SMC2614

glofitamab concentrate for solution for infusion (Columvi®)

Roche Products Ltd

10 May 2024

The Scottish Medicines Consortium (SMC) has completed its assessment of the above product and advises NHS Boards and Area Drug and Therapeutic Committees (ADTCs) on its use in NHSScotland. The advice is summarised as follows:

ADVICE: following a full submission assessed under the end of life and orphan medicine process

glofitamab (Columvi®) is accepted for use within NHSScotland.

Indication under review: as monotherapy for the treatment of adult patients with relapsed or refractory (R/R) diffuse large B-cell lymphoma (DLBCL), after two or more lines of systemic therapy.

In a phase I/II open-label study, 40% of patients treated with glofitamab who had R/R DLBCL after two or more lines of systemic therapy had a complete response.

This advice applies only in the context of an approved NHSScotland Patient Access Scheme (PAS) arrangement delivering the cost-effectiveness results upon which the decision was based, or a PAS/ list price that is equivalent or lower.

This advice takes account of the views from a Patient and Clinician Engagement (PACE) meeting.

Vice Chair
Scottish Medicines Consortium

1. Clinical Context

1.1. Medicine background

Glofitamab is a bispecific antibody that binds bivalently to CD20 expressed on the surface of B cells and monovalently to CD3 in the T-cell receptor complex expressed on the surface of T cells. The simultaneous binding to CD20 and CD3 mediates glofitamab's formation of an immunological synapse with subsequent T-cell activation and proliferation, secretion of cytokines and release of cytolytic proteins that result in the lysis of CD20-expressing B cells.[1]

Glofitamab is administered by intravenous infusion up to a maximum of 12 cycles (each cycle is 21 days) or until disease progression or unmanageable toxicity. Dosing begins with a step-up dosing schedule leading to the recommended dose of 30 mg (on day one only of the 21-day cycles). For full information on administration of glofitamab, including pre-treatment with obinutuzumab, pre-medication/prophylaxis treatment, and glofitamab dose step-up schedule, refer to Summary of Product Characteristics (SPC).[1]

1.2. Disease background

Diffuse large B-cell lymphoma (DLBCL) is the most common non-Hodgkin lymphoma (NHL), accounting for approximately 30% to 40% of all cases. The incidence increases with age with a median age at diagnosis of 64 years. Risk factors include a family history of lymphoma, autoimmune disease, human immunodeficiency virus (HIV) infection, hepatitis C virus (HCV) seropositivity, a high body mass as a young adult and some occupational exposures. Although approximately half of newly diagnosed patients with DLBCL receive curative treatment, the disease is aggressive and approximately 30% of cases relapse and 10% to 15% are refractory to first-line therapy.[3, 4, 8, 9]

1.3. Treatment pathway and relevant comparators

Primary treatment of relapsed/refractory DLBCL depends on the individual's eligibility for transplant. Enrolment in clinical trials is usually considered where possible. Guidelines recommend that patients deemed fit for transplant receive salvage chemotherapy followed by autologous stem cell transplant (ASCT). For patients with relapsed or refractory DLBCL after two or more lines of systemic therapy, the CAR-T cell products axicabtagene ciloleucel and tisagenlecleucel should be considered; SMC has accepted axicabtagene ciloleucel (SMC2189) and tisagenlecleucel (SMC2200) in this setting. For patients who are not candidates for haematopoietic stem cell transplant (HSCT), polatuzumab vedotin in combination with bendamustine and rituximab is a treatment option (SMC2524). Gemcitabine or etoposide-based chemotherapy regimens may also be used in this setting in combination with rituximab. Tafasitamab in combination with lenalidomide followed by tafasitamab monotherapy for the treatment of adult patients with relapsed or refractory DLBCL who are not eligible for ASCT is not recommended by SMC (SMC2522). SMC has also recently accepted polatuzumab vedotin in combination with rituximab, cyclophosphamide, doxorubicin, and prednisone (R-CHP), for restricted use for patients with previously untreated DLBCL. Therefore, the treatment pathway for relapsed or refractory DLBCL is changing and availability of polatuzumab vedotin first line may displace its use in later lines of therapy.[2]

1.4. Category for decision-making process

Eligibility for interim acceptance decision option
Glofitamab has conditional marketing authorisation from the Medicines and Healthcare Products Regulatory Agency (MHRA).

Glofitamab received an Innovation Passport allowing entry into the Innovative Licensing and Access Pathway (ILAP).
Glofitamab received a positive scientific opinion under the Early Access to Medicines Scheme (EAMS) with the Medicines and Healthcare Products Regulatory Agency (MHRA).

