CADTH

CADTH REIMBURSEMENT REVIEW

Clinician Input

daratumumab (Darzalex)

(Janssen Inc.)

Indication: Acute hepatic porphyria (AHP) in adults

August 9, 2021

CADTH Reimbursement Review
Clinician Group Input Template

CADTH Project Number	**PC0257-000**
Generic Drug Name (Brand Name)	**daratumumab (Darzalex); Manufacturer: Janssen**
Indication	**Indications:** Darzalex SC in combination with bortezomib, cyclophosphamide, and dexamethasone, for the treatment of adult patients with newly diagnosed light chain (AL) amyloidosis. **Manufacturer Requested Reimbursement Criteria[1]:** Darzalex SC in combination with bortezomib, cyclophosphamide, and dexamethasone, for the treatment of adult patients with newly diagnosed light chain (AL) amyloidosis
Name of the Clinician Group	**Ontario Health (Cancer Care Ontario) Hematology Cancer Drug Advisory Committee**
Author of the Submission	**Dr. Tom Kouroukis, Dr. Pierre Villeneuve, Dr. Lee Mozessohn**
Contact information	Name: Dr. Tom Kouroukis Title: Provincial Head – Complex Malignant Hematology (OH-CCO) [redacted] Phone:

1. About Your Clinician Group

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

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

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

Discussed jointly via emails.

3. Current treatments

3.1. 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. Are such treatments supported by clinical practice guidelines?

Treatments available through special access programs are relevant.

Do current treatments modify the underlying disease mechanism? Target symptoms?

Response:

Treatments usually align with treatments for multiple myeloma, including PI or IMid-based induction with or without autologous stem cell transplant.

Ontario currently does not have provincial funding for amyloidosis patients unless they also have concurrent myeloma.

Access to compassionate drugs may be available – e.g., bortezomib

4. Treatment goals

4.1. 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.

Response:

Prolong life, delay disease progression, improve end organ function

5. Treatment gaps (unmet needs)

5.1. Considering the treatment goals in Section 4, please describe goals (needs) that are not being met by currently available treatments.

Examples:

- *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*
- *Treatment are needed to improve compliance*
- *Formulations are needed to improve convenience*

Response:

Lack of provincial funding for amyloidosis (as described in 3.1)

Treatments are needed that are better tolerated – patients may also have heart failure, renal failure and neuropathy

5.2. Which patients have the greatest unmet need for an intervention such as the drug under review?

Would these patients be considered a subpopulation or niche population?

Describe characteristics of this patient population.

Would the drug under review address the unmet need in this patient population?

Response:

All amyloidosis patients could benefit from this treatment

6. Place in therapy

6.1. 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?

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

Response:

This protocol would enhance first line therapy. No downstream impact on subsequent treatments.

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

If so, please describe which treatments should be tried, in what order, and include a brief rationale.

Response:

Not applicable. This is intended for first line therapy.

6.3. How would this drug affect the sequencing of therapies for the target condition?

If appropriate for this condition, please indicate which treatments would be given after the therapy has failed and specify whether this is a significant departure from the sequence employed in current practice.

Would there be opportunity to treat patients with this same drug in a subsequent line of therapy? If so, according to what parameters?

Response:

No downstream impact on subsequent treatments

6.4. Which patients would be best suited for treatment with the drug under review?

Which patients are most likely to respond to treatment with the 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)?

Response:

Applicable to all amyloidosis patients. Treatment may be challenging to administer in patients with significant neuropathy.

6.5. How would patients best suited for treatment with the drug under review be identified?

Examples: *Clinician examination or judgement, laboratory tests (specify), diagnostic tools (specify)*

Is the condition challenging to diagnose in routine clinical practice?

Are there any issues related to diagnosis? (e.g., tests may not be widely available, tests may be available at a cost, uncertainty in testing, unclear whether a scale is accurate or the scale may be subjective, variability in expert opinion.)

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

Should patients who are pre-symptomatic be treated considering the mechanism of action of the drug under review?

Response:

Standard diagnosis of amyloidosis. Sometimes amyloid subtyping can be challenging.

6.6. Which patients would be least suitable for treatment with the drug under review?

Response:

Advanced comorbidities where treatment delivery will be challenging.

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

If so, how would these patients be identified?

Response:

NA

6.8. What outcomes are used to determine whether a patient is responding to treatment in clinical practice?

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

Response:

Standard amyloid response criteria

6.9. What would be considered a clinically meaningful response to treatment?

Examples:

- *Reduction in the frequency or severity of symptoms (provide specifics regarding changes in frequency, severity, and so forth)*
- *Attainment of major motor milestones*
- *Ability to perform activities of daily living*
- *Improvement in symptoms*
- *Stabilization (no deterioration) of symptoms*

Consider the magnitude of the response to treatment. Is this likely to vary across physicians?

Response:

Symptom improvement and end organ function improvement

6.10. How often should treatment response be assessed?

Response:

Every cycle (monthly)

6.11. What factors should be considered when deciding to discontinue treatment?

Examples:

- *Disease progression (specify; e.g., loss of lower limb mobility)*
- *Certain adverse events occur (specify type, frequency, and severity)*
- *Additional treatment becomes necessary (specify)*

Response:

disease progression, adverse events

6.12. What settings are appropriate for treatment with the drug under review?

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

Response:

outpatient cancer clinics

6.13. For non-oncology drugs, is a specialist required to diagnose, treat, and monitor patients who might receive the drug under review?

If so, which specialties would be relevant? ***Response:*** NA
7. Additional information
7.1. Is there any additional information you feel is pertinent to this review?
Response: Click here to enter response.

8. 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 DAC in completing this input.

