Glofitamab with gemcitabine and oxaliplatin for treating relapsed or refractory diffuse large B-cell lymphoma [ID6202]

For screen – contains redacted information

Technology appraisal committee C - 14th October 2025

Chair: Richard Nicholas

External assessment group: Southampton Health Technology Assessments Centre

Technical team: George Millington, Alexandra Filby, Lorna Dunning

Company: Roche

Glofitamab with gemcitabine and oxaliplatin for treating relapsed or refractory diffuse large B-cell lymphoma

- ✓ **Background and key issues**
- ❑ Clinical effectiveness
- ❑ Modelling and cost effectiveness
- ❑ Other considerations
- ❑ Summary

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Background on diffuse large B-cell lymphoma (DLBCL)

Disease overview

DLBCL is a type of blood cancer that affects white blood cells (B lymphocytes or B cells). It is the most common subtype of Non-Hodgkins lymphoma

Diagnosis and classification

Diagnosis is by surgical biopsy. Disease stages are classified according to the Ann Arbor or Lugano Staging Classification

Symptoms and prognosis

Common symptoms include painless swellings at single or multiple sites (lymph node and non-lymph node), excessive night sweating, unexplained fever and weight loss. Prognosis assessed by international prognostic index based on clinical features that predict overall survival

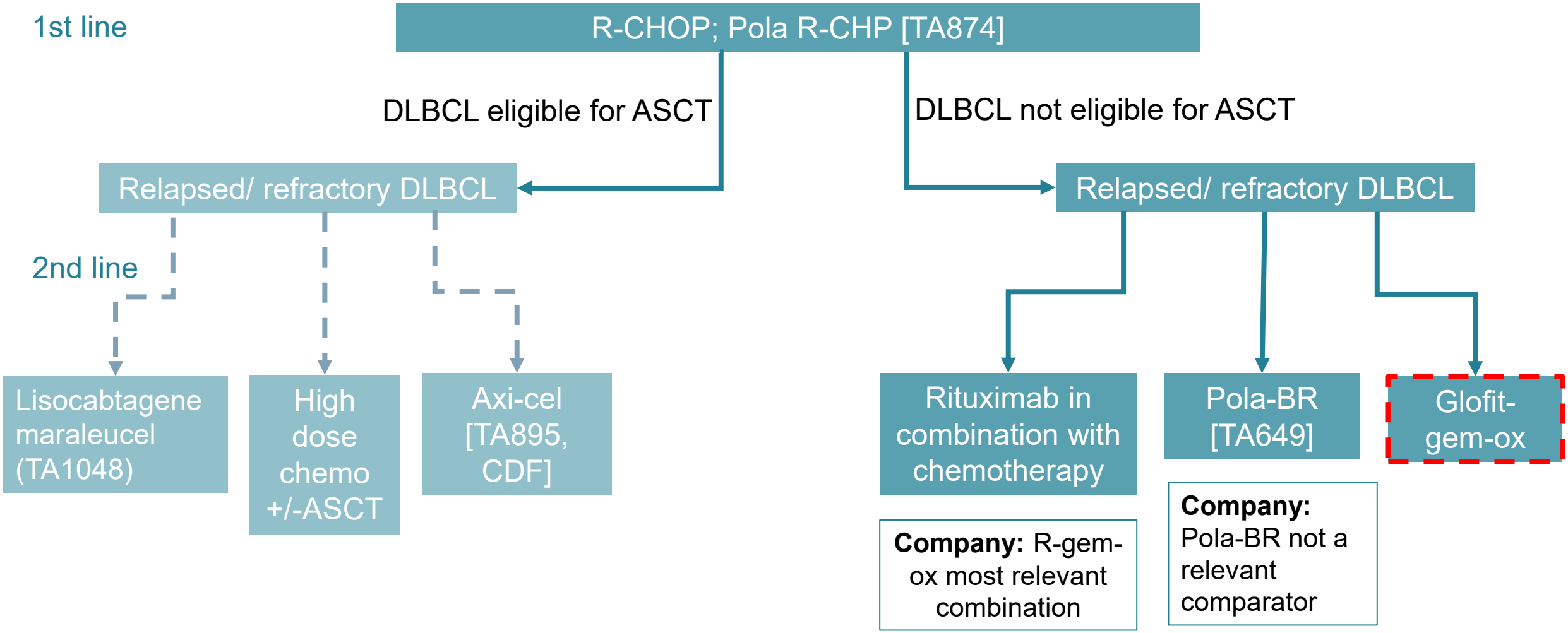
Abbreviations: DLBCL, diffuse large B-cell lymphoma; HIV, human immunodeficiency virus; NOS, not otherwise specified

Glofitamab in combination with gemcitabine and oxaliplatin (Columvi, Roche)

Recap

Marketing authorisation	• 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 • Extension of indication granted by MHRA through IRP in July 2025
Mechanism of action	• Glofitamab is a monoclonal antibody that binds to the CD20 protein on B-cells and the CD3 protein on T-cells. This facilitates immunological synapses, activates T-cells and releases cytolytic proteins that result in lysis of CD20-expressing B-cells • Gemcitabine is a nucleoside analogue that is incorporated into DNA of cells undergoing DNA replication • Oxaliplatin is a platinum-based alkylating compound that causes DNA lesions
Admin	• All patients must have obinutuzumab pre-treatment to mitigate cytokine release syndrome • Dose step-up schedule leads to recommended dose of 30 mg administered as IV infusion
Price	• List price: £687.00 (2.5 mg vial); £2,748 (10 mg vial); • Approx annual cost of glofitamab (excluding gem-ox and obinutuzumab): £94,119 (list price) (cycle 1: 2.5mg day 8, 10mg day 15; cycle 2 to 12: 30mg day 1) • Company have a patient access scheme discount applicable

Treatment pathway for relapsed or refractory DLBCL



Abbreviations: ASCT, autologous stem cell transplant; Axi-cel, axicabtagene ciloleucel; DLBCL, diffuse large B-cell lymphoma; Glofit-gem-ox, glofitamab, gemcitabine and oxaliplatin; IPI, international prognostic index; Pola-R-CHP; polatuzumab vedotin with rituximab, doxorubicin, cyclophosphamide and prednisolone; R-CHOP, rituximab with cyclophosphamide, doxorubicin, vincristine and prednisolone; R-gem-ox, Rituximab, gemcitabine, and oxaliplatin

Responses to draft guidance consultation

- Lymphoma Action - noted uncertainty in data but requested further discussions take the patient experience into account.
- Company (Roche)

Embargoed data

ACM 1 – draft guidance recommendation

Glofitamab plus gemcitabine and oxaliplatin should not be used to treat relapsed or refractory diffuse large B-cell lymphoma not otherwise specified in adults who are not eligible for autologous stem cell transplant.

Committee concluded there was not enough evidence to determine whether glofitamab with gemcitabine and oxaliplatin is value for money in this population.

