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Reimbursement Recommendation

Polatuzumab Vedotin (Polivy)

Indication: Polivy (polatuzumab vedotin for injection) in combination with rituximab, cyclophosphamide, doxorubicin, and prednisone (R-CHP) is indicated 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 that are classified as activated B-cell-like (ABC) lymphoma subtype

Sponsor: BC Cancer Lymphoma and Myeloma Tumour Group

Final recommendation: Reimburse with conditions

Summary

What Is the Reimbursement Recommendation for Polivy?

Canada's Drug Agency (CDA-AMC) recommends that Polivy in combination with rituximab, cyclophosphamide, doxorubicin , and prednisone (R-CHP) should be reimbursed by public drug plans for the treatment of adult patients with previously untreated large B-cell lymphoma (LBCL), including diffuse large B-cell lymphoma (DLBCL) not otherwise specified, high-grade B-cell lymphoma, Epstein-Barr virus–positive DLBCL not otherwise specified, and T-cell/histiocyte-rich LBCL that is classified as activated B cell–like (ABC) subtype if certain conditions are met.

Which Patients Are Eligible for Coverage?

Polivy in combination with R-CHP should only be covered to treat adult patients who have previously untreated ABC subtype of LBCL confirmed with appropriate testing. Eligible patients should have low to intermediate risk of survival on the International Prognostic Index scale and good performance status. Patients with LBCL not classified as ABC subtype of LBCL are not eligible for Polivy in combination with R-CHP.

What Are the Conditions for Reimbursement?

Polivy in combination with R-CHP should only be reimbursed if prescribed by clinicians with experience in the management of aggressive lymphomas and the side effects of treatment with curative intent and the cost of Polivy is reduced.

Why Did CDA-AMC Make This Recommendation?

Evidence from a clinical trial showed that Polivy in combination with R-CHP was better than treatment with rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) in delaying cancer progression and potentially prolonging survival.

Based on the CDA-AMC assessment of the health economic evidence, Polivy may not represent good value to the health care system at the public list price, given the substantial amount of uncertainty with the available evidence. A price reduction is therefore required.

Patients expressed a need for new treatments that prolong life and extend the duration without disease progression. The pan-Canadian Oncology Drug Review Expert Review Committee (pERC) found that Polivy in combination with R-CHP meets patient needs of delaying disease progression and potentially prolonging survival.

Summary

Based on public list prices, Polivy is estimated to result in additional cost to the public drug plans of approximately $70 million to $107 million depending on range of estimates for immunohistochemistry testing accuracy over the next 3 years. However, the actual budget impact is uncertain and depends on reduced subsequent treatment costs and does not include additional costs required to implement gene expression profiling testing to accurately identify patients with DLBCL with the ABC subtype.

Additional Information

What Is LBCL?

LBCL, a type of non-Hodgkin lymphoma, is a cancer that grows in lymph nodes, affecting other organs such as the spleen, liver, and bone marrow. Patients with the ABC subtype of LBCL experience poor outcomes with the available treatment. In Canada, it was estimated that 11,700 people would be diagnosed with non-Hodgkin lymphoma in 2024 and 3,100 people would die of the disease.

Unmet Needs in LBCL

There is a need for effective treatments that prolong survival, extend the duration of disease remission and symptom control, and improve quality of life.

How Much Does Polivy Cost?

Treatment with Polivy in combination with R-CHP is expected to cost approximately $23,605 per patient per 28 days.

Recommendation

The Canada's Drug Agency (CDA-AMC) pan-Canadian Oncology Drug Review Expert Review Committee (pERC) recommends that polatuzumab vedotin be reimbursed 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 (EBV)–positive DLBCL NOS, and T-cell/histiocyte-rich LBCL that is classified as activated B cell–like (ABC) subtype only if the conditions listed in Table 1 are met.

Rationale for the Recommendation

A subgroup analysis of patients with ABC subtype of LBCL in the phase III, multicentre, randomized controlled POLARIX trial (n = 235 of 897 randomized) suggested that treatment with polatuzumab vedotin combined with R-CHP (pola-R-CHP) resulted in potentially clinically important progression-free survival (PFS) benefit compared to rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP). The 5-year PFS rate was 72.5% in patients treated with pola-R-CHP versus 45.8% in those treated with R-CHOP, resulting in a 67% risk reduction in investigator-assessed PFS (stratified hazard ratio [HR] = 0.33; 95% confidence interval [CI], 0.21 to 0.53). pERC observed that although the median overall survival (OS) had not been reached at the time of analysis, results of the 5-year follow-up analysis suggested a significant OS improvement in patients with ABC subtype of LBCL who were treated with pola-R-CHP compared with those treated with R-CHOP (OS rate 84.6% versus 69.9%, respectively; stratified HR = 0.49; 95% CI, 0.27 to 0.90). Regarding adverse events (AEs) of special interest, pERC noted that peripheral neuropathy occurred at similar frequency between the treatment groups; however, neutropenia and infections occurred more frequently with treatment with pola-R-CHP than with R-CHOP. pERC determined that, overall, AEs were consistent with the known and manageable safety profile of the treatments.

Unmet needs identified by patients and clinicians include early effective treatments that prolong survival, extend the duration of disease remission and symptom control, and improve quality of life. pERC concluded that regardless of the limitations of the subgroup analyses, pola-R-CHP meets some of these needs for patients with the ABC subtype of LBCL as suggested by the larger PFS and OS benefit compared to R-CHOP.

The committee considered analyses conducted by the sponsor and CDA-AMC that considered the cost-effectiveness of pola-R-CHP relative to R-CHOP based on data from a subgroup of patients from the POLARIX trial. Based on the sponsor's submitted price for polatuzumab and publicly listed prices for all other drug costs, the incremental cost-effectiveness ratio (ICER) for pola-R-CHP was estimated to be less than $50,000 per quality-adjusted life-year (QALY) gained compared with R-CHOP. However, due to the uncertainty associated with the magnitude of clinical benefit, inability of the sponsor's model to adequately assess the impact of testing implications, limitations with the sponsor's economic model structure and programming, concerns regarding the generalizability of the trial population to the population in Canada,

and presence of negotiated prices for subsequent therapies (e.g., chimeric antigen receptor [CAR] T-cell therapy), the cost-effectiveness results are highly uncertain. A price reduction may be required to ensure that pola-R-CHP is a cost-effective regimen for patients with ABC subtype of LBCL that is previously untreated.

Table 1: Reimbursement Conditions and Reasons

Reimbursement condition	Reason	Implementation guidance
Initiation		
1. Treatment with pola-R-CHP should be reimbursed in adult patients with previously untreated *CD20*-positive DLBCL, including DLBCL NOS, high-grade B-cell lymphoma, EBV-positive DLBCL NOS, and T-cell/histiocyte-rich LBCL classified as ABC subtype confirmed with GEP testing.	Evidence from the subgroup analysis of the POLARIX trial demonstrated that treatment with pola-R-CHP resulted in a clinical benefit in patients with these characteristics.	—
2. Patients should have both of the following: 2.1. IPI score of 2 to 5 2.2. good performance status.	Patients with an IPI score of 2 to 5 and an ECOG performance status of 0 to 2 were included in the POLARIX trial.	The clinical experts stated that a patient with an ECOG performance status of 3 would likely improve with their first cycle of treatment (e.g., to achieve an ECOG performance status of 2 or better), such that they should be considered eligible for treatment with pola-R-CHP.
3. Ineligibility criteria: Patients with LBCL not classified as ABC subtype.	The reviewed evidence from the POLARIX trial did not indicate additional clinical benefit in patients with other types of LBCL, in particular GCB or indeterminate, besides the ABC subtype.	—
Discontinuation		
4. Treatment with pola-R-CHP should be discontinued upon disease progression, unacceptable toxicities or upon completion of 6-cycles of treatment.	In the POLARIX trial, polatuzumab vedotin was administered as 1.8 mg/kg given as an IV infusion every 21 days for 6 cycles in combination with R-CHP. The Health Canada recommended dose is the same. Patients in the POLARIX trial discontinued treatment with pola-R-CHP upon disease progression and severe toxicities, and there are no data to support continued treatment with pola-R-CHP beyond progression.	According to the clinical experts, dose reductions of polatuzumab vedotin or other components of the pola-R-CHP regimen may be warranted for patients who experience AEs (e.g., infections, neutropenia, and/or thrombocytopenia).
Prescribing		
5. Pola-R-CHP should be prescribed by clinicians experienced in the management of aggressive lymphomas and the side effects of treatment.	This is meant to ensure that pola-R-CHP is prescribed for appropriate patients and that adverse effects are managed in an optimized and timely manner.	pERC agreed with the clinical experts' observation that management of treatment with pola-R-CHP will be appropriate at community or tertiary cancer centres with access to a hematologist or medical oncologist who treats DLBCL.

