pCODR PAN-CANADIAN ONCOLOGY DRUG REVIEW

pCODR EXPERT REVIEW COMMITTEE (pERC)
INITIAL RECOMMENDATION

The CADTH pan-Canadian Oncology Drug Review (pCODR) was established by Canada's provincial and territorial Ministries of Health (with the exception of Quebec) to assess cancer drug therapies and make recommendations to guide drug reimbursement decisions. The pCODR process brings consistency and clarity to the assessment of cancer drugs by looking at clinical evidence, cost-effectiveness, and patient perspectives.

Providing Feedback on This Initial Recommendation
Taking into consideration feedback from eligible stakeholders, the pCODR Expert Review Committee (pERC) will make a Final Recommendation. Feedback must be provided in accordance with *pCODR Procedures*, which are available on the pCODR website. The Final Recommendation will be posted on the pCODR website once available, and will supersede this Initial Recommendation.

Drug: Polatuzumab vedotin (Polivy)

Submitted Reimbursement Request: In combination with bendamustine and rituximab for the treatment of adult patients with relapsed or refractory diffuse large B-cell lymphoma, not otherwise specified, who are not eligible for autologous stem cell transplant and have received at least 1 prior therapy.

Submitted by: Hoffmann-La Roche Limited

Manufactured by: Hoffmann-La Roche Limited

NOC Date: July 9, 2020

Submission Date: September 29, 2020

Initial Recommendation Issued: April 1, 2021

Approximate per patient drug costs, per month (28 days)	Polatuzumab vedotin: $14,750.00 per 140 mg vial When used in combination with bendamustine and rituximab, the estimated cost per 28 days is $28,272 to $30,001 (this cost is prorated from the cost per 21-day cycle of $21,204 to $22,251).

pERC RECOMMENDATION

☐ **Reimburse**
☒ **Reimburse with clinical criteria and/or conditions[a]**
☐ **Do not reimburse**

[a] If the condition(s) cannot be met, pERC does not recommend reimbursement of the drug for the submitted reimbursement request.

pERC conditionally recommends the reimbursement of polatuzumab vedotin in combination with bendamustine and rituximab (pola-BR) for the treatment of adult patients with relapsed/refractory (R/R) diffuse large B-cell lymphoma (DLBCL), not otherwise specified, who are not eligible for autologous stem cell transplant (ASCT), if the following conditions are met:

- cost-effectiveness is improved to an acceptable level
- feasibility of adoption (budget impact) is addressed.

Eligible patients should have good performance status (PS) and a life expectancy greater than or equal to 24 weeks. Patients must have received at least 1 prior therapy. Treatment with pola-BR should continue for a maximum of 6 cycles (21 days per cycle) or until unacceptable toxicity or disease progression, whichever comes first.

pERC made this recommendation because it was satisfied that pola-BR may have a net clinical benefit compared with bendamustine and rituximab (BR) based on clinically meaningful improvements in complete response (CR), progression-free survival (PFS), and overall survival (OS) rates; a manageable toxicity profile; and a need for treatment options that lead to long-term disease control for R/R DLBCL. However, pERC acknowledged that there was uncertainty in its assessment of the net clinical benefit of pola-BR. This assessment was based on 1 randomized phase II trial with a limited sample size that used BR as the comparator, which is not considered the standard of care in this population in Canada.

	pERC agreed that pola-BR aligns with patient values in that it offers longer remission and survival and has manageable side effects. pERC concluded that, at the submitted price, pola-BR was not cost-effective. pERC noted that the submitted economic evaluation compared pola-BR to a basket of treatment regimens. Given the uncertainties in the indirect evidence and the small sample size from the trial informing the efficacy of pola-BR, pERC could not determine the expected magnitude of clinical benefit associated with pola-BR compared to a basket comparator. Although pERC was unable to identify a plausible base case, pERC noted that the exploratory reanalyses suggested that the incremental cost-effectiveness ratio (ICER) of pola-BR was higher than estimated by the sponsor. pERC noted that CADTH's reanalysis of the sponsor's budget impact analysis suggests that the budget impact of introducing polatuzumab vedotin to the market is substantial and underestimated.
POTENTIAL NEXT STEPS FOR STAKEHOLDERS	**Pricing arrangements to improve cost-effectiveness and budget impact** Given that pERC considered there may be a net clinical benefit of pola-BR, jurisdictions may want to consider pricing arrangements and/or cost structures that would improve the cost-effectiveness of the combination. pERC concluded that a reduction in drug price would be required to improve the cost-effectiveness of pola-BR to an acceptable level and to improve the budget impact. **Please note:** Provincial Advisory Group (PAG) questions are addressed in detail in the Summary of pERC Deliberations and in a summary table in Appendix 1.

SUMMARY OF pERC DELIBERATIONS

Non-Hodgkin lymphoma (NHL) is a cancer of the immune system that encompasses more than 60 types of lymphoma. In 2018, the projected incidence of NHL was 8,300 cases annually, with an age-standardized incidence rate of 20.8 cases per 100,000 Canadians. DLBCL is an aggressive form of NHL that constitutes approximately 30% of lymphoma cases in Canada. Prognosis varies by molecular subtype: activated B-cell type, double-hit lymphoma (concurrent translocations of *MYC* and either *BCL2* or *BCL6*), and double-expressor lymphoma (overexpression of *MYC* and *BCL2*) are all associated with particularly poor prognosis. In Canada, after standard first-line chemotherapy with rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP), or a similar regimen, the longer-term survival is approximately 60%. Unfortunately, 30% to 40% of patients will relapse or experience refractory disease and require subsequent treatment. Selected patients with R/R DLBCL are treated with salvage chemotherapy followed by high-dose therapy and ASCT. However, eligibility for salvage treatment largely depends on performance status (PS), age, and comorbidities; eligibility for ASCT is also dependent on the response to salvage chemotherapy. Approximately half of patients starting salvage chemotherapy become ineligible for ASCT due to inadequate response, and of those patients who proceed to ASCT, more than 50% will ultimately relapse. Until recently, treatment for patients not eligible for ASCT or who have relapsed after ASCT has largely been palliative; however, there is no standard palliative approach. Various single-agent or multi-agent therapy regimens are currently used depending on tolerance and are associated with a median survival that ranges between 3 months and 6 months. CAR T-cell therapy has recently become available to patients with R/R DLBCL. However, it is currently approved for patients who have experienced treatment failure after 2 or more lines of therapy, and thus it would not be available for the transplant-ineligible population after 1 line of therapy. For other patients, there will be challenges in accessing this therapy in a timely manner or they will be ineligible due to comorbidities, disease burden, or PS. Considering the limited treatment options available to most patients with R/R DLBCL, pERC agreed that there is a significant unmet need for treatment options that offer long-term disease control for this patient population.

