CADTH

CADTH REIMBURSEMENT REVIEW

Stakeholder Feedback on Draft Recommendation

polatuzumab vedotin (Polivy)

(Hoffmann La-Roche)

Indication: Polatuzumab vedotin in combination with rituximab, cyclophosphamide, doxorubicin, and prednisone (R-CHP) for the treatment of adult patients with previously untreated large B-cell lymphoma (LBCL), including diffuse large B-cell lymphoma (DLBCL) not otherwise specified (NOS), high grade B-cell lymphoma, Epstein-Barr virus-positive (EBV+) DLBCL NOS, and T-cell/histiocyte rich LBCL.

September 15, 2023

CADTH

CADTH Reimbursement Review
Feedback on Draft Recommendation

Stakeholder information	
CADTH project number	PC0313-000
Brand name (generic)	Polivy (polatuzumab vedotin)
Indication(s)	in combination with rituximab, cyclophosphamide, doxorubicin, and prednisone (R-CHP) for the treatment of adult patients with previously untreated large B-cell lymphoma (LBCL), including diffuse large B-cell lymphoma (DLBCL) not otherwise specified (NOS), high grade B-cell lymphoma, Epstein-Barr virus-positive (EBV+) DLBCL NOS, and T-cell/histiocyte rich LBCL
Organization	Ontario Health (Cancer Care Ontario) Hematology Cancer Drug Advisory Committee
Contact information[a]	Name: Dr. Tom Kouroukis

Stakeholder agreement with the draft recommendation		
1. Does the stakeholder agree with the committee's recommendation.	Yes	☒
	No	☐
Please explain why the stakeholder agrees or disagrees with the draft recommendation. Whenever possible, please identify the specific text from the recommendation and rationale.		

Expert committee consideration of the stakeholder input		
2. Does the recommendation demonstrate that the committee has considered the stakeholder input that your organization provided to CADTH?	Yes	☒
	No	☐
If not, what aspects are missing from the draft recommendation?		

Clarity of the draft recommendation		
3. Are the reasons for the recommendation clearly stated?	Yes	☒
	No	☐
If not, please provide details regarding the information that requires clarification.		
4. Have the implementation issues been clearly articulated and adequately addressed in the recommendation?	Yes	☒
	No	☐
If not, please provide details regarding the information that requires clarification.		
5. If applicable, are the reimbursement conditions clearly stated and the rationale for the conditions provided in the recommendation?	Yes	☐
	No	☐
If not, please provide details regarding the information that requires clarification.		

[a] CADTH may contact this person if comments require clarification.

Appendix 1. Conflict of Interest Declarations for Patient Groups

- 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 feedback from patient groups and clinician groups.
- CADTH may contact your group with further questions, as needed.
- Please see the *Procedures for CADTH Drug Reimbursement Reviews* for further details.

A. Patient Group 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 patient group with a company, organization, or entity that may place this patient group in a real, potential, or perceived conflict of interest situation.

B. Assistance with Providing Feedback		
1. Did you receive help from outside your patient group to complete your feedback?	No	☐
	Yes	☐
If yes, please detail the help and who provided it.		
2. Did you receive help from outside your patient group to collect or analyze any information used in your feedback?	No	☐
	Yes	☐
If yes, please detail the help and who provided it.		

C. Previously Disclosed Conflict of Interest		
1. Were conflict of interest declarations provided in patient group input that was submitted at the outset of the CADTH review and have those declarations remained unchanged? If no, please complete section D below.	No	☐
	Yes	☐

D. New or Updated Conflict of Interest Declaration

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.

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	☐	☐	☐	☐

Appendix 2. Conflict of Interest Declarations for Clinician Groups

- 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 feedback from patient groups and clinician groups.
- CADTH may contact your group with further questions, as needed.
- Please see the *Procedures for CADTH Drug Reimbursement Reviews* for further details.
- For conflict of interest declarations:
  - Please 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 declarations are required for each clinician that contributed to the input.
  - If your clinician group provided input at the outset of the review, only conflict of interest declarations that are new or require updating need to be reported in this form. For all others, please list the clinicians who provided input are unchanged
  - Please add more tables as needed (copy and paste).
  - All new and updated declarations must be included in a single document.