Committee highlighted uncertainty	Company response
2L OS results compared to R-GemOx	Company provided updated data cut from STARGLO showing statistically significant OS difference in 2L population
ITC with Pola-BR	Propensity score analysis ITC has been updated with from latest STARGLO data cut
Variability in outcomes by region	Provided post-hoc analysis produced for EMA and other analysis identifying factors that may have caused differences in results by region

Abbreviations: 2L, second line; EMA, European Medicines Agency; ITC, indirect treatment comparison; OS, overall survival; Pola-BR, polatuzumab vedotin in combination with bendamustine and rituximab; R-gem-ox, Rituximab, gemcitabine, and oxaliplatin

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Summary of company response

Committee preference	Company response
Inclusion of Pola-BR as a comparator	Company note their reservations about including Pola-BR as a comparator. Included more recent data in ITC
Providing an updated data cut from STARGLO, especially for the 2L population	Company provided updated data cut from STARGLO showing statistically significant OS difference in 2L population
Cure point set to 6 years	Included in company base case
15% in Glofit-GemOx arm receive palliative care	Included in company base case
One-off end of life costs applied	Included in company base case
Fully incremental analysis between Glofit-GemOx, R-GemOx, and Pola-BR	Included in company base case but company note that R-GemOx is dominated by Pola-BR and so the comparison is essentially a pairwise comparison between Glofit-GemOx and Pola-BR

Abbreviations: 2L, second line; Glofit-GemOx, Glofitamab plus gemcitabine and oxaliplatin; ITC, indirect treatment comparison; OS, overall survival; Pola-BR, polatuzumab vedotin in combination with bendamustine and rituximab; R-gem-ox, Rituximab, gemcitabine, and oxaliplatin

Key issues

Issue	ICER impact
Generalisability of the results from STARGLO	Unknown ?
Are the results from STARGLO generalisable to NHS practice?	
Pola-BR as a comparator	Unknown ?
Is Pola-BR an appropriate comparator?	
How should uncertainty be accounted for in comparing Pola-BR and Glofit-GemOx?	
Updated modelling assumptions	Unknown ?
Is a fully incremental analysis appropriate?	

Abbreviations: ICER, incremental cost-effectiveness ratio; Glofit-GemOx, Glofitamab plus gemcitabine and oxaliplatin; Pola-BR, polatuzumab vedotin in combination with bendamustine and rituximab;

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Embargoed data

New evidence

Clinical trial results – latest data cut OS - 2L population

Data cut 3 analysis shows OS now significant in 2L population

At ACM1, committee noted analyses from STARGLO latest data cut would help to reduce the uncertainty of both comparisons

Kaplan-Meier OS, data cut 3 analyses STARGLO (2L population)

See ITT OS KM here

Abbreviations: 2L, second line; CI, confidence interval; Glofit-GemOx; glofitamab with gemcitabine and oxaliplatin HR, hazard ratio; ITT, intention to treat; KM, Kaplan-Meier; OS, overall survival; R-GemOx, rituximab with gemcitabine and oxaliplatin

Analysis	HR (95% CI, P-value)
Data cut 2 - median follow-up 20.2 months	0.67 (0.41, 1.07); p=0.092
Data cut 3 - median follow-up 34.9 months	0.58 (0.38, 0.89); *********

Embargoed data

New evidence

Clinical trial results – latest data cut PFS - 2L population

Data cut 3 2L PFS analysis shows similar results to previous analysis

At ACM1, committee noted analyses from STARGLO latest data cut would help to reduce the uncertainty of both comparisons

Kaplan-Meier PFS, data cut 3 analyses STARGLO (2L population)

See ITT PFS KM here

Abbreviations: 2L, second line; CI, confidence interval; Glofit-GemOx; glofitamab with gemcitabine and oxaliplatin HR, hazard ratio; ITT, intention to treat; KM, Kaplan-Meier; PFS, progression-free survival; R-GemOx, rituximab with gemcitabine and oxaliplatin

Analysis	HR (95% CI, P-value)
Data cut 2 - median follow-up 15.5 months	0.41 (0.25, 0.67); p=0.0002
Data cut 3 - median follow-up 26.3 months	**********

Embargoed data

New evidence

Clinical trial results – 2L subpopulation

Significant results are listed in **bold**

Outcome	Overall survival				Progression-free survival			
	2L population Median follow-up CCOD2 - 20.2 months		2L population Median follow-up CCOD3 - 34.9 months		2L population Median follow-up CCOD2 - 15.5 months		2L population Median follow-up CCOD3 - 26.3 months	
	Glofit-GemOx N=115/183	R-GemOx N=57/91	Glofit-GemOx N=115/183	R-GemOx N=57/91	Glofit-GemOx N=115/183	R-GemOx N=57/91	Glofit-GemOx N=115/183	R-GemOx N=57/91
Median, months (95% CI)	NE (20.4, NE)	15.7 (10.3, NE)	NE (22.8, NE)	14.4 (10.3, 26.8)	20.4 (9.2, NE)	5.6 (3.0, 13.1)	20.4 (9.2, NE)	5.5 (2.6, 9.7)
Stratified HR (95% CI)	0.67 (0.41, 1.07); p=0.092		**0.58 (0.38, 0.89)** [redacted]		**0.41 (0.25, 0.67); p=0.0002**		[redacted]	

2L subpopulation is 63% of total pop (both arms)

See full ITT results here

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Abbreviations: 2L, second line; CCOD, clinical cut-off date; CI, confidence interval; Glofit-GemOx; glofitamab with gemcitabine and oxaliplatin HR, hazard ratio; ITT, intention to treat; N, sample size; NE, not evaluable; R-GemOx, rituximab with gemcitabine and oxaliplatin

Key Issue: Generalisability of the results from STARGLO

Company provide EMA submission including further analysis of generalisability of results from STARGLO

ACM1

- Committee raised concerns about the generalisability of the STARGLO results
- Committee requested further statistical analyses to inform conclusions about the applicability of the STARGLO 2L data to UK clinical practice

Company

- Provided submission given to EMA to support generalisability of STARGLO data to EU
- Notes that NALTs appeared to be one main confounding factor - given more frequently in the European population following R-GemOx vs. Glofit-GemOx (at least 1 NALT = 57.7% vs. 29.0%), particularly CAR-T – provided PFS, EFS and IPCW analysis by region
- Deaths due to COVID-19 also identified as a main confounder – provided 3 sensitivity analyses using different methods of censoring COVID-19 events
- Analysis provided also included comparison of baseline characteristics of ITT and European population and comparison with the Europe-based NIVEAU trial
- MHRA, EMA and ESMO were satisfied that results were generalisable to their regions
- Does not appear to be a biological rationale for outcomes to differ by race

Abbreviations: 2L, second line; CAR-T, chimeric antigen receptor T-cell; EFS, event free survival; EMA, European Medicines Agency; ESMO, European Society For Medical Oncology; Glofit-GemOx; glofitamab with gemcitabine and oxaliplatin; IPCW, inverse probability of censoring weighting; ITT, intention to treat; MHRA, Medicines and Healthcare products Regulatory Agency; NALT, new anti-lymphoma therapy; PFS, progression free survival; R-GemOx, rituximab with gemcitabine and oxaliplatin

Key Issue: Generalisability of the results from STARGLO

Company provide EMA submission including further analysis of generalisability of results from STARGLO

EAG

- Unclear how company came to conclusion that NALT use and COVID-19 events were main confounding factors
- Relevance of company analysis is based on assumption that European practice is similar to UK practice, which company do not explicitly discuss
- Unclear whether other studies could have been used for comparative purposes
- Unclear if IPCW approach is suitable - no unmeasured confounders assumption not shown to apply – company did not explore other methods of adjustment for treatment switching
- Data comes from data cut 2 ITT population not data cut 3 2L population, which is population of key interest identified in the draft guidance

Abbreviations: 2L, second line; EMA, European Medicines Agency; IPCW, inverse probability of censoring weighting; ITT, intention to treat; NALT, new anti-lymphoma therapy

Significant results are listed in **bold**

Key Issue: Generalisability of the results from STARGLO

Company provide EMA submission including further analysis of generalisability of results from STARGLO

Table: Baseline characteristics differing between ITT population and European population in STARGLO

Characteristic	ITT population	European population
Ann Arbor stage (3/4)	58.4%	75%
Prior CAR-T therapy	7.7%	13.6%
Refractory to last therapy	64.5%	52.3%
Primary refractory or within 12 months of 1L	75.8%	63.6%
Double refractory (anti-CD20 and anthracycline-based regimen)	58.6%	48.9%

Characteristics listed above were differences between European and ITT populations that may impact efficacy. Other characteristics were similar or not expected to impact efficacy

Table: Unstratified HRs and 95% CIs of PFS and EFS for ITT and geographic regions in STARGLO

