Canada's Drug and
Health Technology Agency

Provisional Funding Algorithm

Indication: Multiple myeloma

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

Background

Following a request from jurisdictions, CADTH will design or update an algorithm depicting the sequence of funded treatments for a particular tumour type. These algorithms are proposals for the jurisdictions to implement and adapt to the local context. As such, they are termed "provisional." Publishing of provisional algorithms is meant to improve transparency of the oncology drug funding process and promote consistency across jurisdictions.

Provisional funding algorithms are based on 3 principal sources of information:

- CADTH pCODR Expert Review Committee (pERC) reimbursement recommendations and/or implementation guidance regarding drug place in therapy and sequencing
- implementation advice from panels of clinicians convened by CADTH concerning sequencing of drugs in the therapeutic space of interest
- existing oncology drug reimbursement criteria and legacy funding algorithms adopted by jurisdictional drug plans and cancer agencies.

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. All 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 also 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.

Jurisdictional cancer drug programs requested a CADTH provisional funding algorithm on multiple myeloma. However, no outstanding implementation issues were identified, and no additional implementation advice is provided in this report. The algorithm depicted herein is meant to reflect the current and anticipated funding landscape based on the previously mentioned sources of information.

History and Development of the Provisional Funding Algorithm

CADTH first published a provisional funding algorithm report for multiple myeloma in May 2022. This was a panel algorithm where the implementation advice panel comprised 5 specialists in Canada with expertise in the diagnosis and management of patients with multiple myeloma. The aim of the panel was to address various outstanding implementation issues, as outlined in the report.

Jurisdictional cancer drug programs have recently requested a rapid algorithm to update and incorporate the CADTH recommendation for Selinexor (Xpovio) to be used in combination with bortezomib and dexamethasone for the treatment of adult patients with multiple myeloma.

In addition, it was noted after publishing the first provisional funding algorithm that carfilzomib-lenalidomide-dexamethasone (KRd) should not be a third-line option under "Sensitive to R but not V". As such, an amendment has been made in this algorithm. This is to align with the CADTH recommendation from PC0067-000.

Table 1: Relevant CADTH Recommendations

Generic name (brand name)	Date of recommendation	Recommendation and guidance on treatment sequencing
Newly diagnosed		

Selinexor (Xpovio) + bortezomib (Velcade) + dexamethasone	August 17, 2022	pERC recommends that selinexor in combination with bortezomib and dexamethasone (SVd) be reimbursed for the treatment of adult patients with multiple myeloma who have received at least one prior therapy if the following conditions are met:
		• Adult (≥ 18 years) patients who have all of the following:
		  ○ Histologically confirmed multiple myeloma
		  ○ received at least one prior therapy
		• SVd should only be prescribed by clinicians with expertise and experience in all of the following:
		  ○ the management of patients with multiple myeloma
		  ○ the adverse effects associated with selinexor
		• Selinexor should only be prescribed and reimbursed in combination with bortezomib and dexamethasone.
		As per the BOSTON trial, prior treatment with bortezomib or other proteasome inhibitor (PI) should be permitted, provided all of the following criteria are met:
		• Best response achieved with prior bortezomib at any time was ≥ partial response (PR) and the last PI therapy (alone or in combination) was ≥ PR
		• Patient did not discontinue bortezomib due to grade ≥ 3 related toxicity
		• Must have had a PI treatment-free interval of at least 6 months prior to the first day of SVd.
		Based on clinical expert opinion, patients with plasma cell leukemia and systemic light chain amyloidosis should be permitted to receive

Generic name (brand name)	Date of recommendation	Recommendation and guidance on treatment sequencing
		SVd as these patients would be treated in clinical practice and could receive benefit from therapy with SVd.
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 evidence-based

Generic name (brand name)	Date of recommendation	Recommendation and guidance on treatment sequencing
		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

Generic name (brand name)	Date of recommendation	Recommendation and guidance on treatment sequencing
		• 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 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	September 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	October 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

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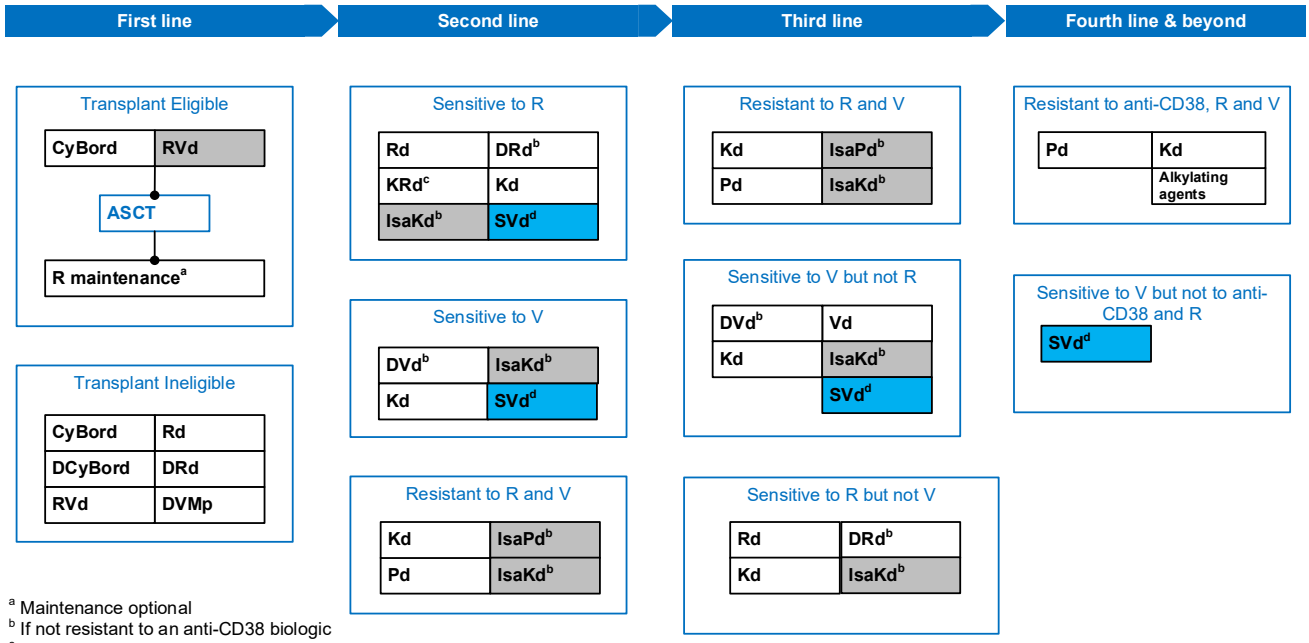
		bortezomib-dexamethasone may be a favourable second-line option over triplet therapy with carfilzomib; however, the committee acknowledged that there is no appropriate treatment sequence for daratumumab and carfilzomib for the treatment of MM after failure of 1 prior therapy. Therefore, pERC was unable to make an evidence-informed recommendation on sequencing of treatments for RRMM. However, pERC recognized that provinces would need to address 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	March 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	November 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.

