NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Polatuzumab vedotin with rituximab and bendamustine for treating relapsed or refractory diffuse large B cell lymphoma [ID1576]

Committee Papers

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

Polatuzumab vedotin with rituximab and bendamustine for treating relapsed or refractory diffuse large B cell lymphoma [ID1576]

Contents:
The following documents are made available to consultees and commentators:

The **final scope and final stakeholder list** are available on the NICE website.

1. **Company submission** from Roche

2. **Clarification questions and company responses**
   a. Main response
   b. Economic appendix

3. **Patient group, professional group and NHS organisation submission** from:
   a. Lymphoma Action
   b. Royal College of Physicians (NCRI-ACP-RCP-RCR)

4. **Expert personal perspectives** from:
   a. Dr Sridhar Chaganti, Consultant Haematologist – clinical expert, nominated by NCRI-ACP-RCP
   b. Dr Kate Cwynarski, Consultant Haematologist – clinical expert, nominated by NCRI-ACP-RCP
   c. Mr Stephen Scowcroft, Director of Operations & External Affairs – patient expert, nominated by Lymphoma Action

5. **Evidence Review Group report** prepared by Kleijnen Systematic Reviews

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7. **Technical report for engagement**

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

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

ID1576: Polatuzumab vedotin with rituximab and bendamustine for treating relapsed or refractory diffuse large B-cell lymphoma

Document B

Company evidence submission

July 2019

File name	Version	Contains confidential information	Date
ID1576_polatuzumab vedotin RR DLBCL_ACIC_Document B	1	Yes	26 July 2019

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This submission must not be longer than 150 pages, excluding appendices and the pages covered by this template. If it is too long it will not be accepted.

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Abbreviations

ADA	Anti-drug antibodies
AE	Adverse event
AIC	Akaike Information Criterion
ALT	Alanine aminotransferase
ANC	Absolute neutrophil count
ASCO	American Society of Clinical Oncology
ASCT	Autologous stem cell transplant
ASH	American Society of Hematology
AST	Aspartate aminotransferase
AUC	Area under the curve
BEAC	Carmustine, etoposide, cytarabine and cyclophosphamide
BEAM	Carmustine, etoposide, cytarabine and melphalan
BIC	Bayesian Information Criterion
BNF	British National Formulary
BOR	Best overall response
BR	Bendamustine with rituximab
BS	Biosimilar
BSA	Body surface area
BSH	British Society of Haematology
CAR-T	Chimeric antigen receptor-T cell
CCOD	Clinical cut-off date
CDF	Cancer Drugs Fund
CEAC	Cost-effectiveness acceptability curve
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence interval
CMH	Cochran Mantel-Haenszel
CMM	Cure-mixture model
CNS	Central nervous system
CR	Complete response
CSR	Clinical study report
CTCAE	Common Terminology Criteria for Adverse Events
DLBLC	Diffuse large B-cell lymphoma
DOR	Duration of response
DSA	Deterministic sensitivity analysis
DSU	Decision support unit

EAMS	Early access to medicine scheme
ECG	Electrocardiogram
ECOG PS	Eastern Co-operative Oncology Group performance status
EFS	Event-free survival
EHA	European Haematology Association
EMA	European Medicines Agency
EPAR	European Public Assessment Report
ERG	Evidence Review Group
ESMO	European Society for Medical Oncology
FDA	Food and Drug Administration
FDG-PET	18F-fluorodeoxyglucose-positron emission tomography
FFS	Failure-free survival
FL	Follicular lymphoma
GCP	Good clinical practice
HMRN	Haematological Malignancy Research Network
HR	Hazard ratio
HRG	Healthcare resource group
ICER	Incremental cost-effectiveness ratio
INV	Investigator
IPI	International Prognostic Index
IRC	Independent Review Committee
ITT	Intention-to-treat
LACE	Lomustine, cytarabine, cyclophosphamide, etoposide
LDH	Lactate dehydrogenase
LEAM	Lomustine, etoposide, cytarabine, melphalan
LYG	Life-years gained
MHRA	Medicines and Healthcare Products Regulatory Agency
MMAE	Monomethyl auristatin E
MRI	Magnetic resonance imaging
NALT	New anti-lymphoma treatment
NCCN	National Comprehensive Cancer Network
NF	New formulation
NHL	Non-Hodgkin lymphoma
OR	Overall response
ORR	Objective response rate
OS	Overall survival
PD	Progressive disease

PET-CT	Positron emission tomography – computed topography
PFS	Progression-free survival
PIM	Promising innovative medicine
PN	Peripheral neuropathy
PR	Partial response
PRO	Patient-reported outcomes
PSA	Probabilistic sensitivity analysis
PSSRU	Personal Social Services Research Unit
PTT	Partial thromboplastin time
QALY	Quality-adjusted life year
R-CHOP	Rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone
R-DECC	Rituximab, dexamethasone, etoposide, chlorambucil, lomustine
R-DHAP	Rituximab, dexamethasone, cytarabine, cisplatin
R-ESHAP	Rituximab, etoposide, methylprednisolone, cytarabine, cisplatin
R-GDP	Rituximab, gemcitabine, dexamethasone, cisplatin
R-GemOx	Rituximab, gemcitabine, oxaliplatin
R-ICE	Rituximab, ifosfamide, etoposide, carboplatin
R-P-MitCEBO	Rituximab, prednisolone, mitoxantrone, cyclophosphamide, etoposide bleomycin, vincristine
RCT	Randomised clinical trial
R/R	Relapsed/refractory
SCT	Stem cell transplant
SD	Standard deviation
SE	Standard error
SLR	Systematic literature review
SOC	Standard of care
TINAS	Therapy-Induced Neuropathy Assessment Scale
TLS	tumour lysis syndrome
TTOT	Time-to-off-treatment
TTP	Time-to-progression
ULN	Upper limit of normal
WTP	Willingness to pay

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

B.1.1 Decision problem

The submission covers the technology's full marketing authorisation for this indication.

Table 1: The decision problem

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
Population	Adults with relapsed or refractory diffuse large B-cell lymphoma for whom hematopoietic stem cell transplant is not suitable.	As per final scope issued by NICE	N/A
Intervention	Polatuzumab vedotin (with rituximab and bendamustine)	As per final scope issued by NICE	N/A
Comparator(s)	Rituximab in combination with one or more chemotherapy agents such as: • R-GemOx (rituximab, gemcitabine, oxaliplatin), • R-Gem (rituximab gemcitabine), • R-P-MitCEBO (rituximab, prednisolone, mitoxantrone, cyclophosphamide, etoposide bleomycin, vincristine), • (R-)DECC (rituximab, dexamethasone, etoposide, chlorambucil, lomustine), • BR (bendamustine, rituximab).	Rituximab in combination with one or more chemotherapy agents such as: • BR (bendamustine, rituximab). • R-GemOx (rituximab, gemcitabine, oxaliplatin).	There is no clear standard of care regimen for the population. BR was the comparator in the randomised phase II study GO29365. It was not feasible to conduct a robust treatment comparison with other comparator regimens in the scope because of the limited evidence available (section B.2.9). Clinical opinion and the limited data available suggest that there is no significant difference in outcomes between the comparator regimens. A scenario with an assumption of equal efficacy of BR and R-GemOx was implemented in the economic model (section B.3.2.3).
Outcomes	The outcome measures to be considered include: • overall survival • progression-free survival • response rates • adverse effects of treatment • health-related quality of life	As per final scope issued by NICE	N/A

B.1.2 Description of the technology being appraised

The technology being appraised is described in Table 2. See Appendix C for details of the draft summary of product characteristics (SmPC) and European Public Assessment Report (EPAR).

Table 2: Description of the technology

UK approved name and brand name	Polatuzumab vedotin (Polivy™)
Mechanism of action	Polatuzumab vedotin (Pola) is an antibody-drug conjugate composed of a CD79b-directed monoclonal antibody (recombinant humanised immunoglobulin G1 [IgG1]), that is covalently linked to the antimicrotubule agent monomethyl auristatin E (MMAE). Pola binds to cell surface antigen CD79b, a component of the B-cell receptor, which is expressed only on B-cells and in most B-cell non-Hodgkin lymphomas (1-3). Binding of pola to CD79b triggers internalisation of the pola molecule (Figure 8). The stable valine-citrulline (VC) linker within pola is cleaved, releasing MMAE (2). MMAE binds to microtubules and exerts cytotoxicity by inhibiting polymerisation, disrupting cell division, and triggering apoptosis (4-6). See section B.2.12 for more information on the mechanism of action of pola.
Marketing authorisation/CE mark status	An application for marketing authorisation was made for pola in combination with bendamustine and rituximab on December 21 2018. Committee for Medicinal Products for Human Use (CHMP) opinion is anticipated in [redacted], with regulatory approval expected in [redacted].
Indications and any restriction(s) as described in the summary of product characteristics (SmPC)	The anticipated indication is as follows: • Polivy in combination with bendamustine and rituximab is indicated for the treatment of adult patients with relapsed/refractory diffuse large B-cell lymphoma (DLBCL) who are not candidates for haematopoietic stem cell transplant (7) As noted in the draft summary of product characteristics (SmPC), pola will only be contraindicated in people who demonstrate hypersensitivity to the medicinal product or any of its excipients.
Method of administration and dosage	Polatuzumab vedotin in combination with bendamustine and rituximab every 3 weeks for 6 cycles: ***Polatuzumab vedotin*** • 1.8 mg/kg intravenous infusion (IV) on day 1 • The initial dose should be administered as a 90-minute infusion

	• If well tolerated, subsequent doses may be administered as a 30-minute infusion ***Bendamustine*** • 90 mg/m^2 IV on days 1 and 2 ***Rituximab*** • 375 mg/m^2 IV on day 1
Additional tests or investigations	No additional test or investigations are required.
List price and average cost of a course of treatment	[redacted] per 140mg vial. [redacted] average treatment costs
Patient access scheme (if applicable)	A patient access scheme is not in place.

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

B.1.3.1 Disease overview

Non-Hodgkin lymphoma (NHL) is a heterogeneous group of lymphoproliferative malignancies, with 80–95% of cases arising from B-clls and the remaining from T-cells. NHL is divided between high and low grade NHL subtypes (8). Diffuse large B-cell lymphoma (DLBCL), a high grade B-cell NHL, represents approximately 40% of all lymphoma cases globally and 30–58% of NHL cases (9, 10).

DLBCL is itself heterogeneous and composed of large neoplastic B lymphoid cells that generally express pan B-cell antigens (CD19, CD20, CD22, CD79a) (11). The majority have genetic abnormalities, but there is no single cytogenetic change that is typical or diagnostic.

The clinical heterogeneity of DLBCL has also been recognised at a molecular level by assigning DLBCL into two cell-of-origin categories based on gene expression patterns indicative of different stages of B cell development. One subgroup expresses genes reminiscent of germinal centre B cells (GCB-like DLBCL), the second group expresses genes normally induced during the activation of peripheral blood cells (ABC-like DLBCL). Patients with GCB-like DLBCL have a significantly better prognosis than those with ABC-like DLBCL (12).

Incidence, prevalence and survival statistics

The Haematological Malignancy Research Network (HMRN) estimates that there will be 5,510 new cases of DLBCL each year in the UK, which accounts for approximately 40% of all UK NHL cases (13, 14). The median age at diagnosis of DLBCL in the UK is approximately 70 years (15) and there is a slightly higher incidence among males compared with females.

The 10-year prevalence is estimated at 28,291 cases (43.4 patients per 100,000 people), again with more male patients affected (16).

Approximately 591 patients per annum are estimated to be treated for relapsed or refractory (R/R) DLBCL not suitable for hematopoietic stem cell transplant[1].

Prognosis for first-line DLBCL patients

DLBCL is an aggressive, high grade lymphoma with a life expectancy of weeks to months if not treated (18). The prognosis is varied among DLBCL patients; overall response rates to standard chemoimmunotherapy are high, ranging from 88–91% (19), but 5-year overall survival varies significantly according to the Revised International Prognostic Index (R-IPI) score (51–96%) and NCCN-IPI score (33%-96%) (20, 21). Overall, the five-year survival rate following first-line treatment in the UK is approximately 61% (22).

Prognosis for relapsed/refractory (R/R) DLBCL patients

The prognosis is poor for patients with R/R DLBCL, with a median survival of 10 months. Fewer than half of relapsed patients (41%) survive for 12 months. Age is an important prognostic indicator in DLBCL patients who relapse; patients aged ≥65 years have a poorer prognosis compared to those aged <65 years (23).

Outcomes are even worse for patients who are refractory to first-line therapy. The SCHOLAR-1 study, the largest pooled retrospective analysis of patients with refractory DLBCL, showed that median overall survival was just 6.3 months for these patients, with 22% of patients alive at 2 years (24).

Impact on patients

Patients with DLBCL typically present with a rapidly enlarging symptomatic mass, most commonly a nodal enlargement in the neck or abdomen, or, in the case of primary mediastinal large B cell lymphoma, the mediastinum. Systemic "B" symptoms (i.e., fever, weight loss, drenching night sweats) are observed in approximately 30% of patients, with elevated serum lactate dehydrogenase, a well known poor prognostic factor for NHL, in over 50% of patients. Approximately 60% of patients present with advanced stage DLBCL (stage III or IV disease) while 40% have localised disease, usually defined as that which can be contained within one irradiation field (25).

[1] This figure is based on the Office of National Statistics reported incidence of 6391 newly diagnosed patients with DLBCL 17. Office for National Statistics. Cancer Registration Statistics 2017. 2018..

There are limited data on the impact of DLBCL on patients' quality of life (QoL), however patients with high grade NHL demonstrate a lower QoL compared to patients with low grade NHL, including physical, social/family, and emotional factors, functional well-being, as well as higher anxiety (26). This is partly related to uncertainties towards the prognosis of their disease, side effects of treatment and fear of relapse (27), especially given the disappointing efficacy of standard salvage regimens prior to transplant (28). Patients who achieve a complete response (CR) after first-line treatment have demonstrated significant improvements in QoL compared to non-complete responders (29). Patients who are refractory to or relapse following first-line treatment experience even greater anxiety due to the poorer prognosis of their condition and the need for further, often more intensive treatment. This will also increase the demand on hospital services and the use of skilled nursing facilities and hospice services (30). Therefore, there remains an unmet need for additional treatments for R/R DLBCL patients that offer better outcomes over existing treatments, can reduce psychological distress and improve QoL (31).

B.1.3.2 Current treatment practice

Terminology

Salvage therapy: a treatment for cancer that has not responded to other treatments. Note, the use of this term is not consistent within the R/R DLBCL setting – UK clinical experts advised Roche that the term 'salvage' is reserved for more intensive therapy aimed at delivering a patient to a potentially curative transplant.

Conditioning regimen: transplant eligible patients who respond to salvage chemotherapy undergo conditioning treatment to consolidate their response. Conditioning regimens include chemotherapy +/- monoclonal antibody therapy or radiotherapy.

Autologous stem cell transplant (ASCT): a procedure in which blood-forming stem cells are removed, stored and later given back to the same patient.

Allogenic stem cell transplant: a procedure in which a patient receives blood-forming stem cells from a genetically similar, but not identical, donor.

A number of treatment guidelines are available for DLBCL including the NICE clinical pathway (NG52) (32), the British Society for Haematology (BSH) (33), ESMO (9) and National Comprehensive Cancer Network (NCCN) (34); however, advice obtained from UK clinical experts at an advisory board meeting[2] confirmed that there is no universal guideline

[2] In October 2018, Roche Products Ltd. held an advisory board meeting with nine clinical experts from across the UK to discuss current treatment practice in the management of R/R DLBCL and to gain feedback on approaches to the cost-effectiveness analysis for this submission.

followed for the treatment of R/R DLBCL. The advisors confirmed that current clinical practice for this population is likely to vary across the country, depending on the expertise of the treatment centre and will also likely be informed by individual clinician and patient choice (35).

First-line DLBCL treatment

The R-CHOP regimen (rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone) has been the gold standard in the management of DLBCL for over 15 years (36). However, approximately 30–50% of patients are not cured by this treatment, depending on disease stage or prognostic index. Among patients for whom R-CHOP therapy fails, 20% suffer from primary refractory disease (disease does not enter complete remission and/or progresses during or soon after treatment) whereas 30% relapse after achieving complete remission (37).

Relapsed/refractory disease

Relapsed/refractory patients have a poor outcome and most will die from their disease (38). Relapses commonly occur within the first two years, however late relapses are possible for approximately 10% of patients (39) and may be associated with an initial favourable International Prognostic Index (IPI) score and extranodal involvement at diagnosis (40).

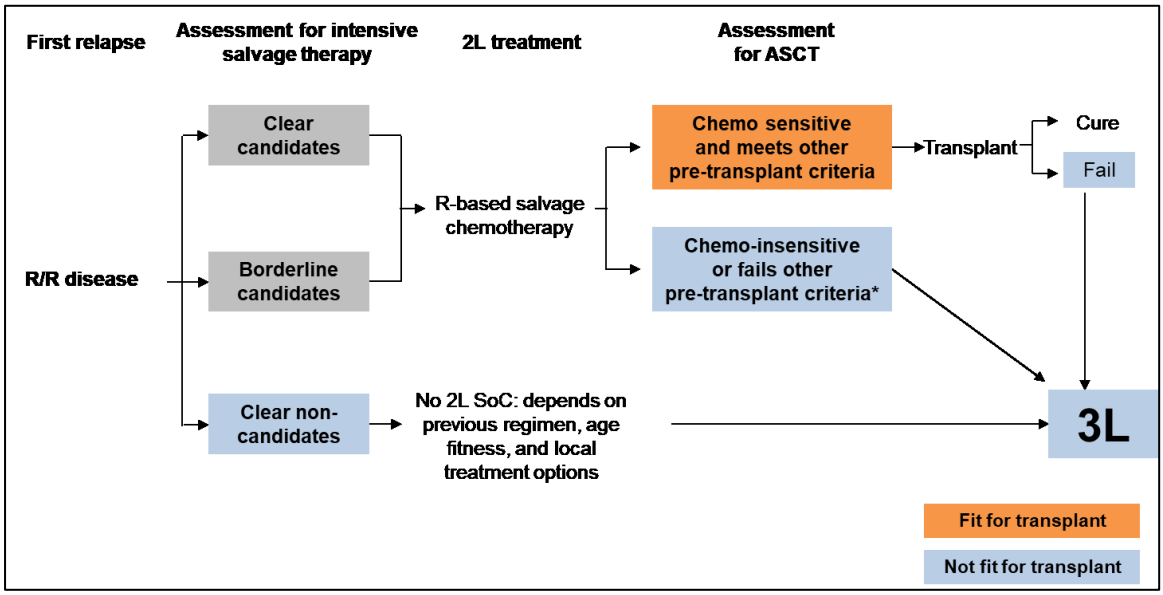
Refractory disease is defined as a <50% decrease in lesion size with initial therapy, or the occurrence of new lesions. Patients with progressive or relapsed disease present with new or enlarging lesions after the attainment of complete remission. Therefore, there are three groups of patients who fail first-line therapy:

1. Relapse after complete remission (relapse >3 months after CR)
2. Partial responders with persistent but not progressive disease
3. Refractory to first-line treatment (patients with stable disease or progressive disease, i.e. failure to achieve CR or relapse ≤3 months after CR) (41)

Prognosis varies among these groups, with refractory patients generally having a worse outlook, as demonstrated in SCHOLAR-1. This international multi-cohort retrospective study of pooled data from two Phase III clinical trials demonstrated a median OS of 6.3 months and response rate of 26% (CR 7%) to the next line of therapy among patients with refractory DLBCL (24).

The initial approach to R/R DLBCL is to assess whether the patient is fit for intensive salvage therapy and potentially autologous stem cell transplant (ASCT). The decision flow presented below was compiled following advice obtained from UK clinical experts and reflects how patients are identified as being eligible for transplant in UK clinical practice (35).

Figure 1: Decision flow for transplant eligibility among R/R DLBCL patients



*per institutional guidelines, considering salvage treatment tolerance, performance status, adequacy of organ function, satisfactory stem cell collection, patient choice, etc.
2L, second-line; 3L, third-line; ASCT, autologous stem cell transplant; R, rituximab; R/R, relapsed or refractory; SoC, standard of care

Treatment of clear or borderline candidates for transplant

In the PARMA trial, salvage chemotherapy followed by ASCT resulted in significantly superior event-free survival and OS in patients with relapsed DLBCL compared with salvage chemotherapy alone, which led to salvage chemotherapy plus ASCT being adopted as the SOC for R/R patients (42). However, ASCT is typically only available for younger, fit patients, although age alone should not be an absolute contraindication to ASCT (43). Eligibility for ASCT should also take into account other factors such as comorbidities e.g. severe pulmonary compromise or left ventricular dysfunction (44, 45). In UK clinical practice, there is no universal guidance on how to assess whether a patient is a suitable candidate for intensive therapy. This is typically an individualised decision, taking into account age (<70–75 years), if the patient has chemo-sensitive disease, if stem cells can be harvested, and if the patient has sufficient organ fitness to receive such treatment (35).

For patients who are eligible for ASCT, the first approach is to administer a rituximab-based salvage chemotherapy regimen to minimise disease burden and demonstrate chemo-sensitivity, followed by consolidation with a high-dose regimen. Response to, and tolerance of, salvage chemotherapy may also confirm eligibility of borderline candidates to receive ASCT since demonstration of response to such treatment is a highly predictive factor of outcome following ASCT.

There are many salvage therapies available, mostly involving rituximab in combination with standard antineoplastic agents (43), as highlighted in the ESMO guidelines for treating R/R

DLBCL (although UK clinical experts confirmed that these are not routinely followed in UK clinical practice) (Table 3) (9). For patients fit enough to tolerate high-intensity salvage therapy, NICE guidance recommends offering salvage therapy with multi-agent immunochemotherapy, with R-GDP (rituximab with gemcitabine, dexamethasone and cisplatin) specifically mentioned due to its more tolerable toxicity profile compared to other salvage regimens (32).

Table 3: ESMO guidelines for patients with first and second relapse or progression

Eligible for Transplant	Ineligible for Transplant
First relapse or progression	
• Platinum-based chemotherapy regimens (i.e., R-DHAP, R-ICE, R-GDP) as salvage therapy • For chemo-sensitive patients R-high dose chemotherapy with ASCT as remission consolidation • Consider allogeneic transplantation in patients relapsed after intensive salvage chemotherapy with ASCT or in patients with poor-risk factors at relapse	• Platinum*- and/or gemcitabine-based regimens • Clinical trials with novel drugs
>2 relapse or progression	
• Allogeneic transplantation • CAR-T cells	• Clinical studies with novel drugs • Palliative care

*Following advice from UK clinical experts, oxaplatin is the preferred platinum regimen for transplant-ineligible patients in UK clinical practice (35)

There remains no clear evidence regarding the superiority of one salvage regimen over another in randomised studies (Table 4). For instance, the Phase III Collaborative Trial in Relapsed Aggressive Lymphoma (CORAL) study, which compared the efficacy of R-ICE (rituximab with ifosfamide, carboplatin, etoposide) or R-DHAP (rituximab with cisplatin, cytarabine and dexamethasone) followed by ASCT with or without rituximab maintenance, demonstrated no difference in 2-year OS between salvage regimens, with only 50% of patients being able to proceed to ASCT (36).

Table 4: Salvage chemotherapy regimens in randomised studies for DLBCL

Study	Salvage regimen	n	RR, %	Transplant rate, %	PFS, %
CORAL (28)	R-ICE	202	64	51	3-year: 31
	R-DHAP	194	63	55	3-year: 42
LY-12 (46)	R-DHAP	304	45	49	3-year: 28
	R-GDP	306	44	52	3-year: 28
ORCHARRD (47)	R-DHAP	223	42	37	2-year: 26
	O-DHAP	222	38	33	2-year: 24

R-GDP, rituximab-gemcitabine, dexamethasone, cisplatin; DLBCL, diffuse large B cell lymphoma; O-DHAP, Ofatumumab- dexamethasone, cytarabine, cisplatin; PFS, progression-free survival; R-DHAP, rituximab-dexamethasone, cytarabine, cisplatin; R-ICE, rituximab-ifosfamide, etoposide, carboplatin; RR, relative risk

Clinical experts confirmed to Roche that there is no standard of care in UK clinical practice for patients who are considered fit for intensive salvage therapy (estimated to be 50–60% of all R/R DLBCL patients). Patients in the UK are typically treated with platinum-based

regimens, irrespective of whether they are clear or borderline candidates for ASCT, such as R-GDP, R-DHAP, R-ICE and R-ESHAP (rituximab with etoposide, methylprednisolone, cytarabine and cisplatin) (35). Clinical experts also reported that R-Gem-Ox (rituximab with gemcitabine and oxaliplatin), an option considered by NHS England for older patients, is not widely used in UK clinical practice although familiarity with the regimen may increase among treatment centres that are enrolling patients to the ARGO study (35, 48).

Intensive salvage chemotherapy is followed by a conditioning regimen, typically carmustine, etoposide, cytarabine and melphalan (BEAM) or lomustine, etoposide, cytarabine and melphalan (LEAM), although alternative, less toxic regimens e.g. carmustine, etoposide, cytarabine and cyclophosphamide (BEAC) and lomustine, cytarabine, cyclophosphamide and etoposide (LACE) may be used for older patients (>70 years of age) (9, 35, 43).

Salvage chemotherapy is an area of high unmet need given the poor rate and duration of response; only 30–40% will respond and proceed to ASCT (28, 46, 47). Furthermore, the outcome for patients who do not respond to salvage regimens is very poor, with a median OS for non-responding patients of only 4 months (49).

Treatment options for patients who fail salvage chemotherapy are limited to clinical trials of novel agents, if available, or an additional line of salvage chemotherapy for younger patients who are willing to receive another treatment (35). Novel therapies for R/R DLBCL are in development, including chimeric antigen receptor T-cell (CAR-T) therapies, which have demonstrated activity in DLBCL in single arm studies (50, 51). However, CAR-T therapies are only available to those patients who have had two or more prior lines of systemic therapy, have sufficient disease control to await the manufacturing times, and can tolerate the conditioning regimen (usually fludarabine/cyclophosphamide), treatment emergent cytokine-release syndrome and sometimes severe neurotoxicities (52)

For patients who do respond to salvage chemotherapy, ASCT offers a second chance of cure. However, the overall benefit of ASCT as an option is limited by the fact that a substantial proportion of patients will be deemed ineligible or will relapse after ASCT. The CORAL study, conducted in the pre-PET era, demonstrated a 3-year event free survival of just 21% for patients in the prior rituximab-treated group (28). A more recent study evaluating the prognostic value of PET prior to ASCT demonstrated improved long term outcomes for patients achieving a complete metabolic response to salvage therapy by contemporary Deauville scoring (DS) (3-year PFS 77% for DS 1-3 vs 49% for DS 4) (53). Nevertheless, the prognosis of those patients who relapse after ASCT is poor (median survival of approximately 8 months among patients who relapse within 12 months of transplant (54)) with very little consensus on the optimal subsequent therapy. Although

allogenic stem-cell transplant is an option for some patients (33), it is rarely used in UK clinical practice and is associated with treatment-related mortality and limited disease control (55-57).

Treatment of transplant-ineligible patients

A substantial proportion of patients are not eligible for intensive therapy followed by ASCT due to age, comorbidities or chemotherapy-insensitive disease – UK clinical experts estimate this to be 40–50% of all R/R DLBCL patients (35). The treatment approach is palliative for such patients in the second or subsequent line setting, although there is still a goal of improving survival, albeit not necessarily with curative intent.

There are no universally established therapies for patients with R/R DLBCL who are ineligible for transplant or who relapse after transplant. There is a considerable amount of variability on the selected regimen for these patients with bendamustine with rituximab and gemcitabine and/or platinum-based therapies (such as oxaliplatin) among the most commonly used regimens. However, outcomes of such transplant-ineligible patients (including patients who relapse after ASCT) remain poor, with median OS of approximately 6 months (24, 58) (Table 5). Furthermore, there is no evidence of one chemotherapy regimen demonstrating superiority over another. The combination of bendamustine with rituximab (BR) has been shown to be active in transplant-ineligible patients with R/R DLBCL with a manageable haematological toxicity profile; median PFS has been reported to be 3.5–6.7 months and median OS reported to be 6.7–9.5 months (59-62). It should be noted however that direct comparison with prior studies investigating chemotherapy-based regimens has several severe limitations; namely different inclusion/exclusion criteria (i.e., limitations on prior lines of therapy, refractoriness) as well as historical context (e.g., how many patients had prior exposure to rituximab, differences in assessing response or what the first-line therapy was), leading to potentially significant differences in prognostic factors between different trial cohorts.

Table 5: Selected regimens for transplant-ineligible R/R DLBCL patients

Regimen	Pts with recurrent NHL	ORR		PFS and OS	Toxicity
		CR (%)	PR (%)		
Rituximab-containing regimens					
Gemcitabine + oxaliplatin + rituximab (63)	16	56	19	Median FFS, 18.5 months	Neutropenia Grade 3/4, 29%/18% Thrombocytopenia Grade 3, 17% Vomiting Grade 2–3, 34% Infection Grade 2–3, 25%
Rituximab + gemcitabine + oxaliplatin (58)	49	44	17	Median PFS, 5 months	Neutropenia Grade 3/4 31%/42% Thrombocytopenia Grade 3/4 32%/21% Grade 3–4 infection, 22% of cycles

				5-year PFS, 12%	
Bendamustine + rituximab (61)	59	37	25	Median PFS, 6.7 months	Neutropenia Grade 3/4 30%/46% Thrombocytopenia Grade 3/4 15%/7% CD 4 lymphopenia Grade 3/4 22%/44% Infection Grade 3, 12%
Bendamustine + rituximab (62)	61	15[h]	31[h]	Median PFS, 3.6 months Median OS NR	Neutropenia Grade 3/4, 29%/7% Thrombocytopenia Grade 3/4, 17%/5% Anaemia Grade 3 12% Febrile neutropenia, 7%
Bendamustine + rituximab (59)	137	21	28	Median PFS, 3.5 months Median OS, 9.5 months	Neutropenia Grade ≥ 3 40% Thrombocytopenia Grade ≥3 16% Lymphopenia Grade ≥ 3 22%
Bendamustine + rituximab (60)	58	31	23	Median PFS, 3.9 months Median OS 6.7 months	Neutropenia Grade 3-4 69%; Anaemia 33% Thrombocytopenia 59% Febrile neutropenia 19%
Rituximab-free regimens					
Gemcitabine, dexamethasone + cisplatin (64)	17	23	29	Median PFS, 3 months Median OS, 9 months	Neutropenia Grade 3/4: 33%/31% Thrombocytopenia Grade 3/4: 26%/4% Grade 2 ototoxicity: 25% Grade 2 creatinine 6%
Gemcitabine + oxaliplatin (63)	17	47	12	Median FFS, 9 months	Neutropenia Grade 3/4, 35%/16% Thrombocytopenia Grade 3–4, 26% Vomiting Grade 2–3, 34% Infection Grade 2–3, 14%
Gemcitabine + vinorelbine (65)	22	14	35	Median TTP, 8 months Median OS, 13 months	Neutropenia Grade 3–4, 41% Thrombocytopenia Grade 3–4, 18%

CD4, cluster of differentiation 4; CR, complete response; FFS, failure-free survival; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; PR, partial response; TTP, time-to-progression

Treatments beyond second-line are further limited and include gemcitabine, bendamustine and palliative oral combinations (66). Pixantrone monotherapy is recommended by NICE as a third- or fourth-line treatment option for adult patients with R/R DLBCL (TA306) (67). However, UK clinical experts confirmed that pixantrone is not widely used in the UK compared with the rest of Europe (an observation corroborated by the exclusion of pixantrone as a treatment option for patients with R/R DLBCL in the BSH guidelines (33)), with real-world data reporting disappointing efficacy (median OS 3.4 months) (66). Furthermore, a Phase III trial (PIX306) investigating the efficacy or R+pixantrone compared with R-gemcitabine failed to demonstrate superiority in terms of progression free survival (PFS) in patients with R/R DLBCL (68).

(50, 51)The novel CAR-T cell therapies represent an additional treatment option for R/R DLBCL patients (52)who have had two or more prior lines of systemic therapy. However, in

practice many patients with progressive DLBCL have a rapid clinical disease course rendering them unsuitable for CAR-T therapy. Importantly also, due to the complex manufacturing and distribution and the need for intense monitoring, this treatment modality is currently limited to specialised tertiary centres and not available to the broad population. Emerging real world evidence will continue to inform the safety and efficacy profile of these new treatment options.

NICE currently recommends two CAR-T therapies. Axicabtagene ciloleucel is recommended for use in the Cancer Drugs Fund (CDF) as an option for adult patients with R/R DLBCL or primary mediastinal large B-cell lymphoma who have previously received two or more systemic therapies (TA559) (69), although this will only be initially available for 200 patients per year in eight specialised centres that are able to administer it. Tisagenlecleucel is also recommended for use in the CDF as an option for treating R/R DLBCL in adults after 2 or more systemic therapies (TA567) (70).

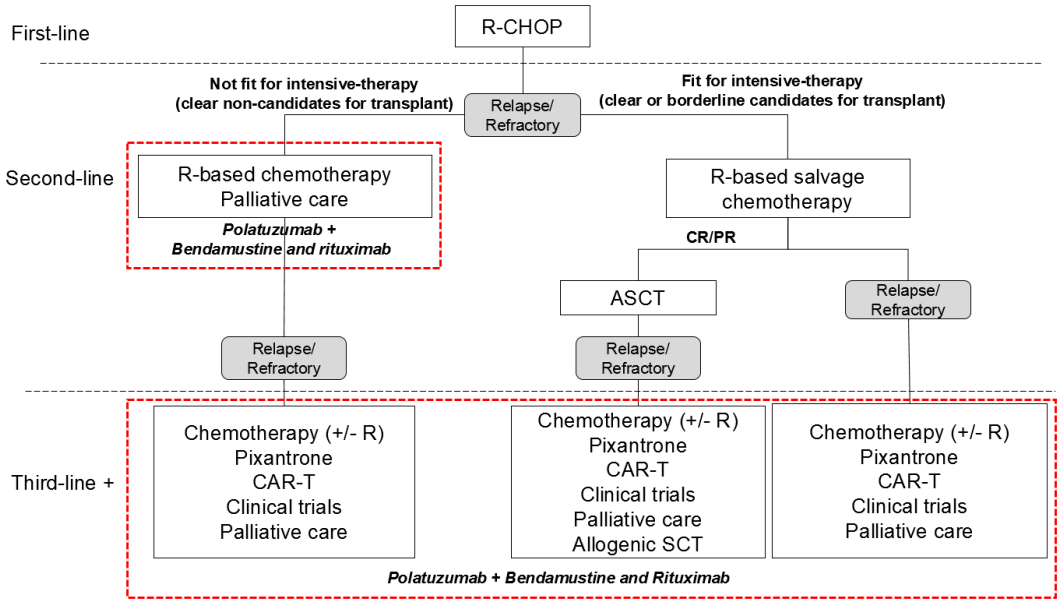
Overall, the outcome for this large group of R/R DLBCL patients who are ineligible for ASCT is poor; patients tend to be older therefore conventional salvage regimens offer little benefit in disease control and have substantial morbidity (71). There are no established therapies for patients with R/R DLBCL who are ineligible for transplant or who relapse after transplant, therefore there is a significant need for new and more effective treatments that extend survival with at least acceptable, if not superior, safety and tolerability profiles for these patients.

B.1.3.3 Proposed position of polatuzumab vedotin in the treatment pathway

The proposed treatment pathway and position of pola in combination with bendamustine and rituximab (pola+BR) is summarised below in Figure 2. In summary, the following patients will be considered eligible for pola+BR:

- R/R patients who are clear non-candidates for transplant (unfit for intensive therapy based on physician assessment), either as second-line treatment or as a third-line treatment and beyond for patients who have relapsed following or are refractory to their last-line of therapy
- R/R patients who would be candidates for transplant but fail to respond to salvage therapy (and are therefore transplant ineligible)
- R/R patients who receive salvage therapy and ASCT but subsequently relapse

Figure 2: Proposed positioning of pola+BR in DLBCL treatment pathway



Evidence for the efficacy of pola+BR in UK clinical practice is sourced from the GO29365 study, in which patients with R/R DLBCL were enrolled (NCT02257567) (72). Patients enrolled must have either relapsed or have been refractory to a prior regimen for DLBCL and were ineligible for stem cell transplant (as assessed by the physician). Sixteen patients with R/R DLBCL enrolled in GO29365 were refractory to or relapsed after prior transplant.

B.1.4 Equality considerations

No equality issues related to the use of pola+BR have been identified.

B.2 Clinical effectiveness

B.2.1 Identification and selection of relevant studies

See appendix D for full details of the process and methods used to identify and select the clinical evidence relevant to the technology being appraised.

B.2.2 List of relevant clinical effectiveness evidence

Table 6: Clinical effectiveness evidence

Study	GO29365 (NCT02257567) (72) **Study publications:** • Phase Ib/II preliminary results (CCOD 15 Aug 2016), ASH 2016 (73) • Phase Ib/II updated results (CCOD 28 Feb 2017), EHA 2017 (74) • Phase II results (CCOD 03 May 2017), ASH 2017, ASCO 2018 and EHA 2018 (75-77) • Phase II updated results CCOD (30 April 2018), ASH 2018 (78) • Interim CSR (CCOD 30 April 2018) (79)				
Study design	Phase Ib/II, multicentre, open-label study				
Population	Patients with R/R DLBCL • Age ≥18 years' old • ECOG PS 0–2 • At least 1 bi-dimensionally measureable lesion ≥1.5 cm in its longest dimension • Adequate haematologic function • If received prior bendamustine, response duration must have been >1 year				
Intervention(s)	Polatuzumab vedotin plus bendamustine and rituximab (pola+BR)				
Comparator(s)	Bendamustine and rituximab (BR)				
Indicate if trial supports application for marketing authorisation	Yes	✓	Indicate if trial used in the economic model	Yes	✓
	No			No	
Rationale for use/non-use in the model	GO29365 is a Phase Ib/II trial providing efficacy and safety evidence for the combination of pola+BR in patients with R/R DLBCL. Data from GO29365 were used to inform the efficacy and safety of pola+BR in the economic model. Data for PFS and OS from the most recent data cut (11 October 2018) were used to inform the economic model – this data and analysis for other endpoints from the previous data cut (30 April 2018) is reported in this submission				
Reported outcomes specified in the decision problem	Overall survival Progression-free survival Response rates Adverse effects of treatment Health-related quality of life				
All other reported outcomes	Duration of response Event-free survival				

DLBCL, diffuse large B cell lymphoma; ECOG PS, Eastern Cooperative Oncology Group performance status; pola+BR, polatuzumab vedotin plus bendamustine and rituximab; R/R, relapsed/refractory

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

Unless otherwise stated, information on the GO29365 study was sourced from the interim clinical study report and protocol (79, 80).

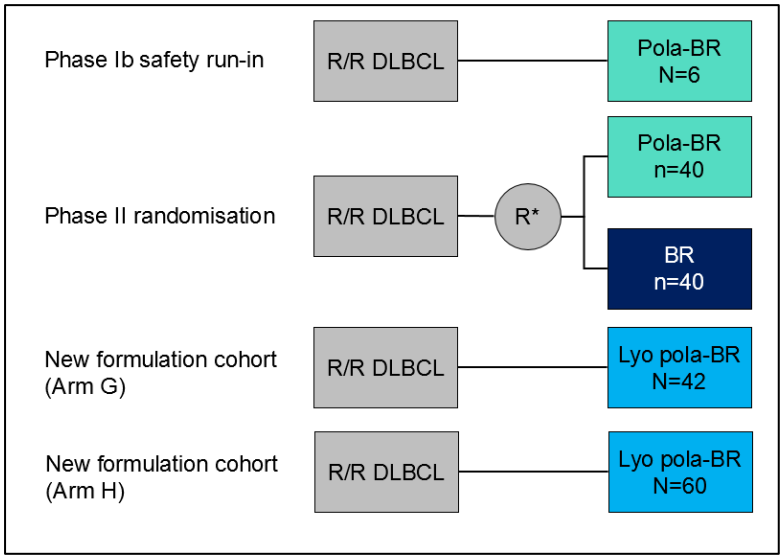
B.2.3.1 Study design

GO29365 is a Phase Ib/II, multicentre, open-label study of pola in combination with BR in patients with R/R DLBCL, and pola in combination with bendamustine and obinutuzumab (BG) in patients with R/R follicular lymphoma. **This submission will focus on the combination of pola+BR in patients with R/R DLBCL only in accordance with the proposed marketing authorisation indication.** The study was conducted in accordance with the principles of the "Declaration of Helsinki" and Good Clinical Practice (GCP) according to the regulations and procedures described in the following sections of the protocol.

The R/R DLBCL component of the study consisted of two stages that ran sequentially (Figure 3):

- **Phase Ib safety run-in stage:** to determine the safety, tolerability, and PK of pola+BR and to identify the recommended Phase II dose (RP2D) of pola to be used in the Phase II stage
- **Phase II randomised and expansion stage**: to evaluate the efficacy, further assess the safety and tolerability, and to characterise the PK of pola+BR.

Figure 3: GO29365 study design schema (R/R DLBCL pola and BR populations only)



*1:1 randomisation, stratified by DOR ≤12 months or >12 months
Lyo, lyophilised formulation
Treatment administered every 21 days x 6 cycles: pola 1.8 mg/kg, C1D2, then D1 for C2+; bendamustine: 90 mg/m2, C1D2/3 then D1/2 for C2+; rituximab: 375 mg/m2, D1 for C1+

During the Phase Ib safety run-in, six patients were treated with pola+BR and monitored for adverse events (AEs) during a safety observation period corresponding to one treatment cycle (from Cycle 1 Day 1 to Cycle 2 Day 1 for a minimum of 21 days). An Internal Monitoring Committee (IMC) performed a safety analysis after the six patients had completed the safety observation period and provided a recommendation on whether to continue into Phase II, and on the RP2D for pola+BR regimen to be used.

For the Phase II randomised portion, patients were randomised to either pola+BR (investigative arm) or to BR alone (control arm).

All patients had tumour assessments including 18F-fluorodeoxyglucose-positron emission tomography (FDG-PET) and a diagnostic-quality CT scan with both oral and IV contrast (referred to as PET-CT) at screening and at an interim response assessment (between Cycle 3 Day 15 and Cycle 4 Day 1), and at primary response assessment: 6–8 weeks after completion of study treatment (i.e., Day 1 of Cycle 6 or after last dose of study medication).

The primary objective of the Phase II portion of the study was to evaluate the efficacy of pola+BR compared with BR alone in patients with R/R DLBCL as measured by PET-defined CR rate using modified Lugano 2014 response criteria (PET-CT criteria) (81) at the primary response.

Data from the Phase Ib and the randomised Phase II portion of GO29365 was generated with a liquid formulation of pola; however, a lyophilised formulation of pola suitable for commercialisation and use in ongoing and future clinical studies was subsequently developed. In late 2017, the protocol was amended to add a new formulation (NF) cohort (Arm G [N=42]), which was designed primarily to assess pharmacokinetic and safety of the lyophilised formulation of pola in combination with BR in R/R DLBCL. Efficacy was evaluated as a secondary objective; [redacted]. In October 2018, another arm was added to the NF cohort (Arm H) recruiting an additional 60 R/R DLBCL patients using the lyophilised formulation of pola in combination with BR. [redacted]

Results reported in this submission are from patients treated with the liquid formulation of polatuzumab vedotin; however, this is not anticipated to be different from that seen with the lyophilised formulation, as reflected by preliminary safety and PK data that has been submitted to EMA. Furthermore, the FDA and EMA have allowed Hoffmann-La Roche to file for marketing authorisation based on results from the liquid formulation.

The BR regimen, chosen to be combined with pola as the investigative treatment, and as the comparator in the randomised Phase II portion of this study, has demonstrated clinical activity in transplant ineligible patients with R/R DLBCL and is associated with manageable haematologic toxicity (59-62). The bendamustine backbone was also selected to minimise the overlapping toxicity of peripheral neuropathy (PN) that may occur with platinum-based therapies.

The dose and schedule of bendamustine used in combination with rituximab in this study (90 mg/m^2 administered on two consecutive days for six 21-day cycles for patients with with R/R DLBCL) was consistent with the recommendations from an international consensus panel based on data in the relapsed setting at the time the study was initiated (82).

The dose of pola was limited to 1.8 mg/kg every 21 days for 6 cycles. Limiting the pola dose regimen for ≤8 cycles may enhance tolerability and mitigate the risk of PN compared with longer treatment durations and higher doses (83). Time-to-event modelling data suggest that 6–8 cycles of 1.8 mg/kg pola has a predicted incidence of grade ≥2 PN of 17.8–28.8%; this is comparable with other antimicrotubule agents for lymphoma treatment (84).

B.2.3.2 Summary of study methodology

	GO29365 (NCT02257567)
Settings and locations of data collection	86 patients were enrolled at 38 study sites in 11 countries for the pola+BR vs BR in R/R DLBCL portion of study: **Countries, number of patients (centres)** • United States 29 (9) • France 7 (5) • Turkey 8 (4) • Spain 6 (3) • Czech Republic 7 (3) • Canada 5 (3) • Italy 3 (3) • Australia 3 (2) • UK 3 (2) • Hungary 5 (2) • South Korea 10 (2)
Trial design	Phase Ib/II, multicentre, open-label study of pola+BR in patients with R/R DLBCL. Six patients enrolled to receive pola+BR in Phase I safety run, 80 patients randomised 1:1 to pola+BR vs BR in Phase II randomisation.
Eligibility criteria	**Inclusion criteria** • Age ≥18 years' old • ECOG PS 0–2 • Histologically confirmed DLBCL

	• Must have received at least one prior therapy for DLBCL. Patients must have either relapsed or have become refractory to a prior regimen, defined as:
	  o Patients who were ineligible for second-line stem cell transplant, with progressive disease or no response (stable disease) <6 months from start of initial therapy (2L refractory)
	  o Patients who were ineligible for second-line stem cell transplant, with disease relapse after initial response ≥6 months from start of initial therapy (2L relapsed)
	  o Patients who were ineligible for third-line (or beyond) stem cell transplant, with progressive disease or no response (stable disease) <6 months from start of prior therapy (3L+ refractory)
	  o Patients who were ineligible for third-line (or beyond) stem cell transplant, with disease relapse after initial response ≥6 months from start of prior therapy (3L+ relapsed)
	• Response duration on prior bendamustine must have been >1 year (for patients who had relapse disease after a prior regimen)
	• At least one bi-dimensionally measurable lesion on imaging scan defined as >1.5cm in its longest duration
	• Life expectancy of at least 24 weeks
	• Adequate haematologic function unless inadequate function is due to underlying disease e.g. extensive bone marrow involvement. Adequate haematologic function defined as:
	  o ANC ≥1.5 ×10^9/L
	  o Platelet count ≥75 ×10^9/L
	  o Haemoglobin ≥9.0 g/dL
	• For women who were not post-menopausal or surgically sterile, agreement to remain abstinent or to use single highly effective or combined contraceptive methods that result in a failure rate of <1% per year during the treatment period and for ≥12 months after the last dose of rituximab
	• For men, agreement to remain abstinent or to use a combination of contraceptive methods that together result in a failure rate of <1% per year during the treatment period and for at least 6 months after the last dose of study drug
	• Able and willing to provide written informed consent and to comply with the study protocol
	
	<u>Key exclusion criteria (please refer to CSR for further detail) (79)</u>
	• History of severe allergic or anaphylactic reactions to humanised or murine monoclonal antibodies (or recombinant antibody-related fusion proteins)
	• Contraindication to bendamustine or rituximab
	• Prior use of any monoclonal antibody, radioimmunoconjugate, or ADC within five half-lives or four weeks, whichever was longer, before Cycle 1 Day 1
	• Ongoing corticosteroid use >30mg/day prednisone or equivalent, for purposes other than lymphoma symptom control
	• Completion of autologous stem cell transplant within 100 days prior to Cycle 1 Day 1
	• Prior allogenic stem cell transplant
	• Eligibility for autologous stem cell transplant

	• History of transformation of indolent disease to DLBCL • Primary or secondary central nervous system lymphoma • Current grade >1 peripheral neuropathy • History of other malignancy that could affect compliance with the protocol or interpretation of results • Evidence of significant, uncontrolled concomitant diseases that could affect compliance with the protocol or interpretation of results, including significant cardiovascular disease (such as New York Heart Association Class III or IV cardiac disease, myocardial infarction within the last 6 months, unstable arrhythmias, or unstable angina) or significant pulmonary disease (including obstructive pulmonary disease and history of bronchospasm) • Known active bacterial, viral, fungal, mycobacterial, parasitic, or other infection (excluding fungal infections of nail beds) at study enrolment or any major episode of infection requiring treatment with intravenous antibiotics or hospitalisation (relating to the completion of the course of antibiotics) within 4 weeks prior to Cycle 1 Day 1 • Positive test results for chronic hepatitis B virus or hepatitis C virus • Known history of human immunodeficiency virus • Any of the following abnormal laboratory values, unless abnormal laboratory values were due to underlying lymphoma per the investigator: • Creatinine >1.5 X ULN or a measured creatinine clearance < 40 mL/min • AST or ALT >2.5 X ULN • Total bilirubin ≥1.5 X ULN • INR or prothrombin time >1.5 X ULN in the absence of therapeutic anticoagulation • PTT or aPTT >1.5 X ULN in the absence of a lupus anticoagulant
Trial drugs and concomitant medications	**Trial drugs** • **Polatuzumab vedotin:** IV, 1.8 mg/kg on Day 2 of Cycle 1 and then Day 1 of subsequent Cycles 2-6**;** • **Bendamustine:** IV, 90 mg/m^2 q3w on two consecutive days, Days 2 and 3 of Cycle 1, then Days 1 and 2 of subsequent Cycles 2–6; • **Rituximab:** IV, 375 mg/m^2, on Day 1 of Cycles 1–6 **Dose modifications** • Permanent dose reduction of **pola** (from 1.8 mg/kg to 1.4 mg/kg) was mandated for Grade 2 or 3 PN (including its signs and symptoms) which had recovered following dose delay to Grade ≤1 within ≤14 days of the scheduled date of the next cycle. Dose reductions below 1.8 mg/kg of pola for neutropenia or thrombocytopenia were not allowed • No dose modifications (reductions) of **rituximab** were allowed • The **bendamustine** dose (90 mg/m^2) could be reduced to 70 mg/m^2 in the event of Grade 3 or 4 neutropenia or thrombocytopenia (first episode or recurrent), if ANC recovered to >1 X 10^9/L (for neutropenia) or platelet count recovered to >75 X

	10^9/L (for thrombocytopenia) on or after Day 8 of the scheduled date for the next cycle. If prior bendamustine dose reduction had occurred, bendamustine dose could be further reduced to 50 mg/m^2 for recurrent Grade 3 or 4 neutropenia or thrombocytopenia. No more than two dose reductions of bendamustine were allowed. **Pre-medications** • All rituximab infusions were to be preceded by premedication with oral acetaminophen/paracetamol and an antihistamine 30–60 minutes before the start of each infusion (unless contraindicated) to minimise the risk of IRRs. **Concomitant medications** **Permitted concomitant medications included:** • Continued use of oral contraceptives, hormone-replacement therapy, or other maintenance therapies • Use of G-CSF for the treatment of neutropenia • Mandatory premedication with acetaminophen/paracetamol and antihistamine prior to administration of each rituximab infusion • Mandatory premedication with oral allopurinol or a suitable alternative treatment (with adequate hydration) prior to Cycle 1, Day 1 and subsequent cycles of treatment if deemed appropriate by the investigator for all patients with high tumour burden and considered to be at high risk for TLS • Anti-infective prophylaxis for viral, fungal, bacterial, or *Pneumocystis* infections • Necessary supportive measures for optimal medical care throughout study according to institutional standards, including growth factors (e.g., erythropoietin) and anti-emetic therapy, if clinically indicated **Prohibited concomitant medications:** • Cytotoxic chemotherapy, other than bendamustine and intrathecal chemotherapy for CNS prophylaxis • Immunotherapy or immunosuppressive therapy, other than study treatments • Radioimmunotherapy or radiotherapy • Hormone therapy, other than contraceptives, stable hormone-replacement therapy, or megestrol acetate • Biologic agents other than haematopoietic growth factors, which are allowed if clinically indicated and used in accordance with instructions provided in the package inserts • Any therapy (other than intrathecal CNS prophylaxis) intended for the treatment of lymphoma
Primary outcome	**Primary endpoint:** • PET-defined CR rate at the time of primary response assessment (6–8 weeks after Cycle 6 Day 1 or last dose of study medication) as defined by the IRC

Other outcomes used in the economic model/specified in the scope	**Secondary endpoints:** • CR at the time of primary response assessment based on PET-CT, as determined by investigator • OR (CR or PR) at the time of primary response assessment, based on PET-CT, as determined by investigator and IRC • CR at the time of primary response assessment based on CT only, as determined by investigator and IRC • OR at the time of primary response assessment based on CT only, as determined by investigator and IRC • BOR (CR or PR) while on study either by PET-CT or CT only, as determined by investigator and IRC • DOR, based on PET-CT or CT, as determined by IRC • PFS, based on PET-CT or CT, as determined by IRC **Exploratory objectives:** • DOR based on PET-CT or CT only as determined by the investigator • PFS based on PET-CT or CT only as determined by the investigator • EFS based on PET-CT or CT only as determined by the investigator • OS **Safety endpoints:** • Safety and tolerability of pola+BR • Immunogenicity of pola+BR, as measured by the formation of ADAs **Patient-reported outcomes:** • Peripheral neuropathy symptom severity and interference on daily functioning and to better understand treatment impact, tolerability, and reversibility, as measured by the Therapy-Induced Neuropathy Assessment Scale (TINAS) v1.0
Pre-planned subgroups	**Pre-planned subgroup analyses** • OS and PFS efficacy of pola+BR in pre-specified demographic and baseline characteristics

ADA, anti-drug antibodies; ALT, alanine aminotransferase; ANC, absolute neutrophil count; AST, aspartate aminotransferase; BOR, best overall response; BR, bendamustine + rituximab; CNS, central nervous system; CR, complete response; DLBCL, diffuse large B-cell lymphoma; DOR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance status; EFS, event-free survival; G-CSF, granulocyte-colony stimulating factor; IRC, Independent Review Committee; IRR, infusion-related reaction; OR, overall response; OS, overall survival; PET-CT, positron emission tomography-computed tomography; PFS, progression-free survival; PN, peripheral neuropathy; Pola, polatuzumab vedotin; PR, partial response; (a)PTT, (activated) partial thromboplastin time; R/R relapsed/refractory; TINAS, Therapy-Induced Neuropathy Assessment Scale; TLS, tumour lysis syndrome; ULN, upper limit of normal

B.2.3.3 Patient demographics and baseline characteristics

Demographic characteristics were generally well balanced across cohorts of patients between treatment arms. Any differences in incidence of demographic characteristics by category observed between BR and pola+BR treatment arms in the randomised Phase II was less than 10% (accounted for by four patients or fewer).

In the randomised Phase II, a higher proportion of patients with R/R DLBCL in the BR arm, compared to the pola+BR arm had bulky disease (≥7.5 cm) (BR: 15/40 patients [37.5%] vs. pola+BR: 10/40 patients [25.0%]), ECOG PS 2 (8/40 [20.0%] vs 6/40 [15.0%], and IPI high risk (4 or 5 risk factors; 17/40 [42.5%] vs 9/40 [22.5%]).

The most common reasons for transplant ineligibility fell into two categories: patient characteristics such as age, comorbidity, or inadequate performance status (BR: 22/40 patients [55.0%]; pola+BR: 14/40 patients [35.0%]), and disease status, including inadequate response to salvage therapy or relapsing after prior autologous transplant (BR: 15/40 patients [37.5%]; pola+BR: 22/40 patients [55.0%]).

Table 7: GO29365 - key demographic and baseline disease characteristics

	Phase Ib (safety run-in)	Phase II (randomised)		Phase Ib/II (total)
	pola+BR n=6	pola+BR n=40	BR n=40	pola+BR N=46
Baseline demographics				
Median age, years (range)	65.0 (58–79)	67.0 (33–86)	71.0 (30–84)	66.5 (33–86)
Male, n (%)	4 (66.7)	28 (70.0)	25 (62.5)	32 (69.6)
Race, n (%)				
White	5 (83.3)	26 (65.0)	31 (77.5)	31 (67.4)
Asian	1 (16.7)	6 (15.0)	4 (10.0)	7 (15.2)
American Indian or Alaska Native	0	0	1 (2.5)	0
Black or African American	0	3 (7.5)	0	3 (6.5)
Unknown	0	5 (12.5)	4 (10.0)	5 (10.9)
ECOG PS, n (%)				
0 or 1	6 (100.0)	33 (82.5)	31 (77.5)	39 (84.7)
2	0	6 (15.0)	8 (20.0)	6 (13.0)
Unknown	0	1 (2.5)	1 (2.5)	1 (2.2)
Primary reason for SCT ineligibility, n (%):				
Age	1 (16.7)	13 (32.5)	19 (47.5)	14 (30.4)
Comorbidities	0	1 (2.5)	1 (2.5)	1 (2.2)
Failed prior transplant	0	10 (25.0)	6 (15.0)	10 (21.7)
Insufficient response to salvage tx	2 (33.3)	12 (30.0)	9 (22.5)	14 (30.4)
Other	1 (16.7)	2 (5.0)	1 (2.5)	3 (6.5)
Patient refusal	2 (33.3)	2 (5.0)	2 (5.0)	4 (8.7)
Performance status	0	0	2 (5.0)	0
Baseline disease characteristics				
Median months since diagnosis at study entry (range)	0.5 (0–1)	0.7 (0–20)	0.8 (0–15)	0.7 (0–20)
Ann Arbor Stage III or IV, n (%)	4 (66.7)	34 (85.0)	36 (90.0)	38 (82.6)
Bulky disease (≥7.5 cm), n (%)	1 (16.7)	10 (25.0)	15 (37.5)	11 (23.9)
Extranodal involvement, n (%)	4 (66.6)	27 (67.5)	29 (72.5)	31 (67.4)
IPI score at enrollment, n (%)				
0–1 (low)	1 (16.7)	9 (22.5)	3 (7.5)	10 (21.7)
2 (low-intermediate)	3 (50.0)	9 (22.5)	8 (20.0)	12 (26.1)
3 (high-intermediate)	2 (33.3)	13 (32.5)	12 (30.0)	15 (32.6)

4–5 (high)	0	9 (22.5)	17 (42.5)	9 (19.6)
Prior anti-lymphoma chemotherapy, n (%)	6 (100.0)	40 (100.0)	40 (100.0)	46 (100.0)
Median no. of lines (range)	2.0 (1–2)	2.0 (1–7)	2.0 (1–5)	2.0 (1–7)
1 line	2 (33.3)	11 (27.5)	12 (30.0)	13 (28.3)
2 lines	4 (66.7)	11 (27.5)	9 (22.5)	15 (32.6)
≥3 lines	0	18 (45.0)	19 (47.5)	18 (39.1)
Prior treatments, n (%)				
Anti-CD20	6 (100.0)	39 (97.5)	40 (100.0)	45 (97.8)
Bendamustine	0	1 (2.5)	0	1 (2.2)
Stem cell transplant	0	10 (25.0)	6 (15.0)	10 (21.7)
Cancer radiotherapy	1 (16.7)	11 (27.5)	10 (25.0)	12 (26.1)
Refractory to last prior anti-CD20 tx[a] n (%)	4 (66.7)	18 (45.0)	18 (45.0)	22 (47.8)
No	1 (16.7)	10 (25.0)	6 (15.0)	11 (23.9)
Unknown	1 (16.7)	12 (13.0)	16 (40.0)	13 (28.3)
Refractory to last prior anti-lymphoma therapy[b], n (%)	5 (83.3)	30 (75.0)	34 (85.0)	35 (76.1)
Median time from last anti-lymphoma therapy[c], days (range)	53.0 (43–1477)	131.0 (17–11744)	82.0 (21–2948)	114.0 (17–11744)
Duration of response to prior tx[d], n (%)				
≤12 months	5 (83.3)	32 (82.0)	33 (82.5)	37 (80.4)

[a] Defined as no response or progression or relapse within 6 months of last anti-lymphoma therapy end date among patients whose last prior regimen contained anti−CD20
[b] Defined as no response or progression or relapse within 6 months of last anti−lymphoma therapy end date
[c] Defined as time from end date of last anti−lymphoma therapy to first dose date
[d] Duration of response to prior therapy based on IxRS for randomised cohorts and CRF for non-randomised cohorts
ECOG PS, Eastern Cooperative Oncology Group performance status; IPI, international prognostic index; IxRS, Interactive Voice/Web Response System; SCT, stem cell transplant

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

Unless otherwise stated, information on the GO29365 study was sourced from the interim clinical study reports and protocol (79, 80). The participant flow and details on patient study and treatment withdrawal for GO29365 is presented in Appendix D.

Determination of sample size

In total, enrolment of approximately 224 patients was planned in order to evaluate the safety and efficacy of pola when combined with BR or BG in DLBCL and FL:

- Twenty-four patients in total were planned to be enrolled during the Phase Ib safety run-in portion of the study, with a minimum of six patients for the pola+BR DLBCL run-in. Less than two observed safety events in a given 6-patient cohort was considered to be deemed safe for the purpose of moving to the Phase II part of the study; this is consistent with requirements for identification of a candidate RP2D based upon a standard 3+3 design

- Forty patients were planned for each treatment arm in the Phase II randomisation phase in patients with R/R DLBCL in order to evaluate the safety and efficacy of pola+BR compared with BR with acceptable accuracy.

The primary analysis was an estimation of treatment-specific CR rates as well as the difference in PET CR rates between patients randomised to treatment with pola+BR and those randomised to treatment with BR alone.

With 40 patients per arm, 95% exact Clopper-Pearson confidence intervals (CIs) for estimation of the true CR rate for would have a margin of error not exceeding ±17%. With 40 patients and an observed CR rate of at least 60%, a true CR rate below 43% can be ruled out with 95% confidence (Table 8). In addition, with 40 patients in each arm, assuming a 40% CR rate in the BR arm, and a 25% increase in CR rate when pola is added to BR, the 95% CI for the difference in CR rates is 3.8%, 46.2%.

Table 8: Clopper-Pearson exact 95% confidence intervals for assumed observed CR rates based on sample size of 40 patients

pola+BR CR rate, %	No. of patients with CR (95% CI for rate)
80	32 (64%, 91%)
75	30 (59%, 87%)
70	28 (53%, 83%)
65	26 (48%, 79%)
60	24 (43%, 75%)

CI, confidence interval; CR, complete response

With respect to assessment of safety based on a sample size of 40 patients in each of the BR arms, there is at least an 87% chance of observing at least one AE with a true incidence of ≥5%.

Analysis populations

Efficacy analyses for the randomised component of the Phase II (BR and pola+BR) were based on the intent-to-treat (ITT) population and conducted in accordance with the ITT principle (i.e., including all randomised patients irrespective of whether they received study treatment, with patients grouped according to treatment assignment at randomisation).

Safety analyses were based on the safety-evaluable population which included all treated patients (i.e., patients who received any amount of study medication) according to actual treatment received.

Efficacy analysis

Analysis methodology for primary, secondary and exploratory efficacy endpoints in the GO29365 study is summarised below.

Table 9: Efficacy outcome measures and analysis methodology

Outcome measure	Analysis methodology
Primary efficacy endpoint	
• CR at primary response assessment (6−8 weeks after Cycle 6 Day 1 or last dose of study medication) based on PET-CT, as determined by the investigator and IRC	CR rate, defined as the percentage of patients with CR, was estimated and the corresponding Clopper-Pearson exact 95% CI was constructed for each treatment arm. The difference in PET CR rates between pola+BR and BR arms was estimated along with the corresponding 95% CI on the basis of normal approximation to the binomial distribution. An exploratory comparison of CR rates for the pola+BR and BR regimens was conducted using the Cochran Mantel-Haenszel (CMH) chi-square test adjusted for randomisation stratification factors.
Secondary efficacy endpoints	
Response rates measured at the primary response assessment: • CR (INV-assessed) and OR (INV- and IRC assessed CR or PR) based on PET alone • CR and OR (INV- and IRC-assessed) based on CT alone • BOR (INV-assessed) at any assessment while on study based on PET alone or CT alone • DOR (IRC-assessed) • PFS (IRC-assessed)	Patients without a post−baseline tumour assessment were considered non-responders. Analyses of secondary efficacy endpoints identical to those described above for the primary efficacy endpoint described above.
Exploratory efficacy endpoints	
Time-to-event outcome measures: • DOR (INV-assessed)	Median DOR was estimated, along with the corresponding 95% CI using the method of Brookmeyer and Crowley. No formal comparisons of DOR across treatment arms were conducted.
• PFS (INV-assessed) • EFS (INV-assessed) • OS	Distribution of durations for PFS, EFS and OS summarised descriptively using Kaplan-Meier (KM) methodology to estimate median (if analytically possible), 1-year, and 2-year PFS and 95% CIs using Greenwood's formula. There was no pre-specified alpha control plan; p-values are provided for descriptive purpose only.

BOR, best overall response; CR, complete response; DOR, duration of response; EFS, event-free survival; IRC, Independent Review Committee; KM, Kaplan-Meier; OR, overall response; OS, overall survival; PET-CT, positron emission tomography-computed tomography; PFS, progression-free survival; PR, partial response

Handling of missing data and censoring methods

For response endpoints, patients with no response assessments (for any reason) were considered non-responders.

For the PFS analyses, patients who did not have documented disease progression or death had observations censored on the date of the last tumour assessment or, if no tumour assessments were performed after the baseline visit, at the time of randomisation and enrolment +1 day.

For OS, patients for whom death had not been documented had observations censored on the last date at which they were known to be alive.

Patient-reported outcome analysis

The PRO analyses included patients in the intent-to-treat population and were analysed according to assigned treatment. For the total score and each of the Therapy-Induced Neuropathy Assessment Scale (TINAS) single symptom items, descriptive statistics for recorded values at each visit and changes from baseline were calculated.

In the event of patients not completing individual TINAS items, missing data were handled per developer scoring instructions, such that a prorated total score was calculated if ≥50% of items were answered using the following formula:

Prorated total score = [Sum of item scores] x [Total no. of items] / [No. of items answered]

B.2.5 Quality assessment of the relevant clinical effectiveness evidence

Critical appraisal of the included randomised clinical trials was performed using established risk of bias tools recommended for HTA submissions. The complete quality assessment is presented in Appendix D. A summary is presented below.

Table 10: Clinical effectiveness evidence quality assessment

Study question	GO29365 (NCT02257567)
Was randomisation carried out appropriately?	Yes
Was the concealment of treatment allocation adequate?	Yes
Were the groups similar at the outset of the study in terms of prognostic factors?	Yes
Were the care providers, participants and outcome assessors blind to treatment allocation?	N/A (open label study)
Were there any unexpected imbalances in drop-outs between groups?	No
Is there any evidence to suggest that the authors measured more outcomes than they reported?	No
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Yes

B.2.6 Clinical effectiveness results of the relevant trials

- Pola+BR resulted in higher response rates and longer DOR, PFS, EFS, and OS compared to BR in the randomised Phase II portion of GO29365. Efficacy results in patients with R/R DLBCL (CCOD 30 April 2018) can be summarised as follows:
- The primary efficacy endpoint of CR rate at the primary response assessment (PRA) based on PET-CT, as determined by the IRC, was higher in the pola+BR arm (40.0% [16/40 patients]; 95% CI: 24.9%, 56.7%) compared with the BR arm (17.5% [7/40 patients]; 95% CI: 7.3%, 32.8%) (Δ22.5% in favour of pola+BR; 95% CI: 2.6%, 40.2%; p=0.0261).
- Secondary efficacy endpoints of response rates (CR and objective response [OR; CR or PR]) whether measured with or without PET and assessed by the investigator or by the IRC remained consistent with primary efficacy results, with a higher proportion of patients with R/R DLBCL achieving CR or OR in the pola+BR arm compared to the BR arm
    - INV-assessed CR (PET-CT): 42.5% vs. 15.0%
    - IRC-assessed OR (PET-CT): 45.0% vs. 17.5%
    - IRC-assessed response rates (CT only): CR, 22.5% vs. 2.5%; OR, 42.5% vs. 15.0%
    - INV-assessed response rates (CT only): CR: 20% vs. 5.0%; OR, 45.0% vs. 15.0%
    - INV-assessed BOR (PET-CT or CT): CR: 57.5% vs. 20.0%; ORR: 70.0% vs. 32.5%
    - IRC-assessed median DOR 12.6 months (95% CI: 7.2, NE) vs. 7.7 months (95% CI: 4.0, 18.9) (stratified HR=0.47; 95% CI: 0.19, 1.14]; p=0.0889)
    - IRC-assessed median PFS: 9.5 months (95% CI: 6.2, 13.9) vs. 3.7 months (95% CI: 2.1, 4.5) (stratified HR=0.36; 95% CI: 0.21, 0.63; p=0.0004)
- Exploratory time-to-event analyses demonstrated a consistent treatment effect favouring the pola+BR arm compared to the BR arm for DOR, PFS, EFS, and OS:
    - INV-assessed median DOR: 10.3 months (95% CI: 5.6, NE) vs. 4.1 months (95% CI: 2.6, 12.7) (stratified HR=0.44; 95% CI: 0.20, 0.95)
    - INV-assessed median PFS: 7.6 months (95% CI: 6.0, 17.0) vs. 2.0 months 95% CI: 1.5, 3.7) (stratified HR=0.34; 95% CI: 0.20, 0.57; p<0.0001). The updated INV-assessed PFS analysis (CCOD 11 October 2018) was consistent with that seen in the interim analysis: [redacted]
    - Median EFS: 6.4 months (95% CI: 4.0, 11.1) vs. 2.0 months (95% CI: 1.5, 3.1)
    - Median OS was extended to 12.4 months (95% CI: 9.0, NE) in the pola+BR arm, from 4.7 months (95% CI: 3.7, 8.3) in the BR arm (stratified HR=0.42; 95% CI: 0.24, 0.75; p=0.0023. [redacted]
    - The treatment effect for survival was consistently observed across all subgroups of patients with R/R DLBCL tested.

The primary analysis presented in this submission is from the clinical cut-off date 30 April 2018, although data for PFS and OS from the most recent data cut (11 October 2018) is also presented.

B.2.6.1 Primary efficacy endpoint

In the randomised Phase II part of the GO29365 study, the proportion of patients with R/R DLBCL with a CR at the primary response assessment by PET-CT as assessed by the IRC was higher in the pola+BR arm (40.0% [16/40 patients]; 95% CI: 24.9%, 56.7%) compared to patients in the BR arm (17.5% [7/40 patients], 95% CI: 7.3%, 32.8%). The difference in CR rates between arms was statistically significant (Δ22.5%; p=0.0261, CMH chi-square).

Table 11: CR rate with PET at primary response assessment (IRC-assessed)

	pola+BR n=40	**BR n=40**
Complete response, n (%) 95% CI	16 (40.0) (24.86, 56.67)	7 (17.5) (7.34, 32.78)
Difference in response rates, n (%) (95% CI) p value	22.5 (2.62, 40.22) p=0.0261	

CCOD: 30 April 2018

B.2.6.2 Secondary efficacy endpoints

Response rates at primary response assessment based on PET

The objective response (CR or PR) rate at the primary response assessment based on PET by IRC was 45.0% (18/40 patients) in the pola+BR arm and 17.5% (7/40 patients) in the BR arm, a difference of 27.5% (p=0.0069, CMH chi-square test). Most patients who had an objective response at the primary response assessment in each treatment arm achieved a CR (BR arm: 7 CRs, 0 PRs vs pola+BR arm: 16 CRs, 2 PRs).

Table 12: Objective response (CR/PR) rates by PET at primary response assessment (IRC-assessed)

	pola+BR n=40	**BR n=40**
Overall response, n (%) 95% CI	18 (45.0) (29.26, 61.51)	7 (17.5) (7.34, 32.78)
Complete response, n (%) 95% CI	16 (40.0) (24.86, 56.67)	7 (17.5) (7.34, 32.78)
Partial response, n (%) 95% CI	2 (5.0) (0.61, 16.92)	0 (0.0, 8.81)
Difference in OR response rates, % (95% CI) p value	27.5 (7.17, 45.02) p=0.0069	

CR, complete response; OR, overall response; PR, partial response
CCOD: 30 April 2018

INV-assessment of response by PET at the primary response assessment was highly consistent with IRC assessment. Complete response rates were 42.5% (17/40 patients) in the pola+BR arm and 15.0% (6/40 patients) in the BR arm, a difference of 27.5% (p=0.0061, CMH chi-square test). Objective response rates, driven by CRs, were 47.5% (19/40 patients) and 17.5% (7/40 patients), respectively (Δ30.0%; p=0.0036, CMH chi-square test).

Table 13: Complete response and objective response (CR/PR) rates by PET at primary response assessment (INV-assessed)

	pola+BR n=40	BR n=40
Overall response, n (%) 95% CI	19 (47.5) (31.51, 63.87)	7 (17.5) (7.34, 32.78)
Complete response, n (%) 95% CI	17 (42.5) (27.04, 59.11)	6 (15.0) (5.71, 29.84)
Partial response, n (%) 95% CI	2 (5.0) (0.61, 16.92)	1 (2.5) (0.06, 13.16)
Difference in OR response rates, % (95% CI) p value	30.0 (9.48, 47.37) p=0.0036	

CR, complete response; OR, overall response; PR, partial response
CCOD: 30 April 2018

Response rates at primary response assessment based on CT

Complete response rates for patients with R/R DLBCL, measured by CT and as assessed by IRC, were 22.5% (9/40 patients) in the pola+BR arm and 2.5% (1/40 patients) in the BR arm (Δ20.0%; p= 0.0078, CMH chi-square test).

Overall response rates were 42.5% and 15.0%, respectively (Δ27.5%; p=0.0051, CMH chi-square test) and compared with objective responses by PET, were made up of proportionately more partial responses (BR arm: 1 CR, 5 PRs vs. pola+BR arm: 9 CRs, 8 PRs).

Table 14: Complete response and objective response (CR/PR) rates by CT at primary response assessment (IRC-assessed)

	pola+BR n=40	BR n=40
Overall response, n (%) 95% CI	17 (42.5) (27.04, 59.11)	6 (15.0) (5.71, 29.84)
Complete response, n (%) 95% CI	9 (22.5) (10.84, 38.45)	1 (2.5) (0.06,13.16)
Partial response, n (%) 95% CI	8 (20.0) (9.05, 35.65)	5 (12.5) (4.19, 26.80)
Difference in OR response rates, % (95% CI) p value	27.5 (7.66, 44.74) p=0.0051	

CR, complete response; OR, overall response; PR, partial response
CCOD: 30 April 2018

Investigator assessment of response by CT at primary response assessment was similar to the IRC assessment. The proportions of patients with CR and OR were 20.0% (8/40 patients) in the pola+BR arm versus 5.0% (2/40 patients) in the BR arm (Δ15.0%; p=0.0454, CMH chi-square test), and 45.0% (18/40 patients) in the pola+BR arm versus 15.0% (6/40 patients) in the BR arm (Δ30.0%; p= 0.0032, CMH chi-square test) respectively.

Table 15: Complete response and objective response (CR/PR) rates by CT at primary response assessment (INV-assessed)

	pola+BR n=40	BR n=40
Overall response, n (%) 95% CI	18 (45.0) (29.26, 61.51)	6 (15.0) (5.71, 29.84)
Complete response, n (%) 95% CI	8 (20.0) (9.05, 35.65)	2 (5.0) (0.61,16.92)
Partial response, n (%) 95% CI	10 (25.0) (12.69, 41.20)	4 (10.0) (2.79, 23.66)
Difference in OR response rates, % (95% CI) p value	30.0 (9.94, 47.12) p=0.0032	

CR, complete response; OR, overall response; PR, partial response
CCOD: 30 April 2018

Best overall response while on study

For analyses of BOR, the tumour assessment result was based on PET-CT or CT results. A best response of CR or PR as assessed by IRC was achieved by 25/40 patients (62.5%) in the pola+BR arm and 10/40 patients (25.0%) in the BR arm while on study. The proportion achieving a best response of CR was 20/40 patients (50.0%) and 9/40 patients (22.5%), respectively.

Table 16: Best overall response rate (IRC-assessed)

	pola+BR n=40	BR n=40
Best overall response, n (%) 95% CI	25 (62.5) (45.80, 77.27)	10 (25.0) (12.69, 41.20)
Complete response, n (%) 95% CI	20 (50.0) (33.80, 66.20)	9 (22.5) (10.84, 38.45)
Partial response, n (%) 95% CI	5 (12.5) (4.19, 26.80)	1 (2.5) (0.06, 13.16)
Stable disease, n (%) 95% CI	5 (12.5) (4.19, 26.80)	9 (22.5) (10.84, 38.45)
Progressive disease, n (%) 95% CI	6 (15.0) (5.71, 29.84)	8 (20.0) (9.05, 35.65)
Missing or unevaluable, n (%) 95% CI	4 (10.0) (2.79, 23.66)	13 (32.5) (18.57, 49.13)
Difference in BOR response rates, % (95% CI) p value	37.50 (15.82, 54.62) p=0.0005	

BOR, best overall response
CCOD: 30 April 2018

A best response of CR or PR as assessed by the investigator was achieved by 28/40 patients (70.0%) in the pola+BR arm and 13/40 patients (32.5%) in the BR arm while on study. The proportion achieving a best response of CR was 23/40 patients (57.5%) and 8/40 patients (20.0%), respectively.

Table 17: Best overall response rate (INV-assessed)

	pola+BR n=40	**BR n=40**
Best overall response, n (%) 95% CI	28 (70.0) (53.47, 83.44)	13 (32.5) (18.57, 49.13)
Complete response, n (%) 95% CI	23 (57.5) (40.89, 72.96)	8 (20.0) (9.05, 35.65)
Partial response, n (%) 95% CI	5 (12.5) (4.19, 26.80)	5 (12.5) (4.19, 26.80)
Stable disease, n (%) 95% CI	1 (2.5) (0.06, 13.16)	2 (5.0) (0.61, 16.92)
Progressive disease, n (%) 95% CI	7 (17.5) (7.34, 32.78)	22 (55.0) (38.49, 70.74)
Missing or unevaluable, n (%) 95% CI	4 (10.0) (2.79, 23.66)	3 (7.5) (1.57, 20.39)
Difference in BOR response rates, % (95% CI) p value	37.5 (15.64, 54.71) p=0.0006	

BOR, best overall response
CCOD: 30 April 2018

Duration of response by IRC

Among patients who achieved an OR (CR/PR) at any time (23 patients in the pola+BR arm and 10 patients in the BR arm), 13 patients in the pola+BR arm (52.0% of responders) and eight patients in the BR arm (80.0% of responders) subsequently had progressive disease or died.

The median IRC-assessed DOR was 12.6 months in the pola+BR arm (95% CI: 7.2 months, NE]) compared to the BR arm (7.7 months [95% CI: 4.0 months, 18.9 months]). The risk of responders progressing or dying was reduced by 53% in patients treated with pola+BR compared to BR (stratified hazard ratio [HR]=0.47; 95% CI: 0.19, 1.14).

Table 18: Duration of response (CR/PR) (IRC-assessed)

	pola+BR n=25	**BR n=10**
Patients with event, n (%)	13 (52.0)	8 (80.0)
Earliest contributing event, n Disease progression Death	 7 6	 3 5
Median time to event, months 95% CI	12.62 (7.16, NE)	7.66 (3.98, 18.89)

Stratified HR % (95% CI) p value (log-rank)	0.47 (0.19, 1.14) p=0.0889

Tumour assessment is based on PET-CT wherever it is available and valid and uses CT only result if PET-CT is missing
HR, hazard ratio
CCOD: 30 April 2018

[redacted]

Progression-free survival by IRC

More patients with R/R DLBCL in the BR arm compared with the pola+BR arm had a PFS event (PD or death) at the time of the clinical cut-off (80.0% [32/40 patients] vs. 62.5% [25/40 patients]). Deaths accounted for most of the PFS events (19/32 patients) in the BR arm and 13 patients in the BR arm had disease progression. PFS events in the pola+BR arm included 11 deaths and 14 patients with disease progression.

The risk of PD or death was reduced by 64% in patients treated with pola+BR compared to BR (stratified HR=0.36; 95% CI: 0.21, 0.63; p<0.0002). Median PFS was over two-fold the duration in patients treated with pola+BR (9.5 months [95% CI: 6.2, 13.9]) compared to BR (3.7 months [95% CI: 2.1, 4.5]).

Table 19: Progression-free survival (IRC-assessed)

	pola+BR n=40	**BR n=40**
Patients with event, n (%)	25 (62.5)	32 (80.0)
Earliest contributing event, n Disease progression Death	 14 11	 13 19
Median time to event, months 95% CI	9.46 (6.24, 13.93)	3.71 (2.07, 4.53)
Stratified HR % (95% CI) p value (log-rank)	0.36 (0.21, 0.63) p<0.0002	

Tumour assessment is based on PET-CT wherever it is available and valid and uses CT only result if PET-CT is missing
HR, hazard ratio
CCOD: 30 April 2018

See section B.2.6.4 for sensitivity analyses of PFS by IRC based on two additional censoring rules that were applied.

B.2.6.3 Exploratory efficacy endpoints

Duration of response by investigator

Among patients who achieved an OR (CR/PR) at any time (28 patients in the pola+BR arm and 13 patients in the BR arm), 17 patients in the pola+BR arm (60.7% of responders) and 11 patients in the BR arm (84.6% of responders) subsequently had progressive disease or died.

The median DOR was over two-fold the duration in the pola+BR arm (10.3 months [95% CI: 5.6 months, NE]) compared to the BR arm (4.1 months [95% CI: 2.6 months, 12.7 months]).

The risk of responders progressing or dying after response to treatment was reduced by 56% in patients treated with pola+BR compared to BR (stratified HR=0.44; 95% CI: 0.2, 0.95).

Table 20: Duration of response (INV-assessed)

	pola+BR n=28	**BR n=13**
Patients with event, n (%)	17 (60.7)	11 (84.6)
Earliest contributing event, n Disease progression Death	 13 4	 7 4
Median time to event, months 95% CI	10.32 (5.59, NE)	4.1 (2.56, 12.68)
Stratified HR % (95% CI) p value (log-rank)	0.44 (0.20, 0.95) p=0.0321	

Tumour assessment based on PET-CT wherever available and valid, CT only if PET-CT is missing
HR, hazard ratio, NE, not estimated
CCOD: 30 April 2018

Progression-free survival by investigator

More patients with R/R DLBCL in the BR arm, compared to the pola+BR arm of the randomised Phase II, had a PFS event (PD or death) at the time of the clinical cut-off (87.5% [35/40 patients] vs. 67.5% [27/40 patients]). The risk of PD or death was reduced by 66% in patients treated with pola+BR compared to BR (stratified HR=0.34 (95% CI: 0.20, 0.57); p<0.0001).

Median PFS was over three-fold the duration in patients treated with pola+BR (7.6 months [95% CI: 6.0, 17.0]) compared to BR (2 months [95% CI: 1.5, 3.7]).

Table 21: Progression-free survival (INV-assessed)

	pola+BR n=40	BR n=40
Patients with event, n (%)	27 (67.5)	35 (87.5)
Earliest contributing event, n Disease progression Death	 21 6	 30 5
Median time to event, months 95% CI	7.62 (5.98, 16.95)	2.04 (1.54, 3.71)
Stratified HR % (95% CI) p value (log-rank)	0.34 (0.20, 0.57) p<0.0001	

Tumour assessment based on PET-CT wherever available and valid, CT only if PET-CT is missing
HR, hazard ratio
CCOD: 30 April 2018

The updated efficacy analysis (CCOD 11 October 2018) provide approximately 5 months of additional data, with an estimated median follow-up of [redacted].

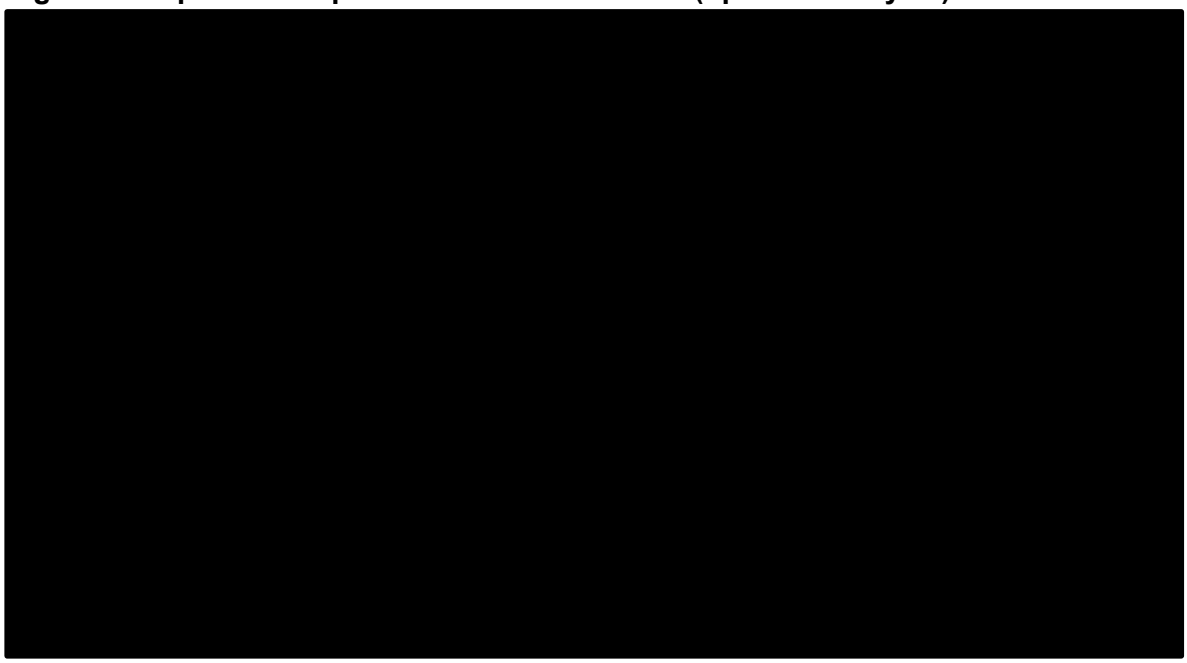
[redacted]

Table 22: INV-assessed progression-free survival (updated analysis)

	pola+BR n=40	BR n=40
Patients with event, n (%)	[redacted]	[redacted]
Earliest contributing event, n Disease progression Death	 [redacted]	 [redacted]
Median time to event, months 95% CI	[redacted]	[redacted]
Stratified HR % (95% CI) p value (log-rank)	[redacted]	

Tumour assessment based on PET-CT wherever available and valid, CT only if PET-CT is missing
HR, hazard ratio
CCOD: 11 October 2018

Figure 4: Kaplan-Meier plot of INV-assessed PFS (updated analysis)



CCOD 11 October 2018

Event-free survival by investigator

As with PFS, more patients with R/R DLBCL in the BR arm, compared to the pola+BR arm of the randomised Phase II had an EFS event (new anti-lymphoma treatment [NALT], PD or death) at the time of the clinical cutoff (95.0% [38/40] vs. 72.5% [29/40]). The risk of PD, death or starting a new antilymphoma treatment was reduced by 70% in patients treated with pola+BR compared to BR (stratified HR=0.30; 95% CI: 0.18, 0.50; p<0.0001).

Table 23: Event-free survival (INV-assessed)

	pola+BR n=40	**BR n=40**
Patients with event, n (%)	29 (72.5)	38 (95.0)
Earliest contributing event, n		
New anti-lymphoma treatment	5	3
Disease progression	20	30
Death	4	5
Median time to event, months	6.36	2.04
95% CI	(3.98, 11.07)	(1.54, 3.06)
Stratified HR %	0.30	
(95% CI)	(0.18, 0.50)	
p value (log-rank)	p<0.0001	

Tumour assessment based on PET-CT wherever available and valid, CT only if PET-CT is missing
HR, hazard ratio
CCOD: 30 April 2018

Overall survival

At the time of the clinical cutoff, a total of 51 patients with R/R DLBCL in the randomised Phase II had died; 28 patients (70.1%) in the BR arm and 23 patients (57.5%) in the

pola+BR arm. The main cause of death in both arms was disease progression (17 patients in the BR arm and 14 patients in the pola+BR arm). A further two patients with R/R DLBCL in the pola+BR safety run-in died of progressive disease.

The risk of death was reduced by 58% in patients treated with pola+BR compared to BR (stratified HR=0.42; 95% CI: 0.24, 0.75; p=0.0023). Median overall survival was 12.4 months (95% CI: 9.0, NE) in patients in the pola+BR arm compared to 4.7 months (95% CI: 3.7, 8.3) in the BR arm.

The duration of survival follow-up for patients with R/R DLBCL as assessed by reverse KM methodology was same in the two treatment arms (median follow-up 22.3 months in both treatment arms).

Table 24: Overall survival

	pola+BR n=40	**BR n=40**
Patients with event, n (%)	23 (57.5)	28 (70.0)
Median time to event, months 95% CI	12.39 (9.04, NE)	4.73 (3.71, 8.31)
Stratified HR % (95% CI) p value (log-rank)	0.42 (0.24, 0.75) p=0.0023	

HR, hazard ratio; NE, not estimated
CCOD: 30 April 2018

At the time of the updated CCOD (11 October 2018),

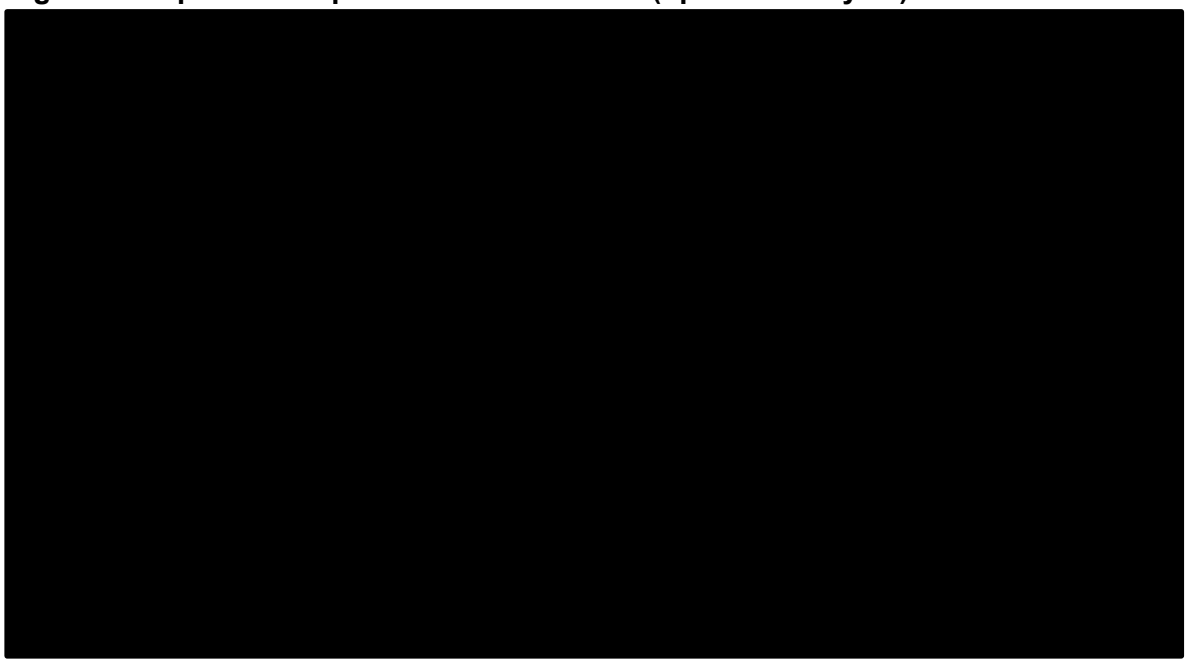
[redacted]

Table 25: Overall survival (updated analysis)

	pola+BR n=40	**BR n=40**
Patients with event, n (%)	[redacted]	[redacted]
Median time to event, months 95% CI	[redacted]	[redacted]
Stratified HR % (95% CI) p value (log-rank)	[redacted]	

HR, hazard ratio; NE, not estimated
CCOD: 11 October 2018

Figure 5: Kaplan-Meier plot of overall survival (updated analysis)



CCOD 11 October 2018

B.2.6.4 PFS sensitivity analyses

To assess the robustness of the results of PFS by IRC in the randomised Phase II portion, two additional censoring rules were applied. For the patients who had missed one or more assessments before their recorded event of disease progression or death, the data were censored at the date of the last non-missing disease assessments prior to the events. For patients who started NALT prior to the disease progression, the data were censored at the date of the last non-missing diease assessments before the NALT. The estimates of the PFS by IRC using these additional censoring rules are consistent with the results of using the standard PFS censoring rule.

Table 26: Progression-free survival (IRC-assessed) – censoring for one or more missing responses

	pola+BR n=40	**BR n=40**
Patients with event, n (%)	21 (52.5)	27 (67.5)
Earliest contributing event, n Disease progression Death	 12 9	 12 15
Median time to event, months 95% CI	10.45 (6.24, NE)	3.71 (1.87, 4.73)
Stratified HR % (95% CI) p value (log-rank)	0.33 (0.18, 0.59) p<0.0001	

Tumour assessment is based on PET-CT wherever it is available and valid and uses CT only result if PET-CT is missing
HR, hazard ratio, NE, not estimated
CCOD: 30 April 2018

Table 27: Progression-free survival (IRC-assessed) – censoring for NALT

	pola+BR n=40	BR n=40
Patients with event, n (%)	19 (47.5)	29 (72.5)
Earliest contributing event, n Disease progression Death	 13 6	 13 16
Median time to event, months 95% CI	11.07 (4.93, NE)	3.68 (2.00, 4.53)
Stratified HR % (95% CI) p value (log-rank)	0.28 (0.15, 0.53) p<0.0001	

Tumour assessment is based on PET-CT if available and valid and uses CT only result if PET-CT is missing
HR, hazard ratio, NE, not estimated
CCOD: 30 April 2018

B.2.6.5 Multiple Cox-regression

To further assess the robustness of the treatment effects observed on pola+BR compared to BR in the randomised Phase II portion, multiple Cox-regression analyses were conducted for PFS and OS. The prognostic factors included in the final models were selected based on the statistical threshold (p<0.2) and clinical consideration while controlling for the multi-collinearity among the factors.

Two sets of factors were used for PFS and OS:

- PFS: Ann Arbor stage, baseline ECOG and IPI
- OS: Ann Arbor stage, baseline ECOG, bulky disease and IPI

After adjusting for the potential prognostic factors and baseline characteristics the treatment effect of pola+BR remains robust:

- For investigator-assessed PFS, the adjusted HR is between 0.34 (95% CI: 0.20, 0.58; p<0.0001) and 0.38 (95% CI: 0.22, 0.64; p=0.0003)
- For IRC-assessed PFS, the adjusted HR is between 0.37 (95% CI: 0.21, 0.66; p=0.0009) and 0.40 (95% CI: 0.23, 0.70; p=0.0012)
- For OS, the adjusted HR is between 0.43 (95% CI: 0.24, 0.78; p=0.005) and 0.46 (95% CI: 0.26, 0.82; p= 0.008)

Table 28: Mulitple Cox regression models for PFS

Multiple Cox regression models (statified*)	pola+BR vs BR				
	n	INV-assessed		IRC-assessed	
		HR (95% CI)	p value	HR (95% CI)	p value
Adjusted for stage (III/IV vs. I/II); ECOG (≥2, <2, unknown†)	80	0.34 (0.20, 0.58)	<0.0001	0.37 (0.21, 0.66)	0.0007
Adjusted for IPI score (≥3 vs. <3)	80	0.38 (0.22, 0.64)	0.0003	0.40 (0.23, 0.70)	0.0012

*stratification factor: duration of response ≤12 months; †two patients missed baseline ECOG
CCOD: 30 April 2018

Table 29: Mulitple Cox regression models for OS

Multiple Cox regression models (statified*)	pola+BR vs BR		
	n	HR (95% CI)	p value
Adjusted for stage (III/IV vs. I/II); ECOG (≥2, <2, unknown†); bulky disease (yes vs no)	80	0.43 (0.24, 0.78)	<0.005
Adjusted for IPI score (≥3 vs. <3)	80	0.46 (0.26, 0.82)	0.008

*stratification factor: duration of response ≤12 months
†two patients missed baseline ECOG
CCOD: 30 April 2018

B.2.6.6 Patient-reported outcomes

The severity of symptoms of neuropathy related to pola treatment and impact on daily functioning were self-reported by the patient on the TINAS v1.0 instrument (85). The TINAS is an 11-item questionnaire that assesses the severity of neuropathy-related symptoms in the last 24 hours. Each item is scored on a 0–10 scale, with 0 being the symptom is not present, and 10 being the symptom is as bad as the patient can imagine. Responses were entered electronically by the patient either while on-site or at home, using the patient's own electronic device or a device provided to them for the purpose of this study.

Patient-reported outcome completion over the course of the trial was generally limited for both Phase Ib and Phase II parts of the study; the proportion of R/R DLBCL patients completing at least one item of the TINAS at each weekly assessment was typically not greater than 50%. During the Phase II randomisation phase, compliance in the BR arm declined more rapidly than the pola+BR arm.

As PN in the study is assumed to be specific to pola, data from pola+BG and pola+BR arms were pooled across the Phase Ib and Phase II stages to maximise the sample size available for analyses given the extent of missing data.

Mean scores for individual TINAS items were low (≤1.5) at the beginning of treatment in both the pola+BR/BG and BR arms, indicating that patients were experiencing relatively little PN burden (range is 0–10 for each item), and generally stayed low during treatment. By the end of treatment, the severity of PN symptoms was rated as low, with the highest means observed for numbness/tingling in hands/feet, although still ≤2.

When exploring mean TINAS scores over time, several sensory (i.e., hot/burning sensations in hands/feet, pins/needles in arms/legs, numbness/tingling in hands/feet, cramps in hands/feet) and motor items (i.e., trouble grasping small objects, trouble walking, and difficulty with balance) showed slight elevations during treatment with pola+BR/BG, whereas

trajectories for the remaining items were largely flat. However, the mean scores rarely exceeded 3.0 during treatment, indicating that overall, patients perceived PN symptoms to be mild. Trends for the BR arm across all items were relatively flat.

B.2.7 Subgroup analysis

Exploratory subgroup analyses of PFS and OS in patients with R/R DLBCL evaluated the potential impact of demographic and baseline disease characteristics, e.g. cell of origin category, duration of response to prior therapy, disease stage, and other prognostic factors on the treatment effect (see Appendix E).

Overall, the treatment effect for PFS was consistent and in the same direction as for the overall R/R DLBCL population with point estimates of HR <0.50 across all except two subgroups, patients with Ann Arbor Stage I/II disease at study entry (HR=0.7 [95% CI: 0.1, 4.98]) and patients with prior transplant (HR=0.86 [95% CI: 0.26, 2.88]). However, the number of patients in each of these subgroups was very small (10 and 16 patients, respectively).

Exploratory subgroup analysis of OS in patients with R/R DLBCL by baseline risk factor shows that for all patient subgroups tested, the treatment effect for survival was consistent with and in the same direction (point estimates of HR were generally ≤0.50) as for the overall R/R DLBCL population.

