

CADTH Reimbursement Recommendation

Selinexor (Xpovio)

Indication: Multiple myeloma

Sponsor: FORUS Therapeutics Inc.

Final recommendation: Reimburse with conditions

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

What Is the CADTH Reimbursement Recommendation for Xpovio?

CADTH recommends that Xpovio should be reimbursed by public drug plans for the treatment of multiple myeloma if certain conditions are met.

Which Patients Are Eligible for Coverage?

Xpovio should only be covered to treat adult patients with multiple myeloma who have received at least 1 prior therapy.

What Are the Conditions for Reimbursement?

Xpovio should only be reimbursed if prescribed by a specialist, given in combination with bortezomib and dexamethasone, and the cost of Xpovio is reduced.

Why Did CADTH Make This Recommendation?

- Evidence from a clinical trial demonstrated that Xpovio delayed progression of multiple myeloma when added to bortezomib and dexamethasone.
- Xpovio meets some of the needs that were identified by patients; it is an additional treatment option that is in part oral therapy and it has proven to delay disease progression.
- Based on CADTH's assessment of the health economic evidence, Xpovio does not represent good value to the health care system at the public list price. A price reduction is therefore required.
- Due to limitations in the submitted budget impact analysis, CADTH was unable to determine the total cost to the drug plans.

Additional Information

What Is Multiple Myeloma?

Multiple myeloma is a cancer of plasma cells (the white blood cells that make antibodies) that is more common in older adults and accounts for 10% to 15% of all blood cancers.

Unmet Needs in Multiple Myeloma

Many patients with multiple myeloma do not respond to initial treatments and their disease worsens, resulting in the need to try different treatments.

How Much Does Xpovio Cost?

Treatment with Xpovio is expected to cost approximately \$11,000 per patient per 28 days. When used in combination with bortezomib and dexamethasone, treatment is expected to cost \$13,629 per patient per 28 days.

Recommendation

The CADTH pCODR Expert Review Committee (pERC) recommends that selinexor in combination with bortezomib and dexamethasone (SVd) be reimbursed for the treatment of adult patients with multiple myeloma (MM) who have received at least 1 prior therapy if the conditions listed in [Table 1](#) are met.

Rationale for the Recommendation

One multi-centre, phase III, open-label, randomized controlled study (BOSTON; N = 402) demonstrated that treatment with SVd resulted in added clinical benefit compared with bortezomib and dexamethasone (Vd) in patients with MM who have received at least 1 prior therapy. In the interim analysis, which was considered the final analysis, the BOSTON trial showed a statistically significant and clinically meaningful improvement in progression-free survival (PFS) with SVd compared with Vd (hazard ratio [HR] = 0.7020; 95% confidence interval [CI], 0.5279 to 0.9335; P = 0.0075). Health-related quality of life (HRQoL) was assessed but not formally compared between the treatment groups in the trial; however, the available evidence suggested that there were no differences in HRQoL between patients in the SVd and Vd treatment groups. There were more frequent rates of thrombocytopenia, gastrointestinal toxicities (e.g., diarrhea, nausea, and vomiting), decreased appetite and weight, and ocular toxicities (e.g., cataracts) in the SVd group compared with the Vd group. pERC acknowledged that although these adverse events (AEs) were not insignificant, they can be managed through supportive care, monitoring, and dose reduction.

pERC agreed that there is an unmet need for additional effective treatments beyond first and second line because treatment options are limited and associated with short remissions. Patients identified that the need for effective treatments was greatest beyond the second-line setting. Other needs important to patients included manageable side effects and access to a supportive and communicative care team. Patients expressed the importance of quality of life and the preference for accessible and portable treatment (highlighting a preference for oral therapy as opposed to subcutaneous [SC] and IV injection, and reduction in hospital visits due to treatment). Given all the evidence, pERC concluded that SVd meets some of these needs identified by patients in terms of an additional treatment option that is in part oral therapy and has shown to improve PFS.

The cost-effectiveness of SVd is highly uncertain due to limitations with the chosen modelling approach, the lack of head-to-head comparative clinical information for most comparators, and uncertainty associated with the use of subsequent therapy after disease progression. As such, a base case cost-effectiveness estimate could not be derived in patients with MM who have received 1 to 3 prior lines of therapy.

The committee considered exploratory analyses conducted by CADTH, which considered the cost-effectiveness of SVd relative to Vd based on data from the BOSTON trial and determined that the incremental cost-effectiveness ratio could be as high as \$10,884,623 per quality-adjusted life-year (QALY). As such, a price reduction would be required for SVd to achieve an incremental cost-effectiveness ratio of \$50,000 per QALY compared with Vd. There is not sufficient evidence to suggest that SVd provides additional clinical benefit compared with

funded treatments used to treat MM. Therefore, SVd should not be priced more than currently funded alternatives.

Table 1: Reimbursement Conditions and Reasons

Reimbursement condition	Reason	Implementation guidance
Initiation		
<p>1. Treatment with SVd should only be reimbursed when initiated in adult (≥ 18 years) patients who have all of the following:</p> <ul style="list-style-type: none"> 1.1. histologically confirmed multiple myeloma 1.2. received at least 1 prior therapy. 	<p>Evidence from the BOSTON trial demonstrated that treatment with SVd resulted in statistically significant and clinically meaningful improvement in PFS in adult patients with multiple myeloma who have received at least 1 prior therapy.</p>	<p>As per the BOSTON trial, prior treatment with bortezomib or another proteasome inhibitor should be permitted, provided all of the following criteria are met:</p> <ul style="list-style-type: none"> 1. best response achieved with prior bortezomib at any time was equal to or greater than partial response PR and the last proteasome inhibitor therapy (alone or in combination) was equal to or greater than partial response 2. patient did not discontinue bortezomib due to grade ≥ 3-related toxicity 3. must have had a proteasome inhibitor treatment-free interval of at least 6 months before the first day of SVd. <p>Based on clinical expert opinion, patients with plasma cell leukemia and systemic light chain amyloidosis should be permitted to receive SVd because these patients would be treated in clinical practice and could receive benefit from therapy with SVd.</p>
Renewal		
<p>2. SVd should be renewed for patients who exhibit a response and for whom treatment is tolerable:</p> <ul style="list-style-type: none"> 2.1. a response is defined as stable disease or better according to IMWG criteria. 	<p>pERC acknowledged response according to IMWG criteria (i.e., partial response or better) used in the BOSTON trial; however, the committee felt that at least stable disease was also a reasonable criterion for response.</p>	—
<p>3. Patients should be assessed for treatment response every 4 to 5 weeks initially then every 2 to 3 months as per physician discretion.</p>	<p>Based on clinical expert opinion, patients may initially be assessed for response every 4 weeks, with less frequent monitoring of patients (every 2 or 3 months) if patients demonstrate stable long-term response and predictable and manageable toxicity.</p>	—

Reimbursement condition	Reason	Implementation guidance
Prescribing		
4. SVd should only be prescribed by clinicians with expertise and experience in all of the following: 4.1. the management of patients with multiple myeloma 4.2. the adverse effects associated with selinexor.	To ensure that SVd is prescribed only for appropriate patients and that adverse effects are managed in an optimized and timely manner. pERC noted the incidence of gastrointestinal toxicities (e.g., diarrhea, nausea, and vomiting), decreased appetite and weight, and ocular toxicities (e.g., cataracts) require supportive care and monitoring.	—
5. Selinexor should only be prescribed and reimbursed in combination with bortezomib and dexamethasone.	As per its Health Canada–approved indication, selinexor is indicated in combination with bortezomib and dexamethasone.	—
Pricing		
6. A reduction in price	CADTH undertook a price reduction analysis using the sponsor’s model based on an alternative set of assumptions around PFS, OS, and health state utility values. This analysis indicated that a 93% reduction in the price of selinexor may achieve an ICER of \$50,000 per QALY compared with Vd. If SVd led to a sustained and durable OS benefit, then a price reduction of 81% may be sufficient to achieve cost-effectiveness relative to Vd. There is insufficient evidence to suggest that SVd provides greater benefit than other funded treatments used to treat multiple myeloma. Therefore, SVd should not be priced more than currently funded alternatives.	—

ICER = incremental cost-effectiveness ratio; IMWG = International Myeloma Working Group; OS = overall survival; PFS = progression-free survival; QALY = quality-adjusted life-year; SVd = selinexor in combination with bortezomib and dexamethasone; Vd = bortezomib and dexamethasone.

Discussion Points

- pERC discussed the current Canadian treatment landscape for MM and agreed with the clinical experts that lenalidomide-containing regimens are not a relevant comparator and that daratumumab-containing regimens will likely shift to first line for transplant-ineligible patients. pERC agreed with clinicians and patient groups that treatment options are limited for patients with MM beyond the second line of therapy.
- pERC discussed the relevance of the comparator in the BOSTON trial (Vd) and agreed with the clinical experts that Vd is not an appropriate comparator in the current Canadian

treatment landscape for MM. However, pERC acknowledged that, at the time of enrolment in the BOSTON trial, the standard of care may have been different.

