

Reimbursement Recommendation

Belantamab Mafodotin, Pomalidomide, Dexamethasone

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

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 pomalidomide 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, including lenalidomide, if certain conditions are met.

Which Patients Are Eligible for Coverage?

Blenrep in combination with pomalidomide and dexamethasone should only be covered to treat adults with relapsed or refractory multiple myeloma who are in relatively good health and have already tried at least 1 other lenalidomide-containing regimen for this disease. Blenrep in combination with pomalidomide and dexamethasone should not be reimbursed in patients who were previously treated with an anti-BCMA therapy or pomalidomide.

What Are the Conditions for Reimbursement?

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

Why Did CDA-AMC Make This Recommendation?

- Evidence from a clinical trial demonstrated that Blenrep in combination with pomalidomide and dexamethasone may delay disease progression and prolong life in adults with relapsed or refractory multiple myeloma compared to bortezomib in combination with pomalidomide and dexamethasone.
- Blenrep meets some patient needs as it is an alternative treatment option that may offer disease control benefits.
- 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 \$485 million over the next 3 years. However, the actual budget impact is uncertain and will depend on several factors, including real-world dosing patterns, the extent of uptake across jurisdictions, and the distribution of subsequent therapies in the treatment pathway.

Summary

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 were diagnosed with multiple myeloma.

Unmet Needs in Multiple Myeloma

Multiple myeloma is an incurable disease, and patients commonly experience relapse or have disease that 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.

How Much Does Blenrep Cost?

Treatment with Blenrep in combination with pomalidomide and dexamethasone is expected to cost approximately \$58,249 per 28 days per patient in the first cycle, and \$49,909 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 pomalidomide and dexamethasone for the treatment of adults with relapsed or refractory multiple myeloma who have received at least 1 prior line of therapy, including lenalidomide, only if the conditions listed in [Table 1](#) are met.

Rationale for the Recommendation

Evidence from an ongoing phase III open-label, randomized controlled trial (RCT) (DREAMM-8; N = 302) demonstrated that treatment with belantamab mafodotin in combination with pomalidomide and dexamethasone (BPd) likely results in an added clinical benefit compared to bortezomib in combination with pomalidomide and dexamethasone (PVd) for adults with multiple myeloma who have received at least 1 prior line of a lenalidomide-containing treatment.

At the time of the interim analysis, with a median follow-up of 21.8 months, median progression-free survival (PFS) (the primary outcome) had not been reached in the BPd arm versus 12.7 months (95% confidence interval [CI], 9.1 to 18.5) in the PVd arm. The estimated hazard ratio (HR) for PFS was 0.52 (95% CI, 0.37 to 0.73) in favour of BPd. [REDACTED] sensitivity or supplemental analyses yielded consistent results with the primary PFS analysis, with HRs ranging from [REDACTED]. Similarly, the PFS probability rates were higher with BPd than with PVd at 12 months (71% versus 51%; risk difference [RD] = [REDACTED]) and 18 months ([REDACTED] versus [REDACTED]; [REDACTED]). The median overall survival (OS) had not been reached in either treatment arm. However, the OS probability rate was numerically higher with BPd than with PVd at 12 months (83% versus 76%; RD = [REDACTED]) and 18 months ([REDACTED] versus [REDACTED]; RD = [REDACTED]).

Patients identified a need for new effective treatment options that prolong survival, delay disease progression, improve quality of life, minimize the number or frequency of hospital visits for treatment, and have a manageable toxicity profile. Based on the evidence reviewed, pERC concluded that BPd met some patients' needs, such as improving PFS and providing an alternative treatment option. pERC agreed with the clinical experts that ocular toxicities with belantamab therapy can negatively impact quality of life. However, pERC observed that the health-related quality of life (HRQoL) outcomes were inconclusive and noted that ocular adverse events (AEs) were significantly more frequent and severe with BPd than with PVd, often requiring more frequent treatment modifications in patients receiving BPd. pERC agreed with the clinical experts that the frequency and severity of ocular AEs with BPd is significant, though they appear to be largely reversible and may be manageable with careful monitoring, dose modification, and supportive care. Additionally, pERC noted that the relative impact of BPd compared to other treatment options remains uncertain with respect to HRQoL and toxicities.

Using the sponsor-submitted price for belantamab mafodotin and publicly listed prices for all other drugs, the incremental cost-effectiveness ratio (ICER) for BPd was \$2,661,253 per quality-adjusted life-year (QALY) gained compared with carfilzomib in combination with dexamethasone (Kd). At this ICER, BPd 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 therapy, including lenalidomide. A price reduction is required for the cost of belantamab mafodotin as part of the BPd 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 BPd should be initiated in patients with relapsed or refractory multiple myeloma who meet all the following criteria: 1.1. 18 years of age or older 1.2. have received at least 1 prior line of treatment for multiple myeloma including a lenalidomide-containing regimen 1.3. have disease progression during or after their most recent treatment.	Evidence from the DREAMM-8 trial demonstrated that treatment with BPd likely resulted in a clinical benefit in patients with these characteristics.	—
2. Patients should not have had a previous treatment with either of the following: 2.1. anti-BCMA therapy 2.2. pomalidomide.	The DREAMM-8 trial excluded patients with prior anti-BCMA therapy, and 1 patient in the study (in the PVd arm) had received a prior treatment with pomalidomide. Thus, no evidence was presented regarding the safety and efficacy of BPd in patients with multiple myeloma who had previously been treated with anti-BCMA therapy or pomalidomide.	pERC acknowledged the clinical experts' input that immunotherapies targeting BCMA work through distinct mechanisms from belantamab mafodotin and resistance to 1 anti-BCMA therapy does not imply a lack of responsiveness to the other. However, pERC noted that the degree of benefit of BPd after anti-BCMA or pomalidomide therapy in patients with multiple myeloma is unknown and not supported by data.
3. Patients should have a good performance status.	Most participants in the DREAMM-8 trial had an ECOG PS of 0 or 1, with about 3% of the study population having an ECOG PS of 2.	pERC agreed with the clinical experts that deciding patient suitability for treatment with BPd based on ECOG PS should be at the discretion of the treating clinician.
Discontinuation		
4. Treatment with BPd should be discontinued on the occurrence of any of the following: 4.1. objective disease progression 4.2. unacceptable toxicity.	In the DREAMM-8 trial, treatment with BPd was discontinued on disease progression or unacceptable toxicity.	—
5. If 1 component of BPd (i.e., belantamab mafodotin or pomalidomide plus dexamethasone) is discontinued permanently because of tolerability	This condition reflects the treatment discontinuation criteria used in the DREAMM-8 trial.	—

