Single Technology Appraisal

Glofitamab for treating relapsed or refractory diffuse large B-cell lymphoma after 2 or more systemic treatments [ID3970]

Committee Papers

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

Glofitamab for treating relapsed or refractory diffuse large B-cell lymphoma after 2 or more systemic treatments [ID3970]

Contents:

The following documents are made available to stakeholders:

Access the **final scope** and **final stakeholder list** on the NICE website.

1. **Company submission** from Roche Products:
   a. Full submission
   b. Summary of Information for Patients (SIP)

2. **Clarification questions and company responses**

3. **Patient group, professional group, and NHS organisation submission** from:
   a. Lymphoma Action
   b. National Cancer Research Institute-Association of Cancer Physicians-Royal College of Physicians-Royal College of Radiologists

4. **External Assessment Report** prepared by Centre for Reviews and Dissemination and Centre for Health Economics – York

5. **External Assessment Group response to factual accuracy check of EAR**

6. **Technical engagement response** from Roche Products
   a. Technical engagement response
   b. Technical engagement supplementary evidence

7. **Technical engagement response & personal statement from experts:**
   a. Dr Wendy Osborne – clinical expert, nominated by Roche
   b. Dr William Townsend – clinical expert, nominated by National Cancer Research Institute-Association of Cancer Physicians-Royal College of Physicians-Royal College of Radiologists

8. **Technical engagement response from consultees and commentators:**
   a. Royal College of Pathologists

9. **External Assessment Group critique of company response to technical engagement** prepared by Centre for Reviews and Dissemination and Centre for Health Economics – York

Any information supplied to NICE which has been marked as confidential, has been redacted. All personal information has also been redacted.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Glofitamab for treating relapsed or refractory diffuse large B-cell lymphoma after 2 or more systemic treatments [ID3970]

Document B

Company evidence submission

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B.1 Decision problem, description of the technology and clinical care pathway

B.1.1 Decision problem

The submission covers the technology's full marketing authorisation for this indication: glofitamab as monotherapy for the treatment of adult patients with relapsed or refractory diffuse large B-cell lymphoma (DLBCL), after two or more lines of systemic therapy.

Table 1: The decision problem

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
Population	Adults with relapsed or refractory diffuse large B-cell lymphoma	Adults with relapsed or refractory diffuse large B-cell lymphoma who have had two or more systemic treatments	To align with the anticipated wording of the glofitamab marketing authorisation.
Intervention	Glofitamab	Glofitamab	NA
Comparator(s)	Established clinical management without glofitamab, including but not limited to: • Chemotherapy with or without rituximab and with or without stem cell transplantation, such as: - DHAP (cisplatin, cytarabine, dexamethasone) - GDP (cisplatin, gemcitabine, dexamethasone) - ICE (ifosfamide, carboplatin, etoposide) - IVE (ifosfamide, epirubicin and etoposide)	• Rituximab-based chemotherapy (bendamustine plus rituximab [BR]) • Polatuzumab vedotin with rituximab and bendamustine (pola-BR) • Axicabtagene ciloleucel (axi-cil)	The three comparators were considered to be the most relevant to the decision problem based upon feedback from eight clinical experts at an Advisory Board. The consensus was that these treatments covered at least 80% of patients treated for DLBCL in the 3L+ setting. The remaining 20% comprised of best supportive care, or clinical trial enrolment, neither of which were listed in the scope, or would be considered appropriate comparators (1). Clinical expert feedback from an Advisory Board conducted by Roche in January 2023 suggested that rituximab with gemcitabine and oxaliplatin (R-GemOx) was the most widely used R-based chemotherapy regimen for the treatment of 3L+ DLBCL (1). However, in the absence of available evidence to put forward a comparison to R-GemOx, bendamustine

	• Polatuzumab vedotin with rituximab and bendamustine (if haematopoietic stem cell transplantation is not possible) • Pixantrone monotherapy • Axicabtagene ciloleucel (subject to ongoing NICE evaluation) • Tafasitamab with lenalidomide (if haematopoietic stem cell transplantation is not possible and subject to ongoing NICE evaluation)		plus rituximab (BR) has been used as a proxy for rituximab-based chemotherapy. In support of this approach, a retrospective analysis of the National Cancer Institute's Surveillance, Epidemiology and End Results (SEER) cancer registry database concluded OS outcomes were similar between patients with R/R DLBCL treated with BR or R-GemOx (2). Clinical experts consulted by Roche agreed that the approach taken was reasonable, and agreed that outcomes would likely be similar for 3L+ DLBCL patients treated with either of BR or R-GemOx (1). NCCN guidelines (3) and ESMO guidelines (4) suggest that patients who relapse after 2L therapy are unlikely to respond to subsequent therapy and therefore generally are not eligible for ASCT. As such, ASCT was not considered a relevant comparator in an appraisal of 3L+ DLBCL treatments. This view was supported by clinical experts consulted by Roche, who suggested that stem cell transplantation may be used in specific circumstances, but that the 3 main treatment options 3L+ were those chosen (1). Lastly, pixantrone was excluded as it is associated with poor outcomes and as a

			result is not commonly used in clinical practice in the UK; and tafa-len was excluded as it is subject to NICE evaluation/re-assessment following appeal.
Outcomes	The outcome measures to be considered include: • Overall survival • Progression-free survival • Response rates • Adverse effects of treatment • Health-related quality of life	In line with NICE scope	NA
Economic analysis	The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year. The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. Costs will be considered from an NHS and Personal Social Services perspective.	In line with NICE scope	NA

	The availability of any commercial arrangements for the intervention, comparator and subsequent treatment technologies will be taken into account. The availability of any managed access arrangement for the intervention will be taken into account.		
Special considerations including issues related to equity or equality	Not included in scope.	Existing geographical and sociodemographic inequity issues should be considered.	Glofitamab has the potential to be more accessible by a larger range of clinical centres than CAR-T-cell therapies (axicabtagene ciloleucel), helping reduce regional, rural–urban, and sociodemographic inequity issues resulting from uneven geographical allocation of CAR-T-cell therapy administration sites (see Section B.1.4).

B.1.2 Description of the technology being evaluated

Table 2: Technology being evaluated

UK approved name and brand name	Glofitamab (brand name to be determined)
Mechanism of action	Glofitamab is a full-length, fully humanised IgG1 bispecific monoclonal antibody that recognises and binds bivalently to CD20 expressed on the surface of B-cells, and monovalently to CD3 in the T-cell receptor (TCR) complex expressed 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 T-cell activation and proliferation, secretion of cytokines and release of cytolytic proteins that results in the lysis of CD20-expressing B-cells (5). The CD3-binding region of glofitamab is fused to one of the CD20-binding regions in a head-to-tail fashion via a flexible linker; this head-to-tail fusion format is designed to increase potency and stabilise the T-cell-target-cell immune synapse (6, 7). The immunoglobulin G format of glofitamab prolongs its half-life, while the silent Fc region is designed to avoid the activation of nonspecific immunomodulatory anti-tumour effects (6, 7).
Marketing authorisation/CE mark status	On 10th October 2022, a Promising Innovative Medicine (PIM) Designation was granted and an Early Access To Medicines Scheme (EAMS) dossier was submitted to the MHRA. A positive CHMP opinion is anticipated in [redacted], and a marketing authorisation (MA) is expected in [redacted].
Indications and any restriction(s) as described in the summary of product characteristics (SmPC)	The indication from the granted MHRA PIM Designation and submitted to the European Medicines Agency (EMA): *Glofitamab as monotherapy is indicated for the treatment of adult patients with relapsed or refractory diffuse large B-cell lymphoma (DLBCL), after two or more lines of systemic therapy.*
Method of administration and dosage	***Pre-treatment with obinutuzumab*** All patients must receive a single 1000 mg dose of obinutuzumab on Cycle 1 Day 1 (7 days prior to initiation of glofitamab treatment). This is to deplete circulating B cells

	and thereby reduce the frequency and severity of cytokine release syndrome (CRS). Obinutuzumab should be administered as an intravenous (IV) infusion at 50 mg/h. The rate of infusion can be escalated in 50 mg/h increments every 30 minutes to a maximum of 400 mg/h. ***Premedication and prophylactic medications*** To reduce the risk of CRS, IV glucocorticoid premedication should be administered at least 60 minutes prior to the administration of glofitamab; oral analgesic, anti-pyretic and/or anti-histamine should be administered at least 30 minutes before glofitamab infusion. ***Glofitamab posology*** After completion of pre-treatment with obinutuzumab on Cycle 1 Day 1, Glofitamab must be administered as an IV infusion according to the dose step-up schedule leading to the recommended dose of 30 mg. Each cycle is 21 days. The glofitamab dose step-up schedule is detailed below: • On Cycle 1 Day 8, 2.5 mg of glofitamab is administered over 4 hours; on Cycle 1 Day 15, 10 mg of glofitamab is administered over a period of 4 hours; • On Cycle 2 Day 1, 30 mg of glofitamab is administered over a period of 4 hours; • On Cycles 3–12 Day 1, 30 mg of glofitamab is administered over a period of 2 hours if the previous infusion was well tolerated. If the patient experienced CRS with a previous dose, the duration of infusion should be maintained at 4 hours.
Additional tests or investigations	All patients must be monitored for signs and symptoms of potential CRS during infusion and for at least 10 hours after completion of the infusion of the first glofitamab dose (2.5 mg on Cycle 1 Day 8). Patients who experienced Grade ≥ 2 CRS with their previous infusion should be monitored after completion of the infusion. No additional requirements are needed for the administration of glofitamab other than those already required for the administration of other conventional cancer treatments.

List price and average cost of a course of treatment	List price: • £687.00 (2.5 mg vial) • £2,748 (10 mg vial) Average course of **glofitamab** treatment, based on a median of 5 treatment cycles: • £46,536 (including obinutuzumab pre-treatment)
Patient access scheme (if applicable)	[redacted] (simple discount)

B.1.3 Health condition and position of the technology in the treatment pathway

B.1.3.1 Disease overview

B.1.3.1.1 Incidence and prevalence

Non-Hodgkin lymphoma (NHL) consists of a heterogeneous group of lymphoproliferative disorders arising from the lymphoid system, and is the most prevalent haematological malignancy (8, 9). Diffuse large B-cell lymphoma (DLBCL) is a heterogeneous disease and is the most common histologic subtype of NHL, accounting for up to 40% of all newly diagnosed NHL cases (10). In the UK, around 4,850 people are diagnosed with DLBCL each year (11). The UK prevalence per 100,000 population is estimated at 38.1, with the 10-year prevalence estimated at 25,010 cases (12). The natural behaviour of the aggressive lymphomas, such as DLBCL, is characterised by faster progression and reduced survival compared with indolent NHL (13).

The incidence of DLBCL increases with age with the disease typically occurring in adults aged over 60 years (especially the 65–74 years age group) (10, 14). In the UK, the median age at diagnosis for DLBCL patients is 70.2 years (15). Nevertheless, DLBCL can also occur in younger patients, including young adults and children (16). Elderly patients with DLBCL have a poorer prognosis and inferior outcomes compared with younger patients with DLBCL, even with similar treatment (17). The disease symptoms (e.g. fever, recurrent night sweats, weight loss and/or local effects of lymph node enlargement), as well as those of bone marrow failure, along with treatment-related side effects, often lead to impairments in aspects of health-related quality of life (HRQoL), including physical functioning and fatigue (18). Initial treatment aims to be curative; however, about 10–15% of patients are refractory to the first-line (1L) standard of care - rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP); and a further 20–30% of patients relapse after a period of remission (19).

B.1.3.1.2 Pathophysiology

DLBCL has distinct morphology, immunophenotype and genetic features with various subtypes defined in the 2016 World Health Organization (WHO) Classification (20). DLBCL is a neoplasm of large B-lymphoid cells that shows a diffuse growth pattern. Morphologically, the disease is characterised by complete or partial effacement of the nodal architecture by sheets of large atypical lymphoid cells. Immunophenotypically, the disease is characterised by the expression of pan B-cell antigens (cluster of differentiation [CD]19, CD20, CD22, CD79a) and surface and/or cytoplasmic immunoglobulin expression (21).

DLBCL arises from centroblasts or immunoblasts and is associated with genetic abnormalities that are relatively specific to the disease. Although there is no single somatic genetic change that defines the disease, the majority of cases have alterations in the immunoglobulin-heavy genes (22). The most frequently dysregulated genes include *BCL6* (rearrangement in 35−40% of cases; mutation in 5' noncoding region in 70%), *BCL2* (translocation in 15%; amplification in 24%) and *cMYC* (5−15%) (23). Gene expression profiling has identified gene expression patterns that lead to further subtypes of the disease that have different oncogenic pathways, including germinal center B-cell and activated B-cell-like (ABC) subgroups (24). As such, DLBCL is a heterogeneous disease with a number of histological, proteomic and molecular subsets with distinctive prognostic profiles, including cell of origin (germinal centre B-cells and ABC), double-expressor DLBCL, defined as overexpression of MYC and BCL2 proteins, and double- or triple-hit lymphoma, defined as a dual translocation of *MYC* together with *BCL2* and/or *BCL6* (25-29).

B.1.3.1.3 Diagnosis and staging

According to the British Society of Haematology (BSH) (30) and the NICE NHL Diagnosis and Management Guidelines (31), DLBCL 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 categorises lymphomas on the basis of cytology, immunophenotype, and genetic and clinical features (20). A morphological diagnosis of DLBCL should be confirmed by immunohistochemistry or flow cytometry. If there is a low level of confidence in the diagnosis, for example owing to a small biopsy specimen or if the

putatively neoplastic population has a normal phenotype by immunohistochemistry, demonstration of B-cell monoclonality by polymerase chain reaction-based methods should be considered (4).

For patients diagnosed with DLBCL, the extent of the disease is evaluated by staging, which is crucial to determine the best therapeutic option and predict prognosis. DLBCL can be classified into one of four disease stages according to the Ann Arbor (Table 3) and/or Lugano Staging Classification (Table 4) (4, 32, 33). The Ann Arbor staging classification is used routinely to classify the extent of disease on the basis of the distribution and number of involved sites, as well as the presence or absence of extranodal involvement and constitutional symptoms. A consensus study developed by the clinical and imaging working groups of the International Conference of Malignant Lymphomas (Lugano classification) recommends fluorodeoxyglucose positron emission tomography-computed tomography (PET-CT) scan as the gold standard for staging patients with DLBCL (32, 34).

Table 3: Ann Arbor staging classification

Stage	
I	Involvement of a single lymphatic region (I) or localised involvement of single extralymphatic organ or site (IE)
II	Involvement of two or more lymphatic regions on the same side of the diaphragm (II) or localised involvement of a single extralymphatic organ or site and of one or more lymphatic regions on the same side of diaphragm (IIE)
III	Involvement of lymphatic regions on both sides of the diaphragm
IV	Diffuse or disseminated involvement of one or more extralymphatic organs with or without lymphatic involvement

Source: Tilly et al. 2015 (4).

Table 4: Lugano staging classification

Stage	Involvement	Extranodal status
Limited		
Stage I	One node or a group of adjacent nodes	Single extranodal lesions without nodal involvement
Stage II	Two or more nodal groups on the same side of the diaphragm	Stage I or II by nodal extent with limited contiguous extranodal involvement
Stage II bulky[a]	II as above with 'bulky' disease	Not applicable

Advanced		
Stage III	Nodes on both sides of the diaphragm; nodes above the diaphragm with spleen involvement	Not applicable
Stage IV	Additional noncontiguous extralymphatic involvement	Not applicable

Note: extent of disease is determined by positron emission tomography-computed tomography for avid lymphomas and computed tomography for non-avid lymphomas. The tonsils, Waldeyer's ring and spleen are considered nodal tissue.

[a]Whether Stage II 'bulky' disease is treated as limited or advanced disease may be determined by histology and a number of prognostic factors.

Source: Cheson et al. 2014 (32).

B.1.3.1.4 Prognosis factors

The most commonly used prognostic index for aggressive NHL, including DLBCL, is the International Prognostic Index (IPI). This index is based on five clinical features that are independent predictors of OS:

- Age (≤ 60 versus > 60 years)
- Serum lactate dehydrogenase (normal versus elevated) level
- ECOG PS (0 or 1 versus 2–4)
- Ann Arbor stage (I or II versus III or IV)
- Number of extranodal sites (0 or 1 versus 2–4).

On the basis of the number of negative prognostic features present at the time of diagnosis (age > 60 years, elevated serum lactate dehydrogenase, ECOG PS ≥ 2, stage III/IV disease, > 1 extranodal sites of disease), four discrete risk groups were identified before rituximab was introduced, with 5-year overall survival (OS) ranging from 26% to 73% (Table 5**: The International Prognostic Index (IPI)**) (35).

Sehn *et al*. confirmed the validity of the IPI for DLBCL in the rituximab era in a cohort of 365 patients treated with the R-CHOP regimen (the current standard of care treatment for DLBCL) (36). However, the IPI was able to distinguish only three rather than four risk groups in the original IPI. The authors proposed a revised IPI by redistributing the IPI factors into three prognostic groups: 'very good' (0 risk factors), 'good' (1–2 factors) and 'poor' (3–5 factors). The 4-year OS was 94%, 79% and 55% in the three groups, respectively. Although the original IPI remains valid in the R-CHOP era, it now has more limited ability to predict patients who will experience a

particularly aggressive course, because even the ‘high-risk’ group has a 4-year OS greater than 50% (37).

Table 5: The International Prognostic Index (IPI)

IPI			
Number of risk factors	**Risk group**	**5-year OS, %(Without rituximab)**	**3-year OS, %(With rituximab)**
0 or 1	Low risk	73	91
2	Low–intermediate risk	51	81
3	Intermediate–high risk	43	65
4 or 5	High risk	26	59
Revised IPI			
Number of risk factors	**Risk group**	**–**	**4-year OS, %(With rituximab)**
0	Very good	–	94
1 or 2	Good	–	79
3, 4 or 5	Poor	–	55

IPI, International Prognostic Index; OS, overall survival.

Source: International Non-Hodgkin’s Lymphoma Prognostic Factors Project (1993) for 5-year OS (35), Vaidya and Witzig (2014) for 3-year OS (37), Sehn et al. 2007 for 4-year OS (36).

DLBCL has a multiplicity of prognostic profiles. Evidence suggests that bulky disease is an adverse prognostic factor and the activated B-cell (ABC) subtype of DLBCL has been shown to be associated with a more aggressive clinical course than the germinal centre B-cell subtype (38). Individual biomarkers assessed by immunohistochemistry or gene expression profiling have been identified as having prognostic significance in DLBCL, such as *TP53* mutations (39), *MYC* rearrangement and *BCL2* expression (40), although the introduction of rituximab to standard chemotherapy seems to ameliorate the negative prognostic impact of *BCL2* expression (41). ‘Double-hit’ lymphomas, with dual translocations involving both *MYC* and *BCL2* or *BCL6* genes, have a particularly aggressive clinical course and poor response to standard chemotherapy (37). Cell of origin profiles (ABC/germinal centre B-cell like [GCB]) do not currently influence treatment choices, even though retrospective analyses have suggested worse outcomes in patients with ABC sub-type compared with the GCB subtype (42). There is no standard of care for patients

with ‘double-hit’ lymphomas, however, 1L treatment may be intensified, including R-CHOP with central nervous system (CNS) prophylaxis, R-CHOP with addition of etoposide every 2 weeks (R-CHOEP-14), dose-adjusted etoposide with R-CHOP (DA-EPOCH-R), or rituximab with cyclophosphamide, doxorubicin, vincristine, methotrexate/ifosfamide, etoposide and high dose cytarabine (R-CODOX-M/R-IVAC) (19).

Evaluation of prognostic markers in practice is difficult because their use is not integrated into standard treatment pathways, but some evidence suggests that IPI score has predictive value in several subgroups (25, 27, 43, 44). Thus, the unmet need in such a heterogeneous disease cannot be defined by only one biological or clinical risk factor; there are patients at low risk according to IPI score who have poor outcomes owing to biological risk factors (e.g. ABC, double-hit lymphoma [DHL]) and patients who are low risk according to biological risk factors who have poor outcomes owing to IPI clinical risk factors. Patients with the poorest outcomes with current therapies are those who are high risk both in terms of biological factors and high IPI score. After adjusting for biological risk factors of severity, IPI scores remain an important indicator of disease severity and prognosis (44).

B.1.3.1.5 Risk factors

For the vast majority of patients, the aetiology of DLBCL is unknown. Factors thought to potentially incur increased risk include hereditary and acquired immunodeficiencies, such as human immunodeficiency virus (HIV) and rheumatoid arthritis (RA), and pharmacological immunosuppression in the setting of transplantation or treatment of autoimmune diseases (45). Exposure to a variety of environmental factors, including pesticides, may also play a role (46), and a subset of DLBCL cases is associated with Epstein–Barr virus (EBV) (47). DLBCL often arises *de novo* but it can also represent a malignant progression or transformation of a less aggressive lymphoma (e.g. follicular lymphoma [FL], chronic lymphocytic leukaemia [CLL), small lymphocytic lymphoma [SLL] and mucosa-associated lymphoid tissue lymphoma [MALT]) (48). It is estimated that 10−15% of patients are refractory to standard 1L treatment for DLBCL and 20−25% of patients will relapse within 12−18 months (49). B-symptoms and high levels of β2 microglobulin (β2-MG) have also been reported to be risk factors for R/R DLBCL (50).

B.1.3.1.6 Clinical signs and symptoms

Although DLBCL is often asymptomatic, it may be associated with constitutional symptoms, such as non-specific 'B-symptoms', including fever, recurrent night sweats and weight loss, and/or local effects of lymph node enlargement and bone marrow failure (10, 51). DLBCL is marked by rapidly growing tumours in the lymph nodes, spleen, liver, bone marrow or other organs. As such, patients with DLBCL typically present with rapidly enlarging masses at nodal or extranodal sites. This results in damage to the involved and surrounding tissues and organs and requires immediate treatment. The swollen nodes can form large lumps, known as bulky disease (10, 51). The majority of cases (60%) originate in the lymph nodes, with the remaining (40%) presenting at extranodal sites (52). The most common extranodal sites are the gastrointestinal tract, head and neck, and skin and soft tissue. Bone marrow is involved in 10–30% of cases (4). Relapsed DLBCL is characterized by the appearance of any new lesion after a complete response to treatment along with the return of symptoms (enlarged lymph nodes, night sweats, unexplained fever and unintentional weight loss), while refractory DLBCL is characterised by progressive disease or no response from the start of previous treatment (53).

B.1.3.1.7 Quality of life

Without treatment, DLBCL has an aggressive natural history and is fatal, with a median survival of less than a year (54). The clinical course can be debilitating owing to constitutional symptoms, local symptoms of lymphadenopathy and bone marrow failure that may lead to infections, anaemia and thrombocytopenia. Most patients present with advanced disease (Stage III or IV) and adverse prognostic features (e.g. risk scores of 2–5 on the IPI). Approximately 60% of patients with DLBCL can be cured with 1L standard of care R-CHOP; the remaining 40% of patients will either relapse or be refractory to 1L treatment, or will die owing to treatment-related complications (49, 55).

Many patients with DLBCL treated with R-CHOP experience treatment-related AEs. These AEs include peripheral neuropathy (PN), nausea, neutropenia, constipation, fatigue, anaemia, and alopecia (56). Patients treated with a greater number of cycles of chemotherapy reported increased symptoms (pain, neuropathy and dyspnoea) compared with patients treated with a lower number of cycles (57). Among higher-

risk populations, less than half of patients experience long-term remission after R-CHOP. For these populations in clinical trial settings, the 10-year progression-free survival (PFS) rate following 1L R-CHOP or R-CHOP-like treatment was 36.5%, with a corresponding 10-year OS rate of 43.5% (58). However, following the recent recommendation in May 2022 for polatuzumab vedotin with rituximab, cyclophosphamide, doxorubicin and prednisolone (pola-R-CHP) for patients with previously untreated DLBCL; hence, the 1L+ DLBCL treatment pathway is expected to evolve over the course of 2023 (59).

Relapsing or being refractory to 1L treatment remains a major cause of morbidity and mortality for patients with DLBCL. Most relapses occur within 24 months of starting treatment (55, 60) and the majority of patients with relapsed or refractory (R/R) disease have poor outcomes (61-63). Patients who require 2L and subsequent lines of therapy have a particularly poor prognosis, and experience disease progression with an increased risk of side effects of treatments (64). Salvage therapy for R/R DLBCL is limited by a patient's ability to tolerate the therapy and the limited efficacy of treatment.

Disease symptoms, along with treatment-related side effects, often lead to impairments in aspects of HRQoL, including physical functioning and fatigue (18, 56). More patients with DLBCL experience anxiety and depression than their counterparts in the general population; younger patients reported higher anxiety scores, whereas older patients reported higher depression scores over time (65). Reduced HRQoL has also been reported in younger versus older survivors of DLBCL relative to the age-matched normative population (66). Findings suggest that men may be impacted more by DLBCL than women, as reported in a recent study by Paunescu *et al*., whereby women with DLBCL had significantly higher scores on the post-traumatic growth inventory than men at one year post diagnosis. This indicated more positive changes and self-improvement in women than men (57). However, women had significantly worse physical functioning than men at 1 year post diagnosis (57). At the same time point, patients with comorbidities had increased physical fatigue and symptom burden, increased emotional impact, mental fatigue and depression, and reduced physical functioning and global health status compared with patients without comorbidities (57).

B.1.3.2 Current clinical practice in the UK

Approximately 80% of patients with DLBCL receive treatment in the 1L setting, and around 60% can be cured with the current standard of care, R-CHOP (49, 55). As an alternative to R-CHOP, pola-R-CHP (replacement of vincristine in the R-CHOP regimen with polatuzumab vedotin) was also recently approved for the 1L treatment of DLBCL; as a result, the 1L+ DLBCL treatment pathway is expected to evolve over the course of 2023–2024 (59). In the POLARIX registration Phase III study, pola-R-CHP demonstrated a clinically meaningful absolute improvement in 2 year PFS of 6.5% (76.7% [95% confidence interval (CI), 72.7 to 80.8] vs. 70.2% [95% CI, 65.8 to 74.6] for pola-R-CHP and R-CHOP, respectively, at 2 years), and a statistically significant hazard ratio for PFS of 0.73 (95% CI 0.57, 0.95; p=0.02) (67). As such, the approximate 60% 1L cure rate cited above is expected to increase in the coming years.

Of the patients in the UK's Haematological Malignancy Research Network (HMRN) database, 31% of patients were estimated to receive 2L treatment, and 18% of 2L-treated patients were estimated to receive 3L treatment (68). For patients who are not cured with 1L therapy (relapse occurring after > 6 months and biopsy shows continued CD20 expression), 2L+ treatment will depend largely on whether the patient is eligible for high dose chemotherapy and autologous stem-cell transplantation (ASCT), as ASCT is only available for young, fit patients who demonstrate chemosensitive disease (4). However, even if patients are eligible for high-dose chemotherapy and ASCT, less than half will be cured (69, 70). For patients not eligible for transplantation, 2L treatment options include polatuzumab vedotin in combination with bendamustine and rituximab (pola-BR), tafasitamab and lenalidomide (tafa-len), and rituximab in combination with chemotherapy (gemcitabine plus oxaliplatin or bendamustine). That said, current BlueTeq criteria stipule that retreatment with polatuzumab vedotin is not permitted unless used only as bridging to CAR-T therapy with the 6 cycles being completed, after CAR-T has failed. As such, the recent recommendation for pola-R-CHP for 1L DLBCL (GID-TA10785) will rapidly reduce the relevance of pola-BR as an appropriate treatment option 3L and beyond (59). Lastly, patients may also have the option to enter clinical trials of novel therapies.

B.1.3.2.1 3L+ treatments

Guidelines from the European Society for Medical Oncology (ESMO) (4) and the National Comprehensive Cancer Network (NCCN) (71) suggest that patients who relapse after 2L therapy are unlikely to respond to subsequent therapy, and therefore generally are not eligible for ASCT. The outcome in patients not eligible for ASCT is dismal with generally no chance of prolonged periods of disease control (72). Poor outcomes have been reported for patients with R/R DLBCL who respond to salvage therapy, but are ineligible for transplant. In these patients, overall survival (OS) was reported between 4–13 months (73-77).

In the absence of ASCT as a treatment option, patients may be treated with R-chemo at 3L+. However, many patients may have already received rituximab-based regimens in previous lines. In this case, alternative treatments which have emerged more recently for R/R DLBCL may be used at 3L+, including chimeric antigen receptor T-cell (CAR-T) therapies (axicabtagene ciloleucel, tisagenlecleucel), pixantrone, pola-BR (if not already used in 2L) and tafa-len (if not already used in 2L):

I. Rituximab-based chemotherapy

Rituximab- and a platinum-based chemotherapy regimen (e.g. rituximab combined with gemcitabine and oxaliplatin [R-GemOx], or rituximab plus bendamustine [BR]) might be given to DLBCL patients who are not eligible for ASCT, after failure of 1L treatment. However, direct comparison with prior studies investigating chemotherapy-based regimens has several limitations. There are differences in these studies based on inclusion/exclusion criteria (i.e. limitations on prior lines of therapy, refractoriness), patients actually enrolled, as well as historical context (e.g. how many patients had prior exposure to rituximab or what the 1L therapy was).

Although small numbers of R-GemOX are used in the UK, due to the lack of a feasible comparison of glofitamab versus R-GemOx (and other chemotherapy combinations), BR is used a proxy for the value assessment of glofitamab. This proxy approach was supported by NICE in previous submissions (78), during which clinical experts explained that although BR is not commonly used to treat DLBCL in the UK any more, and is not routinely funded, it is standard of care in other

indications, such as chronic lymphocytic leukaemia (CLL). The clinical experts explained that there is a lack of information on the relative effectiveness of different treatments used in R/R DLBCL, but BR would not be expected to have inferior efficacy or tolerability to other treatments, and therefore it would be reasonable to use it as a proxy for standard care. The committee concluded that BR is a reasonable proxy for standard of care in the National Health Service (NHS) in R/R DLBCL when a hematopoietic stem cell transplant (HSCT) is not an option.

To support this position, Roche developed and presented an analysis to assess comparative effectiveness of BR and R-GemOx in R/R DLBCL (2). This study consisted in a retrospective analysis using real-world data from the National Cancer Institute's Surveillance, Epidemiology and End Results (SEER) cancer registry linked to Medicare enrolment data and insurance claims, and included patients with cancer diagnoses from 2004–2016. Patients diagnosed with DLBCL, NOS who received 2L BR or R-GemOx alone, were included. Survival was assessed by Kaplan-Meier (KM) and Cox regression analysis. The inverse probability treatment weighting (IPTW) method was applied to balance baseline characteristics, such as age at the start of 2L treatment, gender, stage of disease, race, Charlson Comorbidity Index, relapsed or refractory status, time from initial treatment to 2L treatment initiation, calendar year of 2L start, and health maintenance organization.

The investigators concluded that OS was not significantly different between patients with R/R DLBCL treated with BR or R-GemOx in the real-world data analysis from the SEER Medicare database. This was also confirmed by clinical experts at a recent Advisory Board, who had no concerns that R-GemOX would produce different results to BR (1).

The safety profile for R-GemOx and BR are comparable: in a Phase II Lymphoma Study Association trial, 49 R/R DLBCL patients were enrolled to receive up to 8 cycles of R-GemOx (79). The most common toxicities were haematologic, with grade 3/4 neutropenia reported in 73% of patients, and grade 3/4 thrombocytopenia reported in 44% of patients. A total of 26 serious adverse events were experienced by 19 patients (40%). Similarly, in the control arm of a Phase 1b/2 study, 39 patients with R/R DLBCL were treated with BR (80). Of which, the most common Grade 3/4

AE was neutropenia (n=13; 33.3%). Thrombocytopenia was observed in 9 patients (23.1%). Fatal AEs occurred in 10 patients (25.6%).

II. CAR T-cells

CAR-T therapy is a treatment in which T-cells are collected from patients by apheresis, genetically engineered to express receptors that bind to tumour antigens, and then returned to the patient so their T-cells can act against their cancer (81). Axicabtagene ciloleucel (Yescarta®) and tisagenlecleucel (Kymriah®) are CAR T-cell therapies that are directed against the CD19 protein, which is present on malignant B-cells. Both therapies are approved in the UK for the treatment of adults with R/R DLBCL after two or more lines of systemic therapy (i.e., at 3L+) and are recommended by NICE in this indication (TA559 and TA567).

The key limitations of CAR-T therapies include manufacturing times, delivery and access issues, and high costs, resulting in reduced feasibility of these treatments being available for patients (82-84). In the UK, if a clinician intends to use CAR-T cell therapy to treat R/R DLBCL, each patient must be assessed by the National CAR-T Clinical Panel (NCCP) (85). If approved, the patient is scheduled for T-cell harvesting (apheresis), then the personalised CAR-T cells need to be manufactured, which is a process that takes place outside of the UK. If successful, the patient is scheduled for in-patient hospitalisation to receive the CAR-T infusion. The treatment must be delivered in one of a few approved, specialised centres (NHS England, Cancer Drugs Fund, CAR-T Therapy). This process takes approximately 8 weeks in the UK (86). Patients referred for CAR-T cell therapy have active R/R DLBCL to the most recent therapy, indicating aggressive disease biology, and hence are at risk of disease progression or death while awaiting CAR-T manufacturing. Therefore, most patients require bridging therapy ahead of the CAR-T infusion. Typically, one or two cycles of pola-BR bridging therapy as necessary until CAR T-Cell product is available, as confirmed by clinical experts at an Advisory Board (1).

Outcomes have been reported for the first 404 patients with R/R DLBCL approved by the NCCP for CAR-T cell therapy with either tisagenlecleucel or axicabtagene ciloleucel between December 2018 and November 2020 (86). The median time from NCCP CAR-T approval to infusion was 57 days (interquartile range [IQR], 49–71)

and from apheresis to CAR-T infusion, 42 days (IQR, 37–53). Of the 404 patients approved for CAR-T cell therapy, 74% (n=300) actually received the infusion, whilst 26% (n=104) did not. The most frequent reason for not receiving infusion was clinical deterioration due to progressive disease. Of the 300 infused patients, 87% (n=260) required bridging therapy with corticosteroids only (11%, n=29), systemic therapies (64%, n=167), radiotherapy (21%, n=54) or combined modality treatment (4%, n=10). The ORR/CR rates were 41%/38% in the infused population, and 30%/27% in the ITT population. Median OS for the ITT population was 10.5 months from the time of approval, 16.2 months for infused patients, and 2.1 months (95% CI: 1.94–2.69) for patients not infused. The 12-month (from time of NCCP approval) OS rates for ITT, infused, and not infused patients, were 44.9%, 58.2% and 5.9%, respectively. An earlier analysis of the UK NCCP dataset reported outcomes in patients whose disease progressed following CAR-T cell therapy (87). Of the 294 patients who received infusion of CAR-T cells and were available for this analysis, 52% (n=153) progressed with 93% (n=143) of progressions occurring within 6 months of infusion. Of the 153 patients who progressed, 54% (n=82) received subsequent treatment for DLBCL. The median OS was 3.7 months for patients who progressed, with 1.4 months for patients not receiving further treatment and 7.8 months for treated patients.

In the modified intent-to-treat (mITT) populations (patients who were infused) in the pivotal trials for tisagenlecleucel (N=115) and axicabtagene ciloleucel (N=101), objective response rate (ORR)/complete response (CR) rates of 54.5%/41.4% and 72%/51% were reported, respectively (Kymriah SmPC (88); Yescarta SmPC (89)). The 12- and 24- month OS for tisagenlecleucel was 48.2% and 40.4%, respectively; and the 12- and 24- month OS for axicabtagene ciloleucel was 60.4% and 50.5%, respectively. Whilst these results are promising for patients who had successfully received infusion of their CAR-T cells, they are not a true representation of the treatment efficacy as they fail to incorporate outcomes for the patients who do not receive reinfusion. As such, the ITT population, which included all patients referred for CAR-T cell therapy, should be the benchmark for comparing CAR-T cell therapy to new treatments, such as bispecific antibodies (86). Specifically, the ORR/CR rate in all patients enrolled to the tisagenlecleucel pivotal study (n=147) were

36.7%/27.9% and 12- and 24- month OS rates were 41.0% and 33.3%, respectively (Kymriah SmPC). The ORR/CR rate in patients enrolled to the axicabtagene ciloleucel pivotal study who underwent leukapheresis (n=111) were 66%/47% and 12- and 24- month OS rates were 59.3% and 47.7%, respectively (Yescarta SmPC).

The main CAR-T related toxicities are cytokine release syndrome (CRS), immune effector cell-associated neurotoxicity syndrome (ICANS), and prolonged cytopenias (86). In the infused patients from the UK real world dataset (N=300), 88.0% (n=264) of patients experienced CRS of any grade, including 7.7% (n=23) reporting Grade ≥3 CRS. A total of 36.8% (n=110) of patients experienced ICANS of any grade, including 15.7% (n=47) of grade ≥ 3. Of the 131 patients who experienced Grade ≥ 3 cytopenias, 19.8% (n=26) and 14.5% (n=19) were still experiencing Grade ≥ 3 neutropenia and thrombocytopenia at 3 months, respectively. ICU admission was required by 27.8% of patients.

While the response rates and long term outcomes are promising for patients who do receive reinfusion of CAR-T cells, the treatment is intensive, with the need for bridging therapy, hospitalisation far from home at times, and often prolonged toxicity. The prognosis for patients who progress following CAR-T and are unable to receive further treatment for their DLBCL (approximately 24% of the infused patients), is extremely poor, with a median OS of 1.4 months (87). For the substantial proportion of patients (26% in the UK dataset) who are referred for CAR-T cell therapy but do not receive reinfusion, the prognosis is also extremely poor with a median OS of less than 2.1 months (86). Therefore, CAR-T cell therapies are not suitable for many patients with R/R DLBCL due to the logistical issues, frailty or need for immediate treatment.

III. Pola-BR

Polatuzumab vedotin (Polivy®), a CD79b-targeted antibody-drug conjugate, in combination with BR (pola-BR) is indicated for the treatment of adult patients with R/R DLBCL who are not candidates for haematopoietic stem cell transplant and is recommended by NICE in this indication (TA649).

In a pivotal Phase II study, pola-BR demonstrated a satisfactory efficacy and safety profile in R/R DLBCL patients. However, patients enrolled to receive pola-BR in the

study had only received ≥ 1 prior line of prior therapy (required per protocol, median of 2 lines) (Polivy SmPC) (90). Comparatively, lower response rates were observed with pola-BR in later lines and in a recent exploratory analysis (N=102), among R/R DLBCL patients with ≥ 2 prior lines of therapy, the observed best overall response (BOR) CR rate was 42.2% and ORR was 50% (63). The median duration of response (DOR) in the overall population of the pivotal cohort (≥ 1 prior lines) was 12.6 months at the time of approval (Polivy SmPC) (90). Based on an updated exploratory analysis in a subgroup of DLBCL patients ≥ 2 prior lines, [redacted] (unpublished internal analyses).

With regard to safety of pola-BR, the occurrence of neutropenia and febrile neutropenia (any grade and Grade ≥3) were reported at 49%, Grade ≥3 neutropenia at 40.4%, and febrile neutropenia at 4%. Discontinuation of all treatment due to adverse events (AEs) was reported in 30.8% of patients.

The recent recommendation of pola-R-CHP for untreated DLBCL (GID-TA10785) (59) is expected to result in rapidly reduced usage of pola-BR as a 3L+ DLBCL treatment option. At an Advisory Board conducted by the company, clinical experts pointed out that pola-BR usage is uncommon and relatively low in the 3L setting, and that they would not consider pola-BR as a 3L+ treatment if pola could be used in earlier lines (1). As such, the applicability of pola-BR as a relevant comparator is expected to decrease throughout the appraisal process. Consideration should be given to the relevance of this comparison at the point of decision making.

IV. Tafa-len

Tafasitamab (Minjuvi®), a fragment crystallized (Fc)-enhanced, anti-CD19 monoclonal antibody, is indicated in combination with lenalidomide (for twelve 28 day cycles) followed by tafasitamab monotherapy until disease progression or unacceptable toxicity, for the treatment of adult patients with R/R DLBCL who are not eligible for autologous stem cell transplant. There is currently an ongoing technology appraisal at NICE (GID-TA10645) for this indication, therefore, it was excluded as a relevant comparator for glofitamab in the present submission.

In a pivotal Phase II study, tafa-len demonstrated a satisfactory efficacy profile in R/R DLBCL patients. However, 49.4% of patients enrolled to receive tafa-len had received only one prior line of therapy, and patients with ≥ 3 prior lines and/or those who had primary refractory DLBCL were excluded from enrolment in the study (91); 44% of patients enrolled to tafa-len were refractory to their last line of therapy. As with pola-BR, tafa-len had demonstrated a best overall CR rate of 39.5% by IRC in patients with DLBCL who had received ≥ 1 prior line of therapy (Minjuvi SmPC) (92), while a lower CR rate, 32.5%, was reported in patients who received ≥ 2 prior lines of therapy (93).

In terms of safety profile, several notable adverse events (AEs) were reported in the tafa-len registration study, including infections (73%), neutropenia (51%), diarrhoea (36%), and febrile neutropenia (12%). A treatment discontinuation rate of 15% was reported in patients enrolled to receive tafa-len.

V. Pixantrone

Pixantrone, a new anthracycline-like drug, is indicated as a monotherapy for the treatment of adult patients with multiply R/R aggressive NHL. It is recommended by NICE for 3L or 4L treatment (TA306). Pixantrone has demonstrated efficacy in heavily treated patients, along with reduced cardiotoxicity compared with other drugs (94); however, clinical experts have advised that pixantrone is rarely used in clinical practice, has poor efficacy, and should not be considered as a standard of care (4, 95). The pivotal randomised Phase III PIX306 study of pixantrone plus rituximab compared with gemcitabine plus rituximab, demonstrated no improvement in efficacy and safety outcomes for patients with relapsed B-cell NHL (96). Therefore, it was excluded as a relevant comparator for glofitamab in the present submission.

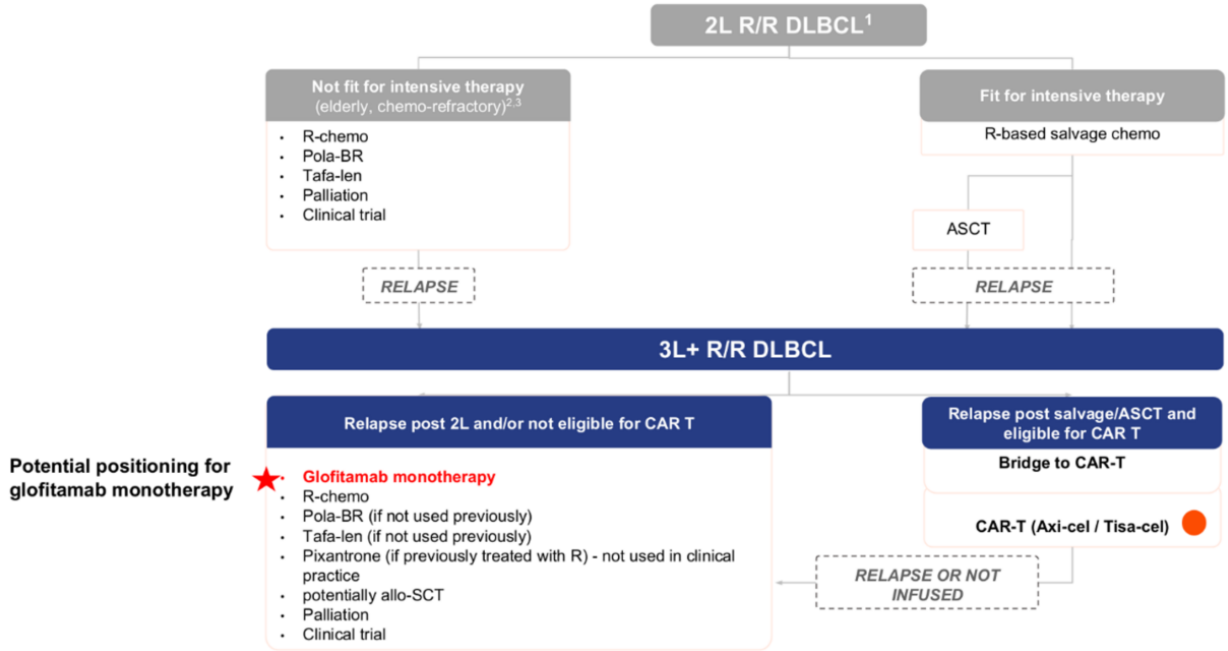
B.1.3.3 Disease management pathway

The proposed treatment pathway and position of glofitamab is summarised below (Figure **1**).

It is proposed that 12 cycles of glofitamab may be used as a treatment line ahead of CAR-T therapy, or in patients who are ineligible for CAR-T therapy, in the 3L+ DLBCL setting. Glofitamab could also be used in patients who have failed CAR-T

therapy in prior treatment lines. This is supported by clinical experts consulted by the Company (1), and in the subgroup analysis of the glofitamab pivotal study, which demonstrated similar CR rates in patients regardless of whether they had received prior CAR-T cell therapy. As most of the treatments licensed for 2L or 3L R/R DLBCL therapy can be used in the 3L+ setting (i.e. 2L+ for pola-BR, tafa-len; 3L+ for CAR-T cell therapy; 3L or 4L for pixantrone), glofitamab is not intended to replace existing treatments, but to provide an additional line of treatment so patients may be eligible for other treatments after receiving glofitamab.

Figure 1: Current treatment pathway for 2L and 3L+ R/R DLBCL patients, including glofitamab positioning



Two CAR-T trials vs ASCT have met primary endpoint, which could shift the treatment algorithm in 2023+ to become a treatment option after first relapse. NICE assessment of axicabtagene ciloleucel is currently ongoing (GID-TA10580).

2L, second-line; 3L+, third-line and higher; allo-SCT: allogeneic stem cell transplantation; ASCT, autologous stem-cell transplantation; Axi-cel: axicabtagene ciloleucel (Yescarta); CAR-T, chimeric antigen receptor T-cell; Pola-BR, polatuzumab vedotin, bendamustine and rituximab; Tafa-len, tafasitamab and lenalidomide; Tisa-cel: tisagenlecleucel (Kymriah).

B.1.4 Equality considerations

Although some patients with R/R DLBCL may have a potentially curative treatment option via high-dose chemotherapy and ASCT, or a potentially durable response with CAR T-cell therapy, the majority of 3L+ patients will not be eligible for these treatments or treatment will fail.

Due to the limited number of clinical centres that can offer CAR-T-cell therapies, patient access to therapy may be limited on the basis of geographic location or be associated with long travel time for many patients with DLBCL and caregivers. Extended travel distances to therapy or inconvenient care locations are significant barriers to patient care, particularly for those receiving later-line oncology therapy who may have poorer performance status.

In addition, CAR-T treatment can be associated with significant out-of-pocket indirect costs, making it infeasible or burdensome for some patients to receive optimal treatment. These costs are driven by expenses needed to travel to the few certified centres and the requirement to remain within proximity to a certified health facility for a long period (at least 4 weeks) following infusion. This results in a postcode lottery, with patients who live further away from CAR-T centres facing increased costs, which could represent a barrier to treatment access.

Given its immediate availability, glofitamab has the potential to be more accessible by a larger range of clinical centres than CAR-T-cell therapies, helping reduce regional, rural–urban, and sociodemographic inequity issues resulting from the uneven geographical allocation of CAR-T-cell therapy administration sites.

B.2 Clinical effectiveness

B.2.1 Identification and selection of relevant studies

See Appendix D (ITC report) for full details of the process and methods used to identify and select the clinical evidence relevant to the technology being evaluated.

B.2.2 List of relevant clinical effectiveness evidence

Table 6: Clinical effectiveness evidence

Study	NP30179
Study design	A Phase I/II, multicentre, open-label, study to evaluate the safety, efficacy, tolerability and pharmacokinetics of escalating doses of glofitamab as a single agent and in combination with obinutuzumab administered after a fixed, single dose pre-treatment of obinutuzumab (Gazyvaro®) in patients with relapsed/refractory (R/R) B cell non-Hodgkin's lymphoma. Pivotal data for the current indication and Company submission are derived from 3 cohorts of this multi-cohort study, which enrolled patients with R/R DLBCL after at least 2 prior systemic therapies who were treated with glofitamab monotherapy at the recommended phase II dose (step up dosing with 2 mg, 10 mg and 30 mg, following a single pre-treatment dose of obinutuzumab 1,000 mg).
Population	Adult patients with relapsed or refractory diffuse large B-cell lymphoma (DLBCL), after two or more lines of systemic therapy.
Intervention(s)	Glofitamab as single agent for up to twelve 21-day cycles following single dose pre-treatment with obinutuzumab.
Comparator(s)	This is a single arm study with an external control comparison of CR rate based on a meta-analysis of 19 studies of R/R DLBCL.
Indicate if study supports application for marketing authorisation	Yes

Study	NP30179
Indicate if study used in the economic model	Yes
Rationale if study not used in model	This pivotal study provided key clinical efficacy and safety data supporting the modelling.
Reported outcomes specified in the decision problem	• Overall survival • Progression-free survival • Response rates • Adverse effects of treatment • Health-related quality of life
All other reported outcomes	• Duration of response • Pharmacokinetics

B.2.3 Summary of methodology of the relevant clinical effectiveness evidence

B.2.3.1 Study methodology

B.2.3.1.1 Study overview

Study NP30179 was a Phase I/II, multicentre, open-label, study to evaluate the safety, efficacy, tolerability and pharmacokinetics of escalating doses of glofitamab as a single agent and in combination with obinutuzumab, administered after a fixed, single dose pre-treatment of obinutuzumab (Gazyvaro®) in patients with relapsed/refractory (R/R) B cell non-Hodgkin's lymphoma.

The study was divided in three parts (Figure 2):

- Part I, dose escalation (single patient Cohort A_1: glofitamab fixed doses 0.005−0.810 mg). Increments were 3-fold until a dose of 0.405 mg was reached, at which time the increment was changed to 2-fold. Thus, the 0.005 mg starting dose was to be followed by doses of 0.015 mg, 0.045 mg, 0.135 mg, 0.405 mg and 0.810 mg.

- Part II, dose-escalation (multiple patient Cohorts A_2, B_2, D_2, F_2: glofitamab fixed doses of 0.015−25 mg and step-up dosing up to 30 mg) in patients with

R/R NHL (mixed histologies). Subcohort D2 included 3L+ R/R DLBCL patients treated with the proposed registration dose of 2.5/10/30mg glofitamab monotherapy (n=7) and is included in the primary study population for the Company Submission.

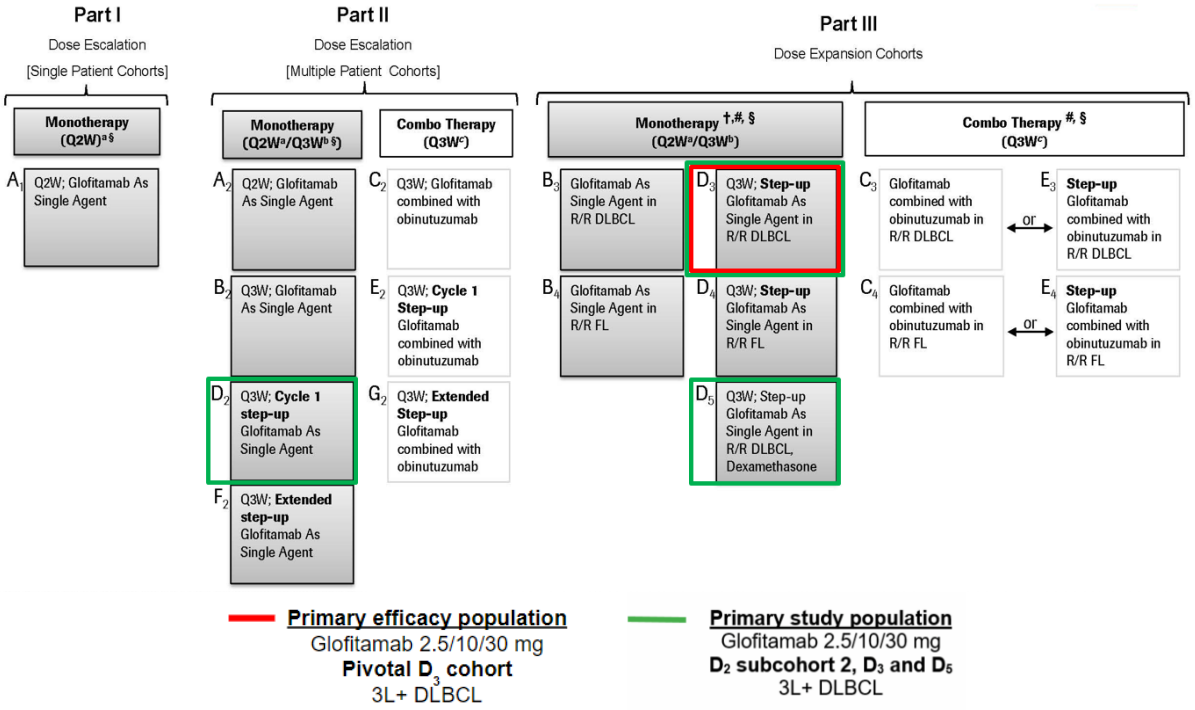
- Part III, dose expansion cohorts in patients with R/R DLBCL or R/R FL treated with glofitamab step-up dosing of 10/16 mg (Cohort B_3 and B_4) and 2.5/10/30 mg (Cohorts D_3, D_4 and D_5). Cohort D3 is the pivotal cohort for expansion, including 3L+ R/R DLBCL patients treated with the proposed registration dose, 2.5/10/30 mg of glofitamab monotherapy (n=108). Cohort D5 had the same eligibility criteria and patients were treated with the same step-up dosing regimen of glofitamab monotherapy but the pre-treatment corticosteroid was mandated as dexamethasone (n=40).

Obinutuzumab pre-treatment was given to all patients in the study 7 days before the first dose of glofitamab, to reduce circulating B-cells and thus the risk of cytokine release syndrome (CRS).

This submission focuses on the primary study populations only, which included 3L+ R/R DLBCL patients treated with the proposed registration dose of 2.5/10/30 mg glofitamab monotherapy (Part II D2 subcohort 2 [Sub. 2], Part III D3 and D5; N=155; (Figure 2), in accordance with the marketing authorisation indication submitted to the EMA. This 2023 Company submission includes updated trial data from the primary study population at the latest clinical cutoff date (CCOD) on 15th June 2022, as well as certain data from the primary analysis of the pivotal efficacy cohort (Part III D2) at CCOD 14th September 2021.

The study schema of NP30179 is shown below (Figure 2).

Figure 2: NP30179 study design schema (3L+ R/R DLBCL primary study populations highlighted)



B.2.3.1.2 Study design

An increment based dose escalation was used in Part I (single patient cohorts) with dosing initiated at 0.005 mg (flat dose). Increments were 3-fold until a dose of 0.405 mg was reached, at which time the increment was changed to 2-fold. Thus, the 0.005 mg starting dose was to be followed by doses of 0.015 mg, 0.045 mg, 0.135 mg, 0.405 mg and 0.810 mg.

The study design was then switched to Part II (multiple patient cohorts) when either a flat dose of 0.810 mg was reached or a glofitamab-related Grade ≥ 2 adverse event (or dose limiting toxicity [DLT]) occurred, whichever came first. Part II initially investigated escalating fixed doses of glofitamab on a Q2W or Q3W regimen up to 25 mg. Accumulated data showed an association between the first glofitamab dose and cytokine-release syndrome (CRS); when administered at 25 mg Q3W, glofitamab was associated with an increasing number of first administration CRS events. Glofitamab 25 mg was declared to exceed the maximum tolerated dose (MTD) when given as the first glofitamab dose.

The dose expansion cohorts (Part III) were to be initiated when the MTD/optimal biological dose (OBD) was defined to further evaluate the safety, pharmacokinetics, and therapeutic activity of glofitamab when given as a single agent. The final MTD/OBD was to be estimated on the basis of an analysis of the data for all patients evaluable for DLTs in Parts I and II of the study.

Based on the observed safety and efficacy during the Part II dose escalation and exposure response analyses, a dosing regimen of obinutuzumab 1,000 mg pre-treatment on Cycle (C)1, Day (D)1, glofitamab 2.5 mg on C1D8, glofitamab 10 mg on C1D15 (3 week cycle) and glofitamab 16–30 mg on C2D1. Subsequent three week cycles (16/30 mg, Q3W) for up to 12 cycles was chosen for the Part III expansion cohorts. Following evaluation of the observed CRS frequency and severity and initial efficacy data, step-up dosing with 2.5/10/30 mg was considered to be safe and tolerable and was selected as the recommended phase II dose and proposed dose for registration.

B.2.3.1.3 Inclusion/exclusion criteria

The key inclusion and exclusion criteria for the NP30179 study are summarised in Table 7; see Appendix E for the full list.

Table 7: Key inclusion and exclusion criteria for the NP30179 study

	Inclusion criteria	Exclusion criteria
Disease Subtype	• Patients with R/R NHL: - For study parts I and II: Grades 1–3b FL, MZL (splenic, nodal and extra-nodal), MCL, DLBCL, PMBCL, Richter's transformation and trFL - For DLBCL cohort of study part III: DLBCL NOS, HGBCL, PMBCL and DLBCL transformed from FL (trFL) - For FL cohort of study part III: Grades 1–3a FL	• Patients with CLL, Burkitt lymphoma, lymphoplasmacytic lymphoma or CNS lymphoma
Organ Function	• Renal: creatine ≤ 1.5 ULN or CrCl ≥ 50 mL/min	• CNS disease

	Inclusion criteria	Exclusion criteria
	• Haematological: neutrophil count ≥ 1.5 × 10^9 cell/L, Hb ≥ 10 g/dL, Platelet count ≥ 75 000/μL • Hepatic: AST/ALT ≤ 3 × ULN, total bilirubin ≤ 1.5 × ULN	
Medical History	• History of haematological malignancy that is expected to express CD20	• History of autoimmune disease, HLH, PML, CNS lymphoma, CNS disease or cardiovascular disease
Infectious	• Hepatitis B: RNA-negative and core Ab-negative • Hepatitis C: RNA-negative (if core Ab-positive)	• HIV-positive
Exposures	• Relapse after or failure to respond to at least one prior treatment regimen and no available treatment options that are expected to prolong survival • Pivotal data comes from cohorts that included patients with DLBCL who had relapsed after or failed at least 2 prior systemic therapies and who were to be treated with the recommended phase II dose (2.5/10/30 mg)	• Prior treatment with systemic immunotherapeutic agents, within 4 weeks or five half-lives of the drug before obinutuzumab (Gazyvaro) pre-treatment (Gpt) infusion on C1D-7 • Treatment with standard radiotherapy, any chemotherapeutic agent, or treatment with any other investigational anti-cancer agent within 4 weeks prior to Gpt infusion
Patient	• Age ≥ 18 years • ECOG PS 0–1 • Life expectancy ≥ 12 weeks	• Age < 18 years • ECOG PS > 1 • Life expectancy < 12 weeks

Ab, antibody; AST, aspartate aminotransferase; ALT, alanine aminotransferase; C1D-7, 7 days in advance of the first dose of glofitamab; CLL, chronic lymphocytic leukemia; CNS, central nervous system; CrCl, creatinine clearance; DLBCL, diffuse large B-cell lymphoma; ECOG PS, Eastern Cooperative Oncology Group performance status; FL, follicular lymphoma; Gpt, obinutuzumab (Gazyvaro) pre-treatment; Hb, hemoglobin; HGBCL, high-grade B-cell lymphoma; HIV, human immunodeficiency virus; HLH, hemophagocytic lymphohistiocytosis; MCL, mantle cell lymphoma; MZL, marginal zone lymphoma; NOS, not otherwise specified; PMBCL, primary mediastinal B-cell lymphoma; PML, progressive multifocal leukoencephalopathy; RNA, ribonucleic acid; R/R, relapsed or refractory; trFL, transformed follicular lymphoma; ULN, upper limit of normal.

B.2.3.2 Patient demographics and baseline characteristics

B.2.3.2.1 Study population and disposition

Patient disposition from study NP30179 is summarised in Table 8. The study population included in this analysis was recruited in cohorts enrolling patients with DLBCL with at least 2 prior systemic therapies who were to be treated with the proposed registration step up dosing (2.5/10/30 mg). A total of 155 patients were recruited (primary efficacy population) and 154 patients received at least one dose of study medication (primary safety population). All patients had completed study treatment by the time of the June 2022 CCOD and the median follow up for PFS was 13.4 months.

Table 8: Patient disposition from study NP30179

	Primary study population: Glofitamab 2.5/10/30mg Cohorts D2 [Sub. 2]+D3+D5 (N=154)
Ongoing in study	63 (40.9%)
Discontinued from study	91 (59.1%)
Completed treatment	41 (26.6%)
Active on treatment	4* (2.6%)
Discontinued treatment (most common) PD Death Adverse event Physician decision	109 (70.8%) 63 (40.9%) 11 (7.1%) 11 (7.1%) 9 (5.8%)
Median follow-up PFS (reverse KM), months (range)	13.4 (0–28)

*PD, progressive disease; PFS, progression-free survival. * The 4 patients had completed all cycles but the disposition page had not been updated at the time of the analysis.*

B.2.3.2.2 Demographics and baseline characteristics

Key demographic and baseline disease characteristics from the most updated analysis (CCOD June 2022) are provided in Table 9. The relevant cohorts from Study NP30179 enrolled a heavily pre-treated and highly treatment-refractory population;

[redacted]

[redacted]

Table 9: Summary of key demographic data and disease characteristics at baseline for the NP30179 study

n (%) (unless otherwise specified)		Primary study population: Glofitamab 2.5/10/30mg Cohorts D2 [Sub. 2]+D3+D5 (N=154)
Age	Median, years (min–max)	[redacted]
Gender	Male Female	[redacted]
Race	White Asian Black or African American Unknown	[redacted]
ECOG	0 1 2	[redacted]
Histology	DLBCL trFL HGBCL PMBCL	[redacted]
Prior cancer treatment		
Number of prior lines of cancer therapy	Median (range)	[redacted]
Prior lines of therapy	2 3 >3	[redacted]
Prior cancer therapy	Chemotherapy Anti-CD20 Non Anti-CD20 Conditioning regimen for SCT Signalling pathway inhibitor Immunotherapy non-SCT CAR T-cell therapy Autologous SCT Other	[redacted]
Prior radiotherapy		[redacted]
Disease characteristics		
Ann Arbor stage at study entry	I II III	[redacted]

	IV	[redacted]
Refractory status to any prior regimen*	Refractory Relapsed	[redacted]
Refractory status to latest prior regimen*	Refractory Relapsed	[redacted]
Refractory status to any prior CD20 regimen*	Refractory Relapsed	[redacted]
Primary refractory		[redacted]
Time since last therapy <3 months		[redacted]
Time since last CD20 therapy <3 months		[redacted]
Bulky disease, at least one lesion	>6cm >10cm	[redacted]

Note: D3 cohort: received 2.5/10/30mg; D2 [Sub. 2]: received 2.5/10/30mg, D5 cohort: received 2.5/10/30mg with mandatory dexamethasone premedication. Patients in cohorts D3 and D2 [Sub. 2] received Investigator choice of corticosteroid premedication.

** Patients who had PD or SD as best response to prior therapy and patients that had unknown or missing response but relapsed within 6 months from last dose of therapy.*

CAR, chimeric antigen receptor; SCT, stem cell transplant.

B.2.4 Statistical analysis and definition of study groups in the relevant clinical effectiveness evidence

B.2.4.1 Analysis population

All patients with R/R DLBCL (DLBCL not otherwise specified [NOS], high-grade B-cell lymphoma [HGBCL], transformed follicular lymphoma [trFL] and primary mediastinal B-cell lymphoma [PMBCL]) enrolled in the study were included in the intent-to-treat (ITT) population. The efficacy-evaluable population comprised patients with R/R DLBCL enrolled in the D2 [Sub. 2], D3 and D5 cohorts. The safety-evaluable population comprised patients with R/R DLBCL from the D2 [Sub. 2], D3 and D5 cohorts, who received at least one dose of study medication. The pivotal D3 cohort had a target sample size to enable a statistical test of the study hypothesis. The target sample size of 100 was in order to provide the study with 92% power to detect an increase from 20% to 35% in the percentage of patients with a CR, at a two-sided alpha level of 5%. The observed percentage of patients with a CR in the ITT population (which included all the patients enrolled in this cohort) was compared with a pre-specified value of 20% (for CR in a historical control), which was established on the basis of a meta-analysis of 19 studies of R/R DLBCL, with the use of an exact binomial test. This external control comparison of CR rates was conducted at the September 2021 CCOD. The PRO-evaluable population comprised

patients with R/R DLBCL from the B3, B4, D3 and D5 cohorts. The definitions of the efficacy, safety and PRO-evaluable populations are provided in Table 10.

Table 10: Definitions of the analysis populations included in the NP30179 study

Population	Definition
ITT	All patients enrolled in the study
Efficacy-evaluable	All patients who have been assessed for response at any time during the study, who have withdrawn from treatment or the study prior to reaching their first response assessment or who have been in the study long enough to have reached their first scheduled response assessment (defined as having a minimum of 49 days since the first dose of glofitamab or 56 days since the first dose of obinutuzumab pre-treatment, at the time of data cut-off)
Safety-evaluable	All patients who have received at least one dose of the study medication, whether prematurely withdrawn from the study or not
PRO-evaluable	All patients with a baseline and at least one post-baseline PRO assessment

ITT, intent-to-treat; PRO, patient-reported outcome.

B.2.4.2 Analysis methods

B.2.4.2.1 Efficacy endpoints

The primary efficacy endpoint was independent review committee (IRC)-assessed complete response (CR) rate, defined as the proportion of patients whose best overall response (BOR) was a CR based on IRC assessment of PET-CT scans using the Lugano criteria (32). Key secondary efficacy endpoints were overall response rate (ORR), duration of complete response (DOCR), duration of response (DOR), progression free survival (PFS) and overall survival (OS).

The definitions and analysis methodology of these endpoints are summarised in Table 11.

Table 11: Key efficacy endpoint definitions and analysis methodology

Endpoint	Definition	Analysis methodology	Analysis population
Primary efficacy endpoint			

IRC-assessed CR rate	The proportion of patients whose BOR was a CR based on IRC assessment of PET-CT scans using the Lugano criteria (32).	• Comparison of CR between the efficacy-evaluable population and historical controls was conducted using an exact binomial test with two-sided α level of 5% • The historical CR rate for patients in the DLBCL cohort was assumed to be 20%	Efficacy-evaluable population
Secondary efficacy endpoints			
ORR	The proportion of patients whose BOR is a PR or CR using standard criteria for NHL	• Assessed by the IRC and by the Investigator using the Lugano classification (32) • The exact 95% CIs using the Clopper–Pearson method for CR rate were provided	Efficacy-evaluable population
DOCR	The time from the initial occurrence of a documented CR until documented disease progression or death due to any cause, whichever occurs first	• Assessed by the IRC and by the Investigator, using the Lugano Classification (32) • The Kaplan-Meier estimate was provided • The Brookmeyer-Crowley method was used to construct the 95% CI for the median DOCR	Efficacy-evaluable population
DOR	The time from the initial occurrence of a documented PR or CR until documented disease progression or death due to any cause, whichever occurs first	• Assessed by the IRC and by the Investigator, using the Lugano Classification (32) • The Kaplan-Meier estimate was provided • The Brookmeyer-Crowley method was used to construct the 95% CI for the median DOR	Efficacy-evaluable population
PFS	The time from the first study treatment to the first occurrence of disease progression or death from any cause, whichever occurs first	• Assessed by the IRC and by the Investigator, using the Lugano Classification (32). • The Kaplan-Meier estimate was provided • The Brookmeyer-Crowley method was used to construct the 95% CI for the median PFS • The Kaplan-Meier method was used to estimate 6-month PFS and 1-year PFS, along with the standard error and the	Efficacy-evaluable population

		corresponding 95% CIs using Greenwood's formula	
OS	The time from the first study treatment to the date of death from any cause	• The Kaplan-Meier estimate was provided • The Brookmeyer-Crowley method was used to construct the 95% CI for the median OS • The Kaplan-Meier method was used to estimate 6-month OS and 1-year OS, along with the standard error and the corresponding 95% CIs using Greenwood's formula	Efficacy-evaluable population

BOR, best overall response; CI, confidence interval; CR, complete response; DLBCL, diffuse large B-cell lymphoma; DOCR, duration of complete response; DOR, duration of response; IRC, independent review committee; NHL, non-Hodgkin's lymphoma; ORR, objective response rate; OS, overall survival; PET-CT, positron emission tomography-computed tomography; PFS, progression-free survival; PR, partial response.

B.2.4.2.2 Patient reported outcomes (PROs)

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) were the PRO scales analysed in the PRO-evaluable population.

The EORTC QLQ-C30 is a validated, reliable self-report measure (97). It consists of 30 questions that assess five domains of patient functioning (physical, emotional, role, cognitive and social), three symptom scales (fatigue, nausea and vomiting, and pain), global health status/quality of life (GHS/QoL) and six single items (dyspnoea, insomnia, appetite loss, constipation, diarrhoea and financial difficulties). Scores are transformed to a 0–100 scale, with higher scores on the five domains and GHS/QoL reflecting a good HRQoL and higher scores on the symptom scales and single items reflecting poor HRQoL.

The 15-item FACT-Lym LymS was developed to assess HRQoL in patients with NHL. The FACT-Lym LymS enables assessment of the changes from baseline with respect to B-symptoms and impact on HRQoL caused by symptom worsening or alleviation and treatment toxicity. The scale range is 0–60, with a higher score reflecting better HRQoL. The validity and reliability of the FACT-Lym LymS for patients with NHL has been established (98).

The EORTC QLQ-C30 and FACT-Lym LymS assessments were performed at baseline and every 3 months during the post treatment follow-up. The scales were scored according to the user manual. Summary statistics and changes from baseline scores were calculated for all time points. The proportion of patients who reported changes from baseline or exceeding the minimal important difference for each measure was also reported.

For the EORTC QLQ-C30 physical and role functioning, GHS/QoL subscales, a clinically meaningful change at any time was defined as a difference of at least 10 points (99). For the FACT-Lym LymS, a clinically meaningful change at any time was defined as a difference of at least 3–5 points (98).

B.2.4.2.3 Safety reporting and analyses

The primary safety endpoints of the study were pharmacokinetics and AE profiles, including dose-limiting toxicity (DLT) and the maximum tolerated dose (MTD).

Safety was assessed through summaries of AEs, changes in laboratory test results, changes in electrocardiograms (ECGs), presence of anti-drug antibodies (ADAs), and changes in vital signs.

Information on AEs was recorded at each patient contact on the adverse event electronic case report form. The National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) v4.03 was used for assessing AE severity.

A summary of the AEs, SAEs, AESIs and DLTs is provided in Table 12.

Table 12: Safety endpoint data recorded in the NP30179 study

Safety data	Methods of analysis
AEs	AEs included: • Any unfavourable and unintended sign, symptom or disease temporally associated with the use of a medicinal product, regardless of whether it is considered to be related to the medicinal product • Any new disease or exacerbation of an existing disease • Recurrence of an intermittent medical condition not present at baseline • Any deterioration in a laboratory value or other clinical test that is associated with symptoms or leads to a change in study treatment or concomitant treatment or discontinuation from study drug • AEs that are related to a protocol-mandated intervention, including those that occur prior to assignment of study treatment
SAEs	SAEs included AEs meeting the following criteria: • Fatal • Life-threatening • Requires or prolongs in-patient Hospitalisation • Results in persistent or significant disability/incapacity • Congenital anomaly/birth defect in a neonate/infant born to a mother exposed to study drug • Significant medical event in the Investigator's judgment SAEs were required to be reported by the Investigator to the sponsor immediately (no more than 24 hours after learning of the event)

Safety data	Methods of analysis
AESIs	AESIs included: • Cases of an elevated ALT or AST in combination with either an elevated bilirubin or clinical jaundice • Suspected transmission of an infectious agent by the study drug AESIs specific for glofitamab: • Grade ≥ 2 CRS • Grade ≥ 2 neurologic adverse event • Any suspected hemophagocytic lymphohistiocytosis • TLS (minimum grade 3 by definition) • Febrile neutropenia (minimum grade 3 by definition) • Grade ≥ 2 AST, ALT or total bilirubin elevation • Any grade disseminated intravascular coagulation (minimum grade 2 by definition) • Grade ≥ 2 tumor inflammation/flare • Any grade pneumonitis or ILD • Colitis of any grade AESIs specific for obinutuzumab: • Secondary malignancies • TLS Non-serious AESIs were required to be reported by the Investigator to the sponsor immediately (no more than 24 hours after learning of the event).
DLTs	DLTs included: • Any grade ≥ 3 AE not considered by the Investigator to be attributable to another clearly identifiable cause • Any hepatic function abnormality (AST or ALT > × 3 ULN in combination with total bilirubin > × 2 ULN; any grade 3 AST or ALT elevation) During the DLT assessment window (4-week window of treatment with glofitamab), DLTs were required to be reported by the Investigator to the sponsor immediately (no more than 24 hours after learning of the event)

AE, adverse event; AESI, adverse event of special interest; AST, aspartate aminotransferase; ALT, alanine aminotransferase; CRS, cytokine release syndrome; DLs, dose-limiting toxicity; ILD, interstitial lung disease; SAE, serious adverse event; TLS, tumour lysis syndrome; ULN, upper limit of normal.

B.2.5 Critical appraisal of the relevant clinical effectiveness evidence

Critical appraisal of the NP30179 study was performed using established risk of bias tools recommended for HTA submissions. The complete quality assessment is presented in Appendix D (ITC report). A summary is presented below in Table 13.

Table 13: Clinical effectiveness evidence quality assessment

Study question	NP30179
Was randomisation carried out appropriately?	N/A
Was the concealment of treatment allocation adequate?	N/A
Were the groups similar at the outset of the study in terms of prognostic factors?	N/A
Were the care providers, participants and outcome assessors blind to treatment allocation?	N/A
Were there any unexpected imbalances in drop-outs between groups?	N/A
Is there any evidence to suggest that the authors measured more outcomes than they reported?	No
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Yes

B.2.6 Clinical effectiveness results of the relevant studies

Pivotal efficacy data were from Cohort D3 (N=108). The pre-specified primary analysis of the primary efficacy endpoint of complete response (CR) rate in Cohort D3 (glofitamab monotherapy, R/R DLBCL ≥ 2 prior lines), and the hypothesis test versus a historical control, was performed based on a CCOD of 14th September 2021, corresponding to a median follow-up duration of 9.0 months (range: 0–16 months). Patients received a median of 5 cycles of glofitamab (range: 1–12 cycles), and the median treatment duration was 77.5 days (range: 1–315 days).

Following health authority feedback, an updated analysis was conducted based on a CCOD of 15th June 2022, which provided up to 9 months of additional follow-up data compared with the primary analysis.

[redacted] No hypothesis testing versus historical control was performed on the CR rate in the updated analysis per the statistical analysis plan. As described in Section B.2.3.1 Study methodology, additional cohorts that included 3L+ R/R DLBCL patients treated with glofitamab monotherapy at the proposed registration dose (2.5/10/30 mg) from Cohorts D2 [Sub. 2] and D5 were added to the primary efficacy population (N=155), which had a median duration of follow up for PFS of 13.4 months (range: 0-28 months). The primary safety population included

patients from the same cohorts who received at least one dose of study medication (N=154).

B.2.6.1 Primary efficacy endpoint

In the primary analysis of the pivotal D3 cohort (CCOD of 14th September 2021), the primary efficacy endpoint of CR rate assessed by IRC was 35.2% (38/108 patients; 95% CI: 26.2%, 45.0%) as per Lugano 2014 criteria (32). The CR rate was tested against a pre-specified historical control of 20%, using an exact binominal test. The two sided p-value was <0.0001 and the null hypothesis was rejected, thus the primary endpoint was met. The historical control CR rate of 20% was derived from a systematic literature review of regimens used in the treatment of R/R DLBCL across 19 studies (1373 patients) where the majority of patients had received at least two prior lines of therapy and included therapies like pola-BR, R-chemo and CAR-T cell therapies.

At the CCOD of 15th June 2022,

[redacted] **14**[redacted]

Results in the pooled, primary efficacy population of 155 patients with R/R DLBCL treated with glofitamab 2.5/10/30 mg after ≥ 2 prior lines from Cohorts D2 [Sub. 2], D3, and D5 were consistent with the results in Cohort D3 at the 15th June 2022 CCOD. The IRC-assessed CR rate in the pooled population was 40.0% ([redacted] 62/155 patients) (Table 14). The primary efficacy outcome result was comparable with the CR rate determined by the Investigator ([redacted]) (Table 14).

Table 14: Summary of primary efficacy endpoint data in R/R DLBCL patients treated with glofitamab 2.5/10/30 mg after ≥ 2 lines of systemic therapy (ITT population)

	Primary analysis (CCOD 14th Sep 2021)	Updated analysis (CCOD 15th June 2022)	
	Cohort D3 (N=108)	Cohort D3 (N=108)	Glofitamab 2.5/10/30mg Cohort D2 [Sub. 2]+D3+D5 (N=155)

	IRC	INV	IRC	INV	IRC	INV
CR rate[a] [95% CI]	35.2% [26.2, 45.0]	33.3% [24.6, 43.1]	[redacted]	[redacted]	40.0% [32.2, 48.2]	[redacted]

[a]Lugano classification (32). CCOD, clinical cut-off date; CI, confidence interval; CR, complete response; INV, Investigator; IRC, Independent Review Committee.

B.2.6.2 Secondary efficacy endpoints

The clinical benefit of glofitamab monotherapy was observed across the secondary endpoints at the updated analysis at the CCOD of 15th June 2022 (Table 15). The overall response rate (ORR) as assessed by IRC and Investigator was 51.6% ([redacted]; 80/155 patients) and [redacted], respectively.

An overview of the secondary endpoint results is shown below in Table 15**.**

Table 15: Overview of secondary efficacy endpoint data in R/R DLBCL patients treated with glofitamab 2.5/10/30 mg after ≥ 2 lines of systemic therapy (ITT population)

Secondary efficacy endpoints	Glofitamab 2.5/10/30mg Cohorts D2 [Sub. 2]+D3+D5 (N=155)	
	IRC	INV
CR rate[a] [95% CI]	40.0% [redacted]	[redacted]
ORR (CR+PR)[a] [95% CI]	51.6% [redacted]	[redacted]
Median DOCR[a] (months) [95% CI]	[redacted]	[redacted]
Event-free at 12 months [95% CI]	73.1% [redacted]	[redacted]
Event-free at 18 months [95% CI]	[redacted]	[redacted]
Median DOR[a] (months) [95% CI]	[redacted]	[redacted]
Event-free at 12 months [95% CI]	[redacted]	[redacted]
Event-free at 18 months [95% CI]	[redacted]	[redacted]
Median TFCR[a] (days) [95% CI]	[redacted]	[redacted]
Median TFOR[a] (days) [95% CI]	[redacted]	[redacted]
Median PFS (months) [95% CI]	[redacted]	[redacted]
1-year PFS rate [95% CI]	[redacted]	[redacted]
Median OS (months) [95% CI]	[redacted]	[redacted]

1-year OS rate [95% CI]	[redacted]	[redacted]

[a] *Lugano classification (32).*

CCOD, clinical cutoff date; CI, confidence interval; CR, complete response; DOCR, duration of complete response; DOR, duration of response; INV, Investigator; IRC, Independent Review Committee; NE, not evaluable; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; PR, partial response; TFCR, time to first complete response; TFOR, time to first overall response.

B.2.6.2.1 Duration of complete response (DOCR), duration of overall response (DOR) and time to first response by IRC

At the CCOD of 15th June 2022, DOCR and DOR achieved by glofitamab demonstrated durable response that extended beyond the length of the fixed treatment duration. Per IRC-assessment, the median DOCR and DOR follow-up was [redacted], respectively.

The median IRC-assessed DOCR was not reached (Table 16). The Kaplan-Meier estimated event-free rates among complete responders (estimated proportion still in CR and alive) at 12 and 18 months after the first CR were 73.1% and [redacted], respectively. The median will change with increased follow-up as [redacted] CRs were ongoing at the 15th June 2022 CCOD.

The median IRC-assessed DOR was [redacted] at the time of CCOD on 15th June 2022. The Kaplan-Meier estimated event-free rates among complete responders at 12 months after the first OR was [redacted] (Table 16). The median is expected to change with further follow up as [redacted] ORs were ongoing at the CCOD.

[redacted]

(Table 16), suggesting that if patients are going to respond to glofitamab, responses are achieved early.

In the supporting efficacy population of patients with R/R DLBCL who received glofitamab doses ≥ 10 mg after ≥ 2 prior lines (n=35) and were enrolled earlier than those in Cohort D3, the median duration of CR follow-up was [redacted] in the updated analysis (Table 16). The median DOCR per IRC was not reached and KM estimated event-free rates showed that [redacted] of CRs were still maintained at 12 and 24 months, respectively, further supporting the durability of

complete responses achieved with glofitamab. At the CCOD, [redacted] were ongoing.

Table 16: DOCR by IRC (CCOD 15th June 2022)

DOCR	Glofitamab 2.5/10/30mg Cohorts D2 [Sub. 2]+D3+D5 (N=155)	Supporting efficacy population: Glofitamab ≥ 10mg (N=35)
Median, months [95% CI]	[redacted]	[redacted]
9-month DOCR [95% CI]	[redacted]	[redacted]
12-month DOCR [95% CI]	[redacted]	[redacted]
15-month DOCR [95% CI]	[redacted]	[redacted]
24-months DOCR [95% CI]	[redacted]	[redacted]
Ongoing CR's at time of CCOD, n [%]n [%]	[redacted]	[redacted]
Median Duration of CR follow-up, months [range]	[redacted]	[redacted]

CCOD, clinical cutoff date; CI, confidence interval; CR, complete response; DOCR, duration of complete response; DOR, duration of response; IRC, Independent Review Committee; NE, not evaluable.

B.2.6.2.2 Progression free survival (PFS) by IRC

At the CCOD of 15th June 2022, the median IRC-assessed PFS was [redacted] in the primary efficacy population (n=155). PFS event-free rates at 12 months were [redacted] (Figure 3). INV-assessed 12-month PFS event-free rates were [redacted]. The majority of events occurred in patients who did not achieve a response. A plateau in

the KM PFS curve emerged at an approximate [redacted] but this is to be determined with longer follow up, as there were [redacted].

Figure 3: Kaplan-Meier plot of time to IRC-assessed PFS (CCOD 15th June 2022)

[redacted]

B.2.6.2.3 Overall survival (OS) by IRC

At the CCOD of 15th June 2022, the median OS of the primary efficacy population was [redacted], which had remained consistent with the previous analysis (Figure 4). The presence of a survival plateau was observed at [redacted], however, with [redacted], further follow up is required to support this. At the CCOD,

[redacted]

Figure 4. Kaplan-Meier plot of time to IRC-assessed OS (CCOD 15th June 2022)

[redacted]

B.2.6.3 Patient-reported outcome (PRO) endpoints

Health-related quality of life (HRQoL) was assessed using the EORTC QLQ-C30 v3.0 questionnaire and the 15-item FACT-Lym LymS subscale. In the EORTC QLQ-C30, higher scores are reflective of higher functioning and overall HRQoL on the function and GHS/QoL scales, but a greater degree of symptoms on the symptom scales. On the FACT-Lym LymS, higher scores are reflective of better HRQoL (i.e., lower lymphoma-specific symptoms or concerns).

The PRO analyses were performed for the Part III monotherapy expansion cohorts (B3: DLBCL patients, glofitamab 10/16 mg, B4: FL patients, glofitamab 10/16 mg, D3: DLBCL patients, glofitamab 2.5/10/30 mg, D4: FL patients, glofitamab 2.5/10/30 mg, and D5: DLBCL patients (dexamethasone pretreatment), glofitamab 2.5/010/30 mg) in patients who had a baseline assessment and at least one post-baseline assessment of PRO scales.

B.2.6.3.1 Completion rates

I. EORTC QLQ-C30

For the EORTC QLQ-C30, a patient was counted if they completed at least one question. For EORTC QLQ-C30 the proportion of patients with R/R DLBCL completing at least one question at baseline was [redacted]. During treatment, [redacted].

II. FACT-Lym LymS

For the FACT-Lym LymS, a patient was considered counted if they completed at least 50% of the questions. For FACT-Lym LymS the proportion of patients with R/R DLBCL completing at least 50% of questions at baseline was [redacted]. During treatment, [redacted].

B.2.6.3.2 Mean and mean change from baseline

In all study cohorts, mean baseline scores in all cohorts showed moderate to moderate-high levels of functioning and overall HRQoL, and low to low-moderate levels of symptoms. In particular, the baseline mean (SD) physical functioning, role functioning, Global Health Status (GHS)/QoL and fatigue scores from the EORTC QLQ-C30 questionnaire for patients with R/R DLBCL in primary efficacy Cohort D3 and Cohort D5 were:

[redacted]

[redacted]

In addition, at baseline (defined as C1D1 pre-infusion of study treatment), in the majority of patients in Cohort D3 and D5, the following treatment-related symptoms from the EORTC QLQ-C30 were reported as ‘’not at all’:

[redacted]

Over the course of treatment, in Cohort D3 (C1D1 to C7D1) and Cohort D5 (C1D1 to C7D1),

[redacted]

B.2.6.3.3 Responder analysis (clinically meaningful change from baseline)

The proportion of patients with R/R DLBCL in Cohorts D3 and D5 reporting a clinically meaningful change

[redacted]

During treatment, the proportion of patients with R/R DLBCL in Cohort D3 reporting a meaningful improvement between C1D1 and C7D1 in EORTC QLQ-C30 physical functioning ranged from

[redacted]. Those in Cohort D3 reporting meaningful deterioration in physical functioning ranged from

[redacted]

[redacted]. In addition, on the FACT-Lym LymS, the proportion of patients in Cohort D3 reporting meaningful improvement ranged from [redacted].

During treatment, the proportion of patients with R/R DLBCL in Cohort D5 reporting meaningful improvement between C1D1 and C7D1 in EORTC QLQ-C30 physical functioning ranged from [redacted]. Those in Cohort D5 reporting meaningful deterioration in physical functioning ranged from [redacted]. In addition, on the FACT-Lym LymS, the proportion of patients in Cohort D5 reporting meaningful improvement ranged from [redacted].

B.2.7 Subgroup analysis

At the CCOD of 15th June 2022, pre-specified subgroup analyses of the primary endpoint (CR rate) in the pooled primary efficacy population, per IRC, demonstrated consistency of the treatment effect across relevant subpopulations defined by demographics (gender, age range categories, race/ethnicity, ECOG PS), prior CAR-T therapy, number of prior lines of therapy and risk factors for IPI (Figure 5):

- [redacted]
- [redacted]
- [redacted]
- [redacted]

Figure 5: Forest plot of the subgroup analysis based on IRC CR rate (CCOD 15th June 2022)

Figure 5: Forest plot of the subgroup analysis based on IRC CR rate (CCOD 15th June 2022) – continued

Figure 5: Forest plot of the subgroup analysis based on IRC CR rate (CCOD 15th June 2022) – continued

B.2.8 Meta-analysis

At the time of submission, clinical evidence supporting the use of glofitamab for the treatment of R/R DLBCL was available solely from the pivotal cohort of the NP30179 study, so no meta-analysis was performed.

B.2.9 Indirect and mixed treatment comparisons

B.2.9.1 Indirect treatment comparison methods

In the absence of head-to-head data comparing glofitamab with relevant comparators described in the NICE scope, a series of indirect treatment comparisons (ITCs) was conducted to estimate the relative efficacy of glofitamab (based on the pivotal cohort of the NP30179 study (100, 101) and its key comparators. As described in Section **Error! Reference source not found.**, BR, pola-BR and axi-cel were deemed to be the most relevant comparators for the treatment of 3L+ DLBCL; as such, these ITCs are presented in the following sections. Given the single-arm design of NP30179 (100, 101), matching-adjusted indirect comparisons (MAICs) were conducted for those comparators for which only published aggregate data were available, and propensity score analyses were conducted for comparators with available individual patient data (IPD).

All analyses were conducted using R statistical software. For details of the ITC methodology and additional scenario results beyond those presented in this submission, please see the ITC report provided in Appendix D (ITC report).

B.2.9.1.1 MAIC

In the MAIC analyses, the individual patient data (IPD) of patients with DLBCL after ≥ 2 prior lines of therapy from the D2 [Sub. 2], D3 and D5 glofitamab step-up dosing cohorts of the NP30179 trial were weighted to match reported prognostic factors and effect modifiers from each of the comparator studies (100, 101) (see Section B.2.4). Where necessary, the NP30179 population was aligned in terms of eligibility criteria related to the factors of interest with that of the comparator studies before estimating the weights (100, 101). The matching-adjusted data were then used to provide an estimate of the outcomes that might have occurred if the comparator studies had included a glofitamab arm.

Full details of the methodology used in the MAIC analyses are presented in Appendix D (ITC report).

B.2.9.1.2 Propensity score analysis

Propensity score analyses provide an estimate of treatment effect after accounting for differences in covariates believed to be potential prognostic factors or treatment-effect modifiers across treatment groups. The preferred target estimand was the average treatment effect (ATE). Methodologies including matching on the propensity score and the inverse probability of treatment weighting (IPTW) were used to minimise imbalances between glofitamab and comparator groups, as recommended in NICE DSU TSD 17 (102). The matching method resulting in better covariance balance, i.e. the one that minimised the absolute standardised mean differences, was selected as the preferred matching method for the base case scenario.

Full details of the methodology used in the propensity analyses are presented in Appendix D (ITC report).

B.2.9.1.3 Data sources

Based on a systematic literature review (SLR) and feasibility assessment (see Section B.2.4 and Appendix D, ITC report for details), the following ITCs were performed against the following comparators specified in the NICE scope:

- A MAIC vs **axicabtagene ciloleucel (axi-cil)**, based on the ZUMA-1 trial (103). Note that while 3 other studies were identified in the feasibility assessment (Frank 2021, Sanderson 2020, and ZUMA-9), ZUMA-1 was deemed the most appropriate source of data for the comparison of axicabtagene ciloleucel to glofitamab (103-106). This was because ZUMA-1 included the largest number of patients, had the largest number of baseline factors available to be considered for adjustment in MAIC analyses (n=16), and reported the most (all) outcomes of interest at the longest follow-up time (103).

- As noted in in Section **Error! Reference source not found.**, **rituximab with bendamustine (BR)** has been put forward as a proxy for R-Chemotherapy to enable a comparison with glofitamab. In the absence of alternative data to

support a robust comparison to R-GemOX, clinical experts agreed that the approach taken was reasonable (1). Furthermore, BR has been shown to demonstrate similar efficacy to R-GemOx, the most widely used R-Chemotherapy regimen for 3L+ DLBCL (2). As such, a MAIC based on the Hong 2018 study (107) has been put forward. Hong 2018 was considered the most appropriate source of data (where IPD were not available) vs BR (107). Note that whilst Hong 2018 was conducted in South Korea, and Western studies are preferred for the MAIC, Hong 2018 was considered the highest quality study available for the comparison (107), because it included fewer patients who received only one prior line of therapy and had an ECOG PS of 2+, as well as more baseline characteristics to control for compared with the other studies considered in the feasibility assessment. See Appendix E for full details.

- A propensity score analysis vs **polatuzumab vedotin with rituximab and bendamustine (pola-BR)** based on the GO29365 study (77) safety run-in, randomised Arm G + Arm H pola-BR cohorts. As GO29365 is a Roche sponsored study, it was possible to conduct more robust matching in this comparison.

For reasons described in Section **Error! Reference source not found.**, and given the availability of data to support these analyses, the comparisons presented are deemed to be the most relevant and robust to the support decision making.

The comparator studies included in the ITCs described in this submission are summarised in Table 17. Note, that for studies with available IPD, only the size of the population corresponding to anticipated glofitamab label (i.e., R/R DLBCL after ≥ 2 treatment lines) is reported in the table.

The source of glofitamab data were the patients with DLBCL (DLBCL NOS, HGBCL, PMBCL and tFL) who received ≥ 2 prior lines of therapy from the D2 [Sub. 2], D3 and D5 glofitamab step-up dosing (2.5/10/30 mg) cohorts of the NP30179 study (n=155), based on a clinical cut-off date of June 2022 (100, 101). Where appropriate, patients may have been further selected from the glofitamab

study to align with the eligibility criteria of the comparator studies, thus improving population overlap and comparability before adjustment (for example, excluding ineligible histologies).

Table 17: List of performed ITCs

Comparator	Study name	Study design	Analysis population	ITC type	Results location in the submission	Likely direction of bias in the ITC
Axicabtagene ciloleucel	ZUMA-1 (103)	A prospective cohort study conducted in the US and Israel, investigating axicabtagene ciloleucel in 101 patients with DLBCL, PMBCL, HGBCL, or tFL	101 patients with R/R DLBCL who had received ≥2 prior lines of treatment	Unanchored MAIC	B.2.9.2.1	The mITT cohort used in the ITC excluded patients who progress before infusion, therefore biasing results in favour of axicabtagene ciloleucel.
Bendamustine and rituximab	Hong 2018 (107)	A multi-centre retrospective analysis conducted in South Korea, investigating bendamustine plus rituximab in 58 patients with DLBCL	58 patients with R/R DLBCL who had received ≥2 prior lines of treatment	Unanchored MAIC	B.2.9.2.1	Imbalances in the number of prior therapies and ECOG PS are likely to bias the ITC in opposite directions, thereby offsetting one another. As such, the overall direction of bias is unclear.
Polatuzumab vedotin plus bendamustine plus rituximab	GO29365 (77)	A randomised phase II trial of polatuzumab vedotin plus rituximab + bendamustine vs rituximab + bendamustine alone in transplant-ineligible patients with R/R FL or DLBCL	152 patients with R/R DLBCL who had received ≥3 prior lines of treatment	Propensity score analysis	B.2.9.2.2	Bias is expected to be well controlled for in this propensity score analysis.

CR, complete remission; DLBCL, diffuse large B-cell lymphoma; FAS, Full analysis set; FL, follicular lymphoma; IPD, individual patient data; ITC, indirect treatment comparison; MAIC, matching-adjusted indirect comparison; OS, overall survival; PFS, progression-free survival; PR, partial remission; R/R, relapsed or refractory.

B.2.9.1.4 Outcomes included in the analyses

The outcomes of interest included OS and PFS as time-to-event endpoints, as well as ORR, CR, DOR, DOCR and treatment discontinuation due to AEs as binary endpoints. Endpoints reported in NP30179 (100, 101) were matched to the definitions available from the comparator trials whenever possible.

B.2.9.1.5 Prognostic factors and effect modifiers

Prognostic factors and effect modifiers were classified as either high priority, low priority, or deprioritised according to clinical feedback. High-priority prognostic factors and effect modifiers included:

- International prognostic index (IPI) (0–2 vs 3–5)/AA-IPI (0–1 vs 2–3) and/or any of its components:
    - Age (mean, or median if mean not reported, or % ≥ 60 years, if neither reported)
    - ECOG PS (0–1 vs ≥ 2) [0 vs 1 not that important prognostically]
    - Ann Arbor Stage (I–II versus III–IV)
    - High lactate dehydrogenase (LDH) levels
    - Presence of extranodal disease (yes/no or number of lesions reported)
- Refractoriness (definition may vary across studies) to first line of treatment
- Refractoriness (definition may vary across studies) to last line of treatment
- Refractoriness (definition may vary across studies) to any line of treatment
    - Some advisors ranked this as lower priority compared to the previous two and as somewhat lower priority compared with early relapse/refractory status to individual agents
- Histological subtype (e.g. HGBCL, PMBCL, or DLBCL/tFL)
- Double/triple hit lymphoma (to be prioritised over histological subtype, if both reported)

- This has a similar importance to histological subtype, as double/triple hit lymphoma typically corresponds to having HGBCL (their definitions can vary across studies, though), so controlling for both may not always be needed and only one may be prioritised

- Early relapse after SCT (e.g. defined as duration of response [DOR] or time since completion of transplant to next treatment line <12 months)
    - Not many patients had this condition in NP30179 (100, 101) D3 cohort; if controlling for this was not feasible as resulting in low ESS, controlling for prior ASCT was considered by the analyst, as a proxy

- Number of prior treatment lines (e.g. 3 vs >3 [no clinically established threshold], or median)

Medium- and low-priority prognostic factors are presented in Appendix D (ITC report).

If key covariates were defined differently in NP30179 and the comparator trials, attempts to readjust the covariate definitions in NP30179 were made, where feasible (100, 101). Full details of the handling of prognostic factors and effect modifier definitions and missing data are presented in Appendix D (ITC report).

B.2.9.2 ITC Results

Only base case analysis results for each ITC are presented in the following sections. Please see Appendix D (ITC report) for results of the scenario analyses performed.

B.2.9.2.1 Glofitamab vs axicabtagene ciloleucel MAIC

B.2.9.2.1.1 Populations and baseline characteristics

The population from ZUMA-1 (103) used for the MAIC included patients with chemo-refractory disease according to ZUMA-1 (103) criteria (progressive or stable disease as the best response to first line or to the most recent chemotherapy regimen or disease progression or relapse within 12 months after autologous stem-cell transplantation) (n=115).

The modified intention- to- treat (mITT) population was used for the comparison, covering patients treated with at least 1.0×10^6 anti-CD19 CAR-T cells/kg in phase II. The mITT population excludes all patients submitted to the NCCP for consideration of CD19 CAR-T who do not ultimately receive treatment. A UK study exploring real world CAR-T experience found that 26% did not proceed to infusion, usually because of rapid disease progression before the infusion could take place (86). If a patient fails to reach infusion following further progression, outcomes are poor and further treatment option are limited. Consequently, because the mITT comparison excludes a significant proportion of patients whose disease progressed before infusion, the results of the MAIC are likely biased in favour of axicabtagene ciloleucel. While recognising these limitations, the results of this comparison are not a true reflection of comparative efficacy and safety. Due to the restrictions on accessing data from the ITT cohort of ZUMA-1, a more robust comparison cannot be presented (103). As such, the direction and magnitude of this bias should be considered when interpreting the results of this MAIC, and any other analyses where they are used. Acknowledging these limitations, a scenario analysis adjusting the relative effectiveness in favour of glofitamab vs axicabtagene ciloleucel has been explored. This was done by assuming proportional hazards, and taking the mid-point HR for PFS and OS between 1 and the ITC estimate, thereby reducing the relative efficacy benefit assumed for axi-cel from the biased ITC results.

The base-case maximises the bias/variance trade-off whilst controlling for all high and medium priority prognostic factors that were feasible (excluding low priority factors). The proportion of patients with double/triple hit lymphoma was not included for adjustment in any analyses presented, because only double/triple hit HGBCL was reported rather than for all patients with double/triple hit tumours, not just those with HGBCL. Therefore, histology subtype was used instead, as the proportion of HGBCL patients also included patients with HGBCL not otherwise specified (NOS), so it was deemed to be a more inclusive covariate. Additionally, two definitions for the refractory to last line variable were available: 1) best response as progressive disease to last previous therapy and 2) best response to last previous therapy as progressive disease or stable disease after at least 2 therapy cycles with duration of stable disease no longer than 6 months. Both were explored, but the latter resulted

in a very small sample size. Consequently, the refractory definition of best response as progressive disease to last previous therapy was selected for the base case analysis. An additional scenario analysis is presented in Appendix D (ITC report) that explores the impact of controlling for all possible matching covariates (addition of low priority factors: cell type of origin, bone marrow involvement and prior SCT).

Baseline characteristics before and after weighting are presented in Table 18.

Table 18: Pre- and post-weighting baseline characteristics in the glofitamab vs axicabtagene ciloleucel MAIC

Variable	Glofitamab unweighted (N=115)	Glofitamab - weighted (ESS=27.9) Base-case	Axicabtagene ciloleucel (N=101)
Age (mean)	[redacted]	[redacted]	[redacted]
ECOG PS ≥1 (%)	[redacted]	[redacted]	[redacted]
Ann Arbor Stage III–IV (%)	[redacted]	[redacted]	[redacted]
High LDH (%)	[redacted]	[redacted]	[redacted]
Extranodal disease (%)	[redacted]	[redacted]	[redacted]
IPI 3–5 (%)	[redacted]	[redacted]	[redacted]
Refractory to 1st line (%)	[redacted]	[redacted]	[redacted]
Best response of PD to last line (%)	[redacted]	[redacted]	[redacted]
HGBCL histology (%)	[redacted]	[redacted]	[redacted]
PMBCL histology (%)	[redacted]	[redacted]	[redacted]
Early relapse after SCT (%)	[redacted]	[redacted]	[redacted]
>2 prior therapies (%)	[redacted]	[redacted]	[redacted]
Bulky disease ≥10cm (%)	[redacted]	[redacted]	[redacted]
Cell type GCB (%)	[redacted]	[redacted]	[redacted]
Cell type ABC/non-GCB (%)	[redacted]	[redacted]	[redacted]
Bone marrow involvement (%)	[redacted]	[redacted]	[redacted]
Prior SCT (%)	[redacted]	[redacted]	[redacted]

ABC, activated B cell; ECOG PS, Eastern Cooperative Oncology Group Performance Status; ESS, effective sample size; GCB, germinal B cell; HGBCL, high grade B cell lymphoma; IPI, International Prognostic Index; LDH, lactate dehydrogenase; NA, not applicable; PD, progressed disease; PMBCL, primary mediastinal large B cell lymphoma; SCT, stem cell transplant.

B.2.9.2.1.2 Response rates (per IRC assessment)

Tumour responses were assessed using the Lugano criteria (32) in NP30179 (100, 101), whereas ZUMA-1 (103) used the International Working Group (IWG) criteria (108).

[redacted]

B.2.9.2.1.3 PFS and OS (per INV assessment)

The Kaplan-Meier plots for PFS and OS are presented in Figure 6 and

[redacted]

Figure 7, respectively.

[redacted]

Figure 6: PFS (per INV assessment) in the glofitamab vs axicabtagene ciloleucel (Yescarta) MAIC

Figure 7: OS in the glofitamab vs axicabtagene ciloleucel (Yescarta) MAIC

B.2.9.2.1.4 Safety

With regards to safety, data relating to discontinuation due to AEs was not available for the MAIC against axicabtagene ciloleucel, so an OR could not be estimated. Treatment-related grade 3 or higher AEs were extracted from the ZUMA-1 study, and considered in the analysis.

B.2.9.2.2 Glofitamab vs bendamustine plus rituximab MAIC

B.2.9.2.2.1 Population and baseline characteristics

The analyses were conducted in a population where HGBCL and PMBCL histologies were excluded in order to align with Hong 2018 (n=139) (107).

The base-case maximises the bias/variance trade-off whilst controlling for all priority prognostic factors that were feasible. Refractory to all lines was used as a proxy for refractory to first line (as reported in the Hong et al 2018 publication (107)), but also

to last line. Note that Hong 2018 (107) enrolled ~30% second line patients, which it is not possible to adjust for since such patients were not enrolled in the NP30179 cohorts used for the analyses. This is likely to introduce a major bias in the results in favour of bendamustine plus rituximab. Additionally, Hong 2018 (107) included ~22% ECOG PS 2+ patients, which, as in the case of number of prior therapies, it is not possible to adjust for, as such patients were not enrolled in the NP30179 cohorts. Therefore, ECOG was excluded from the analysis (as only the split between 0-1 and 2-4 was reported), resulting in a residual imbalance in ECOG PS 1+, which is likely to bias results in favour of glofitamab.

Baseline characteristics before and after weighting are presented in Table 19.

Table 19: Pre- and post-weighting baseline characteristics in the glofitamab vs BR MAIC

Variable	Glofitamab unweighted (N=139)	Glofitamab weighted (ESS=67.6) Base-case	Bendamustine plus rituximab (BR) (N=58)
Age > comparator median (%)	[redacted]	[redacted]	[redacted]
Ann Arbor Stage III–IV (%)	[redacted]	[redacted]	[redacted]
High LDH (%)	[redacted]	[redacted]	[redacted]
Extranodal sites ≥2 (%)	[redacted]	[redacted]	[redacted]
IPI 3–5 (%)	[redacted]	[redacted]	[redacted]
Refractory to all lines (%)	[redacted]	[redacted]	[redacted]
>2 prior therapies (%)	[redacted]	[redacted]	[redacted]
Cell type GCB (%)	[redacted]	[redacted]	[redacted]
Cell type ABC/non-GCB (%)	[redacted]	[redacted]	[redacted]
Prior SCT (%)	[redacted]	[redacted]	[redacted]

ABC, activated B cell; ESS effective sample size; GCB, germinal B cell; IPI, International Prognostic Index; SCT, stem cell transplant.

B.2.9.2.2.2 Response rates (per INV assessment)

Tumour responses were assessed using the Lugano criteria (32) in NP30179 (100, 101) whereas Hong 2018 (107) used the International Working Group (IWG) criteria or revised criteria (108, 109).

[redacted]

[redacted]

B.2.9.2.2.3 PFS and OS (per INV assessment)

The Kaplan-Meier plots for PFS and OS are presented in Figure 8 and

Figure 9, respectively.

[redacted]

Figure 8: PFS (per INV assessment) in the glofitamab vs BR MAIC

Figure 9: OS in the glofitamab vs BR MAIC

B.2.9.2.2.4 Safety

With regards to safety, data relating to discontinuation due to AEs was not available for the MAIC against BR, so an OR could not be estimated. Treatment-related grade 3 or higher AEs were extracted from the Hong 2018 study, and considered in the analysis.

B.2.9.2.3 Glofitamab vs pola-BR propensity score analysis

B.2.9.2.3.1 Population and baseline characteristics

The population used for indirectly comparing glofitamab with pola-BR was the combination of the 1) safety run-in, 2) randomised, 3) Arm G and 4) Arm H DLBCL cohorts from GO29365 (n=152) (77). As GO29365 is a Roche sponsored study IPD was available; therefore, it was possible to better match baseline characteristics in this comparison.

In order to ensure that the patient cohorts used for the analyses were as homogeneous as possible before attempting any indirect comparisons, a filtering procedure based on applying common inclusion/exclusion criteria was adopted. This consisted of excluding those patients histologically incompatible with the glofitamab cohort (excluding "EBV+ DLBCL, NOS", "T-CELL/HISTIOCYTE-RICH LARGE B-CELL LYMPHOMA", "FOLLICULAR LYMPHOMA"), and excluding patients with ECOG PS ≥2 and patients who received only one prior line of therapy from the pola-BR cohort (to align with the inclusion/exclusion criteria of NP30179) (100, 101). In addition, patients with PMBCL histology were excluded from the glofitamab cohort as no such patients were enrolled in the pola-BR cohort.

This resulted in 149 patients in the glofitamab arm and 84 patients in pola-BR arm.

Potentially prognostic baseline characteristics available for these patient cohorts (as per the list of covariates identified in Section B.2.9.1.4) and their imbalances prior to any adjustment are reported in Table 20. As seen in Table 20, several baseline characteristics were imbalanced prior to any adjustment between glofitamab and pola-BR (absolute standardised mean difference [aSMD] >0.1), with the exception of extranodal disease, number of prior therapies, size of the largest node lesion and refractory to any prior anti-CD20 monoclonal antibody (mAb) containing regimen (age and IPI were borderline balanced).

Table 20: Unadjusted and IPTW-adjusted baseline characteristics in the propensity score analysis of glofitamab vs pola-BR

Variable	Unadjusted					IPTW adjusted				
	Glofitamab (n=149)		Pola-BR (n=84)		aSMD	Glofitamab [redacted]		Pola-BR [redacted]		aSMD
	Mean	SD	Mean	SD		Mean	SD	Mean	SD	
Age (mean)	[redacted]									
ECOG PS (1 vs 0) (%)										
Ann Arbor Stage III/IV (Yes) (%)										
High LDH (Yes) (%)										
Extranodal disease (Yes) (%)										
IPI (3-5) %										
Refractory to first line (Yes) (%)										
Refractory to any line (Yes) (%)										
Refractory to last line (Yes) (%)										
HGBCL (Yes) (%)										
Refractory to ASCT (Yes) (%)										
Prior therapies, >2 (%)										

Variable	Unadjusted					IPTW adjusted				
	Glofitamab (n=149)		Pola-BR (n=84)		aSMD	Glofitamab [redacted]		Pola-BR [redacted]		aSMD
	Mean	SD	Mean	SD		Mean	SD	Mean	SD	
Size of the largest node lesion, cm (mean)	[redacted]									
Refractory to any prior anti-CD20 mAb and anthracycline (Yes) (%)	[redacted]									
Refractory to any prior anti-CD20 mAb containing regimen (Yes) (%)	[redacted]									
Time since last treatment [months] (mean)	[redacted]									
Cell type GCB (%)	[redacted]									
Cell type ABC/non-GCB (%)	[redacted]									
Bone marrow involvement (Yes) (%)	[redacted]									
Prior ASCT (yes) (%)	[redacted]									

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

Different adjustment methods were explored in an attempt to balance covariates. Full details of the approaches explored can be seen in Appendix D (ITC report). Covariate balance improved significantly for many prognostic factors both after full matching and inverse probability of treatment weighting (IPTW). The most significant improvements were observed after IPTW, with balance being achieved for all prognostic factors considered, and for this reason IPTW was selected as the adjustment method of preference for the base case analysis. On the other hand, full matching failed in achieving good balance for age, IPI, extranodal disease, number of prior therapies and prior ASCT, with balance being worse than in the unadjusted sample for the first four covariates (Ann Arbor stage, high LDH, and time since last treatment were borderline balanced). For this reason, residual imbalances in these covariates between the two groups were further controlled for in subsequent outcome analyses.

B.2.9.2.3.2 Response rates (per INV assessment)

Tumour responses were assessed using the Lugano criteria (32) in both GO29365 (77) and NP30179 (100, 101).

[redacted]

B.2.9.2.3.3 PFS and OS (per INV assessment)

The Kaplan-Meier plots from the unadjusted analysis and IPTW analysis are presented in Figure 10 and Figure 11. As the IPTW analysis was selected as the adjustment method of preference for the base case analysis, Kaplan-Meier plots from the matching adjusted analysis are not presented in this section, but can be seen in Appendix D (ITC report).

[redacted]

[redacted]

Figure 10: PFS (per INV assessment) in the glofitamab vs pola-BR propensity score analysis

Figure 11: OS in the glofitamab vs pola-BR propensity score analysis

B.2.9.2.3.4 Safety

For the pola-BR arm, a patient was classified as having discontinued treatment due to AEs if that patient had discontinued any of the study treatments due to AEs, as this was deemed to be a more representative outcome for the overall tolerability of the combination regimen.

[redacted]

B.2.9.3 Discussion of ITC results

B.2.9.3.1 Summary of results

The benefit of a treatment in the ITC was considered relatively strong or weak depending on if the confidence intervals (CIs) around the point estimates crossed 1. This was also conducted to consider potential differences in study design that could not be resolved via these methods. In the context of limited patient numbers, and recognising that some imbalances could not be accounted for, where statistical significance was not demonstrated, numerical differences should not be considered as a signal of no relative benefit. The conclusions from the ITCs are broadly summarised as:

- For overall response rate ORR,
  [redacted]
- In the CR analyses,
  [redacted]

[redacted]

- For PFS,

  [redacted]

- In the OS analyses,

  [redacted]

The results of the ITC demonstrate glofitamab has the potential to improve response (OR and CR), and survival (PFS and OS) rates compared with BR and pola-BR. While statistical significance was not always demonstrated, likely due to limited patient numbers or because of covariate imbalances, numerical differences should be considered as a signal of relative benefit, not disregarded with equivalence assumed. In the comparison with axi-cel, the results of the ITC suggest there is weak or strong evidence to suggest response and survival rates could be improved for axi-cel vs glofitamab. However, as discussed in section B.2.9.2.1.1 Populations and baseline characteristics comparing to the axi-cel mITT cohort from ZUMA-1 is expected to significantly bias the results against glofitamab. As such, the direction and magnitude of this bias should be considered when interpreting the results of this MAIC, and any other analyses where they are used.

Top-line results of the ITC are visualised in Figure 12.

Figure 12: Summary of ITC results

CR, complete response; disc, discontinuation; DOCR, duration of complete response; ORR, overall response rate; OS, overall survival; PFS, progression-free survival.

B.2.9.3.2 Limitations and uncertainties

Generally, the conclusions from the ITC results were consistent between the base case analyses and the sensitivity analyses conducted (see Appendix D, ITC report), although a few exceptions were noted where the trends observed in the base case analysis were not confirmed by one or more of the sensitivity analyses (See Appendix D, ITC report).

It is important to interpret the ITC results in the context of the limitations associated with the analyses.

- There were often misalignments across NP30179 and comparator studies in terms of inclusion/exclusion criteria (100, 101). Although not always feasible, filtering procedures using common eligibility criteria related to the prognostic factors/effect modifiers of interest were applied across cohorts to improve population overlap prior to conducting any ITCs. For example:
    - All studies included in the MAICs (with the exception of ZUMA-1 (103) and JULIET (111) also enrolled patients with ECOG PS >1 (the proportion ranged from ~1% to ~54%). These patients were not enrolled in the NP30179 (100, 101) 3L+ DLBCL step-up dosing cohorts [D2 [Sub. 2], D3 and D5] but could not be excluded from the analysis, which may have biased the results
    - All comparator data used for the MAICs were on R/R DLBCL patients rather than 3L+ patients only (the proportion of 2L patients was not always reported for Hong 2018 (107)), which may have significantly

biased the results against glofitamab, given the prognostic importance of the number of prior therapies, particularly for PFS and OS

    - The comparator populations used to compare glofitamab to the CAR-T therapies did not include all leukapheresed patients, but only those patients who eventually received an infusion. These populations do not fully reflect the patients who are eligible to be treated with CAR-Ts in clinical practice and their use in the comparisons likely introduced some selection bias in favour of the comparators (as the patients in worse health who progress or die between leukapheresis and infusion are excluded from the analysis). Such bias cannot be resolved in absence of both baseline characteristics and outcome data on the full population eligible to receive CAR-Ts

- In all MAICs, it was not possible to adjust for all known prognostic factors and effect modifiers, as they were either not available or there was not sufficient overlap between study populations, which resulted in a very low ESS. Compromises had to be made in some cases to maximise the bias-variance trade-off, which may have inevitably biased the results

- The matching and/or weighting adjustments conducted as part of the propensity score analysis did sometimes result in residual imbalances for multiple prognostic factors. Although these might have been further controlled for in subsequent outcome analyses, it is important to note that the second adjustment could only be performed for summary statistics (i.e. HRs or odds ratios [ORs]) but not for KM curves, which should thus be interpreted with caution

    - For the comparison versus pola-BR, full matching failed to achieve a good balance for the following factors: age, IPI, extranodal disease, number of prior therapies and prior ASCT (balance observed to be worse compared with the unadjusted sample for the first four covariates)

- There were misalignments across NP30179 (100, 101) and some comparator studies in terms of endpoint definitions. For example, ORR and CR results for the comparisons versus axicabtagene ciloleucel and BR should be interpreted with caution, as tumour responses were assessed using the Lugano criteria (32) in NP30179 (100, 101) versus the IWG criteria (108) in the other studies.

- In some of the MAICs, the resulting (effective) sample sizes after adjustment were relatively small, which may have led to wide CIs and thus uncertain estimates, thereby limiting the interpretation and the generalisability of the results

- The results from the sensitivity analyses conducted in many MAICs were not always supportive of the conclusions of the respective base-case analyses (as (1) the numerical trends were inverted, or (2) the CIs did not cross 1 in one analysis but they did in at least one of the others, or (3) the CIs from the bias corrected accelerated (BCa) and percentile methods were not in agreement, or (4) any combination of these three reasons). The most notable cases for this were for the comparisons versus the CAR-T cell therapies. This, together with the fact that responses in some studies were evaluated using different assessment criteria than in NP30179 (100, 101), further reinforces that some results should be interpreted with a high degree of caution

- In some OS/PFS/DO(C)R ITCs, adjusted and/or unadjusted analyses resulted in survival curves crossing at one or more points, therefore suggesting that the proportional hazard assumption may not hold and that the relative HRs should be interpreted with caution. When hazards are not constant over time, it is not appropriate to use HRs for the purpose of survival analysis. As discussed in Section B.3.3.2., the proportional hazards assumption does not hold in all comparisons, meaning alternative approaches are required to predict relative long-term survival outcomes. Therefore, while the HR estimated from the ITC analysis provide a signal of relative effects, they are until to be reflective of the magnitude of relative benefit when modelled over a lifetime horizon. As such, HRs were not used to model long-term relative benefits in the economic analysis.

- Some studies used for the MAICs did not report the total number of OS/PFS/DO(C)R events (i.e. ZUMA-1 (103)) and/or the numbers at risk for the KM plots (i.e. Hong 2018 (107)). This can lead to sub-optimal results following the digitisation of the survival curves and the generation of pseudo IPDs required for the MAICs, which may have biased the results.

Despite these limitations, the analyses presented were conducted using the highest quality available evidence, following accepted methodologies and using previously accepted precedents were appropriate, so can be viewed as a robust comparison of glofitamab to treatments currently used in NHS clinical practice.

B.2.9.3.2.1 Sensitivity and scenario analyses

Sensitivity analyses were performed to determine the impact of altering specific inputs on the conclusions of the base-case analyses. When some covariates had to be excluded, sensitivity analyses have been conducted to show the impact of including these on the analysis results. Other sensitivity analyses explored the impact of using alternative definitions for certain covariates around which there was uncertainty regarding how the respective covariate was defined in the comparator data source, or when multiple alternative definitions were available.

In addition, a number of scenario analyses were performed to test the robustness of the ITC results. Please see Appendix D (ITC report) for details of the scenario analyses performed.

B.2.10 Adverse reactions

B.2.10.1 Exposure to study treatment

The exposure of the primary safety-evaluable population to glofitamab at the CCOD of 15th June 2022 is summarised below in Table 21. The safety-evaluable population includes patients who have received at least one dose of study medication [obinutuzumab pre-treatment, glofitamab]) treated with 2.5/10/30 mg step-up doses of glofitamab, pooled from cohorts D2 ([Sub.2], Part II), D3 (Part III) and Cohort D5 (Part III) (N=154 patients). One patient recruited into the primary analysis cohorts did not receive study medication.

[redacted] The median treatment duration among all patients in the primary safety population was [redacted] which supports glofitamab to be a tolerable regimen.

Table 21: Summary of glofitamab exposure in the NP30179 study (CCOD 15th June 2022

Glofitamab	Primary safety population: Glofitamab 2.5/10/30mg Cohorts D2 [Sub. 2]+D3+D5 (N=154)
Number of cycles, median (range)	[redacted]
Categorised number of cycles, n (%) Less than 8 cycles 8 cycles 9-11 cycles 12 cycles >12 cycles	[redacted]
Number of infusions, median (range)	[redacted]
Dose intensity [%], median (range) Dose intensity ≥90%	[redacted]
Total duration [days], median (range)	[redacted]

Dose intensity is the number of doses actually received divided by the expected number of doses.

B.2.10.2 Overview of safety

The AE profile of the primary safety-evaluable population (N=154) is summarised below in Table 22.

The glofitamab monotherapy step-up dosing regimen 2.5/10/30 mg was well-tolerated with a manageable safety profile. Overall, glofitamab discontinuation rates due to AEs were low. The majority of CRS events and the most frequently reported AE were [redacted]. At the CCOD of 15th

June 2022, [redacted]

[redacted]

[redacted]

[redacted] **22**[redacted]

Table 22. Overview of AE profile in the primary safety-evaluable population of the NP30179 study (CCOD 15th June 2022)

	Primary safety population: Glofitamab 2.5/10/30mg Cohorts D2 [Sub. 2]+D3+D5 (N=154)
Any AE, n (%) Glofitamab-related, n (%)	[redacted]
SAE, n (%) Glofitamab-related, n (%)	[redacted]
Grade 3+ AEs, n (%) Glofitamab-related, n (%)	[redacted]
Grade 5 AEs, n (%) Glofitamab-related, n (%)	[redacted]
AE leading to treatment discontinuation, n (%) Glofitamab-related, n (%)	[redacted]
Infections, n (%)	[redacted]
CRS (ASTCT grading), n (%)	[redacted]
Neurological AEs*, n (%) Grade 3+, n (%)	[redacted]

*[#] 3 x COVID-19 pneumonia, 3 x COVID-19, 2 x sepsis, delirium. *AEs within in Nervous System SOC and Psychiatric Disorders SOC. **GI Haemorrhage, Myelitis, CRS (all Grade 4 events) and 2 x neutropenia (1 x Grade 3, 1 x Grade 4).*

AE, adverse event; SAE, serious adverse event; CRS, cytokine release syndrome.

B.2.10.3 Adverse events of special interest (AESIs)

The key clinically significant AESIs related to glofitamab treatment, which may have implications for prescribing decisions and patient management, included CRS, serious infections, tumour flare and tumour lysis syndrome (TLS). An overview of these AESIs in the primary safety-evaluable population at the CCOD of 15th June 2022 are summarised below in Table 23. These events are consistent with the known existing safety profile of glofitamab.

Table 23: Overview of AESIs in the primary safety population (CCOD 15th June 2022)

Patients experienced at least one AE	Primary safety population: Glofitamab 2.5/10/30mg Cohorts D2 [Sub. 2]+D3+D5 (N=154)
Grade ≥ 2 CRS (ASTCT grade)	[redacted]
Grade ≥ 2 neurologic adverse event	[redacted]
Grade ≥ 2 tumour flare events	[redacted]
Grade ≥ 2 AST, ALT, or total bilirubin elevation	[redacted]
Grade ≥ 3 TLS	[redacted]
Grade ≥ 3 febrile neutropenia	[redacted]
Pneumonitis*	[redacted]
Colitis	[redacted]

**Pneumonitis AE were retrieved using interstitial lung disease (SMQ).*

B.2.10.3.1 Cytokine release syndrome (CRS)

The following CRS events were assessed by the American Society for Transplantation and Cellular Therapy (ASTCT) grading criteria (112) (Table 24). At the CCOD of 15th June 2022,

[redacted]

Table 24: CRS after each dose of glofitamab in C1 and C2 (CCOD 15th June 2022)

	Cycle 1		Cycle 2	
	After glofitamab 2.5mg dose [C1D8] (N=145)	After glofitamab 10mg dose [C1D15] (N=135)	After glofitamab 30mg dose [C2D1] (N=127)	Overall across all cycles, most extreme grade
Any grade, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
1	[redacted]	[redacted]	[redacted]	[redacted]
2	[redacted]	[redacted]	[redacted]	[redacted]
3	[redacted]	[redacted]	[redacted]	[redacted]
4	[redacted]	[redacted]	[redacted]	[redacted]

D3 cohort received 2.5/10/30mg; D2 [Sub. 2] received 2.5/10/30mg, D5 cohort received 2.5/10/30mg with mandatory dexamethasone premedication.

By ASTCT grade (112); No Grade 5 CRS reported.

In the supporting populations comprising the primary safety population, i.e., patients with R/R DLBCL with ≥ 2 prior therapies who received 2.5/10/30 mg step-up dosing in Cohorts D2 [Sub. 2] + D3 (N=114), the profile of CRS events was consistent with the primary safety population. However, at the CCOD of 15th June 2022, Cohort D5 (N=40), where patients received mandatory dexamethasone premedication, [redacted] (Table 25).

Table 25: CRS after each dose of glofitamab in C1 and C2, by steroid premedication option (CCOD 15th June 2022)

		Cycle 1		Cycle 2
		1st dose	2nd dose	3rd dose
"Any corticosteroid"*	Dosage	[redacted]	[redacted]	[redacted]
Glofitamab 2.5/10/30mg, Cohorts D2 [Sub. 2]+D3 (N=114)	Any grade	[redacted]	[redacted]	[redacted]
	Grade 1	[redacted]	[redacted]	[redacted]

	Grade 2	[redacted]	[redacted]	[redacted]
	Grade 3	[redacted]	[redacted]	[redacted]
	Grade 4	[redacted]	[redacted]	[redacted]
Mandatory Dexamethasone **Glofitamab 2.5/10/30mg, Cohort D5 (N=40)**	Dosage	[redacted]	[redacted]	[redacted]
	Any grade	[redacted]	[redacted]	[redacted]
	Grade 1	[redacted]	[redacted]	[redacted]
	Grade 2	[redacted]	[redacted]	[redacted]
	Grade 3	[redacted]	[redacted]	[redacted]
	Grade 4	[redacted]	[redacted]	[redacted]

**Any corticosteroid - Investigator could choose one of methylprednisolone, prednisone or dexamethasone; CRS grade by ASTCT criteria; ** D5 cohort had mandatory dexamethasone.*

[redacted]

26

Table 26: CRS management of the primary safety population (CCOD 15th June 2022)

Management in patients with CRS	Primary safety population: Glofitamab 2.5/10/30mg Cohorts D2 [Sub. 2]+D3+D5 (N=99)
Tocilizumab	[redacted]
Corticosteroids	[redacted]
Tocilizumab + Corticosteroids	[redacted]

Single pressor	[redacted]
Multiple pressors	[redacted]
Oxygen low flow	[redacted]
Oxygen High flow	[redacted]
ICU admittance	[redacted]

By ASTCT grade (112). ICU, intensive care unit.

B.2.10.3.2 Neurological adverse events (NAEs)

Neurological adverse events (NAEs) included preferred terms (PTs) reported from the Nervous System Disorders and Psychiatric Disorders system organ classes (SOCs).

[redacted]

27 [redacted]

[redacted]

Table 27: NAEs in the primary safety population (CCOD 15th June 2022)

	Primary safety population: Glofitamab 2.5/10/30mg Cohorts D2 [Sub. 2]+D3+D5 (N=154)
Any Grade AE, n (%)	[redacted]
Grade ≥ 3, n (%)*	[redacted]
SAEs, n (%)	[redacted]
Individual AE terms in ≥3% patients, n (%)	
Headache	[redacted]
Dizziness	[redacted]
Anxiety	[redacted]
Paraesthesia	[redacted]

D3 cohort received 2.5/10/30mg; D2 [Sub. 2] received 2.5/10/30mg, D5 cohort received 2.5/10/30mg with mandatory dexamethasone premedication.

**AEs within in Nervous System SOC and Psychiatric Disorders SOC.*

B.2.10.4 Deaths

At the CCOD of 15th June 2022,

[redacted]

Further information can be found in Appendix G.

B.2.11 Ongoing studies

Follow up for study NP30179 (described in the present submission) is ongoing, with a minimum of 2 years of follow-up from the end of treatment for the last patient enrolled in Cohort D5. This will mean a CCOD in approximately [redacted] and provision of an updated CSR in [redacted] for the primary efficacy and safety populations.

Study GO41944 (NCT04408638; 'STARGLO') is an ongoing phase III, open-label, multicentre, randomised study evaluating the efficacy and safety of glofitamab in combination with gemcitabine plus oxaliplatin (glofit-GemOx) versus rituximab in combination with gemcitabine and oxaliplatin (R-GemOx) in patients with R/R DLBCL. Approximately 270 eligible patients will be randomised in a 2:1 ratio to receive either glofit-GemOx or R-GemOx. The primary endpoint is overall survival.

[redacted]

B.2.12 Interpretation of clinical effectiveness and safety evidence

Despite recent approvals, there remains a need for alternative therapies for patients with R/R DLBCL who continue to relapse or become refractory to treatment. Glofitamab is a novel bispecific antibody with a new mechanism of action for R/R DLBCL patients, redirecting T-cells against the cancer cells. Glofit represents a new treatment option in the 3L+ DLBCL setting with a different mode of action compared with currently available therapies, is chemotherapy-free, and is available at the time of need ("off-the-shelf"). Clinical experts at an Advisory Board praised glofit for its ease of delivery compared to other 3L treatments, specifically when comparing to CAR-T (1).

Glofitamab was well-tolerated and demonstrated a manageable safety profile with a low incidence of treatment discontinuations due to AEs, as shown from study NP30179 - a multicentre, open-label, Phase I/II study to evaluate the safety, efficacy, tolerability, and pharmacokinetics of escalating doses of glofitamab in patients with R/R B-cell NHL.

At the primary analysis of study NP30179 (CCOD 14th September 2021), the primary efficacy endpoint was met with an IRC-assessed CR rate in Cohort D3 of 35.2% (95% CI: 26.2%, 45.0%), which was statistically significantly higher than the pre-specified historical control CR rate of 20% (p-value < 0.0001). Responses were achieved rapidly and were durable beyond the end of the fixed treatment duration.

Results of the updated analysis of study NP30179 (CCOD 15th June 2022) provide up to 9 months of additional follow-up data, supporting the conclusions from the primary analysis (CCOD 14th September 2021), and further confirm the durability of responses achieved with glofitamab monotherapy. At the CCOD of 15th June 2022, 73.7% of patients with a CR and 55.6% of patients with a response in Cohort D3 were still in remission after a median of 12.8 months follow-up for response (IRC). Responses were durable (median not reached for IRC-CR; median 14.4 months for IRC-OR) and extended beyond the end of the fixed treatment duration: the KM-estimated event-free rate at 18 months was 68.8% for complete responders and 48.5% for all responders.

Results in the pooled efficacy population (N=155) were consistent with Cohort D_3, with an IRC-assessed CR rate of 40.0% (95% CI: 32.2%, 48.2%) observed in patients with R/R DLBCL (≥ 2 prior lines of systemic therapy) treated with glofitamab 2.5/10/30 mg in Cohorts D2 [Sub. 2], D3, and D5. Consistent with Cohort D3, responses in the pooled efficacy population were also usually achieved rapidly and were durable.

The safety profile of glofitamab monotherapy in the primary safety population (N=154) was also confirmed with up to 9 months of additional follow-up:

- CRS, although the most common AE for glofitamab, was predominantly a first-cycle phenomenon, mostly of low grade, and manageable with only 1 patient in the primary safety population discontinuing treatment due to this AE. There were no additional treatment discontinuations due to CRS since the primary analysis.

- Due to its mode of action resulting in B-cell depletion, serious infections are anticipated with glofitamab administration. Some Grade 5 AEs, including sepsis (1.3%) and pneumonia (1.9%), were observed, although these were not determined to be related to glofitamab by the investigator.

- Tumour flare, likely due to the influx of T-cells into tumour sites following glofitamab administration, occurred in 11.0% of patients, and the majority of events resolved without requiring glofitamab dose modifications. TLS was

reported rarely (1.3%), and no Grade 4 events were observed. No additional patients reported tumour flare or TLS in the updated analysis.

In conclusion, glofitamab monotherapy (2.5/10/30 mg) demonstrates clinically meaningful benefit along with a manageable safety profile in a high unmet need population; a population of heavily pre-treated high-risk patients with R/R DLBCL who have received at least two prior systemic therapies and are refractory to multiple classes of prior therapy (including refractory to CAR-T). The CR rate and durability were clinically meaningful with a well-tolerated safety profile in the context of currently available therapies in the enrolled populations, supporting a positive benefit risk profile for glofitamab monotherapy in this population. In addition to its positive benefit-risk, glofitamab monotherapy is a readily available ('off-the-shelf') chemotherapy-free regimen with a fixed duration of treatment length to treat R/R DLBCL patients with ≥ 2 prior therapies. Clinical experts at an Advisory Board deemed glofitamab innovative and has the potential to enhance equity of access across the UK, both geographically and chronologically, in a heavily pre-treated DLBCL population (1).

B.3 Cost effectiveness

B.3.1 Published cost-effectiveness studies

In line with the NICE health technology evaluations: the manual (2022) (113), an SLR was conducted to identify cost-effectiveness studies on the management of patients with R/R DLBCL. In brief, electronic database searches (Embase, MEDLINE< EconLit and Evidence Based Medicine [EBM] Reviews) were conducted in September 2022. Supplementary sources were also hand searched for completeness, including reference lists of included studies, conference proceedings, relevant additional databases and websites, and global health technology assessment (HTA) body websites. In total, 29 relevant economic evaluations were identified (Figure 13), reporting 19 published analyses (Table 28) and 10 HTAs (Table 29). Details of the SLR can be found in Appendix H.

The majority of included studies were cost-effectiveness analyses (CEAs) and cost-utility analyses (CUAs), having reported incremental cost-effectiveness ratios (ICERs) as cost per quality-adjusted life years (QALYs) and cost per life years gained (LYGs) (N=12), and six studies were cost-utility analyses as they reported cost per QALY only (N=6). Only one study was a cost-effectiveness analysis; however, this was not explicitly stated and inferred from the outcomes. Of the 19 economic evaluations identified, a range of models were used to model costs and outcomes: partitioned survival models (PSMs) or models with a PSM component (N=14, including a hybrid decision tree and PSM (N=1) a hybrid decision tree and semi-Markov PSM, a partitioned survival mixture cure model (N=1), and a semi-Markov PSM (N=1)), a Markov model (N=3), a decision tree (N=1), and a discrete event simulation (N=1).

Figure 13: PRISMA flow diagram for SLR of economic evaluations

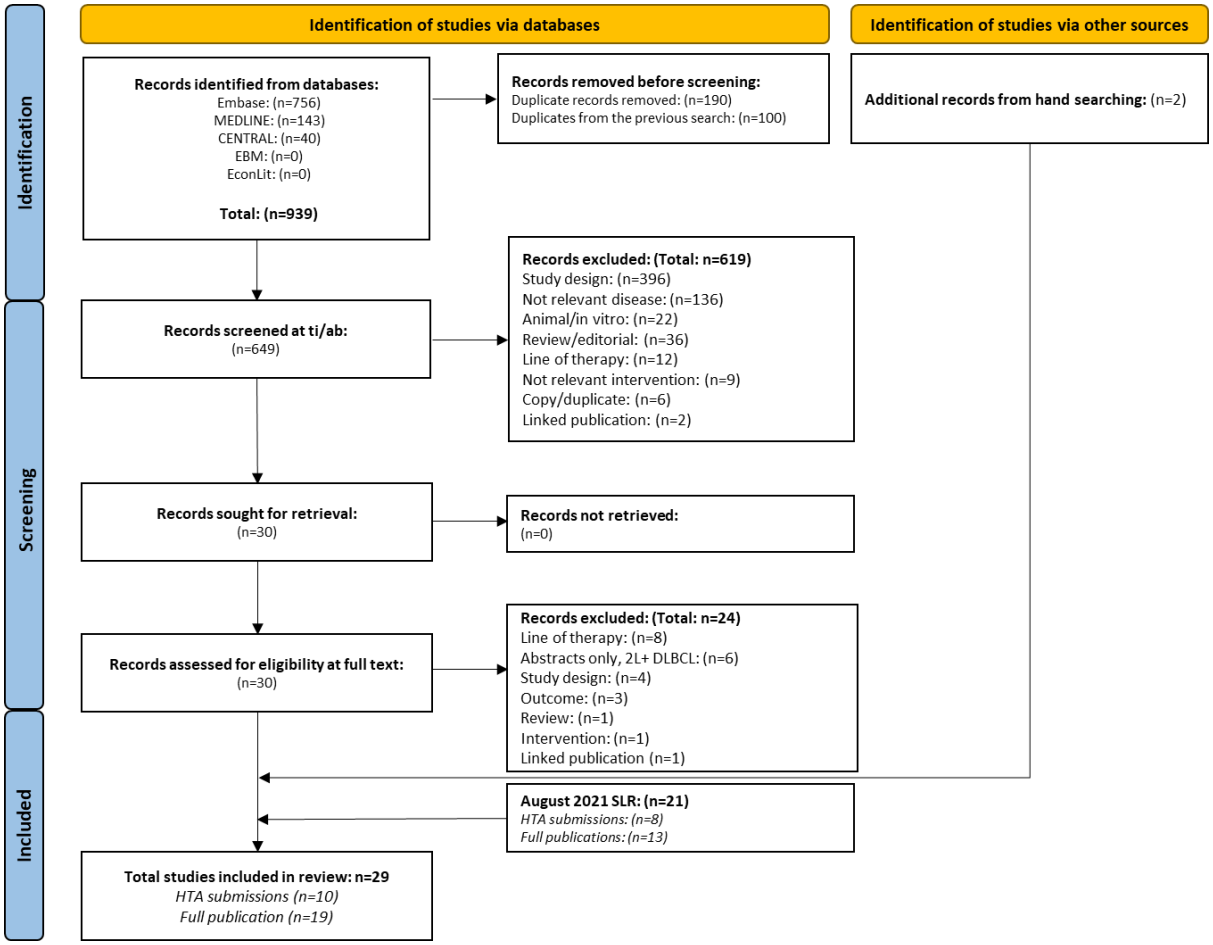


Table 28: Summary list of published cost-effectiveness studies

Study	Model structure	Population	Intervention(s)
Bastos-Oreiro, 2022 (114)	PSM	Patients with R/R DLBCL (mean age 58 years)	• Axi-cel • Tisagenlecleucel
Betts, 2020 (115)	PSM	Patients with R/R DLBCL after ≥1 line of chemotherapy, aged ≥18 years old, who were ineligible for HSCT based on the GO29365 trial	• Polatuzumab vedotin + bendamustine + rituximab • Bendamustine + rituximab
Calamia, 2021 (116)	PSM	Patients with R/R DLBCL who were ineligible for ASCT	• Polatuzumab vedotin + bendamustine + rituximab • Tafasitamab + lenalidomide
Cher, 2020 (117)	Hybrid decision tree and PSM	Patients (median age 56 years) who have failed two or more lines of systemic therapies, consistent with the trial population reported in the JULIET study	• Tisagenlecleucel • Salvage chemotherapy
Cummings-Joyner, 2022 (118)	Decision tree	Patients with R/R DLBCL treated with CAR-T cell therapies	• 1) Axi-cel • 2) Liso-cel • Tisagenlecleucel
Hillis, 2022 (119)	PSM	Patients with R/R DLBCL, aged ≥18 years, after ≥2 lines of treatment	• Axi-cel • BSC (cyclophosphamide, etoposide, and gemcitabine)
Kymes, 2012 (120)	Markov model	Patients with relapsed DLBCL, undergoing HSCT	• G-CSF + plerixafor • G-CSF alone
Li, 2022 (121)	Decision tree and semi-Markov PSM	Patients with R/R DLBCL, aged ≥18 years, after ≥2 lines of systemic therapy	• Axi-cel • Salvage chemotherapy (R-DHAP)
Lin, 2019 (122)	Markov model	Patients (mean age 58 years) with R/R DLBCL after ≥2 lines of therapy or relapsed ≤12 months after SCT	• Axi-cel • Tisagenlecleucel

Study	Model structure	Population	Intervention(s)
Liu, 2021 (123)	PSM (partitioned-survival mixture cure modelling)	Patients with RR LBCL after ≥2 lines of systemic therapy	• Axi-cel • Tisagenlecleucel
Moradi-Lakeh, 2021 (124)	PSM	Patients (paediatric and young adult patients up to 25 years) with B-cell precursor RR ALL and adult patients with R/R DLBCL who have received ≥2 lines of chemotherapy, including rituximab and anthracycline, and either have failed ASCT or were ineligible for or did not consent to ASCT	• Tisagenlecleucel • Salvage chemotherapy
Oluwole, 2022 (125)	PSM	Patients with R/R DLBCL, aged ≥18 years, after ≥2 lines of systemic therapy	• Axi-cel • Liso-cel
Patel, 2020 (126)	Markov model	Patients (median age 69 years, 66% male) with R/R DLBCL and median 2 lines of prior therapy who were ineligible for HSCT due to age, comorbidity, performance status, insufficient response to salvage therapy, failed prior transplantation, or patient refusal	• Polatuzumab vedotin + bendamustine + rituximab • Bendamustine + rituximab
Qi, 2021 (127)	PSM	Patients with RR LBCL after ≥2 lines of systemic therapy	• Tisagenlecleucel • Salvage chemotherapy
Roth, 2018 (128)	PSM	Patients with RR LBCL meeting the ZUMA-1 inclusion criteria	• Axi-cel • Salvage chemotherapy
Wakase, 2021 (129)	PSM	Patients with R/R DLBCL who were ineligible for, or relapsed after, ASCT	• Tisagenlecleucel • Salvage chemotherapy

Study	Model structure	Population	Intervention(s)
Wang, 2017 (68)	DES	Patients with newly diagnosed DLBCL	• Initial decision to administer 1L chemotherapy for curative intent • Manage supportively with a palliative approach
Wang, 2021 (130)	PSM	Patients with R/R DLBCL after ≥2 lines of systemic therapies	• Tisagenlecleucel • Salvage chemotherapy with or without HSCT
Whittington, 2019 (131)	Semi-Markov PSM	Patients with RR B-cell lymphoma	• Axi-cel • Chemotherapy

Abbreviations: 1L, first-line; 2L, second-line; ALL, acute lymphoblastic leukaemia; ASCT, autologous stem cell transplant; CAR-T, chimeric antigen receptor T cell; CEA, cost-effectiveness analysis; CUA, cost-utility analysis; DES, discrete event simulation; DLBCL, diffuse large B cell lymphoma; G-CSF, granulocyte colony stimulating factor; HSCT, haematopoietic stem cell transplantation; LBCL, large B-cell lymphoma; liso-cel, lisocabtagene maraleucel; PSM, partitioned survival model; R-DHAP, rituximab – dexamethasone, high dose cytarabine, and cisplatin; RR, relapsed/refractory; SCT, stem cell transplant

Table 29: Summary table of HTA submissions

HTA submission	Model structure	Population	Intervention(s)
CADTH, 2022a (132) Canada	Decision tree + PSM	Adult patients with R/R DLBCL who failed at least 2 prior lines of treatment (3L+)	• liso-cel • axi-cel, tisagenlecleucel
CADTH, 2022b (133) Canada	PSM	Patients with R/R DLBCL who are not eligible for ASCT	• tafasitamab + lenalidomide • R-GEMOX, R-GDP, GDP

HTA submission	Model structure	Population	Intervention(s)
CADTH, 2019 (134) Canada	PSM	Adult patients with R/R DLBCL who are ineligible for or relapsed after ASCT (2L+)	• Tisagenlecleucel • salvage chemotherapy (consisting of rituximab, gemcitabine, cisplatin, and dexamethasone)
NICE TA306 (135) England/Wales	Semi-Markov model	Adult patients with multiply RR aggressive non-Hodgkin's B-cell lymphoma (2L+)	• Pixantrone • physician's choice (comparator)
NICE TA559 (136) England/Wales	PSM	Adult patients with R/R DLBCL, PMBCL, and transformed FL who are ineligible for ASCT (2L+)	• axi-cel • BSC (blended comparator of different treatment regimens [GEM, GEM-P, R-GCVP, RVP])
NICE TA567 (137) England/Wales	Decision tree + PSM	Adult patients with R/R DLBCL after two or more lines of systemic therapy (3L+)	• Tisagenlecleucel • salvage chemotherapy or pixantrone monotherapy
NICE TA649 (138) England/Wales	PSM	Adults patients with R/R DLBCL who are ineligible for HSCT (2L+)	• polatuzumab vedotin + bendamustine + rituximab • bendamustine + rituximab
SMC 2189 (139) Scotland	PSM	Adult patients with R/R DLBCL and PMBCL after two or more lines of therapy (3L+)	• axi-cel • BSC (blended comparator of different treatment regimens [GEM, GEM-P, R-GCVP, RVP])
SMC 2200 (140) Scotland	Decision tree + PSM	Adult patients with R/R DLBCL after two or more lines of systemic therapy (3L+)	• Tisagenlecleucel • salvage chemotherapy (GEMOX and GDP)

HTA submission	Model structure	Population	Intervention(s)
SMC 2282 (141) Scotland	PSM	Adult patients with R/R DLBCL who are ineligible for HSCT (2L+)	• polatuzumab vedotin + bendamustine + rituximab • bendamustine + rituximab

Abbreviations: 2L/3L/4L+, second-line/third-line/fourth-line and later lines; ASCT, autologous stem cell transplant; BSC, best supportive care; CAD, Canadian Dollars; CADTH, Canadian Agency for Drugs and Technologies in Health; DLBCL, diffuse large B-cell lymphoma; FL, follicular lymphoma; GDP, gemcitabine, dexamethasone, and cisplatin; GEM, gemcitabine and methylprednisolone; GEM-P, gemcitabine, methylprednisolone, and cisplatin; GEMOX, gemcitabine and oxaliplatin; HRQoL, health related quality of life; HSCT, haematopoietic stem cell transplant; INESSS, Institut national d'excellence en santé et services sociaux; LBCL, large B-cell lymphoma; LYG, life year gained; MAIC, matching adjusted indirect comparison; NHS, National Health Service; NICE, National Institute for Health and Care Excellence; NR, not reported; PD, progressed disease; PFS, progression free survival; PMBCL, primary mediastinal large B-cell lymphoma; PSM, partitioned survival model; QALY, quality adjusted life years; R-GCVP, rituximab, gemcitabine, cyclophosphamide, vincristine, prednisolone; RVP, rituximab, vincristine, and prednisolone; RR, relapsed/refractory; SMC, Scottish Medicines Consortium.

B.3.2 Economic analysis

The economic case presented in this submission is based on a cost-utility analysis assessing the use of glofitamab versus various active comparators (see Section B.2.5 Critical appraisal of the relevant clinical effectiveness evidence) for the treatment of adult patients with R/R DLBCL who have received at least two prior systemic therapies (hereafter referred to as third or subsequent line [3L+]). The analysis takes into account a patient access scheme (PAS) discount for glofitamab (detailed in Section B.3.5.2.2 Patient access scheme (PAS)).

The cost-effectiveness studies identified in Section B.3.1 Published cost-effectiveness studies were examined to inform the economic analysis presented in this submission. Previously published modelling approaches were mostly PSMs or Markov models with the majority of models adhering to the common oncology three-state framework (pre-progression, progressed disease, and death), regardless of modelling type, as this represents the most important clinical outcomes for patients.

PSMs are commonly used in oncology, as detailed in NICE TSD 19 (142), and lend themselves to situations where transitions between all states cannot be explicitly identified and modelled, for example, where post-progression survival cannot be estimated from reported data as only PFS and OS are reported, and comparator data may not be available. It has been demonstrated that there is little difference in estimated outcomes between partitioned survival and Markov models and that the assumptions underpinning analysis are more relevant than the choice of the modelling approach (143, 144). The largest consideration is whether time to progression or death is expected to be inherently different between arms and whether the model is able to capture these endpoints appropriately (143, 144). PSMs can reflect these relevant clinical endpoints well and is appropriate where data is not available to inform alternative approaches that require more granularity (143, 144). A PSM can therefore capture long-term impact of oncology interventions in terms of both PFS and OS, which were key secondary outcomes in the NP30179 study (see Section B.2.6.2 Secondary efficacy endpoints). However, the trial's primary endpoint, response rate, is not adaptable to use in PSM.

Importantly, PSMs do not require any PFS to OS surrogacy assumptions and do not translate any PFS benefit into an OS benefit. Therefore, PFS and OS data, being taken directly from the NP30179 trial, better reflect the impact of glofitamab on the clinical course of R/R DLBCL.

Taking into account the above considerations a *de novo* three-state PSM was built to inform decision making. This modelling approach is in line with previous TAs in the same indication and literature identified in the related SLR (135-137).

B.3.2.1 Clinical evidence used in the model

In the model, data from the NP30179 study (Sections B.2.6 Clinical effectiveness results of the relevant studies and B.2.10.2 Overview of safety have been used to inform the clinical efficacy, safety and time on treatment of glofitamab for the treatment of adult patients with R/R DLBLC who have received ≥2 prior systemic therapy lines. The NP30179 study is currently the only study available to provide clinical evidence for glofitamab in the intended population and can therefore be considered the best available evidence to inform the modelling. All analyses in this submission have been conducted from a National Health Service (NHS)/ Personal Social Services (PSS) perspective.

While NP30179 is the source of glofitamab data for the cost-effectiveness analysis, it is a single-arm trial therefore no comparator data are available. Consequently, an ITC was required to provide comparative evidence versus the potential comparators identified in the scope of this appraisal. The ITC employed a propensity score analysis for those comparators with available patient-level data, and a MAIC where only published aggregate data were available (Section B.2.9.1 Indirect treatment comparison methods).

B.3.2.2 Patient population

Glofitamab is proposed for use within the NHS in England as an alternative to any third- or later-line therapy option. The cost-effectiveness model makes use of efficacy data from the 3L+ R/R DLBCL patients enrolled in NP30179 cohorts D3, D5 and D2 [Sub. 2] (N=155, henceforth called pooled efficacy population). These patients have the same target pivotal histologies (DLBCL NOS, trFL, PMBCL,

HGBCL), have all received at least 2 prior lines of therapy, have an ECOG PS 0–1, and were all intended to be administered the same target dosing regimen of glofitamab as in the D3 pivotal cohort. Pooling was performed to maximize the sample size available for the ITCs. For safety data, the cost-effectiveness model (CEM) makes use of the safety-evaluable population from NP30179.

In the base case analysis, baseline patient parameters were derived from the baseline characteristics of the pivotal cohort of patients enrolled in NP30179, as detailed in Table 30. Given challenges in enrolling 3L+ DLBCL patients, NP30179 did not have any UK centres. Despite this, the baseline characteristics of the cohort used for economic modelling were considered generalisable to patients treated in UK clinical practice, with experts consulted by Roche also agreeing the characteristics were broadly representative of those treated in the UK.

Table 30: Baseline parameters in base case

Parameter	Mean	Source
Age (years)	63.19	NP30179 Trial
Baseline body weight (kg)	74.95	NP30179 Trial
Baseline height (cm)	170.52	NP30179 Trial
Baseline BSA (m^2)	1.86	NP30179 Trial
Proportion of cohort male	64.94%	NP30179 Trial

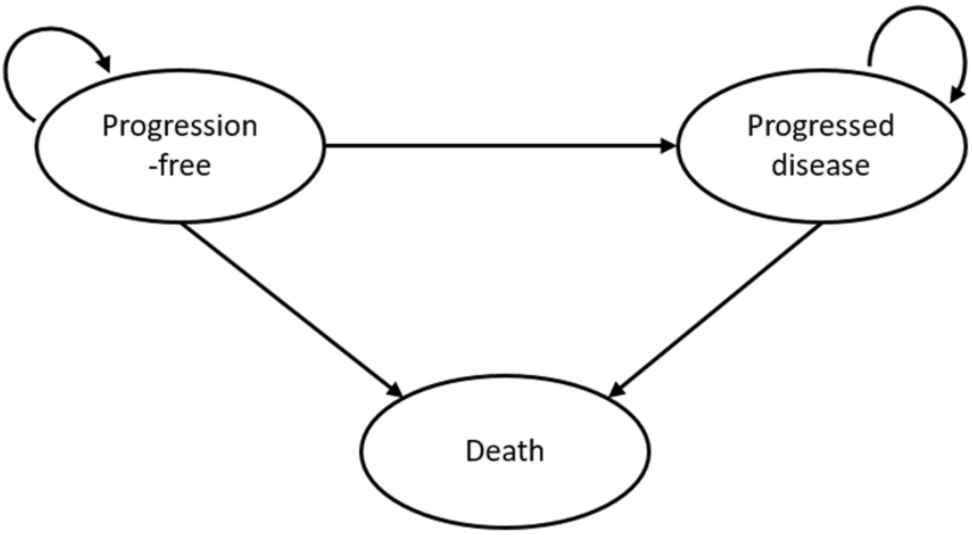
BSA, body surface area; SE: standard error.

B.3.2.3 Model structure

A *de novo* partitioned survival (area under the curve [AUC]) model structure was developed representing PFS, progressive disease (PD), and death. These health states reflect the disease severity and clinical landmarks, as well as key distinctions in mortality, HRQoL, and the use of healthcare resources.

The economic modelling of glofitamab and the relevant comparators in this indication required that comparative efficacy be pieced together from numerous sources with ITCs. Within the AUC model, health state occupancy was determined by partitioning the proportion of patients alive into PFS and PD at discrete time points based on the OS and PFS curves from the NP30179 study and relevant comparator data, identified from the ITC. The model structure is shown in Figure 14.

Figure 14. Model schematic



All patients entered the model in the PFS health state and remained in this health state until their disease progressed, or they died. Once in the progressed health state, patients could either remain in the progressed health state or move to the death state. Patients in the model could not transition to an improved health state, i.e., from PD to PFS.

The economic model uses a 60-year time horizon, which was expected to be sufficiently long to capture all important differences in costs or clinical outcomes between the technologies being compared as all patients in the model were expected to be in the death state by the end of 60 years. In the base case scenario, background mortality is modelled as a function of the age distribution rather than the mean age of the cohort; this requires a relatively longer time model horizon. As such, the 60-year time horizon can be essentially considered equivalent of a lifetime horizon.

The model uses weekly cycles with the proportion of patients in each health state calculated after each cycle. A cycle duration of one week was considered appropriate for this evaluation because it enables the model to reflect differing timings of drug administrations between arms and the time scale over which patients

may experience changes in their symptoms. In addition, transitions between health states can occur at any time within the cycle. In order to account for the over- or underestimation of transitions occurring at the beginning or end of the cycle, half-cycle correction was applied, in line with previous NICE technology appraisals in this disease area (135-137).

In line with the NICE Technology Evaluations Manual, model results are reported in terms of costs, quality-adjusted life-years (QALYs) gained, life-years (LYs) gained, net-health benefit (NHB), net-monetary benefit (NMB), and incremental cost-effectiveness ratios (ICERs) (113).

Costs and health-related utilities were allocated by health state to calculate the weighted cost and QALYs per cycle. Cost and health outcomes were discounted at a 3.5% discount rate and, according to the NICE reference case, an NHS and PSS perspective was assumed (113).

B.3.2.3.1 Derivation of health state occupancy estimates

The decrease in the proportion of patients residing in the progression-free state over time (starting from 100%) was determined by parametric models fit to the PFS curves from the NP30179 data and ITC analysis. The PFS curves indicate, for each time point, the proportion of patients who have not progressed or died.

The PD state accommodates all patients who have experienced disease progression but have not yet died. The proportion of patients in this state was calculated as the difference between the proportion of living patients and the proportion of patients who were both living and pre-progression. The transitions into and out from the progression health state were thus not modelled explicitly, a defining feature of PSMs.

Death was modelled as an absorbing state meaning that all patients eventually enter this state and cannot leave it. The transition rate of patients from the progression-free and progressed disease heath states into the death state was determined by parametric models fit to the OS curves derived from the NP30179 trial and the relevant comparator data (identified by ITC). A correction to ensure the hazard of death estimated from the OS curves could not be lower than that from the

background mortality of an age- and sex-adjusted cohort from the general population was applied at every model cycle. OS curves indicate the proportion of patients who are alive at a given point in time or, equivalently, the proportion of patients who die during a model cycle dependent on the time since treatment initiation. Clinicians supported these assumption and felt that the resulting OS curves reflected the survival that they would expect to see in clinics.

B.3.2.3.2 Derivation of treatment line occupancy

Time-to-off-treatment (TTOT) data from either NP30179 or other comparator studies (i.e., GO29365) was used to model the actual duration on treatment. For other treatments where direct TTOT information was not available, the respective TTOT was set equal to the selected parametric distribution for PFS and capped at the treatment-specific maximum number of cycles, as per label. For a one-off treatment, such as axi-cel, the duration on treatment was assumed to last for a single model cycle.

While patients remained progression free, they could be on or off treatment. Once in the PD health state, it was assumed that patients would move to a further line of treatment. The proportions of patients on certain subsequent therapies, and the duration for which they receive them, was informed by NP30179. The proportion of patients receiving subsequent treatments for each comparator is determined by the proportion who move into the PD state in each arm. This is not equivalent across treatment arms, as it is linked to the long-term remission assumptions applied (see section B.3.3.2.5 Long-term remission/survivorship).

In previous TAs where treatment stopping rules have been applied (145-147), treatment effect waning has also been applied; this is a common approach in modelling immunotherapies. However, relative treatment effect for PFS/OS is assumed not to wane over time in the current model base-case. This was selected as most of the patients have been off-treatment long enough that substantial changes in the observed hazards for PFS/OS (steeply declining with no signal of increase over time) are not expected to occur beyond the end of the observed data.

B.3.2.3.3 Outcome measures

The primary model output is the incremental cost-effectiveness ratio (ICER) expressed as incremental costs per quality-adjusted life-year (QALY) gained. The model provides an overview of other health economic outcomes such as total QALYs, costs, NMB, NHB, and life-years associated with each treatment in total and in a disaggregated form.

B.3.2.4 Comparison of the *de novo* analysis with previous appraisals

An SLR was undertaken to evaluate modelling approaches for R/R DLBCL to identify relevant literature, including previous technology appraisals (TAs).**Error! Reference source not found.** Table 31 provides a comparison of the current submission versus several previous appraisals for DLBCL.

The *de novo* analysis followed precedent from existing submissions as well as the NICE reference case. A lifetime horizon was used to capture all potential costs and benefits and efficacy and utility data were derived from the key trial or sourced from the literature when trial data were not suitable.

Table 31: Features of the economic analysis

Factor	Previous evaluations				Current evaluation	
	TA306	TA559	TA567	TA649	Chosen values	Justification
Time horizon	Lifetime (23 years)	Lifetime (44 years)	Lifetime (46 years)	Lifetime (45 years)	60 years	The reference case stipulates that the time should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared.
Treatment waning effect?	No (PFS: log-normal; OS: lognormal)	No (PFS: Gompertz; OS: CMM, Weibull)	No. A mixture cure model was used in the base case to extrapolate OS and PFS using pooled data from JULIET and Schuster 2017 (PFS: CMM, lognormal; OS: CMM, lognormal)	No (PFS: CMM generalised gamma; OS: CMM generalised gamma informed by PFS cure fraction)	No treatment waning effect. (PFS generalised gamma; OS generalised gamma – PSM)	Not modelled as most of the patients have been off-treatment long enough that substantial changes in the observed hazards for PFS/OS (steeply declining with no signal of increase over time) are not expected to occur beyond this point.

Source of utilities	Literature values (PFS: 0.76; PD: 0.68)	ZUMA-1 study, NICE TA306, NICE TA169, published literature (PFS: 0.72; PD: 0.65)	JULIET, published literature (PFS: 0.83; PD: 0.71)	ZUMA-1, NICE TA559, published literature (PFS: 0.72; PD: 0.65)	PFS on-treatment: 0.729 PFS off-treatment: 0.774 PPS: 0.629	Following approach used in previous appraisals mapping trial utility data (EORTC-QLQ-C30) to EQ-5D (reference case).
Source of costs	Clinician survey on type and frequency of resource use in DLBCL. Unit costs from BNF, NHS reference costs, and PSSRU	Type and frequency of resource based on TA306 for SOC (135). Intervention incurred additional service costs. Unit costs from eMIT, NHS reference costs and PSSRU.	Type and frequency of resource based on clinical trial and NICE guideline (NG52) (31). Intervention incurred additional service costs. Unit costs from eMIT, BNF, NHS reference costs and PSSRU.	Based on TA306 for SOC and intervention (135). Unit costs from NHS reference costs, PSSRU and BNF	Unit costs from eMIT, BNF, NHS reference costs (2020/2021).	NHS Reference Costs, PSSRU, BNF and eMIT are standard sources of UK-relevant costs and were used where possible. Where costs were not reported in these sources, cost inputs were sourced from appropriate literature.

BNF: British National Formulary; eMIT: drugs and pharmaceuticals electronic market information tool; NHS: National Health Service; NICE: National Institute for Health and Care Excellence; PFS: progression-free survival; PPS: post-progression state; PSSRU: Personal Social Services Research Unit; TAs: technology appraisals.

B.3.2.5 Intervention technology and comparators

The health economic model was developed to compare the cost-effectiveness of glofitamab versus the following comparators (see Section **Error! Reference source not found.**):

- Axicabtagene ciloleucel (axi-cel)
- Polatuzumab-vedotin plus rituximab in combination with bendamustine (pola-BR)
- Rituximab in combination with bendamustine (BR), representing rituximab in combination with chemotherapy.

NCCN guidelines (3) and ESMO guidelines (4) suggest that patients who relapse after 2L therapy are unlikely to respond to subsequent therapy and therefore generally are not eligible for ASCT. The outcome in patients not eligible for ASCT is dismal with generally no chance of prolonged periods of disease control (72). Poor outcomes have been reported for patients with R/R DLBCL who respond to salvage therapy, but are ineligible for transplant. In these patients, OS was 4–13 months (73-77).

In the absence of ASCT as a treatment option, patients may be treated with R-chemo in the 3L+ setting. However, many patients may have already received rituximab-based regimens in previous lines. In this case, alternative treatments which have emerged more recently for R/R DLBCL, may be used in at 3L+. At present, the following treatments are broadly recommended by NICE for the treatment of 3L+ R/R DLBCL:

- Rituximab-based chemotherapy
- Chimeric antigen receptor T-cell (CAR-T) therapies
- Polatuzumab vedotin in combination with bendamustine and rituximab (pola-BR)
- Tafasitamab and lenalidomide (tafa-len)
- Pixantrone

Of which, rituximab plus bendamustine [BR], pola-BR, and CAR-T are considered relevant comparators for this submission.

The three selected comparators were considered to be the most relevant to the decision problem (Section B.1.1 Decision problem) based upon feedback from eight clinical experts at an Advisory Board, where the consensus was that these treatments covered at least 80% of patients treated for DLBCL in the 3L+ setting (1).

R-GemOx was identified as a relevant comparator by clinicians who noted it is used widely in clinical practice for the treatment of 3L+ DLBCL. However, it was not feasible to include R-GemOx in the ITC as the identified studies were not comparable to NP30179, due to differences based on histolgy or line of therapy (see Section B.2.9Indirect and mixed treatment comparisons). As such, BR was presented as a proxy, to represent rituximab with chemotherapy as closely as the data allowed. A retrospective analysis of the National Cancer Institute's SEER cancer registry database concluded OS outcomes were similar between patients with R/R DLBCL treated with BR or R-GemOx (2). The results of this analysis therefore suggest that the use of BR as a proxy for R-Chemo is unlikely to bias results in favour of glofitamab, and its use as a proxy to inform this comparison could be appropriate for the purposes of decision making. Clinical experts consulted by Roche agreed that the approach taken was reasonable, and agreed that outcomes for people treated with BR or other R-Chemotherapy regimens, would likely be similar for 3L+ DLBCL patients (1).

While pola-BR is currently used in the 3L+ setting, pola-R-CHP has recently been recommended by NICE for use as a 1L option for patients with DLBCL (59). As current BlueTeq criteria does not permit polatuzumab vedotin to be used as a treatment option for those who have already received it, the relevance of pola-BR as a comparator is expected to rapidly decrease as the uptake of pola-BR in the 1L setting increases.

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B.3.3 Clinical parameters and variables

B.3.3.1 Evidence synthesis

Evidence to describe the characteristics of the patient population and the effectiveness of glofitamab was primarily derived from the NP30179 trial, a Phase I/II, multi-centre, open-label dose escalation and expansion single arm study. Comparator efficacy was informed by an SLR followed by an ITC, as described in Sections B.3.1 Published cost-effectiveness studies and **Error! Reference source not found.**, respectively. Full details of the ITC are provided in Appendix D (ITC report).

B.3.3.2 Survival analysis approach

For survival endpoints of interest, study publication KM curves were scanned and digitised using WebPlotDigitizer 4.5. Survival analysis was conducted and plots were created using the R packages 'survival' and 'survminer' (148). Following the digitisation of the individual curves, by combing the scraped data with the number at risk it was possible to estimate the individual patient data by using an algorithm proposed by Guyot et al, 2012 (110).

The data used for all outcomes and arms is derived from the ITC (see Section **Error! Reference source not found.**), adjusted glofitamab KM and the comparators' unadjusted KM data. Initially, proportional hazards were assessed for each set of reconstructed comparator data and the glofitamab data to determine the suitability of the application of HRs and model choices. As described in Sections B.3.3.2.1 Glofitamab base-case survival distributions–B.3.3.2.4 Glofitamab vs pola-BR, in all cases the proportional hazard assumption was not accepted. As such, independent parametric models were fit to each OS and PFS outcome for the respective comparator (unadjusted) and glofitamab (adjusted).

Fitting independent models is recommended, regardless of the proportional hazards assessment as, if proportional hazards are warranted, the independent models should reflect this regardless (149). This was done for all comparators and outcomes (aside from TTOT) to ensure a consistent approach. Despite the PH assumption not holding, the HRs generated by the ITC are included in the model to facilitate

scenario analyses. A more robust assessment of the proportional hazards assumption may be possible as more data with longer follow up becomes available. The results of these scenarios are shown in Section B.3.14 Validation

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Extrapolation beyond the clinical follow-up period for each treatment was performed by fitting the following parametric distributions to the observed data:

- Exponential
- Weibull
- Log-normal
- Generalised gamma
- Log-logistic
- Gompertz
- 2-parameter gamma

These parametric extrapolations can be used directly for the entire time horizon of the model.

For the base case, parameters for each treatment were selected in line with recommendations in TSD 14 (150). The base case parametric extrapolation for each treatment was selected on the basis of goodness of fit to the data using the Akaike Information Criterion and Bayesian Information Criterion (AIC and BIC), as well as by graphical assessment of each parametric function. The AIC ranking was followed by graphical assessment of the visual fit of the distribution to the adjusted (glofitamab) and unadjusted (comparator) data and assessment of the empirical hazard data to see if it was suggestive of specific distributions (such as a constant hazard suggesting an exponential). Distributions that were poor visual fits or produced clearly implausible projections were discarded, with the remaining distribution with the lowest AIC statistic chosen in the base case. The chosen distributions were validated for long-term plausibility by eight clinical experts at an Advisory Board (1).

B.3.3.2.1 Glofitamab base-case survival distributions

In the base-case, parametric distributions are used to extrapolate PFS and OS over the time horizon of the model. The glofitamab base-case distributions were selected based on the overall goodness of fit and clinical plausibility of the extrapolations across all the populations used for each adjusted comparison. The rationale behind the choice of base-case glofitamab PFS and OS distributions is as follows:

- For PFS, when visually evaluating the curves, a generalised gamma was assessed as providing the best fit across all glofitamab populations used in the model comparisons. Generalised gamma generally fits the steeply declining nature of the observed hazard based on AIC and BIC (see Table 32), the Gompertz and Log-normal are also shown to fit well. However, in many glofitamab populations the Log-normal does not fit the tail of the observed data as it underestimated the PFS (see Figure 15). Therefore, all the glofitamab ITC populations use the same distribution (generalised gamma) as the glofitamab ITT population.

- For OS, when visually evaluating the curves, the Log-normal and Gompertz were assessed as providing the best fit overall across all glofitamab populations used in the model comparisons (see Table 32); however, they yielded very different long-term predictions (see xxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxx xxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxx xxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxx xxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxx xxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxx xxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxx xxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxx

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- **Figure *16***). The Gen Gamma is preferred for the base-case as it fits the observed data equally well (see Table 32) (particularly the steeply declining nature of the hazard) and yields reasonable long-term predictions, in between those of Gompertz and Log-normal (see xxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxx xxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxx xxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxx xxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxx xxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxx xxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxx xxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxx
-
- **Figure *16***).

Table 32: Goodness of fit of glofitamab PFS and OS distributions

Distribution	PFS		OS	
	AIC	BIC	AIC	BIC
Exponential	639.034	642.077	641.485	644.528
Weibull	631.380	637.467	641.893	647.979
Log-normal	612.349	618.436	635.965	642.052
Gen gamma	608.079	617.210	637.963	647.094
Log-logistic	617.424	623.510	636.478	642.564
Gompertz	616.873	622.960	636.197	642.284
Gamma	635.191	641.278	642.654	648.741

Figure 15: PFS distributions considered for glofitamab

[redacted]

Figure 16: OS distributions considered for glofitamab

For the comparator treatments, the choice and justification for the base-case PFS and OS parametric distributions, and the consideration of the proportional hazards assumption in each comparison, are presented in Sections B.3.3.2.2 Glofitamab vs axicabtagene ciloleucel–B.3.3.2.4 Glofitamab vs .

B.3.3.2.2 Glofitamab vs axicabtagene ciloleucel

B.3.3.2.2.1 Progression-free survival

The comparison between glofitamab and axicabtagene ciloleucel is informed by the MAIC adjusted glofitamab population (ESS, n=27.9) and the unadjusted axicabtagene ciloleucel population (n=101) as presented in Section B.2.9.2.1 Glofitamab vs axicabtagene ciloleucel MAIC.

It was not feasible to fully harmonise the inclusion and exclusion criteria between the ZUMA-1 trial and the NP30179 trial as this led to unacceptably low ESS numbers. The limitations associated with the MAIC vs axicabtagene ciloleucel, are summarised in Sections B.2.9.2.1.1 Populations and baseline characteristics and B.2.9.3.2Limitations and uncertainties. In brief, differences in study eligibility criteria, endpoint definitions, and the exclusion of leukapheresed patients who do not reach infusion in the ZUMA-1 mITT cohort represent key limitations which could not be addressed in the MAIC. As such, caution should be taken when interpreting the results of this comparison, giving consideration to the aforementioned limitations and the direction of the probable bias.

Figure 17 displays the PFS KM for glofitamab (adjusted) and axicabtagene ciloleucel (unadjusted) and shows that glofitamab is consistently estimated to be less effective than axicabtagene ciloleucel. Given there are notable differences in the underlying populations and with patients whose disease progressed before infusion excluded from the axi-cel mITT cohort, it is expected that those in the ZUMA-1 study that reached infusion would experience improved PFS (see Section B.2.9.2.1 Glofitamab vs axicabtagene ciloleucel MAIC). The Schoenfeld test (p= 0.2158) would allow acceptance of the proportional hazards assumption, but as the log negative log plot (Figure 18) shows some convergence in the latter time periods, the proportional hazards assumption was rejected, and the PFS curves were fitted independently.

Figure 17: PFS Kaplan-Meier for glofitamab (adjusted) and axicabtagene ciloleucel (unadjusted)

[redacted]

Figure 18: PFS log negative log plot for glofitamab (adjusted) and axicabtagene ciloleucel (unadjusted)

[redacted]

AIC and BIC statistics were calculated for the seven axicabtagene ciloleucel distributions considered (xxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxx xxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxx xxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxx xxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxx xxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxx

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Table ***33***). Based on AIC and BIC, Gompertz was the best fitting distribution, with generalised gamma also found to be a good statistical fit and fits the underlying decreasing hazard quite well (Figure 19). Analysis of survival and hazard plots (Figure 19) suggests Gompertz is a good fit to the KM data. Clinical experts at the Advisory Board considered that Gompertz produced the most plausible PFS estimates for axicabtagene ciloleucel (1). Taking the above into account, the Gompertz distribution was chosen to model axicabtagene ciloleucel PFS.

Figure 19: PFS hazard and survival plots for distributions considered for glofitamab (adjusted) and axicabtagene ciloleucel (unadjusted)

[redacted]

Table 33: AIC and BIC for PFS (axicabtagene ciloleucel)

Distribution	PFS	
	AIC	BIC
Exponential	481.525	484.140
Weibull	464.213	469.444
Log-normal	447.591	452.821
Gen gamma	437.783	445.628
Log-logistic	451.517	456.747
Gompertz	431.177	436.407
Gamma	469.618	474.848

B.3.3.2.2.2 Overall survival

The available data to inform axicabtagene ciloleucel survival was longer than for glofitamab. Figure 20 displays the OS KM for glofitamab (adjusted) and axicabtagene ciloleucel (unadjusted) and shows that the survival probability for patients treated with glofitamab is estimated to be lower than those receiving axicabtagene ciloleucel. Similar to the PFS findings, these results are not unexpected as the observed OS data for axi-cel excludes a significant proportion of patients whose disease progressed ahead of infusion, who would also have had the

highest mortality risk of the full ZUMA-1 ITT population. As such, observed differences in OS are likely an overestimate, biased in favour of axi-cel vs glofitamab. The log negative log plot indicate that the proportional hazards assumption may hold,
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Figure ***21***) and the Schoenfeld test indicated no reason to reject the proportional hazards assumption (p=0.07502). However, assuming proportional hazards holds, and fitting OS extrapolations simultaneously for glofitamab and axicabtagene ciloleucel had a negligible impact on the results (see Section B.3.11.3). Therefore, in order to remain consistent with the approach applied in the other comparisons, the OS distributions for glofitamab and axicabtagene ciloleucel were independently fitted in the base-case analysis.

Figure 20: OS Kaplan-Meier for glofitamab (adjusted) and axicabtagene ciloleucel (unadjusted)

[redacted]

Figure 21: Log negative log plot for glofitamab (adjusted) and axicabtagene ciloleucel (unadjusted)

[redacted]

AIC and BIC statistics were calculated for the seven axicabtagene ciloleucel distributions considered (xxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxx xxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxx xxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxx xxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxx xxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxx xxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxx x

Table ***34***). As with PFS, based on AIC and BIC, Gompertz was the best fitting distribution. The generalised gamma was also a good statistical fit as it fits the underlying decreasing hazard (Figure 22). Analysis of survival and hazard plots (Figure 22**Error! Reference source not found.**) suggest that the Gompertz is the best fit to the KM data. Clinical experts at the Advisory Board considered that they expected a difference in OS when comparing the glofitamab ITT OS data with the axi-cel mITT cohort, and agreed that Gompertz produced the most plausible OS estimates for axicabtagene ciloleucel (1). Taking the above into account, the Gompertz distribution was chosen to model axicabtagene ciloleucel OS.

Figure 22: OS hazard and survival plots for distributions considered for glofitamab (adjusted) and axicabtagene ciloleucel (unadjusted)

Table 34: AIC and BIC for OS (axicabtagene ciloleucel)

Distribution	OS	
	AIC	BIC
Exponential	599.278	601.894
Weibull	584.107	589.338
Log-normal	572.288	577.519
Gen gamma	569.356	577.201
Log-logistic	575.819	581.050
Gompertz	564.014	569.244
Gamma	587.958	593.188

B.3.3.2.3 Glofitamab vs bendamustine plus rituximab

B.3.3.2.3.1 Progression-free survival

As noted in Section B.3.2.5 Intervention technology and comparators, it was not feasible to perform a robust ITC between glofitamab and R-GemOx. BR was therefore used as a proxy to represent rituximab in combination with chemotherapy in the model as it was feasible to perform a comparison between glofitamab and this regimen. As noted in Sections **Error! Reference source not found.** and B.3.2.5 Intervention technology and comparators, BR was considered a suitable proxy for R-Chemotherapy for the purposes of this analysis. Clinical experts consulted by Roche agreed that the comparison to BR to be reflective of other R-Chemotherapy regimens used to treat 3L+ DLBCL (1). The comparison between glofitamab and BR is informed by the MAIC adjusted glofitamab population (ESS, n=67.6), and the unadjusted BR population (n=58), as presented in Section With regards to safety, data relating to discontinuation due to AEs was not available for the MAIC against axicabtagene ciloleucel, so an OR could not be estimated. Treatment-related grade 3 or higher AEs were extracted from the ZUMA-1 study, and considered in the analysis.

B.2.9.2.2 Glofitamab vs bendamustine plus rituximab MAIC.

It was not possible to adjust all covariates to align the cohorts from NP30179 and Hong 2018 (107), notably, imbalances in the number of prior therapies and baseline ECOG PS could not be addressed (see Section With regards to safety, data relating to discontinuation due to AEs was not available for the MAIC against axicabtagene ciloleucel, so an OR could not be estimated. Treatment-related grade 3 or higher AEs were extracted from the ZUMA-1 study, and considered in the analysis.

B.2.9.2.2 Glofitamab vs bendamustine plus rituximab MAIC). With the imbalance in 2L patients biased in favour of BR, and the imbalance in ECOG PS favouring glofitamab, it is expected that these imbalances will partially offset one another. However, given the presence of the bias, it is important to view results of the efficacy estimates with this in mind.

Figure 23 displays the PFS KM for glofitamab (adjusted) BR (unadjusted). Follow up was longer for BR than for glofitamab for both PFS and OS. The log negative hazard plots indicate that the proportional hazards assumption is unlikely to hold with early crossing and divergence in the later time points for PFS (xxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxx xxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxx xxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxx xxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxx xxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxx xxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxx x

Figure ***24***). The Schoenfeld test did not require the proportional hazards assumption to be rejected (p=0.2979) though the crossing in the log negative log plot meant it was deemed sensible to fit independent models.

Figure 23: PFS Kaplan-Meier for glofitamab (adjusted) and BR (unadjusted)

[redacted]

[redacted]

Figure 24: PFS log negative log plot for glofitamab (adjusted) and BR (unadjusted)

[redacted]

AIC and BIC statistics were calculated for the seven distributions considered (xxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxx xxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxx xxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxx xxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxx xxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxx xxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxx x

Table ***35***). For BR, the generalised gamma was the highest ranked distribution, but the log-normal and log-logistic were within five points of the generalized gamma distribution. On observing the OS and PFS predictions based on the generalized gamma distribution, it was found that the PFS curve crossed the OS curve after approximately 3.5 years, which if PFS is not capped by OS, would lead to implausible results. Analysis of survival and hazard plots (Figure 25) suggests that the shape of the hazard in the KM data in the BR arm indicates a concave shaped parametric hazard, which is compatible with log-normal and log-logistic models. Clinical experts at the Advisory Board considered that both extrapolations produced plausible PFS estimates for BR (1). Taking the above into account, the log-logistic distribution was chosen to model BR.

Figure 25: PFS hazard and survival plots for distributions considered for glofitamab (adjusted) and BR (unadjusted)

[redacted]

[redacted]

Table 35: AIC and BIC for PFS (BR)

Distribution	PFS	
	AIC	BIC
Exponential	343.398	345.458
Weibull	336.595	340.716
Log-normal	318.090	322.211
Gen gamma	313.681	319.862
Log-logistic	316.758	320.879
Gompertz	323.524	327.645
Gamma	341.580	345.701

B.3.3.2.3.2 Overall survival

Figure 26 displays the OS KM for glofitamab (adjusted) and BR (unadjusted). Follow up for OS was longer for BR than glofitamab. Even so, the KM data shows that the mortality risk is reduced for people treated with glofitamab more than with BR. Similar to PFS, despite the Schoenfeld test not requiring the proportional hazards assumption to be rejected (p=0.2757), the log negative hazard plots indicate that the proportional hazards assumption is unlikely to hold with early crossing and divergence in later time points for OS (Figure 27). Therefore, it was considered appropriate to fit models independently.

Figure 26: OS Kaplan-Meier for glofitamab (adjusted) and BR (unadjusted)

[redacted]

Figure 27: OS log negative log plot for glofitamab (adjusted) and BR (unadjusted)

[redacted]

AIC and BIC statistics were calculated for the seven distributions considered (xxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxx xxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxx xxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxx xxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxx xxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxx xxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxx x

Table ***36***). For BR, the log-normal model was the highest ranked distribution, and the exponential had similar AIC and BIC scores. Analysis of survival and hazard plots (Figure 28) suggested that the shape of the hazard in the KM data in the BR arm indicates a concave shaped parametric hazard, which is compatible with log-normal and log-logistic models. Clinical experts at the Advisory Board also considered that log-normal produced the plausible OS estimates for BR (1). Taking the above into account the log-normal distribution was chosen to model BR.

Figure 28: PFS hazard and survival plots for distributions considered for glofitamab (adjusted) and BR (unadjusted)

[redacted]

Table 36: AIC and BIC for OS (BR)

Distribution	OS	
	AIC	BIC
Exponential	379.411	381.471
Weibull	381.324	385.445
Log-normal	374.756	378.877
Gen gamma	376.744	382.926
Log-logistic	374.821	378.942
Gompertz	379.766	383.887
Gamma	381.371	385.492

B.3.3.2.4 Glofitamab vs pola-BR

B.3.3.2.4.1 Progression-free survival

The comparison between glofitamab and pola-BR is informed by the propensity score analysis in the IPTW adjusted glofitamab (ESS, n=123) and the pola-BR (ESS=53.9) populations as presented in Section With regards to safety, data relating to discontinuation due to AEs was not available for the MAIC against BR, so an OR could not be estimated. Treatment-related grade 3 or higher AEs were extracted from the Hong 2018 study, and considered in the analysis.

B.2.9.2.3 Glofitamab vs pola-BR propensity score analysis.

In order to ensure that the patient cohorts used for the analysis were as homogenous as possible, patients were filtered until an acceptable balance of all prognostic factors was achieved. Baseline characteristics for glofitamab and pola-BR in the IPTW adjusted populations can be seen in Table 20.

Figure 29 displays the PFS KM for glofitamab and pola-BR. Follow up was considerably longer for pola-BR than for glofitamab for both PFS and OS. PFS is similar until approximately 10 months, where there is separation and glofitamab begins to track above pola-BR. The log negative hazard plots converge and then cross, indicating that the proportional hazards assumption is unlikely to hold for PFS (Figure 30). The Schoenfeld test did not require the proportional hazards assumption to be rejected (p=0.2757), but given the convergence and crossing observed in the log negative log plots, it was considered appropriate to fit models independently.

Figure 29: PFS Kaplan-Meier for glofitamab and pola-BR

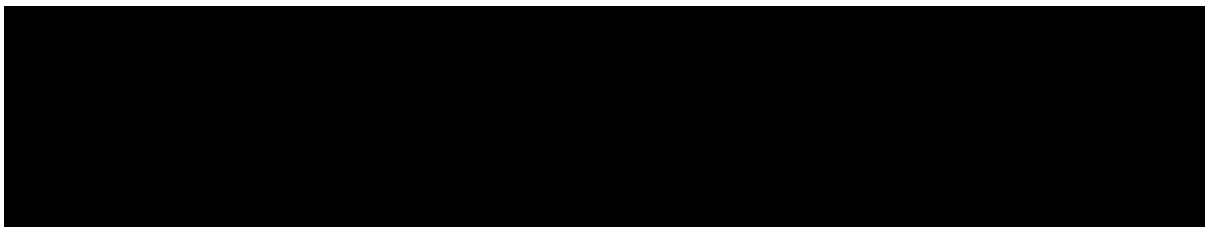

Figure 30: PFS log negative log plot for glofitamab (adjusted) and pola-BR (unadjusted)

[redacted]

AIC and BIC statistics were calculated for the seven distributions considered (xxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxx xxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxx xxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxx xxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxx xxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxx xxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxx x

Table ***37***). For pola-BR, the generalised gamma was the highest ranked distribution, with Log-Normal also found to be a reasonable fit. Analysis of survival and hazard plots (Figure 31**Error! Reference source not found.**) suggests all curves are reasonable fits to the pola-BR KM data. Clinical experts at the Advisory Board considered that several extrapolations, including generalised gamma, produced plausible PFS estimates for pola-BR (1). Taking the above into account, the generalised gamma distribution was chosen to model pola-BR.

Figure 31: PFS hazard and survival plots for distributions considered for glofitamab (adjusted) and pola-BR (unadjusted)

[redacted]

Table 37: AIC and BIC for PFS (pola-BR)

Distribution	PFS	
	AIC	BIC
Exponential	324.749	327.180
Weibull	320.450	325.311
Log-normal	306.647	311.508
Gen gamma	301.974	309.266
Log-logistic	307.534	312.396

Gompertz	311.003	315.865
Gamma	323.861	328.723

B.3.3.2.4.2 Overall survival

Figure 32 displays the OS KM for glofitamab and pola-BR. While there was more follow up data for pola-BR, in the period in which glofitamab OS was observed, the KM data suggests the improved OS for glofitamab compared to pola-BR. As with PFS, the Schoenfeld test did not require the proportional hazards assumption to be rejected (p=0.1587), but as the log negative hazard plots converge and then cross, the proportional hazards assumption is unlikely to hold for OS (Figure 33). Therefore, it was considered appropriate to fit models independently.

Figure 32: OS Kaplan-Meier for glofitamab (adjusted) and pola-BR (unadjusted)

Figure 33: OS log negative log plot for glofitamab (adjusted) and pola-BR (unadjusted)

AIC and BIC statistics were calculated for the seven distributions considered (Table 38). For pola-BR, the generalised gamma was the highest ranked distribution, but a number of alternative distributions (log-normal, log-logistic and Gompertz) had similar AIC and BIC scores. Analysis of survival and hazard plots (Figure 34) suggests all curves are reasonable fits to the pola-BR KM data. Clinical experts at the Advisory Board considered that the observed OS data looked promising for glofitamab, but agreed that further follow-up was needed before conclusions around the relative survival benefits vs pola-BR could be reached (1). Generalised gamma

and log-normal distributions were both considered, with log-normal producing long-term survival predictions in line with estimates elicited from clinical experts, unlike the generalised gamma which produced overly optimistic predictions. Taking the above into account, the log-normal distribution was chosen for pola-BR.

Figure 34: OS hazard and survival plots for distributions considered for glofitamab (adjusted) and pola-BR (unadjusted)

Table 38: AIC and BIC for OS (pola-BR)

Distribution	OS	
	AIC	BIC
Exponential	303.267	305.698
Weibull	303.487	308.348
Log-normal	292.637	297.499
Gen gamma	290.049	297.341
Log-logistic	293.343	298.204
Gompertz	294.525	299.387
Gamma	304.824	309.686

B.3.3.2.5 Long-term remission/survivorship

Long-term remission/survivorship was deemed clinically plausible for R/R DLBCL in previous 2L+ and 3L+ DLBCL NICE submissions (TA649, TA559, TA567), irrespective of the technology being assessed (136-138). To account for this in the model, patients alive and progression free at 2 years are assumed to enter long-term remission. On entering long-term remission, patients do not continue to progress, revert to near general population utility values (assumed 10% lower vs general population, are considered reasonable by clinical experts consulted at the advisory board) (1), and do not accrue any further costs. After 3.5 years, when the majority of progressed patients in the model have died, mortality risks for the remaining patients reverts to a near general population level (9% excess vs general population [in line with value applied from TA559 and TA567, based on a standardised mortality rate

identified from Maurer 2014] (55), adjusted to account for potential excess comorbidities (136, 137). These assumptions were validated as reasonable by clinical experts at an Advisory Board meeting conducted by Roche (1). A scenario in which patients do not enter long-term remission was explored as a scenario analysis (see Section B.3.14 Validation

). To maintain consistency, long-term remission is assumed to be treatment independent, with the same assumptions applied to all treatment arms in the model. However, in some instances, most notably for pola-BR and BR, continuing progression was observed after 2 years, suggesting that survival and subsequent QALY estimates for these treatments may be overestimated when treatment independent long-term remission is assumed.

B.3.3.3 All-cause mortality

Background mortality was calculated using age-and gender-specific all-cause mortality rates by year in the general UK population, obtained from the National Life Tables, England & Wales (period expectation of life based on data for the years 2017-2019) (151). A correction was applied at every model cycle to ensure the hazard of death estimated from each OS extrapolation would not be lower than background mortality. Background mortality is modelled as a function of the age distribution rather than the more standard approach which assumes the mean age of the cohort. This approach is considered to be more realistic than the average cohort age, as it better reflects the slower increase in the average age of the cohort due to the fact that younger patients have a lower risk of death compared to older patients. One-year mortality rates were calculated as a weighted average of sex-specific mortality rates from the National Life Tables, adjusted by the relevant cohort sex distribution from NP30179 and a standardised mortality rate (SMR) adjustment to account for increased morality risk due to excess comorbidities.

The CEM allows the use of different data sources for the applied SMR, as per previous NICE TAs (e.g., TA559/TA567), and are shown as scenarios in Section B.3.14 Validation

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B.3.3.4 Treatment discontinuation

In the base case, time to off treatment (TTOT) data from either NP30179 or other comparator studies was used to model the actual duration on treatment. For other treatments where direct TTOT information was not available, the respective TTOT was set equal to the selected parametric distribution for PFS, capped at the treatment-specific maximum number of cycles, as per the treatment label. For a one-off treatment such as the CAR-T cell therapies, the duration on treatment was assumed to last for a single model cycle.

Base case TTOT model estimates are provided in Table 39.

Table 39: Base case estimates for TTOT

	Glofitamab*	BR (Rituximab)	BR (Bendamustine)	Pola-BR (Pola)	Pola-BR (Bendamustine)	Pola-BR (Rituximab)	Yescarta
Model results, time on treatment							
Mean number (cycles)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mean time (months)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Median time (months)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Proportion still on treatment							
0 months	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
6 months	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
12 months	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

*Note: * that this corresponds to the unfiltered, unweighted pooled efficacy population from the NP30179 trial; therefore, it cannot be directly compared with the comparators.*

RB, rituximab and bendamustine; Pola, polatuzumab-vedotin.

B.3.3.5 Adverse events

Adverse events (AEs) are an inevitable consequence of any intervention. To reflect this, AEs were applied in the model affecting costs and QALYs accrued with each intervention. Only treatment-related AEs with a severity grade of 3 or higher were considered in the model (see Table 40) to reflect those events that are most likely to impact cost-effectiveness. This is in line with the approach used in NICE TA559 and TA567, as well as with how data on treatment-related/emergent AEs were reported in comparator studies. Note that although the actual number of AEs observed were used to estimate the AE incidence for glofitamab, for all other treatments excluding pola-BR, only the number of patients experiencing certain adverse events was reported. This is considered to be a conservative approach likely resulting in increased AE costs for glofitamab compared to most comparators (not pola-BR). Furthermore, only AEs occurring in over 1% of patients were considered.

Table 40: Adverse events considered in the model

Grade 3–5 AEs	Total number of AEs			
	Glofit	BR	Pola-BR	Yescarta
Agitation	0	0	0	4
Anemia	5	19	20	43
Aphasia	0	0	0	7
CRS	5	0	0	13
Diarrhea	0	0	4	4
Encephalopathy	0	0	0	21
Hypocalcemia	0	0	0	6
Hypokalemia	0	0	0	3
Hyponatremia	0	0	0	10
Hypophosphatemia	11	0	0	0
Hypotension	0	0	0	14
Febrile neutropenia	5	11	7	31
Leukopenia	0	0	16	0
Lymphopenia	6	0	12	0
Lymphocyte count decreased	0	0	12	0
Neutrophil count decreased	0	0	22	0
Neutropenia	49	40	101	79
Pneumonia	0	0	8	0
Platelet count decreased	0	0	8	0
Pyrexia	0	0	0	14
Septic shock	0	0	7	0
Somnolence	0	0	0	7
Thrombocytopenia	4	34	42	38

Vomiting	0	0	4	1
White blood cell count decreased	0	0	17	29

Pola, polatuzumab vedotin; RB, rituximab and bendamustine; R2, rituximab and lenalidomide; TTOT, time to off treatment; Yescarta, Axicabtagene ciloleuce.

B.3.4 Measurement and valuation of health effects

B.3.4.1 Health-related quality-of-life studies

An SLR was conducted to identify studies evaluating HRQoL in the target population. Further details of the SLR can be found in the report provided as Appendix I. A total of six relevant HSUV studies were identified for inclusion, for both 2L and 3L DLBCL (full publications, N=2; conference abstracts, N=4). Three studies (reported in four publications) specifically reported results for the 3L+ setting (152-154).

- A full publication and a conference abstract reporting utility values for patients with DLBCL in the 3L+ settings from the TRANSCEND NHL 001 trial who received prior lisocabtagene maraleucel in the US (153, 155)
- A full publication reporting utility values for multi-national patients with DLBCL who had received at least 2 and no more than 5 previous systemic regimens for enrolment in the SADAL trial (154)
- A conference abstract reporting non-treatment specific utilities for patients with DLBCL in the 1L, 2L, and 3L+ settings in the UK (152).

Full detail of these studies, their limitations and conclusions, can be seen in Appendix I.

B.3.4.2 Health-related quality-of-life from clinical trials

In the NP30179 study, the EORTC QLQ-C30 and the FACT-Lym LymS were the PRO scales analysed in the PRO-evaluable population. The EORTC QLQ-C30 and FACT-Lym LymS assessments were administered at baseline and every 3 months during the post treatment follow-up. The scales were scored according to the user manual. Summary statistics and changes from baseline scores were calculated for all time points. Full details of the methods and results can be seen in Appendix I, and a summary in Section B.2.4 Statistical analysis and definition of study groups in the relevant clinical effectiveness evidence.

Health-related quality-of-life information, such as that captured in the EORTC QLQ-C30, was needed for economic modelling purposes. As such, subsequent sections focus on this measure and how it was incorporated into the cost-effectiveness analysis.

B.3.4.3 NP30179 HRQoL data analysis

EQ-5D data was not collected in the NP30179 study. Therefore, the base case analysis uses utility values estimated through EORTC-QLQ-C30 mapped to EQ5D-3L (as per NICE recommendations) (156). Details of the approach used and choice of mapping algorithm can be seen in the following section.

B.3.4.4 Mapping

Given the absence of lymphoma specific algorithms estimating utility values from Western country tariffs, a targeted literature search of EQ-5D-3L mapping algorithms for haematological malignancies was conducted to identify the best candidates for use in the mapping exercise – See Appendix I for details.

Several mapping algorithms were identified, with 2 considered for use in the economic analysis:

- Mapping from EORTC-QLQ-C30 to EQ-5D-3L, using the direct mapping algorithm published by Proskorovsky et al, 2014 (157) (full model).
- Mapping from EORTC-QLQ-C30 to EQ-5D-3L, using the indirect mapping algorithm published in Longworth et al, 2014 (158).

Both of the preferred mapping algorithms were estimated in patients with multiple myeloma (or with multiple tumors where multiple myeloma was the predominant cancer). These were preferred over other potentially available options for the following reasons:

- Good predictive ability (based on model performance statistics and accuracy of predicted values)
- Relevance and size of the patient sample used to estimate the algorithm

- Sufficient amount of detail on how the regression was estimated and on the baseline characteristics of the sample
- External validation
- Use in previous NICE submissions

Both Proskorovsky et al, 2014 (157) and Longworth et al, 2014 (158) algorithms were accepted in previous NICE TAs for haematological malignancies (TA695, TA657, TA450 and TA399), with the former being the one most frequently used. However, the model base case uses the algorithm from Longworth *et al*, 2014 as, unlike Proskorovsky et al, 2014, this has recently been externally validated (159).

Mapping was performed using a complete case perspective, i.e., by excluding those visits in which at least one of the EORTC-QLQ-C30 scores required to run the selected mapping algorithms was missing. Note that only patients with 3L+ R/R DLBCL from the pooled efficacy population (N=155) were considered in the analysis, rather than the PRO-evaluable population. This approach was taken as the PRO-evaluable population included patients who had R/R FL (Cohort B4) or patients with DLBCL who received a different dose of glofitamab (fixed 10/16mg Q3W), compared to the target registrational dose (Cohort B3).

The mapped EQ-5D-3L index values based on UK tariffs were used to estimate utilities for three health states: PFS on-treatment, PFS off-treatment and PPS. A distinction between PFS on- and off-treatment was made to account for the potential impact of treatment-related factors (such as toxicities, burden of administration, etc.) on utility. This approach is also likely to better capture the impact of treatment-related toxicities on utility compared to estimating individual AEs disutilities, as utility measurements are typically rarely available for the same visits at which AEs take place.

At baseline, 139 observations of 155 were available and a mean of 0.687 (SE 0.20) was reported, indicating a reduced utility for patients compared to an age-matched general population (0.816).

As only a small number of patients were available from NP30179 to inform the analysis, a pragmatic approach was taken, and health state utilities were calculated for PFS and PPS. Estimates by progression status are informed by the date of progression for each patient unless it cannot be assigned due to censoring, in which case it is considered unknown and is not included in analysis.

Linear mixed regression models on post baseline utilities, controlling for centralised baseline utilities, using random intercepts for each patient were used. This approach was taken as it is considered robust to violations of distributional assumptions (160). Results are shown in Table 41.

A brazier age-adjusted health state utility value coefficient was also applied (Table 42). This age-adjustment is a linear estimation of how utility changes in the general population as a function of sex and age. In this model, the linear function was used to calculate a multiplier, corresponding to proportional utility loss as a function of age, which was used in the final calculation of QALYs for each cycle in each treatment model.

Table 41. Utility estimates from NP30179 (EORTC-QLQ-C30 to EQ-5L-3L)

State	Utility value (SE)	95% CI
PFS – on treatment	0.729	0.011
PFS – off treatment	0.774	0.020
PPS	0.629	0.019

CI, confidence interval; PFS, progression free survival; PPS, post progression survival; SE, standard error.

Table 42. Brazier age-adjusted coefficients

Parameter	Estimate (SE)
(Intercept)	0.95086
sexM	0.02121
age	-0.00026
age2	-0.00003

CI, confidence interval; SE, standard error.

B.3.4.5 Adverse reactions

It was not possible to conduct an ITC for safety outcomes due to data sparsity. As such, the information relating to AEs contained within the CEM and reported in this

document is taken directly from literature and represents a naïve comparison with glofitamab.

The PFS values estimated from this trial analysis are considered to represent the HRQoL experienced by patients pre-progression and are further considered to account for any potential adverse reactions. Therefore, it was not considered sensible to include specific disutilities for any adverse reactions as this would constitute double counting.