	ITT population (N=274)	Europe (N=88)	North America (N=25)	RoW (N=161)
PFS	**0.46 (0.32, 0.65)**	0.84 (0.44, 1.59)	2.25 (0.48, 10.54)	**0.27 (0.17, 0.42)**
EFS	**0.40 (0.29, 0.55)**	0.76 (0.42, 1.38)	1.03 (0.35, 3.06)	**0.23 (0.15, 0.36)**

Abbreviations: CI, confidence interval; EFS, event free survival; HR, hazard ratio; ITT, intention to treat; N, sample size; PFS, progression free survival; RoW, rest of world

Key Issue: Generalisability of the results from STARGLO

Company present IPCW analysis to adjust for higher rate of NALT use in European R-GemOx arm

Table: Original and IPCW results for OS by geographic region and ITT

Pop	R-GemOx original N	R-GemOx IPCW N	Glofit-GemOx original N	Glofit-GemOx IPCW N	Original HR (95% CI)	IPCW HR (95% CI)
ITT	91	[redacted]	183	[redacted]	**0.62 (0.43, 0.88)**	[redacted]
Europe	26	[redacted]	62	[redacted]	1.09 (0.54, 2.18)	[redacted]
NA	10	[redacted]	15	[redacted]	2.62 (0.56, 12.34)	[redacted]
RoW	55	[redacted]	106	[redacted]	**0.41 (0.27, 0.64)**	[redacted]

Table: Original and IPCW results for PFS by geographic region and ITT

Pop	R-GemOx original N	R-GemOx IPCW N	Glofit-GemOx original N	Glofit-GemOx IPCW N	Original HR (95% CI)	IPCW HR (95% CI)
ITT	91	[redacted]	183	[redacted]	**0.46 (0.32, 0.65)**	[redacted]
Europe	26	[redacted]	62	[redacted]	0.83 (0.44, 1.59)	[redacted]
NA	10	[redacted]	15	[redacted]	2.25 (0.48, 10.54)	[redacted]
RoW	55	[redacted]	106	[redacted]	**0.27 (0.17, 0.42)**	[redacted]

Abbreviations: CI, confidence interval; Glofit-GemOx; glofitamab with gemcitabine and oxaliplatin HR, hazard ratio; IPCW, inverse probability of censoring weighting; ITT, intention to treat; N, sample size; NA, North America; NALT, new anti-lymphoma therapy; OS, overall survival; PFS progression free survival; R-GemOx, rituximab with gemcitabine and oxaliplatin; RoW, rest of world

Key Issue: Generalisability of the results from STARGLO

Company present COVID-19 sensitivity analysis – identified as a main confounder in post-hoc analysis

Table: STARGLO COVID-19 sensitivity analysis for OS by geographic region and ITT

	ITT (N=274)	Europe (N=88)	NA (N=25)	RoW (N=161)
Naïve analysis	**0.62 (0.43, 0.88)**	1.09 (0.54, 2.18)	2.62 (0.56, 12.34)	**0.41 (0.27, 0.64)**
Sensitivity analysis 1	**0.57 (0.40, 0.82)**	[redacted]	[redacted]	[redacted]
Sensitivity analysis 2	**0.56 (0.39, 0.81)**	[redacted]	[redacted]	[redacted]
Sensitivity analysis 3	**0.60 (0.42, 0.88)**	[redacted]	[redacted]	[redacted]

Naïve analysis = Patients not censored due to COVID-19.
Sensitivity analysis 1 = Patients who died due to COVID-19 (within 3 months of treatment discontinuation) censored to study treatment discontinuation.
Sensitivity analysis 2 = OS for patients who died due to COVID-19 censored on their date of death.
Sensitivity analysis 3 = OS for patients who experienced a COVID-19 adverse event censored to study treatment discontinuation date

EAG

- Agrees that OS HRs more favourable but notes all results are [redacted] for the European subgroup

Abbreviations: HR, hazard ratio; ITT, intention to treat; N, sample size; NA, North America; OS, overall survival; PFS progression free survival; RoW, rest of world

Key Issue: Generalisability of the results from STARGLO

Company present results from Europe-based NIVEAU study indicating similar results to STARGLO

Table: OS and PFS rates in the NIVEAU trial compared to the ITT and European populations in STARGLO

	NIVEAU Trial R-GemOx arm (N=90)	STARGLO Trial ITT population R-GemOx arm (N=91)	STARGLO Trial European subgroup R-GemOx arm (N=26)
Overall survival			
1-year rate, % (95% CI)	48% (38, 59)	[redacted]	[redacted]
2 year rate, % (95% CI)	34% (22, 46)	33.5% (22, 45)	[redacted]
Progression-free survival			
1-year rate, % (95% CI)	28% (18, 37)	25.2% (14, 37)	[redacted]
2 year rate, % (95% CI)	15% (7, 23)	[redacted]	[redacted]

EAG

- No UK centres were included in the NIVEAU trial – unclear relevance to NHS practice
- Uncertainty due to differences in baseline characteristics between NIVEAU and STARGLO
- Unclear from publication whether NIVEAU represents European clinical practice

NICE Are the results from STARGLO generalisable to NHS practice?

Key Issue: Pola-BR as a comparator

ITC updated with data from latest STARGLO cut, results remain similar

ACM1

- Committee concluded that Pola-BR was a relevant comparator
- Committee concluded that the latest data from STARGLO and more evidence on its generalisability would help reduce the uncertainty of the appropriateness of the ITC

Company

- IPTW analysis updated to include latest data cut from STARGLO
- Clear separation in OS and PFS curves although [redacted]
- Maintains the use of IPTW without multiple imputation as its main analysis
- Notes several uncertainties remain in the evidence:
  - Remaining imbalances in covariates of interest
  - The small effective sample size for Pola-BR ([redacted])
  - Clinical expert opinion that GO29365 study evidence outperforms Pola-BR in practice

EAG

- Agrees that ITC results should be interpreted with caution, given uncertainties
- HRs give an indication of difference in KMs but are not used in modelling

NHSE

- Notes majority of Pola-BR use is at 2L – Pola-BR use pre-SCT is likely very small and use of Pola-BR prior to 2L CAR-T has in effect stopped
- Considers Pola-BR to be a comparator to Glofit-GemOx

Key Issue: Pola-BR as a comparator

ITC updated with data from latest STARGLO cut, results remain similar

Figure: KM OS, IPTW without MI analysis (2L population)

Figure: KM PFS, IPTW without MI analysis (2L population)

Table: OS, ITC results from different methods

Method for estimating HR	HR (95% CI)
Unadjusted	[redacted]
IPTW without MI (**company** pref)	[redacted]
IPTW with MI (**EAG** pref)*	[redacted]
Full matching	[redacted]

Table: PFS, ITC results from different methods

Method for estimating HR	HR (95% CI)
Unadjusted	[redacted]
IPTW without MI (**company** pref)	[redacted]
IPTW with MI (**EAG** pref)*	[redacted]
Full matching	[redacted]

*EAG prefer including MI, but not necessarily company approach

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Is Pola-BR an appropriate comparator?
How should uncertainty be accounted for in comparing Pola-BR and Glofit-GemOx?

