



CADTH Reimbursement Recommendation

Glofitamab (Columvi)

Indication: For the treatment of adult patients with relapsed or refractory DLBCL not otherwise specified, trFL, or PMBCL, who have received 2 or more lines of systemic therapy and are ineligible to receive or cannot receive CAR-T cell therapy or have previously received CAR-T cell therapy

Sponsor: Hoffmann-La Roche Limited

Final recommendation: Reimburse with conditions



Summary

What Is the CADTH Reimbursement Recommendation for Columvi?

CADTH recommends that Columvi be reimbursed by public drug plans for the treatment of adult patients with relapsed or refractory (R/R) diffuse large B-cell lymphoma (DLBCL) not otherwise specified, DLBCL arising from follicular lymphoma (trFL), or primary mediastinal B-cell lymphoma (PMBCL), who have received 2 or more lines of systemic therapy and are ineligible to receive or cannot receive CAR-T-cell therapy or have previously received CAR-T-cell therapy if certain conditions are met.

Which Patients Are Eligible for Coverage?

Columvi should only be covered to treat adult patients who have DLBCL not otherwise specified, trFL, or PMBCL that has come back or that did not respond to 2 or more previous treatments for their cancer, and who have also previously received CAR-T-cell therapy, declined CAR-T-cell therapy, or cannot receive CAR-T-cell therapy.

What Are the Conditions for Reimbursement?

Columvi should only be reimbursed for a maximum of 12 treatment cycles, after a single dose of obinutuzumab to reduce the risk of cytokine release syndrome (CRS) and should not be given in combination with other anticancer drugs. Reimbursement of Columvi should be discontinued if a patient's cancer grows or spreads or if treatment is unacceptably toxic to the patient. Columvi should only be reimbursed when prescribed by specialists with experience managing DLBCL, and if its cost is reduced.

Why Did CADTH Make This Recommendation?

- Evidence from 1 clinical trial suggested that treatment with Columvi may improve survival and increase the time until the cancer grows or spreads. Additionally, 40% of patients treated with Columvi experienced a disappearance of all signs and symptoms of cancer (i.e., completely responded to treatment).
- Columvi may meet some important patient needs by providing another treatment option that delays disease progression and has manageable side effects.
- Based on CADTH's assessment of the health economic evidence, Columvi does not represent good value to the health care system at the public list price. A price reduction is therefore required.



Summary

- Based on public list prices, Columvi is estimated to cost the public drug plans approximately \$3 million over the next 3 years, but it may cost \$18 million or more, depending upon whether Columvi displaces a comparator treatment and which comparator treatment Columvi displaces.

Additional Information

What Is R/R DLBCL?

Non-Hodgkin lymphoma (NHL) is a type of cancer that forms in the lymphatic system. DLBCL is an aggressive type of NHL that accounts for 30% to 40% of NHL cases in Canada. DLBCL occurs when a type of white blood cell, called a B-cell, grows or divides abnormally, causing tumours in the lymph nodes or other organs, including the spleen, liver, or bone marrow. R/R DLBCL is cancer that has come back after treatment (relapsed) or has not responded to certain treatments (refractory).

Unmet Needs in R/R DLBCL

Not all patients with DLBCL respond to or are cured by first-line treatment with R-CHOP, which is a combination of chemotherapy treatments. Approximately 30% to 50% of patients will experience disease progression or relapse within the first 2 years and will require additional treatments for their disease. There is also a need for accessible treatments for patients who progress after CAR-T-cell therapy or those who cannot or cannot receive CAR-T-cell therapy.

How Much Does Columvi Cost?

Treatment with Columvi is expected to cost \$5,200 per patient for the first 21-day cycle and \$12,480 per patient for each subsequent 21-day cycle. The cost of pretreatment before the first dose of Columvi is \$5,479 per patient.

Recommendation

The CADTH pCODR Expert Review Committee (pERC) recommends that glofitamab be reimbursed for the treatment of adult patients with relapsed or refractory DLBCL not otherwise specified, DLBCL arising from follicular lymphoma (trFL), or PMBCL, who have received 2 or more lines of systemic therapy and are ineligible to receive or cannot receive CAR-T-cell therapy or have previously received CAR-T-cell therapy only if the conditions listed in [Table 1](#) are met.

Rationale for the Recommendation

Evidence from 1 ongoing phase I/II open-label, single-arm study (NP30179), which included 155 patients with R/R DLBCL in the primary efficacy population [Cohorts D2 Subcohort 2, D3, and D5] suggested that treatment with glofitamab may result in clinically meaningful improvements in median overall survival (OS, 12.0 months [95% CI, 8.0 to 16.1]) and progression-free survival (PFS, 4.9 months [95% CI, 3.4 to 8.1]). Additional landmark analyses of OS and PFS at 12- (OS, 50.4%; PFS, 34.9%) and 24 months (OS, 39.1%; PFS, 23.9%) the survival analyses. Glofitamab was associated with a clinically meaningful complete response (CR) rate of 40% (95% CI, 32.22 to 48.17), and durable response (median duration of response [DOR], 16.8 months [95% CI, 10.4 to not estimable]). The results of the NP30179 study suggested no detriment in health-related quality of life (HRQoL).

Patients identified a need for additional treatments that result in longer disease remission and improved survival, disease symptom control, and improvement in HRQoL. Furthermore, patients indicated a need for easier access to new treatments that can be received closer to home and are aligned with their preferred treatment goals. Based on the evidence reviewed, pERC concluded that glofitamab may meet some of these needs, including potentially extending disease remission and survival, as well as providing an alternative treatment that is more accessible than other options in this palliative setting; no definitive conclusion could be reached regarding the effects of glofitamab on HRQoL.

Using the sponsor-submitted price for glofitamab and publicly listed prices for all other drug costs, the incremental cost-effectiveness ratio (ICER) for glofitamab was \$230,682 per quality-adjusted life-year (QALY) compared with salvage chemotherapy. At this ICER, glofitamab is not cost-effective at a \$50,000 per QALY gained willingness to pay (WTP) threshold for patients with R/R DLBCL after at least 2 prior lines of therapy. A price reduction is required for glofitamab to be cost-effective at a \$50,000 per QALY gained threshold.

Table 1: Reimbursement Conditions and Reasons

Reimbursement condition	Reason	Implementation guidance
Initiation		
1. Adult (≥ 18 years) patients with both of the following: <ol style="list-style-type: none"> 1.1. Relapsed or refractory DLBCL not otherwise specified, trFL, or PMBCL. 1.2. Have received 2 or more lines 	In the NP30179 trial, treatment with glofitamab monotherapy demonstrated a clinical benefit in the cohorts of patients with DLBCL not otherwise specified, HGBCL, PMBCL and trFL who relapsed after or failed to respond to at least 2 prior	As outlined in the product monograph for glofitamab, all patients must receive a single 1,000 mg dose of obinutuzumab on cycle 1 Day 1 (7 days before initiation of glofitamab treatment) to deplete

Reimbursement condition	Reason	Implementation guidance
of systemic therapy and have previously received CAR-T-cell therapy; declined, are ineligible to receive, or cannot receive CAR-T-cell therapy.	systemic treatment regimens (including at least one prior regimen containing anthracycline, and at least one containing an anti-CD20-directed therapy).	circulating and lymphoid tissue B-cells and minimize the risk of CRS.
Discontinuation		
2. Treatment with glofitamab should be discontinued upon the occurrence of any of the following: 2.1. Objective disease progression or a maximum of 12 cycles 2.2. Unacceptable toxicity	In the NP30179 study, treatment with glofitamab was discontinued if a patient experienced disease progression or intolerable or serious adverse events, which aligned with clinical practice.	—
3. Patients should be initially assessed clinically at least every 3 months until disease progression or fixed treatment duration of 12 cycles, with imaging based on local standards.	In the NP30179 trial, response was evaluated through the assessment of PET-CT scans using the Lugano criteria. Based on clinical expert opinion, patients would undergo interim imaging every 3 months to confirm response using Lugano criteria.	—
Prescribing		
4. Glofitamab should be prescribed by clinicians (hematologists or oncologists) with expertise in managing DLBCL.	This is to ensure that glofitamab is prescribed only for appropriate patients and that adverse effects (e.g., CRS) are managed optimally and timely.	Based on expert opinion, patients should be treated in a facility familiar with aggressive histology lymphomas and with experience managing CRS/ICANS, where possible. Additionally, tocilizumab should be available to treat severe or life-threatening CRS.
5. Glofitamab should not be reimbursed when combined with other systemic anticancer drugs.	Aside from obinutuzumab pre-treatment, there is no evidence to demonstrate the benefit of glofitamab in combination with other anticancer drugs in the target population. In the cohorts of interest in this review of the NP30179 trial, glofitamab was administered as monotherapy.	—
Pricing		
6. A reduction in price.	The ICER for glofitamab is \$230,682 per QALY gained when compared with salvage chemotherapy. A price reduction of 82% would be required for glofitamab to achieve an ICER of \$50,000 per QALY gained compared to salvage chemotherapy.	—
Feasibility of adoption		
7. The feasibility of the adoption of glofitamab must be addressed.	At the submitted price, the magnitude of uncertainty in the budget impact must be addressed to ensure the feasibility of	—

Reimbursement condition	Reason	Implementation guidance
	adoption, given the difference between the sponsor's and CADTH's estimates.	