A conservative assumption was made that the HRQoL experienced is consistent across all treatment arms and is related to the health state rather than toxicity. The most impactful AEs are evident early after treatment onset (such as CRS, which occurred predominantly after the first dose of glofitamab in Cycle 1, see Section B.2.10.3.1 Cytokine release syndrome (CRS)) and these will be captured within the PFS health state measurement.

While it may have been possible to collect disutility estimates for some AEs experienced, these were not collected within a comparative trial. It was therefore considered that including disutilities and combining these with rates from a naïve comparison, would introduce unnecessary uncertainty to the decision problem.

If one wants to assess the impact of the toxicity profiles of individual treatments, then it is recommended to use the PFS/PPS health state utilities based on literature/previous NICE TAs in the CEM. If switched on, AE disutilities are applied in the model for the time patients are on-treatment. The only exception to this is for CAR-T cell therapies, whose main AEs tend to occur in the first 2–3 weeks after injection, and thus these were all assumed to occur within the first model cycle, as a modelling simplification. The impact of applying AE disutilities, while using health state utilities from NICE TA306 so as to not reflect the impact of CRS in the PFS health state, is explored in a scenario analysis (see Section B.3.14) (136). ***Validation***

B.3.4.6 Health-related quality-of-life data used in the cost-effectiveness analysis

In the base case, the health state utility values from the Glofit trial NP30179, (EORTC-QLQ-C30 mapped to EQ-5D-3L [see Section B.3.4.3 NP30179 HRQoL data analysis]), were used for all arms and therefore, it was assumed that the utility of patients in each treatment arm is comparable (Table 43***). It is acknowledged that values using an alternative mapping algorithm (see Section B.3.4.3 NP30179 HRQoL data analysis) and from previous NICE technology appraisals differ. As such, scenarios are presented where health state utility is based on estimates from NP30179 values using the direct mapping algorithm (Proskorovsky et al, 2014), and from previous NICE technology appraisals of axi-cel (TA559) and pixantrone (TA306) (see Section B.3.14 Validation***) (135, 136, 157).

Table 43. Base case utility values and scenario utility values

Scenario	State	Utility values	Standard error
Base case	PFS – on treatment	0.729	0.011
	PFS – on treatment	0.774	0.020
	PPS	0.629	0.019
Scenario (EORTC-QLQ-C30 to EQ-5D 3L Mapped Utility Values, direct Mapping (UK tariff) (157)	PFS – on treatment	0.772	0.010
	PFS – on treatment	0.836	0.017
	PPS	0.673	0.016
Scenario (TA559) (136)	PFS	0.72	0.06
	PPS	0.65	0.03
Scenario (TA306 - FAD) (135)	PFS	0.76	0.06
	PPS	0.68	0.03

FAD, final appraisal determination; NICE, National Institute for Health and Care Excellence PFS, progression free survival; PPS, post progression survival; SE, standard error; TA, NICE technology appraisal.

B.3.5 Cost and healthcare resource use identification, measurement and valuation

B.3.5.1 Published costs and resources studies

An SLR was conducted to identify studies describing the costs and resource use associated with the management of patients with DLBCL. In brief, electronic database searches (Embase, MEDLINE, Evidence Based Medicine [EBM], and EconLit) were conducted in August 2021 and September 2022. Supplementary sources were hand searched for completeness, including reference lists of included studies, conference proceedings, relevant additional databases and websites, and global HTA body websites. Full details of the SLR are described in detail in Appendix J.

A total of 46 studies were identified reporting cost and resource use data for patients with DLBCL in the R/R setting (161-205). The majority of studies had a retrospective study design (N=37) (161-177, 179, 180, 182, 183, 185, 186, 188, 189, 191-193, 195, 198-203, 205, 206). The remaining studies consisted of cost analyses (n=4) (181, 184, 187, 196), a longitudinal study (N=1) (178), a cross-sectional study (N=1) (194), a real-world evidence study (N=1) (204), an economic framework for therapy valuation (N=1) (197), and an analysis of Phase 1 pivotal trial results (N=1) (190). Five studies analysed data from the clinical studies TRANSCEND NHL 001 [NCT02631044] (176, 190, 191) and JULIET [NCT02445248] (202, 203).

A wide range of patients with R/R DLBCL were reported to have been considered across the 46 included studies. Largely, patients were described to be R/R, although some publications provided additional descriptions of the number of prior lines of treatment. Six publications reported that results were for patients in the R/R setting specifically (175, 192-195, 206) and 25 publications reported results for patients in the 3L+ settings (165, 167-169, 171, 174, 176-178, 180-182, 185-187, 190, 191, 196, 198-203).

B.3.5.2 Intervention and comparators' costs and resource use

B.3.5.2.1 Glofitamab costs

The costs of glofitamab, including drug procurement (Table 44), administration (Table 45), and monitoring (Table 46) were applied in the CEM, at specific cycles, based on acquisition, administration and monitoring costs. Unit costs are costed per resource as reported in the NHS reference costs for 2020-2021 (207).

The administration of glofitamab is assumed to take place under supervision at hospital and has been costed as a prolonged infusion, first attendance for all appointments taking place in line with the dosing schedule. Subsequent administration is assumed to take place in an outpatient setting, costed as subsequent elements of chemotherapy cycle.

Glofitamab is administered via intravenous infusion for a maximum of 12 21-day cycles, according to a step-up dosing schedule in cycle 1 (2.5 mg in D8, 10 mg in D15) and at a dose of 30 mg in cycles 2−12. The glofitamab step-up dosing schedule also includes pre-treatment with a single dose of obinutuzumab (1000 mg) 7 days prior to first dose of glofitamab to mitigate the risk of CRS. As such, vial sharing was not assumed as the step up dosing regimen for glofitamab does not require the 2.5mg or 10mg vials to be split.

As per the draft glofitamab SmPC (208), all patients must be monitored for at least 10 hours after completion of the first infusion. For subsequent doses, patients who experienced Grade ≥2 CRS (17.50%, average between rates according to Lee and ASTCT grading scales in the pooled efficacy population) with the previous infusion should be monitored for at least 22 hours after completion of the infusion. Glofitamab additional monitoring costs can be seen in Table 46.

Table 44. Glofitamab dosing and acquisition

Dosing	2.5/10/30
Dose per cycle	As above
Cost (excluding PAS)	£687.00 (2.5mg); £2748.00 (10mg)
Pre-treatment – obinutuzumab (excluding PAS)	1000mg: £3312.00 (Cycle 1: Day1)
Cost per dose (excluding PAS)	2.5mg: £687.00 (Cycle 1: Day 8)

	10mg: £2748.00 (Cycle 1: Day 15) 30mg: £8244.00 (Cycle 2: Day 1)
Administration costs	See PAS: patient access scheme. **Table *45***
Monitoring costs	See Table 46

PAS: patient access scheme.

Table 45. Administration costs for glofitamab

Component	National cost collection for the NHS	Cost	Inflated costs
Administration (first appointment)	Deliver complex chemotherapy, including prolonged infusional treatment, at first attendance (SB14Z)	£526.52	NHS Reference Costs 2020 to 2021 (207)
Administration (subsequent appointments)	Subsequent elements of chemotherapy cycle (SB15Z)	£470.62	NHS Reference Costs 2020 to 2021 (207)

Table 46. Monitoring costs for glofitamab

Component	% pts	Cycles applied for	National NHS cost collection	Cost	Inflated costs
Monitoring (10 hours after first glofitamab infusion)	100	1	Average of malignant lymphoma (currency codes SA31A-F): day case	£620.14	NHS Reference Costs 2020 to 2021 (207)
Monitoring (22 hour for patients experiencing Grade ≥2 CRS after first glofitamab infusion)	17.5	2	2 x average of malignant lymphoma (currency codes SA31A-F): day case	£1240.28	NHS Reference Costs 2020 to 2021 (207)

B.3.5.2.2 Patient access scheme (PAS)

A PAS has been applied, comprising a simple discount of [redacted] from the glofitamab list price. In order to best replicate the true economic impact of a positive recommendation for glofitamab, the economic evaluation presented in this submission applies the PAS in the base case analysis (Table 47).

Table 47. Acquisition costs of glofitamab following application of PAS

Vial size	No PAS	PAS

2.5mg	£687	[redacted]
10mg	£2,748	[redacted]

mg, milligrams; PAS, patient access scheme.

Obinutuzumab is used as a pre-treatment ahead of glofitamab administration. As obinutuzumab is a Roche product, the confidential discount is known. Therefore, the PAS price for obinutuzumab ([redacted]) is applied to all of the results reported in Sections B.3.10-11.

B.3.5.3 Comparator costs

Comparator dosing and schedule were estimated in accordance with BNF recommendations and assumed no vial sharing where applicable (Table 48). As the dosing for some treatments was weight or body surface area (BSA) dependent, wastage may occur and impacting the cost per treatment cycle. To account for this, an algorithm has been applied in the economic model which calculates the combination of small and large vials to minimise the overall treatment cost. Furthermore, for treatments that are BSA dependent, the base-case analysis assumes that drug dosing is estimated as the planned dosing according to treatment protocols, calculated using individual patient characteristics from the NP30179 trial.

Rituximab and chemotherapy was assumed to comprise bendamustine and rituxumab (BR). In this regimen, rituximab was assumed to be given at 375mg/m^2 every 21 days. Bendamustine was given at 90-120 mg/m^2 on two consecutive days with dose de-escalation (120-90-70 mg/m2) in case of toxicity as recommended in the R/R DLBCL setting, as per Cheson et al 2016 (209). This regimen was assumed to be given up to a maximum of 12 cycles, with an assumed cycle length of 21 days.

In the regimen of Pola-BR, polatuzumab-vedotin was given at 1.8 mg/kg (total dose not recommended to exceed 240 mg due to limited clinical experience), every 21 days in combination with bendamustine and rituximab. In the same regimen, rituximab was assumed to be given at 375 mg/m^2 on Day 1 of each cycle, and bendamustine was given 90 mg/m^2 on days 1 and 2 of each cycle. This regimen was assumed to be given up to a maximum of 6 cycles, with an assumed cycle length of 21 days.

Axicabtagene ciloleucel was assumed to be given as a single intravenous dose on the first cycle.

Administration costs for the comparators, apart from axicabtagene ciloleucel, were assumed to be the same as for glofitamab for the first cycle and then costed as subsequent elements of a chemotherapy cycle for all subsequent administrations (Table 50).

Table 48. Comparator dosing and acquisition

Comparator	Unit cost	Source
Rituximab (200mg)	£314.33	BNF (210)
Rituximab (500mg)	£785.84	BNF (210)
Bendamustine (25mg)	£6.81	eMIT (211)
Bendamustine (100mg)	£16.57	eMIT (211)
Polatuzumab vedotin (30mg)	£2370.00	BNF (210)
Polatuzumab vedotin (140mg)	£11060.00	BNF (210)
Axicabtagene ciloleucel	£280451.00	NHSBSA DM+D (212)

DM+D, dictionary of medicines and devices browser; NHSBSA, NHS Business Services Authority.

Table 49. Comparator cost per cycle

Comparator	Cost per cycle
Rituximab	£1,452.27
Bendamustine	£329.24
Polatuzumab vedotin	£11,316.49
Axicabtagene ciloleucel	£280,451.00 (one-off)

Table 50. Comparator administration costs

Component	National cost collection for the NHS	Cost	Inflated costs
Administration (first appointment)	Deliver Complex Chemotherapy, including Prolonged Infusional Treatment, at First Attendance (SB14Z)	£526.52	NHS Reference Costs 2020 to 2021 (207)
Administration (Subsequent appointments)	Subsequent Elements of Chemotherapy Cycle (SB15Z)	£470.62	NHS Reference Costs 2020 to 2021 (207)
Administration (oral treatment)	Deliver Exclusively Oral Chemotherapy (SB11Z)	£245.23	NHS Reference Costs 2020 to 2021 (207)

B.3.5.3.1 Axicabtagene ciloleucel administration costs

Given the complexities associated with the administration of axicabtagene ciloleucel it was necessary to assign separate administration costs for this comparator. The costs associated with the delivery of CAR-T therapies are represented in the revised NHS England CAR-T Tariff, as seen in the committee documents for the ongoing technology appraisal of axicabtagene ciloleucel for treating DLBCL after 1 systemic therapy (213). The NHS tariff captures the resource use and costs at given proportions, as presented in Table 51.

Table 51: Summary of revised CAR-T tariff cost breakdown

Resource category	Value (GBP, 2022)	Proportion of tariff distributed
Identification and work-up	£6,514	9.96%
Leukapheresis	£2,459	3.76%
Pre-conditioning	£6,935	10.60%
Inpatient admission up to day 28	£19,499	29.81%
Early follow up close to treatment centre up to day 28	£11,588	17.71%
Adverse events up to day 28	£13,070	19.98%
Follow up post discharge to day 100	£5,451	8.18%
Total	**£65,415**	100%

GBP, Great British Pounds.

Given the availability of the revised CAR-T tariff, calculated by NHS England, the largest entity involved in the purchase and delivery of CAR-T in England, for use specifically in NICE appraisals, it was deemed appropriate to apply this cost estimate in the economic model. As such, in the base-case analysis, it is assumed that the administration costs for axicabtagene ciloleucel are equal to that of the revised NHS England CAR-T Tariff (Table 51). An alternative cost estimate for the delivery of axicabtagene ciloleucel was considered [redacted], informed by an ERG scenario analysis presented in the ongoing appraisal of

axicabtagene ciloleucel for treating diffuse large B-cell lymphoma after 1 systemic therapy (214). This was estimated as a one-off cost of £41,101 for the first 100 days plus the costs of conditioning chemotherapy drugs, stem cell transplantation and intravenous immune globulin (IVIg). The impact of applying this alternative administration cost estimate for the delivery of axicabtagene ciloleucel to the mITT cohort, excludes those who did not reach infusion, was explored in a scenario analysis (see Section B.3.11.3). Components of the NHS CAR-T tariff will be incurred by a proportion of patients deemed eligible to receive treatment, but who do not reach infusion. As such, a scenario is presented where costs are multiplied for the resource categories (identification and work-up, leukapheresis and pre-conditioning) which take place before infusion. The magnitude of the multiplier was derived from an analysis of real world CAR-T outcomes in the UK which showed that 26% of patients do not reach infusion (86). Applying a multiplier of 135% (see Equation 1) ensures the cost of the aforementioned resource categories, not captured in the analysis compared with the mITT cohort, are fully accounted for. A breakdown of costs applied in the scenario analysis can be seen in Table 51.

Equation 1: CAR-T cost multiplier

$$\frac{100\%\ (ITT\ population)}{74\%(mITT\ population)} \times 100 = 135\%$$

Table 52: Summary of revised CAR-T tariff cost breakdown

Resource category	Value (GBP, 2022)	Proportion of patients cost applies to	Total
Identification and work-up	£6,514	135%	£8,793
Leukapheresis	£2,459	135%	£3,319
Pre-conditioning	£6,935	135%	£9,362
Inpatient admission up to Day 28	£19,499	100%	£19,499
Early follow up close to treatment centre up to Day 28	£11,588	100%	£11,588
Adverse events up to Day 28	£13,070	100%	£13,070
Follow up post discharge to Day 100	£5,451	100%	£5,451

Total	£71,082

GBP, Great British Pounds.

B.3.5.4 Treatment costs at subsequent lines of therapy

Once patients in the model discontinued their initial treatment line after progression, they were assumed to be eligible for all other treatments available at fourth and subsequent lines of DLBCL treatment. These are represented in the model as a pool of treatments that can be taken in any order after discontinuation from any arm. The post discontinuation therapy cost was applied once to the proportion of patients who move from the PFS to PPS health state each cycle. This takes into account the mean duration of treatment, the proportion assumed to use each treatment option and the associated cost.

The mean duration on treatment and proportion of patients receiving different subsequent treatments upon progression on each induction treatment are listed in Table 53 and based on NP30179. The costs associated with each subsequent treatment is listed in

Table ***54***, and Table 55 shows total cost post discontinuation for glofitamab and all included comparators.

Administration costs were assumed to be the same as for glofitamab (Table 45) for the first cycle and costed as subsequent elements of a chemotherapy cycle for all subsequent administrations (Table 50).

Subsequent treatment costs are assumed to not apply for patients in long-term remission (progression free after 24 months – see Section B.3.3.2.5). As different proportions of people are assumed to be in long-term remission in each treatment arm, post discontinuation costs are therefore estimated to be different for each modelled treatment (Table 55).

Table 53: Proportion assumed to take each subsequent therapy by arm

		Base-case

Subsequent therapy	Mean duration in weeks	% on glofit	% on axi-cel	% on BR	% on pola-BR
BR	5.14	1.79%	1.79%	1.79%	1.79%
R-GemOX	4.50	2.68%	2.68%	2.68%	2.68%
R-CHOP	2.81	2.68%	2.68%	2.68%	2.68%
Average R-chemo	4.11	8.93%	8.93%	8.93%	8.93%
Other chemo regimens (non-R)	5.07	22.32%	22.32%	22.32%	22.32%
Pola-BR	4.71	8.93%	8.93%	8.93%	8.93%
Lenalidomide	2.00	1.79%	1.79%	1.79%	1.79%
Pixantrone	0.14	0.89%	0.89%	0.89%	0.89%
Clinical trial/other	5.62	17.86%	17.86%	17.86%	17.86%
Radiotherapy	1.00	15.18%	15.18%	15.18%	15.18%
Allogenic SCT	1.00	6.25%	6.25%	6.25%	6.25%
Autologous SCT	1.00	1.79%	1.79%	1.79%	1.79%
Axi-cel	1.00	8.93%	8.93%	8.93%	8.93%

Table 54. Weekly treatment costs for post-discontinuation including administration (list price)

Treatment	Total cost (£)	Comments
BR	1126.86	Average cost of BR
R-GemOX	1274.09	Average cost of R-GemOX
R-CHOP	734.37	Average cost of R-CHOP
Average R-chemo	1045.10	Mean cost of R-B, R-CHOP, R-GemOX
Other chemo regimens (non-R)	830.21	Average of the anti-CD20 based therapies (excluding rituximab. costs), pixantrone and lenalidomide
Pola-BR	5076.70	Average cost of pola-BR
Lenalidomide	1226.04	Average cost of lenalidomide
Pixantrone	1928.18	Average cost of pixantrone
Clinical trial/other	6315.88	Mean of all therapies, excluding one-off, and BSC

Radiotherapy	5446.60	One off, following approach from tafa-len NICE submission (10*admins), costed with NHS reference cost 20/21
Allogenic SCT	64539.89	One-off cost, estimated as per CAR-T NICE TA559/TA567
Autologous SCT	26169.43	One-off cost, estimated as per CAR-T NICE TA559/TA567
Axi-cel	345866.00	One off cost

Table 55. Total post-discontinuation costs

Treatment	Total cost (£)
Glofitamab	32,083
Axi-cel	25,598
BR	34,755
Pola-BR	39,249

In the base-case, data on post-discontinuation regimen shares and treatment duration for glofitamab were taken from the NP30179 trial. Comparator shares and duration were assumed to be the same as glofitamab. Total therapy costs were calculated using mean duration (weeks) and weekly cost estimates (including administration costs) using NHS reference costs (2020-2021) (207).

B.3.5.5 Supportive care costs

Supportive care costs were applied to each model cycle a patient was alive. These costs were different between the progression-free survival and post-progression health states and were independent of treatment arm (Table 56). They are therefore considered to represent health care resource use that is specific to disease status rather than treatment arm.

A microcosting approach to supportive care costs was taken to determine the resources used in supportive care for each health state or event. Resource use for PFS was extracted from the appraisal of pola-BR for R/R DLBCL (TA649), and discussed with clinicians who felt that the approach and costs were reasonable. These resource estimates were then costed using NHS reference costs or applying an appropriate inflation to 2021 costs, based on the NHS Cost Inflation Index (NHSCII) from the Personal Social Services Research Unit (PSSRU) (215).

Resources used, and one-off costs applied at progression were also extracted from TA649, and validated by clinicians as an appropriate representation of the main costs which would apply at progression. These resource estimates were then costed using NHS reference costs for 2020/2021. No separate terminal care costs were applied in the model, as these costs are expected to be captured in the supportive care costs. Furthermore, including terminal care costs in the economic model has a negligible impact on the results.

The costs applied for supportive care, including the costs associated with the PFS and PPS health state, are reported in Table 56. Table 57 shows the one-off costs associated with disease progression. This one-off cost was applied in the cycle that progression takes place.

Table 56: Weekly supportive care costs

Unit	Unit cost	Resource use of PFS state on treatment	Resource use of PFS state off treatment	Resource use of progression state	Source
Professional and social services					
Residential care (day)	120.63	0.75	0.19	0.00	TA649 (138)
Day care (day)	61.11	0.28	0.07	0.47	
Home care (day)	35.11	1.17	0.43	2.34	
Hospice (day)	198.10	0.01	0.00	0.23	
Health care professionals and hospital resource use					
Oncologist (visit)	214.56	0.42	0.11	0.08	TA649 (138)
Haematologist (visit)	224.55	0.20	0.05	0.25	
Radiologist (visit)	185.20	0.42	0.08	0.00	
Nurse (visit)	51.84	1.00	0.25	0.00	

Specialist nurse (visit)	51.84	0.17	0.04	0.63	
GP (visit)	39.23	0.50	0.13	0.83	
District nurse (visit)	51.84	0.38	0.10	1.00	
CT scan	106.79	0.08	0.08	0.00	
Inpatient day	404.02	0.06	0.06	0.05	
Palliative care team	124.15	0.00	0.00	0.33	
Treatment follow-up					
Full blood counts	3.63	0.83	0.83	0.25	TA649 (138)
LDH	3.63	0.50	0.50	0.08	
Liver function	3.63	0.83	0.83	0.25	
Renal function	3.63	0.83	0.83	0.08	
Immunoglobulin	3.63	0.17	0.17	0.08	
Calcium phosphate	3.63	0.17	0.17	0.25	
Hematologist (visit)	224.55	0.06	0.06	0.05	
Oncologist (visit)	193.24	0.01	0.01	0.01	
Nurse (visit)	51.84	0.09	0.09	0.04	
Radiologist (visit)	185.20	0.00	0.00	0.00	
GP (visit)	39.23	0.00	0.00	0.00	
Total weekly supportive costs used in model					

Model state	Used cost (£)
Progression-free state	**528.90**
Progression-free state off treatment	**182.59**
Progression state	**428.72**

PSA, probabilistic sensitivity analysis; SE, standard error.

Table 57: One-off progression costs

Unit	Unit cost (£)	Proportion of patients requiring resource	Source
ECG	181.83	15.90%	NHSSRC 2020/21; EY51Z
MUGA	438.39	7.90%	NHSSRC 2020/21; RN22Z
MRI	212.41	4.00%	NHSSRC 2020/21; RD01A
PET-CT	775.76	1.70%	NHSSRC 2020/21;RN01A
Bone marrow biopsy	928.96	13.60%	NHSSRC 2020/21; RD01A; SA33Z; DC

Total one-off progression costs	% of patients	Used cost (£)
	100	**211.57**

B.3.5.6 Adverse reaction unit costs and resource use

The costs of AEs during the time on treatment were calculated based on the average number of treatment-related AEs per patient per week in the relevant trial (Section B.3.3.5) and the unit cost of these AEs (Table 58). The only exception to this is for CAR-T cell therapies, where the main AEs tend to occur in the first 2–3 weeks after infusion. As the NHS England delivery of CAR-T tariff covers adverse events up to day 28 after infusion (see Section B.3.5.3.1), to avoid double counting of AE costs for axicabtagene ciloleucel, additional AE costs were not separately modelled. For glofitamab and the remaining comparators, costs were assumed in line with relevant recent technology appraisals and costed using the most recent reference costs.

As noted in Section B.3.4.5, only treatment-related AEs with a severity grade of 3 and higher were costed in the model. Furthermore, any AEs related to axi-cel were not costed.

Table 58: Costs of AEs included in the model

Grade 3–5 AEs	Mean cost (£)	Source(s)
Acute kidney injury	524.49	Weighted average of LA07M-P; DC
Anemia	409.10	Weighted average of SA01G-K, SA03G-H, SA04G-L, SA05G-J; DC
CRS	12,049.15	Table 59
Diarrhoea	576.27	Weighted average of FD10J-M; DC
Hypophosphatemia	462.58	Weighted average of KC05G-N; DC
Febrile neutropenia	2,153.89	TA306 (£1,627) ; inflated to 2022 using PRRSU
Leukopenia	366.66	Weighted average of SA35A-E; DC
Lymphopenia	557.42	Weighted average of SA08G-J; DC
Lymphocyte count decreased	557.42	Weighted average of SA08G-J; DC
Neutrophil count decreased	366.66	Weighted average of SA35A-SA35E; DC
Neutropenia	366.66	Weighted average of SA35A-SA35E; DC

Pneumonia	782.27	Weighted average of DZ11K-V; NES
Platelet count decreased	414.46	Weighted average of SA12G-SA12K; DC
Septic shock	1,978.27	Weighted average of WJ06A-F, NES
Thrombocytopenia	414.46	Weighted average of SA12G-SA12K; DC
Vomiting	632.98	Weighted average FD10D-M, DC
White blood cell count decreased	366.66	Weighted average of SA35A-SA35E; DC

See reference (207) for NHS Reference costs 2020/2021.

The costing of cytokine release syndrome (CRS) management was based on the approach used in NP30179, with the most significant cost components considered. It was assumed everyone experiencing CRS as a treatment-related AE with a severity grade of 3 or higher would require 2 doses of tocilizumab. Tocilizumab administration costs are assumed to consist of pharmacist time and rheumatologist time (see Table 59). In line with what was accepted in TA559, it is also assumed that these patients would require 4 days of intensive care unit (ICU) hospitilisation (see Table 59) (136). While corticosteroids (methylprednisolone and dexamethasone) are used in the management of CRS, given the relative cost of these compared to other cost components, including these costs in the calculation had a negligible impact, and were therefore excluded for simplicity.

AE costs for axicabtagene ciloleucel, including CRS, are assumed to be captured in the NHS CAR-T tariff. Therefore, to avoid double counting, CRS related AE costs do not apply separately for axicabtagene ciloleucel.

Table 59: CRS AE management

Cost component	Cost per unit	Unit	Total cost	Source
Tocilizumab	£767.49	2	£1,534.98	74.95kg (average weight from trial); £1.28/mg for the IV (BNF); Tocilizumab 8 mg/kg intravenously (not to exceed 800 mg), as administered in Study NP30179
Pharmacist time	£31.20	2	£62.40	Cost of preparation taken from TA812; tocilizumab infusion time is 1 hour

Rheumatology	£230.27	2	£460.54	NHSSRC 2020/21; WF02A; Multiprofessional Non-Admitted Face-to-Face Attendance, Follow-up
Intensive care unit (ICU) hospitalisation	£2,497.81	4	£9,991.24	NHSSRC 2020/21;weighted average of HRGs for non-specific, general adult critical care
Total cost			**£12,049.15**	

The probability of events was combined with the cost of each AE in each treatment arm (see Table 40). These costs were then applied in the model to the proportion who remain on treatment in each cycle.

Table 60: Adverse event costs per cycle

Drug regimen	Cost per model cycle (weekly) (£)
Glofitamab	39.73
Axicabtagene ciloleucel	0.00 (AEs to day 28 captured in NHS CAR-T Tariff – see B.3.5.3.1)
Rituximab and bendamustine	111.06
Polatuzumab-vedotin with rituximab and bendamustine	65.36

B.3.5.7 Miscellaneous unit costs and resource use

No additional costs were considered in this analysis.

B.3.6 Severity

In line with the NICE Methods Manual, an adjustment to the value of a QALY can apply where there is a shortfall in QALYs for people living with a condition, compared with a person without the condition, over the remaining lifetime of the patients.

Baseline characteristics from the glofitamab trial were used to inform the expected total discounted QALYs for the general population (Total QALYs for people living with 3L+ DLBCL, under current treatments, were informed by the discounted QALYs from the glofitamab cost-effectiveness model Consistent with previous appraisals, the base case assumes a therapy area specific long-term remission assumption: irrespective of treatment, if a patient remains progression free at 2 years, no further progression is assumed and utility reverts to near general population utility; and at 3.5 years, mortality risk reverts to a near general population level (see Section B.3.3.2.5 Long-term remission/survivorship). However, upon publication of more

recent data for some comparators, this assumption can be considered more uncertain, with progression being observed beyond the 2 year time point (Figure 29**: PFS Kaplan-Meier for glofitamab and pola-BR**). As a result, the total QALYs for pola-BR and BR are likely to be overestimated. To account for this, the total QALYs under current treatments were based on the model predictions when the survival is not adjusted by assuming long-term remission can occur. This resulted in a proportional QALY shortfall in the comparison vs BR and pola-BR, but not vs axicabtagene-ciloleucel (Table 62). As such, an adjustment to the value of glofitamab QALYs (x1.2) can apply for these comparisons.

Table *61*). Expected QALYs for a person free from R/R DLBCL were then calculated using the QALY shortfall calculator from McNamara et al 2022, applying the reference case HRQoL norms based on EQ-5D data from the Health Survey for England (waves 2017-2018) (216).

Total QALYs for people living with 3L+ DLBCL, under current treatments, were informed by the discounted QALYs from the glofitamab cost-effectiveness model Consistent with previous appraisals, the base case assumes a therapy area specific long-term remission assumption: irrespective of treatment, if a patient remains progression free at 2 years, no further progression is assumed and utility reverts to near general population utility; and at 3.5 years, mortality risk reverts to a near general population level (see Section B.3.3.2.5 Long-term remission/survivorship). However, upon publication of more recent data for some comparators, this assumption can be considered more uncertain, with progression being observed beyond the 2 year time point (Figure 29**: PFS Kaplan-Meier for glofitamab and pola-BR**). As a result, the total QALYs for pola-BR and BR are likely to be overestimated. To account for this, the total QALYs under current treatments were based on the model predictions when the survival is not adjusted by assuming long-term remission can occur. This resulted in a proportional QALY shortfall in the comparison vs BR and pola-BR, but not vs axicabtagene-ciloleucel (Table 62). As such, an adjustment to the value of glofitamab QALYs (x1.2) can apply for these comparisons.

Table 61: Baseline characteristics informing general population QALYs

Factor	Value (reference to appropriate table or figure in submission)	Reference to section in submission
Proportion males	64.9%	Section B.2.3.2 Patient demographics and baseline characteristics
Starting age	63.19	Section B.2.6 Clinical effectiveness results of the relevant studies

Table 62: QALY shortfall analysis

Expected total QALYs for the general population	Assumed current treatment	Total QALYs expected for people living with the condition, under current treatment	Absolute QALY shortfall	Proportional QALY shortfall
11.62	Axi-cel	5.03	6.59	56.71%
	BR	0.90	10.72	92.25%
	Pola-BR	1.44	10.18	87.61%

B.3.7 Uncertainty

Due to data sparsity and immaturity, there is some uncertainty regarding the efficacy estimates included within the economic model. Data sparsity and immaturity are common obstacles in indications where there are small patient numbers and this situation highlights the requirement for treatments that provide alternative options for patients.

The NP30179 phase 1/2 trial is a single arm trial with no comparator arm, which means that data from population-adjusted ITCs had to be used to assess the cost-effectiveness of glofitamab versus the comparators of interest. The extent to which such data can be considered reliable for head-to-head comparisons depends on the quality of the respective studies, how comparable these were to NP30179 and how well the adjustment procedures used (MAIC or IPTW) were able to resolve differences in prognostic factors and effect modifiers. Notably, some of the ITC results used to inform the parametric extrapolations for glofitamab displayed residual bias in favour of axicabtagene-ciloleucel, and potentially rituximab and

bendamustine. Consequently, cost-effectiveness results versus these comparators are likely biased against glofitamab.

EQ-5D data was not collected in the NP30179 study. Therefore, the CEM base case uses utilities estimated through EORTC-QLQ-C30 to EQ5D-3L mapping (as per NICE recommendations) (156), with utility values used in previous NICE submissions in R/R DLBCL available for use in sensitivity analyses. While in line with NICE recommendations, utility mapping is known to be associated with increased uncertainty.

Long-term remission/survivorship was deemed clinically plausible for R/R DLBCL in previous 2L+ and 3L+ DLBCL NICE submissions (TA649, TA559, TA567), irrespective of the technology being assessed (136-138). There remains uncertainty around what constitutes the threshold after which patients with durable remissions can be considered as long-term survivors. Given the impact of potential excess comorbidities in this population, the actual HRQoL and mortality risk in these patients compared to the general population is also uncertain.

B.3.8 Managed access proposal

A managed access proposal is being considered by Roche. If pursued, a proposal for further data collection in the framework of the Cancer Drugs Fund will be provided.

B.3.9 Summary of base-case analysis inputs and assumptions

B.3.9.1 Summary of base-case analysis inputs

A summary of all values, and their respective distributions applied, used in the base case analysis is presented in Table 63.

Table 63: Summary of variables applied in the economic model

Variable	Value (reference to appropriate table or figure in submission)	Measurement of uncertainty and distribution: confidence interval (distribution)	Reference to section in submission
Baseline parameters			
Baseline parameters	Table 9	None	B.2.3.2
Survival and progression functions			
PFS -	Table 32	Distributi	B.3.3.

glofit		on specific	2.1
OS - glofit	Table 32	Distribution specific	B.3.3.2.1
PFS - axi - cel	xxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxx xxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxx xxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxx xxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxx xxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxx xxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxx xxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxx Table ***33***	Distribution specific	B.3.3.2.2.1
OS - axi - cel	xxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxx xxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxx xxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxx xxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxx xxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxx xxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxx xxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxx Table ***34***	Distribution specific	B.3.3.2.2.2
PFS - BR	xxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxx xxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxx xxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxx xxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxx xxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxx xxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxx xxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxx Table ***35***	Distribution specific	B.3.3.2.3.1
OS - BR	xxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxx xxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxx xxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxx xxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxx xxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxx xxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxx xxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxx Table ***36***	Distribution specific	B.3.3.2.3.2
PFS - pola-BR	xxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxx xxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxx xxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxx xxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxx xxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxx xxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxx xxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxx	Distribution specific	B.3.3.2.4.1

	Table ***37***		
OS-pola-BR	Table 38	Distribution specific	B.3.3.2.4.2
All-cause mortality	None	None	B.3.3.3
TTOT	Table 39	Distribution specific for glofitamab. Fixed or related to PFS for comparators.	B.3.3.4
Clinical parameters			
Adverse event rates	Table 40**: Adverse events considered in the modelError! Reference source not found.**	Normal	B.3.3.5
Utility values			

NP 30 17 9 utility values (base-case)	Table 41	Beta	B. 3. 4. 5
Brazier age-adjusted coefficients	Table 42	None	B. 3. 4. 3
Utility scenarios	Table 43	Beta	B. 3. 4. 5
Cost and resource use			
Glofitamab-dosing and acquisition	Table 44	None	B. 3. 5. 2. 1
Glofitamab-ad	Table 45	Generalised ga	B. 3. 5. 2. 1

ministration costs		mma	
Glofitamab-monitoring costs	Table 46	None	B.3.5.2.1
Comparators - dosing and acquisition	Table 48	None	B.3.5.3
Comparators - costs per cycle	DM+D, *dictionary of medicines and devices browser; NHSBSA, NHS Business Services Authority.* **Table *49***	None	B.3.5.3
Comparators - administration	Table 50	Generalised gamma	B.3.5.3

costs			
CAR-T administration costs	Table 51	Generalised gamma	B.3.5.3.1
Proportion assumed to take subsequent therapy	Table 53**: Proportion assumed to take each subsequent therapy by arm**	None	B.3.5.4
Post discontinuation-weekly treatment costs	Table 54	None	B.3.5.4
Post-disco	Table 55	Generalise	B.3.

ntinuation costs		d gamma	5.4
Supportive care costs - weekly	Table 56	Generalised gamma	B.3.5.5
Supportive care one-off costs	Table 57	None	B.3.5.5
Adverse event costs	Table 60	Log-normal	B.3.5.6

B.3.9.2 Assumptions

During the construction of the economic model, it was necessary to make some assumptions, both structural and related to model inputs. The assumptions underlying the economic model presented in this submission (Table 64) were tested, where possible, in the sensitivity analyses described in Section B.3.11 Exploring uncertainty.

Table 64. Summary of model assumptions

Topic	Assumption	Justification/reason

ITC	In using ITC methods, it is assumed that there is sufficient overlap between trial populations	Data sparsity is a considerable problem in indications where there are low patient numbers. The ITC was conducted in line with recommended methods and population matching was performed with as close a population as reasonable without impacting the viability of estimates, though it is acknowledged that there may be some bias against glofitamab in the presented analysis. This was considered unavoidable given the limitations of the available data.
Efficacy	Efficacy generated from the ITC represents the likely comparative estimates that will be realised in practice	Though the efficacy outputs generated by the ITC is considered to bias against glofitamab, the efficacy estimates included in the economic model are considered to be the most robust source of data available at this time.
Treatment effect	No treatment waning applied after treatment cessation.	Treatment waning was not included as the majority of patients taking glofitamab had completed their regimen within the observed period.
Utilities	Same utility values applied to all treatment arms	No evidence was available to suggest that the HRQL experienced by patients on comparator therapies would differ when compared with those taking glofitamab. Further, incidence and type of adverse events experienced are similar between arms.
Dosing	Cheapest combination of vial sizes will be administered	This assumption is in line with the reference case though it is acknowledged that in practice, it may sometimes be necessary to use more expensive options.
Vial sharing	No vial sharing is considered	This assumption was validated by clinicians who were interviewed.
Long-term remission/survivorship	Patients alive and progression free at 2 years are assumed to enter long-term remission with no further progression or costs, and revert to near general population utility. After 3.5 years, mortality risk reverts to near general population levels. Both HRQoL and mortality are adjusted to take account	Long-term remission/survivorship was deemed clinically plausible for R/R DLBCL in previous 2L+ and 3L+ DLBCL NICE submissions (TA649, TA559, TA567), irrespective of the technology being assessed (136-138).

	of expected comorbidities.	

HRQL; health-related quality of life, ITC: indirect treatment comparison.

B.3.10 Base-case results

B.3.10.1 Base-case incremental cost-effectiveness analysis results

Table 65 presents the base case cost-effectiveness results for glofitamab with the proposed PAS discount (see Section B.3.5.2.2). Glofitamab is shown to be cost-effective at a £20,000 threshold versus all comparators. Glofitamab is shown to be dominant, more effective and less costly, compared to pola-BR (list price), and is shown to be cost-effective compared to BR (list price). When compared to axi-cel (list price), while associated with a loss of QALYs, due to the magnitude of the incremental cost savings, glofitamab is shown to be cost-effective. While associated with a QALY loss vs axi-cel, the magnitude of these losses is expected to be overestimated due to presence of residual bias in the ITC from comparing to the ZUMA-1 mITT population, which excludes a significant proportion of progressed patients (see Section B.2.9.2.1.1 Populations and baseline characteristics).

In the comparisons vs BR and pola-BR, a modifier of 1.2 has been applied to the estimated QALY gains for glofitamab (see Section B.3.6).

Table 65: Deterministic base-case cost-effectiveness results (glofitamab PAS price, comparator list price)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)	NMB at 30k
Glofit vs BR								
Glofit	[redacted]	[redacted]	[redacted]					
BR	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Glofit vs pola-BR								
Glofit	[redacted]	[redacted]	[redacted]					
Pola-BR	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Glofit vs axi-cel								
Glofit	[redacted]	[redacted]	[redacted]					
Axi-cel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

**1.2 QALY modifier applied. ICER, incremental cost-effectiveness ratio; LYG, life years gained; NMB, net monetary benefit; QALYs, quality-adjusted life years.*

B.3.11 Exploring uncertainty

B.3.11.1 Probabilistic sensitivity analysis

Probabilistic sensitivity analysis (PSA) was performed for 1,000 iterations. In each iteration, the model inputs were randomly drawn from the specific distributions, summarised in Table 63.

The median probabilistic incremental costs and QALYs gained from glofitamab with the PAS discount considered for 1,000 iterations are given in Table 66. The pairwise cost-effectiveness acceptability curves are presented in Figure 35. Assuming a WTP threshold of £30,000 per QALY gained, the probability of glofitamab being the most cost-effective treatment or dominant treatment option was

[redacted] The incremental results of each iteration in the PSA are displayed in Figure 36. The results from the probabilistic analysis are in line with those of the deterministic analysis in terms of the estimated QALY and LY gains and the estimated incremental costs. This demonstrates that the deterministic base case results are robust as they are likely to represent the average experience per person treated with glofitamab.

Table 66: Probabilistic base-case cost-effectiveness results (glofitamab PAS price, comparator list price)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)	NMB at 30k
Glofit vs BR								
Glofit	[redacted]	[redacted]	[redacted]					
BR	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Glofit vs pola-BR								
Glofit	[redacted]	[redacted]	[redacted]					
Pola-BR	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Glofit vs axi-cel								
Glofit	[redacted]	[redacted]	[redacted]					
Axi-cel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

**1.2 QALY modifier applied. ICER, incremental cost-effectiveness ratio; LYG, life years gained; NMB, net monetary benefit; QALYs, quality-adjusted life years.*

Figure 35: Cost-effectiveness acceptability curve (glofitamab PAS price, comparator list price)

Figure 36: Incremental cost-effectiveness plane (glofitamab PAS price, comparator list price)

B.3.11.2 Deterministic sensitivity analysis

Figure 37 to Figure 39 present the ten most influential parameters on cost-effectiveness with descending sensitivity when glofitamab is compared to BR, pola-BR and axi-cel, respectively.

The parameter that had the largest impact on the results for glofitamab vs BR and vs pola-BR, was the time point at which the PFS and OS long-term remission assumptions were applied. This is expected to be a key driver of results given how influential it is on the QALY calculations. Similarly, the results in all comparisons are shown to be sensitive to the time point at which progression free patients were assumed to be in long-term remission. In the comparison of glofitamab vs axi-cel, axi-cel acquisition cost was the key driver of results. This was an expected result given that incremental costs, largely driven by axi-cel acquisition cost, was a key driver of cost-effectiveness in this comparison. Other important parameters were the cost of glofitamab after the loading doses and to a lesser extent, post progression costs.

Figure 37: Tornado diagram showing OWSA results on NMB – Glofit vs BR (glofitamab PAS price, comparator list price)

Figure 38: Tornado diagram showing OWSA results on NMB – Glofit vs pola-BR (glofitamab PAS price, comparator list price)

Figure 39: Tornado diagram showing OWSA results on NMB – Glofit vs axi-cel

Summary of sensitivity analyses results

Sensitivity analysis is of particular importance where data is sparse and there is potential for the decision to be subject to uncertainty. The deterministic sensitivity analysis determines which parameters exert the most influence over these findings. These show that assumptions relating to long-term remission are influential in the results. This was expected in the case of the of PFS and OS cure point, as setting these too early leads to inflated QALY gains by disregarding observed progression, or unrealistically assuming patients with progressed disease have a length of life similar to the general population. This highlights the importance of adjusting the PFS and OS remission points to clinically plausible time-points, as was applied in the base-case. Treatment cost and subsequent treatment cost are also shown to be influential, particularly in the comparison of glofitamab vs axi-cel. Though there is some challenge with limited data in indications with small populations, the probabilistic sensitivity analysis estimates that the deterministic results are likely to be reliable and demonstrates that glofitamab offers a cost-effective alternative to all of the comparators considered.

B.3.11.3 Scenario analysis

Scenarios using alternative utility data sets, different costs, and survival analysis approaches were explored as described below, with the results summarised in Table 67.

To avoid challenges with interpretation, NMB applying a WTP threshold of 30K per QALY gained, is reported in Table 67. A positive % change in NMB suggests improved cost-effectiveness, and vice versa. Reporting NMB was preferred as many scenarios in the comparison of glofitamab vs pola-BR led to negative ICERs (glofit dominant) limiting the possibility to interpret the impact of the scenario on cost-effectiveness. Similarly in the comparison of glofitamab vs axi-cel, the majority of ICERs reported are SW quadrant/cost saved per QALY lost, again leading to interpretational challenges. For completeness, ICERs for each scenario are also reported in Table 68. Given the aforementioned challenges, the results of the scenario analysis in Table 68 should be interpreted with caution.

Table 67: Scenario analysis results (NMB) (glofitamab PAS price, comparator list price)

Parameter modifier	NMB vs BR (£)	% change from base-case	NMB vs pola-BR (£)	% change from base-case	NMB vs axi-cel (£)	% change from base-case
Base case	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Model time horizon						
Time horizon, 30 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Time horizon, 40 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Time horizon, 50 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Patient baseline characteristics						

Average cohort age background mortality (35 year time horizon)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Utilities						
EORTC-QLQ-C30 Mapping (Direct)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TA306 (FAD values)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TA559	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Costs						
Axi-cel admin cost (EAG derived [£41,101])	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Axi-cel admin cost (135% pre-infusion cost multiplier applied [£71,083])	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Survival modelling						
Proportional hazards assumed	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Midpoint HR (OS, PFS) between 1 and ITC estimate: glofit vs axi-cel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
No long-term remission (PFS cure point)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
No long-term remission (OS cure point)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
No PFS cure point for BR and Pola-BR	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
No QoL adjustment in LTR	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
No excess mortality in LTR	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Discounting						
1.5% discounting for costs and effects	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Table 68: Scenario analysis results (ICER)

Parameter modifier	ICER vs BR (£)	% change from base-case	ICER vs pola-BR (£)	% change from base-case	ICER vs axi-cel (£)	% change from base-case
Base case	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Model time horizon						
Time horizon, 30 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Time horizon, 40 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Time horizon, 50 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Patient baseline characteristics						
Average cohort age background mortality (35 year time horizon)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Utilities						
EORTC-QLQ-C30 Mapping (Direct)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TA306 (FAD values)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TA559	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Costs						
Axi-cel admin cost (EAG derived [£41,101])	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Axi-cel admin cost (135% pre-infusion cost multiplier applied [£71,083])	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Survival modelling						
Proportional hazards assumed	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Midpoint HR (OS, PFS) between 1 and ITC estimate: glofit vs axi-cel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

No long-term remission (PFS cure point)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
No long-term remission (OS cure point)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
No PFS cure point for BR and Pola-BR	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
No QoL adjustment in LTR	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
No excess mortality in LTR	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Discounting						
1.5% discounting for costs and effects	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

B.3.11.3.1 Confidential discounts for comparators

Where it is known that confidential discounts are in place for comparators, the NICE user manual for the submission template recommends presenting scenarios with a range of potential discounts to aid decision making. ICER ranges have been presented in the comparisons of BR and axi-cel with varying levels of discount applied to the assumed list price. As noted in Section B.3.11.3, due to interpretational issues of the ICERs in the comparison vs axi-cel, NMB is also reported in Table 69 with a WTP threshold of £30k per QALY gained assumed. In the comparison of glofitmab vs BR and glofitamab vs pola-BR, a modifier of 1.2 is applied to the glofitamab QALY gains, and is therefore reflected in the ICER and NMB estimates in this comparison.

[redacted]

Table 69: Comparator discount level threshold analysis

Comparator discount applied	ICER vs BR (£)	NMB vs BR (£)	ICER vs axi-cel (£)	NMB vs axi-cel (£)
Base case (0%)	[redacted]	[redacted]	[redacted]	[redacted]
10%	[redacted]	[redacted]	[redacted]	[redacted]
20%	[redacted]	[redacted]	[redacted]	[redacted]
30%	[redacted]	[redacted]	[redacted]	[redacted]
40%	[redacted]	[redacted]	[redacted]	[redacted]
50%	[redacted]	[redacted]	[redacted]	[redacted]
60%	[redacted]	[redacted]	[redacted]	[redacted]
70%	[redacted]	[redacted]	[redacted]	[redacted]
80%	[redacted]	[redacted]	[redacted]	[redacted]
90%	[redacted]	[redacted]	[redacted]	[redacted]
100%	[redacted]	[redacted]	[redacted]	[redacted]

In the comparison of pola-BR, as polatuzumab vedotin is owned by Roche, and the agreed discount is known, a scenario where the confidential discount is applied is shown in Table 70. Given the level of confidential discount which could apply for bendamustine and/or rituximab, is unknown, Table 70 presents the results where the list price of these treatments are assumed with PAS prices applied for polatuzumab vedotin, glofitamab, and obinutuzumab.

Table 70: Base-case results with comparator discount applied (Glofit PAS price, Pola PAS price, BR list price)

Treatment	Costs	QALYs	Incremental costs (£)	Incremental QALYS	ICER vs pola-BR (£)	NMB vs pola-BR (£)
Glofitamab	[redacted]	[redacted]				
Pola-BR	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

B.3.12 Subgroup analysis

No subgroup analysis has been conducted for this decision problem.

B.3.13 Benefits not captured in the QALY calculation

Clinical advice to the company was that there is no accepted standard of care for 3L+ DLBCL treatment and that clinical practice in England can vary. Patients with DLBCL who are heavily pre-treated and often refractory to multiple available therapies represent a population in which there is a substantial unmet need for novel therapeutic treatment options. While axi-cel, and other CAR-T therapies are an option for some of this population, a significant proportion of those deemed eligible for treatment do not go on to receive it.

Despite new treatment options, patients with DLBCL who have failed two or more prior lines of systemic therapy continue to have a poor prognosis, and therefore there is an urgent need for innovative treatment options that offer effective, durable remissions and are readily available.

Glofitamab is a first-in-class ready to use CD20xCD3 T-cell engaging bispecific antibody, with a unique 2:1 binding format designed to deliver potent antitumor efficacy, in a fixed duration treatment regimen. In patients with 3L+ DLBCL, glofitamab monotherapy offers early and durable CRs, that remain durable even

after treatment with glofitamab is completed, with a manageable safety profile. As a partitioned survival model was used for the economic analysis of glofitamab and the relevant comparators, observed benefits linked to response are not likely to be accounted for in the QALY calculation, as PFS and OS drive the results.

When compared with the other treatments available for the treatment of patients with R/R DLBCL after two or more prior lines of systemic therapy, glofitamab tends to show superiority against pola-BR and BR, in all of the outcomes assessed. While axi-cel, and other CAR-T therapies are an option for some of this population, a significant proportion of those deemed eligible for treatment do not go on to receive it (i.e. an analysis of UK real world practice found 26% did not reach infusion) (86). For those who progress before CAR-T infusion, outcomes are poor and further treatment option are limited. As a result, estimates of relative efficacy and cost-effectiveness vs axi-cel, where these patients are excluded, are biased against glofitamab, and should be deliberated with caution. Overall, glofitamab can offer a suitable clinical and more affordable alternative to CAR T-cell therapies and novel combinations for patients with 3L+ DLBCL. Further to this, glofitamab has the potential to be more accessible by a larger range of clinical centres than CAR-T-cell therapies (axicabtagene ciloleucel), helping reduce regional, rural-urban, and sociodemographic inequity issues resulting from uneven geographical allocation of CAR-T-cell therapy administration sites. Glofitamab's potential to address these inequalities is not expected to be captured in this analysis, but should be given careful consideration.

While all aforementioned benefits of glofitamab may not be fully captured in the QALY calculations, from an economic perspective, glofitamab can be considered the most favourable treatment options, being dominant or cost-effective when compared with the relevant options available.

B.3.14 Validation

B.3.14.1 Validation of cost-effectiveness analysis

The model methodology was designed to align with NICE's preferred methods. As described in Section B.3.2.3, an AUC (or partitioned survival analysis) structure was selected for the analysis based on guidance provided in TSD 19 (142) and the precedents of committee acceptance in recent technology appraisals in DLBCL (136-138). The model was built to align with the NICE reference case, adopting an NHS and PSS perspective, a lifetime time horizon to fully capture all costs and QALY gains associated with the interventions, and discount rates for costs and benefits of 3.5% (113). Finally, health state utilities were based on those collected in NP30179, a trial including patients representative of the decision problem, which when mapped to EQ-5D-3L following recommended methods, were shown to be consistent with previously accepted values.

The model was subject to an external quality assurance procedure, which included technical validation of key model inputs and calculations. Any issues or errors were documented and addressed in the final version of the models.

Clinical expert opinion was sourced during model development to inform model assumptions, to ensure they were clinically valid and/or aligned with UK clinical practice for 3L+ R/R DLBCL. Specifically, an advisory board of eight UK clinicians was held in January 2023 to discuss the natural history of 3L+ R/R DLBCL and standard clinical practice in the UK, in order to inform the model (1).

B.3.15 Interpretation and conclusions of economic evidence

The patient population included in the analysis reflects the NP30179 trial and those of the comparator studies and is aligned with the population specified in the NICE final scope.

The choice of comparators was informed by the NICE scope, and following consultation with clinical experts, was refined to the treatments options most commonly used in clinical practice for the treatment of 3L+ DLBCL. The relevant comparators, and those presented in this analysis include R-based chemotherapy, pola-BR and CAR-T (axi-cel) (see Section **Error! Reference source not found.**). In

the absence of suitable data to inform a comparison against R-GemOx, a regimen commonly used for 3L+ DLBCL, BR was deemed a suitable proxy for R-chemotherapy, an approach validated as reasonable by clinical experts (see Section **Error! Reference source not found.**).

As such, a *de novo* economic analysis was conducted to evaluate the cost-effectiveness of glofitamab vs BR, pola-BR and axi-cel for the treatment of 3L+ R/R DLBCL patients in the UK.

However, while a comparison to pola-BR has been put forward given its current usage in the 3L+ setting, its relevance as a treatment option at 3L+, and therefore its applicability as an appropriate comparator, is expected to reduce quickly ([redacted]) following the recent recommendation for polatuzumab vedotin use in untreated DLBCL (59).

Where ITC populations were not completely aligned, population inclusion criteria were expanded conservatively so that the comparator estimates were not biased towards glofitamab. Estimates from the model have been extensively validated; the outcomes were shown and discussed with clinical experts at an advisory board meeting, with experts accepting of the key model inputs and predictions.

Based on the analysis of the economic evidence presented, treatment with glofitamab is expected to be associated with comparable or greater QALY gains while being cost saving or not substantially increasing costs compared to BR and pola-BR. Compared to axi-cel, glofitamab is expected to produce lower QALY gains while being substantially cost saving to the point where axi-cel would not be likely to be considered a cost-effective option unless a discount to the acquisition cost of axi-cel of more than [redacted] applies.

The model results were generally robust across scenario and sensitivity analyses tested. However, there are some areas of uncertainty with respect to a few parameter inputs and key modelling assumptions, with the most notable being the limited NP30179 follow up, uncertainty around long-term remissions/survivorship, and residual bias from the ITCs in favour of some comparators. With this in mind, the cost-effectiveness estimates can be considered conservative against glofitamab,

particularly in the comparison vs axi-cel, where a significant proportion of progressed patients were excluded from the axi-cel mITT cohort used in the analysis. In the absence of data which better represents the true effects of axi-cel in the patients covered by the decision problem, a deliberative and cautious approach should be taken when considering the cost-effectiveness results in this comparison.

Despite recently recommended new treatment options becoming available, patients with DLBCL who have failed two or more lines of therapy continue to have a poor prognosis; therefore, there is an urgent need for innovative treatment options that offer effective, durable remissions and are ready to use without delay. As such, glofitamab would be a welcome treatment option to the clinical and patient community, and offers a suitable clinical alternative to BR, pola-BR and axi-cel for patients with 3L+ DLBCL.

Overall, the findings of the economic analysis indicate that glofitamab can be considered one of the most favourable treatment options from both an economic and efficacy standpoint for patients with 3L+ DBLCL, particularly for those who have limited alternatives left available to them. Therefore, based on the available evidence, glofitamab should be recommended as an option for the treatment of 3L+ DLBCL.

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Glofitamab for treating relapsed or refractory diffuse large B-cell lymphoma after 2 or more systemic treatments [ID3970]

Summary of Information for Patients (SIP)

May 2023

File name	Version	Contains confidential information	Date
ID3970_Glofit_DLBCL_SIP_[Redacted]_ RPL030523	2.0	Yes	03 May 2023

Summary of Information for Patients (SIP):

The pharmaceutical company perspective

What is the SIP?

The Summary of Information for Patients (SIP) is written by the company who is seeking approval from NICE for their treatment to be sold to the NHS for use in England. It is a plain English summary of their submission written for patients participating in the evaluation. It is not independently checked, although members of the public involvement team at NICE will have read it to double-check for marketing and promotional content before it is sent to you.

The **Summary of Information for Patients** template has been adapted for use at NICE from the Health Technology Assessment International – Patient & Citizens Involvement Group (HTAi PCIG). Information about the development is available in an open-access IJTAHC journal article.

SECTION 1: Submission summary

1a) Name of the medicine (generic and brand name):

Active ingredient: Glofitamab **Brand name:** To be confirmed

1b) Population this treatment will be used by. Please outline the main patient population that is being appraised by NICE:

Adults with relapsed or refractory diffuse large B-cell lymphoma after 2 or more systemic treatments.

1c) Authorisation: Please provide marketing authorisation information, date of approval and link to the regulatory agency approval. If the marketing authorisation is pending, please state this, and reference the section of the company submission with the anticipated dates for approval.

Authorisation (licence) On 10th October 2022, a Promising Innovative Medicine (PIM) Designation was granted and an Early Access To Medicines Scheme (EAMS) dossier was submitted to the Medicines and Healthcare products Regulatory Agency (MHRA). A marketing authorisation (MA) is pending and is expected in [redacted].

1d) Disclosures. Please be transparent about any existing collaborations (or broader conflicts of interest) between the pharmaceutical company and patient groups relevant to the medicine. Please outline the reason and purpose for the engagement/activity and any financial support provided:

In 2022, Roche provided the following support to UK-based patient groups that are relevant to glofitamab/treatment of B cell lymphoma. These included providing funds for the purpose of supporting patients, healthcare, scientific research or education that is independent and free from Roche influence, where Roche did not receive any direct benefit or gains. These included:

- A £50,000 grant to **Maggie's Cancer Centres** to support their creation of a suite of videos for eight of their centres, to be used during 'Getting Started with Treatment' sessions;
- A £25,000 grant to **Lymphoma Action** to further develop and deliver their clinical trials information service, education programmes, focus day and patient workshops;
- A £25,000 grant to **Blood Cancer UK** to support their online Health Transformation Project;
- A £15,000 grant to **Blood Cancer Alliance** for to support their campaigning for increased recognition of blood cancer amongst policy makers;
- A £1,000 sponsorship to **Lymphoma Action** to support their Lymphoma Management Webinar educational series.

SECTION 2: Current landscape

2a) The condition – clinical presentation and impact

Please provide a few sentences to describe the condition that is being assessed by NICE and the number of people who are currently living with this condition in England.

Please outline in general terms how the condition affects the quality of life of patients and their families/caregivers. Please highlight any mortality/morbidity data relating to the condition if available. If the company is making a case for the impact of the treatment on carers this should be clearly stated and explained.

Main condition that the medicine plans to treat

Diffuse large B-cell lymphoma (DLBCL) is a fast-growing form of non-Hodgkin lymphoma (NHL), which is a cancer that affects white blood cells called B-lymphocytes. These lymphocytes are a type of white blood cell that normally help to fight infections. DLBCL patients have abnormal B-lymphocytes that build up in lymph nodes or other body organs.

Glofitamab is a cancer treatment that is intended for adult patients with DLBCL that has come back (relapsed) or did not get better (refractory) following initial treatment (also called relapsed/refractory [R/R] DLBCL), after 2 or more systemic cancer treatments that target the entire body.

Main symptoms of disease

The main symptom of DLBCL is swollen glands (lymph nodes), most commonly in the head, neck, armpit or groin. Depending on where the swollen lymph nodes are located,

patients may also notice symptoms such as pain in the chest, abdomen, or bone, skin lumps, coughing or breathlessness.

In addition, patients might also experience some of the following symptoms, known as 'B-symptoms', such as fever (higher than 38ºC), recurrent night sweats, or unexplained weight loss.

How many people have the condition

In the UK, around 4,850 people are diagnosed with DLBCL each year (1). Out of every million people, around 380 people will develop DLBCL, and around 25,000 cases are estimated within a 10-year period (2). People are more likely to develop DLBCL when they get older, and the disease occurs more commonly in those who are over 60 years of age. In the UK, the average age at diagnosis for DLBCL patients is 70 years (3). Men are slightly more likely to develop DLBCL than women.

Burden of disease

Most patients with DLBCL are diagnosed in the advanced stages of the disease and have features that suggest a poor chance of recovery (prognosis). Around 60% of patients with DLBCL will get better with an initial (first-line, or 1L) combination treatment of chemotherapy given with antibody therapy (chemo-immunotherapy). However, the treatment of DLBCL can be really hard on the body as it causes symptoms like fever, fatigue, and swollen lymph nodes. It can also affect the bone marrow, which could lead to infections, and low red blood cell (anaemia) and platelet count (thrombocytopenia).

Relapsing or being refractory to 1L treatment is a major cause of sickness and, in some cases, death in patients with DLBCL. Most relapses happen within 24 months of starting treatment (4, 5), and patients who experience a relapse or do not respond to initial treatment have a poorer prognosis (6-8). Patients who require multiple rounds of therapy after 1L treatment are more likely to experience disease progression and side effects of treatments (9). The options for treating relapsed or refractory DLBCL are limited and may not be effective for some patients.

Emotional effects

When someone has DLBCL, they may experience symptoms and side effects from the treatment that can impact their quality of life. DLBCL patients may experience increased anxiety and depression than the general population, and younger patients tend to feel more anxious while older patients tend to feel more depressed (10). Younger DLBCL survivors tend to have worse quality of life than older survivors (11), and men may be more affected than women. Women may have more positive changes and self-improvement after being diagnosed with DLBCL, but they may also have worse physical functioning than men (12). Patients with other health problems in addition to DLBCL may experience increased fatigue, emotional impact, depression, and reduced physical and mental health compared to those without other health problems (12).

2b) Diagnosis of the condition (in relation to the medicine being evaluated)

Please briefly explain how the condition is currently diagnosed and how this impacts patients. Are there any additional diagnostic tests required with the new treatment?

How DLBCL is diagnosed

DLBCL is diagnosed by taking a sample of an affected lymph node or tissue through a surgical biopsy. The sample is then analysed under a microscope and tested to determine the specific type of lymphoma. This is done by looking at the cells and their characteristics and genetic features. To confirm the diagnosis of DLBCL, additional tests such as antibody-testing (immunohistochemistry) or cell analysis (flow cytometry) are performed. In cases where the diagnosis is uncertain, additional testing may be done to look for signs of cancer using DNA testing (polymerase chain reaction, PCR) methods (13).

Staging of DLBCL

Staging is an important process for patients diagnosed with DLBCL to determine the best treatment option and make a prognosis. DLBCL is classified into one of four stages based on the Ann Arbor or Lugano Staging Classification systems (13-15). The Ann Arbor system looks at the spread of affected sites, the number of lymph nodes involved, involvement outside of lymph nodes, and presence of 'B-symptoms'. The Lugano classification, recommended by experts, suggests using a PET-CT scan as the best way to determine the staging for patients with DLBCL (14, 16).

2c) Current treatment options:

The purpose of this section is to set the scene on how the condition is currently managed:

- What is the treatment pathway for this condition and where in this pathway the medicine is likely to be used? Please use diagrams to accompany text where possible. Please give emphasis to the specific setting and condition being considered by NICE in this review. For example, by referencing current treatment guidelines. It may be relevant to show the treatments people may have before and after the treatment under consideration in this SIP.
- Please also consider:
    - If there are multiple treatment options, and data suggest that some are more commonly used than others in the setting and condition being considered in this SIP, please report these data.
    - Are there any drug–drug interactions and/or contraindications that commonly cause challenges for patient populations? If so, please explain what these are.

What treatment are currently used, how they work and their side effects

Around 80% of DLBCL patients receive 1L treatment and most are treated with a chemo-immunotherapy called R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone). Around 60% of patients have reduced cancer symptoms after receiving R-CHOP (4, 17).

Recently, another treatment, called pola-R-CHP, was approved as an alternative 1L treatment for DLBCL. Pola-R-CHP is similar to R-CHOP, but the vincristine chemotherapy ('O' in R-CHOP) is replaced with polatuzumab vedotin, an antibody joined to a strong anticancer drug (antibody-drug conjugate). This is expected to increase the long term remission rate after 1L treatment in the coming years (20). However, a substantial

proportion of patients either do not respond to 1L treatment, experience a relapse, or experience treatment-related complications and require further treatment for relapsing DLBCL (4, 17).

The Haematological Malignancy Research Network (HMRN) database in the UK shows that approximately 31% of DLBCL patients receive subsequent (second-line, or 2L) treatment; and of those, about 18% receive further (third-line, or 3L) treatment.

Most patients who have relapsed or refractory DLBCL will be offered more chemo-immunotherapy, aiming to reduce the active cancer as much as possible. If patients are fit enough and if they respond well to 2L chemo-immunotherapy, they may be offered a stem cell transplant (autologous stem-cell transplantation, ASCT), a medical procedure where some of the patient's stem cells are collected from their own bone marrow or blood and saved for later use. This treatment can increase the chance of a long-lasting remission.

When ASCT is not an option or if relapse occurs following ASCT, patients with R/R DLBCL may receive further chemo-immunotherapy as a 3rd or later line (3L+) treatment. However, many patients may have already received chemo-immunotherapy in earlier lines, making this treatment less effective. In this case, newer treatments for R/R DLBCL may be used instead. Currently, the National Institute for Health and Care Excellence (NICE) recommends several treatments for 3L+ R/R DLBCL, including:

- Rituximab-based chemotherapy
- Chimeric antigen receptor T-cell (CAR-T) therapies
- Polatuzumab vedotin in combination with bendamustine and rituximab (pola-BR)
- Pixantrone

Of these, rituximab-based chemotherapy (rituximab plus bendamustine [BR]), pola-BR, and CAR-T are considered relevant comparators for glofitamab. Therefore, glofitamab will be compared with these treatments to assess whether it can provide good value for its cost (cost-effectiveness).

Rituximab-based chemotherapy

- For DLBCL patients who cannot receive a stem cell transplant after their first treatment has failed, there are two treatment options - R-GemOx or BR. It is difficult to compare the two treatments directly because they were tested in different clinical trials. BR is not commonly used for DLBCL in the UK, but it is used to treat other types of cancer, such as such as chronic lymphocytic leukaemia (CLL). Experts think that BR works similarly to other treatments for DLBCL, and a study of real-world data showed that there is no significant difference in patient survival between BR and R-GemOx. Both treatments have similar side effects, with the most common one being neutropenia (18, 19).

CAR-T therapies

- CAR-T therapy is a type of cancer treatment where T-cells are removed from a patient, modified to fight cancer cells, and then returned to the patient (20). Two types of CAR-T therapy are approved in the UK for patients with R/R DLBCL - axicabtagene ciloleucel (brand name Yescarta®) and tisagenlecleucel (brand name Kymriah®). CAR-T therapy is expensive and has some limitations, such as long manufacturing times and issues with delivery and access. Patients in the UK must be assessed by a national panel to receive CAR-T treatment, and it takes around 8 weeks to go through this process (21). The therapy can cause side effects like cytokine release syndrome, immune system-related neurotoxicity, and prolonged blood cell deficiencies (cytopenias) (21). In the UK, around 90% of patients experienced these side effects and some required admission to the intensive care unit.

Polatuzumab vedotin in combination with bendamustine and rituximab (pola-BR)

- Polatuzumab vedotin (brand name Polivy®) is a type of cancer treatment that is used in combination with BR (pola-BR) for adult patients with R/R DLBCL who are not eligible for stem cell transplant. Pola-BR has shown satisfactory results in clinical trials, but its effectiveness was lower in patients who had received multiple prior treatments. Almost half of the patients who received pola-BR experienced neutropenia and fever with neutropenia (febrile neutropenia), and 30% had to stop treatment due to side effects. Pola-BR may be used less often in the future as a 3L+ treatment option, as a new treatment option (pola-R-CHP) is now available for patients with untreated DLBCL (22, 23).

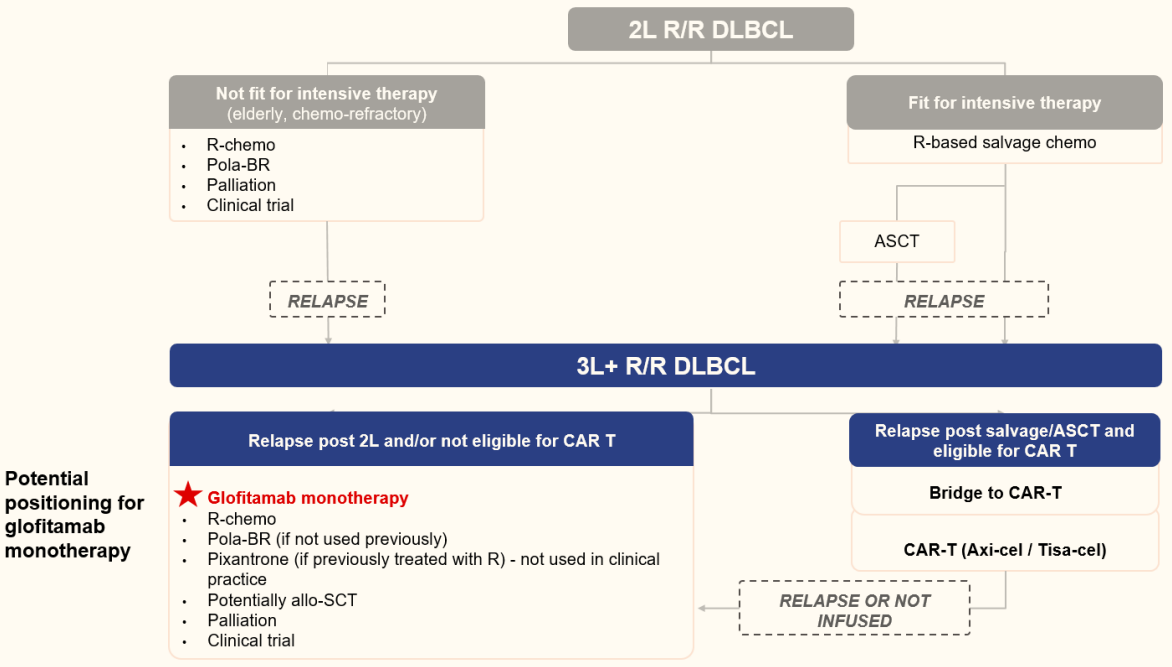
Pixantrone

- Pixantrone is a treatment that can be used to treat aggressive non-Hodgkin's lymphoma in adult patients who have not responded to other treatments. It has less risk of causing heart damage than other drugs. However, it is not commonly used in practice because it is not very effective (13, 24), so it is not being compared to glofitamab in this review.

Proposed position for glofitamab in the DLBCL treatment pathway

The proposed use of glofitamab is for the treatment of patients with R/R DLBCL who have failed at least 2 previous systemic treatments. Specially, as a 3L+ treatment line ahead of CAR-T therapy, in patients who are ineligible for CAR-T therapy, or in patients who have failed CAR-T therapy in prior treatment lines. Glofitamab is not meant to replace other treatments but to provide an additional treatment option for patients, so they may still be eligible for other treatments in the future if they relapse after glofitamab. This positioning is supported by clinical experts (23). The treatment pathway for glofitamab is summarised below (Figure 1).

Figure 1: Current treatment pathway for 2L and 3L+ R/R DLBCL patients, including glofitamab positioning



Abbreviations: 2L, second-line; 3L+, third-line and higher; allo-SCT: allogeneic stem cell transplantation; ASCT, autologous stem-cell transplantation; Axi-cel: axicabtagene ciloleucel (Yescarta); CAR-T, chimeric antigen receptor T-cell; Pola-BR, polatuzumab vedotin, bendamustine and rituximab; Tisa-cel: tisagenlecleucel (Kymriah).

2d) Patient-based evidence (PBE) about living with the condition

Context:

- **Patient-based evidence (PBE)** is when patients input into scientific research, specifically to provide experiences of their symptoms, needs, perceptions, quality of life issues or experiences of the medicine they are currently taking. PBE might also include carer burden and outputs from patient preference studies, when conducted in order to show what matters most to patients and carers and where their greatest needs are. Such research can inform the selection of patient-relevant endpoints in clinical trials.

In this section, please provide a summary of any PBE that has been collected or published to demonstrate what is understood about **patient needs and disease experiences**. Please include the methods used for collecting this evidence. Any such evidence included in the SIP should be formally referenced wherever possible and references included.

The Lymphoma Coalition is a group of patient organisations around the world that help support people with lymphoma, including patients in the UK. They conduct a survey every 2 years to learn more about the experiences of people with lymphoma and their caregivers. In 2022, 488 people from the UK (434 patients and 54 caregivers) responded to the survey (25).

Although the proportion of DLBCL patients who responded to the Lymphoma Coalition survey was relatively low (13%), the results may still be relevant across all subtypes of lymphoma. This is because some of the chemo-immunotherapy treatments used to treat lymphoma have similar side effect profiles, regardless of the specific subtype of lymphoma. Therefore, the survey results can provide valuable insights into the

experiences and challenges faced by lymphoma patients and their caregivers, regardless of the subtype of lymphoma they are dealing with.

The key findings from this research in terms of impact on patients and carers is as follows:

- The most common side effects reported by patients (>50%) are fatigue (80%), hair loss (63%), constipation (50%) and changes in sleeping patterns/trouble sleeping (53%).
- Side effects that affected patients' wellbeing the most were hair loss, infections and constipation and approximately three quarters of those affected by hair loss or constipation experienced these side effects for more than a year.
- For the majority of those patients with affected sleep patterns, this continued for more than a year and in approximately 30% of these patients it lasted more than 2 years.
- In those patients affected by fatigue, for over 70% this was experienced for over a year, with 40% continuing to experience it over 2 years.
- In those patients reporting lymphoma symptoms and/or treatment side effects, 56% agreed or strongly agreed that symptoms/side effects negatively impacted on close family or friends, 60% agreed or strongly agreed that they had a negative effect on their social life, 65% agreed or strongly agreed that they negatively impacted on every day activities (e.g. exercise, shopping, household chores) and 53% agreed or strongly agreed that they were unable to work or had to change working pattern because of symptoms and/or side effects.
- Psychosocial issues were experienced by 82% of patients over the prior year, with over half of patients (56%) in remission reporting fear of cancer relapse as their biggest concern; other reported effects included anxiety (47%), isolation (38%) and loss of self-esteem (35%).

SECTION 3: The treatment

3a) How does the new treatment work?

What are the important features of this treatment?

Please outline as clearly as possible important details that you consider relevant to patients relating to the mechanism of action and how the medicine interacts with the body

Where possible, please describe how you feel the medicine is innovative or novel, and how this might be important to patients and their communities.

If there are relevant documents which have been produced to support your regulatory submission such as a summary of product characteristics or patient information leaflet, please provide a link to these.

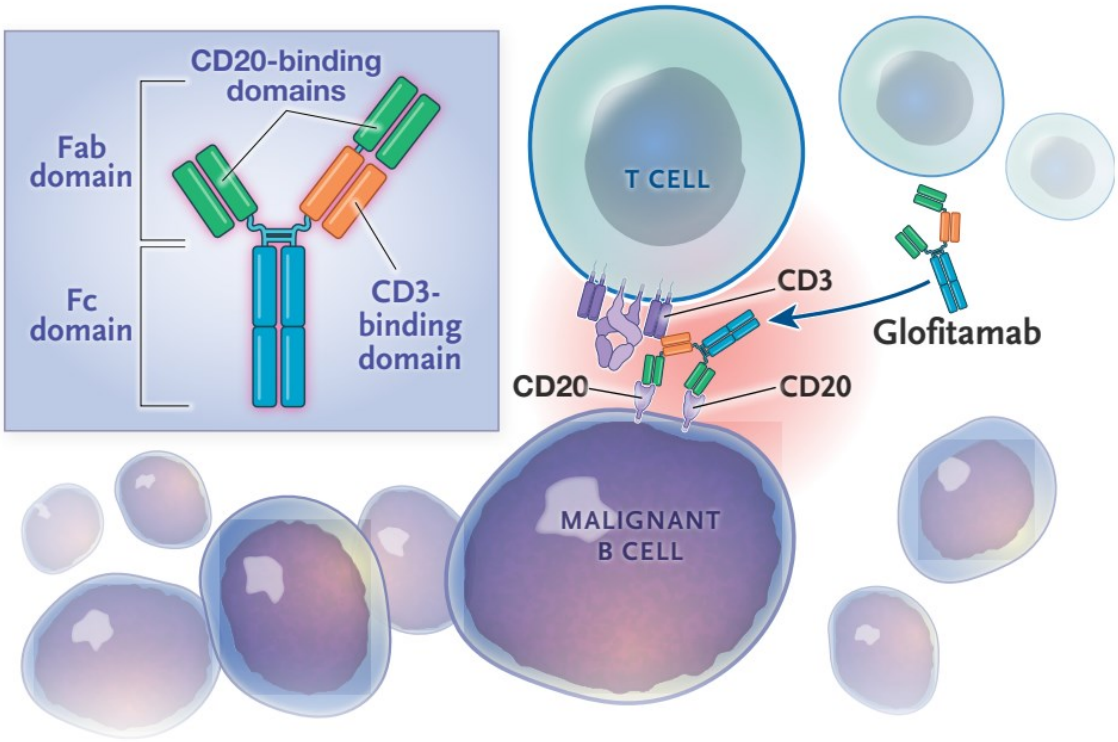
Glofitamab's key features and how it works

Glofitamab is a monoclonal (man-made) antibody that binds to different proteins (bispecific) on the surface of two different cells in the immune system: CD20 on B-cells

and CD3 on T-cells. By binding to both types of cells, it activates the patient's own T-cells to multiply and destroy the cancerous B-cells that express CD20 (26). This is a unique mechanism of action for the treatment of R/R DLBCL that supports the patient's own immune system to fight the lymphoma. This is important for later line (i.e. 3L+) treatment of DLBCL when a patient's disease has become refractory to other therapies.

See Figure 2 for an illustrated diagram to show how glofitamab works on T-cells and B-cells.

Figure 2: How glofitamab works (27)



3b) Combinations with other medicines

Is the medicine intended to be used in combination with any other medicines?

- No

If yes, please explain why and how the medicines work together. Please outline the mechanism of action of those other medicines so it is clear to patients why they are used together.

If yes, please also provide information on the availability of the other medicine(s) as well as the main side effects.

If this submission is for a combination treatment, please ensure the sections on efficacy (3e), quality of life (3f) and safety/side effects (3g) focus on data that relate to the combination, rather than the individual treatments.

Glofitamab is not used in combination with other medicines. However, a pre-treatment with one dose of another antibody, obinutuzumab, is given to patients one week before starting glofitamab. Obinutuzumab is used to lower the amount of the patients B cells, which has been shown to reduce the risk of a specific side effect of glofitamab known as cytokine release syndrome (27).

3c) Administration and dosing

How and where is the treatment given or taken? Please include the dose, how often the treatment should be given/taken, and how long the treatment should be given/taken for. How will this administration method or dosing potentially affect patients and caregivers? How does this differ to existing treatments?
Patients will receive glofitamab under the supervision of a doctor experienced in cancer treatment, in the haematology unit of a hospital. **Medicines given before glofitamab treatment** Seven days before starting glofitamab treatment, patients will be given a single dose of another medicine, obinutuzumab. This is to lower the number of the B-cells in the blood in order to reduce the risk of cytokine release syndrome (CRS) (27), which is a side effect of glofitamab that some patients may experience and can be severe. Shortly before glofitamab is given, patients will be given other medicines (pre-medication) to help reduce reactions associated with cytokine release syndrome. These medicines may include: • A corticosteroid, such as dexamethasone • A fever-reducing medicine, such as paracetamol • An antihistamine, such as diphenhydramine **How much and how often glofitamab will be given** Patients will receive 12 treatment cycles of glofitamab. Each cycle lasts 21 days. Treatment with glofitamab will begin with a low dose and will gradually increase to the full dose. A typical schedule is shown below. Cycle 1: This will include a pre-treatment and 2 low doses of glofitamab during the 21 days: • Day 1 ‑ Pre-treatment with obinutuzumab • Day 8 ‑ starting low glofitamab dose of 2.5 mg • Day 15 ‑ the second low glofitamab dose of 10 mg Cycle 2 to Cycle 12: This will be just one dose in each 21 day cycle: • Day 1 ‑ full glofitamab dose of 30 mg **How glofitamab is given and monitoring** Glofitamab is given as drip into a vein (intravenous [IV] infusion). The time required for infusion will depend on how the patients respond to the treatment.

The first infusion will be given over 4 hours. Patients will be monitored carefully during the first infusion and for 10 hours after completion of infusion. This is to watch for any signs or symptoms of cytokine release syndrome and the patient will remain in hospital overnight.

For following infusions, patients may be monitored after completion of infusion. This will be necessary if patients experienced CRS with the previous dose.

If patients showed no signs of any cytokine release syndrome after 3 doses, they may receive the following infusions over 2 hours.

3d) Current clinical trials

Please provide a list of completed or ongoing clinical trials for the treatment. Please provide a brief top-level summary for each trial, such as title/name, location, population, patient group size, comparators, key inclusion and exclusion criteria and completion dates etc. Please provide references to further information about the trials or publications from the trials.

Trial NP30179 (NCT03075696)

The clinical trial NP30179, which is being used as evidence for the safety and effectiveness of glofitamab, is still ongoing. This trial evaluates different doses of glofitamab either alone or in combination with obinutuzumab in patients with B-cell non-Hodgkin's lymphoma (NHL) who have not responded to previous treatments.

The evidence for this NICE submission is taken from the group of patients in this trial who had R/R DLBCL to at least 2 prior therapies, and received glofitamab alone (with obinutuzumab pre-treatment). Follow-up assessments of patients in the trial will continue for at least 2 years after the end of their treatment. This means that an analysis of the final results of the trial is expected to be completed in [redacted], and an updated report of the results will be available in the [redacted]. Further details of NP30179 can be found in the following sections in this report and on the ClinicalTrial.gov website (28). Initial results have been published in the New England Journal of Medicine (27).

Trial GO41944 (STARGLO; NCT04408638)

The clinical trial GO41944, also known as STARGLO, is currently ongoing and is testing the effectiveness and safety of using glofitamab in combination with gemcitabine and oxaliplatin (glofit-GemOx) compared to using rituximab in combination with gemcitabine and oxaliplatin (R-GemOx) in patients with R/R DLBCL after at least one prior systemic therapy.

R-GemOx is a chemo-immunotherapy treatment that is currently used in many patients with R/R DLBCL. Around 270 eligible patients will be randomly assigned to receive either glofit-GemOx or R-GemOx in a 2:1 ratio. The main objective (primary endpoint) of the trial is overall survival (OS), and the results are expected to be reported in the [redacted] Further information on this is available on the ClinicalTrial.gov website (29).

3e) Efficacy

Efficacy is the measure of how well a treatment works in treating a specific condition.

In this section, please summarise all data that demonstrate how effective the treatment is compared with current treatments at treating the condition outlined in section 2a. Are any of the outcomes more important to patients than others and why? Are there any limitations to the data which may affect how to interpret the results? Please do not include academic or commercial in confidence information but where necessary reference the section of the company submission where this can be found.

Glofitamab efficacy

Glofitamab was studied in a clinical trial (NP30179) to see if it is safe and effective in treating patients with R/R B-cell NHL. The trial looked at how well glofitamab works on its own and when given with obinutuzumab, and how the body processes the drug.

In this trial, researchers investigated a group of 108 R/R DLBCL patients who had received at least two previous treatments. After receiving feedback from the U.S. Food and Drug Administration (FDA), an updated analysis was carried in June 2022 with more follow-up time and more patients were added to the analysis. A total of 155 patients were assessed at the updated analysis.

The primary endpoint of the NP30179 trial was to see how many patients had a complete response to treatment with glofitamab. It was found that 35% of patients (38 out of 108) with R/R DLBCL achieved a complete response (CR) rate with the treatment glofitamab. This result was better than the pre-set historical control of 20% (based on results from several other clinical trials for R/R DLBCL), and met the trial's main goal. In the updated analysis, the CR rate remained the same. When the results of several groups of patients were pooled together, the Independent Review Committee (IRC)-assessed CR rate was 40% (62 out of 155 patients) and the result was similar to the investigator-assessed CR rate. In clinical trials, an IRC is a group of independent experts who review and evaluate the trial data to ensure accuracy and consistency of the results.

In the June 2022 updated analysis, the clinical benefit of glofitamab was observed across several additional objectives (secondary endpoints). More than half of the patients responded to the treatment; and in the patients who responded, the response lasted longer than the length of the treatment. The average length of time before the disease progressed or worsened was around 5 months, and the average survival time was 12 months. Around half of the enrolled patients had died, and the majority of deaths occurred in patients who did not respond to treatment.

Indirect treatment comparisons (ITCs)

The NP30179 trial was a single-arm study, which means it did not have a control group for comparison. Therefore, to estimate the effectiveness of glofitamab compared with current treatments, several indirect treatment comparisons (ITCs) were conducted. Results from other studies were analysed and compared to the NP30179 data. Different ITC methods were used depending on the type of data available. See below (Table 1) for a list of ITCs performed:

Table 1: List of performed ITCs between glofitamab and current treatments

Comparator	Trial name	Trial design	Analysis population
Axicabtagene ciloleucel (Yescarta®)	ZUMA-1 (30)	• A prospective cohort study conducted in the United States and Israel. • It included 101 patients with different types of blood cancer, including DLBCL, primary mediastinal large B-cell lymphoma (PMBCL), high-grade B-cell lymphoma (HGBCL), and transformed follicular lymphoma (tFL). • The purpose of the study was to look at how well axicabtagene ciloleucel worked in these patients.	101 patients with R/R DLBCL who had received ≥2 prior lines of treatment
Rituximab and bendamustine (BR)	Hong 2018 (31)	• This study was conducted in South Korea and analysed the data of 58 patients with DLBCL who were treated with BR. • The analysis was done after the patients had received the treatment, and the aim was to evaluate the effectiveness and safety of this treatment in these patients.	58 patients with R/R DLBCL who had received ≥2 prior lines of treatment
Polatuzumab-vedotin plus bendamustine and rituximab (pola-BR)	GO29365 (32)	• This was a study that randomly assigned patients with R/R FL or DLBCL who were not eligible for a stem cell transplant into two treatment groups: one receiving a combination of pola-BR, and the other receiving BR alone. • The study aimed to compare the effectiveness of the two treatments.	102 patients with R/R DLBCL who had received ≥2 prior lines of treatment

ITC results

A summary of the top-line results of the ITC can be found in Document B, Section B.2.9.2. Overall, the ITC results suggest that glofitamab has the potential to improve response and survival rates compared to BR and pola-BR, although statistical significance was not always achieved. The results also suggest that axicabtagene ciloleucel may be superior to glofitamab for overall response rate (ORR) and complete response (CR) rate, but these results should be interpreted with caution as the ITC excluded patients who progress before axicabtagene ciloleucel infusion, therefore biasing results in favour of axicabtagene ciloleucel. Numeric differences should also be considered as a signal of relative benefit, even if statistical significance was not achieved.

ITC limitations

It is important to consider the limitations associated with the ITC analyses when interpreting the results. Some limitations include differences in study criteria and

definitions, inability to adjust for all factors across studies, and sometimes small sample sizes. Some studies also did not report important information which may have affected the results. It is important to note that while the measure of the relative risk (hazard ratios, HRs) provide a signal of relative effects, they are not reflective of the long-term benefit. Despite these limitations, the ITC analyses represent the most robust comparisons of glofitamab to the most widely used treatments in NHS clinical practice at the time of this report. The ITCs do not take into account the treatment-related side effects and the frequency and severity of side effects is lower with glofitamab than the comparators.

3f) Quality of life impact of the medicine and patient preference information

What is the clinical evidence for a potential impact of this medicine on the quality of life of patients and their families/caregivers? What quality of life instrument was used? If the EuroQol-5D (EQ-5D) was used does it sufficiently capture quality of life for this condition? Are there other disease specific quality of life measures that should also be considered as supplementary information?

Please outline in plain language any quality of life related data such as **patient reported outcomes (PROs).**

Please include any **patient preference information (PPI)** relating to the drug profile, for instance research to understand willingness to accept the risk of side effects given the added benefit of treatment. Please include all references as required.

The NP30179 trial assessed the health-related quality of life (HRQoL) of patients with R/R DLBCL using two questionnaires - the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC QLQ-C30) v3.0 and the 15-item Functional Assessment of Cancer Therapy – Lymphoma (FACT-Lym) Lymphoma Subscale (LymS).

In the EORTC QLQ-C30, higher scores are reflective of higher functioning and overall HRQoL on the function and GHS/QoL scales, but a greater degree of symptoms on the symptom scales. On the FACT-Lym LymS, higher scores are reflective of better HRQoL (i.e., lower lymphoma-specific symptoms or concerns). In all study groups, the average scores at the beginning of the study showed moderate to moderate-high levels of functioning and overall HRQoL, and low to low-moderate levels of symptoms.

The NP30179 trial found that the proportion of patients reporting a clinically meaningful change on the QLQ- and FACT-Lym LymS over the first three cycles was similar.

[redacted]

Health-related quality-of-life information, such as that captured in the EORTC QLQ-C30, was needed for economic modelling purposes. Data using NICE's preferred quality of life measure EQ-5D was not collected in the glofitamab NP30179 trial. Therefore, to support NICE's decision making, it was necessary to convert EORTC-QLQ-C30 data from the glofitamab trial to NICE's preferred EQ-5D-3L values (following methods recommended by NICE).

3g) Safety of the medicine and side effects

When NICE appraises a treatment, it will pay close attention to the balance of the benefits of the treatment in relation to its potential risks and any side effects. Therefore, please outline the main side effects (as opposed to a complete list) of this treatment and include details of a benefit/risk assessment where possible. This will support patient reviewers to consider the potential overall benefits and side effects that the medicine can offer.

Based on available data, please outline the most common side effects, how frequently they happen compared with standard treatment, how they could potentially be managed and how many people had treatment adjustments or stopped treatment. Where it will add value or context for patient readers, please include references to the Summary of Product Characteristics from regulatory agencies etc.

Each medicine has its own side effects, and the same medicine can produce different reactions in different people.

The NP30179 trial looked at patients who received at least one dose of study medication (obinutuzumab pre-treatment and glofitamab) and were treated with different doses of glofitamab. The results showed that the step-up dosing regimen of 2.5/10/30 mg of glofitamab was well-tolerated with a manageable safety profile:

- Common side effects (over 5% incidence) reported from the NP30179 trial included [redacted] Symptoms of CRS may range from a high temperature (fever), nausea and fatigue to low blood pressure and breathlessness that requires treatment in an intensive care unit.
- [redacted]
- [redacted]
- [redacted]
- Overall, the study concluded that glofitamab was safe and well-tolerated (27).

3h) Summary of key benefits of treatment for patients

Issues to consider in your response:

- Please outline what you feel are the key benefits of the treatment for patients, caregivers and their communities when compared with current treatments.
- Please include benefits related to the mode of action, effectiveness, safety and mode of administration

Glofitamab offers a new mode of action

Glofitamab used on its own (as monotherapy) is expected to be positioned next to CAR-T cell therapies in the 3L+ DLBCL setting (treatment of patients with 2 prior lines of therapy), where the next best option in this setting is participation in a clinical trial. Glofitamab is a novel bispecific antibody with a new mechanism of action for R/R DLBCL patients,

redirecting T-cells against the cancer cells, which may be helpful for patients who have not responded well to the usual treatments.

Unlike CAR-T cell therapies, which have to be manufactured individually for patients, glofitamab can be used quickly after the decision has been made that a further line of treatment is needed. CAR-T cell therapy can only be given in a restricted number of centres in the England (approximately 10–15, although this is increasing). Glofitamab should be accessible for patients in most hospitals with haematology units, so treatment can be delivered more locally for many patients.

Glofitamab is effective and well tolerated in clinical trial

Glofitamab was found to be well-tolerated and had a low incidence of severe side effects in the NP30179 trial. The trial showed that glofitamab had a high complete response rate; and in the 50% of patients who responded, these responses were achieved rapidly and lasted for a long time.

The safety profile of glofitamab was manageable, and severe side effects were rare. Glofitamab is a readily available treatment that does not require chemotherapy and has a fixed duration of treatment. Glofitamab has been well-received by clinical experts who believe it has the potential to enhance access and equity in the treatment of R/R DLBCL (23).

3i) Summary of key disadvantages of treatment for patients

Issues to consider in your response:

- Please outline what you feel are the key disadvantages of the treatment for patients, caregivers and their communities when compared with current treatments. Which disadvantages are most important to patients and carers?
- Please include disadvantages related to the mode of action, effectiveness, side effects and mode of administration
- What is the impact of any disadvantages highlighted compared with current treatments

As with other treatments for DLBCL, glofitamab might not work for all patients. Clinical trial evidence suggests that approximately half of the patients will respond to the treatment, while the remaining patients will not. Unfortunately there is no way to predict whether a patient will respond to the treatment at the time their doctor decides to treat them with glofitamab.

Most of the side effects of glofitamab are mild, including the cytokine release syndrome (CRS) described earlier. However, some patients may experience severe CRS that requires treatment in hospital. As a result, all patients receiving glofitamab must stay in the hospital for their first treatment, unlike some other treatments for DLBCL.

3i) Value and economic considerations

Introduction for patients:

Health services want to get the most value from their budget and therefore need to decide whether a new treatment provides good value compared with other treatments. To do this

they consider the costs of treating patients and how patients' health will improve, from feeling better and/or living longer, compared with the treatments already in use. The drug manufacturer provides this information, often presented using a health economic model.

In completing your input to the NICE appraisal process for the medicine, you may wish to reflect on:

- The extent to which you agree/disagree with the value arguments presented below (e.g., whether you feel these are the relevant health outcomes, addressing the unmet needs and issues faced by patients; were any improvements that would be important to you missed out, not tested or not proven?)
- If you feel the benefits or side effects of the medicine, including how and when it is given or taken, would have positive or negative financial implications for patients or their families (e.g., travel costs, time-off work)?
- How the condition, taking the new treatment compared with current treatments affects your quality of life.

How the model reflects the condition

- The economic case presented in this submission is based on an analysis assessing the use of glofitamab compared with rituximab-based chemotherapy (R-Chemotherapy), pola-BR, and axicabtagene ciloleucel (axi-cel) for the treatment of adult patients with R/R DLBCL who have received at least two prior systemic therapies.
- The approach taken to model costs and health benefits is done by splitting patients into 3 different health states, pre-progression, progressed disease, and death. This is a common approach used to model the lifetime benefits and costs of treatments used to treat different types of cancer.
- The data used to predict how long patients treated with each treatment would remain in each health state, which informs the amount of costs and health gains they would accrue, is based on data from the glofitamab and comparator studies.

Modelling how much a treatment extends life

- Based on the economic modelling, it is predicted that people with 3L+ DLBCL treated with glofitamab will live longer than those treated with R-Chemotherapy or pola-BR. These gains mostly occur from delaying disease progression. The model predicts a larger extension to life for people treated with axi-cel than glofitamab. However, because the axi-cel population considered excluded people whose disease progressed before infusion, it is expected that extensions to life observed in the NHS are likely to be more modest than the model predicts.
- Data on progression free survival, overall survival, time on treatment, quality of life, and adverse events all feed into the economic model. Observed data from the glofitamab study and comparator studies is used to predict long-term outcomes. The amount of observed data available to inform these predictions varied by treatment, with approximately 1 year of data available for glofitamab, and nearly 5 years for pola-BR. The model predicts disease progression, costs and health outcomes over the lifetime of all patients in the model (60 year time horizon).

- Anyone still alive at 5 years is assumed to enter long term remission, and reverts to a life expectancy near that of the general population (9% increased risk to account for comorbidities).

Modelling how much a treatment improves quality of life

- Quality of life in the economic model is determined by the health state a patient is in, and whether or not they are receiving treatment. The quality of life values assigned to each health state is based on the values collected in the glofitamab study which was assessed using the EORTC-QLQ-C30 quality of life measure. The data from the glofitamab study were converted to NICE's preferred EQ-5D-3L measure for the economic analysis.
- Quality of life improvements are achieved if a patient remains progression free and alive for longer.
- If a person remains progression free after 2 years, they are assumed to be cured, with their quality of life reverting to near general population levels (10% reduction compared to the general population to account for comorbidities).
- As a partitioned survival model was used for the economic analysis of glofitamab and the relevant comparators, observed benefits linked to treatment response rates are not likely to be accounted for in the quality of life calculations, as survival outcomes drive the results. Furthermore, glofitamab has the potential to be more accessible by a larger range of clinical centres than CAR-T-cell therapies (axicabtagene ciloleucel), offering an effective alternative, to current treatments. Despite new treatment options, patients with DLBCL who have failed two or more prior lines of systemic therapy continue to have a poor prognosis, and therefore there is an urgent need for innovative treatment options that offer effective, durable remissions and are readily available. As such, the availability of glofitamab has the potential to improve quality of life for patients who may have challenges accessing, or benefiting from, existing treatment options. The full extent of these benefits are not expected to be fully captured in the economic analysis.

Modelling how the costs of treatment differ with the new treatment

- The total costs of treatment related to glofitamab is expected to be greater than that of R-Chemotherapy. This is driven by increased costs in the progression free state, where disease progression takes longer to occur for people who receive glofitamab compared to R-Chemotherapy. Compared to pola-BR, glofitamab is predicted to be cost saving, driven by fewer people reaching the progressed disease state. Glofitamab is also predicted to be cost-saving compared with axi-cel due to the significant drug and administration cost associated with CAR-T therapies.
- There is the potential for out of pocket costs to patients to be reduced compared to CAR-T as glofitamab is likely to be accessible at more centres than CAR-T cell therapies. As such, savings from reduced travel expenses are possible.

Uncertainty

- Due to limited data availability and short term trial follow-up, there is some uncertainty regarding the efficacy estimates included within the economic model. These are common obstacles in indications where there are small patient numbers
- The glofitamab study is single arm trial with no comparator arm, which means that data from comparator studies had to be compared, indirectly, to estimate cost-effectiveness.
- The economic analysis included long-term remission/survivorship assumptions which were plausible for R/R DLBCL in previous 2L+ and 3L+ DLBCL NICE appraisals. There remains uncertainty around the time point after which patients can be considered as long-term survivors. Given the impact of potential excess comorbidities in this population, the actual quality of life and survival predictions in these patients compared to the general population is also uncertain. Adjusting these time points in the economic analysis had a large impact in the comparisons with R-Chemotherapy and pola-BR.

Cost-effectiveness results

- In the company's base-case analysis, glofitamab is shown to be dominant, providing more QALYs and costing less, compared to pola-BR (list price). It is shown to be more costly than BR (list price), but provides greater QALY gains. When compared to axi-cel (list price), while associated with a loss of QALYs, glofitamab is shown to be significantly cost saving. These results do not take into account any confidential commercial discounts for the comparator treatments, or the committee's preferred assumptions which may differ to those applied in the base-case analysis.

Additional factors

- This indication is expected to meet the criteria to make adjustments to the value of a QALY, in line with the NICE Methods Manual, in the comparisons vs BR and pola-BR. Consideration of the QALY shortfall resulted in a proportional QALY shortfall in the comparison vs BR and pola-BR, but not vs axi-cel. As such, an adjustment to the value of glofitamab QALYs (x1.2) can apply for these comparisons.

3j) Innovation

NICE considers how innovative a new treatment is when making its recommendations. If the company considers the new treatment to be innovative please explain how it represents a 'step change' in treatment and/ or effectiveness compared with current treatments. Are there any QALY benefits that have not been captured in the economic model that also need to be considered (see section 3f)

Innovation in patient care

- Glofit is the first bispecific treatment with a unique mode of action in a multi-treated patient population, which has not been seen since CAR-T therapy.

- Glofit is available "off-the-shelf" and does not need to be manufactured specifically for each patient.
- Glofitamab has shown to be effective in clinical trials.
- Glofitamab could help provide more equal access to treatment across the country and over time.
- Glofitamab is easier to give compared to other 3L treatments, especially when compared to CAR-T therapy.

3k) Equalities

Are there any potential equality issues that should be taken into account when considering this condition and this treatment? Please explain if you think any groups of people with this condition are particularly disadvantaged.
Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics

More information on how NICE deals with equalities issues can be found in the NICE equality scheme
Find more general information about the Equality Act and equalities issues here

Although some patients with R/R DLBCL may have a potentially curative treatment option via high-dose chemotherapy and ASCT, or a potentially durable response with CAR T-cell therapy, the majority of 3L+ patients will not be eligible for these treatments or treatment will fail.

Due to the limited number of clinical centres that can offer CAR-T-cell therapies, patient access to therapy may be limited on the basis of geographic location or be associated with long travel time for many patients with DLBCL and caregivers. Extended travel distances to therapy or inconvenient care locations are significant barriers to patient care, particularly for those receiving later-line oncology therapy who may have poorer performance status.

In addition, CAR-T treatment can be associated with significant out-of-pocket indirect costs, making it infeasible or burdensome for some patients to receive optimal treatment. These costs are driven by expenses needed to travel to the few certified centres and the requirement to remain within proximity to a certified health facility for a long period (at least 4 weeks) following infusion. This results in a postcode lottery, with patients who live further away from CAR-T centres facing increased costs, which could represent a barrier to treatment access.

Given its immediate availability, glofitamab has the potential to be more accessible by a larger range of clinical centres than CAR-T-cell therapies, helping reduce regional, rural-urban, and sociodemographic inequity issues resulting from the uneven geographical allocation of CAR-T-cell therapy administration sites.

SECTION 4: Further information, glossary and references

4a) Further information

Feedback suggests that patients would appreciate links to other information sources and tools that can help them easily locate relevant background information and facilitate their effective contribution to the NICE assessment process. Therefore, please provide links to any relevant online information that would be useful, for example, published clinical trial data, factual web content, educational materials etc. Where possible, please provide open access materials or provide copies that patients can access.
Patient groups and charities: • Blood Cancer Alliance • Blood Cancer UK • Cancer Research UK • Lymphoma Action • Macmillan Cancer Support • Maggie's Cancer Centres **Further information on NICE and the role of patients:** • Public involvement at NICE • NICE's guides and templates for patient involvement in HTAs • EUPATI guidance on patient involvement in NICE • EFPIA – working together with patient groups • National Health Council Value Initiative • INAHTA • European Observatory on Health Systems and Policies. Health technology assessment - an introduction to objectives, role of evidence, and structure in Europe

4b) Glossary of terms

Term	Acronym	Description
Ann Arbor Classification System	-	A staging system used for the diagnosis and management of Hodgkin's lymphoma and non-Hodgkin's lymphoma. The system defines four stages of lymphoma, based on the extent of the disease in the body.
Antibody	-	A protein that plays an important role in the body's immune system. Each antibody is unique and recognises a specific part of a germ or other invader. Antibodies can be custom designed for use as drugs.

Autologous stem-cell transplantation	ASCT	A procedure that involves collecting and storing a patient's own stem cells, usually from the bone marrow or blood, and then returning them to the patient after they have undergone intensive chemotherapy or radiation therapy.
Biopsy	-	A process in which a very small part of tissue in the body is removed to look for signs of disease.
Bispecific	-	An antibody or protein that has the ability to bind to two different targets at the same time. In cancer treatment, bispecific antibodies can be designed to recognise and bind to both cancer cells and immune cells, directing the immune cells to attack the cancer cells.
B-lymphocytes/B-cells	-	A type of white blood cell that plays a key role in the immune system. B-lymphocytes are responsible for producing antibodies, which are proteins that help the body identify and neutralise foreign substances such as bacteria and viruses.
Chimeric antigen receptor T-cell therapy	CAR-T	A type of cancer treatment that involves genetically modifying a patient's own immune cells to recognise and attack cancer cells. The process involves removing T-cells (a type of white blood cell) from a patient's blood, modifying them to produce a receptor called a chimeric antigen receptor (CAR) that can recognise and attach to a specific protein on the surface of cancer cells, and then infusing the modified T-cells back into the patient's bloodstream. Once infused, the CAR-T cells can identify and destroy cancer cells that express the targeted protein.
Clinical trial	-	A type of research study that tests how well new medical approaches work in people. These studies test new methods of screening, prevention, diagnosis, or treatment of a disease. Also called clinical study. When it is called “Phase III clinical trial”, it tests the safety and how well a new treatment works compared with a standard treatment.
Complete response	CR	A complete disappearance of all signs and symptoms of cancer after treatment. It indicates that no cancer cells can be detected by any of the tests used for the diagnosis of the specific type of cancer that the patient had.
Cytokine release syndrome	CRS	A type of immune system reaction that can occur in some patients receiving certain types of

		immunotherapy, including CAR-T cell therapy and bispecific antibodies. It happens when the immune system is activated and releases high levels of cytokines, which are proteins that act as messengers between cells. This excessive release of cytokines can cause a range of symptoms, including fever, chills, low blood pressure, difficulty breathing, and organ dysfunction. In severe cases, CRS can be life-threatening and require hospitalization and treatment in an intensive care unit.
Early Access To Medicines Scheme	EAMS	A regulatory pathway in the UK that provides patients with life-threatening or seriously debilitating conditions access to promising new medicines that are not yet licensed or approved.
European Medicines Agency	EMA	The regulatory body that evaluates, approves, and supervises medicines throughout the European Union.
European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30	EORTC QLQ-C30	A quality of life questionnaire used to assess the well-being of cancer patients. It was developed by the European Organisation for Research and Treatment of Cancer (EORTC) and is widely used in clinical trials and routine care to measure the impact of cancer and its treatment on patients' daily lives.
Food and Drug Administration	FDA	A government agency that helps make sure the food, drugs, and medical products are safe and effective. The FDA reviews information about these products and tests them to make sure they are safe to use. They also make sure that the labels on these products are accurate and easy to understand.
Functional Assessment of Cancer Therapy – Lymphoma – Lymphoma Subscale	FACT-Lym LymS	A patient-reported outcome measure developed by the Functional Assessment of Cancer Therapy (FACT) group to assess the health-related quality of life in patients with lymphoma. It consists of a 44-item questionnaire that covers areas such as physical, social, emotional, and functional well-being, as well as lymphoma-specific symptoms and concerns. LymS is an abbreviated version of FACT-Lym that includes 15 items.
Flow cytometry	-	A technique used to analyse cells in a liquid suspension. It measures multiple physical and chemical characteristics of cells, such as size, shape, and surface markers, using fluorescently labelled antibodies. The cells are passed in a single

		file through a laser beam and the scattered light and fluorescence is detected by a detector.
Haematological Malignancy Research Network	HMRN	A collaboration of clinicians, scientists, and researchers in the UK who work together to improve the diagnosis, treatment, and outcomes of patients with haematological cancers.
Hazard ratio	HR	A statistical measure used in survival analysis to compare the time it takes for a particular event, such as death or disease progression, to occur between two groups. It is commonly used in medical research to evaluate the effectiveness of a treatment or intervention.
Immune system	-	A complex network of cells, tissues, organs, and the substances they make that helps the body fight infections and other diseases.
Immunohistochemistry	-	A technique used to visualize proteins, antigens, or other molecules within tissue samples. It involves the use of antibodies that bind to specific protein targets, followed by a detection system to identify the bound antibody. The antibodies can be labelled with dyes, enzymes, or fluorescent molecules, which allow them to be visualised under a microscope.
Indirect treatment comparison	ITC	A method used in healthcare research to compare two or more treatments that have not been directly compared in a head-to-head clinical trial. Instead of a direct comparison, this method uses data from different studies, which may have different designs, patient populations, or outcomes, to estimate the relative effectiveness of the treatments being compared.
Lugano Classification	-	A staging system used to assess the spread and severity of lymphoma, particularly non-Hodgkin lymphoma. It was developed in Lugano, Switzerland in 2014, as an update to the previous Ann Arbor classification.
Medicines and Healthcare products Regulatory Agency	MHRA	A UK government agency responsible for ensuring that medicines, medical devices, and blood components for transfusion meet applicable standards of safety, quality, and efficacy.
Monoclonal antibody	-	Man-made molecules that mimic the immune system's ability to fight off harmful pathogens, such as viruses or cancer cells. They are designed to target specific proteins on the surface of cells and act as a "lock and key" mechanism to bind to these proteins and trigger an immune response to destroy

		the cells. Monoclonal antibodies are used in the treatment of various medical conditions, including cancer, autoimmune disorders, and infectious diseases.
Overall response rate	ORR	A measure of the proportion of patients in a clinical trial or other study who experience a significant reduction in the size of their tumour or other disease.
Positron Emission Tomography-Computed Tomography scan	PET-CT	A medical imaging technique that combines two types of scans to provide more detailed information about the structure and function of tissues and organs in the body. A PET scan uses a small amount of radioactive tracer to highlight areas of the body with high metabolic activity, while a CT scan provides a detailed image of the body's internal structures.
Polymerase chain reaction	PCR	A laboratory technique used to amplify a specific DNA segment, allowing scientists to generate many copies of a particular DNA sequence.
Prognosis	-	A medical term that refers to the likely course or outcome of a disease or condition. It is an estimate of how the disease will progress in an individual patient, based on factors such as the patient's age, medical history, severity of the disease, and response to treatment.
Promising Innovative Medicine Designation	PIM	A program by the UK MHRA that provides early stage support for innovative drugs that are in development and have the potential to address an unmet medical need.
Quality of life	QoL	The overall enjoyment of life. Many clinical trials assess the effects of cancer and its treatment on the quality of life. These studies measure aspects of an individual’s sense of well-being and ability to carry out activities of daily living.
Relapsed or refractory	R/R	Refers to the status of a disease, often cancer, which has either come back (relapsed) after a period of remission or has not responded to initial treatment (refractory). In the context of lymphoma, patients who are R/R to first-line therapy (the initial treatment) are often given more aggressive therapies, including clinical trials and stem cell transplantation.
Side effect	-	An unexpected medical problem that arises during treatment with a drug or other therapy. Adverse events may be mild, moderate, or severe.

Stem cell transplant	-	The process of providing a patient with healthy stem cells that can replace diseased cells intentionally destroyed by therapy.
Systemic treatments	-	Medications or therapies that affect the entire body instead of just one specific part or organ.

4c) References

Please provide a list of all references in the Vancouver style, numbered and ordered strictly in accordance with their numbering in the text:

1. Haematological Malignancy Research Network (HMRN). HMRN, Incidence - Diffuse large B-cell lymphoma (DLBCL), NOS [
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6. Nowakowski GS, Blum KA, Kahl BS, Friedberg JW, Baizer L, Little RF, et al. Beyond RCHOP: a blueprint for diffuse large B cell lymphoma research. J Natl Cancer Inst. 2016;108(12):djw257.
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Single technology appraisal

Glofitamab for treating relapsed or refractory diffuse large B-cell lymphoma after 2 or more systemic treatments [ID3970]

Company response to clarification questions

May 2023

File name	Version	Contains confidential information	Date
Glofitamab 3L+ company response to clarification questions_Redacted	V2.0	Yes	19 May 2023

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Section A: Systematic reviews

A1. The EAG requests more information on how trials of glofitamab were identified. If a systematic review was performed, please supply full details of this, including search strategies, a PRISMA flow diagram, and tables of included and excluded trials. If no systematic search was performed, please provide a full explanation of why that was the case.

A systematic literature review (SLR) was performed to assess the clinical evidence available for glofitamab trials. Details of the methodology and results from the search are discussed in the following sections.

A1.1 Methodology – Clinical SLR

A1.1.1 Eligibility criteria

The studies were selected for inclusion according to the criteria detailed in Table 1.

Table 1: Eligibility criteria for the clinical SLR

Criteria	Include	Exclude
Population	Adult patients with R/R DLBCL (3L+) Publications reporting data for the following populations were reviewed to check whether data for a relevant subgroup are reported (baseline characteristics and outcome data): • Mixed 2L/3L+ patients (likely to be relevant if median ≥2 prior lines (≥50% 3L) or with results for 3L+)	• Paediatric patients • Adult patients treated at 1L or 2L setting only
Intervention & comparators	Studies with at least one treatment arm investigating one of the following pharmacological treatments for R/R DLBCL : • Glofitamab CAR-T cell therapies • Axicabtagene ciloleucel (Yescarta™) • Tisagenlecleucel (Kymriah™) • Liso-cel (Breyanzi™) Immuno/chemotherapy • Polatuzumab vedotin (Polivy™) • Tafasitamab • Lenalidomide (Revlimid™) • R-DHAP (rituximab, dexamethasone, cytarabine, cisplatin) • R-GemOx (rituximab, gemcitabine, oxaliplatin)	• Pharmacological interventions not listed in the “include” column • Non-pharmacological interventions (e.g. surgery, radiotherapy, diagnostic/screening)

Criteria	Include	Exclude
	• GemOx (gemcitabine, oxaliplatin) • Bendamustine + rituximab (BR) • Pixantrone Treatments could be used as monotherapy or in combination with other interventions (both pharmacological and non-pharmacological [e.g. radiotherapy or surgery])	
Outcomes	Included, but not restricted to: • Response rates (CR, PR, PD, stable disease, ORR) – include the response criteria and imaging modality used and whether the criteria are aligned with published criteria • Duration of response (to include DOCR and DOR) • Measurement of minimal residual disease (to include method of measurement) • Survival (OS/PFS/EFS) • Time to treatment discontinuation/trial withdrawal • Time to patient progression • Time to first complete response • Time to first overall response • Drug exposure time • Duration of follow up/time on study • Time to next anti-lymphoma treatment • Safety (to include incidence of treatment emergency AEs, serious AEs, grade 5 AEs, AEs and serious AEs reported in ≥5% of patients, and discontinuation rate due to AE/serious AEs) • Tolerability: dose reductions and interruptions, discontinuation (any reason), discontinuation (due to AEs) • Health-related quality of life as reported in eligible studies (to include both disease-specific and generic questionnaires)	Outcomes not listed in the "include" column
Study design	• RCTs (Phase 1/2/3) • Prospective clinical trials (non-RCTs, non-comparative) • Extension phases of trials • Observational/registry studies (prospective/retrospective) • Case-control studies • Cross-sectional surveys • Case series • Treatment guidelines	• Economic evaluations • Case reports • Pharmacokinetic studies • Animal/in vitro studies

Criteria	Include	Exclude
	• SLR, meta-analyses, and narrative review publications of interventional and/or observational studies (for citation-chasing and baseline data gap filling only)	
Geography	No restriction	-
Publication date	No restriction	-
Language	No restriction. English language publications or non-English language publications with an English abstract were of primary interest.	-

Abbreviations: AE, adverse event; CAR-T, chimeric antigen receptor T cell; CR, complete response; DLBCL, diffuse large B-cell lymphoma; DOCR, duration of complete response; DOR, duration of response; EFS, event-free survival; ORR, overall response rate; OS, overall survival; PD, progressive disease; PFS, progression free survival; PR, partial response; RCT, randomised controlled trial; RR, relapsed refractory; SC, subcutaneous.

A1.1.2 Information sources

The following sources were searched to identify potentially relevant publications:

- Electronic databases
- Reference lists of eligible clinical studies
- Global HTA bodies
- Conference proceedings
- Regulatory documents
- Clinical trial registries

A1.1.2.1 Electronic databases

The following electronic databases were interrogated on the 14th December 2021 and 15th September for the clinical SLR via the OVID platform:

- Embase, 1974 to present
- MEDLINE, 1946 to present, including:
  - MEDLINE Epub Ahead of Print
  - MEDLINE In-Process & Other Non-Indexed Citations
  - MEDLINE Daily
- EBM Reviews, incorporating:
  - American College of Physicians (ACP) Journal Club
  - Cochrane Central Register of Controlled Trials (CENTRAL)
  - Cochrane Database of Systematic Reviews
  - Cochrane Clinical Answers
  - Cochrane Methodology Register
  - Database of Abstracts of Reviews of Effects (DARE)
  - HTA database
  - NHS Economic Evaluation Database (NHS EED)

A1.1.2.2 Conference proceedings

The following conference proceedings were reviewed for the last 3 years:

- American Society of Clinical Oncology (ASCO)
- American Society of Hematology (ASH)
- European Hematology Association (EHA)
- European Society for Medical Oncology (ESMO)
- International Conference on Malignant Lymphoma (ICML)
- International Society for Pharmacoeconomics and Outcomes Research (ISPOR) [International, Asia Pacific, and European meeting]
- Health Technology Assessment international (HTAi)
- Society for Medical Decision Making (SMDM)

A1.1.2.3 HTA body websites

The following HTA bodies were searched to identify previous relevant submissions:

- NICE: https://www.nice.org.uk/
- Scottish Medicines Consortium (SMC): https://www.scottishmedicines.org.uk/
- Canadian Agency for Drugs and Technologies in Health (CADTH), including the pan-Canadian Oncology Drugs Review (pCODR): https://www.cadth.ca/
- Pharmaceutical Benefits Advisory Committee (PBAC): https://www.pbs.gov.au/pbs/home
- Agencia Española de Medicamentos y Productos Sanitarios (AEMPS): https://www.aemps.gob.es/
- Agenzia Italiana del Farmaco (AIFA): https://www.aifa.gov.it/
- Haute Autorité de Santé (HAS): https://www.has-sante.fr/
- Institute for Quality and Efficiency in Health Care (IQWiG): https://www.iqwig.de/
- Institute for Clinical and Economic Review (ICER): https://icer-review.org/

A1.1.2.4 Regulatory data and clinical trial registries

The following resources were searched:

- European public assessment reports (EPARs): https://www.ema.europa.eu/en/glossary/european-public-assessment-report
- Supporting documents from the Food and Drug Administration (FDA): https://www.fda.gov
- US National Institutes of Health (US NIH) registry & results database (https://clinicaltrials.gov)
- World Health Organization International Clinical Trials Registry Platform (WHO ICTRP) registry (http://apps.who.int/trialsearch/)

A1.1.3 Study selection

Publications identified through the SLR were evaluated in a pre-defined process to assess if they met the inclusion criteria:

1) Following completion of electronic searches, citations were exported into an Excel® database
2) Individual citations were then screened against the pre-defined inclusion/exclusion criteria (as per Table 1) based on the title and abstract. The citations excluded at this stage were assigned an appropriate exclusion code to include:
    - Not relevant intervention
    - Not relevant disease
    - Not relevant line of therapy
    - Pre-2019 conference abstract
    - Not relevant outcome (used at full publication review stage only)
    - Duplicate publication
    - Not relevant study design
    - Animal/*in vitro* study
    - Linked publication (e.g. a conference abstract that had been superseded by a full journal article and that does not report any unique data)
    - Review publication
    - Study protocol
3) The full text of citations included at abstract screening stage were obtained to ascertain whether the publications did meet the eligibility criteria (as per Table 1). Again, citations excluded at this stage were assigned a code together with a more detailed explanation of the reason for exclusion at full publication review.

Citations were screened by two independent analysts at both the title/abstract and full publication stage. Any discrepancies were resolved by consensus or referred to the project manager. This procedure complies with HTA guidelines for conducting a robust SLR (1).

A1.1.3.1 Assessment of study bias

Quality (risk of bias) assessment of eligible randomised controlled trials (RCTs) was conducted using the seven-criteria checklist provided in Section 2.5 of the NICE single technology appraisal user guide (2). Quality (risk of bias) assessment of non-randomised studies was conducted using the Downs and Black checklist (3). This approach is based on guidance provided by the Centre for Reviews and Disseminations (CRD) for assessing the quality of studies included in SLRs (1).

A1.1.4 Search strategies

A1.1.4.1 December 2021

Table 2: Embase (Ovid): 1974 to 2021 December 13: searched 14.12.2021

#	Searches	Results
1	exp diffuse large B cell lymphoma/	18414
2	exp large cell lymphoma/	48395
3	(((bcell or b-cell or b cell) adj3 lymphoma*) or (diffuse adj3 (bcell or b-cell or b cell) adj3 lymphoma*)).ti,ab.	64386
4	(DLBCL or anaplastic large cell lymphoma* or disseminated large cell lymphoma* or intravascular large b cell lymphoma* or large b cell lymphoma* or large cell diffuse lymphoma or large cell follicular lymphoma or large cell ki-1 lymphoma or primary cutaneous anaplastic large cell lymphoma or b cell non-hodgkin* or diffuse mixed lymphoma or immunoblastic lymphoma or aggressive non-hodgkin$ lymphoma).ti,ab.	45860
5	or/1-4	85300
6	Clinical trial/	1020456
7	Randomized controlled trial/	686389
8	controlled clinical trial/	464611
9	multicenter study/	308080
10	Phase 3 clinical trial/	57634
11	Phase 4 clinical trial/	4568
12	exp RANDOMIZATION/	92603
13	Single blind procedure/	44557
14	Double blind procedure/	190342
15	Crossover procedure/	68884
16	Placebo/	374494
17	Randomi?ed controlled trial$.tw.	272159
18	Rct.tw.	44540
19	(random$ adj2 allocat$).tw.	48332
20	single blind$.tw.	27962
21	double blind$.tw.	225584
22	((treble or triple) adj blind$).tw.	1463
23	Placebo$.tw.	335298
24	Prospective study/	730938
25	or/6-24	2604533
26	Case study/	82627
27	Case report.tw.	469688

28	letter/	1129402
29	Editorial.pt.	709984
30	review.pt.	2826221
31	Note.pt.	874539
32	or/26-31	6049055
33	25 not 32	2214655
34	Clinical study/	156822
35	Case control study/	180958
36	Longitudinal study/	164489
37	Cohort analysis/	782992
38	(Cohort adj (study or studies)).mp.	377155
39	(Case control adj (study or studies)).tw.	149433
40	(follow up adj (study or studies)).tw.	67755
41	single arm.tw.	21181
42	(observational adj (study or studies)).tw.	204799
43	(epidemiologic$ adj (study or studies)).tw.	113598
44	(cross sectional adj (study or studies)).tw.	270863
45	((comparative or evaluation) adj (study or studies)).tw.	136941
46	or/34-45	2055636
47	46 not 32	1918686
48	33 or 47	3727446
49	5 and 48	12141
50	cancer recurrence/	225118
51	((second or third or fourth or 2nd or 3rd or 4th) adj3 line).tw.	59372
52	(refractory or intoleran* or failure* or resistan* or recurren* or metasta* or progress* or invasive* or chemorefractory or advanced or relapse*).tw.	6279874
53	((previous* or prior or salvage) adj3 (treat* or therap* or regimen*)).tw.	225068
54	50 or 51 or 52 or 53	6415164
55	49 and 54	8147

Table 3: Ovid MEDLINE(R) and Epub Ahead of Print, In-Process, In-Data-Review & Other Non-Indexed Citations, Daily and Versions(R): 1946 to December 13, 2021: searched 14.12.2021

#	Searches	Results
1	exp Lymphoma, Large B-Cell, Diffuse/	21407
2	exp lymphoma, b-cell/	51641

3	(((bcell or b-cell or b cell) adj3 lymphoma*) or (diffuse adj3 (bcell or b-cell or b cell) adj3 lymphoma*)).ti,ab.	41084
4	(DLBCL or anaplastic large cell lymphoma* or disseminated large cell lymphoma* or intravascular large b cell lymphoma* or large b cell lymphoma* or large cell diffuse lymphoma or large cell follicular lymphoma or large cell ki-1 lymphoma or primary cutaneous anaplastic large cell lymphoma or b cell non-hodgkin* or diffuse mixed lymphoma or immunoblastic lymphoma or aggressive non-hodgkin$ lymphoma).ti,ab.	25442
5	or/1-4	76445
6	Randomized Controlled Trials as Topic/	150736
7	randomized controlled trial/	552270
8	Random Allocation/	106260
9	Double Blind Method/	168681
10	Single Blind Method/	31279
11	clinical trial/	532565
12	clinical trial, phase i.pt.	22730
13	clinical trial, phase ii.pt.	36439
14	clinical trial, phase iii.pt.	19504
15	clinical trial, phase iv.pt.	2228
16	controlled clinical trial.pt.	94572
17	randomized controlled trial.pt.	552270
18	multicenter study.pt.	309790
19	clinical trial.pt.	532565
20	Clinical Trials as topic/	198261
21	or/6-20	1459603
22	(clinical adj trial$).tw.	419945
23	((singl$ or doubl$ or treb$ or tripl$) adj (blind$3 or mask$3)).tw.	184861
24	PLACEBOS/	35784
25	placebo$.tw.	231128
26	randomly allocated.tw.	32450
27	(allocated adj2 random$).tw.	35977
28	or/22-27	706466
29	21 or 28	1769151
30	case report.tw.	349979
31	letter/	1162443
32	historical article/	366738
33	or/30-32	1861784

34	29 not 33	1729710
35	Epidemiologic studies/	8917
36	exp case control studies/	1258011
37	exp cohort studies/	2258648
38	Case control.tw.	139133
39	(cohort adj (study or studies)).tw.	255927
40	Cohort analy$.tw.	9736
41	(Follow up adj (study or studies)).tw.	52523
42	(observational adj (study or studies)).tw.	132032
43	Longitudinal.tw.	280697
44	Retrospective.tw.	630176
45	Cross sectional.tw.	425891
46	Cross-sectional studies/	401687
47	or/35-46	3400493
48	34 or 47	4670500
49	5 and 48	13382
50	((second or third or fourth or 2nd or 3rd or 4th) adj3 line).tw.	31206
51	(refractory or intoleran* or failure* or resistan* or recurren* or metasta* or progress* or invasive* or chemorefractory or advanced or relapse*).tw.	4557635
52	((previous* or prior or salvage) adj3 (treat* or therap* or regimen*)).tw.	118715
53	or/50-52	4626027
54	49 and 53	6731

Table 4: EBM Reviews (Ovid): ACP Journal Club 1991 to November 2021, Cochrane Central Register of Controlled Trials November 2021, Cochrane Database of Systematic Reviews 2005 to December 09, 2021, Cochrane Clinical Answers November 2021, Cochrane Methodology Register 3rd Quarter 2012, Database of Abstracts of Reviews of Effects 1st Quarter 2016, Health Technology Assessment 4th Quarter 2016, NHS Economic Evaluation Database 1st Quarter 2016: searched 14.12.2021

#	Searches	Results
1	exp Lymphoma, Large B-Cell, Diffuse/	452
2	exp lymphoma, b-cell/	742
3	(((bcell or b-cell or b cell) adj3 lymphoma*) or (diffuse adj3 (bcell or b-cell or b cell) adj3 lymphoma*)).ti,ab.	2421
4	(DLBCL or anaplastic large cell lymphoma* or disseminated large cell lymphoma* or intravascular large b cell lymphoma* or large b cell lymphoma* or large cell diffuse lymphoma or large cell follicular lymphoma or large cell ki-1 lymphoma or primary cutaneous anaplastic large cell lymphoma or b cell non-hodgkin* or	2558

	diffuse mixed lymphoma or immunoblastic lymphoma or aggressive non-hodgkin$ lymphoma).ti,ab.	
5	or/1-4	3314
6	((second or third or fourth or 2nd or 3rd or 4th) adj3 line).tw.	9327
7	(refractory or intoleran* or failure* or resistan* or recurren* or metasta* or progress* or invasive* or chemorefractory or advanced or relapse*).tw.	432473
8	((previous* or prior or salvage) adj3 (treat* or therap* or regimen*)).tw.	37647
9	or/6-8	449292
10	5 and 9	2142

A1.1.4.2 September 2022

Table 5: Embase (Ovid): 1974 to 2022 September 14: searched 15.9.22

#	Searches	Results
1	exp diffuse large B cell lymphoma/	22096
2	exp large cell lymphoma/	52509
3	(((bcell or b-cell or b cell) adj3 lymphoma*) or (diffuse adj3 (bcell or b-cell or b cell) adj3 lymphoma*)).ti,ab.	69015
4	(DLBCL or anaplastic large cell lymphoma* or disseminated large cell lymphoma* or intravascular large b cell lymphoma* or large b cell lymphoma* or large cell diffuse lymphoma or large cell follicular lymphoma or large cell ki-1 lymphoma or primary cutaneous anaplastic large cell lymphoma or b cell non-hodgkin* or diffuse mixed lymphoma or immunoblastic lymphoma or aggressive non-hodgkin$ lymphoma).ti,ab.	49562
5	or/1-4	91390
6	Clinical trial/	1044958
7	Randomized controlled trial/	727689
8	controlled clinical trial/	467065
9	multicenter study/	336841
10	Phase 3 clinical trial/	62884
11	Phase 4 clinical trial/	4932
12	exp RANDOMIZATION/	95347
13	Single blind procedure/	47513
14	Double blind procedure/	198668
15	Crossover procedure/	71425
16	Placebo/	385410
17	Randomi?ed controlled trial$.tw.	295045
18	Rct.tw.	48605
19	(random$ adj2 allocat$).tw.	51183

20	single blind$.tw.	29511
21	double blind$.tw.	233623
22	((treble or triple) adj blind$).tw.	1645
23	Placebo$.tw.	348580
24	Prospective study/	794457
25	or/6-24	2751254
26	Case study/	88268
27	Case report.tw.	497654
28	letter/	1162857
29	Editorial.pt.	737019
30	review.pt.	2948400
31	Note.pt.	906632
32	or/26-31	6295096
33	25 not 32	2349133
34	Clinical study/	160312
35	Case control study/	192739
36	Longitudinal study/	178085
37	Cohort analysis/	894607
38	(Cohort adj (study or studies)).mp.	420349
39	(Case control adj (study or studies)).tw.	157699
40	(follow up adj (study or studies)).tw.	70331
41	single arm.tw.	24364
42	(observational adj (study or studies)).tw.	226128
43	(epidemiologic$ adj (study or studies)).tw.	117396
44	(cross sectional adj (study or studies)).tw.	301511
45	((comparative or evaluation) adj (study or studies)).tw.	143644
46	or/34-45	2251975
47	46 not 32	2104581
48	33 or 47	4001089
49	5 and 48	13976
50	cancer recurrence/	245885
51	((second or third or fourth or 2nd or 3rd or 4th) adj3 line).tw.	63533
52	(refractory or intoleran* or failure* or resistan* or recurren* or metasta* or progress* or invasive* or chemorefractory or advanced or relapse*).tw.	6620760
53	((previous* or prior or salvage) adj3 (treat* or therap* or regimen*)).tw.	238423
54	50 or 51 or 52 or 53	6762656

55	49 and 54	9606
56	limit 55 to dc=20211214-20220915	1558
57	limit 55 to yr="2022 -Current"	636
58	56 or 57	1564

Table 6: Ovid MEDLINE(R) and Epub Ahead of Print, In-Process, In-Data-Review & Other Non-Indexed Citations, Daily and Versions: 1946 to September 13, 2022: searched 15.9.22

#	Searches	Results
1	exp Lymphoma, Large B-Cell, Diffuse/	22614
2	exp lymphoma, b-cell/	53646
3	(((bcell or b-cell or b cell) adj3 lymphoma*) or (diffuse adj3 (bcell or b-cell or b cell) adj3 lymphoma*)).ti,ab.	43472
4	(DLBCL or anaplastic large cell lymphoma* or disseminated large cell lymphoma* or intravascular large b cell lymphoma* or large b cell lymphoma* or large cell diffuse lymphoma or large cell follicular lymphoma or large cell ki-1 lymphoma or primary cutaneous anaplastic large cell lymphoma or b cell non-hodgkin* or diffuse mixed lymphoma or immunoblastic lymphoma or aggressive non-hodgkin$ lymphoma).ti,ab.	27079
5	or/1-4	79579
6	Randomized Controlled Trials as Topic/	157732
7	randomized controlled trial/	577088
8	Random Allocation/	106880
9	Double Blind Method/	173068
10	Single Blind Method/	32183
11	clinical trial/	536104
12	clinical trial, phase i.pt.	24234
13	clinical trial, phase ii.pt.	38617
14	clinical trial, phase iii.pt.	20964
15	clinical trial, phase iv.pt.	2362
16	controlled clinical trial.pt.	95028
17	randomized controlled trial.pt.	577088
18	multicenter study.pt.	325584
19	clinical trial.pt.	536104
20	Clinical Trials as topic/	200377
21	or/6-20	1512413
22	(clinical adj trial$).tw.	448737
23	((singl$ or doubl$ or treb$ or tripl$) adj (blind$3 or mask$3)).tw.	191265

24	PLACEBOS/	35924
25	placebo$.tw.	239146
26	randomly allocated.tw.	34376
27	(allocated adj2 random$).tw.	38010
28	or/22-27	743970
29	21 or 28	1840399
30	case report.tw.	372051
31	letter/	1193235
32	historical article/	368725
33	or/30-32	1915887
34	29 not 33	1799646
35	Epidemiologic studies/	9185
36	exp case control studies/	1353248
37	exp cohort studies/	2394360
38	Case control.tw.	146460
39	(cohort adj (study or studies)).tw.	285076
40	Cohort analy$.tw.	10714
41	(Follow up adj (study or studies)).tw.	54375
42	(observational adj (study or studies)).tw.	145891
43	Longitudinal.tw.	300861
44	Retrospective.tw.	685048
45	Cross sectional.tw.	467662
46	Cross-sectional studies/	440302
47	or/35-46	3603026
48	34 or 47	4921036
49	5 and 48	14215
50	((second or third or fourth or 2nd or 3rd or 4th) adj3 line).tw.	33268
51	(refractory or intoleran* or failure* or resistan* or recurren* or metasta* or progress* or invasive* or chemorefractory or advanced or relapse*).tw.	4800428
52	((previous* or prior or salvage) adj3 (treat* or therap* or regimen*)).tw.	123791
53	or/50-52	4871567
54	49 and 53	7265
55	limit 54 to dt=20211214-20220915	409
56	limit 54 to yr="2022 -Current"	487
57	55 or 56	516

Table 7: EBM Reviews (Ovid): ACP Journal Club 1991 to July 2022, Cochrane Central Register of Controlled Trials August 2022, Cochrane Database of Systematic Reviews 2005 to September 14, 2022 Cochrane Clinical Answers August 2022: searched 15.9.22

#	Searches	Results
1	exp Lymphoma, Large B-Cell, Diffuse/	477
2	exp lymphoma, b-cell/	764
3	(((bcell or b-cell or b cell) adj3 lymphoma*) or (diffuse adj3 (bcell or b-cell or b cell) adj3 lymphoma*)).ti,ab.	2401
4	(DLBCL or anaplastic large cell lymphoma* or disseminated large cell lymphoma* or intravascular large b cell lymphoma* or large b cell lymphoma* or large cell diffuse lymphoma or large cell follicular lymphoma or large cell ki-1 lymphoma or primary cutaneous anaplastic large cell lymphoma or b cell non-hodgkin* or diffuse mixed lymphoma or immunoblastic lymphoma or aggressive non-hodgkin$ lymphoma).ti,ab.	2534
5	or/1-4	3282
6	((second or third or fourth or 2nd or 3rd or 4th) adj3 line).tw.	8697
7	(refractory or intoleran* or failure* or resistan* or recurren* or metasta* or progress* or invasive* or chemorefractory or advanced or relapse*).tw.	430641
8	((previous* or prior or salvage) adj3 (treat* or therap* or regimen*)).tw.	37667
9	or/6-8	445977
10	5 and 9	2167
11	limit 10 to yr="2022 -Current"	54

A1.2 Results – Clinical SLR

A1.2.1 Identification of studies

The electronic database search for the original SLR was conducted on the 14th December 2021 and identified a total of 17,020 articles. After the removal of 3,795 duplicates, 13,225 articles were screened by title and abstract. In total, 12,790 articles were excluded, and 435 articles were deemed potentially relevant; these were screened based on the full publication. At this stage, a further 210 citations were excluded. Hand searching yielded 23 additional relevant citations. Therefore, a total of 248 publications were included in the SLR.

The SLR was updated on the 15th September 2022. Across all databases a total of 2,134 articles were identified and 2,045 screened by title and abstract following removal of duplicates. In total, 1,933 articles were excluded, and 112 articles were deemed potentially relevant and screened based on the full publication. At this stage, a further 50 citations were excluded. Hand searching yielded 10 additional relevant citations. Therefore, a total of 72 publications were included in the SLR update.

In summary, a total of 320 articles (related to 232 unique studies) were eligible for inclusion across both the original and updated SLR (Section A1.2.3).

The flow of studies through the review is summarised in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram in Figure 1, with separate flow diagrams for the original and updated SLR reported in

A1.2.3.1 December 2021

Figure 2 and A1.2.3.2 September 2022

Figure 3, respectively. A list of studies excluded at full publication review, together with an exclusion code and additional rationale for exclusion, is provided in Table 9. Note that relevant meta-analysis publications are indicated in this list of excluded studies so that these could be revisited for citation chasing and baseline data gap filling.

A1.2.2 Summary of studies

A list of all publications included in the SLR (n=320 reporting on 232 unique studies) and details of the interventions investigated is provided in Table 8. The 320 publications comprised 187 full publications and 131 abstract publications.

In summary, the 232 unique studies in the SLR investigated a total of 256 treatment arms of interest (several studies had multiple treatment arms):

- Axicabtagene (n=73)
- Lenalidomide (n=37)
- Polatuzumab vedotin (n=34)
- Tisagenlecleucel (n=30)
- Bendamustine plus rituximab (n=26)
- R-GemOx (n=17)
- Pixantrone (n=15)
- R-DHAP (n=14)
- Lisocabtagene (n=4)
- Tafasitamab (n=3)
- Glofitamab (n=3)

In total, 115 studies included in the SLR (reported in 123 publications) were either related to glofitamab or polatuzumab vedotin (Roche have access to the full trial data; n=34), investigated a non-relevant combination therapy (n=61) or line of therapy (n=3), were reported in non-English language publications (n=3), or reported insufficient data (n=13) or non-relevant outcomes (n=1) for consideration in the feasibility assessment. The remaining 117 studies (reported in reported in 197 publications; reporting on 129 unique treatment arms of interest) underwent a preliminary top-line extraction to obtain details of study design, sample size, study population (in terms of histology, prior therapy, prior rituximab exposure), and the reporting of key outcomes of interest.

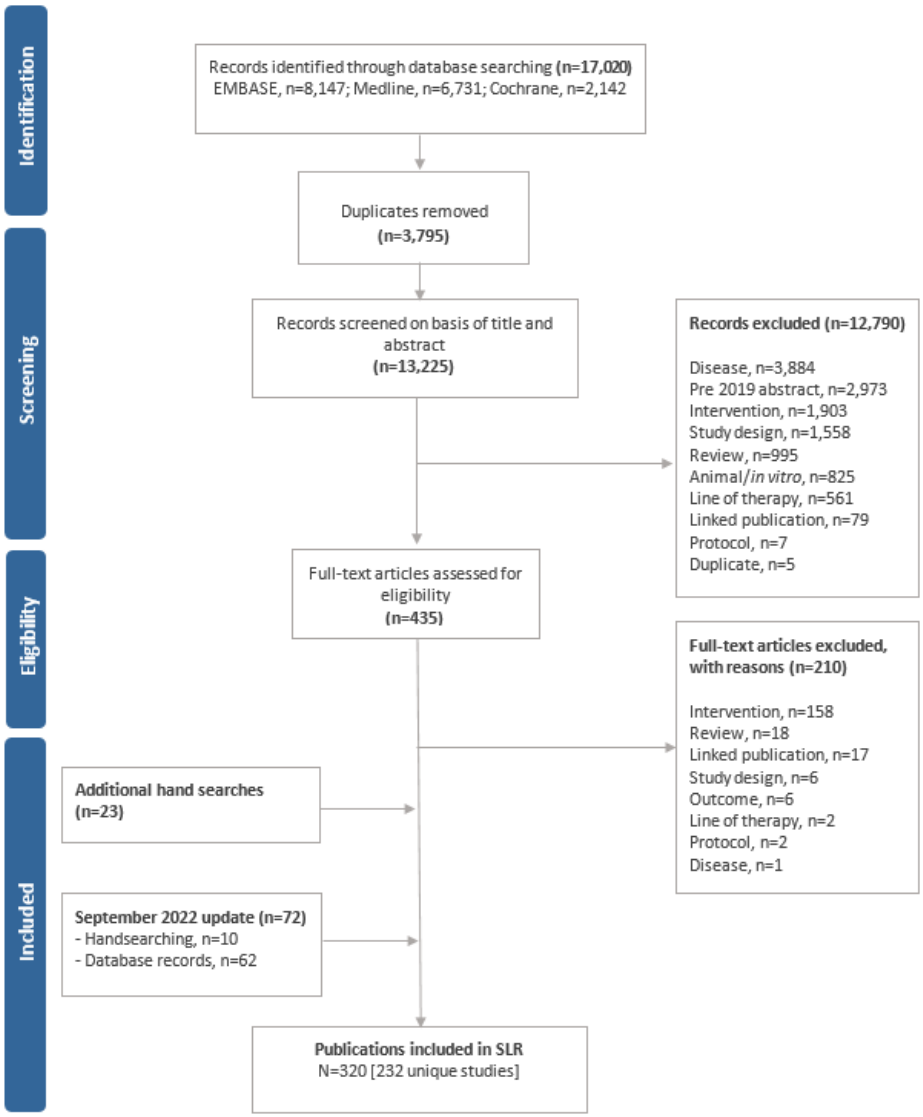
The 117 studies considered in the feasibility assessment were predominantly retrospective studies (n=77). The majority of the 40 prospective studies were single-arm phase I/II trials, with only four RCTs included. Few studies were conducted internationally (n=13) and notably a large proportion of the studies were conducted in the US (n=45).

In 86 of the studies, the population enrolled was exclusively DLBCL and the percentage of the DLBCL subgroup ranged from 19 to 97% of the total study population in the remaining studies. There was a substantial range in the size of the DLBCL cohort across the 117 studies, ranging from 4 to 1,389 patients (median, 61).

In the majority of studies (n=97) pivotal histologies (diffuse large B-cell lymphoma, not otherwise specified [DLBCL NOS], high-grade b-cell lymphoma [HGBCL], primary mediastinal b-cell lymphoma [PMBCL], and transformed follicular lymphoma [tFL]) were aligned or ≥80% aligned with the NP30179 pivotal histologies; and 73/97 of these studies were conducted in the 2L+ setting. The most commonly reported outcome across the studies was safety (n=82), followed by response outcomes (n=75), overall survival (OS, n=57), progression-free survival (PFS, n=57), duration of response (DOR, n=16) and duration of complete response (DOCR, n=6).

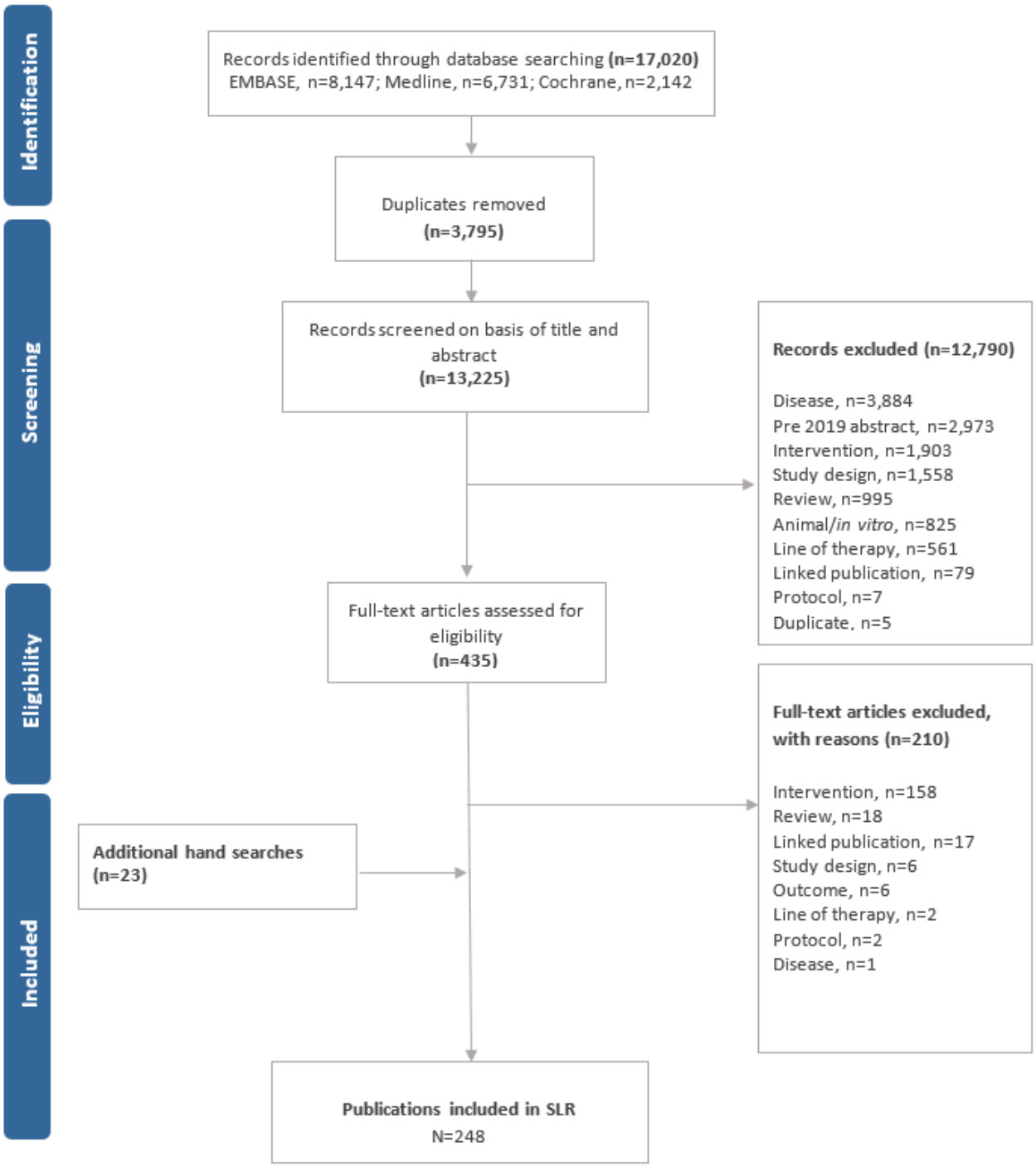
A1.2.3 PRISMA flow diagram

Figure 1: PRISMA flow diagram for the clinical SLR



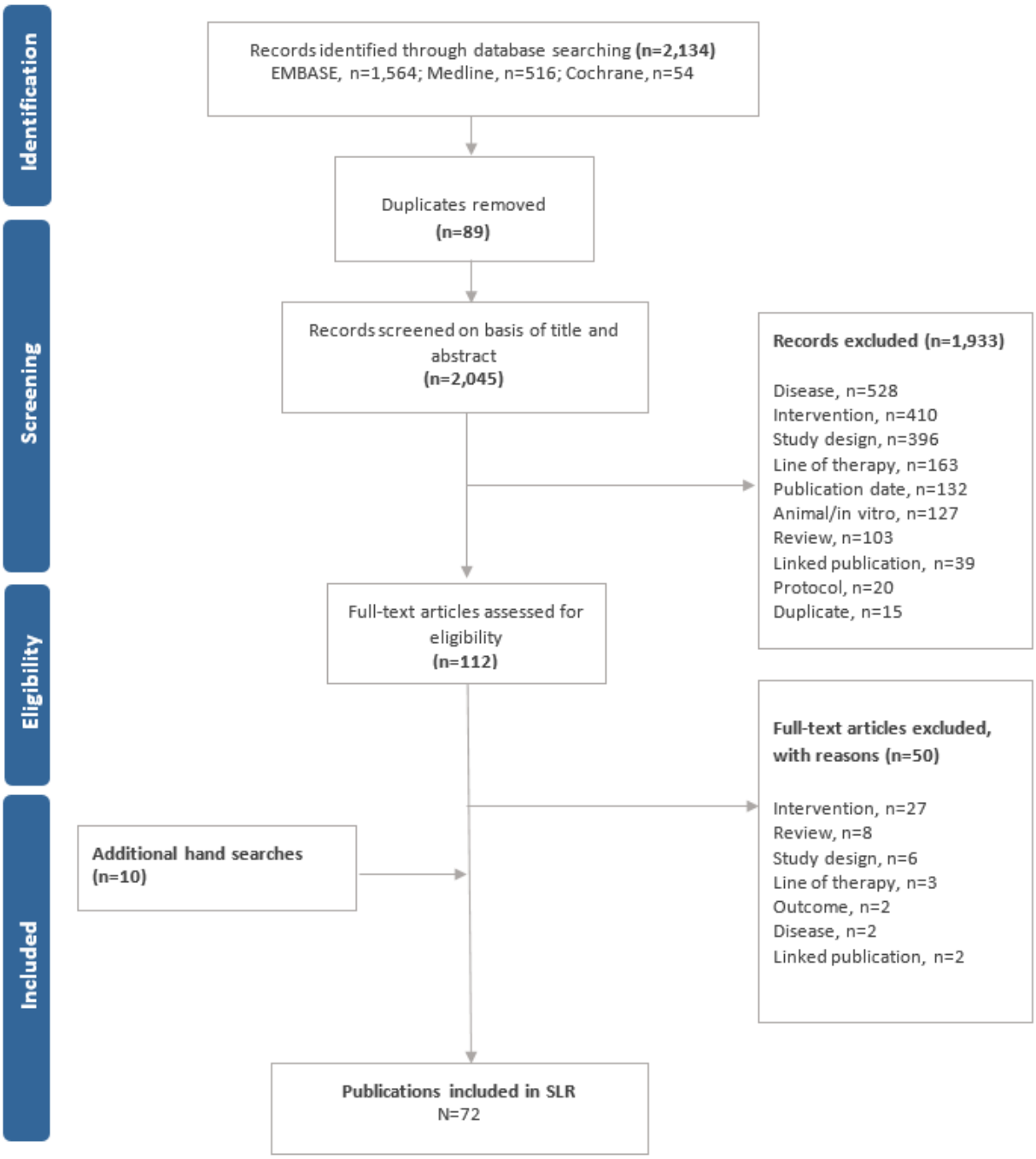
A1.2.3.1 December 2021

Figure 2: PRISMA flow diagram for the clinical SLR-December 2021



A1.2.3.2 September 2022

Figure 3: PRISMA flow diagram for the clinical SLR- September 2022



A1.2.4 List of included and excluded trials

Table 8: List of included trials in the clinical SLR

Author	Title	Citation	Full publication/ abstract	Trial name	Intervention	Included on topline extraction	Reason for exclusion from topline extraction	Explanation	Source
Abbasi, A.	Axicabtagene ciloleucel CD19 CAR-T cell therapy results in high rates of systemic and neurologic remissions in ten patients with refractory large B cell lymphoma including two with HIV and viral hepatitis	J Hematol Oncol. 2020 Jan 3;13(1):1.	Full publication		Axicabtagene	Yes	NA		Original SLR
Ahmed, S.	Efficacy of Chimeric Antigen Receptor (CAR) T-Cell Therapy, Axicabtagene Ciloleucel (axi-cel), in Patients with Refractory Large B-Cell Lymphoma (LBCL)	Transplantation and Cellular Therapy. 27(3 Supplement):S403-S404.	Abstract		Axicabtagene		Line of therapy	Unclear line of therapy	SLR update
Al Zaki, A.	Day 30 SUVmax Predicts Progression in Lymphoma Patients Achieving PR/SD After CAR T-cell Therapy	Blood Advances. 2022. 11:11.	Full publication		Axicabtagene	Yes	NA		SLR update
Ayuk, F. A.	Axicabtagene ciloleucel in vivo expansion and treatment outcome in aggressive B-cell lymphoma in a real-world setting	Blood Adv. 2021 Jun 8;5(11):2523-2527	Full publication		Axicabtagene	Yes	NA		Original SLR

Borogovac, A.	Successful development of an outpatient chimeric antigen receptor (CAR) t cell therapy program	Blood. 2021. 138(SUPPL 1):4821.	Abstract		Axicabtagene		Limited reporting	Baseline and outcome data not reported for a single intervention	SLR update
Breen, W.	Metabolic Kinetics of Non-Hodgkin Lymphoma Prior to CAR-T Infusion: Prognostic Factors and Risk Stratification	International Journal of Radiation Oncology Biology Physics. 2021. 111(3 Supplement):S131-S132.	Abstract		Axicabtagene		Limited reporting	Not included on topline extraction as very limited data and unclear the % of patients with DLBCL	Original SLR
Cappell, K. M.	Long-Term Follow-Up of Anti-CD19 Chimeric Antigen Receptor T-Cell Therapy	J Clin Oncol. 2020 Nov 10;38(32):3805-3815.	Full publication	NCT00924326	Axicabtagene	Yes	NA		Original SLR
Dean, E. A.	High metabolic tumor volume is associated with decreased efficacy of axicabtagene ciloleucel in large B-cell lymphoma	Blood Adv. 2020 Jul 28;4(14):3268-3276	Full publication		Axicabtagene	Yes	NA		Original SLR
Forero-Forero, J. V.	Predictors and management of relapse to Axicabtagene Ciloleucel in patients with aggressive B-cell lymphoma	Hematol Oncol Stem Cell Ther . 2021 Sep 20;S1658-3876(21)00084-4	Full publication		Axicabtagene	Yes	NA		Original SLR
Frank, M. J.	Monitoring of Circulating Tumor DNA Improves Early Relapse Detection After Axicabtagene Ciloleucel Infusion in Large B-Cell Lymphoma: Results of	J Clin Oncol. 2021 Sep 20;39(27):3034-3043	Full publication		Axicabtagene	yes	NA		Original SLR

	a Prospective Multi-Institutional Trial								
Gaut, D.	Granulocyte Colony-Stimulating Factor (G-CSF) Interactions with Chimeric Antigen Receptor (CAR) T-Cell Therapy for Diffuse Large B-Cell Lymphoma	Blood. 2019. 134(Supplement 1):4109.	Abstract		Axicabtagene	Yes	NA		Original SLR
Gouni, S.	Axicabtagene ciloleucel in relapsed or refractory large B-cell lymphoma patients in complete metabolic response at time of infusion	Blood. 2021. 138(SUPPL 1):1740.	Abstract		Axicabtagene	Yes	NA		SLR update
Grana, A.	Safety of Axicabtagene Ciloleucel for the Treatment of Relapsed or Refractory Large B-Cell Lymphoma	Clin Lymphoma Myeloma Leuk. 2021 Apr;21(4):238-245	Full publication		Axicabtagene	Yes	NA		Original SLR
Greenbaum, U.	The easix (endothelial activation and stress index) score predicts for CAR T related toxicity in patients receiving axicabtagene ciloleucel (axi-cel) for non-Hodgkin lymphoma (NHL)	Blood. 2020. 136(SUPPL 1):17-18.	Abstract		Axicabtagene	Yes	NA		Original SLR
Hamadani, M.	Allogeneic Transplant and CAR-T Therapy After Autologous Transplant Failure in DLBCL: A Noncomparative Cohort Analysis	Blood Adv. 2022 Jan 25;6(2):486-494	Full publication		Axicabtagene	Yes	NA		SLR update
Hashmi, H.	Fever Characteristics Associated with Toxicity and Outcome	Blood. 2019. 134(Supplement 1):1612.	Abstract		Axicabtagene	Yes	NA		Original SLR

	after Anti-CD19 CAR T-Cell Therapy for Aggressive Lymphoma								
Jacobson, C. A.	Real-world Evidence of Axicabtagene Ciloleucel for the Treatment of Large B-Cell Lymphoma in the United States	Transplantation and Cellular Therapy. 2022	Full publication		Axicabtagene	Yes	NA		SLR update
Jacobson, C. A.	Outcomes of Patients (Pts) in ZUMA-9, a Multicenter, Open-Label Study of Axicabtagene Ciloleucel (Axi-Cel) in Relapsed/Refractory Large B Cell Lymphoma (R/R LBCL) for Expanded Access and Commercial Out-of-Specification (OOS) Product	Blood. 2020. 136(SUPPL 1):2-3.	Abstract	ZUMA-9	Axicabtagene	Yes	NA		Original SLR
Jacobson, C. A.	Axicabtagene Ciloleucel in the Non-Trial Setting: Outcomes and Correlates of Response, Resistance, and Toxicity	J Clin Oncol. 2020 Sep 20;38(27):3095-3106	Full publication		Axicabtagene	Yes	NA		Original SLR
Jacobson, C. A.	Phase 1/2 primary analysis of ZUMA-6: Axicabtagene ciloleucel (Axi-Cel) in combination Withatezolizumab (Atezo) for the treatment of patients (Pts)with refractory diffuse large B cell lymphoma (DLBCL)	Cancer Research. 2020. 80(16 SUPPL).	Abstract	ZUMA-6	Axicabtagene		Treatment regimen	Not extracted as axicabtagene + atezolizumab	Original SLR

Jain T	Safety and feasibility of chimeric antigen receptor T celltherapy aNer allogeneic hematopoietic cell transplantation inrelapsed/refractory B cell non-Hodgkin lymphoma.	Leukemia2019;33(10):2540-4.	Full publication		Axicabtagene	Yes	NA		Original SLR
Kato K	Phase 2 study of axicabtagene ciloleucel in Japanese patients with relapsed or refractory large B-cell lymphoma	Int J Clin Oncol. 2022 Jan;27(1):213-223.	Full publication	JapicCTI-183914	Axicabtagene	Yes	NA		SLR update
Khurana, A.	Impact of type of salvage therapy (ST) and response to bridging therapy (BT) on CAR-T therapy outcomes for relapsed/refractory aggressive B-cell non-Hodgkin lymphoma (NHL)	Journal of Clinical Oncology. 2020. 38(15).	Abstract		Axicabtagene	Yes	NA		Original SLR
Khurana, A.	Lines of therapy before autologous stem cell transplant and CAR-T affect outcomes in aggressive Non-Hodgkin's lymphoma	Am J Hematol. 2021 Oct 1;96(10):E386-E389.	Full publication		Axicabtagene		Treatment regimen	Of the CAR-T cohort, all those who were third line had received ASCT	Original SLR
Khurana, A.	Response to bridging therapy as a predictor of outcomes for chimeric antigen receptor therapy in large B-cell lymphoma	Blood. 2021. 138(SUPPL 1):3841.	Abstract		Axicabtagene	Yes	NA		SLR update
Kochenderfer, J. N.	Chemotherapy-refractory diffuse large	J Clin Oncol. 2015 Feb 20;33(6):540-9	Full publication	NCT00924326	Axicabtagene	Yes	NA		Original SLR

	B-cell lymphoma and indolent B-cell malignancies can be effectively treated with autologous T cells expressing an anti-CD19 chimeric antigen receptor								
Kwon, M.	Real World of Experience Axicabtagene Ciloleucel for the Treatment of Relapsed or Refractory Large B-Cell Lymphoma in Spain	Bone Marrow Transplantation. 2021. 56:37-39.	Abstract		Axicabtagene	Yes	NA		Original SLR
Locke FL	Real-world outcomes of axicabtagene ciloleucel for the treatment of large B-cell lymphoma by race and ethnicity	ASCO 2022	Abstract/poster		Axicabtagene	Yes	NA		SLR update
Logue, J. M.	Immune reconstitution and associated infections following axicabtagene ciloleucel in relapsed or refractory large B-cell lymphoma	Haematologica. 2021 Apr 1;106(4):978-986	Full publication		Axicabtagene	Yes	NA		Original SLR
Maakaron, J.	Icans prophylaxis with simvastatin and intrathecal dexamethasone in adults receiving axicabtagene ciloleucel (Axi-cel) treatment	Blood. 2021. 138(SUPPL 1):1744.	Abstract		Axicabtagene	Yes	NA		SLR update
Melody, M.	Impact of hypoalbuminemia on the prognosis of relapsed/refractory B-cell lymphoma treated	Eur J Haematol. 2021 Jul;107(1):48-53	Full publication		Axicabtagene	Yes	NA		Original SLR

	with axicabtagene ciloleucel								
Melody, M.	C-reactive protein and ferritin levels and length of intensive care unit stay in patients with B-cell lymphomas treated with axicabtagene ciloleucel	Hematol Oncol Stem Cell Ther . 2021 Jun;14(2):141-146	Full publication		Axicabtagene	Yes	NA		Original SLR
Melody, M.	Incidence of thrombosis in relapsed/refractory B-cell lymphoma treated with axicabtagene ciloleucel: Mayo Clinic experience	Leukemia & Lymphoma. 2022	Full publication		Axicabtagene	Yes	NA		SLR update
Mian A	Outcomes and factors impacting use of axicabtagene ciloleucel in patients with relapsed or refractory large B-cell lymphoma: results from an intention-to-treat analysis	Leuk Lymphoma. 2021 Jun;62(6):1344-1352	Full publication		Axicabtagene	Yes	NA		Original SLR
Mumtaz, A. A.	Ocular adverse events associated with chimeric antigen receptor T-cell therapy: a case series and review	British Journal of Ophthalmology. 2022. 10:10	Full publication		Axicabtagene	Yes	NA		SLR update
Nastoupil, L. J.	Standard-of-care axicabtagene ciloleucel for relapsed or refractory large B-cell lymphoma: Results from the US lymphoma CAR T consortium	J Clin Oncol. 2020 Sep 20;38(27):3119-3128	Full publication	US Lymphoma CAR T Consortium	Axicabtagene	Yes	NA		Original SLR
Neelapu SS	Axicabtagene Ciloleucel CAR T-Cell	N Engl J Med. 2017 Dec 28;377(26):2531-2544.	Full publication	ZUMA-1	Axicabtagene	Yes	NA		Original SLR

	Therapy in Refractory Large B-Cell Lymphoma								
Panaite, L.	Predictors of cytopenia after treatment with axicabtagene ciloleucel in patients with large cell lymphoma	Blood. 2020. 136(SUPPL 1):1-2.	Abstract		Axicabtagene	Yes	NA		Original SLR
Pasquini, M. C.	Post-Marketing Use Outcomes of an Anti-CD19 Chimeric Antigen Receptor (CAR) T Cell Therapy, Axicabtagene Ciloleucel (Axi-Cel), for the Treatment of Large B Cell Lymphoma (LBCL) in the United States (US)	Blood. 2019. 134(Supplement 1):764.	Abstract	Center for International Blood & Marrow Transplant Research (CIBMTR) Cellular Therapy (CT) Registry	Axicabtagene	Yes	NA		Original SLR
Pinnix, C. C.	Bridging therapy prior to axicabtagene ciloleucel for relapsed/refractory large B-cell lymphoma	Blood Adv. 2020 Jul 14;4(13):2871-2883	Full publication		Axicabtagene	Yes	NA		Original SLR
Quinn, R.	Neurotoxicity of axicabtagene ciloleucel and long-term outcomes-in a minority rich, ethnically diverse real world cohort	Blood. 2021. 138(SUPPL 1):4842.	Abstract		Axicabtagene	Yes	NA		SLR update
Sanderson, R.	Axicabtagene ciloleucel CD19 CAR T-cells for relapsed/refractory large B-cell lymphoma:	Bone Marrow Transplantation. 2020. 55:234-235.	Abstract		Axicabtagene	Yes	NA		Original SLR

	Realworld outcomes, toxicity and predictors of response from a prospective UK cohort								
Schubert, M. L.	Feasibility and Safety of CD19 Chimeric Antigen Receptor T Cell Treatment for B Cell Lymphoma Relapse after Allogeneic Hematopoietic Stem Cell Transplantation	Biol Blood Marrow Transplant . 2020 Sep;26(9):1575-1580	Full publication		Axicabtagene	Yes	NA		Original SLR
Shadman, M.	Autologous transplant vs chimeric antigen receptor T-cell therapy for relapsed DLBCL in partial remission	Blood. 2022. 139(9):1330-1339.	Full publication		Axicabtagene	Yes	NA		SLR update
Shapiro LC	Safety of axicabtagene ciloleucel for relapsed/refractory large B-cell lymphoma in an elderly intercity population	Bone Marrow Transplant. 2021 Jul;56(7):1761-1763.	Full publication		Axicabtagene	Yes	NA		Original SLR
Shouse, G.	Incidence and causes of prolonged hematologic toxicity after chimeric antigen receptor T cell therapy: A city of hope (COH) experience	Blood. 2020. 136(SUPPL 1):40-41.	Abstract		Axicabtagene	Yes	NA		Original SLR
Sohlbach, K.	Cd19-cart (Axicabtagene Ciloleucel) in patients with highly refractory diffuse large b-cell lymphoma-a single center experience	HemaSphere. 202. 4(Supplement 1):1007.	Abstract		Axicabtagene	Yes	NA		Original SLR
Spanjaart A	Population-based real world results of CD19-	ESMO 2022	Abstract/poster		Axicabtagene	Yes	NA		SLR update

	directed CAR T-cell therapy for patients with relapsed or refractory large B-cell lymphoma: The Dutch CAR T-cell tumorboard experience								
Spiegel, J. Y.	CAR T cells with dual targeting of CD19 and CD22 in adult patients with recurrent or refractory B cell malignancies: a phase 1 trial	Nat Med 27, 1419–1431 (2021)	Full publication		Axicabtagene	Yes	NA		Original SLR
Strati P	Axicabtagene Ciloleucel in combination with rituximab for the treatment of refractory large B-cell lymphoma: outcomes of the phase 2 ZUMA-14 study	Journal of Clinical Oncology 40, no. 16_suppl (June 01, 2022) 7567-7567.	Abstract/poster	ZUMA-14	Axicabtagene		Treatment regimen	Combination treatment	SLR update
Strati, P.	Clinical and radiologic correlates of neurotoxicity after axicabtagene ciloleucel in large B-cell lymphoma	Blood Advances. 2020. 4(16):3943-3951	Full publication		Axicabtagene	Yes	NA		Original SLR
Tabbara, N.	Decreased chimeric antigen receptor T-cell efficacy with severe or prolonged post-infusion cytopenias	Blood. 2021. 138(SUPPL 1):3869.	Abstract		Axicabtagene	Yes	NA		SLR update
Thakkar, A.	Patterns of leukocyte recovery predict infectious complications after CD19 CAR-T cell therapy in a real-world setting	Stem Cell Investig . 2021 Sep 6;8:18	Full publication		Axicabtagene	Yes	NA		Original SLR

Wang, M.	Characterizing outcomes of patients receiving axicabtagene ciloleucel and risk factors associated with survival	Transfusion. 2021. 61(SUPPL 3):94A	Abstract		Axicabtagene	Yes	NA		Original SLR
Wang, M.	Real-world safety and effectiveness of axicabtagene ciloleucel in patients with diffuse large B cell lymphoma	Clinical Pharmacology and Therapeutics. 2021. 109(SUPPL 1):S50.	Abstract		Axicabtagene	Yes	NA		Original SLR
Wudhikarn K	The impact of obesity and body weight on the outcome of patients with relapsed/refractory large B-cell lymphoma treated with axicabtagene ciloleucel	Blood Cancer J. 2021 Jul 1;11(7):124	Full publication		Axicabtagene	Yes	NA		Original SLR
Zareef, S.	Cardiovascular side effects of chimeric antigen receptor (CAR) T-cell products: A single center experience in a minority rich, ethnically diverse real-world cohort	Blood. 2021. 138(SUPPL 1):3840.	Abstract		Axicabtagene		Limited reporting	Limited to reporting of CV AEs only	SLR update
Ahmed, G.	Impact of Chronic Kidney Disease and Acute Kidney Injury on Safety and Outcomes of CAR T-Cell Therapy in Lymphoma Patients	Clinical lymphoma, myeloma & leukemia. 2022. 18:18.	Full publication		Axicabtagene, Tisagenlecleucel		Limited reporting	Histology not reported for treatment groups and only data for ICANS	SLR update
Bachy, E.	A real-world comparison of tisagenlecleucel and axicabtagene ciloleucel CAR T cells in relapsed or refractory diffuse large B cell lymphoma	Nature Medicine	Full publication	DESCAR-T	Axicabtagene, Tisagenlecleucel	Yes	NA		Original SLR

Bastos-Oreiro, M.	Best Treatment Option for Patients With Refractory Aggressive B-Cell Lymphoma in the CAR-T Cell Era: Real-World Evidence From GELTAMO/GETH Spanish Groups	Frontiers in Immunology. 2022. 13:855730.	Full publication		Axicabtagene, Tisagenlecleucel	Yes	NA		SLR update
Bethge, W. A.	GLA/DRST real-world outcome analysis of CAR-T cell therapies for large B-cell lymphoma in Germany	Blood. 2022.22	Full publication		Axicabtagene, Tisagenlecleucel	Yes	NA		SLR update
Chiappella, A.	Real-life CAR-T cell treatment in large B-cell lymphomas indicates that axi-cel and tisa-cel have similar outcomes, but long-term cytopenia is an emerging problem	Blood. 2021. 138(SUPPL 1):3867.	Abstract		Axicabtagene, Tisagenlecleucel		Limited reporting	No baseline data by treatment	Original SLR
Gauthier, J.	Impact of CD19 CAR T-cell product type on outcomes in relapsed or refractory aggressive B-NHL	Blood. 2022	Full publication		Axicabtagene, Tisagenlecleucel	Yes	NA		SLR update
Kuhnl, A.	A national service for delivering CD19 CAR-Tin large B-cell lymphoma - The UK real-world experience	British Journal of Haematology. 2022	Full publication		Axicabtagene, Tisagenlecleucel	Yes	NA		SLR update
Kwon, M.	Axicabtagene ciloleucel compared to tisagenlecleucel for the treatment of aggressive B-cell lymphoma	Haematologica. 2022	Full publication		Axicabtagene, Tisagenlecleucel	Yes	NA		SLR update
Riedell, P. A.	Patterns of Use, Outcomes, and Resource Utilization among Recipients of Commercial	Transplantation and Cellular Therapy. 2022	Full publication		Axicabtagene, Tisagenlecleucel	Yes	NA		SLR update

	Axicabtagene Ciloleucel and Tisagenlecleucel for Relapsed/Refractory Aggressive B-cell Lymphomas								
Riedell, P. A.	A multicenter analysis of outcomes, toxicities, and patterns of use with commercial axicabtagene ciloleucel and tisagenlecleucel for relapsed/refractory aggressive B-cell lymphomas	Blood. 2021. 138(SUPPL 1):2512.	Abstract		Axicabtagene, Tisagenlecleucel	Yes	NA		SLR update
Sanderson, R.	Car-t toxicity management and steroid use in high-grade b-cell lymphoma: Impact on real-world survival outcomes in the uk	Blood. 2021. 138(SUPPL 1):531.	Abstract		Axicabtagene, Tisagenlecleucel		Limited data	No baseline data by treatment	SLR update
Sesques P	CAR T-cell associated toxicity in large B-cell non-hodgkin lymphoma: a real world multicentric experience (DESCAR-T ANCILLARY study)	EHA 2022			Axicabtagene, Tisagenlecleucel	Yes	NA		SLR update
Sesques, P.	Commercial anti-CD19 CAR T cell therapy for patients with relapsed/refractory aggressive B cell lymphoma in a European center	Am J Hematol. 2020 Nov;95(11):1324-1333	Full publication		Axicabtagene, Tisagenlecleucel	Yes	NA		Original SLR
Steiner, R. E.	Cardiovascular events in patients treated with chimeric antigen receptor T-cell therapy	Haematologica. 2021. 11	Full publication		Axicabtagene, Tisagenlecleucel		Limited reporting	No data reported by intervention (although	SLR update

	for aggressive B-cell lymphoma							94% did have axi)	
Stolz, S.	Introducing innovative cellular therapies into the clinic: a 2-year retrospective experience of a chimeric antigen receptor T-cell programme at a single centre in Switzerland	Swiss Medical Weekly. 2022	Full publication		Axicabtagene, Tisagenlecleucel		Limited reporting	No data reported by intervention	SLR update
Wudhikarn, K.	Outcomes of aggressive B cell lymphoma patients with no evidence of measurable disease at the time of CD19 chimeric antigen receptor T cell therapy: The experience from the CAR T cell consortium	Blood. 2021. 138(SUPPL 1):2843.	Abstract	CAR T-cell consortium	Axicabtagene, Tisagenlecleucel		Limited reporting	No baseline or outcome data reported for individual CAR-Ts	Original SLR
Arcari, A.	Safety and efficacy of rituximab plus bendamustine in relapsed or refractory diffuse large B-cell lymphoma patients: an Italian retrospective multicenter study	Leukemia & Lymphoma. 2016. 57(8):1823-30.	Full publication		BR	Yes	NA		Original SLR
Budde, L. E.	Bendamustine with rituximab, etoposide and carboplatin (T(R)EC) in relapsed or refractory aggressive lymphoma: a prospective multicentre phase 1/2 clinical trial	British Journal of Haematology. 2018. 183(4):601-607.	Full publication		BR		Treatment regimen	Not extracted as combination treatment with bendamustine with rituximab, etoposide	Original SLR

								and carboplatin	
Cheson, B. D.	A phase I study of bendamustine, lenalidomide and rituximab in relapsed and refractory lymphomas	British Journal of Haematology. 2015. 169(4):528-33.	Full publication		BR		Treatment regimen	Not extracted as combination treatment with rituximab-bendamustine-lenalidomide	Original SLR
De Vos, S.	Venetoclax, bendamustine, and rituximab in patients with relapsed or refractory NHL: A phase Ib dose-finding study	Annals of Oncology. 2018. 29(9):1932-1938.	Full publication		BR		Treatment regimen	Not extracted as combination treatment of venetoclax in combination with bendamustine-rituximab	Original SLR
Hawkes, E. A.	Avelumab in Combination Regimens for Relapsed/Refractory DLBCL: Results from the Phase Ib JAVELIN DLBCL Study	Targeted Oncology. 2021. 16(6):761-771.	Full publication		BR		Treatment regimen	Not extracted as combination treatment with avelumab	Original SLR
Hitz, F.	Rituximab, bendamustine and lenalidomide in patients with aggressive B-cell lymphoma not eligible for anthracycline-based therapy or intensive salvage chemotherapy - SAKK 38/08	British Journal of Haematology. 2016	Full publication		BR		Treatment regimen	Not extracted as combination treatment with rituximab-bendamustine-lenalidomide	Original SLR
Hong JY	Bendamustine plus rituximab for relapsed or refractory diffuse large B cell lymphoma:	Ann Hematol. 2018 Aug;97(8):1437-1443	Full publication		BR	Yes	NA		Original SLR

	a multicenter retrospective analysis								
Ishizawa, K.	A phase I/II study of 10-min dosing of bendamustine hydrochloride (rapid infusion formulation) in patients with previously untreated indolent B-cell non-Hodgkin lymphoma, mantle cell lymphoma, or relapsed/refractory diffuse large B-cell lymphoma in Japan	Cancer Chemotherapy & Pharmacology. 2022. 90(1):83-95.	Full publication		BR	Yes	NA		SLR update
Kambhampati, S.	A Phase 1b Dose Escalation Trial of Carfilzomib in Combination with Bendamustine and Rituximab in Patients with Relapsed or Refractory Non-Hodgkin Lymphoma	Blood. 2019. 134(Supplement 1):2828.	Abstract		BR		Treatment regimen	Not extracted as carfilzomib in combination with bendamustine and rituximab	Original SLR
Karadurmus N	Effectiveness of bendamustine in relapsed or refractory lymphoma cases: a Turkish Oncology Group study	Arch Med Sci 2021;17(4):920–927	Full publication		BR	Yes	NA		Original SLR
Kedmi, M.	Ibrutinib, bendamustine, rituximab for relapsed and refractory aggressive B cell lymphoma - Final analysis of phase II clinical trial	HemaSphere. 2021. 5(SUPPL 2):213-214.	Abstract		BR		Treatment regimen	Not extracted as combination treatment with ibrutinib, bendamustine, and rituximab	Original SLR
Kiguchi, T.	MO12-5 Phase III trial of bendamustine plus	Annals of Oncology. 2021. 32(Supplement 4):S304.	Abstract		BR	Yes	NA		Original SLR

	rituximab for relapsed or refractory diffuse large B-cell lymphoma in Japan								
Maddocks, K.	A phase 1/1b study of rituximab, bendamustine, and ibrutinib in patients with untreated and relapsed/refractory non-Hodgkin lymphoma	Blood. 2015. 125(2):242-8.	Full publication		BR		Treatment regimen	Not extracted as combination treatment with ibrutinib, bendamustine, and rituximab	Original SLR
Merchionne, F.	Bendamustine plus rituximab for relapsed or refractory diffuse large B cell lymphoma: a retrospective analysis	Leukemia Research. 2014. 38(12):1446-50.	Full publication		BR	Yes	NA		Original SLR
Murayama, K.	Bendamustine plus rituximab in Japanese patients with relapsed or refractory diffuse large B-cell lymphoma	Annals of Hematology. 2022. 101(5):979-989.	Full publication		BR	Yes	NA		SLR update
Novo, M.	Copanlisib in combination with rituximabbendamustine in patients with relapsed-refractory diffuse large b-cell lymphoma: A multicentric phase ii trial of the fondazione italiana linfomi (fil-copa-rb)	HemaSphere. 2021. 5(SUPPL 2):692.	Abstract		BR		Treatment regimen	Not extracted as copanlisib +BR	Original SLR
Ogura, M.	Feasibility and pharmacokinetic study of bendamustine hydrochloride in combination with rituximab in relapsed or refractory aggressive B	Cancer Science. 2011. 102(9):1687-1692.	Full publication		BR	Yes	NA		Original SLR

	cell non-Hodgkin's lymphoma								
Ohmachi K	Multicenter Phase II Study of Bendamustine Plus Rituximab in Patients With Relapsed or Refractory Diffuse Large B-Cell Lymphoma	Journal of Clinical Oncology 31, no. 17 (June 10, 2013) 2103-2109.	Full publication	NCT01118845	BR	Yes	NA		Original SLR
Rigacci, L.	Bendamustine with or without rituximab for the treatment of heavily pretreated non-Hodgkin's lymphoma patients: A multicenter retrospective study on behalf of the Italian Lymphoma Foundation (FIL)	Annals of Hematology. 2012. 91(7):1013-1022.	Full publication		BR	Yes	NA		Original SLR
Soumerai, J. D.	The PARP inhibitor veliparib can be safely added to bendamustine and rituximab and has preliminary evidence of activity in B-cell lymphoma	Clinical Cancer Research. 2017 23(15):4119-4126.	Full publication		BR		Treatment regimen	Not extracted as combination treatment of venetoclax in combination with bendamustine-rituximab	Original SLR
Vacirca JL	Bendamustine combined with rituximab for patients with relapsed or refractory diffuse large B cell lymphoma	Ann Hematol. 2014 Mar;93(3):403-9	Full publication		BR	Yes	NA		Original SLR
Weidmann, E.	Bendamustine is effective in relapsed or refractory aggressive non-Hodgkin's lymphoma	Annals of Oncology. 2002. 13(8):1285-1289.	Full publication		BR		Treatment regimen	Not extracted as bendamustine mono	Original SLR

Sehn LH	Polatuzumab Vedotin in Relapsed or Refractory Diffuse Large B-Cell Lymphoma	J Clin Oncol. 2020 Jan 10;38(2):155-165	Full publication	GO29365	BR, Polivy		IPD available	GO29365 data obtained directly from Roche	Original SLR
Nowakowski, G. S.	Improved Efficacy of Tafasitamab plus Lenalidomide versus Systemic Therapies for Relapsed/Refractory DLBCL: RE-MIND2, an Observational Retrospective Matched Cohort Study	Clinical Cancer Research 2022	Full publication	RE-MIND2	BR, R-GemOx	Yes	NA		SLR update
Hutchings, M.	Glofitamab, a Novel, Bivalent CD20-Targeting T-Cell-Engaging Bispecific Antibody, Induces Durable Complete Remissions in Relapsed or Refractory B-Cell Lymphoma: A Phase I Trial	J Clin Oncol. 2021 Jun 20;39(18):1959-1970	Full publication	NCT03075696	Glofitamab		IPD available		Original SLR
Rentsch, V.	Glofitamab Treatment in Relapsed or Refractory DLBCL after CAR T-Cell Therapy	Cancers (Basel). 2022 May 20;14(10):2516	Full publication		Glofitamab		IPD available		SLR update
Hutchings, M.	Glofitamab (Glofit) in combination with polatuzumab vedotin (POLA): Phase ib/ii preliminary data support manageable safety and encouraging efficacy in relapsed/refractory (R/R) diffuse large b-cell lymphoma (DLBCL)	Blood. 2021. 138(SUPPL 1):525.	Abstract	NCT03533283	Glofitamab, Polivy		IPD available		SLR update

Ayers EC	Real World Outcomes in Patients With Relapsed/Refractory Diffuse Large B-cell Lymphoma Receiving Palliative Intent Therapies	Clin Lymphoma Myeloma Leuk. 2020. 20(10):661-667	Full publication		Lenalidomide	Yes	NA		Original SLR
Broccoli A	Lenalidomide in Pretreated Patients With Diffuse Large B-Cell Lymphoma: An Italian Observational Multicenter Retrospective Study in Daily Clinical Practice	Oncologist (2019) 24:1246–52	Full publication		Lenalidomide	Yes	NA		Original SLR
Casulo, C.	Durvalumab as monotherapy and in combination therapy in patients with lymphoma or chronic lymphocytic leukemia: The FUSION NHL 001 trial	Cancer Reports. 2022	Full publication		Lenalidomide		Treatment regimen	Not extracted as in combination with durvalumab	SLR update
Conde-Royo, D.	Lenalidomide-rituximab in high risk relapsed/refractory diffuse large b cell lymphoma: A single institution experience	HemaSphere. 2020. 4(Supplement 1):603.	Abstract		Lenalidomide		Treatment regimen	Not extracted as len + RTX	Original SLR
Czuczman MS	A Phase 2/3 Multicenter, Randomized, Open-Label Study to Compare the Efficacy and Safety of Lenalidomide Versus Investigator's Choice in Patients with Relapsed or Refractory Diffuse Large B-Cell Lymphoma	Clin Cancer Res.2017. 23(15):4127-4137.	Full publication		Lenalidomide	Yes	NA		Original SLR

Ferreri AJM	Lenalidomide maintenance in patients with relapsed diffuse large B-cell lymphoma who are not eligible for autologous stem cell transplantation: an open label, single-arm, multicentre phase 2 trial	Lancet Haematol. 2017. 4(3):e137-e146	Full publication		Lenalidomide	Yes	NA		Original SLR
Hernandez-Ilizaliturri FJ	Higher response to lenalidomide in relapsed/refractory diffuse large B-cell lymphoma in nongerminal center B-cell-like than in germinal center B-cell-like phenotype	Cancer. 2011 Nov 15;117(22):5058-66	Full publication		Lenalidomide	Yes	NA		Original SLR
Houot, R.	Obinutuzumab plus Lenalidomide (GALEN) for the treatment of relapse/refractory aggressive lymphoma: a phase II LYSA study	Leukemia. 2019. 33(3):776-780	Full publication		Lenalidomide		Treatment regimen	Not extracted as len + obinutuzumab	Original SLR
Ivanov V	Efficacy and safety of lenalinomide combined with rituximab in patients with relapsed/refractory diffuse large B-cell lymphoma	Leuk Lymphoma. 2014 Nov;55(11):2508-13	Full publication		Lenalidomide		Treatment regimen	Not extracted as len + RTX	Original SLR
Koh, Y.	Rituximab, lenalidomide and acalabrutinib (R2A) for relapsed/refractory aggressive B-cell lymphoma: Interim analysis reporting good	HemaSphere. 2020. 4(Supplement 1):596-597.	Abstract		Lenalidomide		Treatment regimen	Not extracted as rituximab, lenalidomide and acalabrutinib	Original SLR

	tolerability and potential durable response								
Kuhnl, A.	R-GEM-Lenalidomide versus R-GEM-P as second-line treatment of diffuse large B-cell lymphoma: results of the UK NRCI phase II randomised LEGEND trial	Annals of Hematology. 2020. 99(1):105-112.	Full publication		Lenalidomide		Treatment regimen	Not extracted as R-GEM-Lenalidomide	Original SLR
Lakshmaiah KC	Lenalidomide in relapsed refractory non-Hodgkin's lymphoma: An Indian perspective	J Cancer Res Ther. 2015. 11(4):857-61	Full publication		Lenalidomide	Yes	NA		Original SLR
Lee Y-P	Real-World, Single-Center Data for Lenalidomide Plus Rituximab in Relapsed or Refractory Diffuse Large B-Cell Lymphoma and Transformed Follicular Lymphoma	Cancer Manag Res. 2021 May 28;13:4241-4250	Full publication		Lenalidomide		Treatment regimen	Not extracted as len + RTX	Original SLR
Lemoine, J.	Lenalidomide exposure at time of CAR T-cells expansion enhances response of refractory/relapsed aggressive large B-cell lymphomas	Blood. 2021. 138(SUPPL 1):1433.	Abstract		Lenalidomide		Treatment regimen	Not extracted as len + CAR-T	Original SLR
Major, A.	Phase I/II clinical trial of temsirolimus and lenalidomide in patients with relapsed and refractory lymphomas	Haematologica. 2021. 29	Full publication		Lenalidomide		Treatment regimen	Not extracted as temsirolimus + lenalid	Original SLR
Marangon, M.	Lenalidomide Combination Therapy in Relapsed/Refractory Diffuse Large B Cell	Clinical lymphoma, myeloma & leukemia. 2019. 19(7):e321-e323	Full publication		Lenalidomide		Treatment regimen	Not extracted as combination therapy	Original SLR

	Lymphoma: The Italian Real-Life Experience								
Martin, A.	Lenalidomide in combination with R-ESHAP in patients with relapsed or refractory diffuse large B-cell lymphoma: A phase 1b study from GELTAMO group	British Journal of Haematology. 2016. 173(2):245-252.	Full publication		Lenalidomide		Treatment regimen	Not extracted as len + R-ESHAP	Original SLR
Mehta-Shah, N.	Romidepsin and lenalidomide-based regimens have efficacy in relapsed/refractory lymphoma: Combined analysis of two phase I studies with expansion cohorts	American Journal of Hematology. 2021. 96(10):1211-1222.	Full publication		Lenalidomide		Treatment regimen	Not extracted as len combination therapy	Original SLR
Mondello P	Lenalidomide in Relapsed or Refractory Diffuse Large B-Cell Lymphoma: Is It a Valid Treatment Option?	Oncologist. 2016 Sep;21(9):1107-12.	Full publication		Lenalidomide	Yes	NA		Original SLR
Morschhauser, F.	An open-label phase 1b study of obinutuzumab plus lenalidomide in relapsed/refractory follicular B-cell lymphoma	Blood. 2018. 132(14):1486-1494.	Full publication		Lenalidomide		Treatment regimen	Not extracted as obinutuzumab plus lenalidomide	Original SLR
Padrnos, L.	A Novel Combination of the mTORC1 Inhibitor Everolimus and the Immunomodulatory Drug Lenalidomide Produces Durable Responses in Patients With Heavily Pretreated Relapsed Lymphoma	Clinical Lymphoma, Myeloma and Leukemia. 2018. 18(10):664-672.e2.	Full publication		Lenalidomide		Treatment regimen	Not extracted as len + everolimus	Original SLR
Palazon-Carrion, N.	Lenalidomide plus R-GDP (R2-GDP) in	Clinical Cancer Research. 2022	Full publication		Lenalidomide		Treatment regimen	Not extracted as	SLR update

	Relapsed/Refractory Diffuse Large B Cell Lymphoma. Final Results of the R2-GDP-GOTEL Trial and Immune Biomarker subanalysis							lenalidomide + R-GDP	
Phipps, C.	Phase I/II dose-escalation study of lenalidomide in combination with R-GDP for treatment of transplant-ineligible relapsed/refractory diffuse large B-cell lymphoma followed bymaintenance lenalidomide	Blood. 2020. 136(SUPPL 1):25-26.	Abstract		Lenalidomide		Treatment regimen	Not extracted as lenalidomide + R-GDP	Original SLR
Sabirou, F.	Lenalidomide and rituximab combined with CEP chemotherapy (r2CEP) for patients with relapsed b-cell lymphoma	HemaSphere. 2020. 4(Supplement 1):1005.	Abstract		Lenalidomide		Treatment regimen	Not extracted as lenalidomide and rituximab combined with CEP chemotherapy	Original SLR
Sigmund, A. M.	Assessment of Salvage Regimens Post-Chimeric Antigen Receptor T Cell Therapy for Patients with Diffuse Large B Cell Lymphoma	Transplantation and Cellular Therapy. 2022. 04:04	Full publication		Lenalidomide		Limited reporting	No baseline characteristic reported based on Tx received	SLR update
Thieblemont, C.	Lenalidomide enhance CAR T-cells response in patients with refractory/relapsed large B cell lymphoma experiencing	Blood. 2020. 136(SUPPL 1):16-17.	Abstract		Lenalidomide		Treatment regimen	Not extracted as len combination	Original SLR

	progression after infusion								
Vose, J. M.	Single-agent lenalidomide is active in patients with relapsed or refractory aggressive non-Hodgkin lymphoma who received prior stem cell transplantation	British Journal of Haematology. 2013. 162(5):639-47.	Full publication		Lenalidomide		Treatment regimen	Patients had received prior transplant	Original SLR
Wang M	Oral lenalidomide with rituximab in relapsed or refractory diffuse large cell, follicular and transformed lymphoma: a phase II clinical trial	Leukemia. 2013 Sep;27(9):1902-9	Full publication		Lenalidomide		Treatment regimen	Not extracted as len + RTX	Original SLR
Wiernik PH	Lenalidomide monotherapy in relapsed or refractory aggressive non-Hodgkin's lymphoma	J Clin Oncol. 2008. 26(30):4952-7	Full publication		Lenalidomide	Yes	NA		Original SLR
Wilson, W. H.	Phase 1b/2 study of ibrutinib and lenalidomide with dose-adjusted EPOCH-R in patients with relapsed/refractory diffuse large B-cell lymphoma*	Leukemia and Lymphoma. 2021. 62(9):2094-2106.	Full publication		Lenalidomide		Treatment regimen	Not extracted as ibrutinib and lenalidomide with dose-adjusted EPOCH-R	Original SLR
Witzig TE	An international phase II trial of single-agent lenalidomide for relapsed or refractory aggressive B-cell non-Hodgkin's lymphoma	Ann Oncol. 2011. 22(7):1622-1627	Full publication		Lenalidomide	Yes	NA		Original SLR
Xiao, F.	Efficacy and safety of lenalidomide, rituximab combined with second-line chemotherapy (R2-chemo) in patients with	Blood. 2020. 136(SUPPL 1):6-7.	Abstract		Lenalidomide		Treatment regimen	Not extracted as lenalidomide, rituximab combined	Original SLR

	relapsed/refractory diffuse large-B cell lymphoma							with second-line chemotherapy	
Zinzani PL	Combination of lenalidomide and rituximab in elderly patients with relapsed or refractory diffuse large B-cell lymphoma: a phase 2 trial	Clin Lymphoma Myeloma Leuk. 2011 Dec;11(6):462-6.	Full publication		Lenalidomide		Treatment regimen	Not extracted as len + RTX	Original SLR
Zinzani PL	Lenalidomide monotherapy in heavily pretreated patients with non-Hodgkin lymphoma: an Italian observational multicenter retrospective study in daily clinical practice	Leuk Lymphoma.2015. 56(6):1671-6.	Full publication		Lenalidomide	Yes	NA		Original SLR
Zinzani PL	RE-MIND: Comparing Tafasitamab + Lenalidomide (L-MIND) with a Real-world Lenalidomide Monotherapy Cohort in Relapsed or Refractory Diffuse Large B-cell Lymphoma	Clin Cancer Res. 2021. 27(22):6124-6134.	Full publication		Lenalidomide	Yes	NA		Original SLR
Tomas, A. A.	Novel agents may be preferable to chemotherapy for large b-cell lymphoma progressing after cd19-car-t: A multicenter observational study	Blood. 2021. 138(SUPPL 1):883.	Abstract		Lenalidomide, Polivy		Limited reporting	Not extracted as abstract just says 'len-based' therapy	Original SLR
Zurko, J. C.	Outcomes and treatment patterns in patients with aggressive b-cell	Blood. 2021. 138(SUPPL 1):884.	Abstract		Lenalidomide, Polivy, Tafasitamab		Limited reporting	No baseline characteristics reported	SLR update

	lymphoma after failure of anti-cd19 car t-cell therapy							for patients by treatment	
Abramson, J.	Safety and efficacy results from transcend NHL 001, a multicenter phase 1 study of lisocabtagene maraleucel (Liso-Cel) in relapsed/refractory large B-cell lymphoma	Presented at Transplantation & Cellular Therapy Meeting 2020	Abstract	TRANSCEND NHL 001	Lisocabtagene	Yes	NA		Original SLR
Godwin, J.	Outreach: Preliminary safety & efficacy results from a phase 2 study of lisocabtagene maraleucel (LISO-CEL) in the nonuniversity setting	HemaSphere. 2021. 5(SUPPL 2):235-236.	Abstract	OUTREACH	Lisocabtagene	Yes	NA		Original SLR
Makita, S.	Phase 2 results of lisocabtagene maraleucel in Japanese patients with relapsed/refractory aggressive B-cell non-Hodgkin lymphoma	Cancer Medicine. 2022	Full publication	TRANSCEND WORLD	Lisocabtagene	Yes	NA		SLR update
Siddiqi, T.	Safety of lisocabtagene maraleucel given with durvalumab in patients with relapsed/refractory aggressive B cell non Hodgkin lymphoma: First results from the platform study	Hematological Oncology. 2019. 37(Supplement 2):171-172.	Abstract	PLATFORM	Lisocabtagene		Treatment regimen	Not extracted as liso-cel + durvalumab (dose escalation part of Arm A)	Original SLR
Borchmann, P.	Phase I/II study of pixantrone in combination with cyclophosphamide, vincristine, and prednisone in patients with relapsed	Leukemia and Lymphoma. 2011. 52(4):620-628.	Full publication		Pixantrone		Treatment regimen	CPOP: not extracted	Original SLR

	aggressive non-Hodgkin lymphoma								
Cencini E	Pixantrone in patients with relapsed/refractory diffuse large B-cell lymphoma: A real-life, retrospective, multicenter trial on behalf of the "RTL" (Regional Tuscan Lymphoma network)	Eur J Haematol. 2022 Jan 20. doi: 10.1111/ejh.13745.	Full publication		Pixantrone	Yes	NA		SLR update
D'Amore, F.	Final analysis of a nordic lymphoma group phase Ib/IIa trial of pixantrone, etoposide, bendamustine and, in CD20-positive tumors, rituximab in relapsed aggressive B-or T-cell lymphomas	Hematological Oncology. 2021. 39(SUPPL 2):327.	Abstract		Pixantrone		Treatment regimen	Not extracted as combination treatment with pixantrone, etoposide, bendamustine and RTX	Original SLR
Dlugosz-Danecka, M.	Pixantrone, etoposide, bendamustine, rituximab (P[R]EBEN) as an effective salvage regimen for relapsed/refractory aggressive non-Hodgkin lymphoma-Polish Lymphoma Research Group real-life analysis	Pharmacological Reports: PR. 2019. 71(3):473-477.	Full publication		Pixantrone		Treatment regimen	Not extracted as combination treatment with pixantrone, etoposide, bendamustine and RTX	Original SLR
Eyre TA	Results of a multicentre UK-wide retrospective study evaluating the efficacy of pixantrone in relapsed, refractory diffuse large B cell lymphoma	Br J Haematol. 2016; 173(6):896-904	Full publication		Pixantrone	Yes	NA		Original SLR
Herbrecht R	Comparison of pixantrone-based	Ann Oncol. 2013 Oct;24(10):2618-2623	Full publication		Pixantrone		Treatment regimen	CPOP-R: not extracted	Original SLR

	regimen (CPOP-R) with doxorubicin-based therapy (CHOP-R) for treatment of diffuse large B-cell lymphoma								
Hess, G.	A phase II trial to evaluate the combination of pixantrone and obinutuzumab for patients with relapsed aggressive lymphoma: Final results of the prospective, multicentre GOAL trial	British Journal of Haematology. 2022	Full publication		Pixantrone		Treatment regimen	Not extracted as pixantrone + obinutuzumab, not all pts 3rd line and beyond	SLR update
Heyman, B.	Phase I Study of the Combination of Bendamustine, Rituximab, and Pixantrone in Patients With Relapsed/Refractory B-cell Non-Hodgkin Lymphoma	Clinical Lymphoma, Myeloma and Leukemia. 2018. 18(10):679-686.	Full publication		Pixantrone		Treatment regimen	Not extracted as combination treatment with pixantrone, etoposide, bendamustine and RTX	Original SLR
Leivonen, S. K.	Molecular Profiling of Aggressive Non-Hodgkin Lymphoma - Results from a Phase 1/2 Preben Study	Blood. 2019. 134(Supplement 1):5314.	Abstract		Pixantrone		Treatment regimen	Not extracted as combination treatment with pixantrone, etoposide, bendamustine and RTX	Original SLR
Lim, S. T.	A phase I/II trial of pixantrone (BBR2778), methylprednisolone, cisplatin, and cytosine arabinoside (PSHAP) in relapsed/refractory	Leukemia and Lymphoma. 2007. 48(2):374-380.	Full publication		Pixantrone		Treatment regimen	Pixantrone substituted for etoposide in the ESHAP regimen	Original SLR

	aggressive non-Hodgkin's lymphoma								
Novakovic A	Limited efficacy of pixantrone in refractory diffuse large B-cell lymphoma	Oncol Lett. 2020 Mar;19(3):2028-2034	Full publication		Pixantrone	Yes	NA		Original SLR
Pettengell R	Pixantrone dimaleate versus other chemotherapeutic agents as a single-agent salvage treatment in patients with relapsed or refractory aggressive non-Hodgkin lymphoma: a phase 3, multicentre, open-label, randomised trial	Lancet Oncol. 2012. 13(7):696-706	Full publication	NCT00088530	Pixantrone	Yes	NA		Original SLR
Pettengell R	Pixantrone plus rituximab versus gemcitabine plus rituximab in patients with relapsed aggressive B-cell non-Hodgkin lymphoma not eligible for stem cell transplantation: a phase 3, randomized, multicentre trial (PIX306)	Br J Haematol. 2020 Jan;188(2):240-248	Full publication		Pixantrone		Treatment regimen	Not extracted: pixa + RTX	Original SLR
Sancho J-M	Efficacy and safety of pixantrone for the treatment of multiply relapsed or refractory aggressive non-Hodgkin B-cell lymphomas	Eur J Haematol. 2020. 104(5):499-508	Full publication		Pixantrone	Yes	NA		Original SLR
Zinzani PL	Effectiveness and Safety of Pixantrone for the Treatment of	Acta Haematol. 2021. 144(3):259-263	Full publication		Pixantrone	Yes	NA		Original SLR

