CADTH REIMBURSEMENT REVIEW

Patient and Clinician Group Input

belantamab mafodotin, bortezomib, dexamethasone

GlaxoSmithKline Inc.

Indication: Belantamab mafodotin is indicated for the treatment of multiple myeloma in combination with bortezomib and dexamethasone (BVd) in adult patients who have received at least one prior therapy.

November 7, 2024

This document compiles the input submitted by patient groups and clinician groups for the file under review. The information is used by CADTH in all phases of the review, including the appraisal of evidence and interpretation of the results. The input submitted for each review is also included in the briefing materials that are sent to expert committee members prior to committee meetings.

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CADTH

CADTH Reimbursement Review Patient Input

Name of Drug: belantamab mafodotin (BLENREP) in combination with bortezomib (Velcade) and dexamethasone

Indication: Adult patients with relapsed-refractory multiple myeloma

Name of Patient Group: Myeloma Canada

Author of Submission: [redacted]

1. About Your Patient Group

Multiple myeloma, also known as myeloma, is the second most common form of blood cancer. Myeloma affects plasma cells, which are a type of immune cell found in the bone marrow. Every day, 11 Canadians are diagnosed with myeloma, yet despite its growing prevalence the disease remains relatively unknown. People with myeloma experience numerous relapses; with successful treatment it can enter periods of remission, but myeloma will always ultimately return and require further treatment. Myeloma patients also become refractory to treatment, meaning it can no longer control their myeloma, and they require a new regimen. Myeloma Canada has existed for over 15 years to support the growing number of Canadians diagnosed with myeloma, and those living longer than ever with the disease can access new and innovative therapies. Over the years, as a part of this mission Myeloma Canada has collected data on the impact of myeloma and its treatments on patients and caregivers by conducting surveys. The data are then presented to the pERC.

www.myeloma.ca

2. Information Gathering

Myeloma Canada is sharing the input received from a patient and caregiver survey regarding belantamab mafodotin in combination with bortezomib and dexamethasone (BVd) therapy for the treatment of relapsed refractory multiple myeloma. Our patient and caregiver survey included questions regarding both combinations including belantamab mafotodin (BVd and BPd), was available from August 26 – September 30, 2024. It was shared via email and social media by Myeloma Canada, and the Leukemia and Lymphoma Society of Canada. Of 356 total responses to the survey, 64 incomplete responses

wherein a respondent did not finish answering survey questions were removed from the dataset, leaving 292 complete and eligible responses. All respondents were initially asked similar questions regarding disease experience. Upon verifying their eligibility for, or experience with, the treatment under review, respondents were divided into two subsets, and correspondingly posed different questions. The subsets and their demographic characteristics are as follows:

1. **Subset E**. Patients who would be eligible for treatment with BVd and their caregivers (282)
    i. Respondents were from Ontario (115), British Columbia (52), Quebec (43), Alberta (36), Manitoba (10), Nova Scotia (7), Newfoundland and Labrador (6), Prince Edward Island (4), New Brunswick (3), Saskatchewan (3), Yukon (3), and 5 from outside of Canada (France, USA, UK, Algeria, Ivory Coast).
    ii. 254 respondents were patients, and 28 were caregivers.
    iii. 140 Subset E respondents identified themselves as assigned male at birth (further referred to in this report as male), 140 as assigned female at birth (further referred to as female), and 2 selected 'Prefer not to say'.
    iv. 72% (202) of Subset E respondents resided in an urban area, 30% (77) in a rural area, and 2 in a remote area (1 respondent skipped the question).
    v. 40% (113) of Subset E respondents were between '70—79' years of age, 36% (101) were between '60–69', 13% (37) were between '50–59', 8% (21) were between '80–89' years, 6 were between '40-49', 2 were between '30-39' and one final respondent was '90+' years old. (one respondent skipped the question).

    Note: the survey had open eligibility considering all patients currently on their 1st line of treatment will eventually relapse and need to consider a new treatment. Based on the applied-for indication, the treatment would also be available to patients at subsequent lines of therapy. There was no significant difference in responses based on prior lines of therapy.
2. **Subset T**: Patients who have experience with belantamab mafodotin and their caregivers (10):
    Note: Though there were no survey respondents who had experience with BVd, 10 respondents indicated they had experience with belantamab mafodotin, 7 with BPd and 3 as monotherapy/ with dexamethasone. The responses to select questions about general experience with belantamab mafodotin will be presented in the final section.
    i. Respondents **(10)** were from Ontario (5), British Columbia (3), and Manitoba (2).
    ii. 5 respondents were patients, and 5 were caregivers.
    iii. 6 respondents identified themselves as female, 4 as male.
    iv. 6 respondents were located in an urban area, and 4 in a rural area.

v. 5 respondents were between ‘70–79’ years of age, 2 were between ‘60–69’, 2 between ‘50–59’ and 1 respondent was between ’40—49’ years of age. (Note: the respondents in their 40’s and 50’s were all patients)

3. Disease Experience

All respondents (292) were asked “*How important it is to control various symptoms related to myeloma? Please rate on a scale of 1 - Not important to 5 - Extremely important”,* by weighted average rating, respondents indicated that ‘Infections’ (4.49) were the most important aspect to control, followed by ‘Mobility’ (4.41), ‘Kidney problems’ (4.38), and ‘Pain’ (4.20).

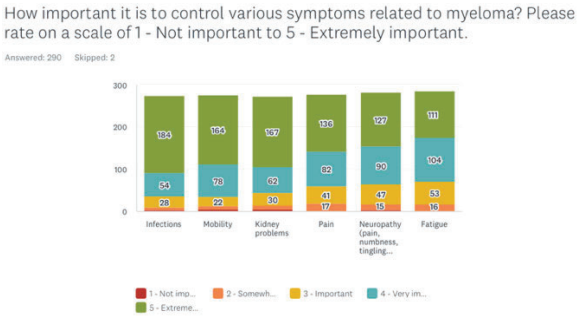


Figure 1 – Importance of controlling myeloma symptoms (All respondents; 290)

When asked “*Do symptoms associated with myeloma, or caring for someone with myeloma impact or limit your day-to-day activities and quality of life? Please rate on a scale of 1 - No impact to 5 - Extreme impact.”*, by weighted average rating, respondents (292) indicated that their ‘ability to travel’ (3.48) and ability to work (3.46) were most significantly impacted, followed by ‘ability to exercise’ (3.24), and ‘ability to conduct volunteer activities’ (3.17).

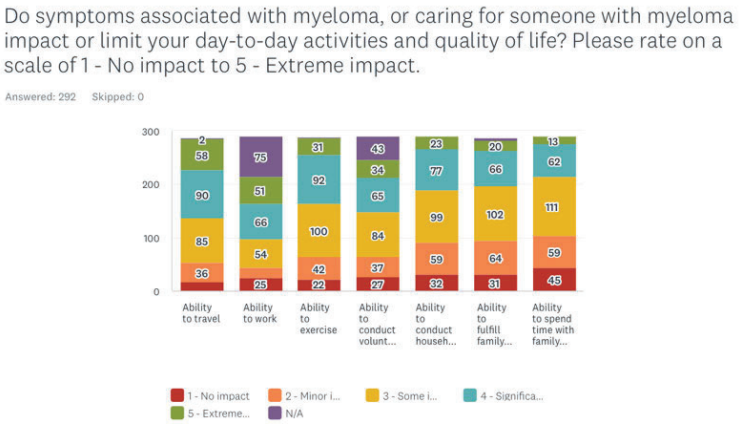


Figure 2 – Impact of myeloma on daily activities and quality of life (All respondents; 292)

When all respondents (287) were asked "*How long does it take you to travel to the hospital/cancer centre where you, or the person you care for, receive(s) treatment?",* 47% of respondents (135) indicated 'Less than 30 minutes', 35% (103) of respondents chose '30 mins – 1 hour', 27 chose '1-2 hours', 11 chose '3-4 hours', and 11 respondents chose 'Other' commenting that they self-administer treatment at home, or are not currently receiving treatment.

When asked "I*f you are currently receiving active treatment for your myeloma, or you care for someone who is, please indicate how often you/they visit a hospital/cancer centre for treatment."* respondents (273) most frequently selected, 'once a month (105), followed by 'once a week' (39), 'every two weeks' (33), 'never (treatment administered at home)' (25) and 'every two months' (22). 21 respondents selected 'other' and provided comments. Among these comments, four described receiving their treatments every six months, nine described taking their treatment(s) at home, and eight described receiving their treatment(s) every three months.

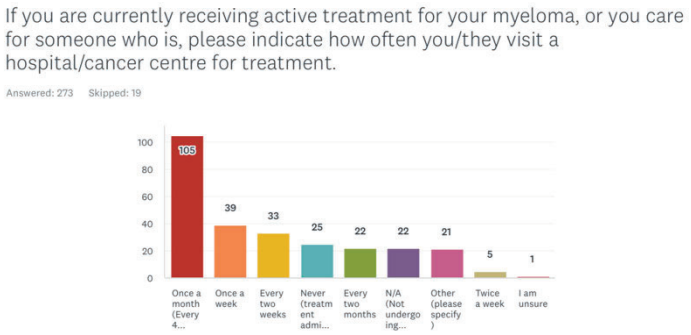


Figure 3 –Frequency of hospital visits for treatment (All respondents; 273)

When all patients and caregivers (292) were asked, "*What have been the most significant financial implications of myeloma treatment on you and your household? Please check all that apply"*; respondents indicated lost income/pension funds due to absence from work, disability, or early retirement (94), travel costs (86), followed by parking costs (85), drug costs (74), and accommodation costs (28) were the most significant financial implications of myeloma treatment.

