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Reimbursement Recommendation

Glofitamab (Columvi)

Indication: Columvi (glofitamab), in combination with gemcitabine and oxaliplatin, is indicated for the treatment of adult patients with relapsed or refractory diffuse large B-cell lymphoma not otherwise specified (DLBCL NOS) who are not candidates for autologous stem cell transplant (ASCT)

Sponsor: Hoffmann-La Roche Limited

Final recommendation: Reimburse with conditions

Summary

What Is the Reimbursement Recommendation for Columvi?

Canada's Drug Agency (CDA-AMC) recommends that Columvi in combination with gemcitabine and oxaliplatin be reimbursed by public drug plans for the treatment of adult patients with relapsed or refractory (r/r) diffuse large B-cell lymphoma not otherwise specified (DLBCL NOS) who are not candidates for autologous stem cell transplant (ASCT), if certain conditions are met.

Which Patients Are Eligible for Coverage?

Columvi in combination with gemcitabine and oxaliplatin should only be covered to treat adult patients with r/r DLBCL NOS who are not candidates for ASCT and have received at least 1 prior line of therapy, or 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.

What Are the Conditions for Reimbursement?

Columvi in combination with gemcitabine and oxaliplatin should only be reimbursed if prescribed by clinicians experienced in the treatment of aggressive lymphomas and the side effects of treatment, and if the cost of Columvi is reduced.

Why Did CDA-AMC Make This Recommendation?

Evidence from a clinical trial demonstrated that treatment with Columvi in combination with gemcitabine and oxaliplatin resulted in significantly greater improvement in overall survival (OS) and progression-free survival (PFS) compared with rituximab in combination with gemcitabine and oxaliplatin (R-GemOx) in adult patients with r/r DLBCL NOS who have experienced treatment failure with 1 line of therapy and are not candidates for transplant, or have experienced treatment failure at least 2 lines of therapy.

- The pan-Canadian Oncology Drug Review Expert Review Committee (pERC) noted that Columvi in combination with gemcitabine and oxaliplatin met some key needs identified by patients and clinicians by prolonging life, achieving durable remission, and delaying disease progression.
- Based on the CDA-AMC assessment of the health economic evidence, Columvi plus gemcitabine and oxaliplatin does not represent good value

Summary

to the health care system at the public list price. A price reduction is therefore required.

- Based on public list prices, Columvi plus gemcitabine and oxaliplatin is estimated to cost the public drug plans approximately $43 million over the next 3 years.

Additional Information

What Is r/r DLBCL NOS?

r/r DLBCL NOS refers to a form of DLBCL that does not fit into more specific subtypes of DLBCL and returns after a period of remission following initial treatment or does not respond to initial treatment or relapses very quickly after treatment. DLBCL is a heterogeneous group of aggressive B-cell malignancies that account for approximately 30% to 40% of all non-Hodgkin lymphoma cases in Canada.

Unmet Needs in r/r DLBCL NOS

r/r DLBCL NOS is not curable, and there is an unmet need for treatments that delay progression, provide durable remission, prolong life, and improve health-related quality of life (HRQoL), including the ability to perform daily activities.

How Much Does Columvi With Gemcitabine and Oxaliplatin Cost?

Treatment with Columvi is expected to cost approximately $12,480 (cycles 2 to 12) per patient per 21-day cycle. When used in combination with gemcitabine and oxaliplatin, the 21-day cost is expected to be $13,200 per patient in cycles 2 to 8 and $12,480 per patient in cycles 9 to 12.

Recommendation

pERC recommends that glofitamab in combination with gemcitabine and oxaliplatin (Glofit-GemOx) be reimbursed for the treatment of adult patients with relapsed or refractory diffuse large B-cell lymphoma not otherwise specified (DLBCL NOS) who are not candidates for ASCT, only if the conditions listed in Table 1 are met.

Rationale for the Recommendation

One ongoing phase III, multicentre, open-label, parallel-group, randomized controlled trial (RCT) (the STARGLO trial; N = 274) has demonstrated that treatment with Glofit-GemOx results in added clinical benefit compared with R-GemOx in adult patients with r/r DLBCL NOS who have experienced treatment failure with 1 line of therapy and are not candidates for transplant, or have experienced treatment failure with at least 2 lines of therapy. The primary analysis indicated a statistically significantly greater improvement in OS with Glofit-GemOx than with R-GemOx (hazard ratio [HR] = 0.59; 95% confidence interval [CI], 0.40 to 0.89), although the median OS had not been reached for the Glofit-GemOx arm and was 9.0 months (95% CI, 7.3 months to 14.4 months) in the R-GemOx arm. The updated analysis confirmed the statistically significantly better OS benefit with Glofit-GemOx compared with R-GemOx (HR = 0.62; 95% CI, 0.43 to 0.88), after a median follow-up of 22.5 months and 19.7 months, respectively. Similarly, improvement in PFS was statistically significantly greater with Glofit-GemOx than R-GemOx at the primary analysis (HR = 0.37; 95% CI, 0.25 to 0.55), with a median follow-up of 9.0 months and 6.1 months, respectively. The superior PFS benefit with Glofit-GemOx over R-GemOx was maintained at the updated analysis (HR = 0.40; 95% CI, 0.28 to 0.57) after a median follow-up of 16.3 months and 8.6 months in the Glofit-GemOx and R-GemOx arms, respectively. However, results of the HRQoL analyses demonstrated little to no difference between Glofit-GemOx and R-GemOx in the effect on patients' HRQoL.

Patients in the Glofit-GemOx arm experienced more adverse events (AEs) and serious adverse events (SAEs) than those in the R-GemOx arm. Notably, while there was no incidence of cytokine release syndrome (CRS) in patients treated with R-GemOx, 42.4% of patients in the Glofit-GemOx arm experienced CRS requiring hospitalization, including 20.3% who experienced a serious CRS event. However, pERC determined that the harms profile of Glofit-GemOx was known and generally considered manageable in the appropriate clinical settings.

The sponsor-submitted indirect treatment comparison (ITC) did not show a conclusive benefit of Glofit-GemOx over polatuzumab vedotin plus bendamustine rituximab (pola-BR) or glofitamab monotherapy with regard to efficacy and discontinuation due to AEs.

pERC acknowledged the needs identified by patients and clinicians for therapy options that prolong survival, provide durable disease remission, delay progression, and improve HRQoL, including performance of daily activities. Based on the evidence reviewed, pERC determined that Glofit-GemOx met some of these needs, such as offering a meaningful clinical benefit in OS and PFS.

Using the sponsor-submitted price for glofitamab and publicly listed prices for all other drug costs, the incremental cost-effectiveness ratio (ICER) for Glofit-GemOx is $79,881 per quality-adjusted life-year (QALY) gained compared with R-GemOx, and $141,006 per QALY gained compared with pola-BR. Glofit-GemOx is thus not cost-effective at a $50,000 per QALY willingness-to-pay (WTP) threshold for r/r DLBCS NOS in adults who are not candidates for ASCT. A price reduction for glofitamab is required for Glofit-GemOx to be considered cost-effective at a $50,000 per QALY gained threshold.