Key Issue: Pola-BR as a comparator

EAG concerned with reliability of company IPTW with MI analysis

Company

- Did IPTW analysis with MI for cell-of-origin and bone marrow involvement - used MICE technique because level of missing data was too high to impute with the mode for those inputs – repeated 5 times
- IPTW with MI produces different KMs to IPTW without MI (which affects modelling) but inclusion of MI introduces uncertainty and is not suitable for decision making
  - MI is only appropriate when missing covariates are prognostic - cell-of-origin and bone marrow involvement considered low-priority prognostic variables by clinicians
  - Literature states MI is not appropriate when missing data exceeds 40% - bone marrow involvement is 24% missing, cell-of-origin is 51% missing
  - KM curves cannot be adjusted for imbalances - causes large variation in costs and QALYs

EAG

- Company's MI analysis is poorly explained – unclear what other data were available, how much of this is missing, what assumptions were included, why the approach was chosen and why no additional methods were attempted
- Standard practice to explicitly define the imputation and analysis model and justify appropriateness
- Unclear why company included cell-of-origin and bone marrow involvement in MI if not prognostically important
- Not clear why company did not exclude cell-of-origin as a covariate as it is above the 40% threshold for missingness – may have contributed to heterogeneity of results
- MICE approach would still not be suitable for level of missing data for cell-of-origin
- The inability to adjust for imbalances does not just apply to MI, applies to entire ITC approach

Abbreviations: CI, confidence interval; HR, hazard ratio; IPTW, inverse probability of treatment weighting; ITC, indirect treatment comparison; OS, overall survival; PFS, progression free survival; Pola-BR, polatuzumab vedotin in combination with bendamustine and rituximab

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Updated modelling assumptions

Company updated model to include latest STARGLO data cut and committee preferred assumptions

Company

- For the comparison with Pola-BR, PFS and OS curves for the Glofit-GemOx arm plateau later in the updated analysis so applied the log-normal distribution at 25 months for both PFS and OS with approximately 30% and 50% of patients remaining at risk, respectively
- Based on the results of the fully incremental analysis, R-GemOx should be excluded because it is dominated by Pola-BR, leaving Pola-BR as the sole comparator for consideration in this appraisal
- The cost-effectiveness of Glofit-GemOx in comparison to R-GemOx should be considered because clinical experts have confirmed it represents SoC

EAG

- Company's choice of parametric curve and applying the distribution at 25 months for both PFS and OS are reasonable
- Acknowledges the difficulties of providing an incremental analysis in this case and considers that pairwise comparisons are worthwhile in this instance

Is a fully incremental analysis appropriate?

Abbreviations: Glofit-GemOx; glofitamab with gemcitabine and oxaliplatin; OS, overall survival; PFS, progression free survival; Pola-BR, polatuzumab vedotin in combination with bendamustine and rituximab; R-GemOx, rituximab with gemcitabine and oxaliplatin; SoC, standard of care

Cost-effectiveness results

All ICERs are reported in PART 2 slides

because they include confidential

PAS discounts

For the comparison with R-GemOx, company and EAG base case ICERs are below the range normally considered an acceptable use of NHS resources

For the comparison with Pola-BR, the ICERs are above the lower end of the range normally considered a cost-effective use of NHS resources

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Other issues

Equality issues:

No equality issues were raised in the submissions

Severity:

The threshold for the severity modifier has not been reached and no adjustment has been applied in the model

Managed access:

The company has not submitted a managed access proposal but have said it is open to consideration for a managed access agreement

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Key issues

Issue	ICER impact
Generalisability of the results from STARGLO	Unknown ?
Are the results from STARGLO generalisable to NHS practice?	
Pola-BR as a comparator	Unknown ?
Is Pola-BR an appropriate comparator?	
How should uncertainty be accounted for in comparing Pola-BR and Glofit-GemOx?	
Updated modelling assumptions	Unknown ?
Is a fully incremental analysis appropriate?	

Abbreviations: ICER, incremental cost-effectiveness ratio; Glofit-GemOx, Glofitamab plus gemcitabine and oxaliplatin; Pola-BR, polatuzumab vedotin in combination with bendamustine and rituximab;

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Supplementary appendix

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Key clinical trial: STARGLO

Clinical trial design

	Characteristics
Design	Phase 3 open label RCT
Population	Adults with histologically confirmed relapsed or refractory DLBCL who had at least 1 line of systemic therapy and who are not eligible for ASCT N=274 at 62 sites (UK: N=16 at 5 sites)
Intervention	• Pre-treatment 1000mg obinutuzumab; • 8 cycles glofit-gem-ox followed by up to 4 cycles glofitamab monotherapy
Comparator	• Up to 8 cycles R-gem-ox
Primary outcome	• Overall survival
Key secondary outcomes	• Progression free survival • Complete response rate (proportion whose best overall response is CR on PET/CT) • Duration of complete response (time from CR to disease progression, or death)
Locations	Worldwide (13, countries, including UK)
Used in model?	Yes: 2L population only

Abbreviations: ASCT, autologous stem cell transplant; Glofit-gem-Ox; glofitamab with gemcitabine and oxaliplatin; RCT, randomised controlled trial; R-gem-cx; rituximab with gemcitabine and oxaliplatin

* link

Embargoed data

New evidence

Clinical trial results – latest data cut OS - ITT

Data cut 3 ITT OS analysis shows similar results to previous analysis

Kaplan-Meier OS, data cut 3 analyses STARGLO (ITT population)

Abbreviations: CI, confidence interval; Glofit-GemOx; glofitamab with gemcitabine and oxaliplatin HR, hazard ratio; ITT, intention to treat; OS, overall survival; R-GemOx, rituximab with gemcitabine and oxaliplatin

Analysis	HR (95% CI, P-value)
Data cut 2 - median follow-up 20.7 months	0.62 (0.43, 0.88); p=0.006
Data cut 3 - median follow-up 35.1 months	0.60 (0.43, 0.83) [redacted]

Embargoed data

New evidence

Clinical trial results – latest data cut PFS - ITT

Data cut 3 ITT PFS analysis shows similar results to previous analysis

Kaplan-Meier PFS, data cut 3 analyses STARGLO (ITT population)

Glofit-GemOx

R-GemOx

Abbreviations: CI, confidence interval; Glofit-GemOx; glofitamab with gemcitabine and oxaliplatin HR, hazard ratio; ITT, intention to treat; PFS, progression-free survival; R-GemOx, rituximab with gemcitabine and oxaliplatin

Analysis	HR (95% CI, P-value)
Data cut 2 - median follow-up 15.7 months	0.40 (0.28, 0.57); p<0.000001
Data cut 3 - median follow-up 26.3 months	0.41 (0.29, 0.57); [redacted]

Embargoed data

New evidence

Clinical trial results – latest data cut - ITT

Outcome	Overall survival				Progression-free survival			
	Data cut 2 analysis Median follow-up 20.7 months		Data cut 3 analysis Median follow-up 35.1 months		Data cut 2 analysis Median follow-up 15.7 months		Data cut 3 analysis Median follow-up 26.3 months	
	Glofit-GemOx N=183	R-GemOx N=91	Glofit-GemOx N=183	R-GemOx N=91	Glofit-GemOx N=183	R-GemOx N=91	Glofit-GemOx N=183	R-GemOx N=91
Median OS, months (95% CI)	25.5 (18.3, NE)	12.9 (7.9, 18.5)	25.5 (17.0, NE)	12.5 (7.9, 16.5)	13.8 (8.7, 20.5)	3.6 (2.5, 7.1)	14.4 (8.8, 27.4)	3.3 (2.3, 5.6)
Stratified HR (95% CI)	0.62 (0.43, 0.88); p=0.006		0.60 (0.43, 0.83) [redacted]		0.40 (0.28, 0.57); p<0.000001		0.41 (0.29, 0.57); [redacted]	

NICE

Abbreviations: CI, confidence interval; Glofit-GemOx; glofitamab with gemcitabine and oxaliplatin HR, hazard ratio; ITT, intention to treat; N, sample size; NE, not evaluable; OS, overall survival; R-GemOx, rituximab with gemcitabine and oxaliplatin

Key Issue: Pola-BR as a comparator

EAG concerned with reliability of company IPTW with MI analysis

Table: Median PFS and percentage progression free at 5 years for company base case and each MI iteration

Analysis	Median PFS (months)	5-year progression-free (%)
Base case (no MI, [redacted])	[redacted]	[redacted]
Imputation 1 [redacted]	[redacted]	[redacted]
Imputation 2 [redacted]	[redacted]	[redacted]
Imputation 3 [redacted]	[redacted]	[redacted]
Imputation 4 [redacted]	[redacted]	[redacted]
Imputation 5 [redacted]	[redacted]	[redacted]
Average result of imputations	[redacted]	[redacted]