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 <u>each clinician</u> that 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

Clinician Information	
Name	*Dr. Tom Kouroukis*
Position	*Provincial Head – Complex Malignant Hematology (OH-CCO)*
Date	*8-07-2021*

☒	**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.

Conflict of Interest Declaration				
Company	**Check Appropriate Dollar Range**			
	$0 to 5,000	**$5,001 to 10,000**	**$10,001 to 50,000**	**In Excess of $50,000**
No COI	☐	☐	☐	☐
	☐	☐	☐	☐
	☐	☐	☐	☐

Declaration for Clinician 2

Clinician Information	
Name	*Pierre Villeneuve*
Position	*Hematologist, The Ottawa Hospital*
Date	*12-07-2021*
☒	**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.

Conflict of Interest Declaration				
Company	**Check Appropriate Dollar Range**			
	$0 to 5,000	**$5,001 to 10,000**	**$10,001 to 50,000**	**In Excess of $50,000**
No COI	☐	☐	☐	☐
	☐	☐	☐	☐
	☐	☐	☐	☐

Declaration for Clinician 3

Clinician Information	
Name	*Dr. Lee Mozessohn*
Position	*Hematologist/oncologist*
Date	*05-08-2021*
☒	**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.

Conflict of Interest Declaration				
Company	**Check Appropriate Dollar Range**			
	$0 to 5,000	**$5,001 to 10,000**	**$10,001 to 50,000**	**In Excess of $50,000**
No COI	☐	☐	☐	☐

Add company name	☐	☐	☐	☐
Add or remove rows as required	☐	☐	☐	☐

Declaration for Clinician 4

Clinician Information	
Name	*Please state full name*
Position	*Please state currently held position*
Date	*Please add the date form was completed (DD-MM-YYYY)*
☐	**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.

Conflict of Interest Declaration

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	☐	☐	☐	☐

Declaration for Clinician 5

Clinician Information	
Name	*Please state full name*
Position	*Please state currently held position*
Date	*Please add the date form was completed (DD-MM-YYYY)*
☐	**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.

Conflict of Interest Declaration

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	☐	☐	☐	☐

CADTH

CADTH Reimbursement Review
Clinician Group Input Template

Instructions

Input from clinicians is submitted to CADTH by **groups or associations of health care professionals**. Individual clinicians who wish to provide input are encouraged to work with a group that represents their profession to prepare a group submission.

CADTH will accept input from individual clinicians only when there is no relevant group or association that could provide input for the drug under review. Individuals who wish to submit input for a drug review should first contact CADTH (at requests@cadth.ca) to confirm the absence of a relevant group or association.

Completing the Template

Please complete all applicable sections of the clinician input template.

Ensure that all contributing clinicians have completed the conflict of interest declaration in the clinician input template. Input **will not be accepted without the conflict of interest section** completed for all contributors.

Complete the template by the deadline given on the Open Calls page.

Filing the Completed Template:

Send the completed template by using the *Submit* link next to the drug listed on the Open Calls page. The input must be filed as a Microsoft Word document by the posted deadline date for the information to be used by CADTH.

CADTH Reimbursement Review
Clinician Group Input Template

CADTH Project Number	
Generic Drug Name (Brand Name)	**Daratumumab + Cyclophosphamide, Bortezomib and Dexamethasone (Dara-CyBorD)**
Indication	**Frontline therapy of AL amyloidosis**
Name of the Clinician Group	**Canadian Myeloma Research Group**
Author of the Submission	**Dr. Christopher Venner**

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), previously named the Myeloma Canada Research Network (MCRN), is a charitable organization whose membership consists of physicians specializing in plasma cell dyscrasias--including multiple myeloma and AL amyloidosis--from 22 major academic medical centres in Canada. The three main purposes of CMRG consist of: 1) conducting investigator-initiated academic clinical trials to improve the outcome of patients with multiple myeloma and other plasma cell dyscrasias; 2) maintenance of a national Plasma Cell Dyscrasias 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 the management of multiple myeloma and related plasma cell dyscrasias.

2. Information Gathering

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

The information for this submission was gathered from the network via virtual discussion of the data at hand and relevant questions as per the Clinician Input submission document. The final draft was further refined with the input of members and signed by them.

3. Current treatments

3.1. 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. Are such treatments supported by clinical practice guidelines?

Treatments available through special access programs are relevant.

Do current treatments modify the underlying disease mechanism? Target symptoms?

Response:

AL amyloidosis is a rare plasma cell dyscrasia related to the more common disease of multiple myeloma. It must be differentiated from other causes of amyloid such as hereditary and wild type ATTR (transthyretin amyloidosis) which require completely different approaches. AL amyloidosis is caused by a clonal/neoplastic population of plasma cells that causes variable and deleterious effects on multiple organs that, in turn, can cause significant morbidity and mortality. In AL amyloidosis, the clonal plasma cells, although usually not representing a high percentage of marrow cells, secrete a toxic clonal light chain protein which forms very stable and resilient light chain fibrils that deposit in affected tissues causing them to malfunction and eventually fail. The most commonly affected organs include the heart, kidney, liver and nerves but skin, GI tract and the microvasculature can also be affected. The goal of therapy is to minimize the clonal plasma cells population so that the production of the toxic light chains is halted. This prevents further organ damage and, over time, can allow their “egress” from the affected organs and providing them a chance to ”heal”. Similar to multiple myeloma, AL amyloidosis is not curable with any current therapy. Thus, achieving the deepest response possible is crucial as it correlates directly with durability of response which, in turn, allows a longer opportunity for the organs to heal. Additionally, it should be noted that outcomes in this disease are directly linked with the severity of cardiac involvement. Patients with advanced cardiac deposition have 50% chance or more of dying within the first year. Thus, therapies that can give rise to not only deeper but more rapid responses are crucial in addressing the unmet need in this ultra-high-risk population of patients. If such patients can survive long enough to derive maximal benefit from the chemotherapy, long-term data has demonstrated that they can live for years with excellent disease control and ongoing functional improvement.