	Relapsed or Refractory Diffuse Large B-Cell Lymphoma in Every-Day Clinical Practice: The Italian Cohort of the PIXA Registry								
Avivi, I.	Polatuzumab-based regimen or CAR T cell for patients with refractory/relapsed DLBCL-a matched cohort analysis	Annals of Hematology. 2022. 101(4):755-762.	Full publication		Polivy		IPD available		SLR update
Diefenbach, C.	Promising clinical data from dose escalation in a phase ib/II ongoing study of mosunetuzumab with polatuzumab vedotin for relapsed/refractory B-cell Non-Hodgkin's lymphoma	Hematological Oncology. 2021. 39(SUPPL 2):330-332.	Abstract		Polivy		IPD available		Original SLR
Diefenbach, C. S. M.	Polatuzumab vedotin (Pola) + rituximab (R) + lenalidomide (Len) in patients (pts) with relapsed/refractory (R/R) diffuse large B-cell lymphoma (DLBCL): Primary analysis of a phase 1b/2 trial	Journal of Clinical Oncology. Conference: Annual Meeting of the American Society of Clinical Oncology, ASCO. 2021. 39(15 SUPPL).	Abstract	GO29834; NCT02600897	Polivy		IPD available		Original SLR
Dimou, M.	Real-life experience with the combination of polatuzumab vedotin, rituximab, and bendamustine in aggressive B-cell lymphomas	Hematological Oncology. 2021. 39(3):336-348.	Full publication		Polivy		IPD available		Original SLR
Dimou, M.	Polatuzumab-vedotin in combination with	HemaSphere. 2020. 4(Supplement 1):581-582.	Abstract		Polivy		IPD available		Original SLR

	rituximab/bendamustine in a greek multicenter cohort of relapsed/refractory aggressive B-cellnon-Hodgkin lymphoma patients:real-life data on efficacy & safety								
Dujmovic, D.	Polatuzumab-vedotin combined with immunochemotherapy in R/R patients with DLBCL: A retrospective, non-interventional, real-life study of krohem, the croatian cooperative group for hematologic diseases	HemaSphere. 2020. 4(Supplement 1):586.	Abstract		Polivy		IPD available		Original SLR
Farina, K. A.	Bendamustine, rituximab, and polatuzumab vedotin for relapsed or refractory diffuse large bcell lymphoma: Single-center real-world experience	Hematological Oncology. 2021. 39(SUPPL 2):249-251.	Abstract		Polivy		IPD available		Original SLR
Flories Avile C	Real-world characteristics and clinical outcomes in relapse/refractory diffuse large B-cell lymphoma post CAR-T failure	ESMO 2022	Abstract/poster		Polivy		IPD available		SLR update
Gouni, S.	A Multicenter Retrospective Study of Polatuzumab Vedotin in Patients with Large B-cell Lymphoma After CAR T-cell Therapy	Blood advances. 2022. 03	Full publication		Polivy		IPD available		SLR update

Gritti, G.	Polatuzumab vedotin plus venetoclax with rituximab in relapsed/refractory diffuse large B-cell lymphoma: Primary efficacy analysis of a phase IB/II study	Blood. 2020. 136(SUPPL 1):45-47.	Abstract		Polivy		IPD available		Original SLR
Kinoshita, T.	Safety and pharmacokinetics of polatuzumab vedotin in Japanese patients with relapsed/refractory B-cell non-Hodgkin lymphoma: A phase 1 dose-escalation study	Japanese Journal of Clinical Oncology.2021. 51(1):70-77.	Full publication		Polivy		IPD available		Original SLR
Liebers, N.	Polatuzumab vedotin as a salvage and bridging treatment in relapsed or refractory large B-cell lymphomas	Blood Advances. 2021. 5(13):2707-2716.	Full publication		Polivy		IPD available		Original SLR
Lu T	Exposure-safety and exposure-efficacy analyses of polatuzumab vedotin in patients with relapsed or refractory diffuse large B-cell lymphoma	Leuk Lymphoma. 2020 Dec;61(12):2905-2914	Full publication		Polivy		IPD available		Original SLR
Morschhauser, F.	Polatuzumab vedotin or pinatuzumab vedotin plus rituximab in patients with relapsed or refractory non-Hodgkin lymphoma: final results from a phase 2 randomised study (ROMULUS)	The Lancet Haematology. 2019. 6(5):e254-e265.	Full publication		Polivy		IPD available		Original SLR
Northend, M.	Polatuzumab vedotin with bendamustine and rituximab for	Hematological Oncology. 2021. 39(SUPPL 2):248-249.	Abstract		Polivy		IPD available		Original SLR

	relapsed/refractory high-grade B-cell lymphoma: The UK experience								
Palanca-Wessels, M. C. A.	Safety and activity of the anti-CD79B antibody-drug conjugate polatuzumab vedotin in relapsed or refractory B-cell non-Hodgkin lymphoma and chronic lymphocytic leukaemia: A phase 1 study	The Lancet Oncology. 2015. 16(6):704-715.	Full publication		Polivy		IPD available		Original SLR
Pincha, R.	Polatuzumab vedotin in relapsed/refractory high-grade b-cell non hodgkin lymphoma	Indian Journal of Hematology and Blood Transfusion. 2020. 36(1 SUPPL):S139.	Abstract		Polivy		IPD available		Original SLR
Segman, Y.	Outcome of Relapsed DLBCL Patients, Treated with Polatuzumab-BR or Polatuzumab-R: Real Life Data	Blood. 2019. 134(Supplement 1):5321.	Abstract		Polivy		IPD available		Original SLR
Smith, S. D.	Polatuzumab Vedotin for Relapsed/Refractory Aggressive B-cell Lymphoma: A Multicenter Post-marketing Analysis	Clinical lymphoma, myeloma & leukemia. 2021. 21(3):170-175.	Full publication		Polivy		IPD available		Original SLR
Smykova, O.	Polatuzumab vedotin in combination with bendamustine and rituximab in patients with relapsed or refractory B-cell non-Hodgkin lymphoma: Interim analysis	HemaSphere. 2021. 5(SUPPL 2):237.	Abstract		Polivy		IPD available		Original SLR
Sodhi, L.	Outcome of rituximab-polatuzumabbendamus	HemaSphere. 2021. 5(SUPPL 2):243.	Abstract		Polivy		IPD available		Original SLR

	tine in the treatment of relapsed/ refractory high grade lymphoma and transformed high grade lymphoma - A multi-centre analysis								
Strati, P.	Clinical efficacy of polatuzumab vedotin in patients with relapsed/refractory large B-cell lymphoma after standard of care axicabtagene ciloleucel	Blood. 2020. 136(SUPPL 1):16-17.	Abstract		Polivy		IPD available		Original SLR
Terui, Y.	A phase 2 study of polatuzumab vedotin + bendamustine + rituximab in relapsed/refractory diffuse large B-cell lymphoma	Cancer Science. 2021. 112(7):2845-2854.	Full publication		Polivy		IPD available		Original SLR
Thuresson, P. O.	Quality of Life (QoL) in Patients With Relapsed/Refractory Non-Hodgkin Lymphoma (NHL) Treated with Polatuzumab Vedotin Plus Rituximab in the ROMULUS Study	Blood. 2019. 134(Supplement 1):4767.	Abstract	ROMULUS	Polivy		IPD available		Original SLR
Topp, M. S.	Anti-CD20-atezolizumab-polatuzumab vedotin in relapsed/refractory follicular and diffuse large B-cell lymphoma	Journal of Cancer Research and Clinical Oncology. 2022	Abstract		Polivy		IPD available		SLR update
Tsai, C. H.	Polatuzumab vedotin-based salvage chemotherapy in the third-line or above	Blood. 2020. 136(SUPPL 1):12.	Abstract		Polivy		IPD available		Original SLR

	treatment for diffuse large B-cell lymphoma								
Vodicka, P.	Polatuzumab vedotin plus bendamustine and rituximab in patients with relapsed/refractory diffuse large B-cell lymphoma in the real world	European Journal of Haematology. 2022	Full publication		Polivy		IPD available		SLR update
Wang, Y. W.	Polatuzumab vedotin-based salvage immunochemotherapy as third-line or beyond treatment for patients with diffuse large B-cell lymphoma: a real-world experience	Annals of Hematology. 2021	Full publication		Polivy		IPD available		Original SLR
Wu, J.	A multicenter real-life study of polatuzumab vedotin combined with immunochemotherapy in patients with R/R DLBCL: Preliminary data on efficacy and safety in Chinese cohort	Blood. 2020. 136(SUPPL 1):50-51.	Abstract		Polivy		IPD available		Original SLR
Wu, J.	Cohort study of efficacy and safety of polatuzumab vedotin combined with immunochemotherapy in patients with relapse/refractory diffuse large B cell lymphoma. [Chinese]	National Medical Journal of China. 2021. 101(25):1985-1990.	Full publication		Polivy		IPD available		Original SLR
Bonnet, C.	Ibrutinib Associated with Rituximab-Platinum Salt-Based Immunochemotherapy in B-Cell Lymphomas:	Cancers. 2022. 14(7) (no pagination)(1761).	Full publication		R-DHAP		Treatment regimen	Not extracted as combination therapy	SLR update

	Results of a Phase 1b-II Study of the LYSA Group								
Chiappella, A.	The Addition of Bortezomib to R-DHAP Does Not Improve the Response Pre-Stem Cell Transplantation Compared to Standard R-DHAP in Young Patients with Relapsed/Refractory Diffuse Large B-Cell Lymphoma: Preliminary Results of the Phase II Randomized Trial FIL-VERAL12 of the Fondazione Italiana Linfomi	Blood. 2019. 134(Supplement 1):2025.	Abstract		R-DHAP		Treatment regimen	Treatment prior to transplant	Original SLR
Cuccuini, W.	MYC+ diffuse large B-cell lymphoma is not salvaged by classical R-ICE or R-DHAP followed by BEAM plus autologous stem cell transplantation	Blood. 2012. 119(20):4619-24.	Full publication		R-DHAP		Treatment regimen	Not extracted as R-DHAP followed by high-dose therapy and ASCT	Original SLR
Gisselbrecht C	Rituximab Maintenance Therapy After Autologous Stem-Cell Transplantation in Patients With Relapsed CD20+ Diffuse Large B-Cell Lymphoma: Final Analysis of the Collaborative Trial in Relapsed Aggressive Lymphoma	J Clin Oncol. 2012 Dec 20; 30(36): 4462–4469.	Full publication	CORAL	R-DHAP		Treatment regimen	Not extracted as R-DHAP given as three courses and pts then treated with ASCT and randomised to maintenance RTX or observation	Original SLR

Hatano, K.	Clinical interaction between dexamethasone and aprepitant in chemotherapy for lymphoma	Annals of Hematology. 2022. 101(6):1211-1216.	Full publication		R-DHAP	Yes	NA		SLR update
Hu, J.	Combination of decitabine and modified DHAP regimen: A potential salvage regimen for relapsed/ refractory diffuse large B-cell lymphoma after second-line treatment failure	Hematological Oncology. 2021. 39(SUPPL 2):416.	Abstract		R-DHAP		Treatment regimen	Not extracted as decitabine and modified DHAP	Original SLR
Jeon SY	The effect of the dexamethasone, cytarabine, and cisplatin (DHAP) regimen on stem cell mobilization and transplant outcomes of patients with non-Hodgkin's lymphoma who are candidates for up-front autologous stem cell transplantation	Korean J Intern Med. 2018 Nov;33(6):1169-1181.	Full publication		R-DHAP		Treatment regimen	Not extracted: reports on stem cell mobilisation with DHAP only	Original SLR
Lacout N	R-DHA-oxaliplatin (R-DHAOx) versus R-DHA-cisplatin (R-DHAP) regimen in B-cell lymphoma treatment: A eight-year trajectory study	Eur J Haematol. 2020 Aug;105(2):223-230	Full publication		R-DHAP		Outcome	Not extracted: reports nephrotoxicity only	Original SLR
Lisenko K	Minimal renal toxicity after Rituximab DHAP with a modified cisplatin application scheme in patients with relapsed	BMC Cancer 16, 267 (2016). https://doi.org/10.1186/s12885-016-2289-y	Full publication		R-DHAP		Line of therapy	Not extracted as 2L only	Original SLR

	or refractory diffuse large B-cell lymphoma								
Mey UJM	DHAP in combination with rituximab vs DHAP alone as salvage treatment for patients with relapsed or refractory diffuse large B-cell lymphoma: a matched-pair analysis	Leuk Lymphoma. 2006 Dec;47(12):2558-66	Full publication		R-DHAP	Yes	NA		Original SLR
Schirmbeck NGD	Salvage Chemotherapy with R-DHAP in Patients with Relapsed or Refractory Non-Hodgkin Lymphoma	Cancer Invest. 2016 Sep 13;34(8):361-72	Full publication		R-DHAP	Yes	NA		Original SLR
Vellenga, E.	Rituximab improves the treatment results of DHAP-VIM-DHAP and ASCT in relapsed/progressive aggressive CD20+ NHL: a prospective randomized HOVON trial	Blood. 2008. 111(2):537-43.	Full publication		R-DHAP		Treatment regimen	Not extracted as R-DHAP followed by ASCT	Original SLR
Witzens-Harig M	The mTOR Inhibitor Temsirolimus Added to Rituximab Combined With Dexamethasone, Cytarabine, and Cisplatinum (R-DHAP) for the Treatment of Patients With Relapsed or Refractory DLBCL - Results From the Phase-II STORM Trial	Hemasphere. 2021 Sep 23;5(10):e636	Full publication	STORM	R-DHAP		Treatment regimen	Not extracted as temsirolimus + R-DHAP	Original SLR
Witzig TE	Salvage chemotherapy with rituximab DHAP for relapsed non-Hodgkin lymphoma: a phase II trial in the	Leuk Lymphoma. 2008 Jun;49(6):1074-80	Full publication		R-DHAP	Yes	NA		Original SLR

	North Central Cancer Treatment Group								
Balzarotti, M.	A phase Ib, open-label, dose-escalation trial of the anti-CD37 monoclonal antibody, BI 836826, in combination with gemcitabine and oxaliplatin in patients with relapsed/refractory diffuse large B-cell lymphoma	Investigational New Drugs. 2021. 39(4):1028-1035.		NCT02624492	R-GemOx		Treatment regimen	Not extracted as BI 836826 in combination with GemOx	Original SLR
Bua, B. R.	ABCL-181: Updated Results of a Phase 2 Study from GELTAMO Investigating the Combination of Ibrutinib with R-GemOx in Patients with Relapsed or Refractory Diffuse Large B-Cell Lymphoma	Clinical Lymphoma, Myeloma and Leukemia. 2021. 21(Supplement 1):S381.	Abstract	NCT02692248	R-GemOx		Treatment regimen	Not extracted as combination of ibrutinib with R-GemOx-D	Original SLR
Cai, Q.	Chidamide plus R-GemOx(rituximab, gemcitabine and oxaliplatin) regimen as salvage treatment for transplant-ineligible patients with relapsed/refractory diffuse large B-cell lymphoma: A preliminary analysis of a multicenter, single arm, phase II study	Blood. 2020. 136(SUPPL 1):52-53.	Abstract	NCT04022005	R-GemOx		Treatment regimen	Not extracted as chidamide plus R-GemOx	Original SLR
Castro, F.	Comparative effectiveness of bendamustine plus rituximab (BR) and	Blood. 2020. 136(SUPPL 1):41-42.	Abstract		R-GemOx		Line of therapy	Not extracted as 2L only	Original SLR

	rituximab plus gemcitabine and oxaliplatin (R-GemOx) in relapsed/refractory diffuse large B-cell lymphoma								
Cazelles C	Rituximab plus gemcitabine and oxaliplatin (R-GemOx) in refractory/relapsed diffuse large B-cell lymphoma: a real-life study in patients ineligible for autologous stem-cell transplantation	Leuk Lymphoma. 2021 Sep;62(9):2161-2168.	Full publication		R-GemOx	Yes	NA		Original SLR
Corazzelli, G.	Long-term results of gemcitabine plus oxaliplatin with and without rituximab as salvage treatment for transplant-ineligible patients with refractory/relapsing B-cell lymphoma	Cancer Chemotherapy and Pharmacology. 2009. 64(5):907-916.	Full publication		R-GemOx	Yes	NA		Original SLR
Davies, A.	9p gain predicts outcomes in patients with relapsed/refractory (r/r) diffuse large b-cell lymphoma (DLBCL) treated with R-GemOx +/- atezolizumab. argo: A randomised phase ii study	Hematological Oncology. 2021. 39(SUPPL 2):155-156.	Abstract	ARGO	R-GemOx	Yes	NA		Original SLR
Dhanapal V	Outcome for patients with relapsed/refractory aggressive lymphoma treated with gemcitabine and oxaliplatin with or	Leuk Lymphoma. 2017;58(9):1-9.	Full publication		R-GemOx	Yes	NA		Original SLR

	without rituximab; a retrospective, multicentre study.								
El Gnaoui T	Rituximab, gemcitabine and oxaliplatin: an effective salvage regimen for patients with relapsed or refractory B-cell lymphoma not candidates for high-dose therapy.	Ann Oncol. 2007;18(8):1363-8.	Full publication		R-GemOx	Yes	NA		Original SLR
Fan, Q.	GemOx+/-R regimen for the patients with relapsed or refractory aggressive non-Hodgkin's lymphoma. [Chinese]	Chinese Journal of Clinical Oncology. 2010. 37(24):1476-1478.	Full publication		R-GemOx		Non-English language publication		Original SLR
Lopez A	GemOx-R regimen is a highly effective salvage regimen in patients with refractory/relapsing diffuse large-cell lymphoma: a phase II study	Eur J Haematol. 2008 Feb;80(2):127-32	Full publication		R-GemOx	Yes	NA		Original SLR
Mounier N	Rituximab plus gemcitabine and oxaliplatin in patients with refractory/relapsed diffuse large B-cell lymphoma who are not candidates for high-dose therapy. A phase II Lymphoma Study Association trial.	Haematologica. 2013;98(11):1726-31.	Full publication		R-GemOx	Yes	NA		Original SLR
Schade, J. R.	Retrospective Analysis of Gemcitabine and Oxaliplatin (GemOx)-Based Treatment in Patients with	Blood. 2019. 134(Supplement 1):2904.	Abstract		R-GemOx	Yes	NA		Original SLR

	Relapsed/Refractory Aggressive B-Cell Non-Hodgkin Lymphoma								
Thurner, L.	Pre-planned interim safety analysis of the niveau trial, a randomized phase 3 study for patients with aggressive non-Hodgkin lymphoma in first relapse or progression not eligible for high-dose chemotherapy (HDT), testing nivolumab in combination with gemcitabine, oxaliplatin (GemOx) plus rituximab (R) in case of B-cell lymphoma	Blood. 202. 136(SUPPL 1):32.	Abstract	Niveau	R-GemOx	Yes	NA		Original SLR
Yan, S. B.	Efficacy Analysis of GemOx Regimen for Treatment of Refractory Non-Hodgkin's Lymphoma. [Chinese]	Zhongguo shi yan xue ye xue za zhi. 2017. 25(5):1415-1419.	Full publication		R-GemOx		Non-English language publication		Original SLR
Yang, J.	[Efficacy and safety evaluation of gemcitabine combined with oxaliplatin in lymphoma patients after failure of multiple chemotherapy regimens]	Chung-Hua Chung Liu Tsa Chih [Chinese Journal of Oncology]. 2014. 36(2):137-40.	Full publication		R-GemOx		Non-English language publication		Original SLR
Duell J	Long-term outcomes from the Phase II L-MIND study of tafasitamab (MOR208) plus lenalidomide in patients with relapsed	Haematologica. 2021 Sep 1;106(9):2417-2426.	Full publication	L-MIND	Tafasitamab	Yes	NA		Original SLR

	or refractory diffuse large B-cell lymphoma								
Jurczak, W.	Phase IIa study of the CD19 antibody MOR208 in patients with relapsed or refractory B-cell non-Hodgkin's lymphoma	Annals of Oncology. 2018. 29(5):1266-1272	Full publication	NCT01685008	Tafasitamab		Treatment regimen	Tafasitamab monotherapy	Original SLR
Chavez, J. C.	Ibrutinib before apheresis may improve tisagenlecleucel manufacturing in relapsed/refractory adult diffuse large B-cell lymphoma: Initial results from a phase 1b study	Blood. 2020. 136(SUPPL 1):3-4.	Abstract		Tisagenlecleucel		Treatment regimen	Not extracted as tisa + ibrutinib	Original SLR
Fried, S.	Patients with out of specification tisagenlecleucel can be salvaged with point-of-care car-T cells: An observational intention-to-treat single-center analysis		Abstract		Tisagenlecleucel	Yes	NA		Original SLR
Ghilardi, G.	Bendamustine is Safe and Effective for Lymphodepletion Before Tisagenlecleucel in Patients with Refractory or Relapsed Large B-Cell Lymphomas	Annals of oncology : official journal of the European Society for Medical Oncology. 2002. 08	Full publication		Tisagenlecleucel	Yes	NA		SLR update
Iacoboni, G.	Real-world evidence of tisagenlecleucel for the treatment of relapsed or refractory large B-cell lymphoma	Cancer Med. 2021 May;10(10):3214-3223	Full publication		Tisagenlecleucel	Yes	NA		Original SLR

Jager, U.	Safety and efficacy of tisagenlecleucel (tisa-cel) plus pembrolizumab (pembro) in patients (pts) with relapsed/refractory diffuse large B-cell lymphoma (r/r DLBCL): Updated analysis of the phase 1b PORTIA study	Journal of Clinical Oncology. 2021. 39(15 SUPPL).	Abstract	PORTIA	Tisagenlecleucel		Treatment regimen	Not extracted as tisa + pembro	Original SLR
Jaglowski, S.	Tisagenlecleucel Chimeric Antigen Receptor (CAR) T-Cell Therapy for Adults with Diffuse Large B-Cell Lymphoma (DLBCL): Real World Experience from the Center for International Blood & Marrow Transplant Research (CIBMTR) Cellular Therapy (CT) Registry	Blood. 2019. 134(Supplement 1):766.	Abstract	Center for International Blood & Marrow Transplant Research (CIBMTR) Cellular Therapy (CT) Registry	Tisagenlecleucel	Yes	NA		Original SLR
Landsburg, D. J.	Real-World Efficacy and Safety Outcomes for Patients with Relapsed or Refractory (R/R) Aggressive B-Cell Non-Hodgkin's Lymphoma (aBNHL) Treated with Commercial Tisagenlecleucel: Update from the Center	Blood. 2021. 138(Supplement 1):429.	Abstract		Tisagenlecleucel	Yes	NA		SLR update

	for International Blood and Marrow Transplant Research (CIBMTR) Registry								
Mohn N	Neurological management and work-up of neurotoxicity associated with CAR T cell therapy	Neurol Res Pract. 2022 Jan 10;4(1):1	Full publication		Tisagenlecleucel	Yes	NA		SLR update
Pasquini MC	Real-world evidence of tisagenlecleucel for pediatric acute lymphoblastic leukemia and non-Hodgkin lymphoma.	Blood Adv. 2020 Nov 10;4(21):5414-5424.	Full publication	CIBMTR	Tisagenlecleucel	Yes	NA		Original SLR
Schuster, S. J.	Chimeric Antigen Receptor T Cells in Refractory B-Cell Lymphomas	N Engl J Med. 2017 Dec 28;377(26):2545-2554	Full publication	NCT02030834	Tisagenlecleucel	Yes	NA		Original SLR
Schuster SJ	Tisagenlecleucel in Adult Relapsed or Refractory Diffuse Large B-Cell Lymphoma	N Engl J Med. 2019 Jan 3;380(1):45-56.	Full publication	JULIET	Tisagenlecleucel	Yes	NA		Original SLR
Svoboda, J.	Use of Bendamustine for Lymphodepletion before Tisagenlecleucel (anti-CD19 CAR T cells) for Aggressive B-Cell Lymphomas	Blood. 2019. 134(Supplement 1):1606.	Abstract		Tisagenlecleucel	Yes	NA		Original SLR
Yamasaki-Morita, M.	Relative hypercoagulation induced by suppressed fibrinolysis after tisagenlecleucel infusion in malignant lymphoma	Blood advances. 2022	Full publication		Tisagenlecleucel	Yes	NA		SLR update
Zettler, M. E.	Real-world adverse events associated with tisagenlecleucel in	Blood. 2020. 136(SUPPL 1):12	Abstract		Tisagenlecleucel		Limited reporting	Not included for topline extraction	Original SLR

	acute lymphoblastic leukemia and large B-cell lymphoma							due to limited reporting of any data of interest (AE only)	

Table 9: List of excluded trials in the clinical SLR

Author	Title	Journal	Year	Citation	Full publication review	Reason for exclusion
Original SLR (n=210)						
Abramson, J.	Safety and efficacy results from transcend NHL 001, a multicenter phase 1 study of lisocabtagene maraleucel (Liso-cel) in relapsed/refractory (R/R) large B-cell lymphoma (LBCL)	Oncology Research and Treatment	2020	43(Supplement 1):215.	E8 - Linked publication	Superseded by full publication
Abu-Sbeih, H.	Gastrointestinal Adverse Events Observed After Chimeric Antigen Receptor T-Cell Therapy	American Journal of Clinical Oncology: Cancer Clinical Trials	2019	42(10):789-796.	E3 - Not relevant intervention	General CAR-T
Alderuccio, J. P.	ABCL-396: Incidence, Onset, and Management of Edema and Effusion in Patients Treated with Loncastuximab Tesirine for R/R DLBCL in the LOTIS Clinical Trial Program	Clinical Lymphoma, Myeloma and Leukemia	2021	21(Supplement 1):S397-S398.	E3 - Not relevant intervention	Loncastuximab
Apap Mangion, S.	Real world clinical features and management of neurotoxicity in CD19 targeted chimeric antigen receptor (CAR) T-cell therapy for high grade lymphoma with off-label use of anakinra	European Journal of Neurology	2020	27(Supplement 1):94.	E3 - Not relevant intervention	General CAR-T
Avigdor, A.	Baseline clinical and PET-CT tumor burden parameters do not predict outcome of relapse/refractory aggressive B cell lymphoma patients treated with anti-CD19 car T-cells	Hematological Oncology	2019	37(Supplement 2):504-505.	E3 - Not relevant intervention	General CAR-T

Author	Title	Journal	Year	Citation	Full publication review	Reason for exclusion
Avivi, I.	Polatuzumab vedodtin vs. Car-t cell for patients with relapsed/ refractory diffuse large b cell lymphoma - A propensity score matched analysis	HemaSphere	2021	5(SUPPL 2):85-86.	E8 - Linked publication	Superseded by full publication(MAIC)
Bailen, R.	Multi-technique follow-up of lymphoma patients undergoing commercial car-t cell therapy: Experience from a single centre	HemaSphere	2020	4(Supplement 1):692.	E3 - Not relevant intervention	General CAR-T
Baird, J. H.	CD22-directed CAR T-cell therapy mediates durable complete responses in adults with relapsed or refractory large B-cell lymphoma after failure of CD19-directed CAR T-cell therapy and high response rates in adults with relapsed or refractory B-cell acute lymphoblastic leukemia	Blood	2020	136(SUPPL 1):28-29.	E3 - Not relevant intervention	General CAR-T
Bannerji, R.	Odronextamab (REGN1979), a human CD20 x CD3 bispecific antibody, induces durable, complete responses in patients with highly refractory B-cell non-Hodgkin lymphoma, including patients refractory to CAR T therapy	Blood	2020	136(SUPPL 1):42-43.	E3 - Not relevant intervention	Odronextamab
Bao, F.	Autologous CD19-directed chimeric antigen receptor-T cell is an effective and safe treatment to refractory or relapsed diffuse large B-cell lymphoma	Cancer Gene Therapy	2019	26(7-8):248-255.	E3 - Not relevant intervention	Not relevant CAR-T construct (different production process to CAR=Ts of interest)
Beider, K.	Senescent/exhausted phenotype of CD19-targeted cart cells and immunoregulatory environment correlate with reduced response to CAR-T cell therapy in relapsed/refractory B cell malignancies	Bone Marrow Transplantation	2020	55:237-238.	E3 - Not relevant intervention	General CAR-T
Beider, K.	Upregulation of Senescent/Exhausted Phenotype of CAR T Cells and Induction of Both Treg and Myeloid Suppressive Cells Correlate with Reduced Response to CAR T Cell Therapy in Relapsed/Refractory B Cell Malignancies	Blood	2019	134(Supplement 1):3234.	E3 - Not relevant intervention	General CAR-T
Bethge, W. A.	Standard-of-care CAR-T cell therapy for large B-cell lymphoma: Real world data Germany	Bone Marrow Transplantation	2021	56:19-20.	E3 - Not relevant intervention	General CAR-T

Author	Title	Journal	Year	Citation	Full publication review	Reason for exclusion
Beyar-Katz, O.	Early infections following commercial anti-CD19 CAR-T Cells infirm population - A single center retrospective study	HemaSphere	2021	5(SUPPL 2):100-101.	E3 - Not relevant intervention	Data not reported for individual CAR-T
Bonner, A.	Pcn34 Compatibility of Chimeric Antigen Receptor (Car) T-Cell Therapy Studies in the Treatment of Patients with Relapsed/Refractory Large B-Cell Lymphoma (Lbcl) for Indirect Treatment Comparison (Itc) Analyses	Value in Health	2020	23(Supplement 1):S28.	E11 - review	
Brady, J.	Feasibility and outcome of bridging RT pre CAR-T in DLBCL in one centre with a wide referral network	Radiotherapy and Oncology	2021	161(Supplement 1):S241-S242.	E3 - Not relevant intervention	Details of CAR-T not reported (primary focus is radiotherapy as bridging therapy)
Bramanti, S.	Management of single site localized early relapse after CART cell therapy in DLBCL: A single center experience	Tumori	2021	107(2 SUPPL):153.	E3 - Not relevant intervention	Data not reported for individual CAR-T
Bucklein, V.	Extranodal disease is an independent negative predictive marker for progressionfree survival after CD19-CAR T-CELL therapy for relapsed/refractory diffuse large B-cell lymphoma	HemaSphere	2021	5(SUPPL 2):239.	E3 - Not relevant intervention	Data not reported for individual CAR-T
Bucklein, V.	Extranodal disease is associated with shorter progression-free survival after CD19-CAR T-cell therapy for relapsed/refractory diffuse large B-cell lymphoma	Hematological Oncology	2021	39(SUPPL 2):366-367.	E3 - Not relevant intervention	General CAR-T
Bucklein, V.	CD19 car T-cells for relapsed/refractory diffuse large b-cell lymphoma: Real-world data from LMU Munich	Journal for ImmunoTherapy of Cancer	2020	8(SUPPL 2):A48-A49.	E3 - Not relevant intervention	General CAR-T
Bucklein, V.	Cd19 car t-cell therapy for relapsed/ refractory diffuse large b-cell lymphoma-the munich real life experience	HemaSphere	2020	4(Supplement 1):699-700.	E3 - Not relevant intervention	General CAR-T
Budka, J.	Pretreatment (PreTx) immune cell phenotypes in peripheral blood associated with the tumor immune contexture, product attributes, and durable clinical efficacy in patients with large B-cell lymphoma (LBCL) treated with axicabtagene ciloleucel (axi-cel)	Cancer Research. Conference: AACR Annual Meeting	2021	81(13 SUPPL).	E12 - outcome	In vitro study

Author	Title	Journal	Year	Citation	Full publication review	Reason for exclusion
Buecklein, V.	Single-center experience with axicabtagene-ciloleucel (AXI-Cel) and tisagenlecleucel (TISA-Cel) for relapsed/refractory diffuse large B-cell lymphoma: Comparable response rates and manageable toxicity	Blood	2020	136(SUPPL 1):34-35.	E3 - Not relevant intervention	General CAR-T
Caimi, P. F.	Duration of response to loncastuximab tesirine in relapsed/refractory diffuse large B-cell lymphoma by demographic and clinical characteristics: Subgroup analyses from LOTIS-2	HemaSphere	2021	5(SUPPL 2):223.	E3 - Not relevant intervention	Loncastuximab
Caimi, P. F.	Loncastuximab tesirine in relapsed or refractory diffuse large B-cell lymphoma (LOTIS-2): a multicentre, open-label, single-arm, phase 2 trial	The Lancet Oncology	2021	22(6):790-800.	E3 - Not relevant intervention	Loncastuximab
Cao, Y.	CD19/CD22 Chimeric Antigen Receptor T Cell Cocktail Therapy following Autologous Transplantation in Patients with Relapsed/Refractory Aggressive B Cell Lymphomas	Transplantation and Cellular Therapy.	2021		E3 - Not relevant intervention	CAR-T therapy following ASCT
Cao, Y.	CD19/CD22 CAR-T cell cocktail therapy following autologous transplantation in patients with relapsed/refractory B-cell lymphomas	Blood	2020	136(SUPPL 1):11.	E3 - Not relevant intervention	General CAR-T
Cao, Y.	Anti-CD19 chimeric antigen receptor T cells in combination with nivolumab are safe and effective against relapsed/refractory B-cell non-hodgkin lymphoma	Frontiers in Oncology	2019	9(AUG) (no pagination)(767).	E3 - Not relevant intervention	Data not reported for individual CAR-T; CAR-T therapy administered in combination with nivolumab
Cappell, K.	Long-term follow-up of anti-CD19 CAR T-cell therapy for B-cell lymphoma and chronic lymphocytic leukemia	Journal of Clinical Oncology. Conference	2020	38(15).	E8 - Linked publication	Superseded by full publication
Carlo-Stella, C.	Initial results of a phase 2 study of loncastuximab tesirine, a novel pyrrolobenzodiazepine-based antibody-drug conjugate, in patients with relapsed or refractory diffuse large B-cell lymphoma	HemaSphere	2020	4(Supplement 1):75-76.	E3 - Not relevant intervention	Lonca: LOTIS-2

Author	Title	Journal	Year	Citation	Full publication review	Reason for exclusion
Casadei, B.	Real world evidence of car t-cell therapies for the treatment of relapsed/refractory b-cell non-hodgkin lymphoma: A monocentric experience	Cancers	2021	13(19) (no pagination)(4789).	E3 - Not relevant intervention	Limited data reported for individual CAR-Ts (only data for median time to onset of cytokine release syndrome)
Chapman, R.	PMU55 Methods and Acceptability of Comparator Arms for CAR-T HTA Submission	Value in Health	2020	23(Supplement 2):S612.	E11 - review	
Chen, X.	A Phase I clinical trial of chimeric antigen receptor-modified T cells in patients with relapsed and refractory lymphoma	Immunotherapy	2020	12(10):681-696.	E3 - Not relevant intervention	General CAR-T
Cheng, R.	Patient Perspectives on Health-Related Quality of Life in Diffuse Large B-Cell Lymphoma Treated with Car T-Cell Therapy: A Qualitative Study	Oncology & Therapy	2021		E3 - Not relevant intervention	General CAR-T
Chiappella, A.	Car-t cell in diffuse large b-cell and primary mediastinal lymphomas in real life setting: A report from the prospective observational study of the italian society of hematology	HemaSphere	2021	5(SUPPL 2):333-334.	E3 - Not relevant intervention	General CAR-T
Chiappella, A.	First report of the real-life prospective observational study CAR-T cell in diffuse large B-cell and primary mediastinal lymphomas of the italian society of hematology	Hematological Oncology	2021	39(SUPPL 2):371.	E3 - Not relevant intervention	General CAR-T
Chien, H. C.	Real-world practice patterns and outcomes in Veterans with relapsed/refractory diffuse large B-cell lymphoma	Future Oncology	2021	17(4):411-422.	E12 - outcome	Outcomes reported by line of therapy, but not for particular treatments
Chong, E. A.	Anti-CD19 CAR-T for treatment of double expressor and double hit large B-cell lymphomas: A single institution real-world analysis	Blood	2020	136(SUPPL 1):19-20.	E3 - Not relevant intervention	General CAR-T
Chong, E. A.	Clinical outcomes for anti-CD19 CAR T cell (CTL019) products not meeting commercial release specifications	Cytotherapy	2020	22(5 Supplement):S29.	E3 - Not relevant intervention	General CAR-T
Chong, E. A.	Outcomes in Aggressive B-Cell Non-Hodgkin Lymphomas with Anti-CD19 CAR	Blood	2019	134(Supplement 1):594.	E8 - Linked publication	Linked to Chong 2020

Author	Title	Journal	Year	Citation	Full publication review	Reason for exclusion
	T-Cell (CTL019) Products Not Meeting Commercial Release Specifications					
Cordeiro, A.	Late Events after Treatment with CD19-Targeted Chimeric Antigen Receptor Modified T Cells	Biology of Blood and Marrow Transplantation	2020	26(1):26-33.	E3 - Not relevant intervention	Data not reported for individual CAR-T
Cuadrado, M.	Early pet response predicts outcome in large bcell lymphoma patients treated with CD19 CAR-T	Hematological Oncology	2021	39(SUPPL 2):137-138.	E3 - Not relevant intervention	General CAR-T
De la Cruz-Merino, L.	Lenalidomide plus R-GDP (R2-GDP) in relapsed/refractory diffuse large b cell lymphoma. Preliminary results of the R2-GDP-gotel trial	Hematological Oncology	2019	37(Supplement 2):258-259.	E3 - Not relevant intervention	Combination therapy
Delgado, J.	The European Medicines Agency Review of Tafasitamab in Combination With Lenalidomide for the Treatment of Adult Patients With Relapsed/Refractory Diffuse Large B-cell Lymphoma	HemaSphere	2021	5(12):e666.	E11 - review	EMA review of tafasitamab in R/R DLBCL
Deng, Q.	Characteristics of anti-CD19 CAR T cell infusion products associated with efficacy and toxicity in patients with large B cell lymphomas	Nature Medicine	2020	26(12):1878-1887.	E3 - Not relevant intervention	Limited outcome data reported for axi-cel and number of pts with DLBCL subtype not reported
Depaus, J.	Clinical activity of loncastuximab tesirine plus ibrutinib in Non-Hodgkin lymphoma: Updated lotis 3 phase 1 results	Hematological Oncology	2021	39(SUPPL 2):325-327.	E3 - Not relevant intervention	loncastuximab tesirine + ibrutinib
Depaus, J.	Interim results of a phase 1/2 study of loncastuximab tesirine (Lonca) combined with ibrutinib in advanced diffuse large b-cell lymphoma (DLBCL) or mantle cell lymphoma (MCL)	HemaSphere	2020	4(Supplement 1):601-602.	E3 - Not relevant intervention	loncastuximab tesirine + ibrutinib
Dreger, P.	Outcome determinants of commercial CAR-T cell therapy for large B-cell lymphoma: Results of the GLA/DRST real world analysis	Hematological Oncology	2021	39(SUPPL 2):370-371.	E3 - Not relevant intervention	General CAR-T
Duell, J.	Long-term analyses from l-mind, a phase ii study of tafasitamab plus lenalidomide (LEN) in patients (PTS) with relapsed or	Hematological Oncology	2021	39(SUPPL 2):58-61.	E8 - Linked publication	Superseded by 2021 full pub

Author	Title	Journal	Year	Citation	Full publication review	Reason for exclusion
	refractory diffuse large b-cell lymphoma (r/R DLBCL)					
Dwivedy Nasta, S.	A Characterization of Bridging Therapies Leading up to Commercial CAR T-Cell Therapy	Blood	2019	134(Supplement 1):4108.	E3 - Not relevant intervention	General CAR-T
Enblad, G.	A phase I/IIa trial using CD19-targeted third-generation CAR T cells for lymphoma and leukemia	Clinical Cancer Research	2018	24(24):6185-6194.	E3 - Not relevant intervention	Third-generation CAR-T
Ernst, M.	Chimeric antigen receptor (CAR) T-cell therapy for people with relapsed or refractory diffuse large B-cell lymphoma	Cochrane Database of Systematic Reviews	2021	2021(9) (no pagination)(CD013365).	E11 - review	
Fan, L.	Phase I study of CBM.CD19 chimeric antigen receptor T cell in the treatment of refractory diffuse large B-cell lymphoma in Chinese patients	Fronteras en Medicina	2021	02:02.	E3 - Not relevant intervention	Not relevant CAR-T construct (C-CAR011)
Feldman, T.	Addition of lenalidomide to rituximab, ifosfamide, carboplatin, etoposide (RICER) in first-relapse/primary refractory diffuse large B-cell lymphoma	British Journal of Haematology	2014	166(1):77-83.	E4 - Not relevant line of therapy	Second line study
Figura, N. B.	Patterns and Predictors of Failure in Recurrent or Refractory Large B-Cell Lymphomas After Chimeric Antigen Receptor T-Cell Therapy	International Journal of Radiation Oncology, Biology, Physics	2021	111(5):1145-1154.	E3 - Not relevant intervention	Data not reported for individual CAR-T
Follows, G.	Effect of prior therapy on the efficacy and safety of oral selinexor in patients with relapsed/ refractory (R/R) diffuse large B-cell lymphoma (DLBCL): A post-hoc analysis of the sadal study	HemaSphere	2020	4(Supplement 1):582-583.	E3 - Not relevant intervention	Selinexor
Fox, C.	Clinical outcomes in patients with relapsed/ refractory large B-cell lymphoma receiving conventional third-line therapy: A multicenter, retrospective, real-world study in the United Kingdom	HemaSphere	2021	5(SUPPL 2):234-235.	E12 - outcome	Data not presented for individual treatments
Gajra, A.	Neurological adverse events following CAR T-cell therapy: a real-world analysis	Immunotherapy	2020	12(14):1077-1082.	E3 - Not relevant intervention	Limited data reported for individual CAR-Ts (only data for

Author	Title	Journal	Year	Citation	Full publication review	Reason for exclusion
						incidence of neurological AEs)
Garcia-Recio, M.	The International Prognostic Index Is Associated with Outcomes in Diffuse Large B Cell Lymphoma after Chimeric Antigen Receptor T Cell Therapy	Transplantation and Cellular Therapy	2021	27(3):233-240.	E3 - Not relevant intervention	Data not reported for individual CAR-T
Gauthier, J.	CRS and ICANS risk across three CD19 car-T cell products in patients with aggressive NHL	HemaSphere	2021	5(SUPPL 2):217-218.	E3 - Not relevant intervention	General CAR-T
Gauthier, J.	CD19 CAR T-cell product type independently impacts CRS and ICANS severity in patients with aggressive NHL	Journal of Clinical Oncology. Conference: Annual Meeting of the American Society of Clinical Oncology, ASCO	2021	39(15 SUPPL).	E3 - Not relevant intervention	General CAR-T
Ghafouri, S.	Real-World Experience of Axicabtagene Ciloleucel and Tisagenlecleucel for Relapsed or Refractory Aggressive B-cell Lymphomas: A Single-Institution Experience	Clinical lymphoma, myeloma & leukemia	2021	21(12):861-872.	E3 - Not relevant intervention	Data not reported for individual CAR-T
Ghafouri, S. N.	CD19/CD20 bispecific chimeric antigen receptor (CAR) in naive/memory T-cells for the treatment of relapsed or refractory B-cell lymphomas	Cancer Research. Conference: AACR Annual Meeting	2021	81(13 SUPPL).	E3 - Not relevant intervention	General CAR-T
Ghosh, N.	Lisocabtagene maraleucel for treatment of second-line transplant noneligible relapsed/ refractory aggressive large B-cell non-hodgkin lymphoma: Updated results from the pilot study	HemaSphere	2020	4(Supplement 1):82.	E4 - Not relevant line of therapy	Second line study
Godwin, J. E.	Outcomes of treatment with the chimeric antigen receptor (CAR) T cell therapy lisocabtagene maraleucel (LISO-Cel) in the nonuniversity setting: Initial results from the outreach study	Blood	2020	136(SUPPL 1):50-52.	E3 - Not relevant intervention	General CAR-T
Good, Z.	Identification of Two CAR T-Cell Populations Associated with Complete Response or Progressive Disease in Adult Lymphoma Patients Treated with Axi-Cel	Blood	2019	134(Supplement 1):779.	E12 - outcome	In vitro measurement of surface/cellular proteins

Author	Title	Journal	Year	Citation	Full publication review	Reason for exclusion
Guha, A.	Cardiovascular Events Associated with Chimeric Antigen Receptor T Cell Therapy: Cross-Sectional FDA Adverse Events Reporting System Analysis	Biology of Blood & Marrow Transplantation	2020	26(12):2211-2216.	E3 - Not relevant intervention	Limited data reported for individual CAR-Ts (only data for incidence of overall AEs)
Guidetti, A.	Long term cytopenia and infections in patients treated with anti-cd19 car t-cells: An analysis of bone marrow and clinical risk factors	HemaSphere	2021	5(SUPPL 2):340-341.	E3 - Not relevant intervention	General CAR-T
Guidetti, A.	Quantitative metabolic parameters evaluation in patients with aggressive B-cell lymphomas treated with anti-CD19 CAR T-cells	Hematological Oncology	2021	39(SUPPL 2):372-373.	E3 - Not relevant intervention	General CAR-T
Gupta, S.	Acute Kidney Injury and Electrolyte Abnormalities After Chimeric Antigen Receptor T-Cell (CAR-T) Therapy for Diffuse Large B-Cell Lymphoma	American Journal of Kidney Diseases	2020	76(1):63-71.	E3 - Not relevant intervention	Limited data reported for individual CAR-Ts (only data for incidence of AKI)
Halford, Z.	Axicabtagene Ciloleucel: Clinical Data for the Use of CAR T-cell Therapy in Relapsed and Refractory Large B-cell Lymphoma	Annals of Pharmacotherapy	2021	55(3):390-405.	E11 - review	
Hamadani, M.	Final results of a phase 1 study of loncastuximab tesirine in relapsed/refractory B-cell non-Hodgkin lymphoma	Blood	2021	137(19):2634-2645.	E3 - Not relevant intervention	Loncastuximab
Hathway, J.	Budget impact model of axicabtagene ciloleucel (Axi-cel) in a us population of patients with relapsed or refractory large B-Cell lymphoma (R/R-LBCL)	Bone Marrow Transplantation	2019	53:878-879.	E12 - outcome	BIM
Held, G.	Analysis of a Safety Run-in Cohort from Niveau, a Phase 3 Study for Patients with Aggressive Non-Hodgkin Lymphoma in First Relapse or Progression Not Eligible for High-Dose Chemotherapy (HDT), Testing Nivolumab in Combination with Gemcitabine, Oxaliplatin (GemOx) Plus Rituximab (R) in Case of B-Cell Lymphoma	Blood	2019	134(Supplement 1):4085.	E3 - Not relevant intervention	Nivolumab + R-GemOx
Hess, B.	Relationship between exposure and safety/efficacy of loncastuximab tesirine	Cancer Research. Conference:	2021	81(13 SUPPL).	E3 - Not relevant intervention	Loncastuximab

Author	Title	Journal	Year	Citation	Full publication review	Reason for exclusion
	(Lonca) in B-cell non-Hodgkin lymphoma (B-NHL)	AACR Annual Meeting				
Hirayama, A. V.	The response to lymphodepletion impacts PFS in patients with aggressive non-Hodgkin lymphoma treated with CD19 CAR T cells	Blood	2019	133(17):1876-1887.	E3 - Not relevant intervention	Data not reported for individual CAR-T
Hockings, C.	Characterisation of early and late cytopenias in lymphoma patients following treatment with anti-CD19 CAR-T therapy	Bone Marrow Transplantation	2020	55:238-239.	E3 - Not relevant intervention	General CAR-T
Hu, Y.	CD19/CD22 dual-targeted chimeric antigen receptor T-cell therapy for relapsed/refractory aggressive B-cell lymphoma: A safety and efficacy study	Blood	2020	136(SUPPL 1):34.	E3 - Not relevant intervention	General CAR-T
Hutchings, M.	O17-1 Subcutaneous (SC) epcoritamab induces complete responses across R/R B-cell NHL subtypes: Updated dose-escalation data	Annals of Oncology	2021	32(Supplement 4):S292.	E3 - Not relevant intervention	Epcoritamab
Hutchings, M.	Subcutaneous epcoritamab induces complete responses with an encouraging safety profile across relapsed/refractory B-cell non-Hodgkin lymphoma subtypes, including patients with prior CAR-T therapy: Updated dose escalation data	Blood	2020	136(SUPPL 1):45-46.	E3 - Not relevant intervention	Epcoritamab
Imber, B. S.	Clinical impact of bridging therapy prior to commercial chimeric antigen receptor (CAR) T-cell therapies for relapsed/refractory lymphomas	Blood	2020	136(SUPPL 1):1-2.	E3 - Not relevant intervention	General CAR-T
Inam, S.	Real-world clinical features of neurotoxicity complicating CD19-targeted chimeric antigen receptor (CAR) T-cell therapy for high grade lymphoma and management including the off-label use of anakinra	Bone Marrow Transplantation	2020	55:229-230.	E3 - Not relevant intervention	General CAR-T
Jacobson, C. A.	Long-term survival and gradual recovery of B cells in patients with refractory large B-cell lymphoma treated with axicabtagene ciloleucel	British Journal of Haematology	2021	193(SUPPL 1):143-145.	E8 - Linked publication	Superseded by full publication
Jaeger, U.	Safety and efficacy of tisagenlecleucel plus pembrolizumab in patients with relapsed/	HemaSphere	2021	5(SUPPL 2):222.	E3 - Not relevant intervention	PORTIA: combination of tisa + pembro

Author	Title	Journal	Year	Citation	Full publication review	Reason for exclusion
	refractory diffuse large B-cell lymphoma: Updated analysis of the phase 1B portia study					
Jain, T.	CAR-Induced Cytopenia	Clinical Lymphoma, Myeloma and Leukemia	2021	21(Supplement 1):S80.	E3 - Not relevant intervention	General CAR-T
Jain, T.	Hematopoietic recovery in patients receiving chimeric antigen receptor T-cell therapy for hematologic malignancies	Blood Advances	2020	4(15):3776-3787.	E3 - Not relevant intervention	Limited data reported for individual CAR-Ts (only data for number of patients with complete count recovery at 1 month, incidence of cytokine release syndrome, or immune effector cell–associated neurological syndrome)
Janakiram, M.	ABCL-339: Clinical Activity of Loncastuximab Tesirine (Lonca) Plus Ibrutinib in Non-Hodgkin Lymphoma: Updated LOTIS-3 Phase 1 Results	Clinical Lymphoma, Myeloma and Leukemia	2021	21(Supplement 1):S392.	E3 - Not relevant intervention	Loncastuximab
Johnsrud, A.	Bleeding and thrombosis are associated with endothelial dysfunction in CAR-T cell therapy and are increased in patients experiencing neurologic toxicity	Blood	2020	136(SUPPL 1):32-33.	E3 - Not relevant intervention	General CAR-T
Kahl, B. S.	ABCL-022: LOTIS-2 Follow-Up Analysis: Updated Results from a Phase 2 Study of Loncastuximab Tesirine (Lonca) in Relapsed or Refractory Diffuse Large B-Cell Lymphoma	Clinical Lymphoma, Myeloma and Leukemia	2021	21(Supplement 1):S377-S378.	E3 - Not relevant intervention	Loncastuximab
Kahl, B. S.	A phase I study of ADCT-402 (loncastuximab tesirine), a novel pyrrolobenzodiazepine-based antibody-drug conjugate, in relapsed/ refractory B-cell non-Hodgkin lymphoma	Clinical Cancer Research	2019	25(23):6986-6994.	E3 - Not relevant intervention	Loncastuximab

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Kalakonda, N.	Selinexor in patients with relapsed or refractory diffuse large B-cell lymphoma (SADAL): a single-arm, multinational, multicentre, open-label, phase 2 trial	The Lancet Haematology	2020	7(7):e511-e522.	E3 - Not relevant intervention	Selinexor
Kenderian, S. S.	ZUMA-19: A phase 1/2 multicenter study of lenzilumab use with axicabtagene ciloleucel (Axi-Cel) in patients (Pts) with relapsed or refractory large B cell lymphoma (R/R LBCL)	Blood	2020	136(SUPPL 1):6-7.	E9 - Protocol	
Kersten, M. J.	Comparative efficacy of tisagenlecleucel (TISA-CEL) and lisocabtagene maraleucel (LISO-CEL) in patients with relapsed/refractory diffuse large b-cell lymphoma (R/R DLBCL)	HemaSphere	2021	5(SUPPL 2):218-219.	E11 - review	
Kilgore, K. M.	Burden of illness and outcomes in the 2nd line treatment of large B-cell lymphoma: A real-world comparison of medicare beneficiaries with and without stem cell transplants	Blood	2020	136(SUPPL 1):1-2.	E3 - Not relevant intervention	
Kittai, A. S.	Comorbidities Predict Inferior Survival in Patients Receiving Chimeric Antigen Receptor T Cell Therapy for Diffuse Large B Cell Lymphoma: A Multicenter Analysis	Biology of Blood and Marrow Transplantation.	2020		E3 - Not relevant intervention	Data not reported for individual CAR-T
Kittai, A. S.	Comorbidities Predict Inferior Survival in Patients Receiving CAR T-Cell Therapy for Relapsed/Refractory DLBCL: A Multicenter Retrospective Analysis	Blood	2019	134(Supplement 1):780.	E3 - Not relevant intervention	General CAR-T
Klein, C.	FDG-PET/CT is a powerful tool to evaluate response to chimeric antigen receptor T-cell therapy in Diffuse Large B-Cell Lymphoma (DLBCL)	NuklearMedizin	2021	60(2):153.	E3 - Not relevant intervention	General CAR-T
Klink, A.	Real-world treatment with car t-cell therapy of united states (us) patients with large b cell lymphoma (lbcl)	HemaSphere	2021	5(SUPPL 2):337.	E3 - Not relevant intervention	General CAR-T
Knight, J. M.	Quality of life, tryptophan metabolites, and neurotoxicity assessments of patients with relapsed or refractory B cell malignancies undergoing CAR 20/19-T cell therapy	Blood	2020	136(SUPPL 1):42-43.	E3 - Not relevant intervention	General CAR-T

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Kochenderfer, J. N.	Donor-derived CD19-targeted T cells cause regression of malignancy persisting after allogeneic hematopoietic stem cell transplantation	Blood	2013	122(25):4129-4139.	E3 - Not relevant intervention	Limited details of CART-T regimen; only 2 DLBCL subjects
Kochenderfer, J. N.	Treating B-cell cancer with T cells expressing anti-CD19 chimeric antigen receptors	Nature Reviews Clinical Oncology	2013	10(5):267-76.	E11 - review	Narrative review od CART-Ts
Kuhnl, A.	Radiotherapy Bridging in Patients With R/R High-Grade Lymphoma Receiving CD19 CAR-T in the UK	International Journal of Radiation Oncology Biology Physics	2021	111(3 Supplement):S130.	E3 - Not relevant intervention	Data not reported for individual CAR-T
Kuhnl, A.	Outcome of high-grade lymphoma patients treated with cd19 car-t-updated real-world experience in the UK	HemaSphere	2020	4(Supplement 1):81-82.	E3 - Not relevant intervention	General CAR-T
Kuhnl, A.	Real-World Data of High-Grade Lymphoma Patients Treated with CD19 CAR-T in England	Blood	2019	134(Supplement 1):767.	E3 - Not relevant intervention	General CAR-T
Lamure, S.	Clinical and product features associated with outcome of dlbcl patients to cd19-targeted car t-cell therapy	Cancers	2021	13(17) (no pagination)(4279).	E3 - Not relevant intervention	Data not reported for individual CAR-T
Leivonen, S. K.	Molecular Profiling of Aggressive Non-Hodgkin Lymphoma - Results from a Phase 1/2 Preben Study	Blood	2019	134(Supplement 1):5314.	E3 - Not relevant intervention	Combination treatment with pixantrone, etoposide, bendamustine and RTX
Li, C.	Comparison of CAR-T19 and autologous stem cell transplantation for refractory/relapsed non-Hodgkin's lymphoma	JCI Insight	2019	4(17) (no pagination)(e130195).	E3 - Not relevant intervention	General-CAR-T
Lin, R. J.	Impact and Safety of Chimeric Antigen Receptor T Cell Therapy in Vulnerable Older Patients with Relapsed/Refractory Diffuse Large B-Cell Lymphoma	Blood	2019	134(Supplement 1):1603.	E3 - Not relevant intervention	General CAR-T
Liu, F. F.	Use of chimeric antigen receptor t cell therapies in patients with large b-cell lymphoma in the real-world setting: Systematic literature review	HemaSphere	2021	5(SUPPL 2):562.	E11 - review	

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Liu, H.	A phase i trial using CD19 CAR-T expressing PD-1/CD28 chimeric switch-receptor for refractory or relapsed B-cell lymphoma	Journal of Clinical Oncology. Conference	2019	37(Supplement 15).	E3 - Not relevant intervention	General CAR-T
Liu, W.	Anti-CD19 CAR T-cell (CNCT19) infusion following HDT/ASCT is safe and effective in patients with relapsed/refractory large B-cell lymphoma	Blood	2020	136(SUPPL 1):2.	E3 - Not relevant intervention	General CAR-T
Maillet, D.	Evaluation of mid-term (6-12 months) neurotoxicity in B-cell lymphoma patients treated with CAR T cells: A prospective cohort study	Neuro-Oncology	2021	23(9):1569-1575.	E3 - Not relevant intervention	Data not reported for individual CAR-T
Maloney, D. G.	Matching-adjusted indirect treatment comparison of liso-cel versus axi-cel in relapsed or refractory large B cell lymphoma	Journal of Hematology and Oncology	2021	14(1) (no pagination)(140).	E5 - Not relevant study design	MAIC
Maloney, D. G.	Matching-Adjusted Indirect Comparison (MAIC) of Lisocabtagene Maraleucel (liso-cel) Vs Axicabtagene Ciloleucel (axi-cel) and Tisagenlecleucel in Relapsed/Refractory (R/R) Large B-Cell Lymphoma (LBCL)	Blood	2020	136(Supplement 1):18-19.	E11 - review	MAIC
Maloney, D. G.	Systematic Literature Review of the Clinical Evidence in Relapsed/Refractory (R/R) Large B-Cell Lymphoma	Blood	2019	134(Supplement 1):5821.	E11 - review	
Maziarz, R. T.	Comparative efficacy of tisagenlecleucel (TISACEL) and lisocabtagene maraleucel (LISO-CEL) in relapsed/refractory diffuse large B-cell lymphoma (r/r DLBCL)	Hematological Oncology	2021	39(SUPPL 2):367-368.	E11 - review	
Melody, M.	Baseline Hypoalbuminemia Does Not Appear to be an Adverse Prognostic Factor in Patients with Relapse/Refractory B-Cell Lymphomas Treated with Axicabtagene Ciloleucel (axi-cel)	Blood	2019	134(Supplement 1):5343.	E8 - Linked publication	Superseded by full publication
Minard-Colin, V.	BIANCA: Phase 2, single-arm, global trial to determine efficacy and safety of tisagenlecleucel in pediatric/young adult patients with relapsed/ refractory B-cell non-Hodgkin lymphoma	HemaSphere	2020	4(Supplement 1):585.	E2 - Not relevant disease	Enrolled paediatric/young adults and unclear if any of the DLBCL patients were young adults.

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Mirza, A. S.	Incidence and Management of Effusions Before and After CD19-Directed Chimeric Antigen Receptor (CAR) T Cell Therapy in Large B Cell Lymphoma	Transplantation and Cellular Therapy	2021	27(3):242.e1-242.e6.	E3 - Not relevant intervention	Data not reported for individual CAR-T
Moignet, A.	Life after CAR-T cells: A prospective study evaluating the personal, social and professional outcomes after CAR-T cell therapy in lymphoma patients	Hematological Oncology	2021	39(SUPPL 2):467.	E3 - Not relevant intervention	General CAR-T
Monfrini, C.	Monitoring commercial anti-cd19 car t-cell product expansion kinetics: Real-world applications of a novel droplet digital pcr assay and of multiparametric flow cytometry	HemaSphere	2021	5(SUPPL 2):331.	E3 - Not relevant intervention	General CAR-T
Mous, R.	Subcutaneous epcoritamab in patients with relapsed/refractory B-cell non-Hodgkin lymphoma: Safety profile and anti-tumor activity	HemaSphere	2021	5(SUPPL 2):212.	E3 - Not relevant intervention	Epcoritamab
Nader, A.	Association of PET/CT response assessment prior to CAR T-cell infusion with outcomes after CAR T-cell therapy in aggressive B-cell lymphomas	Journal of Clinical Oncology. Conference: Annual Meeting of the American Society of Clinical Oncology, ASCO	2021	39(15 SUPPL).	E3 - Not relevant intervention	General CAR-T
Nagle, S. J.	Prolonged hematologic toxicity following treatment with chimeric antigen receptor T cells in patients with hematologic malignancies	American Journal of Hematology	2021	96(4):455-461.	E3 - Not relevant intervention	Data not reported for individual CAR-T
Nagler, A.	Update on chimeric antigen receptor - T cells (CAR-T) CD19 therapy: the Sheba experience	Hematology, Transfusion and Cell Therapy	2020	42(Supplement 1):7-8.	E3 - Not relevant intervention	General CAR-T
Neelapu, S. S.	Outcomes of patients aged 65 years in ZUMA-1, a pivotal phase 1/2 study of axicabtagene ciloleucel (Axi-Cel) in refractory large B cell lymphoma	American Journal of Hematology	2019	94(Supplement 2):S19-S20.	E8 - Linked publication	Superseded by 2020 publication
Neill, L.	Steroid use, advanced stage disease and >=3 lines of prior chemotherapy are associated with a higher risk of infection following CD19 CAR T-cell therapy for B-	Blood	2020	136(SUPPL 1):20-21.	E3 - Not relevant intervention	General CAR-T

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	NHL: Real world data from a large UK center					
Novo, M.	Copanlisib in combination with rituximabbendamustine in patients with relapsed-refractory diffuse large b-cell lymphoma: A multicentric phase ii trial of the fondazione italiana linfomi (fil-copa-rb)	HemaSphere	2021	5(SUPPL 2):692.	E3 - Not relevant intervention	Copanlisib
Nowakowski, G. S.	ABCL-346: Overall Survival with Tafasitamab + Lenalidomide (LEN) vs Routinely Administered Therapies for ASCT-Ineligible Relapsed or Refractory (R/R) Diffuse Large B-Cell Lymphoma (DLBCL): Outcomes from the Observational RE-MIND2 Study	Clinical Lymphoma, Myeloma and Leukemia	2021	21(Supplement 1):S392-S393.	E5 - Not relevant study design	Propensity match analysis
Oiwa, K.	Utility of the Geriatric 8 for the Prediction of Therapy-Related Toxicity in Older Adults with Diffuse Large B-Cell Lymphoma	Oncologist	2021	26(3):215-223.	E5 - Not relevant study design	First line subjects
Oluwole, O. O.	Comparing Efficacy, Safety, and Preinfusion Period of Axicabtagene Ciloleucel versus Tisagenlecleucel in Relapsed/Refractory Large B Cell Lymphoma: Comparative Study of Axicabtagene Ciloleucel and Tisagenlecleucel	Biology of Blood and Marrow Transplantation	2020	26(9):1581-1588.	E5 - Not relevant study design	MAIC
Oluwole, O. O.	Prophylactic corticosteroid use with axicabtagene ciloleucel in patients with relapsed/refractory large B-Cell lymphoma	British Journal of Haematology	2021	193(SUPPL 1):147-148.	E8 - Linked publication	Superseded by 2021 full pub
Ram, R.	Toxicity and efficacy of chimeric antigen receptor T-cell in patients with diffuse large B cell lymphoma above the age of 70 years compare to younger patients - a matched control multi-center cohort study	Haematologica.	2021	08.	E3 - Not relevant intervention	Data not reported for individual CAR-T
Ramos, C. A.	In Vivo Fate and Activity of Second- versus Third-Generation CD19-Specific CAR-T Cells in B Cell Non-Hodgkin's Lymphomas	Molecular Therapy: the Journal of the American Society of Gene Therapy	2018	26(12):2727-2737.	E3 - Not relevant intervention	General CAR-T
Ravella, R.	Car T-cell therapy in relapsed/refractory diffuse large B-cell lymphoma (R/R DLBCL):	Blood	2020	136(SUPPL 1):22-23.	E3 - Not relevant intervention	Role of bridging therapy

Author	Title	Journal	Year	Citation	Full publication review	Reason for exclusion
	A 'real-world' analysis of patterns of failure and role of bridging therapy					
Rejeski, K.	CAR-HEMATOTOX: A model for CAR T-cell related hematological toxicity in relapsed/refractory large B-cell lymphoma	Blood.	2021	24.	E3 - Not relevant intervention	Limited data reported for individual CAR-Ts (only data for incidence of anaemia, neutropenia, and severe thrombocytopenia)
Rejeski, K.	Identification of predictive markers of severe and prolonged neutropenia after CD19-specific CAR T-cell treatment in patients with relapsed/refractory B-cell malignancies	Blood	2020	136(SUPPL 1):41-42.	E3 - Not relevant intervention	General CAR-T
Riedell, P. A.	A Multicenter Retrospective Analysis of Outcomes and Toxicities with Commercial Axicabtagene Ciloleucel and Tisagenlecleucel for Relapsed/Refractory Aggressive B-Cell Lymphomas	Biology of Blood and Marrow Transplantation	2020	26(3 Supplement):S41-S42.	E12 - outcome	Limited safety data reported
Riedell, P. A.	A Multicenter Retrospective Analysis of Clinical Outcomes, Toxicities, and Patterns of Use in Institutions Utilizing Commercial Axicabtagene Ciloleucel and Tisagenlecleucel for Relapsed/Refractory Aggressive B-Cell Lymphomas	Blood	2019	134(Supplement 1):1599.	E8 - Linked publication	Superseded by full publication
Rodgers, T.	ABCL-135: RE-MIND: A Comparison of Tafasitamab (MOR208) + Lenalidomide (L-MIND) Versus Lenalidomide Monotherapy (Real-World Data) in Transplant-Ineligible Patients with Relapsed/Refractory Diffuse Large B-Cell Lymphoma	Clinical Lymphoma, Myeloma and Leukemia	2020	20(Supplement 1):S265-S266.	E8 - Linked publication	Superseded by Zinzani full pub
Ruff, A.	18F-Fluorodeoxyglucose Positron Emission Tomography/Computed Tomography Following Chimeric Antigen Receptor T-cell Therapy in Large B-cell Lymphoma	Molecular Imaging and Biology	2021	23(6):818-826.	E3 - Not relevant intervention	Data not reported for individual CAR-T
Saini, N.	Gut bacterial diversity associates with efficacy of anti-CD19 CAR T-cell therapy in patients with large B-cell lymphoma	Blood	2020	136(SUPPL 1):34-35.	E3 - Not relevant intervention	General CAR-T

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Salles, G.	Indirect Treatment Comparison of Liso-Cel vs. Salvage Chemotherapy in Diffuse Large B-Cell Lymphoma: TRANSCEND vs. SCHOLAR-1	Advances in Therapy	2021	38(6):3266-3280.	E5 - Not relevant study design	MAIC
Salles, G.	Estimation of long-term survival with tafasitamab + lenalidomide in relapsed/refractory diffuse large B-cell lymphoma	Blood	2020	136(SUPPL 1):9-10.	E8 - Linked publication	Superseded by 2021 full pub
Salles, G.	Estimation of long-term survival with tafasitamab + lenalidomide (LEN) in relapsed/ refractory diffuse large B-cell lymphoma (R/R DLBCL)	Hematological Oncology	2021	39(SUPPL 2):254-256.	E8 - Linked publication	Superseded by 2021 full pub
Sang, W.	Phase II trial of co-administration of CD19- and CD20-targeted chimeric antigen receptor T cells for relapsed and refractory diffuse large B cell lymphoma	Cancer Medicine	2020	9(16):5827-5838.	E3 - Not relevant intervention	Coadministration of anti-CD19 and anti-CD20 CAR-T
Schaefer, A.	Cytopenias After CD19 Chimeric Antigen Receptor T-Cells (CAR-T) Therapy for Diffuse Large B-Cell Lymphomas or Transformed Follicular Lymphoma: A Single Institution Experience	Cancer Management and Research	2021	13:8901-8906.	E3 - Not relevant intervention	Data not reported for individual CAR-T
Schmitz, N.	The phase 3, randomized study of axicabtagene ciloleucel (Axi-Cel) versus standard-of-care therapy in patients with relapsed/refractory diffuse large B cell lymphoma: ZUMA-7	British Journal of Haematology	2019	185(Supplement 1):90-91.	E9 - Protocol	
Schubert, M. L.	CAR T cell therapy directed against CD19 in patients with B-cell lymphoma after an allogeneic hematopoietic stem cell transplantation (alloHCT) is feasible and safe	Bone Marrow Transplantation	2020	55:246-247.	E3 - Not relevant intervention	General CAR-T
Schuster, S. J.	ABCL-166: Tisagenlecleucel and Lisocabtagene Maraleucel: Comparative Efficacy in Patients with Relapsed/Refractory Diffuse Large B-Cell Lymphoma	Clinical Lymphoma, Myeloma and Leukemia	2021	21(Supplement 1):S380-S381.	E11 - review	
Schuster, M. W.	Effect of age on the efficacy and safety of single agent oral selinexor in patients with	Blood	2020	136(SUPPL 1):5-6.	E3 - Not relevant intervention	Selinexor

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	relapsed/refractory diffuse large B-cell lymphoma (DLBCL): A post-hoc analysis of the sadal pivotal study					
Schuster, M. W.	Selinexor efficacy and safety are independent of renal function in patients with relapsed/refractory diffuse large B-cell lymphoma (DLBCL): A post-hoc analysis from the pivotal phase 2b sadal study	Blood	2020	136(SUPPL 1):34-35.	E3 - Not relevant intervention	Selinexor
Schuster, M.	Lymphocyte count effect on efficacy and safety of single agent oral selinexor in patients with relapsed/refractory diffuse large B-cell lymphoma (DLBCL): A Post-hoc analysis from phase 2b sadal study	HemaSphere	2021	5(SUPPL 2):230.	E3 - Not relevant intervention	selinexor
Schuster, S. J.	Comparative efficacy of tisagenlecleucel (tisa-cel) and lisocabtagene maraleucel (liso-cel) in patients with relapsed/refractory diffuse large B-cell lymphoma (r/r DLBCL)	Journal of Clinical Oncology. Conference: Annual Meeting of the American Society of Clinical Oncology, ASCO	2021	39(15 SUPPL).	E11 - review	
Sermer, D.	Outcomes in patients with DLBCL treated with commercial CAR T cells compared with alternate therapies	Blood Advances	2020	4(19):4669-4678.	E3 - Not relevant intervention	Data not reported for individual CAR-T
Sesques, P.	Real-world results of anti-CD19 CAR T cells use for patients with relapsed/refractory large B-cell lymphoma in lyon sud hospital	HemaSphere	2020	4(Supplement 1):565-566.	E3 - Not relevant intervention	General CAR-T
Shadman, M.	Immunotherapy using a 3rd generation cd20 targeted car t-cell (mb-106) for treatment of b-cell non-hodgkin lymphoma (b-nhl) and chronic lymphocytic leukemia (cll)	HemaSphere	2021	5(SUPPL 2):335.	E3 - Not relevant intervention	General CAR-T
Shah, J.	Health-related quality of life and utility outcomes with selinexor in relapsed/refractory diffuse large B-cell lymphoma	Future Oncology	2021	17(11):1295-1310.	E3 - Not relevant intervention	Selinexor
Shah, N. N.	Bispecific anti-CD20, anti-CD19 CAR T cells for relapsed B cell malignancies: a phase 1 dose escalation and expansion trial	Nature Medicine	2020	26(10):1569-1575.	E3 - Not relevant intervention	Not relevant CAR-T construct (tandem, bispecific CD-19, CD-20 construct)

Author	Title	Journal	Year	Citation	Full publication review	Reason for exclusion
Shouval, R.	Impact of TP53 Genomic Alterations in Large B-Cell Lymphoma Treated With CD19-Chimeric Antigen Receptor T-Cell Therapy	Journal of Clinical Oncology	2021		E3 - Not relevant intervention	General CAR-T
Smedby, K. E.	Evaluation of eligibility for CAR-T cell therapy in a population-based cohort of 3550 patients with incident diffuse large B-cell lymphoma (DLBCL) in Sweden	Blood	2020	136(SUPPL 1):38-39.	E3 - Not relevant intervention	Data not reported for individual CAR-T
Smith, K.	Experiences of providing commercial Chimeric Antigen Receptor (CAR-T) cell therapy at the Northern Centre for Cancer Care	British Journal of Haematology	2020	189(Supplement 1):226.	E3 - Not relevant intervention	General CAR-T
Solh, M.	ABCL-362: Incidence, Onset, and Management of Myelosuppression in Patients Treated with loncastuximab Tesirine for R/R DLBCL in a Pooled Safety Analysis	Clinical Lymphoma, Myeloma and Leukemia	2021	21(Supplement 1):S394-S395.	E3 - Not relevant intervention	Loncastuximab
Spira, A.	Health-Related Quality of Life, Symptoms, and Tolerability of Loncastuximab Tesirine in Patients With Relapsed or Refractory Diffuse Large B-Cell Lymphoma	Clinical Lymphoma, Myeloma and Leukemia.	2021		E3 - Not relevant intervention	Loncastuximab
Steiner, R.	Cardiovascular events among adult patients with aggressive B-cell lymphoma treated with standard of care axicabtagene ciloleucel and tisagenlecleucel	Hematological Oncology	2021	39(SUPPL 2):356-358.	E3 - Not relevant intervention	General CAR-T
Steiner, R. E.	Cardiovascular events in patients treated with chimeric antigen receptor t-cell therapy for aggressive B-cell lymphoma	Haematologica	2021	11:11.	E3 - Not relevant intervention	Data not reported for individual CAR-T
Stephens, D. M.	Selinexor Combined with Ibrutinib Demonstrates Tolerability and Efficacy in Advanced B-Cell Malignancies: A Phase I Study	Blood	2019	134(Supplement 1):4310.	E8 - Linked publication	Superseded by full publication
Thakkar, A.	Dynamics of leukocyte subpopulations reconstitution predict infection propensity in a multiethnic real world cohort treated with anti-CD19 CAR-T cell therapy (axicabtagene-ciloleucel)	Blood	2020	136(SUPPL 1):10-11.	E3 - Not relevant intervention	General CAR-T

Author	Title	Journal	Year	Citation	Full publication review	Reason for exclusion
Thieblemont, C.	Real-world results on CD19 car tcell for 60 french patients with relapsed/refractory diffuse large B-cell lymphoma included in a temporary authorization for use program	Hematological Oncology	2019	37(Supplement 2):301.	E3 - Not relevant intervention	Data not reported for individual CAR-T
Thiel, G.	Assessment of Time to Insurance Approval and Distance Traveled in Patients Treated with CAR T-Cell Therapy for Relapsed or Refractory Diffuse Large B-Cell Lymphoma	Biology of Blood and Marrow Transplantation	2020	26(3 Supplement):S272.	E3 - Not relevant intervention	General CAR-T
Tholouli, E.	Phase I Alexander study of AUTO3, the first CD19/22 dual targeting CAR.T cell, with pembrolizumab in patients with relapsed/refractory (r/r) DLBCL	Annals of Oncology	2020	31(Supplement 4):S651.	E3 - Not relevant intervention	General CAR-T
Thuresson, P. O.	A Systematic Review of the Clinical Efficacy of Treatments in Relapsed or Refractory Diffuse Large B Cell Lymphoma	Advances in Therapy	2020	37(12):4877-4893.	E11 - review	
Tong, C.	Optimized tandem CD19/CD20 CAR-engineered T cells in refractory/relapsed B-cell lymphoma	Blood	2020	136(14):1632-1644.	E3 - Not relevant intervention	Not relevant CAR-T construct
Topp, M. S.	Earlier Steroid Use with Axicabtagene Ciloleucel (Axi-Cel) in Patients (Pts) with Relapsed/Refractory Large B Cell Lymphoma (R/R LBCL)	Molecular Therapy	2020	28(4 Supplement 1):577-577.	E8 - Linked publication	Superseded by 2021 full pub
Topp, M. S.	Earlier steroid use with axicabtagene ciloleucel (axi-cel) in patients with relapsed/refractory large B cell lymphoma	Current Oncology	2020	27(6):E669.	E8 - Linked publication	Superseded by 2021 full pub
Tytorenko, I.	Analysis of the use of different chemotherapy regimens in the treatment of patients with relapse and refractory DLBCL in real practice (Ukrainian Retrospective Study)	HemaSphere	2020	4(Supplement 1):1007-1008.	E3 - Not relevant intervention	
Valade, S.	CAR-T cell therapy in ICU patients: A single-center experience	Annals of Intensive Care. Conference: French Intensive Care Society International Congress	2020	10(Supplement 1).	E3 - Not relevant intervention	General CAR-T

Author	Title	Journal	Year	Citation	Full publication review	Reason for exclusion
Vercellino, L.	Predictive factors of early progression after CAR T-cell therapy in relapsed/refractory diffuse large B-cell lymphoma	Blood Advances	2020	4(22):5607-5615.	E3 - Not relevant intervention	Limited data reported for individual CAR-Ts (only data for incidence of relapse)
Walker, C.	Comprehensive assessment of molecular markers of selinexor response in patients with diffuse large b-cell lymphoma (DLBCL)	HemaSphere	2020	4(Supplement 1):621-622.	E3 - Not relevant intervention	Selinexor
Wang, S.	Outcomes in refractory diffuse large B-cell lymphoma: results from a multicenter real-world study in China	Cancer Communications	2021	41(3):229-239.	E3 - Not relevant intervention	Outcome data not reported by treatment
Wang, J.	Comparison of Survival Between Autologous and Allogeneic Stem Cell Transplantation in Patients with Relapsed or Refractory B-Cell Non-Hodgkin Lymphoma: A Meta-Analysis	Cell Transplantation	2020	29(no pagination).	E11 - review	
Wang, T.	Hematopoietic stem cell transplantation and chimeric antigen receptor T cell for relapsed or refractory diffuse large B-cell lymphoma	Immunotherapy	2020	12(13):997-1006.	E3 - Not relevant intervention	Not relevant CAR-T construct
Wang, X.	Phase 1 studies of central memory-derived CD19 CAR T-cell therapy following autologous HSCT in patients with B-cell NHL	Blood	2016	127(24):2980-90.	E3 - Not relevant intervention	Not relevant CAR-T construct
Wang, Y.	Effective response and delayed toxicities of refractory advanced diffuse large B-cell lymphoma treated by CD20-directed chimeric antigen receptor-modified T cells	Clinical Immunology	2014	155(2):160-175.	E3 - Not relevant intervention	Not relevant CAR-T construct (CD-20 construct)
Wei, G.	CD19/CD22 dual-targeted car t-cell therapy for relapsed/refractory aggressive b-cell lymphoma: A safety and efficacy study	Cancer Immunology Research	2021	9(9):1061-1070.	E3 - Not relevant intervention	Not relevant CAR-T construct (CD-19/CD-22 dual targeting)
Wei, J.	Anti CD19/22 cocktail CAR T-cell therapy can improve the outcomes of patients with TP53-mutated relapsed/refractory B-cell lymphoma	Blood	2020	136(SUPPL 1):43.	E3 - Not relevant intervention	General CAR-T
Westin, J. R.	Efficacy and safety of CD19-directed CAR-T cell therapies in patients with relapsed/refractory aggressive B-cell lymphomas: Observations from the JULIET, ZUMA-1, and TRANSCEND trials	American Journal of Hematology	2021	96(10):1295-1312.	E11 - review	

Author	Title	Journal	Year	Citation	Full publication review	Reason for exclusion
Wright, C. M.	Bridging Radiation Therapy Before Commercial Chimeric Antigen Receptor T-Cell Therapy for Relapsed or Refractory Aggressive B-Cell Lymphoma	International Journal of Radiation Oncology Biology Physics	2020	108(1):178-188.	E3 - Not relevant intervention	Limited data reported for individual CAR-Ts (only data for cytokine release syndrome/neurotoxicity grade and incidence of unplanned hospitalisations)
Wu, J. Q.	[Cohort study of efficacy and safety of polatuzumab vedotin combined with immunochemotherapy in patients with relapse/refractory diffuse large B cell lymphoma]	Chung-Hua i Hsueh Tsa Chih [Chinese Medical Journal]	2021	101(25):1985-1990.	E5 - Not relevant study design	Non-English
Wudhikarn, K.	Infectious Complications in Aggressive B Cell Non-Hodgkin Lymphoma after CD-19 Chimeric Antigen Receptor T Cell Therapy	Biology of Blood and Marrow Transplantation	2020	26(3 Supplement):S326.	E3 - Not relevant intervention	General CAR-T
Wudhikarn, K.	Burden and Impact of Toxicities on Outcomes for Aggressive B Cell Non-Hodgkin Lymphoma Patients after CD19-Directed Chimeric Antigen Receptor T Cell: Real-World Experience	Biology of Blood and Marrow Transplantation	2020	26(3 Supplement):S263-S264.	E3 - Not relevant intervention	General CAR-T
Yan, Z. X.	Clinical Efficacy and Tumor Microenvironment Influence in a Dose-Escalation Study of Anti-CD19 Chimeric Antigen Receptor T Cells in Refractory B-Cell Non-Hodgkin's Lymphoma	Clinical Cancer Research	2019	25(23):6995-7003.	E3 - Not relevant intervention	Not relevant CAR-T construct (JWCAR029 [relma-cel])
Yassine, F.	Real world experience of approved chimeric antigen receptor T-cell therapies outside of clinical trials	Current Research in Translational Medicine	2020	68(4):159-170.	E11 - review	Review of RWE
Ye, S.	Early clinical results of a novel anti-CD20 chimeric antigen receptor (CAR)-T cell therapy for B-cell NHL patients who are relapsed/resistant following CD19 CAR-T therapy	Blood	2020	136(SUPPL 1):8-9.	E3 - Not relevant intervention	General CAR-T
Ying, Z.	Relmacabtagene autoleucel (relma-cel) CD19 CAR-T therapy for adults with heavily pretreated relapsed/refractory large B-cell lymphoma in China	Cancer Medicine	2021	10(3):999-1011.	E3 - Not relevant intervention	Data for relmacabtagene autoleucel (relma-cel)

Author	Title	Journal	Year	Citation	Full publication review	Reason for exclusion
Ying, Z.	Clinical Response in Relapsed/Refractory (R/R) B-NHL Treated with the CD19-Directed CAR T-Cell Product JWCAR029	Blood	2019	134(Supplement 1):2876.	E8 - Linked publication	Linked to Yan 2020
Yuen, C.	Clinical predictors of chimeric antigen receptor T-cell therapy neurotoxicity: A single-center study	Immunotherapy	2021	13(15):1261-1269.	E3 - Not relevant intervention	Data not reported for individual CAR-T
Yuen, C.	Neurotoxicity as surrogate marker for Car Tcell therapy treatment response	Neurology. Conference: 72nd Annual Meeting of the American Academy of Neurology, AAN	2020	94(15 Supplement).	E3 - Not relevant intervention	General CAR-T
Zettler, M. E.	Real-world adverse events associated with CAR T-cell therapy among adults age>=65years	Journal of Geriatric Oncology	2021	12(2):239-242.	E3 - Not relevant intervention	Limited data reported for individual CAR-Ts (AEs by age group for each treatment)
Zhang, J.	A Review of Two Regulatory Approved Anti-CD19 CAR T-Cell Therapies in Diffuse Large B-Cell Lymphoma: Why Are Indirect Treatment Comparisons Not Feasible?	Advances in Therapy	2020	37(7):3040-3058.	E11 - review	
Zhang, R.	Improved safety and efficacy of a multi-target chimeric antigen receptor modified T cell therapy (4SCAR2.0) against relapsed or refractory lymphomas	Blood	2020	136(SUPPL 1):47.	E3 - Not relevant intervention	General CAR-T
Zhang, Y.	A Prospective Investigation of Bispecific CD19/22 CAR T Cell Therapy in Patients With Relapsed or Refractory B Cell Non-Hodgkin Lymphoma	Frontiers in Oncology	2021	11 (no pagination)(664421).	E3 - Not relevant intervention	Data for a bispecific CD19/22 CAR-T
Zhang, Y.	Long-term activity of tandem CD19/CD20 CAR therapy in refractory/relapsed B-cell lymphoma: a single-arm, phase 1-2 trial	Leukemia.	2021		E3 - Not relevant intervention	Not relevant CAR-T construct (tandem CD19/CD20 construct)
Zheng, P.	Bendamustine is a favorable lymphodepleting chemotherapy regimen prior to car t cells immunotherapy as fludarabine	HemaSphere	2021	5(SUPPL 2):686.	E3 - Not relevant intervention	General CAR-T
Zhou, L.	Developing a novel anti-CD19/CD20 Bi-specific chimeric antigen receptor T (CAR-	Blood	2020	136(SUPPL 1):8.	E3 - Not relevant intervention	General CAR-T

Author	Title	Journal	Year	Citation	Full publication review	Reason for exclusion
	T) cell therapy for relapsed/refractory (R/R) B-cell NHL					
Zhou, X.	Phase I Trial of Fourth-Generation Anti-CD19 Chimeric Antigen Receptor T Cells Against Relapsed or Refractory B Cell Non-Hodgkin Lymphomas	Frontiers in Immunology	2020	11 (no pagination)(564099).	E3 - Not relevant intervention	Fourth generation CAR-T
Zhu, J.	Clinical response of CD19 CAR-T cells (relmacabtagene autoleucel, relma-cel) in adults with heavily-pre-treated relapsed/refractory(R/R) large B-cell lymphoma in China	Blood	2020	136(SUPPL 1):39-40.	E3 - Not relevant intervention	General CAR-T
Zhu, J.	Radiotherapy in Combination with Chimeric Antigen Receptor T Cell Therapy Is a Safe and Promising Approach in Relapsed/Refractory Diffuse Large B Cell Lymphoma Patients with High Tumor Burden	International Journal of Radiation Oncology Biology Physics	2019	105(1 Supplement):S67.	E3 - Not relevant intervention	General CAR-T plus radiotherapy
Zijlstra, J. M.	Efficacy and safety of single agent oral selinexor in patients with primary refractory diffuse large B-cell lymphoma (DLBCL): A post-hoc analysis of the SADAL study	HemaSphere	2020	4(Supplement 1):574.	E3 - Not relevant intervention	Selinexor
Zinzani, P. L.	Lotis 2 follow-up analysis: Updated results from a phase 2 study of loncastuximab tesirine in relapsed or refractory diffuse large B-cell lymphoma	Hematological Oncology	2021	39(SUPPL 2):252-254.	E3 - Not relevant intervention	Loncastuximab
SLR update (n=50)						
Alderuccio, J. P.	Clinical characteristics and responses of patients with relapsed or refractory high-grade B-cell lymphoma treated with loncastuximab tesirine in the LOTIS-2 clinical trial	Blood	2021	138(SUPPL 1):3575.	E3 - Not relevant intervention	Not relevant intervention (loncastruximab)
Baltadakis, I.	Chimeric antigen receptor t cells for refractory/relapsed diffuse large b cell lymphoma and acute lymphoblastic leukemia: The hellenic real-world experience in adult patients	Blood	2021	138(SUPPL 1):4840.	E3 - Not relevant intervention	Data not reported for individual CAR-Ts

Author	Title	Journal	Year	Citation	Full publication review	Reason for exclusion
Bannerji, R.	Odronextamab, a human CD20xCD3 bispecific antibody in patients with CD20-positive B-cell malignancies (ELM-1): results from the relapsed or refractory non-Hodgkin lymphoma cohort in a single-arm, multicentre, phase 1 trial	The Lancet. Haematology.	2022	31.	E3 - Not relevant intervention	Not relevant intervention (odronextamab)
Bliven, S. P.	Patterns of Utilization and Outcomes of Autologous Stem Cell Transplantation and Chimeric Antigen Receptor T-Cell Therapy in Relapsed or Refractory Diffuse Large B-cell Lymphomas with MYC and BCL2 and/or BCL6 Rearrangements	Clinical lymphoma, myeloma & leukemia	2022	29:29.	E3 - Not relevant intervention	Data not reported for individual CAR-T therapies
Caimi, P. F.	The AntiCD19 Antibody Drug Immunoconjugate Loncastuximab Achieves Responses in DLBCL Relapsing After AntiCD19 CAR-T Cell Therapy	Clinical Lymphoma, Myeloma and Leukemia.	2022	Introduction: Chimeric antigen receptor T (CAR-T) cells targeting CD19 result in durable responses in approximately 40% of DLBCL patients. Loncastuximab tesirine, an antibody drug conjugate targeting CD19 with a pyrrolobenzodiazepine payload, has activity against DLBCL. Patients and Methods: We evaluated the outcomes of 13 DLBCL patients relapsed after CAR-T cells treated with loncastuximab in the LOTIS-2 trial. Result(s): Six patients (46%) had responses to loncastuximab (CR, n = 2). Median OS, PFS and duration of response	E3 - Not relevant intervention	Not relevant intervention (loncastruximab) [LOTIS-2]

Author	Title	Journal	Year	Citation	Full publication review	Reason for exclusion
				after loncastuximab were 8.2, 1.4 and 8 months, respectively. Conclusion(s): Loncastuximab can achieve responses in patients progressing after CAR-T cells. Sequencing CD19-targeting therapies is possible in cases without CD19 loss.Copyright © 2021 Elsevier Inc.		
Cao, Y.	CD19/CD22 Chimeric Antigen Receptor T Cell Cocktail Therapy following Autologous Transplantation in Patients with Relapsed/Refractory Aggressive B Cell Lymphomas: Y. Cao et al	Transplantation and Cellular Therapy	2021	27(11):910.e1-910.e11.	E3 - Not relevant intervention	Not relevant CAR-T
Carlo-Stella, C.	Planned interim analysis of a phase 2 study of loncastuximab tesirine plus ibrutinib in patients with advanced diffuse large b-cell lymphoma (Lotis-3)	Blood	2021	138(SUPPL 1):54.	E3 - Not relevant intervention	Not relevant intervention (loncastruximab) [LOTIS-3]
Cartron G	Matching-adjusted indirect treatment comparison of chimeric antigen receptor T-cell therapies for third-line or later treatment of relapsed or refractory large B-cell lymphoma: lisocabtagene maraleucel versus tisagenlecleucel.	Exp Hematol Oncol.	2022	11(1):17.	E11 - review	MAIC
Cencini, E.	Pixantrone in patients with relapsed/refractory diffuse large B-cell lymphoma: A real-life, retrospective, multicenter trial on behalf of the RTL (Regional TUSCAN Lymphoma Network)-Authors' reply to Morris and colleagues	European Journal of Haematology	2022	18:18	E11 - review	Review of current treatments
Chaganti, S.	Primary Analysis of ZUMA-7: A Phase 3 Randomized Trial of Axicabtagene Ciloleucel (Axi-Cel) Versus Standard-of-Care (SOC) Therapy in Patients (Pts) With	British Journal of Haematology	2022	197(SUPPL 1):20-22.	E4 - Not relevant line of therapy	Second-line study: ZUMA-7

Author	Title	Journal	Year	Citation	Full publication review	Reason for exclusion
	Relapsed/Refractory (R/R) Large B-Cell Lymphoma (LBCL)					
Chen, A. J.	Value of Reducing Wait Times for Chimeric Antigen Receptor T-Cell Treatment: Evidence From Randomized Controlled Trial Data on Tisagenlecleucel for Diffuse Large B-Cell Lymphoma	Value in Health	2022	25(8):1344-1351.	E12 - outcome	Study reported on the survival benefits of expediting treatment access to tisa
ClinicalTrials.gov	Pembrolizumab plus chemotherapy for diffuse large B-cell lymphoma that has come back or does not respond to treatment	2022		E5 - Not relevant study design	Trial registry record	
ClinicalTrials.gov	Phase 2 Study of Plamotamab Combined With Tafasitamab Plus Lenalidomide Versus Tafasitamab Plus Lenalidomide in R/R DLBCL	2022		E5 - Not relevant study design	Trial registry record	
ClinicalTrials.gov	Study of Mivavotinib (CB-659) in Relapsed/Refractory Diffuse Large B-Cell Lymphoma (DLBCL)	2022		E5 - Not relevant study design	Trial registry record	
Cordoba R	Tafasitamab Plus Lenalidomide Versus 3 Rituximab-Based Treatments for Non-Transplant Eligible Relapsed/Refractory Diffuse Large B-Cell Lymphoma: A Matching-Adjusted Indirect Comparison.	Adv Ther.	2022	39(6):2668-2687.	E11 - review	MAIC
Cortes-Bullich, A.	Outcomes of CD19 Chimeric Antigen Receptor T Cell Therapy in Patients with Gastrointestinal Tract Involvement of Large B Cell Lymphoma	Transplantation and Cellular Therapy	2021	27(9):768.e1-768.e6.	E3 - Not relevant intervention	Data not reported for individual CAR-Ts
Cwynarski, K.	Patient-Reported Outcomes in ZUMA -7, a Phase 3, Randomised, Open-Label Study Evaluating the Efficacy of Axicabtagene Ciloleucel (Axi-Cel) Versus Standard-of-Care Therapy in Relapsed/ Refractory Large B-Cell Lymphoma	British Journal of Haematology	2022	197(SUPPL 1):154-156.	E4 - Not relevant line of therapy	Second-line study: ZUMA-7
Dickinson, M.	Glofitamab monotherapy provides durable responses after fixed-length dosing in relapsed/refractory (R/R) non-Hodgkin lymphoma (NHL) patients (pts)	Blood	2021	138(SUPPL 1):2478.	E5 - Not relevant study design	Proportion of patienst in relevant indication

Author	Title	Journal	Year	Citation	Full publication review	Reason for exclusion
Galtier, J.	PET-imaging assessment for guiding strategy in patients with relapsed/refractory large B-cell lymphoma receiving CAR T-cells	Haematologica.	2022	09.	E3 - Not relevant intervention	Results not reported separately for axi and tisa
Greil, R.	Pola-R-ICE: open-label, prospective phase III clinical study to compare polatuzumab vedotin + rituximab, ifosfamide, carboplatin + etoposide(Pola-R-ICE) with rituximab, ifosfamide, carboplatin + etoposide(R-ICE) alone as salvage-therapy in patients with primary refractory or relapsed diffuse large B-cell-lymphoma (DLBCL)	Memo magazine of european medical oncology	2022	15:2022-04.	E5 - Not relevant study design	Trial registry record
Guarino, M.	CAR T-cell therapy in BOlogNa - NEUrotoxicity TReatment and Assessment in Lymphoma: the CARBONNEUTRAL study	European Journal of Neurology	2022	29(Supplement 1):165.	E3 - Not relevant intervention	Data not reported for individual CAR-Ts
Hamadani, M.	Characteristics and Clinical Outcomes of Patients With Relapsed/Refractory Diffuse Large B-cell Lymphoma Who Received At Least 3 Lines of Therapies	Clinical Lymphoma, Myeloma and Leukemia.	2021		E3 - Not relevant intervention	Data not reported for individual CAR-Ts
Hamadani, M.	Matching-adjusted Indirect Comparison of the Efficacy of Loncastuximab Tesirine Versus Treatment in the Chemoimmunotherapy Era for Relapsed/Refractory Diffuse Large B-cell Lymphoma	Clinical Lymphoma, Myeloma and Leukemia.	2022	Background: Loncastuximab tesirine (Lonca) and chemoimmunotherapy (CIT) have been assessed in patients with relapsed/refractory diffuse large B-cell lymphoma (R/R DLBCL), but direct evidence from head-to-head randomized clinical trials is not available. Material(s) and Method(s): Matching-adjusted indirect comparison (MAIC) was used to evaluate the	E11 - review	MAIC

Author	Title	Journal	Year	Citation	Full publication review	Reason for exclusion
				efficacy of Lonca versus CIT-era treatment in R/R DLBCL. The analysis used individual patient data from the phase II LOTIS-2 trial of Lonca (NCT03589469) and pooled aggregated data from 2 extension studies of the CORAL trial for CIT. The LOTIS-2 trial included 145 patients who had relapsed or progressed following 2 or more multi-agent systemic treatment regimens; the CORAL extension studies included 203 patients who received 2 prior lines of therapy and 75 patients who relapsed after autologous hematopoietic cell transplantation. MAIC analyses were performed to adjust for cross-trial differences in inclusion/exclusion criteria and the distribution of observed baseline characteristics. Overall response rate (ORR) and overall survival (OS) were compared between the balanced trial populations.		

Author	Title	Journal	Year	Citation	Full publication review	Reason for exclusion
				 Result(s): A total of 80 patients in LOTIS-2 were included in the analysis. After matching to the characteristics of 278 patients from the pooled CORAL extension studies, the ORR was significantly higher for Lonca compared with CIT-era treatment (53.4% vs. 40.3%, P < .05). Lonca was also associated with a significantly improved OS compared with CIT-era treatment (median OS 10.8 vs. 6.4 months; adjusted hazard ratio: 0.67 [95% CI: 0.48, 0.92], P < .05). Conclusion(s): This study indicates that Lonca was associated with significantly improved efficacy compared with CIT-era treatments for R/R DLBCL. Copyright © 2022 Elsevier Inc.		
Hamadani, M.	Long-term survival projections of loncastuximab tesirine-treated patients in relapsed or refractory (R/R) diffuse large B-cell lymphoma (DLBCL)	Journal of Clinical Oncology. Conference: Annual Meeting of the American Society of Clinical Oncology, ASCO	2022	40(16 Supplement 1).	E3 - Not relevant intervention	Not relevant intervention (loncastruximab) [LOTIS-2]

Author	Title	Journal	Year	Citation	Full publication review	Reason for exclusion
Harrysson, S.	Outcomes of relapsed/refractory diffuse large B-cell lymphoma and influence of chimaeric antigen receptor T trial eligibility criteria in second line-A population-based study of 736 patients	British Journal of Haematology	2022	198(2):267-277.	E3 - Not relevant intervention	Data not reported for intervention of interest
Ho, J.	A phase 1 study of the safety, pharmacokinetics and pharmacodynamics of escalating doses followed by dose expansion of the selective inhibitor of nuclear export (SINE) selinexor in Asian patients with advanced or metastatic malignancies	Therapeutic Advances in Medical Oncology	2022	14(no pagination).	E3 - Not relevant intervention	Not relevant intervention (selinexor) and only 11% of patients had lymphoma
Jager, U.	DSHNHL-NIVEAU: improvement of outcome in elderly-patients or patients not eligible for high-dose-chemotherapy with aggressive-Non-Hodgkin-Lymphoma in frst-relapse or progression by adding nivolumab to gemcitabine, oxaliplatin + rituximab by CD20+-disease	Memo magazine of european medical oncology	2022	15:2022-04.	E5 - Not relevant study design	Trial registry record
Kedmi, M.	Point-of-care anti-CD19 CAR T-cells for treatment of relapsed and refractory aggressive B-cell lymphoma	Transplantation and Cellular Therapy	2022	23:23.	E3 - Not relevant intervention	Not relevant CAR-T
Korell, F.	Easix predicts severe cytokine release syndrome (CRS) and immune effector cell-associated neuro-toxicity syndrome (ICANS) in patients receiving CD19-directed chimeric antigen receptor T (CAR-T) cell therapy	Blood	2021	138(SUPPL 1):3861.	E3 - Not relevant intervention	Data not reported for individual CAR-Ts
Maerevoet, M.	Selinexor in combination with R-GDP for patients with relapsed/refractory B-cell lymphoma: Results of the SELINDA phase Ib lysa study	Blood	2021	138(SUPPL 1):1411.	E3 - Not relevant intervention	Not relevant intervention (selinexor)
Maziarz, R. T.	Indirect comparison of tisagenlecleucel and historical treatments for relapsed/refractory diffuse large B-cell lymphoma	Blood Advances	2022	Vol.6(8):2536-2547p.	E11 - review	MAIC
Nath, K.	Vitamin D Insufficiency and Clinical Outcomes with Chimeric Antigen Receptor	Transplantation and Cellular Therapy	2022	06:06.	E3 - Not relevant intervention	Data not reported for individual CAR-Ts

Author	Title	Journal	Year	Citation	Full publication review	Reason for exclusion
	T-Cell Therapy in Large B-cell Lymphoma: Vitamin D insufficiency and CAR-T in LBCL					
Nuvvula, S.	The Novel Therapeutic Landscape for Relapsed/Refractory Diffuse Large B Cell Lymphoma	Clinical lymphoma, myeloma & leukemia	2021	20:20.	E11 - review	Review of theraeutic landscape
Ram, R.	Toxicity and efficacy of chimeric antigen receptor T-cell therapy in patients with diffuse large B-cell lymphoma above the age of 70 years compared to younger patients - a matched control multicenter cohort study	Haematologica	2022	107(5):1111-1118.	E3 - Not relevant intervention	Data not reported separately for individual CAR-Ts
Rejeski, K.	Clinical phenotypes of CAR-T-cell related hematotoxicity in relapsed/refractory large B-cell lymphoma	Oncology Research and Treatment	2021	44(SUPPL 2):45-46.	E3 - Not relevant intervention	Data not reported separately for individual CAR-Ts
Sancho, J. M.	Axicabtagene ciloleucel compared to tisagenlecleucel for the treatment of relapsed or refractory large B-cell lymphoma in the real world setting in Spain	Blood	2021	138(SUPPL 1):1742.	E8 - Linked publication	Superseded by Kwon 2022
Sang, W.	Anti-PD-1 Therapy Enhances the Efficacy of CD30-Directed Chimeric Antigen Receptor T Cell Therapy in Patients With Relapsed/Refractory CD30+ Lymphoma	Frontiers in Immunology	2022	13:858021.	E2 - Not relevant disease	Majority of patients had HL
Schuster SJ	Comparative efficacy of tisagenlecleucel and lisocabtagene maraleucel among adults with relapsed/refractory large B-cell lymphomas: an indirect treatment comparison.	Leuk Lymphoma.	2022	63(4):845-854	E11 - review	MAIC
Sehgal, A.	Lisocabtagene maraleucel as second-line therapy in adults with relapsed or refractory large B-cell lymphoma who were not intended for haematopoietic stem cell transplantation (PILOT): an open-label, phase 2 study	The Lancet. Oncology.	2022	12.	E4 - Not relevant line of therapy	Second-line pts only
Sigmund, A. M.	Outcomes of large B-cell lymphoma patients by post CAR-T salvage regimen at a single institution	Blood	2021	138(SUPPL 1):3851.	E3 - Not relevant intervention	Data not reported separately for individual CAR-Ts

Author	Title	Journal	Year	Citation	Full publication review	Reason for exclusion
Silverman, E. A.	Five-year experience using bridging radiotherapy prior to chimeric antigen receptor (CAR) T-cell therapies for B-cell malignancies at Memorial Sloan Kettering Cancer Center	Blood	2021	138(SUPPL 1):2507.	E3 - Not relevant intervention	Data not reported separately for individual CAR-Ts
Stephens, D. M.	Selinexor combined with ibrutinib demonstrates tolerability and safety in advanced B-cell malignancies: A phase I study	Clinical cancer research : an official journal of the American Association for Cancer Research.	2022	24.	E3 - Not relevant intervention	Not relevant intervention (selinexor)
Thakkar, A.	Dynamics of Leukocyte Subpopulations Reconstitution Predict Infection Propensity in a Multiethnic Real World Cohort Treated with Anti-CD19 CAR-T Cell Therapy (Axicabtagene-Ciloleucel)	Transplantation and Cellular Therapy	2021	27(3 Supplement):S422-S423.	E8 - Linked publication	Related to Thakkar 2021 full publication
Ursu, R.	Long-Term Neurological Safety in B-Cell Lymphoma Patients Treated With Anti-CD19 CAR T-Cell Therapy	Neurology.	2022	18.	E3 - Not relevant intervention	Data not reported for individual CAR-T therapies
Weinstein, B.	Efficacy and Safety of Innovative Experimental Chimeric Antigen Receptor (CAR) T-cells versus Axicabtagene ciloleucel (Yescarta) for the Treatment of Relapsed/Refractory Large B-Cell Lymphoma (LBCL): Matching Adjusted Indirect Comparisons (MAICs) and Systematic Review	Innovations in Pharmacy	2021	12(4).	E11 - review	MAIC
Weinstock, M.	Complete responses to odronextamab in two patients with diffuse large B-cell lymphoma refractory to chimeric antigen receptor T-cell therapy	British Journal of Haematology.	2022		E3 - Not relevant intervention	Not relevant intervention (odronextamab)
Xie, J.	Characteristics and treatment patterns of relapsed/refractory diffuse large B-cell lymphoma in patients receiving >=3 therapy lines in post-CAR-T era	Current Medical Research and Opinion	2021	37(10):1789-1798.	E12 - outcome	Relevant outcome data not reported for treatment of interest
Yuen, C.	Dysgraphia as the earliest presenting symptom of severe chimeric antigen	Neuro-Oncology	2021	23(SUPPL 6):vi149.	E2 - Not relevant disease	Patients with secondary CNS lymphoma

Author	Title	Journal	Year	Citation	Full publication review	Reason for exclusion
	receptor (CAR) T-cell therapy neurotoxicity: A single center experience					
Zhu, M.	Translational findings for odronextamab: From preclinical research to a first-in-human study in patients with CD20+ B-cell malignancies	Clinical and Translational Science	2022	15(4):954-966.	E3 - Not relevant intervention	Not relevant intervention (odronextamab); no relevant in vivo outcome data reported
Zijlstra, J. M.	The Association between Patient Characteristics and the Efficacy and Safety of Selinexor in Diffuse Large B-Cell Lymphoma in the SADAL Study	Cancers	2022	14(3) (no pagination)(791).	E3 - Not relevant intervention	Not relevant intervention (selinexor)

A2. Priority question: A systematic review of "CR rate based on a meta-analysis of 19 studies of R/R DLBCL." (CS Section B.2.4.1, Page 43) is mentioned but no detail provided. Please supply full details of this review, including search strategies, a PRISMA flow diagram, tables of included and excluded trials, data extraction, and the meta-analysis.

An initial SLR was performed on 4th September 2018, aiming at identifying studies evaluating the efficacy of licensed or investigational pharmaceutical treatment available for adult patients ≥ 18 years with transplant ineligible R/R DLBCL who received second or third-line (or beyond) therapy.

This initial SLR was performed according to Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Guidelines on 4th September 2018, covering Embase, MEDLINE, and the Cochrane Library. These electronic databases were used to identify relevant publications using a pre-defined search string.

The eligibility criteria used to determine relevance for inclusion of publications in the SLR were in the form of the patient, intervention, comparison, outcome (PICO) model, and are detailed in Table 10.

Table 10: Eligibility criteria used in the initial screening to identify studies relating to any pharmacological treatment for patients with R/R DLBCL

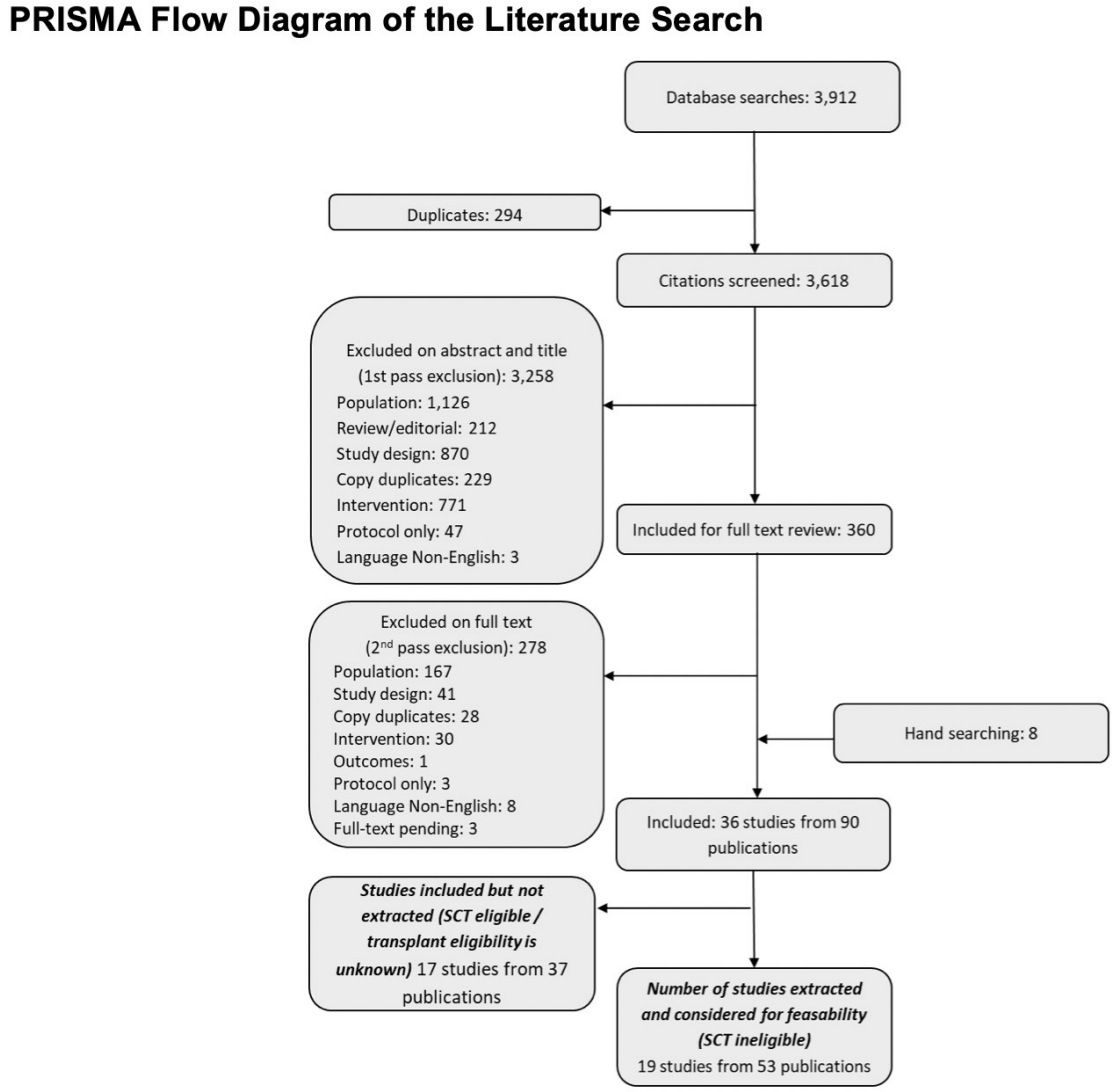
Criteria	Inclusion criteria	Exclusion criteria
Population	Adult patients (≥18years) with R/R DLBCL who are receiving second or third-line (or beyond) therapy Subgroups of interest includes: SCT ineligible Failed transplant patients Duration of response to prior therapy: ≤12 months vs. >12 months Disease burden: high vs. low Age (≤60 vs. >60) Stage of Disease (I–II vs. III–IV) Prior systemic therapy Refractory vs. relapse Extranodal-site involvement (0–1 vs. 2–4) Eastern Cooperative Oncology Group (ECOG) Score	Animal/in vitro studies
Intervention	Polatuzumab vedotin in combination with bendamustine plus rituximab	-
Comparators	Licensed or investigational pharmaceutical treatment available for R/R DLBCL patients: Bendamustine+/–rituximab Brentuximab vedotin CEPP (Cyclophosphamide, Etoposide, Procarbazine) +/– rituximab	First-line treatments Non-pharmacological therapies

	CEOP (Cyclophosphamide, Etoposide, Vincristine) +/– rituximab DA-EPOCH (Cyclophosphamide, Doxorubicin, Etoposide, Vincristine) +/– rituximab GDP (Cisplatin, Dexamethasone, Gemcitabine) +/– rituximab Carboplatin, Dexamethasone, Gemcitabine +/– rituximab Gemox (Gemcitabine, Oxaliplatin) +/– rituximab Gemcitabine + vinorelbine +/– rituximab Lenalidomide +/– rituximab Rituximab Ibrutinib Pixantrone CAR-T (Axicabtagene ciloleucel or Tisagenlecleucel) MOR208 Venetoclax Apatinib DHAP (dexamethasone, cytarabine, cisplatin) +/– rituximab ICE (ifosfamide, etoposide, carboplatin) +/– rituximab MINE (mesna, ifosfamide, mitoxantrone, etoposide) +/– rituximab ESHAP (etoposide, methylprednisolone, cytarabine, cisplatin) +/– rituximab IME (ifosfamide, mitoxantrone, etoposide) +/– rituximab IVE (ifosfamide, epirubicin and etoposide) +/– rituximab CEPP R+/–PECC (Rituximab-Prednisone, Etoposide, Chlorambucil, Lomustine) BSC/placebo Note: any study which evaluates only one arm of interest were taken forward into the initial phase of the ITC feasibility assessment as it may serve as a bridging study to connect two comparators which are relevant to the decision problem.	
Outcomes	Efficacy: OS PFS TTP EFS Duration of response Response rates (CR, PR, SD) Any response rates reported as PET-CR (i.e. metabolic CR) or using older criteria (e.g. CRu), or a mixture of various different criteria [(4), Lugano	Outcome(s) not listed

	(5), modified Lugano (6)] ORR DCR Duration of treatment and duration of treatment beyond progression Safety All-grade treatment related AE Treatment related Grade 3 or 4 AEs Treatment related SAEs Tolerability: dose reductions and interruptions, discontinuation (any reason), discontinuation (due to AEs) HRQoL and PRO measures (e.g. EORTC QLQ-C30)	
Study design/setting	RCTs, any duration (irrespective of blinding) Prospective single arm studies Comparative observation studies	Reviews/editorials, case reports/case series Retrospective single arm studies
Language of publication	English language publications	Non-English language publications without an English abstract.
Date of publication	No restriction	-
Countries	No restriction	-

This initial systematic literature review identified 19 unique studies reporting efficacy data for 1552 patients exposed to 27 regimens (Figure 4).

Figure 4: PRISMA Flow Diagram of the initial literature search



This initial systematic literature review was updated to reflect clinical trial data published up to 2019 (NP30179 SAP version 1) and further refined to restrict the efficacy patient population to studies with majority of 3L+ R/R DLBCL patients, defined as "median prior lines of therapy ≥2, or number of patients who have two or more prior therapies ≥ 50%". This SLR has been considered for the determination of the historical control CR mentioned in the the NP30179 SAP version 1.

Consequently, 13 clinical trials evaluated 19 regimens were identified (Table 11).

Table 11: Summary of clinical trial data in patients with R/R DLBCL/tFL included in the SLR

Study reference	Regimen	Efficacy (n)
Sehn 2019	BR	40
	Pola-BR	40

	Pola-BG	27
Schuster 2019	Tisangelecleucel	93
Zinzani 2011	R-Lenalidomide	23
Neelapu 2017	Axicabtagene ciloleucel	101
Dang 2017	Investigator Choice (R-G)	35
	Investigator Choice (BR)	137
Wiernik 2008	Lenalidomide	49
Schuster 2017	CTL019	14
El Gnaoui 2007	R-GemOx	46
Czuczman 2017	Lenalidomide	51
	IC (R, Gem, Ox, Etop)	51
Pettengell 2012	Pixantrone	70
	IC (Vin, Ox, Ifos, Etop, Mitoxantrone, Gem)	70
Lakshmaiah 2015	Lenalidomide	15
Crump 2017	Refractory to 2nd line or greater	318
	Refractory to auto SCT	140
Viardot 2016	Blinatumomab	25

Source: Statistical Analysis Plan NP30179, version 1.

A3. Priority question: The EAG requests more information on the systematic review used to identify trials of comparator treatments (Appendix D, ITC report). Please supply the search strategies, a PRISMA flow diagram and a table of included and excluded trials. Also, please supply, the SLR and MAIC feasibility assessment report "MtA_3L_DLBCL_SR and FA report_261022_clean" mentioned on Page 23 of the ITC report.

A matching-adjusted indirect comparison (MAIC) feasibility assessment was to assess the clinical evidence available for the treatment of patients with R/R 3L+ DLBCL to allow a comparison of glofitamab with comparators of interest.

A3.1 Methodology – MAIC

The only feasible approach to generate indirect comparisons with an evidence base that is comprised primarily of single-arm studies is to conduct either naïve indirect comparisons or population adjusted ITCs such as 'unanchored' MAICs.

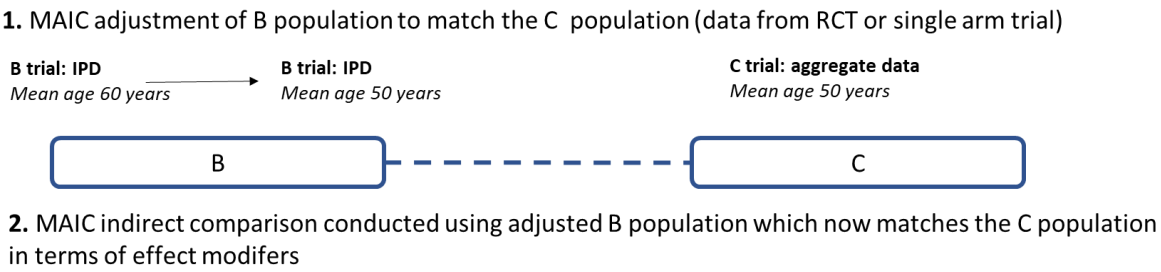
Briefly, a naïve comparison is a comparison of study arms from different trials as if they were from the same RCT. Naïve indirect comparisons are generally avoided due to the susceptibility of bias; the effect of a treatment may be over- or underestimated due to bias.

MAIC is a recently developed population adjustment method that uses individual patient-level data (IPD) from a subset of trials to form population-adjusted indirect comparisons between treatments in a specific target population (7). MAIC essentially adjusts for between-trial differences in baseline characteristics. MAIC requires IPD for at least one of the trials to form predictors of the summary outcomes that would be observed in patients

receiving the treatment if the population were the same as that in the comparator trial population of interest. There must also be sufficient patient numbers in the trial with IPD to confirm the summary outcomes. The predicted outcomes that may be used were as follows:

- To generate estimates of relative treatment effect (when based on RCT data) in 'anchored' indirect comparisons (referred to as 'anchored MAIC'), which is not applicable here as only single-arm study data are available for glofitamab at this time
- To generate estimates of relative treatment effect (when based on single-arm data) in 'unanchored' indirect comparisons (referred to as 'unanchored MAIC') as shown in Figure 5.

Figure 5: Overview of MAIC unanchored indirect comparisons



Abbreviations: IPD, individual patient-level data; MAIC, matching adjusted indirect comparison; RCT, randomised controlled trial.

Unanchored MAICs assume that absolute treatment effects are constant regardless of the level of effect modifiers and prognostic variables (and all of these are required to be known; referred to as conditional constancy of absolute effects). These effect modifiers and prognostic factors must be reported in each study included in the MAIC to enable population adjustment in the trial with IPD. Glofitamab results are available from a single-arm study, so it is not possible to use a common comparator for indirect treatment comparisons. Therefore, any analyses will use unanchored methods.

A comparison between glofitamab and each comparator treatment requires re-weighting the glofitamab patients (i.e. each patient is assigned a weight estimated from a statistical model) to reflect their over- or under-representation relative to the comparator study population. Post-weighting, average baseline characteristics should match those from the comparator study under investigation. MAIC weights are estimated based on a propensity scoring model, based on the odds of being enrolled in the glofitamab or the comparator study. This uses the methods of moments approach. The weights from the matching process are then used to estimate weighted treatment-effects by comparing outcomes in balanced treatment arms.

An assessment of the weights should be considered alongside the MAIC analysis results; investigating the distribution of weights can help to determine whether certain patients are particularly influential in the analysis. The effective sample size (ESS), which is a measure of the sample size post-matching, should also be considered. The ESS may be compared

with the original sample size as a measure of robustness; a small ESS is an indication that the weights are highly variable due to a lack of population overlap, and that the treatment-effect estimate may be unstable. The ESS was calculated utilising the weights from the matching process and was estimated as follows:

$$ESS = \frac{(\sum_{i=1}^{n} weight_i)^2}{\sum_{i=1}^{n} weight_i^2},$$

Where $weight_i$ is the weight assigned to patient i.

A3.1.1 Prognostic factors and effect modifiers in DLBCL

An unanchored MAIC should adjust for known prognostic variables and effect modifiers. Based on discussion with the Roche internal and external medical advisors, a list of potential prognostic factors and effect modifiers for relapsed/refractory (R/R) DLBCL to be considered in the MAIC was generated. These prognostic factors were further validated by the results of an SLR that was conducted to assess the prognostic factors of patients with R/R DLBCL. Those in the list of prognostic factors were classified as either high priority, medium or low priority.

High priority[a]

- International Prognostic Index (IPI) (0–2 vs 3–5)/AA-IPI (0–1 vs 2–3) and/or any of its components:
  - Age (mean, or median if mean not reported, or % ≥60 years, if neither reported)
  - ECOG PS (0–1 vs ≥2) [0 vs 1 not that important prognostically]
  - Ann Arbor Stage (I–II versus III–IV)
  - High lactate dehydrogenase (LDH) levels
  - Presence of extranodal disease (yes/no or number of lesions reported)
- Refractoriness (definition may vary across studies) to first line of treatment
- Refractoriness (definition may vary across studies) to last line of treatment
- Refractoriness (definition may vary across studies) to any line of treatment
  - Some advisors ranked this as lower priority compared to the previous two and as somewhat lower priority compared with early R/R status to individual agents
- Histological subtype (e.g. HGBCL, PMBCL, or DLBCL/tFL)
- Double/triple hit lymphoma[b] (to be prioritised over histological subtype, if both reported)
  - This has a similar importance to histological subtype, as double/triple hit lymphoma typically corresponds to having HGBCL (their definitions can vary across studies, though), so controlling for both may not always be needed and only one may be prioritised

[a] Note that CNS involvement was also flagged as an important prognostic factor, though it is not possible to control for it due to it being an exclusion criteria in NP30179.

[b] Tumours with double-/triple-hit rearrangements, which do not correspond to double-/triple-expressor tumours, whose actual prognostic value is unclear.

- Early relapse after stem cell transplant (SCT) (e.g. defined as duration of response [DOR] or time since completion of transplant to next treatment line <12 months)
  - Not many patients had this condition in NP30179 D3 cohort; if controlling for this was not feasible as resulting in low ESS, consider controlling for prior autologous SCT (ASCT) instead, as a proxy
- Number of prior treatment lines (e.g. 3 vs >3 [no clinically established threshold], or median)

Medium priority

- Bulky disease (definition can vary across studies [no clinically established threshold])[c]
- Chemotherapy refractoriness
- Prior treatment with (or refractoriness to) rituximab and an anthracycline therapy
- This has likely a slightly lower (or similar) importance to chemotherapy refractoriness, so when both are reported there is likely no need to control for both and chemotherapy refractoriness can be prioritized, otherwise they can be used as proxies for one another Rituximab refractoriness
- Early relapse from last line of treatment (e.g. defined as DOR or time since last completion of therapy treatment <12 months), or, alternatively, time since completion of last therapy)

Low priority

- Primary diagnosis (DLBCL versus non-DLBCL/indolent lymphoma)
- Cell type of origin of the disease (by immunohistochemistry [IHC] or gene expression profiling [GEP]; when both reported, GEP to be prioritised)
  - If values like GCB, non-GCB and ABC are reported, then non-GCB and ABC can be pooled; this somewhat applies also to the “unclassified” category, though it is not clear
  - If ABC is reported as a category, then the method of assessment is by definition GEP
  - This variable can have a lot of missing values, particularly for GEP results. In those cases, prioritise the variable definition featuring <50% missing
- Bone marrow involvement
- Primary bone marrow transplant
  - Occurs very rarely and is also very rarely reported, plus only one patient with this in the NP30179 trial, so most likely it cannot be controlled for
- Prior SCT

[c] Bulky disease is generally constructed from the size of largest lymph node lesion (longest dimension) involved; as none of the thresholds typically used to define bulky disease have been established as being superior prognostically over the others (based on medical feedback), then adjusting for bulky disease in the MAICs should be de-prioritised in favour of size of largest lymph node lesion when information on both is available.

A3.1.2 Selection of studies for inclusion into the full MAIC feasibility assessment

The comparators of interest for the feasibility assessment included:

- Axicabtagene ciloleucel
- Bendamustine plus rituximab (BR)
- Lenalidomide
- Lisocabtagene maraleucel
- Pixantrone
- Polatuzumab vedotin
- R-DHAP
- R-GemOx/GemOx
- Tafasitamab + lenalidomide
- Tisagenlecleucel

In instances where IPD was available for a comparator of interest, indirect treatment comparisons will be conducted using propensity score analysis methods as recommended by NICE DSU TSD 17; thus no additional studies reporting on the same comparator (where IPD was available) were considered further in the MAIC feasibility assessment except for the comparator of bendamustine plus rituximab (as the size of this cohort enrolled in GO29365 only included a small number of patients, many of which were 2L, and it was anticipated that the filtering process to align the eligibility criteria across trials would potentially result in an insufficient sample size to inform any reliable propensity score analyses).

The feasibility of conducting MAICs was assessed in a robust, stepwise process for all remaining comparator studies with no IPD available. Studies reporting results for 3L+ R/R DLBCL were of primary interest for inclusion in the MAIC feasibility assessment. However, as evidence for some comparator treatments was scarce, this criterion had to be relaxed so as to include certain relevant treatments, such as those that were relevant comparators due to being broadly reimbursed or prescribed in the 3L+ R/R DLBCL setting.

A preliminary top-line extraction of all studies included in the SLR and relevant for the MAIC feasibility assessment (i.e. investigating a comparator of interest with no IPD available for the studies) was conducted to obtain details pertaining to study design, sample size, study population (in terms of histology, prior therapy, prior rituximab exposure), and the reporting of key outcomes of interest). Selected studies were then reviewed to identify those most appropriate for inclusion in the full MAIC feasibility assessment and were selected using the following hierarchical criteria based on internal medical and clinical science feedback:

1) DLBCL histologies: those aligned with the glofitamab trial [NCT03075696][d] to be ≥80%

[d] https://www.clinicaltrials.gov/ct2/show/NCT03075696: The four pivotal histologies included DLBCL not otherwise specified (NOS) (trFL), PMBCL and HGBCL.

2) Line of therapy: median of 2 prior therapies or at least 50% of patients at third line plus
3) Prior rituximab exposure: cut off of 80% (applicable to studies initiated prior to 2010, or where it is reasonable to assume that patients might have not received rituximab)

Note that the thresholds of the above criteria were selected so as to exclude studies which would inevitably introduce an unacceptable bias in the comparison, as per medical and clinical science feedback.

In instances where >1 candidate study was still eligible for a given comparator:

1) Prospective studies were to be prioritised over retrospective studies (with a view to revisiting if it was not feasible to use a prospective study following full feasibility assessment for example due to too few baseline characteristics for adjustment)
2) Studies enrolling more than 40 patients were to be prioritised over smaller studies

A3.1.3 Full data extraction and MAIC feasibility assessment

Full data extraction was conducted for all studies selected for inclusion into the full MAIC feasibility assessment. The selected studies for each comparator were then assessed for inclusion in a MAIC, with a focus on (i) the trial key eligibility criteria and availability of baseline characteristics (to confirm sufficient overlap to permit a MAIC and potential variables that could be used in an analysis) and (ii) the availability and alignment of outcomes reported between the comparator studies and NCT03075696 (data permitting). The outcomes included in the feasibility assessment were OS, PFS, overall response rate (ORR), complete response (CR), DOCR, DOR, and treatment discontinuation due to adverse events (AEs). Note that some studies may report AEs leading to treatment discontinuation and/instead of treatment discontinuation due to AEs; in instances where both were available discontinuation due to AEs was prioritised.

A3.2 Results – MAIC

The current MAIC feasibility assessment restricted to the following comparators of interest for glofitamab:

- Axicabtagene ciloleucel
- Bendamustine plus rituximab
- Lenalidomide
- Lisocabtagene maraleucel
- Pixantrone
- R-DHAP
- R-GemOx/GemOx
- Tafasitamab + lenalidomide
- Tisagenlecleucel

Although bendamustine plus rituximab (± polatuzumab vedotin) are comparators of interest for the current SLR and subsequent indirect treatment comparison, Roche have

access to data from the Phase 2 GO29365 RCT (NCT02257567)[e] for these comparators (polatuzumab + BR versus BR alone); therefore, the indirect treatment comparisons will be conducted using propensity score analysis methods as recommended by NICE DSU TSD 17. Owing to the availability of IPD from this trial, and thus the possibility of filtering patients to make them more comparable to the 3L+ DLBCL patients enrolled in NP30179, polatuzumab vedotin (+BR) is not considered further in the MAIC feasibility assessment and the similarity in baseline characteristics and outcomes available will be described directly in the indirect treatment comparison report. A point similar to that one for polatuzumab vedotin around the availability of IPD can also be made for BR, using the cohort of 40 patients on BR enrolled in in the randomized part of GO20365. However, as the size of this cohort only included a small number of patients, many of which were 2L, it was anticipated that the filtering process to align the eligibility criteria across trials would potentially result in an insufficient sample size to inform any reliable propensity score analyses. Therefore, BR was also included as a treatment of interest for the MAIC FA, to identify the most suitable candidate study to perform a MAIC should a propensity score analysis turn out not to be feasible.

A3.2.1 Summary of study selection for full MAIC feasibility assessment

A visual summary of the selection of studies from the SLR for top-line extraction and selection for inclusion into the full MAIC feasibility assessment is provided in Figure 6. A list of all publications included in the SLR (n=320), details of the interventions investigated and the inclusion or exclusion of each publication in the top-line extraction for the feasibility assessment (complete with full rationale for exclusions) is provided in Table 8 and Table 9, respectively.

In summary, 115/232 studies (123/320 publications) in the SLR were excluded from further consideration for the following reasons:

- IPD available (n=34) [36 publications]
- Non-relevant combination therapy (n=61) [67 publications]
- Line of therapy (n=3) [3 publications]
- Insufficient data (n=13) [13 publications]
- Outcome (n=1) [1 publication]
- Non-English language publication (n=3) [3 publications]

A top-line extraction of the 117/232 (197/320 publications) studies in the SLR (reporting on 117 unique studies with 129 unique study arms of interest) was conducted. Full details of the selection of candidate studies for each comparator of interest by applying the selection criteria is presented in the following sections. In total, 113 study arms (reported across 101 unique studies) [reported across 117 publications] were excluded from the full feasibility assessment for the following reasons:

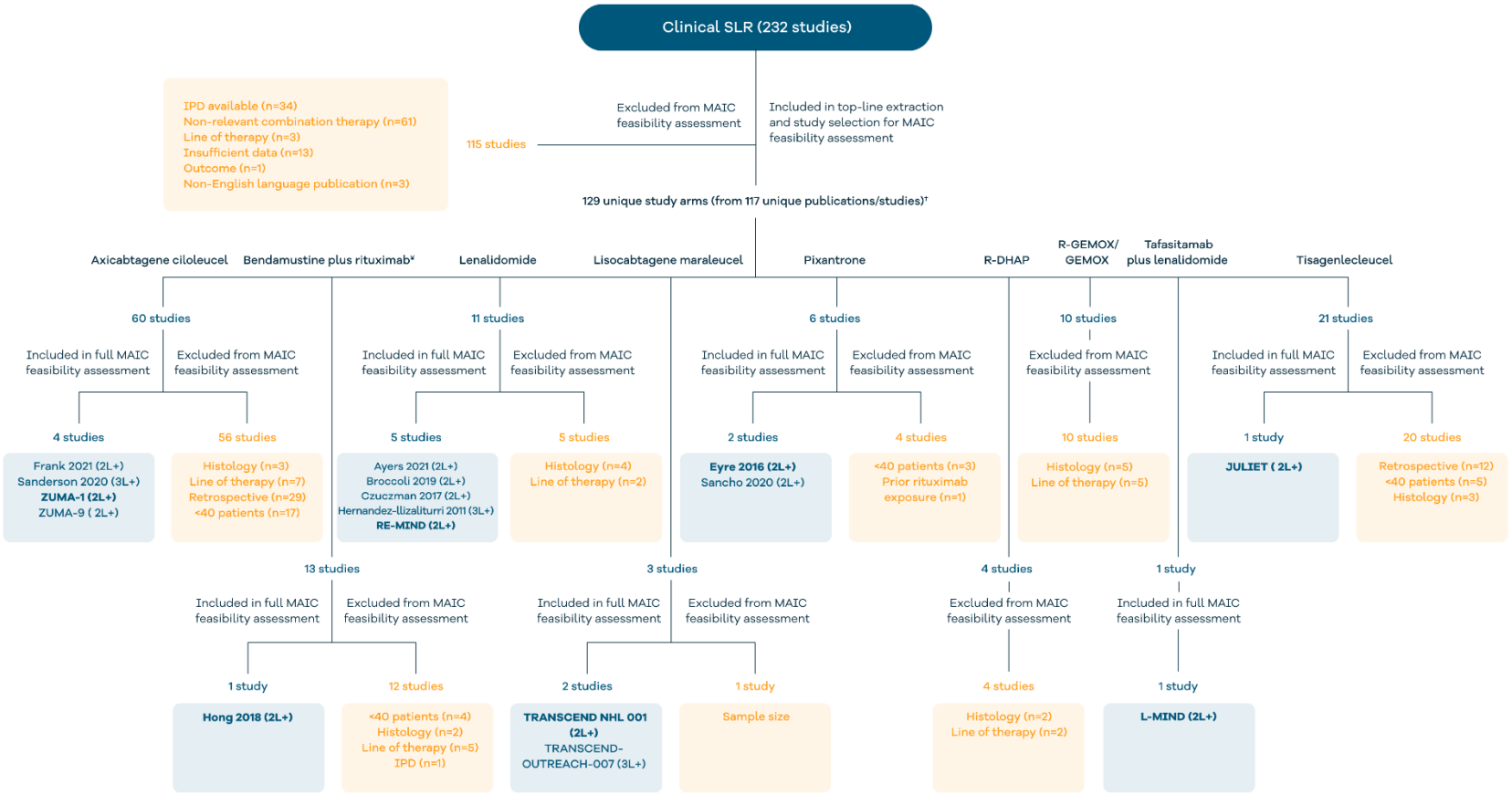
- Histology, n=19

[e] https://clinicaltrials.gov/ct2/show/NCT02257567

- Line of therapy, n=21
- Retrospective study, n=41
- Sample size <40 patients, n=30
- Prior rituximab exposure, n=1
- IPD available, n=1

A total of 16 studies (reported across 80 publications) were identified for inclusion in the full feasibility assessment.

Figure 6: Flow diagram for the selection of studies from the SLR into the full MAIC feasibility assessment



Abbreviations: DLBCL, diffuse large B-cell lymphoma; MAIC, matching-adjusted indirect comparison; SLR, systematic literature review.
† A total of 12 studies in the top-line extraction included two treatment arms of interest.
¥ Whilst IPD are available for NCT02257567 (BR) the MAIC feasibility for BR was still conducted due to issues with the sample. Studies in bold ultimately selected for inclusion into MAIC analyses on completion of the full feasibility assessment.

A3.2.1.1 Axicabtagene ciloleucel

A total of 60 studies included in the SLR investigated axicabtagene ciloleucel. Three studies were excluded based on histology, seven studies were excluded based on the line of therapy, 30 studies were excluded as they were retrospective, and 17 studies were excluded as they included <40 patients. Four remaining prospective studies were selected for inclusion into the full MAIC feasibility assessment (8-11).

A3.2.1.2 Bendamustine + rituximab

Note that IPD is available for NCT02257567 using the cohort of 40 patients on BR enrolled in the randomized part of GO29365. However, as the size of this cohort only included a small number of patients, many of which were 2L, it was anticipated that the filtering process to align the eligibility criteria across trials would potentially result in an insufficient sample size to inform any reliable propensity score analyses. Therefore, BR was also included as a treatment of interest for the MAIC FA, so as to identify the most suitable candidate study to perform a MAIC should a propensity score analysis turn out not to be feasible. A total of 13 studies included in the SLR investigated bendamustine plus rituximab. Two studies were excluded based on histology, five studies were excluded based on the line of therapy (two of which are also briefly reviewed in the full feasibility assessment; RE-MIND2 and Vacirca 2014), and four studies were excluded as they included <40 patients. The single study for which IPD was available was also excluded (12).

A single remaining retrospective study were selected for inclusion into the full MAIC feasibility assessment (13).

A3.2.1.3 Lenalidomide

A total of 11 studies included in the SLR investigated lenalidomide. Four studies were excluded based on histology and two studies were excluded based on the line of therapy. Five remaining studies were selected for inclusion into the full MAIC feasibility assessment (14-18).

A3.2.1.4 Lisocabtagene maraleucel

Three studies included in the SLR investigated lisocabtagene maraleucel. A single study was excluded form feasibility assessment as it included <40 patients. The two remaining studies were deemed relevant for inclusion into the full MAIC feasibility assessment (TRANSCEND NHL 001 and TRANSCEND-OUTREACH-007) (19, 20).

A3.2.1.5 Pixantrone

A total of six studies included in the SLR investigated pixantrone. Three studies were excluded as they included <40 patients, and a single study was excluded due to low rituximab exposure. Two remaining studies were selected for inclusion into the full MAIC feasibility assessment (8-11, 21, 22).

A3.2.1.6 R-DHAP

A total of four studies included in the SLR investigated R-DHAP. These were not included in the full MAIC feasibility assessment based on histology (n=2) and line of therapy (n=2).

A3.2.1.7 R-GemOx/GemOx

A total of 10 studies included in the SLR investigated R-GemOx (or R-GemOx and GemOx). These were not included in the full MAIC feasibility assessment based on histology (n=5) or line of therapy (n=5).

A3.2.1.8 Tafasitamab plus lenalidomide

A single study (L-MIND) was included in the SLR that investigated tafasitamab + lenalidomide and was deemed relevant for inclusion into the full MAIC feasibility assessment (23).

A3.2.1.9 Tisagenlecleucel

A total of 21 studies included in the SLR investigated tisagenlecleucel. Twelve studies were excluded as they were retrospective, three studies were excluded based on histology and five studies were excluded as they included <40 patients. The remaining study (JULIET) was selected for inclusion into the full MAIC feasibility assessment (11).

A3.2.2 Full MAIC feasibility assessment

A total of 16 studies were included in the full feasibility assessment:

- Axicabtagene ciloleucel, n=4
- bendamustine plus rituximab, n=1
- Lenalidomide, n=5
- Lisocabtagene maraleucel, n=2
- Pixantrone, n=2
- R-DHAP/R-GemOx/GemOx, n=0
- Tafasitamab + lenalidomide, n=1
- Tisagenlecleucel, n=1

A summary of the trial designs, populations, baseline characteristic and outcomes reported for each of the comparator studies considered in the full feasibility assessment is provided in Table 12. A comparison of the glofitamab study (NP30179) to each comparator study regarding the similarity of key inclusion/exclusion criteria, baseline patient characteristics for each of the prognostic factors specified in Section A3.1.1, the availability of outcomes reported, and the comparability of their definitions is provided in the following sections. Recommendations regarding the suitability of each of the studies for MAIC analyses are also provided.

Table 12: Summary of MAIC feasibility assessment (16 total studies, those recommended for use in MAIC analyses for each comparator indicated in green)

Comparator	Trial (perspective) & key inclusion criteria	Population (histology and line of therapy)	N	Baseline characteristics reported and source of data (unique additional characteristics indicated consecutively)	Outcomes available (KM curves and response criteria indicated if available; ✓/ ✕ to indicate if response criteria aligned with NP30179) [Data source]						
					CR	DOCR	ORR	DOR	PFS	OS	Disc due to AEs
Axicabtagene ciloleucel	Frank 2021 (prospective) •Age ≥18 years •Measurable •Enrolled prior to receiving lymphodepleting chemotherapy for standard of care axicel •PET-avid disease	DLBCL, tFL, PMBCL Median 3 (range 1–7) therapies	72	Frank 2021 (8) •Age •Ann Arbor stage •High LDH •Double/tripe hit •No. of prior lines of treatment •Bulky disease •Prior SCT •Histology	NR	NR	NR	NR	KM curve (by initial concentration of circulating tumour DNA) [Frank 2021 (8); median 10.9 months]	KM curve (by initial concentration of circulating tumour DNA) [Frank 2021 (8); median 10.9 months]	NA

Comparator	Trial (perspective) & key inclusion criteria	Population (histology and line of therapy)	N	Baseline characteristics reported and source of data (unique additional characteristics indicated consecutively)	Outcomes available (KM curves and response criteria indicated if available; ✓/ ✕ to indicate if response criteria aligned with NP30179) [Data source]						
					CR	DOCR	ORR	DOR	PFS	OS	Disc due to AEs
Axicabtagene ciloleucel	Sanderson 2020 (prospective) •Age >18 years •At least two prior lines of therapy including anthracyclines	DLBCL, tFL and PMBCL All patients had ≥2 prior therapies	42	Sanderson 2020 (9) •Age •ECOG PS •Histology •Prior SCT •No. of prior lines of treatment	NR	NR	82% and 84% at 1 and 3 months [Sanderson 2020 (9); median 6 months' follow up]	NR	Median 3.8 months [Sanderson 2020 (9); median 6 months' follow up]	NR	NA
Axicabtagene ciloleucel	ZUMA-1 (prospective) •Age ≥18 years •ECOG PS 0–1	DLBCL (DLBCL NOS, HGBCL, PMBCL, and tFL) Median 3 (range 1–	101 (mITT)	Locke 2019 (11) (n=101) •IPI (0-2, 3-4) •Age (median ,≥65 years) •ECOG PS •Ann Arbor stage (I-II/III-IV)	IRC 55 (54%) & INV 59 (58%) Cheson 2007✕	INV KM curve Median not reached	IRC 75 (74%) & INV 84 (83%) Cheson 2007✕	INV & IRC KM curve INV: 11.1 (95% CI: 4.2,	INV KM curve 5.9 (95% CI: 3.3, 15.0)	KM curve 25.8 (95% CI: 12.8, NE)	NA

Comparator	Trial (perspective) & key inclusion criteria	Population (histology and line of therapy)	N	Baseline characteristics reported and source of data (unique additional characteristics indicated consecutively)	Outcomes available (KM curves and response criteria indicated if available; ✓/ ✕ to indicate if response criteria aligned with NP30179) [Data source]						
					CR	DOCR	ORR	DOR	PFS	OS	Disc due to AEs
	•RR disease after 2 systemic lines of therapy (anti-CD20 and anthracycline containing regimen) •Patients had to be chemo refractory defined as either no response to first-line therapy, no response to second	10) therapies		•No. of prior lines of trt •Double hit/triple hit •Histology •Cell of origin •Relapse after prior ASCT •Primary refractory disease •Refractory to second-line or later therapy •Best response as progressive disease to last previous therapy EPAR 2018 (24) (N=101) •Age (mean) •Ann Arbor stage (I, II etc) •IPI (0, 1, 2, etc.) •Histology (HGBCL) •Extranodal disease •Bulky disease	[Locke 2019; median 27.1 months follow up]	[Neelapu 2017; median 15.4 months follow up]	[Locke 2019; median 27.1 months follow up]	NE) & IRC: NE [Locke 2019; median 27.1 months follow up]	[Locke 2019; median 27.1 months follow up]	[Jacobson 2021, median 63.1 months follow up]	

Comparator	Trial (perspective) & key inclusion criteria	Population (histology and line of therapy)	N	Baseline characteristics reported and source of data (unique additional characteristics indicated consecutively)	Outcomes available (KM curves and response criteria indicated if available; ✓/ ✕ to indicate if response criteria aligned with NP30179) [Data source]						
					CR	DOCR	ORR	DOR	PFS	OS	Disc due to AEs
	line + or refractory post - ASCT			•Bone marrow involvement •Prior SCT Maloney 2021 (25) (MAIC) (n=101) •Refractory to last therapy (differs to value reported in Locke 2019 for best response as progressive disease to last therapy) Locke 2022 (26) •High LDH No additional characteristics reported in the long-term OS poster publication - Jacobson 2021 (27)							

Comparator	Trial (perspective) & key inclusion criteria	Population (histology and line of therapy)	N	Baseline characteristics reported and source of data (unique additional characteristics indicated consecutively)	Outcomes available (KM curves and response criteria indicated if available; ✓/ ✕ to indicate if response criteria aligned with NP30179) [Data source]						
					CR	DOCR	ORR	DOR	PFS	OS	Disc due to AEs
Axicabtagene ciloleucel	ZUMA-9 (prospective) •Age ≥18 years •ECOG PS 0–1 •RR disease	DLBCL, PMBCL, HGBCL, tFL >3 lines of therapy- Cohort 1: 64% Cohort 2: 69%	Cohort 1, 25 Cohort 2, 36	Jacobson 2020 (10) •IPI •Age •ECOG PS •Histology •No. of prior lines of treatment	64% and 36% for cohorts 1 and 2 [Jacobson 2020 (10); median 27.1 months (cohort 1) and 13.2 months (cohort 2) months follow up]	NR	76% and 53% for cohorts 1 and 2 [Jacobson 2020 (10); median 27.1 months (cohort 1) and 13.2 months (cohort 2) months follow up]	NR	NR	Median 23.8 (95% CI: 13.5, NE) and NR (3.4, NE) [Jacobson 2020 (10); median 27.1 months (cohort 1) and 13.2 months (cohort 2) months follow up]	NA

Comparator	Trial (perspective) & key inclusion criteria	Population (histology and line of therapy)	N	Baseline characteristics reported and source of data (unique additional characteristics indicated consecutively)	Outcomes available (KM curves and response criteria indicated if available; ✓/ ✕ to indicate if response criteria aligned with NP30179) [Data source]						
					CR	DOCR	ORR	DOR	PFS	OS	Disc due to AEs
Bendamustine plus rituximab	Hong 2018 (retrospective) •Relapsed or refractory DLBCL •Ineligible for intensive chemotherapy with ASCT	DLBCL (de novo or transformed) % prior therapy: 1: 29.3% 2: 31% ≥3: 39.7%		Hong 2018 (13) (n=58): •Age (median: ≥65 years) •ECOG PS •Extranodal disease •High LDH •Ann Arbor stage (I–II/III–IV) •IPI (0–2, 3–4) •Histology •Primary refractory disease •No. of prior lines of treatment •Prior SCT •Cell of origin •Refractory to all lines (relapsed disease)	18 (31%) Cheson 1999/2007✕ [Hong 2018; follow up NR]	NR	32 (55.1%) Cheson 1999/2007✕ [Hong 2018; follow up NR]	NR 3.7 months (95% CI: 1, 47.2) [Hong 2018; follow up NR]	KM curve 3.9 (95% CI: 2.4, 5.4) [Hong 2018; follow up NR]	KM cuve 6.7 (95% CI: 4.7, 8.7) [Hong 2018; follow up NR]	NR
Lenalidomide	Ayers 2020 (retrospective)	DLBCL	83	Ayers 2020 (14) (n=83) •Age (median: >70 years)	NR	NR	NR	NR	NR (Event-free	KM curve (2nd	NR

Comparator	Trial (perspective) & key inclusion criteria	Population (histology and line of therapy)	N	Baseline characteristics reported and source of data (unique additional characteristics indicated consecutively)	Outcomes available (KM curves and response criteria indicated if available; ✓/ ✕ to indicate if response criteria aligned with NP30179) [Data source]						
					CR	DOCR	ORR	DOR	PFS	OS	Disc due to AEs
	•Age 18–90 years RR	% prior therapy: 1: 39.8% 2: 37.3% 3: 22.9%		•ECOG PS (0–1, 2–3) •Ann Arbor stage (I–II, III–IV) •Extranodal disease •IPI (0–2, >2) •High LDH •Cell of origin •No. of prior lines of treatment •Histology (transformed disease) •Prior SCT (in second-line) [reported at diagnosis and not at baseline]					survival reported)	line versus 3/4th line] 15.4 months (95% CI: 9.4, 24.2) - all patients also reported for 2nd line and 3/4th lines] [Ayers 2021; median 22.7 months	

Comparator	Trial (perspective) & key inclusion criteria	Population (histology and line of therapy)	N	Baseline characteristics reported and source of data (unique additional characteristics indicated consecutively)	Outcomes available (KM curves and response criteria indicated if available; ✓/ ✕ to indicate if response criteria aligned with NP30179) [Data source]						
					CR	DOCR	ORR	DOR	PFS	OS	Disc due to AEs
										’ follow up]	
Lenalidomide	Broccoli 2019 (retrospective) RR disease	DLBCL Median 2 (range: 1–6) therapies	153	Broccoli 2019 (15) (n=153) •Age (median) •Ann Arbor stage (I–II, III, IV) •ECOG PS (0–1, 2, 3) •Bulky disease •Refractory to first line of therapy •Refractory to last line of therapy •Prior SCT	INV 36 (23.5%) Cheson 2007✕ [Broccoli 2019; 36 months’ follow up]	NR	INV 45 (29.4%) Cheson 2007✕ [Broccoli 2019; 36 months follow up]	NR	KM curve 6 months [Broccoli 2019; 36 months follow up]	KM curve 12 months [Broccoli 2019; 36 months follow up]	30/153
Lenalidomide	Czuczman 2017 (prospective)	DLBCL % prior therapy: 1: 9.8% 2: 41.2%	51	Czuczman 2017 (16) (all patients [n=51] and for GCB [n=23] and non-GCB patients [n=28])	IRC 5, (9.8%) IWRC 1999 ✕	NR	IRC 14, (27.5%)	No KM 3.9 weeks (95%	KM curve 13.6 weeks (95% CI:	KM curve 31 weeks (95% CI:	NR

Comparator	Trial (perspective) & key inclusion criteria	Population (histology and line of therapy)	N	Baseline characteristics reported and source of data (unique additional characteristics indicated consecutively)	Outcomes available (KM curves and response criteria indicated if available; ✓/ ✕ to indicate if response criteria aligned with NP30179) [Data source]						
					CR	DOCR	ORR	DOR	PFS	OS	Disc due to AEs
	•Age ≥18 years •ECOG PS 0–2 •RR disease to 1 chemotherapy regimen containing rituximab and an anthracycline and at least 1 additional combination chemotherapy regimen	≥3: 49%		•Age (median/≥65 years) •ECOG PS •No. of prior lines of treatment •Cell type of origin •Prior SCT •Double hit-lymphoma Baseline data and results reported for overall population and cell of origin subgroup	[Czuczman 2017; follow-up NR]		IWRC 1999 ✕ [Czuczman 2017; follow-up NR]	CI: 6.4, NE)	0.41, 0.99) [Czuczman 2017; follow-up NR]	0.59, 1.41) [Czuczman 2017; follow-up NR]	

Comparator	Trial (perspective) & key inclusion criteria	Population (histology and line of therapy)	N	Baseline characteristics reported and source of data (unique additional characteristics indicated consecutively)	Outcomes available (KM curves and response criteria indicated if available; ✓/ ✕ to indicate if response criteria aligned with NP30179) [Data source]						
					CR	DOCR	ORR	DOR	PFS	OS	Disc due to AEs
Lenalidomide	Hernandez-Ilizaliturri 2011 (retrospective) •RR disease	DLBCL (de novo, secondary, or associated with FL) Median 4 (range: 2–13)	40	Hernandez-Ilizaliturri 2011 (17) (all patients [n=40] and for GCB [n=23] and non-GCB patients [n=17]) •Age (median /<60 years) •Histology •No. of prior lines of treatment •Ann Arbor stage (I, II etc) •IPI score •Cell type of origin •Rituximab refractoriness	7 (17.5%) Cheson 2007✕ [Hernandez-Ilizaliturri 2011; follow-up until death of last clinic visit]	NR	11 (27.5%) Cheson 2007✕ [Hernandez-Ilizaliturri 2011; follow-up until death of last clinic visit]	NR	KM curve (GCB versus non-GCB) 2.6 months (95% CI: 0.9, 4.2) [all patients] [Hernandez-Ilizaliturri 2011; follow-up until death of last clinic visit]	KM curve (GCB versus non-GCB) 14 months (95% CI: 7.3, 20.6) [GCB] 13.5 months (95% CI : 0, 0.33) [non—GCB] [Hernandez-Ilizaliturri 2011;	NR

Comparator	Trial (perspective) & key inclusion criteria	Population (histology and line of therapy)	N	Baseline characteristics reported and source of data (unique additional characteristics indicated consecutively)	Outcomes available (KM curves and response criteria indicated if available; ✓/ ✕ to indicate if response criteria aligned with NP30179) [Data source]						
					CR	DOCR	ORR	DOR	PFS	OS	Disc due to AEs
										follow-up until death of last clinic visit]	
Lenalidomide	RE-MIND (retrospective) •Age ≥18 years •RR after 1–3 prior systemic therapies •Were not candidates for ASCT •Exclusion of known 'double/triple-hit' DLBCL	DLBCL (including transformed indolent lymphoma with a subsequent relapse	76	Zinzani 2021 (18) (n=76) •Age (median ,<70 years) •Ann Arbor stage •Refractory to last therapy •No. of prior lines of treatment •Primary refractory disease •Prior SCT •High LDH •ECOG PS •Cell of origin (IHC) •Rituximab refractoriness •IPI (0–2, 3–5)	INV 10 (13.2%) Cheson 2007✕ [Zinzani 2021; 32 months]	NR	INV 26 (34.2%) Cheson 2007✕ [Zinzani 2021; 32 months]	INV KM curve 6.6 months (95% CI: 4.1, 17.2) [Zinani; NR 2021]	INV KM curve 4.0 months [Zinzani 2021; median 12.6 months f.up]	KM curve 9.4 months [Zinzani 2021; median 20.9 months f.up]	7 (9.2%)

Comparator	Trial (perspective) & key inclusion criteria	Population (histology and line of therapy)	N	Baseline characteristics reported and source of data (unique additional characteristics indicated consecutively)	Outcomes available (KM curves and response criteria indicated if available; ✓/ ✕ to indicate if response criteria aligned with NP30179) [Data source]						
					CR	DOCR	ORR	DOR	PFS	OS	Disc due to AEs
				•Time since last treatment/ASCT							
Liso-cabtagene maraleucel	TRANSCEND NHL 001 (prospective) •Age ≥18 years •ECOG PS 0–1 •RR disease after 2 systemic lines of therapy (anti-CD20 and anthracycline containing regimen)	DLBCL (de novo or tiNHL), HGBCL, PMBCL or FL grade 3b Median 3 (range: 1–8) therapies	270 safety set 257 efficacy evaluable set	Abramson 2021 (28) (n=270) •Age (median/≥65 years) •ECOG PS •Histology (PMBCL, HGBCL & FL 3b) •Chemo refractory •No. of prior lines of treatment •Prior SCT Abramson 2020 publication (20) (n=269) •High LDH •Histology (HGBCL & PMBCL)	IRC 186 (73%) Lugano 2014✓ [Abramson 2021; 2-year follow up]	IRC KM curve 26.1 months (95% CI: 23.1, NE) [Abramson 2021; 2-year follow up]	IRC 136 (53%) Lugano 2014✓ [Abramson 2021; 2-year follow up]	IRC KM curve 23.1 months (95% CI: 8.6, NE) [Abramson 2021; 2-year follow up]	IRC KM curve 6.8 months (95% CI: 3.3, 12.7) [Abramson 2021; 2-year follow up]	KM curve 27.3 months (95% CI: 16.2, 45.6) [Abramson 2021; 2-year follow up]	NA

Comparator	Trial (perspective) & key inclusion criteria	Population (histology and line of therapy)	N	Baseline characteristics reported and source of data (unique additional characteristics indicated consecutively)	Outcomes available (KM curves and response criteria indicated if available; ✓/ ✕ to indicate if response criteria aligned with NP30179) [Data source]						
					CR	DOCR	ORR	DOR	PFS	OS	Disc due to AEs
	•Patients with secondary CNS involvement were eligible •Patients who received prior allogenic transplant were eligible			Salles 2021 (29)/Moloney 2021 (25) (n=256) •Age (mean) •Ann Arbor stage •Bulky disease •IPI score •Extranodal disease •Prior SCT •Early relapse after SCT •Refractory to last therapy EPAR 2022 (30) (n=270) •Double or triple hit •Cell of origin (n=256) •Primary refractory							

Comparator	Trial (perspective) & key inclusion criteria	Population (histology and line of therapy)	N	Baseline characteristics reported and source of data (unique additional characteristics indicated consecutively)	Outcomes available (KM curves and response criteria indicated if available; ✓/ ✕ to indicate if response criteria aligned with NP30179) [Data source]						
					CR	DOCR	ORR	DOR	PFS	OS	Disc due to AEs
Liso-cabtagene maraleucel	TRANSCEND - OUTREACH-007 (prospective) •Age ≥18 years •ECOG PS 0–1 •RR after ≥2 systemic lines of therapy or after auto-HSCT	DLBCL nos, HGBCL, PMBCL, and FL grade 3b	46	Godwin 2021 (19) (n=46) •Age •Histology •Refractory last line	50% and 61% for inpatients and 138outpatients [Godwin 2021 (19); follow up NR]	NR	75% and 79% for inpatients and 138outpatients [Godwin 2021 (19); follow up NR]	NR	NR	NR	NA

Comparator	Trial (perspective) & key inclusion criteria	Population (histology and line of therapy)	N	Baseline characteristics reported and source of data (unique additional characteristics indicated consecutively)	Outcomes available (KM curves and response criteria indicated if available; ✓/ ✕ to indicate if response criteria aligned with NP30179) [Data source]						
					CR	DOCR	ORR	DOR	PFS	OS	Disc due to AEs
Pixantrone	Eyre 2016 (retrospective) •RR disease Respond to anthracycline based chemotherapy for ≥24 weeks	DLBCL (de novo, 63%; transformed iNHL, 33%; Richter's transformation, 4%) Median 2 (range 1–6) chemotherapies	90	Eyre 2016 (21) (n=90) •Age (median, >60 years) •ECOG PS •Histology •Ann Arbor stage •IPI score •No. of prior lines of treatment •Prior SCT •Time from last chemotherapy to randomisation (proxy for time since last treatment) •Refractory to last line •Time to first relapse post R-CHOP or equivalent (surrogate for refractoriness to first line)	INV (24%) [Eyre 2016; unclear follow up]	NR	INV (10%) [Eyre 2016; unclear follow up]	NR	KM curve 2 months (95% CI: 1.5, 2.4) [Eyre 2016; unclear follow up]	KM curve 3.4 months (95% CI: 2.7, 4.5) [Eyre 2016; unclear follow up]	NR

Comparator	Trial (perspective) & key inclusion criteria	Population (histology and line of therapy)	N	Baseline characteristics reported and source of data (unique additional characteristics indicated consecutively)	Outcomes available (KM curves and response criteria indicated if available; ✓/ ✕ to indicate if response criteria aligned with NP30179) [Data source]						
					CR	DOCR	ORR	DOR	PFS	OS	Disc due to AEs
Pixantrone	Sancho 2020 (retrospective) •Age ≥18 years •RR B-cell NHL •Progressed on ≥2 prior lines of therapy	NHL (94.9% DLBCL) Median 3 (range: 1–5) therapies	79	Sancho 2020 (22) (n=79) •Age (mean) •ECOG PS •Refractory to first line (primary refractory) •Refractory to last line •No. of prior lines of treatment •Prior SCT	10 (13.2%) Cheson 2007✕ [Sancho 2020; unclear follow up]	NR	22 (29%) Cheson 2007✕ [Sancho 2020; unclear follow up]	NR (4.9 months) [Sancho 2020; unclear follow up]	KM curve 2.8 months (95% CI: 2.1, 3.6) [Sancho 2020; median 8.6 months follow up]	KM curve 4 months (95% CI: 3.6, 4.4) [Sancho 2020; median 6.7 months follow up]	3 (3.8)
Tafasitamab plus lenalidomide	L-MIND (prospective) •Age ≥–18 years	DLBCL (including transformed lymphoma with a DLBCL relapse);	81 safety set 80 efficacy set	Duell 2021 (23) (n=81) •IPI (3–5) •Age (median/>70 years) •Ann Arbor stage (III–IV)	IRC 32 (40%) & INV 29 (36 %)	IRC KM curve Median not	IRC 46 (57.5%) & INV 51 (64%)	IRC KM curve 43.9 (95%	IRC KM curve 11.6 (95%	KM curve 33.5 (95% CI:	15 (18.25) Disc due to AEs

Comparator	Trial (perspective) & key inclusion criteria	Population (histology and line of therapy)	N	Baseline characteristics reported and source of data (unique additional characteristics indicated consecutively)	Outcomes available (KM curves and response criteria indicated if available; ✓/ ✕ to indicate if response criteria aligned with NP30179) [Data source]						
					CR	DOCR	ORR	DOR	PFS	OS	Disc due to AEs
	•ECOG PS 0–2 •RR disease to at least 1 but no more than 3 systemic regimens (with at least one anti-CD20)	any other type of lymphoma including PMBCL excluded Median 2 (range: 1–4) therapies		•High LDH •Cell type or origin •No. of prior lines of treatment •Prior SCT •Histology Salles 2020 (31) (n=81) •Bulky disease •Primary refractory (1st line) •Refractory last line •Rituximab refractory •ECOG PS EPAR 2021 (32) (n=81) •Age (mean) •Ann Arbour stage (I,II etc) •IPI (0, 1, 2 etc) •Double hit/triple hit	Cheson 2007✕ [Duell 2021; ≥35 months' follow up]	reached [Duell 2021; ≥35 months' follow up]	Cheson 2007✕ [Duell 2021; ≥35 months' follow up]	CI:26.1, NR) [Duell 2021; ≥35 months' follow up]	CI:6.3, 45.7) [Duell 2021; ≥35 months' follow up]	18.3, NE) [Duell 2021; ≥35 months' follow up]	20 (24.69 %) AEs leading to disc [Duell 2021; ≥35 months' follow up]

Comparator	Trial (perspective) & key inclusion criteria	Population (histology and line of therapy)	N	Baseline characteristics reported and source of data (unique additional characteristics indicated consecutively)	Outcomes available (KM curves and response criteria indicated if available; ✓/ ✕ to indicate if response criteria aligned with NP30179) [Data source]						
					CR	DOCR	ORR	DOR	PFS	OS	Disc due to AEs
				•Time since completion of last therapy or ASCT Nowakowski 2022 •Extranodal sites							
Tisagen-lecleucel	JULIET (prospective) •Age ≥18 years •ECOG PS 0–1 RR disease after ≥2 lines of chemotherapy, including rituximab and anthracycline	DLBCL (to include HGBCL and tFL) [patients with mediastinal DLBCL excluded] Median: 3 (range: 2–3) therapies	115 (FAS)	Shuster 2021 (33) (n=115) •IPI •Age (median/≥65 years) •ECOG PS •Ann Arbor stage •Cell type or origin (DLBCL) •Double/triple hit •Histology •No. of prior lines of treatment •Refractory last line •Prior ASCT •Bulky disease	IRC 45 (39%) & INV 39 (33.9%) Lugano 2014✓ [Schuster 2021; median 40.3	IRC KM curve Median not reached [Schuster 2019; median 14 months' follow	IRC 61 (43.5%) & INV 55 (47.8%) Lugano 2014✓ [Schuster 2021; median 40.3	IRC KM curve Median not reached [Schuster 2021; median 40.3 months	IRC KM curve 2.9 (95% CI: 2.3, 5.2) [Schuster 2021; median 40.3 months	KM curve 11.1 (95% CI: 6.6, 23.9) Schuster 2021; median 40.3 months' follow up]	NA

Comparator	Trial (perspective) & key inclusion criteria	Population (histology and line of therapy)	N	Baseline characteristics reported and source of data (unique additional characteristics indicated consecutively)	Outcomes available (KM curves and response criteria indicated if available; ✓/ ✕ to indicate if response criteria aligned with NP30179) [Data source]						
					CR	DOCR	ORR	DOR	PFS	OS	Disc due to AEs
				Shuster 2019 (34)/EPAR 2018 (35) (n=111) •Bone marrow involvement •Primary refractory (efficacy analysis set n=73) •Cell type or origin (cancer) Maziarz 2022 (36) MAIC (n=114†) •Age (mean) •Extranodal disease •Refractory all line •High LDH	months ' follow up]	up; **n=93,** *baseline data reported for FAS, n=111*]*	months follow up]	' follow up]	' follow up]		

Abbreviations: AE, adverse event; ASCT, autologous stem cell transplant; CI, confidence interval; 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; FAS, full analysis set; FL, follicular lymphoma; GCB, Germinal Centre B cel ; HGBCL, High-grade B-cell lymphoma; IHC, immunohistochemistry; iNHL, indolent NHL; INV, investigator; IPI, International Prognostic Index; IRC, independent review committee; ITT, intention to treat; IWRC, International working group response criteria; KM, Kaplan–Meier; LDH, lactate dehydrogenase; MAIC, matching-adjusted indirect comparison; mITT, modified intention to treat; NA, not applicable; NE, not estimable; NHL, non-Hodgkin lymphoma; NOS, not otherwise specified; NR, not reported; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; PMBCL, primary mediastinal large B-cell lymphoma; RR, relapsed/refractory; SCT, stem cell transplant; tFL, transformed follicular lymphoma.
†The publication states that in JULIET the original FAS of 115 included a patient with neuroendocrine tumour who was initially misclassified with DLBCL, this patient was excluded in the MAIC.

A3.2.2.1 Axicabtagene ciloleucel

A tabulated summary of the baseline characteristic of the glofitamab and axicabtagene ciloleucel studies considered in the feasibility assessment is provided in Table 13. A summary of each of the studies investigating axicabtagene ciloleucel that were included in the full feasibility assessment is provided in Sections A3.2.2.1.1–4, and details of the final study selection is provided in Section A3.2.2.1.5.

A3.2.2.1.1 Frank 2021

Frank 2021 reports multi-institutional prospective, open label trial of axicabtagene ciloleucel for the treatment of large B-cell lymphoma in the US. The study inclusion/exclusion criteria of Frank 2021 are aligned broadly with that of NCT03075696, enrolling patients aged ≥18 years with DLBCL, tFL or PBMCL. Patients had received a median of 3 prior lines of therapy (range: 1–7) (8).

A total of eight baseline characteristics of interest are reported for all enrolled patients (n=72) (8); thus, there are up to eight baseline factors which may be considered for adjustment in MAIC analyses.

Limited data are reported at a median of 10.9 months' follow-up; PFS and OS Kaplan–Meier (KM) curves reported by initial concentration of circulating tumour DNA. Thus, MAIC analyses may be feasible for PFS and OS only for the total populations and respective subgroups.

A3.2.2.1.2 Sanderson 2020

Sanderson 2020 reports a prospective, open-label, single-arm study of real world axicabtagene ciloleucel for the treatment of R/R large B-cell lymphoma in the UK. The study inclusion inclusion/exclusion criteria of Sanderson 2020 are aligned broadly with that of NCT03075696, enrolling patients aged >18 years with DLBCL, tFL or PMBCL after 2 previous lines of treatment, including anthracyclines (9).

A total of five baseline characteristics of interest are reported for the ITT population (n=42) in the single abstract publication (9); thus, there are up to five baseline factors which may be considered for adjustment in MAIC analyses.

Limited data are reported at a median of 6 months follow-up; ORR at 1 and 3 months and the median PFS at 3.6 months (no associated measure of uncertainty reported or KM curve). Thus, MAIC analyses may be feasible for ORR only.

A3.2.2.1.3 ZUMA-1

ZUMA-1 reports a prospective, open-label, single-arm study of axicabtagene ciloleucel for the treatment of refractory large B-cell lymphoma in the US and Israel. The study inclusion/exclusion criteria of ZUMA-1 are aligned broadly with that of NCT03075696, enrolling patients aged ≥18 years with R/R DLBCL (DLBCL not otherwise specified [NOS], HGBCL, PMBCL, and tFL) after two prior systemic lines of therapy (including an anti-CD20

and an anthracycline containing regimen), with ECOG PS of 0–1, and no evidence of CNS lymphoma. Notably ZUMA-1 only allowed enrolment of patients who were “chemotherapy-refractory”, defined as refractoriness to first line, second or greater line or transplant.

A total of 12 baseline characteristics of interest are reported for the modified-intention-to-treat (mITT) population (n=101) in the long-term follow-up publication (11). A further 4 unique factor of interests for the mITT population (n=101) were reported in the EPAR 2018 assessment report (24), (which also reported additional factors in a more granular format compared with the long-term publication). Notably the data reported for refractory to last therapy for ZUMA-1 in a MAIC publication differs to that in the long-term publication (reported as best response as progressive disease to last therapy) and therefore is highlighted for potential consideration (25). Finally Locke 2022 also reports elevated LDH levels (26). Thus, there are up to 16 baseline factors that may be considered for adjustment in MAIC analyses (note that whilst there are 18 unique factors listed in Table 13 it is only necessary to control for either histology or double/triple hit as one may be already inclusive of the other depending on their definition [as in this case with HGBCL being inclusive of double/triple hit]; refractory to second-line or later therapy [which corresponds to refractory to last line, based on the definition reported] and best response as progressive disease to last previous therapy are two different definitions of the same factor; thus, the number of factors for adjustment is 16).

Long-term data are reported at a median follow-up of 27.1 months (IQR 25.7, 28.8) for response rates (IRC & INV), DOR (IRC & INV) and PFS (INV) (11) and at a median follow-up of 63.1 months for OS (27) for the mITT population (all patients that received product; n=101). The response endpoints were assessed according to the modified IWG criteria (4) in comparison with the Lugano classification used in NP30179 (6). Notably, whilst median DOCR is reported at a median follow-up of 27.1 months (11), a KM curve is only reported for the interim analysis (median 15.4 months with a maximum follow-up of approximately 23 months; INV only) in the primary analysis publication for ZUMA-1 (in the ITT population; n=111) (37).

Thus, MAIC analyses may be feasible for all outcomes of interest.

A3.2.2.1.4 ZUMA-9

ZUMA-9 reports a prospective, open-label, multi-centre, single-arm study of axicabtagene ciloleucel for the treatment of RR large B-cell lymphoma for expanded assess and commercial out of specification product in the US. The study inclusion/exclusion criteria of ZUMA-9 are aligned broadly with that of NCT03075696, enrolling patients aged ≥18 years with R/R DLBCL (DLBCL NOS, HGBCL, PMBCL, and tFL), who received prior CD20-targeting and an anthracycline-containing regimen, and with ECOG PS of 0–1 (10). Patients received axicabtagene ciloleucel via an expanded access program until the treatment was commercially available (cohort 1) and later, if commercially manufactured product did not meet commercial release specification (cohort 2).

A total of five baseline characteristics of interest are reported for the ITT population (n=25 cohort 1; n=36 cohort 2) in the single abstract publication (10); thus, there are up to five baseline factors that may be considered for adjustment in the MAIC analyses.

Limited data are reported at a median of 27.1 (cohort 1) and 13.2 (cohort 2) months follow-up; ORR, CR and median OS (no KM curve). Thus, MAIC analyses may be feasible for CR and ORR only for both cohorts.

Table 13: Summary of baseline characteristics across the glofitamab and axicabtagene ciloleucel cohorts

Covariate	Glofitamab cohort	Axicabtagene ciloleucel			
	Total (N=155)	ZUMA-1 (n=101)	Frank 2021 (n=72)	Sanderson 2020 (n=42)	ZUMA-9 (cohort 1, n=25; cohort 2, n=36)
High priority					
IPI, n (%)	0: 5 (3.2%) 1: 24 (15.5%) 2: 45 (29.0%) 3: 55 (35.5%) 4: 26 (16.8%)	0: 4 (3.96%) 1: 23 (22.77%) 2: 26 (25.74%) 3: 30 (29.70%) 4: 18 (17.82%)	NR	NR	Cohort 1 ≥3: 44% Cohort 2 ≥3: 56%
Mean (SD) age, years	63.1 (14.7)	56.3 (12.0)	Median: 62	Median: 55 (range: 18–73)	Cohort 1: median: 56 (range: 28–76) Cohort 2: median: 61 (range: 24–81)
ECOG PS, n (%)	0: 77 (49.7%) 1: 78 (50.3%) 2: 1 (0.6%) [at screening]	0: 42 (41.58%) 1: 59 (58.42%)	NR	0–1: 92 (100%)	Cohort 1 1: 48% ≥2: 0% Cohort 2 1: 58% ≥2: 17%
Ann Arbor Stage, n (%)	I: 10 (6.5%) II: 25 (16.1%) III: 31 (20.0%) IV: 85 (54.8%) Unknown: 4 (2.6%)	I: 4 (3.96%) II: 11 (10.89%) III: 28 (27.72%) IV: 58 (57.43%) I–II: 15 (14.85%) III–IV: 86 (85.15%)	III–IV: 52 (72%)	NR	NR

Covariate	Glofitamab cohort	Axicabtagene ciloleucel			
	Total (N=155)	**ZUMA-1 (n=101)**	**Frank 2021 (n=72)**	**Sanderson 2020 (n=42)**	**ZUMA-9 (cohort 1, n=25; cohort 2, n=36)**
High LDH, n (%) [>ULN]	High: 101 (65.2%) Low-Normal: 52 (33.5%) Missing: 2 (1.3%) [at screening]	Elevated LDH: 62 (61.39%) LDH > ULN per local laboratory reference range	37 (51%)	NR	NR
Extranodal disease, n (%) [yes, or number of sites]	95 (61.3%)	70 (69.31%)			
Refractory to 1st line, n (%)	91 (58.7%) (Failure to respond to first treatment or progression within 6 months)	26 (25.74%) ['primary refractory'] Definition of primary refractory in the refractory subgroup according to the ZUMA-1 protocol: experienced disease progression as best response to first line therapy or had stable disease after at least 4 cycles of first line therapy	NR	NR	NR
Refractory to last line, n (%)	131 (84.5%)	67 (66.34%) [best response as PD to last	NR	NR	NR

Covariate	Glofitamab cohort	Axicabtagene ciloleucel			
	Total (N=155)	**ZUMA-1 (n=101)**	**Frank 2021 (n=72)**	**Sanderson 2020 (n=42)**	**ZUMA-9 (cohort 1, n=25; cohort 2, n=36)**
	(Failure to respond to previous treatment or progression within 6 months)	previous therapy; Locke 2019] 77 (76.24%) ['refractory to second-line or later'; a subject is considered to be refractory to 2nd or greater line therapy if the patient experienced PD as best response to the most recent therapy regimen; Locke 2019] 79.2% refractory to last line of treatment; Maloney 2021			
Refractory to any line, n (%)	139 (89.7%) (Failure to respond to any treatment or progression within 6 months)	NR	NR	NR	NR
Histological subtype: HGBCL, PMBCL or	DLBCL: 110 (71.0%) HGBCL: 10 (6.5%)	PMBCL: 8 (7.92%) HGBCL: 6 (5.94) [defined as double-hit or triple-hit or NOS]	DLBCL: 49 (68%) tFL: 17 (24%)	DLBCL: 27 (64%) tFL: 12 (29%) PMBCL: 3 (7%)	Cohort 1 DLBCL: 80% Cohort 2 DLBCL: 78%

Covariate	Glofitamab cohort	Axicabtagene ciloleucel			
	Total (N=155)	ZUMA-1 (n=101)	Frank 2021 (n=72)	Sanderson 2020 (n=42)	ZUMA-9 (cohort 1, n=25; cohort 2, n=36)
DLBCL/tFL, n (%)	PMBCL: 6 (3.9%) FL: 29 (18.7%)				
Double/triple hit lymphoma, n (%)	19 (12.3%) Missing: 1 (0.6%)	5 (4.95%) [among patients with HGBCL-assumed]	16 (22%) Double-hit	NR	NR
Refractory to prior ASCT/Early relapse after SCT (<12 months), n (%)	7 (4.5%) unknown: 127 (81.9%)	21 (20.79%) relapse after prior ASCT (not specified as early)	NR	NR	NR
Number of prior treatment lines, n (%) and median (range)	2: 61 (39.4%) 3: 49 (31.6%) 4: 27 (17.4%) 5: 10 (6.5%) 6: 5 (3.2%) 7: 3 (1.9%) ≥3: 94 (60.6%)	1: 3 (2.97%) 2: 28 (27.72%) ≥3: 70 (69.31%) ≥5: 12 (11.88%) Median 3 (1-10)	≥3: 43 (60%) Median: 3 (range: 1–7)	≥2: 42 (100%)	Cohort 1 ≥3: 64% Cohort 2 ≥3: 69%
Medium priority					
Bulky disease, n (%)	>6 cm: 64 (41.6%) >10 cm: 19 (12.3%)	≥10 cm: 16 (15.84%)	13 (18%)	NR	NR

Covariate	Glofitamab cohort	Axicabtagene ciloleucel			
	Total (N=155)	ZUMA-1 (n=101)	Frank 2021 (n=72)	Sanderson 2020 (n=42)	ZUMA-9 (cohort 1, n=25; cohort 2, n=36)
	Missing: 1 (0.6%)				
Refractory to chemotherapy, n (%)	133 (85.8%)	NR	NR	NR	NR
Refractory to rituximab and anthracycline, n (%)	88 (56.8%)	NR	NR	NR	NR
Refractory to rituximab, n (%)	129 (83.2%)	NR	NR	NR	NR
Time since last treatment, mean (SD)	6.49 (15.41)	NR	NR	NR	NR
Low/unclear priority					
Primary diagnosis, n (%)	DLBCL: 112 (72.3%) FL: 28 (18.1%) HGBCL: 8 (5.2%) PMBCL: 6 (3.9%) tFL: 1 (0.6%)	NR	NR	NR	NR
Cell type of origin, n (%)	ABC: 17 (11.0%)	GCB: 52 (70.27%) ABC: 18 (24.32%)	NR	NR	NR

Covariate	Glofitamab cohort	Axicabtagene ciloleucel			
	Total (N=155)	**ZUMA-1 (n=101)**	**Frank 2021 (n=72)**	**Sanderson 2020 (n=42)**	**ZUMA-9 (cohort 1, n=25; cohort 2, n=36)**
	GCB: 66 (42.6%) Miss/unclassified: 38 (24.5%) Non-GCB: 34 (21.9%)	Missing: 4 (5.5%) [n=74]			
Bone marrow involvement, n (%)	18 (11.6%)	Positive: 11 (10.89%) Negative: 82 (82.18) Not assessed: 7(6.93%)			NR
Prior SCT, n (%)	29 (18.7%)	25 (24.75%)	8 (11%)	11 (26%)	

Abbreviations: ABC, activated B-cell-like; ASCT, autologous stem cell transplant; CART-T, chimeric antigen receptor T-cell; GCB, germinal centre B cell; 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; IQR, interquartile range; LDH, lactate dehydrogenase; MAIC, matching adjusted indirect comparison; NOS, not otherwise specified; NR, not reported; PMBCL, primary mediastinal large B-cell lymphoma; RR, relapsed/refractory; SCT, stem cell transplant; SD, standard deviation; tFL, transformed FL.

A3.2.2.1.5 Final study selection for MAIC

ZUMA-1 is selected as the most appropriate source of data for axicabtagene ciloleucel for use in MAIC analyses for the following reasons:

- ZUMA-1 included the largest number of patients (n=101) (versus n=42–72 across the three other studies)
- ZUMA-1 had the largest number of baseline factors which may be considered for adjustment in MAIC analyses (n=16) (versus n=5-8 across the three other studies)
- ZUMA-1 reported all outcome of interest (versus limited outcome reporting across each of the three other studies)
- ZUMA-1 reported outcome data up to the longest follow-up of 63.1 months for OS (versus n=6–27.1 months across the other three studies)

A3.2.2.2 Bendamustine + rituximab

A tabulated summary of the baseline characteristic of the glofitamab and bendamustine plus rituximab studies considered in the feasibility assessment is provided in Table 15.

A3.2.2.2.1 Hong 2018

Hong 2018 reports a multi-centre retrospective analysis of bendamustine plus rituximab for R/R DLBCL in South Korea (13). The study reviewed medical records of each patient treated at 11 tertiary hospitals, who were ineligible for intensive chemotherapy with ASCT. A total of 58 patients were included that were treated with bendamustine plus rituximab, and of these, 29.3% received second-line therapy, and 31% and 39.7% of patients received third and fourth-line treatments, respectively. Notably, 22% of patients had an ECOG PS OF 2+.

A total of 11 baseline characteristics of interest are reported for the PP population (n=58) in the single publication at an unclear follow-up (although KM curves would suggest up to 50 months' follow-up); thus, there are up to 11 baseline factors that may be considered for adjustment in MAIC analyses.

Outcome data are reported for OS, PFS and response outcomes. Further, KM curves are reported for PFS and OS by line of therapy (second, third and fourth); although, as baseline data are not reported by line of therapy, it will not be appropriate to include these data in a potential MAIC. Whilst median DOR is reported, no KM curve is available. The response endpoints were assessed according to the Cheson 2007 classification in comparison with the Lugano classification used in NP30179 (17). Thus, MAIC analyses may be feasible for CR, ORR, PFS and OS.

Table 14: Summary of baseline characteristics across the glofitamab and bendamustine plus rituximab cohorts

Covariate	Glofitamab cohort	Bendamustine plus rituximab
	Total (N=155)	Hong 2018 (n=58)
High priority		
IPI, n (%)	0: 5 (3.2%) 1: 24 (15.5%) 2: 45 (29.0%) 3: 55 (35.5%) 4: 26 (16.8%)	0–2: 19 (33%) 3–5: 39 (67%)
Mean (SD) age, years	63.1 (14.7)	Median: 69 (18–86)
ECOG PS, n (%)	0: 77 (49.7%) 1: 78 (50.3%) 2: 1 (0.6%) [at screening]	0–1: 45 (78%) 2–4: 13 (22%)
Ann Arbor Stage, n (%)	I: 10 (6.5%) II: 25 (16.1%) III: 31 (20.0%) IV: 85 (54.8%) Unknown: 4 (2.6%)	I–II: 15 (26%) III–IV: 43 (74%)
High LDH, n (%) [>ULN]	High: 101 (65.2%) Low-Normal: 52 (33.5%) Missing: 2 (1.3%) [at screening]	38 (66%)
Extranodal disease, n (%) [yes, or number of sites]	95 (61.3%)	0–1: 32 (55%) 2+: 26 (45%)
Refractory to 1st line, n (%)	91 (58.7%) (Failure to respond to first treatment or progression within 6 months)	NR
Refractory to last line, n (%)	131 (84.5%) (Failure to respond to previous treatment or progression within 6 months)	NR
Refractory to any line, n (%)	139 (89.7%) (Failure to respond to any treatment or progression within 6 months)	NR

Covariate	Glofitamab cohort	Bendamustine plus rituximab
	Total (N=155)	Hong 2018 (n=58)
Histological subtype: HGBCL, PMBCL or DLBCL/tFL, n (%)	DLBCL: 110 (71.0%) HGBCL: 10 (6.5%) PMBCL: 6 (3.9%) FL: 29 (18.7%)	Pathoplogy: De novo DLBCL: 54 (93%) trDLBCL: 4 (7%)
Double/triple hit lymphoma, n (%)	19 (12.3%) Missing: 1 (0.6%)	
Refractory to prior ASCT/Early relapse after SCT (<12 months), n (%)	7 (4.5%) unknown: 127 (81.9%)	NR
Number of prior treatment lines, n (%) and median (range)	2: 61 (39.4%) 3: 49 (31.6%) 4: 27 (17.4%) 5: 10 (6.5%) 6: 5 (3.2%) 7: 3 (1.9%) ≥3: 94 (60.6%)	1: 17 (29.3%) 2: 18 (31%) ≥3: 23 (39.7%)
Medium priority		
Bulky disease, n (%)	>6 cm: 64 (41.6%) >10 cm: 19 (12.3%) Missing: 1 (0.6%)	NR
Refractory to chemotherapy, n (%)	133 (85.8%)	6 (10%) ['Primary refractory'] Defined as no objective response to previous chemotherapies
Refractory to rituximab and anthracycline, n (%)	88 (56.8%)	NR
Refractory to rituximab, n (%)	129 (83.2%)	NR
Time since last treatment, mean (SD)	6.49 (15.41)	NR
Primary diagnosis, n (%)	DLBCL: 112 (72.3%) FL: 28 (18.1%) HGBCL: 8 (5.2%) PMBCL: 6 (3.9%) tFL: 1 (0.6%)	NR
Cell type of origin, n (%)	ABC: 17 (11.0%) GCB: 66 (42.6%) Mis-/unclassified: 38 (24.5%) Non-GCB: 34 (21.9%)	GCB: 6 (10%) Non-GCB: 29 (50%) Unknown: 23 (40%)

Covariate	Glofitamab cohort	Bendamustine plus rituximab
	Total (N=155)	Hong 2018 (n=58)
Bone marrow involvement, n (%)	18 (11.6%)	NR
Prior SCT, n (%)	29 (18.7%)	13 (22%)

Abbreviations: GCB, germinal centre B cell; 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; LDH, lactate dehydrogenase; NOS, not otherwise specified; NR, not reported; PMBCL, primary mediastinal large B-cell lymphoma; SD, standard deviation; tFL, transformed FL.

A3.2.2.2.2 Final study selection for MAIC

It is challenging to identify which source of data for bendamustine plus rituximab is most appropriate for inclusion into MAIC analysis. A summary of all potentially relevant data sources considering key elements to help identify the most robust data source are provided in Table 15. Note that in addition to Hong 2018 included for the full feasibility assessment two additional studies that were considered potentially relevant from the topline extraction are included for completeness (Nowakowski 2022 and Vacirca 2014). These studies were not considered in the full feasibility assessment for the following reasons:

- **Nowakowski 2022 (RE-MIND2):** There are notable differences in the DLBCL population included in RE-MIND2 to include the exclusion of any other types of lymphoma including PMBCL, capped the maximum number of prior therapies and enrolled patients with an ECOG PS 0–2 (30.7% of patients had an ECOG PS 2). Thus, the population enrolled excluded higher risk DLBCL histologies and included significantly less pre-treated patients than in NP30179
- **Vacirca 214:** Reports fewer baseline characterises and outcomes compared with the other studies, and included <50% of patients on third-line therapy

On reflection it is suggested that Hong 2018 is the most appropriate source of data for bendamustine plus rituximab because it included fewer patients who received only one prior line of therapy and with an ECOG PS of 2+, as well as more baseline characteristic to control for compared with the other studies. Note that whilst Hong 2018 was conducted in South Korea and Western studies are preferred for the MAIC, this would not be at the cost of compromising on study quality.

Table 15: Summary of studies investigating bendamustine and rituximab

Criteria	Hong 2018	Nowakowski 2022	Vacirca 2014
Country	South Korea (11 hospitals)	International (multi-centre)	USA (26 centres)
Sample size	58	75	61
Prospective/ Retrospective	Retrospective	Retrospective	Prospective
Histology	DLBCL: DLBCL NOS 93.1% 6.9% tfFL	DLBCL (excluding other types of high-	DLBCL

		risk lymphoma such as PMBCL)	
Rituximab exposure	Yes	Unclear (assumed)	95%
Prior line of therapy	2+, 70.7%	2+, 48%	2+, 49%
ECOG PS 2+	22%	30.7%	6%
Number of prognostic factors reported	11	9	7
Patient characteristics reported	Baseline	Baseline	Baseline
Outcomes reported	OS, PFS & responses	OS, PFS & responses	PFS & responses
Responses clearly defined?	Yes (Cheson 2007)	Yes (1999, 2007 & 2014 IWG)	Yes (Cheson 2007)

Abbreviations: DLBCL, diffuse large C cell lymphoma; ECOG PS, Eastern Cooperative Oncology Group performance status; NOS, not otherwise specified; OS, overall survival; PFS, progression-free survival; PMBCL, primary mediastinal large B-cell lymphoma; PS, performance status; tFL, transformed follicular lymphoma.

A3.2.2.3 Lenalidomide

A tabulated summary of the baseline characteristic of the glofitamab and lenalidomide studies considered in the feasibility assessment is provided in Table 16. A summary of each of the studies investigating lenalidomide that were included in the full feasibility assessment is provided in Sections A3.2.2.3.1–5 and details of the final study selection is provided in Section A3.2.2.3.6.

A3.2.2.3.1 Czuczman 2017

Czuczman 20017 reports an open-label, Phase 2/3 RCT of lenalidomide versus investigators choice of therapy in patients with R/R large B-cell lymphoma conducted internationally (16). The study enrolled patients aged ≥18 years with R/R DLBCL, with ECOG PS of 0–2 (13% of patients had an ECOG PS of 2+). Most of the patients (90.2%) had 2 or more prior therapies at enrolment. The 5 patients (9.8%) with 1 prior therapy were exempt from the requirement for second combination chemotherapy or stem cell transplant on the basis of advanced age alone (n=1) or in combination with poor PS (n=1), major organ dysfunction (n=4) or patients decision to decline second-line combination chemotherapy (n=3).

A total of 5 baseline characteristics of interest are reported for the mITT population that were randomized to lenalidomide (n=51). The study reports baseline data and outcome data for all patients and for the GCB and non-GCB subgroups. Outcome data are reported for all outcomes of interest except for DOR (median DOR only), DOCR and discontinuations due to Aes (follow-up unclear). The response outcomes were assessed according to the International working group criteria (IWRC) criteria at an unclear follow-up. Thus, MAIC analyses may be feasible for CR, ORR, OS and PFS.

Note that this RCT was initially anticipated to be the preferred candidate comparator study for lenalidomide as it is prospective. However, it is anticipated that with only 5 baseline characteristics reported it would not allow for a robust MAIC, and

therefore, other retrospective studies were also considered in the feasibility analysis in the following sections.

A3.2.2.3.2 Ayers 2021

Ayers 2021 reports a retrospective cohort study of lenalidomide for the treatment of RR large B-cell lymphoma in the US (14). The study reviewed records from the nationwide de-identified electronic health record-derived Flatiron Health database. A total of 83 R/R DLBCL patients that received lenalidomide monotherapy were included in the study and of the patients 40% received second-line treatments and 37% and 23% of patients received third and fourth-line treatments, respectively. Notably 47% of patients had an ECOG PS of 2+.

A total of 10 baseline characteristics of interest are reported for the PP population (n=83) in the single publication at a follow-up of 22.7 months, but these are at diagnosis only and not at baseline. The outcome of OS was reported with KM curves available for the patients that received second line therapy (33/83) versus those that received third- or fourth-line therapy (50/83). No further outcomes of interest were reported (KM curves for event-free survival was reported); defined as the interval between the start of current therapy and the start of the next line of therapy, last follow-up while on current therapy, or death). Thus, MAIC analyses may be feasible for OS only.

A3.2.2.3.3 Broccoli 2019

Broccoli 2019 reports a retrospective observational study of lenalidomide for the treatment of R/R large B-cell lymphoma in Italy (15). The study included 153 patients that had received lenalidomide monotherapy according to the law (median number of prior therapies was 2 [range: 1–6]). Notably 29% of patients had an ECOG PS of 2+.

A total of seven baseline characteristics of interest were reported for the total population (n=153) in the single publication for which the follow-up duration was 36 months. Outcome data were reported for all outcomes of interest except for DOR and DOCR; notably, OS and PFS curves were reported for all patients and for age subgroups (elderly versus non-elderly) and relapsed and refractor subgroups. Thus, MAIC analyses may be feasible for CR, ORR, OS, PFS and discontinuations due to AEs.

A3.2.2.3.4 Hernandez-Ilizaliturri 2011

Hernandez-Ilizaliturri 2011 reported a retrospective cohort study of lenalidomide for the treatment of RR large B-cell lymphoma in the US (17). The study reviewed records from patients with R/R DLBCL treated with lenalidomide monotherapy and a total of 40 cases were included in the study population (85% DLBCL, 15% composite transformed histology; 23 GCB and 17 non-GCB) that had received a median of 4 prior treatments (range: 2–13). The study reports baseline data and outcome data for all patients and for the GCB and non-GCB subgroups.

A total of 7 baseline characteristics of interest were reported for the PP population (n=40) in the single publication at an unclear follow-up duration (patients were followed until death or their last clinical visit). Outcome data were reported for all outcomes of interest except for DOR, DOCR and discontinuations due to AEs. Thus, MAIC analyses may be feasible for CR, ORR, OS and PFS.

A3.2.2.3.5 RE-MIND

RE-MIND reports a retrospective observational study that generated a historic control of lenalidomide monotherapy for L-MIND (lenalidomide plus tafasitamab) to compare the contribution of tafasitamab in Italy, the US, Spain and France (18). The eligibility criteria for the lenalidomide cohort were aligned with the L-MIND and broadly aligned with some aspects of NCT03075696; including patients aged ≥18 years with R/R DLBCL (including transformed indolent lymphoma with a subsequent DLBCL relapse), after at least one, but no more than four systemic regimens [at least one anti-CD20]). However, notable differences in the populations include that L-MIND/RE-MIND excluded any other types of lymphoma including PMBCL and HGBCL, enrolled a significant number of patients that were less pre-treated (with a cap to the maximum number of prior therapies) and less refractory to previous therapies, as well as patients with an ECOG PS 0–2. Thus, the population enrolled excluded higher risk DLBCL histologies and included significantly less pre-treated and less refractory patients than in NP30179 (and 33% of patients had an ECOG PS of 2+).

A total of 12 baseline characteristics of interest were reported for the PP population (n=76) in the single publication for which a 32-month analysis window from the index date was applied. Outcome data were reported for all outcomes of interest except for DOCR. Thus, MAIC analyses may be feasible for CR, ORR, OS and PFS.

