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CADTH Reimbursement Review

Glofitamab (Columvi)

Sponsor: Hoffmann-La Roche Limited
Therapeutic area: Relapsed or refractory diffuse large B-cell lymphoma

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Abbreviations

AE	adverse event
ASTCT	American Society for Transplantation and Cellular Therapy
ATE	average treatment effect
CAR	chimeric antigen receptor
CCOD	clinical cut-off date
CI	confidence interval
CR	complete response
CRS	cytokine release syndrome
D2S2	cohort D2 subcohort 2
DLBCL	diffuse large B-cell lymphoma
DOCR	duration of complete response
DOR	duration of response
ECOG PS	Eastern Cooperative Oncology Group performance status
EORTC QLQ-C30	European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30
ESS	effective sample size
FACT-Lym	Functional Assessment of Cancer Therapy–Lymphoma
GHS/QoL	global health status/quality of life
GRADE	Grading of Recommendations, Assessment, Development, and Evaluation
HGBCL	high-grade B-cell lymphoma
HRQoL	health-related quality of life
IPI	International Prognostic Index
IPTW	inverse probability treatment weighting
IRC	independent review committee
ITC	indirect treatment comparison
LymS	lymphoma-specific subscale
mAb	monoclonal antibody
MAIC	matching-adjusted indirect comparison
NHL	non-Hodgkin lymphoma
NICE	National Institute for Health and Care Excellence
NOC/c	Notice of Compliance with conditions
OH-CCO	Ontario Health–Cancer Care Ontario
ORR	overall response rate

OS	overall survival
PFS	progression-free survival
PMBCL	primary mediastinal B-cell lymphoma
Pola-BR	polatuzumab vedotin, bendamustine, and rituximab
PR	partial response
PRO	patient-reported outcome
PSA	propensity score analysis
R-CHOP	rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone
R-GemOx	rituximab plus gemcitabine and oxaliplatin
r/r	relapsed or refractory
SAE	serious adverse event
SAP	Statistical Analysis Plan
SCT	stem cell transplant
SD	standard deviation
SLR	systematic literature review
trFL	transformed follicular lymphoma

Executive Summary

An overview of the submission details for the drug under review is provided in Table 1.

Table 1: Background Information of Application Submitted for Review

Item	Description
Drug product	Glofitamab (Columvi), concentrate for solution for infusion, 2.5 mg/2.5 mL vial and 10 mg/10 mL vial, IV infusion
Sponsor	Hoffmann-La Roche Limited
Indication	Columvi (glofitamab) is indicated for the treatment of adult patients with relapsed or refractory DLBCL not otherwise specified, arising from follicular lymphoma (trFL), or PMBCL, who have received two 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.
Reimbursement request	Glofitamab is indicated for the treatment of adult patients with relapsed or refractory DLBCL not otherwise specified, 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, following obinutuzumab pretreatment.
Health Canada approval status	NOC/c
Health Canada review pathway	Standard
NOC date	NOC/c received March 24, 2023
Recommended dose	Step-up dosing beginning with obinutuzumab 1,000 mg on cycle 1 day 1, followed by glofitamab 2.5 mg on cycle 1 day 8, 10 mg on cycle 1 day 15, and 30 mg on day 1 of each subsequent cycle for a maximum of 12 cycles. Each treatment cycle is 21 days.

CAR = chimeric antigen receptor; DLBCL = diffuse large B-cell lymphoma; NOC = Notice of Compliance; NOC/c = Notice of Compliance with Conditions; PMBCL = primary mediastinal B-cell lymphoma; trFL = transformed follicular lymphoma.

Introduction

Diffuse large B-cell lymphoma (DLBCL) is the most common type of non-Hodgkin lymphoma (NHL), accounting for approximately 30% to 40% of all NHL cases in Canada.[1] DLBCLs are a heterogeneous group of aggressive B-cell malignancies that differ in clinical presentation, molecular features, prognosis, and treatment options.[1,2]

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 bones, brain, and gastrointestinal tract, among other locations. DLBCL can also cause systemic B symptoms (i.e., unexplained fever, weight loss, and night sweats) and elevated serum lactate dehydrogenase.[3]

There are few estimates of DLBCL incidence and prevalence in Canada. The Canadian Cancer Society estimated that 11,400 people living in Canada were diagnosed with NHL in 2022, with 3,000 dying from the disease.[4] International studies have estimated the incidence of DLBCL in the US and England at approximately 7 cases per 100,000 persons per year.[3]

Based on statistics from 1975 through 2017, the estimated 5-year relative survival at diagnosis of DLBCL was 63.8% in the US.[5] First-line treatment for DLBCL is relatively standardized across Canada, with most patients receiving rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) every 3 weeks.[6,7] Although the cure rate for DLBCL is high (60% to 70%), approximately 30% to 50% of patients will experience relapse, or have disease that is refractory to treatment with standard first-line R-CHOP or a similar regimen.[8,9] Patients with disease that relapses early (within 12 months) or patients with refractory disease have a worse prognosis than those with disease that does not relapse within 12 months, even if they receive second-line therapy.[6,10] For patients with disease that is refractory to R-CHOP or who experience relapse after 12 months of R-CHOP, the standard approach if those patients have chemosensitive disease and meet eligibility criteria for transplant consists of salvage platinum-based chemotherapy followed by high-dose chemotherapy and autologous stem cell transplant (SCT). For patients who are ineligible for SCT, second-line treatment options include chemotherapy with or without rituximab, or polatuzumab vedotin, bendamustine, and rituximab (Pola-BR).[1,7] Currently, chimeric antigen receptor (CAR) T-cell therapy is approved in Canada for patients with relapsed or refractory (r/r) DLBCL after 2 or more lines of therapy. As such, CAR T-cell therapy is the standard treatment approach for patients with r/r DLBCL that is not responding to salvage chemotherapy (meaning those patients are ineligible for transplant) or patients with r/r DLBCL that relapses post-SCT.[1,7] Though not currently funded in the second-line setting, CAR T-cell therapy could be a second-line treatment option for eligible patients.[11] For patients who do not have chemosensitive disease and who are ineligible for autologous SCT or who experience relapse post-SCT or post–CAR T-cell therapy, the prognosis is poor and there is no standard approach to treatment. Available options, if accessible, are currently limited to palliative chemotherapies — including rituximab plus gemcitabine and oxaliplatin (R-GemOx), Pola-BR, and tafasitamab with lenalidomide — or clinical trials with novel drugs.[1,7]

Glofitamab (Columvi) is a bispecific monoclonal antibody (mAb) (recombinant humanized immunoglobulin G1) 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. By simultaneously binding to CD20 on the B-cell and CD3 on the T-cell, glofitamab mediates the formation of an immunological synapse, with subsequent potent T-cell activation and proliferation, secretion of cytokines, and release of cytolytic proteins, which results in the lysis of CD20-expressing B-cells.[12]

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 for the treatment of adult patients with r/r DLBCL not otherwise specified, DLBCL arising from transformed 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, following pretreatment with obinutuzumab.

Stakeholder Perspectives

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

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 detection of disease, discover new and improved treatments for lymphoma, improve access to those treatments, and find a cure for lymphoma. Information for this patient group input was collected from June 5, 2023, to July 10, 2023, through an online survey of 27 patients. Thirteen patients included in the survey (48%) were diagnosed with DLBCL not otherwise specified, 8 (30%) were diagnosed 3 to 5 years before the survey, 8 (30%) were living in Canada, and 6 (22%) were aged 45 to 54 years. At diagnosis, the following disease symptoms were most reported by the patients included in the survey as having a significant impact on their health-related quality of life (HRQoL): enlarged lymph nodes (32% of patients), bodily swelling (27% of patients), fatigue (27% of patients), shortness of breath (27% of patients), bodily aches and pains (23% of patients), and night sweats (23% of patients), 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 experiencing 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 confirmation of their diagnosis (e.g., wait time between testing and results and scheduling appointments for biopsy). According to 15 patients included in the survey, their ability to do the following was impacted by their disease: 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; and 6 were in a clinical trial. Most patients (62%) were very satisfied or satisfied with their first-line treatment options; in comparison, 39% were very satisfied or satisfied with their second-line treatment options and 31% with their third-line treatment options. Lymphoma Canada also suggested that patients are less satisfied with their treatment options in the second-line and third-line settings than in the first-line setting. The most common financial implications associated with treatment for large B-cell lymphoma were drug costs (reported by 60% of the patients who responded to the survey), travelling costs (reported by 40% of the patients), and absence from work (reported by 40% of the patients).

Two patients included in the survey reported experience with glofitamab, accessed through private insurance and public health care. Both patients were in remission. One patient reported no side effects, while the other reported cytokine release syndrome (CRS), hypotension, and low platelet count. Both patients indicated that they had experienced financial impacts due to the cost of the drug and the cost of supplemental medication.

Lymphoma Canada referred to a separate patient survey submitted for the CADTH Reimbursement Review of polatuzumab vedotin (Polivy). In this separate survey, patients with large B-cell lymphoma identified longer disease remission, longer survival, control of disease symptoms, normalization of blood counts, and improved HRQoL and ability to perform daily activities as the most important outcomes of treatment.

Clinician Input

Input From Clinical Experts Consulted by CADTH

The clinical experts consulted by CADTH stated that the goal of treatment for patients with r/r DLBCL 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 is palliative and generally includes maintaining HRQoL by 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 patients in the palliative setting who are not eligible for curative treatment or for patients with disease that has relapsed or is refractory to second-line treatment consisting of SCT or CAR T-cell therapy, as there are limited treatment options for disease control and the currently available options are often associated with significant toxicity that limits their usefulness and applicability. Additionally, patients who are posttransplant and/or post–CAR T-cell therapy 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.

If first-line treatment with R-CHOP (curative intent) fails, for patients who are eligible for transplant and have chemosensitive disease, second-line treatment consists of salvage rituximab-based chemotherapy and autologous SCT (curative intent) and third-line therapy consists of CAR T-cell therapy (curative intent). There is no standard of care following these treatment options. Patients who are ineligible for transplant tend to receive palliative rituximab-based chemotherapy (e.g., Pola-BR or R-GemOx) with noncurative intent as second-line and third-line treatment, and/or radiation or enrol in clinical trials. The clinical experts highlighted that there is 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 are a major problem of palliative treatment options. The experts highlighted that glofitamab should be restricted to patients who are not eligible for other curative therapies, patients who have already received CAR T-cell therapy or who would not be able to receive it later (i.e., as third-line therapy for patients post–CAR T-cell therapy or patients who are ineligible for CAR T-cell therapy), and patients who are unable to receive CAR T-cell therapy for logistical and nonmedical reasons, and the experts envisioned glofitamab occupying the same therapeutic space as Pola-BR.

The experts noted that eligible patients would be identified in routine practice by clinicians familiar with the treatment of patients with lymphoma who are 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 intensive cellular therapies (i.e., SCT or CAR T-cell therapy) or for whom intensive cellular therapies have failed would be considered for treatment with glofitamab. The experts could not identify a specific subgroup of patients that would likely receive an enhanced benefit or a reduced benefit from glofitamab treatment.

The experts highlighted that repeat biopsy is generally not required in cases of suspected relapse of DLBCL, unless it was a remote relapse or unless the patient had prior history of indolent lymphoma and it was unclear which lymphoma had relapsed.

The clinical experts stated that response to treatment would include standard assessment of lymphoma response using the Lugano criteria. Patients would undergo interim imaging every 3 months to confirm response, which would lead to either ongoing treatment or discontinuation. Patients are also assessed for lymphoma-related symptoms at each visit; the clinical experts noted that these outcomes are more subjective but that they do factor into patients' decisions for continuation of therapy. The experts also noted that the frequency of these assessments and the collection of data may vary across Canada. In terms of meaningful response to treatment, the clinical experts stated that a response of 6 months or more with improved symptoms can be considered meaningful. The experts did not consider temporary shrinking of tumours beneficial to patients and believed that initial responses (either partial response [PR] or complete response [CR]) should exceed 6 months, otherwise the treatment should be discontinued. Additionally, with a current median overall survival (OS) of 6 months in this patient population, the experts considered a benefit of at least 6 months and at least 3 months over current standard of care to be clinically meaningful for OS and progression-free survival (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 that resolution of severe AEs can allow for resumption of therapy, so the decision to discontinue due to AEs should be left to physician judgment and patient request.

The clinical experts indicated that patients with r/r DLBCL are typically under the care of hematologists or oncologists who are familiar with the treatment of patients with lymphoma. The experts 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 the Ontario Health–Cancer Care Ontario (OH-CCO) Hematology Cancer Drug Advisory Committee, with 1 clinician contributing to the submission. 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.

The input from the clinician groups generally aligned with that of the clinical experts consulted by CADTH. The clinician groups highlighted the need for additional accessible and effective treatment options beyond Pola-BR (as well as for patients with disease progression after CAR T-cell therapy or those who are ineligible for or are unable to receive CAR T-cell therapy) and for 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 the use of glofitamab as a third-line option for patients who are ineligible for or unable

to receive CAR T-cell therapy or for 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 for patients with disease progression after CAR T-cell therapy or patients who are ineligible for or unable to receive CAR T-cell therapy.

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 similarly to DLBCL and that, as such, patients with these subtypes may benefit from glofitamab treatment. The clinician groups suggested that patients who are eligible for and able to receive CAR T-cell therapy would not be suitable for treatment with glofitamab.

The clinician groups highlighted that response to treatment with glofitamab 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 input from the clinical experts consulted by CADTH, the clinician groups considered improvement in the standard lymphoma response measures, improved survival, and symptom improvement to be important outcomes of treatment. 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 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 drug programs identified implementation issues relating to relevant comparators, considerations for initiation of therapy, considerations for discontinuation of therapy, considerations for prescribing of therapy, generalizability, care provision issues, and system and economic issues. Refer to Table 5 for more details.

Clinical Evidence

Systematic Review

Description of Study

One study, the NP30179 study[13] — an ongoing phase I/II, multicentre, open-label, single-arm study of glofitamab monotherapy after a fixed single-dose pretreatment of obinutuzumab in patients with r/r NHL — was included in this review. The study was divided into 3 parts: Part I (single-patient cohorts) and Part II (multiple-patient cohorts), composing 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] patients were assigned to dose cohorts in the order in which they were enrolled in the NP30179 study. Cohort D2 subcohort 2 (D2S2), cohort D3, and cohort D5 were the cohorts of interest to this review and composed the primary efficacy population (n = 155), which included patients with r/r DLBCL who had had 2 or more prior lines of systemic therapy and were treated with the phase II recommended dosage of glofitamab of 2.5 mg, then 10 mg, then 30 mg every 3 weeks for a fixed treatment duration of 12 cycles. The

end points from the NP30179 study of interest to this review were the primary end point of proportion of patients experiencing CR and the secondary end points of overall response rate (ORR), PFS, OS, duration of response (DOR), and HRQoL.[13]

In the primary safety analysis population (n = 154), most patients were diagnosed with DLBCL (110 [71.4%]). The median age of the patients enrolled was 66.0 years, and there were slightly more patients with an Eastern Cooperative Oncology Group Performance Status (ECOG PS) of 1 (84 [54.5%]) than of 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 having received anthracycline (151 [98.1%]) therapies. Nearly all patients had disease that was refractory to the last prior therapy (131 [85.1%]) and that was also refractory to prior anti-CD20 therapies (128 [83.1%]).[13]

An interim Clinical Study Report was provided for the NP30179 study, detailing the results up to the CCOD of September 14, 2021. At CADTH's request, an updated Clinical Study Report detailing the results to a CCOD of June 15, 2022, was provided.

Efficacy Results

Efficacy results for the NP30179 study were presented for the primary efficacy population, composed of cohorts D2S2, D3, and D5 (n = 155), as of the June 15, 2022, CCOD.[13]

Overall Survival

At the June 15, 2022, CCOD, [redacted] patients had died, resulting in a median OS of [redacted]. The OS rate at 12 months and 24 months was [redacted] respectively.[13]

Progression-Free Survival

The median duration of follow-up for independent review committee (IRC)-assessed PFS was [redacted]. [redacted] PFS events had occurred in the primary efficacy population, [redacted] categorized as disease progression and [redacted] as death. The median PFS was [redacted]. The PFS rate at 12 months and 24 months was [redacted] and [redacted] respectively.[13]

Health-Related Quality of Life

European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30: At baseline, [redacted]% of patients completed at least 1 question of the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC QLQ-C30). At baseline, the mean EORTC QLQ-C30 physical functioning, role functioning, global health status/quality of life (GHS/QoL), and fatigue scores for [redacted] patients in cohort D3 were [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]) was [redacted], the mean change from baseline in GHS/QoL score ([redacted] was 6.86 points (standard deviation [SD] = 20.86), and the mean change from baseline in fatigue score ([redacted]) was [redacted]. At the end of treatment, the mean change from baseline in the physical functioning, role functioning, GHS/QoL, and fatigue scores ([redacted]) was [redacted].[13]

Functional Assessment of Cancer Therapy–Lymphoma, Lymphoma Subscale: At baseline, 88.9% of the patients completed at least 50% of the questions in the Functional Assessment of Cancer Therapy–Lymphoma (FACT-Lym) lymphoma subscale (LymS). The mean FACT-Lym LymS score at baseline was ( ). At cycle 5 day 1 ( ), the mean change from baseline in the total score was . At the end of treatment assessment, the mean change from baseline in the total score was .[13]

Clinical Response

Complete Response: The proportion of patients experiencing 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% confidence interval [CI], 32.2 to 48.2) at the June 15, 2022, CCOD.[13]

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 population of patients with r/r DLBCL.[13]

Results for the subgroup analyses were generally consistent with those of the primary analysis, albeit ranging from 0% to 100% due to small sample sizes, with overlapping CIs.[13]

Overall 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), 80 patients (51.6%; 95% CI, 43.46% to 59.70%) experienced an overall response: 62 (40.0%) experienced CR, 18 (11.6%) experienced PR. Of the remaining patients, 21 (13.5%) had stable disease, and 42 (27.1%) had progressive disease.[13]

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 experienced an IRC-assessed response (CR or PR), the median DOR was 16.8 months (95% CI, 10.4 to not estimable). Fifty 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 these 80 patients at 12 months and 24 months after the first response was , respectively.[13]

Harms Results

At the June 15, 2022, CCOD, 152 patients (98.7%) in the primary safety population had experienced at least 1 AE. The most frequently reported AEs were CRS (103 patients [66.9%]), neutropenia (58 patients [37.7%]), and anemia (47 patients [30.5%]). Fifty-four patients (35.1%) had experienced grade 1 to 2 AEs, 89 patients (57.8%) had experienced grade 3 to 4 AEs, and 9 patients (5.8%) had experienced grade 5 AEs. The most frequently reported grade 3 to 4 AEs were neutropenia or decreased neutrophil count (42 patients [27.3%]), anemia (12 patients [7.8%]), hypophosphatemia (9 patients [5.8%]), and thrombocytopenia or decreased platelet count (12 patients [7.8%]).[13]

Seventy-five patients (48.7%) experienced a serious AE (SAE). The most frequently reported SAE was CRS (34 patients [22.1%] according to Lee [2014] grading criteria; 32 patients [20.8%] according to American Society for Transplantation and Cellular Therapy [ASTCT] 2019 grading criteria), followed by sepsis (6 patients [3.9%]); COVID-19, COVID-19 pneumonia, and tumour flare (5 patients [3.2%] each); and anemia,

febrile neutropenia, neutropenia, and pleural effusion (3 patients [1.9%] each). SAEs resulted in dose modifications or interruptions in 9 patients (5.8%).[13]

In the primary safety population, 14 patients (9.1%) reported an AE leading to study treatment discontinuation, primarily due to [redacted].[13]

At the June 15, 2022, CCOD, 81 patients (52.6%) had died. The most frequent cause of death was progressive disease (61 patients [75.3%]), followed by AEs (8 patients [5.19%]), including COVID-19 pneumonia (3 patients [1.9%]), COVID-19 (3 patients [1.9%]), sepsis (2 patients [1.3%]), and delirium (1 patient [0.6%]). Other causes of death included [redacted].[13]

Notable Harms

As of the June 15, 2022, CCOD, 103 patients (66.9%) had reported at least 1 CRS AE according to Lee (2014) grading, and 99 patients (64.3%) had reported at least 1 CRS AE according to ASTCT 2019 grading. Serious CRS events according to ASTCT 2019 grading were reported by 32 patients (20.8%). Serious CRS events according to Lee (2014) grading were reported by 34 patients (22.1%). According to ASTCT 2019 grading, grade 2 CRS AEs occurred in 19 patients (12.3%), and grade 3 or 4 CRS AEs were reported in 6 patients (3.9%). According to the Lee (2014) grading system, 24 patients (15.6%) experienced grade 2 CRS, and 5 patients (3.2%) experienced grade 3 and 4 CRS. As of the CCOD, grade 2 or higher CRS events had been resolved in 24 of 25 patients according to ASTCT grading and in 27 of 29 patients according to Lee (2014) grading.[13]

Infection and infestation AEs were reported in 62 patients (40.3%). Grade 3 to 4 infection and infestation AEs were reported in 18 patients (11.7%). Eight patients (5.2%) reported grade 5 infection and infestation AEs. Twenty-eight patients (18.2%) experienced serious infection and infestation AEs. The most frequently reported infection and infestation SAEs were sepsis (6 patients [3.9%]), COVID-19 pneumonia (5 patients [3.2%]), COVID-19 (5 patients [3.2%]), pneumonia (2 patients [1.3%]), infection (2 patients [1.3%]), and vascular device infection (2 patients [1.3%]).[13]

Critical Appraisal

The NP30179 study is an ongoing phase I/II, multicentre, open-label, single-arm study of glofitamab. The choice to conduct a single-arm trial was justified because the study was designed as an early phase I/II study, where an internal comparator group is not required, and because of the severity of illness for patients with r/r DLBCL. However, the decision to conduct a single-arm study also has implications for the overall strength and interpretability of the results. With a single-arm study, there is an increased risk of bias in the estimation of treatment effects due to the potential for confounding related to natural history and prognostic factors. The potential influence of selection bias is also difficult 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 results for these end points can only be considered as exploratory and supportive.

In addition to glofitamab monotherapy, based on the results of preclinical data, all patients received 1,000 mg of obinutuzumab as pretreatment to minimize the risk of CRS. The Health Canada reviewers report noted that no noticeable antitumour effect was observed for obinutuzumab; however, due to the single-arm design

of the NP30179 study, it is impossible to determine whether the effects observed in the study are attributable to glofitamab or obinutuzumab. Additionally, the true effect of obinutuzumab on CRS remains unknown for this reason.

In addition to its single-arm design, the NP30179 study was open label, whereby the investigator and the study participants were aware of their treatment status, potentially increasing the risk of detection bias and performance bias. As such, the open-label trial design limits the interpretability of the subjective study outcomes such as patient-reported outcomes (PROs) including HRQoL, as well as AEs. However, to mitigate the impact of this bias, all outcomes except for OS were assessed by both the IRC and the investigator. Though the NP30179 study was powered for the primary end point, the magnitude of the treatment effect estimates observed in the 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 hematologic cancers. Historically, in hematologic tumours, response has been considered a direct measure of a drug's antitumour activity in oncology clinical trials. The sponsor provided multiple studies that suggested that end of treatment CR was a predictor of PFS and OS and that 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 for DLBCL. The outcomes from the NP30179 study of critical importance to this review were 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 a relevant outcome. At the June 15, 2022, CCOD, 52.3% of patients experienced OS events and 61.3% of patients experienced PFS events (the median follow-up duration was 17.0 months for OS and 13.4 months for PFS). Although 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 estimate of treatment effect than could be observed in clinical practice. Despite the PFS and OS results being 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 means that the results for survival end points should be interpreted with caution and should only be considered supportive of the overall antitumour effect of glofitamab. For HRQoL outcomes, no time of assessment was specified, and there were high rates of attrition for HRQoL outcomes throughout the analysis, which limited the interpretability of the effect of glofitamab on HRQoL.

The clinical experts consulted by CADTH noted that some eligibility criteria — such as ECOG PS, 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 patient population, although they are typically specific clinical trial enrolment criteria. The clinical experts also noted that at this advanced stage of the disease, there are few relevant prognostic factors, though they indicated that ECOG PS remains important. The clinical experts also noted that the baseline characteristics of the included population were generally reflective of Canadian clinical practice, though they noted there to be a high proportion of patients with disease that was refractory to any prior therapy (89.6%) compared to clinical practice, where they would expect more patients

to present with relapsed disease. This may indicate a sicker population in contrast to the eligibility criteria of the NP30179 study. While the experts considered response outcomes to be important in the treatment of r/r DLBCL and considered that the response observed in the NP30179 study was better than they would expect with other currently available treatments, they noted that survival and prevention of progression are of the greatest importance to patients in advanced stages of the disease. As previously mentioned, the results for PFS and OS may be overestimated due to the relatively small information fraction and the overall immaturity of the data, which may impact generalizability to the population of patients with r/r DLBCL living in Canada.

GRADE Summary of Findings and Certainty of the Evidence

For the pivotal study 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 the 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.[16,17] Although GRADE guidance is not available for noncomparative studies, the CADTH review team assessed pivotal single-arm trials for study limitations (which refers 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 starts at very low certainty with no opportunity for rating up.

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

Table 2: Summary of Findings for Glofitamab for Patients With Relapsed or Refractory DLBCL

Outcome and follow-up	Patients, N (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 to 16.1) **12-month OS rate (95% CI):** [redacted] **24-month OS rate (95% CI):** [redacted]	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 to 8.1) **12-month PFS rate (95% CI):** [redacted] **24-month PFS rate (95% CI):** [redacted]	Very low[b,c]	The evidence is very uncertain about the effects of glofitamab on PFS vs. any comparator.
Health-related quality of life				
EORTC QLQ-C30 Follow-up (median): NR	[redacted] (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 Follow-up (median): NR	[redacted] (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 (IRC-assessed) Follow-up (median): 12.0 months	155 (1 single-arm trial)	400 per 1,000 patients (322 to 482)	Low[e]	Glofitamab may result in a large CR rate, although the evidence is still uncertain.
ORR (IRC-assessed) Follow-up	155 (1 single-arm trial)	516 per 1,000 patients (430 to 597)	Low[e]	Glofitamab may result in a large ORR, although the evidence is still uncertain.

Outcome and follow-up	Patients, N (studies, N)	Effect	Certainty[a]	What happens
(median): 12.0 months				
DOR (IRC-assessed) Follow-up (median): 12.0 months	155 (1 single-arm trial)	**Median (95% CI) DOR:** 16.8 months (10.4 to NE) **12-month event-free rate (95% CI):** 76.97% (67.34 to 86.60) **24-month event-free rate (95% CI):** 43.37% (26.14 to 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)	669 per 1,000 patients	Low[f]	Glofitamab may result in CRS, although the evidence is still uncertain.
Serious infection Follow-up: NR	154 (1 single-arm trial)	182 per 1,000 patients	Very low[d]	The evidence is very uncertain about the effects of glofitamab on serious infections vs. any comparator.

CFB = change from baseline; CI = confidence interval; CR = complete response; CRS = cytokine release syndrome; DLBCL = diffuse large B-cell lymphoma; DOR = duration of response; EORTC QLQ-C30 = European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30; FACT-Lym = Functional Assessment of Cancer Therapy–Lymphoma; GHS/QoL = global health status/quality of life; IRC = independent review committee; LymS = lymphoma subscale; NE = not estimable; NR = not reported; ORR = overall response rate; OS = overall survival; PFS = progression-free survival; SD = standard deviation.

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

[a]In 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."

[b]Rated 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.

[c]In the trial, statistical testing for this outcome was not adjusted for multiplicity. The results are considered as supportive evidence.

[d]Rated 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.

[e]Despite the study limitations resulting in the certainty of evidence starting at "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. The outcome could be rated down 1 level for serious indirectness as the 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, this evidence is restricted to its use in instances of previously untreated disease, which is not reflective of the population under review.

[f]Despite the study limitations resulting in the certainty of evidence starting at "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 pretreatment. As such, the CADTH clinical review team considered the certainty of evidence for this outcome to be higher.

Source: NP30179 Clinical Study Report.[13]

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) conducted to compare, for outcomes of interest, the efficacy of glofitamab versus relevant comparators in the third-line treatment setting and beyond for DLBCL. The sponsor-submitted ITC began with 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:[18]

- a propensity score analysis (PSA) comparing glofitamab to Pola-BR in the third-line treatment setting and beyond for DLBCL using individual patient data from the NP30179 study and the GO29365 trial
- an unanchored matching-adjusted indirect comparison (MAIC) comparing glofitamab to salvage chemotherapy in the third-line treatment setting and beyond for DLBCL using individual patient data from the NP30179 study and aggregated-level data from the SCHOLAR-1 retrospective study.

PSAs were conducted when individual patient data were available for both comparators, and a MAIC was conducted for comparators for which only aggregate data were available.[18]

Efficacy Results

Propensity Score Analysis

The sponsor conducted PSAs using individual patient data from 2 of its own studies — the NP30179 and GO29365 studies — due to the possibility of filtering patients from the GO29365 study by characteristic to make them more comparable to the patients with DLBCL in the third-line treatment setting and beyond enrolled in the NP30179 study. Prior to adjustment of the selected patient characteristics, patients were filtered by applying common inclusion and exclusion criteria. Most baseline characteristics were imbalanced between the glofitamab and Pola-BR groups. 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 the ability to achieve covariate balance.[18]

For the end points of OS, PFS, DOR, duration of CR (DOCR), CR, ORR, and discontinuation due to AEs, there was no difference after adjustment between glofitamab and Pola-BR under either full matching or IPTW.[18]

Matching-Adjusted Indirect Comparison

Based on market research and consultation with a clinician, a MAIC was conducted to compare glofitamab with salvage chemotherapy using data from the SCHOLAR-1 study. 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.[18]

Critical Appraisal

Given the lack of direct evidence comparing glofitamab to relevant treatments in the r/r DLBCL third-line treatment setting and beyond, 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 study of glofitamab was a phase I/II, single-arm study, whereas the GO29365 study was a comparative phase Ib/II, randomized, open-label study and the SCHOLAR-1 study was a retrospective research study, and no formal quality assessment was conducted on the comparator studies. Given that the

differences in the design of the studies included in the analyses conducted could not be adjusted for in the weighting procedures, these differences were 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 an ECOG PS of 2. In the SCHOLAR-1 study, patients were enrolled from various sources, and patients with 1 or more prior lines of therapy, including prior SCT, and patients with an ECOG PS of 0 to 4 were included. In the MAIC, it was not possible to adjust for patients receiving second-line treatment or for patients with an ECOG PS of 2 or more as these patients were not included in the NP30179 study; thus, these potentially important prognostic factors were not 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 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. Covariate adjustment resulted in a reduction in sample size of [redacted]% in the glofitamab group and [redacted]% in the Pola-BR group and of [redacted]% in the glofitamab group and [redacted]% in the Pola-BR group, in the full matching scenario and the IPTW analysis, respectively. In the MAIC, the ESS for the glofitamab group was reduced [redacted]% in the base-case analysis, [redacted]% for scenario 1, and [redacted]% for scenario 2. Thus, either there was considerable heterogeneity between studies among the variables included in the weighting process or the inclusion and exclusion criteria differed greatly between the studies.

The results of 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. The results of the MAIC comparing glofitamab to salvage chemotherapy using data from the SCHOLAR-1 study were consistent across models and adjustment scenarios, favouring glofitamab for the outcome of ORR. While the 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, the differences in the included patient populations, and the heterogeneity in baseline characteristics across studies, as well as the reduction in sample sizes — led to uncertainty about the overall generalizability of the results to the patient 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

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

Conclusions

One phase I/II, single-arm, open-label trial (the NP30179 study) provided evidence for the efficacy and safety of glofitamab in adult patients with r/r DLBCL that has relapsed after or failed to respond to at least 2 prior systemic therapies. Clinicians and patients highlighted the need for accessible, alternative treatment options for patients in this setting. Improvements in survival were considered the most important outcomes of treatment by patients and clinicians. Although OS and PFS were evaluated in the study, the single-arm design and the immature data from limited follow-up preclude the ability to attribute the study results to treatment with glofitamab. Moreover, the short duration of the NP30179 study may result in survival being overestimated. Nonetheless, the study suggested that some patients (40%) will experience CR, which is likely a clinically important result, although the evidence is still uncertain. Though HRQoL was an outcome important to patients, due to the noncomparative design and high patient attrition rates in the NP30179 study, the effect of glofitamab on HRQoL remains uncertain. The harms associated with glofitamab were largely consistent with the mechanism of action, including a high frequency of patients who experienced CRS and serious infections. While all patients received pretreatment with obinutuzumab to mitigate the risk of CRS, given the high rate of CRS events, it remains unclear what effect obinutuzumab pretreatment had in reducing CRS. Despite the high CRS rates, most events were treated, and the side effect profile of glofitamab was considered manageable according to the clinical experts consulted by CADTH. The CADTH clinical assessment identified limitations with the sponsor's ITCs used to assess the comparative effectiveness and safety of glofitamab. There were no apparent differences in efficacy between glofitamab and Pola-BR in the PSA; however, substantial limitations in the MAIC — including small sample sizes, heterogeneity across study designs and included populations, the inability to adjust for important potential confounders and prognostic variables, and wide 95% CIs — substantially limited the ability to interpret the relative treatment effects observed between glofitamab and salvage chemotherapy. Overall, the evidence was very uncertain about the effects of glofitamab on any outcomes versus any comparator, and the ability to draw firm conclusions about the magnitude of clinical benefit of glofitamab was hindered by the limitations in the evidence.

Introduction

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 for solution for IV infusion for the treatment of r/r DLBCL not otherwise specified, DLBCL arising from trFL, or PMBCL in adult 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, following obinutuzumab pretreatment.

Disease Background

Contents within this section have been informed by materials submitted by the sponsor and clinical expert input. The following has been summarized and validated by the CADTH review team.

DLBCL is the most common type of NHL, accounting for approximately 30% to 40% of all NHL cases in Canada.[1] DLBCLs are a heterogeneous group of aggressive B-cell malignancies that differ in clinical

presentation, molecular features, prognosis, and treatment options. Some types of indolent B-cell lymphomas (e.g., follicular lymphoma) can transform into DLBCL.[1,2]

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 bones, brain, and gastrointestinal tract, among other locations. DLBCL can also cause systemic B symptoms (i.e., unexplained fever, weight loss, and night sweats) and elevated serum lactate dehydrogenase.[3]

DLBCL is an aggressive disease that is typically diagnosed in more advanced stages, with 30% to 40% of patients diagnosed when the disease is localized (stage I or II).[2] It is diagnosed through surgical biopsy, usually of an involved lymph node or extranodal site. Histological evaluation is performed in accordance with the WHO classification of lymphoid neoplasms, which categorizes lymphomas on the basis of cytology, immunophenotype, and genetic and clinical features.[19] A morphological diagnosis of the cell of origin to distinguish between activated B-cell type (approximately 25% to 30% of DLBCL cases) and germinal centre B-cell type (approximately 60% of DLBCL cases) is generally confirmed by immunohistochemistry or flow cytometry and has been considered a major prognostic factor in the first-line treatment of DLBCL.[7,9,20-22] Other molecular subtypes with prognostic implications have been identified, including double-hit lymphoma (concurrent translocations of *MYC* and either *BCL2* or *BCL6*), which is a particularly aggressive, high-risk subtype with poor prognosis.[19,23] Double-expressor lymphoma (overexpression of *MYC* and *BCL2*) is not considered a separate entity but has also been associated with worse prognosis.[24,25] However, the prognostic significance of these subtypes remains controversial, and optimal clinical management has not been established.[25-28]

Disease staging is crucial for determining the appropriate treatment and assessing prognosis. The gold standard for staging DLBCL is by PET or CT scan. DLBCL is initially divided into 2 groups by stage: limited stage or advanced stage. The extent of DLBCL is determined using the Ann Arbor classification system, which further categorizes the disease into 4 stages according to the extent of lymph node and extranodal site involvement. For prognostic purposes, the International Prognostic Index (IPI) and age-adjusted IPI are calculated to assign a prognosis to patients undergoing treatment with chemotherapeutic regimens.[29]

There are few estimates of DLBCL incidence and prevalence in Canada. The Canadian Cancer Society estimated that 11,400 people living in Canada were diagnosed with NHL in 2022, with 3,000 dying from the disease.[4] International studies have estimated the incidence of DLBCL in the US and England at approximately 7 cases per 100,000 persons per year.[3]

Although the cure rate of DLBCL is high (60% to 70%), approximately 30% to 50% of patients will experience relapse, or have disease that is refractory to, treatment with standard first-line R-CHOP or a similar regimen.[8,9] The estimated 5-year relative survival at diagnosis of DLBCL was 63.8% in the US, based on statistics from 1975 through 2017.[5] Until recent approval of CAR T-cell therapy, treatment for patients not eligible for SCT or who have experienced relapse after SCT had been largely palliative, with median survival being approximately 6 months.[30]

Standards of Therapy

Contents within this section have been informed by materials submitted by the sponsor and clinical expert input. The following has been summarized and validated by the CADTH review team.

First-line treatment for DLBCL is relatively standardized across Canada, with most patients receiving R-CHOP every 3 weeks.[6,7] While most patients respond well to R-CHOP, 30% to 50% of patients will have disease that is refractory to or relapses following first-line therapy. Patients with disease that relapses early (within 12 months) or patients with refractory disease have a worse prognosis than those with disease that does not relapse within 12 months, even if they receive second-line therapy.[6,10]

Patients requiring second-line treatment for r/r DLBCL are classified based on their eligibility to receive SCT. Based on the *Canadian Evidence-Based Guideline for the Treatment of Relapsed/Refractory Diffuse Large B-Cell Lymphoma*, for patients with disease that is refractory to R-CHOP or who experience relapse after 12 months of R-CHOP, the standard approach if those patients have chemosensitive disease and meet eligibility criteria for transplant consists of salvage platinum-based chemotherapy followed by high-dose chemotherapy and autologous SCT. For patients who are ineligible for SCT, second-line treatment options include chemotherapy with or without rituximab, or Pola-BR.[1,7]

Currently, CAR T-cell therapy is approved in Canada for patients with r/r DLBCL after 2 or more lines of therapy. As such, CAR T-cell therapy is the standard treatment approach for patients with r/r DLBCL that is not responding to salvage chemotherapy (meaning those patients are ineligible for transplant) or patients with r/r DLBCL that relapses post-SCT.[1,7] Although it is currently not adopted, CAR T-cell therapy could be offered as second-line treatment to eligible patients.[11]

For patients who do not have chemosensitive disease and who are ineligible for autologous SCT or who experience relapse post-SCT or post–CAR T-cell therapy, the prognosis is poor and there is no standard 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.[1,7]

According to the input from the clinician groups, novel drugs including ibrutinib, lenalidomide, tafasitamab, and obinutuzumab have compassionate access programs in Canada but generally do not have Health Canada approvals or provincial funding for use in the treatment of r/r DLBCL.

Drug Under Review

Glofitamab (Columvi) is a bispecific mAb (recombinant humanized immunoglobulin G1) 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. By simultaneously binding to CD20 on the B-cell and CD3 on the T-cell, glofitamab mediates the formation of an immunological synapse, with subsequent potent T-cell activation and proliferation, secretion of cytokines, and release of cytolytic proteins which results in the lysis of CD20-expressing B-cells.[12]

Glofitamab 1 mg/mL is administered intravenously at a step-up dose of 2.5 mg to 10 mg to 30 mg (Table 3). To minimize the risk of CRS and to deplete circulating and lymphoid tissue B-cells, all patients must receive a

single pretreatment 1,000 mg dose of obinutuzumab on cycle 1 day 1 (7 days before initiation of glofitamab treatment). Glofitamab administration begins with 2.5 mg on cycle 1 day 8, followed by 10 mg on cycle 1 day 15, followed by 30 mg on cycle 2 day 1. All subsequent infusions are administered at a dose of 30 mg on day 1 of each cycle. Each treatment cycle is 21 days.[12]

Table 3: Glofitamab Monotherapy Dose Step-Up Schedule for Patients With r/r DLBCL

Treatment schedule		Dose (mg)	Duration
Cycle	Day		
1	1	Obinutuzumab pretreatment: 1,000	Obinutuzumab should be administered as an IV infusion at 50 mg per hour. The rate of infusion can be escalated in 50 mg per hour increments every 30 minutes to a maximum of 400 mg per hour.
	8	2.5	4 hours[a]
	15	10	
2	1	30	
3 to 12	1	30	2 hours[b]

DLBCL = diffuse large B-cell lymphoma; r/r = relapsed or refractory.

[a]For patients who experienced cytokine release syndrome with their previous dose of glofitamab, the duration of infusion may be extended up to 8 hours.

[b]At the discretion of the treating physician, if the previous infusion was well tolerated. If the patient experienced cytokine release syndrome with a previous dose, the duration of infusion should be maintained at 4 hours.

