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 08 July 2025

Chair: Steve O'Brien

Lead team: Elizabeth Thurgar, Amit Parekh, Stella O'Brien

External assessment group: Southampton Health Technology Assessments Centre

Technical team: Vicky Gillis-Elliott, Alexandra Filby, Ross Dent

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

NICE National Institute for Health and Care Excellence

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

Causes

Cause is largely unknown. Risk factors include hereditary and acquired immunodeficiencies such as HIV and rheumatoid arthritis, immunosuppression from transplantation or treatment of autoimmune diseases, exposure to environmental factors such as pesticides

Epidemiology

Around 4850 people are diagnosed with DLBCL (NOS) each year. Incidence increases with age; median age at diagnosis, 70 years. DLBCL is slightly more common in males

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

Patient perspectives

Relapsed or refractory DLBCL often has a poor response to treatment with a poor prognosis

Submission from Lymphoma Action

Symptoms

- Initially painless lumps (enlarged lymph nodes) in neck, groin or armpit
- Cancer developing can cause cough, shortness of breath and abdominal pain

Impact of diagnosis

- Psychological impact is enormous. People describe worry of relapsing or not responding to treatment and worry that there will no further treatment options. It can also be mentally difficult for family members
- Having to wait for multiple relapses makes the chance of cure smaller and can cause more physical side effects and prolonged mental impact

Current treatment

- Chemo-immunotherapy can have short and long-term side effects. There are multiple treatments. But people's options run out as the diseases relapses or become refractory to treatment
- Having another treatment option available after the first relapse or treatment failure would be an advantage

Worrying about how long I have raises its head…from a mental health perspective

When I was given R-ICE I lost [my] hair … I think the most annoying aspect of this was the fact it didn't work, so I did not need to lose my hair

the difference the medication made to my lymph nodes and the mass growing on the side of my neck

Abbreviations: DLBCL, diffuse large B-cell lymphoma; R-ICE, rituximab in combination with ifosfamide, carboplatin and etoposide

Clinical perspectives

Treatment will represent a step forward for patients with relapsed/refractory DLBCL

Submission from 2 consultant haematologists

- Current treatment options are all non-curative and have a short-lived response. The new treatment provides a potentially curative 2nd line option
- Glofit-gem-ox offers survival benefit compared to current care for relapsed or refractory DLBCL who are not eligible for stem cell transplant or CAR T
- Glofit-gem-ox would be delivered in secondary/tertiary health care settings. Centres already deliver gem-ox chemotherapy and glofitamab as individual treatments and administration is similar to current care
    - likely to be no difference in healthcare resource required to deliver this new treatment compared with current care in the NHS
- The combination has a manageable safety/toxicity profile but there are side effects for bispecific antibodies with cytokine release syndrome and neurotoxicity

There is…a gap in treatment for the majority of…transplant ineligible patients [who relapse] due to inferior 2nd line treatments

In the UK practice [glofit-gem-ox] would be an important option and replace [R-gem-ox] chemotherapy

Abbreviations: DLBCL, diffuse large B-cell lymphoma; CAR T; chimeric antigen receptor T-cell therapy; gem-ox, gemcitabine and oxaliplatin; glofit, glofitamab; R-gem-ox, Rituximab, gemcitabine, and oxaliplatin

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

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 EMA 14th April 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
Administration	• 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

Key issues

Issue	Resolved?	ICER impact
Comparators: Glofit-gem-ox positioned as 2L only, whereas it could be used 2L+ in the MA. Is positioning appropriate? Should pola-BR be a relevant comparator? Is glofit-gem-ox effective compared with pola-BR?	No – for discussion	Large 
Cure assumptions: Should the cure point in the model be set to 3 years or 6 years?	No – for discussion	Large 
Proportion having subsequent treatment Should third-line therapy costs be applied for everyone whose disease has progressed or would a proportion have palliative care?	No – for discussion	Large 