Abbreviations: CI, confidence interval; HR, hazard ratio; IPTW, inverse probability of treatment weighting; ITC, indirect treatment comparison; OS, overall survival; PFS, progression free survival; Pola-BR, polatuzumab vedotin in combination with bendamustine and rituximab

Key Issue: Pola-BR as a comparator

EAG concerned with reliability of company IPTW with MI analysis

Figure: Imputation 1 PFS

Figure: Imputation 2 PFS

Figure: Imputation 5 PFS

Figure: Imputation 3 PFS

Figure: Imputation 4 PFS

Abbreviations: PFS, progression free survival

Key Issue: Pola-BR as a comparator

EAG concerned with reliability of company IPTW with MI analysis

Figure: Imputation 1 OS

Figure: Imputation 2 OS

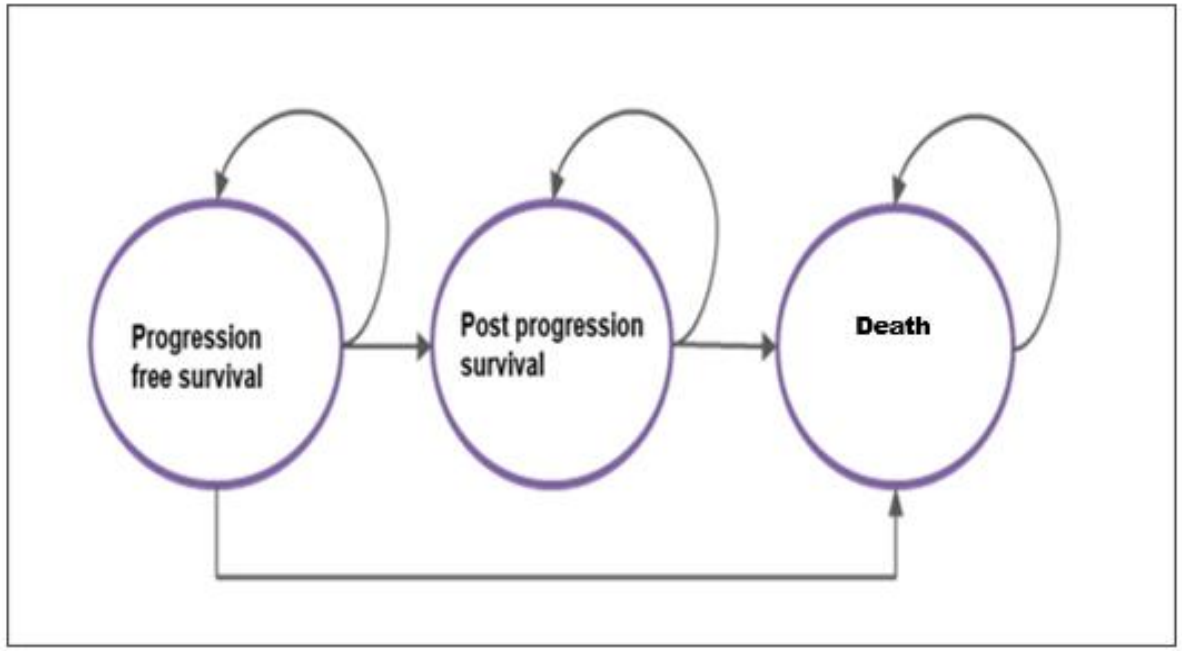
Figure: Imputation 3 OS

Figure: Imputation 4 OS

Figure: Imputation 5 OS

 Abbreviations: OS, overall survival

Company's model overview



Company model:

- Partitioned survival analysis with 3 health states
- 60-year time horizon; STARGLO 2L sub population;
  - Mean age [redacted] years; [redacted] male
- Background mortality modelled as a function of age distribution rather than mean age of cohort
- Weekly cycles with half-cycle correction

Assumptions with greatest impact on ICER:

- Most sensitive to using the same mortality as the general population after six years
  - and assuming 30% of people do not have third-line treatment.
- End of life care costs become a key driver if cure point set to 3 years

All other changes have minimal impact on results

EAG:

- Partitioned survival analysis is appropriate
- Population of STARGLO broadly representative of people with r/r DLBCL
- Time horizon is adequate
- No concerns using age distribution to calculate background mortality
- Half-cycle correction not needed due to short cycle length

Abbreviations: DLBCL, diffuse large B-cell lymphoma; ICER, incremental cost-effectiveness ratio; r/r, relapsed or refractory

Summary of modelling concerns from ACM1

Company align model to committee preferences

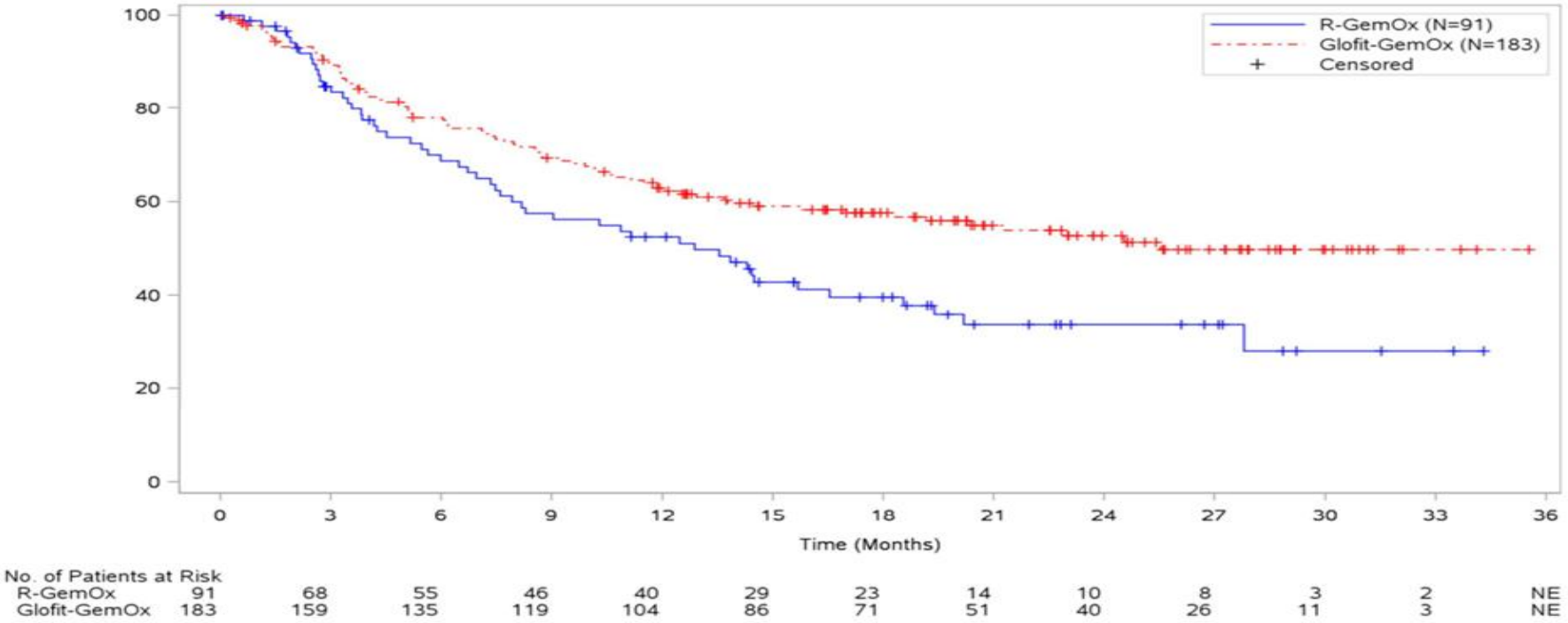
Committee preference	Company response
Cure point set to 6 years (SMR of 1.09)	Included in company base case
15% in Glofit-GemOx arm receive palliative care	Included in company base case
One-off end of life costs applied	Included in company base case
Fully incremental analysis between Glofit-GemOx, R-GemOx, and Pola-BR	Included in company base case but company note that R-GemOx is dominated by Pola-BR and so the comparison is essentially a pairwise comparison between Glofit-GemOx and Pola-BR