Table 1: Reimbursement Conditions and Reasons

Reimbursement condition	Reason	Implementation guidance
Initiation		
1. Treatment with Glofit-GemOx should be reimbursed in adult patients with r/r DLBCL NOS who meet both of the following criteria: 1.1. are not candidates for ASCT and have received at least 1 prior line of therapy, or 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 1.2. have a good performance status.	Evidence from the STARGLO trial demonstrated (and clinical experts consulted by CDA-AMC indicated) that treatment with Glofit-GemOx provides clinical benefit in patients with these characteristics. The STARGLO trial required patients to have an ECOG Performance Status score of ≤ 2.	The product monograph states that at least 1 dose of tocilizumab should be readily available for use before glofitamab infusion at cycles 1 and 2 in the event of CRS. In addition, all patients should receive a regimen involving obinutuzumab 1 week before the first dose of glofitamab, as well as appropriate premedications as outlined in the product monograph to reduce the risk of CRS.
2. Patients are ineligible for treatment with Glofit-GemOx if they have: 2.1. experienced treatment failure with only 1 prior line of therapy and are candidates for ASCT 2.2. current or previous primary or secondary CNS lymphoma 2.3. disease refractory to a CD20 × CD3 bispecific antibody or to GemOx.	These were key exclusion criteria in the STARGLO trial and the review did not assess any evidence suggesting that Glofit-GemOx provides clinical benefit in patients with these characteristics.	According to the clinical experts consulted by CDA-AMC, patients with DLBCL transformed from indolent lymphoma, high-grade B-cell lymphoma with *MYC* and *BCL2* and/or *BCL6* rearrangements, high-grade B-cell lymphoma NOS, and PMBCL are treated with R-GemOx as standard of care. Therefore, they should be considered for Glofit-GemOx given its superior clinical benefits over R-GemOx in the STARGLO trial. Also, patients whose disease is not refractory to second-line glofitamab (i.e., if relapse is at least 6 months from stopping treatment) should be eligible for re-treatment with bispecifics in later lines. pERC agreed with both, noting that patients with grade 3B follicular lymphoma should also be considered for glofitamab.

Reimbursement condition	Reason	Implementation guidance
Discontinuation		
3. Treatment with Glofit-GemOx should be discontinued upon any of the following: 3.1. objective disease progression 3.2. unacceptable toxicity 3.3. completion of 8 cycles of treatment with the combination Glofit-GemOx, followed by 4 cycles of glofitamab monotherapy for a maximum of 12 cycles of glofitamab.	In the STARGLO trial, Glofit-GemOx treatment was discontinued if a patient experienced disease progression or intolerable AEs.	—
Prescribing		
4. Glofit-GemOx should be prescribed by clinicians experienced in the management of aggressive lymphomas and the side effects of treatment.	This condition is meant to ensure that Glofit-GemOx is prescribed for appropriate patients and that adverse effects (e.g., CRS) are managed in an optimized and timely manner.	According to the clinical experts consulted by CDA-AMC, treatment with Glofit-GemOx requires inpatient admission at a setting with emergency facilities for acute complications and the ability to implement specialized management protocols such as premedications and careful monitoring during dose step-up, where the risk of CRS or ICANS is most significant. The requirement for experienced care in the proper settings to manage these AEs restricts the use and availability of Glofit-GemOx in Canada. pERC noted that the drug plans may use protocols to manage the risk of CRS or ICANS as applicable in the jurisdictions.
Pricing		
5. A reduction in price.	The ICER for Glofit-GemOx is $79,881 per QALY gained when compared with R-GemOx and $141,006 when compared with pola-BR. Price reductions greater than 30% will be required for Glofit-GemOx to achieve an ICER below $50,000 per QALY gained. Price reductions for different thresholds vs. R-GemOx and pola-BR are available in Appendix 4 in the Pharmacoeconomic Report.	—

AE = adverse event; ASCT = autologous stem cell transplant; CDA-AMC = Canada's Drug Agency; CNS = central nervous system; CRS = cytokine release syndrome; DLBCL NOS = diffuse large B-cell lymphoma not otherwise specified; ECOG = Eastern Cooperative Oncology Group; Glofit-GemOx = glofitamab plus gemcitabine and oxaliplatin; ICANS = immune effector cell-associated neurotoxicity syndrome; ICER = incremental cost-effectiveness ratio; NOS = not otherwise specified; pERC = pan-Canadian Oncology Drug Review Expert Review Committee; pola-BR = polatuzumab vedotin plus bendamustine rituximab; PMBCL = primary mediastinal large B-cell lymphoma; QALY = quality-adjusted life-year; R-GemOx = rituximab plus gemcitabine and oxaliplatin; r/r = relapsed or refractory; vs. = versus.

Discussion Points

- **Unmet needs**: pERC discussed the input from patient groups and clinician groups and noted that there is an unmet need for more effective and well-tolerated treatment options for patients with r/r DLBCL NOS who are ineligible for, unable to receive, or have already received intensive treatments with ASCT or CAR T-cell therapy. The committee noted that the Grading of Recommendations Assessment, Development and Evaluation (GRADE) assessment of the OS and PFS outcomes of the STARGLO trial indicated with high certainty that the gains were likely clinically meaningful. pERC deliberated on the higher incidence of AEs, SAEs, and notable harms with Glofit-GemOx compared with R-GemOx, noting that measures required to manage or minimize the risk of some AEs associated with Glofit-GemOx are not routinely available at many clinical settings in Canada. However, pERC determined that the AEs were consistent with the known and manageable safety profile of glofitamab, gemcitabine, and oxaliplatin. Therefore, the committee concluded that overall, Glofit-GemOx provides a valuable treatment option for patients with r/r DLBCL NOS who have experienced treatment failure with 1 line of therapy and are not candidates for transplant or have experienced treatment failure with at least 2 lines of therapy.
- **Eligibility of patients outside trial inclusion**: pERC observed that the STARGLO trial excluded patients with DLBCL transformed from indolent lymphoma; high-grade B-cell lymphoma with *MYC* and *BCL2* and/or *BCL6* rearrangements, and high-grade B-cell lymphoma NOS; grade 3B follicular lymphoma, and primary mediastinal large B-cell lymphoma (PMBCL). pERC acknowledged that those criteria may be necessary for the clinical study; however, pERC considered the input from the clinical experts consulted by CDA-AMC that patients with high-risk or transformed lymphoma may be treated with R-GemOx as standard of care. Therefore, the committee agreed with the clinical experts that these patients with high risk should be eligible for treatment with Glofit-GemOx, especially if their disease is refractory and they are unable to tolerate CAR T-cell therapy, given that Glofit-GemOx significantly improved clinical benefit compared with R-GemOx. pERC also noted that the STARGLO trial excluded patients who had experienced treatment failure with only 1 prior line of therapy and were candidates for ASCT. The committee emphasized the importance of an informed discussion between the patient and their clinician about the clinical implications of Glofit-GemOx compared to ASCT. pERC noted that if a patient decides to decline ASCT following such a discussion, this choice should not disqualify them from accessing Glofit-GemOx because that could present ethical challenges.
- **HRQoL**: pERC noted that patients and clinicians highlighted improvement in quality of life (QoL) as an important outcome and treatment goal for patients with r/r DLBCL. However, pERC was unable to draw definitive conclusions regarding the effects of Glofit-GemOx compared to R-GemOx on HRQoL due to concerns about imprecision and missing outcome data in the STARGLO trial. Additionally, HRQoL was not assessed in the sponsor-submitted ITC; therefore, pERC could not determine if Glofit-GemOx offered a benefit in HRQoL compared to other comparators like pola-BR or glofitamab monotherapy.

- **Uncertainty in the economic analysis**: The cost-effectiveness estimates for Glofit-GemOx versus R-GemOx and pola-BR are uncertain because of the uncertainty in the comparative efficacy, long-term survival estimates, and economic model structure. Because of limitations with the submitted model structure and the uncertainty in the long-term efficacy data, the CDA-AMC analysis may not accurately reflect the impact of Glofit-GemOx on patient health and health care resources. Thus, the cost-effectiveness estimates are uncertain and higher price reductions than those noted in the CDA-AMC Pharmacoeconomic Review report may be required to achieve a given WTP threshold.

Background

DLBCL is the most common type of non-Hodgkin lymphoma (NHL) in North America, accounting for approximately 30% to 40% of all NHL cases in Canada. DLBCL is a heterogeneous group of aggressive B-cell malignancies that differ in clinical presentation, molecular features, prognosis, and treatment options. The disease often presents with rapidly enlarging lymph nodes, elevated serum lactate dehydrogenase (LDH), and systemic “B symptoms” such as fever, night sweats, and unexplained weight loss. In 2024, it was estimated that approximately 11,700 new cases of NHL would occur in Canada. Up to 40% of patients with DLBCL have r/r disease, with most patients experiencing rapid disease progression. While the 5-year OS rate for DLBCL is approximately 60% to 70%, in patients who experience r/r DLBCL it is estimated to be as low as 6.6 months, particularly for those who are ineligible for ASCT or who have experienced relapse after second-line therapy.