Eligibility for a PACE meeting
Glofitamab meets SMC end of life and orphan criteria for this indication.

2. Summary of Clinical Evidence

2.1. Evidence for the licensed indication under review

Evidence to support the efficacy and safety of glofitamab for the treatment of R/R DLBCL comes from study NP30179.

Table 2.1. Overview of relevant studies[3, 5]

Criteria	Study NP30179 (DLBCL expansion cohorts)
Study design	International, multicentre, open-label, phase I/II study.
Eligible patients	The following key criteria apply specifically to the patients relevant to the submission: • Histologically confirmed DLBCL (not otherwise specified), transformed follicular lymphoma, high-grade B-cell lymphoma, or primary mediastinal large B-cell lymphoma. • Age ≥ 18 years. • ECOG performance status of 0 or 1. • Disease that had relapsed after, or was refractory to, at least two previous lines of therapy including at least one anti-CD20 antibody-containing regimen and at least one anthracycline-containing regimen.
Treatments	Pre-treatment with obinutuzumab 1,000 mg IV seven days before the first dose of glofitamab to alleviate the extent of cytokine release and associated safety issues as well as ADA formation. Glofitamab was then administered IV as 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). Patients were treated for a maximum of 12 cycles or until disease progression or unacceptable toxicity.
Randomisation	Not applicable.
Primary outcome	Complete response (CR) as assessed by independent review committee according to standard NHL response criteria (Lugano classification).
Secondary outcomes	CR as assessed by investigator, ORR, DOCR, DOR, PFS, OS.
Statistical analysis	Efficacy analyses were performed in the intention-to-treat population, which included all patients who were intended to be treated at the established phase 2 dose (2.5/10/30 mg step-up dosing schedule).

Abbreviations: ADA = antidrug antibodies; DLBCL = diffuse large B-cell lymphoma; DOCR = duration of complete response; DOR = duration of response; ECOG = Eastern Cooperative Oncology Group; IV = intravenously; NHL = non-

Hodgkin's lymphoma; ORR = objective response rate; OS = overall survival; PFS = progression-free survival; R/R = relapsed/refractory.

Results from study NP30179 are presented in Table 2.2 below. The company provided data at a later cutoff (16 January 2023) which are confidential.

Table 2.2 Key efficacy results from NP30179 for the primary study population (n=155).[3, 5]

	Glofitamab 2.5 mg/10 mg/30 mg step-up dosing schedule			
Data-cut	**14 March 2022 (n=155)**		**15 June 2022 (n=155)**	
	IRC	**INV**	**IRC**	**INV**
Primary outcome: CR (as per Lugano criteria)				
CR	39%	37%	40%	38%
ORR	52%	57%	52%	59%
Secondary outcome: DOCR				
Median DOCR (months)	NE	19.8	NE	NE
Response at 12 months	78%	72%	73%	NR
Secondary outcome: DOR*				
Median DOR (months)	18.4	10.4	16.8	10.4
Response at 12 months	64%	49%	60%	NR
Secondary outcome: PFS				
Median PFS (months)	4.9	3.8	4.9	3.8
PFS rate at 12 months	37%	30%	35%	31%
Secondary outcome: OS				
Median OS (months)	11.5		12.0	
OS rate at 12 months	50%		50%	

Abbreviations: CR = complete response; DOCR = duration of complete response; DOR = duration of objective response; INV = investigator-assessed; IRC = independent review committee; NE = not evaluable; NR = not reported; ORR = objective response rate (complete response and partial response); OS = overall survival; PFS = progression-free survival.

2.2. Health-related quality of life outcomes

Health Related Quality of Life (HRQoL) was assessed using the following questionnaires: the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC QLQ-C30) and the Functional Assessment of Cancer Therapy – Lymphoma (FACT-Lym) Lymphoma Subscale (LymS). These instruments were used at baseline and every 3 months during the post treatment follow-up. Very slight benefit was inconsistently observed in patient reported outcomes based on the small number of patients that completed the questionnaires and continued treatment. These results should be interpreted with caution.[3]

2.3. Indirect evidence to support clinical and cost-effectiveness comparisons

In the absence of direct evidence comparing glofitamab with relevant comparators, the submitting company presented an indirect treatment comparison (ITC). This has been used to inform the economic case.

Table 2.3: Summary of indirect treatment comparison

Criteria	Overview
Design	Three unanchored matching adjusted indirect treatment comparisons (MAICs) and one propensity score analysis.