Reimbursement condition	Reason	Implementation guidance
6. Polatuzumab vedotin should only be prescribed in combination with R-CHP administered with curative intent.	There were no data to support the use of polatuzumab vedotin with potentially curative regimens, such as R-CEOP, R-mini-CHOP, or DA-R-EPOCH.	The clinical experts felt combination of polatuzumab with R-CEP (no vincristine) was reasonable; there are no safety or efficacy data from combining pola with DA-R-EPOCH.
Pricing		
7. A reduction in price.	The cost-effectiveness of pola-R-CHP is highly uncertain. When partially considering the impact of testing, and revising subsequent treatment use assumptions, pola-R-CHP may be considered cost-effective vs. R-CHOP at a willingness-to-pay threshold of $50,000 per QALY gained. However, this was based on the sponsor's model which assumed 3 incremental life-years for pola-R-CHP compared to R-CHOP. The committee concluded there was substantial uncertainty as to whether there was a survival benefit, and the magnitude of the impact on subsequent treatment use. A reduction in price may be required to address the uncertainty regarding the cost-effectiveness of pola-R-CHP in patients with previously untreated LBCL with the ABC subtype.	—
Feasibility of adoption		
8. The economic feasibility of adoption of pola-R-CHP must be addressed.	At the submitted price, the incremental budget impact of pola-R-CHP is expected to be greater than $40 million in year 1 assuming 52% testing specificity and the magnitude of uncertainty in the budget impact must be addressed to ensure the feasibility of adoption because of the difference between the sponsor's estimate and the CDA-AMC estimate(s). If the cost of testing was included, the budget impact would be higher than has been estimated.	—
Organizational feasibility	GEP testing is required to determine patients with the ABC subtype of LBCL who are eligible for therapy with pola-R-CHP. Because GEP testing for ABC subtype of LBCL is currently not available in most jurisdictions in Canada, implementing the use of GEP testing to decide eligibility for treatment with pola-R-CHP is anticipated to impact human and other health care resources. Nonetheless, it may also help	pERC acknowledged that it may require considerable time, other resources, and preparations for jurisdictions to make GEP testing available for identifying patients with ABC subtype of LBCL. pERC agreed with the drug plans that until the GEP scarcity issue is resolved, IHC (though suboptimal for purpose) will be an

Reimbursement condition	Reason	Implementation guidance
	reduce costs and patient harm by avoiding unnecessary treatments for those who would not benefit and minimizing additional toxicities.	appropriate test to identify patients with ABC subtype of LBCL.

ABC = activated B cell–like; AE = adverse event; BR = bendamustine plus rituximab; CDA-AMC = Canada's Drug Agency; DA-R-EPOCH = dose-adjusted rituximab, etoposide, prednisone, vincristine, cyclophosphamide, and doxorubicin; DLBCL = diffuse large B-cell lymphoma; EBV = Epstein-Barr virus; ECOG = Eastern Cooperative Oncology Group; GCB = germinal centre B cell–like; GEP = gene expression profiling; IHC = immunohistochemistry; LBCL = large B-cell lymphoma; NOS = not otherwise specified; pERC = pan-Canadian Oncology Drug Review Expert Review Committee; pola = polatuzumab vedotin; QALY = quality-adjusted life-year; R-CEOP = rituximab, cyclophosphamide, etoposide, vincristine, and prednisone; R-CHP = rituximab, cyclophosphamide, doxorubicin, and prednisone; R-CHOP = rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone.

Discussion Points

- **Unmet needs**: pERC acknowledged patients identified unmet needs for treatments that prolong life, disease remission, and symptom control, as well as normalize blood counts and improve quality of life. pERC noted that although the results of the subgroup analysis suggest that pola-R-CHP could delay disease progression and prolong life in patients with the ABC subtype of LBCL, there was no evidence to indicate that the treatment normalized blood counts in or improved the quality of life of this population of patients with LBCL.
- **Quality of evidence**: pERC noted that the evidence evaluated was uncertain because it was from an exploratory subgroup analysis. Therefore, a phase III trial in this subset is desirable to provide more definitive data; however, it is unlikely that the sponsor will initiate such a trial. pERC acknowledged that the patients with the ABC subtype have an inferior response to conventional treatment (e.g., OS rate in the ABC subtype has been reported to range from 45% to 56% compared with 78% to 80% for the germinal centre B cell–like [GCB] subtype). The committee noted that the findings from the subgroup analysis suggest that pola-R-CHP could be a better option than R-CHOP for patients with the ABC subtype of LBCL.
- **Testing procedure considerations and patient selection**: pERC discussed that treatment with pola-R-CHP in patients with the ABC subtype requires cell-of-origin (COO) testing to identify patients appropriately because there is no evidence that the therapy works in patients with other subtypes of LBCL. The committee noted that although immunohistochemistry (IHC) testing is generally available with the LBCL diagnostic testing, its specificity for identifying the ABC subtype varies from 52% to 82%, which may lead to overtreating patients with the GCB subtype or with unclassified COO status. Also, IHC testing simply dichotomizes patients into GCB and non-GCB subtypes, in which patients with the non-GCB classification would include both the ABC subtype (eligible for pola-R-CHP) and unclassified subtype (ineligible for pola-R-CHP). pERC noted that the optimal patient identification requires the more accurate gene expression profiling (GEP) testing, which is currently not available in most jurisdictions in Canada. pERC noted that although IHC-based testing could lead to potential overtreatment in a proportion of patients, mandating GEP-based testing in other jurisdictions could result in inequitable and delayed access to the treatment due to the barriers to implementing GEP testing (e.g., high start-up cost for infrastructure and staff training).

- **Economic considerations:** pERC discussed the uncertainty associated with the economic evaluation. pERC noted the uncertainty associated with the clinical evidence that was used to inform the economic evaluation, and acknowledged that the magnitude of benefit observed based on the POLARIX trial ABC subgroup may not be observed in practice in Canada, in particular if IHC is used to identify patients with LBCL who have the ABC subtype. pERC noted limitations with the sponsor's economic model which could not adequately assess the impact of testing implications and was programmed such that OS associated with pola-R-CHP compared with R-CHOP was likely overestimated. pERC also considered the uncertainty associated with the assumptions regarding subsequent treatment and the presence of negotiated prices for several treatments (e.g., CAR T-cell therapy) meant that estimates of cost offsets were highly uncertain. As a result, pERC noted that although the economic evaluation estimates suggested the ICER for pola-R-CHP may be less than $50,000 per QALY gained, a price reduction may be required to address the uncertainty.
- **Budget impact:** pERC discussed that the budget impact of reimbursing pola-R-CHP as a first-line treatment is expected to be very high (between $290 million and $447 million over the first 3 years of reimbursement), but that the sponsor assumed large cost offsets based on less use of subsequent treatments (cost savings of $221 million to $340 million over the first 3 years of reimbursement), resulting in a budget impact of $69 million to $107 million. pERC noted that the budget impact is highly uncertain and will be influenced by diagnostic test accuracy (which affects the number of individuals who are treated) and realization of estimated cost offsets. pERC also noted that the cost of testing was not considered in the sponsor's budget impact model. Based on available pricing, the cost to implement GEP testing may be $1.7 million, but this does not take into account the costs associated with the infrastructure to incorporate this test; thus, this estimate is associated with substantial uncertainty. Because IHC testing is generally available across the country and may be used to test for the ABC subtype, pERC considered that the availability of pola-R-CHP is not expected to impact costs associated with IHC testing.

Background

It was estimated that 11,700 people in Canada would be diagnosed with non-Hodgkin lymphoma (NHL) and 3,100 people would die of it in 2024. LBCL is a type of NHL that has a number of histologic, proteomic, and molecular subsets with distinctive prognostic profiles, including COO subtypes ABC and GCB, elevated protein expression of *MYC* and *BCL2* seen in double-expressor lymphoma, and gene rearrangements involving *MYC* and *BCL2* and/or *BCL6* (double-hit lymphoma or triple-hit lymphoma). DLBCL NOS is the most common subtype of LBCL, accounting for 35% of NHL cases and 80% of aggressive lymphomas. DLBCL may be classified as limited-stage disease (stage I or II) or advanced-stage disease (stage III or IV); approximately two-thirds of patients with DLBCL present with stage III or IV disease. Patients with LBCL experience debilitating symptoms and psychosocial impacts (e.g., fatigue, drenching night sweats, loss of appetite, anxiety, and depression) that negatively affect their health-related quality of life (HRQoL). Evaluations of patients with newly diagnosed DLBCL to determine treatment options include assessment

of disease stage, comorbid conditions and performance status, cytogenetic or molecular features, risk for central nervous system involvement, and International Prognostic Index (IPI) score. First-line treatment of DLBCL is 6 cycles of R-CHOP for those with high-risk and advanced-stage disease and for a proportion of those with limited-stage disease (e.g., age > 60 years, bulky disease, Eastern Cooperative Oncology Group [ECOG] performance status score of 2 to 4). Although treatment with R-CHOP achieves cure in approximately 60% of patients with DLBCL, about 40% of patients experience relapse or disease progression. The clinical experts highlighted that patients with refractory disease or early relapse may proceed to salvage therapy (e.g., stem cell transplant or CAR T-cell therapy), which is associated with increased toxicity, poor outcomes, and increased costs.