Given the rarity of this disease there is currently no formal Health Canada-approved therapy for AL amyloidosis. There is, however, a long track record of using many of the approved therapies for multiple myeloma in this disease. Historically, melphalan (either in low doses delivered orally or in high-dose in the context of an autologous stem cell transplant [ASCT]) has been the standard of care. It should be noted, however, that only a minority of AL patients are suitable transplant candidates and that the risk of transplant-related mortality is relatively high even in selected patients. With the advent of novel therapies such the proteasome inhibitors, combinations of alkylator-steroid backbone therapy with agents such as bortezomib have achieved considerably better outcomes than older treatments. Specifically, like cyclophosphamide, bortezomib and dexamethasone (CyBorD) and bortezomib, melphalan and dexamethasone (VMDex) were therefore widely accepted in AL amyloidosis on the basis of small phase II studies and retrospective series. These pilot studies demonstrated marked and unprecedented activity which led to a recent phase III clinical trial comparing VMDex to MDex. The results showed clear

improvements in response depth, organ responses and progression-free survival (PFS) [1] with the addition of bortezomib. This trial formally established bortezomib-based triplet therapy as the new standard of care in AL amyloidosis. It also justified what many jurisdictions in Canada had already adopted as the frontline treatment of choice, albeit with the substitution of cyclophosphamide as the preferred alkylator (similar to the evolution of such therapy in multiple myeloma). Compared with melphalan, the alternative alkylating agent cyclophosphamide has more predictable and less profound blood count suppression, easier administration in the setting of renal compromise and less permanent damaging effects on the bone marrow, thus preserving one's ability to collect stem cells in patients in case ASCT becomes an option in the future. Thus, CyBorD has become the most widely used regimen for the frontline treatment of AL amyloidosis in Canada.

Therefore, CyBorD is the initial treatment in the majority of AL patients. If a deep remission is achieved, fixed-duration therapy for 6-12 cycles may be administered and the patient then monitored for relapse off therapy. ASCT is reserved for a minority of patients with limited (1 or 2 organ) involvement, excellent KPS and no significant cardiac disease, orthostatic hypotension, Factor X deficiency or extensive gastrointestinal involvement who may not have achieved a sufficiently deep remission with CyBorD yet still meet all the previous criteria.

There is no consensus second-line treatment for relapsed AL, nor are there any approved or funded regimens. Some patients may have become transplant-eligible if their organs improved sufficiently during the first remission to meet the above criteria, but this is uncommon. More often, patients will be offered, and some will respond, to another course of CyBorD although data for this approach is lacking; consolidation of a response with ASCT, after re-induction with CyBorD, particularly if less than a CR is achieved, might be considered to try to deepen and/or prolong response—a very uncommon scenario. Lenalidomide plus dexamethasone may be used but has many disadvantages. Specifically, it may result in peripheral edema, may precipitate CHF in some patients, and is associated with considerable fatigue which limits the ability to administer an adequate dose. However, its main disadvantage is that it rarely produces the deep remissions, particularly the CRs, necessary to control light chain production and further organ damage. Pomalidomide is a more potent IMiD but is technically available/funded in myeloma only after failure of lenalidomide, is not funded for AL *per se*, and thereby is difficult to procure. However, it is felt to produce deeper remissions and be better tolerated than lenalidomide and is preferred when patients can obtain it via private insurance.

Ideally, daratumumab regimens would be available for relapsed AL, as a number of retrospective series as well as phase I/II studies clearly demonstrated efficacy in AL amyloidosis with profound rapidity and depth of responses seen. Several CMRG member physicians have used daratumumab to successfully treat a limited number of relapsed Canadian AL patients who had private insurance coverage, including individuals progressive after all the other regimens mentioned above and, at least anecdotally, preventing dialysis-dependency. Unfortunately, daratumumab is not routinely available for this indication via compassionate or special access.

With the recent successes using daratumumab in the treatment of multiple myeloma in a variety of settings, its utility in AL amyloidosis has also been explored. A number of retrospective series as well as phase I/II studies clearly demonstrated efficacy in AL amyloidosis with profound rapidity and depth of responses seen. This led to the development of the pivotal frontline study (ANDROMEDA trial) which serves as the foundation for this CADTH proposal. In this study, which included even advanced cardiac patients, daratumumab was added to CyBorD and compared to CyBorD alone in a standard phase III clinical trial. The responses have been remarkable, achieving a depth of response to unprecedented levels (even surpassing those of ASCT) and leading to marked improvements in organ function--all of which translated into prolonged PFS and survival free of major organ deterioration. The basis for these improvements was the much more robust control of the underlying plasma cell clone achieved with the

addition of the more targeted anti-plasma cell monoclonal antibody daratumumab. The ANDROMEDA findings clearly define a paradigm shift in the management of this disease and represent a monumental step forward in treatment of AL patients.

Presently, there is no availability of daratumumab for the AL indication via compassionate or special access. For this reason, we eagerly await the CADTH review in hopes that it will lead to provincial approvals.

4. Treatment goals

4.1. 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.

