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Reimbursement Recommendation

Belantamab Mafodotin (Blenrep), Bortezomib, Dexamethasone

Indication: Belantamab mafodotin is indicated in combination with bortezomib and dexamethasone for the treatment of adults with relapsed or refractory multiple myeloma who have received at least 1 prior line of therapy.

Sponsor: GlaxoSmithKline Inc.

Final recommendation: Reimburse with conditions

Summary

What Is the Reimbursement Recommendation for Blenrep?

Canada's Drug Agency (CDA-AMC) recommends that Blenrep in combination with bortezomib and dexamethasone be reimbursed by public drug plans for the treatment of adults with relapsed or refractory multiple myeloma who have received at least 1 prior line of therapy, if certain conditions are met.

Which Patients Are Eligible for Coverage?

Blenrep in combination with bortezomib and dexamethasone should only be covered to treat adult patients with relapsed or refractory multiple myeloma who are in relatively good health and have already tried at least 1 other treatment for this disease. Blenrep in combination with bortezomib and dexamethasone should not be reimbursed in patients who were previously treated with an anti-BCMA therapy, patients who have experienced intolerance to bortezomib, or patients whose disease is refractory to bortezomib.

What Are the Conditions for Reimbursement?

Blenrep in combination with bortezomib and dexamethasone should only be reimbursed if it is prescribed under the care of clinicians with expertise in the diagnosis and management of patients with multiple myeloma, and if the cost of Blenrep in combination with bortezomib and dexamethasone is reduced.

Why Did CDA-AMC Make This Recommendation?

- Evidence from a clinical trial demonstrated that Blenrep in combination with bortezomib and dexamethasone may delay disease progression and prolong life in adult patients with relapsed or refractory multiple myeloma, compared to daratumumab in combination with bortezomib and dexamethasone (DVd).
- Blenrep meets some patient needs, as it is an alternative treatment option that may offer benefits in delaying progression of disease and improved survival compared to DVd.
- Based on the CDA-AMC assessment of the health economic evidence, Blenrep does not represent good value to the health care system at the public list price. A price reduction is therefore required.
- Based on public list prices, Blenrep is estimated to cost the public drug plans approximately $940 million over the next 3 years. However, the actual budget impact is uncertain and will depend on several

Summary

factors, including real-world dosing patterns, the extent of uptake across jurisdictions, and the distribution of subsequent therapies in the treatment pathway.

Additional Information

What Is Multiple Myeloma?

Multiple myeloma is a cancer of plasma cells (the white blood cells that make immunoglobulins) in the bone marrow. In 2024, it was estimated that 4,100 people in Canada had been diagnosed with multiple myeloma.

Unmet Needs in Multiple Myeloma

Multiple myeloma is an incurable disease, and patients commonly experience relapse or their disease eventually becomes refractory to treatment. There is a need for additional effective therapies that can prolong survival, delay disease progression, and improve quality of life (QoL).

How Much Does Blenrep Cost?

Treatment with Blenrep in combination with bortezomib and dexamethasone is expected to cost approximately $77,656 per 28 days per patient in the first cycle, and $74,133 per 28 days per patient in subsequent cycles.

Recommendation

The pan-Canadian Oncology Drug Review Expert Review Committee (pERC) recommends that belantamab mafodotin be reimbursed in combination with bortezomib and dexamethasone for the treatment of adults with relapsed or refractory multiple myeloma who have received at least 1 prior line of therapy, only if the conditions listed in Table 1 are met.

Rationale for the Recommendation

One ongoing phase III, open-label, randomized controlled trial (RCT) (the DREAMM-7 trial; N = 494) showed that treatment with belantamab mafodotin in combination with bortezomib and dexamethasone (BVd) resulted in added clinical benefit in patients with relapsed or refractory multiple myeloma who had received at least 1 prior therapy, compared to DVd. At the primary (first interim) analysis (IA1), after a median follow-up time of 28.2 months, the median progression-free survival (PFS) was 36.6 months (95% CI, 28.4 to not estimable) in the BVd group and 13.4 months (95% CI, 11.1 to 17.5) in the DVd group (hazard ratio [HR] = 0.41; 95% CI, 0.31 to 0.53). At the second planned interim analysis (IA2), after a median follow-up time of 40.2 months, improvement in PFS was sustained for BVd versus DVd (HR = 0.46; 95% CI, 0.35 to 0.59). The Kaplan-Meier (KM) estimated between-group differences in probabilities of PFS at 24 months and 36 months were [redacted] and [redacted], respectively, in favour of BVd. Although the median overall survival (OS) had not been reached in either treatment group at the interim analyses, BVd showed a statistically significant and clinically meaningful improvement in overall survival (OS) compared with DVd at IA2 (HR = 0.58, 95% CI, 0.43 to 0.79). The KM-estimated between-group differences in probabilities of OS at 24 months and 36 months were [redacted] and [redacted] in favour of BVd.

In the absence of direct comparative evidence for the comparisons of BVd with other publicly funded treatments for multiple myeloma in the second and later lines of therapy in Canada, pERC considered evidence from 1 sponsor-submitted indirect treatment comparison (ITC). Results of the ITC suggested that the treatment effect estimates for PFS favoured BVd over several relevant comparators, such as isatuximab plus high-dose carfilzomib and daratumumab (IhKd), high-dose carfilzomib plus dexamethasone (hKd), pomalidomide plus bortezomib plus dexamethasone (PVd), selinexor plus bortezomib plus dexamethasone (SVd), carfilzomib plus dexamethasone (Kd), and bortezomib plus dexamethasone (Vd). Similarly, the treatment effect estimates for OS favoured BVd relative to IhKd, PVd, SVd, and Vd. However, pERC noted that the magnitude of these differences remains uncertain, as the indirect evidence was associated with notable limitations, including significant heterogeneity across the included trials in terms of study design, baseline patient characteristics, dosing regimens, and duration of follow-up.

Patients identified a need for new effective treatment options that prolong survival, delay disease progression, improve QoL, require fewer clinic visits, and have fewer side effects. pERC concluded that BVd may meet some patient needs because it offers an additional treatment option that delays disease progression and may improve survival, compared to DVd. Based on exploratory analyses, treatment with

BVd did not result in a decline in health-related quality of life (HRQoL) from baseline to week 175 compared to DVd. pERC agreed with the clinical experts that ocular toxicity with belantamab therapy can negatively impact QoL. However, pERC noted that HRQoL results for BVd compared with DVd were inconclusive due to high attrition rates, particularly at longer follow-up. pERC noted that ocular adverse events (AEs) were more common and severe in the group receiving BVd, often requiring more frequent treatment modifications than the DVd group. The committee agreed with the clinical experts that the toxicity profile of BVd is significant but may be manageable with careful monitoring, dose modification, and supportive care for ocular AEs, which occurred with high frequency but appeared to be largely reversible. Additionally, pERC noted that the relative impact of BVd compared to other treatment options remains uncertain with respect to HRQoL and toxicity.

Using the sponsor-submitted price for belantamab mafodotin and publicly listed prices for all other drug costs, the incremental cost-effectiveness ratio (ICER) for BVd was $1,758,284 per quality-adjusted life-year (QALY) gained, compared with Kd. At this ICER, BVd is not cost-effective at a $50,000 per QALY gained willingness-to-pay threshold for patients with relapsed or refractory multiple myeloma who have received at least 1 prior line of therapy. A price reduction is required for belantamab mafodotin as part of the BVd regimen to be considered cost-effective at a $50,000 per QALY gained threshold.

Table 1: Reimbursement Conditions and Reasons

Reimbursement condition	Reason	Implementation guidance
Initiation		
1. Treatment with BVd should be reimbursed in patients with relapsed or refractory multiple myeloma who meet all the following criteria: 1.1. aged 18 years or older 1.2. have received at least 1 prior therapy 1.3. documented disease progression during or after their most recent therapy.	In the DREAMM-7 trial, BVd demonstrated a clinical benefit over DVd in adult patients with relapsed or refractory multiple myeloma who fulfilled the characteristics listed in this condition.	—
2. Treatment with BVd should not be initiated in patients who have any of the following: 2.1. intolerant to, or disease that is refractory to, bortezomib 2.2. history of prior treatment with anti-BCMA therapy.	No evidence was available to support the benefit of BVd in patients with these characteristics because those patients were excluded from the DREAMM-7 trial.	pERC acknowledged the clinical experts' input that immunotherapies targeting BCMA work through distinct mechanisms from belantamab mafodotin and resistance to 1 does not imply a lack of responsiveness to the other. However, pERC noted that the degree of benefit of BVd after anti-BCMA therapy in patients with multiple myeloma is unknown and not supported by data.
3. Patients should have a good performance status.	The DREAMM-7 trial included patients with an ECOG Performance Status score of 0 to 2.	—