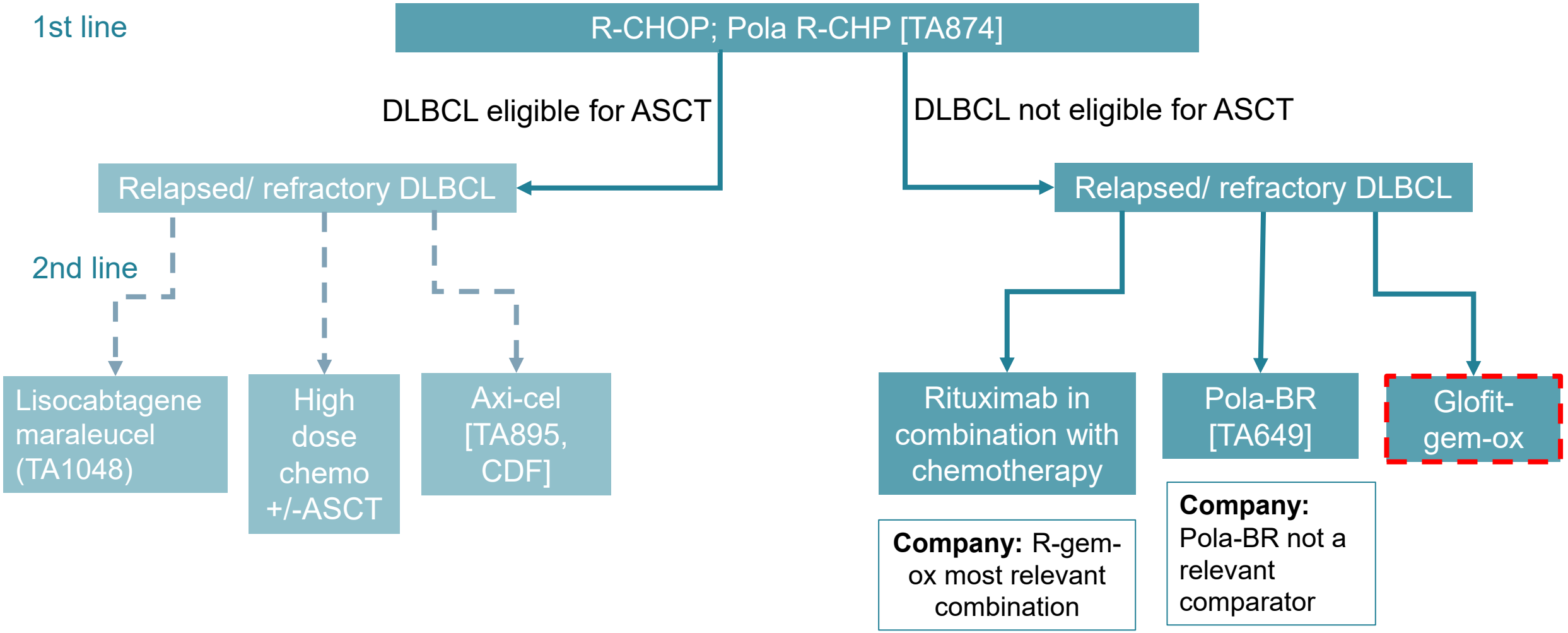
- Issues are key drivers but company and EAG base case ICERs vs R-gem-ox including all discounts are below the upper end of the range normally considered cost-effective use of NHS resources
- Some results for pola-BR are above the upper end of the range normally considered cost-effective

Other issues	Resolved?	ICER impact
End of life care costs: Should end of life care costs be captured in weekly resource use or as one-off cost?	No – for discussion	Status as key driver is contingent on cure point being set to 3 years 

NICE

Abbreviations: ICER, incremental cost-effectiveness ratio; Pola-BR, polatuzumab vedotin in combination with bendamustine and rituximab; R-gem-ox, Rituximab, gemcitabine, and oxaliplatin

Treatment pathway for relapsed or refractory DLBCL



Glofit-gem-ox positioned as 2L only, whereas it could be used 2L+ in the MA. Is positioning appropriate? Should pola-BR be a relevant comparator? (slide 16)

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

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

NICE National Institute for Health and Care Excellence

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

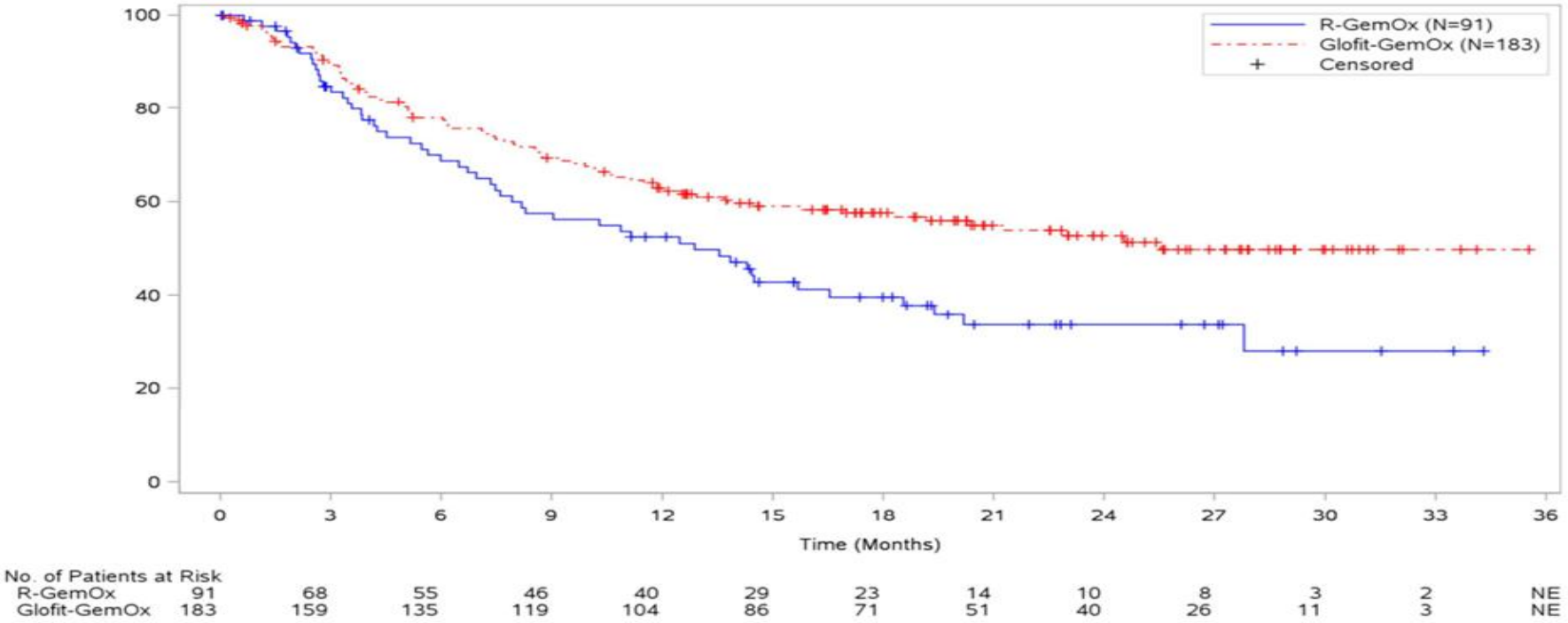
Abbreviations: ASCT, autologous stem cell transplant; Glofit-gem-Ox; glofitamab with gemcitabine and oxaliplatin; RCT, randomised controlled trial; R-gem-cx; rituximab with gemcitabine and oxaliplatin