Reimbursement condition	Reason	Implementation guidance
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.		
Prescribing		
6. BPd should be prescribed under the care of clinicians with expertise in the diagnosis and management of patients with multiple myeloma.	This condition is meant to ensure that BPd 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 toxicities associated with belantamab mafodotin, BPd should only be prescribed for use in a setting with access to facilities and clinician specialists to monitor and manage the ocular toxicities. Additionally, the product monograph recommends that ophthalmic exams are conducted before each dose of BPd, with modifications to the frequency of monitoring as clinically indicated.
Pricing		
7. A reduction in price.	The ICER for BPd is \$2,661,253 when compared with Kd. Price reductions in excess of 90% will be required for the cost of belantamab mafodotin as part of the BPd 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 BPd must be addressed.	At the submitted price, the incremental budget impact of BPd is expected to be greater than \$40 million in years 1, 2, and 3.	—
9. The feasibility of adoption of BPd 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 the sponsor's estimate and the CDA-AMC estimate.	—
10. The organizational feasibility of assessing and managing ocular toxicities associated with belantamab mafodotin should be addressed.	Managing ocular toxicities 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 toxicities during treatment and regular monitoring of	—

Reimbursement condition	Reason	Implementation guidance
	ocular toxicities by an ophthalmologist or an optometrist are needed.	

BPd = belantamab mafodotin in combination with pomalidomide with dexamethasone; CDA-AMC = Canada's Drug Agency; ECOG PS = Eastern Cooperative Oncology Group Performance Status; ICER = incremental cost-effectiveness ratio; Kd = carfilzomib in combination with dexamethasone; pERC = pan-Canadian Oncology Drug Review Expert Review Committee; PVd = pomalidomide in combination with bortezomib and dexamethasone; QALY = quality-adjusted life-year.

Discussion Points

- **Unmet needs:** pERC noted that multiple myeloma is an incurable disease, and patients commonly have disease that relapses or eventually becomes refractory to treatment. pERC discussed the unmet needs identified by the patients and clinicians, including new effective therapies for patients with multiple myeloma who have disease that has progressed on prior drugs, including lenalidomide. Based on the evidence reviewed, pERC concluded that BPd may meet some of the unmet needs by delaying disease progression and prolonging survival.
- **Certainty of evidence:** pERC noted that the data for the interim OS analyses were immature, and the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) assessment indicated a low certainty in the evidence regarding the OS probability rate benefit of BPd compared to PVd at 12 and 18 months. However, the GRADE assessment indicated with moderate certainty that treatment with BPd likely results in a clinically meaningful improvement in PFS at 12 and 18 months. pERC acknowledged that PFS is generally considered a valid surrogate end point for OS in patients with multiple myeloma; however, results from analyses using matured OS data are warranted to address the uncertainty regarding the OS benefit of BPd in patients with multiple myeloma.
- **Adverse effects:** pERC discussed the safety profile of BPd, acknowledging that patients' expressed a need for treatments associated with fewer side effects. pERC noted that ocular AEs are the major side effects associated with belantamab mafodotin and occurred at a significantly more frequent rate with BPd than PVd (89% versus 30%) in the DREAMM-8 trial, despite measures taken by the investigators to reduce the incidence of ocular AEs. pERC acknowledged the clinical experts' input that the side effects of belantamab mafodotin are generally manageable. However, pERC noted that the clinical resources, monitoring, and dose modifications necessary to manage the ocular AEs associated with belantamab mafodotin are not routinely used in the care of patients with multiple myeloma. pERC noted that measures to manage ocular AEs and prevent permanent drug discontinuation, including dose reductions and treatment delays, regular monitoring for ocular AEs, and professional support from ophthalmologists and/or optometrists are needed to safely use BPd in the treatment of patients with multiple myeloma.
- **HRQoL:** pERC noted that patients and clinicians identified improvement in quality of life as an important outcome and treatment goal for patients with multiple myeloma. pERC concluded that the evidence on HRQoL from the DREAMM-8 trial had significant uncertainty due to limitations and was insufficient to determine whether BPd might result in a clinically meaningful improvement in HRQoL compared to PVd.

- **Indirect evidence:** pERC discussed the indirect evidence from the indirect treatment comparison (ITC) submitted by the sponsor, which compared BPd with several comparator therapies through a network meta-analysis (NMA). pERC noted that the results from NMA suggested that in patients with multiple myeloma who had received at least 1 prior lenalidomide-containing therapy, treatment with BPd may result in a more favourable PFS benefit compared with high-dose carfilzomib plus dexamethasone (hKD), selinexor plus bortezomib and dexamethasone (SVd), and bortezomib plus dexamethasone (Vd). However, pERC was unable to draw any conclusions on the comparative efficacy of BPd versus any of the comparators due to limitations with the NMA, such as the significant heterogeneity in patient demographics and disease characteristics among the included studies. The NMA did not assess safety or HRQoL outcomes.
- **Place in therapy:** pERC discussed the place in therapy of BPd, given alternative treatments, and determined that it was necessary to clarify its place in therapy, particularly with regards to proteasome inhibitors, which are required before pomalidomide in some provinces. The benefits in later lines of therapy after a proteasome inhibitor is uncertain.
- **Economic considerations:** pERC expressed significant concerns regarding the cost-effectiveness of BPd. The CDA-AMC base case estimated an ICER of \$2,661,253 per QALY gained for BPd 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 \$485 million, with total spending on BPd projected to reach \$680 million 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 BPd, 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 the ocular toxicities associated with belantamab mafodotin and noted that implementation of a reimbursement recommendation for BPd 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 and cooling masks during infusions to alleviate symptoms). pERC also noted that public coverage for required eye care to support using BPd 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 thorough eye exams by ophthalmologists or optometrists, including slit lamp evaluation and best corrected visual acuity assessment, artificial tears, and potentially prescription lenses to manage ocular toxicities. Ensuring comprehensive coverage for these services is crucial to mitigate potential financial burden

on patients and maintain their quality of life 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:** BPd was a pre-Notice of Compliance 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). During the meeting, the subcommittee discussed the serious warning included in the product monograph about safety concerns related to ocular toxicities. The monitoring requirements related to adverse reactions and 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 an incurable, progressive, malignant plasma cell cancer, characterized by the abnormal proliferation of clonal B cells in the bone marrow and overproduction of the abnormal immunoglobulin M-protein. Multiple myeloma accounts for approximately 1% of all cancers and about 10% of all hematologic malignancies. Multiple myeloma is more common in males than females and about twice as common in Black people compared to those who are white or Asian. The incidence of multiple myeloma is related to older age. In 32,065 patients with multiple myeloma in Canada between 1992 and 2010, approximately 80% were diagnosed at the age of 60 years or older. It is estimated that 4,100 new cases of multiple myeloma were diagnosed in 2024 in Canada. The 5-year net survival for patients with multiple myeloma in Canada is approximately 50%. The clinical course of multiple myeloma, although variable, typically includes periods of treatment and remission separated by inevitable relapses, with the duration of response to treatment decreasing with each subsequent line of therapy. Relapsed or refractory multiple myeloma is defined as multiple myeloma that is nonresponsive to therapy or has progressed within 60 days of the last line of treatment in patients who previously achieved a minimal response or better.