A. Assistance with Providing the Feedback		
2. Did you receive help from outside your clinician group to complete this submission?	No	☐
	Yes	☒
If yes, please detail the help and who provided it. OH-CCO provided a secretariat function to the group.		
3. Did you receive help from outside your clinician group to collect or analyze any information used in this submission?	No	☒
	Yes	☐
If yes, please detail the help and who provided it.		
B. Previously Disclosed Conflict of Interest		
4. Were conflict of interest declarations provided in clinician group input that was submitted at the outset of the CADTH review and have those declarations remained unchanged? If no, please complete section C below.	No	☐
	Yes	☒
If yes, please list the clinicians who contributed input and whose declarations have not changed: • Dr Tom Kouroukis • Dr. Pierre Villeneuve		

On behalf of Lymphoma Canada Scientific Advisory Board (SAB) members, we strongly oppose the recent negative CADTH recommendation for RCHP-polatuzumab in the front-line treatment of large B-cell lymphoma. This is a great disservice to patients in Canada to not have this regimen available and represents an inconsistency with prior recommendations. Specific responses to pERC comments are outlined below:

1. PFS endpoint: '*pERC was uncertain whether the observed between-group difference of 6.64% at 24 months (95% CI: 0.70 to 12.58) is clinically meaningful'*

   As a reminder this equated to a HR .76 (p=0.0298) and it is the SAB's opinion that this is a clinically meaningful benefit and reflects the log rank difference as opposed to choosing a specific point estimate. Regardless, we do feel 6.64% is clinically meaningful and a previous pERC opinion also previously determined a similar magnitude of benefit to be clinically meaningful in the front-line treatment of advanced stage Hodgkin lymphoma with AVD-BV in Echelon-1 where the absolute modified PFS benefit (and endpoint that also included treatment for incomplete response by central review) was 4.7% at 2y. It is unclear why a higher magnitude of benefit in another curative lymphoma would lead a different conclusion especially given the downstream treatments required to cure relapsed/refractory large B-cell lymphoma (auto-SCT, CART-cell therapy). This inconsistency is confusing for practitioners and patients.

   If the magnitude of the benefit is of concern, the pERC committee can also reference subgroups that benefit. Not surprisingly, those with an IPI 3-5 (planned stratification factor) drove the benefit observed (HR .7) and thus consideration could be given to restricting use to these patients. There is another obvious caveat; it would appear this rationale was used with the Echelon-1 study to restrict approval and funding to stage IV patients based on the initial subgroup analysis. Subsequent follow-up demonstrated benefit in all patient subgroups. Scientifically, we appreciate that while interesting, subgroup analyses remain only hypothesis generating.

   The other group that appears to derive significant benefit is those with ABC DLBCL where the HR is striking .4 (2 y PFS 83.9 % vs 58.8% compared to 1.0 for GCB 75.1% vs 76.9%) although it is important to note that this was not a stratification factor. Supporting a differential effect in ABC/GCB is an accompanying recent commentary by Alizadeh and colleagues in the NEJM (August 24, 2023) that likely was not available during the pERC review. The authors point out that this data was presented to the FDA There is data from other trials also supporting this differential effect. Given that COO in this study was by molecular diagnostics and many diagnostic labs in Canada only report immunohistochemical cell of origin by the less robust immunohistochemical assignment, it may be challenging to tie approval to COO at this time but can be used by practioners who do have this test available.

Collectively, although we support approval based on the ITT population, we would prefer at the very least funding it in subgroups that derive the greatest benefit than not having it at all.

2. OS: *'-pERC noted that **overall survival (OS) is an important outcome to patients and clinicians**, and no OS benefit was observed in the POLARIX trial. The HR for OS was 0.94 (95% CI: 0.67 to 1.33) with the upper CI crossing unity, and a key limitation for the OS results was the insufficient number of events observed'*
   The study was powered to evaluate PFS not OS. Although we agree that OS is an important endpoint, approval should not be based on the demonstration of superior OS. Again, this is inconsistent with the positive recommendation for AVD-BV in the frontline treatment of advanced HL without an OS benefit at first report although later verified) but the committee recognized the importance of the mPFS benefit. It cannot be underestimated what the downstream costs, toxicity and QOL impact of treating relapsed/refractory DLBCL may have on patients and the health care system. The only curative options are auto-SCT and CART-cell therapy, costly and challenging therapies for provincial systems to deliver. Improving PFS the cure rate) with 6 months of front-line therapy means that patients would not have undergo second-line therapies. Older patients and those with comorbidities are frequently unable to access these therapies resulting in a median OS is < 6 months.

3. QOL: *pERC could not reach definitive conclusions regarding the effects of pola-R-CHP compared to R-CHOP on disease symptoms, normalized blood counts and HRQOL*

   This comment is difficult to understand. Health related quality of life was assessed in this clinical trial and was found to not be inferior in the control arm. It was similar to standard therapy with R-CHOP. As the pola-R-CHP arm was associated with favourable disease control without a decrement in QOL, this would be typically interpreted as a positive clinical finding. The comments from pERC regarding disease sympoms and normalized blood counts are irrelevant – pola-R-CHP had similar QOL and better lymphoma control thus disease-related symptoms could not be worsened in the experimental arm. Similarly blood counts reflect numbers and not symptoms nor QOL. These toxicities are generally irrelevant and rather the consequences (febrile neutropenia, transfusion rates etc.) should be considered.