Source: Glofitamab product monograph.[12]

Glofitamab received a Notice of Compliance with Conditions (NOC/c) from Health Canada on March 24, 2023. The NOC/c was granted on the condition that the sponsor commit 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 acknowledge that marketing authorization may be revoked if the trial fails to demonstrate an improvement in OS.[31] The Health Canada indication for glofitamab is for the treatment of adult patients with r/r DLBCL not otherwise specified, DLBCL arising from 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.[12]

Wording specific to the reimbursement request for glofitamab differs from the Health Canada indication, specifying the requirement of obinutuzumab pretreatment. The reimbursement request is for the treatment of adult patients with r/r DLBCL not otherwise specified, DLBCL arising from 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, following obinutuzumab pretreatment.

Glofitamab has not been previously reviewed by CADTH. Key characteristics of glofitamab are summarized in Table 4, along with other treatments available for r/r DLBCL.

Table 4: Key Characteristics of Glofitamab and Combination Chemotherapy

Characteristic	Glofitamab	Combination chemotherapy	
		Pola-BR	Rituximab-based chemotherapy
Mechanism of action	Glofitamab is a bispecific mAb that simultaneously binds to CD20 on the B-cell and CD3 on the T-cell to mediate the formation of an immunological synapse with subsequent potent T-cell activation and proliferation, secretion of cytokines, and release of cytolytic proteins that result in the lysis of CD20-expressing B-cells.	Polatuzumab vedotin is a CD79b-targeted ADC that preferentially delivers an antimitotic drug, MMAE, to B-cells, which results in the killing of malignant B-cells. MMAE binds to microtubules and kills dividing cells by inhibiting cell division and inducing apoptosis.	Rituximab is a chimeric mAb that binds to the antigen CD20, a transmembrane protein found on the surface of normal and malignant B lymphocytes. CD20 regulates an early step in the activation of cell cycle initiation and differentiation.
Indication[a]	For the treatment of adult patients with R/R DLBCL not otherwise specified, DLBCL arising from 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.	For the treatment of adult patients with R/R DLBCL, not otherwise specified, who are not eligible for autologous stem cell transplant and have received at least 1 prior therapy.	Not approved in Canada in the r/r setting of DLBCL.
Route of administration	IV infusion	IV infusion	IV infusion
Recommended dose	Dosing begins with a step-up dosing schedule to minimize the risk of CRS. The recommended dose after step-up is 30 mg.	Polatuzumab vedotin, bendamustine, and rituximab can be administered in any order on day 1 of each cycle. • The recommended dosage of polatuzumab vedotin is 1.8 mg/kg given as IV infusion every 21 days in combination with bendamustine and rituximab for 6 cycles. • The recommended dose of bendamustine is 90 mg/m^2/day on day 1 and day 2 when administered with polatuzumab vedotin and rituximab. • The recommended dose of rituximab is 375 mg/m^2 on day 1 of each cycle.	Not approved in Canada for DLBCL in the r/r setting.
Serious adverse effects or safety issues	CRS	**Polatuzumab vedotin**: Infections and myelosuppression	**Rituximab**: Infusion reactions, PML, TLS, HBV reactivation, mucocutaneous reactions, infections, cardiovascular events

Characteristic	Glofitamab	Combination chemotherapy	
		Pola-BR	Rituximab-based chemotherapy
Other	All patients must receive a single 1,000 mg dose of obinutuzumab on cycle 1 day 1 (7 days before initiation of glofitamab treatment). Premedication should be administered according to the product monograph to reduce the risk of CRS.	NA	NA

ADC = antibody-drug conjugate; CAR = chimeric antigen receptor; CRS = cytokine release syndrome; DLBCL = diffuse large B-cell lymphoma; HBV = hepatitis B virus; mAb = monoclonal antibody; MMAE = monomethyl auristatin E; NA = not applicable; PMBCL = primary mediastinal B-cell lymphoma; PML = progressive multifocal leukoencephalopathy; Pola-BR = polatuzumab vedotin plus bendamustine, and rituximab; r/r = relapsed or refractory; TLS = tumour lysis syndrome; trFL = follicular lymphoma.

[a]Health Canada–approved indication.

Note: Examples of rituximab-based chemotherapy include rituximab plus gemcitabine, dexamethasone, and cisplatin (R-GDP), rituximab plus ifosfamide, carboplatin, and etoposide (R-ICE), and rituximab plus gemcitabine and oxaliplatin (R-GemOX).

Sources: Product monographs for glofitamab,[12] polatuzumab vedotin,[32] and rituximab.[33]

Stakeholder Perspectives

Patient Group Input

This section was prepared by the CADTH review team based on the input provided by 1 patient group. The full original patient input received by CADTH has been included in the Stakeholder section of this report.

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 detection of disease, discover new and improved treatments for lymphoma, improve access to those treatments, and find a cure for lymphoma.

Information for this patient group input was collected from June 5, 2023, to July 10, 2023, through an online patient survey. In total, 27 patients responded to the survey: 5 females (19%), 6 males (22%), and 16 (59%) undisclosed. Thirteen patients included in the survey (48%) were diagnosed with DLBCL not otherwise specified, 8 (30%) were diagnosed 3 to 5 years before the survey, 8 (30%) were living in Canada, and 6 (22%) were aged 45 to 54 years.

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% of patients), bodily swelling (27% of patients), fatigue (27% of patients), shortness of breath (27% of patients), bodily aches and pains (23% of patients) and night sweats (23% of patients). Following diagnosis, 26% and 20% of patients rated fatigue and enlarged lymph nodes, respectively, as having the most significant impact on their current HRQoL. Patients included in the survey also reported challenges with mental health at diagnosis, including stress of diagnosis, fear of progression, and inability to continue daily activities (14 out of 22 [64%]) and anxiety and

worry (13 out of 22 [59%]). Following diagnosis, 66%, 56%, and 42% of patients reported experiencing 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 confirmation of their diagnosis (e.g., wait time between testing and results and scheduling appointments for biopsy). According to 15 patients included in the survey, their ability to do the following was impacted by their disease: 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%).

Of the 27 patients who responded to the survey, 9 (33%) indicated that they had received 1 line of treatment, 4 (15%) indicated that they had received 3 or more lines of treatment, and 14 skipped the question. In the third-line setting, 6 patients had received CAR T-cell therapy; 1 had received polatuzumab plus rituximab, cyclophosphamide, doxorubicin, and prednisone; and 6 were in a clinical trial. Most patients (62%) were very satisfied or satisfied with their first-line treatment options; in comparison, 39% were very satisfied or satisfied with their second-line treatment options and 31% with their third-line treatment options. Based on these results, Lymphoma Canada suggested that patients are less satisfied with their treatment options in the second-line and third-line settings than in the first-line setting. Only 10 patients from the survey provided information on accessing treatment for their DLBCL; half (5 [50%]) reported difficulty, while the other half indicated no to minimal difficulties in access. The most common financial implications associated with treatment for large B-cell lymphoma were drug costs (reported by 60% of patients who responded to the survey), travelling costs (reported by 40% of the patients), and absence from work (reported by 40% of the patients).

Two patients included in the survey reported experience with glofitamab, accessed through private insurance and public health care. One patient had received treatment less than 6 months before the survey, and the other had been treated 3 to 5 years prior. Both patients were in remission, 1 for less than 6 months to 1 year and the other for 1 to 2 years. One patient reported no side effects, while the other reported CRS, hypotension, and low platelet count. Both patients indicated that they had experienced financial impacts due to the cost of the drug and the cost of supplemental medication. Despite these challenges, the patients rated their overall experience with glofitamab as good and very good.

Since the section on improved outcomes in the survey was largely incomplete, Lymphoma Canada referred to a separate patient survey submitted for the CADTH Reimbursement Review of polatuzumab vedotin (Polivy). In this separate survey, patients with large B-cell lymphoma identified longer disease remission, longer survival, control of disease symptoms, normalization of blood counts, and improved HRQoL and ability to perform daily activities as the most important outcomes of treatment. Eight patients from this separate survey indicated that they would be willing to tolerate side effects to access a new treatment, and 7 patients indicated that having a choice is important to them when deciding to take a drug based on known side effects and expected outcomes of treatment. Furthermore, Lymphoma Canada indicated that most patients experience relapse after first-line treatment, suggesting there is a need for new and improved therapeutic options for patients with DLBCL that has relapsed.

Clinician Input

Input From Clinical Experts Consulted by CADTH

All CADTH review teams include at least 1 clinical specialist with expertise in the diagnosis and management of the condition for which the drug is indicated. Clinical experts are a critical part of the review team and are involved in all phases of the review process (e.g., providing guidance on the development of the review protocol, assisting in the critical appraisal of clinical evidence, interpreting the clinical relevance of the results, and providing guidance on the potential place in therapy). The following input was provided by 2 clinical specialists with expertise in the diagnosis and management of DLBCL.

Unmet Needs

r/r DLBCL is associated with a poor prognosis, and in patients who are not eligible for cellular therapy (i.e., CAR T-cell therapy and/or autologous SCT) or for whom cellular therapy has failed, the outcomes are poor (OS < 6 months). The clinical experts indicated that the goal of treatment at this stage is palliative and generally includes maintaining HRQoL by 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 experts noted that there is an unmet need for safe and effective treatments for patients in the palliative setting who are not eligible for curative treatment or for patients with disease that has relapsed or is refractory to second-line treatment consisting of SCT or CAR T-cell therapy, as there are limited treatment options for disease control and the currently available options are often associated with significant toxicity that limits their usefulness and applicability. Additionally, patients who are posttransplant and/or post–CAR T-cell therapy often have poor prognosis and very poor bone marrow function that prevents them from receiving or tolerating further cytotoxic therapy.

Input from the experts suggested that there is also 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.

Place in Therapy

If first-line treatment with R-CHOP (curative intent) fails, for patients who are eligible for transplant and have chemosensitive disease, second-line treatment consists of salvage rituximab-based chemotherapy and autologous SCT (curative intent) and third-line therapy consists of CAR T-cell therapy (curative intent). There is no standard of care following these treatment options. As second-line and third-line treatment, patients who are ineligible for transplant tend to receive palliative rituximab-based chemotherapy (e.g., Pola-BR or R-GemOx) with noncurative intent and/or radiation or enrol in clinical trials. The clinical experts highlighted that there is 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 are a major problem of palliative treatment options.

The experts highlighted that glofitamab should be restricted to patients who are not eligible for other curative therapies, patients who have already received CAR T-cell therapy or who would not be able to receive it later (i.e., as third-line therapy for patients post–CAR T-cell therapy or patients who are ineligible for CAR T-cell therapy), and patients who are unable to receive CAR T-cell therapy for logistical and nonmedical reasons, and the experts envisioned glofitamab occupying the same therapeutic space as Pola-BR.

Patient Population

The experts noted that eligible patients would be identified in routine practice by clinicians familiar with the treatment of patients with lymphoma who are undergoing surveillance for relapse (clinical and/or imaging).

Per the indication for glofitamab, patients with r/r DLBCL requiring third-line or later treatment who are not eligible for intensive cellular therapies (i.e., SCT or CAR T-cell therapy) or for whom intensive cellular therapies have failed would be considered for treatment with glofitamab. The experts could not identify a specific subgroup of patients that would likely receive an enhanced benefit or a reduced benefit from glofitamab treatment.

The experts highlighted that repeat biopsy is generally not required in cases of suspected relapse of DLBCL, unless it was a remote relapse or unless the patient had prior history of indolent lymphoma and it was unclear which lymphoma had relapsed.

Assessing the Response Treatment

The clinical experts stated that response to treatment would include standard assessment of lymphoma response using the Lugano criteria. Patients would undergo interim imaging every 3 months to confirm response, which would lead to either ongoing treatment or discontinuation. Patients are also assessed for lymphoma-related symptoms at each visit; the clinical experts noted that these outcomes are more subjective but that they do factor into patients' decisions for continuation of therapy. The experts also noted that the frequency of these assessments and the collection of data may vary across Canada.

In terms of meaningful response to treatment, the clinical experts stated that a response of 6 months or more with improved symptoms can be considered meaningful. The experts did not consider temporary shrinking of tumours beneficial to patients and believed that initial responses (either PR or CR) should exceed 6 months, otherwise the treatment should be discontinued.

Additionally, with a current median OS of 6 months in this patient population, the experts considered a benefit of at least 6 months and at least 3 months over current standard of care to be clinically meaningful for OS and PFS, respectively.

Discontinuing Treatment

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 AEs may vary, and that resolution of severe AEs can allow for resumption of therapy, so the decision to discontinue due to AEs should be left to physician judgment and patient request.

Prescribing Considerations

The clinical experts indicated that patients with r/r DLBCL are typically under the care of hematologists or oncologists who are familiar with the treatment of patients with lymphoma. The experts 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 training of site staff before implementation. The clinical experts noted that after the first few cycles, treatment may continue within regional centres as the risk of CRS decreases.

Clinician Group Input

This section was prepared by the CADTH review team based on the input provided by clinician groups. The full original clinician group inputs received by CADTH have been included in the Stakeholder section of this report.

Two clinician groups provided input for this review: Lymphoma Canada, with 4 clinicians contributing to the submission, and the OH-CCO Hematology Cancer Drug Advisory Committee, with 1 clinician contributing to the submission. 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.

The unmet needs identified by the clinician groups were generally similar to those identified by the clinical experts consulted by CADTH, highlighting the need for additional accessible and effective treatment options beyond Pola-BR (as well as for patients with disease progression after CAR T-cell therapy or those who are ineligible for or are unable to receive CAR T-cell therapy) and for an effective therapy that can achieve disease remission for prolonged periods to improve OS and HRQoL in patients with r/r DLBCL.

The input from the clinician groups generally aligned with that of the clinical experts consulted by CADTH on the anticipated place in therapy of glofitamab, highlighting its use as a third-line option for patients who are ineligible for or unable to receive CAR T-cell therapy or for 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 for patients with disease progression after CAR T-cell therapy or patients who are ineligible for or unable to receive CAR T-cell therapy.

According to the clinician group inputs, and in line with the current indication and the input of the clinical experts consulted by CADTH, patients best suited for treatment with glofitamab are those with DLBCL that has progressed after 2 or more lines of systemic therapy who are ineligible to receive, cannot receive, or have previously received CAR T-cell therapy. One clinician group also suggested that patients who have had prior allogeneic SCT may also be eligible for treatment with glofitamab. The clinician groups highlighted that other histologic subtypes of large B-cell lymphoma are generally treated similarly to DLBCL and that, as such, patients with these subtypes may benefit from glofitamab treatment. The clinician groups suggested that patients who are eligible for and able to receive CAR T-cell therapy would not be suitable for treatment with glofitamab.

The clinician groups highlighted that response to treatment with glofitamab 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 input from the clinical experts consulted by CADTH, the clinician groups considered improvement in the standard lymphoma response measures (using Lugano criteria and confirmed by CT or PET-CT), improved survival, and symptom improvement to be important outcomes of treatment. The clinician groups highlighted that disease progression and unacceptable toxicity would be the primary factors when deciding to discontinue treatment.

Regarding the appropriate treatment setting for glofitamab, the clinician groups and clinical experts consulted by CADTH agreed that glofitamab should be administered in hospitals or cancer centres by a hematologist or oncologist familiar with managing the potential AEs of bispecific antibodies, with staff trained to manage CRS. One clinician group further suggested that both inpatient and outpatient settings may be appropriate for treatment with glofitamab. Lymphoma Canada highlighted that though 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 drug programs provide input on each drug being reviewed through CADTH's reimbursement review processes by identifying issues that may impact their ability to implement a recommendation. The implementation questions and corresponding responses from the clinical experts consulted by CADTH are summarized in Table 5.

Table 5: Summary of Drug Plan Input and Clinical Expert Response

Drug program implementation questions	Clinical expert response
Relevant comparators	
The pivotal trial (NP30179) was an open-label, multicentre, single-arm, phase I/II trial. 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.	The clinical experts agreed that the only currently available publicly funded comparator is Pola-BR. CAR T-cell therapy is not considered a relevant comparator for glofitamab because 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 who decline or cannot access CAR T-cell therapy, glofitamab may be given.
Considerations for initiation of therapy	
Per the pivotal trial, patients were required to have been previously treated with at least 2 prior lines of therapy including at least 1 anthracycline-containing regimen and 1 anti-CD20 antibody–containing regimen.	No response required. For pERC consideration.
Should patients with other types of indolent lymphomas besides FL that have transformed into DLBCL be eligible? Should the patients with the following be eligible for glofitamab? • FL grade 3B • High-grade B-cell lymphoma	Patients with grade 3B FL and high-grade B-cell lymphoma were included in the NP30179 study, though patients with grade 3B FL were not included the cohorts of interest to this review. The clinical experts noted that these uncommon subtypes are treated in the same manner as DLBCL, and these patients should be eligible for treatment with glofitamab.

Drug program implementation questions	Clinical expert response
The following indications were excluded from the NP30179 study: • CL • Burkitt lymphoma • lymphoplasmacytic lymphoma • prior allogeneic SCT What evidence is there for using glofitamab in patients with these indications, and could these indications be considered for treatment with glofitamab?	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. The clinical experts noted that these indications are rare; thus, there are few to no prospective clinical trials for these indications. Therefore, there is a paucity of data available for these patients. With regard to prior allogeneic SCT, the clinical experts highlighted that certain caveats, including the absence of GVHD or no longer taking immunosuppressive therapies, would be required to use glofitamab for these patients; however, no evidence exists.
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?	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 (complete or partial) or stable disease at the end of the full initial glofitamab treatment regimen. No time frame for relapse was specified. The clinical experts noted that, in line with the clinical trial, if patients experienced a good outcome following the initial treatment with glofitamab, then experienced relapse, the experts would consider re-treatment with glofitamab.
Considerations for discontinuation of therapy	
The trial protocol allowed patients to continue study treatment if they were deriving clinical benefit despite radiographic evidence of disease progression. When should treatment with glofitamab be discontinued, including in the presence of suspected pseudoprogression?	As with other bispecific T-cell engager therapies, treatment with glofitamab should be discontinued upon evidence of disease progression or unacceptable toxicity. In the NP30179 study, treatment during suspected pseudoprogression was able to be continued; however, if radiographic disease progression was confirmed at a subsequent tumour assessment, treatment with glofitamab was discontinued. The clinical experts noted that pseudoprogression is rare and that there may be some initial swelling or worsening of symptoms; however, they highlighted that treatment should continue if the symptoms were considered pseudoprogression.
In the event of prolonged dosing delays, obinutuzumab pretreatment is required again.	No response required. For pERC consideration.
Considerations for prescribing of therapy	
Pretreatment 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 patients with r/r DLBCL?	Beyond the NP30179 trial, there is no evidence for the use of obinutuzumab to minimize the risk of CRS in patients with r/r DLBCL.

Drug program implementation questions	Clinical expert response
Generalizability	
Patients with an ECOG PS greater than 1 were excluded from the NP30179 trial. Should patients with an ECOG PS 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 that select patients with an ECOG PS 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 needs to 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.

CAR = chimeric antigen receptor; CLL = chronic lymphocytic leukemia; CRS = cytokine release syndrome; DLBCL = diffuse large B-cell lymphoma; ECOG PS = Eastern Cooperative Oncology Group Performance Status; FL = follicular lymphoma; GVHD = graft-vs.-host disease; pCPA = pan-Canadian Pharmaceutical Alliance; pERC = CADTH pan-Canadian Oncology Drug Review Expert Review Committee; Pola-BR = polatuzumab vedotin, bendamustine, and rituximab; r/r = relapsed or refractory; SCT = stem cell transplant.

Clinical Evidence

The objective of CADTH's Clinical Review Report is to review and critically appraise the clinical evidence submitted by the sponsor on the beneficial and harmful effects of glofitamab 1 mg/mL for IV infusion in the treatment of adult patients with r/r 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 focus will be placed on comparing glofitamab to relevant comparators and identifying gaps in the current evidence.

A summary of the clinical evidence included by the sponsor in the review of glofitamab is presented in 2 main sections, with CADTH's critical appraisal of the evidence included at the end of each section. The first main section, the systematic review, includes 1 pivotal study that was selected according to the sponsor's systematic review protocol. CADTH's assessment of the certainty of the evidence in this first section using the GRADE approach follows the critical appraisal of the evidence. The second main section includes indirect evidence from the sponsor. No long-term extension studies or additional studies that were considered to address important gaps in the systematic review evidence were submitted by the sponsor.

Included Studies

Clinical evidence from the following is included in the CADTH review and appraised in this document:

- 1 pivotal study identified in the systematic review (the NP30179 study)[13]
- 2 ITCs (1 PSA and 1 MAIC).[18]

Systematic Review

Contents within this section have been informed by materials submitted by the sponsor. The following has been summarized and validated by the CADTH review team.

Description of Study

Characteristics of the included study are summarized in Table 6.

Table 6: Details of Study Included in the Systematic Review

Study characteristic	NP30179
Design and populations	
Study design	Phase I/II, open-label, multicentre, single-arm study
Locations	13 countries (Spain and US [6 centres each]; France [5 centres]; Italy and Poland [3 centres each]; Australia, Belgium, and Taiwan [2 centres each]; Canada, Czech Republic, Denmark, Finland, and New Zealand [1 centre each])
Patient enrolment dates	Start date: January 2020 End date: June 2022
Enrolled (N)	Primary efficacy population: N = 155 Primary safety population: N = 154 The main analysis included 108 patients in the pivotal cohort (cohort D3), 40 patients in the mandatory dexamethasone cohort (cohort D5), and 7 patients who had been treated at the phase II dose in the dose escalation part of the study (cohort D2S2)
Inclusion criteria	• Age ≥ 18 years. • Depending on study part, a history or status of a histologically confirmed hematologic malignancy that was expected to express CD20, and disease that relapsed after or did not respond to at least 1 prior treatment regimen, and having no available treatment options that were expected to prolong survival (e.g., standard chemotherapy or autologous SCT). Eligible patients with r/r NHL included: ◦ part I and part II dose escalation cohorts: grade 1 to 3b FL, MZL (splenic, nodal, or extranodal), MCL, DLBCL, PMBCL, Richter transformation, and trFL ◦ part III expansion cohorts: ▪ DLBCL cohort: DLBCL not otherwise specified, HGBCL, PMBCL, and trFL. Patients must have disease that relapsed after or did not respond to at least 2 prior systemic treatment regimens (including at least 1 prior regimen containing anthracycline and at least 1 containing an anti-CD20–directed therapy) ▪ FL cohort: grade 1 to 3a FL. Patients must have disease that relapsed after or did not respond to at least 2 prior lines of systemic therapy and must have received prior treatment with rituximab and alkylating agents. • Measurable disease, defined as at least 1 bi-dimensionally measurable nodal lesion, defined as > 1.5 cm in its longest dimension, or at least 1 bi-dimensionally measurable extranodal lesion, defined as > 1.0 cm in its longest dimension. • Able to provide a fresh biopsy from a safely accessible site, per investigator determination, providing the patient had more than 1 measurable target lesion (or, in the absence of a fresh biopsy, the most recent archival tumour tissue samples). • ECOG PS of 0 or 1. • Life expectancy (in the opinion of the investigator) of ≥ 12 weeks.

Study characteristic	NP30179
	• Adequate liver function: total bilirubin ≤ 1.5 × ULN. Patients with documented history of Gilbert syndrome and in whom total bilirubin elevations are accompanied by elevated indirect bilirubin are eligible. Patients with AST/ALT ≤ 3 × ULN. • Adequate hematological function: neutrophil count of ≥ 1.5 × 109 cells/L; platelet count of ≥ 75,000/μL (and platelet transfusion free within 14 days before administration of obinutuzumab); hemoglobin ≥ 10.0 g/dL (6.2 mmol/L); transfusion free within 21 days before administration of obinutuzumab. • Adequate renal function: serum creatinine ≤ 1.5 × ULN or a creatine clearance of ≥ 50 mL/min (calculated by Cockroft-Gault formula) for patients in whom, in the investigator's judgment, serum creatinine levels did not adequately reflect renal function. • Negative serologic or PCR test results for acute or chronic HBV infection.
Exclusion criteria	• Known or suspected history of HLH. • Acute bacterial, viral, or fungal infection at baseline. • Known active infection, or reactivation of a latent infection, or any major episode of infection requiring hospitalization or treatment with IV antibiotics within 4 weeks of study dosing. • Pregnant, breastfeeding, or intending to become pregnant during the study. • Prior treatment with systemic immunotherapeutic agents, such as radio-immunoconjugates, antibody-drug conjugates, immune/cytokines and monoclonal antibodies, within 4 weeks or 5 half-lives of the drug, whichever was shorter, before obinutuzumab infusion. • Treatment with standard radiotherapy or any chemotherapeutic drug, or treatment with any other investigational anticancer agent, including CAR T-cell therapy, within 4 weeks before obinutuzumab infusion. • Prior allogeneic SCT. • Autologous SCT within 100 days before obinutuzumab infusion. • Current or history of CNS lymphoma. • Significant cardiovascular disease, such as NYHA Class III or IV cardiac disease, myocardial infarction within the last 6 months, unstable arrhythmias, or unstable angina. • History of autoimmune disease. • Another invasive malignancy in the past 2 years (except for BCC and tumours deemed by the investigator to have low likelihood of recurrence). • Treatment with systemic immunosuppressive medications within 2 weeks before obinutuzumab infusion. Treatment with corticosteroid (≤ 25 mg/day prednisone or equivalent) was allowed. Inhaled and topical steroids were permitted.
Drugs	
Intervention	Cycle 1 day 1: Pretreatment with obinutuzumab (1,000 mg) administered IV Cycle 1 day 8 to day 15: Glofitamab administered intravenously as step-up doses on day 8 (2.5 mg) and day 15 (10 mg) Cycle 2 to cycle 12: 30 mg glofitamab on day 1 of cycles 2 through 12 (cycles lasted 21 days)
Comparator(s)	NA
Study duration	
Screening phase	28 days before initial treatment
Treatment phase	12 cycles (8.3 months)
Follow-up phase	Patients followed until disease progression, death, or new anticancer therapy

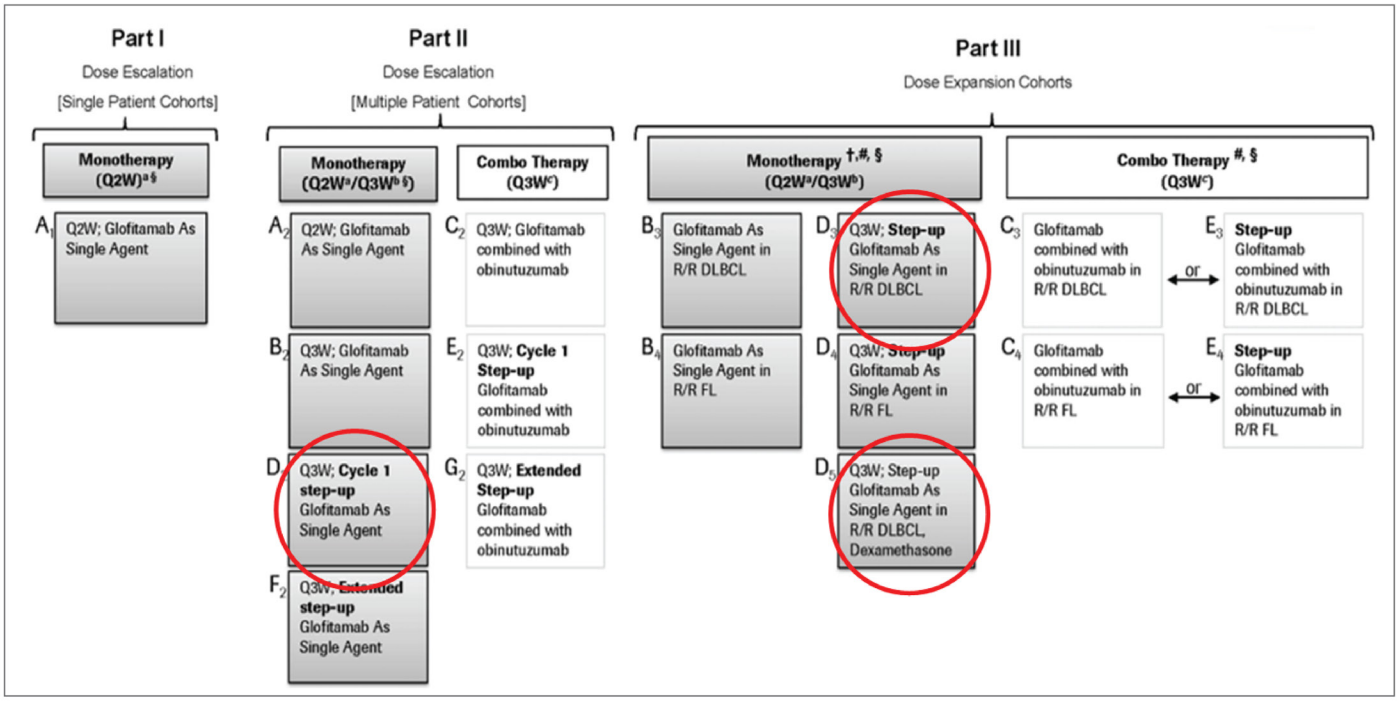
Study characteristic	NP30179
Outcomes	
Primary end point	The primary efficacy end point was IRC-assessed CR rate, defined as the proportion of patients best overall response was a CR based on IRC assessment of PET-CT scans using the Lugano criteria
Secondary and exploratory end points	Secondary: ORR, DOCR, DOR, PFS, OS, safety, and PROs Exploratory: • To evaluate the relationship between glofitamab, as a single drug (and in combination with obinutuzumab) following obinutuzumab exposure, and appropriate progressive disease biomarkers such as soluble mediators, peripheral B-cell and T-cell number, and T-cell activation status • To make a preliminary assessment of tumour burden and/or biological markers that might act as predictors of the safety or antitumour activity of glofitamab as a single drug (and in combination with obinutuzumab), such as MRD status, immune-modulatory phenotypic markers, and soluble mediators • To assess the antitumour activity of re-treatment with glofitamab as a single drug (and in combination with obinutuzumab) in patients who experienced an objective response (CR or PR) or stable disease and who subsequently experienced disease progression or relapse
Publication status	
Publications	Dickinson et al. (2022)[34] Sponsor's Clinical Study Report Trial ID numbers: EudraCT number: 2016-0011845-28 ClinicalTrials.gov identifier: NCT03075696

ALT = alanine transaminase; AST = aspartate transaminase; BCC = basal cell carcinoma; CAR = chimeric antigen receptor; CNS = central nervous system; CR = complete response; DLBCL = diffuse large B-cell lymphoma; DOCR = duration of complete response; DOR = duration of response; ECOG PS = Eastern Cooperative Oncology Group Performance Status; FL = follicular lymphoma; HBV = hepatitis B virus; HGBCL = high-grade B-cell lymphoma; HLH = hemophagocytic lymphohistiocytosis; IRC = independent review committee; MCL = mantle cell lymphoma; MRD = minimal residual disease; MZL = marginal zone lymphoma; NA = not applicable; NHL = non-Hodgkin lymphoma; NYHA = New York Heart Association; ORR = overall response rate; OS = overall survival; PCR = polymerase chain reaction; PFS = progression-free survival; PMBCL = primary mediastinal B-cell lymphoma; PR = partial response; PRO = patient-reported outcome; r/r = relapsed or refractory; SCT = stem cell transplant; trFL = transformed follicular lymphoma; ULN = upper limit of normal.

Source: NP30179 Clinical Study Report.[13]

One study was included in the review. The NP30179 study is an ongoing phase I/II, multicentre, open-label, single-arm study of glofitamab monotherapy after a fixed, single dose pretreatment of obinutuzumab in patients with r/r NHL. The study was divided into 3 parts: Part I (single-patient cohorts) and Part II (multiple-patient cohorts), composing 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.[13] The overall study design of the NP30179 study is shown in Figure 1.

Figure 1: Study Design of the NP30179 Study



DLBCL = diffuse large B-cell lymphoma; FL = follicular lymphoma; Q2W = every 2 weeks; Q3W = every 3 weeks; r/r = relapsed or refractory.

§ Mandatory paired fresh baseline (cycle 1, day 7) and on-treatment tumour biopsies (cycle 1, day 9) are collected in a subset of patients.

† Patients in Part III dose expansion monotherapy cohorts may receive glofitamab on an every-2-week dosing schedule with fixed dosing or every 3 weeks with step-up dosing (cycle 1 step-up or extended step-up), if supported by emerging data and/or recommended by the independent monitoring committee.

Based on determined maximally tolerated dose or optimal biological dose, both expansion cohorts or 1 expansion cohort may be selected for monotherapy B3 and/or D3, or B4 and/or D4, while cohorts C3 or E3 and C4 or E4 may be selected.

[a] Monotherapy schedule every 2 weeks.

[b] Monotherapy therapy schedule every 3 weeks.

[c] Combination therapy schedule every 3 weeks.

Source: NP30179 Clinical Study Report.[13]

An interim Clinical Study Report was provided for the NP30179 study, detailing the results from the first patient enrolment date (February 14, 2017) up to the CCOD of September 14, 2021, from a snapshot taken on November 19, 2021. At CADTH's request, an updated Clinical Study Report detailing the results from the first patient enrolment date to a CCOD of June 15, 2022, was provided. All results within this section are reported as of the June 15, 2022, CCOD, unless otherwise specified.

At the June 15, 2022 CCOD, [redacted] patients were assigned to dose cohorts in the order in which they were enrolled in the NP30179 study and had received treatment with glofitamab monotherapy (246 patients in Parts I and II, and 257 patients in Part III). Multiple cohorts were initiated in the NP30179 study, evaluating non–Health Canada–approved dosages; thus, only cohorts with dosages in line with the Health Canada indication were of interest to this review. Cohorts from the NP30179 study of interest to this review were cohort D2S2 [redacted], cohort D3 [redacted], and cohort D5 [redacted]. The combined D2S2, D3, and D5 cohorts composed the primary efficacy population [redacted], which included patients with r/r DLBCL who had received 2 or more prior lines of systemic therapy and who were treated with the phase II recommended dosage of glofitamab

of 2.5 mg, then 10 mg, then 30 mg every 3 weeks for a fixed treatment duration of 12 cycles, or 8.3 months, and with obinutuzumab 1,000 mg 7 days before the first dose of glofitamab. The primary safety population consisted of all patients from the primary efficacy population, except 1 patient who was enrolled in error and did not receive the study treatment (n = 154). The NP30179 study was conducted in 13 countries, including 1 Canadian study site, which enrolled 9 patients.[13]

Populations

Inclusion and Exclusion Criteria

The key inclusion and exclusion criteria for the NP30179 study are summarized in Table 6. Patients eligible for the cohorts of interest to this review were adults (aged ≥ 18 years) diagnosed with DLBCL not otherwise specified, high-grade B-cell lymphoma (HGBCL), PMBCL, or trFL who had disease that had relapsed after or not responded to at least 2 prior systemic treatment regimens (including ≥ 1 prior regimen containing anthracycline and ≥ 1 containing an anti-CD20–directed therapy) and who had an ECOG PS of 0 or 1. Patients were excluded if they had received prior allogeneic SCT or if they had received prior autologous SCT within 100 days of the study. Additionally, patients with a history of central nervous system lymphoma or autoimmune disease were excluded.[13]

Interventions

Glofitamab

An increment-based dose escalation was used for the single-patient cohorts in Part I and II of the NP30179 study, with dosing initiated at 0.005 mg (flat dose) until the maximally tolerated dose of glofitamab of 25 mg was declared. Based on the observed safety and efficacy during the Part II dose escalation and exposure-response analyses, a step-up dosing regimen was introduced to reduce the incidence and severity of CRS. Thus, the recommended phase II dose was determined in Part II to be glofitamab 2.5 mg, then 10 mg, then 30 mg. Following the selection of the recommended phase II dose for step-up dosing, the dose expansion cohort D3 for patients with r/r DLBCL was initiated.[13]

During the parts of the NP30179 study of interest to this review, glofitamab was administered every 3 weeks, with step-up doses on day 8 (2.5 mg) and day 15 (10 mg) of cycle 1, followed by a dose of 30 mg on day 1 of cycles 2 through 12 (cycles lasted 21 days). Glofitamab was administered by IV infusion using a dedicated infusion line and a catheter in a clinic or hospital equipped for systemic cancer treatment. The first administration of glofitamab was administered over 4 hours. Glofitamab infusion was to be discontinued immediately in patients who developed CRS, with no further restarts of the infusion for this administration, unless the CRS was limited to grade 1. Glofitamab was permanently discontinued if patients experienced grade 4 CRS. If patients experienced grade 3 CRS, then the current infusion was discontinued and not resumed. If the symptoms resolved within 72 hours, glofitamab was administered at the planned dose at the next scheduled infusion, though a slower infusion rate was considered. Patients were monitored for at least 22 hours postinfusion, and if grade 3 or higher CRS recurred at subsequent infusion, the infusion was stopped, and treatment was discontinued. In the absence of infusion-related AEs, infusion time in subsequent glofitamab cycles could be reduced to 2 hours. For patients who could be at an increased risk of CRS, patients who experienced infusion-related reactions or CRS with their previous dose of glofitamab,

or patients who were at increased risk of recurrent infusion-related reactions or CRS with subsequent doses, the time of infusion could be extended to up to 8 hours.[13]

Premedication with oral acetaminophen (500 mg to 1,000 mg) and an antihistamine (e.g., diphenhydramine 50 mg to 100 mg) was administered at least 30 minutes before the start of each infusion (unless contraindicated). Premedication with corticosteroids (80 mg IV methylprednisolone [or equivalent dose of prednisone, prednisolone, or 20 mg IV dexamethasone]) was administered at least 60 minutes before the administration of obinutuzumab and glofitamab. Corticosteroid premedication was optional at later cycles, based on investigator's assessment, for patients who had tolerated the step-up doses and 2 target doses of glofitamab without experiencing any grade of CRS. If a patient experienced CRS, premedication with steroids was required for subsequent doses until no additional CRS events were observed. Tocilizumab was administered to manage potential safety risks for patients who experienced severe CRS during or after any infusion of glofitamab. Starting from version 10 of the NP30179 study protocol, dexamethasone (20 mg IV before obinutuzumab and glofitamab infusion) was included as an option for corticosteroid premedication (in addition to prednisolone and methylprednisolone). Cohort D5 was introduced to investigate if mandated premedication with dexamethasone could further reduce the occurrence and severity of CRS.[13]

Glofitamab Re-treatment

Patients who initially experienced response (PR or CR) or had stable disease following the study treatment were eligible to receive re-treatment, per version 10 of the study protocol. Patients who experienced response were required to complete the end of treatment assessments for the initial glofitamab treatment course before entering the "follow-up until progression" phase, where they were followed until disease progression or death or until they were lost to follow-up. While in the "follow-up until progression" phase, patients with investigator-assessed disease progression or relapse, confirmed by radiographic imaging, were eligible for glofitamab re-treatment at the highest dose found to be safe at the time of re-treatment, provided they met the re-treatment eligibility criteria.[13]

Patients who withdrew from the study because of disease progression or pseudoprogression but who later experienced PR or CR without receiving any other therapy after the last dose of glofitamab were allowed to enter the "follow-up until progression" phase and could be eligible for re-treatment provided they met the re-treatment eligibility criteria. Patients who experienced pseudoprogression were allowed to continue the initial treatment course provided there was an absence of symptoms and signs (including worsening of laboratory values) indicating progression of disease, there was no decline in ECOG PS, and there was an absence of tumour progression at critical anatomic sites. If radiographic disease progression was confirmed at a subsequent tumour assessment or at the end of treatment, these patients were ineligible to receive further glofitamab treatment.[13]

In the event of a delayed response (e.g., following pseudoprogression that led to premature discontinuation or interruption of the study treatment), re-treatment or resumption of treatment could be allowed. As safety measures, obinutuzumab was reinitiated 7 days before resuming treatment with glofitamab and, for patients enrolled in the step-up dosing regimen, mandatory hospitalization was required with the step-up dosing of glofitamab for the first cycle after the dosing delay.[13]

Patients eligible for re-treatment had to meet all eligibility criteria at the time glofitamab was reinitiated, with the following exceptions:[13]

- Prior therapy with glofitamab is allowed.
- Serology tests to confirm viral status (HIV or hepatitis B or C) do not need to be repeated unless clinically indicated.
- Manageable and reversible immune-related AEs with prior cycles of glofitamab treatment are allowed (with the exception of glofitamab-suspected hypersensitivity type 1 events) and do not constitute an exclusionary history of autoimmune disease.
- Patients must have a radiographically documented, investigator-assessed objective response (CR or PR) or stable disease at the end of the full initial glofitamab treatment regimen.
- Patients must not have experienced grade 4 nonhematologic AEs during the initial glofitamab treatment period. Consideration for further treatment with glofitamab may be warranted and would need to be discussed with the medical monitor, taking into consideration benefits and risks for a given patient as well as ad hoc and patient-specific risk mitigation.
- For patients who experienced grade 2 or 3 AEs during the initial treatment period, these toxicities must have been resolved to grade 1 or lower.
- Patients are required to receive obinutuzumab again, and hospitalization will be required as per the schedule of assessments of the assigned regimen.
- No intervening systemic anticancer therapy can have been administered between the time of completion of initial glofitamab and the reinitiation of obinutuzumab and/or glofitamab treatment.
- If clinically feasible and safe, a biopsy of the recurrent or progressing tumour should be obtained before glofitamab re-treatment for retrospective assessment of CD20 expression status and assessment of the tumour microenvironment. Patients who reconsent to the re-treatment but who have no lesion amenable for biopsy at disease progression may still be considered for glofitamab re-treatment.

