Canadian Journal of Health Technologies
January 2024 Volume 4 Issue 1

CADTH Reimbursement Recommendation

Polatuzumab Vedotin (Polivy)

Indication: Large B-cell lymphoma
Sponsor: Hoffman-La Roche Ltd.
Final recommendation: Do not reimburse

Summary

What Is the CADTH Reimbursement Recommendation for Polivy?

CADTH recommends that Polivy in combination with rituximab, cyclophosphamide, doxorubicin, and prednisone (R-CHP) not 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 (NOS), high-grade B-cell lymphoma, Epstein-Barr virus–positive DLBCL NOS, and T-cell/histiocyte-rich LBCL.

Why Did CADTH Make This Recommendation?

- Evidence from a clinical trial showed that 6.6% more patients with newly diagnosed moderate- to high-risk LBCL were alive without their disease progressing 2 years after treatment with Polivy in combination with R-CHP compared to those treated with traditional chemoimmunotherapy (rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone [R-CHOP]). However, there is uncertainty whether this difference observed in the clinical trial translates to a meaningful difference in the real world. The evidence from the trial did not show that Polivy combined with R-CHP prolonged survival compared to R-CHOP. It is also unknown if Polivy in combination with R-CHP would reduce disease symptoms or improve functioning compared to R-CHOP because there were no differences between the 2 groups.
- Patients identified a need for treatments that prolong disease remission, prolong survival, control disease symptoms, normalize blood counts, and improve quality of life. Based on the evidence submitted, it is not clear that Polivy in combination with R-CHP would provide a meaningful benefit in prolonging remission or meet the other important needs in LBCL.

Additional Information

What Is LBCL?

Non-Hodgkin lymphoma (NHL) is a type of cancer that forms in the lymph system. It is the fifth most common cancer. LBCL refers to several subtypes of NHL. DLBCL, which is a cancer that develops from the B cells in the lymphatic system, accounts for approximately 25% of NHL cases.

Unmet Needs in LBCL

Newly diagnosed patients with LBCL have limited treatment options. Not all patients are cured by treatment with R-CHOP. Approximately 30% to 50%

Summary

of patients will have disease progression or will relapse typically within the first 2 years, and will require additional treatments for their disease.

How Much Does Polivy Cost?

Treatment with Polivy in combination with R-CHP is expected to cost $23,480 per patient per 28 days.

Recommendation

The CADTH pan-Canadian Oncology Drug Review Expert Review Committee (pERC) recommends that polatuzumab vedotin in combination with rituximab, cyclophosphamide, doxorubicin, and prednisone (pola-R-CHP) not be reimbursed 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.

Rationale for the Recommendation

One phase III, multicentre, randomized controlled trial (RCT) (POLARIX) demonstrated that treatment with pola-R-CHP resulted in a benefit in progression-free survival (PFS) compared to rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) in adult patients with previously untreated LBCL. However, pERC was uncertain whether the observed between-group difference of 6.64% at 24 months (95% confidence interval [CI], 0.70% to 12.58%) is clinically meaningful. After a median follow-up time of approximately 31 months, 118 (26.8%) patients had experienced disease progression or died as assessed by the investigator in the pola-R-CHP group versus 143 (32.6%) patients in the R-CHOP group (stratified hazard ratio [HR] = 0.76; 95% CI, 0.60 to 0.97; P = 0.0298). pERC noted that overall survival (OS) is an important outcome to patients and clinicians, and no OS benefit was observed in the POLARIX trial. The HR for OS was 0.94 (95% CI, 0.67 to 1.33), with the upper CI crossing unity. However, the OS analysis was immature due to the limited duration of follow-up.

Patients identified a need for new treatments for LBCL that prolong disease remission, prolong survival, control disease symptoms, normalize blood counts, and improve quality of life so they can participate in daily activities. As described previously, pERC could not conclude that pola-R-CHP would meaningfully prolong remission compared to standard-of-care R-CHOP and an OS benefit compared to R-CHOP was not observed in the POLARIX trial. Furthermore, pERC could not reach definitive conclusions regarding the effects of pola-R-CHP compared to R-CHOP on disease symptoms, normalized blood counts, and health-related quality of life (HRQoL). HRQoL and symptoms were assessed as secondary and exploratory outcomes in the POLARIX trial; there were no differences between the groups treated with pola-R-CHP or R-CHOP for HRQoL, functioning, or key symptoms experienced by patients.

Discussion Points

- The sponsor requested a reconsideration of the initial draft recommendation to not reimburse pola-R-CHP 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. pERC discussed each of the issues identified by the sponsor in their request for reconsideration. pERC also discussed the feedback from patient groups, clinical experts, and clinician groups on the initial draft recommendation.