Reimbursement condition	Reason	Implementation guidance
Discontinuation		
4. Treatment with BVd should be discontinued upon the occurrence of any of the following: 4.1. disease progression 4.2. unacceptable toxicity.	In the DREAMM-7 trial, treatment with BVd was continued until disease progression, unacceptable toxicity, patient withdrawal, or death.	—
5. If 1 component of BVd (i.e., belantamab mafodotin or bortezomib plus dexamethasone) is discontinued permanently because of tolerability concerns, the patient may continue to receive the other component at the discretion of the treating physician, until the discontinuation criteria in condition 4 are met.	This condition reflects the treatment discontinuation criteria used in the DREAMM-7 trial.	—
Prescribing		
6. BVd should be prescribed under the care of clinicians experienced in diagnosing and managing multiple myeloma.	This is meant to ensure that treatment is prescribed only for appropriate patients and that adverse effects are managed in an optimized and timely manner.	pERC noted that due to the ocular toxicity associated with belantamab mafodotin, BVd should only be used in a setting with access to facilities and clinician specialists to monitor and manage the ocular toxicity. Additionally, the product monograph recommends that ophthalmic exams be conducted before each dose of BVd, with modifications to the frequency of monitoring as clinically indicated.
Pricing		
7. A reduction in price.	The ICER for BVd is $1,758,284 when compared with Kd. Price reductions in excess of 90% will be required for belantamab mafodotin as part of the BVd regimen to achieve an ICER below $50,000 per QALY gained compared to therapies in current use. Price reductions for different thresholds are available in Appendix 4 in the Pharmacoeconomic Review report.	—
Feasibility of adoption		
8. The economic feasibility of adoption of BVd must be addressed.	At the submitted price, the incremental budget impact of BVd is expected to be greater than $40 million in years 1, 2, and 3.	—
9. The feasibility of adoption of BVd must be addressed.	At the submitted price, the magnitude of uncertainty in the budget impact must be addressed to ensure the feasibility of adoption, given the difference between	—

Reimbursement condition	Reason	Implementation guidance
	the sponsor's estimate and the CDA-AMC estimate.	
10. The organizational feasibility of assessing and managing ocular toxicity associated with belantamab mafodotin must be addressed.	Managing ocular toxicity associated with belantamab mafodotin requires clinical resources, assessments, and interventions not routinely needed in the care of patients with multiple myeloma. Therefore, access to measures for reducing ocular toxicity during treatment and regular monitoring of ocular toxicity by an ophthalmologist or an optometrist are needed.	—

ASCT = autologous stem cell transplant; BVd = belantamab mafodotin in combination with bortezomib and dexamethasone; CDA-AMC = Canada's Drug Agency; DVd = daratumumab plus bortezomib and dexamethasone; ECOG = Eastern Cooperative Oncology Group; ICER = incremental cost-effectiveness ratio; pERC = pan-Canadian Oncology Drug Review Expert Review Committee; QALY = quality-adjusted life-year.

Discussion Points

- **Unmet needs**: pERC acknowledged the unmet need for more effective treatments for second or later lines of therapy, given that multiple myeloma remains an incurable disease. pERC noted a critical treatment gap for patients whose disease is refractory to lenalidomide or anti-CD38 therapies, particularly in older adults, who often experience suboptimal outcomes with existing regimens and may be ineligible for more aggressive treatments, such as CAR T-cell therapy or bispecific antibodies. pERC agreed with the patient and clinician groups that there is a need for new, effective, and accessible therapies that can result in deepened response, durable remission, and prolonged survival, while having a reasonable tolerability profile.
- **Certainty of evidence**: pERC noted that the Grading of Recommendations Assessment, Development and Evaluation (GRADE) assessment of the evidence from the pivotal DREAMM-7 trial demonstrated with high certainty that BVd resulted in a clinically meaningful improvement in PFS at 12 months and 36 months, when compared with DVd. The GRADE assessment also indicated that, with moderate certainty of evidence, BVd likely resulted in a clinically meaningful improvement in OS at 36 months, when compared with DVd. However, pERC noted that median OS had not been reached in either treatment group. Furthermore, pERC noted that that the OS results at the data cut-off represent interim analyses and, due to the immaturity of the data, longer-term follow-up is needed to inform the true effect of BVd on survival compared with DVd. pERC also noted that longer follow-up for OS is likely to be confounded by subsequent treatments.
- **Adverse effects**: pERC discussed the safety profile of BVd, acknowledging that patients expressed a need for treatments associated with fewer side effects. pERC acknowledged high-certainty evidence indicating an increased risk of ocular adverse events with BVd compared to DVd. pERC agreed with the clinical experts that the ocular toxicity associated with belantamab mafodotin therapy requires specialized support from eye care professionals — such as ophthalmologists or optometrists — along with more intensive monitoring and treatment modifications than typically needed for other systemic

therapies used for multiple myeloma. pERC noted that several strategies have been developed to manage the ocular toxicity of belantamab mafodotin and prevent permanent drug discontinuation, including dose reductions, treatment delays, early detection of corneal toxicity, and the use of cooling masks, corticosteroid eye drops, and artificial tears. pERC also agreed that, unlike other therapies, belantamab mafodotin was associated with less significant myelosuppressive toxicities, making it a good option for older patients who are more vulnerable to the adverse effects of other treatments. After considering the clinical expert input, pERC concluded that the adverse effects of belantamab mafodotin are generally manageable with appropriate measures. The clinical experts consulted for this review indicated that AEs are often reversible and can be mitigated with dose modifications (e.g., dose reduction, or extended intervals between doses). pERC was unable to draw conclusions about the safety of BVd relative to other relevant comparators, as the sponsor-submitted ITC did not include harms data.

- **HRQoL**: Patients and clinicians highlighted maintenance or improvement in HRQoL as an important outcome and treatment goal in multiple myeloma. pERC noted that despite the low certainty of evidence for HRQoL, there did not appear to be detriment to HRQoL. However, a substantial amount of missing data due to attrition limited the interpretation of these findings. Additionally, the submitted ITC did not assess HRQoL outcomes, precluding pERC from drawing conclusions on this important aspect of treatment.
- **Indirect evidence**: pERC discussed the indirect evidence submitted for this review, comparing BVd to comparators beyond DVd that are currently considered relevant comparators in the Canadian clinical setting for patients with relapsed or refractory multiple myeloma in the second-line setting and later settings. pERC noted that although the ITC suggested a favourable treatment effect of BVd on PFS and OS compared to several other regimens, it was associated with several major limitations in the design and methods that precluded any definitive conclusion about the magnitude of effect against other comparators. pERC agreed that while the ITC suggested a favourable effect of BVd on PFS in lenalidomide-exposed and lenalidomide-refractory populations (compared to regimens such as DVd, hKD, and Vd), the magnitude of this effect remains uncertain. It was also noted that no comparative effect estimates for patient-reported outcomes (e.g., HRQoL) and harms outcomes were included in the ITC. The committee noted that these limitations preclude a balanced assessment of the benefits and harms of BVd compared to other treatment options available in Canada for the patient population under review.
- **Place in therapy**: pERC discussed the place in therapy of BVd given the current treatment landscape and considering the differences between BVd and other treatment options, including CAR T-cell therapies or bispecific antibodies when choosing treatment options in the second-line setting and beyond. pERC agreed with the clinical experts that systemic treatment selection of multiple myeloma depends on several factors, including patient factors (i.e., age, comorbidity, prior toxicity), line of therapy, transplant eligibility, and prior therapies received.
- **Economic considerations**: pERC expressed significant concerns regarding the cost-effectiveness of BVd. The CDA-AMC base case estimated an ICER of $1,758,284 per QALY gained for BVd

compared to Kd. This estimate was considered to be unacceptably high, based on the magnitude of the incremental cost and the clinical benefit observed. Concerns also extended to the budget impact. The estimated incremental budget impact over the first 3 years of reimbursement is approximately $940 million, with total spending on BVd projected to reach $1.3 billion over this period. This represents a substantial increase compared to current expenditures on available treatment options. pERC also acknowledged that the actual budget impact will depend on several factors, including real-world dosing patterns of BVd, the extent of uptake across jurisdictions, and the distribution of subsequent therapies in the treatment pathway. Variability in these assumptions introduces uncertainty into the budget impact projections and may further affect the feasibility of adoption for public drug plans.