CAR-T = chimeric antigen receptor T-cell; CRS = cytokine release syndrome; DLBCL = diffuse large B-cell lymphoma; HGBCL = high-grade B-cell lymphoma; ICANS = immune effector cell-associated neurotoxicity syndrome; ICER = incremental cost-effectiveness ratio; PET-CT = PET – CT; PMBCL = primary mediastinal B-cell lymphoma; QALY = quality-adjusted life-year; trFL = transformed follicular lymphoma.

Discussion Points

- pERC discussed the poor prognosis for patients with R/R DLBCL, the need for effective therapies in this patient population, and the uncertainty of the evidence given the lack of a comparator in the NP30179 trial. pERC agreed with clinical experts that the CR rate, which was the primary end point of the NP30179 trial, and median and landmark OS, PFS, and DOR observed in the NP30179 trial appeared compelling, durable, and clinically meaningful compared to historical data in patients in an otherwise palliative setting.
- The committee acknowledged that patients highlighted the need for easier access to treatments and noted that glofitamab may meet this need. Although the treatment landscape for R/R DLBCL may be changing with the availability of CAR-T cell therapy as second-line therapy (for patients with early relapse or refractory disease), pERC considered that not all patients would be able to access CAR-T cell therapy for various logistical and non-medical reasons and that this should not disqualify patients from receiving glofitamab. pERC discussed the subgroup of patients in the NP30179 trial who received prior CAR-T cell therapy (N = 52 [33.5%]), noting that the CR rate in this subgroup (36.5% [95% CI, 23.6 to 51.0]) was comparable with the overall CR rate (40.0% [95% CI, 32.2 to 48.2]) from the NP30179 trial. Based on input from clinical experts, an unmet need for patients in the third or fourth-line setting was also identified. pERC noted that glofitamab may also meet this need, particularly as an option for patients who have received intensive therapies such as CAR-T or stem cell therapy who are more likely to experience tolerability issues with Pola-BR.
- pERC discussed a submitted indirect treatment comparison that compared glofitamab to Pola-BR via propensity scoring analysis and salvage chemotherapy via matching adjusted indirect comparison. The results of the propensity score analysis suggested no difference between glofitamab and Pola-BR for the outcomes of interest to this review (OS, PFS, DOR, or CR rate, ORR). Conversely, in the MAIC analysis, glofitamab was favoured over salvage chemotherapy regimens for the outcomes of OS, ORR, and CR rates. However, numerous limitations (including small sample sizes, heterogeneity across study designs and populations, and the inability to adjust for important potential confounders and prognostic variables) in the analyses meant that no firm conclusions could be drawn on the efficacy of glofitamab versus relevant comparators in this setting. Also, pERC discussed the sequencing of glofitamab and Pola-BR, and based on the results of the ITC, there is no evidence to suggest a difference between these treatments or to inform decisions about treatment sequencing.
- In line with pERC's assessment of evidence comparing glofitamab and Pola-BR and discussion regarding their place in therapy and sequencing, there is no robust clinical evidence to suggest

the total drug cost of glofitamab should exceed the total drug cost of Pola-BR paid by CADTH-participating drug plans.

- pERC discussed the sponsor-submitted economic evaluation and noted concerns with the sponsor's modelling approach. These concerns with the modelling approach, along with the uncertainty associated with the comparative clinical efficacy and exclusion of subsequent lines of treatment, lead to uncertainty associated with the incremental cost-effectiveness estimates of glofitamab. pERC noted that treatment sequencing was not considered in the budget impact analysis and discussed that if glofitamab does not displace other treatments but delays the time to use of those treatments, the analyses underestimate the expected budget impact of reimbursing glofitamab by CADTH-participating drug plans. pERC noted that evidence is needed to inform the sequencing of Pola-BR, glofitamab, and CAR-T cell therapy in clinical practice.

Background

DLBCL is the most common type of NHL, accounting for approximately 30% to 40% of all NHL cases in Canada. Patients with DLBCL typically present with an enlarged symptomatic mass in the lymph nodes, typically in the neck or abdomen. However, widespread DLBCL can also arise in tissues outside the lymph nodes (i.e., extranodal involvement) in the bone marrow, bones, brain, and gastrointestinal tract, among others. Diffuse large B-cell lymphoma can also cause systemic B symptoms (i.e., unexplained fever, weight loss, night sweats) and elevated serum lactate dehydrogenase.

There are limited estimates of DLBCL incidence and prevalence in Canada. The Canadian Cancer Society estimated that 11,400 Canadians were diagnosed with NHL in 2022, with 3000 dying from the disease. International studies have estimated the incidence of DLBCL in the US and England to be approximately 7 cases per 100,000 persons per year.

First-line treatment for DLBCL is relatively standardized across Canada, with most patients receiving R-CHOP Q3W. While most patients often respond well to R-CHOP, 30% to 50% of patients will either be refractory to or relapse following first-line therapy. Patients who relapse early (within 12 months) or patients with refractory disease have a worse prognosis than those who did not relapse within 12 months, even with second-line therapy. Patients requiring second-line treatment for R/R DLBCL are classified based on their eligibility for stem cell therapy (SCT). Based on the Canadian Evidence-Based Guideline for the Treatment of R/R DLBCL, for patients who are refractory to or relapse after 12 months of R-CHOP, the historical standard approach for patients with chemosensitive disease and who meet eligibility criteria for transplant consists of salvage platinum-based chemotherapy followed by high-dose chemotherapy and autologous SCT. In patients who are ineligible for SCT, second-line treatment options include chemotherapy with or without rituximab or Pola-BR. Currently, CAR-T cell therapy is approved in Canada for patients with R/R DLBCL following 2 or more lines of therapy. As such, CAR-T cell therapy is the standard treatment approach for patients with R/R DLBCL not responding to salvage chemotherapy (i.e., transplant-ineligible) or who relapse post-SCT. Though not adopted at this review, CAR-T may be offered as a second-line treatment to eligible patients. For patients

who are not chemosensitive and who are ineligible for autologous SCT, who relapse post-SCT or post-CAR-T, the prognosis is poor. There is no standard treatment approach to treatment. Available options are currently limited to palliative chemotherapies, including R-GemOx, Pola-BR, and tafasitamab with lenalidomide or clinical trials with novel drugs.

Glofitamab received a Notice of Compliance with Conditions (NOC/c) from Health Canada on March 24, 2023, for the treatment of adult patients with relapsed or refractory DLBCL not otherwise specified, trFL, or PMBCL who have received 2 or more lines of systemic therapy and are ineligible to receive or cannot receive CAR-T-cell therapy or have previously received CAR-T-cell therapy. The NOC/c was granted on the basis that the sponsor commits to submitting the results of the confirmatory phase III study of glofitamab plus gemcitabine and oxaliplatin compared to R-GemOx in R/R DLBCL and acknowledges that marketing authorization may be revoked if the trial fails to demonstrate an improvement in OS. Glofitamab is a bispecific monoclonal antibody that binds bivalently to CD20, expressed on the surface of B-cells, and monovalently to CD3 in the T-cell receptor complex on the surface of T-cells. It is available as a 1 mg/mL concentrate for solution for IV infusion, and the glofitamab dosage recommended in the product monograph is a step-up dosing schedule beginning with 2.5 mg on cycle 1 day 8, followed by 10 mg on cycle 1 day 15, and 30 mg on cycle 2 day 1. All subsequent infusions are administered at 30 mg on day 1 of each cycle. To minimize the risk of CRS and deplete circulating lymphoid B-cells, all patients must receive a pre-treatment 1,000 mg dose of obinutuzumab on cycle 1 day 1. Each treatment cycle is 21 days.