Health care centres across Canada do not have routine access to COO-based molecular testing with GEP to determine ABC subtype and instead rely on IHC with the Hans algorithm as a surrogate to dichotomize LBCL into GCB subtype and non-GCB subtypes, with the latter primarily representing the ABC subtype. However, there is limited diagnostic accuracy with the immunostaining algorithm to caution its use in guiding treatment. The clinical experts consulted for the review highlighted that non-GCB subtypes of LBCL are more likely to have high-risk disease features (e.g., advanced-stage disease at diagnosis, IPI score of 3 to 5) that is associated with higher rates of relapse and less favourable prognosis compared to those with the GCB subtype. Patients with the ABC subtype of LBCL experience significantly poorer outcomes with standard upfront chemoimmunotherapy. Because there is no specific treatment approach for patients with the ABC subtype, the current treatment paradigm for patients with LBCL, regardless of COO classification, is R-CHOP for 6 cycles. According to the clinical experts, goals of treatment for DLBCL are cure or prolonging survival, minimizing treatment-related toxicities, alleviating disease-related symptom burden, and maintaining HRQoL. Patients with high-risk disease (e.g., IPI score 3 to 5, ABC subtype) need improved front-line treatment options to achieve cure and avoid the need for toxic salvage therapies. Pola-R-CHP has been approved by Health Canada for the treatment of adult patients with previously untreated LBCL, including DLBCL NOS, high-grade B-cell lymphoma, EBV-positive DLBCL NOS, and T-cell/histiocyte-rich LBCL. Polatuzumab vedotin is a CD79b-targeted antibody-drug conjugate. It is available as an IV infusion, and the dosage recommended in the product monograph is 1.8 mg/kg every 21 days for 6 cycles in combination with R-CHP.

Submission History

Pola-R-CHP was previously reviewed by CADTH in December 2023 for the treatment of adult patients with previously untreated LBCL, including DLBCL NOS, high-grade B-cell lymphoma, EBV-positive DLBCL NOS, and T-cell/histiocyte-rich LBCL, and received a recommendation not to be reimbursed from pERC. The original review of pola-R-CHP included 1 randomized controlled trial of 879 adult patients with previously untreated LBCL. Key reasons for the recommendation included uncertainty in whether the between-group difference in PFS at 24 months was clinically meaningful as well as a lack of demonstrated benefit in OS based on the evidence from the POLARIX trial. Additionally, pERC could not conclude that treatment with pola-R-CHP would meaningfully prolong remission compared with standard-of-care R-CHOP. Finally,

pERC could not reach conclusions regarding the effects of pola-R-CHP compared to R-CHOP on disease symptoms, normalized blood counts, or HRQoL.

This resubmission is based on the sponsor's rationale that patients with LBCL who have the ABC subtype experience poorer outcomes with standard-of-care treatment R-CHOP and, thus, would benefit from treatment with pola-R-CHP. The sponsor submitted an exploratory subgroup analysis of the POLARIX trial according to COO status, including a cohort of patients with ABC subtype. The sponsor also indicated that because the ABC subtype of LBCL is more common in older adults who may not be candidates for second- or later-line treatment options, the potential for curative first-line treatment is important in this patient population. Although the sponsor had included a subgroup analysis of COO status for PFS at 2-year follow-up (unstratified results with a forest plot) in the original Polivy submission, new evidence provided in the resubmission pertaining to the ABC subtype included the following: patient information (study disposition, baseline characteristics, treatment exposure, concomitant treatments, and new antilymphoma treatments), efficacy results (PFS at 2 years and 5 years [stratified results with Kaplan-Meier plot] and OS at 2 years [stratified results] and at 5 years [stratified results with Kaplan-Meier plot]), and harms.

Sources of Information Used by the Committee

To make its recommendation, the committee considered the following information:

- a review of 1 randomized controlled trial in adult patients with previously untreated *CD20*-positive DLBCL
- patients' perspectives gathered by 1 patient group, Lymphoma Canada
- input from public drug plans that participate in the reimbursement review process
- input from 2 clinical specialists with expertise diagnosing and treating patients with LBCL
- input from 2 clinician groups, Lymphoma Canada Scientific Advisory Board (LC-SAB) and Ontario Health – Cancer Care Ontario (OH-CCO) Hematology Cancer Drug Advisory Committee
- a review of the pharmacoeconomic model and report submitted by the sponsor.

Perspectives of Patients, Clinicians, and Drug Programs

Patient Input

Lymphoma Canada provided input from an online survey among patients with LBCL (N = 89). Lymphoma Canada is a national Canadian registered charity that empowers the lymphoma community through education, support, advocacy, and research. Information from the survey was used to identify the main areas of concern for patients with LBCL. The subtype of LBCL according to COO status was not identified for the respondents. Most patients lived in Canada (94%) and were aged 55 years to 74 years (64%); 58% were female and 42% were male and most were diagnosed 1 year to 5 years ago (61%) with DLBCL (89%).

Symptoms that impacted quality of life among patients with LBCL included fatigue, bodily aches and pain, night sweats, enlarged lymph nodes, reduced appetite, and headache. Patients experienced mental health challenges, including fear of progression or relapse, stress of having cancer, and anxiety or worry. Patients also identified activities that impacted their daily life, such as their ability to exercise, travel, spend time with family, volunteer, and attend work or school.

More survey respondents indicated that they received 2 or more lines of therapy than those who received first-line therapy only. In the first-line setting, 48% of patients received chemoimmunotherapy with R-CHOP, while others received R-CHP or etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin, and rituximab (EPOCH-R). Although 28% of patients were satisfied with their first-line treatment options and 57% of patients were very satisfied with the number of available treatment options, 15% of patients expressed dissatisfaction with the available treatment options. Many patients indicated no difficulty accessing treatment for their lymphoma in Canada; however, many patients reported having challenges, such as delays, cost of travelling long distances for treatment, absence from work, and financial burden of drugs for treatment and supplementary drugs for managing side effects.

Four individuals had experience with pola-R-CHP treatment, of whom 2 patients indicated a good overall experience and 3 patients indicated that they would recommend the treatment to other individuals with LBCL. Side effects of pola-R-CHP treatment reported by at least 2 patients included fatigue, neutropenia, thrombocytopenia, decreased appetite, and diarrhea.

Most patients felt there was a need for more treatment options for LBCL. Many patients were willing to tolerate side effects to access new treatment and sought choice in their selection of treatment. Factors important to patients with LBCL when considering new treatments include longer disease remission, controlled disease symptoms, longer survival, normalized blood counts, and improved quality of life to enable activities of daily living.

Clinician Input

Input From Clinical Experts Consulted for This Review

The clinical experts outlined that although many patients with LBCL experience cure with R-CHOP as a first-line standard-of-care treatment, many patients with high-risk disease (i.e., IPI score of 3 to 5, ABC lymphoma subtype) experience poor outcomes with standard of care. The clinical experts reported that patients with non-GCB subtype of lymphoma (mainly comprising ABC subtype) commonly exhibit high-risk disease features (e.g., high IPI score); compared with the GCB subtype, high-risk molecular features are associated with poorer outcomes using standard-of-care treatment for LBCL. Furthermore, patients with refractory disease or early relapse require salvage therapy (e.g., stem cell transplant, CAR T-cell therapy, bispecific T-cell engager [BiTE] therapy) which is intensive, toxic, and costly, with limited curative potential. Altogether, the experts indicated that patients with high-risk LBCL, regardless of subtype, would benefit from more efficacious first-line treatments that avoid the need for toxic salvage therapies. The current treatment in the first-line setting for patients with ABC subtype is the same as for patients with LBCL (regardless of subtype): 6 cycles of R-CHOP. The experts anticipate that if pola-R-CHP is approved, it would supplant the

current standard of care, R-CHOP, resulting in a shift in the current treatment paradigm for patients with COO of ABC. The clinical experts indicated that all patients who are eligible for treatment with R-CHOP (generally fit and without significant comorbidities), including patients with ABC subtype, would be suited for treatment with pola-R-CHP. Individuals considered ineligible for treatment with pola-R-CHP due to its toxicity include those with reduced cardiac function (e.g., ejection fraction) and/or significant comorbidities, and for whom other treatments are more appropriate (e.g., more intensive treatments for patients with double-hit or double-expressor lymphoma).

According to the clinical experts, eligibility for treatment with pola-R-CHP per proposed reimbursement population requires COO determination to ascertain ABC subtype. In Canada, COO testing is routinely conducted using IHC-based testing with the Hans algorithm. IHC testing distinguishes GCB from non-GCB and although it has demonstrated high concordance with GEP (gold standard for COO diagnostic testing), it is regarded as a proxy for identifying ABC subtype. However, misclassification can occur in approximately 10% to 15% of patients.

According to the experts, treatment response is assessed radiographically at 2 time points: after 3 or 4 cycles of treatment (with CT scan) and at the end of treatment (with PET scan). Upon attaining remission at end of treatment, patients are clinically monitored every 3 months (e.g., physical examination, symptom assessment, laboratory testing) to screen for relapse, with any additional imaging assessments guided by the clinical assessment. The experts reported that, because of the low likelihood of disease relapse 2 years after completing treatment, patients are generally followed up for at least 2 years (or up to 5 years after completing treatment). For those patients whose disease has not progressed or relapsed by 2 years, their disease is considered to be cured. Routine patient imaging is not typically conducted after complete disease remission. The experts expressed that because the goal of treatment for DLBCL is curative intent, OS is the most important outcome for patients, although PFS is also a critical outcome to assess given that disease progression or relapse is common within the first 2 years of treatment. According to the clinical experts, treatment for patients with the ABC subtype of LBCL would be discontinued due to lack of efficacy or unacceptable toxicity. The clinical experts indicated that it would be appropriate for any hematologist or oncologist who treats DLBCL in a community or tertiary care centre to manage patients with ABC subtype using pola-R-CHP. The clinical experts reiterated that restricting polatuzumab vedotin treatment to those with ABC subtype would be impractical based on current diagnostic testing practice in Canada (IHC with the Hans algorithm) and potentially inequitable due to the exclusion of eligible patient populations that would otherwise benefit from this treatment (e.g., patients with high-risk LBCL including those with non-GCB subtype and/or IPI score of 3 to 5).

