Medicinrådet

Bilag til Medicinrådets vurdering af glofitamab i kombination med gemcitabine og oxaliplatin til behandling af diffust storcellet B-cellelymfom, ikke nærmere specificeret (DLBCL NOS)

Vers. 1.0

Bilagsoversigt

1. Ansøgers notat til Rådet vedr. glofitamab i kombination med gemcitabin og oxaliplatin
2. Forhandlingsnotat fra Amgros vedr. glofitamab i kombination med gemcitabin og oxaliplatin
3. Ansøgers endelige ansøgning vedr. glofitamab i kombination med gemcitabin og oxaliplatin

Response to the DMC assessment report

Response to concerns regarding study population characteristics and impact on ITT results

Roche acknowledges the concern that the inclusion of patients potentially eligible for CAR-T or ASCT could introduce bias. However, extensive analyses demonstrate that the overall ITT results are highly robust and do not overestimate the treatment effect.

Impact of eligibility criteria on outcomes

Exploratory post-hoc analyses were conducted to assess the impact of specific eligibility criteria:

- **CAR-T eligibility:** Analyses comparing countries with and without CAR-T candidate exclusion criteria, as well as splitting the ITT population into CAR-T eligible vs. ineligible patients (based on EU-approved indications), indicated that these criteria did not significantly impact results of STARGLO. Efficacy outcomes across these subgroups were consistent with the overall ITT population.
- **ASCT ineligibility (including patient refusal):** The justification for including patient refusal was examined. While 95 patients cited refusal, clinical adjudication algorithm revealed that 66 of these also had additional clinical reasons for ASCT non-candidacy. Exploratory analyses of these patients showed OS, PFS, and CR rates comparable to the overall ITT population.

Robustness confirmed by Multivariable Analysis (MVA)

To rule out the possibility that imbalances in baseline prognostic factors drove the observed efficacy, an MVA was performed. This analysis adjusted for key risk factors, including geographic region, IPI score, bulky disease (≥10 cm), SPD, prior lines of therapy, refractory status, and sex. After adjusting for these factors, the MVA demonstrated a highly consistent and significant OS benefit for Glofit-GemOx, with an OS HR of 0.63.

Comparison with the NIVEAU study (external validation)

To further validate the ITT population, baseline characteristics and outcomes were compared to the Phase 3 NIVEAU study, conducted in a similar transplant-ineligible R/R DLBCL population in Europe. The comparison demonstrated that the STARGLO ITT population is highly comparable to the NIVEAU population. Furthermore, the efficacy outcomes for the R-GemOx control arm in STARGLO were consistent with the R-GemOx arm in NIVEAU. As recognized by the EMA, these consistencies show that STARGLO did not overestimate efficacy due to a fitter patient population.

Conclusion

The clinical data confirm that the inclusion of specific subgroups did not overestimate the treatment effect. The STARGLO ITT population is highly representative of European R/R DLBCL patients, supporting the EMA's decision to grant full authorisation based on the demonstrated clinically meaningful benefits.

Response to the DMC's conclusion on efficacy

Long-term efficacy of Glofit-GemOx

The DMC expresses uncertainty regarding the long-term effect of Glofit-GemOx, despite the survival plateau in the 3-year data. Roche wishes to address these points by highlighting the following evidence:

- **Robust survival plateau:** The 3-year data (median follow-up 35.1 months) shows a doubling of the median OS from 12.5 to 25.5 months. At 36 months, 41 patients remain at risk in the Glofit-GemOx arm vs. 10 in the control arm. The plateau is sustained by a substantial group, not by outliers.
- **Adjustment for subsequent therapies (NALT):** An Inverse Probability of Censoring Weighting (IPCW) analysis was performed to isolate the impact of Glofit-GemOx from NALT. When adjusting to remove the

effect of NALT, the OS HR improved from 0.62 to 0.42. This confirms the survival advantage is inherently tied to Glofit-GemOx and indicates the control arm derived the greatest survival benefit from subsequent therapies.

- **Independent disease control:** Before any subsequent interventions, the PFS (censored before NALT) for Glofit-GemOx was 14.4 months vs. 3.3 months in the control arm. Finally, 58.5% of Glofit-GemOx patients achieved a Complete Response (CR), and the median duration of response (DOCR) has not yet been reached, reflecting a very deep and long-lasting response.

Regional subgroup analyses

The DMC acknowledges an expected relative effect difference for Danish patients but notes uncertainty regarding the magnitude, placing emphasis on geographical subgroup analyses. Roche believes it is necessary to provide further nuance regarding these results:

- **Study power:** STARGLO was powered for the ITT population. Small subgroups are not powered to conclusively assess outcomes, as reflected in the wide confidence intervals.
- **Randomization and stratification:** These subgroups were not defined by stratification variables. Interpretation of non-stratified results is inherently uncertain, as analyzing these subsets breaks the benefits of randomization.
- **Multiplicity:** Given the large number of subgroups examined, numerical inconsistencies in OS could arise purely by chance.

Impact of NALT

In response to regional numerical differences, Roche's exploratory post-hoc analyses—previously presented to the EMA and DMC—identified baseline characteristics, NALT, and COVID-19 as primary confounders. While the DMC focuses on baseline differences, Roche notes that NALT was a major confounding factor that disproportionately impacted efficacy outcomes by influencing the performance of the control arm (R-GemOx):

- **Frequency and initiation:** Across all regions, NALT was initiated more frequently and earlier in the R-GemOx arm. The longer time to NALT initiation for Glofit-GemOx indicates superior disease control that delayed the need for salvage therapies.
- **Regional variations:** In Europe, 46.2% of R-GemOx patients received highly efficacious subsequent therapies (e.g., CAR-T, bispecifics) compared to 34.6% in the Rest of World (RoW) subgroup.
- **Contribution to OS:** Swimlane plots reveal NALT contributed significantly more to OS for R-GemOx patients. In Europe, the median survival time while on NALT was 8.7 months for R-GemOx, vs. 4.3 months for Glofit-GemOx.
- **Adjustment for NALT:** IPCW analyses adjusting for NALT showed consistent OS benefit for Glofit-GemOx (HR < 1) across all regions, including Europe. Similarly, Event-Free Survival (EFS) analysis consistently showed improved HRs favoring Glofit-GemOx.

Interpretation of interaction tests

Regarding the interaction tests mentioned by the DMC, STARGLO was neither designed nor powered to test for subgroup interactions. These post-hoc analyses, conducted without adjustment for multiplicity, are subject to significant uncertainty. The FDA has remarked that these results should be interpreted with caution as hypothesis-generating rather than conclusive.

Conclusion

Observed regional differences should be interpreted with caution due to the lack of power and absence of stratification. Post-hoc analyses demonstrate that when correcting for the confounding effects of NALT, a consistent treatment benefit for Glofit-GemOx is observed across all geographic regions, including Europe.

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28.05.2026

LSC/DBS

Forhandlingsnotat

Dato for behandling i Medicinrådet	24.06.2026
Leverandør	Roche
Lægemiddel	Columvi (glofitamab)
Ansøgt indikation	Glofitamab i kombination med gemcitabin og oxaliplatin til behandling af voksne patienter med recidiverende eller refraktært diffust storcellet B-celle lymfom, ikke nærmere specificeret (DLBCL NOS), som er uegnede til autolog stemcelletransplantation (ASCT).
Nyt lægemiddel / indikationsudvidelse	Indikationsudvidelse

Prisinformation

Amgros har forhandlet følgende pris på Columvi:

Tabel 1: Forhandlingsresultat

Lægemiddel	Styrke (pakningsstørrelse)	AIP (DKK)	Nuværende SAIP, (DKK)	Nuværende rabat ift. AIP	Forhandlet SAIP (DKK)	Forhandlet rabat ift. AIP
Columvi	2,5 mg (1 stk.)	6.228,98	[redacted]	[redacted]	[redacted]	[redacted]
Columvi	10 mg (1 stk.)	24.624,72	[redacted]	[redacted]	[redacted]	[redacted]

Prisen er betinget af Medicinrådets anbefaling. Det betyder, at hvis Medicinrådet ikke anbefaler Columvi, indkøbes lægemidlet til nuværende SAIP.

Aftaleforhold

Amgros har en aftale på Columvi. Aftalen gælder frem til den 31.12.2026. Der er inkluderet mulighed for prisregulering i aftalen.

[redacted]

Konkurrencesituationen

Nuværende standardbehandling er forskellige rituximab-baserede kemoterapier bl.a. rituximab i kombination med gemcitabin og oxaliplatin (R-GemOx).

Både Columvi og rituximab gives i kombination med gemcitabin og oxaliplatin. Kombinationslægemidlerne gemcitabin og oxaliplatin er derfor ikke inkluderet i beregningen af de årlige lægemiddeludgifter.

Tabel 2 viser lægemiddeludgifter til et behandlingsforløb med hhv. Columvi og rituximab. Bemærk at behandlingsvarigheden er forskellig for de to lægemidler. Columvi gives i maksimalt 12 serier af hver 3 ugers varighed, mens rituximab gives i maksimalt 8 serier af hver 3 ugers varighed.

Den gennemsnitlige behandlingsperiode for Columvi er 6,1 måneder, mens den gennemsnitlige behandlingsperiode for rituximab er 3,2 måneder, jf. Medicinrådets vurdering af glofitamab i kombination med gemcitabine og oxaliplatin til behandling af diffust storcellet B-cellelymfom, ikke nærmere specificeret (DLBCL NOS).

Tabel 2: Sammenligning af lægemiddeludgifter pr. patient for en gennemsnitlig behandlingsperiode

Lægemiddel	Styrke (pakning)	Dosering*	Pris pr. pakning (SAIP, DKK)	Lægemiddeludgift pr. behandlingsperiode (SAIP, DKK)
Columvi (glofitamab)	2,5 mg (1 stk.) 10 mg (1 stk.)	Opstart: 2,5 mg på dag 8, 10 mg på dag 15 i cyklus 1, i.v. Derefter 30 mg på dag 1 i hver cyklus, i.v. Behandlingsperiode: 6,1 mdr.	[redacted]	[redacted]
Ruxience (rituximab)	500 mg (1 stk.)	375 mg/m^2 hver 3. uge, i.v.** Behandlingsperiode: 6,1 mdr.	[redacted]	[redacted]

*Cykluslængde: 21 dage (3 uger)

**Kropsoverfladeareal (BSA) 1,97m^2 jf. Medicinrådets anbefaling vedrørende axicabtagene ciloleucel til andenlinjebehandling af patienter med DLBCL

Status fra andre lande

Tabel 3: Status fra andre lande

Land	Status	Link
Norge	Ikke anbefalet	Link til vurdering
England	Anbefalet	Link til vurdering
Sverige	Anbefalet	Link til vurdering

Opsummering

Amgros har en gældende aftale på Columvi.

[redacted]

Application for the assessment of Columvi (glofitamab) in combination with gemcitabine and oxaliplatin for the treatment of adult patients with relapsed or refractory diffuse large B-cell lymphoma not otherwise specified, who are ineligible for autologous stem cell transplant

Color scheme for text highlighting	
Color of highlighted text	Definition of highlighted text
	Confidential information
[Other]	[Definition of color-code]

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Tables and Figures

Abbreviations

ABC	activated B-cell-like
AE	adverse event
AESI	adverse event of special interest
AIC	Akaike Information Criterion
Ara-C	cytarabine
ASCT	autologous stem-cell transplant
AUC	area under curve

Axi-cel	Axicabtagene ciloleucel
BIC	Bayesian Information Criterion
CAR-T	chimeric antigen receptor T-cell
CCOD	clinical cut-off date
CD	cluster of differentiation
CEA	Cost Effectiveness Analysis
CHMP	Committee for Medicinal Products for Human Use
CI	confidence interval
CMH	Cochran-Mantel-Haenszel
CR	complete response
CRS	cytokine release syndrome
DLBCL	diffuse large B-cell lymphoma
DLG	Danish Lymphoma Group
DMC	Danish Medicines Council
DOCR	duration of complete response
DOR	duration of response
DRG	Diagnosis-Related Group
DSA	deterministic sensitivity analysis
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group performance status
EMA	European Medicines Agency
EORTC QLQ-C30	European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30
EuroQoL EQ-5D-5L	European Quality of Life 5-Dimension 5-Level Version questionnaire
Fab	fragment antigen-binding
FACT-Lym LymS	Functional Assessment of Cancer Therapy-Lymphoma Lymphoma Subscale
GCB	germinal center B-cell

GemOx	gemcitabine plus oxaliplatin
GHS	global health status
Glofit-GemOx	glofitamab combined with gemcitabine and oxaliplatin
HR	hazard ratio
HRQoL	health-related quality of life
HSCT	hematopoietic stem-cell transplant
HSUV	health state utility value
HTA	health technology assessment
ICANS	immune effector cell-associated neurotoxicity syndrome
ICER	incremental cost-effectiveness ratio
INV	investigator
IPD	individual patient data
IPI	International Prognostic Index
IQR	interquartile range
IRC	independent review committee
ITT	intention-to-treat
KM	Kaplan–Meier
LDH	lactate dehydrogenase
Liso-cel	Lisocabtagene maraleucel
LYFO	Danish Lymphoma Database
MCAR	Missing Completely at Random
NALT	new anti-lymphoma treatment
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NE	not estimable
NHL	non-Hodgkin’s lymphoma
NICE	National Institute for Health and Care Excellence
NOS	not otherwise specified

ORR	objective response rate
OS	overall survival
PCR	polymerase chain reaction
PD	progressed disease
PET-CT	positron emission tomography-computed tomography
PFS	progression-free survival
Pola+BR	polatuzumab, bendamustine, rituximab
PPS	post-progression survival
PR	partial response
PRO	patient-reported outcome
PS	Performance status
PSA	probabilistic sensitivity analysis
PSM	partitioned survival model
PT	preferred term
QALY	quality-adjusted life year
QoL	quality of life
R/R	relapsed or refractory
R-CHOP	rituximab with cyclophosphamide, doxorubicin, vincristine and prednisone
RCT	randomized controlled trial
R-DHAP	rituximab, cisplatin, cytarabine, dexamethasone
R-GDP	rituximab, cisplatin, gemcitabine, dexamethasone
R-GemOx	rituximab combined with gemcitabine and oxaliplatin
R-ICE	rituximab, ifosfamide, carboplatin, etoposide
SAE	serious adverse event
SAP	statistical analysis plan
SCT	stem-cell transplantation
SD	standard deviation

SE	Standard Error
SmPC	Summary of Product Characteristics
SMR	Standardized Mortality Ratio
TLS	tumor lysis syndrome
TTD	time to deterioration
VAS	visual analogue scale
WHO	World Health Organization

1. Regulatory information on the medicine

Overview of the medicine	
Proprietary name	Columvi
Generic name	Glofitamab
Therapeutic indication as defined by EMA	Glofitamab in combination with gemcitabine and oxaliplatin is indicated for the treatment of adult patients with relapsed or refractory diffuse large B-cell lymphoma not otherwise specified (R/R DLBCL NOS), who are ineligible for autologous stem cell transplant (ASCT)
Marketing authorization holder in Denmark	Roche Registration GmbH, Emil-Barell-Strasse 1, 79639 Grenzach-Wyhlen,Tyskland
ATC code	L01FX28
Combination therapy and/or co-medication	Combination therapy (glofitamab in combination with gemcitabine and oxaliplatin)
(Expected) Date of EC approval	April 14, 2025
Has the medicine received a conditional marketing authorization?	Columvi received conditional marketing authorization for 3L+ DLBCL monotherapy due to its public health benefit and ability to meet an unmet medical need, despite less comprehensive data than normally required.
Accelerated assessment in the European Medicines Agency (EMA)	No
Orphan drug designation (include date)	Columvi received EU orphan designation for DLBCL on 15 Oct 2021, which was withdrawn on 19 Mar 2025.
Other therapeutic indications approved by EMA	Columvi as monotherapy is indicated for the treatment of adult patients with R/R DLBCL, after two or more lines of systemic therapy.
Other indications that have been evaluated by the DMC (yes/no)	Columvi as monotherapy for the treatment of adult patients with R/R DLBCL, after two or more lines of systemic therapy.
Joint Nordic assessment (JNHB)	Not relevant for JNHB, as the current treatment practices are not similar across the Nordic countries.
Dispensing group	BEGR

Overview of the medicine	
Packaging – types, sizes/number of units and concentrations	Columvi 2.5 mg concentrate for solution for infusion. Each vial of 2.5 mL of concentrate contains 2.5 mg of glofitamab at a concentration of 1 mg/mL. Columvi 10 mg concentrate for solution for infusion. Each vial of 10 mL of concentrate contains 10 mg of glofitamab at a concentration of 1 mg/mL.

2. Summary table

Summary	
Indication relevant for the assessment	Glofitamab in combination with gemcitabine and oxaliplatin (Glofit-GemOx) is indicated for the treatment of adult patients with R/R DLBCL NOS, who are ineligible for ASCT.
Dosage regimen and administration	Obinutuzumab 1000 mg intravenously (IV) is given on Day 1, 7 days before the first glofitamab dose. Treatment follows 21-day cycles: **Cycle 1:** Gemcitabine IV 1000 mg/m² + oxaliplatin IV 100 mg/m² (Day 2), Glofitamab IV 2.5 mg (Day 8), 10 mg (Day 15) **Cycles 2-8:** Glofitamab IV 30 mg + gemcitabine IV 1000 mg/m² + oxaliplatin IV 100 mg/m² **Cycles 9-12:** Glofitamab IV 30 mg
Choice of comparator	The comparator in the phase III clinical trial, STARGLO (NCT04408638), is rituximab-gemcitabine-oxaliplatin (R-GemOx). As this aligns with Danish clinical practice, R-GemOx will be used as the comparator in this application R-GemOx is administered every 3 weeks for 8 cycles: Rituximab IV at 375 mg/m^2, gemcitabine IV at 1000 mg/m^2 and oxaliplatin IV at 100 mg/m^2.
Prognosis with current treatment (comparator)	DLBCL is an aggressive malignancy that typically responds to first-line therapy (R-CHOP); however, approximately 30-40% of patients develop R/R disease. In these patients, the disease course is generally progressive and associated with significantly reduced life expectancy and impaired health-related quality of life. Prognosis is particularly poor for those ineligible for ASCT or chimeric antigen receptor T-cell (CAR-T) therapy. Published data indicate that median overall survival (OS) in this population is typically less than 12 months in the second-line (2L) setting, and even shorter in third-line or later (3L+), depending on patient fitness, disease biology, and treatment intensity (1-3). These outcomes highlight the need for more effective therapeutic options for this patient group.

Summary	
Type of evidence for the clinical evaluation	Head-to-head, phase III, randomized controlled trial (STARGLO) in patients with R/R DLBCL NOS ineligible for ASCT.
Most important efficacy endpoints (Difference/gain compared to comparator)	**Overall survival (OS):** [redacted] **Independent review committee (IRC)-assessed progression-free survival (PFS):** [redacted] **Complete response (CR) rate:** [redacted] **Duration of complete response (DOCR):** [redacted]
Most important serious adverse events for the intervention and comparator	Cytokine release syndrome (CRS): 19.4% with Glofit-GemOx vs 0%; Pneumonia: 6.7% vs 4.5%; Pyrexia: 6.1% vs 1.1%
Impact on health-related quality of life	Based on EQ-5D-5L shows no statistically significant difference in QoL. At base the difference is [redacted], at cycle 7 the difference is [redacted] and at 12 months of follow up the difference is [redacted]. In the health economic model, the utility is assumed to be dependent on health states and is assumed equal. Differences will arise indirectly as Glofit-GemOx survival and progression-free survival compared to GemOx.
Type of economic analysis that is submitted	Type of analysis: Cost-utility Type of model: Partitioned survival model
Data sources used to model the clinical effects	STARGLO study (4)
Data sources used to model the health-related quality of life	STARGLO study (4)
Life years gained	[redacted]
QALYs gained	[redacted]
Incremental costs	[redacted]

Summary	
ICER (DKK/QALY)	[redacted]
Uncertainty associated with the ICER estimate	Extrapolation and long-term survivor.
Number of eligible patients in Denmark	40 new patients a year.
Budget impact (in year 5)	[redacted]

3. The patient population, intervention, choice of comparator and relevant outcomes

3.1 The medical condition

Overview

Diffuse large B-cell lymphoma (DLBCL) is the most common lymphoid malignancy in adults and accounts for approximately 35% of all non-Hodgkin lymphomas (NHL), with an annual incidence of around 500 new cases in Denmark (5). The disease primarily affects older adults, with a median age at diagnosis of 67 years (5, 6) although it can also occur in younger individuals (7). While DLBCL is considered aggressive, it is potentially curable with standard immunochemotherapy. Without treatment, life expectancy is less than one year (8), but with first-line (1L) therapy, 60-65% of patients can achieve cure (5, 9, 10).

DLBCL typically arises de novo but may also represent transformation from indolent B-cell lymphomas, such as follicular lymphoma. Morphologically, it is characterized by large neoplastic B cells that grow in a diffuse pattern and disrupt normal tissue architecture (8). Based on molecular, immunophenotypic, and cytogenetic features, several subtypes exist, including the germinal center B-cell-like (GCB) and activated B-cell-like (ABC) subtypes, although these currently do not influence treatment decisions in routine Danish practice (6, 11, 12).

Clinical presentation

DLBCL often presents with rapidly enlarging lymph nodes or masses at extranodal sites such as the gastrointestinal tract, head and neck, or skin (13, 14). Bone marrow involvement occurs in 10-30% of cases (14). Systemic symptoms include fever, night

sweats, fatigue, weight loss, loss of appetite, and extreme itchiness (8, 15) and these can significantly impair patients' health-related quality of life (HRQoL) (16).

Relapsed disease is defined by new lesions after complete response and return of symptoms. Refractory disease refers to persistent progression despite treatment (17).

Diagnosis and risk stratification

DLBCL is diagnosed through surgical biopsy, typically of an involved lymph node or extranodal site. Histopathological evaluation follows WHO classification criteria, which integrate cytological, immunophenotypic, genetic, and clinical features (11). Diagnosis is confirmed by immunohistochemistry or flow cytometry, and in cases of diagnostic uncertainty – such as limited tissue or non-representative phenotypes – polymerase chain reaction (PCR) testing for B-cell clonality may be used (14). Staging with positron emission tomography-computed tomography (PET-CT), based on the Ann Arbor Classification, is essential for prognosis and treatment planning. Approximately 70% of patients present with advanced-stage disease (stage III or IV) at diagnosis (9). In relapsed disease, biopsy confirmation is required, typically by core needle sampling, followed by full restaging using the same diagnostic procedures (14).

The International Prognostic Index (IPI) remains a key clinical tool for assessing risk in patients with DLBCL. It incorporates five baseline factors: age, serum lactate dehydrogenase (LDH) level, Eastern Cooperative Oncology Group (ECOG) performance status, Ann Arbor stage, and number of extranodal (8, 14). The age-adjusted IPI is used for younger patients and includes a simplified set of three risk factors. Although IPI does not guide treatment selection in the R/R setting, it continues to provide important prognostic information.

Burden of disease

DLBCL is a fast-growing (aggressive) lymphoma, but it often responds well to first-line treatment. The standard 1L regimen – rituximab plus cyclophosphamide, doxorubicin, vincristine and prednisone (R-CHOP) – is potentially curative. Nevertheless, around 30-40% of patients relapse or are refractory to treatment (5, 9, 10, 18). Relapsed or refractory disease is associated with poor outcomes and contributes significantly to DLBCL-related morbidity and mortality (8). Most relapses occur within 12-18 months of initial treatment. Second-line (2L) treatment options include chimeric antigen receptor T-cell (CAR-T) therapy, rituximab-based salvage chemotherapy, and autologous stem cell transplantation (ASCT). However, long-term survival is achieved in only a minority of patients (19, 20).

The prognosis for patients with R/R DLBCL who are ineligible for ASCT or CAR-T therapy remains poor. Published data show that median overall survival (OS) in this population is typically less than 12 months in the 2L setting and even shorter in later lines of therapy, depending on fitness, comorbidities, and disease biology (1-3, 21, 22). In a Danish population-based study, the 5-year OS for patients treated with salvage chemotherapy was 31%. This varied by transplant eligibility: 46% in patients who received ASCT versus 18% in those who did not (2). More recent data from Al-Mashhadi et al. (2024) report a median OS of 5.8 months and a 2-year OS of 25.1% in the third-line or later (3L+) population, emphasizing the limited benefit of available therapies in this setting.

The disease course is often debilitating. Constitutional symptoms, lymphadenopathy, and bone marrow failure can lead to infections, anemia, thrombocytopenia, organ failure, and death. In addition, treatment-related side effects – particularly from repeated cycles of chemotherapy – add to the clinical burden. Patients undergoing more intensive regimens report greater incidences of neuropathy, dyspnea, and pain (23). Combined, these factors negatively impact HRQoL (24, 25), reinforcing the need for more effective and tolerable treatment alternatives.

3.2 Patient population

Glofit-GemOx is indicated for the treatment of adult patients with R/R DLBCL NOS, who are ineligible for ASCT (26). The European Commission granted formal approval on April 14, 2025, based on results from the Phase III STARGLO study. This study included patients with DLBCL NOS who had relapsed after, or were refractory to, one or more prior lines of systemic therapy (27).

Patient characteristics

Danish registry studies demonstrate that a substantial proportion of patients with R/R DLBCL are elderly, have comorbidities, poor performance status, and present with early relapse or primary refractory disease. These factors significantly limit eligibility for intensive therapies such as ASCT or CAR-T therapy (1, 2).

In the study by Arboe et al., which evaluated 277 patients treated for R/R DLBCL following rituximab-based therapy, the median age was 65 years, and only 46% of patients receiving salvage chemotherapy proceeded to ASCT. Among those who did not, the median age was 62 years, 48% had primary refractory disease, 24% had ≥2 comorbidities, and 63% were male. Age ≥65, comorbidity burden, and primary refractory disease were all independently associated with reduced likelihood of undergoing ASCT. Patients receiving non-salvage therapy were older still (median age 74 years), more frequently single, and more likely to have multiple comorbidities (2).

Similarly, in a Danish population-based study by Al-Mashhadi et al., which included 189 patients with ≥3L R/R DLBCL, the median age was 71 years; 76% were refractory to previous line of therapy, and 29.6% had an ECOG performance status ≥2 (1).

Together, these findings underscore that many patients requiring 2L or later therapy – particularly those ineligible for ASCT or CAR-T therapy – represent a population with significant clinical unmet need.

Incidence and prevalence

According to the 2023 annual report from the Danish Lymphoma Group (DLG) and the Danish Lymphoma Registry (LYFO), approximately 500 patients are diagnosed with DLBCL annually in Denmark (5).

Based on insights from clinical experts (28) and their familiarity with LYFO data, it is estimated that approximately 15% of DLBCL patients progress to 2L therapy, corresponding to around 75 patients per year. Of these, an estimated 25 patients are

considered fit for treatment but ineligible for ASCT or CAR-T therapy, representing the population that could benefit from Glofit-GemOx (28).

In the 3L setting, it is further estimated that 6-10% of DLBCL patients progress to 3L therapy, corresponding to approximately 30-50 patients per year (28). Among these, an estimated 15 patients are considered fit for treatment with Glofit-GemOx (28).

Incidence and prevalence data in the past five years are presented in Table 1. The expected number of patients eligible for treatment with Glofit-GemOx in the five coming years is presented in Table 2.

Table 1 Incidence and prevalence in the past 5 years

Year	2019	2020	2021	2022	2023
Incidence in Denmark[1]	501	482	525	509	471
2L	75	72	79	76	71
3L	30	29	32	31	28
Prevalence in Denmark[2]	-	4068	-	-	-
Global prevalence	N/A	N/A	N/A	N/A	N/A

[1] Incidence data for 2019 are sourced from the National LYFO report from 2021 (10) and incidence data for 2020-2023 is sourced from the National LYFO report from 2023 (5). According to clinical expert input (28), approximately 15% of DLBCL patients progress to 2L therapy and 6-10% to 3L therapy. For estimation purposes, 2L and 3L incidence have been calculated as 15% and 6% of the annual DLBCL incidence, respectively. [2] Data for 2020 were extracted directly from the LYFO database by a clinical expert. Data for other years are not available. Abbreviations: NA, not applicable; 2L, second-line; 3L, third-line.

Table 2 Estimated number of patients eligible for treatment

Year	Year 1	Year 2	Year 3	Year 4	Year 5
Number of patients in Denmark who are eligible for treatment in the coming years	40	40	40	40	40

Estimates are based on clinical expert input (28) and LYFO data. Of approximately 75 patients per year in 2L, 25 are considered ineligible for ASCT or CAR-T therapy but fit for treatment with Glofit-GemOx. In 3L, of approximately 30-50 patients per year, 15 are considered fit for Glofit-GemOx.

3.3 Current treatment options

Treatment selection for patients with R/R DLBCL in Denmark is guided primarily by the patient's eligibility for ASCT or CAR-T cell therapy, the 1L treatment, and the timing of relapse.

According to the Danish national clinical guidelines for DLBCL (6), there is no single recommended standard regimen for 2L treatment in patients who are ineligible for ASCT or CAR-T therapy. For patients with good performance status and limited comorbidities,

protocol-based regimens should be offered where possible and available. Suggested options include rituximab-based chemotherapy combinations such as: R-GDP (rituximab, gemcitabine, dexamethasone, cisplatin); R-DHAOx (rituximab, dexamethasone, high-dose cytarabine, oxaliplatin); R-GemOx (rituximab, gemcitabine, oxaliplatin); R-ICE (rituximab, ifosfamide, carboplatin, etoposide) (6). For patients requiring 3L treatment, clinical options are more limited. Rituximab-based chemotherapy may be considered, particularly in cases where relapse occur more than 18 months after the last treatment.

In clinical practice, treatment patterns vary. Al-Mashhadi et al. (2024) reported that the most commonly used 2L regimens were GDP, DHAP (cisplatin, cytarabine, dexamethasone), or ICE (43.4%), followed by low-intensity chemotherapy (including GemOx) in 24.3%, and other treatments in 24.9%. Rituximab was administered to 83.1% of patients in 2L (1). In the same study, the most prevalent 3L+ treatments were: Best supportive care (19.5%); Platinum-based salvage chemotherapy (ICE, DHAP, GDP: 12.7%), and Gemcitabine or GemOx in 4.2% of cases (1). Clinical experts note that R-GemOx has become increasingly used in 2L in recent years (29). A summary of the current treatment algorithm is presented in Figure 1.

As described in section 3.2, the prognosis for patients with R/R DLBCL who are ineligible for ASCT or CAR-T therapy remains poor. Published data suggest that median OS in these populations is typically less than 12 months in 2L and even lower in 3L+ settings, depending on patient fitness, disease biology, and treatment intensity (1-3, 30, 31).

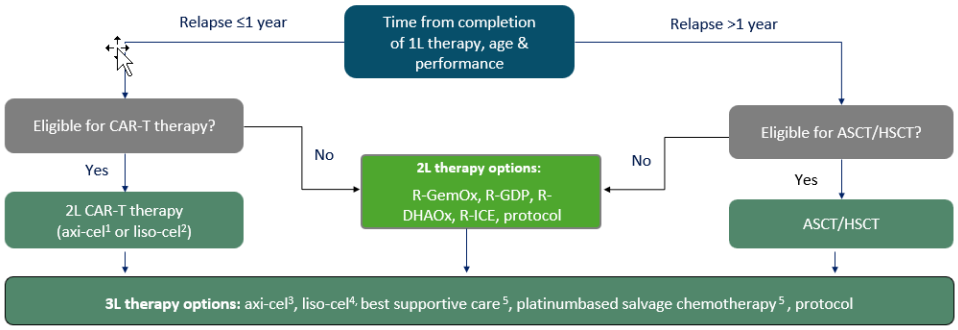

Figure 1 Treatment algorithm in R/R DLBCL in Denmark

Figure adapted from the Danish National Clinical Guidelines for DLBCL (6). [1](32), [2](33), [3](34), [4](35), [5](1). Axi-cel, axicabtagene ciloleucel; ASCT, autologous stem cell transplant; CAR-T, chimeric antigen receptor T-cell; HSCT, hematopoietic stem cell transplant; Liso-cel, lisocabtagene maraleucel; R-DHAOx, rituximab, dexamethasone, high-dose cytarabine, oxaliplatin; R-GDP, rituximab, gemcitabine, dexamethasone, cisplatin; R-GemOx, rituximab, gemcitabine, oxaliplatin; R-ICE, rituximab, ifosfamide, carboplatin, etoposide.

3.4 The intervention

Glofitamab is a cluster of differentiation (CD)20xCD3 T-cell bispecific antibody with a unique '2:1' format that enables simultaneous binding to CD20 on B-cells via two fragment antigen-binding (Fab) domains and to CD3 on T-cells via a single Fab domain (36). This bivalent CD20 binding enhances tumor antigen avidity (37). By engaging both T-cells and malignant B-cells, glofitamab forms immunological synapses, triggers CD3

cross-linking, and activates T-cells - leading to cytokine and chemokine release, proliferation, cytotoxic granule secretion, and target cell lysis (38). The recruitment of additional T-cells further amplifies tumor killing. Unlike classical anti-CD20 antibodies (e.g. rituximab, obinutuzumab), glofitamab redirects T-cell cytotoxicity and does not rely on antibody-dependent cytotoxicity or phagocytosis (38-40).

Glofitamab must be administered as an intravenous (IV) infusion according to a dose step-up schedule leading to the recommended dose of 30 mg, following completion of obinutuzumab pre-treatment on Cycle 1 Day 1. Glofitamab is administered in combination with gemcitabine and oxaliplatin in Cycles 1–8, and as monotherapy in Cycles 9-12. Each treatment cycle has a duration of 21 days (41).

To reduce the risk of cytokine release syndrome (CRS), premedication prior to glofitamab infusion should include 20 mg IV dexamethasone, an oral analgesic/antipyretic, and an antihistamine in Cycles 1-3, and an oral analgesic/antipyretic plus an antihistamine in all subsequent cycles (41).

For CRS management, at least one dose of tocilizumab (8 mg/kg IV; maximum 800 mg) must be available prior to glofitamab infusion in Cycles 1 and 2, with access to an additional dose within 8 hours of the previous administration. Tocilizumab should be administered in accordance with the CRS management guidance in the SmPC (41).