Sources of Information Used by the Committee

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

- a review of 1 phase I/II open-label, single-arm study in patients with R/R NHL
- patients perspectives gathered by patient groups, Lymphoma Canada
- input from public drug plans and cancer agencies that participate in the CADTH review process
- Two clinical specialists with expertise in diagnosing and treating patients with R/R DLBCL
- input from 2 clinician groups, including Lymphoma Canada and OH-CCO Hematology Cancer Drug Advisory Committee
- a review of the pharmacoeconomic model and report submitted by the sponsor.

Stakeholder Perspectives

Patient Input

One patient group, Lymphoma Canada, provided input for this review. Lymphoma Canada is a national Canadian registered charity whose mission is to empower patients and the lymphoma community through education, support, advocacy, and research. Lymphoma Canada collaborates with patients, caregivers, health care professionals, and other organizations to promote early disease detection, discover new and

improved treatments, improve access to those treatments, and find a cure for lymphoma. Information was collected from June 5 to July 10, 2023, through an online survey of 27 patients. Most patients included in the survey were diagnosed with DLBCL not otherwise specified (13 [48%]), diagnosed 3 years to 5 years before the survey (8 [30%]), living in Canada (8 [30%]), and in the age range of 45 years to 54 years (6 [22%]). At diagnosis, the following disease symptoms were most reported by the patients included in the survey as having a significant impact on their HRQoL: enlarged lymph nodes (32%), bodily swelling (27%), fatigue (27%), shortness of breath (27%), bodily aches and pains (23%) and night sweats (23%), with fatigue and enlarged lymph nodes highlighted as having the most significant impact on their current HRQoL. Following diagnosis, 66%, 56%, and 42% of patients reported fear of progression and relapse, stress of having cancer, and anxiety and worry, respectively. Patients further commented on the challenges they faced at diagnosis, including symptoms (e.g., difficulty swallowing and sleeping) and time to confirm their diagnosis (e.g., wait time between testing and results and scheduling appointments for biopsy). According to 15 patients included in the survey, the following aspects of day-to-day activities were affected by their disease: the ability to work, attend school, and volunteer (54%); perform day-to-day activities (47%), spend time with family and friends (47%), and attend to household chores (40%).

In the third-line setting, 6 patients received CAR-T cell therapy, 1 received polatuzumab plus rituximab, cyclophosphamide, doxorubicin, and prednisone (Pola-R-CHP), and 6 were in a clinical trial. Most patients were very satisfied or satisfied with their first-line treatment options (62%), compared to second-line treatment options (39%) and third-line treatment options (31%). Lymphoma Canada suggested that patients are less satisfied with their treatment options in the second- and third-line settings compared to the first-line setting. The most common financial implications associated with treatment for large B-cell lymphoma included drug costs (60%), travelling costs (40%), and absence from work (40%).

Two patients in the survey reported experience with glofitamab accessed through private insurance and public care. Both patients were in remission. One patient reported no side effects. The other reported CRS, hypotension, and low platelet count. Both patients indicated financial impact due to the costs of the drug and supplemental medication with treatment.

LC referred to a separate patient survey submitted for the CADTH submission of Pola-R-CHP. In this separate survey, patients with large B-cell lymphoma identified longer disease remission, more prolonged survival, control of disease symptoms, normalization of blood counts, and improved HRQoL to perform daily activities as the most important treatment outcomes.

Clinician Input

Input From Clinical Experts Consulted by CADTH

The clinical experts consulted by CADTH stated that the goal of treatment at this stage is palliative and generally includes maintaining HRQoL through relieving lymphoma-related symptoms, delaying disease progression, and balancing the toxicities of therapy. There is no standard of care in this setting, but options include chemotherapy (e.g., Pola-BR), radiation, and clinical trials. The clinical experts stated that there is an unmet need for safe and effective treatments for palliative patients who are not eligible for curative

treatment or those who have failed second-line treatment consisting of SCT or CAR-T, as there are limited treatment options for disease control, and currently available options are often associated with significant toxicity that limits their usefulness and applicability. Additionally, posttransplant and post-CAR-T cell therapy patients often have poor prognosis and very poor bone marrow function that prevents them from receiving or tolerating further cytotoxic therapy. The clinical experts also noted that there is a significant group of patients who may be eligible for intensive treatments but are unable to access them due to barriers based on location. Many patients are unable to travel with caregivers to specialized cellular therapy sites and choose not to have this treatment as they wish to be treated closer to home. As such, there is an additional unmet need for treatments that patients can access and receive closer to home.

After the failure of first-line R-CHOP (curative intent), second-line treatment consists of salvage rituximab-based chemotherapy and autologous SCT for transplant-eligible chemosensitive patients (curative intent), and third-line therapy consisting of CAR-T cell therapy (curative intent). There is no standard of care following these treatment options, and transplant-ineligible patients in second- and third-line treatment tend to receive palliative rituximab-based chemotherapy (e.g., Pola-BR or R-GemOx) with non-curative intent, radiation, and clinical trials. The clinical experts highlighted a planned shift to use CAR-T cell therapy as second-line therapy for primary refractory or early relapsed DLBCL pending funding in Canada. The clinical experts emphasized that cytopenias constitute a significant problem of palliative treatment options. The experts highlighted that glofitamab should be restricted to patients who are not eligible for other curative therapies and for patients who already received CAR-T-cell therapy or who would not be able to receive it later (i.e., as third-line for post-CAR-T cell therapy or patients unable to do CAR-T cell therapy). They envisioned glofitamab occupying the same space as Pola-BR.

The experts noted that these patients would be identified in routine practice by clinicians familiar with treating lymphoma patients undergoing surveillance for relapse (clinical and/or imaging). Per the indication for glofitamab, patients with R/R DLBCL requiring third-line treatment who are not eligible for or failed intensive cellular therapies (i.e., SCT or CAR-T) would be considered for glofitamab. The experts could not identify a specific subgroup of patients demonstrating an enhanced or reduced benefit from glofitamab treatment. The experts highlighted that repeat biopsy is generally not required in cases of suspected relapses of DLBCL unless it is a remote relapse or if the patient had a prior history of indolent lymphoma. It was unclear which lymphoma had relapsed.

The clinical experts stated that response to treatment would include a standard assessment of lymphoma response using the Lugano criteria. Patients undergo interim imaging every 3 months to confirm response, leading to ongoing treatment or discontinuation. Patients are also assessed for lymphoma-related symptoms at each visit; however, the clinical experts noted that these outcomes are more subjective but factor into patients' decisions to continue therapy. The experts also noted that the frequency of these assessments and collection of data may vary across Canada. In terms of meaningful response to treatment, the clinical experts stated that a 6-month or more response with improved symptoms can be considered meaningful. The experts did not consider temporary shrinking of tumours beneficial to patients and believed that the initial responses (either partial or complete responses) should exceed 6 months; otherwise, they should be discontinued. Additionally, with a current median OS of 6 months in this population, the experts

considered a benefit of at least 6 months and 3 months over the current standard of care to be clinically meaningful for OS and PFS, respectively.

The clinical experts suggested that treatment with glofitamab should be discontinued upon overt disease progression or lack of response to treatment. The experts noted that adverse events (AEs) may vary, and resolution of severe AEs can still allow for resumption of therapy, so this is more variable and should be left to physician judgment and patient request before discontinuation.

The clinical experts indicated that patients with R/R DLBCL are typically under the care of hematologists or oncologists familiar with treating lymphoma patients. They also noted that the monitoring and treatment of these patients must be conducted at tertiary centres with the means to monitor and treat CRS, which may require some initial training of site staff before implementation.

Clinician Group Input

Two clinician groups provided input for this review: Lymphoma Canada, with 4 clinicians contributing to the submission, and Ontario Health-Cancer Care Ontario (OH-CCO) Hematology Cancer Drug Advisory Committee, with 1 clinician contributing. Lymphoma Canada is a national Canadian registered charity whose mission is to empower patients and the lymphoma community through education, support, advocacy, and research. The OH-CCO Hematology Cancer Drug Advisory Committee provides evidence-based clinical and health system guidance on drug-related issues.