Generic name (brand name)	Date of recommendation	Recommendation and guidance on treatment sequencing
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 submitted price and based on the Economic Panel's range of best estimates of the incremental cost-effectiveness ratio, pomalidomide could not be considered cost-effective compared with best supportive care.
Idecabtagene vicleucel (Abecma)	November 12, 2021	CADTH recommends that Abecma should not be reimbursed by public drug plans for the treatment of MM.
Daratumumab (Darzalex)	December 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 have failed or are intolerant to an IMiD.

ASCT = autologous stem cell transplant; CGP = clinical guidance panel; 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; KRd = carfilzomib-lenalidomide-dexamethasone; LVEF = left ventricular ejection fraction; MM = multiple myeloma; Pd = pomalidomide-dexamethasone; PVd = pomalidomide-dexamethasone-bortezomib; R = lenalidomide; Rd = lenalidomide-dexamethasone; RVd = lenalidomide-bortezomib-dexamethasone; SVd = Selinexor-bortezomib-dexamethasone; V = bortezomib; Vd = bortezomib-dexamethasone.

Provisional Funding Algorithm

Figure 1: Provisional Funding Algorithm Diagram for Multiple Myeloma



[a] Maintenance optional
[b] If not resistant to an anti-CD38 biologic
[c] only if also sensitive to R & V
[d] must have a proteasome inhibitor treatment-free interval of at least 6 months before 1st day of SVd

Notes:
1) Patients with drug resistance cannot be re-treated with same drug(s)
2) Cyclophosphamide may be added to Kd, Pd and Rd

Legend

Therapy funded across most jurisdictions	Therapy funding pending (pCPA or province/ cancer agency)	Therapy under review for funding (pCPA or province/cancer agency)

ASCT = autologous stem cell transplant; CyBord = cyclophosphamide-bortezomib-dexamethasone; d = dexamethasone; D = daratumumab; I = isatuximab; P = pomalidomide; R = lenalidomide; S = selinexor; V = bortezomib.

Description of the Provisional Funding Algorithm

Figure 1 depicts the provisional funding algorithm proposed. 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 cyclophosphamide-bortezomib-dexamethasone (CyBord) or lenalidomide-bortezomib-dexamethasone (RVd), if funded by the jurisdictions. After transplant,

maintenance with lenalidomide is available. Patients who are ineligible for transplant can be given CyBord or lenalidomide-dexamethasone (Rd) (with or without daratumumab), or RVd or daratumumab-bortezomib-melphalan-prednisone (DVMp).

Relapsed or Refractory

Treatment in the relapsed or refractory setting depends on response to prior therapies. As a rule, 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 carfilzomib-dexamethasone (Kd) or pomalidomide-dexamethasone (Pd) (combination with isatuximab is under jurisdictional review), KRd, Rd, daratumumab-lenalidomide-dexamethasone (DRd), daratumumab-bortezomib-dexamethasone (DVd), or selinexor-bortezomib-dexamethasone (SVd). SVd is under review for funding.

Subsequently, alternate regimens with a different proteasome inhibitor (PI) or immunomodulator backbone can be offered in the third and fourth line, depending on drug sensitivity. Cyclophosphamide may be added to some regimens such as Pd, Kd, and Rd.

Additional Remarks

- pERC does not anticipate SVd will displace previous and subsequent lines of therapies that are reimbursed; rather, pERC agreed with the clinical experts that daratumumab-containing regimens will likely shift to first line for transplant-ineligible patients, which would be the place in therapy of drugs reimbursed in first line and beyond. pERC noted that bortezomib-refractory would likely preclude reimbursement of other bortezomib-containing regimen options.
- pERC agreed with the clinical experts that SVd could be administered to patients in the second line or later, but that other treatment options may be preferred. pERC highlighted if DRd was used in frontline transplant-ineligible patients, SVd is a potential second-line option for these patients. Other funded options are Pd, CyBord, and Kd.
- pERC agreed with the clinical experts that patients who are refractory to bortezomib would be unlikely to respond to therapy with SVd. pERC felt that, as per the BOSTON trial, prior treatment with bortezomib or other PI should be permitted, provided all of the following criteria are met:
    - best response achieved with prior bortezomib at any time was at least a partial response, and with the last PI therapy (alone or in combination) was at least a partial response
    - the patient did not discontinue bortezomib due to grade 3 or higher related toxicity
    - must have had a PI treatment-free interval of at least 6 months before the first day of SVd.