Table 3 Overview of intervention

Overview of intervention (41)	
Indication relevant for the assessment	Columvi in combination with gemcitabine and oxaliplatin is indicated for the treatment of adult patients with R/R DLBCL NOS, who are ineligible for ASCT (26).
ATMP	N/A
Method of administration	IV
Dosing	**Premedication before glofitamab infusion:** **Cycle 1 (Day 8, Day 15), Cycle 2 (Day 1) and Cycle 3 (Day 1):** 20 mg IV dexamethasone, oral analgesic/antipyretic, and antihistamine, in accordance with the glofitamab SmPC. **All subsequent infusions:** Oral analgesic/anti-pyretic and anti-histamine, in accordance with the glofitamab SmPC. **Dosing schedule** **Cycle 1:** Obinutuzumab 1000 mg IV (Day 1), gemcitabine IV 1000 mg/m² + oxaliplatin IV 100 mg/m² (Day 2), Glofitamab IV 2.5 mg (Day 8), Glofitamab IV 10 mg (Day 15)

Overview of intervention (41)	
	Cycles 2-8: Glofitamab IV 30 mg + gemcitabine IV 1000 mg/m² + oxaliplatin IV 100 mg/m² **Cycles 9-12:** Glofitamab IV 30 mg
Dosing in the health economic model (including relative dose intensity)	Same as above.
Should the medicine be administered with other medicines?	Glofitamab is given in combination with gemcitabine and oxaliplatin at Cycles 1-8 and as monotherapy at Cycles 9-12.
Treatment duration / criteria for end of treatment	12 cycles administered every 3 weeks, corresponding to a total treatment period of approximately 33 weeks.
Necessary monitoring, both during administration and during the treatment period	Normal monitoring during administration
Need for diagnostics or other tests (e.g. companion diagnostics). How are these included in the model?	N/A
Package size(s)	Columvi 2.5 mg concentrate for solution for infusion. Each 2.5 mL vial contains 2.5 mg of glofitamab (1 mg/mL). Columvi 10 mg concentrate for solution for infusion. Each 10 mL vial contains 10 mg of glofitamab (1 mg/mL).

3.4.1 The intervention in relation to Danish clinical practice

Glofit-GemOx is intended for use in adult patients with R/R DLBCL who are ineligible for ASCT, in accordance with its EMA-approved indication. The regimen is expected to be introduced in the 2- and 3L treatment settings and will replace currently used chemotherapy-based regimens such as R-GemOx in Danish clinical practice (Figure 1). This treatment algorithm is in line with the recently updated National Comprehensive Cancer Network (NCCN) guidelines on DLBCLs (42) as well as the recently updated European Hematology Association (EHA) guidelines on the management of aggressive large B-cell lymphomas (LBCLs) in 2L and 3L+ (presented at the EHA congress in 2025).

In 2L, Glofit-GemOx is a treatment option for patients who relapse after more than 12 months since treatment ended and are ASCT-ineligible. It is also a treatment option for patients who are primary refractory or relapse before 12 months, and for whom there is no intention to proceed to CAR-T. In 3L, Glofit-GemOx is a treatment option for patients where there is no intention to proceed to CAR-T.

The introduction of Glofit-GemOx will not add a new line of therapy but will serve as a substitution for existing 2L and 3L treatment options in transplant-ineligible patients. As such, no major shifts in the overall treatment algorithm are anticipated beyond replacement of current regimens in the relevant lines.

3.5 Choice of comparator

R-GemOx has been selected as the comparator as it reflects current Danish clinical practice in both the 2- and 3L treatment settings for patients with R/R DLBCL who are ineligible for ASCT. While several rituximab-based chemotherapy regimens are used in this population, clinical experts consider R-GemOx to be the most widely used option. Therefore, no other comparators have been included. Information on R-GemOx is provided in Table 4 below.

Table 4 Overview of comparators: rituximab, gemcitabine and oxaliplatin

Overview of comparator: Rituximab (43)	
Generic name	Rituximab
ATC code	L01X C02
Mechanism of action	Rituximab is a monoclonal antibody that specifically binds CD20, a non-glycosylated transmembrane phosphoprotein expressed on pre-B and mature B lymphocytes, including >95% of B-cell non-Hodgkin's lymphomas. It induces B-cell lysis through complement-dependent cytotoxicity, antibody-dependent cellular cytotoxicity, and apoptosis.
Method of administration	IV
Dosing	375 mg/m^2 body surface area per cycle
Dosing in the health economic model (including relative dose intensity)	375 mg/m^2 body surface area per cycle
Should the medicine be administered with other medicines?	Premedication with an antipyretic and antihistamine (e.g. paracetamol and diphenhydramine) should be given before each rituximab dose **Cycles 2–8**: Rituximab 375 mg/m^2 plus gemcitabine (8 cycles) 1000 mg/m^2 and oxaliplatin 100 mg/m^2
Treatment duration/ criteria for end of treatment	8 cycles every 3 weeks
Need for diagnostics or other tests (i.e. companion diagnostics)	N/A

Overview of comparator: Rituximab (43)	
Package size(s)	Rituximab concentrate for solution for infusion: 100 mg (10 mL vial) and 500 mg (50 mL vial), both at a concentration of 10 mg/mL.

Overview of comparator: Gemcitabine (44)	
Generic name	Gemcitabine
ATC code	L01BC05
Mechanism of action	Gemcitabine is a pyrimidine antimetabolite that is converted intracellularly to active metabolites. It inhibits DNA synthesis by blocking deoxynucleotide production and incorporating into DNA, leading to chain termination and cell death.
Method of administration	IV
Dosing	1000 mg/m^2 for 8 cycles
Dosing in the health economic model (including relative dose intensity)	1000 mg/m^2 for 8 cycles
Should the medicine be administered with other medicines?	**Cycles 2–8:** Rituximab 375 mg/m^2 plus gemcitabine (8 cycles) 1000 mg/m^2 and oxaliplatin 100 mg/m^2
Treatment duration/ criteria for end of treatment	8 cycles every 3 weeks
Need for diagnostics or other tests (i.e. companion diagnostics)	N/A
Package size(s)	25 ml conc. for infusion liquid solution (40 mg/ml) (other sizes depending on supplier)

Overview of comparator: Oxaliplatin (45)	
Generic name	Oxaliplatin
ATC code	L01XA03
Mechanism of action	Oxaliplatin is a platinum-based agent that forms crosslinks within and between DNA strands, disrupting replication and transcription and leading to cell death. Its chemical structure contributes to activity in tumors resistant to other platinum therapies.

Overview of comparator: Rituximab (43)	
Method of administration	IV
Dosing	100 mg/m^2 for 8 cycles
Dosing in the health economic model (including relative dose intensity)	100 mg/m^2 for 8 cycles
Should the medicine be administered with other medicines?	**Cycles 2–8:** Rituximab 375 mg/m^2 plus gemcitabine (8 cycles) 1000 mg/m^2 and oxaliplatin 100 mg/m^2
Treatment duration/ criteria for end of treatment	8 cycles every 3 weeks
Need for diagnostics or other tests (i.e. companion diagnostics)	N/A
Package size(s)	20 ml conc. for infusion, liquid (5 mg/ml) (other sizes depending on supplier)

3.6 Cost-effectiveness of the comparator

The comparator (R-GemOx) has not been evaluated by the Danish Medicines Council (DMC) in this setting. The comparator is standard of care in Denmark. Rituximab, gemcitabine and oxaliplatin are rather cheap off-patent products. Hence, it is a reasonable assumption that R-GemOx as a standard of care in Denmark can be assumed to be cost-effective.

This health economic evaluation provides relevant and comprehensive information about cost-effectiveness of the comparator.

3.7 Relevant efficacy outcomes

3.7.1 Definition of efficacy outcomes included in the application

All outcomes assessed by the Independent Review Committee (IRC) are presented in the main application, while those assessed by investigators (INV) are included in Appendix B. Median follow-up times for all included clinical cut-off dates (CCODs) are reported alongside the corresponding results.

Table 5 Efficacy outcome measures relevant for the application

Outcome measure	Time point*	Definition	How was the measure investigated/method of data collection

OS [STARGLO, GO41944; NCT04408638]	CCOD, 1 May 2025: 35.1 mo. (95% CI: 33.6, 37.6)	OS was defined as the time from randomization to date of death from any cause	Events were monitored throughout the study. For long-term follow-up, OS information was collected systematically via telephone calls, patient medical records, and/or clinic visits approximately every 90 days (±14 days) until death.
Progression-free survival (PFS) [STARGLO, GO41944; NCT04408638]	CCOD, 1 May 2025: IRC: 26.3 mo (95% CI: 21.2, 27.2)	PFS was defined as the time from randomization to the first occurrence of disease progression, or death due to any cause, whichever occurred first.	PFS was assessed by both the IRC and INV through the evaluation of PET-CT scans using the Lugano criteria (35).
Complete response (CR) [STARGLO, GO41944; NCT04408638]	CCOD, 1 May 2025	CR rate was defined as the proportion of patients whose best overall response (BOR) was a CR	CR was assessed by both the IRC and INV through the evaluation of PET-CT scans using the Lugano criteria (35).
Duration of complete response (DOCR) [STARGLO, GO41944; NCT04408638]	CCOD, 1 May 2025: IRC: 24.0 mo (95% CI: 21.4, 26.9)	DOCR was defined as the time from the initial occurrence of a documented CR until documented disease progression or death due to any cause, whichever occurs first.	CR and disease progression were assessed by both the IRC and INV through the evaluation of PET-CT scans using the Lugano criteria (35).
Objective response rate (ORR) [STARGLO, GO41944; NCT04408638]	CCOD, 1 May 2025	ORR was defined as the proportion of patients whose BOR is a partial response (PR) or CR based.	ORR was assessed by both the IRC and INV through the evaluation of PET-CT scans using the Lugano criteria (35).
Duration of response (DOR) [STARGLO, GO41944; NCT04408638]	CCOD, 1 May 2025: IRC: 24.0 mo (95% CI: 21.4, 25.3)	DOR was defined as the time from the initial occurrence of a documented objective response (PR or CR) until documented disease progression or death, whichever occurs first.	ORR and disease progression were assessed by both the IRC and INV through the evaluation of PET-CT scans using the Lugano criteria (35).

* Time point for data collection used in analysis (follow up time for time-to-event measures). Results from the primary analysis at the CCOD of 29 Mar 2023 and the updated analysis at 16 Feb 2024 are also included in this application. However, the main emphasis is placed on the most recent CCOD (1 May, 2025). Median follow-up times for each CCOD are provided in the results section.

Validity of outcomes

The validity and clinical relevance of the endpoints included in STARGLO (Table 5) are consistent with established practices in oncology and previous DMC assessments.

OS is considered the gold-standard endpoint for establishing clinical benefit in oncology trials. While it can be influenced by subsequent therapies, its direct measure of patient survival makes it a critical outcome.

PFS is a widely accepted primary endpoint in oncology, including DLBCL, as confirmed by regulatory bodies like the FDA and EMA (46, 47). It is less affected by subsequent treatments compared to OS. Evidence from randomized controlled trials and meta-analyses supports PFS and Event-Free Survival (EFS) as valid surrogates for OS in DLBCL (48, 49). Specifically, studies indicate that patients remaining progression-free for 24 months post-treatment initiation have survival comparable to the general population (19, 50).

CR and ORR are important endpoints demonstrating the immediate efficacy of treatment. No minimal important differences are universally established for these endpoints, their consistent use in clinical trials underscores their relevance.

DOCR and DOR are crucial for evaluating the durability of treatment effect. DOCR is particularly significant as lasting remissions for at least two years are considered a strong indicator for favorable long-term prognosis in DLBCL (50).

The consistent use of these well-defined and clinically relevant endpoints, assessed by established criteria, supports the validity of the outcomes reported in the STARGLO trial for evaluating Glofit-GemOx in R/R DLBCL.

4. Health economic analysis

4.1 Model structure

In this submission, a decision analytic modelling is needed, and it's applied according to the local economic evaluation guidelines. A three-health state model is the typical structure used in the cost-effectiveness analysis to estimate long-term costs and health benefits on cancer and R/R DLBCL treatments. Partitioned survival models (PSM) are often used in economic evaluations of oncology drugs and have been commonly used in DLBCL submissions also for DMC. A partitioned survival model (PSM) was used to estimate the cost-effectiveness of Glofit-GemOx versus R-GemOx. Partitioned survival models are particularly suitable for situations where a substantial proportion of events have been observed during the trial period and when individual patient level data (IPD) is available. The model was built based on STARGLO phase 3 trial (27).

PSMs use time-to-event data to model the proportion of patients who are in the progression-free, post-progression and death state dependent on time since trial

initiation. OS is partitioned into PFS and post-progression survival (PPS) based on the PFS curve (Figure 2). The proportion of patients in the post-progression health state at a given point in time is calculated as the difference of the proportion of patients who are alive and the proportions of patients who are progression free.

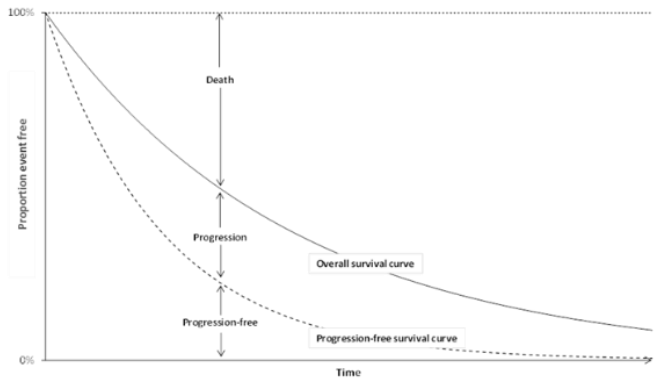

Figure 2 Partitioned survival model structure

Patients enter the model in the progression-free state (Figure 3). In each cycle, patients can either remain in the progression-free health state, or transition to the post-progression or death health state. Patients who have progressed can remain in the post-progression state or transition to the death state but never go back to the progression-free state. All patients eventually enter the death state.

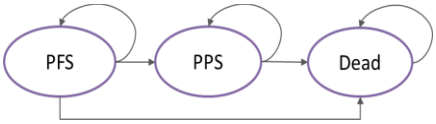

Figure 3 Diagram of the model for a partitioned survival model

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.

Progression free survival

Progression-free survival was the initial state in which all patients entered the model. The decrease in the proportion of patients who remained in the progression-free state over time was determined by the progression-free survival curves estimated based on the STARGLO trial data. The PFS curves indicate for each point in time the proportion of patients who have not progressed and not died yet.

Post-progression

The post-progression state accommodated all patients who have experienced disease progression but have not died yet. The proportion of all patients in this state was calculated as the difference between the proportion of patients who were alive and the

proportion of patients who were in the progression-free health state. The transitions into and out of the post-progression health state were thus not modelled explicitly but as a residual proportion of patients.

Death

Death was modelled as an absorbing state meaning that all patients eventually enter this state and cannot leave it. The transitions of patients from the progression-free and post-progression health states into the death state were determined by the overall survival curves derived from the STARGLO trial. A correction to ensure the hazard of death estimated from the OS curves would not be lower than that from the background mortality of an age- and sex-adjusted cohort from the general Danish population was applied at every model cycle. Overall survival 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.

4.2 Model features

The comparators differ in terms of expected long-term costs and effectiveness. Therefore, we apply a cost-utility analysis. The model features are reported in Table 6.

Table 6 Features of the economic model

Model features	Description	Justification
Patient population	Adult patients with 2L+ DLBCL	STARGLO study
Perspective	Limited societal perspective	According to DMC guidelines
Time horizon	Lifetime (60 years)	To capture all health benefits and costs in line with DMC guidelines.
Cycle length	7 days	Consistent with length of treatment cycle (day 1 every 14 days). A weekly cycle length is used in the model. By applying a relatively short cycle length of weekly cycle, the difference between the actual transition time and the model predicted transition time is reduced.
Half-cycle correction	Yes	Due to the short cycle length of one week, the half-cycle correction is not expected to have a large impact on the results.
Discount rate	3.5 % / 2.5 %	According to DMC guidelines
Intervention	Glofitamab + R-GemOx	STARGLO study

Model features	Description	Justification
Comparator(s)	R-GemOx	According to national treatment guidelines / standard of care (15)
Outcomes	OS, PFS, QALY	Consistent with the STARGLO study and the partitioned survival model

5. Overview of literature

5.1 Literature used for the clinical assessment

This application is based on the head-to-head study, STARGLO (GO41944), which compares glofitamab plus GemOx with R-GemOx for the treatment of adult patients with R/R DLBCL NOS who are ineligible for ASCT. In Danish clinical practice, R-GemOx is used for both 2L and 3L DLBCL patients. Therefore, it is considered a relevant comparator, and a systematic literature review has not been conducted.

Table 7 Relevant literature included in the assessment of efficacy and safety

Reference (Full citation incl. reference number)	Trial name*	NCT identifier	Dates of study (Start and expected completion date, data cut-off and expected data cut-offs)	Used in comparison of*
Abramson, J. S., et al. (2024). Glofitamab plus gemcitabine and oxaliplatin (GemOx) versus rituximab-GemOx for relapsed or refractory diffuse large B-cell lymphoma (STARGLO): a global phase 3, randomised, open-label trial. The Lancet 404 (10466): 1940-1954 (27)	STARGLO	NCT04408638	Start: 23 Feb 2021 Completion: 15 Feb 2026 First CCOD: 29 Mar 2023; second CCOD: 16 Feb 2024; third CCOD: 1 May 2025	Glofitamab + R-GemOx vs. R-GemOx for adult patients with R/R DLBCL NOS who are ineligible for ASCT

5.2 Literature used for the assessment of health-related quality of life

HRQoL data was obtained from the head-to-head STARGLO study with the intervention and comparator of interest. Therefore, there was no need to do a systematic literature review for HRQoL.

Table 8 Relevant literature included for health-related quality of life (See section 10)

Reference (Full citation incl. reference number)	Health state/Disutility	Reference to where in the application the data is described/applied
Abramson, J. S., et al. (2024). Glofitamab plus gemcitabine and oxaliplatin (GemOx) versus rituximab-GemOx for relapsed or refractory diffuse large B-cell lymphoma (STARGLO): a global phase 3, randomised, open-label trial. The Lancet 404 (10466): 1940-1954 (27)	Utility applied by health states (PFS, PD).	See section 10

5.3 Literature used for inputs for the health economic model

Literature research was not used as all the parameters were based on the STARGLO study or local inputs.

Table 9 Relevant literature used for input to the health economic model

Reference (Full citation incl. reference number)	Input/estimate	Method of identification	Reference to where in the application the data is described/applied
Abramson, J. S., et al. (2024). Glofitamab plus gemcitabine and oxaliplatin (GemOx) versus rituximab-GemOx for relapsed or refractory diffuse large B-cell lymphoma (STARGLO): a global phase 3, randomised, open-label trial. The Lancet 404 (10466): 1940-1954 (Abramson, Ku et al. 2024)	OS, PFS	Only head-to-head study of Glofit-GemOx versus R-GemOx for R/R DLBCL	Section 8

6. Efficacy

6.1 Efficacy of Glofitamab plus GemOx compared to R-GemOx for patients with R/R DLBCL NOS who are ineligible for ASCT

6.1.1 Relevant studies

Study design

The STARGLO study (GO41944; NCT04408638) is a phase 3, open-label, multicenter, randomized controlled trial to evaluate the efficacy, safety and tolerability of Glofit-GemOx after a fixed, single-dose pre-treatment of obinutuzumab (Gazyvaro) compared with R-GemOX in patients with R/R DLBCL NOS. Eligible participants included those who had failed one prior line of therapy and were ineligible for ASCT, as well as those who had failed at least two prior lines of therapy.

Patients were enrolled from 13 countries: Australia, Belgium, China, Denmark, France, Germany, Poland, Republic of Korea, Spain, Switzerland, Taiwan, the United Kingdom, and the United States.

A total of 274 eligible patients were randomized in a 2:1 ratio to receive glofitamab plus GemOx (n = 183) or rituximab plus GemOx (n = 91). Randomization was stratified according to the following stratification factors:

- Number of previous lines of systemic therapy for DLBCL (1 vs ≥ 2)
    - CAR T-cell plus bridging therapy were counted as one line of therapy
    - Local therapies (e.g. radiotherapy) were not considered as a line of therapy
- Outcome of last systemic therapy (relapsed vs refractory)
    - Relapsed disease was defined as disease that had recurred following a response that lasted ≥ 6 months after completion of the last line of therapy.
    - Refractory disease was defined as disease that did not respond to or that progressed < 6 months after completion of the last line of therapy.

Patients who discontinued the last line of therapy before sufficient time for response assessment (for example, owing to toxicity) were assessed for refractoriness based on the previous line of therapy.

The primary outcome measure was OS. Secondary measures included efficacy by PFS, CR rate, ORR, DOCR and DOR, as well as safety, tolerability and patient-reported-outcomes (PROs). An overview of the study design of STARGLO is presented in Table 10. Details of the rationale for the study design are presented in section 3.3 of the STARGLO Study Protocol (51).

Table 10 Overview of study design for studies included in the comparison

Trial name, NCT-number (reference)	Study design	Study duration	Patient population	Intervention	Comparator	Outcomes and follow-up time
STARGLO (GO41944), NCT04408638 (27)	Phase 3, open-label, multicenter, RCT in patients with R/R DLBCL NOS	The study is expected to last about 3.5 years, from first patient screening to study end	Adult patients with R/R DLBCL NOS, who are ineligible to ASCT	**Glofitamab plus GemOx** (n=183) **Obinutuzumab IV:** 1000 mg on Day 1 of Cycle 1 (7 days before first glofitamab dose) **Glofitamab IV**: 2.5 mg on Day 8, 10 mg on Day 15 of Cycle 1; then 30 mg on Day 1 of Cycles 2–12 (21-day cycles). **Gemcitabine and Oxaliplatin IV:** 1000 mg/m² and 100 mg/m² on Day 2 of Cycle 1; then Day 1 of Cycles 2–8 (21-day cycles).	**R-GemOx** (n=91) **Rituximab IV**: 375 mg/m2 on Day 1 of Cycles 1-8 (21-day cycles) **Gemcitabine and Oxaliplatin IV:** 1000 mg/m² and 100 mg/m² on Day 2 of Cycle 1; then Day 1 of Cycles 2–8 (21-day cycles).	**Primary outcome measures**: OS; median follow-up: 35.1 mo (95% CI: 33.6, 37.6) **Secondary outcome measures**: IRC- and INV-assessed efficacy outcomes: • PFS; median follow-up, IRC: 26.3 (95% CI: 21.2, 27.2), INV: 29.2 mo (95% CI: 26.3, 32.3) • CR rate • ORR • DOCR; median follow-up, IRC: 24.0 mo (95% CI: 21.4, 26.9), INV: 26.9 mo (95% CI: 24.0, 28.5) • DOR; median follow-up: IRC: 24.0 mo (95% CI: 21.4, 25.3), INV: 27.7 mo (95% CI: 24.5, 29.7) Patient reported outcomes: • Time to deterioration in physical functioning and fatigue measured by EORTC QLQ-C30 and in lymphoma symptoms measured by FACT-Lym LymS

ASCT, autologous stem-cell transplant; DLBCL, diffuse large B-cell lymphoma; CR, complete response; DOCR, duration of complete response; DOR, duration of response; EORTC QLQ-C30, European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30; FACT-Lym LymS, Functional Assessment of Cancer Therapy-Lymphoma Lymphoma Subscale; GemOx, rituximab plus gemcitabine and oxaliplatin; Glofit-GemOx, glofitamab plus gemcitabine and oxaliplatin; IRC, independent review committee; INV, investigator; PFS, progression-free survival; NOS, not otherwise specified; ORR, objective response rate; OS, overall survival; RCT, randomized controlled trial; R/R, relapsed/refractory.

Data cut-off and respective objectives

The efficacy and safety data presented in the application are based on data from the CCOD of 29 March 2023, CCOD of 16 February 2024 and CCOD of 1 May 2025. Main emphasis is on data from the most recent CCOD. A summary of the CCODs is presented in Table 11.

Table 11 STARGLO study clinical data cut-offs and respective objectives

CCOD	Objectives	Availability
1 May 2025	Long-term analysis, including full safety and efficacy data from the date of first patient enrolled (23 February 2021) up to a CCOD of 1 May 2025. Median follow-up time: 35.1 mo. (95% CI: 33.6, 37.6)	Data on file (4)
16 Feb 2024	Updated analysis (defined in SAP), including full safety and efficacy data from the date of first patient enrolled (23 February 2021) up to a CCOD of 16 February 2024 when all patients had completed therapy. Median follow-up time: 20.7 mo. (95% CI: 19.9, 23.3)	Abramson et al 2024, (27), EMAs assessment report (52), Clinical study report (CSR) 2024 (53)
29 Mar 2023	Primary analysis (defined in SAP) to evaluate the efficacy and safety of Glofit-GemOx compared with R-GemOx in patients with R/R DLBCL NOS. Median follow-up time: 11.3 mo. (95% CI: 9.6, 12.7)	Abramson et al 2024, (27), EMAs assessment report (41), CSR 2023 (54)

DLBCL, diffuse large B-cell lymphoma; CCOD, clinical cut-off date; Glofit, glofitamab; GemOx, gemcitabine plus oxaliplatin; R, rituximab; R/R, relapsed or refractory; SAP, statistical analysis plan; NOS, not otherwise specified.

6.1.2 Comparability of studies

Not applicable, since comparisons are based on a head-to-head study.

6.1.2.1 Comparability of patients across studies

Baseline demographic and disease characteristics were generally well balanced between the Glofit-GemOx and R-GemOx groups across most parameters. The median age was 68.0 years in both arms, and the majority were aged ≥65 (Glofit-GemOx: 63.4%; R-GemOx: 61.5%). Most patients were male (Glofit-GemOx: 57.4%; R-GemOx: 58.2%). Among enrolled patients, 47.0% (Glofit-GemOx) and 56.0% (R-GemOx) were Asian, and 44.8% and 36.3%, respectively, were White.

In both arms, the majority had an ECOG PS of 0-1 (Glofit-GemOx: 89.4%; R-GemOx: 90.9%), while 10.6% and 9.1% of patients, respectively, had a PS of 2.

Most patients presented with advanced-stage disease. Ann Arbor Stage III was reported in 12.6% (Glofit-GemOx) and 8.8% (R-GemOx); Stage IV in 54.6% and 68.1%, respectively. Bulky disease (≥10 cm) was observed in 12.6% and 15.4% of patients, respectively.

Similar proportions of patients were refractory to first-line therapy (Glofit-GemOx: 57.4%; R-GemOx: 51.6%), last line of therapy (61.2% vs. 59.3%), and any prior therapy

(67.8% vs. 63.7%). One prior line of systemic therapy for R/R DLBCL had been received by 62.8% of patients in the Glofit-GemOx arm and 62.6% in the R-GemOx arm; 37.2% and 37.4%, respectively, had received two or more prior lines.

Prior ASCT had been administered to 4.4% (Glofit-GemOx) and 3.3% (R-GemOx). The most common reasons for stem-cell transplantation (SCT) ineligibility were patient refusal (Glofit-GemOx: 35.0%; R-GemOx: 33.0%), age (34.4% vs. 27.5%), age ≥70 years (8.2% vs. 14.3%), and insufficient response to salvage therapy (8.2% vs. 12.1%). Among patients with one prior line of therapy (Glofit-GemOx: n=115; R-GemOx: n=57), the main reasons for SCT ineligibility were age (Glofit-GemOx: 55.7%; R-GemOx: 59.6%) and patient refusal (33.9% vs. 33.3%).

Baseline characteristics for the ITT population are summarized in Table 12.

Table 12 Baseline characteristics of patients in studies included for the comparative analysis of efficacy and safety

	STARGLO, ITT population	
	Intervention: Glofit-GemOx (n=183)	**Comparator: R-GemOx (n=91)**
Age, years		
Median (IQR)	68 (59–74)	68 (55–73)
Age <65	67 (37%)	35 (39%)
Age ≥65	116 (63%)	56 (62%)
Gender		
Male	105 (57%)	53 (58%)
Female	78 (43%)	38 (42%)
Race		
Asian	86 (47%)	51 (56%)
Black or African American	2 (1%)	1 (1%)
White	82 (45%)	33 (36%)
Unknown	13 (7%)	6 (7%)
Geographical region		
Europe	62 (34%)	26 (29%)
North America	15 (8%)	10 (11%)
Asia or Australia*	106 (58%)	55 (60%)
ECOG performance status		

	STARGLO, ITT population	
	Intervention: Glofit-GemOx (n=183)	**Comparator: R-GemOx (n=91)**
0	72 (39%)	44 (48%)
1	89 (49%)	36 (40%)
2	19 (10%)	8 (9%)
Unknown	3 (2%)	3 (3%)
Ann Arbor stage†		
I–II	60 (33%)	20 (22%)
III–IV	123 (67%)	70 (77%)
Unknown	0	1 (1%)
Number of risk factors for IPI‡		
0-1	48 (26%)	13 (14%)
2	42 (23%)	28 (31%)
3	49 (27%)	30 (33%)
4-5	38 (21%)	17 (19%)
Unknown	6 (3%)	3 (3%)
Cell of origin		
Germinal centre B cell	60 (33%)	29 (32%)
Non-germinal centre B cell§	103 (56%)	50 (55%)
Unknown	20 (11%)	12 (13%)
Bulky disease¶		
Yes	23 (13%)	14 (16%)
No	160 (87%)	76 (84%)
Unknown	0	1 (1%)
Number of previous lines of therapy||		
Median (IQR)	1 (1–2)	1 (1–2)
1	115 (63%)	57 (63%)
≥2	68 (37%)	34 (37%)
Previous CAR T-cell therapy		

	STARGLO, ITT population	
	Intervention: Glofit-GemOx (n=183)	**Comparator: R-GemOx (n=91)**
No	170 (93%)	83 (91%)
Yes	13 (7%)	8 (9%)
Previous ASCT		
Yes	8 (4%)	3 (3%)
No	175 (96%)	88 (97%)
Relapsed or refractory to any previous therapy**		
Refractory	125 (68%)	58 (64%)
Relapsed	58 (32%)	33 (36%)
Relapsed or refractory to last line of therapy||		
Refractory	112 (61%)	54 (59%)
Relapsed	71 (39%)	37 (41%)
Relapsed or refractory to first line of therapy		
Refractory	106 (58%)	47 (52%)
Relapsed	77 (42%)	44 (48%)
Relapsed or refractory to any previous anti-CD20 therapy		
Refractory	117 (64%)	55 (60%)
Relapsed	64 (35%)	34 (37%)
Unknown	2 (1%)	2 (2%)

ASCT, autologous stem-cell transplant; CAR, chimeric antigen receptor; ECOG, Eastern Cooperative Oncology Group; Glofit-GemOx, glofitamab plus gemcitabine–oxaliplatin; IPI, International Prognostic Index; IQR, Interquartile range; R-GemOx, rituximab plus gemcitabine–oxaliplatin. *Includes: China, Taiwan, South Korea, and Australia. †Stages range from I to IV, with higher stages indicating more extensive disease. ‡IPI risk factors were derived from clinical data provided at screening; IPI score indicates low (0 or 1), low–intermediate (2), high–intermediate (3), or high (4 or 5) risk of a poor outcome on the basis of a scoring system that gives one point for each of the following risk factors: age older than 60 years, one or more extranodal areas of disease, an ECOG performance status of 2 or higher, a blood lactate dehydrogenase concentration above the upper limit of the normal range, and Ann Arbor stage III or IV disease. §Primarily classified by immunohistochemistry (n=147 [54%]; R-GemOx: n=48 [53%]; Glofit-GemOx: n=99 [54%]); also includes six patients classified as activated B-cell subtype via gene expression profiling (R-GemOx: n=2 [2%]; Glofit-GemOx: n=4 [2%]). ¶Defined as the presence of one or more lesions that were 10 cm or larger in greatest dimension. ||Stratification factor. **Patients who had both relapsed and been refractory to previous lines of therapy are shown as refractory.

6.1.3 Comparability of the study population with Danish patients eligible for treatment

As outlined in the section on patient characteristics, Danish registry studies (1, 2) show that patients with R/R DLBCL eligible for 2L+ treatment but ineligible for ASCT or CAR-T therapy are typically older, often male, and frequently affected by comorbidities and refractory disease. These characteristics align with those reported in the STARGLO trial population. Clinical experts have reviewed the STARGLO data and consider the study population comparable to Danish patients eligible for treatment with glofitamab plus GemOx (29). Key characteristics are summarised in Table 13.

Table 13 Characteristics in the relevant Danish population and in the health economic model

	Value in Danish population (1, 2)	Value used in health economic model (27)
Age	62 in 2L (2), 71 in 3L+ (1)	65
Gender	63% male (2)	57.3 % male
Patient weight	No available information	68.83
≥2 comorbidities	24% (2)	NA
Refractory disease	48% (2)	NA

6.1.4 Efficacy – results per STARGLO (GO41944)

In the following, we present efficacy results from three analyses: the primary analysis (CCOD: March 29, 2023), an updated analysis after all patients had completed study therapy (CCOD: February 16, 2024), and a recently available long-term analysis (CCOD: May 1, 2025). These data are confidential and intended for presentation at the 67th ASH Annual Meeting and Exposition in December 2025. Only the long-term analysis results are included in Appendix B.

Primary efficacy endpoint

Overall survival (OS)
The primary efficacy endpoint evaluating Glofit-GemOx compared with R-GemOx was OS, defined as the time from randomization to date of death from any cause.

The Kaplan–Meier (KM) method was used to estimate the median OS, if reached, and OS distribution for each treatment arm. The Brookmeyer-Crowley method was used to construct the 95% CI for the median OS for each treatment arm. Cox proportional-hazards model was used to estimate the stratified hazard ratio (HR) and its 95% CI. Treatment comparison was made using a two-sided level 0.05 stratified log-rank test. The analysis population was the intention-to-treat (ITT) population, which included all patients randomized in the study (51).

At the primary analysis, after a median follow-up of 11.3 months (95% CI: 9.6, 12.7), STARGLO met its primary endpoint, demonstrating a statistically significant and clinically meaningful improvement in OS with Glofit-GemOx compared to R-GemOx. Median investigator-assessed OS was not reached in the Glofit-GemOx arm (95% CI: 13.8, NE) and was 9.0 months (95% CI: 7.3, 14.4) in the R-GemOx arm. The HR was 0.59 (95% CI: 0.40, 0.89; p = 0.011) (27).

At the updated analysis, after a median follow-up of 20.7 months (95% CI: 19.9, 23.3), the OS benefit with Glofit-GemOx remained consistent. Median investigator-assessed OS was 25.5 months (95% CI: 18.3, NE) in the Glofit-GemOx arm versus 12.9 months (95% CI: 7.9, 18.5) in the R-GemOx arm. The HR was 0.62 (95% CI: 0.43, 0.88; p = 0.006) (27). KM-plot of OS is shown in Figure 18, Appendix B.