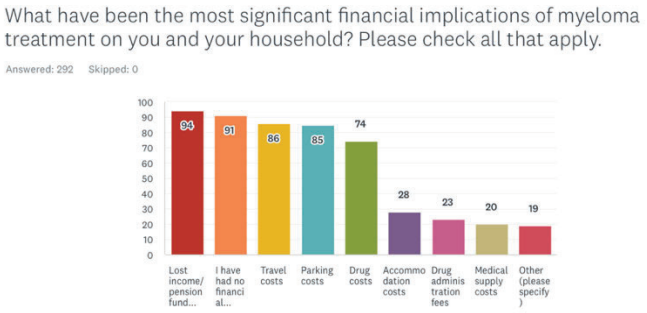


Figure 4 – Financial implications of myeloma (All respondents; 292)

All patients and caregivers were asked "*Have you experienced any of the following psychological / social difficulties due to multiple myeloma, or caring for someone with myeloma? Please rate how severely they impacted your quality of life on a scale of 1 - No impact to 5 - Extreme impact."* By the weighted average of responses, respondents (291) felt that that 'Interruption of life goals/accomplishments (career, retirement, etc.)' (3.45) had the most impact on quality of life, followed by 'Loss of sexual desire' (3.39) which was the option most frequently (61) rated 5 – Severe impact, 'Anxiety/worry' (3.19), and 'difficulty sleeping' (2.91)

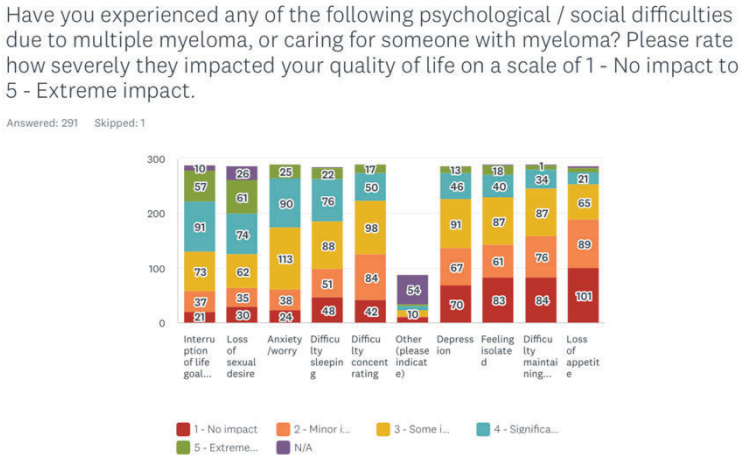


Figure 5 – Psychosocial impact of myeloma (All respondents; 291)

When all patients (259) were asked "*Do you need the support of a caregiver or family member to help you manage your myeloma or your treatment-related symptoms?"*, 124 answered 'No' they did not need a caregiver (48%), 20 chose 'No', but I would benefit from a caregiver's help, 8 chose 'Yes but I am unable to access the help I need', and 107 chose 'Yes' (41%).

All patients and caregivers were asked to identify the factors they consider to be most important to (any) myeloma treatment. Respondents (260) frequently mentioned maintaining quality of life and making side effects manageable, along with the effectiveness of treatment, especially in achieving remission and having a long, durable, response, and accessibility/portability of treatment (including fewer/minimal visits to the hospital/cancer centre), to be key factors. Responses to this effect are as follows:

- *"data-confidence that it is a currently innovative or well tested treatment over time that promises results and has limited side effects, extends life expectancy"*

- *"How often the treatment requires me to go to hospital/ cancer clinic. This impacts my ability to travel and see family. I prefer an oral medication that allows me to visit family. Secondly the side effects of the treatment."*
- *"That the benefit far out weighs the risk/side affects. No one wants a treatment that makes you feel terrible and may have lasting affects to other organs or cause other forms of cancer. It needs to give longer and better quality of life.."*
- *"that there will always be another treatment/option/horse to pick.....living w an incurable cancer means having to stay positive and access to new drugs plays a BIG part...."*

4. Experiences With Currently Available Treatments (eligible population Subset E)

Of 282 respondents 38% (108) had received 1 line of therapy, 31% (87) had received 2 lines of therapy, 40 indicated they received 3 lines, 26 responded 4 lines, 13 respondents indicated they or the person they care for had received 5 lines of therapy or more, and 8 indicated they were unsure.

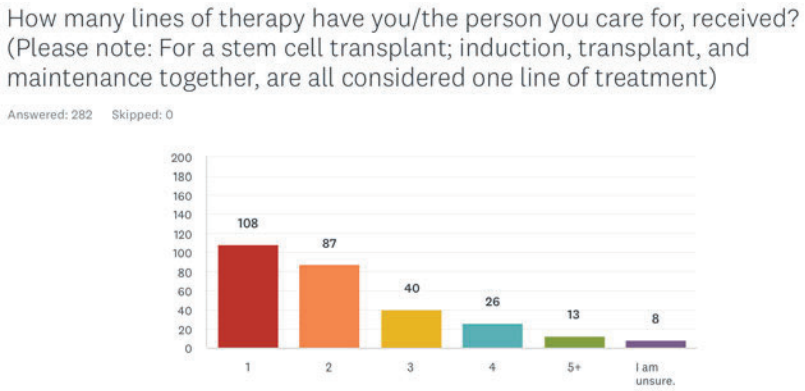


Figure 6 – Prior lines of therapy (Subset E; 282)

When asked, "*Have you/the person you care for, received an autologous stem-cell transplant (ASCT) to treat your myeloma?"* 68% (190) of respondents (282) said yes, 30% (85) indicated they/the person they care for was not eligible for an ASCT, and 7 respondents indicated they were preparing to have an ASCT soon. Those who did not receive an ASCT were asked "Why did you, or the person care for, not receive an autologous stem cell transplant (ASCT)?" 61% (52) of respondents (85) indicated 'Age', 7 chose 'Was not offered', 6 indicated 'Chose not to', 2 indicated 'I am unsure', and 18 selected 'Other; and provided comments, many of which described co-morbidities (renal, pulmonary, hypotension) that prevented them from benefiting from an ASCT.

When asked *"Which of the following classes of myeloma treatment have you or the person you care for received? Please select all that apply."*, 87% (246) of respondents (282) had received an immunomodulatory agent, 61% (171) had received a proteasome inhibitor, 37% (104) had received an anti-CD38 monoclonal antibody, 3% (8) had received a BCMA-targeted therapy (CAR T, bispecific, or ADC), and 24% (67) indicated they were unsure and provided comments most of which mentioned dexamethasone, cyclophosphamide, or stem cell transplant.

When asked "*Are you or the person you care for refractory to lenalidomide (Revlimid)?"* 54% (152) of respondents (282) indicated they were not refractory to lenalidomide, 20% (57) indicated they were refractory to lenalidomide, 12% (33) selected 'I have / the person I care for has been treated with lenalidomide in the past, but I am unsure if I am / they are refractory to it', and 40 additional respondents chose 'Other' and most specified that they had tried lenalidomide but could not tolerate it (due to allergy, bad reaction, comorbidities, side effects).

When asked "*Are you worried about having additional treatment options available when you or the person you care for relapse(s)?",* respondents (277) most frequently selected '3 – somewhat worried' (92), followed by '4 – very worried' (73), and '5 - extremely worried' (51).

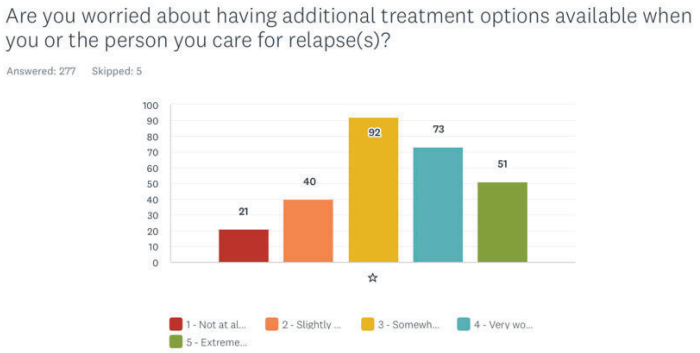


Figure 6 – Worry about subsequent treatment option availability (Subset E; 277)

5. Improved Outcomes – Subset E

Subset E Respondents (281) were asked, "When considering a myeloma treatment, how important is it that the treatment improves overall quality of life for you/the person you care for", 58% (162) chose '5 – extremely important', 34% (95) chose '4- very important', 8% (23) chose '3 – somewhat important', and 1 person chose '2 – slightly important', for a weighted average rating of 4.49.

When asked “When considering a myeloma treatment, how important is it that the treatment increases life expectancy for yourself or the person you care for?”, 67% (187) of respondents (280) chose ‘5 – extremely important’, 24% (68) chose ‘4- very important’, 9% (24) chose ‘3 – somewhat important’, and 1 person chose ‘2 – slightly important’, for a weighted average rating of 4.58.

Subset E (273) was asked “*How desirable is an estimated two - three years (24 - 36 months +) of extended life without myeloma getting worse, for you or the person you care for? (Compared to an estimated 13 months with standard of care treatments.)*” 75% (204) indicated it was ‘5 – extremely desirable’, 19% (51) chose ‘4 – very desirable’, 12 chose ‘3 – somewhat desirable’, 4 chose ‘2 – slightly desirable’ and 2 chose ‘1 – not at all desirable’. (Note: the survey included questions about BVd and BPd, the range in this question represents the data from both trials).