B.2.8 Meta-analysis

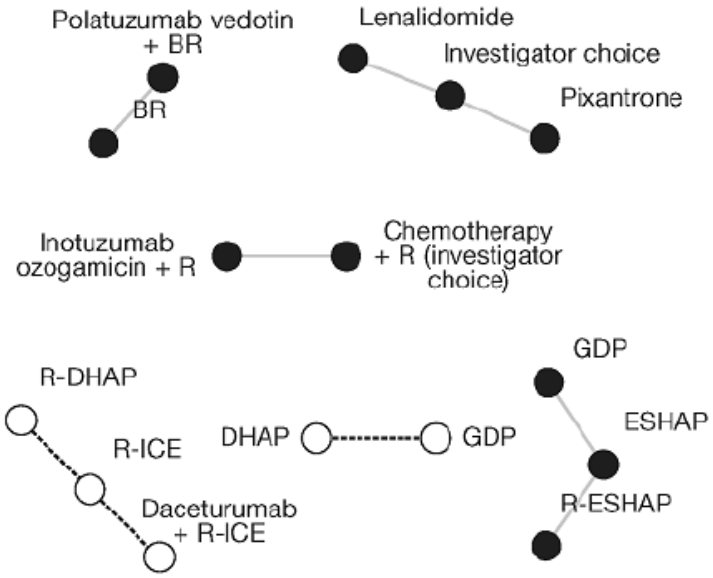
A meta-analysis was not feasible as only one study was identified.

B.2.9 Indirect and mixed treatment comparisons

There is no universally accepted standard of care regimen for treating patients with R/R DLBCL who are not candidates for ASCT. The feasibility of an indirect treatment comparison of Pola+BR with comparators other than BR identified in the NICE scope was investigated based on the results of the systematic review (Appendix D).

However, no connected network of RCTs to other potential treatment options identified in the final scope could be established. As shown below only a limited number of studies were identified for the relevant population of R/R DLBCL patients ineligible for transplant, that did not form a connected network.

Figure 6: Network of evidence, black circles – ASCT ineligible and white circles ASCT eligible



In the review of single arm studies, only one study of R-GemOx was identified that included a group of patients that had received rituximab in a prior treatment line (rituximab pre-treated patients) (58). However, the study did not report KM data for rituximab pre-treated and naïve patients separately and it was therefore not feasible to conduct a robust match-adjusted treatment comparison.

B.2.9.1 Uncertainties in the indirect and mixed treatment comparisons

Not applicable.

B.2.10 Adverse reactions

- Overall, the safety and tolerability profile of pola+BR was acceptable within the context of this pre-treated population of patients with R/R DLBCL; the nature and frequency of the observed AEs were consistent with the known safety profiles of pola and of BR and in line with what might be expected in this patient population
- No new safety signals were identified relative to the known safety profile of pola, bendamustine, or rituximab
- The duration of exposure to study treatment was longer (median 5 vs. 3 cycles received), cumulative exposure higher, and more patients with R/R DLBCL completed their planned number of treatment cycles (46.2% vs. 23.1%) in the pola+BR arm compared to the BR arm because of fewer early discontinuations due to disease progression
- The safety profile of pola+BR in patients with R/R DLBCL, in the context of the clinically significant benefit observed and longer treatment duration, was acceptable and overall was consistent with that observed in the BR arm:
  - Grade ≥3 AEs were reported at a higher overall incidence in patients treated with pola+BR than with BR (84.6% vs. 71.8%), the difference driven mainly by a higher incidence of Grade 3 or 4 cytopenias (neutropenia, thrombocytopenia and anaemia) in the pola+BR arm.
  - Fewer patients died due to disease progression in the pola+BR arm compared to the BR arm (14 patients vs. 17 patients)
  - The overall incidence of serious AEs was almost similar in the pola+BR and BR arms (64.1% vs. 61.5%)
  - In the setting of longer treatment exposure in the pola+BR arm, treatment discontinuations due to AEs were more frequent in the pola+BR arm compared to the BR arm (33.3% vs. 15.4%)
- Of selected AEs/AEs to monitor defined as identified and potential risks of pola:
  - Neutropenia, thrombocytopenia, anaemia (all grade and Grade ≥3) were more frequently reported in the pola+BR arm compared to the BR arm but these were manageable
  - The incidence of infections (all grade, Grade ≥3 and serious) was similar between pola+BR and BR arms; four cases of infection in the pola+BR arm and three cases of infection in the BR arm were fatal.
  - Peripheral neuropathy events were, as expected, more frequently reported in the pola+BR arm compared to the BR arm (43.6% vs. 7.7%, all Grade 1 or 2). A single patient discontinued pola due to muscle atrophy (Grade 1) and 2 patients had their pola dose reduced due to Grade 2 PN

The safety evaluable population in the GO29365 study excluded two patients (one in each treatment arm) who did not receive any study treatment (84 patients in the DLBCL cohort; all six patients in the Phase Ib safety run-in and 78 patients in the Phase II randomisation

cohort). All patients who were administered at least one dose of study drug, received their intended treatment.

Overall, no new safety signals were noted with the addition of pola to BR relative to the known safety profile of Pola, and the safety and tolerability profile of the pola+BR regimen was acceptable within the context of this pre-treated population of patients with R/R DLBCL. An overview of the safety profile of pola+BR in GO29365 is summarised below.

Table 30: Overview of safety profile in GO29365

	Phase Ib	Phase II		Phase Ib/II
n, (%)	pola+BR n=6	pola+BR n=39	BR n=39	pola+BR N=45
Patients with at least one:				
Any AE	6 (100)	39 (100)	38 (97.4)	45 (100)
Grade 3–4 AE	5 (83.3)	33 (84.6)	28 (71.8)	38 (84.4)
Grade 5 AE	0	9 (23.1)	11 (28.2)	9 (20.0)
Serious AE	4 (66.7)	25 (64.1)	24 (61.5)	29 (64.4)
AE leading to discontinuation of:				
Pola	0	12 (30.8)	n/a	12 (26.7)
Any study drug	1 (16.7)	13 (33.3)	6 (15.4)	14 (31.1)
AE leading to modification/interruption of:				
Pola	2 (33.3)	22 (56.4)	n/a	24 (53.3)
Any study drug	3 (50.0)	28 (71.8)	19 (48.7)	31 (68.9)
AEs to monitor:				
Grade ≥2 peripheral neuropathy	0	6 (15.4)	2 (5.1)	6 (13.3)
Grade ≥3 neutropenia	2 (33.3)	23 (59.0)	18 (46.2)	25 (55.6)
Grade ≥3 hepatoxicity	0	2 (5.1)	1 (2.6)	2 (4.4)
Grade ≥3 infections and infestations	2 (33.3)	13 (33.3)	12 (30.8)	15 (33.3)
Total no. of deaths	2 (33.3)	23 (59.0)	28 (71.8)	25 (55.6)
Deaths due to PD	2 (100)	14 (60.9)	17 (60.7)	15 (64.0)

AE, adverse event; PD, progressive disease
CCOD: 30 April 2018

Extent of exposure to study treatment

Planned treatment of patients with R/R DLBCL given pola+BR or BR consisted of 6x21-day cycles during which a total of 6 doses of pola (1.8 mg/kg), 12 doses of bendamustine (90 mg/m^2), and 6 doses of rituximab (375 mg/m^2) were to be administered.

Patients with R/R DLBCL receiving pola+BR completed a median of 5 cycles (46.2% completing all 6 treatment cycles). Median treatment duration for each individual component of study treatment was approximately 2.42 months. Patients receiving bendamustine and rituximab completed a median of 3 cycles for both (23.1% completing all cycles of treatment).

The extent of exposure of patients to bendamustine and rituximab in the comparator BR arm was less than for patients in the pola+BR arm, largely due to a higher rate of early treatment

discontinuations in patients in the BR arm most frequently due to progressive disease. Patients in the BR arm received a median of 3 cycles of treatment; median treatment duration was 1.39 months.

Table 31: Exposure to polatuzumab vedotin, bendamustine and rituximab

n, (%)	Phase Ib	Phase II		Phase Ib/II
	pola+BR n=6	pola+BR n=39	BR n=39	pola+BR N=45
Pola				
Median tx duration, months (range)	2.4 (0.66-3.9)	3.2 (0.0-5.9)	NE	3.2 (0.0-5.9)
Median number of cycles (range)	4.5 (2-6)	5.0 (1-6)	NE	5.0 (1-6)
Mean cumulative dose, mg (SD)	628 (306)	599 (276)	NE	604 (277)
Median dose intensity, % (range)*	101.5 (87.2-103.7)	97.3 (58.4-112.7)	NE	99.5 (58.4-112.7)
Bendamustine				
Median tx duration, months (range)	2.4 (0.7-3.9)	3.2 (0.03-5.1)	1.4 (0.03-4.4)	3.2 (0.03-5.1)
Median number of cycles (range)	4.5 (2-6)	5.0 (1-6)	3.0 (1-6)	5.0 (1-6)
Mean cumulative dose, mg (SD)	1426 (607)	1439 (604)	989 (584)	1438 (598)
Median dose intensity, % (range)*	98.6 (78.1-101.7)	95.4 (53.4-102.1)	95.6 (63.6-103.1)	95.4 (53.4-102.1)
Rituximab				
Median tx duration, months (range)	2.4 (0.7-4.0)	3.2 (0.0-6.0)	1.4 (0.0-4.4)	3.2 (0.0-6.0)
Median number of cycles (range)	4.5 (2-6)	5.0 (1-6)	3.0 (1-6)	5.0 (1-6)
Mean cumulative dose, mg (SD)	3127 (1382)	3099 (1290)	2097 (1280)	3103 (1287)
Median dose intensity, % (range)*	98.5 (70.7-105.2)	94.7 (70.7-105.2)	96.7 (49-102.7)	99.4 (85.7-101.2)

*Adjusted for dose modification and delay
NE, not estimated; SD, standard deviation
CCOD: 30 April 2018

Common adverse events

All patients with R/R DLBCL treated with pola had at least one AE during the study. In the randomised Phase II, AEs of any grade were reported in 100% of patients (39/39) in the pola+BR arm and 97.4% of patients (38/39) in the BR arm.

The AEs by preferred term with a >10% higher incidence in the pola+BR arm compared to the BR arm were neutropenia, thrombocytopenia, anaemia, lymphopenia, diarrhoea, vomiting, upper abdominal pain, pyrexia, chills, pneumonia, hypokalaemia, hypoalbuminaemia, peripheral neuropathy, dizziness, peripheral sensory neuropathy, and pruritus.

Table 32: Most frequently reported adverse events (>10%) with pola+BR

n, (%)	Phase Ib	Phase II		Phase Ib/II
	pola+BR n=6	pola+BR n=39	BR n=39	pola+BR N=45
Total number of patients with at least one AE:	6 (100)	39 (100)	38 (97.4)	45 (100)
Blood and Lymphatic System Disorders				
Neutropenia	0	21 (53.8)	15 (38.5)	21 (46.7)

Anaemia	0	21 (53.8)	10 (25.6)	21 (46.7)
Thrombocytopenia	2 (33.3)	19 (48.7)	11 (28.2)	21 (46.7)
Febrile neutropenia	1 (16.7)	4 (10.3)	5 (12.8)	5 (11.1)
Leukopenia	0	5 (12.8)	5 (12.8)	5 (11.1)
Lymphopenia	0	5 (12.8)	0	5 (11.1)
Pancytopenia	1 (16.7)	2 (5.1)	0	3 (6.7)
Gastrointestinal Disorders				
Diarrhoea	2 (33.3)	15 (38.5)	11 (28.2)	17 (37.8)
Nausea	3 (50.0)	12 (30.8)	16 (41.0)	15 (33.3)
Constipation	1 (16.7)	7 (17.9)	8 (20.5)	8 (17.8)
Vomiting	1 (16.7)	7 (17.9)	3 (7.7)	8 (17.8)
Abdominal pain	1 (16.7)	4 (10.3)	4 (10.3)	5 (11.1)
Abdominal pain upper	0	5 (12.8)	2 (5.1)	5 (11.1)
General disorders and administration site conditions				
Fatigue	4 (66.7)	14 (35.9)	14 (35.9)	18 (40.0)
Pyrexia	2 (33.3)	13 (33.3)	9 (23.1)	15 (33.3)
Chills	1 (16.7)	4 (10.3)	3 (7.7)	5 (11.1)
Asthenia	1 (16.7)	4 (10.3)	6 (15.4)	5 (11.1)
Oedema, peripheral	0	2 (5.1)	3 (7.7)	2 (4.4)
Infections and infestations				
Pneumonia	2 (33.3)	5 (12.8)	4 (10.3)	7 (15.6)
Herpes zoster	1 (16.7)	1 (2.6)	2 (5.1)	2 (4.4)
Upper respiratory tract infection	2 (33.3)	2 (5.1)	1 (2.6)	4 (8.9)
Urinary tract infection	1 (16.7)	1 (2.6)	2 (5.1)	2 (4.4)
Metabolism and nutrition disorders				
Decreased appetite	2 (33.3)	10 (25.6)	8 (20.5)	12 (26.7)
Hypokalaemia	3 (50.0)	4 (10.3)	3 (7.7)	7 (15.6)
Hypoalbuminaemia	1 (16.7)	5 (12.8)	2 (5.1)	6 (13.3)
Hypocalcaemia	2 (33.3)	3 (7.7)	1 (2.6)	5 (11.1)
Hypomagnaesmia	2 (33.3)	1 (2.6)	4 (10.3)	3 (6.7)
Dehydration	2 (33.3)	2 (5.1)	0	4 (8.9)
Hypophosphataemia	1 (16.7)	2 (5.1)	1 (2.6)	3 (6.7)
Musculoskeletal and connective tissue disorders				
Back pain	0	2 (5.1)	4 (10.3)	2 (4.4)
Bone pain	0	0	0	0
Muscular weakness	0	2 (5.1)	1 (2.6)	2 (4.4)
Pain in extremity	0	2 (5.1)	2 (5.1)	2 (4.4)
Nervous system disorders				
Peripheral neuropathy	0	9 (23.1)	1 (2.6)	9 (20.0)
Dizziness	1 (16.7)	5 (12.8)	3 (7.7)	6 (13.3)
Peripheral sensory neuropathy	0	6 (15.4)	0	6 (13.3)
Headache	1 (16.7)	3 (7.7)	2 (5.1)	4 (8.9)
Paresthesia	0	2 (5.1)	0	2 (4.4)
Psychiatric disorders				
Anxiety	0	3 (7.7)	2 (5.1)	3 (6.7)
Respiratory, thoracic and mediastinal disorders				
Cough	1 (16.7)	6 (15.4)	8 (20.5)	7 (15.6)
Dyspnoea	0	3 (7.7)	2 (5.1)	3 (6.7)
Pleural effusion	1 (16.7)	2 (5.1)	4 (10.3)	3 (6.7)

Skin and subcutaneous disorders				
Pruritus	1 (16.7)	5 (12.8)	4 (10.3)	6 (13.3)
Rash	1 (16.7)	2 (5.1)	5 (12.8)	3 (6.7)
Vascular disorders				
Hypotension	0	3 (7.7)	2 (5.1)	3 (6.7)

Table only shows preferred terms reported in >10% of all patients with R/R DLBCL treated with pola+BR (at least 5/45 patients in Phase Ib/II combined)
CCOD: 30 April 2018

Adverse events by intensity

The majority of patients had at least one Grade ≥3 AEs. The proportion of patients with Grade 4 events was slightly higher in patients treated with pola+BR compared to the BR (37.8% vs. 25.6%).

A total of 202 Grade 3–5 AEs were reported in 38/45 patients (84.4%) with R/R DLBCL treated with pola+BR (Phase Ib/II combined). The most frequently reported Grade 3–5 AEs at a frequency of >5% of patients (in at least 3/45 patients with R/R DLBCL treated with pola+BR in Phase Ib/II combined) were neutropenia, thrombocytopenia, anaemia and lymphopenia.

Most frequently reported Grade 3–5 adverse events (>5%)

	Phase Ib	Phase II		Phase Ib/II
n, (%)	pola+BR n=6	pola+BR n=39	BR n=39	pola+BR N=45
Blood and Lymphatic System Disorders				
Neutropenia	0	18 (46.2)	13 (33.3)	18 (40.0)
Thrombocytopenia	1 (16.7)	16 (41.0)	9 (23.1)	17 (40.0)
Anaemia	0	11 (28.2)	7 (17.9)	11 (24.2)
Febrile neutropenia	1 (16.7)	4 (10.3)	5 (12.8)	5 (11.1)
Lymphopenia	0	5 (12.8)	0	5 (11.1)
Leukopenia	0	3 (7.7)	3 (7.7)	3 (6.7)
Gastrointestinal Disorders				
Diarrhoea	1 (16.7)	1 (2.6)	1 (2.6)	2 (4.4)
Nausea	0	0	0	0
General disorders and administration site conditions				
Fatigue	1 (16.7)	1 (2.6)	1 (2.6)	2 (4.4)
Asthenia	0	0	0	0
Infections and infestations				
Pneumonia	1 (16.7)	3 (7.7)*	1 (2.6)*	4 (8.9)
Herpes zoster	0	0	1 (2.6)	0
Metabolism and nutrition disorders				
Hypokalaemia	0	3 (7.7)	1 (2.6)	3 (6.7)
Hypophosphataemia	0	1 (2.6)	1 (2.6)	1 (2.2)
Respiratory, thoracic and mediastinal disorders				
Hypoxia	0	1 (2.6)	1 (2.6)	1 (2.2)
Skin and subcutaneous disorders				
Rash	0	0	3 (7.7)	0
Cardiac disorders				
Atrial fibrillation	0	0	1 (2.6)	0

AE preferred terms reported in >5% of all patients with R/R DLBCL treated with pola+BR (at least 3 patients out of total of 45 in Phase Ib/II combined)

*All AEs shown in this table of most frequently reported Grade 3-5 AEs (with onset from first dose of study drug through 90 days after last dose of study drug) were Grade 3 or 4 except for two fatal (Grade 5) events of pneumonia (one event each in pola+BR arm and BR arm of randomised Phase II)
CCOD: 30 April 2018

Serious adverse events

A total of 57 serious AEs (SAEs) were reported in 29/45 patients (64.4%) with R/R DLBCL treated with pola+BR (Phase Ib /II combined). The most common SAEs by preferred term were febrile neutropenia (five patients, 11.1%), pneumonia, and pyrexia (four patients each, 8.9%).

In the randomised Phase II, the overall incidence of SAEs was similar between the arms (64.1% [25/39 patients] pola+BR arm vs 61.5% [24/39 patients] BR). SAEs by preferred term or by SOC were generally balanced with no more than three patients in either arm accounting for any difference observed.

Deaths

A total of 25/46 patients (54.3%) with R/R DLBCL in the pola+BR arms had died at the time of the clinical cut-off. The main cause of death was disease progression (in 16/25 deaths [64.0%]).

In the randomised Phase II, fewer deaths overall had occurred in the pola+BR arm (23 deaths), compared to the BR arm (28 deaths); the difference can be accounted for by fewer deaths due to disease progression in the pola+BR arm (14 vs 17 patients) and fewer deaths due to AEs (9 vs 11 patients).

Three deaths due to AEs in the pola+BR arm (pneumonia, haemoptysis, and pulmonary oedema) and 4 deaths due to AEs in the BR arm (septic shock and pneumonia) occurred during the study treatment period, after first dose of study treatment and before treatment discontinuation or completion.

Table 33: Summary of deaths in GO29365

	Phase Ib	Phase II		Phase Ib/II
n, (%)	pola+BR n=6	pola+BR n=40	BR n=40	pola+BR N=46
Total number of deaths	2	23	28	25
Adverse events	0	9 (39.1)	11 (39.3)	9 (36.0)
Disease progression	2 (100)	14 (60.9)	17 (60.7)	16 (64.0)
No. of deaths ≤30 days of last dose	1	1	8	2
Adverse events	0	1(100)	3 (37.5)	1 (50.0)
Disease progression	1 (100)	0	5 (62.5)	1 (50.0)
No. of deaths >30 days of last dose	1	22	20	23
Adverse events	0	8 (36.4)	8 (40.0)	8 (34.8)
Disease progression	1(100)	14 (63.6)	12 (60.0)	15 (65.2)

CCOD: 30 April 2018

Selected adverse events to monitor in R/R DLBCL

This section describes the results of the analyses of selected AEs, defined as identified risks and potential risks of pola based on data available at the time of the assessment. Most patients with R/R DLBCL treated with pola+BR had at least one selected AE (95.6% [43/45 patients]). A higher incidence of selected AEs were reported in the pola+BR arm compared to the BR arm of the randomised Phase II (97.4% vs. 87.2%).

No protocol-defined adverse events of special interest (potential drug-induced liver injury, suspected transmission of an infectious agent by the study drug, TLS of any grade or second malignancies) requiring expedited reporting, even if non-serious, was reported for any patient in the GO29365 study.

Table 34: Selected adverse events in patients with R/R DLBCL

	Phase Ib	Phase II		Phase Ib/II
n, (%)	pola+BR n=6	pola+BR n=39	BR n=39	pola+BR N=45
Patients with at least one AE	5 (83.3)	38 (97.4)	34 (87.2)	43 (95.6)
Selected AEs/AEs to monitor category				
Neutropenia	2 (33.3)	25 (64.1)	17 (43.6)	27 (60.0)
Peripheral neuropathy	1 (16.7)	17 (43.6)	3 (7.7)	18 (40.0)
Anaemia	0	21 (53.8)	10 (25.6)	21 (46.7)
Thrombocytopenia	2 (33.3)	20 (51.3)	13 (33.3)	22 (48.9)
Infections and infestations	3 (50.0)	21 (53.8)	20 (51.3)	24 (53.3)
IRRs (during/within 24 hrs of end of infusion)	2 (33.3)	13 (33.3)	9 (23.1)	15 (33.3)
Hepatic toxicity	2 (33.3)	7 (17.9)	5 (12.8)	9 (20.0)
Fatigue asthenia	4 (66.7)	18 (46.2)	19 (48.7)	22 (48.9)
Hyperglycaemia	0	1 (2.6)	1 (2.6)	1 (2.2)
Renal toxicity	1 (16.7)	5 (12.8)	5 (12.8)	6 (13.3)
Gastrointestinal toxicity	4 (66.7)	32 (82.1)	25 (64.1)	36 (80.0)
Pulmonary toxicity	0	2 (5.1)	1 (2.6)	2 (4.4)
Joint pain, arthralgia, and skeletal pain	0	6 (15.4)	1 (2.6)	6 (13.3)
Alopecia	0	0	1 (2.6)	0
Cardiac toxicity and arrhythmias	1 (16.7)	0	5 (12.8)	1 (2.2)
Ocular toxicity	0	0	1 (2.6)	0
Dysguesia	2 (33.3)	1 (2.6)	0	3 (6.7)
Malignancies	1 (16.7)	1 (2.6)	2 (5.1)	2 (4.4)
Myelodysplastic syndrome	0	1 (2.6)	1 (2.6)	1 (2.2)

IRRs, infusion-related reactions
CCOD: 30 April 2018

Adverse events leading to treatment withdrawal or dose modification/interruption

Adverse events led to discontinuation of any study drug in 14/45 patients (31.3%) with R/R DLBCL treated with pola+BR (Phase Ib/II combined), compared with 6/39 patients (15.4%) treated with BR. In most cases (12/14) all drugs (Pola, bendamustine, and rituximab) were discontinued permanently at the same time (in two patients, bendamustine only was discontinued).

The most common events leading to discontinuation of any treatment were cytopenias, (8/14 discontinuations; predominantly Grade ≥3), mainly thrombocytopenia, neutropenia, and pancytopenia.

Adverse events that led to the discontinuation of pola in 12/45 patients (26.7%) with R/R DLBCL treated with pola+BR (Phase Ib/II combined); the most frequent AE by preferred term was thrombocytopenia (four patients), followed by neutropenia (two patients). All other AEs leading to pola withdrawal were unique events affecting single patients.

Drug interruption (dose delays/withholding of dose) was the most common action taken in response to AEs. Approximately one half of patients with R/R DLBCL had any drug interrupted (23/45 patients [51.1%]) due to an AE. The most frequent events leading to drug interruption were neutropenia and thrombocytopenia.

Table 35: Incidence of adverse events leading to discontinuation, drug interruption or dose modification of study drugs in patient with R/R DLBCL

	Phase Ib	Phase II		Phase Ib/II
n, (%)	pola+BR n=6	pola+BR n=39	BR n=39	pola+BR N=45
Any study drug				
Patients with AE leading to:				
Discontinuation	1 (16.7)	13 (33.3)	6 (15.4)	14 (31.1)
Dose reduction	1 (16.7)	7 (17.9)	4 (10.3)	8 (17.8)
Drug interruption (delay/withholding dose)	2 (33.3)	21 (53.8)	15 (38.5)	23 (51.1)
Polatuzumab vedotin				
Patients with AE leading to:				
Discontinuation	0	12 (30.8)	n/a	12 (26.7)
Dose reduction	0	2 (5.1)	n/a	2 (4.4)
Drug interruption (delay/withholding dose)	2 (33.3)	20 (51.3)	n/a	22 (48.9)
Bendamustine				
Patients with AE leading to:				
Discontinuation	0	14 (35.9)	6 (15.4)	14 (31.1)
Dose reduction	1 (16.7)	5 (12.8)	4 (10.3)	6 (13.3)
Drug interruption (delay/withholding dose)	1 (16.7)	18 (46.2)	15 (38.5)	19 (42.2)
Rituximab				
Patients with AE leading to:				
Discontinuation	0	12 (30.8)	6 (15.4)	12 (26.7)
Drug interruption (delay/withholding dose)	2 (33.3)	20 (51.3)	16 (41.0)	22 (51.3)

CCOD: 30 April 2018

Anti-drug antibodies directed against Pola

For all R/R DLBCL patients treated with Pola, the baseline prevalence of ADAs was 4.8% (2/42 evaluable patients). Post-baseline, ADAs were detected in 3/41 evaluable R/R DLBCL patients (7.3%) treated with Pola. All three patients had treatment-induced ADAs (i.e., ADA-negative at baseline or missing a baseline sample for ADA analysis and at least one positive

post-baseline ADA result); however, the emergence of ADAs to pola did not appear to impact efficacy; two of these patients had ongoing long-term responses.

Table 36: Incidence of anti-drug antibodies to Pola

n, (%)	Phase Ib pola+BR n=6	Phase II pola+BR n=40
Baseline prevalence of ADAs:		
Baseline evaluable patients	6	36
Patients with a positive sample at baseline	2 (33.3)	0
Patients with no positive samples at baseline	4	36
Post-baseline incidence of ADAs:		
Post-baseline evaluable patients	6	35
Patients positive for ADA	2 (33.3)	1 (2.9)
Treatment-induced ADA	2	1
Treatment-enhanced ADA	0	0
Patients negative for ADA	4	34
Treatment unaffected	2	0

ADA, anti-drug antibodies
CCOD: 30 April 2018

Adverse events of special interest

In the randomised Phase II, the overall incidence of Grade ≥3 AEs was higher in patients with R/R DLBCL treated with pola+BR than with BR; the difference between arms was driven mainly by cytopenias (neutropenia, thrombocytopenia, and anaemia) in the pola+BR arm. However, descriptive comparisons of incidences of AEs for pola+BR vs BR should take into account the longer median duration of exposure and higher cumulative exposure to study drug in patients with R/R DLBCL treated with pola+BR relative to the BR arm (median 3.2 months vs 1.4 months, with patients completing a median of 5 cycles vs 3 cycles of treatment), due in part to the higher frequency of early treatment discontinuation in the BR arm as a result of disease progression.

Fewer patients treated with pola+BR died due to progressive DLBCL compared to those patients treated with BR. There were 9 deaths due to AEs (Grade 5) in the pola+BR arm and 11 deaths dues to AEs in the BR arm, with no clear pattern of fatal events emerging in any arm. In the pola+BR arm, 4/9 fatal AEs were due to infections, with pneumonia the cause of death of two patients with R/R DLBCL. Deaths due to pneumonia and other infections were also reported in the BR arm.

Neutropenia, an identified risk of Pola, was among the most commonly observed toxicities in patients treated with pola+BR in the study. While neutropenia events, including febrile neutropenia were mainly Grade 3 or 4, they were adequately managed by delaying study drug administration and use of G-CSF support, as mandated by the protocol (80).

Neutropenia events were reversible and did not lead to a high rate of study treatment discontinuation or drug dose reduction. None of the events of neutropenia were fatal.

Thrombocytopenia and anaemia are potential risks of Pola. Grade 3 or 4 thrombocytopenia and anaemia events were frequently reported in patients with R/R DLBCL (40.0% and 24.4% respectively). As with neutropenia, thrombocytopenia was manageable with treatment delays of all study drugs and dose reduction (bendamustine only). Grade ≥3 anaemia usually resolved without specific action taken to the study drug administration.

The incidence of infections (all grade, Grade ≥3, and serious) was comparable between the pola+BR and BR arms. Four cases of infection in the pola+BR arm and three cases of infection in the BR arm were fatal.

Peripheral neuropathy, including peripheral sensory and/or motor neuropathy, is an identified risk of Pola, consistent with the mechanism of action of MMAE and was reported in 39% patients receiving pola+BR (Grade 1: 21%; Grade 2: 18%] vs 3% (all Grade 2) in those receiving BR. However, PN infrequently led to study treatment discontinuation (1 patient) or drug dose reduction (two patients). Moreover, patient-reported severity of PN-related symptoms as captured by mean score of responses to items on the TINAS questionnaire were generally reported to be mild across the majority of the treatment period in both the pola+BR and BR arms (see Section 2.6.6).

Other selected events specifically analysed as potential risks of pola included hepatic toxicity events and diarrhoea, which were mainly Grade 1 or 2 and were tolerated, requiring no specific action to be taken with study treatment. No cases of potential drug-induced liver injury (according to Hy's Law) were reported.

Overall, the combination of 1.8 mg/kg pola with BR for 6 cycles in a pre-treated R/R DLBCL population was acceptable, and consistent with the known safety profiles for each treatment, with no new safety signals identified.

B.2.11 Ongoing studies

The study is ongoing and is scheduled to end at the time point at which all patients enrolled in the study have either had at least 2 years of follow-up from the time of the treatment completion visit or have discontinued the study.

[redacted]

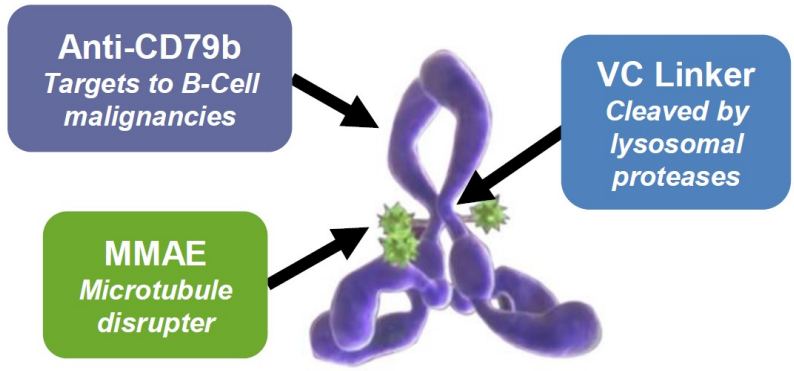
Two cohorts were added to confirm the efficacy, safety, and pharmacokinetics of the new lyophilised formulation of pola in combination with BR (Arm G [N=42] and Arm H [N=60]). [redacted].

B.2.12 Innovation

Antibody-drug conjugates (ADCs) are an innovative class of anticancer treatment agents that comprise a monoclonal antibody targeted to a tumour antigen, a chemical linker, and a potent cytotoxic agent, which is often too toxic to be given as conventional chemotherapy (86). The characteristics of the linker component of an ADC are key to ensuring that the ADC molecule remains relatively stable in the circulation to prevent non-specific release of the cytotoxic agent, yet allowing the linker to be cleaved to release the cytotoxin within a specific microenvironment within the tumour cell (87). Improvements to linker technology associated with highly potent cytotoxic payloads have permitted the development of targeted ADCs that offer meaningful efficacy while minimising side effects (88).

Polatuzumab vedotin is the only ADC targeting CD79b. In doing so it preferentially delivers a potent anti-mitotic agent (monomethyl auristatin E [MMAE]) to B cells, resulting in anti-cancer activity against B cell malignancies. The pola molecule consists of MMAE covalently attached to a CD79b directed humanised IgG1 monoclonal antibody through a protease cleavable linker, maleimidocaproyl valine citrulline p aminobenzyloxycarbonyl (1-3).

Figure 7: Polatuzumab-vedotin

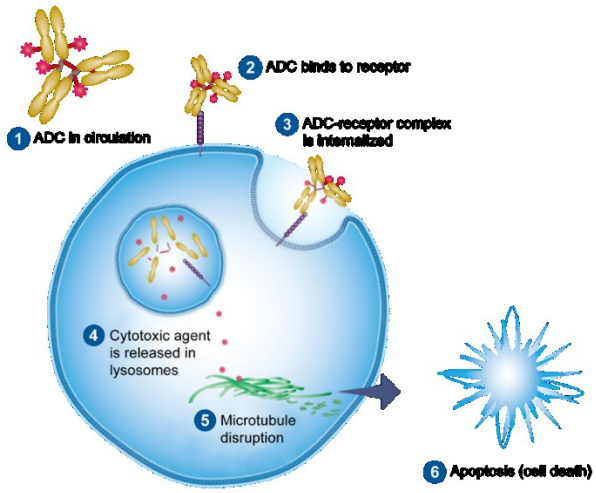


CD79b is a signalling component of the B cell receptor expressed on the surface of B cells and is found in abundance in people with DLBCL. As such, CD79b expression is restricted to

normal cells within the B cell lineage (with the exception of plasma cells) and malignant B-cells; therefore targeted delivery of MMAE is expected to be restricted to these cells (3).

Antibodies bound to CD79b are rapidly internalised, which makes CD79b ideally suited for the targeted delivery of cytotoxic agents (2). After internalisation, the conjugate is cleaved by lysosomal enzymes to release MMAE, which binds to tubulin, disrupts the microtubule network, and results in the inhibition of cell division and cell growth, and induction of apoptosis (3-5). MMAE has a mechanism of action that is similar to vincristine, a cytotoxic agent used in DLBCL therapy.

Figure 8: Mechanism of action of antibody-drug conjugates



Although R-CHOP is the standard of care for patients with previously untreated DLBCL, approximately 30–50% of patients are not cured by this treatment, depending on the stage of disease and prognostic index (37) (see Section B.1.3.2). While high-dose chemotherapy followed by ASCT offers a second chance for cure in some of those patients, approximately half of patients will not respond to subsequent therapy because of refractory disease (28), and a significant number are ineligible for this intensive therapy because of age, comorbidities or chemotherapy-insensitive disease (24, 28). Therefore, there is a significant need for new and more effective treatments with at least acceptable, if not superior, safety and tolerability profiles for patients with DLBCL that relapses or is refractory to treatment.

In the randomised phase of GO29365, pola+BR has clearly demonstrated a significant survival benefit in comparison to BR across all lines of therapy in the R/R DLBCL setting (see Section B.2.6.3; [redacted]), while a clinically meaningful benefit was also observed in terms of IRC- and investigator-assessed PFS. A high CR rate (40%) was also observed with Pola+BR treatment, which has been associated with improved outcomes in DLBCL and may in part explain the durable responses of at least 20

months observed in a proportion of patients receiving pola+BR in the GO29365 study. In view of the survival advantage, high CR rate and prolonged disease control, pola+BR represents a major therapeutic innovation for a patient population with high unmet medical need.

The pola treatment regimen consists of an intravenous infusion of 1.8 mg/kg pola every 21 days for 6 cycles; the first infusion takes 90 minutes, which if tolerated can then be followed by 30 minute infusions for subsequent doses. This infusion duration, coupled with the fact that the individual components of the pola+BR regimen can be administered in any order (unlike some other chemotherapy combinations) ensures optimal administration of pola+BR with same day delivery, negating the need for any additional service provision or healthcare resource. Furthermore, administration of pola for 6 cycles may improve tolerability by reducing PN risks versus longer treatment durations and higher doses (84).

The potential of pola+BR to address the high unmet need in DLBCL was recognised by the EMA and FDA when PRIME and Breakthrough Therapy was granted in June 2017 and September 2017 respectively, which was followed by FDA approval in June 2019. Moreover, pola+BR for the treatment of adult patients with R/R DLBCL was granted a Promising Innovative Medicine (PIM) designation by the Medicines and Healthcare Products Regulatory Agency (MHRA) in December 2018, indicating that this treatment combination has the potential to address an unmet clinical need for patients with a life-threatening condition. In June 2019, the MHRA issued a Positive Final Scientific Opinion for the pola+BR Early Access to Medicines Scheme (EAMS) for adult R/R DLBCL patients who are ineligible for transplant. The lyophilised formulation of pola is being used for this EAMS.

B.2.13 Interpretation of clinical effectiveness and safety evidence

The Phase Ib/II study GO29365 evaluated the efficacy and safety of pola 1.8 mg/kg in combination with rituximab or obinutuzumab plus bendamustine in relapsed or refractory follicular lymphoma or DLBCL. **This submission focuses on the combination of pola+BR in patients with R/R DLBCL only in accordance with the proposed marketing authorisation indication.**

Polatuzumab vedotin has previously demonstrated an acceptable safety and tolerability profile in patients with R/R DLBCL as a monotherapy in a Phase I study (1) as well as clinical efficacy in combination with rituximab in the Phase II Romulus study, with an overall response rate of 54% (median duration of follow-up 17.4 months). The Phase II Romulus study also evaluated the efficacy of a second ADC in combination with rituximab – pinatuzumab vedotin (pina). Following this study, pola was selected for future development

in NHL, based on a longer duration of response and an overall benefit/risk ratio favouring pola in combination with rituximab compared with pina with rituximab (89).

There is no universal standard of care regimen for patients with R/R DLBCL who are ineligible for transplant or who relapse after transplant, as no prior randomised trials have established the superiority of one regimen over another for this population. For instance, one of the largest studies to date, a randomised Phase III study of inotuzumab ozogamicin + rituximab compared with investigator's choice (BR or gemcitabine + rituximab) that included 306 patients with R/R DLBCL, failed to show a benefit in terms of ORR, PFS or OS for patients in the experimental compared to control arms (59). It is noteworthy that 80% of control patients in this study received BR and 20% received gemcitabine + rituximab, perhaps suggesting that investigators perceive bendamustine to have greater efficacy than gemcitabine

Cross trial comparisons of survival outcomes between different regimens have significant limitations in terms of differences in enrolled or observed populations such as numbers of refractory vs relapsed patients, numbers of prior lines of therapy, and when trials were conducted (some earlier trials occurred at a time when a significant proportion of patients had not been exposed to rituximab in first-line therapy). Thus, it remains extremely difficult to definitively conclude that regimens based on platinum or gemcitabine are truly superior to BR in the contemporary setting for transplant-ineligible R/R DLBCL patient population without a randomised trial.

The combination of BR has been shown to be active in transplant-ineligible patients with R/R DLBCL with a manageable haematologic toxicity profile; median PFS has been reported to be 3.5–6.7 months and median OS reported to be 6.7–9.5 months (59-62). Furthermore, guidelines such as those put forth by the NCCN include BR as a treatment option for patients with DLBCL who are not candidates for high-dose therapy with ASCT (34), therefore BR was chosen to be combined with pola and is considered to be a relevant comparator. Furthermore, the bendamustine backbone was selected to minimise the overlapping toxicity of PN that may occur with platinum-based therapies. The bendamustine dose of 90 mg/m^2 on Days 1 and 2 in combination with rituximab was selected due to concerns of additive myelotoxicity of bendamustine at 120 mg/m^2 when used in combination with rituximab. This dose recommendation was also supported by recommendations established by an international consensus panel (82).

The randomised phase of GO29365 demonstrated a clear and consistent clinically meaningful benefit of pola+BR in a pre-treated R/R DLBCL population. The primary endpoint of IRC-assessed CR rates by PET-CT at the primary response assessment was significantly

higher in the pola+BR arm compared to the BR arm (40.0% vs. 17.5%; Δ22.5%, p=0.0261). Most patients who responded to treatment achieved a CR. Objective response rates as measured by the IRC were also higher in the pola+BR arm compared to the BR arm (45.0% vs.17.5%; Δ27.5%, p=0.0069). Of particular interest, a proportion of patients receiving pola+BR had durable responses; [redacted] There were no obvious clinical predictors of response, as all subgroups examined appeared to benefit, including patients with refractory disease and patients who have received multiple prior lines of therapy. It is also notable that at an advisory board meeting, UK clinical experts commented that the CR rate seen in the control arm of GO29365 is in-line with what they would expect to see with other current treatment options for this population (35).

GO29365 is the first randomised study to show survival benefit in transplant-ineligible R/R DLBCL patients as a clinically meaningful benefit was seen in PFS and OS for pola+BR compared with BR. At the latest data cut (11 October 2018), the risk of death was reduced by [redacted] in patients treated with pola+BR compared to BR ([redacted]), with a median OS of [redacted] with pola+BR compared to [redacted] with BR alone.

Forty patients were enrolled into each treatment arm of the randomised Phase II cohorts of GO29365, with the sample size being sufficient to demonstrate a benefit in OS. The number of patients enrolled was calculated to provide meaningful estimates; 40 patients randomised to each treatment arm provided a margin of error not exceeding 17% for the 95% exact CIs for estimation of the true CR rate (primary efficacy endpoint), with at least an 87% chance of observing at least one adverse event with a true incidence of ≥5% (primary safety endpoint). The robustness of the benefit of pola+BR in R/R DLBCL is demonstrated by consistent efficacy findings between IRC and investigator and assessment, while OS benefits with pola+BR were observed across different subgroups defined based on demographic and baseline disease characteristics, duration of response to last therapy and cell of origin, with no difference between ABC- and GCB-like DLBCL.

The CHMP acknowledged that based on the April 2018 CCOD, the benefit-risk profile of pola+BR observed in GO29365 is positive and it was therefore acceptable to file for marketing authorisation based on these data.

Randomisation and stratification are methods used to construct comparable treatment arms by reducing the baseline imbalance over known and unknown factors. However, some baseline imbalance may arise by chance, as seen in the BR treatment arm where more

patients with bulky disease, categorised as IPI high risk and, ECOG PS 2 and refractory to last prior treatment were enrolled compared with the pola+BR arm. However, stratified multiple Cox regression analysis adjusting for this potential imbalance in baseline characteristics also supported the robustness of the treatment effect of pola+BR with the OS HR remaining in the 0.24–0.78 range post-adjustment.

The combination of pola+BR was associated with additional toxicity as expected when an additional therapeutic agent is added to the BR combination, but for the most part was clinically manageable; no new safety signals were identified relative to the known safety profile of pola, bendamustine, or rituximab. The toxicity profile observed with pola+BR in the GO29365 study is also in keeping with adverse events observed with other ADCs for NHL (90). Moreover, the tolerability of the pola+BR combination is demonstrated by the fact that more patients completed all six treatment cycles than those patients in the BR arm (46.2% vs 23.1%). A higher rate of Grade 3–4 cytopenias was observed with pola+BR compared with BR, but this did not result in a higher risk of infection or need for transfusion. This higher rate of AEs was likely contributed to by increased susceptibility in these pre-treated patients, as well as disease progression and subsequent anti-lymphoma therapy in this high-risk population of R/R DLBCL.

Peripheral neuropathy is a recognised toxicity associated with MMAE based antibody-drug conjugates, and was closely monitored during GO29365. The majority of PN observed was low grade and reversible, and led to few patients experiencing dose reduction or delay. Furthermore, patient-reported severity of PN-related symptoms as captured by mean score of responses to items on the TINAS questionnaire were generally reported to be mild across the majority of the treatment period in both the pola+BR and BR arms for patients with R/R DLBCL.

Conclusions

On the basis of the data from the randomised Phase II GO29365 study, the overall benefit-risk assessment of pola+BR in patients with R/R DLBCL ineligible for transplant is considered to be positive. The benefits of durable and higher PET-based CR response rates after completion of treatment and longer median PFS and OS with pola+BR relative to BR are significant and clinically meaningful. Moreover, the analysis of the efficacy findings between investigator and IRC were consistent, thus further supporting the robustness of the benefit of pola+BR in R/R DLBCL.

Overall, pola+BR offers a new treatment option for transplant ineligible patients with a high unmet medical need, who may be rapidly progressing and need urgent disease control. Furthermore, the safety profile of pola+BR is considered to be acceptable as the additional

toxicities observed with the addition of pola to BR are manageable and readily monitored, therefore this regimen may also provide an alternative treatment option for those patients who are unable to tolerate intensive treatments after progressing on platinum-based salvage regimens or who are refractory to or relapse following ASCT.

Table 37: End-of-life criteria

Criterion	Data available	Reference in submission (section and page number)
The treatment is indicated for patients with a short life expectancy, normally less than 24 months	The prognosis for patients with DLBCL who relapse is poor, with median survival 10 months and less than half of patients (41%) who relapse still alive at one-year post relapse. Age is an important prognostic indicator in DLBCL patients who relapse; patients aged ≥65 years have a poorer prognosis compared to those aged <65 years (23). Outcomes are even worse for patients refractory to first-line therapy. The SCHOLAR-1 study showed that median overall survival was just 6.3 months for these patients, with 22% of patients alive at 2 years (24). The median OS for the comparator arm (BR) in the GO29365 study was [redacted] The average survival estimated in the economic analysis was 12.2 months.	Section B.1.3.1 (page 13) Appendix J1.1
There is sufficient evidence to indicate that the treatment offers an extension to life, normally of at least an additional 3 months, compared with current NHS treatment	The estimated mean OS gain of Pola+BR over BR in the model was 4.1 years.	Appendix J1.1

B.3 Cost effectiveness

Summary of Cost-Effectiveness Analysis for Pola+BR vs BR

- No published economic analyses were identified for polatuzumab vedotin or the comparators identified in the NICE final scope in R/R DLBCL, therefore a *de novo* cost-effectiveness model was developed.
- A partitioned survival model was built with three mutually exclusive health states: PFS, PD and Death. The proportion of alive patients falling into PFS or PD was defined by extrapolated PFS and OS survival curves from GO29365.
- The model possesses a cycle length of 1 week, a lifetime (45 year) time horizon and costs and benefits discounted at 3.5% as per the NICE reference case (91).
- In the base case, BR was selected as the comparator to Pola+BR, as it was deemed representative of current standard of care for transplant-ineligible R/R DLBCL patients in the UK, and a robust comparison to Pola+BR using data from the randomised GO29365 trial was possible.
- Survival analysis was performed to identify appropriate parametric survival functions to extrapolate PFS and OS (92). Standard survival functions and cure-mixture models were explored, on the basis of clinical expert opinion and evidence from the literature that patients who achieve 2-years PFS following treatment are likely to experience long-term survival aligned with that of the age- and sex-matched general population.
- Based on visual fit to the GO29365 KM data and plausibility of the long-term extrapolations, cure-mixture models using the generalised gamma distribution were selected for the base case for PFS and OS. The OS extrapolation was informed by the 'cure fraction' for PFS, on the basis that achievement of long-term PFS is an indicator of long-term survival.
- Base case utilities were modelled by health state and were sourced from the recent manufacturer submission for axicabtagene ciloleucel in R/R DLBCL (69). AE disutilities were applied based on CTCAE Grade ≥3 AEs from GO29365 and were sourced from recent NICE appraisals. Patients who remained in PFS for >2 years reverted to age- and sex-matched general population utilities (93).
- Categories of costs included in the model were acquisition, administration, supportive care and subsequent treatment costs. Costs were sourced from NHS Reference Costs 2017–18, PSSRU 2018, and the BNF and eMIT (both accessed June 2019). Patients who remained in PFS for >2 years no longer accrued supportive care costs.
- The base case acquisition costs for polatuzumab vedotin were based on the availability of both 140 mg and 30 mg vials, the latter of which is due to be available in [redacted]. Alternative scenarios, including interim arrangements with compounding services, are explored in scenario analyses.
- The base case results of the analysis demonstrated that Pola+BR is cost-effective vs BR at an ICER of £26,877 per QALY. This was driven by the substantially greater QALY gain vs BR.
- The DSA and scenario analyses demonstrated the robustness of the base case results. DSAs identified no input parameters that resulted in a range of ICER values greater than 12% of the base case. Scenario analyses identified that in general, the ICER value remained relatively unchanged, except where survival modelling extrapolations of reduced clinical plausibility were used.
- Variation in the PSA from the base case was observed, which may be attributed to the parameter uncertainty around the use of the generalised gamma distribution for modelling survival and the independent variation of input parameters for long-term survival and long-term remission.
- The results of the cost-effectiveness analysis support that Pola+BR is a cost-effective treatment option vs BR, which may be considered representative of standard of care for transplant-ineligible R/R DLBCL patients in the UK.

B.3.1 Published cost-effectiveness studies

No published cost-effectiveness analyses were available for the technology or comparator regimens identified in the scope. Further details on the methodology and results of the SLR are presented in Appendix G.

B.3.2 Economic analysis

As noted in Section B.3.1, no prior cost-effectiveness analyses that assessed Pola+BR in patients with R/R DLBCL who are ineligible for transplant were identified in the SLR. A *de novo* economic model was therefore built to inform decision making.

B.3.2.1 Patient population

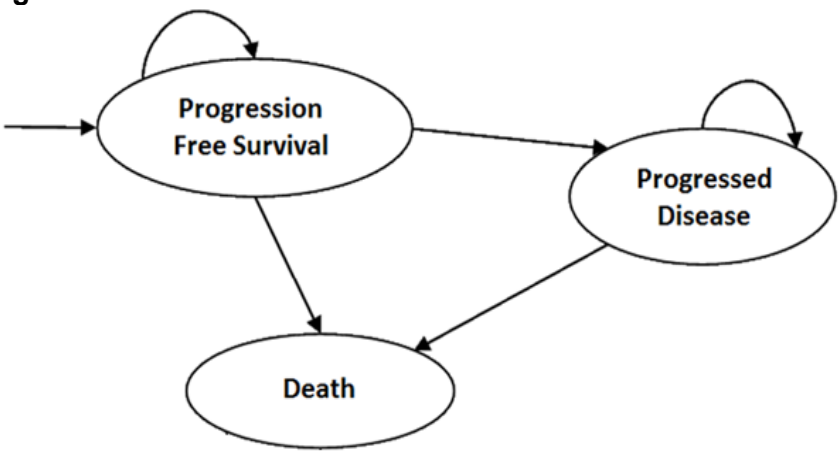
Patients with R/R DLBCL ineligible for SCT were included in the economic evaluation. This patient population is in line with the expected licensed indication for Pola+BR, the decision problem addressed in this submission (see Section B.1), and the patient population included in the GO29365 trial.

B.3.2.2 Model structure

An Area-Under-the-Curve (AUC) or partitioned survival analysis model was developed in Microsoft Excel. The AUC model structure is in line with NICE Decision Support Unit (DSU) guidance (94) and is consistent with previous appraisals conducted in this disease setting (67, 69, 70). An important benefit of the partitioned survival approach is that modelling of OS and PFS is based on study-observed events, which is expected to accurately reflect disease progression and the long-term expected survival profile of patients treated with Pola+BR.

The model includes three mutually exclusive health states: “Progression-Free Survival (PFS)”, “Progressed Disease (PD)” and “Death” as shown in Figure 9.

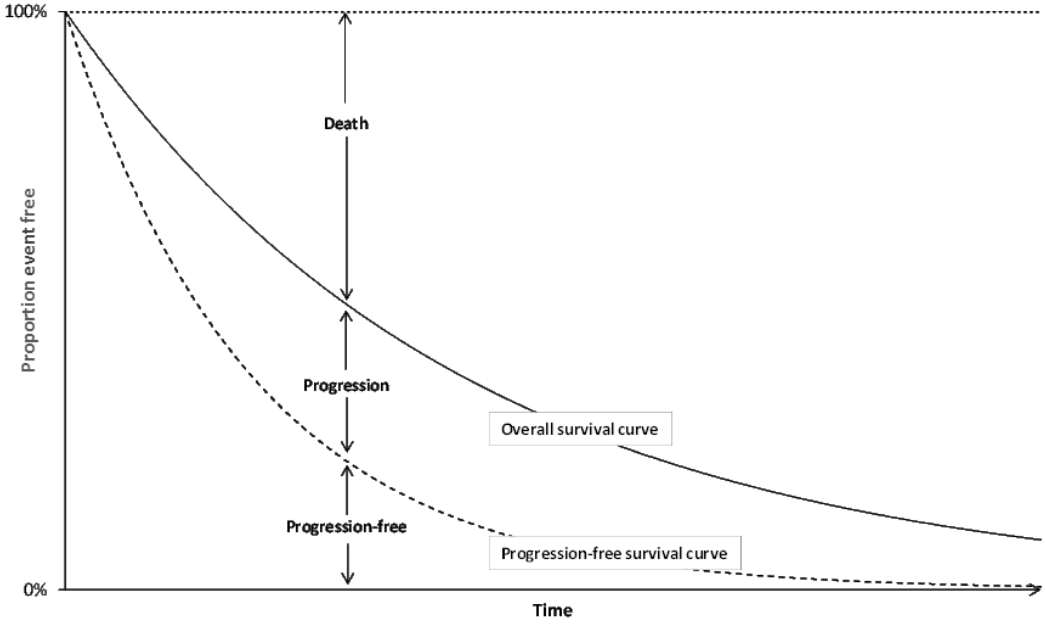
Figure 9: Economic model structure



All patients enter the model in the PFS health state and remain in this health state until they progress. Upon progression, patients either transition into the PD health state or enter the absorbing health state of Death. Patients in the PD health state stay in that health state until Death. Patients cannot transition to an improved health state (i.e. from PD to PFS); a restriction that is consistent with previous economic modelling in oncology.

The proportion of patients in each health state at any time is defined by the partitioning of alive patients alive into “PFS” and “PD” at discrete time points, based on the PFS and OS survival curves from GO29365. The proportion of patients falling into the “PD” health state is the difference between OS and PFS, as illustrated in Figure 10. The “PD” health state also includes any further lines of treatment, as described in Section B.3.5.5.

Figure 10. Example of a partitioned survival model



Features of the *de novo analysis*

The model has been designed to use a weekly cycle, with the proportion of patients in each health state calculated each week. Transition between health states can occur at any time within the cycle, therefore a half-cycle correction was applied to account for the over- or under-estimation of transitions occurring at the beginning or end of the cycle.

Costs and health-related utilities are allocated to each health state and multiplied by state occupancy to calculate the weighted costs and quality adjusted life years (QALYs) per cycle. Costs and health outcomes are discounted at 3.5% and the perspective of the NHS and Personal Social Services (PSS) is assumed, as per the NICE reference case (91). The model inputs for the Pola+BR versus BR comparison (efficacy, safety and tolerability) are based on the results of the randomised phase II study GO29365 (see Section B.2).

The economic model uses a time horizon of 45 years, which is considered to be appropriate as a lifetime horizon for patients with R/R DLBCL, taking into account the average age of patients at the start of treatment (69 years). This time horizon ensures all benefits and costs accrued by patients are captured from start of treatment to death, and is consistent with the anticipated survival based on the economic model, with less than approximately 1% of patients still alive at 45 years for Pola+BR.

Model results are reported in terms of costs per QALY gained, reflecting the decision problem.

An overview of how the economic analysis for Pola+BR compares to other NICE appraisals in R/R DLBCL is provided in Table 38 below.

Table 38. Features of the economic analysis

	Previous appraisals				Current appraisal
Factor	**TA306 (67)**	**TA567 (70)**	**TA559 (69)**	**Chosen values**	**Justification**
Time horizon	Lifetime (23 years)	Lifetime (46 years)	Lifetime (44 years)	Lifetime (45 years)	To capture costs and benefits over a lifetime horizon, as per the NICE reference case (91).
Treatment waning effect?	No (PFS: log-normal; OS: log-normal)	No (PFS: CMM, log-normal; OS: CMM, log-normal)	No (PFS: Gompertz; OS: CMM, Weibull)	No (PFS: CMM generalised gamma; OS: CMM generalised gamma informed by PFS cure fraction)	Survival distributions for PFS and OS were selected based on model fit statistics, visual fit and long-term clinical validity; full justification is presented in Section B.3.3.
Source of utilities	Literature values (PFS: 0.76; PD: 0.68)	Trial based (PFS: 0.83; PD: 0.71)	Trial based (PFS: 0.72; PD: 0.65)	Values based on previous TAs (PFS: 0.72; PD: 0.65)	Utilities aligned with values presented in TA559, which were sourced from a representative patient population (ZUMA-1) of R/R DLBCL patients using the EQ-5D. Full justification is presented in Section B.3.4
Source of costs	Clinician survey on type and frequency of resource use in DLBCL. Unit costs from BNF, NHS	Type and frequency of resource based on clinical trial and NICE guideline (NG52) (32).Interven	Type and frequency of resource based on TA306 for SOC (67). Intervention incurred additional	Based on TA306 for SOC and intervention (67). Unit costs from NHS reference costs,	Resource use based on accepted values from previous NICE appraisal. NHS Reference Costs and PSSRU are standard sources of UK-relevant costs. See

	reference costs and PSSRU.	tion incurred additional service costs. Unit costs from eMIT, BNF, NHS reference costs and PSSRU.	service costs. Unit costs from eMIT, NHS reference costs and PSSRU.	PSSRU and BNF.	Section B.3.5 for full justification.

BNF, British National Formulary; CMM, cure-mixture model; eMIT, drugs and pharmaceutical electronic market tool; EQ-5D, EuroQol Five Dimensions; OS, overall survival; PD, progressed disease; PFS, progression-free survival; PSSRU, Personal Social Services Research Unit; SOC, standard of care

B.3.2.3 Intervention technology and comparators

Intervention – Pola+BR

The model intervention is Pola+BR, as described in Section B.1.2. Pola+BR was modelled to follow the dosing schedule implemented in GO29365, see Section B.2.3, and in accordance with the anticipated marketing authorisation (7).

Comparators – BR (base case) and R-GemOx (scenario)

In the base case, Pola+BR was compared to BR, the comparator in the randomised GO29365 study (see Section B.2). A scenario analysis was also performed in which R-GemOx was included as a comparator, under the assumption of equivalent efficacy to BR.

As discussed in Sections B1.1 and B.1.3, there is no universally accepted standard of care regimen for R/R DLBCL patients not eligible for SCT, with patients typically prescribed one regimen from a range of available gemcitabine and/or platinum-based therapies, or BR. Choice of chemotherapy in SCT-ineligible patients is dependent upon clinician preference (35), and there is no strong evidence that one regimen is superior to another (see Section B.1.3.2).

In the NICE final scope, a number of potential regimens used in NHS clinical practice were identified (R-GemOx, R-Gem, R-P-MitCEBO and [R])DECC), in addition to BR (95). However, in the clinical SLR, studies were only identified for R-GemOx, please see Appendix D. The possibility of performing a robust indirect comparison between Pola+BR and R-GemOx was found to be unfeasible, as no connected network of randomised studies was identified (see Section B.2.9). A robust unanchored comparison was similarly found to be not feasible due to significant or unknown differences in prognostic factors in the study populations for GO29365 and captured R-GemOx studies, including proportion of refractory patients, prior rituximab exposure and number of prior lines of treatment. A lack of robust and comparable studies assessing therapies for DLBCL is an inherent limitation of the disease area, as identified by the NICE technology appraisals for tisagenlecleucel and

axicabtagene ciloleucel, in which the indirect comparisons performed to chemotherapy (necessitated by the single-arm trials for the interventions) were deemed to be associated with substantial bias, significantly limiting the use of the comparative evidence to inform decision making (69, 70).

As such, given the lack of evidence demonstrating superiority of one chemotherapy regimen over another, clinical opinion that the range of available chemotherapy regimens for DLBCL are considered to be equally effective, and the ability to make a robust comparison with Pola+BR using the data from the GO29365 randomised controlled trial, BR was selected as the comparator to Pola+BR in the base case analysis.

In order to supplement the evidence presented in the base case, a scenario analysis was also performed in which R-GemOx was included as an additional comparator. This scenario assumed equivalent efficacy with BR, which is supported by recent real-world evidence demonstrating no OS difference between people with R/R DLBCL treated with BR and R-GemOx. Limited UK-based data are available, however, in a cohort of DLBCL patients from the US Veterans Health Association database that had been treated with either second-line BR or R-GemOx, and followed-up for 11.3 and 11.7 months, respectively, median OS was estimated at 11 months for BR and 13 months for R-GemOx. Univariate and multivariate analyses both found no significant difference in OS between either regimen (96).

In addition to this recent real-world data, reported outcomes in prospective studies fall into a similar range. In a Phase II study based in France, Mounier et al. reported median PFS and OS values for R-GemOx for transplant-ineligible R/R DLBCL patients who had previously received rituximab of 4 months and 8 months, respectively (58). More recently, Hong et al. reported median PFS and OS values for transplant-ineligible R/R DLBCL patients treated with BR of 3.9 months (95% CI: 2.4–4.5) and 6.7 months (95% CI 4.7–8.7), respectively (60). The GO29365 study BR arm showed a median PFS (investigator-assessed) of 2.0 months (95% CI: 1.5–3.7) and OS of 4.7 months (95% CI: 3.7–8.3) (78).

Finally, BR and R-GemOx are expected to acquire similar acquisition costs, as presented in Table 39. Therefore, the base case analysis for Pola+BR versus BR, supplemented by the scenario including R-GemOx as an additional comparator, is considered to provide a representative analysis of the cost-effectiveness of Pola+BR vs standard of care chemotherapy regimens used in the UK for R/R DLBCL patients who are ineligible for transplant.

Table 39. Drug acquisition costs for BR and R-GemOx

Regimen	Drug	Cost per treatment cycle[a, b]	Total cost per treatment cycle[c]
BR	Bendamustine	£95.95	£677.47
BR	Rituximab	£581.52	
R-GemOx	Gemcitabine	£17.84	£613.24
R-GemOx	Oxaliplatin	£13.87	
R-GemOx	Rituximab	£581.52	

[a]Costs sourced from BNF 2019 (rituximab, bendamustine) (97) and eMIT 2019 (gemcitabine, oxaliplatin) (98); [b]Dosing regimens sourced from GO29365 (BR) and Mournier 2013 (R-GemOx) (58); [c]Full details for how the acquisition costs for each regimen have been calculated can be found in Section B.3.5.2.
BR, bendamustine + rituximab; R-GemOx, rituximab + gemcitabine + oxaliplatin

B.3.3 Clinical parameters and variables

The primary source of clinical data for the Pola+BR and BR arms of the economic model is the GO29365 study. Data from the latest available data cut (October 2018) have been used to inform the clinical parameters for PFS and OS (results data for which are reported in Section B.2.6.3). For treatment duration and treatment-related AE rates, the latest available data were from the clinical cut-off date of April 2018. All patients had completed treatment with Pola+BR or BR by this date.

B.3.3.1 Survival inputs and assumptions

PFS and OS results from GO29365 were extrapolated to the model lifetime time horizon, as lifetime results are not available for patients who participated in this study. NICE DSU Technical Support Document (TSD) 14 (92), which provides guidance on survival analysis, was followed to identify appropriate parametric survival models to model both outcomes. Specifically, the following points were performed:

1. Visual inspection of the OS and PFS log-cumulative hazard plots, based on patient level data for the two arms of GO29365, 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 GO29365
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 and the expectations of clinical experts

For both PFS and OS, application of standard parametric survival models (exponential, Weibull, Gompertz, log-normal, generalised gamma and log-logistic) was explored, in addition to the fitting of cure-mixture models. Cure-mixture models represent an approach to modelling cancer therapies for which there is evidence to support that a proportion of treated patients enter long-term remission, and subsequently experience mortality aligned with that of the general population. This is reflected in the parameterisation of cure-mixture models, which assume the patient population comprises two subpopulations; the first subpopulation is considered to be at the same risk of mortality as the age- and sex-matched general population (sourced from the Office for National Statistics for this model (99), whilst the mortality rate of the second subpopulation is defined by a selected standard parametric survival curve. The proportion of patients falling into the first population (known as the 'cure fraction') is estimated through logistic regression of trial data. The extrapolations for each subpopulation are then combined via the cure fraction to obtain extrapolations for the population as a whole.

Accordingly, evidence to support the exploration of cure-mixture survival modelling in the context of this appraisal is as follows:

A study of the natural history of newly diagnosed DLBCL patients treated with immunochemotherapy identified that patients who did not experience a progression or death event after two years went on to experience subsequent survival equivalent to that of the age- and sex-matched general population (93). Whilst an equivalent study has not been performed in the R/R DLBCL setting, clinical experts confirmed that patients who achieve two years PFS are at very low risk of subsequent progression, and their risk of death can be assumed to have returned to a level close to that of the matched general population (35).

Nevertheless, with current standard of care options, the proportion of patients achieving sustained remission in the transplant-ineligible R/R DLBLC setting is small. Of these, clinical experts estimated that the proportion of patients achieving long-term remission and subsequent long-term survival is approximately 5–10% (35). Similarly, the SCHOLAR-1 study, a multi-national study which combines outcomes from two randomised controlled trials and two academic databases, reported a two-year OS of 11% for refractory DLBCL patients who had not undergone SCT (24).

PFS and OS data from the GO29365 study demonstrate that compared to current standard of care, Pola+BR is likely to offer patients an improved probability of achieving long-term remission (and therefore long-term survival), as evidenced by the statistically significantly improved rate of PFS vs BR. Of note, a very low risk of relapse or death can be observed in the KM plots for PFS and OS for Pola+BR towards the end of follow-up, indicative of a very

low risk of relapse or death for patients who were still alive towards the end of follow-up (Sections B.3.3.2 and B.3.3.3).

Finally, precedent of cure-mixture modelling in NICE appraisals for R/R DLBCL was established in TA567 and TA559, where the respective Committees accepted that patients who are able to demonstrate sustained remission are likely to benefit from long-term survival (69, 70).

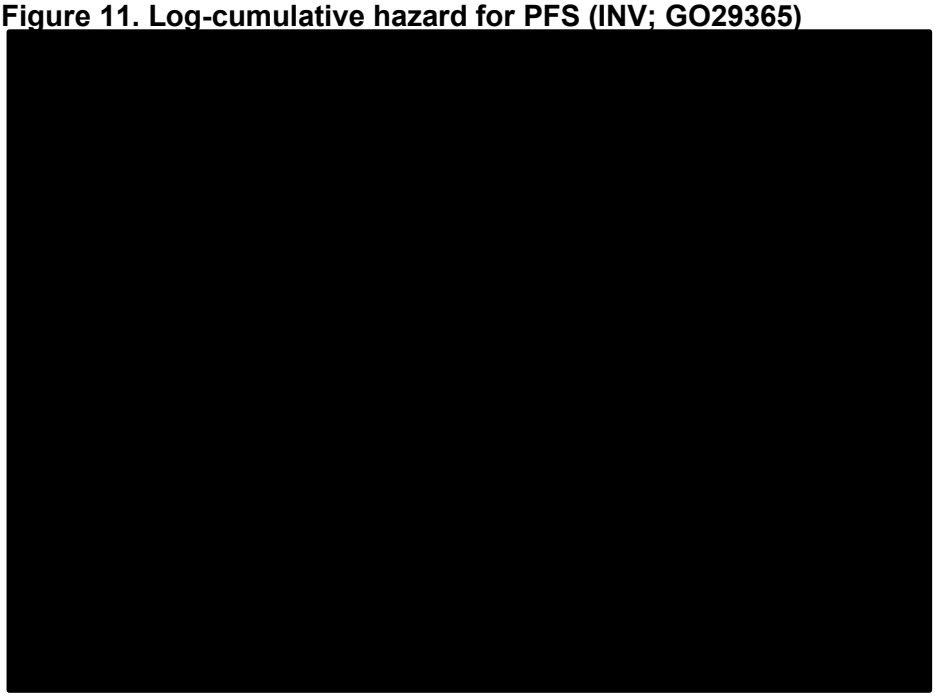
B.3.3.2 Extrapolation of PFS

For the extrapolation of PFS in the model, INV PFS from GO29365 was selected over IRC PFS. The rationale for this selection is that treatment decisions for patients included in the trial, for example, to move a patient to the next line of treatment, were based on progression as measured by the investigator. As such, these data are more consistent with the treatment pathway experienced by patients in the trial and therefore deemed more suitable for inclusion in the model.

Assessment of the proportional hazards assumption

Visual inspection of the log-cumulative hazard plots for PFS from GO29365 (Figure 11) indicates that making the proportional hazards assumption is plausible. This is evidenced by the approximately parallel lines that can be observed for Pola+BR and BR for INV PFS, indicating that the ratio of hazard rates between arms remains approximately constant over the follow-up period.

Figure 11. Log-cumulative hazard for PFS (INV; GO29365)



BR, bendamustine + rituximab; INV, investigator assessed; Pola+BR, polatuzumab + bendamustine + rituximab; PFS, progression-free survival

As such, investigating the fitting of proportional hazards survival functions (exponential, Gompertz or Weibull) to model PFS for Pola+BR and BR was considered appropriate. The fitting of the log-normal, log-logistic and generalised gamma parametric survival functions to the observed data was also explored.

The standard extrapolations were fitted to the GO29356 data using two approaches. The first approach was to model curves independently, and the second, to use a dependent approach, whereby the comparator survival curves were estimated via a treatment effect applied to the intervention curve. For the dependent approach, extrapolations were fitted for both treatment arms in SAS, with treatment as a covariate.

Assessment for cure-mixture modelling

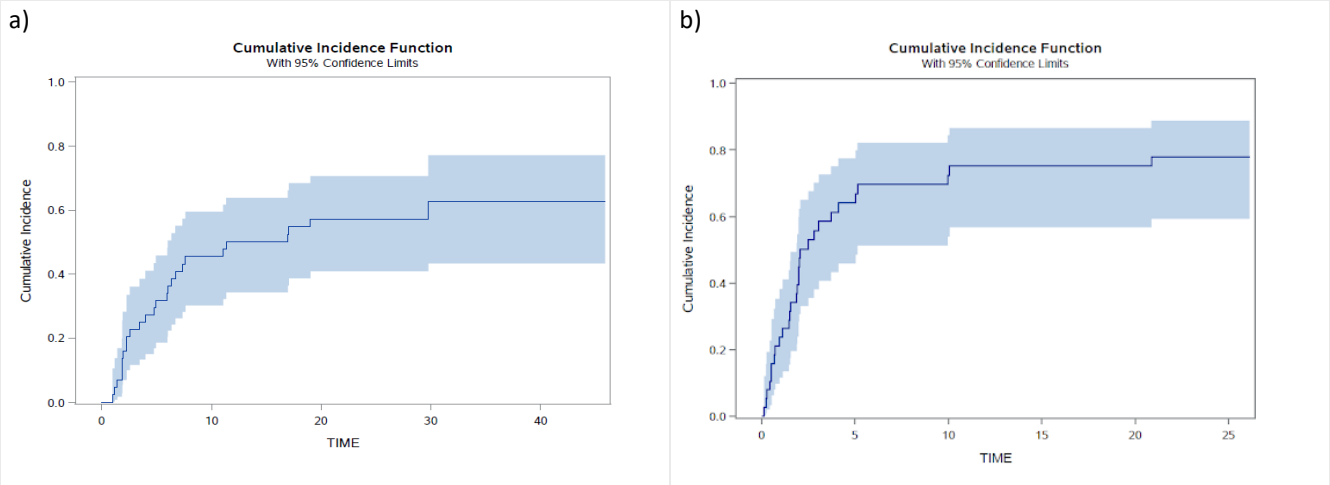
The suitability of the GO29365 PFS data to the application of cure-mixture modelling was assessed. As discussed in Section B.3.3.1, to support the use of cure-mixture modelling, the trial data must indicate that a proportion of patients enter long-term remission (PFS) and are therefore likely to experience long-term survival. In line with this, the KM data for INV PFS presented in Figure 12 demonstrate a very low rate of relapse for both Pola+BR and BR around the 24-month timepoint, suggesting there is a fraction of patients in the GO29365 trial who have achieved long-term remission. As discussed previously (Section 3.3.1), evidence from the literature and clinical opinion suggest that patients remaining progression-free for two years are expected to demonstrate survival aligned with that of the general population. A drop-off in the ‘plateau’ shape of the KM data for the two arms can be observed towards the end of follow-up, however, this can be attributed to the low patient numbers at risk in the trial towards the end of follow-up. Later data cuts are expected to provide more data around this time point.

Figure 12. KM plot for INV PFS (GO29365; data cut: October 2018)

BR, bendamustine + rituximab; CI, confidence interval; INV, investigator-assessed; KM, Kaplan Meier; PFS, progression-free survival; Ph, phase; Pola+BR, polatuzumab + bendamustine + rituximab

Both progression and death are considered as events when assessing PFS. Accordingly, progression events may be analysed alone (i.e. excluding any death events), as presented in Figure 13, in order to further assess the suitability of using cure-mixture modelling. It can be observed from Figure 13 that most progression events occur within the first 12 months in both arms of GO29365, and that patients are at a very low risk of progression after 24 months, further supporting the exploration of using cure-mixture modelling to extrapolate PFS.

Figure 13. Cumulative incidence of progression (INV) from GO29365 a) Pola+BR and b) BR



BR, bendamustine + rituximab; INV, investigator assessed; Pola+BR, polatuzumab + bendamustine + rituximab

Finally, additional rationale for exploring cure-mixture modelling is provided by the log-cumulative hazard plot presented previously to assess the proportional hazards assumption (Figure 11). The plot indicates a decline in the hazard of progression for both interventions at the end of the follow-up period, again suggesting that a proportion of patients enter long-term remission.

The parameterisation of cure-mixture models means this model type is better suited to reflect the potential for a proportion of patients to achieve long-term survival. Accordingly, in addition to the standard parametric models, cure-mixture models were investigated and fitted independently to the two arms of the model.

The proportion of patients achieving long-term remission is a parameter that can be fitted from the observed GO29365 data via logistic regression. The ‘cure fraction’ of patients are assumed not to progress or be susceptible to cancer-related death.

Statistical fit of models to the observed data

Table 40The AIC and BIC goodness of fit results for the functions used to model PFS for Pola+BR and BR in GO29365, as well as a qualitative impression of visual fit to the observed KM curve are provided below.

In the selection of suitable survival functions for PFS, for clinical plausibility, consideration was given to consistency with the extrapolations being explored for OS (discussed in Section B.3.3.3). For all survival functions explored for OS for both arms, parameterisation for the Gompertz model did not converge. Accordingly, given that a Gompertz extrapolation would ultimately not be selected for OS, this function was excluded from consideration for PFS. As such, AIC/BIC values are therefore not presented for this extrapolation.

Table 40. Ranking of PFS distributions for Pola+BR and BR based on AIC, BIC and assessment of their visual fit

Parametric distribution		Pola+BR AIC (rank)	Pola+BR BIC (rank)	Visual fit to KM[a]	BR AIC (rank)	BR BIC (rank)	BR Visual fit to KM
Standard (dependent fit)[b]	Exponential	266.4 (5)	271.1 (5)	×	NA	NA	×
	Weibull	263.1 (4)	270.2 (4)	×	NA	NA	×
	Gompertz	NA[c]	NA[c]	NA[c]	NA[c]	NA[c]	NA[c]
	Log-Normal	250.8 (1)	257.9 (1)	~	NA	NA	✓
	Generalised Gamma	250.8 (2)	260.4 (3)	~	NA	NA	✓
	Log-Logistic	252.6 (3)	259.8 (2)	~	NA	NA	✓
Standard (independent fit)	Exponential	125.8 (4)	127.5 (4)	×	140.5 (5)	142.2 (5)	×
	Weibull	126.9 (5)	130.3 (5)	×	137.8 (4)	141.2 (4)	×
	Gompertz	NA[c]	NA[c]	NA[c]	NA[c]	NA[c]	NA[c]
	Log-Normal	121.6 (2)	125.0 (2)	~	131.2 (1)	134.6 (1)	✓
	Generalised Gamma	120.1 (1)	125.1 (1)	✓	132.8 (3)	137.9 (3)	✓
	Log-Logistic	123.3 (3)	126.7 (3)	~	131.2 (2)	134.6 (2)	✓
Cure-mixture	Exponential	79.7 (5)	161.55 (1)	~	4.57 (3)	86.45 (1)	~
	Weibull	79.6 (4)	182.49 (4)	~	8.43 (5)	111.33 (4)	~
	Gompertz	NA[c]	NA[c]	NA[c]	NA[c]	NA[c]	NA[c]
	Log-Normal	75.9 (1)	179.22 (3)	✓	3.05 (1)	105.95 (2)	✓
	Generalised Gamma	76.0 (2)	194.67 (5)	✓	4.66 (4)	123.42 (5)	✓
	Log-Logistic	78.4 (3)	178.94 (2)	✓	3.08 (2)	105.99 (3)	✓

[a]A ✓ symbol indicates a model has a good fit to the KM data; A ~ symbol indicates a model has an average fit to the KM data; a × indicates a model has an unsuitable fit to the KM data. [b]The presented statistics represent the overall fit of the dependent model to both arms of the trial. [c]The Gompertz extrapolation was not considered for PFS for either arm due failure of parameterisation for this function for OS; AIC/BIC statistics are therefore not presented. AIC, Akaike Information Criterion; BIC, Bayesian Information Criterion; BR, bendamustine + rituximab; KM, Kaplan-Meier; NA, not available; Pola+BR, polatuzumab + bendamustine + rituximab

Among the standard models (dependently and independently fit), the AIC and BIC statistics indicated that all models had a similar statistical fit to the KM data in both arms. The top-ranking models (both arms) for both dependent and independently-fit extrapolations were the log-normal, generalised gamma and log-logistic. Similarly, for the cure-mixture models, minimal variation was observed among the statistics; the best ranking models were the generalised gamma and log-logistic for Pola+BR and the log-normal, log-logistic and exponential for BR.

The fit of the dependently modelled extrapolations was inspected visually (Figure 14). The exponential and Weibull models appeared to overestimate PFS in both the Pola+BR and BR arms early in the extrapolation, and did not capture the decline in progression at the end of the follow-up period. In the Pola+BR arm, the log-logistic, log-normal and generalised gamma appeared to provide a better fit early in the extrapolation, but similarly did not capture the decline in progression in both arms towards the end of follow-up well. The generalised gamma, log-logistic and log-normal curves offered reasonable fits to the BR arm.

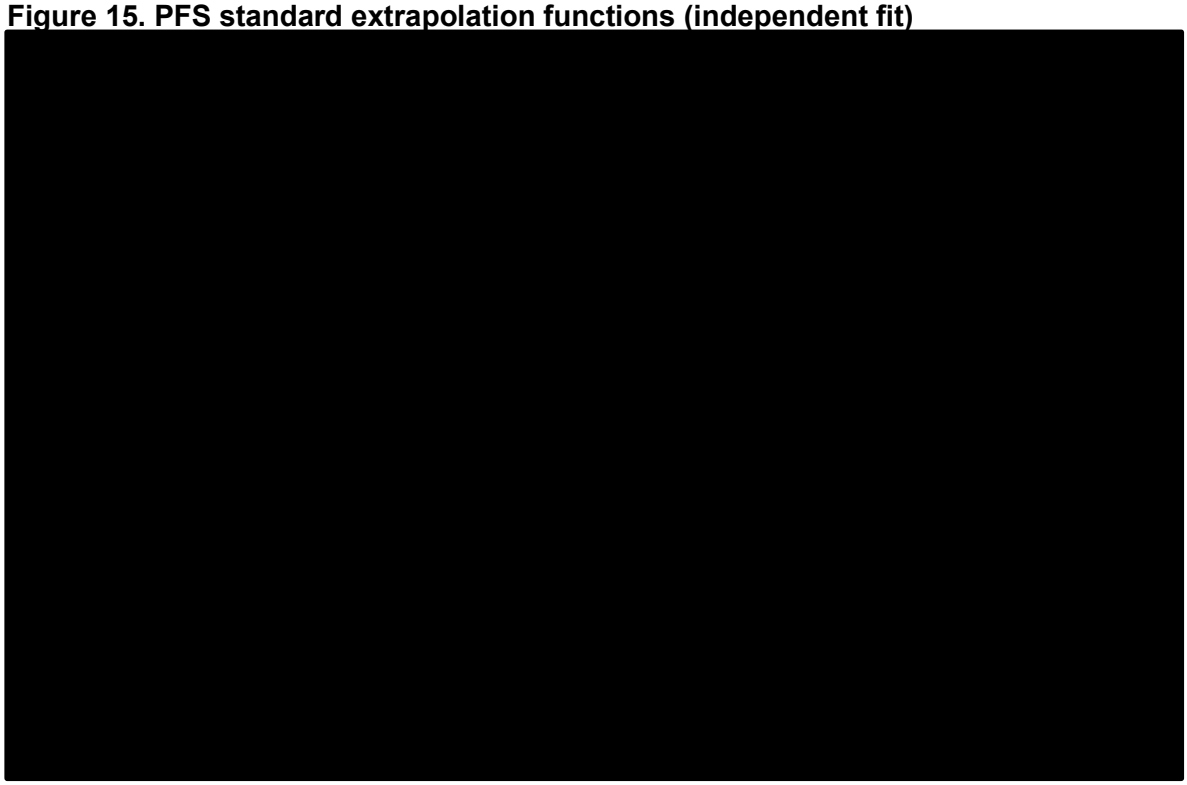
Figure 14. PFS standard extrapolation functions (dependent fit)

The Gompertz extrapolation was not considered for either arm for PFS due failure of parameterisation for this function for OS; this extrapolation is therefore not presented.
BR, bendamustine + rituximab; KM, Kaplan-Meier; Pola+BR, polatuzumab + bendamustine + rituximab

Similar conclusions were made from the visual inspection of the independent fit extrapolations as the dependent fit extrapolations; in the Pola+BR arm, functions typically

either overestimated PFS stages in the earlier months and/or underestimated the decline in patient progression towards the end of follow-up. Of all the functions, the generalised gamma provided the most reasonable fit in the Pola+BR arm. In the BR arm, the generalised gamma, log-logistic and log-normal appeared to fit the observed data reasonably well.

Figure 15. PFS standard extrapolation functions (independent fit)



The Gompertz extrapolation was not considered for either arm for PFS due failure of parameterisation for this function for OS; this extrapolation is therefore not presented. BR, bendamustine + rituximab; Pola+BR, polatuzumab + bendamustine + rituximab

Introducing cure-mixture models improved the visual fit of all models to both arms of the KM data (Figure 16), with log-logistic, log-normal and generalised gamma cure-mixture models providing good fits to the observed data in the Pola+BR arm. The Weibull and exponential overestimated PFS early in the extrapolation. In the BR arm, the Weibull appeared to overestimate PFS at the earliest stages of follow-up, with the exponential overestimating progression at later stages. All other models appeared to provide a relatively good fit to the KM data.

Table 41 presents the cure fractions (i.e. the proportion of patients achieving long-term remission) predicted by each of the cure-mixture extrapolations for each arm. The proportion of patients achieving long-term remission falls into a narrow range from 20.8% to 25.9% in the Pola+BR arm, and 0.0% to 4.4% in the BR arm. A narrow range of values demonstrates consistency in the cure fraction estimation across parametric models, further supporting the suitability of this modelling approach.

Figure 16. PFS cure-mixture extrapolation functions

The Gompertz extrapolation was not considered for either arm for PFS due failure of parameterisation for this function for OS; this extrapolation is therefore not presented. BR, bendamustine + rituximab; KM, Kaplan-Meier; Pola+BR, polatuzumab + bendamustine + rituximab

Table 41. Predicted long-term remission (cure fraction) from PFS cure-mixture model extrapolations

Parametric distribution	Cure fraction Pola+BR	Cure fraction BR
Exponential	25.9%	4.4%
Weibull	24.7%	3.0%
Gompertz	NA	NA
Log-normal	20.8%	0.0%
Generalised gamma	21.2%	0.0%
Log-logistic	22.2%	0.0%

The Gompertz extrapolation was not considered for either arm for PFS due failure of parameterisation for this function for OS; cure fractions for this extrapolation are therefore not presented. BR, bendamustine + rituximab; NA, not available; Pola+BR, polatuzumab + bendamustine + rituximab

Based on visual fit, plausibility of the long-term extrapolation, and alignment with the selected OS distribution (see Section B.3.3.3), the cure-mixture generalised gamma survival curve was selected for the base case for both arms, whilst the log-normal and log-logistic extrapolations were (applied in both arms) were explored in scenarios.

The final base case extrapolations are shown alongside the selected OS extrapolation in Figure 23 in Section B.3.3.3, where the long-term plausibility of the selected extrapolations for both outcomes is also discussed.

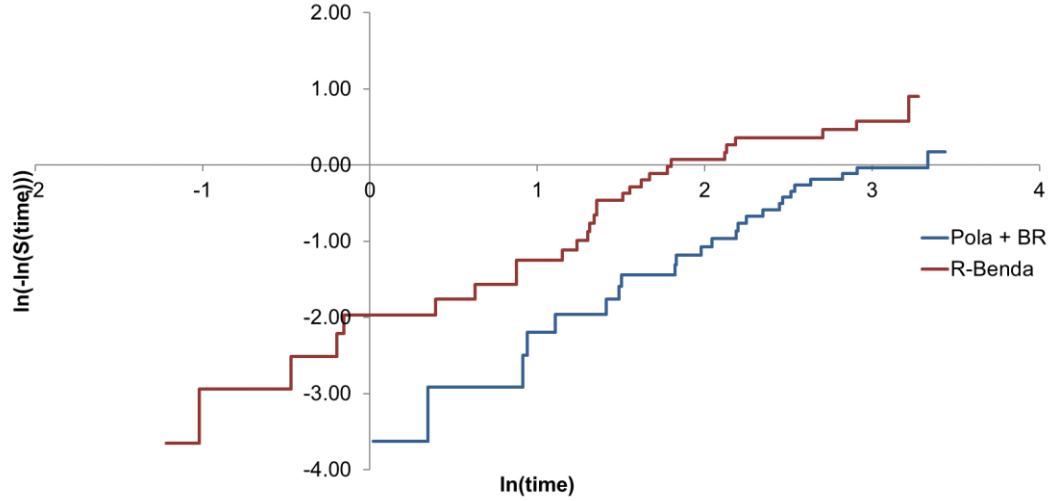
In the scenario where R-GemOx is explored as a comparator, the base case PFS extrapolations for BR are adopted.

B.3.3.3 Extrapolation of OS

Assessment of the proportional hazards assumption

Visual inspection of the log-cumulative hazard plot for OS from GO29365 (Figure 17) indicates that making the proportional hazards assumption is plausible. This is evidenced by the approximately parallel lines that can be observed between Pola+BR and BR, indicating that the ratio of hazard rates between arms remains approximately constant over the follow-up period.

Figure 17. Log-cumulative hazard plot for OS in study GO29365



Pola + BR, polatuzumab + bendamustine + rituximab; R-Benda, rituximab + bendamustine

As such, investigating the fitting of proportional hazards survival functions (exponential, Gompertz or Weibull) to model OS for Pola+BR and BR was considered appropriate. The fit of the log-normal, log-logistic and generalised gamma curves was also explored.

As for PFS, the standard extrapolations were fitted to the GO29356 data using both independent and dependent approaches.

Assessment for cure-mixture modelling

Cure-mixture models were also investigated for the modelling of OS, as long-term remission in R/R DLBCL would be expected to be associated with long-term survival. As was observed for PFS, a decline in the hazard of death can be seen towards the end of follow-up in the OS KM data from GO29365 (Figure 18) for both arms of the trial. The majority of death events can be seen to take place prior to 12 months.

Figure 18. KM plot for OS (GO29365; data cut: October 2018)

BR, bendamustine + rituximab; CI, confidence interval; INV, investigator-assessed; KM, Kaplan Meier; OS, overall survival; Ph, phase; Pola+BR, polatuzumab + bendamustine + rituximab

Further justification for the exploration of cure-mixture modelling is provided by the log-cumulative plots presented in Figure 17. A decline in the hazard of death can be observed towards the end of the follow-up period, similar to the decline in the hazard of progression observed for PFS. Again, this is consistent with a proportion of patients experiencing long-term remission and subsequent long-term survival in the trial.

In prior economic evaluations (69, 70), it was stated that only patients who have not yet progressed can be considered to be long-term survivors, based on the view from clinical experts. As the OS rates in GO29365 were higher than PFS rates at the end of the observed follow-up period, a proportion of patients (those in progression) were expected to be at increased mortality risk, and not long-term survivors. Therefore, two cure-mixture model approaches were implemented, both of which ensured a conservative estimate of long-term survivor rates. Firstly, an approach was implemented whereby the proportion of long-term survivors was constrained to the proportion of patients in long-term remission, as fitted from the PFS data, i.e. the cure-mixture mode was informed by PFS. Treatment arms were fitted independently using this approach. Secondly, a dependent model was explored, whereby OS was not informed by PFS but the survival for patients who were not long-term survivors was assumed to be similar in the Pola+BR and BR arm, to achieve a more conservative estimate of long-term survival in the Pola+BR arm based on OS data alone. Further background on cure-mixture statistical models is provided in Appendix M.

Statistical fit of models to the observed data

Table 42 provides the AIC and BIC goodness of fit results for the functions used to model OS for Pola+BR and BR in GO29365, as well as a qualitative impression of visual fit to the observed KM curve for each arm. For all extrapolations, parameterisation of the Gompertz extrapolation for both arms did not converge, and therefore AIC and BIC statistics are not presented for this extrapolation.

Table 42. Ranking of OS models for Pola+BR and BR based on AIC, BIC and assessment of their visual fit

Model		Pola+BR AIC (rank)	Pola+BR BIC (rank)	Visual fit to KM	BR AIC (rank)	BR BIC (rank)	BR Visual fit to KM
Standard (dependently fit)[b]	Exponential	225.1 (4)	229.8 (4)	×	NA	NA	×
	Weibull	226.6 (5)	233.7 (5)	×	NA	NA	×
	Gompertz	NA[c]	NA[c]	NA[c]	NA[c]	NA[c]	NA[c]
	Log-Normal	218.6 (1)	225.8 (1)	×	NA	NA	~
	Generalised gamma	220.2 (3)	229.7 (3)	×	NA	NA	~
	Log-logistic	219.2 (2)	226.3 (2)	×	NA	NA	~
Standard (independently fit)	Exponential	109.1 (4)	110.8 (1)	×	116.0 (4)	117.7 (3)	×
	Weibull	111.1 (5)	114.5 (5)	×	117.2 (5)	120.6 (5)	×
	Gompertz	NA[c]	NA[c]	NA[c]	NA[c]	NA[c]	NA[c]
	Log-Normal	107.5 (1)	110.9 (2)	×	113.1 (2)	116.5 (2)	~
	Generalised gamma	108.7 (3)	113.8 (4)	×	115.0 (3)	120.1 (4)	~
	Log-logistic	108.4 (2)	111.8 (3)	×	112.8 (1)	116.1 (1)	~
Cure-mixture (dependent, not informed by PFS)[b]	Exponential	123.40 (3)	205.28 (1)	×	NA	NA	×
	Weibull	124.11 (4)	227.02 (4)	×	NA	NA	×
	Gompertz	NA[c]	NA[c]	NA[c]	NA[c]	NA[c]	NA[c]
	Log-Normal	123.19 (2)	226.09 (3)	×	NA	NA	×
	Generalised Gamma	124.76 (5)	243.51 (6)	×	NA	NA	×
	Log-Logistic	122.54 (1)	225.44 (2)	×	NA	NA	×
Cure-mix	Exponential	82.38 (4)	164.27 (1)	~	46.36 (4)	128.24 (1)	×

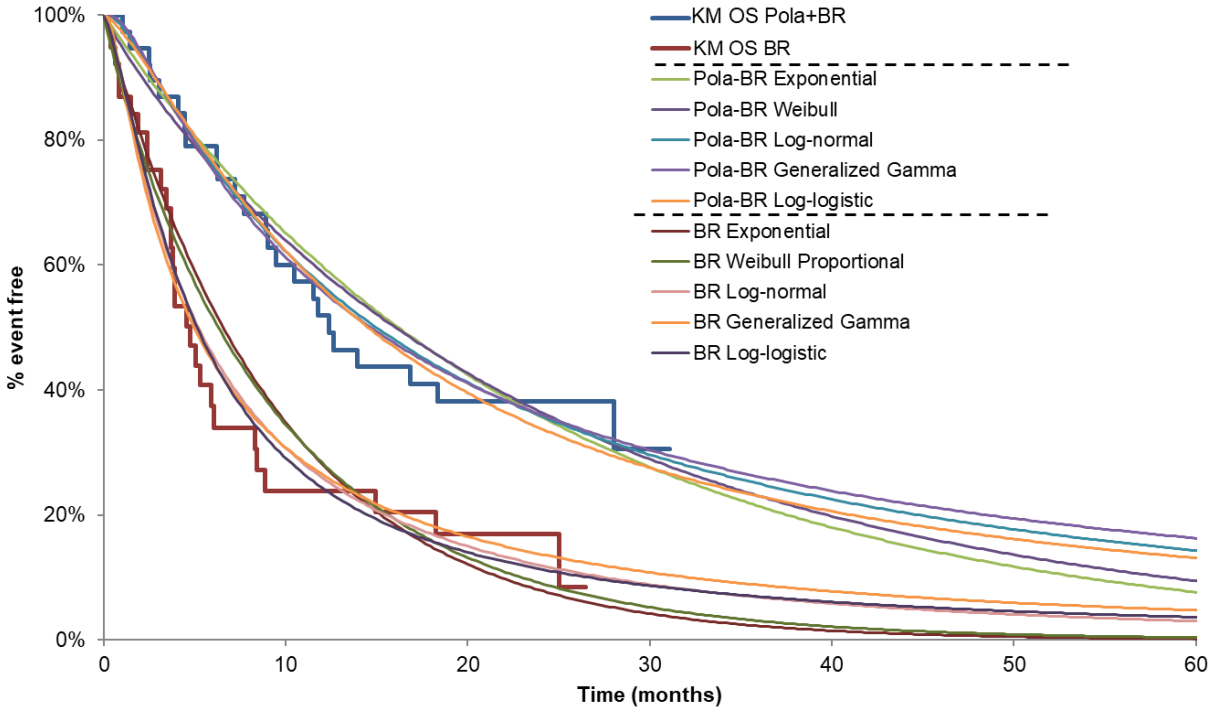
	Weibull	81.62 (3)	184.52 (4)	×	48.47 (6)	151.37 (5)	×
	Gompertz	NA[c]	NA[c]	NA[c]	NA[c]	NA[c]	NA[c]
	Log-Normal	81.21 (2)	184.11 (3)	✓	44.55 (2)	147.45 (3)	✓
	Generalised Gamma	83.32 (5)	202.07 (5)	✓	46.46 (5)	165.21 (6)	✓
	Log-Logistic	81.20 (1)	184.11 (2)	✓	44.27 (1)	147.18 (2)	~

[a]A ✓ symbol indicates a model has a good fit to the KM data; A ~ symbol indicates a model has an average fit to the KM data; a × indicates a model has an unsuitable fit to the KM data. [b]The presented statistics represent the overall fit of the dependent model to both arms of the trial. [c]Parameterisation did not converge for the Gompertz extrapolation in all four modelling approaches; AIC/BIC statistics are therefore not presented. AIC, Akaike Information Criterion; BIC, Bayesian Information Criterion; BR, bendamustine + rituximab; KM, Kaplan-Meier; NA, not available; Pola+BR, polatuzumab + bendamustine + rituximab

As was the case for PFS, AIC and BIC values indicated a similar statistical fit to the KM data for the standard models (dependently and independently fit) for both arms. The best ranking models in both arms were the log-normal, log-logistic and generalised gamma. For the two cure-mixture models, the AIC/BIC statistics also indicated a similar statistical fit among the extrapolations, with the log-logistic and log-normal curves suggesting the best fit in both arms.

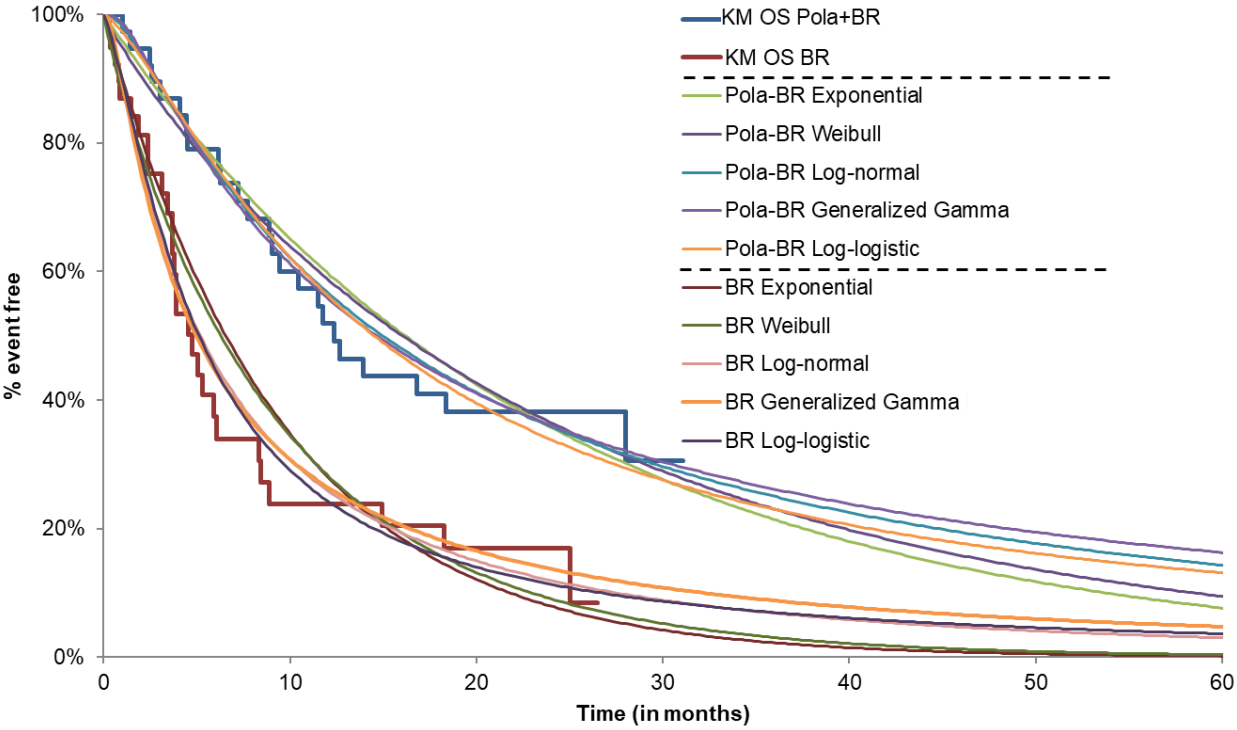
Based on visual inspection, none of the standard models (applied dependently or independently) fitted the observed OS data in Pola+BR arm particularly well, as they tended to overestimate OS early on and did not capture the decline in the observed mortality rate at the end of the follow-up period. In the BR arm, only the log-logistic, log-normal and generalised gamma extrapolations provided a reasonable visual fit (Figure 19 [dependent fit], Figure 20 [independent fit]).