At the long-term analysis, [redacted] (4). A graphical check of the proportional hazards assumption using Schoenfeld residuals is shown in Appendix D.

[redacted] (4).

Figure 4 Kaplan–Meier plot of OS, ITT: CCOD, 1 May 2025

Day 1 is day of randomization. The HR was estimated by Cox regression. Stratified HR and p-values have been adjusted for the randomization stratification variables according to IxRS. CI, confidence interval; CCOD, clinical cut-off date; Glofit-GemOx, glofitamab in combination with gemcitabine and oxaliplatin; OS, overall survival; R-GemOx, rituximab in combination with gemcitabine and oxaliplatin.

Secondary efficacy endpoints

The key secondary efficacy endpoints evaluating Glofit-GemOx compared with R-GemOx were PFS, CR rate, DOCR, ORR and DOR assessed by the IRC and by the INV using the Lugano criteria (55), as assessed on PET-CT scan; the method of analysis is described for each endpoint in the following.

A hierarchical testing procedure was used to adjust for multiple statistical testing of the primary and key secondary efficacy endpoints. Briefly, key secondary endpoints included in the hierarchical order were IRC-assessed PFS, IRC-assessed CR rate and IRC-assessed DOCR; these were only evaluated if the primary efficacy endpoint of OS was statistically significant at the appropriate boundary level. All additional secondary efficacy endpoints were tested without adjusting for multiplicity.

Progression-free survival (PFS)

PFS was defined as the time from randomization to the first occurrence of disease progression, or death due to any cause, whichever occurred first. PFS was assessed by the independent review committee (IRC) and by the investigator, using the Lugano Classification (55). The Kaplan–Meier estimate was used to estimate the median PFS for each treatment arm. The Brookmeyer–Crowley method was used to construct the 95% CI for the median PFS for each treatment arm. Cox proportional-hazards models were used to estimate the stratified HR and its 95% CI. Treatment comparison was made using a two-sided level 0.05 stratified log-rank test. Analyses were conducted on the ITT population (51).

IRC-assessed PFS

Across all CCODs, analyses demonstrated a statistically significant and clinically meaningful improvement in median IRC-assessed PFS in patients treated with Glofit-GemOx compared with those treated with R-GemOx. Findings for INV-assessed PFS were consistent with those of IRC-assessed PFS (Appendix B).

At the primary analysis, the median duration of follow-up was 9.0 months (95% CI, 6.2, 9.7) in the Glofit-GemOx arm and 6.1 months (95% CI, 3.4, 8.8) in the R-GemOx arm. Median IRC-assessed PFS was 12.1 months (95% CI, 6.8, 18.3) in the Glofit-GemOx arm versus 3.3 months (95% CI: 2.5, 5.6) in the R-GemOx arm. The stratified HR was 0.37 (95% CI, 0.25, 0.55; $p < 0.0001$) (27).

At the time of the updated analysis, the median duration of follow-up was 16.3 months (95% CI, 15.3, 20.1) in the Glofit-GemOx arm and 8.6 months (95% CI, 5.9, 14.6) in the R-GemOx arm. The result of the updated analysis was consistent with that of the primary analysis. Median IRC-assessed PFS was 13.8 months (95% CI, 8.7, 20.5) in the Glofit-GemOx arm versus 3.6 months (95% CI, 2.5, 7.1) in the R-GemOx arm. The stratified HR was 0.40 (95% CI, 0.28, 0.57; $p < 0.0001$) (27). KM-plot of IRC-assessed PFS is shown in Figure 19, Appendix B.

[redacted](4).

Figure 5 Kaplan–Meier plot of IRC-assessed PFS censored before NALT, ITT:CCOD, 1 May 2025 Day 1 is day of randomization. The HR was estimated by Cox regression. Stratified HR and p-values have been adjusted for the randomization stratification variables according to IxRS. CI, confidence interval; CCOD, clinical cut-off date; Glofit-GemOx, glofitamab in combination with gemcitabine plus oxaliplatin; IRC, independent review committee; NALT, new anti-lymphoma treatment; NE, not estimable; PFS, progression-free survival, R-GemOx, rituximab in combination with gemcitabine plus oxaliplatin.

Complete response (CR) rate

CR rate was defined as the proportion of patients whose best overall response (BOR) was a CR based on IRC- and investigator-assessment of PET-CT scans using the Lugano criteria (55). An estimate of CR rate and its 95% CI were calculated using the Clopper-Pearson method for each treatment arm. CR rate was compared between treatment arms using the Cochran-Mantel-Haenszel (CMH) test stratified by the randomization stratification factors. Analyses were conducted on the ITT population (51).

IRC-assessed CR rate

Across all CCODs, analyses demonstrated a statistically significant and clinically meaningful improvement in the IRC-assessed CR rate in patients treated with Glofit-GemOx compared with those treated with R-GemOx. Findings for INV-assessed CR rate were consistent with those of IRC-assessed CR rate (Appendix B)

At the primary analysis, the IRC-assessed CR rate was 50.3% (95% CI, 42.8, 57.7) and 22.0% (95% CI, 14.0, 31.9) in the Glofit-GemOx and R-GemOx arms, respectively; the difference in IRC-assessed CR rate was 28.3% (95% CI, 16.3, 40.3; CMH p value < 0.0001) in favor of the Glofit-GemOx arm (27, 54).

At the updated analysis, the IRC-assessed CR rate was 58.5% (95% CI, 51.0, 65.7) and 25.3% (95% CI, 16.8, 35.5) in the Glofit-GemOx and R-GemOx arms, respectively; the difference in IRC-assessed CR rate was 33.2% (95% CI, 20.9, 45.5; CMH p value < 0.0001) in favor of the Glofit-GemOx arm (27, 53).

[redacted]

[redacted](4).

Duration of complete response (DOCR)

DOCR was defined as the time from the initial occurrence of a documented CR until documented disease progression or death due to any cause, whichever occurs first. It was assessed by the IRC and by the investigator, using the Lugano Classification (55). The Kaplan–Meier estimate was used to estimate the median DOR, for each treatment arm. The Brookmeyer–Crowley method was used to construct the 95% CI for the median DOR for each treatment arm. Cox proportional-hazards models were used to estimate the unstratified HR and its 95% CI. Treatment comparison was made using a two-sided level 0.05 stratified log-rank test. Analyses were conducted on the ITT population (51).

IRC-assessed DOCR

IRC-assessed DOCR showed a trend in favor of Glofit-GemOx over R-GemOx across all CCODs. Interpretation was limited by the low number of patients achieving CR in the R-GemOx arm. INV-assessed DOCR results were consistent with those of IRC (Appendix B).

At the time of the primary analysis, the median duration of follow-up for IRC-assessed DOCR was 6.9 months (95% CI, 5.9, 7.6) in the Glofit-GemOx arm (N = 92) and 6.1 months (95% CI, 2.7, 9.8) in the R-GemOx arm (N = 20). IRC-assessed median DOCR was 14.4 months (95% CI, 14.4, NE) in the Glofit-GemOx arm and could not be estimated in the R-GemOx arm (NE; 95% CI, 6.4, NE). The unstratified HR was 0.59 (95% CI, 0.19, 1.83) and did not meet the threshold for statistical significance (p = 0.3560) (27).

At the time of the updated analysis, the median duration of follow-up was 13.6 months (95% CI, 12.9, 17.7) in the Glofit-GemOx arm (N = 107) and 11.8 months (95% CI, 4.0, 12.58) in the R-GemOx arm (N = 23). IRC-assessed median DOCR was not reached in the Glofit-GemOx arm (NE; 95% CI, NE, NE) and was 24.2 months (95% CI, 6.9, NE) in the R-GemOx arm. The unstratified HR was 0.59 (95% CI, 0.25, 1.35; p = 0.2040) (27).

[redacted](4).

[redacted]**(4).**

Figure 6 Kaplan–Meier plot of IRC-assessed DOCR, ITT: CCOD, 1 May 2025 Day 1 is day of documented CR. The HR was estimated by Cox regression. Includes patients with a best overall response by IRC of CR. CI, confidence interval; CCOD, clinical cut-off date; DOCR, duration of complete response; Glofit-GemOx, glofitamab in combination with gemcitabine plus oxaliplatin; IRC, independent review committee; NE, not estimable; R-GemOx, rituximab in combination with gemcitabine plus oxaliplatin.

Objective response rate (ORR)

ORR was defined as the proportion of patients whose BOR is a partial response (PR) or CR based on IRC- or investigator assessment of PET-CT scans using the Lugano criteria (55). An estimate of ORR and its 95% CI were calculated using the Clopper-Pearson method for each treatment arm. ORR was compared between treatment arms using the Cochran-Mantel-Haenszel test stratified by the randomization stratification factors. The analysis population was the ITT, including all patients randomized in the study (51).

IRC-Assessed ORR

Across all CCODs, analyses showed an improvement in IRC-assessed ORR with Glofit-GemOx over R-GemOx. Results of the primary and updated analyses are presented in Appendix B. INV-assessed ORR results were consistent with those of IRC (Appendix B).

[redacted](4).

Duration of response

DOR was defined as the time from the initial occurrence of a documented objective response (PR or CR) until documented disease progression or death, whichever occurs first. DOR was assessed by the IRC and by the investigator, using the Lugano Classification (55). The Kaplan–Meier estimate was used to estimate the median DOR, for each treatment arm. The Brookmeyer–Crowley method was used to construct the 95% CI for the median DOR for each treatment arm. Cox proportional-hazards models were used to estimate the unstratified HR and its 95% CI. Treatment comparison was made using a two-sided level 0.05 stratified log-rank test. The analysis population was the ITT, including all patients randomized in the study (51).

IRC-Assessed DOR

IRC-assessed DOR showed a trend in favor of Glofit-GemOx over R-GemOx across all CCODs. Results of the primary and updated analyses are presented in Appendix B. INV-assessed DOR results were consistent with those of IRC (Appendix B).

[redacted](4).

Subgroup analyses

At the primary analysis, an unstratified exploratory analysis of subgroups was conducted in the STARGLO study. Overall, a directionally consistent treatment effect supporting the OS benefit of Glofit-GemOx was observed in the majority of subgroups (unstratified HR <1). The 95% CIs for the unstratified HR in most subgroups included 0.61, which was the estimated unstratified HR in the ITT population. Consistent efficacy of Glofit-GemOx was demonstrated across other key patient populations, including number of previous lines of systemic therapy for DLBCL [redacted] The treatment effect of Glofit-GemOx in the subgroups was maintained at the updated and long-term analyses. Forest plots of HR for OS with 95% CI within each subgroup are shown for the long-term analysis in Appendix B (Figure 24, Figure 25, Figure 26, Figure 27).

Despite this general consistency, potential inconsistencies in the unstratified OS HR were observed in specific subgroups by [redacted] when compared to the overall ITT population (Appendix B).

These variations should be interpreted with caution due to the known limitations of exploratory subgroup analyses, particularly those with small sample sizes. The observed inconsistencies in OS HRs within the subgroups by race and geographic region are attributable to a combination of these inherent statistical limitations and several confounding factors, which are highlighted in Appendix B. All post hoc exploratory analyses were presented to EMA as part of their assessment. Importantly, EMA concluded that the results from the ITT analysis can be extrapolated to the European population.

7. Comparative analyses of efficacy

Not applicable, since comparisons are based on a head-to-head study. Table 14 is completed with results from STARGLO.

7.1.1 Differences in definitions of outcomes between studies

Not applicable

7.1.2 Method of synthesis

Not applicable

7.1.3 Results from the comparative analysis

Table 14 Results from the comparative analysis of Glofit-GemOx vs. R-GemOx for patients with R/R DLBCL NOS who are ineligible for ASCT

Outcome measure	Glofit-GemOx (N=183)	R-GemOx (N=91)	Result
OS – Median	[redacted]	[redacted]	[redacted]
OS – 24-months rate	[redacted]	[redacted]	[redacted]
IRC PFS – Median	[redacted]	[redacted]	[redacted]
IRC PFS – 12-months rate	[redacted]	[redacted]	[redacted]
INV PFS – Median	[redacted]	[redacted]	[redacted]
IRC CR	[redacted]	[redacted]	[redacted]
INV CR	[redacted]	[redacted]	[redacted]
IRC DOCR – Median	[redacted]	[redacted]	[redacted]

Outcome measure	Glofit-GemOx (N=183)	R-GemOx (N=91)	Result
INV DOCR – Median	[redacted]	[redacted]	[redacted]
IRC ORR	[redacted]	[redacted]	[redacted]
INV ORR	[redacted]	[redacted]	[redacted]
IRC DOR – Median	[redacted]	[redacted]	[redacted]
INV DOR – Median	[redacted]	[redacted]	[redacted]

7.1.4 Efficacy – results per outcome measure

Not applicable

8. Modelling of efficacy in the health economic analysis

8.1 Presentation of efficacy data from the clinical documentation used in the model

Usage of the trial data

The results are based on the most recent CCOD of 1 May 2025 with a median follow-up time of [redacted]. Extrapolation beyond the clinical follow-up period was performed by fitting parametric distributions to the observed time to event data from the trial. Guidance from Latimer et al (2013) (56) was followed to identify the most relevant parametric survival extrapolations for PFS and OS. For Time to off treatment (TTOT), no extrapolation was needed as time on treatment had been observed at the time of the data cut.

The following steps were used to select the most relevant extrapolation for PFS and OS:

1. Visual inspection of the OS and PFS log-cumulative hazard plots and Schoenfeld test, based on patient level data for the two arms of STARGLO, to test for the

plausibility of the proportional hazards assumption and to examine the hazard of progression or death in each arm over time.

2. The Akaike Information Criterion (AIC) and the Bayesian Information Criterion (BIC) goodness-of-fit statistics were calculated to assess statistical fit of the models to both arms of the PFS and OS KM data from STARGLO.
3. The clinical plausibility of the long-term extrapolations for the base case parametric models was validated by comparing the long-term behaviour of the models with suitable data sources, previous submissions and the expectations of clinical experts.

For both PFS and OS, application of standard parametric survival models (exponential, Weibull, Gompertz, log-normal, gamma, generalised gamma and log-logistic) were explored and spline model was considered for OS.

8.1.1 Extrapolation of efficacy data

8.1.1.1 Extrapolation of PFS

Assessment of progression-free survival

IRC-assessed PFS was a secondary endpoint in the STARGLO trial (see 7.1.4). [redacted]

Assessment of proportional hazards

The economic evaluation is based on the most up to date data cut for STARGLO (CCOD: 1 May 2025). Extrapolation beyond the STARGLO clinical follow-up period was needed and performed by fitting parametric distributions to the observed data (parametric survival analysis) to assess long-term impacts of the treatments. The PFS KM curves for Glofit-GemOx and R-GemOx (Figure 5) clearly demonstrate a reduced progression risk for patients treated with Glofit-GemOx compared to R-GemOx.

The first assumption to check when choosing an extrapolation model is whether the PH assumption is valid for PFS. This is tested using the Schoenfeld test and plotting the log-log plot. The Schoenfeld test (p=0.17) (Figure 32) would allow acceptance of the proportional hazard assumption, but the log-log plot shows crossing at the earlier time points (Figure 33). Although the curves cross very early and then stabilize, the proportional hazards assumption was assessed to be violated, and thus consequently the PFS curves were fitted independently.

In the base case, standard parametric distributions were used to extrapolate OS from STARGLO over the time horizon of the model for the Glofit-GemOx and GemOx arm independently. Analysis of survival and hazard plots suggest a monotonic hazard rate for Glofit-GemOx (with a continuous decline in hazard rate), whereas the hazard rate for R-GemOx seems to be somewhat non-monotonic (Figure 34).

Statistical fit of models to the observed data

Table 58 summarizes the AIC and BIC values for each extrapolation, with a lower AIC or BIC value indicating a better fitting model. Based on these values, the Gompertz distribution is shown to be the best fit for Glofit-GemOx. Log-normal was the second-highest ranked distribution, with for instance the log-logistic being within four points of the log-normal distribution, indicating that there is not a strong rationale for this distribution to be selected over log-normal on the basis of statistical fit. For R-GemOx, the generalized gamma and log-normal distributions are the highest ranked AIC and BIC ranked distributions.

Clinical plausibility of long-term extrapolations for PFS

Although the shape of the hazard for Glofit-GemOx was compatible with the exponential and Weibull distributions these distributions may underestimate the long-term PFS for Glofit-GemOx. Furthermore, visual inspection of the curves demonstrates that the exponential distribution overestimates PFS at early stages of the model (Figure 7), which is supported by this distribution having the worst AIC/BIC ranking. Exponential as well as Weibull have a rather poor statistical fit. Moreover, NICE DSU TSD 14 (56) recommends fitting the same distribution to both treatment arms when fitting individual parametric models to each arm, as different distributions allow very different shapes and would require greater justification.

In Figure 7 Gompertz fits the best, but when visually evaluating the curves, this distribution yields clinically rather implausible estimates of long-term PFS for Glofit-GemOx. Both Gompertz and the generalized gamma distributions may also overestimate long-term PFS of R-GemOx.

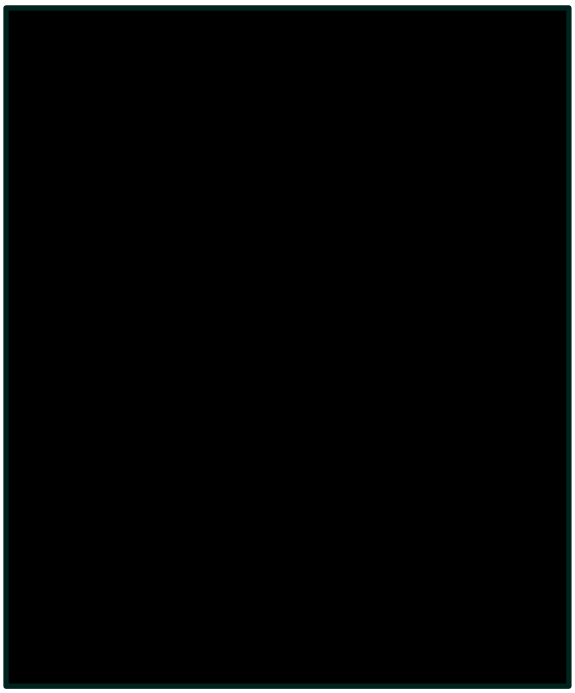

Figure 7 PFS standard functions (independent fit) for Glofit-GemOx and R-GemOx

In Figure 35 plausibility of long-term extrapolations is explored more. The smoothed hazards and survival curve of all fitted distributions for PFS are reported simultaneously on top of the empirical KM curve data. Based on the figures for instance, the Weibull and

exponential distributions perform poorly. The log-normal distribution performs rather well, although it may produce slightly too high a hazard, especially for Glofit-GemOx, indicating conservative results.

Taking all the above factors into account, the log-normal distribution was chosen for both Glofit-GemOx and R-GemOx base case. Alternative distributions have been explored in scenario analyses, which shows that the results are robust. Log-normal has also been a feasible distribution and used earlier on other DLBCL assessments in Denmark and across Nordics, like assessment of glofitamab (COLUMVI) for relapsed or refractory DLBCL and assessment of Polatuzumab vedotin (Polivy®) +R-CHP Previously untreated DLBCL.

Table 15 Summary of assumptions associated with extrapolation of PFS

Method/approach	Description/assumption
Data input	STARGLO (GO41944)
Model	Exponential, Weibull, Log-normal, Generalised Gamma, Log-logistic, Gompertz, 2-parameter gamma
Assumption of proportional hazards between intervention and comparator	No
Function with best AIC fit	[redacted]
Function with best BIC fit	[redacted]
Function with best visual fit	[redacted]
Function with best fit according to evaluation of smoothed hazard assumptions	[redacted]
Validation of selected extrapolated curves (external evidence)	A Danish clinical expert has evaluated that a log-normal distribution would be clinically plausible for patients with R/R DLBCL, which is consistent with the log-normal para-metric function previously chosen by the professional committee of the DMC for both PFS and OS in the polatuzumab + bendamustine + rituximab (pola+BR) submission who assessed the curves to be realistic (57). Choosing log-normal distribution for extrapolation generates a realistic and clinical plausible result.

Method/approach	Description/assumption
Function with the best fit according to external evidence	[redacted]
Selected parametric function in base case analysis	[redacted]
Adjustment of background mortality with data from Statistics Denmark	Yes
Adjustment for treatment switching/cross-over	No
Assumptions of waning effect	No
Assumptions of cure point	Yes: Patients alive and progression-free at 2 years in the current model enter long-term remission but are prone to excess mortality and quality of life decrement

8.1.1.2 Extrapolation of OS

Assessment of overall survival

OS was the primary endpoint in the STARGLO trial (see 7.1.4). Median investigator-assessed OS was [redacted]

Assessment of proportional hazards

The OS KM curves for Glofit-GemOx and R-GemOx clearly demonstrate a reduced mortality risk for patients treated with Glofit-GemOx compared to R-GemOx (Figure 4).

The first assumption to check when choosing an extrapolation model is whether the PH assumption is valid for OS. Again, this is tested using the Schoenfeld test and the log-log plot. The Schoenfeld test ($p = 0.2704$) (Figure 36) would allow acceptance of the proportional hazard assumption, but the log-log plot shows that the curves cross at early time points (Figure 37). Although the crossing occurs very early and the curves stabilize thereafter, the proportional hazards assumption was violated, and the OS curves were fitted independently.

Analysis of hazard plots suggest non-monotonic hazard rates for both Glofit-GemOx and R-GemOx (Figure 38), indicating compatibility with log-normal, log-logistic and generalized gamma distributions.

Statistical fit of models to the observed data

Table 59 summarizes the AIC and BIC values for each OS extrapolation. Based on these values, the Gompertz distribution n is shown to be the best fit for Glofit-GemOx. Log-

normal was the second-highest ranked distribution. For R-GemOx, the log-normal and Generalized Gamma distributions were the highest AIC and BIC ranked distributions, respectively.

Clinical plausibility of long-term extrapolations for OS

Although Gompertz had the best fit based on AIC and BIC, but when visually evaluating the curves, this distribution yields clinically implausible estimates of long-term OS for Glofit-GemOx as well as for R-GemOx. Log-normal distribution has a good fit among chosen distributions, and it also produces more plausible long-term extrapolation for both treatments (Figure 8).

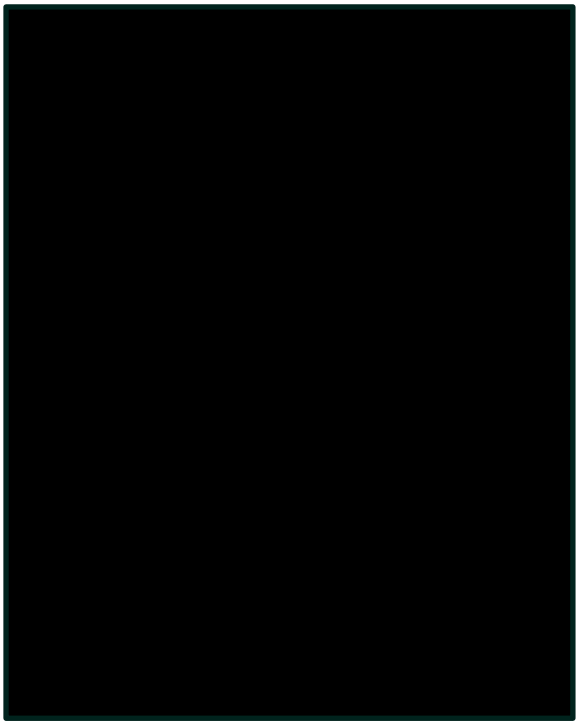

Figure 8 OS extrapolation functions (independent fit) for Glofit-GemOx and GemOx

In Figure 39 plausibility of long-term extrapolations is explored more. The smoothed hazards and survival curve of all fitted distributions for OS are reported simultaneously on top of the empirical KM curve data. Based on the figures, for instance, the Weibull distribution performs poorly. The log-normal distribution performs rather well, although it may produce slightly too high a hazard, especially for Glofit-GemOx, indicating conservative results.

Taking all the above factors into account the log-normal distribution was chosen for both Glofit-GemOx and R-GemOx as a base case. Alternative distributions have been explored in scenario analyses, which shows that the results are quite robust. Also spline model with 2 or 3 knots (knots chosen as equally-spaced quantiles of the log uncensored survival times) was considered but that model wouldn't provide additional value. The hazards in STARGLO are not so complex and do not justify need for spline model for the comparators.

Table 16 Summary of assumptions associated with extrapolation of OS

Method/approach	Description/assumption
Data input	STARGLO (GO41944)
Model	Exponential, Weibull, Log-normal, Generalised Gamma, Log-logistic, Gompertz, 2-parameter gamma
Assumption of proportional hazards between intervention and comparator	No
Function with best AIC fit	[redacted]
Function with best BIC fit	[redacted]
Function with best visual fit	[redacted]
Function with best fit according to evaluation of smoothed hazard assumptions	[redacted]
Validation of selected extrapolated curves (external evidence)	[redacted]
Function with the best fit according to external evidence	[redacted]
Selected parametric function in base case analysis	[redacted]
Adjustment of background mortality with data from Statistics Denmark	Yes

Method/approach	Description/assumption
Adjustment for treatment switching/cross-over	No
Assumptions of waning effect	No
Assumptions of cure point	Yes: Patients alive and progression-free at 2 years in the current model enter long-term remission but are prone to excess mortality and quality of life decrement

8.2 Assumptions of long-term treatment effect

8.2.1 Long-term remission / survivorship

The assumptions related to long-term survivorship and remission are informed by mechanism of action of treatments, biological plausibility, clinical evidence from clinical trials, evidence from observational studies (real world data) and real-life clinical practice.

The genetic heterogeneity of DLBCL suggests some patients may respond better to treatment, leading to prolonged remission. Effective treatments can restore or boost the patient's immune system, contributing to long-term disease control or eradication. Modern DLBCL treatments like anti-CD20 monoclonal antibodies, CAR-T cells and bispecific antibodies target specific mechanisms, have shown to lead to durable responses. These therapies typically result in higher complete response rates, translating into prolonged remission periods and potentially curative outcomes in some patients.

The standard practice in Danish clinics regarding DLBCL patients is that those who remain free of disease progression for two years post-treatment is primarily followed up in primary care (15). Observational studies like SCHOLAR-1 study (18) have shown improved long-term overall survival rates, where many patients maintain remission beyond two years (plateau effect). The same effect is seen in CORAL (22); Maziarz et al. 2022) (59) and ZUMA-7 (60) studies. In the STARGLO study the plateau observed in the KM PFS curve (Figure 5), together with the fact that just 50 (27.3%) of patients in the Glofit-GemOx arm went on to receive at least one subsequent treatment, compared to 52 (57.1%) patients in the R-GemOx arm.

Long-term remission / survivorship or remission (or cure rate) is typically applied in DLBCL modelling. It has been deemed clinically plausible for instance in previous R/R DLBCL in NoMA (ID2017_116 and ID2017_105) and in NICE submissions, irrespective of the technology being assessed (see (NICE TA649/559/567/895/927/947/954). Furthermore, it has been proven in Denmark (50) and it was applied in the previous assessment of Glofitamab in R/R DLBCL 3L+ in Denmark.

To account for the long-term survivorship in DLBCL, we assume in the base case that patients alive and progression-free at 2 years in the current model enter long-term remission. On entering long-term remission, patients do not continue to progress, revert

to near general population utility values, and do not accrue any further costs. In addition, when the majority of progressed patients in the model have died, mortality risk for the remaining patients reverts to a near general population level (9% excess vs. the general population based on a standardized mortality rate (SMR) identified from Maurer 2014 (19) and used e.g. in NICE submission (TA559 and TA567), adjusted to account for potential excess comorbidities together with assuming quality-of-life detriment. Scenarios with alternative remission rates of 3 and 5 years were explored as scenario analyses, and no excess mortality in long-term remission and an alternative source for mortality rate were applied (61). To maintain consistency, long-term remission is assumed to be treatment independent, with the same assumptions applied to both treatment arms in the model. Therefore, the model captures long-term burden of disease in terms of mortality and comorbidities in terms of survival and HRQoL.

8.2.2 Waning effect

See appendix D.2.10

8.3 All-cause mortality

Background mortality was calculated using age- and gender-specific all-cause mortality rates by year in the general Danish population, obtained from the DMC Mortality sheet. Sex-adjusted 1-year mortality rates were calculated from this source, adjusted by the relevant cohort sex distribution and an SMR adjustment to account for increased mortality risk due to excess comorbidities.

A general fact that needs to be considered in the modeling is that the risk of death is not linear but increases exponentially as age increases. Most cost-effectiveness models only consider a cohort of a specific age that produces somewhat unprecise estimate for most of the follow-up period. However, the STARGLO trial included a broad range of ages (22-88 years) and a skewed distribution of patients over different age groups. Therefore, the model presents two options to select the age of the population and to estimate background mortality: (1) cohort with age distribution as observed in STARGLO (the base case); (2) cohort with a specific age of years (option). Using the first option, a time horizon shorter than 60 years will lead to some patients still being alive at the horizon. Thus, considering the distribution of age in STARGLO necessitates the use of at least 60-year time horizon in the base case in order to accurately capture the full impact on health and costs.

8.3.1 Calculation of transition probabilities

We applied PSM model so the transition probabilities are based on the PFS and OS curves from the STARGLO trial. Extrapolation beyond the clinical follow-up period was performed by fitting parametric distributions to the observed time to event data from the trial.

Table 17 Transitions in the health economic model

Health state (from)	Health state (to)	Description of method	Reference

Progression-free survival	Progressed disease	[redacted]	STARGLO (4)
	Death	[redacted]	STARGLO (4)
Progressed disease	Death	[redacted]	STARGLO (4)

The PSM results subject to long-term treatment effect and survival assumptions are demonstrated in Figure 9. These Markov trace figures are based on the model and show the proportion of patients who are in the progression-free, post-progression and death state since modeling initiation. The figures support the chosen lifetime perspective of 60 years.

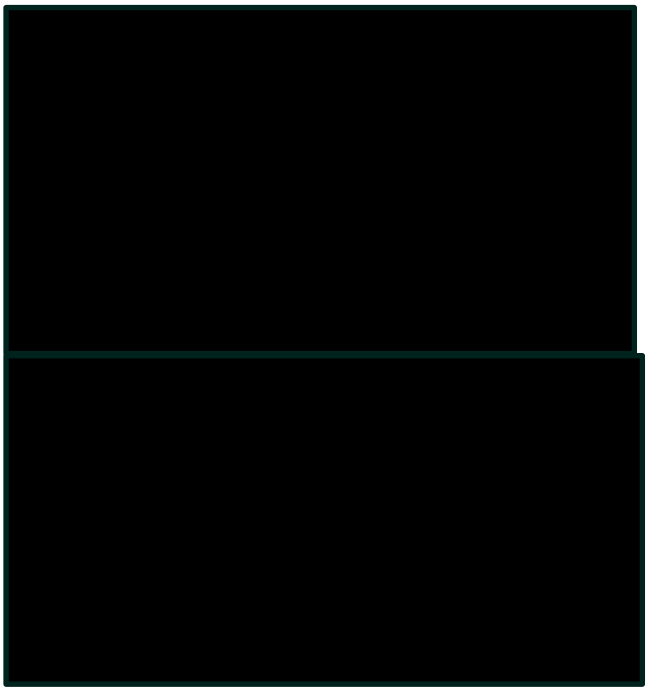

Figure 9 Markov trace – Glofit-GemOx and GemOx

8.4 Presentation of efficacy data from [additional documentation]

Not applicable as STARGLO is the only study on the relative effect between Glofit-GemOx vs GemOx.

8.5 Modelling effects of subsequent treatments

Data on post-discontinuation regimen shares and treatment duration for Glofit-GemOx and R-GemOx were taken from the STARGLO trial (Table 18). As the data is from STARGLO there are some subsequent treatment lines difference between the intervention and the comparator. By using the STARGLO data we can make sure that the internal consistency of the model and the clinical trial results remains. Hence the clinical effects of subsequent treatments are incorporated into STARGLO KM curves and related extrapolations. The effects related to costs are calculated based on the pharmaceutical treatments and health care resource utilisation (unit price x amount).

Table 18 Share of subsequent treatments

Therapy class	Therapy	% on Glofit-GemOx N=52 Number of subsequent treatments = 82	mean duration in weeks	% on R-GemOx N=50 Number of subsequent treatments = 96	mean duration in weeks
Anti-CD20 + chemo	BR	[redacted]	[redacted]	[redacted]	[redacted]
Anti-CD20 + chemo	R-GEMOX	[redacted]	[redacted]	[redacted]	[redacted]
Anti-CD20 + chemo	R-CHOP	[redacted]	[redacted]	[redacted]	[redacted]
Anti-CD20	Rituximab	[redacted]	[redacted]	[redacted]	[redacted]
Anti-CD20 + chemo	Other R-chemo regimens	[redacted]	[redacted]	[redacted]	[redacted]
Chemo (no anti-CD20)	Other chemo regimens (not including R)	[redacted]	[redacted]	[redacted]	[redacted]
Drug-antibody conjugate	Pola-BR	[redacted]	[redacted]	[redacted]	[redacted]
Immunomodulating agent	Tafa-Len	[redacted]	[redacted]	[redacted]	[redacted]
Immunomodulating agent	Lenalidomide	[redacted]	[redacted]	[redacted]	[redacted]
Chemo (no anti-CD20)	Pixantrone	[redacted]	[redacted]	[redacted]	[redacted]
Other	Other/Clinical Trial	[redacted]	[redacted]	[redacted]	[redacted]
Radiotherapy	Radiotherapy	[redacted]	[redacted]	[redacted]	[redacted]
Stem-cell transplant	Allogeneic SCT	[redacted]	[redacted]	[redacted]	[redacted]
Stem-cell transplant	Autologous SCT	[redacted]	[redacted]	[redacted]	[redacted]
CAR-T	CAR-T	[redacted]	[redacted]	[redacted]	[redacted]
Drug-antibody conjugate	Loncastuximab	[redacted]	[redacted]	[redacted]	[redacted]
Bi-specific antibody	Mosunetuzumab	[redacted]	[redacted]	[redacted]	[redacted]
Bi-specific antibody	Epcoritamab	[redacted]	[redacted]	[redacted]	[redacted]
Bi-specific antibody	Glofitamab	[redacted]	[redacted]	[redacted]	[redacted]

8.6 Other assumptions regarding efficacy in the model

The model applies the same general assumptions as the previous Glofitamab 3L model (62).