Response:

As described above, in the absence of curative therapy, the most important goals of any plasma cell-directed therapy is to achieve deep and rapid responses in terms of eliminating the clonal plasma cells and hence the monoclonal protein product it secretes. The need for a deep response - ideally a CR or at least a VGPR with a subsequent organ response - is particularly important for survival in AL amyloidosis, as continued light chain production, even at low levels, causes ongoing organ damage as the amyloidogenic light chain accumulates further in the target tissues. High-grade control of the monoclonal plasma cell population and reduction of the toxic light chains ultimately has the long-term effect of), reversing the target organ dysfunction, and potentially limiting the need for future dialysis, or in some instances, cardiac or renal transplantation patients, and maintaining/improving function and quality-of-life (supported by recent data from the ANDROMEDA study)—overall helping patients resume their place in society. Importantly, the Dara-CyBorD regimen is finite and can be stopped after 2 years yet can provide very prolonged disease/treatment-free intervals measured in many more years. Previous experience with another therapy, ASCT, has demonstrated that AL patients achieving CR can experience very long survivals, as long-term follow-up studies have demonstrated that the median PFS for CR patients is ≥ 8 years. In the Dara-CyBorD arm of the ANDROMEDA study over 50% of patients achieved this key endpoint compared to only 18% in the control arm [2].

5. Treatment gaps (unmet needs)

5.1. Considering the treatment goals in Section 4, please describe goals (needs) that are not being met by currently available treatments.

Examples:

- *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*
- *Treatment are needed to improve compliance*
- *Formulations are needed to improve convenience*

Response:

1. No therapies are specifically funded for AL amyloidosis in Canada.
2. Not all AL amyloidosis patients achieve a sufficient depth of response with currently available therapies to reduce the toxic free light chains, and therefore organ damage continues to worsen.
3. Even in responding patients, the duration of response may be variable, and relapse leads to further deposition of light chains in the affected organs, clinical deterioration, a miserable quality of life and eventual death in many.
4. AL amyloidosis patients tolerate all anti-plasma cell treatments less well than myeloma patients due to the underlying organ damage intrinsic to this disease (with compromise of kidneys, heart, liver, gastrointestinal tract, peripheral or autonomic nervous system, skin, blood vessel walls, lungs, and/or other organs).
5. Full therapeutic doses may not be possible for many agents –particularly IMiDs, steroids and high-dose melphalan—due to compromised organ function or poor clinical condition.
6. No specific treatments are available to help “dissolve” or “disassemble” the light chain fibrils deposited as aggregates of “amyloid” in involved organs; instead, improvements in organ function depend on stopping light chain production and waiting for the deposits to regress on their own.

In the ANDROMEDA study the control arm of CyBorD is the standard of care in Canada. It is clear from the data presented that achieving the deep responses necessary for the organ improvement and prolonged disease control are not optimal with this approach. Furthermore, in advanced cardiac patients, the time to achieving CR may be delayed which may increase the risk of early death if patients do not have access to the addition of daratumumab. In addition, the longer a patient’s disease remains out of control, the more the burden of amyloid deposits accumulates in affected organs. This can be very difficult to reverse and may lead to permanent damage causing organ loss, the need for replacement therapy (such as dialysis or even organ transplantation) or death.

5.2. Which patients have the greatest unmet need for an intervention such as the drug under review?

Would these patients be considered a subpopulation or niche population?

Describe characteristics of this patient population.

Would the drug under review address the unmet need in this patient population?

Response:

The data presented in the Forrest plot in the NEJM paper for ANDROMEDA study clearly demonstrates that virtually all patients with systemic AL amyloidosis would be expected to benefit from the addition of the monoclonal antibody. Of note, the ANDROMEDA study included a heterogeneous population of AL patients so that a wide range of presentations were well-represented. This is very reflective of the real-world clinical setting. While AL amyloidosis is eventually fatal in the majority of patients due to organ failure, those who most desperately need a deep and rapid response are those with cardiac involvement. The ANDROMEDA data demonstrates that the addition of daratumumab markedly improves those with cardiac involvement above the CyBorD control.

6. Place in therapy

6.1. 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?

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

Response:

The combination of alkylator and proteosome inhibitor-based therapies (CYBORD) is the most commonly utilized first line regimen in Canada for AL amyloidosis. A subset of patients may further proceed on to autologous stem cell transplant depending upon several factors including severity of amyloid related organ damage, disease response, as well as any pre-existing co-morbidities and functional status. At subsequent relapses, there are no current standards of care and wide variability exists depending upon access and local guidelines. Unfortunately, there is no funded access to daratumumab for AL amyloidosis currently, in either front line or in the relapsed setting.

The current regimen under review would represent a major shift in the treatment of AL amyloidosis with daratumumab added to the current standard of care CYBORD among all newly diagnosed patients in the first-line setting. This would be widely adopted for AL patients given the favorable and pivotal results of ANDROMEDA study. Given its effectiveness, it is likely fewer AL patients will require ASCT with its attendant risk of morbidity and increased mortality in this disease. The use of less effective, yet expensive regimens, such as IMiDs, would be delayed or perhaps be unnecessary.

An important consideration, and particular concern for CMRG physicians, is the lack of access of daratumumab regimens for the current population of Canadian AL patients who have already received first-line therapy and in whom daratumumab at relapse could well be life-saving or live-extending. This is expected to be a limited group of patients whom we feel deserve the chance to receive daratumumab therapy at progression, given the limited range of other options.

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

If so, please describe which treatments should be tried, in what order, and include a brief rationale.

Response:

Given the toxic effect of the amyloid light chain, it is vital to achieve rapid and deep responses (VGPR or preferably CR) as early in the disease course as possible. This limits the ongoing damage to organs which are potentially irreversible. Therefore, it is imperative to have access to therapies in first line that produce deep and quick responses. Daratumumab-CYBORD is a major breakthrough in this disease which, if not treated quickly and with deep responses, can lead to irreversible organ damage and result in significant morbidity and subsequent poor quality of life. Given the pathophysiology of AL, there is no rationale or justification to try a less effective therapy first. In addition, the subcutaneous administration of daratumumab used in the ANDROMEDA trial reduces the potentially serious effect of volume overloading that can be seen in patients with cardiac and renal amyloid involvement.