The objective of this report is to review and critically appraise the evidence submitted by the sponsor on the beneficial and harmful effects of glofitamab (1 mg/mL concentrate solution for IV infusion) in combination with gemcitabine and oxaliplatin (Glofit-GemOx) in the treatment of adult patients with r/r diffuse DLBCL NOS. In February 2024, glofitamab received a recommendation by CDA-AMC to reimburse with clinical criteria and/or conditions for the treatment of adult patients with r/r DLBCL NOS, transformed follicular lymphoma, or primary mediastinal B-cell lymphoma 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.

Glofit-GemOx was approved by Health Canada for the treatment of adult patients with r/r DLBCL NOS who are not candidates for ASCT. Glofitamab is a bispecific T-cell engager with affinity for a CD3 × CD20 bispecific antibody, available as injection for IV infusion. Gemcitabine is an antimetabolite chemotherapy and oxaliplatin is a platinum-based chemotherapy, and both are available for IV infusion. The product monograph recommends a fixed 8-cycle treatment with the combination Glofit-GemOx, followed by 4 cycles of glofitamab monotherapy for a maximum of 12 cycles of glofitamab.

Sources of Information Used by the Committee

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

- a review of 1 ongoing phase III, multicentre, open-label, parallel-group, RCT (the STARGLO trial; N = 274) in adult patients with r/r DLBCL NOS who have experienced treatment failure with 1 line of therapy and are not candidates for transplant, or have experienced treatment failure with at least 2 lines of therapy, and 1 sponsor-submitted ITC
- patients' perspectives gathered by 1 patient group, from Lymphoma Canada (LC)
- input from public drug plans and cancer agencies that participate in the reimbursement review process
- 2 clinical specialists with expertise in diagnosing and treating patients with r/r DLBCL NOS
- input from 2 clinician groups, from LC and the Ontario Health (Cancer Care Ontario) (OH [CCO]) Hematology Cancer Drug Advisory Committee (DAC)
- a review of the pharmacoeconomic model and report submitted by the sponsor.

Perspectives of Patients, Clinicians, and Drug Programs

The information in this section is a summary of input provided by the patient and clinician groups who responded to our call for input and clinical experts consulted by CDA-AMC for this review.

Patient Input

LC is a national Canadian registered charity whose mission is to empower patients and the lymphoma community through education, support, advocacy, and research. Data for this submission were gathered from an online anonymous patient survey from February 24, 2025, to March 23, 2025. A total of 41 responses were collected, which were used to identify the main areas of concern for patients with DLBCL. Two patients, with an age range of 45 years to 54 years and living in the US, had experience with Glofit-GemOx for DLBCL.

Of the respondents who answered the demographic questions (n = 10), 80% lived in Canada, 40% were between the ages of 65 and 74 years, 60% were male and 40% were female. Six respondents were diagnosed 1 to 2 years ago, 5 respondents each were diagnosed less than a year ago or 3 to 5 years ago, and 7 respondents were diagnosed 5 to 10 years ago. Subtypes of large B-cell lymphoma were identified as DLBCL NOS (n = 13); DLBCL arising from follicular lymphoma (n = 7); and DLBCL arising from primary mediastinal B-cell lymphoma, Richter transformation, or germinal centre B-cell lymphoma (1 respondent each).

The respondents highlighted the following symptoms impacting QoL: fatigue or lack of energy, neutropenia, enlarged lymph nodes, night sweats, shortness of breath, bodily aches and pains, reduced appetite, and weight loss. Regarding psychosocial impacts, respondents (n = 23) noted anxiety, fear of progression, difficulty sleeping, stress of diagnosis, problems concentrating, and inability to continue daily activities.

On a scale of 1 (no impact) to 5 (significant impact), respondents rated the ability to go to work, school and volunteer, ability to contribute financially to household expenses, and ability to travel as 4 or higher. Respondents highlighted fatigue, nausea, vomiting, infections, low white blood cells, bone pain, neutropenia, and hair loss as treatment side effects that were the most difficult to tolerate.

Eleven respondents indicated that they had received 1 (36%), 2 (36%), or 3 or more (27%) lines of treatment. The majority of the respondents (63%) experienced relapse and needed treatment past the first-line setting. In the first-line setting, 10 respondents indicated that they had received treatment with rituximab, cyclophosphamide, doxorubicin, vincristine and prednisone (R-CHOP), and 1 respondent received treatment with R-CHOP and rituximab, etoposide, prednisone, vincristine, cyclophosphamide, and doxorubicin. In the second-line setting, 2 respondents each received treatment with rituximab in combination with gemcitabine, dexamethasone, and cisplatin, and salvage therapy plus ASCT; 3 respondents received radiation; and 4 respondents participated in a clinical trial. In the third-line setting, 3 respondents received CAR T-cell therapy, 1 respondent received pola-BR, 2 respondents received glofitamab, and 5 respondents participated in a clinical trial. The patient group noted that 54% of respondents indicated that they were very satisfied with their treatment options in the first-line setting compared to 20% of respondents in the r/r setting. Eight of the 11 respondents had no difficulty or little difficulty accessing treatment, while 3 respondents had some difficulty. Common financial implications reported by respondents for treatment for DLBCL were absence from work, drug costs, supplementary drug costs for side effects, and travelling costs. Respondents provided positive feedback on the care and expertise provided by the health care teams treating them.

Eleven respondents considered longer disease remission, longer survival, control of disease symptoms, normalization of blood counts, and improved QoL to perform daily activities as important outcomes with new treatments. Seven respondents indicated that they were willing to tolerate side effects to access new treatments. Six respondents indicated that treatment choice based on knowledge of side effects and expected outcomes was an important factor.

Two respondents indicated that they had experience with Glofit-GemOx. One respondent was treated less than 6 months previously, while the other was treated 1 to 2 years previously. Respondents indicated that they were in remission upon receiving the therapy. Side effects, including decreased appetite, nausea, vomiting, and fatigue, were noted by both respondents. One respondent also noted CRS, fever, neutropenia, and low platelet count as experienced side effects. Both respondents experienced financial impacts due to absence from work and travel. The patient group noted that the respondents rated their overall experience with the therapy as good and satisfactory, and that they would recommend the therapy to other patients with DLBCL.

Clinician Input

Input From Clinical Experts Consulted for This Review

Unmet Needs

The clinical experts noted that the goal of treatment in transplant-ineligible, second-line or later, r/r DLBCL is generally palliative despite the treatments available today, and that there is a need for access to new

treatment options (e.g., new immunotherapies and cellular therapies). In the absence of a cure, the goal is to prevent disease progression, prolong life, and improve QoL, as determined by a combination of validated QoL scales, patient reports, and clinical assessment. Furthermore, the side effects of treatment — including cytopenia, infections, and AEs of special interest for immunotherapies (e.g., CRS and immune effector cell-associated neurotoxicity syndrome [ICANS]) — include serious conditions. Lastly, health care system resources are required to monitor new interventions, and the risk of SAEs (e.g., CRS and ICANS) can be a burden on the health care system, requiring additional inpatient capacity to deliver and monitor patients receiving these treatments.

Place in Therapy

According to the clinical experts, given that glofitamab works through mechanisms that are different from the current standard cytotoxic agents, it is expected to be active even in very resistant DLBCL. Furthermore, its combination with gemcitabine and oxaliplatin is believed to enhance T-cell activity and is likely to be a promising option for patients with r/r DLBCL.