As described in chapter 8.2, we assume long-term remission and survivorship for patients who are progression-free after 2 years, whereby such patients are in principle assumed to have the same utility and mortality risk as the general population. However, to model real life better, we apply i) a standardized mortality rate (SMR) adjustment to account for increased mortality risk due to excess comorbidities, and simultaneously ii) a QoL adjustment factor to account for excess disutility related to comorbidities in long-term survivors (see above).

8.7 Overview of modelled average treatment length and time in model health state

Estimates for the modelled average and modelled median of the PFS, PPS and OS predicted by the extrapolation model are reported in Table 19 and Table 20.

Table 19 Estimates in the model

	Modelled average OS	Modelled median OS	Observed median from relevant study
Glofit-GemOx	[redacted]	[redacted]	[redacted]
R-GemOx	[redacted]	[redacted]	[redacted]

Regarding PPS, only mean values are available (see model sheet Model Inputs columns J:K:134-135).

Table 20 Estimates in the model

	Modelled average PPS	Modelled median PPS	Observed median from relevant study
Glofit-GemOx	[redacted]	N/A	N/A
R-GemOx	[redacted]	N/A	N/A

Time to off treatment (TTOT) data from STARGLO was used to model the actual duration on treatment. As TTOT data was complete from STARGLO, there was no need to fit a distribution to the KM data and, as treatment for glofitamab in the Glofit-GemOx combination is limited to a maximum of 12 cycles, so therefore practically there was no need for long-term curve fitting for extrapolation to be used in the modeling. Using the KM TTOT data directly removes adding an unnecessary level of uncertainty resulting from curve fitting although some flexibility related to this aspect is built into the model.

While patients remained progression-free, they could be on or off treatment. Once in the progression health state, it was assumed that patients would move to a further line of treatment. The distribution, proportions of patients on subsequent therapies, and the duration for which they receive them, was informed by the STARGLO trial.

Mean of patients still on treatment are described in Table 21. The data in the model is taken directly from STARGLO study (4, 53) to avoid the inconsistencies due to back calculation of the step-up dosing of Glofitamab

Table 21 Overview of modelled average treatment length and time in model health state, undiscounted and not adjusted for half cycle correction

Treatment	Treatment length, months	PFS, months	PPS, months	OS , months
Glofit-GemOx	[redacted]	[redacted]	[redacted]	[redacted]
R-GemOx	[redacted]	[redacted]	[redacted]	[redacted]

9. Safety

9.1 Safety data from the clinical documentation

This section presents safety data from the STARGLO study, based on the CCODs of 16 February, 2024, and 1 May, 2025. Table 22 and Table 23 present data from both CCODs. While complete data from the 1 May 2025 CCOD was not available at the time of this application, the available information presented demonstrates no significant changes compared to earlier data. This consistency aligns with the median time to first adverse event (AE) following the initial glofitamab/rituximab dose: 2.0 days (range: 1.0–175.0) in the Glofit-GemOx (Glofit Exposed) population and 2.0 days (range: 1.0–85.0) in the R-GemOx population. Therefore, the 16 February 2024 CCOD data remain representative of the safety profile of Glofit-GemOx.

The safety-evaluable population includes all patients, who have received any amount of any study treatment in the treatment or control arm. In the Glofit-GemOx group, 172 (94%) of 183 patients were exposed to glofitamab (Glofit Exposed), while 180 (98%) patients received any study treatment (Any Treatment Exposed). In the R-GemOx group, 88 (97%) of 91 patients were exposed to rituximab. In this section, safety outcomes will be presented for the groups who received any study treatment except for cytokine release syndrome (CRS) and immune effector cell-associated neurotoxicity syndrome (ICANS) for which patients had to be exposed to glofitamab.

At the CCOD of 16 February 2024, the median number of glofitamab cycles received was 11.0 (IQR 4–12) with a median duration of 218.0 days (range: 1-296 days). Overall, the safety profile of patients in the Glofit-GemOx (Glofit Exposed) group was comparable to that of the Glofit-GemOx (Any Treatment Exposed) group. In the R-GemOx group, the

median number of rituximab cycles received was 4.0 (IQR 2–8) with a median duration of 64.0 days (range: 1-183 days) (27, 52).

Table 22 Overview of safety events (STARGLO: Glofit-GemOx (Any Treatment Exposed) vs. R-GemOx). CCODs: 16 Feb 2024 and 1 May 2025

	CCOD: 16 Feb 2024 (27, 53)			CCOD: 1 May 2025 (4)		
	Intervention: Glofit-GemOx N=180	Comparator: R-GemOx N=88	Difference, % (95 % CI)	Intervention: Glofit-GemOx N=180	Comparator: R-GemOx N=88	Difference, % (95 % CI)
Number of AEs, n	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Number and proportion of patients with ≥1 AE, n (%)	180 (100)	84 (95.5)	4.6 (0.2, 8.9)	[redacted]	[redacted]	[redacted]
Number of serious adverse events*, n	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Number and proportion of patients with ≥ 1 SAEs, n (%)	98 (54.4)	15 (17.0)	37.4 (26.7, 48.1)	[redacted]	[redacted]	[redacted]
Number of CTCAE grade ≥ 3 events, n	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Number and proportion of patients with ≥ 1 CTCAE grade ≥ 3 events§, n (%)	140 (77.8)	36 (41.0)	36.9 (24.9, 48.8)	[redacted]	[redacted]	[redacted]
Number of adverse reactions, n	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Number and proportion of patients with ≥ 1 adverse reactions, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

	CCOD: 16 Feb 2024 (27, 53)			CCOD: 1 May 2025 (4)		
	Intervention: Glofit-GemOx N=180	Comparator: R-GemOx N=88	Difference, % (95 % CI)	Intervention: Glofit-GemOx N=180	Comparator: R-GemOx N=88	Difference, % (95 % CI)
Number and proportion of patients who had a dose reduction, n (%)**	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Number and proportion of patients who discontinue treatment regardless of reason, n (%)	106 (58.9)	65 (73.9)	[redacted]	[redacted]	[redacted]	[redacted]
Number and proportion of patients who discontinue treatment due to adverse events, n (%)	48 (26.7)	11 (12.5)	[redacted]	[redacted]	[redacted]	[redacted]

95% CI for risk differences is calculated using the Wald method. CTCAE, Common Terminology Criteria for Adverse Events. * A serious adverse event is an event or reaction that at any dose results in death, is life-threatening, requires hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability or incapacity, or results in a congenital anomaly or birth defect (see the ICH's complete definition). ** Adverse Events that led to dose Modification or interruption. § CTCAE v. 5.0 must be used if available.

Although higher rates of AEs were observed with Glofit-GemOx versus R-GemOx, the safety profile was as expected for this patient population. Moreover, the safety outcomes should be viewed in the context of the evolving COVID-19 pandemic (27, 63).

All adverse events

At the CCOD of 16 February 2024, 180 (100%) patients in the Glofit-GemOx (Any Treatment Exposed) group and 84 (96%) patients in the R-GemOx group had at least one AE. The most common (≥ 20% of patients) reported AEs by preferred term (PT) besides CRS were thrombocytopenia/platelet count decreased (48.3% vs. 47.7%), anaemia (40.6% vs. 21.6%), nausea (39.4% vs. 39.8%), diarrhoea (34.4% vs. 27.3%), aspartate aminotransferase increased (32.8% vs. 19.3%), alanine aminotransferase increased (31.7% vs. 21.6%), [redacted] (27, 53).

Adverse events related to treatment

[redacted](53).

[redacted](53). CRS will be described below in the adverse event of special interest (AESI) section.

Serious adverse events

At the CCOD of 16 February 2024, serious adverse events (SAEs) of any grade were reported in a greater proportion of patients in the Glofit-GemOx (Any Treatment Exposed) arm than in the R-GemOx arm (54.4% vs 17.0%) (27). [redacted](53). All SAEs with a frequency of ≥ 5% are listed in Table 23 (4, 53). At the CCOD of 1 May 2025, there were no changes to the serious adverse events with a frequency of ≥ 5% compared to the CCOD of 16 February 2024.

Table 23 Serious adverse events with a frequency of ≥ 5%. CCODs: 16 Feb 2024.

Adverse events	Intervention (N=180)		Comparator (N=88)	
	Number of patients with adverse events	Number of adverse events	Number of patients with adverse events	Number of adverse events

Adverse events	Intervention (N=180)		Comparator (N=88)	
Immune system disorders	[redacted]	[redacted]	[redacted]	[redacted]
Cytokine release syndrome, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Infections and infestations	[redacted]	[redacted]	[redacted]	[redacted]
Pneumonia, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
COVID-19, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
General disorders and administration site conditions	[redacted]	[redacted]	[redacted]	[redacted]
Pyrexia, n (%)	[redacted]	[redacted]	[redacted]	[redacted]

* A serious adverse event is an event or reaction that at any dose results in death, is life-threatening, requires hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability or incapacity, or results in a congenital anomaly or birth defect (see the ICH's complete definition).

Serious adverse events related to treatment

[redacted] (53).

CTCAE grade ≥3 events

At the CCOD of 16 February 2024, 140 (77.9%) patients in the Glofit-GemOx (Any Treatment Exposed) group and 36 (41.0%) patients in the R-GemOx group had at least one grade 3 or worse AE.

Adverse events leading to dose modification or dose interruption

No dose modifications of glofitamab, obinutuzumab, gemcitabine and rituximab were permitted, however dose interruptions were permitted. The oxaliplatin dose could be reduced for neuropathy per specified instructions in the protocol. In situations where clinical judgment of benefit-risk considerations warranted deviating from protocol guidelines, decisions on study treatments were permitted by the protocol to be taken by the investigator upon consultation with the Medical Monitor (27).

[redacted] (53).

[redacted] (53).

Adverse events leading to treatment discontinuation

At the CCOD of 16 February 2024, 106 patients (58.9%) in the Glofit-GemOx (Any Treatment Exposed) group discontinued treatment compared with 65 patients (73.9%) in the R-GemOx group. The most common reason for discontinuation in both groups was disease progression (22.8% vs. 43.1%) (27, 53).

The proportion of patients with at least one AE, which led to discontinuation of any study treatment, was greater in the Glofit-GemOx (All Treatment Exposed) group compared to the R-GemOx group (26.7% vs 12.5%) (27, 53). The most commonly reported AE leading to discontinuation of study treatment was COVID-19 in both the Glofit-GemOx arm (Any Treatment Exposed) (12.2% vs. 5.7%).

A higher proportion of patients discontinued study treatment due to COVID-19 or COVID-19-associated adverse events in the Glofit-GemOx group (Any Treatment Exposed) (25 [13.9%]) than in the R-GemOx group (5 [5.7%]) (27, 53). 15 patients in the Glofit-GemOx arm and 5 patients in the R-GemOx arm discontinued treatment as per the Protocol v6 mandate, where patients who developed documented SARS-CoV-2 infection during the study were required to permanently discontinue study treatment (27, 53).

Deaths

[redacted] (53).

[redacted] (53).

[redacted]

[redacted] (53).

Adverse Events of Special Interests

The key clinically significant AESIs related to glofitamab treatment, which may have implications for prescribing decisions and patient management, included Grade ≥ 2 CRS, Grade ≥ 2 tumor flare and Grade ≥ 3 TLS.

Cytokine release syndrome

At the CCOD of 16 February 2024, CRS events of any grade were reported in 76 (44.2%) of 172 patients in the Glofit-GemOx (Glofit Exposed) group using the American Society for Transplantation and Cellular Therapy grading criteria (64). The majority of these AEs were of low grade, with 54 (31.4%) of patients experiencing Grade 1 CRS events and 18 (10.5%) of patients experiencing Grade 2 CRS events. Grade 3 CRS AEs were reported in 4 of 172 patients (2.3%) and no grade 4 or 5 CRS AEs were reported. CRS events of any grade occurred predominately in Cycle 1 and occurred mainly after the glofitamab 2.5 mg dose (any grade 59/76 patients [77.6%]) and prior to the 10 mg dose (any grade 24/73 patients [32.9%]).

[redacted]

[redacted] (27, 53).

Immune effector cell-associated neurotoxicity syndrome (ICANS) events (based on CTCAE terms consistent with ICANS) were reported in [redacted] All events were concurrently with CRS and were resolved with CRS resolution (27).

Tumor flare

At the CCOD of 16 February 2024, tumor flare or suspected tumor flare events were experienced by [redacted].

Of these, 1 patient in each group experienced a Grade ≥ 2 tumor flare event. In the Glofit-GemOx group 1 patient had a Grade 3 suspected tumor flare event of non-serious cholestasis in a patient with baseline liver lesions, which had an onset prior to glofitamab infusion on study day 3. The event was considered related to treatment, study treatment

was interrupted, and the event was unresolved or ongoing as of the CCOD. In the R-GemOx group, 1 of 88 patients (1.1%) had a Grade 2 suspected tumor flare event of non-serious thrombocytopenia. The event was considered related to study treatment and had been resolved by the CCOD (27, 53).

Tumor lysis syndrome

At the CCOD of 16 February 2024, [redacted]. All the events were considered related to study treatment by the investigator, and all the patients received treatment for the AE. At the time of the CCOD, all events had been resolved (53).

The median time to onset of TLS in the Glofit-GemOx (Glofit Exposed) group from the first glofitamab dose was 8.5 days (range 7.5–21.5 days), with a median duration of 7.0 days (range 3–10 days). For the R-GemOx arm, the median time to onset of TLS from the first rituximab dose was 3.5 days (range 2.6–7.5 days), with a median duration of 8.0 days (range 6–15 days) (53).

Adverse events in the health economic model

In the health economic model only treatment-related AEs with a severity grade of 3 or higher were considered in the analysis to reflect those events that are most likely to impact cost-effectiveness (Table 17). Furthermore, only AEs occurring in over 1% of patients were considered. As the IPDs from the STARGLO study were available the actual number of AEs observed were used to estimate the AE incidence. The model uses this data to calculate a weekly probability of experiencing each event while on treatment together with an estimate on total follow-up. Therefore, the number of events reported can include several events per patient.

$$P(\text{adverse event}) = 1 - e^{-\text{Total number of events}_x / \text{Total duration of follow-up for AEs}}$$

where x is the adverse event and follow-up is follow-up in weeks. Costs and disutility associated with managing AEs are discussed in chapters further below. The calculation we applied utilises patient level information from the STAGLO study. The difference to the traditional one-time approach in calculation adverse event costs is expected to be marginal. In one time approach, adverse events and related costs occur in the first model cycle as a one-time cost.

Table 24 Adverse events used in the health economic model

Adverse events	Intervention			Comparator				
	Frequency used in economic model for intervention	N patients with AE (SD)	Prob. of event (per week)	Frequency used in economic model for comparator	N patients with AE (SD)	Prob. of event (per week)	Source	Justification
Adverse event, n (%)								
Alanine amino-transferase increased	5	5 (0.00)	0.0069	0	0 (0.00)	0.0000	STARGLO	STAGLO
Anaemia	24	22 (0.29)	0.0327	8	5 (0.89)	0.0599	STARGLO	STARGLO
CRS	4	4 (0.00)	0.0055	0	0 (0.00)	0	STARGLO	STARGLO
Diarrhoea	4	4 (0.00)	0.0055	0	0 (0.00)	0	STARGLO	STARGLO
Febrile neutropenia	6	6 (0.00)	0.0083	0	0 (0.00)	0	STARGLO	STARGLO
Lymphocyte count decreased	24	18 (0.59)	0.0327	0	0 (0.00)	0	STARGLO	STARGLO
Neutrophil count decreased	58	38 (1.13)	0.0771	11	9 (0.67)	0.0814	STARGLO	STARGLO
Neutropenia	36	24 (0.88)	0.0486	6	6 (0.00)	0.0453	STARGLO	STARGLO

Adverse events	Intervention			Comparator				
Pneumonia	7	7 (0.00)	0.0096	0	0 (0.00)	0	STARGLO	STARGLO
Platelet count decreased	54	31 (1.26)	0.0720	9	8 (035)	0.0671	STARGLO	STARGLO
Thrombo-cytopenia	26	17 (0.80)	0.0353	8	6 (0.52)	0.0599	STARGLO	STARGLO
White blood cell count decreased	29	16 (1.05)	0.0393	8	6 (0.82)	0.0599	STARGLO	STARGLO

9.2 Safety data from external literature applied in the health economic model

Not applied.

Table 25 Adverse events that appear in more than X % of patients

Adverse events	Intervention (N=x)			Comparator (N=x)			Difference, % (95 % CI)	
	Number of patients with adverse events	Number of adverse events	Frequency used in economic model for intervention	Number of patients with adverse events	Number of adverse events	Frequency used in economic model for comparator	Number of patients with adverse events	Number of adverse events
Adverse event, n								

10. Documentation of health-related quality of life (HRQoL)

Table 26 Overview of included HRQoL instruments

Measuring instrument	Source	Utilization
EQ-5D-5L	STARGLO	Clinical effectiveness and utility. Section 10.1.
EORTC QLQ-C30	STARGLO	Clinical effectiveness. See Appendix F.
FACT-Lym LymS	STARGLO	Clinical effectiveness. See Appendix F.

EORTC QLQ-C30, European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30; EQ-5D-5L, European Quality of Life 5-Dimension 5-Level Questionnaire; FACT-Lym LymS, Functional Assessment of Cancer Therapy-Lymphoma Lymphoma Subscale

In addition to EQ-5D-5L, STARGLO has collected health-related quality of life (HRQoL) with the generic measuring instrument European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC QLQ-C30) and the disease-specific instrument Functional Assessment of Cancer Therapy-Lymphoma Lymphoma Subscale (FACT-Lym LymS). These are reported as supplementary information in Appendix F.

10.1 Presentation of the health-related quality of life measured by EQ-5D-5L

10.1.1 Study design and measuring instrument

The STARGLO study design is described in Section 6.1.1. The EQ-5D-5L is an exploratory endpoint used to assess health status utility scores in patients treated with Glofit-GemOx or R-GemOx for pharmacoeconomic modeling.

The EQ-5D-5L is a validated self-reported health status questionnaire designed to generate health utility scores for use in health economic analyses (65-68). It consists of five dimensions assessing mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. The health utility component of EQ-5D-5L is scored from 0 to 1, with higher scores indicating better HRQoL. The Visual Analog Scale (VAS) component measures the patient's current health state, ranging from 0 to 100, where higher scores reflect better HRQoL.

10.1.2 Data collection

Assessments of the EQ-5D-5L utility index and VAS were conducted at baseline; Day 1 in cycle 2, 3, 5, and 7; treatment completion; and every three months during post-treatment follow-up. Data was collected in the PRO-evaluable population defined as all

randomized patients with a baseline and at least one post-baseline PRO assessment. Change from baseline at each time point were calculated by treatment arm.

The EQ-5D-5L questionnaire was considered completed for compliance purposes if at least 50% of questions had been answered. In practice, all patients who met this criterion provided responses for all five dimensions, allowing calculation of utility index scores. In both the Glofit-GemOx and R-GemOx populations, compliance was 100% at baseline and remained above 90% up to Cycle 7 Day 1. Compliance rates dropped at treatment completion/early discontinuation to 74.8% and 81.0%, respectively, and continued to decline during long-term follow-up owing to attrition.

Table 27 Pattern of missing data and completion, EQ-5D-5L data: CCOD, 1 May 2025

Time point	HRQoL population N	Missing N (%)	Expected to complete * N	Completion § N (%)
	Number of patients at randomization	Number of patients for whom data is missing (% of patients at randomization)	Number of patients "at risk" at time point X	Number of patients who completed (% of patients expected to complete)
Glofit-GemOx				
Baseline	183	[redacted]	[redacted]	[redacted]
Cycle 2 Day 1	183	[redacted]	[redacted]	[redacted]
Cycle 3 Day 1	183	[redacted]	[redacted]	[redacted]
Cycle 5 Day 1	183	[redacted]	[redacted]	[redacted]
Cycle 7 Day 1	183	[redacted]	[redacted]	[redacted]
Treatment completion / Early discontinuation	183	[redacted]	[redacted]	[redacted]
Long term follow-up month 3	183	[redacted]	[redacted]	[redacted]
Long term follow-up month 6	183	[redacted]	[redacted]	[redacted]
Long term follow-up month 9	183	[redacted]	[redacted]	[redacted]
Long term follow-up month 12	183	[redacted]	[redacted]	[redacted]
Long term follow-up month 15	183	[redacted]	[redacted]	[redacted]
Long term follow-up month 18	183	[redacted]	[redacted]	[redacted]

Time point	HRQoL population N	Missing N (%)	Expected to complete * N	Completion § N (%)
Long term follow-up month 21	183	[redacted]	[redacted]	[redacted]
Long term follow-up month 24	183	[redacted]	[redacted]	[redacted]
Long term follow-up month 27	183	[redacted]	[redacted]	[redacted]
Long term follow-up month 30	183	[redacted]	[redacted]	[redacted]
Long term follow-up month 33	183	[redacted]	[redacted]	[redacted]
Long term follow-up month 36	183	[redacted]	[redacted]	[redacted]
		R-GemOx		
Baseline	91	[redacted]	[redacted]	[redacted]
Cycle 2 Day 1	91	[redacted]	[redacted]	[redacted]
Cycle 3 Day 1	91	[redacted]	[redacted]	[redacted]
Cycle 5 Day 1	91	[redacted]	[redacted]	[redacted]
Cycle 7 Day 1	91	[redacted]	[redacted]	[redacted]
Treatment completion / Early discontinuation	91	[redacted]	[redacted]	[redacted]
Long term follow-up month 3	91	[redacted]	[redacted]	[redacted]
Long term follow-up month 6	91	[redacted]	[redacted]	[redacted]
Long term follow-up month 9	91	[redacted]	[redacted]	[redacted]
Long term follow-up month 12	91	[redacted]	[redacted]	[redacted]
Long term follow-up month 15	91	[redacted]	[redacted]	[redacted]
Long term follow-up month 18	91	[redacted]	[redacted]	[redacted]
Long term follow-up month 21	91	[redacted]	[redacted]	[redacted]
Long term follow-up month 24	91	[redacted]	[redacted]	[redacted]
Long term follow-up month 27	91	[redacted]	[redacted]	[redacted]
Long term follow-up month 30	91	[redacted]	[redacted]	[redacted]

Time point	HRQoL population N	Missing N (%)	Expected to complete * N	Completion § N (%)
Long term follow-up month 33	91	[redacted]	[redacted]	[redacted]
Long term follow-up month 36	91	[redacted]	[redacted]	[redacted]

* Number of patients expected to complete at least 50%. § Completed at least 50% of questions.

10.1.3 HRQoL results

EQ-5D-5L health states from STARGLO have been converted to the Danish population using Danish preference weights for EQ-5D-5L (69).

In both the Glofit-GemOx and R-GemOx populations, there were no changes from baseline in the mean EQ-5D-5L utility index scores and EQ VAS scores at all cycles during treatment and long-term follow-up, indicating maintenance of health status levels reported at baseline.

Table 28 HRQoL summary statistics, EQ-5D-5L utility index scores in STARGLO. PRO-evaluable population: CCOD, 1 May 2025

	Intervention		Comparator		Intervention vs. comparator
	N	Mean (SE)	N	Mean (SE)	Difference (95% CI) p-value
Baseline	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 2 Day 1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 3 Day 1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 5 Day 1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 7 Day 1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Treatment completion / Early discontinuation	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Long term follow-up month 3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Long term follow-up month 6	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

	Intervention	Comparator	Intervention vs. comparator
Long term follow-up month 9	[redacted]	[redacted]	[redacted]
Long term follow-up month 12	[redacted]	[redacted]	[redacted]
Long term follow-up month 15	[redacted]	[redacted]	[redacted]
Long term follow-up month 18	[redacted]	[redacted]	[redacted]
Long term follow-up month 21	[redacted]	[redacted]	[redacted]
Long term follow-up month 24	[redacted]	[redacted]	[redacted]
Long term follow-up month 27	[redacted]	[redacted]	[redacted]
Long term follow-up month 30	[redacted]	[redacted]	[redacted]
Long term follow-up month 33	[redacted]	[redacted]	[redacted]
Long term follow-up month 36	[redacted]	[redacted]	[redacted]

Figure 10 Change from baseline by visit, EQ-5D-5L utility index scores, PRO-evaluable population: CCOD, 1 May 2025

Table 29 HRQoL summary statistics, EQ VAS, PRO-evaluable population: CCOD, 1 May 2025

	Intervention		Comparator		Intervention vs. comparator
	N	Mean (SE)	N	Mean (SE)	Difference (95% CI) p-value
Baseline	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 2 Day 1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 3 Day 1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 5 Day 1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 7 Day 1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Treatment completion / Early discontinuation	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Long term follow-up month 3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Long term follow-up month 6	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Long term follow-up month 9	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Long term follow-up month 12	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Long term follow-up month 15	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Long term follow-up month 18	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Long term follow-up month 21	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Long term follow-up month 24	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Long term follow-up month 27	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Long term follow-up month 30	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

	Intervention	Comparator	Intervention vs. comparator
Long term follow-up month 33	[redacted]	[redacted]	[redacted]
Long term follow-up month 36	[redacted]	[redacted]	[redacted]

Figure 11 Change from baseline by visit, EQ VAS, PRO-evaluable population: CCOD, 1 May 2025

10.2 Health state utility values (HSUVs) used in the health economic model

10.2.1 HSUV calculation

Clinical description of disease specific and generic health-related quality of life (HRQoL), setting and measures in the STARGLO trial are described in the clinical part of this document.

Clinical efficacy data (PFS and OS) for Glofit-GemOx (on target step-up dosing: 2.5mg/10mg/30mg) were taken from the STARGLO phase 3 trial (CCOD, 1 may 2025). Health state utility values (HSUVs) were collected alongside the STARGLO trial using the EQ-5D-5L and were used to estimate utilities for three health states: PFS on-treatment, PFS off-treatment and PPS.

Utility measurements were assigned to PFS or PPS health states by comparing the date of progression with the corresponding date of measurement for the predicted utility. 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.

In both the Glofit-GemOx and R-GemOx populations, compliance for completing at least 50% of the questions in the EQ-5D-5L questionnaire was 100% at baseline and remained high (93.8% / 100%) up to Cycle 7 Day 1 (Table 61). Also, during the whole long-term follow-up compliance for completing remain at a reasonable high level. Sometimes, due to poor compliance, the HRQoL data from the trial suffers from significant missing data. In this case, the compliance remains high, so the EQ-5D-5L data from the STARGLO trial is feasible and the best source to be used in this economic evaluation.

In both the Glofit-GemOx and R-GemOx populations, there were no changes from baseline in the median EQ-5D-5L scores at all cycles during treatment and long-term follow-up at time points with 10 patients in either treatment population completing the questionnaire, indicating maintenance of health status levels reported at baseline (see the clinical part).

In the model, we assume long-term remission and survivorship for patients who are progression-free after a given time threshold, whereby such patients are assumed to have the same utility and mortality risk as the general population. However, in order to model real life better, we apply i) a standardized mortality rate (SMR) adjustment to account for increased mortality risk due to excess comorbidities, and simultaneously ii) a quality of life (QoL) adjustment factor to account for excess disutility related to comorbidities in long-term survivors.

We use SMR of 1.09 in the base case (19), and 1.18 (19) and 1.41 (61) in the scenario analysis. There is no clear evidence or standard approach regarding the appropriate QoL adjustment factor. We do not have information available about the long-term health conditions of those DLBCL 2L+ patients who are remission and are considered as long-term survivors. We used the article by Saarni et al (2008) (70) to inform this assumption. According to Table 2 in Saarni et al 2008, the average EQ-5D loss (3L with UK valuations) across all the listed conditions is approximately -0.04 in absolute terms. If we apply this estimate to the age-adjusted weekly utilities in the model (Sheet ”Utility Values” rows F136-), the adjustment factor of approximately -4% compared to the corresponding general population utility seems to be realistic. Other values are tested in the sensitivity analysis.

10.2.1.1 Mapping

Refer section 10.2.3.

10.2.2 Disutility calculation

Utility estimates are derived from the STARGLO trial. Therefore, AE specific disutility is set to ”no” in the base case to avoid double counting in the model. However, in the model this option is available and AE related cost are taken into account (see Chapter 11.5).

10.2.3 HSUV results

Utilities by state are estimated through a linear mixed effects model on post-baseline utilities while controlling for centralized baseline utilities and health state using random intercepts for each patient. Patients without baseline utilities and observations with undefined health status are dropped from the analysis.

Health states are defined by three states: before progression state while on treatment, before progression state while off treatment, and post progression state. Undefined health state corresponds to observations where the patient had an analysis date for utilities after the patient was censored without a record of progression. 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.

We explored patient specific random terms for intercept and slope and the fit statistics (AIC/BIC) and utility estimates were similar to that of the model with only random intercept. Therefore, we used a simpler model with only random intercept.

We have used the lme4 R package to fit the model. The equation used is as follows

lmer1 <- lmer(UTIL ~ UTIL + HEALTH_STATE + (1|USUBJID), data = util.postbase)

Analyses of utility values were conducted on a complete case dataset. The assumption of missing completely at random (MCAR) was made based on the following considerations: (1) less than 20% of the values were missing, (2) an examination of the missing data patterns revealed no systematic differences between observed and missing data, and (3) external factors and domain knowledge suggested no plausible mechanism by which the missingness was related to the values themselves.

There were 267 patients who had any utility observations (1861 observed utility values including baseline utility). We removed observations with undefined health state. Undefined health state corresponds to observations where the patient had an analysis date for utilities after the patient was censored without a record of progression.

After excluding observations with undefined health states, we had 266 patients with a total of 1,644 observations. Within these remaining data, we examined three groups of patients: those with baseline utility values, those with post-baseline utility values, and those with both baseline and post-baseline utility values.

We assumed the MCAR and conducted the analysis on patients who had both baseline and post-baseline utility values (i.e., complete case analysis without imputation). The analysis included 231 patients with a total of 1,359 post-baseline utility values. Out of these 231 patients, 155 received Glofit-GemOx and 76 received R-GemOx.

We also examined the utility distribution of the 30 patients who only had baseline utility values and were excluded from the analysis. The distribution of these excluded patients was similar to that of the patients included in the analysis. Therefore, we concluded that there was no indication of patient selection bias, supporting the reasonableness of the MCAR assumption.

HSUVs were the same for both Glofit-GemOx and R-GemOx in the model (Table 30) as there was no evidence that there is any treatment specific difference in HRQoL for instance related to the administration. Danish tariff according to Jensen et al (2021) (71) was applied straight to the individual level data from the STARGLO study as well as DMC's age multiplier.

As individual level patient level data was used, it was possible to measure utilities among patients on treatment and off treatment. The utility during on treatment was higher than off treatment but the difference is very marginal and probably due to random variation rather than inconsistency. So practically separating on and off treatment does not affect the results at all.

Table 30 Overview of health state utility values

	Results [95% CI]	Instrument	Tariff (value set) used	Comments
HSUVs				
HSUV On treatment	[redacted]	EQ-5D-5L	DK	Estimate is based on mean of both trial arms.
HSUV Off treatment	[redacted]	EQ-5D-5L	DK	Estimate is based on mean of both trial arms.
HSUV Post-progression	[redacted]	EQ-5D-5L	DK	Estimate is based on mean of both trial arms.

Note: a beta distribution has been used to sample all these utilities in the probabilistic sensitivity analysis. To ensure accurate ordered sampling of health state utilities, the method described in Ren et al 2018 (72) was used. EQ-5D-5L, European Quality of Life 5 Dimensions 5 Level version; PFS, progression-free survival; PPS, post-progression survival; PSA, probabilistic sensitivity analysis; SE, standard error.

10.3 Health state utility values measured in other trials than the clinical trials forming the basis for relative efficacy

10.3.1 Study design

Not relevant.

10.3.2 Data collection

Not relevant.

10.3.3 HRQoL Results

Not relevant.

10.3.4 HSUV and disutility results

Not relevant.

Table 31 Overview of health state utility values [and disutilities]

	Results [95% CI]	Instrument	Tariff (value set) used	Comments

Table 32 Overview of literature-based health state utility values

	Results [95% CI]	Instrument	Tariff (value set) used	Comments

11. Resource use and associated costs

11.1 Medicines - intervention and comparator

Costs and resource use vary depending on the administered treatment and health states. The model includes drug costs, administration costs, subsequent therapy costs, disease management costs, and AE costs. The costs included are consistent with the limited societal perspective as described in the DMC guidelines (73). Drug costs are estimated from Medicinpriser.dk, where administration costs, disease management costs, and AE costs are based on the Danish diagnose relative group (DRG) tariffs 2025.

For all pharmaceuticals administered in the model, pharmacy purchase prices have been used. Drug acquisition costs are applied to patients in each health state. For intravenous therapies, the CEA assumes no vial sharing, and uses the cheapest vial size per mg.

Exposure to study treatments data for patients in the Glofit-GemOx population were similar to that in the Glofit-GemOx (Glofit Exposed) population. Patients could receive up to 12 cycles of glofitamab. In the Glofit-GemOx (Any Treatment Exposed) population, the median number of cycles of glofitamab received was 11.0 (range 1.13); 35.5% of patients received less than 8 cycles, 14.0% of patients received 9-11 cycles and 44.2% of patients received 12 cycles of glofitamab treatment. For 1 patient, 13 cycles were reported; the first step-up dosing cycle was repeated and reported in an Unscheduled Visit, which was counted as an additional cycle. The median number of glofitamab infusions was 12 (range 1.14) due to the step-up dosing schedule in cycle 1. The median treatment

duration was 218.0 days (range: 1-296) with a median total cumulative dose of 303.75 mg (range: 2.5-355.0). The median dose intensity was 100.0% (range: 96.1-116.4).

In the R-GemOx population, the median number of cycles of rituximab received was 4.0 (range: 1-8); 70.5% of patients received less than 8 cycles, and 29.5% of patients received 8 cycles of rituximab treatment. The median number of rituximab infusions was 4.0 (range: 1-8). The median treatment duration was 64.0 days (range: 1-183) with a median total cumulative dose of [redacted]). The median dose intensity was 100.0% (range: 95.2-125.4). All patients (100%) received. 90% of the planned dose of rituximab.