- During the initial and reconsideration meetings, pERC acknowledged and carefully deliberated on the statistically significant improvement in PFS. pERC noted that PFS may be an important outcome to patients and clinicians, which was reflected in their feedback on the initial draft recommendation. However, the majority of pERC remained uncertain regarding whether the magnitude of the improvement compared to R-CHOP was clinically meaningful. The majority of the committee concluded that there is insufficient evidence that pola-R-CHP will extend survival, provide clinically meaningful improvements in HRQoL for patients living with LBCL, or address the unmet needs identified by stakeholders. pERC recognized the impact of LBCL on patients and their unmet needs; pERC acknowledged the need for improved cure rates from first-line treatment to reduce the rate of relapsed or refractory disease and to avoid the need for salvage treatments.
- pERC noted that OS is an important outcome based on patient and clinician input. Although OS was a key secondary end point in the POLARIX trial, the study was not adequately designed or statistically powered for OS. Key limitations of the OS results were the insufficient number of events observed over the follow-up period of nearly 40 months and that the proportional hazards assumption was likely violated. However, during the reconsideration meeting, pERC acknowledged the challenges of detecting an OS benefit in a first-line LBCL trial due to the length of follow-up required and the results being confounded by subsequent treatments. Overall, pERC was uncertain whether the PFS benefit with pola-R-CHP would translate into a meaningful OS benefit compared to R-CHOP with longer follow-up.
- pERC discussed the potential harms associated with pola-R-CHP, such as infections and myelosuppression (neutropenia, febrile neutropenia, thrombocytopenia, and anemia). The clinical experts expressed concerns about neutropenia of any grade, grade 3 anemia, grade 3 diarrhea, and peripheral neuropathy among patients treated with pola-R-CHP. In addition, the clinical experts noted that, in the POLARIX trial, patients treated with pola-R-CHP had a higher rate of febrile neutropenia and infections than patients treated with R-CHOP, despite the prophylactic use of granulocyte-colony stimulating factor for all patients. However, during the reconsideration meeting, pERC noted that clinicians treating aggressive lymphoma are experienced in the management of toxicities, and the toxicities of concern (diarrhea, peripheral neuropathy, and febrile neutropenia) can be manageable.
- pERC noted that R-CHOP was an appropriate comparator in the POLARIX trial because it is the standard of care for most patients with LBCL in the first-line setting. However, the clinical experts noted that patients with frailty or comorbidities are treated with dose-adjusted CHOP as first-line treatment due to intolerability of adverse events (AEs). pERC noted that the POLARIX trial did not examine different doses of the components to assess potential effects on treatment tolerability.
- pERC noted that the International Prognostic Index (IPI) score is used in clinical practice for prognostic assessment. In the POLARIX trial, there were signals that the PFS benefit was primarily driven by treatment effects among the subgroup of patients with an IPI score of 3 to 5 and without bulky disease, but these findings were from exploratory subgroup analyses and may reflect differences in expected risk of progression among patients with an IPI score of 2 versus those with

a higher score. During the reconsideration meeting, pERC considered whether patients with an IPI score of 3 to 5 may be more likely to benefit from treatment with pola-R-CHP. pERC deliberated on the results from prespecified and post hoc subgroup analyses but noted that these were exploratory and hypothesis-generating only. pERC could not draw definitive conclusions from the subgroup analyses of the POLARIX trial. Furthermore, pERC noted that the evidence submitted was focused on the broader population of patients with previously untreated LBCL; therefore, there was limited information available regarding the efficacy, safety, and cost-effectiveness of pola-R-CHP in specific subgroups. As such, pERC could not make an evidence-based recommendation for a specific subgroup of the population. pERC acknowledged that there could be subgroups of patients that may experience a greater clinical benefit from treatment with pola-R-CHP, but this remains a gap in the evidence.

- During the reconsideration meeting, pERC considered the results from secondary end points, including event-free survival (EFS), disease-free survival, duration of response, and subsequent lymphoma therapies. pERC noted that EFS was ranked below blinded independent committee review (BICR)–assessed complete response (CR) rate at end of treatment (EOT) in the statistical analysis hierarchy until a protocol amendment that moved EFS efficacy above CR. Therefore, the declaration of statistical significance for EFS was a change to the statistical testing hierarchy. The POLARIX trial's preplanned, multiplicity-adjusted analysis did not find a difference between groups for CR; the other response rate and duration of response outcomes were analyzed outside the hierarchy. Therefore, the study does not provide adequate evidence that pola-R-CHP provides a better treatment effect on these outcomes versus R-CHOP. The need for new antilymphoma therapies at the time of updated analysis was numerically lower for pola-R-CHP compared with R-CHOP, but these results were not statistically tested.

Background

Non-Hodgkin lymphoma (NHL) is the fifth most common cancer. An estimated 11,400 people are diagnosed annually in Canada, and approximately 3,000 will die from the disease. DLBCL NOS accounts for approximately 25% of NHL cases, and comprises a heterogeneous group of NHL histologic subtypes, including DLBCL transformed from indolent lymphoma or chronic lymphocytic leukemia, high-grade B-cell lymphoma, primary cutaneous DLBCL, EBV-positive DLBCL, and T-cell/histiocyte-rich LBCL. The risk of DLBCL increases with age, with an average age at diagnosis of 65 years. DLBCL presents as a quickly growing, nonpainful enlarged lymph node in the neck, groin, or abdomen which has a high burden of symptoms, including fever, weight loss, night sweats, and poor HRQoL. According to the clinical experts consulted by CADTH for the review, 50% to 60% of patients with advanced stage disease can be cured with first-line standard-of-care treatment for LBCL in Canada using R-CHOP. However, the clinical experts consulted reported that approximately 30% to 50% of patients will have disease progression or relapse (typically within the first 2 years), especially among high-risk subgroups (e.g., higher IPI score, activated B-cell–like DLBCL, double- or triple-hit lymphoma) with poor prognosis. According to the clinical experts, significant morbidity

exists for patients who experience treatment failure in the first-line setting due to the need for salvage chemotherapy or other treatments that are associated with toxicities and lower cure rates. OS for patients with primary refractory disease is estimated to be 15% to 20% at 5 years.