Clinician Group Input

Two clinician groups provided input for this submission: LC-SAB comprising 9 clinicians with expertise in lymphoid cancer and the OH-CCO Hematology Cancer Drug Advisory Committee comprising 7 clinicians. The clinician groups were aligned with the clinical experts in identifying patients at high risk of poor response to standard of care chemoimmunotherapy R-CHOP (e.g., advanced disease stage, IPI score of 2 to 5, relapsed or refractory disease), including patients with ABC subtype, as individuals who would benefit from

treatment with pola-R-CHP. Both LC-SAB and OH-CCO agreed with the clinical experts that pola-R-CHP would replace R-CHOP in the first-line setting for treatment of patients with ABC subtype. OH-CCO reported that an outpatient setting would be most appropriate for treatment administration; however, LC-SAB agreed with the clinical experts that any site that currently administers R-CHOP would be appropriate for managing patients with pola-R-CHP. LC-SAB highlighted that because polatuzumab vedotin has been approved in combination with bendamustine and rituximab for the treatment of relapsed or refractory DLBCL, there is broad experience with the drug and in a combination chemotherapy regimen.

Drug Program Input

Input was obtained from the drug programs that participate in the reimbursement review process. The following were identified as key factors that could potentially impact the implementation of a recommendation for pola-R-CHP:

- considerations for initiation of therapy
- considerations for continuation or renewal of therapy
- considerations for discontinuation of therapy
- considerations for prescribing of therapy
- generalizability of trial populations to the broader populations in the jurisdictions
- care provision issues
- system and economic issues
- potential need for a provisional funding algorithm.

The clinical experts consulted for the review provided advice on the potential implementation issues raised by the drug programs.

Table 2: Responses to Questions From the Drug Programs

Drug program implementation questions	Clinical expert response
Relevant comparators	
R-CHOP, R-CEOP, and R-mini-CHOP are funded as first-line treatment options for patients with DLBCL. Some jurisdictions fund DA-R-EPOCH for first-line treatment of aggressive lymphomas with high-risk features (i.e., double-hit, triple-hit).	The clinical experts agreed that the available first-line treatments for patients with DLBCL are relevant comparators for pola-R-CHP, with most (> 75%) patients treated with R-CHOP. R-mini-CHOP incorporates a dose reduction in some of its components, which may be most appropriate for patients with frailty or significant comorbidities but is not a clinically unique population to preclude them from being eligible for treatment with pola-R-CHP. There is some uncertainty regarding the optimal therapy for patients with double-hit lymphoma or triple-hit lymphoma, for whom alternatives to R-CHOP that are more intensive may be prescribed (e.g., DA-R-EPOCH, Magrath regimen). However, the majority of double-hit lymphomas are of GCB cell origin and would not benefit from addition of polatuzumab. Patients with significant cardiac dysfunction may be more appropriately treated with R-CEOP, thereby removing anthracycline from their treatment regimen. Altogether, R-CEOP and

Drug program implementation questions	Clinical expert response
	R-mini-CHOP were not considered by the experts to be appropriate comparators for pola-R-CHP. pERC agreed with the clinical experts. pERC noted that the degree of benefit of adding polatuzumab to a reduced-dose regimen vs. R-mini-CHOP is unknown and not supported by data.
Considerations for initiation of therapy	
The POLARIX trial included patients with IPI score of 2 to 5. Should patients with ABC subtype have IPI score of 2 to 5 to be eligible for pola-R-CHP?	The clinical experts felt that patients with ABC subtype of LBCL with an IPI score of 2 to 5 should be eligible for treatment with pola-R-CHP, given that they are reflective of patients who were included in the POLARIX trial. The experts added that patients with LBCL who have IPI scores of 0 or 1 have better prognosis compared with those who have higher IPI scores and experience favourable outcomes with R-CHOP. It is unknown whether patients with ABC subtype of LBCL who have an IPI score of 0 or 1 would have meaningful benefit with pola-R-CHP treatment in the absence of evidence. pERC agreed with the clinical experts.
The POLARIX trial included patients 18 to 80 years of age. Would patients older than 80 years of age who have ABC subtype be eligible for pola-R-CHP?	The clinical experts expressed that any patient treated with R-CHOP–like therapy for curative intent should be eligible for treatment with pola-R-CHP, including those older than 80 years who may currently be treated with dose-reduced R-CHOP (i.e., R-mini-CHOP) for improved tolerance. pERC noted that although this may happen in clinical practice, the degree of benefit of adding polatuzumab to a reduced-dose regimen vs. R-mini-CHOP, including in patients older than 80 years, is unknown and not supported by data.
The POLARIX trial excluded patients with indolent lymphoma. PAG would like to confirm the following 2 questions: 1. Would patients with follicular lymphoma grade IIIB (also called follicular large B-cell lymphoma) be eligible for pola-R-CHP provided all other criteria are met? 2. Would patients who received treatment for indolent follicular lymphoma (i.e., bendamustine-rituximab) and then transform to DLBCL be eligible for treatment with pola-R-CHP?	1. According to the clinical experts, follicular lymphoma grade 3B (neither an indolent nor transformed lymphoma) is categorized as a GCB subtype. Patients with follicular lymphoma grade 3B are treated the same way as de novo DLBCL — with R-CHOP chemotherapy. However, this population is not included in the current resubmission of polatuzumab vedotin, which is focused on patients with the ABC subtype of LBCL. pERC stated that eligibility should be based on the study criteria, which excluded patients with follicular lymphoma grade 3B from the trial. 2. The clinical experts felt that although patients with indolent lymphoma whose disease transforms to DLBCL should be treated as de novo DLBCL, most follicular lymphomas that transform to DLBCL are of the GCB subtype such that few patients would be eligible for treatment with polatuzumab vedotin based on the requested reimbursement population of ABC lymphoma subtype. pERC stated that eligibility should be based on the study criteria, which excluded patients with indolent lymphoma from the trial. However, patients in whom the disease has transformed into a confirmed ABC subtype of LBCL should be eligible for treatment with pola-R-CHP.

Drug program implementation questions	Clinical expert response
Considerations for prescribing of therapy	
Cycles 1 to 6: pola-R-CHP every 21 days for 6 cycles; cycles 7 and 8: rituximab only. The drug plans note that polatuzumab vedotin is available in 30 mg and 140 mg vials that require reconstitution. The dose is 1.8 mg/kg IV every 21 days for 6 cycles. Polatuzumab vedotin, rituximab, cyclophosphamide, and doxorubicin can be administered in any order on day 1 after the administration of prednisone. Prednisone is administered on days 1 to 5 of each cycle. Cycles 7 and 8 consist of rituximab as monotherapy, which is an additional 2 cycles of therapy compared to the standard 6 cycles of R-CHOP that is usually administered, adding additional pharmacy workload and chair time visits. The drug plans would like to know if cycles 7 and 8 of single-agent rituximab would be recommended as normally R-CHOP is given every 21 days for 6 cycles (and no cycles 7 and 8) in most jurisdictions.	According to the clinical experts, because rituximab with chemotherapy is administered in current practice for 6 cycles, and there is no evidence to support additional 2 doses of single-agent rituximab (e.g., patients were not randomized to receive rituximab monotherapy 6 cycles vs. 8 cycles), rituximab monotherapy in cycles 7 and 8 of treatment should be omitted. pERC agreed with the clinical experts.
The dose of CHOP in R-CHOP is sometimes reduced in older adult patients (R-mini-CHOP). 1. Is it appropriate to reduce the dose of CHP when used in the pola-R-CHP regimen in older adults or patients who are frail, or substitute etoposide for doxorubicin in patients who may not be able to receive doxorubicin? 2. Can polatuzumab vedotin be used with rituximab SC or rituximab biosimilar as part of the pola-R-CHP regimen?	1. The clinical experts indicated that if an R-CHOP–like regimen is administered at a reduced dose to improve intolerance with curative intent, then it would be reasonable to consider treatment with pola-R-CHP. Moreover, because R-CEOP is a treatment option with curative intent in patients who cannot tolerate doxorubicin (e.g., due to issues with cardiac function such as low ejection fraction), the experts expressed that it would be appropriate to consider treatment with pola-RCEP for those with such contraindications. pERC noted that although this may happen in clinical practice, the degree of benefit of pola-RCEP to this group of patients is unknown without data to support that or the use of polatuzumab vedotin with potentially curative regimens, such as R-CEOP, R-mini-CHOP, or DA-R-EPOCH. 2. The experts had no concerns with polatuzumab vedotin being used with rituximab SC or rituximab biosimilar as part of the pola-R-CHP regimen because rituximab SC is used in combination with either R-CHOP (from cycle 2 onward) or pola-BR in current practice. pERC agreed with the clinical experts.
For cycle 1, it may be difficult for treatment rooms to accommodate the time of administration for slow infusion rituximab, 90 minutes polatuzumab vedotin infusion, 90 minutes observation and cyclophosphamide infusion and doxorubicin IV. For treatment rooms that are only open for 8 hours, would it be advisable to administer R-CHP on day 1 and then polatuzumab vedotin on day 2 or is there a preference of which drugs should be split? Acknowledging there may be no answer to this question, this will be an implementation issue for many treatment rooms that are only open for 8 hours. This would only be for cycle 1.	According to the clinical experts, it would be reasonable to divide cycle 1 of the pola-R-CHP regimen components as necessary for ease of administration (e.g., administer rituximab and polatuzumab vedotin on same day, followed by CHP the next day) and as logistically feasible at each institution. pERC agreed with the clinical experts.