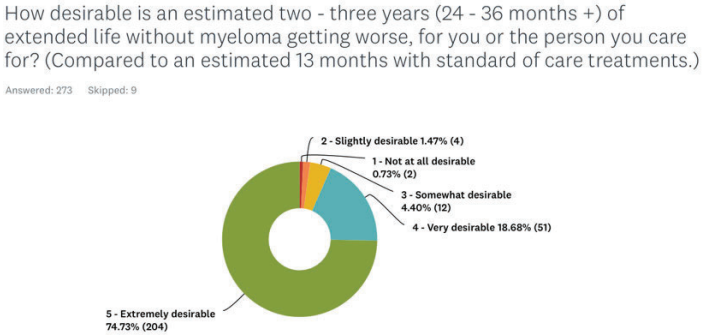


Figure 7 –Desirability of 2-3 years extended life without progression (Subset E; 273)

Subset E was presented information about common side effects of belantamab mafodotin, particularly the eye-related side effects (Blurry vision, eye pain, light sensitivity etc…), and the dosing schedule of BVd was described. Subset E was asked “*Amongst the most common side effects in patients who receive belantamab mafodotin, how tolerable do you expect they would be for you or the person you care for? Please rate on a scale of 1 Not at all tolerable to 5 Extremely tolerable'".* Ordered by weighted average of responses Subset E (275) perceived eye pain (2.10), blurry vision (2.23), and foreign body sensation in eye (2.28), to be the least tolerable side effects, followed by infections (2.42), and eye irritation (2.42). Overall, the median tolerability rating was 2 – Slightly tolerable for all except the hematological side effects which received a median rating of ‘3 – Somewhat tolerable’.

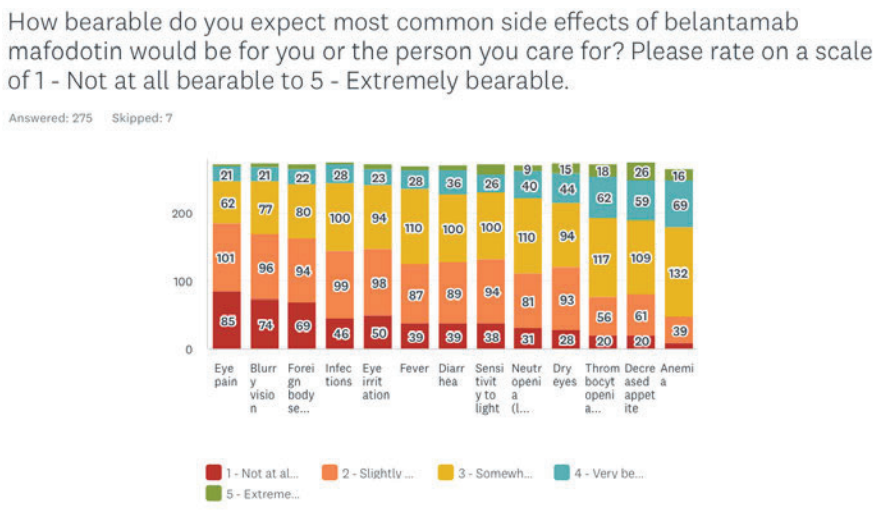


Figure 8 – Perception of belantamab mafodotin side effects (Subset E; 275)

When Subset E was asked, "*How worrisome is the overall side effect profile for belantamab mafodotin, compared to other treatment options available to you or the person you care for? Please rate on a scale of 1 - Not at all worrisome to 5 - Extremely worrisome'.*" Respondents (274) most frequently chose '3 – Somewhat worrisome' (55%; 150), followed by, '2 – Slightly worrisome' (26%; 70), '1 – Not at all worrisome' (8%; 22), '4 – Very worrisome' (7%; 20), and '5 – Extremely worrisome' (4%; 12).

Subset E was presented information about the rates of experience eye related side effects, and permanent vision damage from the DREAMM-7 and DREAMM-8 trials, and asked, "*Does the above information impact your concern about you or the person you care for experiencing eye/vision-related side-effects due to belantamab mafodotin treatment?".* Respondents (279) most frequently chose 'No, my level of concern/worry remains the same' (42%; 118), followed by 'Yes, I am less worried' (32%; 90), and 'Yes', I am more worried (23%; 64). 7 respondents chose 'other' and provided comments:

> *"If my life is extended and quality is good that s all I would be concerned with"*
>
> *"I have Central Serous Retinopathy. Diagnosed 2 years before Myeloma diagnosis. I am very concerned with losing my eye sight.*

When asked, "*If you or the person you care for were eligible to receive belantamab mafodotin in combination with bortezomib (Velcade) and dexamethasone (BVd), what do you believe the advantages and/or disadvantages would be compared to your current treatment?*". Subset E respondents were

provided the following list of factors and asked to indicate if they felt there would be an increase or decrease in that area:

- Treatment side effects (267) – Increased: 73, No change: 93, Decreased: 11, I'm not sure: 90
- Control of myeloma and its symptoms' (270) – Increased: 101, No change: 54, Decreased: 12, I'm not sure: 103),
- Frequency of trips to the hospital or cancer centre for treatment (233) – Increased: 133, No change: 52 , Decreased: 18, I'm not sure: 30).
- Tolerability of the treatment's mode of administration (234) – Increased: 51, No change: 105, Decreased: 28, I'm not sure: 50.
- Quality of life (233) – Increased: 48, No change: 58, Decreased: 53, I'm not sure: 74.

17 respondents provided comments, many of which were related to the perceived travel burden of BVd treatment. Selected comments are as follows:

> *"Have to use public transportation"*
>
> *"Living almost an hour from the nearest cancer center we would be on the road many hours each week."*
>
> *"i would be travelling for injections alot. hard to ask support people when it is a 90 minute round trip"*
>
> *"I live on an island and have to take a ferry to the nearest hospital. The increased trips are not great."*
>
> *"Obligation d'arrêter de travailler pour aller recevoir le traitement"*

To the question "*Based on what you know today, would you consider BVd (belantamab mafodotin combined with bortezomib and dexamethasone) as a potential next treatment for yourself or the person you care for? (Presuming you are eligible and your doctor agrees)..*" 48% (177) of Subset E respondents (244) indicated 'Yes', while 36% (87) said they were unsure, 9 chose 'No' and 31 additional patients indicated they would need more information to decide.

When given the opportunity to share any further thoughts about potential treatment with belantamab mafodotin in combination with bortezomib and dexamethasone, 18 Subset E respondents left comments,

of which some noted the importance of their hematologist/oncologist's opinion about belantamab mafodotin, and the side effects being manageable. Additional comments of note are as follows:

- *" Nous avons besoin de plusieurs options de traitements, car le myelome revient dans 98% des cas. Plus vous autorisez de combinaisons, plus nous vous serons reconnaissance de nous permettre de s'approcher de l'espérance de vie moyenne."*
- *"Bvd is an issue due to ongoing neuropathy issues with Bortezamib and now Carfilzomib"*
- *"To me, the trial results look encouraging for BVd and that is the significant factor weighing in its favour."*
- *"from my understaning BVd or BPd have a good side effect profile, longer remission lenght and is less expesive then methods like CAR-T and Less chane of infecaion then BITES . It would be a good option to have"*

6. Experience With Drug Under Review

As noted previously, there were 10 individuals with belantamab mafodotin experience who responded to the survey, 7 received BPd and 3 indicated they received belantamab mafodotin as a monotherapy / with dexamethasone, and none had received BVd. Responses to select questions from the survey that are non-specific but relevant to BVd are presented below.

Subset T (10) was asked, "*Which of the most frequent belantamab mafodotin side effects listed below have you/the person you care for experienced? Please select all that apply and rate the side effects severity on a scale of 1 Not at all bearable to 5 Extremely bearable'.".* By weighted average of responses, blurry vision (3.10), dry eyes (3.10), eye irritation (3.29), and sensitivity to light (3.10) were considered the least bearable side effects, followed by infections (3.20). Similarly, the weighted average response to all listed side effects was '3 – Somewhat bearable' or higher.

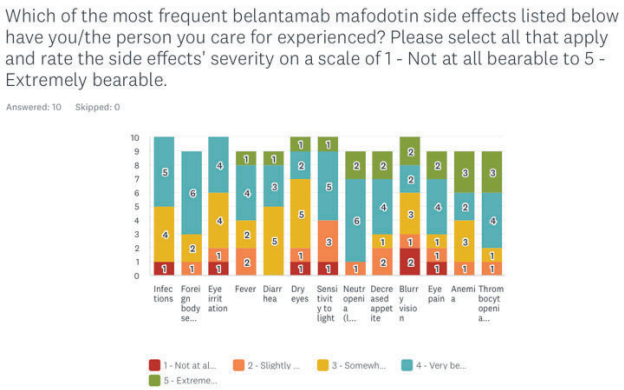


Figure 9 — Experience of belantamab mafodotin side effects (Subset T; 10)

When asked "*How effective was the supportive care you received in managing your side effects from belantamab mafodotin treatment? Please rate on a scale of 1–5 where 1 is Not at all effective and 5 is Extremely effective",* 5 Subset T respondents (10) chose '4 – Very effective', 2 chose '3 – Somewhat effective', 2 chose '2 – Slightly effective', and 1 chose '5 - Extremely effective'.

Following the instructions "*Please answer each of the following questions on your overall experience with belantamab mafodotin, by rating them on a scale of 1- Not at all to 5 - Completely",* Subset T patients (10) responded to the questions:

- "*Were the overall side-effects of belantamab mafodotin manageable?* (Mostly: 5, Somewhat: 3; Slightly: 1, Not at all: 1).
- "*Was belantamab mafodotin effective in controlling myeloma for you/the person you care for?"* (Completely: 5, Mostly: 1, Somewhat: 3; Slightly: 1).

Finally, when asked if there was anything else they would like to share about their experience with belantamab mafodotin, 5 Subset T patients provided the following comments:

"*The weekly 40 mgs of dexamethasone is probably the most negative aspect of the trial*";

"Side affects from the supporting drugs like the anti-biotic that you take for the first month."

"*how to manage the blurry vision and constipation is very important*"

"The patient could not produce enough platelets to continue treatment with Blenrep, therefore it is difficult to know if Blenrep would have been successful."