Table 16: Summary of baseline characteristics across the glofitamab and lenalidomide cohorts

Covariate	Glofitamab cohort	Lenalidomide				
	Total (N=155)	Ayers 2021 (n=83)	Broccoli 2019 (n=153)	Czuczman 2017 (n=51)	Hernandez-Ilizaliturri 2011 (n=40)	RE-MIND (n=76)
High priority						
IPI	0: 5 (3.2%) 1: 24 (15.5%) 2: 45 (29.0%) 3: 55 (35.5%) 4: 26 (16.8%)	0–2: 18 (22%) >2: 65 (78%)	NR	NR	0–1: 11 (28%) 2: 8 (20%) 3: 9 (23%) 4–5: 12 (30%)	0–2: 16 (21%) 3–5: 32 (42%) Missing: 28 (37%)
Age, mean (SD)	63.1 (14.7)	Median: 73.6 (IQR: 66.2–79.8) At diagnosis	Median 72 (25-93)	Median 69 (28-84)	Median 66 (43-80)	70 (8.65)
ECOG PS, n (%)	0: 69 (44.8%) 1: 84 (54.5%) 2: 1 (0.6%)	0-1: 44 (53%) 2-5: 39 (47%)	0-1: 110 (72%) 2: 30 (20%) 3: 13 (9%)	0: 18 (35%) 1: 24 (47%) 2: 7 (14%)	NR	0: 5 (7%) 1: 36 (47%) 2: 19 (25%) 3: 6 (8%) ≥2: 25 (33%) Missing: 10 (13.16%)
Ann Arbor Stage	I: 10 (6.5%) II: 25 (16.1%)	I–II: 15 (18%) III–IV: 68 (82%)	I–II: 37 (24%) III: 35 (23%) IV: 81 (53%)	NR	I: 4 (10%) II: 4 (10%) III: 12 (30%)	I: 0 II: 12 (16%) III: 12 (16%)

Covariate	Glofitamab cohort	Lenalidomide				
	Total (N=155)	Ayers 2021 (n=83)	Broccoli 2019 (n=153)	Czuczman 2017 (n=51)	Hernandez-Ilizaliturri 2011 (n=40)	RE-MIND (n=76)
	III: 31 (20.0%) IV: 85 (54.8%) Unknown: 4 (2.6%)				IV: 20 (50%)	IV: 52 (68%) I–II: 12 (15.79%) III–IV: 64 (84.21%)
High LDH, n (%) [>ULN]	107 (69.03%)	26 (31.3%) LCH>ULN	NR	NR	NR	45 (59%) >ULN
Extranodal disease, n (%) [yes, or number of sites]	95 (61.3%)	>1 site: 30 (36%)	NR	NR	NR	NR
Refractory to 1st line, n (%)	91 (58.7%) (Failure to respond to first treatment or progression within 6 months)	NR	61 (40%)	NR	NR	16 (21%) Primary refractoriness Best response less than PR or PD before or ≤6 months after completion of that treatment (assumed same definition as for L-MIND)

Covariate	Glofitamab cohort	Lenalidomide				
	Total (N=155)	Ayers 2021 (n=83)	Broccoli 2019 (n=153)	Czuczman 2017 (n=51)	Hernandez-Ilizaliturri 2011 (n=40)	RE-MIND (n=76)
Refractory to last line, n (%)	131 (84.5%) (Failure to respond to previous treatment or progression within 6 months)	NR	91 (60%)	NR	NR	34 (45%) Best response less than PR or PD before or ≤6 months after completion of that treatment (assumed same definition as for L-MIND)
Refractory to any line, n (%)	139 (89.7%) (Failure to respond to any treatment or progression within 6 months)	NR	NR	NR	NR	NR
Histological subtype: HGBCL, PMBCL or DLBCL/tFL, n (%)	DLBCL: 110 (71.0%) HGBCL: 10 (6.5%) PMBCL: 6 (3.9%) FL: 29 (18.7%)	Transformed disease: 11 (13%)	NR	NR	DLBCL: 34 (85%) Composite/transformed: 6 (15%)	NR PMBCL & HGBCL: O Split between remaining histologies NR

Covariate	Glofitamab cohort	Lenalidomide				
	Total (N=155)	Ayers 2021 (n=83)	Broccoli 2019 (n=153)	Czuczman 2017 (n=51)	Hernandez-Ilizaliturri 2011 (n=40)	RE-MIND (n=76)
Double-/triple-hit lymphoma, n (%)	19 (12.3%)	NR	NR	NR	NR	NR
Refractory to prior ASCT/Early relapse after SCT (<12 months), n (%)	7 (4.5%)	NR	NR	NR	NR	NR
Number of prior treatment lines, n (%) and median (range)	2: 61 (39.4%) 3: 49 (31.6%) 4: 27 (17.4%) 5: 10 (6.5%) 6: 5 (3.2%) 7: 3 (1.9%) ≥3: 94 (60.6%)	1: 33 (40%) 2: 31 (37%) 3: 19 (23%)	Median: 2 (range: 1–6)	1: 5 (10%) 2: 21 (41%) ≥3: 25 (49%)	Median: 4 (range: 2–13)	1: 28 (37%) 2: 42 (55%) 3: 6 (8%)
Medium priority						
Bulky disease, n (%)	>6 cm: 64 (41.6%)	NR	39 (26%)	NR	NR	NR

Covariate	Glofitamab cohort	Lenalidomide				
	Total (N=155)	Ayers 2021 (n=83)	Broccoli 2019 (n=153)	Czuczman 2017 (n=51)	Hernandez-Ilizaliturri 2011 (n=40)	RE-MIND (n=76)
	>10 cm: 19 (12.3%)					
Refractory to chemotherapy, n (%)	133 (85.8%)	NR	NR	NR	NR	NR
Refractory to rituximab and anthracycline, n (%)	88 (56.8%)	NR	NR	NR	NR	NR
Refractory to rituximab, n (%)	129 (83.2%)	NR	NR	NR	27 (68%) Resistant to rituximab	33 (43%) Defined as a response less than PR to any rituximab-containing regimen during the course of treatment or PD within ≤6 months of treatment completion (assumed same definition as for L-MIND)
Time since last	6.49 (15.41)	NR	NR	NR	NR	13.62 (19.64) Time since discontinuation of

Covariate	Glofitamab cohort	Lenalidomide				
	Total (N=155)	Ayers 2021 (n=83)	Broccoli 2019 (n=153)	Czuczman 2017 (n=51)	Hernandez-Ilizaliturri 2011 (n=40)	RE-MIND (n=76)
treatment, mean (SD)						last prior anti-DLBCL medication or ASCT
Low/unclear priority						
Primary diagnosis, n (%)	DLBCL: 112 (72.3%) FL: 28 (18.1%) HGBCL: 8 (5.2%) PMBCL: 6 (3.9%) tFL: 1 (0.6%)	NR	NR	NR	NR	NR
Cell type of origin, n (%)	ABC: 17 (11.0%) GCB: 66 (42.6%) Mis/unclassified: 38 (24.5%) Non-GCB: 34 (21.9%)	Non-GCB: 26 (31%) GCB: 21 (25%) Unknown: 36 (43%)	NR	GCB: 23 (45%) Non-GCB: 28 (55%)	GCB: 23 (57.5%) Non-GCB: (42.5%)	GCB: 14 (18%) Non-GCB: 16 (21%) Missing: 46 (61%)
Bone marrow involvement, n (%)	18 (11.6%)	NR	NR	NR	NR	NR

Covariate	Glofitamab cohort	Lenalidomide				
	Total (N=155)	Ayers 2021 (n=83)	Broccoli 2019 (n=153)	Czuczman 2017 (n=51)	Hernandez-Ilizaliturri 2011 (n=40)	RE-MIND (n=76)
Prior SCT, n (%)	29 (18.7%)	9 (11%) ASCT in 2nd line	26 (17%)	13 (25%)	NR	6 (8%)

Abbreviations: ASCT, autologous stem cell transplant; ABC, activated B-cell-like ; CART-T, chimeric antigen receptor T-cell; GCB, germinal centre B cell; 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; IQR, interquartile range; LCH, ; LDH, lactate dehydrogenase; NOS, not otherwise specified; NR, not reported; PD, progressed disease ; PMBCL, primary mediastinal large B-cell lymphoma; PR, partial response ; RR, relapsed/refractory; SCT, stem cell transplant; SD, standard deviation; tFL, transformed FL; ULN, upper level normal .

A3.2.2.3.6 Final study selection for MAIC

It is challenging to identify which source of data for lenalidomide is most appropriate for inclusion into the MAIC analysis. A summary of all potentially relevant data sources considering key elements to help identify the most robust data source is provided in Table 17. On reflection, it is suggested that RE-MIND is the most appropriate source of data for lenalidomide because it has the largest number of prognostic factors available. However, it should be noted that a MAIC with this comparator study (RE-MIND) is expected to be associated with important limitations and uncertainties due to the enrolment of patients who were, in general, less pre-treated or with ECOG PS 2 (as the proportion of patients with 1 prior line of therapy and ECOG PS 2 cannot be controlled for) and less refractory to previous therapies, which could introduce significant bias in the analysis and yield very small ESS due to the low population overlap, thereby limiting the interpretation and the generalisability of the results.

Table 17: Summary of studies investigating lenalidomide

Criteria	Ayers 2021	Broccoli 2019	Czuczman 2017	Hernandez-Ilizaliturri 2011	RE-MIND
Country	USA (nationwide database)	Italy (24 centres)	International (multi-centre)	USA (4 institutions)	Italy & US
Sample size	83	153	51	56	76
Prospective/ Retrospective	Retrospective	Retrospective	RCT	Retrospective	Retrospective
Histology	DLBCL; 11.3% tfFL	DLBCL	DLBCL (DLBCL or composite/transformed)	DLBCL; 15% tfFL	DLBCL (excluding other types of high-risk lymphoma such as PMBCL)
Rituximab exposure	Not explicitly stated	Not explicitly stated	Yes	Yes	Yes
Prior line of therapy	≥2, 60.2%	Median 2 (range: 1–6)	≥2, 90.2%	Median 4 (range: 2–13)	≥2, 63.2%
ECOG PS ≥2	47%	29%	13.7%	NR	33%
Number of prognostic factors reported	10	7	5	7	12
Patient characteristics reported	At time of diagnosis	Baseline	Baseline	Baseline	Baseline
Outcomes reported	OS	OS, PFS & responses	OS, PFS & responses	OS, PFS & responses	OS, PFS, responses,

					discontinuation due to AEs
Response assessment criteria definition available	No	Yes (Cheson 2007)	Yes (IWRC 1999)	Yes (Cheson 2007)	Yes (Cheson 2007)

Abbreviations: AE, adverse event; DLBCL, diffuse large B-cell lymphoma; ECOG PS, Eastern Cooperative Oncology Group performance status; IWRC, International working group response committee; OS, overall survival; PFS, progression-free survival; PS, performance status; PMBCL, primary mediastinal large B-cell lymphoma; RCT, randomised controlled trial; tFL, transformed follicular lymphoma.

A3.2.2.4 Lisocabtagene maraleucel

A tabulated summary of the baseline characteristic of the glofitamab and lisocabtagene maraleucel studies considered in the feasibility assessment is provided in Table 18. A summary of each of the studies investigating lisocabtagene maraleucel that were included in the full feasibility assessment is provided in Sections A3.2.2.4.1–2, and details of the final study selection is provided in Section A3.2.2.4.3.

A3.2.2.4.1 TRANSCEND NHL 001

TRANSCEND NHL 001 reports a prospective, open label, Phase 1 single-arm study of lisocabtagene maraleucel for the treatment of R/R large B-cell lymphoma in the US. The study inclusion/exclusion criteria of TRANSCEND NHL 001 are broadly aligned with that of NCT03075696, enrolling patients aged ≥18 years with R/R DLBCL (DLBCL NOS, HGBCL, PMBCL, and tFL) after two or more systemic lines of therapy (including an anti-CD20 and an anthracycline containing regimen with a subsequent relapse), with ECOG PS of 0–1 (it became 0–1 after a protocol amendment so the trial did enroll patients with ECOG PS 2). However, notable differences in the eligibility criteria include that TRANSCEND NHL 001 permitted the inclusion of patients with FL grade 3b, patients that had received previous allogenic haematopoietic SCT and patients with secondary CNS involvement.

A total of six baseline characteristics of interest are reported for the safety population (n=270) in the 2-year follow-up ASH presentation (20). An additional factor of interest (high LDH) was reported in the primary analysis publication plus additional data for histology based on the safety population in that analysis (n=269). Further data for six factors of interest in addition to alternative format of reporting for age and prior SCT data were reported in MAIC publications (n=256) (25, 29), and three in the Breyanzi 2022 EPAR report (n=270). Thus, there are up to 16 baseline factors that may be considered for adjustment in MAIC analyses.

It is noted that there is likely a reporting issue In the covariates of prior ASCT and early relapse (refractoriness) to ASCT as the n and % of patients who had prior SCT is lower than that of those patients who were refractory to it (which lacks face

validity). As the reported proportion is very high, it is anticipated that controlling for refractoriness to ASCT in a MAIC may cause issues. Note that the definition of refractoriness to chemotherapy in TRANSCEND actually includes patients who are early relapsers (refractory) to ASCT. Therefore, adjusting for refractoriness to chemotherapy is likely to also control for at least part of the (unknown) imbalances in early relapse (refractoriness) to ASCT.

Data are reported at 2-year (median: 19.9 months) follow-up for all outcomes in the efficacy evaluable data set (all patients that received product; n=257) of interest except discontinuations due to AEs (IRC for response outcomes, DO[C]R and PFS) (20). The response endpoints were assessed according to the Lugano classification as used in NP30179 (6). Thus, MAIC analyses may be feasible for all outcomes of interest except discontinuation due to AEs.

A3.2.2.4.2 TRANSCEND-OUTREACH-007

TRANSCEND OUTREACH-007 reports a prospective, open-label, Phase 2 single-arm study of lisocabtagene maraleucel for the treatment of RR large B-cell lymphoma at non-University medical centres in the US. The study inclusion/exclusion criteria of TRANSCEND OUTREACH-007 are broadly aligned with that of NCT03075696, enrolling patients aged ≥18 years with ECOG PS of 0–1 and R/R DLBCL (DLBCL NOS, HGBCL, PMBCL, and tFL) after two or more systemic lines of therapy but also enrolled patients after auto-HSCT which is a notable difference versus NCT03075696.

A total of three baseline characteristics are reported for the enrolled population (n=42) in the single abstract publication (19); thus, there are up to three baseline factors that may be considered for adjustment in MAIC analyses.

Limited data are reported an unclear follow-up; ORR for inpatients (n=16) and for outpatients (n=30). Thus, MAIC analyses may be feasible for ORR only.

Table 18: Summary of baseline characteristics across the glofitamab and lisocabtagene maraleucel cohorts

Covariate	Glofitamab cohort	Lisocabtagene maraleucel	
	Total (N=155)	**TRANSCEND (n=256/269/270)**	**TRANSCEND-OUTREACH-007 (n=42)**
High priority			
IPI, n (%)	0: 5 (3.2%) 1: 24 (15.5%) 2: 45 (29.0%) 3: 55 (35.5%) 4: 26 (16.8%)	0–2: 150 (58.60%) 3–4: 102 (39.84%) 5: 2 (0.78%) Missing: 2 (0.78%) [n=256]	NR
Mean (SD) age, years	63.1 (14.7)	60.3 (13.3) [n=256]	Median: 63 (range: 34–83)

Covariate	Glofitamab cohort	Lisocabtagene maraleucel	
	Total (N=155)	TRANSCEND (n=256/269/270)	TRANSCEND-OUTREACH-007 (n=42)
ECOG PS, n (%)	0: 77 (49.7%) 1: 78 (50.3%) 2: 1 (0.6%) [at screening]	0: 104 (40.64%) 1: 148 (57.81%) 2: 4 (1.56%) [N=256]	NR
Ann Arbor Stage, n (%)	I: 10 (6.5%) II: 25 (16.1%) III: 31 (20.0%) IV: 85 (54.8%) Unknown: 4 (2.6%)	I–II: 69 (26.95%) III–IV: 185 (72.27%) Missing: 2 (0.78%) [n=256]	NR
High LDH, n (%) [>ULN]	High: 101 (65.2%) Low-Normal: 52 (33.5%) Missing: 2 (1.3%) [at screening]	58 (21.56%) [n=269] ≥500 U/L	NR
Extranodal disease, n (%) [yes, or number of sites]	95 (61.3%)	Yes: 134 (53.34%) [n=256] No: 120 (46.88%) Missing: 2 (0.78%)	NR
Refractory to 1st line, n (%)	91 (58.7%) (Failure to respond to first treatment or progression within 6 months)	Primary refractory Yes: 205 (75.93%) No: 60 (22.22%) Missing: 5 (1.85%)	NR
Refractory to last line, n (%)	131 (84.5%) (Failure to respond to previous treatment or progression within 6 months)	Yes: 158 (61.72%) No: 92 (35.94%) Missing: 6 (2.34%) [n=256; Maloney 2021] Best response to last therapy of progressive disease or stable disease and relapsed defined as best response to last therapy of partial response or complete response 53 (20.70%) [n=256; Abramson 2020]	91%

Covariate	Glofitamab cohort	Lisocabtagene maraleucel	
	Total (N=155)	TRANSCEND (n=256/269/270)	TRANSCEND-OUTREACH-007 (n=42)
		Relapsed versus refractory is defined as best response of complete response versus best response of partial response, stable disease, or progressive disease to last systemic or transplant treatment with curative intent.	
Refractory to any line, n (%)	139 (89.7%) (Failure to respond to any treatment or progression within 6 months)	NR	NR
Histological subtype: HGBCL, PMBCL or DLBCL/tFL, n (%)	DLBCL: 110 (71.0%) HGBCL: 10 (6.5%) PMBCL: 6 (3.9%) FL: 29 (18.7%)	HGBCL: 36 (13.38%) [HGBCL with gene rearrangements in MYC and either BCL2, BCL6, or both. i.e. these were HGBCL DH-TH (HGBCL NOS not included)] PMBCL: 15 (5.58%) FL3b: 3 (1.11%) [N=269] PMBCL: 14 (5.47%) [N=256]	DLBCL NOS: 63%
Double-/triple-hit lymphoma, n (%)	19 (12.3%) Missing: 1 (0.6%)	36 (13.33%)	NR
Refractory to prior ASCT/Early relapse after SCT (<12 months), n (%)	7 (4.5%) unknown: 127 (81.9%)	Early relapse (≤12 month) post-haematopoeitic SCT [n=256] Yes: 92 (35.94%) No: 158 (61.72%) Missing: 6 (2.34%)	NR

Covariate	Glofitamab cohort	Lisocabtagene maraleucel	
	Total (N=155)	TRANSCEND (n=256/269/270)	TRANSCEND-OUTREACH-007 (n=42)
Number of prior treatment lines, n (%) and median (range)	2: 61 (39.4%) 3: 49 (31.6%) 4: 27 (17.4%) 5: 10 (6.5%) 6: 5 (3.2%) 7: 3 (1.9%) ≥3: 94 (60.6%)	1: 9 (3.35%) 2: 121 (44.98%) 3: 68 (25.28%) ≥4: 71 (26.39% Median: 3 (range: 1–8) [n=269]	NR
Medium priority			
Bulky disease, n (%)	>6 cm: 64 (41.6%) >10 cm: 19 (12.3%) Missing: 1 (0.6%)	≥10 cm (assumed to be aligned with Yescarta definition) Yes: 29 (11.33%) No: 225 (87.89%) Missing: 2 (0.78%) [n=256]	NR
Refractory to chemotherapy, n (%)	133 (85.8%)	171 (66.8%) [n=256] No response to or progressive disease after last chemotherapy-containing regimen, or relapse <12 months after autologous haematopoietic SCT	NR
Refractory to rituximab and anthracycline, n (%)	88 (56.8%)	NR	NR
Refractory to rituximab, n (%)	129 (83.2%)	NR	NR
Time since last treatment, mean (SD)	6.49 (15.41)	NR	NR
Low/unclear priority			
Primary diagnosis, n (%)	DLBCL: 112 (72.3%) FL: 28 (18.1%) HGBCL: 8 (5.2%) PMBCL: 6 (3.9%) tFL: 1 (0.6%)	NR	NR

Covariate	Glofitamab cohort	Lisocabtagene maraleucel	
	Total (N=155)	TRANSCEND (n=256/269/270)	TRANSCEND-OUTREACH-007 (n=42)
Cell type of origin, n (%)	ABC: 17 (11.0%) GCB: 66 (42.6%) Mis/unclassified: 38 (24.5%) Non-GCB: 34 (21.9%)	GCB: 119 (44.07%) ABC, non-GCB: 76 (28.15%) Unknown: 56 (20.74%) NR: 19 (7.04%)	NR
Bone marrow involvement, n (%)	18 (11.6%)	NR	NR
Prior SCT, n (%)	29 (18.7%)	87 (33.98%) [n=256] Included some patients with allogenic SCT	NR

Abbreviations: ABC, activated B-cell-like; ASCT, autologous stem cell transplant; GCB, germinal centre B cell; 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; NOS, not otherwise specified; NR, not reported; PMBCL, primary mediastinal large B-cell lymphoma; SCT, stem cell transplant; SD, standard deviation; tFL, transformed follicular lymphoma.

A3.2.2.4.3 Final study selection for MAIC

TRANSCEND NHL 001 is selected as the most appropriate source of data for lisocabtagene maraleucel for use in MAIC analyses for the following reasons:

- TRANSCEND NHL 001 included the largest number of patients (n=256) (versus n=46 in TRANSCEND-OUTREACH-007)
- TRANSCEND NHL 001 had the largest number of baseline factors that may be considered for adjustment in MAIC analyses (n=16) (versus n=3 in TRANSCEND-OUTREACH-007)
- TRANSCEND NHL 001 reported all outcome of interest (versus ORR only in TRANSCEND-OUTREACH-007)
- TRANSCEND NHL 001 reported data at the longest follow-up of 2 years (assumed longest as only ORR data reported for TRANSCEND-OUTREACH-007 and follow-up was not reported)

A3.2.2.5 Pixantrone

A tabulated summary of the baseline characteristic of the glofitamab and pixantrone studies considered in the feasibility assessment is provided in Table 19. A summary of each of the studies investigating pixantrone that were included in the full feasibility assessment is provided in Sections A3.2.2.5.1–2 and details of the final study selection is provided in Section A3.2.2.5.3.

A3.2.2.5.1 Eyre 2016

Eyre 2016 reports a multi-centre UK-side retrospective study of pixantrone in R/R DLBCL (21). The study included patients 57 (63%) patients with de novo DLBCL, 30 (33%) patients with transformed iNHL (2 MZL, 2 LPL, 2iNHL and 24 FL) and 4 (4%) of patients with Richter's transformation. Patients had received a median of 2 prior therapies, and 49% of patients had an ECOG PS of 2+.

A total of nine baseline characteristics of interest are reported for all patients in the single primary publication for this study; thus, there are up to nine baseline factors that may be considered for adjustment in the MAIC analyses.

Outcome data are reported for CR, ORR, PFS and OS at an unclear follow-up and progression and responses were based on investigator assessment with lack of finalised radiological reporting according to published criteria.

A3.2.2.5.2 Sancho 2020

Sancho 2020 reports a retrospective, observational real-life study of patients who received pixantrone monotherapy for R/R aggressive B-cell NHL in Spain and Italy (22). The study included patients aged ≥18 years that had progressed on ≥2 lines of prior therapy. The majority of patients had DLBCL (94.9%) with a small proportion of patients with FL3b or peripheral T-cell lymphoma (4.1%). A total of 39% of patients had an ECOG PS of 2+.

A total of six baseline characteristics of interest are reported for all patients (n=79) but are also reported for patients who received ≥2 cycles of pixantrone (n=58) and for patients who received 1 cycle of pixantrone (n=21) in the single primary publication for this study; thus, there are up to six baseline factors that may be considered for adjustment in MAIC analyses.

Outcome data are reported for all outcomes of interest except DOR (median response reported only) and DOCR. PFS was reported at a median follow-up of 8.6 months and OS reported at a median OS of 6.7 months. The response endpoints were assessed according to the Cheson 2007 classification in comparison with the Lugano classification used in NP30179 (17). Thus, MAIC analyses may be feasible for all but two outcomes of interest.

Table 19: Summary of baseline characteristics across the glofitamab and pixantrone cohorts

Covariate	Glofitamab cohort	Pixantrone	
	Total (N=155)	Eyre 2016 (n=90)	Sancho 2020 (n=79)
High priority			
IPI, n (%)	0: 5 (3.2%) 1: 24 (15.5%)	0–1: 5 (6%) 2: 19 (21%)	NR

Covariate	Glofitamab cohort	Pixantrone	
	Total (N=155)	Eyre 2016 (n=90)	Sancho 2020 (n=79)
	2: 45 (29.0%) 3: 55 (35.5%) 4: 26 (16.8%)	3–5: 65 (73%) Missing: 1 (1.11%)	
Mean (SD) age, years	63.1 (14.7)	Median: 65.9 (range: 20.3–85.9)	67.5 (95% CI: 64.6, 70.3)
ECOG PS, n (%)	0: 77 (49.7%) 1: 78 (50.3%) 2: 1 (0.6%) [at screening]	0–1: 41 (46%) 2–4: 49 (54%)	0–1: 39/60 (56%) ≥2: 21/60 (35%) Unknown: 47 (62%)
Ann Arbor Stage, n (%)	I: 10 (6.5%) II: 25 (16.1%) III: 31 (20.0%) IV: 85 (54.8%) Unknown: 4 (2.6%)	I–II: 9 (10%) III–IV: 80 (90%)	NR
High LDH, n (%) [>ULN]	High: 101 (65.2%) Low-Normal: 52 (33.5%) Missing: 2 (1.3%) [at screening]	NR	NR
Extranodal disease, n (%) [yes, or number of sites]	95 (61.3%)	NR	NR
Refractory to 1st line, n (%)	91 (58.7%) (Failure to respond to first treatment or progression within 6 months)	Time to first relapse post R-CHOP (or equivalent) <12 months: 36 (40.00%) >12 months: 53 (58.89%) Missing: 1 (1.11%)	47 (62%) ['Primary refractory'] Those that did not chieve a CR to first-line chemotherapy or those that progressed within the first 3 months of completion of treatment
Refractory to last line, n (%)	131 (84.5%) (Failure to respond to previous treatment or progression	Baseline tumour RR: 76 (84.44%) Refractory disease was defined as SD or PD to the immediate prior line of treatment or disease that relapsed within 8	66/78 (15%) Those with <8 months from the end of their most recent previous chemotherapy (irrespective of response) to the initiation of

Covariate	Glofitamab cohort	Pixantrone	
	Total (N=155)	Eyre 2016 (n=90)	Sancho 2020 (n=79)
	within 6 months)	months following a previous documented response (PR/CR)	treatment with pixantrone, or those with stable disease or PD since their most recent previous chemotherapy regimen
Refractory to any line, n (%)	139 (89.7%) (Failure to respond to any treatment or progression within 6 months)	NR	NR
Histological subtype: HGBCL, PMBCL or DLBCL/tFL, n (%)	DLBCL: 110 (71.0%) HGBCL: 10 (6.5%) PMBCL: 6 (3.9%) FL: 29 (18.7%)	De novo DLBCL: 57 (63%) Transformed iNHL: 30 (33%) Richter's transformation: 4 (4%)	NR
Double/triple hit lymphoma, n (%)	19 (12.3%) Missing: 1 (0.6%)	NR	
Refractory to prior ASCT/Early relapse after SCT (<12 months), n (%)	7 (4.5%) unknown: 127 (81.9%)	NR	NR
Number of prior treatment lines, n (%) and median (range)	2: 61 (39.4%) 3: 49 (31.6%) 4: 27 (17.4%) 5: 10 (6.5%) 6: 5 (3.2%) 7: 3 (1.9%) ≥3: 94 (60.6%)	Median: 2 (range: 1–6)	2: 32/75 (43%) 3: 18/75 (24%) >3: 25/75 (33%) Unknown: 4 (5%) Median 3 (1-5)
Medium priority			
Bulky disease, n (%)	>6 cm: 64 (41.6%) >10 cm: 19 (12.3%) Missing: 1 (0.6%)	NR	NR

Covariate	Glofitamab cohort	Pixantrone	
	Total (N=155)	Eyre 2016 (n=90)	Sancho 2020 (n=79)
Refractory to chemotherapy, n (%)	133 (85.8%)	NR	NR
Refractory to rituximab and anthracycline, n (%)	88 (56.8%)	NR	NR
Refractory to rituximab, n (%)	129 (83.2%)	NR	NR
Time since last treatment, mean (SD)	6.49 (15.41)	Median: 4.2 (range: 0.72–78.5) Time from last chemotherapy	NR
Low/unclear priority			
Primary diagnosis, n (%)	DLBCL: 112 (72.3%) FL: 28 (18.1%) HGBCL: 8 (5.2%) PMBCL: 6 (3.9%) tFL: 1 (0.6%)	NR	NR
Cell type of origin, n (%)	ABC: 17 (11.0%) GCB: 66 (42.6%) Mis/unclassified: 38 (24.5%) Non-GCB: 34 (21.9%)	NR	NR
Bone marrow involvement, n (%)	18 (11.6%)	NR	NR
Prior SCT, n (%)	29 (18.7%)	14 (15%)	13 (17%)

Abbreviations: ABC, activated B-cell-like; ASCT, autologous stem cell transplant; CR, complete response; GCB, germinal centre B cell; DLBCL, diffuse large B-cell lymphoma; ECOG PS, Eastern Cooperative Oncology Group performance status; FL, follicular lymphoma; HGBCL, high-grade B-cell lymphoma; iNHL, indolent NHL; NOS, not otherwise specified; NR, not reported; PD, progressed disease; PMBCL, primary mediastinal large B-cell lymphoma; PR, partial response; RR, relapsed/refractory; SCT, stem cell transplant; SD, standard deviation; tFL, transformed follicular lymphoma.

A3.2.2.5.3 Final study selection for MAIC

It is challenging to identify which source of data for pixantrone is most appropriate for inclusion into the MAIC analysis. A summary of all potentially relevant data sources considering key elements to help identify the most robust data source is provided in Table 20. On reflection, it is suggested that Eyre 2016 is the most appropriate source of data for pixantrone because it includes the largest number of patients and has more baseline characteristics available for adjustment, though it enrolled a larger proportion of patients with ECOG PS 2+ versus Sancho 2020 (note that ECOG was missing for ~24% of the patients in Sancho 2020).

Table 20: Summary of studies investigating pixantrone

Criteria	Eyre 2016	Sancho 2020
Country	UK (33 centres)	Spain & Italy (52 sites)
Sample size	90	79
Prospective/ retrospective	Retrospective	Retrospective
Histology	DLBCL: 63% DLBCL NOS; 33% transformed iNHL	NHL: 94.9% DLBCL NOS; 4.1% FL3b or peripheral T cell lymphoma
Rituximab exposure	99%	96.2%
Prior line of therapy	Median: 2 (range: 1–6)	Median: 3 (range: 1–5)
ECOG PS 2+	49%	35%
Number of prognostic factors reported	9	6
Patient characteristics reported	Baseline	Baseline†
Outcomes reported	OS, PFS & responses	OS, PFS & responses
Responses clearly defined?	No	Yes (Cheson 2007)

Abbreviations: DLBCL, diffuse large B-cell lymphoma; ECOG PS, Eastern Cooperative Oncology Group performance status; iNHL,indolent NHL ; NHL, non-Hodgkin's lymphoma; NOS, not otherwise specified; OS, overall survival; PFS, progression-free survival.
†Note some factors were also reported at diagnosis but are not considered in the current feasibility assessment.

A3.2.2.6 Tafasitamab plus lenalidomide

A3.2.2.6.1 L-MIND

A tabulated summary of the baseline characteristic of the glofitamab and tafasitamab plus lenalidomide studies considered in the full feasibility assessment is provided in Table 21.

L-MIND reports a prospective, open-label, Phase 2, single-arm study of tafasitamab plus lenalidomide for the treatment of RR large B-cell lymphoma internationally. The study inclusion/exclusion criteria of L-MIND are aligned with some aspects of NCT03075696; enrolling patients aged ≥18 years with R/R DLBCL (including transformed indolent lymphoma with a subsequent DLBCL relapse), after at least

one, but no more than four systemic regimens (at least one anti-CD20)6 and no CNS lymphoma involvement (present or past). However, notable differences in the populations include that L-MIND/ excluded any other types of lymphoma including PMBCL and HGBCL, enrolled a significant number of patients that were less pre-treated (with a cap to the maximum number of prior therapies) and less refractory to previous therapies, as well as patients with an ECOG PS 0–2. Thus, the population enrolled excluded higher risk DLBCL histologies and included significantly less pre-treated and less refractory patients than in NP30179.

A total of eight baseline characteristics of interest are reported for the safety population (n=81) in the long-term follow-up ≥35 months (23) and an additional five characteristics are reported in the primary analysis publication (31). A further three unique characteristics are reported in the EPAR 2021 assessment report (also reporting age, Ann Arbour stage and IPI in a more granular format compared with the primary and long-term study publications) (32). Thus, there are up to 16 baseline factors which may be considered for adjustment in MAIC analyses.

Long-term data at ≥35 months are reported for all outcomes of interest in the efficacy analysis set (n=80) (IRC for response outcomes), thus MAIC analyses may be feasible for all outcomes (23). The response endpoints were assessed according to the modified IWG criteria (4) in comparison with the Lugano classification used in NP30179 (6).

Table 21: Summary of baseline characteristics across the glofitamab and tafasitamab plus lenalidomide cohorts

Covariate	Glofitamab cohort	Tafasitamab + lenalidomide
	Total (N=155)	L-MIND (N=81/80)
High priority		
IPI, n (%)	0: 5 (3.2%) 1: 24 (15.5%) 2: 45 (29.0%) 3: 55 (35.5%) 4: 26 (16.8%)	0: 5 (6.17%) 1: 11 (13.58%) 2: 24 (29.63%) 3: 24 (29.63%) 4: 14 (17.28%) 5: 3 (3.71%) ≥3: 41 (50.62%)
Mean (SD) age, years	63.1 (14.7)	69.3 (9.53)
ECOG PS, n (%)	0: 77 (49.7%) 1: 78 (50.3%) 2: 1 (0.6%) [at screening]	0: 29 (35.80%) 1: 45 (55.56%) 2: 7 (8.64%)

[6] One patient that had received four prior treatments was included (as a result of a protocol amendment or a protocol violation).

Covariate	Glofitamab cohort	Tafasitamab + lenalidomide
	Total (N=155)	L-MIND (N=81/80)
Ann Arbor Stage, n (%)	I: 10 (6.5%) II: 25 (16.1%) III: 31 (20.0%) IV: 85 (54.8%) Unknown: 4 (2.6%)	I: 4 (4.94%) II: 16 (19.75%) III: 16 (19.75%) IV: 45 (55.56%) I-II: 20 (24.69%) III-IV: 61 (75.31%)
High LDH, n (%) [>ULN]	High: 101 (65.2%) Low-Normal: 52 (33.5%) Missing: 2 (1.3%) [at screening]	45 (55.56%) >ULN (upper limit of normal)
Extranodal disease, n (%) [yes, or number of sites]	95 (61.3%)	0–1 sites: 52 (68.42%) ≥2 sites: 54 (31.58%)
Refractory to 1st line, n (%)	91 (58.7%) (Failure to respond to first treatment or progression within 6 months)	15 (18.52%) ['Primary refractory'] Best response less than PR or PD before or ≤6 months after completion of that treatment Patients with primary refractory disease were excluded, although until a protocol amendment in June 2016, primary refractoriness was defined as no response or PD within <3 months of frontline therapy, rather than 6 months.
Refractory to last line, n (%)	131 (84.5%) (Failure to respond to previous treatment or progression within 6 months)	36 (44.44%) [N=80] Best response less than PR or PD before or ≤6 months after completion of that treatment
Refractory to any line, n (%)	139 (89.7%) (Failure to respond to any treatment or progression within 6 months)	NR
Histological subtype: HGBCL, PMBCL or DLBCL/tFL, n (%)	DLBCL: 110 (71.0%) HGBCL: 10 (6.5%) PMBCL: 6 (3.9%) FL: 29 (18.7%)	HGBCL & PBMCL: 0 DLBCL from transformed low grade lymphoma: 8 (9.88%)
Double-/triple-hit lymphoma, n (%)	19 (12.3%) Missing: 1 (0.6%)	2 (2.47%)
Refractory to prior ASCT/Early relapse	7 (4.5%) unknown: 127 (81.9%)	NR

Covariate	Glofitamab cohort	Tafasitamab + lenalidomide
	Total (N=155)	L-MIND (N=81/80)
after SCT (<12 months), n (%)		
Number of prior treatment lines, n (%) and median (range)	2: 61 (39.4%) 3: 49 (31.6%) 4: 27 (17.4%) 5: 10 (6.5%) 6: 5 (3.2%) 7: 3 (1.9%) ≥3: 94 (60.6%)	1: 40 (49.38%) 2: 35 (43.21%) 3: 5 (6.17%) 4: 1 (1.24%) ≥ 2: 41 (50.62%) Median: 2 (range: 1–4)
Medium priority		
Bulky disease, n (%)	>6 cm: 64 (41.6%) >10 cm: 19 (12.3%) Missing: 1 (0.6%)	≥7.5 cm: 15 (18.52%) Absent: 65 (80.25%) Missing: 1 (1.23%)
Refractory to chemotherapy, n (%)	133 (85.8%)	NR
Refractory to rituximab and anthracycline, n (%)	88 (56.8%)	NR
Refractory to rituximab, n (%)	129 (83.2%)	Yes: 34 (41.98%) No: 46 (56.79%) Unknown: 1 (1.23%) Defined as a response less than PR to any rituximab-containing regimen during the course of treatment or PD within ≤6 months of treatment completion
Time since last treatment, mean (SD)	6.49 (15.41)	16.994 (21.8378) [anti-DLBCL medication or ASCT]
Low/unclear priority		
Primary diagnosis, n (%)	DLBCL: 112 (72.3%) FL: 28 (18.1%) HGBCL: 8 (5.2%) PMBCL: 6 (3.9%) tFL: 1 (0.6%)	NR
Cell type of origin, n (%)	ABC: 17 (11.0%) GCB: 66 (42.6%) Mis/unclassified: 38 (24.5%) Non-GCB: 34 (21.9%)	By GEP GCB: 8 (9.88%) ABC: 20 (24.69%) Unclassified: 6 (7.41%) Not evaluable: 5 (6.17%)

Covariate	Glofitamab cohort	Tafasitamab + lenalidomide
	Total (N=155)	L-MIND (N=81/80)
		Missing: 42 (51.85%) By IHC) GCB: 39 (48.15% Non-GCB: 22 (27.16%) Unknown: 20 (24.69%)
Bone marrow involvement, n (%)	18 (11.6%)	NR
Prior SCT, n (%)	29 (18.7%)	9 (11.11%)

Abbreviations: ABC, activated B-cell-like; ASCT, autologous stem cell transplant; CAR-T, chimeric antigen receptor T-cell; GCB, germinal centre B cell; DLBCL, diffuse large B-cell lymphoma; ECOG PS, Eastern Cooperative Oncology Group performance status; FL, follicular lymphoma; HGBCL, high-grade B-cell lymphoma; IHC, immunohistochemistry; IPI, International Prognostic Index; NOS, not otherwise specified; NR, not reported; PD, progressed disease ; PMBCL, primary mediastinal large B-cell lymphoma; PR, partial response; RR, relapsed/refractory; SCT, stem cell transplant; SD, standard deviation; tFL, transformed follicular lymphoma; ULN, upper level normal .

It should be noted that a MAIC with L-MIND is expected to be associated with important limitations and uncertainties due to the enrolment of patients who were in general less pre-treated (as the proportion of patients with 1 prior line of therapy cannot be controlled for) and less refractory to previous therapies, which could be introduce significant bias against glofitamab in the analysis and yield very small ESS due to the low population overlap, thereby limiting the interpretation and the generalisability of the results.

A3.2.2.7 Tisagenlecleucel

A tabulated summary of the baseline characteristic of the glofitamab and tisagenlecleucel studies considered in the full feasibility assessment is provided in Table 22.

A3.2.2.7.1 JULIET

JULIET reports a prospective, open-label, Phase 2, single-arm study of tisagenlecleucel for the treatment of R/R large B-cell lymphoma internationally. The study inclusion/exclusion criteria of JULIET are aligned broadly with that of NCT03075696, enrolling patients aged ≥18 years with R/R DLBCL (HGBCL and tFL, but not PMBCL) after two or more lines of chemotherapy (including rituximab and anthracycline, either having failed ASCT, or being ineligible for or not consenting to ASCT), with ECOG PS of 0–1, no prior allogenic SCT and no active CNS involvement of their DLBCL.

A total of 11 baseline characteristics of interest are reported for the full analysis set (FAS) population (n=115) in the long-term follow-up publication at a median of 40.3 months (11) and an additional two characteristics (bone marrow involvement and primary refractory) as well as origin of cell of origin data (cancer) were reported in an

earlier analysis 2019 (34) and EPAR 2018 assessment report (35) based on the FAS population (n=111). An additional three factors of interest for the FAS population (n=114) was also reported in a MAIC publication in addition to age reported as a mean (36); in this MAIC analysis the authors highlight that in JULIET the original FAS of 115 included a patient with neuroendocrine tumour who was initially misclassified with DLBCL, this patient was excluded in the MAIC. In total, there are there are up to 15 baseline factors that may be considered for adjustment in MAIC analyses (note that whilst there are 16 factors listed in Table 22 it is only necessary to control for either histology or double-/triple-hit as one may be already inclusive of the other depending on their definition [as in the case with double-/triple-hit being inclusive of HGBCL] thus the list number of factors is 15).

Long-term data are reported at a median follow-up of 40.3 months (IQR: 37.8–43.8) in the FAS population (all patients that received product; n=115) for all outcomes except discontinuation due to AEs (IRC for response outcomes and PFS) (11). The response endpoints were assessed according to the Lugano classification as used in NP30179 (6). Thus, MAIC analyses may be feasible for all outcomes of interest.

Table 22: Summary of baseline characteristics across the glofitamab and tisagenlecleucel cohorts

Covariate	Glofitamab cohort	Kymriah cohort
	Total (N=155)	JULIET (n=115]
High priority		
IPI, n (%)	0: 5 (3.2%) 1: 24 (15.5%) 2: 45 (29.0%) 3: 55 (35.5%) 4: 26 (16.8%)	≥2: 84 (73.4%) ≥3: 41 (44.1%) [n=93]
Mean (SD) age, years	63.1 (14.7)	53.7 (13.1) [n=114]
ECOG PS, n (%)	0: 77 (49.7%) 1: 78 (50.3%) 2: 1 (0.6%) [at screening]	0: 65 (56.52%) 1: 50 (43.48%)
Ann Arbor Stage, n (%)	I: 10 (6.5%) II: 25 (16.1%) III: 31 (20.0%) IV: 85 (54.8%) Unknown: 4 (2.6%)	I: 9 (7.83%) II: 18 (15.65%) III: 23 (20%) IV: 65 (56.52%) I–II: 27 (23.48%) III–IV: 88 (76.52%)
High LDH, n (%) [>ULN]	High: 101 (65.2%) Low-Normal: 52 (33.5%) Missing: 2 (1.3%)	60 (52.17%) > ULN (upper limit of normal) at the closest time before the day of infusion

Covariate	Glofitamab cohort	Kymriah cohort
	Total (N=155)	JULIET (n=115]
	[at screening]	
Extranodal disease, n (%) [yes, or number of sites]	95 (61.3%)	0: 64 (51.14%) ≥2: 50 (43.86%) Missing: 1 (1%) [n=114]
Refractory to 1st line, n (%)	91 (58.7%) (Failure to respond to first treatment or progression within 6 months)	41% (assumed to be on the efficacy analysis set who met the refractory criteria of SCHOLAR-1 for the MAIC in the EPAR, n=73) Definition was assumed to be from 1L therapy as per SCHOLAR-1 publication. In SCHOLAR-1, refractory DLBCL (including subtypes PMBCL and tFL) was defined as progressive disease (received ≥4 cycles of first-line therapy)
Refractory to last line, n (%)	131 (84.5%) (Failure to respond to previous treatment or progression within 6 months)	63 (54.78%) Refractory disease indicates either progressive or stable disease as the best response to the last therapy before enrolment or an unknown response status.
Refractory to any line, n (%)	139 (89.7%) (Failure to respond to any treatment or progression within 6 months)	NR
Histological subtype: HGBCL, PMBCL or DLBCL/tFL, n (%)	DLBCL: 110 (71.0%) HGBCL: 10 (6.5%) PMBCL: 6 (3.9%) FL: 29 (18.7%)	HGBCL: 17 (14.78%) Defined as patients with diffuse large B-cell lymphoma and double- or triple-hit rearrangements in either MYC and BCL2, MYC and BCL6, or MYC, BCL2, and BCL6
Double-/triple-hit lymphoma, n (%)	19 (12.3%) Missing: 1 (0.6%)	20 (17.4%)
Refractory to prior ASCT/Early relapse after SCT (<12 months), n (%)	7 (4.5%) Unknown: 127 (81.9%)	NR
Number of prior treatment lines, n (%) and median (range)	2: 61 (39.4%) 3: 49 (31.6%) 4: 27 (17.4%) 5: 10 (6.5%) 6: 5 (3.2%)	1: 5 (4.35%) 2: 51 (44.35%) 3: 36 (31.3%) 4–6: 23 (20%) 4: 14 (12.3%) [n=114]

Covariate	Glofitamab cohort	Kymriah cohort
	Total (N=155)	JULIET (n=115]
	7: 3 (1.9%) ≥3: 94 (60.6%)	5: 8 (7%) [n=114] 6: 1 (0.9%) [n=114] Median: 3 (range: 1–6) [n=114]
Medium priority		
Bulky disease, n (%)	>6 cm: 64 (41.6%) >10 cm: 19 (12.3%) Missing: 1 (0.6%)	>10 cm: 9 (7.83%)
Refractory to chemotherapy, n (%)	133 (85.8%)	NR
Refractory to rituximab and anthracycline, n (%)	88 (56.8%)	NR
Refractory to rituximab, n (%)	129 (83.2%)	NR
Time since last treatment, mean (SD)	6.49 (15.41)	6 (7.29) [n=93]
Low/unclear priority		
Primary diagnosis, n (%)	DLBCL: 112 (72.3%) FL: 28 (18.1%) HGBCL: 8 (5.2%) PMBCL: 6 (3.9%) tFL: 1 (0.6%)	NR
Cell type of origin, n (%)	ABC: 17 (11.0%) GCB: 66 (42.6%) Miss/unclassified: 38 (24.5%) Non-GCB: 34 (21.9%)	Cell of origin in DLBCL reported for the DLBCL NOS patients [n=92] GCB: 50 (54.35%) ABC: 41 (44.56%) Other: 1 (1.09%) Cell of origin of cancer [n=111] GCB: 63 (56.76%) Non-GCB: 45 (40.54%) Missing: 3 (2.7%)
Bone marrow involvement, n (%)	18 (11.6%)	8 (7.21%) [n=111]
Prior SCT, n (%)	29 (18.7%)	56 (48.7%)

Abbreviations: ABC, activated B-cell-like; ASCT, autologous stem cell transplant; GCB, germinal centre B cell; DLBCL, diffuse large B-cell lymphoma; ECOG PS, Eastern Cooperative Oncology Group performance status; EPAR, European public assessment report; FL, follicular lymphoma; HGBCL, high-grade B-cell lymphoma; IPI, International Prognostic Index; IQR, interquartile range; LDH, lactate dehydrogenase; NOS, not otherwise specified; NR, not reported; PMBCL, primary mediastinal large B-cell lymphoma; RR, relapsed/refractory; SCT, stem cell transplant; SD, standard deviation; tFL, transformed follicular lymphoma; ULN, upper level normal.

A3.2.3 Summary of MAIC feasibility assessment

A tabulated summary of the full MAIC feasibility assessment is provided in Table 12.

- For the comparators of bendamustine plus rituximab (Hong 2018), tisagenlecleucel (JULIET) and tafasitamab plus lenalidomide (L-MIND), single studies were included in the full feasibility assessment
- Four prospective studies investigating axicabtagene ciloleucel were considered in the feasibility assessment (8-11). However, ZUMA-1 is selected as the most appropriate source of data for axicabtagene ciloleucel for use in MAIC analyses
- Five studies investigating lenalidomide were considered in the feasibility assessment (14-18). However, RE-MIND is selected as the most appropriate source of data for lenalidomide for use in MAIC analyses
- Two studies investigating lisocabtagene maraleucel were considered in the feasibility assessment (19, 20). However, TRANSCEND NHL 001 is selected as the most appropriate source of data for lisocabtagene maraleucel for use in MAIC analyses
- Two studies investigating pixantrone considered in the feasibility assessment (21, 22). However, Eyre 2016 is selected as the most appropriate source of data for pixantrone for use in MAIC analyses

In summary, MAIC analyses are feasible for all efficacy outcomes of interest for the comparators of interest; axicabtagene ciloleucel (ZUMA-1), bendamustine plus rituximab (Hong 2018), lenalidomide (RE-MIND), lisocabtagene maraleucel (TRANSCEND NHL 001), pixantrone (Eyre 2016), tafasitamab plus lenalidomide (L-MIND) and tisagenlecleucel (JULIET).

The comparator trials selected for most of the interventions of interest are broadly aligned with NCT03075696 in terms of the inclusion/exclusion criteria (with a few exceptions) and report 9 to 16 baseline characteristics which may be used to adjust for in MAIC analyses (sources of each of the characteristics are indicated in Table 12). All comparator studies report most (if not all of) the efficacy outcome of interest and details of the response assessments (criteria and INV/IRC) are indicated in Table 12.

Section A: The NP30179 trial

A4. Please supply the Protocol, Clinical Study Report (CSR) and Statistical Analysis Plan (SAP) for this trial, or indicate where they can be found.

Please see the attached supplementary documents for the glofitamab Protocol version 11, CSR (CCOD June 2022) and SAP version 5 of the NP30179 trial.

A5. Please supply a quality assessment of the trial using the NICE seven-criteria checklist, as was used for the comparator trials (in Appendix D.1 Table 2).

A quality assessment for the NP30179 trial was previously provided alongside comparator trials (Appendix D.1, Table 2, last column). It is included here again for reference.

Table 23: Quality assessment results for NP30179

Trial name, author, journal, year	NP30179, Roche, CSR, 2022
1. Is the hypothesis/aim/objective of the study clearly described?	Yes
2. Are the main outcomes to be measured clearly described in the Introduction or Methods section?	Yes
3. Are the characteristics of the patients in the study clearly described?	Unclear
4. Are the interventions of interest clearly described?	Yes
5. Are the distributions of principal confounders in each group of subjects to be compared clearly described?	Unclear
6. Are the main findings of the study clearly described?	Yes
7. Does the study provide estimates of the random variability in the data for the main outcome?	Yes
8. Have all important adverse events that may be a consequence of the intervention been reported?	Yes
9. Have the characteristics of patients lost to follow-up been described?	No
10. Have actual probability values been reported (e.g. 0.035 rather than < 0.05) for the main outcomes except where the probability value is less than 0.001?	No
11. Were the subjects asked to participate in the study representative of the entire population from which they were recruited?	Unable to determine
12. Were those subjects who were prepared to participate representative of the entire population from which they were recruited?	Unable to determine
13. Were the staff, places and facilities where the patients were treated, representative of the treatment the majority of the patients receive?	Unable to determine
14. Was an attempt made to blind study subjects to the intervention they have received?	No

Trial name, author, journal, year	NP30179, Roche, CSR, 2022
15. Was an attempt made to blind those measuring the main outcomes of interest?	Yes
16. If any of the results of the study were based on "data dredging", was this made clear?	Yes
17. In trials and cohort studies, do the analyses adjust for different lengths of follow-up of patients, or in case-control studies, is the time period between the intervention and outcome the same for cases and controls?	Yes
18. Were the statistical tests used to assess the main outcomes appropriate?	Yes
19. Was compliance with the interventions reliable?	Unable to determine
20. Were the main outcome measures used accurate (valid and reliable)?	Yes
21. Were study subjects in different intervention groups (trials and cohort studies) or were the cases and controls (case-control studies) recruited from the same population?	Yes
22. Were study subjects in different intervention groups (trials and cohort studies) or were the cases and controls (case-control studies) recruited over the same period of time?	Yes
23. Were study subjects randomised to intervention groups?	No
24. Was the randomised intervention assignment concealed from both patients and health care staff until recruitment was complete and irrevocable?	No
25. Was there adequate adjustment for confounding in the analyses from which the main findings were drawn?	Unclear
26. Were losses of patients to follow-up taken into account?	Yes
27. Did the study have sufficient power to detect a clinically important effect where the probability value for a differences being due to chance is less than 5%?	Yes

A6. The EAG would like to see greater detail on the various cohorts of the NP30179 trial, and why they were or were not included in the primary efficacy or safety populations. Please supply a table describing the size, population, treatment and dosing pattern in each cohort, with a justification of why the cohort was or was not included.

The NP30179 trial had several cohorts, but only three were relevant to this submission: D3, D5, and D2 [Sub. 2] (see Table 24). These cohorts were included because:

- They enrolled patients with R/R DLBCL (i.e. DLBCL NOS, tFL, HGBCL or PMBCL) who had received at least two prior systemic therapies (i.e., 3L+)

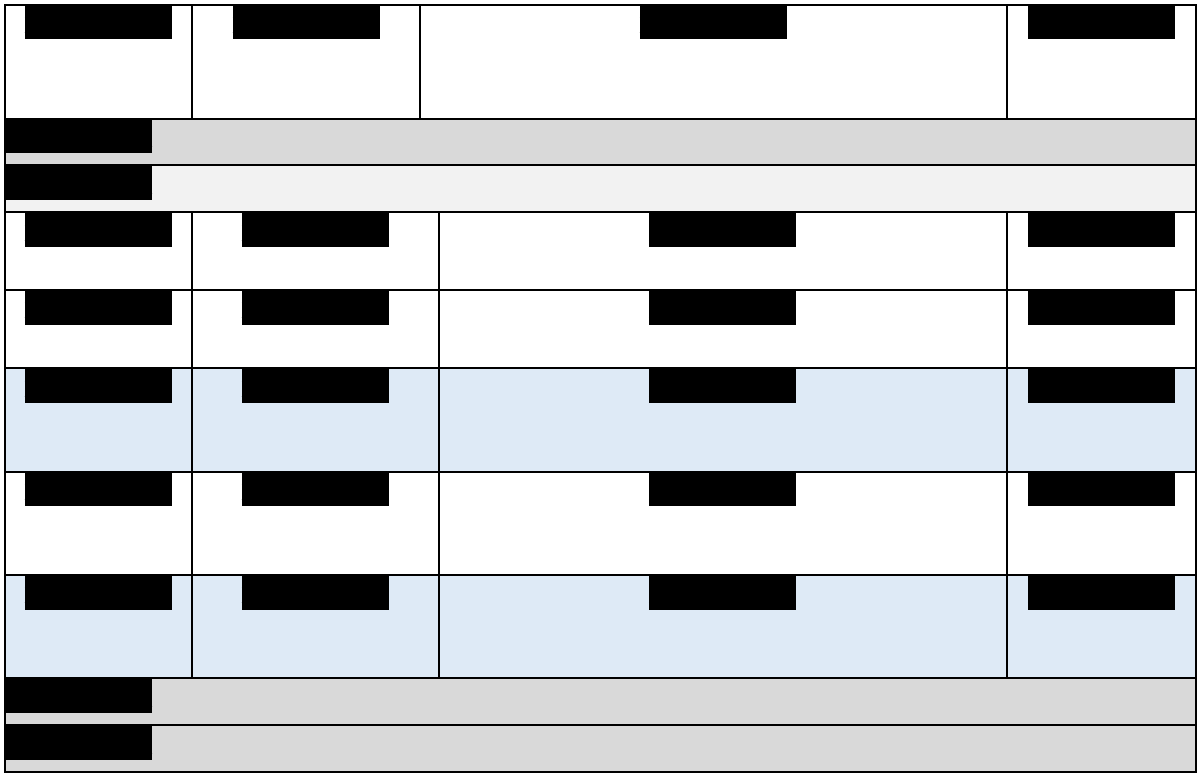
and

- Patients in these cohorts were treated with the target dosing regimen for registration, which consisted of step-up dosing: 2.5 mg on C1D8, 10 mg on C1D15, and 30 mg on D1 Q3W from C2 onward.

The other cohorts were not included in the primary efficacy or safety populations for various reasons: some included patients with histologies other than DLBCL or mixed R/R NHL histologies, while others had the inclusion criterion of at least one prior systemic treatment (i.e., 2L+ rather than 3L+). Additionally, some cohorts were treated with dosing regimens that differed from the target dosing regimen for registration, such as fixed dosing or different step-up dosing regimens. A table providing details on the size, population, treatment, and dosing pattern of each cohort is provided below (Table 24).

Table 24: Overview of R/R NHL patients: glofitamab monotherapy cohorts in Parts I, II and III of study NP30179 (safety-evaluable population) (CCOD 15 June 2022)

Cohort (diagnosis)	Dose of Glofitamab[a]	Glofitamab dosing regimen	Number of patients treated
[redacted]			
[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]
[redacted]			
[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]



[a] All patients received a single fixed dose of obinutuzumab (Gpt: 1000 mg IV) pre-treatment, given 7 days (C1D1) prior to the initial dose of glofitamab, except for patients in Cohort D2 Subcohort 4 who received two doses of Gpt.[b] Q2W dosing including dosing on C1D8 and C1D15 followed by Q2W dosing on Day 1 in each cycle from C2 onward. [c] Q2W dosing without dosing on C1D15. [d] Safety population in Cohort D3 includes one R/R FL patient who was enrolled into this Cohort in error and excludes 1 patient who did not receive any study treatment with Gpt or glofitamab (enrolled in error).[e] Dexamethasone pre-medication. [f] Safety population in Cohort D5 includes one R/R FL patient who was enrolled into this Cohort in error.

Key: C = cycle; D = day; R/R FL = relapsed/refractory follicular lymphoma; Gpt = obinutuzumab pre- treatment; Q2W = every two weeks; Q3W = every three weeks; R/R DL8CL = relapsed/refractory diffuse large 8-cell lymphoma; R/R NHL= relapsed/refractory non-Hodgkin's lymphoma.

A7. Priority question: If available, please provide summary outcome data covering all trial cohorts of R/R DLBCL patients. Please provide data on CR, ORR and Kaplan-Meier curves for OS and PFS. We suggest specifically providing pooled outcome data for the cohorts:

a. With different dosing schedules (Cohorts B3 and A2, B2, F2);

The dosing schedules for Cohorts A2, B2, B3 and F2 can be found in the previous response to Question A6 (Table 24). However, it is important to note that these cohorts are not applicable to the regulatory submission as they significantly differ from the intended dosing regimen for registration, which is a glofitamab step-up dosing of 2.5/10/30 mg. This particular dosing regimen is the only one that has been submitted to the European Medicines Agency (EMA) for regulatory review.

In addition, Cohorts A2, B2 and F2 recruited mixed NHL histologies (including indolent lymphomas, such as FL and marginal zone lymphoma) and had the inclusion criterion of R/R NHL with at least one prior systemic therapy (i.e. 2L+). As such, these cohorts are not relevant to the current submission.

b. Combination therapy cohorts (Cohorts C3, E3, and C2, E2, G2);

The indication submitted for regulatory review pertains only to the use of glofitamab as a monotherapy. Therefore, the cohorts that administered glofitamab in combination with obinutuzumab are not relevant for this submission.

Please note that all relevant cohorts in this submission included a single pre-treatment with obinutuzumab on C1D1, followed by step-up dosing of glofitamab monotherapy. To distinguish it from the combination therapy with obinutuzumab, this pre-treatment with obinutuzumab is referred to as "GpT" (i.e. obinutuzumab (Gazyvaro®) pre-treatment) in the submission.

c. The "supporting efficacy population" (as in CS Table 16);

It is important to note that the data from the supporting efficacy population of patients with R/R DLBCL who received glofitamab doses ≥10 mg (n=101), was specifically presented to support the DOCR endpoint, with a longer median follow-up of 26.0 months compared to the primary efficacy population. The IRC-assessed response rates and PFS outcomes are presented below in Table 25. No Kaplan-Meier (KM) plots were generated for this population.

Additionally, OS data was not reported for patients who received a target dose of ≥10 mg of glofitamab, as survival information was not collected for some patients before its implementation in the NP30179 Protocol version 8.

Table 25: IRC-assessed response rates and PFS outcomes for the glofitamab supporting efficacy population (CCOD 15 June 2022)

	Supporting efficacy population Glofitamab ≥10 mg* (N=101)
Response rates	
Overall response rate (ORR) (95% CI)	[redacted]
Complete response (CR) (95% CI)	[redacted]
Progression-free survival (PFS)	
Patients with event Earliest contributing event: Death Disease Progression	[redacted]
Time to event (months) Median (95% CI)	[redacted]

**Includes patients treated with glofitamab 10 mg, 16 mg, 25 mg, 10/16 mg and 2.5/10/16 mg.*

d. Cohort D3 (also include DCOR and DOR Kaplan Meier curves for this cohort).

The IRC-assessed response rates, PFS, and OS outcomes are presented below in Table 26. The requested KM curves are presented from Figure 7 to Figure 10.

Table 26: IRC-assessed response rates, PFS, and OS outcomes for Cohort D3 (CCOD 15 June 2022)

	Glofitamab 2.5/10/30 mg Cohort D3 (N=108)
Response rates	
Overall response rate (ORR) (95% CI)	[redacted]
Complete response (CR) (95% CI)	[redacted]
Progression-free survival (PFS)	
Patients with event Earliest contributing event: Death Disease Progression	[redacted]
Time to event (months) Median (95% CI)	[redacted]
Overall survival (OS)	
Patients with event	[redacted]
Time to event (months) Median (95% CI)	[redacted]

Figure 7: Kaplan-Meier plot of IRC-assessed PFS for Cohort D3 (ITT population)

Figure 8: Kaplan-Meier plot of IRC-assessed OS for Cohort D3 (ITT population)

Figure 9: Kaplan-Meier plot of IRC-assessed DOCR for Cohort D3 (complete responder population)

Figure 10: Kaplan-Meier plot of IRC-assessed DOR for Cohort D3 (responder population)

A8. Please explain why the cohort receiving dexamethasone treatment (D5) was originally excluded from analysis and later included. Please provide all outcome data (CR, ORR, DOR, DOCR, OS and PFS) for cohort D5 on its own.

During the interim CSR in September 2021, a pre-planned statistical analysis was conducted to assess the primary efficacy outcome measure of CR rate between the intention-to-treat (ITT) population in Cohort D3 and a historical control. The interim CSR also included preliminary data from Cohort D5 (i.e. 3L+ R/R DLBCL with 2.5/10/30mg step up dosing and pre-treatment steroid mandated as dexamethasone), which was still in the active enrollment phase (n=38) as supportive data. By the time of the updated primary analysis in June 2022, all of the participants in Cohort D5 had been enrolled (n=40) and had received at least one response assessment. Consequently, the Company presented safety and efficacy data based on the updated primary analysis population dataset (Cohorts D2 [Sub. 2] + D3 + D5), which included a larger sample of patients with 3L+ DLBCL (n=155) receiving glofitamab at the registrational dose (2.5/10/30 mg) to provide more comprehensive information for prescribers.

The NP30179 trial incorporated dexamethasone premedication to reduce the frequency and severity of cytokine release syndrome (CRS), based on previous studies conducted in mice and data obtained from the GO41943 trial (NCT04313608). Starting from NP30179 Protocol v10, dexamethasone (20 mg IV administered prior to obinutuzumab and glofitamab infusion) was included as an option for corticosteroid premedication, as an alternative to prednisolone and methylprednisolone for all patients. Moreover, an R/R DLBCL expansion cohort (D5)

was introduced to assess the exploratory objective of determining whether mandatory dexamethasone pre-medication could further reduce the incidence and severity of CRS.

Of the 40 patients recruited in Cohort D5, 37 received glofitamab with 3 patients discontinuing study treatment before the first dose of glofitamab (after obinutuzumab pre-treatment); 2 due to adverse events and 1 due to physician decision. All 37 glofitamab-exposed patients (100%) received at least one dose of dexamethasone as premedication (36 patients [97.3%; dexamethasone] and 1 patient [2.7%; dexamethasone phosphate]). Of those 37 patient, 33 patients exclusively received dexamethasone and 4 patients received at least one dose of steroids other than dexamethasone as pre-medication including methylprednisolone (3 patients), prednisolone (2 patients), and methylprednisolone sodium succinate (1 patient).

The requested outcomes for patients in Cohort D5 are reported in Table 27, and from Figure 11 to Figure 14. The shorter duration of follow-up for IRC-assessed duration of CR and of OR in patients in Cohort D5 was due to the fact that they were enrolled into the study later than patients in the other cohorts included in the primary efficacy population (Cohort D2 [Sub. 2] and D3). Note that the KM plots for PFS, DOR and DOCR have a sharp drop to zero due to the fact the last uncensored patient had an event.The shape of these curves is expected to change with longer follow-up.

Table 27: IRC-assessed response rates in Cohort D5 (ITT population)

	Glofitamab 2.5/10/30 mg Cohort D5 (N=40)
Overall response rate (ORR) (95% CI)	[redacted]
Complete response (CR) (95% CI)	[redacted]

Figure 11: Kaplan-Meier plot of IRC-assessed DOR in Cohort D5 (ITT population)

[redacted]

Figure 12: Kaplan-Meier plot of IRC-assessed DOCR in Cohort D5 (ITT population)

Figure 13: Kaplan-Meier plot of IRC-assessed PFS in Cohort D5 (ITT population)

Figure 14: Kaplan-Meier plot of IRC-assessed OS in Cohort D5 (ITT population)

A9. Given possible differences in response between DLBCL, PMBCL and HGBCL subtypes, please provide outcome data (CR, ORR, and PFS/OS if feasible) for each subtype.

Table 28 represents the IRC-assessed response rates for patients with DLBCL, PMBCL, tFL, and HGBCL subtypes. The KM plots of IRC-assessed PFS and OS for patients with DLBCL are presented in Figure 15 and Figure 16; and these are reflective of the PFS and OS KM curves for the primary efficacy population in the submission (Document B, Figure 3 and Figure 4, respectively).

However, there is insufficient data to draw meaningful conclusions regarding PFS and OS outcomes for the rest of the subtypes. It should be noted that the subgroup sizes for PMBCL and HGBCL were particularly small (n≤10); therefore, it was not possible to report PFS or OS outcomes for these subtypes with confidence.

Table 28: IRC-assessed response rates by histology subtype (ITT population)

n (%)	Glofitamab 2.5/10/30 mg Cohorts D2 (Sub. 2), D3, D5 (N=155)				
	DLBCL (n=110)	PMBCL (n=6)	tFL (n=29)	HGBCL (n=10)	All patients (N=155)
Overall response rate (ORR) (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Complete response (CR) (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Figure 15: Kaplan-Meier plot of IRC-assessed PFS in DLBCL patients (ITT population)

Figure 16: Kaplan-Meier plot of IRC-assessed OS in DLBCL patients (ITT population)

A10. Priority question: If available, please provide full subgroup analysis results (CR, ORR, PFS, OS) according to the number of previous lines of treatment.

The IRC-assessed CR rates of the primary efficacy population in patients who had received 2 (n=61) vs ≥3 (n=94) prior lines of therapy have been provided in the forest plot in Document B, Figure 5 (2 prior, 33% [21, 46] vs ≥3 prior, 45% [34, 55]). Additional ORR, PFS, and OS outcomes are presented in Table 29, and from Figure 17 to Figure 20 below.

Table 29: IRC-assessed ORR by prior lines of therapy (2 vs ≥3)

	Glofitamab 2.5/10/30 mg Cohorts D2 (Sub. 2), D3, D5 (N=155)		
	Patients, n (%)	Patients with event	
		n (%)	95% CI
All	[redacted]	[redacted]	[redacted]
Prior lines of therapy			
2	[redacted]	[redacted]	[redacted]
≥3			

Figure 17: Kaplan-Meier plot of IRC-assessed PFS in the primary efficacy population, with 2 prior lines of therapy

Figure 18: Kaplan-Meier plot of IRC-assessed PFS in the primary efficacy population, with ≥3 prior lines of therapy

Figure 19: Kaplan-Meier plot of IRC-assessed OS in the primary efficacy population, with 2 prior lines of therapy

Figure 20: Kaplan-Meier plot of IRC-assessed OS in the primary efficacy population, with ≥3 prior lines of therapy

[redacted]

A11. Priority question: Please provide the DOR and DCOR Kaplan Meyer curves (including numbers at risk over time) from the primary study efficacy population.

The KM plots of IRC-assessed DOR and DOCR in the primary efficacy population (glofitamab 2.5/10/30 mg, Cohorts D2 [Sub. 2] + D3 + D5) are shown in Figure 21 and Figure 22, respectively.

The KM estimated DOR among responders at 6, 12, and 18 months after the first response was [redacted] respectively (Figure 21).

The KM estimated DOCR among complete responders at 6, 12, and 18 months after the first CR were [redacted], respectively (Figure 22).

Figure 21: Kaplan-Meier plot of IRC-assessed DOR in the primary efficacy population (responder population)

[redacted]

Figure 22: Kaplan-Meier plot of IRC-assessed DCOR in the primary efficacy population (complete responder population)

[redacted]

A12. Priority question: Please provide the PFS and OS Kaplan-Meier curves (including numbers at risk over time) from the:

a. Individuals without prior CAR-T in the primary study efficacy population, and report the number of these individuals who received CAR-T subsequently to glofitamab;

The KM plots of IRC-assessed PFS and OS in patients who did not receive prior CAR-T therapy in the primary efficacy population (glofitamab 2.5/10/30 mg, Cohorts D2 [Sub. 2] + D3 + D5) are shown in Figure 23 and Figure 24, respectively.

A total of 103 patients did not receive prior CAR-T therapy; of which, 9 individuals underwent CAR-T therapy after completing their glofit treatment.

Figure 23: Kaplan-Meier plot of IRC-assessed PFS of the primary study efficacy population, without prior CAR-T therapy

[redacted]

Figure 24: Kaplan-Meier plot of IRC-assessed OS of the primary study efficacy population, without prior CAR-T therapy

b. Individuals with prior CAR-T, in the primary study efficacy population, and report the number of these individuals who also received CAR-T subsequently to glofitamab.

The KM plots of IRC-assessed PFS and OS in patients who received prior CAR-T therapy in the primary efficacy population are shown in Figure 25 and Figure 26, respectively.

A total of 52 out of 155 patients received prior CAR-T therapy, and none of them received further CAR-T therapy after completing their glofit treatment.

Figure 25: Kaplan-Meier plot of IRC-assessed PFS of the primary study efficacy population, with prior CAR-T therapy

Figure 26: Kaplan-Meier plot of IRC-assessed OS of the primary study efficacy population, with prior CAR-T therapy

A13. Please explain why people with cardiovascular disease, HIV and ECOG status >1 were excluded from the trial. Please comment on the impact for treatment of such patients, and any equality issues that may arise.

The NP30179 trial marks the first in-human study for glofitamab. As such, there was no clinical experience at the initiation of the study (i.e. first patient enrolled in February 2017). Early glofitamab trials recommended precautions based on nonclinical studies with glofitamab, and previous clinical experience with CD20- and CD3e-targeting antibodies.

Considering the anticipated mechanism of action for CD3/CD20 T-cell engaging bispecific antibodies, and the risk of cytokine release syndrome (which may present symptoms such as hypotension or hemodynamic instability despite intravenous fluid), patients with a significant or extensive cardiovascular disease history (e.g. New York Heart Association Class III or IV or Objective Class C or D cardiac disease, myocardial infarction within the last 6 months, unstable arrhythmias, or unstable angina) were deemed inappropriate for inclusion.

Additionally, immunosuppressed patients (including those with human immunodeficiency virus [HIV]) were not considered suitable for this trial; therefore, the Company currently lacks data regarding the impact of

immunosuppression on glofitamab's activity. Exploratory analyses were conducted to understand the role of T-cells in glofitamab's activity. Specifically, in an exploratory analysis of baseline peripheral blood biomarkers from Cohort D3 in NP30179, a positive association with response to glofitamab was observed for CD4 T-cells and CD4 effector memory cells (38). However, these analyses offer limited information on the functionality of circulating immune cells, and no response association was observed with CD8 T-cells, regulatory T-cells, and NK cells (38). These findings suggest that the number of available T-cells may play a role in driving response, but other mechanisms are likely involved. In the absence of clinical data for immunosuppressed patients, the impact of T-cell count on glofitamab's activity can be provided based on preclinical data. Although results indicate that T-cell count in a humanised mouse preclinical model did not play an important role on glofitamab glofitamab's activity, clinical data is necessary to confirm the translation to humans.

Similarly, at the time of designing this first in-human trial, patients with performance status other than 0 (i.e. fully active, capable of performing all pre-disease activities without restriction) and 1 (i.e. limited in physically strenuous activity but ambulatory and able to perform light or sedentary work) were deemed ineligible due to the lack of prior clinical experience with glofitamab (39).

In the absence of clinical data in immunosuppressed patients, a discussion on the impact of the number of T-cells on the activity of glofitamab can be provided based on preclinical data. Although results indicate the number of T-cells in a Humanized NSG mice preclinical model did not play an important role on the activity of glofitamab, clinical data is needed for confirmation of how this translates to humans.

As part of glofitamab's ongoing clinical development, the Company plans to generate data for immunosuppressed patients and patients with ECOG 0, 1, and 2 within the glofitamab development program.

A14. Please comment on the observed difference in CR between men and women (Figure 5). Have any checks been performed for possible confounding with other factors (e.g. ECOG status, IPI risk factors)? If possible, please also provide outcome data for ORR, PFS and OS by sex.

In the primary efficacy population (N=155) of the NP30179 trial, there was a greater proportion of male patients (n=101 [65.1%]) compared to female patients (N=54 [34.9%]). In this population, a numerically higher CR rate was observed in female patients, but it is important to note that the 95% confidence interval (CI) overlapped between male and female patients (40).

Table 30 presents an overview of demographics and baseline disease characteristics by gender in the primary safety population (N=154). In this subgroup analysis we observed, a higher proportion of male patients exhibited higher risk factors compared to female patients. For example, a larger percentage of male patients had extranodal disease (65.0% vs. 55.6%) and bulky disease >6 cm (45.0% vs. 35.2%). Additionally, a higher proportion of male patients had HGBCL (8.0% vs. 3.7%) and among the female patients a higher number of trFL patients.

Overall, subgroup analyses of CR demonstrated consistency in treatment effects across various subpopulations, including those defined by gender (40).

Table 30: Summary of key demographic data and disease characteristics by sex (male vs female)

	Primary safety population[a] Glofitamab 2.5/10/30 mg Cohorts D2 (Sub. 2), D3, D5 (N=154)	
	Male (n=100)	**Female (n=54)**
Age (years), n Median Min–Max	100 65.5 21–90	54 71.0 26–86
Age Group (years), n (%) < 65 > 65	100 49 (49.0%) 51 (51.0%)	54 21 (38.9%) 33 (61.1%)
Race, n (%) Asian Black/African American White Unknown	100 5 (2.7%) 4 (2.2%) 153 (82.3%) 24 (12.9%)	54 7 (6.9%) 0 82 (81.2%) 12 (11.9%)
Body Mass Index (kg/m2), n Median Min–Max	98 24.9 17.6–45.1	54 24.5 17.6–44.5
ECOG status, n (%) 0 1 2	 50 (50.0%) 49 (49.0%) 1 (1.0%)	 19 (35.2%) 35 (64.8%) 0

Cancer Histology Subtype II, n (%) DLBCL FL Grade 3B FL Grades 13A HGBCL MCL PMBCL Richter's transformation trFL trMZL Transformed other	 71 (71.0%) 0 0 8 (8.0%) 0 5 (5.0%) 0 16 (16.0%) 0 0	 39 (72.2%) 0 0 2 (3.7%) 0 1 (1.9%) 0 12 (22.2%) 0 0
Ann Arbor Staging, n (%) Stage I Stage II Stage III Stage IV Unknown	100 7 (7.0%) 15 (15.0%) 21 (21.0%) 55 (55.0%) 2 (2.0%)	54 3 (5.6%) 10 (18.5%) 10 (18.5%) 30 (55.6%) 1 (1.9%)
Risk Factors for IPI (non-FL patients only), n (%) 0 1 2 3 4	100 3 (3.0%) 16 (16.0%) 29 (29.0%) 33 (33.0%) 19 (19.0%)	54 1 (1.9%) 8 (14.8%) 16 (29.6%) 22 (40.7%) 7 (13.0%)
Extranodal Disease, n (%) No Yes	100 35 (35.0%) 65 (65.0%)	54 24 (44.4%) 30 (55.6%)
Bulky Disease >6 cm, n (%) No Yes	100 55 (55.0%) 45 (45.0%)	54 35 (64.8%) 19 (35.2%)
Absence of Circulating Malignant Cells, n (%) No Yes Missing	100 3 (3.0%) 20 (20.0%) 77 (77.0%)	54 2 (3.7%) 10 (18.5%) 42 (77.8%)

[a] *Primary safety population: patients with R/R DLBCL (includes DLBCL NOS, trFL, PMBCL, HGBCL; 2 prior lines) from Cohorts D2 Subcohort 2, D3, and D5.*

Additional ORR, PFS, and OS outcomes are presented in Table 31, and from Figure **27** to Figure 30 below.

Table 31: IRC-assessed ORR by sex (male vs female)

	Primary efficacy population Glofitamab 2.5/10/30 mg Cohorts D2 (Sub. 2), D3, D5 (N=155)		
	Patients, n (%)	Patients with event	
		n (%)	95% CI
All	155 (100%)	80 (51.6%)	43.8, 59.3
Sex Male Female	 101 (65.2%) 54 (34.8%)	 46 (45.5%) 34 (63.0%)	 36.2, 55.2 49.6, 74.6

Figure 27: Kaplan-Meier plot of IRC-assessed PFS of the primary study efficacy population, male

[redacted]

Figure 28: Kaplan-Meier plot of IRC-assessed PFS of the primary study efficacy population, female

[redacted]

Figure 29: Kaplan-Meier plot of IRC-assessed OS of the primary study efficacy population, male

[redacted]

Figure 30: Kaplan-Meier plot of IRC-assessed OS of the primary study efficacy population, female

[redacted]

A15. Priority question: Please provide more detail on the treatment duration with glofitamab. Specifically, please provide numbers of patients completing 1 month, 2 months, 3 months etc. of treatment, and data on why patients stopped receiving treatment (e.g. numbers with progression and numbers with adverse events at each month).

The disposition of patients on- and off-treatment by month (CCOD June 2022) is shown in Figure 31.

The reasons for treatment discontinuation by month for patients who received glofitamab are shown in Table 32. Please note that one patient discontinued treatment in Month 7 due to treatment completion, which is why the number of patients on treatment in Month 7 is 43 instead of 44.

Figure 31: Patients on- and off-treatment by month (CCOD 15 June 2022)

Table 32: Reasons for study treatment discontinuation by month (CCOD 15 June 2022)

Study duration	<1 month	Month 1	Month 2	Month 3	Month 4	Month 5	Month 6	Month 7
Patients on glofitamab treatment, n	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Reasons for study treatment discontinuation (events per month)								
Progressive disease	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Adverse event	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Death	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Lack of efficacy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Physician decision	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Protocol deviation	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Symptomatic deterioration	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Withdrawal by subject	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Other/not recorded	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

A16. Page 90 of the CS states

“[redacted]”. Please provide reasons for why patients with a CR discontinued treatment before receiving 12 cycles.

In the NP30179 trial, [redacted] patients in the primary efficacy population achieved a CR but received fewer than 12 cycles due to glofitamab treatment discontinuation. The reasons for discontinuation by month are shown in Table 33 below.

Table 33: Reasons for study treatment discontinuation by month, for patients with a CR who underwent less than 12 glofitamab cycles (CCOD 15 June 2022)

Study duration	<1 month	Month 1	Month 2	Month 3	Month 4	Month 5

Patients on glofitamab treatment, n	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Reasons for study treatment discontinuation (events per month)						
Progressive disease	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Adverse event	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Death	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Lack of efficacy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Physician decision	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Protocol deviation	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Symptomatic deterioration	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Withdrawal by subject	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Other/not recorded	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Section A: Indirect treatment comparisons (ITCs)

A17. Priority question: In several of the MAIC adjusted analyses the 95% confidence interval is similar in extent, or sometimes narrower, than for the unadjusted analysis. This is particularly apparent in Section B.2.9.2.2.2, but is also the case elsewhere. Given the decline in effective sample size when performing an adjusted MAIC obtaining a narrower confidence interval after adjustment is statistically highly implausible.

a. Please check that the results of indirect treatment comparisons have been reported correctly.

The Company confirms that all indirect treatment comparison results have been correctly reported in the company submission.

b. Please check that appropriate methods have been used to calculate confidence intervals (such as sandwich estimators) and provide details of the methods used.

The Company confirms that appropriate methods have been used for the estimation of confidence intervals in all presented results. Specifically, two main methods were used for the estimation of confidence intervals in the Company's ITCs, i.e. "regular" standard errors (from the coxph() function of the R package survival) and bootstrapping for the unweighted and weighted analyses, respectively. These are described in Section 3 of the ITC report.

For the weighted analyses, CIs for relative treatment effects of interest were estimated using bootstrapping, as cluster-robust SEs can be biased for ORs

and should be used with caution ((41)). Accordingly, bootstrapping was used for both binary and survival outcomes, for consistency, as it is a simple and straightforward method to implement and has been shown to be valid in many cases through several simulation studies ((42), (43), (41)). Furthermore, bootstrapping was used for the weighted analyses as it can be considered somewhat preferable to robust standard errors, in that it allows to sample the uncertainty inherent to the estimation of the matching/balancing weights without requiring to resort to any distributional assumptions. Also, it was found to be more suited to small sample sizes, as robust SEs are reported to underestimate variability when the ESS is small ((44, 45)). Accordingly, NICE TSD 18 suggests bootstrapping as a valid method to incorporate all sources of uncertainty in MAICs.

The Company would like to point out that the approach used for this submission to estimate CIs for weighted and unweighted analyses has also been applied in several previous TAs (e.g. TA643 and more recently ID3931, TA of mosunetuzumab for treating relapsed or refractory follicular lymphoma - ongoing) (46) and it was accepted by both the respective EAGs and Committees.

c. If errors have been made, please supply corrected results.

Please see response to Question A17a.

d. If results are correct, please provide some commentary on why this unexpected result might have occurred.

The Company believes that the discrepancy raised by the EAG may be due to having employed two different methods for the estimation of the confidence intervals between the unweighted and weighted analyses. The Company confirms that if the same bootstrapping method used for the MAIC weighted analyses had also been used for the unweighted analyses, this would have resulted in narrower confidence intervals for the unweighted analyses compared to the ones obtained using regular standard errors. The bootstrapping method employed for the weighted analyses was not used in the case of the unweighted analyses primarily for computational efficiency reasons (due to the high number of endpoints analyzed), also considering that the unweighted results are normally only presented for comparative purposes. In fact, the weighted analyses provide all the information that should be of primary interest for decision making.

A18. Priority question: When performing adjusted indirect comparisons, it is usual to perform multiple scenario analyses

adjusting for different factors, to balance between number of factors adjusted for and effective sample size. It appears that only one such scenario analysis (other than the base cases) has been reported (in appendix D, ITC report).

a. Please provide summary results of all scenario analyses (other than the base case) performed for the indirect comparisons. Please summarise the factors adjusted for, the effective sample size and the effect estimate, confidence intervals and any measures of goodness of fit (AIC or BIC) in each case.

The Company would like to clarify that summary results, as well as diagnostic and methodological information, for all the scenario analyses conducted that were deemed relevant and informative have been already provided in the ITC report submitted as part of Appendix D. In this respect, the Company would also like to clarify that the main criteria considered to decide on the nature and number of sensitivity analyses that would involve a change in the list of factors considered for adjustment were the following (as already explained in Section 3.1.5 of the report):

1. The need to exclude certain covariates (primarily those identified as low-priority) to maximise the bias/variance trade-off and have an acceptable ESS in the base case scenario, which would warrant exploring the impact of their re-inclusion on the results
2. Uncertainty regarding how certain covariates were defined in the comparator data source, or when multiple alternative definitions were available, which would warrant exploring the impact of using alternative definitions for these covariates on the results

The Company believes that, in the context of ITCs, generating goodness of fit statistics (such as AIC and BIC) for different scenario analyses does not provide any particularly informative insights, so these metrics have not been estimated. This is because the criteria to judge the suitability of the different scenarios should be mainly based on their relative ability to achieve covariate balance (without resulting in weight instability). In this respect, all the relevant information to assess these two factors is already provided in the submitted ITC report.

b. If no other scenario analyses were performed, please provide a justification for why that was the case.

In line with the approach described in the response to question A18a, only 1) the MAIC vs axi-cel using data from the ZUMA-1 study and 2) the propensity score analysis versus BR using data from the GO29365 study, would warrant

exploring the use of different factors (in number and/or type) in sensitivity analyses.

In the case of the MAIC versus axi-cel, two main analyses were conducted:

1. The base case analysis, which only controlled for all available high-and medium- priority factors, to maximize the bias/variance tradeoff
2. A sensitivity analysis which included all available covariates (including low-priority ones)

The ESS of the base-case analysis was borderline acceptable and that of the sensitivity analysis was already very low. The use of a different definition for refractory to last line was explored, but it would only lower the ESS even further (<10), so these analyses were deemed uninformative. Controlling for both double/triple hit and HGBCL at the same time would result in collinearity issues, considering that these generally identify the same patients. Controlling for double / triple hit instead of HGBCL would have made no clinical sense given how these factors were defined in ZUMA-1 (refer to Sections 3.1.2 and 4.1.1 of the ITC report for the reasons).

In the case of the PSA versus BR based on GO29365 data, four analyses were reported:

1. IPTW (ATE weights), using all covariates
2. Matching method yielding the best covariate balance, using all covariates
3. IPTW (ATE weights), using only high- and medium-priority covariates
4. Matching method yielding the best covariate balance, using only high- and medium-priority covariates

None of these analyses yielded satisfactory covariate balance (all the relevant diagnostic information is reported in Section 4.2.1 or Appendices I-K of the ITC report). For this reason, only unadjusted analyses were conducted and reported for transparency. No analyses exploring the impact of different covariate definitions were needed, as we had access to IPDs for both trials and we could thus align these prior to conducting any adjustment, as per good practices. Controlling for double / triple hit or HGBCL was not possible, as only information on double / triple hit HGBCL was reported in GO29365 and no patients were found to have HGBCL in the patient cohort considered in the analyses (i.e. these factors identify the same patients). Also the refractory to chemotherapy variable was very highly correlated with refractory to any line leading to very large SEs in the PS generating model if both were used, hence only the latter was included as it was flagged to be of higher prognostic relevance.

In the cases of the MAIC versus BR based on Hong et al 2018 and the PSA versus Pola-BR based on GO29365 data, only the respective base case analyses (with respect to the factors considered for adjustment) were reported. This was done as these already maximized the bias/variance tradeoff whilst controlling for all priority prognostic factors that were feasible (see Sections 4.1.2 and 4.2.2 of the ITC report). Conducting scenario analyses by excluding confounding factors that were identified as low priority wouldn't have provided any particularly more informative scenarios. This is because it would have resulted in a higher ESS but at the cost of unnecessarily introducing bias in the analyses, which was deemed not to be beneficial overall given that the ESS achieved in the base case scenarios were already rather acceptable.

For the MAIC vs BR, the definitions of all reported confounding factors were clear enough to allow the corresponding variable definitions for the NP30179 patient cohort used for the comparison to be properly aligned prior to the matching. No sensitivity analyses could be conducted to explore the impact of enrolling patients with only 1 prior line (these were excluded in NP30179) or with ECOG >1 (ECOG 0-1 split not reported, and no ECOG >1 patients included in NP30179) in Hong et al 2018. The Company could not think of other sensitivity analyses that may have been considered given the available data sources.

For the PSA versus Pola-BR, we had access to IPDs for both trials and we could thus align the baseline characteristic definitions across the two treatment arms prior to conducting any adjustment, as per good practices and in line with what was done for the PSA vs BR. Controlling for double / triple hit and HGBCL at the same time was not possible due to collinearity issues, and controlling for double / triple hit instead of HGBCL would have made no clinical sense given that only information on double / triple hit HGBCL was reported in GO29365 (see the above point for Yescarta). Again, the refractory to chemotherapy variable was very highly correlated with refractory to any line leading to very large SEs in the PS generating model if both were used, hence only the latter was included as it was flagged to be of higher prognostic relevance.

The Company would like to clarify that additional scenario analyses where fewer factors were controlled for could have been performed for the MAIC versus Yescarta and the PSA versus BR to improve sample sizes. However, covariate balance in these comparisons would have been worse than what was originally presented and therefore more likely to be subject to higher bias.

The Company would also like to clarify that, strictly speaking, the submitted ITC report does not only report the results of the base case scenario (IPTW) for the PSA versus Pola-BR, as a sensitivity analysis using a different balancing method (full-matching) is also described. This was conducted to align with the recommendations in TSD 17 (Q1 of the QuEENS checklist). A similar point also applies to the PSA analyses vs BR described above.

Despite not being any more informative than the base case results described in the ITC report, the Company decided to also run the PSA and MAIC vs Pola-BR and BR, respectively, using a reduced set of adjustment factors (only those identified as high- and medium-priority). This was done for full transparency, although the Company would like to reinforce that their results are inevitably subject to higher bias compared to the base case analyses.

The same methodologies as described in the ITC report and in the responses to the clarification questions was employed. Full diagnostic information and results are provided in Figure 32 to Figure 53, and Table 34 to Table 50 below.

PSA vs Pola-BR (GO29365) using high- and medium-priority covariates only

Figure 32: Propensity score distribution before matching

Figure 33: Propensity score distribution after matching

Figure 34: IPT weights and stabilised IPT weights distribution

Figure 35: Love plots for covariate balance after full matching and IPTW

Figure 36: Covariate distribution balance plots

Figure 37: KM plot of OS for the matched sample

Figure 38: KM plot of OS for IPTW sample

Figure 39: KM plot of IRC-assessed PFS for the matched sample

Figure 40: KM plot of IRC-assessed PFS for IPTW sample

Figure 41: KM plot of INV-assessed PFS for the matched sample

Figure 42: KM plot of INV-assessed PFS for IPTW sample

Figure 43: KM plot of IRC-assessed DOR for the matched sample

Figure 44: KM plot of IRC-assessed DOR for IPTW sample

Figure 45: KM plot of INV-assessed DOR for the matched sample

Figure 46: KM plot of INV-assessed DOR for IPTW sample

Figure 47: KM plot of IRC-assessed DOCR for the matched sample

Figure 48: KM plot of IRC-assessed DOCR for IPTW sample

Figure 49: KM plot of INV-assessed DOCR for the matched sample

Figure 50: KM plot of INV-assessed DOCR for IPTW sample

Table 34: Summary of PSA results for OS

Method for estimating HR	HR (95% CI)
Full matching plus covariate adjustment	[redacted]
Inverse probability of treatment weighting	[redacted]

Table 35: Summary of PSA results for IRF-assessed PFS

Method for estimating HR	HR (95% CI)
Full matching plus covariate adjustment	[redacted]
Inverse probability of treatment weighting	[redacted]

Table 36: Summary of PSA results for INV-assessed PFS

Method for estimating HR	HR (95% CI)
Full matching plus covariate adjustment	[redacted]
Inverse probability of treatment weighting	[redacted]

Table 37: Summary of PSA results for IRF-assessed DOR

Method for estimating HR	HR (95% CI)
Full matching plus covariate adjustment	[redacted]
Inverse probability of treatment weighting	[redacted]

Table 38: Summary of PSA results for INV-assessed DOR

Method for estimating HR	HR (95% CI)
Full matching plus covariate adjustment	[redacted]

Inverse probability of treatment weighting	[redacted]

Table 39: Summary of PSA results for IRF-assessed DOCR

Method for estimating HR	HR (95% CI)
Full matching plus covariate adjustment	[redacted]
Inverse probability of treatment weighting	[redacted]

Table 40: Summary of PSA results for INV-assessed DOCR

Method for estimating HR	HR (95% CI)
Full matching plus covariate adjustment	[redacted]
Inverse probability of treatment weighting	[redacted]

Table 41: Summary of PSA results for IRF-assessed ORR

Method for estimating OR	OR (95% CI)
Full matching plus covariate adjustment	[redacted]
Inverse probability of treatment weighting	[redacted]

Table 42: Summary of PSA results for (INV-assessed) OR

Method for estimating OR	OR (95% CI)
Full matching plus covariate adjustment	[redacted]
Inverse probability of treatment weighting	[redacted]

Table 43: Summary of PSA results for IRF-assessed CR

Method for estimating OR	OR (95% CI)
Full matching plus covariate adjustment	[redacted]
Inverse probability of treatment weighting	[redacted]

Table 44: Summary of PSA results for INV-assessed CR

Method for estimating OR	OR (95% CI)
Full matching plus covariate adjustment	[redacted]

Inverse probability of treatment weighting	[redacted]

Table 45: Summary of PSA results for discontinuation due to AEs

Method for estimating OR	OR (95% CI)
Full matching plus covariate adjustment	[redacted]
Inverse probability of treatment weighting	[redacted]

MAIC vs BR (Hong et al 2018) using high- and medium-priority covariates only

Table 46: Summary of baseline characteristics

Variable	Glofitamab unweighted (n=139)	Glofitamab weighted (ESS=99.1)	Bendamustine plus rituximab (n=58)
Age > comparator median (%)	[redacted]	[redacted]	[redacted]
Ann Arbor Stage III–IV (%)	[redacted]	[redacted]	[redacted]
High LDH (%)	[redacted]	[redacted]	[redacted]
Extranodal sites ≥2 (%)	[redacted]	[redacted]	[redacted]
IPI 3–5 (%)	[redacted]	[redacted]	[redacted]
Refractory to all lines (%)	[redacted]	[redacted]	[redacted]
>2 prior therapies (%)	[redacted]	[redacted]	[redacted]

Figure 51: Histograms of MAIC weights

[redacted]

Figure 52: KM plot of OS

[redacted]

Figure 53: KM plot of INV-assessed PFS

[redacted]

Table 47: Summary of MAIC results for OS

Method for estimating HR	HR (95% CI)
Bootstrap median (95% percentile CI) weighted Cox model	[redacted]
Bootstrap median HR (95% BCa CI) weighted Cox model	[redacted]

Table 48: Summary of MAIC results for (INV-assessed) PFS

Method for estimating HR	HR (95% CI)
Bootstrap median (95% percentile CI) weighted Cox model	[redacted]
Bootstrap median HR (95% BCa CI) weighted Cox model	[redacted]

Table 49: Summary of MAIC results for (INV-assessed) ORR

Method for estimating OR	OR (95% CI)
Bootstrap median OR (95% percentile CI) weighted logistic regression model	[redacted]
Bootstrap median OR (95% BCa CI) weighted logistic regression model	[redacted]

Table 50: Summary of MAIC results for (INV-assessed) CR

Method for estimating OR	OR (95% CI)
Bootstrap median OR (95% percentile CI) weighted logistic regression model	[redacted]
Bootstrap median OR (95% BCa CI) weighted logistic regression model	[redacted]

A19. Priority question: Please provide the results of the propensity score analysis comparing glofitamab with the BR arm of the GO29365 trial, which was excluded from the ITC report. Specifically, please supply a version of Table 2 in the ITC report (Appendix D) with the requested analysis included, and adjusted and unadjusted Kaplan-Meier curves for OS and PFS.

Section 4.2.1 of the ITC report provides the results of the propensity score analysis (PSA) vs the BR arm of the G029365 study.

The population used for indirectly comparing glofitamab with BR was the randomised DLBCL cohort from GO29365 (n=40).

To ensure that patient cohorts used for the analyses were as homogeneous as possible before performing any indirect comparisons, a filtering procedure was employed. This involved applying common inclusion and exclusion criteria, which excluded patients with histologies that were not compatible with the glofitamab cohort (e.g. "EBV+ DLBCL, NOS", "T-CELL/HISTIOCYTE-RICH LARGE B-CELL LYMPHOMA", and "FOLLICULAR LYMPHOMA"), excluded patients with ECOG PS ≥2, and excluded patients who had only received one prior line of therapy from the BR cohort (to align with the inclusion/exclusion criteria of NP30179). Additionally, patients with PMBCL and HGBCL histology (except HGBCL NOS) were excluded from the glofitamab cohort since they were not present in the BR cohort (to align with the inclusion/exclusion criteria of GO29365).

This resulted in 140 patients in the glofitamab arm and 21 patients in the BR arm.

Potentially prognostic baseline characteristics of these patient cohorts and their imbalances prior to any adjustment are reported in Table 51. As can be noticed from Table 51, several baseline characteristics were imbalanced prior to any adjustment between the glofitamab and bendamustine plus rituximab groups (aSMD >0.1), with the exception of ECOG PS, Ann Arbour stage, extranodal disease, IPI, and cell type of origin (age and refractory to first line were borderline balanced).

Table 51: Summary of baseline characteristics (PSA BR)

Variable	Glofitamab (n=140)		Bendamustine plus rituximab (n=21)		aSMD	VR
	Mean	SD	Mean	SD		
Age (mean)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ECOG PS (1 vs 0) (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
Ann Arbor Stage III/IV (Yes) (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
High LDH (Yes) (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
Extranodal disease (Yes) (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	

IPI (3–5) %	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
Refractory to first line (Yes) (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
Refractory to any line (Yes) (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
Refractory to last line (Yes) (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
Refractory to ASCT (Yes) (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
Prior therapies, >2 (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
Size of the largest node lesion [cm] (mean)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Refractory to any prior anti-CD20 mAb and anthracycline (Yes) (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
Refractory to any prior anti-CD20 mAb containing regimen (Yes) (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
Time since last treatment, months (mean)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cell type GCB (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
Cell type ABC/non-GCB (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
Bone marrow involvement (Yes) (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
Prior ASCT (yes) (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	

Unsuccessful attempts to match covariates when using either optimal pair or IPTW matching methods, indicate that the results of any adjusted outcome analysis are likely to be highly unreliable. For this reason, and for transparency, the results from unadjusted analyses are provided, which should be interpreted with extreme caution in light of the several limitations highlighted above. Given the aforementioned limitations with the BR PSA, the results from the MAIC analyses were preferred for use in the submission base case comparison with BR.

Results

The results from the PSA comparison with the unadjusted BR cohort from G029365 can be seen in Sections 4.2.1-12 of the ITC report.

After filtering, several imbalances in potentially prognostic baseline characteristics were noted. Prior to any adjustment, only 21 patients were included in the BR arm. Adjustment attempts to balance these characteristics, through full matching or ITPW, resulted in unacceptably low effective sample sizes (ESS <10), and poor covariate balance. With extremely small sample sizes in the BR arm after adjustment, it is not appropriate to interpret the results of the analyses based on the adjusted populations.

A20. Please clarify for which comparator studies data on prognostic factors and effect modifiers was missing, the extent of missingness for each variable and how was this handled. Please discuss how the imputation of missing information may impact the ITC results.

Handling of missing data

The Company would like to clarify that a full explanation of the general methodology employed to handle missing data in MAICs and PSAs can be found in Sections 3.1.2.2 and 3.2.2.2 of the submitted ITC report, respectively. This is briefly summarised below:

In the case of missing values for categorical covariates from comparator studies (used in MAICs), the proportions for the categories of that covariate were renormalised without the missing data. In the case of missing values for categorical or continuous covariates in NP30179 (or GO29365), the values were imputed based on the most frequently occurring value (mode) or the mean value without the missing data points in the data set, respectively, so that the patients did not have to be dropped from the analysis. The imputation was performed prior to 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 (e.g. for the cell of origin type), in which case missing was treated as a separate category in its own right for both treatments rather than imputed. In some MAICs, it was not possible to control for ECOG PS 2 due to the NP30179 inclusion criteria (all patients had ECOG PS<2). In instances where ECOG PS 2 was reported in comparator studies, this could have either been imputed as ECOG PS 1 (maximally conservative assumption), or ECOG may have been excluded from the analysis (depending on whether the proportion was low or

high, respectively or how the split between ECOG PS values was reported, e.g. 0-1 and 2-4).

Extent of data missingness and implication of data imputations on ITC results

Full information on what factors, among those deemed relevant for the ITCs based on clinical / medical feedback (see Section 3.1.2.1 of the ITC report), were reported for the comparator studies eventually considered suitable for the MAICs can be found in the Clinical SLR and MAIC Feasibility Assessment report (see response to question A1).

- Yescarta (ZUMA-1) (Table 13)
- BR (Hong et al 2018) (Table 14)

Among all the relevant confounding factors reported in the above mentioned publications, missing values were only reported for one factor (cell of origin) in Hong et al 2018 and two factors (cell of origin and bone marrow involvement) in ZUMA-1. The extent of missingness was low for bone marrow involvement in ZUMA-1 (~6.9%) and low to moderate for cell of origin (~5.5% and ~39.7% in ZUMA-1 and Hong et al 2018, respectively). In the absence of protocol mandated cell of origin testing, missing data for this parameter is not necessarily unexpected based on reported adherence to guidelines-recommended diagnostic testing in the real world clinical setting (47). As both factors were flagged as low priority, the extent of their missingness was generally low and, when not, missingness was treated as a separate category in the adjustment; the Company does not believe that covariate data missingness would have a significant impact on the ITC results.

In the glofitamab patient population that was considered for the ITCs (N = 155), information was not available for the following factors:

- Ann Arbor Stage (4 patients)
- High LDH (2 patients)
- Double-/triple-hit lymphoma (1 patient)
- Bulky disease (1 patient)
- Time since completion of previous therapy (5 patients)
- Cell type of origin (24.5% of the patients)

In the Pola-BR patient population that was considered for the ITCs (N =84), information was not available for the following factors:

- High LDH (1 patient)
- HGBCL histology (1 patient)
- Cell type of 45/84 (53.5% of the patients)

Again, the rate of missingness was generally very low for high- and medium-priority confounding factors and, when not (cell type of origin - low priority factor), missingness was treated as a separate category in the adjustment. Therefore, the Company does not believe that covariate data missingness would have a significant impact on the ITC results.

A21. For the comparisons where a propensity score analysis was performed the preferred target estimand was the average treatment effect (ATE). Given that the glofitamab cohort varied depending on which comparator was being matched, could the Company clarify and justify their methodology.

The NICE TSD 17 guideline recommends that “The treatment effect which is typically of interest in NICE TAs is the ATE” (NICE TSD 17, page 15). Accordingly, ATE was selected as our preferred target estimand for comparisons based on propensity score analyses (as the availability of both comparator IPDs allowed us to select a target estimand), where feasible (i.e. where satisfactory covariate balance could be achieved by using a method allowing for the estimation of the ATE). This is unfortunately not possible where IPDs are available only for one treatment, as this dictates what target estimand can be computed.

Furthermore, the Company would like to clarify that the exclusion of patients from either the glofitamab or comparator cohorts used for the comparisons due to non-overlapping eligibility criteria is not expected to play any major role in the interpretation/generalisability of the results. In fact, only non-overlapping eligibility criteria with respect to the identified confounding factors of interest for the ITCs were considered. Had the identified patients not been excluded from the cohorts used for the comparisons, they would have most likely been assigned a weight of zero or very close to, which would have made their impact on the final outcomes negligible compared to including them. The Company also would like to clarify that this general approach to ITCs has also been applied in previous TAs (the last of which was ID3931, TA of mosunetuzumab for treating relapsed or refractory follicular lymphoma - ongoing) and was not challenged by either the EAG or the Committee.

Section B: Systematic reviews

B1. Please supply complete search strategies for all databases searched for the following systematic reviews described in the submission:

a. Cost-effectiveness searches (Appendix H)

Details from the original SLR (conducted September 2016) is described below. Details from the SLR update 1 (conducted August 2021) and SLR update 2 (conducted September 2022) were previously detailed in Appendix H.

B1a.1 Methodology – Cost-effectiveness SLR

B1a.1.1 Eligibility criteria

This SLR focused on health economic studies assessing 1L treatment of DLBCL as defined by the PICOS outlined in Table 52.

Table 52: Scope of review defined by PICOS criteria

Criteria	Inclusion
Population	Studies must assess patients with newly diagnosed diffuse large b-cell lymphoma
Interventions	Studies can include any pharmacological intervention used as first-line treatment
Comparisons	No restrictions
Outcomes	Studies must evaluate at least one of the following endpoints in combination with cost outcomes: Clinical outcomes Utilities Quality-adjusted life-years Resource use
Study designs	Studies must be one of the following: Economic evaluations Cost-effectiveness analyses Cost-utility analyses Cost-benefit analyses Cost-minimization analyses Cost of illness analyses Budget impact analyses Economic studies based on clinical studies Modeling studies

Note – no language limitations have been set, however, only English language papers will be included for data extraction (after identification of non-English studies, assessment of eligibility will be conducted to complete a list of potentially relevant non-English studies); studies presented as conference presentations will be listed and will only be included for data extraction if they report sufficient detail.

B1a.1.2 Information sources

- National Health Service Economic Evaluation Database (NHS EED)
    - Discontinued in 2014 – no search executed

- International Network for Agencies for Health Technology Assessment (INAHTA)
    - 28 results searching the 5 terms
    - 10 results MESH term Lymphoma, Large B-Cell, Diffuse
    - 73 results MESH term Lymphoma, Non-Hodgkin
    - Total results = 82

- National Institute for Health and Care Excellence (NICE)
    - Search terms to include: dlbcl OR "large cell lymphoma" OR "diffuse large b cell lymphoma" OR "non-hodgkin lymphoma" OR "non-hodgkin's lymphoma"
    - Total results =5

- National Institute for Health Research (NIHR)
    - NIHR HTA database is funded by the UK National Institute for Health Research (NIHR) and is currently produced by the Centre for Reviews and Dissemination (CRD); therefore this information is in the same database searched for INAHTA (above)

- Canadian Agency for Drugs and Technologies in Health (CADTH)
    - HTA Database Canadian Search Interface searched
    - Search terms to include: dlbcl OR "large cell lymphoma" OR "diffuse large b cell lymphoma" OR "non-hodgkin lymphoma" OR "non-hodgkin's lymphoma"
    - Total results = 10

B1a.1.3 Study selection

All title and abstracts identified through the literature searches were scanned by two investigators independently and in duplicate to assess eligibility according to the PICOS selection criteria corresponding with the research question.

Once title and abstract screening was completed the investigators reconciled any discrepancies between studies selected as eligible as well as reasons for exclusion. If a consensus was not reached, a third investigator provided arbitration. The same two investigators independently screened full texts of all articles deemed eligible for inclusion at the title and abstract screening phase. No articles were excluded at this stage for lack of reporting on an outcome of interest.

Once full-text screening was complete the investigators reconciled any discrepancies between included studies as well as reasons for exclusion. If a consensus was not reached, a third investigator provided arbitration. This

resulted in the final list of included studies that proceeded to the data extraction phase.

A Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram are provided in Figure 54 and Figure 55 show a graphical representation of the abstract screening and full text screening processes for all systematic reviews.

Data extraction

Data for the SLR of health economic studies (research question 3) was extracted into the Report Tables by the two investigators for the final list of included studies. Any discrepancies observed were resolved by consensus. A third investigator provided arbitration as needed.

Information extracted included: model type, disease states and pathway, cycle length, type of analysis, outcomes assessed, model assumptions, input data and data sources, and results.

Study quality

Study quality of health economic studies was assessed according to the Consolidated Health Economic Evaluation Reporting Standards (CHEERS) checklist (48).

B1a.1.4 Search strategies

Table 53: Search strategy for Embase; SLR of health economic studies

Database: Embase (1974 to 2016 May 27) Date searched: May 31, 2016		
1	exp diffuse large b-cell lymphoma/	26112
2	(((bcell or b-cell or b cell) adj3 lymphoma*) or ((diffuse adj3 (bcell or b-cell or b cell)) adj3 lymphoma*)).ti,ab.	37585
3	(DLBCL or anaplastic large cell lymphoma* or disseminated large cell lymphoma* or intravascular large b cell lymphoma* or large b cell lymphoma* or large cell diffuse lymphoma or large cell follicular lymphoma or large cell ki-1 lymphoma or primary cutaneous anaplastic large cell lymphoma or b cell non-hodgkin* or diffuse mixed lymphoma or immunoblastic lymphoma or aggressive non-hodgkin's lymphoma).ti,ab.	25528
4	1 or 2 or 3	50387
5	socioeconomics/	120867
6	cost benefit analysis/	71710
7	cost effectiveness analysis/	114285
8	cost of illness/	16370
9	cost control/	55394
10	economic aspect/	107333
11	financial management/	106183
12	health care cost/	149585
13	health care financing/	12012

14	health economics/	35441
15	hospital cost/	16185
16	(fiscal or financial or finance or funding).tw.	127884
17	cost minimization analysis/	2806
18	cost adj estimate$	2410
19	cost adj variabl$	180
20	unit adj cost$	3092
21	exp economic evaluation/	242441
22	exp health care cost/	233515
23	pharmacoeconomics/	6280
24	(econom$ or cost or costs or costly or costing or price or prices or pricing or pharmacoeconomic$).ti,ab.	735966
25	(expenditure$ not energy).ti,ab.	28508
26	budget$.ti,ab.	28370
27	5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26	1242201
28	4 and 27	687

Table 54: Search strategy for MEDLINE®; SLR of health economic studies

Database: Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) (1946 to Present) Date searched: May 31, 2016		
1	exp diffuse large b-cell lymphoma/	16359
2	(((bcell or b-cell or b cell) adj3 lymphoma*) or ((diffuse adj3 (bcell or b-cell or b cell)) adj3 lymphoma*)).ti,ab.	25890
3	(DLBCL or anaplastic large cell lymphoma* or disseminated large cell lymphoma* or intravascular large b cell lymphoma* or large b cell lymphoma* or large cell diffuse lymphoma or large cell follicular lymphoma or large cell ki-1 lymphoma or primary cutaneous anaplastic large cell lymphoma or b cell non-hodgkin* or diffuse mixed lymphoma or immunoblastic lymphoma or aggressive non-hodgkin's lymphoma).ti,ab.	15546
4	1 or 2 or 3	38997
5	economics/	26713
6	"costs and cost analysis"/	44102
7	cost allocation/	1980
8	cost-benefit analysis/	66016
9	cost control/	20853
10	cost savings/	9770
11	cost of illness/	20536
12	cost sharing/	2112
13	deductibles/	1528
14	medical savings accounts/	497
15	health care costs/	30848
16	direct service costs/	1093
17	drug costs/	13289
18	employer health costs/	1077
19	hospital costs/	8832
20	health expenditures/	15322
21	capital expenditures/	1971

22	value of life/	5500
23	exp economics, hospital/	21462
24	exp economics, medical/	13866
25	economics, nursing/	3937
26	economics, pharmaceutical/	2619
27	exp "fees and charges"/	28214
28	exp budgets/	12827
29	low adj cost	33013
30	high adj cost	9715
31	health?care adj cost$	6276
32	(fiscal or funding or financial or finance).tw.	100040
33	cost adj estimat$	1974
34	cost adj variable	37
35	unit adj cost$	1840
36	(economic$ or pharmacoeconomic$ or price$ or pricing).tw.	209640
37	economics/	26713
38	exp “costs and cost analysis”/	197903
39	exp economics, hospital/	21462
40	economics, medical/	8872
41	economics, nursing/	3937
42	economics, pharmaceutical/	2619
43	(economic$ or cost or costs or costly or costing or price or prices or pricing or pharmacoeconomic$).ti,ab.	553068
44	(expenditure$ not energy).ti,ab.	21532
45	value for money.ti,ab.	1179
46	budget$.ti,ab.	21964
47	5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43 or 44 or 45 or 46	771981
48	4 and 47	236

B1a.2 Results – Cost-effectiveness SLR

B1a.2.1 PRISMA flow diagram

Figure 54. Modified PRISMA flow-chart (RQ3 – Bibliographic DBs)

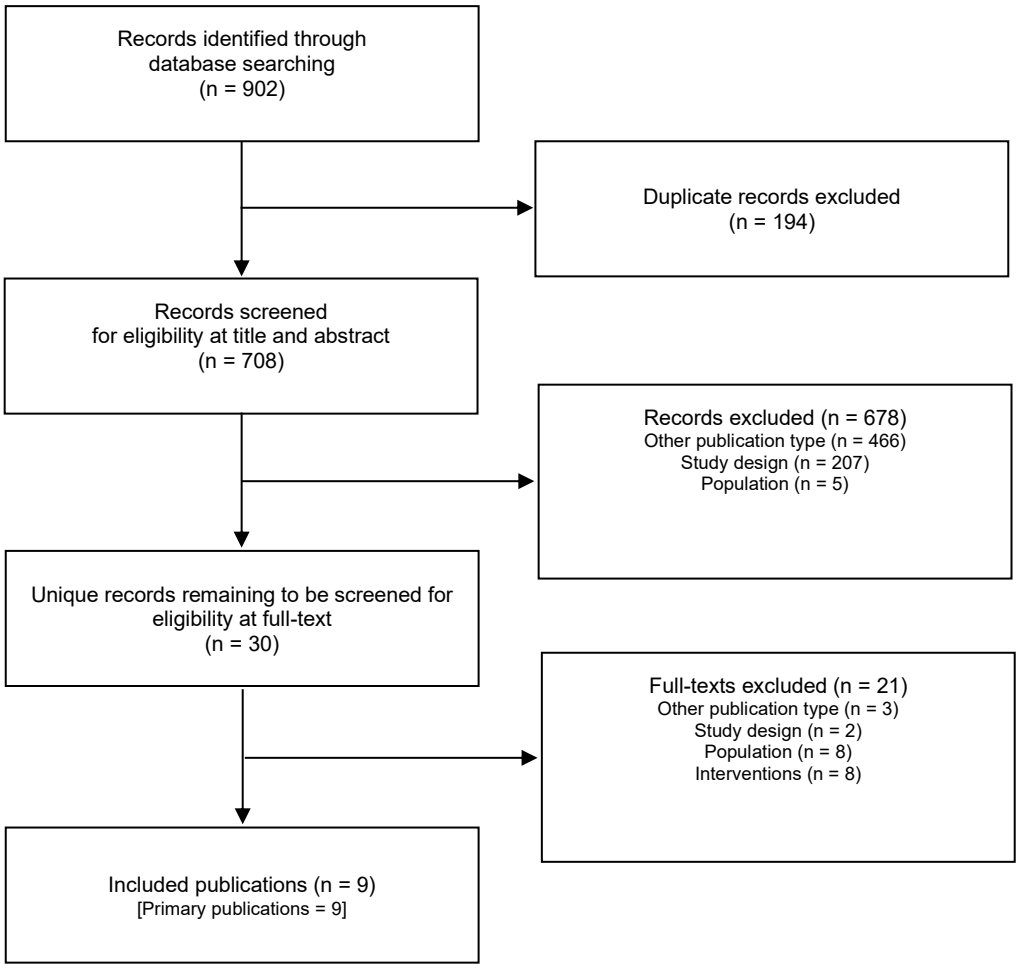
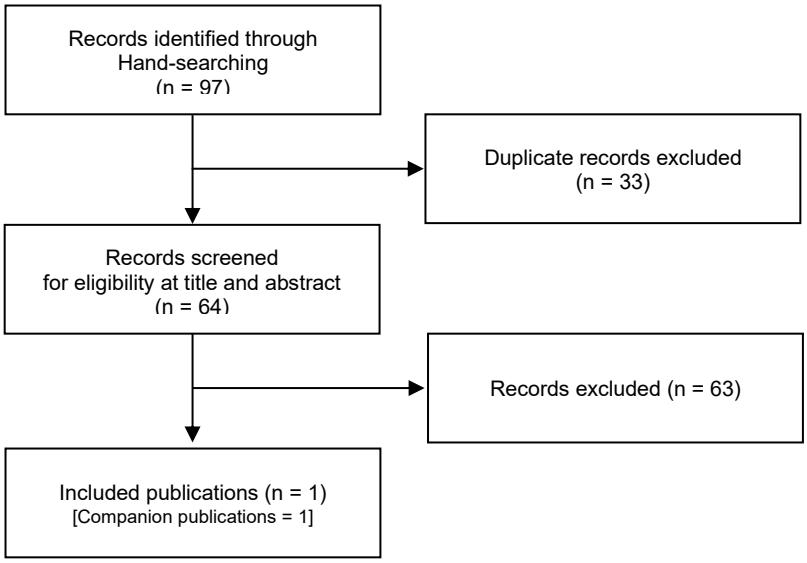


Figure 55. Modified PRISMA flow-chart (RQ3 – Grey lit)



B1a.2.2 Findings of the literature review

The literature search identified 902 citations with 708 titles and abstracts included for screening after duplicates were removed. Six hundred and seventy-eight citations were excluded at the abstract screening phase, leaving 30 records for full-text review. Of these records, 21 were included (9 primary publications and no companion publications) (49-57). An additional 97 records were identified through hand searches, after screening, no additional citations were included. One companion citation was identified that linked to an already included primary publication

The nine included studies are listed in Table 55. One cost-benefit analysis (CBA) took place in the United States using a societal perspective (50), one cost analysis (CA) took place in Canada using a public payer perspective (57), three cost-effectiveness analyses (CEA) took place in Canada (56), the United States (52) and Italy (51) using public payer perspectives, and four studies used a combination of CEA and cost utility analysis (CUA). These studies took place in Canada (55), United States (54), France (49) and the Netherlands (53) using a societal perspective in the latter three studies, with the perspective not reported in the Canadian study.

Table 55: Distribution of economic studies

Bibliographic DBs (published)	
Primary publication	**Companion publications**
Danese, Med Care, 2016	
Khor, BMC Cancer, 2014	Khor, INAHTA, 2014
Griffiths, Cancer, 2012	
Johnston, Value Health, 2010	
Lee, Value Health, 2008	
Ferrara, Clin Drug Invest, 2008	
Best, Value Health, 2005	
Hornberger, Cancer, 2005	
Groot, Eur J Haematol, 2005	

B1a.2.3 Decision problem

The primary intervention of interest in most studies (49, 51, 53-57) included rituximab plus cyclophosphamide, doxorubicin, vincristine and prednisone (R-CHOP) chemotherapy versus CHOP alone for the treatment of DLBCL in patients across varying age groups, although some studies also examined these strategies for additional populations, or examined other/ additional comparators for the DLBCL population. Danese et al (50) were not specific regarding the type of chemotherapy examined in their study, although the

authors did examine the net benefit of rituximab and chemotherapy versus chemotherapy alone in patients diagnosed with DLBCL, follicular lymphoma and chronic lymphocytic leukemia. Griffiths et al (52) examined rituximab and CHOP/ cyclophosphamide, mitoxantrone, vincristine, and prednisone (CNOP) chemotherapy versus three alternatives: CHOP/ CNOP alone, other chemotherapy regimens, or rituximab and other chemotherapy regimens. Table 56 rovides an overview of each of the studies.

The diagnosis and treatment history of populations included in each economic evaluation study were categorised as follows:

1) Newly diagnosed with DLBCL;

2) DLBCL diagnosed as first primary cancer;

3) Previously untreated for DLBCL; and

4) Not reported.

These categories have also been applied in Table 56. Half the included studies (50, 52, 55-57) evaluated the alternative therapies as first-line treatments for DLBCL, the other half of the studies (49, 51, 53, 54) included only previously untreated DLBCL patients and thus the therapies evaluated were considered to be first-line treatments.

Table 56: Overview of included studies

Study	Type of study	Population	Treatment history category	Intervention of interest	Comparators	Country	Perspective
Danese et al 2016 (50)	CBA	US patients (any age, gender, race) diagnosed with DLBCL, follicular lymphoma, or chronic lymphocytic leukemia and who were enrolled in Medicare Parts A and B with no HMO coverage after diagnosis	Previously untreated DLBCL; DLBCL diagnosed as first primary cancer	R+Chemo-therapy	Chemo-therapy Alone	US	Societal (although only direct medical costs from Medicare included)

Study	Type of study	Population	Treatment history category	Intervention of interest	Comparators	Country	Perspective
Khor et al 2014(56)	CEA	Ontario HIV-negative patients (any age, gender, race) newly diagnosed with DLBCL and without a diagnosis of lymphoma one year prior to DLBCL diagnosis	Newly diagnosed with DLBCL; Previously untreated DLBCL	R-CHOP	CHOP	Canada	Public Payer (Ontario)
Griffiths et al 2012(52)	CEA	US patients diagnosed after age 65 with DLBCL as first primary cancer, received treatment within 180 days after diagnosis, and had been enrolled in a fee-for-service Medicare plan (with no HMO coverage) at least one year prior to diagnosis	Previously untreated DLBCL; DLBCL diagnosed as first primary cancer	R-CHOP/ CNOP	CHOP/ CNOP; Other; or R+Other	US	Public payer (Medicare)
Johnston et al 2010 (55)	CEA/ CUA	British Columbia HIV-negative DLBCL patients (>15 years, any gender & race)	Not reported	R-CHOP	CHOP	Canada	Not reported (although only direct medical costs included)

Study	Type of study	Population	Treatment history category	Intervention of interest	Comparators	Country	Perspective
Lee et al 2008(57)	CA	Canadian patients (any age, gender, race) diagnosed with DLBCL	Not reported	R-CHOP	CHOP	Canada	Public Payer (Alberta)
Ferrara et al 2008(51)	CEA	Simulated cohort of DLBCL in young patients with good prognosis	Not reported	R-CHOP	CHOP	Italy	Public Payer (Italian National Health Service)
Best et al 2005(49)	CEA/ CUA	French patients aged 60-80 years with Stage II, III, IV DLBCL diagnosis and performance status 0-2.	Previously untreated DLBCL	R-CHOP	CHOP	France	Public Payer (French National Social Security System)
Hornberger et al 2005 (54)	CEA/ CUA	US patients aged 60-80 years with Stage II, III, IV DLBCL diagnosis and performance status 0-2.	Previously untreated DLBCL	R-CHOP	CHOP	US	Societal
Groot et al 2005(53)	CEA/ CUA	Stage II, III, IV DLBCL patients in the Netherlands (any age, gender, race)	Not reported	R-CHOP	CHOP	Netherlands	Societal (although only direct medical costs included)

B1a.2.4 Model structure and sensitivity analysis

Table 57 presents an overview of the methods used in the included economic evaluations. Two of the studies used a Markov state-transition model (53, 54), one study used a decision tree model (51), and one study used a patient-level simulation model (55). One study reported developing a model, however no details were provided regarding the type of model used or the model structure (49).The remaining studies did not use an economic model, largely due to their reliance on deterministic (administrative) data to populate both the costs and outcomes over the time horizon examined.

In the study by Johnston et al (55), a patient-level simulation model was used evaluating relapse and death outcomes at 15 years for R-CHOP and CHOP. Within this model, individuals moved forward in intervals based on certain pre-specified events, rather than using uniform time cycle. In the study by Ferrara et al 2008(51), a decision-tree model was used to evaluate complete response (or not) at 5 months and relapse (or no relapse) at 3 years. Both Hornberger et al 2005 (54) and Groot et al 2005 (53) used Markov state-transition models in their analyses, but the outcomes differed in each model. Hornberger et al 2005 evaluated event free, salvage, transplantation, end of life care and death as the health states of importance at 5 years, whereas Groot et al 2005 modelled complete and no complete response at 15 years (53, 54). Best et al (49) evaluated the cost per life year gained and the cost per QALY for previously untreated patients, however model details were not reported.

Of the studies that utilised administrative data, the study by Danese et al (50) estimated the clinical value of rituximab in terms of life years saved, estimated the incremental direct medical costs of adding rituximab to standard care, and compared the benefits and costs of rituximab at the population level. Khor et al (56), using extracted deterministic values from the administrative data, examined the value for money of adding rituximab to the treatment protocol for DLBCL. Similarly, Griffiths et al (52) adopted a public payer perspective by using real-world data to evaluate the survival, cost and cost-effectiveness of adding rituximab to treatment. Lee et al (57) estimated and compared direct medical costs associated with R-CHOP versus CHOP, as well as the costs of subsequent treatments, and how patient characteristics influenced costs from a public payer perspective.

Table 57: Overview of methods used for economic evaluations

Study	Model types	Health states	Final outcome(s) assessed	Time horizon	Sensitivity analyses (SA)
Danese et al 2016 (50)	N/A	N/A	Life years gained & overall value of life years gained; incremental cost of adding Rituximab to chemotherapy	10 years	1 way SA Not performed1 Probabilistic Sensitivity Analysis (Monte Carlo simulation; performed to characterize 95% uncertainty intervals)
Khor et al 2014 (56)	N/A	N/A	Cost per life year gained (stratified by all ages; <60 years; 60-79 years; ≥ 80 years)	3 and 5 years	N/A
Griffiths et al 2012 (52)	N/A	N/A	Cost per life year gained (stratified by ages 66-80 years; >80 years)	4 years	No sensitivity analysis conducted on economic evaluation results.
Johnston et al 2010 (55)	Patient-level simulation model	Relapse; Death	Cost per life year gained, cost per disease-free life year gained & cost per QALY (stratified by over or under 60 years of age)	15 years (SA: 5 years)	1-way SA Probabilistic sensitivity analysis
Lee et al 2008 (57)	N/A	N/A	Cost of R-CHOP pathway; cost of CHOP pathway	3 years – R-CHOP 5 years – CHOP	N/A

Study	Model types	Health states	Final outcome(s) assessed	Time horizon	Sensitivity analyses (SA)
Ferrara et al 2008 (51)	Decision-tree	Complete Response (5 months); No Complete Response (5 months); Relapse (at 3 years); No Relapse (at 3 years)	Cost per life years gained (for complete response at 5 months; relapse-free survival at 3 years; overall survival at 3 years)	5 months and 3 years	1-way SA Threshold analyses
Best et al 2005 (49)	Not reported	Not reported	Cost per life year gained & cost per QALY	15 years	1 way SA Probabilistic Sensitivity Analysis
Hornberger et al 2005 (54)	Markov state transition model	Event free; Salvage; Transplantation; End of life care; Death	Cost per life year saved & cost per QALY	5 years (SA: 3-10 years)	1 way SA Subgroup analyses Probabilistic Sensitivity Analysis (Monte Carlo simulation)
Groot et al 2005(53)	Markov state transition model (adopted from NICE)	Complete response; No complete response	Cost per life year gained & cost per QALY (stratified by over or under 60 years of age)	15 years	1 way SA Probabilistic Sensitivity Analysis (Monte Carlo simulation)

B1a.2.5 Methods of deriving the effectiveness data

Table 58 presents a summary of the two clinical trials referenced in the economic models for R-CHOP and CHOP treatment for DLBCL. The Group d'Etude des Lymphomes de l'Adulte Non-Hodgkin's Lymphoma (LNH 98.5) randomized control trial was the most commonly used source of effectiveness data, as it was used to inform three economic studies (49, 53, 54). The second trial, the MabThera International Trial (MInT) was used to inform one economic study (51).

Table 58: Clinical trials referenced in economic evaluations

Trial name	Registry ID	Intervention	Eligible population
Group d'Etude des Lymphomes de l'Adulte Non-Hodgkin's Lymphoma 98.5	GELA-LNH 98.5	R-CHOP vs. CHOP	60-80 years of age; Stage II, III, IV DLBCL Diagnosis; Performance 0-2.
MabThera International Trial (MInT)	NCT 00064116	CHOP-like chemotherapy vs. Rituximab plus CHOP-like chemotherapy	18-60 years of age; no risk factors or one risk factor (according to International Prognostic Index), Stage II, III, IV DLBCL disease; or Stage I disease with bulk

The remaining studies extracted deterministic values from administrative data sources to inform their measures of effectiveness. Danese et al (50) and Griffiths et al (52) used the Surveillance, Epidemiology, and End Results (SEER) cancer registry data to inform incidence rates of DLBCL in the United States and SEER Medicare data to inform survival rates over time. Khor et al (56) and Johnston et al (55) used provincial-specific administrative data sources to inform their measures of effectiveness, whereas Lee et al (57) did not require a measure of effectiveness in their study as they completed a CA.

B1a.2.6 Measurement and valuation of resource data

Resource utilisation and cost data were obtained either from administrative data sources or from locally available published data sources. In Groot et al (53), expert opinion was also sought to inform annual surveillance costs.

Danese et al (50) and Griffiths et al (52) used SEER Medicare data to inform utilization and costs in the United States. Khor et al (56), Johnston et al (55) and Lee et al (57) used provincial-specific administrative data sources to inform local resource utilization and costs, whereas Ferrara et al (51), Best et al (49), and Hornberger et al (54) relied on locally published estimates of resource utilization and costing data. Table 59 presents a summary of the data sources used to inform parameters for the economic evaluation studies.

Table 59: Data sources used to inform parameters for economic evaluation studies

Study	Data Inputs
Danese et al 2016 (50)	- Incidence rates were taken from the SEER cancer registry data - Population counts were taken from US Census data. - Utilization, survival, and costs were estimated using SEER-

Study	Data Inputs
	Medicare data - Value of survival was estimated using the literature.
Khor et al 2014 (56)	- Ontario Cancer Registry - incidence; - Registered Persons Database - patients' demographics and vital statistics - New Drug Funding Program - resource use chemotherapy and cost per case for chemotherapy; - NACRS - average cost and number of ER visits and outpatient surgery visits (based on RIW); - OHIP - physician billing claims and number of visits, ER visits and cost of visits; - CIHI Discharge Abstract Database - inpatient costs and average number of visits; - Ontario Drug Benefit Plan - prescription drugs dispensed and cost of drugs; - Continuing Care Reporting System - cost per weighted day as inpatient; - Ontario Home Care Admin System and Home Care Database - cost of home care; - Activity Level Reporting System - resource use for chemotherapy and radiation therapy.
Griffiths et al 2012 (52)	- Incidence rates were taken from the Surveillance, Epidemiology, and End Results (SEER) cancer registry data, - Population counts were taken from US Census data - Utilization, survival, and costs were estimated using SEER-Medicare data
Johnston et al 2010 (55)	- British Columbia Cancer Agency (BCCA) Lymphoid Cancer Database: routinely-collected treatment and outcomes information on patients with lymphoid cancer - BCCA Provincial Systemic Therapy Drug Database: per-patient chemotherapy costs - BC Radiation Therapy program: unit-based radiotherapy costs for each chemotherapy regimen - Literature: palliative care costs; all other costs (micro-costing study completed in AB – see Lee et al 2008); utilities
Lee et al 2008 (57)	Administrative data: Calgary Health Region (Tom Baker Cancer Centre), physician claims, Calgary Laboratory Services, and through detailed patient chart review for resource utilization.
Ferrara et al 2008 (51)	- MabThera International Trial (MInT): Complete response at 5 months; relapse-free survival at 3 years; overall survival at 3 years; chemotherapy regimens for R-CHOP and CHOP (used for resource consumption). - Literature: clinical pathway; resource consumption for rescue therapy. - Italian-based published data: acquisition costs for chemotherapy agents and rescue therapy; and hospitalization, imaging, histological analysis, haematological, biochemical investigation costs.

Study	Data Inputs
Best et al 2005 (49)	- GELA-LNH 98.5 RCT data: mean overall and disease-free survival; incidence of hospitalizations for adverse events and drug administration; cumulative doses of chemotherapeutic agents - Scottish and Newcastle Lymphoma Group (SNLG) database: tail of the survival distribution beyond the 48 months of median follow-up of the LNH 98-5 data - Published data: costs associated with cancer surveillance care (routine monitoring), salvage therapy (intensive chemotherapy only), bone marrow transplantation, end-of-life care (palliative care), hospitalizations for drug administration and adverse events, and chemotherapy acquisition costs, and to determine adjustments for quality of life
Hornberger et al 2005 (54)	- GELA-LNH 98.5 – RCT data: response rate, efficacy of R-CHOP over CHOP, survival rates (Kaplan-Meier estimates), transition rates; literature: other transition rates - International Non-Hodgkin's Lymphoma Prognostic Factors Project: population mortality rates - US based published data: costing information for drugs, cancer surveillance and end-of-life care.
Groot et al 2005 (53)	- GELA-LNH 98.5 – RCT data: used to calculate the relative increase in complete response rate and relative risk reduction in disease-free and overall survival associated with R- CHOP over CHOP. - The Scottish Newcastle Lymphoma Group (SNLG) database was used to compute the disease-free and overall survival of DLBCL patients treated with conventional CHOP. - Expert opinion was used to determine % receiving second-line treatment, duration of risk reduction, utility of death, and annual surveillance costs after year 4. - The literature was used to determine other utilities, discount rates, and other costs.

B1a.2.7 Measurement and valuation of health benefits (utilities)

Only four studies completed a CUA, thus requiring the use of utilities in the valuation of health benefits. In Johnston et al (55), utilities were obtained from the literature (58) and categorised into complete responder, partial responder, and progressive disease. Best et al (49) and Hornberger et al (54) reported using published utility estimate data to determine adjustments for quality of life from the same source (59), whereas Groot et al (53) reported using quality of life data from the same researchers (59), however via a personal communication (p 201).

B1a.2.8 Quality assessment

The CHEERS checklist (48) was used to assess the quality of each included economic study. Overall, the quality of studies varied. The studies by Johnston et al (55), Lee et al (57), Best et al(49), and Groot et al (53) faired

favorably in terms of the quality assessment. Some concerns were raised for the studies by Danese et al (50) and Griffiths et al (52) and Hornberger et al (54) due to a lack of details provided regarding the methods used in the analysis.

B1a.2.9 Narrative summary by study

Danese et al (2016)

Decision Problem

Danese et al (50) completed a CBA in the United States, evaluating the use of R-chemotherapy versus chemotherapy alone for the treatment of DLBCL, follicular lymphoma and chronic lymphocytic leukemia at the population level. Using administrative data, Danese et al attempted to estimate the clinical value of rituximab in terms of life years saved, to estimate the incremental direct medical costs of adding rituximab to the standard of care, and to compare the benefits and costs of rituximab at the population level in the United States. Patients were included in the analysis if they were diagnosed with DLBCL, FL or CLL as their first primary cancer and if they received R-chemotherapy or chemotherapy as first-line treatment. Patients were also required to be enrolled in Medicare Parts A and B, with no health maintenance organization (HMO) coverage after their diagnosis. Those diagnosed within the same month as their death, or via autopsy, were excluded. No limitations were placed on age at diagnosis. The final outcomes that were analyzed included life years gained and overall value of life years gained, as well as the incremental cost of adding rituximab to chemotherapy at 10 years. All costs were reported in 2013 US dollars.

Overall, they found that the introduction of rituximab into clinical practice produced 279,704 cumulative life years saved (95% uncertainty index (UI), 269,136-293,345) across the three lymphomas: DLBCL, FL and CLL, at an incremental cost of $8.92 billion US dollars (95% UI, $7.28-$10.28 billion). The resulting economic benefit of the life-years saved was $25.44 billion (95% UI, $11.72–$69.16 billion) and the net economic gain from using rituximab was estimated to be $16.52 billion (95% UI, $2.27–$60.44 billion), indicating that the benefits of rituximab exceeded the costs for the US population.

Model structure and sensitivity analysis

An economic model was not used for this analysis. Rather, the authors estimated the costs and benefits of rituximab using real-world, administrative data. A discount rate was not reported, and a one-way sensitivity analysis was not completed, because, according to the authors, “the inputs have a simple, direct effect on the outcomes”(p 347). A probabilistic sensitivity analysis was

completed using Monte Carlo methods to characterize uncertainty by sampling inputs from distributions, although the distributions used for parameters were not reported.

Methods of deriving the effectiveness data

To derive population values, a simulation model was created whereby incidence rates from the SEER cancer registry data were multiplied by the corresponding population values from the US Census data to estimate the total number of diagnosed patients for DLBCL, FL and CLL in each year and within each age, sex, and year stratum. The economic value attached to life years saved was estimated using the literature.

Measurement and valuation of resource data

This study included direct medical costs but did not include any direct nonmedical costs or indirect costs. Costs and utilization were estimated using SEER Medicare data; the incremental direct medical costs of R+chemotherapy versus chemotherapy alone were based on Medicare Part A and B paid amounts using inverse probability weighted regression, accounting for censoring. Costs were estimated over a 6-year time horizon, with the incremental total direct medical cost for year 6 applied to years 7 to 10 to extrapolate to a 10-year timeframe.

Measurement and valuation of health benefits (utilities)

This study did not measure utility values.

Khor et al (2014)

Decision problem

In a CEA that took place in Ontario, Canada, Khor et al (56) evaluated the use of R-CHOP versus CHOP as first-line treatment for newly diagnosed DLBCL patients, with the objective of being able to show the value for money of adding rituximab to the treatment protocol for DLBCL. This study used a public payer perspective with real-world, administrative, data sources. The population eligible for this study were those with newly diagnosed DLBCL within 6 months prior to and up to 30 days after they began their first R-CHOP or CHOP treatment. Those with missing data on histological diagnosis, Ontario Health Insurance Provider (OHIP) number, or sex were excluded from the study. Additionally, patients with a history of HIV infection prior to their first DLBCL diagnosis or lymphoma more than a year prior to their first DLBCL diagnosis were excluded. The final outcomes that were analyzed included cost per life year gained at 3 and 5 years for various age groups: <60 years,

60-79 years, and ≥ 80 years of age. All costs were reported in 2009 Canadian dollars.

Overall, Khor et al found that R-CHOP was associated with a mean improvement in survival compared to CHOP: 3.2 months over a 5-year period. This outcome was associated with a mean additional cost of approximately $16,000 compared to CHOP, resulting in an incremental cost effectiveness ratio (ICER) of approximately $62,000 per additional life year gained. Cost-effectiveness decreased significantly as age increased, suggesting that R-CHOP was not an attractive option for the very elderly population (≥ 80 years of age).

Model structure and sensitivity analysis

An economic model was not used for this analysis. Rather, Khor et al extracted deterministic values from the administrative data for effectiveness, resource use and costs. A discount rate of 3% was used for both costs and outcomes. Sensitivity analyses were not completed.

Methods of deriving the effectiveness data

A multivariate logistic regression model was used to support propensity score matching of R-CHOP and CHOP patients. Once patients were matched, effectiveness was assessed using administrative data. The Ontario Cancer Registry (OCR) provided information on incidence of DLBCL, whereas the Registered Persons Database provided information on vital statistics, including patient demographics and vital statistics. Inverse probability weighting was applied to account for censoring in the survival data.

Measurement and valuation of resource data

Following propensity score matching, costs were assessed using administrative data. The New Drug Funding Program (NDFP) provided information on resource use for chemotherapy as well as the cost per case for chemotherapy. The National Ambulatory Care Reporting System (NACRS) provided information on the average cost and number of emergency room and outpatient surgery visits, based on the Resource Intensity Weighting (RIW) approach. The OHIP provided information on physician billing claims and number of physician visits. The Canadian Institute for Health Information's Discharge Abstract Database (DAD) provided information on inpatient costs and average number of visits. Ontario's Drug Benefit Plan informed resource use around prescription drugs dispensed and cost of drugs, although this data was unavailable for patients less than 65 years of age. The Continuing Care Reporting System informed the cost per weighted day as an inpatient. Ontario's Home Care Administrative System and Home Care Database

provided information on the cost of home care; and, finally, the Activity Level Reporting System informed resource use for chemotherapy and radiation therapy. Inverse probability weighting was applied to account for censoring in the cost data.

Measurement and valuation of health benefits (utilities)

This study did not measure utility values.

Griffiths et al (2012)

Decision problem

In a CEA that took place in the United States, Griffiths et al (52)evaluated the use of R-CHOP/ CNOP versus 1) CHOP/ CNOP alone; 2) other chemotherapy regimens; or 3) rituximab and other chemotherapy regimens, as first-line treatment for patients diagnosed with DLBCL as their first primary cancer. Through their study, Griffiths et al hoped to evaluate the survival, cost and cost-effectiveness of adding rituximab to treatment for DLBCL using data that reflects routine clinical practice in elderly patients. The public payer (Medicare) perspective was adopted using real-world, administrative data. The population eligible for this study included patients diagnosed with DLBCL as their first primary cancer and whose first Medicare claim for immunochemotherapy was within 180 days following their diagnosis. Patients were required to be enrolled in a Medicare fee-for-service plan, with no HMO coverage, for 12 months prior to their DLBCL diagnosis. Patients who received a DLBCL diagnosis prior to the age of 65 years, who received their diagnosis by death certificate or autopsy, who died within the first month following diagnosis, or who were enrolled in Medicare less than 12 months prior to their DLBCL diagnosis were excluded from this study. The final outcomes assessed by Griffiths et al included the cost per life year gained at 4 years for all age groups, those aged 66-80 years and those greater than 80 years of age. All costs were reported in 2009 US Dollars.

Griffiths et al found that rituximab and chemotherapy was associated with lower all-cause mortality (HR, 0.68; 95% CI, 0.61-0.74) compared to chemotherapy alone. The cost per life year gained of rituximab plus chemotherapy was $62,424 ($23,097 of 0.37 life-years) over the 4-year time horizon, compared with chemotherapy alone.

Model structure and sensitivity analysis

An economic model was not used for this analysis. Rather, Griffiths et al extracted deterministic values from the administrative data for effectiveness, resource use and costs. A discount rate was not reported. Although sensitivity analysis was not completed for the economic evaluation results, sensitivity

analysis was applied to the hazard ratios generated from a multivariate survival analysis model.

Methods of deriving the effectiveness data

Multivariate survival analysis was completed using Cox proportional hazards regression, where the primary survival analysis was limited to 4 years. Additional survival analyses were conducted using the entire observation period, with cancer and non-cancer mortality as the outcomes, and restricting the cohort to those who received CHOP or CNOP. All survival analyses were then repeated using propensity score analysis. An adjusted Kaplan Meier curve was created with the difference in survival between rituximab and chemotherapy versus chemotherapy alone using inverse probability of treatment weighting. Relapse-free and progression-free survival were not examined in this study.

The SEER cancer registry data provided information regarding the incidence rates of DLBCL. Population counts were taken from US Census data, whereas survival was estimated using SEER Medicare data.

Measurement and valuation of resource data

Partitioned, inverse probability weighted, least-squares regression analysis took place to examine adjusted associations between cumulative costs (over 4 years) and patient demographic, clinical and treatment factors. Confidence intervals for the cumulative costs were calculated using a bootstrap approach. All utilization and costs were obtained using SEER Medicare data.

Measurement and valuation of health benefits (utilities)

This study did not measure utility values.

Johnston et al (2010)

Decision problem

In a combined CEA and CUA study, Johnston et al (55) evaluated R-CHOP versus CHOP for the first-line treatment of DLBCL using real-world observational data that describe routine clinical practice for a Canadian HIV-negative population above the age of 15 years. Johnston et al did not report the perspective used, although only direct medical costs were included. The final outcomes assessed included the cost per life year gained, the cost per disease-free life year gained and the cost per quality-adjusted life year (QALY) at 15 years for individuals younger than 60 years or 60 years or older. All costs were reported in 2006 Canadian dollars.

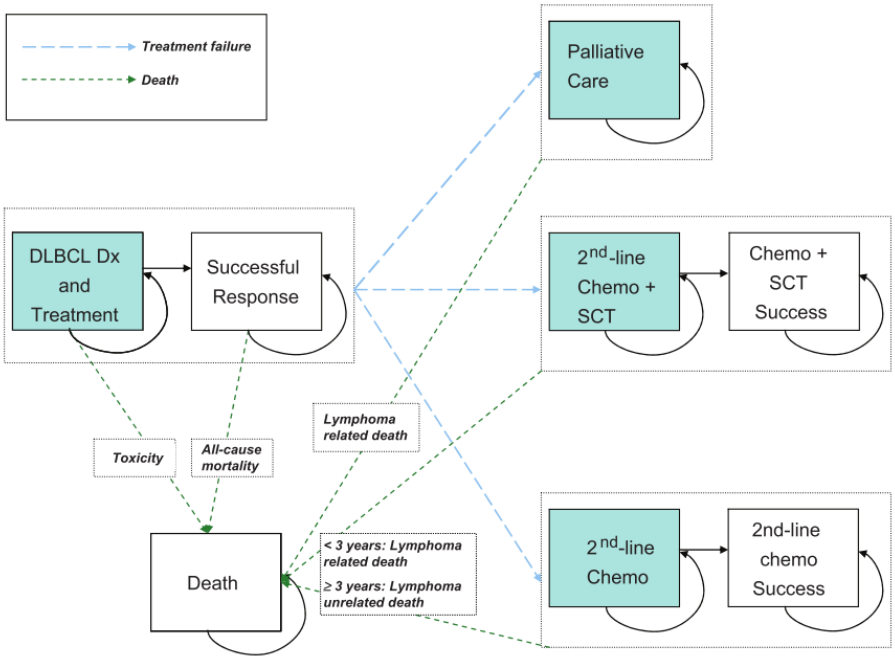
Overall, Johnston et al found that R-CHOP was a cost-effective alternative to CHOP. The ICERs for the 60 years and younger group ranged from $11,965 per disease-free life year gained to $19,144 per QALY gained over 15 years. For the above 60 years of age group, ICERs ranged from $4,313 per disease-free life year gained to $5,853 per QALY over 15 years. The use of R-CHOP as a first-line treatment for DLBCL was recommended.

Model structure and sensitivity analysis

Figure 56 shows the micro, patient level simulation model that was used for this analysis. For this model, time-to-event analyses took place in order to estimate the distributions associated with time spent in various health states, including relapse and death. Within this model, individuals moved forward in intervals based on certain pre-specified events, rather than using uniform time cycles. For individuals who relapsed, time until occurrence of relapse was randomly generated based on a Weibull survival model. A discount rate of 3% was used for both costs and outcomes, although the analysis was also evaluated using undiscounted rates.

Probabilistic sensitivity analysis was performed on all parameters of the survival analysis, as well as the estimated costs and utilities associated with health states. During each iteration of this analysis, new time-to-event parameters were generated based on the means and standard errors estimated within each respective Weibull model. One-way sensitivity analyses were completed using undiscounted rates as well as a time horizon of 5 years.

Figure 56: Patient-level simulation model



Methods of deriving the effectiveness data

All analyses assumed a parametric Weibull form for the underlying hazard function. Each second-line treatment regimen was associated with a corresponding health state and Weibull survival model, which described the time between treatment initiation and death. The British Columbia Cancer Agency (BCCA) Lymphoid Cancer Database provided information on routinely collected treatment and outcomes for patients with DLBCL.

Measurement and valuation of resource data

Costs were assessed using various sources of data. The BCCA Provincial Systemic Therapy Drug Database provided information on unit-based radiotherapy costs for R-CHOP and CHOP. The literature provided information regarding palliative care costs and all other costs. In particular, a micro-costing study completed by Lee et al (57) in Alberta was used to inform costs.

Measurement and valuation of health benefits (utilities)

Utilities were based on the literature (58) and were categorised into complete responder, which included all individuals who took initial therapy and responded successfully, partial responder, which included all individuals receiving second-line therapy with curative intent, and progressive disease, which included all individuals receiving palliative care.

Lee et al (2008)

Decision problem

In a CA study that took place in Canada, Lee et al (57) evaluated the costs of R-CHOP versus CHOP for first-line treatment of DLBCL. In particular, Lee et al used real-world, administrative data to attempt to estimate and compare the direct medical costs associated with each type of treatment, analyze the costs of subsequent treatments, and determine how patient characteristics influenced costs. This study utilized a public payer perspective and all costs were reported using 2004 Canadian dollars. Patients of any age who were receiving R-CHOP or CHOP as first-line treatment for DLBCL were included in this study. CHOP patients were matched to R-CHOP patients based on age, sex, stage of cancer and performance score (based on the criteria established by the Eastern Clinical Oncology Group (ECOG)). Costs were evaluated at 3 years for the R-CHOP sample and 5 years for the CHOP sample.

Based on their analysis, Lee et al found that, for first-line treatment, drug costs were the largest contributor to total cost, followed by hospitalization costs. For treatments subsequent to first-line treatment, no significant cost differences

were found. In addition, patients with advanced stage disease incurred more costs than those with limited stage disease.

Model structure and sensitivity analysis

An economic model was not used for this analysis. Rather, Lee et al extracted deterministic cost values from the administrative data for resource use and costs. A discount rate was not reported and sensitivity analyses were not completed.

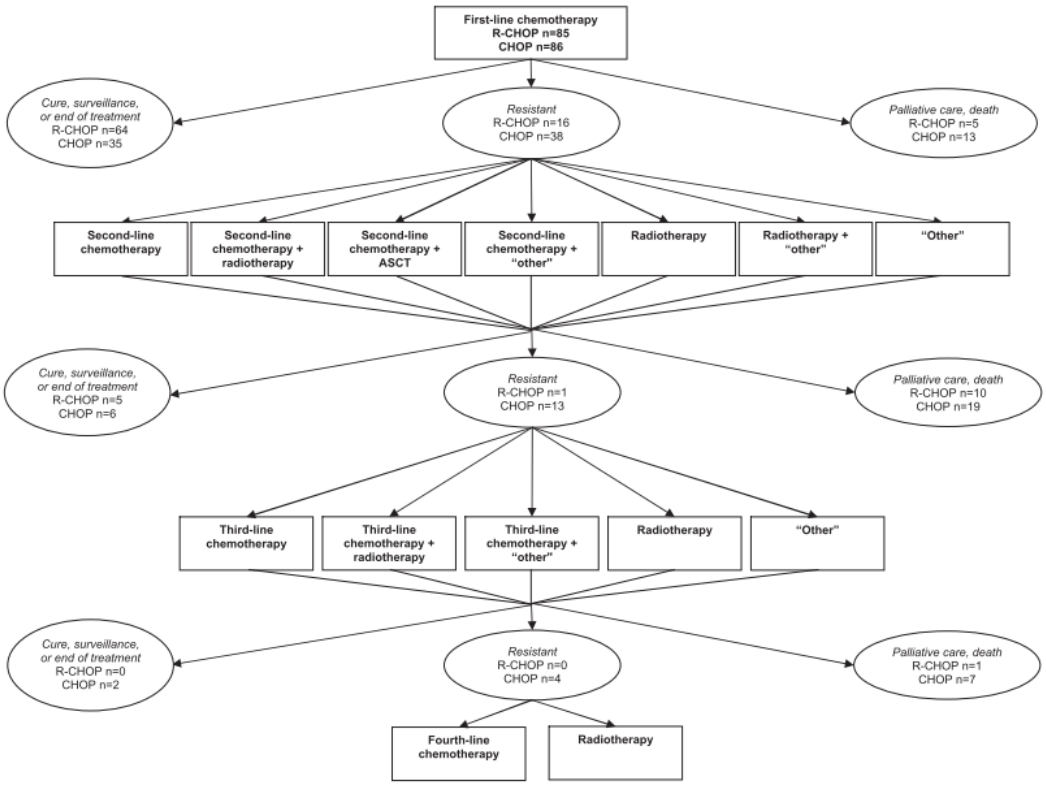
Methods of deriving the effectiveness data

Effectiveness data were not measured for this analysis.

Measurement and valuation of resource data

Microcosting data were obtained from the Calgary Health Region (Tom Baker Cancer Centre), physician claims, Calgary Laboratory Services, and through detailed patient chart review for resource utilization. The authors aimed to quantify the “door to door” costs for patients from the time they entered the cancer care facility until they received a cure, they completed treatment, or they died. Second-, third- and fourth-line treatment costs were also included in this study. Figure 57 provides the flow chart of treatment for DLBCL that was used to inform this study.

Figure 57: Flow chart of treatment using R-CHOP and CHOP



Measurement and valuation of health benefits (utilities)

This study did not measure utility values.

Ferrara et al (2008)

Decision problem

In this CEA that took place in Italy, Ferrera et al (51) evaluated the use of R-CHOP versus CHOP for the treatment of DLBCL at 5 months and 3 years in young patients with a good prognosis. This study used a public payer (Italian National Health Service) perspective with a simulated cohort of patients. No restrictions were placed on the population cohort simulated in this model. Final outcomes assessed included the cost per life year gained for three health states: response at 5 months, relapse-free survival at 3 years, and overall survival at 3 years. All costs were reported using 2007 Euros.

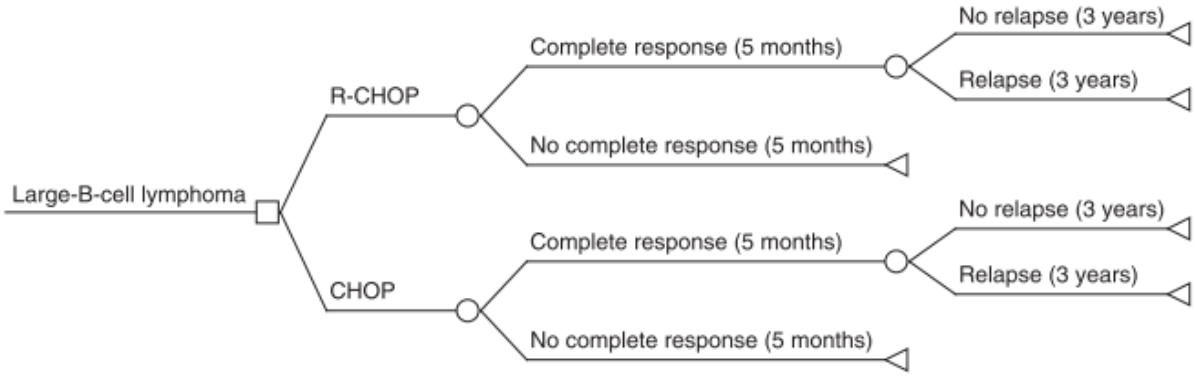
Overall, Ferrera et al found that R-CHOP was the dominant strategy; the incremental life years gained was 0.18 and the overall mean treatment cost was lower for the R-CHOP group (€22,133.44 versus €22,831.17), resulting in an ICER of -€3987.39 per patient.

Model structure and sensitivity analysis

Figure 58 shows the decision-tree model that was used for this analysis. The health states examined include complete or no complete response at 5 months and relapse or no relapse at 3 years. A discount rate of 3% was used for both costs and outcomes.

One-way sensitivity and threshold analyses were completed for this study. The parameters considered in the one-way sensitivity analysis included complete response at 5 months, relapse-free survival at 3 years and overall survival at 3 years; for these variables sensitivity values ranged according to their confidence intervals, where the lower limit, or worst case scenario, was used for the R-CHOP treatment and the upper limit, or best case scenario, was used for the CHOP treatment. The discount rate was also varied from 1% to 5%. A threshold analysis was used to evaluate the impact of the cost of rescue therapy on the results of the model.

Figure 58: Decision-tree model used in Ferrara et al



Methods of deriving the effectiveness data

Data from the MabThera International Trial (MinT) was used to determine complete response at 5 months, relapse-free and overall survival at 3 years and chemotherapy regimens for R-CHOP and CHOP. The literature was used to inform the clinical pathway and resource consumption for rescue therapy. The authors note that the number of cycles administered for rescue therapy was relatively conservative in this study.

Measurement and valuation of resource data

Italian National Health Service (NHS) reimbursement data was used to determine acquisition costs for chemotherapy agents and rescue therapy. The tariffs of the Italian NHS were used to determine hospitalization, imaging, histological analysis, haematological, and biochemical investigation costs. The cost of one day in hospital was determined by a study conducted by the Agenzia Servizi Sanitari Regionali.

Measurement and valuation of health benefits (utilities)

This study did not measure utility values.

Best et al (2005)

Decision problem

In this joint CEA and CUA study that took place in France, Best et al (49)evaluated the cost per life year gained and cost per QALY for patients previously untreated for DLBCL. The population included in the study were French patients aged 60 to 80 years with Stage II to IV DLBCL diagnosis, untreated DLBCL and performance status 0-2 according to the criteria of the ECOG. A representative patient was also assumed to have the initial characteristics as the average patient in the LNH 98.5 randomized control

trial: age, performance status, stage of illness, B symptoms, number of extranodal sites, bone marrow involvement and age-adjusted International Prognostic Index score. The final outcomes assessed include the cost per life year gained and the cost per QALY at 15 years using a public payer (French National Security System) perspective. All costs were reported in 2003 Euros.

Overall, Best et al found that R-CHOP significantly increases the mean survival up to 4 years compared with CHOP, and a projected ICER of less than €20,000 per QALY.

Model structure and sensitivity analysis

Best et al reported developing a model for this analysis, however no details were provided regarding the type of model used or the model structure. A discount rate of 4% was used for both costs and outcomes.

One-way sensitivity analysis was used for each parameter in the model. For this analysis, Best et al assigned extreme values of each parameter according to their distribution. Probabilistic sensitivity analysis was also conducted, where normal or uniform distributions were assigned to each of the key variables in the analysis. For the uniform distribution, the highest and lowest values in the distribution were used, whereas for the normal distribution, the 5^{th} and 95^{th} percentiles of the distributions were used.

Methods of deriving the effectiveness data

LNH 98.5 trial data was used to estimate mean overall and disease-free survival, incidence of hospitalizations for adverse events and drug administration, and cumulative doses of chemotherapeutic agents. Kaplan-Meier curves were used to estimate survival during the trial period, and survival beyond the trial period was projected based on mortality rates obtained from the Scottish and Newcastle Lymphoma Group (SNLG) database.

Measurement and valuation of resource data

French diagnosis-related group (DRG) payment schedules were applied to LNH 98.5 trial data to estimate the cost of adverse events and drug administration. Other published data were used to determine the costs associated with cancer surveillance care, salvage therapy, bone marrow transplantation, end-of-life care, hospitalizations for drug administration and adverse events, and chemotherapy acquisition costs.

Measurement and valuation of health benefits (utilities)

Best et al report using published utility estimate data to determine adjustments for quality of life.

Hornberger et al (2005)

Decision problem

In this joint CEA and CUA that took place in the United States, Hornberger et al (54) evaluated the use of R-CHOP versus CHOP as treatment for previously untreated DLBCL, with the objective of estimating the incremental cost utility at 5 years for patients aged ≥60 years. This study used a societal approach and a Markov state-transition model. The population included in the study were those with characteristics similar to the LNH 98.5 clinical trial: ages 60–80 years with Ann Arbor Stage II, III, or IV disease and with a performance status of 0–2 according to the criteria of the Eastern Cooperative Oncology Group. The final outcomes assessed included the cost per life year saved and cost per QALY at 5 years. The currency and base year used for costs were not reported.

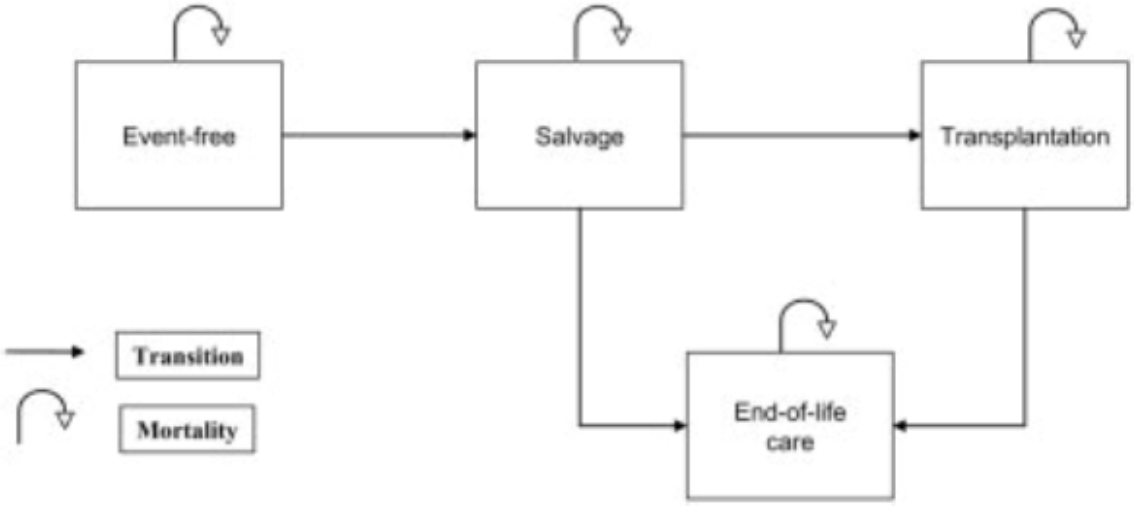
Overall, Hornberger et al found that R-CHOP was cost-effective for the elderly population. Over 5 years, R-CHOP would prolong overall survival by approximately 1.04 years, at an incremental additional cost of $13,867 and an ICER of $19,297 per QALY.

Model structure and sensitivity analysis

Figure 59 shows the Markov-state transition model that was used by Hornberger et al in their study. Five health states were incorporated into the model: event-free, salvage, transplantation, end-of-life care, and death. The term ‘event’ included the progression of lymphoma, declining treatment, or patients with a concurrent illness or adverse event. Salvage treatment follows after an event and consists of chemotherapy with or without radiation therapy. For some patients, transplantation may follow chemotherapy. Patients that fail to respond to salvage therapy may also enter end-of-life care until they reach death. A discount rate of 3% was used for both costs and outcomes.

One-way sensitivity analysis was conducted on costs (CHOP, surveillance, salvage and transplantation, end-of-life care), the probability of salvage therapy, quality of life, time horizon, and the time discount rate. Probabilistic sensitivity analysis was also conducted on select variables, using truncated normal distributions for cost variables, beta distributions for probability variables and uniform distributions for utilities, time discount rate and time horizon.

Figure 59: Markov-state transition model used in Hornberger et al



Methods of deriving the effectiveness data

Published Kaplan-Meier estimates were used, along with transition rates, to estimate survival. The LNH-98.5 clinical trial provided information on the response rate, efficacy of R-CHOP over CHOP, survival rates and transition rates. The literature provided information on other transition rates. The International Non-Hodgkin's Lymphoma Prognostic Factors Project was used to derive population mortality rates.

Measurement and valuation of resource data

US-based published data provided costing information for drugs, cancer surveillance and end-of-life care.

Measurement and valuation of health benefits (utilities)

Hornberger et al used published utility estimate data in the valuation of health benefits. Estimates were adjusted for quality of life based only on cancer stage, in which survival without events was assigned a utility of 0.83, and end-of-life care after recurrence was assigned a utility of 0.38.

Groot et al (2005)

Decision problem

In a joint CEA and CUA that took place in the Netherlands, Groot et al (53) evaluated the use of R-CHOP versus CHOP for the treatment of DLBCL, with the objective of aiding decision-making in the Netherlands. The study used a societal approach, although only direct medical costs were included, and employed a Markov-state transition model that was previously evaluated by

the National Institute for Clinical Excellence (NICE) in the United Kingdom and adapted for use in the Netherlands. The population included in this study were those with stage II, III or IV DLBCL receiving initial treatment with CHOP or R-CHOP. No limitations were placed on age. The final outcomes that were assessed included the cost per life year gained and the cost per QALY at 15 years for two age groups: those under and over the age of 60 years. All costs were reported in 2002 Euros.

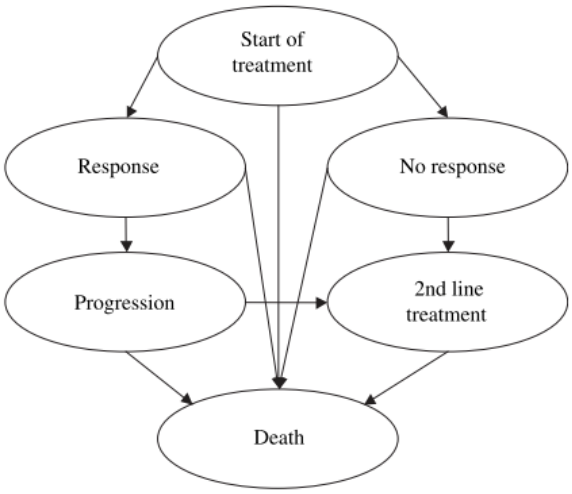
Overall, Groot et al found that the incremental gain in QALYs of R-CHOP compared to CHOP was 0.88 in both the younger and older age groups. The costs were €12 343 higher in the younger group of patients and €15 860 in the older patients, resulting in ICERS of €13 983 and €17 933 per QALY, respectively. Based on these results, Groot et al felt that these results should be seen as acceptable by most policy makers in priority setting for budget allocation.

Model structure and sensitivity analysis

Figure 60 provides a visual of the treatment pathway of DLBCL patients in the Netherlands. A Markov state-transition model was used in this study. This model was previously evaluated by NICE and the outcomes were confirmed by an independent analysis conducted by the School for Health and Related Research (ScHARR) of the university of Sheffield. The model was then adapted for use in the Netherlands. Two health states were assessed in this model: complete response versus no complete response. A discount rate of 4% was used for both costs and outcomes, in accordance with Dutch recommendations.

Several one-way sensitivity analyses were conducted to test baseline assumptions, where the range of values tested varied (see Table 2 in Groot et al). Probabilistic sensitivity analysis was also performed on selected variables using a Monte Carlo simulation with 1000 iterations. A lognormal distribution was assumed for the relative increase in complete response and the relative risk reductions for disease-free and overall survival. A uniform distribution was assumed for the utilities while a normal distribution was used for the follow-up costs.

Figure 60: Treatment path of DLBCL patients



Methods of deriving the effectiveness data

A continuous survival curve using a Weibull distribution was fitted alongside the Scottish Newcastle Lymphoma Group (SNLG) data for both younger and older patients, which was used to compute the disease-free and overall survival of DLBCL patients treated with conventional CHOP. LNH 98.5 data was used to inform the relative increase in complete response rate and relative risk reduction in disease-free and overall survival associated with R-CHOP over CHOP, and expert opinion was used to determine the proportion receiving second-line treatment and duration of risk reduction. The literature informed other discount rates.

Measurement and valuation of resource data

Data on the average number of courses of CHOP and R-CHOP were derived from LNH 98.5 trial. Information on resource use during initial treatment, follow-up during the first 4 years following treatment and second-line treatment costs were derived from detailed cost-effectiveness studies previously performed in patients with aggressive non-Hodgkins Lymphoma in the Netherlands. Costs were then calculated by multiplying the units of resource use by the unit costs. Expert opinion was used to inform annual surveillance costs after year 4, whereas other costs were obtained using the literature.

Measurement and valuation of health benefits (utilities)

Utility estimates were derived using previously published literature values(59). Expert opinion was used to derive additional utility estimates, such as the utility of death.

B1a.2.10 Discussion

The intended SLR identified nine economic evaluation studies for the treatment of DLBCL. The studies were completed in varying countries with varying populations, and utilized different methods, models and sources of data, including trial data from the LNH 98.5 trial as well as the MInT trial, and administrative data which reflected real-world, clinical settings and costs.

The majority of studies found for this SLR compared R-CHOP to CHOP. Despite the varying methods and sources of data, most study conclusions were aligned; R-CHOP appeared to be a more attractive alternative compared to CHOP and was recommended for use with the intended population.

In order for Gazyva® to be adopted widely as first- line treatment for DLBCL, it will be imperative to show that this drug has greater efficacy/ effectiveness than R-CHOP and is more attractive in terms of its cost-effectiveness.

b. Health-related quality of life searches (Appendix I)

Details from the original SLR (conducted September 2018) and SLR update 1 (conducted June 2019) are described below. Details from the SLR update 2 (conducted August 2021) and SLR update 3 (conducted September 2022) were previously provided in Appendix I.

B1b.1 Methodology – Health state utilities SLR

B1b.1.1 Eligibility criteria

The eligibility criteria used to determine relevance for inclusion of publications in the review are detailed in Table 60.

Table 60: Eligibility criteria

Criteria	Include	Exclude
Population	Adult patients with DLBCL receiving first-line therapy or have R/R DLBCL	• Animal/ in vitro studies
Intervention/comparators	No restriction	–
Outcomes	• Utilities derived using generic preference-based instruments (e.g. EQ-5D) for relevant health states	Outcome(s) not listed

Criteria	Include	Exclude
	• Direct utility estimates (e.g. standard gamble, time trade off) • Mapping studies, from disease-specific to generic preference-based measures or between different generic preference-based measures	
Study design/setting	• Any studies reporting original HSUV data for relevant health states	Studies not listed
Language of publication	English language publications	Non-English language publications without an English abstract.
Date of publication	No restriction	-
Countries	No restriction	-

Abbreviations: BSC, best supportive care; EQ-5D, European Quality of Life-5 Dimensions; HSUV, health state utility value; R/R DLBCL, relapse/refractory diffuse large B-cell lymphoma.

B1b.1.2 Information sources

Electronic databases were used to identify relevant publications using a pre-defined search string. The processes for electronic database searching, for screening identified studies and for hand-searching are detailed below. The selection criteria to be applied are then below.

Electronic database searches

The following electronic databases were searched via the Ovid platform on 4th September 2018:

- Embase, 1974 to present
- MEDLINE®
    - MEDLINE In Process & Other Non-Indexed Citations
    - MEDLINE, 1946 to present day
    - MEDLINE, Epub Ahead of Print
- The Cochrane Library, incorporating:
    - the Health Technology Assessment Database (HTA)
    - the National Health Service Economic Evaluation Database (NHS EED)

An update of the search was conducted on 10th June 2019 to identify relevant papers published post-September 2018. The database search strings identified all relevant studies indexed in Medline, and were modified for performing searches in Embase and the Cochrane Library, to account for differences in syntax and thesaurus headings. Searches included terms for free text and

Medical Subject Heading (MeSH) terms. The search strings applied for each database are presented in B1b.1.3.

Citation screening

Citations identified in the electronic database search were reviewed on the basis of title and abstract to assess eligibility based on the predefined inclusion criteria (Table 60). Full publications of potentially relevant citations were then obtained and examined in full to identify publications eligible for inclusion in the SLR. Reasons for exclusion were documented for all excluded citations. Disputes regarding eligibility were resolved through discussion between reviewers.

Hand searching

Hand searching of reference lists from included publications and relevant identified SLRs were screened, in addition to proceedings from the following conferences between 2015 and 2018 inclusive. In the update review, all conferences were included from January to June 2019.

- European Hematology Association (EHA)
- International Conference on Malignant Lymphoma (ICML)
- American Society of Hematology (ASH)
- American Society of Clinical Oncology (ASCO)
- European Society for Medical Oncology (ESMO)
- International Society for Pharmacoeconomics and Outcomes Research (ISPOR): Annual and European Meeting
- Health Technology Assessment International (HTAi)
- Society for Medical Decision Making (SMDM)

Additional sources

The following additional sources were also searched 8th and 9th October 2018:

- Previous Health Technology Assessment (HTA) submissions from following agencies:
    - The National Institute for Health and Care Excellence (NICE)
    - The Scottish Medicines Consortium (SMC)
    - The All Wales Medicines Strategy Group (AWMSG)
    - The Pharmaceutical Benefits Advisory Committee (PBAC)
    - The Canadian Agency for Drugs and Technologies in Health (CADTH), including the pan-Canadian Oncology Drug Review (pCODR)
    - The Institut national d'excellence en sante et en services sociaux (INESSS)
    - The Haute Autorité de Santé (HAS)

- Latin American and Caribbean Health Sciences Literature (LILACS): http://lilacs.bvsalud.org/en/
- The Cost-Effectiveness Analysis (CEA) Registry: http://healtheconomics.tuftsmedicalcenter.org/cear4/Home.aspx
- EconPapers within Research Papers in Economics (RePEc): http://econpapers.repec.org/
- International Network of Agencies for Health Technology Assessment (INAHTA): http://www.inahta.org/
- National Institute for Health Research Health Technology Assessment (NIHR HTA): https://www.nihr.ac.uk/
- University of York Centre for Reviews and Dissemination: https://www.york.ac.uk/crd/
- EuroQoL website: https://euroqol.org/
- University of Sheffield ScHARRHUD database: http://www.scharrhud.org/

B1b.1.3 Search strategies

The study design filter was adapted using Scottish Intercollegiate Guidelines Network (SIGN) filter(60)(60)(13)(60), CADTH database search filters(61)(61)(14)(61), and previous NICE HTA submissions.

Original review (September 2018)

Table 61: Embase (1974 to 2018), assessed on 4th September 2018

#	Searches	Results
1	exp Lymphoma, Large B-Cell, Diffuse/	6204
2	exp large cell lymphoma/	33907
3	(diffuse large B-cell or DLBCL or DLBL).mp.	24060
4	aggressive B-cell*.mp.	1648
5	(large B-cell adj4 lymphoma*).mp.	23997
6	(diffuse adj4 lymphoma*).mp.	25591
7	1 or 2 or 3 or 4 or 5 or 6	42185
8	("EuroQOL 5-Dimension" or "Euroqol 5D" or "EQ-5D" or EQ5D or Euroqol or "EQ 5D" or "european quality of life").mp.	16145
9	(AQOL or "Assessment of Quality of Life" or "quality of life index" or "Australian quality of life" or "Australian qol").mp.	6838
10	("Health utilities index" or HUI or HUI$ or (health adj2 (utilities or utility))).mp.	13675
11	("short form 6D" or "short-form 6D" or SF6D or SF-6D or "SF 6D").mp.	1318

#	Searches	Results
12	(15D or 16D or 17D).mp.	3613
13	("standard gamble" or SG).mp.	13317
14	("time trade off" or "time trade-off" or "time tradeoff" or TTO).mp.	2391
15	("quality of wellbeing" or QWB or "quality of well-being" or "quality of well being").mp.	550
16	disutilit$.mp.	726
17	(health adj1 stat*).mp. or exp Health Status/	248763
18	(utility adj1 (value* or weight*)).mp.	2863
19	exp statistical model/	149965
20	preference$.mp.	175800
21	*patient preference/	3565
22	(utilit* or "health utility index" or "utilities index").mp.	247416
23	(map$ or mapping or regression or "cross walking" or "cross-walking").mp.	1523940
24	("multiattribute utility" or "multi-attribute utility" or "multi attribute utility" or "mau").mp.	1563
25	quality of life index.mp. or exp "quality of life index"/	4195
26	quality adjusted life year.mp. or exp quality adjusted life year/	22828
27	(qaly or daly or "adjusted life").mp.	30360
28	("quality adjusted" or "disability adjusted").mp.	28157
29	disability.mp. or exp disability/	288236
30	disabled person.mp. or exp disabled person/	43349
31	life expectancy.mp. or exp life expectancy/	57744
32	(29 or 30) and 31	3196
33	(QoL or HRQoL or HRQL or "health related quality of life" or "health-related quality of life").mp.	108006
34	quality of life.mp. or exp "quality of life"/	504377
35	or/17-28,32	2233879
36	35 and (33 or 34)	115020
37	or/8-16	53483
38	36 or 37	151931
39	7 and 38	160

Table 62: Ovid MEDLINE(R) Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) (1946 to Present), accessed 4th September 2018

#	Searches	Results
1	exp Lymphoma, Large B-Cell, Diffuse/	17996
2	exp Lymphoma, B-Cell/	45762
3	(diffuse large B-cell or DLBCL or DLBL).mp.	11963
4	aggressive B-cell*.mp.	818
5	(large B-cell adj4 lymphoma*).mp.	23819
6	(diffuse adj4 lymphoma*).mp.	25202
7	1 or 2 or 3 or 4 or 5 or 6	52447
8	("EuroQOL 5-Dimension" or "Euroqol 5D" or "EQ-5D" or EQ5D or Euroqol or "EQ 5D" or "european quality of life").mp.	8684
9	(AQOL or "Assessment of Quality of Life" or "quality of life index" or "Australian quality of life" or "Australian qol").mp.	3236
10	("Health utilities index" or HUI or HUI$ or (health adj2 (utilities or utility))).mp.	8645
11	("short form 6D" or "short-form 6D" or SF6D or SF-6D or "SF 6D").mp.	717
12	("quality of wellbeing" or QWB or "quality of well-being" or "quality of well being").mp.	431
13	("15D" or "16D" or "17D").mp.	2638
14	("standard gamble" or SG).mp.	9125
15	("time trade off" or "time trade-off" or "time tradeoff" or TTO).mp.	1658
16	("quality of wellbeing" or QWB or "quality of well-being" or "quality of well being").mp.	431
17	disutilit$.mp.	380
18	(health adj1 stat*).mp. or exp Health Status/	353501
19	(utility adj1 (value* or weight*)).mp.	1554
20	exp Models, Economic/	13505
21	preference$.mp.	145958
22	exp Patient Preference/	6544
23	(utilit* or "health utility index" or "utilities index").mp.	180050
24	(map$ or mapping or regression or "cross walking" or "cross-walking").mp.	1301493
25	("multiattribute utility" or "multi-attribute utility" or "multi attribute utility" or "mau").mp.	1001
26	quality of life index.mp.	1554
27	quality adjusted life year.mp. or exp Quality-Adjusted Life Years/	12569
28	("qaly" or "daly" or "adjusted life").mp.	18214

#	Searches	Results
29	("quality adjusted" or "disability adjusted").mp.	17617
30	exp Disability Evaluation/ or disability.mp.	207042
31	disabled person.mp. or exp disabled person/	60297
32	life expectancy.mp. or exp life expectancy/	36474
33	(30 or 31) and 32	1860
34	("QoL" or "HRQoL" or "HRQL" or "health related quality of life" or "health-related quality of life").mp.	65381
35	quality of life.mp. or exp "quality of life"/	292153
36	or/18-29,33	1921763
37	36 and (34 or 35)	193051
38	or/8-16	32405
39	37 or 38	213331
40	7 and 39	111

Table 63: The Cochrane Library, incorporating: EBM Reviews - Health Technology Assessment 4th Quarter 2016, EBM Reviews - NHS Economic Evaluation Database 1st Quarter 2016, accessed 4th September 2018

#	Searches	Results
1	exp Lymphoma, B-Cell/	10
2	(diffuse large B-cell or DLBCL or DLBL).mp.	21
3	aggressive B-cell*.mp.	2
4	(large B-cell adj4 lymphoma*).mp.	22
5	(diffuse adj4 lymphoma*).mp.	23
6	1 or 2 or 3 or 4 or 5	31
7	("EuroQOL 5-Dimension" or "Euroqol 5D" or "EQ-5D" or EQ5D or Euroqol or "EQ 5D" or "european quality of life").mp.	744
8	(AQOL or "Assessment of Quality of Life" or "quality of life index" or "Australian quality of life" or "Australian qol").mp.	50
9	("Health utilities index" or HUI or HUI$ or (health adj2 (utilities or utility))).mp.	446
10	("short form 6D" or "short-form 6D" or SF6D or SF-6D or "SF 6D").mp.	55
11	("quality of wellbeing" or QWB or "quality of well-being" or "quality of well being").mp.	59
12	("15D" or "16D" or "17D").mp.	18

#	Searches	Results
13	("standard gamble" or SG).mp.	210
14	("time trade off" or "time trade-off" or "time tradeoff" or TTO).mp.	365
15	("quality of wellbeing" or QWB or "quality of well-being" or "quality of well being").mp.	59
16	disutilit$.mp.	181
17	(health adj1 stat*).mp. or exp Health Status/	2028
18	(utility adj1 (value* or weight*)).mp.	1799
19	exp Models, Economic/	1695
20	preference$.mp.	1044
21	exp Patient Preference/	477
22	(utilit* or "health utility index" or "utilities index").mp.	4821
23	(map$ or mapping or regression or "cross walking" or "cross-walking").mp.	1087
24	("multiattribute utility" or "multi-attribute utility" or "multi attribute utility" or "mau").mp.	11
25	quality of life index.mp.	14
26	quality adjusted life year.mp. or exp Quality-Adjusted Life Years/	3446
27	("qaly" or "daly" or "adjusted life").mp.	5050
28	("quality adjusted" or "disability adjusted").mp.	4937
29	exp Disability Evaluation/ or disability.mp.	771
30	disabled person.mp. or exp disabled person/	75
31	life expectancy.mp. or exp life expectancy/	1300
32	(29 or 30) and 31	73
33	("QoL" or "HRQoL" or "HRQL" or "health related quality of life" or "health-related quality of life").mp.	676
34	quality of life.mp. or exp "quality of life"/	6957
35	or/17-28,32	8965
36	35 and (33 or 34)	5665
37	or/8-16	1584
38	37 or 38	5747
39	7 and 39	6

Update review (June 2019)

Table 64: Embase, assessed on 10th June 2019

#	Searches	Results
1	exp Lymphoma, Large B-Cell, Diffuse/	8605
2	exp large cell lymphoma/	36840
3	(diffuse large B-cell or DLBCL or DLBL).mp.	26676
4	aggressive B-cell*.mp.	1781
5	(large B-cell adj4 lymphoma*).mp.	26607
6	(diffuse adj4 lymphoma*).mp.	27901
7	1 or 2 or 3 or 4 or 5 or 6	45117
8	("EuroQOL 5-Dimension" or "Euroqol 5D" or "EQ-5D" or EQ5D or Euroqol or "EQ 5D" or "european quality of life").mp.	18485
9	(AQOL or "Assessment of Quality of Life" or "quality of life index" or "Australian quality of life" or "Australian qol").mp.	7273
10	("Health utilities index" or HUI or HUI$ or (health adj2 (utilities or utility))).mp.	13997
11	("short form 6D" or "short-form 6D" or SF6D or SF-6D or "SF 6D").mp.	1450
12	(15D or 16D or 17D).mp.	3782
13	("standard gamble" or SG).mp.	14370
14	("time trade off" or "time trade-off" or "time tradeoff" or TTO).mp.	2554
15	("quality of wellbeing" or QWB or "quality of well-being" or "quality of well being").mp.	583
16	disutilit$.mp.	826
17	(health adj1 stat*).mp. or exp Health Status/	263059
18	(utility adj1 (value* or weight*)).mp.	3196
19	exp statistical model/	154840
20	preference$.mp.	185481
21	*patient preference/	4057
22	(utilit* or "health utility index" or "utilities index").mp.	265018
23	(map$ or mapping or regression or "cross walking" or "cross-walking").mp.	1626509
24	("multiattribute utility" or "multi-attribute utility" or "multi attribute utility" or "mau").mp.	1678
25	quality of life index.mp. or exp "quality of life index"/	4461
26	quality adjusted life year.mp. or exp quality adjusted life year/	24984
27	(qaly or daly or "adjusted life").mp.	33229
28	("quality adjusted" or "disability adjusted").mp.	30992

#	Searches	Results
29	disability.mp. or exp disability/	305441
30	disabled person.mp. or exp disabled person/	44600
31	life expectancy.mp. or exp life expectancy/	60542
32	(29 or 30) and 31	3419
33	(QoL or HRQoL or HRQL or "health related quality of life" or "health-related quality of life").mp.	118248
34	quality of life.mp. or exp "quality of life"/	546623
35	or/17-28,32	2375536
36	35 and (33 or 34)	125578
37	or/8-16	57700
38	36 or 37	164947
39	7 and 38	178
40	(Sep* 2018 or Oct* 2018 or Nov* 2018 or Dec* 2018 or Jan* 2019 or Feb* 2019 or Mar* 2019 or Apr* 2019 or May* 2019 or Jun* 2019).dp.	444432
41	39 and 40	11
42	limit 39 to dd=20180904-20190610	7
43	41 or 42	12

Table 65: Ovid MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations and Daily <1946 to June 07, 2019>, Accessed 10th June 2019

#	Searches	Results
1	exp Lymphoma, Large B-Cell, Diffuse/	18653
2	exp Lymphoma, B-Cell/	46925
3	(diffuse large B-cell or DLBCL or DLBL).mp.	12817
4	aggressive B-cell*.mp.	888
5	(large B-cell adj4 lymphoma*).mp.	24806
6	(diffuse adj4 lymphoma*).mp.	26167
7	1 or 2 or 3 or 4 or 5 or 6	53961
8	("EuroQOL 5-Dimension" or "Euroqol 5D" or "EQ-5D" or EQ5D or Euroqol or "EQ 5D" or "european quality of life").mp.	9697
9	(AQOL or "Assessment of Quality of Life" or "quality of life index" or "Australian quality of life" or "Australian qol").mp.	3404

#	Searches	Results
10	("Health utilities index" or HUI or HUI$ or (health adj2 (utilities or utility))).mp.	9075
11	("short form 6D" or "short-form 6D" or SF6D or SF-6D or "SF 6D").mp.	788
12	("quality of wellbeing" or QWB or "quality of well-being" or "quality of well being").mp.	444
13	("15D" or "16D" or "17D").mp.	2666
14	("standard gamble" or SG).mp.	9757
15	("time trade off" or "time trade-off" or "time tradeoff" or TTO).mp.	1766
16	("quality of wellbeing" or QWB or "quality of well-being" or "quality of well being").mp.	444
17	disutilit$.mp.	427
18	(health adj1 stat*).mp. or exp Health Status/	373073
19	(utility adj1 (value* or weight*)).mp.	1702
20	exp Models, Economic/	14164
21	preference$.mp.	154298
22	exp Patient Preference/	7224
23	(utilit* or "health utility index" or "utilities index").mp.	191583
24	(map$ or mapping or regression or "cross walking" or "cross-walking").mp.	1374835
25	("multiattribute utility" or "multi-attribute utility" or "multi attribute utility" or "mau").mp.	1057
26	quality of life index.mp.	1635
27	quality adjusted life year.mp. or exp Quality-Adjusted Life Years/	13406
28	("qaly" or "daly" or "adjusted life").mp.	19715
29	("quality adjusted" or "disability adjusted").mp.	19065
30	exp Disability Evaluation/ or disability.mp.	217118
31	disabled person.mp. or exp disabled person/	62127
32	life expectancy.mp. or exp life expectancy/	38178
33	(30 or 31) and 32	1971
34	("QoL" or "HRQoL" or "HRQL" or "health related quality of life" or "health-related quality of life").mp.	70597
35	quality of life.mp. or exp "quality of life"/	312202
36	or/18-29,33	2030039
37	36 and (34 or 35)	206244

#	Searches	Results
38	or/8-16	34646
39	37 or 38	227703
40	7 and 39	120
41	(2018 Sep* or 2018 Oct* or 2018 Nov* or 2018 Dec* or 2019 Jan* or 2019 Feb* or 2019 Mar* or 2019 Apr* or 2019 May* or 2019 Jun*).dp.	823904
42	40 and 41	3
43	limit 40 to ed=20180904-20190610	9
44	42 or 43	11

Table 66: The Cochrane Library, incorporating: EBM Reviews - Health Technology Assessment, EBM Reviews - NHS Economic Evaluation Database, Accessed 10 June 2019

#	Searches	Results
1	exp Lymphoma, B-Cell/	10
2	(diffuse large B-cell or DLBCL or DLBL).mp.	21
3	aggressive B-cell*.mp.	2
4	(large B-cell adj4 lymphoma*).mp.	22
5	(diffuse adj4 lymphoma*).mp.	23
6	1 or 2 or 3 or 4 or 5	31
7	("EuroQOL 5-Dimension" or "Euroqol 5D" or "EQ-5D" or EQ5D or Euroqol or "EQ 5D" or "european quality of life").mp.	744
8	(AQOL or "Assessment of Quality of Life" or "quality of life index" or "Australian quality of life" or "Australian qol").mp.	50
9	("Health utilities index" or HUI or HUI$ or (health adj2 (utilities or utility))).mp.	446
10	("short form 6D" or "short-form 6D" or SF6D or SF-6D or "SF 6D").mp.	55
11	("quality of wellbeing" or QWB or "quality of well-being" or "quality of well being").mp.	59
12	("15D" or "16D" or "17D").mp.	18
13	("standard gamble" or SG).mp.	210
14	("time trade off" or "time trade-off" or "time tradeoff" or TTO).mp.	365
15	("quality of wellbeing" or QWB or "quality of well-being" or "quality of well being").mp.	59
16	disutilit$.mp.	181
17	(health adj1 stat*).mp. or exp Health Status/	2028
18	(utility adj1 (value* or weight*)).mp.	1799
19	exp Models, Economic/	1695
20	preference$.mp.	1044

#	Searches	Results
21	exp Patient Preference/	477
22	(utilit* or "health utility index" or "utilities index").mp.	4821
23	(map$ or mapping or regression or "cross walking" or "cross-walking").mp.	1087
24	("multiattribute utility" or "multi-attribute utility" or "multi attribute utility" or "mau").mp.	11
25	quality of life index.mp.	14
26	quality adjusted life year.mp. or exp Quality-Adjusted Life Years/	3446
27	("qaly" or "daly" or "adjusted life").mp.	5050
28	("quality adjusted" or "disability adjusted").mp.	4937
29	exp Disability Evaluation/ or disability.mp.	771
30	disabled person.mp. or exp disabled person/	75
31	life expectancy.mp. or exp life expectancy/	1300
32	(29 or 30) and 31	73
33	("QoL" or "HRQoL" or "HRQL" or "health related quality of life" or "health-related quality of life").mp.	676
34	quality of life.mp. or exp "quality of life"/	6957
35	or/17-28,32	8965
36	35 and (33 or 34)	5665
37	or/8-16	1584
38	37 or 38	5747
39	7 and 39	6
40	39 (2018 Year-Current)	0

B1b.2 Results – Health state utilities SLR

B1b.2.1 Search yields

Original review (September 2018)

In total, 277 papers were identified through the electronic searches. Upon the removal of duplicate papers, 258 titles and abstracts were reviewed. A total of 21 were deemed to be potentially relevant and were ordered for full paper review; of these, 17 were excluded (Table 70). Hand searching yielded an additional three publications. This resulted in a total of nine publications which reported utility values for patients with DLBCL. Out of these seven publications reporting utility values for the relapse or refractory DLBCL were extracted.

Update review (June 2019)

An update of the searches was conducted on 10th June 2019 to identify new studies published since the original review was conducted. The decision problem was consistent with that of the original review.

Full details of the searches are provided in Section B1b.1.3. In total, 23 papers were identified through the electronic database searches. After screening of 23 citations on the basis of title and abstract, nine papers were deemed to be potentially relevant and were included for full publication review. At this stage, further six studies were excluded. Hand searching yielded two additional studies for inclusion in the review. This resulted in a total of five publications for final inclusion in the review update. Out of these, data from four publications for relapsed and refractory disease were extracted.

Overall summary

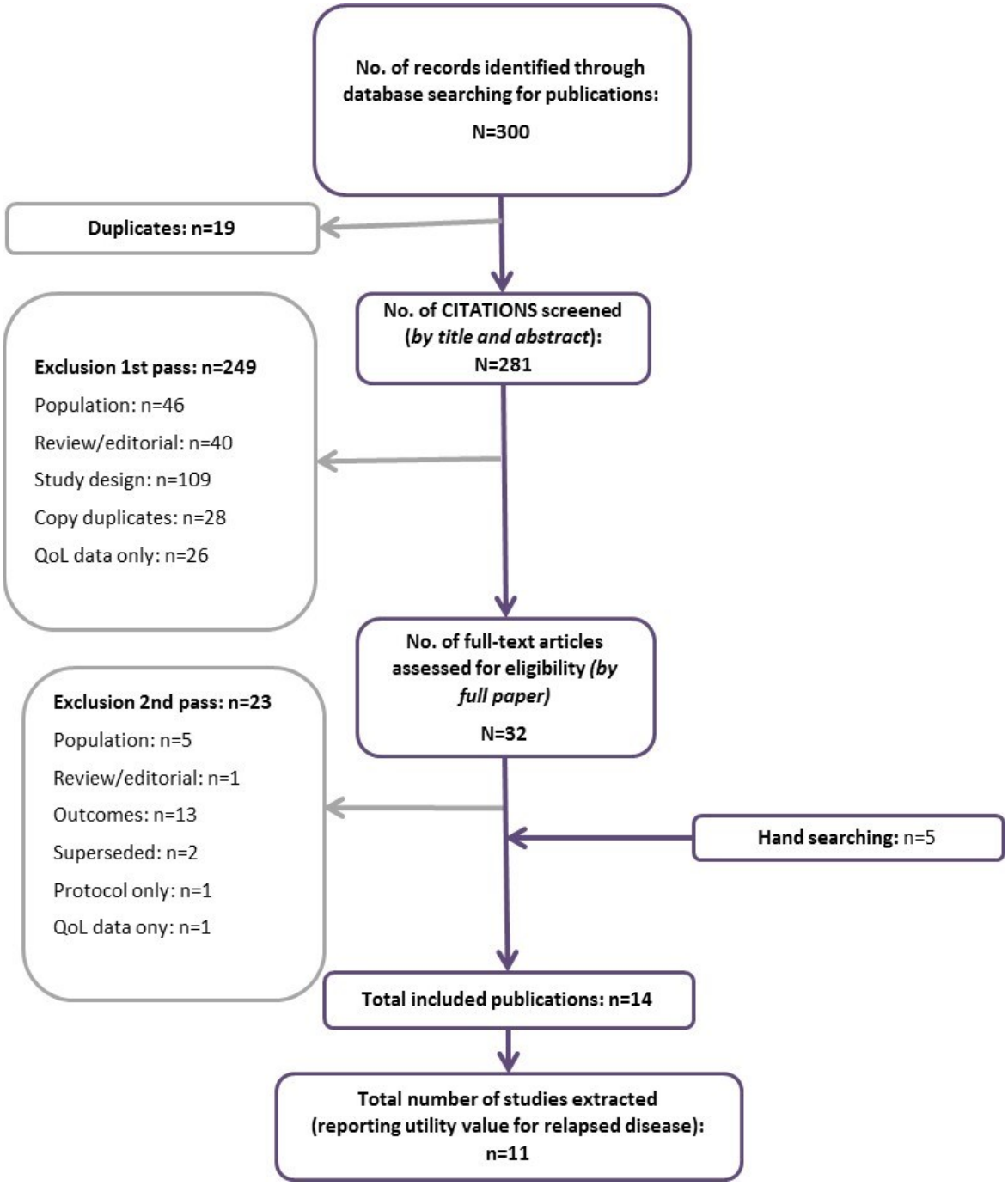
Across the original review and the June 2019 update, a total 14 unique studies were identified, out of which 11 studies in relapsed/refractory population were extracted. The remaining three publications reported utility values in patients with DLBCL in remission (62-64).

B1b.2.2 PRISMA flow diagrams

The process of study selection is depicted in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) overall flow diagram (Figure 61). Separate PRISMA flow diagrams for the original review and the June 2019 update are also provided in Figure 62 and Figure 63, respectively.

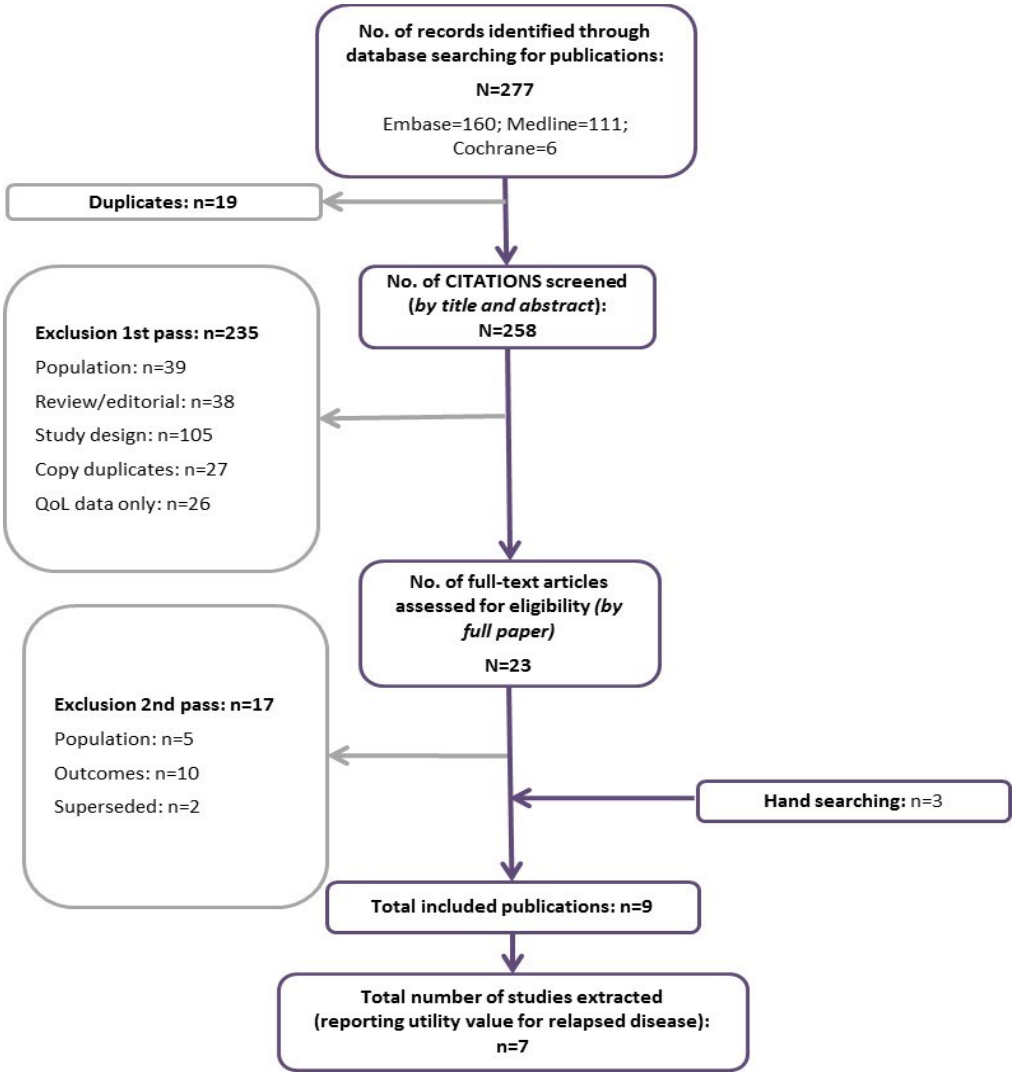
The list of publications, which were excluded are presented in Table 70.