Table 33 Medicines used in the model

Medicine	Dose	Relative dose intensity	Frequency	Vial sharing
Glofit-GemOx	A step-up dosing schedule starting on Day 8 of Cycle 1 (2.5 mg), Day 15 of Cycle 1 (10 mg), followed by 30 mg on Day 1 of Cycles 2–12, with each cycle being 21 days (i.e. every 3 weeks	100 %	see "Dose" column	No
Rituximab biosimilar (Ritemvia)	375 mg/m2 on day 1 of each cycled	100 %	see "Dose" column	No
Gemcitabine	1,000 mg/m2 on day 1 of each cycle	100 %	see "Dose" column	No
Oxaliplatin	100 mg/m2 on day 1 of each cycle	100 %	see "Dose" column	No
Obituzumab	One single dose of 1000 mg as a pre-treatment to deplete B-cells 7 days prior to initiation of glofitamab	100 %	see "Dose" column	No

11.2 Medicines– co-administration

Not applicable.

11.3 Administration costs

The model allows taking complexity of drug administration into account. As per the Glofitamab SmPC (41), infusion time can vary between 2-8 hours (mainly 4) depending on dose and possible infusion reactions. However, we have no detailed information about the complexity of admiration of different i.v. pharmaceuticals.

We assume that all infusion treatment alternatives have the same fixed administration cost in all cycles. The administration cost of 2136 DKK (DRG 2025, 17MA98) in the first

cycle and in the subsequent cycles. The incremental difference in drug administration costs is assumed being marginal when all comparative drugs are infusions. If the patient had experienced Grade ≥2 CRS (12.79 %) in the Glofit-Gemox arm, it was assumed that these patients are monitored after their infusions, and hence an inpatient cost of 2136 DKK (DRG 2025, 17MA98) cycles were assumed. Expected costs per treatment cycle were calculated using the total administration cost per cycle (Table 24) and TTOT KM data.

The unit costs for the mode of administration were obtained from DRG tariffs 2025 and are applied to the administration cost in the model and presented in Table 34.

Table 34 Administration costs used in the model

Administration type	Frequency	Unit cost [DKK]	DRG code	Reference
Oral	Every day	0	-	Assumption
IV	Once per administration	2136 DKK	17MA98	DRG 2025

11.4 Disease management costs

In each cycle that a patient remained alive, supportive care costs were implemented and varied between the PFS and PPS health states, regardless of the treatment arm utilized. These costs are indicative of healthcare resource consumption that is specific to the disease status, rather than the treatment arm employed.

A resource usage for both PFS and PPS states, which included one-time expenses for patient progression, were based on the earlier [redacted] and were deemed to be representative of Danish R/R DLBCL patients.

Resource use of PFS state on treatment

It is postulated that patients who are undergoing treatment and in the PFS state will have 32 consultations with a haematologist/oncologist and with a 16 nurse consultation throughout the course of a year. These 16 consultations are consistent with the number of blood tests and other examinations conducted as outlined in Table 20. Additionally, it is presumed that these patients will engage in four consultations with a radiologist each year, corresponding to the number of CT scans performed annually for these patients. Patients in the PFS health state who receive treatment are anticipated to be hospitalized nine times in the first year due to AEs.

Resource use of PFS state off treatment

For patients who remain in the PFS state, it is assumed that they will have 2 consultations with an oncologist every year and blood tests and other laboratory tests that are performed every three months.

Resource use of PPS state

In the cost-effectiveness analysis of glofitamab monotherapy, patients in the PPS state were primarily assumed to have 12 consultations with an oncologist, as well as consultations with a nurse throughout the course of a year. It was presumed that patients will engage in two consultations with a radiologist each year and blood tests as it was presumed in the PFS state. Based on the clinical expert's assessment, patients in the PPS health state are expected to be hospitalized approximately two times for a duration of three days per year (six in total).

Total weekly supportive costs used in model are reported in Table 35.

Table 35 Disease management costs used in the model

Activity	Frequency of PFS state on treatment (weekly)	Frequency of PFS state off treatment (weekly)	Frequency of progression state (weekly)	Unit cost (DKK)	DRG code	Reference
Health care professionals and hospital resource use						
Oncologist (visit)	0.61	0.04	0.23	1054		Cost of chief physician according to the DMC "Værdisætning af enhedsomkostninger" v1.8
Radiologist (visit)	0.08	0.00	0.04	1054		Cost of chief physician according to the DMC "Værdisætning af enhedsomkostninger" v1.8
Nurse (visit)	0.31	0.00	0.23	462		Cost of nurse according to the DMC "Værdisætning af enhedsomkostninger" v1.8
CT scan	0.08	0.00	0.04	2701	DRG 2025, 30PR06	
Inpatient day	0.17	0.00	0.11	2136	DRG 2025, 17MA98	
Treatment follow-up						

Activity	Frequency of PFS state on treatment (weekly)	Frequency of PFS state off treatment (weekly)	Frequency of progression state (weekly)	Unit cost (DKK)	DRG code	Reference
Full blood counts	0.31	0.08	0.23	21.63		takstkort-29-a-generelle-ydelser.pdf (laeger.dk)
LDH	0.31	0.08	0.23	14.0		https://labportal.rh.dk/LabPortal.asp?Mode=View&Id=3890
Liver function	0.31	0.08	0.23	54.0		https://labportal.rh.dk - ASAT, ALAT, BILIRUBIN, PHOSPHATASE
Renal function	0.31	0.08	0.23	57.0		https://labportal.rh.dk - ALBUMIN, CREACLEA
Immunoglobulin	0.31	0.08	0.23	24.0		RH Laboratorieundersøgelse
Calcium phosphate	0.31	0.08	0.23	88.0		https://labportal.rh.dk/LabPortal.asp?Mode=View&Id=5565

11.5 Costs associated with management of adverse events

In the model disutility are not applied as a onetime event and related cost. AE (event) related disutilities are applied in the model for the time patients are on-treatment taken into account the total patients' months at risk. So patients can realize adverse events continuously while being treated as *1-EXP(-(occurrence/ total patients months at risk))*. The results are not sensitive to this approach compared to the traditional off-time approach.

The CEA calculates the weekly probability of experiencing adverse events across health states and treatment options. This allows it to identify the proportion of patients who experience each AE while on treatment. To calculate the cost of managing adverse events, the CEA applies the costs reported in 29 to the proportion of patients who experienced them.

Total adverse event related costs per patient week was 1347.5 DKK for Glofit-GemOx and 824.93 DKK or R-GemOx patients. Weekly costs are rather marginal in relation to the total costs.

Table 36 Cost associated with management of adverse events

	DRG code	Unit cost/DRG tariff
Alanine aminotransferase increased	DRG 2025, 16MA98	2208 DKK

	DRG code	Unit cost/DRG tariff
Anaemia	DRG 2025, 16MA98	2208 DKK
CRS	DRG 2025, 17MA01	51697 DKK
Diarrhoea	DRG 2025, 06MA11	4977 DKK
Febrile neutropenia	DRG 2025, 16MA03	44978.40 DKK
Lymphocyte count decreased	DRG 2025, 16MA98	533.63 DKK
Neutrophil count decreased	DRG 2025, 16MA98	2208 DKK
Neutropenia	DRG 2025, 16MA98	2208 DKK
Pneumonia	DRG 2025, 16MA98	2208 DKK
Platelet count decreased	DRG 2025, 16MA98	2208 DKK
Thrombocytopenia	DRG 2025, 16MA98	2208 DKK
White blood cell count decreased	DRG 2025, 16MA98	2208 DKK

11.6 Subsequent treatment costs

One-time expenses associated with disease progression were taken into account in the model based on the earlier glofitamab 3L Health technology assessment (HTA) (62). Table 37 presents the one-time expenses associated with disease progression, which were applied in the cycle during which progression occurred.

Data on post-discontinuation pharmaceutical regimen shares and treatment duration for Glofit-GemOx and R-GemOx were taken from the STARGLO trial (see Table 18 in section 8.5). Post-progression treatment costs were estimated applying micro costing by multiplying the selected distributions (% excl. Tx) of each arm with the estimated cost per treatment (Table 37).

In the model, if the product is not on market, the cost is set as 0. The other option is to re-weight proportion presented in Table 37 but this would violate inherent coherence between the trial results and the modeling results. The impact of zero cost for certain therapies is marginal.

Table 37 Medicines of subsequent treatments

Medicine	Relative dose intensity	Dose and Frequency	Vial sharing	Cost/week (incl. admin cost), DKK	Source
Rituximab + Bendamustine (BR)	Not available	90 mg/m2 on days 1 and 2 of each cycle for up to 6 cycles in POLA+BR	No	6.688	Medicinpriser.dk
R-GEMOX	Not available	R-GEMOX: 375 mg/m2 on Day 1 every 14 days	No	8.323	Medicinpriser.dk
R-CHOP	Not available		No	4.172	Medicinpriser.dk
Other R-chemo regimens *	Not available		No	6.395	Average of the three treatments above
Other chemo regimens (not including R) **	Not available		No	2.295	Average of pixantrone and lenalidomide, but pixantrone not of the market.
Pola-BR	Not available		No	27.305	Medicinpriser.dk
Tafa-Len	Not available		No	22.175	Medicinpriser.dk
Lenalidomide	Not available		No	2.725	Medicinpriser.dk
Pixantrone	Not available		No	Not on market	
Other/Clinical Trial (=average of all the treatments above)	Not available		No	0	Assumption
Radiotherapy	Not available		No	6.455	One-off cost; DRG 2025 27MP10
Allogeneic SCT	Not available		No	103.174	One-off cost; DRG 2025, 26MP24

Medicine	Relative dose intensity	Dose and Frequency	Vial sharing	Cost/week (incl. admin cost), DKK	Source
Autologous SCT	Not available		No	103.174	One-off cost; DRG 2025, 26MP24
CAR-T	Not available		No	3.645.319	DRG 2025 26MP21
Loncastuximab	Not available		No	Not on market	
Mosunetuzumab	One-off cost		No	23.374	Medicinpriser.dk
Epcoritamab	One-off cost		No	24.848	Medicinpriser.dk
Glofitamab	One-off cost		No	17.235	Medicinpriser.dk

* Average of the anti-CD20 based therapies; ** Average of the anti-CD20 based therapies (excluding Ritux. costs), pixantrone and lenalidomide

11.7 Patient costs

Patient and transportation costs are included in the model in line with the DMC method guidelines (74). The unit cost per patient hour was estimated to be 203 DKK and the transportation cost was estimated to be 3.51 DKK per km with the assumption of an average distance to the hospital of 40 km (roundtrip) in line with the DMC guidelines. It is further assumed that patients would spend 30 minutes on transportation per visit (roundtrip). Patient time and transportation costs are distributed based on the health states of PFS on/off treatment and PPS.

Table 38 Patient costs used in the model

	Units; Unit cost (DKK)	Source
Patient cost per hour	203.00	(74)
Transport cost per visit	20 km per visit 3.51 DKK per km	(74)

11.8 Other costs (e.g. costs for home care nurses, out-patient rehabilitation and palliative care cost)

One-time expenses associated with disease progression were taken into account in the model. Table 39 presents the one-time expenses associated with disease progression, which were applied in the cycle during which progression occurred.

Table 39 One-off progression costs

Resource	Unit cost (EUR) *	Proportion of patients requiring resource, %	Source
ECG	2 136.00	100.00 %	DRG 2025, 17MA98
MUGA	2 111.00	5.00 %	DRG 2025, 05PR04
MRI	2 603.00	20.00 %	DRG 2025, 30PR02
PET-CT	3 737.00	100.00 %	DRG 2025, 36PR07
Bone marrow biopsy	16 156.00	10.00 %	DRG 2025, 17PR01

12. Results

12.1 Base case overview

An overview of the base case is described in Table 40.

Table 40 Base case overview

Feature	Description
Comparator	Glofit-GemOx vs R-GemOx
Type of model	Partitioned survival model
Time horizon	60 years (life time)
Treatment line	2nd+ line. Subsequent treatment lines are included.
Measurement and valuation of health effects	Health-related quality of life measured with EQ-5D-5L in STARGLO study. Danish population weights were used to estimate health-state utility values
Costs included	Medicine costs Hospital costs Costs of adverse events

Feature	Description
	Patient costs
Dosage of medicine	According to SmPC taken into account weight (41, 43)
Average time on treatment	[redacted]
Parametric function for PFS	[redacted]
Parametric function for OS	[redacted]
Inclusion of waste	Yes, no vial sharing assumed
Average time in model health state	
In PFS	[redacted]
In PD	[redacted]
Death	N/A

12.1.1 Base case results

Table 41 shows base case results for Glofit-GemOx vs R-GemOx using the assumptions presented in Table 40. The mean treatment acquisition cost for Glofit-GemOx was [redacted] DKK. The mean total cost including cost of drug administration, adverse event management, supportive, post progression treatments, patient costs and end-of-life care was [redacted] DKK for the Glofit-GemOx compared to [redacted] DKK for the R-GemOx combination. The mean total incremental cost was therefore [redacted] DKK.

In terms of health outcomes, the Glofit-GemOx vs R-GemOx combinations generated [redacted], resulting in mean life years gained in favour of [redacted] In terms of mean QALYs, Glofit-GemOx generated [redacted] in total, while the R-GemOx combination generated 3.62 QALYs, resulting in a mean QALY gain of [redacted] in favour of Glofit-GemOx.

Base case cost-effectiveness results show a mean cost per life year gained of 200.437 DKK and a mean cost per QALY gained (ICER) of 251.691 DKK at the proposed list price for Columvi (glofitamab).

Table 41 Base case results, discounted estimates

	Glofit-GemOx	R-GemOx	Difference
Medicine costs (treatment)	[redacted]	[redacted]	[redacted]

	Glofit-GemOx	R-GemOx	Difference
Medicine costs – co-administration	0	0	0
Administration	157.709	25.408	132.301
Disease management costs (supportive care)	64.372	48.390	15.981
Costs associated with management of adverse events	25.378	9.123	16.256
Subsequent treatment costs (pharmaceuticals)	224.874	80.268	144.606
Patient costs	27.351	19.404	1.947
Palliative care costs	0	0	0
Total costs	[redacted]	[redacted]	[redacted]
Life years gained (PFS)	[redacted]	[redacted]	[redacted]
Life years gained (PD)	[redacted]	[redacted]	[redacted]
Total life years	[redacted]	[redacted]	[redacted]
QALYs (PFS)	[redacted]	[redacted]	[redacted]
QALYs (PD)	[redacted]	[redacted]	[redacted]
QALYs (adverse reactions)	[redacted]	[redacted]	[redacted]
Total QALYs	[redacted]	[redacted]	[redacted]
Incremental costs per life year gained		[redacted]	
Incremental cost per QALY gained (ICER)		[redacted]	

12.2 Sensitivity analyses

12.2.1 Assessment of uncertainty

The model presents the cost-effectiveness analysis of Glofit-GemOx for the treatment of patients with R/R DLBCL after at least one prior line of therapy. The economic evaluation is informed by the phase III randomised clinical trial comparing Glofit-GemOx vs. R-

GemOx. The phase III head-to-head trial (STARGLO) produced statistically and clinically meaningful results.

However, limitations of the analysis include a somewhat limited follow-up with some uncertainty about the long-term evolution of OS. The STARGLO study is the only study available to provide clinical evidence for Glofit-GemOx in the intended population and can therefore be considered the best available evidence to inform the modelling. Many pharmaceuticals for treating DLBCL have been assessed in HTA, and that information can be used as prior information and for external validation.

The model applies a partitioned survival model based on data from the STARGLO trial. It is unlikely that structural or modelling uncertainty, like applying mixture cure modelling or changing the model structure, would be significant from the perspective of decision uncertainty. Therefore, we do not explore structural or modelling uncertainty in more detail.

The median age in STARGLO might be lower than in the Danish treatable population (not untypical for a clinical trial). So, there is some uncertainty related to generalizability. The wide age range in the study, providing further rationality for modelling background mortality as a function of the age distribution rather than the mean age of the cohort. Moreover, the baseline characteristics of the STARGLO population is broadly representative of Danish clinical practice. We didn't consider it feasible to change the age distribution or average age (e.g. over 70 years) to keep the consistency between the model and STARGLO trial.

There is uncertainty related to key assumptions and other key parameters. Long-term remission/survivorship was deemed clinically plausible for R/R DLBCL in previous R/R DLBCL submissions like for instance in many NICE submissions, irrespective of the technology being assessed. However, 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. However, assuming long-term remission is supported by the plateau observed in the KM PFS curve for the 2L+ population in STARGLO. For instance, Norwegian and UK lymphoma experts who concurred that 2 years is a clinically plausible time point for when transplant ineligible DLBCL patients treated in the 2L+ setting would enter long term remission if progression-free.

Related to the long-term survivorship assumption there is some uncertainty related to long-term cost. Even though the model assumes excess mortality and quality of life adjustment for long-term survivors, the long-term costs during this period are not estimated and assumed to be zero for both comparators. This choice may underestimate the estimated total costs. However, these costs in the future are discounted and are assumed to be marginal in terms of cumulative and incremental total costs in the model.

Typically, a significant modelling uncertainty is caused by extrapolations used for PFS and OS. We assess how selection of the mathematical function affects the results. When extrapolations are varied, covariance between coefficients within one parametric model is typically considered using the variance covariance matrix and the Cholesky decomposition. However, usually correlation between OS and PFS is not considered,

even though correlation is likely, e.g., death is captured by both OS and PFS. Handling of uncertainty in estimates primarily through bootstrapping enables correlations between different endpoints to be preserved in the excel models. For example, if we expect that time to progression correlates positively with survival, then the random draws should also reflect this correlation, rather than just being drawn independently, which could lead to unrealistic iterations with large OS but minimal PFS, and vice versa. Hence, we apply the sampling method for OS/PFS extrapolation parameters in the PSA instead of traditional Cholesky decomposition.

Typically, potentially significant uncertainty is related to utilities. Even though we used reliable trial data, we explored how different utility measures and tariffs may affect the results and decision uncertainty.

The uncertainty described above is explored in the sensitivity analysis. We apply deterministic (DSA) and probabilistic (PSA) sensitivity analysis, and scenario analyses are conducted to assess the robustness of the base case assumptions and parameter uncertainty. For the DSA / univariate sensitivity analysis, the calculation of the lower and upper parameter values is by default based on the parameter distribution from the PSA or assuming standard error of 0.20 more normal-like or mildly skewed variable distribution or 0.25 for potentially more skewed or wider variable distribution. Both can be changed in the model (see e.g. Sensitivity Chart and Cost Inputs sheets).

12.2.2 Deterministic sensitivity analyses

Deterministic sensitivity analyses were performed on key cost-effectiveness parameters from parameter uncertainty point of view. All outcomes are half-cycle corrected and discounted. Table 42 shows the results of the sensitivity analyses in relation to the base case ICER. All factors had a negligible impact on the base case results. Using generalised gamma distribution in extrapolations and proximity of death utilities had the highest impact. Overall, the deterministic sensitivity analyses result consistent results from the decision uncertainty point of view.

Table 42 One-way sensitivity analyses results

Change	Reason / Rational / Source	Incremental cost (DKK)	Incremental benefit (QALYs)	ICER (DKK/QALY)
Base case		[redacted]	[redacted]	[redacted]
PFS extrapolations for both treatments*				
[redacted]	Standard approach and distribution	[redacted]	[redacted]	[redacted]

Change	Reason / Rational / Source	Incremental cost (DKK)	Incremental benefit (QALYs)	ICER (DKK/QALY)
[redacted]	Standard approach and distribution	[redacted]	[redacted]	[redacted]
[redacted]	Standard approach and distribution	[redacted]	[redacted]	[redacted]
[redacted]	Standard approach and distribution	[redacted]	[redacted]	[redacted]
[redacted]	Standard approach and distribution	[redacted]	[redacted]	[redacted]
[redacted]	Standard approach and distribution	[redacted]	[redacted]	[redacted]
OS extrapolations for both treatments*				
[redacted]	Standard approach and distribution	[redacted]	[redacted]	[redacted]
[redacted]	Standard approach and distribution	[redacted]	[redacted]	[redacted]
[redacted]	Standard approach and distribution	[redacted]	[redacted]	[redacted]
[redacted]	Standard approach and distribution	[redacted]	[redacted]	[redacted]
[redacted]	Standard approach and distribution	[redacted]	[redacted]	[redacted]
[redacted]	Standard approach and distribution	[redacted]	[redacted]	[redacted]
[redacted]	Standard approach and distribution	[redacted]	[redacted]	[redacted]

* The same extrapolation is applied to both treatments; ** For all states (PFS on-/off-treatment and progression)

In the scenario analysis we tested different scenarios related to key assumptions (Table 43). These scenarios are based on different valuations or guidelines rather than natural uncertainty related to a specific parameter. Discount rates, quality of life adjustment and long-term survivorship had the biggest impact on the result. However, across all scenarios the decision uncertainty remains low.

Table 43 Scenario analyses results

	Change	Reason / Rational / Source	Incremental cost (DKK)	Incremental benefit (QALYs)	ICER (DKK/QALY)
Base case			[redacted]	[redacted]	[redacted]
General parameters					
Discount rates:	C: 0% E: 0%		[redacted]	[redacted]	[redacted]
Discount rates:	C: 5% E: 5%		[redacted]	[redacted]	[redacted]
Time horizon:	40 years		[redacted]	[redacted]	[redacted]
Long-term survivorship / remission (LTS), mortality					
Set utilities and costs for PFS equal to those in the general population and set mortality for the cohort (PFS + PD) equal to the general population after 3 years		Feasible assumption	[redacted]	[redacted]	[redacted]
Set utilities and costs for PFS equal to those in the general population and set mortality for the cohort (PFS + PD) equal to the general population after 5 years		Feasible assumption	[redacted]	[redacted]	[redacted]
QoL adjustment factor to account for excess comorbidities in long term survivors at 6%		Feasible assumption	[redacted]	[redacted]	[redacted]
QoL adjustment factor to account for excess		Feasible assumption	[redacted]	[redacted]	[redacted]

	Change	Reason / Rational / Source	Incremental cost (DKK)	Incremental benefit (QALYs)	ICER (DKK/QALY)
comorbidities in long term survivors at 10%					
SMR (Standardized mortality ratio) for excess background mortality 1,18		Feasible assumption	[redacted]	[redacted]	[redacted]
SMR (Standardized mortality ratio) for excess background mortality 1,41		Feasible assumption	[redacted]	[redacted]	[redacted]
No excess mortality		Extreme scenario	[redacted]	[redacted]	[redacted]

Tornado diagram summarises most meaningful parameters in terms on their feasible lowest and highest values. The model in Excel provides more options and results for DSA and scenario analysis. In general, the uncertainty remains low from the decision uncertainty point of view.

Figure 12 Tornado diagram

Although Glofitamab is already cost-effective treatment with the list price sensitivity of Columvi® (Glofitamab) unit price on cost-effectiveness is tested in a separate analysis. Figure 13 shows how the ICER decreases as the list price of Glofitamab (Columvi®) is discounted. With discount of approximately 59 % the ICER turns to negative (namely to south-east quadrant in CE plane) indicating savings.

Figure 13 Cost per QALY gained (ICER) for different price levels of Columvi®

12.2.3 Probabilistic sensitivity analyses

Key variables from the parametric uncertainty point of view were included in PSA (see Appendix G).

Figure 14 shows simulated (1000 times) expected values for total costs ( ) and QALYs (51) for Glofit-GemOx and R-GemOx, respectively. The results indicate that the uncertainty is at the same level for both comparators. That means that there is not only uncertainty related to Glofit-GemOx, but also uncertainty regarding how the standard of care (R-GemOx) performs in terms of expected costs and health benefits.

Figure 14 Simulation results in terms of mean costs and QALYs

Figure 15 shows the incremental cost-effectiveness plane for Glofit-GemOx vs. R-GemOx using the base case assumptions. Even though there is some uncertainty around the exact incremental clinical benefit and costs, it seems clear that almost all 1000 simulations are located in the northeast quadrant. Thus, at the established willingness-to-pay threshold for this disease, it is highly likely that GlofitGemOx is a cost-effective alternative to R-GemOx. This is shown clearly in the cost-effectiveness acceptability curve (Figure 16) which indicate high probability of cost-effectiveness at any reasonable willingness to pay thresholds in Denmark.

Figure 15 Cost-effectiveness plane in terms of incremental costs and QALYs

Figure 16 Cost-effectiveness acceptability curve

The convergence of the simulation in terms of incremental NMB is presented in Figure 17.

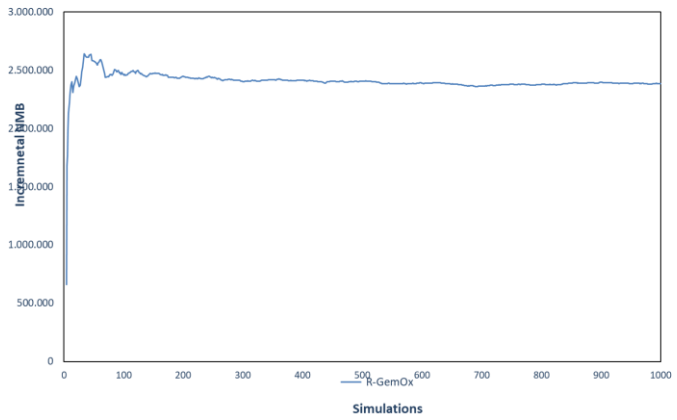

Figure 17 Convergence of the simulations

The model was built of STARGLO head-to-head trial. We utilised patient level data from the trial in modelling and in populating the input parameters. These formed a strong basis for the modelling.

The uncertainty of the model and results was considered from parameter, structural/modeling, and methodological perspectives and was further considered from the decision uncertainty perspective. Decision uncertainty relates to the risk of making the wrong decision about Glofit-GemOx—either adopting a technology that does not provide good value or failing to adopt a technology that does. The cost-effectiveness results were generally robust across scenarios and sensitivity analyses (incl. for instance assumptions related to PFS/OS extrapolations, costs and utilities).

In total, Glofit-GemOx added 3.01 QALYs at an incremental cost 845.356 DKK, resulting in an incremental cost-effectiveness ratio (ICER) of 280.416 DKK using the proposed list price for glofitamab. Net monetary benefit remained positive at the existing willingness-to-pay threshold of 1 000 000 DKK for this indication when key model parameters were varied, which indicates low decision uncertainty.

The base case results were based on the public list price. Even with the list price the ICER is clearly below typical willingness to pay threshold in Denmark.

The conclusion of this analysis is therefore that Glofit-GemOx is, with very high probability, a cost-effective alternative to R-GemOx and the decision uncertainty is reasonable low.

13. Budget impact analysis

Number of patients (including assumptions of market share)

Table 44 Number of new patients expected to be treated over the next five-year period if the medicine is introduced (adjusted for market share)

	Year 1	Year 2	Year 3	Year 4	Year 5
			Recommendation		
Glofitamab+GemOx	40	40	40	40	40
R-GemOx	0	0	0	0	0
			Non-recommendation		
Glofitamab+GemOx	0	0	0	0	0
R-GemOx	40	40	40	40	40

Budget impact

Table 45 Expected budget impact of recommending the medicine for the indication

	Year 1	Year 2	Year 3	Year 4	Year 5
The medicine under consideration is recommended	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
The medicine under consideration is NOT recommended	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Budget impact of the recommendation	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

14. List of experts

Input from clinicians was provided at an advisory board held in January 2025.

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Appendix A. Main characteristics of studies included

Table 46 Main characteristic of studies included

Trial name: STARGLO, GO41944	NCT number: NCT04408638
Objective	STARGLO (GO41944) is a Phase III, open-label, multicenter, randomized controlled trial in patients with R/R DLBCL. It was designed to evaluate the efficacy and safety of Glofit-GemOx compared with R-GemOx in patients who have failed one line of therapy and are not candidates for transplant, as well as those patients who have failed at least two lines of therapy.
Publications – title, author, journal, year	Glofitamab plus gemcitabine and oxaliplatin (GemOx) versus rituximab-GemOx for relapsed or refractory diffuse large B-cell lymphoma (STARGLO): a global phase 3, randomised, open-label trial. Abramson, Jeremy S et al. The Lancet, Volume 404, Issue 10466, 1940 – 1954 (27)
Study type and design	Phase III, open-label, multicenter, randomized study evaluating the efficacy and safety of glofitamab in combination with gemcitabine plus oxaliplatin versus rituximab in combination with gemcitabine and oxaliplatin in patients with relapsed/refractory diffuse large B cell lymphoma
Sample size (n)	274 patients were enrolled. 183 patients were randomized to receive Glofit-GemOx, and 91 patients were randomized to receive R-GemOx.
Main inclusion criteria	Patients must have met the following criteria for study entry: • Age ≥ 18 years at time of signing the ICF • Histologically confirmed DLBCL (NOS) • R/R disease, defined as follows: ○ Relapsed: disease that had recurred following a response that lasted ○ ≥ 6 months after completion of the last line of therapy ○ Refractory: disease that did not respond to, or that progressed 6 months after, ○ completion of the last line of therapy ○ Patients who discontinued last line of therapy before sufficient time for a response assessment (for example, due to toxicity) were assessed for refractoriness based on the previous line of therapy. • At least one (≥ 1) line of prior systemic therapy

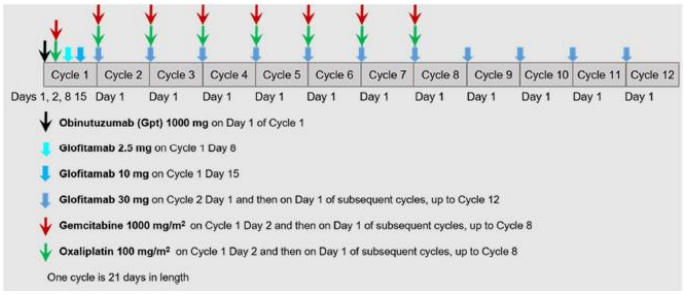
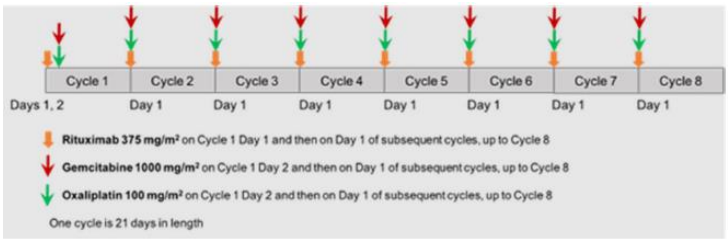
	○ Patients may have undergone ASCT prior to recruitment. ○ CAR T-cell plus bridging therapy were counted as one line of therapy. ○ Local therapies (e.g., radiotherapy) were not considered as lines of therapy. • Patients who had failed only one prior line of therapy and were not a candidate for high-dose chemotherapy followed by ASCT by meeting at least one of the following criteria: ○ Left ventricular ejection fraction ≤ 40% ○ Creatinine clearance (CrCl) or glomerular filtration rate ≤ 45 mL/min ○ Eastern Cooperative Oncology Group (ECOG) Performance Status of ≥ 2 ○ Age ≥ 70 years ○ Patient refused high-dose chemotherapy and/or transplant ○ Patient had insufficient response to pre-transplant chemotherapy to be able to proceed to transplant ○ Other comorbidities or criteria that precluded the use of transplant based on local practice standards or in the investigator's opinion. The rationale for transplant ineligibility had to be recorded in the electronic Case Report Form (eCRF). • At least one bi-dimensionally measurable (≥ 1.5 cm) nodal lesion, or one bi-dimensionally measurable (≥ 1 cm) extranodal lesion, as measured on CT scan • ECOG Performance Status of 0, 1, or 2 • Negative SARS-CoV-2 antigen or PCR test within 7 days prior to enrollment • Adequate renal function, defined as an estimated CrCl ≥ 30 mL/min • For women of childbearing potential: agreement to remain abstinent (refrain from heterosexual intercourse) or use contraceptive measures • For men: agreement to remain abstinent (refrain from heterosexual intercourse) or use contraceptive measures and agreement to refrain from donating sperm
Main exclusion criteria	Patients who met any of the following criteria were excluded from study entry:

Trial name: STARGLO, GO41944	NCT number: NCT04408638

- Patients who had failed only one prior line of therapy and were a candidate for stem cell transplantation
- History of transformation of indolent disease to DLBCL
- High-grade B-cell lymphoma with *MYC* and *BCL2* and/or *BCL6* rearrangements, and high-grade B-cell lymphoma NOS, as defined by 2016 WHO guidelines (Swerdlow et al. 2016)
- Primary mediastinal B-cell lymphoma
- Prior treatment with glofitamab or other bispecific antibodies targeting both CD20 and CD3
- Prior treatment with R-GemOx or GemOx
- Primary or secondary central nervous system lymphoma at the time of recruitment or history of CNS lymphoma
- Current or history of CNS disease, such as stroke, epilepsy, CNS vasculitis, or neurodegenerative disease
- History of other malignancy that could affect compliance with the protocol or interpretation of results
- Significant or extensive cardiovascular disease such as New York Heart Association Class III or IV cardiac disease or Objective Assessment Class C or D, myocardial infarction within the last 3 months, unstable arrhythmias, or unstable angina
- Known active bacterial, viral, fungal, mycobacterial, parasitic, or other infection (excluding fungal infections of nail beds) at study enrollment or any major episode of infection (as evaluated by the investigator) within 4 weeks prior to the first study treatment
- Diagnosis with SARS-CoV-2 infection within 30 days prior to the first study treatment, including asymptomatic SARS-CoV-2 infection
- Documented SARS-CoV-2 infection within 6 months of first study treatment

  Patients may have been eligible if they had no persistent respiratory symptoms, no evidence of lung infiltrates on chest CT, and had a negative PCR during the 30 days prior to first study treatment.
- Known history of HIV seropositive status

  For patients with unknown HIV status, HIV testing was performed at screening if required by local regulations.
- Prior solid organ transplantation
- Prior allogeneic stem cell transplant
- Active autoimmune disease requiring treatment

Trial name: STARGLO, GO41944	NCT number: NCT04408638
	• Ongoing corticosteroid use > 30 mg/day of prednisone or equivalent; stable low dose or short high-dose courses of steroid administration were permissible • Pregnancy or breastfeeding, or intention of becoming pregnant during study treatment or within 18 months after the final dose of study treatment
Intervention	Patients in the Glofit-GemOx arm received a single IV dose of obinutuzumab pretreatment 7 days before the first dose of glofitamab, then up to 8 cycles of glofitamab in combination with gemcitabine plus oxaliplatin, followed by up to 4 cycles of glofitamab monotherapy, to complete up to a total of 12 cycles of glofitamab 
Comparator	Patients in the R-GemOx arm received rituximab in combination with gemcitabine plus oxaliplatin for up to 8 cycles. 
Follow-up time	Median follow-up for primary endpoint, CCOD May 1, 2025: 35.1 mo. (95% CI: 33.6, 37.6)
Is the study used in the health economic model?	Yes
Primary, secondary and exploratory endpoints	**Endpoints included in this application:** OS, IRC- and INV-assessed PFS, IRC- and INV-assessed CR rate, IRC- and INV-assessed DOCR, IRC- and INV-assessed ORR, IRC- and INV-assessed DOR, PROs and safety. **Primary efficacy objective in STARGLO** To evaluate the efficacy of Glofit-GemOx compared with R-GemOx with respect to OS.