6.3. How would this drug affect the sequencing of therapies for the target condition?

If appropriate for this condition, please indicate which treatments would be given after the therapy has failed and specify whether this is a significant departure from the sequence employed in current practice.

Would there be opportunity to treat patients with this same drug in a subsequent line of therapy? If so, according to what parameters?

Response:

As currently there is no access to daratumumab in the relapsed setting in AL amyloidosis in Canada, approval and funding of daratumumab-CYBORD will not impact sequencing in the relapsed setting. However, given the favorable results of ANDROMEDA, it is expected that the need for subsequent line treatment will be delayed given the deep and durable responses following two years of finite treatment with this regimen.

Since frontline Dara-CyBorD would be given as a fixed-duration regimen, it would follow precedent—and be considered ideal-- to consider re-treatment with the same Dara-CyBorD regimen. If that is not possible, the previous options as in section 3.1 would be tried: reinduction with CyBorD, an IMiD (lenalidomide or pomalidomide + dexamethasone), or occasionally ASCT in a small subset of selected patients.

6.4. Which patients would be best suited for treatment with the drug under review?

Which patients are most likely to respond to treatment with the 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)?

Response:

Since the Dara-CyBorD regimen is well-tolerated with subcutaneous dosing of both daratumumab and bortezomib and produces minimal hematologic toxicity, virtually all newly diagnosed AL patients would be potential candidates. The rapid responses it can generate can be associated with rapid organ improvement, with the rate depending on the physiochemical characteristics of the toxic amyloidogenic light chains.

Additionally, the ANDROMEDA trial included a heterogenous group of patients including those with cardiac disease which are often excluded from other clinical trials. Based upon the subgroup analysis, it is expected that most subgroups of patients with AL amyloidosis would be expected to benefit from this treatment regimen, including those with cardiac disease. In the trial, a small proportion of patients with very advanced cardiac concerns were excluded; however, this regimen is expected to be effective, appropriate and potentially life-saving for those patients, depending upon clinical judgement.

6.5. How would patients best suited for treatment with the drug under review be identified?

Examples: *Clinician examination or judgement, laboratory tests (specify), diagnostic tools (specify)*

Is the condition challenging to diagnose in routine clinical practice?

Are there any issues related to diagnosis? (e.g., tests may not be widely available, tests may be available at a cost, uncertainty in testing, unclear whether a scale is accurate or the scale may be subjective, variability in expert opinion.)

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

Should patients who are pre-symptomatic be treated considering the mechanism of action of the drug under review?

Response:

The initial signs and symptoms of AL are often subtle and non-specific. A delay in diagnosis is typical and most patients have seen several specialists before the definitive diagnosis is made. By that time, organ damage has often become significant. Once the diagnosis is considered, confirmation of the AL sub-type requires identification of amyloid deposits in an involved organ or surrogate tissue such as a fat aspirate or bone marrow biopsy. If a cardiac biopsy is needed, it may be limited to specialized centres. While amyloid deposits are identified by staining with an easily available reagent--Congo red --there must be a suspicion of amyloidosis for it to be performed. Expertise may be needed to interpret the unique apple-green birefringence produced under polarized light. To diagnose the light chain origin of the amyloid deposits, and distinguish AL from other forms of amyloidosis (such as hereditary or wild type transthyretin subtypes), initially the same serum and urine assays used to diagnose the monoclonal protein made by myeloma cells (SPEP, UPEP and serum free light chain levels) are performed. In Ontario, this is problematic for community physicians, as the cost of the most important parameter, the serum free light chain assay, is not covered by the provincial health plan; rather, it must be performed in a hospital under its global budget. This contributes to the delay in diagnosis by primary providers.

The detection of an elevated serum free light chain, however, does not guarantee that it is the protein in the tissue amyloid deposit, as incidental monoclonal gammopathies without associated amyloid deposition are common with age (5% of the population over age 70). It is often necessary to analyse the amyloid deposits in the tissue biopsy by mass spectrometry, which is now available in Toronto (or alternatively sent to the Mayo Clinic in the US). The misdiagnosis of the amyloidosis subtype can be catastrophic, as hereditary and wild type transthyretin amyloidosis are not associated with a clonal plasma cell population and are managed without cytotoxic therapy.

However, once the diagnosis of AL amyloidosis is made, given the favorable results of the ANDROMEDA trial and the subgroups examined, it is expected that this treatment will be widely adopted in the front-line setting.

6.6. Which patients would be least suitable for treatment with the drug under review?

Response:

As stated above, the Dara-CyBorD led to superior outcomes in virtually all examined subgroups. This includes patients with advanced cardiac disease-- who are currently routinely offered CyBorD in Canada despite their fragile condition. These patients can still benefit further from the addition of daratumumab, due to the more rapid responses which will limit further organ deterioration and allow a chance for improvement as early as possible. Importantly, even with a small risk of infusion reactions from the IV daratumumab (significantly minimized with the subcutaneous formulation), the agent remains feasible even in those with a potential risk of hemodynamic compromise.

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

If so, how would these patients be identified?

Response:

Again, there are no subgroups who would be expected to respond markedly better than others. As yet, there are no validated biomarkers or other clinical features that help to guide therapeutic choice. There has been prior concern regarding the use of bortezomib in patients with AL amyloidosis possessing the t(11;14) cytogenetic abnormality, given the observation that both myeloma and AL patients with this cytogenetic subtype respond less well to this agent. Given the critical role of bortezomib in AL treatment until now, the t(11;14) abnormality is considered an adverse prognostic factor in AL patients, perhaps for this reason [3]. Encouragingly, the data presented in the ANDROMEDA trial demonstrates superiority of Dara-CyBorD over CyBorD alone even in this subgroup.