* link

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

	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		2 line 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	

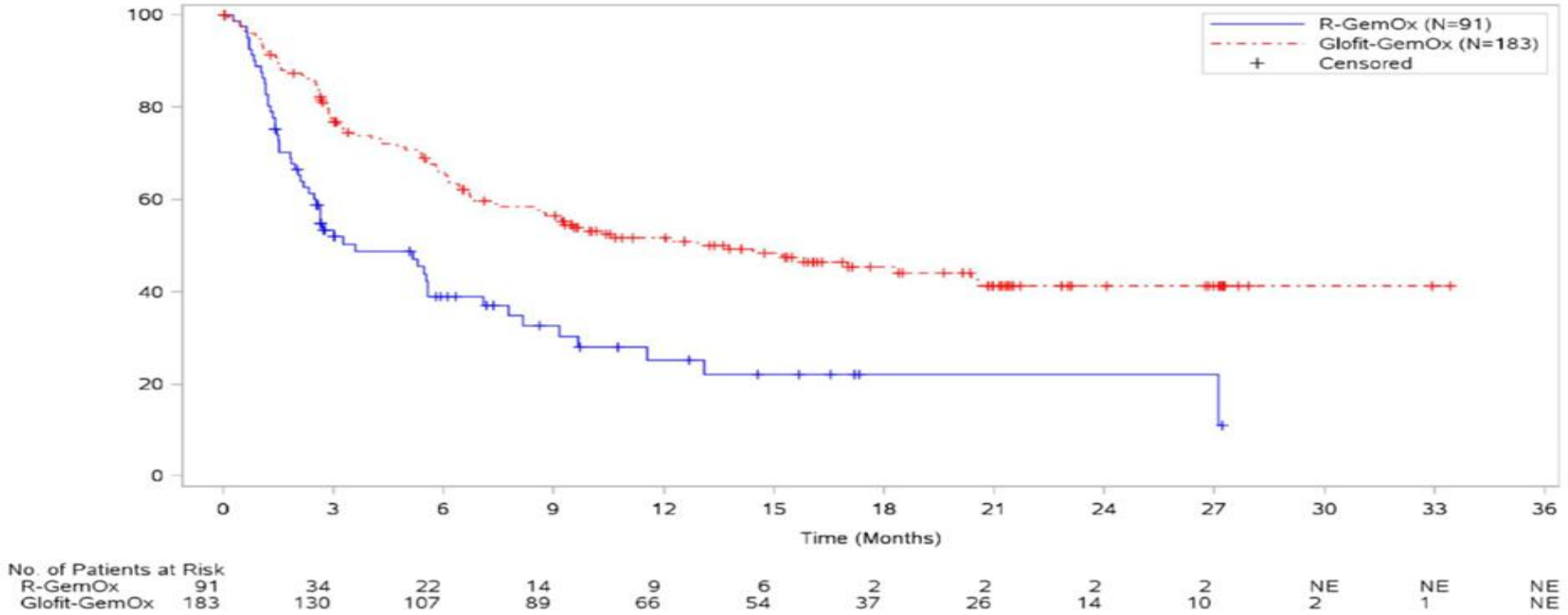
* N for 2 line subpopulation is 63% of total pop (both arms)