Abbreviations:

Clinical trial results - OS analyses

OS for the whole trial (ITT) data showed 41% reduction in risk of death in people treated with glofit-gem-ox compared with R-gem-ox. Analysis for 2L subpopulation are used to inform economic analysis (see later slides)

Kaplan-Meier OS, updated analyses STARGLO (ITT population)



Abbreviations: CI, confidence interval; Glofit-gem-Ox; glofitamab with gemcitabine and oxaliplatin; HR, hazard ratio; ITT, intention to treat; N, sample size; NE, not evaluable; OS, overall survival; R-gem-ox, rituximab with gemcitabine and oxaliplatin

NICE

Analysis	HR (95% CI, P-value)
OS analyses - median follow-up 11.3 months	0.59 (0.40, 0.89); p=0.011
Updated analyses - median follow-up 20.7 months	0.62 (0.43, 0.88); p=0.006

Clinical trial results - OS analyses

Outcome	Primary analysis		Updated analysis			
	ITT population Median follow-up 11.3 months		ITT population Median follow-up 20.7 months		2L sub-population Median follow-up 20.2 months	
	Glofit-gem-ox N=183	R-gem-ox N=91	Glofit-gem-ox N=183	R-gem-ox N=91	Glofit-gem-ox N=115/183*	R-gem-ox N=57/91*
Median OS, months (95% CI)	NE (13.8, NE)	9.0 (7.3, 14.4)	25.5 (18.3, NE)	12.9 (7.9, 18.5)	NE (20.4, NE)	15.7 (10.3, NE)
Stratified HR (95% CI)	0.59 (0.40, 0.89); p=0.011		0.62 (0.43, 0.88); p=0.006		0.67 (0.41, 1.07); p=0.092	

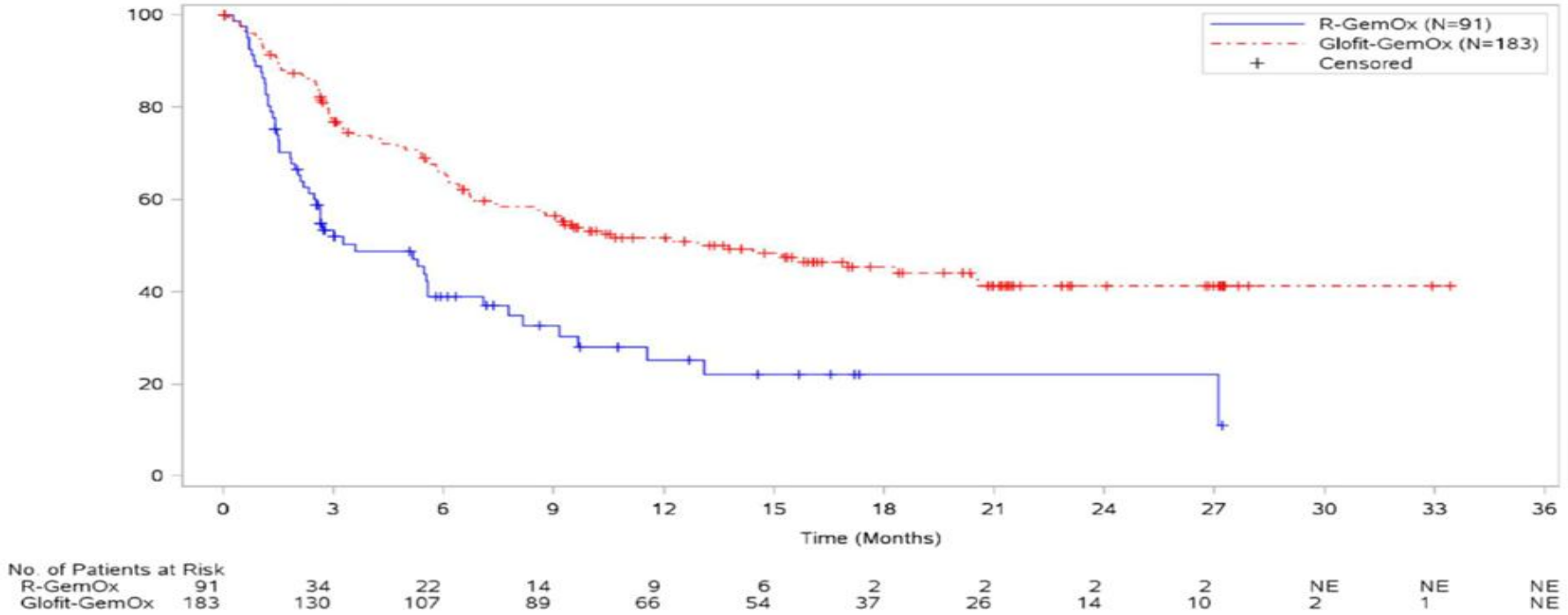
* N for 2 line subpopulation is 63% of total pop (both arms)

NICE Abbreviations: CI, confidence interval; Glofit-gem-Ox; glofitamab with gemcitabine and oxaliplatin HR, hazard ratio; ITT, intention to treat; N, sample size; NE, not evaluable; OS, overall survival; R-gem-ox, rituximab with gemcitabine and oxaliplatin
* Calculated by NICE

Clinical trial results - PFS analyses

PFS for the whole trial (ITT) data showed 63% reduction in risk of PFS event for glofit-gem-ox compared with R-gem-ox. Analysis for 2L subpopulation is used to inform economic analysis (see later slides)

Kaplan-Meier PFS, updated analyses STARGLO (ITT population)



Abbreviations: CI, confidence interval; Glofit-gem-Ox; glofitamab with gemcitabine and oxaliplatin; HR, hazard ratio; ITT, intention to treat; N, sample size; NE, not evaluable; PFS, progression free survival; R-gem-ox, rituximab with gemcitabine and oxaliplatin

NICE

Analysis	HR (95% CI, P-value)
PFS analyses - median follow-up 7.2 months	0.37 (0.25, 0.55); p<0.000001
Updated analyses - median follow-up 15.7 months	0.40 (0.28, 0.57); p<0.000001