- Although improvement in PFS compared with Vd was demonstrated in the BOSTON trial, pERC acknowledged that there remains uncertainty in the clinical benefit of SVd compared with relevant comparators because there are no head-to-head trials versus relevant comparators. pERC discussed the indirect treatment comparisons (ITCs) submitted by the sponsor and published ITCs that compared SVd to relevant comparators. The results of the ITCs stem from uncertain evidence due to methodological limitations (e.g., lack of sensitivity analysis on prior lenalidomide, no adjustments for crossover), wide CIs associated with the point estimates, and heterogeneity across patients.
- pERC noted that certain MM regimens require IV injection (e.g., daratumumab, carfilzomib), SC injection (e.g., bortezomib), and oral administration (e.g., lenalidomide, dexamethasone), and acknowledged that selinexor represents a therapeutic target that is an oral therapy, which is desirable for patients. pERC also discussed patients' preference for a reduction in hospital visits due to treatment, which improves quality of life. SVd is a triple therapy; although selinexor and dexamethasone are oral therapies, bortezomib is administered via SC injection which requires clinic visits.
- pERC discussed the toxicity profile of SVd and noted the incidence of gastrointestinal toxicities (e.g., diarrhea, nausea, and vomiting), decreased appetite and weight, and ocular toxicities (e.g., cataracts). pERC acknowledged that the AEs associated with SVd are not insignificant and can be challenging upon initial uptake; however, pERC felt that the AEs associated with SVd are expected to be manageable through supportive care, monitoring and dose reduction, and clinical experience with SVd over time.
- pERC also discussed that although PFS rates were higher in the SVd treatment group compared with the Vd treatment group, time to treatment discontinuation (TTD) rates were not. It was expected that an improvement in PFS would translate to a longer TTD in the investigational therapy group versus the control group; however, this was not the case in the BOSTON trial. pERC noted that AEs leading to treatment discontinuation were higher in the SVd treatment group compared with the Vd treatment group.
- Although HRQoL was an exploratory analysis in the BOSTON study, results suggested that there were no differences between patients in the SVd and Vd treatment groups; however, pERC noted higher scores for blurred vision in the SVd group. Given the higher rates of cataracts in the SVd treatment group, monitoring of vision is needed.
- pERC discussed uncertainty associated with the cost-effectiveness of SVd due to the sponsor's modelling approach and lack of robust clinical data comparing SVd to more commonly used treatments. pERC noted the lack of clinical evidence to suggest incremental benefit compared with currently funded regimens and how the toxicity profile with SVd may also influence cost-effectiveness.

Background

Selinexor has been approved by Health Canada in combination with bortezomib and dexamethasone for adult patients with MM who have received at least 1 prior therapy. Selinexor is a reversible selective inhibitor of nuclear export (SINE) compound which blocks the exportin 1 (XPO1) protein. Inhibition of the XPO1 protein by selinexor leads to a reduction in cancer cells by stopping the cell cycle, reducing the presence of oncoproteins, and

causing cell death. When combined with bortezomib and dexamethasone, the SVd regimen demonstrates antitumour activity, including in vivo models resistant to proteasome inhibitors (PIs). Selinexor is administered with bortezomib and dexamethasone. Selinexor is available as a 20 mg tablet; the dosage recommended in the product monograph is 100 mg orally once weekly on day 1 of each week.

MM is a plasma cell cancer caused by the growth of cancer cells in the bone marrow. In Canada, more than 3,000 new cases of MM are diagnosed annually, with slightly more cases occurring in men than women. MM is generally incurable with a median survival for patients just over 5 years, and during this time patients can receive 4 or more lines of therapy. MM is a heterogenous condition that typically affects older adults around the age of 65 years. Patients' outcomes can be dependent on many factors, including their disease stage, prognostic indicators, and early treatment of symptomatic disease to limit or avoid organ damage. Patients may initially present with symptoms such as bone pain, lytic lesions, anemia, fatigue, infections, weight loss, hypercalcemia, and renal dysfunction. Patients may also have cytogenetic abnormalities that can influence the course of their disease, response to therapy, and overall prognosis.

The treatment landscape for MM has changed significantly in the past number of years, with the emergence of new therapies in newly diagnosed and relapsed or refractory settings. Treatment choices for patients depend on whether or not they are transplant eligible or ineligible. Most patients in Canadian clinical practice will receive a lenalidomide-based regimen. At relapse, treatment for patients depends on patient factors, including age, comorbidities, and previous treatments. Most patients will receive a daratumumab-containing regimen. As patients continue to progress, other treatment options can include regimens containing carfilzomib, pomalidomide, isatuximab, or belantamab; funding of these regimens is variable across the Canadian jurisdictions and, in some cases, treatments may only be available through special access programs.

Sources of Information Used by the Committee

To make their recommendation, the committee considered the following information:

- a review of 1 multi-centre, phase III, active-controlled, open-label study in adult patients with relapsed or refractory multiple myeloma (RRMM) who received 1 to 3 prior anti-MM regimens
- patients' perspectives gathered by the patient group: Myeloma Canada
- input from public drug plans and cancer agencies that participate in the CADTH review process
- two clinical specialists with expertise diagnosing and treating patients with MM
- input from 2 clinician groups, including the OH-CCO Hematology Drug Advisory Committee (DAC) and the Canadian Myeloma Research Group (CMRG)
- a review of 1 sponsor-submitted network meta-analysis (NMA) and 3 published NMAs
- a review of the pharmacoeconomic model and report submitted by the sponsor.

Stakeholder Perspectives

Patient Input

One patient group, Myeloma Canada, provided input on the combination of selinexor with bortezomib and dexamethasone for the treatment of MM in adult patients. The patient group conducted an online survey distributed through email and social media and made available to patients and caregivers across Canada from December 2021 to January 2022. According to Myeloma Canada, patients considered it extremely important to control symptoms of infections, kidney problems, mobility, and neuropathy related to myeloma. Patients also indicated that symptoms significantly impacted their ability to travel, work, exercise, and concentrate. Patients also indicated parking costs, travel costs, drug costs, lost income due to absence from work, and lost income or pension due to early retirement as the most significant financial implications due to myeloma treatment. Patients receiving treatment with bortezomib and dexamethasone reported fatigue, diarrhea, and nausea as being “totally unbearable.” “Tolerable” side effects were anemia and thrombocytopenia. Peripheral neuropathy was highlighted by many patients as a side effect and an important symptom to control and reduce the severity. Three respondents had experience with SVd through participation in the BOSTON trial; 2 had not relapsed since receiving SVd through the BOSTON trial, while the other relapsed within 3 months and was receiving a different treatment. Nausea was stated to be a “somewhat tolerable” side effect while diarrhea, peripheral neuropathy, and vomiting were “somewhat intolerable.” Other side effects experienced included thrombocytopenia, anemia, fatigue, decreased appetite, and weight loss. One patient indicated the trial regimen was very effective in helping to control their myeloma, while the other patient indicated it was somewhat ineffective. Respondents mentioned the following as being important considerations for new treatments: effectiveness of treatment, quality of life, accessibility and portability of treatment, manageable side effects, and having a supportive and communicative care team accessible to them. The side effects that patients most frequently ranked as important to avoid when considering new treatments included infections, vomiting, pain, confusion, decreased appetite, and neuropathy. Many patients indicated a preference for orally administered treatment versus SC injection or IV infusion. Many respondents indicated that fewer trips to a cancer centre or hospital for treatment would positively impact their quality of life.

Clinician Input

Input From Clinical Experts Consulted by CADTH

The clinical experts highlighted the need for treatments that improve survival, provide deeper and longer-lasting remissions, and improve disease-related symptoms and complications, such as pain and renal failure. In addition, treatments would have less major negative impact on patient’s quality of life and require fewer clinic visits. The clinical experts acknowledged that most patients will relapse with currently available therapies. Treatments are palliative and may prolong patients’ lives, but they do not provide patients with an option of a cure. Patients will eventually become refractory to available treatments. Patients with high-risk cytogenetics and who are transplant ineligible were stated to be at particularly high risk of progression and poor outcomes. The adverse effects of some treatments were stated to affect tolerability and effectiveness. Many treatment options for patients are provided intravenously or subcutaneously at a cancer centre as often as once or twice per week, resulting in significant burden for patients, caregivers, and treatment centres. Selinexor could also be an attractive option for patients because it is administered orally and only once per week, potentially

reducing the need for clinic visits. The clinical experts acknowledged that selinexor would not cause a significant paradigm shift and that other therapies exist which treat MM. However, selinexor operates under a mechanism of action different to other treatments currently available for MM, presenting an opportunity to be effective in patients who have become resistant to treatments which target other pathways. The clinical experts agreed that other regimens would likely be preferred before using a selinexor-based regimen. The toxicity profile of selinexor was also stated to be different from other classes of drugs. The clinical experts agreed that there are no specific features which would make a patient a better candidate for selinexor. Patients with pre-existing anorexia, weight loss, or nausea may not be good candidates for this treatment because the side effect profile of selinexor is associated with these symptoms.