pERC's *Deliberative Framework* for drug reimbursement recommendations focuses on 4 main criteria:

CLINICAL BENEFIT	**PATIENT-BASED VALUES**
ECONOMIC EVALUATION	**ADOPTION FEASIBILITY**

pERC deliberated on the results from a small (N = 80), phase Ib/II, open-label, randomized control trial (RCT), the GO29365 trial, which enrolled patients with R/R DLBCL after at least 1 prior regimen. pERC noted that the trial had several arms; however, the submission was focused on the phase II portion of the study that compared the outcomes of patients with R/R DLBCL who were randomized to treatment with either pola-BR or BR alone. pERC discussed that BR is not an available treatment option for this population in Canada. However, pERC agreed with the Clinical Guidance Panel (CGP) that given there is no standard-of-care regimen in most jurisdictions, the efficacy associated with BR is similar in magnitude to what is expected from currently used regimens in Canada. pERC discussed that the trial demonstrated improvements with pola-BR with respect to the majority of efficacy end points assessed by an independent review committee (IRC). The primary outcome, CR rate at end of treatment (EOT) based on PET-CT scan, as well as secondary outcomes including objective response rate (ORR), PFS, and OS, were all superior in patients treated with pola-BR when compared with patients treated with BR. However, pERC noted there was neither a power calculation nor pre-specified statistical hypothesis testing performed for the comparison of any outcomes between the treatment groups. Given these limitations in trial design, along with notable differences in important baseline characteristics between the treatment groups, pERC considered that there was uncertainty around the magnitude of clinical benefit for all outcomes. Based on the available efficacy data from the trial, and considering the noted limitations, pERC concluded that pola-BR may have a net clinical benefit compared with BR based on clinically meaningful improvements in CR, PFS, and OS.

Since the GO29365 trial lacked a standard-of-care comparator relevant to Canadian clinical practice, the sponsor submitted 2 indirect treatment comparison (ITCs) to estimate the relative efficacy of pola-BR to relevant comparator regimens in Canada. A matching-adjusted indirect comparison (MAIC) was submitted that compared pola-BR to R-GemOx, pixantrone, tisagenlecleucel (CAR T-cell therapy), and axicabtagene

ciloleucel (CAR T-cell therapy). A propensity score-weighted analysis using Canadian patient data from a real-world database (RWD) was also submitted that compared pola-BR to standard-of-care treatments in transplant-ineligible patients with R/R DLBCL. pERC discussed the CGP's and CADTH Methods Team's assessments of these analyses, which indicated that both ITCs had significant limitations in terms of scope of comparators, the use of variable quality and outdated evidence (MAIC), heterogeneity in patient populations with limited adjustment for treatment effect modifiers, and small sample sizes that affected the precision of the estimates obtained. pERC agreed with the CGP and CADTH Methods Team that the limitations of each analysis precluded reliable estimates of comparative efficacy to other treatments currently used in Canada.

pERC deliberated on the safety of pola-BR and noted that all patients in the GO29365 trial experienced at least 1 adverse event (AE), the incidence of grade 3 or grade 4 toxicity was higher in patients treated with pola-BR compared with those treated with BR, and the incidence of serious AEs (SAEs) and patient deaths attributable to AEs were comparable between the treatment groups. The AEs that occurred most frequently among patients treated with pola-BR included anemia, neutropenia, thrombocytopenia, peripheral neuropathy, and diarrhea. pERC discussed that peripheral neuropathy, a known side effect of polatuzumab vedotin, was the only patient-reported outcome assessed in the trial. However, its impact on patients could not be reliably assessed due to a significant amount of missing data for the Therapy-Induced Neuropathy Assessment Scale (TINAS) questionnaire. pERC noted that all cases of peripheral neuropathy in the pola-BR group were low grade and the majority of them resolved or improved when treatment, which was time-limited, was completed. pERC also discussed that when compared to the BR group, the number of AEs requiring dose interruption or dose reduction was higher in the pola-BR group, as were treatment discontinuations. pERC noted that the higher rate of treatment discontinuations in the pola-BR group was mostly due to increased AEs, but rates of febrile neutropenia and fatal AEs were similar between the treatment groups. Based on the trial evidence, as well as input received from registered clinicians and the patient advocacy group, pERC concluded that the toxicity profile of pola-BR appears to be tolerable despite an overall higher incidence of toxicity. The toxicity can be managed through proper dose adjustment and the use of granulocyte colony-stimulating factor, which was received by most patients in the trial. pERC was unable to deliberate on the impact pola-BR had on patient quality of life (QoL), as data on this outcome were not collected in the trial.

In summary, pERC concluded that pola-BR may have a net clinical benefit compared with BR based on clinically meaningful improvements in CR, PFS, and OS rates; a manageable toxicity profile; and a need for treatment options that lead to long-term disease control for R/R DLBCL. However, pERC acknowledged there was uncertainty in its assessment of the net clinical benefit of pola-BR. The assessment was based on 1 randomized phase II trial with a limited sample size that used BR as the comparator, which is not considered the standard of care in this population in Canada.

pERC discussed the patient advocacy input that was received supporting this submission and noted that patients value treatments that provide longer remission and survival compared to current standard-of-care treatments, have manageable side effects, and improve QoL. While pERC noted that there is uncertainty around the magnitude of clinical benefit pola-BR offers over currently available treatments, the Committee was satisfied based on the comparison to BR that the combination improves complete remission rates and survival. pERC discussed that patients indicated a desire for new treatment regimens that offer more favourable dosing schedules, in terms of a reduced number of clinic visits and shorter infusion times, when compared to currently used chemotherapy regimens. Patients stated that the greater number of clinic visits, longer infusion times, as well as the number of infusion reactions and infections associated with chemotherapy negatively impact their QoL. pERC noted, however, that the combined regimen of pola-BR may not provide the treatment dosing schedule patients desire since it requires IV administration, ongoing monitoring and clinic visits, and infections can be a complication of treatment. pERC therefore concluded that pola-BR aligns with patient values because it offers longer remission and survival and has manageable side effects.