Clinical trial results - PFS analyses

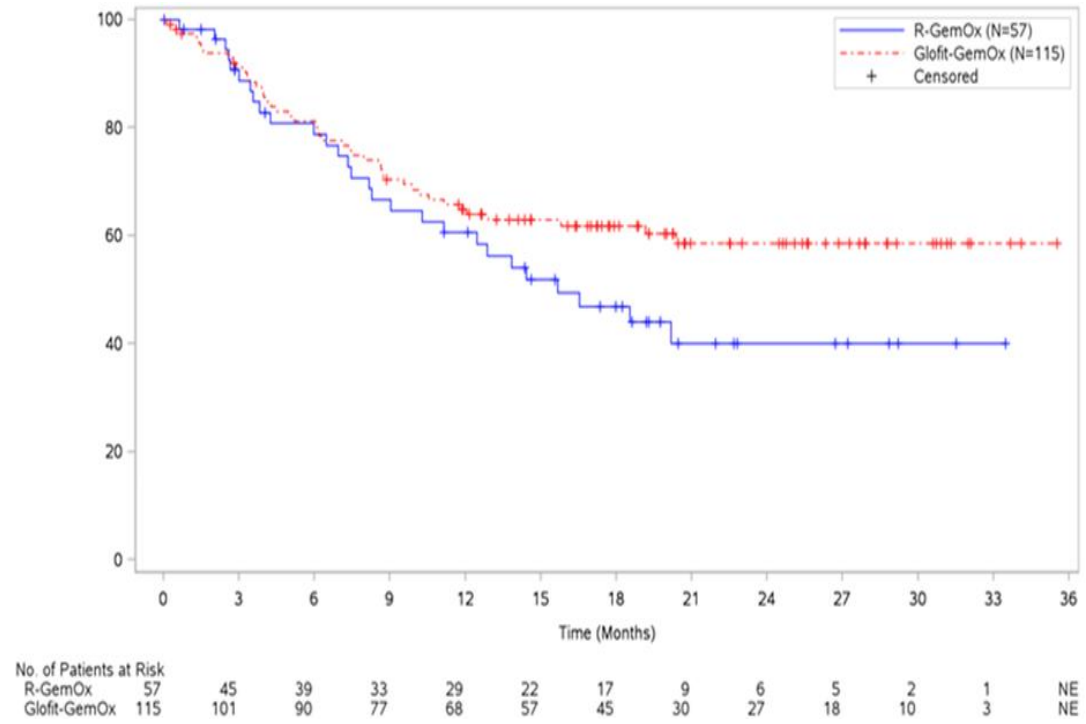
Outcome	Primary analysis		Updated analysis			
	ITT population Median follow-up 7.2 months		ITT population Median follow-up 15.7 months		2L subpopulation Median follow-up 15.5 months	
	Glofit-gem-ox N=183	R-gem-ox N=91	Glofit-gem-ox N=183	R-gem-ox N=91	Glofit-gem-ox N=115/183*	R-gem-ox N=57/91*
Median OS, months (95% CI)	12.1 (6.8, 18.3)	3.3 (2.5, 5.6)	13.8 (8.7, 20.5)	3.6 (2.5, 7.1)	20.4 (9.2, NE)	5.6 (3.0, 13.1)
Stratified HR (95% CI)	0.37 (0.25, 0.55) p<0.000001		0.40 (0.28, 0.57); p<0.000001		0.41 (0.25, 0.67); p=0.0002	

* N for 2 line subpopulation is 63% of total pop (both arms)

NICE Abbreviations: CI, confidence interval; Glofit-gem-Ox; glofitamab with gemcitabine and oxaliplatin; HR, hazard ratio; ITT, intention to treat; N, sample size; NE, not evaluable; OS, overall survival; R-gem-ox, rituximab with gemcitabine and oxaliplatin
* Calculated by NICE

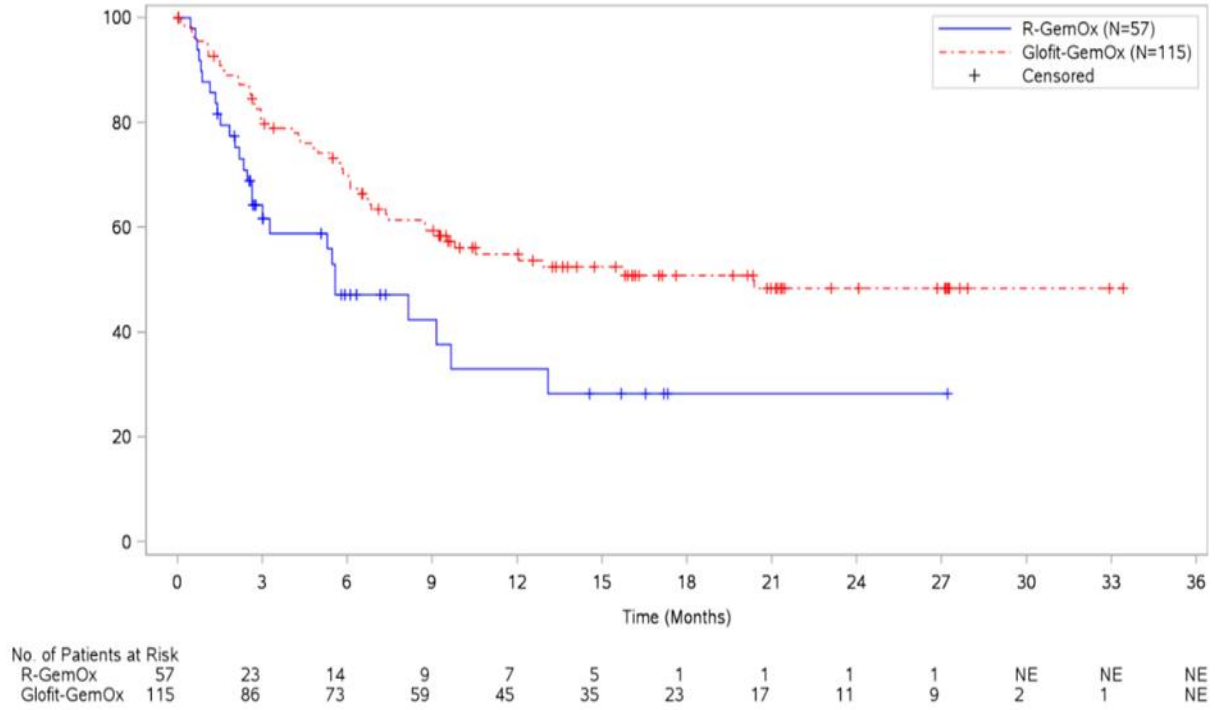
Clinical trial results: 2L only - analysis used in economic model

Kaplan-Meier OS, 2L (STARGLO updated analysis)



	Median follow-up 20.2 months
HR (95% CI, P-value)	0.67 (0.41, 1.07); p=0.092

Kaplan-Meier PFS, 2L (STARGLO updated analysis)



	Median follow-up 15.5 months
HR (95% CI, P-value)	0.41 (0.25, 0.67); p=0.0002

NICE

Abbreviations: CI, confidence interval; gGofit-GemOx, glofitamab, gemcitabine, oxaliplatin; HR, hazard ratio; N, sample size; OS, overall survival; PFS, progression free survival; R-gem-ox, Rituximab, gemcitabine, oxaliplatin

Background on Diffuse large B-cell lymphoma (DLBCL)

Ann Arbor staging classification

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

* See link

NICE

Abbreviations: DLBCL, diffuse large B-cell lymphoma;

Background on Diffuse large B-cell lymphoma

Lugano classification

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

* See link

NICE

Abbreviations: DLBCL, diffuse large B-cell lymphoma;

Background on Diffuse large B-cell lymphoma

International Prognostic Index

Clinical feature	Predictors of OS
Age	Less than 60 years; More than 60 years
Serum lactate dehydrogenase level	Normal level; Elevated level
ECOG performance status	Stage 0 or 1; Stage 2 to 4
Ann Arbor stage	Stage I or II; Stage III or IV
Number of extranodal sites	Stage 0 or 1; Stage 2 to 4

* See link

NICE

Abbreviations: DLBCL, diffuse large B-cell lymphoma; ECOG, Eastern Cooperative Oncology Group; OS, overall survval

Glofitamab in combination with gemcitabine and oxaliplatin Dose set up schedule

Glofitamab posology

- On Cycle 1, Day 8, 2.5 mg of glofitamab is administered over 4 hours; on Cycle 1, Day 15, 10 mg of glofitamab is administered over 4 hours;
- On Cycle 2, Day 1, 30 mg of glofitamab is administered over a period of 4 hours;
- If the patient experienced CRS with their previous dose, the duration of infusion may be extended to up to 8 hours.
- On Cycles 3–12, Day 1, 30 mg of glofitamab may be shortened to 2 hours at the discretion of the treating physician, if the previous infusion was well tolerated. If the patient experienced CRS with the previous dose, the duration of infusion should be maintained at 4 hours

Gemcitabine/oxaliplatin posology

- On Cycle 1, Day 2, 1000 mg/m^2 of gemcitabine and 100 mg/m^2 of oxaliplatin are administered IV.
- On Cycles 2–8, Day 1 or 2 (per local practice), 1000 mg/m^2 of gemcitabine and 100 mg/m^2 of oxaliplatin are administered IV.