Pola-R-CHP has been approved by Health Canada for 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.

Sources of Information Used by the Committee

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

- a review of 1 RCT in adult patients with previously untreated LBCL, including DLBCL NOS, high-grade B-cell lymphoma, EBV-positive DLBCL NOS, and T-cell/histiocyte-rich LBCL
- patients' perspectives gathered by 1 patient group, Lymphoma Canada
- input from public drug plans that participate in the CADTH review process
- input from 2 clinical specialists with expertise diagnosing and treating patients with LBCL
- input from 2 clinician groups, including the Ontario Health (Cancer Care Ontario) Hematology Cancer Drug Advisory Committee and a group of hematologists and oncologists in Canada
- a review of the pharmacoeconomic model and report submitted by the sponsor.

Stakeholder Perspectives

The information in this section is a summary of input provided by the patient and clinician groups who responded to CADTH's call for input and from clinical expert(s) consulted by CADTH for the purpose of this review.

Patient Input

One patient group, Lymphoma Canada, submitted input for this review. Lymphoma Canada is a national Canadian registered charity that empowers the lymphoma community through education, support, advocacy, and research. The input was based on an online anonymous patient survey of patients with a subtype of LBCL. The survey was created and promoted by Lymphoma Canada and was available from February 2 to March 13, 2023. A total of 89 respondents were included in the patient input, with 4 confirmed responses for experience with polatuzumab vedotin. Most patients were living in Canada (94%), were between the ages of 55 and 74 (64%) years, were female (58%), and were diagnosed 1 to 5 years ago (61%).

The most reported symptoms at diagnosis among respondents included fatigue, body aches and pains, night sweats, enlarged lymph nodes, and a reduced appetite. The psychosocial impacts of their diagnosis

included stress, anxiety or worry, fear of progression, inability to continue daily activities, and difficulty sleeping. LBCL symptoms impacted respondents' ability to exercise, travel, spend time with family, volunteer, and attend work or school. Most survey respondents received 1 line of treatment for their LBCL, with R-CHOP as the most common treatment regimen. Most patients were satisfied or very satisfied with their options for frontline treatment. When asked about accessing lymphoma therapy in Canada, many patients indicated they were required to travel long distances, which was challenging financially and required time off work. Among the 4 patients with experience with pola-R-CHP, 3 patients would recommend the treatment to other patients with LBCL and 2 patients indicated their overall experience with the treatment was very good. Side effects experienced by at least 2 patients on pola-R-CHP included fatigue, neutropenia, thrombocytopenia, decreased appetite, and diarrhea. According to the patient input received, expectations for new treatments include longer disease remission, controlled disease symptoms, longer survival, normalized blood counts, and improved quality of life to be able to participate in daily activities.

Clinician Input

Input From Clinical Experts Consulted by CADTH

Two clinical experts provided input on the diagnosis and management of LBCL. The clinical experts identified that patients at high risk (IPI score 3 to 5) with advanced age, frailty, or other comorbidities experience poor outcomes due to a greater likelihood of refractory disease or relapse and would benefit from improved cure rates from first-line treatment. The experts reported using polatuzumab vedotin as a combined regimen with bendamustine and rituximab in the relapsed or refractory setting. The clinical experts regarded pola-R-CHP to have a therapeutic role as frontline treatment in treating the underlying DLBCL disease, thereby reducing the need for salvage treatments (e.g., stem cell transplant and/or chimeric antigen receptor T-cell therapy) among patients. Pola-R-CHP was anticipated by the experts to replace R-CHOP for DLBCL for patients with an IPI score of 3 or greater. Its role in patients with an IPI score of 2 is less certain, but it was not considered to fill an unmet need for patients with limited stage disease (IPI score 0 to 1) who typically experience high cure rates with current approaches including R-CHOP. The clinical experts expressed that those patients eligible for pola-R-CHP would also include those with an Eastern Cooperative Oncology Group Performance Status (ECOG PS) score of 3 or 4 with pathological entities who were typically excluded from clinical trials (e.g., LBCL transformed indolent lymphoma, follicular grade 3B). The clinical experts consulted by CADTH reported the following outcomes to be important for patients with DLBCL: CR at EOT as measured by PET and Lugano criteria; PFS, especially at 2 years posttreatment; and OS. According to the clinical experts, response to treatment is assessed using a CT scan after the first 3 or 4 cycles of therapy to identify responders, and PET at EOT to determine remission or CR. CR maintained for 2 years was considered by the clinical experts to demonstrate cure. The experts indicated that treatment discontinuation should be considered when there is a lack of efficacy (i.e., no response or disease progression despite treatment) or unacceptable toxicity (e.g., severe AEs), and emphasized regular monitoring of patients with supportive care in balancing the benefits versus harms of therapy. The clinical experts consulted by CADTH reported that specialists with experience treating patients with lymphoma could provide care and management of patients with DLBCL, including hematologists or oncologists.