pERC deliberated on the cost-effectiveness of pola-BR compared with a basket comparator of currently used treatment regimens for previously treated patients with R/R DLBCL who are not eligible for ASCT. A key limitation discussed by pERC was the definition of the comparator selected by the sponsor. Given that pola-BR was compared to a basket comparator, an ITC was required to derive comparative clinical efficacy estimates. As pERC noted in the assessment of the clinical evidence, limitations with the indirect evidence precluded reliable estimates of comparative efficacy and useful application of the results. As such, the expected magnitude of clinical benefit (i.e., life-years, quality-adjusted life-years [QALYs]) derived from the indirect evidence is highly uncertain. pERC reviewed the broad range of exploratory

analyses conducted by CADTH alongside the sponsor's submitted analysis which highlighted that assumptions regarding comparative effectiveness were a key driver of the cost-effectiveness of pola-BR compared to the basket comparator. pERC was able to conclude that, at the submitted price of polatuzumab vedotin, pola-BR was not cost-effective at a willingness-to-pay threshold of $50,000 per QALY gained. pERC further commented that the cost-effectiveness results presented by the sponsor and CADTH likely underestimated the ICER of pola-BR when compared to the basket comparator; pERC agreed with the clinical expert feedback that the life-years associated with pola-BR in the post-progression setting are substantially overestimated. Although CADTH suggested a price reduction range based on exploratory analyses, the aforementioned caveats precluded the Committee from determining a reasonable price reduction for pola-BR that would be considered cost-effective.

pERC also discussed the budget impact analysis. pERC considered the estimated budget impact to be associated with substantial uncertainty and underestimated and noted that the budget impact is highly sensitive to assumptions regarding which treatments would be displaced, market uptake, and the cost of currently available treatments.

EVIDENCE IN BRIEF

The CADTH pan-Canadian Oncology Drug Review (pCODR) Expert Review Committee (pERC) deliberated:

- a pCODR systematic review
- other literature in the Clinical Guidance Report that provided clinical context
- an evaluation of the sponsor's economic model and budget impact analysis
- guidance from the pCODR clinical and economic review panels
- input from 1 patient advocacy group: Lymphoma Canada (LC)
- input from 3 registered clinician groups: 2 clinicians on behalf of the Cancer Care Ontario (CCO) Hematology DAC, 20 clinicians on behalf of the BC Cancer Agency and University of British Columbia (UBC), and 3 clinicians on behalf of LC
- input from pCODR's Provincial Advisory Group (PAG).

OVERALL CLINICAL BENEFIT

pCODR review scope

The purpose of the review is to evaluate the efficacy and safety of pola-BR for the treatment of adult patients with R/R DLBCL, not otherwise specified, who are not eligible for ASCT and have received at least 1 prior therapy.

Studies included: One small, open-label, phase Ib/II RCT

The pCODR systematic review included 1 ongoing phase Ib/II, open-label, RCT, the GO29365 trial, that enrolled patients with R/R DLBCL after at least 1 prior regimen. The trial had several arms; however, the submission to CADTH was focused on the phase II portion of the trial that compared the outcomes of patients with R/R DLBCL who were randomized to receive treatment with pola-BR or BR alone. The trial was conducted in 54 centres in 12 countries including 4 Canadian sites that contributed 44 patients.

The key inclusion criteria of the GO29365 trial included the following: age 18 years or older, biopsy-confirmed R/R DLBCL (excluding transformed lymphoma), 1 or more prior lines of therapy, an Eastern Cooperative Oncology Group (ECOG) PS of 0 to 2, peripheral neuropathy assessed as grade 1 or less, transplant-ineligible or treatment failure with prior ASCT, and a life expectancy of 24 weeks or greater. The trial excluded patients who had a history of transformation of indolent disease to DLBCL, primary or secondary central nervous system lymphoma, prior allogeneic stem cell transplantation, and active hepatitis B or C virus, or HIV.

Patient populations: Predominantly White, male, median age of 69 years, and ECOG PS of 0 or 1; imbalances in some baseline characteristics between treatment groups

Study GO29365 enrolled a total of 80 patients, with 40 patients randomized to each treatment group. The trial population was predominantly male (66%), White (71%), and had a median age of 69 years. Most patients (80%) had an ECOG PS of 0 or 1. Although patients were to have DLBCL, there was 1 patient enrolled with follicular lymphoma and another patient with Burkitt lymphoma. In terms of prior therapy, 80% of patients were considered refractory, 84% had a duration of response of 12 months or less, and 20% were considered to have failed hematopoietic stem cell transplant (HSCT). Differences in baseline characteristics between the pola-BR and BR treatment groups of greater than 10% were observed for race (White: 65% versus 78%, respectively), primary reason for HSCT ineligibility (age: 33% versus 48%, respectively; failed prior HSCT: 25% versus 15%, respectively), outcome of last therapy (refractory: 75% versus 85%, respectively), disease features at baseline (bulky disease: 25% versus 38%, respectively), and International Prognostic Index risk at baseline (high: 23% versus 43%, respectively).

Key efficacy results: Clinically meaningful improvements in CR, PFS, and OS

The primary outcome of the trial was achievement of a CR, measured at the primary response assessment (i.e., EOT, which was 6 weeks after day 1 of cycle 6 or last dose of study medication) as measured by PET-CT scan and as determined by an IRC. The secondary outcomes, all assessed by an IRC, included CR rate at EOT based on CT only, ORR at EOT, best overall response, duration of response, and PFS. OS was an exploratory end point. Health-related QoL (HRQoL) was not assessed in the trial; however, peripheral

neuropathy, which is a recognized adverse effect of polatuzumab vedotin, was assessed by patients using the TINAS and by the investigators using the Total Neuropathy Score.

There was no pre-specified statistical hypothesis testing for the randomized phase II portion of trial GO29365. For the primary outcome, the sponsor assumed a 40% CR rate in the BR group and a 25% increase in CRs in the pola-BR group. There was no pre-specified alpha control plan to account for multiple comparison testing, and all time-to-event outcomes were summarized descriptively. The primary analysis cut-off date was April 30, 2018, which occurred after all treated patients had 1 year of follow-up after the preliminary response assessment. The median duration of follow-up at the primary analysis was 22.3 months. The sponsor provided longer-term efficacy data based on an updated data cut-off date of January 2, 2020, at which time the median duration of follow-up was 42.2 months.