* See link

Key issues: Relevant comparators (1)

BSH guidelines 2025: Recommended treatment options for rrLBCL in second-and third-line settings

Assess eligibility and fitness for CAR T-cell therapy and HDT-auto in all patients with rrLBCL

- For CAR T-cell fit patients with primary refractory or relapsed disease ≤12 months of completing first-line CIT, offer CD19-targeting CAR T-cell therapy.
- For HDT-auto fit patients relapsing >12 months after completing first-line CIT, offer a platinum-based regimen (e.g. R-ICE, R-GDP, R-DHAP, R-ESHAP)
  - Assess response to reinduction with a PET-CT scan after two to three cycles. Offer HDT-auto for patients achieving a CMR
  - For patients in PMR, the approach requires individualisation. Consider HDT-auto for patients with a low tumour burden Deauville 4 response
  - Consider radiotherapy consolidation before or after HDT-auto for patients in PMR after reinduction chemotherapy
  - Offer third-line therapy, preferably after further biopsy, for patients with an inadequate response or for those with stable or progressive metabolic disease after two to three cycles of reinduction
- For patients who are not suitable for second-line CAR T-cell therapy or HDT-auto, treatment should be individualisedbased on the level of fitness of the patient, prior first-line therapy and potential suitability for CAR T-cell therapy or anti-CD3xCD20 BsAb therapy in the third-line setting.
  - Offer glofitamab + GemOx if available
  - Consider rituximab-containing regimens without bendamustine such as four to eight cycles of R-GemOx, especially where subsequent CAR T-cell therapy or anti-CD3xCD20 BsAb therapy may be appropriate at third line
  - Consider Pola-BR for selected patients who have not received polatuzumab in first-linetherapy, but **caution is advised with bendamustine** where subsequent CAR T-cell therapy (and possibly anti-CD3xCD20 BsAb) may be appropriate at third line.
  - Where available, consider tafasitamab and lenalidomide for selected patients but caution is advised where CD19-targeting CAR T-cell therapy may be an option in third-line setting
  - In frail patients, consider oral etoposide-based chemotherapy regimens with or without rituximab

link

Abbreviations: ASCT, autologous stem cell transplant; DLBCL, diffuse large B-cell lymphoma; Pola-BR, polatuzumab vedotin in combination with bendamustine and rituximab; Pola-R-CHP; polatuzumab vedotin with rituximab, doxorubicin, cyclophosphamide and prednisolone

Key issues: Relevant comparators (1)

BSH guidelines 2025: Patients unfit for CAR-T or high dose-therapy

- “Where possible, pola-BR should be avoided for patients who may be suitable for third-line CAR T-cell therapy given that bendamustine exposure prior to apheresis is associated with increased risk of CAR T-cell manufacturing failure and inferior outcomes after CAR T-cell therapy.
- Although definitive data are not yet available and current literature is conflicting, there is concern that prior bendamustine exposure may adversely impact the efficacy of subsequent CD3xCD20 BsAb therapy, especially if the interval between these therapies is short”

link

Abbreviations: ASCT, autologous stem cell transplant; DLBCL, diffuse large B-cell lymphoma; Pola-BR, polatuzumab vedotin in combination with bendamustine and rituximab; Pola-R-CHP; polatuzumab vedotin with rituximab, doxorubicin, cyclophosphamide and prednisolone

Key issues: Relevant comparators - ITC glofit-gem-ox compared with pola-BR

EAG:

ITC methods:

- ITC appropriate but reporting of methods lacks detail;
- Key prognostic factors adequately considered but ambiguity how bulky disease covariate was analysed
- Company apply a crude approach to adjust covariate missing values in unadjusted and full matching analyses
- IPTW with multiple imputation is most robust analysis but uncertain of impact of missing data
- Reducing effective sample size is a minor limitation compared to uncertainties in covariate adjustments and missing data

Real world evidence:

- Company do not discuss process for identifying and selecting real world evidence so unclear if Northend et al is only relevant source of real-world evidence for pola-BR
- Results from Northend et al (2022) based on full population sample
  - Includes bridging to CAR T cell therapy; re-induction with planned stem cell; stand-alone treatment (no planned CAR T-cell therapy or SCT)
- Results from Northend et al (2022) stand-alone population are most relevant
  - Median PFS 5.4 months; Median OS 10.2 months

Abbreviations: CI, confidence interval; DLBCL, diffuse large B-Cell lymphoma; ITC, indirect treatment comparison; IPTW, inverse probability of treatment weighting; OS, overall survival; PFS, progression free survival; R/R, relapsed or refractory; SCT, stem cell transplant

Clinical trial G029365

Clinical trial design

	Characteristics
Design	Phase Ib/II, multicentre, open-label study
Population	Adults with relapsed or refractory DLBCL
Intervention	• Pola-BR
Comparator	• Bendamustine with rituximab
Primary outcome	• Complete response
Key secondary outcomes	• Overall survival • Progression-free survival • Event-free survival • Duration of response • Adverse effects of treatment • Health-related quality of life

* link

Abbreviations: Pola-BR, Polatuzumab vedotin plus bendamustine and rituximab; R-GemOx; rituximab with gemcitabine and oxiplatin

Key issues: Relevant comparators - ITC glofit-gem-ox compared with pola-BR

Covariate balance of unadjusted and IPTW analyses

Balanced covariates defined as <0.1 for absolute SMD

* link

Abbreviations: R DLBCL, diffuse large B cell lymphoma; Pola-BR, polatuzumab vedotin plus bendamustine and rituximab; R/R, relapsed or refractory

Key issues: Relevant comparators - ITC glofit-gem-ox compared with pola-BR

Covariates included in main analysis and full matching analysis:

- Age, years
- Eastern Cooperative Oncology Group (ECOG) performance status (PS) 1, %
- Eastern Cooperative Oncology Group (ECOG) PS 2, %
- Ann Arbor Stage III/IV, %
- High Lactate dehydrogenase (LDH), %
- Extranodal disease, %
- International Prognostic Index (IPI) 3–5, %
- Refractory first-line, %
- Bulky disease
- Time since last treatment to first study treatment, months
- Male sex, %

EAG's preferred ITC analysis (IPTW with multiple imputation) included two further covariates: cell type of origin and bone marrow involvement

* link

NICE Abbreviations: R DLBCL, diffuse large B cell lymphoma; Pola-BR, polatuzumab vedotin plus bendamustine and rituximab; R/R, relapsed or refractory

Key issues: ITC glofit-gem-ox compared with pola-BR

Baseline characteristics for the unadjusted sample

Variable	Glofit-GemOx [redacted]		Pola-BR ([redacted])		SMD	VR
	Mean	SD	Mean	SD		
Age, years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ECOG 1, %	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ECOG 2, %	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ann Arbor Stage III/IV, %	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
High LDH, %	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Extranodal disease, %	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
IPI 3–5, %	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Refractory first-line, %	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Bulky disease	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Time since last treatment to first study treatment, months	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Male sex, %	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

NICE

* link

Key issues: Relevant comparators - ITC glofit-gem-ox compared with pola-BR

ITC methods

ITC Analysis	Covariates adjusted for	Missing data adjustment	EAG Notes
Unadjusted	None	Unclear	
IPTW without multiple imputation	2 missing	Crude imputation	Company main analysis
IPTW with multiple imputation	All	Multiple imputation	EAG preferred analysis
Fully matched	2 missing	Crude imputation	Method not fully clear

- Main analysis: Did not adjust for cell type of origin and bone marrow involvement but missing values for all other covariates set equal to mean or mode of each covariate
- IPTW: Used to balance covariates
- IPTW with multiple imputation: Used to estimate values for cell type of origin, bone marrow involvement, and other covariates
- Fully matched analysis: Set all missing values equal to mean or mode of each covariate

link

Abbreviations: ITC, indirect treatment comparison; IPTW, inverse probability of treatment weighting;