6.8. What outcomes are used to determine whether a patient is responding to treatment in clinical practice?

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

Response:

Responses in AL include two components:

Formal response criteria have been established previously and were included in the ANDROMEDA trial. Standard response assessments in AL amyloidosis consist of two components: 1) the hematologic/clonal response (as measured by the serum and urine protein electrophoresis/immunofixation and serum free light chain testing) and 2) organ response (measured by levels of NT-proBNP for cardiac response, a combination of renal function and proteinuria for renal response and the alkaline phosphatase level for liver involvement). Hematologic responses are the first to occur, and it is typically the patients with deep heme responses who experience subsequent organ responses. The light chain amyloid fibrils are able regress from the deposits when their production by plasma cells is halted. Improvement in organ function can be seen relatively quickly in some patients, but it is well described that maximal responses may not be documented for months or even years after a deep hematologic response is achieved.

6.9. What would be considered a clinically meaningful response to treatment?

Examples:

- *Reduction in the frequency or severity of symptoms (provide specifics regarding changes in frequency, severity, and so forth)*
- *Attainment of major motor milestones*
- *Ability to perform activities of daily living*
- *Improvement in symptoms*
- *Stabilization (no deterioration) of symptoms*

Consider the magnitude of the response to treatment. Is this likely to vary across physicians?

Response:

In AL amyloidosis the goal of treatment is ultimately to control the production of the amyloidogenic light chain sufficiently to prevent further organ deterioration and give the organs a chance to heal/improve over time, as the light chain deposits regress. Thus, a clinically meaningful response is, at minimum, preservation of organ function (i.e., no further deterioration) and, at best, improvement of organ function. As above, formal response criteria have been established and were used in the study. Practically speaking, this equates to parameters such as decreased edema, improved exercise tolerance, decrease in frequency/severity of heart failure episodes, and/or less fatigue, orthostatic dizziness, peripheral neuropathy symptoms and gastrointestinal dysfunction. In the more advanced patients, improvements in early cardiac death rate and decreases in renal failure requiring dialysis would represent optimal outcomes.

6.10. How often should treatment response be assessed?

Response:

While on therapy response assessment should be included with standard safety labs. Measurements for hematologic response should be monthly while on treatment and every 1-3 months after therapy to detect relapse as early as possible and prevent further organ damage. Organ responses are performed every 1-3 months depending on the clinical situation. For example, serum cardiac biomarkers (NT-proBNP and troponin I or T) and liver markers (alkaline phosphatase) can easily be assessed monthly. More involved tests such as 24-hour urinary protein excretion may be performed less often.

6.11. What factors should be considered when deciding to discontinue treatment?

Examples:

- *Disease progression (specify; e.g., loss of lower limb mobility)*
- *Certain adverse events occur (specify type, frequency, and severity)*
- *Additional treatment becomes necessary (specify)*

Response:

- Responses to therapy are assessed primarily using the serum free light chain levels, as consensus criteria utilize the difference between the involved and non-involved free light chain levels. A very good partial response (dFLC VGPR) in which the dFLC is < 40mg/L, or preferably, a complete response (CR) in which the light chain ratio is normalized, are the goals. A PR may be satisfactory if organ function stabilizes or improves. However, in some patients with less than a VGPR, organ function continues to decline, and therapy should then be changed to another regimen to try to reduce the toxic light chain further. Even in a CR, the complete 2-year Dara-CyBorD regimen should be completed in order to maximize the response duration. Similarly, if the disease progresses during therapy, as per standard hematologic criteria, therapy should be changed.
- Discontinuation for toxicity with Dara-CyBorD is expected to be infrequent, even in this often relatively fragile population of patients. Specifically, only 4.2% of patients randomized to Dara-CyBorD in the ANDROMEDA trial stopped due to adverse events. This low rate is consistent with the experience of the Canadian CMRG physicians who participated in this trial.

6.12. What settings are appropriate for treatment with the drug under review?

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

Response:

Similar to the current usage of daratumumab in myeloma, the drugs should be delivered within a dedicated oncology program. The regimen is however amenable for delivery in the community oncology setting, outpatient oncology setting as well as inpatient setting. The latter may be required for those patients with advanced organ involvement who require additional supportive care.

6.13. For non-oncology drugs, is a specialist required to diagnose, treat, and monitor patients who might receive the drug under review?

If so, which specialties would be relevant?

Response:

Not applicable as, generally speaking the diagnosis of and therapy for AL amyloidosis is overseen by a malignant hematologist or medical oncologist. Other specialists are often in the supportive care involved given the multi-organ dysfunction accompanying most cases.
7. Additional information
7.1. Is there any additional information you feel is pertinent to this review?
Response: No

References

1. Kastritis E, Leleu X, Arnulf B, Zamagni E, Cibeira MT, Kwok F, Mollee P, Hájek R, Moreau P, Jaccard A, Schönland SO, Filshie R, Nicolas-Virelizier E, Augustson B, Mateos MV, Wechalekar A, Hachulla E, Milani P, Dimopoulos MA, Fermand JP, Foli A, Gavriatopoulou M, Klersy C, Palumbo A, Sonneveld P, Johnsen HE, Merlini G, Palladini G. Bortezomib, Melphalan, and Dexamethasone for Light-Chain Amyloidosis. J Clin Oncol. 2020 Oct 1;38(28):3252-3260. doi: 10.1200/JCO.20.01285. Epub 2020 Jul 30. PMID: 32730181.
2. Efstathios Kastritis, Giovanni Palladini, Monique C. Minnema et al. Daratumumab-Based Treatment for Immunoglobulin Light-Chain Amyloidosis. NEJM. July 2021
3. Brett Dumas, Hassan Yameen, Shayna Sarosiek, J. Mark Sloan & Vaishali Sanchorawala (2020) Presence of t(11;14) in AL amyloidosis as a marker of response when treated with a bortezomib-based regimen, Amyloid, 27:4, 244-249, DOI: 10.1080/13506129.2020.1778461

8. 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.