4. 'POLARIX trial did not examine different doses of the components.'

As pERC pointed out, R-CHOP is the appropriate comparator and only those patients suitable for full dose R-CHOP were enrolled. Dose reduction is used in older patients whether it is strictly R-mini-CHOP or simply choosing a 2ercentage decrease for safety reasons. Evaluating chemotherapy dosing would never be examined in a phase 3 registrational study as it would result in too much heterogeneity to examine the effect of the therapy in question (the dosing of the experimental drug would have been defined by prior trials and the components of

the standard regimen would have been well established by prior studies). This statement could be applied to any phase 3 trial incorporating novel therapy with a standard regimen and would be completely inaccurate. Recent examples in the lymphoma primary therapy setting include Echelon-1 in Hodgkin Lympphoma and Echelon-2in CD30+ periperal T Cell lymphoma In clinical practice there may be dose modification based on physician discretion but this is moot in considering the merit of this phase 3 trial.

CADTH

CADTH Reimbursement Review
Feedback on Draft Recommendation

Stakeholder information	
CADTH project number	PC0313-000-000
Brand name (generic)	POLIVY (polatuzumab vedotin)
Indication(s)	Previously untreated large B-cell lymphoma (LBCL)
Organization	Lead of Clinician Group: Canadian Hematologists/Oncologists Treating DLBCL
Contact information[a]	Name: Laurie H. Sehn MD, MPH

Stakeholder agreement with the draft recommendation		
1. Does the stakeholder agree with the committee's recommendation?	Yes	☐
	No	☒

Please explain why the stakeholder agrees or disagrees with the draft recommendation. Whenever possible, please identify the specific text from the recommendation and rationale.

We do not agree with pERC's negative recommendation. We strongly believe that Polatuzumab vedotin in 1L has tremendous value for two key reasons. First, the magnitude of improvement of pola-R-CHP in 1L is both significant and clinically meaningful as highlighted by clinicians and patients. Second, the PFS benefit observed at 24 months is an appropriate endpoint and its enduring benefits are further supported by the longer-term follow-up data and secondary endpoints, which were not considered in pERC's evaluation. Furthermore, we feel that CADTH's negative recommendation is not consistent with their previous recommendations. We strongly urge CADTH to reconsider the POLARIX file.

The following lays out our reasoning for disagreeing with the rationale provided by pERC:

1. The MAGNITUDE of effect of Pola-R-CHP is significant and clinically meaningful and, thus, we are not aligned with CADTH's comment that it is "uncertain whether magnitude of improvement compared to R-CHOP was clinically meaningful".

    - **Magnitude of effect.** CADTH stated that they found it "difficult to adequately assess the treatment effects". We firmly disagree. POLARIX is the first Phase III trial to demonstrate statistically significant benefit in nearly 20 years. The trial did meet the primary endpoint by demonstrating that pola+R-CHP reduced the risk of disease progression, disease relapse or death by 27% compared to R-CHOP (PFS HR 0.73 [95% CI 0.57, 0.95]; p-value=0.0177). This translates into one of 4 patients that would have relapsed, being prevented from relapse. The curves for PFS were stable over a 3 year period which indicates that Pola-R-CHP is curing a higher proportion of patients in the front-line setting compared with R-CHOP. As clinicians who treat this disease, we all agree that preventing progressive disease, relapse, or death in front-line treatment is clinically meaningful. Therefore, the statistically significant magnitude of improvement observed in the POLARIX trial is an important advancement for the treatment of 1L DLBCL.

- **Meaningfulness of effect.** CADTH concluded Pola-R-CHP did not "address the unmet needs identified by stakeholders". As we underscored in our initial submission, " PFS is a clinically meaningful endpoint that is used in clinical practice, as well as PFS at 2 years, since most progression or relapse events will occur within this time frame". Moreover, CADTH's own Clinical experts noted that PFS especially at 2 years post-treatment was "important for patients with DLBCL" and, similarly the patient input echo this sentiment that "exceptions for new treatments include longer disease remission". Thus, a significant change in PFS is both meaningful to clinicians and patients.
- **Unmet need in IPI 3-5.** CADTH noted that their review "focused on the subgroups of IPI score" but "concrete conclusions cannot be drawn". We agree with CADTH that "benefit of treatment with pola-R-CHP may be most relevant in those with an IPI score of 3 to 5 and no bulky disease". Patients with IPI 3-5 have a higher unmet need and pola-R-CHP is likely to be even more meaningful for these higher risk individuals. Aligned with this view, CADTH's own experts advised that "Pola-R-CHP was anticipated to replace R-CHOP for DLBCL patients with IPI score of 3 and greater". Even CADTH acknowledged that "PFS benefit was primarily driven by treatment effects among the subgroup of patients with an IPI score of 3 or higher". As the ITT population of POLARIX was statistically significant and, according to CADTH, likely driven by IPI 3-5 patients, it remains unclear why CADTH has disregarded the clinical experts and not at least considered supporting access to pola-R-CHP for patients with IPI 3-5.