"*This drug should be approved for treatment of Myeloma in Canada. The eye toxicity side effects are cyclical and do affect day to day activities but the drug works for controlling myeloma and should be administered.*"

7. Anything Else?

1. In a focus group conducted by Myeloma Canada in 2022, two patients had experience with BPd treatment, and described the importance of having additional treatment options available to them. As well, all participants in this focus group described finding it is less difficult to set decision criteria in the abstract, but often, when faced with a treatment decision, this is in the context of their previous treatment failing and/or a decline in their health. Participants said that this situation is frequently met by doctors inquiring, 'what measures are you willing to take to stay alive'; and despite their preference for an improved quality of life, many acknowledged that in the moment, they would likely be more willing to start a new treatment despite its potential impact on quality of life, especially if there is only one treatment option accessible to them, or they perceive

the risks to be less significant those that of another treatment. It is extremely important to allow patients and their care team to weigh risks/side effects for themselves whenever possible. If they perceive the potential consequences of cardiac toxicities, or infections like COVID-19 acquired while in hospital to be greater than potential ocular toxicities, they should be able to make that decision. In support of the focus group's conclusions, 67% of survey respondents felt that the ability of a treatment to prolong life was 'extremely important' while only 58% rated a treatment's ability to improve quality of life as 'extremely important' (see page 8). Patients must balance these interests when choosing treatment but ultimately, many find extending their life to be a more important goal of treatment, and thus choose to accept the (potential) side effects.

2. When Subset T respondents (7) were asked "*How difficult was it to find an optometrist or eye-specialist to monitor eye health and vision changes while you or the person you care for were/are receiving treatment with belantamab mafodotin?"*, 8 answered 'Not at all difficult' and 1 answered 'Somewhat difficult'. This may be influenced by the fact that all respondents were receiving belantamab mafodotin through a clinical trial. In the aforementioned focus group conducted by Myeloma Canada in 2022, one participant reported considerable difficulty finding an optometrist who was comfortable taking on the monitoring of their eyes while receiving BPd.

3. The eye and vision related side effects are of concern to patients, but the comments represented a wide range of views. This underscores the importance of patient preference in weighing the potential costs and benefits of a new treatment, which can only occur when patients have access to different treatment options. As expressed by survey respondents, for those with specific comorbidities impacting their sight, or those for whom vision plays a key role in activities of personal/professional importance, belantamab mafodotin containing regimens may not be an optimal choice. For rural patients though, this calculation may look very different as a higher value may be placed on factors like dose flexibility, or fewer hospital visits/less time spent in hospital. As well, the increasing number of patients receiving 3 or 4 drug combinations *including an anti-CD38 antibody* at the first line of therapy are triple-class exposed and potentially triple-class refractory after their first or second line of treatment, leaving them with fewer treatment effective options when they relapse, and in need of new *classes of therapy* with *different genetic targets and risk profiles* available before the fourth line of therapy.

4. Patients should be proactively informed about vision problems. One patient in the survey commented *" just found out velcade caused vision problems"* , and Myeloma Canada received a similar comment in a focus group we conducted in 2021 about not being informed of the impact bortezomib could have on vision.

Appendix: Patient Group Conflict of Interest Declaration

1. Did you receive help from outside your patient group to complete this submission? If yes, please detail the help and who provided it.

   No

2. Did you receive help from outside your patient group to collect or analyze data used in this submission? If yes, please detail the help and who provided it.

   The Leukemia and Lymphoma Society of Canada assisted with data collection by sharing the link to our survey.

   No help was received from outside Myeloma Canada for data analysis.

3. List any companies or organizations that have provided your group with financial payment over the past 2 years AND who may have direct or indirect interest in the drug under review.

Table 1: Financial Disclosures

Company	$0 to 5,000	$5,001 to 10,000	$10,001 to 50,000	In Excess of $50,000
Abbvie	☐	☒	☒	☒
AstraZeneca	☐	☐	☒	☐
Apotex	☐	☐	☐	☒
Amgen	☐	☐	☐	☒
The Binding Site	☐	☐	☐	☐
BMS	☐	☐	☐	☒
FORUS Therapeutics	☐	☐	☐	☒
GSK	☐	☐	☐	☒
IMC	☐	☒	☐	☒
JAMP	☐	☐	☒	☐
Janssen	☐	☐	☐	☒
Merck	☐	☐	☒	☐
Pfizer	☐	☐	☐	☒
Rapid Novor	☐	☐	☐	☒
Roche	☐	☐	☒	☐
Sanofi	☐	☐	☐	☒

Sebia Diagnostics	☐	☐	☒	☐
Takeda	☐	☐	☒	☐

I hereby certify that I have the authority to disclose all relevant information with respect to any matter involving this patient group with a company, organization, or entity that may place this patient group in a real, potential, or perceived conflict of interest situation.

Name: Aidan Robertson
Position: Advisor, Health Policy and Advocacy
Patient Group: Myeloma Canada
Date: 11-06-2024

CADTH Reimbursement Review

Clinician Group Input

CADTH Project Number: PC0379-000

Generic Drug Name (Brand Name): belantamab mafodotin, bortezomib, dexamethasone

Indication: Belantamab mafodotin is indicated for the treatment of multiple myeloma in combination with bortezomib and dexamethasone (BVd) in adult patients who have received at least one prior therapy.

Name of Clinician Group: OH (CCO) Hematology Cancer Drug Advisory Committee (DAC)

Author of Submission: Dr. Tom Kouroukis and members of the DAC

1. About Your Clinician Group

OH(CCO)'s Drug Advisory Committees provide timely evidence-based clinical and health system guidance on drug-related issues in support of CCO's mandate, including the Provincial Drug Reimbursement Programs (PDRP) and the Systemic Treatment Program.

2. Information Gathering

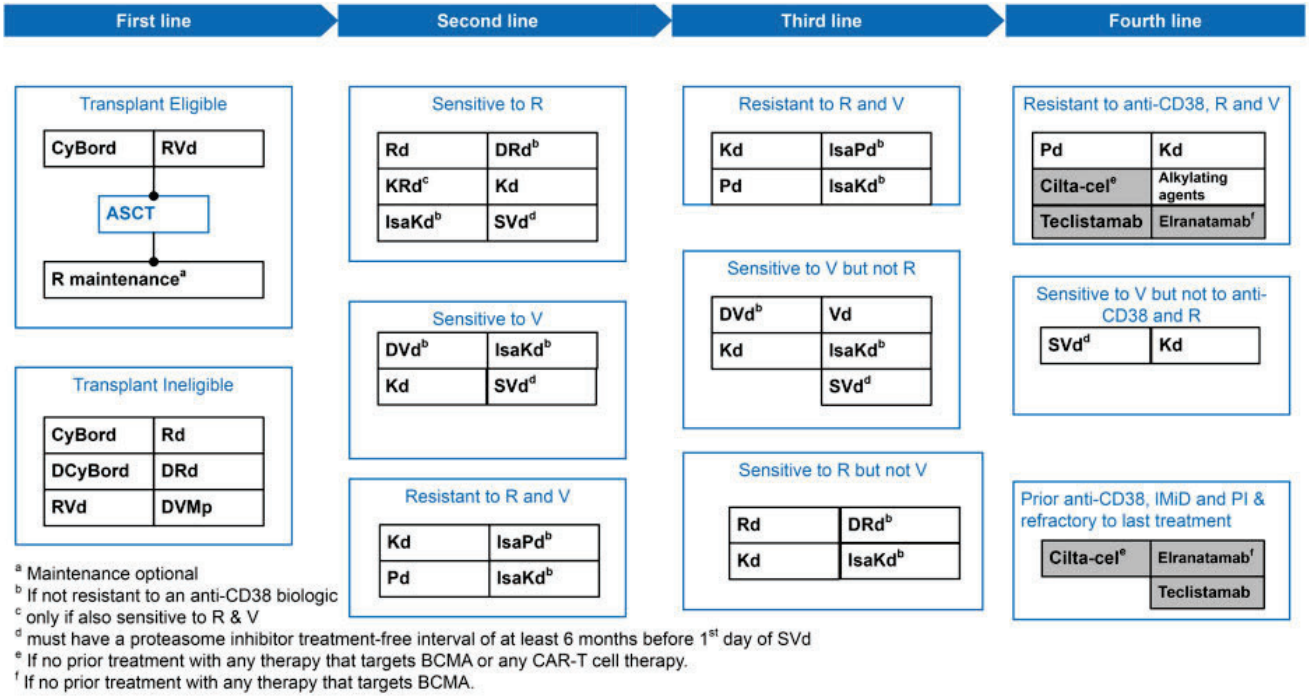
Information was gathered via video-conferencing.

3. Current Treatments and Treatment Goals

Current treatments include DVd, IsaKd, Kd, and SVd (re: Figure 1 – current Provisional Funding Algorithm for Multiple Myeloma (CDA-AMC August 2024)

Treatment goals include disease control, improvement in symptoms, prolonged survival, prevention of end-organ damage.

Figure 1: Provisional Funding Algorithm Diagram for Multiple Myeloma



[a] Maintenance optional
[b] If not resistant to an anti-CD38 biologic
[c] only if also sensitive to R & V
[d] must have a proteasome inhibitor treatment-free interval of at least 6 months before 1st day of SVd
[e] If no prior treatment with any therapy that targets BCMA or any CAR-T cell therapy.
[f] If no prior treatment with any therapy that targets BCMA.

4. Treatment Gaps (unmet needs)

4.1. Considering the treatment goals in Section 3, please describe goals (needs) that are not being met by currently available treatments.

Not all treatments work effectively in relapsed myeloma. Second line BCMA targeted therapy can be an attractive option for some patients.

5. Place in Therapy

5.1. How would the drug under review fit into the current treatment paradigm?

This is another option in Figure 1, second line, “Sensitive to V.” Using this regimen may preclude future use of BCMA targeted CAR-T therapy.

5.2. Which patients would be best suited for treatment with the drug under review? Which patients would be least suitable for treatment with the drug under review?

For patients that are unlikely to get CAR-T cell therapy, this can be a good BCMA targeted therapy.