- **Implementation considerations:** pERC had significant concerns about the capacity of jurisdictions to address ocular toxicities associated with belantamab mafodotin and noted that implementation of a reimbursement recommendation for BVd will require frequent eye exams by ophthalmologists or optometrists (to detect early signs of toxicity) and other supportive care (e.g., use of artificial tears, as well as cooling masks during infusions to alleviate symptoms). pERC also noted that public coverage for required eye care to support using BVd safely is not uniform across jurisdictions, third-party coverage is highly variable, and the disparity could disproportionately impact individuals with limited financial resources and/or access to public coverage. Therefore, pERC noted that jurisdictions may need to evaluate the financial impact of covering additional eye care services and supportive treatments for patients receiving belantamab mafodotin. This includes the costs associated with regular ophthalmologic exams (including slit lamp evaluation and best corrected visual acuity [BCVA] assessment), artificial tears, and potentially prescription lenses to manage ocular toxicities. Ensuring comprehensive coverage for these services is crucial to mitigate the potential financial burden on patients and to maintain their QoL during treatment. The committee also emphasized the importance of vigilant monitoring and patient education regarding potential side effects.
- **Subcommittee discussion following approval by Health Canada:** BVd was a pre-NOC submission that was reviewed and deliberated on by pERC before Health Canada approved the final product monograph. A subcommittee of pERC was convened to review the changes outlined in the final product monograph (authorized July 21, 2025). The subcommittee discussed the serious warning included in the product monograph related to ocular toxicities. The monitoring requirements related to adverse reactions as well as dose administration were also discussed in relation to both clinical and economic impacts. Overall, the subcommittee concluded that the safety concerns were sufficiently discussed during the initial deliberation, and that the recommendation that had been drafted by the full committee remained valid.

Background

Multiple myeloma is a progressive and incurable malignancy characterized by the clonal expansion of malignant plasma cells and the overproduction of monoclonal protein (M protein). Older individuals are more

likely to develop multiple myeloma, with a higher incidence in males compared to females, and it is more prevalent in African American populations relative to white and Asian populations in the US. The incidence rate of multiple myeloma increased in Canada from 2003 to 2019, by about 1.7% per year for males and 1.3% per year for females. In Canada, approximately 3,900 new multiple myeloma cases were diagnosed in 2023, and there were an estimated 1,700 multiple myeloma–related deaths. In 2024, approximately 4,100 new cases were projected, with 2,400 cases in males and 1,750 in females. The 5-year survival rate for patients with multiple myeloma is approximately 50%, although recent therapeutic advancements have improved survival outcomes, despite the lack of a cure.

Multiple myeloma is most commonly diagnosed when patients present with symptoms such as bone pain, fatigue, anemia, kidney dysfunction, and recurrent infections. Multiple myeloma diagnosis requires the presence of 1 or more myeloma-defining events, along with either 10% or more clonal plasma cells in the bone marrow or a biopsy-proven plasmacytoma. Myeloma-defining events include end-organ damage (hypercalcemia, renal insufficiency, anemia, and bone lesions [CRAB criteria]) and 3 biomarkers: clonal bone marrow plasma cell percentage of at least 60%, free light chain ratio of at least 100, and at least 1 focal lesion on MRI. Prognosis is heavily influenced by staging, with the International Staging System (ISS) and the Revised International Staging System (R-ISS) widely used to assess disease progression. The ISS evaluates albumin and B2M levels, with advanced stages correlating with low albumin and high B2M. The R-ISS further incorporates tumour burden and high-risk genetic abnormalities to refine prognostication. Other factors, such as age, kidney function, and overall performance status, also impact prognosis. The build-up of resistance to different classes of therapies represents a significant challenge in clinical management of multiple myeloma, as the disease typically becomes more resistant to treatment with each subsequent line of therapy. In Canada, studies show that remission rates decrease with each line of therapy, and attrition rates increase. These findings underscore the progressive nature of the disease and the growing need for diverse therapeutic options that can effectively manage relapsed or refractory multiple myeloma. Patients with relapsed or refractory multiple myeloma often experience a persistent symptom burden, including fatigue, bone pain, and depression, which can severely affect their QoL.

Belantamab mafodotin is a humanized, afucosylated, BCMA-targeted antibody-drug conjugate. As described in the product monograph, the recommended starting dose schedule of belantamab mafodotin is 2.5 mg/kg administered intravenously once every 3 weeks in combination with bortezomib and dexamethasone for the first 8 cycles (cycle length = 3 weeks) and then continued as a single agent until disease progression or unacceptable toxicity.

Sources of Information Used by the Committee

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

- a review of 1 phase III, randomized, open-label, multicentre trial (the DREAMM-7 trial) in adults with multiple myeloma who had received at least 1 prior therapy
- 1 ITC

- patients' perspectives gathered by 1 patient group (Myeloma Canada)
- input from public drug plans that participate in the reimbursement review process
- input from 3 clinical specialists with expertise diagnosing and treating patients with multiple myeloma
- input from 2 clinician groups, including the Ontario Health (Cancer Care Ontario) (OH [CCO]) Hematology Cancer Drug Advisory Committee and the Canadian Myeloma Research Group (CMRG)
- a review of the pharmacoeconomic model and report submitted by the sponsor.

Perspectives of Patients, Clinicians, and Drug Programs

Patient Input

Patient input was submitted by 1 patient group (Myeloma Canada). Information was gathered from patients and caregivers through an online survey (N = 292). The most important symptoms related to myeloma that respondents wanted to control, in order of importance, included infections, mobility, renal problems, and pain. About 41% of patient respondents indicated that they required the help of a caregiver to manage their disease or treatment-related symptoms. The input noted that patients' disease symptoms impacted their ability to travel, work, exercise, and conduct volunteer activities. Respondents noted that the most significant financial implications due to myeloma treatment were the loss of income and/or pension funds due to absence from work, disability, or early retirement, followed by the costs of travel, parking, drugs, and accommodations. Respondents felt that the interruption of life goals or accomplishments had the greatest impact on their QoL, followed by the loss of sexual desire, and anxiety or worry. Respondents reported a desire for a treatment that would extend their life expectancy without disease progression (67% rated this as "extremely important") and improve their QoL (58% rated this as "extremely important").

No survey respondents had experience with BVd, and 10 respondents indicated that they had experience with belantamab mafodotin (7 with belantamab mafodotin plus pomalidomide and dexamethasone, and 3 either as monotherapy or combined with dexamethasone). Among these respondents, the least bearable side effects reported included blurry vision, dry eyes, eye irritation, sensitivity to light, and infections. Eight of the respondents indicated that the overall side effects of belantamab mafodotin treatment were "somewhat or mostly" manageable. When asked if the treatment was effective in controlling myeloma, 6 respondents reported "mostly or completely," 3 reported "somewhat," and 1 reported "slightly." The input emphasized the importance of patient preference in weighing the potential costs and benefits of any new treatment.

Clinician Input

Input From Clinical Experts Consulted for This Review

The clinical experts consulted by CDA-AMC highlighted several challenges associated with the currently available therapies for multiple myeloma in Canada. First, while various classes of drugs are available to manage multiple myeloma at different stages, no single treatment can offer a definitive cure for the disease. Second, a critical treatment gap exists for patients whose disease becomes refractory to lenalidomide or

anti-CD38 therapies. Third, treatment regimens such as Kd or SVd demonstrate suboptimal outcomes, and many patients may not be candidates for more aggressive therapies like CAR T-cell therapy or bispecific antibodies. Additionally, there is a need for therapies with improved toxicity profiles. Given that patients with multiple myeloma often require treatment regimens with manageable side effects to preserve their QoL, there is an increasing demand for therapies that involve fewer clinic visits and less intensive monitoring. According to the clinical experts consulted, belantamab mafodotin would primarily be used as second-line or later treatment for multiple myeloma, specifically for patients who have experienced relapse or whose disease is refractory to prior therapies. The clinical experts indicated that older patients, particularly those who have previously received lenalidomide plus bortezomib and dexamethasone, or DVd, and whose disease is not refractory to bortezomib, are ideal candidates for belantamab mafodotin. They also emphasized that, aside from ocular toxicities, the toxicity profile of belantamab mafodotin is relatively favourable, particularly in older patients. Unlike other therapies, belantamab mafodotin does not exhibit significant myelosuppressive toxicities, making it a good option for older patients who are more vulnerable to the adverse effects of other treatments. However, the clinical experts indicated that ocular toxicities remain a concern, and patients with pre-existing ocular conditions would be least suitable for belantamab mafodotin.

The clinical experts indicated that assessing response to treatment for multiple myeloma is generally straightforward, with routine blood tests being the primary method of monitoring. According to the clinical experts, ocular toxicity with belantamab mafodotin therapy can negatively impact QoL and requires more intensive monitoring than is standard in care for multiple myeloma. Specifically, regular ophthalmologic assessments and slit lamp examinations are necessary to guide dose adjustments and prevent more severe ocular toxicity, as they are not typically part of standard clinical practice in multiple myeloma. The clinical experts consulted indicated that treatment with BVd would be discontinued for 2 primary reasons: disease progression and intolerable toxicity, with ocular toxicity being the most significant. Furthermore, the clinical experts also noted that ocular toxicity may require extending dosing intervals to every 8 to 12 weeks, and in severe or intolerable cases, treatment may be discontinued. According to the clinical experts, treatment of multiple myeloma with belantamab should be managed by trained hematologist-oncologists, with eye specialists involved in monitoring and managing ocular toxicity.