Figure 61: PRISMA flow diagram of literature search for overall review [Database start (Embase 1974, MEDLINE 1946) to June 2019]



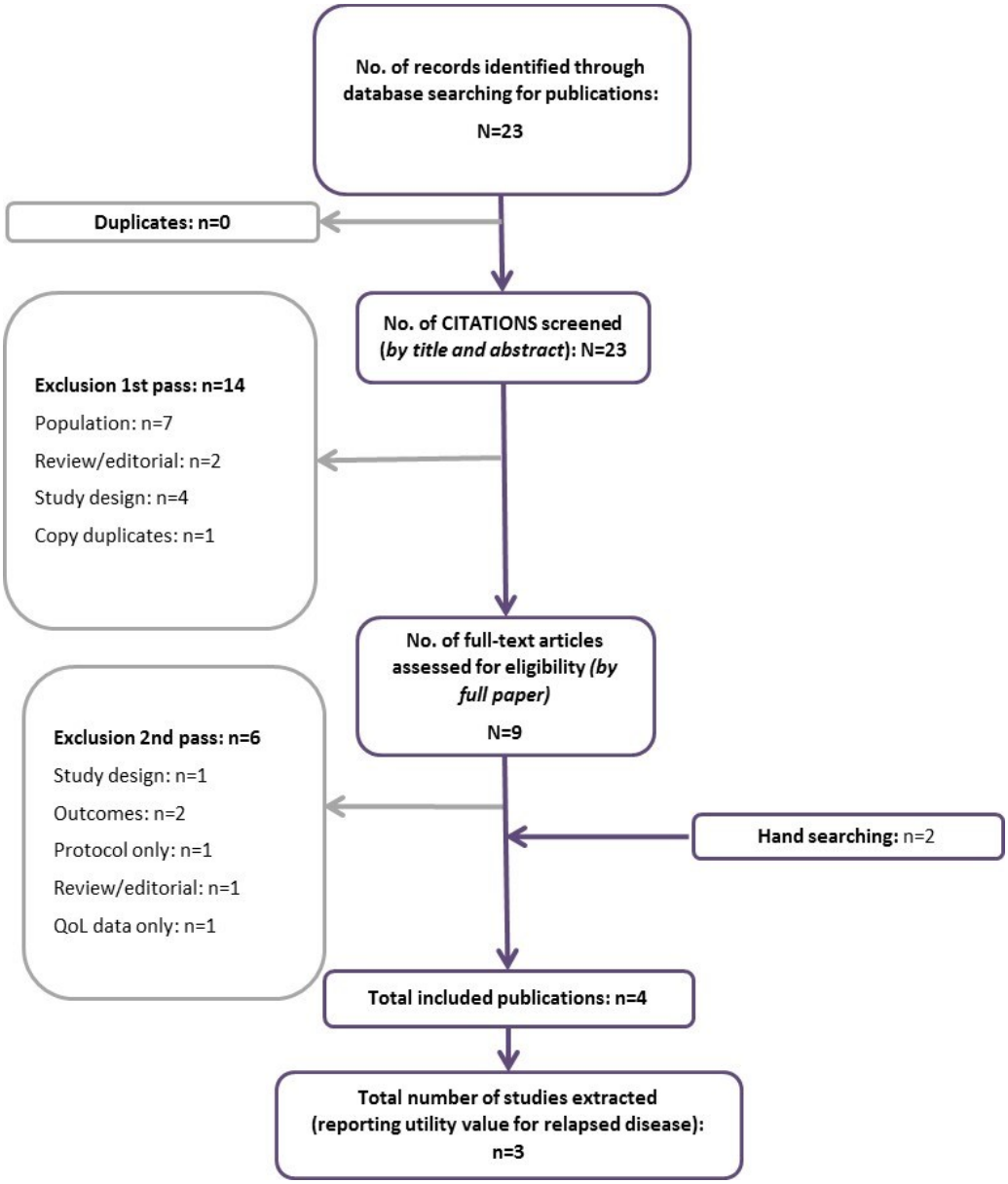
Original review (September 2018)

Figure 62: PRISMA flow diagram of literature search for the original review



Update review (June 2019)

Figure 63: PRISMA flow diagram of literature search for the update review



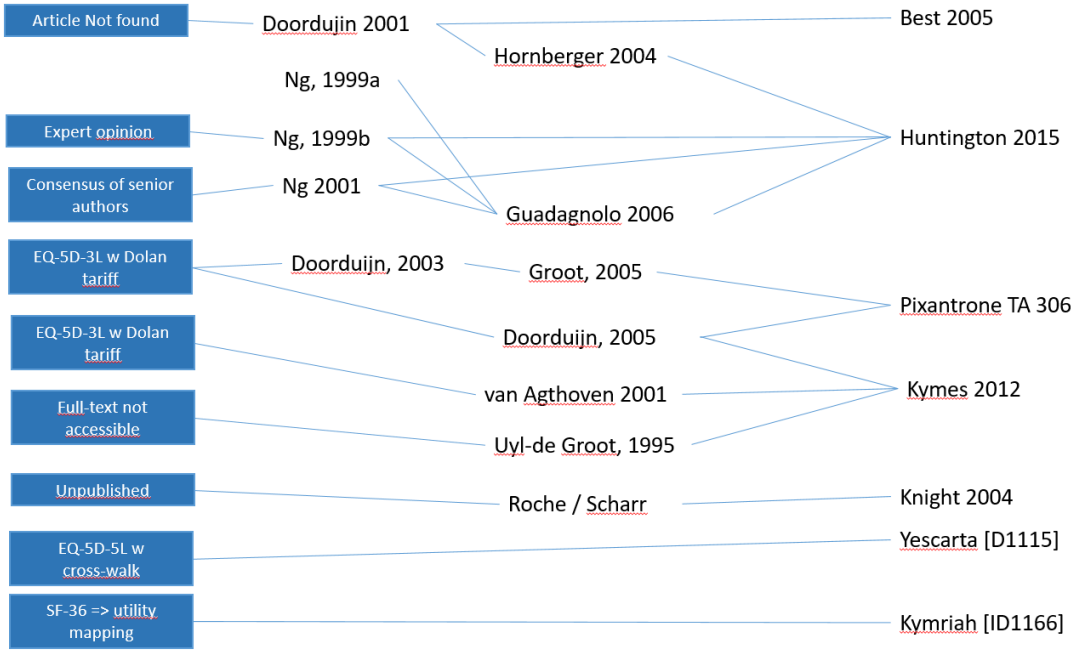
B1b.2.3 Description of studies identified

Overall, a total of 14 studies were eligible for inclusion in the utility review (62-75). Of these, 11 studies reported utility values associated with patients with relapsed or refractory DLBCL. These studies are considered most relevant for decision problem by NICE and are discussed further. The remaining three publications reported utility values in patients with DLBCL in first remission have not been described further (62-64).

The current review identified only one relevant utility study (75), all the remaining 10 included studies were HTAs/economic models. Among the 10 included models, six were published economic evaluations (65, 69, 71-74), while four were NICE technology appraisals (66-68, 70), which reported utility values for patients with relapsed or refractory DLBCL in respective economic models.

Of the 11 included studies, the only one relevant utility study was published as conference abstract (75), while all six published economic evaluations were full publications (65, 69, 71, 72, 74) and four were publications conducted from US payer perspective (65, 69) and one each conducted using UK (73) and French payer perspective (71). All the four NICE technology appraisals, were conducted from UK perspective (66-68, 70). Figure 64 shows how utility was estimated in the original source used and the cross-reference.

Figure 64: Original utility source and cross-reference



B1b.2.4 Relevant HSUV by line of treatment

The review identified seven relevant studies which reported utility data for relapsed or refractory DLBCL patients. A summary of the seven included studies reporting utility values is provided in Table 67 and a summary of their relevance to the NICE reference case is presented in Table 68.

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Table 67: Summary of studies identified in the review

Study name, Country	Population	Interventions/ comparators	Sample size Study type	Original reference source for utility data	Instrument used to derive utilities	Health states	Utility data
Primary utility studies/source							
(75) US	Patients age ≥18 years with R/R DLBCL	Lisocabtagene Maraleucel	N=90 RCT (NHL 001; NCT02631044)	Health state utility values were assessed with the EQ-5D-5L	EORTC QLQ-C30 EQ-5D-5L	• NR	Mean EQ-5D health state utility score • Baseline: 0.8276 • Month 1: 0.8099 • Month 2: 0.9351 • Month 3: 0.8417 • Month 6: 0.8444
Secondary utility studies/source							
(71) France, Belgium, and Switzerland	Untreated patients with DLBCL	R-CHOP CHOP	• GELA LNH CHOP, n: 197 • R-CHOP, n: 202 • SNLG CHOP, n: 816	Utility scores were based on a study by (76)	Utility scores for DFS and progression were based on a study by (76) in patients aged 65 to 90 with aggressive NHL (using EQ-5D)	• Complete responders • Non-responders • Survival	No CR/progression (relapse): 0.39

Study name, Country	Population	Interventions/ comparators	Sample size Study type	Original reference source for utility data	Instrument used to derive utilities	Health states	Utility data
(72) US	Adult patients with R/R LBCL treated with axi-cel vs salvage chemotherapy (R-DHAP)	Axicabtagene ciloleucel Salvage chemotherapy (R-DHAP)	N=NR (ZUMA-1 (NCT02348216) and SCHOLAR trial) Economic evaluation study	Utility scores from a patient-level analysis in the ZUMA-1 trial	EQ-5D-5L scores with US tariffs from a patient-level analysis in the ZUMA-1 trial cohort	• Progression • Post-Progression • Death	• Axi-cel on treatment: 0.740 • Remission with <6 months of follow-up: 0.782 • Remission with ≥6 months of follow-up: 0.823 • Salvage chemotherapy on treatment: 0.673 • Progressive disease: 0.390
(73) UK	Patients with relapsed or refractory aNHL who had failed ≥2 lines, receiving their third or fourth line of treatment	• Pixantrone • Current clinical practice (vinorelbin, oxaliplatin, ifosfamide, etoposide, mitoxantrone,	N=NR (PIX301 trial; NCT00088530)	Due to absence of utility data from PIX301 trial in the literature specific to the modeled population, patients' quality of life (based on	Utilities based on expert opinion. Utility decrements associated with AE were obtained from published literature and	• Stable/no progression, including progression-free patients • Progressive/relapsed disease, including	Utility (SE) • Pre-progression: 0.76 (0.03) • Post-progression: 0.68 (0.04)

Study name, Country	Population	Interventions/ comparators	Sample size Study type	Original reference source for utility data	Instrument used to derive utilities	Health states	Utility data
		and gemcitabine)		expert opinion) was assumed to be similar to that of patients with second line advanced and/or metastatic renal carcinoma	applied to PIX301 trial	living patients who have progressed • Death	
(65) US	Patients with DLBCL in first Remission	• Surveillance Imaging (routine CT/ or PET/CT)	NR Economic modelling study	Clinical utilities for various health states were based on values used in previous studies (77-80)	Not reported; Ranges of clinical utilities were informed by expert opinion and extensively analysed on sensitivity analyses	• Continued first remission • Disease relapse treated with salvage immunoche motherapy • ASCT • Second complete remission • Refractory or relapsed disease treated with palliative immunothera	Long-term utility (Range) • Relapsed disease: 0.90 (0.80 to 0.95) • Refractory disease: 0.80 (0.80 to 0.90) Utility adjustments • False-positive surveillance scan: -0.02 (0 to -0.03) • Salvage cytotoxic chemotherapy: -0.15 (-0.10 to -0.30) • Autologous

Study name, Country	Population	Interventions/ comparators	Sample size Study type	Original reference source for utility data	Instrument used to derive utilities	Health states	Utility data
						py • Death	SCT: -0.20, (-0.10 to -0.30)
(66) UK	Adult patients with DLBCL	R-CHOP CHOP	NR HTA	SCHARR and ROCHE models utilised QoL utility scores from an unpublished data source	The utility scores employed by the ROCHE model, based on the EuroQol. Utility weights for these states were taken from a large UK community sample	• Complete responders • Non-responders • Overall survival	Utility value of Non-responders /relapses • CHOP: 0.38 • R-CHOP: 0.38
(69) US	Relapsed DLBCL patients undergoing ASCT at Washington University	• Granulocyte colony-stimulating factor with plerixafor • Granulocyte colony-stimulating factor plus placebo	N=20 Economic modelling study	Utilities were based on previous studies (81, 82)	EQ-5D-3L and using the Dolan algorithm was used	• 1st apheresis session • 2nd apheresis session • 3rd apheresis session • 4th apheresis session • Rescue transplant	• Day before transplant (Patients while undergoing apheresis): 0.75 • 14 days post-transplant (during high-dose chemotherapy and engraftment): 0.53

Study name, Country	Population	Interventions/ comparators	Sample size Study type	Original reference source for utility data	Instrument used to derive utilities	Health states	Utility data
						• Recurrence • Death	• 3 months post-transplant (post engraftment): 0.78
(74) US	Adults with DLBCL R/R after two or more lines of therapy or relapsed 12 or fewer months after SCT	• Axicabtagene • Tisagenlecleucel • R-DHAP • R-GDP • R-GEMOX • R-ICE	N= NR (ZUMA-1, JULIET trial and SCHOLAR trial	Utility scores were based on a study by: • (81, 83-85) • Expert opinion	EORTC QLQ C-30 scales were converted to the preference-weighted EQ-5D	• Remission • Progression • Remission after transplantation • Progression after transplantation • Long-term remission	Axicabtagene ciloleucel • Month 1-2: 0.50 (0.40-0.60) • Remission after treatment: 0.70 (0.47-0.89) Tisagenlecleucel • Month 1-2: 0.58 (0.55-0.61) • Remission after treatment 0.70 (0.47-0.89) Autologous SCT • Month 1-2: 0.43 (0.23-0.64)

Study name, Country	Population	Interventions/ comparators	Sample size Study type	Original reference source for utility data	Instrument used to derive utilities	Health states	Utility data
							• Month 3 (if in remission): 0.70 (0.47-0.89) • Remission after treatment: 0.70 (0.47-0.89) Allogeneic SCT • Month 1-2: 0.35 (0.16-0.57) • Month 3 (if in remission): 0.45 (0.25-0.65) • Remission after treatment: 0.68 (0.46-0.86) • Progression: 0.45 (0.40-0.50)
NICE TA306 (70) UK	Adults with aggressive de novo or	• Pixantrone • Vinorelbine • Oxaliplatin	NR	Utilities were based on previous studies	Utility data were identified from published	4 health states: • Stable/PFS, on 3rd or 4th	• Pre-progression health state:

Study name, Country	Population	Interventions/ comparators	Sample size Study type	Original reference source for utility data	Instrument used to derive utilities	Health states	Utility data
	transformed NHL that had relapsed after 2 or more chemotherapy regimens, including at least 1 standard anthracycline-containing regimen with a response that had lasted at least 24 weeks	• Ifosfamide • Etoposide • Mitoxantrone • Gemcitabine		(81, 82)	sources for similar patient populations, and for disease areas with similar expected survival, disease progression, nature of the disease and quality of life	line treatment • Stable/PFS, discontinued 3rd or 4th line treatment • Progressive/relapsed disease • Death	0.76 • Post-progression health state: 0.68
NICE TA559 (67) UK	Adults with relapsed or refractory DLBCL, PMBCL or transformed FL	• Axicabtagene ciloleucel • BSC (consists of GEM, GEM-P, RGCVP, RVP)	N=34, with 87 observations HTA (data used for model) Utilities scores also captured from ZUMA-1	Trial collected EQ-5D-5L, and crosswalk algorithm was applied	Single arm trial collected EQ-5D-5L, and crosswalk algorithm was applied to convert estimates to EQ-5D-3L	• Pre-progression • Post progression • Death	**EQ-5d-3L index score:** • Screening: 0.739 (0.257) • Week 4: 0.675 (0.198) • Month 3: 0.756 (0.183) • Month 6: 0.758 (0.317)

Study name, Country	Population	Interventions/ comparators	Sample size Study type	Original reference source for utility data	Instrument used to derive utilities	Health states	Utility data
			(NCT02348216) safety management cohort				• Total: 0.724 (0.228) **Base case, mean utility (SE)** • Progression-free: 0.722 (0.210) • Progressed disease: 0.647(0.136) **Adverse event Disutilities** • Anemia: -0.12 • Neutropenia: -0.09 • Platelet count decreased: -0.11 • Thrombocytopenia: -0.11 • Pyrexia: -0.11 • Febrile neutropenia: -0.15 • Encephalopathy: -0.15 • Hypophosphat

Study name, Country	Population	Interventions/ comparators	Sample size Study type	Original reference source for utility data	Instrument used to derive utilities	Health states	Utility data
							emia: -0.15 • Hypotension: -0.15 • Leukopenia: -0.15 • Lymphocyte count decreased: -0.15 • Neutrophil count decreased: -0.15 • White blood cell count decreased: -0.15
NICE TA567 (68) UK	Adults with relapsed or refractory DLBCL either failed auto SCT or were ineligible for or did not consent to	• Tisagenlecleucel • Pixantrone monotherapy • R-GEMOX • R-GDP	JULIET trial (NCT02445248): N=111 HTA	SF-36 based on the mapping algorithm reported in (86)	Utility scores based on UK preference e-weights were calculated based on individual dimension	• Progression free • Progressed disease • Death	**Utilities** • Progression free state: 0.83 • Progressed disease state: 0.71 **Disutilities** • Treatment disutility per

Study name, Country	Population	Interventions/ comparators	Sample size Study type	Original reference source for utility data	Instrument used to derive utilities	Health states	Utility data
	autologous SCT				scores of SF-36 based on the mapping algorithm reported in (86)		cycle x1 (tisagenlecleucel): -0.011 • For ICU stay (tisagenlecleucel): -0.005 (CRS related); -0.002 (CRS unrelated) • Treatment disutility per cycle x1 (R-GEMOX): -0.017 • Treatment disutility per cycle x 2 (R-GDP): -0.013 • Treatment disutility per cycle x 2 (pixantrone monotherapy): -0.012 • Subsequent SCT disutility

Study name, Country	Population	Interventions/ comparators	Sample size Study type	Original reference source for utility data	Instrument used to derive utilities	Health states	Utility data
							per-cycle (allogenic and autologous): -0.025

Abbreviations: axi-cel, axicabtagene ciloleucel; ASCT, autologous stem cell transplantation; BSC, best supportive care; CT, computed tomography; CR, complete responder; CHOP, cyclophosphamide, doxorubicin, vincristine, and prednisolone; CRS, cytokine release syndrome; DFS, disease free state; DLBCL, diffuse large B cell lymphoma; FL, follicular lymphoma; EQ-5D, EuroQol 5 dimensions; GEM, gemcitabine and methylprednisolone; GEM-P, gemcitabine, methylprednisolone, and cisplatin; HTA, Health technology assessment; ICU, intensive care unit; NHL; on-Hodgkin lymphoma, PET, positron emission tomography; PMBCL, primary mediastinal B-cell lymphoma; R-CHOP, rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisolone; R-GDP, R-DHAP, cyclophosphamide, doxorubicin, vincristine, and prednisolone rituximab, gemcitabine, cisplatin, and dexamethasone; R-GEMOX, rituximab, gemcitabine, and oxaliplatin; RGCVP, rituximab, gemcitabine, cyclophosphamide, vincristine, and prednisolone; RVP, rituximab, vinblastine, and prednisolone; SE, standard error; SNLG, Scottish and Newcastle Lymphoma Group; SE, standard error; UK, United Kingdom; US, United States.

Table 68: Summary of relevance of identified full publications to the NICE reference case

Study	Is the generic preference-based EQ-5D instrument used to describe health states?	Do patients describe the health states?	Are appropriate societal preferences used to value health states?	Is the TTO/SG method used to value health states?	Is the study consistent with the NICE reference case?
(71)	Unclear	Yes	Yes	Unclear	It is unclear if this study meets the requirements of the NICE reference case – The evaluation was conducted in patients receiving first-line DLBCL treatment, and was conducted from French payer perspective
(65)	No; Ranges of clinical utilities were informed by expert opinion and extensively analysed on sensitivity analyses	Yes	Unclear	Unclear	It is unclear if this study meets the requirements of the NICE reference case – it is unclear if UK societal preferences were used to value health states The study was conducted across sites in the US, so it is unclear if the results are generalizable to a UK setting
(66)	Yes	Yes	Yes	No	It is unclear if this study meets the requirements of the NICE reference case – although this is NICE HTA submission and relevant to UK population. However, the evaluation was conducted in patients receiving first-line DLBCL treatment
(75)	Yes	No	Yes	No	It is unclear if this study meets the requirements of the NICE reference case – the study is only published as conference abstract and was conducted across US, so it is unclear if the results are generalizable to a UK setting

(74)	Yes	Yes	Unclear	Unclear	It is unclear if this study meets the requirements of the NICE reference case – The study was conducted with the US perspective, so it is unclear if the results are generalizable to a UK setting
(72)	Yes	Yes	Yes	Unclear	It is unclear if this study meets the requirements of the NICE reference case – as the study was conducted with the US perspective, so it is unclear if the results are generalizable to a UK setting
(73)	Unclear	Yes	Unclear	Unclear	It is unclear if this study meets the requirements of the NICE reference case – although this was conducted using UK payer perspective. However, the evaluation was conducted in patients with mixed population.

(69)	Yes	Yes	Unclear	Unclear	It is unclear if this study meets the requirements of the NICE reference case – it is unclear if UK societal preferences were used to value health states The study was conducted across sites in the US, so it is unclear if the results are generalizable to a UK setting
NICE TA306 (70)	Yes	Yes	Yes	No	The manufacturer's initial results did not meet the requirements of NICE, and ERG considered that the utility weights used by the manufacturer in the original economic model was potentially inappropriate. ERG noted that the utility values were from a population of patients receiving first-line treatment for aggressive non-Hodgkin's lymphoma and were derived from a study that had initially been rejected by the manufacturer in their SLR. Further, the manufacturer's reported utility values that were higher than those derived for healthy older patients in the UK. However, the committee concluded that, although there was some uncertainty as to the true utility value, the utility values used in the manufacturer's revised model with the patient access scheme were acceptable in the committee's decision-making.

NICE TA559 (67)	Yes	Yes	Yes	Yes	This study meets the requirements of the NICE reference case as crosswalk algorithm was applied to convert estimates to EQ-5D-3L. Further this study collected EQ-5D data in a small subgroup of patients. However, the evaluation was conducted in patients with DLBCL, PMBCL, and FL patients. Apart from this, ERG mentioned that for survival data, KM curves were heavily influenced by censoring data after 12 months, with very few patients' remaining at risk. However, the committee's overall observation was that the results were clinically meaningful, but lack of comparative data made the assessment challenging.
NICE TA567 (68)	Yes	Yes	Yes	Yes	This is a NICE HTA submission and relevant to the UK population. NICE concluded that the use of progression-free utility values were consistent with the assumed cure point. The committee also mentioned that ERG's preferred analyses, which includes an age-adjusted utility decrement, may not have major impact on cost-effectiveness results.

Abbreviations: DLBCL, diffuse large B cell lymphoma; EQ-5D, ERG, European Research Group; EuroQol 5 dimensional; FL, follicular lymphoma; HTA, Health technology assessment; NICE, National Institute for Health and Care Excellence; PMBCL, primary mediastinal B-cell lymphoma; SG, standard gamble; TTO, time trade-off; UK, United Kingdom; US, United States

B1b.2.5 Relevant disutilities and decrements

Four studies reported disutilities values, and have been described in Table 69.

Table 69: Disutilities and decrements for adverse event health states in patients with DLBCL

Study name Country	Population	Interventions/ comparators	Instrument used to derive utilities	Disutilities
NICE TA559 (67) UK	Adults with relapsed or refractory DLBCL, PMBCL or transformed FL	• Axicabtagene ciloleucel • BSC (consists of GEM, GEM-P, RGCVP, RVP)	Single arm trial collected EQ-5D-5L, and crosswalk algorithm was applied to convert estimates to EQ-5D-3L	• Anemia: -0.12 • Neutropenia: -0.09 • Platelet count decreased: -0.11 • Thrombocytopenia: -0.11 • Pyrexia: -0.11 • Febrile neutropenia: -0.15 • Encephalopathy: -0.15 • Hypophosphatemia: -0.15 • Hypotension: -0.15 • Leukopenia: -0.15 • Lymphocyte count decreased: -0.15 • Neutrophil count decreased: -0.15 • White blood cell count decreased: -0.15
(72) US	Adult patients with R/R LBCL treated with axi-cel vs salvage chemotherapy (R-DHAP)	• Axicabtagene ciloleucel • Salvage chemotherapy (R-DHAP)	EQ-5D-5L scores with US tariffs from a patient-level analysis in the ZUMA-1 trial cohort	• Salvage chemotherapy on treatment: -0.15
(73) UK	Patients with relapsed or refractory aNHL who had failed ≥2 lines, receiving their third or fourth line of treatment	• Pixantrone • CCP	Utilities based on expert opinion. Utility decrements associated with AE were obtained from published literature and applied to PIX301 trial	Weighted average annual utility decrements associated with grade 2 AEs • Pixantrone: -0.0075 • CCP: -0.0066 Average utility decrements associated with grade 3/4 AEs • Pixantrone: -0.0078 • CCP: -0.0073

Study name Country	Population	Interventions/ comparators	Instrument used to derive utilities	Disutilities
NICE TA567 (68) UK	Adults with relapsed or refractory DLBCL either failed auto SCT or were ineligible for or did not consent to autologous SCT	• Tisagenlecleucel • Pixantrone monotherapy • R-GEMOX • R-GDP	EQ-5D utility scores based on UK preference e-weights were calculated based on individual dimension scores of SF-36 based on the mapping algorithm reported in (86)	• Treatment disutility per cycle x1 (tisagenlecleucel): -0.011 • For ICU stay (tisagenlecleucel): -0.005 (CRS related); -0.002 (CRS unrelated) • Treatment disutility per cycle x1 (R-GEMOX): -0.017 • Treatment disutility per cycle x 2 (R-GDP): -0.013 • Treatment disutility per cycle x 2 (pixantrone monotherapy): -0.012 • Subsequent SCT disutility per-cycle (allogenic and autologous): -0.025

Abbreviations: aNHL, advanced Non-Hodgkin lymphoma; AEs, adverse events; ASCT, autologous stem cell transplantation; BSC, best supportive care; CCP, current clinical practice; DLBCL, diffuse large B cell lymphoma; FL, follicular lymphoma; GEM, gemcitabine and methylprednisolone; GEM-P, gemcitabine, methylprednisolone, and cisplatin; HTA, Health technology assessment; ICU, intensive care unit; PET, positron emission tomography; PMBCL, primary mediastinal B-cell lymphoma; R-CHOP, rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisolone; R-GDP, rituximab, gemcitabine, cisplatin, and dexamethasone; R-GEMOX, rituximab, gemcitabine, and oxaliplatin; RGCVP, rituximab, gemcitabine, cyclophosphamide, vincristine, and prednisolone; RVP, rituximab, vinblastine, and prednisolone; SE, standard error; UK, United Kingdom; US, United States

B1b.2.6 Relevance of identified utility values

The current evidence base suggests limited utility studies in patients with R/R DLBCL. The review identified only one recently published utility study. All the remaining utility values captured within this review have been used in the previously published economic models, some of which were used in NICE technology appraisals (66-68, 70).

B1b.2.7 Excluded studies on the basis of full publication

Table 70: Studies excluded on the basis of full publication

	Reference	Link	Rationale for exclusion
Original review			
1	Cost-effectiveness of rituximab in the treatment of diffuse large B-cell non-hodgkin's lymphoma patients (DLBCL) in China	https://www.valueinhealthjournal.com/article/S1098-3015(16)30851-8/abstract	Outcomes not of interest (Economic evaluation, no relevant utility data reported for patients with R/R DLBCL)

	Reference	Link	Rationale for exclusion
2	Cost-effectiveness of subtype-based treatment strategies for diffuse large b-cell lymphoma patients (DLBCL)	http://www.bloodjournal.org/content/126/23/4476?sso-checked=true	Outcomes (Economic evaluation, no relevant utility data reported for patients with R/R DLBCL)
3	Comparative effectiveness and cost of adding rituximab to first-line chemotherapy for elderly patients diagnosed with diffuse large B-cell lymphoma	PMID: 22648454	Outcomes (Economic evaluation, no relevant utility data reported for patients with R/R DLBCL)
4	Cost-effectiveness of brentuximab vedotin in relapsed or refractory systemic anaplastic large cell lymphoma in Taiwan	https://www.valueinhealthjournal.com/article/S1098-3015(16)31285-2/abstract	Population (patients with lymphoma subtypes other than DLBCL)
5	Health state utilities for relapsed/refractory (rel/ref) Hodgkin's lymphoma (HL) and systemic anaplastic large-cell lymphoma (sALCL): Asian pacific country data	https://www.valueinhealthjournal.com/article/S1098-3015(12)02036-0/abstract	Population (patients with lymphoma subtypes other than DLBCL)
6	Health utilities in relation to treatment response and adverse events in relapsed/refractory Hodgkin lymphoma and systemic anaplastic large cell lymphoma	PMID: 25284490	Population (patients with lymphoma subtypes other than DLBCL)
7	Cost-utility analysis of primary prophylaxis versus secondary prophylaxis with granulocyte colony-stimulating factor in elderly patients with diffuse aggressive lymphoma receiving curative-intent chemotherapy	PMID: 22393098	Outcomes (Economic evaluation, no relevant utility data reported for patients with R/R DLBCL)
8	Estimating health state utilities for patients with relapsed/ refractory (R/R) Hodgkin lymphoma (HL) and systemic anaplastic large-cell lymphoma (SALCL) in Mexico and Brazil	https://www.valueinhealthjournal.com/article/S1098-3015(13)02456-X/fulltext	Population (patients with lymphoma subtypes other than DLBCL)
9	Cost-effectiveness of the addition of rituximab to CHOP chemotherapy in first-line treatment for diffuse large B-	PMID: 20561333	Outcomes (Economic evaluation, no relevant utility data reported for patients with R/R DLBCL)

	Reference	Link	Rationale for exclusion
	cell lymphoma in a population-based observational cohort in British Columbia, Canada		
10	Deriving health utility values from a health-related quality of life instrument in non-Hodgkin lymphoma patients	http://www.bloodjournal.org/content/118/21/2065	Population (patients with lymphoma subtypes other than DLBCL)
11	The cost-effectiveness of plerixafor plus G-CSF for stem cell mobilization in patients with diffuse large B-cell non-Hodgkin Lymphoma (DLBCL)	https://www.bbmt.org/article/S1083-8791(10)00716-0/fulltext	Conference superseded by full paper
12	Cost-utility analysis of routine surveillance imaging of patients in first remission after treatment for diffuse large B-cell lymphoma	http://ascopubs.org/doi/abs/10.1200/jco.2014.32.15_suppl.6526	Conference superseded by full paper
13	Cost-effectiveness of filgrastim and pegfilgrastim as primary prophylaxis against febrile neutropenia in lymphoma patients receiving R-CHOP chemotherapy	PMID: 23873405	Outcomes (Economic evaluation, no relevant utility data reported for patients with R/R DLBCL)
14	Cost-effectiveness analysis of the addition of rituximab to CHOP in young patients with good-prognosis diffuse large-B-cell lymphoma	PMID: 18081361	Outcomes (Economic evaluation, no relevant utility data reported for patients with R/R DLBCL)
15	Cost-effectiveness of rituximab (MabThera) in diffuse large B-cell lymphoma in the Netherlands	PMID: 15693788	Outcomes (Economic evaluation, no relevant utility data reported for patients with R/R DLBCL)
16	Cost utility in the United States of rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone for the treatment of elderly patients with diffuse large B-cell lymphoma	PMID: 15756658	Outcomes (Economic evaluation, no relevant utility data reported for patients with R/R DLBCL)
17	Cost-effectiveness of filgrastim and pegfilgrastim as primary prophylaxis against febrile neutropenia in lymphoma patients	http://www.bloodjournal.org/content/114/22/2475?sso-checked=true	Outcomes (Economic evaluation, no relevant utility data reported for patients with R/R DLBCL)
Update review			
1	What are patients' preferences and satisfaction regarding modes of administration for the treatment of chronic lymphocytic leukemia (CLL),	http://dx.doi.org/10.1182/blood-	Study design

	Reference	Link	Rationale for exclusion
	diffuse large B-cell lymphoma (DLBCL), and follicular lymphoma (FL)?	2018-99-115327	
2	Clinical and quality of life predictors of failure to achieve event free survival at 24 months in patients aged 70 years and older with diffuse large b-cell lymphoma.	http://dx.doi.org/10.1182/blood-2018-99-118356	QoL data only (QOL was assessed at enrollment using a single item Linear Analogue Self-Assessment and the 27-item Functional Assessment of Cancer Treatment-General questionnaire)
3	Patients' decision-making, experiences and preferences regarding pixantrone treatment in relapsed or refractory diffuse large B-cell lymphoma: study protocol for a longitudinal mixed methods study.	https://dx.doi.org/10.1136/bmjopen-2018-026505	Protocol only
4	The burden of relapsed/refractory (R/R) diffuse large B-cell lymphoma (DLBCL): A systematic literature review (SLR).	http://dx.doi.org/10.1182/blood-2018-99-112878	Review/editorial
5	Cost-effectiveness of axicabtagene ciloleucel for relapsed or refractory diffuse large b-cell lymphoma in Italy.	http://dx.doi.org/10.1182/blood-2018-99-113838	Outcomes
6	Cost-Effectiveness of Tisagenlecleucel for Adults with Relapsed or Refractory Diffuse Large B-Cell Lymphoma: A Canadian Societal Perspective.	http://dx.doi.org/10.1016/j.jval.2018.09.260	Outcomes

c. Cost and healthcare resource identification searches (Appendix J)

Two SLR searches were conducted to identify the costs and healthcare resources required for the study. The original search was carried out on 25th August 2021, and the update searches were conducted on 13th September 2022. The complete search strategies for all databases that were searched have already been provided in Appendix J.

B2. Please clarify how was the scenario analysis "No PFS cure point for BR and Pola-BR" performed, as the submitted economic version model does not appear to have the functionality to easily modify the cure assumption settings for the comparators alone. If this functionality is not currently implemented in the electronic version of the model, please update it accordingly.

Functionality has been added to the economic model to allow the implementation of differential long-term survivorship assumptions by treatment arm.

In-line with previously accepted appraisal precedents (TA649 (87), TA567 (88), TA559 (89)), the Company base-case assumes that long-term remission is treatment independent. Clinical experts consulted by the Company also agreed that long-term remission was plausible in 3L+ DLBCL.

Removing the PFS cure point for Pola-BR and BR was explored as a scenario to reflect the fact that continuing progression was observed after 2 years for people with DLBCL receiving these treatments. As such, treatment independent long-term remission assumptions should only be explored where there is continued evidence of progression beyond 2 years.

B3. Regarding the validation of the long-term clinical plausibility of the extrapolated curves for PFS and OS by the clinical experts in the advisory board (see page 186, CS), please clarify the following:

a. Were the clinical experts asked to examine the clinical plausibility of the OS and PFS extrapolation models fitted to the glofitamab Kaplan Meier curves of the three population adjusted curves or just to the unadjusted curves.

Clinical experts consulted at the glofitamab HTA advisory board were presented the adjusted and unadjusted glofitamab Kaplan Meier plots in the context of considering the PFS and OS ITC results.

When considering the clinical plausibility of the glofitamab OS and PFS extrapolation models, clinical experts were asked to examine the plausibility of extrapolations fitted to the unadjusted NP30179 Kaplan Meier curves. With a larger sample size underpinning the unadjusted Kaplan Meier curves, compared to the reduced sample sizes in the population adjusted curves, it was deemed more appropriate to determine the best fitting models to the unadjusted curves. The choice of the best fitting and most clinically plausible models, based on fit to the unadjusted curve, was applied in all analyses of survival, in all comparisons. Furthermore, the risk of death or progression is not expected to be substantially different in the adjusted populations, which contain a subset of the overall NP30179 3L+ DLBCL cohort, from which the choice of most appropriate extrapolation models were based. As can be

seen in the response to Question B4, generalised gamma, the base-case glofitamab PFS and OS parametric distribution, is the best fitting extrapolation fitted to the pola-BR and BR adjusted KM curves, and the second best fitting distribution to the axi-cel adjusted KM curve. The best fitting PFS and OS parametric distribution the axi-cel adjusted population is gompertz, which produced implausible long-term survival predictions, making generalised gamma the most appropriate distribution in all scenarios, across all populations and comparisons.

b. Was the long-term clinical plausibility of the glofitamab and comparators extrapolated curves for PFS and OS assessed exclusively on the seven standard parametric models presented in the submission, or were other extrapolation models considered (e.g., piecewise, mixture-cure, landmark response, spline models, etc.)? Please list all the extrapolation models examined by the clinical experts in the advisory board.

Clinical experts consulted by the Company were asked to consider the clinical plausibility of the glofitamab and comparator PFS and OS extrapolation curves for the seven standard models presented in the company submission.

Other flexible models have been developed in response to question B7. As discussed at the clarification meeting, these models and the results of the analyses will be provided by the 3rd April 2023.

B4. Please report the AIC and BIC for the alternative PFS and OS extrapolation models fitted to the each of the three population-adjusted Kaplan-Meier curves for glofitamab, as well as corresponding survival plots (for a time horizon of 100 months to improve visualisation).

Table 71, and Figure 65 to Figure 70 present the AIC and BIC for PFS and OS extrapolation models fitted to the population adjusted KM curves for glofitamab.

Table 71: Glofitamab population-adjusted AIC and BIC values for extrapolation models of PFS and OS

Extrapolation	Glofit adjusted population (BR)		Glofit adjusted population (Pola-BR)		Glofit adjusted population (Axi-cel)	
	AIC	BIC	AIC	BIC	AIC	BIC
PFS						
Exponential	343.398	345.458	324.749	327.180	481.525	484.140
Weibull	336.595	340.716	320.450	325.311	464.213	469.444
Log Normal	318.090	322.211	306.647	311.508	447.591	452.821

Gen Gamma	313.681	319.862	301.974	309.266	437.783	445.628
Log Logistic	316.758	320.879	307.534	312.396	451.517	456.747
Gompertz	323.524	327.645	311.003	315.865	431.177	436.407
Gamma	341.580	345.701	323.861	328.723	469.618	474.848
OS						
Exponential	279.106	282.041	487.525	490.529	123.553	126.298
Weibull	280.010	285.879	488.135	494.143	122.322	127.812
Log Normal	275.270	281.139	483.388	489.396	120.073	125.562
Gen Gamma	275.843	284.646	485.372	494.384	121.478	129.713
Log Logistic	276.977	282.846	484.244	490.252	120.928	126.418
Gompertz	276.297	282.166	483.809	489.817	120.431	125.921
Gamma	280.530	286.399	488.747	494.755	122.973	128.463

Figure 65: PFS extrapolations for glofitamab weighted population (BR)

Figure 66: OS extrapolations for glofitamab weighted population (BR)

Figure 67: PFS extrapolations for glofitamab weighted population (Pola-BR)

Figure 68: OS extrapolations for glofitamab weighted population (Pola-BR)

Figure 69: PFS extrapolations for glofitamab weighted population (axi-cel)

Figure 70: OS extrapolations for glofitamab weighted population (axi-cel)

B5. Please clarify why the PFS and OS hazard plots for polatuzumab with bendamustine and rituximab (pola-BR) (unadjusted, Figures 31 and

34) and PFS hazard plot for bendamustine and rituximab (BR) (unadjusted, Figure 25) appear to be truncated in the CS. If the hazard plots were truncated, please submit hazard plots for the totality of the follow-up used to inform the PFS and OS with pola-BR, and PFS for BR.

The original KM plots were computed for the overall raw data and the horizontal axis had an upper bound of approximately 90 months, because this covers the timeline of observations across trial populations. As such, the plots provided were not truncated. However, the plots were using the cartesian system with (0, 0) as the reference point which might have led to the axes cluttering with the curves in extreme cases (i.e Weibull near the origin point).

To enhance visibility we procure updated plots so that the horizontal (time) axis extends up to 240 months (showing the behavior of the distribution tails in the limit). In order to avoid the image cluttering which happens at the left hand side, we are also including a 3% buffer between the horizontal and vertical axes to move them away from the origin (0, 0) so that they don't interfere with the graphs from the curves near the origin.

Lastly, regarding the hazard plots, the vertical axis is bounded by the overall range of the predicted hazard (approximately within the interval [0, 0.2]). However, with the Weibull hazard, by definition the probability goes to infinity as time approaches zero in contrast to the remaining distributions. Therefore, further extending the vertical axis e.g [0, 1] would essentially lead to a plot where the empirical estimate and the estimated smooth curves are all squeezed together hence reducing the ability for graphical evaluation of goodness of fit for the hazard.

Figure 71: PFS hazard and survival plots for distributions considered for glofitamab (adjusted) and pola-BR (unadjusted)

Figure 72: OS hazard and survival plots for distributions considered for glofitamab (adjusted) and pola-BR (unadjusted)

Figure 73: PFS hazard and survival plots for distributions considered for glofitamab (adjusted) and BR (unadjusted)

B6. Priority question: The electronic version of the model allows selecting extrapolation models for PFS and OS that are not currently reported in the CS. These include Bayesian average models and piece-wise models (Kaplan Meier + extrapolation standard parametric models).

a. Please clarify why were the results of these alternative extrapolation models not formally included in the CS.

Bayesian average and piece-wise models were included in the economic model for completeness, allowing greater flexibility to explore alternative models if requested. The approach used in the base-case, where survival predictions are informed by the best fitting, most clinically plausible parametric extrapolation, is commonly used in technology appraisals where it is widely accepted. As such, it was deemed that the inclusion of a number of additional extrapolation models would introduce unnecessary additional complexity to the submission.

b. Please provide details on the methodology followed to estimate the Bayesian average models.

A standard approach was used to estimate the Bayesian average model. The Bayesian average was estimated as the weighted average of all the considered parametric extrapolations, where the individual weights are estimated as EXP (-0.5*BIC) and then normalised.

B7. Priority question: The PFS and OS hazard plots in the CS (Figures 19, 22, 25, 28, 31, 34) for glofitamab (adjusted and unadjusted), BR, Pola-BR and axi-cel, suggest that the survival for these treatments may follow complex hazard functions. Previous technology appraisals (TAs) in third-line DLBCL have explored flexible methods for the extrapolation of the PFS and OS, as is currently recommended by the NICE Decision Support Unit (DSU) Technical Support Document (TSD) 21. 1 However, the CS only reports on the assessment of alternative survival extrapolations with standard parametric survival distributions.

a. Please update the electronic version of the model, so as to include flexible survival models for glofitamab (population adjusted and unadjusted), Pola-BR and axi-cel, as per the NICE DSU TSD 21, 1 and report on the assessment of these extrapolation models based on statistical and visual goodness of fit, as well as their clinical plausibility. As a minimum, please include in the analysis parametric mixture-cure and spline-based models.

The electronic version of the model has been updated to allow testing of deterministic and probabilistic scenarios using splines for OS and PFS for all available comparator arms, as well as mixture cure models for OS and PFS for those comparisons for which fitting such models was methodologically feasible (i.e. only glofitamab vs Pola-BR, see below). All flexible parametric models were estimated independently for each treatment arm using the relevant weights estimated from the respective ITCs. In light of the substantial amount of questions that needed to be addressed in the clarification response and the limited time for implementation, it was not possible to test other families of flexible parametric models. Similarly, it was not possible to implement a mixture cure model for the glofitamab unadjusted population.

Restricted cubic spline models were fitted on the log-hazard scale using one, two, and three internal knots, respectively. The internal knots were placed uniformly along the uncensored log-transformed event times. This approach is consistent with the guidance on the number and positioning of knots from Royston and Parmer, which is the default set up of the flexsurvespline function of the flexsurv R package and has been accepted in previous submissions (e.g. TA567)(90, 91).

It should be noted that, whilst these models may display a strong statistical fit to observed survival data, they may produce clinically unrealistic extrapolations in the long-term, as they represent a purely statistical exercise in model fitting rather than an attempt to reflect the clinical mechanisms underlying the observed hazard function (91). Flexible spline models rely heavily on data observed towards the end of the curve where such data are sparse. Therefore, the suitability of extrapolations requires careful consideration as these would be informed mostly by the end of the curve (where potentially few patients are left at risk). For example, here, spline functions fitted for the BR arm yielded clinically implausible crossings of PFS and OS early in the model time horizon.

Mixture-cure models were fitted only for those comparisons where IPDs were available for both treatment arms. Incorporating background mortality into survival models is essential when fitting mixture-cure models (NICE TSD 21), as the likelihood function for mixture cure models requires individual background hazard information for the censored patients (92). Therefore, only comparisons between glofitamab and Pola-BR could be generated because individual background hazards for censored patients cannot be reliably estimated when only aggregate level information and pseudo-IPDs are available for a given treatment, such as in the case

of MAICs. Accordingly, we decided to remain consistent with the approach used in the original Company submission base case, where the same types of parametric models and of CE model assumptions (e.g. for the long-term remission/survivorship scenarios) are considered for all treatments in a comparison.

Mixture-cure models were fitted using the flexsurvcure R package, which is built upon the established flexsurv survival analysis and allows for direct incorporation of ITC weights in the model fitting. Seven standard parametric models were considered (exponential, weibull, log-normal, log-logistic, gompertz, gamma and generalized gamma) to model the survival of the non-cured fraction. An “OS informed by PFS” approach was employed to estimate the cure fraction for OS and ensure this remained consistent across both endpoints. This was done by using the cure proportion predicted for the PFS models as an external parameter input in the fitting of the OS models. This approach is in line with what was done and accepted in previous TAs (e.g. TA874)(93).

Note that parameter estimation for mixture-cure models for OS and PFS fitted using exponential (for glofitamab and Pola-BR), weibull, gamma and gompertz (for Pola-BR only) distributions did not converge (the covariance matrix for Pola-BR gengamma distribution is likely unstable).

b. Please report cost-effectiveness (CE) results for scenario analyses using these flexible parametric survival models.

B7b.1 Spline model approach

In each comparison, spline models with one, two, and three internal knots were assessed to determine which one provided the best fit to the glofitamab population adjusted data and respective treatment comparator. The optimal number of internal knots is determined primarily by the lowest AIC and then by comparing graphically addressing overfitting, consistency and clinical plausibility, especially on long-term survival, where these models might lead to implausible results due to limited data. While higher-knot models may show better goodness of fit based on AIC and early observations, this is an artificial result of model overfitting and might not hold true for long-term predictions, as seen in the case of BR where such models produced unrealistic results. Therefore, where such discrepancies are observed from the plots, more simple models (fewer knots) that reduce complexity and prioritise clinically plausible long-term predictions are preferred.

The rationale behind the base-case selection of model is described in the following sections.

B7b.1.1 Glofitamab vs BR

Progression free survival

The spline 3-knots better fits the observed hazard for glofitamab PFS, with the 2-knots also showing a reasonable fit (see Figure 74 to Figure 76). However, the 2-

knot model has the highest AIC, suggesting a worse overall fit, but generally speaking, the fit can be considered fairly similar across each of the models considered.

The 3-knots model AIC is very close to the lowest (survival fit curve is more or less similar with all splines), so overall the 3-knots model can be considered the best fitting, and is preferred in the base-case.

Spline 3-knot is the best fit to the observed hazard for BR PFS, the survival curve fit is a slightly better with 3-knots, and has the 2nd lowest AIC (very close to lowest) (see Table 72).

Figure 74: PFS cumulative hazard, hazard, and survival plots (1 internal knot spline model) - glofit vs BR

Figure 75: PFS cumulative hazard, hazard, and survival plots (2 internal knot spline model) - glofit vs BR

Figure 76: cumulative hazard, hazard, and survival plots (3 internal knot spline model) - glofit vs BR

Table 72: AIC and BIC (PFS spline models) – glofit vs BR

Distribution	PFS	
	AIC	BIC
Glofitamab (BR weighted population)		
One-knot hazard	280.80	289.61
Two-knot hazard	282.51	294.25
Three-knot hazard	280.59	295.27
BR		
One-knot hazard	314.10	320.28
Two-knot hazard	315.82	324.06
Three-knot hazard	314.45	324.75

Overall survival

Spline 3-knots seems to fit a bit better the observed hazard for glofitamab OS (survival fit curve is similar with all splines), but 2nd highest AIC, though all AICs are very close (see Figure 77 to Figure 79, and Table 73).

As noted in section B7b.1, the BR spline models result in an implausible crossing between BR OS and PFS at ~ 4 years (which cannot be resolved by playing around with any of the distribution options for BR). This issue became more pronounced in the 2-knot and 3-knot models. So, despite leading to implausible results, as the spline 1-knot fits better the observed hazard for BR OS, slightly better fit to the survival plot, and has lowest AIC, the 1-knot model was preferred for OS BR. In the context of limiting the aforementioned issues, it was deemed appropriate to fit models with a different number of knots by arm for this particular comparison.

Note that none of the splines for glofit reflects properly the steeply declining nature of the observed hazard.

Figure 77: OS cumulative hazard, hazard, and survival plots (1 internal knot spline models) - glofit vs BR

Figure 78: OS cumulative hazard, hazard, and survival plots (2 internal knot spline models) - glofit vs BR

Figure 79: OS cumulative hazard, hazard, and survival plots (3 internal knot spline models) - glofit vs BR

Table 73: AIC and BIC (OS spline models) – glofit vs BR

Distribution	OS	
	AIC	BIC
Glofitamab (BR weighted population)		
One-knot hazard	277.05	285.86
Two-knot hazard	278.63	290.37
Three-knot hazard	278.39	293.06
BR		
One-knot hazard	375.77	381.95
Two-knot hazard	376.71	384.95
Three-knot hazard	376.70	387.00

B7b.1.2 Glofitamab vs Pola-BR

Progression free survival

The spline 1-knot model best fits the observed hazard for glofit PFS and has lowest AIC, with the 3-knot model also showing a reasonable fit, but with higher AIC (see Figure 80 - Figure 82, and Table 74). In general the survival curve fit is quite similar across splines. As such, the spline 1-knot PFS model was preferred in for the glofitamab Pola-BR weighted population.

Spline 3-knot fits better the observed hazard and survival curve for Pola-BR PFS and has lowest AIC, though 2-knots is also reasonable and has 2nd lowest AIC (very close to lowest). For Pola-BR, the spline 3-knot PFS model was used.

Figure 80: PFS cumulative hazard, hazard, and survival plots (1 internal knot spline model) - glofit vs Pola-BR

Figure 81: PFS cumulative hazard, hazard, and survival plots (2 internal knot spline model) - glofit vs Pola-BR

Figure 82: PFS cumulative hazard, hazard, and survival plots (3 internal knot spline model) - glofit vs Pola-BR

Table 74: AIC and BIC (PFS spline models) – glofit vs Pola-BR

Distribution	PFS	
	AIC	BIC
Glofitamab (Pola-BR weighted population)		
One-knot hazard	473.53	482.54
Two-knot hazard	474.59	486.61
Three-knot hazard	476.06	491.08
Pola-BR		
One-knot hazard	305.84	313.13
Two-knot hazard	305.49	315.21
Three-knot hazard	304.92	317.07

Overall survival

For overall survival, the spline 3-knots is a better fit to the observed hazard for glofit OS and has lowest AIC, with the 1-knot also fitting well, with a similar AIC score (see Figure 83 to Figure 85, and Table 75). The fit to the glofit survival curve is similar with all splines, and all AICs are very close. However, 1-knot leads to implausible crossing with OS curves for Pola-BR at ~3 years, with 2-knots it crosses at ~4.5

years and with 3-knots it crosses at ~9-10 years. Overall, the 3-knot spline provides the best fit for glofitamab OS (Pola-BR adjusted), and leads to the least implausible long-term predictions.

For Pola-BR, the spline 1-knot model fits reasonably well to the observed hazard for Pola-BR OS and has lowest AIC, but the fit is similar with all knots, with the 1-knot spline fitting the survival curve slightly better.

Note that while the optimal number of knots has been carefully considered, with the current base case, glofit OS and Pola-BR OS cross at approximately 11-12 years, after which survival in the Pola-BR arm is predicted to be higher than that for glofitamab, which can be considered implausible given the observed OS trend.

Figure 83: OS cumulative hazard, hazard, and survival plots (2 internal knot spline model) - glofit vs Pola-BR

Figure 84: OS cumulative hazard, hazard, and survival plots (2 internal knot spline model) - glofit vs Pola-BR

Figure 85: OS cumulative hazard, hazard, and survival plots (3 internal knot spline model) - glofit vs Pola-BR

Table 75: AIC and BIC (OS spline models) – glofit vs Pola-BR

Distribution	OS	
	AIC	BIC
Glofitamab (Pola-BR weighted population)		
One-knot hazard	486.21	495.22
Two-knot hazard	487.25	499.27
Three-knot hazard	485.84	500.86
Pola-BR		
One-knot hazard	287.85	295.14
Two-knot hazard	289.55	299.27
Three-knot hazard	291.61	303.77

B7b.1.3 Glofitamab vs axi-cel

Progression free survival

For progression free survival, the spline 1-knot is the best fit to the observed hazard and survival curve for glofit (axi-cel adjusted population) and has lowest AIC, with the 3-knots spline also showing a reasonable hazard and survival fit, but with a higher AIC value (see Figure 86 to Figure 88, see Table 76). However, the 1-knot spline PFS model leads to implausible crossing with the OS 1-knot curve for glofit (axi-cel adjusted population) at approximately 4 years, and at approximately 3.5 years with the 2-knot and 3-knot models. The 3-knots glofitamab PFS model crosses with glofitamab OS 2-knots and 3-knots curves at approximately 5-6 years, but shows more plausible predictions when considered with the OS 1-knot model. The 2-knot PFS model for glofitamab has the second lowest AIC, and crosses later with glofitmab OS models, with the 2-knots and 3-knots curves crossing PFS at approximately 6-7 years, but again showing more plausible predictions when considered with the OS 1-knot model. As the PFS 2-knot model has the next lowest AIC and gives more realistic curves when considered with OS 1-knot, this was selected for glofitamab PFS (axi-cel population adjusted).

The spline 2-knots and 3-knots models better fit the observed hazard and survival curve for axi-cel PFS. The survival fit is a bit better for 2-knots with a similar fit to the hazard plot for both models. The 3-knots has lowest AIC, though 2-knots has next lowest and very similar AIC while also better fitting the data. So, the 2-knot PFS model was selected for axi-cel.

Figure 86: PFS cumulative hazard, hazard, and survival plots (1 internal knot spline model) - glofit vs axi-cel

Figure 87: PFS cumulative hazard, hazard, and survival plots (2 internal knot spline model) - glofit vs axi-cel

Figure 88: PFS cumulative hazard, hazard, and survival plots (3 internal knot spline model) - glofit vs axi-cel

Table 76: AIC and BIC (PFS spline models) – glofit vs axi-cel

Distribution	PFS	
	AIC	BIC
Glofitamab (axi-cel weighted population		
One-knot hazard	100.66	108.89
Two-knot hazard	101.52	112.50
Three-knot hazard	103.55	117.28
Axi-cel		

One-knot hazard	421.91	429.75
Two-knot hazard	418.85	429.31
Three-knot hazard	418.74	431.81

Overall survival

For overall survival, the spline 2-knots and 3-knots models (particularly 3-knots) were the best fit to the observed hazard for glofit OS and also have a slightly better to the survival curve fit compared to 1-knot, but have the highest AIC (3-knots highest, 2-knots 2nd highest very close to 1-knot) (see Figure 89 to Figure 91, and Table 77). As described in the PFS section above, the 1-knot OS curve resulted in the most plausible long term predictions, avoiding PFS and OS crossing early in the model time horizon, so the 1-knot OS model for glofitamab was preferred.

For axi-cel, the spline 3-knots model was the best fit to the observed hazard for axi-cel OS and has lowest AIC, while the spline 1-knot model also fit well, and had the second lower AIC. The spline 2-knots model had the highest AI, and also showed a worse fit to the survival curve than the other models. As such, the 3-knots model for axi-cel OS was selected as the best fitting model.

It is worth noting, that most likely splines are not a good parametric distribution option for glofit OS/PFS in this comparison, because of the observed PFS and OS crossing in various considered models. Furthermore, as in the case of the comparison versus BR, none of the splines for glofit OS reflects properly the steeply declining nature of the observed hazard.

Figure 89: OS cumulative hazard, hazard, and survival plots (1 internal knot spline model) - glofit vs axi-cel

[redacted]

Figure 90: OS cumulative hazard, hazard, and survival plots (2 internal knot spline model) - glofit vs axi-cel

[redacted]

Figure 91: OS cumulative hazard, hazard, and survival plots (3 internal knot spline model) - glofit vs axi-cel

[redacted]

Table 77: AIC and BIC (OS spline models) – glofit vs axi-cel

Distribution	OS	
	AIC	BIC
Glofitamab (axi-cel weighted population		
One-knot hazard	121.78	130.01

Two-knot hazard	123.48	134.46
Three-knot hazard	125.35	139.08
Axi-cel		
One-knot hazard	559.43	567.27
Two-knot hazard	559.56	570.02
Three-knot hazard	558.59	571.66

B7b.1.4 Spline model results

Table 78: Base-case results, spline modelling approach (glofitamab PAS, comparator list)

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)	NMB at 30k
Glofit	[redacted]	[redacted]				
BR	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Glofit	[redacted]	[redacted]				
Pola-BR	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Glofit	[redacted]	[redacted]				
Axi-cel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

**1.2 QALY modifier applied. ICER, incremental cost-effectiveness ratio; LYG, life years gained; NMB, net monetary benefit; QALYs, quality-adjusted life years.*

Table 79: Scenario analysis, spline modelling approach (glofitamab PAS, comparator list)

Parameter modifier	ICER vs BR (£)*	ICER vs Pola-BR (£)*	ICER vs axi-cel (£)
Base case	[redacted]	[redacted]	[redacted]
Model time horizon			
Time horizon, 30 years	[redacted]	[redacted]	[redacted]
Time horizon, 40 years	[redacted]	[redacted]	[redacted]
Time horizon, 50 years	[redacted]	[redacted]	[redacted]
Patient baseline characteristics			
Average cohort age background mortality (35 year time horizon)	[redacted]	[redacted]	[redacted]
Utility values			

EORTC-QLQ-C30 Mapping (Direct)	[redacted]	[redacted]	[redacted]
TA306 (FAD values)	[redacted]	[redacted]	[redacted]
TA559	[redacted]	[redacted]	[redacted]
Costs			
Axi-cel admin cost (EAG derived [£41,101])	[redacted]	[redacted]	[redacted]
Axi-cel admin cost (135% pre-infusion cost multiplier applied [£71,083])	[redacted]	[redacted]	[redacted]
Survival modelling			
Proportional hazards assumed	[redacted]	[redacted]	[redacted]
Midpoint HR (OS, PFS) between 1 and ITC estimate: glofit vs axi-cel	[redacted]	[redacted]	[redacted]
No long-term remission (PFS cure point)	[redacted]	[redacted]	[redacted]
No long-term remission (OS cure point)	[redacted]	[redacted]	[redacted]
No PFS cure point for BR and Pola-BR	[redacted]	[redacted]	[redacted]
No QoL adjustment in LTR	[redacted]	[redacted]	[redacted]
No excess mortality in LTR	[redacted]	[redacted]	[redacted]
Discounting			
1.5% discounting for costs and effects	[redacted]	[redacted]	[redacted]

**1.2 QALY modifier applied. ICER, incremental cost-effectiveness ratio. LTR, long-term remission. OS, overall survival. PFS, Progression free survival. TA, technology appraisal.*

B7b.2 Mixture cure modelling approach

As noted in response to B7b, mixture-cure models were fitted only for those comparisons where IPDs were available for both treatment arms. In this case, only comparisons between glofitamab and Pola-BR could be generated because individual background hazards for censored patients cannot be reliably estimated when only aggregate level information, such as that available in the comparisons with BR and axi-cel. Accordingly, we decided to remain consistent with the approach used in the original Company submission base case, where the same types of parametric models and of CE model assumptions (e.g. for the long-term remission/survivorship scenarios) are considered for all treatments in a comparison.

B7b.2.1 Survival extrapolation validation

Progression free survival

For progression free survival, log-normal, generalised gamma and log-logistic all fit the observed glofitamab hazard well (see Figure 92). The lowest AIC is with lognormal, next best was generalise gamma and the highest AIC, but still very close, was log-logistic (see Table 80). Log-logistic and log-normal seem to over predict the tail of the observed data, though generalised gamma likely under predicts long term survival. When looked at together with OS, log-logistic is probably implausible, with crossing observed at approximately 12 years, log-normal may be plausible and gives best results but the gap between OS and PFS may be too small, generalise gamma is also plausible but the gap between OS and PFS may be too high. With the lowest AIC, log-normal was selected as the preferred glofitamab (Pola-BR population adjusted) PFS extrapolation distribution.

For Pola-BR PFS, again, generalised gamma has the best visual fit for the hazard and it has the lowest AIC. Log-normal and log-logistic also have a reasonable fit for the hazard, though not as good as generalised gamma, with the first part of the hazard is increasing while the observed hazard is almost always decreasing, and the visual fit for survival is slightly worse than for generalised gamma with both over predicting survival and crossing with OS at approximately 11-12 years. That considered, generalised gamma was selected as the preferred Pola-BR PFS extrapolation distribution.

Exponential, Weibull, Gompertz and Gamma models did not converge for Pola-BR, so were not considered.

Figure 92: PFS hazard and survival plots – glofit (adjusted) vs Pola-BR

Table 80: AIC and BIC (PFS mixture cure model) – glofit vs Pola-BR

Distribution	PFS	
	AIC	BIC
Glofitamab (Pola-BR weighted population)		
LNORMAL	105.93	114.94
LLOGISTIC	107.97	116.98
GEN GAMMA	107.17	119.18
Pola-BR		
LNORMAL	76.13	83.42
LLOGISTIC	77.75	85.04
GEN GAMMA	74.38	84.10

Overall survival

For overall survival, both generalised gamma and log-logistic fit the nature of the observed hazard and survival plots for glofitamab OS (see Figure 93). Log-normal shows a slightly worse fit to the observed data, but generalised gamma has highest AIC and log-logistic lowest (see Table 81).**x**

As such, log-logistic was selected as the preferred OS extrapolation distribution for glofitamab OS (Pola-BR population adjusted). While log-logistic was found to have the best overall fit, none of the models for glofit OS properly reflects the steeply declining nature of the observed hazard.
For Pola-BR OS, generalised gamma shows the best visual fit for the hazard though it has the highest AIC, log-normal and log-logistic both over predict the hazard and under predict the survival. As such, generalised gamma was selected as the preferred Pola-BR PFS extrapolation distribution.

Exponential, Weibull, Gompertz and Gamma models did not converge for Pola-BR, so were not considered.

Figure 93: OS hazard and survival plots – glofit (adjusted) vs Pola-BR

Table 81: AIC and BIC (OS mixture cure model) – glofit vs Pola-BR

Distribution	OS	
	AIC	BIC
Glofitamab (Pola-BR weighted population)		
LNORMAL	174.21	180.22
LLOGISTIC	173.50	179.51

GEN GAMMA	176.05	185.06
Pola-BR		
LNORMAL	103.79	108.66
LLOGISTIC	104.09	108.95
GEN GAMMA	105.01	112.31

B7b.2.2 Mixture cure model results

Table 82: Base-case results, mixture cure modelling approach (glofitamab PAS, pola PAS, BR list)

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)	NMB at 30k
Glofit	[redacted]	[redacted]				
Pola-BR	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

**1.2 QALY modifier applied. ICER, incremental cost-effectiveness ratio; LYG, life years gained; NMB, net monetary benefit; QALYs, quality-adjusted life years.*

Table 83: Scenario analysis, mixture cure modelling approach (glofitamab PAS, pola PAS, BR list)

Parameter modifier	ICER vs Pola-BR (£)*
Base case	[redacted]
Time horizon, 30 years	[redacted]
Time horizon, 40 years	[redacted]
Time horizon, 50 years	[redacted]
Average cohort age background mortality (35 year time horizon)	[redacted]
EORTC-QLQ-C30 Mapping (Direct)	[redacted]
TA306 (FAD values)	[redacted]
TA559	[redacted]
Proportional hazards assumed	[redacted]
No long-term remission (PFS cure point)	[redacted]
No long-term remission (OS cure point)	[redacted]
No PFS cure point for Pola-BR	[redacted]
No QoL adjustment in LTR	[redacted]
No excess mortality in LTR	[redacted]
Removal of all long term remission assumptions	[redacted]
1.5% discounting for costs and effects	[redacted]

**1.2 QALY modifier applied. ICER, incremental cost-effectiveness ratio. LTR, long-term remission. OS, overall survival. PFS, Progression free survival. TA, technology appraisal.*

Flexible model results conclusion

The conclusions that can be drawn from the results of both the spline and mixture cure modelling approaches are consistent with those from the results based on the parametric survival modelling approach used in the company submission. Treatment with glofitamab is expected to be associated with comparable or greater QALY gains while being cost saving or not substantially increasing costs compared to BR and pola-BR. Compared to axi-cel, glofitamab is expected to produce lower QALY gains while being substantially cost saving.

Across all comparisons and modelling approaches considered, in the base-case and all scenario analyses, glofitamab is shown to be cost-effective. Therefore, the results presented in this response demonstrate the robustness of the original economic analyses, further supporting the view that glofitamab represents a cost-effective alternative to currently available alternatives.

B8. Priority question: Please update the electronic version of the model so that the impact on cost-effectiveness of using an alternative approach to informing the glofitamab population adjustment for the comparison against BR (i.e., informed by the propensity score analysis results using the GO29365 study, in line with the request in A19.) can be explored. The assessment of survival model fit (visual, statistical and clinical plausibility for the updated PFS and OS extrapolation models (including mixture-cure and spline based models) for the GO29365 study (BR) adjusted glofitamab, should also be presented.

As detailed in the response to A19, and in Section 4.2.1 of the ITC report (Appendix D), unsuccessful attempts to match covariate matching when using either optimal pair or IPTW matching methods, indicate that the results of any adjusted outcome analysis are likely to be highly unreliable. Furthermore, population adjustment in the attempted propensity score analysis resulted in an unacceptably small sample size in the BR arm, which would lead to highly uncertain survival predictions if attempts were made to fit parametric extrapolations.

For the reasons described above, and in response to A19, the economic model has not been updated to incorporate the propensity score analysis results using the GO29365 study.

Section B: All-cause mortality

B9. The approach taken to model all-cause mortality in this appraisal (i.e. modelled as a function of the age distribution, as opposed to mean cohort age) is similar to the one followed in TA649. However, both the committee and the EAG in TA649 preferred the mean cohort age approach. Please justify the use of the age distribution all-cause mortality approach in the context of a cohort model and using a utility age-adjustment based on mean age, including any further justifications to what was presented for TA649.

The Company acknowledges that the rationale put forward in TA649 to support the suitability of modelling background (also referred to as “all-cause”) mortality as a function of the age distribution instead of the mean age of a cohort may have been explained and referenced suboptimally. Therefore, the Company would like to take the opportunity to invite the EAG and the Committee to consider some additional arguments and justifications on why this approach is suitable.

Firstly, the fact that mortality is a nonlinear function of age, with older patients having a greater risk of death than younger ones, which in turn may translate into a non-linear change in the age composition (and thus the risk of death) of the cohort over time, has been discussed in health economic modeling literature. As proposed by Bullement A and Hatswell AJ in 2018 (94), modeling background mortality as a function of the age distribution of a patient cohort can better reflect heterogeneity in the actual background mortality of patients, as opposed to using the standard average cohort age approach. This approach is consistent with other approaches that use distributions of patient demographic variables to more accurately estimate model parameters in cohort-based economic evaluations (95). Furthermore, approaches similar to this one, where a distribution of patient ages is used to model background mortality, were also employed in previous TAs (e.g., TA530/ID995) and were deemed to be appropriate.

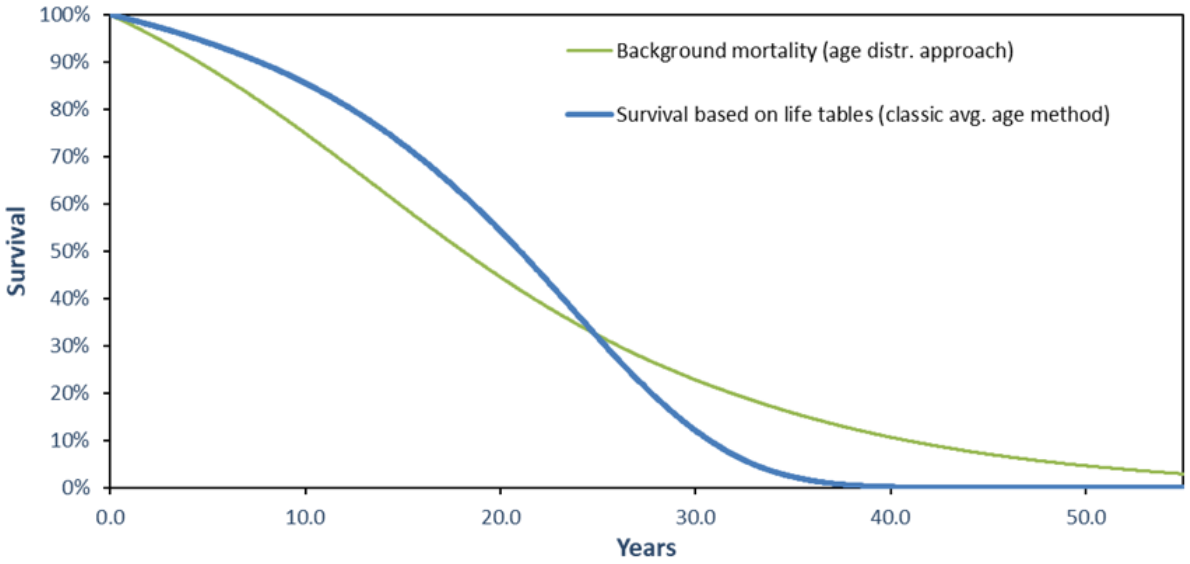
Two main criticisms were raised in the context of TA649 with regards to this approach, which will be addressed below.

1. **Unrealistic long-term survival estimates yielded by modeling all-cause mortality using a distribution of patient ages**

In the case of a generally late-onset disease (such as lung cancer or DLBCL), the age distribution of patients can be reasonably expected to be left-skewed, with a greater number of older than younger patients. Figure 94 provides a visual explanation of how the expected all-cause mortality would look with the two approaches (cohort age distribution vs average cohort age) for a patient population

featuring a left-skewed age distribution, such as the one used in the cost-effective model (CEM) for 3L+ DLBCL.

Figure 94: Comparison of expected all-cause mortality with cohort age distribution and average cohort age approaches

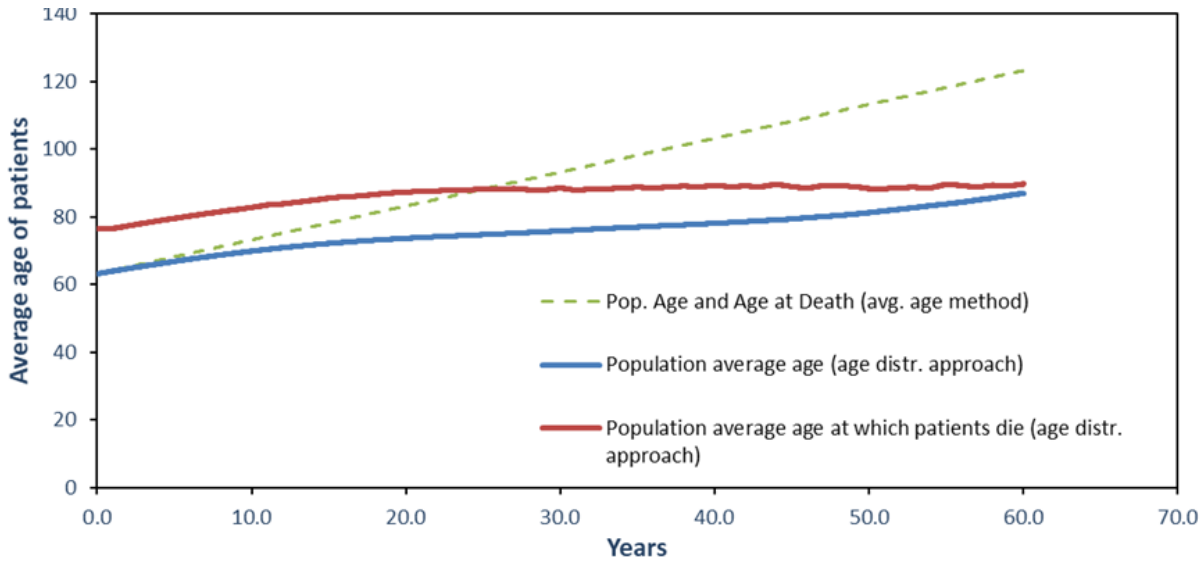


Note that this pattern is specific to a left-skewed distribution: if the age distribution was mildly right-skewed (e.g. where the mean age of the cohort was closer to the minimum of the distribution), the difference between the all-cause mortality curves estimated by the two approaches over a model time horizon would be significantly reduced.

In TA649 it was noted that the cohort age distribution approach would result in an unrealistic all-cause survival curve for a patient cohort featuring a relatively old mean age (in that case ~70 years). Specifically, it was deemed implausible that a cohort of ~70 years of age could still be alive after 50 years, as this would imply that the average age of this cohort would be ~120 years. However, this argument did not take into account what the actual average age of the cohort would be over the model time horizon when estimated with this approach.

Figure 95 (included in the CEM, along with the calculations used to inform it) provides a more accurate representation of what the actual average age of the model cohort is estimated to be using the cohort age distribution approach, versus the average cohort age approach.

Figure 95: Comparison of actual average age estimates in model cohort using cohort age distribution and average cohort age approaches



As evident in Figure 95, with the average cohort age method patients who die have the same age as the average age of the patients alive in the cohort. This is consistent with the expectation that it is implausible for a cohort of ~70 years to still be alive after 50 years. However, in the cohort age distribution approach the average age at which patients die differs from the average age of the patients alive, as the oldest patients have a greater risk of death. As this holds true over time (the red curve is never lower than the blue curve), the actual average age of the cohort is the same (for the first years of the time horizon) or lower and increases less steeply than with the average age method, until the actual age of the cohort and the age at which patients die converge. This occurs as the cohort age distribution approach effectively allows for a change in the age composition of the cohort over time, thereby the actual average age estimated with this approach always remains within the range of plausible values over the model time horizon used.

This is not due to any issues in the calculations, rather it is simply a reflection of that fact that mortality is a nonlinear function of age (as described above) and that there appears to be a non-negligible proportion of patients with DLBCL (at least 36% in our specific case) who present with the disease at a younger age than the average. These patients can plausibly be expected to feature a higher (non-disease related) life-expectancy than patients presenting with the disease at older age.

2. **Lack of consistency between the approach of modeling all-cause mortality using a distribution of patient ages (referred to as “individual patient-level”) and the cohort-based approach used for modeling PFS and OS in the economic model**

In TA649, it was noted that the cohort age distribution approach would be inconsistent with the cohort-based approach used for modeling PFS and OS in the economic model.

The Company would like to clarify that the decision to model all-cause mortality hazard and survival in the cohort age distribution approach by using individual patients is not taken to introduce any inconsistencies in the modelling, but rather to represent the most accurate proxy for the observed patient age distribution.

To better explain this point and clarify why the cohort age distribution approach to model background mortality remains appropriate without making use of the enhanced granularity granted by the use of all patients, the Company has generated an example of a more simplified approach (also added to the electronic version of the model, Life Tables tab). This example (termed as cohort age group approach) uses a discrete series of patient sub-cohorts (to remain consistent with the general cohort approach used in the model), each featuring their own specific mean age, based on the observed trial age distribution. Seven age groups were considered, each featuring age intervals of ~10 years, and these were assigned a weight corresponding to the relative contribution of that subcohort to the overall trial population. Figure 96 to Figure 98 compare how the expected results on the modelled all-cause survival, death hazard, cohort age and age at death would look like if the cohort age distribution approach was applied using this series of patient sub-cohorts.

Figure 96: Projected all-cause survival results for patient sub-cohorts using cohort age distribution approach

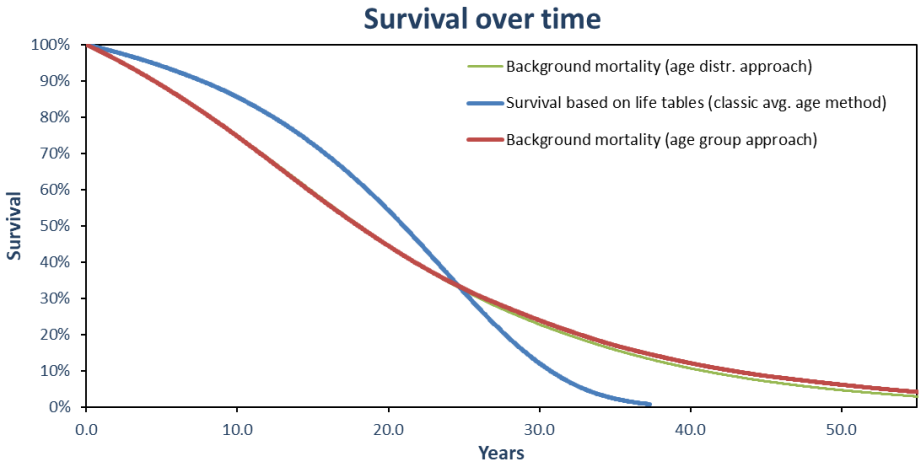


Figure 97: Projected death hazard results for patient sub-cohorts using cohort age distribution approach

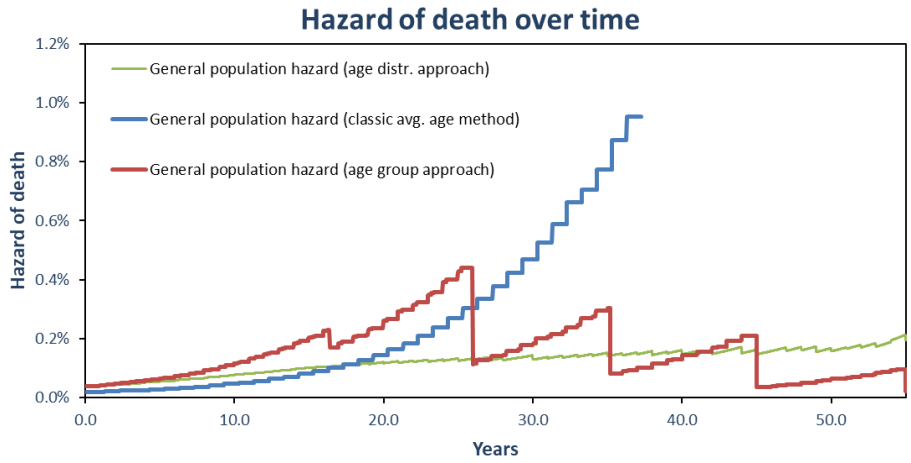
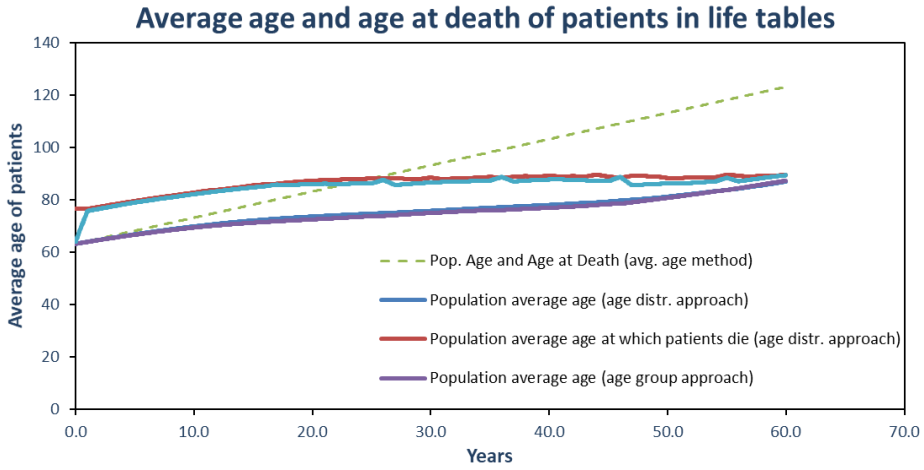


Figure 98: Projected cohort age and age at death results for patient sub-cohorts using cohort age distribution approach



The following conclusions can be drawn from Figure 96 to Figure 98 above:

- Using a distribution of sub-cohort ages rather than individual patient ages to remain consistent with the cohort-based approach used in the economic model does not substantially influence the quantities being estimated over time.
    - The survival due to all-cause mortality displays a very similar trend. This reflects the fact that as the older patient sub-cohorts die faster than the younger ones, the expected mean survival for the observed age distribution of the cohort is first lower and then higher than that estimated using the standard cohort age approach, in line with the expected change in age composition of the overall cohort over time.

    - The average age at death and average age of the patients alive in the overall cohort over time also display a similar trend, in line with the considerations laid out above.
    - The all-cause death hazard over time also follows a similar trend, with the hazard being first higher and then lower than that estimated using the standard cohort age method. This is in line with the fact that as the older sub-cohorts die the younger sub-cohorts become more prominent in the composition of the overall cohort, as well as with the fact that the latter feature a higher (non-disease related) life-expectancy.

- There is a loss in calculation accuracy when using a less granular approach based on sub-cohort ages rather than individual patient ages.
    - Such a loss in accuracy is more prominent when estimating the all-cause death hazard. This is ultimately the most important quantity for the economic model, as it is used for the adjustment of the OS (and indirectly of PFS) estimated using the parametric distributions in the Markov traces.
    - This indicates that applying a more granular approach using the most accurate available proxy for the observed patient age distribution may be beneficial for the model calculations.
    - Furthermore, opting for the use of all the granularity available from the trial data avoids having to take a decision on what is the optimal number of age sub-cohorts to be used and their respective age interval, which represents a rather arbitrary decision that may change depending on the specific problem at hand.

On the point regarding the appropriateness of using of the cohort age distribution approach for all-cause mortality while using a utility age-adjustment based on mean age:

- The Company believes that for an optimal and consistent implementation of this approach throughout the economic model, it would be preferable to also have the estimation of the utility age-adjustment factor based on the same approach.
- However, the Company would like to point out that the suitability of the method itself to the estimation of background mortality and the accuracy of the underlying calculations are unrelated to the specific method employed to estimate the utility age-adjustment factor. Using this method also for the estimation of the latter would result in no change to the quantities estimated for all cause-mortality.
- The Company would also like to clarify that the cohort age distribution approach was not implemented for the estimation of the utility age-adjustment factor in the original version of the cost-effectiveness model for the same reasons described

in the response to question B39b (keep the size of the excel file manageable). However, with fewer comparators, this may now be doable, though unfeasible during the time frame of the Clarification period, given the very high number of questions received. However, if the EAG decides to consider this approach for estimating all-cause mortality suitable in their report, in light of the arguments laid out above, the Company is open to also implement this method for the estimation of the utility age-adjustment factor during the Technical Engagement period.

Section B: Treatment duration

B10. Priority question: Please confirm if the source for the time to off-treatment (TTOT) Kaplan-Meier curves used to inform each of the components (polatuzumab, rituximab, bendamustine) of the comparators (BR and pola-BR) treatment durations was the GO29365 study. Please provide the TTOT Kaplan-Meier curves (including numbers at risk over time) for glofitamab (unadjusted and population adjusted curves) and for the comparators BR and pola-BR.

A plot overlaying the KM curves for TTOT for glofitamab unweighted and weighted populations to match the main comparator populations included in the CEM is reported below (Figure 99). As it can be observed in the plot, the curves are very similar as the treatment duration pattern across weighted and unweighted populations is nearly identical.

Figure 99: Kaplan-Meier plot of TTOT – glofitamab weighted populations

Furthermore, the Company would like to clarify that MAIC/propensity score analyses for TTOT were not originally considered as there are additional limitations with using weights from a matching process that focuses on balancing confounders for efficacy as opposed to treatment duration, as there are other considerations that cannot be taken into account during the matching process. In fact, confounders for these specific events are not known (e.g. if a patient experienced a discontinuation event due to withdrawal of consent or other reasons), and thus residual imbalances in such confounders may have resulted as a consequence of it. This is also the reason why discontinuation due to all causes was not analysed in the context of ITCs.

Below are the plots of unweighted KM curves for TTOT of Pola-BR and BR (both as combined and individual regimens) overlaid, based on data from the GO29365 study using the same patient sets as in the ITCs (Figure 100 and Figure 101). These were used to model Pola-BR and BR duration on treatment, for all individual components in the combination (rituximab, bendamustine, +/- polatuzumab vedotin). See also the response to question B11 as to why this approach was used for BR.

Figure 100: Kaplan-Meier plot of TTOT – Pola-BR unweighted populations

Figure 101: Kaplan-Meier plot of TTOT – BR unweighted populations

B11. The CS states that "where direct TTOT information was not available, the respective TTOT was set equal to the selected parametric distribution for PFS, capped at the treatment-specific maximum number of cycles, as per the treatment label". Please clarify for which treatments was treatment duration informed PFS as proxy for TTOT, as the model appears to be using TTOT data for all treatments under comparison. Please provide the references used to inform the treatment treatment-specific maximum number of cycles.

PFS was not used as a proxy for TTOT for any of the treatments included in the submitted CEM. In the specific case of BR, it was decided to use the time to treatment discontinuation information from patients treated with BR in the DLBCL cohort of GO29365 (3L+ patients only, same cohort used for the propensity score analyses). Despite being inconsistent with the approach used to estimate the AE rate for the regimen, this was done as more granular data is available from GO29365 to model BR individual treatment discontinuation. Furthermore, using this approach would also allow to factor in any potential treatment administration delays or

interruptions (e.g. due to safety reasons). As treatment discontinuation impacts drug and administration costs in addition to AE costs, and the former are expected have a larger contribution to the overall costs than the latter, this approach was preferred over using available data from Hong et al 2018 (13).

The maximum number of treatment cycles for glofitamab was set to be the one expected in the target SmPC (12 cycles).

The maximum number of treatment cycles for Pola-BR was set to be aligned with the polatuzumab vedotin SmPC (6 cycles).

The maximum number of treatment cycles for BR was set to be 6 in line with Ohmachi et al. 2013 (96) and Vacirca et al. 2014 (97), which were used to inform the decision of the comparator study regimen in the DLBCL randomized part of the GO29365 trial. This decision was taken to be consistent with how other anti-CD20 plus bendamustine regimens are used to treat NHL, as this has been shown to be sufficient to provide durable responses (source GO29365 CSR).

Axi-cel is a one-off treatment so only one model cycle was considered.

Section B: Adverse events

B12. Priority question: According to the data provided in Tables 24 and 25 in the CS, most CRS events occur after the first three doses of glofitamab. Since the model accounts for adverse events costs (and disutility in scenario analysis) on a weekly basis for individuals on treatment, it potentially underestimates the impact of CRS on the cost-effectiveness of glofitamab. Please correct the electronic version of the model, so that the disutility and costs associated with Grade≥3 cytokine release syndrome (CRS) are applied as a one-off impact at the first dose of glofitamab in the model and update the CE analysis accordingly.

A switch has been added to the economic model to control how the costs and disutilities associated with Grade ≥3 CRS are applied for glofitamab, as requested by the EAG. CRS costs and disutilities can be applied as a one-off or on a weekly basis for the duration of time on treatment in the glofitamab arm. The former represents a conservative scenario as not all treated patients are expected to experience CRS, given that some may only end up receiving Gpt (see response to Question B23).

The impact of applying CRS related costs and disutilities as a one-off or on a weekly basis on the ICERs can be seen in Table 84.

Table 84: Cost-effectiveness results: adverse event cost and disutilities scenarios

Scenario	ICER vs BR	ICER vs pola-BR (glofitamab dominant)	ICER vs axi-cel (cost saved per QALY lost)
Base-case (weekly AE costs)	[redacted]	[redacted]	[redacted]
One-off AE costs	[redacted]	[redacted]	[redacted]
Weekly AE costs and disutilities (health state utilities based on TA559)	[redacted]	[redacted]	[redacted]
One-off first cycle AE costs and disutilities (health state utilities based on TA559)	[redacted]	[redacted]	[redacted]

**1.2 QALY modifier applied. ICER, incremental cost-effectiveness ratio.*

B13. Priority question: Please clarify how was the total duration of follow-up for AEs estimated for each treatment under comparison, describing data sources used and any assumptions made. Please also clarify any further assumptions made when calculating weekly probabilities of AEs.

For glofitamab, the average number of days of exposure to study treatment in the safety population (N=154) from the CSR was converted to weeks and multiplied by the number of patients in the safety population.

For Pola-BR, the median duration of treatment exposure (3.2 months) to Pola-BR in the pooled cohort from the updated GO29365 data publication (98) was assumed to be equal to the mean, converted to weeks and multiplied by the size of the pooled cohort (N=152). This was done to maintain consistency with the data source used to inform the treatment Grade ≥3 AE incidence (the pooled cohort was selected to maximise sample size and follow-up time).

For BR, the total duration of follow-up was estimated as the weighted average number of treatment cycles (converted to weeks) reported in Hong et al 2018 (the date source used to inform the AE incidence data) multiplied by the number of patients enrolled in Hong et al 2018.

For axi-cel, the total duration of follow-up for AEs was assumed to be one week per patient, to model AE costs as one-off costs applied to the first model cycle, in line with the approach employed and accepted in previous CAR-T cell therapy TAs, as CAR-Ts are one-off treatments. The costs associated with AE related to axi-cel treatment are assumed to be captured in the NHS tariff for the delivery of CAR-T therapies, so are not separately modelled.

All approaches are in line with previously accepted precedents from past TAs.

B14. Priority question: The model considers 5 events of Grade ≥3 CRS, but Tables 24 and 25 in the CS suggest that 6 events occurred in the safety population of the NP30179 trial. Please amend the electronic version of the model and update the CE analysis accordingly.

The model has been updated to account for the 6 CRS events from the glofitamab safety population. The discrepancy occurred because the analysis of AE incidence in the CEM considered all AEs and used a general grading system, where one CRS event was classified as a Grade 2 AE. Conversely, Tables 24 and 25 in Document B are based on the Lee and ASCTC gradings, which are specific to CRS.

B15. The EAG could not replicate the Grade ≥2 CRS rate of 17.5% applied to calculate the glofitamab monitoring costs, from the data contained in Tables 24 and 25 in the CS. Could you please clarify which rates you have averaged across? Please also clarify why the sample size for the patients who received the 2.5mg dose of glofitamab at cycle 1 day 8 is n=145 (Table 24, CS), when the safety population had a sample size of n=154 (all of which received glofitamab).

The rate of Grade ≥2 CRS was estimated to be 17.5% for the D2 [Sub. 2]+D3+D5 safety population (n=154). This estimation was based on an average of two grading systems: the Lee grading (18.8%, Table 72 of the CSR) and the ASTCT grading (16.2%, Table 71 of the CSR).

In Document B, Table 24, the denominator for calculating the proportion of patients who experienced CRS after receiving the 2.5mg and 10mg doses in Cycle 1 and the 30mg dose in Cycle 2 was based on the number of patients who received those doses (n=145, n=135, and n=127, respectively).

In the primary safety population, defined as patients in Cohorts D2 [Sub. 2]+D3+D5 who received at least one dose of study treatment, 154 patients received obinutuzumab pre-treatment, and 9 patients discontinued study treatment before receiving the first dose of glofitamab. Therefore, only 145 patients received glofitamab 2.5mg.

Section B: Health-related quality of life

B16. The CS states that "a targeted literature search of EQ-5D-3L mapping algorithms for haematological malignancies was conducted to identify the best candidates for use in the mapping exercise – see Appendix I for details" and that "Several mapping algorithms were identified". Details on how the targeted literature review on mapping

algorithms was carried out and on the identified algorithms was not provided. Could you please provide that information.

Details of the SLR of 3L+ DLBCL utility evidence is provided in Appendix I.

Given the absence of lymphoma specific algorithms estimating utility values from Western country tariffs, a targeted literature search of EQ-5D-3L mapping algorithms for hematological malignancies was conducted to identify the best candidates for use in the mapping exercise. Please refer to the Appendix I, Section I.5.1.2 for more details on the searches.

Both mapping algorithms eventually selected were estimated in patients with multiple myeloma (or with multiple tumors where multiple myeloma was the predominant cancer). These were preferred over other potentially available options for the following reasons:

- Good predictive ability (based on model performance statistics and accuracy of predicted values)
- Relevance and size of the patient sample used to estimate the algorithm
- Sufficient amount of detail on how the regression was estimated and on the baseline characteristics of the sample
- External validation
- Use in previous NICE submissions

Both Proskorovsky et al, 2014 (99) and Longworth et al, 2014 (100) algorithms were accepted in previous NICE TAs for haematological malignancies (TA695 (101), TA657 (102), TA450 (103) and TA399 (104)), with the former being the one most frequently used. However, the model base case uses the algorithm from Longworth et al, 2014 as, unlike Proskorovsky et al, 2014, this has recently been externally validated (105).

B17. The SLR on HRQoL identified the study by Shah et al, 20212 as the only study that met the requirements of the NICE reference case. Nevertheless, the company did not use evidence from this study to inform the economic model, in neither the base case nor scenarios. Could the company please provide an additional scenario analysis where utilities from Shah et al, 2021 2 are used to inform the economic model health states.

The Company would like to apologise as there is likely a mistake in the Appendix I (Health-related quality-of-life studies SLR) that categorises the utilities identified in Shah et al 2021 as meeting all the requirements of the NICE reference case. While the utility values from Shah et al 2021 (106) were cross-walked to EQ-5D-3L values using the recommended van Hout et al 2021 algorithm (107), they are based on a US tariff, which falls outside of the reference case.

Nevertheless, the utilities from Shah et al 2021 were not considered suitable to inform the economic model because they cannot be directly incorporated in the CEM without resorting on very strong assumptions. In fact, the publication reports model based utility values in the following format:

- By treatment visit for the entire population used in the analysis
- By treatment visit and responder status
- By health state (stable disease, response and progressive disease, with patients being considered to have stable disease at baseline and assigned to these different states based on the best overall response at cycle 2)
    - These utilities are however only reported as mean values at baseline and end of treatment, i.e. longitudinal information in between is discarded
- As difference between health states (progressive vs stable disease, response vs progressive disease, response vs stable disease)

None of these formats is directly compatible with the area under the curve model submitted, as these utilities are more suitable for a response model and their use in a partitioned survival model would require the differentiation of utilities in the progression-free state by treatment arm, which would require strong assumptions to be made.

B18. For the mapping from EORTC-QLQ-C30 to EQ-5D-3L, the company used an indirect mapping (response-based) approach (via the published algorithm in Longworth et al, 2014) and an indirect mapping (index value) approach (via the published algorithm in Proskorovsky et al, 2014). Could the company clarify the following:

a. Provide details on the response-based model (indirect mapping) used from Longworth et al, 2014;

The Longworth indirect mapping algorithm from Young et al 2014 is based on a series of multinomial logistic regression models estimated for each EQ-5D dimension (108). The estimates from these regressions can be used to estimate the probability of respondents to be in levels 1, 2, or 3 of each of the EQ-5D dimensions. These probabilities can be subsequently used to predict the expected utility value of the overall EQ-5D health state at each patient visit.

Data to fit the model were obtained from 771 patients with multiple myeloma (~74%) as well as solid tumors, from an RCT (VISTA study) and a Canadian cancer clinic.

The parameters of the model are provided in Table 85 below.

Table 85: Coefficients for best-fitting mapping model from EORTC QLQ-C30

	Mobility		Self-care		Usual activities		Pain		Anxiety/Depression	
Level	2	3	2	3	2	3	2	3	2	3
Physical functioning	-0.0715241	-0.1666518	-0.0492088	-0.0989941	-0.0358454	-0.0851464	-0.0008494	-0.0128045	-0.0143092	-0.0441950
Role functioning	-0.0109798	-0.0066196	-0.0165511	-0.0295817	-0.0321869	-0.0550817	0.0012198	-0.0013792	0.0049731	0.0187775
Emotional functioning	0.0104307	0.0237461	0.0078666	0.0082215	0.0205527	0.0279876	0.0086091	0.0112924	-0.0781099	-0.1475690
Cognitive functioning	-0.0108672	-0.0059660	-0.0098743	-0.0088678	0.0035504	-0.0007108	0.0027021	0.0150750	-0.0065868	0.0056511
Social functioning	0.0030962	0.0109563	-0.0093543	-0.0054659	-0.0213392	-0.0343679	0.0052084	-0.0006402	0.0055038	0.0084157
Fatigue	0.0059733	0.0022788	-0.0220344	-0.0250514	0.0278376	0.0330008	0.0071305	0.0063537	-0.0063396	0.0072863
Nausea and vomiting	0.0005879	0.0157504	0.0068145	0.0186905	0.0218262	0.0215693	0.0054720	-0.0035358	-0.0074123	-0.0088818
Pain	0.0228164	0.0430386	0.0158179	0.0244974	0.0200722	0.0229097	0.1004407	0.1643611	0.0020242	-0.0118933
Dyspnea	0.0016023	0.0044787	-0.0046077	-0.0153410	-0.0053466	-0.0154350	0.0101103	0.0077207	0.0001655	-0.0177905
Sleep disturbance	0.0020489	0.0104134	0.0015579	-0.0001904	-0.0010660	-0.0021797	0.0125753	0.0212104	-0.0029185	0.0116847
Appetite loss	-0.0092890	0.0041667	-0.0001746	0.0095717	-0.0101199	-0.0109212	-0.0127206	-0.0081893	0.0061518	0.0160904
Constipation	-0.0042172	-0.0115196	-0.0041213	-0.0089580	-0.0004575	0.0041718	0.0058912	0.0098999	0.0042562	0.0006725
Diarrhea	-0.0049971	0.0097861	0.0030265	0.0051304	-0.0088893	-0.0111202	-0.0036955	-0.0076847	0.0018030	0.0019909
Financial impact	-0.0012006	-0.0032977	0.0049986	0.0146949	0.0077058	0.0064971	0.0099762	0.0116569	0.0123720	0.0146184
Age	0.0284672	-0.0206177	0.0480864	0.1312050					0.0259679	0.0081053
Female	-0.3486546	-1.3967005								
Constant	3.1686465	3.5415101	0.4980388	-6.6185420	3.4935399	5.6750937	-3.2549790	-9.8187423	4.5615723	6.0238621

This model had the lowest mean absolute error (MAE) on average and was identified as the best-performing response mapping model, as well as better than models belonging to other family classes (e.g. OLS). The model was validated both internally and, more recently, externally by Woodcock and Doble (109).

The expected value of the EQ-5D can then calculated by multiplying the probability of being in each response level for each EQ-5D domain by the standard UK tariff.

$$\begin{aligned}\text{Expected(EQ-5D)} = {} & 1-(\text{Prmob2}\times 0.069)-(\text{Prmob3}\times 0.314)-(\text{Prcare2}\times 0.104)-(\text{Prcare3}\times 0.214)\\ & -(\text{Pruact2}\times 0.036)-(\text{Pruact3}\times 0.094)-(\text{Prpain2}\times 0.123)-(\text{Prpain3}\times 0.386)\\ & -(\text{Pranx2}\times 0.071)-(\text{Pranx3}\times 0.236)-(1-\text{PrPerfect})\times 0.081-\text{PrN3}\times 0.269\end{aligned}$$

where Prmob2 is the probability of being in mobility level 2 on EQ-5D, Prmob3 is the probability of being in mobility level 3 on EQ-5D, Prcare2 is the probability of being in self-care level 2 on EQ-5D, Prcare3 is the probability of being in self-care level 3 on EQ-5D, Pruact2 is the probability of being in usual activities level 2 on EQ-5D, Pruact3 is the probability of being in usual activities level 3 on EQ-5D, Prpain2 is the probability of being in pain or discomfort level 2 on EQ-5D, Prpain3 is the probability of being in pain or discomfort level 3 on EQ-5D, Pranx2 is the probability of being in anxiety or depression level 2 on EQ-5D and Pranx3 is the probability of being in anxiety or depression level 3 on EQ-5D. PrN3 is the probability of any of EQ-5D dimensions being at level 3.

$$\begin{aligned}&\text{PrPerfect is the probability of being in perfect health}\\ &= \text{Prmob1}\times\text{Prcare1}\times\text{Pruact1}\times\text{Pr pain1}\times\text{Pranx1 and PrN3 is the probability of being}\\ &\text{in level 3} = 1-(1-\text{Prmob3})\times(1-\text{Prcare3})\times(1-\text{Pruact3})\times(1-\text{Prpain3})\times(1-\text{Pranx3})\end{aligned}$$

Where Prmob1 is the probability of being in mobility level 1 on EQ-5D, Prcare1 is the probability of being in self-care level 1 on EQ-5D, Pruact1 is the probability of being in usual activities level 1 on EQ-5D, Prpain1 is the probability of being in pain or discomfort level 1 on EQ-5D and Pranx1 is the probability of being in anxiety or depression level 1 on EQ-5D.

b. Provide details on the index-value model (direct mapping) used from Proskorovsky et al, 2014;

The direct mapping algorithm from Proskorovsky et al 2014 is an OLS-based model that relates HRQoL scores from the EORTC-QLQ-C30 to EQ-5D-3L utility values (UK value set). Data to fit the model were obtained from 154 multiple myeloma patients who had participated in a multicenter cohort study in the UK or Germany. External validation was not possible, thus a 10-fold cross-validation model selection method was also used as an alternative testing means.

The parameters of the model used in the CS (full model) are provided in Table 86 below.

Table 86: Model parameters used in the Company submission

Predictors	Full model	
	Estimate	*p*-value
Intercept	0.15540	0.2192
Global health status/QoL*	0.00198	0.0180
Physcial functioning*	0.00463	<0.0001
Role functioning	0.00058079	0.4512
Emotional functioning*	0.00141	0.0696
Cognitive functioning	-0.00048664	0.5075
Social functioning	0.00059878	0.3536
Fatigue	0.00016137	0.8588
Nausea/Vomiting	0.00041262	0.7764
Pain*	-0.00249	0.0001
Dyspnea	0.00060165	0.2879
Insomnia	0.00082466	0.1039
Appetite loss	-0.00037029	0.5885
Constipation	-0.00050445	0.3468
Financial difficulties	0.00079559	0.1187
Adjusted R-squared values	0.6956	
RMSE indices	0.165	

Another model was also presented (trimmed model), which only included coefficients that were statistically significant at a 0.05 level. Both models had similar and good explanatory power (adjusted R-squared values of 0.6956 for the full model and 0.6941 for the trimmed model). Predictive ability of both models was also comparable (RMSE of 0.165 for both the full and trimmed models). Thus, the full model was preferred as it was considered potentially more robust for extrapolating results to patients with a different condition (lymphoma) from that of the sample used for the original estimation (multiple myeloma), as the statistical significance of the coefficients in the trimmed model may have not been preserved in patients with lymphoma.

c. Clarify why an index-value model (direct mapping) from Longworth et al, 2014 has not been used and preference was given to the direct mapping algorithm from Proskorovsky et al, 2014;

The Company would like to clarify that the model utilised in the CS, as sourced from the original Longworth publication (108), was determined by the authors to be the most suitable model for EORTC-QLQ-C30 data, surpassing other model families tested such as OLS.

The Proskorovsky et al 2014 OLS-based algorithm was selected as the best candidate among all the direct mapping algorithms identified via targeted literature search of mapping algorithms for haematological malignancies described in the HSUV report. In general, the algorithm selection considered the following main factors:

- Good predictive ability (based on model performance statistics and accuracy of predicted values)
- Relevance and size of the patient sample used to estimate the algorithm
- Sufficient amount of detail on how the regression was estimated and on the baseline characteristics of the sample
- External validation
- Use in previous NICE submissions for hematological malignanices

Other factors that were considered were 1) scope of the algorithm (predict EQ-5D-3L values, preferred by NICE, versus EQ-5D-5L values) and 2) target EQ-5D tariff (UK vs other countries).

The final decision to use Proskorovsky et al 2014 was primarily based on the rationale that this algorithm was the most frequently used and accepted in previous NICE TAs in hematological malignancies (see Appendix H of the HSUV report). Unlike some of the other algorithms identified in the targeted review for which full information on model coefficients, how the regression was estimated and what was the patient sample used was available, Proskorovsky et al 2014 was estimated specifically on patients with an hematological malignancy (multiple myeloma). Conversely, the other most frequently used algorithms were estimated in patients with solid cancers (with sometimes a very limited sample size): McKenzie 2009 (esophageal cancer); Kontodimopoulos 2009 (gastric cancer); Crott 2010 (breast cancer). The Longworth algorithm itself was estimated on a mix of patients with solid and hematological tumors, even though the latter represented the majority. For all the reasons mentioned above, Proskorovsky et al 2014 was considered to be the best compromise to explore the impact of using a different mapping algorithm for estimating utilities. However, as Longworth et al 2014 has recently been externally validated (109), it was preferred to Proskorovsky et al 2014 for the CE model base case.

d. Provide results for a scenario analysis where the direct mapping algorithm from Longworth et al, 2014 is used, updating the electronic version of the model accordingly.

The EAG confirmed via email that they would be interested in exploring health state utility values estimated using an additional algorithm from the Longworth et al 2014 review based on a model termed OLS model 8. The necessary information for the

implementation of this method is provided in the Appendices of the review (Table 49, page 221), though not in the original mapping paper (108).

This model seems to have been estimated using selected individual EORTC-QLQ-C30 items (based on statistical significance) and age as coefficients. However, to a closer inspection, it is very challenging to unambiguously identify all the individual EORTC-QLQ-C30 items that were used in the regression. Specifically, two items are available for both the pain and social functioning domains in the EORTC-QLQ-C30 questionnaire, and it is not possible to reconcile with certainty which of the two have been used to estimate the respective regression coefficients, as they are generally referred to as “Pain” and “Social functioning” in Table 49. The Company tried to contact the authors of the two papers mentioned above (Prof. Young and Prof. Longworth) for clarification, but to date no reply has been received.

Nevertheless, the Company still tried to estimate the utilities based on this algorithm by assuming that the ambiguous items termed as “Pain” and “Social functioning” in Table 49 would correspond to Questions 9 and 27 of the EORTC-QLQ-C30 questionnaire (Question 9: “Have you had pain?” and Question 27: “Has your physical condition or medical treatment interfered with your social activities?”). The methodology followed is the same as the one described as part of the responses to clarification questions B19–B21. The results of the mapping, i.e. this newly estimated set of utilities are provided in Table 87 below.

Table 87: Newly estimated set of utilities using algorithm for ambiguous items 'pain' and 'social functioning', based on EORTC-QLQ-C30 questionnaire responses

Health state	Estimate	bStderr	2.5% bCL	97.5% bCL	corr_PFS_ONTRT	corr_PFS_OFFTRT	corr_PPS
PFS_ONTRT	0.73822912	0.0116443	0.71642447	0.76196401	1	0.37804856	0.42978262
PFS_OFFTRT	0.78684592	0.02126842	0.74781051	0.82978158	0.37804856	1	0.21774063
PPS	0.62447896	0.01889961	0.58845178	0.66254829	0.429782616	0.217740634	1

Considering the uncertainty around how this specific mapping algorithm was actually estimated, as well as the fact that this model was identified by the authors in both publications as of inferior performance compared to the response-based mapping algorithm, the Company deems the utility values estimated with this approach not suitable for decision making. Accordingly, a scenario based on this new set of utility values has not been implemented in the CE model.

B19. Please clarify how many patients were excluded when taking a complete case mapping approach, discuss the excluded patients' fitness to fill in the questionnaire and how that may affect the robustness of the utility estimates applied in the model.

Per the NP30179 Protocol, no patient-reported outcome (PROs) were administered to patients in Cohort D2, as these were not part of the PRO evaluable population. Therefore, all potentially relevant D2 [Sub. 2] cohort patients (n=7) had to be excluded from the mapping as no EORTC-QLQ-C30 data were collected.

Of the remaining 148 patients, only 2 patients (in cohort D3) had to be excluded from the analyses, as they had individual EORTC-QLQ-C30 responses missing in all visits and could thus not be used for the mapping exercise. This represents ~1% of the relevant cohort effectively usable for the analysis (patients with pivotal DLBCL histologies on target registrational dose for which PRO measures were collected), hence their exclusion from the mapping is not expected to have a meaningful impact on the utility estimates used in the CEM.

The Company would like to clarify that all available visits for which EORTC-QLQ-C30 response information for the domains/items required for a specific mapping algorithms were used, to maximise sample size, i.e. the complete case approach was based on visits and not patients.

B20. Please provide full detail on how mapped EQ-5D-3L index values were used to estimate PFS on treatment, PFS off treatment and post-progression utilities.

Utility measurements were assigned to PFS or PPS health states by comparing the date of progression (per-investigator assessment) with the corresponding date of measurement for the predicted utility value. If the date of measurement was larger than the date of progression, the patient was set as PPS. If it was not possible to assign a utility measurement to either PFS or PPS due to censoring, then that measurement was classified as unknown, as the patient could have progressed between the date of censoring and the date of measurement. These visits were then excluded from the sample. A similar approach was used for on- and off-treatment states but using the date of treatment discontinuation as reference. A flag was then assigned to patient visits to categorize the relevant health states being modelled in the regressions.

Details on the regression modeling employed to estimate health state utility values are described below, as part of the response to Question B21.

B21. Please provide full detail on how mapped EQ-5D-3L index values were modelled longitudinally using a linear mixed regression model.

All utilities were estimated through a mixed regression model (via the lmer() function of the lme4 R package) on post-baseline utilities only, using the health status variable defined above as the main predictor, while controlling for centralised baseline utilities and using random intercepts for each patient (patient level random effects). This technique is relatively robust to distributional violations and it has been applied and accepted in previous TAs (the last of which was ID3931, TA of mosunetuzumab for treating relapsed or refractory follicular lymphoma – ongoing) (46). 13 patients did not have mapped utilities values at baseline and had to be excluded from the analysis, as it was not possible to estimate a centralised baseline utility for them and could thus not be used to fit a model including this covariate. Given the relatively small number of patients with missing utility value at baseline, the potential impact on the regression outcomes is expected to be minimal. For the proximity to death approach, a similar model was used but the health state variable employed was an interaction term between an on-/off-treatment variable and a proximity to death variable estimated using the time intervals described in the Utility Values CEM sheet. Bootstrapping (2000 resamples) was used to estimate confidence intervals around point estimates in all analyses.

Detailed output of the regressions models are provided from Table 88 to Table 90 below.

Table 88: Longworth et al 2014 - PFS (on-/off-treatment) – PD model

Health state	Estimate	bStderr	2.5% bCL	97.5% bCL	corr_PFS_ONTRT	corr_PFS_OFFTRT	corr_PPS
PFS_ONTRT	0.72854982	0.01099889	0.70688369	0.75053804	1	0.397170616	0.416272548
PFS_OFFTRT	0.77376803	0.02044949	0.73563964	0.81520653	0.397170616	1	0.212981984
PPS	0.62868095	0.01896589	0.59016966	0.66537534	0.416272548	0.212981984	1

Table 89: Longworth et al 2014 – Proximity to death model

Health state	Estimate	bStderr	2.5% bCL	97.5% bCL	corr_PTDTH60+ ONTRT	corr_PTDTH60 ONTRT	corr_PTDTH30 ONTRT	corr_PTDTH10 ONTRT	corr_PTDTH60+ OFFTRT	corr_PTDTH60 OFFTRT	corr_PTDTH30 OFFTRT	corr_PTDTH10 OFFTRT
PTDTH60+ ONTRT	0.727635125	0.01688022	0.695951037	0.762259569	1	0.350375611	0.129961756	0.03559785	0.218557914	0.419308985	0.341060197	0.136876763
PTDTH60 ONTRT	0.729478004	0.01466289	0.701543457	0.759435005	0.350375611	1	0.344086858	0.130310534	0.08143255	0.263134711	0.338934431	0.131290934
PTDTH30 ONTRT	0.733444471	0.01543114	0.704209799	0.764699377	0.129961756	0.344086858	1	0.224685381	0.046809363	0.08105017	0.170367792	0.191978927
PTDTH10 ONTRT	0.683646444	0.02517508	0.634826294	0.730163306	0.03559785	0.130310534	0.224685381	1	-0.066491449	0.022886212	0.072270221	0.146422862
PTDTH60+ OFFTRT	0.796042032	0.04451827	0.709962132	0.881868454	0.218557914	0.08143255	0.046809363	-0.066491449	1	0.193977128	0.080995583	0.053402806
PTDTH60	0.724356162	0.02530966	0.675574783	0.774346907	0.41930898 5	0.263134711	0.08105017	0.022886212	0.193977128	1	0.25983733	0.105873816

OFFTRT												
PTDTH30 OFFTRT	0.719535537	0.02250051	0.675359546	0.763645498	0.341060197	0.338934431	0.170367792	0.072270221	0.080995583	0.259837 33	1	0.110543768
PTDTH10 OFFTRT	0.565166162	0.02973035	0.506118952	0.623260543	0.136876763	0.131290934	0.191978927	0.146422862	0.053402806	0.105873816	0.110543768	1

Table 90: Proskorovsky et al, 2014 - PFS (on-/off-treatment) – PD model

Health state	Estimate	bStderr	2.5% bCL	97.5% bCL	corr_PFS_ONTRT	corr_PFS_OFFTRT	corr_PPS
PFS_ONTRT	0.77213184	0.00962813	0.75475318	0.79209251	1	0.402977584	0.35822292
PFS_OFFTRT	0.83614945	0.01721522	0.80392905	0.87146477	0.402977584	1	0.17564958
PPS	0.67325567	0.01649635	0.6416089	0.70602639	0.35822292	0.175649579	1

B22. The company assumes that the PFS on-treatment utility values estimated from the trial capture the health-related quality of life experienced by patients in pre-progression, including the impact of any potential adverse events for those on treatment. Thus, the company does not include adverse effect specific disutilities in their economic model as to avoid double counting. The EAG finds it likely that most patients with severe adverse effects are unable to complete HRQoL questionnaires. Thus, the double counting issue raised by the company may not be apply under these circumstances. Please update the electronic version of the model so that it is possible to turn on/off the impact of AEs disutilities for all scenarios, i.e., not just the ones where health state utilities were based on previous NICE TAs.

The Company would like to clarify that the concern raised by the EAG regarding the potential underestimation of that impact that a treatment safety profile may have on utilities, due to a presumed inability of most patients with severe adverse effects to complete HRQoL questionnaires, is expected to apply for published disutilities as well. In fact, if the published disutilities were originally derived from data collected outside of a clinical trial setting, where the data collection is not subject to the strict requirements imposed by trial protocols, this issue is even more likely to arise.

Furthermore, due to missing information, the values for most of the AE disutilities used in the model were assigned using conservative assumptions rather than estimated directly from data, which makes the actual potential for double counting even higher. Finally, the Company would like to clarify that the Committees' preferences in several previous TAs (e.g. TA406, TA529) (110) were not to include adverse event disutilities in the economic analyses when health state utilities were estimated using trial data, again to avoid incurring in potential double counting issues. As such, additional functionality has not been included in the economic model to enable to the inclusion of AE disutilities when the utility values used in the economic analysis are set to those collected from NP30179 mapped to EQ-5D.

Section B: Resource use and costs

B23. Priority question: The model appears to underestimate the proportion of individuals treated with glofitamab when calculating its acquisition, administration, and monitoring costs (only 90.9% of patients receive glofitamab the model first cycle while in the trial 154 patients out of 155 received at least one dose of glofitamab [99.4%]). This appears to be in part due to the half-cycle correction. Please adjust the cost calculation in the electronic version of the model the model to avoid underestimating the glofitamab treatment costs and update the CE analysis accordingly.

The Company would like to clarify that it is not factually correct that 154 patients out of 155 had received at least one dose of glofitamab. The misunderstanding is likely caused from a potentially unclear definition of study treatment, which is defined in NP30179 as obinutuzumab pre-treatment plus glofitamab, and not glofitamab alone.

In fact, only 145 patients received at least one dose of glofitamab in the pooled cohort (D2 [Sub. 2]+D3+D5) from the NP30179 trial (glofitamab-received population, SERO). Of the 10 patients excluded from this population, 9 received only obinutuzumab pre-treatment and 1 received neither obinutuzumab pre-treatment nor glofitamab. Additionally, the time of receipt of obinutuzumab pre-treatment was used as the starting time to estimate the TTOT KM curve used to inform the treatment discontinuation of glofitamab in the CEM. The current proportion in the model thus represents the actual proportion of patients expected to receive glofitamab, in line with the ITT principle. Therefore, no changes have been made to the drug cost calculation for glofitamab in the model.

B24. Priority question: The calculation of the acquisition costs of treatments for the base-case assumption of optimised vial sharing (in the electronic version of the model, “Dosing” tab) does not seem to take into consideration the number of vials per package of each drug. For example, for rituximab assumes that the cost per small vial of rituximab (100mg) is £314.33, when this is the cost of a pack with two small vials. The same seems to occur for bendamustine which has 5 vials per package (for both 25mg and 100mg doses). Please check if the number of vials per package is considered for every drug in the “Dosing” tab and correct any errors (including those already identified for rituximab and bendamustine) in the electronic version of the model and update the CE analysis accordingly.

The Company would like to thank the EAG for noting this error. This has been corrected in the latest version of the economic model.

B25. The electronic version of the model ("Dosing" tab) contains individual patient data, namely baseline characteristics for individuals in the NP30179 study. This dataset is used to calculate the planned dose of each treatment component (and the age distribution used to inform the general population mortality rate). In the "Dosing" tab there is text suggesting that "missing values imputed (are) as average among non-missings". The dataset contains 154 observations but the primary study population of NP30179 has 155 patients. Please clarify what was the proportion of missing data for each variable in the dataset contained in the model.

Out of the total 155 patients in the dataset, information regarding body weight and height was unavailable for three of them. The safety population used for the dataset comprised 154 patients who received at least one dose of the study treatment (obintuzumab pre-treatment and glofitamab). One patient enrolled in the primary efficacy population (n=155) did not receive any study treatment. This population was considered the most appropriate for dosing calculation purposes, as they were the ones who received the treatment.

B26. Priority question: The cost of monitoring individuals treated with glofitamab are applied differently in the electronic version of the model depending on the glofitamab model engine (the formulae applied in cells CL13:CL3144 in the "Glofit" tab differs from the ones applied in cells BV13:BV3144 in the "Glofit_pop_BR", "Glofit_pop_Pola-BR" and "Glofit_pop_Yesc" tabs). Please clarify why the formulae differ. If this was an error, please correct it in the electronic version of the model and update the CE analysis accordingly.

The economic model has been updated to correct this monitoring cost error in the sheets highlighted. This correction has been implemented with other changes in the economic model, resulting in updated base-case results, reported in Table 91.

Table 91: Deterministic base-case cost-effectiveness results (glofitamab PAS price, comparator list price)

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)	NMB at 30k
Glofit vs BR						

Glofit	[redacted]	[redacted]				
BR	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Glofit vs pola-BR						
Glofit	[redacted]	[redacted]				
Pola-BR	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Glofit vs axi-cel						
Glofit	[redacted]	[redacted]				
Axi-cel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

**1.2 QALY modifier applied. ICER, incremental cost-effectiveness ratio; LYG, life years gained; NMB, net monetary benefit; QALYs, quality-adjusted life years.*

B27. Priority question: Please report the proportion of patients who required IV immunoglobulin (IVIG) treatment for B-cell aplasia and mean time (standard error) on treatment with IVIG in the primary safety population of the NP30179 study. Please implement the cost associated with IVIG treatment for individuals treated with glofitamab in the electronic version of the model, in accordance with what was observed in the NP30179 study.

The Company would like to clarify that, in previous CAR-T TAs (e.g. TA559), B-cell aplasia occurrence was considered to be specifically associated with this technology, as an expected direct consequence of their mechanism of action, due to its link with CAR T-cells proliferation and their associated durability. Conversely, no available evidence to date suggests that B-cell aplasia would be an expected consequence of treatment with glofitamab. In fact, glofitamab specifically targets CD20 (versus currently approved CAR-Ts which target CD19), and is therefore not expected to target the progenitor (Pro) B-cells in the bone marrow which do not express yet CD20 (111). Accordingly, no specific occurrence of B-cell aplasia was reported in NP30179.

In previous TAs, hypogammaglobulinemia was flagged as the primary manifestation of B-cell aplasia (though, strictly speaking, the two do not coincide). It is worth pointing out that hypogammaglobulinemia has not been raised as a safety concern/important risk for glofitamab in current interactions with regulatory authorities. There is currently no comprehensive evidence of AEs other than hypogammaglobulinemia that could be associated with B-cell aplasia and would require treatment with IVIG. In general, IVIG is primarily administered as 1) treatment of antibody deficiency related conditions, 2) replacement therapy, 3) immunomodulator in immune/inflammatory disorders. No IVIG use other than for the

management of AEs linked with B-cell depletion leading to hypogammaglobulinemia can be expected in NP30179, considering its eligibility criteria (patients with history of autoimmune disease were ineligible). Accordingly, uses of IVIG in NP30179 was mainly done for infection prophylaxis (5 patients) or management of AEs unrelated to hypogammaglobulinemia (2 due to COVID-19 pneumonia, 1 for febrile neutropenia, 1 for myelitis, 1 for lymphopenia and 1 for campylobacter infection).

That being said, the occurrence of hypogammaglobulinemia that required treatment with IVIG in the NP30179 trial safety cohort was very low (only 2 out of 155 patients) and might be different in nature/occurrence compared with CAR-Ts. Moreover, the observed reactions were all classified as grade 2/non-serious.Therefore, the Company believes that including IVIG costs for the management of hypogammaglobulinemia / B-cell aplasia in the economic mode would be inappropriate, also because it would be inconsistent with the general approach used for AE costing across comparators. Finally, with only 2 events observed, this is not expected to meaningfully impact the results.

B28. Priority question: Regarding the costs of managing of cytokine release syndrome (CRS) in Table 59 of the CS, please clarify the following:

a. How was the unit cost of tocilizumab (£767.49) estimated? The reference provided (BNF) lists a price of £913.12 for 4 pre-filled injections (162mg/0.9ml). Given the average weight used (74.95Kg) and the dose (8mg/Kg, maximum per dose 800 mg) indicated for the management of CRS, each administration would require 3.7 units of tocilizumab or 4 units assuming wastage. If the unit cost applied in the model assumes wastage, please update the base-case CE analysis to use a £913.12 unit cost for the acquisition cost of tocilizumab for CRS management.

A cost per mg for tocilizumab of £1.28 was derived from the BNF, where 200mg/10ml concentrate for solution for infusion vials has an NHS indicative price of £256.00. Based on this, a dose of 8mg/kg, the average patient weight from NP30179, and assuming zero wastage, the unit cost of tocilizumab was calculated as £767.49 (£1.28*8[mg/kg]*74.95[kg]). As no wastage has been assumed, no additional analyses have been performed.

b. Why were the cost of two rheumatology outpatient attendances included in the cost of managing CRS (Table 59, CS)? Please provide full details on how this unit cost was sourced, as it does not match the cost of a "Multiprofessional Non-Admitted Face-to-Face Attendance, Follow-up" attendance across all HRGs (£155.88) or for the service code 410 (Rheumatology, £108.04) in the NHS reference costs 2020/21.

The cost of managing CRS included the expenses of two appointments with a rheumatologist, who are experienced in administrering tocilizumab, a treatment used for the management of CRS in DLBCL.

This cost was sourced from the NHS reference costs 2020/2021 (112), as a multiprofessional "Non-Admitted Face-to-Face Attendance, Follow-up, Rheumatology, Consultant Led (currency code: WF02A)".

See Table 93 for more details.

c. The exact Homogeneous Resource Group (HRGs) currency codes used to inform the unit cost of ICU hospitalisations.

The calculation of ICU hospitalisations was derived as the average of critical care currency codes XC01Z-XC07Z for "Non-Specific, General Adult Critical Care Patients Predominate" from the 20/21 schedule of NHS reference costs (Table 92).

After reviewing this component of CRS management costs, this figure has been corrected to reflect a weighted average of these currency costs, resulting in a unit cost of ICU hospitalisation of £2385.78 (Table 93) (112).

Table 92: HRG currency codes used to calculate ICU hospitalisation unit cost

Service description	Currency code	Currency description	Activity	National average cost
Non-specific, general adult critical care patients predominate	XC01Z	Adult Critical Care, 6 or more Organs Supported	7034	£2,625.34
Non-specific, general adult critical care patients predominate	XC02Z	Adult Critical Care, 5 Organs Supported	27962	£2,769.13
Non-specific, general adult critical care patients predominate	XC03Z	Adult Critical Care, 4 Organs Supported	98348	£2,781.83

Non-specific, general adult critical care patients predominate	XC04Z	Adult Critical Care, 3 Organs Supported	220733	£2,612.99
Non-specific, general adult critical care patients predominate	XC05Z	Adult Critical Care, 2 Organs Supported	292889	£2,491.23
Non-specific, general adult critical care patients predominate	XC06Z	Adult Critical Care, 1 Organ Supported	253343	£1,888.73
Non-specific, general adult critical care patients predominate	XC07Z	Adult Critical Care, 0 Organs Supported	15838	£1,977.41

The corrected figure for ICU hospitalisation, and the other cost components of CRS management can be seen in Table 93.

Table 93: CRS AE management

Cost component	Cost per unit	Unit	Total cost	Source
Tocilizumab	£767.49	2	£1,534.98	74.95kg (average weight from trial); £1.28/mg for the IV (BNF); Tocilizumab 8 mg/kg intravenously (not to exceed 800 mg), as administered in Study NP30179
Pharmacist time	£31.20	2	£62.40	Cost of preparation taken from TA812; tocilizumab infusion time is 1 hour
Rheumatology	£230.27	2	£460.54	NHS National Reference Cost schedule 2020-2021 (Multiprofessional Non-Admitted Face-to-Face Attendance, Follow-up, Rheumatology, Consultant Led [currency code: WF02A]).
Intensive care unit (ICU) hospitalisation	£2385.78	4	£9,543.12	NHS National Reference Cost schedule 2020-2021 (weighted average of Non-specific, general adult critical care patients predominate XC01Z to XC07Z; Critical Care)
Total cost		**£11,601.05**		

B29. In table 58 in the CS, the HRG currency codes used to inform adverse events unit costs refer mostly to day cases, but pneumonia and septic shock were costed as non-elective short stays. Could you please

clarify what was the rationale followed to select the type of admission for each adverse event?

In an attempt to follow previously accepted approaches to costing AEs for DLBCL, where available, cost codes and administration type for adverse events followed those used in previous appraisals.

Non-elective short stay admissions were selected when costing pneumonia and septic shock AEs, following the approach used in the appraisal of polatuzumab vedotin with rituxumab and bendamustine (TA649)(87).

B30. Priority question: The mean treatment duration and treatment distribution for subsequent therapy in post-progression (see Table 53, CS) was assumed to be independent of the treatment initially received (i.e., glofitamab, pola-BR, BR or axi-cel). Clinical advice suggests that this is not plausible, as prior lines of treatment will condition subsequent ones. Please update the economic version of the model, so that the mean treatment duration and treatment distribution for subsequent therapy in post-progression is dependent on the treatment received pre-progression. A potential data source to inform these parameters for BR and pola-BR is the GO29365 study, which was sponsored by the company and should therefore be accessible. We also suggest that the cost of subsequent CAR-T is removed for those treated at PFS with axi-cel, as this is not in line with current clinical practice in the NHS.

Mean treatment duration for subsequent therapies in post-progression is dependent on the treatment received pre-progression which cannot be reliably informed by data. Furthermore, basing post-progression treatment shares and treatment duration on information from GO29365, would mean basing post-progression costs on outdated estimates of treatment shares, which would lead to an underestimation of the use of post-discontinuation CAR-T and SCT, for reasons described in more detail below. As such, basing post-discontinuation treatment shares on NP30179 was deemed to be the most representative source for DLBCL 4L+.

The Company would like to highlight that using subsequent therapy information informed by GO29365 trial data may not accurately reflect the current clinical practice, and may also be misleading considering the population relevant for this appraisal. In fact, GO29365 is a relatively old trial, where patients may have ended up not receiving CAR-Ts just because these options weren't approved/available at the time when the trial was conducted, or may have been coded as "Clinical Trial" or similar, whose costs aren’t normally considered in the subsequent therapy costs (the cost is normally covered by the manufacturer). Furthermore, unlike NP30791,

transplant ineligibility was an inclusion criteria for the DLBCL part of GO29365, which may have influenced the observed proportion of subsequent SCTs received by patients with 3L+ DLBCL (although it's possible for patients to become again transplant eligible, past transplant ineligibility may reduce these chances). This would unduly bias the results against glofitamab by selectively increasing its subsequent therapy costs due to unresolvable limitations associated with the requested alternative data source. Therefore, while agreeing with the EAG that the type of prior treatments received may influence the choice of the subsequent ones, the Company deems the subsequent treatment shares informed by NP30179 as the most robust representative data available for the population relevant for this appraisal.

The company acknowledges that there is a low probability of re-treatment 4L and beyond. As such, 2 alternative scenarios have been developed in which the post-discontinuation treatment shares observed in NP30179 have been adjusted to remove the possibility of re-treatment:

- Replacing re-treatment shares with 4L+ glofitamab usage. [redacted], and it is therefore highly likely that if recommended, glofitamab will be utilised in the 4L+ setting. Furthermore, NP30179 contains ~60% of people who had at least 3 prior therapies (see table 9, company submission), therefore the efficacy and safety of glofitamab at this position has been demonstrated.
- Removing re-treatment and re-normalising the remaining treatment shares to 100%. Glofitamab is set as a one-off treatment, with a one-off treatment cost derived as the mean 3L treatment cost taken from the cost-effectiveness model.

These 2 analyses represent treatment-dependent post-discontinuation scenarios based on the most reliable source 4L+ treatment shares.

Table 94: No re-treatment, replace re-treatment proportion with glofitamab

Therapy class	Therapy	mean duration in weeks	% on Glofit	% on BR	% on pola-BR	% on axi-cel
Anti-CD20 + chemo	BR	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Anti-CD20 + chemo	R-GEMOX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Anti-CD20 + chemo	R-CHOP	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Anti-CD20 + chemo	Other R-chemo regimens	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Chemo (no anti-CD20)	Other chemo regimens (not including R)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Drug-antibody conjugate	Pola-BR	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Immunomodulating agent	Lenalidomide	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Chemo (no anti-CD20)	Pixantrone	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Other	Clinical Trial/Other	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Radiotherapy	Radiotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Stem-cell transplant	Allogeneic SCT	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Stem-cell transplant	Autologous SCT	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
CAR-T	Axi-cel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Bi-specific	Glofitamab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Table 95: no re-treatment, re-normalising treatment shares to 100%

Therapy class	Therapy	Mean duration in weeks	% on Glofit	% on BR	% on pola-BR	% on axi-cel
Anti-CD20 + chemo	BR	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Anti-CD20 + chemo	R-GEMOX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Anti-CD20 + chemo	R-CHOP	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Anti-CD20 + chemo	Other R-chemo regimens	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Chemo (no anti-CD20)	Other chemo regimens (not including R)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Drug-antibody conjugate	Pola-BR	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Immunomodulating agent	Lenalidomide	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Chemo (no anti-CD20)	Pixantrone	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Other	Clinical Trial/Other	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Radiotherapy	Radiotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Stem-cell transplant	Allogeneic SCT	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Stem-cell transplant	Autologous SCT	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
CAR-T	Axi-cel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

The impact of implementing these 2 scenarios on the cost-effectiveness results can be seen in Table 96. The treatment shares from the 2 scenarios described above are copied in the post progression therapy cost sheet of the economic model. If the EAG wishes to reproduce these scenarios, copying these treatment shares can in to the Table in rows 36-49 in the post progression treatment costs sheet of the economic model, will update the post discontinuation costs applied in the economic analysis.

The results of the 2 additional post progression treatment scenarios can be seen in Table 96 below.

Table 96: Post progression therapy scenarios

Scenario	ICER vs BR	ICER vs pola-BR	ICER vs axi-cel (cost saved per QALY lost)
Base-case (NP30179 post-discontinuation treatment shares)	[redacted]	[redacted]	[redacted]
No re-treatment, replace re-treatment proportion with 4L+ glofitamab use	[redacted]	[redacted]	[redacted]
No re-treatment, re-normalising treatment shares to 100%	[redacted]	[redacted]	[redacted]

**1.2 QALY modifier applied; ICER, incremental cost effectiveness ratio.*

B31. Please provide details on the calculation the cost of allogeneic and autologous stem cell transplant (SCT) implemented in the 'Post progression therapy' tab. Please also implement the corrections below in the electronic version of the model and update the CE analysis accordingly.

a. Correct the follow-up costs of allogeneic SCT in cell V25 from £2,551.00 to 25,551.00 as per TA559.

The cost of follow-up allogeneic SCT has been corrected in the economic model. These costs have now been inflated to 2020/2021 prices (see response below).

b. Inflate the costs in cells W25:W27 to the cost year of the analysis, as these do not appear to have been inflated from 2013/14 costs.

SCT costs in cells W25:W27 have been inflated in the economic model to 2020/2021 costs using the PSSRU NHS cost inflation index (for details see post progression therapy cost sheet).

The cost of allogeneic and autologous SCT in the post-progression therapy tab follows the approach used in previous TAs (e.g. TA567 and/or TA559). Specifically the cost of transplantation procedure consisted of 3 elements (these were costed all using HRGs rather than elective costs as it was thought to be more reflective of what may actually occur in the UK clinical practice):

1. Cost of stem-cell harvesting
    a) Estimated as the weighted average between SA18Z and SA34Z, as per TA567, TA559 and potentially other subsequent TAs

2. Cost of transplantation procedure
    a) Estimated using SA26A for autologous SCT and the weighted average of SA38A, SA39A and SA40Z, as per TA567, TA559 and potentially other subsequent TAs

3. Follow-up costs:
    a) Allogeneic transplant → the same method and data used in TA559, which cites the NICE regenerative medicines report [ref. UK Stem Cell Strategy Oversight Committee Report] was employed
    b) Autologous transplant → the same procedure as the one used in TA567 was employed, i.e. costs were estimated as a fraction of the follow-up costs for allogeneic stem-cell transplant, based on the relative cost of allogeneic SCT compared to autologous SCT, as reported in Blommestein et al. (2012).

B32. Please provide the dosing regimens, unit costs and corresponding sources (including details on the brand and formulation assumed (e.g., powder for solution for infusion, solution for infusion, etc.) for each component of the subsequent chemotherapies listed in Table 55 of the CS.

It is assumed that this question relates to Dcoument B, Table 54 - “Weekly treatment costs for post-discontinuation including administration (list price)”. The total costs (treatment cost per cycle and administration cost) included in CS were informed by model estimations and assumptions.

Additional detail relating to how these costs were calculated is presented in Table 97.

Table 97: Drug cost and sources informing weekly treatment costs for post progression

Therapy	Tx cost/week (incl. admin cost) (£)	Source / description of drug costs
BR	[redacted]	• Rixanthon (rituximab) 100mg/10ml £314.33 - BNF • Rixanthon (rituximab) 500mg/50ml £785.84 - BNF • Bendamustine 25 mg powder for solution for infusion vials (5 pack) £34.08 • Bendamustine 100 mg powder for solution for infusion vials (5 pack) £82.89 - eMIT
R-GEMOX	[redacted]	• Rituximab (as above) • Gemcitabine 200 mg powder for solution for infusion vials (1 pack) £3.30 - this price has been updated in the economic model using the price from eMIT • Gemcitabine 1200mg/120ml solution for infusion bags (1 pack) £32.99 - this price has been updated in the economic model using the price from eMIT • Oxaliplatin 50mg/10ml solution for infusion vials (1 pack) £20.45 - this price has been updated in the economic model using the price from eMIT • Oxaliplatin 100mg/20ml solution for infusion vials (1 pack) £46.78 - this price has been updated in the economic model using the price from eMIT
R-CHOP	[redacted]	• Rituximab (as above) • Cyclophosphamide 500mg powder for solution for injection vials (1 pack) £8.33 - this price has

		been updated in the economic model using the price from eMIT • Doxorubicin 50mg/25ml solution for injection vials (1 pack) £5.95 - this price has been updated in the economic model using the price from eMIT (10mg/5ml and 200mg/100ml prices also updated from eMIT) • Vincristine 1mg/1ml solution for injection vials (5 pack) £17.24 - this price has been updated in the economic model using the price from eMIT (2mg/2ml price also updated from EMIT [5 pack price]) • Prednisolone 20mg tablets Accord Healthcare Ltd (28 tablets) £19.45 - BNF
Other R-chemo regimens	[redacted]	Average costs of R-Based regimens listed above
Other chemo regimens (not including R)	[redacted]	Average of: • Bendamustine (as above) • Gemcitabine (as above) • Oxalilplatin (as above) • Cyclophosphamide (as above) • Doxorubicin (as above) • Vincristine (as above) • Prednisolone (as above) • Lenalidomide 25mg capsules Zentiva Pharma UK Ltd £3,057.60 (hospital only) - Price updated to lowest available on BNF • Pixuvri (Pixantrone) 29mg powder for concentrate for solution for infusion vials Servier Laboratories Ltd £553.50 - BNF
Pola-BR	[redacted]	• Polivy (polatuzumab vedotin) 30mg powder for concentrate for solution for infusion vials Roche Products Ltd £2,370 - BNF • Polivy (polatuzumab vedotin) 140mg powder for concentrate for solution for infusion vials Roche Products Ltd £11,060 - BNF • Bendamustine (as above) • Rituximab (as above)
Lenalidomide	[redacted]	Lenalidomide (as above)

Pixantrone	[redacted]	Pixantrone (as above)

B33. The unit cost for bone marrow biopsy in Table 57 of the CS only appears to include the cost of one of the currency codes listed in the source column (i.e., £928.96 for currency code SA33Z: Diagnostic Bone Marrow Extraction). Please include the cost for the currency code RD01A: Magnetic Resonance Imaging Scan of One Area, without Contrast, 19 years and over.

MRI costs have been accounted for in the total one-off progression costs, calculated as the sum of different costing components listed in Document B, Table 57. No change has been implemented.

B34. Please provide the unit cost source for the categories of costs in Table 56 of the CS, with sufficient detail for the EAG to be able to validate these values.

The unit cost sources for the costs reported in Document B, Table 56 were excluded from the CS to improve readability, but are provided in the Cost inputs sheet of the economic model. The sources for costs have been reproduced below in Table 98.

Table 98: Weekly supportive care unit costs and sources

Unit	Unit cost	Source
Professional and social services		
Residential care (day)	120.63	Crude average of Local authority & private; Jones, K. & Burns, A. (2021) Unit Costs of Health and Social Care 2021, Personal Social Services Research Unit, University of Kent, Canterbury.DOI: 10.22024/UniKent/01.02.92342
Day care (day)	61.11	Jones, K. & Burns, A. (2021) Unit Costs of Health and Social Care 2021, Personal Social Services Research Unit, University of Kent, Canterbury.DOI: 10.22024/UniKent/01.02.92342
Home care (day)	35.11	Jones, K. & Burns, A. (2021) Unit Costs of Health and Social Care 2021, Personal Social Services Research Unit, University of Kent, Canterbury.DOI: 10.22024/UniKent/01.02.92342
Hospice (day)	198.10	TA306 (based on National Audit Office 2008; Per diem cost of hospice care = £132; Inflated per diem cost of home care to 2022 = £198.10

Health care professionals and hospital resource use		
Haematologist (visit)	224.55	NHSSRC 2020/21; WF01A, Service code 370, Medical oncology, face-to-face, non-admitted
Oncologist (visit)	214.56	NHSSRC 2020/21; WF01A, Service code 303, clinical haematology, face-to-face, non-admitted
Radiologist (visit)	185.20	NHSSRC 2020/21; WF01A, Service code 800, Clinic oncology(Radiotherapy), face-to-face, non-admitted
Nurse (visit)	51.84	NHSSRC 2020/21; N02AF; District Nurse, Adult, Face to face
Specialist nurse (visit)	51.84	NHSSRC 2020/21; N02AF; District Nurse, Adult, Face to face
GP (visit)	39.23	Jones, K. & Burns, A. (2021) Unit Costs of Health and Social Care 2021, Personal Social Services Research Unit, University of Kent, Canterbury. DOI: 10.22024/UniKent/01.02.92342
District nurse (visit)	51.84	NHSSRC 2020/21; N02AF; District Nurse, Adult, Face to face
CT scan	106.79	NHSSRC 2020/21; RD27Z; Complex CT
Inpatient day	404.02	Unit cost from TA649 inflated to 2021 prices using NHSCII from PSSRU 2021
Palliative care team	124.15	Unit cost from TA649 inflated to 2021 prices using NHSCII from PSSRU 2021
Treatment follow-up		
Full blood counts	3.63	NHSSRC 2020/21; DAPS05; 'Haematology
LDH	3.63	NHSSRC 2020/21; DAPS05; 'Haematology
Liver function	3.63	NHSSRC 2020/21; DAPS05; 'Haematology
Renal function	3.63	NHSSRC 2020/21; DAPS05; 'Haematology
Immunoglobulin	3.63	NHSSRC 2020/21; DAPS05; 'Haematology
Calcium phosphate	3.63	NHSSRC 2020/21; DAPS05; 'Haematology
Hematologist (visit)	224.55	NHSSRC 2020/21; WF01A, Service code 370, Medical oncology, face-to-face, non-admitted

Oncologist (visit)	193.24	NHSSRC 2020/21; WF01A, Service code 303, clinical haematology, face-to-face, non-admitted
Nurse (visit)	51.84	NHSSRC 2020/21; N02AF; District Nurse, Adult, Face to face
Radiologist (visit)	185.20	NHSSRC 2020/21; WF01C, Service code 800, Clinic oncology(Radiotherapy), face-to-face, non-admitted
GP (visit)	39.23	Jones, K. & Burns, A. (2021) Unit Costs of Health and Social Care 2021, Personal Social Services Research Unit, University of Kent, Canterbury. DOI: 10.22024/UniKent/01.02.92342

B35. The unit costs for a haematologist visit and an oncologist visit is Table 56 in the CS seem to have been switched around, both in the CS and in the electronic model. Please correct this.

The Company would like to thank the EAG for noting this error. These costs have been corrected in the latest version of the economic model (Table 98).

Section B: Uncertainty

B36. Priority question: The incremental cost-effectiveness ratios (ICERs) and incremental cost-utility ratios (ICURs) are calculated in the electronic version of the model ('Simulation' tab) as the average of the PSA simulated incremental costs and incremental QALYs for each comparison. Please correct the electronic version of the model so that probabilistic ICERs/ICURs are estimated based on the ratio of the mean incremental costs and of the mean incremental life years/QALYs for each comparison.

The Company would like to clarify that in the Simulation Tab (Cells UO8:VD8) ICERs and ICURs are calculated as the mean of the ratios between incremental costs and incremental LYs/QALYs across the PSA iterations and not as described by the EAG. The mean ICERs/ICURs appear not to be used anywhere else in the model, so no changes are required.

Please also see the replies to Questions B37 and B38.

B37. Priority question: The electronic version of the model currently estimates in the 'Simulation' tab mean incremental costs and mean incremental QALYs for each comparison as an average of the PSA simulated incremental costs and QALYs estimated for each total costs

and total QALY pair. Please correct the electronic version of the model so that mean incremental costs and mean incremental QALYs for each comparison are calculated as the difference of the mean total costs and mean total QALYs.

Cells in the Results Table have been added to estimate mean incremental costs and QALY as the difference of mean costs and mean QALYs. Please note that for the purpose of estimating incremental costs and QALY, taking the mean of the difference or the difference of the means from the PSA results in the same values. As we are dealing with linear operations, these quantities are insensitive to changing the sequence of the calculations performed.

B38. The probabilistic CE results in the model and presented in Table 66 of the CS incorrectly refer to median rather than mean values. Please correct Table 66 in the CS so that it reports mean incremental costs and mean incremental quality adjusted life-years (QALYs). If any other median probabilistic CE results are presented in the CS, please also update those to the corresponding mean values. Please ensure that the electronic version of the model is also reporting mean probabilistic CE results in the 'Results table' tab (in the "Discounted probabilistic results" table).

A switch has been added to the Results Table sheet to allow the EAG to select between median ICER/ICUR and ratio between mean incremental costs and QALYs/LYs from the sample generated in the PSA as formats to display the probabilistic results.

The base-case mean PSA ICERs produced from the updated model can be seen in Table 99 below.

Table 99: Probabilistic base-case cost-effectiveness results (glofitamab PAS price, comparator list price)

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)	NMB at 30k
Glofitamab vs BR						
Glofit	[redacted]	[redacted]				
BR	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Glofitamab vs pola-BR						
Glofit	[redacted]	[redacted]				

Pola-BR	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Glofitamab vs axi-cel						
Glofit	[redacted]	[redacted]				
Axi-cel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

**1.2 QALY modifier applied. ICER, incremental cost-effectiveness ratio; LYG, life years gained; NMB, net monetary benefit; QALYs, quality-adjusted life years.*

B39. Priority question: The company has applied in their (probabilistic) base-case CE analysis a sampling method for OS/PFS extrapolation parameters based on bootstrapping. This choice was not stated in the main body of the CS, nor justified, and the methodology used are not provided.

a. Please justify the preference for the bootstrap sampling method, over the usual covariance matrix method, with full details on the methodology used.

The standard way of running probabilistic sensitivity analyses relies on sampling random parameters for parametric functions from distributions around the mean parameter values using covariance-variance matrices to account for between-parameter correlations. However, this method is known to be associated with a few important limitations in general (e.g see reference (113) and references therein), and for area under the curve models in particular:

- It requires to assume that the underlying parameter distribution is multivariate normal.
- It neglects the correlation between OS and PFS, as both the estimation of the covariance matrices and the sampling of the random parameters from their respective distributions in the PSA are performed independently for these two endpoints.
    - In Area Under the Curve models, like the ones typically used in metastatic oncology indications, this may result in some PSA iterations featuring implausible crossings of PFS and OS survival curves, which in turn may have an impact on the estimate of the total QALY gains across treatments (specifically a reduction). As PFS/OS survival curves are the driver of the CEM results and QALYs are at the denominator of the ICER, this may in turn result in PSA iterations featuring extremely high ICER values, skewing the mean probabilistic ICER away from the deterministic ICER and overestimating the uncertainty in the model results.

On the other hand, estimating sets of sampled distribution parameters in a correlated way using non-parametric bootstrapping has some advantages compared to the standard method:

- It does not require to make any assumptions on the true structure of the correlations for the underlying parameter distributions, as the nature of the observed (and unobserved) correlations is already fully captured in the re-sampling from the patient data.
- It allows to take into account the correlations between PFS and OS in each bootstrapped set of estimated parameters, as these are estimated using the same patient data in each bootstrapping step for both endpoints. Furthermore, by sampling all the parameters of interest (e.g. for all PFS and OS distributions for a treatment and its comparator(s)) from the same bootstrapped set in each PSA iteration, these inherent correlations between PFS and OS parameters can also be fully taken into account in the probabilistic results.

The use of non-parametric bootstrapping in probabilistic sensitivity analyses in health economic evaluations is not new and its use is becoming increasingly popular in health economics. The Company followed the approach recommended in the available literature (114), though we only focused on the PFS/OS parametric extrapolations parameters and not on all parameters of potential interest for the PSA which could be estimated using patient data. This was to focus on what is normally the main driver of results in partitioned survival models, as boostrapping over all statistical analyses required for the CEM at the same time would have been unfeasible from a coding, computing and runtime perspective for such a complex decision problem. It is worth nothing that a similar approach was employed and accepted in previous TAs, e.g. TA567.

For an explanation of the specific methodology followed to estimate the bootstrapped samples of parameters included in the CEM for this submission, please refer to the reply to point B.

b. Please clarify how the bootstrapped parameter values in the 'Extrap_Param_Bootstrapping' tab within the electronic version of the model were obtained and justify why 1000 simulated values per parameter are a sufficient number of simulations to fully reflect existing parameter uncertainty.

In the non-parametric bootstrap approach, the distributions' parameters are repeatedly estimated based on different bootstrap samples of the original patient dataset, which are obtained by resampling the original dataset with replacement, such that the size of the bootstrap sample equals the size of the original dataset.

Briefly, this approach consisted of the following steps:

1. Generate a random bootstrap sample for each of the original datasets (weighted and unweighted treatment arms), by resampling these datasets with replacement, such that the sample size of the bootstrap sample equals that of the original datasets (100% resampling with replacement).
2. Fit all the parametric distributions of interest for PFS and OS to the population in the bootstrap sample and record the estimated parameter values.
3. Repeat (1) and (2) r times, where r equals the expected number of required PSA runs.

This was performed for 1000 bootstrap samples, which were generated in R v 4.0.3.

The Company would like to clarify that a smaller sample of 1000 boostrapped parameter values sets had to be eventually selected to keep the size of the original CEM excel file manageable, as several other comparisons that are not in scope for this submission were included. The CEM file has now been updated to include all the 3000 simulated parameter values, which should allow for a sufficient number of simulations to properly reflect existing parameter uncertainty.

c. Please provide a table with all parameter estimates (point estimates and 95% confidence intervals) of parametric survival functions used for PFS and OS when using the 'Bootstrap parameters' option and when using the 'covariance matrix' option.

Parameter estimates from the bootstrapping analysis can be seen in the simulation sheet of the economic model.

d. Please justify differences between the deterministic CE results and the probabilistic CE results using both sampling method options (bootstrap and covariance).

Briefly, the standard PSA approach based on the use of a covariance matrix neglects the correlation between OS and PFS, which are sampled independently and may thus result in extremely high ICER values in some PSA iterations, and in turn skew the mean probabilistic ICER away from the deterministic ICER. Conversely, sampling sets of shared parameters from the same bootstrapped sample using a common random seed for each PSA iteration ensures that the correlations between PFS and OS are preserved in the probabilistic results, which in turn should result in fewer iterations featuring extreme ICER values. Consequently, this can have an impact on both the PSA mean probabilistic ICER value (as the ICER is a non-linear function of QALYs and costs), which should then become closer to the deterministic ICER than with the standard approach, as well as on the uncertainty around it. A more detailed explanation of why this may happen in a partitioned survival model is given as part of the explanation of the difference between these two methods provided in the response to question B39a.

B40. The probabilistic CE results produced by the electronic version using the company's preferred assumptions and based on 1,000 simulations are substantially different from the results when 3,000 simulations are performed. Please comment on potential causes for the apparent lack of stability of the probabilistic sensitivity analysis (PSA) and whether it can fully reflect existing parameter uncertainty at 1,000 simulations. Please also update the electronic version of the model so that the PSA can be run at a high enough number of simulations to allow for results stability and update the probabilistic base-case CE results accordingly. Note that if the bootstrapping method to sample OS and PFS is preferred for the company's base-case, the number of bootstrapped values in the 'Extrap_Param_Bootstrapping' tab, may need to be increased too.

Please see response to Question B39.

Section C: Textual clarification and additional points

C1. There are two conflicting definitions of the efficacy evaluable population in the submission (B2.4.1 on Page 43 vs Table 10). Please either confirm which is correct, or provide a correct definition.

The Company would like to clarify that the efficacy-evaluable population from the NP30179 trial included all patients who had been assessed for response at any time during the study, regardless of their treatment status or time of withdrawal from the study. Patients who had been participating in the study long enough to have reached their first scheduled response assessment (occurring a minimum of 49 days since the first dose of glofitamab, or 56 days since the first dose of obinutuzumab pre-treatment, at the time of data cut-off) were also included in this population.

For the purpose of reimbursement for glofitamab monotherapy and in alignment with regulatory submission, the efficacy-evaluable population in the CS specifically comprised patients with R/R DLBCL who were enrolled in the D2 [Sub. 2]+D3+D5 cohorts.

C2. In Table 15 (CS Page 52), "Event-free at 12 months" and "Event-free at 18 months" both appear twice, with different results. Please provide a corrected version of this table.

The first mention of 'Event-free at 12 months' and 'Event-free at 18 months' relates to the DOCR endpoint (i.e. the proportion of patients estimated to be in CR at 12 and 18 months after achieving their CR); and the second mention of these parameters relates to the DOR endpoint (i.e. the proportion of patients estimated to be in

response [CR or PR] at 12 and 18 months after achieving their response). An updated table with clearer row labels has been included in Table 100 below.

Table 100: Overview of secondary efficacy endpoint data in R/R DLBCL patients treated with glofitamab 2.5/10/30 mg after ≥ 2 lines of systemic therapy (ITT population)

Secondary efficacy endpoints	Glofitamab 2.5/10/30mg Cohorts D2 [Sub. 2]+D3+D5 (N=155)	
	IRC	INV
CR rate[a] [95% CI]	[redacted]	[redacted]
ORR (CR+PR)[a] [95% CI]	[redacted]	[redacted]
Median DOCR[a] (months) [95% CI]	[redacted]	[redacted]
DOCR: event-free at 12 months [95% CI]	[redacted]	[redacted]
DOCR: event-free at 18 months [95% CI]	[redacted]	[redacted]
Median DOR[a] (months) [95% CI]	[redacted]	[redacted]
DOR: event-free at 12 months [95% CI]	[redacted]	[redacted]
DOR: event-free at 18 months [95% CI]	[redacted]	[redacted]
Median TFCR[a] (days) [95% CI]	[redacted]	[redacted]
Median TFOR[a] (days) [95% CI]	[redacted]	[redacted]
Median PFS (months) [95% CI]	[redacted]	[redacted]
1-year PFS rate [95% CI]	[redacted]	[redacted]
Median OS (months) [95% CI]	[redacted]	[redacted]
1-year OS rate [95% CI]	[redacted]	[redacted]

[a] Lugano classification (32).

CCOD, clinical cutoff date; CI, confidence interval; CR, complete response; DOCR, duration of complete response; DOR, duration of response; INV, Investigator; IRC, Independent Review Committee; NE, not evaluable; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; PR, partial response; TFCR, time to first complete response; TFOR, time to first overall response.

C3. There are cross-referencing errors in the submission (e.g. Pages 62, 63, 64). Please check the submission for these errors and provide a correct cross-reference in each case.

All the cross-references mentioned on pages 62–64 correctly refer to the Decision Problem Table (Document B, Section B.1.1, Table 1). When reviewing these pages, please use the content page to navigate to the table.

C4. Please provide the minutes of the Clinical Advisory Board conducted by Roche in January 2023 mentioned in sections B.1.1, B.1.3.2 (Reference 1 of the company submission).

Please see the attached supplementary documents for the glofitamab Clinical Advisory Board report.

C5. In the CS Appendix I, page 62, the company stated that "The methodology associated with SLR update 2 and 3 are detailed in the current report, and results from the original SLR and SLR update 1 are provided in separate files to accompany this submission". These separate files reporting on the original SLR and SLR update 1 have not been provided to the EAG. Could you please provide that information.

Please see response to Question B1.

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NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Glofitamab for treating relapsed or refractory diffuse large B-cell lymphoma after 2 or more systemic treatments [ID3970]

Patient Organisation Submission

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on conditions and their treatment that is not typically available from other sources.

To help you give your views, please use this questionnaire with our guide for patient submissions.

You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type. [Please note that declarations of interests relevant to this topic are compulsory].

Information on completing this submission

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 10 pages.

NICE National Institute for Health and Care Excellence

About you

1.Your name	[redacted]
2. Name of organisation	Lymphoma Action
3. Job title or position	[redacted]
4a. Brief description of the organisation (including who funds it). How many members does it have?	Lymphoma Action is a national charity, established in 1986, registered in England and Wales and in Scotland. We provide high quality information, advice and support to people affected by lymphoma – the 5th most common cancer in the UK. We also provide education, training and support to healthcare practitioners caring for lymphoma patients. In addition, we engage in policy and lobbying work at government level and within the National Health Service with the aim of improving the patient journey and experience of people affected by lymphoma. We are the only charity in the UK dedicated to lymphoma. Our mission is to make sure no one faces lymphoma alone. Lymphoma Action is not a membership organisation. We are funded from a variety of sources predominantly fundraising activity with some limited sponsorship and commercial activity. We have a policy for working with healthcare and pharmaceutical companies – those that provide products, drugs or services to patients on a commercial or profit-making basis. The total amount of financial support from healthcare companies will not exceed 20% of our total budgeted income for the financial year (this includes donations, gifts in kind, sponsorship etc) and a financial cap of £50,000 of support from individual healthcare companies per annum (excluding employee fundraising), unless approval to accept a higher amount is granted by the Board of Trustees. The policy and approach ensures that under no circumstances will these companies influence our strategic direction, activities or the content of the information we provide to people affected by lymphoma. https://lymphoma-action.org.uk/about-us-how-we-work-policies-and-terms-use/working-healthcare-and-pharmaceutical-companies

4b. Has the organisation received any funding from the company bringing the treatment to NICE for evaluation or any of the comparator treatment companies in the last 12 months? [Relevant companies are listed in the appraisal stakeholder list.] **If so, please state the name of the company, amount, and purpose of funding.**	Roche £26,000 BMS £11,000 Gilead £46,170 Pfizer £300
4c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	No
5. How did you gather information about the experiences of patients and carers to include in your submission?	We sent out a questionnaire to people affected by DLBCL and R/R DLBCL to gather their experiences of living with the condition, as well as their thoughts on current and potential treatments. We received 3 responses. We also used our existing knowledge from working with those with DLBCL.

Living with the condition

6. What is it like to live with the condition? What do carers experience when caring for someone with the condition?	<u>Living with DLBCL</u> DLBCL is an aggressive lymphoma. Most people with DLBCL first notice rapidly-enlarging lumps, often in the neck, armpit or groin but they can be in the chest or abdomen. Symptoms can vary depending on where the lymphoma is growing. Systemic symptoms are common, including fevers, night sweats, unexplained weight loss, fatigue, loss of appetite and severe itching. One patient described their symptoms - *"Before diagnosis I had obvious lymph node tumours in my neck, and a large tumour in my chest. I was having issues swallowing, eating and eventually breathing due to the pressure of the tumour."* Symptoms of DLBCL usually develop rapidly and progress quickly. Patients can be extremely unwell for many months. One patient told us*, "For me, progression was very fast and it was a traumatic experience for me and my family."* DLBCL is treated with the aim of cure. However, up to 45% of patients are refractory to treatment or relapse after initial treatment. The prognosis for patients with relapsed or refractory DLBCL is poor, with median survival of around a year. During treatment, patients often spend many weeks in hospital, isolated from family and friends. Side effects of intensive chemotherapy, such as sickness, diarrhoea, hair loss and neutropenia can be extremely debilitating, affecting many aspects of life. Most patients are unable to carry on working during treatment. One patient we spoke to was able to carry on working however it was every *"2 weeks out of every 3 (I had my treatment week off work). Keeping in touch with work did have a positive effect on me while I was having treatment."* It can take months or even years after treatment to recover. Some side effects, especially fatigue and peripheral neuropathy, can last for many years and have a significant impact on quality of life. Younger patients may experience fertility issues or early menopause. Patients report feeling "tired all the time" and a constant lack of energy making everything seem an effort. Younger patients may experience fertility issues or early menopause. Others have told us of repeated infections requiring hospital admission. One patient reported that they *"now have the side-effect of an underactive thyroid due to the radiotherapy."*

	Another patient said they found it *"psychologically very difficult to come to terms with the diagnosis and wondering how and why it happened when I thought I had a health lifestyle."* They also highlighted the severity of side effects that came with treatment for DLBCL. *"Physically, treatment was very challenging: I lost all my hair, had mouth ulcers and lost my sense of taste. I experienced a lot of fatigue, and I don't think I've fully recovered my energy since. I had peripheral neuropathy, during and after treatment. I'm still affected by it at times." "I felt anxious a lot of the time and suffered very badly from insomnia." "I'm still hypervigilant about any signs and symptoms that could be cancer, I live with the constant knowledge that my lymphoma could come back."* Financial impacts were also acknowledged, saying "as a small business owner, I worried a lot about not being able to work during treatment and not earning." DLBCL relapsing can be very challenging for people. One patient described the experience and the physical and emotional impact it had the second time round. *"I had been back at work for about 3 months when niggling symptoms prompted further tests. A relapse was confirmed and I started treatment two weeks later, R-IVE this time, which was to lead to BEAM and SCT. Second time round my anxiety was high during the early weeks; I struggled to sleep and felt very low. Once treatment started I was able to focus on it, and I felt more in control of my treatment; the research I had done earlier was really helpful. Time in hospital for chemo and the SCT meant I was away from work again, this time for about 10 months. Recovery from SCT was easier physically, because I had maintained my fitness up to SCT, but the fatigue remained for several years. Other symptoms included brain fog and memory problems, and ongoing bowel issues."* <u>Caring for someone with DLBCL</u> People with DLBCL can be very ill and require a huge amount of support. Caring for someone with DLBCL is emotionally challenging and time-consuming. Some carers take significant amounts of time off work to transport their loved one to-and-from hospital, care for dependants, collect medications and visit hospital. One patient described the impact of her diagnosis on her family. She said *"Although I coped well with diagnosis and treatment, I know it hit my family hard as this was the second diagnosis of DLBCL in the family. My husband was very strong for me, but I know that wasn't always the case. He used to run a lot of errands, which was him*

	basically seeking comfort from friends. He found it difficult to accompany me to treatment and often I was better on my own." Similarly, another patient we spoke to also described the difficult strain her diagnosis and relapse had on her family. *"My family were all very affected by the separation due to periods of treatment in hospital, and the anxiety and worry caused by the prospect of me not recovering. It was very hard for them to see me going through treatment and have to visit me in hospital. I had BEAM and SCT in December, so the family had to spend Christmas and New Year without me, which was hard on them. My husband had to support the children, care for the dog, house and keep working, as well as visit me and care for me when I was home. His employers were not very supportive and this meant he was often exhausted. He sought help from his GP and accessed some counselling support at that time."* We also spoke to a partner of someone diagnosed with DLBCL, who described being *"very scared about my partner's symptoms until we met the consultant, who reassured us both this was a very treatable cancer, with a likely good outcome." They also describe trying to "support my partner as much as possible emotionally, helping her manage her symptoms, and administering treatment (injections etc) where necessary."*

Current treatment of the condition in the NHS

7. What do patients or carers think of current treatments and care available on the NHS?	Most people with DLBCL are treated with chemo-immunotherapy, sometimes followed by radiotherapy. High-dose chemotherapy regimens might be used. For relapsed or refractory DLBCL, salvage chemotherapy followed by stem cell transplant is the most common treatment option. Treatment is very intense and some people are not able to tolerate it. More recently polatuzumab vedotin with R-CHP or CAR T-cell therapy have been made available options for relapsed or refractory patients on the NHS. Even when a treatment is successful, most people with DLBCL have quite serious and often debilitating side effects. One patient described her experiences of treatment. "The first time I received Rituximab I experienced an allergic reaction (throat swelling and rash). However, after a second attempt with a much lower dose over a long period of time, I was able to tolerate future treatment. Overall, I tolerated the RCHOP regime very well, but I did experience very bad mouth ulcers, tiredness and some nausea. I also had collapsed veins which meant I had a PICC line for the last 2 cycles, which I hated. I suffered from Steroid crashes, when the dose of prednisolone was dramatically reduced between treatments. I also had to give myself injections which I got used to eventually. The anti-sickness meds gave me bad constipation as well, which was very uncomfortable." She went on to acknowledge that whilst R CHOP was successful in this instance, she does not know what treatment options would've been without. *"I have been told that if I relapse, I will need stem-cell treatment. However, maybe Glofitamab may now be an option."* Another patient described her second treatment being difficult, although shorter than her initial 10 weeks of chemotherapy. She said she had a *"3 week-long hospital stays to receive R-IVE, followed by the stem cell harvesting, and then BEAM to get me ready for the SCT. I wasn't really aware of the R-IVE, I think the anti-seizure medication that went with it knocked me out for much of each week. BEAM was harder as it went on, and the week or so between BEAM and my counts rising after SCT was difficult – I wasn't really able to do anything, needed a hand with showering, felt very unwell and was too tired to do anything but listen to the radio."*

8. Is there an unmet need for patients with this condition?	Patients feel there is an unmet need for more effective treatments for relapsed or refractory DLBCL, with a greater prospect of a durable response. Patients also express the need for less demanding treatments with fewer side effects. One patient noted the lack of treatment options for somebody in her position. She said *"At the time of treatment, I was unaware of any alternative treatments (other than the fact my family member had been on a drug trial."* Another patient said *"R-CHOP doesn't work for everyone and DLBCL can recur, so it's important to have a range of second- and third-line treatment options that are effective, widely available and well tolerated."*

Advantages of the technology

9. What do patients or carers think are the advantages of the technology?	Having a single drug treatment was desirable to some patients and the reduced side effects. *"RCHOP is basically a long day of treatment with several drugs (plus a lot of medication to take afterwards). I was often the first and last person in the Chemo suite as RCHOP takes such a long time to receive via IV."* Another patient said, *"The knowledge that new treatment options are being developed is very reassuring."* She also noted that *"It's a treatment option that's likely to be more widely available than CAR-T therapy, so it could help to reduce health inequalities in cancer."*

Disadvantages of the technology

10. What do patients or carers think are the disadvantages of the technology?	The length and number of cycles of the treatment may not be ideal for some patients, with one patient said *"12 months is a long treatment course."* Another patient noted that *"there still may be the possibility of an allergic reaction for some people."*

Patient population

11. Are there any groups of patients who might benefit more or less from the technology than others? If so, please describe them and explain why.	One patient acknowledged that younger people might benefit more from this technology as they *"might prefer a single drug treatment."*

Equality

12. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	

Other issues

13. Are there any other issues that you would like the committee to consider?	

Key messages

14. In up to 5 bullet points, please summarise the key messages of your submission.	• Relapsed or refractory DLBCL has a significant impact on the quality of life of both patients and their families and carers. The psychological, social and economic impact of the disease is considerable. • Many people with DLBCL have limited treatment options and additional options that offer a potential lifeline are desired. • With limited CAR T-cell therapy centres in the UK, this treatment could benefit those unable to travel further.

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Single Technology Appraisal

Glofitamab for treating relapsed or refractory diffuse large B-cell lymphoma after 2 or more systemic treatments [ID3970]

Professional organisation submission

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature.

To help you give your views, please use this questionnaire. You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

Information on completing this submission

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 13 pages.

About you

1. Your name	[redacted]
2. Name of organisation	NCRI-ACP-RCP-RCR
3. Job title or position	[redacted]
4. Are you (please select Yes or No):	An employee or representative of a healthcare professional organisation that represents clinicians.
5a. Brief description of the organisation (including who funds it).	NCRI-ACP-RCP-RCR
5b. Has the organisation received any funding from the manufacturer(s) of the technology and/or comparator products in the last 12 months? [Relevant manufacturers are listed in the appraisal matrix.] **If so, please state the name of manufacturer, amount, and purpose of funding.**	No
5c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	No

The aim of treatment for this condition

6. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability.)	The main aim of treatment with Glofitamab in relapsed or refractory diffuse large B cell lymphoma (DLBCL) after 2 or more lines of prior therapy is to achieve complete remission (CR) and prolong progression-free-survival (PFS) compared to existing therapies. Data from the NP30179 trial that informs this submission indicate that, for many patients who achieve CR, remission will be durable with ongoing CR at 12 months in 78% of patients who achieve CR and for these patients it is anticipated that overall survival (OS) will be prolonged compared to other available therapies. The available data are too immature to know whether patients who achieve a durable remission will be cured of this condition.
7. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount.)	In relapsed DLBCL after 2 or more lines of prior therapy, achieving CR as assessed by FDG-PET scan and reported according to the internationally adopted Lugano criteria is a highly clinically significant treatment response with a significant majority of patients still in remission at 12 months. Although there are no Quality of life data (QoL) yet, the fact that many patients will remain in remission, off treatment and with a reasonable side effect profile indicates that the QoL for patients in remission will be very good. Available evidence indicates that partial remission (PR) is of more limited clinically significant value as conversion of PR to CR is rare and the durability of remissions in pts with a PR is shorter than in patients who achieve CR.

8. In your view, is there an unmet need for patients and healthcare professionals in this condition?	Yes there is an unmet need in RR DLBCL after 2 or more prior lines of systemic treatment. Historical data indicate that the CR rate, PFS, and OS are poor in patients with relapsed or refractory DLBCL after 2 or more prior lines of therapy. For example, data from the SCHOLAR-1 project indicate CR rate of 7% with median OS of only 6 months (Crump et al Blood 2017). Recently published retrospective data from international sites including UK real-world data from 4 academic centres indicates a CR rate of 20.7% for 3rd line treatment of DLBCL with median OS 8 months, and median PFS 2.5 months for non-cellular therapy treatments (van Lee Leukemia and Lymphoma 2022). Although the pivotal trial that informs this submission (NP30179) did not have a control arm, a meta-analysis of 19 previously published studies (including CAR-T) and included in the manuscript also indicates a CR rate of 20% in this population with standard treatment options. This figure was used to power this single-arm trial (Dickinson et al NEJM 2022). CAR-T cell therapy (Axicel and Tisagen) has led to improved outcomes in patients with RR DLBCL after 2 or more prior lines of therapy as demonstrated in single-arm ph2 trials and broadly recapitulated in real-world data series, but this treatment is not possible for all patients due to a range of reasons including: a) rapid pace of disease progression precluding CAR-T (up to 20% of those who undergo apheresis and are intended for CAR-T progress and are unable to proceed with cellular therapy) b) comorbidities that preclude CAR-T c) patient choice including but not limited to geographical / transport reasons as CAR-T is only available in limited centres. Furthermore, up to 60% of patients have suboptimal response or progress post CAR-T and better treatment options are needed for these patients who have very poor OS (12-month OS for patients with PD on scan 1-month post PET 38% in the UK real-world CAR-T dataset) highlighting the need for better therapies in this setting (Ref Kuhnl Blood advances 2021).

What is the expected place of the technology in current practice?

9. How is the condition currently treated in the NHS?	There is no standard of care for the management of relapsed DLBCL in the 3rd line+ setting in the NHS. For patients who are eligible and suitable for CAR-T cell therapy, this is often considered but per the notes above, this is not possible for all patients, we do not have accurate data to indicate what proportion of patients with RR DLCBL are not considered suitable for CAR-T. For patients with relapsed or refractory DLBCL not suitable for CAR-T cell therapy, clinical trials of novel agents are often explored, R-benda-polatuzumab may be used if it was not used in 2nd line. Other options include other non-cross-reacting chemotherapy regimens eg R-Gem-Ox if it was not used in 2nd line but outcomes with this approach are poor, CR is rarely achieved, and remissions are typically not durable (median DoR in 3rd line in real-world data set 7.6 months ref van LEE 2022). Sometimes palliative chemotherapy regimens such as DECC are used with palliative intent. Compassionate access to other agents may be attempted in some patients. For some patients it is most appropriate to pursue palliative care in this setting. Pixantrone is rarely used in the UK. For patients who relapse post CAR-T cell therapy, outcomes are poor and the options for treatment in the NHS are palliation, clinical trials of novel agents, and sometimes radiotherapy for localised relapse.
9a. Are any clinical guidelines used in the treatment of the condition, and if so, which?	The UK BCSH guidelines for the management of DLBCL were published in 2016 and are therefore outdated. The British Society of Haematology is planning an updated version of these guidelines in 2023. There are no other national guidelines for the management of relapsed DLBCL. Local regional guidelines may be followed.
9b. Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience	As above there is no standard of care. Treatment options in the management of DLBCL in the 3rd line plus setting depend on: a) Prior lines of therapy received (eg whether or not received RBPola 2nd line, whether CAR-T previously given or not) b) Fitness c) Patient choice

is from outside England.)	d) Availability of clinical trials / compassionate access schemes for novel approaches e) Local practice with some variability between centres.
9c. What impact would the technology have on the current pathway of care?	Glofitamab would be used in 3 main positions in the DLBCL patient pathway: 1) In patients who have relapsed after or are refractory to 2nd line therapy (eg after R-CHOP/Pola-R-CHOP and either R-Benda-Pola or R-Gem-Ox) as an alternative choice to CAR-T cell therapy 2) In patients who have relapsed after or are refractory to 2nd line therapy who are not suitable/eligible for CAR-T cell therapy as 3rd line+ treatment due to frailty / pace of disease / comorbidities 3) In patients who have relapsed post CAR-T (i.e. 4th line at present although this could move to 3rd line if CAR-T is approved for 2nd line treatment.)
10. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	No. It may sometimes be used instead of CAR-T It may be used in place of palliative options in patients not currently suitable/eligible for CAR-T or for patients who have relapsed post CAR-T
10a. How does healthcare resource use differ between the technology and current care?	This depends on what it is being compared against. Compared to standard of care options that are typically delivered with palliative intent there will be increased resource: in-patient admission to hospital for administration and observation for 24-48 hours is required in cycle 1 (and cycle 2 if high risk of further cytokine release syndrome (CRS)), there is a risk of CRS which may require treatment with tocilizumab in about 1/3 of patients. Treatment will continue for up to 12 cycles for many patients compared to shorter duration with palliative-intent regimens. If being used in place of CAR-T cell therapy, resource utilisation will be significantly lower with glofitamab than with CAR-T. There is no need for NCCP panel review, apheresis, cell manufacturing, bridging treatment, long in-patient stay, and complex follow up arrangements with glofitamab.
10b. In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	Haematology units within hospitals. Due to the risk of cytokine release syndrome (CRS), use may be restricted to centres that are familiar with the identification and management of CRS but with appropriate training, all hospitals with haematology units that are capable and able to deliver high intensity chemotherapy may be able to administer glofitamab.

10c. What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	Training in identification and management of CRS Availability of Tocilizumab for management of CRS Single dose of obinutuzumab pre-treatment in all pts. In-patient admission for 1st dose. Training will need to be given to nursing and medical teams on the dosing / administration structure. IV giving sets are the same as would be used for other systemic therapies.
11. Do you expect the technology to provide clinically meaningful benefits compared with current care?	As detailed above, the data that informs us of the utility of glofitamab is derived from the NP30179 trial which was a single arm trial there are therefore no comparative data against other therapeutic strategies available for comparison. There are no comparative data of CAR-T vs glofitamab. Whilst cross trial comparisons are difficult, it is clear that glofitamab has a high chance of delivering clinically meaningful benefit in a cohort of patients with very high risk DLBCL compared to current care. The CR rate of 39% compares favourably with recently published real-world data confirming that the CR rate in 3rd line treatment of DLBCL is historically about 20% (ref van Lee 2022). The RBPolatuzumab combination gave an ORR 45% and CR 40% in the pivotal trial which is similar to the data on glofitamab but it is clear that the population being treated in NP30179 is higher risk than in the RBP trial data (Ref Sehn JCO 2020). A real-world UK dataset showed CR rate was similar to the published data but durability of remissions was much shorter (Ref Northend and Townsend Blood Advances 2022). Glofitamab will provide clinically meaningful benefits compared to all available therapies.
11a. Do you expect the technology to increase length of life more than current care?	As above - there are no comparative data. However, with more than 12 months median follow up, the median OS is 12 months. This compares favourably with historical control data.
11b. Do you expect the technology to increase health-related quality of life more than current care?	Our experts are not familiar with any publicly available published data relating to the QoL of patients receiving glofitamab yet but this is an important consideration. It may be considered that a treatment with a 40% chance of attaining CR which is durable beyond 1 year in a high proportion of patients with 3-weekly out-patient dosing (beyond cycle 1) and a manageable side-effect profile (again, beyond cycle 1) would have a good chance of improving QoL for patients with RR DLBCL compared to current treatment strategies. Further research into this area would be welcomed.

12. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	The pre-specified subgroup analyses in the published trial data indicate that the effect of glofitamab is broadly consistent across a wide range of variables including age and gender. Whilst this treatment is effective across a range of poor risk variables there appears to be most benefit in those who were not refractory to the last line of therapy. There is probably insufficient evidence to determine the efficacy in certain different histological sub-types of DLBCL including HGBCL, double hit lymphoma, and PMBCL. There is an indication that efficacy is similar whether it is used in patients who are naïve to CAR-T cell therapy or if they have relapsed after CAR-T cell therapy. This is an important finding.

The use of the technology

13. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use (for example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed.)	**See answers to 10a and 10c above.** **Concomitant treatments:** Obinutuzmab: a single dose of 1g iv Obinutuzumab pre-treatment will be required for all patients 7d prior to initial dosing of glofitamab. Most treating centres will be familiar with the administration of Obinutuzumab. Tocilizumab: Tocilizumab will need to be available before treating patients. It will be used in the event of ≥G2 CRS. Available data indicate it will be needed in Dexamethasone: Dexamethasone will be administered to all patients as a pre-medication. Anti-infection prophylaxis: in keeping with other B-cell depleting therapies antimicrobial prophylaxis against PCP and HSV may be required per institutional guidelines. **Practical implications:** Only to be used in centres either familiar in or trained in the identification and management of CRS ICU resource needs to be available Monitoring for CRS after first infusion In-patient admission after first infusion
14. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	No

15. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation?	Difficult to know over and above prolonged remission in a high proportion of patients in a cohort of very high-risk patients with limited other options and short life expectancy
16. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met?	Yes this is innovative, it is the first in class CD3-20 bispecific antibody for the treatment of RR DLBCL. By delivering treatment that is well tolerated with lower risk of severe toxicities than CAR-T cell therapy but with a high level of efficacy I think this will have the potential to make a substantial impacy on health-related benefits.
16a. Is the technology a 'step-change' in the management of the condition?	Yes – see above – it is the first in a class of drugs called CD3-20 bispecific antibodies in the treatment of B-NHL.
16b. Does the use of the technology address any particular unmet need of the patient population?	Yes – it is very hard to get patients with RR DLBCL after 2 or more lines to remission – this treatment therefore meets the unmet need of getting about 40% of patients to CR.
17. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	As mentioned above, the principle toxicity is Cytokine release Syndrome (CRS). CRS is manageable and predictable following the measures that were introduced during the NP30179 trial (dex pre-med, obinutuzumab pre-treatment, step up dosing). G3 CRS is rare and G2 CRS is mainly restricted to the first cycle of treatment. Neurotoxicity is lower than with CAR-T cell therapy. There is a risk of infections

	with all b-cell depleting therapies and this will need to be watched and managed closely. Our experts anticipate that QoL will be superior with this treatment than with other available therapies.

Sources of evidence

18. Do the clinical trials on the technology reflect current UK clinical practice?	The NP301079 trial was not conducted in the UK. Our experts believe that the patient population broadly reflects the UK population with a high proportion of patients displaying high risk disease features eg refractoriness.
18a. If not, how could the results be extrapolated to the UK setting?	As above our experts believe the results are applicable to a UK population of patients with RR DLBCL after 2 or more lines of treatment.
18b. What, in your view, are the most important outcomes, and were they measured in the trials?	CR rate is a valid endpoint and it is supported in this trial with DoCR, PFS and OS data As detailed the only trial (NP30179) had CR rate as the primary end point.
18c. If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	Yes – as evidenced by the prolonged Duration of CR, achieving CR is a very important endpoint in this disease.
18d. Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	No: the principle toxicity is Cytokine release Syndrome (CRS). More mature data with longer follow up (and real world data) will be needed to fully assess the risks of infections in this population of heavily pre-treated patients who receive this b-cell depleting therapy.

19. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	Our experts are not aware of any other data on the use of glofitamab monotherapy in the trial setting or real-world datasets. There are emerging trial data on glofitamab in combination with other agents, but this is not relevant to this application.
20. Are you aware of any new evidence for the comparator treatment(s) since the publication of relevant NICE technology appraisal guidance?	no
21. How do data on real-world experience compare with the trial data?	There are no real-world data on the use of glofitamab as it has only been available internationally via clinical trials up to now. Compassionate access schemes are now available in the UK and elsewhere and the NRCN high grade NHL sub group have planned to collate UK real-world data.

Equality

22a. Are there any potential equality issues that should be taken into account when considering this treatment?	None that I am aware of.
22b. Consider whether these issues are different from issues with current care and why.	NA

Key messages

23. In up to 5 bullet points, please summarise the key messages of your submission.	• Glofitamab is a first-in-class bispecific antibody with a unique mechanism of action • The CR rate of 40% is unprecedented as a monotherapy in 3rd line + DLBCL and represents a major advance in the treatment of relapsed DLBCL • For most patients achieving CR, this is a durable remission • The safety profile is manageable and compared to Axicel the CRS and ICANS risks are much lower and, beyond cycle 1, events are very rare

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External Assessment Group Report

Glofitamab for treating relapsed or refractory diffuse large B-cell lymphoma after 2 or more systemic treatments

Produced by	CRD and CHE Technology Assessment Group, University of York, Heslington, York, YO10 5DD
Authors	Pedro Saramago Goncalves, Senior Research Fellow, CHE, University of York Mark Rodgers, Research Fellow, CRD, University of York Shainur Premji, Research Fellow, CHE, University of York Eleonora Uphoff, Research Fellow, CRD, University of York Minyue Gao, Research Fellow, CHE, University of York Helen Fulbright, Information Specialist, CRD, University of York Ana Duarte, Research Fellow, CHE, University of York Mark Simmonds, Senior Research Fellow, CRD, University of York
Correspondence to	Mark Simmonds, Centre for Reviews and Dissemination, University of York, YO10 5DD
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Rider on responsibility for report

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Contributions of authors

P Saramago Goncalves, critiqued and performed the economic analyses, provided advice, wrote and commented on drafts of the report, led the overall economic sections taking joint responsibility for these.

M Rodgers contributed to sections 2 and 3 of the report.

S Premji critiqued and wrote sections 4.1, 4.2.2, 4.27 and 5 of the report. She also validated the model and performed the economic analyses.

E Uphoff contributed to sections 2 and 3 of the report.

M Gao critiqued and contributed to section 4.2.6.9, 4.2.8.9, and 4.9 of report. She also performed the economic analyses.

H Fulbright provided information expertise and reviewed the company systematic reviews.

A Duarte contributed to Sections 4, 5 and 6 of the report, and took overall responsibility for the economic sections of the report.

M Simmonds contributed to sections 2 and 3 of the report, and took overall responsibility for the clinical sections of the report.

Note on the text

All commercial-in-confidence (CIC) data have been [redacted], all academic-in-confidence (AIC) data are [redacted], all depersonalised data (DPD) are highlighted in pink and underlined.

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List of abbreviations

Admin	Administration
AE	adverse event
AIC	Akaike information criterion
ASCO	American Society of Clinical Oncology
ASCT	Autologous stem cell transplant
ASH	American Society of Hematology
ATE	Average treatment effect
Axi-cel	Axicabtagene ciloleucel
BC	Base case
BCa	Bias corrected accelerated
BIC	Bayesian Information Criterion
BNF	British National Formulary
BR	Bendamustine and rituximab
BSA	Body surface area
CADTH	Canadian Agency for Drugs and Technologies in Health
CAR-T	Chimeric antigen receptor T-cell
CCOD	Clinical cut-off dates
CDF	Cancer Drugs Fund
CE	Cost-effectiveness
CEA	Cost-Effectiveness Analysis Registry
CENTRAL	Cochrane Central Register of Controlled Trials
Chemo	Chemotherapy
CHMP	Committee for Medicinal Products of Human Use
CI	Confidence interval
CR	Complete response
CRS	Cytokine release syndrome
CS	Company submission
CSR	Clinical Study Report
CVD	Cardiovascular disease
Cyc	Cyclophosphamide
D	Day
DARE	Database of Abstracts of Reviews of Effects
DHAP	Cisplatin, cytarabine, dexamethasone
DLBCL	Diffuse large B-cell lymphoma
DOCR	Duration of complete response
DOR	Duration of response
EAG	Evidence Assessment Group
EAMS	Early Access to Medicines Scheme
EBM	Evidence Based Medicine
ECOG PS	Eastern Cooperative Oncology Group Performance Status
EHA	European Hematology Association
EMA	European Medicines Agency
eMIT	Drugs and pharmaceutical electronic market information tool
EORTC QLQ-C30	European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30
ESMO	European Society for Medical Oncology
ESS	Effective sample size
FACT-Lym	Functional Assessment of Cancer Therapy – Lymphoma
FAD	Final Appraisal Document

FL	Follicular lymphoma
GDP	Cisplatin, gemcitabine, dexamethasone
Gem	Gemcitabine
Gen	Generalised
Glofit	Glofitamab
HGBCL	High-grade B-cell lymphoma
HR	Hazard ratio
HRG	Healthcare Resource Group
HRQoL	Health-related quality of life
HTA	Health Technology Assessment
ICANS	Immune effector cell-associated neurotoxicity syndrome
ICE	Ifosfamide, carboplatin, etoposide
ICER	Incremental cost-effectiveness ratio
ICML	International Conference on Malignant Lymphoma
ICU	Intensive Care Unit
INAHTA	International Network for Agencies for Health Technology Assessment
Inc	Incremental
IPD	Individual Participant Data
IPI	International Prognostic Index
IPTW	Inverse probability treatment weighting
IRC	Independent Review Committee
ITC	Indirect treatment comparison
ITT	Intention To Treat
IVE	Ifosfamide, epirubicin and etoposide
IVIG	Intravenous immunoglobulin
KM	Kaplan-Meier
LDH	Lactate dehydrogenase
LYG	Life years gained
LTR/S	Long-term remission/ survivorship
MAIC	Matched-adjusted indirect comparison
MCM	Mixture cure model
MHRA	Medicines and Healthcare products Regulatory Agency
NE	Northeast quadrant of the cost-effectiveness plane
NES	Non-elective short stay
NHL	Non-Hodgkin lymphoma
NHS EED	NHS Economic Evaluation Database
NICE	National Institute for Health and Care Excellence
NIHR	National Institute for Health Research
NMB	Net monetary benefit
ORR	Overall response rate
OS	Overall survival
Ox	Oxaliplatin
PAS	Patient Access Scheme
PBAC	Pharmaceutical Benefits Advisory Committee
PD	Progressed disease status
PF	Progression-free status
PfC	Points for Clarification
PFS	Progression free survival
PH	Proportional hazards
PMBCL	Primary mediastinal large B cell lymphoma
Pola-BR	Polatuzumab vedotin with bendamustine and rituximab

Pola-R-CHP	Polatuzumab vedotin in combination with rituximab, cyclophosphamide, doxorubicin, and prednisone
Post-disc therapy	Post-discontinuation therapy
PPS	Post-progression survival
PR	Partial response
Pred	Prednisolone
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PSA	Probabilistic sensitivity analysis
PSS	Personal Social Services
PRSSRU	Personal Social Services Research Unit
QALY	Quality-adjusted life year
Quadr	Quadrant of the cost-effectiveness plane
R	Rituximab
R/R	Relapsed or refractory
R-CHOP	Rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone
R-Gem-Ox	Rituximab combined with gemcitabine and oxaliplatin
SA	Scenario analysis
SCT	Stem cell transplant
SD	Stable disease
SE	Southeast quadrant of the cost-effectiveness plane
SLR	Systematic literature review
SMC	Scottish Medicine Consortium
SmPC	Summary of Product Characteristics
SMR	Standardised mortality ratio
SW	Southwest quadrant of the cost-effectiveness plane
TA	Technology appraisal
Tafa-len	Tafasitamab plus lenalidomide
TrFL	Transformed follicular lymphoma
TTOT	Time to off treatment
Tx	Treatment
Vin	Vincristine

1 EXECUTIVE SUMMARY

This summary provides a brief overview of the key issues identified by the external assessment group (EAG) as being potentially important for decision making. It also includes the EAG's preferred assumptions and the resulting incremental cost-effectiveness ratios (ICERs).

Section 1.1 provides an overview of the key issues. Section 1.2 provides an overview of key model outcomes and the modelling assumptions that have the greatest effect on the ICER. Sections 1.3 to 1.6 explain the key issues in more detail. Background information on the condition, technology and evidence and information on non-key issues are in the main EAG report.

All issues identified represent the EAG's view, not the opinion of NICE.

Overview of the EAG's key issues

	Summary of issue	Report sections
1 **Position of comparator treatments in care pathway**	Glofitamab was compared to CAR-T therapy (axi-cel) and polatuzumab (pola-BR) in third line therapy; both treatments are likely to be increasingly used in earlier lines of therapy. Consideration should be given to what are suitable comparators for glofitamab if it is used after CAR-T and/or polatuzumab	2.3
2 **Patients who do not receive axi-cel infusion**	The ITC of glofitamab with axi-cel could only include patients who did receive an axi-cel infusion, but may patients will not receive the infusion, so the comparison is not completely fair. Consideration should be given to the outcomes and costs in patients who are considered for, but do not receive CAR-T therapy, and the potential impact of treating such patients with glofitamab	3.4.2.2
3 **Confidence intervals of ITC analyses**	Unadjusted ITCs and adjusted MAICS used different and incomparable confidence intervals (standard forms for unadjusted analyses; bootstrap for MAICs). This prevents comparison of the different ITCs and makes the impact and robustness of the adjustments in the of the MAICs less clear. Standard (non-bootstrap) confidence intervals should be provided for all ITC analyses.	3.4.1
4 **Long-term remission/survivorship**	Consideration should be given to the clinical plausibility of long-term remission/ survivorship, i.e. cure, for all treatments under comparison and to the validity of a no cure assumption. The timing of cure is uncertain as there is no accepted clinical definition for it. Furthermore, if cure is assumed, there is uncertainty around which utility decrement and which excess mortality estimate should be used from the cure point.	0
5 **Average cohort age**	In the economic model, an age distribution approach was preferred by the company as it better reflected heterogeneity in the background mortality of the cohort and the associated background risks of death by age. However, this is a partial implementation of the distributional approach to age, as the age distribution is only reflected on all-cause mortality. A full implementation of the company's preferred approach would have to reflect the age distribution on cancer-related survival and on age-adjusted HRQoL.	4.2.7
6 **Treatment discontinuation**	The company's choice of GO29365 study data to model BR individual treatment discontinuation created inconsistencies across the economic model for this comparator as the estimation of the AE rates of occurrence, which then links up with AE cost were obtained from a different source (Hong et al (2018)). Thus, while BR treatment discontinuation, derived from the study GO29365, impact drug and administration costs, BR effectiveness and AE occurrences are built around the Hong et al (2018) study.	0
7 **Immune effector cell-associated neurotoxicity syndrome (ICANS)**	The cost of monitoring ICANS was not considered by the company, and it is uncertain whether this would increase the level of resource use required to monitor patients treated with glofitamab	0

The key differences between the company's preferred assumptions and the EAG's preferred assumptions are: (i) background mortality using an average cohort age (time horizon reduced from 60 to 37 years); (ii) administration of obinutuzumab delivered as a complex and prolonged treatment at first attendance; (iii) axi-cel administration cost corresponding to £50,550.50 (average between £41,101.00 and £60,000.00); (iv) CAR-T re-treatment not possible as a subsequent therapy; and (v)

long-term remission/survivorship at 3 years for PFS and OS, assuming a SMR of 1.41 (on the age-matched UK general population mortality) and a utility decrement of 10% (on the age-sex UK general population utility) from that time point onwards.

The EAG's preferred assumptions are more consistent with previous NICE TAs for the treatment of R/R DLBCL. Where the company has not presented compelling evidence to support their assumptions, the EAG's preferred base case explores alternatives to those assumptions given the level of evidence available and as informed by clinical advice to the EAG.

1.1 Overview of key model outcomes

NICE technology appraisals compare how much a new technology improves length (overall survival) and quality of life in a quality-adjusted life year (QALY). An ICER is the ratio of the extra cost for every QALY gained.

Overall, the technology is modelled to affect QALYs by:

- Increasing the progression-free and reducing or maintaining the post-progression health state occupancy for the comparisons with BR and Pola-BR.
- The assumptions around long-term remission/survivorship, which increases total QALYs for the treatments that have highest proportion of individuals in pre-progressed disease at the point of cure (i.e., glofitamab when compared to pola-BR and BR, and axi-cel compared to glofitamab).
- PFS and OS extrapolations, particularly when no long-term remission/survivorship is assumed.

Overall, the technology is modelled to affect costs by:

- Its higher treatment costs compared to BR, but lower against Pola-BR and Axi-cel.
- Increasing the supportive care costs for all comparisons.
- Reducing the costs of subsequent therapies delivered post-progression for the BR and Pola-BR comparisons, but increasing against axi-cel.
- The assumptions around long-term remission/survivorship.

The modelling assumptions that have the greatest effect on the ICER are:

- Alternative assumptions to when long-term remission/survivorship occurs and what utility decrement and excess mortality values are assumed from that point onwards.
- Assuming no CAR-T re-treatment at post-progression for individuals initially treated with axi-cel.

- The assumption of no long-term remission/survivorship.

1.2 The decision problem: summary of the EAG's key issues

Issue 1: Position of comparator treatments in care pathway

Report section	2.3
Description of issue and why the EAG has identified it as important	Glofitamab was compared to CAR-T therapy (axi-cel) and polatuzumab (pola BR) in third line therapy. The EAG agree these are reasonable current comparators. However, the CS and clinical advice both suggest that these treatments are likely to be increasingly used in earlier lines of therapy. This makes the choice of comparators uncertain, as it is unclear both whether pola-BR or CAR-T will be used in third line therapy, and how effective pola-BR would be if polatuzumab had been used in previous lines.
What alternative approach has the EAG suggested?	The EAG considers that there are no data available at present to permit any alternative approach. However, consideration should be given to what are suitable comparators for glofitamab if it is used after CAR-T and/or polatuzumab
What is the expected effect on the cost-effectiveness estimates?	Unknown, as cost-effectiveness evidence did not explicitly model the use of either pola-BR or CAR-T at previous lines of therapy.
What additional evidence or analyses might help to resolve this key issue?	Additional data on efficacy of glofitamab when used after polatuzumab may be helpful.

1.3 The clinical effectiveness evidence: summary of the EAG's key issues

Issue 2: Patients who do not receive axi-cel infusion

Report section	**3.4.2.2**
Description of issue and why the EAG has identified it as important	The ITC of glofitamab with axi-cel could only include patients who did receive an axi-cel infusion, but may patients will not receive the infusion, so the comparison is not completely fair. A fairer comparison would include patients who were assigned to axi-cel, but ultimately did not receive the infusion.
What alternative approach has the EAG suggested?	Consideration should be given to the outcomes and costs in patients who are considered for, but do not receive CAR-T therapy, and the potential impact of treating such patients with glofitamab.
What is the expected effect on the cost-effectiveness estimates?	The impact of this on the estimates of cost-effectiveness is largely unknown. The costs associated with axi-cel are likely to increase, as explored in one of the company's scenario. However, the impact on effectiveness remains unknown. While the overall effectiveness of axi-cel may be lower if the full ITT population of ZUMA-1 is used to inform it, the relative effectiveness against a glofitamab adjusted population is still very uncertain given the latter's low effective sample size (27.9).
What additional evidence or analyses might help to resolve this key issue?	Data from the ZUMA-1 trial, or other axi-cel trials, on outcomes of patients who did not receive infusion would be required. These could then be compared to glofitamab using MAICs.

Issue 3: Confidence intervals of ITC analyses

Report section	**3.4.1**
Description of issue and why the EAG has identified it as important	Unadjusted ITCs and adjusted MAICs used different and incomparable methods for calculating confidence intervals; namely, standard regression methods for unadjusted analyses; bootstrap methods for MAICs. This prevents comparison of the different ITCs and makes the impact and robustness of the adjustments in the of the MAICs less clear.
What alternative approach has the EAG suggested?	The EAG recommends that unadjusted and MAIC (or propensity score) analyses should use the same methodology to estimate confidence intervals, to ensure comparability, and to allow the EAG to assess the impact on uncertainty from performing adjusted analyses.
What is the expected effect on the cost-effectiveness estimates?	The use of standard (non-bootstrap) confidence intervals may change the probabilistic cost-effectiveness estimates, but the impact in itself is unknown.
What additional evidence or analyses might help to resolve this key issue?	Standard (non-bootstrap) confidence intervals should be provided for all ITC analyses.

1.4 The cost-effectiveness evidence: summary of the EAG's key issues

Issue 4: Long-term remission/survivorship

Report section	**0**
Description of issue and why the EAG has identified it as important	The assumption of long-term remission/survivorship or cure for all comparisons may not be appropriate, as existing evidence is insufficient to support it.
What alternative approach has the EAG suggested?	The EAG considers that under current levels of evidence and to be consistent with recent NICE appraisals (particularly, TA649), the following definition of cure is applied in the base-case analysis: long-term remission/survivorship at 3 years with a 10% decrement from the age-sex UK general population utilities and an excess mortality from the age-matched UK general population mortality based on a SMR of 1.41. Given the long follow-up required to demonstrate cure, scenario analysis assuming no long-term remission/ survivorship should also be considered by the committee.
What is the expected effect on the cost-effectiveness estimates?	The expected effect of cost-effectiveness estimates for when not assuming long-term remission/survivorship and under the assumptions of the base-case and scenario analyses described above, is a sizeable impact on total costs and total QALYs across all comparisons. Statements on the cost-effectiveness of glofitamab vs. BR may change depending on whether cure is assumed.
What additional evidence or analyses might help to resolve this key issue?	Long-term trial PFS and OS data for glofitamab and comparator treatments.

Issue 5: Average cohort age

Report section	**4.2.7**
Description of issue and why the EAG has identified it as important	Background mortality was modelled as a function of the age distribution of patients in the NP30179 study. An age distribution approach may not be appropriate as, although correctly reflecting the heterogeneity in background mortality of trial patients, it has been partially applied across model input parameters.
What alternative approach has the EAG suggested?	Without having access to evidence that allows a full implementation of the age distribution approach to all relevant model parameters, such as survival and HRQoL, the EAG suggest the use of the commonly accepted approach of assuming that background mortality corresponds to that of the average cohort age.
What is the expected effect on the cost-effectiveness estimates?	Without sizeable impact on total costs and total QALYs across all treatment comparisons.
What additional evidence or analyses might help to resolve this key issue?	Further PFS, OS and HRQoL evidence, reflective of the existing heterogeneity in the background mortality of this population, that could be used for a full implementation of the age distribution approach across the economic model.