Drug program implementation questions	Clinical expert response
Generalizability	
The POLARIX trial enrolled patients with an ECOG of 0, 1, or 2. If a patient has an ECOG performance status of	The clinical experts expressed that a patient with ECOG performance status of 3, although typically excluded from clinical trials due to significant disease or symptom burden at presentation, would likely
3 because of their aggressive lymphoma, would they be recommended to use pola-R-CHP?	improve with their first cycle of treatment (e.g., to achieve ECOG performance status of 2 or better) such that they should be considered eligible for treatment with pola-R-CHP. pERC stated that deciding patient suitability for treatment with pola-R-CHP based on ECOG should be at the discretion of the treating clinician.
Would patients with ABC subtype DLBCL who are currently on treatment with R-CHOP be switched to pola-R-CHP? If so, is there a maximum number of cycles of R-CHOP that would be recommended before allowing treatment to be switched to pola-R-CHP?	The experts indicated that patients with ABC lymphoma subtype who have proceeded further along in therapy with R-CHOP (e.g., have had 2 cycles or more of treatment) should continue with R-CHOP. As there may be delays in receiving results of GEP testing (if GEP diagnostic testing becomes available), initiation of urgent therapy may be warranted; that is, patients could receive 1 cycle of R-CHOP while awaiting diagnostic testing and then be allowed to switch to pola-R-CHP for cycle 2 onward, as long as total duration of treatment was not more than 6 cycles. However, the experts acknowledge that there is a lack of evidence to suggest that switching regimen partway through treatment improves outcomes. pERC agreed with the clinical experts.
Funding algorithm (oncology only)	
Request an initiation of a rapid provisional funding algorithm.	This is a comment from the drug plans to inform pERC deliberations.
Drug may change place in therapy of drugs reimbursed in subsequent lines.	This is a comment from the drug plans to inform pERC deliberations.
Complex therapeutic space with multiple lines of therapy, subpopulations, or competing products.	This is a comment from the drug plans to inform pERC deliberations.
If a patient receives pola-R-CHP as first-line treatment and relapses, would pola-BR be an option for second-line treatment? If so, what would be the minimum time from the last polatuzumab vedotin treatment to new initiation of polatuzumab vedotin in the relapsed setting?	Both clinical experts felt that patients who experienced relapse after first-line treatment with pola-R-CHP should be eligible for second-line treatment with pola-BR. One of the experts outlined that because pola-BR is a palliative regimen, it may be considered in the second-line setting for patients who are ineligible for aggressive salvage therapy (e.g., RGDP followed by ASCT, CAR T-cell therapy) and have not experienced refractory disease (i.e., did not progress on treatment or experience relapse > 3 months from last treatment dose). According to the other expert, their jurisdiction requires that 6 months have elapsed since the last rituximab dose to be eligible for re-treatment with rituximab. As such, patients who experience relapse within 1 year are more likely to proceed to CAR T-cell therapy than to receive pola-BR. Nevertheless, the expert expressed that patients with LBCL need bridging therapy to keep their disease under reasonable control before having to escalate to CAR T-cell therapy; therefore, pola-BR should be available to patients who experience relapse at 6 to 12 months. pERC stated that it will be appropriate to make pola-BR available for patients who experience relapse 12 months or more after completing pola-R-CHP.

Drug program implementation questions	Clinical expert response
Care provision issues	
Jurisdictions are familiar with the preparation of rituximab, polatuzumab vedotin, cyclophosphamide, and doxorubicin. This is an enabler to preparation. From a pharmacy point of view, polatuzumab vedotin requires more compounding time than compounding vincristine. From a nursing point of view, extra chair time is required with the use of polatuzumab vedotin.	This is a comment from the drug plans to inform pERC deliberations.
Growth factor support was mandated for patients in the POLARIX trial for the use of pola-R-CHP and will be required upon implementation of pola-R-CHP. Growth factor support is funded differently across jurisdictions.	The clinical experts recommended that growth factor support be mandated with pola-R-CHP treatment based on the use of G-CSF as primary prophylaxis during cycles 1 to 6 of treatment in the POLARIX trial. The experts highlighted that there was a relatively high occurrence of infectious toxicities among patients in the trial despite G-CSF prophylaxis, particularly in the pola-R-CHP group.
As ABC testing may not be available across all jurisdictions, this is an implementation issue that will need to be addressed by the jurisdictions. What is the turnaround time for ABC testing in lymphoma?	The experts reported that GEP testing to determine ABC subtype of LBCL is not performed across most centres in Canada. IHC testing is required for the diagnosis of LBCL in current practice. Diagnostic testing using the IHC method can differentiate GCB from non-GCB subtypes (non-GCB subtype includes ABC subtype and unclassified COO). pERC noted that GEP testing is required to determine patients with the ABC subtype of LBCL who are eligible for therapy with pola-R-CHP. Because GEP testing for ABC subtype of LBCL is not currently available in most jurisdictions in Canada, implementing the use of GEP testing to decide eligibility for treatment with pola-R-CHP is anticipated to impact human and other health care resources. Nonetheless, it may also help reduce costs and patient harm by avoiding unnecessary treatments and minimizing toxicities.
If a patient experiences neuropathy despite dose reductions of polatuzumab vedotin, and polatuzumab vedotin needs to be discontinued, is it advisable to continue with R-CHP?	The experts agreed that a patient may continue treatment with R-CHP alone if they experienced serious neuropathy with polatuzumab vedotin (as part of pola-R-CHP) or with vincristine (as part of R-CHOP). pERC agreed with the clinical experts.
System and economic issues	
There is concern regarding the substantial budget impact for addition of polatuzumab vedotin as it will replace vincristine (vincristine is generic and the incremental cost of 6 cycles of polatuzumab vedotin per patient is substantial).	This is a comment from the drug plans to inform pERC deliberations.
There are large incremental budget impacts for polatuzumab vedotin.	This is a comment from the drug plans to inform pERC deliberations.

ABC = activated B cell–like; ASCT = autologous stem cell transplant; COO = cell of origin; DA-R-EPOCH = dose-adjusted rituximab, etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin; DLBCL = diffuse large B-cell lymphoma; ECOG = Eastern Cooperative Oncology Group; GCB = germinal centre B cell; G-CSF = granulocyte colony-stimulating factor; GEP = gene expression profiling; IHC = immunohistochemistry; IPI = International Prognostic Index; LBCL = large B-cell lymphoma; PAG = Provincial Advisory Group; pola-BR = polatuzumab vedotin, bendamustine, and rituximab; pERC = pan-Canadian Oncology Drug Review Expert Review Committee; pola-R-CHP: polatuzumab vedotin, rituximab, cyclophosphamide, doxorubicin, and prednisone; R-CEOP = rituximab, cyclophosphamide, etoposide, vincristine, and prednisone; R-CHP = rituximab, cyclophosphamide, doxorubicin, and prednisone; R-CHOP = rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone; RGDP = rituximab, gemcitabine, dexamethasone, cisplatin; R-mini-CHOP = rituximab and reduced-dose CHOP; vs. = versus.

Clinical Evidence

Systematic Review

Description of Study

One phase III, multicentre, randomized, double-blind, placebo-controlled trial (POLARIX) assessed the efficacy and safety of pola-R-CHP compared with standard-of-care R-CHOP in the first-line treatment of adults with previously untreated LBCL, including DLBCL NOS, high-grade B-cell lymphoma, EBV-positive DLBCL NOS, and T-cell/histiocyte-rich LBCL. The focus of this resubmission of polatuzumab vedotin was a subgroup of patients in the POLARIX trial who have the ABC subtype of LBCL. In the POLARIX trial, investigator-assessed PFS was the primary outcome, and OS was a key secondary outcome. OS and PFS were exploratory outcomes in the subgroup analyses of patients with ABC subtype of LBCL. Treatment-emergent AE); serious AEs, including AEs of grade 3 or higher; withdrawals due to AEs; deaths; and AEs of special interest were reported for the subpopulation of patients with ABC subtype of LBCL.

Patients with ABC subtype of LBCL (N = [redacted]) comprised [redacted] of the overall population in the POLARIX trial. The median age of patients with ABC lymphoma subtype was [redacted] years (range, [redacted]). At baseline, patients had an ECOG performance status score of 0 ([redacted]), 1 ([redacted]), and 2 ([redacted]). Patients had disease designated as Ann Arbor stage I ([redacted]), II ([redacted]), III ([redacted]), and IV ([redacted]). At screening, more patients had an IPI score of 3 to 5 ([redacted]) than 1 to 2 ([redacted]). Bulky disease was present at baseline in [redacted] of patients but absent in [redacted] of patients. Most patients were negative for double-hit lymphoma or triple-hit lymphoma ([redacted]). In addition to stratified randomization factors (IPI score, bulky disease, and geographical location), the treatment groups were generally similar in demographics and disease characteristics. However, more patients had disease designated as Ann Arbor stage III in the pola-R-CHP group ([redacted]) than the R-CHOP group ([redacted]) whereas fewer patients had Ann Arbor stage IV in the pola-R-CHP group ([redacted]) compared with the R-CHOP group (69.0%). Additionally, fewer patients had 2 or more extranodal disease sites in the pola-R-CHP group ([redacted]) than the R-CHOP group ([redacted]).