Input from the clinician groups generally aligned with the clinical experts consulted by CADTH. Clinician groups highlighted the need for additional accessible treatment options beyond Pola-BR, and an effective therapy that can achieve disease remission for prolonged periods to improve OS and HRQoL in patients with R/R DLBCL. As such, clinician groups anticipated using glofitamab as a third-line option in patients who are ineligible or unable to receive CAR-T cell therapy or in patients with disease progression after CAR-T-cell therapy. The OH-CCO Hematology Cancer Drug Advisory Committee further suggested that glofitamab may be preferred over Pola-BR.

One clinician group suggested that patients who have had prior allogeneic SCT may also be eligible for treatment with glofitamab, and both clinician groups highlighted that other histologic subtypes of large B-cell lymphoma are generally treated similar to DLBCL, and as such, suggested that these patients may benefit from glofitamab treatment. Conversely, the clinician groups suggested that patients who are eligible and able to receive CAR-T-cell therapy would not be suitable for treatment with glofitamab.

The clinician groups highlighted that response to treatment is generally observed quickly, with the first response assessment performed after cycle 2 and repeat imaging after cycles 5 and 8 and at the end of treatment. In line with the clinical experts consulted by CADTH, the clinician groups considered the standard lymphoma response measures, improved survival, and symptom improvement important treatment outcomes. The clinician groups highlighted that disease progression and unacceptable toxicity would be the primary factors when deciding to discontinue treatment. One clinician group suggested that both inpatient and outpatient settings may be appropriate for treatment with glofitamab. Lymphoma Canada highlighted that though PET-CT (PET-CT) is the preferred imaging modality for DLBCL based on modern lymphoma

response assessment criteria, it may not be feasible in all areas of Canada to perform routine PET-CT in the community setting.

Drug Program Input

The clinical experts consulted by CADTH 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	Response
Relevant comparators	
<p>The pivotal trial (NP30179) was an open-label, multicentre, single-arm, phase I/II trial.</p> <p>Publicly funded relevant comparators include Pola-BR and chemotherapy with or without rituximab. CAR-T-cell therapy is publicly funded in most jurisdictions for R/R DLBCL after 2 prior therapies.</p>	<p>The clinical experts and pERC agreed that the only currently available publicly funded comparator includes Pola-BR.</p> <p>CAR-T-cell therapy is not considered a relevant comparator to glofitamab, as in the treatment sequence, if patients were eligible for CAR-T-cell therapy, they would receive it before glofitamab. For patients who are ineligible for CAR-T-cell therapy, or decline or cannot access CAR-T-cell therapy, glofitamab may be given.</p>
Considerations for initiation of therapy	
<p>Per the pivotal trial, patients were required to have been previously treated with at least 2 prior lines of therapy, including at least one anthracycline-containing regimen and one anti-CD20 antibody-containing regimen.</p>	<p>pERC noted that patients not previously treated with an anthracycline-containing regimen (e.g., indolent disease, contraindication), should still be eligible for treatment with glofitamab.</p>
<p>Should patients with other types of indolent lymphomas besides FL that have transformed into DLBCL be eligible?</p> <p>Should the following patients be eligible for glofitamab:</p> <ul style="list-style-type: none"> • follicular lymphoma grade 3B • high-grade B-cell lymphoma 	<p>Patients with Grade 3B FL and HGBCL were included in the NP30179 study, though patients with Grade 3B FL were not included in the cohorts of interest to this review. The clinical experts and pERC noted that these uncommon subtypes are treated in the same manner as DLBCL, and these patients, i.e., patients with Grade 3B FL, HGBCL, and transformed lymphomas from any indolent lymphoma, should be eligible for treatment with glofitamab. pERC agreed with the clinical experts.</p>
<p>The following indications were excluded from the NP30179 study:</p> <ul style="list-style-type: none"> • CLL • Burkitt lymphoma • lymphoplasmacytic lymphoma • prior allogeneic SCT <p>What evidence is there for using glofitamab in these patients, and could these indications be considered for treatment with glofitamab?</p>	<p>The clinical experts highlighted that patients with these indications are typically excluded from clinical trials in this setting; however, despite the lack of evidence supporting the use of glofitamab in these patients, the clinical experts suggested that glofitamab could be used given the similarities in treatment for these diseases.</p> <p>In contrast, pERC noted that there is no evidence to support including patients with Burkitt lymphoma, CLL or lymphoplasmacytic lymphoma, unless their disease has transformed to DLBCL, as with Grade 3B FL or HGBCL, above.</p> <p>The clinical experts noted that these indications are rare, thus, there are few to no prospective clinical trials in these indications, and therefore, there is a paucity of data available for these patients.</p> <p>Regarding prior allogeneic SCT, the clinical experts highlighted</p>

Drug program implementation questions	Response
	<p>that certain caveats, including the absence of GVHD or no longer taking immunosuppressive therapies, would be required to use glofitamab in these patients. However, no evidence exists.</p>
<p>The trial protocol allowed re-treatment for up to another 12 cycles provided re-treatment criteria were met. What evidence is there to support re-treatment?</p>	<p>In the NP30179 study, patients were eligible for re-treatment with glofitamab provided they met all eligibility criteria and initially had a radiographically documented, investigator-assessed objective response (CR or PR) or SD at the end of the total initial glofitamab treatment regimen. No time frame for relapse was specified.</p> <p>The clinical experts and pERC indicated that re-treatment with glofitamab could be considered in alignment with the clinical trial protocol, i.e., if patients experienced a good outcome following the initial treatment with glofitamab, re-treatment would be given for a maximum of 12 cycles or until progression, whichever occurs first. pERC noted insufficient evidence to define a sufficient durable response that would be reasonable before re-treatment was considered; however, based on clinical experience, a durable response for at least 6 months in a patient who had not progressed on therapy may be considered reasonable.</p>
Considerations for discontinuation of therapy	
<p>The trial protocol allowed patients to continue study treatment if deriving clinical benefit despite radiographic evidence of disease progression.</p> <p>When should treatment with glofitamab be discontinued, including in the presence of suspected pseudoprogression?</p>	<p>As with other BiTE therapies, treatment with glofitamab should be discontinued upon evidence of disease progression or unacceptable toxicity.</p> <p>In Study NP30179, treatment during suspected pseudoprogression could be continued; however, if radiographic disease progression was confirmed at a subsequent tumour assessment, treatment with glofitamab was discontinued.</p> <p>The clinical experts noted that pseudoprogression is rare, and there may be some initial swelling or worsening of symptoms; however, they highlighted that treatment should continue if pseudoprogression is considered. pERC emphasized that this is ultimately based on clinical opinion and must be confirmed with subsequent tumour assessments.</p>
<p>In the event of prolonged dose delays, obinutuzumab pre-treatment is required again.</p>	<p>No response is required. For pERC consideration.</p>
Considerations for prescribing therapy	
<p>Pre-treatment with obinutuzumab is required 7 days before the start of glofitamab cycle 1 to minimize the risk of CRS. Obinutuzumab is not currently publicly funded for this indication. What evidence is there for using obinutuzumab to minimize the risk of CRS in R/R DLBCL patients?</p>	<p>The clinical experts stated that beyond the NP30179 trial, there is no evidence for using obinutuzumab to minimize the risk of CRS in R/R DLBCL.</p> <p>pERC agreed with the experts about the availability of evidence for pre-treatment with obinutuzumab. pERC also noted that the use of glofitamab should align with the Health Canada-approved Product Monograph and clinical trial, and therefore, pre-treatment with obinutuzumab should be considered as part of the glofitamab treatment regimen. In addition, pERC noted</p>

Drug program implementation questions	Response
	that tocilizumab must be available during cycles 1 and 2 of glofitamab to ensure severe CRS can be managed if needed, as described in the product monograph.
Generalizability	
Patients with ECOG performance status greater than 1 were excluded from the NP30179 trial. Should patients with ECOG performance status of 2 or more be considered eligible for glofitamab?	The clinical experts agreed that the requirement for performance status in determining treatment eligibility is less stringent in clinical practice, and select patients with an ECOG performance status of 2 could be considered for treatment with glofitamab.
Care provision issues	
Treatment with glofitamab can cause CRS. The trial protocol recommended hospitalization during the first dose of glofitamab. To ensure equitable access to glofitamab, the cost of treatment in the inpatient setting must be considered.	No response required. For pERC consideration.
System and economic issues	
Polatuzumab vedotin, subcutaneous rituximab, and biosimilar IV rituximab have confidential prices negotiated through pCPA. Generic bendamustine is available.	No response required. For pERC consideration.