Figure 19. OS standard extrapolation functions (dependent fit)



Parameterisation did not converge for the Gompertz extrapolations. BR, bendamustine + rituximab; OS, overall survival; Pola+BR, polatuzumab + bendamustine + rituximab

Figure 20. OS standard extrapolation functions (independent fit)



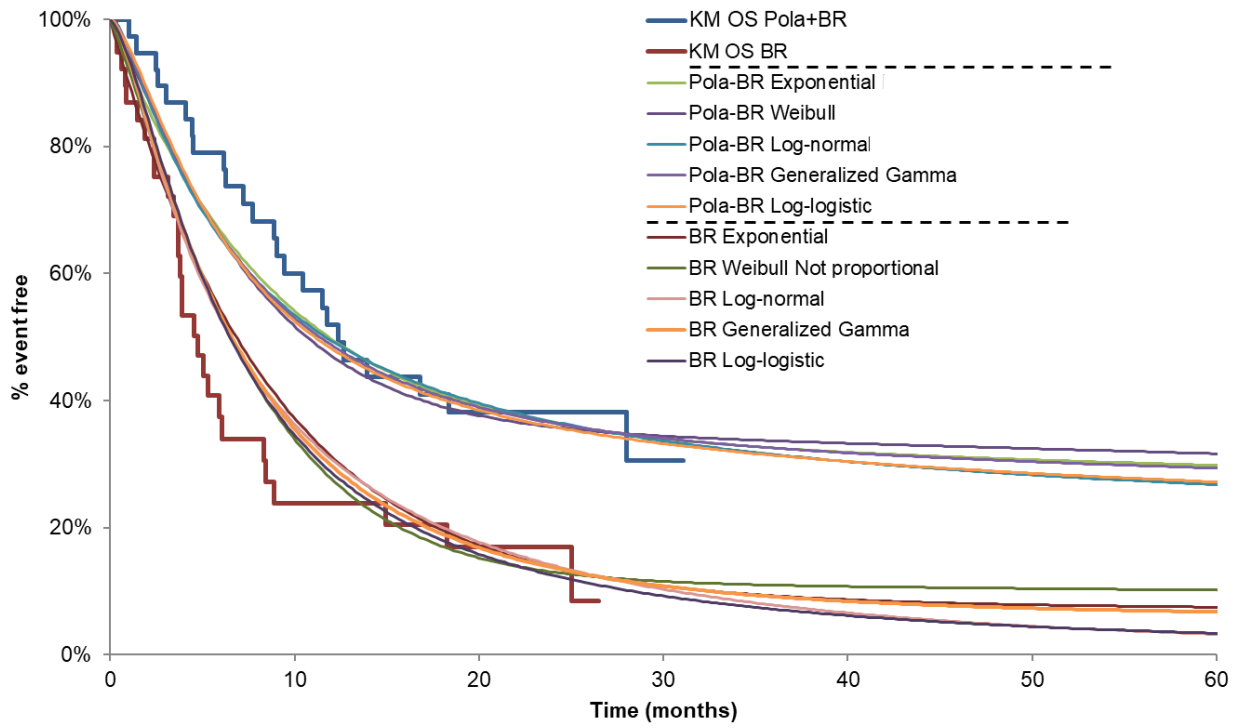
Parameterisation did not converge for the Gompertz extrapolations. BR, bendamustine + rituximab; KM, Kaplan-Meier; OS, overall survival; Pola+BR, polatuzumab + bendamustine + rituximab

Cure-mixture models were subsequently fitted to the OS GO29365 data (Figure 21).

However, all functions were found to have a poor fit to the KM data; in the Pola+BR arm, all

curves underestimated OS early in the extrapolation. In the BR arm, all extrapolations overestimated OS early on, and the majority did not capture the decline in mortality late in follow-up well.

Figure 21. OS cure-mixture extrapolation functions (OS not informed by PFS)



Parameterisation did not converge for the Gompertz extrapolations. BR, bendamustine + rituximab; KM, Kaplan Meier; OS, overall survival; Pola+BR, polatuzumab + bendamustine + rituximab

The cure rates predicted by each model are presented in Table 43. Cure-mixture models fitted directly to OS data produced estimated proportions of patients with long-term survival in the Pola+BR arm ranging from 27.8% to 36.0%. In the BR arm, rates ranged from 0.0% to 11.5%.

Table 43. Predicted long-term survival (cure fraction) from OS cure-mixture model extrapolations (OS not informed by PFS)

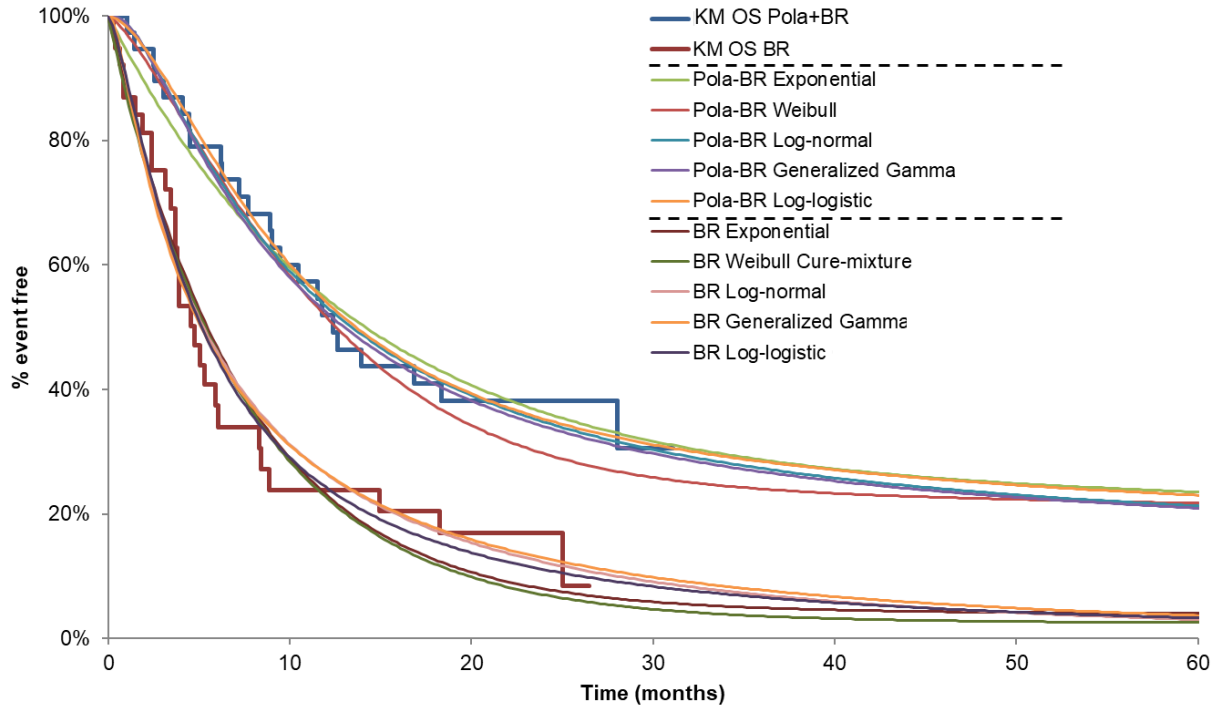
Parametric distribution	Cure fraction Pola+BR	Cure fraction BR
Exponential	33.8%	8.4%
Weibull	36.0%	11.5%
Gompertz	NA	NA
Log-normal	27.8%	0.0%
Generalised Gamma	33.0%	7.1%
Log-logistic	28.2%	0.0%

Parameterisation did not converge for the Gompertz extrapolation, therefore the cure fraction is not presented. BR, bendamustine + rituximab; OS, overall survival; Pola+BR, polatuzumab + bendamustine + rituximab

Given the poor fit of all models explored to this point and guidance provided by clinical experts, cure-mixture models for which the long-term survivor fraction was informed by the

long-term remission fraction (i.e. the OS cure fraction was informed by the PFS cure fraction) were investigated. These models provided an improved fit to the KM data in both arms, with functions providing a closer fit to the OS KM data early on in the extrapolation, and an improved fit to the decline in mortality later in follow-up compared to the standard functions. The best fitting functions for both arms based on visual inspection were the log-normal and generalised gamma (Figure 22).

Figure 22. OS cure-mixture extrapolation functions (OS informed by PFS)



Parameterisation did not converge for the Gompertz extrapolations. BR, bendamustine + rituximab; OS, overall survival; PFS, progression-free survival; Pola+BR, polatuzumab + bendamustine + rituximab

The predicted cure fractions for OS informed by PFS are presented in Table 44.

Table 44. Predicted long-term survival (cure fractions) from OS informed by PFS cure-mixture model extrapolations

Parametric distribution	Cure fraction Pola+BR	Cure fraction BR
Exponential	25.9%	4.5%
Weibull	24.7%	2.8%
Gompertz	NA	NA
Log-normal	21.0%	0.0%
Generalised gamma	20.6%	0.0%
Log-logistic	22.6%	0.0%

Parameterisation did not converge for the Gompertz extrapolation, therefore the cure fraction is not presented. BR, bendamustine + rituximab; NA: not available; Pola+BR, polatuzumab + bendamustine + rituximab

Based on the fit to the observed data of all extrapolations to both the Pola+BR and BR arms, the cure-mixture model informed by PFS approach was selected. The generalised gamma

and log-normal offered the best fits under this approach. Given that of the two extrapolations, the generalised gamma offered the most conservative cure fraction, this function was chosen as the base case for both arms. The log-normal and log-logistic curves (applied in both arms) were investigated in scenario analyses. The selected base case parametric extrapolation functions for PFS and OS are shown in Figure 23.

In the scenario where R-GemOx is explored as a comparator, the base case OS extrapolations for BR are adopted.

Figure 23. Base case PFS and OS extrapolations

BR, bendamustine + rituximab; KM, Kaplan-Meier; PFS, progression-free survival; Pola+BR, polatuzumab + bendamustine + rituximab; OS, overall survival; R-Benda, rituximab + bendamustine

Clinical plausibility of long-term extrapolations for PFS and OS

Whilst statistical tests and visual inspection are useful in determining which models best fit the observed data, they cannot provide information on how suitable a parametric model is for the time period beyond the final trial follow-up. Therefore, the clinical validity of the selected extrapolations for PFS and OS was assessed by comparing the long-term predictions of the model with expected long-term outcomes.

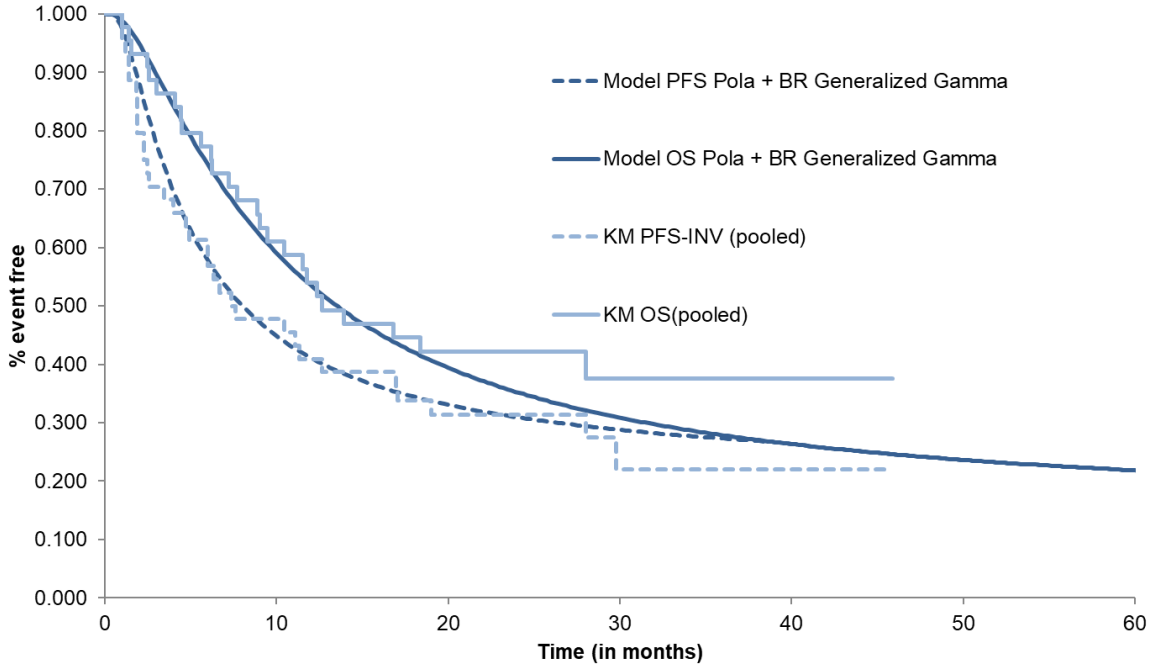
To evaluate the clinical validity of the selected extrapolations for OS and PFS, two additional data sets in R/R DLBCL patients treated with a polatuzumab vedotin regimen over a long-term follow-up were considered.

Firstly, a cohort of six patients received Pola+BR in the safety run-in period prior to start of the randomised phase of GO29365. Data from these patients were pooled with the Pola+BR

arm of the randomised phase of the trial, resulting in a cohort of 46 patients that had been followed for up to 46 months at the October 2018 cut-off date. The KM data for the pooled cohort demonstrates a marked plateau for PFS and OS at the end of the follow-up period (Figure 24), which is more pronounced than that observed in the KM data from the randomised phase of GO29365, due to the longer follow-up time. These data thus further support the presence of a group of patients among the trial population who were treated with a regimen of polatuzumab vedotin and went on to experience sustained remission.

With regards to plausibility of the long-term extrapolations, close alignment can be seen between the model extrapolation and the long-term KM data for OS between 0 and approximately 15 months; following this timepoint, the model extrapolation may be considered a conservative estimation of long-term OS. A close fit between the PFS extrapolation and the KM data can also be seen between 0 and 28 months.

Figure 24. KM for OS and PFS from pooled Pola+BR cohort (N=46) and model extrapolations

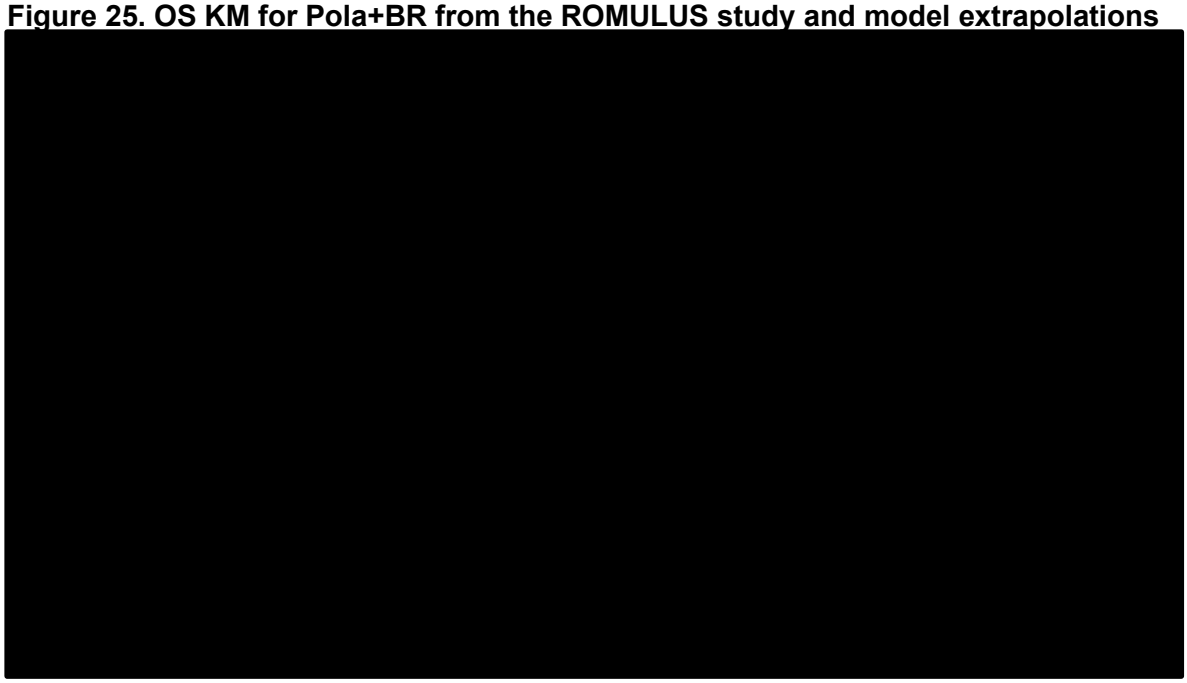


INV, investigator-assessed; KM, Kaplan-Meier; OS, overall survival; PFS, progression-free survival; Pola+BR, polatuzumab + bendamustine + rituximab

Long-term data are also available from the ROMULUS (Phase I/II) study, which included a cohort of R/R DLBCL patients with similar characteristics to those in GO29365 (89) and [redacted]. Patients were treated with polatuzumab vedotin with rituximab (Pola+R), with polatuzumab vedotin given at a higher dose of 2.4 mg/kg. Overall survival data from ROMULUS are presented in Figure 25alongside the model extrapolations for OS. It can be seen that the OS model extrapolation for Pola+BR appears to be

conservative relative to the longer-term ROMULUS data, and that an extended long-term survival on treatment with a polatuzumab vedotin-based regimen is plausible.

Figure 25. OS KM for Pola+BR from the ROMULUS study and model extrapolations



BR, bendamustine + rituximab; KM, Kaplan-Meier; OS, overall survival; Pola-BR, polatuzumab + bendamustine + rituximab; Pola+R, polatuzumab + rituximab

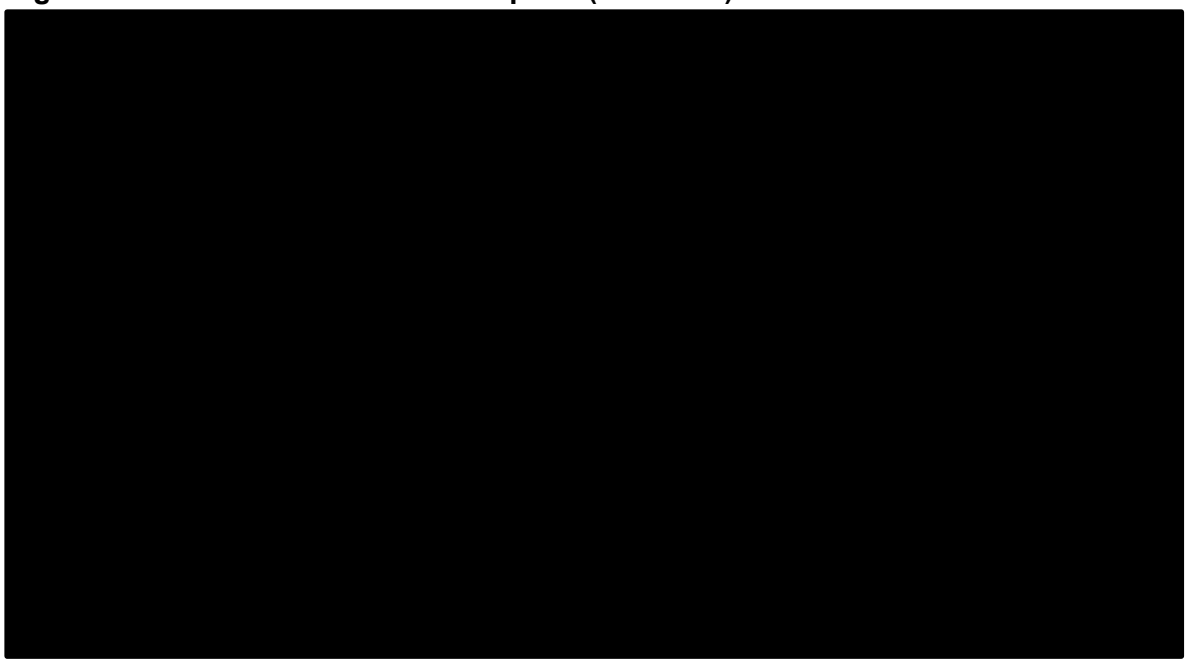
With regards to the plausibility of the long-term BR extrapolations, as discussed in Section B.3.3.1, for transplant-ineligible R/R DLBCL patients treated with current standard of care (represented by the comparator BR arm in this analysis), it is expected that only a small proportion of patients go on to achieve long-term PFS, with clinical experts consulted by Roche indicating estimates of between 5–10% (35). In the BR arm of the model, estimates of the long-term remission rate for the cure-mixture models investigated ranged from 0.0% to 4.4%, indicating that model estimates are in line with clinical expectations.

B.3.3.4 Time on treatment

Time-to-off-treatment (TTOT) data from the GO29365 study were mature, as the Pola+BR and BR arm comprised of treatment for up to 6 cycles only. TTOT KM estimates were therefore used directly in the model base case, using separate curves for each medicine in the respective regimens. The TTOT KM plots for Pola+BR and BR are presented in Figure

26. For the scenario comparing Pola+BR to R-GemOx, 3 cycles of R-GemOx were assumed, based on the assumption used in TA567 (70).

Figure 26. Time to off-treatment KM plots (GO29365)



BR, bendamustine + rituximab; KM, Kaplan-Meier; Pola+BR, polatuzumab + bendamustine + rituximab; TTOT, time-to-off-treatment

B.3.3.5 Adverse events

For Pola+BR and BR, treatment-related AEs of CTCAE Grade 3 or greater from GO29365 that were deemed to be serious were included in the model (data cut-off, April 2018). Serious AEs were defined as those that would require NHS resources to treat them.

The type and frequency of AEs experienced with R-GemOx treatment were derived from Grade 3–5 AEs affecting >5% of patients in a Phase II study on the treatment of R/R DLBCL patients with R-GemOx (58).

Duration of AE data were sourced primarily from GO29365 and also TA306 (67). If duration data were not available from either of these two sources, then the longest duration of an AE from GO29365 was selected (72 days).

Disutilities and costs were applied for each AE to the relevant arm (see Sections B.3.4.4 and B.3.5.6, respectively).

Treatment-related AEs included in the model, their incidence for each arm and duration (and associated source) are reported in Table 45.

Table 45. Incidence of treatment-related AEs included in the model (CTCAE ≥Grade 3, serious)

Treatment-related AEs	Incidence (GO29365 and Mournier 2013 (58))			Duration	
	Pola+BR	BR	R-GemOx	Value, days	Source
Acute kidney injury	2.6%	0.0%	0%	[redacted]	GO29365
Atrial fibrillation	2.6%	0.0%	0%	[redacted]	GO29365
Atrial flutter	2.6%	0.0%	0%	[redacted]	GO29365
Anemia	0.0%	0.0%	33%	16.0	MS TA306
Diarrhoea	0.0%	2.6%	0%	[redacted]	GO29365
Febrile neutropenia	2.6%	2.6%	4%	[redacted]	GO29365
Leukopenia	2.6%	0.0%	0%	[redacted]	GO29365
Neutropenia	2.6%	0.0%	73%	[redacted]	GO29365
Pneumonia	0.0%	2.6%	0%	[redacted]	GO29365
Lower respiratory tract infection	5.1%	0.0%	0%	[redacted]	GO29365
Pyrexia	0.0%	2.6%	0%	[redacted]	GO29365
Septic shock	2.6%	0.0%	0%	[redacted]	Maximum[a]
Thrombocytopenia	0.0%	2.6%	23%	[redacted]	GO29365
Vomiting	0.0%	2.6%	0%	[redacted]	GO29365
Cytomegalovirus infection	2.6%	0.0%	0%	[redacted]	Maximum[a]
Decreased appetite	0.0%	2.6%	0%	[redacted]	Maximum[a]
Supraventricular tachycardia	2.6%	0.0%	0%	[redacted]	GO29365
Herpes virus infection	0.0%	2.6%	0%	[redacted]	GO29365
Meningoencephalitis herpetic	0.0%	2.6%	0%	[redacted]	Maximum[a]
Myelodysplastic syndrome	0.0%	2.6%	0%	[redacted]	Maximum[a]
Neutropenic sepsis	2.6%	0.0%	0%	[redacted]	GO29365
Oedema peripheral	2.6%	0.0%	0%	[redacted]	Maximum[a]
Leukoencephalopathy	2.6%	0.0%	0%	[redacted]	Maximum[a]
Pulmonary oedema	0.0%	2.6%	0%	[redacted]	Maximum[a]

[a]'Maximum' duration indicates equivalence to the longest AE duration from GO29365. AE, adverse event; BR, bendamustine + rituximab; CTCAE, Common Terminology Criteria for Adverse Events; Pola+BR, polatuzumab + bendamustine + rituximab; R-GemOx, Rituximab + gemcitabine + oxaliplatin

B.3.4 Measurement and valuation of health effects

Health-related quality-of-life (HRQoL) data for the model health states were based on values identified in the literature (see Section B.3.4.3), as HRQoL data were not collected in GO29365.

B.3.4.1 HRQoL data from clinical trials

EuroQol Five Dimension (EQ-5D) data, or HRQoL data that could be mapped onto EQ-5D utility values, were not collected in the GO29365 study.

B.3.4.2 Mapping

Mapping from an HRQoL scale to the EQ-5D was not feasible as no HRQoL data were collected in the GO2935 trial.

B.3.4.3 Health-related quality-of-life studies

An SLR was performed to identify studies reporting HRQoL and health state utility data in patients with DLBCL (for detailed methodology and results of the SLR, please see Appendix H). Seven studies reporting HRQoL or utility data in patients with relapsed or refractory disease were identified in the literature review; the results of these studies are presented in Table 46. All studies identified had some limitations with regards to applicability to the cost-effectiveness model, as discussed in Table 46. An additional relevant study was identified after the searches had been performed in September 2018, which was Wang *et al*. 2018 (100). The results of this study are presented in Table 47.

Table 46. HRQoL and utility studies in R/R DLBCL identified in the SLR

Source	Health state utilities			Applicability to current appraisal
	PFS	PD	Other	
TA306 (67)	0.76	0.68	-	Utility values sourced from published European studies of R/R NHL (Doorduijn 2005) and aggressive NHL (van Agthoven 2001). Values relatively dated.
TA567 (70)	0.83	0.71	-	Data sourced from JULIET trial assessing tisagenlecleucel in DLBCL. SF-36 mapped to EQ-5D. Differences in population exist between JULIET and GO29365 (e.g. ECOG, age); CAR-T intervention possesses different AE profile to Pola+BR/BR.
TA559 (69)	0.72	0.65	-	Data sourced from ZUMA-1 trial assessing axicabtagene in mixed histology lymphoma (including DLBCL). EQ-5D-5L was collected, and 5L-3L crosswalk algorithm was applied. Differences in patient population exist between ZUMA-1 and GO29365 (latter included DLBCL patients only); CAR-T intervention possesses different AE profile to Pola+BR/BR.
Best 2005 (101)	NR	No CR/progression (relapse): 0.39	-	Utility values based on published European study for aggressive NHL (Doorduijn 2001). Values not specific to DLBCL. Source publication relatively dated.
Huntington 2015 (102)	NR	Relapsed disease: 0.9, Refractory disease: 0.80	-	Utilities based on published European studies for HL and NHL (Hornberger and Best 2005, Guadagnolo 2006, Ng 2001, Ng 1999). Values not specific

				to DLBCL. Source publications relatively dated.
Knight 2004 (103)	NR	Non-responders/ relapsed patients, treatment with CHOP: 0.38 R-CHOP: 0.38	-	EuroQoL-based utilities sourced from an unpublished data source, therefore validity and reliability could not be assessed. Utility weights were sourced from a large UK community sample. Source publication relatively dated.
Kymes 2012 (104)	NR	NR	Day before transplant (patients undergoing apheresis): 0.75 14 days post-transplant (during high-dose chemotherapy and engraftment): 0.53 3 months post-transplant (post engraftment): 0.78	Utility values sourced from published European studies of R/R NHL (Doorduijn 2005) and aggressive NHL (van Agthoven 2001). Values not specific to DLBCL, or PFS/PD health states. Source publications relatively dated.

3L, 3-level; 5L, 5-level; AE, adverse event; CAR-T, chimeric antigen receptor-T cell; CR, complete response; (R-) CHOP, (rituximab-) cyclophosphamide, doxorubicin, vincristine, prednisolone; DLBCL, diffuse large B cell lymphoma; EQ-5D, Euro-QoL-5 Dimensions; HL, Hodgkin's lymphoma; NHL, non-Hodgkin's lymphoma; NR, not reported; Pola+BR, polatuzumab + bendamustine + rituximab; PD, progressed disease, PFS, progression-free survival; R/R, relapsed/refractory; US, United States

Table 47. HRQoL and utility results from Wang et al. 2018

Source	Health state utilities			Applicability to current appraisal
	PFS	PD	Other	
Wang 2018 (100)	0.69 (2nd remission), 0.58 (3rd remission and beyond)	NR	0.53 (2nd line treatment) 0.53 (3rd line treatment and beyond)	UK real-world data. Analysis not stratified by baseline patient characteristics. Transplant eligible and ineligible patients. PD utility not reported. EQ-5D-3L mapped from EQ-5D-5L.

3L, 3-level; 5L, 5-level; EQ-5D, Euro-QoL-5 Dimensions; PD, progressed disease, PFS, progression-free survival; UK, United Kingdom

B.3.4.4 Adverse reactions

As HRQoL data were not collected in GO29365, the impact of treatment-related AEs was modelled by applying disutilities derived from previous NICE appraisals in R/R DLBCL (67, 69) and brentuximab vedotin in R/R systemic anaplastic large cell lymphoma (TA478) (105). Table 48 presents the disutilities included in the model. As discussed in Section B.3.3.5,

treatment-related AEs of CTCAE Grade 3 or higher that were deemed to be serious were included in the model. Disutilities from AEs for the respective treatments were applied in the model as a weighted average value, with the estimated disutilities (Table 48) being weighted by their corresponding incidence and duration as outlined in Table 45.

Table 48. Disutility values used in the cost-effectiveness model

AE	Disutility	Standard error	Source
Acute kidney injury	0.27	0.03	Assumption same as renal failure in TA306 (67)
Atrial Fibrillation	0.37	0.04	Assumption same as ejection fraction decreased from TA306 (67)
Atrial Flutter	0.37	0.04	Assumption same as ejection fraction decreased from TA306 (67)
Anaemia	0.25	0.03	TA306 (67)
Diarrhoea	0.10	0.01	Lloyd 2006 (106)
Febrile neutropenia	0.15	0.02	Lloyd 2006 (106)
Leukopenia	0.09	0.01	Assumption same as neutropenia
Neutropenia	0.09	0.01	Nafees 2008 (107)
Pneumonia	0.20	0.02	Beusterien 2010 (108)
Lower respiratory tract infection	0.20	0.02	Assumption same as pneumonia
Pyrexia	0.11	0.01	Beusterien 2010 (108)
Septic Shock	0.37	0.04	Assumption (maximum disutility from TA306) (67)
Thrombocytopenia	0.11	0.01	Tolley 2013 (109)
Vomiting	0.05	0.01	Nafees 2008 (107)
Cytomegalovirus infection	0.15	0.02	Assumption same as febrile neutropenia
Decreased appetite	0.37	0.04	Assumption same as anorexia in TA306 (67)
Supraventricular tachycardia	0.37	0.04	Assumption same as ejection fraction decreased from TA306 (67)
Herpes virus infection	0.15	0.02	Assumption same as febrile neutropenia
Meningoencephalitis herpetic	0.15	0.02	Assumption same as febrile neutropenia
Myelodysplastic syndrome	0.37	0.04	Assumption same as malignant neoplasm progression from TA306 (67)
Neutropenic sepsis	0.15	0.02	Assumption same as febrile neutropenia
Oedema peripheral	0.37	0.04	Assumption same as pulmonary oedema

Leukoencephalopathy	0.37	0.04	Assumption (maximum disutility from TA306 (67)
Pulmonary oedema	0.37	0.04	Assumption (maximum disutility from TA306) (67)

AE, adverse event

B.3.4.5 Health-related quality-of-life data used in the cost-effectiveness analysis

In the base case, the recent health state utility values used by the manufacturer in TA559 for PFS and PD were adopted (Table 49) (69). These values were sourced from EQ-5D-5L data captured in the ZUMA-1 study and cross-walked to -3L values, and thus align with the NICE reference case and position statement on the use of the EQ-5D-5L valuation set for England (110). The patient population of ZUMA-1 may be considered similar to that of GO29365; ZUMA-1 contained a subgroup of R/R DLBCL patients (PMBCL and TFL histologies were also included in the trial), the majority of patients had an ECOG performance status of 1 and had received three or more lines of therapy (111).

These values are more conservative than the majority of values identified in the SLR, and the PFS value may be considered to possess face validity given it is below the average utility value for the general population (0.79) (112) at the average baseline age of patients in GO29365.

In agreement with the assumptions adopted in TA559 and TA567, in the base case, patients who have remained in the PFS state for two years revert to age- and sex-matched general population utilities for the UK, which were based on Ara and Brazier 2010 (112). This assumption aligns with clinical expert feedback on the natural history of R/R DLBCL and evidence from Maurer et al. 2014 (93) (as discussed in Section B.3.3.1), that patients who achieve sustained remission for up to two years are considered to experience long-term survival aligned to that of the general population. It is therefore assumed that a similar utility to the general population is accrued in these patients.

Scenario analyses performed with respect to utilities are presented in Table 50. The PFS and PD health state utilities used in TA306 and TA567 were both explored in scenarios. In addition, to explore uncertainty around the time point at which patients are considered to be in long-term remission, application of age- and sex-adjusted general population utility was applied to patients in the PFS state after five years, instead the two-year time point used in the base case. Finally, a scenario was performed in which a decrease in utility in the three months before death was implemented to capture the decline in utility before the end of life. The utility value for this final scenario were sourced from Färkkilä et al. 2014 (113).

AE-related disutilities were applied by treatment arm, as described in Section B.3.4.4.

Table 49. Summary of utility values for cost-effectiveness analysis (base case)

State	Utility value: mean (standard error)	Reference in submission (section and page number)	Justification
PFS	0.72 (0.03)	B.3.4.3, pp 98	Values sourced from ZUMA-1 trial of R/R DLBCL patients not eligible for transplant (114), PFS and PD utility values reported based on clinical trial EQ-5D data.
PD	0.65 (0.06)	B.3.4.3, pp 98	
PFS – long-term follow up (>2 years)	Age- and sex-matched general population utility values from Ara and Brazier 2010 (112)	N/A	As per the assumptions made in TA559 and TA567 (69, 70), patients who achieve sustained remission for >2 years are considered by clinical experts to experience long-term survival in line with the general population. It is therefore assumed that a similar utility to the general population is accrued in these patients.
Treatment-related AEs	Disutility values sourced from relevant NICE appraisals for DLBCL and R/R systemic anaplastic large cell lymphoma		

AE, adverse events; DLBCL, diffuse large B-cell lymphoma EQ-5D: EuroQoL 5 Dimensions; PD, progressed disease; PFS, progression-free survival; R/R, relapsed refractory

Table 50. Summary of utility values for cost-effectiveness analysis (scenario analyses)

Scenario	PFS utility value (standard error)	PD utility value (standard error)	Source
TA306 utility values	0.76 (0.03)	0.68 (0.03)	TA306 (67)
TA567 utility values	0.83 (0.03)	0.71 (0.06)	TA567 (70)
PFS – long-term follow up (>5 years) (115)	Age- and sex-matched general population utility values	0.68 (0.03)	Ara and Brazier 2010 (112)
Decline in utility in the 3 months prior to death	0.490	NA	Färkkilä 2014 (113)

PD, progressed disease; PFS, progression-free survival

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

An SLR was conducted to identify data to inform relevant costs and resource use associated with the treatment of patients with R/R DLBCL.

Full details of the SLR search strategy and process for study selection is reported in Appendix I. Of 235 unique records, the SLR identified a single study by Wang et al. 2017 that met the inclusion criteria (116).

This study reports UK population-based treatment costs for DLBCL patients from a simulation model based upon clinical data from the UK Haematological Malignancy Research Network (HMRN) database. Parameter input costs for the model were derived from NHS reference costs and the unit costs of chemotherapy according to data obtained from the Leeds Teaching Hospital NHS Trust.

B.3.5.1 Costs included in the model

The economic analysis was conducted from the NHS and PSS perspective, with appropriate unit cost sources such as NHS reference costs (2017–18) , British National Formulary (BNF) online (accessed June 2019) and electronic Marketing Information Tool (eMIT) (accessed June 2019) used to inform model cost inputs (97, 98, 117).

The following resource use and cost elements were included for the PFS and PD health states present in the model:

- PFS: drug acquisition and administration, treatment-related AEs and routine supportive care (professional and social services, health care professionals and hospital resource use, treatment follow-up) and subsequent treatment costs
- PD: drug acquisition and administration (for further interventions received), and supportive care (professional and social services, health care professionals and hospital resource use, treatment follow-up) and subsequent treatment costs

The assumptions used for deriving the resource use and costs for supportive care in both PFS and PD health states were aligned with those specified in the previous relevant submissions TA306 (67) and TA559 (69). Based upon the ESMO guidelines recommending routine follow-up of up to 24 months (9), it is assumed that patients remaining in PFS for two years would be discharged and therefore would not incur the further supportive costs that are associated with DLBCL.

B.3.5.2 Intervention and comparators' costs and resource use

Drug acquisition costs and cost per cycle for all interventions in the model are presented in Table 51.

Table 51. Drug acquisition costs for Pola+BR, BR and R-GemOx

Drug	Vial/total pack size (mg)	Vial/pack price	Dosing	Cycle length (days)	Cost per cycle[a]
Polatuzumab vedotin	140	[redacted][c]	1.8 mg/kg on day 1 of each cycle[d]	21	[redacted] (no waste [scenario])
	30[b]	[redacted][c]			[redacted] (140 mg and 30 mg, no vial sharing [base case])
Rituximab biosimilar (Rixathron®/Truxima®)	100	£78.59[e, f]	375 mg/m^2 on day 1 of each cycle[d]	21	£581.52 (no vial sharing)
	500	£392.92[e, f]			
Bendamustine	100	£28.00[e]	90 mg/m^2 per day, on days 1 and 2 of each cycle[d]	21	£95.95 (no vial sharing)
	25	£6.85[e]			
Gemcitabine	200	£2.76[g]	1,000 mg/m^2 on day 1 of each cycle[h]	14	£17.84 (no vial sharing)
	1,000	£7.96[g]			
Oxaliplatin	50	£3.81[g]	100 mg/m^2 on day 1 of each cycle[h]	14	£13.87 (no vial sharing)
	100	£6.44[g]			

[a]Calculated from vial combinations required to match the GO29365 patient dose distribution, informed by weight and BSA; [b]Vial size available in [redacted] [c]Polatuzumab vedotin, planned list price; [d]Dosing source, GO29365; [e]Cost source, BNF 2019; [f]Assumed discount of 50% applied, based on national tendering process for biosimilar rituximab; [g]Cost source, eMIT 2019; [h]Dosing source, Mounier et al. 2013 (58). BNF, British National Formulary; BR, bendamustine + rituximab; BSA, body surface area; Pola+BR, polatuzumab + bendamustine + rituximab; R-GemOx, rituximab + gemcitabine + oxaliplatin

Pola+BR drug acquisition costs and dose calculations

Drug acquisition costs and cost per cycle for Pola+BR are presented in Table 51. For the Pola+BR regimen, patients were assumed to receive up to six cycles (21 days per cycle) of Pola+BR, administered at mean doses of 1.8 mg/kg for polatuzumab vedotin and 375 mg/m^2 for rituximab (both on day 1 of each cycle), with 90 mg/m^2 of bendamustine administered on days 1 and 2 of each cycle. The mean treatment doses were derived from the weight and body surface area (BSA) distribution of patients enrolled in the GO29365 study.

It is planned for polatuzumab vedotin to be available in 140 mg and 30 mg vials (lyophilised product prepared for reconstitution prior to infusion). Due to earlier than anticipated marketing authorisation (expected [redacted]), polatuzumab vedotin will initially be available only with a 140 mg vial size at a list price of [redacted] per vial. The 30 mg vial is in development and is planned to be available at an equivalent per mg price ([redacted] per 30 mg vial) in [redacted].

The use of the 140 mg vial alone prior to the availability of the 30 mg vial could initially create waste for individual NHS Trusts due to a lack of flexibility in vial sizes to tailor the

dose to patients' individual weights. In consultation with NHS compounding service providers, Roche is planning to put arrangements in place so hospitals can obtain bags ready for infusion with the correct patient-specific dosing from these service providers without incurring any wastage costs. Trusts would therefore only be charged on a per mg basis for the drug acquisition costs, resulting in a 'no waste' or 'full vial sharing' scenario. The use of compounders is already common practice for other chemotherapies in an increasing number of NHS Trusts. Upon availability of the 30 mg vial, it is envisaged that NHS Trusts will be able to prepare doses in-house, incurring minimal wastage. Details of the compounding arrangements for polatuzumab vedotin are being discussed with NHS England.

Based on the above, costs per cycle in the model base case were therefore calculated based on the availability of 140 mg and 30 mg vials under the conservative assumption of 'no vial sharing', representing the way in which polatuzumab vedotin will be supplied the long-term. Based on the weight distribution of patients enrolled in the GO29365 study, a mean weight of 74.86 kg resulted in a mean per cycle dose of 143.9 mg polatuzumab vedotin at an average cost of [redacted] per cycle.

A further scenario was also included for completeness, representing the use of 140 mg vials only, with no vial sharing.

Rituximab is available as a biosimilar at a list price of £157.17 for the 100 mg vial and £785.84 for the 500 mg vial (Rixathron®/Truxima®, BNF 2019 (97)). For the economic analysis base case, an estimated discount of 50% was applied to the biosimilar rituximab list price, based on the national tendering process for rituximab biosimilar medicines (precise discount values are kept in confidence by the NHS). In the model base case, the rituximab dose is calculated based on the BSA distribution of the GO29365 patient cohort. Patients were assumed to receive a dose of 375 mg/m^2 of rituximab administered on day 1 of each cycle. Assuming no vial sharing, the average cost per cycle for rituximab was calculated to be £581.52.

Bendamustine is now available as a generic formulation in vials of 25 mg and 100 mg at a cost of £6.85 and £27.77 per vial respectively (BNF 2019 (97)). Patients were assumed to receive a dose of 180 mg/m^2 per cycle (90 mg/m^2 on days 1 and 2 of the cycle) based on the BSA distribution of the GO29365 patient cohort. Assuming no vial sharing, the cost per cycle for bendamustine was calculated to be £95.95.

Comparator drug acquisition costs and dose calculations

Drug acquisition costs for BR are presented in Table 51, with calculations for per cycle cost for bendamustine and rituximab the same as those specified for Pola+BR.

Drug acquisition costs for R-GemOx are presented in Table 51. In the treatment regimen, gemcitabine and oxaliplatin were assumed to be administered on day 1 of each cycle (14 days per cycle) at doses of 1,000 mg/m^2 and 100 mg/m^2, respectively, as reported by Mounier et al. (58). Based on an assumption of no vial sharing, an average cost per cycle was calculated at £17.84 for gemcitabine and £13.87 for oxaliplatin, based on the BSA distribution of the GO29365 patient cohort.

B.3.5.3 Drug administration costs

Administration costs for chemotherapy included in the model are presented in Table 52, with the unit cost per resource as reported in the NHS reference cost schedule 2017–18.

Pharmacy costs for the preparation of IV infusions were not considered separately in previous TAs in R/R DLBCL (67, 69, 70), likely on the basis that there is no unbundled NHS tariff to cover pharmacy service costs in relation to the preparation of IV infusions. In this analysis it was assumed that preparation of each cycle of a regimen containing polatuzumab or rituximab required 39 minutes of pharmacy time, as estimated in a UK-based time and motion study of rituximab in non-Hodgkin's lymphoma (118). An hourly cost for a hospital pharmacist is £48 (119), resulting in a per cycle cost of £31.20.

Table 52. NHS reference costs 2017–18 for chemotherapy administration

HRG tariff[a]	Description	Unit cost
SB13Z	Deliver more complex parenteral chemotherapy at first attendance	£309.22
SB14Z	Deliver complex chemotherapy, including prolonged infusional treatment, at first attendance	£374.52
SB15Z	Deliver subsequent elements of a chemotherapy cycle	£312.34

[a]NHS Improvement. NHS Reference Cost Schedule, 2017–18. HRG, healthcare resource group

The total per cycle drug administration costs for the Pola+BR, BR and R-GemOx treatment regimens are summarised in Table 53. For Pola+BR, the same administration tariff costs are applied up to a maximum of the first six cycles (as determined by the TTOT KM estimate data). Administration tariff costs for BR are separated into administration costs for the first administration (first cycle) and subsequent administrations (subsequent cycles).

Table 53. Drug administration costs per cycle

Administration cycle	Tariff cost (HRG code applicable)[a]	Pharmacy cost	Cost per cycle
Pola+BR (cycles 1–6)	£686.86 (SB14Z + SB15Z; first attendance + additional visit on day 2 for BR)	£62.40	£749.26
BR first cycle	£686.86 (SB14Z + SB15Z)	£31.20	£718.06
BR subsequent cycles	£621.56 (SB13Z + SB15Z)	£31.20	£652.76
R-GemOx (cycles 1–6)	£309.22 (SB13Z)	£31.20	£340.42

[a]NHS Improvement. NHS Reference Cost Schedule, 2017–18. BR, bendamustine + rituximab; HRG, healthcare resource group; Pola+BR, polatuzumab + bendamustine + rituximab; R-GemOx, rituximab + gemcitabine + oxaliplatin

Expected costs per treatment cycle were calculated using the total administration cost per cycle and TTOT KM estimate data (Section B.3.3.3).

B.3.5.4 Health-state unit costs and resource use

The type and frequency of resource utilisation in the PFS and PD health states is based upon data from the manufacturer's submission for TA306, which were derived from questionnaire responses from a set of UK physicians selected based upon publication record in the field of aggressive non-Hodgkin's lymphoma (NHL), prior collaboration, and referrals from other physicians (67). The resources listed consist of three separate categories (professional and social services, healthcare professionals and hospital resource use, and treatment follow-up). Table 54 presents the cost per unit for each type of resource included in the model, whilst Table 55 presents the annual frequency of resource use in each health state. Where required, resource use frequency per model cycle was calculated from the 28-day frequency values as below:

$$Frequency\ (annual) = \left(\frac{28\ day\ frequency}{4}\right) * \left(\frac{365.25}{7}\right)$$

$$Frequency\ (per\ model\ cycle) = \left(\frac{Annual\ frequency}{365.25/7}\right)$$

Table 54. Supportive care resource use unit costs included in the model

Procedure	Cost per unit	Source
Professional and social services		

Residential care (day)	£114.50	Crude average of local authority & private; Curtis and Burns, 2018 (119)
Day care (day)	£58.00	Curtis and Burns, 2018 (119)
Home care (day)	£33.32	National Audit Office 2008 (120); Per diem cost of community care = £28 (assumed by the National Audit Office to be the same as the cost of home care); inflation factor from 2007–08 to 2017–18 = 1.19 (PSSRU inflation index (121); inflated per diem cost of home care = £33.32
Hospice (day)	£157.08	National Audit Office 2008 (120); Per diem cost of hospice care = £132; inflation factor from 2007–08 to 2017–18 = 1.19 (PSSRU inflation index (121)); inflated per diem cost of home care 2007–08 = £157.08
Health care professionals and hospital resource use		
Oncologist (visit)	£165.85	AF01A; Service code 303, clinical haematology, face-to-face, non-admitted[a]
Haematologist (visit)	£164.80	AF01A; Service code 370, medical oncology, face-to-face, non-admitted[a]
Radiologist (visit)	£187.30	AF01A; Service code 800, clinical oncology (radiotherapy), face-to-face, non-admitted[a]
Nurse (visit)	£38.45	N02AF; District nurse, adult, face to face[a]
Specialist nurse (visit)	£38.45	N02AF; District nurse, adult, face to face[a]
GP (visit)	£37.40	Curtis and Burns, 2018 (119)
District nurse (visit)	£38.45	N02AF; District nurse, adult, face to face[a]
CT scan	£163.66	N02AF; District nurse, adult, face to face[a]
Inpatient day	£383.47	SA17G; Malignant disorders of lymphatic or haematological systems, with CC Score 3+, non-elective excess bed day[a]
Palliative care team	£117.84	SD03A; Palliative care team inpatient[a]
Treatment follow-up		
Full blood counts	£2.51	RD28Z; Complex CT[a]
LDH	£2.51	DAPS05; Haematology[a]
Liver function	£2.51	DAPS05; Haematology[a]
Renal function	£2.51	DAPS05; Haematology[a]
Immunoglobulin	£2.51	DAPS05; Haematology[a]
Calcium phosphate	£2.51	DAPS05; Haematology[a]
One-off costs, PD		
Chemotherapy	1,116.40	Assumed GemOx cost for generic chemotherapy and administration
R + chemotherapy	2,860.98	Assumed R-GemOx cost for generic chemotherapy and administration

Rituximab	2,765.83	Assumed R cost for generic chemotherapy and administration
Radiotherapy	162.88	SC42Z, day case
ECG	107.84	RD51A; Imaging:Outpatient
MUGA	285.04	RN03A; Imaging:Outpatient
PET-CT	470.71	RN03A, outpatient
Bone marrow biopsy	519.82	SA33Z, day case
MRI	140.60	RD01A; Imaging:Outpatient

[a]NHS Improvement. NHS Reference Cost Schedule, 2017–18. CT, computed tomography; GP, General Practitioner; LDH, lactate dehydrogenase test; ECG, electrocardiogram; MRI, magnetic resonance imaging; MUGA, multiple-gated acquisition scan; PET-CT, positron emission tomography–computed tomography; PD, progressed disease; PSSRU, Personal Social Services Research Unit; R, rituximab

Resource use was assumed to be the same for both arms, in accordance with clinical expert opinion (35). Clinical expert opinion also considered that patients remaining in PFS for longer than two years were in long-term remission, and it was therefore assumed that no additional supportive costs were incurred beyond this time point (9).

Based on the unit costs and the annual frequencies presented above, the average per cycle supportive care costs for each health state were calculated (Table 56) as shown below:

$$\text{Per cycle supportive care cost} = \text{Per cycle frequency} * \text{Resource unit cost}$$

For the PFS health state, resource use was specified for patients whilst they were on- or off-treatment.

Table 55. Annual frequency of resource use in PFS and PD

Resource utilisation item	PFS on treatment	PFS off-treatment (up to 2 years)	PD	Source
Professional and social services				
Residential care (day)	39.0	9.8	0.0	TA306, ERG Report, Table 37. Annual frequency calculated from 28-day resource use[a]
Day care (day)	14.6	3.7	24.4	TA306, ERG Report, Table 37. Annual frequency calculated from 28-day resource use[a]
Home care (day)	60.9	22.2	121.7	TA306, ERG Report, Table 37[a]
Hospice (day)	0.7	0.2	12.1	TA306, ERG Report, Table 38.

				Annual frequency calculated from 28-day resource use[a]
Health care professionals and hospital resource use				
Oncologist (visit)	21.8	5.5	4.3	TA306, ERG Report, Table 38. Annual frequency calculated from 28-day resource use[a]
Haematologist (visit)	10.2	2.5	13.0	TA306, ERG Report, Table 38. Annual frequency calculated from 28-day resource use[a]
Radiologist (visit)	21.8	4.3	0.0	TA306, ERG Report, Table 38. Annual frequency calculated from 28-day resource use[a]
Nurse (visit)	52.2	13.0	0.0	TA306, ERG Report, Table 38. Annual frequency calculated from 28-day resource use[a]
Specialist nurse (visit)	8.7	2.2	32.6	TA306, ERG Report, Table 38. Annual frequency calculated from 28-day resource use[a]
GP (visit)	26.1	6.5	43.0	TA306, ERG Report, Table 38. Annual frequency calculated from 28-day resource use[a]
District nurse (visit)	19.6	5.0	52.2	TA306, ERG Report, Table 38. Annual frequency calculated from 28-day resource use[a]
CT scan	4.0	4.0	0.0	TA306, ERG Report, Table 38. Annual frequency calculated from 28-day resource use[a]

Inpatient day	3.2	3.2	2.7	TA306, ERG Report, Table 40[a]
Palliative care team	0.0	0.0	17.3	TA306, ERG Report, Table 40[a]
Treatment follow-up				
Full blood counts	43.4	43.4	13.0	TA306, ERG Report, Table 39. Annual frequency calculated from 28-day resource use[a]
LDH	26.1	26.1	4.3	TA306, ERG Report, Table 39. Annual frequency calculated from 28-day resource use[a]
Liver function	43.4	43.4	13.0	TA306, ERG Report, Table 39. Annual frequency calculated from 28-day resource use[a]
Renal function	43.4	43.4	4.3	TA306, ERG Report, Table 39. Annual frequency calculated from 28-day resource use[a]
Immunoglobulin	8.7	8.7	4.3	TA306, ERG Report, Table 39. Annual frequency calculated from 28-day resource use[a]
Calcium phosphate	8.7	8.7	13.0	TA306, ERG Report, Table 39. Annual frequency calculated from 28-day resource use[a]
Haematologist (visit)	3.1	3.1	2.7	TA306, ERG Report, Table 40[a]
Oncologist (visit)	0.6	0.6	0.3	TA306, ERG Report, Table 40[a]
Nurse (visit)	4.9	4.9	2.1	TA306, ERG Report, Table 40[a]
Radiologist (visit)	0.03	0.03	0.03	TA306, ERG Report, Table 40[a]
GP (visit)	0.13	0.13	0.07	TA306, ERG Report, Table 40[a]

One-off costs, PD (Proportion of patients requiring resource)[b]				
	Pola+BR	**BR**	**R-GemOx**	
Chemotherapy	12.5%	12.5%	12.5%	GO29365 NALT data, pooled; assumed the same for R-GemOx
R + chemotherapy	7.5%	7.5%	7.5%	GO29365 NALT data, pooled; assumed the same for R-GemOx
Rituximab	1.3%	1.3%	1.3%	GO29365 NALT data, pooled; assumed the same for R-GemOx
Radiotherapy	2.5%	2.5%	2.5%	TA306, ERG report Table 41[a]
ECG	15.9%	15.9%	15.9%	TA306, ERG report Table 41[a]
MUGA	7.9%	7.9%	7.9%	TA306, ERG report Table 41[a]
MRI	4.0%	4.0%	4.0%	TA306, ERG report Table 41[a]
PET-CT	1.7%	1.7%	1.7%	TA306, ERG report Table 41[a]
Bone marrow biopsy	13.6%	13.6%	13.6%	TA306, ERG report Table 41[a]

[a]TA306 (67). [b]One-off costs weighted by the proportion of patients requiring the respective resource. BR, bendamustine + rituximab; CT, computed tomography; ECG, electrocardiogram; ERG, Evidence Review Group; GP, General Practitioner; LDH, lactate dehydrogenase test; MRI, magnetic resonance imaging; MUGA, multiple-gated acquisition scan; PD, progressed disease; PET-CT, positron emission tomography–computed tomography; PFS, progression-free survival; Pola + BR, polatuzumab + bendamustine + rituximab; R-GemOx, rituximab + gemcitabine + oxaliplatin

Table 56. Per cycle supportive care costs for PFS and PD heath states

PFS on-treatment	PFS off-treatment (up to 2 years)	PFS off-treatment (after 2 years)	PD
£460.22	£160.21	£0.00	£363.64

PD, progressed disease; PFS, progression-free survival

B.3.5.5 Subsequent treatment costs

As discussed in Section B.1.3.3, a small number of third-line and beyond options exist for R/R DLBCL patients, including post-treatment SCT, CAR-T therapy and palliative care.

With regards to post-treatment SCT, GO29365 was not designed to investigate Pola+BR or BR as a salvage regimen for potential transplant candidates, and the comparator regimens identified in the scope are similarly unlikely to be considered as salvage therapies prior to

SCT in clinical practice, as per NICE and ESMO guidance (see Section B.1.3.2). In GO29365, each treatment arm contained only a single patient who received a transplant (2.5% in each arm), both of whom were from the same treatment centre, indicating that subsequent treatment with SCT was not a widespread treatment choice for patients. It is therefore not expected that a significant proportion of patients who meet the decision problem would proceed to transplant after Pola+BR or BR treatment in UK clinical practice. Accordingly, costs for post-treatment SCT were not included in the base case model.

In terms of post-treatment with CAR-T therapy, similarly to SCT, GO29365 was not designed to investigate either Pola+BR or BR as a bridging regimen to CAR-T therapy, although patients could potentially receive CAR-T treatment after progression. An imbalance between the use of curative treatments between treatment arms could potentially bias OS survival estimates. In the Pola+BR treatment arm two patients received CAR-T therapy, one of whom subsequently died, whereas no patients received CAR-T therapy in the BR arm.

The influence of treatments with curative intent (such as CAR-T or SCT) was explored by comparing the GO29365 ITT patient population with a population censored for patients who had received SCT or CAR-T therapies at the time this was received. No difference between the ITT population and the censored population was observed (Figure 27) indicating that OS in the patient population was not affected by post-progression treatments in either arm.

Figure 27. Overall survival for ITT patient population and population censored for those receiving a treatment with curative intent (SCT or CAR-T)

BR, bendamustine + rituximab; CAR-T, chimeric antigen receptor-T cell; ITT, intention-to-treat; OS, overall survival; Pola-BR, polatuzumab + bendamustine + rituximab; SCT, stem cell transplant

As CAR-T therapies are currently funded by the Cancer Drug Fund (CDF), they are not considered as part of standard NHS clinical practice. Accordingly, post-treatment CAR-T costs were not included in the base case model.

In study GO29365, the majority of patients in the randomised phase [redacted]), did not receive any subsequent therapy after Pola+BR or BR. Of those receiving treatment, the majority received chemotherapy with or without rituximab ([redacted]). For the purpose of the economic analysis, the subsequent treatment costs for patients in PD who come off of Pola+BR or BR treatment, were estimated based on the proportion receiving chemotherapy, chemotherapy with rituximab, rituximab alone or radiotherapy. Other regimens, which included investigative treatments or SCT/CAR-T, were not costed. Based on clinical opinion (35) the base case assumes the same subsequent treatments are given in both arms, and pooled estimates across arms from GO29365 for the proportion of patients receiving treatments in the aforementioned categories were used. For the cost of chemotherapy with or without rituximab, the costs of three cycles of GemOx with and without rituximab were assumed, as chemotherapies are available as generic medicines, and costs of different regimens are broadly similar. A weighted average cost was calculated as shown in Table 57. The total cost of subsequent treatments was applied as a one-off cost at the time point of progression in the model.

Table 57. Subsequent treatment costs based on GO29365 data

	Pola+BR N, %		BR N, %		Pooled N, %		Unit cost	Source of cost assumptions
Chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£1116.40	Assumes 3 cycles of chemotherapy and administration[a]
R-chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£2860.98	Assumes 3 cycles of R-chemotherapy and administration[a]
Rituximab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£2765.83	Assumes 3 cycles of rituximab and administration[a]
Radiotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£162.88	National schedule of reference costs 2017–18; SC42Z, day case
Other	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£0	Not costed (see text)
SCT	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£0	Not costed (see text).
CAR-T	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£0	Not costed (see text).

Weighted average cost per patient	**£593.16**	Based on pooled proportions of patients receiving each therapy

[a]Drug acquisition costs and administration for R-chemotherapy were based on those for R-GemOx (see Sections B.3.5.2 and B.3.5.3); for chemotherapy alone and rituximab alone, the costs of rituximab or chemotherapy were excluded as relevant. BR, bendamustine + rituximab; CAR-T, chimeric antigen receptor-T cell; Pola+BR, polatuzumab + bendamustine + rituximab; R-chemotherapy, rituximab-chemotherapy; R-GemOx, rituximab + gemcitabine + oxaliplatin; SCT, stem cell transplant

B.3.5.6 Adverse reaction unit costs and resource use

As discussed in Section B.3.3.5, treatment-related AEs included in the model for Pola+BR and BR were derived from serious treatment-related AEs of CTCAE Grade 3 or higher from the randomised phase of GO29365.

The frequency and unit costs associated with the management of the identified AEs are presented in Table 58.

Table 58. Unit costs of treatment-related AEs included in the economic model

Event (grade)	Unit cost	Source[a]
Acute kidney injury	332.50	Weighted average of LA07M-P; DC
Atrial fibrillation	670.13	Weighted average of EB07A-E; DC
Atrial flutter	670.13	Weighted average of EB07A-E; DC
Anaemia	309.09	Weighted average of SA01G-K, SA03G-H, SA04G-L, SA05G-J; day case
Cytomegalovirus infection	393.65	Weighted average of WH07B-G; DC
Decreased appetite	382.30	Assumed same as vomiting
Diarrhoea	392.26	Weighted average of FD10J, FD10K, FD10L, FD10M; DC
Febrile neutropenia	1,847.50	TA306 (£1,627); inflated to 2018 using PSSRU inflation index (67)
Herpes virus infection	377.90	Weighted average of FD10J, FD10K, FD10L, FD10M; DC
Leukoencephalopathy	3,609.61	Weighted average of AA25C-G; NEL
Leukopenia	291.00	Weighted average of SA35A-E; DC
Lower respiratory tract infection	377.90	Weighted average of FD10J, FD10K, FD10L, FD10M; DC
Meningoencephalitis herpetic	3,652.18	Weighted average of AA22C-G; NEL
Myelodysplastic syndrome	556.99	Weighted average of SA06G-K; NES
Neutropenia	291.00	Weighted average of SA35A-E; DC
Neutropenic sepsis	1,847.50	Assumed same as febrile neutropenia
Oedema peripheral	343.16	Weighted average of WH10A-B; NES
Pneumonia	495.81	Weighted average of DZ11K-V; NES
Pulmonary oedema	2,189.85	Weighted average of DZ20D-F; NEL
Pyrexia	309.56	Weighted average of WJ07A-D; DC

Septic shock	1,037.71	Weighted average of WJ06A-F, NES
Supraventricular tachycardia	670.13	Weighted average of EB07A-E; DC
Thrombocytopenia	281.96	Weighted average of SA12G-SA12K; DC
Vomiting	382.30	Weighted average of FD10C-M; DC

[a]NHS Improvement. NHS Reference Cost Schedule, 2017–18 unless stated otherwise.
AE, adverse event; DC, day case; NEL, non-elective inpatients; NES, non-elective short stay; PSSRU, Personal Social Services Research Unit

B.3.5.7 Miscellaneous unit costs and resource use

A separate cost of death was not applied to the model as it was assumed the costs for supportive care after progression would be accounted for in the cancer-related palliative care costs for progressed patients. Cost and resource use for death from other causes is not included in the model.

B.3.6 Summary of base-case analysis inputs and assumptions

B.3.6.1 Summary of base-case analysis inputs

The inputs and variables of the cost-effectiveness analysis are summarised in Table 59.

Table 59. Summary of variables applied in the economic model base case

Variable	Value	Reference to section in submission
Model settings		
Discount rate (costs), %	3.5%	B.3.2
Discount rate (benefits), %	3.5%	B.3.2
Time horizon, years	45	B.3.2
Patient characteristics		
Starting age, years	69.0	B.3.2
Male, %	50.0	B.3.2
Mean weight, kg	74.86	B.3.5.2
Mean BSA, m^2	1.85	B.3.5.2
Clinical inputs		
PFS (Pola+BR and BR)	Generalised gamma cure-mixture distribution	B.3.2
OS (Pola+BR and BR)	Generalised gamma cure-mixture distribution informed by PFS	B.3.3
TTOT (Pola+BR and BR)	TTOT KM data from GO29365	B.3.3.4
AE frequency	*Various*	B.3.5
AE duration	*Various*	B.3.5
Utilities		
PFS	0.72	B.3.4.5
PFS (>2 years)	Age- and sex-matched general population mortality	B.3.4.5
PD	0.65	B.3.4.5
AE disutilities	*Various*	B.3.4.4
Costs		
Polatuzumab vedotin, acquisition cost per cycle (no vial sharing)	[redacted]	B.3.5.2
Rituximab, acquisition cost per cycle (no vial sharing)	£581.52	B.3.5.2
Bendamustine, acquisition cost per cycle (no vial sharing)	£95.95	B.3.5.2
Gemcitabine, acquisition cost per cycle (no vial sharing)	£17.84	B.3.5.2
Oxaliplatin, acquisition cost per cycle (no vial sharing)	£13.87	B.3.5.2
Pola+BR, administration cost per cycle (cycles 1–6)	£749.40	B.3.5.3
BR, administration cost per cycle (first cycle)	£718.20	B.3.5.3
BR, administration cost per cycle (subsequent cycle)	£652.20	B.3.5.3
R-GemOx, administration cost per cycle (first and subsequent cycles)	£340.42	B.3.5.3
PFS on-treatment supportive care, cost per cycle	£460.22	B.3.5.4

PFS off-treatment (up to 2 years) supportive care, cost per cycle	£160.21	B.3.5.4
PD supportive care, cost per cycle	£363.64	B.3.5.4
Subsequent treatment costs	£593.16	B.3.5.5
Adverse event management costs	*Various*	B.3.6.5

AE, adverse event; BR, bendamustine + rituximab; BSA, body surface area; CI, confidence internal; KM, Kaplan Meier; OS, overall survival; PD, progressed disease; PFS, progression-free survival; Pola+BR, polatuzumab + bendamustine + rituximab, R-GemOx, rituximab + gemcitabine + oxaliplatin; TTOT, time-to-off-treatment

B.3.6.2 Assumptions

The key assumptions of the economic model are summarised in Table 60.

Table 60: Key assumptions in the economic analysis

Assumption	Justification	Addressed in scenario analysis
BR was selected as the key comparator to Pola-BR in the base case, as it was considered representative of standard of care therapy used to treat transplant-ineligible R/R DLBCL patients in the UK.	As discussed in Section B.1.1 and B.1.3, there is no universally accepted regimen for transplant-ineligible R/R DLBCL patients in the UK. The treatment landscape is fragmented, with no clear guideline followed by all UK centres for the treatment of R/R patients, particularly those ineligible for SCT. Patients are offered a chemotherapy regimen with rituximab, with the regimen depending on the expertise of the treatment centre, informed by individual clinician and patient choice. There is no evidence from the literature to suggest that one regimen is superior to another and clinical experts consulted by Roche and in previous TAs in DLBCL deem chemotherapy regimens at this line of treatment to have a similar efficacy level (69, 70). Real-world evidence is available to suggest that efficacy levels between BR and R-GemOx are similar (96). Given the above, and the fact that a reliable comparison based on RCT data between Pola-BR and BR can be made, BR was selected as the key comparator in the base case, to provide an informative analysis for decision-making that is associated with minimal bias.	Inclusion of R-GemOx as a comparator was explored in a scenario analysis, where the same efficacy as BR was assumed.
In the base case, for both treatment arms, PFS is extrapolated using cure-mixture modelling, and OS is extrapolated using cure-mixture modelling informed by PFS. (Both outcomes use the generalised gamma function.)	As discussed in Section B.3.3.1, evidence from the literature and clinical expert opinion is that DLBCL patients have the potential to experience long-term survival aligned with the general population if they achieve two-years' remission following treatment. KM data from GO29365 for PFS and OS demonstrate a decline in the rate of progression and death, respectively, towards the end of follow-up, and this is evident around the 24-month time point. It is therefore assumed that a cure fraction is present among the population, which follows the age- and gender-matched general population mortality. Given the relationship between long-term remission and long-term survival in DLBCL, utilising the PFS cure fraction to inform the OS extrapolation was deemed to be representative of the underlying clinical basis of this relationship.	Best-fitting standard parametric survival functions modelled dependently and independently were explored in scenario analyses for both PFS and OS. For OS, cure-mixture extrapolations not informed by PFS were explored. A scenario in which the background (general population) mortality for patients in the cure fraction is multiplied with a hazard ratio of 1.1, to reflect the fact that

		the intensive therapy that patients have received for DLBCL.
Health state utilities were assumed to be independent of the treatment received. Differences in the AE profile were captured through modelling AEs disutilities for ≥Grade 3 treatment-related AEs deemed to be serious.	In the absence of trial-based by-arm utility data, no differences in health state utility values were assumed. This assumption was supported by clinical expert opinion.	Alternative health state utility values sourced from recent TAs in DLBCL were explored in scenario analyses.
Patients who have remained in the PFS state for two years revert to age- and sex-matched general population utilities for the UK, based on Ara and Brazier 2010 (119).	The natural history of R/R DLBCL and evidence from Maurer et al. 2014 (93) (as discussed in Section B.3.3.1), is that patients who achieve sustained remission for up to two years are considered to experience long-term survival aligned to that of the general population. It is therefore assumed that a similar utility to the age- and sex-matched general population is accrued in these patients.	A scenario in which the time point at which patients switch to general population utility is extended to five years.
In the base case, the drug acquisition costs of supplying 140 mg and 30 mg vials of polatuzumab vedotin with no vial sharing are calculated.	This arrangement represents the way in which it is anticipated polatuzumab vedotin will be supplied in the long-term (upon availability of 30 mg vial sizes [anticipated in [redacted]]).	In a scenario analysis, drug acquisition costs for polatuzumab vedotin were based on an interim supply arrangement (anticipated to be put in place until the availability of 30 mg vials in [redacted]), in which hospitals order IV bags ready for infusion with the correct patient-specific dosing from a compounding facility has been explored. For completeness, a scenario is also included investigation the use of 140 mg vials only, with no vial sharing.

A 50% discount to the acquisition cost of rituximab biosimilar has been applied.	A national tendering process for rituximab biosimilar medicines has been performed, and discounts negotiated between NHS England and providers are commercial in confidence. A 50% discount has therefore been assumed. Given that rituximab is an element of both the intervention and comparators arms, the effect of this discount on cost-effectiveness is neutral.	Given that the effect of this discount on cost-effectiveness is small as rituximab is used in both arms, alteration of this discount has not been explored in sensitivity analyses.
No vial sharing is assumed for rituximab, bendamustine, oxaliplatin and gemcitabine in the base case.	This is a consistent approach for different drugs in the model. For rituximab (biosimilar) or generic chemotherapy, wastage assumptions have little impact on the acquisition costs.	As this approach has little impact on the acquisition costs, it is not explored in a sensitivity analysis.
Patients remaining in PFS for two years do not accumulate further supportive care costs.	As discussed in Section B.3.3.1, evidence from the literature and expert clinician opinion is that patients who achieve sustained remission for a period of two years are no longer at risk of progression, and experience a rate of mortality aligned to that of the general population. Given that such patients are considered to be in long-term remission, it was assumed that they would not accumulate supportive care costs beyond the two-year time point.	A scenario is performed where supportive care costs are extended to three years.
Supportive care costs were modelled independently of treatment.	In the absence of trial-based by-arm resource use data, no differences in health state supportive care costs were assumed. This assumption was supported by clinical opinion (35).	This assumption was deemed to be associated with a minimal impact on cost-effectiveness, and was therefore not tested in a scenario.
CAR-T and SCT are not included as subsequent therapies following Pola+BR or BR.	GO29365 was not designed to investigate Pola+BR or BR as a salvage regimen for potential transplant candidates, and the comparator regimens identified in the scope are similarly unlikely to be considered as salvage therapies prior to SCT in clinical practice, as per NICE and ESMO guidance (see Section B.1.3.2). Only a small number of patients underwent post-treatment SCT in the trial. GO29365 was similarly not designed to investigate either Pola+BR or BR as a bridging regimen to CAR-T therapy, although patients could potentially receive CAR-T treatment after progression. An imbalance between the use of curative treatments between treatment arms could potentially bias OS survival estimates. In the Pola+BR treatment arm one patient received subsequent SCT and two patients received CAR-	Given the demonstrated minimal impact on OS of post-treatment SCT and CAR-T, and the fact that they are unlikely to be used in this position in the treatment pathway in clinical practice, this assumption was not tested in a scenario.

	T cells, one of whom subsequently died. In the BR arm, one patient received SCT and no patients received CAR-T cells. The influence of treatments with curative intent (i.e. CAR-T or SCT) was explored by comparing the GO29365 KM OS data for the ITT patient population with a population censored for patients who had received SCT or CAR-T therapies at the time this was received. No difference between the ITT population and the censored population was observed, indicating that OS in the patient population was not affected by subsequent treatments in either arm. As CAR-T therapies are currently funded by the CDF, they are not considered as part of standard NHS clinical practice.	

AE, adverse events; BR, bendamustine + rituximab; BS, biosimilar; CAR-T, chimeric antigen receptor T-cell; CDF, Cancer Drugs Fund; DLBCL, diffuse large B-cell lymphoma; ESMO, European Society for Medical Oncology; ITT, intent-to-treat; IV, intravenous; KM, Kaplan-Meier; NHS, National Health Service; NICE, National Institute for Health and Care Excellence; Pola+BR, polatuzumab + bendamustine + rituximab; OS, overall survival; PFS, progression-free survival; RCT, randomised controlled trial; R-GemOx, rituximab + gemcitabine + oxaliplatin; R/R, relapsed/refractory; SCT, stem cell transplant; TA, technology appraisal; UK, United Kingdom

B.3.7 Base-case results

B.3.7.1 Base-case incremental cost-effectiveness analysis results

The base case pairwise comparison results for Pola+BR vs BR are presented in Table 61. The clinical outcomes and disaggregated base case cost-effectiveness results are presented in Appendix J.

The base case cost-effectiveness results demonstrate that Pola+BR is cost-effective vs BR, at an incremental cost-effectiveness ratio (ICER) of £26,877 per QALY. Pola+BR accrued a greater health benefit compared to BR, as demonstrated by an incremental QALY value of [redacted].

Table 61. Base case deterministic results

Intervention	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)
Pola+BR	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£26,877
BR	£18,019	1.00	0.68	-	-	-	-

BR, bendamustine + rituximab; ICER, incremental cost-effectiveness ratio; LYG, life years gained; Pola+BR, polatuzumab + bendamustine + rituximab; QALYs, quality-adjusted life years

B.3.8 Sensitivity analyses

B.3.8.1 Probabilistic sensitivity analysis

The uncertainty arising from the imprecision associated with model input parameter estimates was investigated via probabilistic sensitivity analysis (PSA). A Monte-Carlo simulation was conducted using 2,000 iterations based upon model inputs randomly drawn from distributions around the mean (summarised in Table 62). Variation in the parameterisation of the PFS and OS extrapolations was based on normal distributions and where appropriate, covariance matrices.

Where available, the standard error (SE) calculated from the same data used to derive the mean value estimate was used to inform the distribution of the input parameter. Alternatively, the SE was calculated for AE disutility inputs as 10% of the mean estimate, or for cost inputs via the following equation:

$$SE = (LN(mean + 20\%) - LN(mean - 20\%))/4$$

Table 62. PSA parameter inputs

Parameter	Distribution	Mean	SE	Alpha	Beta
Survival modelling					
Parametric estimates for OS and PFS	Normal distribution around parameter estimates, informed where appropriate, by covariance matrices				
Utilities					
Utility in PFS, both treatment arms	Beta	0.72	0.03	62.44	160.56
Utility in PD, both treatment arms	Beta	0.65	0.06	21.76	40.42
Disutility due to adverse events					
Acute kidney injury	Normal	0.27	0.027	N/A Parameter input variation (SE) equal to 10% of mean estimate	
Atrial fibrillation	Normal	0.37	0.037		
Atrial flutter	Normal	0.37	0.037		
Anaemia	Normal	0.25	0.025		
Cytomegalovirus infection	Normal	0.15	0.015		
Decreased appetite	Normal	0.37	0.037		
Diarrhoea	Normal	0.10	0.010		
Febrile neutropenia	Normal	0.15	0.015		
Herpes virus infection	Normal	0.15	0.015		
Leukoencephalopathy	Normal	0.37	0.037		
Leukopenia	Normal	0.09	0.009		
Lower respiratory tract infection	Normal	0.20	0.020		
Meningoencephalitis herpetic	Normal	0.15	0.015		
Myelodysplastic syndrome	Normal	0.37	0.037		
Neutropenia	Normal	0.09	0.009		
Neutropenic sepsis	Normal	0.15	0.015		
Oedema peripheral	Normal	0.37	0.037		
Pneumonia	Normal	0.20	0.020		
Pulmonary oedema	Normal	0.37	0.037		
Pyrexia	Normal	0.11	0.011		
Septic shock	Normal	0.37	0.037		
Supraventricular tachycardia	Normal	0.37	0.037		
Thrombocytopenia	Normal	0.11	0.011		
Vomiting	Normal	0.05	0.005		
Administration costs, Pola+BR (£)					
Administration cost, first treatment cycle	Log-normal	686.86	0.1014		
Pharmacy cost, first treatment cycle	Log-normal	62.40	0.1014		

Administration cost, subsequent treatment cycles	Log-normal	686.86	0.1014	N/A Parameter input variation (SE) calculated from upper and lower estimates of base case value ±20%
Pharmacy cost, subsequent treatment cycles	Log-normal	62.40	0.1014	
Administration costs, BR (£)				
Administration cost, first treatment cycle	Log-normal	686.86	0.1014	N/A Parameter input variation (SE) calculated from upper and lower estimates of base case value ±20%
Pharmacy cost, first treatment cycle	Log-normal	31.20	0.1014	
Administration cost, subsequent treatment cycles	Log-normal	686.86	0.1014	
Pharmacy cost, subsequent treatment cycles	Log-normal	31.20	0.1014	
Supportive care costs (£)				
Residential care (day)	Log-normal	114.50	0.1014	N/A Parameter input variation (SE) calculated from upper and lower estimates of base case value ±20%
Day care (day)	Log-normal	58.00	0.1014	
Home care (day)	Log-normal	33.32	0.1014	
Hospice (day)	Log-normal	157.08	0.1014	
Oncologist (visit)	Log-normal	165.85	0.1014	
Haematologist (visit)	Log-normal	164.80	0.1014	
Radiologist (visit)	Log-normal	187.30	0.1014	
Nurse (visit)	Log-normal	38.45	0.1014	
Specialist nurse (visit)	Log-normal	38.45	0.1014	
GP (visit)	Log-normal	37.40	0.1014	
District nurse (visit)	Log-normal	38.45	0.1014	
CT scan	Log-normal	163.66	0.1014	
Full blood counts	Log-normal	2.51	0.1014	
LDH	Log-normal	2.51	0.1014	
Liver function	Log-normal	2.51	0.1014	
Renal function	Log-normal	2.51	0.1014	
Immunoglobulin	Log-normal	2.51	0.1014	
Calcium phosphate	Log-normal	2.51	0.1014	
Inpatient day	Log-normal	383.47	0.1014	
Palliative care team	Log-normal	117.84	0.1014	
Subsequent care costs, PD				
Chemotherapy	Log-normal	1,116.40	0.1014	
R + chemotherapy	Log-normal	2,860.98	0.1014	
Rituximab	Log-normal	2,765.83	0.1014	

Radiotherapy	Log-normal	162.88	0.1014	N/A Parameter input variation (SE) calculated from upper and lower estimates of base case value ±20%
ECG	Log-normal	107.84	0.1014	
MUGA	Log-normal	285.04	0.1014	
MRI	Log-normal	140.60	0.1014	
PET-CT	Log-normal	470.71	0.1014	
Bone marrow biopsy	Log-normal	519.82	0.1014	
Adverse event management costs (£)				
Acute kidney injury	Log-normal	332.50	0.101	N/A Parameter input variation (SE) calculated from upper and lower estimates of base case value ±20%
Atrial fibrillation	Log-normal	670.13	0.101	
Atrial flutter	Log-normal	670.13	0.101	
Anaemia	Log-normal	309.09	0.101	
Diarrhoea	Log-normal	392.26	0.101	
Febrile neutropenia	Log-normal	1,847.50	0.101	
Leukopenia	Log-normal	291.00	0.101	
Neutropenia	Log-normal	291.00	0.101	
Pneumonia	Log-normal	495.81	0.101	
Lower respiratory tract infection	Log-normal	377.90	0.101	
Pyrexia	Log-normal	309.56	0.101	
Septic shock	Log-normal	1,037.71	0.101	
Thrombocytopenia	Log-normal	281.96	0.101	
Vomiting	Log-normal	382.30	0.101	
Cytomegalovirus infection	Log-normal	393.65	0.101	
Decreased appetite	Log-normal	382.30	0.101	
Supraventricular tachycardia	Log-normal	670.13	0.101	
Herpes virus infection	Log-normal	377.90	0.101	
Meningoencephalitis herpetic	Log-normal	3,652.18	0.101	
Myelodysplastic syndrome	Log-normal	556.99	0.101	
Neutropenic sepsis	Log-normal	1,847.50	0.101	
Oedema peripheral	Log-normal	343.16	0.101	
Leukoencephalopathy	Log-normal	3,609.61	0.101	
Pulmonary oedema	Log-normal	2,189.85	0.101	

BR, bendamustine + rituximab; CD20, B-lymphocyte antigen CD20; CT, computed tomography; ECG, electrocardiogram; GP, General Practitioner; LDH, lactate dehydrogenase test; MRI, magnetic resonance imaging; MUGA, multiple gated acquisition scan; N/A, not applicable; OS, overall survival; PD, progressed disease; PET-CT, positron emission tomography-computed tomography; PFS, progression-free survival; Pola+BR, polatuzumab + bendamustine + rituximab; R, rituximab; PSA, probabilistic sensitivity analysis; SE, standard error

The results of the PSA are presented in Table 63. The mean incremental costs and QALYs from the PSA were £[redacted] and [redacted] respectively, resulting in a mean ICER value of £41,326 per QALY.

Table 63. Mean probabilistic results

Intervention	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)
Pola+BR	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£41,326
BR	£18,076	1.00	0.68	-	-	-	-

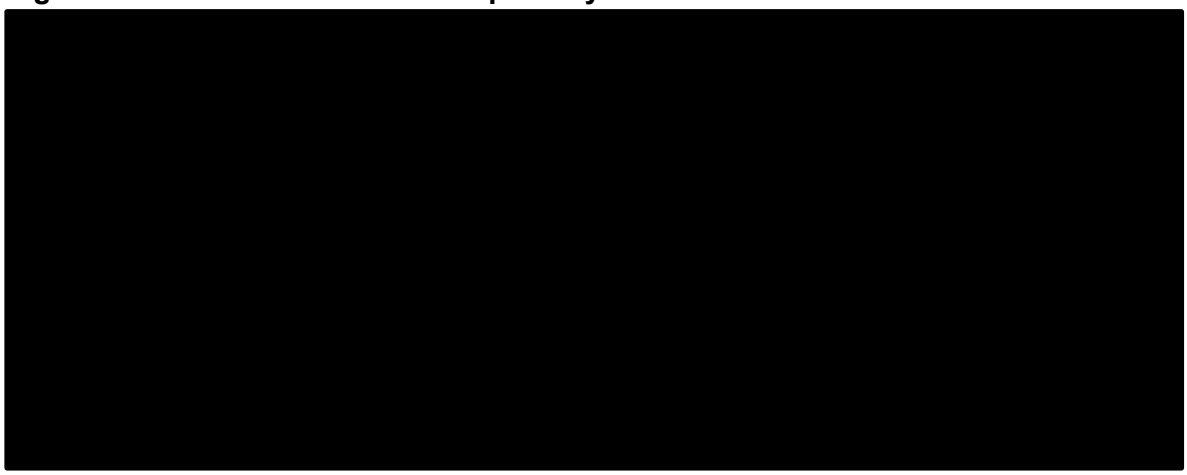
BR, bendamustine + rituximab; ICER, incremental cost-effectiveness ratio; LYG, life years gained; Pola+BR, polatuzumab + bendamustine + rituximab; QALYs, quality-adjusted life years

The cost-effectiveness plane is presented in Figure 28, including the percentile ranges (2.5% and 97.5%) for both incremental costs and QALYs and the 95% credibility ellipse. The cost-effectiveness acceptability curve (CEAC) for Pola+BR versus BR is presented in Figure 29. From the CEAC, at a willingness to pay (WTP) threshold of £50,000, the probability of Pola+BR being cost-effective relative to BR was [redacted].

Figure 28. Cost-effectiveness plane for Pola+BR versus BR

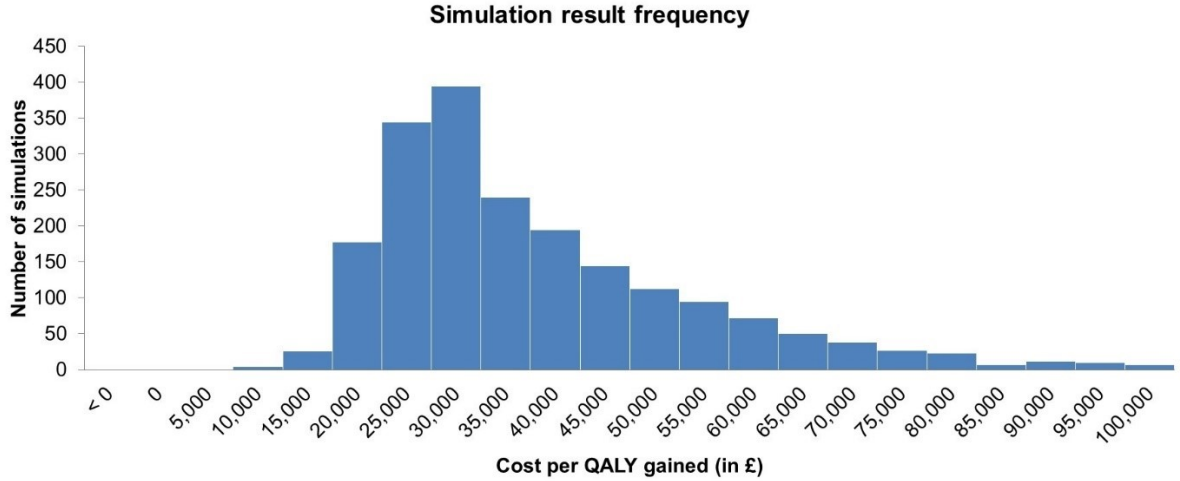
BR, bendamustine + rituximab; Pola+BR, polatuzumab + bendamustine + rituximab; QALY, quality-adjusted life year

Figure 29. Cost-effectiveness acceptability curve for Pola+BR versus BR



BR, bendamustine + rituximab; Pola+BR, polatuzumab + bendamustine + rituximab; WTP, willingness to pay.

Figure 30. Distribution of PSA ICER values for Pola+BR versus BR



BR, bendamustine + rituximab; ICER, incremental cost-effectiveness ratio; Pola+BR, polatuzumab + bendamustine + rituximab; PSA, probabilistic sensitivity analysis; QALY: quality adjusted life year

Selection of the generalised gamma distribution for survival modelling is likely to have contributed to the variation observed in the PSA. Survival models for PFS and OS based upon the generalised gamma distribution were determined to be the best fit for the observed trial data. It should be noted that the generalised gamma distribution may subject to a greater degree of variation under probabilistic analysis, arising from the overall uncertainty in estimating additional parameters relative to other distribution models, which would therefore contribute to increased variation with respect to health benefits and costs. Further variation in the PSA results is likely to have arisen from the fact that input parameters used to model long-term survival and long-term remission are varied independently, whereas these inputs are likely to be correlated.

Whilst the mean probabilistic ICER was elevated relative to the deterministic value, a notable right skew in ICER values from the PSA was observed. It should be noted, however, that the

greatest frequencies of ICER values returned within the £25,000 to £30,000/QALY range (Figure 30).

B.3.8.2 Deterministic sensitivity analysis

Deterministic sensitivity analysis (DSA) was conducted by varying all parameters for which there were single input values. Each input parameter was set to its respective upper or lower bound and the deterministic results for the model recorded. For simplicity, the totals for each cost category were varied for the DSA whilst the impact of AE disutilities was investigated using the average disutility of all AEs, weighted by frequency and duration. The upper and lower bounds around the mean value for each input parameter were based upon the 10% and 90% percentile values obtained from the PSA input distribution. Where percentile estimates were not available, the input parameter was varied by ±20% (alternatively ±5 kg for mean weight, ±5% for mean BSA).

The DSA inputs and corresponding ICER values are summarised in Table 64.

Table 64. DSA results

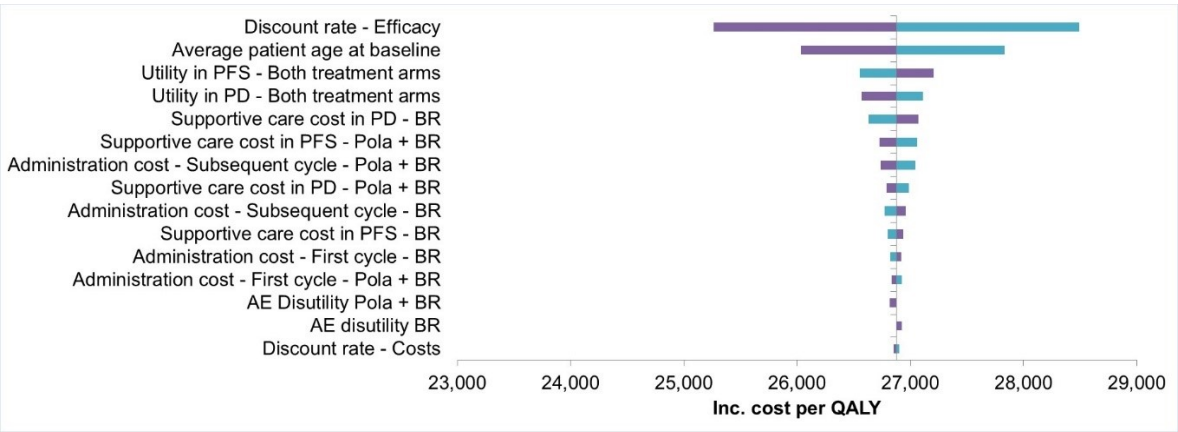
Parameter modified	Base value	Upper value	Lower value	Upper value ICER (£/QALY)	Lower value ICER (£/QALY)	Range (£/QALY)	% of base case
Base case				26,877		-	
Model settings							
Discount rate, costs	3.5%	4.2%	2.8%	26,901	26,854	46	0.17%
Discount rate, effects	3.5%	4.2%	2.8%	28,489	25,267	3,222	11.99%
Patient baseline characteristics							
Average patient age at baseline (+/- 5 years)	69.0	74.0	64.06	27,830	26,037	1,793	6.67%
Utilities							
Utility in PFS, all treatment arms	0.72	0.76	0.68	26,554	27,207	653	2.43%
Utility in PD, all treatment arms	0.65	0.71	0.57	27,112	26,569	542	2.02%
AE disutility, Pola+BR[b]	0.01	0.0175	0.0044	26,877	26,816	61	0.23%
AE disutility, BR[b]	0.01	0.0147	0.0037	26,877	26,928	51	0.19%
AE management costs							
AE management cost per patient, Pola+BR	337.27	356.13	321.93	26,886	26,869	18	0.07%
AE management cost per patient, BR	386.14	409.24	367.39	26,865	26,886	22	0.08%
Administration costs, Pola+BR							
Administration cost (first cycle)	749.40	845.17	666.83	26,926	26,834	92	0.34%
Administration cost (subsequent cycle)	749.40	843.41	670.86	27,044	26,737	307	1.14%

Administration costs, BR							
Administration cost (first cycle)	718.20	818.77	635.38	26,825	26,920	95	0.35%
Administration cost (subsequent cycle)	652.20	742.29	581.19	26,772	26,959	187	0.70%
Supportive care costs							
Supportive care cost in PFS - Pola+BR	160.21	167.29	154.53	27,063	26,727	336	1.25%
Supportive care cost in PFS - Pola+BR on treatment	460.22	483.65	441.42	26,877	26,877	0	0.00%
Supportive care cost in PFS - BR	160.21	167.29	154.53	26,802	26,936	134	0.50%
Supportive care cost in PFS - BR on treatment	460.22	483.65	441.42	26,877	26,877	0	0.00%
Supportive care cost in PD, Pola+BR	363.64	382.02	349.06	26,985	26,791	194	0.72%
Supportive care cost in PD, BR	363.64	382.02	349.06	26,630	27,072	442	1.64%
One-off costs, PD	593.16	474.52	711.79	26,932	26,822	110	0.41%

[a]Input parameter varied ±20% for the DSA; [b]Average of all AEs weighted by frequency and duration. AE, adverse event; BR, bendamustine + rituximab; BSA, body surface area; DSA, deterministic sensitivity analysis; ICER, incremental cost-effectiveness ratio; OS, overall survival; PD, progressed disease; PFS, progression-free survival; Pola+BR, polatuzumab + bendamustine + rituximab; QALY, quality-adjusted life year

A tornado diagram demonstrating the key drivers of ICER value in the comparison between Pola+BR and BR are presented in Figure 31. As shown below, the three parameters most influential on the model ICER value were discount rate for efficacy (i.e. health benefits), average patient age at baseline and utility in PFS. None of the input parameters investigated caused a substantial change in ICER relative to the base case, with the greatest range of ICER value being £3,222 (12.0% of base case; discount rate for efficacy).

Figure 31. Deterministic sensitivity analysis – tornado diagram of the top 15 most influential parameters for Pola+BR versus BR



BR, bendamustine + rituximab; PD, progressed disease; PFS, progression-free survival; Pola+BR, polatuzumab + bendamustine + rituximab; QALY, quality-adjusted life year

B.3.8.3 Scenario analysis

Scenarios using alternative utility data sets, parametric extrapolations and drug acquisition costs were explored as described below, with the results summarised in Table 65.

Deterministic ICER values from the scenario analyses listed ranged from £24,376 to £59,753/QALY. The three most influential (groups of) scenarios were the application of standard parametric survival modelling, the reduction of the model time horizon to 10 years and the use of 140 mg vials polatuzumab vedotin only (no vial sharing), which resulted in approximate increases in ICER of up to 122.3%, 58.8% and 35.8% respectively, relative to the base case. These scenarios are discussed below. No other scenario exceeded a change in ICER value of over 12.3%.

Table 65: Scenario analysis results

Parameter modified	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)	% change from base case ICER
Base case	[redacted]	[redacted]	26,877	0
Model time horizon				
Time horizon, 10 years	[redacted]	[redacted]	42,677	58.8%
Time horizon, 20 years	[redacted]	[redacted]	30,183	12.3%
Time horizon, 30 years	[redacted]	[redacted]	27,629	2.8%
Patient baseline characteristics				
Average patient weight (- 5 kg)	[redacted]	[redacted]	25,399	−5.5%
Average patient weight (+ 5 kg)	[redacted]	[redacted]	28,494	6.0%
Average patient BSA (m^2) (-5%; average body weight set to 66.35 kg)	[redacted]	[redacted]	24,376	−9.3%
Average patient BSA (m^2) (+5%; average body weight set to 83.96 kg)	[redacted]	[redacted]	29,778	10.8%
Utilities				
Utility values PFS/PD from TA567 (70)	[redacted]	[redacted]	26,596	−1.0%
Utility values PFS/PD from TA306 (67)	[redacted]	[redacted]	26,668	−0.8%
PFS – decline in utility in the 3 months prior to death	[redacted]	[redacted]	27,544	2.5%
Long-term survivor utility aligned to general population after 5 years	[redacted]	[redacted]	27,316	1.6%
Survival modelling				
Cure-mixture model (OS, PFS), Log-normal	[redacted]	[redacted]	27,349	1.8%
Cure-mixture model (OS, PFS), Log-logistic	[redacted]	[redacted]	25,721	−4.3%
Dependent parametric distribution function (OS, PFS), generalised gamma	[redacted]	[redacted]	52,178	94.1%
Dependent parametric distribution function (OS, PFS), log-normal	[redacted]	[redacted]	58,191	116.5%
Dependent parametric distribution function (OS, PFS), log-logistic	[redacted]	[redacted]	59,753	122.3%
Independent parametric distribution function (OS, PFS), generalised gamma	[redacted]	[redacted]	33,126	23.3%

Independent parametric distribution function (OS, PFS), log-normal	[redacted]	[redacted]	59,241	120.4%
Independent parametric distribution function (OS, PFS), log-logistic	[redacted]	[redacted]	56,339	109.6%
OS not informed by PFS (cure-mixture extrapolation), generalised gamma (PFS and OS)	[redacted]	[redacted]	26,223	−2.4%
OS not informed by PFS (cure-mixture extrapolation), log-normal (PFS and OS)	[redacted]	[redacted]	27,795	3.4%
OS not informed by PFS (cure-mixture extrapolation), log-logistic (PFS and OS)	[redacted]	[redacted]	26,052	−3.1%
Excess mortality for long-term survivors (>2 years; excess hazard = 1.1)	[redacted]	[redacted]	27,894	3.8%
Costs and resource use				
140 mg vials polatuzumab vedotin only, no vial sharing	[redacted]	[redacted]	36,502	35.8%
140 mg vials polatuzumab vedotin only, 100% vial sharing	[redacted]	[redacted]	25,196	−6.3%
No supportive care costs incurred by long term survivors after 3 years	[redacted]	[redacted]	27,868	3.7%
Alternative comparator				
Pola + BR vs R-GemOx	[redacted]	[redacted]	28,410	5.7%

BR, bendamustine + rituximab; BSA, body surface area; ICER, incremental cost-effectiveness ratio; OS, overall survival; PD, progressed disease; PFS, progression-free survival; Pola+BR, polatuzumab + bendamustine + rituximab; QALY, quality-adjusted life year; R-GemOx, gemcitabine + oxaliplatin + rituximab.

Standard parametric survival scenarios

As a group, the application of standard dependent and independent parametric models for PFS and OS extrapolation produced changes in ICER value of between −2.4% and 122.3%. It should be noted, however, that the standard parametric extrapolations are less clinically plausible based upon clinical expert opinion with regards to long-term patient survival in DLBCL (as described in Sections B.3.3.1 to B.3.3.3). Specifically, the standard parametric survival models do not directly capture patients who go on to achieve sustained remission and subsequent long-term survival following treatment, whereas the parameterisation of cure-mixture models directly captures patients who go on to experience long-term survival aligned to that of the general population. Relative to the base case, application of the standard parametric extrapolations is therefore likely to underestimate the survival benefit and thus the cost effectiveness of Pola+BR vs BR.

10-year time horizon

A reduction in time horizon would be expected to result in a notable difference in ICER value relative to the base case. This is on the basis that a proportion of patients are likely to achieve sustained remission and long-term survival following treatment with Pola+BR (as discussed previously). A short time horizon would therefore not capture the full benefits derived from treatment with Pola+BR. Accordingly, a lifetime horizon of 45 years, as used in

the base case analysis and recommended by the NICE reference case (91), is the most appropriate length of time to capture the full cost and QALYs associated with Pola+BR.

Polatuzumab vedotin 140 mg vials (no sharing)

As discussed in Section B.3.5.2, the drug acquisition costs in the model were explored in scenarios given the anticipated short- and long-term supply arrangements for polatuzumab vedotin. Relative to the base case of 140 mg and 30 mg vial availability (assuming no vial sharing), an increase in ICER value of 35.8% was observed in the scenario using 140 mg vials polatuzumab vedotin only (no vial sharing or compounding costs). This scenario represents the case that a compounding arrangement is not adopted for interim supply of polatuzumab vedotin and vials could not be shared due to a low number of patients. However, since it is planned that temporary arrangements with compounders will be in place resulting in a '100% vial sharing' scenario for the drug acquisition costs until availability of the 30 mg vial (expected in [redacted]), the base case provides the most informative results in terms of the long-term cost-effectiveness of Pola+BR.