Primary outcome:

- The CR rate at EOT by IRC assessment using PET-CT was 40% (n = 16) in the pola-BR group and 18% (n = 7) in the BR group, for a difference between the groups of 22% (95% CI, 3% to 41%).

Secondary outcomes:

- The CR rate at EOT by IRC assessment using CT only was 22.5% (n = not reported [NR]) in the pola-BR group compared to 2.5% (n = NR) in the BR group, for a difference between the groups of 20.0% (95% CI, 5.5% to 35.1%).
- The IRC-assessed ORR at EOT was 45% (n = 18) in the pola-BR group and 17.5% (n = 7) in the BR group. Partial responses were observed in 2 patients (5%) in the pola-BR group and no patients in the BR group at EOT.
- Best overall response was also reported, and there were more patients with a best response of CR in the pola-BR group (50%) compared to the BR group (23%). Partial responses occurred in 5 patients (12.5%) in the pola-BR group and 1 patient (2.5%) in the BR group. The ORR based on best response was 62.5% with pola-BR and 25% with BR. Results for best overall response were unchanged at the time of the updated analysis.
- The median duration of response by IRC was 12.6 (95% CI, 7.2 to not estimable [NE]) months in the pola-BR group and 7.7 (95% CI, 4.0 to 18.9) months in the BR group, corresponding to a hazard ratio (HR) of 0.47 (95% CI, 0.19 to 1.14). At the updated analysis, the median duration of response was 10.9 (95% CI, 5.7 to 40.7) months and 10.2 (95% CI, 4.0 to 19.6) months in the pola-BR and BR groups, respectively, corresponding to a HR of 0.60 (95% CI, 0.25 to 1.43).
- The median PFS by IRC was 9.5 (95% CI, 6.2 to 13.9) months in the pola-BR group and 3.7 (95% CI, 2.1 to 4.5) months in the BR group, corresponding to a HR of 0.36 (95% CI, 0.21 to 0.63). At the time of the updated analysis, the PFS by IRC was 9.2 (95% CI, 6.0 to 13.9) months and 3.7 (95% CI, 2.1 to 4.5) months in the pola-BR and BR groups, respectively, corresponding to a HR of 0.38 (95% CI, 0.22 to 0.65).

Exploratory outcome:

- The median OS was 12.4 (95% CI, 9.0 to NE) months in the pola-BR group and 4.7 (95% CI, 3.7 to 8.3) months in the BR group, corresponding to a HR of 0.42 (95% CI, 0.24, 0.74). At the updated analysis, the OS results were unchanged.

Limitations: Open label, lack of formal power calculation and statistical hypothesis testing, imbalances in important baseline characteristics, no assessment of QoL

The key limitations and potential sources of bias associated with trial GO29365 and the supporting evidence included in the submission are summarized below:

- There was no blinding in Study GO29365. This limitation is less likely to result in biased findings for clinical outcomes such as mortality and IRC-assessed outcomes and more likely to result in biased patient-reported outcomes and assessment of harms. The patient-reported outcome of TINAS used to assess the impact of peripheral neuropathy, and the results of this assessment, may have been biased by lack of blinding, considering that neuropathy is a known AE of polatuzumab vedotin. AEs may have been more likely to be assigned a different degree of severity by investigators based on whether they were experienced by patients in the pola-BR or

BR groups, and patients may have been more or less likely to report AEs if they knew whether they were receiving pola-BR or BR.

- There was no pre-specified statistical hypothesis for the primary outcome nor were adjustments made for multiple statistical comparisons; therefore, the analysis of all outcomes is at risk of type I error.
- There was no formal power calculation performed based on a pre-specified hypothesis. The trial was small, with only 40 patients in each treatment group. The small sample size limits confidence in the analysis and in the results obtained.
- There were imbalances in baseline characteristics for numerous parameters, and the size of these imbalances is difficult to place into perspective given the small sample size of the trial. Notably, the majority of imbalances in the baseline characteristics had the potential to bias results in favour of pola-BR. The sponsor assessed these outcomes in multiple Cox regression models and found that these baseline imbalances did not appear to impact the efficacy results.
- HRQoL was not assessed in the trial. The only patient-reported outcome was TINAS, which was used to assess the impact of peripheral neuropathy. This analysis had limitations, including that baseline data were only available for half the trial patients, and there was a high rate of attrition during the study, with only 29% of patients continually adherent to the questionnaire.
- The lyophilized formulation of pola-BR, which is the formulation that is used in Canada, was not studied in the randomized phase II portion of the GO29365 trial. Instead, it was added as a single arm to the GO29365 trial as a protocol amendment. After conducting a comparative analysis of pharmacokinetics, the FDA concluded that there were no meaningful differences between the lyophilized formulation and the solution.

Comparator information: Lack of robust indirect evidence to inform comparative efficacy of pola-BR to current standard-of-care treatments

In the absence of direct evidence comparing pola-BR to all relevant standard-of-care comparators, the sponsor submitted 2 ITCs that compared the efficacy of pola-BR to that of other treatments for R/R DLBCL:

- The sponsor submitted a MAIC that compared the efficacy of pola-BR to rituximab in combination with gemcitabine and oxaliplatin (R-GemOx), pixantrone, tisagenlecleucel (CAR T-cell therapy), and axicabtagene ciloleucel (CAR T-cell therapy). The MAIC used individual patient data from the GO29365 trial to generate weights for patients to mimic the baseline characteristics reported in the comparator trials. The weighted results showed statistically significant differences in CR between pola-BR and R-GemOx (CR = 37.2%; 95% CI, 15.9% to 76.1%), and tisagenlecleucel (CR = 23.2%; 95% CI, 9.8% to 36.0%). Inversely, the results showed no statistical difference between pola-BR and axicabtagene ciloleucel for both CR (CR = –6.5; 95% CI, –25.5 to 13.5) and OS (OS = 1.38; 95% CI, 0.57 to 3.31). No MAIC was conducted for safety or HRQoL outcomes. Overall, the applicability of the sponsor's analysis is impacted by the limited scope and potential limitations, which are largely attributable to a weak and sparse evidence base. The CADTH Methods Team identified limitations related to population heterogeneity, limited adjustment for all prognostic factors and effect modifiers, reduced precision due to small samples sizes, and inclusion of open-label, non-comparative studies. Overall, the critical appraisal of the MAIC indicated the results of the analysis must be interpreted with caution.
- The sponsor also submitted a propensity score-weighted analysis to compare OS and PFS between pola-BR in the GO29365 trial and a "basket" of chemotherapy regimens used in the Alberta Oncology Outcomes (O2) RWD. This analysis was performed using the inverse probability treatment weighting methodology and numerous sensitivity analyses. The CADTH Methods Team appraised the submitted analysis as having major limitations that hindered the applicability of the results. Identified limitations related to the size of the cohort used, the ability to efficiently weight between RWD and trial data, and important differences in the clinical characteristics of patients between the study arms. Overall, the critical appraisal of the MAIC indicated the results of the analysis should be interpreted with caution.