Autologous stem cell transplant (ASCT) is the standard of care for patients with newly diagnosed multiple myeloma if they are transplant eligible. Patients who are ineligible for ASCT are typically treated with a combination of immunomodulatory drugs, proteasome inhibitors, and monoclonal antibodies. Lenalidomide is used as part of the first-line therapy for newly diagnosed multiple myeloma (regardless of ASCT eligibility) by the International Myeloma Working Group (IMWG) and the Canadian Myeloma Research Group Consensus Guideline Consortium due to the OS benefits seen in clinical trials. Treatment choice in relapsed or refractory multiple myeloma is individualized and multifactorial, taking into consideration prior treatment history and response, timing and aggressiveness of the relapse, patient factors (e.g., performance status, age, frailty, and comorbidities), personal preferences, and jurisdictional funding and rules around reimbursement. The general strategy for treatment beyond the first line includes the use of a drug that the patient has either not been exposed to previously or demonstrated sensitivity to in the treatment regimen. Based on the IMWG

recommendations, for patients whose disease is not refractory to lenalidomide, the preferred options for the second line are daratumumab, lenalidomide, and dexamethasone (DRd) or a combination of carfilzomib, lenalidomide, and dexamethasone, though alternatives are available.

Belantamab mafodotin is a humanized, afucosylated, BCMA-targeted antibody-drug conjugate approved by Health Canada in combination with pomalidomide and dexamethasone for the treatment of adults with relapsed or refractory multiple myeloma who have received at least 1 prior line of therapy including lenalidomide. It is available as powder for solution for infusion. As described in the product monograph, the recommended starting dose schedule for BPd is as follows: cycle 1: 2.5 mg/kg administered once; cycle 2 and onward: 1.9 mg/kg administered once every 4 weeks 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 study (DREAMM-8) in patients with relapsed or refractory multiple myeloma; 1 ITC; and 1 phase I/II, single-arm, open-label study (ALGONQUIN)
- patients' perspectives gathered by 1 patient group, Myeloma Canada
- input from the public drug plans that participate in the reimbursement review process
- 3 clinical specialists with expertise diagnosing and treating patients with multiple myeloma
- input from 2 clinician group(s), 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

- One patient group, Myeloma Canada, submitted input for this review via a survey (N = 100 completed surveys).
- Patients identified infections as the most important symptom to control, followed by kidney problems, mobility, and pain. The daily activities they noted as the most impacted by their disease were ability to travel and work, while the most impacted specific aspects of quality of life were interruptions to life goals or accomplishments and loss of sexual desire.
- The outcomes of most interest to patients were prolonged life expectancy, improved quality of life, and survival without progression of their disease. Various ocular side effects (e.g., eye pain and/or irritation, blurred vision, foreign body sensation, dry eyes) and infections were identified as the worst tolerability issues among 89 patients eligible to receive BPd and the 7 patients who had been treated with BPd.

- The key toxicities of concern identified from the patient input were ocular harms and infections.

Clinician Input

Input From Clinical Experts Consulted for This Review

- The clinical experts noted that because there are no curative therapies for multiple myeloma, it is important to have new therapies with novel mechanisms of action for the patients whose disease becomes resistant to current therapies. The clinical experts added the BPd will mostly be used in patients who have experienced relapse after 1 to 3 prior lines of therapy. According to the clinical experts, older patients who are post DRd would be good candidates for BPd given the favourable toxicity profile with respect to myelosuppression. They added that any patients with pre-existing eye conditions would not be good candidates for belantamab-containing regimens due to its ocular toxicities.
- The clinical experts noted the importance of HRQoL in assessing BPd in multiple myeloma due to the fact that patients survive for a long time with this type of cancer, and due to the ocular toxicities, which may negatively impact quality of life. The clinical experts added that the main reasons to discontinue treatment would be disease progression or toxicity, namely ocular AEs.

Clinician Group Input

- Two clinician groups, the OH (CCO) Hematology Cancer Drug Advisory Committee and CMRG, provided input for this clinical review. The OH (CCO) Hematology Cancer Drug Advisory Committee gathered information from 7 clinicians, while CMRG collected input from 20 clinicians.
- There were no obvious areas of disagreement between the clinician groups and the clinical experts consulted on this review.
- The CMRG noted that BPd would pertain to patients who have had 1 to 3 prior lines of therapy. The OH (CCO) Hematology Cancer Drug Advisory Committee noted that BPd could fit in with current second-line treatments for patients whose disease is resistant to lenalidomide or bortezomib.
- Both clinician groups noted that BPd should be discontinued on disease progression or significant toxicity, especially significant ocular toxicities. Both clinician groups noted that the outpatient setting is the appropriate setting for treatment with BPd, and ophthalmological assessment is needed.