Patients' response to therapy is typically measured through monoclonal protein and serum free light chains; based on these evaluations, a clinically meaningful response would include a sustained PR or better. Stable disease may also be considered an acceptable benefit to patients in some cases. Improvements in cancer-related complications, such as anemia, renal failure, hypercalcemia, and tumour-related pain, are also considered when assessing patient's response. In general, meaningful responses to treatment are expected to translate through improvements in patient's overall survival (OS) and PFS. Improvements in quality of life, myeloma-related symptoms, and treatment toxicity were also stated to be important outcomes when assessing patient's response to treatment. Typically, patients may be assessed for response every 4 weeks, although less frequent monitoring of patients may be warranted if patients demonstrate a stable long-term response and predictable and manageable toxicity.

The clinical experts agreed that discontinuing treatment should be dependent on whether the patient's disease progresses, which is determined when the patient fails to respond to treatment and requires a change in therapy. Significant toxicities or AEs which cannot be managed through supportive care or dose modifications were also stated to result in discontinuation of therapy. Both clinical experts acknowledged that administration of therapies will require a specialty hematology or oncology clinic or equivalent. Physicians with expertise and experience in treating MM, such as a hematologist or oncologist, would treat and monitor patients. The clinical experts highlighted that changes to the treatment paradigm for MM patients are likely to occur with approvals of daratumumab in the first-line setting. Most patients will likely receive daratumumab, lenalidomide, and dexamethasone (DRd) as a first-line therapy; therefore, these patients will not receive daratumumab-based regimens upon relapse. The next line option for patients will likely be a combination of regimens including bortezomib and another PI (e.g., cyclophosphamide, bortezomib, and dexamethasone [CyBorD] or carfilzomib plus dexamethasone). Selinexor could be considered as a second-line option; however, it may be more likely for SVd to be used in later lines of therapy.

Clinician Group Input

Two groups provided clinician input on the review of SVd for the treatment of adult patients with MM: the OH-CCO Hematology DAC (prepared by 7 physicians) and the CMRG (prepared by 13 physicians). Both groups generally agreed that improving OS, PFS, disease-related symptoms, and HRQoL are important goals for an ideal treatment. The OH-CCO group indicated the greatest unmet need for patients currently exists after the second-line setting; patients who failed daratumumab in the second-line setting could have the option to use this regimen in the third-line setting. CMRG expressed the need for new classes of anti-

myeloma drugs to complement available treatments and improve patients' convenience with oral administration and better toxicity profiles. Both groups agreed that patients with the greatest unmet need for a selinexor-based regimen are those with RRMM who are refractory to immunomodulatory inhibitors, PIs, and anti-CD38 monoclonal antibodies. CMRG also specified that patients with renal insufficiency and poor-risk features (e.g., high-risk cytogenetics, extramedullary disease, or highly proliferative disease) have the greatest unmet need for this therapy.

Selinexor was stated to be currently available through special access programs and was acknowledged by CMRG to differ compared to currently available therapies based on the route of administration, side effect profile, and supportive care needs. Canadian physicians stated that therapies which differ from currently available treatment options, such as selinexor, were needed for patients whose disease has progressed on funded treatment options, but they are not yet candidates for palliative care. The OH-CCO DAC expressed uncertainty about the specific placement of SVd into the current treatment paradigm. However, both groups generally agreed that daratumumab- or isatuximab-based treatments would be preferred as second-line regimens before recommending SVd. Both groups agreed that this drug would not impact the treatment sequence employed in current practice.

Both clinician group inputs acknowledged that eligible patients would be identified by their treating physician or hematologist. The OH-CCO DAC did not specify any specific criteria for patients who would be least suited for treatment, although CMRG indicated that newly diagnosed patients with MM would be least suitable for treatment with SVd. Both groups indicated that patients' response to treatment would be assessed using conventional myeloma response criteria. A clinically meaningful response to treatment in the setting of advanced disease was stated to include a reduction in measurable disease. Both groups agreed that patient's response to treatment would be assessed each cycle or approximately every month. Both groups agreed that discontinuation of treatment would be based on disease progression and toxicity. Both groups agreed that SVd would be administered in outpatient clinics, hematology clinics, and in hospitals.

Drug Program Input

The clinical experts consulted by CADTH provided advice on the potential implementation issues raised by the drug programs.

Table 2: Responses to Questions From the Drug Program

Implementation issues	Response
Relevant comparators	
<p>The BOSTON trial compared SVd vs. twice-weekly bortezomib-dexamethasone in myeloma patients who had received at least 1 but no more than 3 prior lines of therapy. At the time of the PAG input, bortezomib-dexamethasone may be more appropriate as a comparator if SVd is used in a much later line setting (e.g., fourth-line regimen).</p> <p>PAG noted that the bortezomib dosing used in the Vd arm of the BOSTON trial was twice weekly, whereas most jurisdictions use once-weekly bortezomib and dexamethasone.</p>	<p>The clinical experts agreed that Vd in the second- or third-line setting is not a relevant comparator based on standard of care in current clinical practice. The twice weekly schedule of Vd used in the comparator group of the BOSTON trial is not often used in clinical practice. In addition, Vd is not often used alone and is usually part of a triplet regimen.</p> <p>pERC agreed with the clinical experts that the twice weekly schedule of Vd used in the comparator group of the BOSTON trial is not commonly used in clinical practice. Jurisdictions may consider weekly bortezomib and dexamethasone. pERC also</p>

Implementation issues	Response
	agreed that Vd is often not used alone and is usually part of a triplet regimen.
Considerations for initiation of therapy	
Should SVd be used in patients who have bortezomib-refractory multiple myeloma?	<p>The clinical experts agreed that patients who are refractory to bortezomib may not continue to experience a response to this therapy. Patients who were refractory to a PI were excluded in the BOSTON trial.</p> <p>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:</p> <ul style="list-style-type: none"> • 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-related toxicity • must have had a PI treatment-free interval of at least 6 months before the first day of SVd.
Patients with plasma cell leukemia and systemic light chain amyloidosis were excluded from the BOSTON trial. Should patients with plasma cell leukemia and systemic light chain amyloidosis be excluded from receiving therapy with SVd?	<p>The clinical experts agreed that the eligibility criteria of the BOSTON trial were restrictive and that while patients with plasma cell leukemia and systemic light chain amyloidosis were excluded from the BOSTON trial, these patients would be treated similarly in clinical practice and could receive benefit from therapy with SVd.</p> <p>pERC agreed with the clinical experts that these patients excluded from the BOSTON trial would likely be treated in clinical practice and could receive benefit from therapy with SVd. Therefore, pERC felt that these patients should be permitted to receive SVd because patients would be treated similarly in clinical practice and could receive benefit from therapy with SVd.</p>
Considerations for prescribing of therapy	
In the trial, a selinexor dose escalation to 120 mg weekly starting on cycle 3 could have been considered for patients on SVd who did not achieve at least a partial response within the first 2 cycles, were tolerating the 100 mg weekly dose well, and did not have any adverse events at the time of dose escalation.	pERC agreed that it would appropriate to dose escalate as per the BOSTON trial.
The cycle length of bortezomib and dexamethasone when combined with selinexor is different than the bortezomib-dexamethasone (28 days cycle) that cancer centres are accustomed to and may lead to medication errors.	pERC acknowledged the drug plan input and also noted that there are other examples of regimens that use a non-28 day cycle, such as VMP. pERC felt this difference in cycle length is manageable.
The incidence of cataracts with the combination of selinexor, bortezomib, and dexamethasone may require consultation with ophthalmologists.	The BOSTON trial also required ophthalmic examination by an optometrist or ophthalmologist before the first dose of treatment and at the end of treatment. This was repeated if clinically indicated during the study (e.g., monitoring of pre-existing cataracts or visual disturbances). The clinical experts agreed that the incidence of cataracts during the treatment period was higher