BiTE = bispecific T-cell engager; CAR-T = chimeric antigen receptor T-cell therapy; CLL = chronic lymphocytic leukemia; CRS = cytokine release syndrome; DLBCL = diffuse large B-cell lymphoma; ECOG = Eastern Cooperative Oncology Group; pCPA = pan-Canadian Pharmaceutical Alliance; pERC = pCODR Expert Review Committee; R/R = relapsed/refractory; SCT = stem cell transplant.

Clinical Evidence

Systematic Review

Description of Studies

One single-arm study, NP30179, an ongoing phase I/II, multicentre, open-label, single-arm study of glofitamab monotherapy after a fixed, single-dose pre-treatment of obinutuzumab in patients with R/R NHL was included in this review. The study was divided in 3 parts: Part I (single patient cohorts) and part II (multiple patient cohorts), comprising the dose-escalation phase of the study, and Part III, the dose-expansion phase of the study. The primary objective of the NP30179 study was to evaluate the efficacy, safety, and tolerability of escalating doses of glofitamab. At the time of the June 2022 clinical cut-off date (CCOD), [REDACTED] were assigned to dose cohorts in the order in which they were enrolled into Study NP30179. The combined D2 Subcohort 2 (D2S2), D3, and D5 cohorts were the cohorts of interest to this review comprised the primary efficacy population (n = 155) which included R/R DLBCL patients with 2 or more prior lines of systemic therapy who were treated with the phase II recommended dose of glofitamab of 2.5mg, 10 mg, 30 mg every 3 weeks for a fixed treatment duration of 12 cycles unless discontinued earlier due to disease progression or toxicity. End points from NP30179 of interest to this review included the primary end point of the proportion of patients achieving CR, with secondary end points of interest consisting of objective response rate (ORR), PFS, OS, DOR, and HRQoL.



In the safety analysis set (n = 154), most patients were diagnosed with DLBCL (110 [71.4%]). The median age of patients enrolled was 66.0 years, and there were slightly more patients with Eastern Cooperative Oncology Group (ECOG) performance status 1 (84 [54.5%]) than 0 (69 [44.8%]). The median number of prior lines of therapy was 3.0, with all patients having received prior chemotherapy, alkylator and an anti-CD20 mAb, and most patients received anthracycline (151 [98.1%]) therapies. Nearly all patients were refractory to their last prior therapy (131 [85.1%]) and were also refractory to prior anti-CD20 therapies (128 [83.1%]).

An interim clinical study report (CSR) was provided for the NP30179 study detailing the results up to the CCOD of September 14, 2021. At CADTH's request, an updated CSR detailing the results to a CCOD of June 15, 2022, was provided.

Efficacy Results

Efficacy results for NP30179 were presented for the primary efficacy population, comprised of cohorts D2S2, D3, and D5 (n = 155) as of the CCOD (June 15, 2022).

Overall Survival

At the June 15, 2022, CCOD, 81 (52.6%) patients had died, resulting in a median OS of 12.0 months (95% CI, 8.0 to 16.1). The OS rate at 12 and 24 months was 50.39% (95% CI, 42.06 to 58.71), [REDACTED].

Progression-Free Survival

The median duration of follow-up for independent review committee (IRC)-assessed PFS was 13.4 months (95% CI, 8.9 to 15.9). [REDACTED] The median PFS was 4.9 months (95% CI, 3.4 to 8.1). The PFS rate at 12 and 24 months were 34.90% (95% CI, 26.48 to 43.31) and [REDACTED], respectively.

Health-Related Quality of Life

European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30 (EORTC QLQ-C30)

At baseline, 89.8% of patients completed at least 1 question of the EORTC QLQ-C30. At baseline, the mean EORTC QLQ-C30 physical functioning, role functioning, GHS/QoL, and fatigue scores for [REDACTED] in Cohort D3 was [REDACTED], respectively. At cycle 5, the mean change from baseline in physical functioning score [REDACTED], the mean change from baseline in role functioning score [REDACTED], the mean change from baseline in GHS/QoL score [REDACTED], and the mean change from baseline in fatigue score [REDACTED]. At the end of treatment, the mean change from baseline in the physical functioning, role functioning, GHS/QoL, and fatigue scores [REDACTED], respectively.

Functional Assessment of Cancer Therapy-Lymphoma Subscale (FACT-Lym LymS)

At baseline, a total of 88.9% of patients completed at least 50% of questions in the FACT-Lym LymS. The mean FACT-Lym LymS score at baseline [REDACTED]. At cycle 5, day 1 [REDACTED], the mean change from

baseline in total score was [REDACTED]. At the end-of-treatment assessment, the mean change from baseline in total score was [REDACTED].

Clinical Response

Complete Response

The proportion of patients achieving CR per IRC assessment was the primary end point of the NP30179 study. In the primary efficacy population, the IRC-assessed CR rate was 40.0% (95% CI, 32.2 to 48.2) at the June 15, 2022 CCOD.

Based on the September 14, 2021 CCOD, the prespecified primary efficacy end point of IRC-assessed CR rate was 35.2% (95% CI, 26.2 to 45.0) in cohort D3 (n = 108), which was greater than the 20% historical control for CR rate in a R/R DLBCL patient population.

Results for the subgroup analyses were generally consistent with the primary analysis, ranging from 0 to 100% due to small sample sizes with overlapping CIs.

Objective Response Rate

The median duration of follow-up for an IRC-assessed response was 12.0 months (95% CI, 7.6 to 16.6). In the primary efficacy population (n = 155), a total of 80 (51.6% [95% CI, 43.46% to 59.70%]) patients achieved an ORR; 62 (40.0%) patients with CR, 18 (11.6%) with partial response (PR), 21 (13.5%) with stable disease, and 42 (27.1%) with progressive disease.

Duration of Response

The median duration of follow-up for IRC-assessed response was 12.0 months (95% CI, 7.6 to 16.6). For the 80 patients who achieved an IRC-assessed response (CR or PR), the median DOR was 16.8 months (95% CI, 10.4 to not estimable [NE]). A total of 50 patients (62.5%) remained in remission, and 30 patients (37.5%) subsequently had disease progression or died. The Kaplan-Meier estimated event-free rate among responders at 12-, and 24-months after the first response was 59.57% (95% CI, 46.85 to 72.28) and 43.37% (95% CI, 26.14 to 60.61), respectively.

Harms Results

On June 15, 2022 CCOD, 152 (98.7%) patients experienced at least 1 AE. The most frequently reported AEs included CRS (103 [66.9%]), neutropenia (58 [37.7%]), and anemia (47 [30.5%]). A total of 54 (35.1%) patients experienced grade 1 to 2 AEs, 89 (57.8%) patients experienced grade 3 to 4 AEs, and 9 (5.8%) patients experienced grade 5 AEs. The most frequently reported grade 3 to 4 AEs included neutropenia or decreased neutrophil count (42 [27.3%]), anemia (12 [7.8%]), hypophosphatemia (9 [5.8%]), and thrombocytopenia or decreased platelet count (12 [7.8%]).

A total of 75 (48.7%) patients experienced a serious AE (SAE). The most frequently reported SAEs included CRS (34 [22.1%] by Lee 2014; 32 [20.8%] by American Society for Transplantation and Cellular Therapy [ASTCT] 2019), followed by sepsis (6 [3.9%]), COVID-19, COVID-19 pneumonia, and tumour flare (5 [3.2%] each), and anemia, febrile neutropenia, neutropenia, and pleural effusion (3 [1.9%] each). SAEs resulted in dose modifications or interruptions in 9 (5.8%) patients.

In the primary safety population, 14 (9.1%) patients reported an AE leading to study treatment discontinuation, primarily due to COVID-19, delirium, and neutropenia (2 [1.3%] each).