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

	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	

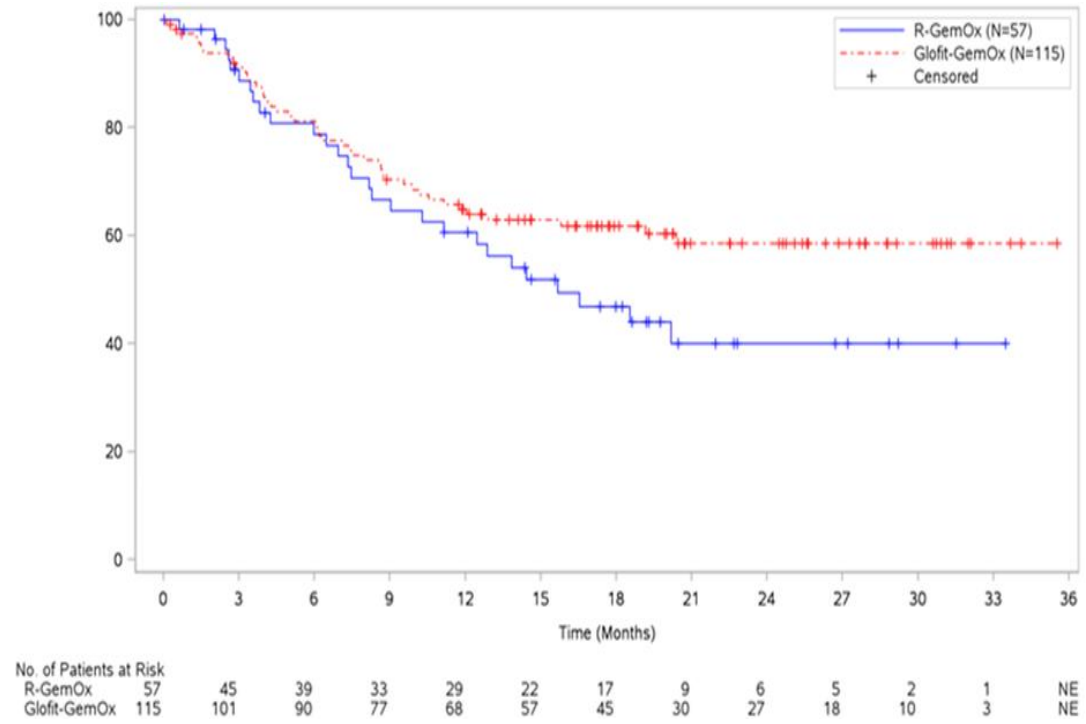
* N for 2 line subpopulation is 63% of total pop (both arms)

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

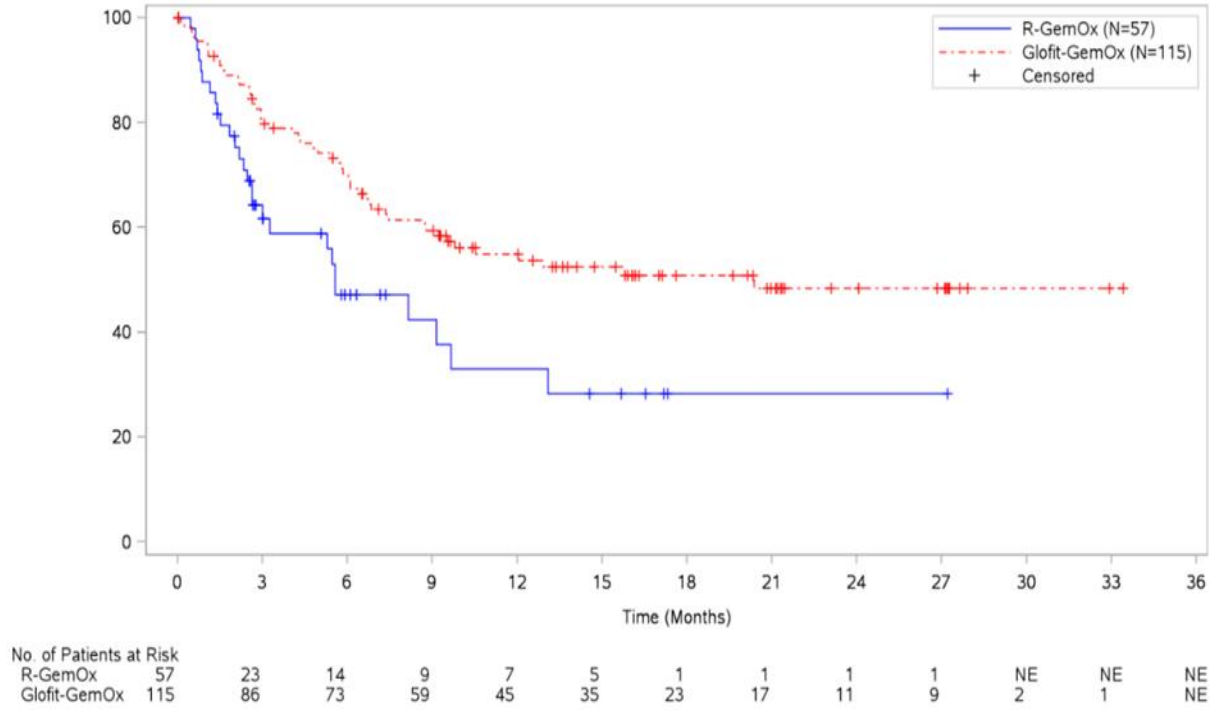
Clinical trial results: 2L only - analysis used in economic model

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; Glofit-Gem-Ox, glofitamab, gemcitabine, oxaliplatin; HR, hazard ratio; N, sample size; OS, overall survival; PFS, progression free survival; R-gem-ox, Rituximab, gemcitabine, oxaliplatin

Key issues: Relevant comparators (1)

Should pola-BR be included as a comparator?