Implementation issues	Response
	<p>than expected. Therefore, clinicians may consider more frequent observation of vision problems for patients.</p> <p>pERC agreed with the clinical experts that additional observation may be required for patients being treated with selinexor due to the greater incidence in cataracts compared with the Vd group in the BOSTON trial.</p>
The incidence of gastrointestinal toxicities, most notably diarrhea, nausea and vomiting, and anorexia, requires supportive care. Additional resources will be required for the monitoring and management of adverse effects with selinexor.	pERC acknowledged the drug plan input. pERC highlighted that SVd should only be prescribed by clinicians with expertise and experience in the management of patients with multiple myeloma and adverse effects associated with selinexor.
Funding algorithm (oncology only)	
SVd may change the place in therapy of drugs reimbursed (in previous lines and in subsequent lines).	pERC acknowledged this input. 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 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.
Multiple myeloma is a complex therapeutic space with multiple lines of therapy, subpopulations, and competing products.	pERC acknowledged the complexity of treating myeloma and the need for clinician expertise to treat these patients.
<p>What is the place in therapy for SVd?</p> <p>Under which clinical circumstances would SVd be preferred over existing funded regimens (e.g., DVd, DRd, KRd, Kd, Pd, lenalidomide-dexamethasone)?</p>	<p>Based on the eligibility criteria from the BOSTON trial, patients would have received SVd in the second line or later. The clinical experts agreed that SVd could be used in the second line, although it would likely be used in third line or later. Other regimens may be preferred over SVd, including daratumumab-based regimens. ITCs were submitted by the sponsor which also suggested that other regimens (i.e., daratumumab-based regimens) may be preferred before using SVd.</p> <p>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 funded in frontline transplant-ineligible patients, SVd is a potential second-line option for these patients. Other funded options are Pd, CyBorD, and Kd.</p>
Care provision issues	
Eye exams are needed due to new onset or worsening of existing cataracts.	pERC agreed with the clinical experts that additional observation may be required for patients being treated with selinexor due to the increased incidence of cataracts.
System and economic issues	
The extent of the budget impact would depend on the eventual place in therapy for SVd and also the prevalent patients who may be treated with SVd in the fourth-line setting.	pERC acknowledged the input from the drug plans.

Implementation issues	Response
High-cost drug.	pERC acknowledged the input from the drug plans.

CyBorD = cyclophosphamide plus bortezomib plus dexamethasone; DRd; daratumumab plus lenalidomide plus dexamethasone; DVd = daratumumab plus bortezomib plus dexamethasone; ITCs = indirect treatment comparisons; Kd = carfilzomib plus dexamethasone; KRd = carfilzomib plus lenalidomide plus dexamethasone; PAG = provincial advisory committee; Pd = pomalidomide and dexamethasone; pERC = CADTH pCODR Expert Review Committee; PI = proteasome inhibitor; SVd = selinexor in combination with bortezomib and dexamethasone; Vd = bortezomib and dexamethasone; VMP = bortezomib, melphalan, and prednisone.

Clinical Evidence

One multi-centre, phase III, active-controlled, open-label study (BOSTON) was included in this CADTH review. The objective of the BOSTON trial was to compare the efficacy, HRQoL, and safety of SVd compared with Vd in adult patients with RRMM who received 1 to 3 prior anti-MM regimens. Patients were randomized to receive SVd or Vd in a 1:1 ratio and were stratified based on prior PI therapy (yes versus no) and number of prior anti-MM regimens (1 versus > 1). Inclusion criteria included adult patients with histologically confirmed MM with measurable disease per International Myeloma Working Group guidelines who had received between 1 and 3 prior anti-MM regimens. Patients had to have documented evidence of progressive MM on or after their most recent regimen. Patients previously treated with bortezomib or other PI were eligible if certain criteria were met. Patients must also have had an Eastern Cooperative Oncology Group Performance Status (ECOG PS) of 2 or lower. Exclusion criteria included previous exposure to SINE compounds, including selinexor, previous malignancies requiring treatment or showing evidence of recurring, and uncontrolled comorbidities. Patients could not have peripheral neuropathy greater than grade 2, or peripheral neuropathy of grade 2 or higher with pain at baseline, regardless of whether or not they were receiving medication. The primary end point of the BOSTON trial was PFS. Key secondary end points included overall response rate (ORR), incidence of grade 2 or higher events of peripheral neuropathy (PN), response rates of very good partial response (VGPR) or better based on independent review committee (IRC) assessment. Other secondary end points included OS, duration of response, time to next treatment, time to response, and HRQoL.

In general, characteristics across both the SVd and Vd treatment groups were well balanced. The mean age of patients was 65 years (SD = 9.56) in the SVd group and 67 years (SD = 9.35) in the Vd group; most patients were in the 51 to 64 years (36% in the SVd group versus 31% in the Vd group), 65 to 74 years (39% versus 41%, respectively), or older than 75 years (17% versus 23%) age categories; fewer patients were between 18 to 50 years (8% versus 5%, respectively). There was a slightly greater proportion of males enrolled in the trial (59% versus 56% in the SVd and Vd groups, respectively). Most patients were White (83% versus 80% in the SVd and Vd groups, respectively), non-Hispanic or Latino (88% versus 91%, respectively), never smokers (73% versus 74%), with an ECOG PS of 0 (35% versus 37%) or 1 (54% versus 55%), a mean creatinine clearance at baseline of greater than 60 mL/min (71% versus 66%), and a status of nonfrail at baseline (66% versus 69%). Approximately one-quarter of patients (25% in the SVd group versus 27% in the Vd group) were diagnosed with stage I disease at diagnosis compared with one-third who were diagnosed with stage II (32% versus 27%, respectively), and one-third at stage III (29% versus 32%). More than half of patients had kappa light chain type of the active myeloma at baseline (56% versus 61% in the SVd group and Vd group, respectively). The R-ISS stage at screening was stage I for 29% of patients in the SVd group versus 25% in the Vd group, stage II for 60% of patients in both groups, and 6%

and 7%, respectively, for stage III. Approximately half of patients had a high-risk chromosomal abnormality, with most being 1q21 (41% versus 34% in the SVd and Vd groups) compared with t(4;14) (11% versus 14%), del (17p)/p53 (11% versus 8%), or t(14;16) (4% versus 5%). The mean number of prior lines of anti-MM therapy was 1.7 in both treatment groups; 51% versus 48% of patients in the SVd and Vd groups, respectively, had 1 prior line of therapy compared with 33% and 31% of patients with 2 prior lines of anti-MM therapy and 16% versus 21% of patients with 3 prior lines of anti-MM therapy. Most patients had received prior PI therapy (76% in the SVd group versus 77% in the Vd group). Other treatments patients had been previously exposed to included bortezomib (69% versus 70% in the SVd and Vd groups, respectively), lenalidomide (40% versus 37%), carfilzomib (10% in both groups), pomalidomide (6% versus 3%), daratumumab (6% versus 3%), and ixazomib (3% versus 1%). Slightly more patients in the SVd group received a stem cell transplant (39%) than patients in the Vd group (30%).

Efficacy Results

Results from the BOSTON trial were reported for 2 data cut-offs. The primary analysis was a pre-specified interim analysis and was based on a data cut-off of February 18, 2020. In agreement with the Data Safety Monitoring Board (DSMB), the results of this interim analysis were considered final because the stopping boundary for PFS had been reached. The updated analysis was based on a data cut-off of February 15, 2021; results of the updated analysis were considered descriptive. The results of the updated analysis were supportive of the primary analysis and are not described here.

Overall Survival

At the time of the primary analysis, results for OS were based on a median follow-up time of 17.28 months (95% CI, 16.56 to 19.27) in the SVd group and 17.51 months (95% CI, 17.08 to 18.23) in the Vd group. Similar proportions of patients experienced death in the SVd (24.1%) and Vd (30.0%) treatment groups. The median OS was not estimable (NE) (95% CI, NE to NE) in the SVd group and 24.97 months (95% CI, 23.49 to NE) in the Vd group. The HR for death was 0.84 (95% CI, 0.57 to 1.23; 1-sided P = 0.1852, stratified log-rank test). At total of 75 patients (36%) from the Vd group had crossed over to the selinexor plus bortezomib plus dexamethasone (SVdX) or selinexor plus dexamethasone after crossover (SdX) groups.

Progression-Free Survival

A median follow-up time of 13.17 months (95% CI, 10.64 to 15.34) was reported for the SVd group and 16.53 months (95% CI, 14.39 to 17.71) in the Vd group. At the primary analysis, a higher proportion of patients in the Vd group experienced a PFS event than patients in the SVd group (59.9% versus 41.0%, respectively). Median PFS was longer in the SVd group at 13.93 months (95% CI, 11.73 to NE) compared with 9.46 months (95% CI, 8.11 to 10.78) in the Vd group. A HR of 0.70 (95% CI, 0.53 to 0.93) was reported for PFS, indicating an increase in PFS of 4.47 months and a 30% reduction in risk of disease progression or death in the SVd group compared with the Vd group (1-sided P = 0.0075, stratified log-rank test).

Duration of Response

At the primary analysis, there were more patients in the SVd group who achieved a PR or better (76.4%) than the Vd group (62.3%). The median duration of response was 20.72 months (95% CI, 12.55 to NE) in the SVd group compared with 12.88 months (95% CI, 9.26 to 15.77) in the Vd group.