Clinician Group Input

Clinician input was received from 2 groups: the Ontario Health (Cancer Care Ontario) Hematology Cancer Drug Advisory Committee, comprised of 7 clinicians, and a group of Canadian hematologists and oncologists who treat DLBCL, comprised of 55 clinicians. Input from the clinician groups was generally aligned with the clinical experts consulted by CADTH. As highlighted by the clinical experts consulted by CADTH, the clinician groups noted that there remains a significant unmet need to improve the cure rate for patients with DLBCL with first-line therapy to reduce the high rate of relapsed or refractory disease, thereby improving outcomes and reducing the need for patients to proceed to more toxic secondary options. The clinician groups stated that pola-R-CHP is an alternative to R-CHOP for patients with previously untreated DLBCL with an IPI score of 2 to 5, echoing the input of the clinical experts consulted by CADTH for the review. Outcomes used to assess patient response to treatment include PFS, which is a clinically meaningful end point that is used in clinical practice, as well as PFS at 2 years because most progressions or relapses will occur within this time frame. Their input stated that response during therapy is typically monitored by CT scan; after treatment, patients are assessed by both CT scan and PET scan. This differed slightly according to the clinical experts consulted by CADTH who indicated posttreatment assessment should be conducted by PET scan. After therapy, the clinician groups and clinical experts consulted by CADTH both reported that patients are typically monitored clinically every 3 months for 2 years, then every 6 to 12 months for evidence of progression. Disease progression or AEs were indicated as the primary reasons to discontinue treatment with the drug under review. The clinician groups also noted that treatment with pola-R-CHP has a similar safety profile as R-CHOP, and it is anticipated that it can be safely administered in similar settings as R-CHOP. However, this opinion was not shared by the clinical experts consulted by CADTH, who highlighted concerns with greater toxicity with pola-R-CHP treatment. In general, pola-R-CHP is an outpatient systemic therapy that can be routinely administered by physicians with experience in oncology therapy (typically hematologists or oncologists).

Drug Program Input

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

- considerations for initiation 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 by CADTH provided advice on the potential implementation issues raised by the drug programs.

Clinical Evidence

Pivotal Studies and RCT Evidence

Description of Studies

One phase III, multicentre, randomized, double-blind, placebo-controlled trial (Study GO39942 or POLARIX; N = 879) assessed the efficacy and safety of polatuzumab vedotin 1.8 mg/kg intravenously in combination with R-CHP (pola-R-CHP) in first-line treatment compared with standard-of-care R-CHOP in the 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. Outcomes identified to be important to patients and most relevant for clinicians included OS, PFS, CR, objective response rate (ORR), and patient-reported outcomes . PFS as assessed by the investigator was the primary outcome in the POLARIX trial, and OS and CR at EOT as assessed by BICR were key secondary outcomes. Additional secondary efficacy outcomes included CR at EOT assessed by the investigator and ORR assessed by BICR and by the investigator. HRQoL was evaluated as secondary outcomes, using time to deterioration and responder analyses for the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC QLQ-C30) physical functioning and fatigue scales, and for the Functional Assessment of Cancer Therapy – Lymphoma (FACT-Lym) Lymphoma Subscale, and assessed using rate of peripheral neuropathy on the FACT/Gynecologic Oncology Group-Neurotoxicity (FACT/GOG-NTX). Treatment-emergent AEs, serious AEs (SAEs), withdrawals due to AEs, and deaths were reported in the POLARIX trial.

The POLARIX trial included 7 sites in Canada. All patients enrolled had CD20-positive DLBCL, an IPI score of 2 to 5, an ECOG PS score of 0 to 2 (84% with score of 0 to 1), and a life expectancy of 12 months or greater. Most patients were male (53.8%) and white (53.6%), with a median study population age of 65 years. Most patients had advanced Ann Arbor stage III to IV disease (88.7%), and baseline lactate dehydrogenase greater than 1 × upper limit of normal (65.4%) at diagnosis. Patients were similar between treatment groups in stratification factors used for randomization (IPI score, bulky disease, and geographical region) and baseline characteristics. All patients in the safety population had at least 1 medical history condition, with similar proportions of patients between groups for the most common conditions.

Efficacy Results

The analysis population for primary and secondary efficacy analyses consisted of the intention-to-treat population (i.e., all randomized patients regardless of treatment received). The analysis population for HRQoL included the patient-reported outcome–evaluable population (i.e., all randomized patients with a baseline and at least 1 postbaseline assessment). The primary analysis included patients followed up to the clinical cut-off date (CCOD) of June 28, 2021, for all efficacy and HRQoL outcomes. The updated analysis followed patients to the CCOD of June 15, 2022, for OS and PFS.

Overall Survival

OS, defined as time from randomization to date of death from any cause, was included in the hierarchical testing procedure as a key secondary end point. At the final analysis (CCOD of June 15, 2022), a total of 131 OS events were observed after a median survival follow-up of 39.7 months and 39.6 months for the pola-R-

CHP and R-CHOP groups, respectively (64 events [14.5%] and 67 events [15.3%], respectively). The stratified HR was 0.94 (95% CI, 0.67 to 1.33; P = 0.7326). OS rates for the pola-R-CHP and R-CHOP groups were 92.2% and 94.6%, respectively, at 12 months and were 88.7% and 88.6%, respectively, at 24 months.