Background: Pola-BR recommended for adults with relapsed or refractory DLBCL who are not eligible for ASCT [TA649] **Company:** do not consider pola-BR to be a relevant comparator. R-gem-ox is only comparator

Company: Advisory board lymphoma experts: pola-BR rarely used at second line and will continue to decline:

- Blueteq criteria: polatuzumab can only be used once in pathway unless bridging for CAR T. Pola-R-CHP is now a first-line therapy [TA874] so pola-BR at second-line has decreased (approx. [redacted]
- Bendamustine precludes CAR T therapy and bispecific monoclonal antibodies (at later lines of therapy) so reluctance to prescribe bendamustine in earlier lines
- Based on NHSE calculations (box below) approx 40% currently have pola-BR in 2L setting
- British Society for Haematology guidelines caution against bendamustine for those needing CAR T *, **
- Provided ITC of glofit-gem-ox vs pola-BR for OS and PFS and an economic scenario analysis

EAG: EAG clinical experts agreed pola-BR use has declined but it is still considered a relevant comparator (estimates of use were less than 10%, 10 to 15%, 10 to 20%).

NHSE CDF clinical lead: Pola-BR remains a comparator, but use is diminishing

- 34 registrations per month Jan to Dec 2024 (n=411); 28 registrations per month Jan to April 2025 (n=112)
- Clinical experts surprised at continued use of pola-BR, may reflect use in more loco-regional centres

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

see appendix for *BSH guidelines ** summary

Key issues: Relevant comparators (2) - ITC glofit-gem-ox compared with pola-BR

Background:

- Company provided ITC and scenario analyses vs pola-BR to consider cost-effectiveness

Company:

- 4 analyses submitted based on 2L STARGLO population (key trial n=[redacted]) and GO29365 (key trial in TA649; n= [redacted])
- See appendix for description of each analysis
- Included subset in GO29365 with DLBCL NOS, large node lesion and had 1 prior line of therapy
- Effective sample size glofit-gem-ox = [redacted] pola-BR =[redacted]

	Overall survival	Progression free survival
Method	**HR (95% CI)**	**HR (95% CI)**
Unadjusted	[redacted]	[redacted]
IPTW	[redacted]	[redacted]
IPTW: multiple imputation	[redacted]	[redacted]
Full matching	[redacted]	[redacted]

EAG:

- HRs and 95% CIs are similar in all analyses, but no results are statistically significant
- IPTW analysis with multiple imputation considered the most robust
- Proportional hazards assumption does not hold, so in the model the treatment arms are modelled separately, so uncertainty reflected by the confidence intervals from the ITC is not captured.

Is glofit-gem-ox effective compared with pola-BR?

Abbreviations: CI, confidence interval; DLBCL, diffuse large B-Cell lymphoma; HR, hazard ratio; ITC, indirect treatment comparison; IPTW, inverse probability of treatment weighting; NOS, not otherwise specified; OS, overall survival; PFS, progression free survival; R/R, relapsed or refractory; RWE, real world evidence

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

Kaplan-Meier graph for OS IPTW analysis

Kaplan-Meier graph for PFS for IPTW analysis

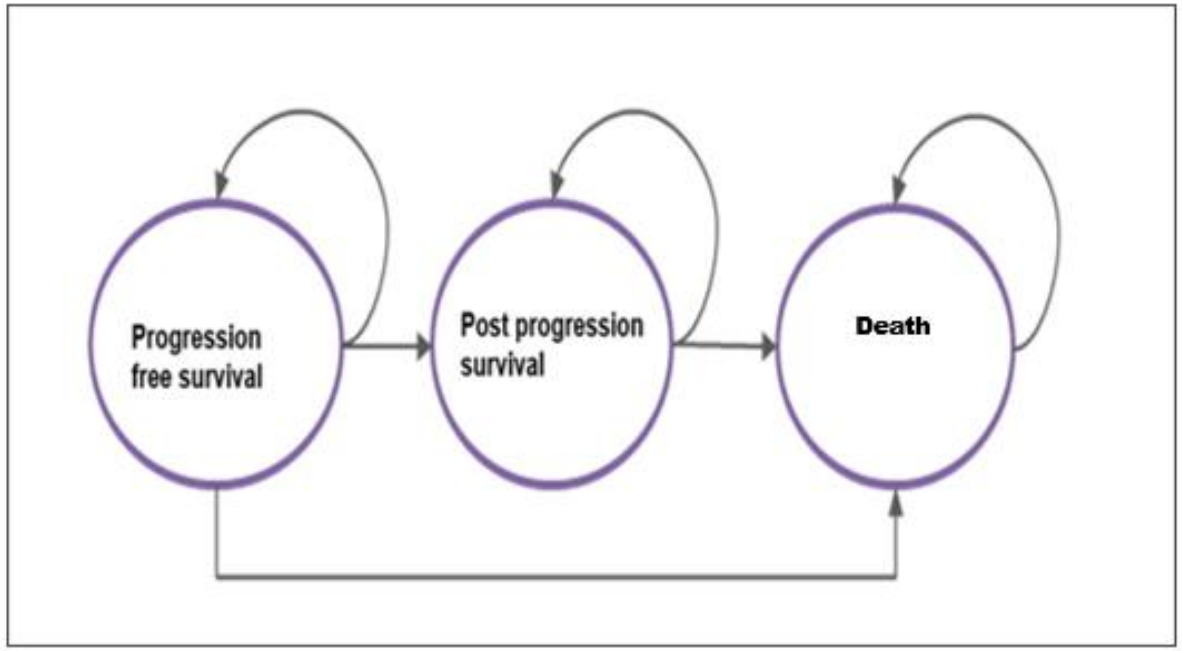
Abbreviations: ITC, indirect treatment comparison; IPTW, inverse probability of treatment weighting;