Population	**MAIC versus axicabtagene ciloleucel** Adults with refractory DLBCL (or relapse within 12 months of autologous stem-cell transplant). **MAIC versus tisagenlecleucel** Adults with R/R DLBCL who had received ≥2 prior lines of treatment (including rituximab and an anthtracycline). **MAIC versus rituximab plus bendamustine** Adults with R/R DLBCL with confirmed CD20 positive DLBCL. **Propensity score analysis versus polatuzumab vedotin plus rituximab plus bendamustine** Adults with R/R DLBCL who had received ≥ 2 prior lines of treatment.
Comparators	Axicabtagene ciloleucel, tisagenlecleucel, rituximab plus bendamustine, polatuzumab vedotin plus rituximab plus bendamustine. The submitting company used rituximab plus bendamustine as a proxy for other rituximab-chemotherapy combinations in the submission.
Studies included	ZUMA-1 (axicabtagene ciloleucel), JULIET (tisagenlecleucel), Hong 2018 (rituximab plus bendamustine), GO29365 (polatuzumab vedotin plus rituximab plus bendamustine).
Outcomes	OS, PFS, ORR, CR, DOR, DOCR, and treatment discontinuation due to AEs.
Results	Glofitamab was significantly inferior to axicabtagene ciloleucel for OS; confidence intervals crossed 1 for PFS suggesting no evidence of a difference. No evidence of a difference was observed between glofitamab and tisagenlecleucel for both OS and PFS. No evidence of a difference was observed between glofitamab and polatuzumab vedotin plus bendamustine plus rituximab for both OS and PFS. Glofitamab was significantly superior to bendamustine plus rituximab for both OS and PFS.

*Other data were also assessed but remain confidential.**

3. Summary of Safety Evidence

No comparative safety data are available. Refer to the SPC for details.[1]

In the NP30179 study at data cut-off 15 June 2022 for the primary safety population (n=154), the median duration of treatment was 79 days (range: 1 to 326 days). Any adverse event (AE) was reported by 99% (n=152) of patients and 91% (n=140) of any AEs were glofitamab-related. Patients reporting any serious AE was 49%, and 30% were glofitamab-related; AEs of grade 3 and above were reported in 64% of patients, and 44% were glofitamab-related; and events that led to discontinuation of glofitamab were reported in 9.1% of patients, 3.2% were glofitamab-related.[3]

The key AEs of interest related to glofitamab included cytokine release syndrome (CRS), neutropenia, serious infections, neurological adverse events and tumour flare. CRS was reported by 64% of patients; neutropenia was reported in 38% of patients; serious infections were reported in 18% of patients; grade ≥ 2 neurological AEs were reported by 14% of patients; and tumour flare was reported by 11% of patients. Hypogammaglobulinemia is a rare AE that may require long-term treatment with immunoglobulins; 2 out of 155 patients in NP30179 required immunoglobulin treatment. The safety profile of glofitamab appears to be manageable and acceptable in this disease setting where patients have poor prognosis and limited treatment options.[3]

4. Summary of Clinical Effectiveness Considerations

4.1. Key strengths

- A CR rate of 40% in patients with R/R DLBCL after two or more lines of systemic therapy is a promising result and suggests clinically meaningful benefit with glofitamab for some patients.[3]
- Patients with difficult-to-treat disease, such as those who had been previously treated with CAR-T treatments (approximately 34% of the relevant study population), also appear to derive benefit from treatment with glofitamab.[3]

4.2. Key uncertainties

- NP30179 was a single-arm, phase I/II study which are prone to various biases. The treatment effect of glofitamab relative to relevant comparators in clinical practice is therefore uncertain.
- There is limited duration of follow-up. For example, at the latest published data-cut (June 2022), the median duration of follow-up for cohort D3 was 15 months.[3] However, the company provided confidential data from a later data cut which provided reassurance.
- The sample size was small (n=155), however this may be expected in an orphan condition in a patient population that has been heavily pre-treated.[3]
- CR and ORR are appropriate outcomes in phase II studies that measure anti-tumour activity. However, it may be unclear to what degree this anti-tumour activity corresponds to more robust measures of clinical benefit, such as overall survival (OS) or progression-free survival (PFS). Given the limitations above, it is difficult to interpret the clinically relevant outcomes PFS and OS.[3, 6]
- There may be generalisability issues with the study population in terms of prior treatments. Due to the evolving treatment pathway, patients in clinical practice may have received different prior treatments compared with the study population of NP30179. The efficacy of glofitamab following treatment with polatuzumab vedotin in combination with bendamustine plus rituximab is unknown.[2]
- In the absence of direct evidence comparing glofitamab with relevant comparators in Scottish clinical practice, the company conducted ITCs, which have some limitations. Unanchored MAICs are inherently at risk of bias. There was no common control arm to anchor the indirect comparisons. Therefore, residual confounding due to unobserved characteristics and other characteristics that were not or could not be adjusted for may bias the results. Effective sample sizes were substantially reduced after matching, suggesting poor overlap between study populations. Confidence intervals were wide suggesting uncertainty in the results. HRQoL was not assessed. In summary, due to these limitations, the results of the ITCs are highly uncertain.