As patients have more courses of cytotoxic agents (e.g., patients receiving treatment in the second or third line or later), their immune systems may not respond as well to combinations such as Glofit-GemOx. As such, it is likely that this combination will be more active earlier in the disease course, given that immune therapies in general require an intact immune system. Nonetheless, it is not yet clear what the comparative efficacy and safety of GemOx to other types of immunotherapies used in practice such as cellular therapies (e.g., CAR T-cell therapy) will be, or what the longer-term outcomes for this combination will be.

With regard to toxicity, 1 clinical expert stated that while Glofit-GemOx is considered to have a worse safety profile than competing treatments that contain noncytotoxic agents (e.g., polatuzumab vedotin, tafasitamab, or lenalidomide), the anticipated efficacy probably favours the use of Glofit-GemOx. There are still concerns about toxicity, potential for CRS or ICANS, and treatment-related deaths from this combination. The clinical experts anticipate that, in the future, the evolution of treatment with Glofit-GemOx may include less need for hospitalization for administration and monitoring of these drugs, minimizing health disparities between provinces and for patients living in rural areas.

According to the clinical experts, the patient population included in the STARGLO trial was relatively young (with a mean age of approximately 65 years) and in good general health (with an ECOG Performance Status score of 0 to 2). The clinical experts stated that a patient with poor functional status may not be able to tolerate toxicities. In addition, the trial excluded important DLBCL groups (e.g., patients who had transformed disease or double-hit genetic rearrangements), and aggressive forms of DLBCL (e.g., with a high international prognostic index bulky disease, and nongerminal centre subtypes) did not respond as well to therapy. Furthermore, in the STARGLO trial, 1 of the most common reasons for transplant ineligibility was patient choice. According to the clinical experts, this is not expected to be a common reason in a typical patient living in Canada, if otherwise eligible.

According to the clinical experts, traditional measures of response (e.g., PFS, OS, duration of objective response (DOR)) can be used to determine the effectiveness of this treatment. Improvement in QoL and disease-related symptoms would be important patient-reported outcomes to assess as well.

According to the clinical experts, disease progression and/or permanent toxicity (e.g., significantly impaired renal dysfunction, worsening neuropathy, and other toxicities with damage to major organs) would be causes for discontinuing treatment. The clinical experts consulted by CDA-AMC noted that treatment would require inpatient admission so that detailed and specialized management algorithms can be followed, similar to other T cell–engaging therapies. This includes premedications, careful monitoring of the step-up dose where the risk of CRS or ICANS is greatest, and ensuring emergency facilities are available for acute complications. Managing CRS requires experienced care in the proper settings, thus restricting the use and availability of glofitamab in the Canadian landscape.

Clinician Group Input

Two clinician groups, from LC and the OH (CCO) Hematology Cancer DAC, provided input for this submission. Information was gathered from a literature search of published clinical trials of Glofit-GemOx as well as other treatments for r/r DLBCL. Four clinicians provided their input to LC. OH (CCO) gathered information via a teleconference and included input from 7 clinicians.

The LC clinician group noted that, for eligible patients, second-line treatment may include CAR T-cell therapy, if they experience relapse within 12 months of receiving R-CHOP. Chemoimmunotherapy and ASCT may be options if a patient experiences relapse more than 12 months after receiving R-CHOP. Those not experiencing a response to second-line chemoimmunotherapy or who experience relapse after ASCT may receive third-line CAR T-cell therapy.

Both clinician groups noted that the goals of therapy were to prolong survival and improve QoL. In addition, the OH (CCO) DAC noted an improvement in disease response and disease-related symptoms as important goals, and the LC clinician group noted a cure for lymphoma as an important goal. The LC clinician group highlighted that most patients with r/r DLBCL would receive pola-BR or R-GemOx, or monotherapy with glofitamab or epcoritamab. They noted that an unmet need exists for effective therapies and well-tolerated treatments among patients who are ineligible for, are unable to receive, or have already received intensive treatments (i.e., ASCT or CAR T-cell therapy). The OH (CCO) DAC noted poor response rates, PFS, and OS with available therapies.

The LC clinician group mentioned that, once funded, Glofit-GemOx would replace R-GemOx or pola-BR as the preferred treatment in the second-line setting for many patients who are ineligible for or do not wish to receive therapies such as ASCT or CAR T-cell therapy. They also noted that Glofit-GemOx would be an appropriate third-line treatment option for r/r DLBCL. However, this choice would depend on various factors such as a patient's age, comorbidities, values and preferences, treatment history, prior response to chemotherapy, tumour burden, and cytopenias.

The LC clinician group mentioned that patients who have r/r DLBCL after 1 or more lines of therapy and are ineligible for, unable to receive, or decline intensive therapies would be best suited for treatment with Glofit-GemOx. They also highlighted that patients would be expected to have adequate performance status, hematopoietic reserve, and organ function to tolerate both components of the Glofit-GemOx treatment. The OH (CCO) DAC noted that patients not eligible for high-dose chemotherapy due to comorbidities would be

best suited to receive Glofit-GemOx. They also mentioned that patients eligible for CAR T-cell therapy in the second line should proceed along that route.

The LC clinician group noted that Glofit-GemOx would not be recommended for patients whose disease is refractory to a CD20 × CD3 bispecific antibody or to GemOx chemotherapy. Other patient factors that may make candidates inappropriate for this regimen were poor performance status, inadequate organ function, active uncontrolled infections, active central nervous system lymphoma, or being eligible to receive intensive therapies (e.g., ASCT). The LC clinician group noted that other histologic subtypes of DLBCL were likely to benefit from Glofit-GemOx. The OH (CCO) DAC noted that patients who are not refractory to second-line glofitamab should be eligible for re-treatment with bispecifics in later lines.

With regard to response assessment, the LC clinician group noted that PET or CT scans would typically be performed after cycle 4 of the treatment. Repeat imaging may be considered after cycle 8 and at the end of the treatment, depending on the initial depth of response and physician discretion. Both clinician groups agreed that treatment should be discontinued if disease progression or unacceptable toxicities occurs.

The LC clinician group noted that glofitamab should be administered by a hematologist or oncologist with experience managing the potential AEs of bispecific antibodies (including CRS, neurotoxicity, cytopenias, tumour lysis syndrome, and tumour flare) and cytotoxic chemotherapy. Both clinician groups agreed that the initial treatment with glofitamab requires inpatient monitoring. The LC clinician group further noted that patients should receive the first 3 doses of glofitamab at a facility with access to tocilizumab and intensive care unit support (to treat high-grade CRS).

Drug Program Input

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

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

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

Table 2: Responses to Questions From the Drug Programs

Drug program implementation questions	Clinical expert response
Relevant comparators	
Other comparators for r/r DLBCL include pola-BR and R-chemo. In the third line or later, other comparators would include CAR T-cell therapy, pola-BR, and glofitamab or epcoritamab monotherapy. CAR T-cell therapy is publicly funded in most jurisdictions for transplant-ineligible r/r DLBCL after 2 prior therapies. Is there evidence comparing Glofit-GemOx to these therapies?	No.
Considerations for initiation of therapy	
Are there circumstances in which patients with only 1 prior line of therapy could be considered ineligible for ASCT, outside of the trial criteria?	Ineligibility for transplant usually includes age or comorbid illnesses. Sometimes, geographic issues also prevent ASCT use.
Considerations for continuation or renewal of therapy	
Should patients treated with Glofit-GemOx be eligible for downstream glofitamab or epcoritamab? If so, should there be a minimum treatment interval between the last cycle of glofitamab and re-treatment?	If patients experience relapse or progress on treatment, they should not receive glofitamab or epcoritamab downstream. If the treatment is stopped and they relapse afterwards, they can still be candidates for the individual drugs, especially if the relapse occurs at least 6 months after stopping the original treatment. pERC agreed with the clinical experts.
Considerations for discontinuation of therapy	
If 1 of the agents has to be discontinued due to intolerance, can the remaining agents be continued?	Yes. pERC agreed with the clinical experts.
Generalizability	
Should patients with the following be considered for treatment with glofitamab? • DLBCL transformed from indolent lymphoma • Double-hit or triple-hit lymphoma • HGBCL NOS	Yes, to all these specific populations. pERC agreed with the clinical experts, noting that patients with grade 3B follicular lymphoma and primary mediastinal lymphoma B-cell lymphoma should also be considered for glofitamab.
Should patients on existing regimens be switched to Glofit-GemOx?	pERC stated that patients who have just started on another treatment may switch to Glofit-GemOx on a time-limited basis.
System and economic issues	
Is there any guidance regarding which patients will need to be admitted vs. some potentially receiving the initial dose in the outpatient setting?	Patients with high tumour burden or very kinetically active tumours (high Ki 67 indexes). pERC stated that the decision should be based on the discretion of the attending clinician.