Efficacy Results

Key efficacy results for patients with ABC subtype of LBCL in the POLARIX trial are summarized in Table 2. The analysis population for OS and PFS included randomized patients regardless of treatment received (intention to treat) who had evaluable COO status at baseline. Patients with ABC subtype of LBCL were included as a subgroup analysis by COO status and followed to the clinical cut-off date on June 15, 2022, for PFS (included as a forest plot in the original submission for polatuzumab vedotin). The resubmission supplemented this with Kaplan-Meier estimates of OS and PFS at this follow-up. The resubmission also provided data for long-term follow-up of patients with ABC subtype of LBCL at the clinical cut-off date on July 5, 2024, for OS and PFS, which were included in this report.

Overall Survival

[redacted]. The 2-year OS rate was 91.4% in the pola-R-CHP group versus 87.11% in the R-CHOP group, with a difference of 4.3% (stratified HR = 0.46; 95% CI, 0.23 to 0.92). At 5-year follow-up (data cut-off on

July 5, 2024), the median duration of follow-up was 63.9 months (range, 0 months to 73 months) in the pola-R-CHP group and 64.2 months (range, 1 month to 78 months) in the R-CHOP group. Median OS had not been reached in the pola-R-CHP group or the R-CHOP group. The 5-year OS was 84.6% in the pola-R-CHP group versus 69.9% in the R-CHOP group, with a difference of 14.7% (stratified HR = 0.49; 95% CI, 0.27 to 0.90). Analyses of OS were uncontrolled for multiplicity and considered supportive.

Investigator-Assessed PFS

At 3-year follow-up, the median duration of follow-up was [redacted] months (range, [redacted]) in the pola-R-CHP group and median [redacted] months (range, [redacted]) in the R-CHOP group. Median investigator-assessed PFS had not been reached in the pola-R-CHP group, and the median PFS was [redacted] months ([redacted]) in the R-CHOP group. The 2-year investigator-assessed PFS rate was [redacted] in the pola-R-CHP group versus [redacted] in the R-CHOP group, with a difference of [redacted] ([redacted]). At 5-year follow-up, the median duration of follow-up was 55.0 months (range, 0 to 71 months) in the pola-R-CHP group and median 56.1 months (range, 0 to 68 months) in the R-CHOP group. Median investigator-assessed PFS was 70.5 months (95% CI, not estimable) in the pola-R-CHP group, compared with 33.2 months (95% CI, 18.9 months to 66.7 months) in the R-CHOP group. The 5-year investigator-assessed PFS was 72.5% in the pola-R-CHP group versus 45.8% in the R-CHOP group, with a difference of 26.7% (stratified HR = 0.33; 95% CI, 0.21 to 0.53). Analyses of investigator-assessed PFS were uncontrolled for multiplicity and considered supportive.

Harms Results

Key harms data for patients with ABC subtype of LBCL in the POLARIX trial are summarized in Table 2. The analysis population for harms included all patients who received at least 1 dose of study treatment, with patients grouped according to the treatment received. Safety data were from the 5-year follow-up data.

In the ABC subpopulation, the number of patients who experienced at least 1 treatment-emergent AE was 105 of 106 patients (99.1%) in the pola-R-CHP group and 127 of 129 patients (98.4%) in the R-CHOP group. The number of patients who experienced at least 1 AE of grade 3 to 5 was 70 patients (66.0%) in the pola-R-CHP group and 81 patients (62.8%) in the R-CHOP group. The number of patients who experienced serious AEs was 34 patients (32.1%) in the pola-R-CHP group and 38 patients (29.5%) in the R-CHOP group. The number of patients who stopped treatment due to AEs was 7 patients (6.6%) in the pola-R-CHP group and 11 patients (8.5%) in the R-CHOP group. Types of treatment-emergent AEs, serious AE, and the reasons for treatment discontinuation due to AEs were not specified. The number of patients who died was 17 patients (16.0%) in the pola-R-CHP group and 39 patients (30.2%) in the R-CHOP group. Reasons for deaths in the pola-R-CHP and R-CHOP groups, respectively, were progressive disease (7.5% and 17.1%, respectively), an AE (4.7% and 6.2%, respectively), and unspecified (3.8% and 7.0%, respectively).

Notable Harms

In the ABC subpopulation, the number of patients who experienced peripheral neuropathy was 56 patients (52.8%) in the pola-R-CHP group and 65 patients (50.4%) in the R-CHOP group. The number of patients who experienced neutropenia, including febrile neutropenia was 56 patients (52.8%) in the pola-R-CHP group and 60 patients (46.5%) in the R-CHOP group. The number of patients who experienced infections

was 58 patients (54.7%) in the pola-R-CHP group and 54 patients (41.9%) in the R-CHOP group. The number of patients who experienced anemia was 30 patients (28.3%) in the pola-R-CHP group and 33 patients (25.6%) in the R-CHOP group.

Table 3: Summary of Key Results in POLARIX Study

Outcome measure	POLARIX ABC subpopulation	
	Pola-R-CHP N = 106	R-CHOP N = 129
OS (global ITT analysis set)		
Data cut-off date	**June 15, 2022**	
Follow-up duration (months), median (range)	[redacted]	[redacted]
Patients with events, n (%)	[redacted]	[redacted]
Censored, n (%)	[redacted]	[redacted]
Time to OS (months), median (95% CI)	[redacted]	[redacted]
Unstratified HR (95% CI)[a]	[redacted]	[redacted]
P value[b]	[redacted]	[redacted]
Stratified HR (95% CI)[c]	[redacted]	[redacted]
P value[d]	[redacted]	[redacted]
OS at 24 months		
Patients remaining at risk at 24 months, n (%)	[redacted]	[redacted]
24-month OS rate (95% CI)	[redacted]	[redacted]
Difference in OS rate at 24 months (95% CI)	[redacted]	[redacted]
Data cut-off date	**July 5, 2024**	
Follow-up duration (months), median (range)	63.9 (0 to 73)	64.2 (1 to 78)
Patients with events, n (%)	17 (16.0)	38 (29.5)
Censored, n (%)	89 (84.0)	91 (70.5)
Time to OS (months), median (95% CI)	NE (NE)	NE (NE)
Unstratified HR (95% CI)[a]	0.49 (0.28 to 0.88)	Reference
P value[b]	0.0136	Reference
Stratified HR (95% CI)[c]	0.49 (0.27 to 0.90)	Reference
P value[d]	0.0190	Reference
OS at 60 months		
Patients remaining at risk at 60 months, n (%)	81 (76.4)	82 (63.6)
60-month OS rate (95% CI)	84.59 (77.64 to 91.54)	69.89 (61.76 to 78.02)

Outcome measure	POLARIX ABC subpopulation	
	Pola-R-CHP N = 106	R-CHOP N = 129
Difference in OS rate at 60 months (95% CI)	14.70 (4.00 to 25.39)	Reference
Investigator-assessed PFS (global ITT analysis set)		
Data cut-off date	**June 15, 2022**	
Follow-up duration (months), median (range)	[redacted]	[redacted]
Patients with investigator-assessed PFS events, n (%)	[redacted]	[redacted]
Disease progression	[redacted]	[redacted]
Death	[redacted]	[redacted]
Censored, n (%)	[redacted]	[redacted]
Time to investigator-assessed PFS event (months), median (95% CI)	[redacted]	[redacted]
Unstratified HR (95% CI)[a]	[redacted]	[redacted]
P value[b]	[redacted]	[redacted]
Stratified HR (95% CI)[c]	[redacted]	[redacted]
P value[d]	[redacted]	[redacted]
PFS at 24 months		
Patients remaining at risk at 24 months, n (%)	[redacted]	[redacted]
24-month PFS rate (95% CI)	[redacted]	[redacted]
Difference in PFS rate at 24 months (95% CI)[e]	[redacted]	[redacted]
Data cut-off date	**July 5, 2024**	
Follow-up duration (months), median (range)	55.0 (0 to 71)	56.1 (0 to 68)
Patients with investigator-assessed PFS events, n (%)	28 (26.4)	69 (53.5)
Disease progression	17 (16.0)	58 (45.0)
Death	11 (10.4)	11 (8.5)
Censored, n (%)	78 (73.6)	60 (46.5)
Time to investigator-assessed PFS event (months), median (95% CI)	70.5 (NE)	33.2 (18.9 to 66.7)
Unstratified HR (95% CI)[a]	0.38 (0.24 to 0.59)	Reference
P value[b]	< 0.0001	Reference
Stratified HR (95% CI)[c]	0.33 (0.21 to 0.53)	Reference
P value[d]	< 0.0001	Reference
PFS at 60 months		
Patients remaining at risk at 60 months, n (%)	28 (26.4)	26 (20.2)
60-month PFS rate (95% CI)	72.46 (62.82 to 82.10)	45.78 (36.47 to 55.08)

Outcome measure	POLARIX ABC subpopulation	
	Pola-R-CHP N = 106	R-CHOP N = 129
Difference in PFS rate at 60 months (95% CI)[e]	26.69 (13.29 to 40.09)	Reference
Harms (safety analysis set)		
Data cut-off date	**July 5, 2024**	
N	106	129
TEAEs, n (%)	105 (99.1)	127 (98.4)
Serious AEs, n (%)	34 (32.1)	38 (29.5)
Treatment discontinuations due to AEs, n (%)	7 (6.6)	11 (8.5)
Deaths, n (%)	17 (16.0)	39 (30.2)
Notable harms, n (%)		
Peripheral neuropathy	56 (52.8)	65 (50.4)
Neutropenia	56 (52.8)	60 (46.5)
Febrile neutropenia	20 (18.9)	7 (5.4)
Infections	58 (54.7)	54 (41.9)
Anemia	30 (28.3)	33 (25.6)
Infusion-related reactions	13 (12.3)	25 (19.4)
Thrombocytopenia	16 (15.1)	16 (12.4)
Hepatic toxicity	13 (12.3)	10 (7.8)
Tumour lysis syndrome	1 (0.9)	2 (1.6)
Progressive multifocal leukoencephalopathy	0	0

ABC = activated B-cell-like; AE = adverse event; CI = confidence interval; HR = hazard ratio; ITT = intention to treat; NE = not estimable; NR = not reported; OS = overall survival; PFS = progression-free survival; pola-R-CHP = polatuzumab vedotin, rituximab, cyclophosphamide, doxorubicin, and prednisone; R-CHOP = rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone; TEAE = treatment-emergent adverse event.