Drug Program Input

The clinical experts consulted for this 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 BPd against PVd in patients with heavily pretreated myeloma (including patients whose disease is refractory to lenalidomide and/or anti-CD38 antibodies).	According to the clinical experts, the efficacy of BPd is very good and likely superior to many of the other listed regimens. However, 1 of the clinical experts noted that it

Drug program implementation questions	Clinical expert response
At the time of the review, PVd is hardly used in Canada. Question: How does BPd compare with Kd, SVd, IsaPd, IsaKd, and Pd?	is difficult to compare to IsaPd and IsaKd, which are also quite effective, noting that the toxicity of BPd is unique but manageable. Another clinical expert noted that BPd appears to have improved PFS compared to many of the regimens listed here. pERC noted the significantly higher incidence of ocular AEs with BPd than with PVd despite measures taken by the investigators to reduce the incidence of ocular AEs in the DREAMM-8 trial. Therefore, pERC determined that access to measures for reducing ocular toxicities during treatment and regular monitoring of ocular toxicities by an ophthalmologist or an optometrist are needed for patients' safety during treatment with BPd.
At the time of this input, first-line quadruplet regimens (daratumumab-VRd for transplant-eligible myeloma and isatuximab-VRd for transplant-ineligible myeloma) are under CDA-AMC review. Ciltacabtagene autoleucel (1 to 3 prior lines; fourth line), 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 (BVd) is also under review, with a different dosing schedule. Caution is needed to ensure that the correct dosing schedule is chosen for BPd, especially in the event of dose reductions.	This is a comment from the drug plans to inform pERC deliberations.
Due to the ocular toxicities, 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.
In the trial, patients who had to stop 1 of the study drugs were permitted to continue with the remaining study drugs at the discretion of the investigator.	This is a comment from the drug plans to inform pERC deliberations.
Generalizability	
Question: Should the following patients be considered for BPd: • those with disease that is intolerant or refractory to bortezomib • those with active plasma cell leukemia • those with systemic light chain amyloidosis.	According to the clinical experts consulted by the CDA-AMC review team: • Patients with active plasma cell leukemia and patients who are intolerant or have disease that is refractory to bortezomib could be considered for BPd. • One clinical expert noted that although data on BPd use in patients with systemic light chain amyloidosis is very limited, its use in these patients is likely acceptable. pERC agreed with the clinical experts.
Question: Should patients receiving pomalidomide-dexamethasone or other alternative treatments be switched to belantamab mafodotin?	The clinical experts indicated that this option could be allowed but not mandatory. pERC noted that the DREAMM-8 trial did not provide evidence demonstrating a beneficial effect in switching patients from pomalidomide-dexamethasone or other alternative treatments to belantamab mafodotin. However,

Drug program implementation questions	Clinical expert response
	patients receiving pomalidomide-dexamethasone whose disease has not progressed on therapy may be considered for belantamab mafodotin on a time-limited basis only.
Funding algorithm	
The drug programs requested the initiation of a rapid provisional funding algorithm. Note that if the final reimbursement recommendation for this drug under review is “Do not reimburse,” the project will be suspended indefinitely.	This is a comment from the drug plans to inform pERC deliberations.
The trial excluded patients who had received prior BCMA-targeted therapies. Question: Is there sufficient evidence to support the sequencing of belantamab mafodotin with other BCMA-targeted therapies? Question: If a patient's disease progresses on a bortezomib-and-lenalidomide-containing regimen in the first-line setting (i.e., RVD), would the patient be eligible for BPd in a later-line setting?	One of the clinical experts noted that there is no evidence yet that immunotherapies work through different mechanisms than ADC; therefore, resistance to 1 does not indicate resistance to the other. Another clinical expert noted that belantamab likely has some efficacy in this case. pERC noted that the degree of benefit of BPd after anti-BCMA therapy in patients with multiple myeloma is unknown and not supported by data. The clinical experts noted that when a patient progresses on a bortezomib-and-lenalidomide-containing regimen in the first line, there would be no reason to exclude them from receiving BPd. pERC agreed with the clinical experts.
Care provision issues	
Belantamab is supplied as 70 mg and 100 mg vials. It has a 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	
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. pERC noted that coverage for required eye care to support using BPd safely is not uniform across jurisdictions, and the disparity could disproportionately impact individuals with limited financial resources.
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.

AE = adverse event; ADC = antibody-drug conjugate; BPd = belantamab mafodotin in combination with pomalidomide and dexamethasone; BVd = belantamab mafodotin in combination with bortezomib and dexamethasone; CDA-AMC = Canada's Drug Agency; cilta-cel = ciltacabtagene autoleucel; IsaKd = isatuximab in combination with carfilzomib and dexamethasone; IsaPd = isatuximab in combination with pomalidomide and dexamethasone; Kd = carfilzomib and dexamethasone; PAG = Provincial Advisory Group; Pd = pomalidomide and dexamethasone; pERC = pan-Canadian Oncology Drug Review Expert Review Committee; PVd = pomalidomide in combination with bortezomib and dexamethasone; RVD = lenalidomide in combination with bortezomib and dexamethasone; SVD = selinexor plus bortezomib and dexamethasone; VRd = daratumumab in combination with bortezomib, lenalidomide, and dexamethasone.

Clinical Evidence

Systematic Review

Description of Studies

DREAMM-8 is an ongoing phase III, open-label, multinational (140 centres in 18 countries, including 3 sites in Canada) RCT evaluating the efficacy and safety of BPd versus PVd in 302 participants with relapsed or refractory multiple myeloma. Patients in the BPd arm received belantamab mafodotin intravenously at a dose of 2.5 mg/kg on day 1 of cycle 1 and 1.9 mg/kg of cycle 2 or more in each 28-day cycle. Following screening, participants were stratified based on the number of prior lines of therapy (1 versus 2 or 3 versus ≥ 4), prior bortezomib treatment (yes or no), and prior anti-CD38 treatment (yes or no). International Staging System (ISS) status (I versus II/III) was a randomization factor but was replaced with prior anti-CD38 treatment (yes or no) in protocol amendment 1. Treatment was continued in both arms until progressive disease per IMWG criteria, death, unacceptable toxicity, start of a new antineoplastic therapy, withdrawal of consent, or the end of the study, whichever occurred first. In the case of progressive disease, participants were followed to ascertain receipt of subsequent antineoplastic therapy, PFS on subsequent line of therapy, and survival status every 12 weeks (± 14 days) until the withdrawal of consent, loss to follow-up, death, or the end of the study. The primary outcome of the DREAMM-8 trial was PFS, while key secondary outcomes included OS, duration of response (DOR), and minimal residual disease (MRD) negativity. The primary and secondary end points of the DREAMM-8 trial were analyzed based on the data cut-off date of January 29, 2024.

The majority of patients were male (60%; female = 40%), 66 years of age, on average, and approximately 61% were 65 years of age or older. The majority of patients (59%) were ISS I at screening, only 10% had extramedullary disease, and [REDACTED]. The most common myeloma immunoglobulin was immunoglobulin G (62% of patients), with immunoglobulin A the next-most common (22%). With respect to prior lines of therapy completed before screening, 53% of patients had 1 line, 34% had 2 or 3 lines, and 14% had 4 lines or more. Most patients (91%) had received a prior proteasome inhibitor, and all patients had received a previous immunomodulatory drug and lenalidomide. In total, 60% of patients had received a prior stem cell transplant. With respect to cytogenetic risk profile, one-third of participants were considered high risk. Most patients (98%) had an Eastern Cooperative Oncology Group Performance Status (ECOG PS) of 0 or 1.

