CADTH

CADTH Reimbursement Review

CADTH Reimbursement Recommendation

(Draft)

Polatuzumab vedotin (Polivy)

Indication: Large B-cell lymphoma

Sponsor: Hoffmann-La Roche Ltd.

Recommendation: Do Not Reimburse

Version: 1.0
Publication Date: August 2023
Report Length: 13 Pages

Single Technology

Redactions: Confidential information in this document may be redacted at the request of the sponsor in accordance with the *CADTH Drug Reimbursement Review Confidentiality Guidelines*.

About CADTH: CADTH is an independent, not-for-profit organization responsible for providing Canada's health care decision-makers with objective evidence to help make informed decisions about the optimal use of drugs, medical devices, diagnostics, and procedures in our health care system.

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

Recommendation

The CADTH pCODR 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-positive (EBV+) DLBCL NOS, and T-cell/histiocyte rich LBCL.

Rationale for the Recommendation

One phase III, multicentre, randomized controlled trial (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% 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% confidence interval [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, and a key limitation for the OS results was the insufficient number of events observed.

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 above, 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 pola-R-CHP and R-CHOP groups for HRQoL, functioning, or key symptoms experienced by patients.

Discussion Points

- Although pERC acknowledged and carefully deliberated on the statistically significant improvement in PFS, they remained uncertain whether the magnitude of the improvement compared to R-CHOP was clinically meaningful. A 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/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. 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). 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, clinical experts noted that patients treated with pola-R-CHP had a higher rate of febrile neutropenia and infections than patients treated with R-CHOP, despite the POLARIX trial having employed granulocyte-colony stimulating factor (G-CSF) prophylaxis for all patients.
- pERC noted that R-CHOP was an appropriate comparator in the POLARIX trial since 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 (R-mini-CHOP) as first-line treatment due to intolerability of AEs. pERC noted that POLARIX trial did not examine different doses of the components to assess potential effects on treatment tolerability.
- pERC noted that the 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 higher.

Background

Non-Hodgkin lymphoma (NHL) is the fifth most common cancer, with an estimated 11,400 people diagnosed annually in Canada, and about 3,000 will die from the disease. Diffuse large B-cell lymphoma (DLBCL) not otherwise specified (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, Epstein-Barr virus positive (EBV+) DLBCL, and T-cell histiocyte-rich large B-cell lymphoma (LBCL). The risk of DLBCL increases with age, with an average age at diagnosis of 65 years. DLBCL presents as a quickly growing, non-painful enlarged lymph node in the neck, groin, or abdomen with high burden of symptoms including fever, weight loss, and night sweats, and poor health-related quality of life (HRQoL). According to the clinical experts consulted by CADTH for the review, nearly 50% to 60% of patients with advanced stage disease can be cured with first-line standard of care (SOC) treatment for LBCL in Canada using rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone (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 International Prognostic Index [IPI] score, ABC, DHL/THL) 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. Overall survival (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+ 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+ 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 among patients with a subtype of LBCL, created and promoted by Lymphoma Canada, 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%), between the age of 55 and 74 (64%), female (58%), and were diagnosed 1 to 5 years ago (61%).

The most reported symptoms at diagnosis among respondents included fatigue, bodily 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 one 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 LBCL patients 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, control 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 front-line treatment in treating the underlying DLBCL disease, thereby reducing the need for salvage treatments (e.g., stem cell transplant and/or chimeric antigen receptors T [CAR-T] therapy) among patients. Pola-R-CHP was anticipated by the experts to replace R-CHOP for DLBCL for patients with IPI score of 3 and 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 these patients eligible for pola-R-CHP would also include those with an ECOG PS 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: complete response (CR) at the end of treatment (EOT) as measured by PET and Lugano criteria, progression-free survival (PFS) especially at 2 years post-treatment, 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 the 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 adverse events), 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 treating 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/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, as most progressions or relapses will occur within this time frame. The input stated that the response during therapy is typically monitored by CT scan, and post-treatment patients are assessed by both CT scan and PET scan. This differed slightly according to the clinical experts consulted by CADTH who indicated post-treatment assessment to be conducted by PET scan. Post-therapy, clinician groups and the clinical experts consulted by CADTH alike 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 adverse events 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 to R-CHOP and it is anticipated that it can be safely administered in similar settings as R-CHOP. However, this opinion was not shared by the clinical experts consulted by CADTH, who highlighted concerns with greater toxicity with pola-R-CHP treatment. In general, pola-R-CHP is an out-patient systemic therapy that can be routinely administered by physicians with experience in oncology therapy (typically hematologists or oncologists).

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, multi-centre, 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 (IV) in combination with R-CHP (pola-R-CHP) compared with SOC in first-line treatment comprising R-CHOP in the treatment of adults with previously untreated LBCL, including DLBCL NOS, high-grade B-cell lymphoma, EBV+ 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 (PROs). PFS as assessed by the investigator was the primary outcome in the POLARIX trial, and OS and CR at EOT as assessed by blinded independent review committee (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, assessed using time to deterioration (TTD) and responder analyses for the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Cancer 30 (EORTC QLQ-C30) physical functioning and fatigue scales, and for the Functional Assessment of Cancer Therapy – Lymphoma Lymphoma subscale (FACT-Lym LymS), and assessed using rate of peripheral neuropathy on the Functional Assessment of Cancer Treatment/Gynecologic Oncology Group-Neurotoxicity (FACT/GOG-NTX). Treatment-emergent adverse events (TEAEs), serious adverse events (SAEs), withdrawals due to adverse events (WDAEs), and deaths were reported in POLARIX.