Clinician Group Input

Two clinician groups consisting of a total of 27 clinicians provided input for this review, including the OH (CCO) Hematology Cancer Drug Advisory Committee and CMRG. Both submissions noted that myeloma remains incurable despite the introduction of new agents over the last 2 decades. Patients' disease eventually becomes refractory to all available funded antimyeloma agents. The clinician groups stated that symptom burden for patients with multiple myeloma is high, with patients experiencing bone pain and destruction, anemia and other cytopenias, renal damage, hypercalcemia, and a high risk of infection. CMRG stated that despite the clear benefits of lenalidomide as part of first-line therapy, progression on this potent agent, even as single-agent maintenance, leads to shorter PFS outcomes with nearly all traditional and reimbursed second-line regimens (including those containing an anti-CD38 monoclonal antibody) compared to the results without such exposure. As such, the clinician groups noted that drug exposure, rather than lines of therapy, more accurately defines the need for access to innovative treatments to forestall

the development of refractory myeloma. CMRG also noted that with the movement of combinations of 3 major drug classes (i.e., an immunomodulatory imide drug [IMiD], proteasome inhibitor [PI], and anti-CD38 monoclonal antibody) to the first-line and second-line treatment settings, exposure and resistance to multiple drug classes now occurs much earlier in the disease course than in the past. As such, the highest unmet need in myeloma continues to be effective treatment for patients who have experienced disease progression despite exposure to effective agents.

The OH (CCO) committee noted that the regimen would be another second-line treatment option for patients who are sensitive to bortezomib. The input noted that the treatment under review would be most suitable for patients who are unlikely to receive CAR T-cell therapy, as BVd may preclude future use of BCMA-targeted CAR T-cell therapy. Standard myeloma response outcomes used in clinical practice would be appropriate to determine if a patient is responding to the treatment under review, based on the monoclonal protein markers in the serum and/or urine, bone marrow biopsy, and, in some instances, imaging studies. Clinically meaningful responses usually correlate with at least a partial remission, as defined by the International Myeloma Working Group (IMWG) Consensus Criteria. These include improvement in symptoms (cessation of bone destruction with less pain, fractures, and need for radiotherapy), improvement in energy, and better ability to perform activities of daily living. Responses are generally assessed every 1 to 3 months, depending on clinical stability and the regimen used for therapy. Factors to consider when deciding to discontinue the treatment under review include significant toxicities, particularly ocular AEs, as well as disease progression. The clinician groups stated that the appropriate setting for BVd treatment is an outpatient setting and that there is also a need for ophthalmological assessments.

Drug Program Input

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

Table 2: Responses to Questions From the Drug Programs

Drug program implementation questions	Clinical expert response
Relevant comparators	
The trial compared BVd to DVd, which has become a less relevant comparator. **Question:** How does BVd compare with Kd, SVd, IhKd, and PVd?	pERC agreed with the clinical experts that IhKd may have been a more appropriate comparator for BVd, as it is considered more potent and associated with a longer PFS than DVd. The clinical experts noted that, in patients with lenalidomide-refractory disease, SVd, Kd, and PVd regimens have shown a median PFS of less than 1 year. pERC agreed with the clinical experts that BVd likely offers better efficacy than most of the listed regimens, with the possible exception of IhKd. However, it was noted that without direct comparisons, and given the methodological limitations associated with the ITC results, the comparative efficacy and safety of BVd relative to alternative regimens remains uncertain.

Drug program implementation questions	Clinical expert response
At the time of this input, first-line quadruplet regimens (daratumumab plus bortezomib plus lenalidomide and dexamethasone for patients with myeloma who are transplant-eligible, and isatuximab plus bortezomib plus lenalidomide and dexamethasone for patients who are transplant-ineligible) are under CDA-AMC review. Ciltacabtagene autoleucel (1 to 3 prior lines, 4L), elranatamab, and teclistamab are also in active negotiations.	This is a comment from the drug plans to inform pERC deliberations.
Considerations for prescribing of therapy	
Another belantamab mafodotin regimen, BPd, is also under review, with a different dosing schedule. Caution is needed to ensure that the correct dosing schedule is chosen for BVd, especially in the event of dose reductions.	This is a comment from the drug plans to inform pERC deliberations.
Due to the ocular toxicity, eye exams are required. PAG is concerned that patients may not be able to access ophthalmologists or optometrists in a timely manner.	This is a comment from the drug plans to inform pERC deliberations.
Question: Can belantamab mafodotin be administered with other bortezomib dosing regimens (e.g., weekly bortezomib)? In the trial, patients who had to stop bortezomib plus dexamethasone were permitted to continue belantamab mafodotin monotherapy (or vice versa) at the discretion of the investigator.	The clinical experts noted that there is substantial evidence showing that once-weekly bortezomib is likely as effective as twice-weekly dosing, with a significantly improved side effect profile. pERC agreed with the clinical experts that it is anticipated that belantamab mafodotin will be used alongside once-weekly bortezomib, without significant concerns about differences in efficacy with twice-weekly bortezomib.
Generalizability	
Question: Should these patients be considered for BVd? • Patients who experience intolerance to, or whose disease is refractory to, bortezomib • Patients whose disease is refractory to anti-CD38 antibodies (note that 1% of trial patients received prior daratumumab) • Patients with active plasma cell leukemia • Patients with systemic light chain amyloidosis	pERC agreed that patients who experience intolerance to, or whose disease is refractory to, bortezomib should not receive the BVd regimen. pERC agreed with the clinical experts that BVd should be considered in patients with anti-CD38–refractory disease, as those patients were excluded from the pivotal trial to be eligible to be randomized into the control arm (i.e., DVd). However, pERC noted that the true efficacy of BVd in patients whose disease is refractory to anti-CD38 therapies remains unknown, as no evidence was included in this review to support the efficacy and safety of BVd in this population. pERC agreed with the clinical experts that BVd can be used in patients with systemic light chain amyloidosis and plasma cell leukemia.
Question: Should patients receiving bortezomib plus dexamethasone or alternative treatments be switched to belantamab mafodotin?	pERC agreed with the clinical experts that if a patient was previously on SVd, switching to BVd would likely not be appropriate. However, if the patient was on bortezomib and dexamethasone alone, the addition of a third agent such as belantamab mafodotin could be considered. According to the clinical experts consulted for this review, very few patients are treated with doublet therapies in current practice. pERC agreed with the clinical experts that newly diagnosed patients who are eligible for transplant and are currently receiving bortezomib are typically doing so as part of an ASCT approach and possibly in the first-line setting; therefore, this regimen would not be indicated in that

Drug program implementation questions	Clinical expert response
	context. For patients who are not eligible for transplant, at the time of relapse, the clinical experts noted that treatment with bortezomib and dexamethasone alone is unlikely, making this a less common scenario that would need to be evaluated separately.
Funding algorithm (oncology only)	
Request an initiation of a rapid provisional funding algorithm.	This is a comment from the drug plans to inform pERC deliberations.
The trial excluded patients with prior BCMA-targeted therapies. **Question:** Is there sufficient evidence to support the sequencing of belantamab mafodotin with other BCMA-targeted therapies?	According to the clinical experts, although data are currently lacking, immunotherapies targeting BCMA work through mechanisms distinct from belantamab mafodotin, so resistance to 1 should not theoretically preclude responsiveness to the other. pERC noted that there was insufficient evidence available to inform the optimal sequencing of belantamab mafodotin with other BCMA-targeted therapies.
Care provision issues	
Belantamab mafodotin is supplied as 70 mg and 100 mg vials. It has relatively short stability. Dose reductions were also needed in the trial to manage side effects. These can result in drug wastage.	This is a comment from the drug plans to inform pERC deliberations.
System and economic issues	
The feasibility of adoption (budget impact) may need to be considered depending on the extent of uptake.	This is a comment from the drug plans to inform pERC deliberations.
There may be potential out-of-pocket eye care costs (e.g., eye exams, eye drops) that are not affordable for some patients. This, in turn, may impact the management of ocular side effects.	This is a comment from the drug plans to inform pERC deliberations.
There are confidential prices for carfilzomib, isatuximab, pomalidomide, and selinexor. Negotiations are ongoing for cilta-cel, elranatamab, and teclistamab.	This is a comment from the drug plans to inform pERC deliberations.

BVd = belantamab mafodotin plus bortezomib and dexamethasone; BPd = belantamab mafodotin plus pomalidomide and dexamethasone; CDA-AMC = Canada's Drug Agency; cilta-cel = ciltacabtagene autoleucel; DVd = daratumumab plus bortezomib and dexamethasone; IhKd = isatuximab plus carfilzomib plus dexamethasone; 4L = fourth line; Kd = carfilzomib plus dexamethasone; PAG = Provincial Advisory Group; pERC = pan-Canadian Oncology Drug Review Expert Review Committee; PFS = progression-free survival; PVd = pomalidomide plus bortezomib plus dexamethasone; SVd = selinexor plus bortezomib plus dexamethasone.