Time to Next Treatment

There were fewer patients in the SVd groups who had time to next treatment events (45.1%) versus the Vd group (65.2%). The median time to next treatment was longer in the SVd group at 16.13 months (95% CI, 13.92 to NE) than the Vd group at 10.84 months (95% CI, 9.82 to 13.40). There was a longer median treatment-free interval for patients with new MM treatment in the SVd group at 28.0 days (range = 1 to 447) than patients in the Vd group at 14.0 days (range = 1 to 419).

Time to Treatment Discontinuation

There were no differences between the SVd and Vd treatment groups in percentage of patients who discontinued treatment (81.0% versus 82.6%, respectively). The median TTD in the SVd group was 7.10 months (95% CI, 6.44 to 8.54) and 7.95 months (95% CI, 6.80 to 9.23) in the Vd group.

Time to Response

A greater proportion of patients in the SVd group had an IRC-confirmed response of PR or greater (76.4%) than the Vd group (62.3%). The median time to response was shorter in the SVd group at 1.41 months (95% CI, 1.35 to 1.51) than the Vd group at 1.61 months (95% CI, 1.51 to 2.14).

Overall Response Rate

At primary analysis, a total of 149 patients had an ORR of 76.4% (95% CI, 69.8 to 82.2) in the SVd group compared with 129 patients (62.3%; 95% CI, 55.3 to 68.9) in the Vd group. There were no differences in the best overall response of patients between the 2 treatment groups. Most patients achieved a PR (31.8% in the SVd group versus 30.0% in the Vd group), VGPR (27.7% versus 21.7%, respectively), or stable disease (12.8% versus 19.3%).

Rate of VGPRs or Better

At the primary analysis, a VGPR, complete response, or stringent complete response was observed in 87 (44.6%) of 195 patients from the SVd group and 67 (32.4%) of 207 patients from the Vd group (odds ratio = 1.6594; 95% CI, 1.0993 to 2.5049; P = 0.0082).

Health-Related Quality of Life

Patient-Reported PN Measured by EORTC QLQ-CIPN20

Baseline scores for the sensory, motor, and autonomic neuropathy symptoms subscales were similar between the 2 treatment groups. Regarding the sensory and motor subscales, a greater proportion of patients in the Vd group had higher post-baseline scores of 10 or greater, 20 or greater, 30 or greater, 40 or greater, and 50 or greater increases from baseline than the SVd group, indicating worse symptoms for patients in the Vd group. Regarding the autonomic subscale, a greater proportion of patients in the SVd group had higher post-baseline scores of 10 or greater, 20 or greater, 30 or greater, 40 or greater, and 50 or greater increases from baseline than the Vd group, indicating worse symptoms for patients in the SVd group. Linear mixed-effect models were also conducted for the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Chemotherapy-Induced Peripheral Neuropathy 20-Item (EORTC QLQ-CIPN20) questionnaire scores; a lower mean change from baseline was observed in the SVd group compared with the Vd group for the sensory, motor symptoms, and autonomic subscale indicating less symptom burden in the SVd treatment group. The results of the autonomic symptom score were broken down to its

3 components of blurred vision, difficulty with erection, and dizzy when standing up. The SVd and Vd groups showed similar scores for the dizziness and erectile function components. The SVd group showed higher scores for blurred vision than the Vd group, indicating greater symptom burden. There were no statistically significant results between the SVd and Vd groups for any of the subscales.

EORTC QLQ-C30

The EORTC QLQ Core 30 (EORTC QLQ-C30) questionnaire was completed at baseline and at least 1 post-baseline time point by 188 patients in the SVd group and 195 patients in the Vd group. The mean baseline scores of patients were similar between the SVd and Vd group for global health status and quality of life. There were no differences in global health status scores over time between the SVd and Vd groups. There were no statistically significant differences in the domains of the EORTC QLQ-C30 between the SVd and Vd treatment groups.

EQ-5D-5L

Baseline scores of patients in the SVd and Vd groups were similar for the visual analogue scale, and there were no differences between treatment groups throughout the trial. No major differences were observed for any other symptom domains.

Harms Results

Adverse Events

The most commonly occurring AEs included thrombocytopenia (60.0% in the SVd group versus 27.0% in the Vd group), nausea (50.2% versus 9.8%), fatigue (42.1% versus 18.1%), diarrhea (32.3% versus 25.0%), anemia (36.4% versus 23.0%), decreased appetite (35.4% versus 5.4%), PN (32.3% versus 47.1%), weight decreased (26.2% versus 12.3%), asthenia (24.6% versus 13.2%), cataract (21.5% versus 6.4%), and vomiting (20.5% versus 4.4%). These AEs were all more commonly reported in the SVd group than the Vd group, except for PN which occurred more frequently in the Vd group. Other AEs that occurred more frequently in the SVd group included neutropenia (14.9% in the SVd group versus 5.9% in the Vd group), dizziness (12.3% versus 3.9%), and nasopharyngitis (11.8% versus 4.9%).

Grade 3 and 4 AEs also occurred more frequently in the SVd group at 79.0% compared with 55.9% of patients in the Vd group. Grade 3 or higher AEs occurred in 85.1% of patients compared with 61.3% of patients. The most commonly occurring grade 3 or higher AEs were thrombocytopenia (39.5% in the SVd group versus 17.2% in the Vd group) and anemia (15.9% versus 10.3%).

Serious Adverse Events

Serious AEs (SAEs) were more frequent in the SVd group at 51.8% compared with 37.7% of patients in the Vd group. The most common SAE was pneumonia, which occurred in 11.8% of patients in each treatment group.

AEs Leading to Dose Modifications

AEs leading to dose modifications were more frequent in the SVd group (88.7%) than the Vd group (76.5%). Specifically, AEs leading to dose reductions or dose interruptions were both more common in the SVd group than the Vd group (72.3% versus 51.0% and 85.6% versus 68.1%, respectively).

Mortality

Deaths were reported for 6.2% of patients in the SVd group and 5.4% of patients in the Vd group. The most common causes of death in the SVd group were septic shock (1.5%) and pneumonia (1.0%). The most common cause of death in the Vd group was pneumonia (1.5%).

Notable Harms

Notable harms pre-specified in the CADTH systematic review protocol included pain, anorexia, nausea, gastrointestinal disorders, thrombocytopenia, and neutropenia. The incidence of pain was similar between both treatment groups (2.6% of patients in the SVd group versus 2.0% in the Vd group). No patients had observations of anorexia. Nausea (50.3% in the SVd group versus 9.8% in the Vd group), gastrointestinal disorders (69.2% versus 44.6%), thrombocytopenia (60.0% versus 27.0%), and neutropenia (15.9% versus 5.9%) more commonly occurred in the SVd group than the Vd group.

The incidence of grade 2 or higher PN events was a key secondary safety end point of the BOSTON trial. PN was also a notable harm pre-specified in the CADTH systematic review protocol. PN was less commonly reported in the SVd group than the Vd group at the primary analysis (21.0% versus 34.3%, respectively). Most events were grade 2. Results at the updated analysis were consistent with the primary analysis.

Critical Appraisal

Two interim analyses were planned for the BOSTON trial. The first interim analysis was for sample size readjustment. At the first interim analysis, it was determined that no readjustment of sample size would be conducted. The second interim analysis was for efficacy analysis based on PFS and would allow for a conclusion of efficacy and stopping for futility (non-binding). There was agreement between the sponsor and the DSMB to use the second interim analysis as the final analysis for PFS. Because more than 75% of planned PFS events occurred, the DSMB determined that the primary end point of PFS was met at a 1-sided alpha of 0.025 which met the stopping boundary.

The sponsor conducted additional analyses of efficacy end points at an updated time point (February 15, 2021). This updated analysis was not pre-specified and was not considered in the statistical analysis plan. All results from the updated analysis should be considered descriptive.

Although not unique to the BOSTON trial, it is possible the choice of subsequent therapies could have affected efficacy assessments of OS because the analyses for OS included patients who received subsequent therapies. A total of 69 patients in the SVd group and 116 patients in the Vd group received subsequent anti-cancer therapies. There were disproportional differences noted between treatment groups in the types of subsequent anti-cancer therapies received because more patients in the SVd group received [REDACTED] than the Vd group. In addition, patients in the Vd group were eligible to crossover to receive a selinexor-based regimen. The differences in subsequent therapies are expected to have introduced bias in the efficacy analyses of OS and other patient outcomes. However, the direction and extent of the biases are difficult to predict. It is possible that crossover also affected safety analyses. Patients crossing over to a selinexor-based regimen would have experienced selinexor-related AEs. Therefore, it is possible that differences between treatment groups in incidence of selinexor-related AEs are underestimated.