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

NICE National Institute for Health and Care Excellence

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

Key Issue: Cure assumptions (1)

Background

- Company base case assumes mortality for all patients **at 3 years** nearly equal to general pop (SMR: 1.09)
- EAG: Company base case results in optimistic OS predictions. It set cure point at **6 years**

Company

- 3-year assumption based on TA927, in-line with TA559 and TA567, applies standardised mortality rate (1.09; Maurer, 2014) adjusted for excess comorbidities. Same assumptions in both treatment arms
- TA927 committee agreed with assumption that people who were still alive 3 years after starting a third treatment, only had a 9% increased risk of mortality

EAG

- EAG set cure point to when all patients with progressed disease have died and remaining patients are progression free at **6 years (SMR: 1.09)**
- EAG's 5-year overall survival estimates for R-gem-ox arm align more closely with literature

Abbreviations: ICER, incremental cost-effectiveness ratio; OS, overall survival; R-gem-ox, Rituximab, gemcitabine, oxaliplatin; SMR, standardised mortality ratio

Key Issue: Cure assumptions (2)

Long-term overall survival estimates

Alive on Glofit-gem-ox	Time point			
	1 year	2 years	5 years	10 years
STARGLO K-M data	65%	59%	-	-
Cure point 3 years; lognormal (company base case)	70%	57%	46%	37%
Cure point 6 years; lognormal (EAG base case)	70%	57%	39%	29%
Alive on R-gem-ox				
STARGLO K-M data	61%	40%	-	-
Cure point 3 years; lognormal (company base case)	60%	39%	26%	21%
Cure point 6 years; lognormal (EAG base case)	60%	39%	17%	11%
Cazalles et al. (2021)	-	32%	-	-
Mounier et al. (2013)	48%	35%	14%	-

Should the cure point be set at 3 years or 6 years?

* See link

Abbreviations: Gofit-GemOx, glofitamab, gemcitabine, oxaliplatin; K-M Kaplan-Meier; R-gem-ox, Rituximab, gemcitabine, oxaliplatin

Key issue: Proportion having subsequent lines of therapy

Background

- Company assume 3L therapy costs apply to everyone in post-progression survival state and this includes 15% after Glofit-GemOx have palliative care or go on to take part in a clinical trial EAG consider a proportion have palliative care (**30%**),

Company

- Subsequent treatment costs are only applied to those in post-progression state
- There are different proportions in long-term remission in each arm, so post discontinuation costs differ for each modelled treatment

EAG

- Assumed **30%** have palliative care 3L
  - EAG experts: approx. 20% to 50% may be too frail to have third-line therapy and have palliative care
  - One EAG expert: new effective treatments at 3L means that fewer patients now move from second-line therapy to full palliation (20% to 25%)
- Scenario analyses 20% and 50% of people have palliative care

Should third-line therapy costs be applied for everyone whose disease has progressed, or would a proportion have palliative care?
What proportion having subsequent therapy should have palliative care?

Abbreviations: 3L, third line

See appendix for Distribution of subsequent treatments

Other issue: End of life care costs

Key driver dependent on cure assumptions

Background

- Company: end of life care costs captured in weekly resource use costs so did not apply separate cost
- EAG: unclear how some end of life care costs are accounted for in weekly resource cost so apply one-off cost

Company

- Resource use for PFS, PPS and one-off costs at progression based on weekly costs used in TA649
- Does not include separate end of life care costs because these are captured in the resource use costs

EAG

- Inpatient bed day cost is not accounted for in weekly resource use costs
- Weekly resource use costs for residential care, day care, home care and hospice care set to zero, and end of life costs modelled using one-off full end of life care costs (Georghiou and Bardsley, 2014)
- Individual impact increases ICER but cumulative impact is outweighed by setting mortality the same as for general population after 6 years so the effect of end of life care costs is much reduced

Should end of life care costs be captured in weekly resource use or as one-off cost?

