosphamide, bortezomib, and dexamethasone:** At the time of implementing a reimbursement recommendation for DVMP, jurisdictions may consider extending the reimbursement to daratumumab in combination with cyclophosphamide, bortezomib, and dexamethasone (DCyBorD) because pERC agreed with the registered clinician input and the CGP that DCyBorD would likely be equally as effective as DVMP and possibly less toxic.
Relapsed or refractory		

Isatuximab (Sarclisa) + carfilzomib (Kyprolis) + dexamethasone	February 15, 2022	pERC recommends that isatuximab combined with carfilzomib and dexamethasone (IsaKd) be reimbursed for the treatment of adult patients with relapsed or refractory MM who have received 1-3 prior lines of therapy, and the following conditions met:
		• measurable disease
		• received at least 1 prior line of therapy
		• good performance status
		• must not:
		  ○ have prior treatment with antiCD38 mab
		  ○ be refractory to carfilzomib
		  ○ have a LVEF < 40%
		
		Treatment should be discontinued if:
		• evidence of disease progression (IMWG)
		• unacceptable toxicity despite dose modification
		• pERC also called for a reduction in price
		• pERC agreed with the clinical experts that the preferred regimen depends on what the patient has received previously. If a patient experienced disease progression on a lenalidomide-based regimen in the first-line setting, then IsaKd and DVd are available options.
		• pERC agreed with the clinical experts that it is preferential to give an anti-CD38 as soon as possible, and therefore second-line IsaKd is preferred over third-line IsaPd for those who have not had a CD38 mAb.
		• pERC agreed with the clinical experts that there is currently no evidence to support sequencing of isatuximab and daratumumab.
		• pERC agreed with the clinical experts that there is currently no evidence in support of sequencing IsaKd and IsaPd.

Isatuximab (Sarclisa) + pomalidomide (Pomalyst) + dexamethasone	April 1, 2021	pERC conditionally recommends the reimbursement of isatuximab in combination with pomalidomide and dexamethasone (IsaPd) in patients with relapsed or refractory MM who have received at least 2 prior lines of therapy including lenalidomide and a PI, if the following conditions are met: • cost-effectiveness improved to an acceptable level • feasibility of adoption (budget impact) being assessed Eligible patients include adults with RRMM who have failed treatment on lenalidomide and a PI, administered either alone or in combination

Generic name (brand name)	Date of recommendation	Recommendation and guidance on sequencing
		in any prior line of treatment, have disease that was refractory to the last line of treatment received, and good performance status. Treatment should be continued until acceptable toxicity or disease progression. **Optimal sequencing of IsaPd with other therapies for RRMM including daratumumab:** pERC noted that the eligibility criteria in the ICARIA-MM trial included patients who had previous treatment with but were not refractory to an anti-CD38 mAb, but that only 1 patient in the IsaPd treatment group of the trial had prior exposure to an anti-CD38 mAb (i.e., daratumumab). In the absence of evidence, pERC concluded that the efficacy of IsaPd in eligible patients who have received at least 2 prior lines of therapy that includes daratumumab is unknown. pERC also concluded that due to the absence of evidence on sequencing of IsaPd and currently available treatments for RRMM, no informed recommendation on optimal sequencing could be made. pERC recognized that jurisdictions would need to address this issue upon implementation of IsaPd reimbursement and noted that collaboration among jurisdictions to develop a common approach to sequencing would be of value.
Pomalidomide (Pomalyst) + bortezomib (Velcade) + dexamethasone	Sep. 18, 2019	pERC conditionally recommends the reimbursement of pomalidomide in combination with dexamethasone and bortezomib (PVd) for the treatment of adults with relapsed or refractory MM who have had at least 1 prior regimen including lenalidomide, if the following condition, cost-effectiveness being improved to an acceptable level, is met. Patients should have good performance status and treatment should be continued until disease progression or unacceptable toxicity. pERC concluded that the optimal sequencing of PVd and other treatments now available for the treatment of MM is currently unknown. pERC was therefore unable to make an evidence-informed recommendation on sequencing. However, pERC recognized that provinces would need to address this issue upon implementation of pomalidomide reimbursement and noted that collaboration among provinces to develop a common approach would be of value.
Daratumumab (Darzalex) + lenalidomide (Revlimid) or bortezomib (Velcade) + dexamethasone	Oct. 5, 2017	pERC recommends the reimbursement of daratumumab in combination with lenalidomide and dexamethasone (DRd) or bortezomib and dexamethasone (DVd) for treatment of patients with MM with good performance status who have received at least 1 prior therapy, conditional on the cost-effectiveness being substantially improved and adoption feasibility being addressed. pERC noted that daratumumab should be continued until disease progression or unacceptable toxicity. pERC concluded that the optimal sequencing of daratumumab plus lenalidomide-dexamethasone or bortezomib-dexamethasone and other treatments now available for the treatment of MM is currently unknown. pERC noted the opinion of the pCODR CGP that daratumumab in combination with lenalidomide-dexamethasone or bortezomib-dexamethasone may be a favourable second-line option over triplet therapy with carfilzomib; however, the committee acknowledged that there is no appropriate treatment sequence for daratumumab and carfilzomib for the treatment of MM after failure of 1 prior therapy. Therefore, pERC was unable to make an evidence-informed recommendation on sequencing of treatments for RRMM. However, pERC recognized that provinces would need to address