Progression-Free Survival

The primary study end point in the POLARIX trial was PFS, defined as the time from randomization to the first occurrence of disease progression or relapse as assessed by the investigator using the Lugano Response Criteria for Malignant Lymphoma or death from any cause, whichever occurred earlier. At the updated analysis with a CCOD of June 15, 2022, median follow-up time for PFS was 30.9 months (range, 0 to 46 months) and 30.8 months (range, 0 to 54 months) in the pola-R-CHP and R-CHOP groups, respectively. At this analysis, 118 (26.8%) patients had disease progression or died in the pola-R-CHP group versus 143 (32.6%) patients in the R-CHOP group (stratified HR = 0.76; 95% CI, 0.60 to 0.97; P = 0.0298).

Subgroup Analyses

Subgroup analyses of PFS were exploratory in the POLARIX study, and the CADTH review focused on the subgroups of IPI score, bulky disease, and DLBCL subtype. Subgroup analysis suggested benefit with pola-R-CHP treatment compared with R-CHOP among patients with IPI scores of 3 to 5 (unstratified HR = 0.71; 95% CI, 0.53 to 0.95) and without bulky disease (unstratified HR = 0.59; 95% CI, 0.42 to 0.83). Unstratified investigator-assessed PFS subgroup analysis by baseline molecular DLBCL subtypes included centrally tested cell of origin, centrally tested immunohistochemistry for BCL2 and MYC (double expressor lymphoma), and centrally tested FISH for rearrangements in MYC, BCL2, and BCL6 (double-hit lymphoma or triple-hit lymphoma), suggesting that treatment with pola-R-CHP compared with R-CHOP was associated with better PFS among patients in higher-risk subgroups: the activated B-cell–like DLBCL subgroup (84.7% versus 56.1%; HR = 0.34; 95% CI, 0.21 to 0.56) and the double expressor lymphoma subgroup (75.8% versus 63.1%; HR = 0.63; 95% CI, 0.42 to 0.94).

Based on the subgroup results for PFS among those with an IPI score of 3 to 5 and no bulky disease, the Health Canada reviewers requested the sponsor conduct additional subgroup analyses to examine the subgroups of patients with DLBCL who have an IPI score of 3 to 5 and no bulky disease. The results suggested that pola-R-CHP may have a greater PFS benefit compared with R-CHOP in this subgroup (unstratified HR = 0.40; 95% CI, 0.25 to 0.63). Although concrete conclusions cannot be drawn on the results of these analyses, there is a signal that the benefit of treatment with pola-R-CHP may be greatest in those with an IPI score of 3 to 5 and no bulky disease.

CR Rate at End of Treatment (PET-CT by BICR and Investigator)

CR rate at EOT assessed using PET-CT by BICR was a key secondary end point included in the statistical testing hierarchy. At EOT, BICR-assessed CR rate was 78.0% for pola-R-CHP (95% CI, 73.79% to 81.74%) versus 74.0% for R-CHOP (95% CI, 69.66% to 78.07%; difference = 3.9%; 95% CI, –1.9% to 9.7%).

CR rate at EOT assessed using PET-CT by investigator assessment was a secondary efficacy end point that was not adjusted for multiplicity. Investigator-assessed CR rates at EOT were 75.0% for pola-R-CHP versus 72.2% for R-CHOP (difference = 2.79%; 95% CI, –3.20% to 8.75%; P = 0.3402).

ORR at End of Treatment (PET-CT by BICR and Investigator)

ORR at EOT assessed using PET-CT by BICR and by investigator were secondary efficacy end points that were not adjusted for multiplicity. BICR-assessed ORR (i.e., partial response or CR) at EOT was 85.5% in the pola-R-CHP group versus 83.8% in the R-CHOP group (difference = 1.63%; 95% CI, −3.32% to 6.57%; P = 0.4828). Investigator-assessed ORR at EOT was 84.5% in the pola-R-CHP group versus 80.9% in the R-CHOP group (difference = 3.68%; 95% CI, −1.49% to 8.84%; P = 0.1345).

Health-Related Quality of Life

HRQoL was assessed as the following secondary end points without adjustment for multiplicity: time to deterioration in the EORTC QLQ-C30 physical functioning (≥ 10-point decrease) and fatigue (≥ 10-point increase), FACT-Lym Lymphoma Subscale (≥ 3-point decrease), and FACT/GOG-NTX; the proportion of patients in each treatment group who achieved clinically meaningful improvement in EORTC QLQ-C30 physical functioning (≥ 7-point increase) and fatigue (≥ 9-point decrease) , and FACT-Lym Lymphoma Subscale (≥ 3-point increase); and a comparison of EORTC QLQ-C30 treatment-related symptoms and FACT/GOG-NTX peripheral neuropathy between the 2 treatment groups. There were no clear differences between the treatment groups for these outcomes.

Harms Results

The analysis population for harms included all patients who received at least 1 dose of any study treatment component, with patients grouped according to the treatment received. Patients were followed for harms to the updated analysis (CCOD of June 15, 2022).