Patients who initiated study re-treatment could continue to receive glofitamab for 12 cycles, until disease progression or unacceptable toxicity, whichever occurred first.[13]

Obinutuzumab

All patients received pretreatment with obinutuzumab 1,000 mg, administered intravenously 7 days before the first dose of glofitamab. Obinutuzumab pretreatment was given as a safety measure to deplete B-cells both in the peripheral blood and in the secondary lymphoid organs to reduce the risk of sudden cytokine release associated with the first administration of glofitamab. Obinutuzumab was administered in a clinic or hospital equipped for systemic cancer treatment.[13]

Prior and Concomitant Therapy

The following concomitant therapies were permitted:[13]

- Oral contraceptives, hormone replacement therapy, or other maintenance therapy

- Hematopoietic growth factors such as erythropoietin, granulocyte colony-stimulating factor filgrastim, pegfilgrastim, granulocyte-macrophage colony-stimulating factor sargramostim, or thrombopoietin
- Anti-infective prophylaxis for viral, fungal, bacterial, or pneumocystis infection
- Treatment of severe CRS or hemophagocytic lymphohistiocytosis according to published recommendations and/or institutional practice
- Symptomatic treatment for patients who experience obinutuzumab or glofitamab infusion-related symptoms
- Concomitant medications that are CYP450 substrates have a narrow therapeutic window in patients who are at the highest risk for drug-drug interactions, and were monitored closely in the NP30179 study with the dose adjusted as necessary. Given the expected pharmacology of obinutuzumab and glofitamab, the release of cytokines in the immediate period after the first infusion of each compound can lead to secondary alteration of CYP450 enzymes, with risk of subsequent drug-drug interactions. Systemic cytokine release is considered a "first-pass effect" that may be related, in part, to levels of circulating CD20+ target cells, and targets will drop with obinutuzumab and continued glofitamab dosing.

The following therapies were prohibited during the study and for 30 days after the last dose of glofitamab: investigational or unlicensed or unapproved agents, biologic agents (e.g., bevacizumab, erlotinib), immunotherapy or radio-immunotherapy, radiotherapy (except for limited-field palliative radiotherapy for bone pain or for soft tissue lesions), chemotherapy, hormone therapy (other than contraceptives, hormone replacement therapy, or megestrol acetate), chronic steroids (inhaled, topical, or systemic [excluding those required for the management of study drug–related AEs]), and non-oncological live viral vaccines. Patients who required the use of any of these agents were discontinued from treatment with glofitamab. Patients who are discontinued from study treatment were to be followed for safety outcomes for 90 days following the patient's last dose of glofitamab or until the patient receives another anticancer therapy, whichever comes first, and thereafter for survival.[13]

Outcomes

A list of efficacy end points assessed in this Clinical Review Report is provided in Table 7; the table is followed by descriptions of the outcome measures. The summarized end points are based on the outcomes included in the sponsor's summary of clinical evidence as well as any outcomes identified as important to this review according to the clinical experts consulted by CADTH and stakeholder input from patient and clinician groups and public drug plans. Using the same considerations, the CADTH review team selected the end points considered most relevant to inform CADTH's expert committee deliberations and finalized this list of end points in consultation with members of the expert committee. All summarized efficacy end points were assessed using GRADE. Select notable harms outcomes considered important for informing CADTH's expert committee deliberations were also assessed using GRADE.

Table 7: End Points Summarized From the NP30179 Study

End point	Time point	Type of outcome
Progression-free survival	Median, 12 months and 24 months	Secondary
Overall survival	Median, 12 months and 24 months	Secondary
HRQoL (EORTC QLQ-C30, FACT-Lym LymS)	Baseline, cycle 3, cycle 5, and cycle 7	Secondary
Complete response	Any	Primary
Overall response rate	Any	Secondary
Duration of response	Median, 12 months and 24 months	Secondary
Notable harms (CRS)	Any	Secondary

CRS = cytokine release syndrome; EORTC QLQ-C30 = European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30; FACT-Lym = Functional Assessment of Cancer Therapy–Lymphoma; HRQoL = health-related quality of life; LymS = lymphoma subscale.

Efficacy Outcomes

According to the clinical expert input, patient group input, and clinician group input received by CADTH, patients for whom second-line and third-line treatments have failed have limited safe and effective treatment options, and the currently available therapies are palliative with poor survival rates (OS < 6 months). Therefore, outcomes related to survival were included as outcomes to be assessed using GRADE. In the NP30179 study, these outcomes were OS and PFS.

HRQoL was identified as an important outcome for patients with r/r DLBCL; thus, the change from baseline in HRQoL outcomes, including the fatigue, physical function, role function, and GHS/QoL scales of the EORTC QLQ-C30 and the FACT-Lym LymS total score, were included in the GRADE assessment.

Per the clinical experts consulted by CADTH, clinical response (particularly the CR rate) is an important outcome of treatment for r/r DLBCL; thus, CR and ORR were included in the GRADE assessment. In addition, the clinical experts suggested that DOR may demonstrate greater treatment effect than response rates alone; thus, it was included in the GRADE assessment.

Primary Efficacy Outcome

The primary efficacy end point of the NP30179 study was CR rate, defined as the proportion of patients whose best overall response was a CR based on IRC assessment of PET-CT scans using the Lugano criteria. Patients included in the primary efficacy population with missing or no PET-CT response assessments were included as patients who did not experience response.[13]

Secondary Efficacy Outcomes

The secondary outcomes of the NP30179 study included additional response outcomes, time-to-event outcomes, and HRQoL outcomes. The additional response end points were:[13]

- investigator-assessed CR rate, defined as the proportion of patients whose best overall experienced response was a CR based on investigator assessment of PET-CT scans using the Lugano classification

- both IRC-assessed and investigator-assessed ORR, defined as the proportion of patients whose best overall experienced response was a CR or PR using the Lugano classification.

The secondary time-to-event end points were only reported for the Part III step-up dosing expansion primary efficacy population of cohort D3 (2.5 mg, then 10 mg, then 30 mg), with relevant supporting data from the Part II cohort with 2.5 mg, then 10 mg, then 30 mg dosing (cohort D2S2). The secondary time-to-event end points were:[13]

- DOR, assessed via PET-CT by the IRC and the investigator using the Lugano criteria and defined as the time from the initial occurrence of a documented CR or PR until documented disease progression or death due to any cause, whichever occurred first
- PFS, assessed by the IRC and the investigator using the Lugano classification (Cheson et al. [2014]) and defined as the time from the first study treatment (obinutuzumab, or glofitamab if obinutuzumab was not taken) to the first occurrence of disease progression or death from any cause, whichever occurred first
- OS, defined as the time from the first study treatment (obinutuzumab, or glofitamab if obinutuzumab was not taken) to the date of death from any cause.

HRQoL outcomes were recorded for the Part III monotherapy expansion cohorts (B3, B4, D3, and D5) and included use of the EORTC QLQ-C30 and the FACT-Lym LymS. The EORTC QLQ-C30 is a validated, reliable self-report measure.[35] It consists of 30 questions that assess 5 domains of patient functioning (physical, emotional, role, cognitive, and social), 3 symptom scales (fatigue, nausea and vomiting, and pain), GHS/QoL, and 6 single items (dyspnea, insomnia, appetite loss, constipation, diarrhea, and financial difficulties). Scores are transformed to a 0 to 100 scale, with higher scores on the 5 domains and GHS/QoL being reflective of better HRQoL and higher scores on the symptom scales and single items reflective of poorer HRQoL. The EORTC QLQ-C30 takes approximately 10 minutes to complete and uses a recall period of the previous week. For the EORTC QLQ-C30 physical and role functioning and GHS/QoL subscales, a clinically meaningful change at any time has been defined as a difference of at least 10 points.[13,36]

The FACT-Lym LymS was developed to assess HRQoL in patients with NHL. The FACT-Lym LymS includes 15 items that assess the changes from baseline with respect to B symptoms and the impact on HRQoL brought about by symptom worsening or alleviation and treatment toxicity. The scale range is 0 to 60, with a higher score reflecting better HRQoL; the recall period is the previous week. The validity and reliability of the FACT-Lym LymS for NHL patients have been established. For the FACT-Lym LymS, a clinically meaningful change at any time has been defined as a difference of at least 3 to 5 points in patients with NHL.[13,37]

The validity, reliability, and responsiveness of the EORTC QLQ-C30 and the FACT-Lym LymS in r/r DLBCL are summarized in Table 8.

Table 8: Summary of HRQoL Outcome Measures and Their Measurement Properties

Outcome measure	Type	Conclusions about measurement properties	MID
EORTC QLQ-C30 version 3.0	A 30-item, patient-reported, cancer-specific questionnaire used to assess HRQoL in response to treatment in clinical trials.[35,38] The questionnaire consists of:[38] • 5 functional scales (physical, role, cognitive, emotional, and social) • 3 symptom scales (fatigue, pain, and nausea and vomiting) • 6 single-item scales (dyspnea, insomnia, appetite loss, constipation, diarrhea, and financial difficulties) • 1 global health status/QoL scale. Items are rated on a 4-point or 7-point Likert scale. Raw scores are transformed to a 0 to 100 scale, with higher scores indicating a high or healthy level of functioning, a good QoL, or a high level of symptomatology or problems, depending on the scale.[38]	Measurement properties of validity, reliability, and responsiveness have not been assessed for patients with NHL.	Using an anchor-based approach based on global ratings of change, patients with breast cancer (n = 246) and small-cell lung cancer (n = 111) who were in clinical trials for chemotherapy reported that "a little," "moderate," and "very much" absolute change corresponded to a mean change in EORTC QLQ-C30 (a previous version) score of 5 to 10, 10 to 20, and > 20, respectively.[36] Based on the 2012 evidence-based guidelines for interpreting change scores for the EORTC QLQ-C30,[39] the following are the thresholds for a trivial difference over time in patients with diversity in cancer type, including hematologic: −5 to 2 for physical functioning, −7 to 6 for role functioning, and −5 to 5 for global QoL. Based on the 2011 evidence-based guidelines for determination of sample size and interpretation of the EORTC QLQ-C30,[40] the following are the thresholds for a trivial difference between groups of patients with diversity in cancer type, including hematologic: 0 to 5 for physical functioning, 0 to 6 for role functioning, and 0 to 4 for global QoL.
FACT-Lym LymS	The FACT-Lym consists of the 27-item FACT-G and the 15-item LymS.[37] The FACT-G questionnaire assesses 4 dimensions of HRQoL: physical, social/family, emotional, and functional well-being.[37] The LymS is an NHL-specific, patient-reported questionnaire used to assess HRQoL in terms of disease-specific symptoms and concerns.[37] Items are rated on a 5-point Likert scale, with higher scores indicating better HRQoL.[37]	In a study[37] of 84 adult patients with NHL, measurements were taken at baseline, at 3 to 7 days, and at 8 to 12 weeks. **Validity:** Known-groups (construct) validity was demonstrated by the LymS score, which differentiated between patients with an ECOG PS of 0, 1, or 2 and between patients on and off active treatment (e.g., radiation and chemotherapy) but did not differentiate between patient groups defined by their NHL	Using distribution-based and anchor-based methods, the investigators suggested the likely MID range for the LymS in patients with NHL is approximately 3 to 5 points, or 5% to 8% of the scale range (0 to 60).[37]

Outcome measure	Type	Conclusions about measurement properties	MID
		grade.[37] Concurrent validity was demonstrated based on correlations between LymS and SF-36 PCS (r = 0.62) and MCS (r = 0.48) scores and the POMS total score (r = 0.60).[37] Divergent validity was demonstrated based on the near-zero association between LymS and the Marlowe-Crowne Social Desirability Scale–Short Form (r = 0.15).[37] **Reliability**: LymS demonstrated good internal consistency, with Cronbach alpha ranging from 0.79 to 0.85 at each assessment time point.[37] LymS demonstrated good test-retest reliability based on an ICC of 0.84 (retested at 3 to 7 days from baseline; n = 74).[37] **Responsiveness:** FACT-LymS was able to differentiate patients in each of the 3 groups (worse, unchanged, better) defined by the patients' retrospective ratings of change at the final assessment, and by change over 3 months in performance status (effect sizes > 0.50).[37]	

ECOG PS = Eastern Cooperative Oncology Group Performance Status; EORTC QLQ-C30 = European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30; FACT-G = Functional Assessment of Cancer Therapy–General; FACT-Lym = Functional Assessment of Cancer Therapy–Lymphoma; HRQoL = health-related quality of life; ICC = intraclass correlation coefficient; LymS = lymphoma subscale; MCS = mental component summary; MID = minimal important difference; NHL = non-Hodgkin lymphoma; PCS = physical component summary; POMS = Profile of Mood States; QoL = quality of life; SF-36 = Short Form (36) Health Survey.

Harms Outcomes

Safety was assessed through summaries of AEs, AEs of special interest, changes in laboratory test results, changes in electrocardiograms, presence of antidrug antibodies, and changes in vital signs using the *Medical Dictionary for Regulatory Activities* version 24.0. The AEs of special interest for glofitamab were CRS (graded using the Lee [2014] grading criteria and summarized by ASTCT 2019 grading criteria); neurologic AEs; any suspected hemophagocytic lymphohistiocytosis; tumour lysis syndrome; febrile neutropenia; aspartate aminotransferase, alanine aminotransferase, or total bilirubin elevation; any grade of disseminated intravascular coagulation; tumour inflammation or flare; any grade of pneumonitis or interstitial lung disease; and colitis.[13]

AEs were defined as any untoward medical occurrence in a participant in a clinical investigation who had been administered a pharmaceutical product, regardless of causal attribution.[13]

An SAE was defined as any AE that is considered fatal or life threatening, or that requires or prolongs inpatient hospitalization, or that results in persistent or significant disability or incapacity or in a congenital anomaly in an infant born to a study participant exposed to the study drug while pregnant, or that was considered a significant medical event in the investigator's judgment.[13]

Patients were assessed clinically for toxicity before receiving each dose of the study drug using the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.03. All AEs and SAEs were recorded for up to 90 days after the last dose of the study drug or until the initiation of another systemic anticancer therapy, whichever came first.[13]

Statistical Analysis

Sample Size and Power Calculation

The sample size calculation for the NP30179 study was based on the primary end point of CR rate for the primary efficacy population of cohort D3 compared to a historical control. An SLR was performed for regimens used in the treatment of r/r DLBCL — CAR T-cell therapy, anti-CD20 therapy plus chemotherapy, lenalidomide, polatuzumab vedotin, and other regimens — in patients who had received 2 or more prior lines of therapy. The SLR identified 19 studies, which together included 1,373 patients, most of whom had received at least 2 prior systemic therapy regimens. A random-effects model meta-analysis was performed, which calculated a historical control rate of 20% (95% CI, 14% to 28%).[13]

A sample size of 100 patients had 92% power to detect an increase in CR rate from 20% to 35%. The primary analysis was to be conducted with 80 to 100 patients. An analysis conducted with 80 patients would have 85% power to detect an increase in CR rate from 20% to 35%.[13]

Interim and Final Analyses

A nonbinding interim analysis for safety and futility was performed for each expansion cohort in Part III of the study. The first such interim analysis was to occur after approximately 15 patients in each treatment cohort had been evaluated for response. Additional analyses would occur after approximately 40 patients had been evaluated for response in the cohort. At each interim analysis, the internal monitoring committee reviewed the response data to decide whether to recommend an early decision to stop enrolment in the study owing to futility.[13]

During the expansion phase (Part III), it was planned that predictive and/or posterior probability methods would be used to compare the efficacy end points obtained using the Lugano classification with those of historical controls that had used the design of Lee and Liu (2008),[41] with the modification that the uncertainty in the historical control data would be fully accounted for by using a distribution on the control response rate. Interim analysis decision rules for each cohort were based on the predictive probability that the cohort would have a positive outcome if they completed the study. The latest data available at the time of the analysis regarding the efficacy of existing therapies in comparable patients were to be used as historical controls for comparison. The possible data sources to be used as historical controls would be publications, real-world data sources, and other reliable information on efficacy from other studies in similar patients. This interim analysis was not undertaken for step-up monotherapy for r/r DLBCL (cohort D3) because an

informal assessment of data from cohort D2S2 indicated that the study would not stop for futility. If at any time the interim analysis suggests that the ORR with study treatment is lower than that of historical controls, enrolment into the expansion cohort could be stopped. Specifically, enrolment may be stopped if an approximately 80% chance exists that the true ORR is 25% or less when the posterior probability approach with a noninformative prior is used.[13]

Statistical and Analytical Plans

Primary End Point

The primary end point of IRC-assessed CR rate in the efficacy-evaluable population in cohort D3 was evaluated using the Lugano criteria, with exact 95% CIs for the CR rate based on the Clopper-Pearson method.[13]

CR rates were compared using an exact binomial test with a 2-sided alpha level of 5%. The historical CR rate for patients in the r/r DLBCL cohort was assumed to be 20%, and was tested at the 5% significance level.[13]

Sensitivity Analyses: Sensitivity analyses were only conducted on the primary efficacy population of cohort D3. If more than 5% of patients discontinued the study because they were starting a new antilymphoma treatment, an event-free survival analysis was planned, with progression, new antilymphoma treatment, and death counted as events.[13]

If more than 5% of patients experienced a confirmed or suspected COVID-19 diagnosis, a sensitivity analysis was performed for the primary end point by removing these patients. An analysis of the safety profile for patients with confirmed or suspected COVID-19 was planned to be performed, and key safety summaries for these patients were produced separately.[13]

Additional sensitivity analyses for PFS and ORR were conducted following the database snapshot using data from November 19, 2021, and were therefore not specified in the Statistical Analysis Plan (SAP) or the Clinical Study Report submitted to CADTH. These analyses are not included in the report.[13]

Subgroup Analyses: Subgroup analyses were performed for the primary end point for cohort D3 only. Forest plots showing the proportions of CRs with 95% CIs within each subgroup were produced on the basis of the primary end point. Prespecified subgroups of interest to this review included ECOG PS (0, 1), prior lines of therapy (≤ 2, ≥ 3), type of NHL (PMBCL, trFL, DLBCL not otherwise specified, HGBCL), post–autologous SCT (yes, no), disease refractory to last line of therapy (refractory, relapsed, unknown, not available), disease refractory to any prior anti-CD20 therapy (refractory, relapsed, unknown, not available), disease refractory to any prior line of therapy (refractory, relapsed, unknown, not available), and prior CAR T-cell therapy (yes, no). Subgroup analyses were not adjusted for multiplicity, and all subgroup analyses were exploratory.[13]

Secondary End Points

The secondary response outcomes of investigator-assessed CR rate and IRC-assessed and investigator-assessed ORR were evaluated using the same method as the primary end point.[13]

For the secondary time-to-event end point of DOR, the Kaplan-Meier method was used, and estimates were provided at 3, 6, 9, 12, 15, 18, 21, and 24 months. The Brookmeyer-Crowley method was used to construct the

95% CI for the median DOR. The Kaplan-Meier method was used to estimate the 6-month and 1-year PFS and OS, along with the standard error and the corresponding 95% CIs, through the use of the Greenwood formula. The Brookmeyer-Crowley method was used to construct the 95% CI for the median PFS and median OS. Kaplan-Meier plots and estimates were provided for all time-to-event end points. For PFS, patients who were progression-free and alive at the time of the analysis had their data censored at the date of the last response assessment. For OS, patients who were alive at the time of analysis had their data censored at the date last seen. If the treatment start date was missing for OS or PFS, the date of consent was used. Patients enrolled in the study before protocol version 8 were not followed up with in the survival follow-up phase; hence, OS was only reported in Part III step-up dosing monotherapy expansion cohort D3. Both PFS and OS were evaluated in the primary efficacy population.[13]

Analysis of HRQoL (EORTC QLQ-C30 and FACT-Lym LymS) was performed for the Part III monotherapy expansion cohorts (B3, B4, D3, and D5). Visit summary and change from baseline analyses were performed for the EORTC QLQ-C30 physical functioning, role functioning, GHS/QoL, and remaining scales, as well as for the FACT-Lym LymS. For the EORTC QLQ-C30, a patient was counted if they completed at least 1 question. For the FACT-Lym LymS, a patient was counted if they completed at least 50% of the questions. Summary statistics of scores and change from baseline at each time point were presented by study part and dose. The 95% CI was calculated by using the Clopper-Pearson method.[13]

Analysis Populations

Multiple cohorts were enrolled into the NP30179 study, with 2 primary populations: the primary efficacy population (also referred to as the intention-to-treat population) and the primary safety population (Table 9).

The efficacy-evaluable population included all patients who had been assessed for response at any time during the study, who had withdrawn from treatment or the study before reaching their first response assessment, or who had been participating in the study long enough to have reached their first scheduled response assessment, defined as occurring a minimum of 49 days after the first dose of glofitamab, or 56 days after the first dose of obinutuzumab pretreatment, at the time of data cut-off. The primary efficacy population from the cohorts of interest to this review comprised 155 patients from cohorts D2S2 (n = 46), D3 (n = 108), and D5 (n = 41), though only 7 of 46 patients were included from cohort D2S2, and 40 of 41 patients from cohort D5, as well as all 108 patients from cohort D3,.[13]

The primary safety population included all patients who had received at least 1 dose of the study medication. Unless otherwise specified, the primary safety population was used as the default analysis set used for the NP30179 study. One patient was enrolled in error in cohort D3 and did not receive study treatment and was therefore excluded from the primary safety population. The primary safety population from the cohorts of interest to this review therefore comprised 154 patients from cohorts D2S2, D3, and D5.[13]

The PRO-evaluable population included all enrolled patients in the Part III cohorts (B3, B4, D3, and D5) who had a baseline assessment, and at least 1 postbaseline assessment, of PRO scales. The PRO-evaluable population was used for descriptive analyses of visit summaries and for change from baseline for the efficacy end points.[13]

Table 9: Analysis Populations of the NP30179 Study

Population	Definition	Application
Primary efficacy (ITT) population	All patients enrolled in the study	All efficacy analyses
Primary safety population	All patients who have received at least 1 dose of the study drug (obinutuzumab or glofitamab), whether prematurely withdrawn from the study or not	The primary safety end points of the study were pharmacokinetics and AE profiles, including DLT and MTD
PRO evaluable	All patients from the Part III cohorts (cohorts B3, B4, D3, and D5) with a baseline, and at least 1 postbaseline, PRO assessment	Used for the descriptive evaluation of visit summaries and change from baseline for efficacy end points

AE = adverse event; DLT = dose-limiting toxicity; ITT = intention to treat; MTD = maximum tolerated dose; PRO = patient-reported outcome.
Source: NP30179 Clinical Study Report.[13]

Protocol Amendments and Deviations

Protocol Amendments

The original study protocol for the NP30179 study (July 21, 2016) was amended 10 times up to the June 15, 2022, CCOD. Key amendments to the study protocol are summarized in Table 10. Additional versions of the protocol were produced specifically for France to provide the doses planned for step-up dosing in cycle 1 and the dose ranges planned for the extended step-up and specifically for the US at the request of the FDA.[13]

The cohorts of interest to this review were added in protocol version 5, though it is uncertain how many patients were enrolled before this change and whether any patients enrolled before protocol version 5 were included in the cohorts of interest to this review. The sponsor-provided Clinical Study Report using the June 15, 2022, CCOD is based on protocol version 11.[13]

Table 10: Summary of Key Changes to the Protocol of the NP30179 Study

Protocol version	Changes
Version 2 October 5, 2016	A dose threshold of 810 mcg (flat dose) in Part I was added to ensure that the multiple-patient cohorts (Part II) would begin enrolling close to the start of the estimated therapeutic dose range of 1 mg to 10 mg. Part II was to begin when either a flat dose of 810 mcg (405 mcg × 2) was reached or a glofitamab-related ≥ grade 2 toxicity occurred, whichever came first.
Version 3 May 24, 2017	Tumour assessments (FDG PET and diagnostic CT scans) at week 6 (cycle 3) were incorporated. This additional assessment was supported by data indicating a strong potential for positive responses that occur before week 12 of treatment.
Version 4 September 29, 2017	Inclusion criterion 10 — "Patient must have a peripheral B-cell count at or below 500 cells/μL at screening" — was removed. The cycle 1 day 8 glofitamab infusion was removed.
Version 5 March 8, 2018	Dose escalation and expansion cohorts were added to assess the safety, PK, and preliminary antitumour activity of glofitamab in combination with obinutuzumab, following pretreatment with obinutuzumab. An every-3-week schedule was to be explored for newly enrolled patients assigned to escalation and expansion cohorts receiving glofitamab either as a single drug or in combination with obinutuzumab.

Protocol version	Changes
Version 6 August 8, 2018	The study design was modified to obtain additional safety, tolerability, PK, and clinical activity data. Based on the clinical activity observed in this study, including complete responses (4 of 45 patients as of May 18, 2018) and partial responses (14 of 45 patients as of May 18, 2018) in indolent as well as aggressive r/r NHL, the expansion phase was modified to further assess and confirm clinical activity of glofitamab in a cohort of patients with r/r follicular NHL and r/r DLBCL. In addition, PRO assessments were added to the expansion cohorts.
Version 7 April 2, 2019	The safety management guidelines were updated for glofitamab and a single-arm monotherapy cohort was added to evaluate the safety, tolerability, and PK of glofitamab when administered using the phase III formulation in a subset of patients with r/r NHL.
Version 8 August 6, 2019	Version 7 (row above) was only released to the health authority in the US; it was subsequently amended to version 8 for global release. Version 8 included all the revisions made in version 7 plus the following: The CRS risk description was updated to include factors that may increase the risk of severe CRS. The CRS management guidelines were updated, including guidance regarding glofitamab infusion and use of tocilizumab and dexamethasone. The investigation of step-up dosing in cycle 1 was introduced as a possible additional safety measure for CRS. The response criteria for malignant lymphoma were updated to the standard Lugano classification (rather than the modified Lugano classification).
Version 9 (France) May 19, 2020	The doses planned for step-up dosing in cycle 1 as well as dose ranges planned for the extended step-up were provided.
Version 9 May 22, 2020	The initial treatment period was updated to 12 cycles of glofitamab with an additional response assessment in cycle 9. New treatment cohorts were incorporated with extended step-up dosing and double pretreatment with obinutuzumab before the first dose of glofitamab. The mandatory hospitalization was reduced to 24 hours in cycle 1. Corticosteroid premedication in later cycles was updated.
Version 10 December 24, 2020	The mandatory hospitalization with step-up dosing was reduced. The study was reclassified as phase I/II to reflect the overall size of the study and the purpose of Part III of the study. A new expansion cohort was incorporated of patients with r/r DLBCL receiving dexamethasone as premedication. Dexamethasone was included as an option for premedication for all patients.
Version 10 (France) January 5, 2021	The protocol for France was amended to align with the global protocol version 10.
Version 10 (US) March 10, 2021	As requested by an FDA review, the mandatory hospitalization required for patients receiving step-up dosing was updated.
Version 11 May 27, 2021	The protocol was amended to align with the glofitamab investigator's brochure version 6, including the incorporation of new AESI categories and the update of identified and potential risks associated with glofitamab. In addition, recommendations regarding SARS-CoV-2 vaccines were added, and the CRS management guidelines were consolidated into a single table.
Version 11 (France) June 3, 2021	The protocol for France was amended to align with the global protocol version 11.

AESI = adverse event of special interest; CCOD = clinical cut-off date; CRS = cytokine release syndrome; DLBCL = diffuse large B-cell lymphoma; FDG = fluorodeoxyglucose; NHL = non-Hodgkin lymphoma; PK = pharmacokinetic; PRO = patient-reported outcome; r/r = relapsed or refractory.

Note: The Clinical Study Report is based on version 10.

Source: NP30179 Clinical Study Report.[13]

Protocol Deviations

As of the June 15, 2022, CCOD, [redacted] protocol deviations had been reported across [redacted] patients in the cohorts of interest to this review. The most frequent major protocol deviations were missed PRO assessment for Part III patients [redacted]; SAEs, AEs of special interest, or dose-limiting toxicity not reported within 24 hours [redacted]; dispensing or dosing errors [redacted]; and tumour tissue samples archival [redacted]. Four patients enrolled in cohort D5 received at least 1 dose of steroids other than dexamethasone as premedication despite the protocol requirement for dexamethasone as premedication.[13]

Table 11: Summary of Major Protocol Deviations (June 15, 2022, CCOD)

Deviation category	[redacted]
At least 1 major protocol deviation, n (%)	[redacted]
PRO assessment at C1D7, C1D1, C3D1, EOT not done for Part III patients	[redacted]
SAEs, AESIs, or DLTs not reported within 24 hours	[redacted]
Dispensing or dosing errors	[redacted]
Archival tumour tissue samples (or fresh biopsy)	[redacted]
Continued administration of glofitamab after reasons warranting discontinuation	[redacted]
Implementation of unapproved recruitment procedures	[redacted]
Assessment (AEs, laboratory tests, physical examination) not done per SOA	[redacted]
Repeated minor deviations that put patients' safety at risk	[redacted]
Administration of prohibited therapies or medication during the study	[redacted]
Adequate hematological function	[redacted]
Loss, theft, or mishandling of study drug at site	[redacted]
Other (including any serious GCP-related deviations)	[redacted]

AE = adverse event; AESI = adverse event of special interest; C1 = cycle 1; C3 = cycle 3; CCOD = clinical cut-off date; D1 = day 1; D7 = day 7; DLT = dose-limiting toxicity; EOT = end of treatment; GCP = good clinical practice; PRO = patient-reported outcome; SAE = serious adverse event; SOA = schedule of assessments.

Source: NP30179 Clinical Study Report.[13]

Changes to Planned Analysis

The primary interim analysis using the September 14, 2021, CCOD was based on SAP version 3. For the updated interim analysis (June 15, 2022, CCOD), the SAP was updated twice, and SAP version 5 was used. SAP versions 4 and 5 included the following key changes:[13]

- SAP version 4:
  - The scope of the SAP was expanded to be applicable to both the primary analysis and the subsequent updated analyses of the r/r DLBCL monotherapy cohorts.
  - Reference to Part III exploratory safety cohort D5 as a supporting cohort for specific end points was added where applicable.

- A new subsection was added to cover expected timelines for analysis updates after the primary analysis.
- Censoring rules under the hypothetical strategy for PFS were updated to remove physical examination if it did not include a scan and so could not be used to determine if the patient had progressed. The censoring rule was updated to censor patients at their last adequate (radiographic) response assessment.
- A sensitivity analysis for PFS was added in which patients who progressed after 2 or more consecutive missed response assessments were censored at the date of their last adequate response assessment before the first missed assessment. This sensitivity analysis was only to be triggered if more than 5% of patients experienced disease progression after 2 or more consecutive missed response assessments.
- Three additional subgroup variables were added to Table 5 in SAP version 4; however, these were superseded by SAP version 5.

- SAP version 5:
  - Analyses, including updates in the efficacy end points, sensitivity analysis, and subgroup analysis sections, was expanded to all patients with r/r DLBCL who had received at least 2 prior lines of therapy and had been treated at the proposed registrational dose (2.5 mg, then 10 mg, then 30 mg glofitamab) across cohorts D2S2, D3, and D5.

Results

Patient Disposition

Patient disposition for the NP30179 study at the June 15, 2022, CCOD is summarized in Table 12. [redacted] patients were screened for the study, with [redacted] patients enrolled and treated with glofitamab monotherapy. The intention-to-treat and safety populations consisted of [redacted] and [redacted] patients enrolled in cohorts D2S2, D3, and D5. Of the [redacted] patients in the primary safety population from the cohorts of interest to this review, [redacted] completed the initial treatment period and [redacted] discontinued initial treatment, primarily due to disease progression ([redacted]). As of the June 15, 2022, CCOD, [redacted] had discontinued the study, with the most frequent reason being death ([redacted]). [redacted] were still ongoing on study treatment, and [redacted] were undergoing re-treatment with glofitamab.[13]

Table 12: Summary of Patient Disposition From the NP30179 Study (Primary Safety Population; June 15, 2022, CCOD)

Patient disposition	Glofitamab (2.5 mg/10 mg/30 mg) q.3.w.
Screened (all cohorts), N	[redacted]
Did not meet screening criteria (all cohorts), N	[redacted]
Enrolled and treated (all cohorts), N	[redacted]
Enrolled (cohorts D2S2, D3, and D5), N (%)	[redacted]
Cohort D2S2	[redacted]

Patient disposition	Glofitamab (2.5 mg/10 mg/30 mg) q.3.w.
Cohort D3	[redacted]
Cohort D5	[redacted]
Completed initial treatment (cohorts D2S2, D3, and D5), n (%)	[redacted]
Discontinued initial treatment (cohorts D2S2, D3, and D5), n (%)	[redacted]
AE	[redacted]
Death	[redacted]
Lack of efficacy	[redacted]
New anticancer therapy	[redacted]
Other	[redacted]
Physician decision	[redacted]
Progressive disease	[redacted]
Protocol deviation	[redacted]
Symptomatic deterioration	[redacted]
Withdrawal by patient	[redacted]
Active on initial treatment (cohorts D2S2, D3, and D5), n (%)	[redacted]
Discontinued from study (cohorts D2S2, D3, and D5), n (%)	[redacted]
Reason for discontinuation (cohorts D2S2, D3, and D5), n (%)	
Death	[redacted]
Lost to follow-up	[redacted]
New anticancer therapy	[redacted]
Other	[redacted]
Physician decision	[redacted]
Progressive disease	[redacted]
Protocol deviation	[redacted]
Symptomatic deterioration	[redacted]
Withdrawal by patient	[redacted]
AE	[redacted]
Ongoing on study (cohorts D2S2, D3, and D5), n (%)	[redacted]
Ongoing on re-treatment (cohorts D2S2, D3, and D5), n (%)	[redacted]

AE = adverse event; CCOD = clinical cut-off date; q.3.w. = every 3 weeks.

Source: NP30179 Clinical Study Report.[13]

Baseline Characteristics

The baseline demographic and disease characteristics of the primary safety population for the cohorts of interest to this review are summarized in Table 13. In the primary safety population, patients were predominantly white (118 [76.6%]) and male (100 [64.9%]); the median age was 66.0 years (range, 21 years to 90 years). There were slightly more patients with an ECOG PS of 1 (84 [54.5%]) than of 0 (69 [44.8%]), with 1 patient (0.6%) enrolled who had an ECOG PS of 2. The majority of patients (110 [71.4%]) had DLBCL at baseline, and most had Ann Arbor stage IV disease (85 [55.2%]) and extranodal disease (95 [61.7%]). Nearly two-thirds of patients had 2 or 3 IPI risk factors (45 [29.2%] and 55 [35.7%], respectively). All patients had received prior chemotherapy, alkylator, and an anti-CD20 mAb, and most patients (151 [98.1%]) had received anthracycline therapies. The mean number of prior lines of therapy was 3.1 (SD = 1.2), with most patients having received 2 or 3 prior lines of therapy (109 [70.7%]). Nearly all patients had disease that was refractory to their last prior therapy (131 [85.1%]) and was also refractory to prior anti-CD20 therapies (128 [83.1%]).[13]

Exposure to Study Treatments

Exposure to study treatments at the June 15, 2022, CCOD is summarized in Table 14. In the safety population (n = 154), the median duration of treatment with glofitamab was [redacted]. The median number of treatment cycles was [redacted], with [redacted] receiving 12 cycles of treatment and [redacted] receiving more than 12 treatment cycles. The median dose intensity with glofitamab was [redacted]. All patients received obinutuzumab pretreatment. The median number of obinutuzumab infusions was [redacted], with a median dose intensity of [redacted]. [redacted] tocilizumab infusions were received in the safety population. The median number of tocilizumab infusions was [redacted], with a median dose intensity of [redacted].[13]

Table 13: Summary of Baseline Characteristics From the NP30179 Study (Primary Safety Population; June 15, 2022, CCOD)

Characteristic	Cohorts D2S2, D3, and D5 (glofitamab 2.5 mg/10 mg/30 mg q.3.w.) n = 154
Age	
Age (years), mean (SD)	[redacted]
Age (years), median (range)	[redacted]
< 65 years, n (%)	[redacted]
≥ 65 years, n (%)	[redacted]
Sex, n (%)	
Female	[redacted]
Male	[redacted]
Race, n (%)	
Asian	[redacted]

Characteristic	Cohorts D2S2, D3, and D5 (glofitamab 2.5 mg/10 mg/30 mg q.3.w.) n = 154
Black or African American	[redacted]
White	[redacted]
Unknown	[redacted]
BMI (kg/m^2)	
Mean (SD)	[redacted]
Median (range)	[redacted]
ECOG PS at baseline[a], n (%)	
0	[redacted]
1	[redacted]
Ann Arbor stage, n (%)	
I	[redacted]
II	[redacted]
III	[redacted]
IV	[redacted]
Bulky disease, n (%)	
> 6 cm	[redacted]
> 10 cm	[redacted]
Extranodal disease, n (%)	[redacted]
IPI risk factors, n (%)	
0	[redacted]
1	[redacted]
2	[redacted]
3	[redacted]
4	[redacted]
Cancer history at baseline, n (%)	
DLBCL	[redacted]
HGBCL	[redacted]
PMBCL	[redacted]
Transformed FL, n (%)	[redacted]
Prior lines of therapy	
Mean (SD)	[redacted]
Median (range)	[redacted]

Characteristic	Cohorts D2S2, D3, and D5 (glofitamab 2.5 mg/10 mg/30 mg q.3.w.) n = 154
2 prior lines, n (%)	[redacted]
3 prior lines, n (%)	[redacted]
> 3 prior lines, n (%)	[redacted]
Prior cancer-related surgery, n (%)	[redacted]
Prior radiotherapy, n (%)	[redacted]
Disease relapsed after or refractory to any prior therapy, n (%)	
Refractory	[redacted]
Relapsed	[redacted]
Disease relapsed after or refractory to last line of prior therapy, n (%)	
Refractory	[redacted]
Relapsed	[redacted]
Disease relapsed after or refractory to any prior anti-CD20 therapy, n (%)	
Refractory	[redacted]
Relapsed	[redacted]
Disease relapsed after or refractory to any prior CAR T-cell therapy, n (%)	
Refractory	[redacted]
Relapsed	[redacted]
Unknown	[redacted]

BMI = body mass index; CAR = chimeric antigen receptor; CCOD = clinical cut-off date; DLBCL = diffuse large B-cell lymphoma; ECOG PS = Eastern Cooperative Oncology Group Performance Status; FL = follicular lymphoma; HGBCL = high-grade B-cell lymphoma; IPI = International Prognostic Index; PMBCL = primary mediastinal B-cell lymphoma; q.3.w. = every 3 weeks; SD = standard deviation.

[a]One patient with an ECOG PS of 2 was enrolled in the primary safety population.

Source: NP30179 Clinical Study Report.[13]

Subsequent Antilymphoma Treatment

After documented disease progression, patients were followed for survival or new antilymphoma treatment. In the safety population (n = 154), [redacted] patients received at least 1 new antilymphoma treatment. The most frequently received subsequent antilymphoma treatments were [redacted] and [redacted]. All other new antilymphoma treatments occurred in [redacted] or fewer patients, including subsequent [redacted] patients.[13]

Efficacy

Efficacy results for the NP30179 study were presented for the primary efficacy population, composed of cohorts D2S2, D3, and D5 ([redacted]) as of the June 15, 2022, CCOD. Per SAP version 5, the prespecified primary analysis of the CR rate was only conducted in cohort D3, and the comparison to a historical control was performed using the September 14, 2021, CCOD. An updated analysis of the CR rate in cohort D3 without comparison to the historical control was also presented in the updated interim Clinical Study Report based

on data at the June 15, 2022, CCOD. All secondary efficacy end point analyses are based on the June 15, 2022, CCOD.[13]

Table 14: Summary of Patient Exposure From the NP30179 Study (Primary Safety Population; June 15, 2022, CCOD)

Characteristic	Cohorts D2S2, D3, and D5 (glofitamab 2.5 mg/10 mg/30 mg q.3.w.) n = 154
Glofitamab	
Number of infusions	
Mean (SD)	[redacted]
Median (range)	[redacted]
Number of cycles	
Mean (SD)	[redacted]
Median (range)	[redacted]
Relative dose intensity (%)	
n	[redacted]
Mean (SD)	[redacted]
Median (range)	[redacted]
Proportion of patients with dose intensity ≥ 90%, n (%)	[redacted]
Total duration (days)	
Mean (SD)	[redacted]
Median (range)	[redacted]
Obinutuzumab	
Number of infusions	
Mean (SD)	[redacted]
Median (range)	[redacted]
Number of cycles	
Mean (SD)	[redacted]
Median (range)	[redacted]
Relative dose intensity (%)	
n	[redacted]
Mean (SD)	[redacted]
Median (range)	[redacted]
Proportion of patients with dose intensity ≥ 90%, n (%)	[redacted]

Characteristic	Cohorts D2S2, D3, and D5 (glofitamab 2.5 mg/10 mg/30 mg q.3.w.) n = 154
Total duration (days)	
Mean (SD)	[redacted]
Median (range)	[redacted]

CCOD = clinical cut-off date; q.3.w. = every 3 weeks; SD = standard deviation.