4.3. GB/EMA conditional marketing authorisation specific obligations

As part of the specific obligations outlined by the EMA, the submitting company will provide updated results from NP30179 with a minimum follow-up of 2 years from the end of treatment of the last patient enrolled in the study. The EMA specific obligations are unlikely to address the key uncertainties identified in the clinical evidence presented.

4.4. Clinical expert input

Clinical experts consulted by SMC considered that glofitamab fills an unmet need in this therapeutic area, as there are limited satisfactory treatment options currently available. Clinical experts considered glofitamab to be a therapeutic advancement as an additional treatment option that can achieve disease control in some patients. Clinical experts state that glofitamab would be used an alternative to CAR-T cell treatments, or in patients where CAR-T cell treatment is inappropriate (for example if a patient was not considered fit enough for CAR-T cell treatment), or in patients who have received CAR-T cell treatment and have experienced disease progression.

4.5. Service implications

Glofitamab may be less burdensome to the service than CAR-T cell treatments and is immediately available (there are lead times associated with making CAR-T cell treatments). However, when compared with other treatment options, it may be associated with considerable service burden. As an intravenous medicine, patients may be hospitalised to administer treatment and will need careful monitoring for adverse events such as CRS. Glofitamab has a fixed treatment duration which may have benefits for the service and patients.

5. Summary of Patient and Carer Involvement

A patient and clinician engagement (PACE) meeting with patient group representatives and clinical specialists was held to consider the added value of glofitamab as an orphan/end of life medicine, in the context of treatments currently available in NHSScotland.

The key points expressed by the group were:

- Relapsed or refractory DLBCL is an aggressive type of lymphoma (blood cancer) associated with poor prognosis and short life expectancy. Patients can experience a wide variety of symptoms, including enlarged lymph nodes, abdominal pain, nausea, cough, breathlessness, and B symptoms such as fevers, night sweats and unexplained weight loss. In addition to the physical symptoms of relapsed or refractory DLBCL, there is a significant mental burden for patients caused by worrying about relapsing or not responding to treatment; this can lead to anxiety or insomnia in some.
- There are a limited number of treatment options at present for relapsed or refractory DLBCL, and these treatments have limited efficacy and considerable side effects. Treatment regimens that include chemotherapy can have challenging and persistent side effects and CAR-T cell therapies are only provided by two hospitals in Scotland, and some patients may experience disease progression whilst they wait for the treatment to be manufactured. There are fewer treatment options for patients who have already received CAR-T therapy or polatuzumab vedotin (at earlier lines of treatment). There is therefore a high unmet need for patients with

relapsed or refractory DLBCL.

- Glofitamab has the potential to benefit patients greatly in this setting. It is believed to be a well-tolerated treatment which may achieve durable disease control in patients, that could result in improvements in survival and help to maintain a high quality of life. Some patients may spend less time in hospital compared with other treatments. The availability of glofitamab as a treatment option when disease relapses or fails to respond to treatment will likely have a large impact on the mental wellbeing of patients. It also provides an immediately and widely available treatment option, which could be particularly beneficial for patients who do not live near to the two specialist CAR-T treatment centres in Scotland.
- Friends, family, and carers experience significant stress and anxiety worrying about relapses or lack of treatment response, and often have to take on financial, caring, and at-home responsibilities. The availability of glofitamab is expected to alleviate some of the anxiety experienced by family members and carers, and if patient respond to treatment, the burden of care may be reduced as patients enjoy more independence.
- PACE participants noted that careful monitoring for CRS adverse events is required with glofitamab. However, these adverse events are mainly mild in severity, easily managed, and ultimately would not deter patients from wanting to commence treatment on glofitamab, since it is a promising treatment that can potentially prevent or prolong disease progression. They also highlighted that some patients might consider the potential duration of treatment with glofitamab (up to 12 cycles via intravenous infusion) to be long, although the fixed duration of treatment is seen as advantageous as patients have the chance of achieving treatment-free remission.

Additional Patient and Carer Involvement

We received a patient group submission from Lymphoma Action, which is a registered charity. Lymphoma Action has received 6.7% pharmaceutical company funding in the past two years, including from the submitting company. A representative from Lymphoma Action participated in the PACE meeting. The key points of their submission have been included in the full PACE statement considered by SMC.

6. Summary of Comparative Health Economic Evidence

6.1. Economic case

The submitting company provided an economic case, as presented in Table 6.1.