At the June 15, 2022, CCOD, 81 (52.6%) patients had died. The most frequent cause of death was progressive disease (61 [75.3%]), followed by AEs (8 [5.19%]), including COVID-19 pneumonia (3 [1.9%]), COVID-19 (3 [1.9%]), sepsis (2 [1.3%]), and delirium (1 [0.6%]). Other causes of death included pneumonia, COVID-19, and pulmonary fungal infection (all n = 1 [0.6%]), and unknown reasons (n = 7 [4.5%]).

Notable Harms

As of the June 15, 2022, CCOD, 103 (66.9%) patients reported at least 1 CRS AE per Lee (2014), while 99 (64.3%) patients reported at least 1 CRS AE by ASTCT 2019 grading. Serious CRS events by ASTCT 2019 grading were reported by 32 (20.8%) patients. Serious CRS events by Lee (2014) were reported by 34 (22.1%) patients. By ASTCT, grade 2 CRS AEs occurred in 19 (12.3%) patients and grade 3 or 4 CRS AEs were reported in 6 (3.9%) patients. According to Lee's (2014) grading system, 24 (15.6%) patients experienced grade 2 CRS, while 5 (3.2%) experienced grade 3 and 4 CRS. As of the CCOD, grade 2 or higher CRS events were resolved in 24 of 25 by ASTCT grading and 27 of 29 patients by Lee 2014.

Infection and infestation of AEs were reported in 62 (40.3%) patients. Grade 3 to 4 infection and infestation AEs were reported in 18 (11.7%) patients. A total of 8 (5.2%) grade 5 infection and infestation AEs were reported. A total of 28 (18.2%) infection and infestation AEs were serious. The most frequently reported infection and infestation SAEs included sepsis (6 [3.9%]), COVID-19 pneumonia (5 [3.2%]), COVID-19 (5 [3.2%]), pneumonia (2 [1.3%]), infection (2 [1.3%]), and vascular device infection (2 [1.3%]).

Critical Appraisal

NP30179 is an ongoing phase I/II, multicentre, open-label, single-arm study of glofitamab. The choice to conduct a single-arm trial was justified considering that the study was designed as an early phase I/II study where an internal comparator group is not required, as well as the severity of illness for patients at this stage. However, the decision to conduct a single-arm study also has implications for the overall strength and interpretability of the results. As a single-arm study, there is an increased risk of bias in estimating treatment effects due to the potential for confounding related to natural history and prognostic factors. The potential influence of selection bias is also complex to ascertain in a single-arm study. Additionally, the effect of glofitamab on time-to-event end points such as PFS, OS, and DOR cannot be interpreted and can only be considered exploratory and supportive.

In addition to glofitamab monotherapy, all patients received 1,000 mg of obinutuzumab as pre-treatment to minimize the risk of CRS based on preclinical data results. The Health Canada reviewers' report noted that no noticeable antitumour effect was observed for obinutuzumab; however, considering the single-arm design of the study, it remains impossible to differentiate whether the effects observed in the study are attributable to glofitamab or obinutuzumab. Additionally, the true effect of obinutuzumab on CRS also remains unknown for this reason.

In addition to the single-arm design, NP30179 was also open-label, whereby the investigator and the study participants were aware of their treatment status, potentially increasing the risk of detection and

performance bias. As such, the open-label trial design limits the interpretability of the subjective study outcomes, such as patient-reported outcomes, including HRQoL and AEs. However, to mitigate the impact of this bias, all outcomes except for OS were assessed by both IRC and the investigator. Though the NP30179 study was powered for the primary end point, the magnitude of the treatment-effect estimates observed in a relatively small study sample may not be replicable in a larger study sample. The primary end point of CR in the NP30179 study was aligned with regulator guidance, such as from the FDA,¹⁴ for market access for hematologic cancers. In hematologic tumours, response directly measures a drug's antitumour activity in oncology clinical trials. The sponsor provided multiple studies which suggested that end-of-treatment CR was a predictor of PFS and OS, and CR could be an effective surrogate end point for survival; however, these studies were conducted in previously untreated patients; thus, it remains unclear whether there is an association between CR rate and survival in patients receiving third-line treatment. Outcomes of critical importance to this review in the NP30179 study included OS and HRQoL. The clinical experts consulted by CADTH and patient input for the review also identified preventing progression as important, and therefore, PFS was also identified as relevant. At the June 15, 2022, CCOD, a total of 52.3% OS events and 61.3% PFS events had occurred (median follow-up duration 17.0 months for OS and 13.4 months for PFS). While the study is still ongoing, CADTH considered there to be a small number of events, reflecting the immaturity of the survival data, particularly for OS. As early analyses of OS data are more likely to overestimate treatment effect,¹⁵ the OS results from the NP30179 study may suggest a higher or better treatment-effect estimate than could be observed in clinical practice. Despite PFS and OS results that were considered clinically meaningful by the clinical experts consulted by CADTH, the combination of the single-arm design, the secondary nature of the outcomes, and the short follow-up duration, the results for survival end points should be interpreted with caution, and only be considered supportive of the overall antitumour effect of glofitamab. No time of assessment was specified for HRQoL outcomes, and there were high rates of attrition for HRQoL outcomes throughout the analysis, limiting the interpretability of the effect of glofitamab on HRQoL.

In discussion with the clinical experts consulted by CADTH, some eligibility criteria such as ECOG performance status, renal function, or required presence of measurable disease may have been restrictive, selecting for ideal, less severely ill patients, which may not reflect the general population, though are typically specific to clinical trials. The clinical experts also noted that at this stage of disease, there are few relevant prognostic factors, though indicated that ECOG performance status remains important at this stage. The clinical experts also noted that the baseline characteristics of the included population was generally reflective of Canadian clinical practice, though they noted there to be a high proportion of patients with refractoriness to any prior therapy (89.6%) compared to clinical practice where they would expect more patients who relapse, which, in contrast to the eligibility criteria, may indicate a sicker population. While the experts considered response outcomes to be important in treatment of R/R DLBCL, and that the response observed in the NP30179 study was better than they would expect with other currently available treatments, they noted that survival and preventing progression are of greatest importance to patients at this stage. As previously mentioned, the estimates for PFS and OS may be overestimated due to the relatively small information fraction and overall immaturity of the data, which may impact the generalizability to the R/R DLBCL population in Canada.

GRADE Summary of Findings and Certainty of the Evidence

For pivotal studies and randomized controlled trials (RCTs) identified in the sponsor's systematic review, Grading of Recommendations Assessment, Development and Evaluation (GRADE) was used to assess the certainty of the evidence for outcomes considered most relevant to inform CADTH's expert committee deliberations, and a final certainty rating was determined as outlined by the GRADE Working Group. Although GRADE guidance is not available for noncomparative studies, the CADTH review team assessed pivotal single-arm trials for study limitations (which refer to internal validity or risk of bias), inconsistency across studies, indirectness, and publication bias to present these important considerations. Because the lack of a comparator arm does not allow for a conclusion to be drawn on the effect of the intervention versus any comparator, the certainty of evidence for single-arm trials started at very low certainty with no opportunity for rating up.

The selection of outcomes for the GRADE assessment was based on the sponsor's Summary of Clinical Evidence, consultation with clinical experts, and input received from patient and clinician groups and public drug plans. The following list of outcomes was finalized in consultation with expert committee members: median OS, median PFS, change from baseline in HRQoL at cycles 3 and 5, and clinical response (CR, ORR, median DOR). For time-to-event outcomes, landmark analyses at 12- and 24-months were also of interest.

When possible, certainty was rated in the context of an important (nontrivial) treatment effect; if this was not possible, certainty was rated in the context of the presence of any treatment effect (i.e., the clinical importance is unclear). In all cases, the target of the certainty of evidence assessment was based on the point estimate and where it was located relative to the threshold for a clinically important effect (when a threshold was available) or to the null.

The target of the certainty of evidence assessment was the presence of a clinically important improvement in survival (OS and PFS) and HRQoL, which were considered the most important outcomes to treatment by the clinical experts consulted by CADTH and the clinician group and patient group inputs. According to the clinical experts consulted by CADTH, clinically importance thresholds for the outcomes of OS and PFS were a benefit of at least 6 months and 3 months over current standard of care for OS and PFS, respectively. Additionally, response to treatment (CR, ORR, DOR) was included in the certainty of evidence assessment based on the potential translation to long-term survival outcomes.