ASCT = autologous stem cell transplant; DLBCL = diffuse large B-cell lymphoma; Glofit-GemOx = glofitamab plus gemcitabine and oxaliplatin; HGBCL = high-grade B-cell lymphoma; NOS = not otherwise specified; pola-BR = polatuzumab vedotin plus bendamustine rituximab; R-chemo = rituximab plus chemotherapy; r/r = relapsed or refractory; vs. = versus.

Clinical Evidence

Systematic Review

Description of Studies

The systematic review included 2 reports of 1 pivotal trial (the STARGLO trial). The STARGLO trial is a phase III, ongoing, prospective, international (no sites in Canada), multicentre, open-label, parallel-group RCT to assess Glofit-GemOx compared with R-GemOx in patients with r/r DLBCL NOS who have experienced treatment failure with 1 line of therapy and are not candidates for transplant, as well as patients who have experienced treatment failure with at least 2 lines of therapy. Patients were randomized in a 2:1 ratio to receive either Glofit-GemOx or R-GemOx. Randomization was stratified by number of previous lines of systemic therapy for DLBCL (1 versus ≥ 2) and outcome of last systemic therapy (relapsed versus refractory). Patients in the investigational arm received an IV dose of obinutuzumab pretreatment 7 days before the first dose of glofitamab, then up to 8 cycles of Glofit-GemOx, followed by up to 4 cycles of glofitamab monotherapy to complete up to 12 cycles of glofitamab, with each cycle being 21 days (i.e., every 3 weeks). Patients in the control arm received R-GemOx for up to 8 cycles with each cycle being 21 days (i.e., every 3 weeks). Patients permanently discontinued study treatment if they experienced any of the following: any medical condition that could have jeopardized the patient's safety if they continued to receive study treatment, documented severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) during the study, pregnancy, use of an anticancer therapy not required per protocol, confirmed disease progression (per investigator assessment according to the 2014 Lugano Response Criteria for Malignant Lymphoma), and unacceptable toxicity. The primary outcome was OS, and the key secondary outcomes included independent review committee (IRC)–assessed PFS, IRC-assessed complete response rate (CRR), and IRC-assessed duration of complete response. Harms including SAEs and notable harms were also measured and reported. Patient-reported outcomes (e.g., HRQoL) were also measured.

A total of 274 patients underwent randomization (Glofit-GemOx: n = 183; R-GemOx: n = 91). At the updated analysis data cut-off (February 16, 2024), 86 patients (47.0%) in the Glofit-GemOx arm and 28 patients (30.8%) in the R-GemOx arm were still in the study. Patients had an average age of 65.0 years (standard deviation [SD] = 13.0 years), 57.7% were male, 42.3% were female, and 50.0% were Asian, followed by white (42.0%), and Black or African American (1.1%). Race was not reported for 6.9% of patients. Most patients (89.9%) had an ECOG Performance Status score of 0 or 1, had 1 previous line of therapy (62.8%), and had disease that was refractory to any prior line of therapy (66.4%). Discontinuation from the study occurred in 97 patients (53.0%) and 63 patients (69.2%) in the Glofit-GemOx and R-GemOx arms, respectively. The most frequent reason for study discontinuation in both treatment arms was death (accounting for 43.7% and 57.1% in the Glofit-GemOx and R-GemOx populations, respectively).

Efficacy Results

Overall Survival

For OS, at the time of the primary analysis, with a median duration of follow-up of 12.0 months (95% CI, 10.2 months to 13.2 months) in the Glofit-GemOx arm and 9.6 months (95% CI, 7.9 months to 12.0 months)

in the R-GemOx arm, the median OS was not reached for the Glofit-GemOx arm (95% CI, 13.8 months to not estimable [NE]) and was 9.0 months (95% CI, 7.3 months to 14.4 months) in the R-GemOx arm. These findings for OS favoured Glofit-GemOx (HR = 0.59; 95% CI, 0.40 to 0.89).

At the time of the updated analysis, with a median duration of follow-up of 22.5 months (95% CI, 20.0 months to 24.5 months) in the Glofit-GemOx arm and 19.7 months (95% CI, 18.0 months to 23.1 months) in the R-GemOx arm, the median OS was 25.5 months (95% CI, 18.3 months to NE) for the Glofit-GemOx arm and 12.9 months (95% CI, 7.9 months to 18.5 months) in the R-GemOx arm. These findings for OS favoured Glofit-GemOx (HR = 0.62; 95% CI, 0.43 to 0.88).

IRC-Assessed PFS

For PFS, at the time of the primary analysis, with a median duration of follow-up of 9.0 months (95% CI, 6.2 months to 9.7 months) in the Glofit-GemOx arm and 6.1 months (95% CI, 3.4 months to 8.8 months) in the R-GemOx arm, the median PFS was 12.1 months (95% CI, 6.8 months to 18.3 months) for the Glofit-GemOx arm and 3.3 months (95% CI, 2.5 months to 5.6 months) in the R-GemOx arm. These findings for PFS favoured Glofit-GemOx (HR = 0.37; 95% CI, 0.25 to 0.55).

At the time of the updated analysis, with a median duration of follow-up of 16.3 months (95% CI, 15.3 months to 20.1 months) in the Glofit-GemOx arm and 8.6 months (95% CI, 5.9 months to 14.6 months) in the R-GemOx arm, the median PFS was 13.8 months (95% CI, 8.7 months to 20.5 months) for the Glofit-GemOx arm and 3.6 months (95% CI, 2.5 months to 7.1 months) in the R-GemOx arm. These findings for PFS favoured Glofit-GemOx (HR = 0.40; 95% CI, 0.28 to 0.57).

IRC-Assessed CRR

At the time of the primary analysis, the CRR was 50.3% (95% CI, 42.8% to 57.7%) for Glofit-GemOx and 22.0% (95% CI, 14.0% to 31.9%) for R-GemOx, with a between-group difference of 28.3% (95% CI, 16.3% to 40.3%) in favour of Glofit-GemOx.

At the time of the updated analysis, the CRR was 58.5% (95% CI, 51.0% to 65.7%) for Glofit-GemOx and 25.3% (95% CI, 16.8% to 35.5%) for R-GemOx, with a between-group difference of 33.2% (95% CI, 20.9% to 45.5%) in favour of Glofit-GemOx.

IRC-Assessed DOR

For DOR at the time of the primary analysis, with a median duration of follow-up of 6.9 months (95% CI, 6.3 months to 7.6 months) in the Glofit-GemOx arm and 5.8 months (95% CI, 2.8 months to 6.1 months) in the R-GemOx arm, the median DOR in patients was 15.4 months (95% CI, 14.4 months to NE) for Glofit-GemOx and 9.1 months (95% CI, 5.3 months to NE) for R-GemOx. There was no evidence of a statistically significant difference between the 2 groups (unstratified HR = 0.58; 95% CI, 0.26 to 1.30) with regard to DOR.