Other scenarios of note that warrant discussion are inclusion of R-GemOx as a comparator, application of general population utility at five years, assuming excess mortality for long-term survivors and no supportive care costs after three years.

Exploration of the Pola+BR cost-effectiveness using R-GemOx as an alternative comparator (as detailed in Section B.3.2.3), resulted in an ICER value of £28,410. Therefore, at a WTP threshold of £50,000/QALY, Pola+BR is considered cost-effective compared to R-GemOx.

The assumption that patient utility in the PFS health state declines in the three months prior to death was found to result in a marginal change in ICER value of only 2.5%. Extending the time point at which long-term survivor utility is assumed to be equal to that of general population to five years, resulted in an increased ICER value of only 1.6%, whereas assuming long-term survivors retained a residual excess risk of mortality compared to the general population changed the deterministic ICER value by approximately 3.8%. Extending the time point at which long-term survivors no longer incurred supportive care costs from two to three years, resulted in an increase in ICER value of approximately 3.7%.

B.3.8.4 Summary of sensitivity analyses results

From the PSA, Pola+BR was cost-effective over BR in more than [redacted] of simulations at a WTP threshold over £35,000/QALY and in [redacted] of simulations at a WTP threshold of £50,000/QALY. Variation in the PSA may be attributed to the parameter uncertainty around the use of the generalised gamma distribution for modelling survival and the independent variation of input parameters for long-term survival and long-term remission.

Whilst the DSA identified that discount rate for efficacy, average patient age at baseline and utility in PFS had the greatest influence on ICER value, none were found to result in a range of ICER values greater than a total of £3,222.

The scenarios considered in Section B.3.8.3 resulted in ICER values that ranged from £24,376 to £59,753. It was noted that standard parametric survival modelling resulted in the largest deviation from the base case ICER value. However, as discussed previously, these models were considered to lack clinical plausibility and did not represent the observed trial data relative to the cure-mixture approach with respect to their ability to reflect long-term patient remission and survival. On the other hand, alternative plausible cure-mixture models confirmed the robustness for the base case findings. After standard parametric survival modelling, the reduction of the model time horizon to 10 years and the use of 140 mg vials polatuzumab vedotin only (no vial sharing), were found to have had the largest effect on ICER values.

In conclusion, the DSA and scenario analyses demonstrate the robustness of the base case results with respect to both the combined uncertainty of the model parameter inputs and the alternative plausible approaches and assumptions explored in the scenario analyses.

B.3.9 Subgroup analysis

No subgroups were evaluated in the economic analysis.

B.3.10 Validation

B.3.10.1 Validation of cost-effectiveness analysis

The model methodology was designed to align with NICE's preferred methods. As described in Section B.3.2, an AUC (or partitioned survival analysis) structure was selected for the analysis based on guidance provided in TSD 19 (94) and precedent of Committee acceptance in recent appraisals for interventions in DLBCL (69, 70). Learnings gleaned from these two appraisals in terms of Committee preferences were taken into account in the building of this model. The model was built to align with the NICE reference case (91), adopting an NHS and PSS perspective, a lifetime time horizon to fully capture all costs and QALY gains associated with the interventions, and discount rates for costs and benefits of 3.5%. Finally, health state utility values were selected based on a trial of representative DLBCL patients, for which utilities were cross-walked from the EQ-5D-5L to the 3L, in line with NICE's position statement (110).

Clinical expert opinion was sourced during model development to guide the making of assumptions in the model, to ensure they were clinically valid and/or aligned with UK clinical practice for transplant-ineligible R/R DLBCL patients. Specifically, an advisory board of nine

UK clinicians was held in October 2018 to discuss the natural history of R/R DLBCL and standard clinical practice in the UK (35) in order to inform the model.

The plausibility of long-term extrapolations for PFS and OS was validated through comparison to long-term data for polatuzumab vedotin regimens in DLBCL (see Section B.3.3.3). The validation illustrated that the base case long-term OS extrapolation for Pola+BR may be deemed conservative.

B.3.10.2 Validation of model clinical outcomes

A comparison of clinical outcomes produced by the model base case versus the results from GO29365 is presented in Table 66.

Table 66. Comparison of model clinical outcomes vs GO29365

Intervention	Median PFS (months)		Median OS (months)	
	Model	GO29365 (95% CI)	Model	GO29365 (95% CI)
Pola+BR	8.0	[redacted]	13.1	[redacted]
BR	2.1	[redacted]	5.1	[redacted]

BR, bendamustine + rituximab; OS, overall survival; PFS, progression-free survival; Pola+BR, polatuzumab + bendamustine + rituximab

B.3.11 Interpretation and conclusions of economic evidence

A *de novo* economic analysis was conducted to evaluate the cost-effectiveness of Pola+BR vs BR in the treatment of transplant-ineligible, R/R DLBCL patients in the UK. The patient population included in the analysis reflects the GO29365 trial and is aligned with the population specified in the NICE final scope (95).

The economic analysis can be considered generalisable to the UK; the patient population in GO29365 is aligned with the population to be treated in UK clinical practice, and three patients from the trial were treated in the UK, with 39/86 enrolled patients treated in Europe. The analysis was conducted from an NHS and PSS perspective, with health state resource utilisation based on a survey of UK physicians (67). Finally, key clinical assumptions in the model were validated in a recent advisory board of clinicians treating DLBCL patients in the UK (35).

Extensive survival analysis was performed during model development to explore a wide range of functions that would provide a close fit to the observed OS and PFS data from GO29365 and a clinically feasible long-term extrapolation. This included the exploration of cure-mixture models, which are able to reflect the natural history expressed by expert clinical opinion (35) that R/R DLBCL patients who achieve two years' PFS are likely to subsequently

experience long-term remission and survival aligned to the general population. The long-term plausibility of the cure-mixture models selected for the base case was validated against long-term survival data currently available for polatuzumab vedotin regimens in DLBCL.

An inherent limitation in the field of DLBCL is the lack of robust and comparable studies assessing therapies for R/R DLBCL, thus limiting the number of interventions from the NICE scope that could be included in the model. However, robust comparative evidence between Pola+BR and BR available from the randomised GO29365 study enabled BR to be selected as the key comparator to Pola+BR in the model base case. Feedback from practising clinicians was that choice of chemotherapy regimen for transplant-ineligible, R/R DLBCL in the UK varies significantly between centres and is guided by the expertise of the treatment centre and patient choice; overall, different regimens are considered to have a similar level of efficacy (35). Given this, and similarity in cost between regimens, BR was considered to be suitably representative of chemotherapy regimens used for the treatment of transplant-ineligible, R/R DLBCL patients in the UK.

Minimal variation from the base case was observed in the deterministic sensitivity and scenario analyses in the majority of cases, demonstrating the robustness of the model. Scenarios in which standard parametric survival models were investigated resulted in the largest deviation from the base case ICER, however, as discussed previously, these models are considered to lack clinical plausibility relative to the cure-mixture modelling approach, which is able to directly capture patients achieving sustained remission following treatment. On the other hand, plausible alternative cure-mixture models confirmed the base case results. Variation in the mean probabilistic results versus the base case was observed, which may be attributed to the parameter uncertainty around the use of the generalised gamma distribution for modelling survival, and the independent variation of input parameters for long-term survival and long-term remission.

Overall, the economic analysis demonstrated that Pola+BR offers a new cost-effective treatment option for transplant-ineligible, R/R DLBCL patients who have a high unmet medical need, who may be rapidly progressing and need urgent disease control. Cost-effectiveness of Pola+BR is driven by the substantially greater survival and associated QALY gain for patients treated with Pola+BR compared to current standard of care.

B.4 References

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Polatuzumab vedotin with rituximab and bendamustine for treating relapsed or refractory diffuse large B-cell lymphoma [ID1576]

Clarification questions

August 2019

File name	Version	Contains confidential information	Date
ID1576_polatuzumab vedotin RR DLBCL_ACIC_ERG Clarification Responses_040919	1.0	Yes	4th September 2019

Notes for company

Highlighting in the template

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Section A: Clarification on effectiveness data

Literature searching

A1. Only search strategies for the 4 September 2018 searches have been provided in Appendix D. For transparency, please supply the update search strategies for clinical effectiveness detailed in Appendix D reported as conducted in June 2019.

Search strategies for the 10 June 2019 searches are provided below.

Table 1: Embase <1980 to 2019 Week 23>; accessed on 10th June 2019

#	Searches	Results
1	exp Lymphoma, Large B-Cell, Diffuse/	8605
2	exp large cell lymphoma/	36840
3	(diffuse large B cell or DLBCL or DLBL).mp.	26676
4	aggressive B cell*.mp.	1781
5	(large B cell adj4 lymphoma*).mp.	26607
6	(diffuse adj4 lymphoma*).mp.	27901
7	1 or 2 or 3 or 4 or 5 or 6	45117
8	Clinical trial/	948271
9	Randomized controlled trial/	548231
10	controlled clinical trial/	462785
11	multicenter study/	217113
12	Phase 3 clinical trial/	40041
13	Phase 4 clinical trial/	3419
14	exp RANDOMIZATION/	82635

#	Searches	Results
15	Single blind procedure/	35254
16	Double blind procedure/	158149
17	Crossover procedure/	59264
18	Placebo/	321142
19	Randomi?ed controlled trial$.tw.	203186
20	Rct.tw.	32491
21	(random$ adj2 allocat$).tw.	39458
22	single blind$.tw.	22693
23	double blind$.tw.	191121
24	((treble or triple) adj blind$).tw.	941
25	Placebo$.tw.	284037
26	Prospective study/	522573
27	or/8-26	2114471
28	Case study/	61484
29	Case report.tw.	371853
30	letter/	988666
31	Editorial.pt.	592700
32	review.pt.	2413221
33	Note.pt.	755341
34	or/28-33	5148814
35	27 not 34	1764058
36	Clinical study/	109470
37	Case control study/	140932
38	Longitudinal study/	125741
39	Cohort analysis/	470719
40	(Cohort adj (study or studies)).mp.	262673
41	(Case control adj (study or studies)).tw.	122767
42	(follow up adj (study or studies)).tw.	56951
43	single arm.tw.	13097
44	(observational adj (study or studies)).tw.	144785
45	(epidemiologic$ adj (study or studies)).tw.	97884
46	(cross sectional adj (study or studies)).tw.	188442
47	or/36-46	1345946
48	47 not 34	1246828
49	35 or 48	2759483
50	exp bendamustine/ or (bendamustine or Treanda* or Treakisym* or Ribomustin* or Levact*).mp.	5943
51	exp rituximab/ or (rituximab or Rituxan* or MabThera).mp.	74666
52	exp brentuximab vedotin/ or (brentuximab or Adcetris* or SGN-35).mp.	3285
53	exp cyclophosphamide/ or (cyclophosphamide or lyophilized Cytoxan or Endoxan* or Cytoxan* or Neosar* or Procytox* or Revimmune* or Cycloblastin).mp.	202622
54	exp etoposide/ or (etoposide or Etopophos*).mp.	86184
55	exp Vincristine/ or (vincristine or Oncovin* or Vincasar*).mp.	97828
56	exp Procarbazine/ or (Procarbazine or Matulane* or Natulan* or Indicarb*).mp.	14120
57	(CEPP or CEOP or DA-EPOCH or EPOCH or GEMOX or CAPOX or PECC or IEV or MINE or ICE or IME).ti,ab.	53278
58	exp doxorubicin/ or (Doxorubicin or Adriamycin* or Caelyx* or Myocet* or Pegylated liposomal doxorubicin or doxil*).mp.	181643
59	exp gemcitabine/ or (gemcitabine or Gemzar*).mp.	53855

#	Searches	Results
60	exp oxaliplatin/ or (oxaliplatin or Eloxatin*).mp.	37170
61	exp cisplatin/ or (cisplatin or cisplatinum* or CDDP or Platin).mp.	181232
62	exp capecitabine/ or (capecitabine or Xeloda*).mp.	28152
63	exp vinorelbine/ or (Vinorelbine or Navelbine*).mp.	17616
64	exp dexamethasone/ or (dexamethasone or Decadron* or Dexasone* or Diodex* or Hexadrol* or Maxidexmp*).mp.	147666
65	exp carboplatin/ or (carboplatin or paraplatin*).mp.	66497
66	exp lenalidomide/ or (lenalidomide or Revlimid*).mp.	17705
67	exp ibrutinib/ or (ibrutinib or Imbruvica*).mp.	5205
68	exp Pixantrone/ or (Pixantrone or Pixuvri* or BBR 2778).mp.	251
69	exp cytarabine/ or (cytarabine or Cytosar-U or Depocyt*).mp.	55738
70	exp ifosfamide/ or (ifosfamide or Ifex*).mp.	29671
71	exp epirubicin/ or (epirubicin or Ellence*).mp.	28158
72	exp methotrexate/ or (methotrexate or Trexall* or MTX or Rheumatrex*).mp.	167580
73	exp mesna/ or (mesna or Mesnex*).mp.	6080
74	exp mitoxantrone/ or (mitoxantrone or Novantrone*).mp.	23173
75	chimeric antigen receptor T cells/ or Axicabtagene/ or (Axicabtagene or tisagenlecleucel or kymriah or CAR-T).tw.	4336
76	axicabtagene ciloleucel/ or yescarta.mp.	243
77	(DHAP or ESHAP).mp.	1524
78	(MOR208 or Xmab-5574).mp.	43
79	exp Prednisone/ or (prednisone or prednisolone or Deltasone* or Prednisone Intensol).mp.	271326
80	exp Polatuzumab vedotin/ or (polatuzumab or DCDS4501A or RG7596).mp.	144
81	Venetoclax/ or (ABT-199 or Venetoclax).mp.	2387
82	Apatinib/ or Apatinib.mp.	670
83	exp Chlorambucil/ or (chlorambucil or leukeran).mp.	15962
84	exp Lomustine/ or (lomustine or CeeNU or CCNU or Gleostine).mp.	10079
85	((best or supportive or standard or usual) adj3 (care or treatment*)).tw.	223993
86	BSC.tw.	3691
87	or/50-86	1242085
88	((second or third or fourth) adj3 line).tw.	42261
89	(refractory or intoleran* or failure* or resistan* or recurren* or metasta* or progress* or invasive* or chemorefractory or advanced or relapse*).tw.	5080049
90	((previous* or prior or salvage) adj3 (treat* or therap* or regimen*)).tw.	179571
91	88 or 89 or 90	5169218
92	((first or new*) adj1 diagnos*).ti,ab.	114651
93	91 not 92	5118437
94	7 and 49 and 87 and 93	2500
95	(Sep* 2018 or Oct* 2018 or Nov* 2018 or Dec* 2018 or Jan* 2019 or Feb* 2019 or Mar* 2019 or Apr* 2019 or May* 2019 or Jun* 2019).dp.	444432
96	94 and 95	154
97	limit 94 to dd=20180905-20190610	185
98	96 or 97	211

Table 2: Ovid MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations and Daily <1946 to June 07, 2019>. Accessed on 10th June 2019

#	Searches	Results
1	exp Lymphoma, Large B-Cell, Diffuse/	18656
2	(diffuse large B cell or DLBCL or DLBL).mp.	12819
3	aggressive B cell*.mp.	888
4	(large B cell adj4 lymphoma*).mp.	24809
5	(diffuse adj4 lymphoma*).mp.	26170
6	1 or 2 or 3 or 4 or 5	28115
7	exp bendamustine/ or (bendamustine or Treanda* or Treakisym* or Ribomustin* or Levact*).mp.	1173
8	exp rituximab/ or (rituximab or Rituxan* or MabThera).mp.	21244
9	exp brentuximab vedotin/ or (brentuximab or Adcetris* or SGN-35).mp.	881
10	exp cyclophosphamide/ or (cyclophosphamide or lyophilized Cytoxan or Endoxan* or Cytoxan* or Neosar* or Procytox* or Revimmune* or Cycloblastin).mp.	72132
11	exp etoposide/ or (etoposide or Etopophos*).mp.	24620
12	exp Vincristine/ or (vincristine or Oncovin* or Vincasar*).mp.	30667
13	exp Procarbazine/ or (Procarbazine or Matulane* or Natulan* or Indicarb*).mp.	4131
14	(CEPP or CEOP or DA-EPOCH or EPOCH or GEMOX or CAPOX or PECC or IEV or MINE or ICE or IME).ti,ab.	46833
15	exp doxorubicin/ or (Doxorubicin or Adriamycin* or Caelyx* or Myocet* or Pegylated liposomal doxorubicin or doxil*).mp.	73247
16	exp gemcitabine/ or (gemcitabine or Gemzar*).mp.	15792
17	exp oxaliplatin/ or (oxaliplatin or Eloxatin*).mp.	10577
18	exp cisplatin/ or (cisplatin or cisplatinum* or CDDP or Platin).mp.	73710
19	exp capecitabine/ or (capecitabine or Xeloda*).mp.	6479
20	exp vinorelbine/ or (Vinorelbine or Navelbine*).mp.	4018
21	exp dexamethasone/ or (dexamethasone or Decadron* or Dexasone* or Diodex* or Hexadrol* or Maxidexmp*).mp.	69080
22	exp carboplatin/ or (carboplatin or paraplatin*).mp.	16706
23	exp lenalidomide/ or (lenalidomide or Revlimid*).mp.	4142
24	exp ibrutinib/ or (ibrutinib or Imbruvica*).mp.	1561
25	exp Pixantrone/ or (Pixantrone or Pixuvri* or BBR 2778).mp.	97
26	exp cytarabine/ or (cytarabine or Cytosar-U or Depocyt*).mp.	16957
27	exp ifosfamide/ or (ifosfamide or Ifex*).mp.	6982
28	exp epirubicin/ or (epirubicin or Ellence*).mp.	7013
29	exp methotrexate/ or (methotrexate or Trexall* or MTX or Rheumatrex*).mp.	53397
30	exp mesna/ or (mesna or Mesnex*).mp.	1752
31	exp mitoxantrone/ or (mitoxantrone or Novantrone*).mp.	6096
32	chimeric antigen receptor T cells/ or Axicabtagene/ or (Axicabtagene or tisagenlecleucel or kymriah or CAR-T).tw.	1848
33	axicabtagene ciloleucel/ or yescarta.mp.	16
34	(DHAP or ESHAP).mp.	818
35	(MOR208 or Xmab-5574).mp.	7
36	exp Prednisone/ or (prednisone or prednisolone or Deltasone* or Prednisone Intensol).mp.	92892
37	exp Polatuzumab vedotin/ or (polatuzumab or DCDS4501A or RG7596).mp.	13
38	Venetoclax/ or (ABT-199 or Venetoclax).mp.	737
39	Apatinib/ or Apatinib.mp.	326
40	exp Chlorambucil/ or (chlorambucil or leukeran).mp.	5049

41	exp Lomustine/ or (lomustine or CeeNU or CCNU or Gleostine).mp.	3091
42	((best or supportive or standard or usual) adj3 (care or treatment*)).tw.	137267
43	BSC.tw.	2227
44	or/7-43	616694
45	((second or third or fourth) adj3 line).tw.	24387
46	(refractory or intoleran* or failure* or resistan* or recurren* or metasta* or progress* or invasive* or chemorefractory or advanced or relapse*).tw.	3828508
47	((previous* or prior or salvage) adj3 (treat* or therap* or regimen*)).tw.	101891
48	or/45-47	3887598
49	((first or new*) adj1 diagnos*).ti,ab.	66973
50	48 not 49	3861746
51	Randomized Controlled Trials as Topic/	124302
52	randomized controlled trial/	483466
53	Random Allocation/	99260
54	Double Blind Method/	151649
55	Single Blind Method/	26863
56	clinical trial/	516496
57	exp Clinical Trials as Topic/	326660
58	or/51-57	1120533
59	(clinical adj trial$).tw.	334470
60	((singl$ or doubl$ or treb$ or tripl$) adj (blind$3 or mask$3)).tw.	164106
61	Placebos/	34368
62	placebo$.tw.	204780
63	randomly allocated.tw.	26341
64	(allocated adj2 random$).tw.	29498
65	or/59-64	591413
66	Case study/	2024016
67	case report.tw.	289195
68	letter/	1029912
69	historical article/	352043
70	editorial.pt.	492824
71	or/66-70	3725101
72	65 not 71	575600
73	exp case control studies/	997508
74	exp cohort studies/	1864726
75	Case control.tw.	115899
76	(cohort adj (study or studies)).tw.	177524
77	Cohort analy$.tw.	7034
78	(Follow up adj (study or studies)).tw.	46985
79	(observational adj (study or studies)).tw.	92799
80	Longitudinal.tw.	223034
81	Cross sectional.tw.	311365
82	Cross-sectional studies/	295859
83	Epidemiologic studies/	7989
84	73 or 74 or 75 or 76 or 77 or 78 or 79 or 80 or 81 or 82 or 83	2665274
85	72 or 84	3144022
86	6 and 44 and 50 and 85	1109
87	animals/ not (humans/ and animals/)	4554892
88	86 not 87	1106

89	(2018 Sep* or 2018 Oct* or 2018 Nov* or 2018 Dec* or 2019 Jan* or 2019 Feb* or 2019 Mar* or 2019 Apr* or 2019 May* or 2019 Jun*).dp.	825105
90	88 and 89	38
91	limit 27 to ed=20180906-20190610	110
92	90 or 91	148

Table 3: The Cochrane Library, incorporating: EBM Reviews - Cochrane Central Register of Controlled Trials, EBM Reviews - Cochrane Database of Systematic Reviews, EBM Reviews - Database of Abstracts of Reviews of Effects, EBM Reviews - NHS Economic Evaluation Database. Accessed 10th June 2019

#	Searches	Results
1	exp Lymphoma, Large B-Cell, Diffuse/	339
2	(diffuse large B cell or DLBCL or DLBL).mp.	1346
3	aggressive B cell*.mp.	132
4	(large B cell adj4 lymphoma*).mp.	1433
5	(diffuse adj4 lymphoma*).mp.	1520
6	1 or 2 or 3 or 4 or 5	1707
7	exp bendamustine/ or (bendamustine or Treanda* or Treakisym* or Ribomustin* or Levact*).mp.	640
8	exp rituximab/ or (rituximab or Rituxan* or MabThera).mp.	4614
9	exp brentuximab vedotin/ or (brentuximab or Adcetris* or SGN-35).mp.	257
10	exp cyclophosphamide/ or (cyclophosphamide or lyophilized Cytoxan or Endoxan* or Cytoxan* or Neosar* or Procytox* or Revimmune* or Cycloblastin).mp.	12530
11	exp etoposide/ or (etoposide or Etopophos*).mp.	4073
12	exp Vincristine/ or (vincristine or Oncovin* or Vincasar*).mp.	4403
13	exp Procarbazine/ or (Procarbazine or Matulane* or Natulan* or Indicarb*).mp.	716
14	(CEPP or CEOP or DA-EPOCH or EPOCH or GEMOX or CAPOX or PECC or IEV or MINE or ICE or IME).ti,ab.	2670
15	exp doxorubicin/ or (Doxorubicin or Adriamycin* or Caelyx* or Myocet* or Pegylated liposomal doxorubicin or doxil*).mp.	9583
16	exp gemcitabine/ or (gemcitabine or Gemzar*).mp.	5562
17	exp oxaliplatin/ or (oxaliplatin or Eloxatin*).mp.	4108
18	exp cisplatin/ or (cisplatin or cisplatinum* or CDDP or Platin).mp.	14163
19	exp capecitabine/ or (capecitabine or Xeloda*).mp.	3586
20	exp vinorelbine/ or (Vinorelbine or Navelbine*).mp.	1855
21	exp dexamethasone/ or (dexamethasone or Decadron* or Dexasone* or Diodex* or Hexadrol* or Maxidexmp*).mp.	10935
22	exp carboplatin/ or (carboplatin or paraplatin*).mp.	6567
23	exp lenalidomide/ or (lenalidomide or Revlimid*).mp.	1799
24	exp ibrutinib/ or (ibrutinib or Imbruvica*).mp.	452
25	exp Pixantrone/ or (Pixantrone or Pixuvri* or BBR 2778).mp.	41
26	exp cytarabine/ or (cytarabine or Cytosar-U or Depocyt*).mp.	2813
27	exp ifosfamide/ or (ifosfamide or Ifex*).mp.	1466
28	exp epirubicin/ or (epirubicin or Ellence*).mp.	3174
29	exp methotrexate/ or (methotrexate or Trexall* or MTX or Rheumatrex*).mp.	11993
30	exp mesna/ or (mesna or Mesnex*).mp.	310
31	exp mitoxantrone/ or (mitoxantrone or Novantrone*).mp.	1439
32	chimeric antigen receptor T cells/ or Axicabtagene/ or (Axicabtagene or tisagenlecleucel or kymriah or CAR-T).tw.	147

#	Searches	Results
33	axicabtagene ciloleucel/ or yescarta.mp.	0
34	(DHAP or ESHAP).mp.	202
35	(MOR208 or Xmab-5574).mp.	9
36	exp Prednisone/ or (prednisone or prednisolone or Deltasone* or Prednisone Intensol).mp.	15731
37	exp Polatuzumab vedotin/ or (polatuzumab or DCDS4501A or RG7596).mp.	31
38	Venetoclax/ or (ABT-199 or Venetoclax).mp.	174
39	Apatinib/ or Apatinib.mp.	228
40	exp Chlorambucil/ or (chlorambucil or leukeran).mp.	745
41	exp Lomustine/ or (lomustine or CeeNU or CCNU or Gleostine).mp.	840
42	((best or supportive or standard or usual) adj3 (care or treatment*)).tw.	79335
43	BSC.tw.	736
44	or/7-43	150834
45	((second or third or fourth) adj3 line).tw.	6306
46	(refractory or intoleran* or failure* or resistan* or recurren* or metasta* or progress* or invasive* or chemorefractory or advanced or relapse*).tw.	337003
47	((previous* or prior or salvage) adj3 (treat* or therap* or regimen*)).tw.	29426
48	or/45-47	350253
49	((first or new*) adj1 diagnos*).ti,ab.	12225
50	48 not 49	344421
51	6 and 44 and 50	815
52	limit 51 to yr="2018 -Current" [Limit not valid in DARE; records were retained]	57

A2. Please provide an updated PRISMA flowchart (Appendix D, Figure 1) to include results of the update searches run in June 2019, and provide revised details of study selection to include the results of the update.

It was not possible to produce an updated PRSIMA flowchart that included the updated searches in the time available. Please find below the individual PRISMA flowcharts for the separate searches that were provided in the original CS.

Figure 1: PRISMA flow diagram showing the study identification process

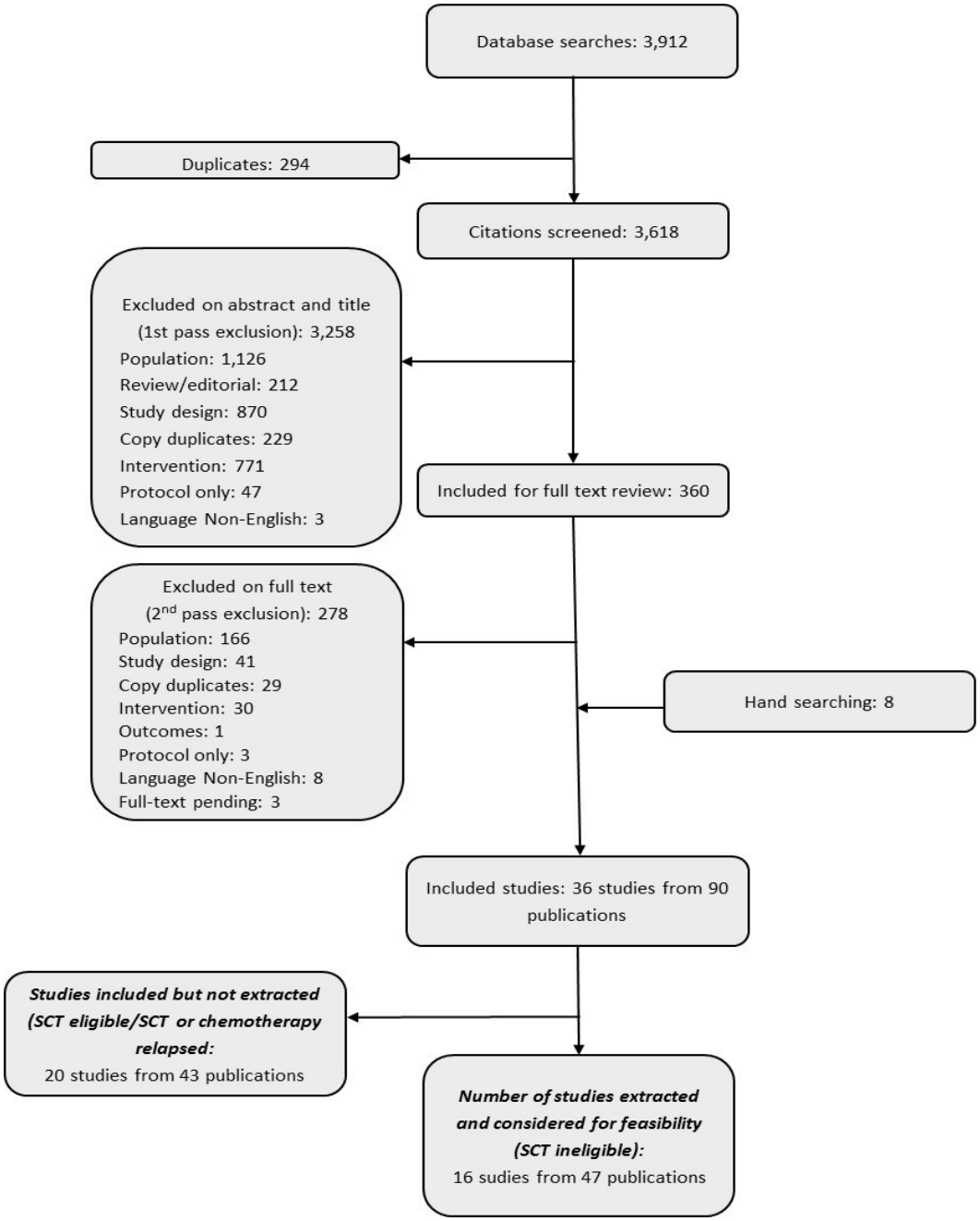
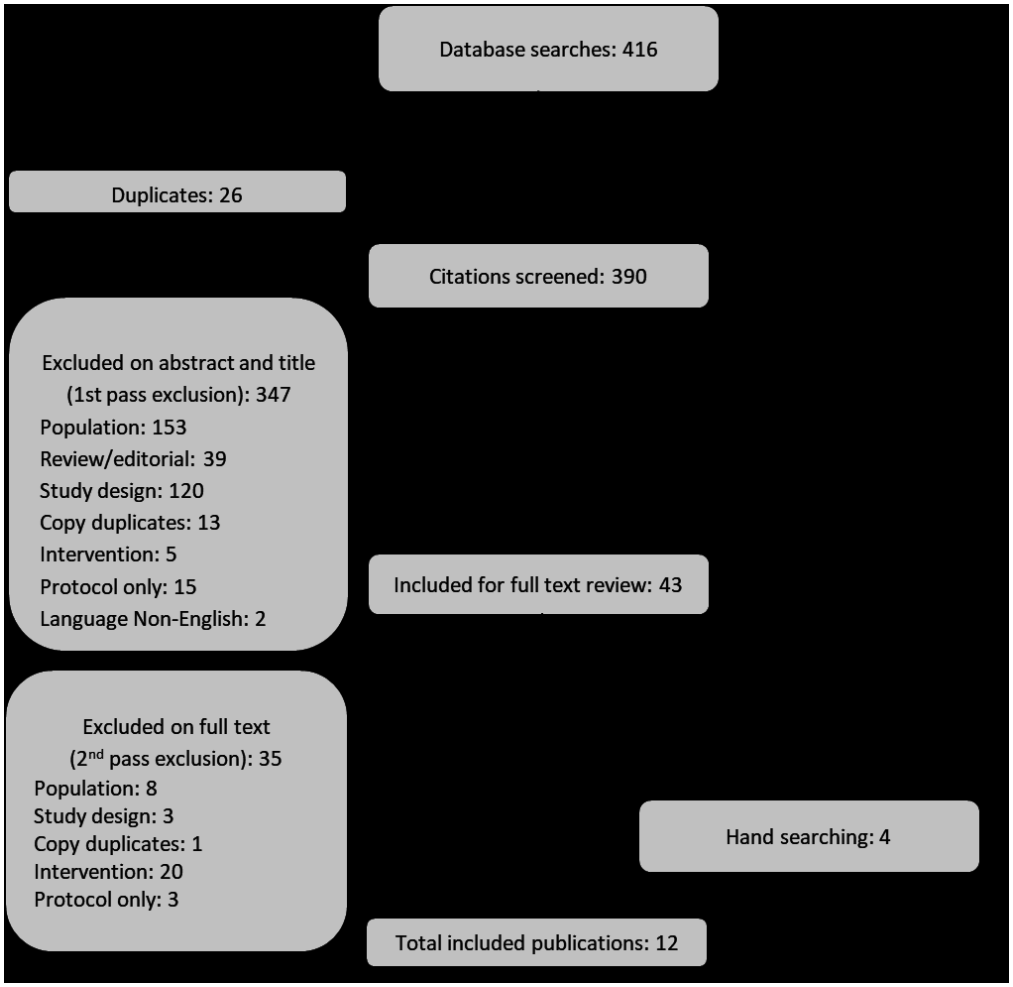


Figure 2: PRISMA flow diagram showing the study identification process



Population

A3. Priority question: The population in the NICE scope is adults with relapsed or refractory diffuse large B-cell lymphoma for whom hematopoietic stem cell transplant (SCT) is not suitable. However, the company submission (CS) states, as indicated in Figure 2, that the position of polatuzumab vedotin with bendamustine, rituximab (pola+BR) includes those who have undergone autologous stem cell transplant (ASCT). Also, Appendix D states that studies were excluded from the review if they *"…enrolled transplant eligible patients or transplant or chemotherapy relapsed patients"* (p.17).

a. **Please confirm that such patients are not within the NICE scope or the decision problem.**

We can confirm that transplant-eligible patients are not within the NICE scope or the decision problem, as per the pivotal trial (patients who were eligible for ASCT or had

completed ASCT within 100 days prior to Cycle 1 Day 1 were excluded from the trial). Patients who had received prior transplant (but have since progressed) are within the expected marketing authorisation for pola+BR if they are not eligible for another transplant at this point.

b. Please conduct an analysis of the GO29365 trial, which excludes the 16 patients who had received an ASCT.

Analysis of the randomised portion of the GO29365 trial, excluding the 16 patients who had received an ASCT is provided below. We have provided data from both the 30 April 2018 and [redacted] data cuts. Data from the 30 April 2018 data cut are provided in the forest plots of Appendix E of the CS.

Table 4: CR rate with PET at primary response assessment (IRC-assessed) endpoint, excluding the 16 patients who had received an ASCT

	pola+BR n=30	BR n=34
Complete response, n (%) 95% CI	[redacted]	[redacted]
Difference in response rates, n (%) (95% CI) p- value (stratified)	[redacted]	

CCOD: 30 April 2018

Table 5: Objective response (CR/PR) rates by PET at primary response assessment (IRC-assessed) endpoint, excluding the 16 patients who had received an ASCT

	pola+BR n=30	BR n=34
Overall response, n (%) 95% CI	[redacted]	[redacted]
Complete response, n (%) 95% CI	[redacted]	[redacted]
Partial response, n (%) 95% CI	[redacted]	[redacted]
Difference in OR response rates, % (95% CI)	[redacted]	

CR, complete response; OR, overall response; PR, partial response
CCOD: 30 April 2018

Table 6: Complete response and objective response (CR/PR) rates by PET at primary response assessment (INV-assessed) endpoint, excluding the 16 patients who had received an ASCT

	pola+BR n=30	BR n=34
Overall response, n (%) 95% CI	[redacted]	[redacted]
Complete response, n (%) 95% CI	[redacted]	[redacted]

Partial response, n (%) 95% CI	[redacted]	[redacted]
Difference in OR response rates, % (95% CI)	[redacted]	

CR, complete response; OR, overall response; PR, partial response
CCOD: 30 April 2018

Table 7: Progression-free survival (IRC-assessed), excluding the 16 patients who had received an ASCT (latest data update)

	pola+BR n=30	BR n=34
Patients with event, n (%)	[redacted]	[redacted]
Earliest contributing event, n Disease progression Death	[redacted]	[redacted]
Median time to event, months 95% CI	[redacted]	[redacted]
Stratified HR % (95% CI)	[redacted]	

HR, hazard ratio
CCOD: [redacted]

Table 8: Progression-free survival (INV-assessed), excluding the 16 patients who had received an ASCT (latest data update)

	pola+BR n=30	BR n=34
Patients with event, n (%)	[redacted]	[redacted]
Earliest contributing event, n Disease progression Death	[redacted]	[redacted]
Median time to event, months 95% CI	[redacted]	[redacted]
Stratified HR % (95% CI)	[redacted]	

HR, hazard ratio
CCOD: [redacted]

Table 9: Overall survival, excluding the 16 patients who had received an ASCT (latest data update)

	pola+BR n=30	BR n=34
Patients with event, n (%)	[redacted]	[redacted]
Median time to event, months 95% CI	[redacted]	[redacted]
Stratified HR % (95% CI)	[redacted]	

HR, hazard ratio; NE, not estimated
CCOD: [redacted]

c. Given that, as stated in Table 3 of the CS, the European Society for Medical Oncology (ESMO) guidelines recommend chimeric antigen receptor-T (CAR-T) cells only for those who are eligible for SCT, please also conduct an analysis of the GO29365 trial, which excludes the

16 patients who had received a transplant and the two patients who had received CAR-T.

To clarify, no patients enrolled in the GO29365 trial received CAR-T therapies prior to receiving pola+BR. In the Pola+BR treatment arm two patients went on to receive subsequent CAR-T therapy, one of whom died.

The influence of treatments with curative intent (such as CAR-T or SCT) was explored by comparing the GO29365 ITT patient population with a population censored for patients who had received SCT or CAR-T therapies after pola+BR or BR at the time this was received. No difference between the ITT population and the censored population was observed (see Figure 27 in the CS) indicating that OS in the patient population was not affected by subsequent treatments in either arm.

Comparators

A4. Priority question: Only one comparator (bendamustine with rituximab; BR) was fully included in the decision problem while rituximab, gemcitabine, oxaliplatin (R-GemOx) were only included in the economic model by assuming equal efficacy with BR. Appendix D reports the results of a systematic review of 16 studies.

a. **Please complete the systematic review by reporting the effectiveness and safety results of the 16 studies.**

An update of the searches to inform the clinical SLR was conducted on 10 June 2019 to identify new studies published since the original review was conducted. The decision problem informing this clinical SLR was consistent with that of the original review. In total, 101 publications (36 unique studies) were identified that met the inclusion criteria of the SLR. Of these 36 unique studies, 19 studies were considered for extraction, representing an additional 3 studies to the 16 studies from the earlier review.

The 19 studies were taken forward into the indirect treatment comparison (ITC) feasibility assessment; 6 RCTs and 13 single-arm studies. The feasibility assessment showed that no connected network of evidence could be constructed

based on evidence identified from the SLR (even when adopting a supplementary process to introduce additional evidence).

An overview of the studies taken forward from the clinical SLR for meta-analysis feasibility assessment can be seen below in Table 10. Of the selected 19 studies, where available, a summary of the overall survival is presented in Table 11, progression free survival in Table 12, and safety availability in Table 13.

Table 10: Overview of studies

Trial	Treatment arm	Number of patients	Study design	Blinding	Study setting	Study phase	Location (site/countries)	Date of trial	Median follow-up time, months
GO29365 (1)	Pola + BR	40	RCT	Open-label	Multicentre international	Phase Ib/II	Australia, Canada, Czechia, France, Germany, Hungry, Italy, Korea, Netherlands, United States, Spain, Turkey, UK	October 2014 – April 2018	22.3
	BR	40							
Aribi (2)	ESHAP	48	RCT	Single-blind	Monocentric	NR	Algeria	January 2005 - December 2008	13
	GDP	48							
Aviles (3)	ESHAP	53	RCT	NR	Single-center	Phase 3	Mexico	March 2009	64.5
	R-ESHAP	47							
Dang (4)^	Inotuzumab ozogamicin plus rituximab	166	RCT	Open-label	Multicentre	Phase 3	United States, Belgium, Bulgaria, Canada, Croatia, Czechia, Czechia, Germany, Hungary, India, Ireland, Japan, Lithuania, Mexico, Poland, Puerto Rico, Russian Federation, Singapore, Slovakia, Spain, Sweden, Taiwan, Thailand, Ukraine, United Kingdom	February 2011 and May 2013	14.9
	Investigator's choice (rituximab plus bendamustine or rituximab plus gemcitabine)	172							15.9
Pettengell (5)	Pixantrone	70	RCT	Open-label	Multicentre	Phase 3			
	Investigator's choice (rituximab, oxaliplatin, ifosfamide, etoposide, mitoxantrone, gemcitabine)	70					Europe, India, Russia, South America, the UK, and the USA.	October 2004 - February, 2010	NR, study treatment + 18 months follow-up
Czuczman (6)	Lenalidomide	51	RCT	Open-label	Multicentre	Phase 2/3	Australia, Austria, Czech Republic, France, Italy, Spain, Sweden and the UK	October 2010 - April 2018	NR
	Investigator's choice (gemcitabine, rituximab,	51							

	etoposide or oxaliplatin)								
El Gnaoui (7)	R-GemOx	33	Observational	Open-label	Monocentric	Phase 2	France	January 2002 – June 2005	28
Lakshmaiah (8)	Lenalidomide	15	Observational	Open-label	NR	NR	India	March 2011 to December 2012	24
Lopez(9)	R-GemOx	32	Observational	NR	Multicentre	Phase 2	Spain	September 2004 – September 2006	13
Schuster JULIET (10)	Tisagenlecleucel	115 treated (99 in main cohort; and 16 in cohort A)	Observational	Open-label	Multicentre international	Phase 2	Australia, United States, Austria, Canada, France, Germany, Italy, Japan, Netherlands, Norway	Data cutoff May 2018	≥3 months
Mounier (11)	R-GemOx	49	Observational	Open-label	Multicentre	Phase 2	France	August 2003 – January 2009	65
Neelapu ZUMA-1 (12)	Axicabtagene ciloceucel	81 enrolled (77 treated)	Observational	Open-label	Multicentre	Phase 2	United States, Israel	November 2015 – September 2016	8.7
Ohmachi (13)	BR	59	Observational	Open-label	Multicentre	Phase 2	Japan, Korea	April 2010 – June 2011	4.7
Papageorgiou (14)	Gemcitabine and Vinorelbine	22	Observational	Open-label	Multicenter	Phase 2	Greece	NR	44
Schuster (15)	Tisagenlecleucel	23 enrolled (14 treated)	Observational	Open-label	Monocentric	Phase 2	United States	March 2014 – August 2018	285
Vacirca (16)	BR	61	Observational	Open-label	Multicentre	Phase 2	United States	December 2008 – January 2011	Up to 36
Wiernik (17)	Lenalidomide	26	Observational	NR	Multicenter	Phase 2	United States	August 2005 to September 2006	3.7
Witzig (18) (18)	Lenalidomide	217	Observational	Open-label	Multicentre	Phase 2	United States, UK, Spain, Germany, France, and Italy, Canada	November 2006 – March 2008	NR
Zinzani (19)	Lenalidomide and rituximab	23	Observational	Open-label NR	Single-center	Phase 2	Italy	March to June 2009	16

^*Data for overall population captured in the study, although the study included only 91% of DLBCL patients*

Abbreviations: Key: BR, bendamustine and rituximab; DHAP, dexamethasone, cytarabine, and cisplatin; ESHAP, etoposide, cisplatin, solumedrol, aracytine; GPD/GDP, gemcitabine, dexamethasone, cisplatine; Pola + BR, polatuzumab plus bendamustine and rituximab; RCT, randomized controlled trial; R-GemOx, Rituximab, gemcitabine and oxaliplatin

Table 11: Summary of overall survival data

Trial	Treatment arm	Median OS [95% CI], months	HR [95% CI]	Kaplan-Meier curve availability	Definition
GO29365 (1)	Pola + BR	12.4 [9.0 – NE]	0.42 [0.24 – 0.75]	Yes; IPD available and Kaplan-Meier curve extracted from abstract	NR
	BR	4.7 [3.7 – 8.3]	1		
Aribi (2)	GDP	17.0* [NR]	NA; digitization methods required to estimate hazard ratio.	Yes (strata by treatment arm)	According to clinical and tomodensitometric criteria.
	ESHAP	7.0* [NR]			
Dang (4) ^	Inotuzumab ozogamicin plus rituximab	9.5 [7.0-14.5]	1.08 [0.82-1.44]	Yes	Response and progression were evaluated according to the revised Cheson Criteria (2007)
	Investigator's choice (rituximab plus bendamustine or rituximab plus gemcitabine)	9.5 [7.7-14.1]	1		
NCT00088530 Pettegell (5)	Pixantrone	10.2 [6.4–15.7]	0·79 [0·53–1·18]	Yes (for ITT population)	NR
	Investigator's choice (rituximab, oxaliplatin, ifosfamide, etoposide, mitoxantrone, gemcitabine)	7.6 [5.4–9.3]	1		
Czuczman (6)	Lenalidomide	7.1** [NR]	0.91 [0.59-1.41]	Yes (no number at risk)	NR
	Investigator's choice (gemcitabine, rituximab, etoposide or oxaliplatin)	5.7** [NR]	1		
El Gnaoui (7)	R-GemOx	Not reached [NR]	NA	Yes	Calculated from the date of enrolment until death from any cause
Lopez(9)	R-GemOx	9.1 [3.0 – 15.0]	NA	Yes	OS were measured from the date of GEMOX-R and were estimated according to the KM method
Mounier (11)	R-GemOx	11.0	NA	Yes	NR

		[NR]			
ZUMA-1 Neelapu (12)	Axicabtagene ciloleucel	15.4 [10.4-15.4]	NA	Yes	Assessed by Investigators according to the International Working Group Response Criteria for Malignant Lymphoma
Ohmachi (13)	BR	NR	NA	No	NR
Papageorgiou (14)	Gemcitabine and vinorelbine	12.9 [Range: 4–54+]	NR	Yes	Time from treatment initiation to the last follow up or until the patient's death from any cause.
Schuster NCT02030834(15)	Tisagenlecleucel	22.2 [NR]	NA	Yes	Response evaluated with the use of the 1999 International Working Group response criteria
Schuster JULIET (10)	Tisagenlecleucel	11.1 [6.6 – NE]	NA	Yes	NR
Vacirca (16)	BR	Not reached. Due to a high number of censored data, as patients withdrew from study follow-up, the median OS was not reached	NA	No	Revised response criteria for malignant lymphoma
Zinzani 2011 (19)	Lenalidomide and rituximab	Not reached	NA	Yes	
Abbreviations: CSR, clinical study report; HR, hazard ratio; IPD, individual patient data; NA, not applicable; NE, not estimable; NR, not reported; OS, overall survival. OS data not reported by Wiernik 2008 and Witzig et al, 2011 ^ *Data for overall population captured in the study, although the study included only 91% of DLBCL patients; * digitized from figure. ** Converted from weeks*					

Table 12: Summary of progression-free survival data

Trial	Treatment arm	Median PFS [95% CI], months	HR [95% CI]	Kaplan-Meier curve availability	Definition
GO29365 (1)	Pola + BR	7.6 [6.0 -17.0]	0.34 [0.20, 0.57]	Yes; IPD available and Kaplan-Meier curve extracted from abstract	Investigator assessed
	BR	2.0 [1.5 – 3.7]	1		

Aribi (2)	GDP	17.1* [NR]	NA: digitization methods required to estimate hazard ratio.	Yes	Progression-free survival is defined as the survival without recurrence and, therefore, without relapse and signs of progression after treatment
	ESHAP	6.0* [NR]			
Dang (4)^	Inotuzumab ozogamicin plus rituximab	3.7 [2.9-5.0]	0.92 [0.72-1.19]	Yes	Response and progression were evaluated according to the revised Cheson Criteria (2007)
	Investigator's choice (rituximab plus bendamustine or rituximab plus gemcitabine)	3.5 [2.8-4.9]	1		
Pettengell (5)	Pixantrone	5.3 [2.3–6.2]	0.60 [0·42–0·86]	Yes	assessment was based upon the 1999 IWG criteria
	Investigator's choice (rituximab, oxaliplatin, ifosfamide, etoposide, mitoxantrone, gemcitabine)	2.6 [1.9–3.5]	1		
Czuczman (6)	Lenalidomide	13.6 wks [8.6 wks –17.7 wks]	0.64 [0.41–0.99]	Yes (no number at risk)	IWRC 1999 for the primary assessment
	Investigator's choice (gemcitabine, rituximab, etoposide or oxaliplatin)	7.9 wks [6.3 wks – 9.0 wks]	1		
El Gnaoui (7)	R-GemOx	NR	NA	No	NR
Lopez (9)	R-GemOx	NR	NA	Yes	NR
Schuster Juliet (10)	Tisagenlecleucel	2.9 [2.2–6.2)	NA	No	IRC based; PFS is defined as the time from date of tisagenlecleucel infusion to the date of first documented disease progression or death due to any cause.
Mounier (11)	R-GemOx	5.0 [NR]	NA	Yes	NR
Neelpau ZUMA-1 (12)	Axicabtagene ciloleucel	INV: 6.0 (3.9, 8.1) IRC: 7.3 (5.2, 12.4)	NA	Reported only for overall population (not for	Investigators according to the International Working Group

				DLBCL patients)	Response Criteria for Malignant Lymphoma
Ohmachi (13)	BR	6.7 [3.6 – 13.7]	NA	Yes	PFS was calculated as the time from day 1 of the first cycle of study treatment to either disease progression, commencement of another treatment, death from any cause, or discontinuation of assessment
Schuster NCT02030834 (15)	Tisagenlecleucel	3.2 [0.9 – NE]	NA	Yes	NR
Vacirca (16)	BR	3.6 [2.7 – 7.2]	NA	Yes	Progression-free survival was measured as the time from the start of treatment to the date of disease progression or death as a result of any cause
Abbreviations: CSR, clinical study report; HR, hazard ratio; IPD, individual patient data; NA, not applicable NE, not estimable; NR, not reported; PFS, progression-free survival. ^ *Data for overall population captured in the study, although the study included only 91% of DLBCL patients;* * digitized from figure.					

A range of safety and tolerability endpoints were extracted as part of the SLR. A summary of the outcomes showing data availability by study is presented here. Many AEs are reported in NCT02257567; however, two comparator studies [(El Gnaoui et al. 2007) and (Schuster, Svoboda, et al. 2017)] do not report data for any safety or tolerability outcomes. Data availability increased when grade 3/4 AEs were considered. The most commonly reported AEs include anaemia, nausea, neutropenia and thrombocytopenia

Table 13: Summary of safety and tolerability endpoints – data availability by study

Trial	Treatment arm	Grade 3/4 adverse events	Serious adverse events (all-cause)	Discontinuation	Discontinuation (due to adverse events)	Discontinuation (due to death)	Adverse events																	
							Anaemia	Constipation	Diarrhoea	Decreased appetite	Dyspnoea	Headache	Fatigue	Fever	Infections	Leukopenia	Nausea	Neutropenia	Febrile neutropenia	Pain	Peripheral neuropathy	Rash	Thrombocytopenia	Vomiting
GO29365 (1)	Pola + BR / BR	✓	✓	✓	✓	✓	✓†	✓	✓ †	✓	✓	✓	✓†	✓	✓†	✓†	✓†	✓†	✓†	✓	✓	✓†	✓†	✓
Aribi (2)	GDP / ESHAP						†								†	†							†	†
Aviles (3)	ESHAP/ R-ESHAP																							
Dang (4)^	R-Ino/IC	✓		✓	✓	✓	✓†	✓†	✓ †	✓†			✓†	✓†		✓†	✓†	✓†	✓	✓†			✓†	✓†
Pettengell (5)	Pixan/IC	✓					✓	✓	✓		✓		✓	✓		✓	✓	✓	✓	✓			✓	✓
Czuczman (6)	Len/IC	✓	✓				✓	✓	✓				✓	✓			✓	✓					✓	
El Gnaoui(7)	R-GemOx																							
Lakshmaiah (8)	Lenalidomide																							
Lopez (9)	R-GemOx						✓†										✓	✓†	†		✓†		✓†	✓
Mounier (11)	R-GemOx		✓	✓														†	†				†	
Neelapu ZUMA-1 (12)	Axicabtagene ciloleucel																	†	†				†	
Ohmachi (13)	BR			✓	✓	✓	✓†	✓†		✓†	†	†	✓†	✓†	✓†	✓†	✓†	✓†	✓†				✓†	✓†	
Papageogiou (14)	GEM plus vinorelbine			✓	✓	✓	✓†							✓†	†	✓†	✓	✓†					✓†	✓
Schuster NCT02030834 (15)	Tisagenlecleucel																							
Schuster	Tisagenlecl	✓													†			†	†					

JULIET (10)	eucel																							
Vacirca (16)	BR			✓		✓	✓†	✓†	✓†	✓†	✓†	✓†	✓†	✓†			✓†	✓†		✓†			✓†	✓†
Wiernik (17)	Lenalidomide																							
Zinzani (19)	Lenalidomide and rituximab																							
Total number of studies (all grade)		3	2	6	4	5	6	4	2	4	2	2	4	5	2	4	6	6	3	3	2	2	6	5
Total number of studies (grade 3/4)		-	-	-	-	-	7	3	2	3	2	2	4	4	5	5	4	9	6	2	1	2	9	3
Abbreviations: ✓ reports data for all grade AEs; † reports data for grade 3/4 AEs. ^*Data for overall population captured in the study, although the study included only 91% of DLBCL patients*																								

b. Please state the reasons for each of the 16 studies as to why the results could not be included in a meta-analysis with those from GO29365.

Table 14: Reasons trial results could not be incorporated into a meta-analysis and the economic model

Study / ID (primary reference)	Arms/Interventions	Reason(s) results could not be incorporated into a meta-analysis/economic model
Original SLR		
Aribi (2)	ESHAP vs GDP	Lack of relevant comparator arm(s) with no connection to the network of the decision problem.
Aviles (3)	ESHAP vs R-ESHAP	Lack of relevant comparator arm(s) with no connection to the network of the decision problem (study explored salvage regimen for transplant eligible patients).
Dang (4)^	Inotuzumab ozogamicin plus rituximab vs investigator choice (BR or R+Gem)	Lack of relevant comparator arm(s) with no connection to the network of the decision problem. The arm containing BR is a mixed arm and so is not suitable for a MAIC. Additionally BR is already included in GO29365 as a direct comparator.
GO29365 (1)	pola + BR vs BR	Not applicable. This study informs the primary NICE decision problem and so is suitable for inclusion. Since this is the only study that would be suitable for inclusion it represents a node and not part of a feasible network to be meta-analyzed.
El Gnaoui (7)	R-GemOx	This single arm study in France between 2002 and 2005 did not have a connection to a potential network for analysis. A matched-adjusted indirect comparison was not feasible since results were not reported separately for prior rituximab experience (of the ITT population [N=46] 26 had prior rituximab therapy representing 57%).

Lopez (9)	R-GemOx	This single arm study did not have a connection to a potential network for analysis. A matched-adjusted indirect comparison was not feasible since results were not reported separately for prior rituximab experience (the ITT population included induction therapies of CHOP [25% of patients], R-CHOP [62%], and R-EPOCH [12%]).
Mounier (11)	R-GemOx	Whilst R-GemOx represented a relevant comparator stipulated within the decision problem scope, this single arm study did not report baseline characteristics or survival results in the form of Kaplan-Meier plots separately based on prior rituxumab experience (37% of patients in the study were rituximab inexperienced). For these reasons the results from the ITT population of this study were not appropriate and a MAIC not feasible.
Ohmachi (13)	BR	This single arm study did not have a connection to a potential network for analysis. A matched-adjusted indirect comparison was not explored since BR is already a comparator within GO29365. Further to this, incorporation of these results which are generated from a median follow-up time of 4.7 months, only from centers in Japan and Korea, would not be generalisable to the current population in scope.
Vacirca (16)	BR	This single arm study did not have a connection to a potential network for analysis. A matched-adjusted indirect comparison was not explored since BR is already a comparator within GO29365.
Neelapu, ZUMA-1 (12)	Axicabtagene ciloleucel (Yescarta)	This single arm study did not have a connection to a potential network for analysis and the treatment did not represent a relevant comparator according to the decision problem set out within the scope.
Papageorgiou (14)	Gemcitabine plus vinorelbine	This single arm study did not have a connection to a potential network for analysis and the treatment did not represent a relevant comparator according to the decision problem set out within the scope.
Schuster NCT02030834 (15)	Tisagenlecleucel (Kymriah)	This single arm study did not have a connection to a potential network for analysis and the treatment did not represent a relevant comparator according to the decision problem set out within the scope.
Schuster JULIET (10)	Tisagenlecleucel (Kymriah)	This single arm study did not have a connection to a potential network for analysis and the treatment did not represent a relevant comparator according to the decision problem set out within the scope.
Lakshmaiah (8)	Lenalidomide	This single arm study did not have a connection to a potential network for analysis and the treatment did not represent a relevant comparator according to the decision problem set out within the scope.
Wiernik (17)	Lenalidomide	This single arm study did not have a connection to a potential network for analysis and the treatment did not represent a relevant comparator according to the decision problem set out within the scope.

Zinzani (19)	Lenalidomide and rituximab	This single arm study did not have a connection to a potential network for analysis and the treatment did not represent a relevant comparator according to the decision problem set out within the scope.
Updated SLR		
Pettengell (5)	Pixantrone vs Inv. choice (rituximab, oxaliplatin, ifosfamide, etoposide, mitoxantrone, gemcitabine)	Lack of relevant comparator arm(s).
Witzig (18)	Lenalidomide	This single arm study did not have a connection to a potential network for analysis and the treatment did not represent a relevant comparator according to the decision problem set out within the scope.
Czuczman (6)	Lenalidomide vs Inv. choice (gemcitabine, rituximab, etoposide or oxaliplatin)	Lack of relevant comparator arm(s). Treatments did not represent a relevant comparator according to the decision problem set out within the scope.

c. Please state the reasons for each of the 16 studies as to why the results could not be incorporated in the economic model.

See above.

d. **The company notes in Table 3 regarding ESMO guidelines for patients with first and second relapse or progression that following advice from UK clinical experts, oxaplatin is the preferred platinum regimen for transplant-ineligible patients in UK clinical practice. However, further in the text clinical experts reported that R-Gem-Ox is not widely used in clinical practice. Please clarify on this point.**

Clinical experts reported that R-Gem-Ox (rituximab with gemcitabine and oxaliplatin), is not widely used in UK clinical practice as a salvage regimen for transplant-eligible patients (20).

However, R-Gem-Ox is an option considered by NHS England for older and/or transplant-ineligible patients. Further advice sought by Roche also reported that the familiarity of this regimen has occurred very recently (in the last few years) and its use in the transplant-ineligible setting may increase among treatment centres that are enrolling patients to the ARGO study (21).

GO29365 trial

A5. Priority question: According to Table 6 of the CS *"Data for PFS and OS from the most recent data cut (11 October 2018) were used to inform the economic model – this data and analysis for other endpoints from the previous data cut (30 April 2018) is reported in this submission"*.

Please provide data, including those analysed by an independent review committee (IRC), on all endpoints including adverse events (AEs), progression free survival (PFS) and overall survival (OS) from a data cut that is as recent as possible.

We can confirm that for key endpoints for the economic submission (PFS and OS) updated analyses (11 October 2018 clinical cut-off) had been submitted along with a comprehensive report on endpoints as reported in the CSR for the 20 April 2018 cut-off date. We also like to point out that the response endpoint or time-to-off-treatment would not have changed as all patients in the randomised phase of GO29356 had completed the response assessments and treatment, respectively. As discussed with

the ERG during the clarification call, further updated analyses are provided in response to A6 below

A6. Priority question: Page 61 of the CS states that

[redacted]

Please provide the most recent efficacy and safety results for pola+BR.

As discussed with the ERG and NICE, data from the unplanned exploratory analysis with a clinical cut-off date [redacted] is now available for analysis [redacted]. In updating the endpoints provided in the submission we have prioritised on the analysis of endpoints relevant for the economic model, i.e. PFS, OS and AEs, as agreed with the ERG in the clarification call, and the update of the economic model. As this data is a long-term follow-up for GO29365, it in particular provides more mature PFS and OS data confirming the analyses in the submission.

Updated PFS by IRC

As PFS was previously shown to be mature, the median PFS [redacted] months (95% CI: [redacted]) for pola+BR and [redacted] months (95% CI: [redacted]) for BR. The stratified HR [redacted]. The 24-month PFS rate was [redacted] (pola+BR) and [redacted] (BR). An updated KM curve is provided in Figure 1.

Table 15: Updated progression-free survival (IRC-assessed)

	pola+BR n=40	BR n=40
Patients with event, n (%)	[redacted]	[redacted]
Earliest contributing event, n Disease progression Death	[redacted]	[redacted]
Median time to event, months 95% CI	[redacted]	[redacted]
Stratified HR % (95% CI) p value (log-rank)	[redacted]	

HR, hazard ratio
CCOD: [redacted]

Figure 3: Updated Kaplan-Meier Curve for PFS by IRC

Updated PFS by Investigator

PFS by investigator assessments . With updated data cutoff, the median PFS was months (95% CI:) for pola+BR and months (95% CI:) for BR. The stratified HR was (95% CI:). The 24-month PFS rate was (pola+BR) and (BR). An updated KM curve is provided in Figure 4.

Table 16: Updated progression-free survival (INV-assessed)

	pola+BR n=40	BR n=40
Patients with event, n (%)		
Earliest contributing event, n Disease progression Death		
Median time to event, months 95% CI		
Stratified HR % (95% CI) p value (log-rank)		

HR, hazard ratio
CCOD:

Figure 4: Updated Kaplan-Meier Curve for PFS by Investigator

Updated OS

As shown in the prior data cuts, OS is mature. With this updated data cutoff, the median OS [redacted] months (95% CI: [redacted]) for pola+BR and [redacted] months (95% CI: [redacted]) for BR. The stratified HR [redacted]). The 24-month OS for pola+BR was [redacted], and [redacted] for BR. An updated KM curve is provided in Figure 5.

Table 17: Updated overall survival

	pola+BR n=40	BR n=40
Patients with event, n (%)	[redacted]	[redacted]
Median time to event, months 95% CI	[redacted]	[redacted]
Stratified HR % (95% CI) p value (log-rank)	[redacted]	

HR, hazard ratio; NE, not estimated
CCOD: [redacted]

Figure 5: Updated Kaplan-Meier Curve for OS

A7. Priority question: Figure 2 in the CS shows that pola + BR might be positioned at either second-line (immediately after rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone; R-CHOP), third-line (after R-based chemotherapy/palliative care) or second-line (after R-based salvage chemotherapy).

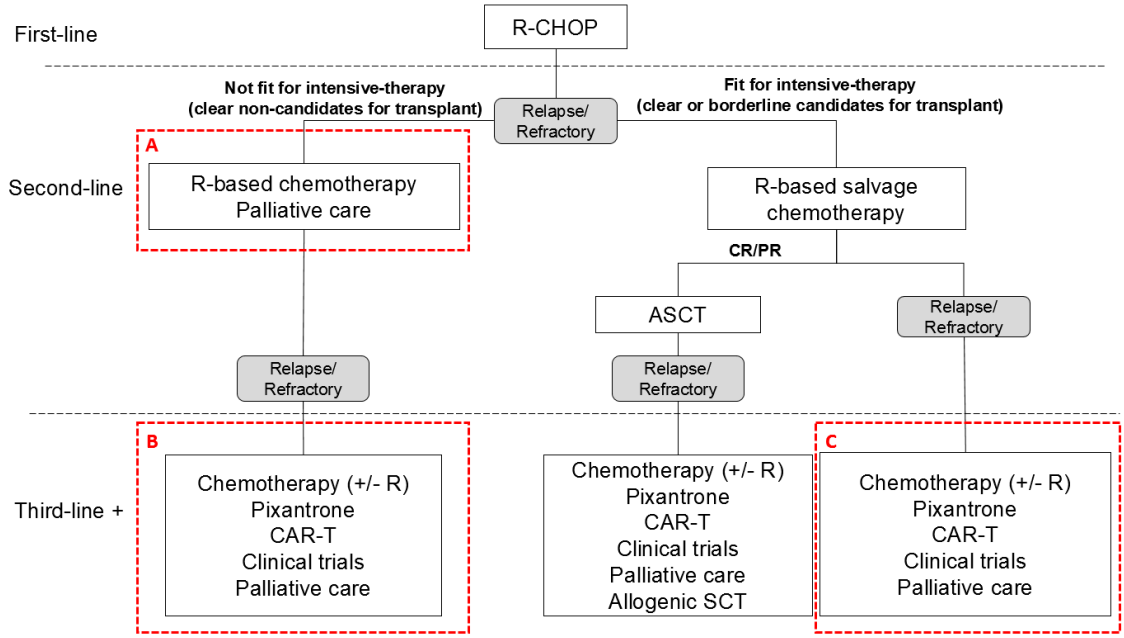
Please conduct subgroup analyses of the GO29365 trial appropriate to each of these three positions.

Subgroup analyses for the following patient populations are provided below:

- Clear non-candidates for transplant (transplant-ineligible), second-line (labelled as box A in Figure 6 below)
- Clear non-candidates for transplant (transplant-ineligible), third-line (Box B)
- Clear or borderline candidate for transplant, third-line after failing salvage therapy and therefore transplant-ineligible (Box C)

It was not possible to perform a subgroup analysis of patients who received pola+BR beyond third-line as these patients could not be clearly defined.

Figure 6: Schematic to define subgroup analyses populations



The small patient numbers of these subgroups demonstrates the difficulty in performing meaningful subgroup analyses and therefore these results should be interpreted with caution.

Table 18: CR rate with PET at primary response assessment (IRC-assessed) endpoint for transplant-ineligible subgroups

Clear non-candidates for transplant (transplant-ineligible)		
2nd line (box A)	**pola+BR n=11**	**BR n=12**
Complete response, n (%) 95% CI	[redacted]	[redacted]
Difference in response rates, % (95% CI) p-value (stratified)	[redacted]	
3rd line (box B)	**pola+BR n=5**	**pola+BR n=5**
Complete response, n (%) 95% CI	[redacted]	[redacted]
Difference in response rates, % (95% CI) p-value (stratified)	[redacted]	
Clear or borderline candidates for transplant		
3rd line after failed salvage therapy (and therefore transplant-ineligible) (box C)	**pola+BR n=6**	**pola+BR n=4**
Complete response, n (%) 95% CI	[redacted]	[redacted]
Difference in response rates, % (95% CI) p-value(stratified)	[redacted]	

Additional analyses for the second-line population are provided below.

Table 19: Additional efficacy endpoints for second-line patients (box A)

	pola+BR n=11	BR n=12
Objective response (CR/PR) rates by PET at PRA (IRC-assessed) (30 April 2018)		
Overall response, n (%) 95% CI	[redacted]	[redacted]
Difference in response rates, % (95% CI) p- value (stratified)	[redacted]	
Investigator assessed CR rates by PET at PRA endpoint (30 April 2018)		
Complete response, n (%) 95% CI	[redacted]	[redacted]
Difference in response rates, % (95% CI) p- value (stratified)	[redacted]	
Progression-free survival (IRC-assessed) [redacted]		
Patients with event, n (%)	[redacted]	[redacted]
Earliest contributing event, n Disease progression Death	[redacted]	[redacted]
Median time to event, months 95% CI	[redacted]	[redacted]
Stratified HR % (95% CI)	[redacted]	
Progression-free survival (INV-assessed) [redacted]		
Patients with event, n (%)	[redacted]	[redacted]
Earliest contributing event, n Disease progression Death	[redacted]	[redacted]
Median time to event, months 95% CI	[redacted]	[redacted]
Stratified HR (95% CI)	[redacted]	
Overall survival [redacted]		
Patients with event, n (%)	[redacted]	[redacted]
Median time to event, months 95% CI	[redacted]	[redacted]
Stratified HR % (95% CI)	[redacted]	

A8. Priority question: The CS states that *"Data from the Phase Ib and the randomised Phase II portion of GO29365 was generated with a liquid formulation of pola; however, a lyophilised formulation of pola suitable for commercialisation and use in ongoing and future clinical studies was*

subsequently developed" **and two arms have been added to the trial to assess this formulation.**

a. Please provide a rationale for the two formulations.

A lyophilised formulation of polatuzumab vedotin was developed to enhance drug product stability and enable administration using standard IV bags and infusion sets. Specifically, the lyophilised formulation was developed to:

- Minimise the increase in acidic region contributed by succinimide linker hydrolysis observed in the liquid dosage form
- Reduce protein oxidation risks associated with the higher polysorbate 20 concentration needed to stabilise polatuzumab vedotin from interfacially mediated protein aggregation during administration of the product using standard IV bags and IV infusion sets.

Three drug product configurations were used during clinical development of polatuzumab vedotin:

- 100 mg/10 mL liquid drug product
- 170 mg/vial lyophilised drug product
- 140 mg/vial lyophilised drug product

The two lyophilised drug products differ only in fill volume and the corresponding reconstitution volume. In all three drug product configurations, polatuzumab vedotin is the only active ingredient in the drug product.

A lyophilised drug product designed to deliver 170 mg of polatuzumab vedotin per vial was introduced into phase Ib/II studies based on an anticipated clinical dose of 2.4 mg/kg.

For later clinical studies and commercialisation (including Arm G of GO29365), a lyophilised drug product designed to deliver 140 mg of polatuzumab vedotin per vial was introduced based on a revised clinical dose of 1.8 mg/kg. The 140 mg/vial lyophilised drug product is stable when stored at the recommended storage temperature of 2°C–8°C for greater than 24 months.

b. Which formulation of pola do you expect to be administered in clinical practice?

The 140 mg/vial lyophilised formulation of polatuzumab vedotin will be administered in clinical practice.

c. Please justify the applicability of the randomised trial data to the efficacy and safety of the lyophilised formulation.

Arm G of Study GO29365 evaluated the pharmacokinetics (PK), safety and efficacy of v1.0-derived lyophilised polatuzumab vedotin in combination with bendamustine plus rituximab in patients with R/R DLBCL. The full analysis of efficacy and safety from Arm G will be available in [redacted], however preliminary safety data from the first 32 patients of Arm G has been provided in Appendix L of the company submission. It is important to note, however, that Arm G was designed with the primary objective of clinically qualifying the commercial lyophilised polatuzumab vedotin drug product (DP) in terms of PK and safety and not designed to provide a comparative efficacy analysis to the randomised cohort. Conclusions from the analysis of Arm G is provided below

Pharmacokinetics:

[redacted]

Safety and Tolerability:

[redacted]

[redacted]

[redacted]

[redacted]

[redacted].

Efficacy:

[redacted]

A9. From which countries is Arm H of GO29365 recruiting? Have the patients taken part in any other trials? Have they received any other interventions for R/R diffuse large B-cell lymphoma (DLBLC)?

Patients were enrolled to Arm H of GO29365 from the following countries: US, Spain, Australia, Italy, Canada, France, Germany, Hungary, Korea, Turkey, UK (n=4, two patients from Kings College Hospital, two patients from Nottingham City Hospital).

Patients enrolled were all 2L or 3L+ patients. While past treatment history was collected, it is unknown if that treatment was part of another clinical trial.

As per the protocol for GO29365, all patients must have received at least one prior therapy for DLBCL.

A10. The number of United Kingdom (UK) patients and centres is provided in the CS.

a. **Please provide information regarding the location of the centres.**

Three patients enrolled onto the R/R DLBCL randomised portion of the study; one patient from Nottingham City Hospital (BR arm), and two patients from The Christie Hospital (one patient per arm).

b. **Please justify the applicability of the GO29365 trial to UK clinical practice.**

The study population from GO29365 is largely reflective of the R/R DLBCL population in the UK. The baseline patient characteristics of R/R DLBCL patients enrolled in GO29365 is very similar to the population enrolled in a retrospective study evaluating the efficacy of pixantrone in R/R DLBCL patients (median age 66.5 vs 65.9, respectively, proportion refractory to last prior anti-lymphoma therapy 76% vs 85%) (22). Furthermore, advice obtained from clinical experts confirmed that the baseline characteristics of patients enrolled in GO29365 are reflective of the population seen in UK clinical practice and corroborates the comparison to the retrospective analysis; clinical experts reported that most patients in their clinic have stage 3–4 disease and 75–80% are refractory to last prior therapy) (20). Moreover, the range of lines of prior therapy ranged from 1 to 7 in the pola+BR arm, reflecting the broad population in the transplant-ineligible setting that is seen in current clinical practice.

There is no universal standard of care regimen for patients with R/R DLBCL who are ineligible for transplant or who relapse after transplant, with no prior randomised trials having established the superiority of one regimen over another for this population. This therefore results in a considerable amount of variability on the selected regimen for these patients. Bendamustine with rituximab is among the most commonly used regimens for these patients therefore it's use as a comparator in the GO29365 can be deemed to be relevant to UK clinical practice. It is also notable that at an advisory board meeting, UK clinical experts commented that the CR rate seen

with BR in the control arm of GO29365 is in-line with what they would expect to see with other current treatment options for this population (35).

Finally, the GO29365 study was designed to capture endpoints which are relevant to UK clinical practice and that address the unmet medical need for this patient population, in particular progression-free survival, overall survival, overall response rate and duration of response.

In summary, Roche concludes that the study population and results generated in the GO29365 study are applicable to UK clinical practice.

A11. There is a large difference in the number of earliest contributing events that are disease progression or death between IRC-assessment and investigator (INV)-assessment, e.g. the number of disease progression events is 14 in Table 19 and 21 in Table 21.

Please explain why this is the case.

The main reason for the difference in the number of IRC- and INV-assessed disease progressions is that non-radiographic PD (clinical progressions) could not be detected by the IRC tumour assessment. There were 14 patients in the randomised BR arm that had clinical progression without confirmatory scans. No patients in the randomised pola+BR arm fell into this category.

A12. Please provide details on treatment-related adverse events aligned to Table 30 in the CS.

Table 20: Overview of treatment-related adverse events in GO29365

	Phase II	
n, (%)	**pola+BR n=39**	**BR n=39**
Patients with at least one:		
Any AE	[redacted]	[redacted]
Grade ≥3	[redacted]	[redacted]
Grade 5 AE	[redacted]	[redacted]
Serious AE	[redacted]	[redacted]
AE leading to discontinuation of:		
Pola	[redacted]	[redacted]
Bendamustine	[redacted]	[redacted]
Rituximab	[redacted]	[redacted]
AE leading to any study drug withdrawal	[redacted]	[redacted]
AEs to monitor:		

Grade ≥2 peripheral neuropathy Grade ≥3 neutropenia Grade ≥3 hepatoxicity Grade ≥3 infections and infestations	[redacted]	[redacted]

A13. The company notes that the justification for using bendamustine to be combined with pola was to minimise the overlapping toxicity of peripheral neuropathy. However, in the adverse events section, peripheral neuropathy was more frequently reported. Please explain this observation.

Peripheral neuropathy (PN) is an identified risk of pola, consistent with the mechanism of action of monomethyl auristatin E (MMAE), the potent anti-mitotic agent delivered to B cells by the polatuzumab vedotin antibody drug conjugate (23-25). Capping the treatment duration of pola to six cycles reduces the risk of PN versus longer treatment durations and higher doses, with the expected incidence of PN comparable to other antimicrotubule agents for lymphoma treatment (26).

Other regimens used in the treatment of R/R DLBCL, such as R-Gem-Ox (a platinum-based regimen) is associated with a high incidence (38%) and severity (Grade 3: 8%) of PN (11). Therefore, there was concern that combining polatuzumab vedotin with R-Gem-Ox would result in significant additive toxicity, specifically PN.

PN is a very rare adverse event for BR, as noted in the respective SmPCs (27, 28) and previous studies of the regimen (incidence of PN 7% vs 29% [$p<0.0001$] for BR compared to R-CHOP in patients with indolent and mantle cell lymphomas) (29). Therefore, bendamustine plus rituximab was chosen to be combined with pola to minimise the overlapping toxicity of PN that may occur with other regimens (30, 31).

Given that PN is an identified risk of pola, it is not unexpected that PN is more frequently reported in the Pola+BR arm compared to BR alone. However, the majority of PN cases were low grade and reversible, and led to few patients experiencing dose reduction or delay. Furthermore, patient-reported severity of PN-related symptoms as captured by mean score of responses to items on the Therapy-Induced Neuropathy Assessment Scale (TINAS) questionnaire were generally reported to be mild across the majority of the treatment period in both the pola+BR and BR arms for patients with R/R DLBCL.

Section B: Clarification on cost-effectiveness data

Cost effectiveness Literature Search

B1. Findings reported in section B.3.1 of the CS are not in line with the findings of Appendix G. In the literature search reported in Appendix G, five studies were considered as relevant.

a. **Please clarify why these five studies (including NICE appraisals in the same indication) in Appendix G were not reported in section B.3.1.**

The five studies identified in the SLR of cost-effectiveness studies were not presented in the main body as they did not evaluate Pola+BR or any of the comparators in the NICE scope as the primary intervention under consideration. However, all information extracted from these five studies is presented in Appendix G.

b. **Please conduct an updated search for the previous HTA submissions and assessments on the Institute for Clinical and Economic Review (ICER), Scottish Medicines Consortium (SMC), All Wales Medicines Strategy Group (AWSMG), Pharmaceutical Benefits Advisory Committee (PBAC), Canadian Agency for Drugs and Technologies in Health (CADTH)/ pan-Canadian Oncology Drug Review (pCODR)/ Institut national d'excellence en santé et services sociaux (iNESS) and Haute Autorité de Santé (HAS) websites for all relevant comparators, not only for the ones reported in the NICE scope, but also for the other treatments potentially used for this indication (e.g. CAR-T therapies).**

An updated search has been conducted to identify HTA submissions and assessments submitted to the requested HTA bodies or health authorities for DLBCL. The identified documents are submitted alongside this response document, and are listed in Table 21.

Table 21: HTA submissions and assessments for interventions treating DLBCL identified in updated searches

HTA Body/Health Authority	Primary interventions assessed	Date
SMC	Tisagenlecleucel	2019

SMC	Axicabtagene ciloleucel	2019
ICER	CAR-T therapies	2017
iNESSS	Tisagenlecleucel	2019
iNESSS	Axicabtagene ciloleucel	2019
CADTH	Tisagenlecleucel	2019
CADTH	Axicabtagene ciloleucel	2019
HAS	Tisagenlecleucel	2018–2019
HAS	Axicabtagene ciloleucel	2018–2019

CADTH, Canadian Agency for Drugs and Technologies in Health; CAR-T, chimeric antigen receptor T-cells; HAS, Haute Autorité de Santé; HTA, Health Technology Assessment; ICER, Institute for Clinical and Economic Review; iNESSS, Institut National D'excellence en Santé et Services Sociaux; SMC, Scottish Medicines Consortium

Population

B2. Priority question:

a. **Please incorporate the analysis in question A3.b (i.e. analysis of the trial, excluding 16 patients who received a transplant previously) and question A3.c (i.e. analysis of the trial, excluding 16 patients who had received a transplant and 2 patients who had received CAR-T previously) into the economic model by updating the relevant model inputs such as PFS, OS, time on treatment and adverse events.**

As discussed in the answer to A3 a. above, patients who had received prior transplant (but have then progressed) are within the expected marketing authorisation for pola+BR if they are not eligible for another transplant at this point. This was an incursion criterion in the GO29365 study. Therefore, an analysis excluding patients who had prior transplant in the GO29365 study was not implemented in the economic model.

b. **Please incorporate the subgroup analyses explained in question A7 to the economic model, with subgroup-specific efficacy (OS, PFS), time-on-treatment and safety (AEs) data.**

As discussed in question A7 and in the submission, the subgroups analysed showed treatment effects consistent with the ITT population in the key PFS and OS endpoints. In addition, current treatment options (comparators) for the different sub-groups would be the same. The GO29365 study was not designed to investigate differences in outcomes for these sub-groups and given the small number of patients

in each sub-group, sub-group scenarios were not implemented in the economic model.

Effectiveness Inputs

B3. Priority question: In the CS, for the justification of the equal effectiveness assumption of R-GemOx and Pola+BR, it was mentioned that limited UK-based data are available and findings from another company-sponsored study based on US Veterans Health Association database (a research poster from Ionescu-Ittu et al. 2018, reference 96 of the CS) were provided.

a. **Please clarify how it was concluded that limited UK-based data were available.**

The clinical SLR had included single arm studies. In addition, the literature was pragmatically search for additional published data. The question on published standard of care data sets was also asked to UK clinicians at an advisory board. However, no other UK published data was mentioned in addition to clinical studies which were subsequently identified in the SLR.

b. **Did you contact UK-based or other research networks (e.g. Haematological Malignancy Research Network) for determining the availability of alternative evidence for the effectiveness of the comparators other than BR?**

[redacted]

B4. Priority question: In the CS, the assessment of the cure mixture modelling application was done mostly by visually assessing the shapes of the Kaplan-Meier and log-cumulative hazard plots.

a. **Please provide (smoothed-kernel) empirical hazard rate plots, cumulative hazard rate estimate plots and Q-Q plots for PFS (both for**

INV and IRC assessments) and OS from the GO29365 trial, using the latest data cut-off points.

We have attached (smoothed-kernel) empirical hazard rate plots for the PFS and OS endpoints ([redacted] data-cut) in the file '[redacted]' as AIC. However, the plots would need to be interpreted with caution due to the small number of events.

Cumulative hazard plots with the parametric estimates are enclosed in the file '[redacted]' and Q-Q plots for cure-mixture models are in the file '[redacted]. All data is based on the [redacted] cut-off date and is provided as AIC.

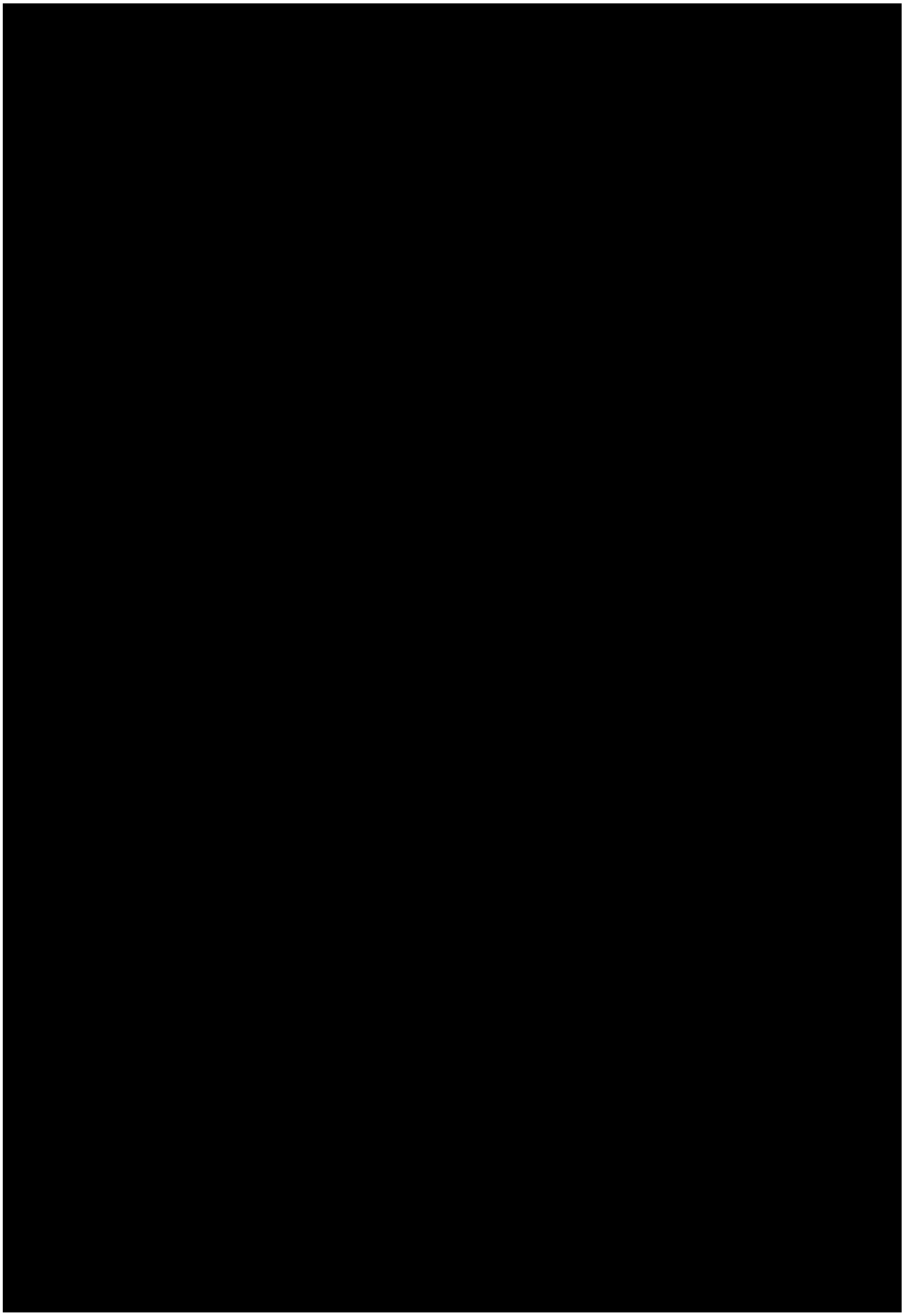
b. **For each fitted cure-mixture model, please provide Kaplan-Meier (KM) plots separately for categorised 'cured' and 'non-cured' patients, together with their associated extrapolation functions (e.g. population level mortality curves for 'cured' and parametric extrapolation curves for 'non-cured').**

The cure-mixture algorithms explained in Appendix M of the submission (including the R flexsurv cure package or our code) do not categorically distinguish between 'cured' and 'non-cured' but rather assign a probability for being in the 'cured' or 'non-cured' proportion (see our responses to B4d and B9). The cure-mixture model is fitted jointly to the observed events and the estimated cure probabilities. As there is no categorical output for 'cured' or 'non-cured' patients it is not possible to provide separate KM curves for these patients.

c. **For each of the tables presenting the cure fractions (i.e. Table 41, Table 43 and Table 44 in the CS), please provide additional histograms, presenting the frequency of the number of times each patient is categorised as 'cured', separately for Pola+BR and BR arms.**

The probability of cure (x axis) for is shown for individual patients (Y axis) for the different parametric functions and endpoint below. Different parametric functions are in general aligned. Correlation between PFS and OS 'cure' estimates is discussion in response to B9.

Figure 7: Probability of 'cure' by individual patient, parametric function and endpoint



d. **Please summarise how the Akaike Information Criterion (AIC) and Bayesian Information Criterion (BIC) values for the mixture models are generated and explain why there is a substantial discrepancy between the standard parametric models' and mixture models' goodness of fit results in Tables 40 and 42 of the CS.**

AIC and BIC values are calculated starting from the likelihood function and the number of parameters and observations used. Differences with respect to the standard parametric extrapolations are due to the fact that the cure-mixture likelihood includes a background-hazard term for each subject and is therefore different from that of the standard parametric function.

B5. Priority question:

a. **Please justify why other methods (e.g. flexible parametric modelling using splines, landmark models based on response or other mixture modelling methods than cure, as explained in Ouwens et al. 2019 Pharmacoeconomics) were not explored while modelling the OS and PFS from the GO29365 trial.**

After clarification from the ERG, the investigation of spline models and the implementation of a fixed cure point as in the scenario described in e) were prioritized for further investigation and analyses in response to the clarifications. Originally, spline models were dismissed as they may fit the observed data, but a better fit may not result in a more plausible extrapolation as noted in the TSD document (1). Our opinion is that by using a spline, the extrapolation would be mainly based on the KM curve at the end of the follow up period with very few patients at risk and therefore be more uncertain and less robust and could change substantially with a small number of additional events. This is less the case for standard parametric functions or cure-mixture models. Furthermore, the use of cure-mixture models was justified by the natural history of the disease.

We have further investigated spline model and a 3-knot spline model for OS in the pola-BR is shown in Figure 8 and Figure 9 (a 4-knot model did not improve the fit) Comparing the spline fit with the cure-mixture functions (Figure 8) shows lower long-

term estimates for OS; compared to standard parametric functions (independent fit as shown in Figure 9), long-term estimates are between Generalised Gamma and Long-Logistic model. However, the spline fit underestimated the observed KM curve from approx. 15 months onwards and, for the aforementioned reasons, did not result in a more plausible long-term extrapolation than the base case using cure-mixture models.

Figure 8: Cure-mixture and spline extrapolation for OS pola+BR

Figure 9: Standard parametric and spline extrapolation for OS pola+BR

b. Please provide these methods listed above and integrate them to the economic model.

In response to the clarification questions the model was updated with the latest now available latest data cut (clinical cut-off date). We have included revised base case, sensitivity and scenario analyses as an appendix to this response (see Appendix for economic section). The results are confirmatory and consistent with the results and predictions from the submission based on the October 2018 data cut.

In light of the substantial amount of analyses that needed to be updated with the original submission model, the findings on splines above, and the limited time for implementation, spline models were not further investigated and fully implemented. The spline model can be selected as an option for pola+BR OS (when choosing independent standard parametric models). However, we were unable to implement and test PSA for this option.

c. **Please provide alternative cure-mixture models, for PFS and OS, where the time threshold for 'cure' is set at 5 years.**

We confirm that the cure models provided do not rely on a specification of a 'threshold' time or time point for cure. As described in the submission and also as per the fit procedure (see B6), cure rates are estimated based on observed patient level data without the need to specify a survival time threshold. Such an explicit specification was implemented in the scenarios described in e) where the long-term extrapolation relies explicitly on external input parameters.

d. **Please provide an alternative model where the OS and PFS distributions can be informed by the KM estimates until the last observed event and any of the explored extrapolation methods can be selected for the time points beyond the last observed event for PFS and OS.**

KM estimates with a piecewise exponential extension have been implemented in the revised model for PFS and OS to allow expiration of such scenarios. However, these scenarios appear less plausible and do not take into account the natural history of the disease whereby more than two years in remission is associated with long-term remission and survival. Moreover, these scenarios are sensitive to the choice of attachment point of the extrapolation to the KM curve and therefore to the length of follow up in the trial. On the other hand, estimates based on cure-mixture models were more robust and the [redacted] data cut confirmed the extrapolation based on the earlier data cut.

e. **Please provide an alternative model, where the OS and PFS distributions can be informed by standard parametric extrapolation models until a specific time point, and after that time point, the mortality is informed by general population mortality (that specific time point has to be justified by the clinical literature, and different options can be explored, such as 2 years, 5 years and 10 years).**

We have attempted to implement such a scenario for OS in the revised model. When selecting 'External Cure option' (sheet 'Model Inputs', cell I205) for the OS extrapolation a cure rate can be set manually (cell J223) and is added to the standard parametric extrapolation selected and a time point can be set where the mortality is set equal to the background mortality (cell J226). This option therefore

allows to generate a wide range of extrapolation scenarios based on these external inputs. However, we were not able to explore scenarios systematically and compare OS estimates with the scenarios already implemented or comment on plausible external inputs.

We were not able to implement this function for PFS as well in the given time. However, PFS is limited by OS in the model, i.e. PFS cannot exceed OS. This function should therefore allow generation of scenarios where long-term PFS equals OS and explore OS scenarios based on external inputs.

B6. Priority question:

a. **Please provide a detailed explanation (line by line) of the cure-mixture models in R and provide the data used in the code so that the analyses can be replicated and modified by the Evidence Review Group (ERG), if needed.**

The flexsurv cure package in R allows for the use of both mixture and non-mixture models. However, the vignette provided for the package is not exhaustive and we could not identify the underlying model used. As the package does not require the inclusion of the background hazard (differently from the standard model by Lambert (32), we assume that the package uses background hazards = 0 in the absence of more detailed info. Therefore, our in-house code was used that allowed speciation of background hazards. The R code posted on github (https://github.com/felizzi/PFS_informed_cure) has now been updated with comment lines for greater clarity. In addition, a data set to test the code has been posted.

b. **Please explain which baseline characteristics are used in the expectation maximisation algorithm in the categorisation of the patients as 'cured' and 'non-cured'.**

The following baseline characteristics were used: AGE, GENDER, COUNTRY, YEAR OF TRIAL in the cure-mixture models. In addition, we use external life tables from mortality.org to build the background hazard for each subject depending on the above-mentioned characteristics.

B7. Priority question: Please confirm that all options were explored for the Gompertz extrapolation for the PFS, including using other software (e.g. in R) and other methods in the flexsurv package, such as 'Nelder-Mead' or other suggestions outlined under the optimisation routine 'optim'. If these methods were not explored, please provide the Gompertz extrapolations in the economic model, using these methods.

We can confirm that alternative methods in the R package or in SAS for standard parametric function were explored without success.

B8. Priority question:

a. **Please provide clinical expert estimates for %PFS and %OS estimates for year 1, year 2, year 5 and year 10 for BR and Pola+BR treatment arms.**

The KM PFS and OS curves for BR and pola-BR together with extrapolations with an earlier version of the model (based on the April 2018 data-cut) was discussed at the clinical advisor board as mentioned in the submission. The main focus of discussion was long-term behaviour of the BR arm and current SOC as long-term outcomes for pola-BR could not have been estimated by experts based on actual clinical experience. The OS for BR was viewed as comparable to other available regimens ~20% survival at 1 year is expected. Long-term survival (i.e. 5 years onwards) was expected for a small proportion of patients (5–10%), as discussed in the submission.

Whereas the response on BR was seen as expected with clinical practice, PFS, which showed 18% of patient's progression free at 6 months in an earlier version of the model, was considered by the advisors to be an underestimate (Please note the current base case estimate is higher at 23%). As discussed in the submission, advisors stated that 2 years PFS was deemed as indicating long-term response and survival (implying a rate of 5-10% in current practice for PFS beyond 2 years).

The clinical validity of the cure-mixture models for the long-term extrapolation and estimation of overall survival was further underpinned by publishing an abstract (33) on the subject with the clinical study investigators of GO29365 (including 1 expert from the UK) who contributed and agreed to the publication and its conclusions.

b. **Please provide clinical expert estimates or findings from literature for the standardized mortality ratio for the 'cured' relapsed or refractory diffuse large B-cell lymphoma patients. Please apply this mortality ratio in the model for the 'cured' patients.**

We are aware that an increased hazard of 9% of mortality, i.e. a ratio of 1.09, being applied to the background mortality in scenarios in TA567 and TA559 for long-term survivors. Application of this ratio was implemented in the model for long-term survivors ('Model Inputs' I86) and application of the 1.09 ratio was investigated in a scenario in the submission (Table 65 in the submission).

B9. Please respond to the points below:

a. **Please provide an independent cure-mixture model for OS, where the OS cure fractions are independently estimated from the OS data of the GO29365 trial and not from the PFS cure-mixture models.**

Independent model scenarios for cure-mixture OS models were implemented in the model as discussed in the submission pp. 90-92. These scenarios resulted in higher cure rates than PFS. These scenarios have been updated in the revised model.

b. **Please compare the level of consistency between these OS and PFS cure mixture models (e.g. showing the percentage among patients who are categorised as both PFS and OS 'cured', those who are categorised PFS 'cured' and OS 'non-cured', those who are categorised OS 'non-cured' and PFS 'cured' and those who are categorised as both PFS and OS 'non-cured').**

Based on the cure probabilities we have calculated an average probability over the different parametric cure-mixture models. Plotting the average probability of 'cure' based on PFS-INV versus the estimates based on the OS model (data shown for both arms) in Figure 10 shows a good concordance for very high probabilities and low values. In line with the higher cure rates in models based on OS (in particular for the pola+BR arm), some patients with intermediate probabilities based on OS were found to have low probabilities based on PFS.

Figure 10: Probability of 'cure' estimates in GO29365 ([redacted] data cut, Pola+BR and BR)

B10. Please respond to the points below:

a. **Please provide details on how time to off-treatment (TTOT) curves in Figure 26 are generated (i.e. by defining the event).**

Time to off-treatment (TTOT) was defined as the time to last treatment dose received, i.e. the event was the last treatment dose received. Events were recorded for each treatment separately within the Pola+BR and BR regimens.

b. **The PFS curves from Figure 26 are missing, please provide the corresponding PFS curves for Pola+BR and BR arms in the same Figure.**

A revised CS Figure 26 with the PFS curves included alongside TTOT is shown in Figure 11 below.

Figure 11: Time to off-treatment KM plots (GO29365; CS Figure 26 revised; [redacted])

BR, bendamustine + rituximab; CS, company submission; KM, Kaplan-Meier; Pola+BR, polatuzumab + bendamustine + rituximab; PFS, progression-free survival, COO, clinical cut off.

c. In the economic model, different KM curves are used for time-to-off-treatment (TTOT) of polatuzumab, bendamustine and rituximab. Please explain how these curves are generated, and explain the calculations performed in the "KM TTOT" sheet of the economic model.

As per the response to part a), the TTOT Kaplan-Meier (KM) curves were generated separately for each treatment within the pola+BR and BR regimens in GO29365. The data for the KM curve for each treatment is presented on the 'KM TTOT' sheet of the model. The medicine that each set of data represents is stated in the title cells in row 8; for example, columns E to K provide data for pola in the pola+BR arm. In the model, medicine acquisition costs are determined by the average cost per treatment cycle and the average proportion of patients on treatment for each medicine within a regimen. The latter is determined directly by the relevant KM curve as the data are mature, i.e. all patients in the randomised phase of GO29365 had completed treatment on the study medicines in the data cut used in the model.

To include the TTOT in the probabilistic sensitivity analysis, probabilistic KM TTOT curves are generated by applying a normal distribution to the log-cumulative hazard at each time point within the respective calculations, e.g. in columns M and N for pola in the pola+BR arm.

Adverse events

B11. Please justify why Mournier et al. 2013 (reference 58 in the CS) was considered to be the only source for the AE type and frequency data. Please check if other sources are available and provide adjusted incidences for AE frequency for R-GemOx. Furthermore, please provide an analysis where the AE type and frequency of R-GemOx and BR are identical.

The clinical SLR identified three studies (11, 34, 35) which included patients treated with R-GemOx, of which two presented AE type and frequency data: Mounier et al. 2013 and López et al. 2008. Both studies were observational, multi-centre, European studies, and included the same dose of R-GemOx (rituximab 375 mg/m^2, gemcitabine 1000 mg/m^2 and oxaliplatin 100 mg/m^2). However, the Mounier et al. 2013 study was deemed to be the most appropriate source of AE data for patients treated with R-GemOx for the following reasons: Mounier et al. 2013 included a longer follow up period compared to López et al. 2008 (65 months versus 13 months) and a larger patient population (48 patients versus 32 patients). Additionally, Mounier et al. 2013 is a more recent study, and is therefore more likely to have a patient population which is representative of current clinical practice. In Mounier et al. 2013, all patients had previously been treated with doxorubicin, 63% had been treated with rituximab and 35% had been treated with high-dose therapy. In addition,all patients had been treated at first line with a CHOP (69%) or ACVBP (31%) regimen, which was combined with rituximab in 28 of 48 patients.