There is potential eye toxicity with this drug which may be a concern for some patients.

5.3 What outcomes are used to determine whether a patient is responding to treatment in clinical practice? How often should treatment response be assessed?

Standard myeloma response outcomes used in clinical practice.

5.4 What factors should be considered when deciding to discontinue treatment with the drug under review?

Significant toxicity (particularly ocular) or disease progression.

5.5 What settings are appropriate for treatment with [drug under review]? Is a specialist required to diagnose, treat, and monitor patients who might receive [drug under review]?

Outpatient setting. There is a need for ophthalmological assessment as well.

6. Additional Information

NA

7. Conflict of Interest Declarations

To maintain the objectivity and credibility of the CADTH drug review programs, all participants in the drug review processes must disclose any real, potential, or perceived conflicts of interest. This conflict of interest declaration is required for participation. Declarations made do not negate or preclude the use of the clinician group input. CADTH may contact your group with further questions, as needed. Please see the *Procedures for CADTH Drug Reimbursement Reviews* (section 6.3) for further details.

1. Did you receive help from outside your clinician group to complete this submission? If yes, please detail the help and who provided it.

   OH-CCO provided secretariat support to the group in completing this submission.

2. Did you receive help from outside your clinician group to collect or analyze any information used in this submission? If yes, please detail the help and who provided it.

   No.

3. List any companies or organizations that have provided your group with financial payment over the past two years AND who may have direct or indirect interest in the drug under review. **Please note that this is required for each clinician who contributed to the input — please add more tables as needed (copy and paste). It is preferred for all declarations to be included in a single document.**

Declaration for Clinician 1

Name: Dr. Tom Kouroukis

Position: Lead, OH (CCO) Hematology Cancer Drug Advisory Committee

Date: 10-10-2024

☒ **I hereby certify** that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Table 1: Conflict of Interest Declaration for Clinician 1

	Check appropriate dollar range*			
Company	**$0 to $5,000**	**$5,001 to $10,000**	**$10,001 to $50,000**	**In excess of $50,000**
Add company name				
Add company name				
Add or remove rows as required				

* Place an X in the appropriate dollar range cells for each company.

Declaration for Clinician 2

Name: Dr. Selay Lam

Position: Member, OH (CCO) Hematology Cancer Drug Advisory Committee

Date: 10-10-2024

☒ I hereby certify that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Table 2: Conflict of Interest Declaration for Clinician 2

	Check appropriate dollar range*			
Company	**$0 to $5,000**	**$5,001 to $10,000**	**$10,001 to $50,000**	**In excess of $50,000**
Add company name				
Add company name				

Add or remove rows as required				

* Place an X in the appropriate dollar range cells for each company.

Declaration for Clinician 3

Name: Dr. Jordan Herst

Position: Member, OH (CCO) Hematology Cancer Drug Advisory Committee

Date: 10-10-2024

☒ I hereby certify that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Table 3: Conflict of Interest Declaration for Clinician 3

	Check appropriate dollar range*			
Company	**$0 to $5,000**	**$5,001 to $10,000**	**$10,001 to $50,000**	**In excess of $50,000**
Add company name				
Add company name				
Add or remove rows as required				

* Place an X in the appropriate dollar range cells for each company.

Declaration for Clinician 4

Name: Dr. Joanna Graczyk

Position: Member, OH (CCO) Hematology Cancer Drug Advisory Committee

Date: 10-10-2024

☒ I hereby certify that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Table 4: Conflict of Interest Declaration for Clinician 4

Company	Check appropriate dollar range*			
	$0 to $5,000	**$5,001 to $10,000**	**$10,001 to $50,000**	**In excess of $50,000**
Add company name				
Add company name				
Add or remove rows as required				

* Place an X in the appropriate dollar range cells for each company.

Declaration for Clinician 5

Name: Dr. Lee Mozessohn

Position: Member, OH (CCO) Hematology Cancer Drug Advisory Committee

Date: 10-10-2024

☒ I hereby certify that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Table 5: Conflict of Interest Declaration for Clinician 5

Company	Check appropriate dollar range*			
	$0 to $5,000	**$5,001 to $10,000**	**$10,001 to $50,000**	**In excess of $50,000**
Add company name				
Add company name				
Add or remove rows as required				

* Place an X in the appropriate dollar range cells for each company.

Declaration for Clinician 6

Name: Dr. Christopher Cipkar

Position: OH (CCO) Hematology Cancer Drug Advisory Committee member

Date: 10-10-2024

☒ I hereby certify that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Table 5: Conflict of Interest Declaration for Clinician 6

Company	Check appropriate dollar range*			
	$0 to $5,000	$5,001 to $10,000	$10,001 to $50,000	In excess of $50,000
Add company name				
Add company name				
Add or remove rows as required				

* Place an X in the appropriate dollar range cells for each company.

Declaration for Clinician 7

Name: Rami El-Sharkaway

Position: OH (CCO) Hematology Cancer Drug Advisory Committee member

Date: 10-10-2024

☒ I hereby certify that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Table 5: Conflict of Interest Declaration for Clinician 7

Company	Check appropriate dollar range*			
	$0 to $5,000	$5,001 to $10,000	$10,001 to $50,000	In excess of $50,000
Add company name				
Add company name				
Add or remove rows as required				

* Place an X in the appropriate dollar range cells for each company.

CADTH

CADTH Reimbursement Review

Clinician Group Input

CADTH Project Number: **PC0379-000**
Generic Drug Name (Brand Name): **belantamab mafodotin, bortezomib, dexamethasone**
Indication:
Name of Clinician Group: Canadian Myeloma Research Group (CMRG)
Author of Submission: Dr. Suzanne Trudel

1. About Your Clinician Group

Please describe the purpose of your organization. Include a link to your website (if applicable).

< The Canadian Myeloma Research Group (CMRG) is a Canada-wide network of researchers aiming to develop better treatments for extending life of myeloma patients, enhancing the quality of life for those living with myeloma and related disorders and working to find a cure for these diseases and other plasma cell disorders. The three main purposes of CMRG consist of: 1) conducting investigator-initiated academic clinical trials to improve the outcome of myeloma patients; 2) maintenance of a national Myeloma Database, now consisting of over 7000 patients, to evaluate real-word patterns of treatment, outcomes, risk factors and areas for future research in myeloma; and 3) generation of consensus statements for myeloma management.>

2. Information Gathering

Please describe how you gathered the information included in the submission.

< CMRG holds monthly teleconferences, and participants agreed to submit a single document for feedback to CADTH which would be signed by the physicians who agreed with the information. The initial draft of the document was prepared in consultation with the CMRG Chief Medical Officer and sent to all members to obtain input. Comments and suggestions were incorporated as appropriate. The final draft was signed by physicians who agreed with all of the content and their Conflict of Interest obtained as required.>

3. Current Treatments and Treatment Goals

Please describe the current treatment paradigm for the disease.

- Focus on the Canadian context.
- Please include drug and non-drug treatments.
- Drugs without Health Canada approval for use in the management of the indication of interest may be relevant if they are routinely used in Canadian clinical practice. Treatments available through special access programs are relevant. Are such treatments supported by clinical practice guidelines?
- Do current treatments modify the underlying disease mechanism? Target symptoms?
- What are the most important goals that an ideal treatment would address?
- **Examples:** Prolong life, delay disease progression, improve lung function, prevent the need for organ transplant, prevent infection or transmission of disease, reduce loss of cognition, reduce the severity of symptoms, minimize adverse effects, improve health-related quality of life, increase the ability to maintain employment, maintain independence, reduce burden on caregivers.

- Initial Therapy: Currently, newly diagnosed Canadian myeloma patients are still divided into those who are transplant-eligible (TE), or transplant-ineligible (TI) based on age and fitness. TE patients receive bortezomib-based induction with RVD (previously CyBorD) followed by high-dose melphalan + ASCT and then lenalidomide-maintenance until disease progression. TI patients preferentially daratumumab-based regimens, typically DRd; a small proportion with renal compromise or poor marrow reserved may comment treatment with Dara-CYBORD. Less often, TI patients may receive Rd or RVd (typically "lite") with single- agent lenalidomide also given until disease progression. Support for these algorithms comes from published phase 3 trials as well as real-world CMRG analyses. These approaches have also been endorsed by CADTH in the recent Provisional Funding Algorithm.

- Second-line therapy (after 1 prior regimen): Second-line therapy depends on whether patients have progressed on lenalidomide (which currently includes the vast majority of Canadian TE and TI patients at first relapse). A key priority to date has been the inclusion of an anti-CD38 antibody at this time if one was not used in the first-line setting. ASCT patients on lenalidomide maintenance usually receive DVd or, more recently, IsaKd, at the time of first progression. These regimens are also utilized in the TI patient if they progressed on lenalidomide in the era before the availability of daratumumab-based regimens such as DRd as initial therapy. In the uncommon TE or TI patient who has not progressed on lenalidomide in first-line, DRd is strongly preferred as the second-line regimen (in the absence of prior daratumumab exposure). Other potential regimens in patients progressing on lenalidomide +/- daratumumab include XVd and Kd (+/- cyclophosphamide). Finally, a small number of patients with private insurance can access pomalidomide + daratumumab + dex (DPd) as an alternative to Isa-Kd in second-line if they have progressed on lenalidomide but not yet received a CD38 monoclonal antibody in initial therapy.