At the time of the updated analysis, with a median duration of follow-up 14.3 months (95% CI, 13.0 months to 18.0 months) in the Glofit-GemOx arm and 5.8 months (95% CI, 3.0 months to 12.5 months) in the R-GemOx arm, the median DOR for Glofit-GemOx arm was not reached (NE months; 95% CI, 17.6 months

to NE) and was 10.3 months (95% CI, 6.5 months to NE) in the R-GemOx arm. There was no evidence of a statistically significant difference between the 2 groups (unstratified HR 0.57, 95% CI, 0.30 to 1.10) with regards to the DOR.

Health-Related Quality of Life

For HRQoL, descriptive summary statistics and the change from baseline were to be calculated by treatment arm at each assessment. The mean difference between groups in change from baseline was not tested statistically.

Change From Baseline in EORTC QLQ-C30 Fatigue Score

At baseline, the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC QLQ-C30) Fatigue scores for Glofit-GemOx and R-GemOx were 32.98 (SD = 25.20) and 32.18 (SD = 21.17), respectively. At the time of the primary analysis, the mean change from baseline was 2.42 (SD = 23.10) in the Glofit-GemOx arm and 4.98 (SD = 22.43) in the R-GemOx arm at the end of treatment (either completion or discontinuation). At the time of the updated analyses, the mean change from baseline in EORTC QLQ-C30 Fatigue score was −1.24 (SD = 25.64) in the Glofit-GemOx arm and 4.59 (SD = 21.64) in the R-GemOx arm at the end of treatment (either completion or discontinuation).

At baseline, the EORTC QLQ-C30 Physical Functioning subscale scores for Glofit-GemOx and R-GemOx were 77.14 (SD = 20.01) and 76.63 (SD = 18.72), respectively. At the time of the primary analysis, the mean change from baseline in EORTC QLQ-C30 Physical Functioning subscale score was −1.65 (SD = 19.97) in the Glofit-GemOx arm and −4.25 (SD = 17.82) in the R-GemOx arm at the end of treatment (either completion or discontinuation). At the time of the updated analyses, the mean change from baseline in EORTC QLQ-C30 Physical Functioning subscale score was 0.36 (SD = 20.29) in the Glofit-GemOx arm and −4.13 (SD = 17.12) in the R-GemOx arm at the end of treatment (either completion or discontinuation).

Change From Baseline in FACT-Lym LymS Score

At baseline, the Functional Assessment of Cancer Therapy – Lymphoma Scoring Guidelines Lymphoma Subscale (FACT-Lym LymS) scores for Glofit-GemOx and R-GemOx were 45.38 (SD = 10.60) and 43.90 (SD = 10.43), respectively. At the time of the primary analysis, the mean change from baseline in FACT-Lym LymS score was 1.71 (SD = 10.58) in the Glofit-GemOx arm and 0.41 (SD = 8.00) in the R-GemOx arm at the end of treatment (either completion or discontinuation). At the time of the updated analyses, the mean change from baseline in FACT-Lym LymS score was 2.32 (SD = 10.05) in the Glofit-GemOx arm and 0.64 (SD = 7.82) in the R-GemOx arm at the end of treatment (either completion or discontinuation).

Harms Results

Adverse Events

At the updated analyses, the majority of patients in both the Glofit-GemOx arm (172 of 172 patients [100%]) and the R-GemOx arm (84 of 88 patients [95.5%]) experienced at least 1 AE. The most frequently reported AEs in the Glofit-GemOx arm were CRS (76 patients [44.2%]), nausea (71 patients [41.3%]), and anemia (71 patients [41.3%]). The most frequently reported AEs in the R-GemOx arm were nausea (35 patients [39.8%]), platelet count reduction (27 patients [30.7%]), and diarrhea (24 patients [27.3%]).

Serious Adverse Events

At the time of the updated analyses, SAEs were reported in a greater proportion of patients in the Glofit-GemOx (any treatment exposed) population (98 patients [54.4%]) compared with the R-GemOx population (15 patients [17.0%]). The most common SAEs (with an incidence rate ≥ 5%) in the Glofit-GemOx and R-GemOx populations were CRS (Glofit-GemOx versus R-GemOx: 20.3% versus 0.0%), pyrexia (Glofit-GemOx versus R-GemOx: 6.4% versus 1.1%), and pneumonia (Glofit-GemOx versus R-GemOx: 5.8% versus 4.5%).

Withdrawals Due to AEs

At the updated analyses, withdrawal of any study treatment was reported in a greater proportion of patients in the Glofit-GemOx arm (any treatment exposed) (48 patients [26.7%]) than the R-GemOx arm (11 patients [12.5%]).

Notable Harms: CRS

At the time of the updated analysis, there were 76 patients (42.2%) and 0 patients experiencing CRS events of any grade in the Glofit-GemOx (Glofit exposed) arm and R-GemOx arm, respectively. Of the patients receiving Glofit-GemOx (any treatment exposed) who experienced CRS, 54 (30.0%) had grade 1 events, 18 (10.0%) had grade 2 events, and 4 (2.2%) had grade 3 events.

Critical Appraisal

The STARGLO trial was planned with adequate power to meet the goals of the study's primary outcome (OS), randomizing 274 patients in a 2:1 ratio to Glofit-GemOx or R-GemOx. The assumptions made when performing power calculations were considered reasonable. The randomization method and allocation concealment appeared adequate. Further, the randomization was stratified based on important prognostic factors to minimize important differences in baseline characteristics between groups and to allow for maintenance of randomization for exploratory subgroup analyses based on these baseline characteristics. The use of IRC assessments for the important outcomes provided objectivity to the outcome assessments. Furthermore, to minimize bias, the IRC remained blinded to treatment assignment and the sponsor did not have access to efficacy and safety summaries, which compared treatment arms before the formal reporting of study results, with the exception that the randomization code may have been made available to facilitate the analysis of pharmacokinetic samples. There were, however, some limitations and potential sources of bias, which are outlined in this section.

The reported results to date were based on an interim analysis at the clinical cut-off date of March 29, 2023, and a follow-up analysis was conducted at the subsequent clinical cut-off date of February 16, 2024. The final data will not be available for several years. Interim analyses are typically at risk of overestimating the true magnitude of benefit.

The STARGLO trial has an open-label design, and the lack of blinding may bias results, particularly for subjective, patient-reported outcomes. HRQoL self-reporting and reporting of more subjective AEs may also be influenced by lack of blinding, as patients may anticipate known adverse effects and thus may be more likely to report them when they do occur. Physician knowledge of their patients' assigned treatment may also

affect the way they treat their patients, and patient knowledge of their assigned treatment may make them more or less likely to remain in the study. An IRC was used to evaluate the study end points of PFS, CRR, and DOR in a blinded manner and would be less likely to be influenced by the lack of blinding. While the median OS was not yet reached and the data were immature with respect to OS at the time of the primary analysis, the median OS was reached at the time of the updated analysis. Estimates of the median DOR were not yet reached at the time of the primary analysis or the updated analysis, remaining immature.

Multiplicity was controlled in the study by using a hierarchical testing procedure. The procedure seemed appropriate for the primary and key secondary outcomes (alpha spending between primary and updated analyses). Statistical significance was reached for the primary analyses; therefore, the subsequent updated clinical cut-off analysis was considered descriptive. The subgroup analyses were not adjusted for multiplicity nor powered to detect effect modification. Nonetheless, the results of most sensitivity and subgroup analyses for OS were generally consistent with the primary analysis supporting the consistency of the effect across subgroups.

Additionally, for OS, new antilymphoma therapy (NALT) was allowed in patients who completed study treatment or discontinued trial medications based on investigator assessment. This can potentially bias the true effect of the interventions on survival and can vary across settings, as the decision on whether or not to use a NALT was not systematically applied across all of the enrolling centres. Patients who started on a NALT were not censored at the time of initiation for the OS end point. Moreover, patients who discontinued therapy remained in the analysis of OS. This was also the case with the analysis of PFS, CRR, and DOR; however, additional sensitivity analyses that explored the potential impact of NALT on treatment differences were conducted and were supportive of the overall findings. However, at the time of the evidence review for OS by CDA-AMC, these sensitivity analyses were not available for review; thus, we could not be certain of the magnitude and direction of the potential bias.