Most patients in the POLARIX study reported at least 1 AE (97.9% in pola-R-CHP group versus 98.4% in R-CHOP group). The most commonly reported AEs in the pola-R-CHP and R-CHOP groups were nausea (41.6% and 36.8%, respectively), constipation (28.7% and 29.2%, respectively), fatigue (25.7% and 26.5%, respectively), diarrhea (31% and 20.1%, respectively), and alopecia (24.4% and 24.0%, respectively).

The percentage of patients who experienced at least 1 SAE was 34.0% in the pola-R-CHP group and 30.6% in the R-CHOP group. The most common SAEs in the pola-R-CHP and R-CHOP groups were febrile neutropenia (9.9% and 6.4%, respectively), pneumonia (4.1% and 3.9%, respectively), diarrhea (2.3% and 0.5%, respectively), and pyrexia (1.6% and 1.8%, respectively).

The percentage of patients who experienced at least 1 AE that led to withdrawal of any study medication was 6.0% in the pola-R-CHP group and 6.4% in the R-CHOP group. The most common AEs that led to withdrawal of any study medication were infections (1.6% in pola-R-CHP group versus 2.3% in R-CHOP group) and nervous system disorders (0.7% in pola-R-CHP group versus 2.5% in R-CHOP group).

A total of 133 (15.2%) deaths occurred in the POLARIX trial, with similar proportions between the pola-R-CHP and R-CHOP groups (14.7% and 15.8%, respectively). The primary cause of death among cases in the pola-R-CHP and R-CHOP groups were disease progression (7.8% and 8.0% of patients, respectively) and AEs (3.0% and 2.5% of patients, respectively).

Notable harms identified in the CADTH review included peripheral neuropathy, infections, neutropenia, anemia, thrombocytopenia, infusion-related reactions, hepatic toxicities, tumour lysis syndrome, and progressive multifocal leukoencephalopathy. The proportion of patients who experienced peripheral neuropathy was 52.9% and 53.9% in the pola-R-CHP and R-CHOP groups, respectively. A higher proportion of patients in the pola-R-CHP group compared with the R-CHOP group experienced infections (49.7% versus 42.7%), neutropenia including febrile neutropenia (46.0% versus 42.9%), and hepatic toxicity (10.6% versus 7.5%). Similar proportions of patients in the pola-R-CHP and R-CHOP groups experienced anemia (28.7% versus 27.2%) and thrombocytopenia (13.3% versus 13.5%). The proportion of patients who reported infusion-related reactions was 13.3% and 16.0% in the pola-R-CHP and R-CHOP groups, respectively. Tumour lysis syndrome was reported by 2 patients (0.5%) and 4 patients (0.9%) in the pola-R-CHP and R-CHOP groups, respectively. No patients reported experiencing progressive multifocal leukoencephalopathy in the POLARIX trial.

Critical Appraisal

POLARIX was a phase III, double-blind, placebo-controlled trial. There was low risk of bias for objective and subjective outcome assessments due to the blinded study design. Between-group proportions were similar in stratification factors for IPI score (2 versus 3 to 5), bulky disease, and geographical region, as well as other baseline demographics and disease characteristics; therefore, the risk of selection bias from inappropriate randomization and allocation concealment was determined to be low. Few protocol deviations occurred to impact study conduct, assessments, or findings. There was a relatively high rate of discontinuations from the study (19.1%) with most losses due to deaths, which was similar between treatment groups. The large reduction in sample size makes it difficult to adequately assess the treatment effects on important outcomes such as PFS and HRQoL. A hierarchical gatekeeping approach was used to account for multiplicity for the primary efficacy outcome (PFS) and key secondary end points (OS and BICR-assessed CR rate). Analyses of additional secondary end points, such as investigator-assessed CR rate, ORR, or HRQoL, were not adjusted for multiplicity; therefore, results for these end points are at increased risk of type I error. OS results were limited by the low number of events observed, relatively short duration of follow-up at the final analysis, and likely violation of the proportional hazards assumption. Most patients were censored for PFS because no progression event or death was recorded at the CCOD. Subgroup analyses were exploratory. HRQoL outcomes were not adjusted for multiplicity, and a high proportion of patients were lost to follow-up for HRQoL assessments at 24 months and later time points without adequate imputation of missing data.

The efficacy end points evaluated in the POLARIX trial were aligned with treatment outcomes important to patients and of relevance in clinical practice as per the clinical experts consulted by CADTH, including PFS, OS, and CR rate. Although the population enrolled in the POLARIX trial was reported by the clinical experts to be representative of patients with DLBCL who they would consider eligible for pola-R-CHP treatment, there were limitations with the representativeness of the study population. Patients with an ECOG PS score of 3 or 4, transformed indolent lymphoma, or with follicular lymphoma grade 3B were excluded from the POLARIX trial but would be considered eligible for treatment in current practice, as per the clinical experts. The clinical experts believed that higher-risk patients (IPI score 3 to 5) who typically experience poor outcomes with standard-of-care R-CHOP are more likely to benefit from treatment with pola-R-CHP. There