Clinical Evidence

Systematic Review

Description of Studies

The sponsor-conducted systematic literature review identified 1 pivotal, open-label, randomized trial (the DREAMM-7 trial; N = 494) that assessed the efficacy and safety of BVd relative to DVd in adult patients with relapsed or refractory multiple myeloma. The primary objective of the DREAMM-7 trial was to demonstrate the superiority of BVd compared to DVd in PFS. Key secondary objectives were to demonstrate superiority in OS, duration of response (DoR), and minimal residual disease (MRD) negativity. The trial enrolled patients

who had received at least 1 prior line of multiple myeloma therapy and had documented disease progression during or after their most recent treatment. Patients were enrolled in the trial across 142 centres in 20 countries, including 5 sites in Canada. In the DREAMM-7 trial, patients were randomized in a 1:1 ratio to receive BVd at the dose of 2.5 mg/kg on day 1 of every 21-day cycle intravenously, or DVd. The DREAMM-7 trial included a screening period, treatment period, and follow-up period.

Efficacy end points of interest to this review included PFS, OS, HRQoL measured by the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC QLQ-C30)'s Global Health Status (GHS) score, DoR, MRD negativity, overall response rate (ORR), complete response rate (CRR), and safety outcomes, including ocular AEs and serious adverse events (SAEs). The trial end points were analyzed using data from the cut-off date of October 2, 2023, and the database lock date of November 6, 2023, for IA1, and from the cut-off date of October 7, 2024, for IA2 or the prespecified primary PFS analysis.

In general, patient demographic and disease characteristics were well balanced between the BVd and DVd treatment groups. The mean age of patients was 64.5 years (standard deviation [SD] = 9.5 years) in the BVd group and 63.6 years (SD = 10.1 years) in the DVd group. Most patients had an Eastern Cooperative Oncology Group Performance Status (ECOG PS) score of 0 or 1 (96% in both groups), and an R-ISS score of I or II (95% and 94% in the BVd and DVd groups, respectively), with immunoglobulin G being the most common myeloma immunoglobulin. Of the 494 patients, 250 (51%) had received 1 prior line of therapy, 117 (24%) had received 2 prior lines of therapy, and 70 (14%) had received 3 prior lines of therapy. Additionally, 257 patients (52%) had prior exposure to lenalidomide, and 166 patients (34%) had disease that was refractory to lenalidomide. High-risk cytogenetic abnormalities were present in 67 patients (28%) in the BVd group and 69 patients (27%) in the DVd group, with t(4;14) and 17p13del being the most common high-risk cytogenetic abnormalities in both groups.

Efficacy Results

PFS per Independent Review Committee Assessment

At the time of IA1, using the October 2, 2023, data cut-off, the median duration of follow-up was 28.2 months. In the intent-to-treat (ITT) population, PFS events were reported for 91 patients (37%) in the BVd group and 158 patients (63%) in the DVd group. The median PFS was 36.6 months (95% CI, 28.4 months to not estimable) in the BVd group and 13.4 months (95% CI, 11.1 months to 17.5 months) in the DVd group, with a between-group hazard ratio (HR) of 0.41 (95% CI, 0.31 to 0.53; P < 0.00001) in favour of the BVd group. The KM-estimated probabilities of being alive or progression-free at 12 months and 18 months were 78.3% (95% CI, 72.2% to 83.2%) versus 53.3% (95% CI, 46.5% to 59.5%) and 68.8% (95% CI, 62.0% to 74.7%) versus 42.8% (95% CI, 36.2% to 49.2%) in the BVd and DVd groups, respectively.

PFS reached the predefined boundary for statistical significance at IA1, and, in accordance with the study protocol, was evaluated as an exploratory end point at the time of IA2. At the time of IA2, using the October 7, 2024, data cut-off, the median PFS was [redacted] in the BVd group and [redacted] in the DVd group. The KM-estimated probabilities of being alive and progression-free at 24 months and 36 months were [redacted] versus [redacted]

and versus , in the BVd and DVd groups, respectively.

The results of predefined exploratory subgroup analyses were consistent with the primary PFS analyses, including for those exposed or refractory to lenalidomide (HR = 0.33 [95% CI, 0.23 to 0.48] and HR = 0.37 [95% CI, 0.24 to 0.56], respectively), those with more than 1 prior line of therapy (HR = 0.33 [95% CI, 0.23 to 0.48]), those with high cytogenetic risk (HR = 0.36 [95% CI, 0.22 to 0.58]) and those categorized as R-ISS stage II or III (HR = 0.45 [95% CI, 0.32 to 0.64]). The results of all sensitivity analyses were consistent with the primary PFS analyses. The results of the PFS analyses per independent review committee (IRC) assessment were consistent with those from the investigator assessment.

OS per IRC Assessment

At the time of IA1, using the October 2, 2023, data cut-off, the median OS was not reached in either treatment group. OS data had reached 29% (141 of 494 participants) for overall maturity. Death was reported in 54 patients (22%) in the BVd group and 87 patients (35%) in the DVd group, with a between-group HR of 0.57 (95% CI, 0.40 to 0.80; P = 0.00049). At the time of IA1, the results for OS did not meet the significance criterion.

At the time of IA2, using the October 7, 2024, data cut-off, the median OS was not reached in either treatment group. Death was reported in 68 patients (28%) in the BVd group and 103 patients in the DVd group, with a between-group HR of 0.58 (95% CI, 0.43 to 0.79; P = 0.00023) in favour of BVd. At the time of IA2, OS data had reached 34.6% (171 of 494 patients) for overall maturity, and the significance criterion was met (P < 0.00112). The KM-estimated probabilities of being alive at 24 months and 36 months were 79.0% (95% CI, 73.2% to 83.7%) versus 67.4% (95% CI, 61.0% to 73.0%) and 71.4% (95% CI, 67.9% to 79.2%) versus 60.2% (95% CI, 53.6% to 66.2%) in the BVd and DVd groups, respectively.

Duration of Response

DoR was analyzed based on the restricted mean duration of response (RMDoR), using a nonparametric approach. RMDoR is a composite end point that integrates overall response data and PFS data, allowing cross-group comparison, and efficiently assesses the treatment effect related to tumour reductions. At the time of IA1, using the October 2, 2023, data cut-off, the RMDoR was 19.0 months (95% CI, 17.7 months to 20.4 months) in the BVd group, and 13.2 months (95% CI, 11.8 months to 14.6 months) in the DVd group, with a ratio of RMDoR of in favour of the BVd group.

At the time of IA1, using the October 2, 2023, data cut-off, the median DoR was 35.6 months (95% CI, 30.5 months to not estimable) in the BVD group and 17.8 months (95% CI, 13.8 months and 23.6 months) in the DVd group. At the time of IA2, using the October 7, 2024, data cut-off, the median DoR was 40.8 months (95% CI, 30.5 months to not estimable) in the BVd group and 17.8 months (95% CI, 13.8 months and 23.6 months) in the DVd group. The KM-estimated probabilities of maintaining response at 12 months and 36 months were versus and versus in the BVd and DVd groups, respectively.

Minimal Residual Disease

MRD is considered to be a biomarker that provides a reliable quantification of tumour burden, independent of the assay used.[19] At the time of IA1, using the October 2, 2023, data cut-off, MRD negativity analysis was considered exploratory because the OS results were not significant at the time of IA1. The proportion of patients who achieved MRD negativity by best response (complete response [CR] or stringent complete response [sCR]) was higher in the BVd group compared with the DVd group (24.7% versus 9.6%, respectively; $P < 0.00001$). Given that the IA2 analysis of OS reached statistical significance, the MRD negativity results from the IA1 primary analysis can be considered statistically significant due to the prespecified hierarchical testing of outcomes. At the time of IA2, using the October 7, 2024, data cut-off, MRD negativity rates by CR or sCR remained consistent with the IA1 results. The BVd group showed higher MRD negativity rates (25.1%) compared with the DVd group (10.4%).

Complete Response Rate

At the time of IA1, using the October 2, 2023, data cut-off, a greater proportion of patients in the BVd group (34.6%) compared with the DVd group (17.1%) achieved CR or sCR, with a between-group difference of 17.4% (95% CI, 8.6% to 26.1%).

Overall Response Rate

At the time of IA1, using the October 2, 2023, data cut-off, a greater proportion of patients in the BVd group (82.7%) compared with the DVd group (71.3%) had a confirmed partial response or better, with a between-group difference of 11.4% (95% CI, 2.6% to 20.1%).