Issue 6: Treatment discontinuation

Report section	**0**
Description of issue and why the EAG has identified it as important	The use of GO29365 study data to model BR individual treatment discontinuation provided more granularity to the analysis, nevertheless a different source of evidence (Hong et al (2018)) was used to inform treatment effectiveness of BR against glofitamab and to inform AE occurrences, creating inconsistencies across the model for this comparison.
What alternative approach has the EAG suggested?	To promote consistency across sources of evidence informing BR, but also consistency with Pola-BR, the EAG has explored the use of evidence from the GO29365 study to inform the effectiveness of BR relative to glofitamab, by: - assuming PH and using the unweighted/unadjusted ITC PFS and OS HR estimates for all comparisons (note that adjusted HR estimates for the comparison with BR using the GO29365 study were not provided to the EAG, only unweighted/unadjusted estimates); and - assuming PH and using evidence on OS and PFS from the recent Sehn et al (2022) study on the GO29365 study for the comparison of Pola-BR and BR to indirectly derive estimates for PFS and OS for the comparison of glofitamab vs BR, via the glofitamab vs Pola-BR estimates derived using propensity score IPTW methods on the GO29365 study.

What is the expected effect on the cost-effectiveness estimates?	The EAG has not considered alternative approaches to the use of the GO29365 study data to model BR individual treatment discontinuation, but has explored the use of evidence from the GO29365 study instead that of the Hong et al (2018) to inform the relative effectiveness of glofitamab and BR. It is expected a sizeable impact on total costs and total QALYs across all treatments for when using the unweighted ITC estimates, and BR for when indirectly using the Sehn et al (2022) data.
What additional evidence or analyses might help to resolve this key issue?	Long-term trial data on treatment discontinuation and HRQoL, together with long-term comparative survival data for glofitamab and comparator treatments.

Issue 7: ICANS

Report section	**0**
Description of issue and why the EAG has identified it as important	Neurological adverse events consistent with immune effector cell-associated neurotoxicity syndrome (ICANS) have been observed in patients treated with glofitamab in the NP30179 study but not considered in the cost-effectiveness analysis. While this may be appropriate if ICANS were not severe or frequent enough, it is unknown whether these AEs may require additional resource use for monitoring (e.g., access to specialised neurological care units). Furthermore, if specialised critical care is potentially needed as part of the monitoring strategy, this may constrain the setting in which glofitamab can be delivered to NHS centres with such facilities.
What alternative approach has the EAG suggested?	NP30179 study data could have been used to quantify the healthcare resource required for ICANS monitoring and management. If this evidence was not collected, clinical opinion on the matter could have been sought more formally. The EAG notes that the company's clinical advisors discussed the ICANS data collected in NP30179. As a minimum, the EAG would expect the company to report how the inclusion of ICANS was considered in the economic analysis.
What is the expected effect on the cost-effectiveness estimates?	Unknown
What additional evidence or analyses might help to resolve this key issue?	NP30179 study data may provide evidence on healthcare resource required for ICANS monitoring and management, which could then be incorporated in the economic analysis. Uncertainty here could also have been explored by seeking clinical opinion to inform a sensitivity analysis.

1.5 Other key issues: summary of the EAG's view

None

1.6 Summary of EAG's preferred assumptions and resulting ICER

Summary of the EAG's preferred assumptions and ICERs

Preferred assumption	Section in EAG report	Incr. cost	Incr. QALYs	Cumulative ICER £/QALY
1. Company's updated base-case	**5.1**			
Glofit vs BR		[redacted]	[redacted]	[redacted]
Glofit vs Pola-BR		[redacted]	[redacted]	[redacted]
Glofit vs Axi-cel		[redacted]	[redacted]	[redacted]
2. Company's corrected base-case	**6.1**			
Glofit vs BR		[redacted]	[redacted]	[redacted]
Glofit vs Pola-BR		[redacted]	[redacted]	[redacted]
Glofit vs Axi-cel		[redacted]	[redacted]	[redacted]
3. Analysis 2 + Background mortality using average age cohort (37 years TH)	**4.2.7**			
Glofit vs BR		[redacted]	[redacted]	[redacted]
Glofit vs Pola-BR		[redacted]	[redacted]	[redacted]
Glofit vs Axi-cel		[redacted]	[redacted]	[redacted]
4. Analysis 3 + Obinutuzumab administered as a complex and prolonged treatment at first attendance	**0**			
Glofit vs BR		[redacted]	[redacted]	[redacted]
Glofit vs Pola-BR		[redacted]	[redacted]	[redacted]
Glofit vs Axi-cel		[redacted]	[redacted]	[redacted]
5. Analysis 4 + Axi-cel administration cost corresponds to £50,550.50	**0**			
Glofit vs BR		[redacted]	[redacted]	[redacted]
Glofit vs Pola-BR		[redacted]	[redacted]	[redacted]
Glofit vs Axi-cel		[redacted]	[redacted]	[redacted]
6. Analysis 5 + CAR-T re-treatment not possible as a subsequent therapy	**0**			
Glofit vs BR		[redacted]	[redacted]	[redacted]
Glofit vs Pola-BR		[redacted]	[redacted]	[redacted]
Glofit vs Axi-cel		[redacted]	[redacted]	[redacted]
7. EAG base-case: Analysis 6 + LTR/S: 3 years, SMR: 1.41, - 10% utility adjustment	**0**			
Glofit vs BR		[redacted]	[redacted]	[redacted]
Glofit vs Pola-BR		[redacted]	[redacted]	[redacted]
Glofit vs Axi-cel		[redacted]	[redacted]	[redacted]

Modelling inconsistencies identified and corrected by the EAG are described in Section 6.1. For further details of the exploratory and sensitivity analyses done by the EAG, see Section 6.2.

EXTERNAL ASSESSMENT GROUP REPORT

2 INTRODUCTION AND BACKGROUND

2.1 Introduction

In this report the EAG has reviewed the company submission (CS) from Roche to NICE on the clinical effectiveness and cost-effectiveness of glofitamab for the treatment of relapsed or refractory diffuse large B-cell lymphoma (DLBCL) after two or more systemic treatments.

The company is awaiting a decision from the MHRA on inclusion of glofitamab in the Early Access to Medicines Scheme (EAMS) and from the European Medicines Agency (EMA) Committee for Medicinal Products of Human Use (CHMP). Glofitamab was recommended for approval by the CHMP in April 2023 and marketing authorisation is expected in August 2023.

In this section the ERG critiques the company's proposed positioning of glofitamab in the treatment pathway and its definition of the decision problem when compared with the NICE scope.

2.2 Background

2.2.1 Description of diffuse large B-cell lymphoma

DLBCL is an aggressive and fast-growing (high grade) type of non-Hodgkin lymphoma (NHL), characterised by abnormal and enlarge B cells which spread through the lymphatic system and to other areas of the body. The condition is described in the CS section B.1.3.1.

The company describe that around 4,850 people are diagnosed with DLBCL each year in the UK (CS section B.3.1.1, p. 17). Our clinical advisor estimated 5,500 people a year. Based on these estimates and assuming around 18% of patients receive third-line treatment (Wang 2017; CS source), the eligible population glofitamab would be 873 to 990 patients a year.

DLBCL affects men more often than women and predominantly occurs in older adults.[1] The most common symptom of DLBCL is one or more painless swellings which may grow quickly. Other symptoms include night sweats, recurrent high temperatures, and substantial weight loss. DLBCL, like other NHLs, is normally diagnosed with a surgical biopsy.[2] As described in the CS section B.1.3.1.3, the disease stage is determined following a diagnosis to determine the best treatment option(s) and to inform a prediction of prognosis. The prognosis is predicted using the five risk factors of the International Prognostic Index (IPI): age at diagnosis, serum lactate dehydrogenase level, ECOG status, Ann Arbor Stage, and number of extranodal sites. The prognosis is poorer for patients

aged 60 and older, with an elevated serum lactate dehydrogenase level, ECOG PS ≥ 2, Ann Arbor Stage III or IV, and patients with more than one extranodal site (CS section B.1.3.1.4).

2.2.2 Description of glofitamab

The CS describes the mechanism of action for glofitamab in CS section B.1.2, Table 2. Glofitamab is an antibody, which binds to protein CD3 on T cells and CD20 on B cells, stimulating the release of cytotoxic T cell proteins into nearby cancerous B cells. After pre-treatment with obinutuzumab and other prophylactic agents, glofitamab is administered as an intravenous (IV) infusion, leading up to a dose of 30 mg in the second treatment cycle. Patients may receive up to 12 treatment cycles.

2.2.3 Position of glofitamab in the clinical pathway

The company proposed positioning for glofitamab in the clinical pathway is described in the CS Section 1.3.2, summarised here as follows.

2.2.3.1 First line

R-CHOP is the current standard of care for first line DLBCL in the UK, for which the company cite a cure rate of around 60% (CS section B.1.3.2, p. 25). This is expected to change with the recent approval of polatuzumab vedotin in combination with rituximab, cyclophosphamide, doxorubicin, and prednisone (pola-R-CHP) in the first line. If first line cure rates improve as a result, fewer patients will be requiring second line and third line treatments.

2.2.3.2 Second line treatment

For patients with relapsed or refractory (R/R) DLBCL after first line treatment, second line treatment differs based on the condition and age of the patient. Those who are fit enough may receive rituximab-based salvage chemotherapy and/or an autologous stem cell transplant (ASCT), as shown in Figure 1 of the CS (section B.1.3.3, p. 33). In addition, it is anticipated that Chimeric antigen receptor T-cell (CAR-T) therapy will soon be approved for second line treatment for patients who are fit enough for intensive therapy.

For patients who are not fit for intensive therapy, treatment options include rituximab-based chemotherapy, polatuzumab vedotin with bendamustine and rituximab (Pola-BR), tafasitamab plus lenalidomide (tafa-len), palliation, or clinical trial participation.

2.2.3.3 Third line and beyond

Glofitamab is proposed for use in third line or later. Current treatment options for third line and beyond are CAR-T (which usually requires pola-BR bridging therapy whilst patients are waiting to start treatment); rituximab-based chemotherapy such as bendamustine and rituximab (BR) and

rituximab combined with gemcitabine and oxaliplatin (R-Gem-Ox); Pola-BR; palliative care; or clinical trial participation.

The EAG's clinical advisor explained that BR is not used regularly to treat R/R DLBCL in the UK clinical setting. The addition of polatuzumab to BR is considered to be more effective and is licensed in the UK and is also more likely to be prescribed as third-line treatment for DLBCL.[3] R-Gem-Ox has some efficacy but is unlikely to achieve long term disease control. The EAG's clinical advisor confirmed the company's description of pixantrone as a treatment which is considered palliative treatment for these patients due to inferior long-term efficacy.

Glofitamab could be used ahead of CAR-T, or for patients who are ineligible for CAR-T therapy, or for patients who progress following CAR-T (CS section B.1.3.3, p. 32). The EAG's clinical advisor explained that patients may be ineligible for CAR-T if T-cells cannot be frozen or if the patients' cancer has progressed and they cannot wait for the treatment to become available.

The EAG are satisfied that the clinical pathway presented in the CS section B.1.3.2 reflects current UK practice. The EAG's clinical advisor agreed that the clinical pathway is currently evolving, after having been relatively static for decades. Pola-BR is likely to become a less common third line treatment, as the introduction of pola-R-CHP in the first line means patients are unlikely to receive pola-BR in subsequent treatments. The anticipated approval for CAR-T therapy as a second line treatment may make glofitamab the treatment of choice after CAR-T, or instead of CAR-T for those not eligible to receive CAR-T therapy.

2.3 Critique of company's definition of decision problem

Table 1 provides an overview of the EAG critique on the company's definition of the decision problem. The company largely adhered to the final scope issued by NICE with regard to the population, intervention, and outcomes. The EAG's critique of the company's economic modelling is presented in Chapter 4.

2.3.1 Population

The population specified in the final scope by NICE is 'adults with relapsed or refractory diffuse large B-cell lymphoma who have had two or more systemic treatments'. The EAG agrees that this population is appropriate for this appraisal, but the population in the pivotal study is more restrictive than the population in scope.

The population in the pivotal study of evidence of clinical effectiveness for this appraisal (NP301799) excluded several subgroups of the population (CS section B.2.3.1.3, p.39-40). At the Points for

Clarification stage, the EAG queried the exclusion of the following groups, who may be eligible to receive glofitamab in practice:

- **Patients who are HIV-positive.** A positive HIV status is linked to a greater risk of DLBCL. The EAG's clinical advisor was not aware of a reason why HIV-positive patients with R/R DLBCL would not be considered for treatment with glofitamab. Guidance from the European Society for Medical Oncology (ESMO) suggests that HIV-positive patients usually receive the same treatment as HIV-negative patients.[4]
- **Patients with cardiovascular disease (CVD).** According to the EAG's clinical advisor patients with CVD would not automatically be excluded from treatment with glofitamab. Patients' ability to tolerate neutropenic sepsis would be considered on an individual basis, depending on the type of CVD.
- **Patients with ECOG PS >1.** The EAG's clinical advisor considers patients with ECOG PS 2 potential candidates for glofitamab, particularly if performance is impaired by the disease. The EAG considers patients with ECOG PS > 1 a relevant group, particularly considering the company's positioning of glofitamab as a potential treatment for patients who are ineligible to receive CAR-T therapy.

In response to the EAG's request for clarification on these exclusions, the company explained that these decisions were justified based on a lack of experience and data regarding the safety of glofitamab in these subgroups. These patient groups are potential future candidates for receiving glofitamab and the company is planning to generate data. At a later stage the company further clarified that only patients with active HIV infection, or those who recently experienced severe infections requiring hospitalisation or IV antibiotics would have been excluded from the trial. Similarly, only patients with a significant or extensive history of CVD would have been excluded.

2.3.2 Intervention

The decision problem describes the intervention as glofitamab monotherapy, in line with the final scope issues by NICE (CS Table 1). Glofitamab monotherapy requires a single dose pre-treatment with obinutuzumab, a targeted cancer drug. Obinutuzumab is administered to reduce the risk of cytokine release syndrome (CRS).

2.3.3 Comparators

Although the NICE scope lists various relevant comparators, including multiple chemotherapies and combination therapies with and without stem cell transplantation, the company restricted their submission to three comparator treatments: bendamustine plus rituximab (BR), polatuzumab vedotin

with rituximab and bendamustine (pola-BR), and CAR-T treatment axicabtagene ciloclecucel (axi-cel) (CS Table 1).

BR was used as a proxy comparator for rituximab, gemcitabine, and oxaliplatin (R-GemOx) given that suitable comparator data for R-GemOx are unavailable. Both BR and R-GemOx are combination therapies treating patients with a monoclonal antibody (rituximab) and chemotherapy (bendamustine or gemcitabine plus oxaliplatin). In a previous NICE appraisal (TA649), BR was considered a reasonable proxy for other rituximab and chemotherapy combinations used in the NHS.

A retrospective analysis of US registry data showing similar median OS for BR and R-GemOx was used to justify the use of BR as a proxy (CS section B.2.9.1.3, p. 63-64). For this study, DLBCL patients > 65 years old treated with second line BR (N=308) or R-GemOx (N=131) were included in the analysis. Compared to pivotal study NP30179, these patients were older and less likely to be in an advanced stage of disease (Ann Arbor stage IV). After adjustment through IPTW, the median OS was 16.39 months (95% CI 13.01; 18.48) for BR and 8.74 months (95% CI 7.00; 12.98) for R-GemOx, suggesting that median overall survival may be longer for BR than R-GemOx. The hazard ratios for adjusted OS however showed no difference between BR and R-GemOx.

The EAG's clinical advisor confirmed that BR is rarely used for the treatment of 3L DLBCL in the UK, and that pola-BR and axi-cel are considered the standard of care for these patients. Given the recent approval of pola-R-CHP for first line treatment, the most relevant comparator for this appraisal is CAR-T for patients fit enough to receive CAR-T, and rituximab-based chemotherapy for those who are not eligible to receive CAR-T.

The EAG notes that pixantrone and tafasitamab plus lenalidomide (tafa-len) were listed in the NICE scope as comparators and had been investigated by the company. The EAG therefore considers both these treatments in its evaluation (see Section 3.4.2). The EAG accepts that it was reasonable to exclude these two treatments from economic analyses. Pixantrone, is not presently used in routine clinical practice in the UK for 3L+ DLBCL. At time of writing, tafa-len has not been approved for use by NICE. Tisagenlecleucel was also initially included by the company in indirect treatment comparisons, but results were not presented. The EAG's clinical advisor explained that axi-cel is more widely used than tisagenlecleucel in UK clinical practice, and the omission of tisagenlecleucel from the comparators is therefore acceptable.

2.3.4 Outcomes

Outcomes presented by the company are in line with the final scope issued by NICE (CS Table 1). The company chose complete response (CR) as the primary outcome.

2.3.5 Special considerations including issues related to equity or equality

In section B.1.4 of the CS, the company draws attention to barriers in the delivery of CAR-T-cell therapies. Glofitamab, in comparison, may be available to patients quicker and from a wider range of clinical centres. However, committees appraising tisagenlecleucel (TA567) and axi-cel (TA559) concluded that no relevant equality issues are related to these treatments in the UK. Both committees were of the opinion that the decision to make these treatments available within the NHS would not have a different effect on people protected by the equality legislation than on the wider population.

Table 1 Summary of decision problem

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	EAG comment
Population	Adults with relapsed or refractory diffuse large B-cell lymphoma who have had two or more systemic treatments.	As per NICE final scope		As per NICE final scope, although several subgroups eligible for glofitamab in practice were excluded in pivotal study.
Intervention	Glofitamab	As per NICE final scope		Pre-treatment with obinutuzumab.
Comparator(s)	Established clinical management without glofitamab, including but not limited to: chemotherapy with or without rituximab and with or without stem cell transplantation, such as: DHAP (cisplatin, cytarabine, dexamethasone) GDP (cisplatin, gemcitabine, dexamethasone) ICE (ifosfamide, carboplatin, etoposide) IVE (ifosfamide, epirubicin and etoposide) polatuzumab vedotin with rituximab and bendamustine (if haematopoietic stem cell transplantation is not possible) pixantrone monotherapy axicabtagene ciloleucel (subject to ongoing NICE evaluation) tafasitamab with lenalidomide (if haematopoietic stem cell transplantation is not possible and subject to ongoing NICE evaluation)	• Rituximab-based chemotherapy (bendamustine plus rituximab [BR]) • Polatuzumab vedotin with rituximab and bendamustine (pola-BR) • Axicabtagene ciloleucel (axi-cel)	(see CS for full rationale) Considered most relevant treatments by clinical experts, covering 80% of 3L+ patients. BR used as proxy for R-GemOx in absence of evidence for R-GemOx. Supported by clinical experts and analysis of registry data suggesting similar OS rates. ASCT not considered a relevant comparator for 3L+. Pixantrone excluded as it is associated with poor outcomes and therefore not commonly used in UK clinical practice. Tafalen excluded as subject to NICE evaluation/ re-assessment following appeal.	The EAG generally agrees with the rationale for prioritising the three comparators provided by the company. BR is rarely used for 3L DLBCL in the UK, and that CAR-T (axi-cel) is the most common 3L therapy. The EAG considers that pixantrone, and tafa-len should be included as comparators, but accepts that they cannot be reasonably included in economic analyses, for the reasons given by the company. The EAG supports the company's choice not to include tisagenlecleucel as a relevant comparator.
Outcomes	The outcome measures to be considered include: overall survival progression-free survival response rates adverse effects of treatment health-related quality of life.	In line with NICE scope.		Complete response (CR) primary endpoint.

Economic analysis	cost-effectiveness of treatments to be expressed in terms of cost per quality-adjusted life year. time horizon sufficiently long to reflect differences in costs or outcomes between intervention and comparators. availability of commercial and/or managed access arrangements to be taken into account.			
Subgroups	Not included in scope.			
Special considerations including issues related to equity or equality	Not included in scope.	Existing geographical and sociodemographic inequity issues should be considered.	Glofitamab has the potential to be more accessible by a larger range of clinical centres than CAR-T-cell therapies (axicabtagene ciloleucel), helping reduce regional, rural–urban, and sociodemographic inequity issues resulting from uneven geographical allocation of CAR-T-cell therapy administration sites (see Section B.1.4).	Previous committee appraisals concluded that no relevant equity issues are related to CAR-T-therapies in the UK.

3 CLINICAL EFFECTIVENESS

3.1 Critique of the methods of review(s)

The company carried out four systematic reviews to identify clinical evidence, information on cost and healthcare resources, and published health state utility values. The two reviews of clinical evidence are discussed in this section. The two reviews relating to evidence on health economics are discussed in Section 4. Details of the systematic reviews were not provided initially and some of this information was obtained by the EAG as part of the clarification response.

3.1.1 Systematic review of clinical evidence

The company performed a systematic review of all possible treatments for R/R DLBCL in second line, third line, or later. This review appeared to be conducted primarily to identify trials for indirect comparison with glofitamab (see Section 3.3), but also searched for trials of glofitamab itself.

3.1.1.1 Searches

The EAG appraisal of the search strategies can be found in Appendix 9.1. The company provided some of the search strategies as part of the clarification response. No search strategies were provided for searches of conference proceedings, Health Technology Assessment (HTA) body websites, or clinical trial registries. We assume that the searches that were performed were used to find clinical evidence as well as evidence on indirect treatment comparisons. However, this remains unclear. Search filters were used but not referenced, so it is unclear whether validated filters were used.

Searches were initially conducted in December 2021 and identified 13,225 unique records. Update searches were carried out in September 2022, with another 2,045 records found.

3.1.1.2 Selection criteria

The eligibility criteria are in line with the decision problem of the company submission. The company investigated studies with a mix of second line and third line R/R DLBCL patients, and these were eligible for inclusion if subgroup data were reported. The EAG considers this approach reasonable.

Screening of titles/ abstracts and full-text manuscripts was carried out in duplicate by two reviewers independently. This will have minimised the potential for errors in the data selection process.

After screening, 232 studies (320 records) were included in the review. A list of included studies and excluded studies with reasons for exclusion was provided in the clarification response (Section A1.2.4, Table 8, p. 27).

3.1.1.3 Data extraction

For 115 out of 232 studies, no data were extracted. The company provided reasons for this in the clarification response (section A1.2.2, p. 22). No full-text papers were retrieved for non-English language abstracts (N=3). Thirteen studies were excluded because reported data were insufficient.

For the remaining 117 studies, data on study design, population, and reporting of key outcomes were extracted. Sixteen of the studies were deemed eligible for inclusion in the Indirect treatment comparison analyses (Section 3.3).

3.1.1.4 Quality assessment

Quality assessments were conducted using checklists appropriate to the primary study design. Results of the quality assessments were provided in Appendix H of the company submission (p. 9).

3.1.1.5 Evidence synthesis

In the clarification response, the company provided a succinct narrative summary of study and participant characteristics of included studies. No synthesis of study results was conducted. Studies selected for the indirect treatment comparison analyses were summarised in-depth and outcome data were extracted.

3.1.2 Systematic review of second and third line R/R DLBCL treatment

The CS briefly mentioned a systematic review of "CR rate based on a meta-analysis of 19 studies of R/R DLBCL." (CS Section B.2.4.1, page 43). Limited information on this review was provided on request from the EAG as part of the clarification response. It appears from the provided Statistical Analysis Plan that it was originally conducted to provide historical control data for comparison with glofitamab (SAP section 5.6.1.1, page 24).

3.1.2.1 Searches

The company performed a systematic review to identify studies evaluating second or third line (or beyond) pharmacological treatments for adult patients with transplant-ineligible R/R DLBCL. No details of the search strategy were provided.

3.1.2.2 Selection criteria

The review was initially inclusive of a wide range of in-human studies of adult patients with R/R DLBCL who received second or third-line (or beyond) therapy. An update search was restricted to studies with a majority of 3L+ R/R DLBCL patients, defined as "median prior lines of therapy ≥2, or number of patients who have two or more prior therapies ≥ 50%".

3.1.2.3 Data extraction

No details on methods of data extraction were provided. In the clarification response, the company has tabulated the studies by type of treatment and states the efficacy population per study arm (Table 11, p. 111-112). Some data appear to have been reported in Table 1 of the Statistical Analysis Plan (page 26).

3.1.2.4 Quality assessment

No information was provided on quality assessment.

3.1.2.5 Evidence synthesis

The company used the 19 included studies to perform a meta-analysis of complete response (CR) in a historical control population. It appears unweighted data from studies evaluating a variety of treatments were used to estimate the CR rate, including treatments such as bendamustine and rituximab (BR) and pixantrone which are not commonly used for this population in UK practice. This CR estimate is unlikely to be meaningful and impossible to interpret without knowing how it was derived from the data. This estimate was used only to determine that the primary endpoint was met in the D3 cohort of the pivotal study (CS section B.2.6.1, p. 51). It was not used in the indirect treatment comparisons that informed the company's model (see Section 3.4).

3.2 Critique of trials of the technology of interest, the company's analysis and interpretation (and any standard meta-analyses of these)

3.2.1 *Glofitamab study* NP30179

Data on the efficacy and safety of glofitamab were based on one study: NP30179, a Phase I/II, multicentre, open-label study evaluating escalating doses of glofitamab as a single agent and in combination with obinutuzumab, administered after a fixed, single dose pre-treatment of obinutuzumab (Gazyvaro®) in patients with relapsed/refractory (R/R) B cell non-Hodgkin's lymphoma.

The EAG requested access to the protocol, clinical study report, and statistical analysis plan for this study (PfC A4). These documents were used to check and/or elaborate on the information provided in the CS.

3.2.1.1 Quality assessment of NP30179

Appendix D of the CS included a quality assessment of NP30179. Table 2 compares the company and EAG judgements of study quality. Given the design of NP30179, the EAGs concerns related to the absence of a concurrent comparator, participant/cohort selection, risks of confounding in subgroup

comparisons, and absence of immune effector cell-associated neurotoxicity syndrome (ICANS) data in the CS. These issues are discussed individually in sections 3.2.1.2 to 3.2.1.7 of this report.

Table 2: Quality assessment results based on NP30179 CSR

Trial name, author, journal, year	Company assessment	EAG assessment
1. Is the hypothesis/aim/objective of the study clearly described?	Yes	Yes
2. Are the main outcomes to be measured clearly described in the Introduction or Methods section?	Yes	Yes
3. Are the characteristics of the patients in the study clearly described?	Unclear	Yes
4. Are the interventions of interest clearly described?	Yes	Yes
5. Are the distributions of principal confounders in each group of subjects to be compared clearly described?	Unclear	Unclear[a]
6. Are the main findings of the study clearly described?	Yes	Yes
7. Does the study provide estimates of the random variability in the data for the main outcome?	Yes	Yes
8. Have all important adverse events that may be a consequence of the intervention been reported?	Yes	Yes[b]
9. Have the characteristics of patients lost to follow-up been described?	No	No[c]
10. Have actual probability values been reported (e.g. 0.035 rather than < 0.05) for the main outcomes except where the probability value is less than 0.001?	No	No[d]
11. Were the subjects asked to participate in the study representative of the entire population from which they were recruited?	Unable to determine	Unable to determine
12. Were those subjects who were prepared to participate representative of the entire population from which they were recruited?	Unable to determine	Unable to determine
13. Were the staff, places and facilities where the patients were treated, representative of the treatment the majority of the patients receive?	Unable to determine	Unable to determine[e]
14. Was an attempt made to blind study subjects to the intervention they have received?	No	No
15. Was an attempt made to blind those measuring the main outcomes of interest?	Yes	No[f]
16. If any of the results of the study were based on "data dredging", was this made clear?	Yes	Yes[g]
17. In trials and cohort studies, do the analyses adjust for different lengths of follow-up of patients, or in case-control studies, is the time period between the intervention and outcome the same for cases and controls?	Yes	Yes
18. Were the statistical tests used to assess the main outcomes appropriate?	Yes	Yes
19. Was compliance with the interventions reliable?	Unable to determine	Yes[h]
20. Were the main outcome measures used accurate (valid and reliable)?	Yes	Yes
21. Were study subjects in different intervention groups (trials and cohort studies) or were the cases and controls (case-control studies) recruited from the same population?	Yes	N/A
22. Were study subjects in different intervention groups (trials and cohort studies) or were the cases and controls (case-control studies) recruited over the same period of time?	Yes	N/A
23. Were study subjects randomised to intervention groups?	No	N/A
24. Was the randomised intervention assignment concealed from both patients and health care staff until recruitment was complete and irrevocable?	No	No
25. Was there adequate adjustment for confounding in the analyses from which the main findings were drawn?	Unclear	Unclear
26. Were losses of patients to follow-up taken into account?	Yes	Yes
27. Did the study have sufficient power to detect a clinically important effect where the probability value for a differences being due to chance is less than 5%?	Yes	Yes[i]

[a]Characteristics reported, but not as potential confounders. No treatment comparator but potential for confounding in subgroup analyses
[b]Yes in CSR, but no ICANS discussion in CS
[c]No, but numbers lost to follow-up are small (1.3%)
[d]Only reported p value is for CR rate vs 'historical control' rate of 20% (p<0.0001)
[e]No UK sites, though study population appears broadly similar to eligible UK patients
[f]IRC was blinded to investigator-assessed data, but not to treatment
[g]Post-hoc analyses were appropriately described
[h]Route of administration (infusion) means measurement of compliance is likely to have been reliable
[i]Power calculation only made for the comparison with historical 20% CR rate

3.2.1.2 Methods

Section B.2.3.1.1 of the CS provides an overview of study NP30179. The study is divided in three parts (i.e., dose-escalation (Parts I and II) and dose-expansion [Part III]). Figure 2 of the CS (p.38) illustrates all the treatment cohorts incorporated in the trial, including the subset selected for inclusion in the CS. Section 3.2.1 of this EAG report provides further detail on how the patient cohorts were selected for the submission.

3.2.1.3 Participants

Participant selection, demographics and baseline characteristics

Section B.2.3.1.3 (p.39) of the CS summarised the main participant selection criteria. The EAG's clinical advisor considered these inclusion criteria to be broadly appropriate. As noted in section 2.3, NP30179 excluded participants with cardiovascular disease (CVD), HIV positive disease, or an ECOG score >1. The EAG's clinical advisor suggested that in practice such patients may be eligible depending on other considerations (type of CVD and risks of potential neutropenic sepsis; potential antiviral treatment interactions or low CD4 count in HIV patients; some ECOG 2 patients might be treated, particularly if impaired performance is due to the disease). An appendix listing reasons for screening failure was not included with the submitted clinical study report, so the EAG could not ascertain the number of patients excluded on the basis of CVS, HIV, or ECOG status.

Section B2.3.3.2 of the CS presented the key demographic and baseline characteristics of participants in NP30179.

The study did not recruit participants from any UK centres. The EAG's clinical advisor broadly agreed with the company's experts that the study patient characteristics were broadly similar to UK patients, while noting the relatively larger proportion of refractory compared to relapsed patients in the trial. However, given the poor prognosis of refractory disease, this is unlikely to bias the observed outcomes in favour of glofitamab.

Patient cohorts included in the company submission

NP30179 included 17 patient cohorts. Nine were glofitamab monotherapy cohorts, of which three were included in the CS clinical effectiveness evaluation. Pivotal data is from cohorts that included

patients with DLBCL who had relapsed after or failed at least two prior systemic therapies and who were to be treated with the recommended phase II dose (2.5/10/30 mg). Figure 2 of the CS (p.38) illustrates the NP30179 patient cohorts within the study schema. The cohorts selected for inclusion in the CS were:

- Part II **sub-cohort D2**: 3L+ R/R DLBCL patients treated with the proposed registration dose of 2.5/10/30mg glofitamab monotherapy (n=7)
- Part III **Cohort D3**: 3L+ R/R DLBCL patients treated with the proposed registration dose, 2.5/10/30 mg of glofitamab monotherapy (n=108)
- Part III **Cohort D5**: 3L+ R/R DLBCL patients treated with the proposed registration dose, 2.5/10/30 mg of glofitamab monotherapy, but the pre-treatment corticosteroid was mandated as dexamethasone (n=40)

Cohort D3 (n=108) was classified in the CS as the 'primary efficacy population'. The combination of sub-cohort D2, cohort D3, and cohort D5 (n=155) was classified as the 'primary study population' or 'efficacy evaluable population' (all patients who have been assessed for response at any time during the study, who have withdrawn from treatment or the study prior to reaching their first response assessment or who had been in the study long enough to have reached their first scheduled response assessment at a minimum of 49 days since the first dose of glofitamab or 56 days since the first dose of obinutuzumab pre-treatment, at the time of data cut-off)).

The 'primary safety population' included patients from the primary study population that had received at least one dose of study medication (n=154). However, it should be noted that although 154 patients received obinutuzumab pre-treatment, nine patients discontinued study treatment before receiving the first dose of glofitamab, so only 145 patients in the safety population received at least one dose of glofitamab (PfC B15).

The EAG requested greater detail on the NP30179 cohorts and their selection for the primary efficacy or safety populations (PfC A6). Fourteen NP30179 study cohorts were excluded from the CS based on histology (non-DLBCL subtypes of B-cell lymphoma, such as follicular, marginal zone, or mantle cell lymphoma), treatment received (glofitamab in combination with obinutuzumab rather than as monotherapy), number of prior lines of systemic therapy and/or dosing schedule (fixed dosing schedules or step-up schedules at doses lower than the 2.5/10/30mg schedule described in the marketing authorisation). The EAG's clinical advisor considered it appropriate to exclude study cohorts with these criteria. Table 3 provides further detail on the cohorts and, where relevant, reasons for their exclusion from the primary efficacy or safety population.

Table 3 Glofitamab monotherapy cohorts in Parts I, II and Ill of study NP30179 (safety-evaluable population) with reasons for exclusion from company evidence submission (CCOD 15 June 2022)

Cohort (diagnosis)	Dose of Glofitamab[a]	Glofitamab dosing regimen	Number of patients treated	Reason for exclusion from CS
Part I: dose escalation cohorts (single patient cohorts)				
A1 (R/R NHL)	0.005 mg	Fixed dosing, C1D8, Q2W	[redacted]	Dose
	0.015 mg	Fixed dosing, C1D8, Q2W	[redacted]	
	0.045 mg	Fixed dosing, C1D8, Q2W	[redacted]	
Part II: dose escalation cohorts (multiple patient cohorts)				
A2 (Q2W) and B2 (Q3W) (R/R NHL)	0.015 mg	Fixed dosing, C1D8, Q2W	[redacted]	Dose, histology (mixed NHL), number of prior therapies
	0.045 mg	Fixed dosing, C1D8, Q2W	[redacted]	
	0.07 mg	Fixed dosing, C1D8, Q2W[b]	[redacted]	
	0.10 mg	Fixed dosing, C1D8, Q2W[b]	[redacted]	
	0.22 mg	Fixed dosing, C1D8, Q2W[b]	[redacted]	
	0.30 mg	Fixed dosing, C1D8, Q2W[b]	[redacted]	
	0.60 mg	Fixed dosing, C1D8, Q2W[b,c]/Q3W	[redacted]	
	1.0 mg	Fixed dosing, C1D8, Q2W[c]/Q3W	[redacted]	
	1.8 mg	Fixed dosing, C1D8, Q2W[c]/Q3W	[redacted]	
	4 mg	Fixed dosing, C1D8, Q2W[c]/Q3W	[redacted]	
	10 mg	Fixed dosing, C1D8, Q2W[c]/Q3W	[redacted]	
	16 mg	Fixed dosing, C1D8, Q3W	[redacted]	
	25 mg	Fixed dosing, C1D8, Q3W	[redacted]	
D2 (R/R NHL)	Subcohort 1: 2.5/10/16mg	Step-up dosing, C1D8 2.5 mg, C1D15 10 mg, C2D1 16 mg. Q3W from C2 onward	[redacted]	Dose escalation to 16mg instead of 30mg
	Subcohort 2: 2.5/10/30 mg	Step-up dosing, C1D8 2.5 mg, C1D15 10 mg, C2D1 30 mg. Q3W from C2 onward	[redacted]	7/46 patients were included in CS. 39 patients excluded on histology and/or number of prior therapies
	Subcohort 4: 2.5/10/30 mg	Step-up dosing, C1D82.5 mg, C1D15 10 mg, C2D1 30 mg. Q3W from C2 onward	[redacted]	Two sequential doses of obinutuzumab
F2 (R/R NHL)	0.5/2.5/10/30 mg	Extended step-up dosing, C1D8 0.5 mg, C1D15 2.5 mg, C2D1 10 mg, C3D1 30 mg. Q3W from C3 onward	[redacted]	Dose and histology (FL), number of prior therapies
Total number of patients treated in Part I and II: 246				
Part Ill: dose expansion cohorts				
B3 (R/R DLBCL)	10/16 mg	Fixed dosing, C1D810 mg, C2D1 16 mg. Q3W from C2 onward	[redacted]	Dose
B4 (R/R FL)	10/16 mg	Fixed dosing, C1D810 mg, C2D1 16 mg. Q3W from C2 onward	[redacted]	Dose and histology (FL)
D3 (R/R DLBCL)	2.5/10/30 mg	Step-up dosing, C1D8 2.5 mg, C1D15 10 mg, C2D1 30 mg. Q3W from C2 onward	108[d]	Included in CS
D4 (R/R FL)	2.5/10/30 mg	Step-up dosing, C1D8 2.5 mg, C1D15 10 mg, C2D1 30 mg. Q3W from C2 onward	[redacted]	Histology (FL)
D5 (R/R DLBCL)	2.5/10/30 mg[e,f]	Step-up dosing, C1D8 2.5 mg, C1D15 10 mg, C2D1 30 mg. Q3W from C2 onward	41	Included in CS
Total number of patients treated in Part Ill: 257				
Total number of patients treated in Parts I, II and Ill: 503				

3.2.1.4Interventions

The proposed marketing authorisation for glofitamab for relapsed or refractory DLBCL recommends a single 1000mg dose of obinutuzumab on Cycle 1 Day 1 (7 days prior to initiation of glofitamab), followed by a glofitamab monotherapy dose step-up schedule of 2.5mg (Cycle 1 Day 8), 10mg (Cycle 1 Day 15), and 30mg (Cycles 2-12 Day 1). The patient cohorts selected for inclusion in the CS followed this schedule (see section 0)

Re-treatment with glofitamab

The proposed marketing authorisation recommends glofitamab for a maximum of 12 cycles or until disease progression or unmanageable toxicity.[5] It does not specifically mention the possibility of re-treatment with glofitamab. However, the study protocol for NP30179 stated "Patients who initially respond or have stable disease following study treatment may benefit from additional treatment" and described the following exploratory objective:

[redacted]

Section 3.1.4.4 (p.95) of the study protocol outlined several glofitamab re-treatment eligibility criteria. These included:

[redacted]

[redacted]

Table 8 of the CS (p.44) partially summarises the patient disposition from NP30179 but does not report the number of re-treated patients. [redacted]

Table 4 Re-treatment with glofitamab in NP30179

	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

3.2.1.5 Clinical effectiveness

Table 11, section B.2.3.2.1 of the CS (p.44) listed the key efficacy endpoints of NP30179. The primary efficacy endpoint was IRC-assessed complete response (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). Key secondary efficacy endpoints were overall response rate (ORR), duration of complete response (DOCR), duration of response (DOR), progression free survival (PFS) and overall survival (OS). Health-related quality of life (HRQoL) outcomes were 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). The reported outcomes were in line with the NICE scope (see Section 2.3).

Section B.2.6 of the CS (p.50) reported the clinical effectiveness results of NP30179 for these efficacy endpoints. For ease of reference, the key primary and secondary efficacy endpoint data are reproduced in Table 5 and Table 6 below.

Table 5: Summary of primary efficacy endpoint data in R/R DLBCL patients treated with glofitamab 2.5/10/30 mg after ≥ 2 lines of systemic therapy (ITT population)

	Primary analysis (CCOD 14th Sep 2021)		**Updated analysis (CCOD 15th June 2022)**			
	Cohort D3 (N=108)		**Cohort D3 (N=108)**		**Glofitamab 2.5/10/30mg Cohort D2 [Sub. 2]+D3+D5 (N=155)**	
	IRC	**INV**	**IRC**	**INV**	**IRC**	**INV**
CR rate[a] [95% CI]	35.2% [26.2, 45.0]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

[a]Lugano classification. CCOD, clinical cut-off date; CI, confidence interval; CR, complete response; INV, Investigator; IRC, Independent Review Committee.

Table 6: Overview of secondary efficacy endpoint data in R/R DLBCL patients treated with glofitamab 2.5/10/30 mg after ≥ 2 lines of systemic therapy (ITT population)

Secondary efficacy endpoints	Glofitamab 2.5/10/30mg Cohorts D2 [Sub. 2]+D3+D5 (N=155)	
	IRC	INV
CR rate[a] [95% CI]	[redacted]	[redacted]
ORR (CR+PR)[a] [95% CI]	[redacted]	[redacted]
Median DOCR[a] (months) [95% CI]	[redacted]	[redacted]
Event-free at 12 months [95% CI]	[redacted]	[redacted]
Event-free at 18 months [95% CI]	[redacted]	[redacted]
Median DOR[a] (months) [95% CI]	[redacted]	[redacted]
Event-free at 12 months [95% CI]	[redacted]	[redacted]
Event-free at 18 months [95% CI]	[redacted]	[redacted]
Median TFCR[a] (days) [95% CI]	[redacted]	[redacted]
Median TFOR[a] (days) [95% CI]	[redacted]	[redacted]
Median PFS (months) [95% CI]	[redacted]	[redacted]
1-year PFS rate [95% CI]	[redacted]	[redacted]
Median OS (months) [95% CI]	[redacted]	[redacted]
1-year OS rate [95% CI]	[redacted]	[redacted]

[a] Lugano classification[776].

CCOD, clinical cutoff date; CI, confidence interval; CR, complete response; DOCR, duration of complete response; DOR, duration of response; INV, Investigator; IRC, Independent Review Committee; NE, not evaluable; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; PR, partial response; TFCR, time to first complete response; TFOR, time to first overall response

Comparison of primary efficacy endpoint with other regimens

The primary efficacy endpoint of CR rate assessed by IRC was reported for two clinical cut-off dates (CCOD): the primary analysis (cohort D3 'primary efficacy population'; n=108; CCOD 14th Sept 2021) and an updated analysis (glofitamab 2.5/10/30mg Cohort D2 [Sub. 2]+D3+D5 'efficacy evaluable population'; n=155; 15th June 2022).

The primary analysis CR rate of 35.2% (95% CI: 26.2, 45.0) was reported to be statistically significantly greater than a "historical control CR rate" of 20% derived from a systematic review of

regimens used in the treatment of R/R DLBCL (p<0.0001). However, this was a simple unadjusted comparison which is likely subject to confounding and bias.

The updated analysis using the efficacy evaluable population reported a CR rate of 40.0% (95% CI: 32.2, 48.2). This analysis population and CCOD was used to inform a more robust indirect comparison done through matching-adjusted indirect comparisons (MAICs) and propensity score analyses (see section 3.4.1 for discussion of the limitations of these comparisons)

Additional outcome data requested by the EAG

Additional data for certain outcomes and/or populations not reported in the CS were requested by the EAG and reported below.

DOR and DOCR Kaplan-Meier plots

The KM plots of IRC-assessed DOR and DOCR in the primary efficacy population (glofitamab 2.5/10/30 mg, Cohorts D2 [Sub. 2] + D3 + D5) are shown in

Figure 1 and Figure 2.

The KM estimated DOR among responders at 6, 12, and 18 months after the first response were [redacted] respectively (

Figure 1).

The KM estimated DOCR among complete responders at 6, 12, and 18 months after the first CR were [redacted] respectively (Figure 2).

Figure 1 Kaplan-Meier plot of IRC-assessed DOR in the primary efficacy population (responder population)

Figure 2 Kaplan-Meier plot of IRC-assessed DCOR in the primary efficacy population (complete responder population)

Outcome data for 'supporting efficacy population' and cohorts D3 and D5

The EAG requested separate outcome data for the 'supporting efficacy population' of patients with R/R DLBCL who received glofitamab doses ≥10 mg (n=101), Glofitamab 2.5/10/30 mg Cohort D3 (n=108), and Glofitamab 2.5/10/30 mg (pre-treatment steroid mandated as dexamethasone) Cohort D5 (n=40). Table 7 brings together data from the CS, response to PfCs (A7 and A8) and clinical study report for these populations. This data (and the additional KM curves provided in the response to PfCs) indicate [redacted]

[redacted]

(see response to PfC A7).

Table 7 IRC-assessed response rates, PFS and OS outcomes (CCOD 15 June 2022)

	Supporting efficacy population **Glofitamab ≥10 mg*** **(N=101)**	**Glofitamab 2.5/10/30 mg** **Cohort D3** **(N=108)**	**Glofitamab 2.5/10/30 mg** **Cohort D5** **(N=40)**	**Glofitamab 2.5/10/30mg** **Cohorts D2 [Sub. 2]+D3+D5** **(N=155)**
Response rates				
Overall response rate (ORR) **(95% CI)**	[redacted]	[redacted]	[redacted]	[redacted]
Complete response (CR) **(95% CI)**	[redacted]	[redacted]	[redacted]	[redacted]
Progression-free survival (PFS)				
Patients with event **Earliest contributing event:** **Death** **Disease Progression**	[redacted]	[redacted]	[redacted]	[redacted]
Time to event (months) **Median** **(95% CI)**	[redacted]	[redacted]	[redacted]	[redacted]
Overall survival (OS)				
Patients with event	[redacted]	[redacted]	[redacted]	[redacted]
Time to event (months) **Median** **(95% CI)**	[redacted]	[redacted]	[redacted]	[redacted]

Subgroup analyses

Figure 5 of the CS (p.59) summarises the pre-specified subgroup analyses of the primary endpoint (IRC-assessed CR rate) in the primary efficacy population.

The CS noted "consistency of the treatment effect across relevant subpopulations defined by demographics (gender, age range categories, race/ethnicity, ECOG PS), prior CAR-T therapy, number of prior lines of therapy and risk factors for IPI", while noting that the relatively small number of patients with relapsed (non-refractory) disease showed a trend towards increased CR (rates ranging between 58%–67%; Table 55).

It should be noted that while the total number risk factors for IPI were not clearly associated with CR rate, there appears a trend toward higher CR rates in patients with ≤1 risk factors for *age-adjusted* IPI (53%, 95% CI 40, 65) than for patients with 2 risk factors (30%, 95% CI 21, 41; see CS, figure 5).

Sex differences

The EAG noted [redacted] and asked the company whether checks had been performed for possible confounding with other factors (PfC A14). The company provided key participant characteristic data by sex, [redacted] (see Table 8).

Table 8 Summary of key demographic data and disease characteristics by sex (male vs female)

	Male	Female
[redacted]		
Age (years), n		
Median		
Min–Max		
Age Group (years), n (%)		
< 65		
> 65		
Race, n (%)		
Asian		
Black/African American		
White		
Unknown		
Body Mass Index (kg/m2), n		
Median		
Min–Max		
ECOG status, n (%)		
0		
1		
2		
Cancer Histology Subtype II, n (%)		
DLBCL		
FL Grade 3B		
FL Grades 13A		
HGBCL		
MCL		
PMBCL		
Richter's transformation		

trFL	[redacted]	[redacted]
trMZL	[redacted]	[redacted]
Transformed other	[redacted]	[redacted]
Ann Arbor Staging, n (%)	[redacted]	[redacted]
Stage I	[redacted]	[redacted]
Stage II	[redacted]	[redacted]
Stage III	[redacted]	[redacted]
Stage IV	[redacted]	[redacted]
Unknown	[redacted]	[redacted]
Risk Factors for IPI (non-FL patients only), n (%)	[redacted]	[redacted]
0	[redacted]	[redacted]
1	[redacted]	[redacted]
2	[redacted]	[redacted]
3	[redacted]	[redacted]
4	[redacted]	[redacted]
Extranodal Disease, n (%)	[redacted]	[redacted]
No	[redacted]	[redacted]
Yes	[redacted]	[redacted]
Bulky Disease >6 cm, n (%)	[redacted]	[redacted]
No	[redacted]	[redacted]
Yes	[redacted]	[redacted]
Absence of Circulating Malignant Cells, n (%)	[redacted]	[redacted]
No	[redacted]	[redacted]
Yes	[redacted]	[redacted]
Missing	[redacted]	[redacted]

[a] Primary safety population: patients with R/R DLBCL (includes DLBCL NOS, trFL, PMBCL, HGBCL; 2 prior lines) from Cohorts D2 Subcohort 2, D3, and D5

The EAG also requested outcome data for IRC-assessed ORR, PFS and OS by sex. [redacted] (see Figure 3 to

Figure 6).

Figure 3 Kaplan-Meier plot of IRC-assessed PFS of the primary study efficacy population, male

Figure 4 Kaplan-Meier plot of IRC-assessed PFS of the primary study efficacy population, female

Figure 5 Kaplan-Meier plot of IRC-assessed OS of the primary study efficacy population, male

Figure 6 Kaplan-Meier plot of IRC-assessed OS of the primary study efficacy population, female

Histology subtypes

The EAG requested CR, OSS, PFS and OS data where available for DLBCL, PMBCL, HGBCL and tFL subtypes (PfC A9). The data in **Error! Not a valid bookmark self-reference.** reflect the expected responsiveness of each subtype to treatment

[redacted]

Table 9: IRC-assessed response rates by histology subtype (ITT population)

n (%)	**Glofitamab 2.5/10/30 mg Cohorts D2 (Sub. 2), D3, D5 (N=155)**				
	DLBCL (n=110)	**PMBCL (n=6)**	**tFL (n=29)**	**HGBCL (n=10)**	**All patients (N=155)**
Overall response rate (ORR) (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Complete response (CR) (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Number of previous lines of treatment

Figure 5 of the CS indicated a (statistically non-significant) higher CR rate among patients with ≥3 prior lines of therapy than for those who had 2 prior lines (2 prior, 33% vs ≥3 prior, 45%).

The EAG requested ORR, PFS and OS results for this subgroup comparison (PfC A10). These data are shown in Table 10 and

Figure 7 to

Figure 10. [redacted]

Table 10: IRC-assessed ORR by prior lines of therapy (2 vs ≥3)

	Glofitamab 2.5/10/30 mg Cohorts D2 (Sub. 2), D3, D5 (N=155)		
	Patients, n (%)	Patients with event	
		n (%)	95% CI
All	[redacted]	[redacted]	[redacted]
Prior lines of therapy 2 ≥3	[redacted]	[redacted]	[redacted]

Figure 7 Kaplan-Meier plot of IRC-assessed PFS in the primary efficacy population, with 2 prior lines of therapy

[redacted]

Figure 8 Kaplan-Meier plot of IRC-assessed PFS in the primary efficacy population, with ≥3 prior lines of therapy

Figure 9 Kaplan-Meier plot of IRC-assessed OS in the primary efficacy population, with 2 prior lines of therapy

Figure 10 Kaplan-Meier plot of IRC-assessed OS in the primary efficacy population, with ≥3 prior lines of therapy

CAR-T prior and/or subsequent to glofitamab

In response to a request from the EAG, the company clarified that none of the 52 patients who received prior CAR-T therapy received further CAR-T after completing glofitamab treatment.

[redacted] see response to PfC A12).

Glofitamab treatment discontinuation

Section B.2.10.1 summarised glofitamab exposure in the primary safety population (as noted in section 3.2.1.2 of this EAG report, nine patients discontinued study treatment before receiving the first dose of glofitamab, so only 145 of 154 patients in the safety population received at least one dose of glofitamab).

Treatment discontinuation in the primary safety population

The EAG requested more information on glofitamab treatment duration, and reasons for treatment discontinuation (PfC A15). The data provided by the company are presented in Figure 11 and

Table 11. the most common reason for glofitamab discontinuation was progressive disease in 63/145 (43.4%) of patients.

Figure 11: Patients on- and off-treatment by month (CCOD 15 June 2022)

[redacted]

Table 11: Reasons for study treatment discontinuation by month (CCOD 15 June 2022)

Study duration	<1 month	Month 1	Month 2	Month 3	Month 4	Month 5	Month 6	Month 7	Total
Patients on glofitamab treatment, n	[redacted]								
Reasons for study treatment discontinuation (events per month)									
Progressive disease	[redacted]								
Adverse event	[redacted]								
Death	[redacted]								
Lack of efficacy	[redacted]								
Physician decision	[redacted]								
Protocol deviation	[redacted]								

Treatment discontinuation in patients achieving CR

Among patients in the primary efficacy population with a CR, [redacted] received 12 cycles of treatment while non-responders received fewer cycles largely due to study treatment discontinuation. The reasons for discontinuation among [redacted] patients who achieved a CR but received fewer than 12 cycles of glofitamab were requested by the EAG (PfC A16) and are reported in Table 12. Of patients achieving a CR, [redacted] subsequently discontinued glofitamab treatment due to progressive disease and [redacted] due to adverse events.

Table 12: Reasons for study treatment discontinuation by month, for patients with a CR who underwent less than 12 glofitamab cycles (CCOD 15 June 2022)

Study duration	<1 month	Month 1	Month 2	Month 3	Month 4	Month 5	Total
Patients on glofitamab treatment, n	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
Reasons for study treatment discontinuation (events per month)							
Progressive disease	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Adverse event	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Death	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Lack of efficacy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Physician decision	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Protocol deviation	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Symptomatic deterioration	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Withdrawal by subject	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Other/not recorded	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Safety

Section B.2.10 of the CS (p.89) summarised safety data from NP30179, including adverse events of special interest (AESIs).

Immune effector cell-associated neurotoxicity syndrome (ICANS)

Immune effector cell-associated neurotoxicity syndrome (ICANS) is a clinical and neuropsychiatric syndrome that can occur in the days to weeks following administration of certain types of immunotherapy, especially immune effector cell and T cell engaging therapies, including glofitamab. While the CS presented some data on neurological adverse events (section B.2.10.3.2), no ICANS were reported.

Advisory Group minutes requested by the EAG (PfC C4) record [redacted] These data were not presented in the CS. However, ICANS data extracted from the clinical study report by the EAG are presented in Table 13.

The clinical study report states that the majority of ICANS events occurred [redacted] though exact data on

relatedness could not be found. [redacted]

The observed rate of ICANS events for glofitamab-treated patients in NP30179 is less than observed for CAR-T treated patients in a UK real world dataset ([redacted] vs 36.8%).[8] The EAG's clinical advisor suggested that the risk of ICANS would be greatest with the first treatment cycle, but that the overall risk of ICANS with glofitamab is likely to be low.

Table 13 Neurological adverse events consistent with ICANS event (CCOD 15th June 2022)

Neurological AEs consistent with ICANS event	Number (%) of events in primary safety population (n=154)
All events **Concurrent with CRS** **Non-concurrent with CRS**	[redacted]
Grade 1-2	[redacted]
Grade 2	[redacted]
Grade 3 (somnolence and delirium)	[redacted]
Grade 5 (fatal delirium)	[redacted]
Unresolved at time of CCOD **Somnolence** **Grade 2 dysphonia**	[redacted]

3.3 Critique of trials identified and included in the indirect comparison and/or multiple treatment comparison

3.3.1 Comparator interventions considered

The CS presented indirect comparisons of glofitamab with:

- Axicabtagene ciloleucel (axi-cel)
- Bendamustine and rituximab (BR)
- Polatuzumab vedotin plus bendamustine plus rituximab (Pola-BR)

A supplied appendix reporting the indirect treatment comparisons (Appendix D ITC report) also presented indirect comparisons with:

- Lenalidomide
- Lisocabtagene maraleucel
- Pixantrone
- Tafasitamab plus lenalidomide (tafa-len)
- Tisagenlecleucel

Two of these therapies (pixantrone and tafa-len) were included in the NICE scope. The CS did not present results for piaxantrone on the grounds that it is associated with poor outcomes and as a result is not commonly used in clinical practice in the UK. Tafa-len was excluded as it was subject to NICE evaluation/re-assessment following appeal. The EAG accepts that these reasons may make comparisons with pixantrone and tafa-len less relevant for consideration. However, as they were specified in the NICE scope, we do consider them in this section. The EAG notes that NICE guidance for tafa-len, rejecting its use was made public shortly before this report was completed, so tafa-len is no longer a relevant comparator. However, we leave discussion of it in this report for the sake of transparency. We also present some summary results for the other comparators, even though they were not in the scope, for reference.

The CS noted that rituximab with gemcitabine and oxaliplatin (R-GemOx) may be the most widely used therapy at present in third-line DLBCL treatment. However, in the absence of available evidence to put forward a comparison to glofitamab, the company considered that bendamustine and rituximab (BR) would have similar efficacy. Based on advice from our clinical expert, the EAG accepts this conclusion.

3.3.2 Trials in the indirect treatment comparisons

The company chose to use only one trial per comparator for the ITC analyses. Details of all eligible trials were presented in the ITC report. The company appear to have used a suitable trial for each comparator. Where more than one trial was available, they generally chose the largest trial that most closely matched the scope (e.g. with patients at 3rd line treatment or later) and reported data on the largest number of prognostic factors. While ideally the ITC should consider all eligible trials, the EAG accepts that this would not be practical for this assessment, and that the company have made appropriate choices of trials for the ITC.

The one exception to this was for the comparison with BR. The company reported an ITC using Hong et al 2018[9] for this comparison, as the largest available study. The company also performed an ITC using the BR arm of the GO29365[3] trial, but did not present it on the grounds that its effective sample size was very small. As the GO29365 trial may be more representative of the UK population, the EAG requested that the results of this ITC be provided for comparison. The company provided the unadjusted comparison for this trial, but declined to provide the results of the propensity score analysis.

Table 14 presents summary of the trials included in the ITC analyses. Only one of the trials was an RCT; all others were single-arm trials, cohort studies or retrospective analyses. This raises the standard concerns that these trials may be biased because of the lack of a control arm, but the EAG

notes that single-arm studies are usual in this field. We note the very small sample sizes, particularly for the BR trials. These may make adjusted comparisons unreliable.

Table 14 Summary of trials included in the ITC analyses

Comparator	Trial	Sample size	Trial design	Lines of therapy	Notes
Axi-cel	ZUMA-1	101	Phase II single arm	3rd line or later	Patients who progressed before infusion were excluded from ZUMA-1 analysis.
Pola-BR	GO29365	152	Phase II RCT	2rd line or later	HGBCL and PMBCL histologies were excluded Patients with ECOG ≥2 were excluded.
BR	Hong 2018	58	Retro. analysis	2th line or later	HGBCL and PMBCL histologies were excluded
	GO29365	40	Phase II RCT	3rd line or later	
Pixantrone	Eyre 2016	90	-	2rd line or later	HGBCL and PMBCL histologies were excluded
Tafa-len	L-MIND	80	Phase II single arm	3rd line or later	HGBCL and PMBCL histologies and >4 lines of therapy were excluded
Lenalidomide	RE-MIND	76	Retro. cohort	3rd line or later	HGBCL and PMBCL histologies and >4 lines of therapy were excluded
Lisocabtagene maraleucel	TRANSCEND	257	Phase II single arm	4th line or later	HGBCL and PMBCL histologies and >4 lines of therapy were excluded
Tisagenlecleucel	JULIET	115	Phase II single arm	3rd line or later	PMBCL histologies were excluded

The quality of the included trials was assessed, (CS Appendix D, Tables 1 and 2). The one RCT (GO29365) was not blinded, and it does not appear to have properly concealed the randomisation process. This raises concerns that the trial may have produced biased estimates of the effectiveness of pola-BR and BR.

All other included trials were non-randomised. The main quality concerns were a lack of blinding of outcome assessors, a lack of clarity as to whether the patients included were representative, and a lack of clarity over treatment compliance. No assessment of the ZUMA-1 or L-MIND trials was reported. These points raise general concerns as to the potential for bias in all the non-randomised trials considered, but these concerns are to be expected in single-arm trials in this field.

3.4 Critique of the indirect comparison and/or multiple treatment comparison

Glofitamab has only been used in on single-arm trial and so has not been directly compared with any other eligible treatment. Therefore, the company used indirect approaches to compare glofitamab to

other treatment, including matched indirect adjusted comparison (MAIC) and propensity score analysis.

3.4.1 Statistical methods for indirect treatment comparisons

Section B.2.9 of the CS described the methods used for the indirect treatment comparisons, with a fuller explanation given it the ITC appendix, The EAG also requested some clarification of the methods used.

For all comparisons an unweighted comparison was presented, which did not adjust for any differences in characteristics between trials, and so may give a biased comparison. Unanchored MAIC analyses were used for most treatments to adjust for differences between trials. Propensity score analysis was possible for comparison with the GO29365 trial, as the company had access to the data for that trial. MAIC analyses appeared to have been performed using standard approaches for matching (as set on in the relevant technical support documents).

The propensity score analysis sought to estimate the average treatment effect (ATE). It used both propensity score matching and inverse probability of treatment weighting (IPTW) to adjust for prognostic factor imbalances between trials. Although other approaches are possible, the EAG considers that the statistical approach to propensity score analysis used was appropriate.

For both propensity score analyses and MAICs, confidence intervals were calculated using bootstrapping. This was justified as providing more robust confidence intervals than conventional methods (such as confidence intervals from weighted Cox models), However, bootstrapping was not used for the confidence intervals for the unweighted comparisons. This meant that confidence intervals for weighted and unweighted analyses were not comparable. Confidence intervals for MAIC or propensity score analyses were of a similar width, or in some cases narrower, than those for unweighted comparisons (see Table 17). This was unexpected because the substantial reduction in effective sample size for weighted analyses should have led to wider confidence intervals. It is unclear to the EAG whether the difference in methodologies could have led to this unexpected result, or whether there were errors in the analysis. The EAG notes that bootstrap procedures are inherently random and have some seed-dependence, and large samples are needed for robust results.[10]

The analyses sought to recategorize covariates appropriately where definitions varied between trials. Where patients in the NP30179 trial of glofitamab had missing data for any covariate the values were imputed by using the average values among all other patients. This is a reasonable approach to missing data, rather than excluding patients entirely, but may inflate the effective sample size, making MAICs appear more robust than they are.

The prognostic factors used when adjusting the trials data were categorised as high, medium or low priority for inclusion in the analyses. The "high priority" factors were:

- International prognostic index (IPI) or any of its components
- Whether patients were refractory to prior lines of therapy
- Histological subtype
- Double/triple hit lymphoma
- Early relapse after SCT
- Number of prior treatment lines

Medium and low priority factors were listed in the ITC report. After consultation with our clinical advisor, the EAG considers that the set of prognostic factors considered, and their prioritisation, was appropriate. Therefore, the ITC analyses are likely to be suitably adjusted for the key prognostic factors, but, as for all indirect comparisons, the possibility that some important factor has been missed cannot be excluded.

For most indirect comparisons only one "base-case" adjusted analysis was reported in the CS. When performing MAICs and propensity score analysis, multiple analyses adjusting for different factors are often performed to investigate the balance between number of factors adjusted for and effective sample size. The company justified not doing this broadly on the grounds that the base-case analyses "maximized the bias/variance tradeoff whilst controlling for all priority prognostic factors that were feasible". The EAG notes that effective sample sizes for most analyses were very low, and analyses adjusting for fewer factors to increase sample size at the cost of possibly greater bias would have been useful. This would have allowed us to investigate how robust the adjusted analyses were.

The CS presented ITC analyses for survival outcomes (OS and PFS), response outcomes (ORR and CR), duration of response (DOR and DOCR) and discontinuation due to AEs. Hazard ratios were calculated, and Kaplan-Meier curves produced for OS and PFS. All other outcomes were reported as odds ratios. The CS noted that outcome definitions were not always consistent across trials, particularly for response (CR and ORR). However, the company sought to match endpoint definitions used in NP30179 to definitions of comparator studies to align them as closely as possible, where feasible. This may impact the validity of the comparisons, but exactly how is uncertain. The ITC report also noted that results for duration of response (DOR and DOCR) may be unreliable because:

"[These analyses]… require the very strong assumption that the baseline characteristics of responders are the same as those of both the responder and non-responder groups combined for the comparator patient population"

The EAG agrees that potential differences between responder and non-responder groups across trials makes duration of response comparisons unreliable. The EAG has presented these results for the sake of completeness, but we suggest that these results not be considered, or be interpreted with extreme caution.

3.4.2 Results of the indirect treatment comparisons

3.4.2.1 Overall summary

Table 15 summarises the prognostic factors that were adjusted for in each treatment comparison (excluding treatments that were not in the NICE scope). In general, analyses were adjusted for most of the "high priority" factors, but for few other factors. Some notable omissions were that most analyses could not adjust for double/triple hit lymphoma. The company clarified that this was because only double/triple hit HGBCL was reported rather than for all patients with double/triple hit tumours; therefore, histology subtype was used instead. Comparisons with BR and pixantrone were not adjusted for ECOG status, and comparison with tafa-len was not adjusted for number of prior therapies. That these factors could not be adjusted for could be a substantial source of bias in the analyses.

Table 15 Prognostic factors adjusted for in indirect treatment comparisons

Factors adjusted for	Axi-cel	Pola-BR	BR (Hong)	Pixantrone	Tafa-len
High priority					
Age	■	■	■	■	■
ECOG	■	■	■	■	■
Ann-Arbor Stage	■	■	■	■	■
High LDH	■	■	■	■	■
Extranodal disease	■	■	■	■	■
IPI	■	■	■	■	■
Refractory to 1st line	■	■	■	■	■
Refractory to previous line	■	■	■	■	■
Refractory to any line	■	■	■	■	■
HGBCL / PMBCL	■	■	■	■	■
Double/triple hit lymphoma	■	■	■	■	■
Early relapse after SCT	■	■	■	■	■
Number of prior therapies	■	■	■	■	■
Others					
Bulky disease	■	■	■	■	■

Best response of PD to last line	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cell type	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Time since last therpay	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Prior SCT (or ASCT)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Refractory to rituximab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Refractory to ASCT or anti-CD20	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Bone marrow involvement	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

* *Adjusted for in sensitivity analysis, but not in base-case*

Table 16 presents the sample sizes for all treatment comparisons, including effective sample sizes for the MAICs. The sample size for glofitamab in unadjusted analyses varies because patients were excluded from analysis where feasible if they would not have been included in the comparator trial. Note that the effective sample size for all MAICs was very low compared to the total sample size.

Table 16 Sample sizes of trials in the ITC analyses

Comparator	Comparator sample size	Glofitamab sample size	
		Unadjusted	Effective sample size after adjustment
Axi-cel	101	[redacted]	[redacted]
Pola-BR	84	[redacted]	[redacted]
BR (Hong)	58	[redacted]	[redacted]
BR (GO29365)	21	[redacted]	[redacted]
Pixantrone	90	[redacted]	[redacted]
Tafa-len	81	[redacted]	[redacted]
Lenalidomide	76	[redacted]	[redacted]
Lisocabtagene maraleucel	256	[redacted]	[redacted]
Tisagenlecleucel	115	[redacted]	[redacted]

Table 17 presents a summary of the results of all the indirect comparisons (unadjusted analyses, MAICs and propensity score analyses) performed. The table gives unadjusted and adjusted comparisons between glofitamab and the comparator interventions for each outcome considered. The colour coding summarises the EAG's conclusions for each analysis as follows:

- Dark green: Evidence favours glofitamab (results are statistically significant)
- Light green: Evidence possibly favours glofitamab (results are not statistically significant)
- Yellow: No clear difference between glofitamab and comparator, or highly uncertain evidence

- Light red: Evidence possibly favours comparator (results are not statistically significant)
- Dark red: Evidence favours comparator (results are statistically significant)

Table 17 is adapted from Table 1 in the ITC report, but uses a different colour coding. In this table we report the independent review committee (IRC) results for glofitamab, wherever they were reported, and the ITPW results for propensity score analyses. In practice, the differences between IRC and investigator results, and between ITPW and matched analyses, were small.

Table 17 Summary of all indirect treatment comparisons

Comparator	Analysis	OS	PFS	DOR	DOCR	ORR	CR	Discontinuation due to AE
Axi-cel	Unadjusted							
	Adjusted							
Pola-BR (Propensity score)	Unadjusted							
	Adjusted (ITPW)							
BR (Hong 2018)	Unadjusted							
	Adjusted							
BR (GO29365)	Unadjusted							
	Adjusted							
Pixantrone	Unadjusted							
	Adjusted							
Tafa-len	Unadjusted							
	Adjusted							
Lenalidomide	Unadjusted							
	Adjusted							
Lisocabtagene maraleucel	Unadjusted							
	Adjusted							
Tisagenlecleucel	Unadjusted							
	Adjusted							

Figure 12 and

Figure 13 present Kaplan-Meier curves for OS and PFS respectively, including both weighted and unweighted analyses. The company submissions only reported these data for glofitamab, axi-cel, pola-BR and BR (from Hong 2018). These figures were created using data digitally extracted from Kaplan-Meier plots in the ITC report, so there may be very minor variations between these figures and the plots supplied by the company.

Figure 12 Kaplan-Meier curves of overall survival (OS) for all treatments

Figure 13 Kaplan-Meier curves of progression-free survival (PFS) for all treatments

We note that the various adjusted versions of the glofitamab survival curves in Figure 12 and

Figure 13 are [redacted] to the unadjusted survival curves. This suggests that survival times with glofitamab are [redacted] to variations in patient populations.

Sections 0 to 0 consider the ITC analyses for each comparator treatment.

3.4.2.2. Axi-cel

The data from the ZUMA-1 trial of axi-cel excluded patients submitted for consideration of CD19 CAR-T but who did not ultimately receive treatment, so the analysis population is only those who successfully received CAR-T infusion. This may mean that the comparison between axi-cel and glofitamab is unfair.

Unadjusted comparisons (see Table 17) [redacted]

In the MAIC analysis, [redacted]

[redacted]

The results of the MAIC were [redacted]

A further MAIC was performed (in the ITC report), adjusting for more prognostic factors, but with a much smaller effective sample size (ESS 15.1). The EAG considers that this ESS is too small to be reliable, and so we do not report its results here. They were broadly similar to those from the base-case MAIC.

Comparing the Kaplan-Meier curves for OS and PFS (Figure 12 and

Figure 13) [redacted]

[redacted], in both unadjusted and adjusted analyses.

3.4.2.3 Pola-BR

The company had access to the data for the GO29365 trial, so they performed a propensity score analysis to compare glofitamab to pola-BR. Patients not relevant to this assessment were removed from the pola-BR arm (e.g. patients with ECOG PS ≥2, or with only one prior line of therapy). After removal of data there were 84 patients in the pola-BR arm, and 149 in the glofitamab arm.

Unadjusted comparisons (see Table 17) found [redacted] between glofitamab and pola-BR. Odds ratios for response (CR and ORR) were [redacted], as were hazard ratios for survival (OS and PFS). [redacted]. The EAG notes that our conclusion differs from that in the CS. Discontinuation due to adverse events was [redacted].

Adjustments were performed for [redacted]

The results of the adjusted IPTW analyses were [redacted]. For survival analyses (OS and PFS) hazard ratios [redacted]. Results for response (CR and ORR) [redacted]

The ITC report also included an indirect comparison based on full matching rather than IPTW. Th matching between glofitamab and pola-BR was less successful using that method, so both company and the EAG prefer the IPTW analysis, and the fully matched analysis is not presented here. Results from the fully matched analysis were broadly similar to both the unadjusted analysis and the IPTW analysis.

Comparing the Kaplan-Meier curves for OS and PFS (Figure 12 and

Figure 13) suggests that there is [redacted]

3.4.2.4. BR

Glofitamab was compared to BR in the Hong 2018 trial and GO29365 trial. For the comparison with Hong 2018 patients with HGBCL and PMBCL histologies were excluded in order to align with Hong 2018.

When compared to Hong 2018, [redacted] Table 17 [redacted] for survival (OS and PFS). Results for response (ORR and CR) [redacted]

When compared to GO29365, [redacted] Table 17 [redacted] for OS and ORR. Results for PFS and CR [redacted]

The unadjusted comparisons with Hong 2018 and GO29365 gave broadly similar results. [redacted] It also suggests that Hong being conducted in South Asia is not a cause of bias.

In the MAIC analysis against Hong 2018, [redacted] The Hong trial included patients with ECOG status over 2, who were absent from NP30179, and the analysis could not be adjusted for ECOG status. This could have led to biased results. [redacted] The effective sample size decreased from 139 unadjusted to 67.6 after adjustment.

The results of the MAIC were [redacted]

The company performed a propensity weighted analysis to compare BR in the GO29365 trial to glofitamab, but did not provide its results. This was on the grounds that the small sample size meant that any matching or weighting attempted was not robust. The EAG accepts that the analysis was unlikely to be robust, but considers that results should have been supplied for completeness.

Comparing the Kaplan-Meier curves for OS and PFS (Figure 12 and

Figure 13) suggests [redacted]

3.4.2.5 Pixantrone

The CS did not present any comparison between glofitamab and pixantrone. Only summary results were presented in the ITC appendix, so the robustness of the analysis is uncertain. The MAIC appeared to adjust for the major "high priority" prognostic factors, but not for any other factors. Patients with HGBCL and PMBCL histologies were excluded. The effective sample size for the MAIC was 42.7, reduced from 139 in the unadjusted comparison.

Results are given in Table 17. [redacted]

3.4.2.6 Tafa-len

The CS did not present any comparison between glofitamab and tafa-len. Only summary results were presented in the ITC appendix, so the robustness of the analysis is uncertain. The MAIC appeared to adjust for most "high priority" prognostic factors, but notably could not adjust for number of prior therapies, which could lead to bias. Patients with HGBCL and PMBCL histologies were excluded, as were patients with over four previous lines of therapy. The effective sample size for the MAIC was 34.6, reduced from 99 in the unadjusted comparison.

Results are given in Table 17 [redacted]

In the MAIC [redacted]

The EAG notes that tafa-len is the only comparator with [redacted] The ITC report notes that the L-MIND trial included patients with only one prior line of therapy, and many patients not refractory to previous therapies. This limited the scope to adjust the glofitamab data to match L-MIND, and may make both unadjusted and MAIC analyses unreliable.

The EAG notes that NICE guidance for tafa-len, rejecting its use was made public shortly before this report was completed, so tafa-len is no longer a relevant comparator. However, we retain discussion of it here for the sake of transparency.

3.4.2.7 Other comparators

Glofitamab was also compared to lenalidomide, lisocabtagene maraleucel and tisagenlecleucel in the ITC report, but these were not included in the CS or the NICE scope. The analyses were not reported in detail, so the robustness and validity of these comparisons is uncertain. See Table 17 for full results.

Lenalidomide was [redacted]

Lisocabtagene maraleucel was [redacted]

Tiagenelcleucel had [redacted]

3.5 Additional work on clinical effectiveness undertaken by the EAG

The EAG has performed two further small analyses: a meta-analysis of the 19 trials used as historical controls (mentioned at CS Page 43), and a comparison of glofitamab with a trial of R-GemOx.

3.5.1 Meta-analysis of "historical control" trials

In the CS a meta-analysis of CR was mentioned as: "CR rate based on a meta-analysis of 19 studies of R/R DLBCL." (CS Section B.2.4.1, Page 43). The EAG requested this meta-analysis but it was not provided. However, the relevant data on CR was reported in the company Statistical Analysis Plan (SAP, Table 1), where it was described as being used as historical control data from comparison with glofitamab. Figure 14 shows a forest plot of CR for all trials.

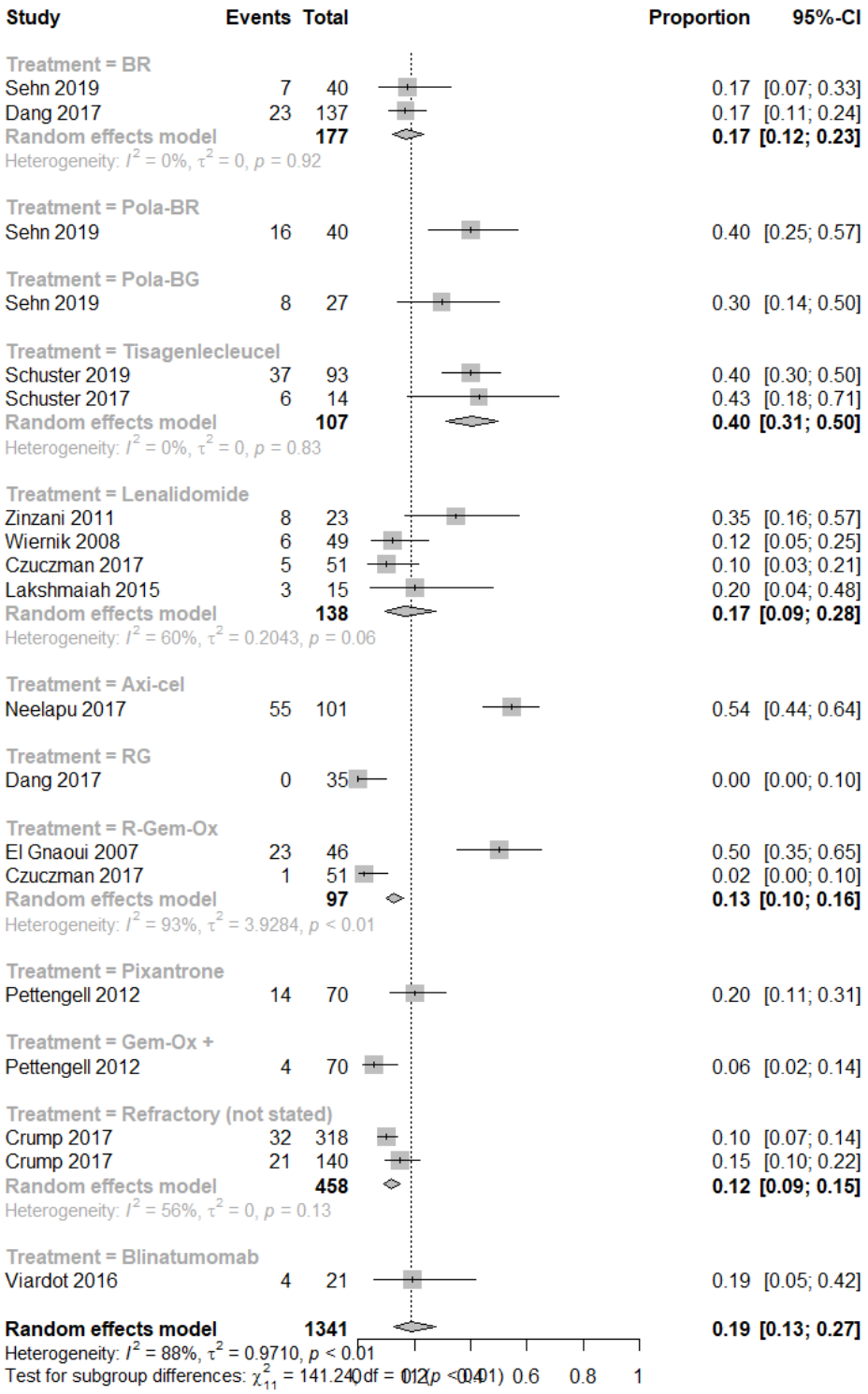
The EAG meta-analysis gives a summary CR of 19% (95% CI 13 to 27), which is marginally different from the 20% reported in the CS. The data included trials of CAR-T and polatuzumab-based treatments. As these are newer, efficacious therapies the EAG considers that including them in a

historical control analysis is unusual. We performed a meta-analysis of just those five trials (of axi-cel, tisagenlecleulcel, pola-BR and pola-BG); that gave a summary CR of 43% (95% CI 39 to 50).

Similarly the EAG performed a meta-analysis of the trials excluding those of CAR-T or polatuzumab (11 trials); that gave a summary CR of 14% (95% CI 9 to 21), but with evidence of substantial heterogeneity (I^2 = 78%).

Comparing these meta-analyses to the trial results for glofitamab (CR 35.2%; 95% CI 26.2 to 45.0) suggests that glofitamab is similar to, but may be inferior to, CAR-T and polatuzumab-based therapies. Glofitamab appears superior to other less-novel therapies (including pixantrone and BR). This is a simple unadjusted indirect comparison, but it is consistent with the findings of the formal indirect treatment comparisons (see Section 3.4.2).

Figure 14 Meta-analysis of "historical control" trials



3.5.2 The El Gnaoui trial of R-GemOx

The EAG noted that the analysis of "historical control" data (Section 3.5.1) included two trials of R-GemOx. On investigating further one of these, by El Gnaoui et al (2007),[11] appeared to be broadly eligible for inclusion in this assessment, and was included in the company's systematic review of R/R DBLCL. The company later clarified that this study did not meet the filtering criteria for histology used (80% DLBCL) to select suitable studies for the MAIC feasibility assessment. However, this raises some doubt regarding the claim in the CS that no suitable data on R-GemOx exists for comparison with glofitamab. (e.g. CS Table 1).

As the EAG only became aware of this trial from information included in the response to our points for clarification, it is currently unclear why this trial was not included in the indirect treatment comparisons performed for the CS. The EAG notes that the trial is somewhat old, having been published in 2007, and was small (a total of 44 patients).

Table 18 summarises the characteristics of the el Gnaoui trial, in comparison with the NP30179 trial. The el Gnaoui trial included patients on their second line of therapy, and patients generally had more severe disease, with many of ECOG status 2. It also had fewer patients of primary refractory status.

Table 18 Baseline characteristics of the el Gnaoui trial of R-GemOx

Factor		Glofitamab (NP30179)	R-GemOx (el Gnaoui)
Age		[redacted]	64
Sex	Female	[redacted]	33%
ECOG	ECOG 0 or 1	[redacted]	67%
	ECOG 2	[redacted]	33%
Histology	Diffuse	[redacted]	72%
	Follicular	[redacted]	17%
	Other	[redacted]	11%
Prior lines	1	[redacted]	34.80%
	2	[redacted]	37.00%
	3 or more	[redacted]	28.30%
Prior therapy	Radiotherapy	[redacted]	26%
Ann Arbor Stage	I or II	[redacted]	22%
	III or IV	[redacted]	78%
Primary refractory		[redacted]	13%

Error! Not a valid bookmark self-reference. summarises the results on CR and ORR reported by el Gnaoui et al, and compares them to results for glofitamab form the CS, where they are comparable.

[redacted]

[redacted]

[redacted].

Table 19 Summary of response outcomes from el Gnaoui trial of R-GemOx

	R-GemOx						Glofitamab		
	N. patients	CR/CRu		ORR			N. patients	CR	ORR
		N	%	N	%			%	%
Overall	46	23	50	38	83		[redacted]	[redacted]	[redacted]
Histological type									
Diffuse	33	19	58	27	82		[redacted]	[redacted]	
Follicular	8	3	38	6	75		[redacted]	[redacted]	
Mantle	5	1	20	5	100				
Previous lines of therapy									
1	16	7	44	12	75				
2	17	9	53	16	94		[redacted]	[redacted]	
3 or more	13	7	54	10	77		[redacted]	[redacted]	
Prior rituximab									
Yes	26	11	42	19	73		[redacted]	[redacted]	
No	20	12	60	19	95				
Duration of previous response									
Primary refractory	6	2	33	2	33		[redacted]	[redacted]	
<1 year	9	2	22	6	67				
>1 year	31	19	61	30	97				

** Assumed to be all patients in NP30179*

*** Refractory to previous line*

Error! Not a valid bookmark self-reference. shows digitally extracted Kaplan-Meier curves for OS and event-free survival (assumed equivalent to PFS) for R-GemOx and glofitamab.

[redacted] The EAG notes that this analysis is not adjusted for any possible confounders.

Figure 15 Kaplan-Meier curves (PFS and OS) for R-GemOx and glofitamab

. The EAG acknowledges that this is a naïve, unadjusted comparison, and may be biased by many factors differing between the two trials. Ideally, a MAIC should be used to compare these trials, but the EAG does not have access to the data to do this. The small sample size in the el Gnaoui trial may make an MAIC analysis uninformative, or unreliable.

3.6 Conclusions of the clinical effectiveness section

3.6.1 *The NP30179 trial*

Evidence for the safety and efficacy of glofitamab solely comes from NP30179 - a multicentre, open-label, Phase I/II study of escalating doses of glofitamab in patients with R/R B-cell non-Hodgkins lymphoma. As an uncontrolled study, it does not provide any evidence on the efficacy or safety of glofitamab to alternative treatment options.

While the trial included 17 patient cohorts, just three matched the decision problem and proposed marketing authorisation i.e. patients with DLBCL who had relapsed after or failed at least two prior systemic therapies and who were to be treated with an escalating dose of 2.5/10/30 mg glofitamab monotherapy. Though restriction to these cohorts reduced the available study sample size (n=155), the selection criteria were appropriate. Despite the study not including any UK centres, the study population appeared broadly similar to UK patients, though possibly with a slightly larger proportion of refractory compared to relapsed patients.

Results relating to the primary efficacy endpoint of IRC-assessed CR rate appear robust, as time to first complete response was consistently early (42 days, 95% CI: 42 to 44). There are insufficient data

to establish whether the small observed differences in CR rates between the patient cohorts are meaningful.

As stated in the CS, there appeared a trend towards higher CR rates were observed in patients with relapsed (non-refractory) disease. Some data indicate possible subgroup effects by sex and number of prior treatments, but small sample sizes and potential confounding mean that these are not definitive.

As the study is ongoing, some treatment duration and time-to-event values (e.g. duration of [complete] response, immature subgroup OS estimates) will change with further follow-up.

The CS conclusion that glofitamab was well-tolerated and demonstrated a manageable safety profile with a low incidence of treatment discontinuations due to AEs, appears reasonable based on the available evidence from NP30179. Immune effector cell-associated neurotoxicity syndrome (ICANS) data from the clinical study report were not reported in the CS. However, [redacted] and the overall risk of ICANS with glofitamab is likely to be low.

3.6.2 *Indirect treatment comparisons*

The company performed a large systematic review to inform the indirect treatment comparisons (ITC), which identified many trials of eligible treatments. However, in most cases only one trial was used per treatment comparison, which restricts interpretation and robustness of the ITCs. The EAG considers that the trials chosen for comparison were appropriate, being generally the largest trials that were most similar to the NP30179 trial of glofitamab.

The EAG considers that MAICs and propensity analyses appear to have been conducted appropriately, with correct statistical methods. The EAG has two minor concerns with the conduct of the ITCs. First, there was inconsistency in methods used to calculate confidence intervals between unadjusted and adjusted ITCs. This means the confidence intervals are not comparable between different analyses, and the true uncertainty around the analyses estimates remains unclear. Second, the CS only presented a single MAIC for most treatment comparisons, rather than a series of MAICs adjusting for different sets of confounding factors. While this is reasonable on space and brevity grounds, it does mean that the robustness of the MAICs to the choice of confounding factors is unclear.

[redacted], but this analysis was restricted to patients who received an axi-cel infusion. As patients may be selected for axi-cel therapy but not receive an infusion, this may be an unfair

comparison. [redacted]

[redacted]. The EAG notes that this conclusion differs slightly from that of the company.

The CS did not include a comparison with pixantrone or tafa-len. The EAG thinks these should have been included as both interventions were included in the NICE scope. MAIC analyses for both treatments were reported in supplementary material. [redacted]

The EAG notes that NICE guidance for tafa-len, rejecting its use was made public shortly before this report was completed, so tafa-len is no longer a relevant comparator. However, we leave discussion of it in this report for the sake of transparency. [redacted]

4 COST EFFECTIVENESS

4.1 EAG comment on company's review of cost-effectiveness evidence

This section will focus on the economic evidence submitted by the company and additional information provided in response to points for clarification (PfCs). The original CS included searches to identify cost-effectiveness evidence for patients with relapsed or refractory (R/R) DLBCL. A description of the searches and some of the search strategies were included in Appendix H (pp. 24-41).

In response to the EAG's PfCs, a further document was provided by the company, which included some additional strategies.

Please note that the EAG does not have access to the Evidence Based Medicine (EBM) Reviews database and therefore cannot fully scrutinise these strategies.

4.1.1 Search strategy

In 2016, the company had commissioned a systematic literature review to identify published economic evaluations in patients with DLBCL. This search was not restricted by line of therapy. The company therefore reviewed the initial search findings and updated the previous search strategy to identify additional economic evaluations in R/R DLBCL. The company provided details of the original SLR (September 2016) and two updated SLRs (August 2021, September 2022), and the review of these can be found in the appendix.

4.1.2 Identified studies

The company noted that studies excluded at full publication review for the original SLR also did not identify any relevant R/R DLBCL economic evaluations. Upon review of the studies included for the original SLR, the EAG notes these studies also did not identify any relevant R/R DLBCL economic evaluations.

SLR Updates 1 and 2 identified a total of 29 relevant economic evaluations for inclusion, which consisted of 19 full publications and 10 previous HTA submissions. Countries in which analysis were conducted included the US (n=11), Singapore (n=2), Switzerland (n=1), Japan (n=1), UK (n=1), Spain (n=1), Canada (n=1), and China (n=1). Patients with R/R DLBCL in the 3L+ setting were evaluated across 11 studies, 2L+ setting across 2 studies, and lines of treatment not specified across 6 studies. With the exception of 1 study, which evaluated mean costs and mean life days/survival time, the remaining studies conducted a cost-effectiveness analysis with ICERs reported as cost per QALY (n=18) and/or cost per LYG (n=12). Axi-cel was most commonly assessed (n=9 studies) relative to chemotherapy (n=4 studies), tisagenlecleucel (n=4 studies), and/or lisocabtagene maraleucel (n=2

studies). Pola-BR was assessed relative to BR in 2 studies and tafasitamab + lenalidomide in one study. Tisagenlecleucel was also assessed relative to salvage chemotherapy in five studies.

Table 15 of the company appendices provides additional information on the populations and treatment comparisons considered for this appraisal. A critical review of the searches conducted to identify cost-effectiveness evidence for patients with relapsed or refractory (R/R) DLBCL can be found in appendix.

4.1.2.1 Points for Critique

The company provided details of eligibility criteria and search strategies for the searches related to published cost-effectiveness studies. The EAG identified some issues with the clarity of reporting the searches, the appropriateness of the search terms used and the referencing of search filters, but has no major concerns about the search strategy.

4.2 Summary and critique of the company's submitted economic evaluation by the EAG

In this section, the EAG summarises and critiques all elements submitted by the company to support their cost-effectiveness results. Areas of uncertainty and/or issues with potential impact on the estimates of cost-effectiveness are emphasised in a series of numbered items, which are then revisited in Section 6.

4.2.1 NICE reference case checklist

Table 20 summarises the EAG's assessment of whether the company's economic evaluation meets NICE's reference case criteria.

Table 20 NICE reference case checklist

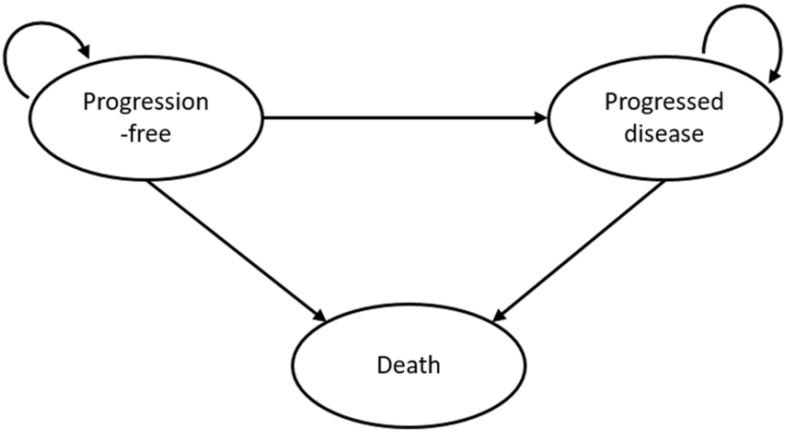
Element of health technology assessment	Reference case	EAG comment on company's submission
Perspective on outcomes	All direct health effects, whether for patients or, when relevant, carers	The CS is appropriate.
Perspective on costs	NHS and PSS	The CS is appropriate.
Type of economic evaluation	Cost–utility analysis with fully incremental analysis	The CS is appropriate.
Time horizon	Long enough to reflect all important differences in costs or outcomes between the technologies being compared	The CS is appropriate. The base case modelled patients according to the age distribution in the NP30179 trial. The time horizon was 60 years.
Synthesis of evidence on health effects	Based on systematic review	The CS is appropriate. As NP30179 was a single-arm trial, ITC methodology was used to obtain comparable survival data for

		comparators through unanchored MAICs and propensity score techniques.
Measuring and valuing health effects	Health effects should be expressed in QALYs. The EQ-5D is the preferred measure of health-related quality of life in adults.	The CS is appropriate.
Source of data for measurement of health-related quality of life	Reported directly by patients and/or carers	The CS is appropriate. No EQ-5D data was collected during NP30179. Indirect mapping was applied between EORTC (collected by patients in NP30179) and EQ-5D-3L using Longworth et al. 2014 algorithm. [12]
Source of preference data for valuation of changes in health-related quality of life	Representative sample of the UK population	The CS is appropriate. The EORTC to EQ-5D-3L mapping utilised a UK tariff.
Equity considerations	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit	The CS is appropriate.
Evidence on resource use and costs	Costs should relate to NHS and PSS resources and should be valued using the prices relevant to the NHS and PSS	The CS is appropriate. The cost perspective and evidence used to inform costing is appropriate. The EAG notes in the relevant sections where costs may have not been appropriately captured.
Discounting	The same annual rate for both costs and health effects (currently 3.5%)	The CS is appropriate.
Abbreviations: PSS: personal social services; MAIC: match-adjusted indirect comparisons; PSA: propensity score analysis; QALYs: quality-adjusted life years; EQ-5D: standardised instrument for use as a measure of health outcome.		

4.2.2 Model structure

The Company developed a *de novo* partitioned survival model with three health states: progression free (PF), progressed disease (PD), and the absorbing health state death. All patients entered the model in the PF health state and remained in this health state until their disease progressed, or they died. Once progressed, patients could not transition back to the progression free disease state (Figure 16).

Figure 16 Model structure



The proportion of patients in each health state were estimated using standard parametric survival models fit to PFS from the NP30179 trial and via indirect treatment comparison (ITC) analysis. The proportion of patients in the death health state were determined using OS curves directly and those in the PD health state were determined using the difference in area between the OS and PFS curves. Time to off treatment (TTOT) data from NP30179 were used to estimate treatment discontinuation with glofitamab. For the BR and Pola-BR comparators, TTOT was determined using data for 3L+ patients from the GO29365 trial. For axi-cel, the duration on treatment was assumed to last for a single model cycle. For other treatments, TTOT was set equal to the treatment-specific maximum number of cycles.

Baseline population parameters for the modelled population are provided in Table 30 of the CS. The model utilised weekly cycles with half-cycle correction. Background mortality was modelled as a function of the age distribution and treatment-related AEs with a severity grade of 3 and higher were costed. The company justified use of the age distribution of patients versus the use of the mean cohort age approach for background mortality as they considered this approach to better reflect the slower increase in the average age of the cohort and the associated risks of death by age.

Model outcomes assessed total costs, total LY, total QALYs, and the incremental cost-effectiveness ratio and net monetary benefit at specific cost-effectiveness threshold values.

Points for Critique

The company's model aligns with the NICE reference case and was structured according to guidance provided in TSD 19.[13] Although no EQ-5D data was collected directly during the NP30179 trial, indirect mapping was applied between EORTC (collected by patients in NP30179) and EQ-5D-3L, and the mapping algorithm utilised a UK tariff – see section 4.2.8.

4.2.3 Population

Glofitamab is indicated for adults with relapsed or refractory diffuse large B-cell lymphoma who have had two or more systemic treatments. Proposed positions for glofitamab in the current treatment pathway include: 3L+ treatment line ahead of CAR-T therapy, patients ineligible for CAR-T therapy, or patients who have failed CAR-T therapy in prior treatment lines. Glofitamab is not intended to replace existing treatments, but to provide an additional line of treatment so patients may be eligible for other treatments after receiving glofitamab.

Points for Critique

The EAG is satisfied the population under consideration for this appraisal represents the eligible population for treatment with glofitamab in the UK.

4.2.4 Interventions and comparators

The key intervention under review was glofitamab. Comparators included: rituximab-based chemotherapy (bendamustine plus rituximab (BR)), which was provided as a proxy for rituximab with gemcitabine and oxaliplatin (R-GemOx) due to lack of evidence and similar efficacy; Polatuzumab vedotin with rituximab and bendamustine (pola-BR); and axicabtagene ciloleucel (axi-cel), a CAR T-cell therapy.

Points for Critique

The EAG notes that the final scope issued by NICE included additional comparators for review, e.g., pixantrone monotherapy and tafasitamab with lenalidomide and notes the company's rationale for excluding these as comparators for this appraisal. The EAG is satisfied the comparators included were most relevant for this appraisal, and this was validated by the EAG's clinical advisor.

4.2.5 Perspective, time horizon and discounting

In line with the NICE reference case criteria, this analysis utilised a National Health Service and Personal Social Services perspective, with a lifetime time horizon (60 years) and costs and outcomes discounted annually at 3.5%.

Points for Critique

The company's perspective, time horizon and discounting for the economic modelling is aligned with the NICE reference case.

4.2.6 Treatment effectiveness and extrapolation

This section considers the following aspects of treatment effectiveness: (i) synthesis of effectiveness evidence, (ii) company's approach to survival analysis, (iii) long-term remission/survivorship, (iv) treatment discontinuation, and (v) adverse events.

Synthesis of effectiveness evidence

Given the characteristics of the pivotal trial NP30179 for glofitamab, a series of ITCs were conducted to provide comparative effectiveness evidence (PFS and OS) versus relevant comparators. The company employed two ITC approaches:

- an unanchored MAIC of individual arms for when published aggregate data were available (comparators: Axi-cel and BR);

- a propensity score analysis for the comparator with available patient-level data (comparator: Pola-BR) using propensity matching methods and the inverse probability of treatment weighting.

Details on these ITC methods are provided and discussed in Sections 3.3 and 3.4, respectively. Details specific to the model implementation are explained below.

For axicabtagene ciloleucel, an unanchored MAIC used ZUMA-1,[14] controlling for all identified and available prognostic factors and modifiers of effect labelled as of high and medium priority in the base case. For bendamustine plus rituximab, an unanchored MAIC used Hong 2018,[9] controlling also for identified and available prognostic factors and effect modifiers labelled as of high and medium priority in the base case, expect for ECOG status. Finally, for polatuzumab-vedotin plus bendamustine plus rituximab, a propensity score approach used the study GO29365, with (high, medium, and low priority) covariate balance better achieved with full matching and inverse probability of treatment weighting. The EAG notes that a propensity score analysis approach was attempted for bendamustine plus rituximab using the patient-level data available from the study GO29365.The propensity scores estimated with this approach featured very poor overlap, which was partially addressed by matching and inverse probability of treatment weighting. However, this was achieved at the costs of small ESS (≤21) for bendamustine plus rituximab. See Sections 3.3 and 3.4 for further detail.

Table 21 provides a summary of the ITC results used within the economic model (data extracted from CS, Appendix I, Tables 1 and 2). The HRs for OS and PFS favour axicabtagene ciloleucel versus glofitamab in both adjusted models, with the former showing statistical significance. The HRs for OS and PFS strongly favour glofitamab versus bendamustine plus rituximab in both adjusted models. The HRs for OS and PFS strongly favour glofitamab versus bendamustine plus rituximab in both adjusted models. The HRs for OS and PFS point to similar efficacy between glofitamab and pola-BR irrespective of the propensity score analysis performed. Similar results were also obtained for the

unadjusted models, which highlights the limited impact of adjusting for prognostic and effect modification factors.

Table 21 Summary of the ITC results informing the economic model (company's preferred estimates in bold)

Comparator (source of data)	Cohort details		Method of estimation	ITC results for the comparison of glofitamab vs comparator	
				OS HR, median (95% CI)	PFS HR, median (95% CI)
Axicabtagene ciloleucel ZUMA-1 (N=101)	ESS = ~27.9 (Glofitamab unweighted, n=115)		**Unanchored MAIC, covariate adjusted, bootstrap percentile CI (base-case)**	[redacted]	[redacted]
			Unanchored MAIC, covariate adjusted, bootstrap BCa CI	[redacted]	[redacted]
Bendamustine plus rituximab Hong et al 2018 (N=58)	ESS = ~67.6 (Glofitamab unweighted, n=139)		**Unanchored MAIC, covariate adjusted, bootstrap percentile CI (base-case)**	[redacted]	[redacted]
			Unanchored MAIC, covariate adjusted, bootstrap BCa CI	[redacted]	[redacted]
Polatuzumab-vedotin plus bendamustine plus rituximab GO29365 (N=152)	Glof. filtered, n=149 Pola-BR filtered, n=84	Glof. ESS = ~97.7 Pola-BR ESS = ~24.2	Propensity score analysis, full matching plus covariate adjustment (ATE)	[redacted]	[redacted]
		Glof. ESS = ~123 Pola-BR ESS = ~53.9	**Propensity score analysis, inverse probability of treatment weighting (base-case)**	[redacted]	[redacted]

Abbreviations: ATE, average treatment effect; BCa, bias corrected accelerated; CI, confidence interval; FL, Follicular lymphoma; Glof., glofitamab; HR, hazard ratio; MAIC, matching-adjusted indirect comparison; PFS, progression-free survival; OS, overall survival. *as assessed by the investigator; **as assessed by the independent review committee

Points for critique

In the company's economic model under base-case assumptions, the relative effect of each comparator vs. glofitamab is obtained via the independent modelling of PFS and OS of the comparator data and the glofitamab adjusted populations (i.e. the ITC-adjusted glofitamab populations), assuming non-proportionality of hazards. If PH is assumed, PFS and OS HRs derived from the ITC analysis (Table 21) are directly used in the model to obtain adjusted OS and PFS parametric estimates for each comparator. Assuming PH holds, the use of the company's preferred PFS and OS HR estimates from the ITC analysis results in an ICER vs BR of [redacted] (£/QALY gained, 38.9% increase from company's base-case after clarifications), an ICER vs axi-cel of [redacted] (£/QALY

gained SW quadrant, 8.5% decrease from company's base-case after clarifications), and with glofitamab still [redacted] vs. Pola-BR.

As highlighted above, the EAG has several concerns relating to the ITC analysis presented by the company (Section 3.3). EAG list of concerns include: the use of three different sources of data for each of the three comparisons of interest; the company's preferred choice of data (Hong et al 2018) [9] for the adjusted comparison with BR; and the use of a different confidence interval estimation method (i.e. bootstrap) between adjusted and unadjusted HR estimates in the ITC analysis.

To promote consistency between comparisons, at points for clarification the EAG questioned the company on the reasons behind not using the same data source for indirectly comparing glofitamab with BR as it did for the comparison with Pola-BR, i.e. the use of PFS and OS data from the GO29365 study for the comparison of glofitamab with BR and with Pola-BR. The company clarified that the use of the randomised DLBCL cohort from GO29365 (n=40) for indirectly comparing glofitamab with BR, reduced the BR arm sample size to 21, after inclusion/exclusion criteria alignment with NP30179 patient characteristics. Furthermore, the company highlighted that, irrespective of the matching methodology used, the approach was unsuccessful in accomplishing an acceptable covariate balance, resulting in low (<10) ESSs. Thus, the company did not provide adjusted HR estimates for the comparison with BR to the EAG, only unadjusted estimates (Table 25 for OS and Table 27 for PFS, CS Appendix D – ITC Technical report). The EAG notes that for all comparisons, the OS and PFS HR point estimates for when performing and not performing covariate adjustment, either via unanchored MAIC or Propensity Score Analysis, are noticeably similar (Tables for OS: 6, 16 and 42; and for PFS: 7, 17 and 43 for each comparison, respectively; CS Appendix D – ITC Technical report). This indicates that the ITC adjustments have minor impact on the PFS and OS derived estimates, and the EAG question the extent to which any adjustments are necessary given the small ESSs these generate, particularly for axi-cel. The use of the PFS and OS ITC unweighted/unadjusted estimates across all comparisons enables the use of data from the GO29365 study for the comparison with BR instead of the adjusted estimates derived from Hong et al 2018 [9] Although, the EAG fully acknowledges that these PFS and OS HR estimates from 'naïvely' comparing glofitamab with alternatives would carry additional biases into the economic model and its results.

Furthermore, the EAG is concerned with the face validity of the OS and PFS adjusted ITC estimates that indirectly compare glofitamab with BR and glofitamab with Pola-BR, and the degree to which these are reflective of the most recent findings of Sehn et al (2022)[15] when analysing the GO29365 study. The EAG notes that Sehn et al (2022){Sehn, 2022 #496 identified a significant survival benefit with Pola-BR vs BR in the randomised DLBCL cohort from GO29365, with a PFS HR of 0.39 (0.23-0.66) and OS HR of 0.42 (0.24-0.72). Given these findings, the EAG believes that the ITC should

have indicated an even stronger evidence in support of glofitamab being superior to BR in progression-free and overall survival.

Item 1: The use of three different sources of data to indirectly compare glofitamab with alternative treatments hinders consistency within the ITC analysis framework.

Item 2: The ITC PFS and OS HR estimates for the indirect comparison of glofitamab with BR and of glofitamab with Pola-BR for may not be reflective of the most recent findings of Sehn et al (2022) when analysing the GO29365 study.

Company's approach to survival analysis

After the ITC were conducted, the company proceeded as follows:

1. KM curves for OS and PFS were scanned and digitised and individual patient data was simulated using Guyot et al{Guyot, 2012 #526} algorithm;
2. For each set of reconstructed comparator data and the glofitamab data, the proportional hazards (PH) assumption was assessed to determine the suitability of the application of HRs and parametric assumptions;
3. If PH holds, the ITC estimated HRs for OS and PFS were inversed and applied on to the respective best fitting glofitamab OS and PFS weighted population curves, to obtain adjusted OS and PFS parametric estimates for each comparator. The approach relies on the PH assumption between glofitamab population and matched populations;
4. When the PH assumption (between glofitamab and a comparator) was considered violated, individual parametric models were fitted to the reconstructed patient data for all comparators. The company further claims that independent model fitting was performed for all comparators and outcomes, except for time to off treatment (TTOT). Furthermore, it states that the HRs generated by the ITC are included in the economic model despite the PH assumption not being always met. The independent modelling of OS and PFS curves for each comparison was considered for the company's base case;
5. Several parametric distributions were fitted independently to the glofitamab adjusted and comparator data, including: exponential, Weibull, Log-normal, Generalised gamma, Log-logistic, Gompertz and 2-parameter gamma. Parametric extrapolation curves, beyond the clinical follow-up period, were obtained. Parametric extrapolations for each treatment were selected based on AIC and BIC, visual fit, and assessed for clinical plausibility by the company's clinical advisors. Bayesian average models and piece-wise models (Kaplan Meier + extrapolation standard parametric models) were also included in the electronic model, which the company included for

completeness, as stated in the response to clarifications. Furthermore, and at response to clarifications, flexible parametric models were fitted independently by the company for all comparisons. The company tested up to three internal knots and selected the approach that offered the best combination between lowest AIC, visual fit, and model complexity. The company also fitted mixture cure models (MCMs) as requested by the EAG at points for clarification. MCMs were fitted to the comparison where individual patient data were available and used in the ITC for both treatment arms, that is, fitted to the comparison between glofitamab and Pola-BR.

6. The economic model allows the estimation of the cost-effectiveness outcomes to be derived from the comparison with the Glofitamab trial ITT population or with the corresponding ITC-adjusted glofitamab populations, with the latter selected as the company's base case.

4.2.6.3 Glofitamab populations

4.2.6.3.1 Progression free survival

For the PFS curve of the glofitamab unweighted population the company considered the generalised gamma as the standard parametric distribution providing the best fit both visually and according to AIC and BIC statistics (Figure 15 and Table 32 of the CS). The company also considered the generalised gamma as the best fitting curve for all PFS adjusted glofitamab populations. The Log-normal and Gompertz distributions also provided a good fit. Both the generalised gamma and the Gompertz were clinically validated by the company's clinical advisors as providing the best fit.

The company also fitted flexible parametric spline models to PFS for all three glofitamab adjusted populations, concluding that the 2-knot, 3-knot and 1-knot were the best fitting models for the glofitamab axi-cel, BR and Pola-BR adjusted PFS data, respectively. MCMs were fitted to the glofitamab Pola-BR adjusted PFS data, with the company considering the Log-normal MCM to offer the best fit. The estimated cure fraction for the Log-normal MCM suggests that approximately 21% of patients receiving glofitamab (Pola-BR adjusted) achieve a long-term remission. As MCMs were fitted only to the comparison between glofitamab and Pola-BR the company decided to not consider the results of MCMs in their base case.

Please see Table 22 for a summary of the company justification for selected PFS glofitamab extrapolation curves. The table shows considerations over the goodness of visual fit, statistical fit and clinical plausibility. Goodness of visual fit and statistical fit are presented per model type, with the later based on AIC statistic within 5 points from the parametric distribution with lowest AIC value. Clinical plausibility considers the input provided from the company's clinical advisors.

Table 22 Summary of company justification for selected PFS Glofitamab extrapolation curves

Treatment	Survival model type*	Cure fraction	Parametric curve	Goodness of visual fit**	Best statistical fit***	Clinical plausibility
Glofitamab unadjusted	Standard Parametric	NA	Exponential	No	No	No
			Weibull	No	No	No
			Log-normal	Yes	Yes	No
			Gen Gamma (BC)	**Yes**	**Yes**	**Yes**
			Log-logistic	Yes	No	No
			Gompertz	Yes	No	Yes
			Gamma	No	No	No
	Flexible Parametric (Splines)	NA	1-knot	Yes	Yes	Unknown
			2-knot	Yes	Yes	Unknown
			3-knot	Yes	Yes	Unknown
	Mixture-cure	NA	not implemented	NA	NA	NA
Glofitamab Axi-cel adjusted	Standard Parametric	NA	**Gen Gamma (BC)**	**Unknown**	**No**	**Unknown**
	Flexible Parametric (Splines)	NA	1-knot	No	Yes	Unknown
			2-knot	No	Yes	Unknown
			3-knot	No	Yes	Unknown
	Mixture-cure	NA	not implemented	NA	NA	NA
Glofitamab BR adjusted	Standard Parametric	NA	**Gen Gamma (BC)**	**Unknown**	**Yes**	**Unknown**
	Flexible Parametric (Splines)	NA	1-knot	Yes	Yes	Unknown
			2-knot	Yes	Yes	Unknown
			3-knot	Yes	Yes	Unknown
	Mixture-cure	NA	not implemented	NA	NA	NA
Glofitamab Pola-BR adjusted	Standard Parametric	NA	**Gen Gamma (BC)**	**Unknown**	**Yes**	**Unknown**
	Flexible Parametric (Splines)	NA	1-knot	Yes	Yes	Unknown
			2-knot	Yes	Yes	Unknown
			3-knot	Yes	Yes	Unknown
	Mixture-cure	25.7%	Weibull	No	No	Unknown
		21.3%	Log-normal	Yes	Yes	Unknown
		22.3%	Gen Gamma	Yes	No	Unknown
		14.9%	Log-logistic	Yes	Yes	Unknown
		26.5%	Gompertz	No	Yes	Unknown
		13.7%	Gamma	No	No	Unknown

* Independent modelling of curves; ** Goodness of visual fit per model type; *** Best statistical fit per model type based on AIC statistic and within 5 points from lowest AIC value; Abbreviations: BC: base-case, Gen: generalised

4.2.6.3.2 Overall Survival

Similar to PFS, for the OS curve of the glofitamab unweighted population the company considered the generalised gamma as the parametric distribution of choice due to reasonable long-term predictions, despite the Log-normal and Gompertz providing the best statistical fit according to AIC and BIC statistics (Figure 16 and Table 32 of the CS). The company also considered the generalised

gamma to be the best fitting curve for all OS adjusted glofitamab populations, while the company's clinical experts considered the Gompertz to be clinically plausible.

The company indicates also that the fitting of spline models with 1-knot, 1-knot and 3-knot were the best fitting models for the glofitamab axi-cel, BR and Pola-BR adjusted OS data, respectively. MCMs were fitted to the glofitamab Pola-BR adjusted OS data, with the company considering the Log-logistic MCM to offer the best fit. The estimated cure fraction for the Log-logistic MCM suggests that approximately 22% of patients receiving glofitamab (Pola-BR adjusted) achieve a long-term remission. As highlighted, MCMs were fitted only to the comparison between glofitamab and Pola-BR and, thus, the company decided to not consider the results of MCMs in their base case.

Please see Table 23 for a summary of the company justification for selected OS Glofitamab extrapolation curves.

Table 23 Summary of company justification for selected OS Glofitamab extrapolation curves

Treatment	Survival model type*	Cure fraction	Parametric curve	Goodness of visual fit**	Best statistical fit***	Clinical plausibility
Glofitamab	Standard Parametric	NA	Exponential	No	No	No
			Weibull	No	No	No
			Log-normal	Yes	Yes	No
			Gen Gamma (BC)	**Yes**	**Yes**	**No**
			Log-logistic	Yes	Yes	No
			Gompertz	Yes	Yes	Yes
			Gamma	No	No	No
	Flexible Parametric (Splines)	NA	1-knot	Yes	Yes	Unknown
			2-knot	Yes	Yes	Unknown
			3-knot	Yes	Yes	Unknown
	Mixture-cure	NA	not implemented	NA	NA	NA
Glofitamab Axi-cel adjusted	Standard Parametric	NA	**Gen Gamma (BC)**	**Unknown**	**Yes**	**Unknown**
	Flexible Parametric (Splines)	NA	1-knot	No	Yes	Unknown
			2-knot	No	Yes	Unknown
			3-knot	No	Yes	Unknown
	Mixture-cure	NA	not implemented	NA	NA	NA
Glofitamab BR adjusted	Standard Parametric	NA	**Gen Gamma (BC)**	**Unknown**	**Yes**	**Unknown**
	Flexible Parametric (Splines)	NA	1-knot	No	Yes	Unknown
			2-knot	No	Yes	Unknown
			3-knot	No	Yes	Unknown
	Mixture-cure	NA	not implemented	NA	NA	NA
Glofitamab Pola-BR adjusted	Standard Parametric	NA	**Gen Gamma (BC)**	**Unknown**	**Yes**	**Unknown**
	Flexible Parametric (Splines)	NA	1-knot	Yes	Yes	Unknown
			2-knot	Yes	Yes	Unknown
			3-knot	Yes	Yes	Unknown

Treatment	Survival model type*	Cure fraction	Parametric curve	Goodness of visual fit**	Best statistical fit***	Clinical plausibility
	Mixture-cure	25.7%	Weibull	No	Yes	Unknown
		21.3%	Log-normal	No	Yes	Unknown
		22.3%	Gen Gamma	No	Yes	Unknown
		14.9%	Log-logistic	No	Yes	Unknown
		26.5%	Gompertz	No	Yes	Unknown
		13.7%	Gamma	No	No	Unknown

* Independent modelling of curves; ** Goodness of visual fit per model type; *** Best statistical fit per model type based on AIC statistic and within 5 points from lowest AIC value; Abbreviations: BC: base-case

4.2.6.3.3. Points for critique

Irrespective of the quality of the adjustments performed to achieve comparability between glofitamab and relevant comparators, the EAG is concerned with the use of what, in effect, are three different cuts of the original glofitamab trial data representing different glofitamab sub-samples, each one being used for each comparison, i.e. a ESS of 27.9 (via unanchored MAIC) for the axicabtagene ciloleucel comparison, a ESS of 67.6 (via unanchored MAIC) for the BR comparison and a ESS of 123 (via PSA - IPTW) for the Pola-BR comparison. The EAG believes that this brings additional uncertainty to the modelling framework and resulting cost-effectiveness results. Furthermore, with exception of the OS glofitamab population axi-cel adjusted, the impact of these population adjustments is marginal, with the PFS and OS KMs for both glofitamab trial and adjusted populations being very similar –

Figure 17a and

Figure 18a. This issue, together with the added uncertainties brought by the ITC analysis, makes the EAG question the validity of each of the adjusted comparisons. The EAG highlights that, under these circumstances, a naïve and unadjusted comparison of each comparator data with the glofitamab ITT trial population may also be relevant in aiding the committee's decision-making process.

The choice between the use of the glofitamab ITC/adjusted populations (company's base-case) and glofitamab ITT trial population is enabled within the company's economic model. With the company's preferred (base-case) assumptions for survival extrapolation and cure, the use of glofitamab ITT trial population in the comparisons results in an ICER vs BR of [redacted] (£/QALY gained, 70% increase from company's base-case after clarifications), an ICER vs axi-cel of [redacted] (£/QALY gained SW quadrant, 17.6% decrease from company's base-case after clarifications), and with glofitamab still [redacted] vs Pola-BR.

The use of the standard parametric generalised gamma model as the preferred choice for survival extrapolation by the company for all adjusted and unadjusted glofitamab populations may be overestimating the survival benefits of glofitamab relative to comparators, particularly extrapolated benefits on OS –

Figure 17b and

Figure 18b. The EAG considers reasonable to assume the same parametric distribution for all glofitamab populations, nevertheless, and as highlighted by the company and for OS, different long-term predictions are obtained across populations when using the best fitting parametric distributions (generalised gamma, Gompertz and Log-normal), with subsequent impact on the cost-effectiveness outcomes. As highlighted in section 0, there is uncertainty around the assumptions relating to long-

term remission/survivorship, and long-term survival predictions will be more impactful when no long-term remission/survivorship is assumed. Table 24 provides the model overall survival estimates at 3, 5, 10 and 20 years, when no long-term remission/survivorship is assumed and for when PFS and OS glofitamab adjusted populations are fitted with the generalised gamma (company's base case), the Log-normal and the Log-logistic. As shown in Table 24, out of the three parametric distributions fitted, the generalised gamma provides the most optimistic overall survival estimates across time.

Table 24 Overall survival model predictions when using different parametric distributions for glofitamab adjusted populations for when assuming no long-term remission/survivorship

Glofitamab adjusted population	Overall survival of glofitamab adjusted populations (OS, %) - No long-term remission/survivorship											
	Generalised Gamma (PFS & OS)				Log-normal (PFS & OS)				Log-logistic (PFS & OS)			
	3 years	5 years	10 years	20 years	3 years	5 years	10 years	20 years	3 years	5 years	10 years	20 years
BR adj	31.4%	24.3%	16.8%	9.9%	25.6%	16.4%	7.8%	3.1%	24.2%	15.5%	8.0%	3.9%
Pola-BR adj	26.9%	17.8%	9.1%	4.0%	26.4%	17.2%	8.4%	3.5%	24.2%	15.5%	7.9%	3.8%
Axi-cel adj	29.2%	23.0%	16.2%	9.6%	25.2%	17.4%	9.5%	4.6%	24.2%	16.9%	9.9%	5.3%

Abbreviations: OS: overall survival; PFS: progression free survival; BR: bendamustine plus rituximab; Pola-BR: polatuzumab vedotin in combination with bendamustine and rituximab; Axi-cel: axicabtagene ciloleucel; adj; adjusted.

Although acknowledging the efforts made by the company in implementing flexible parametric spline models to all glofitamab populations at clarification stage, the EAG understands that these models achieve similar or slightly better fitting to that of the standard parametric models. The EAG agrees with the company that, while these models may have displayed stronger statistical fit to observed survival data, overfitting may occur and clinically unrealistic extrapolations in the long-term may be produced, and thus not reflecting the clinical mechanisms underlying the observed hazards over time.

Please see EAG's full critique on the use of MCMs for survival extrapolation in Section 0 on the comparison of glofitamab and pola-BR and Section 0 on the long-term remission/survivorship.

Item 3: The use of 3 different (adjusted) glofitamab populations by the company, one for each comparison, to indirectly compare the effectiveness of comparators relative to glofitamab adds considerable uncertainty to the cost-effectiveness results.

Item 4: The use of the generalised gamma as the preferred choice for survival extrapolation by the company for all adjusted and unadjusted glofitamab populations may be overestimating the OS benefits of glofitamab relative to Pola-BR and Axi-cel

Figure 17 PFS a) KM; and b) company's base-case (i.e. Gen-Gamma) parametric extrapolations over 10 years (with no 'cure' assumption) for glofitamab trial (unadjusted) and glofitamab ITC (adjusted) populations

Figure 18 OS a) KM; and b) company's base-case (i.e. Gen-Gamma) parametric extrapolations over 10 years (with no 'cure' assumption) for glofitamab trial (unadjusted) and glofitamab ITC (adjusted) populations

4.2.6.4 Glofitamab vs axicabtagene ciloleucel

The comparison between glofitamab and axi-cel is informed by a small MAIC adjusted glofitamab population (ESS, n=27.9) and the unadjusted axicabtagene ciloleucel population (n=101).

4.2.6.4.1 Progression free survival

The PFS KM for glofitamab (adjusted) and axi-cel (unadjusted) shows glofitamab being consistently estimated to be less effective than axi-cel. The PH assumption was assumed valid through Schoenfeld testing, but rejected based on the log-log plot, with the company opting for fitting curves to PFS data independently.

The company considered the generalised gamma as the best fitting standard parametric distribution for the PFS glofitamab axi-cel adjusted population data and the Gompertz distribution to model axi-cel PFS. Splines models applied to glofitamab axi-cel adjusted population PFS data led to implausible long-term predictions with PFS crossing with OS curves. The 2-knot model deemed by the company as the flexible parametric model providing the more 'realistic' predictions for both PFS glofitamab axi-cel adjusted and PFS axi-cel data. MCMs were not fit to PFS glofitamab axi-cel adjusted or PFS axi-cel data.

Please see Table 25 for a summary of the company justification for selected PFS axi-cel extrapolation curves.

4.2.6.4.2 Overall Survival

Similar to PFS, the OS KMs for the axi-cel adjusted glofitamab population and for axi-cel show glofitamab being consistently estimated to be less effective than axi-cel over time (Figure 20 of the CS). The PH assumption was assessed by the company to be valid, although for consistency OS distributions for glofitamab and axi-cel were independently fitted by the company in their base-case analysis.

The company's clinical advisors highlighted the expectation for a difference in OS when comparing the glofitamab ITT OS data with the axi-cel mITT cohort and agreed that Gompertz produced the most plausible OS estimates for axi-cel, being that the distribution chosen for the extrapolation of OS axi-cel data. Spline models were also fit by the company at clarification stage, with 1-knot spline model for glofitamab axi-cel adjusted OS data and the 3-knots model for axi-cel OS data the preferred choices. MCMs were not fit to OS glofitamab axi-cel adjusted or OS axi-cel data.

Please see Table 26 for a summary of the company justification for selected OS axi-cel extrapolation curves.

Table 25 Summary of company justification for selected PFS comparators' extrapolation curves

Treatment	Survival model type*	Cure fraction	Parametric curve	Goodness of visual fit**	Best statistical fit***	Clinical plausibility
Axi-cel	Standard Parametric	NA	Exponential	No	No	No
			Weibull	No	No	No
			Log-normal	No	No	No
			Gen Gamma	Yes	No	No
			Log-logistic	No	No	No
			Gompertz (BC)	**Yes**	**Yes**	**Yes**
			Gamma	No	No	No
	Flexible Parametric (Splines)	NA	1-knot	Yes	Yes	Unknown
			2-knot	Yes	Yes	Unknown
			3-knot	Yes	Yes	Unknown
	Mixture-cure	NA	not implemented	NA	NA	NA

BR	Standard Parametric	NA	Exponential	No	No	Yes
			Weibull	No	No	No
			Log-normal	Yes	Yes	Yes
			Gen Gamma	No	Yes	No
			Log-logistic (BC)	**Yes**	**Yes**	**Yes**
			Gompertz	No	No	No
			Gamma	No	No	No
	Flexible Parametric (Splines)	NA	1-knot	Yes	Yes	Unknown
			2-knot	Yes	Yes	Unknown
			3-knot	Yes	Yes	Unknown
	Mixture-cure	NA	not implemented	NA	NA	NA
Pola-BR	Standard Parametric	NA	Exponential	No	No	No
			Weibull	No	No	No
			Log-normal	Yes	Yes	No
			Gen Gamma (BC)	**Yes**	**Yes**	**Yes**
			Log-logistic	Yes	Yes	No
			Gompertz	No	No	Yes
			Gamma	No	No	No
	Flexible Parametric (Splines)	NA	1-knot	Yes	Yes	Unknown
			2-knot	Yes	Yes	Unknown
			3-knot	Yes	Yes	Unknown
	Mixture-cure	8.0%	Log-normal	Yes	Yes	Unknown
		8.5%	Log-logistic	Yes	Yes	Unknown
		0.0%	Gen Gamma	Yes	Yes	Unknown

* Independent modelling of curves; ** Goodness of visual fit per model type; *** Best statistical fit per model type based on AIC statistic and within 5 points from lowest AIC value; Abbreviations: BC: base-case; Gen: generalised

Table 26 Summary of company justification for selected OS comparators' extrapolation curves

Treatment	Survival model type*	Cure fraction	Parametric curve	Goodness of visual fit**	Best statistical fit***	Clinical plausibility
Axi-cel	Standard Parametric	NA	Exponential	No	No	No
			Weibull	No	No	No
			Log-normal	No	No	No
			Gen Gamma	No	No	No
			Log-logistic	No	No	No
			Gompertz (BC)	**Yes**	**Yes**	**Yes**
			Gamma	No	No	No
	Flexible Parametric (Splines)	NA	1-knot	No	Yes	Unknown
			2-knot	No	Yes	Unknown
			3-knot	No	Yes	Unknown
	Mixture-cure	NA	not implemented	NA	NA	NA
BR	Standard Parametric	NA	Exponential	No	No	No
			Weibull	No	No	No

			Log-normal (BC)	**Yes**	**Yes**	**No**
			Gen Gamma	No	Yes	No
			Log-logistic	Yes	Yes	No
			Gompertz	No	Yes	Yes
			Gamma	No	No	Yes
	Flexible Parametric (Splines)	NA	1-knot	No	Yes	Unknown
			2-knot	No	Yes	Unknown
			3-knot	No	Yes	Unknown
	Mixture-cure	NA	not implemented	NA	NA	NA
Pola-BR	Standard Parametric	NA	Exponential	No	No	No
			Weibull	No	No	No
			Log-normal (BC)	**Yes**	**Yes**	**No**
			Gen Gamma	Yes	Yes	Yes
			Log-logistic	Yes	Yes	No
			Gompertz	Yes	Yes	No
			Gamma	No	No	No
	Flexible Parametric (Splines)	NA	1-knot	Yes	Yes	Unknown
			2-knot	Yes	Yes	Unknown
			3-knot	Yes	Yes	Unknown
	Mixture-cure	8.0%	Log-normal	No	Yes	Unknown
		8.5%	Log-logistic	No	Yes	Unknown
		0.0%	Gen Gamma	Yes	Yes	Unknown

* Independent modelling of curves; ** Goodness of visual fit per model type; *** Best statistical fit per model type based on AIC statistic and within 5 points from lowest AIC value; Abbreviations: BC: base-case

4.2.6.4.3 Points for critique

The modified intention-to-treat (mITT) ZUMA-1 population was used for the comparison between glofitamab and axi-cel. As reported by the company, the mITT ZUMA-1 population excludes a significant proportion of patients whose disease progressed before infusion. Thus, the results of the ITC unanchored MAIC are likely to be biased in favour of axi-cel. The EAG acknowledges the scenario performed by the company to explore the relative effectiveness of glofitamab and axi-cel and the highlighted bias in favour of axi-cel. The scenario implemented by the company reduced the point estimate of the relative effect benefit assumed for axi-cel (from the biased ITC results) from [redacted] and from [redacted] for PFS and OS, respectively. This scenario analysis was performed assuming that hazards proportionality holds and by taking the mid-point HR for PFS and OS between 1 and the ITC estimate. The use of the midpoint for PFS and OS HR for the comparison of glofitamab and axi-cel results in an ICER vs axi-cel of [redacted] (£/QALY gained SW quadrant, 56.4% increase from company's base-case after clarifications).

The majority of survival benefits of axi-cel are conferred during the extrapolation period. Therefore, it is important to consider the assumptions underlying the extrapolation of survival (PFS and OS), and their impact on the magnitude of survival benefits. Considerations from the EAG on the choice of the generalised gamma as the preferred parametric curve for glofitamab axi-cel adjusted PFS and OS

curves have been described in Section 0. As alluded to above, the EAG is concerned with the company's PFS and OS extrapolations due to the use of the mITT from the ZUMA-1 study, but the EAG is concerned also with the immaturity of the ZUMA-1 data, particularly on PFS.

As depicted in

Figure 19, the Gompertz distribution seems to appropriately reflect the initial downward slope of the hazard and the plateau that follows. The axi-cel PFS curve plateaus from approximately month 18 onwards, when the number of patients at risk should be substantially reduced at this stage given the small size of the axi-cel cohort from the start (n=101). The Gompertz distribution extrapolates this plateau for the remaining model time horizon, being quickly capped by axi-cel OS extrapolated curved early, at around 8 years, which would otherwise yield clinically implausible results with the crossing of PFS and OS. Although of much longer follow up compared to PFS, the axi-cel OS curve also shows the beginning of a possible plateau, with events still being registered at later stages that may be reflecting underlying background mortality. Thus, the EAG questions if the existing volume of evidence is sufficient to sustain an assumption of long-term remission and survivorship for axi-cel as it is being advocated by the company in their base case. The glofitamab axi-cel adjusted KM and extrapolated PFS and OS curves are not suggestive of long-term remission or survivorship. Please see Section 0 for further detail on long-term remission/ survivorship.

Similar curve convergence between PFS and OS can be observed for the glofitamab axi-cel adjusted population, however much later, at around 20 years. In the model a constraint is in place that ensures the hazard of death estimated from the OS curves does not go below that from the age-sex adjusted background mortality from the general population. This constraint is also reflected in

Figure 19.

Figure 19 Glofitamab axi-cel adjusted and axi-cel PFS and OS company's base-case extrapolated curves (with 'no cure' assumption)

The EAG acknowledges the difficulties encountered by the company in implementing flexible parametric spline models due to implausible long-term predictions with the crossing of PFS and OS curves and lack of an appropriate reflection of the steeply declining nature of the observed survival hazards. The use of the company's preferred spline models for PFS and OS results in an ICER vs axi-cel of 174,783 (£/QALY gained, 1.7% increase from company's base-case after clarifications).

4.2.6.5 Glofitamab vs bendamustine plus rituximab

BR was considered by the company to be a suitable proxy for R-Chemotherapy for the purposes of this analysis. This was validated by the company's clinical experts. The comparison between glofitamab and BR is informed by an unanchored MAIC adjusted glofitamab population (ESS, n=67.6) and an unadjusted BR population (n=58) from the Hong et al (2018) study. [9] As described in the CS Appendix D and section 2.9.2.2, the company was not successful in correcting for all existing imbalances between the NP30179 and Hong et al (2018) [9] cohorts, which introduces bias in the resulting glofitamab BR adjusted OS and PFS curves and related HR estimates.

4.2.6.5.1 Progression free survival

Except for the first 2 or 3 months where PFS is similar and where curves cross, the PFS KM for glofitamab (adjusted) and BR (unadjusted) shows glofitamab being consistently estimated to be more effective than BR (CS, Figure 23). The PH assumption was rejected based on visual assessment of the log-log plot, with the company opting for fitting curves independently to PFS data.

Out of the set of standard parametric survival models, the company considered the generalised gamma as the best fitting curve for the adjusted axi-cel glofitamab population PFS data and the Log-logistic distribution to model BR PFS data. The generalised gamma was the best fitting curve to the PFS BR data, although as it produced clinically implausible results with crossing OS at 3.5 years, it was not taken forward. The Log-normal distribution was also considered a good fit to the BR PFS curve. The choice of the Log-logistic for the fit of BR PFS data differed from the judgement of most experts in the company's clinical advisors panel that preferred an exponential curve.

The company fitted also spline models to the PFS glofitamab BR adjusted and BR data concluding that a spline model with 3-knots was the best fit relative to other spline models with lower number of knots. MCMs were not fit to PFS glofitamab BR adjusted or BR data.

Please see Table 25 for a summary of the company justification for selected PFS BR extrapolation curves.

4.2.6.5.2 Overall Survival

Similar to PFS, the OS KMs for the BR adjusted glofitamab population and for BR show glofitamab being consistently estimated to be more effective in terms of mortality than BR (Figure 26 of the CS),

except for the first 5 months of follow-up where the curves overlap. The PH assumption was deemed not to hold by the company and OS distributions for glofitamab and BR were independently fitted in the company's base-case analysis.

The Log-normal, Log-logistic and generalised gamma were considered the best fitting standard distributions, with the former being selected for the company's base-case. As detailed by the company at response to clarification stage, BR spline models result in an implausible crossing between BR OS and PFS at approximately 4 years. For glofitamab BR adjusted curve, none of the splines reflects appropriately the steeply declining nature of the observed hazard. MCMs were not fit to OS glofitamab BR adjusted or BR data.

Please see Table 26 for a summary of the company justification for selected OS BR extrapolation curves.

4.2.6.5.3 Points for critique

The EAG is concerned with the immaturity of the PFS and OS BR observed data, limited to approximately 3.5 years for PFS and 3 years for OS, which is being used to fit parametric curves and extrapolate survival for over 50 years. The EAG would like to highlight that it was unable to confirm the BR PFS plateau shown on Figure 23 of the CS, in the KM data contained in the company's electronic model. The BR PFS data to which the EAG had access to within the economic model show a steeply declining hazard up to approximately 10 months and a smoother hazard decline over the remaining observed period. The EAG is satisfied with the preferred parametric choices the company has made, although conscious of the limitations of the extrapolations that these choices implied in terms of PFS and OS crossing which would lead to clinically implausible results if capping rules were not in place. Discarding the built in 'cure' assumptions of the economic model produces the glofitamab BR adjusted and BR PFS and OS extrapolated curves as depicted on

Figure **20** and reflect the expected additional survival benefits glofitamab has over BR.

As for axi-cel, the EAG acknowledges the difficulties encountered by the company in implementing flexible parametric spline models due to unrealistic long-term predictions with the crossing of PFS and OS curves and lack of an appropriate reflection of the steeply declining nature of the observed survival hazards. The use of the company's preferred spline extrapolation models for PFS and OS BR results in an ICER vs BR [redacted]

Figure 20 Glofitamab BR adjusted and BR PFS and OS company's base-case extrapolated curves (with 'no cure' assumption)

[redacted]

4.2.6.6 Glofitamab vs polatuzumab-vedotin plus bendamustine plus rituximab

The comparison between glofitamab and axi-cel is informed by the propensity score IPTW adjusted glofitamab (ESS, n=123) and the pola-BR population (n=53.9) from the Pola-BR cohort in the GO29365 study. Pola-BR has considerably longer follow-up (in excess of 80 months) for PFS and OS than glofitamab and other comparators.

4.2.6.6.1 Progression free survival

PFS is similar between Pola-BR adjusted glofitamab and pola-BR until approximately 6 or 7 months, with curves crossing multiple times during this initial period. After 6 or 7 months, PFS curves separate with the glofitamab curve being above pola-BR curve. The company concluded it was appropriate to fit models independently to each curve, based mainly on the crossing of curves on the log-log plot.

For pola-BR, the generalised gamma was the preferred choice for PFS extrapolation out of the set of standard parametric models, with the Log-Normal also found to be a reasonable fit. The company's clinical advisors considered that several extrapolations, including generalised gamma, produced plausible PFS estimates for pola-BR, giving preference to the Gompertz distribution. A spline 1-knot PFS model was selected by the company for the glofitamab Pola-BR adjusted population and a spline 3-knot PFS model selected for Pola-BR.

MCMs were fitted to PFS curves under this comparison. MCM models of Log-normal, generalised gamma and log-logistic distributions were found to fit well the glofitamab Pola-BR adjusted PFS curve, with the MCM Log-normal being selected by the company as their preferred choice. For Pola-BR PFS, the MCM with generalised gamma distribution was chosen by the company as the best fit.

Exponential, Weibull, Gompertz and Gamma MCM models did not converge for Pola-BR and were not considered.

4.2.6.6.2 Overall Survival

Consistent with PFS findings, the OS KMs for the Pola-BR adjusted glofitamab population and for BR show glofitamab being above BR, from approximately 7 months where curves cross and then separate (Figure 26 of the CS). Before this initial period, the Pola-BR curve is either above or similar to the glofitamab curve.

For Pola-BR, the generalised gamma was the best fitting standard parametric distribution, with the Log-normal, Log-logistic and Gompertz also providing a good fit. The company's clinical advisors considered that the observed OS data looked promising for glofitamab, but that further follow-up was needed before making firm conclusions on the relative survival benefits against Pola-BR. The Log-normal was deemed the distribution that produced long-term survival predictions in line with estimates elicited from the company's clinical experts, unlike the generalised gamma which produced overly optimistic predictions. The EAG did not have access to the elicited OS estimates from the company's clinical experts and, thus, was unable to validate these. The 3-knot spline model provides the best fit for glofitamab OS Pola-BR adjusted although judged by the company to provide implausible long-term predictions. For Pola-BR, the spline 1-knot model was found to fit well the OS data.

MCMs were fitted to OS curves under this comparison. The Log-logistic was found to have the best overall fit although none of the MCM models for glofitamab Pola-BR adjusted OS data properly as none reflected the steeply declining nature of the observed hazard. The MCM with generalised gamma was selected as the preferred Pola-BR OS extrapolation distribution. Exponential, Weibull, Gompertz and generalised gamma MCM models did not converge for Pola-BR and were not considered.

4.2.6.6.3 Points for critique

The EAG notes the much longer follow-up period for OS and PFS for Pola-BR in comparison with glofitamab, with an additional 50 months of observed data for Pola-BR approximately. PFS data for Pola-BR is also substantially longer than follow-up data available for any of the other glofitamab comparators. OS data for Pola-BR is marginally longer to data available for axi-cel (further 10months of data) but substantially longer than data available for BR. This extended Pola-BR survival data, compared to available data for alternatives, provide confidence to the EAG about the parametric curve fitting and subsequent curve extrapolation for the long-term. This extended follow-up for Pola-BR may provide indicative evidence on the plausibility of long-term remission and/or survivorship. In fact, the PFS KM curve for Pola-BR shows the beginning of a plateau on its distal portion from 60-62

months onward (Figure 29 of the CS). However the number of patients at risk by this time point is unknown and assumed small by the EAG given the reduced ESS of 53.9 (Pola-BR IPTW adjusted population) from which the company's base case analysis started with. Judgements on the plausibility of long-term remission/survivorship require both a sufficiently long follow-up and numbers of patient at risk at the end of follow-up, and none of these factors seem to be supported here. The EAG thus understands that the company's base case assumption on long-term remission/survivorship from 2/3.5 years may not be fully justified for this comparison either (see section 0 for further detail).

The EAG considers reasonable the judgements made by the company on the assessment over the PH assumption for both PFS and OS Pola-BR data. The EAG is also satisfied with the fitting of models independently for glofitamab adjusted and Pola-BR PFS and OS curves. The EAG considers the generalised gamma, Log-normal and Log-logistic distributions to provide a good fit to the Pola-BR OS and PFS data. The EAG highlights that the long-term PFS and OS extrapolations are not fully reflected in the economic model results as these are truncated by the company's base case assumptions on long-term remission/survivorship at 2/3.5 years which are built in the economic model (Figure 21).

As there is uncertainty around the assumptions relating to long-term remission/survivorship (see Section 0), and to fully appreciate the implications of different long-term OS predictions when using different parametric distributions for extrapolation, the EAG shows on Table 27, the economic model overall survival predictions at 3, 5, 10 and 20 years when no long-term remission/survivorship is assumed and for when Pola-BR OS curve is fitted with the generalised gamma (company's base case) and the Log-normal. It can be depicted on Table 27 that, compared to the model estimates produced when fitting a Log-normal to the Pola-BR OS, the generalised gamma provides the most optimistic overall survival estimates across time.

Table 27 Overall survival model predictions when using different parametric distributions for Pola-BR OS for when assuming no long-term remission/survivorship

	Overall survival of Pola-BR (OS, %) - No long-term remission/survivorship							
	Generalised Gamma				Log-normal			
Treatment	3 years	5 years	10 years	20 years	3 years	5 years	10 years	20 years
Pola-BR	23.1%	16.1%	9.7%	5.4%	19.8%	10.6%	3.7%	1.0%

Abbreviations: OS: overall survival; PFS: progression free survival; BR: bendamustine plus rituximab; Pola-BR: polatuzumab vedotin in combination with bendamustine and rituximab; Axi-cel: axicabtagene ciloleucel; adj; adjusted.

The EAG acknowledges the limitations in the fitting of flexible parametric spline models for Pola-BR PFS and OS data. Like for the company's base case results, the use of the company's preferred spline extrapolation models for PFS and OS Pola-BR results in glofitamab being dominant over Pola-BR.

A key aspect to consider is whether the existing evidence for pola-BR can robustly support the existence of long-term remission and survivorship, given the limitations highlighted above. The company implemented MCMs to Pola-BR PFS and OS data. The EAG understands that it is important to recognise that MCMs require long follow-up times well beyond the point of cure in order to robustly estimate a cure fraction and sufficient numbers of patient at risk at the end of follow-up.[16] A study exploring cure in DLBCL has been cited in previous TAs where MCMs were considered, that concluded that even with a follow-up period of 11 years it may not have been sufficient to estimate a cure fraction accurately.[17] The EAG would like to note that the cure-fractions estimated for PFS and OS for the glofitamab Pola-BR adjusted population are exactly the same – see last rows of Table 22 for PFS and Table 23 for OS. Similarly, the cure-fractions estimated by the company for the Pola-BR PFS and OS data are also the same – see last rows of Table 25 for PFS and Table 26 for OS. The EAG considers this highly improbable and believes the company may have misreported the estimated cure fractions for PFS and OS for both glofitamab Pola-BR adjusted and Pola-BR populations. The EAG notes that the company may have built in dependency between the PFS and OS cure-fractions, following an approach similar to the one taken in TA649 by the same company where the proportion of long-term survivors was constrained to the proportion of patients in long-term remission. Irrespective of this, from the three implemented MCMs (Log-normal, Log-logistic and generalised gamma) fitted to the Pola-BR data, the company reports similar estimated cure fractions from the Log-normal (8.5%) and Log-logistic (8.0%), but the cure fraction estimated from the generalised gamma MCM was zero (0.00). The PFS extrapolation for the generalised gamma MCM, for example, was similar to the standard independent generalised gamma parametric model – the company's preferred distribution for PFS Pola-BR. Assuming the cure fractions estimates provided are correct, the magnitude and the difference in the cure fractions across the alternative models, suggest that the PFS data may not be sufficiently mature to be able to estimate a robust cure fraction for PFS Pola-BR. Similar conclusions can be attained for OS Pola-BR.

Figure 21 Glofitamab Pola-BR adjusted and Pola-BR PFS and OS company's base-case extrapolated curves (with 'no cure' assumption)

Item 5: Even with longer follow-up for Pola-BR OS and PFS than comparators, there seems to be limited evidence to support an assumption of long-term remission and/or survivorship.

4.2.6.7 Long-term remission / survivorship

The company considered clinically plausible a long-term remission/survivorship for the R/R DLBCL 2L+ population. Supported by previous company's submissions NICE (e.g. in TA649 and TA559), the company assumed for its base case that patients alive and progression free after 2 years enter in a long-term remission stage. This implies that from 2 years onwards it is assumed that progression-free patients at that point in time, will not progress, and, thus, are considered 'cured'. The company's clinical advisors agreed with this assumption on the basis that it *"was previously used in the CAR-T appraisal"*, but were uncertain if the same would be applicable to R/R diseases. When patients enter the long-term remission stage, the company assumed patients return to near general population values, that is, patients experience the utility of the UK general population reduced by 10%, and not incurring any further costs.

Furthermore, the company assumed in its base case that after 3.5 years, and once the large majority of patients who progressed in the model have died, remaining patients return to near UK general population age-matched mortality risk, that is, assuming a standardised mortality ratio (SMR) for excess background mortality of 1.09, as applied in TA559 and TA567 and based on the Maurer et al (2014) study.[18] The company's Advisor Board agreed that long-term survivors could have a 9% excess mortality relative to the general population, although the EAG is not clear about the company's Advisor Board opinion on the 3.5 years cut-off assumption. The company's economic model also allows other SMR assumptions to be applied, including no excess mortality, i.e. SMR=1, SMR=1.18 based on a subset of patients in the Maurer et al (2014) study,[18] and an SMR of 1.41 based on the Howlader et al 2017.[17]

The economic model has the above 'cure' assumptions built-into the model, and were initially treatment independent, but the company revised the model at points for clarification enabling different 'cure' related assumptions being applied to different treatments.

As requested by the EAG, at clarification stage the company implemented mixture-cure models. MCMs were fitted only for those comparisons where IPDs were available for both treatment arms as the likelihood function for MCMs requires individual background hazard information for the censored patients which cannot be reliably estimated when only aggregate level information and pseudo-IPDs are available for a given treatment, such as in the case of MAICs.

4.2.6.7.1 Points for critique

The EAG has several concerns regarding the long-term remission/survivorship company assumptions. First, the EAG is concerned with the clinical plausibility of cure for all treatments under comparison. The EAG considers that the observed PFS and OS survival data may suggest the occurrence of statistical long-term remission and cure for a given treatment when there is a flattening of the PFS and OS KM curves which forms a plateau. As discussed above, the PFS KM curves for glofitamab populations (

Figure 17a), BR and Pola-BR provide only early indications of the existence of a plateau and, thus, the support for a long-term remission assumption is limited. The axi-cel PFS KM curve plateaus from approximately month 18 onwards and the preferred distribution for extrapolation, the Gompertz, reflects that remission over the long-term. Similarly, the OS KM curves for other treatments (excluding Pola-BR) do not suggest that a plateau may be forming and more mature data is required to make strong statements on the existence of long-term survivorship.

Secondly, the EAG is concerned with the MCMs implemented by the company. In situations where a proportion of patients experience long-term durable remissions for their illness, significant heterogeneity in survival data may exist which may not be captured in standard parametric models. While in standard parametric modelling patients are grouped altogether to provide a single prediction of survival for the entire group, MCMs assume that for a proportion of patients (the cure fraction), treatment will have a curative effect, and therefore, patients will have the same mortality rate as the (age-matched) UK general population. Thus, and at points for clarification, the EAG requested the company to implement MCMs in order to assess if these models would be able to capture this potential heterogeneity in the survival data. However, the EAG believes that limited PFS and OS follow-up have hindered an appropriate estimation of the cure-fractions.

The EAG disagrees with the company that MCMs can only be applied to the comparison for which individual-patient data were available. The EAG referred to the NICE DSU TSD 21,[19] reference cited by the company to support the statement above, and having not found a basis for the company's argument, contacted the expert Mark Rutherford (Associate Professor of Biostatistics at the University of Leicester and first author of the NICE DSU TSD 21). Professor Rutherford confirmed that MCMs could be applied to pseudo-IPD as long as the profile of key covariates was accounted for in the adjustment (Rutherford, M, personal communication, 5th April 2023). The EAG understands that the cure fraction estimated for PFS was used to inform the one for OS in the company's analysis, which explains why PFS and OS cure-fraction estimates were the same. However, it considers it improbable that these estimates are a true reflection of PFS and OS cure-fractions.

Thirdly, the EAG considered the timing of long-term remission/survivorship to be uncertain as there is no accepted clinical definition of cure. The company did not fully justify the use of the cut-offs of 2 years for PFS and 3.5 years for OS. Although with reservations, the company's clinical advisors indicated that some clinical consensus existed in relation to long-term remission, considering that patients entered this stage if they were progression-free after 2 years. Committees of recent TAs have considered cut-off points to define cure based on PFS at 2 years (e.g. TA559[20], albeit considered optimistic), 3 years (e.g. TA649)) [21] or as a range from 2-5 years (e.g. TA567)[22], as these were

considered clinically plausible with the 2-years time point seen as optimistic and the 5 years as pessimistic, particularly when excess mortality was also factored in. A range between 2 and 5 years was considered reasonable by the EAG's clinical advisor. Some TAs considered also the timepoint at which OS and PFS converged as being the point of cure (e.g. TA559). [20] In the ongoing NICE appraisal of tafasitamab plus lenalidomide in R/R DLBCL (ID3795) the company conducted extensive scenario analyses on the definition of cure, but did not model cure in their base-case analysis. Thus, the EAG concludes that, if cure is assumed, there is substantial uncertainty around the time-point at which cure can be assumed. Additionally, the EAG believes that there is no clear rationale or new evidence presented to support a differential timing for when long-term remission and survivorship should be assumed, and that the point of cure of 2 years may be considered too optimistic, with the range between 3-5 years cut-off points seen as more appropriate. The EAG would also like to highlight that the company recognises the uncertainty in their own base case long-term remission/survivorship assumptions – see Section 7 for further detail.

Fourthly, related to the time point at which cure is assumed, a model constraint is imposed that makes progression-free patients move from the health state specific utility to near age-gender adjusted general population utility. The general population utility decrement used by the company was of 10%, although the company's clinical advisors deemed a 10 to 20% reduction to be more realistic. Previous TAs have used the age-sex adjusted general population utility directly (e.g. TA649), [21] the age-sex adjusted general population utility with a 10% utility decrement (e.g. scenario analysis in TA559)[20] or PFS utility after the point of cure regardless of health state membership (e.g. TA559). [20] The EAG considers that, if cure is assumed, there is uncertainty around which utility decrement should be used from the cure point.

Finally, the EAG is concerned that, after the point of cure, the excess mortality of 9% over the age-matched general population mortality for long-term survivors may not be reflective of the toxicities of previous chemotherapy treatment that patients were subject to, together with cardiovascular and immunosuppression side effects which are expected to persist for several years. The EAG's clinical advisor considered it unlikely that 'cured' patients would have the same mortality as the general population, due to prior treatment related toxicity, predominantly cardiac related. Committees of more recent TAs (e.g. TA649) [21] have considered the SMR of 1.41 from the Howlader et al study (2017)[17] as being more appropriate. The EAG considers that, if cure is assumed, there is uncertainty around which excess mortality estimate should be used to adjust age-matched general population mortality from the cure point.

Item 6. Except for axi-cel, there is no clinical plausibility of cure for the remaining treatments and limited data exists that supports an assumption of long-term remission/survivorship.

Item 7. There is no accepted clinical definition of cure and substantial uncertainty exists around the time-point at which cure can be assumed.

Item 8. If cure is assumed, there is uncertainty around which utility decrement, if any, should be used.

Item 9. If cure is assumed, there is uncertainty around which excess mortality estimate should be used to adjust age-matched general population mortality from the cure point.

4.2.6.8 Treatment discontinuation

Treatment discontinuation data from the study NP30179 was used to model the duration on treatment for glofitamab. The CS states that for other treatments where direct TTOT information was not available, the respective TTOT was set equal to the selected parametric distribution for PFS, capped at the treatment-specific maximum number of cycles, as per the treatment label, but this is not implemented for any of the treatments under comparison. Treatment in the model stops if progression occurs or at the time point in the model that coincides with the maximum number of treatment cycles (whichever is earliest). The maximum number of treatment cycles for glofitamab was set to according to the target SmPC, i.e. 12 cycles, equating to a maximum number of weeks under treatment of 36. The maximum number of treatment cycles for Pola-BR was based on the polatuzumab vedotin SmPC, i.e. 6 cycles, equating to a maximum number of weeks under treatment of 18. Furthermore, the company clarified that TTOT data from the study GO29365 (company's own data) was used for BR rather than data from Hong et al 2018[9] as more granular data was available from the GO29365 study to model BR individual treatment discontinuation. Thus, and for BR, the company clarified that the maximum number of treatment cycles was set to be 6 (equating to a maximum number of weeks under treatment of 18) in line with published literature used to inform the decision of the comparator study regimen in the DLBCL randomised part of the GO29365 trial. Axi-cel is a one-off treatment so only one model cycle was considered, equating to a maximum number of 1 week under treatment.

At clarification stage the company indicated that the TTOT KM curves for glofitamab unweighted and weighted populations had a similar treatment duration pattern, being almost identical. Similarly, the KM curves for TTOT for Pola-BR and BR (both as combined and individual regimens) overlapped. For pola-BR and BR, TTOT is modelled independently for each drug component in these regimens (i.e. separate TTOD KM are considered for each drug).

4.2.6.8.1 Points for critique

The EAG agrees with the company that although the choice of GO29365 data to model BR individual treatment discontinuation provided more granularity, it created inconsistencies across the model for this comparator as the estimation of the AE rates of occurrence, which then links up with AE cost

were obtained from a different source, the Hong et al (2018) study.[9] Thus, while BR treatment discontinuation, derived from the study GO2936, impact drug and administration costs, BR effectiveness and AE occurrences are built around the Hong et al (2018) study.[9]

Furthermore, the EAG is concerned with limiting treatment discontinuation to the maximum number of treatment cycles for each treatment as this might not be reflective of the respective KM TTOT curves being used. The EAG notes that patients may remain on treatment beyond the time point defined by the maximum number of treatment cycles for each drug component. For example, for glofitamab and as indicated above, the maximum number of weeks under treatment was defined as 36 (12 treatment cycles). Nonetheless, we can observe on the TTOT KM for glofitamab that patients remained on treatment beyond this point, with the last event of interest being recorded at approximately 52 weeks. The EAG confirms that this issue is also observed for Pola-BR and BR but not to the same extent. The issue may relate to treatment delays. This is further discussed in the EAG points for critique of section 0.

Item 10. Different evidence sources inform the modelling of BR individual treatment discontinuation and other important model parameters for this comparator creating inconsistencies.

4.2.6.9 Adverse events

The company included treatment-related AEs grade ≥3 occurring in over 1% of patients for the different treatments under comparison. After PfCs, the option to model the occurrence of CRS was modelled as a one-off probability at the start of the model for glofitamab was included (given these events are more likely to occur in the first 2–3 weeks after infusion); all other AEs were individually modelled as having a treatment specific weekly probability of occurrence for progression-free patients on treatment. In the company's base-case analysis, the AEs are modelled as having an impact on costs only (see Section 0), while the disutility associated to AEs is only accounted for in scenario analysis (see Section 0).

The CS reports the AEs included and the number of events for each treatment under comparison except axi-cel in Table 40. The number of events were sourced from the same sources of evidence used to inform the clinical effectiveness data in the model. The EAG note that for glofitamab and pola-BR the model considers the number of AEs occurrences, while for the other comparators it considers the number of patients experiencing the AEs (as only these estimates were available from the published literature). The company states that this is a conservative approach, likely to increase the AE management costs of glofitamab compared to BR.

The per patient probability of each AE, was calculated by the company based on the number of AEs, patients with AEs and the total duration of follow-up for AEs. Details on how the total duration of follow-up for AEs by treatment was estimated, are presented in the company's response to PfCs (question B13); the EAG considered the estimation of the probabilities appropriate.

The company did not include the axi-cel related AEs in the original version of the model, as the AEs management costs are already captured in the administration costs of axi-cel (see Section 0). These AEs were added to the model at PfCs, but are only linked to the AEs disutilities as is appropriate.

4.2.6.9.1 Points for critique

The EAG was unable to validate the number of treatment-related AEs and patients with treatment-related AEs in the model for glofitamab against the figures presented in the CS and in the NP30179 CSR. This is because we could not identify in the submitted documentation evidence reported for the whole safety population by individual AEs treatment broken down by grade and whether they are treatment related. The number of patients with treatment-related AEs for BR, pola-BR and axi-celwas sourced from Hong et al (2018)[9] Sehn et al (2022)[15] and Neelapu et al(2017),[23] respectively. However, the EAG could not validate the number of treatment-related AEs for pola-BR, as this information is not available in the published literature. Furthermore, there are AEs included in TA649[24] for pola-BR (e.g., acute kidney injury) that have not been included in the model. This may be due to differences in the criteria for inclusion between TAs (TA649 included serious treatment-related AEs grade ≥3 for pola-BR), but the EAG could not ascertain this.

The company did not model any neurological AEs judged to be consistent with ICANS for glofitamab (see section 0); it is unclear whether this was due to no such AEs meeting the criteria for inclusion.

Item 11: It is unclear whether the AEs associated with glofitamab and pola-BR were correctly modelled by the company, as the EAG could not validate all related model inputs.

4.2.7 All-cause mortality

Age and sex adjusted all-cause mortality sourced from national life tables[25] was applied in the company's model as background mortality; survival in the model was constrained so that the OS extrapolated death hazard was never lower than the background mortality at each model cycle.

In the company's base-case analysis background mortality was modelled as a function of the age distribution of patients in the NP30179 study. This is in contrast with single age cohort-based approach of assuming the background mortality corresponds to that of the mean cohort age, which is more commonly used in cohort models. The EAG notes that the age-distribution approach had been previously applied in the company's analyses in TA649.[24] Both the NICE committee and the EAG in TA649 preferred the single age cohort-based approach.

In the company's original CS, the use of the age distribution approach was stated to be preferred to the single-age cohort, as it better reflected heterogeneity in the background mortality of the cohort and the associated background risks of death by age. Following clarification, the company indicated this approach was deemed appropriate, for example, in TA530.[26] Question B9 of the clarification response further addresses two key criticisms raised during TA649 with this approach, which we describe in brief. First, the company addressed the critique that unrealistic long-term survival estimates are yielded by modelling background mortality using an age distribution approach. The company provided a visual comparison of expected background mortality with an age distribution versus a single age cohort-based approach (Figure 74 of PfC), as well as a comparison of the actual age estimates at death for each approach (Figure 75 of PfC), which indicated in the cohort age distribution approach the average age at which patients die differs from the average age of the patients alive, as the oldest patients have a greater risk of death. Using the single age cohort-based approach, patients who die have the same age as the average age of the patients alive in the cohort, which the company considered implausible. Second, to address the concern of potential lack of consistency between using the age distribution versus the single age cohort-based approach for modelling PFS and OS, the company provided an example using a discrete series of patient sub-cohorts featuring their own specific mean age (approximately 10 years a part), based on the observed trial distribution. Figures 76-78 (response to PfCs) compared expected results for survival over time, hazard of death over time, and average age at death. The company concluded that using a distribution of sub-cohort ages rather than individual patient ages does not substantially influence the quantities being estimated over time.

4.2.7.1 Points for critique

Considering the all the evidence provided by the company, the EAG agrees that applying an age distribution approach for the reference case represents an appropriate background risk of mortality for the cohort. However, the EAG considers this is a partial implementation of the distributional approach to age, as the age distribution is only reflected on all-cause mortality. A full implementation of the company's preferred approach would have to reflect the age distribution on cancer-related survival and on age-adjusted HRQoL. The EAG notes that the cost-effectiveness results are not sensitive to this assumption, with similar cost-effectiveness estimates under the two alternative approaches (see Section 5.2, Table 43).

Item 12. The company's preferred approach to model background mortality, is a partial implementation of age as a distribution. For this to be fully and consistently applied, the age distribution would also have to be implemented for the cancer-related mortality and age-adjusted HRQoL.

4.2.8 Health related quality of life

HRQoL data from identified studies

The company conducted an SLR to identify studies evaluating HRQoL in the DLBCL 2L+ setting. A description of the searches and some of the search strategies were included in Appendix I (pp. 62-77). There is mention of a 'targeted review' to identify published algorithms for mapping QLQ-C30 data to the EQ-5D (Appendix I, p. 62), so the EAG assume that the searches to identify health-related quality of life studies were also used to identify evidence for the targeted review; this is, however, not clear.

Six studies, related to seven publications,[27-33] were identified as relevant, with two studies [30-32] reporting results for the R/R DLBCL 3L+ setting. A quality assessment exercise was conducted on the six identified studies. The study by Shah et al[32] was the only study deemed to clearly meet the requirements of the NICE reference case, which reported EQ-5D-5L data from the SADAL trial, a multinational, single-arm, open-label, phase 2b study on patients with R/R DLBCL with 2 to 5 prior therapies who received single-agent selinexor. EQ-5D-5L was used to measure changes in patients' HRQoL, with complete EQ-5D-5L data obtained for responders (N=31) and non-responders (N=44). EQ-5D-5L was scored using the US standard value set and mapped/cross-walked using the Van Hout[34] algorithm. The quality assessment performed on Shah et al[32] highlighted that some patients may not have reached later timepoints as the number of patients with post-baseline HRQoL data decreased in later cycles of treatment with selinexor. This could lead to bias as patients who responded remained in the study, while non-responders, and relapsed patients, could have drop out, not filling in the HRQoL questionnaires. A summary of the health state utility values for Shah et al[32] and for the remaining studies identified in the SLR can be found in the CS, Appendix I, Table 29, pages 79-87.

Points for critique

The search strategies presented were generally appropriate to identify published health state utility values (HSUVs) for DLBCL in the 2L+ setting. The SLR performed by the company provide a satisfactory repository of the current available published utility data relevant to patients with DLBCL in the 2L+ setting. This review highlighted the paucity of robust data in this area. Overall, the identified studies indicated that DLBCL has a substantial impact on patients HRQoL.

In the CS Appendix I, page 62, it is stated that "The methodology associated with SLR update 2 and 3 are detailed in the current report, and results from the original SLR and SLR update 1 are provided in separate (sic) files to accompany this submission.". The separate files reporting on the original SLR and SLR update 1 as well as the findings for these were not provided to the EAG and were requested at points for clarification. Details from the original SLR (conducted in September 2018) and SLR

update 1 (conducted in June 2019) were provided in the company's response, together with a summary of the identified studies and their relevance to the NICE reference case. The EAG believes that the SLR and SLR updates conducted by the company provide a satisfactory repository of the current available published utility data relevant to patients with DLBCL in the 2L+ setting.

The company considers that none of the studies identified in the review can adequately characterise the HRQoL of patients in this indication. This was down to the limitations identified in each individual study. A number of limitations were highlighted by Shah et al[32] in their analyses of HRQoL data, which were reiterated in the CS, and with which the EAG agrees. Although recognising the limitations of this utility data, the EAG emphasises the limited availability of good quality utility data and the existing uncertainty surrounding the mapped utility estimates used by the company in their base case. Thus, the EAG believes that the fact that this study has HRQoL data using the EQ-5D-5L instrument directly elicited from a relevant population to this appraisal and that it is the only one, out of the set of identified studies in the SLR, that clearly meets the NICE criteria, should have been considered by the company for inclusion in the economic model, and this issue was put to the company at clarification stage. The company responded that utility values derived in Shah et al 2021[32] were cross-walked to EQ-5D-3L values using the recommended van Hout et al 2021[34] algorithm but based on a US tariff, thus falling outside of the NICE reference case. Furthermore, the company indicates that it did not consider the utilities by Shah et al 2021[32] suitable to inform the economic model without making use of strong assumptions, as these were better suited to inform a response-based model. The EAG generally agrees with the company's position on this.

HRQoL data from clinical trials

The CS presents data on HRQoL measured in the NP30179 study via the disease-specific European Organization for Research of Cancer Quality of Life Questionnaire Core 30 v3.0 (EORTC QLQ-C30) and the 15-item Functional Assessment of Cancer Therapy – Lymphoma (FACT-Lym) Lymphoma Subscale (LymS) instruments. HRQoL assessments were performed at baseline and every 3 months during the post-treatment follow-up. Completion rates for both instruments in cohorts D3 and D5 were considered high (>85%). Change in mean scores from baseline for both cohorts did not exceed pre-specified clinically meaningful thresholds, defined as a difference of a least 10 points for the EORTC QLQ-C30[35] and of at least 3-5 points for FACT-Lym LymS.[36]

Points for critique

The reported outcomes were in line with the NICE scope. The EAG agrees with the company's interpretation of the HRQoL data from the NP30179 study.

Mapping

As EQ-5D data was not collected in the NP30179 study, patient-reported HRQoL data captured via the EORTC QLQ-C30 instrument was used for the economic modelling. This was achieved by mapping EORTC QLQ-C30 to EQ-5D-3L. A targeted literature search conducted by the company identified two relevant mapping algorithms to map EORTC QLQ-C30 to EQ-5D-3L: a direct mapping algorithm (i.e. mapping to EQ-5D-3L index values) published by Proskorovsky et al, 2014;[37] and an indirect mapping algorithm (i.e. mapping to the dimensions of EQ-5D-3L, also known as response-based mapping) published by Longworth et al, 2014.[12] Both mapping algorithms were estimated in patients with multiple myeloma (MM) or where MM was the predominant cancer. Proskorovsky et al, 2014[37] mapping algorithm uses multiple linear regression analysis to derive EQ-5D index values from EORTC QLQ-C30 elicited from 154 patients (89 (56%) patients from the UK, 97 (63%) male and mean age 66.4years (SD 10.0years)), with UK value sets used for all patients. Longworth et al, 2014[12] mapping algorithm uses a variety of regression models, including response mapping models, to derive EORTC QLQ-C30 elicited at screening from 771 patients pooled from the VISTA trial[38] and the Vancouver Cancer Clinic register (572 [74%] with MM, 44% male and mean age 68 years (SD 9.6years)). The mapping algorithms chosen were considered appropriate by the company for this appraisal given that they were deemed to have a good predictive ability, were estimated in a relevant and reasonably sized population, have been subject to external validation and were previously used in NICE submissions.

The mapping exercises were performed on patients with 3L+ R/R DLBCL from the pooled efficacy population (N=155) in NP30179 and under a complete case perspective, that is, data on patient' visits with at least one of the EORTC-QLQ-C30 scores missing were excluded. At baseline, the company estimated a mapped mean utility of 0.687 (SE 0.20) for 139 patients (i.e. 16 patients were excluded), although not clearly mentioning with which mapping algorithm these mapped baseline utility values were obtain (the EAG assumed these estimates relate to using the response-based mapping algorithm from Longworth et al, 2014[12] considered in the company's base case). This mapped mean utility indicated a reduced utility for patients compared to an age-matched general population (0.816) estimate from Ara and Brazier, 2010.[39]

The company indicates that the mapped utility estimates were used to inform the utilities for three health states: PFS on-treatment, PFS off-treatment and PPS. Simultaneously the company states that, given the small number of patients available from NP30179 to inform this analysis, health state utilities were calculated for PFS and PPS, that is, not distinguishing between PFS on- and off-treatment, though the company presents PFS on-treatment, PFS off-treatment utility related values. Subsequently, the company implemented a linear mixed regression model with random intercept on post-baseline utilities, adjusting for baseline utilities. The estimated mapped utilities (EORTC-QLQ-

C30 to EQ-5L-3L), using the indirect/response-based mapping algorithm (UK tariff) from Longworth et al, 2014,[12] from the NP30179 study by health states are shown on Table 41, page 147 of the CS. The estimated mapped utilities (EORTC-QLQ-C30 to EQ-5L-3L), using the direct mapping algorithm (UK tariff) from Proskorovsky et al, 2014,[37] from the NP30179 study by health states are shown on Table 43, page 149 of the CS. Both indirect and direct mapped utilities are replicated on Table XX below. An age/sex-adjustment of utility values was applied in the calculation of QALYs for each model cycle and in the treatment-specific Markov traces within the model. Age/sex adjustment coefficients were reported on Table 42, page 147 of the CS and correspond to the values found in the relevant literature.[39] As an alternative to the progression-based utility approach, the company implemented in the model a time-to-death utility approach, which was not described in the original CS, but later detailed at clarification stage. The mapped utility estimates (EORTC-QLQ-C30 to EQ-5L-3L) from the NP30179 study by health state are shown in

Table 28.

Table 28 Mapped utility estimates (EORTC-QLQ-C30 to EQ-5L-3L) from the NP30179 study by health state.

Health state	NP30179 mapped utility values, mean (SE)		
	Best indirect mapping (response-based) algorithm from Longworth et al 2014 (company's base case)	**Best direct mapping algorithm from Proskorovsky et al 2014**	**Direct mapping algorithm from Longworth et al 2014***
Progression free – on treatment	0.729 (0.011)	0.772 (0.010)	0.738 (0.012)
Progression free – off treatment	0.774 (0.020)	0.836 (0.017)	0.787 (0.021)
Post-Progression	0.629 (0.019)	0.673 (0.016)	0.624 (0.019)

* Under assumptions due to limited detail provided on the best-fitting direct mapping algorithm by Longworth et al 2014[12]

Points for critique

The EAG has several concerns regarding the mapping study presented in the CS. Firstly, the CS states that "a targeted literature search of EQ-5D-3L mapping algorithms for haematological malignancies was conducted to identify the best candidates for use in the mapping exercise – see Appendix I for details." and that "Several mapping algorithms were identified". Details on how the targeted literature review on mapping algorithms was carried out were not provided to the EAG and were requested at points for clarification. At clarification stage, the company continue not to provide any details on the targeted literature review on mapping algorithms or its results, emphasising only details about the two preferred mapping algorithms by the company (Proskorovsky et al, 2014 and Longworth et al, 2014). Secondly, both Longworth et al 2014 and Proskorovsky et al, 2014 studies assessed several alternative mapping algorithms and it was not clear to the EAG which algorithms were used from each source. The EAG requested further information at points for clarification and the company clarified that it used the best-fitting indirect/response-based mapping model, as defined in Table 21 of Longworth et al 2014[12] and the full multiple regression model (OLS-based) for direct mapping, as defined in Table 5 of Proskorovsky et al, 2014.[37]

Thirdly, the EAG was not clear why the Proskorovsky et al, 2014 was chosen for direct mapping over the use of Longworth et al 2014, as the latter presents both direct and indirect algorithms. At points for clarification, the EAG requested the company to implement a scenario where EORTC-QLQ-C30 data from NP30179 were mapped to EQ-5L-3L using the best-fitting direct mapping algorithm from Longworth et al 2014. In response the company highlighted that the use Proskorovsky et al 2014[37] was primarily based on the rationale that this algorithm was the most frequently used and accepted in previous NICE TAs in haematological malignancies. As requested by the EAG, the company attempted implementing the best-fitting direct mapping algorithm as defined by Longworth et al 2014[12] but, due to limited detail being provided, utility estimates were derived only under assumptions over the 'pain' and 'social functioning' dimensions. Estimated directly mapped utilities using Longworth et al 2014[12] are shown in the last column of

Table 28, not differing much from the indirectly mapped utilities estimated from the same source.

Fourthly, results of the mapped EQ-5D utilities, using either mapping approach and before modelling, were not provided in the CS and thus the EAG is unable to verify and appropriately critique these. Although acknowledging the preference from the company's clinical advisors over the mapped utility values derived from Proskorovsky, the EAG would like to highlight that the estimated utility of 0.836 for 'Progression free – off treatment' lacks face validity as it is higher than the age-adjusted general population utility of 0.816.[39] Thus, the EAG believes that the mapped utilities derived from Proskorovsky et al, 2014[37] may be overestimated and not appropriately representing the HRQoL of patients in this indication in the relevant health states.

Finally, the EAG would like to mention that, as highlighted in Chan et al 2014,[40] a problem of underestimation of uncertainties of health utilities derived from mapping algorithms exist, meaning that confidence intervals based on the derived utility values are tighter than the confidence intervals of the original actual health utilities. This study proposes an adjustment of mapped estimates to account for the proportion of total variation explained by the mapping algorithm, using, for instance, the R^2 or the MSE of the mapping algorithms. For example, the adjusted R^2 (as a proxy for R^2) of the full mapping model from Proskorovsky et al, 2014 is 0.6956 (Table 74 of the company's response to clarification questions), which could have been used as an adjustment of the variance of mapped utility estimates, accounting for the proportion of total variation explained by the mapping algorithm.

It should also be noted that the initial CS did not provide detail on how mapped EQ-5D utilities were used to estimate utilities by progression status and how many observations were consider for each of the three health states PFS on-treatment, PFS off-treatment and PPS. At points for clarification, the company clarified that utility measurements were assigned to PFS or PPS health states by comparing the date of progression (per-investigator assessment) with the corresponding date of measurement for the predicted utility value. Additionally, no detail was provided on the linear mixed regression to model mapped utilities longitudinally. Further details were provided by the company at clarification stage after being sought from the EAG, and the EAG considers the explanations satisfactory.

Item 13: Health state-specific utilities used in the cost-effectiveness model estimated using mapping algorithms are uncertain.

Adverse events disutilities

The company did not include adverse event disutility in their base-case. The company assumed that the PFS utility values estimated from the pivotal trial data represent the HRQoL experienced by patient's pre-progression and considered that it accounted for any potential adverse reactions.

In the economic model, it is possible to consider the impact of treatment's toxicity profiles when choosing scenarios where the source of the PFS/PPS health state utilities are previous NICE TAs –

please see next subsection (0) for further detail. Once these scenarios are enabled in the model, AE related disutilities are applied for the time patients are on-treatment, except for the axi-cel comparator where AEs were all assumed to occur within the first model cycle, as considered within the respective TA (TA559). The company also explored a scenario where the impact of AE disutilities is accounted for within the model but excluding the impact of CRS in the PFS health state.

Table 29 summarises the data applied in the model to estimate the disutility from treatment-related adverse events. The probability of an adverse event occurring was estimated via the number of events occurring and the total duration of follow-up for AEs. Where the number of events and duration of follow-up were sourced from the study NP30179 for glofitamab, Hong et al[9] for BR, the study GO29365 (company's data) for pola-BR and Neelapu et al[23] for axi-cel. The average AE weekly disutility was estimated using the probability of the AE occurring, the disutility value and the AE duration. Disutilities associated with adverse events and estimates of their duration were sourced from a variety of studies and NICE TAs. The majority of utility decrement values were sourced from NICE TA306[41] and Nafees 2008.[42] Standard errors for all adverse events disutilities were assumed to be 20% of the mean disutility value. The CS stated that for adverse events for which no utility estimates were identified, a disutility equal to the maximum of the identified non-CRS AE disutilities was assumed, as per NICE TA306.[41] The disutility assumed for a CRS was assumed to be 50% greater than the maximum in TA306 and reduce a patient's utility by 0.56 (SE 0.11) for the duration of the adverse event.

The average AE weekly disutility was estimated to be of -0.013 for glofitamab, -0.087 for BR, -0.056 for pola-BR and applied at each model cycle (Table 29). The company states that the main AEs for axi-cel tend to occur in the first 2 to 3 weeks after injection, and thus, the model assumed AEs to occur within the first model cycle for axi-cel, i.e. with a disutility of -1.472. See top row of Table 29 for further detail.

Points for critique

The company assumes that the PFS on-treatment utility values estimated from the NP30179 trial capture the HRQoL experienced by patients in pre-progression, including the impact of any potential adverse events for those on glofitamab. This assumption was extended to comparator treatments with no explanation being provided on if, in Hong et al[9] for BR and in GO29365 (company's data) for pola-BR, pre-progression was capturing patients AEs related disutilities. Thus, and as to avoid double counting, the company did not include adverse effect specific disutilities in their economic model base case. The EAG considers it likely that most patients with severe adverse effects are unable to complete HRQoL questionnaires. Thus, the double counting issue raised by the company may not be applicable under these circumstances. However, in the economic model, it is possible to consider the impact of treatment's toxicity profiles when choosing scenarios where the source of the PFS/PPS

health state utilities are previous NICE TAs (TA306, TA567 and TA559). At clarification stage, the EAG requested the company to update the electronic version of the model so that it is possible to turn on/off the impact of AEs disutilities for all scenarios, i.e., not just the ones where health state utilities were based on previous NICE TAs. This would enable the EAG to perform sensitivity analysis on the impact of AE disutilities for all scenarios, and not just to a subset. The company, in response, did not include that model functionality, reinstating the issue of the potential for double counting and highlighting that several Committees preferences in previous NICE TAs (TA406, TA529) were not to include AE disutilities due to potential double counting.

Table 29 Summary of adverse events data applied in the company economic model to estimate disutilities for each treatment

Adverse event, Grade ≥3	Disutility, mean (SE)	Source for AE disutility	AE duration (days)	Source for AE duration	Glofitamab (NP30179)	BR (Hong et al)	Pola-BR (GO29365)	Axi-cel (Neelapu et al)*
Mean AE weekly disutility					**-0.013**	**-0.087**	**-0.056**	**-1.472**
					Probability of AE occurrence during follow-up			
Anaemia	0.25 (0.05)	NICE TA306 (based on Swinburn 2010)	13	Assumed average of TA306 and NP30179	0.002	0.035	0.009	0.347
Anorexia			35	Assumption as per NICE TA306	0.000	0.004	0.000	0.000
Agitation	0.37 (0.07)	Assumption (max of TA306)	72	Assumption as per NICE TA649	0.000	0.000	0.000	0.039
Aphasia			23	Assumed weighted average of AE in NP30179**	0.000	0.000	0.000	0.067
Confusional state					0.000	0.000	0.000	0.085
Constipation					0.000	0.004	0.000	0.000
Decreased appetite					0.000	0.000	0.000	0.020
Encephalopathy			9	Assumption as per NICE TA559	0.000	0.000	0.000	0.188
Fatigue			32	Assumption as per NICE TA306	0.000	0.004	0.000	0.020
Headache			23	Assumed weighted average of AE in NP30179**	0.000	0.000	0.000	0.010
Hypoalbuminemia					0.000	0.000	0.000	0.010
Insomnia					0.000	0.002	0.000	0.000
Memory impairment					0.000	0.000	0.000	0.010
Mental status change					0.000	0.000	0.000	0.020
Septic shock					0.000	0.000	0.003	0.000
Somnolence					0.000	0.000	0.000	0.067
Supraventricular tachycardia			8	Assumption as per NICE TA 649	0.000	0.000	0.000	0.020

Adverse event, Grade ≥3	Disutility, mean (SE)	Source for AE disutility	AE duration (days)	Source for AE duration	Glofitamab (NP30179)	BR (Hong et al)	Pola-BR (GO29365)	Axi-cel (Neelapu et al)*
Tremor			23	Assumed weighted average of AE in NP30179**	0.000	0.000	0.000	0.010
Tumor flare			9	NP30179	0.002	0.000	0.000	0.000
CRS	0.56 (0.11)	Assumed to be 50% greater than max in TA306	7	Assumed average of ZUMA-1, JULIET, TRANSCEND and NP30179	0.002	0.000	0.000	0.121
Diarrhoea	0.10 (0.02)	Lloyd 2006	37	Assumption as per NICE TA649	0.000	0.000	0.002	0.039
Febrile neutropenia	0.15 (0.03)	Lloyd 2006	8	Assumed average between NICE TA559, TA649 and NP30179	0.002	0.021	0.003	0.264
Hypocalcemia		Assumed same as Hypotension (Lloyd 2006)	23	Assumed weighted average of AE in NP30179**	0.000	0.000	0.000	0.058
Hypokalaemia					0.000	0.000	0.000	0.029
Hyponatraemia					0.000	0.000	0.000	0.094
Hypophosphatemia			10	Assumed average between NICE TA559 and NP30179	0.004	0.000	0.000	0.000
Hypotension			7	Assumed average between NICE TA559 and TA306	0.000	0.000	0.000	0.129
Leukopenia	0.09 (0.02)	Assumed same as Neutropenia (Nafees 2008)	15	Assumed average between NICE TA559, TA649 and TA306	0.000	0.000	0.008	0.000
Lymphopenia		Bullement et al 2019	88	Assumed average between TA306 and NP30179	0.002	0.000	0.006	0.000
Lymphocyte count decreased		Assumed same as Neutropenia (Nafees 2008)	64	Assumption as per NICE TA559	0.000	0.000	0.006	0.000
Neutrophil count decreased		Assumed same as Neutropenia (Nafees 2008)	17	Assumption as per NICE TA559	0.000	0.000	0.010	0.000
Neutropenia		Nafees 2008	22	Assumed average between NICE TA559, TA649, TA306 and NP30179	0.019	0.073	0.047	0.543
White blood cell count decreased		Assumed same as Neutropenia (Nafees 2008)	40	Assumption as per NICE TA559	0.000	0.000	0.008	0.250
Pneumonia	0.20 (0.04)	Beusterein 2010	23	Assumed weighted average of AE in NP30179**	0.000	0.000	0.004	0.000

Adverse event, Grade ≥3	Disutility, mean (SE)	Source for AE disutility	AE duration (days)	Source for AE duration	Glofitamab (NP30179)	BR (Hong et al)	Pola-BR (GO29365)	Axi-cel (Neelapu et al)*
Pyrexia	0.11 (0.02)	Beusterein 2010	5	Assumed average between NICE TA559 and TA649	0.000	0.000	0.000	0.129
Platelet count decreased	0.11 (0.02)	NICE TA559 (based on Tolley et al 2013)	30	Assumed average between NICE TA559, TA649, TA306 and NP30179	0.000	0.000	0.004	0.000
Thrombocytopenia					0.002	0.062	0.020	0.314
Vomiting	0.05 (0.01)	Nafees 2008	23	Assumed weighted average of AE in NP30179**	0.000	0.000	0.002	0.010

* Information provided at clarification point. AEs to occur within the first model cycle for axi-cel; **Assumed to be the weighted average of the Grade ≥3 treatment-related AE durations in NP30179 (occurring in at least 2 patients)

Details on the estimation of the average AE weekly disutility, or any of the components which enable its estimation, were not provided in the CS, with limited information being available in the electronic economic model.

The EAG notes that most AE disutility values and durations were subject to assumptions, with no justification provided and with many of which lacking a clinical rationale. However, the disutility associated with adverse events is not considered by the EAG to be an important driver of cost-effectiveness.

Item 14: Disutilities relating to treatment specific adverse events should, in principle, be accounted for in the economic model on all scenarios.

Health states utility values used in the economic model

The indirect/response-based mapping using the Longworth et al, 2014[12] algorithm was considered in the company's base case and the direct mapping using the Proskorovsky et al, 2014[37] algorithm was considered as a scenario analysis. Acknowledging that potential differences may exist between the mapped utility estimates and the utility estimates used in previous NICE TAs, the company implemented two extra scenarios where utility values are sourced from the NICE TAs for axi-cel (TA559[20]) and for pixantrone for R/R aggressive non-Hodgkin's lymphoma (TA306[41]). These scenarios do not distinguish between PFS on- and off-treatment. The base case and scenario analysis assumed no differences in health state utilities by treatment group. Scenario analysis using utility estimates from previous NICE TAs consider AE related disutilities

As described in section 0, the economic model included an important additional structural assumption, specifically that those patients' who remain in the progression free health state for at least 2 years (in either treatment group), will subsequently revert to similar HRQoL as the general population. This is equivalent to a structural 'cure' assumption applied within the model that prevents transitions from the progression free to the post-progression state after 2 years. The company assumes that, after 2 years in 'pre-progression', patients' experience the utility of the age-sex matched UK general population reduced by 10%.

A summary of the health state utility values and related assumptions applied within the economic model in provided in Table 30.

Table 30 Summary of health state utility values applied in the economic model.

Health State	Utility values, mean (SE)	Source/Justification
Pre-progression after 2 years (long-term remission)	10% percentage decrement to general population utility	To reflect the assumption that long-term survivors have similar utility as the UK general population, on entering long-term remission, patients do not progress and revert to near age-sex general population utility values
Base case – Indirect mapping (response-based)		
Progression free – on treatment	0.729 (0.011)	Estimated mapped utilities (EORTC-QLQ-C30 to EQ-5L-3L) from the NP30179 study, using the indirect/ response-based mapping algorithm (UK tariff) from Longworth et al, 2014[12]
Progression free – off treatment	0.774 (0.020)	
Post-Progression	0.629 (0.019)	
Scenario analysis – Direct mapping		
Progression free – on treatment	0.772 (0.010)	Estimated mapped utilities (EORTC-QLQ-C30 to EQ-5L-3L) from the NP30179 study, using the direct mapping algorithm (UK tariff) from Proskorovsky et al, 2014 [37]
Progression free – off treatment	0.836 (0.017)	
Post-Progression	0.673 (0.016)	
Scenario analysis – NICE TA559 (axi-cel)		
Progression free – on treatment	0.72 (0.06)	From ZUMA-1 trial safety management cohort, which collected EQ-5D-5L from participants.
Post-Progression	0.65 (0.03)	
Scenario analysis – NICE TA178 and TA306 (pixantrone)		
Progression free – on treatment	0.76 (0.06)	Assumption in TA178, and applied in TA306, for patients in second- and subsequent-lines of treatment and with renal cell carcinoma
Post-Progression	0.68 (0.03)	

Points for critique

The magnitude of the mapped utility values from using the direct mapping algorithm are higher than the ones derived with the indirect mapping algorithm, although the ranking across health states remains the same. Utility values were estimated to be higher for progression free – off treatment, followed by progression free - on treatment and post-progression. As detailed above, the EAG questions the magnitude of the directly mapped utility estimate for progression free – off treatment as it is higher than the age-sex adjusted UK general population utility values. The use of direct mapping utility estimated results in an ICER vs BR of [redacted]

[redacted].

The utility values sourced from the NICE TA306 were from a sensitivity analysis where utility values from patients receiving second- and subsequent-line treatment for renal cell carcinoma from the NICE TA178 were used. The NICE TA306 committee noted that the utility value for the pre-progression health state (0.76) was similar to that expected for a healthy older population in the UK, and it considered that the HRQoL of patients receiving third- or fourth-line treatment for the relevant indication (aggressive non-Hodgkin's B-cell lymphoma) could be lower than this. This scenario, although not distinguishing the impact on patients' HRQoL from progression free on- and off-treatment, provides utilities for progression free in line with the mapped progression free on-treatment utility estimates. Assumptions were made to obtain standard errors for both progression free and post-progression health state utility values. The use of utility estimates from TA306 and factoring in AE disutilities results in an ICER vs BR of [redacted]).

Another scenario presented by the company included utility values used in the NICE TA559. These utility estimates were sourced from a small (at that point) trial ZUMA-1 (N=34), with few observations informing the pre- and post-progression estimates, with the later likely to have been measured close to the progression event and, thus, potentially not reflective of the entire period of progressive disease. The EAG considers that the uncertainty surrounding the utility of progressive disease unlikely to be a key driver of cost-effectiveness, given that the majority of patients who experience progression will die within a relatively short time frame. The use of TA559 utility estimates and factoring in AE disutilities results in an ICER vs. BR of [redacted]).

The EAG highlights that the majority of QALY gains in the economic model are driven by QALYs accrued in the extrapolation of OS and the HRQoL of patients remaining progression free and/or assumed 'cured'. In particular, the EAG would like to highlight that the uncertainty surrounding the assumption that patients in the 'progression free' health state nearly revert to HRQoL of the general population at 2-years appears to be a critical area of uncertainty. As previously discussed, there appears to be limited evidence to support a cure assumption at two years after treatment initiation, and no guarantee exists that excess mortality does not persist for up to five years. If the survival of 'cured'

patients remains affected by excess mortality, this is also likely to be reflected in lower HRQoL compared to the general population, at least for the period where excess mortality applies. Limited evidence exists to support a 10% decrement from the population norm, and the EAG considers this value to be arbitrary, similarly to the value used in TA559. In fact, the company's clinical advisors considered that the long-term survivors should be between 10% and 20% lower HRQoL than the general population. The EAG notes also that previous TAs (e.g. TA649) considered the use of the general population utility directly without any reduction. The company presents a scenario analysis whereby after 2 years patients in the progression free health state experience the utility of the general population (no HRQoL adjustment / no reduction from the population norm) resulting in an ICER vs BR [redacted]).

4.2.9 Resources and costs

Confidential pricing arrangements

The EAG notes that there are a number of confidential commercial arrangements in place for drugs comprising the intervention and the comparator regimens, and for drugs currently in use as subsequent treatment options. The treatment acquisition costs used in the analyses presented in the company submission and the EAR (Section 6), include only the confidential pricing agreement for glofitamab and obinutuzumab.

Table 31 presents details of which comparator and subsequent treatments have confidential prices which differ from the publicly available list prices used to generate the results in this report. These prices were made available to the EAG, and were used to replicate all analyses presented in the EAR for consideration by the Appraisal Committee. Details of all confidential pricing arrangements and all results inclusive of these arrangements are provided in the confidential appendix to this report. These prices were correct as of 30th March 2023.

Table 31 Source of the confidential prices used in the confidential appendix

Treatment	Therapy	Form	Dose per unit	Pack size	Source of price used in model/type of confidential arrangement sent by NICE
Rituximab	BR & Pola-BR	IV	100mg	2	CMU
			500gm	1	CMU
Polatuzumab vedotin	Pola-BR	IV	30mg	1	PAS

		IV	140mg	1	PAS
Axicabtagene ciloleucel	Axi-cel	IV	1	1	PAS
Pixantrone	Pixantrone	IV	29mg	1	PAS
Lenalidomide	Lenalidomide	Oral(tablets)	25mg	21	CMU

Abbreviations: CMU, commercial medicines unit; PAS, patient access scheme

Resource use and cost evidence in the published literature

The company conducted a systematic review of the literature to identify cost and healthcare resource identification, measurement and valuation evidence in adult patients with R/R DLBCL in the 2L+ setting. Results of this review were reported in the main body of the CS (Section B.3.5.1). A description of the searches and some of the search strategies were included in Appendix J (pp. 96-112).

The searches were initially conducted in August 2021 and updated in September 2022. The updated review included 46 studies (22 full publications and 24 conference abstracts). The EAG does not have access to Evidence Based Medicine (EBM) Reviews and therefore cannot fully scrutinise these strategies.

The included studies were synthesised narratively. The costs and resource use extracted from each study are reported on Table 44 and 45 (Appendix J), respectively, alongside the studies' characteristics. The characteristics and results of the included studies were presented in Appendix J. The majority of studies were retrospective analyses (N=37), followed by cost-analyses (n=4). Other study designs were also included (e.g., longitudinal, cross sectional, economic framework for therapy valuation, etc.) The majority of studies took place in the US (N=31). Only one (multinational) study included UK patients; it reported total healthcare resource use costs from leukapheresis to 2-month post-infusion of tisagenlecleucel for individuals in the JULIET trial.[43]

Points for critique

The EAG presents an appraisal of the evidence identification search strategy in appendix. In brief, the EAG identified some issues with the clarity of reporting for the searches, the appropriateness of the search terms used and the referencing of search filters, but has no major concerns about the search strategy.

While the company identifies limitations for some of the studies (Section J.5.3, Appendix J, the company does not discuss the relevance of the studies to inform the cost-effectiveness analysis and if any of the evidence identified was considered in the model. However, the EAG is not concerned that relevant information may not have been considered, given that the studies identified appear to have limited generalisability to the England and Wales NHS.

Resource use and costs applied in the model

The resource use and costs included in the model comprise those associated with: drug acquisition and administration, glofitamab monitoring, acquisition and administration of treatments delivered post-progression, supportive care costs, and management of adverse events. Resource use estimates are informed by the NP30179 study, summary of product characteristics for each drug, and previous NICE guidance. Unit costs are mostly informed by national published sources, such as the National schedule of NHS costs,[44] the Personal Social Services Research Unit (PSSRU) costs, [45] the British National Formulary (BNF)[46] and the Drugs and pharmaceutical electronic market information tool (eMIT).[47] Costs in the model are expressed as pound sterling at 2020/21 prices (inflated to this price year when appropriate) and discounted at an annual rate of 3.5%.

The EAG identified a few errors in the model implementation of the costs described in the following sections, which were corrected by the company at PfCs. Costs presented in the subsequent sections refer to the version of the electronic model submitted in response to the EAG's PfCs (03 April 2023), unless otherwise stated.

Drug acquisition and administration

Table 32 summarises the resource use and cost associated with the acquisition of the drugs in each treatment under comparison. Given the model weekly cycles, acquisition (and administration) costs are only applied in the model cycles that contain the day of the treatment cycle when a drug is administered. The EAG notes that the original model submitted by the company had an error on the calculation of acquisition costs for rituximab and bendamustine, which was corrected at PfCs.

Table 32 Drug acquisition costs and resource use

Treatment	Drug component	Treatment schedule			Dose administered	Presentation (# units × dose)	List price per pack (PAS price)	Unit costs source	Cost per administration (PAS price)
		Tx cycle	Cycle day	Max # Tx cycles					
Glofitamab	Obinutuzumab	1	1	12	1000mg	1×1000mg	£3,312 ([redacted])	Company	£3,312 ([redacted])
	Glofitamab		8		2.5mg	1×2.5mg	£687 ([redacted])		£687 ([redacted])
			15		10mg	1×10mg	£2,748 ([redacted])		£2,748 ([redacted])
		≥ 2	1		30mg				£8,244 ([redacted])
BR	Bendamustine	Any	1 & 2	6	90mg/m^2	5×25mg	£34.08	eMIT	£65.85
						5×100mg	£82.89		
	Rituximab		1		375mg/m^2	2×100mg	£314.33	BNF	£1,162.41
						1× 500mg	£785.84		
Pola-BR	Bendamustine	Any	1 & 2	6	90mg/m^2	5×25mg	£34.08	eMIT	£65.85
						5×100mg	£82.89		
	Rituximab	Any	1		375mg/m^2	2×100mg	£314.33	BNF	£1,162.41
						1×500mg	£785.84		
	Polatuzumab vedotin				1.8mg/Kg	1×30mg	£2,370	BNF	£11,316.49
						1×140mg	£11,060		
Axi-cel	Axi-cel	One-off Tx	1	1	-	-	£280,451.00	NHSBSA DM+D	£280,451.00

Abbreviations: #, number; DM+D: dictionary of medicines and devices browser; Max, maximum; NHSBSA, NHS Business Services Authority; Tx, treatment.

The drug acquisition cost of the glofitamab treatment included the one-off cost of pre-treatment with obinutuzumab at the start of the model and subsequently the cost of glofitamab. In the first two treatment cycles (21 days per cycle), the glofitamab dose is escalated from 2.5mg to the maintenance dose of 30 mg. The treatment schedule and maximum treatment duration for glofitamab are in line with the provisional SmPC for glofitamab and the NP30179 study. For both glofitamab and obinutuzumab, costs in the model reflect a simple Patient Access Scheme (PAS) price discounts over their list prices of [redacted] and [redacted] respectively. The model estimated cost per administration assumes no wastage for obinutuzumab and glofitamab, which is appropriate given the drug presentations available.

For the pola-BR and BR treatments, the treatment schedule appears to be in line with what was used in TA649.[24]. The EAG notes that the company reported in the CS (Section B.3.5.3) a different dosing schedule for the bendamustine component of the BR treatment (i.e. 90-120 mg/m^2 on two consecutive days with dose de-escalation [120-90-70 mg/m^2] in case of toxicity) and maximum number of treatment cycles (i.e. 12 cycles) than that followed for the same component in the pola- BR treatment. This alternative schedule was sourced from the literature. [48] However, the bendamustine dose per treatment cycle was modelled as 90mg/m^2 for a maximum of 6 cycles in both BR and pola-BR.

For drug dosages dependent on patient characteristics such as weight or body surface area (BSA) (i.e., bendamustine, rituximab and polatuzumab vedotin), the model estimates individual patient dosages based on the distribution of weights and BSA in the safety population of the NP30179 study. Acquisition costs are estimated for each of the 154 individuals, assuming no vial sharing and an optimised combination of small and large vials to minimise the overall treatment cost. The cost per dose applied in the model is an average of the cost of optimised vial combination for each individual. In order to estimate the optimised vial combination, the company assumes that if the number of vials required to make up a planned dose is not an integer and less than 5% of the last vial is required to make up the planned dose, the number of vials is rounded down. Otherwise, the number of vials is rounded up. The approach taken by the company to estimate the acquisition costs for drug dosages dependent on patient characteristics appears to be appropriate and correctly implemented in the most up to date version of the company's model.

The acquisition costs for axi-cel were applied as a one-off cost at the start of the model, effectively assuming that the first administration of these CAR-T takes place at the same time as leukapheresis and pre-conditioning (this is discussed further at a later point in this section).

The administration costs of the drug components of the glofitamab, pola-BR and BR treatments are reported in Table 33. Note that this differs from the information presented in the company CS (Table 50, p153), but match the implementation in the company's model.

The proportion of patients who incur acquisition and administration cost with each drug component (with the exception of one-off treatments) is informed by the respective TTOT curves (see Appendix). Treatment stops if progression occurs or at the time point in the model that coincides with the maximum number of treatment cycles (whatever is earliest).

Table 33 Treatment administration costs for glofitamab, pola-BR and BR

Cost category	Unit cost	Source	Cost per administration
First administration of a drug component	£526.52	NHS reference costs 2020/21, Total HRGs, currency code SB14Z: Deliver Complex Chemotherapy, including Prolonged Infusional Treatment, at First Attendance	£588.92
	£62.40	Assumption (based on NICE TA649) that the preparation of an IV treatment requires ~39 minutes of pharmacist time.	
Subsequent administrations of a drug component	£470.62	NHS reference costs 2020/21, Total HRGs, currency code SB15Z: Deliver Subsequent Elements of a Chemotherapy Cycle	£533.02
	£62.40	Assumption (based NICE TA649) that the preparation of an IV treatment requires ~39 minutes of pharmacist time.	

The drug administration costs applied in the model for the glofitamab, pola-BR and BR treatments include the cost of i) administering and ii) preparing an infusional treatment, although the CS only mentions the first component i). In the model, TA649 is referenced as the source for the unit cost of preparing the infusion and this is assumed to take approximately 39 minutes of a pharmacist time. However, the cost of 39 minutes of a hospital pharmacist time in TA649 was £31.20, so it appears this cost was doubled in the model.