was uncertainty of benefit among patients with an IPI score of 2 based on subgroup analyses, and those with an IPI score of 0 or 1 were excluded from the POLARIX trial. Standard-of-care R-CHOP is not routinely used in patients with specific molecular characteristics (e.g., double- or triple-hit lymphoma); other first-line approaches are preferred for these patients in Canada (e.g., dose-adjusted etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin, and rituximab [DA-EPOCH-R]). Moreover, patients with advanced age and/or frailty or with comorbidities are more likely to experience intolerability of R-CHOP, which would require dose adjustments or alternative treatments, because there is a lack of evidence from the POLARIX trial for treatment with pola-R-CHP in these patients. PFS may be an acceptable surrogate for OS in DLBCL, although the strength of the correlation with OS beyond 5 years is uncertain. Nonetheless, the clinical experts considered PFS at 24 months to be a reasonable outcome for assessing the effects of pola-R-CHP because most disease progression or relapses occur before this time point. However, there was uncertainty regarding whether the between-group difference in PFS observed in the POLARIX trial is clinically meaningful overall or at specific time points.

Long-Term Extension Studies

No long-term extension studies were submitted by the sponsor.

Indirect Evidence

No indirect treatment comparisons were submitted by the sponsor.

Studies Addressing Gaps in the Pivotal and RCT Evidence

No additional studies addressing important gaps in the systematic review evidence were submitted by the sponsor.

Economic Evidence

Cost and Cost-Effectiveness

Table 2: Summary of Economic Evaluation

Component	Description
Type of economic evaluation	Cost-utility analysis Partitioned survival model (PSM)
Target populations	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.
Treatment	Polatuzumab vedotin in combination with rituximab, cyclophosphamide, doxorubicin, and prednisone (pola-R-CHP)
Dose regimen	1.8 mg/kg intravenously of polatuzumab vedotin on day 1 every 21 days for up to 6 cycles
Submitted price	30 mg vial: $3,160.71 140 mg vial: $14,750.00

Component	Description
Treatment cost	$19,666.67 per 28-day cycle, assuming a patient weight of 75.92 kg and BSA of 1.86 m^2 In combination with R-CHP: $23,480.41 per 28-day cycle
Comparator	Rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP)
Perspective	Canadian publicly funded health care payer
Outcomes	QALYs, life-years
Time horizon	Lifetime (60 years)
Key data sources	POLARIX trial to inform PFS and OS for pola-R-CHP vs. R-CHOP GOYA trial extension used to support long-term extrapolation of PFS
Key limitations	• The clinical meaningfulness of the magnitude of benefit of pola-R-CHP on PFS from the trial, and whether it would be maintained long term, was noted to be uncertain in CADTH's clinical review. Further uncertainty was identified with the submitted model's estimates of PFS gains over the modelled lifetime time horizon, as they were likely inaccurately estimated due to the use of external data (from the GOYA trial) and due to the use of KM data directly in the model to inform PFS. • There was no OS benefit observed in the available follow-up period in the POLARIX trial with pola-R-CHP; however, the submitted model estimated an OS benefit with pola-R-CHP which is uncertain. The OS benefit observed in the model was driven by sponsor assumptions and methodological choices, including the uncertain use of PFS gains to inform OS gains, OS benefits related to the use of curative subsequent therapies likely not being captured, the assumption of an indefinite treatment benefit of pola-R-CHP on OS, and the chosen time point up until which KM data for OS from the trial is applied directly in the model. • The sponsor used a PSM to estimate costs and outcomes associated with first-line treatment for LBCL; however, this approach was not suitable for this decision problem where the primary goal of first-line and subsequent treatments is curative. The choice of model structure captures the cost of subsequent therapies but not the health outcomes (i.e., improvements in OS) for patients receiving curative subsequent therapies. This results in the overestimation of the incremental benefit for patients receiving pola-R-CHP in the sponsor's base-case analysis given more patients receiving R-CHOP are estimated to have progressed disease. • In the submitted model, subsequent therapy assumptions were not reflective of Canadian clinical practice: the sponsor assumed that there would be differences in the number and distribution of subsequent therapies received dictated by the first-line treatment received. Clinical experts consulted by CADTH indicated that at the time of disease progression, the number and distribution of subsequent therapies is not dependent on first-line therapy received, and thus would be similar for both treatment groups. • The assumption of perfect vial sharing (no wastage) was inappropriate because the product monograph indicates that vials are intended for single-use only and to discard excess medication.
CADTH reanalysis results	• To account for the key limitations, several changes were made to derive the CADTH base case, which included removal of the GOYA extension data and use of the full parametric survival curve for PFS, adjustments to OS KM data cut-off points and treatment effect duration, modifications to subsequent therapy use, and changes to assumptions about vial sharing and administration times. • CADTH was unable to address issues related to the model structure, the generalizability to other patient populations of interest (e.g., IPI 0 to 1) and the exclusion of appropriate comparators. • ICER = $394,163 per QALY gained (0.19 incremental QALYs; $76,379 incremental cost) for pola-R-CHP vs. R-CHOP in the CADTH base case. • A price reduction of at least 66% for polatuzumab vedotin (i.e., a price less than $5,015 per 21-day cycle) would be required for pola-R-CHP to be cost-effective at a $50,000 per QALY gained threshold.