Source: NP30179 Clinical Study Report.[13]

Table 15: Summary of Subsequent Treatment From the NP30179 Study (Primary Safety Population; June 15, 2022, CCOD)

Characteristic	Cohorts D2S2, D3, and D5 (glofitamab 2.5 mg/10 mg/30 mg q.3.w.) n = 154
Patients with at least 1 new antilymphoma treatment, n (%)	[redacted]
Radiotherapy	[redacted]
R-GemOx	[redacted]
CAR T-cell therapy	[redacted]
CHOP-Pola	[redacted]
IGEV	[redacted]
Rituximab plus ifosfamide and etoposide	[redacted]
R-CHOP	[redacted]

CAR = chimeric antigen receptor; CCOD = clinical cut-off date; CHOP-Pola = cyclophosphamide, doxorubicin, vincristine, and prednisone, plus polatuzumab vedotin; IGEV = ifosfamide, gemcitabine, and vinorelbine; R-CHOP = rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone; R-GemOx = rituximab plus gemcitabine and oxaliplatin.

Note only includes antilymphoma treatments with frequency greater than 1%.

Source: NP30179 Clinical Study Report.[13]

Overall Survival

OS was a secondary end point of the NP30179 study. The results for OS at the June 15, 2022, CCOD in the primary efficacy population are summarized in Table 16 and displayed in Figure 2. At the CCOD, [redacted] patients had died, resulting in a median OS of [redacted]. The OS rate at 12 months and 24 months was [redacted], respectively.[13]

Figure 2: Kaplan-Meier Plot of Overall Survival (Primary Efficacy Population; June 15, 2022, CCOD) [Redacted]

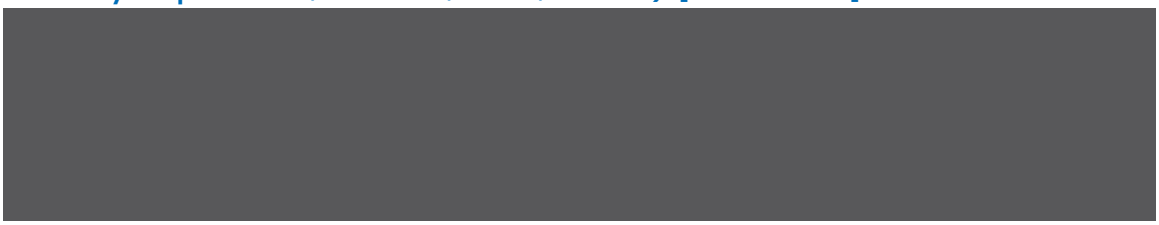
Source: NP30179 Clinical Study Report.[13]

Progression-Free Survival

The results for PFS are summarized in Table 16 and displayed in Figure 3. At the June 15, 2022, CCOD, the median duration of follow-up for IRC-assessed PFS was [redacted]. [redacted] PFS events had occurred in the primary efficacy population, [redacted] categorized as disease progression and [redacted] as death. The median PFS was [redacted]. The PFS rate at 12 months and 24 months was [redacted] and [redacted], respectively.[13]

The results for investigator-assessed PFS were consistent with those of the IRC assessment, with a median PFS of [redacted], based on a median duration of follow-up of [redacted]. [redacted] PFS events had occurred, [redacted] due to disease progression and [redacted] due to death. The PFS rate at 12 months and 24 months was [redacted] and [redacted], respectively.[13]

Figure 3: Kaplan-Meier Plot of IRC-Assessed and Investigator-Assessed PFS (Primary Efficacy Population; June 15, 2022, CCOD) [Redacted]



Source: NP30179 Clinical Study Report.[13]

Sensitivity Analysis

Given that more than 5% of patients discontinued the study because they started a new antilymphoma treatment, an event-free survival analysis was performed, with progression, new antilymphoma treatment, and death counted as events in the investigator assessment. In the primary efficacy population, [redacted] events had occurred; [redacted] The median event-free survival was [redacted].[13]

As less than 5% of patients experienced disease progression or death after 2 or more consecutive missing response assessments, the planned sensitivity analysis in which patients were to be censored at the date of their last adequate response assessment before the first missed assessment was not performed.[13]

Health-Related Quality of Life

HRQoL was a secondary outcome of the NP30179 study and was assessed via the EORTC QLQ-C30 and FACT-Lym LymS. No formal analysis was planned, and based on the availability of data, CADTH considered the results at cycle 5 day 1 (due to its proximity to the midpoint) and at the end of treatment for analysis. The results for HRQoL are summarized in Table 16.

EORTC QLQ-C30

At baseline, [redacted] of patients had completed at least 1 question on the EORTC QLQ-C30. At baseline, the mean EORTC QLQ-C30 physical functioning, role functioning, GHS/QoL, and fatigue scores for 92 patients in cohort D3 were [redacted] and [redacted], respectively.[13]

At cycle 5, the mean change from baseline in the physical functioning score ([redacted]) was [redacted], the mean change from baseline in the role functioning score ([redacted]) was [redacted] the mean change from baseline in GHS/QoL score [redacted] and the mean change from baseline in fatigue score ([redacted]).[13]

At the end of treatment, the mean change from baseline in the physical functioning, role functioning, GHS/QoL, and fatigue scores [redacted] was [redacted], respectively.[13]

FACT-Lym LymS

At baseline, [redacted] of patients had completed at least 50% of the questions on the FACT-Lym LymS. The mean FACT-Lym LymS score at baseline ([redacted]) was [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].[13]

Clinical Response

The results for the clinical response outcomes of interest (CR, PR, ORR, and DOR) are summarized in Table 16.

Complete Response

The proportion of patients experiencing 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.[13]

The CR rate as assessed by the investigator was a secondary outcome of the NP30179 study. The results for investigator-assessed CR were consistent with those of the primary analysis (CR = 38.1%; 95% CI, 30.39% to 46.20%).[13]

Though not specified as an outcome of interest to this review, the results for DOCR have been included in Table 25 of Appendix 1 to add context to the durability of the primary end point.

Historical Control: At 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 population of patients with r/r DLBCL. The 2-sided P value based on an exact binomial test comparing the treated patient population with the historical control was less than 0.0001.[13]

Subgroup Analyses: Subgroup analyses of interest to this review for CR rate as assessed by the IRC are summarized in Table 26 of Appendix 1. The results for the subgroup analyses were generally consistent with those of the primary analysis, albeit ranging from 10% to 71% due to small sample sizes, with overlapping CIs.[13]

The results for subgroup analysis by investigator assessment were generally consistent with those of the IRC-assessed subgroup analyses; however, 2 subgroups had differences of 10% or more compared to the IRC assessment (NHL subtype PMBCL, and refractory to prior autologous SCT).[13]

Prior CAR T-Cell Therapy

Of the 52 patients (33.5%) treated with glofitamab in the primary efficacy population who had received prior CAR T-cell therapy, [redacted] had an IRC-assessed response to treatment, [redacted] of which were CRs and [redacted] were PRs. The results for investigator-assessed subgroups were consistent with those of the IRC assessment.[13]

Overall Response Rate

The median duration of follow-up for an IRC-assessed response was 12.0 months (95% CI, 7.6 to 16.6). ORR assessed by the IRC and by the investigator were secondary end points of the NP30179 study. In the primary efficacy population (n = 155), 80 patients (51.6%; 95% CI, 43.46% to 59.70%) experienced an overall response: 62 (40.0%) experienced CR, 18 (11.6%) experienced PR. Of the remaining patients, 21 (13.5%) had stable disease, and 42 (27.1%) had progressive disease.[13]

The results for ORR per investigator assessment were consistent with those for IRC-assessed ORR, with 91 patients (58.7%; 95% CI, 50.53% to 66.55%) experiencing an overall response: 59 (38.1%) experienced CR, 32 (20.6%) experienced PR. Of the remaining patients, 8 (5.2%) had stable disease, and 44 (28.4%) had progressive disease.[13]

Subgroup Analysis: ORR by Histology Subtype: The consistency of treatment effect was evaluated through assessment of ORR by histological subtype. Of the 155 patients in the primary efficacy population, [redacted] had DLBCL not otherwise specified, [redacted] had trFL, [redacted] had PMBCL, and [redacted] had HGBCL. The ORR in the subtypes of DLBCL not otherwise specified, trFL, PMBCL, and HGBCL was [redacted], respectively. When ORR was assessed by the investigator, the results were consistent with those of the IRC assessment of the ORR in each subtype, with the exception of trFL ([redacted], respectively).[13]

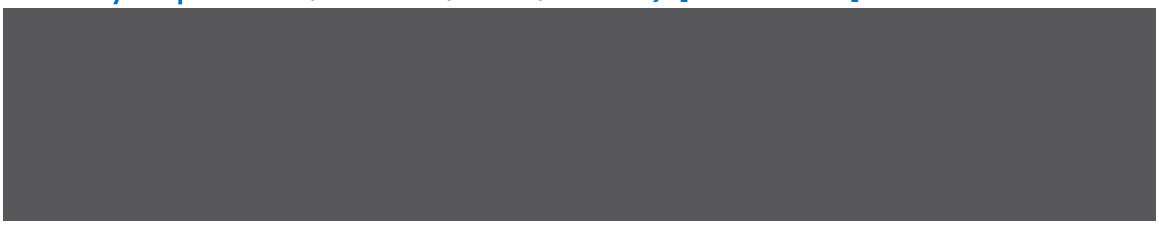
Sensitivity Analysis: In the post hoc sensitivity analysis based on all treated patients (i.e., the safety population), which excluded 1 patient in cohort D3, the results for IRC-assessed ORR were nearly identical to those in the original analysis, with an ORR of 51.9% (95% CI, 43.8% to 60.1%).[13]

Duration of Response

DOR was a secondary outcome of the NP30179 study. Kaplan-Meier plots of DOR per IRC and investigator assessment are summarized in Figure 4. 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 experienced an IRC-assessed response (CR or PR), the median DOR was 16.8 months (95% CI, 10.4 to not estimable). Fifty 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 patients who experienced response at 12 months and 24 months after the first response was [redacted], respectively.[13]

The median duration of follow-up for investigator-assessed DOR was 12.8 months (95% CI, 8.3 to 18.0). For the 91 patients who experienced an investigator-assessed response (CR or PR), the median DOR was 10.4 months (95% CI, 5.4 to not estimable). Forty-eight patients (52.7%) remained in remission, and 43 patients (47.3%) subsequently had disease progression or died. Among patients who experienced response, the event-free rates at 12 months and 24 months after the first response were [redacted].[13]

Figure 4: Kaplan-Meier Plot of IRC-Assessed and Investigator-Assessed DOR (Primary Efficacy Population; June 15, 2022, CCOD) [Redacted]



Source: NP30179 Clinical Study Report.[13]

Harms

Safety results were presented for the primary safety population (n = 154). Refer to Table 17 for harms data.

Adverse Events

At the June 15, 2022, CCOD, 152 patients (98.7%) had experienced at least 1 AE. The most frequently reported AEs were CRS (103 patients [66.9%]), neutropenia (58 patients [37.7%]), and anemia (47 patients [30.5%]). Most AEs (665 of 752 [88.4%]) occurred during the first treatment cycle. The median time to first AE from the first dose of glofitamab was 2.0 days (range, 1.0 day to 120.0 days).[13]

Table 16: Summary of Key Efficacy Results From the NP30179 Study (Primary Efficacy Population; June 15, 2022, CCOD)

Characteristic	Cohorts D2S2, D3, and D5 (glofitamab 2.5 mg/10 mg/30 mg q.3.w.) n = 155
OS	
Deaths, n (%)	[redacted]
OS (months), median (95% CI)	[redacted]
12-month event-free rate (95% CI)	[redacted]
24-month event-free rate (95% CI)	[redacted]
PFS	
Patients with PFS event, n (%)	[redacted]
PFS (months), median (95% CI)	[redacted]
12-month event-free rate[a] (95% CI)	[redacted]
24-month event-free rate[a] (95% CI)	[redacted]
Health-related quality of life[b]	
EORTC QLQ-C30	
Physical functioning	
Baseline	
N	[redacted]
Score, mean (SD)	[redacted]
Cycle 5 day 1	
N	[redacted]
Score, mean (SD)	[redacted]
CFB, mean (SD)	[redacted]
End of treatment	
N	[redacted]
Score, mean (SD)	[redacted]
CFB, mean (SD)	[redacted]
Role functioning	
Baseline	
N	[redacted]
Score, mean (SD)	[redacted]
Cycle 5 day 1	

Characteristic	Cohorts D2S2, D3, and D5 (glofitamab 2.5 mg/10 mg/30 mg q.3.w.) n = 155
N	[redacted]
Score, mean (SD)	[redacted]
CFB, mean (SD)	[redacted]
End of treatment	
N	[redacted]
Score, mean (SD)	[redacted]
CFB, mean (SD)	[redacted]
GHS/QoL	
Baseline	
N	[redacted]
Score, mean (SD)	[redacted]
Cycle 5 day 1	
N	[redacted]
Score, mean (SD)	[redacted]
CFB, mean (SD)	[redacted]
End of treatment	
N	[redacted]
Score, mean (SD)	[redacted]
CFB, mean (SD)	[redacted]
Fatigue	
Baseline	
N	[redacted]
Score, mean (SD)	[redacted]
Cycle 5 day 1	
N	[redacted]
Score, mean (SD)	[redacted]
CFB, mean (SD)	[redacted]
End of treatment	
N	[redacted]
Score, mean (SD)	[redacted]
CFB, mean (SD)	[redacted]

Characteristic	Cohorts D2S2, D3, and D5 (glofitamab 2.5 mg/10 mg/30 mg q.3.w.) n = 155
FACT-Lym LymS	
Baseline	
N	[redacted]
Total score, mean (SD)	[redacted]
Cycle 5 day 1	
N	[redacted]
Total score, mean (SD)	[redacted]
CFB in total score, mean (SD)	[redacted]
End of treatment	
N	[redacted]
Total score, mean (SD)	[redacted]
CFB in total score, mean (SD)	[redacted]
Clinical response	
CR	
IRC-assessed CR, n (%)	[redacted]
95% CI	[redacted]
Investigator-assessed CR, n (%)	[redacted]
95% CI	[redacted]
ORR	
IRC-assessed ORR, n (%)	[redacted]
95% CI	[redacted]
Investigator-assessed ORR, n (%)	[redacted]
95% CI	[redacted]
PR	
IRC-assessed PR, n (%)	[redacted]
95% CI	[redacted]
Investigator-assessed PR, n (%)	[redacted]
95% CI	[redacted]
DOR[a]	
DOR (months), median (95% CI)	[redacted]
12-month event-free rate[b] (95% CI)	[redacted]

Characteristic	Cohorts D2S2, D3, and D5 (glofitamab 2.5 mg/10 mg/30 mg q.3.w.) n = 155
24-month event-free rate[b] (95% CI)	[redacted]

CCOD = clinical cut-off date; CFB = change from baseline; CI = confidence interval; CR = complete response; DOR = duration of response; EORTC QLQ-C30 = European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30; FACT-Lym = Functional Assessment of Cancer Therapy–Lymphoma; GHS/QoL = global health status/quality of life; IRC = independent review committee; LymS = lymphoma subscale; ND = not done; NE = not evaluable; ORR = overall response rate; OS = overall survival; PFS = progression-free survival; PR = partial response; q.3.w. = every 3 weeks; SD = standard deviation.

Note: All patients without response data were considered missing.

[a]IRC-assessed.

[b]Only conducted for cohort D3.

Source: NP30179 Clinical Study Report.[13]

Table 17: Summary of Harms Results From the NP30179 Study (Primary Safety Population; June 15, 2022, CCOD)

Adverse events	Cohorts D2S2, D3, and D5 (glofitamab 2.5 mg/10 mg/30 mg q.3.w) n = 154
Most common adverse events,[a] n (%)	
CRS	[redacted]
Neutropenia/neutrophil count reduction	[redacted]
Anemia	[redacted]
Thrombocytopenia/platelet count reduction	[redacted]
Hypophosphatemia	[redacted]
Pyrexia	[redacted]
Hypomagnesemia	[redacted]
Constipation	[redacted]
Diarrhea	[redacted]
Hypocalcemia	[redacted]
Fatigue	[redacted]
Tumour flare	[redacted]
Hypokalemia	[redacted]
Nausea	[redacted]
Back pain	[redacted]
SAEs,[b] n (%)	
Overall	[redacted]
CRS	[redacted]
Sepsis	[redacted]

Adverse events	Cohorts D2S2, D3, and D5 (glofitamab 2.5 mg/10 mg/30 mg q.3.w) n = 154
COVID-19	[redacted]
COVID-19 pneumonia	[redacted]
Tumour flare	[redacted]
Anemia	[redacted]
Febrile neutropenia	[redacted]
Neutropenia	[redacted]
Pleural effusion	[redacted]
Back pain	[redacted]
Delirium	[redacted]
Gastrointestinal hemorrhage	[redacted]
Infection	[redacted]
Pneumonia	[redacted]
Pyrexia	[redacted]
Vascular device infection	[redacted]
Patients who stopped treatment due to adverse events, n (%)	
Total	[redacted]
COVID-19	[redacted]
Delirium	[redacted]
Neutropenia	[redacted]
Biliary tract infection	[redacted]
Myelitis	[redacted]
Sepsis	[redacted]
COVID-19 pneumonia	[redacted]
CRS	[redacted]
GI hemorrhage	[redacted]
Hepatic cytolysis	[redacted]
Cholestasis	[redacted]
Recurrent melanoma	[redacted]
Deaths, n (%)	
Total	[redacted]
Progressive disease	[redacted]

Adverse events	Cohorts D2S2, D3, and D5 (glofitamab 2.5 mg/10 mg/30 mg q.3.w) n = 154
Adverse event	[redacted]
COVID-19 pneumonia	[redacted]
COVID-19	[redacted]
Sepsis	[redacted]
Delirium	[redacted]
Other	[redacted]
Missing	[redacted]
Notable harms, n (%)	
CRS	[redacted]
Serious infection	[redacted]

CRS = cytokine release syndrome; GI = gastrointestinal; SAE = serious adverse event.

[a]Frequency greater than or equal to 10%.

[b]Frequency greater than or equal to 1%.

Source: NP30179 Clinical Study Report.[13]

In the primary safety population, 89 patients (57.8%) had experienced grade 3 to 4 AEs and 9 patients (5.8%) had experienced grade 5 AEs. The most frequently reported grade 3 to 4 AEs were neutropenia or decreased neutrophil count (42 patients [27.3%]), anemia (12 patients [7.8%]), hypophosphatemia (9 patients [5.8%]), and thrombocytopenia or decreased platelet count (12 patients [7.8%]). In the primary safety population, 28 patients (18.2%) reported an AE leading to dose interruption or modification of glofitamab.[13]

Serious AEs

At the June 15, 2022, CCOD, 75 patients (48.7%) had experienced an SAE. The most frequently reported SAE was CRS (34 patients [22.1%] according to Lee [2014] grading criteria;[42] 32 patients [20.8%] according to ASTCT 2019 grading criteria[43]), followed by sepsis (6 patients [3.9%]); COVID-19, COVID-19 pneumonia, and tumour flare (5 patients [3.2%] each); and anemia, febrile neutropenia, neutropenia, and pleural effusion (3 patients [1.9%] each). Modifications or interruptions to glofitamab occurred in 9 patients (5.8%) because of SAEs.[13]

Withdrawals Due to AEs

At the June 15, 2022, CCOD, 14 (9.1%) patients in the primary safety population reported an AE leading to study treatment discontinuation, primarily due to COVID-19, delirium, and neutropenia (2 [1.3%] each).[13]

Mortality

At the June 15, 2022, CCOD, 81 patients (52.6%) had died. Of these 81 deaths, 61 (75.3%) occurred more than 30 days after the last dose of the study drug and 20 (24.7%) occurred within 30 days of the last dose. The most frequent cause of death was progressive disease (61 patients [75.3%]), followed by AEs [redacted] including COVID-19 pneumonia [redacted], COVID-19 [redacted], sepsis [redacted], and delirium [redacted]. Other causes

of death included pneumonia, COVID-19, pulmonary fungal infection [redacted], and unknown reasons [redacted]. One death due to COVID-19 was categorized as "other" as the date of death was not entered on the AE case report form.[13]

Notable Harms

Notable harms of interest to this review were CRS, and infections. Incidence of notable harms in the primary safety population is summarized in Table 17.

Cytokine Release Syndrome

CRS events were reported according to ASTCT 2019 grading and according to Lee 2014 grading.[42,43] As of the June 15, 2022, CCOD, [redacted] patients had reported at least 1 CRS event according to Lee (2014) grading, and [redacted] patients had reported at least 1 CRS event according to ASTCT 2019 grading. Serious CRS events according to ASTCT 2019 grading were reported by [redacted] patients. Serious CRS events according to Lee (2014) grading were reported by [redacted] patients.[13]

In the primary safety population, [redacted] patients experienced grade 2 or higher CRS events according to ASTCT 2019 grading, and [redacted] according to Lee (2014) grading. According to ASTCT grading, grade 2 CRS events occurred in [redacted] patients, and grade 3 or 4 CRS events were reported in [redacted] patients. According to the Lee (2014) grading system, [redacted] patients experienced grade 2 CRS and [redacted] experienced grade 3 and 4 CRS. As of the CCOD, grade 2 or higher CRS events had been resolved in [redacted] according to ASTCT grading and [redacted] patients according to Lee (2014) grading.[13]

The majority of CRS events of any grade occurred during the first cycle of treatment with glofitamab. CRS events of any grade occurring on or after the first dose of glofitamab (2.5 mg, cycle 1 day 8) and before the second dose of glofitamab (10 mg, cycle 1 day 15) were reported in [redacted] patients according to ASTCT grading and [redacted] according to Lee (2014) grading. [redacted] patients had CRS on or after the second dose of glofitamab and before the third dose (30 mg, cycle 1 day 21) according to ASTCT grading and [redacted] according to Lee (2014) grading. The median duration of any grade CRS following the first dose of glofitamab was [redacted]. Following the second dose, the median duration of CRS was [redacted], and following the third dose, the median duration of CRS was [redacted].[13]

Serious Infections

In the primary safety population, AEs from the grouped terms of infections and infestation were reported in [redacted] patients. Grade 3 to 4 infection and infestation AEs were reported in [redacted] patients. [redacted] grade 5 infection and infestation AEs were reported. [redacted] infection and infestation AEs were serious. The most frequently reported infection and infestation SAEs were sepsis [redacted], COVID-19 pneumonia [redacted], COVID-19 [redacted], pneumonia [redacted], infection [redacted], and vascular device infection [redacted].[13]

Critical Appraisal

Internal Validity

The NP30179 phase I/II trial was the only study included in this review. The NP30179 study is an ongoing phase I/II, multicentre, open-label, single-arm study of glofitamab. The choice to conduct a single-arm trial

was justified because the study was designed as an early phase I/II study, where an internal comparator group is not required, and because of the severity of illness for patients at this advanced stage of r/r DLBCL. However, the decision to conduct a single-arm study also has implications for the overall strength and interpretability of the results. With a single-arm study, there is an increased risk of bias in the estimation of treatment effects due to the potential for confounding related to natural history and prognostic factors. The potential influence of selection bias is also difficult to ascertain in a single-arm study. Additionally, time-to-event end points cannot be adequately assessed in a single-arm trial because all patients receive the same treatment. As such, the effect of glofitamab on time-to-event end points such as PFS, OS, and DOR cannot be interpreted, and results for these end points can only be considered as exploratory and supportive. Consequently, assessment of the comparative clinical value of glofitamab relied on a naive external historical comparison and indirect comparisons (unanchored MAICs), both of which rely on numerous assumptions about the comparability of treatment groups, thereby increasing the uncertainty related to the comparative effectiveness. The limitations noted with the lack of a direct comparison in the NP30179 study meant that the efficacy outcomes contributing to the Health Canada NOC/c for glofitamab in the current setting included response outcomes and no survival end points.

The noncomparative design of the NP30179 trial precludes the ability to assess the relative therapeutic benefit or safety of glofitamab in Canadian clinical practice, though the clinical experts consulted by CADTH did note that it would be difficult to conduct a comparative trial in this setting. In addition to glofitamab monotherapy, based on the results of preclinical data, all patients received 1,000 mg of obinutuzumab as pretreatment to minimize the risk of CRS. The Health Canada reviewers report noted that no noticeable antitumour effect was observed for obinutuzumab; however, due to the single-arm design of the NP30179 study, it is impossible to determine whether the effects observed in the study are attributable to glofitamab or obinutuzumab. Additionally, the true effect of obinutuzumab on CRS remains unknown for this reason.

In addition to its single-arm design, the NP30179 study was also open label, whereby the investigator and the study participants were aware of their treatment status, potentially increasing the risk of detection bias and performance bias. As such, the open-label trial design limits the interpretability of the subjective study outcomes (e.g., PROs) including HRQoL, and AEs. However, to mitigate the impact of this bias, all outcomes included in this review except for OS were assessed by both the IRC and the investigator using the Lugano classification criteria for the response. For response outcomes, there was generally a low discordance rate between IRC-assessed and investigator-assessed response. Instances of discordance on CRs occurred in 11 instances (7.1%) overall: 4 (2.6%) by the investigator and 7 (4.5%) by the IRC. However, for any response (CR or PR), discordance rates were slightly higher (13.5%), with higher rates of discordance in investigator-assessed response (16 [10.3%]) than in IRC-assessed response (5 [3.2%]). The exact magnitude of this bias remains unclear. Discordance between IRC-assessed and investigator-assessed response and the potential influence on outcomes are well documented, including in guidance from the FDA to industry.[14] Given the open-label design of the trial, it is possible that the IRC provided fewer potentially biased tumour assessments compared with investigator's assessments.

A limited number of patients were included in the primary efficacy population (n = 155). Though the NP30179 study was powered for the primary end point, the magnitude of the treatment effect estimates observed in

the 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 hematologic cancers. Historically, in hematologic tumours, response has been considered a direct measure of a drug's antitumour activity in oncology clinical trials. In a retrospective analysis of the GOYA trial[44] and a meta-analysis of studies of DLBCL,[45] the prognostic value of PET-based CR with respect to PFS and OS was assessed. Though the results of these studies suggested that end of treatment CR was a predictor of PFS and OS and that CR could be an effective surrogate end point for survival, 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 for DLBCL. Recent literature has highlighted that the correlation between response rates and survival is variable and that there are gaps in understanding the strength of response as a surrogate outcome in hematologic malignancy trials.[46-48]

The threshold for a positive study outcome for the primary efficacy population in the NP30179 study was based on a historically determined 20% CR rate (95% CI, 14% to 28%), derived from an SLR and meta-analysis using Lugano criteria. However, this threshold was only considered for cohort D3 (n = 108) at the initial September 2021 CCOD. Despite the comparison demonstrating a greater CR rate than the historical control (35.2%), the methodology of the comparison limits the ability to determine comparative effectiveness. Moreover, the results were not applicable to the entire population of interest to this review and can only be viewed as supportive of the overall effect of glofitamab.

The outcomes from the NP30179 study of critical importance to this review were 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 a relevant outcome. These outcomes were secondary outcomes of the NP30179 study. At the June 15, 2022, CCOD, 52.3% of patients experienced OS events and 61.3% of patients experienced PFS events (the median follow-up duration was 17.0 months for OS and 13.4 months for PFS), and although 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 estimate of treatment effect than could be observed in clinical practice. Despite the PFS and OS results being 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 means that the results for survival end points should only be considered supportive of the overall antitumour effect of glofitamab. Quality of life outcomes were also secondary end points of the NP30179 study. At the June 15, 2022, CCOD, HRQoL analyses used the safety population of cohort D3 (n = 107) as opposed to the full safety analysis population (n = 154). No time of assessment was specified for HRQoL outcomes; thus, cycle 5 day 1 was selected as the "midpoint" of treatment based on the schedule of assessments, which occurred every second cycle, and the available sample size, which was notably higher than in cycle 7. Additionally, the results at the end of treatment were considered. There were high rates of attrition in the HRQoL outcomes, with evaluable sample sizes drastically decreasing over time, with as many as [redacted]% of patients reporting baseline values and only [redacted]% and [redacted]% of patients reporting values at cycle 5 and the end of treatment, respectively. As such, the effect of glofitamab on HRQoL remains uncertain.

No methods were incorporated to account for multiple testing; thus, all secondary end points were considered supportive and should be interpreted considering the potential type I error. There was also no control for multiplicity across the cohorts selected for inclusion in the review.

There were multiple amendments to the protocol of the NP30179 study from the original (dated July 21, 2016) to the June 15, 2022, CCOD, though none were expected to severely impact the conduct or results of the study. CADTH reviewers noted that the Health Canada review of glofitamab did not highlight the protocol amendments as limiting the internal validity of the NP30179 study.

External Validity

The NP30179 study was an international, multicentre study that included sites in Australia, Belgium, Canada, Czech Republic, Denmark, Finland, France, Italy, New Zealand, Poland, Spain, and the US. One Canadian treatment centre had enrolled 9 patients as of the June 2022 CCOD. According to the clinical experts consulted by CADTH, the inclusion and exclusion criteria for the NP30179 study were generally as expected for patients with r/r DLBCL, though, the experts noted that some criteria, such as ECOG PS, renal function, or required presence of measurable disease, are typically specific to clinical trials and may have been restrictive, selecting for ideal, less severely ill patients, which may not reflect the general patient population.

The clinical experts also noted that the baseline characteristics of the included population were generally reflective of Canadian clinical practice, though they noted that body mass index in the trial was lower than in the population they treat in their practice settings. Additionally, feedback from the clinical experts suggested that the proportion of patients with disease that was refractory to any prior therapy (89.6%) was greater than what would be expected in clinical practice. In clinical practice, the experts noted that they would expect more patients to present with relapsed disease rather than refractory, which may indicate a sicker population. This was in contrast to certain eligibility criteria of the NP30179 study, which may suggest a less sick population (e.g., ECOG performance status 0 or 1). The clinical experts also noted that at this advanced stage of disease, there are few relevant prognostic factors, though they indicated that ECOG PS remains important at this stage.

The treatment regimen used in cohorts D2S2, D3, and D5 of the NP3019 study aligns with Health Canada–recommended dosage of 2.5 mg, then 10 mg, then 30 mg every 3 weeks for a maximum of 12 cycles. The clinical experts noted that treatment with other bispecific T-cell engager therapies continues until disease progression or unacceptable toxicity; however, they could not comment on whether treatment with glofitamab would diverge from the cap of 12 cycles.

The outcomes included in the NP30179 trial were relevant to the management of r/r DLBCL and were important to clinicians and patients. For tumour response and disease progression, measurement using the Lugano criteria is standardized across jurisdictions. However, it was noted in the clinician group input that PET-CT is not available across all jurisdictions. While the experts considered response outcomes to be important in the treatment of r/r DLBCL and considered that the response observed in the NP30179 study was better than they would expect with other currently available treatments, they noted that survival and prevention of progression are of the greatest importance to patients at this advanced stage of the

disease. As previously mentioned, the results for PFS and OS may be overestimated due to the relatively small information fraction and the overall immaturity of the data, which may impact generalizability to the population of patients with r/r DLBCL living in Canada.

GRADE Summary of Findings and Certainty of the Evidence

Methods for Assessing the Certainty of the Evidence

For the pivotal study identified in the sponsor's systematic review, GRADE was used to assess the certainty of the evidence for the 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:[16,17]

- **High certainty:** We are very confident that the true effect lies close to that of the estimate of the effect.
- **Moderate certainty:** We are moderately confident in the effect estimate. The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different. We use the word "likely" for evidence of moderate certainty (e.g., "X intervention likely results in Y outcome").
- **Low certainty:** Our confidence in the effect estimate is limited. The true effect may be substantially different from the estimate of the effect. We use the word "may" for evidence of low certainty (e.g., "X intervention may result in Y outcome").
- **Very low certainty:** We have very little confidence in the effect estimate. The true effect is likely to be substantially different from the estimate of effect. We describe evidence of very low certainty as "very uncertain."

Although GRADE guidance is not available for noncomparative studies, the CADTH review team assesses pivotal single-arm trials for study limitations (which refers 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 starts at very low certainty with no opportunity for rating up.

When possible, in this assessment certainty was rated in the context of the presence 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 such 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 in HRQoL, which were considered the most important outcomes of treatment by the clinical experts consulted by CADTH and by the clinician groups and patient group that provided input. According to the clinical experts consulted by CADTH, the clinically important thresholds for the outcomes of OS and PFS were a benefit of at least 6 months and at least 3 months, respectively, over current standard of care. 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.

The NP30179 study, a phase I/II, single-arm, open-label study of glofitamab monotherapy was the only study included in the GRADE assessment.

Results of GRADE Assessments

Table 2 presents the narrative GRADE summary of findings for glofitamab monotherapy from the NP30179 study in the treatment of patients with r/r DLBCL that has relapsed after or not responded to at least 2 prior systemic treatment regimens.

Long-Term Extension Studies

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

Indirect Evidence

Contents within this section have been informed by materials submitted by the sponsor. The following has been summarized and validated by the CADTH review team.

Objectives for the Summary of Indirect Evidence

Given the single-arm nature of available glofitamab data from the NP30179 study, there are no direct head-to-head trials comparing glofitamab against relevant comparators. As such, a series of sponsor-submitted ITCs were conducted to compare, for outcomes of interest, the efficacy of glofitamab versus relevant comparators in the third-line treatment setting and beyond for DLBCL (depending on data availability).[18]

Description of Indirect Comparisons

The sponsor-submitted ITC began with an SLR to identify evidence for treatments for the management of r/r DLBCL. A feasibility assessment was performed to identify which studies were available per comparator and which outcomes were reported for comparison. The single-arm nature of the NP30179 study and the results of the feasibility assessment led to the conclusion that conducting an anchored network meta-analysis was not feasible. As such, 2 ITCs were conducted:[18]

- a PSA comparing glofitamab to Pola-BR in the third-line treatment setting and beyond for DLBCL using individual patient data from the NP30179 study and the GO29365 trial
- an unanchored MAIC comparing glofitamab to salvage chemotherapy in the third-line treatment setting and beyond for DLBCL using individual patient data from the NP30179 study and aggregated-level data from the SCHOLAR-1 retrospective study.

PSAs were conducted when individual patient data were available for both comparators, and a MAIC was conducted for comparators for which only aggregate data were available.[18]

ITC Designs

Objectives

The objective of the sponsor-submitted ITCs (PSA and MAIC) was to compare the efficacy of glofitamab to Pola-BR and salvage chemotherapy in the third-line treatment setting and beyond for DLBCL for regulatory and health technology assessment purposes.[18]

Study Selection Methods

Propensity Score Analysis

The sponsor-submitted PSA was informed by an SLR to identify studies investigating third-line and beyond treatments for adult patients with r/r DLBCL. Per the sponsor's report, the scope of the SLR had to be broadened to make sure studies of relevant treatments, such as those that were relevant comparators due to being broadly reimbursed or prescribed in the third-line treatment setting and beyond for r/r DLBCL, were identified and properly assessed for their suitability.[18]

The SLR consisted of planned searches of multiple electronic databases, including MEDLINE, MEDLINE In-Process, Embase, and the Cochrane Library. Additional manual searches of congress proceedings from the past 3 years, reference lists of included publications, regulatory reports, and health technology assessment documents were conducted to identify relevant evidence. Searches were conducted between December 14, 2021, and September 15, 2022. Eligible citations were reviewed based on title and abstract, and those included were reviewed in full. Citations were screened by 2 independent reviewers, with any discrepancies resolved by consensus. Data extraction for studies relevant for full feasibility assessment (including study design, baseline characteristics, and treatment outcomes) was conducted by a single reviewer and independently checked against the source document by a second reviewer. The quality of eligible randomized controlled trials was conducted using the 7-criteria checklist provided in section 2.5 of the National Institute for Health and Care Excellence (NICE) single technology appraisal user guide, and the quality of nonrandomized studies was assessed using the Downs and Black checklist.[18] The eligibility criteria for study selection for the sponsor's SLR can be found in Table 18. Studies of interest included those involving adult patients with r/r DLBCL (third-line treatment setting and beyond) and those that evaluated glofitamab compared to Pola-BR. Outcomes of interest to the PSA included OS, PFS, and ORR.[18]

Table 18: Study Selection Criteria and Methods for ITCs Submitted by the Sponsor

Characteristic	Criteria
Population	Adult patients with RR DLBCL (3L+) (publications reporting data for mixed patients in the 2L/3L+ treatment setting were included if the median was ≥ 2 prior lines (≥ 50% 3L) or if they included results for the 3L+ treatment setting)
Intervention	Glofitamab step-up dosing (2.5 mg, then 10 mg, then 30 mg)
Comparator	Pola-BR (bendamustine 90 mg/m^2 IV on days 2 and 3 of cycle 1 and on days 1 and 2 of subsequent cycles; rituximab IV 375 mg/m^2 on day 1 of each cycle; polatuzumab vedotin 1.8 mg/kg IV on day 2 of cycle 1 and on day 1 of subsequent cycles). Patients received treatment of up to six 21-day cycles.
Outcome	OS, PFS, ORR
Study designs	• RCTs (phase I, II, III) • Prospective clinical trials (non-RCTs, noncomparative) • Extension phases of trials • Observational/registry studies (prospective/retrospective) • Case control studies • Cross-sectional surveys

Characteristic	Criteria
	• Case series • Treatment guidelines • SLR, meta-analyses, and narrative review publications of interventional and/or observational studies (to identify citations and fill baseline data gaps only)
Publication characteristics	For comparators besides glofitamab, only published studies were included
Exclusion criteria	Studies with nonrelevant populations (e.g., pediatric patients, adult patients treated in the 1L or 2L setting only), interventions (pharmacological interventions not listed in the inclusion list or non-pharmacological interventions such as surgery, radiotherapy, or diagnostic/screening), or outcomes (e.g., outcomes not listed in the inclusion list, economic evaluations, case reports, pharmacokinetic studies, animal/in vitro studies) were not included in the SLR

1L = first line; 2L = second line; 3L = third line; 3L+ = third line and beyond; DLBCL = diffuse large B-cell lymphoma; ITC = indirect treatment comparison; ORR = overall response rate; OS = overall survival; PFS = progression-free survival; Pola-BR = polatuzumab vedotin, bendamustine, and rituximab; RCT = randomized controlled trial; r/r = relapsed or refractory; SLR = systematic literature review.