Safety: Higher incidence of grade 3 or grade 4 AEs, and AEs leading to dose modification or interruption and treatment discontinuation with pola-BR

In the safety evaluable population (N = 78), 100% of patients in the pola-BR group and 97% of patients in the BR group experienced an AE; grade 3 or grade 4 AEs occurred in 84% and 72% of patients, respectively. Anemia was the most common AE that occurred in the pola-BR group (54% versus 26% in the BR group; grade 3 or 4: 28% versus 18%) followed by neutropenia (54% versus 39%; grade 3 or 4: 46% versus 33%), thrombocytopenia (49% versus 28%; grade 3 or 4: 41% versus 23%), and peripheral neuropathy (44% versus 8%; no grade 3 or 4). Diarrhea was also a common AE with pola-BR (39% versus 28%; grade 3 or 4: 3% in each group). SAEs occurred in 64% of patients on pola-BR and 62% of patients on BR. The most common SAEs with pola-BR were pneumonia (8% versus 8% in the BR group), febrile neutropenia (10% versus 10%), and pyrexia (10% versus 0). There were more treatment discontinuations due to AEs in patients treated with pola-BR compared to BR; treatment discontinuations occurred in 33% of pola-BR patients and 13% of BR patients, and 31% of patients treated with pola-BR discontinued polatuzumab vedotin. Dose modifications and interruptions due to AEs occurred in 72% and 49% of patients treated with pola-BR and BR, respectively.

There were 4 deaths (9% of patients) in the pola-BR group that were described as AEs and 6 deaths (15%) in the BR group. In the pola-BR group, the fatal AEs all appeared to be related to infection and/or pneumonia. In the BR group, 3 deaths occurred due to infection, and 1 each for cardiac event, unspecified cerebrovascular accident, and sudden death.

At the time of the updated analysis, secondary malignancies were reported in 2 patients (5.1% of patients) in each of the pola-BR and BR treatment groups. Two patients in the pola-BR group and 1 patient in the BR group had a secondary malignancy.

Need and burden of illness: Unmet need for treatments that offer long-term disease control

NHL is a cancer of the immune system that encompasses more than 60 types of lymphoma. In 2018, the projected incidence of NHL was 8,300 cases annually, with an age-standardized incidence rate of 20.8 cases per 100,000 Canadians. DLBCL is an aggressive form of NHL that constitutes approximately 30% of lymphoma cases in Canada. R/R DLBCL occurs in 30% to 40% of patients after first-line treatment. For transplant-ineligible patients, there is no standard treatment approach, and although there are a number of chemotherapy treatments available, none are offered with long-term curative intent. Treatment-ineligible patients represent more than 50% of the R/R population, but a proportion of these patients are too unwell or have too may comorbidities to undergo any further treatment. Transplant-eligible patients who do not respond to salvage chemotherapy or relapse post-ASCT, which is up to 70% of these patients, also have limited treatment options. Until recently, there were no good treatment options for such patients, and they were treated with palliative oral chemotherapy options or radiotherapy, with a prognosis of less than 6 months of life. Most recently, CAR T-cell therapy has become available for patients with DLBCL; however, this therapy requires good PS and lymphoma burden that can last the several weeks it takes to manufacture cells for this therapy. The treatment also has unique toxicities and therefore may not be appropriate for patients with comorbidities and impaired PS. CAR T-cell therapy will only be available in select centres; as a result, travel constraints, resource limitations, and provincial funding restrictions could limit the number of patients who ultimately have access. Finally, a proportion of patients receiving CAR T-cell therapy will eventually experience disease progression and require further treatment. In light of these factors, treatment options that offer long-term disease control for patients with R/R DLBCL are needed.

Registered clinician input: Unmet need for novel treatment options in R/R DLBCL; anticipate pola-BR will be new standard of care

Three joint clinician inputs were provided: two clinicians provided input on behalf of the CCO Hematology DAC, 20 individual clinicians provided input on behalf of the BC Cancer Agency and UBC, and three on behalf of LC. The inputs received indicate that there is currently no standard-of-care regimen for transplant-ineligible R/R DLBCL patients because there have been no randomized trials that establish the superiority of 1 regimen over another for this patient population. Treatment options for these patients include sequential single-agent chemotherapy drugs, or chemotherapy combinations, which are mostly palliative. Steroids and/or radiation may be offered in the palliative setting, mainly for symptom control. The clinicians noted that the most frequently used treatment in the R/R setting is platinum-based combination chemotherapy, but this option is generally unsuitable for older patients or those with comorbidities as it is often too intensive and toxic. The registered clinician input suggested that many patients in the R/R setting have already received platinum-based regimens and therefore require novel

treatment options. The addition of novel agents to chemotherapy may be difficult due to overlapping toxicities, and access to these approaches is often restricted to clinical trials. Clinicians anticipated that pola-BR would represent a new standard of care. The clinician groups also noted other places in the treatment algorithm where pola-BR is anticipated to be used beyond the funding request. In the absence of a universally established standard of care, and based on its efficacy, tolerability, and potential for long-term durable disease control, pola-BR is believed to provide clinicians with a therapeutic option for patients with R/R DLBCL who are not eligible for ASCT and have disease progression after at least 1 prior therapy. The clinicians also remarked on the possibility of pola-BR serving as a bridge to ASCT or CAR T-cell therapy as opposed to standard platinum-based chemotherapy (i.e., R-GDP). They also noted that pola-BR could possibly replace conventional palliative chemotherapy following ASCT relapse.