Efficacy Results

Progression-Free Survival

PFS was assessed by an independent review committee (IRC). After a median follow-up of 21.8 months, progression or death occurred in 62 participants (40%) in the BPd arm versus 80 (54%) participants in the PVd arm, for an HR of 0.52 (95% CI, 0.37 to 0.73; $P < 0.001$). The median PFS was not reached in the BPd arm (95% CI, 20.6 to not reached) and was 12.7 months (95% CI, 9.1 to 18.5) in the PVd arm. The landmark analyses of PFS at 12 months showed a higher PFS rate in the BPd arm than in the PVd arm (71% versus 51%), as well as at 18 months ([REDACTED] versus [REDACTED]). [REDACTED] sensitivity or supplemental analyses were

conducted, all of which yielded results consistent with the primary PFS analysis, with HRs ranging from [REDACTED].

The PFS benefit observed was consistent across all subgroups, with HRs ranging from 0.26 to 0.76. In the protocol-specified subgroups of the DREAMM-8 trial, the HR was 0.52 (95% CI, 0.31 to 0.88) for participants with 1 prior line of therapy and 0.52 (95% CI, 0.33 to 0.80) for those with 1 or more prior lines of therapy. For patients who has exposure to bortezomib, the HR was 0.55 (95% CI, 0.38 to 0.78). Among participants with disease that was refractory to lenalidomide, the HR was 0.45 (95% CI, 0.31 to 0.65). Regarding cytogenetic risk, the HR was 0.57 (95% CI, 0.34 to 0.96) for patients considered high risk, and 0.51 (95% CI, 0.30 to 0.86) for those considered standard risk.

Overall Survival

At the data cut-off date (January 29, 2024), median OS was not reached in either treatment arm. The OS data had reached 34.8% (105 of 302 participants) overall maturity and an information fraction equal to 48.4% (105 of 217), where 217 deaths were planned for OS analysis according to the statistical analysis plan. Follow-up for OS is ongoing and will continue until the next planned interim analysis of OS at approximately 60% information fraction. The 12-month OS survival rate was higher in the BPd arm compared with the PVd arm (83% [95% CI, 76% to 86%] versus 76% [95% CI, 68% to 82%]), for an RD of [REDACTED] and this was also the case at 18 months ([REDACTED] versus [REDACTED] for an RD of [REDACTED]).

European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30

At least 50% of participants in both treatment arms were receiving treatment during the initial 12 months and had regular assessments every 4 weeks. Therefore, the patient-reported outcome dataset is more complete during this time frame. The European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC QLQ-C30) global health status/QoL domain, physical domain, role functioning domain, and fatigue domain remained stable across both treatment arms over time.

Conventional Assessment of DOR

DOR was defined as the time from first documented evidence of partial response or better until progressive disease or death due to any cause based on IRC assessment per IMWG criteria. The median DOR was not reached in the BPd arm (95% CI, 24.9 to not reached) and was 17.5 months (95% CI, 12.1 to 26.4) in the PVd arm. In the BPd arm, 66 participants (55%) with disease response had not experience disease progression or died and had follow-up for PFS ongoing at the data cut-off date compared with 33 participants (31%) in the PVd arm.

MRD Negativity Rate

At the time of the primary analysis, the proportion of participants with a complete response or greater who experienced MRD negativity was higher in the BPd arm (37 of 155 patients; 24%) compared with the PVd arm (7 of 147 patients; 5%). As the OS analysis was not statistically significant at the time of the PFS analysis data cut-off date (because the data were immature), MRD negativity could not be formally tested at

that time. The results of the MRD negativity analysis using investigator-confirmed response or in participants with very good partial response (VGPR) or better were consistent with the primary MRD analysis.

Complete Response Rate

There were 62 patients (40%) in the BPd arm compared to 24 patients (16%) in the PVd arm who had an IRC-assessed complete response or better. No formal testing of this outcome was completed.

Harms Results

When assessing harms, it should be noted that exposure to BPd was longer than exposure to PVd. For example, the median exposure to belantamab was 13.19 months, to pomalidomide was 15.92 months, and to dexamethasone was 14.00 months in the BPd arm, while exposure to bortezomib was 7.62 months, to pomalidomide was 8.51 months, and to dexamethasone was 8.08 months in the PVd arm. The sponsor noted that dosing interruptions and/or reductions were required to manage adverse reactions such as ocular adverse reactions. Although the proportions of patients who had AEs leading to a dose reduction were similar between arms (61% in each), there were more patients in the BPd arm who had AEs leading to dose interruption or delay than in the PVd arm (91% versus 75%). Most ocular toxicities were reversible and improved with dose reductions or delays. The mean number of weeks between doses of belantamab mafodotin increased over the course of the trial: 5.26 during the first 6 months; 11.91 during months 6 to 12; and 14.2 beyond 12 months of therapy.

Adverse Events

Overall, 149 patients (more than 99%) in the BPd arm and 139 patients (96%) in the PVd arm had at least 1 AE, and 136 patients (91%) in the BPd arm and 106 patients (73%) in the PVd arm had a grade 3 or 4 AE. The 3 most frequent AEs, all numerically more common with BPd than PVd, included blurred vision (119 patients [79%] versus 22 patients [15%]), dry eyes (91 patients [61%] versus 14 patients [10%]), and foreign body sensation in eyes (91 patients [61%] versus 9 patients [6%]). Under the category of infections and infestations, the AEs for which there were differences were, for BPd versus PVd, COVID-19 (56 patients [37%] versus 31 patients [21%]), upper respiratory tract infection (40 patients [27%] versus 25 patients [17%]), and pneumonia (36 patients [24%] versus 17 patients [12%]).

The most common grade 3 or greater AEs, all numerically more common with BPd than with PVd, were neutropenia (63 patients [42%] versus 41 patients [28%]), thrombocytopenia (36 patients [24%] versus 29 patients [20%]), and pneumonia (26 patients [17%] versus 11 patients [8%]).