- OS, defined as the time from randomization to date of death from any cause

Secondary efficacy objective in STARGLO

To evaluate the efficacy of Glofit-GemOx compared with R-GemOx with respect to the secondary efficacy endpoints:

- PFS, defined as the time from randomization to the first occurrence of disease progression, or death due to any cause, whichever occurs first
- CR rate, defined the proportion of patients whose BOR was a CR based on IRC assessment of PET-CT scans using the Lugano criteria
- ORR, defined as the proportion of patients whose BOR is a PR or CR based on IRC assessment of PET-CT scans using the Lugano criteria
- DOR, defined as the time from the initial occurrence of a documented objective response (PR or CR) until documented disease progression or death, whichever occurs first
- DOCR, defined as time from the initial occurrence of a documented CR until documented disease progression or death due to any cause, whichever occurs first
- Time to deterioration in physical functioning and fatigue, as measured by the EORTC QLQ-C30, and in lymphoma symptoms, as measured by the FACT-Lym LymS

Explorative efficacy objectives in STARGLO

To evaluate the efficacy of Glofit-GemOx compared with R-GemOx with respect to the exploratory endpoints:

- Descriptive summary statistics of PROs and the change from baseline by treatment arm at each assessment for the following:
    - All remaining scales of the EORTC QLQ-C30
    - FACT-Lym LymS
- Characterization of patients who became hematopoietic stem-cell transplant (HSCT) candidates after study therapy and were in the autologous or allogeneic ASCT, including:
    - Incidence of autologous and allogeneic HSCT after study therapy
    - Survival post-HSCT, defined as the time from date of transplantation to date of death from any cause
- Characterization of patients who received CAR T-cell therapy after study therapy and were in the CAR T-cell therapy, including:

- Incidence of treatment with CAR T-cell therapy
- Survival post-CAR-T-cell therapy, defined as the time from date of CAR T-cell infusion to date of death from any cause

Other endpoints:

Not applicable

Safety Objective

To evaluate the safety and tolerability of Glofit-GemOx compared with R-Gem-Ox:

- Incidence and severity of AEs, with severity determined according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) Version 5.0, including CRS, with severity determined according to the American Society for Transplantation and Cellular Therapy (ASTCT) CRS grading criteria (64) and the GO41944 Protocol v7 (51)
- Change from baseline in targeted vital signs
- Change from baseline in targeted clinical laboratory test results
- Tolerability, as assessed by dose interruptions, dose reductions, and dose intensity, and study treatment discontinuation because of AEs

To evaluate the post-transplant Day 100 non-relapse mortality, for patients who became ASCT candidates after study therapy and were in the autologous or allogeneic ASCT:

- Day 100 non-relapse mortality, defined as the incidence of death not related to disease progression within 100 days of transplantation

To evaluate the post-CAR T infusion Day 100 non-relapse mortality for patients who become candidates for and are in the CAR T-cell therapy after study therapy:

- Day 100 non-relapse mortality, defined as the incident of death not related to disease progression within 100 days of CAR T-cell therapy

To evaluate the safety in patients who are treated with CAR T-cell therapy after study treatment:

- Incidence and severity of the following events in patients in the CAR T-cell therapy after study treatment:
  - CRS
  - ICANS

To evaluate and predict the risk of CRS for patients who are treated with glofitamab:

Accuracy of 8 and 5 parameter CRS risk score models in identifying patients at low risk of experiencing Grade 2 CRS with 2.5 mg dose of glofitamab

Pharmacokinetic Objectives

	To evaluate the pharmacokinetics of glofitamab when administered as a component of Glofit-GemOx: • Minimum serum concentration of glofitamab • Maximum serum concentration of glofitamab • AUC for serum concentration–time profile of glofitamab estimated using a population-PK model, as appropriate and where data allowed To evaluate the PK of obinutuzumab: • Minimum serum concentration of obinutuzumab • Maximum serum concentration of obinutuzumab **Immunogenicity Objectives** To evaluate the immune response to Glofit-GemOx: • Prevalence of anti-drug antibodies (ADAs) against glofitamab at baseline, and incidence of ADAs during the study **Exploratory Immunogenicity Objectives** To evaluate potential effects of ADAs to glofitamab • Relationship between glofitamab ADA status and efficacy, safety, or PK endpoints **Exploratory Biomarker Objectives** To identify and evaluate biomarkers that are predictive of response to Glofit-GemOx (i.e., predictive biomarkers), are associated with progression to a more severe disease state (i.e., prognostic biomarkers) or acquired resistance to study treatment, can provide evidence of Glofit-GemOx activity (i.e., pharmacodynamic biomarkers), or can increase the knowledge and understanding of disease biology and drug safety • Exploratory biomarkers in blood and tumor tissue (e.g., circulating-tumor DNA [ctDNA] and DLBCL prognostic subtypes, such as cell of origin) and endpoints, including efficacy, safety, PK, or other biomarker endpoints To assess minimal residual disease status following administration of Glofit-GemOx or R-GemOx to patients with R/R DLBCL **Exploratory Health Status Utility Objectives** To evaluate health status utility scores of patients treated with Glofit-GemOx or R-GemOx • Change from baseline at each time point in EuroQol 5-Level 5-Dimension Questionnaire (EQ-5D-5L) index-based and visual analog scale scores
Method of analysis	**<u>Primary endpoint</u>:** **OS, ITT population** 1) The Kaplan–Meier estimate was used to estimate the median OS, if reached, and OS distribution for each treatment arm. 2) The Brookmeyer–Crowley method was used to construct the 95%

CI for the median OS for each treatment arm.
3) Cox proportional-hazards models were used to estimate the stratified HR and its 95% CI.
4) Treatment comparison was made using a two-sided level 0.05 stratified log-rank test.

Secondary endpoints:

PFS, ITT population

1) Assessed by the IRC and INV using the Lugano Classification.
2) The Kaplan–Meier estimate was used to estimate the median PFS for each treatment arm.
3) The Brookmeyer–Crowley method was used to construct the 95% CI for the median PFS for each treatment arm.
4) Cox proportional-hazards models were used to estimate the stratified HR and its 95% CI.
5) Treatment comparison was made using a two-sided level 0.05 stratified log-rank test.

CR, ITT population

1) Assessed by the IRC and INV using the Lugano classification.
2) An estimate of CR rate and its 95% CI were calculated using the Clopper-Pearson method for each treatment arm.
3) CR rate was compared between treatment arms using the Cochran-Mantel-Haenszel test stratified by the randomization stratification factors.

ORR, ITT population

1) Assessed by the IRC and INV using the Lugano classification.
2) An estimate of ORR and its 95% CI were calculated using the Clopper-Pearson method for each treatment arm.
3) ORR was compared between treatment arms using the Cochran-Mantel-Haenszel test stratified by the randomization stratification factors.

DOR, ITT population

1) Assessed by the IRC and INV using the Lugano Classification.
2) The Kaplan–Meier estimate was used to estimate the median DOR, for each treatment arm.
3) The Brookmeyer–Crowley method was used to construct the 95% CI for the median DOR for each treatment arm.
4) Treatment comparison was made using a two-sided level 0.05 stratified log-rank test.

DOCR, ITT population

1) Assessed by the IRC and by the investigator, using the Lugano Classification.
2) The Kaplan–Meier estimate was used to estimate the median DOR, for each treatment arm.
3) The Brookmeyer–Crowley method was used to construct the 95%

	CI for the median DOR for each treatment arm. 4) Treatment comparison was made using a two-sided level 0.05 stratified log-rank test. **<u>Patient Reported Outcomes:</u>** **EQ-5D-5L** Assessments of the EQ-5D-5L utility index and Visual Analog Scale (VAS) were conducted at baseline; Day 1 in cycle 2, 3, 5, and 7; treatment completion; and every three months during post-treatment follow-up. Data were collected in the ITT population. **EORTC QLQ-C30 and FACT-Lym LymS** The EORTC QLQ-C30 and FACT-Lym LymS assessments were administered at baseline; Day 1 in cycle 2, 3, 5, and 7; treatment completion; and every 3 months during the post treatment follow-up. Data were collected in the PRO population. The scales were scored according to the user manual. Summary statistics and changes from baseline scores were calculated by treatment arm for all time points. TTD in fatigue was defined as the time from randomization to the first documentation of a 10-point or more increase and TTD in physical functioning was defined as the time from randomization to the first documentation of a 10-point or more decrease. TTD in lymphoma-specific symptoms was defined as the time from randomization to the first documentation of a 3-point or more decrease in mean score. The Cox proportional-hazards model was used to estimate HR and its 95% CI.
Subgroup analyses	**OS** Per the SAP v6, the treatment effect on the primary endpoint of OS was explored in an unstratified exploratory analysis of subgroups. The subgroup analysis of overall survival by baseline risk factors in the updated analysis was pre-specified (ITT population). Forest plots of the HR for OS with 95% CIs within each subgroup were produced based on the primary endpoint of OS sub-grouped by demographic data and baseline characteristics. **PFS** The treatment effect on IRC-assessed PFS was explored in an unstratified exploratory post-hoc subgroup analysis. Forest plots of the HR for IRC-assessed PFS with 95% CIs within each subgroup were produced and sub-grouped by demographic data and baseline characteristics.
Other relevant information	Not applicable

Appendix B. Efficacy results per study

Results per study

Table 47 Results per study

Results of [STARGLO (NCT number)]											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	**Study arm**	**N**	**Result (CI)**	**Difference**	**95% CI**	***P* value**	**Difference**	**95% CI**	***P* value**		
OS	Glofit-GemOx	183	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Median OS was estimated using the KM method and the 95% CIs were constructed using the Brookmeyer-Crowley method. The Cox proportional-hazards model was used to estimate the stratified HR and its 95% CI. Treatment comparison was made by two-sided stratified log-rank test (α = 0.05)	Data on file
	R-GemOx	91	[redacted]								
24 months OS-rate	Glofit-GemOx	183	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Survival rates are based on the Kaplan–Meier estimator. The Cox proportional-hazards model was used to estimate the stratified HR and its 95% CI.	Data on file
	R-GemOx	91	[redacted]								

Results of [STARGLO (NCT number)]											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	Study arm	N	Result (CI)	Difference	95% CI	*P* value	Difference	95% CI	*P* value		
IRC-Assessed PFS	Glofit-GemOx	183	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Median PFS was estimated using the KM method and the 95% CIs were constructed using the Brookmeyer-Crowley method. The Cox proportional-hazards model was used to estimate the stratified HR and its 95% CI. Treatment comparison was made by two-sided stratified log-rank test (α = 0.05)	Data on file
	R-GemOx	91	[redacted]								
12 months PFS-rate	Glofit-GemOx	183	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Event free rates are based on the Kaplan-Meier estimator. The Cox proportional-hazards model was used to estimate the stratified HR and its 95% CI.	Data on file
	R-GemOx	91	[redacted]								
INV-Assessed PFS	Glofit-GemOx	183	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Same as for IRC-Assessed PFS	Data on file
	R-GemOx	91	[redacted]								

Results of [STARGLO (NCT number)]											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	Study arm	N	Result (CI)	Difference	95% CI	*P* value	Difference	95% CI	*P* value		
IRC-Assessed CR	Glofit-GemOx	183	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	An estimate of CR rate and its 95% CI were calculated using the Clopper-Pearson method for each treatment arm. CR rate was compared between treatment arms using the Cochran-Mantel-Haenszel (CMH) test stratified by the randomization stratification factors.	Data on file
	R-GemOx	91	[redacted]								
INV-Assessed CR	Glofit-GemOx	183	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Same as for IRC-Assessed CR	Data on file
	R-GemOx	91	[redacted]								
IRC-Assessed DOCR	Glofit-GemOx	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Median DOCR was estimated using the KM method and the 95% CIs were constructed using the Brookmeyer-Crowley method. The Cox proportional-hazards model was used to estimate the unstratified HR and its 95% CI. Treatment	Data on file
	R-GemOx	[redacted]	[redacted]								

Results of [STARGLO (NCT number)]											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	Study arm	N	Result (CI)	Difference	95% CI	*P* value	Difference	95% CI	*P* value		
										comparison was made by two-sided stratified log-rank test (α = 0.05)	
INV-Assessed DOCR	Glofit-GemOx	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Same as for IRC-Assessed DOCR	Data on file
	R-GemOx	[redacted]	[redacted]								
IRC-Assessed ORR	Glofit-GemOx	183	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	An estimate of ORR and its 95% CI were calculated using the Clopper-Pearson method for each treatment arm. ORR was compared between treatment arms using the Cochran-Mantel-Haenszel test stratified by the randomization stratification factors.	Data on file
	R-GemOx	91	[redacted]								
	Glofit-GemOx	183	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Same as for IRC-Assessed ORR	Data on file

Results of [STARGLO (NCT number)]											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	Study arm	N	Result (CI)	Difference	95% CI	*P* value	Difference	95% CI	*P* value		
INV-Assessed ORR	R-GemOx	91	[redacted]								
IRC-Assessed DOR	Glofit-GemOx	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Median DOR was estimated using the KM method and the 95% CIs were constructed using the Brookmeyer-Crowley method. The Cox proportional-hazards model was used to estimate the unstratified HR and its 95% CI. Treatment comparison was made by two-sided stratified log-rank test (α = 0.05)	Data on file
	R-GemOx	[redacted]	[redacted]								
INV-Assessed DOR	Glofit-GemOx	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Same as for IRC-Assessed DOR	Data on file
	R-GemOx	[redacted]	[redacted]								
TTD in EORCT-	Glofit-GemOx	183	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]		Data on file

Results of [STARGLO (NCT number)]											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	**Study arm**	**N**	**Result (CI)**	**Difference**	**95% CI**	***P* value**	**Difference**	**95% CI**	***P* value**		
QLQ-C30 fatigue	R-GemOx	91	[redacted]							The Cox proportional-hazards model was used to estimate HR and its 95% CI.	
TTD in EORCT-QLQ-C30 physical function-ing	Glofit-GemOx	183	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Same as for TTD in EORCT-QLQ-C30 fatigue	Data on file
	R-GemOx	91	[redacted]								
TTD in FACT-Lym LymS	Glofit-GemOx	183	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Same as for TTD in EORCT-QLQ-C30 fatigue	Data on file
	R-GemOx	91	[redacted]								

Overall survival

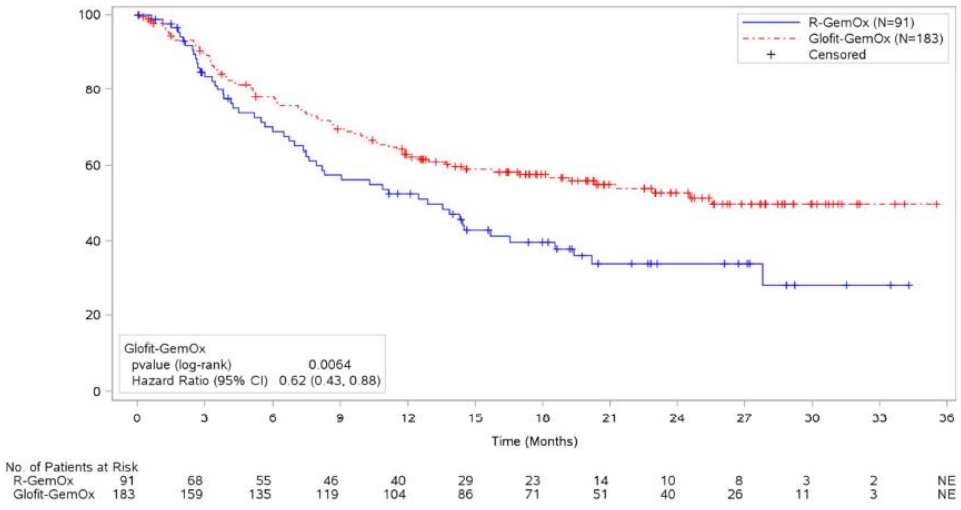


Figure 18 Kaplan–Meier plot of OS, ITT: CCOD, 16 Feb 2024

CI, confidence interval; CCOD, clinical cut-off date; Glofit-GemOx, glofitamab in combination with gemcitabine and oxaliplatin; OS, overall survival; R-GemOx, rituximab in combination with gemcitabine and oxaliplatin.

Progression-free survival

IRC-Assessed PFS

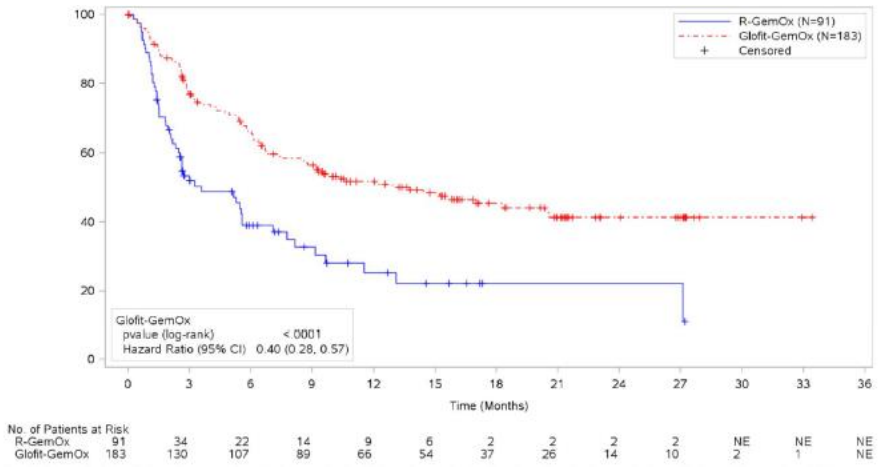


Figure 19 Kaplan–Meier plot of IRC-assessed PFS censored before NALT, ITT: CCOD, 16 Feb 2024

CI, confidence interval; CCOD, clinical cut-off date; Glofit-GemOx, glofitamab in combination with gemcitabine plus oxaliplatin; IRC, independent review committee; NALT, new anti-lymphoma treatment; NE, not estimable; PFS, progression-free survival, R-GemOx, rituximab in combination with gemcitabine plus oxaliplatin (27).

Figure 20 Kaplan–Meier plot of IRC-assessed PFS without censoring for NALT, ITT: CCOD, 16 Feb 2024

CI, confidence interval; CCOD, clinical cut-off date; Glofit-GemOx, glofitamab in combination with gemcitabine plus oxaliplatin; IRC, independent review committee; NALT, new anti-lymphoma treatment; NE, not estimable; PFS, progression-free survival, R-GemOx, rituximab in combination with gemcitabine plus oxaliplatin (data on file).

INV-assessed PFS

The findings for INV-assessed PFS were consistent with those of IRC-assessed PFS.

At the time of the primary analysis, the median duration of follow-up was 10.0 months (95% CI, 9.1, 11.1) in the Glofit-GemOx arm and 8.8 months (95% CI, 6.0, 10.7) in the R-GemOx arm. Median INV-assessed PFS was 17.0 months (95% CI, 8.7, NE) and 2.7 months (95% CI, 2.0, 5.3) in the Glofit-GemOx and R-GemOx arms, respectively. The stratified HR was 0.31 (95% CI, 0.22, 0.45; p < 0.0001) (27).

At the time of the updated analysis, the median duration of follow-up was 17.0 months (95% CI, 15.5, 20.8) in the Glofit-GemOx arm and 12.7 months (95% CI, 8.6, 17.3) in the R-GemOx arm. Median INV-assessed PFS was 14.4 months (95% CI, 9.2, 24.6) and 2.7 months (95% CI, 2.2, 5.3) in the Glofit-GemOx and R-GemOx arms, respectively. The stratified HR was 0.32 (95% CI, 0.23, 0.45; p < 0.0001) (27).

[redacted](4).

Complete response rate

INV-Assessed CR rate

The findings for INV-assessed CR rate were consistent with those of IRC-assessed CR rate.

At the primary analysis, the INV-assessed CR was 51.9% (95% CI, 44.4, 59.3) and 19.8% (95% CI, 12.2, 29.5), in the Glofit-GemOx and R-GemOx arms, respectively; the difference in INV-assessed

CR rate was 32.1% (95% CI, 20.4, 43.9; [redacted] < 0.0001) in favor of the Glofit-GemOx arm (27, 53).

At the updated analysis, the INV-assessed CR rate was 57.4% (95% CI; 49.9, 64.6) and 23.1% (95% CI, 14.9, 33.1) in the Glofit-GemOx (N = 183) and R-GemOx (N = 91) arms, respectively; the difference in CR rate was 34.3% (95% CI, 22.2, 46.4; [redacted] < 0.0001) in favor of the Glofit-GemOx arm (27, 53).

[redacted](4).

Duration of complete response

IRC-assessed DOCR

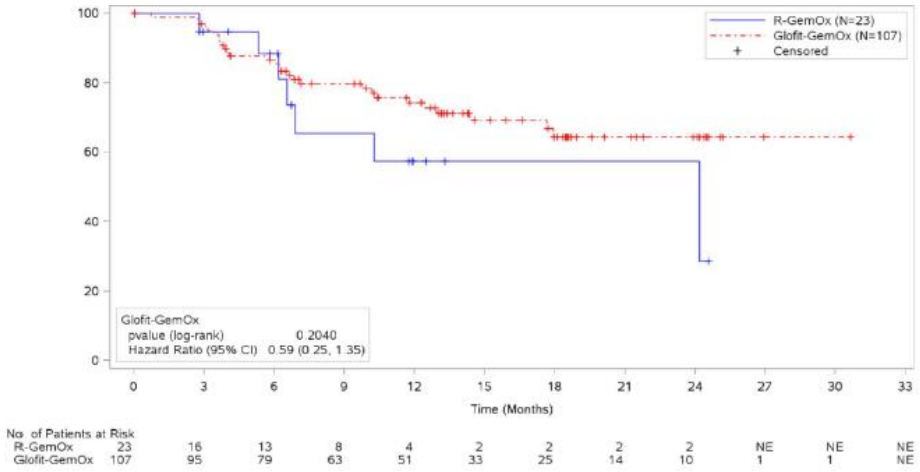


Figure 21 Kaplan–Meier plot of IRC-assessed DOCR, ITT: CCOD, 16 Feb 2024

CI, confidence interval; CCOD, clinical cut-off date; DOCR, duration of complete response; Glofit-GemOx, glofitamab in combination with gemcitabine plus oxaliplatin; IRC, independent review committee; NE, not estimable; R-GemOx, rituximab in combination with gemcitabine plus oxaliplatin. (27).

INV-Assessed DOCR

The findings for INV-assessed DOCR were consistent with those of IRC-assessed DOCR.

At the time of the primary analysis, the median duration of follow-up for INV-assessed DOCR was 6.9 months (95% CI, 6.3, 7.9) in the Glofit-GemOx arm (N = 95) and 6.1 months (95% CI, 5.8, 6.7) in the R-GemOx arm (N = 18). INV-assessed median DOCR could not be estimated in the Glofit-GemOx arm (NE, 95% CI; NE, NE) and was 11.5 months (95% CI, 6.2, NE) in the R-GemOx arm. The unstratified HR was 0.27 (95% CI, 0.09, 0.81; p = 0.0128) (54).

At the time of the updated analysis, the median duration of follow-up was 13.6 months (95% CI, 12.7, 15,9) in the Glofit-GemOx arm (N = 105) and 11.9 months (95% CI, 6.1, 18.1) in the R-GemOx arm (N = 21). INV-assessed median DOCR was not reached in the Glofit-GemOx arm (NE; 95% CI, 21.6, NE) and was 18.9 months (95% CI, 6.6, NE) in the R-GemOx arm, with an unstratified HR of 0.41 (95% CI, 0.18, 0.93; p = 0.0280) (53).

[redacted](4).

Objective response rate

IRC-Assessed ORR

At the time of the primary analysis, the IRC-assessed ORR was 60.1% (95% CI, 52.6, 67.3) and 31.9% (95% CI, 22.5, 42.5), in the Glofit-GemOx and R-GemOx arms, respectively; the difference in IRC-assessed ORR was 28.2% (95% CI, 15.5, 50.0; CMH p value <0.0001) in favor of the Glofit-GemOx arm (27, 54).

At the time of the update analysis, the IRC-assessed ORR was 68.3% (95% CI, 61.0, 75.0) and 40.7% (95% CI, 30.5, 51.5) in the Glofit-GemOx and R-GemOx arms, respectively; the difference in IRC-assessed ORR was 27.7% (95% CI, 14.7, 40.6; CMH p value <0.0001) in favor of the Glofit-GemOx arm (27, 53).

INV-Assessed ORR

Findings for INV-assessed ORR were consistent with those of IRC-assessed ORR.

At the time of the primary analysis, the INV-assessed ORR was 62.3% (95% CI, 54.9, 69.3) and 30.8% (95% CI, 21.5, 41.3), in the Glofit-GemOx and R-GemOx arms, respectively; the difference in ORR was 31.5% (95% CI, 18.9, 44.2; p>0.0001) in favor of the Glofit-GemOx arm (27, 54).

At the time of the update analysis, the INV-assessed ORR was 69.9% (95% CI, 62.7, 76.5) and 37.4% (95% CI, 27.4, 48.1), in the Glofit-GemOx and R-GemOx arms, respectively; the difference in ORR was 32.6% (95% CI, 19.8, 45.3; p>0.0001) in favor of the Glofit-GemOx arm (27, 53).

[redacted](4).

Duration of response (DOR)

IRC-Assessed DOR

At the time of the primary analysis, the median duration of follow-up for IRC-assessed DOR was 6.9 months (95% CI, 6.3, 7.6) in the Glofit-GemOx arm (N = 110) and 5.8 months (95% CI, 2.8, 6.1) in the R-GemOx arm (N = 29). IRC-assessed median DOR was 15.4 months (95% CI, 14.4, NE) and 9.1 months (95% CI, 5.3, NE) in the Glofit-GemOx and R-GemOx arms, respectively. The unstratified HR was 0.58 (95% CI, 0.26, 1.30), which did not meet the threshold for statistical significance (p = 0.1798) (27).

At the time of the updated analysis, the median duration of follow-up was 14.3 months (95% CI, 13.0, 18.0) in the Glofit-GemOx arm (N = 125) and 5.8 months (95% CI, 3.0, 12.5) in the R-GemOx arm (N = 37). IRC-assessed median DOR was not reached (NE; 95% CI, 17.6, NE) in the Glofit-GemOx arm and was 10.3 months (95% CI, 6.5, NE) in the R-GemOx arm. The unstratified HR was 0.57 (95% CI, 0.30, 1.10; p = 0.0892). The KM-plot is shown in Figure 22 (27).

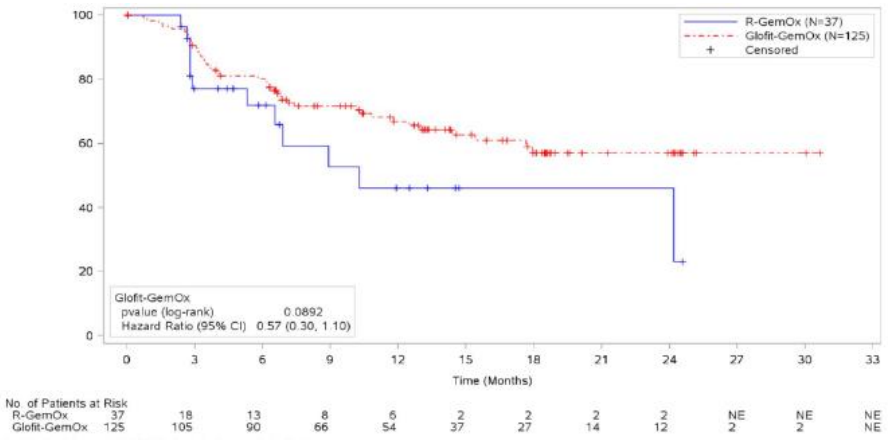


Figure 22 Kaplan–Meier plot of IRC-assessed DOR, ITT: CCOD, 16 Feb 2024

CI, confidence interval; CCOD, clinical cut-off date; DOR, duration of response; Glofit-GemOx, glofitamab in combination with gemcitabine plus oxaliplatin; IRC, independent review committee; NE, not estimable; R-GemOx, rituximab in combination with gemcitabine plus oxaliplatin (27).

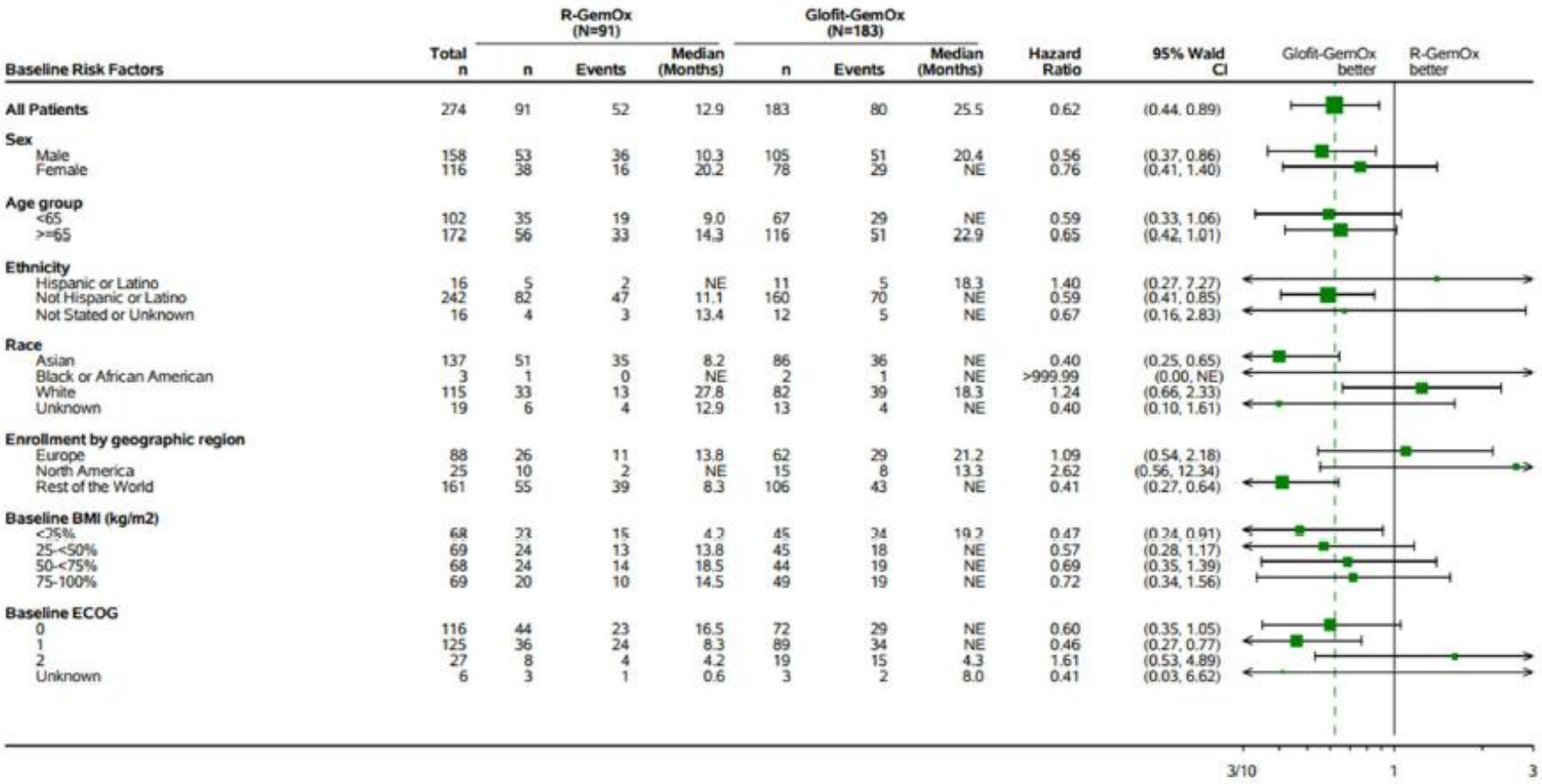
Figure 23 Kaplan–Meier plot of IRC-assessed DOR, ITT: CCOD, 1 May 2025

Day 1 is day of documented CR/PR. The HR was estimated by Cox regression. Includes patients with a best overall response by IRC of CR/PR. CI, confidence interval; CCOD, clinical cut-off date; DOR, duration of response; Glofit-GemOx, glofitamab in combination with gemcitabine plus oxaliplatin; IRC, independent review committee; NE, not estimable; R-GemOx, rituximab in combination with gemcitabine plus oxaliplatin.