All 3 clinician groups indicated that they had prior experience with pola-BR. The LC and BC Cancer Agency/UBC clinicians noted that pola-BR has a similar side effect profile to BR, except for a higher incidence of neutropenia. Clinicians from LC also noted that severe neuropathy (grade 2 or higher) would be a contraindication for polatuzumab vedotin. Overall, it was believed that pola-BR is a more favourable option in R/R DLBCL over currently used platinum-based regimens.

PATIENT-BASED VALUES

Experience of patients with DLBCL: Significant physical symptoms and emotional and financial distress associated with DLBCL that negatively impact QoL
LC provided input from 2 online surveys of DLBCL patients: a survey of those without experience with pola-BR and a survey of patients with pola-BR experience. A total of 114 patients responded to both surveys (107 without and 7 patients witht pola-BR experience).

From the patient perspective, the most debilitating physical symptoms associated with DLBCL and treatment included fatigue, enlarged lymph nodes, drenching night sweats, weight loss, loss of appetite, flu-like symptoms, and persistent cough. Aside from the physical effects of the disease and treatment, DLBCL patients also experienced mental and emotional stress, including fear of disease recurrence, memory loss, anxiety, problems concentrating, difficulty sleeping, loss of sexual desire, stress of diagnosis, and depression. Most patients reported that the symptoms negatively impact their QoL. LC noted that the disease and associated treatments can have an impact on daily life. Many respondents reported a negative impact on their ability to work or go to school and cited early retirement and no finances or income as major sources of life-altering stress and limitation.

Chemoimmunotherapy with R-CHOP was the most commonly reported first-line treatment option, which was received by 83% of respondents as first-line therapy. Other options (second line or beyond) included ASCT or allogeneic stem cell transplant. The most common side effects of treatment reported by more than 50% of patient respondents included hair loss, fatigue, memory problems and/or confusion, neutropenia, and nausea. Patients stated that their associated fatigue is so impactful that they are unable to exert themselves beyond the minimum and they do very little around the house to ensure they have enough energy for work. Patients also noted that the number of clinic visits, infusion time, reactions, and the number of infections negatively impact their QoL.

Patient values, experience on or expectations for treatment: Longer remission and survival, and improved QoL

A total of 7 patients indicated that they had experience with pola-BR for DLBCL. Patients indicated that that the dosing schedule of pola-BR was better than that used for other chemotherapy treatments as the number of treatments was reduced. Two patients reported that they did not experience any side effects with pola-BR. The most commonly reported side effects of pola-BR therapy were nausea and fatigue. Other side effects experienced included neutropenia, thrombocytopenia, low blood pressure, loss of taste, rash, and peripheral neuropathy. One patient required hospitalization to manage side effects, and 2 patients experienced nausea that lasted longer than 2 months. Most patients reported that treatment with pola-BR did not have a significant negative impact on their QoL. Four patients stated their physical health and QoL improved with pola-BR treatment, while 3 respondents indicated their mental health improved by being able to do things they were not able to do before and while on treatment. Two patients stated their mental health remained unchanged with pola-BR therapy. Overall, when asked about pola-BR, patients described their experience as good to excellent and they indicated that they would take the treatment again if it was necessary. All patients reported that they would recommend pola-BR as a therapy to others with DLBCL.

Overall, patients indicated they value longer survival and longer remission than can be achieved with current therapies, followed by better QoL. Close to half of the survey respondents indicated that they would be willing to tolerate the side effects of a new treatment if they were short-term events.

ECONOMIC EVALUATION

Polatuzumab vedotin is administered intravenously, over 90 minutes for the initial dose and over 30 minutes for subsequent doses at 1.8 mg per kg, to be administered in combination with bendamustine and rituximab (regimen referred to as *pola-BR*) for up to 6 treatment cycles of 21 days. A mean number of treatment cycles from the trial was used to estimate average treatment duration for pola-BR (polatuzumab vedotin = 4.44 cycles, bendamustine = 4.51 cycles, rituximab = 4.51 cycles). At the submitted price of $14,750 per 140 mg vial, the estimate cost per patient per 28 days of polatuzumab vedotin is $20,748 and the full regimen (in combination with bendamustine and rituximab) cost per patient per cycle is $28,611.

The sponsor submitted a cost-utility analysis comparing costs and outcomes for pola-BR and a weighted average of currently used treatment regimens ("basket comparator") for patients with R/R DLBCL, not otherwise specified, who are not eligible for ASCT and have received at least 1 prior therapy. The modelled population reflects the GO29365 trial population, sponsor's reimbursement request, and Health Canada–approved indication. The sponsor assumed that the distribution of the GO29365 trial population was generalizable to Canadian R/R DLBCL patients. The submitted partitioned survival model included the following health states: PFS, progressive disease (PD), and death. All patients entered the model in the PFS state. At the end of each weekly cycle, patients could remain in the PFS state, transition to the PD state, or die. The economic analysis was undertaken over a 20-year time horizon from the perspective of a public health care payer. Data from the GO29365 trial (data cut January 2020) were used to inform baseline population characteristics. Efficacy of pola-BR was derived by pooling data from 3 cohorts within the GO29365 trial: pola-BR randomized arm (cohort C), the safety cohort (cohort 1A), and the phase II lyophilized arm (cohort G/H). The sponsor indicated that the pooled analysis was conducted to increase the precision analysis and that cohort G/H had similar inclusion criteria, baseline characteristics, and clinical efficacy results compared with cohort C. The efficacy of the basket comparator was derived from sponsor-identified patients from the Alberta O2 (real-world data) RWD database between 2012 and 2015 who were diagnosed with DLBCL and were transplant-ineligible. Additional selection criteria were applied to align it with the GO29365 trial. The comparative efficacy of pola-BR and the basket comparator was derived using the inverse probability of treatment weighting propensity score approach (pola-BR: n = 91; basket comparator: n = 42). Long-term efficacy was estimated by fitting parametric survival models to patient-level OS and PFS data for each treatment option. Model selection was based on clinical validity and statistical fit via Akaike information criterion and Bayesian information criterion, visual assessment, and clinical plausibility. In the base case, long-term OS and PFS data for pola-BR and the basket comparator were predicted using the generalized gamma function. Patients could receive subsequent treatments once they had progressed.