NICE

Abbreviations: PFS, progression free survival; PPS, post progression survival; PSS, personal and social services

Summary of company and EAG base case assumptions

Assumption	Company base case	EAG base case	Impact
Cure assumption (key issue)	SMR 1.09: Mortality for progression-free or progressed disease after 3 years	SMR 1.09: Mortality for progression-free or progressed disease after 6 years	Increases ICER
Subsequent lines of therapy (key issue)	All with progressed symptoms have 3L therapy (15% after Glofit-gem-ox have palliative care or clinical trial)	30% will not have 3L therapy and have palliative care instead	Increases ICER
End of life care costs (other issue)	Weekly costs for supportive care included in healthcare resource use	One-off cost for end-of-life care	Negligible impact on ICER*
Utility values	Utility scores from STARGLO ITT population	Utility scores specific to 2 line	Negligible impact on ICER
Comparator costs	R-gem-ox given up to 8 cycles (in line with STARGLO)	R-gem-ox given for 6 cycles (in line with clinical advice to EAG)	Negligible impact on ICER
Administration costs	Applied separate costs for each treatment	Applied once for the combination of treatments	Negligible impact on ICER
Adverse event costs	Treatment-related adverse events for grade 3 and higher	TLS included in both R-gem-ox and Glofit-gem-ox	Negligible impact on ICER

NICE

Abbreviations: AE, adverse event; ITT, intention to treat; TLS, tumour lysis syndrome
*Only becomes a key driver if cure point set to 3 years

Cost-effectiveness results

- All cost-effectiveness estimates are reported in Part 2 slides because they include confidential discounts
- For the comparator R-gem-ox, company and EAG base case ICERs are below the upper end of the range normally considered an acceptable use of NHS resources
- For the comparator pola-BR, some results are above the upper end of the range normally considered a cost-effective use of NHS resources

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

NICE National Institute for Health and Care Excellence

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

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**

NICE National Institute for Health and Care Excellence

Key issues

Issue	Resolved?	ICER impact
Comparators: Glofit-gem-ox positioned as 2L only, whereas it could be used 2L+ in the MA. Is positioning appropriate? Should pola-BR be a relevant comparator? Is glofit-gem-ox effective compared with pola-BR?	No – for discussion	Large 
Cure assumptions: Should the cure point in the model be set to 3 years or 6 years?	No – for discussion	Large 
Proportion having subsequent treatment Should third-line therapy costs be applied for everyone whose disease has progressed or would a proportion have palliative care?	No – for discussion	Large 

- Issues are key drivers but company and EAG base case ICERs vs R-gem-ox including all discounts are below the upper end of the range normally considered cost-effective use of NHS resources
- Some results for pola-BR are above the upper end of the range normally considered cost-effective

Other issues	Resolved?	ICER impact
End of life care costs: Should end of life care costs be captured in weekly resource use or as one-off cost?	No – for discussion	Status as key driver is contingent on cure point being set to 3 years 

NICE

Abbreviations: ICER, incremental cost-effectiveness ratio; Pola-BR, polatuzumab vedotin in combination with bendamustine and rituximab; R-gem-ox, Rituximab, gemcitabine, and oxaliplatin

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

Supplementary appendix

NICE National Institute for Health and Care Excellence

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

Unbalanced covariates noted in red

* 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

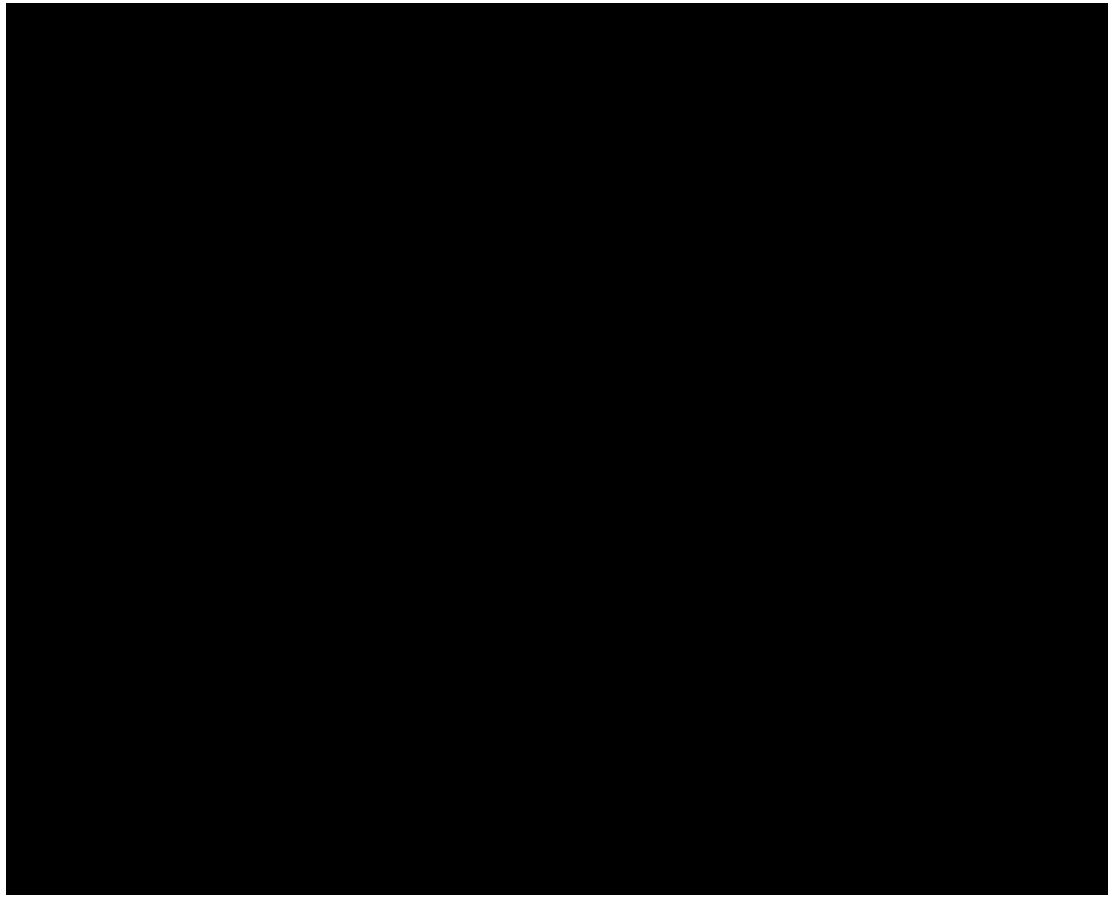
- Main analysis: Did not adjust for cell type of origin and bone marrow involvement but missing values for all other covariates set equal to mean or mode of each covariate
- IPTW: Used to balance covariates
- IPTW with multiple imputation: Used to estimate values for cell type of origin, bone marrow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