The incidence of AEs in López et al. 2008 and Mounier et al. 2013 is presented in Table 22.

Table 22: Incidence of AEs in López et al. 2008 and Mounier et al. 2013

	López et al. 2008	Mounier et al. 2013
Treatment arm	R-GemOx	R-GemOx
N randomised/included	32	48
Anaemia, n (%)	All grade: 29 (91) Grade 3/4: 1 (3)	NR
Febrile neutropenia, n (%)	NR	All grade: NR (4)
Nausea and vomiting, n (%)	All grade: 32 (100) Grade 3/4: NR	NR
Neutropenia, n (%)	All grade: 30 (94) Grade 3/4: 13 (43)	All grade: NR (98) Grade 3/4: NR (73)

Peripheral neuropathy, n (%)	All grade: 30 (94) Grade 3/4: 2 (7)	NR
Thrombocytopenia, n (%)	All grade: 28 (88) Grade 3/4: 12 (43)	All grade: NR (92) Grade 3/4: (44)

AE, adverse event; NR, not reported; R-GemOx, gemcitabine + oxaliplatin + rituximab.

The results of a scenario analysis in which the AE type and frequency of R-GemOx and BR are identical is presented in Table 23.

Table 23: Scenario analysis results (R-GemOx AE data equivalent to BR AE data)

Intervention	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)
Pola+BR	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	26,423
R-GemOx	15,418	0.98	0.67				

AE, adverse event; BR, bendamustine + rituximab; ICER, incremental cost-effectiveness ratio; LYG, life year gained; Pola+BR, polatuzumab + bendamustine + rituximab; QALY, quality-adjusted life year; R-GemOx, gemcitabine + oxaliplatin + rituximab.

Utility/HRQoL

B12. Priority question: In the economic model, when selecting to use utility values based on technology appraisal (TA) 567 (PFS 0.83 PD 0.71), the economic model does not appear to use the PFS value of 0.83 for the first 2 years in PFS, but instead uses the age adjusted general population value.

Please clarify whether this was intentional, as this was not mentioned in the CS. If this was not intentional, please correct.

It was intentional to limit the health state utility value for each health state by the age-adjusted general population utility. The PFS utility value in TA567 (0.83) is higher than the general population value for the starting age of the cohort of 68 years (0.79). Therefore, when the scenario adopting the TA567 utility values is selected, the PFS value becomes the age-adjusted general population utility value from the start, in order to ensure face validity of the utility values used.

B13. Priority question: Please provide information on:

a. **How many patients provided data for the calculation of progression free and progressed utility (separately for each health state utility value) from ZUMA-1?**

The health-related quality of life (HRQoL) data from the ZUMA-1 clinical trial were collected in a safety management cohort, comprised of 87 EQ-5D-5L observations from 34 patients. A cross-walk algorithm was used to convert the EQ-5D-5L data to EQ-5D-3L data, in line with the NICE reference case (36).

The number of observations used to calculate the EQ-5D-3L utility value for the progression-free health state was 49 and the number of observations used for the progressed disease health state was 5 (36).

b. **The characteristics of patients who provided utility data in ZUMA-1 (and how these compare to the characteristics of patients in GO29365).**

The baseline characteristics for the safety management cohort of ZUMA-1 are not publicly available, however, this information was presented by the manufacturer in response to the ERG clarification questions in TA559 (36). This information was mostly redacted, therefore a comparison of the baseline characteristics of DLBCL patients in the Phase II ZUMA-1 population and GO29365 is presented in Table 24. This comparison should be interpreted with caution, as the safety management cohort may not be representative of the Phase II intent-to-treat ZUMA-1 population, with the ERG noting that the safety management cohort was generally younger, and had a higher proportion of males, patients at an earlier stage of disease, and patients with a lower IPI score.

Table 24: Baseline characteristics in ZUMA-1 and GO29365

		ZUMA-1	GO29365	
Treatment arm		Axicabtagene ciloleucel	Pola+BR	BR
N		77	40	40
Age		Median (Range): 58 (25–76) ≥65 years, n (%): 17 (22)	Median (Range): 67 (33–86) ≥65 years, n (%): 23 (57.5)	Median (Range): 71 (30–84) ≥65 years, n (%): 26 (65.0)
Gender, n (%)		M: 50 (65)	M: 28 (70.0)	M: 25 (62.5)
	0	NR	NR	NR

ECOG PS, n (%)	1	49 (64)	NR	NR
	0–1	NR	33 (82.5)	31 (77.5)
	2	NR	6 (15.0)	8 (20.0)
	3	NR	0	0
	Missing	NR	1 (2.5)	1 (2.5)
IPI risk score, n (%)	0–2	40 (52)	18 (45)	11 (27.5)
	3–4	37 (48)	22 (55)	29 (72.5)
Bulky disease, n (%)		NR	10 (25.0)	15 (37.5)
Extranodal involvement, n (%)		NR	27 (67.5)	29 (72.5)

†reported across whole population (not for DLCBL subgroup)
BR, bendamustine + rituximab; ECOG, Eastern Cooperative Oncology Group; F, female; IPI, International Prognostic Index; M, male; NR, not reported; Pola, polatuzumab; PS, performance status SD, standard deviation

B14. Priority question: The economic model assumes that patients who remain progression free for 2 years have the same utility as the general population.

Please provide evidence (specific to patients HRQoL) which justifies this assumption.

The assumption that patients who remain progression free for two years have the same utility as the general population has been used in a previous NICE appraisal (TA559) (36).

The assumption can further be justified by studies on HRQoL in long term cancer survivors from the literature:

Firstly, a recent systematic review carried out by the Office of Health Economics (OHE) (37) concluded that the majority of studies comparing HRQoL in long term cancer survivors with general population levels found these to be similar, and suggested that this could provide some evidence to support an argument for applying general population utilities to long term cancer survivors in economic models. However, it was noted that there was a limited evidence base.

Secondly, a recent systematic review specifically in aggressive non-Hodgkin lymphoma (NHL) concluded that HRQoL of NHL survivors becomes more comparable to general population HRQoL with longer survival (38). One of the studies (39) included in this review also looked at the effect of age and concluded that for older age categories, only differences with trivial or small-size effects in HRQoL to general population norms were found.

B15. In Table 46 of the CS, TA306 is reported as a source of health state utility values (with utilities originally sourced from Doorduijn and van Agthoven). The values reported to be obtained from these sources in the first row of Table 46 (PFS=0.76 and PD=0.68) do not match any values from the Doorduijn study. No reference could be identified for van Agthoven 2001 in the company submission or in TA306 and therefore this source could not be searched. The values presented in the first row of Table 46 do however match values reported in TA306 as sourced from second-line treatment in patients with renal cell carcinoma from the final appraisal determination of TA176.

Please explain how the values presented as sourced from TA306 (in row 1 of Table 46 of the CS) were estimated and clarify their original source.

Thank you for identifying this error in data extraction from the SLR. The utility values presented (PFS=0.76 and PD=0.68) are for the second-line treatment of patients with renal cell carcinoma, from the FAD of TA176, cited in TA306 (40). The utility values which were intended to be extracted from TA306 are those in the base case (PFS=0.81 and PD=0.60) which are sourced from Doordujin et al. 2005, cited in Groot et al. 2005 (41).

The scenario analysis whereby utility values from TA306 are used has been updated to include the base case values from this appraisal. The results of this scenario analysis are presented in Table 25.

Table 25: Scenario analysis results (utility values PFS/PD from TA306)

Intervention	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)
Pola+BR	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	24,714
BR	17,740	0.98	0.67				

BR, bendamustine + rituximab; ICER, incremental cost-effectiveness ratio; LYG, life year gained; PD, progressed disease; PFS, progression-free survival; Pola+BR, polatuzumab + bendamustine + rituximab; QALY, quality-adjusted life year; R-GemOx, gemcitabine + oxaliplatin + rituximab.

B16. Please answer the questions below:

a. **Page 101 of the document B of the CS states that *"In agreement with the assumptions adopted in TA559 and TA567, in the base case, patients who have remained in the PFS state for two years revert to age- and sex-***

***matched general population utilities for the UK"*. Please provide details of where this assumption is stated in TA567.**

After re-reading the respective TA documents, the assumptions relating to patients reverting to general population utility if in remission longer than two years was only explicitly made in TA559. In TA567, it appears the utility for all patients (PD and PFS) beyond 2 years in reverted to the PFS utility (point 3.17 in the FAD document). It should be noted that the PFS utility in this appraisal was 0.83. According to our answer to Question B13, this would in effect mean reverting to the general population utility as this PFS utility is already higher than that of the general population in the model.

b. **Where was the end of life utility value (used in the last 3 months of a patient's life in scenario analysis of 0.49) taken from in the Färkkilä et al. 2014 paper, or how was this value calculated by the company?**

The utility near the end of life (less than 3 months in the model) was derived from figure 1 b) in the Färkkilä et al. 2014 paper (by manually digitizing the graph values) (42). We like to point out a factual inaccuracy in the values reported in the submission: the correct value should read 0.47 and this has been corrected this in the latest version of the model. However, this value is only used in a scenario analysis and not in the base case.

c. **In Table 50 of document B of the CS, why is a progressive disease (PD) utility value of 0.68 chosen for the PFS – long-term follow up >5 years scenario, instead of the base-case PD utility value of 0.65? This change in assumption was not mentioned for this scenario.**

Thank you for spotting this error in Table 50 of the CS. We confirm that the PD utility value in the scenario where patients revert to general population utility after 5 years in the PFS health state remains at 0.65, and this is correct in the model.

Resource use/costs

B17. Priority question: Please clarify the choices made for the calculation of the costs of administration of Pola+BR (cycles 1 to 6), BR first cycle, BR subsequent cycles, R-GemOx (cycles 1 to 6), and one-off costs in PD for chemotherapy, R + chemotherapy, and rituximab, especially how the different HRG tariff codes (i.e. differentiating between administration at first attendance and subsequent administrations) are lined up with the different treatments that are given, and in different model cycles, and how they are combined, considering that some of the administrations should be in different days.

The unit costs applied for drug administration follow the HRG codes for chemotherapy administration in the NHS in England. For regimens on the national regimen list (BR and GemOx) (43), the applicable tariff for the first visit in each cycle, that is the first visit in the first cycle and the first visit in subsequent treatment cycles, are used in the model. For the pola+BR regimen, the tariff corresponding to the longest infusion length (and therefore highest unit costs), SB14Z ("Deliver Complex Chemotherapy, Including Prolonged Infusional Treatment, At First Attendance" (44)) was conservatively used for all first visits in each treatment cycle.

If a treatment cycle included subsequent administration visits, such as bendamustine on day 2 of each cycle for pola+BR and BR, the applicable tariff SB15Z ("Deliver Subsequent Elements of a Chemotherapy Cycle" (44)) was applied.

Unit costs for the administration tariffs were derived from the national schedule of reference costs (44). In the model, the tariff costs for each treatment cycle were added as shown in Table 26 and applied (adding pharmacy costs as described in the CS) in the model cycle (week) where the administration visit(s) occur for the proportion of patients on treatment. Please note that in the original submitted model, SB13Z instead of SB14Z had been applied for the R-GemOx administration; this has now been corrected in the revised version

Table 26: Tariff administration costs per cycle - derivation of Table 53 in submission

Cycle and regimen	Tariff applicable	Tariff unit costs	Total tariff costs per treatment cycle (CS Table 53)
1st Cycle pola+BR			

Day 1: Pola + BR	SB14Z	£374.52	£686.86
Day 2: B	SB15Z	£312.34	
Subsequent cycles pola+BR			
Day 1: Pola + BR	SB14Z	£374.52	£686.86
Day 2: B	SB15Z	£312.34	
1st Cycle BR			
Day 1: BR	SB14Z	£374.52	£686.86
Day 2: B	SB15Z	£312.34	
Subsequent cycles BR			
Day 1: BR	SB13Z	£309.22	£621.56
Day 2: B	SB15Z	£312.34	
1st and subsequent cycles R-GemOx			
Day 1: R-GemOx	SB14Z	£374.52	£374.52

BR, bendamustine + rituximab; CS: company submission; Pola+BR, polatuzumab + bendamustine + rituximab; R-GemOx, gemcitabine + oxaliplatin + rituximab.

B18. Priority question: In the section 'Treatment of clear or borderline candidates for transplant' (p. 17-20 of the CS), different terms relating to one of several forms of salvage chemotherapy are used: 'salvage chemotherapy', 'intensive therapy', 'high-dose regimen', 'high-intensity salvage therapy', 'intensive salvage chemotherapy'. It is not clear to the ERG to what extent these different terms refer to differences between regimens (in terms of treatment, as well as costs) that are specifically relevant for the purpose of the cost-effectiveness model.

Please clarify whether the aforementioned terms refer to the same or different treatments. In case they refer to different treatments, please clarify the implications for the differences in costs of these treatments.

In this section ('Treatment of clear or borderline candidates for transplant') and throughout the CS, the term 'salvage regimen' is used when there is an intention to consolidate with transplant, i.e. the treatment of transplant-eligible patients. This definition of 'salvage regimen' in aligned with UK clinical practice, as advised by UK clinical experts, however there is inconsistency in the use of the term throughout the literature. The term 'salvage' is usually reserved for more intensive therapies, and therefore 'salvage chemotherapy', 'intensive therapy', 'high-dose regimen', 'high-intensity salvage therapy', and 'intensive salvage chemotherapy' are all referring to a 'salvage regimen'.

The section on ‘Treatment of clear or borderline candidates for transplant’ is not directly relevant for the economic model as it deals with the treatment of transplant-eligible patients and therefore does not address the population in the expected indication for polatuzumab vedotin (transplant-ineligible patients). This section was included in the submission to give a full overview of the DLBCL treatment pathway.

The treatments mentioned in this paragraph are therefore not relevant comparators of Pola+BR, which are used in the transplant-ineligible setting. Regarding the costs of chemotherapies with rituximab used for transplant-ineligible patients (as identified in the NICE scope), these can be deemed broadly comparable in terms of acquisition costs as described in B19a) below.

B19. Please respond to the following issues:

a) **For the costs of chemotherapy in PD, costs of GemOx were assumed. This is justified by stating that chemotherapies are available as generic medicines, and that the costs of different regimens are broadly similar. Please clarify whether this assumption has been validated by clinical experts, regarding the representativeness of GemOX as a (generic) chemotherapy in terms of treatment as well as the associated costs.**

The assumption that chemotherapies are available as generic medicines and that the costs of different regimens are broadly similar has not been validated by clinical experts. However, the chemotherapy regimens listed in the final NICE scope (that were not included in the model) have been costed, as presented inTable 27***: Costs of additional chemotherapy regimens included in the final NICE scope***. Costs for therapies from the final NICE scope that were included in the model are presented in Table 51 in the CS. Not considering concomitant administration with rituximab, in can be seen that costs for the chemotherapy regimens included in the final NICE scope is low (<£300 per cycle). Differences in total cost of regimens are therefore unlikely to significantly impact cost-effectiveness results. Furthermore 7/11 individual medicines included in Table 27 were sourced from the NHS Drugs and Pharmaceutical Electronic Market Information Tool (eMIT), from which costs for generic medicines are sourced.

Table 27: Costs of additional chemotherapy regimens included in the final NICE scope

Agent	Milligram (or other unit)	Pack size	Pack price (£)	Source	Dose calculation	Total cycle dose (mg)	Cost per cycle
PMitCEBO (45), 14-day cycle length							
Cyclophosphamide	2000	1	27.50	NHS eMIT	300 mg/m^2 * BSA	555.00	£7.63
Mitoxantrone	20	1	61.42	BNF	7 mg/m^2 * BSA	12.95	£39.77
Etoposide	500	1	8.14	NHS eMIT	150 mg/m^2 * BSA	277.50	£4.52
Bleomycin	15000	10	170	BNF	10.000 IU/m^2 * BSA	18500.00	£20.97
Vincristine	2	5	17.82	NHS eMIT	1.4 mg/m^2 * BSA	2.59	£4.62
Prednisolone	25	56	20.25	NHS eMIT	50 mg per day (14-day cycle)	700.00	£10.13
Total							**£87.63**
DECC (46), 28-day cycle							
Dexamethasone	3.3	10	2.14	NHS eMIT	6 mg/m^2 * BSA	55.50	£3.60
Chlorambucil	2	25	42.87	BNF	15 mg/m^2 * BSA	111.00	£95.17
Etoposide	500	1	8.14	NHS eMIT	150 mg/m^2 * BSA	832.50	£13.55
Lomustine	40	20	780.82	BNF	80 mg/m^2 * BSA	148.00	£144.45
Total							**£256.78**
Gemcitabine (45), 7-day cycle							
Gemcitabine	1000	1	8.66	NHS eMIT	1000 mg/m^2 * BSA	1850.00	£16.02
Total							**£16.02**

Costs of rituximab have not been included with the regimens, however, this cost would be equivalent between regimens.
BNF, British National Formulary; BSA, body surface area; eMIT, electronic market information tool; NHS, National Health Service.

b) **Resource use in PFS, for patients on or off treatment, was assumed to be the same as in a previous TA (in CS referred to as TA306, in economic model referred to as TA308; also see C2 below). Please clarify whether this assumption has been validated by clinical expert opinion.**

With regards to the assumption that resource use for PFS is the same as that specified in TA306; this has not been validated by clinical expert opinion. However, the resource use assumed in the cost-effectiveness analysis for TA306 was carefully derived through questionnaire responses from expert practising clinicians in DLBCL (CS page 107). The resource use for PFS assumed in TA559 (36) was also based on TA306, and this assumption was not commented on by the Committee in this appraisal. The unit costs associated with PFS resource use have been updated to the latest costs available (2017–18).

c) **On page 115 it is mentioned that "The frequency and unit costs associated with the management of the identified AEs are presented in Table 58". However, Table 58 in the CS only shows unit costs, no frequencies. Please provide a table with the frequencies of AEs**

Please accept our apologies for the error regarding the provision of a table with the frequencies of adverse events included in the model. This was instead provided in Table 45 in the CS. Table 28 below is a copy of Table 45 from the submission and presents the incidences and duration of adverse events include in the model.

Table 28: Incidence of treatment-related AEs included in the model (CTCAE ≥Grade 3, serious)

Treatment-related AEs	Incidence (GO29365 and Mournier 2013 (11))			Duration	
	Pola+BR	BR	R-GemOx	Value, days	Source
Acute kidney injury	2.6%	0.0%	0%	[redacted]	GO29365
Atrial fibrillation	2.6%	0.0%	0%	[redacted]	GO29365
Atrial flutter	2.6%	0.0%	0%	[redacted]	GO29365
Anemia	0.0%	0.0%	0%	16.0	MS TA306
Diarrhoea	0.0%	2.6%	0%	[redacted]	GO29365
Febrile neutropenia	2.6%	2.6%	4%	[redacted]	GO29365
Leukopenia	2.6%	0.0%	0%	[redacted]	GO29365
Neutropenia	2.6%	0.0%	73%	[redacted]	GO29365

Pneumonia	0.0%	2.6%	0%	[redacted]	GO29365
Lower respiratory tract infection	5.1%	0.0%	0%	[redacted]	GO29365
Pyrexia	0.0%	2.6%	0%	[redacted]	GO29365
Septic shock	2.6%	0.0%	0%	[redacted]	Maximum[a]
Thrombocytopenia	0.0%	2.6%	44%	[redacted]	GO29365
Vomiting	0.0%	2.6%	0%	[redacted]	GO29365
Cytomegalovirus infection	2.6%	0.0%	0%	[redacted]	Maximum[a]
Decreased appetite	0.0%	2.6%	0%	[redacted]	Maximum[a]
Supraventricular tachycardia	2.6%	0.0%	0%	[redacted]	GO29365
Herpes virus infection	0.0%	2.6%	0%	[redacted]	GO29365
Meningoencephalitis herpetic	0.0%	2.6%	0%	[redacted]	Maximum[a]
Myelodysplastic syndrome	0.0%	2.6%	0%	[redacted]	Maximum[a]
Neutropenic sepsis	2.6%	0.0%	0%	[redacted]	GO29365
Oedema peripheral	2.6%	0.0%	0%	[redacted]	Maximum[a]
Leukoencephalopathy	2.6%	0.0%	0%	[redacted]	Maximum[a]
Pulmonary oedema	0.0%	2.6%	0%	[redacted]	Maximum[a]

[a]'Maximum' duration indicates equivalence to the longest AE duration from GO29365.

AE, adverse event; BR, bendamustine + rituximab; CTCAE, Common Terminology Criteria for Adverse Events; Pola+BR, polatuzumab + bendamustine + rituximab; R-GemOx, Rituximab + gemcitabine + oxaliplatin

Validation

B20: Priority question: Please provide all details of the validation efforts mentioned in section B.3.10 of the CS. Did the validation efforts include all steps (internal validation, cross-validation etc.) as explained for example in the AdvisHE (https://advishe.wordpress.com/) tool? If not, please include these steps as well.

The NICE methods guide does not stipulate a specific tool or steps for the validation of health economic models. Steps taken to ensure the validity of the model were described in the relevant sections of the submission and are summarised below in Table 29.

Table 29: Validation process for the pola+BR model

Item	Key validation steps	Reference in submission/clarification questions
Partitioned survival model concept	• Structure based on previous and recent use in NICE TAs in DLBCL	CS, Section B3.2.2

	• Alignment with NICE DSU guidance for oncology modelling • Model structure was presented at advisory board and no objections were raised by clinical experts	
Input data	• The applicability of the GO29356 clinical trial data to the UK was verified at an advisory board of UK clinical experts • The statistical fit of PFS and OS extrapolations was explored in detail, in line with recommendations in NICE DSU TSD 14 • Cost inputs are from the NHS/PSS perspective, as recommended by the NICE reference case	CS, Sections B3.3 and B3.5
Excel model	• Agency preformed a review of the model including checking formulas and tracing calculation errors in draft versions of the model	NA
Model outcomes	• The long-term extrapolation for BR based on an earlier data cut of GO29365 was validated with expert clinicians at an advisory board • The base case cure mixture extrapolations were validated against available long-term data to ensure their clinical validity • Base case cure-mixture model analysed and published with clinical trial investigators (47)	CS, Section B.3.3.3, Answer to B8

CS, company submission; DLBCL, diffuse large B-cell lymphoma; DSU, Decision Support Unit; NICE: National Institute for Health and Care Excellence; OS, overall survival; PFS, progression-free survival; PSS, Personal and Social Services; TA, technology appraisal; TSD: Technical Support Document.

Sensitivity/scenario/subgroup analyses

B21. Priority question: It seems that many important and relevant parameters (e.g. cure rates or PFS/OS extrapolations) were not included in the one-way sensitivity analysis.

a. Please provide the selection criteria for the parameters to be included in the one-way sensitivity analysis.

Input parameters that were independent were selected for the one-way sensitivity analysis in the CS. Parameters of parametric fits, such as treatment effect, shape parameters or cure rates (as requested in the question) could not be included in a one-way sensitivity analysis, as these were not independent. For example, a change in the cure rate parameter would require the extrapolation to be re-fitted, as the parameters for the parametric function are dependent upon the cure rate. Therefore, any uncertainty associated with the cure rates and parametric models was explored in the PSA (see the response to B22 below). In addition, the uncertainty associated

with the PFS and OS extrapolations was investigated in scenario analyses using alternative cure-mixture or standard parametric functions.

b. **Please provide a new one-way sensitivity analysis where all relevant parameters are included alongside a description of the selection criteria for relevant parameters.**

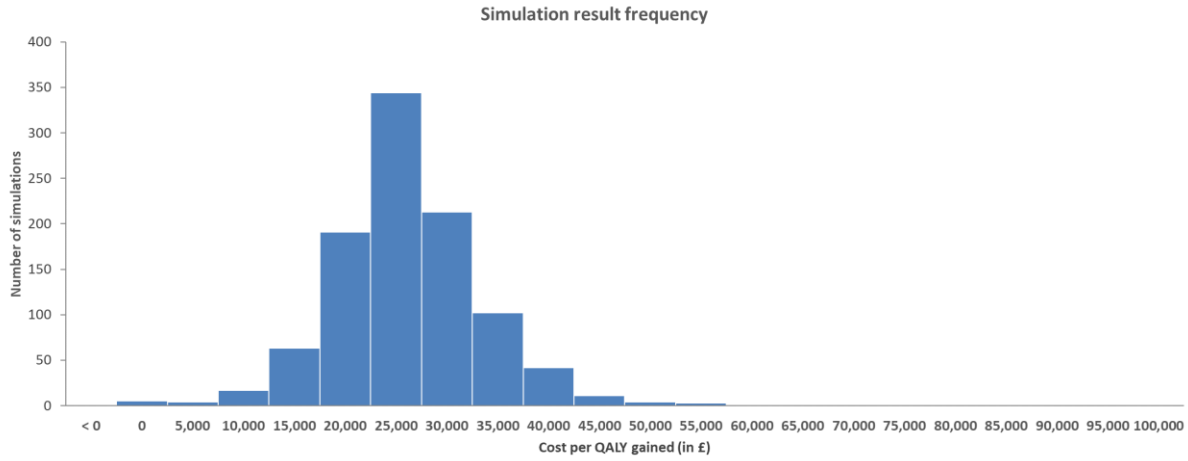
As described in part a, all relevant, independent input parameters were analysed in the one-way sensitivity analysis presented in the CS, therefore a new sensitivity analysis has not been presented in response to this question.

B22. Priority question: Please answer the following PSA and scenario analysis related issues:

a. **Please explain why there is a substantial discrepancy between the results of the PSA and deterministic base case. If the variation is attributed to generalised gamma, please check if the discrepancy is reduced when choosing another distribution.**

There is a difference in the average probabilistic ICER compared to the deterministic base case ICER due to the distribution of probabilistic ICER results being skewed to higher values (CS, Figure 28). This appears to be driven mainly by the distribution/scatter of QALY estimates in the intervention (pola+BR) arm. Through running a small number of probabilistic simulations manually (Cell J53=1 in Sheet 'Settings') it becomes apparent that the OS and PFS extrapolations in the intervention arm vary significantly, with parametric curves showing significant variations and deviating from the observed KM data and the base case Generalised-Gamma distribution (CS, Figure 23). This variation, and the consequent variation in the probabilistic ICER is significantly reduced by selecting an exponential curve for PFS and OS. The reduced number of fit parameters for the exponential curve leads to reduced uncertainty, and consequently reduces the variation in QALYs for the intervention arm, resulting in a narrower and more symmetric distribution of ICER values (Figure 12). This ultimately results in a probabilistic ICER of £28,613, which is closer to the deterministic value of £26,513.

Figure 12: ICER distribution for Exponential cure-mixture scenario



b. Judging from the PSA output in the simulation sheet, cells BP to CA, the parameters for PFS and OS (lambda, gamma, and delta) appear as not being varied. Please provide a corrected version of the model.

We can confirm that all parameters were varied based on the respective covariance matrices. However, in the case of the cure-mixture models, the parameters had not been linked to the simulation sheet (only for standard parametric functions) and therefore, although the parameters and the cure rates were varied, these values did not appear on the sheet. This has now been corrected in the updated version of the model.

c. Please provide the selection criteria for the parameters to be included in the PSA. It seems that many important and relevant parameters (e.g. patient weight and BSA or the correlation between O`S and PFS extrapolations) were not included in the PSA. Please provide a new corrected model with PSA, where all relevant parameters are included, with the description of the selection criteria for relevant parameters.

The demographic variables weight and BSA were not varied as the model base case was already taking into account the actual weight and BSA distribution observed in the trial, rather than average values only. Therefore, a weight and BSA distribution is already incorporated within the deterministic and probabilistic results.

With regards to varying the OS/PFS correlation in the PSA, the two covariate matrices for OS and PFS in the model are treated independently. This methodological limitation of the model therefore means that the OS and PFS correlation cannot be analysed in the PSA. However, as described in the CS (Section B3.8.3), the influence of different extrapolations for PFS and OS (including OS extrapolations that are not informed by the PFS cure rate) on the cost-effectiveness results can be varied through scenario analyses.

d. Please provide the descriptions (referring to the sheet and cell locations etc.) to conduct the scenario analyses presented in section B.3.8.3 of the CS.

Descriptions of the inputs (sheet and specific cell[s]) that require adjusting for each scenario presented in CS Section 3.8.3 are presented below.

Table 30: Descriptions of input locations for scenario analyses

Scenario	Sheet	Cell (name)
Model time horizon		
Time horizon, 10 years	Model Inputs	I21 (t_horizon)
Time horizon, 20 years	Model Inputs	I21 (t_horizon)
Time horizon, 30 years	Model Inputs	I21 (t_horizon)
Patient baseline characteristics		
Average patient weight (- 5 kg)	Model Inputs	I51 (dm_wgt)
Average patient weight (+ 5 kg)	Model Inputs	I51 (dm_wgt)
Average patient BSA (m^2) (-5%; average body weight set to 66.35 kg)	Model Inputs	I56 (dm_hgt)
Average patient BSA (m^2) (+5%; average body weight set to 83.96 kg)	Model Inputs	I56 (dm_hgt)
Utilities		
Utility values PFS/PD from TA567	Model Inputs	I95 (utility)
Utility values PFS/PD from TA306	Model Inputs	I95 (utility)
PFS – decline in utility in the 3 months prior to death	Model Inputs	I97 (u_approach)
Long-term survivor utility aligned to general population after 5 years	Model Inputs	I84 (u_time_gen_pop)
Survival modelling		
Cure-mixture model (OS, PFS), Log-normal	Model Inputs	**PFS:** I165 (prop_hazards_pfs); I168 (dist_pfs); I169 (dist_pfs_comp) **OS**: I209 (dist_os); I210 (dist_os_comp)

Cure-mixture model (OS, PFS), Log-logistic	Model Inputs	**PFS:** I165 (prop_hazards_pfs); I168 (dist_pfs); I169 (dist_pfs_comp) **OS**: I209 (dist_os); I210 (dist_os_comp)
Dependent parametric distribution function (OS, PFS), generalised gamma	Model Inputs	**PFS:** I165 (prop_hazards_pfs)*; I168 (dist_pfs); I169 (dist_pfs_comp) **OS:** I206 (prop_hazards_os)*; I209 (dist_os); I210 (dist_os_comp)
Dependent parametric distribution function (OS, PFS), log-normal	Model Inputs	**PFS:** I165 (prop_hazards_pfs)*; I168 (dist_pfs); I169 (dist_pfs_comp) **OS**: I206 (prop_hazards_os)*; I209 (dist_os); I210 (dist_os_comp)
Dependent parametric distribution function (OS, PFS), log-logistic	Model Inputs	**PFS:** I165 (prop_hazards_pfs)*; I168 (dist_pfs); I169 (dist_pfs_comp) **OS**: I206 (prop_hazards_os)*; I209 (dist_os); I210 (dist_os_comp)
Independent parametric distribution function (OS, PFS), generalised gamma	Model Inputs	**PFS:** I165 (prop_hazards_pfs)*; I168 (dist_pfs); I169 (dist_pfs_comp) **OS**: I206 (prop_hazards_os)*; I209 (dist_os); I210 (dist_os_comp)
Independent parametric distribution function (OS, PFS), log-normal	Model Inputs	**PFS:** I165 (prop_hazards_pfs)*; I168 (dist_pfs); I169 (dist_pfs_comp) **OS**: I206 (prop_hazards_os)*; I209 (dist_os); I210 (dist_os_comp)
Independent parametric distribution function (OS, PFS), log-logistic	Model Inputs	**PFS:** I165 (prop_hazards_pfs)*; I168 (dist_pfs); I169 (dist_pfs_comp) **OS**: I206 (prop_hazards_os)*; I209 (dist_os); I210 (dist_os_comp)
OS not informed by PFS (cure-mixture extrapolation), generalised gamma (PFS and OS)	Model Inputs	**PFS:** I165 (prop_hazards_pfs)*; I168 (dist_pfs); I169 (dist_pfs_comp) **OS:** I212 (cure_rate_os); I206 (prop_hazards_os)*; I209 (dist_os); I210 (dist_os_comp)
OS not informed by PFS (cure-mixture extrapolation), log-normal (PFS and OS)	Model Inputs	**PFS:** I165 (prop_hazards_pfs)*; I168 (dist_pfs); I169 (dist_pfs_comp) **OS:** I212 (cure_rate_os); I206 (prop_hazards_os)*; I209 (dist_os); I210 (dist_os_comp)
OS not informed by PFS (cure-mixture extrapolation), log-logistic (PFS and OS)	Model Inputs	**PFS:** I165 (prop_hazards_pfs)*; I168 (dist_pfs); I169 (dist_pfs_comp) **OS:** I212 (cure_rate_os); I206 (prop_hazards_os)*; I209 (dist_os); I210 (dist_os_comp)
Excess mortality for long-term survivors (>2 years; excess hazard = 1.1)	Model Inputs	I86 (excess_hazard)
Costs and resource use		
140 mg vials polatuzumab vedotin only, no vial sharing	Model Inputs (1); Cost Inputs (2)	(1) I70 (vial_options); (2) H47 (vial_sharing)
140 mg vials polatuzumab vedotin only, 100% vial sharing	Model Inputs (1); Cost Inputs (2)	(1) I70 (vial_options);

		(2) H47 (vial_sharing)
No supportive care costs incurred by long term survivors after 3 years	Model Inputs	I82 (c_no_cost_lts)
Alternative comparator		
Pola + BR vs R-GemOx	Model Inputs	I26 (comparator)

*In the model, the 'proportional' option in the drop-down menu is equivalent to 'dependent' in the CS and the 'not proportional' option in the drop-down is equivalent to 'independent' in the CS

CS, company submission; PFS, progression-free survival; OS, overall survival; Pola+BR, polatuzumab + bendamustine + rituximab; R-GemOx, Rituximab + gemcitabine + oxaliplatin

e. In the economic model, there are some pull-down menu options, which were not explained in the CS, e.g. duration of treatment effect for PFS and OS or selecting population where the SCT and CAR-T received patients are censored. Please explain the details of each of the pull-down menu options in the economic model, and explain why these options were not elaborated in the scenario analysis section of the CS.

The 'duration of treatment effect' option allows the user to explore scenarios that include a waning treatment effect, setting a start month (from start of treatment) for waning and an end month where the is no more difference in treatment effect between treatment arms in terms of PFS and OS. This option is deemed suitable for standard parametric functions only, and was not further explored in the submission as cure-mixture models were selected for the base case. In addition, for the scenarios with standard parametric functions, there was no evidence of a waning treatment effect (as described in the CS, the observed PFS [page 77] and OS [page 85] in GO29365 was consistent with a proportional hazards assumption).

The 'censor SCTs, CAR-Ts' option allows the user to select OS analyses from a data set in which patients who received SCT or CAR-T after pola+BR or BR were censored (4 patients in total), as described on page 113 in the CS. This scenario demonstrated that OS and the ICER did not change significantly when the censored set was used, demonstrating that outcomes and cost-effectiveness was not affected by a small number of patients that received these treatments in the GO29365 study.

Section C: Textual clarification and additional points

C1. The ERG noted a discrepancy between the terminology used in the CS and the electronic model when referring to rituximab (termed as such, or abbreviated to R, in the CS and most model sheets) versus the term AntiCD20 (cell C36) in the model sheet 'Supportive Care Cost'. Please clarify this discrepancy.

For the purpose of modelling the term can be used interchangeably as all post-polatuzumab vedotin regimens considered as AntiCD20 were in fact rituximab.

C2. The ERG noted a discrepancy between references to TA306 (in the CS), and TA308 (in the model). Please clarify which reference is the correct one.

The reference should read TA306 in the model. This is a typographic error.

C3. Rituximab is incorrectly referred to as a generic chemotherapy in the 'Source' column of Table 54 in the CS. Please confirm this reporting error.

This is correct. Rituximab should be referred to as biosimilar.

C4. Figure 5 in the CS – PFS or OS – axis or table is mislabelled. Please confirm this mislabelling error.

We can confirm the axis is Figure 5 is mislabelled and should read 'Overall Survival'. This error is also repeated in Figure 18.

C5. Figure 25 in document B of the CS (OS KM for Pola+BR from the ROMULUS study and extrapolations) is mislabelled since in ROMULUS patients received Pola+R. Please confirm this mislabelling error. Furthermore, please provide a discussion to what extent the patients from the ROMULUS trial are comparable to the patients in the GO29365 trial.

We can confirm that patients in the ROMULUS study received Pola+BR. The patient characteristics of the ROMULUS study have been reported in Morschhauser et al. (48) and compared to GO29365 in Table 24 below.

Table 31: Baseline characteristics in ROMULUS and GO29365

		ROMULUS	GO29365	
Treatment arm		Pola-R (R/R DLBCL)	Pola+BR	BR
N		39	40	40
Age		Median (Range): 68 (55–77)	Median (Range): 67 (33–86) ≥65 years, n (%): 23 (57.5)	Median (Range): 71 (30–84) ≥65 years, n (%): 26 (65.0)
Gender, n (%)		M: 25 (64%)	M: 28 (70.0)	M: 25 (62.5)
ECOG PS, n (%)	0	12 (31%	NR	NR
	1	25 (64%)	NR	NR
	0–1	NR	33 (82.5)	31 (77.5)
	2	2 (5%)	6 (15.0)	8 (20.0)
	3	NR	0	0
	Missing	NR	1 (2.5)	1 (2.5)
IPI risk score, n (%)	0–2	NR	18 (45)	11 (27.5)
	3–4	NR	22 (55)	29 (72.5)
	Median	2	N/R	N/R
Bulky disease, n (%)		12 (31%)	10 (25.0)	15 (37.5)
Extranodal involvement, n (%)		NR	27 (67.5)	29 (72.5)
Refractory to last prior anti-lymphoma therapy, n (%)		31 (80)	30 (75)	34 (85)

†reported across whole population (not for DLCBL subgroup)
BR, bendamustine + rituximab; ECOG, Eastern Cooperative Oncology Group; F, female; IPI, International Prognostic Index; M, male; NR, not reported; Pola, polatuzumab; PS, performance status SD, standard deviation

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Single technology appraisal

ID1576: Polatuzumab vedotin with rituximab and bendamustine for treating relapsed or refractory diffuse large B-cell lymphoma

Economic Model Updated Results Appendix

GO29365 Data Cut: [redacted]

File name	Version	Contains confidential information	Date
ID1576_polatuzumab vedotin RR DLBCL_ACIC_Economic Appendix	1	Yes	4th September 2019

Contents

Tables

Figures

Introduction

A new data cut from GO29365 ([redacted]) became available in August 2019 after the original manufacturer submission was completed and submitted to NICE. The cost-effectiveness model has therefore been updated with clinical trial data from this new data cut. In addition, the functionality of the model has been updated to reflect requests made by the ERG in the clarification questions for this appraisal; this is detailed in Roche's response to the clarification questions document. Finally, a small number of errors have been corrected in the model since the original version, which are presented in Table 1.

Table 1. Corrections to revised cost-effectiveness model

Input	Sheet(s)	Cell(s)	Change
Proximity to death utility values	Model Inputs	I116–I119	Values corrected from 0.490 to 0.470 Reflects corrected utility values from Qual Life Res (2014) 23:1387–1394
Administration costs R-GemOx	Cost Inputs	H83, H88	Value updated from £340.42 to £405.72. Reflects use of correct HRG code (SB13Z replaced with SB14Z)
AE incidence R-GemOx	Utility Values	K57, K69	K57 (anaemia) corrected from 33% to 0%; K69 (thrombocytopenia) corrected from 23% to 44% Reflects correct AE rates in the R-GemOx arm from Mournier 2013

AE, adverse event; R-GemOx, rituximab + gemcitabine + oxaliplatin

Accordingly, updated cost-effectiveness results from the revised model are presented in this economic appendix. The revised model has been submitted alongside this appendix and the clarification questions.

Base-case results

Base-case incremental cost-effectiveness analysis results

The base case pairwise comparison results for Pola+BR vs BR are presented in Table 2.

The base case cost-effectiveness results demonstrate that Pola+BR is cost-effective vs BR, at an incremental cost-effectiveness ratio (ICER) of £25,307 per QALY. Pola+BR accrued a greater health benefit compared to BR, as demonstrated by an incremental QALY value of [redacted].

Table 2. Base case deterministic results

Intervention	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)
Pola+BR	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	25,307
BR	17,740	0.98	0.67	-	-	-	-

BR, bendamustine + rituximab; ICER, incremental cost-effectiveness ratio; LYG, life years gained; Pola+BR, polatuzumab + bendamustine + rituximab; QALYs, quality-adjusted life years

Sensitivity analyses

Probabilistic sensitivity analysis

The uncertainty arising from the imprecision associated with model input parameter estimates was investigated via probabilistic sensitivity analysis (PSA). A Monte-Carlo simulation was conducted using 2,000 iterations based upon model inputs randomly drawn from distributions around the mean (summarised in Table 3). Variation in the parameterisation of the PFS and OS extrapolations was based on normal distributions and where appropriate, covariance matrices.

Where available, the standard error (SE) calculated from the same data used to derive the mean value estimate was used to inform the distribution of the input parameter. Alternatively, the SE was calculated for AE disutility inputs as 10% of the mean estimate, or for cost inputs via the following equation:

$$SE = (LN(mean + 20\%) - LN(mean - 20\%))/4$$

Table 3. PSA parameter inputs

Parameter	Distribution	Mean	SE	Alpha	Beta
Survival modelling					
Parametric estimates for OS and PFS	Normal distribution around parameter estimates, informed where appropriate, by covariance matrices				
Utilities					
Utility in PFS, both treatment arms	Beta	0.72	0.03	62.44	160.56
Utility in PD, both treatment arms	Beta	0.65	0.06	21.76	40.42
Disutility due to adverse events					
Acute kidney injury	Normal	0.27	0.027	N/A Parameter input variation (SE) equal to 10% of mean estimate	
Atrial fibrillation	Normal	0.37	0.037		
Atrial flutter	Normal	0.37	0.037		
Anaemia	Normal	0.25	0.025		
Cytomegalovirus infection	Normal	0.15	0.015		
Decreased appetite	Normal	0.37	0.037		
Diarrhoea	Normal	0.10	0.010		
Febrile neutropenia	Normal	0.15	0.015		
Herpes virus infection	Normal	0.15	0.015		
Leukoencephalopathy	Normal	0.37	0.037		
Leukopenia	Normal	0.09	0.009		
Lower respiratory tract infection	Normal	0.20	0.020		
Meningoencephalitis herpetic	Normal	0.15	0.015		
Myelodysplastic syndrome	Normal	0.37	0.037		
Neutropenia	Normal	0.09	0.009		
Neutropenic sepsis	Normal	0.15	0.015		
Oedema peripheral	Normal	0.37	0.037		
Pneumonia	Normal	0.20	0.020		
Pulmonary oedema	Normal	0.37	0.037		
Pyrexia	Normal	0.11	0.011		
Septic shock	Normal	0.37	0.037		
Supraventricular tachycardia	Normal	0.37	0.037		
Thrombocytopenia	Normal	0.11	0.011		
Vomiting	Normal	0.05	0.005		
Administration costs, Pola+BR (£)					
Administration cost, first treatment cycle	Log-normal	686.86	0.1014		
Pharmacy cost, first treatment cycle	Log-normal	62.40	0.1014		

Administration cost, subsequent treatment cycles	Log-normal	686.86	0.1014	N/A Parameter input variation (SE) calculated from upper and lower estimates of base case value ±20%
Pharmacy cost, subsequent treatment cycles	Log-normal	62.40	0.1014	
Administration costs, BR (£)				
Administration cost, first treatment cycle	Log-normal	686.86	0.1014	N/A Parameter input variation (SE) calculated from upper and lower estimates of base case value ±20%
Pharmacy cost, first treatment cycle	Log-normal	31.20	0.1014	
Administration cost, subsequent treatment cycles	Log-normal	686.86	0.1014	
Pharmacy cost, subsequent treatment cycles	Log-normal	31.20	0.1014	
Supportive care costs (£)				
Residential care (day)	Log-normal	114.50	0.1014	N/A Parameter input variation (SE) calculated from upper and lower estimates of base case value ±20%
Day care (day)	Log-normal	58.00	0.1014	
Home care (day)	Log-normal	33.32	0.1014	
Hospice (day)	Log-normal	157.08	0.1014	
Oncologist (visit)	Log-normal	165.85	0.1014	
Haematologist (visit)	Log-normal	164.80	0.1014	
Radiologist (visit)	Log-normal	187.30	0.1014	
Nurse (visit)	Log-normal	38.45	0.1014	
Specialist nurse (visit)	Log-normal	38.45	0.1014	
GP (visit)	Log-normal	37.40	0.1014	
District nurse (visit)	Log-normal	38.45	0.1014	
CT scan	Log-normal	163.66	0.1014	
Full blood counts	Log-normal	2.51	0.1014	
LDH	Log-normal	2.51	0.1014	
Liver function	Log-normal	2.51	0.1014	
Renal function	Log-normal	2.51	0.1014	
Immunoglobulin	Log-normal	2.51	0.1014	
Calcium phosphate	Log-normal	2.51	0.1014	
Inpatient day	Log-normal	383.47	0.1014	
Palliative care team	Log-normal	117.84	0.1014	
Subsequent care costs, PD				
Chemotherapy	Log-normal	1,116.40	0.1014	
R + chemotherapy	Log-normal	2,860.98	0.1014	
Rituximab	Log-normal	2,765.83	0.1014	

Radiotherapy	Log-normal	162.88	0.1014	N/A Parameter input variation (SE) calculated from upper and lower estimates of base case value ±20%
ECG	Log-normal	107.84	0.1014	
MUGA	Log-normal	285.04	0.1014	
MRI	Log-normal	140.60	0.1014	
PET-CT	Log-normal	470.71	0.1014	
Bone marrow biopsy	Log-normal	519.82	0.1014	
Adverse event management costs (£)				
Acute kidney injury	Log-normal	332.50	0.101	N/A Parameter input variation (SE) calculated from upper and lower estimates of base case value ±20%
Atrial fibrillation	Log-normal	670.13	0.101	
Atrial flutter	Log-normal	670.13	0.101	
Anaemia	Log-normal	309.09	0.101	
Diarrhoea	Log-normal	392.26	0.101	
Febrile neutropenia	Log-normal	1,847.50	0.101	
Leukopenia	Log-normal	291.00	0.101	
Neutropenia	Log-normal	291.00	0.101	
Pneumonia	Log-normal	495.81	0.101	
Lower respiratory tract infection	Log-normal	377.90	0.101	
Pyrexia	Log-normal	309.56	0.101	
Septic shock	Log-normal	1,037.71	0.101	
Thrombocytopenia	Log-normal	281.96	0.101	
Vomiting	Log-normal	382.30	0.101	
Cytomegalovirus infection	Log-normal	393.65	0.101	
Decreased appetite	Log-normal	382.30	0.101	
Supraventricular tachycardia	Log-normal	670.13	0.101	
Herpes virus infection	Log-normal	377.90	0.101	
Meningoencephalitis herpetic	Log-normal	3,652.18	0.101	
Myelodysplastic syndrome	Log-normal	556.99	0.101	
Neutropenic sepsis	Log-normal	1,847.50	0.101	
Oedema peripheral	Log-normal	343.16	0.101	
Leukoencephalopathy	Log-normal	3,609.61	0.101	
Pulmonary oedema	Log-normal	2,189.85	0.101	

BR, bendamustine + rituximab; CD20, B-lymphocyte antigen CD20; CT, computed tomography; ECG, electrocardiogram; GP, General Practitioner; LDH, lactate dehydrogenase test; MRI, magnetic resonance imaging; MUGA, multiple gated acquisition scan; N/A, not applicable; OS, overall survival; PD, progressed disease; PET-CT, positron emission tomography-computed tomography; PFS, progression-free survival; Pola+BR, polatuzumab + bendamustine + rituximab; R, rituximab; PSA, probabilistic sensitivity analysis; SE, standard error

The results of the PSA are presented in Table 4. The mean incremental costs and QALYs from the PSA were £[redacted] and [redacted] respectively, resulting in a mean ICER value of £37,749 per QALY.

Table 4. Mean probabilistic results

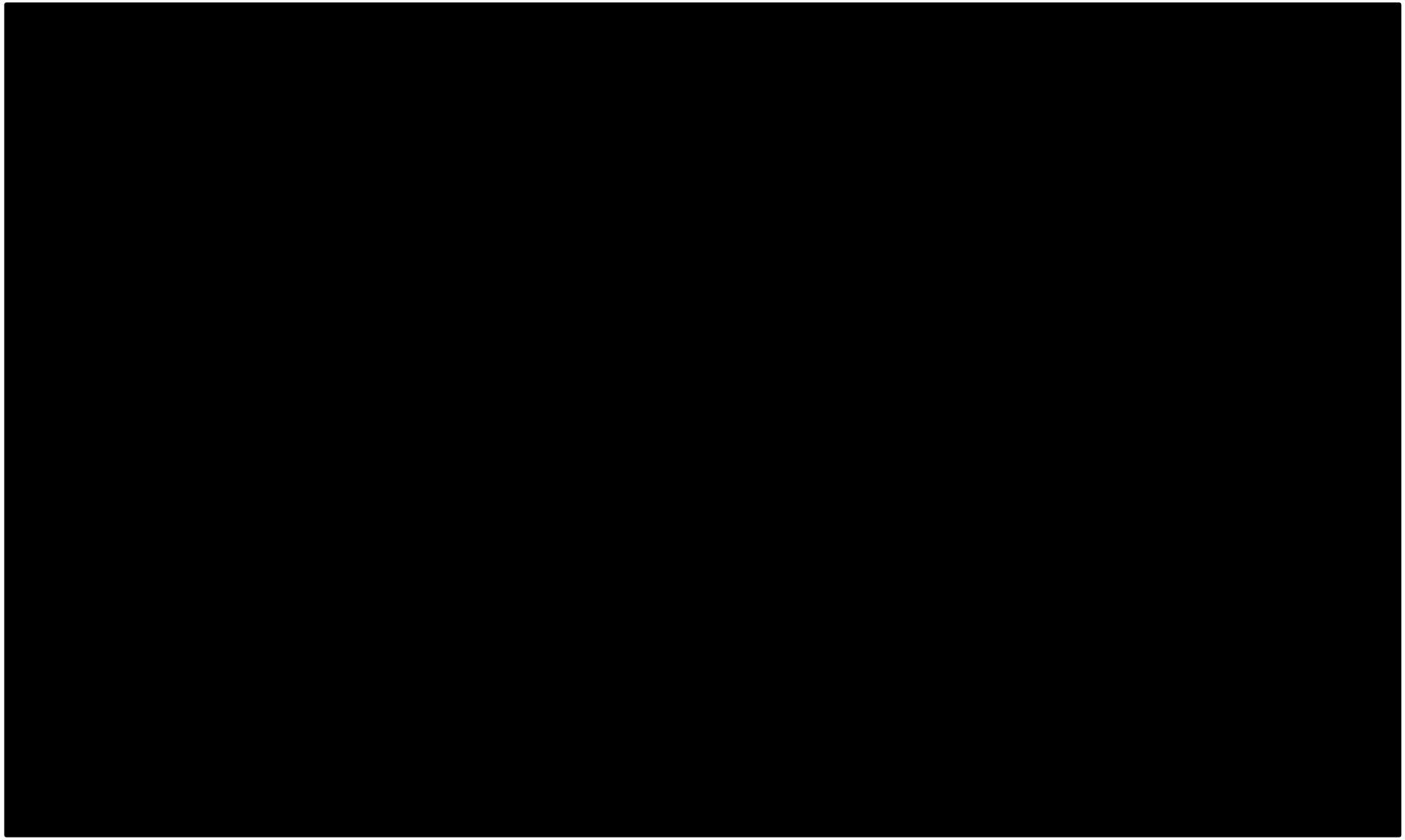
Intervention	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)
Pola+BR	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	37,749
BR	17,762	0.98	0.67	-	-	-	-

Costs and QALYs are discounted at 3.5%.

BR, bendamustine + rituximab; ICER, incremental cost-effectiveness ratio; LYG, life years gained; Pola+BR, polatuzumab + bendamustine + rituximab; QALYs, quality-adjusted life years

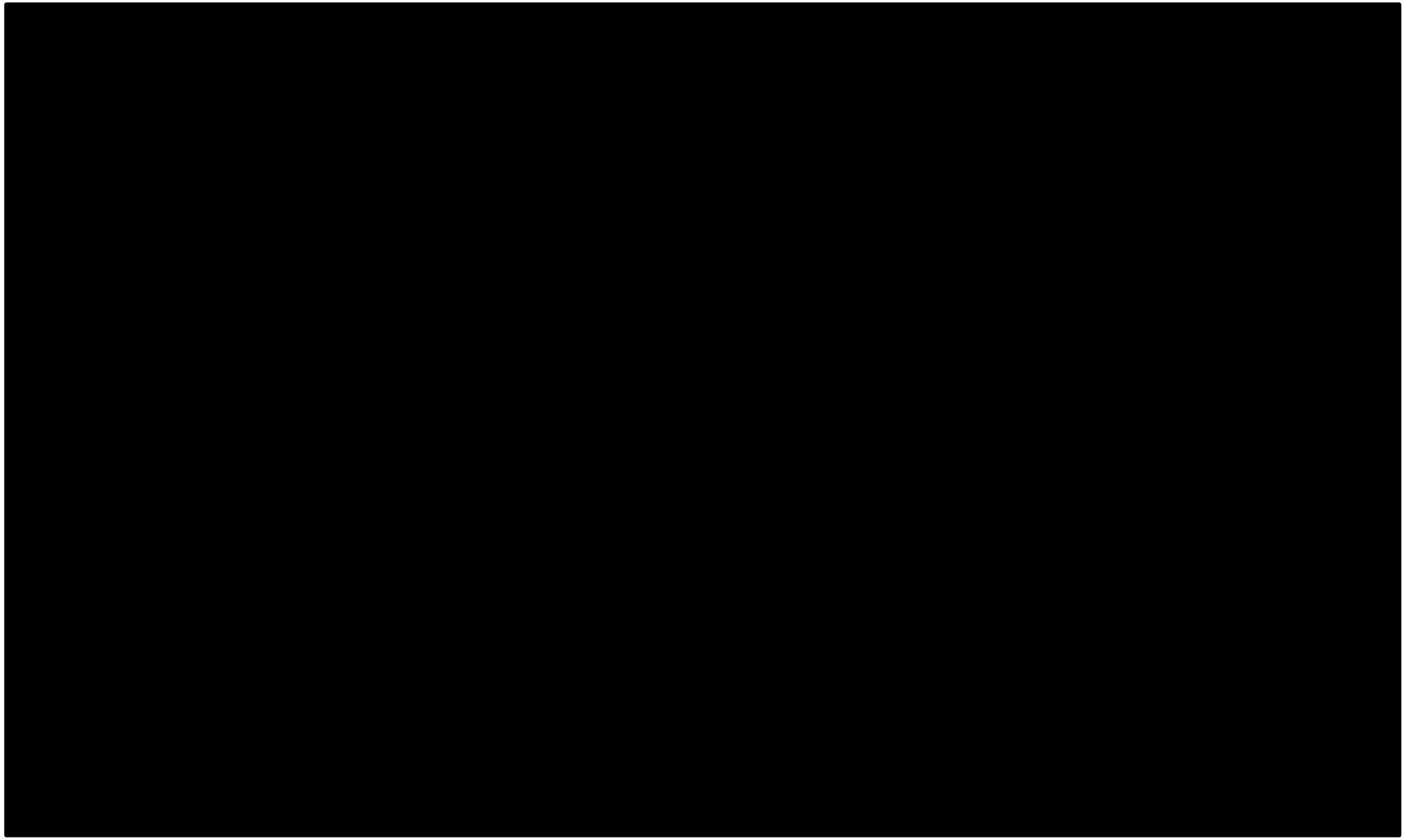
The cost-effectiveness plane is presented in Figure 1, including the percentile ranges (2.5% and 97.5%) for both incremental costs and QALYs and the 95% credibility ellipse. The cost-effectiveness acceptability curve (CEAC) for Pola+BR versus BR is presented in Figure 2. From the CEAC, at a willingness to pay (WTP) threshold of £50,000, the probability of Pola+BR being cost-effective relative to BR was [redacted].

Figure 1. Cost-effectiveness plane for Pola+BR versus BR



BR, bendamustine + rituximab; Pola+BR, polatuzumab + bendamustine + rituximab; QALY, quality-adjusted life year

Figure 2. Cost-effectiveness acceptability curve for Pola+BR versus BR



BR, bendamustine + rituximab; Pola+BR, polatuzumab + bendamustine + rituximab; WTP, willingness to pay.

Deterministic sensitivity analysis

Deterministic sensitivity analysis (DSA) was conducted by varying all parameters for which there were single input values. Each input parameter was set to its respective upper or lower bound and the deterministic results for the model recorded. For simplicity, the totals for each cost category were varied for the DSA whilst the impact of AE disutilities was investigated using the average disutility of all AEs, weighted by frequency and duration. The upper and lower bounds around the mean value for each input parameter were based upon the 10% and 90% percentile values obtained from the PSA input distribution. Where percentile estimates were not available, the input parameter was varied by ±20% (alternatively ±5 kg for mean weight, ±5% for mean BSA).

The DSA inputs and corresponding ICER values are summarised in Table 5.

Table 5. DSA results

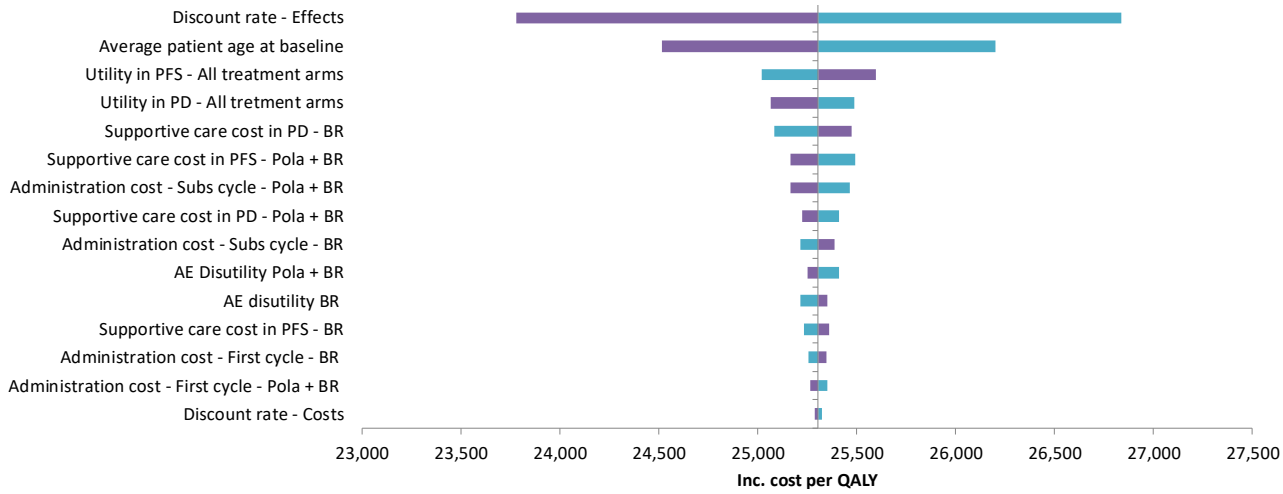
Parameter modified	Base value	Upper value	Lower value	Upper value ICER (£/QALY)	Lower value ICER (£/QALY)	Range (£/QALY)	% of base case
Base case				25,307		-	
Model settings							
Discount rate, costs	3.5%	4.2%	2.8%	25,325	25,290	35	0.14%
Discount rate, effects	3.5%	4.2%	2.8%	26,836	23,781	3,055	12.1%
Patient baseline characteristics							
Average patient age at baseline (+/- 5 years)	69.0	74.0	64.06	26,202	24,517	1,685	7%
Utilities							
Utility in PFS, all treatment arms	0.72	0.76	0.68	25,022	25,598	576	2.3%
Utility in PD, all treatment arms	0.65	0.71	0.57	25,489	25,068	421	1.7%
AE disutility, Pola+BR[b]	0.0088	0.0175	0.0044	25,414	25,253	161	0.64%
AE disutility, BR[b]	0.0074	0.0147	0.0037	25,217	25,351	134	0.53%
AE management costs							
AE management cost per patient, Pola+BR	337.27	355.94	322.54	25,316	25,299	17	0.07%
AE management cost per patient, BR	386.14	409.54	366.50	25,295	25,316	21	0.08%
Administration costs, Pola+BR							
Administration cost (first cycle)	749.26	843.87	666.50	25,352	25,268	84	0.3%
Administration cost (subsequent cycle)	749.26	846.35	664.62	25,467	25,167	300	1.2%
Administration costs, BR							
Administration cost (first cycle)	718.06	816.30	633.84	25,259	25,347	88	0.3%

Administration cost (subsequent cycle)	652.76	736.85	576.53	25,216	25,389	173	0.7%
Supportive care costs							
Supportive care cost in PFS - Pola+BR	160.21	167.29	154.49	25,491	25,165	326	1.3%
Supportive care cost in PFS - Pola+BR on treatment	460.22	483.95	442.01	25,307	25,307	0	0%
Supportive care cost in PFS - BR	160.21	167.69	154.49	25,233	25,363	130	0.5%
Supportive care cost in PFS - BR on treatment	460.22	483.95	442.01	25,307	25,307	0	0%
Supportive care cost in PD, Pola+BR	363.64	382.11	349.75	25,414	25,226	188	0.7%
Supportive care cost in PD, BR	363.64	382.11	349.75	25,085	25,474	389	1.5%
One-off costs, PD	634.88	507.91	761.86	25,301	25,312	11	0.04%

[a]Input parameter varied ±20% for the DSA; [b]Average of all AEs weighted by frequency and duration. AE, adverse event; BR, bendamustine + rituximab; BSA, body surface area; DSA, deterministic sensitivity analysis; ICER, incremental cost-effectiveness ratio; OS, overall survival; PD, progressed disease; PFS, progression-free survival; Pola+BR, polatuzumab + bendamustine + rituximab; QALY, quality-adjusted life year

A tornado diagram demonstrating the key drivers of ICER value in the comparison between Pola+BR and BR are presented in Figure 3.

Figure 3. Deterministic sensitivity analysis – tornado diagram of the top 15 most influential parameters for Pola+BR versus BR



BR, bendamustine + rituximab; PD, progressed disease; PFS, progression-free survival; Pola+BR, polatuzumab + bendamustine + rituximab; QALY, quality-adjusted life year

Scenario analysis

Scenarios using alternative utility data sets, parametric extrapolations and drug acquisition costs were explored as described below, with the results summarised in Table 6.

Table 6: Scenario analysis results

Parameter modified	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)	% change from base case ICER

Base case	[redacted]	[redacted]	25,307	0%
Model time horizon				
Time horizon, 10 years	[redacted]	[redacted]	40,354	59%
Time horizon, 20 years	[redacted]	[redacted]	28,451	12%
Time horizon, 30 years	[redacted]	[redacted]	26,022	3%
Patient baseline characteristics				
Average patient weight (- 5 kg)	[redacted]	[redacted]	23,952	-5%
Average patient weight (+ 5 kg)	[redacted]	[redacted]	26,812	6%
Average patient BSA (m^2) (-5%; average body weight set to 66.35 kg)	[redacted]	[redacted]	22,981	-9%
Average patient BSA (m^2) (+5%; average body weight set to 83.96 kg)	[redacted]	[redacted]	27,999	11%
Utilities				
Utility values PFS/PD from TA567	[redacted]	[redacted]	25,034	-1%
Utility values PFS/PD from TA306	[redacted]	[redacted]	25,110	-1%
PFS – decline in utility in the 3 months prior to death	[redacted]	[redacted]	25,867	2%
Long-term survivor utility aligned to general population after 5 years	[redacted]	[redacted]	25,711	2%
Survival modelling				
Cure-mixture model (OS, PFS), Log-normal	[redacted]	[redacted]	25,983	3%
Cure-mixture model (OS, PFS), Log-logistic	[redacted]	[redacted]	25,932	2%
Dependent parametric distribution function (OS, PFS), generalised gamma	[redacted]	[redacted]	51,413	103%
Dependent parametric distribution function (OS, PFS), log-normal	[redacted]	[redacted]	56,589	124%
Dependent parametric distribution function (OS, PFS), log-logistic	[redacted]	[redacted]	58,520	131%
Independent parametric distribution function (OS, PFS), generalised gamma	[redacted]	[redacted]	33,259	31%
Independent parametric distribution function (OS, PFS), log-normal	[redacted]	[redacted]	55,848	121%
Independent parametric distribution function (OS, PFS), log-logistic	[redacted]	[redacted]	53,530	112%
OS not informed by PFS (cure-mixture extrapolation), generalised gamma (PFS and OS)	[redacted]	[redacted]	24,951	-1%
OS not informed by PFS (cure-mixture extrapolation), log-normal (PFS and OS)	[redacted]	[redacted]	26,361	4%
OS not informed by PFS (cure-mixture extrapolation), log-logistic (PFS and OS)	[redacted]	[redacted]	26,110	3%
Excess mortality for long-term survivors (>2 years; excess hazard = 1.1)	[redacted]	[redacted]	26,270	4%
Costs and resource use				
140 mg vials polatuzumab vedotin only, no vial sharing	[redacted]	[redacted]	34,260	35%
140 mg vials polatuzumab vedotin only, 100% vial sharing	[redacted]	[redacted]	23,743	-6%
No supportive care costs incurred by long term survivors after 3 years	[redacted]	[redacted]	26,261	4%
Alternative comparator				

Pola + BR vs R-GemOx	[redacted]	[redacted]	26,448	5%

BR, bendamustine + rituximab; BSA, body surface area; ICER, incremental cost-effectiveness ratio; OS, overall survival; PD, progressed disease; PFS, progression-free survival; Pola+BR, polatuzumab + bendamustine + rituximab; QALY, quality-adjusted life year; R-GemOx, gemcitabine + oxaliplatin + rituximab.

Subgroup analysis

No subgroups were evaluated in the economic analysis.

NICE National Institute for Health and Care Excellence

Patient organisation submission

Polatuzumab vedotin with rituximab and bendamustine for treating relapsed or refractory diffuse large B-cell lymphoma [ID1576]

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on conditions and their treatment that is not typically available from other sources.

To help you give your views, please use this questionnaire with our guide for patient submissions.

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- Your response should not be longer than 10 pages.

About you	
1.Your name	[redacted]

2. Name of organisation	Lymphoma Action
3. Job title or position	Senior Medical Writer
4a. Brief description of the organisation (including who funds it). How many members does it have?	Lymphoma Action is a national charity, established in 1986, registered in England and Wales and in Scotland. We provide high quality information, advice and support to people affected by lymphoma – the 5th most common cancer in the UK. We also provide education, training and support to healthcare practitioners caring for lymphoma patients. In addition, we engage in policy and lobbying work at government level and within the National Health Service with the aim of improving the patient journey and experience of people affected by lymphoma. We are the only charity in the UK dedicated to lymphoma. Our mission is to make sure no one faces lymphoma alone. Our work is made possible by the generosity, commitment, passion and enthusiasm of all those who support us. In 2018 we raised a total income of £1,432,177 from various fundraising activities. We have a policy for working with healthcare and pharmaceutical companies – those that provide products, drugs or services to patients on a commercial or profit-making basis. This includes that no more than 20% of our income can come from these companies and there is a cap of £50k per company. Acceptance of donations does not mean that we endorse their products and under no circumstances can these companies influence our strategic direction, activities or the content of the information and support we provide to people affected by lymphoma.
4b. Do you have any direct or indirect links with, or funding from, the tobacco industry?	No

5. How did you gather information about the experiences of patients and carers to include in your submission?	We sent a survey to our network of patients and carers asking about their experience of current treatment and their response to this new technology, with particular emphasis on quality of life. We received four responses from patients with a relevant diagnosis, which we have used as the basis of this submission. We have also included information based on our prior experience with patients with this condition.
Living with the condition	
6. What is it like to live with the condition? What do carers experience when caring for someone with the condition?	DLBCL is an aggressive lymphoma. Most people with DLBCL first notice rapidly-enlarging lumps, often in the neck, armpit or groin but they can be in the chest or abdomen. Symptoms can vary depending on where the lymphoma is growing. Systemic symptoms are common, including fevers, night sweats, unexplained weight loss, fatigue, loss of appetite and severe itching. DLBCL is treated with the aim of cure. However, up to 50% of patients are refractory to treatment or relapse after initial treatment. The prognosis for patients with relapsed or refractory DLBCL is poor, with median survival less than a year. Symptoms of DLBCL usually develop rapidly and progress quickly. Patients can be extremely unwell for many months. During treatment, patients often spend many weeks in hospital, isolated from family and friends. One patient commented, ‘Life was completely on hold. I spent progressively more time in hospital, as when I was allowed home, I usually developed neutropenic fevers and was admitted back into hospital.’ Side effects of intensive chemotherapy, such as sickness, diarrhoea, hair loss and neutropenia can be extremely debilitating, affecting many aspects of life. Most patients are unable to carry on working during treatment. It can take months or even years after treatment to recover. Patients report taking a year or more off work to recover from intensive chemotherapy regimens and stem cell transplants. Some side effects, especially

	fatigue and peripheral neuropathy, can last for many years and have a significant impact on quality of life. Younger patients may experience fertility issues or early menopause. The psychological impact of the diagnosis is enormous. Patients report experiencing insomnia, anxiety and a 'constant fear of dying'. Spending many weeks in hospital can have a detrimental effect on the patient and the family as a whole. Even after successful treatment, the relief of getting back into some kind of normal life is marred by the anxiety of relapse. Late effects of treatment are also a psychological and physical challenge. People with DLBCL can be very ill and require a huge amount of support. Caring for someone with DLBCL is emotionally challenging and time-consuming. Some carers take significant amounts of time off work to transport their loved one to-and-from hospital, care for dependants, collect medications and visit hospital. One patient reported preferring to stay in hospital if possible to try to spare their spouse worry. Financially, it can be hard to cope. It can be very difficult for carers to understand what their loved one is experiencing. They often feel helpless, anxious and scared. One patient reported that their spouse turned to the GP for psychological support. DLBCL also has an emotional and psychological impact on any dependants.
Current treatment of the condition in the NHS	
7. What do patients or carers think of current treatments and care available on the NHS?	Most people with DLBCL are treated with chemo-immunotherapy, sometimes followed by radiotherapy. High-dose chemotherapy regimens might be used. For relapsed or refractory DLBCL, salvage chemotherapy followed by stem cell transplant is the most common treatment option. Treatment is very intense and some people are not able to tolerate it. People who experience a subsequent relapse may be eligible to have CAR T-cell therapy. Again, this is a very intensive treatment that can cause serious side effects. Additionally, patients have to remain stable for long enough to receive the treatment. The long-term durability and late effects of CAR T-cell therapy are as yet unknown. Patients feel that current treatment regimens are 'really tough', 'hard and traumatic'. Most patients experience significant side effects and many go on to develop late effects. One commented that the side

	effects can be worse than the cancer. Treatment has a long-lasting impact on physical and mental wellbeing. However, patients are unanimously grateful that treatment has given them another chance. Most patients felt it took many years to recover from their treatment. Some found that aftercare was limited.
8. Is there an unmet need for patients with this condition?	Patients feel there is a definite unmet need for an effective, less demanding treatment with fewer side effects.
Advantages of the technology	
9. What do patients or carers think are the advantages of the technology?	The main advantages patients felt polatuzumab vedotin with rituximab and bendamustine could offer over current treatment options are: • higher response rates • fewer side effects • less time in hospital/more time at home • less time away from work, allowing them to lead a 'normal' life and contribute economically • shorter recovery time.
Disadvantages of the technology	
10. What do patients or carers think are the disadvantages of the technology?	As with all treatments, patients were concerned about the potential side effects. Some were concerned about the durability of response. As with any newer treatment, any potential late effects of polatuzumab vedotin with rituximab and bendamustine are as yet unknown.

Patient population	
11. Are there any groups of patients who might benefit more or less from the technology than others? If so, please describe them and explain why.	Patients felt that people who could not tolerate intensive chemotherapy regimens or stem cell transplants might be more likely to benefit from treatment, as well as people who have not responded to other treatments.
Equality	
12. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	No

Other issues	
13. Are there any other issues that you would like the committee to consider?	No

Key messages

14. In up to 5 bullet points, please summarise the key messages of your submission:

- Prognosis for people with relapsed or refractory DLBCL is extremely poor and any new treatment offers a potential lifeline.
- Current treatments for relapsed or refractory DLBCL are very intensive, requiring long stays in hospital away from the support of family and friends and incurring serious side effects and late effects.
- People with relapsed or refractory DLBCL often take many months to recover from treatment and need significant time off work. The psychological, social and economic impact of this is considerable.
- Polatuzumab vedotin with rituximab and bendamustine has the potential to improve outcomes in people with this very difficult-to-treat disease, particularly for people who are not suitable for stem cell transplantation or who have not responded to other treatments.

Thank you for your time.

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Professional organisation submission

Polatuzumab vedotin with rituximab and bendamustine for treating relapsed or refractory diffuse large B-cell lymphoma [ID1576]

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature.

To help you give your views, please use this questionnaire. You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

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- Your response should not be longer than 13 pages.

About you	
1. Your name	[redacted]
2. Name of organisation	NCRI-ACP-RCP-RCR
3. Job title or position	RCP registrar
4. Are you (please tick all that apply):	An employee or representative of a healthcare professional organisation that represents clinicians?

5a. Brief description of the organisation (including who funds it).	NCRI-ACP-RCP-RCR
5b. Do you have any direct or indirect links with, or funding from, the tobacco industry?	No
The aim of treatment for this condition	
6. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability.)	Main aim: to delay progression. It may provide a durable response (so patients can be bridged to another form of consolidation) or potentially be curative in a cohort of patient The patient cohort 'for whom haematopoietic stem cell transplant is not suitable'. This encompasses 3 main groups of patients: 1. Patient who are older and / or have co-morbidities and who would never be deemed suitable for a stem cell transplant. 2. Patients who have already had a stem cell transplant and have relapsed following it 3. Patients who are young and fit enough for a stem cell transplant but their disease is not in a good enough remission to proceed with this
7. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease	A clinically significant treatment response would be: Reduction in tumour size (CR/PR/ORR) Possible sustained resolution of the tumour so it's not detectable (Complete Response (CR)). Partial responses in DLBCL are rarely sustainable.

activity by a certain amount.)	Prolongation of survival (PFS/OS measured in months)
8. In your view, is there an unmet need for patients and healthcare professionals in this condition?	Yes – there is clearly an unmet need for patients as presently palliative approaches are adopted, or regimens with poor outcome or unacceptable toxicities.
What is the expected place of the technology in current practice?	
9. How is the condition currently treated in the NHS?	Patients who are not fit for transplant are offered low intensity chemotherapy regimens (sometimes with rituximab_ however there is no standard of care. The following comparators can be given with or without rituximab (depending on amount received by patient prior) R-GemOx - R-Gem - R-P-MitCEBO - Pixantrone (although this is not used much around the UK now, and tends to be used at later treatment lines) - (R-)DECC - PEP-C - R-COCKLE - For populations (2) and (3) above there is the option of CAR-T cells (recently introduced in UK in 2019). Benda+R+pola may provide a bridging therapy to CAR T-cell therapy (presently only patients PS 0-1 are eligible for CAR-T therapy so this will be a small cohort). The regimen may be used as part of a strategy to bridge to a potentially curative therapy such as allogeneic transplant – again this will be a small cohort

• Are any clinical guidelines used in the treatment of the condition, and if so, which?	BCSH Guidelines 2013
• Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.)	It is not well defined as this cohort of patients is hard to treat as poor clinical options. Since the introduction of CAR-T therapy in UK (potentially for cohort 2 and 3) in 2019 the national CAR-T panel has been set up and this is being reviewed as it evolves.
• What impact would the technology have on the current pathway of care?	It would dramatically change patient care as it would offer a therapeutic option for a cohort of patients where the options are poor and limited.
10. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	Yes – in the same way. It involves immunotherapy and Lymphoma doctors and Haem-Onc departments have a wealth of experience in this field. It is delivered in the chemotherapy day unit. Bendamustine and rituximab are commonly given across haematology units in the UK and polatuzumab is a straightforward drug to administer.
• How does healthcare resource use differ between the technology and current care?	The main issue we see is that bendamustine is not commissioned for the treatment of relapsed high grade lymphoma. The lymphoma treating community has always been somewhat perplexed why there are such limitations on us using this agent since it became generic. But due to this, currently bendamustine is not a 'standard of care' drug for this indication in England. Often patients remain under consultant haematology / oncology care as well as receiving active palliative care (possible use of palliative radiotherapy for symptoms, possible use of steroids
• In what clinical setting should the technology be used? (For example, primary or	Secondary care as outlined above

secondary care, specialist clinics.)	
• What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	Bendamustine and rituximab are commonly given across haematology units in the UK and polatuzumab is a straightforward drug to administer. It will be delivered in the chemotherapy day unit without patient monitoring of patients as is standard practice
11. Do you expect the technology to provide clinically meaningful benefits compared with current care?	Yes we would expect the technology to provide clinically meaningful benefits compared with current care. Antibody-drug conjugates have been applied successfully to high grade B-cell lymphomas. The trial this evaluation is based on resulted in a significance overall survival difference. These 2 factors combined suggest this does have the potential to have a substantial impact on health-related benefits and is a step-change in the management of this condition. It is innovative in its potential in a population with a poor outcome and limited effective treatment options.
• Do you expect the technology to increase length of life more than current care?	Yes – prolong PFS and OS
• Do you expect the technology to increase health-related quality of life more than current care?	Yes – by improving lymphoma-related symptoms. Also an out-patient/day unit-delivered therapy
12. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	No – the populations as defined above,

The use of the technology	
13. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use (for example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed.)	`It has implications for patients (attending day unit as all 3 agents are given intravenously) whilst presently many of the alternatives may be delivered orally. It has an impact for healthcare professionals: monitoring side effects (peripheral neuropathy or infusional) and opotential infective complications (but latter exists for oral therapies too). This will involve training of staff in day unit but staff experienced in delivering immunochemotherapy regimens. The 1st cycle is delivered over 3 days in day unit, subsequent cycles over 2 days/month. Bendamustine/Rituximab has been associated with infectious complications so appropriate prophylaxis should be given. Monitoring patients closely recommended when they have side effects
14. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	Eligibility: 'Patients who are not fit for transplant' as outlined above. Stop treatment if progressive disease or unacceptable side effects (although the incidence of severe (Grade3 3/ 4) side effects was low. Peripheral neuropathy was usually grade 1-2 and resolved after cessation of therapy.
15. Do you consider that the use of the technology will result in any	Yes – we expect this technology will result in health-related benefits and some may not be included in the quality-adjusted life year (QALY) calculation

substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation?	
16. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met?	Yes we consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and it will improve the way that current need is met. Patients have higher chance of responding to therapy, have prolonged PFS and OS. A cohort of patients may be bridged to a curative line of therapy (CAR-T or allogenetic stem cell transplantation).
• Is the technology a 'step-change' in the management of the condition?	Yes this is a 'step-change' in the management of the condition
• Does the use of the technology address any particular unmet need of the patient population?	Yes – the unmet need of patients who are older and / or have co-morbidities and who would never be deemed suitable for a stem cell transplant where other options are palliative. Also bridging therapy to potentially curative therapies as outlined above.
17. How do any side effects or adverse effects of the technology affect the management of the	Bendamustine/Rituximab has been associated with infectious complications so appropriate prophylaxis should be given. Peripheral neuropathy was usually grade 1-2 and resolved after cessation of therapy.

condition and the patient's quality of life?	
Sources of evidence	
18. Do the clinical trials on the technology reflect current UK clinical practice?	Yes – as there is no standard comparator.
• If not, how could the results be extrapolated to the UK setting?	N/A
• What, in your view, are the most important outcomes, and were they measured in the trials?	Yes – outcomes important to patients involve reduction in tumour size (and associated reduction/resolution of associated symptoms) and prolongation of survival (PFS/OS measured in months). These were measured
• If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	See above
• Are there any adverse effects that were not apparent in clinical trials but have come to	None we are aware of

light subsequently?	
19. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	No
20. How do data on real-world experience compare with the trial data?	Real world data compares well with comparator group
Equality	
21a. Are there any potential equality issues that should be taken into account when considering this treatment?	No equality issues
21b. Consider whether these issues are different from issues with current care and why.	N/A
Key messages	

22. In up to 5 bullet points, please summarise the key messages of your submission.

- Improvement of tumour-associated symptoms
- Prolongation of progression-related survival
- prolongation of overall survival
- Well tolerated (low incidence of severe or persistent symptoms)
- Revolutionises treatment approach for which there is no accepted standard of care

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Clinical expert statement

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- Your response should not be longer than 13 pages.

About you	
1. Your name	**Dr Sridhar Chaganti**
2. Name of organisation	**NCRI and Royal College of Physicians**
3. Job title or position	**Consultant Haematologist**

4. Are you (please tick all that apply):	☒ an employee or representative of a healthcare professional organisation that represents clinicians? ☒ a specialist in the treatment of people with this condition? ☒ a specialist in the clinical evidence base for this condition or technology? ☐ other (please specify):
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	☒ yes, I agree with it ☐ no, I disagree with it ☐ I agree with some of it, but disagree with some of it ☐ other (they didn't submit one, I don't know if they submitted one etc.)
6. If you wrote the organisation submission and/ or do not have anything to add, tick here. (If you tick this box, the rest of this form will be deleted after submission.)	☐ yes
The aim of treatment for this condition	

7. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability.)	To induce a response and improve survival
8. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount.)	Achieving a complete remission or a partial remission with symptom improvement.
9. In your view, is there an unmet need for patients and healthcare professionals in this condition?	Yes. Patients with relapsed /refractory diffuse large B cell lymphoma after 2 or more lines of therapy have very poor outcomes. CART cell therapy may be an option for some patients in this setting but there are no standard treatment options for patients not eligible for CART cell therapy.
What is the expected place of the technology in current practice?	

10. How is the condition currently treated in the NHS?	Patients not fit for transplant but fit to receive further intensive chemotherapy are sometimes treated with either : 1. Rituximab + gemcitabine and cisplatin or oxaliplatin 2. Pixantrone Patients not fit for intensive chemotherapy are treated with a palliative intent with low dose oral chemotherapy regimens.
• Are any clinical guidelines used in the treatment of the condition, and if so, which?	BCSH guidelines 2016
• Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.)	There is no standard of care for treatment of relapsed/ refractory diffuse large B cell lymphoma who are not transplant eligible.
• What impact would the technology have on the current pathway of care?	It will provide an additional treatment option for patients with relapsed/ refractory diffuse large B cell lymphoma.
11. Will the technology be used (or is it already used) in the same way	Yes. BR chemotherapy is already delivered in most haematology centres (for follicular lymphoma) including level 1 centres. Polatuzumab is a short IV infusion given every 3 weeks and its administration is similar in many ways to other antibodies used in the treatment of lymphomas.

as current care in NHS clinical practice?	
• How does healthcare resource use differ between the technology and current care?	This treatment will be delivered on day case unit. The 1st cycle will have to be over 3 days but all other cycles are over 2 days which is standard for BR chemotherapy. Bendamustine is not currently funded for this indication on the NHS. Bendamustine + rituximab is not currently in routine use for r/r DLBCL.
• In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	Secondary care.
• What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	Most haematology units will have the necessary infrastructure in place to deliver this treatment. Bendamustine will need to be funded as well.
12. Do you expect the technology to provide clinically meaningful benefits compared with current care?	CR rates of this regimen are better compared to current treatment options and a proportion of patients may have survival benefit; both are likely to confer a clinically meaningful benefit to patients.
• Do you expect the technology to increase length	Yes, for a proportion of patients.

of life more than current care?	
• Do you expect the technology to increase health-related quality of life more than current care?	Yes, especially for those who achieve a CR.
13. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	No
The use of the technology	
14. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use (for example, any concomitant treatments needed, additional clinical requirements, factors	Pola + BR can be delivered in most haematology centres. Patients may need antibiotic prophyaxis and GSCF injections to reduce risk of infections.

affecting patient acceptability or ease of use or additional tests or monitoring needed.)	
15. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	Lack of response after 3 cycles or progressive disease through treatment at any stage may be a reason to stop treatment. This may need a CT scan assessment.
16. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation?	No
17. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it	Polatuzumab is a novel CD79 antibody targeting and in many ways similar to brentuximab which targets CD30. It is fairly well tolerated in combination with BR chemo regimen and improves response rates and chances of survival for patients with relapsed/ refractory DLBCL.

improve the way that current need is met?	
• Is the technology a 'step-change' in the management of the condition?	It's an incremental improvement.
• Does the use of the technology address any particular unmet need of the patient population?	This may provide a viable treatment option for some patients who are otherwise left with palliative options only.
18. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	May cause significant peripheral neuropathy in a proportion of patients which may have an adverse impact on QoL.
Sources of evidence	
19. Do the clinical trials on the technology reflect current UK clinical practice?	Yes.

• If not, how could the results be extrapolated to the UK setting?	
• What, in your view, are the most important outcomes, and were they measured in the trials?	CR rate and survival. They were both measured in the trial.
• If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	NA
• Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	No
20. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	No
21. Are you aware of any new evidence for the comparator treatment(s) since the publication	No

of NICE technology appraisal guidance [TA306, TA559, TA567]	
22. How do data on real-world experience compare with the trial data?	No data from real world experience as yet that I am aware of.
Equality	
23a. Are there any potential equality issues that should be taken into account when considering this treatment?	No
23b. Consider whether these issues are different from issues with current care and why.	NA
Topic-specific questions	
24. Is polatuzumab vedotin a curative treatment, and if so at what stage can cure be assumed?	It is too early to comment if this will be a curative treatment. Only 7 patients in the Pola + BR arm were in continuing CR at 20 months follow up one of whom had received stem cell transplant consolidation. In diffuse large B cell lymphoma, the chance of cure is high with ongoing CR lasting >24 months.

25. The economic model predicts that 21.2% of patients on polatuzumab vedotin+BR have long-term remission and 20.6% are long term survivors (compared with 0% for BR). Are these proportions for polatuzumab vedotin+BR and BR clinically plausible and reflective of the clinical trial?	It is as per the data from the trial and clinically plausible but the model is based on very small number of patients and includes patients who have had further treatments such as stem cell transplants after Pola + BR. Also with R-Gem Ox, around 10-15% had responses lasting > 24 months (Mounier N, Haematologica 2013)
26. Would patients be likely to have polatuzumab vedotin treatment beyond 6 cycles in clinical practice?	No.
27. Is the lyophilised formulation of polatuzumab vedotin (to be supplied by the company) expected to have similar efficacy and safety to the liquid formulation	Unable to comment. Not my area of expertise.

that was assessed in the clinical trial?	
28. Are bendamustine + rituximab (BR) and rituximab, gemcitabine and oxaliplatin (R-GemOx) a reasonable reflection of the treatments used in clinical practice to treat people who would be eligible for polatuzumab vedotin+BR?	Yes, but bendamustine is not routinely funded in the UK for this indication. However, since bendamustine is now generic, the use of BR in this setting is increasing.
29. Are there any other relevant treatments used in this population? if so, how would the efficacy and safety of these be expected to differ from BR in clinical practice?	ICE – like, DHAP – like, other gemcitabine containing regimens are all used in 3rd line setting for treatment of diffuse large B cell lymphoma in patients who are otherwise fit and could be considered for a stem cell transplant if a remission were achieved (Neste et al Bone Marrow Transplant 2016; Neste et al, Bone Marrow Transplant 2017). CR rate depends on a number of factors but is generally around 20% in the 3rd line setting. Pixantrone is NICE approved for this indication but not often used in clinical practice in the UK. Low dose oral combination chemotherapy regimens (eg; PEP-C) are often used, especially for frail patients.

	There will be an overlap between patients meeting eligibility for Pola + BR and CART therapy. It is possible Pola + BR may be preferentially offered to patients who are considered “not fit” to receive CART therapy either due to patient related factors (such as age, performance status, organ function) or disease specific factors (rapidly progressive/ bulky disease with vital organ compromise).
30. Is it reasonable to assume that BR and R-GemOX have similar efficacy?	Probably yes though there is no published evidence of direct comparison of the 2 regimens
31. Does the assumption that a maximum number of 3 treatment cycles of 3 weeks of R-GemOx reflect treatment in clinical practice?	No. R-Gem OX is used ever 2-3 weeks for up to 8 cycles.
Key messages	

32. In up to 5 bullet points, please summarise the key messages of your statement.

- There is a significant unmet need in treatment of relapsed/ refractory DLBCL. So new treatment options are welcome.
- CART therapy may be an option for some patients but will only serve a small proportion of patients with r/r DLBCL.
- Pola + BR is an attractive option as it comes with a good chance of CR and improves survival.
- Pola + BR is relatively easy to deliver and can be given in most haematology centres around the country.
- Though there is accepted standard arm in this setting, BR chemo is not in routine use in the UK.

Thank you for your time.

Please log in to your NICE Docs account to upload your completed statement, declaration of interest form and consent form.

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NICE National Institute for Health and Care Excellence

Clinical expert statement

Polatuzumab vedotin with rituximab and bendamustine for treating relapsed or refractory diffuse large B-cell lymphoma [ID1576]

Thank you for agreeing to give us your views on this technology and its possible use in the NHS.

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature.

To help you give your views, please use this questionnaire. You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

Information on completing this expert statement

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 13 pages.

About you	
1. Your name	Dr Kate Cwynarski
2. Name of organisation	UCLH and NCRI Lymphoma Clinical Studies Group and NCRI-ACP-RCP
3. Job title or position	Consultant Haematologist: Lymphoma, UCLH Department of Haematology

	UCLH 3rd floor West 250 Euston Road London NW1 2PG and Chair of British Society of Haematology Lymphoma Specialist Interest group
4. Are you (please tick all that apply):	**YES** an employee or representative of a healthcare professional organisation that represents clinicians?: NCRI Lymphoma Clinical Studies Group and Chair of British Society of Haematology Lymphoma Specialist Interest group **YES** a specialist in the treatment of people with this condition? Lymphoma Consultant at UCLH **YES** a specialist in the clinical evidence base for this condition or technology? 'Cliical Expert' for this appraisal and involved in technical appraisal ☐ other (please specify):
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	☐ yes, I agree with it (and I wrote it with my national Lymphoma colleagues' input)
6. If you wrote the organisation submission and/ or do not have anything to add, tick here. (If you tick this box, the	☐ I wrote the organisation submission but there are additional questions in this template which I will address

rest of this form will be deleted after submission.)	
The aim of treatment for this condition	
7. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability.)	Main aim: to delay progression. It may provide a durable response (so patients can be bridged to another form of consolidation) or potentially be curative in a cohort of patient The patient cohort 'for whom haematopoietic stem cell transplant is not suitable'. This encompasses 3 main groups of patients: 1. Patient who are older and / or have co-morbidities and who would never be deemed suitable for a stem cell transplant. 2. Patients who have already had a stem cell transplant and have relapsed following it 3. Patients who are young and fit enough for a stem cell transplant but their disease is not in a good enough remission to proceed with this
8. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount.)	A clinically significant treatment response would be: reduction in tumour size (CR/PR/ORR) possible sustained resolution of the tumour so it's not detectable (Complete Response (CR)). Partial responses in DLBCL are rarely sustainable. prolongation of survival (PFS/OS measured in months)
9. In your view, is there an unmet need for patients and healthcare professionals in this condition?	Yes – there is clearly an unmet need for patients as presently palliative approaches are adopted, or regimens with poor outcome or unacceptable toxicities.

What is the expected place of the technology in current practice?	
10. How is the condition currently treated in the NHS?	Patients who are not fit for transplant are offered low intensity chemotherapy regimens (sometimes with rituximab, however there is no standard of care. The following comparators can be given with or without rituximab (depending on amount received by patient prior) R-GemOx - R-Gem - R-P-MitCEBO - Pixantrone (although this is not used much around the UK now, and tends to be used at later treatment lines) - (R-)DECC - PEP-C - R-COCKLE For populations (2) and (3) above there is the option of CAR-T cells (recently introduced in UK in 2019). Benda+R+pola may provide a bridging therapy to CAR T-cell therapy (presently only patients PS 0-1 are eligible for CAR-T therapy so this will be a small cohort). The regimen may be used as part of a strategy to bridge to a potentially curative therapy such as allogeneic transplant – again this will be a small cohort. Clinical trials (novel agents, other immunotherapeutic strategies) are another option
• Are any clinical guidelines used in the treatment of the condition, and if so, which?	BCSH Guidelines 2013

• Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.)	It is not well defined as this cohort of patients is hard to treat as there are poor clinical options. Since the introduction of CAR-T therapy in UK (potentially for cohort 2 and 3) in 2019 the national CAR-T panel was set up although it's likely to be dismantled. Many patients will be discussed in their local MDT and some in regional MDTs
• What impact would the technology have on the current pathway of care?	It would dramatically change patient care as it would offer a therapeutic option for a cohort of patients where the options are poor and limited.
11. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	Yes – in the same way. It involves immunotherapy and many Lymphoma doctors and Haem-Onc departments have a wealth of experience in this field. It is delivered in the chemotherapy day unit. Bendamustine and rituximab are commonly given across haematology units in the UK and polatuzumab is a straightforward drug to administer. Some smaller units may be less experienced in administering polatuzumab, but since the EAMS scheme was established this year, many units are gaining experience.
• How does healthcare resource use differ between the technology and current care?	The main issue we see is that bendamustine is not commissioned for the treatment of relapsed high grade lymphoma. The lymphoma treating community has always been somewhat perplexed why there are such limitations on us using this agent in treating a number of Lymphoma subtypes since it became generic. But due to this, currently bendamustine is not a 'standard of care' drug for this indication in England. Often patients remain under consultant haematology / oncology care as well as receiving active palliative care (possible use of palliative radiotherapy for symptoms, possible use of steroids
• In what clinical setting should the technology be used? (For example,	Secondary care as outlined above

primary or secondary care, specialist clinics.)	
• What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	Bendamustine and rituximab are commonly given across haematology units in the UK and polatuzumab is a straightforward drug to administer. It will be delivered in the chemotherapy day unit with out patient monitoring of patients as is standard practice
12. Do you expect the technology to provide clinically meaningful benefits compared with current care?	Yes I would expect the technology to provide clinically meaningful benefits compared with current care. Antibody-drug conjugates have been applied successfully to high grade B-cell lymphomas. The trial this evaluation is based on resulted in a significance overall survival difference. These 2 factors combined suggest this does have the potential to have a substantial impact on health-related benefits and is a step-change in the management of this condition. It is innovative in it's potential efficacy in a population with a poor outcome and limited effective treatment options.
• Do you expect the technology to increase length of life more than current care?	Yes – prolong PFS and OS
• Do you expect the technology to increase health-related quality of life more than current care?	Yes – by improving lymphoma-related symptoms. Also an out-patient/day unit-delivered therapy
13. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	No – the populations as defined above,
The use of the technology	

14. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use (for example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed.)	It has implications for patients (attending day unit as all 3 agents are given intravenously) whilst presently many of the alternatives may be delivered orally. It has an impact for healthcare professionals: monitoring side effects (peripheral neuropathy or infusional) and potential infective complications (but latter exists for oral therapies too). This will involve training of staff in day unit but staff experienced in delivering immunochemotherapy regimens. The 1st cycle is delivered over 3 days in day unit, subsequent cycles over 2 days/month. Bendamustine/Rituximab has been associated with infectious complications (that may extend beyond completion of therapy) so appropriate prophylaxis should be given. Monitoring patients closely is recommended when they have side effects
15. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	Eligibility: 'Patients who are not fit for transplant' or ''Patients who are not eligible for transplant' as outlined above. Stop treatment if progressive disease or unacceptable side effects (although the incidence of severe (Grade3 3/ 4) side effects was low. Peripheral neuropathy was usually grade 1-2 and resolved after cessation of therapy.
16. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely	Yes – I expect this technology will result in health-related benefits and some may not be included in the quality-adjusted life year (QALY) calculation

to be included in the quality-adjusted life year (QALY) calculation?	
17. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met?	Yes I consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and it will improve the way that current need is met. Patients have higher chance of responding to therapy, have prolonged PFS and OS. A cohort of patients may be bridged to a curative line of therapy (CAR-T or allogeneic stem cell transplantation).
• Is the technology a 'step-change' in the management of the condition?	Yes this is a 'step-change' in the management of the condition
• Does the use of the technology address any particular unmet need of the patient population?	Yes – the unmet need of patients who are older and / or have co-morbidities and who would never be deemed suitable for a stem cell transplant where other options are palliative. Also bridging therapy to potentially curative therapies as outlined above.
18. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	Bendamustine/Rituximab has been associated with infectious complications so appropriate prophylaxis should be given. Peripheral neuropathy was usually grade 1-2 and resolved after cessation of therapy.

Sources of evidence	
19. Do the clinical trials on the technology reflect current UK clinical practice?	Yes – as there is no standard comparator.
• If not, how could the results be extrapolated to the UK setting?	N/A
• What, in your view, are the most important outcomes, and were they measured in the trials?	Yes – outcomes important to patients involve reduction in tumour size (and associated reduction/resolution of associated symptoms) and prolongation of survival (PFS/OS measured in months). These were measured
• If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	See above
• Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	None that I am aware of
20. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	No

21. Are you aware of any new evidence for the comparator treatment(s) since the publication of NICE technology appraisal guidance [TA306, TA559, TA567]	No However the EAMS scheme that opened a number of months ago in the UK means that many patients/specialists/units have access to this novel combination.
22. How do data on real-world experience compare with the trial data?	Real world data compares well with comparator group
Equality	
23a. Are there any potential equality issues that should be taken into account when considering this treatment?	No equality issues
23b. Consider whether these issues are different from issues with current care and why.	N/A
Topic-specific questions	
24. Is polatuzumab vedotin a curative treatment, and if so at what stage can cure be assumed?	A proportion of patients may be cured – especially in those patients with duration of response > 2 years . However the follow up is short and it's difficult to be exact (see data below).