EORTC QLQ-C30 Scores

GHS Domain

In the DREAMM-7 trial, HRQoL was assessed using the EORTC QLQ-C30. EORTC QLQ-C30 data reported in this section are from IA1, with the data cut-off date of October 2, 2023. EORTC QLQ-C30 GHS domain scores remained stable across both treatment groups over time. Both groups showed a slight mean deterioration in GHS scores between week 4 and week 43, after which scores stabilized and remained consistent throughout the treatment period. Between week 43 and week 100, 24% to 35% of patients in the BVd group experienced an improvement in GHS or QoL scores (a 10-point increase or greater). Small sample sizes at later time points limit the ability to interpret the results.

At week 43, for the GHS domain, patients in the BVd group experienced a mean change of [redacted] from baseline compared with a change of [redacted] in the DVd group, with a least squares (LS) mean difference between groups [redacted] At week 121, in the GHS score, patients in the DVd group experienced a mean change of [redacted] from baseline compared with a change of [redacted] in the DVd group, with an LS mean difference between groups [redacted]

Harms Results

In the DREAMM-7 trial, all patients in both groups experienced at least 1 AE. At the time of IA1, a higher proportion of patients in the BVd group experienced at least 1 SAE compared to the DVd group (50% versus 37%, respectively). The most common SAEs in the BVd and DVd groups were pneumonia (11% versus 4%,

respectively), COVID-19 (5% versus 4%, respectively), pyrexia (5% versus 4%, respectively), and COVID-19 pneumonia (93% in both groups). The IA2 data on SAEs were not available at the time of the submission to CDA-AMC. At the time of IA1 and IA2, a higher proportion of patients in the BVd group discontinued treatment due to AEs compared to the DVd group (31% versus 19%, and 32% versus 19%, respectively). At the time of IA1 and IA2, a higher proportion of patients in the BVd group experienced a dose interruption or delay of study treatment compared to the DVd group (94% versus 75%, and 95% versus 76%, respectively). The sponsor also noted dosing interruptions and/or dosing reductions were required to manage adverse reactions such as ocular adverse reactions. Adverse reactions with BVd, including ophthalmic examination findings, led to dose reductions of any component of therapy in 81% (n = 197) of patients in the DREAMM-7 trial. Also, the mean number of weeks between doses of belantamab mafodotin increased over the course of the trial: 4.78 weeks during the first 6 months; 6.80 weeks during months 6 to 12; and 10.91 weeks beyond 12 months of therapy. At the time of IA2, deaths were reported in 29% of patients in the BVd group and in 41% of patients in the DVd group. The causes of death were similar between groups, with the exception of those attributed to cancer. The majority of deaths in both groups were attributed to cancer, with 10% in the BVd group and 22% in the DVd group, primarily due to multiple myeloma.

Notable Harms

At the time of IA1 and IA2, a higher proportion of patients in the BVd group experienced at least 1 ocular AE of any grade compared to the DVd group (79% versus 29%, and [redacted] respectively). Blurred vision and dry eye were reported in more than half of the patients in this treatment group. Ocular AEs in the BVd group were more severe, with [redacted] classified as grade 3 or 4, while the majority in the DVd group were classified as grade 1 ([redacted]). At the time of IA2, treatment discontinuations due to ocular AEs were reported in [redacted] of patients in the BVd group, compared to none in the DVd group. Treatment modifications due to corneal AEs were more common in the BVd group, with 52% of patients experiencing ocular AEs having doses interrupted, delayed, or reduced, compared to only 2% in the DVd group. At the time of IA1, investigator-assessed corneal events and BVCA events, as evaluated by the Keratopathy and Visual Acuity (KVA) scale, were reported exclusively in patients in the BVd group. A total of 201 patients (83%) in the BVd group had an incidence of corneal events (overall KVA grade). The severity of the corneal events was high, with [redacted] of the 201 patients classified as grade 3 and [redacted] as grade 4. Most corneal events were managed through dose modifications, with 89% of affected patients having doses interrupted or delayed, and 31% experiencing dose reductions. The incidence of investigator-assessed BCVA events, as evaluated by the KVA scale, was [redacted] in the BVd group, with the majority of events classified as grade 2.

At the time of IA1 and IA2, a higher proportion of patients in the BVd group experienced thrombocytopenia compared to the DVd group (87% versus 65%, and 88% versus 65%, respectively). At the time of IA2, of the 212 patients in the BVd group and 160 patients in the DVd group who experienced thrombocytopenia, grade 3 and 4 thrombocytopenia were more frequent in the BVd group (83%) compared to the DVd group (71%). Grade 4 thrombocytopenia events were reported in 53% of patients receiving BVd, versus 33% of patients receiving DVd. In the DREAMM-7 trial, [redacted] of patients in the BVd group an [redacted]. At the time of IA2, despite the high incidence, few patients (5% or less) in either group experienced SAEs related to thrombocytopenia, and treatment discontinuation rates due to

thrombocytopenia were low [redacted] in the BVd group and [redacted] in the DVD group). Dose reductions and interruptions or delays were more common in the BVd group compared to the DVd group (43% versus 20% and 53% versus 39%, respectively). At the time of IA1, neutropenia events (regardless of grade) were reported in [redacted] of patients in the BVd group and [redacted] of patients in the DVd group. Grade 4 neutropenia events were more common in the BVd group ([redacted]) compared to the DVd group ([redacted]). A higher proportion of patients in the DVd group experienced infusion-related reactions ([redacted]) compared to the BVd group ([redacted]), with more than [redacted] of patients in both treatment groups having grade 2 events.

Critical Appraisal

Randomization was performed using appropriate methodology with adequate allocation concealment; randomization stratification was prespecified. Knowledge of the assigned treatment due to the open-label design of the trial could have led to bias in the reporting and measurement of subjective outcomes, including patient-reported outcomes (e.g., HRQoL) and subjective AEs. However, the extent and direction of bias due to treatment knowledge is uncertain. Based on the enrolled sample size, the study was powered to test its primary and key secondary end points. The statistical analysis methods appeared to be acceptable. Results for the primary outcome were based on a prespecified interim analysis (249 PFS events), which occurred at an 89% information fraction, relative to the planned final PFS analysis (280 PFS events). The OS data were immature at both interim analyses, and the median OS was not reached in either treatment group. Given that the study outcomes were based on interim analyses, there is a risk that the effect of BVd compared with DVd was overestimated; however, the existence and extent of any overestimation remains uncertain.[20-22] Patients were allowed to receive post-treatment anticancer medications after discontinuing study treatment, which could influence the assessment of OS. Subgroup analyses were prespecified and conducted only for PFS; however, there was no multiplicity control for the subgroup analyses. A large number of patients in the DREAMM-7 trial discontinued treatment, with fewer discontinuations (both monotherapy and combination) in the BVd group (66%) compared to the DVd group (78%), which may influence the interpretation of harms outcomes. The clinical experts consulted indicated that the main reasons for treatment discontinuation were as expected, and included disease progression and AEs, with ocular toxicity being the main concern associated with belantamab mafodotin treatment. They also noted that several strategies have been developed to manage the ocular toxicity of belantamab mafodotin and prevent permanent drug discontinuation. No strong conclusions could be drawn about the effect of BVd compared with DVd on HRQoL due to an increased risk of type I error and a high risk of attrition bias, particularly at longer follow-up.

According to the clinical experts consulted by CDA-AMC for this review, the patient population in the DREAMM-7 trial generally reflected patients in clinical practice in this setting. Patients were eligible for inclusion in the DREAMM-7 trial if they met 1 of the measurability parameters, including having a serum M protein concentration of 0.5 g/dL or higher. The clinical experts noted that some patients with serum M protein concentration below 0.5 g/dL would still be eligible for the treatment with BVd in clinical practice. The clinical experts indicated that, aside from refractoriness to daratumumab as a comparator in this trial, all other exclusion criteria were consistent with clinical practice. According to the clinical experts consulted, the demographic and disease characteristics of the DREAMM-7 trial population were reflective of patients living in Canada with refractory or relapsed multiple myeloma. The mean age of patients in the DREAMM-7 trial

was 64 years, with clinical experts noting that, in the real-world setting, patients eligible for transplant would likely be younger, while patients with relapsed or refractory disease would typically be older. Most patients in the DREAMM-7 trial had an ECOG PS score of 0 or 1, and an R-ISS score of I or II. The clinical experts consulted indicated that this would be reflective of clinical practice in the second-line setting, but not in later relapse. Only 34% of patients in the trial had disease that was refractory to lenalidomide. The clinical experts indicated that, in the real-world setting, the proportion of patients whose disease is refractory to lenalidomide as a second-line or later therapy would be higher, as it is commonly used as maintenance therapy after experiencing a response to initial treatment. They also noted that these patients may have a poorer response to second-line or third-line treatments compared to those whose disease is not refractory to lenalidomide.