Table 6.1 Description of economic analysis

Criteria	Overview
Analysis type	Cost-utility analysis.
Time horizon	60 years.
Population	The submitting company requested SMC consider glofitamab as monotherapy for the treatment of adult patients with R/R DLBCL, after two or more lines of systemic therapy.

Comparators	• Rituximab in combination with bendamustine, representing rituximab in combination with chemotherapy. • Polatuzumab vedotin in combination with bendamustine and rituximab • CAR-T therapies of tisagenlecleucel and axicabtagene ciloleucel.
Model description	The model was a three-state partitioned survival model with progression free, progressed disease, and death health states. All patients entered the model in the progression free health state and remained in this health state until disease progression or death. In the progressed disease health state, patients either remained in this health state or transitioned to the death state. The model used weekly cycles and a half cycle correction.
Clinical data	Glofitamab PFS, OS, and time to off treatment (TTOT) data were from the NP30179 study (Jan 2023 data cut-off).[3, 5] Rituximab in combination with bendamustine PFS and OS data were from Hong et al., 2018[10] with TTOT data from the GO29365 study[11]. Polatuzumab vedotin in combination with bendamustine and rituximab PFS, OS and TTOT data were from the GO29365 study.[11] PFS and OS data for the CAR-T therapies of tisagenlecleucel and axicabtagene ciloleucel were from the ZUMA-1[12] and JULIET studies[13], respectively. Treatment-related AEs with a severity Grade of 3 or higher occurring in over 1% of patients were included in the model and were sourced from the NP30179 or comparator studies.
Extrapolation	PFS, OS, and TTOT data were extrapolated independently in each treatment arm. Glofitamab PFS and OS Kaplan- Meier data were adjusted using the matching adjusted indirect treatment comparison (MAIC) method in comparisons with rituximab in combination with bendamustine and CAR-T therapies, with the inverse probability of treatment weighting method used in the polatuzumab vedotin in combination with bendamustine and rituximab comparison. Glofitamab PFS and OS were extrapolated using the generalised gamma distribution in all comparisons, with TTOT extrapolated using the Kaplan- Meier data with an exponential tail. Rituximab in combination with bendamustine PFS and OS extrapolations used the log-logistic and log-normal distributions, respectively. Polatuzumab vedotin in combination with bendamustine and rituximab PFS and OS extrapolations used the generalised gamma distribution. Axicabtagene ciloleucel PFS and OS extrapolation used the Gompertz distribution. Tisagenlecleucel PFS and OS extrapolations used the generalised gamma distribution. TTOT for comparators used the observed data from the comparator studies, except for CAR-T therapies where the duration on treatment was assumed to last for a single model cycle. Background mortality was calculated using age-and gender-specific all-cause mortality rates by year in the general UK population. Background mortality was modelled as a function of the age distribution from NP30179, to reflect the slower increase in the average age of the cohort since younger patients have a lower risk of death compared to older patients. The mortality rates were also adjusted with a standardised mortality rate (SMR) adjustment of 9% to account for increased mortality risk due to excess comorbidities. A long-term remission assumption was included in the model. Patients alive and progression free at 3 years were assumed to enter long term remission. On entering remission, patients did not progress, reverted to general population utility values (assuming a 10% decrement), and did not accrue further costs. In addition, mortality risks for the remaining patients reverted to near general population (with the 9% SMR adjustment to account for comorbidities).

Quality of life	Utility values were derived from mapping EORTC QLQ-C30 data from the NP30179 study to EQ-5D-3L using the Longworth et al, 2014 mapping algorithm.[14] Utility values were estimated for PFS on treatment (0.729), PFS off treatment (0.751), and progressed disease (0.637) and were treatment independent. Utilities were adjusted for age in the model using an age-adjusted health state utility value coefficient.[15] Adverse event dis-utilities were not included in the base case as the company viewed these as being captured within the PFS on treatment utility values.
Costs and resource use	The model included treatment acquisition, administration, subsequent treatments, adverse reaction costs, supportive care, and one-off progression costs.
PAS	A Patient Access Scheme (PAS) was submitted by the company and assessed by the Patient Access Scheme Assessment Group (PASAG) as acceptable for implementation in NHSScotland. Under the PAS, a discount was offered on the list price. A PAS discount is in place for polatuzumab vedotin, axicabtagene ciloleucel, and tisagenlecleucel, and these were included in the results used for decision-making by using estimates of the comparator PAS price.

6.2. Results

The base case results are presented in the table below. The majority of incremental QALYs were generated in the progression free health state across comparisons. The majority of incremental costs were attributed to treatment acquisition costs across comparisons.