Results of GRADE Assessments

[Table 3](#) presents the narrative GRADE summary of findings for glofitamab monotherapy from the NP30179 study in treating R/R DLBCL patients who have relapsed after or failed to respond to at least 2 prior systemic treatment regimens.

Table 3: Summary of Findings for Glofitamab for Patients with R/R DLBCL

Outcome and follow-up	Patients (studies), N	Effect	Certainty ^a	What happens
Survival				
OS Follow-up: 17.0 months	155 (1 single-arm trial)	Median (95% CI) OS: 12.0 months (8.0, 16.1) 12-Month OS Rate (95% CI): 50.39% (42.06, 58.71)	Very Low ^{b,c}	The evidence is very uncertain about the effects of glofitamab on OS vs. any comparator.
PFS (IRC-Assessed) Follow-up (median): 13.4 months	155 (1 single-arm trial)	Median (95% CI) PFS: 4.9 months (3.4, 8.1) 12-Month PFS Rate (95% CI): 34.9% (26.48, 43.31)	Very Low ^{b,c}	The evidence is very uncertain about the effects of glofitamab on PFS vs. any comparator.
HRQoL				
EORTC QLQ-C30	107 (1 single-arm trial)	Fatigue CFB Mean (SD) CFB to cycle 3: [redacted] Mean (SD) CFB to cycle 5: [redacted] Physical Function: Mean (SD) CFB to cycle 3: [redacted] Mean (SD) CFB to cycle 5: [redacted] Role Function: Mean (SD) CFB to cycle 3: [redacted] Mean (SD) CFB to cycle 5: [redacted] GHS/QoL: Mean (SD) CFB to cycle 3: [redacted] Mean (SD) CFB to cycle 5: [redacted]	Very Low ^{b,c,d}	The evidence is very uncertain about the effects of glofitamab on EORTC QLQ-C30 domains vs. any comparator.
FACT-Lym LymS	107 (1 single-arm trial)	Total Score: Mean (SD) CFB to cycle 3: [redacted] Mean (SD) CFB to cycle 5: [redacted]	Very Low ^{b,c,d}	The evidence is very uncertain about the effects of glofitamab on FACT-Lym LymS vs. any comparator.
Clinical Response to Treatment				
CR (95% CI) (IRC-Assessed) Follow up (median): 12.0 months	155 (1 single-arm trial)	400 per 1,000 (322 to 482)	Low ^e	Glofitamab may result in a large CR rate, although the evidence is still uncertain.
ORR (IRC-Assessed) Follow up (median): 12.0 months	155 (1 single-arm trial)	516 per 1,000 (430 to 597)	Low ^e	Glofitamab may result in a large ORR, although the evidence is still uncertain.

Outcome and follow-up	Patients (studies), N	Effect	Certainty ^a	What happens
DOR (IRC-Assessed) Follow up (median): 12.0 months	155 (1 single-arm trial)	Median (95% CI) DOR: 16.8 months (10.4, NE) 12-Month Event-Free Rate (95% CI): 76.97% (67.34, 86.60) 24-Month Event-Free Rate (95% CI): 43.37% (26.14, 60.61)	Very Low ^{b,c}	The evidence is very uncertain about the effects of glofitamab on DOR vs. any comparator.
Notable Harms				
CRS Follow-up: NR	154 (1 single-arm trial)	Glofitamab: 669 per 1,000	Low ^f	Glofitamab may result in CRS, although the evidence is still uncertain.
Serious Infection Follow-up: NR	154 (1 single-arm trial)	Glofitamab: 182 per 1,000	Very low ^d	The evidence is very uncertain about the effects of glofitamab on serious infections vs. any comparator.

CI = confidence interval; CR = complete response; CRS = cytokine release syndrome; EORTC QLQ-C30 = European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30; FACT-Lym LymS = Functional Assessment of Cancer Therapy–Lymphoma Subscale; HRQoL = health-related quality of life; IRC = independent review committee; NE = not evaluable; NR = not reported; ORR = objective response rate; OS = overall survival; PFS = progression-free survival.

Note: All serious concerns with study limitations (which refers to internal validity or risk of bias), inconsistency across studies, indirectness, and publication bias are documented in the table footnotes.

^aIn the absence of a comparator group, conclusions about efficacy relative to any comparator cannot be drawn, and the certainty of evidence is started at very low.

^bRated down 1 level for serious internal validity limitations as results are based on an interim analysis. Although not necessarily due to bias, interim analyses can overestimate treatment effects.

^cIn the trial, statistical testing for this outcome was not adjusted for multiplicity. The results are considered as supportive evidence.

^dRated down 1 level for serious risk of bias due to potential for bias arising from the open-label nature of the study and the subjective nature of the outcome.

^eDespite the study limitations resulting in the certainty of evidence starting as 'very low', the outcomes of CR and ORR are demonstrative of an antitumour effect, which is supported by the FDA.¹⁴ As such, given the effect size, which was believed to be large and clinically important, the CADTH review team considered the certainty of this evidence to be higher. Note that the outcome could be rated down 1 level for serious indirectness as a surrogate outcome of CR was used as the primary outcome in the place of OS and PFS. Though there is evidence to support CR as a surrogate outcome in DLBCL, it is restricted to previously untreated disease and not the population under review.

^fDespite the study limitations resulting in the certainty of evidence starting as 'very low', CRS because of glofitamab is a serious warning in the product monograph and occurred in nearly 70% of patients despite premedication and obinutuzumab pre-treatment. As such, the CADTH clinical review team considered the certainty of evidence for this outcome to be higher.

Long-Term Extension Studies

No long-term extension studies were submitted to CADTH or identified in the literature.

Indirect Comparisons

Description of Studies

Given the lack of direct head-to-head trials comparing glofitamab against relevant comparators, the sponsor submitted a series of indirect treatment comparisons (ITCs) that were conducted to compare efficacy of glofitamab in 3L+ DLBCL to relevant comparators for outcomes of interest. The sponsor-submitted ITC first conducted a systematic literature review (SLR) and feasibility assessment to identify evidence available for

comparison for the management of R/R DLBCL. Given the single-arm nature of the NP30179 study, 2 ITCs were conducted:

- A propensity score analysis (PSA) comparing glofitamab in 3L+ DLBCL to Pola-BR using individual patient data (IPD) from the NP30179 study and G029365 trials, respectively.
- An unanchored matching adjusted indirect comparison (MAIC) comparing glofitamab to salvage chemotherapy in 3L+ DLBCL using IPD from the NP30179 study and aggregated level data from the SCHOLAR-1 retrospective study.

PSAs were conducted when IPD was available for both comparators, and a MAIC was conducted for comparators for which only aggregate data were available.

Efficacy Results

Propensity Score Analysis

The sponsor conducted PSA using IPD from 2 of their own studies; NP30179 and G029365, given the possibility of filtering patients to make them more comparable to the 3L+ DLBCL patients enrolled in NP30179. Before adjustment, patients were filtered by applying common inclusion and exclusion criteria. Most baseline characteristics between the glofitamab and Pola-BR groups were imbalanced. Two matching analyses: full matching (average treatment effect [ATE]) and inverse probability treatment weighting (IPTW) were selected as the matching methods of preference for the indirect comparison of glofitamab versus Pola-BR based on the greatest effective sample size (ESS), and ability to achieve covariate balance.

For end points of OS, PFS, DOR, duration of CR, CR, ORR, and discontinuation due to AEs, there was no difference after adjustment between glofitamab and Pola-BR for all end points by either full matching or IPTW.

Matching Adjusted Indirect Comparison

A MAIC was conducted to compare glofitamab with salvage chemotherapy from the SCHOLAR-1 study, informed by market research and consultation with clinicians. Before and after adjustment for prognostic factors and effect modifiers using various methods glofitamab was favoured over salvage chemotherapy for OS, ORR, and CR, though 95% CIs were wide for the outcomes of ORR and CR.

Critical Appraisal

Given the lack of direct evidence comparing glofitamab to relevant treatments in the R/R DLBCL third-line setting, the choice to conduct an ITC was justified; however, there were several limitations with the analyses that precluded the ability to draw strong conclusions about the efficacy of glofitamab compared with other treatments.

The NP30179 of glofitamab was a phase I/II, single-arm study, whereas G029365 was a comparative phase Ib/II randomized, open-label study, and SCHOLAR-1 was a retrospective research study, though no formal quality assessment was conducted on the comparator studies. Given the differences in the design of the included studies for the analyses conducted, which could not be adjusted for in the weighting procedures, this was an important limitation.