Results of GRADE Assessments

Table 3 presents the GRADE summary of findings for BVd versus DVd.

Table 3: Summary of Findings for BVd vs. DVd for Patients With Relapsed or Refractory Multiple Myeloma

Outcome and follow-up	Patients (DREAMM-7 trial), N	Relative effect (95% CI)	Absolute effects (95% CI)			Certainty	What happens
			DVd	BVd	Difference		
Progression-free survival							
Probability of being alive and progression-free at 12 months Median follow-up: 40.2 months[a,b]	494 (1 RCT)	NA				High[c]	BVd results in a clinically important higher probability of being alive and progression-free at 12 months when compared with DVd.
Probability of being alive and progression-free at 36 months Median follow-up: 40.2 months[a,b]	494 (1 RCT)	NA				High[c]	BVd results in a clinically important higher probability of being alive and progression-free at 36 months when compared with DVd.
							
Probability of being alive at 12 months Median follow-up: 40.2 months[a,d]	494 (1 RCT)	NA				Low[e]	BVd may result in a clinically important higher probability of being alive at 12 months when compared with DVd.

Outcome and follow-up	Patients (DREAMM-7 trial), N	Relative effect (95% CI)	Absolute effects (95% CI)			Certainty	What happens
			DVd	BVd	Difference		
Probability of being alive at 36 months Median follow-up: 40.2 months[a,d]	494 (1 RCT)	NA				Moderate[e]	BVd likely results in a clinically important higher probability of being alive at 36 months when compared with DVd.
HRQoL (EORTC QLQ-C30 GHS or QoL score)							
GHS or QoL score, change from baseline (95% CI) Median follow-up: 148 weeks[f]	494 (1 RCT)	NA	EORTC QLQ-C30 GHS domain scores[j] remained stable across both treatment groups over time. Both groups showed a slight mean deterioration in GHS scores between week 4 and week 43, after which scores stabilized and remained consistent throughout the treatment period.			Very low[g,h]	The evidence is very uncertain about the effect of BVd on GHS or QoL when compared with DVd.
Harms							
Proportion of patients with ocular adverse events Median follow-up: 40.2 months[a]	488 (1 RCT)	NR				High[i]	BVd results in an increase in ocular adverse events when compared with DVd.
Proportion of patients with serious adverse events Median follow-up: 28.2 months[f]	488 (1 RCT)	NR				Moderate[j]	BVd likely results in a clinically meaningful increase in serious adverse events when compared with DVd.

BVd = belantamab mafodotin plus bortezomib and dexamethasone; CDA-AMC = Canada's Drug Agency; CI = confidence interval; DVd = daratumumab plus bortezomib and dexamethasone; EORTC QLQ-C30 = European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30; GHS = Global Health Status; HRQoL = health-related quality of life; IA1 = first interim analysis; IA2 = second interim analysis, KM = Kaplan-Meier; MID = minimal important difference; NA = not applicable; NR = not reported; OS = overall survival; PFS = progression-free survival; QoL = quality of life; RCT = randomized controlled trial; vs. = versus.

Notes: Study limitations (which refer to internal validity or risk of bias), inconsistency across studies, indirectness, imprecision of effects, and publication bias were considered when assessing the certainty of the evidence. All serious concerns in these domains that led to the rating down of the level of certainty are documented in the table footnotes.

Estimates of the absolute between-group differences were calculated using the KM method at CDA-AMC's request.

[a]IA2, using the October 7, 2024, data cut-off.

[b]PFS reached the predefined boundary for statistical significance at IA1, and, in accordance with the study protocol, was evaluated as an exploratory end point at the time of IA2.

[c]An empirically derived MID was not identified for the between-group difference for this outcome. A difference of 10% (100 per 1,000) between the groups was identified by the clinical experts consulted by CDA-AMC as a threshold of clinical importance for this outcome.

[d]At the time of IA2, using the October 7, 2024, data cut-off, OS met the significance criterion of $P < 0.00112$.

[e]Rated down 2 levels for serious study limitations. Results were based on an interim analysis, so there was potential for the effect to be overestimated, and the OS data were immature. The median OS was not reached in either treatment group. There is a risk of bias due to confounding as a result of transition of patients to subsequent

treatment following progression. There is no established between-group MID for OS, and the clinical experts considered that a 5% (50 per 1,000) difference between groups in the probability of patients being alive could be considered a threshold of clinical importance. The point estimate suggests a clinically important benefit while the lower boundary of the 95% CI suggests little to no difference.

[f]IA1, using the October 3, 2023, data cut-off.

[g]Rated down 2 levels for very serious risk of bias due to a relatively high amount of missing data (direction unclear) over time, and due to assessor knowledge of treatment assignment. Rated down 2 levels for very serious imprecision; CIs were wide, especially at later time points, and included potential for benefit and harm. As no single time point was of highest importance, the trend over time was appraised.

[h]The statistical testing for HRQoL was not adjusted for multiplicity in the DREAMM-7 trial and should be considered as supportive evidence.

[i]There is no established MID for this outcome and clinical experts consulted by CDA-AMC could not provide a threshold of important difference. In the absence of a known threshold, the null was used.

[j]A large number of patients in the DREAMM-7 trial discontinued treatment, with fewer discontinuations (both monotherapy and combination) in the BVd group (66%) compared to the DVd group (78%), and the BVd group had longer exposure to the study drug than the DVd group. Rated down 1 level for imprecision: An empirically derived MID was not identified for the between-group difference for this outcome. Based on the MID identified by clinical experts (a difference of 10% between the groups), the 95% CI for the between-group difference crossed the MID threshold.

Source: Clinical Study Reports for the DREAMM-7 trial, 2024 and 2025.

Long-Term Extension Studies

No long-term extension studies were identified by the sponsor.

Indirect Comparisons

Description of Studies

In the absence of direct comparative data for belantamab mafodotin versus comparators used in clinical practice aside from daratumumab, 1 report that included ITCs was supplied by the sponsor. The primary objective of the ITC was to assess the comparative efficacy of BVd in a population matching the ITT population of the DREAMM-7 trial, relative to other comparators for which PFS data were available. The secondary objectives of the network meta-analysis (NMA) were to assess the comparative efficacy of BVd in a population of patients with prior exposure to lenalidomide, based on available data for OS and ORR, and in a population of patients whose disease was refractory to lenalidomide, relative to comparators for which data were available for PFS and ORR. The following outcomes were reported to address the objectives of the NMA: PFS, OS, and ORR for the ITT population, and PFS and ORR for the populations with prior exposure to lenalidomide and with disease that was refractory to lenalidomide.

Efficacy Results

The NMA results presented in this report were limited to comparisons between BVd and regimens relevant to Canada for this submission:

- IhKd
- hKd
- PVd
- SVd
- DVd
- Vd
- Kd.

Progression-Free Survival

In the ITT population, results from the fixed-effects models indicated that BVd demonstrated a favourable improvement in PFS compared with all 7 comparators, with HRs ranging from 0.13 (95% credible interval [CrI], 0.09 to 0.18) versus Vd to 0.42 (95% CrI, 0.26 to 0.69) versus IhKd. The results from the corresponding random-effects model showed a favourable improvement in PFS for BVd compared with DVd, hKd, PVd, SVd, and Vd, with HRs ranging from 0.13 (95% CrI, 0.06 to 0.28) versus Vd to 0.41 (95% CrI, 0.22 to 0.75) versus DVd. However, the evidence regarding PFS between BVd and IhKd, as well as Kd, was insufficient to show a difference between groups. The point estimates were comparable across both the fixed-effects and random-effects models.

Among patients with prior exposure to lenalidomide, results from the fixed-effects models found that BVd demonstrated a favourable improvement in PFS versus all comparators. The results from the corresponding random-effects model showed a favourable improvement in PFS for BVd versus DVd, hKd, and Vd; evidence versus other comparators (IhKd, Kd, PVd, and SVd) was insufficient to show a difference between groups. Among patients with disease that was refractory to lenalidomide, results from the fixed-effects models found that BVd demonstrated a favourable improvement in PFS versus all comparators. The results from the corresponding random-effects model showed a favourable improvement in PFS with BVd versus DVd, hKd, and Vd; evidence versus other comparators (IhKd, Kd, and PVd) was insufficient to show a difference between groups.

Overall Survival

In the ITT population, results from the fixed-effects models indicated that BVd demonstrated a favourable improvement in OS compared with DVd, hKd, PVd, SVd, and Vd, with HRs ranging from 0.39 (95% CrI, 0.26 to 0.59) compared to Vd to 0.57 (95% CrI, 0.40 to 0.80) compared to DVd. However, results from the corresponding random-effects model for OS showed that the evidence for a difference between BVd and other comparators was insufficient to show a difference between groups. No secondary or subgroup analyses for OS were conducted or reported in the sponsor-submitted NMA.