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.

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 <u>each clinician</u> that 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

New or Updated Declaration for Clinician 1	
Name	*Dr. Christopher Venner*
Position	*MD (Hematology Tumor Group lead, Cross Cancer Institute, Edmonton, Alberta*
Date	*09-08-2021*
☒	**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.

Conflict of Interest Declaration

Company	**Check Appropriate Dollar Range**			
	$0 to 5,000	**$5,001 to 10,000**	**$10,001 to 50,000**	**In Excess of $50,000**
Celgene/BMS	☒	☐	☐	☐
Takeda	☒	☐	☐	☐
Janssen	☒	☐	☐	☐
Amgen	☒			
Sanofi	☒			
GSK	☒			

Declaration for Clinician 2

New or Updated Declaration for Clinician 2	
Name	*Hira Mian*
Position	*Assistant Professor*
Date	*09-08-2021*
☒	**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.

Conflict of Interest Declaration

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.

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)	☐	☒	☐	☐
Jansen Research Funding	☐	☐	☐	☒
Add or remove rows as required	☐	☐	☐	☐

Declaration for Clinician 3

New or Updated Declaration for Clinician 3	
Name	*Kevin Song MD*
Position	*Hematologist, Vancouver General Hospital*
Date	*09-08-2021*
☒	**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.

Conflict of Interest Declaration

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.

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	☐	☒	☐	☐
Janssen	☐	☒	☐	☐
Amgen	☐	☒	☐	☐

Declaration for Clinician 4

New or Updated Declaration for Clinician 4	
Name	*Nicole Laferriere*
Position	Hematologist/ Chief of Oncology
Date	*09-08-2021*
☒	**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.

Conflict of Interest Declaration

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.

Company	Check Appropriate Dollar Range			
	$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	☒	☐	☐	☐

Declaration for Clinician 5

New or Updated Declaration for Clinician 5	
Name	*Mohammed Aljama*
Position	*Hematologist, JCC. Assistant Professor, Department of Oncology*
Date	*09-08-2021*
☒	**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.

Conflict of Interest Declaration

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.

Company	Check Appropriate Dollar Range			
	$0 to 5,000	**$5,001 to 10,000**	**$10,001 to 50,000**	**In Excess of $50,000**
Jansen	☐	☒	☐	☐

Declaration for Clinician 6

New or Updated Declaration for Clinician 6	
Name	Suzanne Trudel
Position	Oncologist
Date	09-08-2021
☒	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.

Conflict of Interest Declaration

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.

Company	Check Appropriate Dollar Range			
	$0 to 5,000	**$5,001 to 10,000**	**$10,001 to 50,000**	**In Excess of $50,000**
Sanofi	☒	☐	☐	☐
BMS	☐	☐	☒	☐
Add or remove rows as required	☐	☐	☐	☐

Declaration for Clinician 7

New or Updated Declaration for Clinician 7	
Name	*Anette Hay*
Position	*Associate Professor, Queens University*
Date	*09-08-2021*
☒	**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.

Conflict of Interest Declaration

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.

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	☐	☐	☐	☐

Declaration for Clinician 8

New or Updated Declaration for Clinician 8	
Name	*Dr. Donna Reece*
Position	*Chief Medical Officer, CMRG*
Date	*09-08-2021*
☒	**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.

Conflict of Interest Declaration

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/Celgene	☐	☐	☒	☐
Janssen	☐	☐	☒	☐
Amgen	☐	☐	☒	☐
Sanofi	☒	☐	☐	☐
GSK	☒	☐	☐	☐
Takeda	☒	☐	☐	☐

Declaration for Clinician 9

New or Updated Declaration for Clinician 9	
Name	*Irwindeep Sandhu*
Position	*MD, Associate Professor Dept of Oncology University of Alberta*
Date	*09-08-2021*
☒	**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.

Conflict of Interest Declaration

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.

Company	Check Appropriate Dollar Range			
	$0 to 5,000	$5,001 to 10,000	$10,001 to 50,000	In Excess of $50,000

Celgene/BMS	☒	☐	☐	☐
Janssen	☒	☐	☐	☐
Amgen	☒	☐	☐	☐
Takeda	☒			
Sanofi	☒			
Kite/Gilead	☒			

Declaration for Clinician 10

New or Updated Declaration for Clinician 10	
Name	*Dr. Anthony Reiman*
Position	*MD Oncologist*
Date	*09-08-2021*
☒	**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.

Conflict of Interest Declaration

Company	**Check Appropriate Dollar Range**			
	$0 to 5,000	**$5,001 to 10,000**	**$10,001 to 50,000**	**In Excess of $50,000**
Nothing to Declare	☐	☐	☐	☐
	☐	☐	☐	☐
	☐	☐	☐	☐

Declaration for Clinician 11

New or Updated Declaration for Clinician 11	
Name	*Christine Chen*
Position	*Hematologist, Princess Margaret Cancer Centre*
Date	*09-08-2021*
☒	**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.

Conflict of Interest Declaration

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.