Table 6.2 : Base-case results at list prices

Technologies	ICER (£/QALY)
Glofitamab versus BR	20,644
Glofitamab verus polatuzumab vedotin-BR	Dominant
Glofitamab versus axicabatagene ciloleucel	167,750 (SW)
Glofitamab versus tisagenlecleucel	Dominant

Abbreviations: B: bendamustine; ICER: incremental cost-effectiveness ratio; R: rituximab; QALYs: quality-adjusted life years; Dominant= The assessed medicine was estimated as having lower costs and greater health outcomes than the comparator; SW quadrant: The estimated result sits in the South-West quadrant of the cost-effectiveness plane meaning the assessed medicine had lower costs and lower health outcomes than the comparator.

6.3. Sensitivity analyses

The base case results were most sensitive to a shortened time horizon, alternative glofitamab PFS extrapolation distributions, the removal of the long-term remission assumption, and the application of the proportional hazards assumption.

Table 6.3: Scenario analysis results at list prices

	Base case	Scenario	ICER vs BR (£)	ICER vs pola-BR (£)	ICER vs axi-cel. (£)	ICER vs tisagen. (£)
	Base Case	-	**20,644**	**Dominant**	**167,750 (SW)**	**Dominant**
1	60-year time horizon	10-year time horizon	37,733	2,290	291,518 (SW)	Dominant
2	60-year time horizon	30-year time horizon	22,255	Dominant	176,611 (SW)	Dominant

3	Glofitamab PFS extrapolation – Generalised gamma	Glofitamab PFS extrapolation - Log-normal	29,235	23,456	153,407 (SW)	Dominant
4	Glofitamab OS extrapolation – Generalised gamma	Glofitamab OS extrapolation - Gompertz	21,672	7,345	178,165 (SW)	Dominant
5	Pola-BR PFS extrapolation – Generalised gamma	Pola-BR PFS extrapolation – Gompertz	22,644	Dominant	167,750 (SW)	Dominant
6	Pola-BR OS extrapolation – Generalised gamma	Pola-BR OS extrapolation – Gompertz	20,644	Dominant	167,750 (SW)	Dominant
7	Independent extrapolation	Proportional hazards applied for PFS and OS (all comparators)	27,324	13,543	154,217 (SW)	Dominant
8	Independent extrapolation	Proportional hazards applied using HRs of PFS=OS=1 for tisagen. and pola-BR only	20,644	Dominated	167,750 (SW)	37,217,588 (SW)
9	Long term remission – included	Long term remission – excluded	36,180	10,965	133,378 (SW)	Dominant
10	Age distribution background mortality	Average cohort age background mortality (37 year time horizon)	23,346	Dominant	170,143 (SW)	Dominant

Abbreviations: axi-cel = axicabtagene ciloleucel; BR = rituximab in combination with bendamustine; EORTC-QLQ-C30 = European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire; ITC = indirect treatment comparison; OS = overall survival; PFS = progression-free survival; pola-BR = polatuzumab-vedotin plus rituximab in combination with bendamustine; SW = south-west; tisagen = tisagenlecleucel; TTOT = time to off treatment.

Dominant: The assessed medicine was estimated as having lower costs and greater health outcomes than the comparator. Dominated: The assessed medicine was estimated as having higher costs and lower outcomes than the comparator. SW quadrant: The estimated result sits in the South-West quadrant of the cost-effectiveness plane meaning the assessed medicine had lower costs and lower health outcomes than the comparator.

6.4. Key strengths

- The model structure was appropriate to capture disease progression for patients receiving treatment for R/R DLBCL.
- The submitting company conducted a systematic literature review for relevant health state utility value studies showing consistency with those used in the base case.
- The company used a costing algorithm to calculate the combination of small and large vials to minimise the comparator treatment acquisition costs.

6.5. Key uncertainties

- The indirect treatment comparison was subject to limitations, with small effective sample sizes for glofitamab data after matching. There were wide confidence intervals for PFS and OS hazard ratios. Although results demonstrated glofitamab had the potential to improve PFS and OS compared to tisagenlecleucel and polatuzumab vedotin in combination with bendamustine and rituximab, the PFS and OS differences in these comparisons were insignificant. Fully assessing all ITC limitations was challenging, but there were scenarios considered to seek to understand the uncertainty generated. If applying proportional hazards and setting PFS and OS hazard ratios to 1 in the polatuzumab vedotin in combination with bendamustine and rituximab and tisagenlecleucel comparisons, economic results were impacted (Scenario 8). Although the submitting company provided evidence to question the use of a proportional hazards assumption in the extrapolation of comparative efficacy data, there remains some uncertainty over the comparative efficacy of glofitamab and face validity of economic results.