Overall, we believe that CADTH has disregarded a statistically significant Phase III trial that has shown a meaningful magnitude of improvement, particularly in patients with IPI 3-5. This recommendation will undoubtedly deprive Canadian patients from accessing the meaningful clinical benefits of pola-R-CHP.

2. POLARIX primary endpoint is meaningful and is further strengthened by the long-term follow-up data and secondary endpoints.
    - **PFS is a meaningful endpoint.** CADTH noted that "strength of the correlation with OS beyond 5 years is uncertain". This is not aligned to the data that is currently available. Data by Maurer et al., 2014 demonstrated that patients who are event-free at 2 years have OS comparable to the general population. Moreover, improvement of PFS at 2 years is clinically meaningful because relapsing or being refractory to 1L treatment remain the main causes of morbidity and mortality [Maurer, et al. 2018]. Thus, we believe that PFS at 2 years in 1L DLBCL is thus a surrogate for cure rate in the front-line setting.
    - **Maintenance of effect longer-term.** CADTH noted that pERC "could not conclude that pola-R-CHP would meaningfully prolong remission". There are 4 lines of evidence that demonstrate the long-term benefit of Pola-R-CHP on remission and related endpoints:
        - Difference in PFS curves were maintained over 3 years (Herrera, et al. ASH 2022)
        - POLARIX trial has also translated into less subsequent therapies needed in the pola-R-CHP arm vs R-CHOP. This information was omitted from the CADTH draft recommendation. 30.3% of patients in the R-CHOP arm required subsequent treatment, whereas only 22.5 % of patients in the Pola-R-CHP arm required subsequent treatment, which means less radiotherapy, ASCT or CAR-T cell therapy for these patients.

- POLARIX trial secondary time-to-event endpoints, such as EFS, disease-free survival (DFS) and duration of response (DOR) all showed improvement. EFS was consistent with the results of the primary endpoint (HR, 0.75; 95% CI: 0.58–0.96; P=0.02). The 2-year EFS rate was 75.6% (95% CI: 71.5–79.7) with Pola-R-CHP vs 69.4% (95% CI: 65.0–73.8) with R-CHOP
- Pola-R-CHP in 1L reduces the risk of undergoing 2L treatment compared with R-CHOP by 27%. (Boissard et al., 2022)

Taken together, these results support the sustained remission seen in patients treated with pola+R-CHP vs R-CHOP. It's worth underscoring that these endpoints were <u>not</u> included in the CADTH report. We strongly urge pERC to reconsider their evaluation in light of this data.

- **"OS benefit compared to R-CHOP was not observed in the POLARIX".** CADTH noted that "insufficient evidence that pola-R-CHP will extend survival". As CADTH themselves noted, an OS benefit is not expected given that the "trial was not powered to detect improvements in OS". Historically, the benefit of PFS and OS was believed to be correlative as patients who progressed on treatment typically had poorer survival outcomes. However, the recent availability of a greater number and better therapeutic options in relapsed/refractory DLBLC makes it more challenging to show an overall survival benefit when patients do progress on treatment. Therefore, we strongly believe that PFS has become the accepted primary endpoint of clinical trials and we will not improve the treatment of 1L DLBLC in Canada if CADTH demands a statistically significant overall survival benefit.

In summary, we feel that pERC has not adequately reviewed the existing data available from both the POLARIX trial secondary endpoints, long-term follow-up as well as the wider literature on DLBCL endpoints. In light of this, we request pERC reconsider the POLARIX file.