INV-Assessed DOR

Subgroup analyses

Figure 24 Forest Plot by subgroup (Unstratified), OS, ITT: CCOD, 16 Feb 2024 (part 1 of 4)



Baseline Risk Factors	Total n	R-GemOx (N=91) n	Events	Median (Months)	Glofit-GemOx (N=183) n	Events	Median (Months)	Hazard Ratio	95% Wald CI
All Patients	274	91	52	12.9	183	80	25.5	0.62	(0.44, 0.89)
Sex									
Male	158	53	36	10.3	105	51	20.4	0.56	(0.37, 0.86)
Female	116	38	16	20.2	78	29	NE	0.76	(0.41, 1.40)
Age group									
<65	102	35	19	9.0	67	29	NE	0.59	(0.33, 1.06)
>=65	172	56	33	14.3	116	51	22.9	0.65	(0.42, 1.01)
Ethnicity									
Hispanic or Latino	16	5	2	NE	11	5	18.3	1.40	(0.27, 7.27)
Not Hispanic or Latino	242	82	47	11.1	160	70	NE	0.59	(0.41, 0.85)
Not Stated or Unknown	16	4	3	13.4	12	5	NE	0.67	(0.16, 2.83)
Race									
Asian	137	51	35	8.2	86	36	NE	0.40	(0.25, 0.65)
Black or African American	3	1	0	NE	2	1	NE	>999.99	(0.00, NE)
White	115	33	13	27.8	82	39	18.3	1.24	(0.66, 2.33)
Unknown	19	6	4	12.9	13	4	NE	0.40	(0.10, 1.61)
Enrollment by geographic region									
Europe	88	26	11	13.8	62	29	21.2	1.09	(0.54, 2.18)
North America	25	10	2	NE	15	8	13.3	2.62	(0.56, 12.34)
Rest of the World	161	55	39	8.3	106	43	NE	0.41	(0.27, 0.64)
Baseline BMI (kg/m2)									
<25%	68	23	15	4.2	45	24	19.2	0.47	(0.24, 0.91)
25-<50%	69	24	13	13.8	45	18	NE	0.57	(0.28, 1.17)
50-<75%	68	24	14	18.5	44	19	NE	0.69	(0.35, 1.39)
75-100%	69	20	10	14.5	49	19	NE	0.72	(0.34, 1.56)
Baseline ECOG									
0	116	44	23	16.5	72	29	NE	0.60	(0.35, 1.05)
1	125	36	24	8.3	89	34	NE	0.46	(0.27, 0.77)
2	27	8	4	4.2	19	15	4.3	1.61	(0.53, 4.89)
Unknown	6	3	1	0.6	3	2	8.0	0.41	(0.03, 6.62)

Figure 25 Forest Plot by subgroup (Unstratified), OS, ITT: CCOD, 16 Feb 2024 (part 2 of 4)

Baseline Risk Factors	Total n	R-GemOx (N=91) n	Events	Median (Months)	Glofit-GemOx (N=183) n	Events	Median (Months)	Hazard Ratio	95% Wald CI
All Patients	274	91	52	12.9	183	80	25.5	0.62	(0.44, 0.89)
No. of previous lines of systemic therapy for DLBCL									
1	172	57	28	15.7	115	44	NE	0.68	(0.42, 1.09)
>=2	102	34	24	6.7	68	36	18.3	0.55	(0.33, 0.93)
Prior CAR-T therapy									
Yes	21	8	4	27.8	13	6	13.7	0.84	(0.23, 3.01)
No	253	83	48	12.9	170	74	NE	0.62	(0.43, 0.89)
Relapse or refractory to last line of therapy									
Refractory	166	54	36	7.5	112	61	11.9	0.65	(0.43, 0.99)
Relapsed	108	37	16	27.8	71	19	NE	0.51	(0.26, 0.98)
Refractory to any line of therapy									
Yes	183	58	40	7.9	125	66	12.1	0.63	(0.43, 0.94)
No	91	33	12	NE	58	14	NE	0.50	(0.23, 1.09)
Refractory to first line of therapy									
Yes	153	47	34	7.3	106	59	10.2	0.60	(0.40, 0.92)
No	121	44	18	27.8	77	21	NE	0.54	(0.29, 1.01)
Relapsed or refractory to any prior platinum therapy									
Refractory	53	21	15	7.6	32	16	13.7	0.54	(0.27, 1.10)
Relapsed	14	3	2	6.7	11	6	18.3	0.22	(0.03, 1.62)
Unknown	207	67	35	14.4	140	58	NE	0.68	(0.45, 1.03)
Relapsed or refractory to any prior anti-CD20 therapy									
Refractory	172	55	38	7.9	117	63	11.5	0.65	(0.43, 0.97)
Relapsed	98	34	14	NE	64	17	NE	0.48	(0.24, 0.98)
Unknown	4	2	0	NE	2	0	NE	NE	NE
Primary refractory or relapse within 1 year after initial diagnosis date									
Yes	164	52	36	7.6	112	59	11.9	0.61	(0.40, 0.93)
No	110	39	16	27.8	71	21	NE	0.60	(0.31, 1.15)
Primary Refractory or Relapse within 12 months after 1L Therapy									
Yes	197	63	42	8.2	134	69	14.4	0.62	(0.43, 0.92)
No	77	28	10	NE	49	11	NE	0.47	(0.20, 1.12)

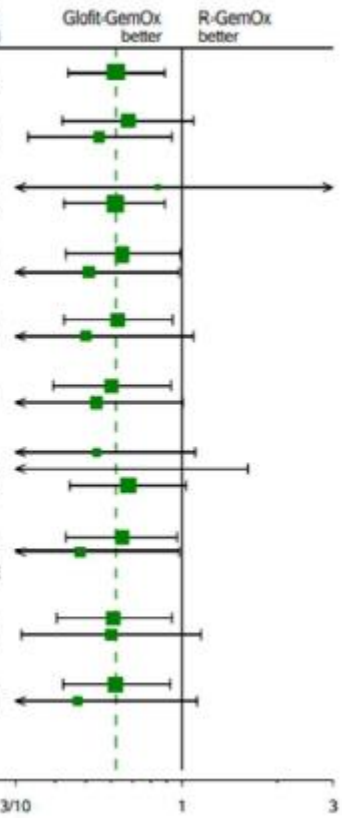


Figure 26 Forest Plot by subgroup (Unstratified), OS, ITT: CCOD, 16 Feb 2024 (part 3 of 4)

Baseline Risk Factors	Total n	R-GemOx (N=91) n	R-GemOx (N=91) Events	R-GemOx (N=91) Median (Months)	Glofit-GemOx (N=183) n	Glofit-GemOx (N=183) Events	Glofit-GemOx (N=183) Median (Months)	Hazard Ratio	95% Wald CI
All Patients	274	91	52	12.9	183	80	25.5	0.62	(0.44, 0.89)
Early relapse from ASCT (PD <=12 months from completion)									
Yes	6	2	2	21.1	4	1	NE	0.82	(0.05, 13.24)
No	5	1	0	NE	4	1	NE	>999.99	(0.00, NE)
No prior ASCT	263	88	50	12.5	175	78	25.5	0.63	(0.44, 0.90)
Double refractory to any prior anti-CD20 and anthracycline based regimen									
Refractory	152	48	34	7.5	104	57	11.1	0.61	(0.40, 0.94)
Relapse (No Refractory)	113	40	17	27.8	73	21	NE	0.55	(0.29, 1.04)
Unknown	9	3	1	NE	6	2	NE	0.99	(0.09, 11.01)
Initial diagnosis									
ABC	17	7	5	20.2	10	4	NE	0.69	(0.18, 2.60)
GCB	84	29	15	10.3	55	25	20.4	0.66	(0.35, 1.25)
Non-GCB	33	10	7	9.9	23	10	25.5	0.44	(0.17, 1.17)
Unclassified	140	45	25	12.9	95	41	NE	0.66	(0.40, 1.08)
Ann Arbor staging at study entry									
Stage I	29	8	3	18.5	21	3	NE	0.27	(0.05, 1.35)
Stage II	51	12	6	6.0	39	17	NE	0.46	(0.18, 1.20)
Stage III	33	8	5	3.4	25	13	22.9	0.51	(0.17, 1.52)
Stage IV	160	62	38	13.8	98	47	19.2	0.75	(0.49, 1.15)
Unknown	1	1	0	NE				NE	NE

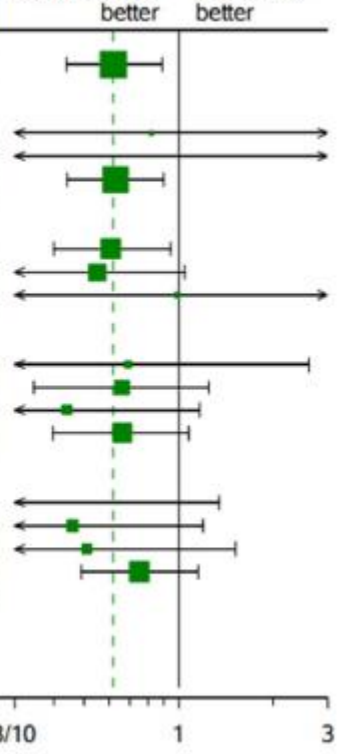
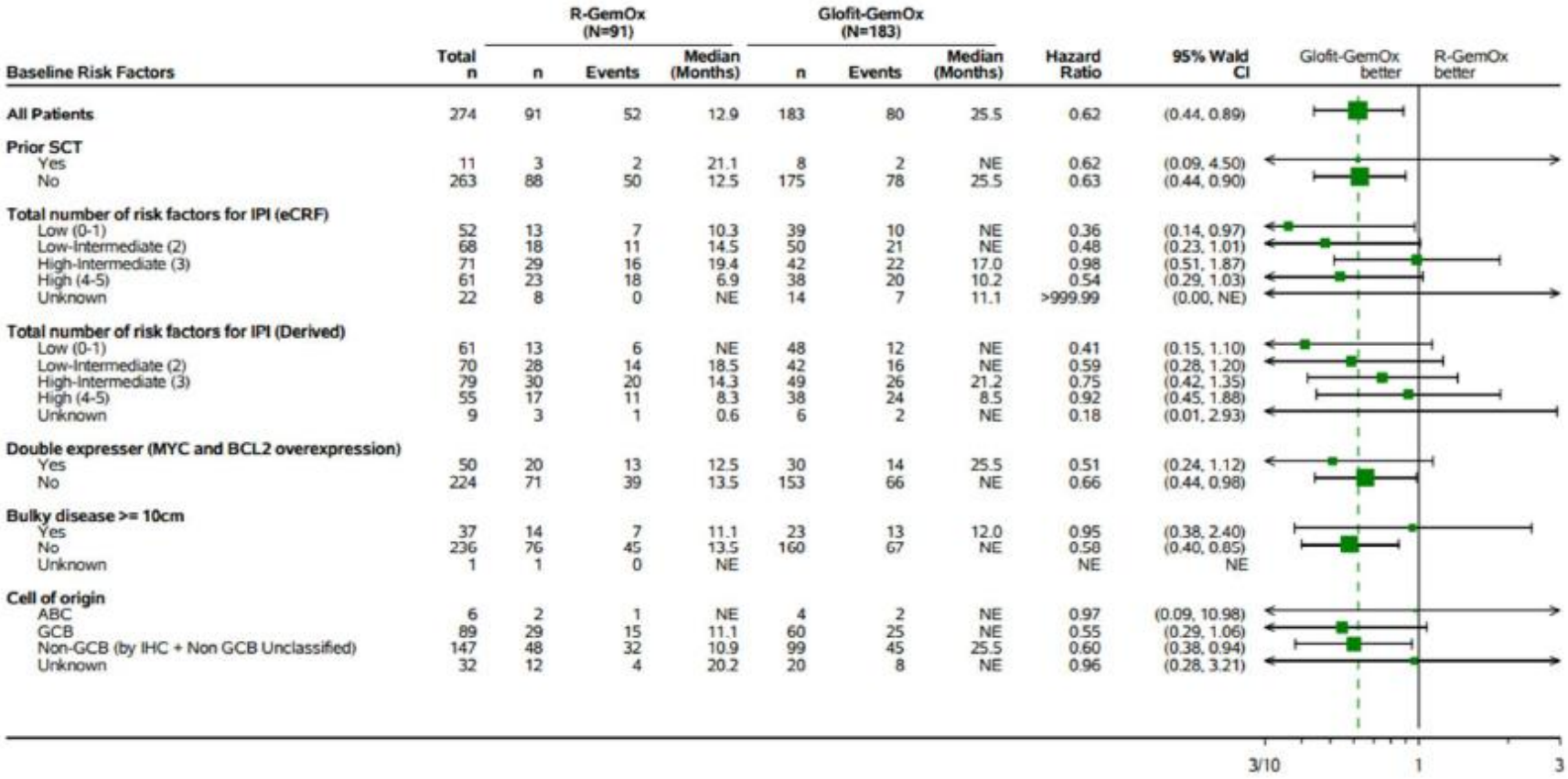


Figure 27 Forest Plot by subgroup (Unstratified), OS, ITT: CCOD, 16 Feb 2024 (part 4 of 4)



Note: Day 1 is day of randomization. Hazard ratios and the associated Wald confidence intervals were estimated using Cox regression. The vertical dashed line indicates the hazard ratio for all patients.

Factors influencing regional and racial subgroup outcomes

Inherent limitations of exploratory subgroup analyses

Exploratory subgroup analyses are not statistically powered to conclusively assess outcomes within specific patient subsets. The STARGLO study was designed and powered for its ITT population. Consequently, drawing definitive conclusions about treatment efficacy in smaller subgroups is challenging due to wide confidence intervals, reflecting high uncertainty. Race and geographic region were not stratification factors, increasing the likelihood of chance imbalances. Given the large number of pre-specified subgroups examined, there is a high statistical probability that some observed OS inconsistencies could arise purely by chance.

Interplay of race and geographic region and lack of biological rationale

The observed differences in OS HRs across racial subgroups are closely linked to geographic enrollment patterns rather than inherent biological variations. In STARGLO, patients of Asian race were almost exclusively enrolled in Asian countries (part of the RoW region), while the majority of patients in the European and North American subgroups were of White race. All 19 patients with "unknown" race were enrolled in European countries. Overall, this strong association suggests that apparent racial differences are primarily a reflection of regional factors.

Furthermore, there is no clear biological reason for outcomes to glofitamab-based therapy to differ by race. Population pharmacokinetic and exposure-response analyses for glofitamab consistently showed similar characteristics and relationships across different racial groups; race was not identified as a significant covariate for OS, PFS, or CR rate. This is consistent with glofitamab monotherapy data (26, 63).

Performance of the control arm in the RoW region

Glofit-GemOx performed consistently across regions. However, the R-GemOx comparator arm showed regional variations in its performance. Specifically, there was a trend toward lower efficacy results in the R-GemOx arm in the RoW subgroup compared to other regional subgroups. This can be explained by the impact of confounding factors, including differences in baseline disease characteristics and variations in NALT usage across the regions. Importantly, the OS, PFS, and CR results observed in the R-GemOx arm in the RoW subgroup are within the expected ranges reported in more recent published literature.

A systematic literature review identified a wide range of response rates for R-GemOx in R/R large B-cell lymphoma (LBCL), influenced by factors such as patient populations and prior therapies. More recent studies, where the majority of patients had received prior rituximab treatment, show CR rates ranging between 20-29%, and overall survival OS and PFS rates consistent with the STARGLO findings. For instance, the Phase 3 NIVEAU study reported a CR rate of 20%, a 24-month PFS rate of 15%, and a 24-month OS rate of 34% for its R-GemOx arm (n=90) in transplant-ineligible R/R LBCL patients who had all been exposed to prior rituximab (75). Similarly, recent retrospective studies using the Flatiron database (n=281) reported a CR rate of 22%, a median PFS of 2.8 months (with 12-month and 18-month PFS rates of 21% and 15% respectively), and a median OS of 12.7 months (with 12-month and 18-month OS rates of 54% and 43% respectively) (30). The LEO consortium database (n=100) reported a CR rate of 18%, a median PFS of 2.0 months (with a 12-month PFS rate of 14%), and a median OS of 9.5 months (with 12-month and 24-month OS rates of 45% and 29% respectively) (31). [redacted] (Figure 24,

Figure 25, Figure 26, Figure 27, Table 48, Table 49). This consistency suggests that the performance of the RoW R-GemOx arm was not unusually low compared to contemporary benchmarks, aligning with expectations for R-chemo in the current treatment landscape.

Impact of specific eligibility criteria on outcomes

Post-hoc exploratory analyses were conducted to assess the impact of specific eligibility criteria on the study outcomes, including CAR-T eligibility and reasons for ASCT ineligibility.

- **CAR-T eligibility:** Analyses comparing countries with and without CAR-T candidate exclusion criteria and splitting the ITT population into CAR-T eligible versus ineligible patients based on EU-approved indications, indicated that these CAR-T eligibility criteria did not significantly impact the interpretation of Study GO41944 results. Efficacy outcomes were comparable across these subgroups and consistent with the overall ITT population.

- **ASCT ineligibility (including patient refusal):** The justification for considering patient refusal of ASCT as a valid reason for ineligibility was also examined. While 95 patients primarily cited refusal, a clinical adjudication algorithm revealed that the majority (66 out of 95) also had other clinical reasons for ASCT non-candidacy. Exploratory analyses of patients who refused ASCT (with or without additional clinical reasons) showed comparable efficacy outcomes (OS, PFS, CR rates) to the overall ITT population. This indicates that patient refusal, as a reason for ASCT ineligibility, did not significantly impact the efficacy results in the ITT population

Imbalances in baseline characteristics by region

While the overall ITT population was generally well-balanced, some differences in prognostic factors were observed across regional subgroups, both between treatment arms within specific regions and across different regions within the same treatment arm. These imbalances can confound results in smaller subgroups. The RoW subgroup in the R-GemOx arm had a higher proportion of patients with high-risk disease characteristics compared to the European and North American R-GemOx subgroups (Table 50, Table 51, Table 52, Table 53). [redacted] These factors are associated with poorer prognosis. Consequently, the R-GemOx arm in RoW inherently faced a higher risk of poor OS outcomes, contributing to the more favorable OS HR observed for Glofit-GemOx in this subgroup (HR=0.41). The performance of the R-GemOx arm in RoW is, however, within the expected range based on recent literature.

Imbalance in the usage of NALTs by region

The use and timing of NALTs significantly influenced OS and PFS, particularly in the R-GemOx control arm. NALT utilization was less frequent and initiated substantially later in the Glofit-GemOx arm compared to the R-GemOx arm across all regions. This indicates superior disease control with Glofit-GemOx.

- **Differential usage and contribution:** NALT usage was less frequent in the Glofit-GemOx arm (Table 54) and median time to NALT initiation or death was substantially longer in the Glofit-GemOx arm. Furthermore, NALT initiation prior to an IRC-assessed PD (e.g., following PR or SD to study therapy, or in context of symptomatic deterioration) occurred at a higher rate among R-GemOx recipients than Glofit-GemOx recipients

([redacted] (53). This led to greater IRC-assessed PFS censoring followed by NALT in the R-GemOx arm. NALTs contributed more significantly to OS time in the R-GemOx arm (quantification of Swimlane plots (Figure 28, Figure 29). [redacted] This suggests that R-GemOx patients often required "rescue" therapies earlier, which can artificially inflate their OS and mask the true efficacy difference.

- **Regional variations in NALT types:** [redacted] (Table 54) (53). CAR-T is a highly efficacious subsequent treatment, and it's greater use in the European R-GemOx arm could extend survival, diminishing the apparent relative benefit of Glofit-GemOx (HR=1.09) in Europe.

- **Inverse probability of censoring weighting (IPCW) analysis:** To account for NALT confounding, IPCW analyses were performed. For OS, IPCW-adjusted HRs consistently demonstrated a benefit for Glofit-GemOx (HRs <1) across the ITT population and all geographic regions. [redacted] (Figure 30) (53). IPCW IRC-assessed PFS HRs were consistently <1 in the ITT population [redacted] and in the Europe [redacted] and RoW [redacted] subgroups. In North America, the IPCW IRC-assessed PFS HR was [redacted] (Figure 31) (53). Overall, these adjustments provide statistical evidence that NALT was a major confounding factor in the naive analyses.

- **Event free survival analyses:** To account for NALT confounding, EFS analyses where designated events included progression, death, or initiation of NALT were performed. The analyses showed improved HRs favoring Glofit-GemOx vs. PFS in the ITT population and across regional subgroups. For Europe, the EFS [redacted] (Table 55) (53).

Influence of the COVID-19 Pandemic

The study was conducted during the COVID-19 pandemic, with varying restrictions and prior to widespread effective COVID-19 therapies. Sensitivity analyses revealed a potentially uneven impact on OS across regions, with the Glofit-GemOx arm in Europe appearing most impacted. For instance, when all COVID-19 deaths were censored, Europe's OS HR numerically shifted from 1.09 to [redacted]. This numerical shift indicates that this external factor disproportionately affected the Glofit-GemOx arm in Europe, making its performance appear less favorable than its true efficacy. In contrast, RoW and North America showed limited impact from COVID-19.

Multivariate analysis (MVA) for overall ITT population

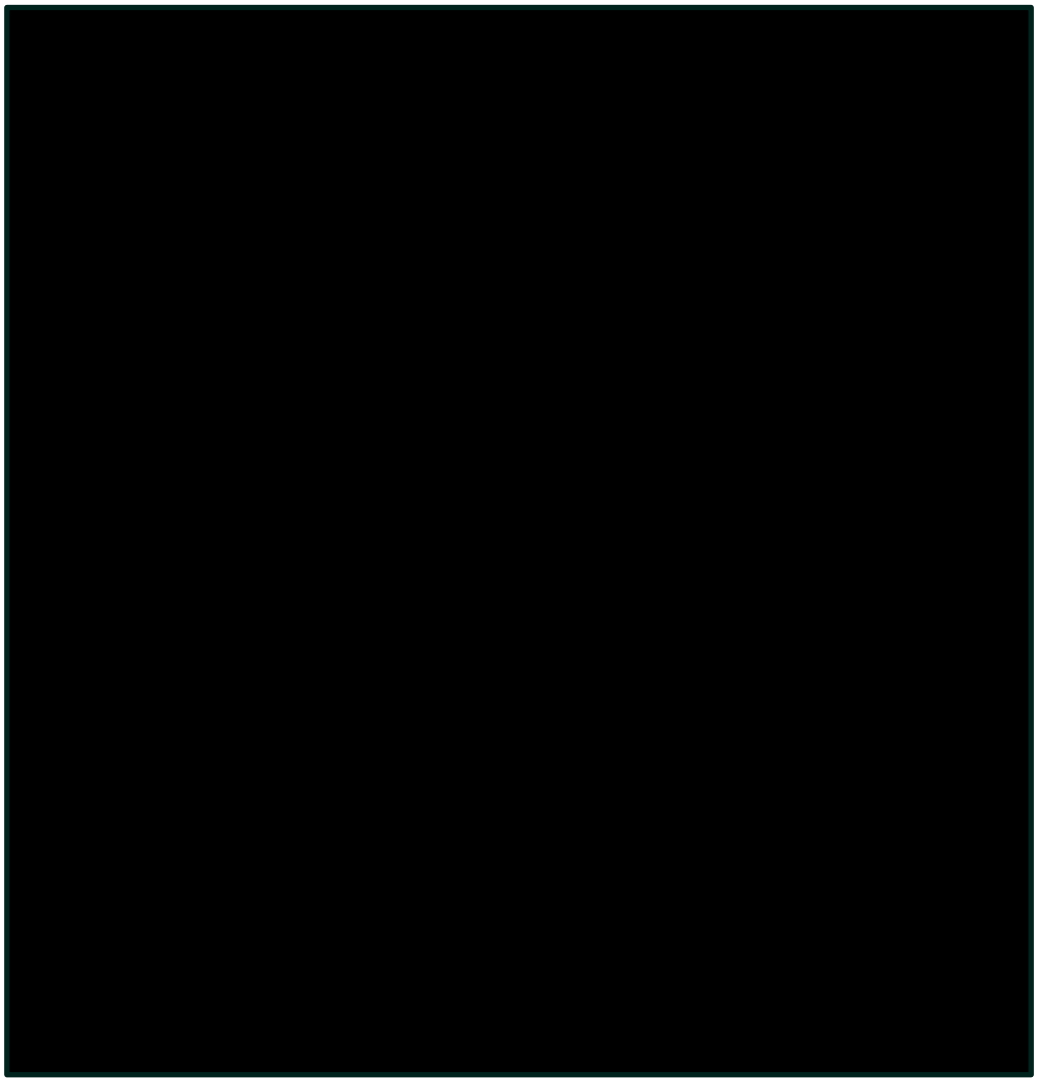
To assess the robustness of the overall ITT population results, a MVA was performed, adjusting for known prognostic and clinically relevant baseline factors. These factors included geographic region, derived IPI score, bulky disease of ≥10 cm, SPD, prior lines of therapy, refractory status to last systemic therapy, and sex. The OS HR for the ITT population after adjusting for these variables through MVA was [redacted] (Table 56) (27, 53). This result remained highly consistent with the unstratified OS HR observed in the updated analysis for the ITT population, which was 0.62 (95% CI: 0.44, 0.89). The consistency of the ITT HR before and after

MVA adjustment indicates that the primary finding of Glofit-GemOx's benefit is robust and not unduly influenced by the distribution of these prognostic factors across the overall study population.

Conclusion on applicability

The EMA concluded that the results from the ITT analysis can be extrapolated to the European population. This is supported by the broad comparability of patient characteristics and treatment outcomes between the European subgroup and the overall ITT population of Study GO41944. Furthermore, cross-trial comparison with the NIVEAU study, a recent Phase 3 trial conducted almost exclusively in Europe with a similar patient population, showed comparable efficacy outcomes for the R-GemOx arm, strengthening the argument that STARGLO's findings are relevant and applicable to the European clinical context.

Table 48 IRC-Assessed PFS by geographic region: CCOD, 16 Feb 2024



CI, confidence interval; HR, hazard ratio; PFS, progression-free survival. [a] This median PFS is considered unreliable as it was reached with one patient at risk and a median follow-up of only three months. [b] Censored observation.

Table 49 Summary of IRC-Assessed best overall and complete response by geographic region: CCOD, 16 Feb 2024

Best Overall Response is the patient's best response assessment recorded from the start of the study treatment until disease progression. Note: All patients without response data are included in the Not Done/Missing category. Responders refer to patients with CR or PR. The differences in objective and complete response rates are unstratified.

Table 50 Demographics and baseline characteristics of patients by geographic region: CCOD, 16 Feb 2024

Table 51 Demographics and baseline characteristics of patients by geographic region: CCOD, 16 Feb 2024 (cont.)

Table 52 Demographics and baseline characteristics of patients by geographic region: CCOD, 16 Feb 2024 (cont.)

ASCT, Autologous stem cell transplant; CAR-T, chimeric antigen receptor T-cell therapy; IPI, Internation Prognostic Index; SCT, stem cell transplant. Source: Update CSR, Report No. 1130634

Table 53 Cell of Origin by geographic region: CCOD, 16 Feb 2024

	R-GemOx (N=91)			Glofit-GemOx (N=183)		
	Europe (N=26)	North America (N=10)	Rest of World (N=55)	Europe (N=62)	North America (N=15)	Rest of World (N=106)
[redacted]						

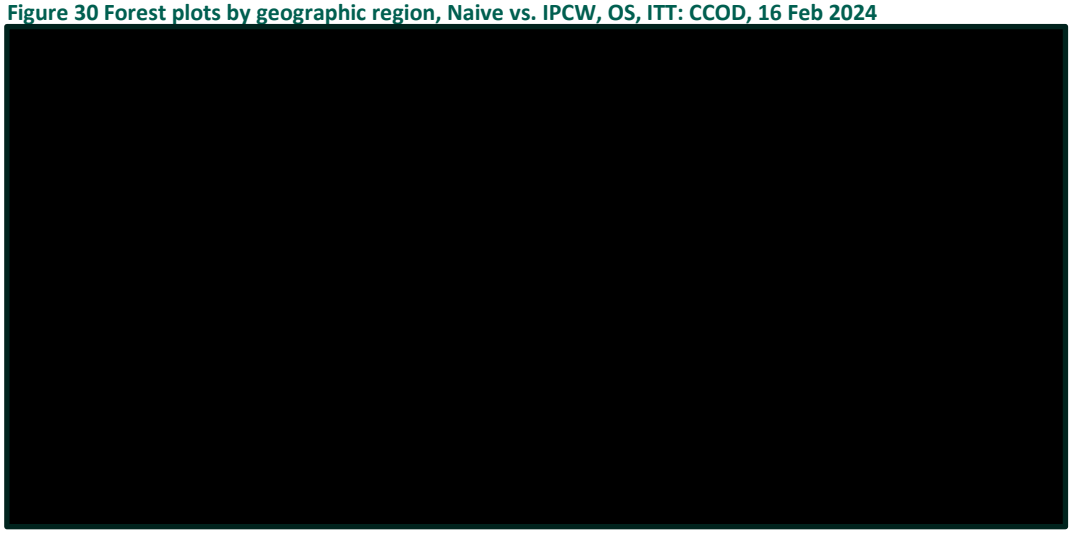
Table 54 Summary of NALT by geographic region: CCOD, 16 Feb 2024

CAR-T. chimeric antigen receptor T-cell therapy; NALT. new anti-lymphoma therapy; RoW. Rest of World; SCT. stem cell transplant. [a] Includes radiotherapy, excision of tumor, and lysis of intestinal adhesions. [b] Includes acalabrutinib, Cc99282. Rituximab, Cdk9 Inhibitor. Btk Inhibitor, cedaramine, zanubrutinib . Selinexor, and other clinical trials. Notes: Patients could have received more than one NALT. Multiple uses of a specific medication for a patient were counted once in the frequency for the medication. For frequency counts in "Total number of treatments", multiple uses of the same medication for a patient were counted separately. Different therapies started on the same date have been included. Source: Update CSR, Report No. 1130634.

Figure 28 Swimlane Plot of OS including all NALT, Europe

Figure 29 Swimlane Plot of OS including all NALT, RoW

Figure 30 Forest plots by geographic region, Naive vs. IPCW, OS, ITT: CCOD, 16 Feb 2024



Naive results are based on censoring OS at the time of first NALT. Missing data in the adjusted baseline covariates were removed from IPCW, leading to a reduced n vs. the original and naive analyses. Sample sizes for IPCW represent the number of unique patients prior to reweighting.

Figure 31 Forest plots by geographic region, naive vs. IPCW, IRC-assessed PFS, ITT: CCOD, 16 Feb 2024

Missing data in the adjusted baseline covariates were removed from IPCW, leading to a reduced n vs. the original/naive analysis. Original/naive results are based on censoring IRC-assessed PFS at the time of first NALT. Sample sizes for IPCW represent the number of unique patients prior to reweighting.

Table 55 EFS by geographic region: CCOD, 16 Feb 2024

CI, confidence interval; NALT, New Anti-Lymphoma Treatment. Note: In these analyses, NALT initiation, disease progression, and death were each included as designated events.

Table 56 Multivariate Cox Regression, OS, ITT: CCOD, 16 Feb 2024

N includes the 265 patients with non-missing values for every covariable. * Wald confidence interval/test.

Appendix C. Comparative analysis of efficacy

Not applicable.

Table 57 Comparative analysis of studies comparing [intervention] to [comparator] for patients with [indication]

Outcome		Absolute difference in effect			Relative difference in effect			Method used for quantitative synthesis	Result used in the health economic analysis?
	Studies included in the analysis	Difference	CI	P value	Difference	CI	P value		

Appendix D. Extrapolation

Extrapolation of PFS

D.1.1 Data input

See section 8

D.1.2 Model

See section 8

D.1.3 Proportional hazards

Figure 32 Visual check of PH assumption - Schoenfeld Individual Test

Figure 33 Visual check of PH assumption - log-log plot

Figure 34 Visual check of PH assumption – hazard plots

D.1.4 Evaluation of statistical fit (AIC and BIC)

Table 58 Ranking of PFS distributions for Glofit-GemOx and R-GemOx based on AIC and BIC

	Parametric distribution	Glofit-GemOx AIC (rank)	Glofit-GemOx BIC (rank)	R-GemOx AIC (rank)	R-GemOx BIC (rank)
Standard (independent fit)	Exponential	[redacted]	[redacted]	[redacted]	[redacted]
	Weibull	[redacted]	[redacted]	[redacted]	[redacted]
	Log-Normal	[redacted]	[redacted]	[redacted]	[redacted]
	Generalised Gamma	[redacted]	[redacted]	[redacted]	[redacted]
	Log-Logistic	[redacted]	[redacted]	[redacted]	[redacted]
	Gompertz	[redacted]	[redacted]	[redacted]	[redacted]
	Gamma	[redacted]	[redacted]	[redacted]	[redacted]

* The presented statistics represent the overall fit of the dependent model to both arms of the trial. AIC, Akaike Information Criterion; BIC, Bayesian Information Criterion

D.1.5 Evaluation of visual fit

See section 8

D.1.6 Evaluation of hazard functions

See section 8

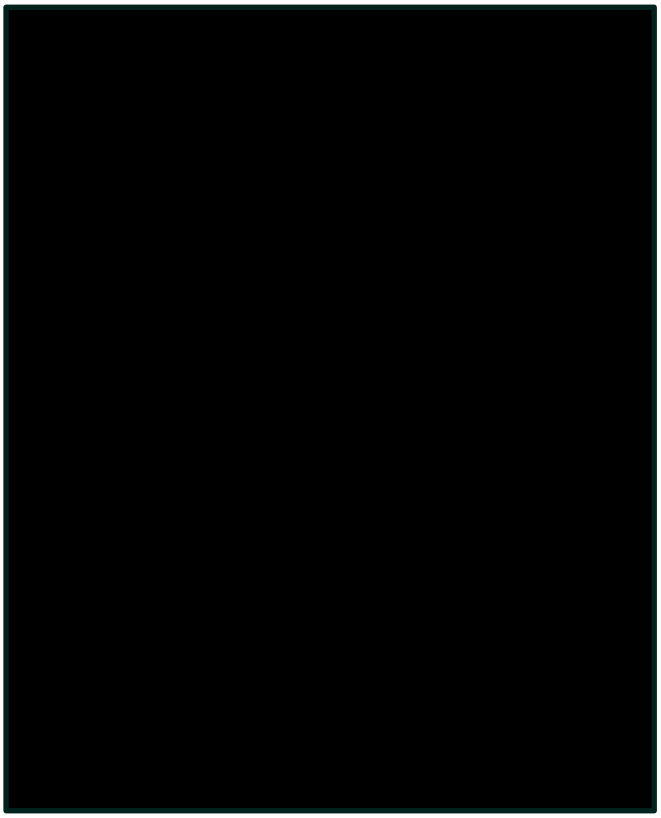


Figure 35 PFS Hazard rate and survival plots considered for Glofit-GemOx and R-GemOx.