Source: Sponsor-submitted ITC.[18]

Matching-Adjusted Indirect Comparison

No literature review was conducted to inform the MAIC. The comparator for the MAIC was informed by market research and consultation with a clinician, as salvage chemotherapies are commonly used in Canada in the third-line treatment setting and beyond for r/r DLBCL. Additionally, the sponsor used the SCHOLAR-1 study as a comparator as it was used to characterize standard of care outcomes in Canada for the CADTH Reimbursement Reviews for Yescarta and Kymriah.[18]

Feasibility Assessment

Following the SLR, the feasibility of conducting an ITC was assessed. An initial feasibility assessment was conducted based on a top-line extraction of the citations identified by the SLR. Given the availability of individual patient data from the GO29365 study for polatuzumab vedotin, this comparator was not considered further in the MAIC feasibility assessment and was only used for the PSA. Following initial assessment of the comparators from the included studies, the feasibility assessment evaluated DLBCL histology, line of therapy, and prior rituximab exposure.[18]

Based on the Canadian indication and appropriate comparators in the Canadian context, none of the studies identified in the SLR were eligible for inclusion in the ITC. It was concluded that conducting an ITC against chemotherapy regimens other than polatuzumab plus bendamustine and rituximab was not feasible. Ten studies included in the SLR investigated R-GemOx (or gemcitabine and oxaliplatin) and 4 evaluated rituximab plus dexamethasone, cytarabine, and cisplatin. Studies evaluating R-GemOx were not included in the full MAIC feasibility assessment due to histology (n = 5 studies) or line of therapy (n = 5 studies), and the studies included in the SLR investigating rituximab plus dexamethasone, cytarabine, and cisplatin were not included in the MAIC due to their histology not being aligned with the NP30179 trial (n = 2 studies) and due to line of therapy, with more than 50% of studies being in the second-line treatment setting and without data for a third-line treatment subgroup (n = 2 studies). In the absence of a feasible ITC comparing glofitamab directly with salvage chemotherapy regimens, the sponsor considered the SCHOLAR-1 study, which had been leveraged in other CADTH reimbursement reviews relating to third-line treatment settings and beyond for r/r

DLBCL. As the SLR had aimed to identify individual treatment regimens, the SCHOLAR-1 study had not been identified.[18]

Analysis Methods: PSA

The studies included in the PSA were both conducted by the sponsor:

- the NP30179 study, enrolling patients with DLBCL (DLBCL not otherwise specified, HGBCL, PMBCL, and trFL) who had received at least 2 prior lines of therapy, specifically the D2S2, D3, and D5 glofitamab step-up dosing (2.5 mg, then 10 mg, then 30 mg) cohorts ([redacted]), based on a CCOD of June 2022
- the comparator GO29365 study, evaluating patients with r/r DLBCL (DLBCL not otherwise specified, HGBCL, PMBCL, or trFL) receiving Pola-BR ([redacted]) or bendamustine and rituximab alone ([redacted]) in the third-line setting or later.[18]

The outcomes of interest for the PSA were CRR, ORR, DOCR, DOR, and PFS assessed by the IRC or the investigator, as well as OS and discontinuation due to AEs. Analyses of DOCR end points were included in the scope of the ITCs as such analyses had been requested to support regulatory activities outside the US. When necessary and possible, end point definitions used in the NP30179 study were matched to the definitions of comparator studies, which may have required a redefinition of the end point. For example, the GO29365 trial reported DOR in a subset of patients who experienced CR, rather than DOCR; DOR can be longer than DOCR if a patient had a PR that later became a CR. Therefore, to improve comparability when indirectly comparing glofitamab to Pola-BR and to bendamustine and rituximab alone, an alternative version of this outcome variable was created and used in the analyses; the alternative used the time of onset of a CR to calculate the response duration. DOR and DOCR are normally analyzed in the subsets of patients who experience a response and patients who experience a CR. It was decided to use the overall populations from both the NP30179 and GO39365 studies to perform the adjustment and then filter to these 2 response subsets for analysis. This approach was preferred as it replicates a randomized controlled trial, where treatment arms are expected to be balanced in the overall population due to randomization, and response subsets are then selected for analysis.[18]

For unadjusted comparisons, DOR, DOCR, PFS, and OS were analyzed using survival analysis methods. The Kaplan-Meier method was used to estimate the DOR, DOCR, PFS, and OS distributions for each treatment group. Estimates of the treatment effect for these outcomes were expressed as hazard ratios and 95% CIs using a Cox proportional hazards model (Efron method for handling ties). Estimates of the treatment effect for ORR and CR, as well as withdrawal due to AE, were expressed as odds ratios and 95% CI.[18]

Per NICE Technical Support Document 17, adjusted comparisons via propensity score matching, as well as IPTW adjustments, were used to minimize between-group imbalances between glofitamab, Pola-BR, and bendamustine and rituximab alone. If, postadjustment, key covariates were still imbalanced, those covariates could also be considered for inclusion in the outcome model. Problematic covariates with regression coefficient standard errors that were extremely large were identified and excluded from the outcome model. CIs for relative treatment effects of interest in the propensity score matched and IPTW samples were estimated using bootstrapping, as cluster-robust standard errors can be biased for odds ratios and

should be used with caution. Accordingly, bootstrapping was used for both binary and survival outcomes for consistency. In total, 2,000 resamples of the datasets were taken, and the propensity scores, matching weights, and mean effects were re-estimated in each of these resamples.[18]

Propensity Score Estimation

A logistic regression model was used to estimate the propensity scores. Baseline characteristics were selected so that the outcome variable of interest was independent of treatment, depending on the propensity score. Only variables that can influence both the treatment indicator and outcomes were included. While selecting baseline characteristics, the danger of including variables that can be affected by the treatment indicator variable (e.g., instrumental variables) was avoided. Several models were tested, including 2-way interaction terms. Specifically, all possible 2-way covariate interactions were generated, and the resulting model was iteratively backward tested on which covariates were to be included, using a stepwise Akaike information criterion selection procedure, which removes the covariate at each stage, leading to the greatest reduction in the model's Akaike information criterion. Models with poor convergence (e.g., iteration limits reached) were excluded, as were models with implausibly large regression coefficients or SES. Two-way interactions were explored in this stepwise Akaike information criterion procedure to ensure that a sufficiently flexible propensity score model could be used and because it was not clear which covariate interactions were of established prognostic value. Alternatives to this procedure were also tested in the following ways: using a stepwise forward selection; using a forward and backward selection procedure; ensuring only covariates with statistically significant P values for the coefficients were retained during the stepwise procedure; using a probit model; or both. For simplicity, all these exploratory analyses were conducted using only 1 matching method (i.e., the 1 resulting in the highest covariate balance) and IPTW as the methods of reference. The final distribution of estimated propensity scores was inspected to assess the overlap between treatment groups, as well as to identify the presence and frequency of propensity scores with potentially extreme values, which could create issues during the matching or weighting process. The propensity score distribution prematching and postmatching was also evaluated to assess which patients (and their propensity scores) would be discarded or would carry greater weight after the matching process (particularly relevant if the starting size of the control unit group was smaller than the starting size of the treated unit group).[18]

Covariate balance was assessed as measured by the absolute standardized mean differences, using a threshold of 0.1,[49] and the complements of overlapping coefficients prematching and postmatching.[50] The distributional balance for each of the covariates used to estimate the propensity scores was also inspected and compared for the 2 main adjustment methods.[51]

Several different matching methods were tested owing to the limited and relatively comparable sample sizes across the 2 treatment groups. The following methods were explored: nearest neighbour matching with and without replacement, optimal pair matching, and full matching. The matching method resulting in better covariance balance — i.e., the 1 that minimized the absolute standardized mean differences and complements of overlapping coefficients for the greatest number of covariates (with major emphasis on the ones with higher prognostic value) — was selected as the preferred matching method for the base-case

scenario. The ESSs were also compared across methods to ensure an acceptable bias-variance trade-off. If, postadjustment, key covariates were still found to be imbalanced, those covariates could also be considered for inclusion in the outcome model.[18]

Inverse Probability Treatment Weighting

IPTW is an alternative method to adjust for imbalances in baseline characteristics as it does not discard any patients from the sample. When using IPTW to estimate the ATE, weights are computed that denote the probability of receiving the actual treatment that was received. Weights can then be used in a Cox proportional hazards model or in a logistic regression model to estimate the relative treatment effects of interest. Stabilized weights were used in all analyses to avoid a few observations with very large weights potentially causing the resulting IPTW-ATE estimator to have large variance and to not be approximately normally distributed. Stabilized weights were not expected to have an impact on the results in the absence of large IPTW-ATE weights, although it could still help in reducing large variances and increasing precision.[18]

Weight truncation for patients with large weights was also considered if, upon visual inspection of the distribution of stabilized IPTW, some very large weights were found to persist. The use of patient trimming was avoided as much as possible due to the limited sample size available for the comparisons. If, postadjustment, key covariates were still found to be imbalanced, those covariates could also be considered for inclusion in the outcome model.[18]

Prognostic Factors and Treatment Effect Modifiers

The prognostic factors and treatment effect modifiers considered in the analyses were classified as either high, medium, or low priority according to clinical feedback:[18]

- High priority:
  - IPI (0 to 2 versus 3 to 5), age-adjusted IPI (0 to 1 versus 2 to 3), and/or any of the components that are included within the IPI (age, ECOG PS, Ann Arbor stage, high lactate dehydrogenase levels, presence of extranodal disease)
  - Refractoriness to first line, last line, or any line of treatment
  - Histological subtype
  - Double-hit or triple-hit lymphoma
  - Early relapse after SCT
  - Number of prior treatment lines
- Medium priority:
  - Bulky disease (definition may vary across studies [no clinically established threshold])
  - Refractoriness to chemotherapy
  - Prior treatment with (or refractoriness to) rituximab and an anthracycline therapy
  - Refractoriness to rituximab
  - Early relapse from last line of treatment

- Low priority:
  - Primary diagnosis
  - Cell type of origin of the disease
  - Bone marrow involvement
  - Primary bone marrow transplant
  - Prior SCT

If key covariates were reported using different definitions in the NP30179 and GO29365 studies, attempts were made to readjust the covariate definitions in either trial to ensure they were aligned or to facilitate model fitting, where possible. When readjusting a covariate definition was not possible or when there was uncertainty about the definition of a covariate, the respective covariates could be considered for testing in sensitivity analyses.[18]

In the case of missing values for categorical or continuous covariates in the NP30179 or GO29365 studies, the values were imputed based on the most frequently occurring value or the mean value without the missing data points in the dataset, so that the patients did not have to be dropped from the analysis. The imputation was performed before any additional filtering of patients to align with the eligibility criteria between studies, so that the same imputed values were used in all comparisons. An exception to this general approach was made if there was also a large amount of missing data for glofitamab, in which case "missing" was treated as a separate category for both treatments rather than the values being imputed.[18]

Analysis Methods: MAIC

The second ITC was a MAIC of glofitamab in the third-line treatment setting and beyond for DLBCL versus salvage chemotherapy from the SCHOLAR-1 retrospective study. In the MAIC, the individual data of patients with DLBCL after at least 2 prior lines of therapy from the D2S2, D3, and D5 glofitamab step-up dosing cohorts from the NP30179 trial were weighted to match reported prognostic factors and effect modifiers from the SCHOLAR-1 study. Where necessary, the NP30179 population was aligned in terms of eligibility criteria related to the factors of interest with the population of the SCHOLAR-1 study before estimating the weights. Inputs for glofitamab were based on the June 15, 2022, CCOD.[18]

The SCHOLAR-1 study is an international, multicohort, retrospective NHL research study to characterize outcomes for a population of patients with refractory DLBCL (including PMBCL and trFL). In the SCHOLAR-1 study, refractory DLBCL was defined as progressive disease or stable disease as best response at any point during chemotherapy (> 4 cycles of first-line or 2 cycles of later-line therapy) or relapsed disease within 12 months after autologous SCT. The SCHOLAR-1 study pooled data from 2 phase III clinical trials (the Lymphoma Academic Research Organization [CORAL] study and the Canadian Cancer Trials Group [LY.12] study) and 2 observational cohorts (MD Anderson Cancer Center and University of Iowa/Mayo Clinic Lymphoma Specialized Program of Research Excellence). For the University of Iowa/Mayo Clinic cohort and the LY.12 and CORAL studies, patients were included at the first instance of disease meeting refractory criteria, whereas for the MD Anderson Cancer Center cohort, patients with disease that first met refractory criteria from second-line therapy onward were included (636 patients in total on the basis of the

refractory criteria in the SCHOLAR-1 study cohorts). Patients must have received an anti-CD20 mAb and an anthracycline as 1 of their qualifying regimens and must not have had primary central nervous system lymphoma. Covariates were determined at diagnosis or at random assignment for the observational and randomized study cohorts, respectively. For all cohorts, in some cases, covariates were also measured later in the treatment course, depending on data availability and accessibility or study design. For summaries of patient characteristics, the covariate measured closest in time to the determination of refractory status was used. For subgroup analyses, patients were included in the covariate subgroup analysis only if the covariate was measured within 3 months of the determination of refractory status. When covariates assessed after the start of therapy for refractory status were used in survival models, survival time was calculated from the day of covariate assessment. Response to therapy for refractory disease was determined by the 1999 International Working Group response criteria, while response to therapy for the observational cohorts was determined by investigator assessment, also using the International Working Group response criteria. Response rates and OS were estimated from the time of initiation of salvage therapy for refractory disease. Kaplan-Meier curves were reported for OS by response, refractory and postrefractory transplant status, ECOG PS, disease stage, and IPI score, and response data were reported by age, ECOG PS, disease stage, and IPI score. However, baseline data were not reported for these subgroups; thus, MAICs could not be conducted. Response end points were assessed according to the 1999 International Working Group response criteria rather than the Lugano classification used in the NP30179 study. MAICs were deemed feasible for CR, ORR, and OS.[18]

In general, the primary sources of data on baseline patient characteristics were the major publications in which the most up-to-date data on efficacy and tolerability outcomes were reported for the efficacy analysis population of interest. When data on specific covariates were unavailable for the population of interest but were available for another similar population (e.g., major versus supportive publications or different data cut-offs), or when there was insufficient clarity on the actual definition of a covariate, consideration was given to imputing the missing value using the mean or proportion from this alternative population. Where multiple values for the same factors could be selected, priority was given to the values reported for the population that was most similar to the main population for which the most up-to-date outcome data were reported.[18]

If key covariates were reported using different definitions in the NP30179 study and the comparator trials, attempts were made to readjust the covariate definitions in the NP30179 study to match the comparator study definition or to facilitate model fitting, where feasible. When readjusting a covariate definition was not possible or when there was uncertainty about the actual definition of a covariate, the respective covariates might have been considered for testing in sensitivity analyses. In consultation with clinical experts, no known clinically important 2-way interactions between covariates were identified; therefore, interactions were not considered in the analysis.[18]

In the case of missing values for categorical covariates from comparator studies, the proportions for the categories of that covariate were renormalized without the missing data. In the case of missing values for categorical or continuous covariates in the NP30179 study, the values were imputed based on the most frequently occurring value or the mean value without the missing data points in the dataset, respectively, so that the patients did not have to be dropped from the analysis. The imputation was performed before any

additional filtering of patients to align with the eligibility criteria of a specific comparator study, so that the same imputed values were used in all comparisons. An exception to this general approach was made if there was also a large amount of missing data for glofitamab, in which case "missing" was treated as a separate category in its own right for both treatments rather than the values being imputed.[18]

In the MAIC, it was not possible to control for an ECOG PS of 2 due to the inclusion criteria for the NP30179 study, under which all patients had an ECOG PS of less than 2. In instances where an ECOG PS of 2 was reported in comparator studies, either an ECOG PS of 1 could be imputed (maximally conservative assumption) or ECOG PS could be excluded from the analysis, depending on whether the proportion of patients with these characteristics was low or high, respectively.[18]

An iterative approach was employed to identify the most appropriate base-case analysis for each comparison. First, the primary analysis attempted to maximize use of the full glofitamab population ([redacted]). To maximize the between-trial comparability before conducting the analyses, the eligibility criteria of the SCHOLAR-1 trial were applied to the glofitamab cohort, unless this resulted in an unacceptably small starting sample size. This process consisted of excluding patients who did not have chemo-refractory disease according to the SCHOLAR-1 study criteria (progressive or stable disease as the best response to first-line treatment or to the most recent chemotherapy regimen, or disease progression or relapse within 12 months after autologous SCT). Furthermore, patients with HGBCL histology or who had received 4 or more prior lines of therapy were also excluded, to align with the population enrolled in the SCHOLAR-1 study.[18]

The general approach was to then try fitting the base case using all available covariates. However, due to the high number of factors to control for, and the important imbalances preadjustment in some of these factors between the NP30179 study and a few of the studies identified in the MAIC feasibility assessment, it was anticipated that this approach may not always be feasible. If the ESS was too low when using all covariates, then the base-case scenario considered the use of high-priority and medium-priority covariates only. If adjustment with only high-priority and medium-priority factors resulted in an ESS that was still too small (e.g., < 30 patients), then the list of variables used for adjustment could be reduced further by excluding some additional covariates in the high-priority or medium-priority set. To maintain the maximum number of the most clinically important variables in the adjustment, several combinations of variables were explored. For continuous covariates, consideration was also given to balancing the standard deviation when reported, via the inclusion of squared covariate terms in the weight calculation, or to converting a median value to a mean, providing this did not substantially reduce the ESS. This approach maximized the bias-variance trade-off, while properly controlling for as many high-priority and medium-priority prognostic factors as possible and selecting the most appropriate base-case scenario for each comparison. However, it was noted that excluding known imbalanced covariates from matching may result in populations with imbalanced levels of effect modification or prognostic value between treatments, which could bias the analysis results.[18]

The base case maximizes the bias-to-variance trade-off while controlling for all priority prognostic factors that were feasible as well as controlling for age as a mean. The following scenario analyses were also conducted:[18]

- Scenario 1, including all available factors and controlling for age as a median (i.e., value as reported and not converted to mean using Hozo et al. [2005][52])
- Scenario 2, including patients who had received up to 4 prior therapies ([redacted]) (patients with ≥ 4 lines were reported to be < 1% in the SCHOLAR-1 study, but this was estimated by excluding patients with disease that relapsed post–autologous SCT, leading to uncertainty) while controlling for all available factors and for age as a mean.

When some covariates had to be excluded, sensitivity analyses could be conducted to show the impact of including these covariates on the analysis results. Other sensitivity analyses that may have been conducted explored the impact of using alternative definitions for certain covariates when multiple alternative definitions were available. These analyses may or may not have been conducted within the context of an "all covariate" sensitivity analysis, depending on the impact that excluding low-priority covariates had on the ESS. Sensitivity analyses may have also been conducted when patients in the matched dataset unambiguously had outlier weights, for example using truncated weights or excluding patients with extreme weights. Finally, the covariate distributions for the glofitamab data prematch and postmatch, as well as the ESS, were summarized and compared to the aggregate study data.[18]

For binary outcomes (i.e., ORR, CR, AEs), the relative treatment effect in the form of odds ratios was estimated using generalized linear models; for continuous outcomes (i.e., OS and PFS), the relative treatment effect in the form of hazard ratios was estimated using Cox proportional hazard models. PFS was of interest, but such data were not available for the SCHOLAR-1 study. Patients were weighted using a method of moments propensity score algorithm for each comparison. CIs were calculated using bootstrapping to account for estimated weights. Two methods were tested for bootstrapping CIs for weighted hazard ratios and odds ratios using 2,000 samples: the percentile method and the bias-corrected accelerated method. Estimates from the percentile-bootstrapped hazard ratio were considered the base case. In instances where the histogram of percentile-bootstrapped hazard ratios is not indicative of a normal distribution, this may suggest that the bias-corrected accelerated method is more appropriate.[18]

Results of Sponsor-Submitted ITCs

Propensity Score Analysis

Summary of Included Studies

A total of 320 publications were identified in the SLR, of which 117 evaluated key interventions of interest and reported sufficient data to be considered. Owing to the availability of individual patient data from the GO29365 study for the comparators of interest, the sponsor conducted a PSA using individual patient data from that study, given the possibility of filtering patients to make them more comparable to the patients with DLBCL in the third-line treatment setting and beyond enrolled in the NP30179 study.[18] The PSA was therefore conducted using individual patient data from 2 of the sponsor's own sponsored studies.

The NP30179 study has previously been described. The population of interest to the PSA from the NP30179 study came from the D2S2, D3, and D5 cohorts, comprising [redacted] patients.[18]

The GO29365 study is a phase Ib/II, open-label, multicentre, randomized study evaluating the safety, efficacy, and pharmacokinetic profile of Pola-BR, bendamustine and rituximab, and polatuzumab vedotin plus bendamustine and obinutuzumab in patients with r/r DLBCL or follicular lymphoma. Patients aged 18 years or older were eligible if they had histologically confirmed r/r DLBCL (excluding trFL), had received at least 1 prior line of therapy, had an ECOG PS of 0 to 2, and were considered ineligible for transplant by the treating physician or had experienced treatment failure with prior autologous SCT. Patients with current peripheral neuropathy higher than grade 1 were excluded. The primary end point of the randomized arms was the CR rate by PET-CT imaging at the end of treatment (6 to 8 weeks after cycle 6 day 1, or last dose of the study treatment) determined by the IRC using the modified Lugano criteria. The secondary objectives included ORR, best overall response, DOR, PFS, OS, and safety. The population used to indirectly compare glofitamab with Pola-BR was the combined population of the safety run-in, randomized, Arm G, and Arm H cohorts of patients with DLBCL from the GO29365 study [redacted].[18]

Prior to adjustment, patients were filtered by applying common inclusion and exclusion criteria. Patients with certain histological characteristics were excluded from the glofitamab cohort (i.e., patients with Epstein-Barr virus DLBCL, DLBCL not otherwise specified, T-cell or histocyte-rich large B-cell lymphoma, follicular lymphoma, and PMBCL were excluded) as no such patients were enrolled in the Pola-BR cohort; patients with an ECOG PS of 2 or higher and patients who had received only 1 prior line of therapy were excluded from the Pola-BR cohort. This resulted in [redacted] patients in the glofitamab arm and [redacted] patients in the Pola-BR arm.[18]

Prior to adjustment, most baseline characteristics were imbalanced between the glofitamab and Pola-BR groups (absolute standardized mean difference > 0.1), except for extranodal disease, number of prior therapies, size of the largest node lesion, and disease refractory to any prior anti-CD20 mAb–containing regimen (Table 19).[18]

None of the approaches to incorporate 2-way interaction terms resulted in improved covariate balance compared with a simpler approach that did not make use of interaction terms, likely due to model overfitting (i.e., several propensity scores were equal to 0 or 1). Therefore, a final model including only linear predictors was selected to estimate the propensity score.[18]

Results

Nearest neighbour matching with or without replacement and optimal pair matching methods resulted in poor balancing of covariates and a small ESS. The final ESS after nearest neighbour matching with replacement was [redacted] for glofitamab and [redacted] for Pola-BR. The final ESS after nearest neighbour matching without replacement and optimal pair matching was 168 (as no weights are involved). As a result, full matching (ATE) was selected as the matching method of preference over nearest neighbour matching for the indirect comparison of glofitamab versus Pola-BR.[18]

Table 19: Summary of Baseline Characteristics Before Adjustment

Variable	Glofitamab (n =)		Pola-BR (n =)		aSMD	VR
	Mean	SD	Mean	SD		
Age (years)						
ECOG PS 1 vs. 0 (%)						
Ann Arbor stage III/IV (%)						
High LDH (%)						
Extranodal disease (%)						
IPI 3 to 5 (%)						
Refractory to first line (%)						
Refractory to any line (%)						
Refractory to last line (%)						
HGBCL (%)						
Refractory to ASCT (%)						
Prior therapies > 2 (%)						
Size of the largest node lesion (cm)						
Refractory to any prior anti-CD20 mAb and anthracycline (%)						
Refractory to any prior anti-CD20 mAb–containing regimen (%)						
Time since last treatment (months)						
GCB (%)						
ABC/non-GCB (%)						
Bone marrow involvement (%)						
Prior ASCT (%)						

ABC = activated B-cell; ASCT = autologous stem cell transplant; aSMD = absolute standardized mean difference; ECOG PS = Eastern Cooperative Oncology Group Performance Status; GCB = germinal centre B-cell; HGBCL = high-grade B-cell lymphoma; IPI = International Prognostic Index; LDH = lactate dehydrogenase; mAb = monoclonal antibody; NA = not applicable; Pola-BR = polatuzumab vedotin, bendamustine, and rituximab; SD = standard deviation; VR = variance ratio; vs. = versus.

Source: Sponsor-submitted indirect treatment comparison.[18]

The covariate balance after full matching and IPTW methods is shown in Table 20 and Table 21, respectively. For the chosen matching analyses, the final ESS after the full matching method was for glofitamab and for Pola-BR. The final ESS after IPTW and weight trimming was for glofitamab and for Pola-BR. IPTW was selected as the adjustment method of preference for the base-case analysis as balance was achieved for all the prognostic factors considered. Full matching failed to achieve good balance for age, IPI, extranodal disease, number of prior therapies, and prior autologous SCT, with the balance being worse than in the unadjusted sample for the first 4 covariates (Ann Arbor stage, high lactate dehydrogenase, and time since

last treatment were borderline balanced). For this reason, residual imbalances in these 3 covariates between the 2 groups were further controlled for in subsequent outcome analyses.[18]

The results from the propensity score matched analyses for all end points are summarized in Table 22. There was no difference after adjustment between glofitamab and Pola-BR for all end points by either full matching or IPTW.[18]

Matching-Adjusted Indirect Comparison

Summary of Included Studies

The SCHOLAR-1 study was not identified in the sponsor's literature search as the search was based on individual treatment regimens. Based on market research and consultation with a clinician, the comparison of the NP30179 study and the SCHOLAR-1 study was conducted via MAIC.[18]

The NP30179 study has previously been described. The population of interest to the MAIC from the NP30179 study came from the D2S2, D3, and D5 cohorts, comprising 155 patients.

Table 20: Summary of Baseline Characteristics After Full Matching for Pola-BR Comparison

Variable	Glofitamab (ESS =)		Pola-BR (ESS =)		aSMD	VR	KS test statistic	Overlapping coefficient complement
	Mean	SD	Mean	SD				
Age (years)								
ECOG PS 1 vs. 0 (%)								
Ann Arbor stage III/IV (%)								
High LDH (%)								
Extranodal disease (%)								
IPI 3 to 5 (%)								
Refractory to first line (%)								
Refractory to any line (%)								
Refractory to last line (%)								
HGBCL (%)								
Refractory to ASCT (%)								
Prior therapies > 2 (%)								
Size of the largest node lesion (cm)								
Refractory to any prior anti-CD20 mAb and anthracycline (%)								
Refractory to any prior anti-CD20 mAb–containing regimen (%)								

Variable	Glofitamab (ESS = [redacted])		Pola-BR (ESS = [redacted])		aSMD	VR	KS test statistic	Overlapping coefficient complement
	Mean	SD	Mean	SD				
Time since last treatment (months)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
GCB (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ABC/non-GCB (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Bone marrow involvement (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Prior ASCT (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

ABC = activated B-cell; ASCT = autologous stem cell transplant; aSMD = absolute standardized mean difference; ECOG PS = Eastern Cooperative Oncology Group Performance Status; ESS = effective sample size; GCB = germinal centre B-cell; HGBCL = high-grade B-cell lymphoma; IPI = International Prognostic Index; KS = Kolmogorov-Smirnov; LDH = lactate dehydrogenase; mAb = monoclonal antibody; NA = not applicable; Pola-BR = polatuzumab vedotin, bendamustine, and rituximab; SD = standard deviation; VR = variance ratio; vs. = versus.

Note: Covariates were considered "balanced" as defined an aSMD less than 0.1, and VR less than 2.

Source: Sponsor-submitted indirect treatment comparison.[18]

Table 21: Summary of Baseline Characteristics After IPTW for Pola-BR Comparison

Variable	Glofitamab (ESS = [redacted])		Pola-BR (ESS = [redacted])		aSMD	VR	KS test statistic	Overlapping coefficient complement
	Mean	SD	Mean	SD				
Age (years)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ECOG PS 1 vs. 0 (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ann Arbor stage III/IV (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
High LDH (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Extranodal disease (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
IPI 3 to 5 (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Refractory to first line (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Refractory to any line (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Refractory to last line (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
HGBCL (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Refractory to ASCT (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Prior therapies > 2 (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Size of the largest node lesion (cm)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Refractory to any prior anti-CD20 mAb and anthracycline (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Refractory to any prior anti-CD20 mAb–containing regimen (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Variable	Glofitamab (ESS = [redacted])		Pola-BR (ESS = [redacted])		aSMD	VR	KS test statistic	Overlapping coefficient complement
	Mean	SD	Mean	SD				
Time since last treatment (months)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
GCB (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ABC/non-GCB (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Bone marrow involvement (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Prior ASCT (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

ABC = activated B-cell; ASCT = autologous stem cell transplant; aSMD = absolute standardized mean difference; ECOG PS = Eastern Cooperative Oncology Group Performance Status; ESS = effective sample size; GCB = germinal centre B-cell; HGBCL = high-grade B-cell lymphoma; IPI = International Prognostic Index; IPTW = inverse probability treatment weighting; KS = Kolmogorov-Smirnov; LDH = lactate dehydrogenase; mAb = monoclonal antibody; NA = not applicable; Pola-BR = polatuzumab vedotin, bendamustine, and rituximab; SD = standard deviation; VR = variance ratio; vs. = versus.

Note: Covariates were considered "balanced" as defined with an aSMD less than 0.1, and VR less than 2.

Source: Sponsor-submitted indirect treatment comparison.[18]

Table 22: Summary of PSA Results for End Points of Interest for Comparison of Glofitamab to Pola-BR

End Point	Unadjusted	Full matching plus covariate adjustment	IPTW
OS, HR (95% CI)	[redacted]	[redacted]	[redacted]
PFS (IRC), HR (95% CI)	[redacted]	[redacted]	[redacted]
PFS (INV), HR (95% CI)	[redacted]	[redacted]	[redacted]
DOR (IRC), HR (95% CI)	[redacted]	[redacted]	[redacted]
DOR (INV), HR (95% CI)	[redacted]	[redacted]	[redacted]
DOCR (IRC), OR (95% CI)	[redacted]	[redacted]	[redacted]
DOCR (INV), OR (95% CI)	[redacted]	[redacted]	[redacted]
CR (IRC), OR (95% CI)	[redacted]	[redacted]	[redacted]
CR (INV), OR (95% CI)	[redacted]	[redacted]	[redacted]
ORR (IRC), OR (95% CI)	[redacted]	[redacted]	[redacted]
ORR (INV), OR (95% CI)	[redacted]	[redacted]	[redacted]
Discontinuation due to AEs, OR (95% CI)	[redacted]	[redacted]	[redacted]

AE = adverse event; CI = confidence interval; CR = complete response; DOCR = duration of complete response; DOR = duration of response; HR = hazard ratio; INV = investigator; IPTW = inverse probability treatment weighting; IRC = independent review committee; OR = odds ratio; ORR = overall response rate; OS = overall survival; PFS = progression-free survival; Pola-BR = polatuzumab vedotin, bendamustine, and rituximab; PSA = propensity score analysis.

Notes: HRs less than 1 presented for the comparison of glofitamab vs. Pola-BR favour glofitamab. ORs greater than 1 presented for the comparison of glofitamab vs. Pola-BR favour glofitamab.

Source: Sponsor-submitted indirect treatment comparison.[18]

The SCHOLAR-1 study is an international, multicohort, retrospective NHL research study and 1 of the largest patient-level pooled analyses to characterize outcomes for patients with refractory DLBCL (including PMBCL

and trFL). Refractory DLBCL was defined as progressive disease or stable disease as best response at any point during chemotherapy (> 4 cycles of first-line or 2 cycles of later-line therapy) or relapsed disease within 12 months from autologous SCT. The SCHOLAR-1 study pooled data from 2 phase III clinical trials (the Lymphoma Academic Research Organization [CORAL] study and the Canadian Cancer Trials Group [LY.12] study) and 2 observational cohorts (MD Anderson Cancer Center and University of Iowa/Mayo Clinic Lymphoma Specialized Program of Research Excellence). For the University of Iowa/Mayo Clinic cohort and the LY.12 and CORAL studies, patients were included at the first instance of disease meeting refractory criteria, whereas for the MD Anderson Cancer Center cohort, patients with disease that first met refractory criteria from second-line therapy onward were included. To be enrolled in the study, patients must have received an anti-CD20 mAb and an anthracycline as 1 of their qualifying regimens and must not have had primary central nervous system lymphoma. Response to therapy for refractory disease was determined by the 1999 International Working Group response criteria. Response to therapy for the observational cohorts was determined by investigator assessment, also using International Working Group response criteria. Response rates and OS were estimated from the time of initiation of salvage therapy for refractory disease, with the ORR being 26% (CR rate = 7%) to the next line of therapy, and the median OS being 6.3 months. Response end points were assessed according to the 1999 International Working Group response criteria rather than the Lugano classification used in the NP30179 study. Thus, MAICs were deemed feasible for CR, ORR, and OS, though with some limitations that may limit the interpretation and generalizability of the results.[18]

Results

To ensure that the glofitamab patient cohort used for the analyses was as homogeneous as possible, a filtering procedure was conducted in which the SCHOLAR-1 study eligibility criteria were applied to patients from the NP30179 study. Patients who did not have chemo-refractory disease according to the SCHOLAR-1 study criteria (progressive or stable disease as the best response to first-line treatment or to the most recent chemotherapy regimen, or disease progression or relapse within 12 months after autologous SCT), who had HGBCL histology, or who had received 4 or more prior lines of therapy were excluded. As such, the population from the NP30179 study included [redacted] patients.[18]

The baseline characteristics that were selected based on availability before and after adjustment for the SCHOLAR-1 and NP30179 studies are summarized in Table 23. Eight baseline characteristics of interest were available for adjustment from the SCHOLAR-1 study pooled population (n = [redacted]). Prior to adjustment, there were differences across nearly all baseline characteristics between the SCHOLAR-1 and NP30179 studies. The SCHOLAR-1 study cohort (Crump et al. [2017]) enrolled approximately [redacted] patients in the second-line treatment setting, and approximately [redacted] of patients had an ECOG PS of 2 or more. Conversely, the NO30179 study [redacted] patients in the second-line treatment setting or patients with an ECOG PS of 2 or more. As such, it was not possible to adjust for these variables in the analyses, and these characteristics were excluded. Following adjustment, most baseline characteristics were balanced, though differences remained for patients who received 2 to 3 prior therapies (SCHOLAR-1 study, [redacted]). The resulting ESS in the glofitamab arm of each analysis was [redacted] for the base-case analysis, [redacted] for Scenario 1, and [redacted] for Scenario 2.[18]

Table 23: Summary of Baseline Characteristics Available for Comparison of Glofitamab and the Salvage Chemotherapy From the SCHOLAR-1 Study

Variable	SCHOLAR-1 (n =)	Glofitamab unadjusted (n =)	Glofitamab weighted		
			Base case ( )	Scenario 1 ( )	Scenario 2 ( )
Age (years), mean					
Age (years), median					
ECOG PS > 1 (%)					
Ann Arbor stage III/IV (%)					
IPI 3 to 5 (%)					
PMBCL histology (%)					
1 prior therapy (%)					
2 to 3 prior therapies (%)					
Refractory to first line (%)					
Refractory to last line (%)					
Early relapse after SCT (%)					

ECOG PS = Eastern Cooperative Oncology Group Performance Status; ESS = effective sample size; IPI = International Prognostic Index; NA = not applicable; PMBCL = primary mediastinal B-cell lymphoma; SCT = stem cell transplant.

Source: Sponsor-submitted indirect treatment comparison.[18]

The results for the MAIC comparing glofitamab to the SCHOLAR-1 study are summarized in Table 24. For OS, glofitamab was favoured over the SCHOLAR-1 cohort for all analyses, regardless of model method. Results for the response end points of ORR and CR also favoured glofitamab over the SCHOLAR-1 study, regardless of model method, though the 95% CIs were imprecise.[18]

Critical Appraisal of Sponsor-Submitted ITCs

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. Two ITCs, a PSA and an unanchored MAIC, were conducted by the sponsor. The sponsor-submitted ITCs were initially informed by an SLR, which included planned searches of multiple databases and grey literature up to September 2022. However, per the sponsor's report, no trials identified in the SLR were available for inclusion in the ITC based on the predefined Population, Intervention, Comparator, Outcome, and Study Design (PICOS) framework. As such, the evidence bases for the PSA and MAIC evaluating the comparative efficacy of glofitamab from the NP30179 study included the GO29365 study and the SCHOLAR-1 study, respectively, which were selected by the sponsor. Thus, although the comparator studies made the ITCs feasible, there is a high risk of selection bias in the comparator trials chosen.

Table 24: Summary of MAIC Results for End Points of Interest for Comparison of Glofitamab to Salvage Chemotherapy From the SCHOLAR-1 Study

End point	Unadjusted Cox model	Bootstrap median OR (95% percentile CI) weighted Cox model	Bootstrap median OR (95% bCa CI) weighted Cox model
OS, HR (95% CI)			
Base case	[redacted]	[redacted]	[redacted]
Scenario 1	[redacted]	[redacted]	[redacted]
Scenario 2	[redacted]	[redacted]	[redacted]
ORR (investigator assessed), OR (95% CI)			
Base case	[redacted]	[redacted]	[redacted]
Scenario 1	[redacted]	[redacted]	[redacted]
Scenario 2	[redacted]	[redacted]	[redacted]
CR (investigator assessed), OR (95% CI)			
Base case	[redacted]	[redacted]	[redacted]
Scenario 1	[redacted]	[redacted]	[redacted]
Scenario 2	[redacted]	[redacted]	[redacted]

bCa = bias-corrected accelerated; CI = confidence interval; CR = complete response; HR = hazard ratio; MAIC = matching-adjusted indirect comparison; OR = odds ratio; ORR = overall response rate; OS = overall survival.

Notes: HRs less than 1 presented for the comparison of glofitamab vs. the SCHOLAR-1 study favour glofitamab. ORs greater than 1 presented for the comparison of glofitamab vs. the SCHOLAR-1 study favour glofitamab.

Source: Sponsor-submitted indirect treatment comparison.[18]

There were important differences in the design of the included studies and the cohorts evaluated that limit the ability to draw strong conclusions about the efficacy of glofitamab compared with other treatments. The NP30179 study of glofitamab was a phase I/II, single-arm study, whereas the GO29365 study was a comparative phase Ib/II randomized, open-label study, and the SCHOLAR-1 study was a retrospective research study. Previously outlined critical appraisal points raised for the NP30179 study apply to the results of the sponsor-submitted ITC. A formal quality assessment using various validated tools was planned; however, only the results for the NICE QuEENS (Quality of Effectiveness Estimates From Nonrandomized Studies) checklist was reported for the NP30179 study. Differences in the design of the included studies for the analyses conducted, which could not be adjusted for in the weighting procedures, was an important limitation.

In addition to differences in study design, there were notable differences in the eligibility criteria of the included studies, which resulted in heterogeneity in baseline characteristics across populations. The inclusion criteria for the NP30179 study have previously been described. The comparator in the PSA, the GO29365 study, enrolled patients who had received 1 or more prior lines of therapy and included patients with an ECOG PS of 2. The comparator study for the MAIC, the SCHOLAR-1 study, enrolled patients from various sources, and patients with 1 or more prior lines of therapy, including prior SCT, and with an ECOG PS

of 0 to 4 were enrolled. Though the SCHOLAR-1 study had strong representation of patients living in Canada, the exact makeup of the therapies included in the salvage chemotherapy arm in the MAIC was not reported. Additionally, the clinical experts consulted by CADTH suggested that in the third-line setting, salvage chemotherapy is generally not used due to toxicity and the 2 prior treatment failures; thus, they would not rechallenge the patient with chemotherapy regimens. In the PSA, when different definitions for key covariates were reported between the NP30179 and GO29365 studies, covariate definitions were readjusted where possible in either trial to ensure they were aligned or to facilitate model fitting, though it was unclear how this readjustment was conducted.

For both analyses, a comprehensive list of prognostic factors and treatment effect modifiers was identified through appropriate channels and was included in the report. As the NP30179 study did not enrol any patients receiving second-line therapy or any patients with ECOG PS of 2 or more, it was not possible to adjust for these variables in the analyses in the ITCs, and these characteristics were excluded. As noted by the clinical experts consulted by CADTH, ECOG PS is an important prognostic factor in later-line r/r DLBCL, and limiting the adjustments because of lack of evidence for this factor is therefore 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 based on the available data; a more comprehensive list was possible for the PSA. Prior to adjustment, there were notable differences in the proportion of patients with 1 or with 2 to 3 prior therapies, as well as in the proportion of patients with disease that was refractory to the last line of treatment. Following adjustment, most factors were balanced; however, differences remained in these same factors. The key limitation of the sponsor-submitted MAIC, which is a limitation inherent to all unanchored MAICs, is that it assumes that all effect modifiers and prognostic factors are accounted for in the model. This assumption is largely considered impossible to meet, according to the NICE Decision Support Unit technical guidance report on the methods for population-adjusted indirect comparisons.[53]

Prior to adjustment in both the PSA and the MAIC, a filtering process applying the eligibility criteria of the comparator trials to the NP30179 study (and vice versa for the comparison of glofitamab to Pola-BR [the GO29365 study]) was conducted to achieve a more homogenous base population. In the PSA, applying the eligibility criteria to each group resulted in [redacted] patients in the glofitamab arm and [redacted] patients in the Pola-BR arm. In the full matching scenario and IPTW (base-case) analysis, adjustment resulted in a reduction in sample size of [redacted]% in the glofitamab group and [redacted]% in the Pola-BR group and of [redacted]% in the glofitamab group and [redacted]% in the Pola-BR group, respectively. Following adjustment, some differences remained in the full matching scenario in age, proportion of patients with Ann Arbor stage III and IV disease, proportion of patients with high lactate dehydrogenase, proportion of patients with extranodal disease, proportion of patients with an IPI score between 3 and 5, proportion of patients who had received 2 or more prior therapies, the mean time since the last treatment, and patients who had received prior autologous SCT. Following adjustment, there were no differences between groups in the baseline characteristics for the IPTW analysis.

In the MAIC, after applying the eligibility criteria for the SCHOLAR-1 study to the individual patient data of the NP30179 study, the eligible population was reduced from [redacted] patients. In the PSA, before adjustment, most baseline characteristics were unbalanced. Compared to the eligible sample size from the NP30179 study, the

ESS from all matching scenarios was substantially reduced: [redacted]% for the base-case analysis, [redacted]% for Scenario 1, and [redacted]% for Scenario 2. It is uncertain how much of this reduction is due to the exclusion of patients or to loss of precision due to the weighting process. Thus, either there was considerable heterogeneity between studies among the variables included in the weighting process or the inclusion and exclusion criteria differed greatly between the studies. Aside from the 2 additional analysis scenarios that controlled for differences in age reporting and for patients who had received up to 4 prior therapies, no consideration was given to the potential bias introduced as a result of any exclusion, which is an important limitation in the relative treatment effect estimates. In the absence of such evidence, the NICE Decision Support Unit considers the amount of bias in an unanchored MAIC likely to be substantial.

The 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.

The results for the MAIC comparing glofitamab to salvage chemotherapy from the SCHOLAR-1 study were conducted using 3 separate models: an unadjusted Cox model, a bootstrapping weighted Cox model, and a bootstrapping unweighted Cox model. The results for OS were consistent across models and adjustment scenarios, favouring glofitamab over salvage chemotherapy regimens from the SCHOLAR-1 study. While the 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 sponsor-submitted ITCs, particularly the MAIC, had multiple limitations, including differences in inclusion and exclusion criteria, heterogeneity in baseline characteristics across studies, and notable reductions in sample sizes due to matching and weighting; thus, there was significant uncertainty about the overall generalizability of the results to the patient population living in Canada. Additionally, wide 95% CIs led to imprecision and uncertainty in the results.