CADTH identified the following key limitations with the sponsor's pharmacoeconomic analysis:

- Given the lack of direct evidence, the sponsor derived the comparative efficacy using a propensity score approach. CADTH identified major limitations related to the size of the cohort used, the ability to efficiently weight between RWD and trial data, and the differences between study arms. This introduced significant uncertainty into the indirect comparison that could not be sufficiently accounted for within the submitted economic analysis. Therefore, any analyses based on these data must be viewed with caution.
- The sponsor pooled the efficacy data for pola-BR from different patient cohorts within the GO29365 trial. CADTH identified concerns with the data pooling, such as notable differences in the trial design that could introduce heterogeneity (methodological and clinical) between cohorts. Without proper adjustment for the heterogeneity, pooling these cohorts could introduce biases into the results.
- The clinical experts consulted on this review suggested that the predicted survival rates in the sponsor's model, especially for patients with progressed disease, were overestimated and not aligned with the observed and expected survival for this patient population for either treatment arm.

- CADTH identified errors in the sponsor's model: use of a non-approved vial size (30 mg); excluding subsequent entry biologic price for rituximab, including anti-CD20 use as subsequent treatment; and using a small number of iterations. CADTH was able to correct for these errors.

CADTH was unable to address several major limitations, including the quality of the comparative data and use of a basket comparator. The issues with the clinical data prohibit a reasonable assessment of cost-effectiveness; as such, a CADTH base case could not be derived. CADTH presented a corrected sponsor's base case, which increased the submitted ICER. In addition, CADTH undertook a series of exploratory reanalyses that suggested that the ICER of pola-BR was likely to be higher than estimated by the sponsor and could range from $67,000 per QALY to $147,000 per QALY. However, this suggests that pola-BR controls the disease better than a basket comparator post-progression, which was considered hypothetical and without biological support by clinical experts consulted by CADTH. Based on this range of exploratory analyses, a price reduction for polatuzumab vedotin of between 35% and 84% would be required for pola-BR to become cost-effective at a willingness-to-pay threshold of $50,000 per QALY compared with the basket comparator. However, the uncertainty identified with the comparative clinical information and modelling approach suggest using caution when interpreting these results.

ADOPTION FEASIBILITY

Considerations for implementation and budget impact: Budget impact is substantial and underestimated

CADTH identified the following key limitations with the sponsor's analysis: the comparators used in Canadian clinical practice may differ from those included in the sponsor's analysis, the market share for pola-BR was underestimated, and other components did not align with the economic evaluation (e.g., subsequent therapies were excluded). CADTH reanalysis increased the proportion of eligible patients and assumed that biosimilar rituximab would be used in place of the branded product. CADTH reanalysis of the sponsor's submitted budget impact analysis suggests that the estimated budget impact of introducing pola-BR would be $66,588,692 over the first 3 years.

Factors related to currently funded treatments, the eligible patient population, implementation, and sequencing and priority of treatments are described in Appendix 1.

ABOUT THIS RECOMMENDATION

The pCODR Expert Review Committee

Recommendations are made by the CADTH pan-Canadian Oncology Drug Review (pCODR) Expert Review Committee (pERC) following the pERC Deliberative Framework. pERC members and their roles are as follows:

Dr. Maureen Trudeau, Oncologist (Chair)
Dr. Catherine Moltzan, Oncologist (Vice-Chair)
Daryl Bell, Patient Member
Dr. Jennifer Bell, Bioethicist
Dr. Kelvin Chan, Oncologist
Dr. Michael Crump, Oncologist
Dr. Matthew Cheung, Oncologist
Dr. Winson Cheung, Oncologist
Dr. Avram Denburg, Pediatric Oncologist
Dr. Leela John, Pharmacist
Dr. Christine Kennedy, Family Physician
Dr. Christian Kollmannsberger, Oncologist
Cameron Lane, Patient Member
Dr. Christopher Longo, Health Economist
Valerie McDonald, Patient Member
Dr. Marianne Taylor, Oncologist
Dr. W. Dominika Wranik, Health Economist

All members participated in deliberations and voting on the Initial Recommendation, except:

- Dr. Kelvin Chan, who was not present for the meeting
- Dr. Maureen Trudeau, who was excluded from voting due to her role as pERC Chair.

Avoidance of conflicts of interest

All members of the pCODR Expert Review Committee must comply with the *pCODR Conflict of Interest Guidelines*; individual conflict of interest statements for each member are posted on the pCODR website and pERC members have an obligation to disclose conflicts on an ongoing basis. For the review of pola-BR for DLBCL, through their declarations, no members had a real, potential, or perceived conflict and, based on application of the *pCODR Conflict of Interest Guidelines*, no members were excluded from voting.

Information sources used

pERC is provided with a pCODR Clinical Guidance Report and a pCODR Economic Guidance Report, which include a summary of patient advocacy group and Provincial Advisory Group input, as well as original patient advocacy group input submissions, to inform its deliberations. pCODR guidance reports are developed following the pCODR review process and are posted on the pCODR website. Please refer to the pCODR guidance reports for more detail on their content.

Consulting publicly disclosed information

pCODR considers it essential that pERC recommendations be based on information that may be publicly disclosed. All information provided to the pCODR Expert Review Committee for its deliberations was handled in accordance with the *pCODR Disclosure of Information Guidelines*.

Use of This Recommendation

This Recommendation from pERC is not intended as a substitute for professional advice, but rather to help Canadian health systems leaders and policy-makers make well-informed decisions and improve the quality of health care services. While patients and others may use this Recommendation, it is for informational and educational purposes only, and should not be used as a substitute for the application of clinical judgment respecting the care of a particular patient, for professional judgment in any decision-making process, or for professional medical advice.