Key Issue: Cure assumptions

Modelled overall survival and progression free survival in company base case (A) Glofit-GemOx, (B) R-GemOx



* See link

Abbreviations: OS, overall survival; Glofit-GemOx, glofitamab with gemcitabine and oxaliplatin; R-GemOx, rituximab with gemcitabine and oxaliplatin

Key Issue: Cure assumptions

Overall survival estimates for (A) Glofit-GemOx and (B) R-GemOx, company base case

[redacted]

Overall survival estimates for (A) Glofit-GemOx and (B) pola-BR, company scenario

[redacted]

* See link

Abbreviations: OS, overall survival; Glofit-GemOx, glofitamab with gemcitabine and oxaliplatin; R-GemOx, rituximab with gemcitabine and oxaliplatin

Key issue: Treatment costs at subsequent lines of therapy

Proportion in company base having each subsequent therapy after 2nd line therapy

Subsequent therapy	% on Glofit-GemOx	Mean duration in weeks	% on R-GemOx	Mean duration in weeks
BR	5.0	0.4	1.0	4.3
Average R-chemo	10.0	2.6	4.5	2.1
Other chemo regimens (non-R)	5.0	3.2	1.0	2.1
Pola-BR	5.0	10.6	5.0	2.2
Clinical trial/other	15.0	6.1	2.5	6.1
Radiotherapy	4.0	1.0	5.0	1
Allogenic SCT	1.0	1.0	1.0	1*
Axicabtagene ciloleucel	30.0	1.0	30.0	1*
Loncastuximab tesirine	25.0	4.8	5	40.9
Glofitamab	0	0	25	14.6
Epcoritamab	0	0	20	3.6

* See link

Abbreviations: SCT, stem cell transplant;

Other issue: End of life care costs - link

Weekly resource costs applied in company model

Unit	Unit cost	Resource use on treatment	Resource use off treatment	Resource use of progression state
Professional and social services				
Residential care (day)	£190.00	0.75	0.19	0.00
Day care (day)	£78.00	0.28	0.07	0.47
Home care (day)	£35.71	1.17	0.43	2.34
Hospice (day)	£198.10	0.01	0.00	0.23
Health care professionals and hospital resource use				
Oncologist (visit)	£204.00	0.33	0.11	0.08
Haematologist (visit)	£193.00	0.20	0.05	0.25
Radiologist (visit)	£157.00	0.08	0.08	0.00
Nurse (visit)	£57.00	0.38	0.10	0.00
Specialist nurse (visit)	£57.00	0.58	0.19	0.63
GP (visit)	£49.00	0.10	0.13	0.83
District nurse (visit)	£57.00	0.38	0.10	1.00
CT scan	£184.00	0.08	0.08	0.00
Inpatient day	£319.00	0.10	0.04	0.05
Palliative care team	£194.00	0.00	0.00	0.33
Treatment follow-up				
Full blood counts	£7.00	0.83	0.83	0.25
LDH	£7.00	0.50	0.50	0.08
Liver function	£7.00	0.83	0.83	0.25
Renal function	£7.00	0.83	0.83	0.08
Immunoglobulin	£7.00	0.17	0.17	0.08
Calcium phosphate	£7.00	0.17	0.17	0.25

Other issue: End of life care costs

One-off end of life costs applied rather than weekly healthcare resource use costs

Cost	Patients with a cancer diagnosis
GP visits	£453
District nurse	£729
Nursing and residential care	£567
Hospital care – inpatient	£682
Hospital care – final 3 months of life	£7,301
Marie Curie nursing service	£672
Total	£10,403

link

NICE

Abbreviations: PFS, progression free survival; PPS, post progression survival;