For both OS and PFS, patients could be censored for several reasons, including missed assessments. The amount of censoring in both arms was very high, which can introduce bias and reduce the validity of the assessments. At the time of the evidence review by CDA-AMC, sensitivity analyses addressing each reason for censoring data and the direction of potential bias were not available for review; thus, we could not be certain of the magnitude and direction of the potential bias.

At the time of the second interim analysis, most patients had discontinued treatment, mainly due to disease progression or death. This large level of treatment discontinuation may influence any potential comparative evaluation and interpretation of HRQoL and harms outcomes. Also, the number of patients remaining to complete HRQoL assessments declined over time, resulting in a risk of bias due to missing outcome data. As such, HRQoL was likely biased due to the large number of participants that did not complete the assessments during the follow-up period.

GRADE Summary of Findings and Certainty of the Evidence

The selection of outcomes for 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 (Table 3). The following list of outcomes was finalized in consultation with expert committee members:

- OS: 6, 12, and 18 months
- PFS: 6, 12, and 18 months
- HRQoL using the FACT-Lym LymS: change from baseline; 6, 12, and 18 months
- individuals with SAEs: up to the data cut-off.

Table 3: Summary of Findings for Glofit-GemOx vs. R-GemOx for Patients With DLBCL NOS

Outcome and follow-up	Patients (studies), N	Absolute effects (95% CI)			Certainty	Interpretation
		R-GemOx	Glofit-GemOx	Difference		
Survival outcomes						
Probability of OS by IRC at 6 months	274 (1 RCT)	687 per 1,000 (587 to 787 per 1,000)	780 per 1,000 (719 to 841 per 1,000)	93 per 1,000 (25 less to 201 more per 1,000)	Moderate[a]	Glofit-GemOx likely results in an improvement in OS compared to R-GemOx.
Probability of OS by IRC at 12 months	274 (1 RCT)	525 per 1,000 (416 to 633 per 1,000)	629 per 1,000 (557 to 701 per 1,000)	104 per 1,000 (26 less to 234 more per 1,000)	Moderate[a]	Glofit-GemOx likely results in an improvement in OS compared to R-GemOx.
Probability of OS by IRC at 18 months	274 (1 RCT)	397 per 1,000 (287 to 507 per 1,000)	576 per 1,000 (502 to 651 per 1,000)	180 per 1,000 (47 to 312 more per 1,000)	High[b]	Glofit-GemOx likely results in an improvement in OS compared to R-GemOx.
Probability of PFS by IRC at 6 months	274 (1 RCT)	390 per 1,000 (276 to 504 per 1,000)	659 per 1,000 (587 to 730 per 1,000)	269 per 1,000 (134 to 403 more per 1,000)	High[b]	Glofit-GemOx likely results in an improvement in PFS compared to R-GemOx.
Probability of PFS by IRC at 12 months	274 (1 RCT)	252 per 1,000 (136 to 369 per 1,000)	517 per 1,000 (440, 594 per 1,000)	265 per 1,000 (125 to 405 more per 1,000)	High[b]	Glofit-GemOx likely results in an improvement in PFS compared to R-GemOx.
Probability of PFS by IRC at 18 months	274 (1 RCT)	221 per 1,000 (104 to 338 per 1,000)	454 per 1,000 (373 to 535 per 1,000)	233 per 1,000 (91 to 376 more per 1,000)	High[b]	Glofit-GemOx likely results in an improvement in PFS compared to R-GemOx.
Patient-reported outcomes (HRQoL)						
FACT-Lym LymS at 6 months	274 (1 RCT)	4.30 points lower (SD = 8.35)	2.80 points lower (SD = 9.42)	The mean difference between groups in change from baseline was not tested statistically.	Very low[c]	Glofit-GemOx may result in little to no difference in FACT-Lym LymS scores compared to R-GemOx.

Outcome and follow-up	Patients (studies), N	Absolute effects (95% CI)			Certainty	Interpretation
		R-GemOx	Glofit-GemOx	Difference		
FACT-Lym LymS at 12 months	274 (1 RCT)	5.81 points lower (SD = 11.47)	3.30 points lower (SD = 10.66)	The mean difference between groups in change from baseline was not tested statistically.	Very low[c]	Glofit-GemOx may result in little to no difference in FACT-Lym LymS scores compared to R-GemOx.
FACT-Lym LymS at 18 months	274 (1 RCT)	5.43 points lower (SD = 11.44)	6.60 points lower (SD = 8.00)	The mean difference between groups in change from baseline was not tested statistically.	Very low[c]	Glofit-GemOx may result in little to no difference in FACT-Lym LymS scores compared to R-GemOx.
Safety outcomes (treatment-emergent SAEs)						
SAEs Follow-up: Up to data cut-off	260 (1 RCT)	150 per 1,000	544 per 1,000	The absolute difference between groups was not tested statistically.	High[b]	Glofit-GemOx may result in an increase in SAEs compared to R-GemOx.

CI = confidence interval; DLBCL NOS = diffuse large B-cell lymphoma not otherwise specified; FACT-Lym LymS = Functional Assessment of Cancer Therapy – Lymphoma Scoring Guidelines Lymphoma Subscale; Glofit-GemOx = glofitamab plus gemcitabine and oxaliplatin; HRQoL = health-related quality of life; IRC = independent review committee; NA = not applicable; OS = overall survival; PFS = progression-free survival; RCT = randomized controlled trial; R-GemOx = rituximab plus gemcitabine and oxaliplatin; SAE = serious adverse event; SD = standard deviation; vs. = versus.

Note: Study limitations (which refer to internal validity or risk of bias), inconsistency across studies, indirectness, imprecision of effects, and publication bias were considered when assessing the certainty of the evidence. All serious concerns in these domains that led to the rating down of the level of certainty are documented in the table footnotes.

[a]No threshold of clinical importance could be established; effects were appraised using the null. Rated down 1 level for imprecision; there is the possibility for both benefit and harm.

[b]No threshold of clinical importance could be established; effects were appraised using the null.

[c]Rated down 3 levels for study limitations; there is risk of bias due to lack of blinding and a subjective outcome, substantial missing outcome data, and imprecision; there is the possibility for both benefit and harm.

Source: Details included in the table are from the sponsor's Summary of Clinical Evidence and additional information provided by the sponsor.

Long-Term Extension Studies

There is no long-term extension phase planned for the STARGLO trial at this time.

Indirect Comparisons

Description of Studies

The sponsor submitted an ITC report with 2 comparisons considered of relevance for the current CDA-AMC review. These analyses used individual patient data from the pivotal STARGLO (GO41944) trial and 2 other trials (the GO29365 study for pola-BR and the NP30179 study for glofitamab monotherapy). Propensity score analyses (PSAs) were performed to provide an estimate of treatment effects after accounting for differences in covariates considered to be potential prognostic factors or treatment-effect modifiers across treatment groups. The analyzed outcomes were OS, PFS, DOR, objective response rate (ORR), and discontinuation due to AEs.

Efficacy Results

Overall Survival

The HR for OS between Glofit-GemOx and pola-BR was [redacted] As the CIs crossed 1, there was no evidence of a statistically significant difference between the 2 treatments. These results were confirmed in the sensitivity analyses.

The HR for OS between Glofit-GemOx and glofitamab monotherapy was [redacted] As the CIs crossed 1, there was no evidence of a statistically significant difference between the 2 treatments. These results were confirmed in the sensitivity analyses.

IRC-Assessed PFS

The HR for PFS between Glofit-GemOx and pola-BR was [redacted] As the CIs crossed 1, there was no evidence of a statistically significant difference between the 2 treatments. These results were confirmed in the sensitivity analyses.