D.1.7 Validation and discussion of extrapolated curves

See section 8

D.1.8 Adjustment of background mortality

See section 8

D.1.9 Adjustment for treatment switching/cross-over

See section 8

D.1.10 Waning effect

See section 8

D.1.11 Cure-point

See section 8

D.2 Extrapolation of OS

D.2.1 Data input

See section 8

D.2.2 Model

See section 8

D.2.3 Proportional hazards

Figure 36 Visual check of PH assumption - Schoenfeld Individual Test

Figure 37 Visual check of PH assumption - log-log plot

Figure 38 Visual check of PH assumption – hazard plots

D.2.4 Evaluation of statistical fit (AIC and BIC)

Table 59 Ranking of OS distributions for Glofit-GemOx and R-GemOx based on AIC and BIC

	Parametric distribution	Glofit-GemOx AIC (rank)	Glofit-GemOx BIC (rank)	R-GemOx AIC (rank)	R-GemOx BIC (rank)
Standard (independent fit)	Exponential	[redacted]	[redacted]	[redacted]	[redacted]
	Weibull	[redacted]	[redacted]	[redacted]	[redacted]
	Log-Normal	[redacted]	[redacted]	[redacted]	[redacted]
	Generalised Gamma	[redacted]	[redacted]	[redacted]	[redacted]
	Log-Logistic	[redacted]	[redacted]	[redacted]	[redacted]
	Gompertz	[redacted]	[redacted]	[redacted]	[redacted]
	Gamma	[redacted]	[redacted]	[redacted]	[redacted]

The presented statistics represent the overall fit of the dependent model to both arms of the trial. AIC, Akaike Information Criterion; BIC, Bayesian Information Criterion

D.2.5 Evaluation of visual fit

See section 8

D.2.6 Evaluation of hazard functions

See section 8

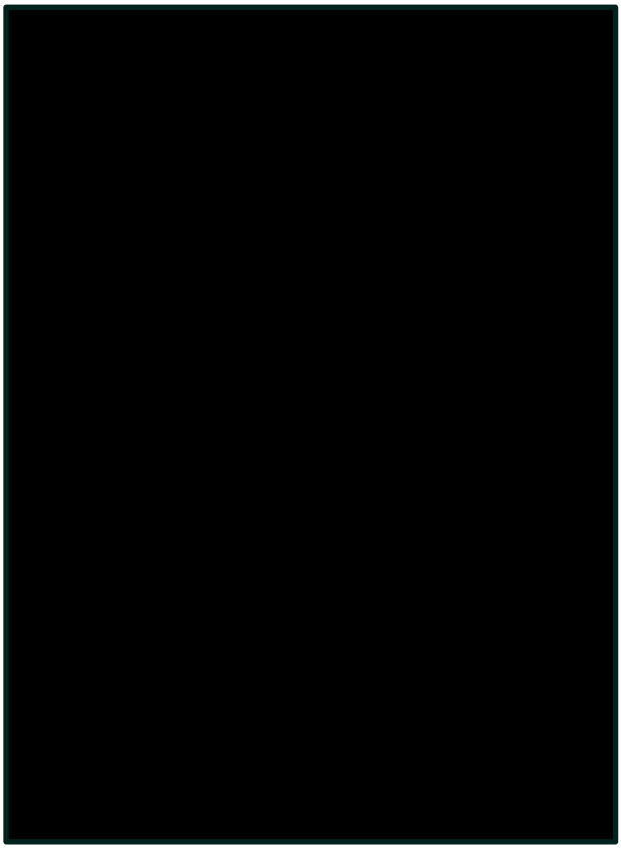


Figure 39 OS Hazard rate and survival plots considered for Glofit-GemOx and R-GemOx.

D.2.7 Validation and discussion of extrapolated curves

See section 8

D.2.8 Adjustment of background mortality

See section 8

D.2.9 Adjustment for treatment switching/cross-over

See section 8

D.2.10 Waning effect

In some economic evaluations where treatment stopping rules have been applied, various treatment effect waning assumptions has been applied to the intervention. This means in the context of this submission that the weekly hazard of the intervention (see Figure 39) would gradually and linearly decreases to the level of comparator's hazard. However, the existence waning assumption and it's starting and stopping parameters are rather arbitrary and typically difficult to justify unequivocally based on clinical evidence.

In this economic evaluation relative treatment effect for PFS or OS are assumed not to wane over time in the current base-case. This was justified as most of the patients have been off-treatment long enough that substantial changes in the observed hazards for PFS

or OS (steeply declining with no signal of increase over time) are not expected to occur beyond the end of the observed data. In average those patients that are not long-term survivors and who's disease have progressed (rather shortly) after the 2L+ treatments, have rather limited life expectancy. Therefore, it does not seem clinically feasible to assume that the hazard associated with Glofit-GemOx would behave differently from the hazard associated with R-GemOx beyond the end of the observed data and during the long-term survivorship period when the patient has been off treatment for months or years.

D.2.11 Cure-point

See section 8

Appendix E. Serious adverse events

SAEs for STARGLO for patients in the Glofit-GemOx (All Treatment Exposed) and R-GemOx arms are presented in Table 60 below

Table 60 STARGLO: Summary of Serious AEs by Preferred Term: CCOD, Feb 16, 2024.

Safety Outcome; MedDRA System Organ Class and MedDRA Preferred Term	**Glofit-GemOx (Any Treatment Exposed) n = 180**	**R-GemOx n = 88**
Total number of patients with at least one serious adverse event, n (%)	98 (54%)	15 (17%)
Overall total number of events	215	35
Blood and lymphatic system disorders		
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
Cardiac disorders		
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
Eye disorders		
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
Gastrointestinal disorders		
[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]

General disorders and administration site conditions		
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
Hepatobiliary disorders		
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
Immune system disorders		
[redacted]	[redacted]	[redacted]
Infections and infestations		
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
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[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
Injury, poisoning and procedural complications		
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
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[redacted]	[redacted]	[redacted]
Investigations		
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
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[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
Metabolism and nutrition disorders		
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
Neoplasms benign, malignant and unspecified (incl cysts and polyps)		
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
Nervous system disorders		
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
Psychiatric disorders		
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
Renal and urinary disorders		
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
Respiratory, thoracic and mediastinal disorders		
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
Vascular disorders		
[redacted]	[redacted]	[redacted]

[redacted]	[redacted]	[redacted]
Product issues		
[redacted]	[redacted]	[redacted]

Investigator text for AEs encoded using MedDRA version 26.1. Only treatment emergent AEs are displayed. AE, adverse event; MedDRA, Medical Dictionary for Regulatory Activities.

Appendix F. Health-related quality of life

F.1 Presentation of the health-related quality of life measured by EORTC QLQ-C30

F.1.1 Study design and measuring instrument

The study design of STARGLO is described in section 6.1.1. Secondary efficacy endpoints include time to deterioration (TTD) in physical functioning and fatigue, as measured by the EORTC QLQ-C30. Exploratory efficacy outcomes consist of descriptive summary statistics and changes from baseline by treatment arm at each assessment for all EORTC QLQ-C30 scales. In this application, we will only report results for the physical functioning and fatigue scales, as these domains are commonly considered the most relevant for capturing the HRQoL impact in patients with R/R DLBCL (76).

EORTC QLQ-C30 is a general instrument designed to assess overall functioning and symptom impact in patients with cancer. The questionnaire comprises a global health status/quality of life (GHS/QoL) scale, five functional scales (cognitive, emotional, physical, role and social functioning), three symptom scales (fatigue, nausea/vomiting and pain), six single items assessing additional symptoms (appetite loss, dyspnea, constipation, diarrhoea and sleep disturbance) and perceived financial impact in the previous 7 days. The questionnaire uses a four-point response format, except for the GHS/QoL scale, which has a seven-point response format. All scale scores range from 0 to 100. Higher scores on the functional and general health status scales indicate better health. Higher scores on the symptom scales indicate more severe symptoms. For the EORTC QLQ-C30 role and physical functioning scales and the GHS/QoL scale, a clinically meaningful change at any time was defined as a difference of at least 10 points (77).

F.1.2 Data collection

The EORTC QLQ-C30 assessments were conducted at baseline; Day 1 in cycle 2, 3, 5, and 7; treatment completion; and every three months during post-treatment follow-up. Data was collected in the PRO-evaluable population. The EORTC QLQ-C30 questionnaires were considered completed if at least 50% of questions had been answered. Completion rates for all questionnaires were high (100%) at baseline in both treatment arms and remained more than 90% until treatment completion. Completion rates dropped at treatment completion / early discontinuation to below 85% and continued to decline during long-term follow-up, as expected due to attrition.

Table 61 Pattern of missing data and completion. CCOD, May 1, 2025

Time point	HRQoL population N	Missing N (%)	Expected to complete * N	Completion § N (%)
	Number of patients at randomization	Number of patients for whom data is missing (% of patients at randomization)	Number of patients "at risk" at time point X	Number of patients who completed (% of patients expected to complete)
		Glofit-GemOx		
Baseline	183	[redacted]	[redacted]	[redacted]
Cycle 2 Day 1	183	[redacted]	[redacted]	[redacted]
Cycle 3 Day 1	183	[redacted]	[redacted]	[redacted]
Cycle 5 Day 1	183	[redacted]	[redacted]	[redacted]
Cycle 7 Day 1	183	[redacted]	[redacted]	[redacted]
Treatment completion / Early discontinuation	183	[redacted]	[redacted]	[redacted]
Long term follow-up month 3	183	[redacted]	[redacted]	[redacted]
Long term follow-up month 6	183	[redacted]	[redacted]	[redacted]
Long term follow-up month 9	183	[redacted]	[redacted]	[redacted]
Long term follow-up month 12	183	[redacted]	[redacted]	[redacted]
Long term follow-up month 15	183	[redacted]	[redacted]	[redacted]
Long term follow-up month 18	183	[redacted]	[redacted]	[redacted]
Long term follow-up month 21	183	[redacted]	[redacted]	[redacted]
Long term follow-up month 24	183	[redacted]	[redacted]	[redacted]

Time point	HRQoL population N	Missing N (%)	Expected to complete * N	Completion § N (%)
Long term follow-up month 27	183	[redacted]	[redacted]	[redacted]
Long term follow-up month 30	183	[redacted]	[redacted]	[redacted]
Long term follow-up month 33	183	[redacted]	[redacted]	[redacted]
Long term follow-up month 36	183	[redacted]	[redacted]	[redacted]
		R-GemOx		
Baseline	91	[redacted]	[redacted]	[redacted]
Cycle 2 Day 1	91	[redacted]	[redacted]	[redacted]
Cycle 3 Day 1	91	[redacted]	[redacted]	[redacted]
Cycle 5 Day 1	91	[redacted]	[redacted]	[redacted]
Cycle 7 Day 1	91	[redacted]	[redacted]	[redacted]
Treatment completion / Early discontinuation	91	[redacted]	[redacted]	[redacted]
Long term follow-up month 3	91	[redacted]	[redacted]	[redacted]
Long term follow-up month 6	91	[redacted]	[redacted]	[redacted]
Long term follow-up month 9	91	[redacted]	[redacted]	[redacted]
Long term follow-up month 12	91	[redacted]	[redacted]	[redacted]
Long term follow-up month 15	91	[redacted]	[redacted]	[redacted]
Long term follow-up month 18	91	[redacted]	[redacted]	[redacted]

Time point	HRQoL population N	Missing N (%)	Expected to complete * N	Completion § N (%)
Long term follow-up month 21	91	[redacted]	[redacted]	[redacted]
Long term follow-up month 24	91	[redacted]	[redacted]	[redacted]
Long term follow-up month 27	91	[redacted]	[redacted]	[redacted]
Long term follow-up month 30	91	[redacted]	[redacted]	[redacted]
Long term follow-up month 33	91	[redacted]	[redacted]	[redacted]
Long term follow-up month 36	91	[redacted]	[redacted]	[redacted]

* Number of patients expected to complete at least 50%. § Completed at least 50% of questions.

F.1.3 HRQoL results

The PRO scales were analyzed in the PRO-evaluable population, which included all randomized patients with a baseline assessment and at least one post-baseline PRO measurement. Summary statistics and changes from baseline scores were calculated by treatment arm at all time points. Additionally, mean differences between treatments were assessed. TTD in fatigue was defined as the time from randomization to the first documentation of a 10-point or more increase and TTD in physical functioning was defined as the time from randomization to the first documentation of a 10-point or more decrease. The Cox proportional-hazards model was used to estimate HR and its 95% CI. Results for fatigue and physical functioning are available from all CCOD analyses. Results from the CCOD of 1 May, 2025, are presented in the section below.

Fatigue

Patients in both treatment arms reported low levels of fatigue at baseline [redacted]) (Table 62). No trends towards improvements were seen while on treatment (Figure 40) (4).

A total of [redacted] patients in the R-GemOx arm experienced a clinically meaningful deterioration in fatigue during the study period. Median TTD in fatigue was [redacted] (Figure 41) (4). Results indicate that patients in both treatment arms experienced similar levels of deterioration of fatigue while on treatment.

Table 62 HRQoL summary statistics, EORTC QLQ-C30 fatigue, PRO-evaluable population: CCOD, 1 May 2025

	Intervention		Comparator		Intervention vs. comparator
	N	Mean (SE)	N	Mean (SE)	Difference (95% CI) p-value
Baseline	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 2 Day 1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 3 Day 1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 5 Day 1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 7 Day 1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Treatment completion / Early discontinuation	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Long term follow-up month 3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Long term follow-up month 6	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Long term follow-up month 9	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Long term follow-up month 12	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Long term follow-up month 15	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Long term follow-up month 18	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Long term follow-up month 21	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Long term follow-up month 24	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Long term follow-up month 27	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

	Intervention	Comparator	Intervention vs. comparator
Long term follow-up month 30	[redacted]	[redacted]	[redacted]
Long term follow-up month 33	[redacted]	[redacted]	[redacted]
Long term follow-up month 36	[redacted]	[redacted]	[redacted]

Figure 40 Change from baseline in EORTC QLQ-C30 fatigue by visitPRO-evaluable population: CCOD, 1 May 2025

Figure 41 Kaplan–Meier Plot of EORTC QLQ-C30-assessed clinically meaningful deterioration in fatigue ITT: CCOD, 1 May 2025 Day 1 is day of randomization. An event is defined as a clinically meaningful deterioration in EORTC QLQ-C30 score, calculated for the fatigue item as an increase of 10 or more points. Patients who do not have an observed deterioration at the time of CCOD will be censored at the last non-missing assessment date. Patients without a post-baseline assessment will be censored at randomization. CI, confidence interval; CCOD, clinical cut-off date; EORTC QLQ-C30, European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30; Glofit-GemOx, glofitamab in combination with gemcitabine and oxaliplatin; ITT, intent-to-treat; NE, not estimable; R-GemOx, rituximab in combination with gemcitabine and oxaliplatin. Source: Update CSR GO41944, Report 1130634.

Physical functioning

Patients in both treatment arms reported moderately high levels of physical functioning at baseline ([redacted] in the R-GemOx arm) (Table 63). No trends towards improvements were seen while on treatment (Figure 42) (4).

During the study [redacted] patients in the R-GemOx arm had a clinically meaningful deterioration in physical functioning. [redacted] (Figure 43) (4). Results indicate that patients in both treatment arms experienced similar levels of deterioration of physical functioning while on treatment.

Table 63 HRQoL summary statistics, EORTC QLQ-C30 physical functioning, PRO-evaluable population: CCOD, 1 May 2025

	Intervention		Comparator		Intervention vs. comparator
	N	Mean (SE)	N	Mean (SE)	Difference (95% CI) p-value
Baseline	[redacted]				
Cycle 2 Day 1	[redacted]				
Cycle 3 Day 1	[redacted]				
Cycle 5 Day 1	[redacted]				
Cycle 7 Day 1	[redacted]				
Treatment completion / Early discontinuation	[redacted]				

	Intervention	Comparator	Intervention vs. comparator
Long term follow-up month 3	[redacted]	[redacted]	[redacted]
Long term follow-up month 6	[redacted]	[redacted]	[redacted]
Long term follow-up month 9	[redacted]	[redacted]	[redacted]
Long term follow-up month 12	[redacted]	[redacted]	[redacted]
Long term follow-up month 15	[redacted]	[redacted]	[redacted]
Long term follow-up month 18	[redacted]	[redacted]	[redacted]
Long term follow-up month 21	[redacted]	[redacted]	[redacted]
Long term follow-up month 24	[redacted]	[redacted]	[redacted]
Long term follow-up month 27	[redacted]	[redacted]	[redacted]
Long term follow-up month 30	[redacted]	[redacted]	[redacted]
Long term follow-up month 33	[redacted]	[redacted]	[redacted]
Long term follow-up month 36	[redacted]	[redacted]	[redacted]

Figure 42 Change from baseline in EORTC QLQ-C30 physical functioning by visitPRO-evaluable population: CCOD, 1 May 2025

Figure 43 Kaplan–Meier Plot of EORTC QLQ-C30-assessed clinically meaningful deterioration in physical functioning, ITT: CCOD, 1 May 2025 Day 1 is day of randomization. An event is defined as a clinically meaningful deterioration in EORTC QLQ-C30 score, calculated for the physical functioning scale as a decrease of 10 or more points. Patients who do not have an observed deterioration at the time of CCOD will be censored at the last non-missing assessment date. Patients without a post-baseline assessment will be censored at randomization. CI, confidence interval; CCOD, clinical cut-off date; EORTC QLQ-C30, European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30; Glofit-GemOx, glofitamab in combination with gemcitabine and oxaliplatin; ITT, intent-to-treat; NE, not estimable; R-GemOx, rituximab in combination with gemcitabine and oxaliplatin. Source: Update CSR GO41944, Report 1130634.

F.2 Presentation of the health-related quality of life measured by FACT-Lym LymS

F.2.1 Study design and measuring instrument

The study design of STARGLO is described in section 6.1.1. In the STARGLO study, lymphoma symptoms, as measured by the FACT-Lym LymS, was included as a secondary efficacy endpoint and all the remaining scales of the FACT-Lym LymS were included as explorative efficacy endpoints. Only results from the secondary efficacy endpoint will be presented in this application.

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 (78). A clinically meaningful change at any time was defined as a difference of at least 3-5 points (78).

F.2.2 Data collection

The FACT-Lym LymS assessments were conducted at baseline; Day 1 in cycle 2, 3, 5, and 7; treatment completion; and every three months during post-treatment follow-up. Data was collected in the PRO-evaluable population. Change from baseline at each time point were calculated by treatment arm.

The FACT-Lym LymS questionnaires were considered completed if at least 50% of questions had been answered. Completion rate for FACT-Lym LymS was high (100%) at baseline in both treatment arms and remained more than 90% until treatment completion. Completion rates dropped at treatment completion / early discontinuation to below 85% and continued to decline during long-term follow-up, as expected due to attrition.

Table 64 Pattern of missing data and completion, FACT-Lym LymS: CCOD, 1 May 2025

Time point	HRQoL population N	Missing N (%)	Expected to complete * N	Completion § N (%)
	Number of patients at randomization	Number of patients for whom data is missing (% of patients at randomization)	Number of patients "at risk" at time point X	Number of patients who completed (% of patients expected to complete)
		Glofit-GemOx		
Baseline	183	[redacted]	[redacted]	[redacted]
Cycle 2 Day 1	183	[redacted]	[redacted]	[redacted]

Time point	HRQoL population N	Missing N (%)	Expected to complete * N	Completion § N (%)
Cycle 3 Day 1	183	[redacted]	[redacted]	[redacted]
Cycle 5 Day 1	183	[redacted]	[redacted]	[redacted]
Cycle 7 Day 1	183	[redacted]	[redacted]	[redacted]
Treatment completion / Early discontinuation	183	[redacted]	[redacted]	[redacted]
Long term follow-up month 3	183	[redacted]	[redacted]	[redacted]
Long term follow-up month 6	183	[redacted]	[redacted]	[redacted]
Long term follow-up month 9	183	[redacted]	[redacted]	[redacted]
Long term follow-up month 12	183	[redacted]	[redacted]	[redacted]
Long term follow-up month 15	183	[redacted]	[redacted]	[redacted]
Long term follow-up month 18	183	[redacted]	[redacted]	[redacted]
Long term follow-up month 21	183	[redacted]	[redacted]	[redacted]
Long term follow-up month 24	183	[redacted]	[redacted]	[redacted]
Long term follow-up month 27	183	[redacted]	[redacted]	[redacted]

Time point	HRQoL population N	Missing N (%)	Expected to complete * N	Completion § N (%)
Long term follow-up month 30	183	[redacted]	[redacted]	[redacted]
Long term follow-up month 33	183	[redacted]	[redacted]	[redacted]
Long term follow-up month 36	183	[redacted]	[redacted]	[redacted]
		R-GemOx		
Baseline	91	[redacted]	[redacted]	[redacted]
Cycle 2 Day 1	91	[redacted]	[redacted]	[redacted]
Cycle 3 Day 1	91	[redacted]	[redacted]	[redacted]
Cycle 5 Day 1	91	[redacted]	[redacted]	[redacted]
Cycle 7 Day 1	91	[redacted]	[redacted]	[redacted]
Treatment completion / Early discontinuation	91	[redacted]	[redacted]	[redacted]
Long term follow-up month 3	91	[redacted]	[redacted]	[redacted]
Long term follow-up month 6	91	[redacted]	[redacted]	[redacted]
Long term follow-up month 9	91	[redacted]	[redacted]	[redacted]
Long term follow-up month 12	91	[redacted]	[redacted]	[redacted]

Time point	HRQoL population N	Missing N (%)	Expected to complete * N	Completion § N (%)
Long term follow-up month 15	91	[redacted]	[redacted]	[redacted]
Long term follow-up month 18	91	[redacted]	[redacted]	[redacted]
Long term follow-up month 21	91	[redacted]	[redacted]	[redacted]
Long term follow-up month 24	91	[redacted]	[redacted]	[redacted]
Long term follow-up month 27	91	[redacted]	[redacted]	[redacted]
Long term follow-up month 30	91	[redacted]	[redacted]	[redacted]
Long term follow-up month 33	91	[redacted]	[redacted]	[redacted]
Long term follow-up month 36	91	[redacted]	[redacted]	[redacted]

* Number of patients expected to complete at least 50%. § Completed at least 50% of questions.

F.2.3 HRQoL results

Summary statistics and changes from baseline scores were calculated by treatment arm at all time points. Additionally, mean differences between treatments were assessed. TTD in lymphoma-specific symptoms was defined as the time from randomization to the first documentation of a 3-point or more decrease in mean score. The Cox proportional-hazards model was used to estimate HR and its 95% CI. Results for fatigue and physical functioning are available from all CCOD analyses. Results from the CCOD of 1 May, 2025, are presented in the section below.

In both treatment arms, mean baseline scores showed low to low-moderate levels of lymphoma-specific symptoms ([redacted] in the R-GemOx arm) (Table 65). Trends towards improvements were seen while on treatment,

with clinical meaningful improvement seen on Day 1 of Cycles 3, 5 and 7 in Glofit-GemOx and Day 1 of Cycles 5 and 7 in R-GemOx (Figure 44) (4).

During the study [redacted] patients in the R-GemOx arm had a clinically meaningful deterioration in lymphoma-specific symptoms. The median TTD was [redacted] in the R-GemOx arm. While Glofit-GemOx patients experienced a deterioration in lymphoma symptoms at a later time point than R-GemOx patients [redacted] the results were not statistically significant (Figure 45) (4). Overall, there were no clinically meaningful differences in median time to deterioration between arms in lymphoma symptoms, demonstrating that Glofit-GemOx does not add additional burden on these symptoms.

Table 65 HRQoL summary statistics, FACT-Lym LymS, PRO-evaluable population: CCOD, 1 May 2025

	Intervention		Comparator		Intervention vs. comparator
	N	Mean (SE)	N	Mean (SE)	Difference (95% CI) p-value
Baseline	[redacted]				
Cycle 2 Day 1	[redacted]				
Cycle 3 Day 1	[redacted]				
Cycle 5 Day 1	[redacted]				
Cycle 7 Day 1	[redacted]				
Treatment completion / Early discontinuation	[redacted]				
Long term follow-up month 3	[redacted]				
Long term follow-up month 6	[redacted]				
Long term follow-up month 9	[redacted]				
Long term follow-up month 12	[redacted]				
Long term follow-up month 15	[redacted]				

	Intervention	Comparator	Intervention vs. comparator
Long term follow-up month 18	[redacted]	[redacted]	[redacted]
Long term follow-up month 21	[redacted]	[redacted]	[redacted]
Long term follow-up month 24	[redacted]	[redacted]	[redacted]
Long term follow-up month 27	[redacted]	[redacted]	[redacted]
Long term follow-up month 30	[redacted]	[redacted]	[redacted]
Long term follow-up month 33	[redacted]	[redacted]	[redacted]
Long term follow-up month 36	[redacted]	[redacted]	[redacted]

Figure 44 Change from baseline by visit, FACT-Lym LymS, lymphoma symptoms,PRO-evaluable population:CCOD, 1 May 2025

Figure 45 Kaplan–Meier Plot of FACT-Lym LymS-assessed clinically meaningful deterioration in lymphoma-specific symptoms, ITT: CCOD, 1 May 2025 Day 1 is day of randomization. An event is defined as a clinically meaningful deterioration in FACT-Lym LymS score, calculated as decrease in mean score of 3 or more points (reverse scoring). Patients who do not have an observed deterioration at the time of CCOD will be censored at the last non-missing assessment date. Patients without a post-baseline assessment will be censored at randomization. CI, confidence interval; CCOD, clinical cut-off date; Glofit-GemOx, glofitamab in combination with gemcitabine and oxaliplatin; ITT, intent-to-treat; NE, not evaluable; R-GemOx, rituximab in combination with gemcitabine and oxaliplatin.

Appendix G. Probabilistic sensitivity analyses

Parameters, values and distributions used in PSA are reported in Table 66. Model detailed information is available in the Excel model sheets.

Table 66. Overview of parameters in the PSA

Input parameter	Point estimate	Lower bound	Upper bound	Probability distribution
Probabilities				
PFS log-normal parameters	Different for all distributions (see model sheet "OS parameters – NPH")	Different for all distributions (see model sheet "OS parameters – NPH")	Different for all distributions (see model sheet "OS parameters – NPH")	Bootstrapped parameters for lambda and gamma
OS log-normal parameters	Different for all distributions (see model sheet "OS parameters – NPH")	Different for all distributions (see model sheet "OS parameters – NPH")	Different for all distributions (see model sheet "OS parameters – NPH")	Bootstrapped parameters for lambda and gamma
HSUV				
Utility of PFS/ on treatment – Glofit-GemOx	[redacted]	Not reported (see model sheet "Utility Values")	Not reported (see model sheet "Utility Values")	A beta distribution has been used to sample all these utilities in the probabilistic sensitivity analysis. To ensure accurate ordered sampling of health state utilities, the method described in Ren et al 2018 was used
Utility of PFS/ on treatment - R-GemOx	[redacted]	Not reported (see model sheet "Utility Values")	Not reported (see model sheet "Utility Values")	A beta distribution has been used to sample all these utilities in the probabilistic sensitivity analysis. To ensure accurate ordered sampling of health state utilities, the method described in Ren et al 2018 was used

Utility of PFS/ off treatment – Glofit-GemOx	[redacted]	Not reported (see model sheet "Utility Values")	Not reported (see model sheet "Utility Values")	A beta distribution has been used to sample all these utilities in the probabilistic sensitivity analysis. To ensure accurate ordered sampling of health state utilities, the method described in Ren et al 2018 was used
Utility of PFS/ off treatment - R-GemOx	[redacted]	Not reported (see model sheet "Utility Values")	Not reported (see model sheet "Utility Values")	A beta distribution has been used to sample all these utilities in the probabilistic sensitivity analysis. To ensure accurate ordered sampling of health state utilities, the method described in Ren et al 2018 was used
Utility of Progression/ Off treatment	[redacted]	Not reported (see model sheet "Utility Values")	Not reported (see model sheet "Utility Values")	A beta distribution has been used to sample all these utilities in the probabilistic sensitivity analysis. To ensure accurate ordered sampling of health state utilities, the method described in Ren et al 2018 was used
Costs				
Administration Cost per treatment administration	2136	1708,8	2562,2	Gamma
One off progression cost	8115	6492	9738	Gamma
AE costs	1078 824.93	871 660	1308 990	Log-normal assuming SE of +/- 20 %
Post progression therapies costs	428.564 496.107	Bootstrapped	Bootstrapped	Gamma

Appendix H. Literature searches for the clinical assessment

H.1 Efficacy and safety of the intervention and comparator(s)

This application is based on the head-to-head study, STARGLO (GO41944), which compares glofitamab plus GemOx with R-GemOx for the treatment of adult patients with R/R DLBCL NOS who are ineligible for ASCT. In Danish clinical practice, R-GemOx is used for both 2L and 3L DLBCL patients. Therefore, it is considered a relevant comparator, and a systematic literature review has not been conducted and thus this appendix is not applicable.

Table 67 Bibliographic databases included in the literature search

Database	Platform/source	Relevant period for the search	Date of search completion

Abbreviations:

Table 68 Other sources included in the literature search

Source name	Location/source	Search strategy	Date of search

Abbreviations:

Table 69 Conference material included in the literature search

Conference	Source of abstracts	Search strategy	Words/terms searched	Date of search

H.1.1 Search strategies

Not applicable

Table 70 of search strategy table for [name of database]

No.	Query	Results
#1		

H.1.2 Systematic selection of studies

Not applicable

Table 71 Inclusion and exclusion criteria used for assessment of studies

Clinical effectiveness	Inclusion criteria	Exclusion criteria	Changes, local adaption
Population			
Intervention			
Comparators			
Outcomes			
Study design/publication type			
Language restrictions			

Table 72 Overview of study design for studies included in the analyses

Study/ID	Aim	Study design	Patient population	Interven-tion and compara-tor (sample size (n))	Primary outcome and follow-up period	Secondary outcome and follow-up period
Study 1						

H.1.3 Excluded fulltext references

Not applicable

H.1.4 Quality assessment

Not applicable

H.1.5 Unpublished data

Not applicable

Appendix I. Literature searches for health-related quality of life

I.1 Health-related quality-of-life search

Health-related quality of life data was obtained from STARGLO (GO41944) (see Table 5) which compares glofitamab plus GemOx with R-GemOx for the treatment of adult patients with R/R DLBCL NOS who are ineligible for ASCT. In Danish clinical practice, R-GemOx is used for both 2L and 3L DLBCL patients. Therefore, it is considered a relevant comparator, and a literature review has not been conducted and thus this appendix is not applicable.

Table 73 Bibliographic databases included in the literature search

Database	Platform	Relevant period for the search	Date of search completion

Abbreviations:

Table 74 Other sources included in the literature search

Source name	Location/source	Search strategy	Date of search

Table 75 Conference material included in the literature search

Conference	Source of abstracts	Search strategy	Words/terms searched	Date of search

I.1.1 Search strategies

Not applicable

Table 76 Search strategy for [name of database]

No.	Query	Results
#1		

Literature search results included in the model/analysis:

Not applicable

I.1.2 Quality assessment and generalizability of estimates

Not applicable

I.1.3 Unpublished data

Not applicable

Appendix J. Literature searches for input to the health economic model

J.1 External literature for input to the health economic model

Input to the Health Economic Model was obtained from STARGLO (GO41944) (see Table 5) which compares glofitamab plus GemOx with R-GemOx for the treatment of adult patients with R/R DLBCL NOS who are ineligible for ASCT. In Danish clinical practice, R-GemOx is used for both 2L and 3L DLBCL patients. Therefore, it is considered a relevant comparator, and a literature review has not been conducted and thus this appendix is not applicable.

J.1.1 Example: Systematic search

Not applicable

Table 77 Sources included in the search

Database	Platform/source	Relevant period for the search	Date of search completion
Embase			
Medline			
CENTRAL			

Abbreviations:

J.1.2 Example: Targeted literature search

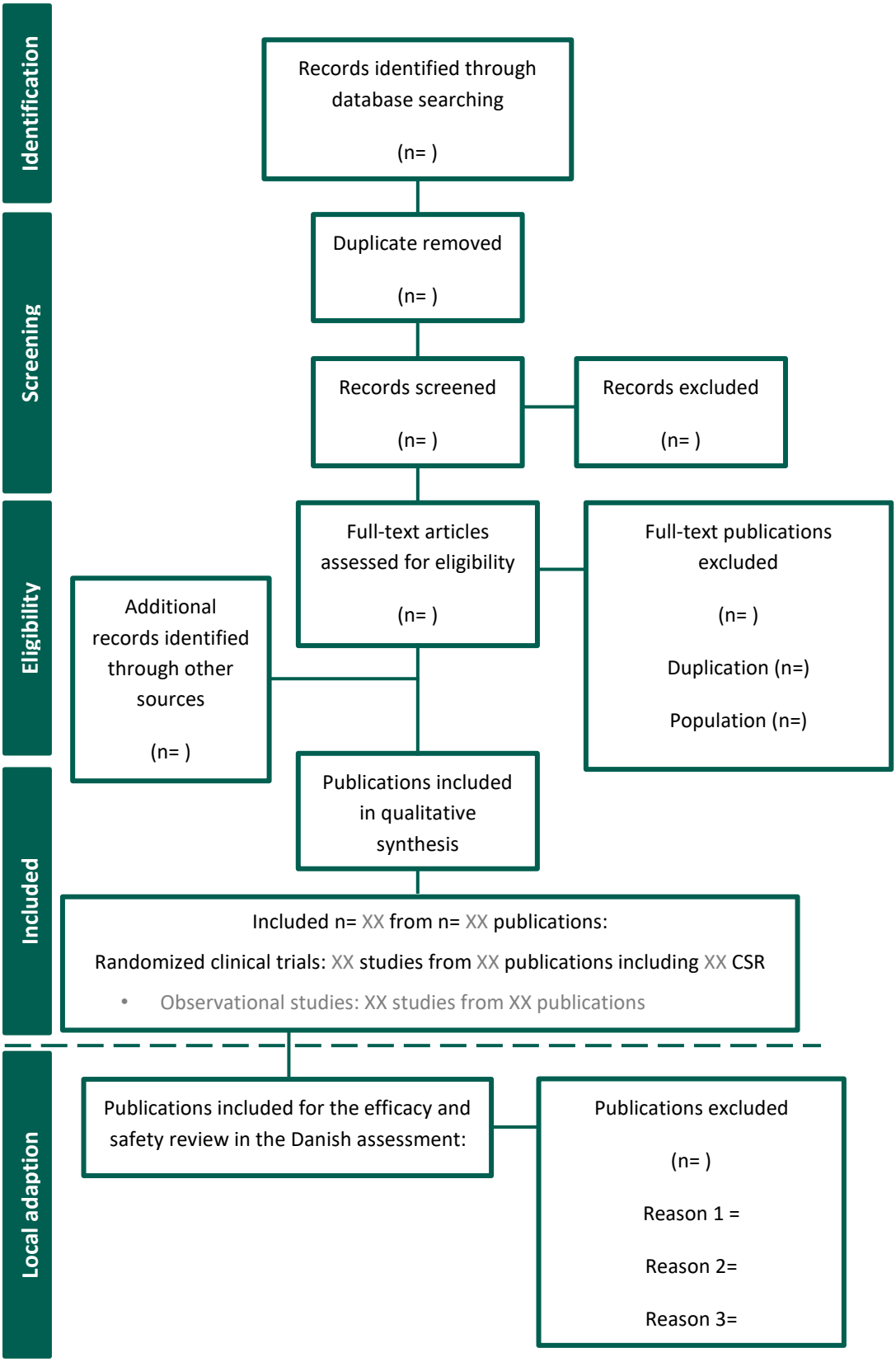
N/A

Table 78 Sources included in the targeted literature search

Source name/ database	Location/source	Search strategy	Date of search

Abbreviations:

Example of PRISMA diagram. The diagram is editable and may be used for recording the records flow for the literature searches and for the adaptation of existing SLRs.



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