25. The economic model predicts that 21.2% of patients on polatuzumab vedotin+BR have long-term remission and 20.6% are long term survivors (compared with 0% for BR). Are these proportions for polatuzumab vedotin+BR and BR clinically plausible and reflective of the clinical trial?	Important to read the updated outcome from the randomised study available online from JCO this month. J Clin Oncol. 2019 Nov 6: JCO1900172. doi: 10.1200/JCO.19.00172. [Epub ahead of print] Polatuzumab Vedotin in Relapsed or Refractory Diffuse Large B-Cell Lymphoma. Sehn LH[1], Herrera AF[2], Flowers CR[3], Kamdar MK[4], McMillan A[5], Hertzberg M[6], Assouline S[7], Kim TM[8], Kim WS[9], Ozcan M[10], Hirata J[11], Penuel E[11], Paulson JN[11], Cheng J[12], Ku G[11], Matasar MJ[13] In the randomly assigned cohort (n = 80; 40 per arm), pola-BR patients had a significantly higher IRC-assessed CR rate (40.0% v 17.5%; P = .026) and longer IRC-assessed PFS (median, 9.5 v 3.7 months; hazard ratio [HR], 0.36, 95% CI, 0.21 to 0.63; P < .001) and **OS (median, 12.4** v 4.7 months; HR, 0.42; 95% CI, 0.24 to 0.75; P = .002; median follow-up, 22.3 months). In the phase Ib pola-BR arm, EOT IRC-assessed CR rate was 50% (3/6), with **all 3 patients remaining in remission at a median follow-up of 37.6 months** (DOR, > 28.9 to ≥ 38.2 months). In the combined phase Ib/II pola-BG cohort, the EOT IRC-assessed CR rate was 29.6%. At a median follow-up of 27.0 months, median PFS (IRC) and OS were 6.3 and 10.8 months, respectively. Two patients proceeded to consolidative stem-cell transplantation (SCT; 1 autologous and 1 allogeneic). Four patients (15%) had documented responses lasting at least 20 months (range, > 20.7 to ≥ 22.5 months) without additional therapy. At last follow-up, 8 patients remained alive, 17 had died (12 PD; 5 AEs), and 2 discontinued the study (1 physician decision; 1 AE). OS was significantly improved in the pola-BR arm, with risk of death reduced by 58% (HR, 0.42; 95% CI, 0.24 to 0.75; P = .002) and a longer median OS with pola-BR (12.4 months; 95% CI, 9.0 to not evaluable) compared with BR alone (4.7 months; 95% CI, 3.7 to 8.3 months; Fig 2C). **Eleven pola-BR–treated patients and 4 BR-treated patients remained alive in follow-up.** Post hoc subgroup analyses demonstrated consistent survival benefit across all clinical and biological subgroups

	examined (Fig 2D; Appendix Fig A1, online only). Importantly, patients benefited regardless of refractory status and number of prior lines of therapy, although sample sizes were small and statistical significance could not be established. **Seven pola-BR patients (18%) had ongoing DOR of > 20 months (range, > 20.0 to ≥ 22.5 months) and remained in complete remission at last follow-up. One patient underwent consolidative allogeneic SCT; the other 6 received no additional therapy.** Only 2 BR patients (5%) remained in follow-up without progression; both received consolidative therapy (1 allogeneic SCT and the other radiation). Benefit was seen regardless of age, performance status, IPI score, and the presence of bulky disease. 25% of pola-BR–treated patients had received prior ASCT **re proportions for polatuzumab vedotin+BR and BR being clinically plausible and reflective of the clinical trial?** **I agree that 21.2% of patients on polatuzumab vedotin+BR have long-term remission and 20.6% are long term survivors (although some will have had other forms of consolidation) and I do not agree with 0% for BR – but maybe more 5-10%**
26. Would patients be likely to have polatuzumab vedotin treatment beyond 6 cycles in clinical practice?	No - because we don't give > 6 courses of bendamustine-containing chemotherapy (for follicular lymphoma etc).
27. Is the lyophilised formulation of polatuzumab vedotin (to be supplied by the company) expected to have similar	Yes – although advice from a Pharmacist is recommended

efficacy and safety to the liquid formulation that was assessed in the clinical trial?	
28. Are bendamustine + rituximab (BR) and rituximab, gemcitabine and oxaliplatin (R-GemOx) a reasonable reflection of the treatments used in clinical practice to treat people who would be eligible for polatuzumab vedotin+BR?	We can not access BR for DLBCL in the UK. As noted above 'The main issue we see is that bendamustine is not commissioned for the treatment of relapsed high grade lymphoma. The lymphoma treating community has always been somewhat perplexed why there are such limitations on us using this agent in treating a number of Lymphoma subtypes since it became generic. But due to this, currently bendamustine is not a 'standard of care' drug for this indication in England.' Patients who are not fit for transplant are offered low intensity chemotherapy regimens (sometimes with rituximab, however there is no standard of care. The following comparators can be given with or without rituximab (depending on amount received by patient prior) R-GemOx - R-Gem - R-P-MitCEBO - Pixantrone (although this is not used much around the UK now, and tends to be used at later treatment lines) - (R-)DECC - PEP-C - R-COCKLE For populations (2) and (3) above there is the option of CAR-T cells (recently introduced in UK in 2019). Benda+R+pola may provide a bridging therapy to CAR T-cell therapy (presently only patients PS 0-1 are eligible for CAR-T therapy so this will be a small cohort).
29. Are there any other relevant treatments used in this population? if so,	See above

how would the efficacy and safety of these be expected to differ from BR in clinical practice?	Pola-BR patients had rates of grade 3-4 neutropenia of 46.2%, anemia 28.2% and thrombocytopenia 41%, and grade 3-4 infections 23.1%. Peripheral neuropathy associated with polatuzumab vedotin was observed in 43.6% of patients but was grade 1-2 and resolved in most patients.
30. Is it reasonable to assume that BR and R-GemOX have similar efficacy?	Difficult to assume this without experience of the use of BR for this indication.
31. Does the assumption that a maximum number of 3 treatment cycles of 3 weeks of R-GemOx reflect treatment in clinical practice?	No maybe more than 3 treatment cycles of R-Gem-Ox (ie usually 4 cycles but maybe even 6 (or rarely 8 cycles) of Gem-Ox Sometimes 4-6 cycles of others - R-P-MitCEBO - Pixantrone (although this is not used much around the UK now, and tends to be used at later treatment lines) - (R-)DECC - PEP-C - R-COCKLE
Key messages	

32. In up to 5 bullet points, please summarise the key messages of your statement.

- Improvement of tumour-associated symptoms
- Prolongation of progression-related survival
- prolongation of overall survival
- Well tolerated (low incidence of severe or persistent symptoms)
- Revolutionises treatment approach for which there is no accepted standard of care

Thank you for your time.

Please log in to your NICE Docs account to upload your completed statement, declaration of interest form and consent form.

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NICE National Institute for Health and Care Excellence

Patient expert statement

Polatuzumab vedotin with rituximab and bendamustine for treating relapsed or refractory diffuse large B-cell lymphoma [ID1576]

Thank you for agreeing to give us your views on this technology and its possible use in the NHS.

You can provide a unique perspective on conditions and their treatment that is not typically available from other sources.

To help you give your views, please use this questionnaire with our guide for patient submissions.

You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

Information on completing this expert statement

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- Your response should not be longer than 10 pages.

About you	
1.Your name	**Stephen Scowcroft**

2. Are you (please tick all that apply):	☐ a patient with the condition? ☐ a carer of a patient with the condition? ☒ a patient organisation employee or volunteer? ☐ other (please specify):
3. Name of your nominating organisation	Lymphoma Action
4. Did your nominating organisation submit a submission?	☒ yes, they did ☐ no, they didn't ☐ I don't know
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	☒ yes, I agree with it ☐ no, I disagree with it ☐ I agree with some of it, but disagree with some of it ☐ other (they didn't submit one, I don't know if they submitted one etc.)

6. If you wrote the organisation submission and/ or do not have anything to add, tick here. (If you tick this box, the rest of this form will be deleted after submission.)	☒ yes
7. How did you gather the information included in your statement? (please tick all that apply)	☐ I have personal experience of the condition ☐ I have personal experience of the technology being appraised ☐ I have other relevant personal experience. Please specify what other experience: ☐ I am drawing on others' experiences. Please specify how this information was gathered:
Living with the condition	
8. What is it like to live with the condition? What do carers experience when caring for someone with the condition?	

in collaboration with:

ERASMUS UNIVERSITEIT ROTTERDAM
INSTITUTE OF HEALTH POLICY & MANAGEMENT

Maastricht University

ID1576: Polatuzumab vedotin with rituximab and bendamustine for treating relapsed or refractory diffuse large B-cell lymphoma

Produced by

Kleijnen Systematic Reviews Ltd. in collaboration with Erasmus University Rotterdam (EUR) and Maastricht University

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Date completed 01/10/2019

Source of funding: This report was commissioned by the NIHR HTA Programme as project number 12/96/88

Declared competing interests of the authors
None.

Acknowledgements
None.

[redacted]

Rider on responsibility for report
The views expressed in this report are those of the authors and not necessarily those of the NIHR HTA Programme. Any errors are the responsibility of the authors.

This report should be referenced as follows:
Armstrong N, Büyükkaramikli N, Penton H, Fayter D, Wetzelaer P, Corro Ramos I, Chalker A, Worthy G, Ross J, Wolff R, Al M, Kleijnen J. Polatuzumab vedotin with rituximab and bendamustine for treating relapsed or refractory diffuse large B-cell lymphoma: a Single Technology Assessment. York: Kleijnen Systematic Reviews Ltd, 2019.

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Nigel Armstrong acted as project lead, health economist and systematic reviewer on this assessment, critiqued the clinical effectiveness and cost effectiveness methods and evidence and contributed to the writing of the report. Nasuh Büyükkaramikli acted as health economic project lead, critiqued the company's economic evaluation and contributed to the writing of the report. Hannah Penton, Pim Wetzelaer and Isaac Corro Ramos acted as health economists on this assessment, critiqued the company's economic evaluation and contributed to the writing of the report. Debra Fayter, Annette Chalker and Robert Wolff acted as systematic reviewers, critiqued the clinical effectiveness methods and evidence and contributed to the writing of the report. Gill Worthy acted as statistician, critiqued the analyses in the company's submission and contributed to the writing of the report. Janine Ross critiqued the search methods in the submission and contributed to the writing of the report. Maiwenn Al acted as health economist on this assessment, critiqued the company's economic evaluation, contributed to the writing of the report and provided general guidance. Jos Kleijnen critiqued the company's definition of the decision problem and their description of the underlying health problem and current service provision, contributed to the writing of the report and supervised the project.

Abbreviations

ADA	Anti-drug antibodies
AE	Adverse event
AF	Acceleration factor
AIC	Akaike information criterion
ALT	Alanine aminotransferase
ANC	Absolute neutrophil count
ASCO	American Society of Clinical Oncology
ASCT	Autologous stem cell transplant
ASH	American Society of Haematology
AST	Aspartate aminotransferase
AWMSG	All Wales Medicines Strategy Group
bd/b.i.d	Twice daily
BI	Budget impact
BIC	Bayesian information criterion
BNF	British National Formulary
BOR	Best overall response
BR	Bendamustine plus rituximab
BSA	Body surface area
BSC	Best supportive care
BSH	British Society of Haematology
CADTH	Canadian Agency for Drugs and Technologies in Health
CAR-T	Chimeric antigen receptor-T cell
CDF	Cancer Drugs Fund
CDSR	Cochrane Database of Systematic Reviews
CE	Cost effectiveness
CEA	Cost effectiveness analysis
CEAC	Cost effectiveness acceptability curve
CHMP	Committee for Medicinal Products for Human Use
CT	Computed tomography
CI	Confidence interval
CNS	Central nervous system
CR	Complete response
CRD	Centre for Reviews and Dissemination
CrI	Credible interval
CS	Company's submission
CSR	Clinical study report
CHMP	Committee for Medicinal Products for Human Use
CTCAE	Common Terminology Criteria for Adverse Events (National Cancer Institute)
CUA	Cost-utility analysis
DALY	Disability-adjusted life year
DC	Day case
DCR	Disease control rate
Den	Denominator
df	Degrees of freedom
DLBCL	Diffuse large B-cell lymphoma
DOR	Duration of response
DPG	Disease population group
DSU	Decision Support Unit
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
ECOG-PS	Eastern Cooperative Oncology Group performance status
EED	Economic Evaluation Database
EFS	Event-free survival

EHA	European Haematology Association
EMA	European Medicines Agency
eMIT	Electronic Market Information Tool
EORTC	European Organisation for Research and Treatment of Cancer
EORTC QLQ-C30	European Organisation for Research and Treatment of Cancer quality of life questionnaire
EPAR	European public assessment report
EQ-5D	European Quality of Life-5 Dimensions
EQ-5D-3L	European Quality of Life-5 Dimensions, three-level scale
ERG	Evidence Review Group
ESMO	European Society for Medical Oncology
EUR	Erasmus University Rotterdam
FDA	Food and Drug Administration
5-FU	5-Fluorouracil
G-CSF	Granulocyte colony stimulating factor
GP	General Practitioner
HAS	Haute Autorité de Sante
HMRN	Haematological Malignancy Research Network
HMRN	Haematological Malignancy Research Network
HR	Hazard ratio
HRQoL	Health-related quality of life
HTA	Health technology assessment
HTAi	Health Technology Assessment International
IC	Indirect comparison
ICD	International Classification of Diseases
ICER	Incremental cost effectiveness ratio
ICML	International Conference on Malignancy Lymphoma
IDMC	Independent data monitoring committee
INAHTA	International Network of Agencies for Health Technology Assessment
Incr	Incremental
INESSS	Institut National D'excellence en services sociaux
INV	Investigator
IPI	International Prognostic Index
IRC	Independent review committee
IRR	Infusion-related reaction
ISPOR	International Society for Pharmacoeconomics and Outcomes Research
ITT	Intention to treat
IV	Intravenous
KM	Kaplan–Meier
KSR	Kleijnen Systematic Reviews
LDH	Lactate dehydrogenase test
LYGs	Life years gained
LYO	Lyophilised formulation
LYS	Life year saved
MAH	Marketing authorisation holder
MedDRA	Medical Dictionary for Regulatory Activities
MeSH	Medical subject headings
MHRA	Medicines and Healthcare Products Regulatory Agency
mg	Milligram
MR	Minimal response
MRI	Magnetic resonance imaging
MRU	Medical resource utilisation
MTC	Mixed treatment comparison

MUGA	Multiple-gated acquisition scan
NA	Not applicable
NCCN	National Comprehensive Cancer Network
NE	Not estimable
NEL	Non-elective inpatient
NES	Non-elective short stay
NHL	Non-Hodgkin lymphoma
NHS	National Health Services
NICE	National Institute for Health and Care Excellence
NIHR	National Institute for Health Research
NR	Not reported
Num	Numerator
od	Once daily
OR	Odds ratio
ORR	Overall response rate
OS	Overall survival
PBAC	Pharmaceutical Benefits Advisory Committee
PCT	Primary Care Trust
PD	Progressive disease
PET-CT	Positron emission tomography – computed tomography
PFS	Progression-free survival
PK	Pharmacokinetic
PN	Peripheral neuropathy
PMBCL	Primary mediastinal B-cell lymphoma
Pola	Polatuzumab vedotin
PR	Partial response
PRESS	Peer Review of Electronic Search Strategies
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PRO	Patient-reported outcome
PS	Performance status
PSA	Probabilistic sensitivity analyses
PSS	Personal Social Services
QALY(s)	Quality-adjusted life year(s)
PSSRU	Personal Social Services Research Unit
QoL	Quality of life
R	Rituximab
RCT	Randomised Controlled Trial
RECIST	Response Evaluation Criteria In Solid Tumours
RePEc	Research Papers in Economics
RGCVP	Rituximab, gemcitabine, cyclophosphamide, vincristine and prednisolone
R-GDP	Rituximab, gemcitabine, cisplatin and dexamethasone
R-GemOx	Rituximab plus gemcitabine plus oxaplatin
RPSFTM	Rank preserving structure failure time model
RR	Relative risk; risk ratio
R/R	Relapsed or refractory
SAE	Serious adverse events
SC	Subcutaneous
ScHARR	School of Health and Related Research
sCR	Stringent complete response
ScHARRHUD	School of Health and Related Research Health Utilities Database
SCT	Stem cell transplant
SD	Standard deviation
SF-36	Short form 36
SHTAC	Southampton Health Technology Assessments Centre

SIGN	Scottish Intercollegiate Guidelines Network
SLR	Systematic literature review
SMC	Scottish Medicines Consortium
SMDM	Society for Medical Decision Making
SPC	Summary of product characteristics
STA	Single technology appraisal
UMC	University Medical Centre
TA	Technology appraisal
TCS	Treatment continuation scheme
TEAEs	Treatment-emergent adverse events
TESAEs	Treatment-emergent serious adverse events
TINAS	Therapy-Induced Neuropathy Assessment Scale
TLS	Tumour lysis syndrome
TSD	Technical Support Document
TTF	Time to failure
TTOT	Time to off treatment
TTP	Time to progression
UK	United Kingdom
ULM	Upper limit of normal
US	United States (of America)
USA	United States of America
VEGF	Vascular endothelial growth factor
VGPR	Very good partial response
WHO	World Health Organisation
WTP	Willingness-to-pay

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1. EXECUTIVE SUMMARY

1.1 Critique of the decision problem in the company's submission

The population defined in the National Institute for Health and Care Excellence (NICE) scope is 'adults with relapsed or refractory diffuse large B-cell lymphoma (R/R DLBCL) for whom hematopoietic stem cell transplant is not suitable'. The company considered the following patients to be eligible for polatuzumab vedotin with rituximab and bendamustine (Pola+BR):

- R/R patients who are clear non-candidates for transplant (unfit for intensive therapy based on physician assessment), either as second-line treatment or as a third-line treatment and beyond for patients who have relapsed following or are refractory to their last-line of therapy
- R/R patients who would be candidates for transplant but fail to respond to salvage therapy (and are therefore transplant ineligible)
- R/R patients who receive salvage therapy and autologous stem cell transplant (ASCT) but subsequently relapse

Patient numbers in the main trial in the company submission (CS) (GO29365) were too small to provide meaningful subgroup results by type of patient or line of therapy.

Although the NICE scope specifies that the population is those for whom hematopoietic stem cell transplant is not suitable, 16 of the patients in the included trial had received prior autologous stem cell transplant (ASCT) and as seen above the company did consider this group to be relevant to the decision problem. The company did provide some results excluding those patients in response to clarification. Since it is not clear if patients who have undergone ASCT (and become ineligible because of that) are part of the population eligible for Pola+BR in clinical practice, it is also unclear which results are most appropriate. However, removal of those 16 patients only seems to improve outcomes.

The company is to supply polatuzumab vedotin in its lyophilised formulation. GO29365 used the liquid formulation although two ongoing arms are to evaluate the lyophilised formulation. In the absence of full evidence, the committee will need to decide if it is satisfied that the lyophilised formulation of polatuzumab will have similar efficacy and safety to the liquid formulation.

Whilst the comparator in the main GO29365 trial is consistent with the scope, it seems likely that it is not the only suitable one, rituximab plus gemcitabine plus oxaplatin (R-GemOx) also being likely to be increasingly used in clinical practice. In the absence of direct evidence, it is not clear if R-GemOx can be assumed to have equal efficacy and safety outcomes to BR.

1.2 Summary of the key issues in the clinical effectiveness evidence

The company conducted a systematic review to identify evidence relevant to this appraisal. They considered 16 studies for inclusion (four RCTs, 12 observational studies). The Evidence Review Group (ERG) examined the four RCTs identified and agreed that a network could not be constructed to inform an indirect comparison between Pola+BR and other relevant treatments. Equally, in examination of the observational studies a match-adjusted indirect comparison did not appear to be appropriate given the differences identified by the company in populations and line of treatment across the studies.

Therefore, the only study presented in relation to clinical effectiveness was a Phase Ib/II, multicentre, open-label trial (GO29365) of polatuzumab in combination with BR in patients with R/R DLBCL, and polatuzumab in combination with bendamustine and obinutuzumab (BG) in patients with R/R follicular

lymphoma (the latter not relevant to this appraisal). Issues relating to the population, intervention and comparator in the trial have been discussed in the previous section.

GO29365 was randomised and was well conducted. It was, however, open label. Both patients and healthcare professionals involved in their care were aware of treatment allocation. The ERG considers the independent review committee outcome results to be more appropriate and has highlighted these in the report. Although the trial was multinational, it was relatively small (40 patients were randomised to Pola+BR) so the evidence on which results are based is limited. Three patients were included from the UK. The company was asked to justify the applicability of the trial to UK clinical practice. They stated that the baseline characteristics of the population of G029365 were similar to a UK study of pixantrone in R/R DLBCL patients.[1] The company also obtained advice from clinical experts who '*confirmed that the baseline characteristics of patients enrolled in GO29365 are reflective of the population seen in UK clinical practice and corroborates the comparison to the retrospective analysis*'[2] The ERG considered this reasonable but noted that non-white participants were underrepresented in the trial and that most patients had Eastern Cooperative Oncology Group (ECOG status) of 0 or 1. The ERG also noted that there were some baseline imbalances between the treatment groups including more patients in the Pola+BR having a lower International Prognostic Index (IPI) score and more patients in the BR group having bulky disease. Adjustment to overall survival (OS) was performed for both of these factors, but not to progression-free survival (PFS) for bulky disease, which could favour Pola+BR.

Pola+BR showed superior results to BR in outcomes relevant to this appraisal. At 24 months there was an increase in median PFS of approximately [redacted] and an increase in median survival of about [redacted]. Given the limited life expectancy of patients with relapsed or refractory DLBCL, the intervention does meet end-of-life criteria specified by NICE. Adverse events were similar although peripheral neuropathy was more frequently reported with Pola+BR. As yet no information is available on long-term 'cure' rates and longer-term rarer adverse events. The trial is ongoing.

1.3 Summary of the key issues in the cost effectiveness evidence

To assess the cost effectiveness of polatuzumab vedotin (Pola), in combination with bendamustine and rituximab (BR), compared to BR alone, the company developed a three-state partitioned survival model that includes the following health states: progression-free, progressed disease and death. Transitions between health states were informed by extrapolated survival curves for PFS and OS from the GO29365 trial. Patients started in the progression-free state, where they remained until progression or death. Upon progression, patients either remained in the progressed disease state, or they died. After 2 years in the progression-free state, patients were considered to have characteristics similar to the general population. Therefore, age/sex adjusted general population utility values and zero healthcare resource use cost values were assigned to those patients who did not progress in their first two years. Cost and health outcomes were discounted at 3.5%.

In the progression-free state, patients received treatment according to time-to-off-treatment (TTOT) data from GO29365. However, also a maximum number of six treatment cycles of three weeks was applied for Pola+BR, as well as for BR. An additional scenario was performed to assess cost effectiveness against a different comparator, R-GemOx. For R-GemOx, effectiveness was assumed equivalent to BR, and a maximum number of three treatment cycles of three weeks was assumed. It is unclear to what extent these assumptions, particularly that of equivalent effectiveness, reflect the actual comparative effectiveness in clinical practice. Therefore, the ERG is cautious about the use of the R-GemOx comparator in this model.

The company base-case assumed cure-mixture models for both OS and PFS extrapolation. Instead of using standard cure-mixture modelling codes available in statistical programs, the company developed its own code, which was not transparent and clear enough for the ERG to assess the correctness of the implementation of the methods in the provided code. The "cure" assumption of the company was based on: literature from the natural history of newly diagnosed DLBCL patients, which suggested no significant difference between the mortality of those patients event free at two years and the age- and gender-matched general population; clinical expert opinion; the company's observation of low risk of relapse or death in the Kaplan–Meier (KM) plots for Pola+BR towards the end of follow-up and the precedent for cure-mixture modelling accepted in previous NICE appraisals in R/R DLBCL patients.[3-5] However, the ERG felt that there was a lack of robust long-term evidence to be confident in a cure assumption, especially given the small number of patients remaining alive and event free at the end of a relatively short follow-up period. The ERG also note that the previous technology appraisals were for Chimeric antigen receptor-T cell (CAR-T) therapies which represent a distinct form of therapy and alternative literature suggests that excess mortality in DLBCL remains for at least five years. [6] Additionally, the company's base-case assumptions of cure-mixture models led to OS and PFS hazard ratios, which were not in line with the empirical hazard plots for OS and PFS from the GO29365 trial and which conferred an overly optimistic treatment benefit, even decades after the treatment is received. Therefore, the ERG explored alternative independent standard parametric survival extrapolation models in their base-case and scenario analyses, and also a logical constraint was enforced, which ensured that the OS extrapolation from the trial provided a lower survival estimate from the age/sex adjusted general population at any given point time.

The ERG considered the company's assumption of no excess mortality in DLBCL long-term survivors compared to the general population to be overly optimistic. This assumption was based on a US study by Maurer et al (2014) which found no statistically significant difference between the mortality of newly diagnosed DLBCL who survived event free to two years and the age- and gender-matched general population. [4] However a more recent study based on a substantially larger sample of DLBCL patients suggests that excess mortality remains up to five years and that overall, DLBCL survivors are at excess risk of mortality due to non-cancer causes as well as the risk of late relapse. [6] Therefore this excess mortality due to non-cancer causes was incorporated into the ERG base-case.

Another important issue was the way the non-cancer background mortality was included in the model. In contrast to the cohort-based approach followed for modelling the cancer-related progression and death events, the company followed an individual patient-level approach while modelling the non-cancer, background mortality risks. The economic model calculates the weighted mortality risk from the individual age- and sex-matched specific mortality risks from a cohort of 160 patients (50%-50% male-female, characterizing the age distribution of the GO29365 trial). This created an inconsistency, as the relatively younger patients' lifetable based survival estimates are taken into the weighted average, hence leading to instances where a significant proportion is still alive after 40 or 50 years, which is not realistic from a cohort modelling perspective, as the average age of the cohort was 69. Therefore, the ERG switched to cohort based modelling for non-cancer background mortality risks.

Additional important sources of uncertainty in the model are the assumptions made regarding the health-related quality of life (HRQoL) and costs of long-term survivors. In the company submission, the argument of a lack of statistically significant excess mortality at two years, was extended to argue that the HRQoL of DLBCL patients would be equivalent to that of the age- and gender-matched general population after two years in the PFS state. When the ERG requested evidence specific to HRQoL, the company provided two literature reviews which provided some support for equivalence in HRQoL in long-term survivors.[7, 8] However one of these explicitly specified that HRQoL between these two groups

was more comparable after three years. [8] Given the parallel uncertainty regarding the assumption of equivalent healthcare costs after two years, which have been previously noted in TA559, in the ERG base-case the assumption of two years was extended to three years for both HRQoL and costs to provide a more conservative estimate.

Adverse events (AEs) were incorporated for Pola+BR and BR based on incidences from GO29365, and for R-GemOx based on findings from the study by Mournier et al., 2013. [9] The ERG identified several inconsistencies between the AE incidences used in the model and the incidences presented in clinical effectiveness section of this ERG report for the GO29365 trial, in terms of the number of serious AEs reported in each treatment arm. Therefore, the ERG updated the model incidences to reflect the incidences for the most frequently reported Grade 3-5 adverse events (>5%).

In response to a lack of HRQoL data collection in the GO29365 trial, the company conducted a thorough literature search for relevant health state utility values. The base-case utility values, estimated from the safety management population of the ZUMA-1 trial using the EQ-5D-5L were based on a small sample (34 patients provided 87 observations) of mixed histology lymphoma patients. The progressed disease value in particular was based on a very small sample as it was estimated from only five observations. The patient characteristics of the members of the ZUMA-1 trial who provided HRQoL data were not available and therefore it is unclear how similar this group were to the GO29365 population or the R/R DLBCL patients who would be expected to receive polatuzumab in clinical practice. However, despite these limitations, the ERG agrees that none of the alternative utility sources identified provided a better alternative, when considering the alignment with the NICE reference case and therefore this source of utility values was retained in the ERG base-case. Disutilities for those adverse events (AEs) included in the model were appropriately sourced from previous appraisals in R/R DLBCL.

The economic analysis was performed from the National Health Service (NHS) and Personal and Social Services (PSS) perspective and included state-specific costs for drug acquisition and administration, treatment-related AEs, routine supportive care (professional and social services, health care professionals and hospital resource use, treatment follow-up; for a maximum of two years), and subsequent treatment costs. Healthcare unit costs were obtained from the National Audit Office 2008[10], Personal Social Services Research Unit (PSSRU) 2018[11], and NHS reference costs.[12] The frequencies of healthcare resource use were primarily sourced from TA306.[13] Drug costs were taken from the British National Formulary (BNF) and electronic Market Information Tool (eMIT) databases. The dose information was derived from the GO29365 trial, whereas for the R-GemOx, it was obtained from Mounier et al.[9] Administration and adverse event costs were mostly obtained from NHS reference costs and percentage of the treatments used in the subsequent treatments were from the GO29365 trial and clinical expert opinion.

The ERG was also concerned with several assumptions made in the company base-case regarding costs and resource use. Polatuzumab is currently only available in 140 mg vials. However, in the company base-case, the company also included 30 mg vials, stating that they plan to provide these from [redacted]. However, given that this statement is subject to uncertainty and no formal agreement is in place, the ERG feel that the base-case should conservatively assume that the current situation will remain. The ERG also felt that the costing of a maximum of six cycles of Pola+BR and BR, contrary to the included TTOT data from the trial was incorrect. Since the treatment effectiveness from the trial is based on the application of the treatment longer than six cycles, not including the costs of these treatments beyond cycle six would create a bias. In the ERG base-case these treatments were costed according to the TTOT data provided. The company also excluded the costs of stem-cell transplant (SCT) and CAR-T treatment, despite these having been received by trial participants. The ERG feels

that this was inappropriate and therefore attempted to include these costs in the ERG base-case. CAR-Ts are currently available of the NHS only under confidential PAS and therefore the cost of SCT was utilised for both treatments.

Alongside their clarification response the company submitted an updated model using data from the latest data cut-off point of the clinical trial, corrected utility values for the proximity to death scenario, corrected administration costs for R-GemOx and corrected AE incidences for R-GemOx. This resulted in an updated company base-case incremental cost effectiveness ratio (ICER) of £25,307.

1.4 Summary of the ERG's preferred assumptions and resulting ICER

The changes made by the ERG to the company base-case (after clarification) are described in Section 7.1.2 and summarised below:

1. General population mortality based on "average patient" (i.e. cohort approach instead of individual patient level approach).
2. OS from the general population with excess mortality must always be higher than or equal to the OS extrapolations from the GO29365 survival data.
3. PFS extrapolation to independent review committee (IRC) data was selected from a standard lognormal distribution independently fitted to both arms. OS extrapolation was selected from a standard generalised gamma distribution independently fitted to both arms.
4. A standardised mortality ratio of 1.41 was applied to model excess mortality compared to age- and gender-matched general population mortality.
5. The time point at which equivalence in HRQoL and costs with the general population was changed from two to three years.
6. Acquisition costs of polatuzumab based on the current availability of vial sizes (140 mg vials only, with no vial sharing).
7. Treatment costs for the Pola+BR and BR regimens were applied for as long as patients in the trial received treatment (i.e. based on TTOT data) instead of up to a maximum of six treatment cycles.
8. Costs for post-progression treatment with SCT and CAR-T, were based on the incidence that follows from the trial data.
9. Adverse event incidences from the most frequently reported Grade 3-5 adverse events (Table 4.16 in the ERG report) were utilised in the model.

The discounted cost effectiveness results of the ERG preferred base-case are presented in Table 1.3. The implementation of the ERG preferred assumptions resulted in Pola+BR generating [redacted] more quality adjusted life years (QALYs) than BR at higher costs ([redacted]). The resulting ICER was £67,499. Therefore, Pola+BR was not cost effective at a threshold ICER of £50,000 in the ERG base-case. The assumption with the largest impact on the incremental ICER was changing the OS and PFS extrapolations from cure-mixture models to standard independently fitted parametric models (using IRC PFS data). This resulted in an ICER increased by £14,664. Calculating polatuzumab treatment costs based on the currently available vial size (140 mg) increased the ICER by £12,851. Following a cohort approach to model background mortality, instead of a patient-level approach, increased the ICER by £10,480. All the other changes made by the ERG resulted in in changing the ICER with less than £3,000 (in absolute value). The base-case ICER in the company submission was £26,877. The ICER based on the ERG preferred assumptions was £67,499.

Table 1.3: ICER resulting from ERG's preferred assumptions (discounted)

Technologies	Total costs (£)	Total LYGs	Total QALYs	Incr. costs (£)	Incr. LYGs	Incr. QALYs	ICER versus baseline (£/QALY)
Pola+BR	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£67,499
BR	£19,904	1.00	0.68				

ERG = Evidence Review Group; ICER = incremental cost effectiveness ratio; Incr. = incremental; LYGs = life years gained; QALY = quality-adjusted life year

1.5 Summary of exploratory and sensitivity analyses undertaken by the ERG

The ERG conducted a PSA using the ERG preferred base-case assumptions mentioned in the previous section. Furthermore, the ERG corrected the following errors in the economic model:

1. Errors in the implementation of alternative survival curves in the PSA
2. Errors in the reporting of the probabilistic ICER in the model results sheets
3. Adverse event incidences varied using beta distributions in the PSA

These errors had an impact on the probabilistic results only but did not change the deterministic results. The probabilistic ICER was £68,619, which was in line with the deterministic ICER. The vast majority of the 1,000 simulations ([redacted]) fell in the north-east quadrant of the CE (cost effectiveness)-plane, the remaining simulations were in the north-western quadrant of the CE-plane. The cost effectiveness acceptability curve (CEAC) indicated that at thresholds of £20,000 and £30,000, the probability that Pola+BR is cost effective was [redacted]. At a willingness-to-pay (WTP) of £50,000 this probability was [redacted].

The ERG conducted additional scenario analyses to explore several sources of uncertainty that seem to be relevant for the model results. From these results, the ERG concluded that the ICER was most sensitive to changes in the selection of parametric survival curves for extrapolating of PFS and OS, the duration of the treatment effect (maintained or declined) and the assumptions about polatuzumab vial size and wastage. Scenarios considering alternative assumptions on the time where costs and HRQoL equal those of the general population, the choice of different standardized mortality ratios to model excess mortality compared to general population, and different utility sources were also explored by the ERG. However, the impact of these assumptions on the cost effectiveness results was minor. The cost effectiveness results of the ERG exploratory analyses are summarised in Table 1.4.

Table 1.4: Exploratory analyses undertaken by the ERG

Scenario	Section in main ERG report	Pola + BR		BR		ICER £/QALY
		QALYs	Costs (£)	QALYs	Costs (£)	
Parametric distribution to model PFS						
Cure mixture generalised gamma (CS)	7.2.2.1	[redacted]	[redacted]	0.68	£19,291	£53,088
Independent log-logistic model		[redacted]	[redacted]	0.68	£19,344	£65,920
Independent log-normal model (ERG)		[redacted]	[redacted]	0.68	£19,904	£67,499

Scenario	Section in main ERG report	Pola + BR		BR		ICER £/QALY
		QALYs	Costs (£)	QALYs	Costs (£)	
Parametric distribution to model PFS						
Cure mixture generalised gamma (CS)	7.2.2.2	[redacted]	[redacted]	0.66	£19,462	£63,867
Independent log-normal model		[redacted]	[redacted]	0.65	£19,185	£82,399
Independent generalised gamma model (ERG)		[redacted]	[redacted]	0.68	£19,904	£67,499
Treatment effect duration assumptions						
Treatment effect maintained (CS and ERG BC)	7.2.2.3	[redacted]	[redacted]	0.68	£19,904	£67,499
Declining OS treatment effect duration		[redacted]	[redacted]	0.68	£19,904	£78,312
Declining PFS treatment effect duration		[redacted]	[redacted]	0.68	£19,904	£69,711
Declining OS and PFS treatment effect duration		[redacted]	[redacted]	0.68	£19,904	£81,245
Long-term survivor assumptions (time where costs and HRQoL equal the general population)						
2 years (Company BC)	7.2.2.4	[redacted]	[redacted]	0.68	£19,625	£66,151
3 years (ERG BC)		[redacted]	[redacted]	0.68	£19,904	£67,499
5 years (Howlader)		[redacted]	[redacted]	0.67	£20,115	£69,068
10 years		[redacted]	[redacted]	0.67	£20,231	£70,523
Changing excess mortality compared to general population						
SMR = 1 (Company BC)	7.2.2.5	[redacted]	[redacted]	0.68	£19,906	£66,662
SMR = 1.09 (Company SA)		[redacted]	[redacted]	0.68	£19,906	£66,845
SMR = 1.18		[redacted]	[redacted]	0.68	£19,905	£67,031
SMR = 1.41 (ERG BC)		[redacted]	[redacted]	0.68	£19,904	£67,499
Source of utility values						
TA559 (PFS=0.72 PD=0.65) (ERG BC)	7.2.2.6	[redacted]	[redacted]	0.68	£19,904	£67,499

Scenario	Section in main ERG report	Pola + BR		BR		ICER £/QALY
		QALYs	Costs (£)	QALYs	Costs (£)	
TA567 (PFS=0.83 PD=0.71)		[redacted]	[redacted]	0.74	£19,904	£63,353
TA306 (PFS=0.81 PD=0.60)		[redacted]	[redacted]	0.69	£19,904	£67,596
TA176 FAD (PFS=0.76 PD=0.68)		[redacted]	[redacted]	0.71	£19,904	£65,085
Costs and resource use						
140mg vial only and no vial sharing (ERG BC)	7.2.2.7	[redacted]	[redacted]	0.68	£19,904	£67,499
140 mg and 30 mg vial sizes for polatuzumab vedotin available (CS BC)		[redacted]	[redacted]	0.68	£19,904	£53,910
No wastage / 100% vial sharing for polatuzumab vedotin		[redacted]	[redacted]	0.68	£19,904	£51,574

ERG = Evidence Review Group; ICER = incremental cost effectiveness ratio, iDFS = invasive disease-free survival; Incr. = incremental, PDRS = post-distant recurrence survival; QALY = quality-adjusted life years; TP = transition probability

2. BACKGROUND

2.1 Introduction

In this report, the ERG provides a review of the evidence submitted by Roche in support of polatuzumab vedotin, trade name Polivy™, for patients with relapsed or refractory diffuse large B-cell lymphoma for whom hematopoietic stem cell transplant is not suitable. In this section, the ERG summarises and critiques the company's description of the underlying health problem and the company's overview of the current provision of service. The information for this critique is taken from Document B of the Company Submission (CS). [14]

2.2 Critique of company's description of underlying health problem

The health problem at the focus of this appraisal is a specific subtype of non-Hodgkin lymphoma (NHL), diffuse large B-cell lymphoma (DLBCL). The company notes DLBCL comprises 30-58% of NHL cases. [14] According to the CS, [14] 5,510 new cases of DLBCL are identified in the United Kingdom (UK) each year. [15] Five hundred and ninety-one patients are reported to be treated for relapsed or refractory (R/R) per year, but are unsuitable for a stem cell transplant. [14] In the UK the median age at diagnosis is 70 years old. [16]

The CS [14] describes R/R DLBCL as having a poor prognosis with an estimated median survival of 10 months. The company emphasises age as being a relevant prognostic indicator, with patients over 65 years old having a poorer prognosis than younger patients. [14] Outcomes worsen further for patients who are refractory at the first-line therapy stage, with a median overall survival of 6.3 months and 22% of patients alive at two years. [14, 17]

According to the CS, patients with DLBCL will typically note symptoms including a rapidly enlarging symptomatic mass, typically a nodal enlargement, in the neck, abdomen, or mediastinum. [14] Symptoms reported for 30% of patients include the systemic "B" symptoms such as fever, weight loss, and night sweats, while 50% of patients experience elevated serum lactate dehydrogenase.

The company highlights the limited availability of data regarding the impact of quality of life (QoL) on DLBCL patients. [14] However, the CS notes the relationship between patients with high grade NHL who experience a lower QoL. This is attributed to the uncertainty of the prognosis of the disease, treatment side effects, and relapse-related fears. [14, 18, 19] The QoL can be further impacted in patients who are R/R at first-line treatment. The company emphasises that diminishing QoL and prognosis among R/R DLBCL patients can increase the demand on further treatments and hospital or hospice services.[14, 20]

ERG comment: The ERG checked the references cited by the company and considers the company to have provided an appropriate description of the underlying health problem of this appraisal.

2.3 Critique of company's overview of current service provision

The company notes numerous treatment guidelines are available for DLBCL, including the NICE clinical guideline (NG52) [21], the British Society for Haematology (BSH) [22], ESMO [23], and the National Comprehensive Cancer Network (NCCN) [24]. However, there are currently no universal guidelines in place for R/R DLBCL. [14] Due to this, current clinical practice will likely vary according to location of the treatment centre, the expertise of the health provider, and preference of the clinician and the patient.[14]

The gold standard for the management of DLBCL is rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) regimen. However, in the event the R-CHOP regimen fails, a

reported 20% of patients experience primary refractory disease, while 30% of patients relapse after complete remission. [14, 25] The next step will be to determine if the patient is fit for salvage therapy or is a suitable candidate for an autologous stem cell transplant (ASCT). Factors including age and fitness will determine suitability for ASCT. However, in UK clinical practice, there is no guidance to assist in assessing patients regarding suitability for intensive therapy.

Patients who are deemed suitable, or are borderline candidates, for ASCT will receive rituximab-based salvage chemotherapy and eventually a high-dose regimen. Tolerance of and response to the treatment is used to determine if ASCT is suitable for borderline candidates.

For patients who are suitable for salvage chemotherapy NICE recommends multi-agent immunochemotherapy with rituximab with gemcitabine, dexamethasone and cisplatin (R-GDP). [21] The company emphasises the evidence regarding superiority over different types of salvage therapy is lacking. Patients in the UK typically receive platinum-based treatment regimens, R-GDP, R-DHAP, R-ICE and R-ESHAP, with R-Gem-Ox being an option for older patients. If a patient fails salvage chemotherapy, additional treatment options are limited.

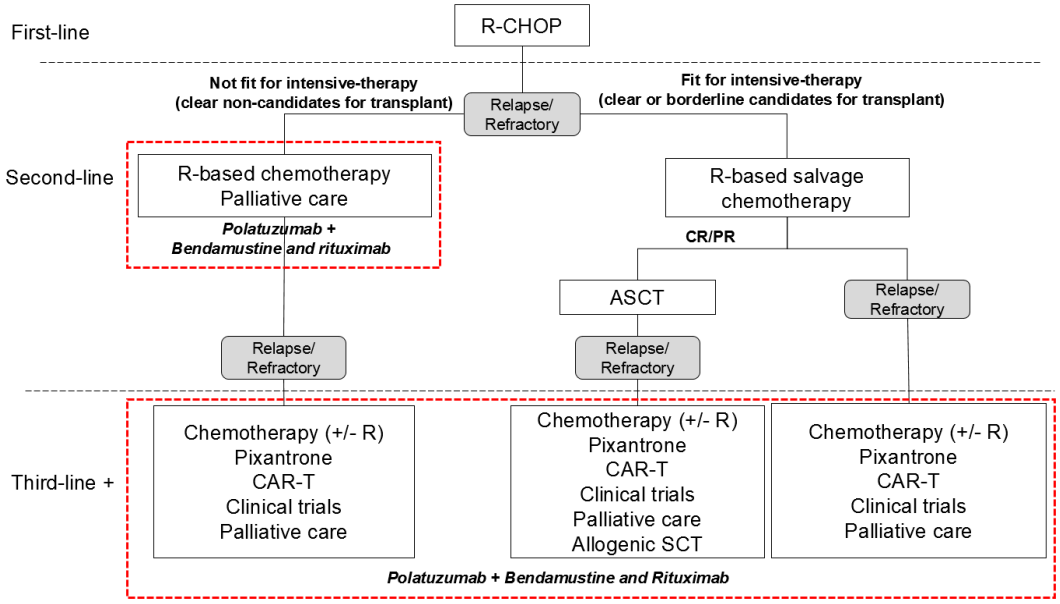
For patients who are ineligible for ASCT after intensive therapy, palliative care is the typical treatment approach. The company states that there is variability in the regimen and lists the rituximab and rituximab-free regimens that may be used. Pixantrone monotherapy is recommended by NICE as a third- or fourth-line option for adults with R/R DLBCL but the company state that, based on clinical expert opinion, it is not widely used. CAR-T cell therapies may be offered to those who have had two or more systemic therapies. However, patients may not be suitable for these treatments. Two CAR-T therapies have recently been approved by NICE for use in the Cancer Drugs Fund (CDF).[3, 5]

The company concludes that there are no universally established therapies for R/R DLBCL patients who are ineligible for ASCT. The company also highlights the need for treatment of patients who relapse after ASCT.

The proposed position in the treatment pathway is shown in Figure 2.1. The company stated that the following would be considered eligible for Pola+BR:

- R/R patients who are clear non-candidates for transplant (unfit for intensive therapy based on physician assessment), either as second-line treatment or as a third-line treatment and beyond for patients who have relapsed following or are refractory to their last-line of therapy
- R/R patients who would be candidates for transplant but fail to respond to salvage therapy (and are therefore transplant ineligible)
- R/R patients who receive salvage therapy and ASCT but subsequently relapse

Figure 2.1: Proposed positioning of Pola+BR in the DLBCL treatment pathway



Source: Figure 2 of the CS
ASCT = autologous stem cell transplant; CR = complete response; PR = partial response; R = rituximab

ERG comment

- The ERG considered that the company highlighted the need for new treatment options in this difficult to treat group of patients.
- Although the company performed subgroup analysis for the different patient groups in the pathway at the request of the ERG, numbers of patients were too small to be reliable.
- The company reiterated at clarification that patients who had received prior transplant (but have since progressed) are within the expected marketing authorisation if they are not eligible for another transplant at this point. However they stated that '*It was not possible to perform a subgroup analysis of patients who received pola+BR beyond third-line as these patients could not be clearly defined.*'[2] The committee will need to consider if those patients who have previously received an ASCT will form part of the population eligible for Pola+BR in clinical practice.

3. CRITIQUE OF COMPANY'S DEFINITION OF DECISION PROBLEM

The company's decision problem is shown in Table 3.1.

Table 3.1: The decision problem

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	ERG comment
Population	Adults with relapsed or refractory diffuse large B-cell lymphoma for whom hematopoietic stem cell transplant is not suitable.	As per final scope issued by NICE	N/A	The ERG consider that it remains unclear if patients who have undergone ASCT (and become ineligible because of that) are part of the population eligible for Pola+BR in clinical practice.
Intervention	Polatuzumab vedotin (with rituximab and bendamustine)	As per final scope issued by NICE	N/A	In the absence of complete evidence, the ERG concludes that there is some doubt as to whether the lyophilised formulation of pola will offer similar efficacy and safety to the liquid formulation when used in clinical practice.
Comparator(s)	Rituximab in combination with one or more chemotherapy agents such as: R-GemOx (rituximab, gemcitabine, oxaliplatin), R-Gem (rituximab gemcitabine), R-P-MitCEBO (rituximab, prednisolone, mitoxantrone, cyclophosphamide, etoposide bleomycin, vincristine), (R-)DECC (rituximab, dexamethasone, etoposide, chlorambucil, lomustine),	Rituximab in combination with one or more chemotherapy agents such as: BR (bendamustine, rituximab). R-GemOx (rituximab, gemcitabine, oxaliplatin).	There is no clear standard of care regimen for the population. BR was the comparator in the randomised phase II study GO29365. It was not feasible to conduct a robust treatment comparison with other comparator regimens in the scope because of the limited evidence available (section B.2.9). Clinical opinion and the limited data available suggest that there is no significant difference in outcomes between	In the absence of direct evidence, it is not clear that R-GemOx can be assumed to have equal efficacy and safety to BR. Furthermore, it is also not clear that the two comparators in the CS are a reasonable reflection of the comparators currently used in practice.

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	ERG comment
	BR (bendamustine, rituximab).		the comparator regimens. A scenario with an assumption of equal efficacy of BR and R-GemOx was implemented in the economic model (section B.3.2.3).	
Outcomes	The outcome measures to be considered include: overall survival progression-free survival response rates adverse effects of treatment health-related quality of life	As per final scope issued by NICE	N/A	Quality of life was not measured in the key clinical trial, GO29365.
Source: Table 1, CS[14] ASCT = autologous stem cell transplant; Pola+BR = polatuzumab plus bendamustine and rituximab				

3.1 Population

ERG comment: The population appeared to be consistent with that in the NICE scope which is adults with relapsed or refractory diffuse large B-cell lymphoma for whom hematopoietic stem cell transplant (SCT) is not suitable.[26] However, the company submission (CS) stated, as indicated in Figure 2 of the CS, that the position of polatuzumab vedotin with bendamustine, rituximab (Pola+BR) includes those who have undergone autologous stem cell transplant (ASCT).[14] In contrast, Appendix D of the CS stated that studies were excluded from the systematic review of relevant clinical evidence if they *"…enrolled transplant eligible patients or transplant or chemotherapy relapsed patients"* (p.17).[27] Therefore, the company were requested in the clarification letter to:

- confirm that such patients are not within the NICE scope or the decision problem.
- conduct an analysis of the GO29365 trial, which excludes the 16 patients who had received an ASCT.

The company confirmed that transplant-eligible patients were not within the NICE scope and the decision problem. In GO29365, the main trial in the submission, the company clarified that '*patients who were eligible for ASCT or had completed ASCT within 100 days prior to Cycle 1 Day 1 were excluded from the trial.*'[2] However, they stated that patients who had received prior transplant (but have since progressed) are within the expected marketing authorisation if they are not eligible for another transplant at this point. The ERG therefore consider that it remains unclear if such patients are part of the population eligible for Pola+BR in clinical practice.

The company provided results of the GO29365 trial excluding the 16 patients who had received an ASCT. These results are provided in Section 4.2.5. Unfortunately, despite request at the clarification stage, the economic analysis was not updated with survival analyses excluding these patients.[2]

GO29365 enrolled 86 patients at 38 study sites in 11 countries including three patients from the UK. The company was asked to justify the applicability of the trial to UK clinical practice. They stated that the baseline characteristics of the population of G029365 were similar to a UK study of pixantrone in R/R DLBCL patients.[1] The company also obtained advice from clinical experts who '*confirmed that the baseline characteristics of patients enrolled in GO29365 are reflective of the population seen in UK clinical practice and corroborates the comparison to the retrospective analysis*'[2] The ERG considered this reasonable.

3.2 Intervention

As described in Table 2 of the CS, the anticipated marketing indication for Pola+BR is for the treatment of adult patients with relapsed/refractory diffuse large B-cell lymphoma (DLBCL) who are not candidates for haematopoietic stem cell transplant.[14] The dosing is as follows:

Polatuzumab vedotin

- 1.8 mg/kg intravenous infusion (IV) on day 1
- The initial dose should be administered as a 90-minute infusion
- If well tolerated, subsequent doses may be administered as a 30-minute infusion

Bendamustine

- 90 mg/m^2 IV on days 1 and 2

Rituximab

- 375 mg/m^2 IV on day 1

ERG comment: The intervention appeared to be as in the final scope. However, The CS states that '*Data from the Phase Ib and the randomised Phase II portion of GO29365 was generated with a liquid formulation of pola; however, a lyophilised formulation of pola suitable for commercialisation and use in ongoing and future clinical studies was subsequently developed and two arms have been added to the trial to assess this formulation*.[14] Therefore, the company were asked in the clarification letter to:

- provide a rationale for the two formulations.
- state which formulation of polatuzumab vedotin (pola) they expected to be administered in clinical practice.
- justify the applicability of the randomised trial data to the efficacy and safety of the lyophilised formulation.

Briefly, the company stated that '*A lyophilised formulation of polatuzumab vedotin was developed to enhance drug product stability and enable administration using standard IV bags and infusion sets.*' The company clarified that '*The 140 mg/vial lyophilised formulation of polatuzumab vedotin will be administered in clinical practice*.'[2]

In relation to the two arms (G and H) added to GO29365 the company stated in the CS that '[redacted]'[14]

The company stated that '[redacted]'[14] The ERG agrees that these comparisons should be treated with caution, but noted that response rates, median PFS and OS tended to be numerically lower (worse) in Arm G, the lyophilised formulation arm. The company stated that '[redacted]'[14] and it is also noted that follow up was shorter in the lyophilised group ([redacted]). In regard to safety the company stated at clarification that '[redacted]'Full details of the safety and efficacy results of Arm G are provided in Appendix L of the CS.

In the absence of complete evidence, the ERG concludes that there is some doubt as to whether the lyophilised formulation of Pola will offer similar efficacy and safety to the liquid formulation when used in clinical practice.

3.3 Comparators

ERG comment: Only one comparator (bendamustine with rituximab; BR) was fully included in the decision problem while rituximab, gemcitabine, oxaliplatin (R-GemOx) were only included in the economic model by assuming equal efficacy with BR. The ERG questioned whether evidence might be available on other comparators given that Appendix D of the CS reported a systematic review of 16 studies considered in an indirect comparison feasibility assessment. The company were requested in the clarification letter to:[27]

- complete the systematic review by reporting the effectiveness and safety results of the 16 studies.
- state the reasons for each of the 16 studies as to why the results could not be included in a meta-analysis with those from GO29365.
- state the reasons for each of the 16 studies as to why the results could not be incorporated in the economic model.

The company provided the above data.[2] The ERG examined the RCTs identified and agreed that a network could not be constructed to inform an indirect comparison based on the RCTs of other treatments available. Equally, in examination of the observational studies a match-adjusted comparison did not appear to be appropriate given the differences identified by the company in populations and line of treatment across the studies. Indeed, studies for only one additional comparator in the scope, R-GemOx, were presented. However, all of these studies included a large proportion of non-rituximab experienced patients, the effect of which would be difficult to estimate given that data were not reported separately by rituximab experience.

Nevertheless, the company noted in Table 3 of the CS regarding European Society for Medical Oncology (ESMO) guidelines for patients with first and second relapse or progression that following advice from UK clinical experts, oxaplatin is the preferred platinum regimen for transplant-ineligible patients in UK clinical practice.[14] However, further in the text, clinical experts reported that R-Gem-Ox is not widely used in clinical practice. They were therefore requested to clarify this apparent discrepancy. The company reiterated that '*Clinical experts reported that R-Gem-Ox…. is not widely used in UK clinical practice as a salvage regimen for transplant-eligible patients*' but did not provide the data to support this assertion.[2] They further stated that '*R-Gem-Ox is an option considered by NHS England for older and / or transplant-ineligible patients. Further advice sought by Roche also reported that the familiarity of this regimen has occurred very recently (in the last few years) and its use in the transplant-ineligible setting may increase among treatment centres that are enrolling patients to the ARGO study.*' [2]

Although there are no comparative data, in the two trials of R-Gem-Ox where it was reported, median OS was considerably higher, at 9.1 and 11.0 months (see Table 11 of the response to clarification), than the [redacted] months for BR in the GO29365 trial.[2, 14] However, it was reported by the company that two clinical advisors stated: "…the responses seen in the BR (control) arm of the GO29365 study is in-line with what they would expect in this population with the use of other treatment options." (p. 5)[28] Also, at clarification the company stated that '*Other regimens used in the treatment of R/R DLBCL, such as R-Gem-Ox (a platinum-based regimen) is associated with a high incidence (38%) and severity (Grade 3: 8%) of PN ([9]). Therefore, there was concern that combining polatuzumab vedotin with R-Gem-Ox would result in significant additive toxicity, specifically PN.*'[2]

Therefore, in the absence of direct evidence, it is not clear that R-GemOx can be assumed to have equal efficacy and safety to BR. Furthermore, it is also not clear that the two comparators in the CS are a reasonable reflection of the comparators currently used in practice.

3.4 Outcomes

ERG comment: The outcomes in the CS were as per the NICE scope.[26] However, health-related quality of life was not directly assessed in the main trial, GO29365.

Primary outcomes in the main trial GO29365 were assessed by IRC and by investigators.[14] Independent outcome assessment is the method preferred by the ERG and these results are presented in Section 4.2.5 of the ERG report.

3.5 Other relevant factors

Equity considerations were not mentioned by the company and there is no patient access scheme.

4. CLINICAL EFFECTIVENESS

4.1 Critique of the methods of review(s)

The company conducted a systematic review to identify evidence relevant to this appraisal. Section 4.1 critiques the methods of the review including searching, inclusion criteria, data extraction, quality assessment and evidence synthesis.[14]

4.1.1 Searches

Appendix D of the CS details a systematic search of the literature used to identify clinical effectiveness literature undertaken on 4 September 2018, the search was updated (electronic databases and congress proceedings) on 4 June 2019.[27] A summary of the sources searched is provided in Appendix 2, Table 1.

ERG comment

- The selection of databases searched was comprehensive, and searches were on the whole clearly reported and reproducible. The database name, host and date searched were provided for most searches. An extensive range of resources additional to database searches was included in the SLR to identify further relevant studies and grey literature.
- Reporting of dates searched are unclear. The text in Appendix D.1 states that searches took place on 4 September 2018, but the search strategies report a search date of 6 September 2018.
- The Cochrane Library Central Register of Controlled Trials (CENTRAL) date span was reported as up to October 2017, but the searches took place on 6 September 2018 so it is unclear why a longer date span was not searched.
- The Cochrane Database of Systematic Reviews (CDSR) date span is reported as 2005-November 2016, but again the searches took place on 6 September 2016 so it is unclear why longer date spans were not searched.
- Study design filters to identify clinical trials were applied. The filters were not referenced, so it was unclear whether they were published objectively-derived filters. The filters contained a combination of subject heading terms (MeSH and Emtree) and free text terms, and the ERG deemed them to be adequate. Additional terms were also employed in the strategy to identify non-randomised studies.
- A broad range of additional sources were 'hand' searched, the sources and terms used were not reported in full detail (i.e. website addresses and terms used to search them).

4.1.2 Inclusion criteria

As stated above, the company conducted a systematic review to identify evidence relevant to this appraisal, the details of which were presented in Appendix D.[27] A summary of the eligibility criteria is given in Appendix 1 of this report.

ERG comment

- The inclusion criteria of the review were slightly different to the inclusion criteria specified by NICE in the scope. The population in the review was '*Adult patients (≥18years) with R/R DLBCL who are receiving second or third-line (or beyond) therapy*' [14] whereas in the scope it was '*Adults with relapsed or refractory diffuse large B-cell lymphoma for whom hematopoietic stem cell transplant is not suitable*'[26]. However, no comparators appear to have been excluded.

- The study designs in the review included RCTs, prospective (but not retrospective) single arm studies and comparative observational studies. The inclusion of non-RCTs was appropriate given the smaller number of RCTs available in this population and to allow the possibility of exploring a mixed-treatment comparison.

- There were no date or country restrictions but only English language publications were eligible which meant that studies could have been missed. It was noted that across the review and its subsequent update search that five papers were excluded based on title and abstract and eight based on the full paper. It was unclear if these studies would have been otherwise eligible for inclusion.

- It was unclear if more than one reviewer was involved in selecting studies for inclusion in the review which helps to minimise bias and error.

- The company reported that 36 unique studies met the eligibility criteria of the review. Sixteen studies were considered for extraction. Twenty were not as they enrolled either transplant eligible patients or transplant or chemotherapy relapsed patients. This appeared initially appropriate to the ERG given the NICE scope. However, the company stated in the clarification letter that '*Patients who had received prior transplant (but have since progressed are within the expected marketing authorisation for pola+BR if they are not eligible for another transplant at this point.*'[2] If NICE considers this population to be part of the scope then some of the non-extracted studies could be relevant especially as the main trial in the submission also included 16 of 80 patients who had received an ASCT.

- Four of the 16 extracted studies in the CS were RCTs and 12 were observational/single arm trials. Two of the RCTs were not specifically in transplant ineligible but '*included elderly, frail patients that could be considered as transplant ineligible*'[14] according to the company. This appeared reasonable to the ERG.

- The company performed an update search on 10 June 2019 which generated three new studies to be extracted and considered in the indirect comparison feasibility assessment (see section 4.1.5). The 19 studies now comprised six RCTs and 13 single arm studies.[2] The company was asked to report on the effectiveness and safety of the studies considered for the indirect comparison. These results are available in the response to clarification letter.[2]

4.1.3 Critique of data extraction

No information was provided on the number of reviewers who extracted data from included studies.

ERG comment: It is normally recommended that two reviewers are involved in data extraction for a systematic review to avoid bias and error.

4.1.4 Quality assessment

The company assessed the quality of GO29365, the main trial of polatuzumab in combination with BR in patients with R/R DLBCL, and the three original RCTs to be considered for the indirect comparison. The quality tool used was as recommended in the NICE STA user guide.[29] Elements assessed were randomisation procedures, allocation concealment, blinding of participants, personnel and outcome assessors, methods of dealing with incomplete outcome data, selective outcome reporting and any other biases. The company gave the trial positive ratings in all categories but one – blinding of participants and personnel as the trial was open label.

Observational studies considered for indirect comparison were also assessed by the company using the Quality Assessment Tool for Quantitative Studies produced as part of the Effective Public Health Practice Project (EPHPP).[30]

No information was provided on the number of reviewers who assessed the quality of included studies.

ERG comment

- It is normally recommended that two reviewers are involved in the assessment of study quality to avoid bias and error.
- The ERG agrees with the company's quality assessment of the main trial, GO29365. It is drawn to the attention of the committee that this is an open label trial so both patients and healthcare professionals involved in their care are aware of treatment allocation.
- Primary outcomes were assessed by independent review committee and by investigators. Independent outcome assessment is the method preferred by the ERG and these results are presented in the report.
- The ERG did not re-assess the quality of the studies (RCTs and observational) considered for the indirect comparison given that no indirect comparison was undertaken.

4.1.5 Evidence synthesis

As the company identified only one relevant trial, no meta-analysis was possible. As stated above, the company investigated the feasibility of an indirect treatment comparison of Pola+BR with comparators in the NICE scope. However a limited number of RCTs were eligible and the company reported that no connected network of evidence could be constructed. The company also stated that three single arm studies of R-GemOx was identified, but as the study did not report KM data for rituximab pre-treated and naïve patients separately it was not possible to conduct a robust matching-adjusted indirect comparison.[2]

ERG comment: The ERG examined the RCTs identified and agreed that a network could not be constructed to inform an indirect comparison based on the RCTs available. Equally a matching-adjusted indirect comparison did not appear to be appropriate given the differences identified by the company in populations and line of treatment across the studies (Also see Section 3.3 of ERG report).

4.2 Critique of trials of the technology of interest, the company's analysis and interpretation (and any standard meta-analyses of these)

4.2.1 Included studies

One study is mentioned in the CS as relevant to the technology being appraised:

- A Phase Ib/II, multicentre, open-label study (GO29365) of polatuzumab in combination with BR in patients with R/R DLBCL, and polatuzumab in combination with bendamustine and obinutuzumab (BG) in patients with R/R follicular lymphoma.

Details of the study are listed in Table 4.1.

Table 4.1: Study details, GO29365

Study	GO29365 (NCT02257567)				
Study design	Phase Ib/II, multicentre, open-label study				
Population	Patients with R/R DLBCL Age ≥18 years' old ECOG PS 0–2 At least 1 bi-dimensionally measurable lesion ≥1.5 cm in its longest dimension Adequate haematologic function If received prior bendamustine, response duration must have been >1 year				
Intervention(s)	Polatuzumab vedotin plus bendamustine and rituximab (Pola+BR)				
Comparator(s)	Bendamustine and rituximab (BR)				
Indicate if trial supports application for marketing authorisation	Yes	✓	Indicate if trial used in the economic model	Yes	✓
	No			No	
Rationale for use/non-use in the model	GO29365 is a Phase Ib/II trial providing efficacy and safety evidence for the combination of Pola+BR in patients with R/R DLBCL. Data from GO29365 were used to inform the efficacy and safety of Pola+BR in the economic model. Data for PFS and OS from the most recent data cut (11 October 2018) were used to inform the economic model – this data and analysis for other endpoints from the previous data cut (30 April 2018) is reported in this submission				
Reported outcomes specified in the decision problem	Overall survival Progression-free survival Response rates Adverse effects of treatment Health-related quality of life				
All other reported outcomes	Duration of response Event-free survival				

Source: CS, Table 6, page 24[14]
DLBCL = Diffuse large B-cell lymphoma; ECOG PS = Eastern Co-operative Oncology Group performance status; R/R = Relapsed/refractory

ERG comment

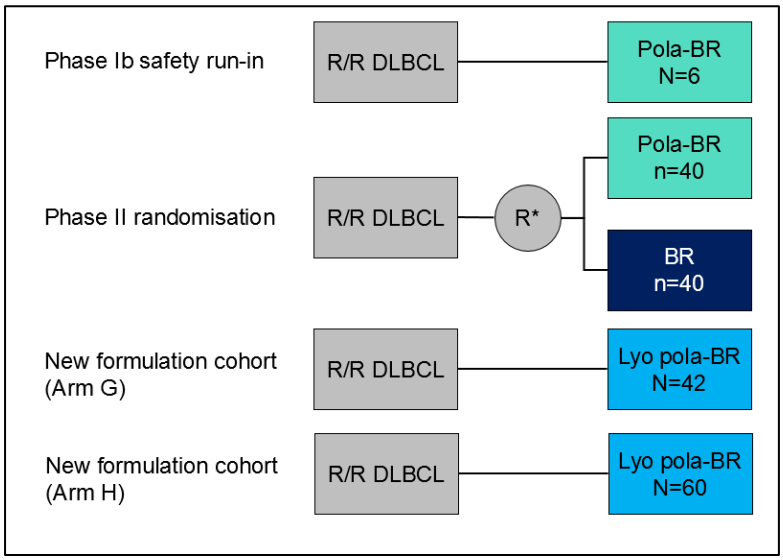
- According to these characteristics, the population is in line with the scope except insofar as it is not stated that hematopoietic stem cell transplant is not suitable.[26] However, this aspect is addressed in Section 4.1.2.
- The intervention is consistent with the scope.
- The comparator is one of those in the scope, although none of the other comparators were included in the trial.
- The outcomes are those that are listed in the scope. However, HRQoL is not assessed in the trial.

- The trial is open-label so treatment assignment was known to patients and care providers. See Section 4.1.4 for a discussion of this aspect.
- The methodology of the GO29365 trial is described in more detail in Appendix 3. The ERG noted that patients needed to have received at least one prior therapy for DLBCL and that they must have relapsed or have become refractory to a prior regimen. Thus, in the trial, patients were receiving treatment at second-line and beyond. Patients needed to have a life expectancy of at least 24 weeks which is reasonable for the trial but in clinical practice this treatment is to be offered as end-of-life care. Importantly, patients could have received a prior ASCT over 100 days previously. Implications of including this population are discussed within this report. Outcomes were assessed by investigators and an IRC and it is the IRC results which are preferred by the ERG and are presented in this report.

4.2.2 Design of the included study

The GO29365 trial study design is summarised in the Figure 4.1 below.

Figure 4.1: GO29365 study design schema (R/R DLBCL polatuzumab and BR populations only)



Source: CS, Figure 3, page 25[14].
Lyo = lyophilised formulation
*1:1 randomisation, stratified by DOR ≤12 months or >12 months.
Treatment administered every 21 days x 6 cycles: pola 1.8 mg/kg, C1D2, then D1 for C2+; bendamustine: 90 mg/m2, C1D2/3 then D1/2 for C2+; rituximab: 375 mg/m2, D1 for C1+

ERG comment

- Six patients enrolled to receive Pola+BR in a Phase I safety run. In a phase II randomisation 40 patients were randomised to Pola+BR and 40 patients to the BR arm. Where results include the six patients in the Phase I study this will be indicated.
- The GO29365 trial is ongoing and issues relating to the new formulation cohort in Arms G and H are discussed in Sections 3.2 and 4.2.7.

4.2.3 Baseline characteristics

A total of 86 patients were enrolled in the GO29365 trial and were randomly assigned to the polatuzumab + BR group (n=40) or the BR group (n=40), whilst six patients received polatuzumab+BR in a Phase I safety run. The median age of patients in the Pola+BR group was 66.5 and in the BR group was 71. Approximately 66% of the trial participants are male. The majority are white and have an ECOG status of 0 or 1. The median number of prior treatment lines is two and approximately 30% have received one prior treatment. See Table 4.2).

Table 4.2: Key demographic and baseline disease characteristics in GO29365

Characteristics	Phase Ib (safety run-in)	Phase II (randomised)		Phase Ib/II (total)
	Pola+BR n=6	Pola+BR n=40	BR n=40	Pola+BR N=46
Baseline demographics				
Median age, years (range)	65.0 (58–79)	67.0 (33–86)	71.0 (30–84)	66.5 (33–86)
Male, n (%)	4 (66.7)	28 (70.0)	25 (62.5)	32 (69.6)
Race, n (%) White Asian American Indian or Alaska Native Black or African American Unknown	 5 (83.3) 1 (16.7) 0 0 0	 26 (65.0) 6 (15.0) 0 3 (7.5) 5 (12.5)	 31 (77.5) 4 (10.0) 1 (2.5) 0 4 (10.0)	 31 (67.4) 7 (15.2) 0 3 (6.5) 5 (10.9)
ECOG PS, n (%) 0 or 1 2 Unknown	 6 (100.0) 0 0	 33 (82.5) 6 (15.0) 1 (2.5)	 31 (77.5) 8 (20.0) 1 (2.5)	 39 (84.7) 6 (13.0) 1 (2.2)
Primary reason for SCT ineligibility, n (%): Age Comorbidities Failed prior transplant Insufficient response to salvage tx Other Patient refusal Performance status	 1 (16.7) 0 0 2 (33.3) 1 (16.7) 2 (33.3) 0	 13 (32.5) 1 (2.5) 10 (25.0) 12 (30.0) 2 (5.0) 2 (5.0) 0	 19 (47.5) 1 (2.5) 6 (15.0) 9 (22.5) 1 (2.5) 2 (5.0) 2 (5.0)	 14 (30.4) 1 (2.2) 10 (21.7) 14 (30.4) 3 (6.5) 4 (8.7) 0
Baseline disease characteristics				
Median months since diagnosis at study entry (range)	0.5 (0–1)	0.7 (0–20)	0.8 (0–15)	0.7 (0–20)
Ann Arbor Stage III or IV, n (%)	4 (66.7)	34 (85.0)	36 (90.0)	38 (82.6)
Bulky disease (≥7.5 cm), n (%)	1 (16.7)	10 (25.0)	15 (37.5)	11 (23.9)
Extranodal involvement, n (%)	4 (66.6)	27 (67.5)	29 (72.5)	31 (67.4)
IPI score at enrolment, n (%) 0–1 (low) 2 (low-intermediate)	 1 (16.7) 3 (50.0)	 9 (22.5) 9 (22.5)	 3 (7.5) 8 (20.0)	 10 (21.7) 12 (26.1)

Characteristics	Phase Ib (safety run-in)	Phase II (randomised)		Phase Ib/II (total)
	Pola+BR n=6	Pola+BR n=40	BR n=40	Pola+BR N=46
3 (high-intermediate)	2 (33.3)	13 (32.5)	12 (30.0)	15 (32.6)
4–5 (high)	0	9 (22.5)	17 (42.5)	9 (19.6)
Prior anti-lymphoma chemotherapy, n (%)	6 (100.0)	40 (100.0)	40 (100.0)	46 (100.0)
Median no. of lines (range)	2.0 (1–2)	2.0 (1–7)	2.0 (1–5)	2.0 (1–7)
1 line	2 (33.3)	11 (27.5)	12 (30.0)	13 (28.3)
2 lines	4 (66.7)	11 (27.5)	9 (22.5)	15 (32.6)
≥3 lines	0	18 (45.0)	19 (47.5)	18 (39.1)
Prior treatments, n (%)				
Anti-CD20	6 (100.0)	39 (97.5)	40 (100.0)	45 (97.8)
Bendamustine	0	1 (2.5)	0	1 (2.2)
Stem cell transplant	0	10 (25.0)	6 (15.0)	10 (21.7)
Cancer radiotherapy	1 (16.7)	11 (27.5)	10 (25.0)	12 (26.1)
Refractory to last prior anti-CD20 tx[a] n (%)	4 (66.7)	18 (45.0)	18 (45.0)	22 (47.8)
No	1 (16.7)	10 (25.0)	6 (15.0)	11 (23.9)
Unknown	1 (16.7)	12 (13.0)	16 (40.0)	13 (28.3)
Refractory to last prior anti-lymphoma therapy[b], n (%)	5 (83.3)	30 (75.0)	34 (85.0)	35 (76.1)
Median time from last anti-lymphoma therapy[c], days (range)	53.0 (43–1477)	131.0 (17–11744)	82.0 (21–2948)	114.0 (17–11744)
Duration of response to prior tx[d], n (%)				
≤12 months	5 (83.3)	32 (82.0)	33 (82.5)	37 (80.4)

Source: CS, Table 7, pages 32-33.
[a] Defined as no response or progression or relapse within 6 months of last anti-lymphoma therapy end date among patients whose last prior regimen contained anti−CD20
[b] Defined as no response or progression or relapse within 6 months of last anti−lymphoma therapy end date
[c] Defined as time from end date of last anti−lymphoma therapy to first dose date
[d] Duration of response to prior therapy based on IxRS for randomised cohorts and CRF for non-randomised cohorts
ECOG PS = Eastern Cooperative Oncology Group performance status; IPI = international prognostic index; IxRS = Interactive Voice/Web Response System; SCT = stem cell transplant

ERG comment

- As only three patients were from the UK it is important to consider whether the baseline characteristics of the patients in the trial reflect those typically seen in clinical practice in this country. The ERG noted an underrepresentation of non-white participants. The majority of patients had an ECOG status of 0 or 1. The primary reasons for SCT ineligibility were age and insufficient response to salvage therapy.

- The ERG noted that there were some baseline imbalances between the treatment groups including variation in IPI score with more patients in the Pola+BR having a lower score. More patients in the BR group had bulky disease. These factors could be advantageous for outcomes in the Pola+BR group. The company conducted multivariable Cox regression analysis to adjust for Ann Arbor stage, baseline ECOG status and IPI (OS and PFS) and also bulky disease (OS only) and concluded that these results were robust and similar to the unadjusted results.

However, bulky disease showed the greatest imbalance at baseline (25% vs. 37.5%) and this was not included in the PFS analysis so this imbalance could favour Pola+BR.

4.2.4 Statistical analyses

Forty patients were planned for each treatment arm in the Phase II randomisation phase in patients with R/R DLBCL in order to evaluate the safety and efficacy of polatuzumab+BR compared with BR with acceptable accuracy. The primary outcome was CR and the sample size was based on the estimation of the CR rate for each treatment. Forty patients per treatment arm would provide a confidence interval of +/- 17% assuming an observed CR of at least 60% and an exact Clopper-Pearson 95% CI of 43% to 75%. Assuming 40% CR with BR and an increase to 65% with Pola+BR then the estimated 95% CI for the difference is 3.8% to 46.2%.

Efficacy analyses were based on two populations: intention-to-treat (ITT) population which was all randomised patients analysed in the group to which they were randomised and the safety-evaluable population, which was all patients who received any study medication, analysed according to treatment received. The primary, secondary and exploratory efficacy endpoints in the GO29365 study are summarised in Table 4.3.

Table 4.3: Efficacy outcome measures

Primary efficacy endpoint	Secondary efficacy endpoints	Exploratory efficacy endpoints
• CR at primary response assessment (6−8 weeks after Cycle 6 Day 1 or last dose of study medication) based on PET-CT, as determined by the investigator and IRC The percentage with CR and the Clopper-Pearson exact 95% CI was calculated for each arm. Differences between arms were compared with a CMH chi-square test adjusted for the randomisation stratification factors	Response rates measured at the primary response assessment: • CR (INV-assessed) and OR (INV- and IRC assessed CR or PR) based on PET alone • CR and OR (INV- and IRC-assessed) based on CT alone • BOR (INV-assessed) at any assessment while on study based on PET alone or CT alone • DOR (IRC-assessed) • PFS (IRC-assessed) Binary outcomes were analysed using the same method as CR Median DOR with 95% CI were estimated using the Brookmeyer and Crowley method, no treatment comparisons were made.	Time-to-event outcome measures: • DOR (INV-assessed) • PFS (INV-assessed) • EFS (INV-assessed) • OS PFS, EFS and OS durations and estimates of one and two-year survival were estimated using the Kaplan-Meier method. There was no pre-specified alpha control plan; p-values are provided for descriptive purposes only.

Source: based on CS, Table 9, page 35
BOR = best overall response; CMH = Cochran-Mantel-Haenszel; CR = complete response; DOR = duration of response; EFS = event-free survival; IRC = Independent Review Committee; OR = overall response; OS = overall survival; PET-CT = positron emission tomography-computed tomography; PFS = progression-free survival; PR = partial response

Patients who did not have response assessments (for any reason) were considered as non-responders. For OS, patients for whom death had not been documented had observations censored on the last date at which they were known to be alive. Also, patients had observations censored on the date of the last tumour assessment or, if no tumour assessments were performed after the baseline visit, at the time of randomisation and enrolment day +1 if they did not have documented disease progression or death.

The patient-reported outcome analyses included patients in the intent-to-treat population and were analysed according to assigned treatment. For the total score and each of the Therapy-Induced Neuropathy Assessment Scale (TINAS) single symptom items, descriptive statistics for recorded values at each visit and changes from baseline were calculated. In cases, where TINAS data were missing, per developer scoring instructions, such that a prorated total score was calculated if ≥50% of items were answered, were used.

ERG comment: The statistical analyses used appropriate methods. However, the sample size calculation was based on estimating the CR rate in each arm and was not powered for detecting differences between the treatment arms. It only considered CR and not time to event outcomes such as PFS, OS and EFS which, given the small sample size of this phase II study, were likely to be underpowered. The analysis methods for the exploratory endpoints (OS, investigator-assessed PFS and EFS) specified that p-values were provided for descriptive purposes only, although they have been presented and used in the conclusion of the CS.

4.2.5 Results

The Phase Ib/II study GO29365 evaluated the efficacy and safety of pola 1.8 mg/kg in combination with rituximab or obinutuzumab plus bendamustine in relapsed or refractory follicular lymphoma or DLBCL in patients with R/R DLBCL. The primary analysis presented in the CS was from the clinical cut-off date 30 April 2018, although data for PFS and OS from the most recent data cut (11 October 2018) were also presented. Because the ERG believe that they are more reliable, only the results of the IRC are presented below.

4.2.5.1 Complete response rate

In the randomised Phase II part of the GO29365 study, polatuzumab+BR (40.0% [16/40 patients]; 95% CI: 24.9%, 56.7%) demonstrated a statistically significant improvement in CR at the primary response assessment by PET-CT as assessed by the IRC compared to patients in the BR arm (17.5% [7/40 patients], 95% CI: 7.3%, 32.8%) (see Table 4.4).

Table 4.4: CR rate with PET at primary response assessment (IRC-assessed)

Outcome	Pola+BR n=40	BR n=40
Complete response, n (%) 95% CI	16 (40.0) (24.86, 56.67)	7 (17.5) (7.34, 32.78)
Difference in response rates, n (%) (95% CI) p value	22.5 (2.62, 40.22) p=0.0261	
Source: CS, Table 11, page 38		

4.2.5.2 Progression-free survival

The number of patients with R/R DLBCL who had a PFS event (PD or death) at the time of the clinical cut off was higher in the BR arm in comparison to polatuzumab+BR arm (80.0% [32/40 patients] vs. 62.5% [25/40 patients]) (see Table 4.5). The risk of PD or death was reduced in patients treated with Pola+BR compared to BR (stratified HR=0.36; 95% CI: 0.21, 0.63).

Table 4.5: Progression-free survival (IRC-assessed)

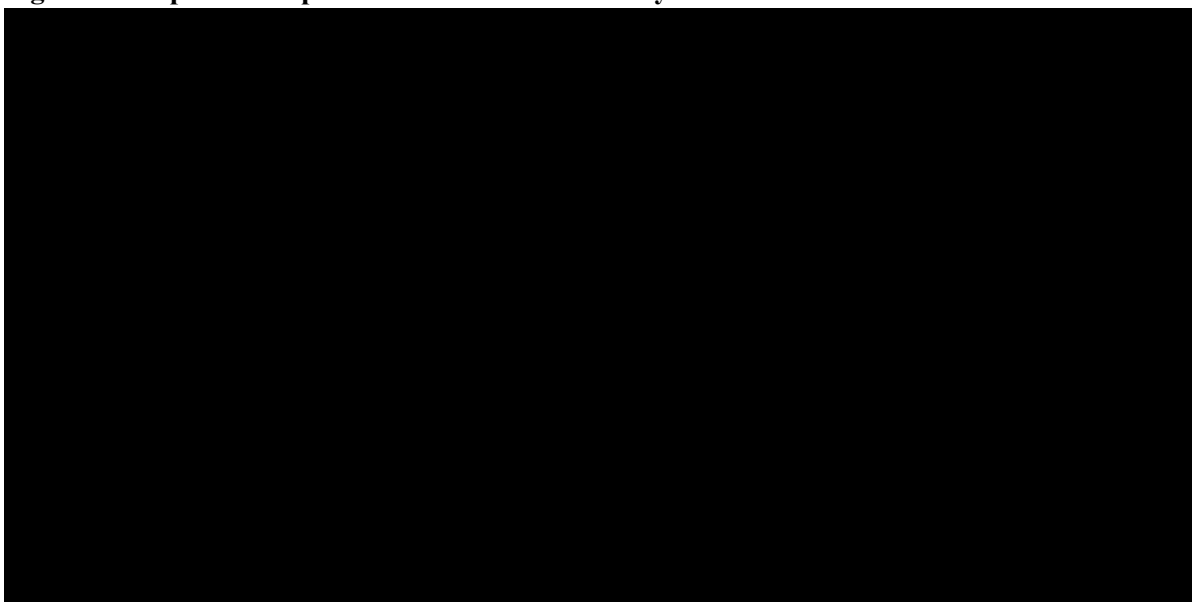
Outcome	Pola+BR n=40	BR n=40
Patients with event, n (%)	25 (62.5)	32 (80.0)
Earliest contributing event, n Disease progression Death	 14 11	 13 19
Median time to event, months 95% CI	9.46 (6.24, 13.93)	3.71 (2.07, 4.53)
Stratified HR % (95% CI) p value (log-rank)	0.36 (0.21, 0.63) p<0.0002	
Source: CS, Table 19, page 42 CCOD: 30 April 2018 Tumour assessment is based on PET-CT wherever it is available and valid and uses CT only result if PET-CT is missing HR = hazard ratio		

The updated PFS by IRC was provided to the ERG with the clarification response.[2] This time the clinical cut-off date was [redacted]. After 30 months the number of patients with a PFS event (PD or death) was higher in the BR arm ([redacted]) compared to the Pola+BR arm ([redacted] (see Table 4.5). The risk of PD or death was reduced compared to BR (stratified [redacted] The results of the updated PFS analysis are shown in Table 4.6. An updated KM curve is provided in Figure 4.2.

Table 4.6: Updated progression-free survival (IRC-assessed)

Outcome	Pola+BR n=40	BR n=40
Patients with event, n (%)	[redacted]	[redacted]
Earliest contributing event, n Disease progression Death	[redacted]	[redacted]
Median time to event, months 95% CI	[redacted]	[redacted]
Stratified HR % (95% CI) p value (log-rank)	[redacted]	
Source: Response to clarification, Table 15, page 26 [redacted] HR, hazard ratio		

Figure 4.2: Updated Kaplan-Meier Curve for PFS by IRC



Source: Response to clarification, Figure 3, page 27

4.2.5.3 Overall survival

A total of 51 patients with R/R DLBCL in the randomised Phase II had died at the time of the clinical cut-off of 30 April 2018 (28 patients in the BR arm and 23 patients in the Pola+BR arm). The risk of death was reduced by 58% in patients treated with Pola+BR compared to BR (stratified HR=0.42; 95% CI: 0.24, 0.75) (see Table 4.7).

Table 4.7: Overall survival

Outcome	Pola+BR n=40	BR n=40
Patients with event, n (%)	23 (57.5)	28 (70.0)
Median time to event, months 95% CI	12.39 (9.04, NE)	4.73 (3.71, 8.31)
Stratified HR % (95% CI) p value (log-rank)	0.42 (0.24, 0.75) p=0.0023	
Source: CS, Table 24, page 46. CCOD: 30 April 2018 HR = hazard ratio; NE = not estimated		

An updated OS was provided to the ERG with clarification response.[2] The clinical cut-off date was [redacted] The results of the updated OS analysis are shown in Table 4.9. An updated KM curve is provided in Figure 4.3.

Table 4.8: Updated overall survival cut-off date [redacted]

Outcome	Pola+BR n=40	BR n=40
Patients with event, n (%)	[redacted]	[redacted]
Median time to event, months 95% CI	[redacted]	[redacted]
Stratified HR % (95% CI) p value (log-rank)	[redacted]	
Source: Response to clarification, Table 17, page 28. [redacted] HR = hazard ratio; NE = not estimated		

Figure 4.3: Updated Kaplan-Meier Curve for OS cut-off date [redacted]

[redacted]

Source: Response to clarification, Figure 5, page 29.[2]

4.2.5.4 Patient-reported outcomes

Patients self-reported the severity of symptoms and neuropathy related to polatuzumab treatment impact on daily functioning by using the TINAS v1.0 instrument.[31] The company made an assumption that peripheral neuropathy (PN) is specific to polatuzumab, therefore, data from Pola+BR and Pola+BG arms were pooled across the Phase Ib and Phase II stages to maximise the sample size available for analyses given the extent of missing data. Patients in both the Pola+BR/BG and BR arms reported low mean scores for individual TINAS items (≤1.5) at the beginning of treatment. Moreover, the severity of PN symptoms was rated as low by the end of treatment, with the highest means observed for numbness/tingling in hands/feet, although still ≤2.

ERG comment: There was a clear and statistically significant advantage with Pola+BR in comparison to BR in all outcomes. This included an increase in median OS of about [redacted] and an increase in median PFS of about [redacted], as shown in Table 4.6. However, the ERG noted an error in the KM curve for OS where the curve for BR reached zero when it should have remained at approximately 17%.

4.2.5.5 Results from GO29365 excluding 16 patients who had received an ASCT

The company was asked at clarification to conduct an analysis excluding the 16 patients from GO29365 who had received an ASCT.[2] The company provided data from both the 30 April 2018 data cut and the [redacted] data cut. The data provided are given below.

Table 4.9: CR rate with PET at primary response assessment (IRC-assessed) endpoint, excluding the 16 patients who had received an ASCT (30 April 2018)

Outcome	Pola+BR n=30	BR n=34
Complete response, n (%) 95% CI	[redacted]	[redacted]
Difference in response rates, n (%) (95% CI) p- value (stratified)	[redacted]	
Source: Response to clarification[2] BR = bendamustine, rituximab; CI = confidence interval		

Table 4.10: Objective response (CR/PR) rates by PET at primary response assessment (IRC-assessed) endpoint, excluding the 16 patients who had received an ASCT (30 April 2018)

Outcome	Pola+BR n=30	BR n=34
Overall response, n (%) 95% CI	[redacted]	[redacted]
Complete response, n (%) 95% CI	[redacted]	[redacted]
Partial response, n (%) 95% CI	[redacted]	[redacted]
Difference in OR response rates, n (%) (95% CI)	[redacted]	
Source: Response to clarification[2] BR = bendamustine, rituximab; CI = confidence interval; OR = overall response		

Table 4.11: Progression-free survival (IRC-assessed), excluding the 16 patients who had received an ASCT ([redacted])

Outcome	Pola+BR n=30	BR n=34
Patients with event, n (%)	[redacted]	[redacted]
Earliest contributing event, n Disease progression Death	[redacted]	[redacted]
Median time to event, months 95% CI	[redacted]	[redacted]
Stratified HR % (95% CI)	[redacted]	
Source: Response to clarification[2] BR = bendamustine, rituximab; CI = confidence interval; HR = Hazard ratio		

Table 4.12: Overall survival, excluding the 16 patients who had received an ASCT (latest data update) ([redacted])

Outcome	Pola+BR n=30	BR n=34
Patients with event, n (%)	[redacted]	[redacted]
Median time to event, months 95% CI	[redacted]	[redacted]
Stratified HR % (95% CI)	[redacted]	
Source: Response to clarification[2] BR = bendamustine, rituximab; CI = confidence interval; HR = Hazard ratio		

ERG comment: The ERG considers that the results appear comparable to those including the 16 who had received an ASCT prior to entering the trial.

4.2.5.6 Subgroups according to line of treatment

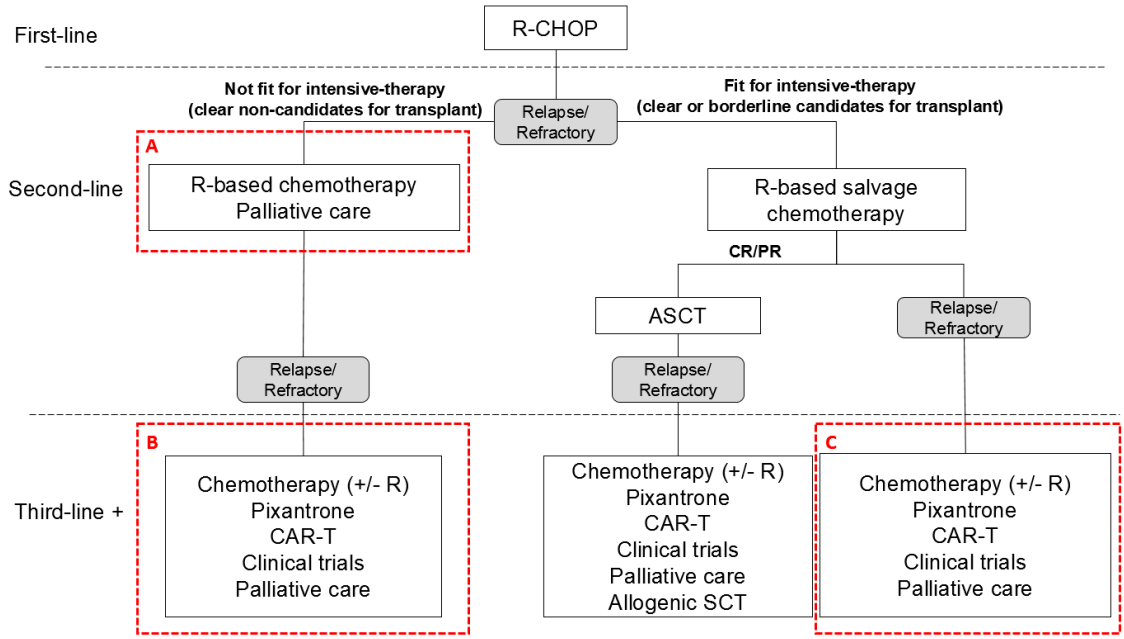
ERG comment: Although the NICE scope did not specify any subgroups of interest, the ERG considered that the committee might need to consider data on the effectiveness of Pola+BR at the different lines of treatment in the proposed pathway. Accordingly, the ERG asked:

'Figure 2 in the CS shows that pola + BR might be positioned at either second-line (immediately after rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone; R-CHOP), third-line (after R-based chemotherapy/palliative care) or second-line (after R-based salvage chemotherapy).

Please conduct subgroup analyses of the GO29365 trial appropriate to each of these three positions.'[2]

The company provided subgroup analyses as illustrated in the Figure 4.4.[2]

Figure 4.4: Company subgroup analyses according to line of treatment



Source: Clarification response[2]
Clear non-candidates for transplant (transplant-ineligible), second-line (Box A in Figure)
Clear non-candidates for transplant (transplant-ineligible), third-line (Box B)
Clear or borderline candidate for transplant, third-line after failing salvage therapy and therefore transplant-ineligible (Box C)

The company stated '*It was not possible to perform a subgroup analysis of patients who received pola+BR beyond third-line as these patients could not be clearly defined.*'[2]

The company concluded that patient number in the subgroups were too small to provide reliable results. The ERG agrees with this conclusion.

4.2.6 Adverse events

The population that could be evaluated for safety included 45 patients who received at least one dose of study drug during Phase Ib/II and 39 patients who only received BR in the Phase II randomisation. The company stated that '*Overall, no new safety signals were noted with the addition of pola to BR relative to the known safety profile of Pola, and the safety and tolerability profile of the pola+BR regimen was acceptable within the context of this pre-treated population of patients with R/R DLBCL.*'[14] A summary of the safety profile of Pola+BR in GO29365 is shown in Table 4.13. Treatment related adverse events were provided by the company in response to clarification (See Table 4.14).[2]

Table 4.13: Overview of safety profile in GO29365

n, (%)	Phase Ib	Phase II		Phase Ib/II
	Pola+BR n=6	Pola+BR n=39	BR n=39	Pola+BR n=45
Patients with at least one:				
Any AE	6 (100)	39 (100)	38 (97.4)	45 (100)
Grade 3–4 AE	5 (83.3)	33 (84.6)	28 (71.8)	38 (84.4)
Grade 5 AE	0	9 (23.1)	11 (28.2)	9 (20.0)
Serious AE	4 (66.7)	25 (64.1)	24 (61.5)	29 (64.4)
AE leading to discontinuation of:				
Pola	0	12 (30.8)	n/a	12 (26.7)
Any study drug	1 (16.7)	13 (33.3)	6 (15.4)	14 (31.1)
AE leading to modification/interruption of:				
Pola	2 (33.3)	22 (56.4)	n/a	24 (53.3)
Any study drug	3 (50.0)	28 (71.8)	19 (48.7)	31 (68.9)
AEs to monitor:				
Grade ≥2 peripheral neuropathy	0	6 (15.4)	2 (5.1)	6 (13.3)
Grade ≥3 neutropenia	2 (33.3)	23 (59.0)	18 (46.2)	25 (55.6)
Grade ≥3 hepatoxicity	0	2 (5.1)	1 (2.6)	2 (4.4)
Grade ≥3 infections and infestations	2 (33.3)	13 (33.3)	12 (30.8)	15 (33.3)
Total no. of deaths	2 (33.3)	23 (59.0)	28 (71.8)	25 (55.6)
Deaths due to PD	2 (100)	14 (60.9)	17 (60.7)	15 (64.0)

Source: CS, Table 30, page 53.[14]
CCOD: 30 April 2018
AE = adverse event; PD = progressive disease

ERG comment

- In the randomised Phase II trial, all patients treated with pola and 38 out of 39 patients in the BR arm had at least one AE during the study.
- Adverse events appeared similar although there appeared to be more discontinuation and modification of study drugs in the Pola+BR group.
- In the randomisation Phase Ib and Phase II, a total of 57 serious AEs (SAEs) were reported in 29/45 patients (64.4%) with R/R DLBCL treated with Pola+BR. In the randomisation Phase II, the rate of SAEs was similar between the arms (64.1% [25/39 patients] Pola+BR arm vs 61.5% [24/39 patients] BR)
- The ERG noted that Grade ≥2 peripheral neuropathy was more frequently reported with Pola+BR.

Table 4.14: Overview of treatment-related adverse events in GO29365

n, (%)	Phase II	
	Pola+BR n=39	BR n=39
Patients with at least one:		
Any AE	[redacted]	[redacted]
Grade ≥3	[redacted]	[redacted]
Grade 5 AE	[redacted]	[redacted]
Serious AE	[redacted]	[redacted]
AE leading to discontinuation of:		
Pola	[redacted]	[redacted]
Bendamustine	[redacted]	[redacted]
Rituximab	[redacted]	[redacted]
AE leading to any study drug withdrawal	[redacted]	[redacted]
AEs to monitor:		
Grade ≥2 peripheral neuropathy	[redacted]	[redacted]
Grade ≥3 neutropenia	[redacted]	[redacted]
Grade ≥3 hepatoxicity	[redacted]	[redacted]
Grade ≥3 infections and infestations	[redacted]	[redacted]

Source: Response to clarification, Table 20, page 36[2]
AE = adverse event

ERG comment

- It is clear from the treatment-related adverse events that more patients had AEs leading to discontinuation as a result of pola, bendamustine and rituximab in the Pola+BR group.
- The majority of occurrences of peripheral neuropathy and neutropenia were deemed treatment-related.
- The ERG asked about the frequency of peripheral neuropathy in the Pola+BR group as the company noted that using bendamustine with pola was to minimise the overlapping toxicity of peripheral neuropathy. The company replied '*Peripheral neuropathy (PN) is an identified risk of pola…..Capping the treatment duration of pola to six cycles reduces the risk of PN versus longer treatment durations and higher doses, with the expected incidence of PN comparable to other antimicrotubule agents for lymphoma treatment*.'[2] They further stated that '*Other regimens used in the treatment of R/R DLBCL, such as R-Gem-Ox (a platinum-based regimen) is associated with a high incidence (38%) and severity (Grade 3: 8%) of PN ([9]). Therefore, there was concern that combining polatuzumab vedotin with R-Gem-Ox would result in significant additive toxicity, specifically PN*.'[2] The company stated that '*the majority of PN cases were low grade and reversible, and led to few patients experiencing dose reduction or delay*'.Patients receiving pola+BR will need to be cautioned about the increased risk of peripheral neuropathy.

The most frequently reported adverse events (>10%) are shown in the table below.

Table 4.15: Most frequently reported adverse events (>10%)

n, (%)	Phase Ib	Phase II		Phase Ib/II
	Pola+BR n=6	Pola+BR n=39	BR n=39	Pola+BR n=45
Total number of patients with at least one AE:	6 (100)	39 (100)	38 (97.4)	45 (100)
Blood and Lymphatic System Disorders				
Neutropenia	0	21 (53.8)	15 (38.5)	21 (46.7)
Anaemia	0	21 (53.8)	10 (25.6)	21 (46.7)
Thrombocytopenia	2 (33.3)	19 (48.7)	11 (28.2)	21 (46.7)
Febrile neutropenia	1 (16.7)	4 (10.3)	5 (12.8)	5 (11.1)
Leukopenia	0	5 (12.8)	5 (12.8)	5 (11.1)
Lymphopenia	0	5 (12.8)	0	5 (11.1)
Pancytopenia	1 (16.7)	2 (5.1)	0	3 (6.7)
Gastrointestinal Disorders				
Diarrhoea	2 (33.3)	15 (38.5)	11 (28.2)	17 (37.8)
Nausea	3 (50.0)	12 (30.8)	16 (41.0)	15 (33.3)
Constipation	1 (16.7)	7 (17.9)	8 (20.5)	8 (17.8)
Vomiting	1 (16.7)	7 (17.9)	3 (7.7)	8 (17.8)
Abdominal pain	1 (16.7)	4 (10.3)	4 (10.3)	5 (11.1)
Abdominal pain upper	0	5 (12.8)	2 (5.1)	5 (11.1)
General disorders and administration site conditions				
Fatigue	4 (66.7)	14 (35.9)	14 (35.9)	18 (40.0)
Pyrexia	2 (33.3)	13 (33.3)	9 (23.1)	15 (33.3)
Chills	1 (16.7)	4 (10.3)	3 (7.7)	5 (11.1)
Asthenia	1 (16.7)	4 (10.3)	6 (15.4)	5 (11.1)
Oedema, peripheral	0	2 (5.1)	3 (7.7)	2 (4.4)
Infections and infestations				
Pneumonia	2 (33.3)	5 (12.8)	4 (10.3)	7 (15.6)
Herpes zoster	1 (16.7)	1 (2.6)	2 (5.1)	2 (4.4)
Upper respiratory tract infection	2 (33.3)	2 (5.1)	1 (2.6)	4 (8.9)
Urinary tract infection	1 (16.7)	1 (2.6)	2 (5.1)	2 (4.4)
Metabolism and nutrition disorders				
Decreased appetite	2 (33.3)	10 (25.6)	8 (20.5)	12 (26.7)
Hypokalaemia	3 (50.0)	4 (10.3)	3 (7.7)	7 (15.6)
Hypoalbuminaemia	1 (16.7)	5 (12.8)	2 (5.1)	6 (13.3)
Hypocalcaemia	2 (33.3)	3 (7.7)	1 (2.6)	5 (11.1)
Hypomagnaesmia	2 (33.3)	1 (2.6)	4 (10.3)	3 (6.7)
Dehydration	2 (33.3)	2 (5.1)	0	4 (8.9)
Hypophosphataemia	1 (16.7)	2 (5.1)	1 (2.6)	3 (6.7)
Musculoskeletal and connective tissue disorders				
Back pain	0	2 (5.1)	4 (10.3)	2 (4.4)
Bone pain	0	0	0	0
Muscular weakness	0	2 (5.1)	1 (2.6)	2 (4.4)
Pain in extremity	0	2 (5.1)	2 (5.1)	2 (4.4)

n, (%)	Phase Ib	Phase II		Phase Ib/II
	Pola+BR n=6	Pola+BR n=39	BR n=39	Pola+BR n=45
Nervous system disorders				
Peripheral neuropathy	0	9 (23.1)	1 (2.6)	9 (20.0)
Dizziness	1 (16.7)	5 (12.8)	3 (7.7)	6 (13.3)
Peripheral sensory neuropathy	0	6 (15.4)	0	6 (13.3)
Headache	1 (16.7)	3 (7.7)	2 (5.1)	4 (8.9)
Paresthesia	0	2 (5.1)	0	2 (4.4)
Psychiatric disorders				
Anxiety	0	3 (7.7)	2 (5.1)	3 (6.7)
Respiratory, thoracic and mediastinal disorders				
Cough	1 (16.7)	6 (15.4)	8 (20.5)	7 (15.6)
Dyspnoea	0	3 (7.7)	2 (5.1)	3 (6.7)
Pleural effusion	1 (16.7)	2 (5.1)	4 (10.3)	3 (6.7)
Skin and subcutaneous disorders				
Pruritus	1 (16.7)	5 (12.8)	4 (10.3)	6 (13.3)
Rash	1 (16.7)	2 (5.1)	5 (12.8)	3 (6.7)
Vascular disorders				
Hypotension	0	3 (7.7)	2 (5.1)	3 (6.7)

Source: CS, Table 32, page 54-55.
Table only shows preferred terms reported in >10% of all patients with R/R DLBCL treated with Pola+BR (at least 5/45 patients in Phase Ib/II combined)
CCOD: 30 April 2018

The most frequently reported Grade 3-5 adverse events (>5%) are shown in Table 4.16 and deaths in Table 4.17.