3. We feel that there is a strong inconsistency of this CADTH recommendation for POLARIX trial compared to the Echelon trial. There are substantial parallels between the two trials. Yet, the recommendation for Echelon was positive whereas in this case POLARIX recommendation was negative. Importantly, unlike the Echelon data, in the POLARIX trial the toxicity profile was similar between the 2 groups.
    - **Parallel between trial endpoints.** There are three important trial endpoints that were disparately evaluated by pERC: OS endpoint, PFS as a meaningful endpoint, use of exploratory endpoints.
        - **OS endpoint.** Similar to the POLARIX trial, in the Echelon trial the OS data were immature at the time of the primary efficacy analysis. During their review pERC noted that with additional follow-up in Echelon the OS data will likely still be confounded by the post-trial treatments given after disease progression. As we've articulated above, the post-trial treatment following progression is likely to impact POLARIX. Therefore, there is inconsistency in the evaluation of the necessity of OS as an endpoint.
        - **PFS as a meaningful endpoint.** While pERC expressed some concerns about modified PFS in the Echelon trial, they ultimately concluded that mPFS is a clinically meaningful endpoint in advanced HL given it includes progression events and that it reflects the curative intent of front-line therapy. This evaluation of Echelon PFS endpoint differs from the evaluation of the POLARIX PFS endpoint. It should be noted that a standard definition of PFS

was used in POLARIX and the absolute improvement observed was higher than that reported in the Echelon trial at the time of approval.

- **Exploratory secondary endpoints.** For pERC's evaluation of the Echelon trial they also considered a post-hoc analysis of the exploratory outcome PFS, at three- and four-years follow-up. Similar to the POLARIX data, the Echelon data secondary endpoint also suggested that the benefit was maintained in the overall trial population and also suggested favourable effects in subgroups of patients with both stage III and IV disease. As stated above, the secondary endpoints for POLARIX were not considered by pERC.

We strongly believe that pERC is inconsistently evaluating files and providing drastically different recommendations. We would request that CADTH reconsider the file aligned with the same fairness as was provided to the Echelon trial.

Pola-R-CHP in front-line DLBCL is quickly becoming the standard of care worldwide and not having this regimen available to Canadian patients is harming our patients. Considering (1) the magnitude of the effect observed in POLARIX, (2) the appropriateness of endpoints demonstrated and (3) for consistency with other recommendations, CADTH should reconsider their assessment of the net-clinical benefit associated with Polatuzumab vedotin and provide a positive listing recommendation for at the very least high-risk patients with IPI 3-5.

Expert committee consideration of the stakeholder input		
2. Does the recommendation demonstrate that the committee has considered the stakeholder input that your organization provided to CADTH?	Yes	☐
	No	☒

If not, what aspects are missing from the draft recommendation?

This recommendation did not take in consideration the stakeholder feedback. Mainly the following points are contradicting with the pERC negative recommendation:

- The clinicians consulted clearly stated where Polatuzumab vedotin would fit in the DLBCL treatment landscape and where it provides clinical meaningfulness.
- According to the clinical experts, the preference is to employ pola-R-CHP as a front-line therapy for increasing cure rates rather than as a later-line treatment to avoid salvage treatments
- The Importance of 2-year PFS & the potential of cure if CR is maintained for 2 years. There's no further explanation on appropriateness of 2 year PFS and the feasibility of conducting an OS primary endpoint trial in this disease area.
- Throughout the recommendation, it was noted that PFS is an appropriate endpoint. "PFS is a clinically meaningful endpoint that is used in clinical practice as well as PFS 2 years, as most progressions or relapses will occur within this time frame". Clinical experts considered PFS at 24 months to be a reasonable outcome for assessing pola-R-CHP because most disease progression or relapses occur before this time point."
- Pola-R-CHP was anticipated by the experts to replace R-CHOP for DLBCL for patients with IPI score of 3 and greater
- Harms was reported to be a concern with pola-R-CHP: Clinicians input mentioned that pola-R-CHP has a similar safety profile to R-CHOP and it is anticipated that it can be safely administered in similar settings as R-CHOP. However, this opinion was not shared by the clinical experts consulted by CADTH, who highlighted concerns with greater toxicity with pola-R-CHP treatment. In general, pola-R-CHP is an out-patient systemic therapy that can be

routinely administered by physicians with experience in oncology therapy (typically hematologists or oncologists).		
Clarity of the draft recommendation		
3. Are the reasons for the recommendation clearly stated?	Yes	☐
	No	☒
If not, please provide details regarding the information that requires clarification. No, as described above, the recommendation contradicts the evidence that demonstrated pola-R-CHP to be more effective than the SOC R-CHOP. It also contradicts the stakeholder feedback. pERC recommends that pola-R-CHP not be reimbursed for the treatment of adult patients with previously untreated LBCL on the basis that "pERC was uncertain whether the observed between-group difference of 6.64% at 24 months (95% CI: 0.70 to 12.58) is clinically meaningful". There is also no further rationale on why this is uncertain. Is there a benchmark that CADTH is using? What level of improvement would make it certain enough?		
4. Have the implementation issues been clearly articulated and adequately addressed in the recommendation?	Yes	☒
	No	☐
If not, please provide details regarding the information that requires clarification.		
5. If applicable, are the reimbursement conditions clearly stated and the rationale for the conditions provided in the recommendation?	Yes	☐
	No	☐
If not, please provide details regarding the information that requires clarification.		