Generic name (brand name)	Date of recommendation	Recommendation and guidance on sequencing
		this issue upon implementation of daratumumab reimbursement and noted that collaboration among provinces to develop a common approach would be of value.
Carfilzomib (Kyprolis) + dexamethasone	Mar. 30, 2017	pERC recommends reimbursement of carfilzomib in combination with dexamethasone for patients with relapsed MM with a good performance status who have received 1 to 3 prior treatments, on the condition that the cost-effectiveness be improved to an acceptable level. pERC concluded that optimal sequencing of carfilzomib plus dexamethasone and other treatments now available for the treatment of MM is currently unknown. pERC was therefore unable to make an evidence-informed recommendation on sequencing. However, pERC recognized that provinces would need to address this issue upon implementation of carfilzomib reimbursement and noted that collaboration among provinces to develop a common approach would be of value. pERC acknowledged that carfilzomib plus dexamethasone would be an alternative therapy for patients who are ineligible to receive triplet therapy and not an add-on to the existing sequence of treatments.
Carfilzomib (Kyprolis) + lenalidomide (Revlimid) + dexamethasone	Nov 11, 2016	pERC recommends reimbursement of carfilzomib in combination with lenalidomide and dexamethasone for patients with MM who have received at least 1 prior treatment, on condition that the cost-effectiveness be improved to an acceptable level. Patients must not have had disease progression during treatment with bortezomib or if previously treated with lenalidomide and dexamethasone patients must not have: • discontinued therapy because of adverse effects • disease progression during the first 3 months of treatment, or • progression at any time during treatment if lenalidomide plus dexamethasone was their most recent treatment Treatment should be in patients who have good performance status and are deemed to have adequate renal function. Treatment with carfilzomib should continue until disease progression or unacceptable toxicity, up to a maximum of 18 cycles. pERC concluded that the optimal sequencing of carfilzomib plus lenalidomide-dexamethasone and other treatments now available for the treatment of MM is currently unknown. pERC was therefore unable to make an evidence-informed recommendation on sequencing. However, pERC recognized that provinces would need to address this issue upon implementation of carfilzomib reimbursement and noted that collaboration among provinces to develop a common approach would be of value.
Pomalidomide (Pomalyst) + dexamethasone	July 31, 2014	pERC recommends funding pomalidomide (Pomalyst) in patients with relapsed and/or refractory MM who have previously failed at least 2 treatments, including both bortezomib and lenalidomide, and demonstrated disease progression on the last treatment, conditional on the cost-effectiveness being improved to an acceptable level. Pomalidomide should also be an option in rare instances where bortezomib is contraindicated, or when patients are intolerant to it but, in all cases, patients should have failed lenalidomide. pERC made this recommendation because it was satisfied that there is a net clinical benefit of pomalidomide in this setting. However, at the

Generic name (brand name)	Date of recommendation	Recommendation and guidance on sequencing
		submitted price and based on the Economic Panel's range of best estimates of the incremental cost-effectivess ratio, pomalidomide could not be considered cost-effective compared with best supportive care.
Idecabtagene vicleucel (Abecma)	Nov. 12, 2021	CADTH recommends that Abecma should not be reimbursed by public drug plans for the treatment of MM.
Daratumumab (Darzalex)	Dec 1, 2016	pERC does not recommend daratumumab for the treatment of patients with MM who 1) have received at least 3 prior lines of therapy including a proteasome inhibitor (PI) and an immunomodulatory agent (IMiD); or 2) have failed or are intolerant to a PI and who have failed or are intolerant to an IMiD.

ASCT = autologous stem cell transplant; CGP = Clinical Guidance Panel; DCyBorD = daratumumab, cyclophosphamide, bortezomib, and dexamethasone; DRd = daratumumab, lenalidomide and dexamethasone; DVd = daratumumab, bortezomib and dexamethasone; DVMP = daratumumab, bortezomib, melphalan, and prednisone; IsaKd = isatuximab, carfilzomib, dexamethasone; IsaPd = Isatuximab, pomalidomide, dexamethasone; LVEF = left ventricular ejection fraction; MM = multiple myeloma; PVd = pomalidomide, dexamethasone and bortezomib.

Note: This table has not been copy-edited.

See published recommendation reports for full details, including conditions and criteria.

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