- There was some uncertainty in the extrapolation of glofitamab PFS outcome data. An appropriate alternative PFS survival curve, the log-normal, generated an increased ICER (Scenario 3). Although meeting statistical fit criteria and reflective of the declining observed hazard, this curve was not selected based on the reasoning that it did not fit the tail of the observed data and underestimated the PFS and was not supported by the submitting company's clinical experts. However, this underestimation does not appear to be substantial in the extrapolation plots. Although the base case PFS extrapolation may be reasonable, it should be noted that there is some ICER uncertainty generated from potential alternatives. Furthermore, hazard plots across various extrapolations in the model also indicated complex hazard shapes, where flexible models may have been appropriate for consideration. The company confirmed these were not considered due to an expected limited impact on conclusions, although no results were provided.

- SMC experts highlighted glofitamab may be used in those that receive CAR-T cell treatments and experience disease progression. Although the NP30179 study data for glofitamab contained 33% who had received prior CAR-T cell therapy, as these patients were not considered a subgroup in the economic analysis no ICER results were available to isolate cost-effectiveness of glofitamab in patients that receive CAR-T cell treatments and

experience disease progression. The subgroup analysis was requested from the submitting company, but this was not provided due to challenges of performing such analysis.

*Other data were also assessed but remain confidential.**

7. Conclusion

The Committee considered the benefits of glofitamab in the context of the SMC decision modifiers that can be applied when encountering high cost-effectiveness ratios and agreed that as glofitamab is an orphan medicine, SMC can accept greater uncertainty in the economic case. After considering all the available evidence and the output from the PACE process, the Committee accepted glofitamab for use in NHSScotland.

8. Guideline and Protocols

The National Institute for Health and Care Excellence (NICE) published clinical guideline NG52: Non-Hodgkin's lymphoma: diagnosis and management in July 2016, which was last updated in October 2021.[7]

The British Committee for Standards in Haematology published guidelines on the management of large B-cell lymphoma in 2016.[8]

The European Society for Medical Oncology published guidelines for diagnosis, treatment and follow-up of diffuse large B-cell lymphoma in 2015.[9]

9. Additional Information

9.1. Product availability date

16 October 2023

Table 9.1 List price of medicine under review

Medicine	Dose regimen	Cost per cycle (£)
glofitamab	**2.5 mg IV on day 8 and 10 mg IV on day 15 of cycle 1, then 30 mg IV on day 1 of 21-day cycle for 11 cycles[1]**	**£3,435 - cycle 1 £8,244 – cycle 2-11**

IV = intravenous; Costs from MIMS online on 02 February 2024. Costs do not take any patient access schemes into consideration.

10. Company Estimate of Eligible Population and Estimated Budget Impact

The submitting company estimated there would be 16 patients eligible for treatment with glofitamab in year 1 and 17 patients eligible for treatment in year 5. The estimated uptake rate was 1% in year 1 and 12% in year 5 with no discontinuation rate. This results in 0 patients estimated to receive treatment in year 1 rising to 2 patients in year 5.

SMC is unable to publish the with PAS budget impact due to commercial in confidence issues. A budget impact template is provided in confidence to NHS health boards to enable them to estimate the predicted budget with the PAS. This template does not incorporate any PAS discounts

associated with comparator medicines or PAS associated with medicines used in a combination regimen.