Serious Adverse Events

Overall, there were 95 patients (63%) in the BPd arm and 65 patients (45%) in the PVd arm who had a serious adverse event (SAE). The exposure-adjusted incidence rate for SAEs was comparable between the 2 treatment arms (45.87 per 100 person-years in the BPd arm versus 47.87 per 100 person-years in the PVd arm). The most frequently reported SAE in both treatment arms was pneumonia, which occurred in [REDACTED] in the BPd arm and [REDACTED] in the PVd arm.

Withdrawals Due to Adverse Events

The incidence of AEs leading to discontinuation of the study treatment (any component of the study treatment) was 15% (22 patients) in the BPd arm and 12% (18 patients) in the PVd arm. The most common AEs leading to treatment discontinuation in the BPd arm were fatigue, keratopathy, muscular weakness, and neuralgia (■■■■■).

Mortality

The incidence of fatal SAEs (related and not related to the study treatment) was similar between the 2 treatment arms (11% in both the BPd and PVd arms). The most common fatal SAE was COVID-19 pneumonia (3% [5 patients] in the BPd arm versus 1% [2 patients] in the PVd arm) and death due to unknown cause (0 in the BPd arm versus 2% [3 patients] in the PVd arm). All other fatal SAEs were reported in 1% or less of participants.

Notable Harms

Ocular exams were performed regularly in all participants in both treatment arms throughout the study; they were performed more frequently in the BPd arm (every 4 weeks, then decreased to every 3 months if there were no significant ocular findings after the sixth dose) than in the PVd arm (every 6 months). Under the original trial protocol, all ocular symptoms and examination findings were to be reported as AEs and graded by the Common Terminology Criteria for Adverse Events (CTCAE) criteria; belantamab dose modification was based on these assessments.

Ocular AEs (CTCAE grade) occurred in 89% of participants in the BPd arm; vision blurred, dry eyes, foreign body sensation in eye(s), and eye irritation were each reported in 50% or more of the participants in this treatment arm. The incidence of ocular AEs (CTCAE grade) in the PVd arm was lower (30%); the most frequently reported ocular AE in this treatment arm was vision blurred (15%). Grade 3 or 4 ocular AEs (CTCAE grade) were reported in more participants in the BPd arm (43%) than in the PVd arm (2%). The most common grade 3 or greater ocular AE, all occurring in more patients receiving BPd than those receiving PVd, were blurred vision (26 patients in the BPd arm [17%] versus none), reduced visual acuity (20 patients [13%] in the BPd arm versus 1 patient [less than 1%] in the PVd arm), impaired vision (■■■■■) corneal epithelial microcysts, and dry eyes (12 patients each in the BPd arm [8%] versus none in the PVd arm), cataracts (9 patients [6%] in the BPd arm versus 6 patients [4%] in the PVd arm), foreign body sensation (9 patients in the BPd arm [6%] versus none in the PVd arm), and punctate keratitis (9 patients in the BPd arm [6%] versus 1 patient [less than 1%] in the PVd arm).

Critical Appraisal

The open-label design of the DREAMM-8 trial introduces the potential for bias, particularly with respect to patient-reported outcomes such as HRQoL. Assessment of HRQoL was also complicated by high attrition rates and missing data from patients who were unable to complete assessments due to disease progression or death, with data reported for less than half of the original intention-to-treat population by week 53. Although study withdrawals were relatively low (less than 10%) across arms, there was a large number of patients who discontinued treatment in both arms; therefore, there was a large imbalance in those going on

to subsequent treatment in the BPd arm compared to the PVd arm (27% versus 52%), and this complicated interpretation of OS.

OS data are not yet mature, which limits any conclusions that can be drawn about these data. PFS is considered a valid surrogate for OS and is frequently used as a primary outcome in pivotal trials, consistent with FDA guidance.

GRADE Summary of Findings and Certainty of the Evidence

For pivotal studies and RCTs identified in the sponsor's systematic review, GRADE was used to assess the certainty of the evidence for outcomes considered most relevant to inform expert committee deliberations, and a final certainty rating was determined as outlined by the GRADE Working Group.

Following the GRADE approach, evidence from RCTs started as high-certainty evidence and could be rated down for concerns related to study limitations (which refers to internal validity or risk of bias), inconsistency across studies, indirectness, imprecision of effects, and publication bias.

When possible, certainty was rated in the context of the presence of an important (nontrivial) treatment effect; if this was not possible, certainty was rated in the context of the presence of any treatment effect (i.e., the clinical importance is unclear). In all cases, the target of the certainty of evidence assessment was based on the point estimate and where it was located relative to the threshold for a clinically important effect (when a threshold was available) or to the null. The minimal important difference for PFS and OS were obtained by asking the clinical experts for their impression of what it should be. For PFS, the clinical experts suggest that a 10% difference between arms would be considered clinically significant, while for OS they suggested it should be 5% because any gain in survival would be considered clinically meaningful to patients. For HRQoL, a minimal important difference of 10 points was identified by the sponsor as clinically significant and the clinical experts agreed that this seemed reasonable. However, given the challenges in trying to identify 1 specific time point in which to assess response to the EORTC QLQ-C30 given the constant attrition over the course of the study, it was decided that instead of seeking 1 specific target of certainty, an overall impression of the direction of effect over time would be ascertained.

The selection of outcomes for GRADE assessment was based on the sponsor's Summary of Clinical Evidence, consultation with clinical experts, and input received from patient and clinician groups and public drug plans. The following list of outcomes was finalized in consultation with the expert committee members:

- PFS
- OS
- HRQoL (EORTC QLQ-C30 global health status/QoL)
- harms (ocular AEs, SAEs).

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

Outcome and follow-up	Patients (studies), N	Relative effect (95% CI)	Absolute effects (95% CI)			Certainty	What happens
			PVd	BPd	Difference		
PFS (median follow-up: 21.8 months)							
Probability of being progression free at 12 months	N = 302 (1 RCT)	NR				Moderate ^a	BPd likely results in a clinically important improvement in the probability of being progression free compared to PVd.
Probability of being progression free at 18 months	N = 302 (1 RCT)	NR				Moderate ^a	BPd likely results in a clinically important improvement in the probability of being progression free compared to PVd.
OS							
Probability of being alive at 12 months	N = 302 (1 RCT)	NR				Low ^b	BPd may result in a clinically important improvement in the probability of being alive compared to PVd.
Probability of being alive at 18 months	N = 302 (1 RCT)	NR				Low ^b	BPd may result in a clinically important improvement in the probability of being alive compared to PVd.
HRQoL							
EORTC QLQ-C30 global health status/ QoL Patients with improvement of ≥ 10 points from baseline	N = 302 (1 RCT)	NR	There was no clear difference between arms for this instrument, although there appeared to be a trend where both arms remained relatively stable over the follow-up period.			Very low ^c	The evidence is very uncertain regarding whether BPd may result in a clinically important improvement in HRQoL compared to PVd.
Harms							
Patients with an ocular AE Follow-up:	N = 302 (1 RCT)	NR				High	BPd results in a clinically important increase in ocular AEs compared to PVd.