  Despite the preferential use of triplet regimens for second-line treatment, prior progression on first-line lenalidomide by itself constitutes an adverse risk even in the absence of other recognized high-risk features. The phase 3 trials that established the efficacy of the regimens listed above that are now an option for second-line use in Canada contained relatively low numbers of patients progressing on lenalidomide simply due to the era in which they were performed. Data on the subset of patients progressing on first-line lenalidomide has become available for many of these regimens, and consistently describes a shorter PFS than for the entire group and those without progression on lenalidomide. Specifically, the median PFS has been less than 18 months for Kd, KCd, DVd, DPd, XVd and PVd (the latter of which is not formally funded but which can occasionally be accessed via compassionate means). Real-world evidence from CRMG Database analyses confirms the suboptimal results of these regimens used in second-line after lenalidomide (references here). The longest median PFS reported in a prospective trial of relapsed/refractory patients, before the newest immunotherapeutics, was seen with IsaKd in the IKEMA trial (Martin T, et al. Blood Cancer J. 2023 May 9;13(1):72). In this study, the median PFS for all myeloma patients progressing after 1-3 prior lines of therapy was 35.7 months. However, subset analyses noted that the 18-month PFS in patients refractory to lenalidomide was only 53% compared to 77% in all patients with only 1 prior line of therapy and 68% in those with greater that 1 line (Dimopoulos MA, et al. Am J Hematol 2023;98:E15–E19). Additionally, not all individuals are eligible for this carfilzomib-based regimen due to cardiovascular, renal, or logistic issues. Due to the relatively recent funding of IsaKd, real-world Canadian results are not yet available.

  Finally, Health Canada recently granted the BCMA CAR-T cell construct cilta-cel an expanded indication to include patients that have received 1 to 3 prior lines of therapy (LoT) including a proteasome inhibitor (PIs) and an immunomodulatory agent (IMiDs), and who are refractory to lenalidomide. This option is not yet fund in second line nor is it marketed in Canada yet. Cilta-cel's administration is much more complex than administration of other immunotherapies such as bispecifics and antibody drug conjugates (ADCs) due to its need for T-cell collection, bridging therapy while waiting for CAR-T processing, lymphodelpletion therapy and CAR-T cell infusion, even though it is given only once. Resources will need to be built into the current system to accommodate: 1) the increasing proportion of patient who will receive this treatment; 2) the specific early toxicities which are more severe than those seen with the other treatments including ADCs and bispecifics; and

3) the need for patients to remain close to the treating centre during the early post-administration days. Finally, even if reimbursement negotiations are achieved we expect ongoing bottlenecks due to production limitations and challenges with capacity at the institutional level.

- Third-line therapy (after 2 prior regimens): If patients have not yet received an anti-CD38 monoclonal antibody by the time of third-line treatment is needed, every effort is made to procure a combination containing such agents such as IsaPd. Of note, this represents a dwindling population of patients. Otherwise, POM, carfilzomib or selinexor can be administered with dex and a third agent which may have been utilized before. Funded options include POM + dex +/- cyclophosphamide (PCd), carfilzomib + dex +/- cyclophosphamide (Kd or KCd). or XVd. Again, triplet regimens are generally preferable. The median PFS with any of these regimens is less than 12 months.

- Fourth-line therapy: Until recently, the options have been extremely limited. A pomalidomide- or carfilzomib-based regimen such as Pd or Kd may be utilized if not used earlier in the third line. Additional treatment options include a regimen of bortezomib + steroids (Vd) yields a short PFS and often cannot be revisited in many jurisdictions if patients are previously refractory to proteasome inhibitors. XVd is approved and funded after1 prior line and can be used in the setting of advanced myeloma. Although cyclophosphamide can be added to many regimens or even used with steroids as a doublet (CyDex or cyclo/prednisone), the cumulative lifetime exposure to cyclophosphamide is limited to 1 to 2 years for each patient due to the risks of bladder cancer or secondary MDS/AML from this alkylating agent; the latter risk may restrict use of alternative alkylating agents like melphalan. A CMRG database analysis indicated that the median PFS for patients who had been triple-class exposed or refractory was 4.4 and 4,6, respectively. Given these findings, palliation/best supportive care and/or local radiotherapy may be appropriate in some individuals.
- Belantamab mafodotin (belamaf), a BCMA ADC had previously been available via a Health Canada SAP. Single agent belamaf was initially granted accelerated/conditional approval by the United States Food and Drug Administration (FDA) and European Medicines Agency (EMA) in 2020 for patients with RRMM who have received at least 4 prior LoTs; including an immunomodulatory agent, PI and anti-CD38 monoclonal antibody). Approval was based on the overall response rates (ORRs) observed in the Phase I DREAMM-1 (NCT02064387) and Phase II DREAMM-2 (NCT03525678) clinical trials. The subsequent Phase III, confirmatory DREAMM-3 (NCT04162210) study of belamaf monotherapy versus the doublet of POM with dex in patients with RRMM who had received two or more prior LoTs did not meet the primary endpoint of superiority for progression-free survival (PFS), and as a result of not fulfilling confirmatory requirements, belamaf was withdrawn from US and European markets in 2023 and is no longer available by Health Canada SAP. It is important to note that the median PFS in DREAMM-3 was numerically longer at 11.2 months for belamaf compared to 7.0 months for POM and dexa; however, the overall difference between arms in the risk of disease progression or death did not reach statistical significance at the primary analysis (hazard ratio (HR), 1.03; 95% CI, 0.72–1.47; P=0.56) (18). However, with longer follow up, the HR for PFS has lowered to 0.86 (95% CI, 0.63–1.18). As a result, belamaf continues to be investigated in several other Phase III trials as a treatment for patients with RRMM and in patients that are newly diagnosed in combination with standard of care therapies.

The recent approvals of the anti-BCMA bispecific antibodies teclistamab and elranatamab offer a longer PFS than the prior treatments listed above. These 2 agents are approved by Health Canada but are not yet funded publicly. There are ongoing drug access programs provided by pharma in Canada that allow a few select patients to receive them. These agents require special expertise during the step-up period to properly manage unique complications such as CRS and ICANS. Widespread integration of these bispecific antibodies into provincial myeloma algorithms requires additional infrastructure in terms of more physical resources and staffing to address the specialized needs of these patients.

Similarly, the BCMA CAR-T cell construct cilta-cel is approved by Health Canada but is not yet funded in fourth-line therapy. Although supportive care considerations overlap with those of the bispecifics, cilta-cel's administration as mentioned above is much more complex and it can be exceedingly challenging in this setting to bridge patients for the 5-6 weeks required to manufacture the product.

Finally, the GPRC5d targeting bispecific, talquetamab has recently received Health Canada in this space. It has recently received a negative review by CADTH and there is no drug access program for this agent and it is not available via SAP.

- Clinical trials are key to improving survival of Canadian patients through early access to promising agents in this setting but clinical trial participation is markedly limited by: 1) strict eligibility criteria such as platelets over 75 x 10^9/L or near-normal renal function that may be challenging to meet in advanced myeloma; 2) the decision by pharma to open promising trials in only a few Canadian sites, or, as in the case of some CAR-T cell studies, to bypass Canada completely in favor of European or US sites; 3) the policy of pharma to offer a time-limited trial spot for only few days so if a patient is not available immediately, the opening is removed and given to a centre in another country; 4) slow trial accrual to promising agents undergoing evaluation in a phase 1 study as DSMB reviews need to take place before a new cohort can be opened.

4. Treatment Gaps (unmet needs)

4.1. Considering the treatment goals in Section 3, please describe goals (needs) that are not being met by currently available treatments.

Please describe goals (needs) that are not being met by currently available treatments. Examples of unmet needs:

- Not all patients respond to available treatments
- Patients become refractory to current treatment options
- No treatments are available to reverse the course of disease
- No treatments are available to address key outcomes
- Treatments are needed that are better tolerated
- Treatments are needed to improve compliance
- Formulations are needed to improve convenience

Please describe limitations associated with current treatments (e.g., adverse events, administration, etc., if applicable).

< Myeloma remains incurable despite the introduction of new agents over the last 2 decades. Patients eventually become refractory to all available funded anti-myeloma agents. At this point, the symptom burden for patients is high with bone pain/destruction, anemia and other cytopenias, renal damage, hypercalcemia and a high risk of infection. The highest unmet need in myeloma continues to be adequate treatment for patients who have progressed despite exposure to effective agents. In the past, this group largely consisted of those who had already received the three major classes drugs -- an IMID, PI and anti-CD38 monoclonal antibody ("triple-class exposed or triple-class refractory"). Initially, these 3 agents were given in sequential regimens, and the unmet need was most apparent after 3 or more lines of treatment. However, with the movement of combinations of three major drug class to the first- and second-line setting, exposure (and resistance) to multiple drug classes now occurs much earlier in the disease course. Specifically, the funding of RVd induction in TE and DRd in TE patients as first-line regimens means that patients may be triple-class exposed/refractory after 2 lines of therapy (or even 1 line in the case of the few patients in Canada who can access daratumumab plus RVd (DVD) before ASCT via clinical trials or private insurance).

Importantly, as discussed above, more information has become apparent 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 of 11-18 months with virtually all traditional and reimbursed second-line regimens (including those containing an anti-CD38 monoclonal antibody) compared to the results without such exposure. With subsequent regimens, periods of myeloma control become progressively shorter. In summary, the unmet need in myeloma has shifted much earlier in the disease course and warrants the use of the more powerful immunotherapies earlier in sequencing. From a clinical perspective, Canadian hematologists perceive that drug exposure, rather than lines of therapy, more accurately defines the need for access to the innovative immunotherapeutics in order to forestall the development of refractory myeloma and its detrimental effects on patient quality of life, caregiver burden and a shortened lifespan.