Tumour Response Variables

For IRC-assessed CRR, the OR between Glofit-GemOx and pola-BR was [redacted] As the CIs crossed 1, there no evidence of a statistically significant difference between the 2 treatments. These results were confirmed in the full matching analysis, but inverse probability of treatment weighting with multiple imputation analysis showed a more favourable benefit with Glofit-GemOx.

For IRC-assessed CRR, the OR between Glofit-GemOx and glofitamab was [redacted] As the CIs crossed 1, there was no evidence of a statistically significant difference between the 2 treatments. These results were confirmed in the sensitivity analyses.

For IRC-assessed DOR, the OR between Glofit-GemOx and pola-BR was [redacted] As the CIs crossed 1, there was no evidence of a statistically significant difference between the 2 treatments. These results were confirmed in the sensitivity analyses.

For IRC-assessed DOR, the OR between Glofit-GemOx and glofitamab was [redacted] As the CIs crossed 1, there was no evidence of a statistically significant difference between the 2 treatments. These results were confirmed in the sensitivity analyses.

Harms Results

Treatment Discontinuation Due to AEs

The OR between Glofit-GemOx and pola-BR for treatment discontinuation due to an AE was [redacted] As the OR crossed 1, there was no evidence of a statistically significant difference between the 2 treatments. These results were confirmed in the sensitivity analyses.

The OR between Glofit-GemOx and glofitamab for treatment discontinuation due to an AE was [redacted] As the OR CIs were wide and crossed 1, there was no evidence of a statistically significant difference between the 2 treatments. These results were confirmed in the sensitivity analyses.

Critical Appraisal

No major issues were identified with regard to the systematic search for identifying relevant studies for the ITC. The ITC analyses were preceded by a feasibility assessment, with a predefined hierarchy of evidence to guide study inclusion. In addition, out of all of the indirect comparisons submitted by the sponsor, only 2 PSAs were considered to be relevant to the current CDA-AMC review.

The choice of the matching factors was based on external clinical experts on an advisory board run by the sponsor. For the glofitamab monotherapy comparison, only high- and medium-priority variables were included due to the limitations of the adjusted model, whereby the Glofit-GemOx arm had a very small estimated sample size (ESS) (< 30) when including high-, medium-, and low-priority variables, which adds uncertainty to these analyses.

While the ITC evaluated important clinical outcomes like OS, PFS, CRR or ORR, DOR, and treatment discontinuation due to AEs, other important outcomes for decision-making, such as HRQoL and SAEs, were not included in the analyses. This limits the ability to evaluate the true balance of comparative benefits and harms. Even for the evaluated outcomes, in most cases the CIs were wide and crossed the null, introducing further imprecision and uncertainty in the comparative effects.

Before the ITC adjustments, there were notable observed differences between the trial patient characteristics. Following adjustment, the populations were balanced. Nonetheless, adjustment methods cannot overcome methodological or design differences (e.g., study design, region or setting, length of follow-up, outcome definitions [event and censoring rules, schedule and method of assessments], cointerventions, and subsequent treatments) across the comparators, which can introduce bias. For example, the study designs for the 3 trials differed with the GO29365 study being a phase Ib/II study, the NP30179 study being a phase II study, and the STARGLO trial being a phase III study. In the GO29365 study, patients who received pola-BR had different histologies, such as DLBCL NOS, high-grade B-cell lymphoma (HGBCL), PMBCL, and transformed follicular lymphoma. However, the NP30179 study (with glofitamab monotherapy) included patients with DLBCL NOS, transformed follicular lymphoma, PMBCL, and HGBCL, and the STARGLO trial only included patients with DLBCL NOS. Further, the NP30179 study only included individuals with r/r DLBCL receiving third-line or later-line therapy (including only DLBCL NOS and 2, 3, or 4 prior treatment lines only). As these factors could not be accounted for in the PSA models, differences between the study samples would be expected to introduce bias into the estimates, although the magnitude and direction is unclear.

The matching adjustments conducted as part of the PSAs did sometimes result in residual imbalances for multiple prognostic factors. Although these are further controlled for in subsequent outcome analyses (following a doubly robust approach), it is important to note that the second adjustment could only be performed for summary statistics (HR or OR) but not for Kaplan-Meier curves.

Generalizability may be an issue due to the small sample size remaining after the exclusions and weighting in some of the analyses. For example, after subsetting the STARGLO trial and the GO29365 study patient cohorts used for the comparisons, there were 170 patients in the Glofit-GemOx arm and 132 patients in the pola-BR arm. Following inverse probability of treatment weighting adjustment, the ESS for Glofit-GemOx was

132.60 and the ESS for pola-BR was 107.36, which could affect the power of the analysis resulting in wide CIs and a lack of ability to find true differences.

Studies Addressing Gaps in the Evidence From the Systematic Review

No additional studies were submitted by the sponsor.

Economic Evidence

Cost and Cost-Effectiveness

- Glofitamab is available as 2.5 mL and 10 mL vials (1 mg/mL) of solution for IV infusion. At the submitted price of $1,040 per 25 mL vial (2.5 mg glofitamab) and $4,160 per 10 mL vial (10 mg glofitamab), the cost of glofitamab per 21-day cycle is expected to be $5,200 per patient in the first cycle of treatment ($12,480 in subsequent cycles), based on the Health Canada–recommended dosage. When used in combination with gemcitabine and oxaliplatin, the 21-day cost is expected to be $11,672, $13,200, and $12,480 per patient in cycle 1, cycles 2 to 8, and cycles 9 to 12, respectively.
- Clinical efficacy in the economic analysis for Glofit-GemOx versus R-GemOx was derived from the STARGLO trial. Evidence submitted by the sponsor suggests that Glofit-GemOx likely results in an improvement in OS and PFS compared with R-GemOx among patients with r/r DLBCL NOS who are not candidates for ASCT. Comparative clinical efficacy for Glofit-GemOx versus pola-BR and glofitamab monotherapy was informed by sponsor-submitted ITCs, which do not support an improvement in OS or PFS with Glofit-GemOx. HRQoL and AEs were not included in the sponsor's ITC.
- The results of the CDA-AMC base case suggest:
  - Glofit-GemOx is predicted to be associated with higher costs to the health care system than R-GemOx (incremental costs = $165,684) and pola-BR (incremental costs = $49,252), primarily driven by increased costs associated with drug acquisition costs associated with Glofit-GemOx.
  - Glofit-GemOx is predicted to be associated with a gain of 2.96 life-years (LYs) compared to R-GemOx and 0.43 LYs compared to pola-BR. When the impact on HRQoL is also considered, Glofit-GemOx is predicted to be associated with a gain of 2.07 and 0.35 QALYs compared to R-GemOx and pola-BR, respectively.
  - The ICER for Glofit-GemOx compared to R-GemOx was $79,881 per QALY gained in the CDA-AMC base case. Compared to pola-BR, the ICER for Glofit-GemOx was $141,006 per QALY gained. The estimated ICER is uncertain because of the uncertainty in the comparative efficacy, long-term survival estimates, and economic model structure. Given the identified limitations with the submitted model structure and the uncertainty in the long-term efficacy data, the economic analysis may not accurately assess the impact on patient health and health care resources. Thus,

the cost-effectiveness estimates are uncertain and higher price reductions may be required to achieve a given WTP threshold.

- CDA-AMC estimates that the budget impact of reimbursing Glofit-GemOx for the Health Canada–indicated population will be approximately $43 million over the first 3 years of reimbursement compared to the amount currently spent on comparators, with an estimated expenditure of $127 million on Glofit-GemOx over this period (expenditure on glofitamab alone = $108 million). The actual budget impact of reimbursing Glofit-GemOx will depend on the number of patients eligible for treatment, the market uptake of Glofit-GemOx, and the treatment duration of therapies in clinical practice.

pERC Information

Members of the Committee

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

Meeting date: August 13, 2025

Regrets: Four expert committee members did not attend.

Conflicts of interest: None

Canada's Drug Agency
L'Agence des médicaments du Canada
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Questions or requests for information about this report can be directed to Requests@CDA-AMC.ca.