Outcome and follow-up	Patients (studies), N	Relative effect (95% CI)	Absolute effects (95% CI)			Certainty	What happens
			PVd	BPd	Difference		
Patients with an SAE	N = 302 (1 RCT)	NR				Low ^d	BPd may result in a clinically important increase in SAEs compared to PVd.

AE = adverse event; BPd = belantamab mafodotin in combination with pomalidomide with dexamethasone; CI = confidence interval; EORTC QLQ-C30 = European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30; HRQoL = health-related quality of life; ITT = intention to treat; MID = minimal important difference; NR = not reported; OS = overall survival; PFS = progression-free survival; PVd = pomalidomide in combination with bortezomib and dexamethasone; RCT = randomized controlled trial; SAE = serious adverse event; 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 following footnotes.

^aRated down 1 level for imprecision because the lower boundary of the 95% CI did not exceed the MID (10%) identified by the clinical experts.

^bRated down 1 level for study limitations; the results are from an interim analysis and there is a risk of bias due to confounding as a result of transition of patients to subsequent treatment postprogression. Rated down 1 level for imprecision.

^cRated down 2 levels for study limitations; assessments of HRQoL may have been biased by lack of blinding, and there was a significant amount of attrition and missing data; rated down 1 level for imprecision because of low sample size relative to the ITT population.

^dRated down 1 level for study limitations as exposure to BPd was longer than exposure to PVd; rated down 1 level for imprecision because the lower boundary of the 95% CI did not exceed the MID (10%) identified by the clinical experts.

Sources: Details included in the table are from the sponsor's Summary of Clinical Evidence and from an additional information request.

Indirect Comparisons

Description of Studies

Direct evidence of comparative efficacy and safety comparing BPd with PVd has been established in the pivotal study (i.e., the DREAMM-8 trial). However, due to the lack of direct evidence comparing the combination of BPd with other existing relevant comparators in the treatment of multiple myeloma in adults who have received at least 1 prior lenalidomide-containing therapy, the sponsor submitted an NMA comparing BPd with the relevant comparators in the treatment of patients with multiple myeloma who were lenalidomide-exposed. Analyses were also performed for a subgroup of the lenalidomide-refractory population. According to the investigators, a fixed-model approach was preferable over the random-effect model of analysis because the networks were sparse (with only 1 study informing most treatment comparisons) and had insufficient sample data to inform the between-study standard deviation in treatment effects.

Efficacy Results

In the treatment of lenalidomide-exposed multiple myeloma, based on the fixed-effect model analysis, a favourable effect was observed when comparing BPd with some of the comparator therapies (such as BPd versus hKd and BPd versus SVd for PFS and overall response rate [ORR]; as well as BPd versus Vd for some outcomes [PFS and/or OS and/or ORR]).

In the lenalidomide-refractory population, in terms of PFS, a favourable effect was observed for BPd based on the fixed-effect model analysis when comparing BPd with hKd, Kd, and Vd.

No ITC comparing BPd with isatuximab in combination with pomalidomide and dexamethasone (IsaPd) or BPd versus pomalidomide and dexamethasone (Pd) was conducted, because the studies assessing the efficacy of IsaPd and Pd could not form a connected network with the DREAMM-8 trial.

No HRQoL outcome was assessed in the NMA.

Harms Results

In the NMA, safety outcomes were not assessed.

Critical Appraisal

Overall, the sponsor's NMA was conducted according to accepted methodological guidance. The potential key limitation of the NMA was the considerable heterogeneity across the included studies due to factors such as the prior line of therapy, ISS stages, ECOG PS, and follow-up time at which outcomes were assessed. The heterogeneity suggests that the assumption of similarity across the included studies may not hold true for the NMA, increasing the likelihood of bias and uncertainty about the validity of the comparative efficacy results for BPd versus relevant comparator therapies used in Canada. Another important limitation is the sparsity of the networks, with most treatment comparisons informed by only 1 trial. These limitations undermine the robustness of the NMA and could bias the treatment effect estimates. Therefore, the results of the NMA should be interpreted with consideration of the previously noted limitations. In addition, HRQoL (which patients have identified as an important outcome) and harms outcomes were not assessed in the NMA. In the lenalidomide-refractory population, only PFS was assessed, OS and ORR were not assessed due to lack of data to form a network.

Studies Addressing Gaps in the Evidence from the Systematic Review

Description of Studies

The sponsor submitted 1 phase I/II, single-arm, open-label, multicenter study (ALGONQUIN) to address gaps in the evidence.

The ALGONQUIN study evaluated various doses and schedules of BPd for patients with multiple myeloma who had disease that was refractory to lenalidomide and were proteasome inhibitor exposed. The ALGONQUIN study comprised a dose-escalation phase (part 1) and a dose-expansion phase (part 2). A total of 87 patients with relapsed or refractory multiple myeloma from 9 sites in Canada were enrolled, with 61 patients in the dose-escalation phase (part 1) and 26 in the dose-expansion phase (part 2). The primary objectives of the ALGONQUIN study were to determine the recommended part 2 dose and the schedule of belantamab in the dose-escalation phase (part 1), as well as to establish the efficacy, as determined by ORR, for participants treated at the recommended part 2 dose in the dose-expansion phase (part 2). The secondary objectives were to assess the safety and tolerability of BPd in the dose-escalation phase (part 1) and to assess additional efficacy outcomes, including PFS, DOR, and OS at the recommended part 2 dose in the dose-expansion phase (part 2).

Efficacy Results

Maximum Tolerated Dose and Recommended Part 2 Dose

The maximum tolerated dose based on the first cycle (28 days) of treatment was determined to be 2.5 mg/kg of belantamab mafodotin. The regimen of 2.5 mg/kg every 8 weeks combined with 4 mg of pomalidomide and 40 mg of dexamethasone was selected as the recommended part 2 dose.