Regarding patient disposition in the BOSTON trial, a greater proportion of patients in the SVd group discontinued treatment due to withdrawal by the patients (■■■■) than in the Vd group (■■■■). The sponsor clarified the reasons for patient withdrawal were due to AEs (■■ in the SVd group versus ■■ in the Vd group), logistical reasons (■■ versus ■■), poor health or entered hospice care (■■ versus ■■), burden of assessments (■■ versus ■■), and IRC-confirmed disease progression (■■ versus ■■); an additional ■■ patients in the SVd group versus ■■ patients in the Vd group did not provide any additional information.⁵ Discontinuation due to AEs or toxicity were initially reported by 16.9% of patients in the SVd group versus 11.3% of patients in the Vd group. The clarification provided by the sponsor regarding reasons behind withdrawal due to “withdrawal by the patient” may indicate that there is additional toxicity related to SVd as an additional ■■ patients in the SVd group versus ■■ patients in the Vd group discontinued due to AEs. It is possible that these differences in patient disposition may have affected some efficacy end points because this imbalance in discontinuations may be a result of informative censoring. PFS was the primary end point; therefore, it is possible that the analyses were conducted on a population of patients in the SVd group who could better tolerate the investigational treatment. The sponsor conducted a number of sensitivity analyses for which the results continued to support the primary analysis of PFS and favoured treatment with SVd over Vd. However, it should be noted that the sponsor also conducted a sensitivity analysis which considered treatment discontinuation as an event; this analysis was the only sensitivity analysis for PFS that did not demonstrate a statistically significant improvement in PFS for the SVd group (HR = 0.95, 95% CI, 0.76 to 1.19). The imbalance in patient discontinuations may also have affected other secondary outcomes, namely TTD. The median TTD was 7.10 months (95% CI, 6.44 to 8.54) in the SVd group and 7.95 months (95% CI, 6.80 to 9.23) in the Vd group (HR = 0.99, 95% CI, 0.79 to 1.23). It was expected that an improvement in PFS would translate to a longer TTD in the investigational therapy group versus the control; however, this was not the case in the BOSTON trial.

The clinical experts consulted by CADTH for this review acknowledged that the eligibility criteria of the BOSTON trial, although similar to other clinical trials for MM, were restrictive and likely excluded patients who would be candidates for SVd in clinical practice. For example, the trial excluded patients who received radiation, chemotherapy immunotherapy, or other anti-cancer therapy 2 weeks or less prior to receiving study treatment. The eligibility criteria also excluded patients with severe PN, plasma cell leukemia, and comorbidities. Other patients excluded were those with spinal cord compression, documented systemic light chain amyloidosis, and major surgery within 4 weeks prior to receiving study therapy. In general, exclusion criteria were acknowledged to be restrictive and exclude patients who could potentially benefit from treatment with SVd.

The demographic and clinical characteristics of patients randomized in the BOSTON trial were generally considered representative of Canadian patients, as confirmed through consultation with clinical experts for this review. However, it was noted by the clinical experts that the proportion of patients with previous exposure to lenalidomide was low (39.5% in the SVd group and 37.2% in the Vd group). In Canadian clinical practice, lenalidomide would be administered to most patients as a first-line therapy in the metastatic setting. Therefore, it is expected that nearly all Canadian patients would have had previous exposure to lenalidomide.

The BOSTON trial was a phase III trial that compared SVd to Vd. The comparator of Vd was not considered to be appropriate in the current Canadian context. In particular, the dose of bortezomib was highlighted as being different between the 2 treatment groups. Bortezomib was administered at a dose of 1.3 mg/m² SC on days 1, 8, 15, and 22 of each 35-day cycle in the SVd group. In the Vd group, bortezomib was administered at a dosage of 1.3 mg/m² SC

on days 1, 4, 8, and 11 of each 21-day cycle for the first 8 cycles; after cycle 8, bortezomib was administered at a dosage of 1.3 mg/m² SC on days 1, 8, 15, and 22 of each 25-day cycle. The clinical experts consulted by CADTH confirmed that the twice-weekly dosing of Vd in the Vd group is not commonly used in clinical practice. In addition, Vd is not a common regimen administered to patients. The clinical experts confirmed that Vd is often administered to patients as part of a triplet regimen. Overall, the clinical experts agreed that the Vd was not an appropriate comparator in the current Canadian treatment landscape for MM. However, it was acknowledged that enrolment for the BOSTON trial began in 2017 when the standard of care may have been different, and that global variation in reimbursement of treatments may have led to the decision to choose Vd as the comparator for the BOSTON trial.

Indirect Comparisons

Description of Studies

Sponsor's ITC

All 66 studies included patients with RRMM. Most studies were phase II or III trials, including 19 (29%) phase II trials and 45 (68%) phase III trials. Details about trial phase were not reported for 1 study. Another study was a retrospective matched-pair analysis that was included to complete the treatment networks. Of these studies, 50 (76%) were open label, 12 (18%) were double blind, and 4 did not report blinding procedures. The median follow-up ranged from 8.0 to 85.1 months (median = 15.9 months). Sample sizes in the treatment groups ranged from 46 to 465 patients (median = 152 per treatment group). The median age ranged between 59 and 74 years (median = 65 years); the median ages were similar across most trials. The proportion of males across the trials ranged from 30.0% to 91.7% (median = 56.0%).

Dolph et al.

A total of 21 studies were included in the network for PFS for second line, including 14 randomized controlled trials (RCTs) with only second-line patients, 5 studies with a mixed population of which the majority were second-line patients, and 2 studies in which the majority of patients were in the third line or later. The 2 studies with majority third-line or later patients were stated to be necessary to connect dexamethasone with Rd. A total of 24 studies were included in the network for PFS in the third line or later, including 19 studies with outcomes reported exclusively in the third line or later. Four studies included patients in the second line and third line or later, and 1 study included exclusively second-line patients but was necessary to link Vd with bortezomib.

A total of 15 studies were included in the network for OS in the second line; 4 of these studies reported only second-line OS information. A mixed population was enrolled for 9 studies with the majority of patients in second line, and 1 study enrolled primarily patients in the third line or later. A total of 22 studies were included in the network for OS in the third line, including 11 studies that included outcomes in the third line or later, and 10 studies with a mixed population of which the majority were in the third line or later. One study reported results exclusively in the second line but was required to connect bortezomib with Vd.

A total of 20 studies were included in the network for ORR in the second line, including 12 RCTs reporting outcomes exclusively in the second line. A mixed population was reported in 8 of the studies with a majority of second-line patients. A total of 27 studies were included in the network for ORR in the third line, including 17 studies that included outcomes exclusively in the third line or later. A mixed population was reported for 9 studies with the majority of

patients being in the third line or later. One study was included that reported exclusively second-line results but was required to link bortezomib with Vd.

Arcuri et al.

A total of 6 studies included lenalidomide in the control group and 8 studies included bortezomib in the control group; only 3 studies did not include either of these treatments but instead included carfilzomib (n = 1) or pomalidomide (n = 2) in the control group. Interventions assessed in the studies included vorinostat (n = 1), panobinostat (n = 1), pomalidomide (n = 1), pegylated doxorubicin (n = 1), cyclophosphamide (n = 1), elotuzumab (n = 1), pembrolizumab (n = 1), autologous stem cell transplantation (n = 1), venetoclax (n = 1), carfilzomib (n = 2), ixazomib (n = 2), daratumumab (n = 3), isatuximab (n = 1), and selinexor (n = 1). There were a range of follow-up times in the studies from 6 months to 36.8 months. The studies also included patients who had received a range of 1 to 3 prior therapies. Studies were published between 2007 and 2020. No further assessment of heterogeneity was conducted by the authors.

Botta et al.

A total of 6 phase III RCTs (CASTOR, ENDEAVOR, OPTIMISM, CANDOR, IKEMA, BOSTON) were included, representing 1,615 RRMM patients who were previously exposed to lenalidomide and 984 patients who were refractory to lenalidomide. The authors reported that studies were well balanced for presence of lenalidomide-refractory patients; these patients accounted for approximately 70% of patients, except for the CASTOR trial, which included 50% of lenalidomide-refractory patients. Studies were also well balanced in terms of exposure to bortezomib, which was approximately 65% of patients, except for the IKEMA trial in which 85% to 93% of patients had previous bortezomib exposure. The proportion of patients in second-line therapy was well balanced across trials and accounted for approximately 45% of patients in the trials. No further assessment of study and patient characteristics was provided.