[a]Based on Kaplan-Meier estimates with 95% CI for median computed using the method of Brookmeyer and Crowley.

[b]Based on an unstratified Cox regression model.

[c]One-sided P value based on an unstratified log-rank test. P value has not been adjusted for multiplicity.

[d]Based on a stratified Cox regression model with stratification factors for geographical region, IPI score, and bulky disease defined as 1 lesion of 7.5 cm or larger.

[e]One-sided P value based on a stratified log-rank test. P value has not been adjusted for multiplicity.

Source: POLARIX Clinical Study Report. Details included in the table were additional data provided from the sponsor.

Critical Appraisal

Findings for PFS and OS for the ABC subpopulation were based solely on exploratory subgroup analyses that, in principle, should be interpreted as hypothesis generation would require a well-designed and adequately powered trial to further confirm the findings. Although patients in the overall global ITT population were allocated into treatment groups by stratified randomization (for IPI score, bulky disease, and geographical location), the randomization principle might not have been preserved for patients with ABC subtype who were not randomized by the stratification factors. There were between-group differences

in the proportion of patients with Ann Arbor stage III ([redacted] in the pola-R-CHP versus R-CHOP groups, respectively) and IV ([redacted] in the pola-R-CHP versus R-CHOP groups, respectively). However, it was unclear whether these imbalances had any impact on patients' prognosis or treatment effects. [redacted]. Despite the adjustment of stratified factors, it is unknown if additional covariates (i.e., disease status) may have biased the findings. Multiplicity is a concern because it could result in inflated type I error, leading to inappropriate conclusion of statistical inference, given that the observed P values for both stratified and unstratified OS were less than the significance level of 0.05. Although both investigator and independent review assessments of PFS would be preferred, the double-blinded study design may limit potential bias (e.g., more frequent assessments, subjective interpretation of radiographic images and clinical assessments) arising from assessment by investigator. [redacted]. Findings should be interpreted cautiously given the small sample sizes.

The clinical experts indicated that patients with ABC subtype enrolled in the POLARIX trial were representative of patients in clinical practice, and 65% of the patients having an IPI score of 3 to 5 aligned with the experts' expectation of high-risk disease among individuals in the ABC subpopulation. Overall, the experts agreed with the inclusion criteria of the POLARIX study although excluding patients with some comorbidity conditions as well as patients with poorer performance status at presentation (i.e., ECOG performance status of 3 or 4) may have resulted in a selected population that is healthier.

Testing Procedure Considerations

According to the sponsor and the clinical experts consulted for this review, GEP is the gold standard method for determining COO subtype; however, it is not widely available in Canada. Instead, IHC using the Hans algorithm (*CD10*, *BCL6*, and *MUM1*) can be used to categorize LBCL into GCB or non-GCB subtypes. The clinical experts confirmed that, in Canada, IHC-based COO testing is routinely performed for most LBCL cases as part of the standard of care during the diagnostic workup except for certain rare subtypes.

Key considerations and relevant information available from materials submitted by the sponsor, input from the clinical experts, and sources from the literature were validated by the review team when possible and are summarized in Table 4.

Table 4: Considerations for LBCL Subtype Classification and COO Testing by GEP and IHC for Establishing Treatment Eligibility With Pola-R-CHOP

Consideration	Criterion	Available Information
Health system–related	Number of individuals in Canada expected to require the test (e.g., per year)	Based on the sponsor-provided estimates confirmed by the clinical experts, approximately 8,973 new cases of NHL are expected to be diagnosed across Canada (excluding Quebec) in 2025, of which approximately 30% are likely to be classified as LBCL. Therefore, it is estimated that 2,692 patients will undergo COO testing.
	Availability and reimbursement status of the testing procedure in jurisdictions across Canada	According to the sponsor and clinical experts, IHC-based COO testing is readily available and funded in jurisdictions across Canada through hematopathology or cancer centres. The clinical experts indicated that GEP is currently only available in British Columbia, but it is unclear if it is consistently available across all centres within the jurisdiction.
	Testing procedure as part of routine care	According to the clinical experts, COO testing is routinely performed for most LBCL cases as part of the standard of care during the diagnostic workup except for certain rare subtypes (e.g., anaplastic lymphoma kinase-positive LBCL, plasmablastic lymphoma).
	Repeat testing requirements	The clinical experts confirmed that COO testing is typically performed once at the time of diagnosis.
	Impacts on human and other health care resources by provision of the testing procedure	Because IHC-based COO testing is currently a routine diagnostic procedure for most patients with LBCL, use of the test result to establish treatment eligibility for pola-R-CHP is not anticipated to impact human and other health care resources. No impact on the volume of COO testing is anticipated if pola-R-CHP were to be funded. However, incorporating GEP-based COO testing may require upscaling testing infrastructure.
Patient-related	Accessibility of the testing procedure in jurisdictions across Canada	As IHC-based COO testing is widely accessible across Canada as a routine diagnostic procedure for patients with LBCL, there is no additional impact of access anticipated from the testing as part of establishing treatment eligibility for pola-R-CHP.
	Expected turnaround times for the testing procedure	According to the clinical experts, IHC-based COO testing results are generally available concurrently with the LBCL diagnostic report and would not delay the clinical diagnosis, including subtype identification or treatment initiation. However, GEP-based COO testing is not currently included in routine diagnostic procedures in most jurisdictions in Canada. According to 1 source in British Columbia, GEP testing can be completed within 24 hours, although the total turnaround time may be longer depending on the entire clinical workflow and the need for centres to send biopsy samples to referral centres for GEP.

Consideration	Criterion	Available Information
	Burden associated with the testing procedure for patients, families, and/or caregivers	Because COO testing is performed on tissue samples already collected during routine biopsy, no additional tissue biopsy would be required.
Clinical	Clinical utility of the testing procedure	IHC-based COO testing is less accurate than GEP in identifying ABC subtypes because the former simply dichotomizes patients into GCB and non-GCB subtypes and the patients with the non-GCB classification would include both ABC (eligible for pola-R-CHP) and unclassified subtypes (ineligible for pola-R-CHP). GEP-based testing provides more accurate COO classification than IHC by specifically identifying the ABC subtype.
	Clinical validity of the testing procedure	Compared with GEP, IHC-based COO testing using the Hans algorithm showed 65% to 86% concordance with 85% to 90% sensitivity and 52% to 82% specificity for detecting the ABC subtype. The Hans algorithm can correctly identify most patients with the ABC subtype but also includes unclassified subtypes within the non-GCB category. Thus, it may misclassify some GCB subtypes as non-GCB subtypes in 18% to 48% of cases. GEP-based COO testing assay performed on FFPE tissues demonstrated 92% to 95% concordance with traditional GEP using fresh frozen tissues for classifying the ABC subtype. This suggests the assay can classify the ABC subtype with high accuracy. Evidence also indicated that the assay has a lower COO misclassification rate in patients with DLBCL compared to IHC-based COO testing using the Hans algorithm (2% and 9%, respectively).
	Risks of harm associated with the testing procedure	The clinical experts and 1 clinician group confirmed the risk of misclassifying some LBCL cases as the ABC subtype using IHC-based COO testing, which may lead to overtreating patients who, in fact, have the GCB or unclassified COO subtype of lymphoma.
Cost	Projected cost of the testing procedure	Depending on the size and number of slides, the cost of IHC for lymphoma diagnosis may range from $30 to $550 in Canada. No information regarding the specific cost of IHC-based COO testing could be obtained. According to sponsor-submitted materials, the cost of GEP is approximately $570 per tumour in British Columbia. This cost includes RNA extraction, machine maintenance, and all related components. However, because COO testing is already part of the standard of care, there is no additional cost anticipated from the testing as part of establishing treatment eligibility for pola-R-CHP.

ABC = activated centre B cell–like; COO = cell of origin; DLBCL = diffuse large B-cell lymphoma; FFPE = formalin-fixed paraffin-embedded; GCB = germinal centre B cell–like; GEP = gene expression profiling; IHC = immunohistochemistry; LBCL = large B-cell lymphoma; NHL = non-Hodgkin lymphoma; pola-R-CHP = polatuzumab vedotin, rituximab, cyclophosphamide, doxorubicin, and prednisone.