There were notable differences in the eligibility criteria of the included studies, which resulted in heterogeneity in baseline characteristics across populations. The GO29365 study enrolled patients who had received 1 or more prior lines of therapy and included patients with ECOG performance status of 2. In SCHOLAR-1, patients were enrolled from various sources; however, patients with 1 or more prior lines of therapy, including prior SCT, and ECOG performance status of 0 to 4 were included. In the MAIC analysis, it was not possible to adjust for patients receiving second-line treatment, or patients with an ECOG score of 2 or more in the NP30179 study; thus, these potentially important prognostic factors weren't included in the adjustment, which was an important limitation of the analysis. Despite the comprehensive list of prognostic factors and effect modifiers identified, only 8 baseline characteristics were included in the MAIC analysis based on the available data, limiting the comparability of the populations.

In both analyses, there were notable differences in populations before and after adjustment, despite filtering patients by inclusion and exclusion criteria. In the full matching scenario and IPTW analysis, covariate adjustment resulted in a reduction in sample size of 34.4% in the glofitamab group and 71.2% in the Pola-BR group, and 17.5% in the glofitamab group and 35.8% in the Pola-BR group, respectively. In the MAIC, the ESS for the glofitamab group was reduced ■ in the base-case analysis, ■ for scenario 1, and ■ for scenario 2. Thus, there was either considerable heterogeneity between studies among the variables included in the weighting process, or the inclusion and exclusion criteria differed greatly between the studies.

Results for the PSA suggested no difference between glofitamab and Pola-BR for any outcomes evaluated before or after adjustment via full matching or IPTW. Additionally, point estimates were associated with wide 95% CIs, particularly after adjustment, suggesting notable imprecision in the results likely due to the reduction in sample sizes. Results for the MAIC comparing glofitamab to salvage chemotherapy from SCHOLAR-1 were consistent across models and adjustment scenarios, favouring glofitamab for the outcome of ORR. While results consistently favoured glofitamab over salvage chemotherapy across adjustment scenarios and models for ORR and CR outcomes, there were differences in the magnitude of effect, and the 95% CIs were extremely wide, suggesting notable imprecision in comparative efficacy estimates from the MAIC.

Overall, the limitations of the sponsor-submitted ITCs, particularly the MAIC, including the differences in study design, included patient populations and heterogeneity in baseline characteristics across studies, as well as the reduction in sample sizes, leads to uncertainty about the overall generalizability of the results to the population living in Canada. Additionally, wide 95% CIs led to imprecision and uncertainty in the results.

Studies Addressing Gaps in the Evidence from the Systematic Review

The sponsor submitted no studies addressing gaps in the systematic review evidence.

Economic Evidence

Cost and Cost-Effectiveness

Table 4: Summary of Economic Evaluation

Component	Description
Type of economic evaluation	Cost-utility analysis Partitioned survival model
Target population	Relapsed/Refractory Diffuse Large B-cell Lymphoma after at least 2 prior lines of therapy
Treatment	Glofitamab (Columvi)
Dose regimen	Glofitamab is given in 21-day cycles. For the first cycle: 2.5 mg on day 8 and 10 mg on day 15 Subsequent cycles: 30 mg on day 1 Patients may be treated for up to 12 cycles. Patients are required to receive pretreatment with Obinutuzumab 1,000 mg as a single dose on day 1 of the first cycle, and premedication with Acetaminophen 100 mg, Diphenhydramine 50 mg and Prednisolone 100 mg before each dose.
Submitted price	Glofitamab, 2.5 mg/2.5 mL vial: \$1,040.00 per vial Glofitamab, 10 mg/10 mL vial: \$4,160.00 per vial
Treatment cost	First cycle: \$5,200 Subsequent cycles: \$12,480 Pretreatment (with obinutuzumab), and premedication (with acetaminophen, diphenhydramine and prednisolone) for first dose of first cycle: \$5,479
Comparators	<ul style="list-style-type: none"> Salvage chemotherapy (rituximab-based regimens represented by R-GDP) Pola-BR Comparisons with glofitamab are pairwise
Perspective	Canadian publicly funded health care payer
Outcomes	QALYs, LYs
Time horizon	Lifetime (20 years)
Key data sources	Sponsor's unpublished indirect treatment comparison comprising NP30179 clinical trial (Glofitamab), SCHOLAR-1 multicohort study (salvage chemotherapy), GO29365 clinical trial (Pola-BR)
Key limitations	<ul style="list-style-type: none"> The clinical evidence for both glofitamab and Pola-BR for this comparison were from small sample, short-term, nonrandomized, early phase studies. As there was no direct head-to-head evidence the sponsor, the sponsor relied on an adjusted indirect comparison to compare these treatments which was associated with substantial limitations. Based on the available evidence, and in line with clinical expert feedback, glofitamab was considered to be similarly effective as Pola-BR. The sponsor's modelling approach does not adequately capture the causal relationships between treatment, progression-free survival and overall survival, which leads to results that lack face validity. For example, patients receiving glofitamab are assumed to gain more years of life (and QALYs) postprogression than patients receiving salvage chemotherapy. There was no justification for this result provided by the sponsor. There is discordance between the number of treatment cycles between the submitted economic evaluation and the submitted budget impact analysis, which underestimates the duration of

Component	Description
	<p>treatment for glofitamab and Pola-BR.</p> <ul style="list-style-type: none"> The sponsor incorporated modelling approaches that inhibit validation of the model, which lead to concerns regarding the reliability of the model. One key concern is the discordance between the results of the deterministic and probabilistic analyses which severely undermines the validity of the submitted model.
<p>CADTH reanalysis results</p>	<p>CADTH base case was derived by making changes to the following model parameters: assume equal efficacy between glofitamab and Pola-BR, revise long-term disease progression and mortality for glofitamab and salvage chemotherapy, revised treatment costs to align with those in the budget impact analysis. Given the underlying concerns with the sponsor's submitted probabilistic analysis, CADTH focused on the deterministic analyses:</p> <ul style="list-style-type: none"> When compared to Pola-BR, glofitamab is associated with lower costs (\$158,322 vs. \$169,708) and similar QALYs (3.66 vs. 3.66). When compared to salvage chemotherapy, glofitamab is associated with an ICER of \$230,682 per QALY gained (higher costs \$147,749 vs. \$69,901; and greater QALYs 1.17 vs. 0.83). <p>Given the limitations, overall uncertainty associated with the comparative clinical evidence, and the modelling techniques used by the sponsor which limit the ability to validate the model, there remains uncertainty that could not be accounted for in the model.</p>

ICER = incremental cost-effectiveness ratio; LY = life-year; Pola-BR = polatuzumab, bendamustine and rituximab; QALY = quality-adjusted life-year; R-GDP = rituximab, gemcitabine, dexamethasone and cisplatin.

Budget Impact

CADTH identified the following key limitations with the sponsor's analysis: the distribution of salvage chemotherapy regimens does not align with clinical expectations, the market share of Pola-BR is underestimated and the market share of salvage chemotherapy is overestimated, and the uptake of glofitamab is underestimated.

CADTH reanalysis included revising the distribution of salvage chemotherapy to align with clinical expectations, revising the market shares of Pola-BR and salvage chemotherapy in both the reference and new drug scenario, as well as increasing the market uptake of glofitamab. Based on the CADTH reanalysis, the reimbursement of glofitamab for the treatment of R/R DLBCL patients who have received 2 or more lines of systemic therapy and are ineligible to receive or cannot receive CAR-T-cell therapy or have previously received CAR-T-cell therapy would be associated with a budgetary increase of \$1,099,459 in year 1, \$314,808 in year 2, \$1,919,279 in year 3, with a 3-year incremental budget impact of \$3,333,546. The results are sensitive to the number of cycles of treatment used, and whether glofitamab displaces Pola-BR or salvage chemotherapy. If glofitamab is more likely to replace salvage chemotherapy as the sponsor originally assumed, the budget impact may be as high as \$18,168,510.

pERC Information

Members of the Committee

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.

Meeting date: December 6, 2023

Regrets: Two of the expert committee members did not attend.

Conflicts of Interest: Of the 2 committee members who did not attend, 1 expert committee member did not participate due to considerations related to conflict of interest.



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