The company does not describe in the CS how administration and preparation costs were implemented. Examining the electronic version of the model, it seems that for pola-BR was assumed that polatuzumab vedotin, bendamustine and rituximab are being administered jointly at the first day in the treatment cycle (i.e. only one administration was costed for the three drug components) with another administration costed for the delivery of bendamustine at the second day of the treatment cycle. For the BR treatment, bendamustine (day one and two of the treatment cycle) and rituximab were costed as two separate administrations at the first day in the cycle and another administration cost for the administration of bendamustine at the second day in the treatment cycle. This suggests that for pola-BR, it was assumed that the cost of all three drug components is captured as a single administration, provided the administration takes place in the same day in the treatment cycle, whereas for BR it was assumed that each individual drug component will incur the cost of a separate administration. The administration cost approach for pola-BR is in line with how this cost element was implemented in TA649.

The CS states that the first administration of a drug would be done in hospital under clinical supervision and costed as the delivery of a complex chemotherapy, while subsequent administrations being conducted in an outpatient setting are costed as the delivery of a subsequent chemotherapy elements. However, this does not seem to apply to obinutuzumab, as its administration cost corresponds to that of a subsequent element of a chemotherapy, despite it being administered as a one-off.

The EAG also notes that the unit cost applied in the model for the subsequent administration of a drug component (£470.62) do not reflect administration in an outpatient setting. The administration unit costs in the model correspond to a weighted average of the respective currency code (SB14Z or SB15Z) in the NHS reference costs[44] across three settings (day case/ regular day night, outpatient, and other).

The administration costs for axi-cel were included as a one-off cost at model entrance, similarly to how the corresponding acquisition costs were modelled. In the company's base-case analysis, the axi-cel administration cost (£65,415) was informed by the revised NHS England CAR-T tariff,[49] which was applied in an ongoing appraisal of axi-cel for DLBCL after the first-line of treatment. The tariff (see CS, Table 51) comprises costs incurred before the administration of axi-cel (i.e. identification and work-up, leukapheresis and pre-conditioning) but also those associated with subsequent resource use directly related to receiving axi-cel (inpatient admission up to 28 days, follow-up in the vicinity of the centre and management adverse events up to day 28, and follow-up post discharge up to day 100). It is worth noting that the draft guidance to this appraisal acknowledges that £65,415 cost provided by NHS England may include double-counting and concluded that a total cost of £60,000 per person was a reasonable estimate to capture the costs of delivering axi-cel, but the company did not use this estimate for the current appraisal. The company conducted two scenario analysis varying the axi-cel administration cost to: i) £41,101, which was the value preferred by the committee in the CDF review of axi-cel for R/R DLBCL after the second line of treatment[20] and ii) £71,082, which adjusts the costs of elements of the revised NHS CAR-T tariff prior to axi-cel administration to reflect the costs incurred by the proportion of patients deemed eligible to receive axi-cel, but who do not reach infusion (see breakdown of costs in Table 52 of the CS).

The EAG notes that there is an error in the cost attributed to the 'follow-up post discharge up to 100 days' item of the NHS revised tariff, which is £5,351 in the source reference rather than £5,451. Since the total cost of £65,415 is not affected, this does not impact on the company's base-case (only the scenario analysis where the itemised costs are reweighted to £71,082 when it should have been £70,984).

Points for critique

The EAG noted above some inaccuracies and inconsistencies in the reporting of the administration costs for glofitamab, pola-BR and BR. First, the cost of preparing infusional treatments appears to have been doubled in comparison to what was used in TA649, [24] without a justification. Second, the costs of administering BR (assuming one administration cost per drug component) is not consistent with how pola-BR administration costs were implemented in the model (one single administration cost for all drug components administered in the same days), and is not in line with NICE TA649. This is likely to have overestimated the administration costs of the BR treatment. Third, the administration of obinutuzumab was costed as a subsequent treatment, without the company providing any justification. According to the clinical advisor to the EAG, obinutuzumab is delivered as a complex and prolonged treatment. This is also supported by the draft glofitamab SmPC [50], which states that [redacted]. The obinutuzumab SmPC[51] describes the need for premedication with oral and IV drugs, so as to mitigate the risk of adverse events. Therefore, the EAG considers that the administration of obinutuzumab should have been costed as a first administration (i.e, £526.52). Finally, the administration setting in the CS does not match the unit costs applied in the model for subsequent treatments. However, the EAG assumes this was a matter of inaccurate reporting, rather than an error.

In addition to the issues above, the EAG is concerned that no justification was provided for the implicit assumption that some drug components are administered jointly and costed as a single administration while others are costed as two separate administrations. We note that this is in contrast with the approach taken in TA649,[24] where all drug components administered in the same day of the treatment cycle incurred the cost of a single administration and infusion preparation.

Item 15. The administration costs for the glofitamab, pola-BR and BR treatments are based on unjustified assumptions, including inconsistencies across treatments and generally are not in line with a previous TA. Overall, the administration cost for BR may be overestimated and that of glofitamab underestimated.

The EAG is concerned that the cost of axi-cel administration may have been overestimated. In the most recently published NICE guidance for axi-cel in R/R DLBCL (TA872),[52] published in February 2023, the committee accepted the one-off cost of £41,101 for axi-cel administration. However, the final appraisal document (FAD) also suggests that the costs of conditioning chemotherapy drugs, stem cell transplantation and IV immunoglobulin (IVIG) were considered separately. So this £41,101 estimate may not be appropriate for the base-case analysis, as the conditioning chemotherapy and IVIG costs for axi-cel are not captured in the model used in the current appraisal. However, the draft

guidance for axi-cel for R/R DLBCL after one line of systemic therapy[53] clearly states the committee's preference for an axi-cel administration cost of approximately £60,000. The EAG considers, therefore, that the cost of axi-cel administration lies between £41,101 and £60,000.

Item 16. The administration cost for axi-cel is not in line with the most recent TA of axi-cel in the indication of this appraisal, and may have been overestimated.

In Section 3.2.1.4, the EAG described the criteria for glofitamab re-treatment in the NP30179 study protocol and noted that it was not clear whether glofitamab re-treatment observed in this study (n=[redacted]) took place at pre or post-progression. The company does not explicitly address the costs of re-treatment in the economic analysis. Re-treatment with glofitamab was not considered in the subsequent treatments' costs in the company's base-case analysis (see Table 35). It is unclear whether re-treatment was captured in the acquisition and administration costs (as well as monitoring costs, which are discussed in the next subsection)in the 'PF on-treatment' health state. Furthermore, and as noted above for glofitamab delayed doses, re-treatment may require repeating pre-treatment and step up dosing, depending on the gap between the last dose of glofitamab treatment and the first re-treatment dose.

Item 17. It is unclear whether the model capture the costs of glofitamab retreatment, and these costs may have been underestimated.

As noted in Section 0, the TTOT curves which inform the number of patients on treatment with glofitamab, pola-BR and BR, suggest that a small proportion of patients remain on treatment beyond the time point defined by the maximum number of treatment cycles for each drug component. In TA649, the committee considered it appropriate to limit the treatment duration with pola-BR by the maximum number of cycles (6) despite the TTOT curve suggesting patients remained on the treatment beyond that 4.15 months (the time point corresponding to 6 cycles). This was according to the company due to delayed doses with no patients having more than 6 cycles in the pivotal trial. The EAG had concerns as to how the TTOT KM curve had been constructed and the delayed doses included in the model. The committee accepted the company's approach as in line with clinical practice and the polatuzumab vedotin marketing authorisation, but noted the small impact on the ICERs (<£2,000 per QALY). Nevertheless, notes that there is a considerable gap between the maximum number of cycles for glofitamab ([redacted]) and the point at which the TTOD KM curve suggests there are no more patient on treatment ([redacted]). Furthermore, the draft glofitamab SmPC mentions that delayed or missed glofitamab doses may require repeating pre-treatment with obinutuzumab and in some cases also repeating the step-up dosing. If the gap between the maximum number of cycles and maximum observed treatment duration is due to delayed doses, it is unclear whether the delay resulted in repeated obinutuzumab pre-treatment or step-up dosing as these were

not costed in the model. The EAG does not, however, have sufficient information on to address this issue in scenario analysis.

Item 18. The truncation of TTOT for the drug components on treatment with glofitamab, pola-BR and BR by the maximum number of cycles assumed in the model, may artificially reduce costs of treatment if delayed doses are not appropriately captured in the model.

Finally, the EAG notes that the company did not consider the costs of the premedication and prophylactic medications to mitigate the risk of adverse events with obinutuzumab and glofitamab (described in Table 1 of the obinutuzumab SMPC[51] and Table 2 of the CS, respectively). In brief, these medications include intravenous and oral corticosteroids, oral analgesics, anti-pyrectics and/or anti-histamines. However, the magnitude of the costs associated with these medications are small and unlikely to impact on the estimates of cost-effectiveness. Furthermore, the company also did not include premedication and prophylactic medication costs for the comparators, so there seems to be an implicit assumption that the level of resource use for these medications is similar across treatments. This is in line with feedback received from the clinical adviser to the EAG, and therefore, we are not concerned about the exclusion of these costs.

Glofitamab monitoring

The company included the costs of monitoring for CRS in patients treated with glofitamab. This cost is not included for other comparators. This is appropriate because the comparators are either not known to present a risk of CRS (pola-BR and BR) or the cost of CRS monitoring is already considered in another category of costs (i.e., axi-cel). Details on how the monitoring costs were applied in the model are shown in Table 34. Note that the implementation of the monitoring cost for the glofitamab adjusted model engines was incorrectly applied by the company in the original version of the model but were corrected at clarification stage.

Table 34 Monitoring costs for glofitamab

Model Cycle	Tx cycle	Type of monitoring	Resource description	% Patients	Unit cost	Source
1	1: .day 8	At 1st glofitamab infusion	At least 10 hours after first Glofitamab infusion	100%	£620.14	NHS reference costs 2020/21, day case, activity weighted average of currency codes SA31-A-F: malignant
		For patients who have had a grade ≥2 CRS at glofitamab infusion	22 hours after infusion	17.5%	2 × £620.14	

2	1: .day 15	For patients who have had a grade ≥2 CRS at glofitamab infusion	22 hours after infusion	17.5%	2 × £620.14	lymphoma including Hodgkin's and Non-Hodgkin's

Abbreviations: Tx, treatment

The draft glofitamab SmPC[50] states that all patients must be monitored for CRS during infusion and for at least 10 hours after completion of the first glofitamab dose. It also states that individuals who experienced grade≥2 CRS with their previous infusion should be monitored after completion of the infusion.

Monitoring for the first glofitamab infusion was costed by the company as a day case admission for malignant lymphoma applying to all patients at model cycle 1 (model cycles start at zero) , but it is unclear why a day case setting was chosen. The EAG notes that the first infusion of glofitamab takes a minimum of 4 hours but can extend up to 8 hours, so it is debatable whether the 10 hours (or more) of monitoring could be achieved without admitting the individual for a night at the hospital.

The company applied a monitoring cost for the first and second glofitamab infusion to reflect the proportion of individuals who have had grade≥2 CRS with their previous glofitamab infusion. The unit cost applied to this corresponded to double that of day case admission due to malignant lymphoma; the company assumed this represented the cost of 22 hours of monitoring. This unit cost was then adjusted by the proportion of patients in the NP30179 study who had a grade≥2 CRS (the company estimated this as the average of [redacted] the rates with the Lee grading and the ASTCT grading systems, respectively, and applied to patients on treatment at cycle 1 and 2 in the model.

Points for critique

The EAG is concerned that the cost of monitoring for CRS with glofitamab may have been underestimated due to the assumption that this would take place in a day case setting rather than as an inpatient (particularly for the first glofitamab infusion; doubling the cost of a day case may have been an acceptable proxy of the true cost). However, the EAG did not identify a more appropriate source for this unit costs, as the cost of an elective admission (for the same currency codes as used by the company to cost the day case) appears to be too high (£11,169) to be representative of the resource use required for monitoring patients overnight. Given this cost is only applied for a limited number of cycles, the EAG considers that it is unlikely that correcting it would impact on the estimates of cost-effectiveness.

The company does not discuss in the CS whether monitoring for ICANS would require additional healthcare resources, although the potential for this was raised by the company's clinical advisors

organised by the company. [54] The company's Advisory Board noted that there might be some shift on the monitoring resource use for CRS and ICANS, but it was unclear how this is likely to occur in clinical practice. The EAG notes that the type of resource use potentially needed to monitor ICANS may also impact on the setting of delivery for glofitamab. For example, if monitoring for these AEs were to require provision for specialised neurological critical care units, this may limit the type of NHS centres where glofitamab can be administered (at least for the initial treatment infusions where ICANS are more likely to occur). The EAG does not have sufficient evident in order to address this concern more formally.

Item 19. The cost of monitoring ICANS was not considered by the company, and it is uncertainty whether this would increase the level of resource use required to monitor patients treated with glofitamab

Treatment costs at subsequent lines of therapy

The costs of subsequent lines of therapy are applied in the model as a one-off cost at the cycle for the proportion of patients who transition from the pre-progression to the post-progression health state. In the company's base-case analysis this cost is independent of treatment received in PFS (i.e., glofitamab, pola-BR, BR or axi-cel), and assumes the distribution of post-progression treatments (regardless of line at which they were delivered) and mean duration per type of treatment as was observed in the NP30179 safety population (n=154). The details for the post-progression treatments cost calculation are presented in Table 35; unit costs for the drug components for each regimen are reported in Table 85 of the company's response to PfCs.

The treatment schedules reported in Table 35 for R-GemOx, R-CHOP, lenalidomide and pixantrone treatments were extracted from the company's post PfCs model (3rd April 2023); these treatment schedules were not described in the CS and their sources were not referenced. The estimated costs per week include the acquisition, administration, and preparation costs for each treatment (as applicable).

Table 35 Costs of subsequent lines of therapy

Post-discontinuation therapies	Tx schedule	Tx distribution	Mean duration (weeks)	Tx cost per week *,**	One-off cost*,**	Assumptions
BR	See Table 32	1.79%	5.14	[redacted]	NA	Tx cycle cost distributed evenly over the cycle duration (as cost per Tx cycle divided by the Tx cycle duration)
R-GemOx	R 375mg/m^2 D1,Gem 100mg/m^2 D2, Ox 100mg/m^2 D2; every 14 days	2.68%	4.50	[redacted]	NA	
R-CHOP	R 375mg/m^2 D1, Cyc 750mg/m^2 D1, Doxo 50mg/m^2 D1, Vin 1.4mg/m^2 D1, Pred 100mg D1-5; every 21 days	2.68%	2.81	[redacted]	NA	
Other R-chemo	NA	8.93%	4.11	[redacted]	NA	Average of BR, R-GemOX & R-CHOP weekly Tx costs
Other chemo excluding R	NA	22.32%	5.07	[redacted]	NA	Average of bendamustine, GemOX, CHOP, lenalidomide & pixantrone weekly Tx costs
Pola-BR	See Table 32	8.93%	4.71	[redacted]	NA	Cost per Tx cycle appears to be divided by the Tx cycle duration
Lenalidomide	25mg/m^2 D1-21; every 28 days	1.79%	2.00	[redacted]	NA	Tx cycle cost distributed evenly over the cycle duration (as cost per Tx cycle divided by the Tx cycle duration)[redacted]
Pixantrone	50mg/m^2 D1, D8, D15; every 28 days	0.89%	0.14	[redacted]	NA	
Clinical Trial/Other	NA	17.86%	5.62	[redacted]	NA	Average of the weekly Tx costs of all regimens above
Radiotherapy	NA	15.18%	1	NA	[redacted]	Stated to take same costing approach as per the Tafa-Len NICE TA
Allogeneic SCT	NA	6.25%	1	NA	[redacted]	Estimated as per NICE TA559/TA567
Autologous SCT	NA	1.79%	1	NA	[redacted]	
CAR-T	See Table 32	8.93%	1	NA	[redacted]	Same cost as calculated for axi-cel at PFS
Glofitamab	See Table 32	SA only	1	NA	[redacted](SA)	Calculated as the total costs of drug acquisition costs and administration costs estimated by the glofitamab unadjusted engine***
	Total cost applied at transition to PP (base-case analysis)				[redacted]	Weighted average of the cost of each regimen for its duration by the Tx distribution (% patients)

*, extracted from the company's post PfCs model (3rd April 2023); **, includes acquisition, administration and preparation costs; ***, model output estimated over the time horizon (includes adjustments for discounting, half-cycle correction and TTOT). **Abbreviations:** chemo, chemotherapy; ; Cyc, cyclophosphamide; D, day; Gem, gemcitabine; NA, not applicable; NR, not reported; Ox, oxaliplatin; Pred, prednisolone; R, rituximab; SA, scenario analysis; SCT, stem cell transplant, Tafa-Len; tafasitamab plus lenalidomide; Tx, treatment; Vin, vincristine.

At PfCs, the EAG expressed concerns about the clinical plausibility of assuming the post-progression treatment distribution (and treatment duration) is independent from treatment received in the PFS state, and asked the company to explore alternative assumptions (potentially using other sources of data to inform the comparators' post-progression treatments). The company argued that "basing post-progression treatment shares and treatment duration on information from GO29365, would mean basing post-progression costs on outdated estimates of treatment shares, which would lead to an underestimation of the use of post-discontinuation CAR-T and SCT" and that using NP30179 as the source of evidence for these parameters is likely to be more representative source for DLBCL 4L+. However, the company did present two scenarios analysis where the following assumptions were explored, where it is assumed that no patient is retreated with the treatment received in PFS, and instead retreatment for each comparator is:

1. Replaced with glofitamab (see Table 82, response to PfCs).
2. Set to zero and the remaining treatments are re-weighted so the displaced treatment proportion is equally distributed across all remaining post-progression treatments (see Table 83, response to PfCs).

The company's base case results were robust to either of the scenarios, but results favour the cost-effectiveness of glofitamab less when compared to the company's base-case analysis (see Table 84, response to PfCs).

Points for critique

The EAG remains concerned about the clinical plausibility of assuming the same post-progression treatments for all regimens under comparison. Although the company considers that the post-progression treatments observed in NP30179 trial are more reflective of current DLBCL 4L+ treatment shares, the EAG notes that the clinical effectiveness data may not reflect the benefits of more recent treatments. Thus, to reflect current day 4L+ treatments on costs alone for the comparators without adjusting the clinical effectiveness data too, may bias the cost-effectiveness analysis in favour of treatments for which the clinical evidence was more recently collected. For example, CAR-T cell therapy was not routinely available when Hong et al (2018) study collected the data (2011-2015) which informs the clinical effectiveness of BR.[9] Therefore, the post-progression survival with BR may not include the benefits of downstream CAR-T treatment, and if it does not, the estimates of cost-effectiveness may be biased against BR. This concern is not addressed by the company's scenarios described above.

For axi-cel including the costs of subsequent CAR-T is not current clinical practice, according to advice to the EAG, and therefore, it is debatable if the distribution of post-progression subsequent

therapies in NP30179 can be considered representative of DLBCL 4L+ treatment for patients previously treated with CAR-T.

Item 20. The distribution of subsequent treatments across the comparator regimens under comparison is an area of uncertainty, and the cost of subsequent treatments for axi-cel in particular may have been overestimated.

The EAG believes there is a model error affecting the cost of R-CHOP, other R-chemotherapy and other chemo excluding rituximab in Table 35. Although the tab 'Cost inputs' in the model suggests that cyclophosphamide was administered at a 750mg/m^2 (administered every 21 days) as part of the R-CHOP (and CHOP) regimen, the model implements the cost of cyclophosphamide 500 mg/m^2 (administered for 3 days). Furthermore, the EAG was unable to validate the unit costs applied in the company's model for some of the drug components of the CHOP regimen, namely those of cyclophosphamide, doxorubicin, vincristine and prednisolone. This may be due to the source data, available as online resources (BNF and eMIT) being updated in the period between the submission of the company's documentation and the EAG updating the model. In addition, one of the presentations of vincristine presentations included in the model (5mg/5mL, 5 units) has been discontinued.[55] The EAG corrects the dosage of cyclophosphamide and the unit costs for the drug components of the CHOP regimen in Section 6.

In Section 3.2.1.4, the EAG described the criteria for glofitamab re-treatment in the NP30179 study protocol and noted that it was not clear whether glofitamab re-treatment observed in this study (n=[redacted]) took place at pre or post-progression. The company does not explicitly address re-treatment in the economic analysis. Re-treatment with glofitamab was not considered in the subsequent treatments in the company's base-case analysis (see Table 35). The EAG is not able to formally explore the impact of re-treatment with glofitamab, given the uncertainties in whether it took place at pre or post-progression and required repetition of pre-treatment and step-up dosing.

Supportive care costs

The company included resource and cost estimates for the pre- progression (PFS-on and PSF-off treatment) and progression health states. The same health state costs were assumed for each treatment, with differences between treatments and hence differences between treatment determined by differences in the proportion of patients i) residing or ii) transitioning to each state over time. The resource use was largely informed by the assumptions in TA649, which were sourced originally from a key opinion leader survey in TA306. Unit costs were sourced from NHS reference costs 2020/21[56] and PSSRU, 2021.[45]

These costs were labelled supportive care costs and include the following categories of medical resource use and associated costs: i) professional and social services, ii) health care professionals and hospital resource use, iii) treatment follow-up, and iv) tests undergone at the point of transitioning to the post-progression health state. The cost categories i) to iii) are applied as weekly costs for the duration of health state permanence, whereas category iv) is applied as a one-off cost applied to the proportion of individuals who transition to the post-progression health state at each model cycle. The company reports the resource use and costs applied in the model for categories i) to iii), and for category iv) in the CS (Table 56 and 57, respectively); the costs applied in the model are summarised in Table 36.

Table 36 Supportive care costs applied in the model

	PFS-on treatment	PFS-off treatment	Post-progression	Transition to progression
Weekly cost	£528.90	£182.59	£428.72	-
One-off cost	-	-	-	£211.57

In the company's base-case analysis, the costs of PFS-off treatment is set to zero from the point of long-term remission on PFS (i.e. 2 years) onwards.

Points for critique

The EAG considers the supportive care costs were modelled in line with previous NICE appraisals, but notes that the assumption that the cost of supportive care becomes zero for patients in long-term remission may be too optimistic, regardless of when remission is assumed to occur. The clinical advisor to the EAG suggested that patients might still be followed-up in oncology or haematology services for up to 5 years, given the uncertainties around long term remission with glofitamab. The EAG does not explore this uncertainty in Section 6.2, because it is unclear how frequently this follow-up would take place and for how long. Furthermore, it is expected that the long-term remission assumptions around mortality and HRQoL are likely to have a greater impact on the estimates of cost-effectiveness.

Adverse events

As mentioned in Section 0, the company considered in their base-case analysis the costs of managing treatment-related adverse events. The unit costs are applied to the AEs modelled as weekly probabilities (see Table 30) and are summarised in Table 37.

Table 37 Adverse events unit costs

Adverse Event	Unit costs	Source
Anemia	£409.10	**NHS reference costs 2020/21, day case, activity weighted average of currency codes: SA01G-K, SA03G-H, SA04G-L, SA05G-J**
CRS	£11,601.05	**Calculated based on assumptions (see Table 38)**
Diarrhoea	£576.27	**NHS reference costs 2020/21, day case, activity weighted average of currency codes: FD10J-M**
Hypophosphatemia	£462.58	**NHS reference costs 2020/21, day case, activity weighted average of currency codes: KC05G-N**
Febrile neutropenia	£2,153.89	TA306 (£1,627); inflated to 2022
Leukopenia	£366.66	**Same as for neutropenia**
Lymphopenia	£557.42	**NHS reference costs 2020/21, day case, activity weighted average of currency codes: SA08G-J**
Lymphocyte count decreased	£557.42	**Same as for lymphopenia**
Neutrophil count decreased	£366.66	**Same as for neutropenia**
Neutropenia	£366.66	**NHS reference costs 2020/21, day case, activity weighted average of currency codes: SA35A-E**
Pneumonia	£782.27	**NHS reference costs 2020/21,** NES**, activity weighted average of currency codes**: DZ11K-V
Platelet count decreased	£414.46	**Same as for thrombocytopenia**
Septic shock	£1,978.27	**NHS reference costs 2020/21, NES, activity weighted average of currency codes**: WJ06A-F
Thrombocytopenia	£414.46	**NHS reference costs 2020/21, day case, activity weighted average of currency codes: SA12G-K**
Vomiting	£632.98	**NHS reference costs 2020/21, day case, activity weighted average of currency codes: FD10D-M**
White blood cell count decreased	£366.66	**Same as for neutropenia**

NES, non-elective short stay

The company stated (response to PfCs question B29) that they attempted to follow the same approach to inform the unit costs for the AEs, as per previous TAs. The EAG notes that the currency codes selected largely match those applied in TA649 [24] but costed as per the NHS reference costs 2020/21 in line with the current appraisal cost year. The exception are the unit costs for two adverse events which were not identified in TA649 (white blood cell count decreased and hypophosphatemia) and required additional assumptions from the company.

The cost of managing CRS for glofitamab was calculated based on the costs detailed in Table 38.

Table 38 Calculation of CRS management costs for glofitamab

Cost category	Unit	Unit cost	Total cost	Unit cost source	Assumptions
Tocilizumab acquisition	2	£767.49	£1,534.98	BNF	.No wastage: £1.28/mg of drug .Based on a dosage of 8 mg/kg and a weight of 74.95Kg (average weight in NP30179)
Tocilizumab preparation	2	£31.20	£62.40	TA812*	.Pharmacist time .1 hour infusion time
Tocilizumab administration	2	£230.27	£460.54	NHS reference costs 2020/21,	.Outpatient Multiprofessional Non-Admitted Face-to-Face Attendance, Follow-up, Rheumatology, Consultant Led, currency codes**:** WF02A .Rheumatologist administers tocilizumab
ICU hospitalisation	4	£2385.78	£9,543.12	NHS reference costs 2020/21	.Critical care, 'Non-specific, general adult critical care patients predominate' service: currency codes: XC01Z- XC07Z
Total cost			£11,601.05		

*, EAG could not validated this source – note that the unit cost appears consistent with 39 minutes of pharmacist time for the preparation of the infusion as applied in TA649 for the preparation of infusional treatments[24]

The cost of managing CRS for glofitamab was calculated as a one-off cost applied at the start of the model for the company's scenario analyses presented in response to PfCs (question B12). The company noted that this approach to modelling the costs of CRS is a conservative one, as not all patients in the glofitamab arm are expected to experience CRS, due to the proportion that discontinues treatment before the first glofitamab dose.

Points for critique

The EAG notes a number of uncertainties affecting the cost of managing CRS for glofitamab patients has been underestimated in the company's base-case analysis. Firstly, the EAG believes that spreading the cost of CRS over the treatment follow-up is not consistent with the time profile for the occurrence of this AE in the NP30179 study, [redacted] Modelling CRS as a weekly probability for those patients still on treatment may underestimate the costs of managing this AE. Secondly, the assumption of no wastage when calculating the acquisition costs of tocilizumab is unlikely to hold, given that this drug is a solution prepared for infusion that should be used immediately and can only be stored for 24 hours to two weeks once diluted (depending on preparation conditions) according to its SmPC.[57] Therefore, it is debatable whether any tocilizumab remnants could be used for another patient. Thirdly, it is unclear to the EAG why it was assumed that the drug administration was performed by rheumatology consultant in an outpatient setting. The company justified this at PfCs (response to question B28), as being due to rheumatologist being experienced in administering tocilizumab. Fourthly, the clinical advisor to the EAG considered that in addition to the cost categories included, patients would also require additional ward days after ICU. Finally, the cost of

managing CRS was applied as an aggregated cost and does not incorporate the PAS price for tocilizumab (as the list price for tocilizumab was not reported originally in the CS and, therefore, the PAS price could not be obtained within the timeline for the EAG appraisal).

Overall, the EAG considers that the uncertainties affecting the acquisition and administration costs of tocilizumab are unlikely to impact on the cost-effectiveness estimates. It is unknown whether the uncaptured costs of hospitalisation after ICU may be more impactful as to the EAG could not identify evidence on the length of stay for these admissions. Thus, this issue is not explored in sensitivity analysis.

The company did not include the costs of intravenous immunoglobulin (IVIG) for the management of B-cell aplasia, and AE that has been previously included in the CAR-T cell NICE appraisals (e.g., TA559 and TA567). [20, 22] The company argued in response to PfCs question B27 that there is no mechanistic evidence to support the occurrence of B-cell aplasia with glofitamab given it targets CD20 (as opposed to CAR-Ts which target CD19) and that no B-cell aplasia was observed in NP30179. While hypogammaglobulinemia could have been used as a proxy for B-cell aplasia requiring treatment with IVIG, the company stated that only 2 patients in the NP30179 safety cohort had grade 2/non-serious hypogammaglobulinemia that required treatment with IVIG. Thus, the EAG notes the omission of this cost as an uncertainty, but agrees that existing evidence does not suggest this will have a considerable impact on cost-effectiveness.

Finally, not all adverse events included in the model were costed by the company. This suggests that the company judged these AEs unlikely to result in the consumption of healthcare resource use. However, this assumption was not justified by the company. The EAG summarises in Table 39 the adverse events that were not costed, alongside their estimated weekly probabilities in the model.

Table 39 Adverse events not costed in the model

Adverse event	Weekly probability		
	Glofitamab	BR	Pola-BR
Anorexia	[redacted]	[redacted]	[redacted]
Constipation	[redacted]	[redacted]	[redacted]
Fatigue	[redacted]	[redacted]	[redacted]
Insomnia	[redacted]	[redacted]	[redacted]
Tumour flare	[redacted]	[redacted]	[redacted]

It is unclear whether the company decided to not cost these AEs deliberately, because they considered it unlikely to result in the consumption of healthcare resource use or if these costs were omitted by

mistake. Given that the EAG did not identify unit costs for these AEs in other relevant NICE appraisals (TA872, TA649, TA567, TA559, and the ongoing appraisal of tafasitamab plus lenalidomide)[20-22, 52, 58] and that it is unclear if the company assumed these AEs do not result in costs to the healthcare system, the EAG has not explored this issue further. The EAG believes that failing to include these costs will have a negligible impact on the cost-effectiveness estimates.

Item 21. The costs of managing adverse events associated with glofitamab is an area of uncertainty, particularly for CRS.

5 COST EFFECTIVENESS RESULTS

5.1 Company's cost effectiveness results

Following the clarification stage, the company provided an updated model with several revisions and corrections. The company's deterministic base-case model results are summarised in Table 40 and are based on the updated version of the model. The company's base case results assume a QALY weight of 1.2 for BR and a QALY weight of 1.0 for pola-BR and axi-cel.

The updates to the company's original base-case analysis (reported in Table 65, CS) included corrections requested by the EAG at the clarification stage to the following elements:

- Number of CRS events in the glofitamab population from 5 to 6;
- Dosage calculations to account for number of vials per package for each drug;
- Implementation of the cost of monitoring individuals treated with glofitamab across all weighted glofitamab engines;
- Unit costs of allogeneic SCT.
- Unit costs for haematologist and oncologist visits in supportive care.

In addition to these, the company's updated base-case analysis also included revisions to the:

- List prices of lenalidomide 25 mg, cyclophosphamide 500 mg, doxorubicin 10, 50, and 200 mg, vincristine 1 and 2 mg, gemcitabine 1200 mg, oxaliplatin 50 and 100 mg (see response to question B32 in PfCs).
- The unit cost for ICU hospitalisation for patients with CRS (see response to question B28 in PfCs).

Table 40 Company deterministic updated base-case analysis – deterministic results

	Total Costs	Total LYG	Total QALYs	Incr. Costs	Incr. LYG	Incr. QALYs	ICER (£ per QALY gain)	NMB at £30,000
Glofit vs BR								
Glofit								
BR								
Glofit vs Pola-BR								
Glofit								
Pola-BR								
Glofit vs Axi-cel								
Glofit								

	Total Costs	Total LYG	Total QALYs	Incr. Costs	Incr. LYG	Incr. QALYs	ICER (£ per QALY gain)	NMB at £30,000
Axi-cel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: Glofit: glofitamab; BR: bendamustine plus rituximab; Pola-BR: polatuzumab vedotin in combination with bendamustine and rituximab; Axi-cel: axicabtagene ciloleucel; LYG: life years gained; QALY: quality-adjusted life year; Inc.: incremental; ICER: incremental cost-effectiveness ratio; NMB: net monetary benefit; NE: northeast quadrant of the cost-effectiveness plane; SE: southeast quadrant of the cost-effectiveness plane; SW: southwest quadrant of the cost-effectiveness plane.

Glofitamab was more costly ([redacted]) and more effective ([redacted] QALYs and [redacted] LYG) relative to BR, less costly ([redacted]) but more effective ([redacted] QALYs and [redacted] LYG) compared to pola-BR, and less costly ([redacted]) and less effective ([redacted] QALYs and [redacted] LYG) relative to axi-cel. This resulted in a deterministic ICER of [redacted] per QALY for glofitamab versus BR, which lies within the northeast quadrant of the cost-effectiveness plane, glofitamab being dominant versus pola-BR, which lies in the SE quadrant and where pola-BR is dominated by glofitamab, and an ICER of [redacted] per QALY for glofitamab versus axi-cel, which lies within the SW quadrant of the cost-effectiveness plane.

The majority of QALY gains for each intervention were generated within the progression-free health state, as can be seen in Table 41.

Table 41 Summary of QALY gains by health state.

Comparator	PF	PD	Total
Glofitamab-adjusted BR	[redacted]	[redacted]	[redacted]
BR	[redacted]	[redacted]	[redacted]
Glofitamab-adjusted Pola-BR	[redacted]	[redacted]	[redacted]
Pola-BR	[redacted]	[redacted]	[redacted]
Glofitamab-adjusted Axi-cel	[redacted]	[redacted]	[redacted]
Axi-cel	[redacted]	[redacted]	[redacted]

Abbreviations: Glofit: glofitamab; BR: bendamustine plus rituximab; Pola-BR: polatuzumab vedotin in combination with bendamustine and rituximab; Axi-cel: axicabtagene ciloleucel; PF: progression-free status; PD: progressed disease status.

Mean costs in the PF health state included treatment, drug administration, adverse events, and supportive care costs. Mean costs in the PD health state included supportive care and post-discontinuation therapy costs. A summary of disaggregated costs for each health state is shown in Table 42.

Table 42 Summary of disaggregated costs.

Comparator	Progression Free				Progressed Disease		Total costs
	Treatment	Drug Admin	Adverse Events	Supportive Care	Supportive Care	Post-disc therapy	
Glofit vs BR							
Glofitamab-adjusted BR	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BR	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Glofit vs BR							
Glofitamab-adjusted Pola-BR	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pola-BR	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Glofit vs Axi-cel							
Glofitamab-adjusted Axi-cel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Axi-cel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: Glofit: glofitamab; BR: bendamustine plus rituximab; Pola-BR: polatuzumab vedotin in combination with bendamustine and rituximab; Axi-cel: axicabtagene ciloleucel; Admin: administration; Post-disc therapy: post-discontinuation therapy.

Main cost drivers of cost-effectiveness results are treatment costs, particularly for axi-cel with mean treatment costs being estimated at [redacted], and post-discontinuation therapy costs. Mean costs were higher in the PF health state relative to PD for all glofitamab-adjusted populations, Pola-BR, and axi-cel. The PD health state for BR generated greater mean costs ([redacted]) relative to the PF health state ([redacted]). The majority of this mean cost difference for BR is driven by a low treatment cost ([redacted]) and high post-discontinuation therapy cost ([redacted]). AE costs for axi-cel are assumed to be captured in the NHS CAR-T tariff and thus, considered to be £0 to avoid double counting.

5.2 Company's sensitivity analyses

5.2.1 One-Way Deterministic Sensitivity Analysis

The company presented a series of one-way deterministic sensitivity analyses in Figures 37-39 of the CS, one for each comparison, to assess the impact of varying key model input parameters on net monetary benefit (NMB) at a cost-effectiveness threshold of £30,000 per additional QALY. The company indicated this analysis suggests the model was most sensitive to assumptions relating to long-term remission for PFS and OS, the treatment and subsequent treatment costs of axi-cel, and the HRQoL adjustment factor for excess comorbidities in long-term remission, i.e., utility of the age-matched UK general population reduced by 10%.

The CS did not provide a justification for the lower and upper threshold values chosen for the one-way deterministic sensitivity analysis. In the cost-effectiveness model, the company reported using an

arbitrary range of ±20% variation around the base case deterministic mean values over which to run the sensitivity analysis, with the exception of the long-term remission/survivorship timepoints for PFS and OS, which were varied across a wider range of estimates (0 to 5 years). *The EAG was able to replicate the one-way deterministic sensitivity analysis provided in the original submission.*

Following clarifications, the company submitted an updated model with several changes and corrections which implied updated cost-effectiveness results (as reported in Table 40), but did not report updated one-way deterministic sensitivity analyses.

Points for Critique

The EAG was satisfied with the approach used to vary the long-term remission/survivorship timepoints for PFS and OS across 0 to 5 years, as it provided a robust range of estimates in line with previous TAs for DLBCL. The EAG were not provided with any rationale for why all other parameters were varied across an arbitrary approach of ±20% around the mean value.

5.2.2 Scenario Analyses

The company presented a series of scenario analyses in Tables 67 and 68 of the original submission. These analyses provided information on the overall robustness of the model results to uncertainty relating to the model time horizon, patient baseline characteristics, sources for utility values, axi-cel administration costs, assumptions underlying survival modelling, and discounting.

Following clarifications, although the company model was updated, the company did not provide updated scenario analyses. The EAG has therefore updated these scenarios and provide results in Table 43.

Table 43 Updated Scenario Analysis (ICER, £ per additional QALY)

Parameter	ICER vs. BR	CE plane quadr.	ICER vs. Pola-BR	CE plane quadr.	ICER vs. Axi-cel	CE plane quadr.
Base Case	[redacted]	NE	Dominant	SE	[redacted]	SW
Model time horizon						
30 years	[redacted]	NE	Dominant	SE	[redacted]	SW
40 years	[redacted]		Dominant		[redacted]	
50 years	[redacted]		Dominant		[redacted]	
Patient baseline characteristics						
Average cohort age background mortality (35 year time horizon)	[redacted]	NE	Dominant	SE	[redacted]	SW
Utilities						
EORTC-QLQ-C30 Mapping (Direct)	[redacted]		Dominant		[redacted]	
TA306 (FAD values)	[redacted]		Dominant		[redacted]	

Parameter	ICER vs. BR	CE plane quadr.	ICER vs. Pola-BR	CE plane quadr.	ICER vs. Axi-cel	CE plane quadr.
Base Case	[redacted]	NE	Dominant	SE	[redacted]	SW
TA559	[redacted]	NE	Dominant	SE	[redacted]	SW
Costs						
Axi-cel admin cost (£41,101)	[redacted]	NE	Dominant	SE	[redacted]	SW
Axi-cel admin cost (£71,083)	[redacted]		Dominant		[redacted]	
Survival modelling						
Proportional hazards assumed (use of ITC HRs for PFS and OS)	[redacted]	NE	Dominant	SE	[redacted]	SW
Midpoint HR (OS, PFS) between 1 and ITC estimate: glofit vs. axi-cel	-	-	-	-	[redacted]	
No long-term remission (PFS cure point)	[redacted]	NE	[redacted]	**NE**	[redacted]	
No long-term survivorship (OS cure point)	[redacted]		Dominant	SE	[redacted]	
No PFS cure point for BR and Pola-BR	[redacted]		Dominant		[redacted]	
No HRQoL adjustment in LTR/S	[redacted]		Dominant		[redacted]	
No excess mortality in LTR/S (SMR=1.0)	[redacted]		Dominant		[redacted]	
Discounting						
1.5% discounting for costs and effects	[redacted]	NE	Dominant	SE	[redacted]	SW

Abbreviations: BR: bendamustine plus rituximab; Pola-BR: polatuzumab vedotin in combination with bendamustine and rituximab; Axi-cel: axicabtagene ciloleucel; CE: cost-effectiveness; HR: hazard ratio; admin: administration; OS: overall survival; PFS: progression-free survival; ITC: indirect treatment comparison; Quadr.: quadrant of the cost-effectiveness plane; QoL: quality of life; LTR/S: long-term remission/survivorship; vs.: versus; NE: northeast; SE: southeast; SW: southwest.

For the comparison with BR, ICERs from the scenario analyses ranged between [redacted] per QALY gained (No PFS cure point) to [redacted] per QALY gained (No long-term remission PFS cure point). Despite the variation, all ICERs remained in the NE quadrant of the cost-effectiveness plane, i.e. glofitamab is estimated to be more costly and effective than BR. For the glofitamab vs pola-BR comparison, ICERs from the scenario analyses ranged between glofitamab being dominant (No PFS cure point) and [redacted] per QALY gained (No long-term remission PFS cure point). With the exception of the latter scenario (No long-term remission PFS cure point), for which the ICER was in the NE quadrant of the cost-effectiveness plane, all remaining scenarios remained within the SE quadrant, i.e. glofitamab is cost saving and more effective than pola-BR. For the glofitamab vs axi-cel comparison, ICERs from the scenario analyses ranged between [redacted] per QALY gained (1.5% discounting for costs and effects) and [redacted] per QALY gained (Midpoint HR for PFS and OS between 1 and ITC estimate for glofitamab vs axi-cel). Despite the variation, all ICERs remained in

the SW quadrant of the cost-effectiveness plane, i.e. glofitamab less costly and also less effective than axi-cel. A note that ICERs in the SW quadrant of the cost-effectiveness plane above pre-defined cost-effectiveness thresholds indicate that the new technology is cost-effective.

The impact of the key drivers of cost-effectiveness in the scenario analyses were primarily related to assumptions around the long-term remission/survivorship and the extrapolation of treatment effects on survival. This is in line with findings from the one-way deterministic sensitivity analysis.

Points for Critique

The EAG notes the company did not provide updated scenario analyses following clarification and has therefore provided updated analyses here. Key drivers of uncertainty relate to assumptions around the long-term remission/survivorship and the extrapolation of treatment effects on survival.

5.2.3 Probabilistic Sensitivity Analysis

In their original submission, the company performed a probabilistic sensitivity analysis (PSA) where parameters were sampled probabilistically based on 1000 iterations. The company conducted their PSA using a bootstrap sampling method with 1000 bootstrapped parameter samples, although this approach was not justified in the CS. Upon clarification, the company indicated that this approach was preferred over the standard approach of using variance-covariance matrices. The bootstrap approach accounts for between-parameter correlations (e.g. PFS and OS correlation), while the standard approach has several limitations when applied to area-under-the-curve models, such as the partitioned state model used for this submission.

According to the PSA provided by the company in Table 66 of the CS, the mean probabilistic ICER was [redacted] per QALY gained for glofitamab versus BR, which is higher than that of the deterministic analysis ([redacted] per QALY gained), but still lies within the NE quadrant of the CE plane. The mean probabilistic ICER was [redacted] per QALY gained for glofitamab versus Pola-BR, which is also higher than the deterministic value ([redacted] per QALY gained), but still lies within the SE quadrant of the CE plane. Similarly, the mean probabilistic ICER was [redacted] per QALY gained for glofitamab versus axi-cel, which was lower than the deterministic value ([redacted] per QALY gained) and still lies within the SW quadrant of the CE plane.

Following clarification, the company provided 3000 bootstrapped parameter samples to support conducting PSA with up to 3000 iterations but did not provide updated probabilistic ICERs from their updated economic model. Using the updated economic model, the EAG conducted multiple PSA analyses for different scenarios, i.e., 1000 and 3000 PSA iterations using both the bootstrap sampling method and the variance-covariance method. The EAG notes that under different PSA conditions,

using 3000 iterations with either method resulted in stable parameter estimates compared to 1000 iterations. Results for the updated PSA model are presented in Table 44.

Table 44 PSA results for 3000 iterations using the bootstrapped approach

	Total Costs	Total LYG	Total QALYs	Incr. Costs	Incr. LYG	Incr. QALYs	ICER (£ per QALY gain)	NMB at £30,000
Glofit vs BR								
Glofit	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BR	[redacted]	[redacted]	[redacted]					
Glofit vs Pola-BR								
Glofit	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Glofitamab dominant	[redacted]
Pola-BR	[redacted]	[redacted]	[redacted]					
Glofit vs Axi-cel								
Glofit	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Axi-cel	[redacted]	[redacted]	[redacted]					

Abbreviations: Glofit: glofitamab; BR: bendamustine plus rituximab; Pola-BR: polatuzumab vedotin in combination with bendamustine and rituximab; Axi-cel: axicabtagene ciloleucel; LYG: life years gained; QALY: quality-adjusted life year; Inc.: incremental; ICER: incremental cost-effectiveness ratio; NMB: net monetary benefit; NE: northeast quadrant of the cost-effectiveness plane; SE: southeast quadrant of the cost-effectiveness plane; SW: southwest quadrant of the cost-effectiveness plane.

According to these findings, the mean probabilistic ICER was [redacted] per QALY gained for glofitamab versus BR, which is about the same as the deterministic analysis ([redacted] per QALY. The mean probabilistic ICER was [redacted] per QALY gained for glofitamab versus Pola-BR, which is slightly lower than the deterministic value ([redacted] per QALY gained. Finally, the mean probabilistic ICER was [redacted] per QALY gained for glofitamab versus axi-cel, which is lower than the deterministic value ([redacted] per QALY gained), but still lies within the SW quadrant of the CE plane, indicating glofitamab is less costly and less effective relative to Axi-cel.

Points for Critique

The EAG is satisfied with the rationale provided for using a bootstrapped approach to reflect second order uncertainty and correlation between model input parameters. However, the EAG notes that in their response to clarifications, the company did not provide information on which cohorts or data cuts of the NP30179 study were used to derive the bootstrapped parameter samples used to run the probabilistic analysis. The EAG also notes that updated results for the sensitivity analyses (one-way, probabilistic and scenario analysis) were not provided according to the updated economic model after points for clarification. The EAG conducted updated model sensitivity analyses and found that 3000 iterations of the PSA resulted in stable cost-effectiveness estimates.

5.3 Model validation and face validity check

The company describes the model validation process in Section B.3.14 of the CS. The company states that the cost-effectiveness model was subject to an external quality assurance procedure, involving technical validation of key model inputs and calculations. Clinical expert opinion was sourced during model development to inform model assumptions and ensure they were clinically valid and/or aligned with UK clinical practice for 3L+ R/R DLBCL. The company further states the model was developed to align with the NICE final scope and in line with NICE reference case requirements.

Points for Critique

The EAG undertook further validation checks, including face validity checks between the model and CS and/or clarification response. As described in Section 5.1, the EAG identified a series of inaccuracies within the model that have been corrected after points for clarification.

The EAG subsequently identified a few additional inaccuracies in the electronic version of the model (submitted on the 3rd April 2023). These are described in Section 6.1. together with the EAGs preferred alternative assumptions to those employed in the company's base-case.

6 EXTERNAL ASSESSMENT GROUP'S ADDITIONAL ANALYSES

As noted in Section 0 there are a number of confidential commercial arrangements in place for drugs comprised in the comparator treatments, as well as subsequent treatments, which are not incorporated in the analyses presented in the EAR. We report the results of corresponding analyses to the ones reported in this section and including these confidential commercial arrangements in a confidential appendix separate to the EAR.

6.1 Corrections to the company's updated base-case analysis

The EAG identified a few minor errors and inconsistencies in the updated version of the company's model (submitted on the 3rd April 2023) used to perform the analyses reported in Section 5. The corrections and revisions applied to the company's updated model are summarised in Table 45, alongside the sections of the EAR where this is discussed.

Table 45 Correction/revision to the company's updated base-case model

Parameter	Correction / Revision	Section
BR administration cost	A single administration cost for bendamustine and rituximab on day one of each treatment cycle	0
Preparation cost of IV infusion applied to glofitamab, pola-BR and BR	Corrected to reflect the cost of 39 minutes of a pharmacist time (as opposed to 2 ×39 minutes).	0
Unit costs of vincristine, doxorubicin, and cyclophosphamide	Revised to reflect the costs in the latest version of eMIT (see Appendix)	0
Cost of subsequent R-CHOP and CHOP	Corrected the cost of cyclophosphamide so that it is consistent with its use in R-CHOP and CHOP regimens (i.e. 750mg/m^2 every 21 days).	0

In addition to this corrections, the EAG also identified that the severity multiplier had been incorrectly implemented for comparison between glofitamab and pola-BR (see Section 7), so a further correction was made to the model so that a severity modifier of 1.00 was applied to both glofitamab and pola-BR.

The deterministic results of the corrected company's base-case analysis (including corrections described in Table 45 and to the severity modifier) are reported in Table 46.

Table 46 Cost-effectiveness results for company's corrected base-case analysis

	Total Costs	Total LYG	Total QALYs	Incr. Costs	Incr. LYG	Incr. QALYs	ICER (£/ QALY gain)
Glofit vs BR							
Glofit	[redacted]	[redacted]	[redacted]				
BR	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Glofit vs Pola-BR							
Glofit	[redacted]	[redacted]	[redacted]				
Pola-BR	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Glofit vs Axi-cel							
Glofit	[redacted]	[redacted]	[redacted]				
Axi-cel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: Glofit: glofitamab; BR: bendamustine plus rituximab; Pola-BR: polatuzumab vedotin in combination with bendamustine and rituximab; Axi-cel: axicabtagene ciloleucel; LYG: life years gained; QALY: quality-adjusted life year; Inc.: incremental; ICER: incremental cost-effectiveness ratio; NE: northeast quadrant of the cost-effectiveness plane; SE: southeast quadrant of the cost-effectiveness plane; SW: southwest quadrant of the cost-effectiveness plane.

The cost corrections and revisions (Table 45) had a small impact on the cost-effectiveness results, and on average lowered the costs for all treatments compared to the company's updated base-case results (Section 5.1). The greatest reduction in total costs was observed for the BR treatment [redacted]), which results both from the reduction in administration costs in the PF health state, but also to the reduction in the costs of subsequent therapies. Despite this the impact on the ICER for the glofitamab vs. BR comparison is modest, with this increasing to [redacted] per QALY compared to the company's updated base-case.

The comparison of glofitamab vs. pola-BR is the most affected by the corrections, and this is driven by the removal of the severity multiplier which had incorrectly been applied to the glofitamab total QALYs. The removal of the multiplier reduced the glofitamab total mean QALYs from [redacted] compared to the company's base-case results, thus reducing the incremental QALYs for glofitamab vs. pola-BR to [redacted] in the company's base-case analysis). The ICER for glofitamab vs. pola-BR remains in the SE quadrant, despite this.

6.2 Exploratory and sensitivity analyses undertaken by the EAG

A summary of the main issues identified and critiqued in Section 4 along with the scenario where the EAG addresses each issue in its additional analyses is shown in Table 47.

Table 47 Summary of the main issues identified by the EAG.

Critique item from Section 4 and description The EAG considers:		Dealt with in scenario	In EAG's base case (Y/N)	Area of remaining uncertainty	Significant impact on ICER (Y/N/Unknown)		
					vs BR	vs Pola-BR	vs Axi-cel
Item 1	The use of three different sources of data to indirectly compare glofitamab with alternative treatments hinders consistency within the ITC analysis framework.	1	N	X	N	Y	Y
Item 2	The ITC PFS and OS HR estimates for the indirect comparison of glofitamab with BR and of glofitamab with Pola-BR for may not be reflective of the most recent findings of Sehn et al (2022) when analysing the GO29365 study.	2	N	X	Y	NA	NA
Item 3	The use of 3 different (adjusted) glofitamab populations by the company, one for each comparison, to indirectly compare the effectiveness of comparators relative to glofitamab adds considerable uncertainty to the cost-effectiveness results.		N	X	Unknown, but assumed small for the comparison against BR and Pola-BR		
Item 4	The use of the generalised gamma as the preferred choice for survival extrapolation by the company for all adjusted and unadjusted glofitamab populations may be overestimating the OS benefits of glofitamab relative to Pola-BR and Axi-cel.		N	X	Unknown, potentially impactful when no long-term remission/survivorship is assumed		
Item 5	Even with longer follow-up for Pola-BR OS and PFS than comparators, there seems to be limited evidence to support an assumption of long-term remission and/or survivorship.	3	Y	X	Y	Y	Y
Item 6	Except for axi-cel, there is no clinical plausibility of cure for the remaining treatments and limited data exists that supports an assumption of long-term remission/survivorship.	3	N	X	Unknown, potentially impactful		
Item 7	There is no accepted clinical definition of cure and substantial uncertainty exists around the time-point at which cure can be assumed.	3	Y	X	Y	Y	Y
Item 8	If cure is assumed, there is uncertainty around which utility decrement, if any, should be used.	3	Y	X	N	N	N
Item 9	If cure is assumed, there is uncertainty around which excess mortality estimate should be used to adjust age-matched general population mortality from the cure point.	3	Y	X	N	N	N
Item 10	Different evidence sources inform the modelling of BR individual treatment discontinuation and other important model parameters for this comparator creating inconsistencies.		N	X	Unknown	NA	NA
Item 11	It is unclear whether the AEs associated with glofitamab and pola-BR were correctly modelled by the company, as the EAG could not validate all related model inputs.		N		N	N	N
Item 12	The company's preferred approach to model background mortality, is a partial implementation of age as a distribution. For this to be fully and consistently applied, the age distribution would also have to be implemented for the cancer-related mortality and age-adjusted HRQoL.	4	Y	X	Unknown		

Critique item from Section 4 and description The EAG considers:		Dealt with in scenario	In EAG's base case (Y/N)	Area of remaining uncertainty	Significant impact on ICER (Y/N/Unknown)		
					vs BR	vs Pola-BR	vs Axi-cel
Item 13	Health state-specific utilities used in the cost-effectiveness model estimated using mapping algorithms are uncertain.		N	X	Unknown, but assumed small		
Item 14	Disutilities relating to treatment specific adverse events should, in principle, be accounted for in the economic model on all scenarios.	5	N		N	N	N
Item 15	The administration costs for the glofitamab, pola-BR and BR treatments are based on unjustified assumptions, including inconsistencies across treatments and generally are not in line with a previous TA. Overall, the administration cost for BR may be overestimated and that of glofitamab underestimated.	6	Y	X	N	N	N
Item 16	The administration cost for axi-cel is not in line with the most recent TA of axi-cel in the indication of this appraisal, and may have been overestimated.	7	Y	X	N	N	N
Item 17	It is unclear whether the model capture the costs of glofitamab retreatment, and these costs may have been underestimated.	8	Y	X	Unknown, but assumed small		
Item 18	The truncation of TTOT for the drug components on treatment with glofitamab, pola-BR and BR by the maximum number of cycles assumed in the model, may artificially reduce costs of treatment if delayed doses are not appropriately captured in the model.		N		Unknown		
Item 19	The cost of monitoring ICANS was not considered by the company, and it is uncertainty whether this would increase the level of resource use required to monitor patients treated with glofitamab		N		Unknown		
Item 20	The distribution of subsequent treatments across the comparator regimens under comparison is an area of uncertainty, and the cost of subsequent treatments for axi-cel in particular may have been overestimated.	7	Y	X	Y	Unknown	N
Item 21	The costs of managing adverse events associated with glofitamab is an area of uncertainty, particularly for CRS.		N		Unknown, but assumed small		

Abbreviation: Y: yes; N: no; X: area where remaining uncertainty exists

As shown in Table 47, the EAG identified a number of limitations and areas of uncertainty in the company's cost-effectiveness analysis. Where the EAG considered that further exploration of the impact of these areas of uncertainty was warranted, scenario analysis was performed (scenarios 1 to 8). Following that and where the EAG considered that there was a more appropriate alternative approach, modifications were implemented in a cumulative manner and formed part of the EAG's preferred base case (Section 6.4) Thorough descriptions of the scenarios that were considered for the definition of the EAG's base case are presented in Section 6.2.1, and the impact on the ICERs is detailed in Section 6.3. The cumulative impact on the ICERs of the EAG preferred assumptions are

presented in Section 6.4 and a subsequent analysis over the EAG base-case assumptions is shown in Section 175.

6.2.1 Developing the EAG base case

The scenario analyses which the EAG considered in defining our base-case are described below and summarised in Table 48. The EAG notes that not all assumptions tested in the scenario analysis were considered in the EAG base case.

Table 48 Building the EAG base-case - description of implemented scenarios.

Scenarios	Description
1. Using unweighted ITC estimates for all comparisons	The use of three different sources of data to indirectly compare glofitamab with alternative treatments hinders consistency within the ITC analysis framework. This scenario explores the use of the unweighted/unadjusted ITC estimates from all comparisons.
2. Indirectly using evidence from the Sehn et al (2022) study [15] to inform the relative effect of glofitamab vs BR	The face validity of the OS and PFS adjusted ITC estimates that indirectly compare glofitamab with BR and glofitamab with Pola-BR were questioned. This scenario explores the impact of using indirectly PFS and OS estimates from Sehn et al (2022) [15] for the comparison with BR.
3. Considering different long-term remission/survivorship assumptions	Given the uncertainties surrounding the assumption of long-term remission/survivorship, the EAG considers a scenario where different combinations of the following are explored: • no long-term remission/survivorship; • timing of long-term remission/survivorship at 3 and 5 years • utility decrement of 10% and 20% from the age-sex UK general population utility, if long-term remission is assumed • excess mortality of 9% and 41% from the age-matched UK general population mortality, if long-term remission is assumed
4. Use of average cohort age to inform the model	This scenario is used instead of the company's preferred approach of modelling background mortality as a function of the age distribution of patients in the NP30179 study. A full implementation of the company's preferred approach would have to reflect the age distribution on cancer-related survival and on age-adjusted HRQoL. This scenario explores the use of the single age cohort-based approach of assuming the background mortality corresponding to that of the mean cohort age, which is more commonly used in cohort models.
5. Accounting for disutilities relating to treatment specific adverse events in the economic model on all utility scenarios.	The company did not include adverse effect specific disutilities in their economic model base case as to avoid double counting. The EAG finds it likely that most patients with severe AEs are unable to complete HRQoL questionnaires and thus, believes these should, in principle, be considered on all utility scenarios of the model.
6. Assuming obinutuzumab is administered as a prolonged and complex treatment at 1st attendance	Obinutuzumab administration takes over 4 hours and requires pre-treatment with IV and oral drugs. Therefore, the EAG considers its administration to be both long and complex. Thus, scenario assumes a cost of £526.52 for the administration of obinutuzumab, corresponding to the NHS reference costs 2020/21 currency code SB14Z (Deliver Complex Chemotherapy, including Prolonged Infusional Treatment, at First Attendance). This is in contrast with the company's approach, which costed obinutuzumab administration using the currency code SB15Z (£470.62, Deliver Subsequent Elements of a Chemotherapy Cycle).
7. Assuming an axi-cel administration cost based on preferred assumptions in previous TAs	The EAG tests two alternatives to the company's preferred value for the administration cost of axi-cel (£65,415), based on preferred assumptions in previous NICE TAs: 1. £60,000 as per the ongoing axi-cel TA[49] 2. £50,550.50, the midpoint between £60,000[49] and £41,101 (TA872)[52]
8. Assuming CAR-T not available as a post-progression treatment for those initially treated with BR or axi-cel	The EAG considers implausible that the distribution of treatments at post-progression is the same across treatments. In this scenario, we test the impact of excluding CAR-T from the subsequent treatments distribution for individuals initially treated with BR or axi-cel

Scenario 1: Using unweighted ITC estimates

In the company's economic model under base-case assumptions, the relative effect of each comparator vs. glofitamab is obtained via the independent modelling of PFS and OS of the comparator data and the glofitamab adjusted populations (i.e. the ITC-adjusted glofitamab populations), assuming non-proportionality of hazards. If PH is assumed, PFS and OS HRs derived

from the ITC analysis (Table 21) are directly used in the model to obtain adjusted OS and PFS parametric estimates for each comparator. The use of three different sources of data to indirectly compare glofitamab with alternative treatments hinders consistency within the ITC analysis framework. To promote evidence consistency between comparisons, the EAG believes that better use of the evidence from the GO29365 study could have been made. The use of the PFS and OS ITC unweighted/unadjusted estimates across all comparisons enables the use of data from the GO29365 study for the comparison with BR instead of the ITC adjusted estimates derived from Hong et al 2018.[9] The current analysis explores the use of the unweighted/unadjusted ITC estimates across comparisons and its impact on cost-effectiveness. The unweighted/unadjusted ITC estimates are shown in Table 49 for completeness. The EAG fully acknowledges that these PFS and OS HR estimates from 'naïvely' comparing glofitamab with alternatives would carry additional biases into the economic model and its results and that the results from this analysis should be performed with care. This scenario was not considered for the EAG's base-case.

Table 49 Summary of ITC unweighted/unadjusted results

Comparator (source of data)	Cohort details	Method of estimation	ITC results for the comparison of glofitamab vs comparator	
			OS HR, median (95% CI)	PFS HR, median (95% CI)
Axicabtagene ciloleucel (ZUMA-1 (N=101))	Glofitamab unweighted, n=115	**Unadjusted Cox proportional-hazards model**	**1.467 (1.007, 2.137)**	**1.333* (0.945, 1.888)**
Bendamustine plus rituximab (GO29365 (N=40))	Glofitamab unweighted, n=140)	**Propensity score analysis, unadjusted analysis**	**0.54 (0.31, 0.94)**	**0.59* (0.36, 0.97)**
Polatuxumab-vedotin plus bendamustine plus rituximab (GO29365 (N=152))	Glof. filtered, n=149 Pola-BR filtered, n=84	**Propensity score analysis, unadjusted analysis**	**0.98 (0.69, 1.40)**	**0.99** (0.72, 1.37)**

Abbreviations: ATE, average treatment effect; BCa, bias corrected accelerated; CI, confidence interval; FL, Follicular lymphoma; Glof., glofitamab; HR, hazard ratio; MAIC, matching-adjusted indirect comparison; PFS, progression-free survival; OS, overall survival. *as assessed by the investigator; **as assessed by the independent review committee

Scenario 2: Indirectly using evidence from the Sehn et al (2022) study to inform the relative effect of glofitamab vs BR

As highlighted in Section 0, the EAG is concerned with the face validity of the OS and PFS adjusted ITC estimates that indirectly compare glofitamab with BR and glofitamab with Pola-BR, and the degree to which these are reflective of the most recent findings of Sehn et al (2022)[15]when analysing the GO29365 study. The EAG notes that Sehn et al identified a significant survival benefit with Pola-BR vs BR in the randomised DLBCL cohort from GO29365, with a PFS HR of 0.39 (0.23-0.66) and OS HR of 0.42 (0.24-0.72). Given these findings, the EAG believes that the ITC should have

indicated an even stronger evidence in support of glofitamab being superior to BR in PFS and OS. Thus, using the results from the propensity score analysis using IPTW for pola-BR [PFS HR of 0.85 (0.57-1.26) and OS HR of 0.90 (0.62-1.26)] and the PFS and OS Sehn et al (2022)[15] results above for the comparison Pola-BR vs BR, the EAG indirectly derived estimates for PFS and OS for glofitamab vs BR: PFS HR of 0.36 (0.18-0.70) and OS HR of 0.35 (0.19-0.66). This scenario explores the impact of using these indirectly estimated PFS and OS values from Sehn et al (2022)[15] for the comparison with BR on the cost-effectiveness of glofitamab vs. BR. This scenario was not considered for the EAG's base-case.

Scenario 3: Considering different long-term remission/survivorship assumptions

As highlighted in section 4.2.6.3, the EAG has several concerns regarding the long-term remission/survivorship company assumptions. The EAG is concerned with the clinical plausibility of cure for all treatments under comparison. The company recognises that the assumption of cure is considerably uncertain and the EAG believes that a no long-term remission/survivorship assumption could be valid.

The company did not fully justify their use of cut-offs of 2 years for PFS and 3.5 years for OS. The EAG believes that there is no clear rationale or new evidence presented to support a differential timing for when long-term remission and survivorship should be assumed. The EAG considers the timing of long-term remission/survivorship to be uncertain as there is no accepted clinical definition of cure. This analysis explores the use of the cut-off points of 3 years and 5 years, assuming no differential timing for long-term remission and survivorship.

Furthermore, attached to the time point at which cure is assumed, a model constraint is imposed that makes progression-free patients move from the health state specific utility to near age-gender adjusted general population utility, with a decrement of 10%. The EAG considers that, if cure is assumed, there is uncertainty around which utility decrement should be used from the cure point. This analysis explores the use of a decrement of 20% from the age-sex UK general population utilities, in addition to the 10% decrement used by the company in their base case.

The EAG is concerned that, after the point of cure, the excess mortality of 9% over the age-matched general population mortality for long-term survivors may not be reflective of the added mortality risk individuals in this indication may experience. The EAG considers that, if cure is assumed, there is uncertainty around which excess mortality estimate should be used to adjust age-matched general population mortality from the cure point. This analysis explores the use of the SMR of 1.41 from the Howlader et al study (2017),[17] in addition to the SMR of 1.09 used by the company in their base case.

Scenario 4: Assuming background mortality corresponds to that of an average cohort age

The company's base-case analysis assumes that background mortality is as a function of the age distribution of patients in the NP30179 study. The use of the age distribution approach was preferred as it better reflected heterogeneity in the background mortality of the cohort and the associated background risks of death by age. The EAG agrees that applying an age distribution approach represents an appropriate background risk of mortality for the cohort. However, the EAG considers this is a partial implementation of the distributional approach to age, as the age distribution is only reflected on all-cause mortality. A full implementation of the company's preferred approach would have to reflect the age distribution on cancer-related survival and on age-adjusted HRQoL. This analysis considers the background mortality corresponding to that of an average cohort age.

Scenario 5: Accounting for disutilities relating to treatment specific adverse events in the economic model on all utility scenarios.

The company assumes that the PFS on-treatment utility values estimated from the NP30179 trial capture the HRQoL experienced by patients in pre-progression, including the impact of any potential adverse events for those on glofitamab. This assumption was extended to comparator treatments. Thus, and as to avoid double counting, the company did not include adverse effect specific disutilities in their economic model base case. The EAG finds it likely that most patients with severe adverse effects (grade ≥3) are unable to complete HRQoL questionnaires. Thus, the EAG believes that adverse events' related disutilities should, in principle, be considered on all utility scenarios of the model. The current analysis explores the impact on cost-effectiveness of including disutilities relating to treatment specific adverse events (as described in Table 29) in the economic model on the company's base case scenario of using the indirect mapping (response-based) algorithm to derive utility estimates (EORTC-QLQ-C30 to EQ-5L-3L) from the NP30179 study by health state. This scenario was not considered for the EAG's base-case.

Scenario 6: Assuming obinutuzumab is administered as a prolonged and complex treatment

The company derived the administration cost of obinutuzumab, assuming this drug would incur the cost of delivering a subsequent chemotherapy cycle (£470.62; currency code SB15Z, NHS reference costs 2020/21.[56] As detailed in Section 0, obinutuzumab is administered over a period of time in excess of 4 hours and requires pre-treatment with oral and IV drugs, so as to mitigate the risk of adverse events. Obinutuzumab is also administered as a first treatment, before patients can be treated with glofitamab. Thus, the EAG believes the administration obinutuzumab should be costed as £526.52, corresponding to currency code for the delivery of a complex chemotherapy, including prolonged infusional treatment, at first attendance (SB14Z, NHS reference costs 2020/21)[56]. In this scenario, we cost the administration of obinutuzumab at £526.52. This scenario is considered for the EAG's base-case.

Scenario 7: Assuming an axi-cel administration cost based on preferred assumptions in previous TAs

The company's base-case estimate for the axi-cel administration cost (£65,415) was informed by the revised NHS England CAR-T tariff used in the ongoing appraisal of axi-cel for DLBCL after failure of one line of systemic treatment.[49] As described in Section 0, the committee to this appraisal considered an estimate of £60,000 more appropriate to cost the administration of axi-cel. Another relevant estimate of the axi-cel administration costs is the one preferred by the committee in TA872 (£41,101), which was explored in the company's scenario analysis (see Section 5.2). However, the estimate preferred in TA872 does not include the costs of i) IVIG treatment, ii) conditioning chemotherapy or ii) subsequent stem cell treatment for individuals treated originally with axi-cel, which was modelled separately in that appraisal. Since the company's model in the current appraisal does not consider the costs associated with i) and ii), the EAG believes that the most appropriate estimate for the cost of axi-cel administration lies somewhere between £41,101 and £60,000. As part of this scenario analysis, the EAG explores two alternative values for the administration of axi-cel:

1. £60,000, in line with the committee preference in the ongoing appraisal of axi-cel for DLBCL after failure of one line of systemic treatment.
2. £50,550.50, the midpoint between £41,101 and £60,000 (the two estimates preferred in previous appraisals of axi-cel).

This scenario is considered for the EAG's base-case.

Scenario 8: Assuming CAR-T are not available as a post-progression treatment for those initially treated with BR or axi-cel

In Section 0, the EAG highlighted that the company's assumption that subsequent treatments delivered post-progression have the same distribution regardless of treatment received in pre-progression is clinically implausible. While the EAG recognises the difficulties in informing treatment distributions conditional on treatment at pre-progression from available evidence, we consider this to be an important area of uncertainty that requires further exploration. In this scenario, we assume that treatment with CAR-T at post-progression is not possible for individuals treated at pre-progression with axi-cel or BR. For individuals treated with axi-cel at pre-progression, re-treatment with CAR-T is not an option under current UK clinical practice. For individuals treated with BR at pre-progression, the clinical effectiveness is unlikely to reflect the use of CAR-T and including the cost of CAR-T may bias the cost-effectiveness analysis against BR. This scenario is implemented by applying an alternative subsequent treatment distribution for individuals treated at pre-progression with axi-cel or BR, where the proportion of individuals treated with CAR-T is set to zero and the subsequent treatment distribution is reweighted so that it adds to 100%. The subsequent treatment distributions

applied in this scenario are illustrated in Table 50. This scenario is considered for the EAG's base-case.

Table 50 Subsequent treatment distribution in Scenario 8

Subsequent Tx	Tx distribution conditional on pre-progression Tx with	
	Glofitamab	Axi-cel or BR
BR	1.79%	1.97%
R-GEMOX	2.68%	2.94%
R-CHOP	2.68%	2.94%
Other R-chemo regimens	8.93%	9.80%
Other chemo regimens (not including R)	22.32%	24.50%
Pola-BR	8.93%	9.80%
Lenalidomide	1.79%	1.97%
Pixantrone	0.89%	0.98%
Clinical Trial/Other	17.86%	19.61%
Radiotherapy	15.18%	16.66%
Allogeneic SCT	6.25%	6.86%
Autologous SCT	1.79%	1.97%
CAR-T	8.93%	0.00%

Abbreviations: Tx, treatment

6.3 Impact on the ICER of additional clinical and economic analyses undertaken by the EAG

All results for the EAG's scenarios are based on a deterministic analysis because the time required to run the model probabilistically across all scenarios was not feasible within the time constraints of the STA. The scenario results presented in Table 51 to Table 57 refer to the incremental costs, incremental QALYs and ICER for each of the relevant comparisons. For completeness and to add to the interpretation of the results, each table presents at the top the company's corrected base-case analysis results. The results of the full incremental analysis for each scenario are presented in Appendix.

For the comparison of glofitamab versus BR, the scenarios in which an ICER above £20,000/QALY gained is estimated are: no-long-term remission/survivorship, a long-term remission/survivorship at 5 years with a SMR of 1.09 and a utility decrement of 20%, a long-term remission/survivorship at 5 years with a SMR of 1.41 and a utility decrement of 10 or 20% and the scenario assuming no CAR-T administration as a subsequent treatment. These cure scenario results are driven mainly by increases in glofitamab total costs and consequently in incremental costs, which, for the no-long-term

remission/survivorship scenario implies the doubling of incremental costs when compared to the company's corrected base-case analysis. This increase in total costs occurs because, without the long-term remission/survivorship, differences in survival between the two treatments are substantially reduced. In scenario 8, where it is assumed that subsequent treatment with CAR-T is not available for individuals previously treated with BR or axi-cel, the mean total costs for BR decrease substantially leading to an increase in the incremental costs [redacted]) and the ICER of glofitamab vs. BR (£[redacted]), compared to the company-base.

For the comparison of glofitamab against Pola-BR, the only scenario suggesting that glofitamab does not dominate over Pola-BR is the one assuming no-long-term remission/survivorship. In this scenario the mean total costs for glofitamab exceed the costs for Pola-BR, when in the company's corrected base-case analysis glofitamab was estimated to be cost saving. Again, the no long-term remission/survivorship reduces the differences in survival between the two treatments, with both now having higher, but similar, total costs for similar incremental benefits to that estimated in the company's corrected base-case analysis.

For the comparison of glofitamab against axi-cel, all scenarios reinforce the findings from the company's corrected base-case analysis, where glofitamab is less costly but it is also estimated to confer less benefits than axi-cel. The cost savings of glofitamab vs. axi-cel are reduced in scenarios 7 and 8, particularly for the latter scenario where it is assumed that individuals initially treated with axi-cel cannot be retreated with CAR-T. Despite this contraction of the cost-savings, results still suggest the QALY gains with axi-cel are not enough to off-set the cost-savings with glofitamab.

6.3.1 Alternative source of relative treatment effects

For completeness Table 51 shows at the top the company's corrected base-case analysis using independent modelling of survival curves and the scenario when proportionality of hazard is assumed and, thus, estimated ITC HRs are used. Table 51 shows also the results from scenario 1 of using the ITC unweighted estimates for all comparisons and from scenario 2 of indirectly using evidence from the Sehn et al (2022) study[15] to inform the relative effect of glofitamab vs BR.

Table 51 Summary cost-effectiveness results for scenarios 1 & 2 - using alternative relative treatment effects

Assumption	Section in EAG report	Incremental cost	Incremental QALYs	ICER £/QALY gained
Company's corrected base-case analysis – independent modelling of survival curves (shown for completeness)				
Glofit vs BR	6.1	[redacted]	[redacted]	[redacted]
Glofit vs Pola-BR		[redacted]	[redacted]	[redacted]
Glofit vs Axi-cel		[redacted]	[redacted]	[redacted]

Company's corrected base- case + proportionality of hazards is assumed and estimated ITC HRs used (shown for completeness)				
Glofit vs BR	0	[redacted]	[redacted]	[redacted]
Glofit vs Pola-BR		[redacted]	[redacted]	[redacted]
Glofit vs Axi-cel		[redacted]	[redacted]	[redacted]
Scenario 1 – using unweighted ITC estimates for all comparisons				
Glofit vs BR	0	[redacted]	[redacted]	[redacted]
Glofit vs Pola-BR		[redacted]	[redacted]	[redacted]
Glofit vs Axi-cel		[redacted]	[redacted]	[redacted]
Scenario 2 – Indirectly using evidence from the Sehn et al (2022) study to inform the relative effect of glofitamab vs BR				
Glofit vs BR	0	[redacted]	[redacted]	[redacted]
Glofit vs Pola-BR		[redacted]	[redacted]	[redacted]
Glofit vs Axi-cel		[redacted]	[redacted]	[redacted]

6.3.2 Long-term remission/survivorship assumptions

Table 52 reports the key cost-effectiveness results for scenario analysis 3, considering no long-term remission/survivorship and long-term remission/survivorship for different cure points, excess mortality and HRQoL for the cured. The results of the full incremental analysis for each scenario are presented in Appendix.

Table 52 Summary cost-effectiveness results for scenario 3 – using alternative cure assumptions

Assumption	Section in EAG report	ICER (per additional QALY), CE plane quadrant	
Company's corrected base-case analysis (shown for completeness)			
Glofit vs BR	6.1	[redacted]	
Glofit vs Pola-BR		[redacted]	
Glofit vs Axi-cel		[redacted]	
Scenario 3.1: No long-term remission/survivorship (i.e. no cure)			
Glofit vs BR	0	[redacted]	
Glofit vs Pola-BR		[redacted]	
Glofit vs Axi-cel		[redacted]	
Assumption	**Section in EAG report**	**Utility adjustment: -10%**	**Utility adjustment: -20%**
Scenario 3.2 - LTR/S: 3 years, SMR: 1.09			
Glofit vs BR	0	[redacted]	[redacted]
Glofit vs Pola-BR		[redacted]	[redacted]
Glofit vs Axi-cel		[redacted]	[redacted]
Scenario 3.3 - LTR/S: 5 years, SMR: 1.09			

Glofit vs BR	0	[redacted]	[redacted]
Glofit vs Pola-BR		[redacted]	[redacted]
Glofit vs Axi-cel		[redacted]	[redacted]
Scenario 3.4 - LTR/S: 3 years, SMR: 1.41			
Glofit vs BR	0	[redacted]	[redacted]
Glofit vs Pola-BR		[redacted]	[redacted]
Glofit vs Axi-cel		[redacted]	[redacted]
Scenario 3.5 - LTR/S: 5 years, SMR: 1.41			
Glofit vs BR	0	[redacted]	[redacted]
Glofit vs Pola-BR		[redacted]	[redacted]
Glofit vs Axi-cel		[redacted]	[redacted]

Abbreviations: Glofit: glofitamab; BR: bendamustine plus rituximab; Pola-BR: polatuzumab vedotin in combination with bendamustine and rituximab; Axi-cel: axicabtagene ciloleucel; CE: cost-effectiveness; ICER: incremental cost-effectiveness ratio; LTR/S: long-term remission/survivorship assumed; NE: northeast quadrant of the cost-effectiveness plane; QALY: quality adjusted life years; SE: southeast quadrant of the cost-effectiveness plane; SMR: standardised mortality ratio; SW: southwest quadrant of the cost-effectiveness plane.

6.3.3 Background mortality based on average cohort age

Table 53 summarises cost-effectiveness results for scenario analysis 4, assuming that the background mortality corresponds to that of an average cohort age rather than age distribution as in the NP30179 trial. In this scenario, the time horizon also needs to be reduced from 60 to 37 years compared to the company's base-case assumptions. This assumption does not imply a sizeable impact on the cost-effectiveness estimates for any of comparisons. The results of the full incremental analysis for each scenario are presented in Appendix.

Table 53 Summary cost-effectiveness results for scenario 4 - assuming background mortality corresponds to that of an average cohort age

Assumption	Section in EAG report	Incremental cost	Incremental QALYs	ICER £/QALY gained
Company's corrected base-case analysis – age distribution as in the NP30179 trial (shown for completeness)				
Glofit vs BR	6.1	[redacted]	[redacted]	[redacted]
Glofit vs Pola-BR		[redacted]	[redacted]	[redacted]
Glofit vs Axi-cel		[redacted]	[redacted]	[redacted]
Scenario 4 - background mortality corresponds to that of an average cohort age – time horizon reduced from 60 to 37 years.				
Glofit vs BR	4.2.7	[redacted]	[redacted]	[redacted]
Glofit vs Pola-BR		[redacted]	[redacted]	[redacted]
Glofit vs Axi-cel		[redacted]	[redacted]	[redacted]

Abbreviations: Glofit: glofitamab; BR: bendamustine plus rituximab; Pola-BR: polatuzumab vedotin in combination with bendamustine and rituximab; Axi-cel: axicabtagene ciloleucel; CE: cost-effectiveness; ICER: incremental cost-effectiveness

ratio; NE: northeast quadrant of the cost-effectiveness plane; QALY: quality adjusted life years; SE: southeast quadrant of the cost-effectiveness plane; SMR: standardised mortality ratio; SW: southwest quadrant of the cost-effectiveness plane.

6.3.4 Adverse event disutilities

Table 54 summarises cost-effectiveness results for scenario analysis 5, applying the company's preferred mapping algorithm and accounting for disutilities due to AEs. This assumption does not imply a sizeable impact on the cost-effectiveness estimates for any of comparisons. The results of the full incremental analysis for each scenario are presented in Appendix.

Table 54 Summary cost-effectiveness results for Scenario 5 - indirect mapping of EQ-5D-3L and accounting for AE disutilities for all regimens

Assumption	Section in EAG report	Incremental cost	Incremental QALYs	ICER £/QALY gained
Company's corrected base-case analysis – indirect mapping of EQ-5D-3L and no AE related disutilities (shown for completeness)				
Glofit vs BR	6.1	[redacted]	[redacted]	[redacted]
Glofit vs Pola-BR		[redacted]	[redacted]	[redacted]
Glofit vs Axi-cel		[redacted]	[redacted]	[redacted]
Scenario 5 – indirect mapping of EQ-5D-3L and accounting for AE disutilities for all regimens				
Glofit vs BR	4.2.8	[redacted]	[redacted]	[redacted]
Glofit vs Pola-BR		[redacted]	[redacted]	[redacted]
Glofit vs Axi-cel		[redacted]	[redacted]	[redacted]

Abbreviations: Glofit: glofitamab; BR: bendamustine plus rituximab; Pola-BR: polatuzumab vedotin in combination with bendamustine and rituximab; Axi-cel: axicabtagene ciloleucel; CE: cost-effectiveness; ICER: incremental cost-effectiveness ratio; NE: northeast quadrant of the cost-effectiveness plane; QALY: quality adjusted life years; SE: southeast quadrant of the cost-effectiveness plane; SMR: standardised mortality ratio; SW: southwest quadrant of the cost-effectiveness plane.

6.3.5 Obinutuzumab administration cost

Table 55 summarises cost-effectiveness results for scenario analysis 6, where the administration of obinutuzumab is costed as that of a complex, prolonged infusional treatment at first attendance (i.e. £526.52) instead of as a subsequent attendance (£470.62; company's assumption). This assumption does not imply a sizeable impact on the cost-effectiveness estimates for any of comparisons. The results of the full incremental analysis for each scenario are presented in Appendix.

Table 55 Summary cost-effectiveness results for scenario 6 - assuming obinutuzumab is administered as a complex and prolonged treatment at 1st attendance

Assumption	Section in EAG report	Incremental cost	Incremental QALYs	ICER £/QALY gained
Company's corrected base-case analysis - assumes obinutuzumab is administered as subsequent attendance				

Glofit vs BR	6.1	[redacted]	[redacted]	[redacted]
Glofit vs Pola-BR		[redacted]	[redacted]	[redacted]
Glofit vs Axi-cel		[redacted]	[redacted]	[redacted]
Scenario 6 - assuming obinutuzumab is administered as a complex and prolonged treatment at 1st attendance				
Glofit vs BR	0	[redacted]	[redacted]	[redacted]
Glofit vs Pola-BR		[redacted]	[redacted]	[redacted]
Glofit vs Axi-cel		[redacted]	[redacted]	[redacted]

6.3.6 Axi-cel administration cost

Table 56 summarises cost-effectiveness results for scenario analysis 7, where two alternative values are assumed for the administration of axi-cel. Neither of the scenarios imply a sizeable impact on the cost-effectiveness estimates for any of comparisons. The results of the full incremental analysis for each scenario are presented in Appendix.

Table 56 Summary cost-effectiveness results for scenario 7 - assuming alternative administration costs for axi-cel

Assumption	Section in EAG report	Incremental cost	Incremental QALYs	ICER £/QALY gained
Company's corrected base-case analysis – assumes administration cost of axi-cel= £65,415 (shown for completeness)				
Glofit vs BR	6.1	[redacted]	[redacted]	[redacted]
Glofit vs Pola-BR	6.1	[redacted]	[redacted]	[redacted]
Glofit vs Axi-cel	6.1	[redacted]	[redacted]	[redacted]
Scenario 7.1 - assuming administration cost of axi-cel= £60,000				
Glofit vs BR	0	[redacted]	[redacted]	[redacted]
Glofit vs Pola-BR	0	[redacted]	[redacted]	[redacted]
Glofit vs Axi-cel	0	[redacted]	[redacted]	[redacted]
Scenario 7.2 - assuming administration cost of axi-cel= £50,500.50				
Glofit vs BR	0	[redacted]	[redacted]	[redacted]
Glofit vs Pola-BR	0	[redacted]	[redacted]	[redacted]
Glofit vs Axi-cel	0	[redacted]	[redacted]	[redacted]

6.3.7 Subsequent therapies

Table 57 summarises cost-effectiveness results for scenario analysis 8, where it is assumed that CAR-T is not available as a subsequent therapy at post-progression for individuals initially treated with either axi-cel or BR. This scenario has a significant impact on the cost-effectiveness estimates for

glofitamab vs BR. The results of the full incremental analysis for each scenario are presented in Appendix.

Table 57 Summary cost-effectiveness results for scenario 8 - assuming CAR-T are not available as a post-progression treatment for those initially treated with BR or axi-cel

Assumption	Section in EAG report	Incremental cost	Incremental QALYs	ICER £/QALY gained
Company's corrected base-case analysis – assumes same distribution of subsequent therapies independent of pre-progression treatment (shown for completeness)				
Glofit vs BR	6.1	[redacted]	[redacted]	[redacted]
Glofit vs Axi-cel	6.1	[redacted]	[redacted]	[redacted]
Scenario 8 - assuming CAR-T are not available as a post-progression treatment for those initially treated with BR or axi-cel				
Glofit vs BR	0	[redacted]	[redacted]	[redacted]
Glofit vs Axi-cel	0	[redacted]	[redacted]	[redacted]

6.4 EAG's preferred assumptions

The EAG considers that the assumptions around long-term remission/survivorship remain a key of uncertainty in the current appraisal, and that these uncertainties affect both the definition of long-term remission/survivorship and whether long-term remission/survivorship can be demonstrated based on available evidence for the treatments under comparison. Furthermore, the EAG considers that the company's preferred assumptions on long-term remission/survivorship are not wholly consistent with the NICE committees' preferences in most recent appraisals in R/R DLBCL. The EAG incorporates in the base-case the following assumptions on long-term remission/survivorship:

i. A single time point after which individuals are assumed to achieve long-term remission/survivorship of 3 years for any of the treatments under comparison;
ii. Survival post time point from which long-term remission/survivorship is assumed is equivalent to that of the UK general population adjusted by a SMR=1.41;
iii. Utility in long-term remission/survivorship corresponds to that of the UK general population adjusted by a 10% decrement.

The EAG considers that i. and ii. are consistent with the preferences of the committee in TA649. [24], while iii. corresponds to the most optimistic decrement of the range proposed by company's clinical advisors.[54]

Overall, the scenario analyses in Section 6.3, suggest that the estimates of cost-effectiveness are robust to alternative assumptions relating to background mortality (scenario 4) and administration costs (scenarios 6 and 7). The assumptions of these scenarios are incorporated into the EAG base-

case. For the administration of axi-cel, the EAG prefers the estimate of £50,550.50 as being more aligned with how the company chose to model the axi-cel component (i.e. not including the costs of IVIG and conditioning chemotherapy, but including the costs of subsequent stem cell transplant).

The EAG base-case assumes that individuals treated at pre-progression with axi-cel do not receive CAR-Ts at post-progression (in line with scenario 8), because that reflects UK clinical practice. We do not assume the same for individuals treated at pre-progression with BR (also explored in Scenario 8), because it is uncertain whether post-progression treatment with CAR-T was used in the Hong et al (2018) study.[9]

The cost-effectiveness results of scenario 1 (using unweighted ITC HRs from each comparison) and scenario 2 (allowing the incorporation of the relative treatment effects from Sehn et al (2021)[15] for the glofitamab vs pola-BR comparison) were broadly similar to the company's scenario analysis when assuming proportional hazards. These two EAG scenarios also rely on the assumption of proportional hazards holding, in contrast with the company's base case that is based on the independent modelling of PFS and OS curves for each comparison. Given the scenario results and that the company demonstrated that the proportional hazards assumption does not hold across all comparisons (see Section 4.2.6), the EAG did not incorporate scenario 1 or 2 in the EAG base-case and should be seen as exploratory.

Scenario 5, including the AE disutilities for all treatments, did not have an impact on the estimates of cost-effectiveness for any of the treatments under comparison and the EAG maintains that it would in principle be more appropriate to include these within the economic model. Nevertheless, the EAG decided to exclude these disutilities in the EAG's base-case, as it would not address uncertainties stemming from not being able to validate the number of AEs with glofitamab and pola-BR from the evidence sources (Section 0).

This section presents the results of the EAG's analyses that formed the EAG's base case. As in Section 6.3, all presented cumulative results are based on a deterministic analysis, except for the EAG's base case for which both deterministic (Table 58) and probabilistic results (Table 59) are presented. The full cost-effectiveness results of the EAG base-case analysis are presented in Appendix.

Table 58 illustrates the results of the analyses that the EAG undertook as separate steps to form the EAG's base case.

For the cumulative analyses result across all analyses and within each comparison, incremental costs remained similar to the ones estimated in the company's corrected base case, suggesting that glofitamab has the potential to result in higher costs against BR but in cost-savings against pola-BR

and axi-cel, and higher benefits against BR and pola-BR but offering less benefits than axi-cel. These results suggest that glofitamab may be considered a cost-effective treatment against all comparators.

Table 58 Deterministic cost-effectiveness results for the EAG's preferred model assumptions

Preferred assumption	Section in EAG report	Incr. cost	Incr. QALYs	Cumulative ICER £/QALY
1. Company's updated base-case	**5.1**			
Glofit vs BR		[redacted]	[redacted]	[redacted]
Glofit vs Pola-BR		[redacted]	[redacted]	[redacted]
Glofit vs Axi-cel		[redacted]	[redacted]	[redacted]
2. Company's corrected base-case	**6.1**			
Glofit vs BR		[redacted]	[redacted]	[redacted]
Glofit vs Pola-BR		[redacted]	[redacted]	[redacted]
Glofit vs Axi-cel		[redacted]	[redacted]	[redacted]
3. Analysis 2 + Background mortality using average age cohort (37 years TH)	**4.2.7**			
Glofit vs BR		[redacted]	[redacted]	[redacted]
Glofit vs Pola-BR		[redacted]	[redacted]	[redacted]
Glofit vs Axi-cel		[redacted]	[redacted]	[redacted]
4. Analysis 3 + Obinutuzumab administered as a complex and prolonged treatment at first attendance	**0**			
Glofit vs BR		[redacted]	[redacted]	[redacted]
Glofit vs Pola-BR		[redacted]	[redacted]	[redacted]
Glofit vs Axi-cel		[redacted]	[redacted]	[redacted]
5. Analysis 4 + Axi-cel administration cost corresponds to £50,550.50	**0**			
Glofit vs BR		[redacted]	[redacted]	[redacted]
Glofit vs Pola-BR		[redacted]	[redacted]	[redacted]
Glofit vs Axi-cel		[redacted]	[redacted]	[redacted]
6. Analysis 5 + CAR-T re-treatment not possible as a subsequent therapy	**0**			
Glofit vs BR		[redacted]	[redacted]	[redacted]
Glofit vs Pola-BR		[redacted]	[redacted]	[redacted]
Glofit vs Axi-cel		[redacted]	[redacted]	[redacted]
7. EAG base-case: Analysis 6 + LTR/S: 3 years, SMR: 1.41, - 10% utility adjustment	**0**			
Glofit vs BR		[redacted]	[redacted]	[redacted]
Glofit vs Pola-BR		[redacted]	[redacted]	[redacted]
Glofit vs Axi-cel		[redacted]	[redacted]	[redacted]

*Under this assumption, the severity multiplier for the pola-BR comparison, becomes 1.2

When considering the probabilistic results of the EAG base-case analysis in Table 59, the interpretation of the cost-effectiveness estimates for the glofitamab vs. BR comparison changes compared to the deterministic results. The results suggest that the increase in QALY gains with glofitamab vs BR offset the additional costs, at the lower bound of the cost-effectiveness threshold range recommended by NICE (i.e., £20,000/QALY gained). The interpretation of probabilistic results for the remaining comparisons remains the same as for the deterministic ones.

Table 59 Probabilistic cost-effectiveness results for the EAG's preferred set of model assumptions

Preferred assumption	Section in EAG report	Incr. cost	Incr. QALYs	ICER £/QALY	Probability of glofitamab being CE**
7. Analysis 6 + LTR/S: 3 years, SMR: 1.41, - 10% utility adjustment	**0**				
Glofit vs BR		[redacted]	[redacted]	[redacted]	[redacted]
Glofit vs Pola-BR		[redacted]	[redacted]	[redacted]	[redacted]
Glofit vs Axi-cel		[redacted]	[redacted]	[redacted]	[redacted]

*Under this assumption, the severity multiplier for the pola-BR comparison, becomes 1.2; **, at £20,000 per QALY

Abbreviations: CE, cost-effective

6.5 Further scenario analysis over the EAG's preferred base-case analysis

The EAG also explored the impact of the assumption of no long-term remission/survivorship or no cure (for all treatments) over the EAG's base-case analysis; the deterministic results for this analysis (numbered analysis 8) are presented in Table 60 alongside the company's updated and corrected base-case results. This alternative assumption is in line with the ongoing TA for tafasitamab plus lenalidomide,[58] where cure as only explored in scenario analysis. The full cost-effectiveness results of analysis 8 are presented in Appendix.

Table 60 Summary deterministic cost-effectiveness results for analysis 8: assuming no long-term remission/ survivorship

Preferred assumption	Section in EAG report	Incr. cost	Incr. QALYs	Cumulative ICER £/QALY
1. Company's updated base-case	**5.1**			
Glofit vs BR		[redacted]	[redacted]	[redacted]
Glofit vs Pola-BR		[redacted]	[redacted]	[redacted]
Glofit vs Axi-cel		[redacted]	[redacted]	[redacted]
2. Company's corrected base-case	**6.1**			
Glofit vs BR		[redacted]	[redacted]	[redacted]

Glofit vs Pola-BR		[redacted]	[redacted]	[redacted]
Glofit vs Axi-cel		[redacted]	[redacted]	[redacted]
8. Analysis 6 + No cure*	**0**			
Glofit vs BR		[redacted]	[redacted]	[redacted]
Glofit vs Pola-BR		[redacted]	[redacted]	[redacted]
Glofit vs Axi-cel		[redacted]	[redacted]	[redacted]

6.6 Conclusions of the cost effectiveness section

The company submitted *a de novo* partitioned survival model which is consistent with the model structures used in previous NICE appraisals of R/R DLBCL. The company systematic review of cost-effectiveness identified 19 publications and 10 HTA submissions, and states that this evidence was used to inform the economic analysis in the current appraisal. Although, it is not always clear how the cost-effectiveness systematic review informed the company's cost-effectiveness analysis, the EAG notes that many parameters (particularly cost and resource use parameters) seem to be informed by NICE TA649.[21] The EAG deems that the submitted evidence reflects the decision problem defined in the final scope.

Despite this, it is important to emphasise that all cost-effectiveness results presented in the company's submissions and the EAR are affected by the uncertainty in the underpinning clinical effectiveness evidence. The estimates of comparative effectiveness are informed by two different methods depending on the availability of comparator data (unanchored MAIC, when published aggregate data were available, and propensity score analysis, when patient-level data was available and adjustments feasible). The use of three separate sources of data to inform each of the comparisons, implies that the glofitamab population against which the alternative treatments are being compared to varies across comparison (see Section 0). This precludes the performance of a fully incremental comparison of the four treatments under comparison. Furthermore, the EAG notes in Section 3.6 the robustness of the MAICs to the choice of confounding factors is unclear and that there is currently insufficient evidence to distinguish between glofitamab and pola-BR (and these are likely to be of similar efficacy). Finally, it was not possible to adjust to a number of high priority prognostic patient characteristics for the BR unanchored MAIC (including refractory to first line and refractory to previous line) used to inform the company's base-case analysis. While the company's approach to estimate clinical effectiveness seems broadly appropriate, the findings of the cost-effectiveness analysis need to be interpreted in the context of substantial uncertainty in the indirectly estimated clinical effectiveness evidence.

The EAG base-case suggests that glofitamab is more effective and more costly than BR, and when probabilistic estimates are considered the ICER lies above the lower bound of the cost-effectiveness

threshold recommended by NICE (i.e. £20,000 per QALY gained). Compared to Pola-BR, glofitamab appears to be cost-saving and generate a small QALY gain, meaning glofitamab is dominant over pola-BR. For the axi-cel comparison, glofitamab seems to be less costly and less effective, resulting in southwest quadrant ICERs above the cost-effectiveness threshold range, that is, suggesting that glofitamab is cost-effective against axi-cel. The company's base-case analysis results is mostly robust to the assumptions in the EAG base-case; the only exception is for the glofitamab vs. BR comparison which produces a probabilistic ICER above £20,000 per additional QALY.

The EAG considers that the assumptions around long-term remission/survivorship remain a key uncertainty in the current appraisal, and that these uncertainty affects both the definition of long-term remission/survivorship and whether long-term remission/survivorship can be demonstrated based on available evidence for the treatments under comparison. As discussed in Section 0, the PFS KM curves for glofitamab populations, BR and Pola-BR provide only early indications of the existence of a plateau (even with the longer Pola-BR follow-up) and, thus, the support for a long-term remission assumption is limited. The axi-cel PFS KM curve plateaus from approximately 18 months onward and the preferred distribution for extrapolation, the Gompertz, reflects remission over the long-term. Similarly, the OS KM curves for other treatments (excluding Pola-BR) do not suggest the formation of a plateau. More mature data is required to make strong statements on the existence of long-term survivorship. The scenario analysis using the set of EAG's preferred assumptions and no long-term remission/survivorship, suggests that the ICER for the comparison of glofitamab vs BR exceeds the upper bound of the cost-effectiveness threshold recommended by NICE (i.e. £30,000 per QALY gained). For the pola-BR comparison, glofitamab appears to become more costly and slightly more effective than pola-BR (with the ICER shifting quadrants in the cost-effectiveness plane). The ICER for glofitamab vs pola-BR is still below the NICE cost-effectiveness threshold range.

When it is assumed that long-term remission/survivorship does not apply to any of the treatments under comparison, the impact of PFS and OS alternative extrapolations becomes more relevant. The EAG did not explore in scenario analysis the impact of varying the company's preferred distributional forms for the PFS and OS, because we assumed that the clinical validation of the company's extrapolation assumptions by their panel of clinical experts would have been more appropriate than the EAG's own assessment. We have expressed our concerns about particular extrapolation choices for glofitamab and pola- BR in Sections 0 and 0, based on their statistical and visual fit. We also provide in those sections a summary of extrapolation predictions over 20 years, so the committee can examine their clinical plausibility.

Overall, the cost-effectiveness analysis suggests that the finding that glofitamab may be cost-effective compared to axi-cel is robust to the assumptions being varied in the company's and the EAG's sensitivity analysis. The EAG would like to emphasise the uncertainties of the comparative clinical

effectiveness data for this particular comparison. First, the mITT population of ZUMA-1,[23] rather than the ITT population, was used to inform the clinical effectiveness of axi-cel. This introduces bias, as the mITT of ZUMA-1 is unlikely to be reflective of the whole population eligible to receive axi-cel, particularly of those who did not receive axi-cel despite being initially eligible (due to disease progression, death or other reasons). The company attempted to explore this in their scenario analysis, but only from the costs side (see Table 43). While this suggests a bias against glofitamab, it also need to be noted that the glofitamab adjusted population for the axi-cel comparison, obtained through an unanchored MAIC, had the lowest ESS (27.9) across all ITCs, limiting the comparability against axi-cel.

The EAG notes that other uncertainties remain unaddressed in the company's cost-effectiveness analysis, namely the potential impact of:

i. a full implementation of the age distribution approach to all survival and HRQoL parameters;
ii. not using the same data sources to inform TTOT and clinical effectiveness for BR;
iii. ICANS monitoring and management.

7 SEVERITY MODIFIER

In Tables 61 of the company's main submission, baseline characteristics from the pivotal glofitamab study NP30179 are reported. The summary data was a mean age of 63.19 years and with 64.9% of patients being male. The company used the online application linked to the publication by Schneider et al (2021)[59] (https://shiny.york.ac.uk/shortfall/) to calculate the absolute and proportionate shortfall. It was estimated that for a population aged 63 years and with 35% female, 11.62 QALYs would be gained for a population without the disease. The estimated QALYs gained for patients receiving treatment for relapsed or refractory DLBCL after ≥2 systemic treatments, and the estimated absolute and proportional QALY shortfalls were treatment dependent, as detailed in Table 62 of the CS and replicated on the top rows of Table 61 for completeness.

Table 61 QALY shortfall analysis for each comparison and for different long-term remission/survivorship assumptions

Expected total QALYs for the general population	Assumed current treatment	Total QALYs expected for people living with the condition, under current treatment	Absolute QALY shortfall	Proportional QALY shortfall	QALY weight for the comparison
Not assuming long-term remission/survivorship (no cure)					
11.62	Axi-cel	5.03	6.59	56.71%	1
	BR	0.75	10.87	93.54%	1.2
	Pola-BR	1.44	10.18	87.61%	1.2
Company's base case assumptions on long-term remission/survivorship (after corrections)					
11.62	Axi-cel	4.91	6.71	57.74%	1
	BR	1.11	10.51	90.45%	1.2
	Pola-BR	2.3	9.32	80.20%	1

The EAG notes that the shortfall analysis for BR as reported on Table 62 of the CS already considers a QALY weight of 1.2. Thus, the top rows of Table 61 considers the original value for expected total QALYs for BR (0.75) and revised absolute (10.87) and proportional (93.54%) QALY shortfalls. Thus, when not assuming long-term remission/survivorship for any of the treatments here under consideration, the QALY shortfalls presented on the top rows of Table 61 warrant a weighting associated with severity which is a QALY weight of 1 for axi-cel and a weight of 1.2 for both BR and Pola-BR. That is, an adjustment to the value of glofitamab QALYs (1.2) can apply for these comparisons.

7.1 Points for critique

The EAG notes that for the QALY shortfall analysis the company assumed that the standard of care for each comparison with glofitamab is the respective comparator, e.g. for the comparison of glofitamab vs BR, the standard of care considered was BR. Also, the EAG would like to highlight that the company's QALY shortfall analysis is based on the assumption of no long-term remission/survivorship (i.e. no cure assumed), and that the conclusions of their QALY shortfall analysis was not fully carried through to the economic model for Pola-BR. That is, in the economic model a QALY weight of 1.2 was applied to glofitamab Pola-BR adjusted and a QALY weight of 1 was applied to Pola-BR, creating a disjoint comparison where the intervention is weighted but the comparator is not.

However, the company's base case assumes long-term remission/survivorship to be plausible for the condition at 2 years for PFS and at 3.5 years for OS. The bottom rows of Table 61 show the QALY shortfall analysis for when these assumptions apply. The analysis shows that the comparison with Pola-BR does not warrant a weighting associated with severity, and a QALY weight of 1 should be applied. Thus, as indicated above in Section 6.1, the EAG corrected the company's base case to consider a QALY weight of 1 for the glofitamab Pola-BR adjusted and for Pola-BR. Moreover, due to the uncertainties around the assumption of cure and as highlighted in Section 6.2, the EAG carried out a series of scenarios considering different time points for cure (3 and 5 years), and different utility decrements from the age/gender general population utility (10 and 20%) and excess mortality from the age-matched general population mortality (SMR of 1.09 and of 1.41). Each of these scenarios generate different total QALYs estimates for each comparator for the people living with the condition, and thus, each warrant a QALY shortfall analysis. Table 62 shows the results of performing QALY shortfall analysis for different cure assumptions for the BR and Pola-BR comparisons. The EAG concludes that for the large majority of cure assumption sets the QALY shortfall analysis indicates a QALY weighting of 1.2 for BR and a QALY weighting of 1 for Pola-BR. The only scenario that indicates that a QALY weight of 1.2 for both BR and Pola-BR should be applied is the scenario that considers a point of cure at 5 years, with a 20% reduction in utility and an excess mortality of 41% compared to the general population. The EAG notes that axi-cel was not considered in this analysis as the magnitude of the total expected QALYs of axi-cel always warrants a QALY weight of 1. For the purposes of obtaining cost-effectiveness results for each relevant comparison, the EAG applied the QALY weights accordingly to each of the scenarios implemented.

Table 62 QALY shortfall analysis for each comparison and for different long-term remission/survivorship assumptions around the cure time point, utility decrement and excess mortality values.

Cure assumptions	QALY shortfall analysis			
	Utility adjustment -10%		Utility adjustment -20%	
	Total QALYs expected for people living with the condition, under current treatment	QALY weight	Total QALYs expected for people living with the condition, under current treatment	QALY weight
LTR/S: 3 years, SMR: 1.09				
Glofit vs BR	1.2	1.2	1.16	1.2
Glofit vs Pola-BR	2.49	1	2.35	1
LTR/S: 5 years, SMR: 1.09				
Glofit vs BR	0.9	1.2	0.88	1.2
Glofit vs Pola-BR	1.88	1	1.8	1
LTR/S: 3 years, SMR: 1.41				
Glofit vs BR	1.14	1.2	1.1	1.2
Glofit vs Pola-BR	2.32	1	2.19	1
LTR/S: 5 years, SMR: 1.41				
Glofit vs BR	0.87	1.2	0.86	1.2
Glofit vs Pola-BR	1.79	1	1.72	1.2

8 REFERENCES

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9 APPENDICES

9.1 Systematic review searches and processes

This section summarises the EAG's views on the quality and conduct of the searches and study selection processes used in the various company systematic reviews.

The original company submission refers to searches to identify clinical evidence for patients with relapsed or refractory diffuse large B-cell lymphoma. However, neither a description of the searches or any of the search strategies were included. Some details were presented in the ITC report. In response to the EAG's points for clarification (PfCs), a further document was provided by the company, which included some of the search strategies and some further information. The EAG view is summarized in Table 63.

Table 63 EAG appraisal of clinical evidence identification

TOPIC	EAG RESPONSE	NOTE
Is the report of the search clear and comprehensive?	PARTLY	**Missing Search Strategies:** In the original company submission. no clinical evidence search strategies were reported in Appendix D. This was raised as a PfC. In response, the company provided details of some of the search strategies. However, no strategies were provided for the searches of conference proceedings, Health Technology Assessment (HTA) body websites, or clinical trial registries. Strategies for the ITC report were asked for in a separate PfC, but none were provided. The EAG are assuming that the searches that were performed were used to find clinical evidence as well as evidence on indirect treatment comparisons. However, it is unclear. **Vague PRISMA:** The searches of conference proceedings, HTA body websites, clinical trial registries are not shown in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) diagram.
Were appropriate sources searched?	YES	Details of the sources searched were not included in the original company submission but were provided in response to PfCs. The company listed a very good selection of relevant databases, conference proceedings, grey literature, HTA and trials sources that were used.
Was the timespan of the searches appropriate?	YES	The original searches were not limited by date in the strategy.
Were appropriate parts of the PICOS included in the search strategies?	YES	The searches combined the population with the study types.
Were appropriate search terms used?	YES	Search terms were comprehensive but there are some missing text word terms for the condition throughout all strategies listed: centroblastic lymphoma, plasmablastic lymphoma, diffuse histiocytic lymphoma, diffuse large lymphoid lymphoma, diffuse large cell lymphoma. There are also several missed subject headings and text words for the concept of condition recurrence. However, a large number of results were retrieved with the strategies, and the EAG accepts that these missed terms are unlikely to have made a difference to the results.
Were any search restrictions applied appropriate?	YES	Irrelevant paper types were removed appropriately. It was appropriate to use date restrictions on the update searches.
Were any search filters used validated and referenced?	UNCLEAR	Various search filters were used but not referenced. There was no mention of whether filters were validated.

The original company submission included searches to identify cost-effectiveness evidence for patients with patients with relapsed or refractory diffuse large B-cell lymphoma. A description of the searches and some of the search strategies were included in Appendix H (pp. 24-41). In response to the EAG's points for clarification (PfCs), a further document was provided by the company, which included some additional strategies.

A description of the searches and some of the search strategies to identify health-related quality of life studies were included in Appendix I (pp. 62-77). There is mention of a 'targeted review' (Appendix I, p. 62), so the EAG assume that the searches to identify health-related quality of life studies were also used for evidence for the targeted review. However, it is unclear.

A description of the searches and some of the search strategies to identify cost and healthcare resource identification, measurement and valuation evidence were included in Appendix J (pp. 96-112).

Please note that the EAG does not have access to Evidence Based Medicine (EBM) Reviews and therefore cannot fully scrutinise these strategies.

The EAG views on the searches performed for health economic evidence are summarized in Table 64, Table 65, Table 66 and Table 67.

Table 64 Cost-effectiveness search strategies

Criteria	SLR September 2016	SLR August 2021/ September 2022
Population	Patients with newly diagnosed DLBCL	Patients with DLBCL being treated in the 2L+ setting
Interventions	Any pharmacological intervention used as first-line treatment	No restriction. Studies reporting results for patients in the 2L setting only were considered out of scope
Comparisons	No restrictions	
Outcomes	One of the following endpoints in combination with cost outcomes: - Clinical outcomes - Utilities - Quality-adjusted life-years - Resource use	- Summary costs and health outcomes (e.g., QALYs, LYG, life years lost) - ICERs Model summary and structure, including: - Model type - Perspective - Time Horizon - Discounting - Cycle Length - Assumptions underpinning model structures - Sources of key model inputs (to include cost data, utilities etc.)
Study Design	Economic evaluations Cost-effectiveness analyses	Cost-effectiveness analyses Cost-utility analyses

Criteria	SLR September 2016	SLR August 2021/ September 2022
	Cost-utility analyses Cost-benefit analyses Cost-minimization analyses Cost of illness analyses Budget impact analyses Economic studies based on clinical studies Modeling studies	
Databases Searched	Not provided.	Embase, 1974 to present MEDLINE® 1946 to present, incorporating: - MEDLINE® Epub Ahead of Print - MEDLINE® In-Process & Other Non-Indexed Citations - MEDLINE® Daily EBM Reviews, incorporating: - The HTA database - The Cochrane Central Register of Controlled Trials (CENTRAL) - Cochrane Database of Systematic Reviews - Cochrane Clinical Answers - Cochrane Methodology Register - Database for Abstracts of Reviews of Effects (DARE) - NHS Economic Evaluation Database (NHS EED) EconLit, 1886 to present
Supplementary Sources	HTA body websites: - National Institute for Health and Care Excellence (NICE) - Canadian Agency for Drugs and Technologies in Health (CADTH) Additional databases: - International Network for Agencies for Health Technology Assessment (INAHTA) - National Institute for Health Research (NIHR) HTA database	Reference lists of eligible studies from full publication screening stage 2019-2022 conference proceedings: - American Society of Clinical Oncology (ASCO) - American Society of Hematology (ASH) - European Hematology Association (EHA) - European Society for Medical Oncology (ESMO) - International Conference on Malignant Lymphoma (ICML) HTA body websites: - National Institute for Health and Care Excellence (NICE) - Scottish Medicines Consortium (SMC) - Canadian Agency for Drugs and Technologies in Health (CADTH)

Criteria	SLR September 2016	SLR August 2021/ September 2022
		- Pharmaceutical Benefits Advisory Committee (PBAC) Additional databases: - The Cost-Effectiveness Analysis (CEA) Registry - EuroQoL website - Research Papers in Economics - MAPI Institute - National Institute for Health and Care Research (NIHR) - International Network of Agencies for Health Technology Assessment - University of Sheffield School of Health and Related Research utility database

Table 65 EAG appraisal of cost-effectiveness evidence identification

TOPIC	EAG RESPONSE	NOTE
Is the report of the search clear and comprehensive?	PARTLY	**Missing Search Strategies**: No search strategies were included for the searches of conference proceedings, Health Technology Assessment (HTA) body websites, or any of the databases listed under 'additional databases' (Appendix H, p. 26). The company were asked to provide all strategies in a PfC but did not provide strategies for the searches of conference proceedings or any of the sources listed under 'additional databases' (Appendix H, p. 26). Strategies for only some of the HTA body websites were provided but these were not clearly documented in a table with dates. **Vague PRISMA**: The searches of conference proceedings, HTA body websites, and the databases listed under 'additional databases' (Appendix H, p. 26) are not shown individually in the PRISMA. However, a Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) diagram showing records identified from hand-searching was included in the company's response to PfCs. In the original company submission, the PRISMA in Figure 3, Appendix H is supposed to be the overall economic evaluation but repeats the database hits from the first update only.
Were appropriate sources searched?	YES	A good selection of relevant databases and other sources were searched.
Was the timespan of the searches appropriate?	YES	Timespan was 2016 onwards for the original searches with regular update searches.
Were appropriate parts of the PICOS included in the search strategies?	YES	The searches combined the population (condition) with the study types.
Were appropriate search terms used?	PARTLY	Search terms are mostly comprehensive but there are some missing text word terms for the condition throughout all strategies listed: centroblastic lymphoma, plasmablastic lymphoma, diffuse histiocytic lymphoma, diffuse large lymphoid lymphoma, and diffuse large cell lymphoma. Moreover, throughout all strategies listed, truncation is applied to lymphoma inconsistently, there are several instances of lymphoma* but many instances without truncation, which could have missed relevant papers. However, the EAG accepts that is unlikely to have made much of a difference to the results.

Were any search restrictions applied appropriate?	YES	Yes, no restrictions were applied.
Were any search filters used validated and referenced?	UNCLEAR	Various search filters were used but not referenced. There was no mention of whether filters were validated.

Table 66 EAG appraisal of health-related quality of life evidence identification

TOPIC	EAG RESPONSE	NOTE
Is the report of the search clear and comprehensive?	PARTLY	**Missing Search Strategies**: In the original company submission, no search strategies were included for any of the sources in the supplementary searches section (pp. 63-64). This includes the searches of conference proceedings, or any of the databases listed under 'additional databases' (Appendix I, p. 64). The company were asked to provide all strategies in a PfC but did not provide them. Appendix I refers to a 'targeted review' (p. 62), so the EAG assume that the searches to identify health-related quality of life studies were also used for evidence for the targeted review. Further information on this targeted review was asked for in a PfC but no additional strategies were provided. **Vague PRISMA**: The searches of everything listed in the supplementary searches section (pp. 63-64) are not shown individually in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) diagram. The PRISMA in Figure 3, Appendix I (p. 77) is supposed to be the overall studies but repeats the database hits from the first update only.
Were appropriate sources searched?	YES	A good selection of relevant databases and other sources were searched.
Was the timespan of the searches appropriate?	PARTLY	Timespan was 2019 onwards for the original searches with regular update searches. More evidence could have been retrieved with a wider date range.
Were appropriate parts of the PICOS included in the search strategies?	YES	The searches combined the population (condition) with the study types.
Were appropriate search terms used?	PARTLY	Search terms are mostly comprehensive but there are some missing text word terms for the condition throughout all strategies listed: centroblastic lymphoma and plasmablastic lymphoma, anaplastic large cell lymphoma, disseminated large cell lymphoma, large cell follicular lymphoma, large cell ki-1 lymphoma, immunoblastic lymphoma, aggressive non-hodgkin's lymphoma, and b cell non-hodgkin lymphoma. However, the EAG accepts that is unlikely to have made much of a difference to the results.
Were any search restrictions applied appropriate?	YES	Yes, no restrictions were applied.
Were any search filters used validated and referenced?	UNCLEAR	Various search filters were used but not referenced. There was no mention of whether filters were validated.

Table 67 EAG appraisal of cost and healthcare resource evidence identification

TOPIC	EAG RESPONSE	NOTE
Is the report of the search clear and comprehensive?	PARTLY	**Missing Search Strategies**: In the original company submission, no search strategies were included for any of the sources in the supplementary searches section (pp. 96-97). This includes the searches of conference proceedings, or any of additional databases listed (Appendix J, p. 97). The company were asked to provide all strategies in the points for clarification (PfCs) but did not provide them. **Vague PRISMA**: The searches of the sources in the supplementary searches section (Appendix H, pp. 96-97) are not shown individually in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) diagram. In the original company submission, the PRISMA in Figure 10, Appendix J is supposed to be the overall economic evaluation but repeats the database hits from the first update only.
Were appropriate sources searched?	YES	A good selection of relevant databases and other sources were searched.
Was the timespan of the searches appropriate?	YES	No date restrictions were applied to the original searches.
Were appropriate parts of the PICOS included in the search strategies?	YES	The searches combined the population (condition) with the study types.
Were appropriate search terms used?	PARTLY	Search terms are mostly comprehensive but there are some missing text word terms for the condition throughout all strategies listed: centroblastic lymphoma and plasmablastic lymphoma, anaplastic large cell lymphoma, disseminated large cell lymphoma, large cell follicular lymphoma, large cell ki-1 lymphoma, immunoblastic lymphoma, aggressive non-hodgkin's lymphoma, and b cell non-hodgkin lymphoma. However, the EAG accepts that is unlikely to have made much of a difference to the results.
Were any search restrictions applied appropriate?	YES	Yes, animal papers and irrelevant paper types were removed appropriately.
Were any search filters used validated and referenced?	UNCLEAR	Various search filters were used but not referenced. There was no mention of whether filters were validated.

Additional material for Section 4

Figure 22 TTOT KM curves (extracted from the company's electronic model, 3rd April, 2023 version

Abbreviations: Benda, bendamustine; Pola, polatuzumab vedotin; Ritux, rituximab

9.2 Additional material for Section 6

9.2.1 Unit costs

Table 68 Unit costs in most recent version of eMIT (26/04/2023)

9.2.2 Scenario analysis results

Table 69 Cost-effectiveness results for Company's corrected base-case + proportionality of hazards is assumed and estimated ITC HRs used (shown for completeness)

	Total Costs	Total LYG	Total QALYs	Incr. Costs	Incr. LYG	Incr. QALYs	ICER (£/ QALY gain)
Glofit vs BR							
Glofit	[redacted]	[redacted]	[redacted]				
BR	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Glofit vs Pola-BR							
Glofit	[redacted]	[redacted]	[redacted]				
Pola-BR	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Glofit vs Axi-cel							
Glofit	[redacted]	[redacted]	[redacted]				
Axi-cel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: Glofit: glofitamab; BR: bendamustine plus rituximab; Pola-BR: polatuzumab vedotin in combination with bendamustine and rituximab; Axi-cel: axicabtagene ciloleucel; LYG: life years gained; QALY: quality-adjusted life year; Inc.: incremental; ICER: incremental cost-effectiveness ratio; NE: northeast quadrant of the cost-effectiveness plane; SE: southeast quadrant of the cost-effectiveness plane; SW: southwest quadrant of the cost-effectiveness plane.

Table 70 Cost-effectiveness results for scenario 1 – using unweighted ITC estimates for all comparisons

	Total Costs	Total LYG	Total QALYs	Incr. Costs	Incr. LYG	Incr. QALYs	ICER (£/ QALY gain)
Glofit vs BR							
Glofit	[redacted]	[redacted]	[redacted]				
BR	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Glofit vs Pola-BR							
Glofit	[redacted]	[redacted]	[redacted]				
Pola-BR	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Glofit vs Axi-cel							
Glofit	[redacted]	[redacted]	[redacted]				
Axi-cel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: Glofit: glofitamab; BR: bendamustine plus rituximab; Pola-BR: polatuzumab vedotin in combination with bendamustine and rituximab; Axi-cel: axicabtagene ciloleucel; LYG: life years gained; QALY: quality-adjusted life year; Inc.: incremental; ICER: incremental cost-effectiveness ratio; NE: northeast quadrant of the cost-effectiveness plane; SE: southeast quadrant of the cost-effectiveness plane; SW: southwest quadrant of the cost-effectiveness plane.

Table 71 Cost-effectiveness results for scenario 2 - Indirectly using evidence from the Sehn et al (2022) study to inform the relative effect of glofitamab vs BR

	Total Costs	Total LYG	Total QALYs	Incr. Costs	Incr. LYG	Incr. QALYs	ICER (£/ QALY gain)
Glofit vs BR							
Glofit	[redacted]	[redacted]	[redacted]				
BR	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Glofit vs Pola-BR							
Glofit	[redacted]	[redacted]	[redacted]				
Pola-BR	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Glofit vs Axi-cel							
Glofit	[redacted]	[redacted]	[redacted]				
Axi-cel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: Glofit: glofitamab; BR: bendamustine plus rituximab; Pola-BR: polatuzumab vedotin in combination with bendamustine and rituximab; Axi-cel: axicabtagene ciloleucel; LYG: life years gained; QALY: quality-adjusted life year; Inc.: incremental; ICER: incremental cost-effectiveness ratio; NE: northeast quadrant of the cost-effectiveness plane; SE: southeast quadrant of the cost-effectiveness plane; SW: southwest quadrant of the cost-effectiveness plane.

Table 72 Cost-effectiveness results for scenario 3.1 - No long-term remission/survivorship

	Total Costs	Total LYG	Total QALYs	Incr. Costs	Incr. LYG	Incr. QALYs	ICER (£/ QALY gain)
Glofit vs BR							
Glofit	[redacted]	[redacted]	[redacted]				
BR	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Glofit vs Pola-BR							
Glofit	[redacted]	[redacted]	[redacted]				
Pola-BR	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Glofit vs Axi-cel							
Glofit	[redacted]	[redacted]	[redacted]				

	Total Costs	Total LYG	Total QALYs	Incr. Costs	Incr. LYG	Incr. QALYs	ICER (£/ QALY gain)
Axi-cel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: Glofit: glofitamab; BR: bendamustine plus rituximab; Pola-BR: polatuzumab vedotin in combination with bendamustine and rituximab; Axi-cel: axicabtagene ciloleucel; LYG: life years gained; QALY: quality-adjusted life year; Inc.: incremental; ICER: incremental cost-effectiveness ratio; NE: northeast quadrant of the cost-effectiveness plane; SE: southeast quadrant of the cost-effectiveness plane; SW: southwest quadrant of the cost-effectiveness plane.

Table 73 Cost-effectiveness results for scenario 3.2 – Timing of long-term remission/survivorship at 3 years, SMR: 1.09

	Total Costs	Total LYG	Total QALYs	Incr. Costs	Incr. LYG	Incr. QALYs	ICER (£/ QALY gain)
Utility decrement 10%							
Glofit vs BR							
Glofit	[redacted]	[redacted]	[redacted]				
BR	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Glofit vs Pola-BR							
Glofit	[redacted]	[redacted]	[redacted]				
Pola-BR	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Glofit vs Axi-cel							
Glofit	[redacted]	[redacted]	[redacted]				
Axi-cel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Utility decrement 20%							
Glofit vs BR							
Glofit	[redacted]	[redacted]	[redacted]				
BR	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Glofit vs Pola-BR							
Glofit	[redacted]	[redacted]	[redacted]				
Pola-BR	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Glofit vs Axi-cel							
Glofit	[redacted]	[redacted]	[redacted]				
Axi-cel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: Glofit: glofitamab; BR: bendamustine plus rituximab; Pola-BR: polatuzumab vedotin in combination with bendamustine and rituximab; Axi-cel: axicabtagene ciloleucel; LYG: life years gained; QALY: quality-adjusted life year; Inc.: incremental; ICER: incremental cost-effectiveness ratio; NE: northeast quadrant of the cost-effectiveness plane; SE: southeast quadrant of the cost-effectiveness plane; SW: southwest quadrant of the cost-effectiveness plane.

Table 74 Cost-effectiveness results for scenario 3.3 – Timing of long-term remission/survivorship at 5 years, SMR=1.09

	Total Costs	Total LYG	Total QALYs	Incr. Costs	Incr. LYG	Incr. QALYs	ICER (£/ QALY gain)
Utility decrement 10%							
Glofit vs BR							
Glofit	[redacted]	[redacted]	[redacted]				
BR	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Glofit vs Pola-BR							
Glofit	[redacted]	[redacted]	[redacted]				
Pola-BR	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Glofit vs Axi-cel							
Glofit	[redacted]	[redacted]	[redacted]				
Axi-cel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Utility decrement 20%							
Glofit vs BR							
Glofit	[redacted]	[redacted]	[redacted]				
BR	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Glofit vs Pola-BR							
Glofit	[redacted]	[redacted]	[redacted]				
Pola-BR	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Glofit vs Axi-cel							
Glofit	[redacted]	[redacted]	[redacted]				

	Total Costs	Total LYG	Total QALYs	Incr. Costs	Incr. LYG	Incr. QALYs	ICER (£/ QALY gain)
Axi-cel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: Glofit: glofitamab; BR: bendamustine plus rituximab; Pola-BR: polatuzumab vedotin in combination with bendamustine and rituximab; Axi-cel: axicabtagene ciloleucel; LYG: life years gained; QALY: quality-adjusted life year; Inc.: incremental; ICER: incremental cost-effectiveness ratio; NE: northeast quadrant of the cost-effectiveness plane; SE: southeast quadrant of the cost-effectiveness plane; SW: southwest quadrant of the cost-effectiveness plane.

Table 75 Cost-effectiveness results for scenario 3.4 – Timing of long-term remission/survivorship at 3 years, SMR=1.41

	Total Costs	Total LYG	Total QALYs	Incr. Costs	Incr. LYG	Incr. QALYs	ICER (£/ QALY gain)
Utility decrement 10%							
Glofit vs BR							
Glofit	[redacted]	[redacted]	[redacted]				
BR	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Glofit vs Pola-BR							
Glofit	[redacted]	[redacted]	[redacted]				
Pola-BR	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Glofit vs Axi-cel							
Glofit	[redacted]	[redacted]	[redacted]				
Axi-cel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Utility decrement 20%							
Glofit vs BR							
Glofit	[redacted]	[redacted]	[redacted]				
BR	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Glofit vs Pola-BR							
Glofit	[redacted]	[redacted]	[redacted]				
Pola-BR	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Glofit vs Axi-cel							
Glofit	[redacted]	[redacted]	[redacted]				
Axi-cel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: Glofit: glofitamab; BR: bendamustine plus rituximab; Pola-BR: polatuzumab vedotin in combination with bendamustine and rituximab; Axi-cel: axicabtagene ciloleucel; LYG: life years gained; QALY: quality-adjusted life year; Inc.: incremental; ICER: incremental cost-effectiveness ratio; NE: northeast quadrant of the cost-effectiveness plane; SE: southeast quadrant of the cost-effectiveness plane; SW: southwest quadrant of the cost-effectiveness plane.

Table 76 Cost-effectiveness results for scenario 3.5 – Timing of long-term remission/survivorship at 5 years, SMR=1.41

	Total Costs	Total LYG	Total QALYs	Incr. Costs	Incr. LYG	Incr. QALYs	ICER (£/ QALY gain)
Utility decrement 10%							
Glofit vs BR							
Glofit	[redacted]	[redacted]	[redacted]				
BR	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Glofit vs Pola-BR							
Glofit	[redacted]	[redacted]	[redacted]				
Pola-BR	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Glofit vs Axi-cel							
Glofit	[redacted]	[redacted]	[redacted]				
Axi-cel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Utility decrement 20%							
Glofit vs BR							
Glofit	[redacted]	[redacted]	[redacted]				
BR	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Glofit vs Pola-BR							
Glofit	[redacted]	[redacted]	[redacted]				
Pola-BR	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Glofit vs Axi-cel							

	Total Costs	Total LYG	Total QALYs	Incr. Costs	Incr. LYG	Incr. QALYs	ICER (£/ QALY gain)
Utility decrement 10%							
Glofit	[redacted]	[redacted]	[redacted]				
Axi-cel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: Glofit: glofitamab; BR: bendamustine plus rituximab; Pola-BR: polatuzumab vedotin in combination with bendamustine and rituximab; Axi-cel: axicabtagene ciloleucel; LYG: life years gained; QALY: quality-adjusted life year; Inc.: incremental; ICER: incremental cost-effectiveness ratio; NE: northeast quadrant of the cost-effectiveness plane; SE: southeast quadrant of the cost-effectiveness plane; SW: southwest quadrant of the cost-effectiveness plane.

Table 77 Cost-effectiveness results for scenario 4 – Background mortality corresponds to that of an average cohort age – time horizon reduced from 60 to 37 years

	Total Costs	Total LYG	Total QALYs	Incr. Costs	Incr. LYG	Incr. QALYs	ICER (£/ QALY gain)
Glofit vs BR							
Glofit	[redacted]	[redacted]	[redacted]				
BR	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Glofit vs Pola-BR							
Glofit	[redacted]	[redacted]	[redacted]				
Pola-BR	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Glofit vs Axi-cel							
Glofit	[redacted]	[redacted]	[redacted]				
Axi-cel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: Glofit: glofitamab; BR: bendamustine plus rituximab; Pola-BR: polatuzumab vedotin in combination with bendamustine and rituximab; Axi-cel: axicabtagene ciloleucel; LYG: life years gained; QALY: quality-adjusted life year; Inc.: incremental; ICER: incremental cost-effectiveness ratio; NE: northeast quadrant of the cost-effectiveness plane; SE: southeast quadrant of the cost-effectiveness plane; SW: southwest quadrant of the cost-effectiveness plane.

Table 78 Cost-effectiveness results for scenario 5 - indirect mapping of EQ-5D-3L and accounting for AE disutilities for all regimens

	Total Costs	Total LYG	Total QALYs	Incr. Costs	Incr. LYG	Incr. QALYs	ICER (£/ QALY gain)
Glofit vs BR							
Glofit	[redacted]	[redacted]	[redacted]				

	Total Costs	Total LYG	Total QALYs	Incr. Costs	Incr. LYG	Incr. QALYs	ICER (£/ QALY gain)
BR	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Glofit vs Pola-BR							
Glofit	[redacted]	[redacted]	[redacted]				
Pola-BR	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Glofit vs Axi-cel							
Glofit	[redacted]	[redacted]	[redacted]				
Axi-cel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: Glofit: glofitamab; BR: bendamustine plus rituximab; Pola-BR: polatuzumab vedotin in combination with bendamustine and rituximab; Axi-cel: axicabtagene ciloleucel; LYG: life years gained; QALY: quality-adjusted life year; Inc.: incremental; ICER: incremental cost-effectiveness ratio; NE: northeast quadrant of the cost-effectiveness plane; SE: southeast quadrant of the cost-effectiveness plane; SW: southwest quadrant of the cost-effectiveness plane.

Table 79 Cost-effectiveness results for scenario 6 - assuming obinutuzumab is administered as a complex and prolonged treatment at 1st attendance

	Total Costs	Total LYG	Total QALYs	Incr. Costs	Incr. LYG	Incr. QALYs	ICER (£/ QALY gain)
Glofit vs BR							
Glofit	[redacted]	[redacted]	[redacted]				
BR	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Glofit vs Pola-BR							
Glofit	[redacted]	[redacted]	[redacted]				
Pola-BR	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Glofit vs Axi-cel							
Glofit	[redacted]	[redacted]	[redacted]				
Axi-cel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: Glofit: glofitamab; BR: bendamustine plus rituximab; Pola-BR: polatuzumab vedotin in combination with bendamustine and rituximab; Axi-cel: axicabtagene ciloleucel; LYG: life years gained; QALY: quality-adjusted life year; Inc.: incremental; ICER: incremental cost-effectiveness ratio; NE: northeast quadrant of the cost-effectiveness plane; SE: southeast quadrant of the cost-effectiveness plane; SW: southwest quadrant of the cost-effectiveness plane.

Table 80 Cost-effectiveness results for scenario 7.1 - assuming administration cost of axi-cel= £60,000

	Total Costs	Total LYG	Total QALYs	Incr. Costs	Incr. LYG	Incr. QALYs	ICER (£/ QALY gain)
Glofit vs BR							
Glofit	[redacted]	[redacted]	[redacted]				
BR	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Glofit vs Pola-BR							
Glofit	[redacted]	[redacted]	[redacted]				
Pola-BR	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Glofit vs Axi-cel							
Glofit	[redacted]	[redacted]	[redacted]				
Axi-cel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: Glofit: glofitamab; BR: bendamustine plus rituximab; Pola-BR: polatuzumab vedotin in combination with bendamustine and rituximab; Axi-cel: axicabtagene ciloleucel; LYG: life years gained; QALY: quality-adjusted life year; Inc.: incremental; ICER: incremental cost-effectiveness ratio; NE: northeast quadrant of the cost-effectiveness plane; SE: southeast quadrant of the cost-effectiveness plane; SW: southwest quadrant of the cost-effectiveness plane.

Table 81 Cost-effectiveness results for scenario 7.2 - assuming administration cost of axi-cel= £50,500.50

	Total Costs	Total LYG	Total QALYs	Incr. Costs	Incr. LYG	Incr. QALYs	ICER (£/ QALY gain)
Glofit vs BR							
Glofit	[redacted]	[redacted]	[redacted]				
BR	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Glofit vs Pola-BR							
Glofit	[redacted]	[redacted]	[redacted]				
Pola-BR	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Glofit vs Axi-cel							
Glofit	[redacted]	[redacted]	[redacted]				
Axi-cel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: Glofit: glofitamab; BR: bendamustine plus rituximab; Pola-BR: polatuzumab vedotin in combination with bendamustine and rituximab; Axi-cel: axicabtagene ciloleucel; LYG: life years gained; QALY: quality-adjusted life year; Inc.: incremental; ICER: incremental cost-effectiveness ratio; NE: northeast quadrant of the cost-effectiveness plane; SE: southeast quadrant of the cost-effectiveness plane; SW: southwest quadrant of the cost-effectiveness plane.

Table 82 Cost-effectiveness results for scenario 8 - assuming CAR-T are not available as a post-progression treatment for those initially treated with BR or axi-cel

	Total Costs	Total LYG	Total QALYs	Incr. Costs	Incr. LYG	Incr. QALYs	ICER (£/ QALY gain)
Glofit vs BR							
Glofit	[redacted]	[redacted]	[redacted]				
BR	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Glofit vs Axi-cel							
Glofit	[redacted]	[redacted]	[redacted]				
Axi-cel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: Glofit: glofitamab; BR: bendamustine plus rituximab; Pola-BR: polatuzumab vedotin in combination with bendamustine and rituximab; Axi-cel: axicabtagene ciloleucel; LYG: life years gained; QALY: quality-adjusted life year; Inc.: incremental; ICER: incremental cost-effectiveness ratio; NE: northeast quadrant of the cost-effectiveness plane; SE: southeast quadrant of the cost-effectiveness plane; SW: southwest quadrant of the cost-effectiveness plane.

9.2.3 Results of EAG preferred assumptions

Table 83 Deterministic cost-effectiveness results for the EAG base-case

	Total Costs	Total LYG	Total QALYs	Incr. Costs	Incr. LYG	Incr. QALYs	ICER (£/ QALY gain)
Glofit vs BR							
Glofit	[redacted]	[redacted]	[redacted]				
BR	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Glofit vs Pola-BR							
Glofit	[redacted]	[redacted]	[redacted]				
Pola-BR	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Glofit vs Axi-cel							
Glofit	[redacted]	[redacted]	[redacted]				

	Total Costs	Total LYG	Total QALYs	Incr. Costs	Incr. LYG	Incr. QALYs	ICER (£/ QALY gain)
Axi-cel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: Glofit: glofitamab; BR: bendamustine plus rituximab; Pola-BR: polatuzumab vedotin in combination with bendamustine and rituximab; Axi-cel: axicabtagene ciloleucel; LYG: life years gained; QALY: quality-adjusted life year; Inc.: incremental; ICER: incremental cost-effectiveness ratio; NE: northeast quadrant of the cost-effectiveness plane; SE: southeast quadrant of the cost-effectiveness plane; SW: southwest quadrant of the cost-effectiveness plane.

Table 84 Probabilistic cost-effectiveness results for the EAG base-case (3000 simulations, bootstrapped parameters)

	Total Costs	Total LYG	Total QALYs	Incr. Costs	Incr. LYG	Incr. QALYs	ICER (£/ QALY gain)	Probability cost-effective at WTP £20,000
Glofit vs BR								
Glofit	[redacted]	[redacted]	[redacted]					
BR	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Glofit vs Pola-BR								
Glofit	[redacted]	[redacted]	[redacted]					
Pola-BR	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Glofit vs Axi-cel								
Glofit	[redacted]	[redacted]	[redacted]					
Axi-cel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: Glofit: glofitamab; BR: bendamustine plus rituximab; Pola-BR: polatuzumab vedotin in combination with bendamustine and rituximab; Axi-cel: axicabtagene ciloleucel; LYG: life years gained; QALY: quality-adjusted life year; Inc.: incremental; ICER: incremental cost-effectiveness ratio; NE: northeast quadrant of the cost-effectiveness plane; SE: southeast quadrant of the cost-effectiveness plane; SW: southwest quadrant of the cost-effectiveness plane. WTP: willingness to pay.

Table 85 Summary deterministic cost-effectiveness results for analysis 8: assuming no long-term remission/ survivorship

	Total Costs	Total LYG	Total QALYs	Incr. Costs	Incr. LYG	Incr. QALYs	ICER (£/ QALY gain)
Glofit vs BR							
Glofit	[redacted]	[redacted]	[redacted]				
BR	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Glofit vs Pola-BR							
Glofit	[redacted]	[redacted]	[redacted]				
Pola-BR	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

	Total Costs	Total LYG	Total QALYs	Incr. Costs	Incr. LYG	Incr. QALYs	ICER (£/ QALY gain)
Glofit vs Axi-cel							
Glofit	[redacted]	[redacted]	[redacted]				
Axi-cel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: Glofit: glofitamab; BR: bendamustine plus rituximab; Pola-BR: polatuzumab vedotin in combination with bendamustine and rituximab; Axi-cel: axicabtagene ciloleucel; LYG: life years gained; QALY: quality-adjusted life year; Inc.: incremental; ICER: incremental cost-effectiveness ratio; NE: northeast quadrant of the cost-effectiveness plane; SE: southeast quadrant of the cost-effectiveness plane; SW: southwest quadrant of the cost-effectiveness plane.

Single Technology Appraisal

Glofitamab for treating relapsed or refractory diffuse large B-cell lymphoma after 2 or more systemic treatments [ID3970]

EAG report – factual accuracy check and confidential information check

"Data owners may be asked to check that confidential information is correctly marked in documents created by others in the evaluation before release." (Section 5.4.9, NICE health technology evaluations: the manual).

You are asked to check the EAG report to ensure there are no factual inaccuracies or errors in the marking of confidential information contained within it. The document should act as a method of detailing any inaccuracies found and how they should be corrected.

If you do identify any factual inaccuracies or errors in the marking of confidential information, you must inform NICE by **5pm on Wednesday 17 May 2023** using the below comments table.

All factual errors will be highlighted in a report and presented to the Appraisal Committee and will subsequently be published on the NICE website with the committee papers.

Please underline all confidential information, and separately highlight information that is submitted as 'commercial in confidence' in turquoise, all information submitted as 'academic in confidence' in yellow, and all information submitted as 'depersonalised data' in pink.

Issue 1 Accurate representation of 3L+ DLBCL treatment landscape

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
[Page 28] "Neither R-Gem-Ox nor BR are used regularly to treat R/R DLBCL in the UK clinical setting."	Amend text to read as follows: "Although R-GemOx is used regularly for the treatment of 3L+ DLBCL, BR was used as a proxy given that suitable comparator data for R-GemOx were unavailable."	This statement is incorrect – R-GemOx is deemed the most prevalent R-based chemotherapy regimen for the treatment of 3L+ DLBCL in the UK, as per clinical expert feedback from an Advisory Board. In the absence of sufficient data for R-GemOx, BR was used as a proxy. This approach is backed by clinical experts and supported by registry data analysis indicating similar OS rates.	We have revised this section on Page 28 regarding R-Gem-Ox, based on discussions with our clinical advisor.

Issue 2 Subgroup exclusion criteria

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
[Pages 28-29] The EAG questioned the exclusion of several subgroups in study NP301799, and noted	Give details of any corrections that should be made	In the referenced CS section B.2.3.1.3 (pages 39-40), only an overview of the NP301799 inclusion/exclusion criteria was provided. These are further elaborated upon in the full list of	We thank the company for this clarification. The EAG notes that this detail was not in the CS, so this is not a factual inaccuracy, given the information supplied to us.

they may be potential candidates for glofitamab treatment in real-world practice. However, only the overview of the NP301799 inclusion/exclusion criteria was considered from the referenced CS section B.2.3.1.3 (pages 39-40).		inclusion/exclusion criteria, which is detailed in Study Protocol v11 (page 33), providing a more nuanced understanding of the specific patient profiles that were considered eligible or ineligible for the study. This detailed breakdown ensures clarity and precision in the patient selection process for the study, allowing for a more accurate interpretation and application of the study findings. 1. We concur with the EAG's clinical advisor and ESMO that a positive HIV status should not automatically exclude patients with R/R DLBCL from glofitamab treatment. However, Study Protocol v11 only excludes those with an **active HIV infection, or those who recently experienced severe infections requiring hospitalisation or IV antibiotics.** This approach aims to balance patient safety with the need to provide access to potentially	We have added additional clarification to Section 2.3.1 (Page 29) to cove this issue.

		beneficial treatments like glofitamab, particularly given the higher risk of DLBCL among the HIV-positive population. 2. We concur that a diagnosis of CVD should not automatically preclude patients from being considered for glofitamab treatment. Study Protocol v11 explains that "**only patients with a significant or extensive history of CVD, such as New York Heart Association Class III or IV, or Objective Assessment Class C or D cardiac disease, myocardial infarction within the last 6 months, unstable arrhythmias, or unstable angina, are excluded from study entry."** We agree that the potential for patients to tolerate neutropenic sepsis, a	

		possible side effect of glofitamab, should be evaluated on an individual basis, taking into consideration the specifics of their CVD condition. This approach is in line with our Study Protocol v11, which aims to ensure the safety and wellbeing of all participants while maximising the potential therapeutic benefits of glofitamab.	

Issue 3 Special equity/equality considerations

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
[Pages 30-31] Previous appraisal committees for tisagenlecleucel (TA567) and axi-cel (TA559) concluded that there are no relevant equality issues associated within the delivery of CAR-T-cell	Give details of any corrections that should be made	In response to the appraisal committees' conclusions based on tisagenlecleucel (TA567) and axi-cel (TA559), it is crucial to acknowledge that the DLBCL treatment landscape has evolved significantly since their approval in 2019 when there were extremely limited therapeutic options for 3L+ treatment of R/R DLBCL.	Not a factual inaccuracy. The EAG thinks that the company response here does not relate specifically to equity and equality.

therapies within the UK context. They believed that the decision to provide these treatments via the NHS would not disproportionately affect those protected by equality legislation compared to the wider population.		The preference of patients and their carers to stay close to home during treatment was highlighted by clinical experts at an Advisory Board conducted by the Company, who often prefer receiving treatment at their local hospitals, minimising travel and the associated stress and costs. Patients and an accompanying carer, if available, are hospitalised for up to 10 days post CAR-T infusion and are then required to remain within an hour of the CAR-T centre for another 2 weeks (1). For patients who do not live close to a CAR-T centre, or who can't afford to stay near a CAR-T centre for two weeks, there is no equitable access to 3L+ DLBCL treatments, until alternative treatments (such as glofitamab) become available. In the current environment, it is important to consider these patient preferences and real-world practicalities. Glofitamab, being potentially available at a wider range of clinical centres and not requiring out of pocket stays, aligns	

		with this perspective, offering a solution that balances both efficacy, equity and patient convenience.	

Issue 4 Study population definition

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
[Page 39] Definition of the 'primary study population' or 'efficacy evaluable population': "...all patients who had been assessed for response at any time during the study, regardless of their treatment status or time of withdrawal from the study; patients who had been participating in the study long enough to have reached their first scheduled response assessment – at a minimum of 49 days since the first dose of glofitamab, or 56	Amend text to read as follows: "All patients who have been assessed for response at any time during the study, who have withdrawn from treatment or the study prior to reaching their first response assessment or who have been in the study long enough to have reached their first scheduled response assessment (defined as having a minimum of 49 days since the first dose of glofitamab or 56 days since the first dose of obinutuzumab pre-treatment, at the time of data cut-off)"	Clarification of definition	We thank the company for this clarification. We have amended the report as suggested on page 39.

days since the first dose of obinutuzumab pre-treatment, at the time of data cut-off”			

Issue 5 Inaccuracies reporting of trials included in the ITC (Table 14)

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
[Table 14, Page 69] ● G029365: should be 2L+ ● Hong 2018: should be 2L+ ● Eyre 2016: includes 2L+ patients ● Transcend: sample size incorrect, should be 257/256 (datacut dependent)	Review and correct the summary of the trials included in the ITC analysis	Factual accuracy	We thank the company for this clarification. We have amended Table 14 as suggested.

Issue 6 Inaccurate reporting of trials included in the ITC

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
[Page 71] Bulleted list of “high-priority” factors considered in the ITC is incomplete.	Please update the bulleted list of high-priority factors to include all those listed on page 67 of the company submission (section B.2.9.1.5).	Factual accuracy / completeness	[NB: This issue is on page 62, not 71] Not a factual inaccuracy. In our view the list on page 62 of the EAG report is a complete and reasonable precis of the list in the CS. We note that table 15 gives exact factors adjusted for.

Issue 7 Unfair statement relating to ESS from ITC analyses

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
[Page 71] “The EAG notes that effective sample sizes for <u>most</u> analyses were very low”	Please specify which analyses had a low effective sample size (ESS). The company does not believe that most of the analyses relevant to this	Factual accuracy / completeness	[NB: This issue is on page 62, not 71] Not a factual inaccuracy.

	appraisal would be deemed to have a low ESS.		We consider this statement to be reasonable given the results (see Table 16)

Issue 8 Incomplete statement relating to consideration of outcome definitions

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
[Page 71] "The CS noted that outcome definitions were not always consistent across trials, particularly for response (CR and ORR)."	Please amend this statement for transparency, given that outcome definitions were aligned when feasible. Suggested amendment: "The CS noted that outcome definitions were not always consistent across trials, particularly for response (CR and ORR), although endpoint definitions used in NP30179 were matched to the definitions of comparator studies to align them as closely as possible, where feasible."	Factual accuracy / completeness	[NB: This issue is on page 63, not 71] This was not an inaccuracy, but we have edited the report at page 63 broadly in line with the company's suggestion.

Issue 9 Missing information in table 15

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
[Table 15, Page 72] Double/triple hit lymphoma is noted as not being adjusted for in the axi-cel comparison.	Presented in this way it is not clear that this was considered, and a decision was made to not adjust for this factor. Please consider adding the following explanation as a footnote to table 15: "Note that the proportion of patients with double/triple hit lymphoma was not included for adjustment, because only double/triple hit HGBCL was reported rather than for all patients with double/triple hit tumours. Therefore, histology subtype was used instead, as the proportion of HGBCL patients also included patients with HGBCL NOS, so it was deemed to be a more inclusive covariate. This was consistent with the feedback received on the ranked list of confounders."	Factual accuracy / completeness	We thank the company for clarifying this issue. We have added a clarification on this at Section 3.4.2.1 Page 64.

Issue 10 Typo

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
[Page 74] "In practice, the differences between ITC and investigator results, and between ITPW and matched analyses, were small."	ITC should be replaced with IRC "In practice, the differences between **IRC** and investigator results, and between ITPW and matched analyses, were small."	Factual accuracy / completeness	We have corrected this typo at Page 66.

Issue 11 Inaccurate description of approach to population adjustments

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
[Page 78] "Adjustments were performed for [redacted]	The wording "some others" is misleading in this passage. All factors that were available were controlled for, (in total 19) not just the high priority and some others. Suggested amendment" "Adjustments were performed for [redacted]	Factual accuracy / completeness	We have clarified this at Section 3.4.2.3 page 70.

[redacted]			

Issue 12 Inaccurate representation of PFS results in axi-cel comparison

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
[Page 79] "Comparing the Kaplan-Meier curves for OS and PFS (Figure 12 and Figure 13) [redacted] for both OS and PFS in both unadjusted and adjusted analyses."	It is inaccurate to suggest that there is a clear PFS benefit for axi-cel over glofitamab where HR crosses one plus the curves get next to each other or cross at ~3, ~6 and ~8 months. Suggested rewording: • Comparing the Kaplan-Meier curves for OS (Figure 12) [redacted] for OS in both unadjusted and adjusted analyses. • Comparing the Kaplan-Meier curves for PFS (Figure 13) [redacted]	Factual accuracy / completeness	We have amended section 3.4.2.2 (Page 70) to address this.

	[redacted] for PFS in the unadjusted analysis, which is however less clear in the adjusted analysis, where the curves approach or cross at ~3, ~6 and ~8 months (at multiple timepoints).		

Issue 13 Not reporting the company's considerations of El Gnaoui et al (2007) study

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
[Page 84] "On investigating further one of these, by El Gnaoui et al (2007), appeared to be broadly eligible for inclusion in this assessment, and was included in the company's systematic review of R/R DBLCL. This raises some doubt regarding the claim in the CS that no suitable	The El Gnaoui study was considered for top-line extraction but subsequently excluded for full extraction as it did not meet the filtering criteria for histology (72% DLBCL and 17% +11% MCL and FL, respectively). Suggested amendment: "On investigating further one of these, by El Gnaoui et al (2007), appeared to be broadly eligible	Factual accuracy / completeness	This was not a factual inaccuracy. For the sake of clarity, we have added text describing why the company did not consider this study to Section 3.5.2 (Page 76).

data on R-GemOx exists for comparison with glofitamab. (e.g. CS Table 1). As the EAG only became aware of this trial from information included in the response to our points for clarification, it is currently unclear why this trial was not included in the indirect treatment comparisons performed for the CS. The EAG notes that the trial is somewhat old, having been published in 2007, and was small (a total of 44 patients)."	for inclusion in this assessment, however it eventually did not meet the filtering criteria for histology used by the Company (80% DLBCL) to select suitable studies for the MAIC feasibility assessment (72% DLBCL)."		

Issue 14 Inaccurate representation of PFS results in axi-cel comparison

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
[Page 88]	Same comment as above. It is inaccurate to suggest that there	Factual accuracy / completeness	[NB: This text is on Page 88]

“Axi-cel was consistently superior to glofitamab across survival (PFS, OS)”	is a clear PFS benefit for axi-cel over glofitamab where HR crosses one plus the curves get next to each other or cross at ~3, ~6 and ~8 months. Suggested amendment: “Axi-cel was consistently superior to glofitamab in terms of overall survival, but the benefit in PFS is less clear.”		This text refers to the hazard ratio estimates (Table 17) rather than the K-M curves. We have deleted “consistently” for sake of clarity.

Issue 15 Incomplete description of information provided

Description of problem	**Description of proposed amendment**	**Justification for amendment**	**EAG response**
[Page 90] “The EAG notes that the company did not provide a full list of exclusion criteria for the search strategy conducted for cost-effectiveness studies. The EAG identified some issues with the clarity of reporting the searches, the	Details of the eligibility criteria and search strategies were provided in appendix H “Published cost-effectiveness studies”, which was shared with the company submission. Suggested amendment: “The company provided details of eligibility criteria and search strategies for the searches	Factual accuracy / completeness	We thank the company for detecting this inaccuracy. We have made the recommended amendment to the text based on factual completeness.

appropriateness of the search terms used and the referencing of search filters, but has no major concerns about the search strategy.”	related to published cost-effectiveness studies. The EAG identified some issues with the clarity of reporting the searches, the appropriateness of the search terms used and the referencing of search filters, but has no major concerns about the search strategy.”		

Issue 16 Typo

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
[Page 92] “For other treatments, TTOT was set equal to the treatment-specific maximum number of cycles”	Minor wording correction. Suggested amendment: “For **all** treatments, TTOT was set equal to the treatment-specific maximum number of cycles”	Factual accuracy	We thank the company for highlighting this issue. However, the EAG feels this is factually incorrect, as the report currently indicates the following: “Time to off treatment (TTOT) data from NP30179 were used to estimate treatment discontinuation with glofitamab. For the BR and Pola-BR comparators, TTOT was determined using data for 3L+ patients from the GO29365 trial. For axi-cel, the duration on treatment was assumed to last for a single

			model cycle. For other treatments, TTOT was set equal to the treatment-specific maximum number of cycles." No changes have been made.

Issue 17 Inaccurate description of PSA analysis

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
[Page 94] "Finally, for polatuzumab-vedotin plus bendamustine plus rituximab, a propensity score approach used the study GO29365, with (**high and medium priority**) covariate balance better achieved with full matching and inverse probability of treatment weighting."	Minor wording correction. Suggested amendment: "Finally, for polatuzumab-vedotin plus bendamustine plus rituximab, a propensity score approach used the study GO29365, with (**high, medium and low priority**) covariate balance better achieved with full matching and inverse probability of treatment weighting.	Factual accuracy	We thank the company for highlighting this inaccuracy. The EAG has made the recommended amendment.

Issue 18 Inaccurate description of PSA matching

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
[Page 94] "The propensity scores estimated with this approach featured very poor overlap, which was addressed by matching and inverse probability of treatment weighting."	Minor wording correction. Suggested amendment: "The propensity scores estimated with this approach featured very poor overlap, which was **partially** addressed by matching and inverse probability of treatment weighting."	Factual accuracy	We thank the company for highlighting this inaccuracy. The EAG has made the recommended amendment.

Issue 19 Inaccurately describing available information as unknown

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
[Tables 22-23, Pages 99-101] Note that the statistical fit of standard parametric models was "unknown" for the glofitamab adjusted populations. However, AIC/BIC for each distribution, in all populations can be	Consider updating Tables 22 and 23 to include information on which distribution was the best statistical fit in each of the glofitamab population adjusted analyses.	It is inaccurate to state that information pertaining to statistical goodness of fit was unknown, when it was available to the EAG in the economic model.	We thank the company for highlighting this issue. The EAG has made the recommended amendment.

seen in the economic model sheets “OS parameters - NPH” and “PFS parameters - NPH”.			

Issue 20 Inaccurately reporting base-case OS distribution

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
[Table 26, Page 108] Highlights generalised gamma as the base-case OS distribution for pola-BR.	Highlight log-normal as the base-case OS distribution for pola-BR.	Factual accuracy	We thank the company for highlighting this inaccuracy. The EAG has made the recommended amendment.

Issue 21 Unfair description and interpretation of the information provided relating to the MCM

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
[Page 118] “The EAG considers that the MCMs and estimated cure-fractions for glofitamab Pola-BR adjusted and Pola-BR populations cannot be	This is inaccurate as in the company response to clarification questions from April 3rd, the response to question B7a describes the approach taken to estimate cure-fractions for OS and PFS, which gives	Factual accuracy	We thank the company for highlighting this inaccuracy. The EAG has made the recommended amendment.

fully interpreted, given insufficient information was provided to understand why the PFS and OS MCM models have the same cure-fraction estimates.”	rationale as to why the estimated cure-fractions could be the same: “An “OS informed by PFS” approach was employed to estimate the cure fraction for OS and ensure this remained consistent across both endpoints. This was done by using the cure proportion predicted for the PFS models as an external parameter input in the fitting of the OS models. This approach is in line with what was done and accepted in previous TAs (e.g. TA874)” Suggested amendment: “The EAG understands that the cure fraction estimated for PFS was used to inform the one for OS in the company’s analysis, which explains why PFS and OS cure-fraction estimates were the same. However, it considers it improbable that these estimates are a true reflection of PFS and OS cure-fractions.””		

Issue 22 Typo / incomplete description of model functionality

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
[Page 121] "After PfCs, the occurrence of CRS was modelled as a one-off probability at the start of the model for axi-cel (given these events are more likely to occur in the first 2–3 weeks after infusion); all other AEs were individually modelled as having a treatment specific weekly probability of occurrence for progression-free patients on treatment"	Minor wording correction. Suggested amendment: "After PfCs, **the option to model** the occurrence of CRS as a one-off probability at the start of the model for **glofitamab was included** (given these events are more likely to occur in the first 2–3 weeks after infusion); all other AEs were individually modelled as having a treatment specific weekly probability of occurrence for progression-free patients on treatment"	Factual accuracy	We thank the company for highlighting this typo. The EAG has made the recommended amendment.

Issue 23 Typo / incomplete sentence

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
[Page 122] "The number of patients with treatment-related AEs for BR, pola-BR and axi-cel in Hong et al (2018), Sehn et al (2022), and Neelapu et al(2017), respectively."	Sentence incomplete. Propose reviewing this wording to ensure the sentence is complete.	Typo / missing word	We thank the company for highlighting this issue. The EAG has completed the sentence, which now reads: "The number of patients with treatment-related AEs for BR, pola-BR and axi-cel was sourced from Hong et al (2018), Sehn et al (2022) and Neelapu et al(2017), respectively."

Issue 24 Typo / incomplete wording

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
[Page 135] "As detailed above, the EAG questions the magnitude of the mapped utility estimate for progression free – off treatment as it is higher than the age-sex adjusted UK general population utility values."	Proposed amendment: "As detailed above, the EAG questions the magnitude of the **directly** mapped utility estimate for progression free – off treatment as it is higher than the age-sex adjusted UK general population utility values."	Accuracy / completeness	We thank the company for highlighting this inaccuracy. The EAG has made the recommended amendment.

Location of incorrect marking	Description of incorrect marking	Amended marking	EAG response
Table 3, Page 40 - Glofitamab monotherapy cohorts in Parts I, II and III of study NP30179 (safety-evaluable population) with reasons for exclusion from company evidence submission (CCOD 15 June 2022)	Mark AIC.	All numbers of patients treated (except Cohorts D3 and D5) and total number of patients treated should be marked AIC.	We thank the company for highlighting this. The EAG has made the recommended amendment.
Table 5, Page 43 - Summary of primary efficacy endpoint data in R/R DLBCL patients treated with glofitamab 2.5/10/30 mg after ≥ 2 lines of systemic therapy (ITT population)	Mark AIC.	The INV-assessed CR rate in the primary analysis and all data in the updated analysis should be marked AIC.	We thank the company for highlighting this. The EAG has made the recommended amendment.
Table 6, Page 44 - Overview of secondary efficacy endpoint data in R/R DLBCL patients	Mark AIC.	All data should be marked AIC.	We thank the company for highlighting this. The EAG has made the recommended amendment.

treated with glofitamab 2.5/10/30 mg after ≥ 2 lines of systemic therapy (ITT population)			
Page 46 - Outcome data for 'supporting efficacy population' and cohorts D3 and D5: ● "...slightly better estimates of CR, median PFS and OS for the efficacy evaluable population presented in the CS than for the "supporting efficacy" or D3 populations." ● "Median DOCR and DOR values for the D3 cohort and efficacy evaluable population appeared similar"	Mark AIC.	"This data (and the additional KM curves provided in the response to PfCs) indicate [redacted] (see response to PfC A7)."	We thank the company for highlighting this. The EAG has made the recommended amendment.

Table 7, Page 47 - IRC-assessed response rates, PFS and OS outcomes (CCOD 15 June 2022)	Mark AIC.	All data should be marked AIC.	We thank the company for highlighting this. The EAG has made the recommended amendment.
Table 8, Pages 48-49 - Summary of key demographic data and disease characteristics by sex (male vs female), as well as the following: ● "...a trend toward higher CR rates in female (52%) than male (34%) patients." ● "...noting a higher proportion of male patients exhibited higher risk factors compared to female patients. For example, a larger percentage of male patients	Mark AIC.	All data from Table 8 should be marked AIC. "The EAG noted [redacted] and asked the company whether checks had been performed for possible confounding with other factors (PfC A14). The company provided key participant characteristic data by sex, [redacted] (see Table 8)."	We thank the company for highlighting this. The EAG has made the recommended amendment.

had extranodal disease (65.0% vs. 55.6%) and bulky disease >6 cm (45.0% vs. 35.2%). Additionally, a higher proportion of male patients had HGBCL (8.0% vs. 3.7%) and a higher proportion of female patients had trFL." ● "ORR was higher in females (63.0%; 95% CI 49.6, 74.6) than males (45.5%; 95% CI 36.2, 55.2), as were median PFS (9.88 vs 3.73 months) and OS values (median not reached vs 9.9 months)		"The EAG also requested outcome data for IRC-assessed ORR, PFS and OS by sex. [redacted] (see Figure 3 to Figure 6)."	

estimated from KM curves."			
Page 52 - Histology subtypes: ● "E.g. higher response rates for PMBCL than HGBCL." ● "However, the small number of patients in NP30179 with these subtypes means these estimates are imprecise." ● "The company noted that the small number of patients with subtypes other than DLBCL precluded reporting PFS or OS outcomes for these subtypes with confidence."	Mark AIC.	"The EAG requested CR, OSS, PFS and OS data where available for DLBCL, PMBCL, HGBCL and tFL subtypes (PfC A9). The data in Table 9 reflect the expected responsiveness of each subtype to treatment [redacted]	We thank the company for highlighting this. The EAG has made the recommended amendment.

Page 55 - CAR-T prior and/or subsequent to glofitamab: ● "Of the 103 participants who had not received prior CAR-T therapy, nine (8.7%) went on to receive CAR-T after completing glofitamab. The company also provided PFS and OS KM plots for patients with/without prior CAR-T therapy (median PFS 4.62 vs 5.92 months; median OS 9.77 vs 14.70 months"	Mark AIC.	"[redacted]; see response to PfC A12)."	We thank the company for highlighting this. The EAG has made the recommended amendment.
Table 18, Page 84 ● Mark glofitamab data AIC	Mark AIC.	Mark all glofitamab data AIC.	We thank the company for highlighting this. The EAG has made the recommended amendment.

Pages 84-86 **“**Overall R-Gemox had higher response rates (for both CR and ORR) than glofitamab. This remained the case for CR even when considering only patients with at least 2, or at least 3 prior lines of therapy. CR rates were more similar when restricted to patients who had received rituximab before (assumed to be all in NP30179), at 42% for R-GemOX and 40% for glofitamab. CR rates were also similar when considering only refractory patients. Figure 15 shows digitally extracted Kaplan-Meier curves for OS and event-free survival (assumed equivalent to PFS) for	The results of this analysis, comparing glofitamab to R-Gemox, should be marked AIC.	[redacted] Figure 15 shows digitally extracted Kaplan-Meier curves for OS and event-free survival (assumed equivalent to PFS) for R-GemOx and glofitamab. [redacted] The EAG notes that this analysis is not adjusted for any possible confounders. [redacted]	We thank the company for highlighting this. The EAG has made the recommended amendment.

R-GemOx and glofitamab. Survival rates for R-GemOx are substantially better for R-GemOx (although the confidence interval is unknown). The EAG notes that this analysis is not adjusted for any possible confounders. The EAG notes that, in no analysis or subgroup was there any evidence that glofitamab was superior to R-GemOx, as was found when comparing glofitamab to BR (See Section 3.4.2.4). The EAG acknowledges that this is a naïve, unadjusted comparison, and may be biased by many factors differing between the two trials. Ideally, a MAIC should be used to compare these trials, but the EAG does not have		The EAG acknowledges that this is a naïve, unadjusted comparison, and may be biased by many factors differing between the two trials. Ideally, a MAIC should be used to compare these trials, but the EAG does not have access to the data to do this. The small sample size in the el Gnaoui trial may make an MAIC analysis uninformative, or unreliable.”	

access to the data to do this. The small sample size in the el Gnaoui trial may make an MAIC analysis uninformative, or unreliable.**”**			
Table 19, Page 85 ● Mark glofitamab data AIC	Mark AIC.	Mark all glofitamab data AIC.	We thank the company for highlighting this. The EAG has made the recommended amendment.
Figure 15, Page 86 ● Contains glofitamab data which should be marked AIC	Mark AIC.	Mark AIC.	We thank the company for highlighting this. The EAG has made the recommended amendment.
Page 88 **“**Axi-cel was consistently superior to glofitamab across survival (PFS, OS) and response (ORR, CR) outcomes, but this analysis was restricted to patients who received an axi-cel infusion. As	ITC results should be marked AIC.	[redacted]but this analysis was restricted to patients who received an axi-cel infusion. As patients may be selected for axi-cel therapy but not receive an infusion, this may be an unfair comparison. [redacted]	We thank the company for highlighting this. The EAG has made the recommended amendment.

patients may be selected for axi-cel therapy but not receive an infusion, this may be an unfair comparison. Glofitamab was consistently superior to BR for both survival and response outcomes. Glofitamab was broadly similar in efficacy to pola-BR for all outcomes. Although the direction of effect favoured glofitamab the differences in effectiveness were small and confidence intervals were wide. The EAG concludes that there is currently insufficient evidence to distinguish between glofitamab and pola-BR, but they are likely to be of similar efficacy. The EAG notes that this conclusion differs		[redacted] [redacted]The EAG notes that this conclusion differs slightly from that of the company. The CS did not include a comparison with pixantrone or tafa-len. The EAG thinks these should have been included as both interventions were included in the NICE scope. MAIC analyses for both treatments were reported in supplementary material. [redacted] The EAG notes that NICE guidance for tafa-len, rejecting its	

slightly from that of the company. The CS did not include a comparison with pixantrone or tafa-len. The EAG thinks these should have been included as both interventions were included in the NICE scope. MAIC analyses for both treatments were reported in supplementary material. The MAIC for pixantrone found glofitamab to be superior to pixantrone for both survival and response outcomes. The EAG notes that NICE guidance for tafa-len, rejecting its use was made public shortly before this report was completed, so tafa-len is no longer a relevant comparator. However, we leave discussion of it		use was made public shortly before this report was completed, so tafa-len is no longer a relevant comparator. However, we leave discussion of it in this report for the sake of transparency. [redacted]	

in this report for the sake of transparency. The MAIC performed for tafa-len found inconclusive evidence that glofitamab may be superior in response (CR and ORR). However, there was also inconclusive evidence that glofitamab may be inferior to tafa-len for survival (particularly OS). The MAIC could not be adjusted for previous lines of therapy, which might substantially bias the comparison. Therefore, the EAG considers that any possible difference in efficacy between tafa-len and glofitamab remains uncertain.”			

Pages 92-93 ● "Assuming PH holds, the use of the company's preferred PFS and OS HR estimates from the ITC analysis results in an ICER vs BR of 18,229 (£/QALY gained, 38.9% increase from company's base-case after clarifications), an ICER vs axi-cel of 157,277 (£/QALY gained SW quadrant, 8.5% decrease from company's base-case after clarifications), and with glofitamab still dominant vs. Pola-BR."	Mark ICERs CIC.	"Assuming PH holds, the use of the company's preferred PFS and OS HR estimates from the ITC analysis results in an ICER vs BR of [redacted](£/QALY gained, 38.9% increase from company's base-case after clarifications), an ICER vs axi-cel of [redacted](£/QALY gained SW quadrant, 8.5% decrease from company's base-case after clarifications), and with glofitamab still[redacted] vs. Pola-BR."	We thank the company for highlighting this. The EAG has made the recommended amendment.

Table 21, Page 95 • ITC results in table 21 should be marked AIC	Mark AIC.	All results and CI in OS HR and PFS HR columns should be marked AIC.	We thank the company for highlighting this. The EAG has made the recommended amendment.
Page 101 • "With the company's preferred (base-case) assumptions for survival extrapolation and cure, the use of glofitamab ITT trial population in the comparisons results in an ICER vs BR of 22,321 (£/QALY gained, 70% increase from company's base-case after clarifications), an ICER vs axi-cel of 141,732 (£/QALY gained	Mark ICERs CIC.	"With the company's preferred (base-case) assumptions for survival extrapolation and cure, the use of glofitamab ITT trial population in the comparisons results in an ICER vs BR of [redacted] (£/QALY gained, 70% increase from company's base-case after clarifications), an ICER vs axi-cel of [redacted] (£/QALY gained SW quadrant, 17.6% decrease from company's base-case after clarifications), and with glofitamab still [redacted] vs Pola-BR."	We thank the company for highlighting this. The EAG has made the recommended amendment.

SW quadrant, 17.6% decrease from company's base-case after clarifications), and with glofitamab still dominant vs Pola-BR."			
Figure 17, Page 104 ● Contains ITC adjusted populations, results should be marked AIC	Mark figure AIC.	Mark figure AIC.	We thank the company for highlighting this. The EAG has made the recommended amendment.
Figure 18, Page 105 ● Contains ITC adjusted populations, results should be marked AIC	Mark figure AIC.	Mark figure AIC.	We thank the company for highlighting this. The EAG has made the recommended amendment.
Pages 108-109 ● "The scenario implemented by the company reduced the point	Mark HRs AIC.	The scenario implemented by the company reduced the point estimate of the relative effect benefit assumed for axi-cel (from the biased ITC results) from	We thank the company for highlighting this. The EAG has made the recommended amendment.

estimate of the relative effect benefit assumed for axi-cel (from the biased ITC results) from 1.33 to 1.16 and from 1.74 to 1.37 for PFS and OS, respectively."		[redacted] and from [redacted] for PFS and OS, respectively.	
Page 109 ● "The use of the midpoint for PFS and OS HR for the comparison of glofitamab and axi-cel results in an ICER vs axi-cel of 268,855 (£/QALY gained SW quadrant, 56.4% increase from company's base-case after clarifications)."	Mark ICERs CIC.	The use of the midpoint for PFS and OS HR for the comparison of glofitamab and axi-cel results in an ICER vs axi-cel of [redacted] (£/QALY gained SW quadrant, 56.4% increase from company's base-case after clarifications).	We thank the company for highlighting this. The EAG has made the recommended amendment.

Figure 19, Page 110 ● Survival extrapolations should be marked AIC	Mark figure AIC.	Mark figure AIC.	We thank the company for highlighting this. The EAG has made the recommended amendment.
Figure 20, Page 112 ● Survival extrapolations should be marked AIC	Mark figure AIC.	Mark figure AIC.	We thank the company for highlighting this. The EAG has made the recommended amendment.
Figure 21, Page 116 ● Survival extrapolations should be marked AIC	Mark figure AIC.	Mark figure AIC.	We thank the company for highlighting this. The EAG has made the recommended amendment.

References

1. CAR T-cell therapy [Accessed May/2023]. Access from: https://lymphoma-action.org.uk/about-lymphoma-treatment-lymphoma/car-t-cell-therapy

NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Glofitamab for treating relapsed or refractory diffuse large B-cell lymphoma after 2 or more systemic treatments [ID3970]

Technical Engagement response form

As a stakeholder you have been invited to comment on the External Assessment Report (EAR) for this evaluation.

Your comments and feedback on the key issues below are really valued. The EAR and stakeholders' responses are used by the committee to help it make decisions at the committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

Information on completing this form

We are asking for your views on key issues in the EAR that are likely to be discussed by the committee. The key issues in the EAR reflect the areas where there is uncertainty in the evidence, and because of this the cost effectiveness of the treatment is also uncertain. The key issues are summarised in the executive summary at the beginning of the EAR.

You are not expected to comment on every key issue but instead comment on the issues that are in your area of expertise.

If you would like to comment on issues in the EAR that have not been identified as key issues, you can do so in the 'Additional issues' section.

If you are the Company involved in this evaluation, please complete the 'Summary of changes to the Company's cost-effectiveness estimates(s)' section if your response includes changes to your cost-effectiveness evidence.

Please do not embed documents (such as PDFs or tables) because this may lead to the information being mislaid or make the response unreadable. Please type information directly into the form.

Do not include medical information about yourself or another person that could identify you or the other person.

We are committed to meeting the requirements of copyright legislation. If you want to include journal articles in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.

Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.

Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise, all information submitted under 'academic in confidence' in yellow, and all information submitted under 'depersonalised data' in pink. If confidential information is submitted, please also send a second version of your comments with that information redacted. See the NICE health technology evaluation guidance development manual (sections 5.4.1 to 5.4.10) for more information.

The deadline for comments is **5pm** on **Wednesday 28 June 2023**. Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Thank you for your time.

We reserve the right to summarise and edit comments received during engagement, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received during engagement are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

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About you

Table 1: About you

Your name	[redacted]
Organisation name: stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder, please leave blank)	Roche Products Limited
Disclosure Please disclose any funding received from the Company bringing the treatment to NICE for evaluation or from any of the comparator treatment companies in the last 12 months [Relevant companies are listed in the appraisal stakeholder list.] Please state the name of the Company, amount, and purpose of funding.	Roche Products Limited is the Sponsor Company of glofitamab (Columvi®)
Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry	None

Key issues for engagement

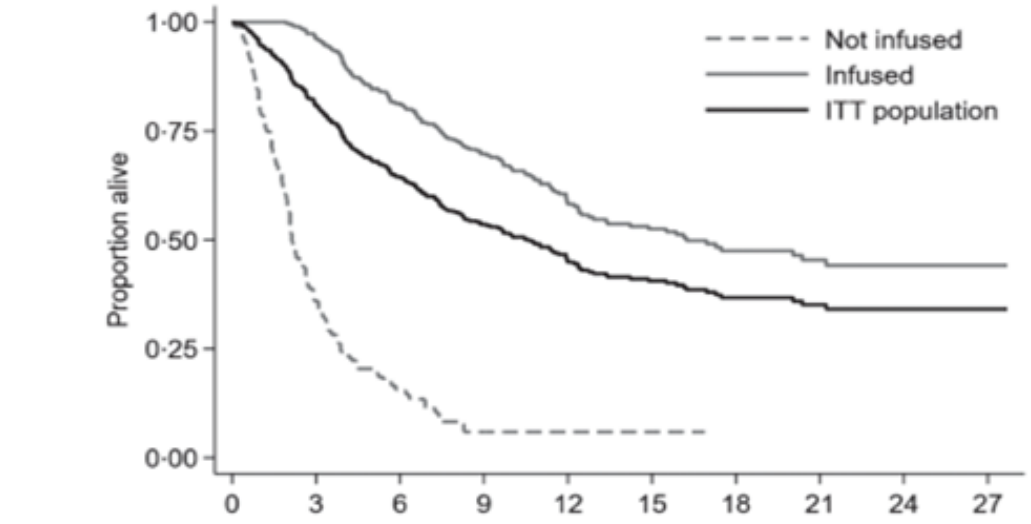
Table 2: Key issues

Key issue	Does this response contain new evidence, data or analyses?	Response
1. Position of comparator treatments in care pathway	Yes - recent approval of pola in 1L and 2L+	The Company agrees with the ERG that the use of pola-BR in R/R DLBCL will reduce in the future due to the following: • There is no defined standard of care (SOC) for 3L+ DLBCL and the current landscape is not well established. In choosing the most appropriate treatment, a careful evaluation of each patient's eligibility for CAR-T therapy, along with an examination of their previous first and second line (1L and 2L) therapies, is essential. With new treatments being introduced and others shifting to earlier lines of therapy, the traditional frameworks for comparison are becoming less relevant. • The recent recommendation of pola-R-CHP for untreated DLBCL (1) and pola-BR for 2L+ DLBCL (2) is expected to lead to a rapid decrease in the usage of pola-BR in the 3L+ setting in the upcoming years. This implies that pola-BR will become less relevant as a comparator in the future. The current Blueteq Approval Criteria for pola-BR does not allow for use of pola-BR if a patient has received 1L treatment with pola-R-CHP (3), and pola-BR is typically not administered to those on track for CAR-T therapy. In addition, according to an Advisory Board conducted by the Company, clinical experts noted the use of pola-BR in the 3L setting is

Key issue	Does this response contain new evidence, data or analyses?	Response
		already relatively uncommon, and questioned the continued relevance of pola-BR as a comparator (4). This perspective was affirmed by the EAG's clinical advisor. ● Against this backdrop, glofitamab has emerged as a promising alternative. It is proposed for use in 3L or later, where there are fewer well-established treatments. Notably, clinical experts agreed that glofit could be particularly valuable for patients who have not responded to CAR-T therapy, one of the few other treatment options for these patients. The EAG has also highlighted glofitamab's potential and acknowledged that it represents a valuable treatment option for 3L+ DLBCL patients, as pola-BR becomes a less common 3L treatment. ● As previously mentioned, the Company agrees that the use of pola-BR in R/R DLBCL will reduce in future due to the approval of pola-R-CHP for 1L treatment earlier this year. As a result, the demand for innovative, off-the-shelf treatment options like glofitamab, which presents a unique mechanism of action, is anticipated to increase for 3L+ DLBCL therapy in the near future.
2. Patients who do not receive axi-cel infusion	Yes	● The Company agrees that the overall effectiveness of axi-cel may be lower in an ITT analysis compared with the modified ITT analysis that included only patients who received CAR-T infusion. ● However, in order to be able to conduct a MAIC versus a full ITT patient population of patients treated with axi-cel, information on both baseline characteristics and outcomes on patients eligible for and willing to undergo leukapheresis and CAR-T infusion should be available for the

Key issue	Does this response contain new evidence, data or analyses?	Response
		indication of relevance. The Company is not aware of the existence of such data, but would like to bring some additional evidence to the consideration of the EAG and the Committee on the actual rates of CAR-T infused vs eligible patients and their respective outcomes that could be expected in the current UK clinical practice. ● As stated in the initial glofitamab Company Submission, all patients in the UK treated with axi-cel in the NHS are assessed for eligibility by the National CAR-T Clinical Panel (NCCP). Real world data have been published on the first 404 patients with R/R DLBCL approved for treatment with either axi-cel or tisagenlecleucel (N=292 and N=112, respectively) (5) by the NCCP between December 2018 and November 2020. A total of 104 (26%) of these patients (68 for axi-cel and 36 for tisagenlecleucel) did not receive CAR-T infusion, mainly due to rapid disease progression. This subset of the CAR-T ITT population has a worse prognosis compared with the patients who did receive their CAR-T cell infusion. This is highlighted in Figure 1, which shows survival curves for the patients who did not receive infusion, those who did receive infusion and the ITT population as a whole. Table 3 compares the survival outcomes in these 3 UK real world populations. The 'not infused' cohort represents the patients that are missing from an ITT analysis of CAR-T in the modified ITT that is available for the MAIC in this Submission. Median overall survival for this group is very poor at 2.1 months, with only 5.9% of these patients alive at 12 months. When these patients are included with the infused patients in the ITT analysis of these UK real world data, the median survival is substantially shorter than the infused cohort

Key issue	Does this response contain new evidence, data or analyses?	Response
		(10.5 months in the ITT compared with 16.2 months in the infused cohort) and 12-month OS proportion substantially less (44.9% versus 58.2%). In context of the MAIC that compares ZUMA-1 with the NP30179 population, these UK real world data suggest that there is substantial bias against glofitamab when the ITT principle is assumed. **Figure 1: Overall survival in patients approved for CAR-T cell therapy by the UK NCCP between Dec 2018 and Nov 2020 (5)**

Key issue	Does this response contain new evidence, data or analyses?	Response
		 Number at risk Not infused 104 37 15 5 3 2 0 0 0 0 Infused 300 289 242 194 123 89 56 39 18 2 ITT population 404 326 257 199 126 91 56 39 18 2

<table>
<tr><th>Key issue</th><th>Does this response contain new evidence, data or analyses?</th><th>Response</th></tr>
<tr><td></td><td></td><td>
Table 3: UK Real World overall survival by ITT, infused and not infused cohort (5)
<table>
<tr><th rowspan="2"></th><th colspan="3">Population Cohort</th></tr>
<tr><th>ITT (n=404)</th><th>Infused (n=300)</th><th>Not infused (n=104)</th></tr>
<tr><td>Median OS, months (95% CI)</td><td>10.5 (8.3, 12.0)</td><td>16.2 (12.4, NR)</td><td>2.1 (1.94, 2.69)</td></tr>
<tr><td>12-month OS (95% CI)</td><td>44.9% (39.7, 49.9)</td><td>58.2% (52.1, 63.9)</td><td>5.9% (2.3, 11.9)</td></tr>
<tr><td>24-month OS (95% CI)</td><td>34.1% (28.4, 40.0)</td><td>44.1% (36.8, 51.2)</td><td>N/A</td></tr>
</table>
</td></tr>
<tr><td>3. Confidence intervals of</td><td>Yes</td><td>• As agreed during the Technical Engagement call, the Company has generated confidence intervals (CIs) for the unadjusted MAIC and propensity-score analyses using the same bootstrapping method used in their respective adjusted analyses, to ensure consistency in the approach used to estimate the uncertainty around the point estimates.</td></tr>
</table>

<table>
<tr><th>Key issue</th><th>Does this response contain new evidence, data or analyses?</th><th>Response</th></tr>
<tr><td>ITC analyses</td><td></td><td>
The below tables present the ITC results for the unadjusted analyses, with both standard 95% confidence intervals and bootstrapped confidence intervals (Table 4, Table 5, and Table 6).
Table 4: Summary of unadjusted MAIC results and 95% CIs (glofitamab vs axi-cel)
<table>
<tr><th>Method for estimating</th><th>OR/HR (95% CI) (Jan 23 CCOD)</th></tr>
<tr><td colspan="2">ORR (IRC-assessed)</td></tr>
<tr><td>OR unadjusted Cox model (standard 95% CI)</td><td>[redacted]</td></tr>
<tr><td>Bootstrap median OR (95% percentile CI) unadjusted cox model</td><td>[redacted]</td></tr>
<tr><td>Bootstrap median OR (95% BCa CI) unadjusted cox model</td><td>[redacted]</td></tr>
<tr><td colspan="2">CR (IRC-assessed)</td></tr>
<tr><td>OR unadjusted Cox model (standard 95% CI)</td><td>[redacted]</td></tr>
<tr><td>Bootstrap median OR (95% percentile CI) unadjusted cox model</td><td>[redacted]</td></tr>
<tr><td>Bootstrap median OR (95% BCa CI) unadjusted cox model</td><td>[redacted]</td></tr>
<tr><td colspan="2">PFS (INV-assessed)</td></tr>
</table>
</td></tr>
</table>

Key issue	Does this response contain new evidence, data or analyses?	Response

HR unadjusted Cox model (standard 95% CI)	[redacted]
Bootstrap median HR (95% percentile CI) unadjusted cox model	[redacted]
Bootstrap median HR (95% BCa CI) unadjusted cox model	[redacted]
OS	
HR unadjusted Cox model (standard 95% CI)	[redacted]
Bootstrap median HR (95% percentile CI) unadjusted cox model	[redacted]
Bootstrap median HR (95% BCa CI) unadjusted cox model	[redacted]

Abbreviations: BCa, Bias corrected accelerated; CI, confidence interval; CR, complete response; HR, hazard ratio; INV, investigator; IRC, independent review committee; MAIC, matching-adjusted indirect comparison; OR, odds ratio; ORR, overall response rate; OS, overall survival; PFS, progression free survival.

Table 5: Summary of unadjusted MAIC results and 95% CIs (glofitamab vs BR)

Method for estimating	OR/HR (95% CI) (Jan 23 CCOD)
ORR (INV-assessed)	

Key issue	Does this response contain new evidence, data or analyses?	Response	
		OR unadjusted Cox model (standard 95% CI)	[redacted]
		Bootstrap median OR (95% percentile CI) unadjusted cox model	[redacted]
		Bootstrap median OR (95% BCa CI) unadjusted cox model	[redacted]
		CR (INV-assessed)	
		OR unadjusted Cox model (standard 95% CI)	[redacted]
		Bootstrap median OR (95% percentile CI) unadjusted cox model	[redacted]
		Bootstrap median OR (95% BCa CI) unadjusted cox model	[redacted]
		PFS (INV-assessed)	
		HR unadjusted Cox model (standard 95% CI)	[redacted]
		Bootstrap median HR (95% percentile CI) unadjusted cox model	[redacted]
		Bootstrap median HR (95% BCa CI) unadjusted cox model	[redacted]

Key issue	Does this response contain new evidence, data or analyses?	Response

OS	
HR unadjusted Cox model (standard 95% CI)	[redacted]
Bootstrap median HR (95% percentile CI) unadjusted cox model	[redacted]
Bootstrap median HR (95% BCa CI) unadjusted cox model	[redacted]

Abbreviations: BCa, Bias corrected accelerated; CI, confidence interval; CR, complete response; HR, hazard ratio; INV, investigator; AIC, matching-adjusted indirect comparison; OR, odds ratio; ORR, overall response rate; OS, overall survival; PFS, progression free survival.

Table 6: Summary of unadjusted PSA results and 95% CIs (glofitamab vs pola-BR)

Method for estimating	OR/HR (95% CI) (Jan 23 CCOD)
ORR (INV-assessed)	
OR unadjusted Cox model (standard 95% CI)	[redacted]
Bootstrap median OR (95% percentile CI) unadjusted cox model	[redacted]
CR (INV-assessed)	

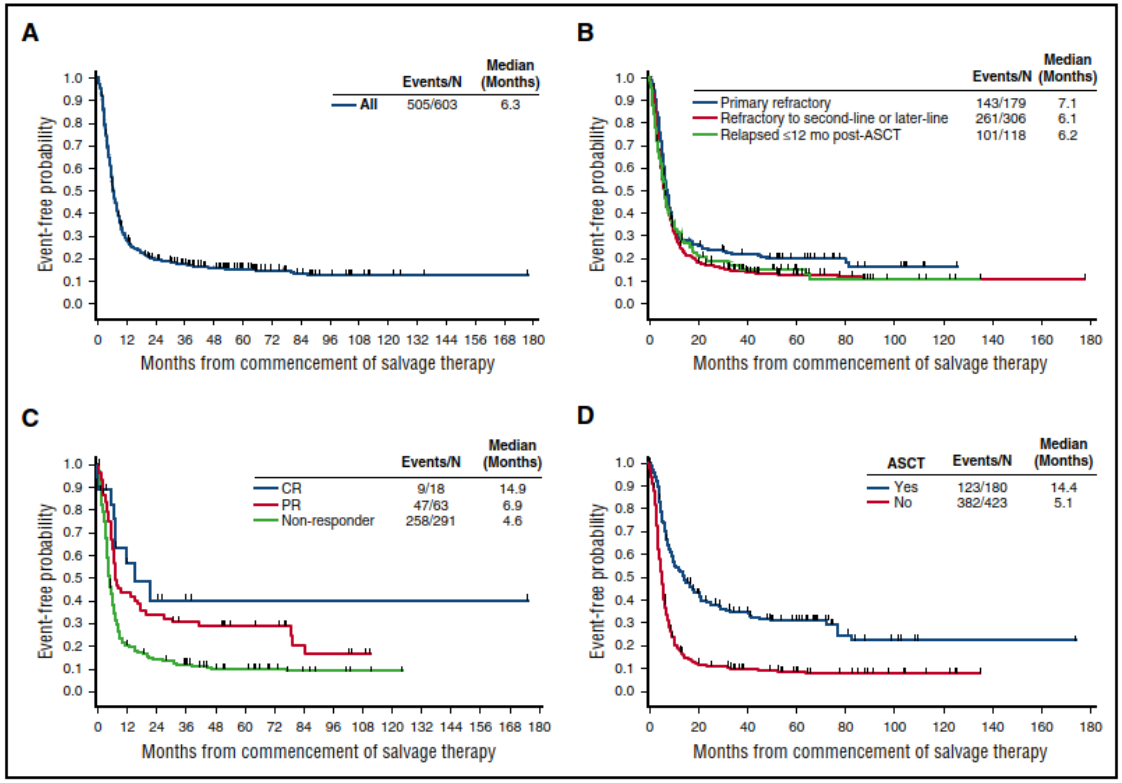
<table>
<tr><th>Key issue</th><th>Does this response contain new evidence, data or analyses?</th><th>Response</th></tr>
<tr><td></td><td></td><td>
<table>
<tr><td>OR unadjusted Cox model (standard 95% CI)</td><td>[redacted]</td></tr>
<tr><td>Bootstrap median OR (95% percentile CI) unadjusted cox model</td><td>[redacted]</td></tr>
<tr><td colspan="2">PFS (INV-assessed)</td></tr>
<tr><td>HR unadjusted Cox model (standard 95% CI)</td><td>[redacted]</td></tr>
<tr><td>Bootstrap median HR (95% percentile CI) unadjusted cox model</td><td>[redacted]</td></tr>
<tr><td colspan="2">OS</td></tr>
<tr><td>HR unadjusted Cox model (standard 95% CI)</td><td>[redacted]</td></tr>
<tr><td>Bootstrap median HR (95% percentile CI) unadjusted cox model</td><td>[redacted]</td></tr>
</table>
Abbreviations: BCa, Bias corrected accelerated; CI, confidence interval; CR, complete response; HR, hazard ratio; INV, investigator; IRC, independent review committee; MAIC, matching-adjusted indirect comparison; OR, odds ratio; ORR, overall response rate; OS, overall survival; PFS, progression free survival.

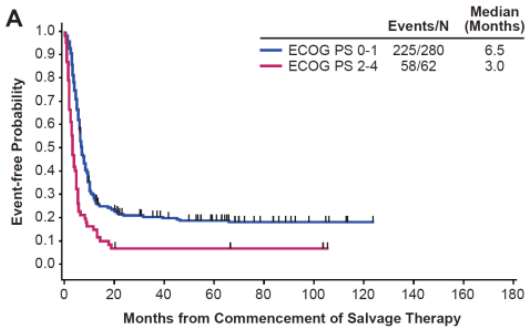
● A trend of increase in the uncertainty around the point estimates between adjusted and unadjusted analyses should now be observed across all comparisons. The Company wishes to point out that the method used to estimate CIs in the unadjusted analyses does not influence the conclusions of the adjusted results. The Company also wishes to clarify that in the current
</td></tr>
</table>

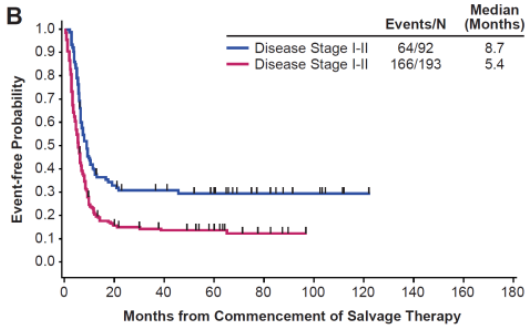
Key issue	Does this response contain new evidence, data or analyses?	Response
		EAG's and Company's base case analyses, the methods used to estimate HR CIs in the ITCs should have no impact on the uncertainty around the cost-effectiveness estimates (as both use independent modelling rather than HRs from the ITCs).
4. Long-term remission/survivorship	Yes	● The Company agrees with the EAG that both a sufficiently long follow-up and numbers of patients at risk at the end of that follow-up are needed to be able to make judgements on the plausibility of long-term remission/survivorship (noting, however, that a formal minimum threshold for both these parameters needed to make such assessments has [to date] not yet been established). Although we broadly acknowledge that this may not be confirmed with certainty for all treatments in the respective data sources used to inform the CEA, the Company disagrees with the EAG that the totality of the existing evidence is currently insufficient to support the clinical plausibility of having patients with relapsed/refractory DLBCL who may be long-term survivors, unless these were treated with a CAR-T cell based therapy (as also highlighted as part of Item 6 in the EAG report). ● First of all, the Company wishes to clarify that the absence of a robust plateau being detected for all treatments informing the CEA (i.e. featuring a sufficiently high number of patient at risk towards the tail of a KM curve), does not imply that this is not clinically plausible for a certain treatment in this disease setting. In fact, this may simply be due to the small sample sizes of the specific studies or patient cohorts that were selected as the most appropriate ones to use in an ITC (which had to take into account a series of considerations in addition to just study sample size and follow-up) and/or to the weighting of IPD needed to ensure balance in patient

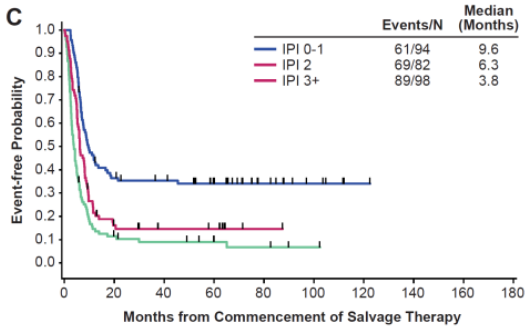
Key issue	Does this response contain new evidence, data or analyses?	Response
		characteristics could be achieved. In this respect, such a weighting of IPD (which results in an unavoidable reduction in the number of patients at risk across a KM curve) can be misleading and is not required to assess the "robustness" or plausibility of an emerging plateau. A more thorough assessment would indeed warrant the use of unweighted data, also considering data sources other than those used for the ITCs. This contrasts with fitting mixture-cure models, which instead requires both the emergence of a robust plateau and balance in patient characteristics to be able to estimate robust cure fractions and ensure a fair comparison. This is one of the reasons why fitting a mixture-cure model was not considered in the original Company submission. ● Secondly, clinical experts consulted in the context of this and past appraisals, as well as the EAG in TA649 (2), agreed that some patients with R/R DLBCL may have long-term survival that is better than that implied solely by the trial data, and that this would be independent of the technology in use. ● Finally, in the Company's opinion the current body of evidence available is actually supportive of the plausibility of having relapsed/refractory DLBCL patients who may be long-term survivors even if they have not been treated with a CAR-T cell based therapy. A summary is provided below. In the international, multi-cohort, retrospective SCHOLAR-1 study (which represents one of the largest pooled analyses in DLBCL, featuring ~600 patients) the emergence of a plateau between 1 and 2 years, which was maintained for several years, can be evidenced in the OS KM curve and it

Key issue	Does this response contain new evidence, data or analyses?	Response
		was consistent across the vast majority of subgroups analysed. None of the patients enrolled received CAR-T cell therapies, as these were not yet available at the time (6). **Figure 2: Overall survival from commencement of salvage therapy – (A) overall population, (B) refractory subgroups, (C) tumour response, (D) post-refractory transplantation status (Kaplan-Meier)**

Key issue	Does this response contain new evidence, data or analyses?	Response
		 **Figure 3: Overall survival from commencement of salvage therapy - (A) ECOG performance status, (B) disease stage, (C) IPI risk classification**

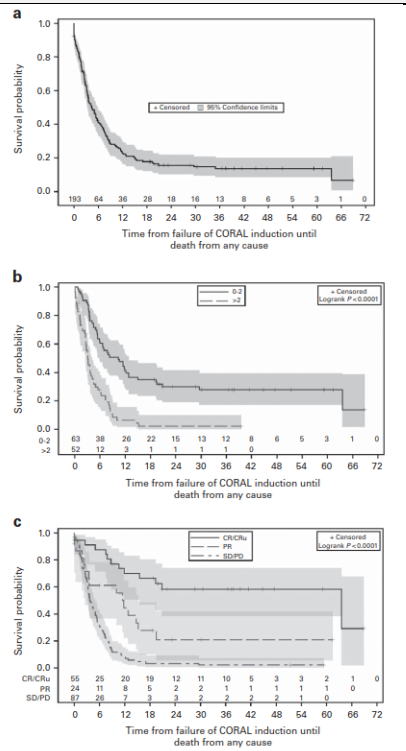


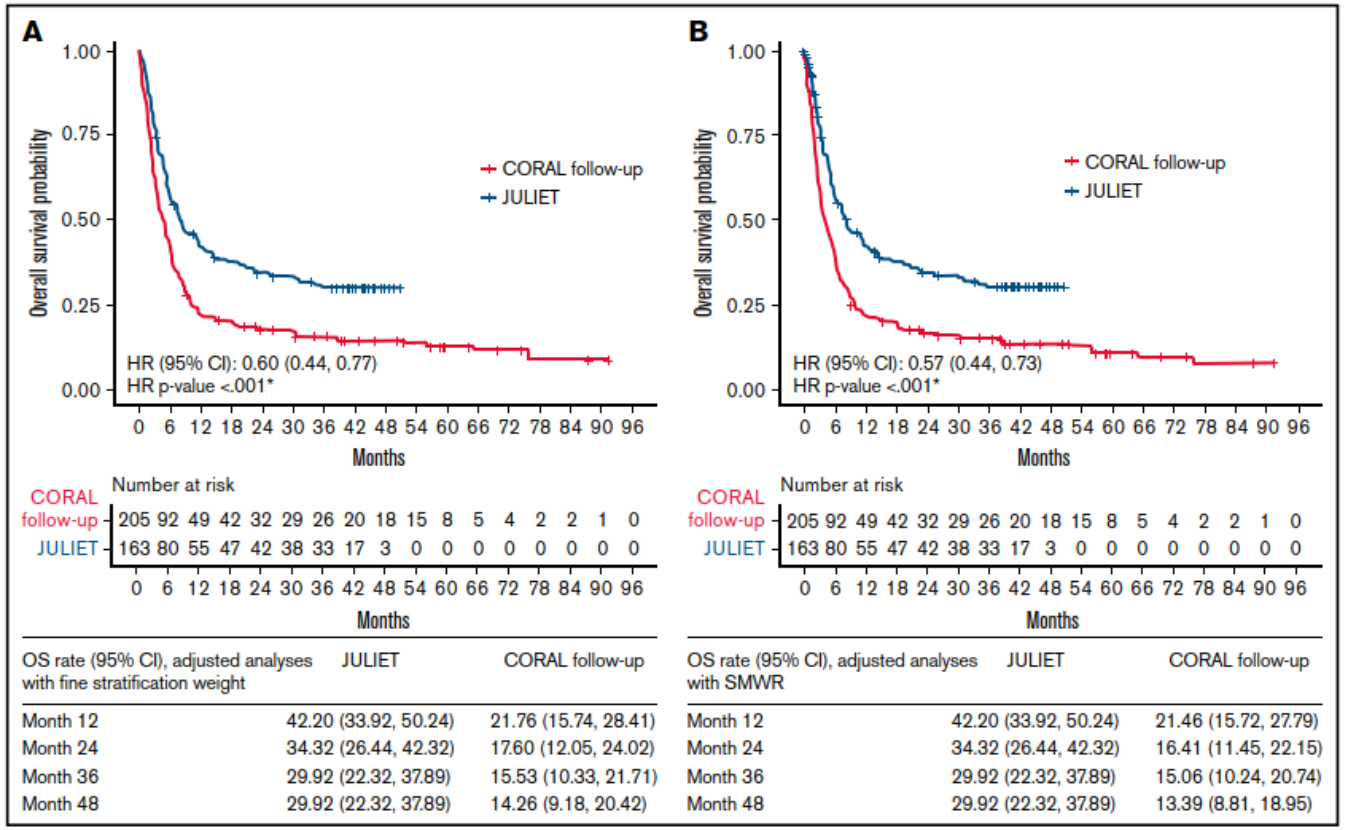




- Somewhat similar findings can also be observed in the third-line patients who failed second-line salvage regimens that were enrolled in the CORAL extension study (7). This

Key issue	Does this response contain new evidence, data or analyses?	Response
		was also somewhat confirmed in a recently published external control arm study, which used the CORAL follow-up to build a comparator arm for tisagenlecleucel (8). **Figure 4: Overall survival from time to treatment failure of CORAL induction until death from any cause**

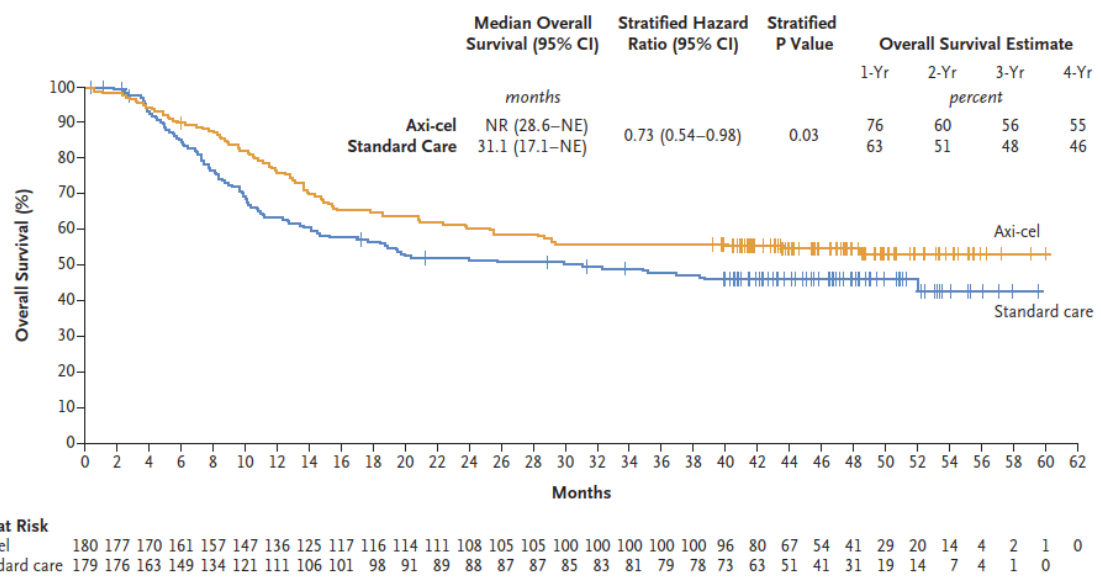
Key issue	Does this response contain new evidence, data or analyses?	Response
		 **Figure 2.** (**a**) OS of 203 patients from time to treatment failure of CORAL induction until death from any cause. (**b**) OS of 115 patients from time to treatment failure of CORAL induction according to tertiary IPI. (**c**) OS of 116 patients from time to treatment failure of CORAL induction according to response to third-line regimen. **Figure 5: Overall survival for the JULIET ITT vs CORAL follow-up ITT populations**

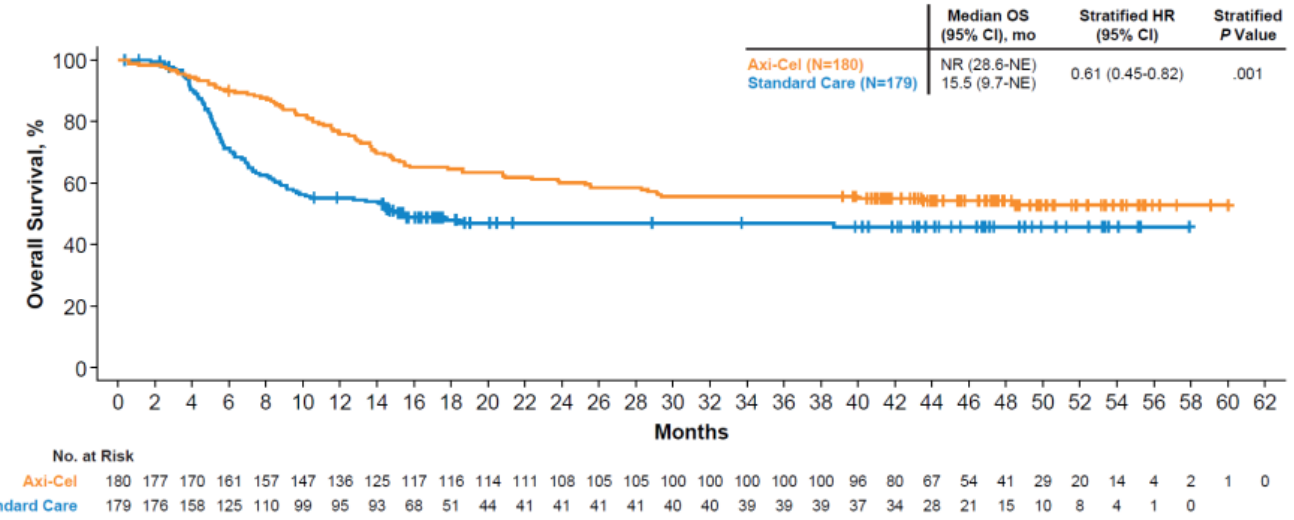
Key issue	Does this response contain new evidence, data or analyses?	Response
		

OS rate (95% CI), adjusted analyses with fine stratification weight	JULIET	CORAL follow-up
Month 12	42.20 (33.92, 50.24)	21.76 (15.74, 28.41)
Month 24	34.32 (26.44, 42.32)	17.60 (12.05, 24.02)
Month 36	29.92 (22.32, 37.89)	15.53 (10.33, 21.71)
Month 48	29.92 (22.32, 37.89)	14.26 (9.18, 20.42)

OS rate (95% CI), adjusted analyses with SMWR	JULIET	CORAL follow-up
Month 12	42.20 (33.92, 50.24)	21.46 (15.72, 27.79)
Month 24	34.32 (26.44, 42.32)	16.41 (11.45, 22.15)
Month 36	29.92 (22.32, 37.89)	15.06 (10.24, 20.74)
Month 48	29.92 (22.32, 37.89)	13.39 (8.81, 18.95)

Key issue	Does this response contain new evidence, data or analyses?	Response
		○ The control arm (i.e. standard of care, defined as 2 or 3 cycles of investigator-selected, protocol-specified chemoimmunotherapy followed by HDT-ASCT in patients who had a complete or partial response) of the recent ZUMA-7 study also featured a stabilisation of the OS KM curve after the first few (~2) years of follow-up (Figure 6) (9). It is worth noting that even though crossover between treatment groups was not allowed by the study protocol, patients could receive subsequent off-protocol therapy, including cellular immunotherapy (~57% in the standard of care arm, ~77.5% of which was axi-cel). Nevertheless, in a pre-specified sensitivity analysis to adjust for the effect of subsequent cellular immunotherapy in the standard of care arm using a rank preserving structural failure time model (RPSFTM), the OS KM curve for the standard of care arm continued to display an (even more) stable plateau lasting up until ~5 years (Figure 7). **Figure 6: Overall survival estimates of patients who received axi-cel compared with standard care**

Key issue	Does this response contain new evidence, data or analyses?	Response
		 **Figure 7: Prespecified overall survival sensitivity analysis to adjust for the effect of subsequent cellular immunotherapy in the stand-care arm using the rank preserving structural failure time model**

Key issue	Does this response contain new evidence, data or analyses?	Response
		Kaplan-Meier estimate of overall survival with sensitivity analysis using the Rank Preserving Structural Failure Time method, which was performed to address the confounding effect from treatment switching in the standard-care arm. The treatment switching rate was defined as the proportion of patients randomized to the standard-care arm who received commercially available or investigational cellular immunotherapy after nonresponse to or relapse after standard care. Two-sided P value from the log-rank test is reported. Axi-cel, axicabtagene ciloleucel; HR, hazard ratio; NE, not estimable; NR, not reached; OS, overall survival. 