BSA = body surface area; DLBCL = diffuse large B-cell lymphoma; ICER = incremental cost-effectiveness ratio; LBCL = large B-cell lymphoma; KM = Kaplan-Meier; NOS = not otherwise specified; OS = overall survival; pola-R-CHP = polatuzumab vedotin + rituximab + cyclophosphamide + doxorubicin + prednisone; PFS = progression-free survival; PSM = partitioned survival model; QALY = quality-adjusted life-year; R-CHOP = rituximab + cyclophosphamide + doxorubicin + vincristine + prednisone.

Budget Impact

CADTH identified the following key limitations with the sponsor's analysis: the market shares for pola-R-CHP were likely underestimated for patients with IPI scores of 2 to 5, the subsequent therapy assumptions were not reflective of Canadian clinical practice, and the assumption of perfect vial sharing is inappropriate. The CADTH reanalysis revised the market uptake for patients with IPI scores of 2 to 5, aligned the number and distribution of subsequent therapies with Canadian clinical practice, and accounted for drug wastage. Based on the CADTH reanalysis, the 3-year budget impact to the public drug plans of introducing pola-R-CHP 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 is expected to be $412,920,515 (year 1: $80,865,544; year 2: $164,205,857; year 3: $167,849,115).

Request for Reconsideration

The sponsor filed a request for reconsideration for the draft recommendation to not reimburse polatuzumab vedotin in combination with R-CHP 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. In their request, the sponsor identified the following issues:

- The sponsor highlighted that PFS is a clinically meaningful primary end point to patients with DLBCL and is used in clinical practice. The sponsor requested that patient and clinician group input regarding the meaningfulness of PFS as an end point be considered during the reconsideration meeting.
- The sponsor noted that the initial recommendation indicated there was uncertainty in the clinical meaningfulness of the magnitude of PFS benefit observed in the POLARIX trial. The sponsor requested clarity regarding pERC's uncertainty in whether the magnitude of the PFS benefit was clinically meaningful, particularly in light of clinician group input that supports pola-R-CHP as a frontline treatment for patients with DLBCL.
- The sponsor outlined results from secondary end points (EFS, disease-free survival, DOR, and subsequent lymphoma therapies) that should be considered by pERC because the sponsor indicated they support the clinical benefit of pola-R-CHP on PFS in demonstrating sustained remission.
- The sponsor noted that the initial recommendation from pERC highlighted the increased toxicity of pola-R-CHP. The sponsor requested that contextual information related to safety be added to include clinician group input and global quality of life during treatment.
- The sponsor requested a positive recommendation for patients who can benefit from treatment with pola-R-CHP. Although the sponsor stated there is a clinical benefit of pola-R-CHP among patients with an IPI score of 2 to 5 as per the POLARIX trial population, they acknowledged that patients with an IPI score of 3 to 5 are considered at high risk for disease progression or relapse and could potentially benefit the most from treatment with pola-R-CHP based on input from clinical experts.

In the meeting to discuss the sponsor's request for reconsideration, the committee considered the following information:

- feedback on the draft recommendation from the sponsor
- information from the initial submission relating to the issues identified by the sponsor
- feedback from 2 clinical specialists with expertise in diagnosing and treating patients with LBCL
- feedback on the draft recommendation from 2 patient groups: Lymphoma Canada and the Leukemia & Lymphoma Society of Canada
- feedback on the draft recommendation from 2 clinician groups: the Ontario Health (Cancer Care Ontario) Hematology Cancer Drug Advisory Committee and a group of hematologists and oncologists in Canada
- feedback on the draft recommendation from the public drug plans.

pERC Information

Members of the Committee at the Initial Meeting

Dr. Maureen Trudeau (Chair), Mr. Daryl Bell, Dr. Jennifer Bell, Dr. Matthew Cheung; Dr. Winson Cheung, Dr. Michael Crump, Dr. Leela John, Dr. Christian Kollmannsberger, Mr. Cameron Lane, Dr. Christopher Longo, Dr. Catherine Moltzan, Ms. Amy Peasgood, Dr. Anca Prica, Dr. Adam Raymakers, Dr. Patricia Tang, Dr. Marianne Taylor, and Dr. W. Dominika Wranik.

Initial meeting date: August 9, 2023

Regrets: Three expert committee members did not attend.

Conflicts of interest: None

Members of the Committee at the Reconsideration Meeting

Dr. Maureen Trudeau (Chair), Mr. Daryl Bell, Dr. Jennifer Bell, Dr. Phillip Blanchette, Dr. Kelvin Chan, Dr. Matthew Cheung, Dr. Michael Crump, Dr. Jennifer Fishman, Mr. Terry Hawrysh, Dr. Yoo-Joung Ko, Dr. Christian Kollmannsberger, Dr. Catherine Moltzan, Ms. Amy Peasgood, Dr. Anca Prica, Dr. Adam Raymakers, Dr. Patricia Tang, Dr. Marianne Taylor, and Dr. W. Dominika Wranik.

Reconsideration meeting date: December 6, 2023

Regrets: None

Conflicts of interest: One expert committee member did not participate due to considerations of conflict of interest.

ISSN: 2563-6596

Funding: CADTH receives funding from Canada's federal, provincial, and territorial governments, with the exception of Quebec.