Table 4.16: Most frequently reported Grade 3-5 adverse events (>5%)

n, (%)	Phase Ib	Phase II		Phase Ib/II
	Pola+BR n=6	Pola+BR n=39	BR n=39	Pola+BR n=45
Blood and Lymphatic System Disorders				
Neutropenia	0	18 (46.2)	13 (33.3)	18 (40.0)
Thrombocytopenia	1 (16.7)	16 (41.0)	9 (23.1)	17 (40.0)
Anaemia	0	11 (28.2)	7 (17.9)	11 (24.2)
Febrile neutropenia	1 (16.7)	4 (10.3)	5 (12.8)	5 (11.1)
Lymphopenia	0	5 (12.8)	0	5 (11.1)
Leukopenia	0	3 (7.7)	3 (7.7)	3 (6.7)
Gastrointestinal Disorders				
Diarrhoea	1 (16.7)	1 (2.6)	1 (2.6)	2 (4.4)
Nausea	0	0	0	0
General disorders and administration site conditions	1 (16.7)	1 (2.6)	1 (2.6)	2 (4.4)
Fatigue	0	0	0	0
Asthenia				

n, (%)	Phase Ib	Phase II		Phase Ib/II
	Pola+BR n=6	Pola+BR n=39	BR n=39	Pola+BR n=45
Infections and infestations				
Pneumonia	1 (16.7)	3 (7.7)*	1 (2.6)*	4 (8.9)
Herpes zoster	0	0	1 (2.6)	0
Metabolism and nutrition disorders				
Hypokalaemia	0	3 (7.7)	1 (2.6)	3 (6.7)
Hypophosphataemia	0	1 (2.6)	1 (2.6)	1 (2.2)
Respiratory, thoracic and mediastinal disorders Hypoxia	0	1 (2.6)	1 (2.6)	1 (2.2)
Skin and subcutaneous disorders				
Rash	0	0	3 (7.7)	0
Cardiac disorders				
Atrial fibrillation	0	0	1 (2.6)	0

Source: CS, page 56.
AE preferred terms reported in >5% of all patients with R/R DLBCL treated with Pola+BR (at least 3 patients out of total of 45 in Phase Ib/II combined)
*All AEs shown in this table of most frequently reported Grade 3-5 AEs (with onset from first dose of study drug through 90 days after last dose of study drug) were Grade 3 or 4 except for two fatal (Grade 5) events of pneumonia (one event each in Pola+BR arm and BR arm of randomised Phase II)
CCOD: 30 April 2018

Table 4.17: Summary of deaths in GO29365

n, (%)	Phase Ib	Phase II		Phase Ib/II
	Pola+BR n=6	Pola+BR n=40	BR n=40	Pola+BR n=46
Total number of deaths	2	23	28	25
Adverse events	0	9 (39.1)	11 (39.3)	9 (36.0)
Disease progression	2 (100)	14 (60.9)	17 (60.7)	16 (64.0)
No. of deaths ≤30 days of last dose	1	1	8	2
Adverse events	0	1(100)	3 (37.5)	1 (50.0)
Disease progression	1 (100)	0	5 (62.5)	1 (50.0)
No. of deaths >30 days of last dose	1	22	20	23
Adverse events	0	8 (36.4)	8 (40.0)	8 (34.8)
Disease progression	1(100)	14 (63.6)	12 (60.0)	15 (65.2)

Source: CS, Table 33, page 57.
CCOD: 30 April 2018

ERG comment: It can be observed that in the Pola+BR group that deaths due to adverse events and disease progression tend to occur ≥30 days after the last dose of treatment.

4.2.7 Ongoing studies

The main study in the CS, GO29365, is ongoing. As stated earlier in the report, the company provided data from a [redacted] data cut which gave a median follow up of [redacted]. These data have been included in the ERG's report.

The CS stated that '*Two cohorts were added to confirm the efficacy, safety and pharmacokinetics of the new lyophilised formulation of pola in combination with BR (Arm G [N=42]), w and Arm H [N=60])* [redacted]' [14]

The company did not mention any further ongoing studies.

ERG comment: In the absence of full evidence, the committee will need to decide if it is satisfied that the lyophilised formulation of pola will have similar efficacy and safety to the liquid formulation. See Section 3.2 for a fuller discussion of this issue.

4.3 Critique of trials identified and included in the indirect comparison and/or multiple treatment comparison

Not applicable.

4.4 Critique of the indirect comparison and/or multiple treatment comparison

Not applicable.

4.5 Additional work on clinical effectiveness undertaken by the ERG

No additional work was undertaken by the ERG.

4.6 Conclusions of the clinical effectiveness section

The company conducted a systematic review to identify evidence relevant to this appraisal. They considered 16 studies for inclusion (four RCTs, 12 observational studies). The ERG examined the four RCTs identified and agreed that a network could not be constructed to inform an indirect comparison between Pola+BR and other relevant treatments. Equally, in examination of the observational studies a match-adjusted comparison did not appear to be appropriate given the differences identified by the company in populations and line of treatment across the studies.

One study was mentioned in the CS as relevant to the technology being appraised, a Phase Ib/II, multicentre, open-label trial (GO29365) of polatuzumab in combination with BR in patients with R/R DLBCL, and polatuzumab in combination with bendamustine and obinutuzumab (BG) in patients with R/R follicular lymphoma. The data from this trial do seem to be consistent with the scope in term of population, intervention, comparator and outcomes.[14, 26] However, the ERG had a number of concerns detailed below.

The company considered the following patients to be eligible for Pola+BR:

- R/R patients who are clear non-candidates for transplant (unfit for intensive therapy based on physician assessment), either as second-line treatment or as a third-line treatment and beyond for patients who have relapsed following or are refractory to their last-line of therapy
- R/R patients who would be candidates for transplant but fail to respond to salvage therapy (and are therefore transplant ineligible)
- R/R patients who receive salvage therapy and ASCT but subsequently relapse

However patient numbers in the main trial were too small to provide meaningful subgroup results by type of patient or line of therapy. The committee will need to decide if overall results are equally relevant to all groups and lines of therapy.

Although the NICE scope specifies that the population is those for whom hematopoietic stem cell transplant is not suitable, 16 of the patients in the trial had received prior ASCT and as seen above the company did consider this group to be relevant to the decision problem. The company did provide some results excluding those patients in response to clarification.[2] Since it is not clear to the ERG if patients who have undergone ASCT (and become ineligible because of that) are part of the population eligible for Pola+BR in clinical practice, it is also unclear which results are most appropriate. However, removal of those 16 patients only seems to improve outcomes.

The ERG also would highlight some doubt as to the suitability of the intervention, at least in its lyophilised formulation. In the absence of full evidence (relevant arms with this formulation are ongoing), the committee will need to decide if it is satisfied that the lyophilised formulation of pola will have similar efficacy and safety to the liquid formulation.

Whilst the comparator in the GO29365 trial is consistent with the scope, it seems likely that it is not the only suitable one, R-GemOx also being likely to be increasingly used in clinical practice. In the absence of direct evidence, it is not clear if R-GemOx can be assumed to have equal efficacy and safety outcomes to BR.

The main trial, GO29365, was randomised and was well conducted. It was, however, open label. Both patients and healthcare professionals involved in their care were aware of treatment allocation. The ERG considers the independent review committee outcome results to be more appropriate and has highlighted these in the report. Although the trial was multinational, it was relatively small (40 patients were randomised to Pola+BR) so the evidence base on which results are based is limited. Three patients were included from the UK. The company was asked to justify the applicability of the trial to UK clinical practice. They stated that the baseline characteristics of the population of G029365 were similar to a UK study of pixantrone in R/R DLBCL patients.[1] The company also obtained advice from clinical experts who '*confirmed that the baseline characteristics of patients enrolled in GO29365 are reflective of the population seen in UK clinical practice and corroborates the comparison to the retrospective analysis*'[2] The ERG considered this reasonable but noted that non-white participants were underrepresented and that most patients had ECOG status of 0 or 1.

Pola+BR showed superior results to BR in outcomes relevant to this appraisal. After [redacted] median follow up months there was an estimated increase in median PFS of about [redacted] and an increase in median OS of [redacted] for patients treated with Pola+BR compared to patients treated with BR. Given the limited life expectancy of patients with relapsed or refractory DLBCL, the intervention does meet end-of-life criteria specified by NICE. Adverse events were similar although there appeared to be more modification of study drugs in the Pola+BR group in the trial. Peripheral neuropathy was more frequently reported with Pola+BR. As yet no information is available on long-term 'cure' rates and longer-term rarer adverse events. The trial is ongoing.

5. COST-EFFECTIVENESS

5.1 ERG comment on company's review of cost effectiveness evidence

5.1.1 Searches performed for cost effectiveness section

The following paragraphs contain summaries and critiques of all searches related to cost effectiveness, HRQoL and cost and healthcare resource identification presented in the company submission.

Appendix G of the CS details systematic searches of the literature used to identify cost effectiveness studies. Appendix H of the CS details systematic searches of the literature used to identify HRQoL studies. Appendix I of the CS details systematic searches of the literature used to identify cost and healthcare resource identification, measurement and valuation studies.[14]

Database searches for cost effectiveness and HRQoL were undertaken on 4 September 2018 and those for cost and healthcare resource identification, measurement and valuation took place on 19 November 2018. A summary of the sources searched is provided in Table 5.1 and Table 5.2 below.

Table 5.1: Data sources for the cost effectiveness and HRQoL systematic reviews

Search strategy element	Resource	Host/source	Date range	Date searched
Electronic databases	Medline	OVID	1946-Present	4 Sept 2018
	Medline Epub Ahead of Print, In-Process & Other Non-Indexed Citations		Not provided	
	Medline Daily			
	Embase		1974- Present	4 Sept 2018
	HTA Database	OVID	Not provided	4 Sept 2018
	NHS EED		Not provided	
	Econlit	OVID	1961-present	4 Sept 2018
Conference proceedings	EHA	Not reported	2015-2018	8/9 October 2018
	ICML			
	ASH			
	ASCO			
	ESMO			
	ISPOR			
	HTAi			
	SMDM			
HTA Agencies	NICE, SMC, AWMSG, PBAC, CADTH, INESSS, HAS	Not reported	2015-2018	8/9 October 2018 Updated search conducted list sent with clarification response
Additional resources	CEA Registry, RePEc,	Websites links provided		8/9 October 2018

Search strategy element	Resource	Host/source	Date range	Date searched
	INAHTA, NIHR HTA database, CRD databases, ScHARRHUD, Latin American and Caribbean Health Sciences Literature			
Bibliographies of all included studies and relevant SLRs were manually searched to identify additional primary studies.				
Source: Appendices G and H of the CS.[14] Abbreviations: ASCO = American Society of Clinical Oncology; ASH = American Society of Hematology; AWMSG = All Wales Medicines Strategy Group; CADTH = Canadian Agency for Drugs and Technologies in Health; CRD = Centre for Reviews and Dissemination; EHA = European Hematology Association; ESMO = European Society for Medical Oncology; HAS = Haute Autorite de Sante; HTA Database = Health Technology Assessment Database; HTAi = Health Technology Assessment International; ICML = International Conference on Malignancy Lymphoma; INAHTA = International Network of Agencies for Health Technology Assessment; INESSS = Institut National D'excellence en services sociaux; ISPOR= International Society for Pharmacoeconomics and Outcomes Research; NHS EED = NHS Economic Evaluation Database; NICE = National Institute for Health and Care Excellence; NIHR = National Institute for Health Research; PBAC = Pharmaceutical Benefits Advisory Committee; RePEc = Research Papers in Economics; ScHARRHUD = School of Health and Related Research Health Utilities Database; SMC = Scottish Medicine Consortium; SMDM = Society for Medical Decision Making.				

Table 5.2: Data sources for the cost and healthcare resource identification, measurement and valuation

Search strategy element	Resource	Host/source	Date range	Date searched
Electronic databases	Medline	OVID	1946-Nov 16 2018	19 November 2018
	Medline Epub Ahead of Print, In-Process & Other Non-Indexed Citations		Up to Nov 16 2018	
	Medline Daily			
	Embase		1974- 16 Nov 2018	19 November 2018
	HTA Database	OVID	CRD York	19 November 2018
	NHS EED		CRD York	
	Econlit	EBSCO	1866-Nov 2018	19 November 2018
Conference proceedings	ESMO	Website links provided	2016-2018	Searched between 21 Nov/4 Dec 2018
	ASCO			
	EHA			
	ASH			
	ICML			

Search strategy element	Resource	Host/source	Date range	Date searched
	ISPOR			
	HTAi			
	SMDM			
HTA Agencies	NICE	NICE website	No date provided	29 Nov 2018
Bibliographies of all included studies and relevant SLRs were manually searched to identify additional primary studies.				
Source: Appendix I of the CS.[14] Abbreviations: ASCO = American Society of Clinical Oncology; ASH = American Society of Hematology; EHA = European Hematology Association; ESMO = European Society for Medical Oncology; HTA Database = Health Technology Assessment Database; HTAi = Health Technology Assessment International; ICML = International Conference on Malignancy Lymphoma; ISPOR= International Society for Pharmacoeconomics and Outcomes Research; NHS EED = NHS Economic Evaluation Database; NICE = National Institute for Health and Care Excellence SMDM = Society for Medical Decision Making.				

ERG comment: The ERG considers the database searches and methodology reported in the CS to support the systematic review of cost effectiveness data, HRQoL and resource use on the whole to be comprehensive, transparent, reproducible and fit for purpose. There were a few minor reporting issues as follows:

- Date spans for NHS EED and HTA databases were not reported.
- The search strategy for Econlit was not provided for the cost effectiveness search.
- Additional economics terms were included in the strategies designed to find economic studies and HRQoL studies in NHS EED and the HTA database. These are already filtered sources and therefore the ERG considers the use of such additional terms redundant since it could impose unnecessary restrictions on the search in these databases.
- The cost effectiveness and HRQoL searches utilised study design filters and terms from previous NICE HTA submissions, although references were provided for the filters used.
- A broad range of additional sources were 'hand' searched, the sources and terms used were reported in detail for the resource use strategies in Appendix I (i.e. website addresses and terms used to search them), but not reported for the searches in Appendix G or H.

5.1.2 Inclusion/exclusion criteria

The predefined eligibility criteria for the cost effectiveness, HRQoL and cost/resource use SLRs are detailed in Table 10 (Appendix G), Table 18 (Appendix H) and Table 28 (Appendix I) of the CS respectively.[14] The inclusion/exclusion criteria were based on the PICOS criteria, to identify the population and disease, interventions, comparators, outcomes, and study designs of interest, as well as publication types, publication dates and language. Non-English language papers without an English abstract were excluded for all three SLRs, except in the case of the cost/resource use SLR where, if the full text was non-English, but the abstract contained enough data to be eligible in its own right, this could be included. There were no exclusions based on the geographical setting of studies in the cost effectiveness and HRQoL SLRs. However, the cost/resource use SLR excluded studies set outside of the UK or, in the case of pooled data, where UK data was not presented separately.

The title-abstract and full-text screening were conducted by two independent reviewers. For studies meeting the eligibility criteria after the second (full text) screening stage, data were extracted by a single

reviewer and 20% of data elements were verified by a second independent reviewer, with disputes referred to a third reviewer if necessary.

ERG comment: The exclusion of non-UK settings in the cost/resource use SLR is very restrictive and could have excluded useful evidence. The SLR could have identified costs and resource use evidence for this population from other countries and converted costs to UK costs using standard and accepted techniques.

5.1.3 Identified studies

Cost effectiveness SLR

In total, 243 papers were identified from electronic database searches for the cost effectiveness SLR. Upon the removal of duplicate papers, 227 records were reviewed at the title/abstract review stage. A total of 36 were deemed to be potentially relevant and were reviewed in full; of these, 15 were excluded. Hand searching yielded an additional three publications. This resulted in a total of 24 publications included in the SLR of economic evaluations. Out of these, five studies reporting data for relapsed and refractory disease were extracted. The strategy and corresponding in- and exclusions are presented schematically in the PRISMA flow diagram in Figure 5 from Appendix G of the CS.

The review identified five relevant studies which reported data for patients with R/R DLBCL. These studies are considered most relevant for the decision problem by NICE and are discussed further. A summary of the five studies is provided in Table 5.3 below.

Table 5.3: Summary of included studies in the economic evaluations SLR

Study name Country Study design	Patient population	Interventions and comparators	Model settings	Model summary	QALYs (Interventions, comparator)	Costs (currency) (Intervention, comparator)	ICER (per QALY gained)
Kymes 2012 [32] USA	R/R DLBCL patients undergoing ASCT at Washington University N=20 Mean age (SD): 56.5 (11.6) years	G-CSF with plerixafor G-CSF + Placebo	Perspective: Societal perspective Time horizon: Lifetime Cycle length: 1 year Discounting: 3% (cost and benefits)	Markov model using a microsimulation approach. The model was made up of 8 health states: 1st apheresis 2nd apheresis 3rd apheresis 4th apheresis Rescue Transplant Recurrence Death	**QALYs:** G-CSF alone: 5.05 Plerixafor and G-CSF: 6.80 **Incremental QALYs:** Plerixafor plus G-CSF vs G-CSF alone: 1.75	**Total cost:** G-CSF alone: $67,730 Plerixafor and G-CSF: $93,180 **Incremental cost:** Plerixafor plus G-CSF vs G-CSF alone: $25,450	**ICER (per QALY gained):** Plerixafor and G-CSF vs G-CSF alone: $14,574
NICE TA306 UK [13]	Adults with relapsed DLBCL after 2 or more chemotherapy regimens, including at least 1 standard anthracycline-containing regimen with a response that had lasted at least 24 weeks N=104	Pixantrone Physician's choice	Perspective: Payer perspective (NHS) Time horizon: Lifetime (23 years) Cycle length: 1 week Discounting: 3.5% (cost and benefits)	Semi-Markov model that contained 4 health states: Stable/PFS, on 3rd or 4th line treatment Stable/PFS, discontinued 3rd or 4th line treatment Progressive/ relapsed disease Death	**QALYs:** Pixantrone: 1.25 Physician choice: 0.83 **Incremental QALYs:** Pixantrone vs physician choice: 0.42	**Total cost:** Pixantrone: £62,795 Physician choice: £52,953 **Incremental cost:** Pixantrone vs physician choice: £9,841	**ICER (per QALY gained):** Pixantrone vs physician choice: £23,699

Study name Country Study design	Patient population	Interventions and comparators	Model settings	Model summary	QALYs (Interventions, comparator)	Costs (currency) (Intervention, comparator)	ICER (per QALY gained)
NICE ID1115/TA559 UK [5]	Adults with R/R DLBCL who either failed auto SCT or were ineligible for or did not consent to autologous SCT	Axicabtagene ciloleucel (Axi-cel) BSC	Perspective: Payer perspective (NHS) Time horizon: Lifetime (44 years) Cycle length: 1 month Discounting: 3.5% (cost and benefits)	De novo model with 3 health states: Pre-progression Post progression Death	**QALYs:** Axi-cel vs BSC: 4.30	**Incremental cost:** Axi-cel vs BSC: £289,571	**ICER (Cost/QALY):** Axi-cel vs BSC: £67,323
NICE ID1166/TA567 UK [3]	Adults with R/R DLBCL who either failed auto ASCT or were ineligible for or did not consent to autologous ASCT N=111	Tisagenlecleucel Pixantrone monotherapy R-GEMOX R-GDP	Perspective: Payer perspective (NHS) Time horizon: Lifetime (46 years) Cycle length: 1 month Discounting: 3.5% (cost and benefits)	A de novo cost-utility model with 3 health states: Progression free Progressed disease Death	NR (all values in submission were secured)	NR (all values in submission were secured)	**ICER (Cost/QALY):** Tisagenlecleucel vs R-GemOx: £47,684 Tisagenlecleucel vs R-GDP: £47,526 Tisagenlecleucel vs Pixantrone monotherapy: £44,648
Wang 2017 UK [33]	Patients newly diagnosed with DLBCL in the UK's population-based Haematological Malignancy Research Network Second-line treatment: N=577 Third-line treatment: N=106	Not specific to particular treatment, overall treatment pathway costs (including first-line, second-line plus ASCT, without ASCT, and untreated patients)	Perspective: NHS and social service perspective Time horizon: Lifetime Cycle length: NR Discounting: 3.5% (cost and benefits)	Discrete event based micro-simulation model The model structure was based on patient treatment pathways determined from empirical HMRN data, expert opinion and clinical guidelines	**Life days, mean cost (95% CI):** Second-line with ASCT: 6,837 (6,797–6,877) Second-line without ASCT: 2,628 (2,610–2,646)	**Mean cost (95% CI):** Second-line treatment: £23,449 (£23,365–£23,534) With ASCT: £56,442 (£56,409–£56,474) Without ASCT: £9,956 (£9,932–£9,981) End-of-life care: For untreated patients: £2,930 (£2,918–2,942) For treated patients: £4,767 (£4,755–£4,780)	NR
Source: Table 11 in Appendix G of the CS.[14]							

Study name Country Study design	Patient population	Interventions and comparators	Model settings	Model summary	QALYs (Interventions, comparator)	Costs (currency) (Intervention, comparator)	ICER (per QALY gained)
Abbreviations: ASCT = autologous stem cell transplantation; BSC = best supportive care; CI = confidence interval; CUA = cost-utility analysis; DLBCL = diffuse large B cell lymphoma; G-CSF = granulocyte colony-stimulating factor; HMRN = Haematological Malignancy Research Network; ICER = incremental cost-effectiveness ratio; NHS = National Health Service; NR = not reported; PMBCL = primary mediastinal B-cell lymphoma; QALY =quality-adjusted life year; R-GDP = rituximab, gemcitabine, cisplatin and dexamethasone; R-GEMOX = rituximab, gemcitabine and oxaliplatin; RGCVP = rituximab, gemcitabine, cyclophosphamide, vincristine and prednisolone; R/R = relapsed/refractory; SCT = stem cell transplant; SD = standard deviation; UK = United Kingdom; USA = United States of America.							

Quality assessment of the five economic evaluations extracted was performed using the 36-item checklist in Section 5.1.3 of the NICE Single Technology Appraisal (STA) Specification for manufacturer/sponsor submission of evidence (January 2015), adapted from Drummond and Jefferson, 1996.[34] The results are presented in Table 14 in Appendix G of the CS.

The five studies identified in the SLR of cost effectiveness studies were not presented in the main body as they did not evaluate polatuzumab vedotin in combination with bendamustine and rituximab or any of the comparators in the NICE scope as the primary intervention under consideration.

HRQoL SLR

The electronic database searches for the HRQoL SLR identified 258 unique records to be screened at title and abstract level, of which 23 were deemed potentially relevant and read at full text. Six of these were included and an additional three studies were identified by hand searching. Of these nine publications, seven reported utility values for R/R DLBCL and were extracted. A summary of the seven included studies is shown in Table 19 in Appendix H of the CS and a summary of each, with regards to their relevance to the NICE reference case, is provided in Table 20 in the CS.[14]

Cost/Resource use SLR

Two hundred and thirty-five unique records were identified from electronic database searching and screened at the title and abstract stage, of which 18 records were reviewed at full test. Only one study was identified which met the inclusion criteria as it included patients with R/R DLBCL and presented data relevant to the UK NHS and PSS. The company did not identify any additional studies that met the eligibility criteria through manual searching of relevant congresses and NICE Technology Appraisals or through hand searching the bibliographies of relevant SLRs, meta-analyses and economic evaluations. Details and results of the included study are displayed in Table 29 in Appendix I of the CS.

ERG comment: The review was generally well reported and identified a range of cost effectiveness, HRQoL, cost/resource use evidence relevant to the indication and potentially useful for the cost effectiveness analysis. However, none of the identified studies were investigating pola, specifically. Therefore, the identified evidence did not negate the necessity to develop a de novo economic model.

5.2 Summary and critique of company's submitted economic evaluation by the ERG

Table 5.4: Summary of the company submission economic evaluation

	Approach	Source/Justification in the company submission	Signpost (location in ERG report)
Model	Three state partitioned survival model. The states are progression-free survival, progressed disease and death.	The approach is in line with NICE Decision Support Unit (DSU) guidance[35] and consistent with previous appraisals conducted in this disease setting (TA306, TA559, TA567).[13],[5],[3] The modelling of OS and PFS is based on study-observed events, which should accurately reflect disease progression and the long-term expected survival profile of patients treated with Pola+BR.	Section 5.2.2
States and events	Patients start in the progression-free survival state, where they remain until progression or death. Upon progression, patients either remain in the progressed disease state, or they die.	Consistent with previous appraisals in oncology.	Section 5.2.2
Comparators	Base-case comparator is a combination of bendamustine and rituximab (BR). In a scenario analysis R-GemOx was included as an additional comparator, assuming equivalent efficacy with BR.	BR was the comparator in the randomised phase II GO29365 trial, thus enabling a robust direct comparison with Pola+BR. R-GemOx was the only additional comparator from the NICE scope, for which the company identified efficacy evidence. The company stated that no connected network was available for indirect comparison. Due to the differences between study populations, the company stated that robust unanchored comparison was not possible. Therefore, equal efficacy with BR was assumed.	Section 5.2.4
Natural history	Based on partitioned survival model. Transitions between	PFS and OS estimates were modelled independently, with the proportion of progressed patients at each	Section 2.1 and 5.2.2

	Approach	Source/Justification in the company submission	Signpost (location in ERG report)
	states were based on GO29365 trial, also it is assumed that after 2 years in the PFS state, patients are assumed as cured and general population mortality, utility and cost values are assigned.	cycle calculated as the difference between the OS and the PFS curves. The cure assumption was justified by the company according to consultation with clinical experts and previous literature.	
Treatment effectiveness	Treatment effectiveness (in terms of OS and PFS) of Pola+BR and BR treatments are based on the extrapolation curves fitted to the OS and PFS KM from the GO29365 study. In terms of TTOT, the survival probabilities that were calculated from the KM curves are used for Pola+BR and BR treatment arms. For the R-GemOx treatment, same effectiveness as BR treatment was assumed.	A de novo cure-mixture modelling method was used in the extrapolation of PFS and OS from the GO29365 study. The cure assumption was justified by the company according to the clinical experts and literature.	Section 5.2.6
Adverse events	The effects of AEs are captured by applying a one-off cost and a utility decrement over a stated time period based on data from the clinical trial, previous NICE technology appraisals, and other related literature.	For Pola+BR and BR, while calculating the type and frequency of the treatment-related AEs, the grade 3-5 AE data from the GO29365 study, using the clinical cut-off date of April 2018, were used. The type and frequency of AEs experienced with R-GemOx treatment were derived from Grade 3–5 AEs affecting >5% of patients in a Phase II study on the treatment of R/R DLBCL patients with R-GemOx. [9] Duration of the AEs were sourced primarily from GO29365 and also TA306 [13]	Section 5.2.7
Health related QoL	HRQoL data was not collected in GO29365. The company conducted a systematic review to identify utility values for R/R DLBCL patients in the progression-free and progressed disease health states as well as	Base-case utility values were taken from the previous NICE technology appraisal TA559, which used HRQoL data collected in the ZUMA-1 trial, investigating the efficacy of axicabtagene in patients	Section 5.2.8

	Approach	Source/Justification in the company submission	Signpost (location in ERG report)
	utility decrements associated with AEs experienced in the GO29365 trial.	with mixed histology lymphoma (including DLBCL).[5]	
Resource utilisation and costs	The economic analysis was performed from the NHS and PSS perspective. The following state-specific costs were included: • drug acquisition and administration • treatment-related AEs • routine supportive care (professional and social services, health care professionals and hospital resource use, treatment follow-up; for a maximum of two years) • subsequent treatment costs.	Healthcare unit costs were obtained from the National Audit Office 2008[10], PSSRU 2018[11], and NHS reference costs. [12] The frequency of the healthcare resource use is primarily sourced from TA306.[13] Drug costs were taken from the BNF and eMIT databases. The dose information was derived from the GO29365 trial, whereas for the R-GemOx, it is obtained from Mounier et al.[9] Administration costs and adverse event were mostly obtained from NHS reference costs and percentage of the treatments used in the subsequent treatments were from the GO29365 trial and clinical expert opinion.	Section 5.2.9
Discount rates	Cost and health outcomes discounted at 3.5%	As per NICE reference case	Section 5.2.5
Sensitivity analysis	Probabilistic, deterministic one-way sensitivity analysis and scenario analyses conducted	As per NICE reference case	Section 6.2.1

Abbreviations: AE = adverse event; BNF = British National Formulary; BR = bendamustine + rituximab; DLBCL = diffuse large B cell lymphoma; eMIT = electronic Market Information Tool; HRQoL = health-related quality of life; KM = Kaplan-Meier; NHS = National Health Service; NICE = National Institute for Health and Care Excellence; OS = overall survival; PFS = progression-free survival; Pola+BR = polatuzumab + bendamustine + rituximab; PSS = personal social services; PSSRU = Personal Social Services Research Unit; R-GemOx = rituximab + gemcitabine + oxaliplatin; R/R = relapsed/refractory; TTOT = time to off treatment.

5.2.1 NICE reference case checklist (TABLE ONLY)

Table 5.5: NICE reference case checklist

Element of health technology assessment	Reference case	ERG comment on company's submission
Perspective on outcomes	All direct health effects, whether for patients or, when relevant, carers.	Direct health effects for patients included.
Perspective on costs	NHS and PSS.	NHS and PSS perspective taken.
Type of economic evaluation	Cost–utility analysis with fully incremental analysis.	Cost-utility analysis with fully incremental analysis undertaken.
Time horizon	Long enough to reflect all important differences in costs or outcomes between the technologies being compared.	The model time horizon of 45 years is appropriate for a lifetime horizon as the average age of patients at the start of treatment was 69 years.
Synthesis of evidence on health effects	Based on systematic review.	Systematic review conducted to identify evidence on health effects.
Measuring and valuing health effects	Health effects should be expressed in QALYs. The EQ-5D is the preferred measure of health-related quality of life in adults.	Health effects expressed in QALYs. HRQoL measured using the EQ-5D-5L.
Source of data for measurement of health-related quality of life	Reported directly by patients and/or carers.	HRQoL reported by R/R DLBCL patients in a previous trial (treatments differ).
Source of preference data for valuation of changes in health-related quality of life	Representative sample of the UK population.	Representative sample of UK population. Van Hout mapping algorithm used to translate EQ-5D-5L utility values to EQ-5D-3L values.[36]
Equity considerations	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit.	No equity issues have been identified.
Evidence on resource use and costs	Costs should relate to NHS and PSS resources and should be valued using the prices relevant to the NHS and PSS.	Costs were sourced from NHS Reference Costs 2017–18, PSSRU 2018, and the BNF and eMIT.
Discounting	The same annual rate for both costs and health effects (currently 3.5%).	Costs and health effects are discounted at 3.5%.

Abbreviations: BNF = British National Formulary; eMIT = electronic Market Information Tool; EQ-5D-3/5L = EuroQol, 5 dimensions, 3/5 levels; NHS = National Health Service; PSS = personal social services; PSSRU = Personal Social Services Research Unit; QALYs = quality-adjusted life years;

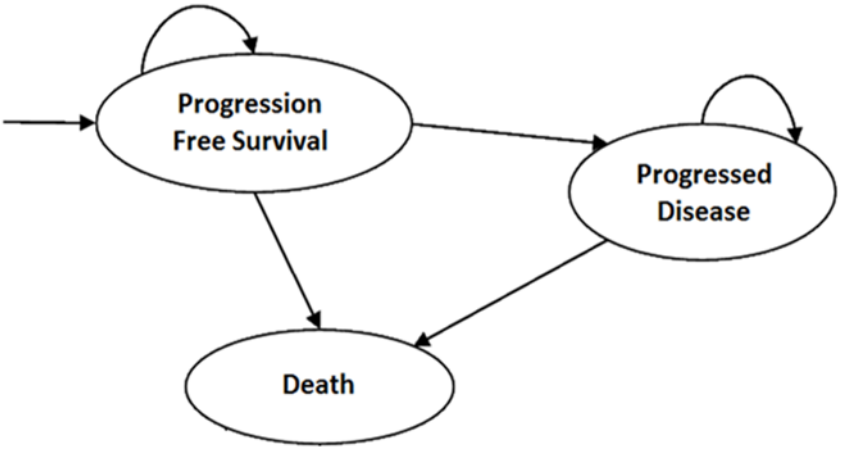
5.2.2 Model structure

The company model, developed in Excel, is a partitioned survival model containing three states, as shown in Figure 5.1. All patients start in the PFS state. They remain there until progression or death. At

progression, patients enter the progressed disease (PD) state. Patients who enter the progressed disease state, remain there until their death. Transitions between health states are determined by PFS and OS survival curves calculated from the GO29365 trial data, with the proportion of patients in the PD health state calculated as the difference between OS and PFS at any given time point. The proportion of the patients that are on treatment is informed by the TTOT curves.

The company employed a cure mixture modelling approach, where it is implicitly assumed that a proportion of patients entered long-term remission (PFS) and are therefore likely to experience long-term survival similar to the general population. In line with this assumption, for the patients who are still in the PFS state after two years, it is assumed that there is no healthcare resource utilisation and also age/gender adjusted general population utilities are assigned to them.

Figure 5.1: Company model structure



Source: Figure 9 in CS.[34]

The model has a cycle length of one week. Half-cycle correction is applied to account for the fact that events can happen at any time during the cycle. Costs and utilities are applied to each health state, weighted according to half-cycle corrected state occupancy, to calculate per-cycle costs and QALYs.

ERG comment: The modelling approach considered by the company is in line with previous NICE technology appraisals in R/R DLBCL (TA306[13], TA567[3] and TA559[5]). Among these three appraisals, only in TA567 and TA559 (both CAR-T therapies), cure mixture modelling approach was followed. The ERG has concerns about the cure assumption in this CS, but it will be discussed further in Section 5.2.6.

5.2.3 Population

The company stated that the population considered in the economic evaluation is patients with R/R DLBCL, who are ineligible for SCT.

The baseline characteristics of the patients used in the model are given in Table 5.6 below:

Table 5.6: Baseline characteristics of the patients used in the model

Patient characteristics	
Starting age, years	69.0
Male, %	50.0
Mean weight, kg	74.86
Mean BSA, m^2	1.85
Source: Based on Table 59 from the CS.[14] Abbreviation: BSA = body surface area.	

ERG comment: Even though the population considered is R/R DLBCL patients who are ineligible for SCT, in section B.3.5.5 of the CS it was stated that two patients received SCT after progression from their assigned first-line treatment. It is not clear to the ERG how an SCT-ineligible patient at baseline can become SCT-eligible at a later point in the disease course.

Most of the baseline population characteristics used in the model are based on the GO29365 trial. In contrast to the trial data, the percentage of males in the model is assumed to be equal to 50%, whereas the percentage of male patients was 66% in the trial. This deviation has a negligible impact on the cost effectiveness results, as it was being solely used for the background, non-cancer related mortality in the model. However, the ERG has corrected this for consistency.

5.2.4 Interventions and comparators

Intervention

The intervention considered in the model is polatuzumab vedotin in combination with bendamustine and rituximab (Pola+BR), given to patients every three weeks (i.e. one treatment cycle consists of three weeks) for a maximum number of six treatment cycles. The dosing for Pola+BR assumed in the model matches the dosing schedule implemented in GO29365 and the anticipated marketing authorisation. Doses for each component are as follows:

- Polatuzumab vedotin - 1.8 mg/kg intravenous infusion (IV) on day 1. The initial dose should be administered as a 90-minute infusion. If well tolerated, subsequent doses may be administered as a 30-minute infusion.
- Bendamustine - 90 mg/m^2 IV on days 1 and 2.
- Rituximab - 375 mg/m^2 IV on day 1.

No additional tests or investigations are required alongside the provision of Pola+BR.

Comparator

The company argued that there is no universally accepted standard of care for patients with R/R DLBCL who are ineligible for SCT. These patients are usually prescribed one of the available gemcitabine and/or platinum-based therapies, or BR according to clinician preference. The company stated that there is no strong evidence that one regimen is superior to another. The NICE scope listed a number of treatments used in NHS clinical practice including BR, R-GemOx, R-Gem, R-P-MitCEBO and (R-)DECC.[26] However the company only identified studies for R-GemOx in the clinical SLR. There was no connected network of randomised studies available to perform an indirect comparison between Pola+BR and R-GemOx. The company also argued that a robust unanchored comparison was infeasible "*due to significant or unknown differences in prognostic factors in the study populations for GO29365*

and captured R-GemOx studies, including proportion of refractory patients, prior rituximab exposure and number of prior lines of treatment"p.73.[14]

The base-case comparator chosen by the company is a combination of bendamustine and rituximab (BR). The company argue that this choice enabled a robust comparison with Pola+BR using data from the GO29365 trial. The choice was further justified by reference to clinical opinion that the range of available chemotherapy regimens for R/R DLBCL are considered equally effective. In a scenario analysis the company also included R-GemOx as an additional comparator, assuming equivalent efficacy to BR.

ERG comment: In the final scope, there are many comparators (i.e. R-Gem, R-P-MitCEBO and (R-)DECC) that were not included in the cost effectiveness analyses conducted by the company.[14]

Other than BR, only R-GemOx was included, assuming same effectiveness as BR. This assumption was based on a recent real-world evidence study using the US Veterans Health Association database which found no statistically significant difference in OS between patients with R/R DLBCL treated with BR and R-GemOx (i.e. median OS of 11 and 13 months, respectively).[37]

The ERG has concerns regarding the inclusion of only BR and R-GemOx as relevant treatment options for the SCT ineligible R/R DLBCL patients in the UK. Therefore, the ERG asked whether UK-specific studies were searched in the literature and whether any of the UK based databases, such as Haematological Malignancy Research Network (HMRN). were consulted. In their response to the ERG's clarification questions, the company mentioned that the clinical SLR had included single arm studies and the literature was pragmatically searched for additional published data. Additionally, the company stated that the question on published standard of care data sets was also asked to UK clinicians at an advisory board. However, no other UK published data were mentioned in addition to the clinical studies that were subsequently identified in the SLR. Since the meeting transcripts of the advisory board and the details of the pragmatic literature search approach were not provided in the reference pack, the ERG could not verify the claims by the company regarding the lack of UK specific data on the UK clinical practice for this population. Following the ERG's suggestion, [redacted]

The ERG also considers that the equal effectiveness assumption between the R-GemOx and the BR therapy was not sufficiently substantiated (comparable OS based on a database study from USA and clinical experts).[37] Therefore, the ERG finds the scenario analyses with R-GemOx comparator (having equal effectiveness as BR) as uninformative, and therefore this scenario analysis is not explored in Section 7.

5.2.5 Perspective, time horizon and discounting

The economic analyses were conducted from the perspective of the NHS and Personal Social Services (PSS). The model has a time horizon of 45 years, which is considered appropriate as a lifetime horizon given that the average age of patients at the start of treatment is 69 years. Costs and QALYs were discounted at 3.5% per annum according to the NICE method guidance.

5.2.6 Treatment effectiveness and extrapolation

5.2.6.1 Survival analysis

General approach

The primary source of clinical data for the Pola+BR and BR arms of the economic model is the GO29365 study. In the original CS, data from the October 2018 data cut point was used to inform the clinical parameters for PFS and OS. For treatment duration and treatment-related AE rates, the data from the clinical cut-off date of April 2018 were used, which is when all the patients had completed treatment with Pola+BR or BR.

PFS and OS results from GO29365 were extrapolated to the model lifetime time horizon. The company mentioned that the recommendations outlined in NICE DSU Technical Support Document (TSD) 14 [38] were followed to identify appropriate parametric survival models. For this purpose, the company claimed that the following steps were taken while deciding for the appropriate extrapolation choice for the OS and PFS to be used in the economic model:

- Visual inspection of the log-cumulative hazard plots, based on patient level data for the two arms of GO29365, to test for the plausibility of the proportional hazards assumption and to examine the hazard of progression or death in each arm over time
- 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 GO29365
- 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 and the expectations of clinical experts

For both PFS and OS, standard parametric survival models (exponential, Weibull, Gompertz, log-normal, generalised gamma and log-logistic for both joint and independent modelling) were explored. In addition, cure-mixture models were explored.

Cure-mixture modelling justification

In the CS, a discussion for the justification of the cure-mixture modelling was provided. The company used the following arguments for the justification of the use of the cure-mixture models:

- A study of the natural history of newly diagnosed DLBCL patients treated with immunochemotherapy that indicated that the survival of patients who did not experience a progression or death event after two years was equivalent to that of the age- and gender-matched general population [4].
- The clinical experts that the company consulted confirmed that patients who achieve two years PFS are at a very low risk of subsequent progression, and their risk of death can be assumed as similar to that of the age- and gender-matched general population. [28]
- The company considered the risk of relapse or death that was observed in the KM plots for PFS and OS for Pola+BR towards the end of follow-up as very low, which is indicative of a very low risk of relapse or death for patients who were still alive towards the end of follow-up.

- The company claimed that the precedent of cure-mixture modelling in NICE appraisals for R/R DLBCL was established in TA567 and TA559, where the respective committees accepted that patients who are able to demonstrate sustained remission are likely to experience long-term survival.

Cure-mixture modelling method

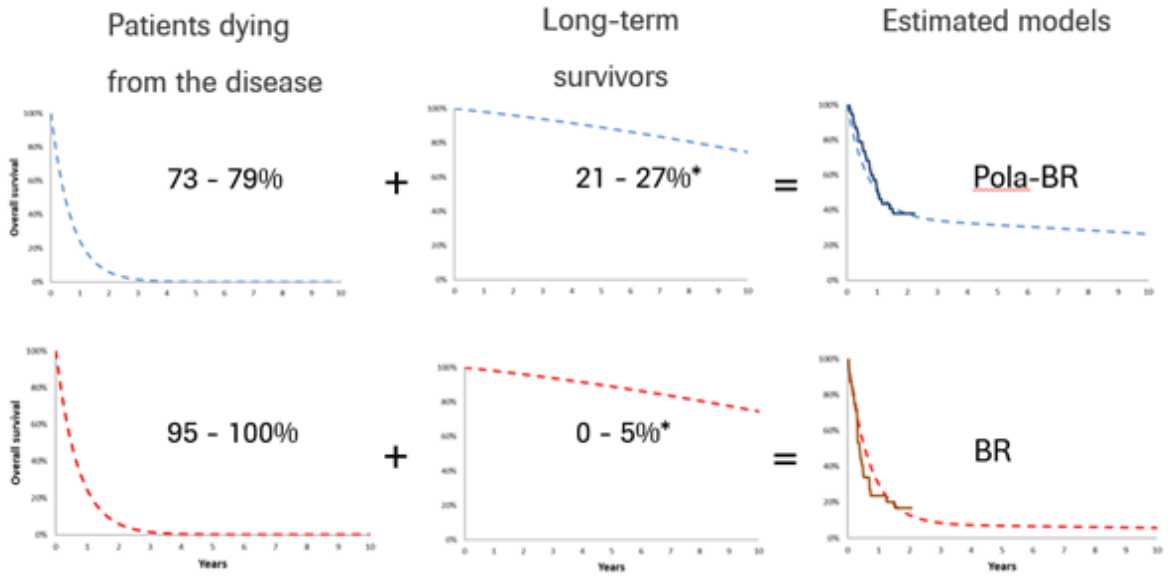
In the CS, the company did not use any of the standard available statistical packages (e.g. flexsurvcure in R) while fitting mixture cure models, but instead used code that was developed by the company in-house. In the CS, the mixture models were fitted according to the following steps:

- Classifying patients into either long-term survivor or not.

In the CS, it was reported that the classification was done by applying standard machine learning methods such as clustering using the expectation–maximisation (EM) algorithm. The purpose of the clustering is to create two clusters (long-term survivors and non-long-term survivors) based upon a logistic regression with a number of exploratory variables from the baseline characteristics such as age, sex, and country., to determine the probability that a patient becomes a long-term survivor or not.

- After the classification, long-term survivors are assumed to be free from disease-specific mortality whereas parametric survival curves are fitted to the survival data from non-long-term survivors.
- The weighted mixture of the long-term survivor and non-long-term survivors' survival data provide the survival extrapolation for the whole population (See Figure 5.2 for visualisation)

Figure 5.2: Example of the how the cure-mixture model estimates OS by combining estimates (illustration only)



Source: based on Figure 9 from the Appendix M from the company submission.[14]

ERG comment: The critique of the ERG on the general survival analysis approaches are listed under the subheadings below:

Exclusion of other flexible parametric models

The ERG considers that the company could have explored other survival modelling options in addition to cure mixture modelling (e.g. flexible parametric modelling using splines, landmark models based on response, cure non-mixture models or other mixture modelling methods than cure), however the company chose to explore only cure-mixture models when they considered that standard parametric models were not appropriate.

Upon the request from the ERG for a justification for excluding other flexible parametric models, the company stated that the spline models were originally dismissed as *"they may fit the observed data, but a better fit may not result in a more plausible extrapolation... Our opinion is that by using a spline, the extrapolation would be mainly based on the KM curve at the end of the follow up period with very few patients at risk and therefore be more uncertain and less robust and could change substantially with a small number of additional events. This is less the case for standard parametric functions or cure-mixture models. Furthermore, the use of cure-mixture models was justified by the natural history of the disease."*[2]

The ERG disagrees with the company and considers that the justification of the company for not using spline models (i.e. extrapolation would be mainly based on the KM curve at the end of the follow-up period) was in conflict with their own justification for using cure-mixture models, which indeed use the low number of deaths/progressions observed in the KM curve at the end of the follow-up period.

Upon the request of the ERG, the company provided the visual fit of a 3-knot spline model to the KM survival curves for Pola+BR and BR arms, in their response to the clarification letter.[2] Without providing the details of the spline modelling exercise followed (e.g. the distribution used, how the knots were determined etc.) the company concluded that spline models would not result in a more plausible long-term extrapolation and therefore they were not included in the economic model. The ERG considers that a conclusion on the implausibility of the spline models that is based only on a single example, and without providing further details, as questionable. Therefore, the ERG considers that other type of extrapolation methods should have been investigated next to the cure-mixture modelling.

Not using available standard codes for cure mixture modelling

The company used their in-house developed cure-mixture modelling code in R, instead of the standard packages available such as "flexsurv cure" package in R. The in-house codes were accessible on github. However, the explanation of the code provided by the company upon the ERG's request did not provide sufficient clarity. Therefore, the ERG could not verify the correctness and plausibility of the in-house code of the company.

From the description of the in-house code in the Appendix M of the CS, the ERG has concerns on the clustering algorithm (expectation maximisation) used by the company. First of all, the company stated that the clustering algorithm uses "age", "gender", "country" and "year of the trial" to determine the chances of an individual being a long-term survivor or not, separately for Pola+BR and BR arms. The ERG thinks that many other prognostic factors exist that could have been used while predicting the chances of "cure" for PFS and OS. Furthermore, the ERG has doubts if machine learning based algorithms (such as expectation maximisation) that were originally designed for applications that are characterised by the availability of big data, would be suitable for determining the cure probabilities based on a dataset that is limited to 80 patients. Also, it is unclear to the ERG how the individual cure probabilities are translated to the cure fractions used in the parametric extrapolations of the cure-mixture models.

Arguments used for the justification of the "cure" assumption by the company

The ERG would like to comment on the arguments provided by the company for the justification of the "cure" assumption. The other arguments, based on the particular PFS and OS data from the trial will be discussed in the following subsections.

The company referred to the long-term survival pattern observed in a study of the natural history of newly diagnosed DLBCL patients treated with immunochemotherapy.[4] The ERG is doubtful if the findings of this study would hold for the indicated population for Pola+BR, which is R/R DLBCL.

Secondly, the company claimed that the precedent of cure-mixture modelling in NICE appraisals for R/R DLBCL was established in TA567 and TA559, where the respective committees accepted that patients who are able to demonstrate sustained remission are likely to experience long-term survival. The ERG considers that the acceptance of cure-mixture modelling in previous appraisals does not provide a convincing argument, as each case should be handled separately. Furthermore, the ERG noted that these two appraisals were focusing on CAR-T type interventions, which are very different from the intervention considered in this appraisal.

5.2.6.2 Progression free survival

For the extrapolation of PFS in the model, the company has chosen the investigator-assessed PFS from the October 2018 data cut-off from the GO29365 trial. The company considered that the investigator-assessed PFS was more suitable for inclusion in the model, since providing a patient with the next line of treatment was often based on progression as measured by the investigator. Therefore, investigator-assessed data were considered as more consistent with the treatment pathway.

Assessment of the proportional hazards assumption

The log-cumulative hazard plots for the investigator assessed PFS from GO29365 was provided in Figure 11 of the CS.[14] Based on the approximately parallel lines, the company deemed the proportional hazards assumption to be plausible. Therefore, the company considered both independent and dependent (joint) models (in the latter, treatment received is the covariate), for the PFS extrapolation, using standard distributions (e.g. exponential, Weibull, lognormal, loglogistic, generalised gamma) to be plausible.

Assessment of the cure-mixture modelling

The company considered that the cure-mixture modelling for the PFS extrapolation is justifiable, because the company interpreted from the KM PFS curves and log cumulative hazard plots that the relapse rates after the 24 month time-point were very low, that the hazard of progression declines toward the end of the follow-up period, and that the cumulative incidence of the progression events (Figure 13 in the CS[14]) suggested that most of the events occurred within the first 12 months. Therefore, the company investigated independently fitted cure-mixture parametric models. In these models, it is assumed that a proportion of patients achieving long-term remission is a parameter that can be fitted from the observed GO29365 data via logistic regression. This 'cure fraction' of patients is assumed not to progress or be susceptible to cancer-related death.

Statistical fit of the data

The company provided the AIC and BIC goodness of fit results for the functions used to model PFS for Pola+BR and BR in GO29365, as well as the subjective qualitative impression of visual fit to the observed KM curve in Table 40 from the CS.[14]

The company did not include the Gompertz distribution in the extrapolation of the PFS curves, as the parameterisation for the Gompertz model did not converge for OS in both arms.

Among the standard models (dependently and independently fit), the AIC and BIC statistics indicated that all models had a similar statistical fit to the KM data in both arms. The top-ranking models (both arms) for both dependent and independently-fitted extrapolations were the log-normal, generalised gamma and log-logistic. Similarly, for the cure-mixture models, minimal variation was observed among the goodness of fit statistics. The best ranking models, in terms of AIC, were the generalised gamma and log-logistic for Pola+BR, and the log-normal, log-logistic and exponential for BR.

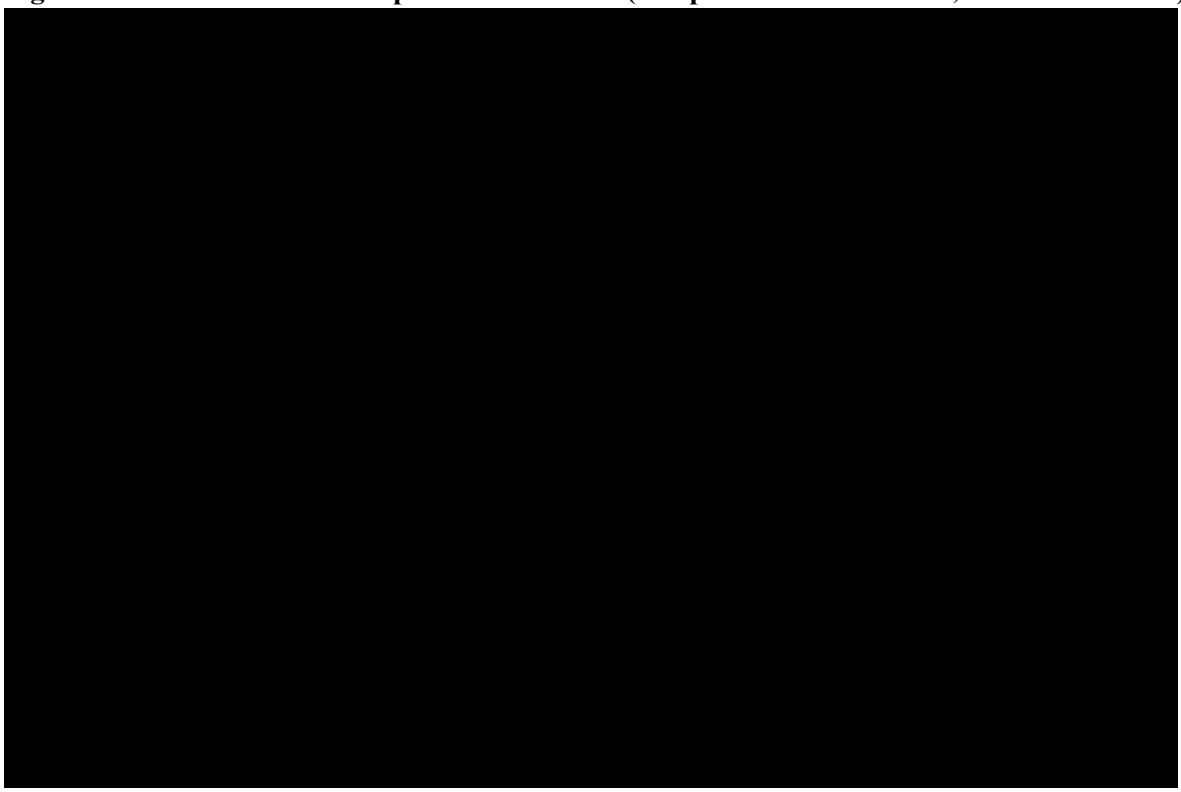
Investigation of the visual fit of the extrapolations

The visual fit investigation of the extrapolations were conducted separately for dependent, independent and cure-mixture models. The fitted dependent and independent standard parametric extrapolations, as well as the cure-mixture models, are presented in Figure 5.3, Figure 5.4 and Figure 5.5 below respectively.

Figure 5.3: PFS standard extrapolation functions (dependent fit, GO29365, Oct. 2018 cut-off)

Source: Figure 14 from the CS.[14]
The Gompertz extrapolation was not considered for either arm for PFS due failure of parameterisation for this function for OS; this extrapolation is therefore not presented.
Abbreviations: BR = bendamustine + rituximab; KM = Kaplan-Meier; Pola+BR = polatuzumab + bendamustine + rituximab.

Figure 5.4: PFS standard extrapolation functions (independent fit GO29365, Oct. 2018 cut-off)



Source: Figure 15 from the CS.[14]
The Gompertz extrapolation was not considered for either arm for PFS due failure of parameterisation for this function for OS; this extrapolation is therefore not presented.
Abbreviations: BR = bendamustine + rituximab; KM = Kaplan-Meier; Pola+BR = polatuzumab + bendamustine + rituximab.

Figure 5.5: PFS cure mixture model extrapolation functions (GO29365, October 2018 cut-off)

Source: Figure 16 from the CS.[14]
The Gompertz extrapolation was not considered for either arm for PFS due failure of parameterisation for this function for OS; this extrapolation is therefore not presented.
Abbreviations: BR = bendamustine + rituximab; KM = Kaplan-Meier; Pola+BR = polatuzumab + bendamustine + rituximab.

For the dependently modelled standard extrapolations (Figure 5.3), the company considered that the exponential and Weibull models appeared to overestimate PFS KM in both the Pola+BR and BR arms initially, and that those extrapolations did not capture the expected decline in progression rates at the end of the follow-up period. In the Pola+BR arm, the log-logistic, log-normal and generalised gamma appeared to provide better visual fits in the first 24 months, but those also did not capture the expected decline in progression rates, in both arms towards the end of the follow-up duration. For dependently modelled extrapolations, the company concluded that the generalised gamma, log-logistic and log-normal curves offered reasonable fits to the BR arm.

The company drew similar conclusions from the visual inspection of the independent fit extrapolations as the dependent fit extrapolations (Figure 5.4); in the Pola+BR arm, functions typically either overestimated PFS stages in the earlier months and/or underestimated the decline in patient progression towards the end of follow-up. Of all the explored functions, the company found that the generalised gamma provided the most reasonable fit in the Pola+BR arm, and in the BR arm, the generalised gamma, log-logistic and log-normal appeared to fit the observed data reasonably well.

The company suggested that introducing cure-mixture models had improved the visual fit of all models to both arms of the KM data (Figure 5.5). According to the company, log-logistic, log-normal and generalised gamma cure-mixture models provided good fits to the observed data in the Pola+BR and BR arms.

The predicted cure fractions by the cure mixture models (i.e. the proportion of patients achieving long-term remission) are presented in Table 41 of the CS.[14] The proportion of patients achieving long-term remission were between 20.8% and 25.9% in the Pola+BR arm, and between 0.0% and 4.4% in the BR arm.

Based on visual fit, plausibility of the long-term extrapolation, and alignment with the selected OS distribution, the company chose cure-mixture generalised gamma survival curve for the base case for both arms, whilst the log-normal and log-logistic extrapolations were considered in the scenario analyses from the company.

In the economic model, minimum value of the PFS and OS extrapolations was used while determining the proportion of the patients that were not progressed at a given cycle.

ERG comment: The critique of the ERG on the PFS extrapolation approaches are listed under the subheadings below:

Choosing investigator assessed PFS as the base case

The company has chosen investigator assessed PFS data for the base-case. In line with the clinical effectiveness section, the company considered the IRC assessed PFS data to be more reliable.

Not including Gompertz PFS in the economic model

The company did not include Gompertz PFS extrapolations in the economic model, because the OS extrapolation for Gompertz distributions did not converge. The ERG could not understand the rationale of the company to exclude Gompertz distribution for PFS, since the distribution of choice for OS and PFS extrapolations can be different.

Disagreement on the interpretation that PFS evidence demonstrated "cure" type of behaviour towards the end of the follow-up period.

The company justified the use of the cure-mixture model, because the company interpreted from the KM PFS curves that the relapse rates after 24 months were very low. The ERG disagrees with the company, as at least two events could be observed after 24 months in the Pola+BR arm from the PFS KM curve (Figure 4.2 in this report). Furthermore, the ERG asked the company to provide empirical hazard rate plots for the PFS data from the GO29365 trial, which are presented below (Figure 5.6). As the company did not provide any further explanation, the ERG does not know which plot corresponds to the Pola+BR treatment. However, the empirical hazard does not seem to approach zero in either of the plots.

Figure 5.6: Empirical hazard plots of the investigated PFS curves

Source: appendix in company's response to the clarification letter.[2]

5.2.6.3 Overall survival

For the extrapolation of OS in the model, the company used OS data from the October 2018 data cut-off from the GO29365 trial.

Assessment of the proportional hazards assumption

The log-cumulative hazard plots for the OS from GO29365 was presented in Figure 17 of the CS.[14] Based on the approximately parallel lines, the company deemed the proportional hazards assumption to be plausible and therefore considered both independent and dependent (joint) models (in the latter, treatment received is the covariate), for the OS extrapolation, using standard distributions (e.g. exponential, Weibull, lognormal, loglogistic, generalised gamma) to be plausible.

Assessment of the cure-mixture modelling for OS

The company followed similar steps to PFS, while providing justifications for the cure-mixture modelling for the OS extrapolation. The company argued that judging from the KM OS curves and log cumulative hazard plots, the death rates after 24-month time-point were very low, and the hazard of death declines toward the end of the follow-up period. Therefore, the company investigated cure-mixture parametric models.

In these models, it is assumed that a proportion of patients achieving long-term survival is a parameter that can be fitted from the observed GO29365 trial data via logistic regression. This 'cure fraction' of patients is assumed not to be susceptible to cancer-related death.

For the OS cure-mixture modelling, two different approaches were followed in comparison to the cure-mixture modelling of the PFS (cure modelling informed by PFS and cure modelling assuming same non-long-term survivor OS).

In the first approach, OS cure-mixture modelling was informed by PFS. In previous economic evaluations (TA559, TA567) it was stated that only patients that have not yet progressed could be

considered to be long-term survivors based on clinical expert opinion. Hence, in this approach, an additional constraint was added while categorising the patients to long-term and non-long-term survivors, in such a way that only those subjects which did not progress can be classified as potential long-term survivors.

In the second OS cure-mixture model by the company (same non-long-term survivor OS), it was considered that OS was not constrained by PFS, but it was assumed that non-long-term survivors in the Pola+BR and BR arms would essentially follow the same survival function but that there would be a difference solely in the proportion of long-term survivors.

Statistical fit of the data

The company provided the AIC and BIC goodness of fit results for the functions used to model OS for Pola+BR and BR in GO29365, as well as the subjective qualitative impression of visual fit to the observed KM curves in Table 42 from the CS.[14]

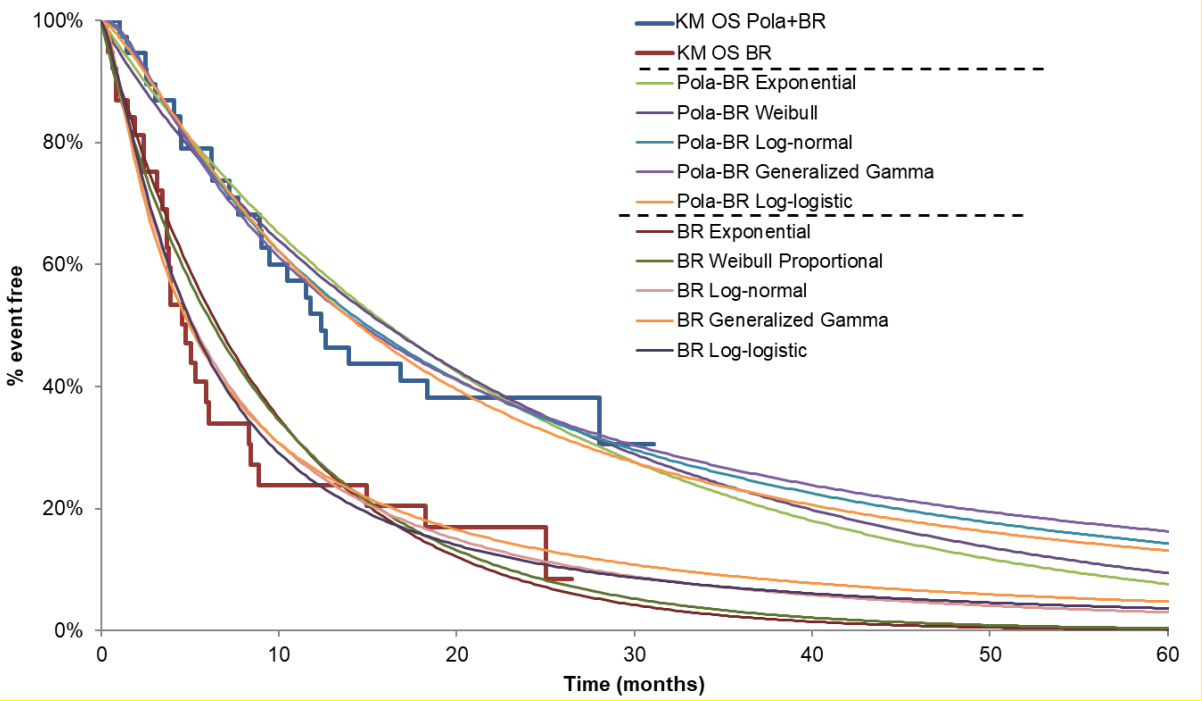
The company mentioned that for all extrapolations, parameterisation of the Gompertz extrapolation for both arms did not converge, and therefore AIC and BIC statistics were not presented for any of the Gompertz extrapolations.

The company considered that the main conclusions from the AIC and BIC values for OS were similar to those from PFS. They indicated a similar statistical fit to the KM data for the standard models (dependently and independently fit) for both arms. The best ranking models in both arms for standard parametric extrapolation were the log-normal, log-logistic and generalised gamma distributions. For the two cure-mixture models, the AIC/BIC statistics also indicated a similar statistical fit among different extrapolations, with the log-logistic and log-normal curves suggesting the best statistical fit in both arms.

Investigation of the visual fit of the extrapolations

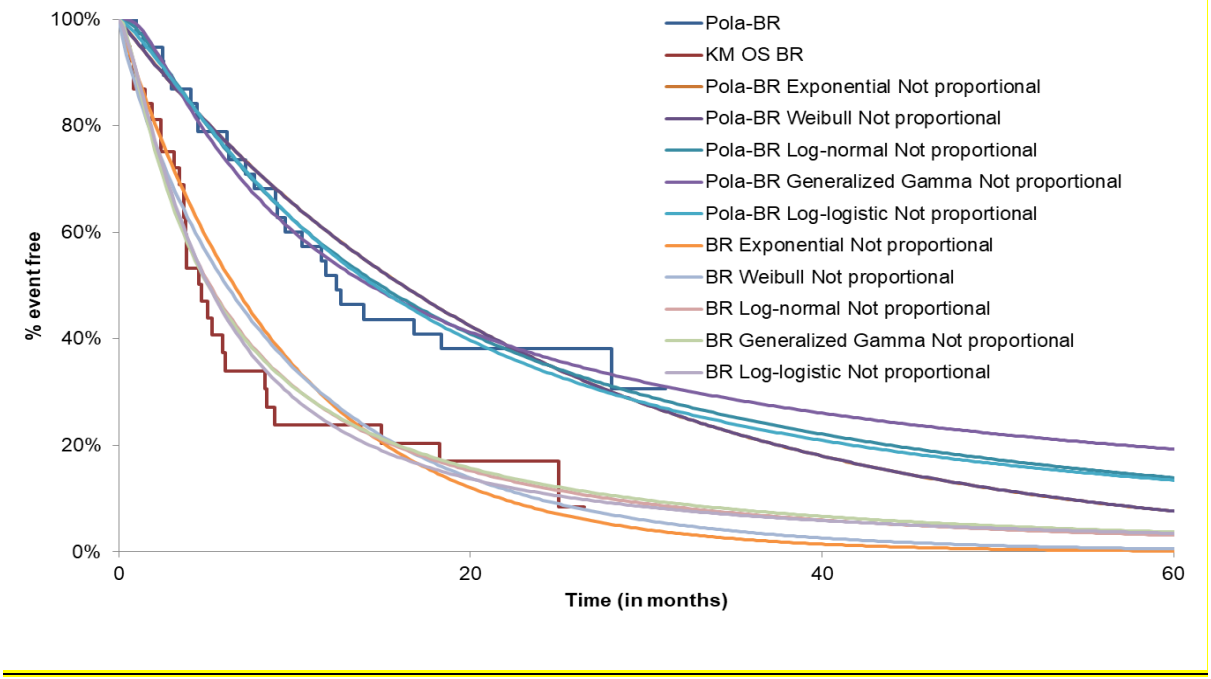
The visual fit investigation of the extrapolations was conducted separately for dependent, independent and cure-mixture models. The fitted dependent and independent standard parametric extrapolations as well as the cure-mixture models are presented in Figure 5.7, Figure 5.8, Figure 5.9 and Figure 5.10 below.

Figure 5.7: OS standard extrapolation functions (dependent fit, GO29365, Oct. 2018 cut-off)



Source: Figure 19 from the CS.[14]
The Gompertz extrapolation was not considered for either arm for OS due failure of parameterisation for this function for OS; this extrapolation is therefore not presented.
Abbreviations: BR, bendamustine + rituximab; KM, Kaplan-Meier; Pola+BR, polatuzumab + bendamustine + rituximab

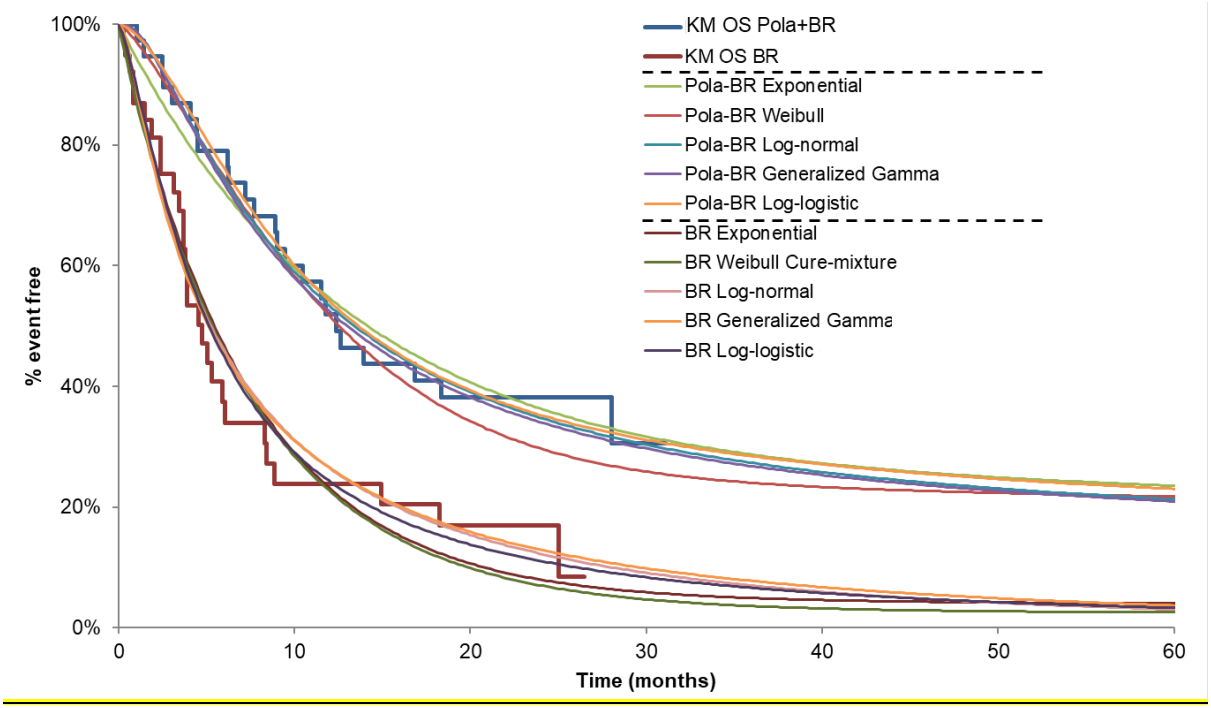
Figure 5.8: OS standard extrapolation functions (independent fit GO29365, Oct. 2018 cut-off)



Source: Recreated from the original economic model as the Figure 20 was the same as Figure 19 from the CS.[14]

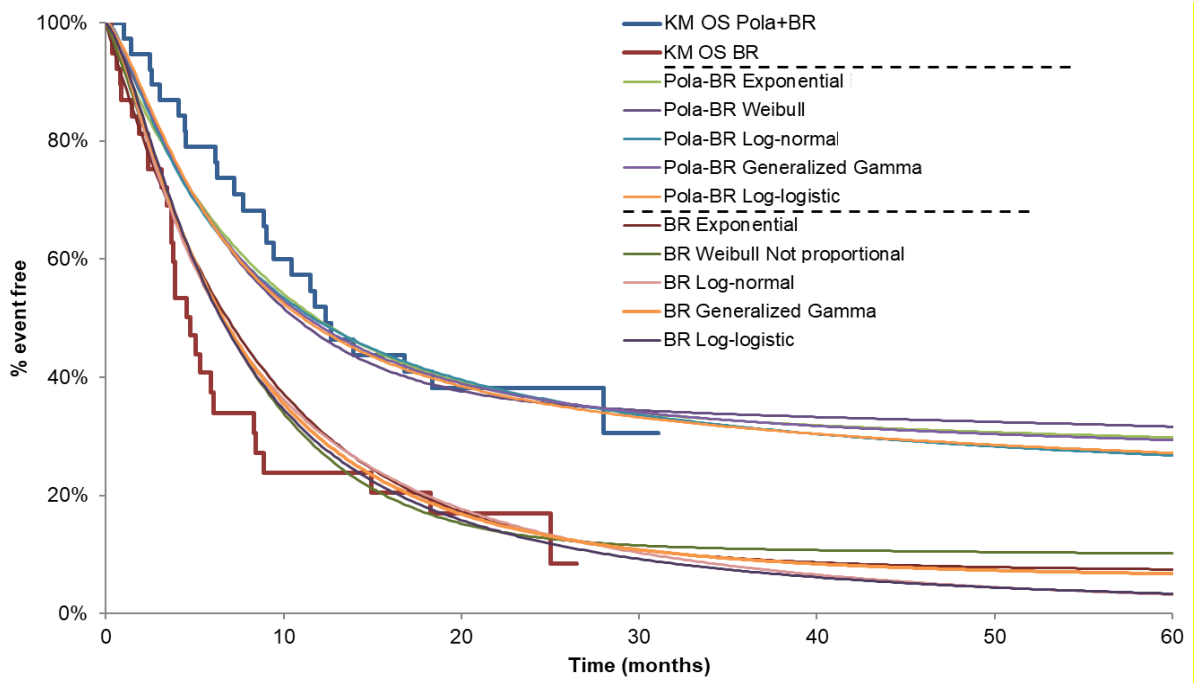
The Gompertz extrapolation was not considered due failure of parameterisation for this function for OS. Abbreviations: BR = bendamustine + rituximab; KM = Kaplan-Meier; Pola+BR = polatuzumab + bendamustine + rituximab.

Figure 5.9: OS cure-mixture model extrapolation functions (OS informed by PFS, from GO29365, Oct 2018 cut-off)



Source: Figure 22 from the CS.[14]
Gompertz extrapolation was not considered for either arm due to the failure of parameterisation for this function. Abbreviations: BR = bendamustine + rituximab; KM = Kaplan-Meier; Pola+BR = polatuzumab + bendamustine + rituximab.

Figure 5.10: OS cure-mixture model extrapolation functions (OS not informed by PFS, same OS for not-long-term survivors, data from GO29365, Oct 2018 cut-off)



Source: Figure 21 from the CS.[14]
The Gompertz extrapolation was not considered for either arm for PFS due to failure of convergence for this parameterisation function for OS; this extrapolation is therefore not presented.
Abbreviations: BR = bendamustine + rituximab; KM = Kaplan-Meier; Pola+BR = polatuzumab + bendamustine + rituximab.

Based on visual inspection, according to the company, none of the standard models (applied dependently or independently) fitted the observed OS data in Pola+BR arm particularly well, as they tended to overestimate OS initially and did not capture the decline in the observed mortality rate at the end of the follow-up period. In the BR arm, the company considered that only the log-logistic, log-normal and generalised gamma extrapolations provided a reasonable visual fit (Figure 5.7 and Figure 5.8).

For the cure-mixture models, the company found that the functions estimated by the second approach (i.e. OS not informed by PFS, same OS for non-long-term survivors) were all found to have a poor fit to the KM data (see Figure 5.10). In the Pola+BR arm, all curves underestimated OS initially. In the BR arm, all extrapolations overestimated OS initially, and the majority of them were not considered to be sufficiently capturing the decline in mortality late in follow-up. On the other hand, the functions estimated by the first method (OS informed by PFS), provided an improved fit to the KM data in both arms (see Figure 5.9). The company claimed that these functions also better reflect the expected decline in mortality later in the follow-up compared to the standard functions.

The predicted cure fractions by the cure mixture models (i.e. the proportion of patients achieving long-term remission) are presented in Table 43 (first cure mixture modelling approach) and Table 44 (second cure-mixture modelling approach) of the CS.[14] The proportion of patients achieving long-term survival were between 20.8% and 36% in the Pola+BR arm, and between 0.0% and 11.5% in the BR arm.

Based on the fit to the observed data of all extrapolations to both the Pola+BR and BR arms, the cure-mixture model informed by PFS approach was selected in the company base-case. The company chose generalised gamma because of the better visual fit, statistical fit, and more conservative cure fraction.

In the scenario where R-GemOx is explored as a comparator, the base case OS extrapolations for BR are adopted.

The best fitting functions for both arms based on visual inspection were the log-normal and generalised gamma (Figure 5.11). Note that the generalised gamma with cure mixture modelling was chosen for the company base-case for both PFS and OS, in the latter one, the cure fractions were informed by PFS (Figure 5.11).

Figure 5.11: Base case PFS and OS extrapolations

Source: Figure 22 from the CS.[14]

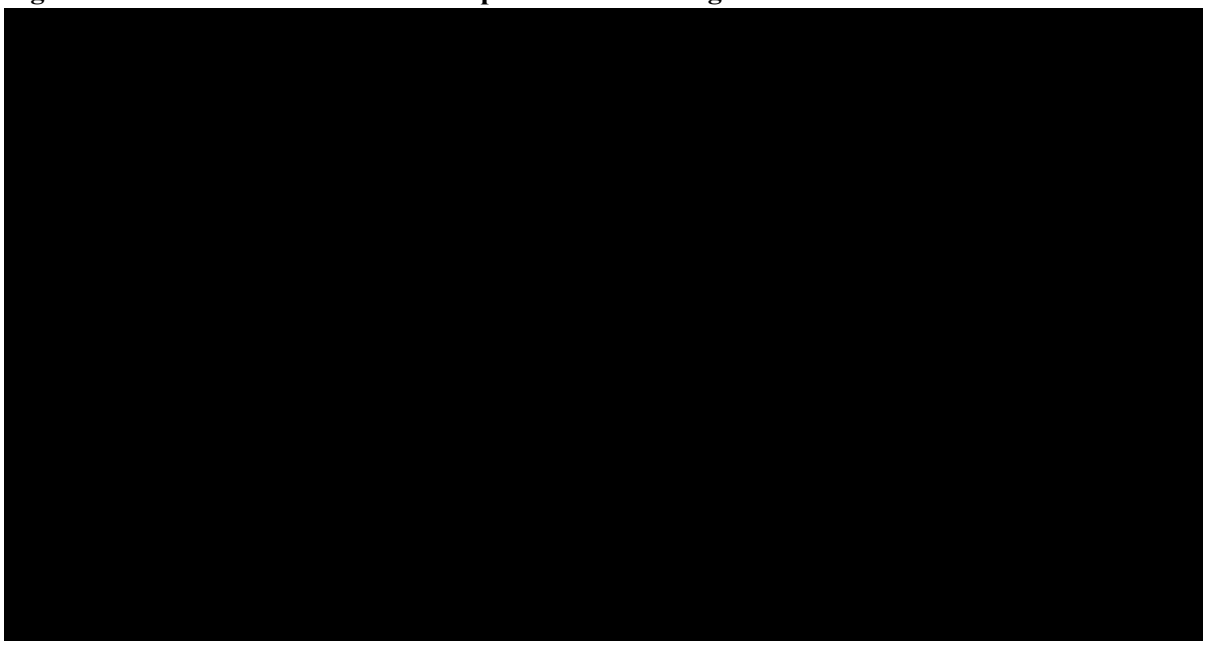
Abbreviations: BR = bendamustine + rituximab; KM = Kaplan-Meier; PFS = progression-free survival; Pola = polatuzumab.

ERG comment

Disagreement on the interpretation that OS evidence demonstrated "cure" type of behaviour towards the end of the follow-up period.

The company used similar arguments for the justification of the cure-mixture models for OS extrapolation as were used for PFS. However, the ERG considers that the evidence is not sufficiently convincing, since death events could be observed towards the end of the follow-up time in the OS KM curve (Figure 4.3 in this report). Also, the empirical hazard rate plots for the OS data from the GO29365 trial presented as below (Figure 5.12) do not seem to approach zero in either of the plots.

Figure 5.12: Kernel smoothed hazard plots of the investigated OS curves



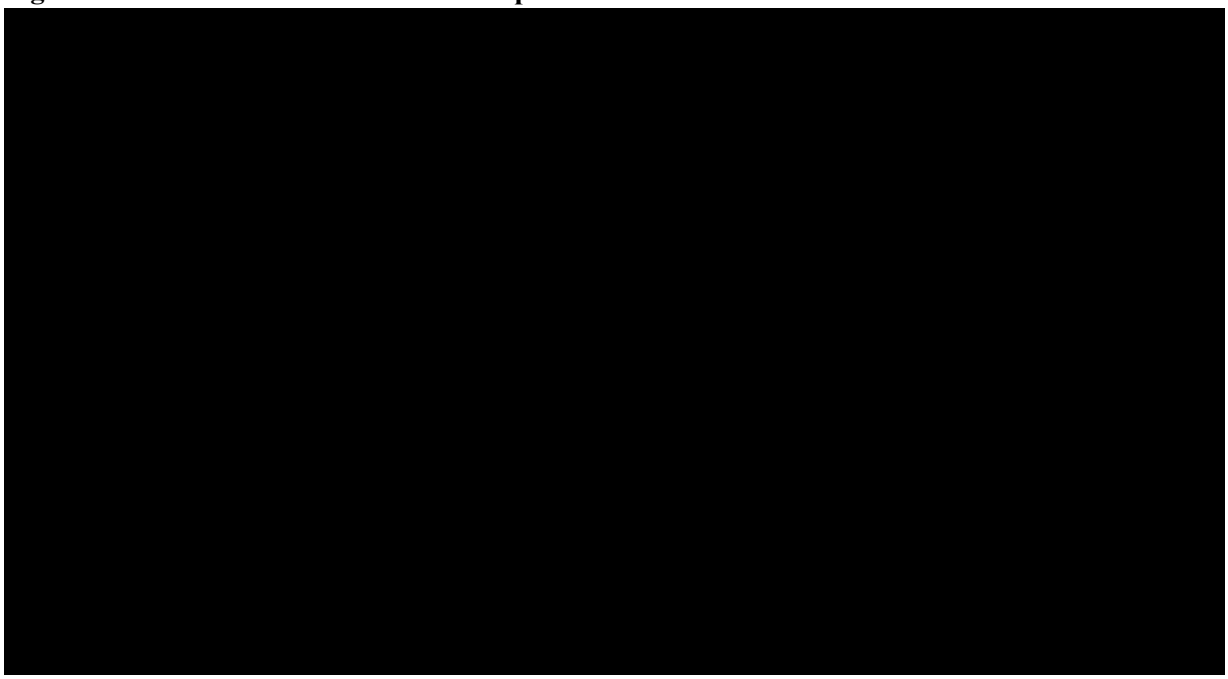
Source: appendix in company's response to the clarification letter.[2]

Doubts on the choice of the distributions for extrapolations

The ERG is doubtful on whether the most appropriate distribution was chosen (generalised gamma) for the OS and PFS extrapolation. The ERG considers that the visual fit of the generalised gamma distribution for the PFS was particularly poor (Figure 5.11) and the goodness of fit of the generalised gamma distribution with cure-mixture was worse than other distributions for the OS (Table 42 in the CS). [14]

In order to assess long-term plausibility, the ERG plotted the OS and PFS base-case extrapolations together with the general population survival of a 69-year-old cohort, reflecting the same male to female ratio as in the GO29365 trial (see Figure 5.13). It can be seen that the OS extrapolation from the company for Pola+BR overestimated the overall survival from the general population after 20 years, which was deemed implausible by the ERG. Hence, the ERG enforces the OS included in the model at a given time to be always smaller than or equal to the OS estimated from a general population in its preferred analyses.

Figure 5.13: Base case PFS and OS extrapolations



Source: ERG analysis.
Abbreviations: BR = bendamustine + rituximab; KM = Kaplan-Meier; PFS = progression-free survival; Pola = polatuzumab.

In addition, the ERG plotted the OS hazard ratio estimates from the company's OS extrapolation at different time points, which is presented below in Figure 5.14.

Figure 5.14: Hazard ratio values, from the company's OS extrapolation at different time points

Source: ERG analysis.
Abbreviations: HR = hazard ration, OS = overall survival, t = time (in years).

From Figure 5.14, it can be seen that the OS extrapolation of the company would result in an increased treatment effect for Pola+BR vs. BR, in terms of preventing death, even years after the Pola+BR treatment is given. The ERG considers that such a claim was not substantiated by the available evidence.

Finally, the company provided some arguments for the long-term survival justification from the ROMULUS trial.[39] However, the ERG noted that the intervention investigated in the ROMULUS trial is different from Pola+BR. Therefore, the ERG is unsure if the findings from the ROMULUS trial are applicable to Pola+BR.

Due to the lack of convincing arguments for the cure-mixture modelling, the ERG preferred standard parametric models and independent lognormal and generalised gamma distributions for the PFS and OS extrapolation, respectively. This is based on statistical goodness-of-fit, visual assessment of fit, as well as the long-term extrapolation plausibility.

In all the models, it was assumed that the treatment effect would be maintained throughout a patient's lifetime. However, in the exploratory analyses, the ERG explored scenarios in which the treatment effect decreases over time and becomes null at given time points.

5.2.6.4 Non-cancer related mortality

In their base-case, the company assumed a cure-mixture model for OS, which assumed that a proportion of patients were long-term survivors. The long-term survivor patients were subject to non-cancer related mortality in the model. Additionally, the patients who did not die among the non-long-term survivors were also subject to non-cancer related mortality in the model.

The company assumed that the non-cancer mortality risks would be equivalent to the age- and gender-matched general population mortality risks. This was based on a study from the US by Maurer et al (2014), who found no statistically significant difference between the mortality of 767 newly diagnosed DLBCL patients who survived event free to two years and the age- and gender-matched general population (SMR=1.09).[4] The company used the 1.09 mean estimate from Maurer et al (2014) in a scenario analysis, as this value had been used in scenario analyses in appraisals TA559 and TA567 as well.[4]

In contrast to the cohort-based approach followed for modelling the cancer-related progression and death events, the company followed an individual patient-level approach while modelling the non-cancer, background mortality risks. The economic model calculates the weighted mortality risk from the individual age- and gender-matched specific mortality risks from a cohort of 160 patients (50%-50% male-female, characterising the age distribution of the GO29365 trial).

ERG comment: The ERG found a more recent US study of 18,047 DLBCL patients that reported an excess risk of mortality in DLBCL patients up to five years.[6] This excess mortality was not only due to the chance of late relapse, but DLBCL patients were also found to be at a higher risk of death due to non-cancer causes such as gastrointestinal and blood diseases and infections (SMR=1.41; 95% CI (1.35, 1.48). Given that this SMR only includes non-cancer mortality, it is likely to be an underestimate of the overall excess mortality in these patients. Given the fact that this study includes more recent data (up to 2012 versus 2009 and 2010 in the US and French studies respectively) and a substantially larger number of patients, the ERG feel that this study should have been considered by the company in their base-case.

The ERG considers that the application of non-cancer mortality to the non-long-term survivors who did not die in a cycle in the economic model might have led to a double counting, since the death events in the OS data from the GO29365 trial might have included non-cancer related deaths as well.

Finally, the ERG disagrees with the individual modelling approach followed by the company for the background mortality risks, as it led to unrealistic mortality estimates. Furthermore, the ERG considers that this individual patient level modelling approach for background mortality created an inconsistency with the cohort-level approach followed while estimating the progression and cancer-related deaths. Therefore, in the preferred analysis conducted by the ERG, the background (non-cancer-related) mortality is calculated based on an average patient that is reflective of the GO29365 trial, instead of finding the weighted average of individually calculated background mortality risks.

5.2.6.5 Time on treatment

Time-to-off-treatment (TTOT) data from the GO29365 study were mature, at the end of the six months all patients stopped treatment for both Pola+BR and BR arms. TTOT KM estimates were therefore used directly in the model base case, using separate curves for each medicine in the respective regimens. The TTOT KM plots for Pola+BR and BR are presented in Figure 5.15 below. For the scenario comparing Pola+BR to R-GemOx, three cycles of R-GemOx were assumed, based on the assumption used in TA567.[3]

Figure 5.15: Time to off-treatment KM plots (GO29365, [redacted])

[redacted]

Source: Figure 11 from the response to the clarification letter.[2]
Abbreviations: BR = bendamustine + rituximab; KM = Kaplan-Meier; Pola+BR = polatuzumab + bendamustine + rituximab; TTOT, time-to-off-treatment.

5.2.7 Adverse events

Adverse event (AE) data were sourced from GO29365 wherever possible. The economic model includes treatment-related (TR) AEs of common terminology criteria adverse events (CTCAE) Grade 3 or greater, which were deemed serious, for both Pola+BR and BR (GO29365 data cut-off April 2018), where serious AEs were assumed to be those requiring NHS resources to treat them. For R-GemOx, TRAEs of Grade 3–5 affecting more than 5% of patients in the Mournier 2013 study (a Phase II study on the treatment of R/R DLBCL patients with R-GemOx) were included in the model.[9] Duration of AEs was sourced from GO29365 and TA306.[13] When unavailable, the company assumed the longest duration of an AE observed in GO29365 (72 days). A summary of the TRAEs included in the model is presented in Table 5.7.

Table 5.7: Incidence of TRAEs included in the model (CTCAE ≥ Grade 3, serious)

TRAE	Incidence (GO29365 and Mournier 2013[9])			Duration	
	Pola+BR	BR	R-GemOx	Value, days	Source
Acute kidney injury	2.6%	0.0%	0%	[redacted]	GO29365
Atrial fibrillation	2.6%	0.0%	0%	[redacted]	GO29365
Atrial flutter	2.6%	0.0%	0%	[redacted]	GO29365
Anemia	0.0%	0.0%	33%	16.0	TA306
Diarrhoea	0.0%	2.6%	0%	[redacted]	GO29365
Febrile neutropenia	2.6%	2.6%	4%	[redacted]	GO29365
Leukopenia	2.6%	0.0%	0%	[redacted]	GO29365
Neutropenia	2.6%	0.0%	73%	[redacted]	GO29365
Pneumonia	0.0%	2.6%	0%	[redacted]	GO29365
Lower respiratory tract infection	5.1%	0.0%	0%	[redacted]	GO29365
Pyrexia	0.0%	2.6%	0%	[redacted]	GO29365
Septic shock	2.6%	0.0%	0%	[redacted]	Assumption
Thrombocytopenia	0.0%	2.6%	23%	[redacted]	GO29365
Vomiting	0.0%	2.6%	0%	[redacted]	GO29365
Cytomegalovirus infection	2.6%	0.0%	0%	[redacted]	Assumption
Decreased appetite	0.0%	2.6%	0%	[redacted]	Assumption
Supraventricular tachycardia	2.6%	0.0%	0%	[redacted]	GO29365
Herpes virus infection	0.0%	2.6%	0%	[redacted]	GO29365
Meningoencephalitis herpetic	0.0%	2.6%	0%	[redacted]	Assumption
Myelodysplastic syndrome	0.0%	2.6%	0%	[redacted]	Assumption
Neutropenic sepsis	2.6%	0.0%	0%	[redacted]	GO29365
Oedema peripheral	2.6%	0.0%	0%	[redacted]	Assumption
Leukoencephalopathy	2.6%	0.0%	0%	[redacted]	Assumption
Pulmonary oedema	0.0%	2.6%	0%	[redacted]	Assumption

Source: Based on Table 45 from the CS[14]
Abbreviations: AE = adverse event; BR = bendamustine + rituximab; CTCAE = Common Terminology Criteria for Adverse Events; Pola+BR = polatuzumab + bendamustine + rituximab; R-GemOx = Rituximab + gemcitabine + oxaliplatin; TRAE = treatment-related adverse event.

ERG comment: Enterocolitis viral was included as an AE in the model, but not reported in the company submission (Table 5.7). This has an effect on the Pola+BR arm only with an incidence of 2.6% (one occurrence in 39 patients observed).

The ERG found the 5% threshold used by the company to be included in the model rather arbitrary. In addition, the ERG has doubts about the assumption of the company that whenever data was unavailable the longest duration observed in the GO29365 trial was assumed.

Furthermore, the ERG was not able to validate the incidence values used in the model (those in Table 5.7 above), which do not seem to be in line with the incidence values presented in the clinical effectiveness section of this report. For instance, Table 4.14 reported 11 serious AEs in the Pola+BR arm, while in the model 15 AE incidences were included. There is a discrepancy in the BR arm, as well. For instance, there are nine serious AEs in Table 4.14 vs. 14 in the model. Therefore, it is unclear to the ERG, how the serious TRAE incidences of Grade 3-5 were included in the model. The categorisation of the Grade 3-5 adverse events as "serious" and "not serious" was not clear and transparent to the ERG.

For the reasons mentioned above, the ERG preferred to use in the model the incidence values reported in Table 4.16 (column Phase II) whenever possible. These incidence values from Table 4.16 refer to the most frequently reported Grade 3-5 adverse events (>5%), under the assumption that all these AEs can occur regardless of whether considered "treatment-related" and, hence, require NHS resources to treat them. In the ERG base-case, all AE incidences in Table 4.16 were updated in the model. For those AEs included in the model but not in Table 4.16, the incidence values remained unchanged. The AEs in Table 4.16 that were not originally in the model were not included in the ERG base-case. Since a limited impact on the incremental results is expected, different assumptions on AE incidences were not explored by the ERG in this report.

5.2.8 Health-related quality of life

5.2.8.1 Identification and selection of utility values

Health-related quality of life data was not collected in the GO29365 trial. The company searched for published sources of health state utility values in patients with DLBCL through a systematic literature review. The systematic review identified seven studies which reported HRQoL data in patients with relapsed or refractory disease. An additional relevant study was identified after searches had been performed [40]. Details of all studies identified are provided in Tables 46 and 47 of the CS [14] Three of the eight utility sources identified were previous NICE appraisals (TA306, TA567 and TA559) [3, 5, 13]. These three studies each provided utility values for the required PFS and PD health states. TA567 and TA559 obtained utility data directly from trials, while TA306 utilised published sources of utility data. TA567 used SF-36 data (mapped to EQ-5D) from 34 patients from the JULIET trial, assessing tisagenlecleucel in DLBCL patients. TA559 used EQ-5D-5L data (mapped to EQ-5D-3L) from 34 patients (87 observations) from the ZUMA-1 trial assessing axicabtagene in mixed histology lymphoma, (including DLBCL). TA306 provided several sources of utility values. The company chose to include the base-case utility values, estimated in R/R NHL patients from Doorduijn et al (2005), cited in Uyl de Groot et al (2005) and values sourced from the FAD of TA176 estimated in patients with renal cell carcinoma. [41, 42]

Of the remaining five sources of utility values, three utilised existing published sources of utility values[43], one used an existing but non-published source of utility data [44] and one based its utility values on real world data [40]. None of these five potential sources of values provided relevant utility values for both required model health states. Additionally, studies based on existing published sources of utility data tended to be based on older data, with the most recent source being from 2006[45] and the oldest from 1999. [46] Values were also often not specific to DLBCL patients. Since the source data used in the Knight 2004 study was unpublished, the validity and reliability of this source could not be assessed.[44]

In the base-case the company chose to adopt the TA559 health state utility values obtained from the ZUMA-1 trial data. This source was chosen as the use of the van Hout mapping algorithm[36] to estimate EQ-5D-3L values from 5L values aligns with the NICE reference case and position statement on the use of the EQ-5D-5L valuation set for England. [40] The company also considered the patient population

of the ZUMA-1 to be similar to that of the GO29365 trial as it contained a subgroup of relapsed/refractory DLBCL patients, the majority of patients had an ECOG performance status of 1 and had received three or more lines of therapy [47]. The TA559 values were also noted by the company to be more conservative than the majority of values identified in the systematic literature review and the PFS value is considered to have face validity as it is below the average utility value for the general population at the mean baseline age in the GO29365 trial.

In line with the company's modelling of survival, in the base-case, patients who have remained progression-free for two years revert to age- and gender-matched general population utilities for the UK (obtained from Ara and Brazier 2010[48]). The company state that this HRQoL assumption was also adopted in TA559.

The company conducted several scenario analyses to test HRQoL assumptions made in the base-case. First the utility values sourced from the two alternative NICE appraisals (TA306 and TA567) were tested. To explore the uncertainty surrounding the time-point at which patients are considered to be in long-term remission (cured), the company tested switching patients in the progression-free health state to the gender- and age-matched general population utility value at five years, instead of two years. Lastly, the company tested the impact of assuming a decrease in utility in the last three months before death. The end of life utility value of 0.47 (initially presented at 0.49 in the company submission but altered to 0.47 when queried by the ERG at the clarification stage) was sourced from Färkkilä et al. 2014.[49]

ERG comment: Given that HRQoL data was not collected in the GO29365 trial, the ERG consider that the company conducted a thorough search for relevant health state utility values. The TA559 utility values utilised in the base-case were obtained from the safety population of the single arm ZUMA-1 trial. This was a small sample, including only 34 patients and 87 observations. The PFS utility value was estimated from 49 observations, while the PD health state utility value was estimated from only five observations. The ERG in appraisal TA559, noted that this very small sample size for progressed disease may suggest that progressed utility was measured soon after occurrence. They were therefore concerned that the value may not be reflective of the full progression period. However, the ERG also noted that despite substantial uncertainty surrounding this value, patients tend to remain in the progressed state for a relatively short period before death and therefore it is unlikely that the progressed disease value is a key driver in the model.[5]

Another issue with the use of utilities from this source is that no information is available to the ERG on the characteristics of the patients who provided HRQoL data in the ZUMA-1 safety management sample. ZUMA-1 included patients with a variety of forms of lymphoma. It is unclear how many (if any) of the 34 patients who provided HRQoL data had DLBCL and how the age, sex and other clinical characteristics of these patients compare to the patients in GO29365. The ERG report in TA559 shows that in comparison to the ZUMA-1 population, the safety management population were younger, with a higher proportion of males, were at an earlier stage of disease and had a better prognostic IPI score. Therefore, it is clear (from comparing to the characteristics of the entire ZUMA-1 population) that the median age of the safety population of ZUMA-1 was less than 58, at least 33% were male, more than 15% of patients had stage I or II disease and more than 27% had a prognostic IPI score of 0-1. However, exact percentages for the safety population have been redacted.

Despite uncertainties related to the use of the utility values from the ZUMA-1 trial, the ERG does not feel that the other utility sources identified would have more appropriate for the base-case. While the utility values from the JULIET trial were obtained from solely R/R DLBCL patients (rather than mixed histology lymphoma in ZUMA-1), the sample size was still small (34 patients – the same as the ZUMA-

1 safety management population). The company also noted that the PFS utility value of 0.83 from the JULIET data and the PFS value from TA306 of 0.81 are both above the age adjusted general population utility value of 0.79 at the starting age of the model (age 68), which lacks face validity. The ERG also feel that HRQoL measured using the EQ-5D-5L, converted into EQ-5D-3L using the recommended cross-walk algorithm (as adopted using the ZUMA-1 data), more closely aligns with the NICE reference case than utilising SF-36 data, mapped to EQ-5D-3L (as used for the JULIET data). Other sources of utility values identified by the company do not provide values for both required health states, and would therefore require the ERG to mix data sources, which is not preferred to sources which provide both required values. Therefore, given the data available, the ERG is satisfied to leave the base-case source of utility values as those estimated from ZUMA-1, despite the acknowledged issues.