POLARIX included 7 sites in Canada. All patients enrolled had CD20-positive DLBCL, IPI score of 2 to 5, Eastern Co-operative Oncology Group Performance Status (ECOG PS) 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 (88.7%), and baseline lactate dehydrogenase > 1x ULN (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 between groups for the most common conditions.

Efficacy Results

The analysis population for primary and secondary efficacy analyses consisted of the intention-to-treat (ITT) population (i.e., all randomized patients regardless of treatment received). The analysis population for HRQoL included the PRO-evaluable population (i.e., all randomized patients with a baseline and at least 1 post-baseline 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.

OS

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 hazard ratio (HR) was 0.94 (95% confidence interval [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 88.7% and 88.6%, respectively at 24 months.

PFS

The primary study end point in POLARIX 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) and 30.8 months (range, 0 to 54) 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 score 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 (COO), centrally tested IHC for BCL2 and MYC (double expressor lymphoma [DEL]), and centrally tested FISH for rearrangements in MYC, BCL2, and BCL6 (double-hit lymphoma/triple hit lymphoma [DHL/THL]), suggesting that treatment with pola-R-CHP compared with R-CHOP was associated with better PFS among patients in higher-risk subgroups: activated B-cell like DLBCL (ABC-DLBCL) subgroup (84.7% versus 56.1%; HR = 0.34; 95% CI, 0.21 to 0.56), and DEL 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 IPI score 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). While 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 most noticed in those with an IPI score of 3 to 5 and no bulky disease.

CR rate at EOT (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 the 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 EOT (PET-CT, by BICR and by 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 [PR] 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).

HRQoL

HRQoL was assessed as the following secondary end points without adjustment for multiplicity: TTD in the EORTC QLQ-C30 physical functioning (10-point decrease or greater) and fatigue (10-point increase or greater), FACT-Lym LymS (3-point decrease or greater), and FACT-GOG-NTX; proportion of patients in each treatment group achieving clinically meaningful improvement in EORTC QLQ-C30 physical functioning (7-point increase or greater) and fatigue (9-point decrease or greater), and FACT-Lym LymS (3-point increase or greater); and a comparison of EORTC QLQ-C30 treatment-related symptoms and FACT/GOG-NTX peripheral neuropathy between the two 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 adverse event (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 versus R-CHOP groups were nausea (41.6% versus 36.8%, respectively), constipation (28.7% versus 29.2%, respectively), fatigue (25.7% versus 26.5%, respectively), diarrhea (31% versus 20.1%, respectively), and alopecia (24.4% versus 24.0%, respectively).

The percentage of patients who experienced at least 1 serious adverse event (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% versus 6.4%, respectively), pneumonia (4.1% versus 3.9%, respectively), diarrhea (2.3% versus 0.5%, respectively), and pyrexia (1.6% versus 1.8%, respectively).

The percentage of patients who experienced at least one 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 POLARIX, 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 adverse events (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 (IRRs), hepatic toxicities, Tumor Lysis Syndrome (TLS), and Progressive Multifocal Leukoencephalopathy (PML). 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 IRRs was 13.3% and 16.0% in the pola-R-CHP and R-CHOP groups, respectively. TLS was reported by 2 patients (0.5%) and 4 patients (0.9%) in the pola-R-CHP and R-CHOP groups, respectively. No patient reported experiencing PML 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 1 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 clinical cut-off date. 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. While the population enrolled in POLARIX were 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 ECOG PS 3 or 4, transformed indolent lymphoma, or with follicular lymphoma Grade 3B, were excluded from POLARIX but considered to be 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 SOC R-CHOP are more likely to benefit from treatment with pola-R-CHP. There was uncertainty of benefit among patients with IPI score of 2 based on subgroup analyses, and those with IPI score of 0 to 1 were excluded from POLARIX. SOC R-CHOP is not routinely used in patients with specific molecular characteristics (e.g., DHL or THL) as 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 comorbidities are more likely to experience intolerability of R-CHOP requiring dose adjustments or alternative treatments, since there is a lack of evidence from POLARIX for treatment with pola-R-CHP in these patients. PFS may be an acceptable surrogate for OS in DLBCL, though 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 and 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 1. Summary of Economic Evaluation

Component	Description
Type of economic evaluation	Cost-utility analysis Partitioned survival model (PSM)
Target populations	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.
Treatment	Polatuzumab vedotin in combination with rituximab, cyclophosphamide, doxorubicin, and prednisone (Pola-R-CHP)
Dose Regimen	1.8 mg/kg intravenously (IV) 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
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, LYs
Time horizon	Lifetime (60 years)
Key data sources	POLARIX trial to inform progression-free survival (PFS) and overall survival (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 modeled 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, as the product monograph indicates that vials are intended for single use only and to discard excess medication.

Component	Description
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 0-1) 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; LY = life-year; 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 2-5; the subsequent therapy assumptions were not reflective of Canadian clinical practice; the assumption of perfect vial sharing is inappropriate. The CADTH reanalysis revised the market uptake for patients with IPI 2-5, aligned the number and distribution of subsequent therapies with Canadian clinical practice, and accounted for drug wastage. Based on the CADTH reanalysis, the three-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+ 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).

pERC Information

Members of the Committee:

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. Catherine Moltzan, Ms. Amy Peasgood, Dr. Anca Prica, Dr. Adam Raymakers, Dr. Patricia Tang, Dr. Marianne Taylor, and Dr. W. Dominika Wranik.

Meeting date: August 9, 2023

Regrets:

Three expert committee members did not attend.

Conflicts of interest:

None