As mentioned above, Health Canada recently granted the BCMA CAR-T cell construct cilta-cel an expanded indication to include patients that have received 1 to 3 prior lines of therapy (LoT) including a proteasome inhibitor (PIs) and an immunomodulatory agent (IMiDs), and who are refractory to lenalidomide. This option has received a a positive CADTH recommendation in second line but is not yet funded or marketed in Canada. As already discussed, cilta-cel's administration is much more complex than administration of other immunotherapies such ADCs due to its need for T-cell collection, bridging therapy while waiting for CAR-T processing, lymphodelpletion therapy and CAR-T cell infusion. Resources will need to be built into the current system to accommodate and it is not expected that all second line patients will be able to receive cilta-cel. Further given the geography of Canada many patients will not be able to relocate to certified centres for CAR-T cell administration and others may not have the supports to undergo such treatment. These patients are in need for treatment strategies that are highly effective and can be given locally, without need for caregivers. Finally, a subgroup analysis of CARTITUDE-1 demonstrated an initial inferior overall survival for patients receiving Cilta-cel after 1 prior line of therapy compared to standard of care with cross-over favoring cilta-cel not occurring until 18 months of follow-up (FDA Carvykti ODAC Materials 15 Mar 2024) showing the need for treatments in early relapse that can rapidly lead to disease control.

>

5. Place in Therapy

5.1. How would the drug under review fit into the current treatment paradigm?

Is there a mechanism of action that would complement other available treatments, and would it be added to other treatments?

Is the drug under review the first treatment approved that will address the underlying disease process rather than being a symptomatic management therapy?

Would the drug under review be used as a first-line treatment, in combination with other treatments, or as a later (or last) line of treatment?

Would the drug under review be reserved for patients who are intolerant to other treatments or in whom other treatments are contraindicated?

Is the drug under review expected to cause a shift in the current treatment paradigm?

Please indicate whether or not it would be appropriate to recommend that patients try other treatments before initiating treatment with drug under review. Please provide a rationale for your perspective.

<The drug combination in question would be appropriate for myeloma patients who have received one prior LofT and are lenalidomide exposed. Based upon the latest phase 3 trial data, the results of adding a drug with a novel mechanism of action and therapeutic target (belamaf) to standard of care pom and dexa—provides a treatment option that has a superior PFS and a strong trend to overall survival benefit over the health Canada approved option of PVd. The availability of BPd in the proposed setting would pertain to patients who have had 1 to 3 prior lines of therapy. This combination offers a highly effective off the shelf treatment option for patients progressing after stem cell transplant and lenalidomide maintenance. Given the inferior prognosis of progression on lenalidomide even with anti-CD38 based combinations such as IsaKd, patients would have access BPd after 1 prior line rather than receiving suboptimal regimen exposing patients to unnecessary side-effects in addition to an unwanted burden on the health care system.

Further the treatment would also greatly benefit those progressing after DRd first or second line where currently available anti-CD38 sparing options offer PFS of 18 months or less at best. This is also supported by data from the Canadian Algonquin trial of BPd that enrolled 100% lenalidomide exposed patients of which 78.9% of patients were anti-CD38 exposed. The estimated-2 year PFS was 52.8% at the recommended part 2 dose (Trudel et al, Nat Med 2024; 30:543). A subgroup analysis of PFS for patients that had received 1 prior LoT and were the lenalidomide refractory in DREAMM-8 revealed a PFS that was not reached (21.1-NR months). While cilta-cel is approved but not yet funded for this indication-limitations for its use second line are listed above. Finally, other anti-BMCA therapies have been Health Canada approved for relapsed myeloma it is important to acknowledge that there is attrition with each line of therapy and therefore we should not risk treating patients with suboptimal therapy for the potential to use other anti-BMCA therapies (cilta-cel or bispecifics) in later lines.>

5.2. Which patients would be best suited for treatment with the drug under review? Which patients would be least suitable for treatment with the drug under review?

Which patients are most likely to respond to treatment with drug under review?

Which patients are most in need of an intervention?

Would this differ based on any disease characteristics (e.g., presence or absence of certain symptoms, stage of disease)?

How would patients best suited for treatment with drug under review be identified (e.g., clinician examination/judgement, laboratory tests (specify), diagnostic tools (specify))

Are there any issues related to diagnosis?

Is a companion diagnostic test required?

Is it likely that misdiagnosis occurs in clinical practice (e.g., underdiagnosis)?

Is it possible to identify those patients who are most likely to exhibit a response to treatment with drug under review?

<

The least suitable patients would include be patients that are refractory to pomalidomide. Patients exposed to anti-BCMA therapies were not included in the DREAMM-8 study so there is uncertainty of activity in this patient population. Subgroup analysis demonstrated a benefit favouring BPd in patients refractory to lenalidomide (HR 0.45;0.31-0.65) and those refractory to anti-CD38s (HR.65; 0.36-1.18) supporting that these patients should be eligible. There is uncertainty in patients who are bortezomib refractory as these patients were excluded from the study because of the control arm but the PFS favoured BPD for the bortezomib exposed patients (HR 0.55; 0.38-0.78) and it is not expected that belamaf would have cross resistance with bortezomib.

Patients with adequate performance status and organ function and older patients are likely to have the good outcomes.

Patients with other disease-related adverse prognostic factors, such as high-risk cytogenetics, extramedullary disease ISS II/III and functional high risk patients do not fare significantly worse and should be eligible for BPd.

>

5.3 What outcomes are used to determine whether a patient is responding to treatment in clinical practice? How often should treatment response be assessed?

Are outcomes used in clinical practice aligned with the outcomes typically used in clinical trials?

What would be considered a clinically meaningful response to treatment? Consider the magnitude of the response to treatment. Is this likely to vary across physicians?

Examples: improved survival; reduction in the frequency/severity of symptoms (provide specifics regarding changes in frequency, severity, etc.); attainment of major motor milestones; ability to perform activities of daily living; improvement of symptoms; and stabilization (no deterioration) of symptoms.

<

Responses are based on the monoclonal protein markers in the serum and/or urine, bone marrow biopsy and, in some instances, by imaging studies (standardized International Myeloma Working Group Criteria (IMWG)). These parameters are aligned with those used in the clinical trials, which also included the emerging parameter of marrow minimal residual disease (MRD).

Clinically meaningful responses usually correlate with at least a partial remission by 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. In myeloma, responses are generally assessed every 1-3 months depending on clinical stability and regimen used for therapy.

>

5.4 What factors should be considered when deciding to discontinue treatment with the drug under review?

Examples: disease progression (specify, e.g. loss of lower limb mobility); certain adverse events occur (specify type/frequency/severity); or additional treatment becomes necessary (specify).

< Similar to more conventional myeloma therapies, the combination of BPd is presently given until disease progression. Treatment is continued based on ongoing efficacy, as measured above, and, additionally, long-term tolerability is required. Notably the management of ocular toxicities which are common with MMAF-containing ADCs including with belamaf are managed with dose holds. In the DREAMM-8 study median interval between doses increased over time from 4 to 8 to 12 and to maximally to 16 weeks. With this dose modification strategy the incidence of patients experiencing a decrease in best corrected visual acuity (BCVA) to ≥20/50 remained below 17% over time and led to low discontinuation rate (9%) with no patients discontinuing treatment due to ocular adverse events after 12 months on treatments. Importantly, efficacy was maintained in patients requiring extended belamaf dosing. Ocular toxicities were reversible in nearly all patients (85% resolved, 92% improved) with those patients not resolving having completed follow up with event ongoing. Finally, the safety profile did not negatively impact quality of life. This data is consistent with results we reported in the Algonquin trial. At the recommended part 2 dose no patients discontinued treatment for ocular toxicity. To date 110 patients have been enrolled across 9 sites in Canada (Trudel et al, Nat Med 2024; 30:543). No patient has had permanent loss of vision. All sites have successfully worked with eye care professionals to manage the ocular toxicities>

5.5 What settings are appropriate for treatment with [drug under review]? Is a specialist required to diagnose, treat, and monitor patients who might receive [drug under review]?

Examples: Community setting, hospital (outpatient clinic), specialty clinic

If a specialist is required, which specialties would be relevant?

< We suggest that belamaf be administered and monitored by hematologists/oncologists who have the knowledge and expertise to manage the potential adverse events that can be associated its use. We also recommend that patients undergo an eye exam by an eye care professional (ophthalmologists or optometrists) prior to first dosing of belamaf and before each planned dose to established

if dose can be administered based on the keratopathy and visual acuity scale and patient symptoms or if delay is required to allow for recovery of ocular toxicities. Administration is intravenous over 30 minutes in the outpatient community setting. Pomalidomide and dexamethasone are home medications taken orally.>

6. Additional Information

Is there any additional information you feel is pertinent to this review?

<Enter Response Here>

7. Conflict of Interest Declarations

To maintain the objectivity and credibility of the CADTH drug review programs, all participants in the drug review processes must disclose any real, potential, or perceived conflicts of interest. This conflict of interest declaration is required for participation. Declarations made do not negate or preclude the use of the clinician group input. CADTH may contact your group with further questions, as needed. Please see the *Procedures for CADTH Drug Reimbursement Reviews* (section 6.3) for further details.

1. Did you receive help from outside your clinician group to complete this submission? If yes, please detail the help and who provided it.

   <Enter Response Here>

2. Did you receive help from outside your clinician group to collect or analyze any information used in this submission? If yes, please detail the help and who provided it.

   <Enter Response Here>

3. List any companies or organizations that have provided your group with financial payment over the past two years AND who may have direct or indirect interest in the drug under review. **Please note that this is required for each clinician who contributed to the input — please add more tables as needed (copy and paste). It is preferred for all declarations to be included in a single document.**

Declaration for Clinician 1

Name: Dr. Donna Reece
Position: Chief Medical Officer, CMRG
Date: 11-10-2022

☒ **I hereby certify** that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Table 1: Conflict of Interest Declaration for Clinician 1

	Check appropriate dollar range*			
Company	**$0 to $5,000**	**$5,001 to $10,000**	**$10,001 to $50,000**	**In excess of $50,000**
BMS/Celgene			X	

Janssen			X	
Amgen			X	
Sanofi	X			
GSK	X			
Takeda	X			

* Place an X in the appropriate dollar range cells for each company.