[a] CADTH may contact this person if comments require clarification.

Appendix 2. Conflict of Interest Declarations for Clinician Groups

- 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 feedback from patient groups and clinician groups.
- CADTH may contact your group with further questions, as needed.
- Please see the *Procedures for CADTH Drug Reimbursement Reviews* for further details.
- For conflict-of-interest declarations:
  - Please 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 declarations are required for each clinician that contributed to the input.
  - If your clinician group provided input at the outset of the review, only conflict of interest declarations that are new or require updating need to be reported in this form. For all others, please list the clinicians who provided input are unchanged
  - Please add more tables as needed (copy and paste).
  - All new and updated declarations must be included in a single document.

A. Assistance with Providing the Feedback		
1. Did you receive help from outside your clinician group to complete this submission?	No	☒
	Yes	☐
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?	No	☒
	Yes	☐
If yes, please detail the help and who provided it. N/A		
B. Previously Disclosed Conflict of Interest		
3. Were conflict of interest declarations provided in clinician group input that was submitted at the outset of the CADTH review and have those declarations remained unchanged? If no, please complete section C below.	No	☐
	Yes	☒
If yes, please list the clinicians who contributed input and whose declarations have not changed: 1. Dr. Laurie H. Sehn, Chair, Lymphoma Tumour Group, BC Cancer Centre for Lymphoid Cancer, Clinical Professor of Medicine, Division of Medical Oncology, University of British Columbia, Vancouver, BC 2. Dr. Alina Gerrie, Assistant Professor of Medicine, Division of Medical Oncology, University of British Columbia, Vancouver, BC 3. Dr. Mohamed Elemary, Professor, Division of Oncology, University of Saskatchewan, Saskatoon, SK		

4. Dr. Daniel Ontko, Hematologist, Island Health, Nanaimo, BC
5. Dr. Graeme Fraser, Associate Professor, Department of Oncology, McMaster University, Hamilton ON
6. Randeep Sangha, Associate Professor, Division of Medical Oncology, University of Alberta, Edmonton, AB
7. Dr. Ardashes Avanessian, Clinical Assistant Professor of Medicine, Division of Medical Oncology, University of British Columbia, Vancouver, BC
8. Dr. Sathish Kumar Gopalakrishnan, Director, Complex Malignant Haematology, Health Sciences North, Sudbury, ON
9. Dr. Philip George Kuruvilla, Oncologist, William Osler Health System, Brampton, ON
10. Dr. Kuljit Grewal, Associate Professor of Medicine (Hematology), Memorial University, NS
11. Dr. Pam Skrabek, Associate Professor, Department of Medical Oncology and Hematology, Max Rady College of Medicine, University of Manitoba, Winnipeg, MB

C. New or Updated Conflict of Interest Declarations – N/A

CADTH

CADTH Reimbursement Review

Feedback on Draft Recommendation

Stakeholder information	
CADTH project number	PC0313
Name of the drug and Indication(s)	polatuzumab vedotin for large B-cell lymphoma
Organization Providing Feedback	PAG

1. Recommendation revisions Please indicate if the stakeholder requires the expert review committee to reconsider or clarify its recommendation.		
Request for Reconsideration	**Major revisions:** A change in recommendation **category** or patient **population** is requested	☐
	Minor revisions: A change in reimbursement **conditions** is requested	☐
No Request for Reconsideration	**Editorial revisions:** Clarifications in recommendation **text** are requested	☐
	No requested revisions	X

2. Change in recommendation category or conditions Complete this section if major or minor revisions are requested
Please identify the specific text from the recommendation and provide a rationale for requesting a change in recommendation.

3. Clarity of the recommendation Complete this section if editorial revisions are requested for the following elements
a) Recommendation rationale
Please provide details regarding the information that requires clarification.
b) Reimbursement conditions and related reasons
Please provide details regarding the information that requires clarification.

c) Implementation guidance
Please provide high-level details regarding the information that requires clarification. You can provide specific comments in the draft recommendation found in the next section. Additional implementation questions can be raised here.

Outstanding Implementation Issues

In the event of a positive draft recommendation, drug programs can request further implementation support from CADTH on topics that cannot be addressed in the reimbursement review (e.g., concerning other drugs, without sufficient evidence to support a recommendation, etc.). Note that outstanding implementation questions can also be posed to the expert committee in Feedback section 4c.