Efficacy Results

Sponsor's ITC

PFS: Regarding the NMA conducted in the second line, compared with Vd, [REDACTED]
[REDACTED]
The remaining regimens did not show any difference. Pairwise comparisons against selinexor [REDACTED] Regarding the NMA conducted in the third line or later that compared to Vd, [REDACTED]
[REDACTED] Pairwise comparisons against selinexor [REDACTED]

OS: Regarding the NMA conducted in the second line, there were [REDACTED]
[REDACTED] Pairwise comparisons against selinexor [REDACTED]. Regarding the NMA conducted in the third line or later, compared with Vd, [REDACTED]
[REDACTED] Pairwise comparisons against selinexor suggested that SVd was [REDACTED]

ORR: Regarding the NMA conducted in the second line, compared to Vd, [REDACTED]
[REDACTED] The remaining regimens did not show any difference. Pairwise comparisons suggested that ORR was [REDACTED] compared to SVd against other comparators specified in the CADTH systematic review protocol. Regarding the NMA conducted in the third line or later, compared with Vd, [REDACTED]

PFS: In the second line, compared with Vd, the greatest benefit was from DVd, followed by DRd, and Kd. There were no differences between the remaining treatments of interest, including SVd. In the third line, compared with Vd, treatments which were favoured included DRd, DVd, Kd, and PVd. There were no differences between the remaining treatments of interest, including SVd. The specific estimates for comparisons were not provided.

ORR: In the second line, treatments favoured over Vd included DKd, DVd, and SVd. There were no differences between the remaining interventions of interest. In the third line, DVd, DKd, and Kd were favoured over Vd. The remaining treatments did not show any differences, including SVd. The treatment effects were not reported.

PFS: There were no differences between selinexor and any of the comparators of interest: carfilzomib (HR = 0.86, 95% CI, 0.50 to 1.48), daratumumab (HR = 0.65, 85% CI, 0.38 to 1.10), high-dose chemotherapy (HR = 1.24, 95% CI, 0.65 to 2.38), isatuximab (HR = 0.85, 95% CI, 0.44 to 1.65), ixazomib (HR = 0.98, 95% CI, 0.55 to 1.75), and pomalidomide (HR = 0.97, 95% CI, 0.50 to 1.87). The heterogeneity measured for PFS, as assessed by I^2 , was 64%.

PFS: Results suggested that PFS among lenalidomide-exposed patients was higher with Isa-Kd (HR = 0.34, 95% CI, 0.18 to 0.64) followed by DKd (HR = 0.36, 95% CI, 0.22 to 0.61), DVd (HR = 0.38, 95% CI, 0.26 to 0.56), PVd (HR = 0.61, 95% CI, 0.49 to 0.76), SVd (HR = 0.63, 95% CI, 0.41 to 0.96), and Kd (HR = 0.69, 95% CI, 0.52 to 0.92) compared with Vd. Among patients who were lenalidomide refractory, PFS was higher with treatment with DVd (HR = 0.36, 95% CI, 0.21 to 0.62) followed by DKd (HR = 0.38, 95% CI, 0.21 to 0.68), Isa-Kd (HR = 0.48, 95% CI, 0.25 to 0.92), and PVd (HR = 0.65, 95% CI, 0.50 to 0.84) compared with Vd. There was no difference observed between Kd (HR = 0.80, 95% CI, 0.57 to 1.12) and Vd.

The authors conducted an analysis for SAEs. However, the analysis for SAEs did not include selinexor; therefore, these results are not reported.

Botta et al.

No analyses for harms were conducted in the ITC conducted by Botta et al.

Critical Appraisal

Sponsor's ITC

The sponsor included 17 trials in their ITC. There is likely high heterogeneity across study and patient characteristics. Differences in these study and patient characteristics may result in uncertainty in the analyses as the studies may not necessarily be comparable. In addition, the proportion of patients in different lines of therapy may not be similar across treatment groups within studies and across studies. It is likely that variations in patient characteristics were present in the trials and unaccounted for.

The clinical experts consulted by CADTH for this review also highlighted the importance of considering subgroups of patients who would be lenalidomide exposed versus lenalidomide refractory. The sponsor did not conduct any sensitivity analyses to determine the differences in treatment effect for these patient groups. These patient subgroups were highlighted because it is expected that most Canadian patients will receive a lenalidomide-based regimen in the first line, and that subsequent therapy should consider patient's initial response to first-line therapy.

Networks of evidence were separated by line of therapy (second line and third or later line) which was considered appropriate given that patients in later lines of therapy tend to have worse outcomes. However, within networks, studies that included a mix of patients in multiple lines of therapy were included in networks where the majority of patients represented patients in either second line or later lines of therapy. This may introduce bias because patients in earlier or later lines of therapies can influence each network differently. Patients receiving second-line therapy may overestimate the efficacy of treatments included in studies in the third-line or later networks, while patients receiving later lines of therapy may underestimate efficacy of treatments included in the second-line networks.

Trials were phase II and III trials — earlier phased trials may not be powered for hypothesis testing. The inclusion of phase II trials is expected to introduce bias into the NMAs that may not be present in phase III trials which are typically designed to detect differences between different treatment groups. Also, inclusion of the retrospective matched-pair analysis was required to link bortezomib to bortezomib plus dexamethasone (there were no RCTs available for this link). Inclusion of this retrospective study does not satisfy the transitivity assumption of the ITC because all other studies were clinical trials. The sponsor considered the connection between bortezomib and bortezomib plus dexamethasone to be necessary and, thus, included this retrospective matched-case analysis to allow for comparisons of included regimens. The inclusion of this retrospective matched-case analysis is expected to introduce considerable uncertainty into the NMAs.

Overall, the networks of the NMAs were complex, leading to a high degree of variability. Methodological limitations are likely to have introduced further uncertainty into the analyses. For example, the sponsor did not conduct adjustments for crossover. Crossover to investigational treatment from a control is expected to underestimate the treatment effect observed in that trial and influence the analyses of the ITC. Important effect modifiers were not controlled for. Subgroup analyses were not performed due to small sample sizes. However, the lack of adjustment may introduce bias, which may affect treatment comparisons.

Dolph et al.

The ITC conducted by Dolph et al. was similar the ITC provided by the sponsor. Because the methodology was very similar to the ITC provided by the sponsor, the results were compared to the sponsor's submitted ITC. In general, the results led to the same or similar conclusions regarding favoured treatments and the efficacy of SVd relative to other interventions. The consistency between these 2 analyses provides support that the analyses conducted by the sponsor and Dolph et al. are replicable. However, limitations associated with the sponsor's ITC are similar to the limitations in the ITC conducted by Dolph et al. Critiques of the sponsor's ITC as reported previously should also be considered for the ITC published by Dolph et al.

The authors conducted an additional NMA which included only Vd-containing regimens. This was preferred methodologically because it did not rely on the retrospective study to link treatments and allowed for comparisons between regimens with 1 shared common anchor; in this case, all regimens were compared with Vd. The authors also stated that this analysis was highly relevant because lenalidomide is used in most patients as a first-line option and would not likely be used in later lines. Therefore, lenalidomide-based regimens are likely not important comparators in the second and later lines. The clinical experts consulted by CADTH for this review supported this statement and agreed that lenalidomide-based regimens would not be competing with other regimens in the second or later lines because it would most likely be used in the first line. However, the authors did not report specific results; therefore, it is unclear which interventions were actually favoured over the others.

The authors also reported that the CASTOR study, which was included in some networks, incorporated 2 trial characteristics that were not consistent with usual clinical practice, and magnified the effect of daratumumab in the study. Specifically, the CASTOR study administered bortezomib twice weekly when most clinical practices administer bortezomib once weekly, and the trial required that bortezomib be discontinued after 24 weeks in both the DVd and Vd treatment groups which resulted in treatment with daratumumab compared with no treatment after the 24 weeks. The clinical experts consulted by CADTH for this review also confirmed that treatment with bortezomib is often administered beyond 24 weeks (or 8 cycles) for patients who can tolerate and respond well to treatment. The CADTH team agreed that this likely amplified the treatment effects of daratumumab and biased results, which did support most daratumumab-based regimens in the NMAs.

Arcuri et al.

There is likely high variation in patient characteristics across the trials, which likely introduced biases and results in considerable uncertainty in the analyses. The authors did not report a thorough assessment of heterogeneity. However, there were variations reported across trial characteristics. Studies were published between 2007 and 2020; treatment practices from 2007 are likely not the same as current treatment practices, and the patient groups compared are likely not the same because new therapies have been introduced which alter the treatment pathways for patients and their outcomes. There were differences in treatment durations which were not accounted for in the analyses. The authors acknowledged that prolonged treatment duration may lead to increased PFS and higher rates of near-complete or complete responses. It is possible that effect modifiers which could affect efficacy analyses may be present but were unaccounted for. For example, the authors included patients across multiple lines of therapies. The clinical experts consulted by CADTH for this review confirmed that patients in later lines of therapy likely will have poorer outcomes; differences in patients across different lines of therapy may under- or overestimate the treatment effects.