Declaration for Clinician 2

Name: Dr. Christopher Venner
Position: Hematologist Lymphoma and Myeloma Program, BC Cancer Vancouver Centre
Date: 11-10-2022

☒ I hereby certify that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Table 2: Conflict of Interest Declaration for Clinician 2

	Check appropriate dollar range*			
Company	**$0 to $5,000**	**$5,001 to $10,000**	**$10,001 to $50,000**	**In excess of $50,000**
Celgene/BMS	X			
Takeda	X			
Janssen	X			
Amgen	X			
Sanofi	X			
GSK	X			

* Place an X in the appropriate dollar range cells for each company.

Declaration for Clinician 3

Name: Hira Mian
Position: Assistant Professor
Date: 11-10-2022

☒ I hereby certify that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Table 3: Conflict of Interest Declaration for Clinician 3

Company	Check appropriate dollar range*			
	$0 to $5,000	$5,001 to $10,000	$10,001 to $50,000	In excess of $50,000
Takeda, Jansen, BMS, Sanofi, Amgen, GSK (advisory board fees)		X		
Jansen Research Funding				X
Add or remove rows as required				

* Place an X in the appropriate dollar range cells for each company.

Declaration for Clinician 4

Name: Dr. Kevin Song
Position: Hematologist, Vancouver General Hospital
Date: 11-10-2022

☒ I hereby certify that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Table 4: Conflict of Interest Declaration for Clinician 4

Company	Check appropriate dollar range*			
	$0 to $5,000	$5,001 to $10,000	$10,001 to $50,000	In excess of $50,000
Bristol Myers Squibb		X		
Janssen		X		
Amgen		X		

* Place an X in the appropriate dollar range cells for each company.

Declaration for Clinician 5

Name: Dr. Sita Bhella
Position: Hematologist, Princess Margaret Cancer Centre
Date: 11-10-2022

☒ I hereby certify that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Table 5: Conflict of Interest Declaration for Clinician 5

Company	Check appropriate dollar range*			
	$0 to $5,000	$5,001 to $10,000	$10,001 to $50,000	In excess of $50,000
Gilead	X			

Novartis	X			
Sanofi	X			
Amgen	X			
Celgene/Bristol Myers Squibb	X			

* Place an X in the appropriate dollar range cells for each company.

Declaration for Clinician 6

Name: Dr. Michael Pavic
Position: Hematologist
Date: 10-10-2022

☒ I hereby certify that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Table 5: Conflict of Interest Declaration for Clinician 6

	Check appropriate dollar range*			
Company	**$0 to $5,000**	**$5,001 to $10,000**	**$10,001 to $50,000**	**In excess of $50,000**
Add company name				
Add company name				
Add or remove rows as required				

* Place an X in the appropriate dollar range cells for each company.

Declaration for Clinician 7

Name: Dr. Amaris Balitsky
Position: Malignant Hematologist, Juravinski Hospital and Cancer Centre
Date: 11-10-2022

☒ I hereby certify that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Table 5: Conflict of Interest Declaration for Clinician 7

	Check appropriate dollar range*			
Company	**$0 to $5,000**	**$5,001 to $10,000**	**$10,001 to $50,000**	**In excess of $50,000**
BMS	X			

Novartis			X	

* Place an X in the appropriate dollar range cells for each company.

Declaration for Clinician 8

Name: Dr. Rami Kotb
Position: Hematologist, Oncologist, Cancer Care Manitoba
Date: 11-10-2022

☒ I hereby certify that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Table 5: Conflict of Interest Declaration for Clinician 8

	Check appropriate dollar range*			
Company	**$0 to $5,000**	**$5,001 to $10,000**	**$10,001 to $50,000**	**In excess of $50,000**
BMS, Amgen, JNJ		X		
Takeda	X			
Sanofi, Merck				X
Karyopharm				X

* Place an X in the appropriate dollar range cells for each company.

Declaration for Clinician 9

Name: Dr. Arleigh Mccurdy
Position: Hematologist, Oncologist
Date: 11-10-2022

☒ I hereby certify that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Table 5: Conflict of Interest Declaration for Clinician 9

	Check appropriate dollar range*			
Company	**$0 to $5,000**	**$5,001 to $10,000**	**$10,001 to $50,000**	**In excess of $50,000**
BMS/Celgene	X			
Takeda	X			

Amgen	X			
Janssen	X			
Sanofi	X			
Forus Therapeutics	X			

* Place an X in the appropriate dollar range cells for each company.

Declaration for Clinician 10

Name: Dr. Richard LeBlanc
Position: Hematologist, Oncologist at Hopital Maisonneuve-Rosemont, Montreal Associate Professor of Medicine, Universite de Montreal
Date: 11-10-2022

☒ I hereby certify that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Table 5: Conflict of Interest Declaration for Clinician 10

	Check appropriate dollar range*			
Company	**$0 to $5,000**	**$5,001 to $10,000**	**$10,001 to $50,000**	**In excess of $50,000**
Janssen	X			

* Place an X in the appropriate dollar range cells for each company.

Declaration for Clinician 11

Name: Dr. Nicole Laferriere
Position: Hematologist / Chief of Oncology
Date: 12-10-2022

☒ I hereby certify that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Table 5: Conflict of Interest Declaration for Clinician 11

	Check appropriate dollar range*			
Company	**$0 to $5,000**	**$5,001 to $10,000**	**$10,001 to $50,000**	**In excess of $50,000**
Astra Zeneca, AMGEN Canada, ROCHE, Abbvie, Sanofi Canada, Lundbeck, Janssen, Celgene, Teva Pharm, Novartis, KiTE, AbbVie, Incyte	X			

* Place an X in the appropriate dollar range cells for each company.

Declaration for Clinician 12

Name: Dr. Jean Roy
Position: Full professor, Université de Montréal, hematologist, Maisonneuve-Rosemont Hospital
Date: 12-10-2022

☒ I hereby certify that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation

Table 5: Conflict of Interest Declaration for Clinician 12

	Check appropriate dollar range*			
Company	**$0 to $5,000**	**$5,001 to $10,000**	**$10,001 to $50,000**	**In excess of $50,000**
Add company name				
Add company name				
Add or remove rows as required				

* Place an X in the appropriate dollar range cells for each company.

Declaration for Clinician 13

Name: Dr. Irwindeep Sandhu
Position: MD, Associate Professor Dept of Oncology University of Alberta
Date: 12-10-2022

☒ I hereby certify that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Table 5: Conflict of Interest Declaration for Clinician 13

	Check appropriate dollar range*			
Company	**$0 to $5,000**	**$5,001 to $10,000**	**$10,001 to $50,000**	**In excess of $50,000**
Celgene/BMS	X			
Janssen	X			
Amgen	X			
Takeda	X			
Sanofi	X			
Kite / Gilead	X			

* Place an X in the appropriate dollar range cells for each company.

Declaration for Clinician 14

Name: Dr. Julie Côté
Position: Hematologist/Oncologist
Date: 12-10-2022

☒ I hereby certify that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Table 5: Conflict of Interest Declaration for Clinician 14

	Check appropriate dollar range*			
Company	**$0 to $5,000**	**$5,001 to $10,000**	**$10,001 to $50,000**	**In excess of $50,000**
BMS	X			
Janssen	X			
Sanofi	X			

* Place an X in the appropriate dollar range cells for each company.

Declaration for Clinician 15

Name: Dr. Anthony Reiman
Position: MD/Oncologist
Date: 12-10-2022

☒ I hereby certify that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Table 5: Conflict of Interest Declaration for Clinician 15

	Check appropriate dollar range*			
Company	**$0 to $5,000**	**$5,001 to $10,000**	**$10,001 to $50,000**	**In excess of $50,000**
Nothing to declare				

* Place an X in the appropriate dollar range cells for each company.

Declaration for Clinician 16

Name: Dr. Heather Sutherland

Position: Hematologist, Vancouver General Hospital
Date: 12-10-2022

☒ I hereby certify that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Table 5: Conflict of Interest Declaration for Clinician 16

	Check appropriate dollar range*			
Company	**$0 to $5,000**	**$5,001 to $10,000**	**$10,001 to $50,000**	**In excess of $50,000**
Sanofi	X			
Amgen	X			

* Place an X in the appropriate dollar range cells for each company.

Declaration for Clinician 17

Name: Dr. Debra Bergstrom
Position: Associate Professor
Date: 13-10-2022

☒ I hereby certify that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Table 5: Conflict of Interest Declaration for Clinician 17

	Check appropriate dollar range*			
Company	**$0 to $5,000**	**$5,001 to $10,000**	**$10,001 to $50,000**	**In excess of $50,000**
Janssen	X			

* Place an X in the appropriate dollar range cells for each company.

Declaration for Clinician 18

Name: Dr. Anca Prica
Position: Hematologist
Date: 13-10-2022

☒ I hereby certify that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Table 5: Conflict of Interest Declaration for Clinician 18

Company	Check appropriate dollar range*			
	$0 to $5,000	$5,001 to $10,000	$10,001 to $50,000	In excess of $50,000

* Place an X in the appropriate dollar range cells for each company.

Declaration for Clinician 19

Name: Dr. Rodger Tiedemann
Position: Consultant Hematologist, Senior Scientist, Princess Margaret Cancer Centre, UHN, Toronto
Date: 13-10-2022

☒ I hereby certify that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Table 5: Conflict of Interest Declaration for Clinician 19

Company	Check appropriate dollar range*			
	$0 to $5,000	$5,001 to $10,000	$10,001 to $50,000	In excess of $50,000
Janssen	X			

* Place an X in the appropriate dollar range cells for each company.

Declaration for Clinician 20

Name: Christine Chen
Position: Hematologist, Princess Margaret Cancer Centre
Date: 13-10-2022

☒ I hereby certify that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Table 5: Conflict of Interest Declaration for Clinician 20

Company	Check appropriate dollar range*			
	$0 to $5,000	$5,001 to $10,000	$10,001 to $50,000	In excess of $50,000
BMS	X			
Janssen	X			

* Place an X in the appropriate dollar range cells for each company.