ORR, OS, PFS in Patients Treated at Recommended Part 2 Dose

In the dose-expansion phase (part 2), the median duration of follow-up for patients treated with the recommended part 2 dose (n = 38) was 13.9 months (range, 1.1 to 28.2). Of these 38 patients treated with the recommended part 2 dose, 34 had 2 consecutive assessments and were considered response evaluable. The ORR for patients who were response evaluable was 85.3% (29 of 34), with 33.9% (11 of 34) reaching complete response or stringent complete response, 42.4% (14 of 34) experiencing VGPR, and 11.8% (4/34) having partial response. In the 38 patients treated with the recommended part 2 dose, the median OS (months) was not reached (95% CI, not reached to not reached) and the median PFS (months) was not reached (95% CI, 13.7 to not reached).

Of the 38 patients treated with the recommended part 2 dose during the dose-expansion phase (part 2), 12 were from the dose-escalation phase (part 1). The median duration of follow-up for the 12 patients was 17.2 months (range, 6.0 to 28.2). The ORR was 91.7% (11 of 12), with 33.3% (4 of 12) reaching complete response or stringent complete response, 50.0% (6 of 12) experiencing VGPR, and 8.3% (1 of 12) having partial response. The median OS was not reached (95% CI, not reached to not reached) and the median PFS was 18.3 months (95% CI, 10.8 to not reached).

ORR, OS, PFS in All Treated Patients

The median duration of follow-up for all treated patients was 14.5 months (range, 0.9 to 42.5). Out of the 87 patients, 81 had 2 consecutive assessments and were considered response evaluable. The ORR for the patients who were response evaluable was 87.7% (71/81), with 33.3% (27 of 81) reaching complete response or stringent complete response, 39.5% (32 of 81) experiencing VGPR, and 14.8% (12 of 81) having partial response. The median OS was 34.0 months (95% CI, 24.4 to not reached) and the median PFS was 21.8 months (95% CI, 17.8 to 32.5).

Harms Results

In patients treated with the recommended part 2 dose, the most common treatment-emergent AE of any grade was decreased visual acuity (71.1%; 27 of 38), followed by keratopathy (65.8%; 25 of 38), fatigue (57.9%; 22 of 38), infection (47.4%; 18 of 38), neutropenia (39.5%; 15 of 38), and thrombocytopenia (39.5%; 15 of 38). The most common treatment-emergent grade 3 to 4 AEs included keratopathy (52.6%; 20 of 38), decreased visual acuity (39.5%; 15 of 38), neutropenia (36.8%; 14 of 38), and thrombocytopenia (34.2%; 13 of 38). Of patients treated with the recommended part 2 dose, 55.3% (21 of 38) had an objective decrease in grade 3 to 4 best corrected visual acuity, 13.2% (5 of 38) had grade 3 to 4 blurred vision, and 10.5% (4 of 38) had other ocular AEs, including dry eyes, photophobia, and eye pain.

Critical Appraisal

The ALGONQUIN study provided insights into the use of various doses of belantamab mafodotin (1.92 mg/kg, 2.5 mg/kg, and 3.4 mg/kg) and schedules (every 4 weeks, every 8 weeks, and every 12 weeks). However, it did not address major gaps or limitations in the pivotal DREAMM-8 trial (e.g., immaturity of OS data, high uncertainty in HRQoL outcomes due to the open-label design). Overall, the certainty of the evidence generated from the ALGONQUIN study is very low due to the single-arm design. Lacking comparative data made the inferences on the efficacy and safety of BPd over currently available therapies challenging and unreliable. For instance, when there were no comparison groups, the interpretation of the OS results could be prone to bias because OS can be sensitive to natural history and progression of the disease as well as heterogeneity of patient characteristics. The ALGONQUIN study was open label, in which investigators and patients were aware of the treatment received. The assessment for response and progression end points, such as ORR and PFS, which relies on investigators' knowledge and experience, was prone to the impact of detection bias due to the open-label design. Additionally, the risk of reporting bias due to the open-label study design could not be ruled out for subjective harms outcomes.

Economic Evidence

Cost and Cost-Effectiveness

- Belantamab mafodotin is available as a 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 \$55,600 per patient in the first cycle of treatment and \$47,260 in subsequent cycles, based on the Health Canada–recommended dosage.
- Clinical efficacy in the economic analysis was derived from the DREAMM-8 trial, which compared BPd with PVd. Evidence from the DREAMM-8 trial suggests that BPd likely results in a clinically important improvement in PFS and may improve OS compared to PVd for patients with multiple myeloma. However, the OS data remain immature, with only 48% of events observed at the time of the interim analysis. For comparisons with other regimens, the sponsor submitted an ITC. The results from the fixed-effects model suggest a numerically favourable PFS and OS benefit for BPd when compared to relevant comparators. The results from the random-effects model, however, did not demonstrate a clear PFS or OS advantage for BPd over these comparators. These findings should be interpreted with consideration of the limitations associated with the ITC, including significant heterogeneity across the studies included.
- The results of the CDA-AMC base case suggest:
 - The following treatments are on the cost-effectiveness frontier: Vd, PVd, Kd, and BPd. Notably, daratumumab in combination with bortezomib and dexamethasone is not included on the frontier, as it was dominated by Kd in the analysis.
 - BPd will be associated with higher costs to the health care system than Kd (incremental costs = \$1,113,326), primarily driven by increased drug acquisition costs associated with BPd.

- BPd will be associated with a gain of 0.63 life-years compared to Kd and is anticipated to improve HRQoL based on time in health states, whereas BPd may result in a gain of 0.42 QALYs compared to Kd.
- The ICER of BPd compared to Kd is \$2,661,253 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 BPd, and more than 55% of the incremental benefit was gained in the extrapolated period (i.e., after 36 months). In the absence of comparative evidence beyond this time point and uncertainty in the comparative clinical evidence, the QALYs gained for patients receiving BPd 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 BPd for the treatment of relapsed or refractory multiple myeloma who have received at least 1 prior therapy, including lenalidomide, will be approximately \$485 million over the first 3 years of reimbursement compared to the amount currently spent on comparators, with an estimated expenditure of \$680 million on BPd over this period. The actual budget impact of reimbursing BPd will depend on BPd dosing assumptions, drug utilization, and distribution of subsequent therapies. At the submitted price, the incremental budget impact of BPd is expected to be greater than \$40 million in year 1, 2, and 3 of reimbursement, and the economic feasibility of adoption must be addressed. Additionally, the magnitude of uncertainty in the budget impact must be addressed to ensure the feasibility of adoption, given the difference between the sponsor's estimate and the CDA-AMC estimate.

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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