Studies Addressing Gaps in the Systematic Review Evidence

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

Discussion

Summary of Available Evidence

One ongoing, phase I/II, open-label, single-arm study (the NP30179 study) was included in this review. The review for glofitamab was based on cohorts D2S2, D3, and D5 of the NP30179 study, which consisted of [redacted] with r/r DLBCL that has relapsed after or failed to respond to at least 2 prior systemic treatment regimens (including at least 1 prior regimen containing anthracycline and at least 1 containing an anti-CD20–directed therapy). The patients were treated with glofitamab monotherapy at the step-up recommended phase II dosage of 2.5 mg, then 10 mg, then 30 mg every 3 weeks. Patients were excluded if they had

received prior allogeneic SCT, or autologous SCT within 100 days of treatment. The primary end point of the NP30179 study was CR rate; the secondary end points were ORR, DOR, PFS, OS, HRQoL, and safety.[13]

At baseline, the patients included in the NP30179 study (cohorts D2S2, D3, and D5) were primarily white (76.6%) and male (64.9%) and had a median age of 66.0 years. Most patients had received 2 or 3 prior lines of therapy (70.7%) and had disease that was refractory to the last prior therapy (85.1%) and to prior anti-CD20 therapies (83.1%).[13]

One sponsor-submitted ITC report consisting of 2 separate ITC methodologies was summarized and critically appraised. Two ITCs were conducted: 1 comparing glofitamab from the NP30179 study to Pola-BR from the GO29365 study via PSA methods, and 1 comparing glofitamab from the NP30179 study to salvage chemotherapy from the SCHOLAR-1 study via MAIC. The outcomes evaluated in the PSA were OS, PFS, DOR, DOCR, CR, ORR, and discontinuation due to AEs, while the MAIC evaluated OS, ORR, and CR.[18]

No long-term extension studies or studies addressing gaps in the systematic review were included.

Interpretation of Results

Efficacy

Patients with DLBCL that is refractory to or relapses after first-line and second-line treatments have poor prognosis due to the aggressive and quickly progressing nature of the disease. Beyond established first-line therapies, treatment for r/r DLBCL is an evolving landscape, with novel CAR T-cell therapies currently emerging in both second-line and third-line settings, as well as Pola-BR recently being recommended as a third-line option ahead of salvage chemotherapy. The clinical experts consulted by CADTH and the clinician group input highlighted that other than Pola-BR, rituximab-based chemotherapies are currently the only remaining option; however, these are associated with significant toxicities, limiting their use. The clinical experts consulted by CADTH suggested that treatment at this stage of disease would likely be palliative, though glofitamab may replace Pola-BR as the preferred treatment option for such patients in Canada. Patients highlighted a considerable need for alternative treatments that can extend life and improve HRQoL.

The efficacy of glofitamab in patients with r/r DLBCL was assessed by the NP30179 phase I/II trial, which enrolled 155 patients with r/r DLBCL into 3 cohorts of interest to this review (cohorts D2S2, D3, and D5). The overall interpretation of the efficacy results from the NP30179 study was limited given the internal and external validity issues identified, led primarily by the single-arm, open-label design, which precludes the ability to attribute the study results to treatment with glofitamab. As noted in the GRADE assessment, conclusions about efficacy relative to any comparator cannot be drawn from single-arm studies; thus, the certainty of evidence is started at “very low” and cannot be rated up. Furthermore, the nonrandomized, early-phase study design of the NP30179 study makes the trial susceptible to selection bias. The clinical experts consulted by CADTH noted that the eligibility criteria suggested a population that was likely less sick than would be seen in the real world; for example, no patients with an ECOG PS of 2 or more were included, but these patients would be included in any available real-world data. However, there was a high proportion of patients with refractory disease, which may, conversely, suggest a sicker population.

As part of the NP30179 study, based on the results of nonclinical data, all patients also received pretreatment with obinutuzumab at the beginning of cycle 1 to minimize the risk of CRS. Obinutuzumab has not been previously studied in this patient population and is therefore not indicated for use in this population in Canada. Though the antitumour effect of obinutuzumab was considered negligible, as noted in the Health Canada reviewers report it is impossible to differentiate between the effects of obinutuzumab and glofitamab, further challenging the interpretation of the results.

Per the clinical experts consulted by CADTH and the patient group and clinician group input, improved survival was considered the most important outcome of treatment, with the clinical experts noting that landmark analyses (i.e., 12-month and 24-month event-free rates) were potentially more suggestive of benefit than median survival. No established thresholds of clinical importance for survival have been identified, though it was the clinical experts' opinion that the observed OS and PFS were potential improvements over the expected 3-month and 6-month PFS and OS for currently used treatments for r/r DLBCL. The median follow-up duration was 17.0 months for OS; however, because the results were based on an interim analysis with a limited number of survival events, the results for OS in the NP30179 study were considered immature and should be interpreted with caution. Though the certainty of evidence for OS and PFS was already rated "very low" by GRADE, the interim analysis of the NP30179 study further reduces the certainty of the survival estimates. Overall, due to the single-arm nature of the NP30179 trial, the ability to interpret the results for OS and PFS was significantly limited. Similar conclusions were drawn by Health Canada, reflected by the issuance of an NOC/c for this indication.

HRQoL was also considered an important outcome by patients, and improvement of HRQoL was identified as a treatment goal by clinicians. End points for HRQoL in the NP30179 study were secondary, and there was no prespecified analysis plan for HRQoL outcomes. These outcomes had high attrition rates, with dropouts upward of [redacted]% at cycle 5 and [redacted]% at the end of treatment assessment. As such, the evidence for the effects of glofitamab on HRQoL was considered by CADTH reviewers to have very low certainty and, as with OS and PFS, no firm conclusions could be made on the observed results.

The primary end point of the study, CR rate, was noted by the clinical experts consulted by CADTH to be greater than expected based on their clinical experience, with 40% of patients in the NP30179 experiencing CR. The clinical experts' opinion was that CRs are more important than PRs in large B-cell lymphomas, as PRs generally do not translate to delayed progression or improved survival outcomes. The current literature suggests some correlation between response and improved survival; however, the results are highly variable and have not specifically been studied in the population under review. The clinical experts also noted that DOR is important. The clinical experts considered the median DOR of 16.8 months to be noteworthy, again emphasizing that an estimated [redacted] remain in response at 12 months and 24-months, respectively. But as with the other time-to-event outcomes, DOR was considered by CADTH to not be evaluable given the very low certainty of the evidence from the NP30179 study.

In the absence of comparative evidence from a randomized trial, and to further contextualize the results of the NP30179 study, the sponsor submitted 2 ITCs, a PSA and a MAIC, to evaluate the comparative efficacy and safety of glofitamab. In the PSA compared to Pola-BR, there were notable differences between

studies; however, following adjustment, there was no difference between glofitamab and Pola-BR in efficacy, though there was a substantial decrease in the ESS. In the MAIC of glofitamab and salvage chemotherapy, glofitamab was favoured for all outcomes. However, given the limitations identified in the sponsor-submitted MAIC, including the overall heterogeneity in study design, inclusion and exclusion criteria, and baseline characteristics, as well as the reduction in sample sizes due to weighting resulting in uncertainty and imprecision in the results, it remained uncertain whether glofitamab provided additional benefits versus currently available therapies.

The NOC/c for glofitamab was granted on the condition that the sponsor provide Health Canada with the results of a phase III trial evaluating glofitamab plus gemcitabine and oxaliplatin compared to R-GemOx in r/r DLBCL. According to the clinical experts consulted by CADTH and the recently published provisional funding algorithm,[11] the most relevant comparator in the third-line r/r DLBCL treatment space is Pola-BR; the use of rituximab-based chemotherapy for a third time is very infrequent. In the sponsor's ITC, it was noted that 10 studies investigating R-GemOx had been identified but not included in any analyses based on histology (n = 5) or line of therapy (n = 5). In the MAIC, R-GemOx was likely included under the basket of salvage chemotherapy regimens in the comparator SCHOLAR-1 study; however, whether it was included is unclear.

Harms

Analysis of safety for glofitamab was based on the safety analysis set, which included 154 patients treated with glofitamab in the NP30179 study. Nearly all patients in the NP30179 study (152 [98.7%]) experienced an AE with glofitamab, though the clinical experts consulted by CADTH did not consider the list of AEs to be concerning, citing that most AEs are manageable and consistent with chemotherapies in this heavily pretreated population. However, the clinical experts also noted that the severity and the grade of individual AEs may be the most important factor in this population, particularly considering that patients enrolled in the trial were considered to have greater functioning than the population expected in clinical practice, according to the clinical experts. Overall, the frequency of grade 3 or higher AEs was high (98 patient [63.6%]); such AEs typically result in hospitalization and are therefore a concern. Within the patient group input, patients noted that they would be willing to tolerate side effects to access new treatment options.

Per the clinical experts consulted by CADTH, the most important AE for glofitamab is CRS, which was experienced in as many as 103 patients (66.9%). Though cases of CRS were high, they were also manageable, with most resolved by the CCOD; however, the clinical experts highlighted that these cases require experienced care in the proper settings, which restricts the use and availability of glofitamab in the Canadian landscape. Additionally, obinutuzumab was given to mitigate the risk of CRS; however, based on the design of the study, it is unclear what effect obinutuzumab had on CRS.

The safety of glofitamab compared with other relevant treatments for r/r DLBCL was not assessed in the single-arm NP301790 study. As such, the sponsor submitted an ITC to attempt to determine the safety of glofitamab compared to Pola-BR in terms of discontinuation of treatment due to AEs. The results of the ITC suggested that there was no difference between glofitamab and Pola-BR in discontinuations due to AEs; however, the results were uncertain given the wide 95% CI.

Conclusion

One phase I/II, single-arm, open-label trial (the NP30179 study) provided evidence for the efficacy and safety of glofitamab in adult patients with r/r DLBCL that has relapsed after or failed to respond to at least 2 prior systemic therapies. Clinicians and patients highlighted the need for accessible, alternative treatment options for patients in this setting. Improvements in survival were considered the most important outcomes of treatment by patients and clinicians. Although OS and PFS were evaluated in the study, the single-arm design and the immature data from limited follow-up preclude the ability to attribute the study results to treatment with glofitamab. Moreover, the short duration of the NP30179 study may result in survival being overestimated. Nonetheless, the study suggested that some patients (40%) will experience CR, which is likely a clinically important result, although the evidence is still uncertain. Though HRQoL was an outcome important to patients, due to the noncomparative design and high patient attrition rates in the NP30179 study, the effect of glofitamab on HRQoL remains uncertain. The harms associated with glofitamab were largely consistent with the mechanism of action, including a high frequency of patients who experienced CRS and serious infections. While all patients received pretreatment with obinutuzumab to mitigate the risk of CRS, given the high rate of CRS events, it remains unclear what effect obinutuzumab pretreatment had in reducing CRS. Despite the high CRS rates, most events were treated, and the side effect profile of glofitamab was considered manageable according to the clinical experts consulted by CADTH. The CADTH clinical assessment identified limitations with the sponsor's ITCs used to inform the comparative effectiveness and safety of glofitamab. There were no apparent differences in efficacy between glofitamab and Pola-BR in the PSA; however, substantial limitations in the MAIC — including small sample sizes, heterogeneity across study designs and included populations, the inability to adjust for important potential confounders and prognostic variables, and wide 95% CIs — substantially limited the ability to interpret the relative treatment effects observed between glofitamab and salvage chemotherapy. Overall, the evidence was very uncertain about the effects of glofitamab on any outcomes versus any comparator, and the ability to draw firm conclusions about the magnitude of clinical benefit of glofitamab was hindered by the limitations in the evidence.

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Appendix 1: Detailed Outcome Data

Note that this appendix has not been copy-edited.

Table 25: Summary of DOCR Results From the NP30179 Study (June 15, 2022, CCOD)

Outcome	Glofitamab (2.5/10/30 mg) q.3.w. Cohorts D2S2, D3, and D5 (n = 155)
IRC-assessed DOCR	
Number of complete responders	62
Responders with subsequent event, n (%)	[redacted]
Responders without subsequent event, n (%)	[redacted]
Median (95% CI), months	[redacted]
12-month event-free rate (95% CI)	[redacted]
24-month event-free rate (95% CI)	[redacted]
Investigator-assessed DOCR	
Number of complete responders	59
Responders with subsequent event, n (%)	[redacted]
Responders without subsequent event, n (%)	[redacted]
Median (95% CI), months	[redacted]
12-month event-free rate (95% CI)	[redacted]
24-month event-free rate (95% CI)	[redacted]

CI = confidence interval; DOCR = duration of complete response; IRC = independent review committee; NE = not estimable; q.3.w. = every 3 weeks.
Source: NP30179 Clinical Study Report.[13]

Table 26: Subgroup Analysis of IRC-Assessed CR Rate (ITT Population)

Subgroup	N (%)	CR, % (95% CI)
Overall	155 (100)	40 (32 to 48)
Prior CAR T-cell therapy		
Yes	52 (34)	37 (24 to 51)
No	103 (66)	42 (32 to 52)
NHL subtype		
DLBCL	110 (71)	40 (31 to 50)
HGBCL	10 (6)	10 (0 to 45)
PMBCL	6 (4)	50 (12 to 88)
trFL	29 (19)	48 (29 to 67)

Subgroup	N (%)	CR, % (95% CI)
Baseline ECOG performance status		
0	69 (45)	43 (32 to 56)
≥ 1	85 (55)	38 (27 to 49)
Unknown/Missing	1 (1)	0
Relapse or refractory to last prior therapy		
Refractory	131 (85)	35 (27 to 44)
Nonrefractory	24 (15)	67 (45 to 84)
Relapse or refractory to any prior anti-CD20 therapy		
Refractory	129 (83)	36 (28 to 45)
Nonrefractory	26 (17)	58 (37 to 77)
Relapse or refractory to any prior therapy		
Refractory	139 (90)	37 (29 to 46)
Nonrefractory	16 (10)	63 (35 to 85)
Prior autologous SCT		
Unknown	127 (82)	34 (26 to 43)
Refractory	7 (5)	71 (29 to 96)
Nonrefractory	21 (14)	67 (43 to 85)
Number of prior lines of therapies		
2	61 (39)	33 (21 to 46)
≥ 3	94 (61)	45 (34 to 55)

ABC = activated B-cell; BMI = body mass index; CAR = chimeric antigen receptor; CI = confidence interval; CR = complete response; DLBCL = diffuse large B-cell lymphoma; ECOG = Eastern Cooperative Oncology Group; GCB = germinal centre B-cell; HGBCL = high-grade B-cell lymphoma; IPI = International Prognostic Index; LDH = lactate dehydrogenase; NHL = non-Hodgkin lymphoma; PMBCL = primary mediastinal B-cell lymphoma; SCT = stem cell transplant; trFL = transformed follicular lymphoma.

Source: NP30179 Clinical Study Report.[13]

Pharmacoeconomic Review

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Abbreviations

BIA	budget impact analysis
CAR	chimeric antigen receptor
CI	confidence interval
CRS	cytokine release syndrome
DLBCL	diffuse large B-cell lymphoma
HR	hazard ratio
ICER	incremental cost-effectiveness ratio
OS	overall survival
pERC	pan-Canadian Oncology Review Expert Review Committee
PFS	progression-free survival
Pola-BR	polatuzumab vedotin, bendamustine, and rituximab
QALY	quality-adjusted life-year
R-GDP	rituximab plus gemcitabine, dexamethasone, and cisplatin
r/r	relapsed or refractory

Executive Summary

The executive summary comprises 2 tables (Table 1 and Table 2) and a conclusion.

Table 1: Submitted for Review

Item	Description
Drug product	Glofitamab (Columvi), concentrate for solution for IV infusion
Submitted price	Glofitamab (Columvi), 2.5 mg/2.5 mL vial: $1,040.00 per vial Glofitamab (Columvi), 10 mg/10 mL vial: $4,160.00 per vial
Indication	For the treatment of adult patients with relapsed or refractory DLBCL not otherwise specified, trFL, or PMBCL, who have received two 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
Health Canada approval status	NOC/c
Health Canada review pathway	Standard
NOC date	NOC/c received March 24, 2023
Reimbursement request	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, following obinutuzumab pretreatment
Sponsor	Hoffmann-La Roche Limited
Submission history	Previously reviewed: No

CAR = chimeric antigen receptor; DLBCL = diffuse large B-cell lymphoma; NOC = Notice of Compliance; NOC/c = Notice of Compliance with Conditions; PMBCL = primary mediastinal B-cell lymphoma; trFL = transformed follicular lymphoma; vs. = versus.

Table 2: Summary of Economic Evaluation

Component	Description
Type of economic evaluation	Cost-utility analysis Partitioned survival model
Target population	Patients with relapsed or refractory diffuse large B-cell lymphoma after at least 2 prior lines of therapy
Treatment	Glofitamab (Columvi)
Comparators	• 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), and GO29365 clinical trial (Pola-BR)

Component	Description
Submitted results	• The ICER for glofitamab vs. salvage chemotherapy is $33,342 per QALY gained (incremental costs of $82,604; incremental QALYs of 2.48) • Glofitamab is associated with lower costs (cost savings of $16,900) and higher QALYs (gain of 0.55) than Pola-BR (i.e., glofitamab is dominant)
Key limitations	• 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 relied on an adjusted indirect comparison to compare these treatments; the indirect comparison was associated with substantial limitations. Based on the available evidence, and in line with clinical expert feedback, glofitamab and Pola-BR were considered to be similarly effective. • 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. No justification for this result was provided by the sponsor. • There is discordance between the number of treatment cycles in the submitted economic evaluation and the submitted budget impact analysis, which underestimates the duration of treatment for glofitamab and Pola-BR. • 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.
CADTH reanalysis results	The CADTH base case was derived by making changes to the following model parameters: assumed equal efficacy between glofitamab and Pola-BR; revised 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: • 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]) Given the limitations, the overall uncertainty associated with the comparative clinical evidence, and the modelling techniques used by the sponsor, which limit the ability to validate the model, uncertainty remains that could not be accounted for in the model.

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

Conclusions

Evidence from the phase I/II, single-arm, open-label NP30179 trial indicated that patients receiving glofitamab may experience clinically important improvements in progression-free survival (PFS) and overall survival (OS), but due to the study design and immature data, it is unclear whether these results are attributable to glofitamab. While the CADTH review acknowledged that the proportion of patients experiencing complete response may be clinically important, the reviewers noted that the included population of patients may be less sick than patients likely to receive glofitamab in Canadian clinical practice and that the short duration of the NP30179 study may lead to survival outcomes being overestimated. The CADTH review also noted a high rate of cytokine release syndrome (CRS) events, such that it was unclear

whether pretreatment with obinutuzumab — which was used to mitigate CRS — had an effect on reducing CRS events. CADTH identified limitations with the sponsor's indirect comparisons, including the following: small sample sizes, heterogeneity across study designs and included populations, inability to adjust for important potential confounders and prognostic variables, and wide 95% confidence intervals (CIs). Given these limitations, the expected magnitude of any potential clinical benefit associated with glofitamab compared with salvage chemotherapy and with polatuzumab vedotin, bendamustine, and rituximab (Pola-BR) is uncertain.

Although the key limitations associated with the sponsor's economic evaluation predominantly relate to the aforementioned limitations with the clinical evidence, CADTH also identified several key limitations with the sponsor-submitted model, which led to concerns about the validity and reliability of the model results. CADTH revised assumptions with respect to relative efficacy, long-term disease progression, and mortality, following recommendations from the clinical experts, and adopted the same treatment costs in the economic evaluation as in the budget impact analysis (BIA).

Compared to salvage chemotherapy, glofitamab is associated with an incremental cost-effectiveness ratio (ICER) of $230,682 per quality-adjusted life-year (QALY) gained. A price reduction of at least 82% is required for glofitamab to be considered cost-effective at a willingness-to-pay threshold of $50,000 per QALY gained. The results are primarily driven by the assumptions relating to delay in disease progression and the cost of glofitamab.

Compared to Pola-BR, glofitamab is associated with lower costs and similar QALYs. This result aligned with clinical feedback that there is no robust evidence of clinical differences between glofitamab and Pola-BR. The expected proportion of patients currently treated with Pola-BR and salvage chemotherapy differed between the sponsor's submission and the clinical expert feedback obtained by CADTH. The results are primarily driven by the assumptions relating to delay in disease progression and the relative costs of glofitamab and Pola-BR. CADTH notes that a price reduction may still be required for glofitamab to be no more costly than Pola-BR, as the price of polatuzumab vedotin was based on the public list price, and the pan-Canadian Oncology Review Expert Review Committee (pERC) recommended the Pola-BR regimen for this indication with the condition of a price reduction for polatuzumab vedotin.

Stakeholder Input Relevant to the Economic Review

This section is a summary of the feedback received from the patient groups, registered clinicians, and drug plans that participated in the CADTH review process.

Patient input was received from Lymphoma Canada, which conducted an online anonymous patient survey with 27 respondents, 8 of whom (30%) resided in Canada. The patients ranged in age from 25 to 84 years; 30% were diagnosed 1 to 5 years ago; and 48% had diffuse large B-cell lymphoma (DLBCL) subtype. The majority of patients indicated they had received 1 (69%) or 3 or more (31%) lines of treatment to treat their large B-cell lymphoma. Front-line therapy included the following: rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone; dose-adjusted etoposide, prednisone, vincristine,

cyclophosphamide, doxorubicin, and rituximab; and doxorubicin, bleomycin, vinblastine, and dacarbazine plus radiation. Second-line therapy included the following: rituximab plus gemcitabine, dexamethasone, and cisplatin (R-GDP); salvage therapy plus autologous stem cell transplant and radiation. Third-line therapy included the following: chimeric antigen receptor (CAR) T-cell therapy; polatuzumab vedotin, rituximab, cyclophosphamide, doxorubicin, and prednisolone. The majority of patients (62%) indicated that they were very satisfied or satisfied with their front-line treatment, although this percentage decreased for second-line treatment options (39%) and third-line treatment options (31%). The most common financial implications of treatment reported by patients were drug costs (60% of patients), travelling costs (40% of patients), and absence from work (40% of patients). Of the survey respondents, 2 patients indicated that they were treated with glofitamab, with 1 patient treated less than 6 months ago and the other treated 3 to 5 years ago. One patient did not experience any side effects and the other experienced CRS, hypotension, and low platelet count. One patient experienced financial impacts from the cost of glofitamab, and the other experienced financial impact from the cost of supplemental medication during treatment. Overall, patients rated their experience with glofitamab as good and very good. Only 2 respondents provided feedback on what they are seeking from new treatments, although a previously published survey suggested that longer disease remission, longer survival, and improved quality of life were very important to patients.

CADTH received 2 registered clinician group input submissions for this review: 1 from the Ontario Health–Cancer Care Ontario Hematology Cancer Drug Advisory Committee and 1 from Lymphoma Canada. Ontario Health–Cancer Care Ontario noted that based on the recent CADTH provisional funding algorithm for DLBCL, there are no other treatment options for patients who are not eligible for CAR T-cell therapy and no treatment options other than Pola-BR for patients with disease that is relapsed or refractory (r/r) to prior treatment. The clinician group highlighted that treatment with glofitamab may be preferred to treatment with Pola-BR. Ontario Health–Cancer Care Ontario noted that centres that have expertise in managing CRS would be the most appropriate setting for treatment with glofitamab and that disease progression and toxicities should be considered when deciding to discontinue treatment. The Lymphoma Canada clinician group highlighted that, in Canada, not all provinces provide third-line CAR T-cell therapy and that access to local treatment centres is limited. The group noted that there is a substantial unmet need for new, effective, and well-tolerated treatments for patients with disease that progresses after CAR T-cell therapy as well as for patients who are ineligible for or unable to receive CAR T-cell therapy. The Lymphoma Canada clinician group agrees with the reimbursement request that patients who are eligible to receive CAR T-cell therapy would not be suitable for glofitamab. The group highlighted that glofitamab has a 12-cycle duration; however, it is generally well tolerated among patients.

The drug plan input for this review noted interest in whether patients with chronic lymphocytic leukemia, Burkitt lymphoma, or lymphoplasmacytic lymphoma, or who had received prior allogeneic stem cell transplant, should be considered for glofitamab, as they were excluded from the NP30179 study. CADTH-participating drug plans wondered if evidence exists to support re-treatment for an additional 12 cycles provided the re-treatment criteria from the trial were met and if patients with an Eastern Cooperative Oncology Group Performance Status greater than 1 should be considered eligible for treatment. Additionally, the drug plan input highlighted that obinutuzumab is not currently publicly funded for this indication and

that will need to be addressed if glofitamab is recommended for reimbursement. The drug plans noted the presence of confidential negotiated prices for comparators.

- The sponsor's model assesses the cost-effectiveness of glofitamab in the patient population aligned with the stakeholders' comments. CADTH could not address the generalizability to patients with other conditions (e.g., chronic lymphocytic leukemia, prior allogeneic stem cell transplant).
- Several areas of feedback were addressed in the sponsor's model, as the sponsor considered survival outcomes, adverse events, and relevant comparators.
- CADTH was unable to address feedback regarding treatment in an expanded patient population, the potential for re-treatment beyond 12 cycles, and potential clinical criteria considerations.

Economic Review

The current review is for glofitamab (Columvi) for patients with r/r DLBCL after at least 2 prior lines of therapy.

Economic Evaluation

Summary of Sponsor's Economic Evaluation

Overview

The sponsor submitted a cost-utility analysis to assess the cost-effectiveness of glofitamab compared to both salvage chemotherapy (rituximab-based regimens, represented as the R-GDP regimen by the sponsor) and Pola-BR.[1] The population modelled was patients with r/r DLBCL who had received at least 2 prior lines of therapy who are ineligible for or unable to access CAR T-cell therapy. This aligns with the Health Canada–indicated population.[2]

The intervention under review is glofitamab, which is given in 21-day cycles: 2.5 mg on day 8 and 10 mg on day 15 in the first cycle, and 30 mg on day 1 of each subsequent cycle for up to 12 cycles, unless discontinued earlier due to toxicity. In addition to glofitamab, patients will receive pretreatment with obinutuzumab 1,000 mg and premedication with acetaminophen 100 mg, diphenhydramine 50 mg, and prednisolone 100 mg as single doses on day 1. The costs for glofitamab are $5,479 for pretreatment, $5,200 in the first 21-day cycle, and $12,480 in subsequent cycles. Glofitamab is infused over 4 hours in cycles 1 and 2 and over 2 hours in cycles 3 through 12. Premedication obinutuzumab 1,000 mg should be infused at 50 mg per hour, which can be increased in 50 mg increments every 30 minutes to a maximum of 400 mg per hour.

Salvage chemotherapy is represented by R-GDP, which can be given for up to three 21-day cycles and comprises rituximab at a dose of 375 mg/m^2 IV on day 1 of each 21-day cycle, gemcitabine at a dose of 1,000 mg/m^2 IV on days 1 and 8 of each 21-day cycle, dexamethasone at a dose of 40 mg on days 1 to 4 of each 21-day cycle, and cisplatin at a dose of 75 mg/m^2 on day 1 of each 21-day cycle. The cost for R-GDP is $3,740 per cycle, based on the sponsor's assumptions relating to vial sharing.

Pola-BR is assumed to consist of no more than six 21-day cycles comprising polatuzumab vedotin at a dose of 1.8 mg/kg (total dose not recommended to exceed 240 mg), bendamustine at a dose of 90 mg/m^2 on days 1 and 2 of each cycle, and rituximab at a dose of 375 mg/m^2 IV on day 1 of each cycle. The cost for Pola-BR is $20,294 per cycle, based on the sponsor's assumptions relating to vial sharing.

Outcomes are modelled in terms of the proportion of patients each week who are progression-free on treatment, progression-free off treatment, and progressive disease. Analysis is conducted from a Canadian health care payer perspective, with a lifetime horizon of 20 years and a discount rate of 1.5% applied to both costs and benefits.

Model Structure

The submitted model takes the form of a partitioned survival model, which independently models the proportion of patients in the population who are progression-free on treatment, progression-free off treatment, have progressive disease, and are dead.

Partitioned survival models model the proportion of patients in each state, which are independent at specific times, rather than model the transition from 1 state to another. This requires the assumption that the proportion of the population who experience PFS is independent of the proportion of patients who remain on treatment. Similarly, partitioned survival models also require the assumption that the proportion of patients who remain alive is independent of the proportion of patients who are alive without progression.

Model Inputs

Due to the lack of head-to-head evidence comparing glofitamab with relevant comparators for patients with DLBCL, the sponsor presented indirect evidence comparing glofitamab with salvage chemotherapy (via a matched-adjusted indirect comparison) and Pola-BR (via a propensity score analysis). Due to the sponsor's approach, data for glofitamab differed for each comparison.

For the comparison with salvage chemotherapy, patients from cohorts D3, D5, and D2 (subcohort 2) from the NP30179 trial for glofitamab [redacted] are weighted to allow replication of the patient characteristics from the SCHOLAR-1 study, which comprised a pooled population of patients with refractory DLBCL from 2 phase III clinical trials (the Lymphoma Academic Research Organization [CORAL] study and the Canadian Cancer Trials Group [LY.12] study) and 2 observational cohorts (MD Anderson Cancer Center and University of Iowa/ Mayo Clinic Lymphoma Specialized Program of Research Excellence).[3,4] The patient population was weighted to match the SCHOLAR-1 study in terms of mean age, Eastern Cooperative Oncology Group Performance Status, disease stage, International Prognostic Index, histology, proportion of patients with disease that is refractory to the first line and last line of therapy, and proportion of patients who experienced early relapse after stem cell transplant. This approach reduces the effective sample size for glofitamab [redacted].

For the comparison with Pola-BR, the sponsor had access to individual patient data from the GO29365 clinical trial for Pola-BR [redacted].[5] The sponsor excluded patients with primary mediastinal large B-cell lymphoma histology from the glofitamab cohort, as no such patients were enrolled for Pola-BR [redacted]. Patient groups across the trials were balanced using propensity score matching and inverse probability treatment weighting. This approach reduces the effective sample size for glofitamab [redacted] and for Pola-BR [redacted].

The sponsor reported that, based on these analyses, glofitamab improved OS compared to salvage chemotherapy (hazard ratio [HR] = [redacted]; 95% CI, [redacted]), but no analysis pertaining to PFS was possible. Further analysis found that glofitamab was associated with a nonsignificant improvement in both OS (HR = [redacted]; 95% CI, [redacted]) and PFS (HR = [redacted]; 95% CI, [redacted]) when compared to Pola-BR.

Data from the matching-adjusted indirect comparison was used to estimate long-term OS and PFS curves for glofitamab for the comparison with salvage chemotherapy. The sponsor adopted a generalized gamma distribution based on a combination of visual inspection and model fit; for both curves, a generalized gamma distribution was adopted. For salvage chemotherapy, although the sponsor suggested that an independent approach using a lognormal distribution was adopted, the OS was obtained by weighting the OS curve for glofitamab by the HR derived from the indirect comparison (i.e., assuming a proportional hazard for the modelled time period). To obtain a PFS curve for salvage chemotherapy, as 1 could not be derived from the indirect comparison, the sponsor weighted the OS by an HR for PFS versus OS from the CORAL study.[6] The validity of this approach was not demonstrated by the sponsor. For all treatments, the estimated curves were used for the first 2 years in the model; after 2 years, the sponsor assumed no further progression and mortality as being equivalent to that of the general population. This has the indirect effect of assuming no deaths for patients who are progression-free up to 19 years and limited mortality in patients with disease that has progressed.

Data from the propensity score approach were used to estimate long-term OS and PFS curves for glofitamab for the comparison with Pola-BR. The sponsor adopted a generalized gamma distribution based on a combination of visual inspection and model fit. For Pola-BR, survival curves were obtained by the same approach, with generalized gamma distributions also adopted. The same assumptions used in the comparison with salvage chemotherapy were adopted beyond 2 years for the analysis comparing glofitamab with Pola-BR, which has the same implications for the analysis.

Time on treatment was based on trial data for glofitamab and Pola-BR and was set to be equal to PFS for salvage chemotherapy, to which the sponsor fit parametric distributions. The sponsor used this approach to estimate a mean of 5.5 cycles of glofitamab, 3.46 cycles of polatuzumab vedotin, 3.60 cycles of bendamustine, 3.77 cycles of rituximab, and 3.88 cycles of salvage chemotherapy. The sponsor noted that the time on treatment for glofitamab was derived from the unfiltered, unweighted pooled efficacy population from the NP30179 trial. As a result, the data represent a different patient population than the rest of the comparative evidence.

Utility values for patients who were progression-free when on treatment, progression-free when off treatment, and patients who had progressed disease were obtained by applying an algorithm to map European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 data to the 3-Level EQ-5D instrument to data from the NP30179 trial.[4,7] Future utility values are adjusted for age.[8]

The analysis includes the following costs: drug acquisition costs, drug administration costs, therapy after discontinuation of treatment, adverse event management, and supportive care. Both the model and the report are unclear as to how drug acquisition costs are considered. The report implies that perfect vial sharing is both implemented and not implemented in the base case. Within the model, it was assumed that

for 5% of patients any leftover drugs within a vial would be used for later patients and for 95% it would be wasted. Other cost categories appear appropriately valued and have little impact on the results.

Summary of Sponsor's Economic Evaluation Results

The sponsor submitted probabilistic analyses with 1,000 replications. The sponsor also presented deterministic analyses, which did not align with the probabilistic results. The sponsor suggested that this was due to uncertainty associated with treatment efficacy. CADTH noted that the uncertainty associated with treatment efficacy does not appear to fully address the concern because for the comparison of glofitamab to salvage chemotherapy, the sponsor's deterministic estimate for the total QALYs with glofitamab was 4.56, but only 9% of replications were above this value. Similar findings occurred with other estimated outcomes. This finding represents a major inconsistency between the 2 results. Thus, given the concerns relating to the probabilistic findings, CADTH presented the deterministic results below.

Base-Case Results

Based on the deterministic analysis, glofitamab was associated with higher costs ($191,309 versus $87,461) and greater QALYs (4.56 versus 1.82) than salvage chemotherapy (R-GDP). This leads to an estimated ICER of $37,859. Glofitamab was found to be associated with lower costs ($149,913 versus $166,886) and greater QALYs (3.66 versus 3.17) than Pola-BR (Table 3); in other words, glofitamab was dominant.

The incremental QALYs for glofitamab when compared to salvage chemotherapy arise due to increased time in PFS and increased time with progressed disease for glofitamab. The incremental costs associated with glofitamab arise mainly due to increased treatment costs and to higher costs for progressed disease due to the increased time in this state.

The incremental QALYs for glofitamab when compared to Pola-BR arise due to increased time in PFS, though this is partially offset by the increased time with progressed disease for Pola-BR. The incremental costs associated with Pola-BR arise due to increased treatment, adverse event, and progressed disease costs.

For the comparison with salvage chemotherapy, the proportion of QALY gains that fall within the time frame of the trial (assumed as 24 months) and within the median duration of treatment (assumed as 6 months) were 12.7% and 1.6%, respectively. For the comparison with Pola-BR, the proportion of QALY gains that fall within the time frame of the trial was 9.1%, but glofitamab was associated with fewer QALY gains (0.06 fewer QALYs) than Pola-BR over the assumed 6-month duration of treatment.

At the end of the 20-year model time horizon, for the comparison with salvage chemotherapy, 21% of patients receiving glofitamab are estimated to be alive, all of whom are assumed to have progression-free disease (for salvage chemotherapy, 7% are estimated, all of whom have progression-free disease). At the end of the 20-year time horizon, for the comparison with Pola-BR, 16% of patients receiving glofitamab are estimated to be alive, all of whom are assumed to have progression-free disease (for Pola-BR, 14% are estimated to be alive, all of whom have progression-free disease). The submitted analysis is based on the publicly available prices of the comparator treatments.

Table 3: Summary of the Sponsor's Economic Evaluation Results — Deterministic

Drug	Total costs ($)	Incremental costs ($)	Total QALYs	Incremental QALYs	ICER vs. reference ($/QALY)
Pairwise analysis 1 (glofitamab vs. salvage chemotherapy)					
Salvage chemotherapy (R-GDP)	87,461	Reference	1.82	Reference	Reference
Glofitamab	191,309	103,847	4.56	2.74	37,859
Pairwise analysis 2 (glofitamab vs. Pola-BR)					
Pola-BR	166,886	Reference	3.17	Reference	Reference
Glofitamab	149,913	−16,973	3.66	0.49	Dominant

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

Source: Sponsor's pharmacoeconomic submission.[1]

Sensitivity and Scenario Analysis Results

Scenario analyses were conducted for both comparisons, focusing on vial sharing, utility data, assumptions relating to progression after 2 years, discount rate, mortality risk, and chosen survival functions for OS and PFS. The results are consistent across most scenario analyses. For the comparison with salvage chemotherapy, the ICER exceeded $50,000 per QALY when the assumption relating to no mortality in patients who are progression-free was removed, and for the adoption of alternative survival distributions for PFS (exponential, Weibull and Gompertz). For the comparison with Pola-BR, glofitamab was no longer dominant, with an ICER exceeding $50,000 per QALY for the adoption of alternative survival functions for PFS (exponential) and OS (exponential). Analyses combining different scenarios are not presented, and no subgroup analyses are presented. No scenario analyses were conducted using a perspective other than the health care payer.

CADTH Appraisal of the Sponsor's Economic Evaluation

CADTH identified several key limitations to the sponsor's analysis that have notable implications for the economic analysis:

- **Uncertain comparative clinical evidence for glofitamab compared with Pola-BR:** The sponsor's analysis relies heavily on the extrapolation of clinical evidence from 2 small-sample, short-term, nonrandomized, early-phase studies (1 for glofitamab and 1 for Pola-BR) and long-term evidence sourced from phase III data and real-world evidence for salvage chemotherapy. As there is no direct head-to-head evidence comparing these treatments, the sponsor assessed these treatments via indirect comparisons. CADTH identified several concerns with the indirect comparisons, including the limitations related to the NP30179 trial of glofitamab, which were perpetuated through the indirect comparisons and small effective sample sizes. To address the substantial differences in the patient characteristics between the studies, the small sample sizes of patients in the studies were further reduced to allow for adequate matching of characteristics between groups. In addition, the short-term nature of the data for glofitamab and Pola-BR led to concerns regarding the long-term

comparative effectiveness estimates. The proportion of QALY gains for glofitamab that arise during the treatment period, the time horizon of the clinical trial, and the entire time horizon presented in the summary of the sponsor's base case highlight uncertainty in the estimates of long-term outcomes. Based on the CADTH appraisal, the propensity score analysis suggested no difference between glofitamab and Pola-BR for any outcomes evaluated before or after adjustment via full matching or the inverse probability treatment weighting approach. This result aligned with clinical expert feedback obtained by CADTH, which concurred that there is no robust evidence to suggest that glofitamab is associated with greater clinical benefit than Pola-BR.

  - CADTH assumed the same PFS and OS curves for glofitamab and Pola-BR.

- **Overestimated long-term survival assumptions:** The sponsor assumes that if a patient's disease does not progress within the first 2 years after treatment initiation, it will not progress after that time point. After this 2-year time point, the sponsor assumes the mortality rate for all patients is equivalent to that of the general population. These assumptions result in the proportion of patients who are progression-free remaining constant after 2 years (i.e., implying they have no risk of dying), and it is assumed that the mortality rate after 2 years in patients with progressed disease approximates that of the general population. The clinical experts consulted by CADTH suggested that these assumptions lack clinical plausibility and that patients who are progression-free at 2 years post–treatment initiation still experience disease progression, though at a slower rate of progression. Further, patients with disease that remains progression free have a risk of mortality higher than the general population, and mortality in patients with progressed disease will be much higher than that of the general population.
  - CADTH assumed, for the comparison between glofitamab and salvage chemotherapy, a continuing if lower rate of progression and mortality data informed by the chosen survival distributions. The PFS and OS curves were estimated based on adopting generalized gamma distributions for the time horizon of the model. A scenario analysis using a gamma distribution for PFS was conducted and suggested a less rapid decline in the probability of progression, but that did not impact the overall findings.
- **Model fails to capture causal relationships appropriately:** The sponsor's model does not adequately capture the causal relationships between patient characteristics and the probability of progression and death. It is necessary that the chosen model structure directly consider these relationships or bias will be introduced. The clinical experts consulted by CADTH suggested that once treatment is stopped, event rates when progression-free (preprogression mortality and progression) will eventually become equivalent between initial treatments. The partitioned survival model structure adopted within this submission does not allow for such an approach and assumes that the risk of mortality can be estimated independently from the probability of having progressed disease. The clinical experts consulted by CADTH confirmed that there was no robust evidence to suggest that there should be a difference between initial treatments in outcomes after disease has progressed, although they considered that it may be plausible to assume some treatment benefit for up to 2 years beyond treatment completion. Thus, for treatments that delay progression, outcomes postprogression (e.g.,

estimated QALYs) should be equal to or worse than treatment alternatives unless justification is provided. Within the sponsor's analysis, QALYs gained postprogression are shown to be greater for glofitamab than for to salvage chemotherapy, but no justification for this is provided.