Disclaimer

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APPENDIX 1: CADTH PAN-CANADIAN ONCOLOGY DRUG REVIEW EXPERT REVIEW COMMITTEE RESPONSES TO PROVINCIAL ADVISORY GROUP IMPLEMENTATION QUESTIONS

PAG implementation questions	pERC recommendation
Eligible patient population	
PAG is seeking clarity on whether the following patients would be eligible for treatment with pola-BR: • pediatric patients • patients with prior ASCT • patients who progressed on prior treatment with CAR T-cell therapy • patients who failed prior ASCT vs. patients who were not eligible.	Based on the GO29365 trial eligibility criteria, pERC agreed with the CGP on the eligibility of the following groups of patients: • Pediatric patients: Pediatric patients were not included in the trial, and thus would not be eligible for pola-BR. • Prior ASCT: Patients with prior ASCT were eligible for the GO29365 trial, and thus would be eligible for pola-BR. • Progression on CAR T: Patients with prior CAR T-cell therapy were eligible for the trial, and thus would be eligible for pola-BR. • Failed vs. ineligible for ASCT: Per the inclusion criteria, patients who were ineligible for or failed ASCT were eligible for the trial, and thus would be eligible for treatment with pola-BR.
PAG identified additional exclusion criteria in the study, notably patients with transformed follicular lymphoma to DLBCL, patients with CNS lymphoma, and patients with HIV-related aggressive histology lymphoma. PAG would like to know if all these exclusion criteria need to be met for eligibility to pola-BR reimbursement.	pERC agreed with the CGP that while patients with transformed follicular lymphoma to DLBCL and those with HIV-related DLBCL were excluded from the trial, their eligibility for pola-BR should be in the judgment of the clinician to treat these patients, since these patients are otherwise generally eligible for the same treatment approaches as other aggressive B-cell lymphoma patients. However, patients with active CNS lymphoma would not be eligible for treatment.
PAG noted that patients currently on alternate therapies for R/R DLBCL who are not progressing as well as patients who just started second line therapy would need to be addressed in a time-limited basis.	At the time of implementing a funding recommendation for pola-BR, jurisdictions may want to consider addressing the short-term, time-limited need for offering the combination to patients with R/R DLBCL who are currently receiving alternate therapies and have not progressed, as well as patients who have just initiated second-line therapy.
PAG noted potential indication creep to using pola-BR in R/R DLBCL as a bridge to a stem cell transplant or CAR T, R/R DLBCL patients who are eligible for transplant, previously untreated DLBCL patients in first line, and other aggressive non-Hodgkin lymphoma histologies (e.g., Burkitt lymphoma, primary mediastinal B-cell lymphoma, grey zone lymphoma).	pERC agreed with the CGP that there is no evidence to inform on the use of pola-BR in any of these clinical situations. Response to pola-BR may provide the opportunity for CAR T-cell therapy as "bridging" therapy; pERC agreed with the CGP and the registered clinicians that this would be a reasonable outcome of pola-BR. pERC agreed that pola-BR should not be used for patients with previously untreated DLBCL or as salvage therapy for patients who are eligible for ASCT, given the well-established standards of care for these patients. The use of pola-BR in variants of large B-cell lymphoma such as R/R grey zone lymphoma and mediastinal large B-cell lymphoma would be reasonable, although such patients were not explicitly included in the GO29375 trial. The activity of pola-BR in Burkitt lymphoma is not known.
Implementation factors	
PAG seeks advice on: • treatment duration • discontinuation criteria • feasibility of combining polatuzumab vedotin with	Based on the available evidence from the GO29365 trial, pERC agreed with the CGP on the following: • Treatment duration: Patients should be treated for up to 6 cycles. • Discontinuation criteria: Patients should be treated for up to 6 cycles in the absence of unacceptable toxicities.

other chemotherapies or chemoimmunotherapies.	• Combining polatuzumab vedotin with other chemotherapies or chemoimmunotherapies: Studies of polatuzumab vedotin in combination with other therapies have not occurred and/or are ongoing; therefore, currently polatuzumab vedotin should not be combined with other therapies other than BR.
In addition, a needle and syringe are outlined in the product monograph for preparation. PAG is seeking clarity on whether this is compatible with needle-less systems or closed system drug transfer devices.	pERC noted that following clarification with the sponsor, the use of closed system drug transfer devices is not described in the approved labelling or package insert. Therefore, they agreed with the CGP that no recommendation can be made regarding the use of and type of closed system drug transfer device to be used with polatuzumab vedotin. Use of a closed system drug transfer device should be left to the discretion of the health care provider.
PAG is seeking clarity that standard management for tumour lysis syndrome applies in this setting.	pERC agreed with the CGP that standard management for tumour lysis syndrome would apply in this setting.
PAG noted that since obinutuzumab was an option in the phase Ib/II trial, and PAG is seeking clarity on whether obinutuzumab is an option for patients who experienced severe infusion-related reactions in response to rituximab.	The GO29365 trial included arms in the phase Ib and phase II portion (non-randomized expansion) that studied R/R DLBCL patients treated with polatuzumab vedotin in combination with bendamustine and obinutuzumab. Although this evidence was not reviewed in detail nor critically appraised, pERC agreed with the CGP that obinutuzumab is a reasonable substitution for rituximab in patients who are intolerant to rituximab.
Sequencing and priority of treatments	
PAG is seeking to confirm the place in therapy and sequencing of pola-BR, including in the following scenarios: • Options after failure of pola-BR including anti-CD19 CAR T • Use of pola-BR as bridge to CAR T. If appropriate, can bendamustine be omitted to avoid depleting T cells? • Number and types of prior therapies that should be attempted before offering pola-BR • If BR is not tolerated, switching to polatuzumab vedotin plus other chemoimmunotherapies	pERC agreed with the CGP on the following sequencing scenarios: • Options after failure on pola-BR: Treatment options after progression on pola-BR should be up to the treating clinician; however, options such as anti-CD19 or CAR T-cell therapies could be considered. • Use of pola-BR as a bridge to CAR T-cell therapy and omitting bendamustine: Bendamustine can be omitted if appropriate based on clinical judgment. However, there is no evidence to support its use in this way. • Number and types of prior therapies: Consistent with the GO29365 trial, patients who were R/R after at least 1 prior line of therapy and were transplant-ineligible would be eligible for pola-BR. • Switching to polatuzumab vedotin plus other chemoimmunotherapies if BR is not tolerated: As previously noted, there is no evidence to support the safe use of polatuzumab vedotin in combination with other chemoimmunotherapies.

ASCT = autologous stem cell transplant; BR = bendamustine and rituximab; CGP = Clinical Guidance Panel; CNS = central nervous system; DLBCL = diffuse large B-cell lymphoma; PAG = Provincial Advisory Group; pERC = CADTH pan-Canadian Oncology Drug Review (pCODR) Expert Review Committee; pola-BR = polatuzumab vedotin plus bendamustine and rituximab; R/R = relapsed/refractory; vs. versus.