Economic Evidence

Table 5: Cost and Cost-Effectiveness

Component	Description
Type of economic evaluation	Cost-utility analysis Markov model
Target population	Adult patients with previously untreated LBCL, including DLBCL NOS, high-grade B-cell lymphoma, Epstein-Barr virus–positive DLBCL NOS, and T-cell/histiocyte-rich LBCL, that is classified as ABC subtype
Treatments	Pola-R-CHP
Dose regimen	• Polatuzumab vedotin: 1.8 mg/kg on day 1 every 21 days for up to 6 cycles • Cyclophosphamide: 750 mg/m^2 every 21 days for up to 6 cycles • Doxorubicin: 50 mg/m^2 every 21 days for up to 6 cycles • Prednisone: 100 mg every 21 days for up to 6 cycles • Rituximab: 375 mg/m^2 every 21 days for up to 6 cycles, with an option for 2 additional cycles
Submitted price	Polatuzumab vedotin: $3,160.71 per 30 mg vial or $14,750.00 per 140 mg vial
Submitted treatment cost	Pola-R-CHP: $18,289 ($15,247 for polatuzumab vedotin) per 21-day cycle[a]
Comparator	R-CHOP: rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone
Perspective	Canadian publicly funded health care payer
Outcomes	QALYs, life-years
Time horizon	Lifetime (35 years)
Key data source	POLARIX trial
Key limitations	• Testing is required to identify patients with LBCL who have the ABC subtype. The predominant method of testing currently available in Canada is IHC testing using the Hans algorithm. Published evidence indicates that this method of testing will result in a substantial number of misclassifications and overtreatment because this method of testing cannot identify the ABC subtype (only GCB and non-GCB subtypes), and published specificity is low (52% to 82%). CDA-AMC calculated that for every 1.5 to 2.3 people identified by IHC via the Hans algorithm, only 1 is likely to have the ABC subtype. More accurate testing is available (GEP), but it not commonly available across Canada (British Columbia only). The sponsor did not include the impact of testing in their economic analysis, and CDA-AMC was limited in terms of its ability to include this information in the analysis. • The long-term benefit of pola-R-CHP is uncertain due to limitations with the clinical evidence, such as imprecision, assumption of surrogacy between PFS and OS, and being based on exploratory subgroup analyses that were not designed or powered to demonstrate OS or PFS benefit given the sample size. Although the CDA-AMC clinical review and clinical experts consulted by CDA-AMC for this review concluded that pola-R-CHP is expected to result in a clinically important PFS benefit in the ABC subtype, the magnitude of benefit is uncertain. The CDA-AMC clinical review also noted that there is little to no benefit and overall high uncertainty with treating other subgroups (non-ABC) with pola-R-CHP. • There are limitations with the clinical evidence and the sponsor's assumptions that treatment benefit would be maintained indefinitely; therefore, the predicted OS benefit in the model is highly uncertain and does not appear to meet face validity according to clinical expert feedback (e.g., patients living for 17 years after receiving pola-R-CHP). Up to 91% of the incremental benefit was predicted to occur beyond the 46-month trial follow-up used to inform

Component	Description
	the economic model. • Modelling assumptions surrounding cure lacked face validity and likely did not capture the clinical pathway of disease. The sponsor assumed that the risk of mortality after cure is equivalent to the general population which does not meet face validity and contradicts published literature. HRQoL was similarly assumed to be equivalent to the general population after cure which seemed optimistic according to clinical expert feedback obtained by CDA-AMC. The risk of relapse and health care resource utilization after cure was also likely underestimated according to clinical expert feedback. • The distributions of subsequent therapy use did not meet face validity according to clinical expert feedback obtained by CDA-AMC. Clinical expert feedback also indicated that at the time of disease progression, the number and distribution of subsequent therapies is not dependent on first-line therapy received (with exception of pola-BR used more frequently after R-CHOP) and thus would be mostly similar for both treatment groups.
CDA-AMC reanalysis results	• In reanalysis, CDA-AMC incorporated the cost of testing to identify individuals with ABC subtype using IHC and the cost of overtreating with pola-R-CHP because of the likelihood of misdiagnosis due to the inaccuracy of the testing process. Reanalyses tested the impact of including a 52% (lower bound) and 82% specificity value (upper bound) for detecting the ABC subtype. In this analysis, based on the subgroup data for the other subtypes, CDA-AMC assumed no incremental benefit for pola-R-CHP. • CDA-AMC was unable to address issues related to the concerns surrounding face validity of cure assumptions, uncertainty in the clinical evidence, and exclusion of testing costs. • ICER = $25,952 per QALY gained (2.42 incremental QALYs; $62,825 incremental cost) for pola-R-CHP vs. R-CHOP in the CDA-AMC base case assessing 52% testing specificity. • ICER = $1,616 per QALY gained (2.42 incremental QALYs; $3,911 incremental cost) for pola-R-CHP vs. R-CHOP in the CDA-AMC base case assessing 82% testing specificity. • Based on scenario analyses, results are sensitive to alternate distributions of subsequent therapies and the cost of CAR T-cell therapy. Although CDA-AMC did not have adequate evidence to explore alternate impacts on subsequent treatment use, given the sensitivity of the results to costs, we can hypothesize that the results are sensitive to the assumptions regarding changes in subsequent treatment use. • Notably, the analysis does not incorporate the costs of testing; GEP testing is not currently funded across all jurisdictions in Canada. Based on the sponsor's estimated number of patients with confirmed DLBCL in Canada (excluding Quebec) and the cost of GEP testing identified in the TPA review, this would result in an additional cost of approximately $1,761,300 per year to identify patients with the ABC subtype. This estimate only includes the cost per GEP test and does not incorporate costs related to assay development and validation, staff training, equipment procurement and maintenance likely required.

ABC = activated B cell–like; BR = bendamustine + rituximab; CDA-AMC = Canada's Drug Agency; DLBCL = diffuse large B-cell lymphoma; GCB = germinal centre B cell–like; GEP = gene expression profiling; HRQoL = health-related quality of life; ICER = incremental cost-effectiveness ratio; IHC = immunohistochemistry; LBCL = large B-cell lymphoma; NOS = not otherwise specified; pola = polatuzumab vedotin; QALY = quality-adjusted life-year; R-CHP = rituximab, cyclophosphamide, doxorubicin, and prednisone; R-CHOP = rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone; TPA = testing procedure assessment; vs. = versus.

[a]Pola-R-CHP: $23,605 ($19,667 for polatuzumab vedotin) per 28 days.

Budget Impact

CDA-AMC identified the following key limitations with the sponsor's analysis:

- Limitations with current testing methods using IHC likely result in misclassification of the ABC subtype and therefore may result in overtreatment of patients with pola-R-CHP. This was not incorporated in the sponsor's submitted analysis.

- Testing costs for GEP to more accurately identify the ABC subtype were not included.
- The subsequent therapy assumptions were not reflective of clinical practice in Canada.

The CDA-AMC reanalysis included adjusting for the cost implications of the overtreatment of patients due to misclassification of the ABC subtype in which we tested a range of specificity values from 52% to 82% from published literature.

Based on the CDA-AMC reanalysis, the estimated 3-year budget impact of reimbursing pola-R-CHP would be $107,095,178 if assuming 52% specificity for IHC testing used to detect patients with DLBCL for the ABC subtype (Year 1: $43,802,149; Year 2: $33,740,502; Year 3: $29,552,527). When assuming a rate of 82% specificity for IHC testing, the estimated 3-year budget impact of reimbursing pola-R-CHP would be $69,542,323 (Year 1: $28,442,954; Year 2: $21,909,417; Year 3: $19,189,953). The upfront cost of pola-R-CHP in this setting ranges from $290,691,715 to $447,665,241 if assuming 82% and 52% specificity for IHC testing, respectively. The sponsor assumes cost offsets associated with pola-R-CHP relative to R-CHOP due to lower subsequent treatment costs.

When alternate distributions for subsequent therapy are assumed and a price reduction for CAR T-cell therapy is implemented, the 3-year budget impact of reimbursing pola-R-CHP would range from $168,590,084 to $259,628,730 when assuming 82% specificity and 52% specificity, respectively. When subsequent therapy is excluded from the analysis, the 3-year budget impact of reimbursing pola-R-CHP would range from $264,243,382 to $406,934,808 when assuming 82% specificity and 52% specificity, respectively.

The analysis does not incorporate the additional costs required to implement GEP testing to accurately identify patients with DLBCL with the ABC subtype. Based on the sponsor's estimated number of patients with confirmed DLBCL across all CDA-AMC–participating jurisdictions, funding GEP testing to identify patients with ABC subtype would result in additional costs of more than $1,761,300 per year to jurisdictions.

pERC Information

Members of the Committee

Dr. Catherine Moltzan (Chair), Dr. Philip Blanchette, Dr. Kelvin Chan (Vice Chair), Dr. Matthew Cheung, Dr. Michael Crump, Annette Cyr, Dr. Jennifer Fishman, Dr. Jason Hart, Terry Hawrysh, Dr. Yoo-Joung Ko, Dr. Aly-Khan Lalani, Amy Peasgood, Dr. Anca Prica, Dr. Adam Raymakers, Dr. Patricia Tang, Dr. Pierre Villeneuve, and Danica Wasney

Meeting date: May 14, 2025

Regrets: One expert committee member did not attend.

Conflicts of interest: Two expert committee members did not participate due to considerations of conflict of interest.

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Questions or requests for information about this report can be directed to Requests@cda-amc.ca.