  - To address these concerns with the model structure, CADTH adopted 2 assumptions for the comparison of glofitamab and salvage chemotherapy, which were validated based on feedback from clinical experts obtained by CADTH.

    First, CADTH assumed the probability of progression would trend toward being equal regardless of treatment after 2 years post–treatment curtailment. Given the limitations of the model structure in not explicitly modelling patients who are progression-free on and off treatment, CADTH took a simplifying assumption whereby the probability of progression after 30 months was the same for glofitamab and salvage chemotherapy and the probability began to converge after 18 months through linear interpolation.

    Second, CADTH assumed the same outcomes (costs and QALYs) postprogression for patients who survive to this state for both salvage chemotherapy and glofitamab. To facilitate this analysis, CADTH estimated the proportion of patients who would die before progression for both treatments based on data from the NP30179 trial and the expected undiscounted time in the progression-free state from the sponsor's model. From this, CADTH estimated the expected outcomes for a patient who developed progressed disease. This was further adjusted to allow for the later time to progression for glofitamab by applying the ratio of the discount factor for the mean time to progression with salvage chemotherapy to the discount factor for the mean time to progression with glofitamab.

- **Discordance between the BIA and the economic evaluation with respect to treatment costs:** The expected number of doses for each treatment regimen varies between the BIA and the economic evaluation. Within the BIA, the expected number of treatment cycles was 6.5 for glofitamab and, for Pola-BR, 4.44 for polatuzumab vedotin and 4.51 for bendamustine and rituximab. These values were derived from mean data from the NP30179 and GO29365 trials. This differs from the number of cycles within the economic evaluation, which were estimated by fitting a survival curve to treatment continuation data: 5.5 cycles for glofitamab, 3.46 for polatuzumab vedotin, 3.60 for bendamustine, and 3.77 for rituximab. For salvage chemotherapy, the BIA assumed that treatment would be given for 3 cycles as per Cancer Care Ontario recommendations. Within the economic evaluation, the mean number of cycles was 3.88. In addition to discordance in treatment doses between the BIA and the economic evaluation, there is confusion over the sponsor's assumptions regarding vial sharing. Within the sponsor's submitted report, it is stated in 1 instance that full vial sharing is incorporated (as per the BIA), but in another instance it is stated that vial sharing is not incorporated. In the model, it was assumed that for 5% of patients any unused drug within a vial would be used for later patients and for 95% of patients any unused drug would be wasted.
  - Given the lack of clarity regarding vial sharing within the economic evaluation and the discordance associated with duration of treatment, the CADTH base case adopted the expected

treatment costs from the BIA. CADTH noted that the budget impact duration of treatment better aligned with PFS curves.

- **Model results are unreliable and lack validity:** CADTH identified several limitations with the submitted model that inhibit validation of the model and lead to concerns regarding the reliability of the results. In addition to the issues already highlighted in this section and Appendix 2, the sponsor's submitted model included numerous CHOOSE, INDIRECT, INDEX, and OFFSET statements. While the sponsor agreed to remove IFERROR and ISERROR statements throughout the model, the systematic use of these additional statements makes thorough auditing of the sponsor's model impractical.
  - CADTH was unable to address this limitation and notes that a thorough validation of the sponsor's model was not possible.

Table 4: Key Assumptions of the Submitted Economic Evaluation (Not Noted as Limitations to the Submission)

Sponsor's key assumption	CADTH comment
R-GDP was assumed to be representative of salvage chemotherapy.	While there may be numerical differences between salvage chemotherapy treatments, the use of R-GDP was considered reasonable.
Utility values vary by whether patients remain on primary treatment or not and whether they have experienced disease progression or not.	Reasonable.
Analysis assumes the same treatments postprogression.	This appears appropriate but further questions the assumption of differential outcomes postprogression.

R-GDP = rituximab plus gemcitabine, dexamethasone, and cisplatin.

CADTH Reanalyses of the Economic Evaluation

Base-Case Results

CADTH reanalyses were derived by making changes to model parameter values and assumptions in consultation with clinical experts. The following changes were made to address several limitations within the economic model: assuming the same PFS and OS curves for Pola-BR and glofitamab; using the generalized gamma distribution to extrapolate PFS and OS for salvage chemotherapy; removing the assumption of cure after 2 years progression free; revising the time on treatment for all treatments to align with the mean trial doses used in the BIA; and assuming no difference in outcomes for patients who experience disease progression for the comparison of salvage chemotherapy and glofitamab. These changes are summarized in Table 5. CADTH focused on pairwise comparisons for glofitamab versus salvage chemotherapy and for glofitamab versus Pola-BR and conducted the analyses deterministically given the identified uncertainty with the sponsor's probabilistic analysis.

Table 5: CADTH Revisions to the Submitted Economic Evaluation

Stepped analysis	Sponsor's value or assumption	CADTH value or assumption
Corrections to sponsor's base case		
None	—	—
Changes to derive the CADTH base case		
1. Comparative effectiveness for glofitamab compared with Pola-BR	Sponsor assumes benefit for glofitamab vs. Pola-BR in terms of progression-free and overall survival.	CADTH assumes equal progression-free and overall survival for glofitamab and Pola-BR.
2. Long-term survival	Sponsor assumes no progression in disease after 2 years, no mortality in patients who are progression free after 2 years, and the mortality rate after 2 years for patients with progressed disease to only be slightly higher than that of the general population.	For the comparison of glofitamab vs. salvage chemotherapy, CADTH assumed that there would be a declining probability of progression for the time horizon of the model based on a generalized gamma survival distribution. For the comparison of glofitamab vs. salvage chemotherapy, CADTH assumed mortality rates could be modelled based on the same approach as for the first 2 years.
3. Model fails to capture causal relationships appropriately	Sponsor assumes a continued benefit from treatment long after treatment curtailment and that the probability of mortality is independent of treatment status and disease status.	CADTH assumed the impact of initial treatment on the probability of progression would decline over time, with the same probability of progression after 2 years. For the comparison of glofitamab and salvage chemotherapy, the probability of progression would be equivalent across treatments after 30 months. CADTH assumed that outcomes postprogression would be the same regardless of initial treatment for patients with progressed disease.[a]
4. Discordance between the BIA and the economic evaluation with respect to treatment costs	Number of doses is based on modelled time to treatment discontinuation for glofitamab and Pola-BR and on progression-free survival for salvage chemotherapy. There was a lack of clarity as to whether and how vial sharing was incorporated.	CADTH adopted the mean number of doses from the relevant clinical trials and from Cancer Care Ontario guidelines in line with the sponsor's BIA. In line with the BIA, it was assumed that vial sharing was considered for a proportion of patients.
CADTH base case	—	For glofitamab vs. salvage chemotherapy: 2 + 3 + 4 For glofitamab vs. Pola-BR: 1 + 4

BIA = budget impact analysis; Pola-BR = polatuzumab vedotin, bendamustine, and rituximab; vs. = versus.

[a]CADTH did this by taking the undiscounted time in progression-free survival to determine a progression rate and a mortality rate (the latter derived from the 8 of 98 progression-free survival events due to death, per the CADTH clinical report) and determining the proportion of patients alive at progression for each group to derive an adjustment factor, to which discounting is then applied. This weighting is then applied to glofitamab based on number of life-years in postprogression for chemotherapy to derive the time in postprogression for glofitamab.

In the CADTH reanalysis, glofitamab was less costly than Pola-BR ($158,322 versus $169,708) and associated with similar QALYs (3.66 versus 3.66). The ICER for Pola-BR versus salvage chemotherapy is $2,281,494 per QALY gained. Due to the limitations with the sponsor's probabilistic analysis, CADTH could

not assess the probability that glofitamab would be considered the cost-effective option at a willingness-to-pay threshold of $50,000 per QALY gained. The biggest drivers of the results are the relative treatment costs (Table 6).

In the CADTH reanalysis, glofitamab was more costly than salvage chemotherapy ($147,749 versus $69,901) and associated with greater QALYs (1.17 versus 0.83), resulting in an ICER of $230,682 per QALY gained. Due to the limitations with the sponsor's probabilistic analysis, CADTH could not assess the probability that glofitamab would be considered the cost-effective option at a willingness-to-pay threshold of $50,000 per QALY gained. The biggest drivers of the results are the relative efficacy of glofitamab versus salvage chemotherapy in time to progressive disease and the costs of glofitamab.

Table 6: Summary of the Stepped Analysis of the CADTH Reanalysis Results

Stepped analysis	Drug	Total costs ($)	Total QALYs	ICER ($/QALY)
Pairwise analysis 1 (glofitamab vs. salvage chemotherapy [R-GDP])				
Sponsor's base case	Salvage chemotherapy (R-GDP)	87,461	1.82	Reference
	Glofitamab	191,309	4.56	37,859
CADTH reanalysis 2	Salvage chemotherapy (R-GDP)	69,552	0.83	Reference
	Glofitamab	196,623	2.82	63,898
CADTH reanalysis 3	Salvage chemotherapy (R-GDP)	87,461	1.82	Reference
	Glofitamab	150,600	3.54	36,579
CADTH reanalysis 4	Salvage chemotherapy (R-GDP)	87,811	1.82	Reference
	Glofitamab	199,718	4.56	40,797
CADTH base case: 2 + 3 + 4	Salvage chemotherapy (R-GDP)	69,901	0.83	Reference
	Glofitamab	147,749	1.17	230,682
Pairwise analysis 2 (glofitamab vs. Pola-BR)				
Sponsor's base case	Glofitamab	149,913	3.66	Reference
	Pola-BR	166,886	3.17	Dominated
CADTH reanalysis 1	Glofitamab	149,913	3.66	Reference
	Pola-BR	157,880	3.66	1,596,511
CADTH reanalysis 4	Glofitamab	158,322	3.66	Reference
	Pola-BR	178,893	3.17	Dominated
CADTH base case: 1 + 4	Glofitamab	158,322	3.66	Reference
	Pola-BR	169,708	3.66	2,281,494

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

Note: CADTH reanalyses are based on publicly available prices of the comparator treatments.

Scenario Analysis Results

When compared to salvage chemotherapy, the cost of glofitamab would need to be reduced by approximately 83% for glofitamab to be cost-effective based on a willingness-to-pay threshold of $50,000 per QALY gained (Table 7). Based on publicly available prices, no price reduction is required for glofitamab compared to Pola-BR.

A scenario analysis was conducted based on assuming a gamma distribution for PFS for the comparison with Pola-BR. In this scenario, glofitamab is associated with lower costs ($263,012 versus $274,392) and fewer QALYs (3.33 versus 3.34); resulting in an ICER for Pola-BR versus glofitamab of $2,275,153 per QALY gained.

Table 7: CADTH Price Reduction Analyses

Analysis	ICERs for glofitamab vs. salvage chemotherapy ($/QALY)	
Price reduction	**Sponsor base case**	**CADTH reanalysis**
No price reduction	37,859	230,682
10%	35,473	208,801
20%	33,088	186,921
30%	30,702	165,040
40%	28,317	143,159
50%	25,931	121,279
60%	23,546	99,398
70%	21,160	77,517
80%	18,775	55,637
90%	16,390	33,756

ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life-year; vs. = versus.

Issues for Consideration

- The provision of glofitamab is reliant on the availability and coverage of obinutuzumab, which must be provided as a pretreatment for patients to receive glofitamab.
- Results are presented based on publicly available prices. Polatuzumab vedotin was recommended with the condition of a price reduction, as part of which pERC noted that the ICERs estimated by the sponsor and CADTH likely underestimated the ICER. CADTH identified substantial limitations with the sponsor's economic evaluation that precluded a base case but noted that a price reduction of between 35% and 84% may be required for polatuzumab vedotin to be considered cost-effective at a $50,000 per QALY gained threshold.
- Glofitamab received a Notice of Compliance with Conditions on March 24, 2023. The Notice of Compliance with Conditions was granted on the condition that the sponsor commit to submitting the results of the confirmatory phase III study of glofitamab plus gemcitabine and oxaliplatin compared to rituximab plus dexamethasone, cytarabine, and cisplatin in r/r DLBCL and acknowledge that

marketing authorization may be revoked if the trial fails to demonstrate an improvement in OS. CADTH notes that the regimen and studied population for the confirmatory trial differ to the regimen and population for glofitamab currently under review.

Overall Conclusions

Evidence from the phase I/II, single-arm, open-label NP30179 trial indicated that patients may experience clinically important improvements in PFS and OS but that, due to the study design and immature data, it is unclear whether these results are attributable to glofitamab. While the CADTH review acknowledged that the proportion of patients experiencing complete response may be clinically important, the reviewers noted that the included population of patients may be less sick than patients likely to receive glofitamab in Canadian clinical practice and that the short duration of the NP30179 study may lead to survival outcomes being overestimated. The CADTH review also noted a high rate of CRS events, such that it was unclear whether pretreatment with obinutuzumab — which was used to mitigate CRS — had an effect on reducing CRS events. CADTH identified limitations with the sponsor's indirect comparisons, including the following: small sample sizes, heterogeneity across study designs and included populations, the inability to adjust for important potential confounders and prognostic variables, and wide 95% CIs. Given these limitations, the expected magnitude of any potential clinical benefit associated with glofitamab compared with salvage chemotherapy and Pola-BR is uncertain.

Although the key limitations associated with the sponsor's economic evaluation predominantly relate to the aforementioned limitations with the clinical evidence, CADTH also identified several key limitations with the sponsor-submitted model that led to concerns with the validity and reliability of the model results. CADTH revised assumptions with respect to relative efficacy, long-term disease progression, and mortality, following recommendations from the clinical experts, and adopted the same treatment costs in the economic evaluation as in the BIA.

Compared to salvage chemotherapy, glofitamab is associated with an ICER of $230,682 per QALY gained. A price reduction of at least 82% is required for glofitamab to be considered cost-effective at a willingness-to-pay threshold of $50,000 per QALY gained. Results are primarily driven by the assumptions relating to delay in disease progression and the cost of glofitamab. Compared to Pola-BR, glofitamab is associated with lower costs and similar QALYs. This aligned with clinical feedback that there is no robust evidence of a clinical difference between glofitamab and Pola-BR. The expected proportion of patients currently being treated with Pola-BR and salvage chemotherapy differed between the sponsor's submission and clinical expert feedback obtained by CADTH.

The results are primarily driven by the assumptions relating to delay in disease progression and the relative costs of glofitamab and Pola-BR. CADTH notes that a price reduction may still be required for glofitamab to be no more costly than Pola-BR, as the price of polatuzumab vedotin was based on the public list price, and pERC recommended the Pola-BR regimen for this indication with the condition of a price reduction for polatuzumab vedotin.

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Appendix 1: Cost Comparison Table

Note that this appendix has not been copy-edited.

The comparators presented in the following table have been deemed to be appropriate based on feedback from clinical experts and drug plan. Comparators may be recommended (appropriate) practice or actual practice. Existing Product Listing Agreements are not reflected in the table and as such, the table may not represent the actual costs to public drug plans.

Table 8: CADTH Cost Comparison Table for 3L or Later r/r DLBCL (Pola-BR and Glofitamab)

Treatment	Strength / concentration	Form	Price	Recommended dosage	Cost per cycle or 1-time use ($)	Cost per 28 days ($)
Glofitamab						
Glofitamab (Columvi)	2.5 mg/mL vial 10 mg/mL vial	IV infusion	1,040.0000[a] 4,160.0000[a]	21-day cycles: 2.5 mg on day 8 and 10 mg on day 15 of cycle 1. 30 mg on day 1 for cycles 2 to 12.	Initial cycle: 5,200 Subsequent cycles: 12,480	Initial cycle: 6,933 Subsequent cycles: 16,640
Obinutuzumab (Gazyva)	40 mL vial	25 mg/mL solution for infusion	5,477.8400[b]	Premedication: 1,000 mg dose on day 1 of cycle 1.	5,478	7,304
Prednisone (generic)	5 mg 50 mg	Tab	0.0220 0.1735	Premedication: 100 mg on day 8 and 15 for cycle 1. 100 mg on day 1 for cycles 2 to 12.	1	1
Glofitamab regimen cost (21-day cycle)					Initial cycle: 10,679 Subsequent cycles: 12,480	Initial cycle: 14,238 Subsequent cycles: 16,640
Pola-BR						
Polatuzumab (Polivy)	140 mg vial	Lyophilized powder	14,750.0000[b]	21-day cycles: 1.8 mg/m^2 on day 1	14,750	19,667
Bendamustine (generic)	25 mg vial 100 mg vial	Lyophilized powder	250.0000[b] 1,000.0000[b]	21-day cycles: 90 mg/m^2 on day 1 and 2	3,500	4,667
Rituximab (biosimilars)	100 mg vial	IV infusion	297.0000	21-day cycles: 375 mg/m^2 on day 1	2,376	3,168
Pola-BR regimen cost (21-day cycle)					20,626	27,501

3L = third-line; DLBCL = diffuse large B-cell lymphoma; Pola-BR = polatuzumab vedotin plus bendamustine plus rituximab; r/r = relapsed or refractory.

Note: All prices are from the Ontario Drug Benefit Formulary (accessed September 2023), unless otherwise indicated, and do not include dispensing fees.[9]

[a]Sponsor-submitted pricing.[1]

[b]Drug prices from IQVIA (accessed September 2023).[10]

Table 9: CADTH Cost Comparison Table for 3L or Later r/r DLBCL (Salvage Chemotherapy)[a]

Treatment	Strength / concentration	Form	Price ($)	Recommended dosage	Cost per cycle or 1-time use ($)	Cost per 28 days ($)
Salvage chemotherapy						
R-GDP						
Rituximab (biosimilars)	100 mg vial	IV infusion	297.0000	21-day cycles: 375 mg/m^2 on day 1	2,079	2,772
Gemcitabine (generic)	1,000 mg 2,000 mg	Lyophilized powder	270.0000[b] 540.0000[b]	21-day cycles: 1,000 mg/m^2 days 1 and 8	1,080	1,440
Dexamethasone (generics)	4 mg	Tablet	0.6112	21-day cycles: 40 mg days 1 to 4	24	33
Cisplatin (generic)	50 mg vial 100 mg vial	1 mg/mL solution for injection	135.0000[b] 270.0000[b]	21-day cycles: 75 mg/m^2 on day 1	405	540
R-GDP regimen cost (21-day cycle)					3,588	4,785
R-ICE						
Rituximab (biosimilars)	100 mg vial	IV infusion	297.0000	21-day cycles: 375 mg/m^2 on day 1	2,079	2,772
Ifosfamide (Ifex)	1,000 mg vial 3,000 mg vial	Powder for solution	143.8700[b] 440.5899[b]	21-day cycles: 1,667 mg/m^2 on days 1 to 3	1,753	2,338
Carboplatin (generic)	50 mg 150 mg 450 mg 600 mg	10 mg/mL vial for injection	70.0000[b] 210.0000[b] 600.0000[b] 775.0020[b]	21-day cycles: AUC 5 on day 1; maximum dose for AUC 5 is 750 mg	Max: 1,050	1,400
Etoposide (generic)	100 mg	20 mg/mL vial for injection	75.0000[b]	21-day cycles: 100 mg/m^2 on days 1 to 3	450	600
R-ICE regimen cost (21-day cycle)					5,564	7,419
R-DHAP						
Rituximab (biosimilars)	100 mg vial	IV infusion	297.0000	21- or 28-day cycles: 375 mg/m^2 on day 1	2,079	2,079 to 2,772
Dexamethasone (generics)	4 mg	Tablet	0.6112	21-day cycles: 40 mg days 1 to 4	24	33
Cytarabine (generic)	500 mg vial 2,000 mg vial	100 mg/mL IV solution	76.8500[b] 306.5000[b]	21- or 28-day cycles: 2,000 mg/m^2 every 12 hours on day 2	1,230	1,230 to 1,639

Treatment	Strength / concentration	Form	Price ($)	Recommended dosage	Cost per cycle or 1-time use ($)	Cost per 28 days ($)
Cisplatin (generic)	50 mg vial 100 mg vial	1 mg/mL IV solution	135.0000[b] 270.0000[b]	21- or 28-day cycles: 100 mg/m^2 on day 1	540	540 to 720
R-DHAP regimen cost (21- or 28-day cycle)					3,873	3,873 to 5,164
R-DICEP						
Rituximab (biosimilars)	100 mg vial	IV infusion	297.0000	21- or 28-day cycles: 375 mg/m^2 on day 1	2,079	2,079 to 2,772
Dexamethasone (generics)	4 mg	Tablet	0.6112	21-day cycles: 40 mg days 1 to 4	24	33
Etoposide (generic)	100 mg	20 mg/ mL vial for injection	75.0000[b]	21-day cycles: 100 mg/m^2 on days 1 to 3	450	600
Cisplatin (generic)	50 mg vial 100 mg vial	1 mg/mL IV solution	135.0000[b] 270.0000[b]	21- or 28-day cycles: 100 mg/m^2 on day 1	540	540 to 720
Cyclophosphamide (Procytox)	500 mg vial 1,000 mg vial 2000 mg vial	Powder for injection	101.7100[b] 184.3600[b] 339.2000[b]	21-day cycles: 750 mg/m^2 on day 1	339	452
R-DICEP regimen cost (21- or 28-day cycle)					3,432	3,704 to 4,474
R-GemOx						
Gemcitabine (generics)	1,000 mg vial 2000 mg vial	Vial for injection	270.0000[b] 540.0000[b]	14-day cycles: 1,000 mg/m^2 on day 1	540	1,080
Oxaliplatin (generics)	100 mg vial 200 mg vial	Vial for injection	90.0000[b] 180.0000[b]	14-day cycles: 100 mg/m^2 on day 1	145	290
Rituximab (biosimilars)	100 mg vial	IV infusion	297.0000	14-day cycles: 375 mg/m^2 on day 1	2,376	4,752
R-GemOx regimen cost (21-day cycle)					3,061	6,122

3L = third-line; DLBCL = diffuse large B-cell lymphoma; R-DHAP = rituximab plus dexamethasone plus cytarabine plus cisplatin; R-DICEP = rituximab plus dexamethasone plus cytarabine plus cisplatin; R-GDP = rituximab plus gemcitabine plus dexamethasone plus cisplatin; R-GemOx = rituximab plus dexamethasone plus cytarabine plus cisplatin; R-ICE = rituximab plus ifosfamide plus carboplatin plus etoposide; r/r = relapsed or refractory.

Note: All prices are from the Ontario Drug Benefit Formulary (accessed September 2023), unless otherwise indicated, and do not include dispensing fees.[9]

[a]Salvage chemotherapy regimen dosages derived from Cancer Care Ontario.[11-14]

[b]Drug prices from IQVIA (accessed September 2023).[10]

Appendix 2: Submission Quality

Note that this appendix has not been copy-edited.

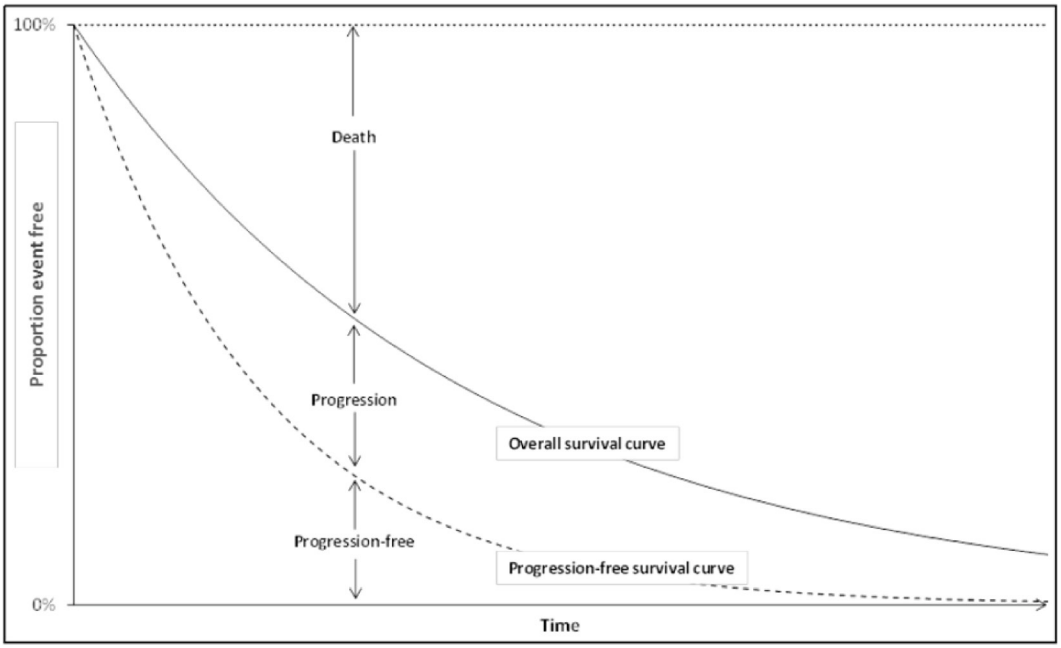
Table 10: Submission Quality

Description	Yes or no	Comments
Population is relevant, with no critical intervention missing, and no relevant outcome missing	Yes	—
Model has been adequately programmed and has sufficient face validity	No	Refer to CADTH appraisal. CADTH noted a thorough validation of the sponsor's model was not possible.
Model structure is adequate for decision problem	No	Model does not adequately capture the causal relationships between patient characteristics and probability of progression and death.
Data incorporation into the model has been done adequately (e.g., parameters for probabilistic analysis)	No	There is a large discordance between the results of the deterministic analysis and the probabilistic analysis. It was not possible for CADTH to address the cause for such discordance, so only the results of the deterministic analysis are presented here. The OS curve for salvage chemotherapy was derived from the OS curve for glofitamab based on an effective sample size for glofitamab of 32.9 patients weighted by a hazard ratio from an indirect treatment comparison using SCHOLAR-1 data. In addition to the use of such a small sample size, the adoption of a proportional hazards assumption lacks face validity given the causal relationship between progression and mortality. The PFS curve was then weighted by a hazard ratio from a NICE Submission relating to the CORAL study. The use of this approach lacks validity. This suggests high degrees of uncertainty. Although the sponsor suggested their approach is valid as SCHOLAR-1 data has been used for previous CADTH submissions, throughout the submission, SCHOLAR-1 is only used to derive a proportional hazard ratio for OS.
Parameter and structural uncertainty were adequately assessed; analyses were adequate to inform the decision problem	No	Refer to CADTH appraisal and comments in the above rows.
The submission was well organized and complete; the information was easy to locate (clear and transparent reporting; technical documentation available in enough details)	No	There were inconsistencies between the submitted report and model.

Appendix 3: Additional Information on the Submitted Economic Evaluation

Note that this appendix has not been copy-edited.

Figure 1: Submitted Model Structure



Patients enter the model in the progression-free state. In each cycle, patients can either remain in the progression-free health state, or transition to the post-progression or death health state. Patients who have progressed can remain in the post-progression state or transition to the death state but never go back to the progression-free state. All patients eventually enter the death state.

Source: Sponsor's Pharmacoeconomic Submission.[1]

CADTH noted that the sponsor's description of the model within the model framework is erroneous. The description implies patients move between states within the model. The submitted model does not model transitions between health states. Rather, it independently models the proportion of the population who are alive and the proportion of the population who are progression free at different time points. This failure to model appropriately the causal relationships between progression status and treatment status on the probabilities of progression and death are fundamental weaknesses of the submitted model.

Detailed Results of the Sponsor's Base Case

Table 11: Summary of the Sponsor's Economic Evaluation Results — Probabilistic

Drug	Total costs ($)	Incremental costs ($)	Total QALYs	Incremental QALYs	ICER vs. reference ($/QALY)
Pairwise analysis 1 (glofitamab vs. salvage chemotherapy)					
Salvage chemotherapy (R-GDP)	74,549	Reference	1.31	Reference	Reference
Glofitamab	157,153	82,604	3.78	2.48	33,342
Pairwise analysis 2 (glofitamab vs. Pola-BR)					
Pola-BR	168,931	Reference	3.13	Reference	Reference
Glofitamab	152,131	−16,800	3.67	0.55	Dominant

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

Source: Sponsor's pharmacoeconomic submission.[1]

Appendix 4: Additional Details on the CADTH Reanalyses and Sensitivity Analyses of the Economic Evaluation

Note that this appendix has not been copy-edited.

Table 12: Disaggregated Summary of the CADTH's Economic Evaluation Results — Glofitamab vs. Salvage Chemotherapy

Treatment	Component	Value	Incremental (vs. salvage chemotherapy)
Discounted LYs			
Salvage chemotherapy (R-GDP)	Progression free	0.65	NA
	Postprogression	0.55	NA
	Total	1.20	NA
Glofitamab	Progression free	1.11	0.47
	Postprogression	0.53	−0.02
	Total	1.64	0.40
Discounted QALYs			
Salvage chemotherapy (R-GDP)	Progression free	0.49	NA
	Postprogression	0.34	NA
	Total	0.83	NA
Glofitamab	Progression free	0.84	0.35
	Postprogression	0.33	−0.01
	Total	1.17	0.34
Discounted costs ($)			
Salvage chemotherapy (R-GDP)	Treatment costs	10,552	NA
	Drug administration	573	NA
	AEs	2,287	NA
	Supportive care – progression free	13,858	NA
	Supportive care – postprogression	17,734	NA
	Post-discontinuation of drug therapy	24,917	NA
	Total	69,901	NA
Glofitamab	Treatment costs	79,321	68,789
	Drug administration	1,015	442
	AEs	4,120	1,833
	Supportive care – progression free	22,483	8,625
	Supportive care – postprogression	16,948	−765

Treatment	Component	Value	Incremental (vs. salvage chemotherapy)
	Post-discontinuation of drug therapy	23,842	−1,076
	Total	147,749	77,848
Treatment		**ICER vs. salvage chemotherapy (R-GDP) ($)**	
Glofitamab		$230,682	

AE = adverse event; ICER = incremental cost-effectiveness ratio; LY = life-year; QALY = quality-adjusted life-year; R-GDP = rituximab, gemcitabine, dexamethasone, and cisplatin; vs. = versus.

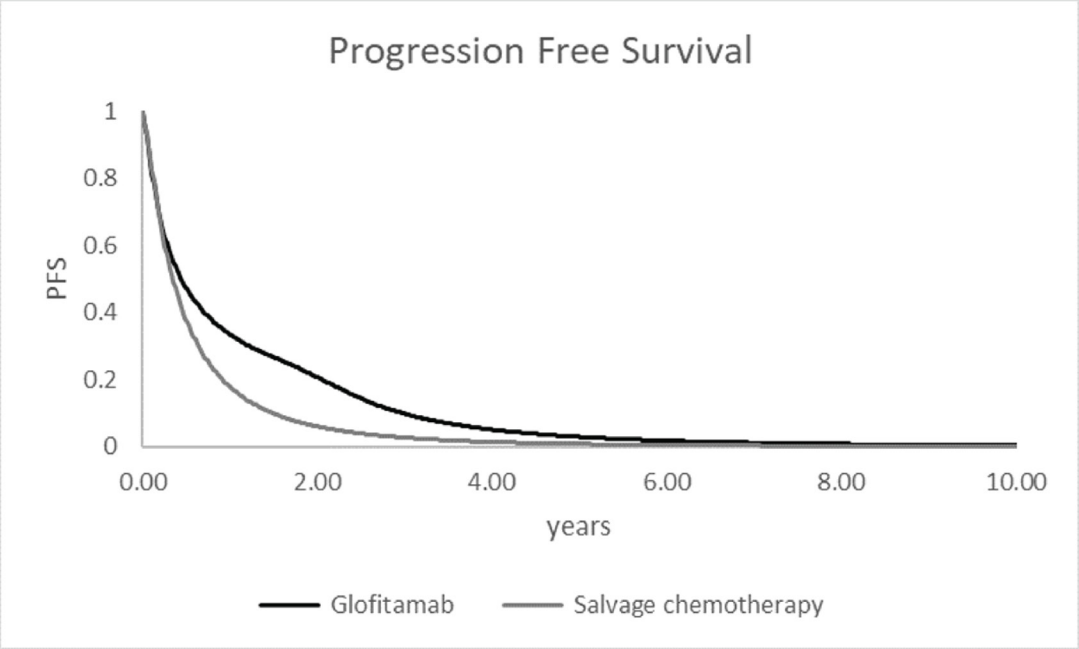
Table 13: Disaggregated Summary of the CADTH's Economic Evaluation Results — Glofitamab vs. Pola-BR

Treatment	Component	Value	Incremental (Pola-BR vs. Glofitamab)
Discounted LYs			
Glofitamab	Progression free	4.15	NA
	Postprogression	1.13	NA
	Total	5.27	NA
Pola-BR	Progression free	4.15	0.00
	Postprogression	1.13	0.00
	Total	5.27	0.00
Discounted QALYs			
Glofitamab	Progression free	2.96	NA
	Postprogression	0.70	NA
	Total	3.66	NA
Pola-BR	Progression free	2.97	0.005
	Postprogression	0.70	0.00
	Total	3.66	0.005
Discounted costs ($)			
Glofitamab	Treatment costs	79,321	NA
	Drug administration	1,105	NA
	AEs	4,120	NA
	Supportive care – progression free	18,293	NA
	Supportive care – postprogression	36,212	NA
	Post-discontinuation of drug therapy	19,361	NA
	Total	158,322	NA
Pola-BR	Treatment costs	87,869	8,368

Treatment	Component	Value	Incremental (Pola-BR vs. Glofitamab)
	Drug administration	816	–199
	AEs	9,827	5,708
	Supportive care – progression free	15,803	2,490
	Supportive care – postprogression	36,212	0
	Post-discontinuation of drug therapy	19,361	0
	Total	158,322	11,386
Treatment		**ICER Pola-BR vs. Glofitamab ($)**	
Pola-BR		2,281,494	

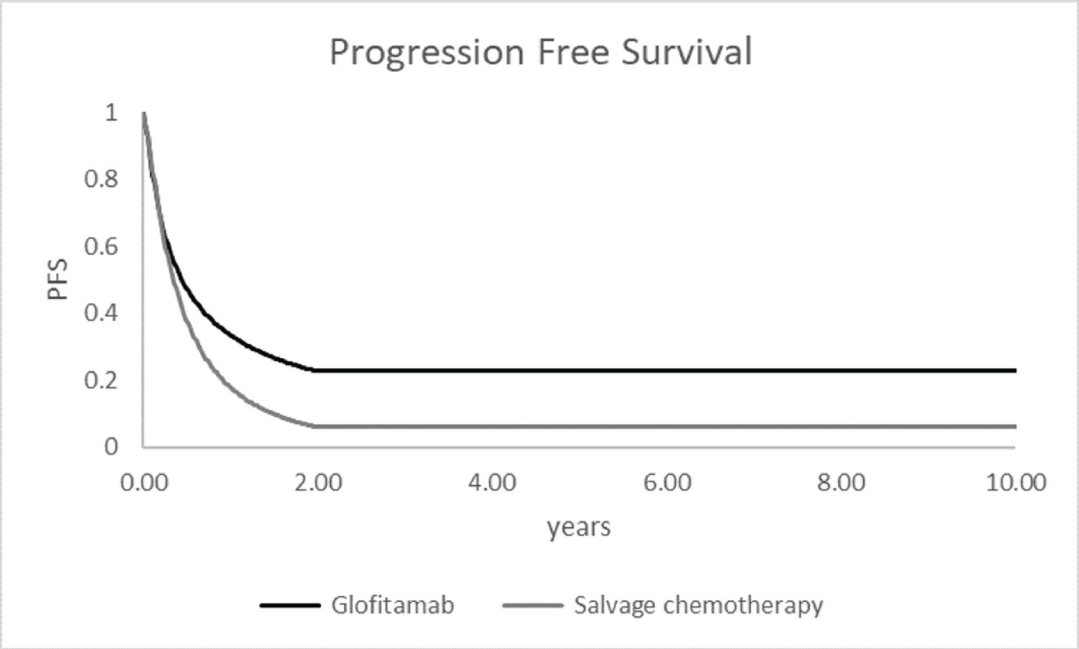
AE = adverse event; ICER = incremental cost-effectiveness ratio; LY = life-year; Pola-BR = polatuzumab, bendamustine, and rituximab; QALY = quality-adjusted life-year; vs. = versus.

Figure 2: Progression-Free Survival Curves Based on the CADTH Reanalysis



Source: Output of the sponsor's economic model.

Figure 3: Progression-Free Survival Curves Based on the Sponsor's Analysis



Source: Output of the sponsor's economic model.

Appendix 5: Submitted BIA and CADTH Appraisal

Note that this appendix has not been copy-edited.

Table 14: Summary of Key Take-Aways

Key take-aways of the BIA

• 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.
  ◦ 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.

Summary of Sponsor's BIA

The submitted BIA assessed expected budgetary impact resulting from reimbursing 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.[15] The BIA was conducted from the perspective of the Canadian public drug plans over a 3-year time horizon using an epidemiological approach. The sponsor's pan-Canadian estimates reflect the aggregated results from provincial budgets (excluding Quebec) as well as the Non-Insured Health Benefits Program. Market distributions were derived through internal assumptions and were validated by sponsor obtained clinicians. Key inputs to the BIA are documented in Table 15.

The following key assumptions were made by the sponsor:

- The cost of each regimen was calculated by assuming perfect vial sharing and excluded administration costs.
- The sponsor assumed 100% of patients would be covered by drug plans.
- The sponsor did not include patients that received second-line treatment with CAR T-cell therapy in the base case.

Summary of the Sponsor's BIA Results

- The sponsor's base case reported that 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 lead to an incremental budget impact of $3,952,969 in Year 1, $6,741,456 in Year 2, and $7,794,413 in Year 3, resulting in a 3-year incremental cost of glofitamab was $18,488,838.

- The sponsor undertook a series of sensitivity analyses including: reporting administration costs, including CRS management costs for glofitamab, assessing alternate duration of treatment and market shares, and including patients that receive treatment after 2L CAR T. The results of the sensitivity analyses demonstrated that the 3-year incremental budget impact may vary from $11,343,098 to $44,689,884. The key assumptions that had a budget impact were the number of glofitamab treatment cycles used, and the assumed market uptake for glofitamab. In the base case, the mean number of cycles were used. In the sensitivity analyses, the range in the 3-year budget impact derived from using the median number and max number of cycles, respectively.

Table 15: Summary of Key Model Parameters

Parameter	Sponsor's estimate (reported as year 1 / year 2 / year 3 if appropriate)
Target population	
NHL cases	9,329[16]
DLBCL cases	35%; 3,265[17]
Patients publicly covered	100%; 3,265[18]
Patients receiving 1L treatment	90%; 2,939[18]
r/r after 1L treatment	40%; 1,175[19]
Eligible for 2L ASCT	50%; 558[19]
Receive 2L CAR T	0%; 0
Intend to receive ASCT and salvage chemotherapy	100%; 558
Receive ASCT	50%; 294[19]
Relapse after ASCT	50%; 147[19]
Refractory to salvage and did not receive ASCT	50%; 294[19]
Ineligible for ASCT	50%; 558[19]
r/r after 2L treatment	73%; 429[20]
Receiving 3L+ that did not receive CAR T in 2L	79%; 687[21]
3L+ treatment other than CAR T	55%; 378
3L CAR T	45%; 309
r/r after 3L CAR T	30%; 93[22]
Number of patients eligible for drug under review	471 / 454 / 437
Market uptake (3 years)	
Uptake (reference scenario)	
Pola-BR	15% / 18% / 20%
Salvage chemotherapy	85% / 83% / 80%

Parameter	Sponsor's estimate (reported as year 1 / year 2 / year 3 if appropriate)
Uptake (new drug scenario)	
Glofitamab	15% / 30% / 40%
Pola-BR	13% / 10% / 8%
Salvage chemotherapy	73% / 60% / 53%
Cost of treatment (per patient)	
Cost of treatment over treatment regimen[a]	
Glofitamab[b]	$79,321
Pola-BR	$87,869
Salvage chemotherapy	
R-GDP	$10,532
R-ICE	$14,340
R-DHAP	$9,384
R-DICEP	$7,728
R-GemOx	$16,680

1L = first-line; 2L = second-line; 3L = third-line; ASCT = autologous stem cell transplant; DLBCL = diffuse large B-cell lymphoma; NHL = non-Hodgkin lymphoma; Pola-BR = polatuzumab vedotin plus bendamustine plus rituximab; R-DHAP = rituximab plus dexamethasone plus cytarabine plus cisplatin; R-DICEP = rituximab plus dexamethasone plus cytarabine plus cisplatin; R-GDP = rituximab plus gemcitabine plus dexamethasone plus cisplatin; R-GemOx = rituximab plus dexamethasone plus cytarabine plus cisplatin; R-ICE = rituximab plus ifosfamide plus carboplatin plus etoposide; r/r = relapsed or refractory.

[a]Regimen length was 6.5 cycles for glofitamab, 4.44 for polatuzumab, 4.51 for BR, and 3 for salvage chemotherapy.

[b]Cost of drug under review including premedication regimen of obinutuzumab, prednisolone, acetaminophen, and diphenhydramine.