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	☒	☐	☐	☐
Janssen	☒	☐	☐	☐

Add or remove rows as required	☐	☐	☐	☐

Declaration for Clinician 12

New or Updated Declaration for Clinician 12	
Name	Sindu Kanjeekal
Position	Hematologist/oncologist
Date	09-08-2021
☒	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.

Conflict of Interest Declaration

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.
no conflicts

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 or remove rows as required	☐	☐	☐	☐

Declaration for Clinician 13

New or Updated Declaration for Clinician 13	
Name	*Dr. Julie Stakiw*
Position	*Oncologist*
Date	*09-08-2021*
☒	**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.

Conflict of Interest Declaration

Company	Check Appropriate Dollar Range			
	$0 to 5,000	**$5,001 to 10,000**	**$10,001 to 50,000**	**In Excess of $50,000**
Sanofi	☒	☐	☐	☐

Declaration for Clinician 14

New or Updated Declaration for Clinician 14	
Name	*Dr. Arleigh McCurdy*
Position	*Hematologist/Oncologist*
Date	*09-08-2021*
☒	**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.

Conflict of Interest Declaration				
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/Celgene	☒	☐	☐	☐
Takeda	☒	☐	☐	☐
Amgen	☒	☐	☐	☐
Janssen	☒	☐	☐	☐
Sanofi	☒	☐	☐	☐

Declaration for Clinician 15

New or Updated Declaration for Clinician 15	
Name	*Dr. Debra Bergstrom*
Position	*Hematologist/ Assistant professor*
Date	*09-08-2021*
☒	**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.

Conflict of Interest Declaration				
Company	**Check Appropriate Dollar Range**			
	$0 to 5,000	**$5,001 to 10,000**	**$10,001 to 50,000**	**In Excess of $50,000**
Nothing to declare	☐	☐	☐	☐

Declaration for Clinician 16

New or Updated Declaration for Clinician 15	
Name	*Dr. Julie Côté*
Position	*Hematologist/ Oncologist*
Date	*09-08-2021*
☒	**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.

Conflict of Interest Declaration				
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	☒	☐	☐	☐
Janssen	☒	☐	☐	☐
Sanofi	☒	☐	☐	☐

Declaration for Clinician 17

New or Updated Declaration for Clinician 17

Name	*Dr. Sita Bhella*
Position	*Hematologist/ Oncologist*
Date	*09-08-2021*
☒	**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.

Conflict of Interest Declaration

Company	**Check Appropriate Dollar Range**			
	$0 to 5,000	**$5,001 to 10,000**	**$10,001 to 50,000**	**In Excess of $50,000**
Celgene	☒	☐	☐	☐
BMS	☒	☐	☐	☐
Sanofi	☒	☐	☐	☐

Declaration for Clinician 18

New or Updated Declaration for Clinician 18	
Name	*Dr. Victor Zepeda*
Position	*Hematologist/ Oncologist*
Date	*09-08-2021*
☒	**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.

Conflict of Interest Declaration

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	☐	☒	☐	☐
BMS	☒	☐	☐	☐
Takeda	☒	☐	☐	☐
Amgen	☒	☐	☐	☐

Declaration for Clinician 19

New or Updated Declaration for Clinician 19	
Name	*Dr. Vishal Kukreti*
Position	*Hematologist/ Oncologist*
Date	*09-08-2021*
☒	**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.

Conflict of Interest Declaration

Company	Check Appropriate Dollar Range			
	$0 to 5,000	$5,001 to 10,000	$10,001 to 50,000	In Excess of $50,000
Amgen	☒	☐	☐	☐
Kirin Kyoto	☒	☐	☐	☐

Declaration for Clinician 19

New or Updated Declaration for Clinician 19	
Name	*Dr. Rami Kotb*
Position	*Hematologist, Oncologist, Cancer Care Manitoba*
Date	*09-08-2021*
☒	**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.

Conflict of Interest Declaration

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.

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, Amgen, JNJ	☐	☒	☐	☐
Takeda	☒	☐	☐	☐
Sanofi, Merck,	☐	☐	☐	☒
Karyopharm	☐	☐	☐	☒

Declaration for Clinician 19

New or Updated Declaration for Clinician 19	
Name	*Dr. Heather Sutherland*
Position	*Please state currently held position*
Date	*08-09-2021*
☒	**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.

Conflict of Interest Declaration

Company	Check Appropriate Dollar Range			
	$0 to 5,000	$5,001 to 10,000	$10,001 to 50,000	In Excess of $50,000
Nothing to Declare	☐	☐	☐	☐

Declaration for Clinician 20

New or Updated Declaration for Clinician 20	
Name	Rodger Tiedemann
Position	Senior Scientist and Hematologist, Princess Margaret Cancer Centre
Date	08-09-2021
☒	**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.

Conflict of Interest Declaration

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.

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 or remove rows as required	☐	☐	☐	☐

Declaration for Clinician 21

New or Updated Declaration for Clinician 21	
Name	Richard LeBlanc
Position	Hematologist and medical oncologist at Hôpital Maisonneuve-Rosemont, Montreal Associate professor of medicine, Université de Montréal
Date	08-09-2021
☒	**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.

Conflict of Interest Declaration

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.

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	☒	☐	☐	☐

Declaration for Clinician 22

New or Updated Declaration for Clinician 22	
Name	Nizar A. Samad
Position	MD hematology
Date	08-09-2021

☒	**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.

Conflict of Interest Declaration

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.

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 or remove rows as required	☐	☐	☐	☐

Declaration for Clinician 23

New or Updated Declaration for Clinician 23	
Name	Dr. Jean Roy
Position	Hematologist
Date	09-08-2021

☒	**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.

Conflict of Interest Declaration

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.

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 or remove rows as required	☐	☐	☐	☐