Overall Response Rate

In the ITT population, results from fixed-effects models found that BVd demonstrated a favourable improvement in ORR compared with DVd, hKd, PVd, SVd, and Vd, with ORs ranging from 1.94 (95% CrI, 1.27 to 2.99) compared to DVd to 5.99 (95% CrI, 3.41 to 10.64) compared to Vd. The results from the corresponding random-effects model for PFS showed that BVd demonstrated a favourable improvement in ORR compared with Vd alone; evidence for other comparisons was insufficient to show a difference between groups. The point estimates were comparable across the fixed and random-effects models. Among patients with prior exposure to lenalidomide, results from fixed-effects models found that BVd demonstrated a favourable improvement in ORR compared with DVd, hKd, hkDd, PVd, SVd, and Vd. The results from the corresponding random-effects model showed a favourable improvement in ORR versus Vd alone; evidence for the other comparisons was insufficient to show a difference between groups. Among patients with disease that was refractory to lenalidomide, results from fixed-effects models found that BVd demonstrated a favourable improvement in ORR compared with SVd and Vd. The results from the corresponding

random-effects model showed a favourable improvement in ORR versus Vd alone; evidence for the other comparisons was insufficient to show a difference between groups. No subgroup analyses for ORR were conducted or reported in the sponsor-submitted NMA.

Harms Results

No comparative effect estimates for harms were provided.

Critical Appraisal

Overall, the systematic literature review conducted to identify potentially relevant studies for the ITC was methodologically robust. The clinical experts indicated that the most relevant comparators included in the NMA were IhKd for patients with multiple myeloma who are eligible for transplant, and SVd for patients with multiple myeloma who are not eligible for transplant. The clinical experts also noted that clinicians would prefer to prescribe IhKd over hKd or Kd to patients in these settings who are not eligible for transplant. Additionally, the clinical experts noted that cyclophosphamide plus bortezomib and dexamethasone (CyVd), cyclophosphamide plus high-dose carfilzomib and dexamethasone (CyhKd), panobinostat plus bortezomib and dexamethasone (PanoVd), high-dose carfilzomib plus daratumumab and dexamethasone (hkDd), and elotuzumab plus bortezomib and dexamethasone (EVd), which were included in this NMA, are not relevant to Canadian clinical practice for relapsed or refractory multiple myeloma.

Several important sources of heterogeneity were noted across the included trials in terms of study design (e.g., crossover, placebo as a comparator, inclusion of phase II trials, time during which trials were undertaken, dosing regimens). Notably, there was considerable variation across studies in the number of prior lines of therapy, prior lenalidomide and IMiD exposures, and high cytogenic risk profile. The observed heterogeneity could have introduced bias that was not adequately accounted for, leading to uncertainty in the analysis. This uncertainty is reflected in the wide CrIs of the comparisons of treatment effects, particularly for ORR and OS. Several important disease-specific characteristics were not reported in some studies within the network, which limits the ability to assess heterogeneity between the studies. While the definitions of end points were similar across the trials, there was considerable variation in the duration of follow-up, and the censoring rules across the PFS analyses were not specified, which may represent a potential source of heterogeneity. The magnitude of the treatment effects appeared consistent across both subgroups (lenalidomide-exposed and refractory); however, the 95% CrIs were wide given the smaller sample sizes, leading to greater uncertainty in the resulting treatment effects. The studies included in the secondary and subgroup analyses for PFS differed from those in the full network, meaning the subgroup analyses did not directly compare the same network as the full population analyses. Narrowing the network could potentially impact the results. The studies within networks included a mix of patients in multiple lines of therapy, which may introduce bias, as patients in earlier or later lines of therapies can influence each network differently. According to the clinical experts consulted by CDA-AMC, patients in earlier lines of therapy are likely to have better outcomes compared with patients in later lines of therapy. There were no closed loops in the network to allow for consistency to be assessed.

Bayesian fixed methods were used as a base-case analysis, with a random-effects model for the exploratory analysis. However, if heterogeneity is present, the CrIs of the fixed-effects model may be narrower and less

conservative, potentially underestimating the uncertainty from between-study variation. The assumptions of the fixed-effects model (e.g., a single true effect size, or no between-study heterogeneity) are likely less realistic than those of the random-effects model (e.g., assuming variation in effect sizes across studies). Secondary analyses were performed for the patient populations with prior lenalidomide exposure and with disease that is refractory to lenalidomide, as it is expected that most patients living in Canada will receive a regimen based on lenalidomide in the first line, with subsequent therapies tailored to the patient's initial response. Some trials had concerns for risk of bias; this assessment was undertaken at the study level, which ignores that risks of bias may vary by effect estimates. It may not be assured that randomization was maintained within subgroups (unless these were stratification factors in contributing trials). Additionally, no patient-reported data for QoL, which was considered an important end point for this review, were evaluated. Furthermore, no comparative effect estimates for harms were provided. These limitations preclude a comprehensive assessment of the balance of benefits and harms and must be considered when drawing conclusions from the NMA results.

Studies Addressing Gaps in the Evidence From the Systematic Review

No studies addressing gaps in the pivotal and RCT evidence were identified by the sponsor.

Economic Evidence

Cost and Cost-Effectiveness

- Belantamab mafodotin is available as powder for solution for injection (50 mg/mL). At the submitted price of $278.00 per mg (available as 70 mg or 100 mg single-use vials), the 28-day cycle cost of belantamab mafodotin is expected to be $74,133 per patient, based on the Health Canada–recommended dosage.
- Clinical efficacy in the economic analysis was derived from the DREAMM-7 trial, which compared BVd with DVd. Evidence from the DREAMM-7 trial suggested that BVd likely results in a clinically important improvement in PFS and OS compared with DVd for patients with multiple myeloma, although OS data remain immature and the effects of BVd on OS beyond 40 months are uncertain. For the comparison between BVd and remaining comparators, clinical efficacy was derived from a sponsor-submitted ITC, which suggested that BVd may result in a favourable PFS or OS benefit versus comparators among patients with multiple myeloma. However, limitations such as considerable heterogeneity among included studies were identified by CDA-AMC, suggesting that the magnitude of benefit could not be determined.
- The results of the CDA-AMC base case suggest the following:
  - The following treatments are on the cost-effectiveness frontier: Vd, PVd, Kd, and BVd. Notably, DVd is not included on the frontier, as it was dominated by Kd in the analysis.
  - BVd is associated with higher total costs to the health care system than Kd (incremental costs = $1,649,889), primarily driven by increased drug acquisition costs associated with BVd.

    - BVd is associated with a gain of 1.27 life-years compared to Kd and is anticipated to improve HRQoL based on time in improved health states, with BVd resulting in a gain of 0.94 QALYs compared to Kd.
    - The ICER of BVd compared to Kd is $1,758,284 per QALY gained in the CDA-AMC base case. The estimated ICER was highly sensitive to the predicted OS benefit and drug acquisition costs of BVd, and more than 75% of the incremental benefit was gained in the extrapolated period (i.e., after 40 months). In the absence of comparative evidence beyond this time point and uncertainty in the comparative clinical evidence, the QALYs gained for patients receiving BVd predicted in the CDA-AMC base case are highly uncertain and may be overestimated. Additional price reductions may therefore be required.
- CDA-AMC estimates that the budget impact of reimbursing BVd for the treatment of relapsed or refractory multiple myeloma in patients who have received at least 1 prior line of therapy will be approximately $940 million over the first 3 years of reimbursement compared to the amount currently spent on comparators, with an estimated expenditure of $1.3 billion on BVd over this period. The actual budget impact of reimbursing BVd will depend on BVd dosing assumptions, drug utilization, and distribution of subsequent therapies. The incremental budget impact of BVd is expected to be greater than $40 million in years 1, 2, and 3 of reimbursement. Given the substantial difference between the sponsor's and CDA-AMC's estimates, and the resulting uncertainty in the projected impact, these issues must be addressed to ensure the feasibility of adoption.

pERC Information

Members of the Committee

Dr. Catherine Moltzan (Chair), Dr. Kelvin Chan (Vice Chair), Dr. Phillip Blanchette, Dr. Matthew Cheung, Dr. Michael Crump, Annette Cyr, Dr. Jennifer Fishman, Dr. Jason Hart, Terry Hawrysh, Dr. Yoo-Joung Ko, Dr. Aly-Khan Lalani, Amy Peasgood, Dr. Anca Prica, Dr. Adam Raymakers, Dr. Patricia Tang, Dr. Pierre Villeneuve, and Danica Wasney.

Meeting date: June 11, 2025

Regrets: None

Conflicts of interest: None

pERC subcommittee meeting date: July 25, 2025

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Drugs. Health Technologies and Systems. Médicaments, technologies de la santé et systèmes.

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Questions or requests for information about this report can be directed to Requests@CDA-AMC.ca.