Source: Sponsor's budget impact analysis.[15]

CADTH Appraisal of the Sponsor's BIA

CADTH identified several key limitations to the sponsor's analysis that have notable implications on the results of the BIA:

- **Distribution of salvage chemotherapy regimens does not align with clinical expectations:** In the sponsor's submitted BIA, the sponsor assumed that there is no difference in the effectiveness of the common chemotherapy regimens in Canada. Due to this assumption, the sponsor used R-GDP as the most commonly used chemotherapy regimen in the model's base case. Feedback obtained from clinical experts consulted by CADTH suggest that while R-GDP is a common regimen used in pan-Canadian clinical practice, R-GemOx may be as common.
    - CADTH addressed this limitation by revising the salvage chemotherapy distribution to 50% of patients using R-GDP and 50% of patients using R-GemOx.
- **The market share estimates in the reference and new drug scenarios do not align with clinical expectations:** In the sponsor's submitted BIA, the sponsor assumed that patients treated with Pola-BR will capture 15% of the market in Year 1, 18% in Year 2 and 20% in Year 3 in the reference scenario. In the new drug scenario, the sponsor assumed that patients treated with Pola-BR will capture 13% of the market in Year 1, 10% in Year 2 and 8% in Year 3. Additionally, the sponsor assumed that patients treated with salvage chemotherapy will capture 85% of the market in Year 1, 83% in Year 2

and 80% in Year 3 in the reference scenario. In the new drug scenario, patients treated with salvage chemotherapy will capture 73% of the market in Year 1, 60% in Year 2 and 53% in Year 3. However, CADTH obtained clinical expert feedback that suggested the distribution of the market shares in the current treatment landscape Pola-BR is the more commonly used therapy.
    - CADTH addressed this limitation by revising the market shares of Pola-BR and salvage chemotherapy in the reference and new drug scenario to reflect the distribution of treatments expected based upon clinical expert feedback.
- **The market uptake of glofitamab is underestimated**: The sponsor's submitted BIA indicated that glofitamab would result in a market uptake of 15% in Year, 30% in Year 2 and 40% in Year 3 based on confidential market insights. However, CADTH obtained clinical expert feedback indicating that the market uptake of 40% in Year 3 does not align with clinical expectation and indicated the sponsor likely underestimated glofitamab uptake. The clinical experts highlighted that by Year 3, salvage chemotherapy will likely not be a 3L+ treatment and the 8% market capture may be absorbed by glofitamab.
    - CADTH addressed this limitation by revising the market distribution in the new drug scenario for glofitamab to absorb Year 3 market capture for salvage chemotherapy.

Additional limitations were identified but were not considered to be key limitations. These limitations include: inaccurate comparator unit costs and the R-ICE regimen comparator included mesna (sodium 2-mercaptoethane sulfonate) in the regimen, which is not included in the regimen per Ontario guidelines.[11]

CADTH Reanalyses of the BIA

The results of the CADTH step-wise reanalysis are presented in summary format in Table 17 and a more detailed breakdown is presented in Table 18. Based on the CADTH base case, the budget impact associated with reimbursement of glofitamab in the indicated target population is expected to be $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.

Table 16: CADTH Revisions to the Submitted Budget Impact Analysis

Stepped analysis	Sponsor's value or assumption	CADTH value or assumption
Corrections to sponsor's base case		
1. Comparator costs	Per treatment cost: Polatuzumab: $14,213.73 Oxaliplatin 100 mg vial: $829.06 Ifosfamide 1,000 mg vial: $136.22 Ifosfamide 3,000 mg vial: $342.47 Carboplatin 50 mg vial: $86.66 Carboplatin 150 mg vial: $318.35 Carboplatin 450 mg vial: $909.56 Cyclophosphamide 500 mg vial: $97.80	Per treatment cost: Polatuzumab: $14,750.00 Oxaliplatin 100 mg vial: $90.00 Ifosfamide 1,000 mg vial: $143.87 Ifosfamide 3,000 mg vial: $440.59 Carboplatin 50 mg vial: $70.00 Carboplatin 150 mg vial: $210.00 Carboplatin 450 mg vial: $600.00 Cyclophosphamide 500 mg vial: $101.71

Stepped analysis	Sponsor's value or assumption	CADTH value or assumption
	Cyclophosphamide 1,000 mg vial: $177.27 Cyclophosphamide 2,000 mg vial: $304.46	Cyclophosphamide 1,000 mg vial: $184.36 Cyclophosphamide 2,000 mg vial: $339.20
2. Incorrect regimen	R-ICE regimen in sponsor's submission included mesna.	R-ICE regimen as indicated in Cancer Care Ontario does not include mesna.[11]
Changes to derive the CADTH base case		
1. Distribution of salvage chemotherapy regimens	Distribution: R-GDP: 100%	Distribution: R-GDP: 50% R-GemOx: 50%
2. Alternate market capture of salvage chemotherapy and Pola-BR	Reference market distribution (year 1 / 2 / 3) Pola-BR: 15% / 17% / 20% Salvage chemotherapy: 85% / 83% / 80% New drug market distribution (year 1 / 2 / 3) Pola-BR: 12% / 10% / 8% Salvage chemotherapy: 73% / 60% / 53%	Reference market distribution (year 1 / 2 / 3) Pola-BR: 83% / 85% / 88% Salvage chemotherapy: 17% / 15% / 12% New drug market distribution (year 1 / 2 / 3) Pola-BR: 73% / 60% / 53% Salvage chemotherapy: 12% / 10% / 8%
3. Increased market uptake of glofitamab in Year 3	New drug market distribution (year 1 / 2 / 3) Glofitamab:15% / 30% / 40% Pola-BR: 12% / 10% / 7% Salvage chemotherapy: 73% / 60% / 53%	New drug market distribution (year 1 / 2 / 3) Glofitamab: 15% / 30% / 47% Pola-BR: 12% / 10% / 8% Salvage chemotherapy: 73% / 60% / 45%
CADTH analysis: revised market shares (2 + 3)	Reference (year 1 / 2 / 3) Glofitamab: 0% / 0% / 0% Pola-BR: 15% / 17% / 20% Salvage chemotherapy: 85% / 83% / 80% New drug (year 1 / 2 / 3) Glofitamab: 15% / 30% / 40% Pola-BR: 12% / 10% / 7% Salvage chemotherapy: 73% / 60% / 53%	Reference (year 1 / 2 / 3) Glofitamab: 0% / 0% / 0% Pola-BR: 83% / 85% / 88% Salvage chemotherapy: 17% / 15% / 13% New drug (year 1 / 2 / 3) Glofitamab: 15% / 30% / 47% Pola-BR: 73% / 60% / 53% Salvage chemotherapy: 12% / 10% / 0%
CADTH base case	1 + 2 + 3	

Pola-BR = polatuzumab vedotin plus bendamustine plus rituximab; R-GDP = rituximab plus gemcitabine plus dexamethasone plus cisplatin; R-GemOx = rituximab plus dexamethasone plus cytarabine plus cisplatin; R-ICE = rituximab plus ifosfamide plus carboplatin plus etoposide.

Table 17: Summary of the CADTH Reanalyses of the BIA

Stepped analysis	Three-year total
Submitted base case	$18,488,838
Corrected base case	$18,249,658
CADTH reanalysis 1	$18,168,510
CADTH reanalysis 2	$1,259,218
CADTH reanalysis 3	$20,352,461
CADTH analysis 2 + 3	$3,362,021
CADTH base case (reanalysis 1 + 2 + 3)	$3,333,546

BIA = budget impact analysis.

Table 18: Detailed Breakdown of the CADTH Reanalyses of the BIA

Stepped analysis	Scenario	Year 0	Year 1	Year 2	Year 3	Three-year total
Submitted base case	Reference	$9,854,843	$10,434,330	$10,935,426	$11,354,094	$32,723,850
	New drug	$9,854,843	$14,387,299	$17,676,882	$19,148,507	$51,212,688
	Budget impact	$0	$3,952,969	$6,741,456	$7,794,413	$18,488,838
Corrected base case	Reference	$10,000,049	$14,527,613	$17,785,072	$19,226,492	$61,539,226
	New drug	$10,000,049	$10,602,706	$11,124,760	$11,562,053	$43,289,568
	Budget impact	$0	$3,924,907	$6,660,313	$7,664,438	$18,249,658
CADTH base case	Reference	$36,280,427	$37,281,015	$35,909,468	$37,169,045	$146,639,955
	New drug	$36,280,427	$36,181,556	$35,594,660	$35,249,767	$143,306,409
	Budget impact	$0	$1,099,459	$314,808	$1,919,279	$3,333,546

BIA = budget impact analysis.

Stakeholder Input

List of Tables

Patient Input

Lymphoma Canada

About Lymphoma Canada

Lymphoma Canada is a national Canadian registered charity whose mission it is to empower patients and the lymphoma community through education, support, advocacy, and research. Based out of Mississauga (ON), we collaborate with patients, caregivers, healthcare professionals, and other organizations and stakeholders, to promote early detection, find new and better treatments for lymphoma patients, help patients access those treatments, learn about the causes of lymphoma, and work together to find a cure. Resources are provided in both English and French. www.lymphoma.ca

Information Gathering

The data presented in this submission was collected from an online anonymous patient survey, created and promoted by Lymphoma Canada (LC) available from June 5 to July 10, 2023. The link was promoted via e-mail to patients registered in the LC national emailing list and made available via social media outlets, including Twitter, Instagram, and Facebook accounts. The survey had a combination of multiple choice, rating, and open-ended questions. Skipping logic was built into the survey so that respondents were asked questions only relevant to them. Open-ended responses were noted in this report verbatim, to provide a deeper understanding of patient perspectives. 27 responses were collected. Information from this survey was used to identify the main areas of concern for patients with Large B-cell lymphoma, with 2 confirmed responses for experience with Glofitamab. 1 of these patients were male, lived in the US and is 35-44 years old, the other patient did not disclose information about their gender, age or location.

Please refer to Tables 1 to 4 below for demographic and relevant information of all survey respondents. The majority of patients lived in Canada (30%), between the age of 45 and 54 (22%), female (19%), and were diagnosed 1-5 years ago (30%) with Diffuse Large B-cell lymphoma subtype (48%).

Table 1: Country of Respondents From Lymphoma Canada Survey

Respondents	CAN	USA	Lebanon	Skipped	Total
Patients with Large B-cell lymphoma	8	2	1	16	27

Table 2: Age Range of Respondents From Lymphoma Canada Survey

	Age (years old)						
Respondents	25-34	35-54	45-54	55-64	75-84	Skipped	Total
Patients with Large B-cell lymphoma	1	5	6	4	1	11	27

Table 3: Gender of Respondents From Lymphoma Canada Survey

Respondents	Gender		Skipped	Total
	Female	Male		
Patients with Large B-cell lymphoma	5	6	16	27

Table 4: Number of Years Ago Respondents Were Diagnosed With Large B-cell Lymphoma

Respondents	Years					Skipped	Total
	<1	1-2	3-5	5-8	9-10		
Patients with Large B-cell lymphoma	4	4	8	2	4	5	27

Table 5: Subtype of Large B-cell Lymphoma of Survey Respondents

Subtype of Large B-cell Lymphoma	Number of respondents
Diffuse Large B-cell Lymphoma, not otherwise specified	13
DLBCL arising from follicular lymphoma	3
DLBCL arising from primary mediastinal B-cell lymphoma	3
95% DLBCL, 5% Hodgkin lymphoma	1
DLBCL arising from Richter's transformation	1
Germinal center B-cell Lymphoma	1
Skipped	5
Total	27

Disease Experience

At Diagnosis

Through the online survey, patients were asked to rate a list of physical symptoms on a scale of 1 (no impact) to 5 (significant impact) in regards to their quality of life upon diagnosis. The most common reported symptoms rated as a five were: enlarged lymph nodes (32%), bodily swelling (27%), fatigue (27%), shortness of breath (27%), bodily aches and pains (23%) and night sweats (23%).

Respondents of the survey were also asked to select from a list of psychosocial impacts they experience when diagnosed with LBCL. Of 22 patients, 64% were impacted by stress of diagnosis, fear of progression and inability to continue daily activities. Additionally, 59% of these patients experienced anxiety/worry. When asked to provide additional details about the challenges faced during diagnosis, several patients commented on difficult symptoms and the time it took to confirm their diagnosis:

> "I had to sleep upright, my face was swollen, and my appearance changed. I was scared that I was going to suffocate."
>
> "The length of time it took to get a diagnosis. To get an appointment for surgery to remove an

enlarged node for biopsy."

"Shock of how fast it progressed (1- 2 weeks), how bad the symptoms got (difficulty breathing, swallowing, sleeping, extreme fatigue), how large the tumour was (14cm x 16 cm mediastinum) and spread (pancreas), and the fact that I thought I was a young (29 y. o.) and healthy individual!"

"The hardest part is the wait time between testing and results of scans."

Current Quality of Life

To understand the factors which currently impact patients with Large B-cell lymphoma, respondents were asked a similar style of questions from the diagnosis section of the survey. On a scale of 1 (no impact) to 5 (significant impact), 26% of patients rated fatigue as a 5 and 20% rated enlarged lymph nodes as a 5. Over 50% of patients did not experience an enlarged spleen, fever, high white blood cell count, low platelet count, weight loss, enlarged lymph nodes, frequent infections, anemia, chest pain, or reduced appetite in their current quality of life. This correlates with the age range of the survey respondents, with most being diagnosed 3-5 years ago.

Patients also indicated they recently experienced mental health challenges such as fear of progression/ relapse (66%), stress of having cancer (56%) and anxiety/worry (42%).

Daily Activities

Regarding day-to-day activities, patients with Large B-cell lymphoma rated several factors on a scale of 1 (no impact) to 5 (very significant impact) which impacted their daily life. The ability to work, school and volunteer (54%), ability to perform day-to-day activities (47%), ability to spend time with family and friends (47%), and ability to attend to household chores (40%) were rated as a 4 or higher by 15 patients. Many patients left comments in this section and a selection of quotes are included below:

"Living my best life!"

"Increased anxiety and mood limit my social interactions."

"I could not go back to full time university studies, after only finishing one year. Very difficult (or I am very slow) at doing many household chores. I have 2 kids that I cannot run or do other sports because of my bone fractures. I feel like I constantly need 10 h of sleep, which I do not get. I developed PTSD from all those cancer experiences and often get triggered/remember/ cry. I am always tired/ fatigued which has become the new normal. My follow ups are made up of "how are you feeling?" questions, and no x-rays, CT scans, pet scans AT ALL! This is extremely frustrating, since I have never had the B symptoms (fever, night sweats, losing weight, enlarged lymph nodes) to begin with, and I get asked if I have them now (which does not make any sense!). So, I am VERY upset about the lack of follow up because of the "protocol" not to do scans. This is unacceptable for a young individual like me (33), with a family and children, work, plans and life in general - to do nothing from the healthcare specialists. "Being immunocompromised I mask indoors still so this limits restaurants or group eating events. I'm grateful for the Evusheld shots protection against covid BA-4 and BA-5. I'm less concerned about covid now than some of the other viruses circulating now. Ir RSV, etc."

Experiences With Currently Available Treatments

Patients who completed the Lymphoma Canada survey were asked how many lines of treatment they received to treat their Large B-cell lymphoma. The majority of 13 patients indicated they received 1 (69%) or 3 or more (31%) lines of treatment, please refer to Table 6.

Table 6: Number of Lines of Therapy Survey Respondents Received

Respondents	1	3+	Skipped	Total
Patients with Large B-cell lymphoma	9	4	14	27

In the front-line setting, 7 patients received R-CHOP, 3 received DA-EPOCH-R, 1 received ABVD + radiation, another patient started on R-CHOP then was switched to DA-EPOCH, and the last patient received R-CHOP + radiation together as first line therapy. In second line, 3 patients received R-GDP, 3 received salvage therapy + autologous stem cell transplant, 4 received radiation, and 3 were on a clinical trial. In the third line of treatment, 6 patients received CAR T-cell therapy, 1 received Pola-R-CHP, and 6 were on a clinical trial.

These patients were asked: "How satisfied were you with the number of treatment options available to you for your lymphoma?" 62% of patients indicated they were very satisfied or satisfied with their frontline treatment options. While 39% of survey respondents gave the same rating in second-line treatment, and 31% with their third-line treatment options. This indicates patients are less pleased with their treatment options in second- and third-line settings.

10 patients provided information about their ability to access their DLBCL treatment. 5 patients found it not difficult at all or not very difficult to access treatment, while 3 patients had some difficulty and 2 had a lot of difficulty. Here are some comments from patients as to why:

> "Location was more than one hour from home."
>
> "I live in Victoria BC but had to travel to Vancouver for chemo treatments. Travel away from family for a week each cycle."
>
> "I got my treatment right away, as I needed it asap! But my grastofill injections would cost $15,000. Luckily, they were covered by t=some angel organization."
>
> "Finances. Not covered by Ohip. Had to beg drug company to cover costs, they agreed on compassionate grounds. Each 30 mins infusion once every three weeks is roughly $10,000.00."

The most common financial implications reported for treatment for LBCL were drug costs (60%), travelling costs (40%), and absence from work (40%). Survey respondents left several comments when asked about the difficulties of accessing treatment in Canada:

> "Da epoch not available in my town. Had to travel and family stayed in hotel. Wish it was outpatient."
>
> "Any follow up is impossible to access. The healthcare system only takes people with symptoms - and since I don't have any standard symptoms (which I never had before my diagnosis), I can NOT get access to ANY follow up scan - x-ray, CT scan, PET scan etc. For the past 3 years nobody knows what is going on inside of my body, and nobody will even at 3, 5, 10-year mark. Very frustrating."

"There was no difficulty, my testing hematologist, and his staff were second to none."

"Keytruda. The cancer had come back a third time within months and the dr decided keytruda was the best course of action took a month and a half to get the drug covered by either my private benefits or the drug company. This involved endless forms and phone calls with the drug company Merck in order to finally have it approved and to start treatment. The drug is also not offered where I live so I do have to travel and hour and a half one way to receive the 30 mins infusion every three weeks. There are no financial aids to cover the price of gas or parking or alternative means of transport in eastern Ontario like the go train as is with the GTA. No other option but to drive."

Improved Outcomes

LBCL patients which completed the Lymphoma Canada survey were asked how important it was for a new drug to control/treat their Large B-cell lymphoma. Unfortunately, only 2 patients provided input to this section of the survey, which did not yield a large consensus of the factors DLBCL patients are looking for improved outcomes.

From a recent patient survey, promoted by Lymphoma Canada, and completed for the CADTH submission of Pola-R-CHP, LBCL patients indicated factors such as longer disease remission (100%), control disease symptoms (91%), longer survival (100%), normalize blood counts (91%), and improved quality of life to perform daily activities (91%), were very important to them (10 out of 10). 8 of these patients indicated they would be willing to tolerate side effects to access new treatment and 7 patients indicated choice is important to them (8 or higher, of 10) in deciding to take a drug based on known side effects and expected outcomes of treatment.

Experience With Drug Under Review

From survey responses, 2 patients indicated they were treated with Glofitamab. 1 patient was treated less than 6 months ago, the other was treated 3-5 years ago. One of these patients accessed the drug through private insurance and the other was through medicare or public care. Both patients are in remission, with 1 less than 6 months to a year, the other for 1-2 years. One patient did not experience any side effects, the other experienced cytokine release syndrome, hypotension, and low platelet count. One LBCL patient experience financial impacts from the cost of Glofitamab, the other experienced costs affording supplemental medication during treatment. Despite these challenges, the patients rated their overall experience with Glofitamab as good and very good. No other responses or comments were provided by these patients.

Companion Diagnostic Test

Not applicable.

Anything Else?

Lymphoma Canada is an advocate for lymphoma patients and their caregivers to have access to novel lymphoma therapies. An increased number of available treatment options gives patients more choice to decide the therapy that is right for their personal goals, with their medical care team. A large majority of

patients relapse from LBCL after first treatment, indicating there is a need for more and better therapeutic options for this subset of patients.

Conflict of Interest Declaration — Lymphoma Canada
To maintain the objectivity and credibility of the CADTH reimbursement review process, all participants in the drug review processes must disclose any real, potential, or perceived conflicts of interest. This Patient Group Conflict of Interest Declaration is required for participation. Declarations made do not negate or preclude the use of the patient group input. CADTH may contact your group with further questions, as needed.

Did you receive help from outside your patient group to complete this submission?

No.

Did you receive help from outside your patient group to collect or analyze data used in this submission?

No.

List any companies or organizations that have provided your group with financial payment over the past 2 years AND who may have direct or indirect interest in the drug under review.

Table 7: Financial Disclosures for Lymphoma Canada

Company	$0 to 5,000	$5,001 to 10,000	$10,001 to 50,000	In Excess of $50,000
Roche	—	—	X	—
Gilead	—	—	—	X
Incyte	—	—	X	—
Novartis	—	—	X	—
BMS	—	—	—	X

Clinician Input

Ontario Health (Cancer Care Ontario) Hematology Cancer Drug Advisory Committee

About Ontario Health (Cancer Care Ontario) Hematology Cancer Drug Advisory Committee
OH-CCO's Cancer Drug Advisory Committees provide timely evidence-based clinical and health system guidance on drug-related issues in support of CCO's mandate, including the Provincial Drug Reimbursement Programs (PDRP) and the Systemic Treatment Program.

Information Gathering
Information was gathered via videoconferencing.

Current Treatments and Treatment Goals

Current treatment options in third line or beyond include Polatuzumab-BR, Rituximab-chemotherapy and radiation.

Treatment Gaps (Unmet Needs)

Considering the treatment goals, please describe goals (needs) that are not being met by currently available treatments.

There are no treatments available for long term remissions if the patient is not CAR-T eligible. And there are no other treatment options than polatuzumab-BR if R/R.

Place in Therapy

How would the drug under review fit into the current treatment paradigm?

This drug can be used in third line or beyond, if the patient was previously treated with CAR T-cell therapy, or ineligible for CAR T-cell therapy, as per the trial.

This may be preferred by clinicians over Pola-BR.

Which patients would be best suited for treatment with the drug under review? Which patients would be least suitable for treatment with the drug under review?

As per the trial criteria.

Patients who have had prior alloSCT, should be eligible for glofitamab.

What outcomes are used to determine whether a patient is responding to treatment in clinical practice? How often should treatment response be assessed?

Standard lymphoma response measures, symptom improvement.

Treatment response should be assessed as per usual practice.

What factors should be considered when deciding to discontinue treatment with the drug under review?

Disease progression, toxicities.

What settings are appropriate for treatment with [drug under review]? Is a specialist required to diagnose, treat, and monitor patients who might receive [drug under review]?

Inpatient and outpatient settings.

Centers with expertise in managing CRS.

Additional Information

We may need to ensure there is adequate tocilizumab supply for CRS management.

Conflict of Interest Declarations — Ontario Health (Cancer Care Ontario) Hematology Cancer Drug Advisory Committee

To maintain the objectivity and credibility of the CADTH drug review programs, all participants in the drug review processes must disclose any real, potential, or perceived conflicts of interest. This conflict of interest declaration is required for participation. Declarations made do not negate or preclude the use of the clinician group input. CADTH may contact your group with further questions, as needed. Please refer to the Procedures for CADTH Drug Reimbursement Reviews (section 6.3) for further details.

OH-CCO provided secretariat function to the group.

Did you receive help from outside your clinician group to complete this submission?

No.

Did you receive help from outside your clinician group to collect or analyze any information used in this submission?

No.

List any companies or organizations that have provided your group with financial payment over the past two years AND who may have direct or indirect interest in the drug under review. Please note that this is required for *each clinician* who contributed to the input.

Declaration for Clinician 1

Name: Dr. Tom Kouroukis

Position: Lead, Ontario Health (Cancer Care Ontario) Hematology Cancer Drug Advisory Committee

Date: 08-06-2023

Table 8: COI Declaration for OH-CCO Hematology Cancer Drug Advisory Committee — Clinician 1

Company	$0 to 5,000	$5,001 to 10,000	$10,001 to 50,000	In Excess of $50,000
No COI	–	–	–	–

Declaration for Clinician 2

Name: Dr. Pierre Villeneuve

Position: Member, Ontario Health (Cancer Care Ontario) Hematology Cancer Drug Advisory Committee

Date: 08-06-2023

Table 9: COI Declaration for OH-CCO Hematology Cancer Drug Advisory Committee — Clinician 2

Company	$0 to 5,000	$5,001 to 10,000	$10,001 to 50,000	In Excess of $50,000
No COI	–	–	–	–

Declaration for Clinician 3
Name: Dr. Joanna Graczyk

Position: Member, Ontario Health (Cancer Care Ontario) Hematology Cancer Drug Advisory Committee

Date: 08-06-2023

Table 10: COI Declaration for OH-CCO Hematology Cancer Drug Advisory Committee — Clinician 3

Company	$0 to 5,000	$5,001 to 10,000	$10,001 to 50,000	In Excess of $50,000
No COI	–	–	–	–

Declaration for Clinician 4
Name: Dr. Lee Mozessohn

Position: Member, Ontario Health (Cancer Care Ontario) Hematology Cancer Drug Advisory Committee

Date: 08-06-2023

Table 11: COI Declaration for OH-CCO Hematology Cancer Drug Advisory Committee — Clinician 4

Company	$0 to 5,000	$5,001 to 10,000	$10,001 to 50,000	In Excess of $50,000
No COI	–	–	–	–

Declaration for Clinician 5
Name: Mark Brown

Position: Member, Ontario Health (Cancer Care Ontario) Hematology Cancer Drug Advisory Committee

Date: 08-06-2023

Table 12: COI Declaration for OH-CCO Hematology Cancer Drug Advisory Committee — Clinician 5

Company	$0 to 5,000	$5,001 to 10,000	$10,001 to 50,000	In Excess of $50,000
No COI	–	–	–	–

Lymphoma Canada

About Lymphoma Canada

Lymphoma Canada is a national organization dedicated to research, education, and raising awareness for the benefit of patients with lymphoma across Canada. (Home - Lymphoma Canada)

Information Gathering

We conducted a literature search of PubMed for published clinical trials of glofitamab for the treatment of diffuse large B-cell lymphoma (DLBCL). In addition, we reviewed abstracts relating to glofitamab presented at recent meetings of the American Society of Hematology. Finally, we conducted a literature search of PubMed for studies evaluating the use of other treatments for patients with DLBCL who have received two or more lines of systemic therapy and are ineligible to receive, cannot receive, or previously received CAR-T cell therapy.

Current Treatments and Treatment Goals

Large B-cell lymphomas (LBCL) are a closely related group of aggressive lymphoid malignancies which account for approximately 30% of all non-Hodgkin lymphomas. First line treatment for eligible patients is typically R-CHOP chemoimmunotherapy (or a variation thereof) which may cure up to 60-70% of patients (1). However, 30-40% of patients will relapse or be refractory to R-CHOP (1). The new standard of care for fit patients who are refractory to or relapse within 12 months of R-CHOP is second-line chimeric antigen receptor (CAR) T-cell therapy, which has demonstrated significant improvements in progression-free survival (PFS) and overall survival (OS) compared to the previous standard of care (2-4). Fit patients relapsing more than 12 months after R-CHOP are treated with second-line chemoimmunotherapy and autologous stem cell transplant (ASCT) (5), while those not responding to second-line chemoimmunotherapy or who relapse after ASCT may go on to receive third-line CAR-T cell therapy (6-8). These intensive therapies are given with curative intent with the goal of prolonging survival and improving quality of life. Patients who are ineligible for intensive, curative-intent therapy due to advanced age, comorbidities, or poor performance status may instead receive palliative-intent chemoimmunotherapy such as R-GemOx or polatuzumab/bendamustine-rituximab (pola-BR) or best supportive care (9, 10).

Although CAR-T cell therapy has significantly improved the outcomes of relapsed LBCL, more than 50% of patients ultimately relapse or die after treatment with CAR-T cells (3, 11). Unfortunately, patients relapsing after CAR-T cell therapy have a poor prognosis, with low response rates to next therapy of 14-30%, median OS of 5-6 months, and 1-year OS of only 20-30% (12, 13).Currently, there are limited effective treatment options for these patients outside of a clinical trial, and many patients opt for palliative- intent therapies as outlined above or best supportive care.

In addition, some patients are ineligible for or are unable to receive CAR-T cell therapy for various reasons, including prohibitive distance from a cellular therapy centre, CAR-T cell manufacturing failure, or inability to tolerate potentially severe toxicities including cytokine release syndrome (CRS) or immune effector cell-associated neurotoxicity syndrome (ICANS) due to advanced age, comorbidities, or poor performance status. In addition, up to 20-30% of patients are unable to proceed to CAR-T cell infusion due to death or

clinical deterioration from rapid disease progression during the 4- to 8-week period between consultation and infusion (14, 15). Some patients who are unable to receive CAR-T cell therapy may instead be treated with palliative-intent regimens such as R-GemOx or pola-BR. However, as noted above, these patients are likely to have been exposed to these treatments earlier in the disease course and now have advanced lymphoma that will be resistant to currently available standard therapy.

Treatment Gaps (Unmet Needs)

Considering the treatment goals, please describe goals (needs) that are not being met by currently available treatments.

It is important to recognize that there are important gaps in the treatment of LBCL for Canadian patients, with some variation based on province of residence. Currently, not all provinces are providing third-line CAR-T cell therapy, and lack of a local treatment centre limits access. Level one evidence supports the use of second-line CAR-T cell therapy in patients with early treatment failure following primary therapy. However, this treatment remains unfunded anywhere in Canada despite the demonstration of significant clinical benefit and more recently improved overall survival (2, 3). Finally, access to novel therapies in patients with relapsed/refractory LBCL remains limited, with the only publicly reimbursed option in Canada being pola-BR.

The current treatment gap in this setting can be broken into two distinct groups: patients who are unable to receive CAR-T cell therapy and patients who experience disease progression post CAR-T. Patients with disease progression after CAR-T cell therapy have a poor prognosis, with most patients dying of disease within months when receiving conventional therapies (12, 13). There is no standard of care in this setting, and currently available chemoimmunotherapy-based treatments are usually ineffective or not tolerated because of CAR-T cell-associated cytopenias. Several retrospective studies have demonstrated low response rates or only short-lasting remissions with chemoimmunotherapy, pola-BR, immune checkpoint inhibitors, or tafasitamab-lenalidomide after failure of CAR-T cell therapy (12, 13, 16-19). Of note, many of these treatments are not reimbursed in Canada. A subset of patients responding to one of these agents may achieve durable remissions following consolidation with autologous or allogeneic hematopoietic cell transplantation (19, 20), but the vast majority of patients relapsing after CAR-T cell therapy are unable to receive these intensive treatments due to older age, comorbidities, or refractory lymphoma. As such, there is a substantial unmet need for new, effective, and well-tolerated treatments for patients progressing after CAR-T cell therapy.

As mentioned above, some patients are ineligible for or unable to receive CAR-T cell therapy for a variety of reasons that could be related to lymphoma (e.g. rapidly progressive disease), poor performance status (due to lymphoma or comorbidities), or lack of feasibility of CAR-T cell administration due to social and/or geographic barriers. Conventional therapies are ineffective in this setting and typically associated with poor survival. Thus, there is a substantial unmet need for effective, rapidly available, and well-tolerated therapies for patients who are ineligible for or unable to receive CAR-T cell therapy.

Place in Therapy

How would the drug under review fit into the current treatment paradigm?

Glofitamab would be used in the patient population that has experienced disease progression after CAR-T or as part of third-line therapy for patients who are unable to receive CAR-T cell therapy.

For patients relapsing after CAR-T cell therapy, bispecific antibodies such as glofitamab appear to be the most promising next line of treatment. In a phase 2 trial evaluating glofitamab in relapsed/refractory LBCL, the 52 patients who progressed after CAR-T cell therapy achieved similarly high complete response rates (35%) as patients who had not received CAR-T cell therapy (42%) (21).

Among these patients who progressed after CAR-T cell therapy, 71% received CAR-T cells as their most recent treatment and 89% were refractory to CAR-T cell therapy, which is representative of patients with CAR-T failure in the real world. Similar findings were reported in a phase 2 trial evaluating another bispecific antibody epcoritamab, which reported a complete response rate of 34% among 61 patients progressing after CAR-T cell therapy (22). Bispecific antibodies have the potential to work synergistically with CAR-T cell therapy by binding to and re-expanding CAR-T cells (23), thereby overcoming CAR-T cell exhaustion and re-inducing a response. In addition, glofitamab has a relatively low risk of myelosuppression which makes it a well-tolerated treatment for patients with CAR-T cell-associated cytopenias. Glofitamab is also a chemotherapy-free regimen which is expected to have lower risks of secondary malignancies compared to other treatments. For these reasons, glofitamab is expected to become the preferred next line of treatment for many patients progressing after CAR-T cell therapy.

For patients who are ineligible for or unable to receive CAR-T cell therapy, glofitamab has an excellent safety profile with low rates of high-grade CRS (4%) or neurotoxicity (3%), making it a suitable treatment for older patients or those with comorbidities who may not tolerate the more severe toxicities of CAR-T cell therapy. Unlike CAR-T cell products which have an approximately 4- to 8-week manufacturing period and risk of manufacturing failure, glofitamab is quickly-available 'off the shelf' which makes it better suited for patients with rapidly progressive or very symptomatic disease who require urgent treatment. In addition, glofitamab is logistically more convenient to administer than CAR-T cell therapy as it does not require apheresis, bridging therapy, lymphodepleting chemotherapy, or central line insertion. Glofitamab can also be given in the outpatient and community hospital settings, making it more accessible to patients across Canada who may not live close by a specialized cellular therapy centre where CAR-T cells are administered. Glofitamab also has a fixed duration of treatment consisting of 12 cycles administered over an 8-month period, which has the potential to reduce toxicity and healthcare costs while also improving quality of life and time-off-treatment compared to other bispecific antibodies which are given indefinitely. Finally, unlike other palliative-intent regimens such as R-GemOx or pola-BR, glofitamab has demonstrated curative potential even in patients with high-risk, refractory lymphoma, with 79% of patients who achieve a complete response at end of treatment remaining in remission for >2 years (24). Glofitamab thus represents a convenient, well-tolerated, and curative-intent treatment to fulfill the unmet needs of patients who are ineligible for or unable to receive CAR-T cell therapy, and it is expected to become the preferred next line of treatment for many patients in this setting.

Which patients would be best suited for treatment with the drug under review? Which patients would be least suitable for treatment with the drug under review?

Patients would be best suited for glofitamab if they have LBCL which has progressed after two 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. Patients should have adequate performance status and organ function to tolerate the potential toxicities of glofitamab. Glofitamab achieved comparable complete response rates in most high-risk subgroups include in the phase 2 trial.

Patients would not be suitable for glofitamab if they are eligible and able to receive CAR-T cell therapy. CAR-T cell therapy has well-established curative efficacy in randomized controlled trials, long-term follow-up studies, and in large real-world retrospective series, hence it should be preferred for most suitable patients before glofitamab unless there are compelling reasons otherwise.

What outcomes are used to determine whether a patient is responding to treatment in clinical practice? How often should treatment response be assessed?

The first response assessment should be performed after cycle 2 of glofitamab. While PET-CT is the preferred imaging modality given modern lymphoma response assessment criteria (25), it is recognized that it may not be feasible in all areas of Canada to perform routine PET-CT in the community setting. Most patients who achieve a complete response to glofitamab do so by the first response assessment, although some patients with an initial partial response may later convert to a complete response. Repeat imaging may be considered after cycle 5 and 8 and at the end of treatment depending on the initial depth of response and physician discretion. Patients who maintain a complete response at the end of treatment are unlikely to relapse and may potentially be cured of their lymphoma, leading to long-term improvement in quality of life and survival.

What factors should be considered when deciding to discontinue treatment with the drug under review?

Treatment with glofitamab should be continued for a total duration of 12 cycles in responding patients or may be discontinued earlier due to disease progression or unacceptable adverse events. Of note, glofitamab is generally well tolerated and only 9% of patients discontinued treatment due to adverse events in the phase 2 trial.

What settings are appropriate for treatment with glofitamab? Is a specialist required to diagnose, treat, and monitor patients who might receive glofitamab?

Glofitamab should be administered by a Hematologist or Oncologist with familiarity managing the potential adverse events of bispecific antibodies, including CRS, neurotoxicity, cytopenias, infections, hypogammaglobulinemia, tumor lysis syndrome, and tumor flare. A brief period of inpatient monitoring for CRS may be required during the dose-ramp up phase, and patients should receive the first three doses in or nearby a facility with access to tocilizumab and intensive care unit support for rare occurrences of high-grade CRS. It is rare for CRS to occur after the third dose of glofitamab. In general, bispecific antibodies such as glofitamab are associated with significantly lower rates of severe CRS and less neurotoxicity than many CAR-T cell products, particularly with obinutuzumab/corticosteroid pre-medication and ramp-up dosing. It is important to recognize that as an ‘off the shelf’ therapy in a common disease, these agents will be used in the community hospital setting, thus improving patient access and convenience.

Education for treatment sites to manage these toxicities is ongoing. Experience to date has been generally limited to a few clinical trial centres, but a larger number of centres (including community practices) will be participating in upcoming studies of bispecific antibodies in lymphoma and myeloma.

Additional Information

We acknowledge the phase 2 trial evaluating glofitamab was non-randomized and did not include a comparator arm, which may introduce uncertainty in determining the clinical effectiveness of glofitamab compared to other existing treatment options. However, glofitamab achieved remarkably durable complete responses in a high-risk cohort of patients with median 3 prior lines of therapy and high rates of primary refractory disease (58%), refractoriness to last therapy (86%), and refractoriness to CAR-T cell therapy (30%). The real-world evidence and clinical trials in this setting with typical populations of relapsed/refractory LBCL are consistent (12, 13, 16, 17, 26), and it appears clear that bispecific antibodies represent an improvement over other currently available therapies.

Glofitamab has a novel immune-based mechanism of action, is quickly-available 'off the shelf', has a favorable safety profile, has a fixed duration of treatment, and may have curative potential, making it the treatment of choice for many Hematologists/Oncologists for patients who have previously received or cannot receive CAR-T cell therapy. Indeed, bispecific antibodies such as glofitamab fulfill an important unmet need and represent the most promising therapeutic breakthrough in the treatment of LBCL since the development of CAR-T cell therapy, the approval of which was also initially based on single-arm phase 2 trials.

We acknowledge the inclusion of DLBCL NOS, transformed follicular lymphoma, and primary mediastinal B-cell lymphoma under the requested indication. However, other histologic subtypes of LBCL are generally treated similarly as DLBCL NOS and are likely to benefit from glofitamab as well. For example, 25% of patients with double-hit lymphoma (high-grade B-cell lymphoma with MYC and BCL2 rearrangements) achieved a complete response to glofitamab in the phase 2 trial, which is a favorable outcome for this poor-prognosis subtype of LBCL.

Conflict of Interest Declarations — Lymphoma Canada

To maintain the objectivity and credibility of the CADTH drug review programs, all participants in the drug review processes must disclose any real, potential, or perceived conflicts of interest. This conflict of interest declaration is required for participation. Declarations made do not negate or preclude the use of the clinician group input. CADTH may contact your group with further questions, as needed. Please refer to the Procedures for CADTH Drug Reimbursement Reviews (section 6.3) for further details.

Did you receive help from outside your clinician group to complete this submission?

No.

Did you receive help from outside your clinician group to collect or analyze any information used in this submission?

No.

List any companies or organizations that have provided your group with financial payment over the past two years AND who may have direct or indirect interest in the drug under review. Please note that this is required for *each clinician* who contributed to the input.

Declaration for Clinician 1
Name: Robert Puckrin

Position: Hematologist, Tom Baker Cancer Centre and University of Calgary

Date: 15-06-2023

Table 13: COI Declaration for Lymphoma Canada — Clinician 1

Company	$0 to 5,000	$5,001 to 10,000	$10,001 to 50,000	In Excess of $50,000
Beigene	X	—	—	—
Kite/Gilead	X	—	—	—

Declaration for Clinician 2
Name: John Kuruvilla

Position: Hematologist, Princess Margaret Cancer Centre

Date: 17-Jun-2023

Table 14: COI Declaration for Lymphoma Canada — Clinician 2

Company	$0 to 5,000	$5,001 to 10,000	$10,001 to 50,000	In Excess of $50,000
Roche	—	—	X	—
Kite/Gilead	—	—	X	—
Abbvie	—	X	—	—
Novartis	—	X	—	—

Declaration for Clinician 3
Name: Carolyn Owen

Position: Hematologist, Tom Baker Cancer Centre and University of Calgary

Date: 15-06-2023

Table 15: COI Declaration for Lymphoma Canada — Clinician 3

Company	$0 to 5,000	$5,001 to 10,000	$10,001 to 50,000	In Excess of $50,000
Roche	X	—	—	—
Abbvie	—	—	X	—
Beigene	—	—	X	—
Astrazeneca	—	—	X	—
Incyte	—	X	—	—
Novartis	—	X	—	—
Merck	—	X	—	—

Declaration for Clinician 4
Name: Mona Shafey

Position: Hematologist, Tom Baker Cancer Centre and University of Calgary

Date: 18-07-2023

Table 16: COI Declaration for Lymphoma Canada — Clinician 4

Company	$0 to 5,000	$5,001 to 10,000	$10,001 to 50,000	In Excess of $50,000
Roche	X	—	—	—
Incyte	X	—	—	—
Kite	X	—	—	—
BMS	X	—	—	—

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