Algorithm and implementation questions
1. Please specify sequencing questions or issues that should be addressed by CADTH (oncology only)
1. 2.
2. Please specify other implementation questions or issues that should be addressed by CADTH
1. 2.
3. Please specify questions or issues that should be addressed by CAPCA. (oncology only)
1. 2.
Support strategy
4. Do you have any preferences or suggestions on how CADTH should address these issues?
May include implementation advice panel, evidence review, provisional algorithm (oncology), etc.

CADTH

CADTH Reimbursement Review
Feedback on Draft Recommendation

Stakeholder information	
CADTH project number	PC0313-000-000
Brand name (generic)	Polivy (Polatuzumab Vedotin)
Indication(s)	Polatuzumab vedotin in combination with rituximab, cyclophosphamide, doxorubicin and prednisone (Pola R-CHP), for the treatment of adult patients with previously untreated large B-cell lymphoma (LBCL), including diffuse large B-cell lymphoma (DLBCL) not otherwise specified (NOS), high grade B-cell lymphoma, Epstein-Barr virus-positive (EBV+) DLBCL NOS, and T-cell/histiocyte rich LBCL
Organization	Lymphoma Canada
Contact information[a]	Name: Antonella Rizza [redacted] and Gurjot Basra [redacted]

Stakeholder agreement with the draft recommendation		
1. Does the stakeholder agree with the committee's recommendation.	Yes	☐
	No	☒

Please explain why the stakeholder agrees or disagrees with the draft recommendation. Whenever possible, please identify the specific text from the recommendation and rationale.

We do not agree with the committee's recommendation that pola-R-CHP not be reimbursed for this indication. We do not agree with pERC's conclusion that PFS is not a valid consideration in determining whether to recommend the drug be funded or not. Pola-R-CHP provides a treatment option for patients in the frontline setting that may be less burdensome for patients than other current standard of care treatment. In the patients we surveyed, QofL was described as important, as was having more treatment options to choose from in this setting. The recommendation goes against these patient preferences in that QofL of pola R-CHP was similar to standard therapy. Of those surveyed the experience of pola-R-CHP from LBCL patients was positive with minimal negative comments left about the ability to access treatment, financial implications, or challenges tolerating side effects, which all positively influence quality of life.

Additionally, in the recommendation, "clinical experts expressed concerns about neutropenia of any grade" as well as "grade three anemia" amongst patients treated with pola-R-CHP. However, amongst the four individuals in our patient survey who received this treatment, none experienced low red blood cell count (anemia), while only one experienced febrile neutropenia.

Expert committee consideration of the stakeholder input		
2. Does the recommendation demonstrate that the committee has considered the stakeholder input that your organization provided to CADTH?	Yes	☐
	No	☒

If not, what aspects are missing from the draft recommendation?

No, our input indicated that patients preferred more options in terms of available treatments. This was not considered. We would like to emphasize responses from the patient survey mentioned in

our original submission. One of the four individuals who received Pola-R-CHP as treatment via clinical trial articulated the following about their experience:

"Grateful to my doctors for being part of this trial"

Additionally, three patients who received Pola-R-CHP therapy agreed that they would recommend it to other patients with Large B-cell lymphoma, rating their experience from "good" to "very good".

Clarity of the draft recommendation

3. Are the reasons for the recommendation clearly stated?	Yes	☒
	No	☐

If not, please provide details regarding the information that requires clarification.

Yes, the reasons are clearly stated although we find it difficult as a patient organization to understand why the committee does not regard 1) a statistically significant improvement in PFS, 2) a comparable QofL to standard of care treatment; as important considerations when making their recommendation – particularly since these considerations might reduce the rate or potentially length of time to relapse for certain patients.
The patient input we provided, particularly of those that had taken pola R-CHP should not be discounted as these patients noted that they would all recommend it to other patients with Large B-cell lymphoma.

4. Have the implementation issues been clearly articulated and adequately addressed in the recommendation?	Yes	☐
	No	☐

If not, please provide details regarding the information that requires clarification.

N/A

5. If applicable, are the reimbursement conditions clearly stated and the rationale for the conditions provided in the recommendation?	Yes	☐
	No	☐

If not, please provide details regarding the information that requires clarification.

N/A

[a] CADTH may contact this person if comments require clarification.

Appendix 1. Conflict of Interest Declarations for Patient Groups

- 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 feedback from patient groups and clinician groups.
- CADTH may contact your group with further questions, as needed.
- Please see the *Procedures for CADTH Drug Reimbursement Reviews* for further details.

A. Patient Group Information	
Name	*Gurjot Basra*
Position	*Manager of Patient Programs, Research, and Advocacy*
Date	*(15-09-2023)*
☒	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.

B. Assistance with Providing Feedback		
1. Did you receive help from outside your patient group to complete your feedback?	No	☒
	Yes	☐
If yes, please detail the help and who provided it.		
2. Did you receive help from outside your patient group to collect or analyze any information used in your feedback?	No	☒
	Yes	☐
If yes, please detail the help and who provided it.		