*Other data were also assessed but remain confidential.**

References

1. Roche Products Ltd. Glofitamab 2.5 mg concentrate for solution for infusion (Columvi®). Summary of product characteristics. Electronics Medicines Compendium. https://www.medicines.org.uk Last updated 16 October 2023.
2. Cancer Research UK. Diffuse large B cell lymphoma. https://www.cancerresearchuk.org/about-cancer/non-hodgkin-lymphoma/types/diffuse-large-B-cell-lymphoma. Last updated 24 November 2020.
3. European Medicines Agency (EMA). European Public Assessment Report. Glofitamab (Columvi). EMA/228393/2023. 26 April 2023 www.ema.europa.eu
4. Sehn LH, Goy A, Offner FC, Martinelli G, Caballero MD, Gadeberg O, et al. Randomized Phase II Trial Comparing Obinutuzumab (GA101) With Rituximab in Patients With Relapsed CD20+ Indolent B-Cell Non-Hodgkin Lymphoma: Final Analysis of the GAUSS Study. J Clin Oncol. 2015;33(30):3467-74. Epub 20150817. 10.1200/jco.2014.59.2139
5. Dickinson MJ, Carlo-Stella C, Morschhauser F, Bachy E, Corradini P, Iacoboni G, et al. Glofitamab for Relapsed or Refractory Diffuse Large B-Cell Lymphoma. N Engl J Med. 2022;387(24):2220-31. Epub 20221211. 10.1056/NEJMoa2206913.
6. European Medicines Agency (EMA). Guideline on the clinical evaluation of anticancer medicinal products. EMA/CHMP/205/95 Rev.6. 18 November 2023. www.ema.europa.eu
7. National Institute of Health and Care Excellence (NICE). Non-Hodgkin's lymphoma: diagnosis and management, NICE guideline NG52. https://www.nice.org.uk/. Last updated October 2021.
8. Chaganti S, Illidge T, Barrington S, McKay P, Linton K, Cwynarski K, et al. Guidelines for the management of diffuse large B-cell lymphoma. Br J Haematol. 2016;174(1):43-56. Epub 20160516. 10.1111/bjh.14136
9. Tilly H, Gomes da Silva M, Vitolo U, Jack A, Meignan M, Lopez-Guillermo A, et al. Diffuse large B-cell lymphoma (DLBCL): ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2015;26 Suppl 5:v116-25. 10.1093/annonc/mdv304
10. Hong JY, Yoon DH, Suh C, Kim WS, Kim SJ, Jo JC, et al. Bendamustine plus rituximab for relapsed or refractory diffuse large B cell lymphoma: a multicenter retrospective analysis. Annals of hematology. 2018;97(8):1437-43
11. Sehn LH, Herrera AF, Flowers CR, Kamdar MK, McMillan A, Hertzberg M, et al. Polatuzumab vedotin in relapsed or refractory diffuse large B-cell lymphoma. J Clin Oncol. 2020;38(2):155–65.
12. Jacobson C. Long-Term (4-and 5-Year) Overall Survival in ZUMA-1, the Pivotal Study of Axicabtagene Ciloleucel in Patients with Refractory Large B-Cell Lymphoma. Presented at the 63rd ASH meeting and exposition, December 11-14 2021, Atlanta, GA, USA. 2021;Poster number 1764 (poster available).

13. Schuster SJ, Bishop MR, Tam CS, Waller EK, Borchmann P, McGuirk JP, et al. Tisagenlecleucel in Adult Relapsed or Refractory Diffuse Large B-Cell Lymphoma. N Engl J Med. 2019;380(1):45-56

14. Longworth L, Yang Y, Young T, Mulhern B, Hernandez Alava M, Mukuria C, et al. Use of generic and condition-specific measures of health-related quality of life in NICE decision-making: a systematic review, statistical modelling and survey. Health Technol Assess. 2014;18(9):1-224.

15. Ara R, Brazier JE. Populating an economic model with health state utility values: moving toward better practice. Value Health. 2010;13(5):509-518. doi:10.1111/j.1524-4733.2010.00700.x.

This assessment is based on data submitted by the applicant company up to and including **15 March 2024**.

**Agreement between the Association of the British Pharmaceutical Industry (ABPI) and the SMC on guidelines for the release of company data into the public domain during a health technology appraisal:*https://www.scottishmedicines.org.uk/about-us/policies-publications/

Medicine prices are those available at the time the papers were issued to SMC for consideration. SMC is aware that for some hospital-only products national or local contracts may be in place for comparator products that can significantly reduce the acquisition cost to Health Boards. These contract prices are commercial in confidence and cannot be put in the public domain, including via the SMC Detailed Advice Document. Area Drug and Therapeutics Committees and NHS Boards are therefore asked to consider contract pricing when reviewing advice on medicines accepted by SMC.

Patient access schemes: A patient access scheme is a scheme proposed by a pharmaceutical company in order to improve the cost-effectiveness of a medicine and enable patients to receive access to cost-effective innovative medicines. A Patient Access Scheme Assessment Group (PASAG), established under the auspices of NHS National Services Scotland reviews and advises NHSScotland on the feasibility of proposed schemes for implementation. The PASAG operates separately from SMC in order to maintain the integrity and independence of the assessment process of the SMC. When SMC accepts a medicine for use in NHSScotland on the basis of a patient access scheme that has been considered feasible by PASAG, a set of guidance notes on the operation of the scheme will be circulated to Area Drug and Therapeutics Committees and NHS Boards prior to publication of SMC advice.

Advice context:

No part of this advice may be used without the whole of the advice being quoted in full.

This advice represents the view of the Scottish Medicines Consortium and was arrived at after careful consideration and evaluation of the available evidence. It is provided to inform the considerations of Area Drug & Therapeutics Committees and NHS Boards in Scotland in determining medicines for local use or local formulary inclusion. This advice does not override the individual responsibility of health professionals to make decisions in the exercise of their clinical

judgement in the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.