The authors connected studies through a common comparator group of either lenalidomide plus dexamethasone or Vd based on the assumption that these 2 treatments are equally effective. This allowed the authors to create a single control group and shorter path for the indirect comparisons; this method allowed for greater power to detect differences. However, 3 studies were also incorporated into this comparison group that did not include either Rd or Vd as a comparator, but instead included Kd or Pd. The authors conducted a sensitivity analysis which separated the control group into 2 categories: 1 group including lenalidomide- or pomalidomide-based regimens and another including bortezomib-based regimens. The authors concluded that both treatments were equivalent, which further supported their decision to group these categories together. The clinical experts consulted by CADTH for this review did not agree with the assumption that Rd and Vd were equally effective treatments. In addition, the clinical experts also disagreed that Kd and Pd were equally effective treatments; however, they also acknowledged that use of Pd would occur after treatment with Rd, and that Pd would be expected to be less efficacious for patients because it is used in a later line in patients previously treated with an immunomodulatory drug. Therefore, the CADTH team considered comparisons conducted in this ITC to be inappropriate because data for treatments that are not considered equivalent were combined to create connections between regimens.

In general, details regarding the methodology used by the authors for the ITC were sparse. It is not possible to provide a full appraisal of these methods. The authors did not report whether they adjusted for crossover in the trials, although it is unlikely. Treatment crossover could have biased efficacy analyses of these trials. However, it was reported that the authors conducted NMAs with fixed effects, unless the I^2 values were greater than 40% where random-effects models were used. The I^2 value of the NMA for PFS was 64%, which indicates that a random-effects model was used. The analyses of OS and SAEs were reported to have an I^2 value of 0; however, a random-effects model was used for the analysis of OS. The use of random effects was considered appropriate given the number of comparators and the high amount of heterogeneity; however, without assessment of model convergence and consistency, it is not possible to know which model was best for these analyses.

Economic Evidence

Table 3: Cost and Cost-Effectiveness

Component	Description
Type of economic evaluation	Cost-utility analysis Partitioned survival model
Target population	Adult patients with multiple myeloma who have received at least 1 prior therapy
Treatment	Selinexor in combination with bortezomib and dexamethasone (SVd)
Submitted price	Selinexor, 20 mg: \$550.00 per tablet
Treatment cost	SVd: \$13,269 per 28-day cycle assuming 100 mg selinexor weekly (days 1, 8, 15, and 22 of each 28-day cycle) alongside bortezomib and dexamethasone (bortezomib: 1.3 mg/m ² subcutaneous on days 1, 8, 15, and 22 for 4 weeks, with 1 week off between 28-day cycles; dexamethasone: 20 mg on days 1, 2, 8, 9, 15, 16, 22, and 23 of each 28-day cycle)

Component	Description
Comparators	<p>Vd (bortezomib + dexamethasone)</p> <p>PVd (pomalidomide + bortezomib + dexamethasone)</p> <p>KCd (carfilzomib + cyclophosphamide + dexamethasone)</p> <p>Kd (carfilzomib + dexamethasone)</p> <p>CyBorD (cyclophosphamide + bortezomib + dexamethasone)</p> <p>DVd (daratumumab + bortezomib + dexamethasone)</p> <p>DRd (daratumumab + lenalidomide + dexamethasone)</p> <p>Rd (lenalidomide + dexamethasone)</p> <p>KRd (carfilzomib + lenalidomide + dexamethasone)</p> <p>Standard of care (assumed to comprise an equally weighted average of Vd, PVd, KCd, Kd, CyBorD, DVd, DRd, Rd, and KRd)</p>
Perspective	Canadian publicly funded health care payer
Outcomes	QALYs, life-years
Time horizon	20 years
Key data source	Network meta-analysis; OS and PFS estimates for SVd informed by the BOSTON trial
Key limitations	<ul style="list-style-type: none"> • The comparative impact of SVd on PFS and OS is highly uncertain because of a lack of head-to-head evidence for SVd compared with the majority of relevant comparators and the high degree of uncertainty in the sponsor's network meta-analysis. • Whether SVd is associated with improved OS, relative to Vd alone, is highly uncertain. Although the sponsor's model predicts an incremental gain of 0.86 life-years with SVd compared to Vd, this is not supported by the results of the BOSTON trial. Additional uncertainty results from the choice of parametric extrapolation curves for the long-term extrapolation of the treatment effects. • The potential impact of subsequent treatment on health outcomes, such as OS, after disease progression was not considered in the sponsor's model. This is inconsistent with clinical expert opinion and likewise inconsistent with the evidence presented to CADTH. • Clinical experts consulted by CADTH noted that the basket of subsequent treatments adopted by the sponsor was not consistent with clinical practice. • Treatment discontinuation was modelled separately from PFS, which assumes that there is no correlation between these parameters. Based on the Health Canada product monograph, SVd should be administered until disease progression or unacceptable toxicity. CADTH notes that the sponsor adopted a higher discontinuation rate for SVd compared to all comparator regimens, which suggests that SVd is either less tolerable or less effective. • The comparative effect of SVd relative to Vd on HRQoL from the trial is uncertain. The sponsor also incorporated an additional response benefit for patients deemed treatment responders which may have resulted in double counting as patients in the progression-free state were already assumed to have higher utility. • RDI was used to reduce drug costs; however, this assumes a direct link between RDI and drug cost which may not hold. Inappropriate methods were also applied to generate RDI as they ignore patients who received a higher dose. • Some regimens included in the sponsor's base case (e.g., those containing lenalidomide [DRd, Rd, KRd]) are unlikely to be used in second- and later line treatment because most patients would receive them in first line and not be rechallenged with the same agent. Other potentially relevant regimens (e.g., Isa-Kd, Isa-Pd) were not included in the sponsor's model. • The model lacked flexibility to assess the cost-effectiveness of SVd by type of prior treatment received

Component	Description
	(e.g., among lenalidomide-refractory patients) and in relevant subgroups (e.g., transplant eligible or ineligible patients). Given that there is considerable heterogeneity across subgroups in terms of comparators and prognosis, this increases the uncertainty of the analysis and may confound the interpretation of OS.
CADTH reanalysis results	<ul style="list-style-type: none"> • CADTH was unable to correct for limitations such as the lack of robust comparative data, the uncertainty associated with the influence of subsequent treatment on OS, and the cost-effectiveness of SVd in relevant subgroups. As such, CADTH was only able to conduct an analysis comparing cost-effectiveness of SVd to Vd. • CADTH's exploratory reanalysis: corrected the price of bortezomib, assumed equivalent OS for SVd and Vd, adopted PFS estimate from the BOSTON trial, adopted alternative parametric distributions for OS and PFS, adopted health state utility values based the BOSTON trial, removed the utility response benefit, and assumed that all patients received the full dose of all drugs. The ICER for SVd compared with Vd, based largely on inputs from the BOSTON trial, was \$10,884,623 per QALY. The results of these reanalyses should be viewed as exploratory because of the limitations highlighted previously. A minimum 93% price reduction of selinexor would be required for SVd to be considered cost-effective at a \$50,000 willingness-to-pay threshold compared to Vd. • Absence of robust data means there is no evidence to justify a price premium for SVd above other treatment regimens used to treat multiple myeloma. To ensure cost-effectiveness, SVd should also be priced at least no more than the lowest cost comparator used to treat multiple myeloma in the Health Canada indicated setting.

Isa-Kd = isatuximab in combination with carfilzomib and dexamethasone, Isa-Pd = isatuximab in combination with pomalidomide and dexamethasone; OS = overall survival; PFS = progression-free survival; PSM = partitioned survival model; QALY = quality-adjusted life-year; SVd = selinexor in combination with bortezomib and dexamethasone; Vd = bortezomib and dexamethasone.

Budget Impact

CADTH identified the following key limitations with the sponsor's analysis: the number of patients eligible for SVd is uncertain and may be underestimated, and all relevant comparators were not considered. Relevant comparators may depend on the line of therapy and prior treatments received; the uptake of SVd is uncertain and may be underestimated. Uptake may differ among patients with and without prior lenalidomide exposure, the duration of SVd treatment is underestimated, and costs associated with subsequent treatment were not considered. Such costs are relevant to the drug plan budget; costs related to selinexor treatment are underestimated, which may increase the cost to the drug plans of reimbursing selinexor.

Owing to the high degree of uncertainty around these model parameters, CADTH did not reanalyze the sponsor's budget impact analysis submission. The impact of reimbursing selinexor to the drug plans is uncertain and will depend on what treatments are currently funded and which are displaced by SVd. CADTH notes the volume of drug costs associated with SVd is highly uncertain when using the sponsor's approach.

pERC Information

Members of the Committee

Dr. Maureen Trudeau (Chair), Mr. Daryl Bell, Dr. Jennifer Bell, Dr. Matthew Cheung; Dr. Winson Cheung, Dr. Michael Crump, Dr. Leela John, Dr. Christian Kollmannsberger, Mr. Cameron Lane,

Dr. Christopher Longo, Dr. Catherine Moltzan, Ms. Amy Peasgood, Dr. Anca Prica, Dr. Adam Raymakers, Dr. Patricia Tang, Dr. Marianne Taylor, and Dr. W. Dominika Wranik.

Meeting date: June 8, 2022

Regrets: None

Conflicts of interest: None