C. Previously Disclosed Conflict of Interest		
1. Were conflict of interest declarations provided in patient group input that was submitted at the outset of the CADTH review and have those declarations remained unchanged? If no, please complete section D below.	No	☒
	Yes	☐

D. New or Updated Conflict of Interest Declaration

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.

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	☐	☐	☐	☒
Incyte	☐	☐	☒	☐
Novartis	☐	☐	☒	☐
BMS	☐	☐	☐	☒
Roche	☒	☐	☐	☐

CADTH

CADTH Reimbursement Review
Feedback on Draft Recommendation

Stakeholder information	
CADTH project number	PC0313-000
Brand name (generic)	polatuzumab vedotin
Indication(s)	Polatuzumab vedotin in combination with rituximab, cyclophosphamide, doxorubicin, and prednisone (R-CHP) for the treatment of adult patients with previously untreated large B-cell lymphoma (LBCL), including diffuse large B-cell lymphoma (DLBCL) not otherwise specified (NOS), high grade B-cell lymphoma, Epstein-Barr virus-positive (EBV+) DLBCL NOS, and T-cell/histiocyte rich LBCL.
Organization	Leukemia & Lymphoma Society of Canada
Contact information[a]	Name: Colleen McMillan [redacted]

Stakeholder agreement with the draft recommendation		
1. Does the stakeholder agree with the committee's recommendation.	Yes	☐
	No	☒

Please explain why the stakeholder agrees or disagrees with the draft recommendation. Whenever possible, please identify the specific text from the recommendation and rationale.

We disagree with the committee's recommendation because our patient group believes that polatuzumab vedotin does meet an unmet need for patients and is in line with patient values. The benefit in PFS is a meaningful endpoint for patients, especially in early-stage disease. PFS is a commonly accepted endpoint in cancer and the benefit that polatuzumab vedotin provides patients regarding PFS is relevant.

Expert committee consideration of the stakeholder input		
2. Does the recommendation demonstrate that the committee has considered the stakeholder input that your organization provided to CADTH?	Yes	☐
	No	☐

If not, what aspects are missing from the draft recommendation?

LLSC did not submit stakeholder input in earlier stages of this review, however, our community supports the input submitted by the clinicians and Lymphoma Canada in their original submissions. We believe that the clinicians and Lymphoma Canada clearly outlined the unmet need that polatuzumab vedotin meets for patients and we wholeheartedly agree with their appeal for a recommendation in favour of the reimbursmenet of polatuzumab vedotin.

Clarity of the draft recommendation		
3. Are the reasons for the recommendation clearly stated?	Yes	☒

	No	☐
If not, please provide details regarding the information that requires clarification.		
4. Have the implementation issues been clearly articulated and adequately addressed in the recommendation?	Yes	☐
	No	☒
We would urge the committee to reconsider the recommendation put forward and reconsider this decision because we believe that polatuzumab vedotin does meet an unmet need for patients in early-stage disease and we do not feel that the significance of the benefit that polatuzumab vedotin has on the impact of PFS for patients as a meaningful endpoint was fully considered. In other CADTH recommendations PFS has been recognized as a significant endpoint and we would urge you to consider that fact in reconsidering this recommendation.		
5. If applicable, are the reimbursement conditions clearly stated and the rationale for the conditions provided in the recommendation?	Yes	☒
	No	☐
If not, please provide details regarding the information that requires clarification.		

[a] CADTH may contact this person if comments require clarification.

Appendix 1. Conflict of Interest Declarations for Patient Groups

- 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 feedback from patient groups and clinician groups.
- CADTH may contact your group with further questions, as needed.
- Please see the *Procedures for CADTH Drug Reimbursement Reviews* for further details.

A. Patient Group Information	
Name	*Colleen McMillan*
Position	*Advocacy Lead*
Date	*15-09-2023*
☒	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.

B. Assistance with Providing Feedback		
1. Did you receive help from outside your patient group to complete your feedback?	No	☒
	Yes	☐
If yes, please detail the help and who provided it.		
2. Did you receive help from outside your patient group to collect or analyze any information used in your feedback?	No	☒
	Yes	☐
If yes, please detail the help and who provided it.		

C. Previously Disclosed Conflict of Interest		
1. Were conflict of interest declarations provided in patient group input that was submitted at the outset of the CADTH review and have those declarations remained unchanged? If no, please complete section D below. **LLSC did not submit input in earlier stages of this review. LLSC does have conflict of interest declarations to report.**	No	☒
	Yes	☐

D. New or Updated Conflict of Interest Declaration

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.

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