Key issue	Does this response contain new evidence, data or analyses?	Response
		In a recent study on the clinical management and outcomes in DLBCL in the UK using data from the HMRN on newly diagnosed patients enrolled from September 2004 to August 2019 (10), submitted as part of TA874 (1), [redacted] Competing risk models for progression free survival from initiation of 2L and 3L therapy with death as a competing risk estimated within the same study (based on Fine and Gray's proportional subhazards [sHR] model) [redacted] **Figure 8: Overall survival from initiation of second line therapy** Redacted **Figure 9: Overall survival from initiation of third line therapy** Redacted

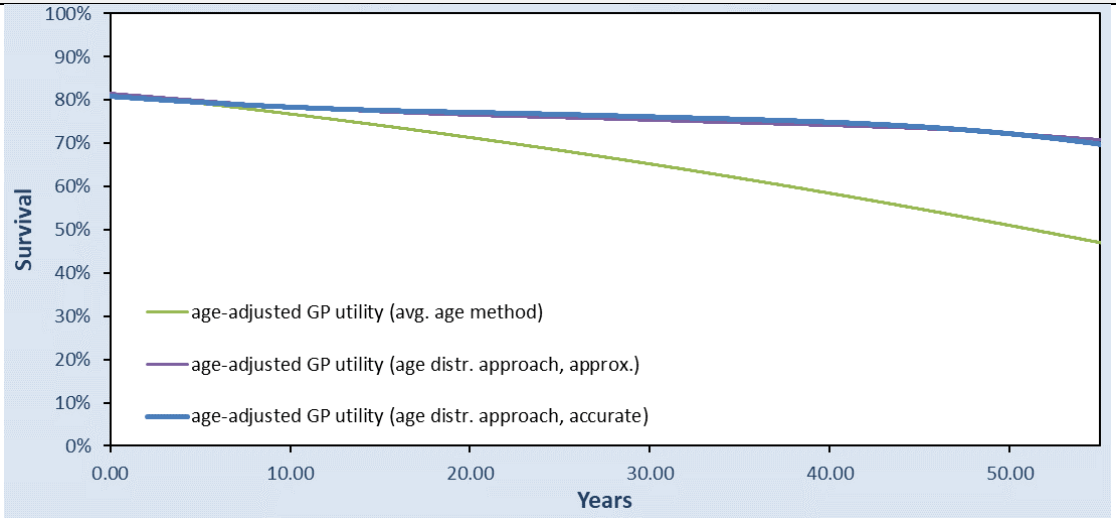
Key issue	Does this response contain new evidence, data or analyses?	Response
		Figure 10: Progression-free survival with death as a competing risk from initiation of second line therapy Redacted **Figure 11: Progression-free survival with death as a competing risk from initiation of third line therapy** Redacted In a re-analysis of the in-house IPD from the GOYA study in 1L DLBCL performed by the Company (11), [redacted] **Figure 12: Kaplan-Meiser plot (OS) of ITT patients (pooled) in GOYA who progressed in 2L+ DLBCL** Redacted

Key issue	Does this response contain new evidence, data or analyses?	Response
		Figure 13: Kaplan-Meiser plot (OS) of ITT patients (pooled) in POLARIX who progressed in 2L+ DLBCL Redacted [redacted]

Key issue	Does this response contain new evidence, data or analyses?	Response
		[redacted]**Figure 14: Overall survival for cohort D2 (sub 2), D3, D5 from NP30179 (ITT population)** Redacted ● In light of the current body of evidence presented as part of this Technical Engagement, the demonstrated superiority of pola-BR versus BR alone (in which TA649 was recognised as a reasonable proxy for standard of care by the Committee) (2) and of the very encouraging CR rates observed with glofitamab in the NP30179 trial, the Company is of the opinion that if long-term remission/survivorship is deemed clinically plausible with standard of care in DLBCL, there is no particularly strong rationale for why this should not also be the case with glofitamab (or pola-BR). Therefore, the Company would like to invite both the EAG and the Committee to only consider exploring treatment dependent long-term remission/survivorship scenarios in the presence of sufficiently robust evidence that this may not actually be applicable to a specific treatment, to ensure fair comparisons across treatments are being made that use similar consistent assumptions.

Key issue	Does this response contain new evidence, data or analyses?	Response
		● To summarise, with respect to the points raised by the EAG on pages 102 and 109 of their report, which highlight 1) the inability to confirm the BR PFS plateau shown on Figure 23 of the CS in the KM data contained in the Company's electronic model and 2) the lack of justification on the use of the cut-offs of 2 years for PFS and 3.5 years for OS: ○ The Company wishes to clarify that this is likely only due to known graphical issues of Excel in handling the proper display of KM steps within its built-in plots. The R codes the Company used to generate the KM data included in the CEM did not include the required statistical inputs in the necessary format to account for this issue. Therefore, confirming that the data sources used to inform the ITCs and the CEA are consistent, the Company recommends referring to other KM plots reported elsewhere in the documents provided as part of the CS or Clarification stage for an assessment of the emergence of a plateau, for their improved graphical quality. ○ The Company wishes to clarify that the primary rationale for using different time points for PFS/OS when running long-term remission / survivorship scenarios is to allow the modelling of more clinically plausible post-progression survival estimates, i.e. OS reverts to background mortality after PFS to allow patients with progressed disease (PD) at the selected time threshold for PFS not to be alive for the entire model time horizon. When setting the OS time threshold to be higher than the PFS one, this allows for an interval during which patients still in PD can die, before mortality for the overall cohort reverts to near general population levels, whilst not having a major impact on the OS of the long-

Key issue	Does this response contain new evidence, data or analyses?	Response
		term survivors. A difference of max 1.5 years between time thresholds was found to be a reasonable compromise and was thus selected for the Company's base case scenario. ● The Company's comments around the points raised by the EAG on the parameters used to inform the long-term remission/survivorship scenarios are provided as part of the response to Additional issues 10-12 (Items 7-9) below.
5. Average cohort age	Yes	● The Company has implemented the age-distribution approach also for the estimation of the age-adjusted GP utility, as offered during the Clarification stage. Two different approaches could be implemented, one more approximate and the other one accurate. Both are implemented in the electronic version of the updated EAG CEM ending with _test, to allow the EAG to verify the correctness of the underlying calculations, if they desire so. As the results are virtually indistinguishable between the two methods (as evidenced in Figure 15 below), but the accurate method increases significantly the complexity and file size of the model, only the approximate method was implemented in the main updated version of the EAG CEM based on the Jan 2023 CCOD that was used to run the updated results. **Figure 15: Age-adjusted GP utility over time**

Key issue	Does this response contain new evidence, data or analyses?	Response
		 • The Company decided not to implement the distributional approach for survival outcomes other than background (all-cause) mortality based on the UK life tables. • In fact, the Company wishes to clarify that, in both the Company's and the EAG's respective base case scenarios, all other survival quantities estimated in the CEM (i.e. OS, PFS and, depending on the comparator, TTOT mean times) that can be informed by trial patient level data are already being directly computed from model inputs that are fully modelled distributionally. This is because survival curves are estimated directly (either via the KM method or by fitting parametric distribution functions) from individual event times in each clinical

Key issue	Does this response contain new evidence, data or analyses?	Response
		study to fully account for their observed distribution (specifically, the complement of their cumulative distribution function). Therefore, all nonlinear effects the distribution of individual event times may have on the final mean survival quantities of interest being estimated in the CEM are already fully accounted for with these methods. • The Company also wishes to clarify that any other attempts to model such quantities in a more "distributional" way than what is done in the CEM (e.g. by using individual patient-level simulation approaches) would lead to inconsistencies with the partitioned survival modelling framework (and more in general with cohort-based modelling). As this is a suitable and well-established framework for economic evaluations in oncology and has been considered appropriate in this and other previous appraisals, the Company opted for maintaining the consistency with the modelling framework used and accepted in the context of this submission. • That being said, the Company believes the distributional approach to now be fully and consistently implemented for all those mean quantities used in the Company's and the EAG's base case scenarios that can be informed by trial patient level data and whose estimation warrants using information of the full distributions, and not just the means, of their input values to take into account nonlinear effects. • Therefore, in light of the evidence and rationale put forward by the Company throughout this appraisal, as well as the recent modifications implemented in the model, the Company would like to invite the EAG and the Committee to consider the use of this approach in their respective preferred analyses. This is also in light of the fact that a less thoroughly

Key issue	Does this response contain new evidence, data or analyses?	Response
		implemented version of this approach (and the extension of the model time horizon needed to capture all costs and benefits over a lifetime horizon to comply with the NICE reference case) (12) has recently been accepted by the respective EAG and Committee as part of TA874 (1).
6. Treatment discontinuation	Yes	● As agreed during the Technical Engagement call, to ensure consistency in the data sources used across all BR model inputs, the Company has implemented a switch in the CEM that allows the user to select Hong et al 2018 as the source to inform BR TTOT (13). The data used to inform treatment discontinuation from Hong et al 2018, was taken from the distribution of the number of cycles completed by each patient, as reported in Table 7 below. **Table 7: Patient disposition**

Key issue	Does this response contain new evidence, data or analyses?	Response

Measure	No. of pts.	(%)
Number of cycles		
Total cycles administered	177	
Median cycles, (range)	2.5	(1–6)
Patients completing cycles		
1	11	(18.9)
2	18	(31.0)
3	10	(17.2)
4	5	(8.6)
5	4	(6.9)
6	10	(17.2)

- In addition to this, when this scenario is selected, the Company has also implemented a switch to turn the half-cycle correction off. As Hong et al 2018 only reports information on the actual maximum number of cycles received by each patient, it would be inappropriate to use this when the latter is selected as the data source to inform BR TTOT. There are two main reasons why the Company believes this would be the case:

Key issue	Does this response contain new evidence, data or analyses?	Response
		○ It would be inconsistent with the data reported - the maximum number of cycles per patient, reflecting the cycles actually administered, as opposed to time on treatment (which would warrant the half-cycle correction to be applied as it could be associated with uncertainty on how many patients actually received a dose at each model cycle) ○ It would underestimate the actual number of cycles received in the CEM compared to what is reported in Hong et al 2018 and thus underestimate the actual costs of treatment (including drug, administration, AE costs) • The Company notes that using Hong et al 2018 to inform the BR TTOT leads to a minor increase in the ICER and thus the cost-effectiveness estimates are fairly insensitive to the use of either data source.

Key issue	Does this response contain new evidence, data or analyses?	Response
7. Immune effector cell-associated neurotoxicity syndrome (ICANS)	Yes	• The incidence of ICANS was low in the primary safety population (N=154) and events were mainly low grade. Information on the ICANS events reported is provided below as rationale for no additional monitoring requirements beyond general clinical management. • All-grade neurological adverse events (NAEs) consistent with the American Society for Transplantation and Cellular Therapies (ASCTC) definition of immune effector cell-associated neurotoxicity syndrome (ICANS; Lee 2019) (14) were reported in a total of [redacted] patients ([redacted]) in the primary safety population (all grades) following treatment with glofitamab step-up dosing. The most commonly reported preferred term (PT) was confusional state ([redacted] The majority of patients experienced Grade 1-2 ICANS event [redacted] reporting Grade 3 NAEs (PTs: somnolence and delirium), and [redacted] reporting a Grade 5 neurologic AE (PT: delirium), which was heavily confounded by concurrent opiate use. In the safety population, only [redacted] experienced ICANS which were related to treatment, all of which were of toxicity grades lower than 3 and none of which were classified as serious adverse events; the incidence of treatment-related ICANS events did not meet the threshold Grade ≥3 event in >1 patient. • In the June 2022 CCOD, one patient had missing toxicity grade, therefore the analysis included only [redacted]. In the new data cut (CCOD Jan 2023), toxicity grade information was available for all 1[redacted] Specifically, the additional patient had a grade 2 toxicity ICAN event which was not an SAE and was not related

Key issue	Does this response contain new evidence, data or analyses?	Response
		to the treatment therapy. Notably, in both data cuts there was [redacted]. **Table 8: NAEs (CCOD June 2022)** Redacted **Table 9: NAEs (CCOD January 2023)** Redacted **Table 10: Relationship of glofitamab treatment to ICANS**

Treatment related ICANs		
AETOXGR	N_ICANS	N_pat
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
ICANS not related to treatment		
AETOXGR	N_ICANS	N_pat

Key issue	Does this response contain new evidence, data or analyses?	Response
		[redacted]

- ICANS is usually treated when it occurs with Grade ≥2 severity. [redacted] in the primary safety population experienced Grade ≥2 ICANS events following treatment with glofitamab step-up dosing. Of the [redacted] patients who reported a Grade ≥2 ICANS event, [redacted] patients reported a Grade 2 event, 2 patients reported a Grade 3 event, and 1 patient experienced the Grade 5 (fatal) event of delirium. AEs in [redacted] was assessed as related to study treatment by the investigator, and [redacted] received treatment for the AE.
- The majority of NAEs consistent with ICANS events were reported in Cycle 1. The patient with Grade 5 delirium experienced the event 2 days after the C1D15 (10 mg) glofitamab dose and this was confounded by concurrent opiate use. No NAEs consistent with ICANS events were reported after Cycle 2.
- The NAEs observed with glofitamab are differentiated from the neurologic toxicity observed for the authorised CAR-T cell therapies. As stated in the initial Company Submission, 110/300 (36.8%) of the infused patients in the UK real world dataset (5) experienced ICANS of any grade with 47 patients (15.7%) reporting Grade ≥3. For axi-cel specifically, the incidence of all grade and Grade ≥3 ICANS was 99/224 (44.4%) and 44/224 (19.6%), respectively (5). The nature of these events (majority low grade and non-serious as described above) does not

Key issue	Does this response contain new evidence, data or analyses?	Response
		warrant specific monitoring recommendations beyond general clinical management. There are no monitoring recommendations in the EU draft SmPC following positive CHMP opinion, which is expected to be the case for the GB SmPC following marketing authorisation. In addition, consultation with haematologists who practice at UK CAR-T centres suggests that links to consultant neurologists at the centre are set up but these are rarely used and it is the haematologist who manages ICANS. Therefore it is expected that ICANS management would not be a limiting factor for location of a haematology specialist unit that would deliver glofitamab treatment.

Additional issues

Table 11: Additional issues from the EAR

Issue from the EAR	Relevant section(s) and/or page(s)	Does this response contain new evidence, data or analyses?	Response
Additional issue 1: CAR-T administration cost	Section 4.2.9.5, Pages 171, 173/174	No	As requested by NICE during the Technical Engagement telephone conference, an administration cost for CAR-T therapies of £41,101 [TA895] has been implemented in the Company's updated base-case (15).
Additional issue 2: Application of QALY modifiers	Section 7, Pages 194-195	No	The EAGs economic model incorrectly applies QALY modifier calculations in the comparisons with BR and pola-BR to both sides of the equation, thereby inflating QALYs (when the modifier is switched on) to glofitamab and the comparator treatment. This has been corrected for in the Company's updated economic model shared with the Technical Engagement response, impacting the incremental QALY calculations in the comparison with BR where a 1.2 QALY modifier applies to glofitamab.
Additional issue 3: Item 1	Section 4.2.6.1.1, Pages 97, 190-192	No	The Company has no particularly major objections on this point. The Company would like to point out the followings for the EAG/Committee's consideration:

Issue from the EAR	Relevant section(s) and/or page(s)	Does this response contain new evidence, data or analyses?	Response
			● The use of different data sources is generally standard practice when conducting ITCs in the presence of disconnected evidence networks and this has not prevented decision making in previous TAs ● The use of different data sources to indirectly compare glofitamab to alternative treatments in this specific case is warranted by the impossibility of achieving covariate balance at an acceptable sample size when trying to use a common data source, where possible, as acknowledged by the EAG ● Although adjustment procedures may show little impact on survival curves compared to unadjusted analyses, the difference on PFS and OS extrapolations may be more important, as also noted by the EAG in TA892 (16) ● Even without any weighting or matching adjustments, a sample size of 21 patients is unlikely to represent a good data source for fitting reasonably robust extrapolations for the long-term survival predictions in the CEM ● Finally, the Company would like to caution against the use of estimates from unadjusted analyses for decision making in those circumstances where well-established and appropriate methods to reduce confounding (as per NICE TSD 17 and 18) can be applied, as this

Issue from the EAR	Relevant section(s) and/or page(s)	Does this response contain new evidence, data or analyses?	Response
			would imply taking decisions based on biased analyses (also acknowledged by the EAG).While the results of the unadjusted analyses are described in the ITC sections of the Company submission, the Company disagrees with the EAG's suggestion of presenting the naive unadjusted comparisons to aide committee decision making. Population adjustments were undertaken to reduce any biases resulting from population imbalances in the presented comparisons. While sample sizes were reduced after adjustments were made, the adjusted samples are sufficiently large and more similar to the comparator population cohorts, to be considered a more robust analysis for committee decision making than the unadjusted analyses.
Additional issue 4: Item 2	Section 4.2.6.1.1, Pages 96 / 97, and Table 47 (Pages 165-166)	No	The Company broadly agrees with the EAG on this point, although we would like to caution against the over interpretation of results from different studies in which different patient populations were enrolled, as they may be confounded by differences in prognostic factors and effect modifiers. For instance, the Hong et al 2018 study enrolled ~30% of 2L patients and this difference could not be controlled for in the MAIC as no 2L patients were enrolled in the D2s2+D3+D5 NP30179 trial cohorts, biasing the results against glofitamab (13). With respect to this, it is worth noting that the number of prior lines of therapy was identified as the most

Issue from the EAR	Relevant section(s) and/or page(s)	Does this response contain new evidence, data or analyses?	Response
			impactful independent prognostic factor for PFS and OS in a recent multivariate analysis of outcomes in a large pool of patients with relapsed / refractory DLBCL treated with standard of care using the COTA Electronic Health Record database (17). Additionally, the Company would like to clarify that the IPTW analysis of glofitamab versus pola-BR showed a mild benefit (though not statistically significant) in favour of the former, after controlling for ~20 covariates and so it can be considered robust. Therefore, in light of these results as well as of the recent results of GO29365 in Sehn et al 2022, if interpretations are to be made these would naturally suggest that true the benefit of glofitamab (and its cost-effectiveness) versus BR is likely being underestimated in the present appraisal, as also suggested by the EAG. Finally, the Company would like to clarify that in absence of formal proportional hazards testing on the curves published in Sehn et al 2022, as well as on the patient cohorts used to inform the PS analyses conducted by the Company using GO29365 latest data, scenarios attempting to reconstruct BR survival curves from the HRs reported in Sehn et al 2022 and the pola-BR 3L+ KM curves are exploratory and should be interpreted with a good degree of caution.

Issue from the EAR	Relevant section(s) and/or page(s)	Does this response contain new evidence, data or analyses?	Response
Additional issue 6: Item 3	Section 4.2.6.3.3, Pages 102-103, and Table 47 (Pages 165-166)	No	The Company would like to clarify that the use of different (adjusted) glofitamab populations, one for each comparison, to indirectly compare a treatment against comparators of interest represents standard practice in the presence of disconnected evidence networks and was accepted in several previous TAs, the last of which being TA892 (16). Furthermore, it may be unavoidable in those situations where the proportional hazards assumption is not found to hold for all endpoints in all comparisons, as this does not allow to apply different adjusted HRs to a common set of survival curves of a given treatment to generate reliable survival estimates for the different comparator arms. In these situations, the only approach that avoids basing decisions on otherwise dangerously biased estimates is to conduct individual pairwise comparisons using the methods recommended in TSD 17 and 18 for propensity-score analyses and population adjusted ITCs, respectively. It is the Company's opinion that any other approaches would increase the uncertainty or, worse, provide a misleading picture, as they would imply taking decisions based on biased analyses. While the results of the unadjusted analyses are described in the ITC sections of the Company submission, the Company disagrees with the EAG's suggestion of presenting the naive unadjusted comparisons to aide committee decision making.

Issue from the EAR	Relevant section(s) and/or page(s)	Does this response contain new evidence, data or analyses?	Response
			Population adjustments were undertaken to reduce any biases resulting from population imbalances in the presented comparisons. While sample sizes were reduced after adjustments were made, the adjusted samples are sufficiently large and more similar to the comparator population cohorts, to be considered a more robust analysis for committee decision making than the unadjusted analyses.
Additional issue 7: Item 4	Section 4.2.6.3.3, Pages 101-102, and Table 47 (Pages 165-166)	No	The choice of preferred survival extrapolations for PFS and OS were based on statistically goodness of fit, and were validated as reasonable in terms of clinical plausibility by 8 UK clinical experts (4).
Additional issue 8: Item 5	Section 4.2.6.6.3, Page 115, and Table 47 (Pages 165-166)	Yes - see response to key issue 4	Please see response to Key Issue 4

Issue from the EAR	Relevant section(s) and/or page(s)	Does this response contain new evidence, data or analyses?	Response
Additional issue 9: Item 6	Section 4.2.6.7.1 Pages 117-119, and Table 47 (Pages 165-166)	Yes - see response to key issue 4	Please see response to Key Issue 4
Additional issue 10: Item 7	Section 4.2.6.7.1 Pages 117-119, and Table 47 (Pages 165-166)	No	The Company acknowledges that there is some uncertainty around the parameters used to inform the long-term remission / survivorship scenarios in the CEA, in agreement with the EAG, and has no particularly major objections on this point. The Company agrees that a 3-year time point after which cure can be assumed (as done in the EAG base case scenario) may also be plausible, as the 2-year time point used in the Company's own base case scenario (as in previous TAs). However, the Company would just like to point out for both the EAG's and the Committee's consideration that most published articles that were used in past TAs as supportive evidence to assess the plausibility of different time points are almost all based on a DLBCL population of newly diagnosed patients. As the population of interest for this appraisal is relapsed / refractory DLBCL (specifically after 2 or more lines of systemic treatments), a 2-3 year time point it is likely to properly account for the time from diagnosis to start of 3rd line and be more clinically plausible

Issue from the EAR	Relevant section(s) and/or page(s)	Does this response contain new evidence, data or analyses?	Response
			(see also response to Key Issue 4) than using 4-5 years as explored in previous TAs, which may thus likely represent overly conservative scenarios.
Additional issue 11: Item 8	Section 4.2.6.7.1 Pages 117-119, and Table 47 (Pages 165-166)	No	The Company acknowledges that there are some uncertainties around the parameters used to inform the long-term remission / survivorship scenarios in the CEA, in agreement with the EAG, and has no particularly major objections on this point. The Company would just like to point out that in light of the evidence and the argumentations provided as part of the response to Item 9, the use of a utility decrement of 0.1 to reflect the continued impact of former disease related comorbidities also in long-term survivors is likely to represent a conservative assumption and that considerations should also be given to scenarios where no penalty to QoL is applied for long-term survivors.
Additional issue 12: Item 9	Section 4.2.6.7.1 Page 117-119, and Table 47 (Pages 165-166)	Yes	The Company acknowledges that there are some uncertainties around the parameters used to inform the long-term remission / survivorship scenarios in the CEA, in agreement with the EAG, and has no particularly major objections on this point. However, the Company would like to bring some additional evidence to the EAG's and Committee's attention that was recently presented as part of TA874 (1). [redacted]

Issue from the EAR	Relevant section(s) and/or page(s)	Does this response contain new evidence, data or analyses?	Response
			[redacted] **Figure 16: Cumulative incidence of all-cause mortality by case-control status in cases who are progression-free at 24 months** Redacted This is in line with the findings of a Danish population based study (18), which suggest that patients who achieve sustained remission for up to 2 years are considered to experience mortality rates and quality of life in line with that of the general population. This in turn also suggests that the residual comorbidity burden in these patients is not likely to differ from that

Issue from the EAR	Relevant section(s) and/or page(s)	Does this response contain new evidence, data or analyses?	Response
			of the general population (also see response to Item 8). The Company also wishes to clarify that, even though both these studies were based on a population of newly diagnosed DLBCL patients, so did the other studies that were considered to inform the SMRs explored in previous TAs (i.e. Maurer et al 2014 (19) and Howlader et al 2017 (20)). Moreover, there is no particular clinical rationale for why if no excess mortality is observed in patients who remain in long-term remission / survivorship from their first line of therapy, this should not also be the case for patients who remain in this status from subsequent lines. A view consistent with UK clinical experts consulted by Roche, who agreed long-term remission and survival was plausible for patients with 3L+ R/R DLBCL. In light of this, the Company believes that greater consideration should be given by the EAG and the Committee to scenarios using an SMR of 1 (or 1.09, to be conservative), as higher SMRs are likely going to be too pessimistic.
Additional issue 13: Item 10	Section 4.2.6.8.1, Pages 120-121, and Table 47 (Pages 165-166)	Yes - see response to Key Issue 6	As discussed during the Technical Engagement call, the Company accepts the EAG reservations on the approach taken in the original CS to model BR treatment discontinuation in the CEM. The Company has revised its approach as part of its response to Key Issue 6 (see above for a description of the scenario implemented in the revised CEM)..

Issue from the EAR	Relevant section(s) and/or page(s)	Does this response contain new evidence, data or analyses?	Response
			With respect to the EAG concern around limiting treatment discontinuation to the maximum number of treatment cycles for each treatment, please refer to the response to Additional issue 21 (Item 18) below.
Additional issue 14: Item 11	Section 4.2.6.9.1, Pages 121-122, and Table 47 (Pages 165-166)	No	The Company confirms that the AEs associated with glofitamab and pola-BR were modelled correctly based on the approach described in the CS and using the same R codes used in previous TAs.
Additional issue 15: Item 12	Section 4.2.7.1, Pages 122-123, and Table 47 (Pages 165-166)	No	Please see response to Key Issue 5
Additional issue 16: Item 13	Section 4.2.8.6, Pages 127-128, and Table 47	No	The Company acknowledges that utility mapping is associated with greater uncertainty compared to estimating HSUVs directly from EQ-5D data collected in a clinical trial and has no particularly major objections on this point. The Company would like to point out that the lack of collection of EQ-5D data is not uncommon in relapsed refractory DLBCL clinical

Issue from the EAR	Relevant section(s) and/or page(s)	Does this response contain new evidence, data or analyses?	Response
	(Pages 165-166)		trials and that the use of mapped utilities has not prevented decision making in previous TAs.
Additional issue 17: Item 14	Section 4.2.8.8, Pages 129-134, and Table 47 (Pages 165-166)	No	The Company disagrees with the EAG that treatment specific adverse event disutilities should also be applied in scenarios where a distinction between PFS on- and off-treatments health states is made. The Company would like to reiterate that the issue raised by the EAG of a potential underestimation of the impact that a treatment safety profile may have on utilities, due to a presumed inability of most patients with severe adverse effects to complete HRQoL questionnaires, is expected to apply also for published disutilities. Actually, if published disutilities were originally derived from data collected outside of a clinical trial setting, where data collection is not subject to the strict requirements usually imposed by trial protocols, it is even more likely for this to be the case. Furthermore, due to missing information, the values for most of the AE disutilities used in the model were imputed using conservative assumptions rather than estimated directly from data, which makes the potential for double counting even higher. Finally, the Committees' preferences in several previous TAs (e.g. TA406, TA529) were not to include adverse event disutilities in the economic analyses when health

Issue from the EAR	Relevant section(s) and/or page(s)	Does this response contain new evidence, data or analyses?	Response
			state utilities were estimated using trial data, again to avoid potential double counting issues. Nevertheless, the Company agrees with the EAG that adverse event disutilities are unlikely to be an important driver of cost-effectiveness.
Additional issue 18: Item 15	Section 4.2.9.6 Page 144, and Table 47 (Pages 165-166)	No	The Company would like to clarify that the costs of BR administration were also originally estimated by considering one single administration cost for all drug components administered in the same days. In fact, it is worth noting that there is some uncertainty around how BR is administered in lymphoma: in some publications, this is done on day 1 for rituximab and on days 2 and 3 for bendamustine, whereas in others bendamustine is administered on Days 1 and 2 (13, 21-23). It is unclear whether this ambiguity in the literature is attributable to geographical variations in practice, different dosing schedules for the 120 or 90 mg administrations or other factors. In the light of this, it was assumed that bendamustine is administered on days 2 and 3, for consistency with what is reported in the study used to inform the MAIC (Hong et al 2018) (13). The costs of pola-BR administration were calculated to align with the dosing schedule originally reported in the GO29365 trial protocol. The Company acknowledges that this should have perhaps been explained more clearly in the notes within the CEM.

Issue from the EAR	Relevant section(s) and/or page(s)	Does this response contain new evidence, data or analyses?	Response
			On the costing of the obinutuzumab administration, the Company wishes to clarify that, in its original approach, the administration costs for all therapies used as pre-treatments were consistently costed as subsequent treatments (including bridging therapy for CAR-Ts before the NHS CAR-T tariff became available), as it was assumed that they would feature fewer pre-medication and monitoring requirements given that they are supposed to be administered for a shorter treatment course than normal, as a simplifying assumption. To estimate the post-progression therapies administration costs, the Company wishes to clarify that this was done as a simplifying assumption to avoid overcomplicating the formulas for the estimation of the total cost per regimen for the subsequent therapies (which would otherwise require something similar to what is done in the model Markov traces, rather than a simple multiplication between unit costs and treatment durations). Recognising that all these changes have a limited impact on the results, and to resolve this issue, the Company accepts the proposed costing amendments that were applied in the EAG updated economic model. These amendments have been also been implemented in the Company's updated base-case.

Issue from the EAR	Relevant section(s) and/or page(s)	Does this response contain new evidence, data or analyses?	Response
Additional issue 19: Item 16	Section 4.2.9.6, Page 145, and Table 47 (Pages 165-166)	No	See response to additional issue 1. An administration cost of £41,101 for axi-cel has been implemented in the economic model at the request of NICE.
Additional issue 20: Item 17	Section 4.2.9.6, Page 145, and Table 47 (Pages 165-166)	No	The Company would like to point out that, although re-treatment under some specific circumstances was allowed by the NP30179 trial protocol (and it is not uncommon in single-arm trials in DLBCL) this is not foreseen in the target SmPC of glofitamab and it is thus not expected to occur in clinical practice. The Company wishes to clarify that the TTOT inputs included in the CEM do consider re-treatment (TTOT defined as time from first to last dose of study treatment), but the cost of re-treatment is not factored in the economic analysis by imposing a cap on the maximum treatment duration as allowed by the respective treatments SmPCs (see also reply to Item 18), to better reflect what would be expected to occur in clinical practice, as well as to ensure a fair comparison is made versus axi-cel and pola-BR. In fact, it is should be noted that ~10% and [redacted] of the patients in the ZUMA-1 and GO29365 trial cohorts that were used in the ITCs also received re-treatment (compared to [redacted] in the NP30179 D2 [Sub 2] +D3+D5 cohorts Jan '23 CCOD), but this is not factored in the subsequent

Issue from the EAR	Relevant section(s) and/or page(s)	Does this response contain new evidence, data or analyses?	Response
			therapy cost assumptions preferred by the EAG. Therefore, considering the cost of re-treatment for glofitamab but no other therapies would result in unfair cost comparisons.
Additional issue 21: Item 18	Section 4.2.9.6, Pages 145-146, and Table 47 (Pages 165-166)	No	The Company confirms that the gap between the treatment duration associated with the maximum number of cycles in the SmPC and the maximum treatment duration (as observed in the NP30179 trial) used as input in the CEA is solely due to delayed doses and/or re-treatment (see also response to Item 17). With respect to this, the Company wishes to clarify that, in the D2 [Sub 2] +D3+D5 NP30179 cohorts, [redacted] (in the step-up dosing period only) and none of these ended up receiving a full treatment course. Therefore, the application of a cap to the maximum treatment duration based on the maximum number of cycles foreseen in the target SmPC would not exclude such dose repetitions observed in the trial data from being fully accounted for in the drug and administration costs, as the treatment duration for the respective patients would not effectively be capped. Also, the Company wishes to clarify that, due to how drug acquisition/administration costs are calculated in the model, costs are charged at each model cycle a patient is expected to be administered a drug based on its dosing schedule, irrespective of whether that patient actually received it or not, for those patients who are on treatment.

Issue from the EAR	Relevant section(s) and/or page(s)	Does this response contain new evidence, data or analyses?	Response
			Therefore, if patients experience one or more dose delays (with or without dose repetitions), the drug acquisition and administration costs incurring in the future are fully charged at the time point when the administration would have occurred had such dose delays not been observed, using the highest available unit cost, which represents a conservative scenario. In fact, after the first treatment cycle (i.e. from model cycle 4 onwards) the full cost of a 30 mg injection is charged for those patients who are on treatment. As the unit cost of a 30 mg injection is substantially higher than that of any other lower dose or obinutuzumab pre-treatment injections (including administration, monitoring and AE costs), this way of estimating drug costs for dose repetitions is conservative. In this respect, a cap on the treatment duration should be in place, as also done in TA649, to avoid one delayed injection being unduly charged as several multiple ones (especially in cases of long delays), with drug acquisition/administration being overcosted, rather than artificially reduced, as suggested by the EAG. As the inclusion of premedication and prophylactic medications costs had a negligible impact on the results, a decision was made to consistently exclude these costs from all treatment arms in the model.

Issue from the EAR	Relevant section(s) and/or page(s)	Does this response contain new evidence, data or analyses?	Response
Additional issue 22: Item 19	Section 4.2.9.8, Page 147-148, and Table 47 (Pages 165-166)	No	The Company agrees with the EAG that the cost of monitoring CRS with glofitamab is unlikely to have a major impact on the cost-effectiveness estimates and that using an elective admission is too high to be representative of the resource use required for monitoring patients overnight. No patients with treatment-related ICANs observed in the D2 [Sub 2]+D3+D5 NP30179 trial cohorts received treatment for neurotoxicity. The Company confirms that the cost of ICANS was not considered in the economic analysis as no Grade 3 or higher treatment related ICANS were observed in the D2 [Sub 2]+D3+D5 NP30179 trial cohorts.
Additional issue 23: Item 20	Section 4.2.9.10, Pages 150-151, and Table 47 (Pages 165-166)	No	The Company accepts the EAGs assumption, which removes CAR-T retreatment as an option. The Company acknowledges that the distribution of subsequent treatments across different regimens under comparison is an area of uncertainty in TAs and that it would generally be preferable to have individualised baskets of subsequent therapies for each comparator based on updated market share information. However, this is rarely the case in TAs, particularly when comparisons are informed by MAICs, as full information on the distribution of subsequent treatments in the indication of interest is almost never available from published articles.

Issue from the EAR	Relevant section(s) and/or page(s)	Does this response contain new evidence, data or analyses?	Response
			Accordingly, the use of broadly comparable clinically relevant subsequent treatment baskets has been accepted in previous TAs. The Company generally agrees with the EAG on the potential underestimation of the benefit of CAR-T cell therapies in the BR comparison due to them not yet being routinely available when the Hong et al (2018) study collected the data (2011-2015). However, considering the sample size in the BR arm (~60 patients), as well as the rate of subsequent CAR-T treatment observed in NP30179 ([redacted] as the best proxy for use in current clinical practice), this is unlikely to have resulted in a dramatic impact on the shape of the BR OS KM curve, considering the follow-up available in Hong et al 2018was roughly similar to the one in the NP30179 Jan '23 CCOD. In fact, in an analysis comparing the OS of all the 155 patients in NP30179 vs the OS of the subset of those who did not receive CAR-T as a subsequent treatment, it can be seen that the two OS survival curves are nearly indistinguishable (Figure 17). This is even more likely to be the case in a smaller dataset such as that of Hong et al 2018. This in turn suggests that the impact on BR OS model extrapolations is also likely to be minimal. **Figure 17: Kaplan-Meier plot of overall survival (by subsequent CAR-T status)**

Issue from the EAR	Relevant section(s) and/or page(s)	Does this response contain new evidence, data or analyses?	Response
			Redacted Finally, the Company would also like to point out that, an issue similar to the one raised by the EAG may also apply to the comparison of glofitamab versus axi-cel, in that a sizeable proportion of patients in ZUMA-1 (~10%) received retreatment, which may bias the survival and cost-effectiveness estimates against glofitamab in the EAG preferred scenario, which excludes the cost of re-treatment for axi-cel. Given the rapidly changing treatment landscape for R/R 3L+ DLBCL in the UK, the Company believes that the analysis of post-discontinuation therapies, informed by NP30179, reflects a robust and current estimate of 4L+ treatment usage in the UK. However, acknowledging the EAG's comments, the Company accepts the EAGs assumption which removes CAR-T retreatment as an option. This amendment has been reflected in the Company's updated base-case (please see the below cost-effectiveness section for more details).
Additional issue 24: Item 21	Section 4.2.9.14, Page 154-156 and Table 47	No	The Company accepts the EAG's critique of the CRS management cost estimates. To address the EAG's comments, an amended cost estimate for the management of CRS, including the tocilizumab PAS, removing vial sharing, and adjusting the cost code for tocilizumab administration is

<table>
<tr><th>Issue from the EAR</th><th>Relevant section(s) and/or page(s)</th><th>Does this response contain new evidence, data or analyses?</th><th>Response</th></tr>
<tr><td></td><td>(Pages 165-166)</td><td></td><td>
provided below (See Table 12). The impact of this amendment has a negligible impact on the ICERs.

The amended cost CRS management estimate, including the tocilizumab PAS is incorporated in the Company’s updated base-case (see cost-effectiveness section below):

Table 12: CRS AE management cost
<table>
<tr><th>Cost component</th><th>Cost per unit</th><th>Unit</th><th>Total cost</th></tr>
<tr><td>Tocilizumab</td><td>£512 (400mg/20ml [without PAS])

[redacted]</td><td>Required dose 8mg/kg = 599.6mg (74.95kg*8mg)

Vials required</td><td>Assuming vial wastage

£1536 (without PAS)</td></tr>
</table>
</td></tr>
</table>

Issue from the EAR	Relevant section(s) and/or page(s)	Does this response contain new evidence, data or analyses?	Response			
				£256 (200mg/10ml [without PAS]) [redacted]	for 2 administrations: **2x400ml 2x200ml**	[redacted]
			Haematologist (visit) NHSSRC 2020/21; WF01A, Service code 303, clinical haematology, face-to-face, non-admitted	£214.56	2	£429.12
			Pharmacist time	£31.20	2	£62.40
			Intensive care unit (ICU)	£2,497.81	4	£9,991.24

Issue from the EAR	Relevant section(s) and/or page(s)	Does this response contain new evidence, data or analyses?	Response
			hospitalisation | | | | **Total cost** | **12,018.76 (without PAS)** [redacted]

Summary of changes to the Company's cost-effectiveness estimate(s)

Company only: If you have made changes to the base-case cost-effectiveness estimate(s) in response to Technical Engagement, please complete the table below to summarise these changes. Please also provide sensitivity analyses around the revised base case. If there are sensitivity analyses around the original base case which remain relevant, please re-run these around the revised base case.

In response to Technical Engagement, an updated economic model, incorporating an updated NP30179 datacut from January 2023 has been provided. The updated economic model has also been updated to implement changes to address key issues (4, 5, and 6). Further to the provision of the updated economic model, an amendment to the glofitamab PAS has been submitted to PASLU, [redacted]

The analyses presented below are based on the updated economic model, including the changes implemented in response to the EAG's key issues and items, a 1.2 QALY modifier for glofitamab QALYs in the comparison with BR, and incorporating the known PAS discounts for, glofitamab, polatuzumab-vedotin, obinutuzumab, and tocilizumab.*

The choice of preferred PFS and OS parametric extrapolations applied in the updated economic model, and updated base-case, are consistent with those presented in the company's submission.

A summary of the clinical outputs from NP30179 (January 2023 CCOD) and updated ITC results can be seen in the supplementary document shared with this response.

Table 13: Changes to the Company's cost-effectiveness estimate

<table>
<tr><th>Key issue(s) in the EAR that the change relates to</th><th>Company's base case before Technical Engagement</th><th>Change(s) made in response to Technical Engagement</th><th>Impact on the Company's base-case incremental cost-effectiveness ratio (ICER)</th></tr>
<tr><td>Issue 4: Long-term remission/survivorship</td><td>The Company's original base-case implemented the following assumptions relating to long-term remission/survivorship:
Long term remission assumed at 2 years (PFS)
Long term survivorship assumed from 3.5 years (OS)
10% utility decrement compared to general population
1.09 standardised mortality rate [SMR] - 9% excess compared to general population</td><td>The Company's updated base-case has been adjusted, with the following assumptions now being applied:
Long term remission assumed at 3 years (PFS)
Long term survivorship assumed from 3 years (OS)
10% utility decrement compared to general population
1.09 standardised mortality rate [SMR] - 9% excess compared to general population</td><td>Incorporating the PAS discounts for glofitamab, polatuzumab-vedotin, obinutuzumab, and tocilizumab. The impact of this change on the ICERs can be seen in Table 14 and Table 15 below.

Table 14: Company original base-case ICERs (LTR/S assumptions)<table><tr><th colspan="2">ICERs (£/QALY)</th></tr><tr><td>vs BR</td><td>[redacted]</td></tr><tr><td>vs pola-BR</td><td>[redacted]</td></tr><tr><td>vs axi-cel</td><td>[redacted]</td></tr></table>*1.2* QALY modifier applied to glofitamab QALYs estimates
**SW ICER (cost saved per QALY lost)</td></tr>
</table>

<table>
<tr>
<td></td>
<td></td>
<td></td>
<td>Table 15: Company updated base-case ICERs
<table>
<tr><th colspan="2">ICERs (£/QALY)</th></tr>
<tr><td>vs BR</td><td>[redacted]</td></tr>
<tr><td>vs pola-BR</td><td>[redacted]</td></tr>
<tr><td>vs axi-cel</td><td>[redacted]</td></tr>
</table>
1.2 QALY modifier applied to glofitamab QALYs estimates
**SW ICER (cost saved per QALY lost)</td>
</tr>
<tr>
<td>Issue 5: Average cohort age</td>
<td>In the Company’s original base-case background mortality was modelled as a function of the age distribution of patients in the NP30179 study.</td>
<td>In the Company’s updated base-case background mortality and health-related quality of life was modelled as a function of the age distribution of patients in the NP30179 study.</td>
<td>It is not possible to present the impact of this amendment in isolation, as this change has been implemented in the updated economic model to apply consistently across all variables, as requested by the EAG. Therefore, functionality hasn’t been included in the model to only adjust the approach used to estimate HRQoL. To illustrate the impact of this approach on the ICERs, an ICER in which the average cohort age approach is</td>
</tr>
</table>

implemented, as applied in the EAG's base-case.

Incorporating the PAS discounts for glofitamab, polatuzumab-vedotin, obinutuzumab, and tocilizumab. The impact of this change on the ICERs can be seen in Table 16 and Table 17 below.

Table 16: Average cohort age approach (37 year time horizon)

ICERs (£/QALY)	
vs BR	[redacted]
vs pola-BR	[redacted]
vs axi-cel	[redacted]

**1.2* QALY modifier applied to glofitamab QALYs estimates*

***SW ICER (cost saved per QALY lost)*

<table>
<tr>
<td></td>
<td></td>
<td></td>
<td>Table 17: Company updated base-case ICERs (distributional approach, 60 year time horizon)
<table>
<tr><th colspan="2">ICERs (£/QALY)</th></tr>
<tr><td>vs BR</td><td>[redacted]</td></tr>
<tr><td>vs Pola-BR</td><td>[redacted]</td></tr>
<tr><td>vs Axi-cel</td><td>[redacted]</td></tr>
</table>
1.2 QALY modifier applied to glofitamab QALYs estimates
**SW ICER (cost saved per QALY lost)</td>
</tr>
<tr>
<td>Issue 6: Treatment discontinuation</td>
<td>The Company’s original base-case modelled BR treatment discontinuation using data from the GO29365 study.</td>
<td>The Company’s updated base-case models BR treatment discontinuation using data from the Hong et al 2018 study, thereby promoting consistency in the sources used to inform the comparative analysis with BR.</td>
<td>Incorporating the PAS discounts for glofitamab, polatuzumab-vedotin, obinutuzumab, and tocilizumab. The impact of this change on the ICERs can be seen in
Table 18 and Table 19 below.

Table 18: Company original base-case ICERs (GO29365 BR discontinuation, half cycle correction)</td>
</tr>
</table>

			ICERs (£/QALY) vs BR [redacted] vs pola-BR [redacted] vs axi-cel [redacted] **1.2* QALY modifier applied to glofitamab QALYs estimates* ***SW ICER (cost saved per QALY lost)* **Table 19: Company updated base-case ICERs (Hong et al BR discontinuation, no half-cycle correction)** **ICERs (£/QALY)** vs BR [redacted] vs pola-BR [redacted] vs axi-cel [redacted] **1.2* QALY modifier applied to glofitamab QALYs estimates* ***SW ICER (cost saved per QALY lost)*
Company's base case	**Table 20: Incremental QALYs**	**Table 21: Incremental costs**	**Table 22: Company updated base-case ICERs**

following Technical Engagement (including glofitamab, polatuzumab vedotin and obinutuzumab PAS discounts, with list prices applied for bendamustine, rituximab and axi-cel)

Incremental QALYs	
vs BR	[redacted]
vs pola-BR	[redacted]
vs axi-cel	[redacted]

**1.2* QALY modifier applied to glofitamab QALYs estimates*

Incremental costs £	
vs BR	[redacted]
vs pola-BR	[redacted]
vs axi-cel	[redacted]

ICERs (£/QALY)	
vs BR	[redacted]
vs pola-BR	[redacted]
vs axi-cel	[redacted]

**1.2* QALY modifier applied to glofitamab QALYs estimates*

***SW ICER (cost saved per QALY lost)*

Sensitivity analyses around revised base case

The development of the Company's base-case, adjusted from the EAG's approach, is presented below.

Table 23: Development of Company updated base-case

Analysis	Description	Cumulative ICERs (£/QALY)		
		ICER vs BR (1.2*QM)	ICER vs pola-BR	ICER vs axi-cel
1. **EAG base-case**	Presented in EAG report	[redacted]	[redacted]	[redacted]
2. Analysis 1 + Updated CRS management cost	Amended cost estimates for glofitamab CRS management (additional issue 24)	[redacted]	[redacted]	[redacted]
3. Analysis 2 + Distributional approach to background mortality and HRQoL	Use more sophisticated approach - 60 year time horizon (key issue 5)	[redacted]	[redacted]	[redacted]
4. Analysis 3 + axi-cel administration cost	NICE requested administration cost £41,101 (additional issue 1)	[redacted]	[redacted]	[redacted]
5. Analysis 4 + Treatment discontinuation	Use Hong et al 2018 to model treatment discontinuation, no half-	[redacted]	[redacted]	[redacted]

	cycle correction (key issue 6)			
6. **Company updated base-case: Analysis 5 + updated long-term remission (LTR) assumptions**	LTR/survival: 3 years, SMR: 1.09, - 10% utility adjustment (key issue 4)	[redacted]	[redacted]	[redacted]

CRS, Cytokine release syndrome; ICER, incremental cost-effectiveness ratio; LTR, long-term remission; LTS, long-term survival; SMR, Standardised mortality rate; QALY, quality adjust life years

**1.2* QALY modifier applied to glofitamab QALYs estimates*

***SW ICER (cost saved per QALY lost)*

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Glofitamab for treating relapsed or refractory diffuse large B-cell lymphoma after 2 or more systemic treatments [ID3970]

Company Technical Engagement Response

Supplementary Material

June 2023

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Section 1: Updated clinical evidence (CCOD January 2023)

The clinical evidence previously provided in the initial Company Submission (CS) and responses to further clarification questions were based on the clinical cutoff date (CCOD) of 15 June 2022. As of this date, all patients had concluded their participation of glofitamab treatment. Please refer to Section B.2.3.1 of the initial CS for information on the study methodology, Section B.2.3.2 for details regarding patient demographics and baseline characteristics, and Section B.2.4.2 for an explanation of the analysis methods used.

The ongoing NP30179 medical data analysis is routinely carried out to pinpoint any safety signals and to confirm that the data is accessible and examined during critical periods, such as during data snapshots. Given the continuing nature of the study, revisions have been made to some patient baseline characteristics and patient outcome data at the new CCOD of 16 January 2023. A summary of these changes is provided below.

- [redacted]
- [redacted]
- [redacted]
- [redacted]

Updated evidence is provided from the NP30179 study for the primary efficacy and safety populations, at the new CCOD of January 2023. The primary endpoint (complete response [CR] rate as determined by IRC) and the objective response rate (ORR) remain unchanged (40.0% [95% CI: 32.2, 48.2] and 51.6% [95% CI: 43.5, 59.7], respectively) (1), as all patients had finished the study treatment by the previous CCOD.

In terms of the median follow up, as per IRC assessment in June 2022, the median duration of follow up for complete response (DOCR) and duration of response (DOR) were [redacted], respectively. By

January 2023, the median time on the study had extended to [redacted], with the median DOCR follow-up also increasing to 18.2 months (range: 0–33).

See Table 1 for a summary of the updated efficacy results from the primary efficacy population who were intended to receive glofitamab doses of 2.5/10/30 mg following ≥ 2 lines of systemic therapy.

Table 1: Overview of efficacy results in the primary efficacy population (CCODs Jun 2022 and Jan 2023)

Efficacy endpoints	Primary efficacy population: Glofitamab 2.5/10/30mg Cohorts D2 [Sub. 2]+D3+D5 (N=155)			
	CCOD 15 June 2022		CCOD 16 January 2023	
	IRC	INV	IRC	INV
CR rate[a] [95% CI]	40.0% [redacted]	[redacted]	[redacted]	[redacted]
ORR (CR+PR)[a] [95% CI]	51.6% [redacted]	[redacted]	[redacted]	[redacted]
Median DOCR[a, c] (months) [95% CI]	[redacted]	[redacted]	[redacted]	[redacted]
Event-free at 12 months [95% CI]	73.1% [redacted]	[redacted]	[redacted]	[redacted]
Event-free at 18 months [95% CI]	[redacted]	[redacted]	[redacted]	[redacted]
Event-free at 24 months [95% CI]	[redacted]	[redacted]	[redacted]	[redacted]
Median DOR[a, d] (months) [95% CI]	[redacted]	[redacted]	[redacted]	[redacted]
Event-free at 12 months [95% CI]	[redacted]	[redacted]	[redacted]	[redacted]
Event-free at 18 months [95% CI]	[redacted]	[redacted]	[redacted]	[redacted]
Event-free at 24 months [95% CI]	[redacted]	[redacted]	[redacted]	[redacted]

Median TFCR[a] (days) [95% CI]	[redacted]	[redacted]	[redacted]	[redacted]
Median TFOR[a] (days) [95% CI]	[redacted]	[redacted]	[redacted]	[redacted]
Median PFS (months) [95% CI]	[redacted]	[redacted]	[redacted]	[redacted]
1-year PFS rate [95% CI]	[redacted]	[redacted]	[redacted]	[redacted]
2-year PFS rate [95% CI]	[redacted]	[redacted]	[redacted]	[redacted]
Median OS (months) [95% CI]	[redacted]	[redacted]	[redacted]	[redacted]
1-year OS rate [95% CI]	[redacted]	[redacted]	[redacted]	[redacted]
2-year OS rate [95% CI]	[redacted]	[redacted]	[redacted]	[redacted]

[a] Lugano classification (2). [b] Data has remained consistent between the two CCODs.

[c] Only included complete responders: n=62 for IRC, n=59 for INV. [d] Only included overall responders: n=80 for IRC, n=90 for INV.

CCOD, clinical cutoff date; CI, confidence interval; CR, complete response; DOCR, duration of complete response; DOR, duration of response; INV, Investigator; IRC, Independent Review Committee; NE, not evaluable; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; PR, partial response; TFCR, time to first complete response; TFOR, time to first overall response.

1.1 IRC-assessed DOCR and DOR

As of CCOD January 2023, the median time on the study was 21.2 months (range: 0–34) and the median DOCR was 26.9 months (95% CI: 18.4, NR) (1).

Between the CCOD in June 2022 and January 2023, the 18-month DOCR showed an upward trend, [redacted] to 67.0% (95% CI: 53.3, 80.8). This suggests that approximately 67% of patients who attained a CR at any stage during the glofitamab treatment sustained their remission for at least 18 months (1). Furthermore, the 24-month results from January 2023 demonstrated a DOCR of [redacted]. However, it is notable that the number of patients contributing to the Kaplan-Meier plot at 24 months is low (12 patients at risk). At the January 2023 CCOD, 42/62 (67.7%) of patients with CR as best response had ongoing CR, so DOCR statistics may change with longer follow up.

The Kaplan-Meier estimated event-free rate among patients who achieved any objective response was similar to the previous CCOD. At the CCOD in June 2022, the median DOR was 16.8 months (10.4, NE) and the 18-month IRC-assessed DOR was [redacted]. By January 2023, to the median DOR was 18.4 months (95% CI: 12.6, NE) and the 18-month DOR was 51.9% [redacted]. At the January 2023 CCOD, 44/80 (55.0%) of patients with a CR or PR had ongoing response.

See Figure 1 and

Figure 2 for the Kaplan-Meier plots of IRC-assessed DOCR and DOR at the latest CCOD in January 2023.

Figure 1: Kaplan-Meier plot of time to IRC-assessed DOCR (CCOD Jan 2023)

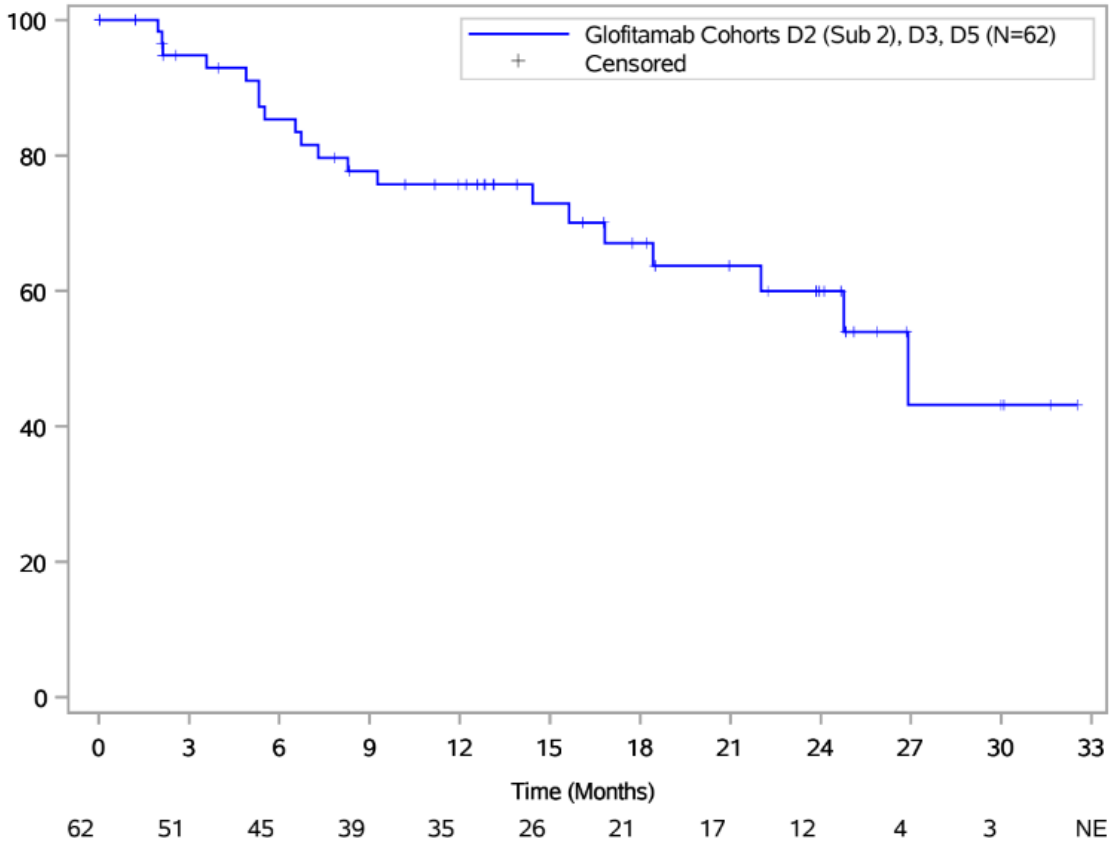
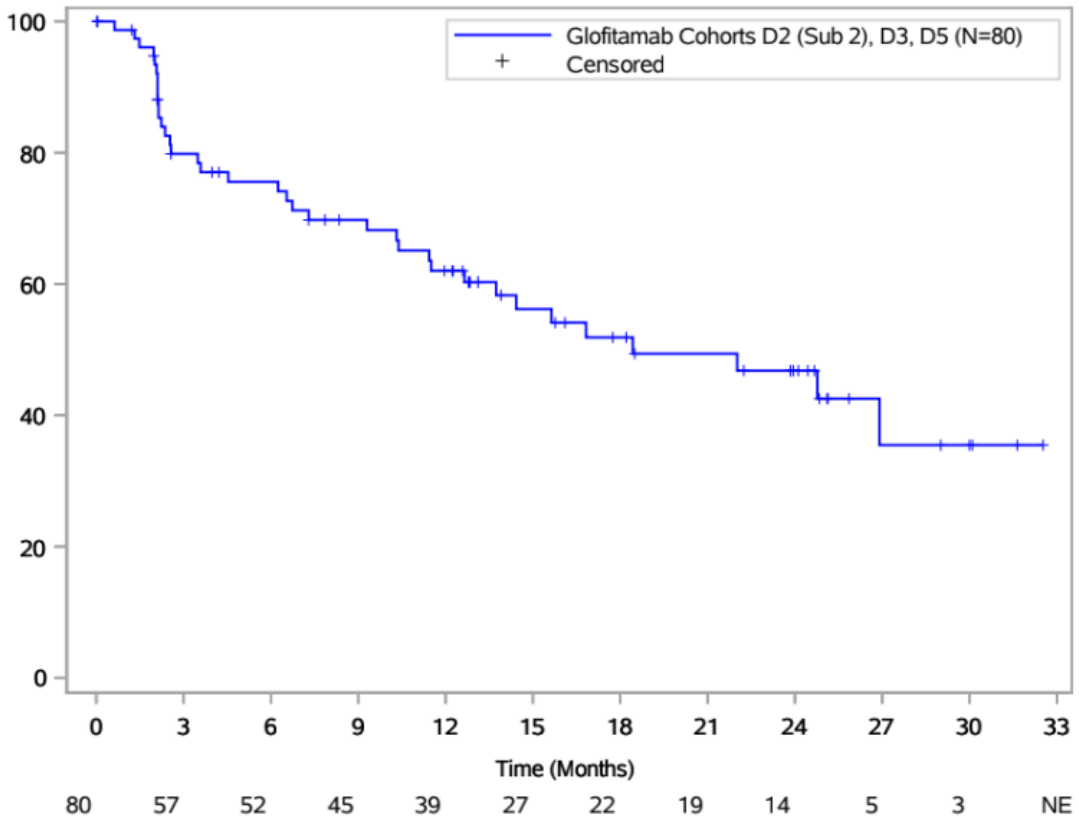


Figure 2: Kaplan-Meier plot of time to IRC-assessed DOR (CCOD Jan 2023)



In the supporting efficacy population for DOCR, 101 patients with R/R LBCL who received glofitamab doses of ≥10mg and less than the recommended Phase 2 dose (RP2D) (1). At the updated CCOD in January 2023, 35 patients (35%) had achieved a CR (no change in CR rate since the June 2022 CCOD). With a median follow up of 32 months (range: 0-49), the median DOCR was not reached (95% CI: 17.9, NR), and 62.6% (95% CI: 45.0, 80.3) of patients remained in remission at 24 months. This demonstrates a sustained response with longer follow up when compared to the previous CCOD in June 2022, which reported a DOCR of [redacted].

1.2 PFS and OS

As of the CCOD in January 2023, the median follow-up for PFS was [redacted].

When compared to the results from the previous CCOD in June 2022, both the PFS and OS rates demonstrate sustained effectiveness of the glofitamab treatment with longer follow up.

Specifically, the median IRC-assessed PFS rate remained stable at [redacted] from June 2022 to January 2023, although there was a minor adjustment in the confidence intervals ([redacted]). The 1-year PFS rate increased from [redacted] ([redacted]) in June 2022 to [redacted]) in January 2023.

Similarly, the median OS rate maintained consistency at [redacted] from June 2022 to January 2023, with a minor variation in confidence intervals ([redacted]). The 1-year INV-OS rate was similar at [redacted] in June 2022 to [redacted] in January 2023.

Additionally, as of January 2023, the 2-year PFS and OS rates were reported as [redacted], respectively. The Kaplan-Meier plots of IRC-assessed PFS and OS are shown in Figure 3 and Figure 4. When observing these rates, it is noticeable that there appears to be a plateauing effect. The plateau in the survival curves, especially in the PFS, suggests a durable response in a subset of patients and is supportive of the DOCR reported above.

Despite disease progression in some patients, a proportion seem to have long-lasting remission, which contributes to the flattened curve over time. The same can be interpreted for the OS rate. These plateaued rates further highlight the potential long-term benefit for patients treated with glofitamab.

Figure 3: Kaplan-Meier plot of time to IRC-assessed PFS (CCOD Jan 2023)

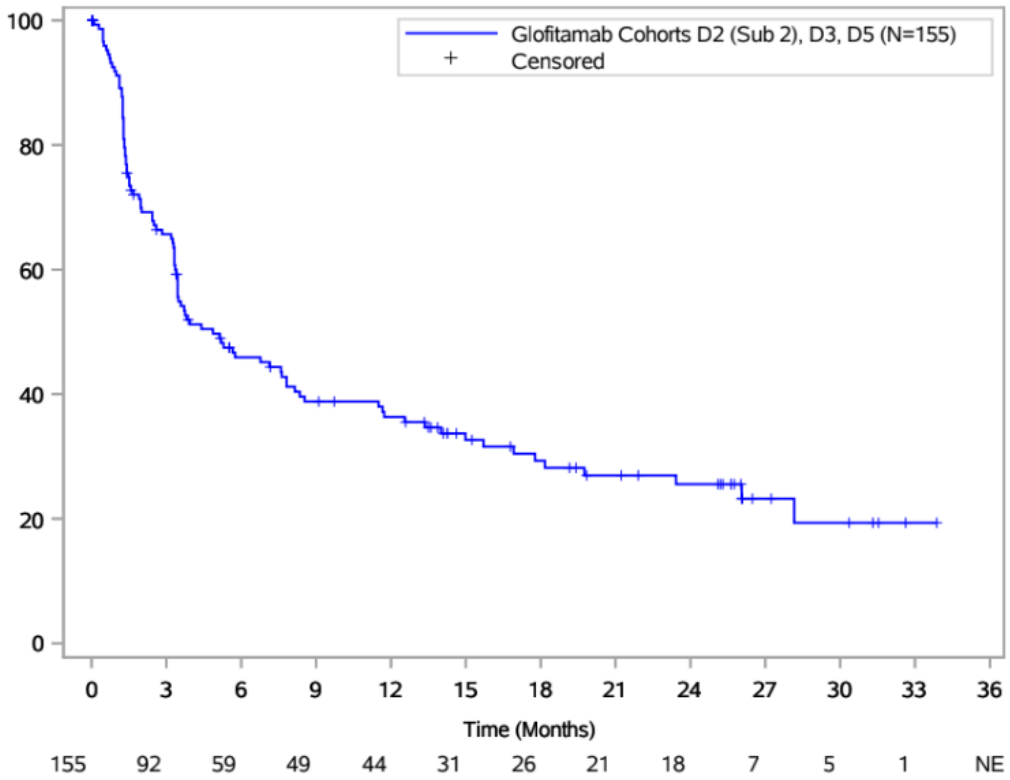
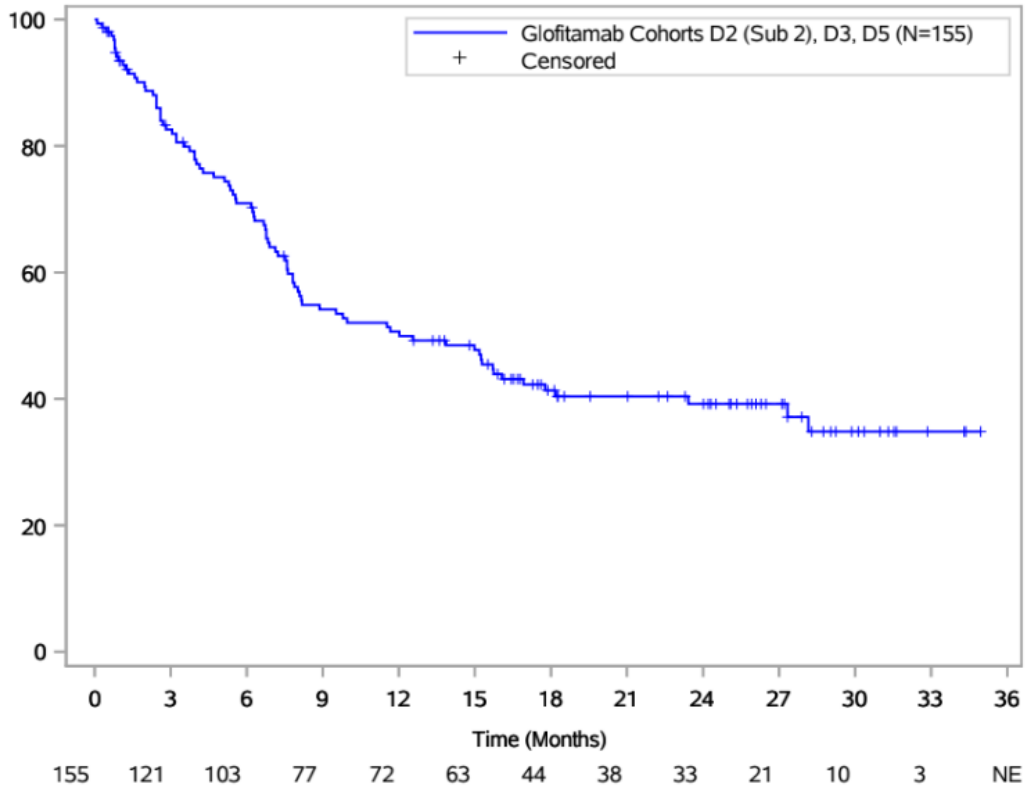


Figure 4: Kaplan-Meier plot of time to OS (CCOD Jan 2023)



Lastly, a landmark analysis was conducted on 45 patients who achieved a CR at the end of

glofitamab treatment (1). Remarkably, these patients exhibited an impressive 80% PFS rate and a 92% OS rate at 12-month. This highlights the potential long-term efficacy of glofitamab in inducing and maintaining remission beyond the fixed duration of up to 12 months' treatment.

1.3 Subgroup analysis

As of the CCOD in January 2023, revisions were made to some of the patient baseline characteristics and patient outcome data (see Section 1). Please refer to Figure 5 for the forest plot from the updated subgroup analysis.

Figure 5: Forest plot of the subgroup analysis based on IRC-CR rate (CCOD Jan 2023)

Figure 5: Forest plot of the subgroup analysis based on IRC-CR rate (CCOD Jan 2023) [continued]

Figure 5: Forest plot of the subgroup analysis based on IRC-CR rate (CCOD Jan 2023) [continued]

1.4 Safety

Exposure to glofitamab remained unchanged since the CCOD in June 2022, as all patients had already completed their treatment by that time. Therefore, the majority of patients did not experience any new adverse events (AEs) in CCOD Jan 2023 following the previous analysis. This suggests stability in the safety profile of glofitamab since the last assessment. See Table 2 for an overview of the updated AE profile from the primary safety population.

Cytokine release syndrome (CRS) remained the most frequently observed AE and was seen in 64% of the patients in the study. The severity of CRS was mostly limited to Grade 1 (48%), or Grade 2 (12%). Higher severity events, such as Grade 3 and Grade 4, were infrequent, with rates of 3% and 1%, respectively.

The overall incidence of AEs and serious adverse events (SAEs) remained stable, compared with the previously analysis at CCOD Jun 2022. One new Grade 3 AE emerged, manifesting as acute kidney injury. Additionally, two new infections were reported. One patient experienced a Grade 4 COVID infection, and another patient had a Grade 2 pneumonia infection. Notably, no glofitamab-related Grade 5 AEs were reported at the latest CCOD from Jan 2023.

Table 2: Overview of safety results in the primary safety-evaluable population (CCOD Jan 2023)

n (%)	Primary safety population: Glofitamab 2.5/10/30mg Cohorts D2 [Sub. 2]+D3+D5 (N=154)
Any AE	[redacted]
Glofitamab-related	[redacted]
Grade ≥3 AE	[redacted]
Glofitamab-related	[redacted]
SAE	[redacted]
Glofitamab-related	[redacted]
Grade 5 (fatal) AE	[redacted]

Glofitamab-related	[redacted]
AE leading to treatment discontinuation Glofitamab-related	[redacted]
AE leading to dose modification/interruption of glofit Glofitamab-related	[redacted]

Section 2: Indirect treatment comparison (ITC)

2.1 Background

As part of Roche's response to technical engagement, additional data from the glofitamab NP30179 study has been provided [January 2023 clinical cut off data]. The additional follow-up from NP30179 has been included in the company's updated economic model, and the indirect treatment comparisons (ITCs) have been conducted again making use of this additional data.

The Company wishes to note that as part of the continuous NP30179 medical data review, which is routinely performed to identify safety signals and ensure data is available and reviewed for key timepoints such as data snapshots, given that the study is still ongoing, some of the patient baseline characteristics were also revised, along with patient outcome data, in the January 2023 CCOD. A summary of these changes is provided below.

- Number of prior lines of therapies for one patient changed to 4 from 3 in the June 2022 CCOD
- Refractory to prior ASCT status changed to Yes for 5 patients
- Double-/triple-hit tumor status changed to Yes for 3 patients
- Cell of origin status for one patient changed to non-GCB from GCB in the June 2022 CCOD

Such changes in baseline characteristics may have impacted the results of the patient filtering conducted to align the eligibility criteria across trials and/or the estimated MAIC or IPT weights, which in turn may have had an impact on the updated effective sample size (ESS) estimates as well as on the conclusions of

some analyses. For transparency, full information on all updated analyses relevant for this appraisal has been provided, with the below sections reporting the results from the ITC analyses, incorporating the updated NP30179 data.

2.2 ITC results

Only base case analysis results for each ITC are presented in the following sections.

2.2.1 Glofitamab vs axicabtagene ciloleucel MAIC

2.2.1.1 Populations and baseline characteristics

Table 3: Pre- and post-weighting baseline characteristics in the glofitamab vs axicabtagene ciloleucel MAIC

Variable	Glofitamab unweighted (n=116)	Glofitamab - weighted (ESS=34.0) Base-case	Axicabtagene ciloleucel (n=101)
Age (mean)	[redacted]	[redacted]	[redacted]
ECOG PS ≥1 (%)	[redacted]	[redacted]	[redacted]
Ann Arbor Stage III–IV (%)	[redacted]	[redacted]	[redacted]
High LDH (%)	[redacted]	[redacted]	[redacted]
Extranodal disease (%)	[redacted]	[redacted]	[redacted]
IPI 3–5 (%)	[redacted]	[redacted]	[redacted]
Refractory to 1st line (%)	[redacted]	[redacted]	[redacted]
Best response of PD to last line (%)	[redacted]	[redacted]	[redacted]
HGBCL histology (%)	[redacted]	[redacted]	[redacted]
PMBCL histology (%)	[redacted]	[redacted]	[redacted]
Early relapse after SCT (%)	[redacted]	[redacted]	[redacted]
>2 prior therapies (%)	[redacted]	[redacted]	[redacted]
Bulky disease ≥10cm (%)	[redacted]	[redacted]	[redacted]
Cell type GCB (%)	[redacted]	[redacted]	[redacted]
Cell type ABC/non-GCB (%)	[redacted]	[redacted]	[redacted]
Bone marrow involvement (%)	[redacted]	[redacted]	[redacted]
Prior SCT (%)	[redacted]	[redacted]	[redacted]

Abbreviations: ABC, activated B cell; ECOG PS, Eastern Cooperative Oncology Group Performance Status; ESS, effective sample size; GCB, germinal B cell; HGBCL, high grade B cell lymphoma; IPI, International

Prognostic Index; LDH, lactate dehydrogenase; NA, not applicable; PD, progressed disease; PMBCL, primary mediastinal large B cell lymphoma; SCT, stem cell transplant.

2.2.1.2 Response rates (per IRC assessment)

Tumour responses were assessed using the Lugano criteria (2) in NP30179 (3, 4), whereas ZUMA-1 (5) used the International Working Group (IWG) criteria (6).

[redacted]

Table 4: Summary of MAIC results for (IRC-assessed) ORR (glofit vs axi-cel)

Method for estimating OR	OR (95% CI)	
	Base-case (June 22 CCOD)	Base-case (Jan 23 CCOD)
Unadjusted logistic regression model	[redacted]	[redacted]
Bootstrap median OR (95% percentile CI) weighted logistic regression model	[redacted]	[redacted]

Abbreviations: BCa, Bias corrected accelerated; CI, confidence interval; MAIC, matching-adjusted indirect comparison; OR, odds ratio; ORR, overall response rate.
ORs presented for the comparison of glofitamab versus axicabtagene ciloleucel. ORs >1 favour glofitamab.

[redacted]

Table 5: Summary of MAIC results for (IRC-assessed) CR (glofit vs axi-cel)

Method for estimating OR	OR (95% CI)	
	Base-case (June 22 CCOD)	Base-case (Jan 23 CCOD)
Unadjusted logistic regression model	[redacted]	[redacted]
Bootstrap median OR (95% percentile CI) weighted logistic regression model	[redacted]	[redacted]

Abbreviations: BCa, Bias corrected accelerated; CI, confidence interval; CR, complete response; IRC, independent review committee; MAIC, matching-adjusted indirect comparison; OR, odds ratio.
ORs presented for the comparison of glofitamab versus axicabtagene ciloleucel. ORs >1 favour glofitamab.

2.2.1.3 PFS (per INV assessment) and OS

The Kaplan-Meier plots for PFS and OS are presented in Figure 6 and Figure 7, respectively.

[redacted]

Table 6: Summary of MAIC results for (INV-assessed) PFS

Method for estimating HR	HR (95% CI)	
	Base-case (June 22 CCOD)	Base-case (Jan 23 CCOD)
Unadjusted logistic regression model	[redacted]	[redacted]
Bootstrap median OR (95% percentile CI) weighted logistic regression model	[redacted]	[redacted]

Abbreviations: BCa, Bias corrected accelerated; CI, confidence interval; HR, hazard ratio; INV, investigator; MAIC, matching-adjusted indirect comparison; PFS, progression free survival.
HRs presented for the comparison of glofitamab versus axicabtagene ciloleucel. HRs <1 favour glofitamab.

[redacted]

Table 7: Summary of MAIC results for OS

Method for estimating HR	HR (95% CI)	
	Base-case (June 22 CCOD)	Base-case (Jan 23 CCOD)
Unadjusted logistic regression model	[redacted]	[redacted]
Bootstrap median OR (95% percentile CI) weighted logistic regression model	[redacted]	[redacted]

Abbreviations: BCa, bias corrected accelerated; CI, confidence interval; HR, hazard ratio; MAIC, matching-adjusted indirect comparison; OS, overall survival.
HRs presented for the comparison of glofitamab versus axicabtagene ciloleucel. HRs <1 favour glofitamab.

Figure 6: PFS (per INV assessment) in the glofitamab vs axicabtagene ciloleucel (Yescarta) MAIC

Figure 7: OS in the glofitamab vs axicabtagene ciloleucel (Yescarta) MAIC

2.2.1.4 Safety

With regards to safety, data relating to discontinuation due to AEs was not available for the MAIC against axicabtagene ciloleucel, so an OR could not be estimated. Treatment-related Grade 3 or higher AEs were extracted from the ZUMA-1 study, and considered in the analysis.

2.2.2 Glofitamab vs bendamustine plus rituximab MAIC

2.2.2.1 Populations and baseline characteristics

Table 8: Pre- and post-weighting baseline characteristics in the glofitamab vs BR MAIC

Variable	Glofitamab unweighted (n=139)	Glofitamab weighted (ESS=67.5) Base-case	Bendamustine plus rituximab (n=58)
Age > comparator median (%)	[redacted]	[redacted]	[redacted]
Ann Arbor Stage III–IV (%)	[redacted]	[redacted]	[redacted]
High LDH (%)	[redacted]	[redacted]	[redacted]
Extranodal sites ≥2 (%)	[redacted]	[redacted]	[redacted]
IPI 3–5 (%)	[redacted]	[redacted]	[redacted]
Refractory to all lines (%)	[redacted]	[redacted]	[redacted]
>2 prior therapies (%)	[redacted]	[redacted]	[redacted]
Cell type GCB (%)	[redacted]	[redacted]	[redacted]
Cell type ABC/non-GCB (%)	[redacted]	[redacted]	[redacted]
Prior SCT (%)	[redacted]	[redacted]	[redacted]

Abbreviations: ABC, activated B cell; ESS effective sample size; GCB, germinal B cell; IPI, International Prognostic Index; SCT, stem cell transplant.

2.2.2.2 Response rates (per INV assessment)

Tumour responses were assessed using the Lugano criteria (2) in NP30179 (3, 4) whereas Hong 2018 (7) used the International Working Group (IWG) criteria or revised criteria (6, 8).

[redacted]

[redacted]

Table 9: Summary of MAIC results for (INV-assessed) ORR (glofit vs BR)

Method for estimating OR	OR (95% CI)	
	Base-case (June 22 CCOD)	Base-case (Jan 23 CCOD)
Unadjusted logistic regression model	[redacted]	[redacted]
Bootstrap median OR (95% percentile CI) weighted logistic regression model	[redacted]	[redacted]

Abbreviations: BCa, Bias corrected accelerated; CI, confidence interval; INV, investigator; MAIC, matching-adjusted indirect comparison; OR, odds ratio; ORR, overall response rate.
ORs presented for the comparison of glofitamab versus bendamustine plus rituximab. ORs >1 favour glofitamab.

[redacted]

Table 10: Summary of MAIC results for (INV-assessed) CR (glofit vs BR)

Method for estimating OR	OR (95% CI)	
	Base-case (June 22 CCOD)	Base-case (Jan 23 CCOD)
Unadjusted logistic regression model	[redacted]	[redacted]
Bootstrap median OR (95% percentile CI) weighted logistic regression model	[redacted]	[redacted]

Abbreviations: BCa, Bias corrected accelerated; CI, confidence interval; CR, complete response; INV, investigator; MAIC, matching-adjusted indirect comparison; OR, odds ratio.
ORs presented for the comparison of glofitamab versus bendamustine plus rituximab. ORs >1 favour glofitamab.

2.2.2.3 PFS (per INV assessment) and OS

The Kaplan-Meier plots for PFS and OS are presented in Figure 8 and Xxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxx xxxxxxxxxx

Xxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxx xxxxxxxxxx

[redacted]

Figure 9, respectively.

[redacted]

Table 11: Summary of MAIC results for PFS (INV-assessed)

Method for estimating HR	HR (95% CI)	
	Base-case (June 22 CCOD)	Base-case (Jan 23 CCOD)
Unadjusted Cox model	[redacted]	[redacted]
Bootstrap median (95% percentile CI) weighted Cox model	[redacted]	[redacted]

Abbreviations: BCa, bias corrected accelerated; CI, confidence interval; HR, hazard ratio; MAIC, matching-adjusted indirect comparison; PFS, progression free survival.
HRs presented for the comparison of glofitamab versus bendamustine plus rituximab. HRs <1 favour glofitamab.

[redacted]

Table 12: Summary of MAIC results for OS

Method for estimating HR	HR (95% CI)	
	Base-case (June 22 CCOD)	Base-case (Jan 23 CCOD)
Unadjusted Cox model	[redacted]	[redacted]
Bootstrap median (95% percentile CI) weighted Cox model	[redacted]	[redacted]

Abbreviations: BCa, bias corrected accelerated; CI, confidence interval; HR, hazard ratio; MAIC, matching-adjusted indirect comparison; OS, overall survival.
HRs presented for the comparison of glofitamab versus bendamustine plus rituximab. HRs <1 favour glofitamab.

Figure 8: PFS (per INV assessment) in the glofitamab vs BR MAIC

Figure 9: OS in the glofitamab vs BR MAIC

2.2.2.4 Safety

With regards to safety, data relating to discontinuation due to AEs was not available for the MAIC against BR, so an OR could not be estimated. Treatment-related Grade 3 or higher AEs were extracted from the Hong 2018 study, and considered in the analysis.

2.2.3 Glofitamab vs pola-BR propensity score analysis MAIC

2.2.3.1 Populations and baseline characteristics

Table 13: Unadjusted and IPTW-adjusted baseline characteristics in the propensity score analysis of glofitamab vs pola-BR

Variable	Unadjusted					IPTW adjusted				
	Glofitamab (n=149)		Pola-BR (n=84)		aSMD	Glofitamab [redacted]		Pola-BR [redacted]		aSMD
	Mean	SD	Mean	SD		Mean	SD	Mean	SD	
Age (mean)	[redacted]									
ECOG PS (1 vs 0) (%)	[redacted]									
Ann Arbor Stage III/IV (Yes) (%)	[redacted]									
High LDH (Yes) (%)	[redacted]									
Extranodal disease (Yes) (%)	[redacted]									
IPI (3-5) %	[redacted]									
Refractory to first line (Yes) (%)	[redacted]									
Refractory to any line (Yes) (%)	[redacted]									
Refractory to last line (Yes) (%)	[redacted]									
HGBCL (Yes) (%)	[redacted]									
Refractory to ASCT (Yes) (%)	[redacted]									
Prior therapies, >2 (%)	[redacted]									

Variable	Unadjusted					IPTW adjusted				
	Glofitamab (n=149)		Pola-BR (n=84)		aSMD	Glofitamab [redacted]		Pola-BR [redacted]		aSMD
	Mean	SD	Mean	SD		Mean	SD	Mean	SD	
Size of the largest node lesion, cm (mean)	[redacted]									
Refractory to any prior anti-CD20 mAb and anthracycline (Yes) (%)	[redacted]									
Refractory to any prior anti-CD20 mAb containing regimen (Yes) (%)	[redacted]									
Time since last treatment [months] (mean)	[redacted]									
Cell type GCB (%)	[redacted]									
Cell type ABC/non-GCB (%)	[redacted]									
Bone marrow involvement (Yes) (%)	[redacted]									
Prior ASCT (yes) (%)	[redacted]									

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

2.2.3.2 Response rates (per INV assessment)

Tumour responses were assessed using the Lugano criteria (2) in both GO29365 (9) and NP30179 (3, 4).

[redacted]

Table 14: Summary of MAIC results for (INV-assessed) ORR (glofit vs pola-BR)

Method for estimating OR	OR (95% CI)	
	Base-case (June 22 CCOD)	Base-case (Jan 23 CCOD)
Unadjusted	[redacted]	[redacted]
Inverse probability of treatment weighting	[redacted]	[redacted]

Abbreviations: CI, confidence interval; INV, investigator; OR, odds ratio; ORR, overall response rate; PSA, propensity score analysis.
ORs presented for the comparison of glofitamab versus polatuxumab-vedotin plus bendamustine plus rituximab.
ORs >1 favour glofitamab.

[redacted]

Table 15: Summary of MAIC results for (INV-assessed) CR (glofit vs pola-BR)

Method for estimating OR	OR (95% CI)	
	Base-case (June 22 CCOD)	Base-case (Jan 23 CCOD)
Unadjusted	[redacted]	[redacted]
Inverse probability of treatment weighting	[redacted]	[redacted]

Abbreviations: CI, confidence interval; CR, complete response; INV, investigator; OR, odds ratio; PSA, propensity score analysis.
ORs presented for the comparison of glofitamab versus polatuxumab-vedotin plus bendamustine plus rituximab.
ORs <1 favour glofitamab.

[redacted]

2.2.3.3 *PFS (per INV assessment) and OS*

The Kaplan-Meier plots from the unadjusted analysis and IPTW analysis are presented in Figure 10 and Xxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxx xxxxxxxxxx

Xxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxx xxxxxxxxxx

[redacted]

Figure *11*. The IPTW analysis was selected as the adjustment method of preference for the base case analysis.

[redacted]

Table 16: Summary of PSA results for PFS (INV-assessed)

Method for estimating HR	HR (95% CI)	
	Base-case (June 22 CCOD)	Base-case (Jan 23 CCOD)
Unadjusted	[redacted]	[redacted]
Inverse probability of treatment weighting	[redacted]	[redacted]

Abbreviations: CI, confidence interval; HR, hazard ratio; PFS, progression free survival; PSA, propensity score analysis.

HRs presented for the comparison of glofitamab versus polatuxumab-vedotin plus bendamustine plus rituximab. HRs <1 favour glofitamab.

[redacted]

Table 17: Summary of PSA results for OS

Method for estimating HR	HR (95% CI)	
	Base-case (June 22 CCOD)	Base-case (Jan 23 CCOD)
Unadjusted	[redacted]	[redacted]
Inverse probability of treatment weighting	[redacted]	[redacted]

Abbreviations: CI, confidence interval; HR, hazard ratio; OS, overall survival; PSA, propensity score analysis. HRs presented for the comparison of glofitamab versus polatuxumab-vedotin plus bendamustine plus rituximab. HRs <1 favour glofitamab.

Figure 10: KM plot of PFS for IPTW sample

[redacted]

Figure 11: KM plot of OS for IPTW sample

[redacted]

[redacted]

2.2.3.4 Safety

For the pola-BR arm, a patient was classified as having discontinued treatment due to AEs if that patient had discontinued any of the study treatments due to AEs, as this was deemed to be a more representative outcome for the overall tolerability of the combination regimen.

[redacted]

Table 18: Summary of PSA results for discontinuation due to AEs

Method for estimating OR	OR (95% CI)	
	Base-case (June 22 CCOD)	Base-case (Jan 23 CCOD)
Unadjusted	[redacted]	[redacted]
Inverse probability of treatment weighting	[redacted]	[redacted]

Abbreviations: AE, adverse event; CI, confidence interval; OR, odds ratio; PSA, propensity score analysis. ORs presented for the comparison of glofitamab versus polatuxumab-vedotin plus bendamustine plus rituximab. ORs <1 favour glofitamab.

2.2.4 Discussion

Overall, the results of the ITC analyses conducted using the January 2023 data-cut from NP30179 are consistent with the original analysis (June 2022 CCOD). With the results based on approximately 6 months additional follow-up, the updated ITC results improve the certainty of the ORs and HRs estimated in these indirect comparisons, providing further evidence to suggest that the initial estimates of glofitamab's relative benefits are likely to be sustained over time.

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Single Technology Appraisal

Glofitamab for treating relapsed or refractory diffuse large B-cell lymphoma after 2 or more systemic treatments [ID3970]

Clinical expert statement and technical engagement response form

Thank you for agreeing to comment on the external assessment report (EAR) for this evaluation, and for providing your views on this technology and its possible use in the NHS.

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature. The EAR and stakeholder responses are used by the committee to help it make decisions at the committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

Information on completing this form

In part 1 we are asking for your views on this technology. The text boxes will expand as you type.

In part 2 we are asking for your views on key issues in the EAR that are likely to be discussed by the committee. The key issues in the EAR reflect the areas where there is uncertainty in the evidence, and because of this the cost effectiveness of the treatment is also uncertain. The key issues are summarised in the executive summary at the beginning of the EAR. You are not expected to comment on every key issue but instead comment on the issues that are in your area of expertise.

A clinical perspective could help either:

- resolve any uncertainty that has been identified OR
- provide missing or additional information that could help committee reach a collaborative decision in the face of uncertainty that cannot be resolved.

In part 3 we are asking you to provide 5 summary sentences on the main points contained in this document.

Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable. Please type information directly into the form.

Do not include medical information about yourself or another person that could identify you or the other person.

We are committed to meeting the requirements of copyright legislation. If you want to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.

Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.

Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise, all information submitted under 'academic in confidence' in yellow, and all information submitted under 'depersonalised data' in pink. If confidential information is submitted, please also send a second version of your comments with that information redacted. See the NICE health technology evaluation guidance development manual (sections 5.4.1 to 5.4.10) for more information.

Please note, part 1 can be completed at any time. We advise that **part 2** is completed after the expert engagement teleconference (if you are attending or have attended). At this teleconference we will discuss some of the key issues, answer any specific questions you may have about the form, and explain the type of information the committee would find useful.

The deadline for your response is **5pm** on **Wednesday 28 June 2023.** Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Thank you for your time.

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We reserve the right to summarise and edit comments received during engagement, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received during engagement are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

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Part 1: Treating diffuse large B-cell lymphoma and current treatment options

Table 1 About you, aim of treatment, place and use of technology, sources of evidence and equality

1. Your name	Wendy Osborne
2. Name of organisation	Newcastle upon Tyne Hospitals NHS Foundation Trust
3. Job title or position	Consultant Haematologist
4. Are you (please tick all that apply)	☐ An employee or representative of a healthcare professional organisation that represents clinicians? ☒ A specialist in the treatment of people with relapsed or refractory diffuse large B-cell lymphoma? ☐ A specialist in the clinical evidence base for relapsed or refractory diffuse large B-cell lymphoma or technology? ☐ Other (please specify):
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	☒ Yes, I agree with it ☐ No, I disagree with it ☐ I agree with some of it, but disagree with some of it ☐ Other (they did not submit one, I do not know if they submitted one etc.)
6. If you wrote the organisation submission and/or do not have anything to add, tick here. (If you tick this box, the rest of this form will be deleted after submission)	☐ Yes
7. Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	Nil

8. What is the main aim of treatment for relapsed or refractory diffuse large B-cell lymphoma? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability)	The main aim is still to obtain a durable response, and in some patients cure. In those patients in whom cure is not achieved then we want to achieve as long as possible with disease control and minimal symptoms allowing a good quality of life.
9. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount)	Any reduction in lymphoma volume is significant but the most important is achieving a complete response as some of these will lead to cure. For patients who achieve a partial response it will lead to months of life for that patient but most patients in a partial response with DLBCL will progress at some stage and there CR is most important.
10. In your view, is there an unmet need for patients and healthcare professionals in relapsed or refractory diffuse large B-cell lymphoma?	Yes, unfortunately current standard second line treatment requires the patient to be fit enough to tolerate high dose chemotherapy and an auto transplant and the responses are only 15-20% durable even in these fit patients. If the patient then has 3rd line CAR T and manages to reach infusion then about 35% of these patients will have a durable response but the rest will progress and will most likely die from DLBCL.
11. How is relapsed or refractory diffuse large B-cell lymphoma currently treated in the NHS? • Are any clinical guidelines used in the treatment of the condition, and if so, which? • Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.) • What impact would the technology have on the current pathway of care?	The BSH guidelines are out of date and are currently being rewritten but are not yet published. The standard pathway is well defined. If a patient is auto fit they will have 2nd line high dose chemo and an auto, if they are auto unfit they will have rgemox if planning 3rd line CAR T or will have Rbenda pola of oral palliative chemo if not planning CAR T 3rd line. Recently 2nd line Axi-Cel has become available on the CDF for auto fit pts who relapse within 12 months of first line treatment. Third line patients will either have CAR T or palliative chemo depending on patients wishes and if it is considered likely that we can keep the patient stable whilst the CAR Ts are being manufactured. If Glofitamab is approved it will be used 3rd line, for pts who had CAR T 2nd line or for those patients who may prefer having treatment close to home and not travelling to a CAR T centre. It will also be used 4th line for those patients who relapse post CAR T.

12. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice? • How does healthcare resource use differ between the technology and current care? • In what clinical setting should the technology be used? (for example, primary or secondary care, specialist clinic) • What investment is needed to introduce the technology? (for example, for facilities, equipment, or training)	This technology is similar to CAR T but significantly easier to deliver which will mean that more patients will choose to access it as they will not have to travel to a CAR T centre. The main side effect is cytokine release syndrome which is predictable and treatable with tocilizumab. Hospitals which can manage patients with neutropenic sepsis can manage CRS and this is why bispecifics have been successfully delivered in a clinical trial setting in hospitals geographically isolated from large CAR T centres or allo centres. Glofitamab can be delivered in secondary care in all centres which deliver chemo at risk of neutropenic sepsis (eg RCHOP). There will be some additional training to ensure CRS is managed appropriately and this has already started as more bispecifics are being used in trials in both haematology and oncology.
13. Do you expect the technology to provide clinically meaningful benefits compared with current care? • Do you expect the technology to increase length of life more than current care? • Do you expect the technology to increase health-related quality of life more than current care?	Yes, the response rates are high and about 40% achieve CR for which many are durable. In my clinical experience using glofitamab in clinical trials the patients have minimal side effects, particularly after the first cycle and they describe excellent quality of life.
14. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	The data shows response even across high risk subgroups (eg double hit lymphoma, relapse post CAR T). There are patients which choose to not travel away from home for a month for CAR T and these patients could benefit from glofitamab because it could be delivered in their local hospital.
15. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use? (For example, any concomitant treatments needed, additional clinical requirements, factors affecting patient	Easier that 3rd line CAR T, if glofit is to be used for relapse post CAR T rather than instead of CAR T then hospital staff will need to be trained in the management of CRS but this is straightforward to do.

acceptability or ease of use or additional tests or monitoring needed)	
16. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	A scan (either CT or PET) will identify that the patient has unfortunately progressed and now needs 3rd line treatment. No other testing is required, just this scan which is done at present to identify progression.
17. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation? • Do the instruments that measure quality of life fully capture all the benefits of the technology or have some been missed? For example, the treatment regimen may be more easily administered (such as an oral tablet or home treatment) than current standard of care	Qualitative data from CAR T and palliative care teams have shown that the requirements for a patient to be 2 hours (previously 1 hour) from a CAR T centre for a month is very difficult for patients. Glofitamab will not have this negative impact.
18. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met? • Is the technology a 'step-change' in the management of the condition? • Does the use of the technology address any particular unmet need of the patient population?	Bispecific antibodies are innovative and allow the benefits of lymphoma response by T cell activation without the need for apheresis, manufacture and long inpatient stays for patients. It also allows true "intention to treat" data whereby you would be able to see the patient in clinic and if eligible start treatment within a few days. This technology allow access irrespective of geography in the UK and also access for those patients who have rapid progression of lymphoma who are not stable enough to wait for CAR T manufacture.
19. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	The CRS will require an overnight stay at the beginning of step up dosing (or a long day unit day) but the patients quality of life is otherwise good for this targeted treatment.
20. Do the clinical trials on the technology reflect current UK clinical practice?	In the UK the trials ate currently focusing on achieving durable responses for patients who relapse and using T cell engagers either as bispecific antibodies or cellular therapies is a primary focus of this research.

• If not, how could the results be extrapolated to the UK setting? • What, in your view, are the most important outcomes, and were they measured in the trials? • If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes? • Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	The most important outcomes are PFS, CR rates and durability of the CR as well as the low toxicity profile suggesting that the months gained (if durable response not achieved) allow the patients to remain out of hospital and have good quality of life. I am not aware of any adverse events not reported.
21. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	No
22. Are you aware of any new evidence for the comparator treatment(s) since the publication of NICE technology appraisal guidance [TA649, TA872]?	No
23. How do data on real-world experience compare with the trial data?	Limited real world data at present.
24. NICE considers whether there are any equalities issues at each stage of an evaluation. Are there any potential equality issues that should be taken into account when considering this condition and this treatment? Please explain if you think any groups of people with this condition are particularly disadvantaged. Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or	In my experience patients who live a long way from a CAR T centre and potentially those who have less income to pay for travel may access 3rd line CAR T less and so glofitamab may reduce some of these inequalities.

belief, sex, and sexual orientation or people with any other shared characteristics. Please state if you think this evaluation could • exclude any people for which this treatment is or will be licensed but who are protected by the equality legislation • lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population • lead to recommendations that have an adverse impact on disabled people. Please consider whether these issues are different from issues with current care and why. More information on how NICE deals with equalities issues can be found in the NICE equality scheme. Find more general information about the Equality Act and equalities issues here.	

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Part 2: Technical engagement questions for clinical experts

We welcome your comments on the key issues below, but you may want to concentrate on issues that are in your field of expertise. If you think an issue that is important to clinicians or patients has been missed in the EAR, please also advise on this in the space provided at the end of this section.

The text boxes will expand as you type. Your responses to the following issues will be considered by the committee and may be summarised and presented in slides at the committee meeting.

For information: the professional organisation that nominated you has also been sent a technical engagement response form (a separate document) which asks for comments on each of the key issues that have been raised in the EAR. These will also be considered by the committee.

Table 2 Issues arising from technical engagement

<u>Position of comparator treatments in care pathway</u> Glofitamab was compared to both CAR-T therapy (axi-cel) and polatuzumab with bendamustine and rituximab (pola-BR) in the third-line. Clinical advice to the EAG suggest these treatments are increasingly being used in earlier lines. 1) **Are CAR-T (axi-cel) and pola-BR relevant third-line comparators?** 2) **Would glofitamab be used after CAR-T and/or pola-BR? If glofitamab was used after CAR-T and/or pola-BR, what**	The main 3rd line comparator will be Axi-cel or Tisa-cel and these are now baseline commissioned. Although only in the CDF, patients who are "auto-eligible" and relapse within 12 months of first line treatment, will now be receiving 2nd line Axi-cel following the ZUMA 7 data and availability on the CDF. If patients have Axi-cel 2nd line, they will not be having it 3rd line. The use of Rituximab polatuzumab bendamustine 3rd line will also reduce in view of the availability if polatuzumab in a first line setting. Pixantrone is not used/very infrequently in the UK due to low durability of response and tafasitamab lenalidomide is not reimbursed in the UK. I agree with the EAG that Axi-cel/Tisacel/ Ritux benda pola/ Tafasitamab lenalidomide/ High dose chemo (eg IVE) as a bridge to allogeneic stem cell transplant are all fair comparators but the patient groups are of different risk in the different studies which need to be considered in the response rates.

would the relevant comparators for glofitamab be? **3) If polatuzumab has been used in a previous line(s) of therapy, would this affect the likelihood of pola-BR being used or being effective in third-line treatment?** **4) Will the efficacy of glofitamab be influenced by using CAR-T or polatuzumab in a prior line?**	In my opinion the main benefit of glofitamb is that it is ITT data and patients that are eligible can be treated quickly without the concern for dropout due to PD in the bridging period which we see sometimes with CAR T. The patients who were assigned to axi-cel, but ultimately did not receive the infusion will die from the lymphoma and this is why ITT are important as often efficacy of patients infused with CAR T are discussed. The patients who do not receive infusion of CAR T are usually apheresed and bridged and so these costs still occur as well as the costs os another line of treatment. The number of patients who drop out prior to CAR T are fewer now compared to a few years ago as we are better at patient selection and bridging. If Polatuzumab has been used first line I don't think that it will be used again either as bridging or 3rd line (unless there was a very long duration of response) In the 179 study about a third of patients had received CAR T 3rd line and then Glofit 4th line and the responses seem to be as good and so prior CAR T does not appear to impact on efficacy. Polatuzumab has a different target and so I think it is unlikely that prior polatzumab will impact efficacy but I have not seen clear data.
<u>Patients who do not receive axi-cel infusion</u> The indirect treatment comparison of glofitamab and axi-cel did not include people who were assigned axi-cel but did **not** receive the infusion. **5) What outcomes would you expect for people who are considered for, but do not receive CAR-T therapy?** **6) What resource use requirements would you expect for people who are considered for, but do not receive CAR-T therapy?**	If patients do not receive CAR T (either because of progression during manufacturing or failed manufacturing) it is like that they will die from RR DLBCL in a short number of months. These patients may be started on oral palliative chemotherapy of may receive ritux benda pola. They will usually still come to the hospital for review and management of their symptoms and so would use resource in this setting.

7) What would the outcomes and resource requirements be for these people if they were treated with glofitamab?	These patients should obtain a 40% CR rate (possibly higher as will be 3rd line and the trial had a higher risk group).The patients would have to be admitted for the first dose but after that would attend every 3 weeks as an outpatient for infusion.
Confidence intervals of ITC analyses The unadjusted and adjusted analyses used different methods for calculating their confidence intervals.	
Long-term remission/survivorship The EAG considers that there is insufficient evidence to support long-term remission, survivorship, and cure estimates. The company's economic model assumes that patients alive and progression free after 2 years enter a long-term remission stage (no progression and considered 'cured') and that after 3.5 years people still alive return to near UK general population age-matched mortality risk (most post-progression patients have died at this point). In the EAG's model, they assumed that people who are alive and progression-free after 3 years have a 10% decrement from the age-sex UK general population utilities (quality of life) and a 41% excess mortality from the age-matched UK general population.	Longer term follow up of glofitmab (Dickinson et al ICML), CR of 40% and estimated rate of CR lasting 18 months was 67%. These data support the clinical plausibility of long term remission/survivorship. In a clinical trial setting I have treated patients who durable response has meant that I am optimistic of cure. It is clinically plausible that patients who are alive and progression free at 2 years enter a long-term remission phase. The long term toxicity of T cell engagers are low and patients have similar utility to the general population, especially if they have not had high dose chemo and an autograft in a second line setting. If a patient remains in CR at 2 years I would consider that they are likely to be cured.

8) **When would a patient be considered to be 'cured'?** 9) **Is it clinically plausible that axi-cel, glofitamab, pola-BR or BR could be curative or lead to long-term remission? Is there evidence to support this?** 10) **For a patient who is cured, how would quality of life and mortality be different to the age-matched general population?**	Yes, it is plausible that Axi-cel and glofitamab can be curative. I think that the cure rate for pola-BR is low and in my experience (and UK real world data) patients remain progression free for 4-8 months but then progression. For patients who are cure their QofLife is very similar to the age matched general population. We also know that immunity recovers well and the mortality is similar to the general population.
<u>Average cohort age</u> Background mortality is modelled as a function of the age distribution seen in the NP30179 study but had been partially applied across parameters of the model. EAG suggests applying mortality associated with average cohort age.	
<u>Treatment discontinuation</u> For bendamustine plus rituximab (BR), different sources are used to estimate efficacy (Hong et al 2018) and treatment discontinuation (GO29365 study). These are then used to inform the indirect treatment comparison with glofitamab. The EAG has explored using the GO29365 study to estimate both the efficacy and discontinuation rate of BR.	Most discontinuations occur due to progressive disease in the

11) What is the most suitable source of data for estimating the efficacy and discontinuation rate of BR?	This is difficult because in the UK we use RBP but not benda ritux frequently and so we do have real world data for this and there are limited trial data.
<u>Immune effector cell-associated neurotoxicity syndrome (ICANS)</u> Neurological adverse events consistent with ICANS have been observed in patients treated with glofitamab in NP30179 but not considered in the cost-effectiveness analysis. While this may be appropriate if ICANS were not severe or frequent enough, it is unknown whether these AEs may require additional resource use for monitoring (e.g., access to specialised neurological care units). Furthermore, if specialised critical care is potentially needed as part of the monitoring strategy, this may constrain the setting in which glofitamab can be delivered to NHS centres with such facilities. **12) What are the healthcare costs associated with the management and monitoring of ICANS?** **13) How frequent and how severe is ICANS in this setting?**	The rates of ICANS in the studies are low and in my clinical experience ICANS is not a concern when using bispecifics. This is very different to using CAR T when we must ensure the patient has a carer with them for the first month and the patient cannot drive for 2 months. With bispecifics, ICANS is very rare, so much so that there are no restrictions in driving and no requirements for care giver or ICANS monitoring. In studies, headaches were considered a “neurological event” and this is not the same as true ICANS. When I have used glofitamab on study I have not managed my patients in the same way as CAR T in terms of ICANS risk (and it is not required in the SpC) and I do not think that observation and hospitalisation for ICANS should be included as it is for CAR T. The ICANS in the clinical trial was about 8% with 3% grade 3 or more but this included all “neurological events” including headache and so in practice using glofitamab on trial or via compassionate access I do not monitor for ICANS.
Are there any important issues that have been missed in the EAR?	Not that I am aware of

Part 3: Key messages

In up to 5 sentences, please summarise the key messages of your statement:

Glofitamab has a high CR rate which appears durable

Glofitamab is easy to deliver and can be delivered in most hospitals following training for CRS management

ICANS is very rare and does not require additional costings, patients do not need a carer with them and can drive on treatment.

It is possible that this improves equity of access for patients with RR DLBCL

This data is intention to treat, unlike comparing with CAR T 3rd line which was patients who reached infusion.

Thank you for your time.

Your privacy

The information that you provide on this form will be used to contact you about the topic above.

☐ **Please tick this box** if you would like to receive information about other NICE topics.

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NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Glofitamab for treating relapsed or refractory diffuse large B-cell lymphoma after 2 or more systemic treatments [ID3970]

Clinical expert statement and technical engagement response form

Thank you for agreeing to comment on the external assessment report (EAR) for this evaluation, and for providing your views on this technology and its possible use in the NHS.

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature. The EAR and stakeholder responses are used by the committee to help it make decisions at the committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

Information on completing this form

In part 1 we are asking for your views on this technology. The text boxes will expand as you type.

In part 2 we are asking for your views on key issues in the EAR that are likely to be discussed by the committee. The key issues in the EAR reflect the areas where there is uncertainty in the evidence, and because of this the cost effectiveness of the treatment is also uncertain. The key issues are summarised in the executive summary at the beginning of the EAR. You are not expected to comment on every key issue but instead comment on the issues that are in your area of expertise.

A clinical perspective could help either:

- resolve any uncertainty that has been identified OR
- provide missing or additional information that could help committee reach a collaborative decision in the face of uncertainty that cannot be resolved.

In part 3 we are asking you to provide 5 summary sentences on the main points contained in this document.

Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable. Please type information directly into the form.

Do not include medical information about yourself or another person that could identify you or the other person.

We are committed to meeting the requirements of copyright legislation. If you want to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.

Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.

Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise, all information submitted under 'academic in confidence' in yellow, and all information submitted under 'depersonalised data' in pink. If confidential information is submitted, please also send a second version of your comments with that information redacted. See the NICE health technology evaluation guidance development manual (sections 5.4.1 to 5.4.10) for more information.

Please note, part 1 can be completed at any time. We advise that **part 2** is completed after the expert engagement teleconference (if you are attending or have attended). At this teleconference we will discuss some of the key issues, answer any specific questions you may have about the form, and explain the type of information the committee would find useful.

The deadline for your response is **5pm** on **Wednesday 28 June 2023.** Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Thank you for your time.

We reserve the right to summarise and edit comments received during engagement, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received during engagement are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

NICE National Institute for Health and Care Excellence

Part 1: Treating diffuse large B-cell lymphoma and current treatment options

Table 1 About you, aim of treatment, place and use of technology, sources of evidence and equality

1. Your name	Dr William Townsend
2. Name of organisation	Employer: University College London Hospitals NHS Trust Representing: NCRI / Royal College of Physicians
3. Job title or position	Consultant haematologist, honorary associate professor
4. Are you (please tick all that apply)	☐ An employee or representative of a healthcare professional organisation that represents clinicians? ☒ A specialist in the treatment of people with relapsed or refractory diffuse large B-cell lymphoma? ☐ A specialist in the clinical evidence base for relapsed or refractory diffuse large B-cell lymphoma or technology? ☐ Other (please specify):
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	☒ Yes, I agree with it ☐ No, I disagree with it ☐ I agree with some of it, but disagree with some of it ☐ Other (they did not submit one, I do not know if they submitted one etc.)
6. If you wrote the organisation submission and/or do not have anything to add, tick here. (If you tick this box, the rest of this form will be deleted after submission)	☒ Yes - I contributed to the submission
7. Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	None to disclose

8. What is the main aim of treatment for relapsed or refractory diffuse large B-cell lymphoma? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability)	The main aim for the treatment of relapsed or refractory diffuse large B cell lymphoma (RR DLBCL) is to attain a complete remission and for that remission to be sustained; the ultimate aim is to cure patients with RR DLBCL. For patients who are not cured the hope is to achieve as durable remission as possible with the least possible toxicity and least time in hospital.
9. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount)	Attaining complete remission on PET scan (CR) is a highly relevant and clinically significant treatment response. ORR (CR and PR) is also relevant although Partial responses are more typically short-lived than complete remissions.
10. In your view, is there an unmet need for patients and healthcare professionals in relapsed or refractory diffuse large B-cell lymphoma?	Yes. The treatment of RR DLBCL remains very challenging. Prior to the advent of CAR-T cell therapy only about 50% of patients with RR DLBCL were considered fit enough to attempt intensive 2nd line chemotherapy and only about 50% of these patients would attain a good enough response to consolidate with autologous stem cell transplant which was considered curative in a proportion of patients. Thus, only a minority of patients with RR DLBCL were cured with this approach. Whilst CAR-T cell therapy, initially in 3rd line treatment and now also in 2nd line treatment (in those with refractory disease or who relapse within 12 months) represents a significant advance in the treatment of RR DLBCL, this approach is not suitable for all patients and up to 50% of patients treated with this approach subsequently have disease progression. Existing options for patients unsuitable/ineligible for CAR-T cell therapy or who experience disease progression post CAR-T are very limited and there is an unmet need for these patients.
11. How is relapsed or refractory diffuse large B-cell lymphoma currently treated in the NHS? • Are any clinical guidelines used in the treatment of the condition, and if so, which?	As above, the treatment pathway for DLBCL has undergone significant change in the last few years, most guidelines (including the BSH national guidelines) are out of date at present and need up-dating to reflect the recent changes to treatment.

• Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.) • What impact would the technology have on the current pathway of care?	Despite the absence of contemporary national guidance, my impression is that the pathway is quite well defined: all pts receive R-CHOP or Pola-R-CHP first-line. As of 2023, at first relapse/primary treatment failure, if that relapse has occurred within 12 months of completing therapy, and they are considered fit for ASCT, Axicel can be used in 2nd line. For those who are not eligible for CAR-T 2nd line but are fit for intensive therapy, we use 2nd line chemotherapy (eg R-GDP/ESHAP/ICE) with a view to AutoSCT if remission is attained and cells can be harvested and the pt remains fit for ASCT post platinum-based chemo. For those not eligible for CAR T 2nd line and not fit for intensive treatment, either R-Gem-Ox or PolaBR are considered 2nd line. Generally, if not fit for ASCT but fit for CAR (see Kuhnl and Townsend BJH 2023 for CAR-T fitness in pts not considered fit for ASCT), I would try to avoid bendamustine in 2nd line as exposure to this may hamper ability to manufacture CAR-T later so, in these pts, I favour R-Gem-Ox 2nd line and if no response / Progression aim to get to CAR-T 3rd line possibly with Pola-BR as a bridge to CAR-T. If glofitamab is approved, I think that it would be used either in 3rd line for pts who have received CAR-T 2nd line and have relapsed, or 4th line for those patients who relapse post CAR T in 3rd line. There is another cohort of pts in 3rd line who could be CAR-T eligible but for various reasons it may be preferable to administer glofitamab instead of CAR-T. I consider that this may occur if a patient has disease that is progressing too rapidly to get to CAR-T, in patients deemed ineligible for CAR-T by the NCCP, or due to pt choice eg choice to have glofitamab administered in a local hospital without need for travel or lengthy in-patient admission.
12. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	**How does healthcare resource use differ between the technology and current care?** Although are similarities in mechanism of action between glofitamab and CAR-T and some overlapping toxicities I think that resource use will be very different to

• How does healthcare resource use differ between the technology and current care? • In what clinical setting should the technology be used? (for example, primary or secondary care, specialist clinic) • What investment is needed to introduce the technology? (for example, for facilities, equipment, or training)	CAR-T: there is no need for bridging when using Glofitamab (compare to high use of bridging chemo +- radiotherapy for CAR-T), there is no need for apheresis and cell manufacturing with glofitamab, there is no need for cytoreductive chemotherapy with glofitamab, however glofitamab does require a single dose of obinutuzumab 7d prior to first dose which will incur some resource use. There is a much shorter in-patient workload with glofitamab than CAR-T with only 1 night stay (or prolonged day unit admission) required in most cases. Although there is a risk of CRS, this is generally more predictable and of lower grade than with CAR-T, tocilizumab may be required in 1/3 of pts with CRS with glofitamab, generally only 1 dose will be needed. ICU will rarely be needed due to drug toxicity. ICANS is much less frequent and of lower grade with glofitamab therefore less resource use. **In what clinical setting should the technology be used? (for example, primary or secondary care, specialist clinic)** I believe that with appropriate training for identification and management of CRS, glofitamab can be delivered in any hospital that is familiar with delivering immunochemotherapy. **What investment is needed to introduce the technology? (for example, for facilities, equipment, or training)** Training in identification and management of CRS. Availability of tocilizumab.
13. Do you expect the technology to provide clinically meaningful benefits compared with current care? • Do you expect the technology to increase length of life more than current care? • Do you expect the technology to increase health-related quality of life more than current care?	**Do you expect the technology to increase length of life more than current care?** It depends which setting and in comparison to what. In pts relapsing after CAR-T I think that the trial data is compelling and indicates a high CR rate which is durable in many cases with impressive OS in a cohort of heavily pre-treated refractory patients including 1/3 of whom have had prior CAR-T. There are few other options which have this level of efficacy post-CAR-T at present

	and I expect glofitamab to increase length of life compared to immunochemotherapy in this setting. There are no data comparing outcomes head-to-head of CAR-T vs glofitamab so it is not possible to say if glofitamab would increase length of life compared to Axicel in 3rd line. If such a trial were done in the future it would have to be done on an ITT basis to capture the outcomes of those who fail to get to CAR-T cell infusion. **Do you expect the technology to increase health-related quality of life more than current care**? Again this depends on what it is being compared against. If comparing to immunochemotherapy in the post CAR-T setting I think it is highly likely that QoL will be superior with glofitamab due to a higher chance of attaining remission, low side effect profile and out-patient delivered treatment (after first dose). It is difficult to compare QoL for this against CAR-T and there is not as much published trial or real world QoL data for glofitamab yet as there is for CAR-T but, in my experience, pts on glofitamab are typically well with few side effects or toxicities and only infrequent visits to the cancer centre for treatment (3 weekly beyond cycle 1). If a trial comparing glofitamab against CAR-T (in 2nd or 3rd line were ever to be conducted, including QoL data would be an important aspect of this trial). I have a cohort of trial pts who I have treated with glofitamab who are in ongoing remission long after completing therapy who are well with no lasting toxicities and appear to be enjoying a good QoL. I don't think the same can be achieved with immunochemotherapy in this cohort of pts.

14. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	The forest plots (for CR rate) show broad efficacy across different sub-groups. There is probably insufficient evidence to assess efficacy or otherwise in HGBCL (double/triple hit).
15. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use? (For example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed)	It is clearly much easier to deliver glofitamab than CAR-T cell therapy. I have described these differences elsewhere in this document. In comparing against immunochemotherapy there are some differences: for glofitamab 1 dose of obinutuzumab will need to be given as an out patient 7d prior to first dose, this is not a challenge for any centre competent and experienced in delivering standard lymphoma treatments as obinutuzumab is routinely used in the treatment of FL. The main challenge will be in admitting the pts to a suitable facility on first dose of glofitamab (2.5mg dose) in d8 to monitor for CRS (either overnight or prolonged day unit admission). Staff will need training in identifying this – although many centres will already be familiar with this from CAR-T cell delivery or from using other T-cell engaging strategies in haematology and oncology. Beyond cycle 1, the delivery of glofitamab does not differ significantly from delivering other antibody therapies for which most UK haematology cancer centres will be familiar with.
16. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	Most responses are observed early (median d42 in the trial data). In most instances a scan after cycle 2 or 3 to assess response would be appropriate however I would strongly guard against stopping treatment early on the basis of sub-optimal response (especially if the patient appears clinically well) due to the possibility of pseudo-progression. I have experienced a few patients on trials who appeared to be progressing radiologically but were deriving clinical benefit and enjoyed sustained responses and prolonged time-to-next treatment after stopping glofitamab. Clinical judgement will be needed. No additional testing is required beyond what would be used in standard treatments.

17. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation? • Do the instruments that measure quality of life fully capture all the benefits of the technology or have some been missed? For example, the treatment regimen may be more easily administered (such as an oral tablet or home treatment) than current standard of care	Treatment more easily delivered closer to home and with shorter in-patient admission than CAR-T.
18. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met? • Is the technology a 'step-change' in the management of the condition? • Does the use of the technology address any particular unmet need of the patient population?	Glofitamab is a first-in class molecule which is innovative in its ability to engage T-cells to mount and anti-tumour response. Other bispecific antibodies with a similar mechanism of action are in development, these include Epcoritamab, Mosunetuzumab (for FL), and Odronextamab; others are also in development. This class of drug delivers a rapid T cell response against the lymphoma without the requirement for apheresis, manufacture, bridging and long inpatient stays associated with CAR-T. With glofitamab we also see a true "intention to treat" data set so the data are not skewed by those who are intended to be treated with CAR-T but do not receive cell therapy (eg due to rapid progression during manufacturing phase). Glofitamab allows patient access irrespective of geography in the UK and also access for those patients who have rapid progression of lymphoma who are not stable enough to wait for CAR T manufacture.
19. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	The main toxicity is the risk of CRS which is highest in cycle 1. The risk of CRS (especially high grade) has been well mitigated by the use of obinutuzumab pre-treatment, step up dosing and steroid pre-medication such that the risk of G3 or higher CRS is now low. Most patients will only require a short admission to hospital on the first day of dosing with no further in patient admission thereafter. If CRS occurs, it is typically short-lived. In my experience of treating >20 pts with glofitamab in the clinical trial setting or via the compassionate access scheme, CRS does not impact QoL beyond cycle 1 d8.

	The other toxicity to consider re QoL is the increased risk of infection. It is hard to quantify how much this is attributable to glofitamab given that patients are heavily pre-treated (often including prior CAR-T which is very immune-suppressive) and the alternative to treatment with glofitamab would be immunochemotherapy which is also immune-suppressive. Nevertheless, infections – sometimes serious – can occur in patients on glofitamab and this can impact QoL.
20. Do the clinical trials on the technology reflect current UK clinical practice? • If not, how could the results be extrapolated to the UK setting? • What, in your view, are the most important outcomes, and were they measured in the trials? • If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes? • Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	Yes. The NP30179 trial was not conducted in the UK (despite our academic endeavours to open it) but the trial population included is similar to patients we would put forward for glofitamab now if it is approved. The trial population comprised a heavily pre-treated, refractory patient cohort that broadly matches the patients we would be aiming to treat with glofitamab if it is approved in the UK. The trial was conducted in some regions where CAR-T (2nd or 3rd line) was not routinely available but 1/3 of patients had had prior CAR-T. I expect that the UK population will have a higher rate of prior CAR-T than the trial due to the availability of this treatment in the UK in 2nd or 3rd line. Most important outcomes is OS, important surrogates include PFS, CR rate, DoCR all of which were measured in this trial. QoL is also important and in this disease is typically driven by time in remission and out of hospital. The trial captures the most relevant adverse effects. There is some concern around infections, sometimes severe infections with long term B cell depletion but it is hard to know how much this relates to prior lines of therapy (including CAR-T). In practice I have all patients on antiviral and PCP prophylaxis and have a low threshold for treating infection if there is clinical concern.
21. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	There is no other source of evidence on the use of glofitamab as it has only been accessible via clinical trials to now. I anticipate that real world data on usage will appear in the coming year as access widens in the UK and internationally.

22. Are you aware of any new evidence for the comparator treatment(s) since the publication of NICE technology appraisal guidance [TA649, TA872]?	No
23. How do data on real-world experience compare with the trial data?	See above, very little real world data so far.
24. NICE considers whether there are any equalities issues at each stage of an evaluation. Are there any potential equality issues that should be taken into account when considering this condition and this treatment? Please explain if you think any groups of people with this condition are particularly disadvantaged. Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics. Please state if you think this evaluation could • exclude any people for which this treatment is or will be licensed but who are protected by the equality legislation • lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population • lead to recommendations that have an adverse impact on disabled people.	The key issue here is around the fact that CAR-T cell therapy remains available in only a relatively small number of specialist centres which involves pt referral from their local hospital to another centre which may be some distance away. There is a significant cost to patients in travelling to CAR-T centres for clinic appointments / apheresis / bridging / admission for treatment and follow up and additional cost to patients' relatives. For this reason some patients may elect not to receive CAR-T and this may bias against those geographically living further from a CAR-T centre, or those who financially can't afford to attend. By contrast, it should be possible to administer glofitamab at many centres with a better geographical spread around the country so that patients who choose not to receive CAR-T can receive effective therapy closer to home. This may overcome some degree of inequity of access.

Please consider whether these issues are different from issues with current care and why. More information on how NICE deals with equalities issues can be found in the NICE equality scheme. Find more general information about the Equality Act and equalities issues here.	

Part 2: Technical engagement questions for clinical experts

We welcome your comments on the key issues below, but you may want to concentrate on issues that are in your field of expertise. If you think an issue that is important to clinicians or patients has been missed in the EAR, please also advise on this in the space provided at the end of this section.

The text boxes will expand as you type. Your responses to the following issues will be considered by the committee and may be summarised and presented in slides at the committee meeting.

For information: the professional organisation that nominated you has also been sent a technical engagement response form (a separate document) which asks for comments on each of the key issues that have been raised in the EAR. These will also be considered by the committee.

Table 2 Issues arising from technical engagement

Position of comparator treatments in care pathway Glofitamab was compared to both CAR-T therapy (axi-cel) and polatuzumab with bendamustine and rituximab (pola-BR) in the third-line. Clinical advice to the EAG suggest these treatments are increasingly being used in earlier lines. 1) **Are CAR-T (axi-cel) and pola-BR relevant third-line comparators?** 2) **Would glofitamab be used after CAR-T and/or pola-BR? If glofitamab was used after CAR-T and/or pola-BR, what**	**Are CAR-T (axi-cel) and pola-BR relevant third-line comparators?** In my opinion, both axicel and PolaBR are valid comparisons in the 3rd line but we need to acknowledge the rapidly changing DLBCL treatment landscape wherein Polatuzumab-R-CHP will increasingly be used 1st line and this will reduce the use of PolaBR in later lines of therapy as there is no available route to fund PolaBR after Pola-R-CHP. In the evolving treatment pathway, Axicel remains a valid comparator in 3rd line as there is a chort of patietns who will not have received it 2nd line either because they received 2nd line treatment before Axicel was approved or because they were ineligible for it in 2nd line. Note that I do not think that Axicel will be re-used in 3rd line if it had been previously used in 2nd line. If a patient with RR DLBCL has had 1st line Pola-R-CHP and 2nd line axicel a valid comparator in 3rd line would most likely be R-chemotherapy and the choice of chemotherapy which is paired with rituximab will vary by centre and according to patient factors. We very rarely use BR. Pixantrone is generally not used in the UK.

would the relevant comparators for glofitamab be? **3) If polatuzumab has been used in a previous line(s) of therapy, would this affect the likelihood of pola-BR being used or being effective in third-line treatment?** **4) Will the efficacy of glofitamab be influenced by using CAR-T or polatuzumab in a prior line?**	**Would glofitamab be used after CAR-T and/or pola-BR? If glofitamab was used after CAR-T and/or pola-BR, what would the relevant comparators for glofitamab be?** I consider that glofitamab may be used after both CAR-T and PolaBR in patients who were fit and eligible to receive both of these therapies. If glofitamab was used after both CAR-T and PolaBR the most relevant comparator would be R-chemotherapy. If used after Pola-RCHP (1L) and Axicel (2L), the most valid comparator 3rd line would be R-chemo. If used after R-CHOP (1L) and Axicel (2L), RBPola would be a relevant comparator. If used after R-CHOP/Pola-R-CHP (1L) and R-Chemo (2L) the most valid comparator would be Axicel 3L. If used after R-CHOP (1L), PolaBR (2L), Axicel (3L), the most valid comparator would be R-chemo. **If polatuzumab has been used in a previous line(s) of therapy, would this affect the likelihood of pola-BR being used or being effective in third-line treatment?** I am not aware of evidence to support or refute the re-use of polatuzumab eg in PolaBR after previous Pola-R-CHOP and there is a need for data on the response rate to Pola-based regimens in patients who have previously received it. It is likely that earlier use of Pola will reduce the frequency of it being used in 3rd line in the PolaBR combination largely due to lack of funding for PolaBR after prior Pola exposure.

	Will the efficacy of glofitamab be influenced by using CAR-T or polatuzumab in a prior line? Further research will be needed to establish the optimal sequencing of all of these treatments in RR DLBCL and to establish whether prior use of one approach impacts on efficacy of a subsequent treatment but, at present, evidence from NP30179 indicates that the efficacy of glofitamab (as measured by CR rate) is not substantially different in patients who have progressed after prior CAR-T vs those who have not received CAR-T (CR rate 35% (22-49) and 42% (32-52) respectively with overlapping 95% confidence intervals), data on durability of remissions with analysis by previous exposure to CAR-T has not – as far as I am aware – been presented or published. Differential response rates by prior exposure to polatuzumab were not reported as far as I am aware. Theoretically T-cell engaging strategies may be most effective earlier in the treatment pathway when T-cell function is maximal and prior to therapies that are known to be long-term lympho-depleting such as bendamustine.
<u>Patients who do not receive axi-cel infusion</u> The indirect treatment comparison of glofitamab and axi-cel did not include people who were assigned axi-cel but did **not** receive the infusion. 1) **What outcomes would you expect for people who are considered for, but do not receive CAR-T therapy?** 2) **What resource use requirements would you expect for people who are considered for, but do not receive CAR-T therapy?**	**What outcomes would you expect for people who are considered for, but do not receive CAR-T therapy?** We know from UK real-world data that outcomes for patients who were eligible for, and approved for CAR-T in 3rd line but did not receive the cellular therapy are very poor with median OS of only 2.1 months and 12 month OS of 5.9% (Ref Kuhnl BJH 2022). In the UK real-world CAR-T experience this applied to 26% of patients approved for CAR-T in 3rd line and although the proportion of patients who do not proceed to CAR-T has decreased with more effective bridging, this is still an important and significant challenge and consideration.

3) What would the outcomes and resource requirements be for these people if they were treated with glofitamab?	**What resource use requirements would you expect for people who are considered for, but do not receive CAR-T therapy?** Of the 75 patients (26%) approved but not infused in the UK real world experience, the main reason for non-infusion was clinical progression and deterioration between approval and time of infusion. Resource use requirements for these patients will vary. Given the very poor OS in this cohort many of these patients will receive palliative and end-of-life care, some will receive further immuno-chemotherapy, a minority of such patients may be able to access clinical trials or compassionate access to novel agents. In addition to further treatment and access to high quality palliative care, patients who are considered for CAR-T but do not receive cell therapy typically incur the resource use and costs of applying for CAR (consultant, administrative, and MDT time), apheresis, and bridging. Glofitamab represents a potential treatment for these patients. **What would the outcomes and resource requirements be for these people if they were treated with glofitamab?** Given that this cohort of patients (eligible for and approved for CAR-T but not infused) typically have rapidly progressive disease they represent a hard-to-treat sub-population of patients with RR DLBCL. Nevertheless, I believe that such patients were represented in the NP30179 clinical trial which recruited a heavily pre-treated and highly refractory patient population. Therefore, I anticipate that the ORR/CR rate for this cohort of patients may be similar to the reported outcomes for the main trial population. Accordingly, the resource requirements for these patients will be the same as for other RR DLBCL pts accessing glofitamab in the 3rd line+ setting.
Confidence intervals of ITC analyses	

The unadjusted and adjusted analyses used different methods for calculating their confidence intervals.	
Long-term remission/survivorship The EAG considers that there is insufficient evidence to support long-term remission, survivorship, and cure estimates. The company's economic model assumes that patients alive and progression free after 2 years enter a long-term remission stage (no progression and considered 'cured') and that after 3.5 years people still alive return to near UK general population age-matched mortality risk (most post-progression patients have died at this point). In the EAG's model, they assumed that people who are alive and progression-free after 3 years have a 10% decrement from the age-sex UK general population utilities (quality of life) and a 41% excess mortality from the age-matched UK general population. 1) **When would a patient be considered to be 'cured'?** 2) **Is it clinically plausible that axi-cel, glofitamab, pola-BR or BR could be curative or lead to long-term remission? Is there evidence to support this?** 3) **For a patient who is cured, how would quality of life and mortality be different**	**When would a patient be considered to be 'cured'?** Given the highly aggressive natural history of DLBCL most relapses typically occur early. In the era of CAR-T cell therapy and now with >5 years follow up, we (the treating community) now have increasing confidence to say that some patients with RR DLBCL treated with CAR-T and in ongoing remission are cured. We don't yet have long enough follow up from the pivotal glofitamab trial to say with confidence that patients are cured but durable CRs are clearly seen (78% of patients in CR have ongoing remission at 12 months – Dickinson NEJM) and I anticipate that a proportion of these patients will be cured. Longer follow up from NP30179 (presented by Dickinson at ICML June 2023) further supports that many patients who achieve CR have durable remissions with 67% ongoing complete remission at 18 months. While some patients may be cured I anticipate that there will be further progression events and I do not think that 'plateau' has yet been reached in the PFS or DoCR curves. Longer follow up is needed to be clear about the proportion of patients who may be cured with glofitamab. **Is it clinically plausible that axi-cel, glofitamab, pola-BR or BR could be curative or lead to long-term remission? Is there evidence to support this?** See above – yes it is now increasingly agreed that axicel may be curative in a proportion of patients with RR DLBCL (longer evidence is available for 3rd line therapy but it is anticipated that the same may be true when axicel is used in 2nd line).

to the age-matched general population?	Accumulating evidence with longer follow up indicates that the same may be true for glofitamab in 3L+ but longer follow up is needed to say this with certainty. BR is not typically used in this setting in the UK and I am unable to say with confidence whether or not it is considered curative. UK real world data published by myself and Dr Northend (Northend et al Blood Advances 2022) indicated that PolaBR in RR DLBCL induces similar rates of remission as the pivotal BRPola trial data (ORR in the stand-alone treatment group 65.8% (CR, 39.7%)) but the median PFS is only 5.4 months when used as a 'stand-alone' therapy i.e. not as bridge to CAR or transplant. This is inferior to the published trial data probably in part due to use in an older population of more heavily pre-treated patients. There does not appear to be a plateau in the PFS or OS curves from this real world data and accordingly I do not think that PolaBR is curative for the majority of patients. Further analysis of this UK real world data set presented at ICML 2023 in abstract form (full paper in development) indicates that ORR, CR rate, and PFS is inferior when PolaBR is used in 3rd line compared to 2nd line (Townsend and Northend ICML 2023). In this analysis the ORR is 73% vs 54% and CR 48% vs 30% for 2nd line compared to 3L+ and the 6-month PFS was 54.2% (95% CI 37.9-67.9) and 35.9% (95% CI 20.1-52.0) for the 2L and ≥3L groups respectively (HR 2.17 (95% CI 1.19-3.95), p=0.01). The 6-month OS in the ≥3L cohort is 49.2% indicating that it is unlikely to be curative in a high proportion of patients. I am unclear if this can be extrapolated to BR but it indicates that ORR, CR, and durability of remission of RBPola in real-world setting in 3rd line and beyond are lower than the published data. **For a patient who is cured, how would quality of life and mortality be different to the age-matched general population?**

	There are few late toxicities from glofitamab, therefore if cured I would anticipate that QoL would be similar to age-matched population. We can extrapolate from earlier studies that life expectancy for patients who are cured is good; subgroup analysis of individual patient data from the CORAL and LY.12 studies in patients with R/R DLBCL who underwent ASCT shows that patients who are event free for 5 years after ASCT achieve a life expectancy similar to that of an age-matched population (Ref: Assouline *Blood Adv* 2020)
<u>Average cohort age</u> Background mortality is modelled as a function of the age distribution seen in the NP30179 study but had been partially applied across parameters of the model. EAG suggests applying mortality associated with average cohort age.	
<u>Treatment discontinuation</u> For bendamustine plus rituximab (BR), different sources are used to estimate efficacy (Hong et al 2018) and treatment discontinuation (GO29365 study). These are then used to inform the indirect treatment comparison with glofitamab. The EAG has explored using the GO29365 study to estimate both the efficacy and discontinuation rate of BR. **4) What is the most suitable source of data for estimating the efficacy and discontinuation rate of BR?**	**What is the most suitable source of data for estimating the efficacy and discontinuation rate of BR?** I am not sure as there is limited data on BR which is infrequently used in the UK for the treatment of RR DLBCL.

Immune effector cell-associated neurotoxicity syndrome (ICANS) Neurological adverse events consistent with ICANS have been observed in patients treated with glofitamab in NP30179 but not considered in the cost-effectiveness analysis. While this may be appropriate if ICANS were not severe or frequent enough, it is unknown whether these AEs may require additional resource use for monitoring (e.g., access to specialised neurological care units). Furthermore, if specialised critical care is potentially needed as part of the monitoring strategy, this may constrain the setting in which glofitamab can be delivered to NHS centres with such facilities. 5) **What are the healthcare costs associated with the management and monitoring of ICANS?** 6) **How frequent and how severe is ICANS in this setting?**	**What are the healthcare costs associated with the management and monitoring of ICANS?** The principle costs associated with the management and monitoring for ICANS in the context of CAR-T cell therapy are from prolonged in-patient admission, nursing care, medical care (including haematology doctor time, neurologist doctor time, potential radiologist time (to interpret neuroimaging), potential ICU doctor time), neuroimaging (CT / MRI head), drug costs (high dose steroids, anti-infection prophylaxis and treatments including anti-fungals consequent on high dose steroids), potential admission to ICU. **How frequent and how severe is ICANS in this setting?** From trial data and my clinical experience, the risk of ICANS is low with glofitamab with 8% events in keeping with ICANS in the trial data and only 3% G≥3 ICANS. Conversely, the risk of ICANS in the UK real-world data set with axicel is 44.4% with 19.6% risk of G≥3 ICANS. Accordingly, whilst ICANS-type events can occur after treatment with glofitamab this is rare and typically of low grade. In practical terms, in the >20 pts I have treated with glofitamab I have not encountered any ICANS events so far and initiate no specific monitoring for ICANS beyond the in-patient admissions to monitor for CRS that were mandated in the clinical trials for which I was an investigator. We are now using Glofitamab in the non-trial setting via a named patient basis scheme and there is only a requirement to monitor patients for CRS on the first administration (2.5mg d8) with no specific requirement to monitor for ICANS.
Are there any important issues that have been missed in the EAR?	Possibly the risk of infections and need for appropriate prophylaxis and treatment of these.

Part 3: Key messages

In up to 5 sentences, please summarise the key messages of your statement:

1) Glofitamab is a first in class bispecific antibody that induces high CR rate in a population of heavily treated, high risk patients with RR DLBCL. Initial evidence indicates that complete responses are durable in a high proportion of patients but longer follow up is required before we can say with confidence what proportion of patients are cured with this treatment.
2) Glofitamab should be deliverable in most haematology units in the UK with appropriate training and staffing to manage CRS.
3) Comparison with Axicel or RBPola are valid with trial data and UK-derived real-world data to inform the utility and efficacy of both of these comparators but we recognise the rapidly changing treatment landscape which affects where these lines of therapy are used.
4) It is important to consider the ITT population for CAR-T and the outcomes and costs incurred for those who are approved but do not go on to receive the cellular therapy.
5) The main toxicities to consider with glofitamab are CRS and infection risk. The risk of ICANS with glofitamab is low.

Thank you for your time.

Your privacy

The information that you provide on this form will be used to contact you about the topic above.

☐ **Please tick this box** if you would like to receive information about other NICE topics.

For more information about how we process your personal data please see our privacy notice.

NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Glofitamab for treating relapsed or refractory diffuse large B-cell lymphoma after 2 or more systemic treatments [ID3970]

Clinical expert statement and technical engagement response form

Thank you for agreeing to comment on the external assessment report (EAR) for this evaluation, and for providing your views on this technology and its possible use in the NHS.

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature. The EAR and stakeholder responses are used by the committee to help it make decisions at the committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

Information on completing this form

In part 1 we are asking for your views on this technology. The text boxes will expand as you type.

In part 2 we are asking for your views on key issues in the EAR that are likely to be discussed by the committee. The key issues in the EAR reflect the areas where there is uncertainty in the evidence, and because of this the cost effectiveness of the treatment is also uncertain. The key issues are summarised in the executive summary at the beginning of the EAR. You are not expected to comment on every key issue but instead comment on the issues that are in your area of expertise.

A clinical perspective could help either:

- resolve any uncertainty that has been identified OR
- provide missing or additional information that could help committee reach a collaborative decision in the face of uncertainty that cannot be resolved.

In part 3 we are asking you to provide 5 summary sentences on the main points contained in this document.

Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable. Please type information directly into the form.

Do not include medical information about yourself or another person that could identify you or the other person.

We are committed to meeting the requirements of copyright legislation. If you want to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.

Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.

Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise, all information submitted under 'academic in confidence' in yellow, and all information submitted under 'depersonalised data' in pink. If confidential information is submitted, please also send a second version of your comments with that information redacted. See the NICE health technology evaluation guidance development manual (sections 5.4.1 to 5.4.10) for more information.

Please note, part 1 can be completed at any time. We advise that **part 2** is completed after the expert engagement teleconference (if you are attending or have attended). At this teleconference we will discuss some of the key issues, answer any specific questions you may have about the form, and explain the type of information the committee would find useful.

The deadline for your response is **5pm** on **Wednesday 28 June 2023.** Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Thank you for your time.

NICE National Institute for Health and Care Excellence

We reserve the right to summarise and edit comments received during engagement, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received during engagement are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

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Part 1: Treating diffuse large B-cell lymphoma and current treatment options

Table 1 About you, aim of treatment, place and use of technology, sources of evidence and equality

1. Your name	Wendy Osborne
2. Name of organisation	The Royal College of Pathologists
3. Job title or position	Consultant Haematologist
4. Are you (please tick all that apply)	☐ An employee or representative of a healthcare professional organisation that represents clinicians? ☒ A specialist in the treatment of people with relapsed or refractory diffuse large B-cell lymphoma? ☐ A specialist in the clinical evidence base for relapsed or refractory diffuse large B-cell lymphoma or technology? ☐ Other (please specify):
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	☒ Yes, I agree with it ☐ No, I disagree with it ☐ I agree with some of it, but disagree with some of it ☐ Other (they did not submit one, I do not know if they submitted one etc.)
6. If you wrote the organisation submission and/or do not have anything to add, tick here. (If you tick this box, the rest of this form will be deleted after submission)	☐ Yes
7. Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	Nil

8. What is the main aim of treatment for relapsed or refractory diffuse large B-cell lymphoma? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability)	The main aim is still to obtain a durable response, and in some patients cure. In those patients in whom cure is not achieved then we want to achieve as long as possible with disease control and minimal symptoms allowing a good quality of life.
9. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount)	Any reduction in lymphoma volume is significant but the most important is achieving a complete response as some of these will lead to cure. For patients who achieve a partial response it will lead to months of life for that patient but most patients in a partial response with DLBCL will progress at some stage and there CR is most important.
10. In your view, is there an unmet need for patients and healthcare professionals in relapsed or refractory diffuse large B-cell lymphoma?	Yes, unfortunately current standard second line treatment requires the patient to be fit enough to tolerate high dose chemotherapy and an auto transplant and the responses are only 15-20% durable even in these fit patients. If the patient then has 3rd line CAR T and manages to reach infusion then about 35% of these patients will have a durable response but the rest will progress and will most likely die from DLBCL.
11. How is relapsed or refractory diffuse large B-cell lymphoma currently treated in the NHS? • Are any clinical guidelines used in the treatment of the condition, and if so, which? • Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.) • What impact would the technology have on the current pathway of care?	The BSH guidelines are out of date and are currently being rewritten but are not yet published. The standard pathway is well defined. If a patient is auto fit they will have 2nd line high dose chemo and an auto, if they are auto unfit they will have rgemox if planning 3rd line CAR T or will have Rbenda pola of oral palliative chemo if not planning CAR T 3rd line. Recently 2nd line Axi-Cel has become available on the CDF for auto fit pts who relapse within 12 months of first line treatment. Third line patients will either have CAR T or palliative chemo depending on patients wishes and if it is considered likely that we can keep the patient stable whilst the CAR Ts are being manufactured. If Glofitamab is approved it will be used 3rd line, for pts who had CAR T 2nd line or for those patients who may prefer having treatment close to home and not travelling to a CAR T centre. It will also be used 4th line for those patients who relapse post CAR T.

12. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice? • How does healthcare resource use differ between the technology and current care? • In what clinical setting should the technology be used? (for example, primary or secondary care, specialist clinic) • What investment is needed to introduce the technology? (for example, for facilities, equipment, or training)	This technology is similar to CAR T but significantly easier to deliver which will mean that more patients will choose to access it as they will not have to travel to a CAR T centre. The main side effect is cytokine release syndrome which is predictable and treatable with tocilizumab. Hospitals which can manage patients with neutropenic sepsis can manage CRS and this is why bispecifics have been successfully delivered in a clinical trial setting in hospitals geographically isolated from large CAR T centres or allo centres. Glofitamab can be delivered in secondary care in all centres which deliver chemo at risk of neutropenic sepsis (eg RCHOP). There will be some additional training to ensure CRS is managed appropriately and this has already started as more bispecifics are being used in trials in both haematology and oncology.
13. Do you expect the technology to provide clinically meaningful benefits compared with current care? • Do you expect the technology to increase length of life more than current care? • Do you expect the technology to increase health-related quality of life more than current care?	Yes, the response rates are high and about 40% achieve CR for which many are durable. In my clinical experience using glofitamab in clinical trials the patients have minimal side effects, particularly after the first cycle and they describe excellent quality of life.
14. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	The data shows response even across high risk subgroups (eg double hit lymphoma, relapse post CAR T). There are patients which choose to not travel away from home for a month for CAR T and these patients could benefit from glofitamab because it could be delivered in their local hospital.
15. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use? (For example, any concomitant treatments needed, additional clinical requirements, factors affecting patient	Easier that 3rd line CAR T, if glofit is to be used for relapse post CAR T rather than instead of CAR T then hospital staff will need to be trained in the management of CRS but this is straightforward to do.

acceptability or ease of use or additional tests or monitoring needed)	
16. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	A scan (either CT or PET) will identify that the patient has unfortunately progressed and now needs 3rd line treatment. No other testing is required, just this scan which is done at present to identify progression.
17. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation? • Do the instruments that measure quality of life fully capture all the benefits of the technology or have some been missed? For example, the treatment regimen may be more easily administered (such as an oral tablet or home treatment) than current standard of care	Qualitative data from CAR T and palliative care teams have shown that the requirements for a patient to be 2 hours (previously 1 hour) from a CAR T centre for a month is very difficult for patients. Glofitamab will not have this negative impact.
18. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met? • Is the technology a 'step-change' in the management of the condition? • Does the use of the technology address any particular unmet need of the patient population?	Bispecific antibodies are innovative and allow the benefits of lymphoma response by T cell activation without the need for apheresis, manufacture and long inpatient stays for patients. It also allows true "intention to treat" data whereby you would be able to see the patient in clinic and if eligible start treatment within a few days. This technology allow access irrespective of geography in the UK and also access for those patients who have rapid progression of lymphoma who are not stable enough to wait for CAR T manufacture.
19. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	The CRS will require an overnight stay at the beginning of step up dosing (or a long day unit day) but the patients quality of life is otherwise good for this targeted treatment.
20. Do the clinical trials on the technology reflect current UK clinical practice?	In the UK the trials ate currently focusing on achieving durable responses for patients who relapse and using T cell engagers either as bispecific antibodies or cellular therapies is a primary focus of this research.

• If not, how could the results be extrapolated to the UK setting? • What, in your view, are the most important outcomes, and were they measured in the trials? • If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes? • Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	The most important outcomes are PFS, CR rates and durability of the CR as well as the low toxicity profile suggesting that the months gained (if durable response not achieved) allow the patients to remain out of hospital and have good quality of life. I am not aware of any adverse events not reported.
21. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	No
22. Are you aware of any new evidence for the comparator treatment(s) since the publication of NICE technology appraisal guidance [TA649, TA872]?	No
23. How do data on real-world experience compare with the trial data?	Limited real world data at present.
24. NICE considers whether there are any equalities issues at each stage of an evaluation. Are there any potential equality issues that should be taken into account when considering this condition and this treatment? Please explain if you think any groups of people with this condition are particularly disadvantaged. Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or	In my experience patients who live a long way from a CAR T centre and potentially those who have less income to pay for travel may access 3rd line CAR T less and so glofitamab may reduce some of these inequalities.

belief, sex, and sexual orientation or people with any other shared characteristics. Please state if you think this evaluation could • exclude any people for which this treatment is or will be licensed but who are protected by the equality legislation • lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population • lead to recommendations that have an adverse impact on disabled people. Please consider whether these issues are different from issues with current care and why. More information on how NICE deals with equalities issues can be found in the NICE equality scheme. Find more general information about the Equality Act and equalities issues here.	

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Part 2: Technical engagement questions for clinical experts

We welcome your comments on the key issues below, but you may want to concentrate on issues that are in your field of expertise. If you think an issue that is important to clinicians or patients has been missed in the EAR, please also advise on this in the space provided at the end of this section.

The text boxes will expand as you type. Your responses to the following issues will be considered by the committee and may be summarised and presented in slides at the committee meeting.

For information: the professional organisation that nominated you has also been sent a technical engagement response form (a separate document) which asks for comments on each of the key issues that have been raised in the EAR. These will also be considered by the committee.

Table 2 Issues arising from technical engagement

<u>Position of comparator treatments in care pathway</u> Glofitamab was compared to both CAR-T therapy (axi-cel) and polatuzumab with bendamustine and rituximab (pola-BR) in the third-line. Clinical advice to the EAG suggest these treatments are increasingly being used in earlier lines. 1) **Are CAR-T (axi-cel) and pola-BR relevant third-line comparators?** 2) **Would glofitamab be used after CAR-T and/or pola-BR? If glofitamab was used after CAR-T and/or pola-BR, what**	The main 3rd line comparator will be Axi-cel or Tisa-cel and these are now baseline commissioned. Although only in the CDF, patients who are "auto-eligible" and relapse within 12 months of first line treatment, will now be receiving 2nd line Axi-cel following the ZUMA 7 data and availability on the CDF. If patients have Axi-cel 2nd line, they will not be having it 3rd line. The use of Rituximab polatuzumab bendamustine 3rd line will also reduce in view of the availability if polatuzumab in a first line setting. Pixantrone is not used/very infrequently in the UK due to low durability of response and tafasitamab lenalidomide is not reimbursed in the UK. I agree with the EAG that Axi-cel/Tisacel/ Ritux benda pola/ Tafasitamab lenalidomide/ High dose chemo (eg IVE) as a bridge to allogeneic stem cell transplant are all fair comparators but the patient groups are of different risk in the different studies which need to be considered in the response rates.

would the relevant comparators for glofitamab be? **3) If polatuzumab has been used in a previous line(s) of therapy, would this affect the likelihood of pola-BR being used or being effective in third-line treatment?** **4) Will the efficacy of glofitamab be influenced by using CAR-T or polatuzumab in a prior line?**	In my opinion the main benefit of glofitamb is that it is ITT data and patients that are eligible can be treated quickly without the concern for dropout due to PD in the bridging period which we see sometimes with CAR T. The patients who were assigned to axi-cel, but ultimately did not receive the infusion will die from the lymphoma and this is why ITT are important as often efficacy of patients infused with CAR T are discussed. The patients who do not receive infusion of CAR T are usually apheresed and bridged and so these costs still occur as well as the costs os another line of treatment. The number of patients who drop out prior to CAR T are fewer now compared to a few years ago as we are better at patient selection and bridging. If Polatuzumab has been used first line I don't think that it will be used again either as bridging or 3rd line (unless there was a very long duration of response) In the 179 study about a third of patients had received CAR T 3rd line and then Glofit 4th line and the responses seem to be as good and so prior CAR T does not appear to impact on efficacy. Polatuzumab has a different target and so I think it is unlikely that prior polatzumab will impact efficacy but I have not seen clear data.
<u>Patients who do not receive axi-cel infusion</u> The indirect treatment comparison of glofitamab and axi-cel did not include people who were assigned axi-cel but did **not** receive the infusion. **5) What outcomes would you expect for people who are considered for, but do not receive CAR-T therapy?** **6) What resource use requirements would you expect for people who are considered for, but do not receive CAR-T therapy?**	If patients do not receive CAR T (either because of progression during manufacturing or failed manufacturing) it is like that they will die from RR DLBCL in a short number of months. These patients may be started on oral palliative chemotherapy of may receive ritux benda pola. They will usually still come to the hospital for review and management of their symptoms and so would use resource in this setting.

7) What would the outcomes and resource requirements be for these people if they were treated with glofitamab?	These patients should obtain a 40% CR rate (possibly higher as will be 3rd line and the trial had a higher risk group).The patients would have to be admitted for the first dose but after that would attend every 3 weeks as an outpatient for infusion.
Confidence intervals of ITC analyses The unadjusted and adjusted analyses used different methods for calculating their confidence intervals.	
Long-term remission/survivorship The EAG considers that there is insufficient evidence to support long-term remission, survivorship, and cure estimates. The company's economic model assumes that patients alive and progression free after 2 years enter a long-term remission stage (no progression and considered 'cured') and that after 3.5 years people still alive return to near UK general population age-matched mortality risk (most post-progression patients have died at this point). In the EAG's model, they assumed that people who are alive and progression-free after 3 years have a 10% decrement from the age-sex UK general population utilities (quality of life) and a 41% excess mortality from the age-matched UK general population.	Longer term follow up of glofitmab (Dickinson et al ICML), CR of 40% and estimated rate of CR lasting 18 months was 67%. These data support the clinical plausibility of long term remission/survivorship. In a clinical trial setting I have treated patients who durable response has meant that I am optimistic of cure. It is clinically plausible that patients who are alive and progression free at 2 years enter a long-term remission phase. The long term toxicity of T cell engagers are low and patients have similar utility to the general population, especially if they have not had high dose chemo and an autograft in a second line setting. If a patient remains in CR at 2 years I would consider that they are likely to be cured.

8) **When would a patient be considered to be 'cured'?** 9) **Is it clinically plausible that axi-cel, glofitamab, pola-BR or BR could be curative or lead to long-term remission? Is there evidence to support this?** 10) **For a patient who is cured, how would quality of life and mortality be different to the age-matched general population?**	Yes, it is plausible that Axi-cel and glofitamab can be curative. I think that the cure rate for pola-BR is low and in my experience (and UK real world data) patients remain progression free for 4-8 months but then progression. For patients who are cure their QofLife is very similar to the age matched general population. We also know that immunity recovers well and the mortality is similar to the general population.
Average cohort age Background mortality is modelled as a function of the age distribution seen in the NP30179 study but had been partially applied across parameters of the model. EAG suggests applying mortality associated with average cohort age.	
Treatment discontinuation For bendamustine plus rituximab (BR), different sources are used to estimate efficacy (Hong et al 2018) and treatment discontinuation (GO29365 study). These are then used to inform the indirect treatment comparison with glofitamab. The EAG has explored using the GO29365 study to estimate both the efficacy and discontinuation rate of BR.	Most discontinuations occur due to progressive disease in the

11) What is the most suitable source of data for estimating the efficacy and discontinuation rate of BR?	This is difficult because in the UK we use RBP but not benda ritux frequently and so we do have real world data for this and there are limited trial data.
<u>Immune effector cell-associated neurotoxicity syndrome (ICANS)</u> Neurological adverse events consistent with ICANS have been observed in patients treated with glofitamab in NP30179 but not considered in the cost-effectiveness analysis. While this may be appropriate if ICANS were not severe or frequent enough, it is unknown whether these AEs may require additional resource use for monitoring (e.g., access to specialised neurological care units). Furthermore, if specialised critical care is potentially needed as part of the monitoring strategy, this may constrain the setting in which glofitamab can be delivered to NHS centres with such facilities. **12) What are the healthcare costs associated with the management and monitoring of ICANS?** **13) How frequent and how severe is ICANS in this setting?**	The rates of ICANS in the studies are low and in my clinical experience ICANS is not a concern when using bispecifics. This is very different to using CAR T when we must ensure the patient has a carer with them for the first month and the patient cannot drive for 2 months. With bispecifics, ICANS is very rare, so much so that there are no restrictions in driving and no requirements for care giver or ICANS monitoring. In studies, headaches were considered a “neurological event” and this is not the same as true ICANS. When I have used glofitamab on study I have not managed my patients in the same way as CAR T in terms of ICANS risk (and it is not required in the SpC) and I do not think that observation and hospitalisation for ICANS should be included as it is for CAR T. The ICANS in the clinical trial was about 8% with 3% grade 3 or more but this included all “neurological events” including headache and so in practice using glofitamab on trial or via compassionate access I do not monitor for ICANS.
Are there any important issues that have been missed in the EAR?	Not that I am aware of

Part 3: Key messages

In up to 5 sentences, please summarise the key messages of your statement:

Glofitamab has a high CR rate which appears durable

Glofitamab is easy to deliver and can be delivered in most hospitals following training for CRS management

ICANS is very rare and does not require additional costings, patients do not need a carer with them and can drive on treatment.

It is possible that this improves equity of access for patients with RR DLBCL

This data is intention to treat, unlike comparing with CAR T 3rd line which was patients who reached infusion.

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Single Technology Appraisal (STA)

Glofitamab for treating relapsed or refractory diffuse large B-cell lymphoma after 2 or more systemic treatments

[ID3970]

EAG addendum: review of company's response to technical engagement

Produced by	CRD and CHE Technology Assessment Group, University of York, Heslington, York, YO10 5DD
Authors	Pedro Saramago Goncalves, Senior Research Fellow, CHE, University of York Mark Rodgers, Research Fellow, CRD, University of York Shainur Premji, Research Fellow, CHE, University of York Eleonora Uphoff, Research Fellow, CRD, University of York Minyue Gao, Research Fellow, CHE, University of York Helen Fulbright, Information Specialist, CRD, University of York Ana Duarte, Research Fellow, CHE, University of York Mark Simmonds, Senior Research Fellow, CRD, University of York
Correspondence to	Mark Simmonds, Centre for Reviews and Dissemination, University of York, YO10 5DD
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Note on the text

All commercial-in-confidence (CIC) data have been [redacted], all academic-in-confidence (AIC) data are [redacted], all depersonalised data (DPD) are highlighted in pink and underlined.

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Overview

This addendum to the External Assessment Report (EAR) report presents the External Assessment Group's (EAG) critique of the additional evidence provided by the company in their response to a number of key issues that were raised by the EAG in its report, which were discussed at technical engagement. The additional evidence provided by the company also includes updated clinical evidence from the NP30179, for which data from a more recent data cut-off date (16th January 2023) has become available, thus extending the follow-up by 7 months. This addendum also reports the results of the company revised base case results (as corrected by the EAG), and the EAG revised base-case and further exploratory analyses. The technical engagement covered seven key issues for consideration.

Table 1: Summary of the key issues

Issue		Resolved?
1	Position of comparator treatments in care pathway	Yes
2	Patients who do not receive axi-cel infusion	Yes
3	Confidence intervals of ITC analyses	Partly
4	Long-term remission/survivorship	No
5	Average cohort age	No
6	Treatment discontinuation	Yes
7	Immune effector cell-associated neurotoxicity syndrome (ICANS)	No

Description and critique of additional evidence

Issue 1: Position of comparator treatments in care pathway

Glofitamab was compared to CAR-T therapy (axicabatagene-ciloleucel [axi-cel]) and polatuzumab plus bendamustine and rituximab (pola-BR) in third line therapy; both comparator treatments are likely to be increasingly used in earlier lines of therapy.

The EAG suggested that suitable comparators for glofitamab when used after CAR-T and/or polatuzumab should be considered.

The company agreed that the recent recommendations of pola-R-CHP for untreated DLBCL (TA874) [1]and pola-BR for 2L+ DLBCL (TA649)[2] are expected to lead to a further decrease in the usage of pola-BR in the 3L+ setting.

The company did not directly address the likely approval of (CAR-T) therapy for second line treatment for patients who are fit enough for intensive therapy, but did cite clinical experts who consider glofitamab to be particularly valuable in patients who have not responded to CAR-T therapy.

Clinical opinion received during technical engagement (Drs Osborne and Townsend) confirms that CAR-T and Pola-BR are likely to be increasingly used in 2nd line therapy, so glofitamab will be most likely be used subsequently to those treatments, particularly for patients where CART-T therapy has not been successful.

EAG response

Given the absence of relevant efficacy data or explicit cost-effectiveness modelling of the impact of pola-BR or CAR-T at previous lines of therapy, the EAG considers that this issue is resolved for the purposes of technical engagement, but it remains an important area of uncertainty for the evaluation of glofitamab.

Issue 2: Patients who do not receive axi-cel infusion

The EAG noted that the ITC of glofitamab versus axi-cel only included patients who received an axi-cel infusion. However, a proportion of patients eligible for axi-cel will not ultimately receive the infusion. The EAG believes the appraisal should address outcomes and costs in patients who are considered for, but do not receive CAR-T therapy, and the potential impact of treating such patients with glofitamab.

The company agreed with the EAG position, but noted that there are currently no data available to fully assess this issue. The EAG agrees with the company on this point. The company instead supplied survival data from the National CAR-T Clinical Panel (NCCP) on the first 404 patients with R/R DLBCL approved for treatment with either axi-cel or tisagenlecleucel.

In Figure 1 the EAG has combined these NCCP data with the overall survival data from the company's updated data cut, and data from ZUMA-1 (patients who were infused with axi-cel). The plot suggests that overall survival with glofitamab is similar to that of the intention-to-treat population in NCCP (i.e the survival once non-infusion with CAR-T is accounted for). This suggests that glofitamab may have a similar survival expectation to CAR-T therapy once the poor prognosis of patients who do not receive infusion is accounted for. However, the EAG notes that the NCCP data includes patients treated with tisagenlecleucel, so may underestimate the effectiveness of axi-cel alone (as suggested by the ZUMA-1 trial data in Figure 1). It is also a naïve, unadjusted comparison; proper matching might alter the conclusions on relative survival across data sources.

Clinical opinion received during technical engagement (Drs Osborne and Townsend) suggests that glofitamab is most likely to be used subsequent to CAR-T therapy, where this has been unsuccessful. Glofitamab might also be used where patients have disease that is progressing too rapidly to get to CAR-T, in patients deemed ineligible for CAR-T, or to avoid high costs or lengthy travel to attend a centre where CAR-T can be administered. The EAG notes that this positioning fits with the evidence that CAR-T is likely to be superior to glofitamab, where infusion is successful.

Figure 1 Summary of overall survival with CAR-T vs glofitamab

EAG response

As there is no further evidence available that could resolve this issue, the EAG considers it resolved for the purposes of technical engagement, but it remains an important area of uncertainty.

Issue 3: Confidence intervals of ITC analyses

In the company submission, unadjusted ITCs and adjusted MAICS used different and incomparable confidence intervals (standard forms for unadjusted analyses; bootstrap for MAICs). The EAG recommended that unadjusted and MAIC (or propensity score) analyses should use the same methodology to estimate confidence intervals, to ensure comparability, and to allow the EAG to assess the impact on uncertainty from performing adjusted analyses. In response to this issue the company supplied unadjusted ITC analyses, with both standard confidence intervals and bootstrap confidence or credible intervals, for survival (OS and PFS) and response (CR and ORR) outcomes, for the updated January 2023 data cut. For ease of interpretation, these results are summarised alongside the adjusted MAIC and PSA analyses (with bootstrap confidence intervals) in Table 2.

The EAG notes that the bootstrap confidence intervals for the unadjusted analyses are generally narrower that the standard confidence intervals. This is unexpected, as bootstrap intervals are intended to be more robust, and would generally be expected to be wider than standard confidence intervals. It is possible that this is due to the data itself, perhaps if the data are underdispersed compared to what would be expected from normality assumptions. However, without access to data and code, the EAG cannot rule out that there are errors in the calculation of the bootstrap confidence intervals.

Bootstrap confidence intervals in the MAIC and PSA analyses are consistently wider than the bootstrap intervals from the unadjusted analyses. This is as expected given the additional uncertainty in performing adjusted analyses. The EAG is therefore reassured that the adjusted analyses have been performed correctly. However, the bootstrap confidence intervals from the MAICs are still consistently narrower than the standard intervals in unadjusted analyses. This suggests that use of bootstrap intervals may be underestimating the true uncertainty in the MAICs, and confidence intervals ought to be at least as wide as the standard intervals for unadjusted analyses.
The EAG notes that, given the observed results, even with wider confidence intervals, there would be no meaningful impact on any clinical conclusions.

EAG response

The EAG considers the issue to be partly resolved. The EAG is reassured that adjusted analyses have been performed correctly, but remains concerned that the use of bootstrap confidence intervals may be underestimating true uncertainty in adjusted analyses. The EAG notes that wider confidence intervals would be unlikely to change any clinical conclusions.

Table 2 Summary of all ITC analyses vs glofitamab (adjusted and unadjusted) for the January 2023 data cut

Dark green: Glofitamab superior to comparator (statistically significant)
Light green: Glofitamab possibly superior to comparator (not statistically significant)
Yellow: No clear evidence of difference
Light red: Comparator possibly superior to glofitamab (not statistically significant)
Dark red: Comparator superior to glofitamab (statistically significant)

Issue 4: Long-term remission/survivorship

The EAG suggested in the EAR that consideration should be given to the clinical plausibility of long-term remission/ survivorship (i.e. cure) for all treatments under comparison, as well as to the validity of a no cure assumption. The EAG noted that the timing of cure is uncertain as there is no accepted clinical definition for it, and furthermore, if cure is assumed, there is uncertainty around which utility decrement and which excess mortality estimate should be used from the cure point.

Given current levels of evidence and to be consistent with recent NICE appraisals (particularly, TA649),[2] the EAG proposed the following definition of cure be applied in the base-case analysis: long-term remission/survivorship at 3 years (for both PFS and OS) with a 10% decrement from the age-sex UK general population utilities and an excess mortality from the age-matched UK general population mortality based on a SMR of 1.41.

Given the long follow-up required to demonstrate cure, the EAG suggested that scenario analysis assuming no long-term remission/survivorship should also be considered by the committee.

The company disagreed with the EAG that the totality of the existing evidence is currently insufficient to support the clinical plausibility of having patients with relapsed/refractory DLBCL who may be long-term survivors, unless these were treated with a CAR-T cell therapy. The company presented several arguments to support this claim, namely:

a) that the absence of a plateau for all relevant treatments in this appraisal does not imply that this is not clinically plausible for a certain treatment in this disease setting;

b) it is supported by clinical experts consulted by the company for this and for past appraisals, indicating that long-term survival would be independent of the technology in use;

c) it is the company's opinion that the current body of evidence is supportive of the plausibility of having long-term survivors in this population even if not treated with CAR-T therapy. The company provided survival curves for studies SCHOLAR-1, CORAL, JULIET, ZUMA-7, GOYA, POLARYX and for a recent HMRN study to support their claim; and

d) the updated data-cut for NP30179 (Jan 2023 CCOD) provided prolonged OS and PFS data, in which the company considers that the former shows a more sustained plateau starting from ~18 months.

The company clarified also that the EAG's inability to confirm BR PFS plateau on Figure 23 of the CS against the KM data available in the company's electronic model was down to graphical issues within Excel to display appropriately the KM data. The company provided also a rationale for differential PFS (2 years) and OS (3.5 years) time-points.

The company acknowledged also that uncertainty exist around the time-points at which cure could be assumed, highlighting that, as the population of interest for this appraisal is R/R DLBCL, a 2 to 3 year time-point should be more clinically plausible. The company justified that the differential time-points allows the modelling of more clinically plausible post-progression survival estimates, that is, allows OS to revert to background mortality after PFS so that patients in the progressed disease (PD) health state at the selected time threshold for PFS would not to be alive for the entire model time horizon.

Furthermore, the company acknowledged that there is uncertainty around which utility decrement, if any, should be used if cure is assumed. The company highlighted that the use of a utility decrement of 0.1, relative to the general population utilities, reflects the continued impact of former disease related comorbidities in long-term survivors and is likely to represent a conservative assumption. The company also considered that considerations should be given to scenarios where no penalty to HRQoL is applied for long-term survivors. No additional evidence has been presented by the company to inform this issue.

Finally, the company acknowledged that there is uncertainty around which excess mortality estimate should be used to adjust age-matched general population mortality from the cure point, if cure is assumed. The company presented new evidence relating to a recent HMRN analysis reported in the context of NICE TA874[3] (polatuzumab vedotin in combination for untreated DLBCL) for which the results are academic in confidence, but which reported [redacted]. The company also provided new evidence relating to a Danish population based study,[4] which, according to the company, suggested that patients who achieve sustained remission for up to 2 years are considered to experience mortality rates and HRQoL in line with that of the general population. The company believes that greater consideration should be given by the Committee to scenarios using an SMR of 1 (or 1.09, to be conservative), as higher SMRs are likely going to be too pessimistic.

EAG response

The EAG acknowledges the points the company has made about the plausibility of long-term remission/survivorship. While the EAG agrees that long-term remission/survivorship for all treatments under comparison is not clinically implausible and that the external clinical evidence submitted further supports this assumption, we also consider that the assumption of no cure still needs to be considered by the appraisal committee. The EAG notes that at least one previous appraisal in R/R DLBCL has not considered cure for the base-case analysis.[5]
The EAG also considers that the latest glofitamab survival evidence from the NP30179 study (new data-cut, Jan 2023 CCOD) presented by the company does not provide additional evidence to support the existence of a plateau and, thus, the support for a long-term remission/survivorship assumption is still limited. This is supported by the TE response from Dr William Townsend, representing NCRI / Royal College of Physicians, which stated that: "*Longer follow up from NP30179 (presented by Dickinson at ICML June 2023) further supports that many patients who achieve CR have durable remissions with 67% ongoing complete remission at 18 months. While some patients may be cured I anticipate that there will be further progression events and I do not think that 'plateau' has yet been reached in the PFS or DoCR curves. Longer follow up is needed to be clear about the proportion of patients who may be cured with glofitamab*".
The EAG also acknowledges the point made by the company that, if long-term remission/survivorship is assumed, it should be considered independent of technology, to ensure that *"a fair comparison is performed across treatments is made with consistent use of assumptions"*. The EAG agrees with the company's statement around the clinical plausibility of a long-term remission/survival time-point of 3 years and is satisfied that the company has adhered to the EAG's base case.
Given the lack of submission of new evidence, the EAG have nothing further to add in relation to the uncertainty around which utility decrement, if any, should be used if cure is assumed. Analyses in Section 0 of this document, only include a 10% utility decrement when long-term remission/survivorship is assumed.
The EAG does not have access to the full methodology and results of the HMRN analysis referenced by the company in their response to technical engagement to support the company's preferred estimate of excess mortality for long-term survivors (i.e., SMR=1.09). Therefore, we cannot examine the methodology of the study and comment on whether the results could be generalisable to the current appraisal. The EAG's interpretation of the results of the Danish population based study,[4] differs from that of the company. Jakobsen et al (2017)[4] estimated a SMR of 1.27 (95% CI: 1.12; 1.44) for patients with DLBCL achieving post-treatment (i.e. after first-line treatment with R-CHOP or equivalently effective regimen) event-free survival at 24 months (n=1,621). The inclusion criteria for Jakobsen et al (2017), required participants to achieve complete response (confirmed or unconfirmed), so the study

population comprises participant who had survived from diagnosis to first line treatment assessment. This is in contrast with Maurer et al (2014)[6] (SMR=1.09; 95% CI: 0.69;1.74, n=820) and Howlader et al (2017),[7] (SMR=1.41; 95% CI:1.35;1.48; n=18,047), which assessed participants from the point of DLBCL diagnosis. None of these studies are on a R/R DLBCL population, but appraisals committees in previous TAs have considered Howlader et al (2017) to be generalisable to R/R DLBCL; the EAG notes that this is also the study with the largest sample size across these three studies. Thus, the EAG retains the SMR of 1.41 over the general population mortality for the long-term survivors, in our set of preferred assumptions. Nevertheless, the EAG recognises that this is an important area of uncertainty and presents a scenario analysis exploring the impact of an alternative estimate of excess mortality in long-term remission/survivorship, as informed by Jakobsen et al (2017).[4]

Issue 5: Average cohort age

In the economic model, an age distribution approach was preferred by the company as it better reflected heterogeneity in the background mortality of the cohort and the associated background risks of death by age. However, the EAG noted in the EAR that this is a partial implementation of the distributional approach to age, as the age distribution is only reflected on all-cause mortality. A full implementation of the company's preferred approach would have to reflect the age distribution on cancer-related survival and on age-adjusted HRQoL. The company has extended their age distributional analysis approach presented in their original submission (where background mortality was modelled as a function of the age distribution of patients in the NP30179 study) for the estimation of age-adjusted general population utility. The company did not implement the distributional approach for the modelled survival outcomes. The company considers that all nonlinear effects that the distribution of individual event times may have on the final mean survival quantities of interest being estimated in the model are already accounted for in KM survival estimates or fitted parametric survival functions.

EAG response

The EAG acknowledges the efforts by the company at technical engagement to extend this approach from partial to complete by applying it for the estimation of the age-adjusted general population utility in one version of the electronic model.
The EAG explored this matter in a bit more detail. Cohort models typically use the mean age of a cohort of individuals to reflect a representative individual with the condition of interest and, by adding the cycle length to their age at every cycle, reflect how this individual's mortality risk would change over time. However, the EAG acknowledges that if the cohort is thought of as a group of individuals, under differential mortality (by age), the cohort's distribution (of ages at the time of first treatment administration) will change over time. The impact will depend on the how mortality affects ages differentially and on the level of heterogeneity over this.
Whilst acknowledging that the commonly used typical single age cohort-based approach provides only an approximation to the average age of a cohort over time, reflecting such heterogeneity within a cohort model requires careful thought and implementation. The EAG report highlighted that heterogeneity exists over a number of dimensions (HRQoL, costs, etc), which all need to be reflected if heterogeneity is to be modelled appropriately. Due to the (cohort) nature of these models, it is not straightforward to reflect such heterogeneity. Additionally, the "age-distribution" approach applied by the company determines the mean age of the cohort over time but, to do so, uses background risk of mortality, and not the

mortality expected for a cohort with the condition being modelled (i.e. the mortality rates observed in the NP30179 trial). The main reason for this is, possibly, that age dependency (i.e., how R/R DLBCL patient's mortality differs across ages) was not explored in the NP30179 trial (which is not powered to do so). Therefore, given that the calculations proposed by the company do not consider the observed differential mortality risk by age (as per NP30179 study), this will also not reflect an accurate calculation of the mean age of the cohort over time.
The EAG considers that, whilst heterogeneity and differential mortality by age may exist and affect mean outcomes of a cohort over time, the appropriate implementation of such heterogeneity in cohort modelling requires further research, particularly over the conditions under which impact on total costs and total QALYs across treatment comparisons are significant. Therefore, the EAG retains the use of the average cohort age as part of our preferred assumptions.

Issue 6: Treatment discontinuation

The EAG noted that the company's choice of GO29365 study data[8] to model BR individual treatment discontinuation created inconsistencies across the economic model for this comparator. This is because the survival outcomes and estimation of the AE rates of occurrence for BR (and, thus, AE costs), were obtained from a different source (Hong et al (2018)).[9] Thus, drug acquisition and administration costs for BR were derived from the study GO29365, while the BR effectiveness and AE costs were informed by the Hong et al (2018) study.[9]
In response to technical engagement, the company updated the electronic model so that treatment discontinuation is informed by the distribution of patients completing treatment cycles (from 1 to a maximum of 6) in the Hong et al (2018) study.[9] When using this data source to inform treatment discontinuation, the company turns off the half-cycle for the BR time to off treatment (TTOT) outcomes. This is according to the company consistent with how the data in Hong et al (2018) is reported and to avoid underestimating the costs of BR treatment.[9]

EAG response

The EAG considers that the company approach to ensure consistency in data sources used to inform the BR related parameters in the electronic model is appropriate, in the absence of published TTOT KM curves from the Hong et al (2018) study.[9] The EAG also considers appropriate to remove the half-cycle correction from the economic model TTOT outcomes for BR to avoid underestimating treatment costs, given how Hong et al (2018)[9] reported treatment duration. However, the EAG also notes that the use of a half-cycle correction across all treatments under comparison is arguable, given the short cycle length (1 week cycle). For the purpose of technical engagement, the EAG considers this issue to be resolved.

Issue 7: Immune effector cell-associated neurotoxicity syndrome (ICANS)

The EAG noted that the cost of monitoring immune effector cell-associated neurotoxicity syndrome (ICANS) was not considered by the company, and it is uncertain whether this would increase the level of resource use required to monitor patients treated with glofitamab. At technical engagement, the company responded by providing detail on the number, grade, and causality classifications of neurological adverse events (NAEs) consistent with the

American Society for Transplantation and Cellular Therapies (ASCTC) definition of ICANS, from both the June 2022 and January 2023 CCODs of NP30179. Values were in both CCODs were similar and the June 2022 values matched those presented in Table 13, section 3.2.1.7 of the EAG report.
The company confirmed that the cost of ICANS was not considered in the economic analysis as no Grade 3 or higher treatment related ICANS were observed in the D2 [Sub 2]+D3+D5 NP30179 trial cohorts.

EAG response

The company's response supports the EAG's original statements that (a) the rate of ICANS events for glofitamab-treated patients in NP30179 is substantially lower than observed for CAR-T treated patients in a UK real world dataset (vs 36.8% ICANS of any grade), and (b) while the risk of ICANS is probably greatest with the first treatment cycle, the overall risk of ICANS with glofitamab is likely to be low.
The uncertainty raised by the EAG relates to whether, given the available evidence, any specific resource should be dedicated to monitoring or managing ICANS risk when using glofitamab in practice. However, the EAG notes that uncertainty remains around the type of resource use potentially needed to monitor ICANS may also impact on the setting of delivery for glofitamab (See section 4.2.9.8 of the EAR). The company states in response to technical engagement that *"consultation with haematologists who practice at UK CAR-T centres suggests that links to consultant neurologists at the centre are set up but these are rarely used and it is the haematologist who manages ICANS. Therefore it is expected that ICANS management would not be a limiting factor for location of a haematology specialist unit that would deliver glofitamab treatment."* While the EAG does not consider these statements necessarily implausible, this remains an area of uncertainty, which requires independent clinical expert input to resolve. The EAG notes that clinical opinion received during technical engagement (Drs Osborne and Townsend) suggested that the level of healthcare resource use to monitor for ICANS due to glofitamab treatment is lower compared to resources required to monitor for these events in patients treated with CAR-T cell therapy.
It is still unclear why the costs of ICANS for the patients who had Grade=3 ICANS in the safety population of the NP30179 study where not included in the economic analysis, as this appears to meet the criteria for AE inclusion defined by the company. However, this may be because of a mismatch between the safety population and the D2 [Sub 2]+D3+D5 NP30179 trial cohorts. Furthermore, the EAG considers that the greatest uncertainty stems from the potential costs of monitoring for ICANS in the initial cycles of treatment with ICANS, as noted above. The EAG maintains that this uncertainty could have been explored by seeking clinical opinion to inform a sensitivity analysis; the company did not conduct any sensitivity analysis to explore this.

Description and critique of the January 2023 data cut

As part of the technical engagement process the company provided an updated analysis of the main NP30179 trial of glofitamab using data as of January 2023. We summarise that new data analysis here.
Some minor corrections were made to patient characteristics, but the EAG thinks these would not meaningfully alter any conclusions. Overall results for key outcomes were largely unchanged in the new analysis, particularly for complete response (CR), overall response rate (ORR) and overall survival (OS). Results for median progression-free survival (PFS)
Generally, the new data cut provided more robust evidence on long-term duration of

response and survival. The company claimed that the new data cut demonstrates a plateauing effect of survival with longer follow-up. The EAG disputes this claim. Particularly for PFS (Figure 3 of the company's new submission), survival is still declining past 24 months, and data beyond that point is too sparse to draw any conclusions about whether, or when, a plateau would be reached. For OS a "cure" plateau is possible, but uncertain. Data is sparse beyond 30 months follow-up, but long-term survival (e.g. over 5 years), for up to 30% of patients is potentially consistent with the data. The technical engagement response submitted by Dr William Townsend on behalf of the NCRI/Royal College of Physicians reaches a similar conclusion to the EAG in relation to the latest data-cut: "I do not think that 'plateau' has yet been reached in the PFS or DoCR curves. Longer follow up is needed to be clear about the proportion of patients who may be cured with glofitamab".
The company re-performed many of the subgroup analyse from the original submission. The new data cut had no substantial impact on these analyses.
The company provided some limited updated safety data. This was broadly consistent with the data in the original submission.
The company repeated the indirect treatment comparisons using the new data cut. As in the original submission, it appears that adjusted indirect comparisons were successfully adjusted for key patient characteristics. A summary of all indirect treatment comparison results is shown in Table 2. Results are not materially changed from the original submission. The EAG's critique of the analyses is therefore also unchanged (but see Section 2.3: Issue 3 above).
Our conclusions from these analyses are therefore unchanged: Axi-cel is superior to glofitamab in those patients who receive an axi-cel infusion (but see Section 2.2: Issue 2 above). The EAG concludes that there is no evidence of difference between glofitamab and pola-BR, noting that this differs from the company's conclusions. Glofitamab appears to be superior to BR.

Updated modelling assumptions

In response to the issues noted in the EAR, and following the additional analyses undertaken by the company, an updated base-case cost-effectiveness model was presented by the company.
The company's revised model includes some of the corrections made by the EAG and detailed in Section 6.1 of the EAR (Table 45). The company also revised the unit cost of CRS management to (with PAS for tocilizumab), as described in Table 12 of their response to technical engagement. The following EAG-preferred assumptions are incorporated within the company's revised model:

- Issue 6: Treatment discontinuation informed by Hong et al (2018);[9]
- Obinutuzumab is administered as a complex and prolonged treatment at first attendance;
- CAR-T are not available as a post-progression treatment for those initially treated with axi-cel;

The company's base-case also incorporated NICE's preferred assumption for the administration cost of axi-cel, i.e., £41,101 in line with TA895.[10]
In addition, the following issues have been partially accommodated in the company's revised model:

- Issue 4: A single time point after which individuals are assumed to achieve long-term remission/survivorship of 3 years for any of the treatments under comparison and

utility in long-term remission/survivorship corresponds to that of the age-matched UK general population adjusted by a 10% decrement.

The company maintain their original position on the following assumptions:

- Issue 4: Excess mortality over the general populations for the long-term survivors of 9% (SMR=1.09).
- Issue: 5: Background mortality based on age distribution.

The EAG notes that data from the NP30179 trial January data cut was not only used to update treatment effectiveness and safety parameters in the economic model, but updates the following parameters: individual patient baseline characteristics to inform drug acquisition costs, health state utilities, and distribution of post-progression treatments. The company did not provide sufficient detail to allow the EAG to validate these changes. Given this, the constrained timelines of technical engagement and the extensive changes to the data informing the economic model, the EAG could only perform a cursory validation of the model. Therefore, we note this as a limitation affecting the robustness of the company and the EAG analyses results.

Finally, the company introduced an error in the implementation of the severity modifier into the version of the electronic model submitted with their technical engagement response, which is reflected in the results of the analyses presented in the company's response. The EAG reiterates that for analyses where the severity modifier criteria apply, the QALY weights should be applied to the total QALYs of both treatments under comparison (which for a pair-wise comparison is equivalent to applying the QALY weight to the incremental QALYs of one treatment vs. its comparator). Results in the main body of the EAG addendum incorporate the relevant severity modifier, when this is applicable, i.e.:

- Severity modifier of 1.2 for the BR comparison for all analyses;
- Severity of 1.2 for the pola-BR comparison for analyses where no cure is assumed (EAG scenario 2).

Corresponding results to those of these analyses but without the severity modifier are presented in Appendix 0.

Results of the company's corrected cost-effectiveness analysis

The results of the company's corrected base case at technical engagement are summarised in Table 3for the deterministic and Table 4 for the probabilistic results, respectively. These results, as well as those of the EAG' analyses are inclusive of the PAS discounts (simple discounts over list price) for glofitamab ([redacted], polatuzumab ([redacted]), tocilizumab [redacted] and obinutuzumab ([redacted]) but are exclusive of confidential PAS discounts and the Department of Health and Social Care Commercial Medicines Unit (CMU) prices for other comparator and subsequent treatments. Results with PAS discounts and CMU prices for all comparators and subsequent treatments are provided in a confidential appendix separate to this document.

Table 3 Cost-effectiveness results for company's corrected base-case analysis – Deterministic results

	Total Costs	Total LYG	Total QALYs	Incr. Costs	Incr. LYG	Incr. QALYs	ICER (£/ QALY gain)
Glofit vs BR							
Glofit	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BR	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Glofit vs Pola-BR							

	Total Costs	Total LYG	Total QALYs	Incr. Costs	Incr. LYG	Incr. QALYs	ICER (£/ QALY gain)
Glofit							
Pola-BR							
Glofit vs Axi-cel							
Glofit							
Axi-cel							

Abbreviations: Glofit: glofitamab; BR: bendamustine plus rituximab; Pola-BR: polatuzumab vedotin in combination with bendamustine and rituximab; Axi-cel: axicabtagene ciloleucel; LYG: life years gained; QALY: quality-adjusted life year; Inc.: incremental; ICER: incremental cost-effectiveness ratio; NE: northeast quadrant of the cost-effectiveness plane; SE: southeast quadrant of the cost-effectiveness plane; SW: southwest quadrant of the cost-effectiveness plane.

Table 4 Cost-effectiveness results for company's corrected base-case analysis – Probabilistic results

	Total Costs	Total LYG	Total QALYs	Incr. Costs	Incr. LYG	Incr. QALYs	ICER (£/ QALY gain)	Probability of glofitamab being CE*
Glofit vs BR								
Glofit								
BR								
Glofit vs Pola-BR								
Glofit								
Pola-BR								
Glofit vs Axi-cel								
Glofit								
Axi-cel								

*at £20,000 per QALY gained; **Abbreviations**: Glofit: glofitamab; BR: bendamustine plus rituximab; Pola-BR: polatuzumab vedotin in combination with bendamustine and rituximab; Axi-cel: axicabtagene ciloleucel; LYG: life years gained; QALY: quality-adjusted life year; Inc.: incremental; ICER: incremental cost-effectiveness ratio; NE: northeast quadrant of the cost-effectiveness plane; SE: southeast quadrant of the cost-effectiveness plane; SW: southwest quadrant of the cost-effectiveness plane.

Results of the EAG's cost-effectiveness analyses

EAG revised base-case

The EAG revised base-case builds on the company base case and adds assumptions not accepted by the company, namely:

- Issue 4: Excess mortality over the general populations for the long-term survivors of 41% (SMR=1.41).

- Issue: 5: Background mortality based on average cohort age.

Deterministic cost-effective results are presented in Table 5, where the impact of each alternative assumption is reported separately and cumulatively. Probabilistic results of the EAG revised base-case are presented in Table 6.

Table 5 Deterministic cost-effectiveness results for the EAG's preferred model assumptions

Preferred assumption	Incr. cost	Incr. QALYs	Cumulative ICER £/QALY
1. Company's corrected base-case at technical engagement			
Glofit vs BR	[redacted]	[redacted]	[redacted]
Glofit vs Pola-BR	[redacted]	[redacted]	[redacted]
Glofit vs Axi-cel	[redacted]	[redacted]	[redacted]
2. Analysis 1 + Background mortality using average age cohort (37 years TH)			
Glofit vs BR	[redacted]	[redacted]	[redacted]
Glofit vs Pola-BR	[redacted]	[redacted]	[redacted]
Glofit vs Axi-cel	[redacted]	[redacted]	[redacted]
3. Analysis 1 + SMR: 1.41			
Glofit vs BR	[redacted]	[redacted]	[redacted]
Glofit vs Pola-BR	[redacted]	[redacted]	[redacted]
Glofit vs Axi-cel	[redacted]	[redacted]	[redacted]
4. EAG revised base-case: Analysis 2 + SMR: 1.41			
Glofit vs BR	[redacted]	[redacted]	[redacted]
Glofit vs Pola-BR	[redacted]	[redacted]	[redacted]
Glofit vs Axi-cel	[redacted]	[redacted]	[redacted]

Table 6 Probabilistic cost-effectiveness results for the EAG's preferred set of model assumptions

Preferred assumption	Incr. cost	Incr. QALYs	ICER £/QALY	Probability of glofitamab being CE*
EAG revised base-case				
Glofit vs BR	[redacted]	[redacted]	[redacted]	[redacted]
Glofit vs Pola-BR	[redacted]	[redacted]	[redacted]	[redacted]
Glofit vs Axi-cel	[redacted]	[redacted]	[redacted]	[redacted]

* at £20,000 per QALY gained; Abbreviations: CE, cost-effective

EAG further analyses

The EAG scenario analysis builds on the EAG base-case and evaluates the impact of alternative assumptions relating to assumption over the long-term remission/survivorship, namely:

- Issue 4: EAG scenario1 - Excess mortality over the general populations for the long-term survivors of 27% (SMR=1.27).
- Issue: 4: EAG scenario 2 - No cure is assumed.

Table 7 Summary of deterministic cost-effectiveness results for scenarios over EAG base-case for EAG scenarios 1 and 2: assuming 1) SMR=1.27, and 2) no cure

Varied assumption	Incr. cost	Incr. QALYs	Cumulative ICER £/QALY
1. EAG base-case + SMR: 1.27			
Glofit vs BR	[redacted]	[redacted]	[redacted]
Glofit vs Pola-BR	[redacted]	[redacted]	[redacted]
Glofit vs Axi-cel	[redacted]	[redacted]	[redacted]
2. EAG base-case + No cure			
Glofit vs BR	[redacted]	[redacted]	[redacted]
Glofit vs Pola-BR	[redacted]	[redacted]	[redacted]
Glofit vs Axi-cel	[redacted]	[redacted]	[redacted]

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Appendix

This appendix presents the results without severity modifier for analyses corresponding to those presented in Section 0 (with the exception of the probabilistic analyses, due to time constraints of the technical engagement).

Table 8 Cost-effectiveness results for company's corrected base-case analysis – Deterministic

	Total Costs	Total LYG	Total QALYs	Incr. Costs	Incr. LYG	Incr. QALYs	ICER (£/QALY gain)
Glofit vs BR							
Glofit	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BR							
Glofit vs Pola-BR							
Glofit	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pola-BR							
Glofit vs Axi-cel							
Glofit	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Axi-cel							

Abbreviations: Glofit: glofitamab; BR: bendamustine plus rituximab; Pola-BR: polatuzumab vedotin in combination with bendamustine and rituximab; Axi-cel: axicabtagene ciloleucel; LYG: life years gained; QALY: quality-adjusted life year; Inc.: incremental; ICER: incremental cost-effectiveness ratio; NE: northeast quadrant of the cost-effectiveness plane; SE: southeast quadrant of the cost-effectiveness plane; SW: southwest quadrant of the cost-effectiveness plane.

Table 9 Deterministic cost-effectiveness results for the EAG's preferred model assumptions

Preferred assumption	Incr. cost	Incr. QALYs	Cumulative ICER £/QALY
1. Company's corrected base-case at technical engagement			
Glofit vs BR	[redacted]	[redacted]	[redacted]
Glofit vs Pola-BR	[redacted]	[redacted]	[redacted]
Glofit vs Axi-cel	[redacted]	[redacted]	[redacted]
2. Analysis 1 + Background mortality using average age cohort (37 years TH)			
Glofit vs BR	[redacted]	[redacted]	[redacted]
Glofit vs Pola-BR	[redacted]	[redacted]	[redacted]
Glofit vs Axi-cel	[redacted]	[redacted]	[redacted]
3. Analysis 1 + SMR: 1.41			
Glofit vs BR	[redacted]	[redacted]	[redacted]
Glofit vs Pola-BR	[redacted]	[redacted]	[redacted]
Glofit vs Axi-cel	[redacted]	[redacted]	[redacted]
4. EAG base-case: Analysis 2 + SMR: 1.41			
Glofit vs BR	[redacted]	[redacted]	[redacted]
Glofit vs Pola-BR	[redacted]	[redacted]	[redacted]
Glofit vs Axi-cel	[redacted]	[redacted]	[redacted]

Table 10 Summary of deterministic cost-effectiveness results for scenarios over EAG base-case for EAG scenarios 1 and 2: assuming 1) SMR=1.27, and 2) no cure

Varied assumption	Incr. cost	Incr. QALYs	Cumulative ICER £/QALY
1. EAG base-case + SMR: 1.27			
Glofit vs BR	[redacted]	[redacted]	[redacted]
Glofit vs Pola-BR	[redacted]	[redacted]	[redacted]
Glofit vs Axi-cel	[redacted]	[redacted]	[redacted]
2. EAG base-case + No cure			
Glofit vs BR	[redacted]	[redacted]	[redacted]
Glofit vs Pola-BR	[redacted]	[redacted]	[redacted]
Glofit vs Axi-cel	[redacted]	[redacted]	[redacted]