A key concern in the HRQoL base-case adopted by the company is the uncertainty surrounding the assumption that patients who have remained progression-free for two years are assumed to have the same utility as the age- and gender-matched UK general population. The assumption of a two-year cure point is based on clinical expert opinion and evidence from the findings of a single study of no statistically significant excess mortality between newly diagnosed DLBCL patients who survive to two years and the general population [4]. However, the details of the clinical expert meeting were not provided and a more recent and larger study suggests that excess mortality remains up to five years.[6] The company do not refer to this more recent study in their CS, despite it being referred in the ERG report of TA559, where the utilities and assumption of the two-year switch to general population utility values were obtained. However, the company do test an extension of the cure point to five years for HRQoL in a scenario analysis.

Furthermore, the company extend the identified evidence of no excess mortality beyond two years, to argue that it is therefore likely that the HRQoL of the two groups (patients who are progression free longer than 2 years and non-cancer patients) would be equivalent from two years. However, no evidence was provided in the company submission to suggest that a lack of difference in mortality between the two groups translates into equivalent HRQoL. Justification for this assumption was requested by the ERG at clarification. In their clarification response the company argued that this approach was used in TA559 and is supported by studies of HRQoL in long-term cancer survivors. The company identified two recent systematic reviews to support their assumption. The first, conducted by the Office of Health Economics (OHE) found that the majority of studies comparing the HRQoL of long-term cancer survival against the HRQoL of the general population found their HRQoL to be similar. The review concluded that, while the evidence base was limited, this finding could provide some support for applying general population utilities to long-term cancer survivors.[7] The other systematic review, carried out in aggressive non-Hodgkin lymphoma (NHL) found that the HRQoL of NHL becomes more comparable with the HRQoL of general population the longer they survive.[8] The company also added that one of the studies included in that review also found that older patients had smaller differences or small-size effects in HRQoL compared to the general population.[50]

However, these arguments presented by the company ignore several important factors within these studies. In the OHE review, it is noted that mean length of survival was five years or more in all but two of the 20 included studies (in the two remaining studies the mean lengths of survival were three and 4.5 years). [7] There are also several warnings about the potential for selection bias, small sample sizes and the low quality of analysis in many of the included studies. Additionally in the NHL-specific review, the abstract states “Compared to the general population, overall HRQoL was more comparable when assessed at ≥3 years from baseline (3/3 better or comparable) versus assessment at <3 years (2/3 better or comparable).” [8] Similarly, the included study referred to by the company as having seen a smaller difference in older age groups, had a mean time since diagnosis of 3.4 years. [50] Therefore, the

ERG would argue that while there may be limited evidence to suggest that HRQoL of long-term survivors does become more comparable with that of the general population over time, there is a lack of evidence presented to suggest that this applies as early as two years.

Additionally, in the previous appraisals there is a tendency to test decrements in utility, even for those assumed to be cured, suggesting that it is thought to be likely that utility may remain lower than the general population over the long-term, due to long lasting effects of the condition and treatments received. The company did not test any scenarios on the utility of long-term survivors.

5.2.8.2 Adverse event disutilities

As HRQoL data were not available from the trial, the company searched for disutilities related to the Grade 3 or higher AEs observed in the trial. These disutilities were sourced from previous NICE appraisals in R/R DLBCL (TA306 and TA559) [13 5] and brentuximab vedotin in R/R systemic anaplastic large cell lymphoma (TA478) [51]. Disutilities, shown in Table 5.8, were weighted according to their incidence and duration for each treatment.

Table 5.8: Adverse event disutility values and durations used in the model

AE	Disutility	Standard error	Source	Duration (days)	Source
Acute kidney injury	0.27	0.03	Assumption same as renal failure in TA306 [13]	[redacted]	GO29365
Atrial Fibrillation	0.37	0.04	Assumption same as ejection fraction decreased from TA306 [13]	[redacted]	GO29365
Atrial Flutter	0.37	0.04	Assumption same as ejection fraction decreased from TA306 [13]	[redacted]	GO29365
Anaemia	0.25	0.03	TA306 [13]	16	TA306
Diarrhoea	0.10	0.01	Lloyd 2006 [52]	[redacted]	GO29365
Febrile neutropenia	0.15	0.02	Lloyd 2006 [52]	[redacted]	GO29365
Leukopenia	0.09	0.01	Assumption same as neutropenia	[redacted]	GO29365
Neutropenia	0.09	0.01	Nafees 2008 [53]	[redacted]	GO29365
Pneumonia	0.20	0.02	Beusterien 2010 [54]	[redacted]	GO29365
Lower respiratory tract infection	0.20	0.02	Assumption same as pneumonia	[redacted]	GO29365
Pyrexia	0.11	0.01	Beusterien 2010 [54]	[redacted]	GO29365
Septic Shock	0.37	0.04	Assumption (maximum disutility from TA306) [13]	[redacted]	Assumption – maximum of reported durations GO29365
Thrombocytopenia	0.11	0.01	Tolley 2013 [55]	[redacted]	GO29365

AE	Disutility	Standard error	Source	Duration (days)	Source
Vomiting	0.05	0.01	Nafees 2008 [53]	[redacted]	GO29365
Cytomegalovirus infection	0.15	0.02	Assumption same as febrile neutropenia	[redacted]	Assumption – maximum of reported durations GO29365
Decreased appetite	0.37	0.04	Assumption same as anorexia in TA306 [13]	[redacted]	Assumption – maximum of reported durations GO29365
Supraventricular tachycardia	0.37	0.04	Assumption same as ejection fraction decreased from TA306 [13]	[redacted]	GO29365
Herpes virus infection	0.15	0.02	Assumption same as febrile neutropenia	[redacted]	GO29365
Meningoencephalitis herpetic	0.15	0.02	Assumption same as febrile neutropenia	[redacted]	Assumption – maximum of reported durations GO29365
Myelodysplastic syndrome	0.37	0.04	Assumption same as malignant neoplasm progression from TA306 [13]	[redacted]	Assumption – maximum of reported durations GO29365
Neutropenic sepsis	0.15	0.02	Assumption same as febrile neutropenia	[redacted]	GO29365
Oedema peripheral	0.37	0.04	Assumption same as pulmonary oedema	[redacted]	Assumption – maximum of reported durations GO29365
Leukoencephalopathy	0.37	0.04	Assumption (maximum disutility from TA306 [13]	[redacted]	Assumption – maximum of reported durations GO29365
Pulmonary oedema	0.37	0.04	Assumption (maximum disutility from TA306) [13]	[redacted]	Assumption – maximum of reported durations GO29365

Source: Table 48 and electronic model in CS.[14]
Abbreviation: AE = adverse event.

ERG comment: The sources used to identify disutilities associated with the included AEs appear appropriate. For a selection of included AEs, the company assume the maximum of reported durations in the GO29365 trial. The model states that this assumption is used where no duration was recorded in the trial or where the issue remained ongoing. The maximum duration seen for an AE in the GO29365

trial was [redacted] days for vomiting, with an assumed associated disutility of 0.05. This assumed AE duration of [redacted] days was used for eight of the included AEs: septic shock, cytomegalovirus infection, decreased appetite, meningoencephalitis herpetic, myelodysplastic syndrome, oedema peripheral, leukoencephalopathy and pulmonary oedema. No evidence is provided to support the likelihood of such a duration for any of these AEs. In addition, six of these eight AEs (with the exception of cytomegalovirus infection and meningoencephalitis herpetic) are also assumed to have the maximum disutility of AEs seen in TA306 of 0.37. [13] Again, there is no reference to evidence to support a disutility of this size in these AEs. The assumption of maximum disutilities in combination with maximum duration for these AEs may overweight the importance of these events. However, AE disutilities and durations have a minimal impact on the ICER and therefore this is unlikely to have a substantial effect on the results.

5.2.8.3 HRQoL data used in the cost-effectiveness analysis

Table 5.9: Health state utility values for base-case

Health state	Base-case Value (SE)	Source
PFS	0.72 (0.03)	ZUMA-1 trial
PD	0.65 (0.06)	
PFS – long-term follow up (>2 years)	Age- and sex-match general population values	Ara and Brazier 2010[48]
Source: Table 49 in CS.[14] Abbreviations: PD = Progressed disease; PFS = Progression free disease; SE = Standard error.		

5.2.9 Resources and costs

The economic analysis was performed from the NHS and PSS perspective. The following costs were included for the PFS health state: drug acquisition and administration, treatment-related AEs, routine supportive care (professional and social services, health care professionals and hospital resource use, and treatment follow-up; for a maximum of two years), and subsequent treatment costs. For the PD health state, the included costs were those for drug acquisition and administration (for further interventions received), supportive care (professional and social services, health care professionals and hospital resource use, and treatment follow-up), and subsequent treatment costs.

5.2.9.1 Drug acquisition costs and administration costs

The acquisition costs and cost per cycle for polatuzumab, rituximab, bendamustine, gemcitabine, and oxaliplatin are listed in Table 5.10.

Table 5.10: Drug acquisition costs and costs per cycle

Drug	Vial / pack size (mg)	Vial / pack price	Cost source	Dosing	Dosing source	Cycle length (days)	Cost per cycle
Polatuzumab vedotin	140	[redacted]	Planned list price	1.8 mg/kg on day 1 of each cycle	GO29365	21	[redacted] (140 mg only, no vial sharing [ERG base case]) [redacted] (140 mg only, 100% vial sharing) [redacted] (140 mg and 30 mg, no vial sharing [Company base case])
	30[a]	[redacted]	Planned list price				
Rituximab biosimilar (Rixathron® / Truxima®)	100	£78.59[b]	BNF 2019[56]	375 mg/m^2 on day 1 of each cycle	GO29365	21	£581.52 (no vial sharing)
	500	£392.92[b]	BNF 2019[56]				
Bendamustine	100	£28.00	BNF 2019[56]	90 mg/m^2 per day, on days 1 and 2 of each cycle	GO29365	21	£95.95 (no vial sharing)
	25	£6.85	BNF 2019[56]				
Gemcitabine	200	£2.76	eMIT 2019[57]	1,000 mg/m^2 on day 1 of each cycle	Mounier et al., 2013[9]	14	£17.84 (no vial sharing)
	1,000	£7.96	eMIT 2019[57]				
Oxaliplatin	50	£3.81	eMIT 2019[57]	100 mg/m^2 on day 1 of each cycle	Mounier et al, 2013[9]	14	£13.87 (no vial sharing)
	100	£6.44	eMIT 2019[57]				

Source: Table 51 and the electronic model of the CS.[14]
a Vial size available in [redacted]
b Assumed discount of 50% applied, based on national tendering process for biosimilar rituximab.
Abbreviations: BNF = British National Formulary, CS = company submission, eMIT = electronic market information tool.

For the Pola+BR regimen as well as for the BR regimen, patients were assumed to receive up to a maximum of six treatment cycles (21 days per cycle). This was determined by the TTOT KM estimate data, and also conforms to the study protocol of GO29365. For the R-GemOx regimen, patients were assumed to receive three treatment cycles. This assumption was based on the one used in TA567.[3]

For Pola+BR, drugs were administered at mean doses of 1.8 mg/kg for polatuzumab vedotin and 375 mg/m^2 for rituximab (both on day 1 of each cycle), with 90 mg/m^2 of bendamustine administered on days 1 and 2 of each cycle. The mean treatment doses were derived from the weight and body surface area (BSA) distribution of patients enrolled in the GO29365 study.

It is planned for polatuzumab vedotin to be available in 140 mg and 30 mg vials (lyophilised product prepared for reconstitution prior to infusion). Polatuzumab vedotin will initially be available only with a 140 mg vial size at a list price of [redacted] per vial. The 30 mg vial is in development and is planned to be available at an equivalent per mg price ([redacted] per 30 mg vial) in [redacted].

The use of the 140 mg vial alone prior to the availability of the 30 mg vial could initially create waste for individual NHS Trusts due to a lack of flexibility in vial sizes to tailor the dose to patients' individual weights. In consultation with NHS compounding service providers, the company is planning to put arrangements in place so hospitals can obtain bags ready for infusion with the correct patient-specific dosing from these service providers without incurring any wastage costs. Trusts would therefore only be charged on a per mg basis for the drug acquisition costs, resulting in a 'no waste' or 'full vial sharing' scenario. The use of compounders is already common practice for other chemotherapies in an increasing number of NHS Trusts. Upon availability of the 30 mg vial, it is envisaged that NHS Trusts will be able to prepare doses in-house, incurring minimal wastage. Details of the compounding arrangements for polatuzumab vedotin are being discussed with NHS England.

Based on the above, costs per cycle in the model base case were therefore calculated based on the availability of 140 mg and 30 mg vials under the conservative assumption of 'no vial sharing', representing the way in which polatuzumab vedotin will be supplied in the long-term. Based on the weight distribution of patients enrolled in the GO29365 study, a mean weight of 74.86 kg resulted in a mean per cycle dose of 143.9 mg polatuzumab vedotin at an average cost of [redacted] per cycle.

In the CS,[14] the company also included a further scenario for completeness that represents the use of 140 mg vials only, with no vial sharing.

The acquisition costs of rituximab, bendamustine, gemcitabine, and oxaliplatin were calculated assuming all available vial sizes, and no vial sharing, and were based on the BSA distribution of the GO29365 patient cohort.

Rituximab (Rixathron®/Truxima®) is available as a biosimilar at a list price of £157.17 for the 100 mg vial and £785.84 for the 500 mg vial.[56] An estimated discount of 50% was applied to the biosimilar rituximab list price, based on the national tendering process for rituximab biosimilar medicines. The rituximab dose is calculated based on the BSA distribution of the GO29365 patient cohort. Patients were assumed to receive a dose of 375 mg/m^2 of rituximab administered on day 1 of each cycle. Assuming no vial sharing, the average cost per cycle for rituximab was calculated to be £581.52.

Bendamustine is available as a generic formulation in vials of 25 mg and 100 mg at a cost of £6.85 and £27.77 per vial respectively.[56] Patients were assumed to receive a dose of 180 mg/m^2 per cycle (90 mg/m^2 on days 1 and 2 of the cycle) based on the BSA distribution of the GO29365 patient cohort. Assuming no vial sharing, the cost per cycle for bendamustine was calculated to be £95.95.

For the R-GemOx regimen, gemcitabine and oxaliplatin were assumed to be administered on day 1 of each cycle (14 days per cycle) at doses of 1,000 mg/m2 and 100 mg/m2, respectively, as reported by Mounier et al., 2013.[9] Based on an assumption of no vial sharing, an average cost per cycle was calculated at £17.84 for gemcitabine and £13.87 for oxaliplatin, based on the BSA distribution of the GO29365 patient cohort.

The unit costs for drug administration corresponded to the tariffs as indicated by the HRG codes for chemotherapy administration in the NHS.[58] For the BR and GemOx regimens, the listed applicable tariff was applied for the first visit in each cycle (i.e. first visit in either first or subsequent cycles): tariff SB14Z for the first cycle of BR, SB13Z for subsequent cycles of BR, and SB14Z for all cycles of R-GemOx. In the original CS, tariff SB13Z was incorrectly applied for R-GemOx. This was corrected in the company's response to clarification questions. For the Pola+BR regimen, the tariff that corresponds to the longest duration of infusion (SB14Z) was conservatively assumed, for all first visits in each treatment cycle. For treatments that included the administration of Bendamustine during a subsequent visit (i.e. day 2 of each treatment cycle for Pola+BR, and BR) the applicable tariff for the delivery of subsequent chemotherapy elements (SB15Z) was applied. Administration costs for each chemotherapy regimen are presented in Table 5.11.

Table 5.11: Drug administration tariffs and costs per cycle

Administration cycle and regimen	Tariff applicable	Tariff unit cost	Total tariff costs per treatment cycle
First cycle Pola+BR			
Day 1: Pola+BR	SB14Z	£374.52	£686.86
Day 2: B	SB15Z	£312.34	
Subsequent cycles Pola+BR			
Day 1: Pola+BR	SB14Z	£374.52	£686.86
Day 2: B	SB15Z	£312.34	
First cycle BR			
Day 1: BR	SB14Z	£374.52	£686.86
Day 2: B	SB15Z	£312.34	
Subsequent cycles BR			
Day 1: BR	SB13Z	£309.22	£621.56
Day 2: B	SB15Z	£312.34	
First and subsequent cycles R-GemOx			
Day 1: R-GemOx	SB14Z	£374.52	£374.52

Source: Table 26 in the clarification response.
Abbreviations: B = Bendamustine; BR = bendamustine + rituximab; CS = company submission; Pola+BR = polatuzumab + bendamustine + rituximab; R-GemOx = rituximab + gemcitabine + oxaliplatin.

For pharmacy costs it was assumed that preparation of each cycle of a regimen containing polatuzumab or rituximab required 39 minutes of pharmacy time, as estimated in a UK-based time and motion study of rituximab in non-Hodgkin's lymphoma.[59] An hourly cost for a hospital pharmacist is £48,[11] resulting in a per cycle cost of £31.20.

Expected costs per treatment cycle were calculated using the total administration cost per cycle, including pharmacy costs, and TTOT KM estimate data.

ERG comment: Due to the unavailability of different vial sizes for polatuzumab, high wastage is expected. Given an average dose of 143.9 mg based on the GO29365 study, nearly half is wasted when only 140 mg vials are available, and no vial sharing is assumed. To prevent this, the company has planned to make available additional vial sizes (i.e. 30 mg from [redacted] onwards), and (in the meantime) to put into place arrangements with compounding service providers who can provide the drug to the hospital in patient-specific doses without incurring wastage costs. Therefore, the company

has assumed the availability of both 30 and 140 mg vial sizes for the base case analysis, and performed two additional scenarios in which only 140 mg vials are used, assuming either no vial sharing or 100% sharing (i.e. no wastage in case of the latter). The ERG considers that a base case analysis that is based on the current availability of vial sizes, and assuming no vial sharing, is a more conservative approach, and that it is more appropriate to explore the impact of the future availability of different vial sizes in scenario analyses.

A maximum number of six treatment cycles was assumed for the Pola+BR and BR regimens, which was reportedly based on TTOT KM estimate data. This also corresponds to the treatments as described in the study protocol for GO29365. The sixth treatment cycle of Pola+BR coincides with a half-cycle corrected TTOT KM estimate of 0.5. This indicates that the assumption of six treatment cycles is a valid reflection of the average treatment time for Pola+BR. It would therefore have been an appropriate option to assume a treatment duration of six cycles for all patients in Pola+BR, irrespective of individual TTOT data. However, when the individual TTOT data are used, as is the case in the electronic model, it is incorrect to only apply costs up to a maximum of six treatment cycles and no costs for the patients that still received additional cycles of treatment thereafter. The ERG therefore has amended the model to apply costs for as long as patients in GO29365 received treatment according to the TTOT KM estimate data, without the assumption of a maximum number of six treatment cycles for Pola+BR and BR.

An estimated discount of 50% was applied to the list price of rituximab. This estimation was "based on the national tendering process for rituximab". Given the uncertainty of this estimate due to discount values being kept confidential by the NHS, the ERG considers that using the regular list price for the base case analysis is a more conservative approach for the costing of rituximab. However, the ERG notes that the impact of this assumption on the cost-effectiveness results is small.

5.2.9.2 Health state unit costs and resource use

The type and frequency of resource utilisation in the PFS and PD health states is based upon data from the manufacturer's submission for TA306,[13] which were derived from questionnaire responses from a set of UK physicians selected based upon publication record in the field of aggressive non-Hodgkin's lymphoma, prior collaboration, and referrals from other physicians. Three categories of resources were included: professional and social services, healthcare professionals and hospital resource use, and treatment follow-up. Table 5.12 presents the cost per unit for each type of resource included in the model, and Table 5.13 presents the annual frequency of resource use in each health state.

Table 5.12: Supportive care unit costs

Procedure	Cost per unit	Source
Professional and social services		
Residential care (day)	£114.50	Crude average of local authority & private; Curtis and Burns, 2018[11]
Day care (day)	£58.00	Curtis and Burns, 2018[11]
Home care (day)	£33.32	National Audit Office 2008[10] Per diem cost of community care = £28 (assumed by the National Audit Office to be the same as the cost of home care); inflation factor from 2007–08 to 2017–18 = 1.19 (PSSRU inflation index[11]; inflated per diem cost of home care = £33.32

Procedure	Cost per unit	Source
Hospice (day)	£157.08	National Audit Office 2008 [60]; Per diem cost of hospice care = £132; inflation factor from 2007–08 to 2017–18 = 1.19 (PSSRU inflation index[11]); inflated per diem cost of home care 2007–08 = £157.08
Health care professionals and hospital resource use		
Oncologist (visit)	£165.85	AF01A; Service code 303, clinical haematology, face-to-face, non-admitted[a]
Haematologist (visit)	£164.80	AF01A; Service code 370, medical oncology, face-to-face, non-admitted[a]
Radiologist (visit)	£187.30	AF01A; Service code 800, clinical oncology (radiotherapy), face-to-face, non-admitted[a]
Nurse (visit)	£38.45	N02AF; District nurse, adult, face to face[a]
Specialist nurse (visit)	£38.45	N02AF; District nurse, adult, face to face[a]
GP (visit)	£37.40	Curtis and Burns, 2018 [61]
District nurse (visit)	£38.45	N02AF; District nurse, adult, face to face[a]
CT scan	£163.66	N02AF; District nurse, adult, face to face[a]
Inpatient day	£383.47	SA17G; Malignant disorders of lymphatic or haematological systems, with CC Score 3+, non-elective excess bed day[a]
Palliative care team	£117.84	SD03A; Palliative care team inpatient[a]
Treatment follow-up		
Full blood counts	£2.51	RD28Z; Complex CT[a]
LDH	£2.51	DAPS05; Haematology[a]
Liver function	£2.51	DAPS05; Haematology[a]
Renal function	£2.51	DAPS05; Haematology[a]
Immunoglobulin	£2.51	DAPS05; Haematology[a]
Calcium phosphate	£2.51	DAPS05; Haematology[a]
One-off costs, PD		
Chemotherapy	1,116.40	Assumed GemOx cost for generic chemotherapy and administration
R + chemotherapy	2,860.98	Assumed R-GemOx cost for generic chemotherapy and administration
Rituximab	2,765.83	Assumed R cost for generic chemotherapy and administration
Radiotherapy	162.88	SC42Z, day case
ECG	107.84	RD51A; Imaging:Outpatient
MUGA	285.04	RN03A; Imaging:Outpatient
PET-CT	470.71	RN03A, outpatient
Bone marrow biopsy	519.82	SA33Z, day case
MRI	140.60	RD01A; Imaging:Outpatient

Procedure	Cost per unit	Source
Source: Table 54 in the CS.[14] [a] NHS Improvement. NHS Reference Cost Schedule, 2017–18.[12] Abbreviations: CS = company submission; CT = computed tomography; ECG = electrocardiogram; GP = General Practitioner; LDH = lactate dehydrogenase test; MRI = magnetic resonance imaging; MUGA = multiple-gated acquisition scan; PD = progressed disease; PET-CT = positron emission tomography–computed tomography; PSSRU = Personal Social Services Research Unit; R = rituximab.		

Resource use was assumed to be the same for both arms, in accordance with clinical expert opinion.[28] Clinical expert opinion also considered that patients remaining in PFS for longer than two years were in long-term remission, and it was therefore assumed that no additional supportive costs were incurred beyond this time point. This assumption was furthermore based on ESMO guidelines[23] that recommend routine follow-up of up to 24 months, and was in line with TA 559.[5]

For the PFS health state, resource use was specified for patients whilst they were on- or off-treatment.

Table 5.13: Annual frequency of resource use in PFS and PD

Resource utilisation item	PFS on treatment	PFS off-treatment (up to 2 years)	PD	Source
Professional and social services				
Residential care (day)	39.0	9.8	0.0	TA306, ERG Report,[13] Table 37[a]. Annual frequency calculated from 28-day resource use
Day care (day)	14.6	3.7	24.4	TA306, ERG Report, [13] Table 37[a]. Annual frequency calculated from 28-day resource use
Home care (day)	60.9	22.2	121.7	TA306, ERG Report, [13] Table 37
Hospice (day)	0.7	0.2	12.1	TA306, ERG Report, [13] Table 38[a]. Annual frequency calculated from 28-day resource use
Health care professionals and hospital resource use				
Oncologist (visit)	21.8	5.5	4.3	TA306, ERG Report, [13] Table 38[a]. Annual frequency calculated from 28-day resource use
Haematologist (visit)	10.2	2.5	13.0	TA306, ERG Report, [13] Table 38[a]. Annual frequency calculated from 28-day resource use
Radiologist (visit)	21.8	4.3	0.0	TA306, ERG Report, [13] Table 38[a]. Annual frequency calculated from 28-day resource use
Nurse (visit)	52.2	13.0	0.0	TA306, ERG Report, [13] Table 38[a]. Annual frequency calculated from 28-day resource use
Specialist nurse (visit)	8.7	2.2	32.6	TA306, ERG Report, [13] Table 38[a]. Annual frequency calculated from 28-day resource use

Resource utilisation item	PFS on treatment	PFS off-treatment (up to 2 years)	PD	Source
GP (visit)	26.1	6.5	43.0	TA306, ERG Report, [13] Table 38[a]. Annual frequency calculated from 28-day resource use
District nurse (visit)	19.6	5.0	52.2	TA306, ERG Report, [13] Table 38[a]. Annual frequency calculated from 28-day resource use
CT scan	4.0	4.0	0.0	TA306, ERG Report, [13] Table 38[a]. Annual frequency calculated from 28-day resource use
Inpatient day	3.2	3.2	2.7	TA306, ERG Report, [13] Table 40
Palliative care team	0.0	0.0	17.3	TA306, ERG Report, [13] Table 40
Treatment follow-up				
Full blood counts	43.4	43.4	13.0	TA306, ERG Report, [13] Table 39[a]. Annual frequency calculated from 28-day resource use
LDH	26.1	26.1	4.3	TA306, ERG Report, [13] Table 39[a]. Annual frequency calculated from 28-day resource use
Liver function	43.4	43.4	13.0	TA306, ERG Report, [13] Table 39[a]. Annual frequency calculated from 28-day resource use
Renal function	43.4	43.4	4.3	TA306, ERG Report, [13] Table 39[a]. Annual frequency calculated from 28-day resource use
Immunoglobulin	8.7	8.7	4.3	TA306, ERG Report, [13] Table 39[a]. Annual frequency calculated from 28-day resource use
Calcium phosphate	8.7	8.7	13.0	TA306, ERG Report, [13] Table 39[a]. Annual frequency calculated from 28-day resource use
Haematologist (visit)	3.1	3.1	2.7	TA306, ERG Report, [13] Table 40
Oncologist (visit)	0.6	0.6	0.3	TA306, ERG Report, [13] Table 40
Nurse (visit)	4.9	4.9	2.1	TA306, ERG Report, [13] Table 40
Radiologist (visit)	0.03	0.03	0.03	TA306, ERG Report, [13] Table 40
GP (visit)	0.13	0.13	0.07	TA306, ERG Report, [13] Table 40
One-off costs, PD (Proportion of patients requiring resource)[a]				
	Pola+BR	BR	R-GemOx	
Chemotherapy	12.5%	12.5%	12.5%	GO29365 NALT data, pooled; assumed the same for R-GemOx

Resource utilisation item	PFS on treatment	PFS off-treatment (up to 2 years)	PD	Source
R + chemotherapy	7.5%	7.5%	7.5%	GO29365 NALT data, pooled; assumed the same for R-GemOx
Rituximab	1.3%	1.3%	1.3%	GO29365 NALT data, pooled; assumed the same for R-GemOx
Radiotherapy	2.5%	2.5%	2.5%	TA306, ERG report,[13] Table 41
ECG	15.9%	15.9%	15.9%	TA306, ERG report,[13] Table 41
MUGA	7.9%	7.9%	7.9%	TA306, ERG report,[13] Table 41
MRI	4.0%	4.0%	4.0%	TA306, ERG report,[13] Table 41
PET-CT	1.7%	1.7%	1.7%	TA306, ERG report,[13] Table 41
Bone marrow biopsy	13.6%	13.6%	13.6%	TA306, ERG report,[13] Table 41

Source: Table 55 in the CS.[14]

[a] One-off costs weighted by the proportion of patients requiring the respective resource.

Abbreviations: BR = bendamustine + rituximab; CS = company submission; CT = computed tomography; ECG = electrocardiogram; ERG = Evidence Review Group; GP = General Practitioner; LDH = lactate dehydrogenase test; MRI = magnetic resonance imaging; MUGA = multiple-gated acquisition scan; PD = progressed disease; PET-CT = positron emission tomography–computed tomography; PFS = progression-free survival; Pola+BR = polatuzumab + bendamustine + rituximab; R-GemOx = rituximab + gemcitabine + oxaliplatin.

The average per cycle supportive care costs for each health state were calculated using the unit costs and the annual frequencies presented above, and are listed in Table 5.14.

Table 5.14: Per cycle supportive care costs for PFS and PD health states

PFS on-treatment	PFS off-treatment (up to 2 years)	PFS off-treatment (after 2 years)	PD
£460.22	£160.21	£0.00	£363.64

Source: Table 56 in the CS.[14]

Abbreviations: CS = company submission; PD = progressed disease; PFS =progression-free survival.

In GO29365, each treatment arm contained a single patient who received a transplant (2.5% in each arm). Both patients were from the same treatment centre, which led the company to assume that subsequent treatment with SCT is not a widespread treatment choice. The company therefore did not expect that a significant proportion of patients who meet the decision problem would proceed to transplant after Pola+BR or BR treatment in UK clinical practice. Accordingly, costs for post-treatment SCT were not included in the company base case model. In the Pola+BR treatment arm two patients received CAR-T therapy, one of whom subsequently died, whereas no patients received CAR-T therapy in the BR arm. The company did not consider CAR-T as part of standard NHS clinical practice since it is currently funded by the Cancer Drug Fund (CDF). Accordingly, post-treatment CAR-T costs were not included in the company base case model.

5.2.9.3 Subsequent therapy costs

In study GO29365, the majority of patients in the randomised phase [redacted]), did not receive any subsequent therapy after Pola+BR or BR. Of those receiving treatment, the majority received

chemotherapy with or without rituximab ([redacted]). For the purpose of the economic analysis, the subsequent treatment costs for patients in PD who come off of Pola+BR or BR treatment, were estimated based on the proportion receiving chemotherapy, chemotherapy with rituximab, rituximab alone or radiotherapy. Other regimens, which included investigative treatments or SCT/CAR-T, were not costed. Based on clinical opinion,[28] the base case assumes the same subsequent treatments are given in both arms. Therefore, pooled estimates across arms from GO29365 for the proportion of patients receiving treatments in the aforementioned categories were used. For the cost of chemotherapy with or without rituximab, the costs of three cycles of GemOx with and without rituximab were assumed, as chemotherapies are available as generic medicines, and costs of different regimens are broadly similar. A weighted average cost was calculated as shown in Table 5.15. The total cost of subsequent treatments was applied as a one-off cost at the time point of progression in the model.

Table 5.15: Subsequent treatment costs based on GO29365 data

	Pola+BR N, %		**BR N, %**		**Pooled N, %**		**Unit cost**	**Source of cost assumptions**
Chemotherapy	[redacted]		[redacted]		[redacted]		£1116.40	Assumes 3 cycles of chemotherapy and administration[a]
R-chemotherapy	[redacted]		[redacted]		[redacted]		£2860.98	Assumes 3 cycles of R-chemotherapy and administration[a]
Rituximab	[redacted]		[redacted]		[redacted]		£2765.83	Assumes 3 cycles of rituximab and administration[a]
Radiotherapy	[redacted]		[redacted]		[redacted]		£162.88	National schedule of reference costs 2017–18[12]; SC42Z, day case
Other	[redacted]		[redacted]		[redacted]		£0	Not costed (see text)
SCT	[redacted]		[redacted]		[redacted]		£0	Not costed (see text).
CAR-T	[redacted]		[redacted]		[redacted]		£0	Not costed (see text).
Weighted average cost per patient							**£593.16**	Based on pooled proportions of patients receiving each therapy

Source: Table 57 in the CS.[14]
[a] Drug acquisition costs and administration for R-chemotherapy were based on those for R-GemOx; for chemotherapy alone and rituximab alone, the costs of rituximab or chemotherapy were excluded as relevant.
Abbreviations: BR = bendamustine + rituximab; CAR-T = chimeric antigen receptor-T cell; CS = company submission; Pola+BR = polatuzumab + bendamustine + rituximab; R-chemotherapy = rituximab-chemotherapy; R-GemOx = rituximab + gemcitabine + oxaliplatin; SCT = stem cell transplant.

ERG comment: Similar to the ERG's concerns regarding patients who have been in PFS for two years being assumed to have the same mortality risk and utility as the general population, this concern also applies to the assumption of the supportive care costs being applicable to patients in PFS for the first two years only. Although the ESMO guidelines indeed emphasise "the need to only specifically monitor the disease in this early period" (i.e. in reference to OS being identical to that of the general population after two event-free years), this does not rule out that further evaluations are performed in case of suspicious symptoms or high-risk patients. In TA559, the corresponding ERG commented that "these assumptions on the costs and HRQoL of PFS patients in the model appear to be overly optimistic and lacking robust evidence to support them".[5] The current ERG agrees to that statement.

Health care resource use is based on TA306,[13] for which in turn it was based on estimates from a survey of three key opinion leaders, commissioned by the company that submitted TA306.[13] As was also noted by the ERG for TA306,[13] this approach is 'subject to higher levels of uncertainty'. For the current submission, the ERG notes that no further validation was done regarding the applicability of these data to the current context.

For the costs of chemotherapy in PD, the costs of GemOx were assumed. This is justified by stating that chemotherapies are assumed 1) to be available as generic medicines and 2) that the costs of different regimens are broadly similar. These assumptions were not validated by clinical experts. Regarding the first assumption, the company pointed out in their response to clarification questions that seven out of the 11 individual medicines that were listed as part of an additional chemotherapy regimen as included in the final NICE scope were indeed generic medicines since their costs were sourced from eMIT (NHS Drugs and Pharmaceutical electronic Market Information Tool). Regarding the second assumption, the company refers to Table 51 in the CS (i.e. Table 5.10 in this report) to point out that the costs for the chemotherapy regimens included in the final NICE scope are below £300 per cycle, and therefore unlikely to significantly impact cost effectiveness results. The ERG notes that the per cycle acquisition costs for gemcitabine and oxaliplatin, £17.84 and £13.87 respectively, do appear as substantially less than those for bendamustine (i.e. £95.95), P-Mit-CEBO (i.e. £87.63), and DECC (i.e. £256.78). However, the ERG confirms that variation in this parameter has a negligible effect on the ICER.

In contrast to the company's decision to leave the costs for SCT and CAR-T out of consideration for the cost effectiveness analysis, the ERG considers it more appropriate to include those costs based on the incidences as indicated by the trial data. Due to uncertainty regarding the costs of CAR-T, the costs are assumed to be the same as the costs of SCT.

5.2.9.4 Adverse event costs

Treatment-related AEs included in the model for Pola+BR and BR were derived from serious treatment-related AEs of CTCAE Grade 3 or higher from the randomised phase of GO29365. The frequencies of AEs are already presented in section 5.2.7. The unit costs associated with the management of the identified AEs are presented in Table 5.16 below.

Table 5.16: Unit costs of treatment-related AEs

Event (grade)	Unit cost (£)	Source[a]
Acute kidney injury	332.50	Weighted average of LA07M-P; DC
Atrial fibrillation	670.13	Weighted average of EB07A-E; DC
Atrial flutter	670.13	Weighted average of EB07A-E; DC
Anaemia	309.09	Weighted average of SA01G-K, SA03G-H, SA04G-L, SA05G-J; day case
Cytomegalovirus infection	393.65	Weighted average of WH07B-G; DC
Decreased appetite	382.30	Assumed same as vomiting
Diarrhoea	392.26	Weighted average of FD10J, FD10K, FD10L, FD10M; DC
Febrile neutropenia	1,847.50	TA306 (£1,627); inflated to 2018 using PSSRU inflation index
Herpes virus infection	377.90	Weighted average of FD10J, FD10K, FD10L, FD10M; DC

Event (grade)	Unit cost (£)	Source[a]
Leukoencephalopathy	3,609.61	Weighted average of AA25C-G; NEL
Leukopenia	291.00	Weighted average of SA35A-E; DC
Lower respiratory tract infection	377.90	Weighted average of FD10J, FD10K, FD10L, FD10M; DC
Meningoencephalitis herpetic	3,652.18	Weighted average of AA22C-G; NEL
Myelodysplastic syndrome	556.99	Weighted average of SA06G-K; NES
Neutropenia	291.00	Weighted average of SA35A-E; DC
Neutropenic sepsis	1,847.50	Assumed same as febrile neutropenia
Oedema peripheral	343.16	Weighted average of WH10A-B; NES
Pneumonia	495.81	Weighted average of DZ11K-V; NES
Pulmonary oedema	2,189.85	Weighted average of DZ20D-F; NEL
Pyrexia	309.56	Weighted average of WJ07A-D; DC
Septic shock	1,037.71	Weighted average of WJ06A-F, NES
Supraventricular tachycardia	670.13	Weighted average of EB07A-E; DC
Thrombocytopenia	281.96	Weighted average of SA12G-SA12K; DC
Vomiting	382.30	Weighted average of FD10C-M; DC

Source: Table 58 in the CS.[14]
[a] NHS Improvement. NHS Reference Cost Schedule, 2017–18[12] unless stated otherwise.
Abbreviations: AE = adverse event; CS = company submission; DC = day case; NEL = non-elective inpatients; NES = non-elective short stay; PSSRU = Personal Social Services Research Unit.

A separate cost of death was not applied to the model as it was assumed the costs for supportive care after progression would be accounted for in the cancer-related palliative care costs for progressed patients. Cost and resource use for death from other causes is not included in the model.

ERG comment: A comprehensive set of AEs were considered and taken into account for the economic analysis. For the frequencies, relevant trial data (serious treatment-related AEs of CTCAE Grade 3 or higher from the randomised phase of GO29365) were used, and costs were valued using the most recent schedule of NHS reference costs. The ERG considers this approach as appropriate.

6. COST-EFFECTIVENESS RESULTS

6.1 Company's cost effectiveness results

The discounted base-case results presented in Table 6.1 indicated that Pola+BR generated [redacted] incremental QALYs, and [redacted] LYGs, with higher incremental costs of [redacted] compared to BR. Therefore, the incremental cost-effectiveness ratio (ICER) was £26,877 per QALY gained.

Table 6.1: Company base-case cost effectiveness results (discounted)

Technologies	Total costs (£)	Total LYGs	Total QALYs	Incr. costs (£)	Incr. LYGs	Incr. QALYs	ICER versus baseline (£/QALY)
Pola+BR	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£26,877
BR	£18,019	1.00	0.68	-	-	-	-

Source: Table 61 of the CS.[14]
Abbreviations: BR = bendamustine + rituximab; CS = company submission; ICER = incremental cost-effectiveness ratio; Incr. = incremental; LYGs = life years gained; pola = polatuzumab; QALYs = quality-adjusted life years.

The disaggregated discounted QALYs by health state are given in Table 6.2. The disaggregated discounted costs by health state and category are given in Tables 6.3 and 6.4, respectively.

Table 6.2: Summary of QALYs disaggregated by health state

Health state	QALYs intervention (Pola+BR)	QALY comparator (BR)	Increment	Absolute increment	% absolute increment
PFS	[redacted]	0.37	[redacted]	[redacted]	[redacted]
PD	0.14	0.32	–0.18	[redacted]	[redacted]
AE disutility[a]	0.009	0.007	0.001	[redacted]	[redacted]
Total	[redacted]	0.68	[redacted]	[redacted]	100.0%

Source: Table 32 in Appendix J of the CS.[62]
[a] Disutility from adverse events as detailed in Section B.3.4.4 of the CS.[14]
Abbreviations: AE = adverse event; BR = bendamustine + rituximab; CS = company submission; PD = progressed disease; PFS = progression-free survival; pola = polatuzumab ; QALY = quality-adjusted life year.

Table 6.3: Summary of costs disaggregated by health state

Health state	Costs intervention (Pola+BR)	Costs comparator (BR)	Increment	Absolute increment	% absolute increment
PFS	[redacted]	£8,019	[redacted]	[redacted]	[redacted]
PD	£4,657	£10,000	−£5,343	£5,343	8.5%
Total	[redacted]	£18,019	[redacted]	[redacted]	100.0%

Source: Table 33 in Appendix J of the CS.[62]
Abbreviations: BR = bendamustine + rituximab; CS = company submission; PD = progressed disease; PFS = progression-free survival; pola = polatuzumab ; QALY = quality-adjusted life year.

Table 6.4: Summary of disaggregated costs by category

Cost category	Costs intervention (Pola+BR)	Costs comparator (BR)	Increment	Absolute increment	% increment
Polatuzumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Bendamustine	£433	£311	£122	£122	[redacted]
Rituximab	£2,624	£1,886	£738	£738	[redacted]
Drug administration	£3,324	£2,181	£1,143	£1,143	[redacted]
AE management	£337	£386	−£49	£49	[redacted]
Supportive care costs	£8,156	£3,254	£4,902	£4,902	[redacted]
Subsequent care costs, PD	£4,657	£10,000	-£5,343	£5,343	[redacted]
Total	[redacted]	[redacted]	[redacted]	[redacted]	100.0%

Source: Table 34 in Appendix J of the CS.[62]
Abbreviations: AE = adverse event; BR = bendamustine + rituximab; CS = company submission; PD = progressed disease; pola = polatuzumab; QALY = quality-adjusted life year.

6.2 Company's sensitivity analyses

6.2.1 Probabilistic sensitivity analysis

The company conducted a PSA based on 2,000 iterations. The input parameters included in the PSA, with their corresponding probability distributions, were reported in Table 62 of the company submission.[14] Parameters of the PFS and OS survival distributions were varied according to multivariate normal distributions with the mean values and covariance matrices reported in the economic model. Standard errors (SEs) for the input parameters, where available, were obtained from the same data source used to derive the point estimates. For AE disutility and cost parameters the SE was calculated as 10% deviation from the mean, and according to the following equation: SE = (LN(mean+20%)-LN(mean-20%))/4, respectively. Additionally, the AE incidence occurrences were also sampled using a lognormal distribution.

The discounted PSA results are shown in Table 6.5. The average incremental costs and incremental QALYs were [redacted] and [redacted] respectively, resulting in an ICER of £41,326 per QALY gained. Compared to the deterministic ICER in Table 6.1, the probabilistic ICER was £14,449 higher.

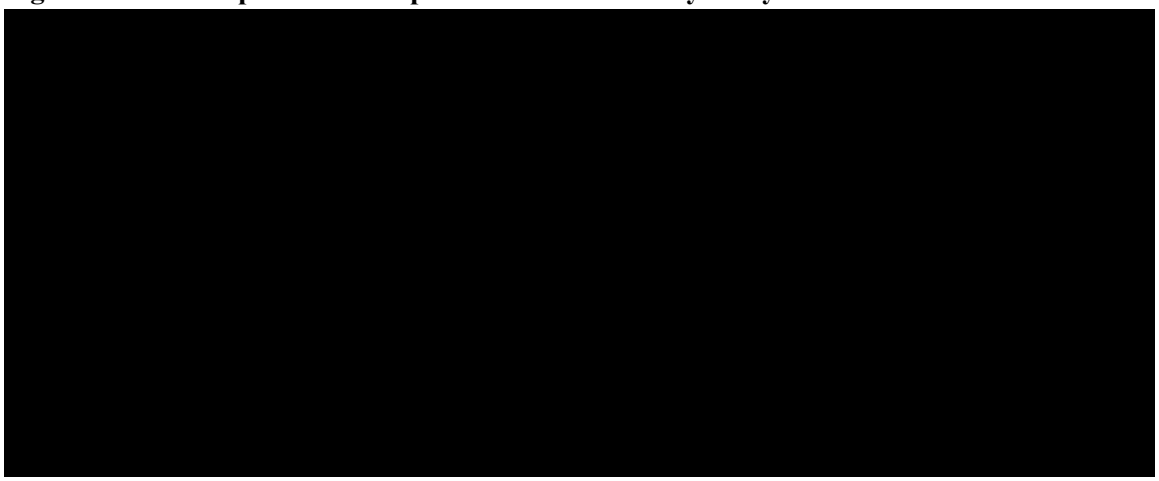
Table 6.5: Company base-case probabilistic cost effectiveness results (discounted)

Technologies	Total costs (£)	Total LYGs	Total QALYs	Incr. costs (£)	Incr. LYGs	Incr. QALYs	ICER versus baseline (£/QALY)
Pola+BR	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£41,326
BR	£18,076	1.00	0.68	-	-	-	-

Source: Table 63 of the CS.[14]
Abbreviations: BR = bendamustine + rituximab; CS = company submission; ICER = incremental cost-effectiveness ratio; Incr. = incremental; LYGs = life years gained; pola = polatuzumab; QALYs = quality-adjusted life years.

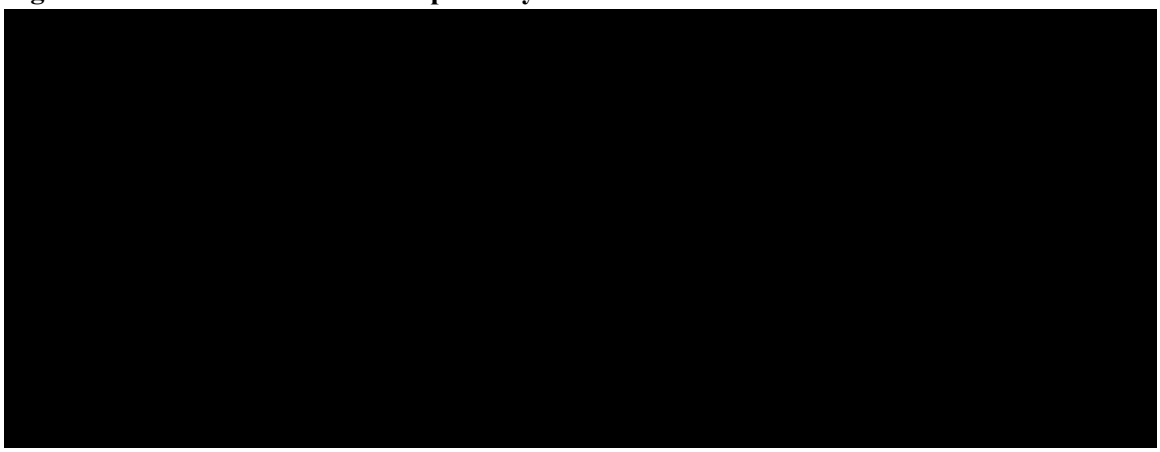
The PSA outcomes were plotted in the CE plane, and, subsequently, a CEAC was derived. These are shown in Figures 6.1 and 6.2, respectively. All the 2,000 PSA iterations provided results in the north-eastern quadrant of the CE plane, where Pola+BR is more effective and more expensive than BR alone. The CEAC showed that Pola+BR has a [redacted]% probability of being cost effective at a threshold of £50,000 per QALY.

Figure 6.1: Scatterplot from the probabilistic sensitivity analysis



Source: Figure 28 of the CS.[14]
Abbreviations: CS = company submission; PSA = probabilistic sensitivity analysis; BR= bendamustine + rituximab; Pola+BR= polatuzumab + bendamustine + rituximab; QALY= quality-adjusted life year.

Figure 6.2: Cost effectiveness acceptability curve



Based on Figure 29 of the CS.[14]
CS = company submission; PSA = probabilistic sensitivity analysis; BR= bendamustine + rituximab; Pola+BR= polatuzumab + bendamustine + rituximab; QALY= quality-adjusted life year; WTP=willingness to pay

ERG comment: The ERG pinpointed the reason for the gap between the probabilistic and the deterministic ICER estimates in the company submission. In the company model, the ICER is calculated at each iteration and the average value of these iteration specific ICERs were calculated. Since the ICER frequently has outlier values, the average of the ICERs from iterations does not converge quickly, and for that purpose, the median of the simulation iteration ICERs or the ratio of the mean incremental costs to mean incremental QALYs would provide a more stable estimate of the probabilistic mean ICER. The ERG corrected this in its exploratory analyses.

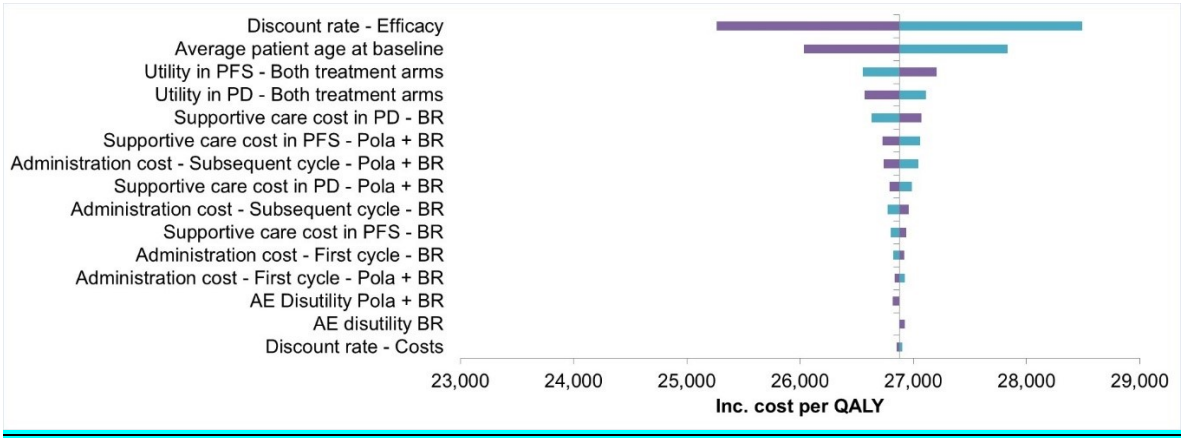
The ERG found the calculation of the SEs for the AE disutilities and costs rather arbitrary, however this is not changed in the base-case as there was no other available source from the literature and the expected impact on the incremental results was minor. Additionally, the ERG considered that sampling the AE incidence probabilities using beta distributions would be methodologically more plausible. Hence in the ERG analyses, the company model is corrected in terms of how AE incidence probabilities were sampled.

6.2.2 Deterministic sensitivity analysis

The company also conducted a deterministic sensitivity analysis (DSA). The value of each parameter included in the analysis was provided in Table 64 of the CS.[14] Total cost categories were varied at once and AE disutilities were varied using the average disutility of all AEs, weighted by frequency and duration. Where available, the upper and lower limits for each input parameter (or group of parameters) were based upon the 10% and 90% percentiles obtained from the probability distributions used in the PSA. Otherwise, parameters were varied by ±20% deviation from the mean (alternatively ±5 kg for mean weight, ±5% for mean BSA).

The tornado diagram in Figure 6.3 shows the impact on the ICER of the 15 parameters which caused the largest changes in the ICER. From this figure, it can be observed that changes in the discount rate for health effects and the average patient age at baseline resulted in the largest changes in the ICER, which remained always between £25,000 and £29,000 per QALY.

Figure 6.3: Tornado diagram – company's preferred assumptions



Source: Figure 31 of the CS.[14]
Abbreviations: AE = Adverse events; BR = bendamustine + rituximab; PD = progressed disease; PFS = progression-free survival; Pola+BR = polatuzumab + bendamustine + rituximab; QALY = quality-adjusted life year.

ERG comment: It should be emphasised that the DSA conducted by the company is not a *one-way* sensitivity analysis. Costs and AE disutilities were treated as a group. Therefore, in the DSA, individual parameters are compared with groups of parameters, which introduces bias in the result of the DSA. The tornado diagram also indicated that the discount rate for the health effects was the most influential parameter. However, discount rates are usually not included in the DSA (because it would assume rate values that are unlikely to occur in reality). Furthermore, in their response to the clarification letter (question B21),[2] the company indicated that only "independent" parameters were included in the deterministic sensitivity analysis. As a result, important parameters like those of the survival curves or cure rates were not included in the DSA. Finally, the range of variation for the input parameters (10% and 90% percentiles from PSA or ±20% deviation from the mean) seems arbitrary and it is unclear

whether it represents a comparable range of variation. Therefore, for the reasons mentioned above, the ERG considers that the DSA results presented by the company can be misleading and should be interpreted with caution.

6.2.3 Scenario analyses

The company undertook a series of scenario analyses in order to test the impact of a number of assumptions on model results. The scenarios tested and results obtained are summarised in Table 6.6.

ERG comment: The scenarios which had the largest impact on results were those involving alternative methods of survival modelling. The largest increases in the ICER were seen for methods involving extrapolation of OS and PFS using dependent and independent parametric distribution functions, which led to ICERs between £33,126 and £59,753. All the other scenarios led to ICERs below £50,000. Therefore, scenarios based on alternative assumptions of survival modelling were the main focus of the ERG in Section 7 of this report.

Table 6.6: Scenario analyses conducted by the company

Scenario	Alternative value	Base-case value	Alternative source for input	Incremental costs (£)	Incremental QALYs	ICER (£)
Base-case				[redacted]	[redacted]	£26,877
1. Model time horizon						
Time horizon (years)	10	45	Assumption	[redacted]	[redacted]	£42,677
	20			[redacted]	[redacted]	£30,183
	30			[redacted]	[redacted]	£27,629
2. Patient baseline characteristics						
Average patient weight (kg)	69.86	74.86	BC – 5kgs (assumption)	[redacted]	[redacted]	£25,399
	79.86		BC + 5kgs (assumption)	[redacted]	[redacted]	£28,494
Average patient BSA (m^2)	1.76	1.85	BC – 5% (assumption)	[redacted]	[redacted]	£24,376
	1.94		BC + 5% (assumption)	[redacted]	[redacted]	£29,778
3. Utilities						
PFS and PD HSUV sources	PFS=0.83 PD=0.71	PFS=0.72 PD=0.65	PFS and PD HSUVs from TA567[3]	[redacted]	[redacted]	£26,596
	PFS=0.76 PD=0.68		PFS and PD HSUVs from TA306[13]	[redacted]	[redacted]	£26,668
End of life	PFS=0.49 in 3 months prior to death	No change in PFS in 3 months prior to death	PFS – decline in utility in the 3 months prior to death Farkkila 2014 [49]	[redacted]	[redacted]	£27,544
Cure point	Match utility to gen pop after 5 years	Match utility to gen pop after 2 years	Assumption	[redacted]	[redacted]	£27,316
4. Survival modelling						
Cure-mixture model (OS, PFS)	Log-normal	Cure-mixture model (OS, PFS), generalised		[redacted]	[redacted]	£27,349
	Log-logistic			[redacted]	[redacted]	£25,721
	Generalised gamma			[redacted]	[redacted]	£52,178

Scenario	Alternative value	Base-case value	Alternative source for input	Incremental costs (£)	Incremental QALYs	ICER (£)
Dependent parametric distribution function (OS, PFS),	Log-normal	gamma. OS informed by PFS.		[redacted]	[redacted]	£58,191
	Log-logistic			[redacted]	[redacted]	£59,753
Independent parametric distribution function (OS, PFS)	Generalised gamma			[redacted]	[redacted]	£33,126
	Log-normal			[redacted]	[redacted]	£59,241
	Log-logistic			[redacted]	[redacted]	£56,339
OS not informed by PFS (cure-mixture extrapolation)	Generalised gamma (PFS and OS)			[redacted]	[redacted]	£26,223
	Log-normal (PFS and OS)			[redacted]	[redacted]	£27,795
	Log-logistic (PFS and OS)			[redacted]	[redacted]	£26,052
Excess mortality for long-term survivors	Excess hazard = 1.1	Excess hazard = 0		[redacted]	[redacted]	£27,894
5. Costs and resource use						
Vial sharing and size assumptions polatuzumab	Only 140 mg vials and no vial sharing	140 mg and 30 mg vials available. No vial sharing.	Based on interim supply arrangement (30 mg vials not anticipated to be available until [redacted])	[redacted]	[redacted]	£36,502
	Only 140 mg vials and 100% vial sharing			[redacted]	[redacted]	£25,196
Supportive care costs	No supportive care costs incurred by long term survivors after 3 years		Assumption	[redacted]	[redacted]	£27,868

Scenario	Alternative value	Base-case value	Alternative source for input	Incremental costs (£)	Incremental QALYs	ICER (£)
6. Alternative comparator						
Alternative comparator	Pola+BR vs R-GemOx	Pola+BR vs BR		[redacted]	[redacted]	£28,410

Source: Table 65 in CS.[14]

Abbreviations: BC = base case; BR= bendamustine + rituximab; BSA = body surface area; gen pop = general population; HSUV = health state utility values; PD = progressed disease; PFS = progression-free survival; Pola+BR= polatuzumab + bendamustine + rituximab; OS = overall survival; QALYs = quality-adjusted life years; R-GemOx = R-GemOx = rituximab + gemcitabine + oxaliplatin.

6.2.4 Subgroup analysis

No subgroup analysis was conducted in the original submission

6.3 Model validation and face validity check

Validation was performed by an advisory board of nine UK clinicians held in October 2018.[28] During this meeting the clinical experts discussed the assumptions made in the model, to ensure their clinical validity and alignment with UK clinical practice.

The plausibility of PFS and OS long-term extrapolations was also validated through comparison to long-term data for polatuzumab vedotin regimens in DLBCL (see Section 5.2.6 of this report).

A comparison of the median PFS and median OS produced by the model base case and those observed in GO29365 was also provided by the company. This can be seen in Table 6.7.

Table 6.7: Comparison of model median PFS and median OS vs. GO29365

Technologies	Median PFS (months)		Median OS (months)	
	Model	GO29365 (95% CI)	Model	GO29365 (95% CI)
Pola+BR	8.0	[redacted]	13..1	[redacted]
BR	2.1	[redacted]	5.1	[redacted]

Source: Table 66 of the CS[14]
Abbreviations: BR = bendamustine + rituximab; CI = confidence interval; OS = overall survival; PFS = progression-free survival; pola = polatuzumab.

ERG comment: A summary of the validation efforts undertaken by the company are summarised in Table 6.8.

The company indicated that a review of the model, including formula and calculation checks, was performed by an agency in draft versions of the model. The specific tests, and whether these were conducted in the final version of the model or not, were not reported. Therefore, the degree of internal validation of the model cannot be assessed by the ERG. The additional validation efforts conducted by the ERG led to the identification of several modelling errors that are described in Section 7.1.2 of this report.

In clarification question B8, the ERG asked the company to provide probability estimates for PFS and OS which can be used to validate the parametric curves used in the model.[2] In their response, the company indicated that during the advisory board held in October 2018, the PFS and OS data from the clinical trial and the plausibility of the parametric extrapolations for both BR and Pola+BR arms was discussed with UK clinicians. However, these extrapolations were based on an earlier version of the model (April 2018 data-cut) and it is, therefore, unclear whether the extrapolations in the final version of the model were validated by experts. Discussion was focused on the long-term behaviour of the BR arm since experts were not able to estimate the long-term behaviour for the Pola+BR arm based on their clinical experience. Regarding OS for the BR arm, the experts consulted by the company considered that survival at year 1 should be comparable to other available regimens and provided an estimate of approximately 20%. Long-term survival (from five years onwards) was estimated to be between 5% – 10%. The experts considered that PFS in the BR arm was underestimated in that earlier version of the model: 18% of patients were in progression-free survival at six months. In the current version of the model this estimate is 23% in the base-case. Whereas this value is higher than the previous 18%, it is

not mentioned whether 23% met the expectations of the clinical experts and, therefore, it is not validated. The clinical experts consulted by the company also mentioned that "*2 years PFS was deemed as indicating long-term response and survival (implying a rate of 5-10% in current practice for PFS beyond 2 years)*".[2]

For the validation of the cure-mixture models, the company referred to an abstract written in collaboration with the clinical study investigators of GO29365 who contributed and agreed to the publication of the abstract and its conclusions.[63]

In clarification question B8, the ERG also asked the company to provide estimates for the standardized mortality ratio for the "cured" relapsed or refractory diffuse large B-cell lymphoma patients and to apply this ratio in the model for the "cured" patients.[2] In their response, the company indicated that they are only aware of a ratio of 1.09, that was applied to the background mortality for long-term survivors in TA567 and TA559.[3, 5] In both STAs, this ratio was applied in scenario analyses but not in the base-case. In line with these STAs, the company implemented this ratio in the model and the impact of it in the model results was investigated in an additional scenario (See Table 6.6).

Table 6.8: Validation efforts undertaken by the company on the economic model

Item	Key validation steps	Reference in ERG report/clarification questions
Partitioned survival model concept	Structure based on previous and recent use in NICE technology appraisals in DLBCL Alignment with NICE DSU guidance for oncology modelling Model structure was presented at advisory board and no objections were raised by clinical experts	Section 5.2.2
Input data	The applicability of the GO29356 clinical trial data to the UK was verified at an advisory board of UK clinical experts The statistical fit of PFS and OS extrapolations was explored in detail, in line with recommendations in NICE DSU TSD 14[38] Cost inputs are from the NHS/PSS perspective, as recommended by the NICE reference case	Section 5.2
Excel model	Agency preformed a review of the model including checking formulas and tracing calculation errors in draft versions of the model	Clarification letter response (question B20).[2]
Model outcomes	The long-term extrapolation for BR based on an earlier data cut of GO29365 was validated with expert clinicians at an advisory board The base case cure mixture extrapolations were validated against available long-term data to ensure their clinical validity Base case cure-mixture model analysed and published with clinical trial investigators[63]	Section 5.2.6, Clarification letter response (question B8).[2]

Source: CS[14] and clarification letter response[2].
Abbreviations: CS = company submission; DLBCL = diffuse large B-cell lymphoma; DSU = Decision Support Unit; NICE = National Institute for Health and Care Excellence; OS = overall survival; PFS = progression-free survival; PSS = Personal and Social Services; TSD = Technical Support Document.

7. EVIDENCE REVIEW GROUP'S ADDITIONAL ANALYSES

7.1 Exploratory and sensitivity analyses undertaken by the ERG

7.1.1 Explanation of the company adjustments after the request for clarification

Following the clarification questions from the ERG, the company made the following amendments to the originally submitted cost effectiveness model:

- The cost effectiveness model has been updated with clinical trial data from the new data cut from GO29365 ([redacted]).
- The utility values for proximity to death in the model are corrected from 0.49 to 0.47. The new values reflect the corrected utility values from the study where it was sourced [49]
- The administration costs for R-GemOx in the model are updated from £340.42 to £405.72. The updated value reflects use of correct HRG code (SB13Z replaced with SB14Z).
- The AE incidence of R-GemOx for anemia and thrombocytopenia, which are used in the utility decrement calculations are corrected from 33% to 0%; and from 23% to 44%, respectively. These values reflect correct AE rates in the R-GemOx arm from Mounier 2013.[9]

After the changes were made in the model, the company has re-run the base-case, sensitivity and scenario analyses. The discounted base-case deterministic and probabilistic results are presented in Table 7.1 and 7.2, respectively. The tornado diagram from the DSA, the CE-plane and CEAC from the PSA and the results of the scenario analyses are similar to those in the original submission and, therefore, not reported here. Further details can be found in the response to the clarification letter (economic appendix) submitted by the company with the responses to the clarification letter.[2]

Table 7.1: Company base-case cost effectiveness results after clarification (discounted)

Technologies	Total costs (£)	Total LYGs	Total QALYs	Incr. costs (£)	Incr. LYGs	Incr. QALYs	ICER versus baseline (£/QALY)
Pola+BR	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£25,307
BR	£17,440	0.98	0.67	-	-	-	-

Source: Table 2 of the response to the clarification letter (economic appendix).[2]
Abbreviations: BR = bendamustine + rituximab; ICER = incremental cost-effectiveness ratio; Incr. = incremental; LYGs = life years gained; pola = polatuzumab; QALYs = quality-adjusted life years.

Table 7.2: Company base-case probabilistic cost effectiveness results after clarification (discounted)

Technologies	Total costs (£)	Total LYGs	Total QALYs	Incr. costs (£)	Incr. LYGs	Incr. QALYs	ICER versus baseline (£/QALY)
Pola+BR	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£37,749
BR	£17,762	0.98	0.67	-	-	-	-

Source: Table 4 of the response to the clarification letter (economic appendix).[2]
Abbreviations: BR = bendamustine + rituximab; ICER = incremental cost-effectiveness ratio; Incr. = incremental; LYGs = life years gained; pola = polatuzumab; QALYs = quality-adjusted life years.

ERG comment: The company, in its updated model in response to the clarification letter, did not provide the details of its re-conducted survival analysis based on the later cut-off point. The distribution types that were chosen in the original economic model for the OS and PFS extrapolation were not changed in the updated model. The ERG did not detect a major difference in terms of the goodness of fit and visual fit results of the updated survival distributions. However the AIC/BIC results and the visual fit assessments of the newly provided data, conducted by the ERG, is presented in Appendix 4.

The ERG noticed, however, that the updated company model did not integrate the necessary PSA parameters of the PFS and OS extrapolations to the calculations. Especially for the covariance matrices of the "non-proportional" standard parametric distributions, which were needed in the PSA, the model was referring to wrong cells. The ERG corrected these errors in its preferred analyses.

7.1.2 Explanation of the ERG adjustments

The changes made by the ERG (to the model received with the response to the clarification letter) were subdivided into the following three categories (according to Kaltenthaler et al. 2016)[64]:

- Fixing errors (correcting the model where the company's electronic model was unequivocally wrong).
- Fixing violations (correcting the model where the ERG considered that the NICE reference case, scope or best practice has not been adhered to).
- Matters of judgement (amending the model where the ERG considered that reasonable alternative assumptions are preferred).

After these changes were implemented in the company's model, additional scenario analyses were explored by the ERG in order to assess the impact of alternative assumptions on the cost effectiveness results.

7.1.2.1 Fixing errors

The following errors were fixed in the economic model used in the ERG preferred analyses.

The correction of these errors has an impact on the probabilistic results but did not change the deterministic results of the updated company base case.

1. Errors in the implementation of alternative survival curves in the PSA (explained in section 7.1.1 in this report)
2. Errors in the reporting of the probabilistic ICER in the model results sheets (explained in section 6.2.1 in this report)
3. AE incidence varied using beta distribution in the PSA (explained in section 6.2.1 in this report)

7.1.2.2 Fixing violations

4. General population mortality is now calculated based on the "average patient", in line with the cohort approach and not based on individual patient level approach (explained in section 5.2.6.4 in this report)
5. A logical constraint is added to OS, such that the OS from the general population with excess mortality is always larger or equal to the OS from the extrapolations from the GO29365 survival data.

7.1.2.3 Matters of judgement

6. Survival modelling – The ERG did not feel that the data could confidently support the use of cure-mixture models. PFS extrapolation to IRC data is selected from standard lognormal distribution independently fitted to both arms (lowest AIC/BIC scores and plausible visual fit and long-term extrapolation) and OS extrapolation is selected from standard generalised gamma distribution independently (plausible AIC/BIC scores, visual fit and long-term extrapolation) fitted to both arms (see ERG comment in section 5.2.6 and Appendix 4 for detailed explanations for the choice of these distributions).
7. Excess mortality SMR = 1.41 compared to age- and gender-matched general population mortality is applied (see ERG comment in section 5.2.6).
8. HRQOL and cost assumptions for long-term survivors – The time point at which equivalence in HRQoL and cost with general population is assumed has been changed from two to three years, given evidence from the literature that HRQoL may be equivalent after three years (see ERG comment in section 5.2.8).[8] Given the uncertainty in the assumption that patients who have remained event-free for two years will not incur any further costs related to treatment follow-up and monitoring, the ERG base-case extends the time period during which such costs are incurred to three years. This assumption is aligned with those regarding the utilities of the same patients in the ERG base-case (also see ERG comment in section 5.2.9.2).
9. As explained in the ERG comment in section 5.2.9.1, the ERG considers a base-case that reflects the current availability of vial sizes for polatuzumab as the most appropriate. Therefore, the ERG base-case is based on the acquisition costs of polatuzumab that follow from the use of 140 mg vials only, with no vial sharing. (See ERG comment in section 5.2.9)
10. The treatment costs for the Pola+BR and BR regimens are applied for as long as patients in the trial receive treatment (i.e. based on TTOT KM data). In contrast to the company's base-case, it is thus not assumed that the Pola+BR and BR regimens are only provided up to a maximum of six treatment cycles (see ERG comment in section 5.2.9.1).
11. The ERG base-case includes the costs for post-progression treatment with SCT and CAR-T, based on the incidence that follows from the trial data. This deviates from the company's base-case, in which these costs were not included (also see ERG comment in section 5.2.9.2).
12. AE incidences from Table 4.16 in this ERG report were utilised in the model.

Table 7.3: Company and ERG base-case preferred assumptions

Base-case preferred assumptions	Company	Justification	ERG	Justification for change
Survival model PFS	Cure-mixture generalised gamma distribution	1. Literature from the natural history of newly diagnosed DLBCL patients. [4]. 2. The clinical experts' expectation 3. The company considered that a very low risk of relapse or death can be observed in the KM plots for PFS and OS for Pola+BR towards the end of follow-up. 4. The precedent of cure-mixture modelling in previous NICE appraisals for R/R DLBCL patients receiving CAR-T therapies	Independent log-normal	Lack of robust long-term evidence for the cure assumption, the ERG chose among the parametric curves in terms of model fit and plausibility of extrapolations.
Survival model OS	Cure-mixture generalised gamma distribution		Independent generalised gamma	Lack of robust long-term evidence for the cure assumption, the ERG chose among the parametric curves in terms of model fit and plausibility of extrapolations.
Treatment effect	Maintained over the duration of patient's remaining life	Exploratory time-to-event analyses demonstrated a consistent treatment effect for DOR, PFS, EFS and OS	Maintained over the duration of patient's remaining life	No change
HRQoL and cost assumptions for long-term survivors	HRQoL and costs of patients in PFS after 2 years equivalent to age- and sex-matched general population	Evidence from literature suggesting no statistically significant difference in mortality for those DLBCL patients event free at 2 years [4] and limited evidence of no difference in HRQoL	HRQoL and costs of patients in PFS after 3 years equivalent to age- and sex-matched general population	Evidence presented in clarification response suggested that HRQoL may be equivalent after 3 years. [8] Given uncertainty surrounding costs of long-term survivors, this was also extended to 3

Base-case preferred assumptions	Company	Justification	ERG	Justification for change
		between long-term survivors and general population [7]		years to remain consistent with HRQoL assumption
Excess mortality	No excess mortality for long-term survivors compared to age- and sex-matched general population[4]	Evidence from literature suggesting no statistically significant difference in mortality for those DLBCL patients event free at 2 years [4]	Excess mortality SMR=1.41, reflecting increased risk of mortality from non-cancer causes[6]	More recent study with a larger sample of CLBCL patients found that excess mortality remained up until 5 years and overall patients experienced excess mortality from non-cancer causes of 1.41[6]
Vial size	Calculated treatment costs according to vial sizes of 140mg and 30mg with no vial sharing	Assumed that 30mg vial will be available in [redacted], as planned.	Calculated treatment costs according to vial sizes of 140mg with no vial sharing	Given that there is no formal guarantee that the 30mg vial will indeed be available the ERG base-case includes only the 140mg vial, which is the only currently available size
Treatment cost duration	Assumed a maximum of 6 cycles for Pola+BR and BR were received in the economic model.	The company considers this to be in line with the license	The treatment costs for the Pola+BR and BR regimens are applied for as long as patients in the trial receive treatment, based on TTOT KM data.	Given that some patients received the treatment more than six cycles, the clinical effectiveness evidence is dependent on it, and therefore these cycle costs should be incorporated as well.
Costs for post-progression treatments	The company ignored the costs related with SCT and CAR-T	The company considered that these were not standard	The ERG incorporated the costs of SCT for these patients.	Since the effectiveness data is based on those patients who received SCT and CAR-T type

Base-case preferred assumptions	Company	Justification	ERG	Justification for change
	therapies received after the progression.	therapies that are applied post-progression		therapies after progression, ignoring these would cause an inconsistency.
AE incidences	The company uses "serious" grade 3 and above adverse events in the GO29365 trial.	"Serious" adverse events are the adverse events that would lead to costs in NHS	The ERG considered all grade 3 and above adverse events reported in the clinical effectiveness section, wherever possible.	The criteria to consider an adverse event as "serious" by the company was not that clear.

7.1.3 Additional scenarios conducted by the ERG

The ERG conducted a series of additional scenario analyses in order to explore important areas of uncertainty in the model. These key uncertainties were related to the survival modelling (in terms of choice of parametric distributions and modelling of cure assumptions), excess mortality, assumptions surrounding the HRQoL and costs of long-term survivors, sources of utility data and cost and resource use assumptions. Other sources of uncertainty were deemed less important and were not explored in this section. A list of scenario analyses conducted by the ERG is provided below.

7.1.3.1 Scenario set 1: changing PFS parametric distributions

The company base-case assumed a cure mixture generalised gamma model. Given the uncertainty surrounding the cure assumption, discussed in section 5.2.6, the ERG examined alternative plausible independent standard parametric models, including the log-normal (ERG BC), generalised gamma and log logistic models as well as the additional cure-mixture extrapolation of the company in ERG base case settings.

7.1.3.2 Scenario set 2: changing OS parametric distributions

The company base-case assumed a cure mixture generalised gamma model. Again, given the uncertainty surrounding the cure assumption, discussed in section 5.2.6, the ERG examined alternative plausible independent standard parametric models, including the log-normal, generalised gamma and log logistic models as well as the additional cure-mixture extrapolation of the company in ERG base case settings.

7.1.3.3 Scenario set 3: alternative approach to modelling long-term mortality (explicit vs. no explicit cure point)

The company and ERG base-cases assume that the future treatment effect could be extrapolated by independently fitted parametric models over the patient's remaining life. This extrapolation led to an increasing treatment effect in the long-term, as can be seen in Figure 5.14 in this report. Given a lack of robust long-term evidence for this assumption, alternative scenarios were tested. Scenarios were run to assume that the treatment effect for PFS, OS and both curves together steadily declines between the end of current follow up (median follow up 30 months) and 10 years (120 months).

7.1.3.4 Scenario set 4: changing HRQoL and costs assumptions for long-term survivors

The company base-case assumed that those patients who remained in PFS for two years would have HRQoL and costs equivalent to the general population, based on a finding of no statistically significant difference in mortality between DLBCL patients who were event free at two years and the general population. [4] However a more recent study suggested that excess mortality remained until five years.[6] In their clarification response, the company found limited evidence from the literature on a lack of statistically significant difference in HRQoL.[7] However, additional literature evidence provided by the company in their clarification response suggested that a longer period was required, suggesting that after three years HRQoL could be suggested to be equivalent to that of the age- and gender-matched general population. Therefore, in the ERG base-case three years in PFS was assumed for the assumption of equivalence in both costs and HRQoL. In scenarios alterative time points of 2, 5 and 10 years were tested.

7.1.3.5 Scenario set 5: alternative SMRs to model HSCT mortality

The company assumed no excess mortality for long-term DLBCL survivors compared to the age- and sex-matched general population in their base-case. This assumption was based on a finding of no

statistically significant difference in mortality between DLBCL patients who were event free at two years and the general population (SMR=1.09 (95% CI (0.69, 1.74)). [4] However a more recent study suggested that excess mortality remained until five years (SMR=1.41 95% CI (1.35, 1.48)), with DLBCL survivors having a higher risk of non-cancer death that the general population.[6, 7] The company included the SMR of 1.09 in a scenario analysis. The ERG selected the SMR of 1.41 for their base-case and tested SMRs of 1, 1.09 and 1.18 (cited in the Maurer paper[4]) in scenario analyses.

7.1.3.6 Scenario set 6: utilities

In this set of scenarios, the ERG tested the impact of utilising different sources of utility values identified by the company, including those values from TA567 and TA306. [5, 13]

7.1.3.7 Scenario set 7: costs and resource use

A set of scenarios analyses is performed to test, first, the impact of the future availability of a 30 mg vial for Pola alongside the 140 mg vial with no vial sharing, and, second, the impact of arrangements with NHS compounding services for correct patient-specific dosing (which are planned for the time period during which only the 140 mg vials are available) to minimize wastage. The latter scenario is tested by assuming a 100 % vial sharing scenario for Pola.

7.2 Impact on the ICER of additional clinical and economic analyses undertaken by the ERG

7.2.1 Results of the ERG preferred base-case scenario

The results of the ERG preferred base-case are provided in Table 7.4. The ERG base-case resulted in a deterministic ICER of £67,499, approximately 2.5 times larger than the company's original base-case ICER of £26,877.

Table 7.4: ERG base-case deterministic results (discounted)

Technologies	Total costs (£)	Total LYGs	Total QALYs	Incr. costs (£)	Incr. LYGs	Incr. QALYs	ICER versus baseline (£/QALY)
Pola+BR	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£67,499
BR	£19,904	1.00	0.68				

BR = bendamustine + rituximab; ERG = Evidence Review Group; ICER = incremental cost-effectiveness ratio, Incr. = incremental, LYGs = life years gained, pola = polatuzumab, QALY = quality-adjusted life year

As shown in Table 7.5, for both treatments, approximately 2/3 of the QALYs were generated in the progression free survival state. QALYs gained in each state and in total were substantially higher for Pola+BR compared to BR, resulting in incremental QALYs of [redacted].

Table 7.5: ERG base-case disaggregated discounted QALYs

QALYs gained	Pola+BR	BR	Incremental
PFS	[redacted]	0.422	[redacted]
PD	[redacted]	0.267	[redacted]
Total QALYs	[redacted]	0.676	[redacted]

Source: electronic model, updated from the response to the clarification letter.[2]
BR = bendamustine + rituximab; ERG = Evidence Review Group; PD = progressed disaease; PFS = progression free survival; pola = polatuzumab; QALY = quality-adjusted life year

Polatuzumab was the largest cost element in the model and is responsible for [redacted] of the [redacted] incremental total cost, as displayed in Table 7.6. The next largest source of differences between the costs of the two treatments arms is supportive care costs in progressive disease, which are [redacted] higher in the polatuzumab arm.

Table 7.6: ERG base-case disaggregated costs

Costs per health state	Pola+BR	BR	Incremental
PFS State			
Polatuzumab	[redacted]	£0	[redacted]
Bendamustine	£455	£321	£134
Rituximab	£2,796	£1,946	£850
Drug administration	£3,516	£2,250	£1,266
AE management	£855	£718	£137
Supportive care	£10,223	£4,523	£5,700
Productivity loss	£0	£0	£0
Travel	£0	£0	£0
Informal care	£0	£0	£0
Total PFS cost	[redacted]	**£9,757**	[redacted]
PD State			
Supportive care	[redacted]	£10,146	[redacted]
Productivity loss	£0	££0	£0
Travel	£0	£0	£0
Informal care	£0	£0	£0
Total PD cost	[redacted]	**£10,146**	[redacted]
End of life cost	£0	£0	£0
Total cost	[redacted]	**£19,904**	[redacted]

Based on electronic model, updated from the response to the clarification letter.[2]
AE = adverse event; BR = bendamustine + rituximab; ERG = Evidence Review Group; PD = progressed disaease; PFS = progression free state; pola = polatuzumab

The ERG also conducted a PSA using their preferred base-case assumptions. Results displayed in Table 7.7 show that the probabilistic ICER is £68,619, slightly higher than the base-case ICER of £67,499.

Table 7.7: ERG base-case probabilistic results (discounted)

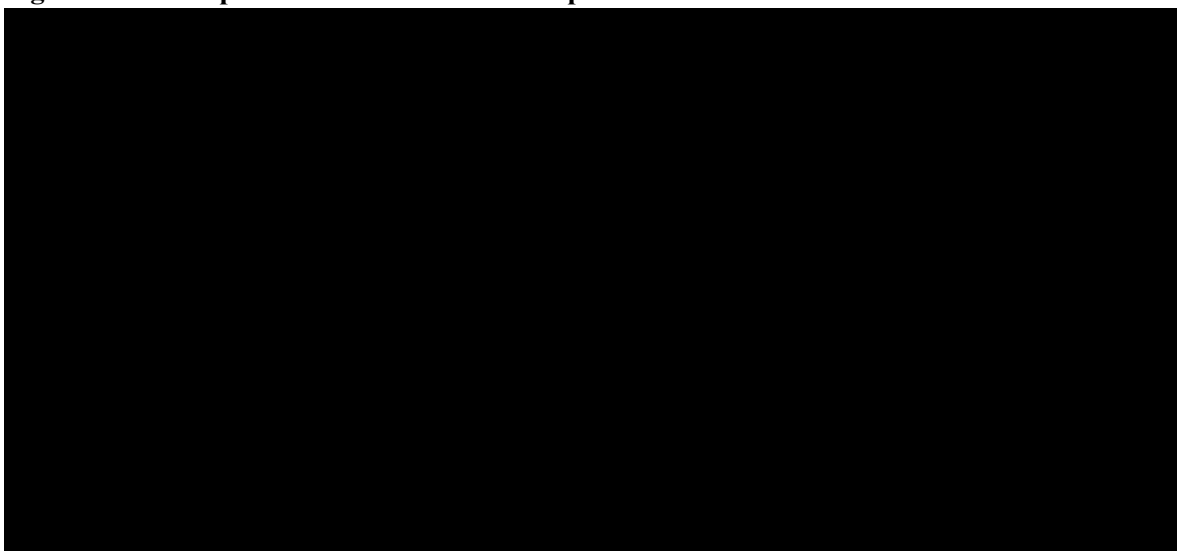
Technologies	Total costs (£)	Total LYGs	Total QALYs	Incr. costs (£)	Incr. LYGs	Incr. QALYs	ICER versus baseline (£/QALY)
Pola+BR	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£68,619
BR	£23,628	1.165	0.782				

BR = bendamustine + rituximab; ERG = Evidence Review Group; ICER = incremental cost-effectiveness ratio; Incr. = incremental; LYGs = life years gained; pola = polatuzumab; QALY = quality-adjusted life year

The incremental costs and QALYs resulting from each of the 1,000 simulations of the ERG PSA are plotted on the cost effectiveness plane displayed in Figure 7.1. The vast majority of the simulations fell

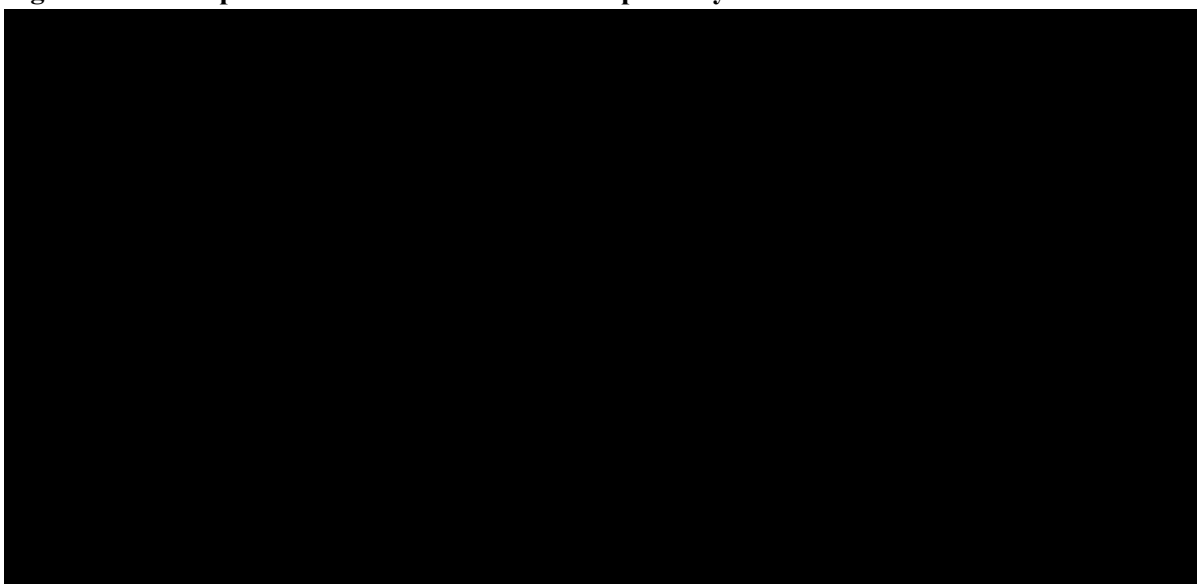
into the north-east quadrant of the CE-plane. The CEAC in Figure 7.2 shows that at WTP thresholds of £20,000 and £30,000, the probability that polatuzumab is cost effective is 0%.

Figure 7.1: ERG preferred cost effectiveness plane



Based on electronic model
BR = bendamustine + rituximab; ERG = Evidence Review Group; Inc. = incremental; pola = polatuzumab; QALY = quality-adjusted life year

Figure 7.2: ERG preferred cost effectiveness acceptability curve



Based on electronic model
BR = bendamustine + rituximab; ERG = Evidence Review Group; pola = polatuzumab; WTP = willingness-to-pay

7.2.2 Results of the ERG additional exploratory scenario analyses

7.2.2.1 Additional scenario 1: changing PFS parametric distributions

Alternative scenarios surrounding the extrapolation of PFS were explored by the ERG, with results displayed in Table 7.8. In the CS the company utilised a cure mixture generalised gamma model for PFS, which led to the lowest ICER of those tested by the ERG (£53,088). Given the uncertainty surrounding the cure assumption, discussed in section 5.2.6, the ERG preferred the use of independent parametric distributions, with the independent log-normal being chosen for the base case. The two most plausible alternative independent parametric model extrapolations for PFS (the log-logistic and log-normal) gave similar ICERs of £65,920 and £67,499 respectively.

Table 7.8: ERG PFS scenario analyses

PFS distribution	Pola+BR		BR		Incr. Costs (£)	Incr. QALYs	ICER (£)
	Costs (£)	QALYs	Costs (£)	QALYs			
Cure-mixture generalised gamma (CS)	[redacted]	[redacted]	£19,291	0.68	[redacted]	[redacted]	£53,088
Independent log-logistic model	[redacted]	[redacted]	£19,344	0.68	[redacted]	[redacted]	£65,920
Independent generalised gamma model	[redacted]	[redacted]	£19,247	0.68	[redacted]	[redacted]	£53,925
Independent log-normal model (ERG)	[redacted]	[redacted]	£19,904	0.676	[redacted]	[redacted]	£67,499

BR = bendamustine + rituximab; CS = company submission; ERG = Evidence Review Group; ICER = incremental cost-effectiveness ratio; Incr. = incremental; PFS = progression free survival; pola = polatuzumab; QALY = quality-adjusted life year

7.2.2.2 Additional scenario 2: changing OS parametric distributions

The company also utilised the generalised gamma cure mixture model in their base-case for OS extrapolation. As shown in Table 7.9, this gave the lowest ICER of the alternatives tested by the ERG (£63,867). Again, given the ERG's uncertainty surrounding the cure assumption, they tested alternative non-cure models. The two most plausible independent extrapolations for OS were the log-normal and the generalised gamma, with the generalised gamma chosen for the ERG base-case. The generalised gamma gave an ICER slightly higher than the company base-case choice, resulting in an ICER of £67,499, while the log-normal gave a substantially higher ICER of £82,399.

Table 7.9: ERG OS scenario analyses

OS scenario	Pola+BR		BR		Incr. Costs (£)	Incr. QALYs	ICER (£)
	Costs (£)	QALYs	Costs (£)	QALYs			
Cure mixture generalised gamma (CS)	[redacted]	[redacted]	£19,462	0.660	[redacted]	[redacted]	£63,867
Independent log-normal model	[redacted]	[redacted]	£19,185	0.651	[redacted]	[redacted]	£82,399
Independent log-logistic model	[redacted]	[redacted]	£19,846	0.67	[redacted]	[redacted]	£81,843
Independent generalised gamma model (ERG)	[redacted]	[redacted]	£19,904	0.676	[redacted]	[redacted]	£67,499

Source: electronic model, updated from the response to the clarification letter.[2]
BR = bendamustine + rituximab; CS = company submission; ERG = Evidence Review Group; ICER = incremental cost-effectiveness ratio; Incr. = incremental; OS = overall survival; pola = polatuzumab; QALY = quality-adjusted life year

7.2.2.3 Additional scenario 3: treatment effect assumptions

Given the ERGs uncertainty surrounding the maintenance of the long-term treatment effect, assumed in both the company and ERG base-cases, scenarios were tested, examining the impact of steadily declining treatments effects from 30 months to zero at 120 months for OS, PSF and both curves together. As shown in Table 7.10, reducing the treatment effect for PFS had little impact on the ICER, however reducing the treatment effect for OS substantially increased the ICER from £67,499 to £78,312, and reducing the treatment effect on both curves simultaneously increased the ICER further to £81,245, with most impact coming from OS. Therefore assumptions surrounding the long-term treatment effect on survival is an important element in the cost-effectiveness of polatuzumab.

Table 7.10: ERG treatment effect scenario analyses

Treatment effect	Pola+BR		BR		Incr. Costs (£)	Incr. QALYs	ICER (£)
	Costs (£)	QALYs	Costs (£)	QALYs			
Treatment effect maintained (CS and ERG BC)	[redacted]	[redacted]	£19,904	0.68	[redacted]	[redacted]	£67,499
Declining OS treatment effect duration	[redacted]	[redacted]	£19,904	0.68	[redacted]	[redacted]	£78,312
Declining PFS treatment effect duration	[redacted]	[redacted]	£19,904	0.68	[redacted]	[redacted]	£69,711

Treatment effect	Pola+BR		BR		Incr. Costs (£)	Incr. QALYs	ICER (£)
	Costs (£)	QALYs	Costs (£)	QALYs			
Declining OS and PFS treatment effect duration	[redacted]	[redacted]	£19,904	0.68	[redacted]	[redacted]	£81,245

Source: electronic model, updated from the response to the clarification letter.[2]
BC = base case; BR = bendamustine + rituximab; CS = company submission; ERG = Evidence Review Group; ICER = incremental cost effectiveness ratio; Incr. = incremental; OS = overall survival; PFS = progression free survival; pola = polatuzumab; QALY = quality-adjusted life year

7.2.2.4 Additional scenario 4: changing long-term survivor assumptions

The company base-case assumed that the costs and HRQoL of long-term survivors were equivalent to those of the general population after two years. However the ERG were concerned that evidence from the literature suggested that, while costs and HRQoL did converge over time, this two-year time point was overly optimistic. Therefore, in the ERG base-case three years was chosen given evidence [8] cited by the company in their clarification response. The ERG also tested scenarios of five years (based on Howlader et al (2017) [6] and 10 years. As seen in Table 7.11, longer time periods gradually increased the ICER, however the impact was fairly small, with the change from two to three years being less than £1,500 and the change from two to 10 years being less than £4,500.

Table 7.11: ERG long-term survivor scenario analyses

Time HRQoL and costs = gen pop	Pola+BR		BR		Incr. Costs (£)	Incr. QALYs	ICER (£)
	Costs (£)	QALYs	Costs (£)	QALYs			
2 (Company BC)	[redacted]	[redacted]	£19,625	0.68	[redacted]	[redacted]	£66,151
3 (ERG BC)	[redacted]	[redacted]	£19,904	0.68	[redacted]	[redacted]	£67,499
5 (Howlader)	[redacted]	[redacted]	£20,115	0.67	[redacted]	[redacted]	£69,068
10	[redacted]	[redacted]	£20,231	0.67	[redacted]	[redacted]	£70,523

Based on electronic model, updated from the response to the clarification letter.[2]
BC = base case; BR = bendamustine + rituximab; CS = company submission; ERG = Evidence Review Group; HRQoL = health related quality of life; ICER = incremental cost effectiveness ratio; Incr. = incremental; pola = polatuzumab; QALY = quality-adjusted life year

7.2.2.5 Additional scenario 5: changing excess mortality compared to general population

In the company base-case it was assumed that long-term survivors experienced no excess mortality as compared to the general population. This assumption was based on a lack of significant difference found in Maurer et al (2014).[4] In this paper the mean estimate was an SMR=1.09, with an alternative mean estimate of SMR=1.18 in a sample of French patients also cited. The ERG identified an alternative estimate of 1.41 from Howlader et al (2017) [6]. Therefore assumptions of SMRs of 1, 1.09, 1.18 and 1.41 were tested, with results displayed in Table 7.12. Again the ICER steadily increased with the larger

SMRs, however the impact was small, with the change from no excess mortality to SMR=1.41 increasing the ICER by less than £1,000.

Table 7.12: ERG excess mortality scenario analyses

SMR	Pola+BR		BR		Incr. Costs (£)	Incr. QALYs	ICER (£)
	Costs (£)	QALYs	Costs (£)	QALYs			
1 (Company BC)	[redacted]	[redacted]	£19,906	0.68	[redacted]	[redacted]	£66,662
1.09 (Company SA)	[redacted]	[redacted]	£19,906	0.68	[redacted]	[redacted]	£66,845
1.18	[redacted]	[redacted]	£19,905	0.68	[redacted]	[redacted]	£67,031
1.41 (ERG BC)	[redacted]	[redacted]	£19,904	0.68	[redacted]	[redacted]	£67,499

Based on electronic model, updated from the response to the clarification letter.[2]
BC = base case; BR = bendamustine + rituximab; ERG = Evidence Review Group; ICER = incremental cost effectiveness ratio; Incr. = incremental; pola = polatuzumab; QALY = quality-adjusted life year; SA = scenario analysis; SMR = standardised mortality ratio

7.2.2.6 Additional scenario 6: Utility values

In this set of scenarios, the ERG tested the impact of using different health state utility values sources identified by the company. As shown in Table 7.13, the utility values from TA306 provided the highest ICER at £67,596, while the utilities from TA567 provided the lowest ICER of £63,353. However, the small variation in ICERs shows that the utility values themselves are not big drivers of model results.

Table 7.13: ERG Utility value scenario analyses

Source of utility values	Pola+BR		BR		Incr. Costs (£)	Incr. QALYs	ICER (£)
	Costs (£)	QALYs	Costs (£)	QALYs			
TA559 (PFS=0.72 PD=0.65) (BC	[redacted]	[redacted]	£19,904	0.68	[redacted]	[redacted]	£67,499
TA567 (PFS=0.83 PD=0.71)	[redacted]	[redacted]	£19,904	0.74	[redacted]	[redacted]	£63,353
TA306 (PFS=0.81 PD=0.60)	[redacted]	[redacted]	£19,904	0.69	[redacted]	[redacted]	£67,596
TA176 FAD (PFS=0.76 PD=0.68)	[redacted]	[redacted]	£19,904	0.71	[redacted]	[redacted]	£65,085

Source: electronic model, updated from the response to the clarification letter.[2]

Source of utility values	Pola+BR		BR		Incr. Costs (£)	Incr. QALYs	ICER (£)
	Costs (£)	QALYs	Costs (£)	QALYs			
BC = base case; BR = bendamustine + rituximab; ERG = Evidence Review Group; FAD = final appraisal determination; ICER = incremental cost effectiveness ratio; Incr. = incremental; PD = progressed disease; PFS = progression free survival; pola = polatuzumab; QALY = quality-adjusted life year							

7.2.2.7 Additional scenario 7: Cost and resource use

Table 7.14 shows the results of a scenario to assess the impact of the future availability of a 30 mg vial for polatuzumab vedotin alongside the 140 mg vial with no vial sharing, and a scenario to assess the impact of arrangements with NHS compounding services for correct patient-specific dosing to minimize wastage. Assuming the availability of 30mg vials decreased the ICER to £53,910, a substantial decrease of £13,500. Assuming individual dosing arrangements to minimise waste also substantially lowered the ICER by approximately £15,000 to £51,574. These scenarios reflect the importance of wastage for the cost-effectiveness of polatuzumab.

Table 7.14: ERG Cost scenario analyses

Cost scenario	Pola + BR		BR		Incr. Costs (£)	Incr. QALYs	ICER (£)
	Costs (£)	QALYs	Costs (£)	QALYs			
140mg vial only and no vial sharing (ERG BC)	[redacted]	[redacted]	£19,904	0.68	[redacted]	[redacted]	£67,499
140 mg and 30 mg vial sizes for polatuzumab vedotin available (CS BC)	[redacted]	[redacted]	£19,904	0.68	[redacted]	[redacted]	£53,910
No wastage / 100% vial sharing for polatuzumab vedotin	[redacted]	[redacted]	£19,904	0.68	[redacted]	[redacted]	£51,574
Based on electronic model, updated from the response to the clarification letter.[2] BC = base case; BR = bendamustine + rituximab; CS = company submission; ERG = Evidence Review Group; ICER = incremental cost effectiveness ratio; Incr. = incremental; pola = polatuzumab; QALY = quality-adjusted life year; SA = scenario analysis; SMR = standardised mortality ratio							

7.3 ERG's preferred assumptions

The ERG preferred changes to the updated company base-case were described in Section 7.1.2 of this report. The cost effectiveness results of the ERG preferred base-case are presented in Table 7.15 in thirteen steps. In each step, the cumulative impact on the model results is shown. The following steps had the largest impact on the ICER: step 4 (following a cohort approach in modelling background mortality), step 6 (changing the OS and PFS extrapolation from cure mixture to the more plausible standard, independent parametric distributions) and step 9 (changing the available vial size to 140 mg only, as it is the only available vial option currently). Steps 6 and 9 have substantial impacts on costs

whereas step 3 has an impact on both costs and QALYs, as it led to shorter life expectancy in both Pola+BR and BR arms.

Table 7.15: ERG's preferred model assumptions

Preferred assumption	Section in ERG report	Pola + BR		BR		Inc. Costs (£)	Inc. QALYs	Cumulative ICER (£/QALY)
		Total Costs (£)	Total QALYs	Total Costs (£)	Total QALYs			
Company base-case	6.1	[redacted]	[redacted]	£18,019	0.68	[redacted]	[redacted]	£26,877
Company updated base-case (after clarification)	7.1.1	[redacted]	[redacted]	£17,440	0.67	[redacted]	[redacted]	£25,307
ERG changes (1 –3): Fixing the errors	7.1.2.1	[redacted]	[redacted]	£17,440	0.67	[redacted]	[redacted]	£25,307
ERG changes (1-3)+4: Following a cohort approach in background mortality	7.1.2.2	[redacted]	[redacted]	£17,249	0.64	[redacted]	[redacted]	£35,787
ERG changes (1-4)+5: Logical constraint on OS (OS from the extrapolation can be at maximum equal to the OS estimated from the age/sex adjusted general population with excess mortality)	7.1.2.2	[redacted]	[redacted]	£17,249	0.64	[redacted]	[redacted]	£35,787
ERG changes (1-5) +6: Changing the OS and PFS extrapolation from cure-mixture models to standard independently fitted parametric models (using IRC PFS data)	7.1.2.3	[redacted]	[redacted]	£17,386	0.68	[redacted]	[redacted]	£50,451
ERG changes (1-6) +7: Changing the excess mortality for non-cancer related deaths from 1.0 to the literature-based value of 1.41	7.1.2.3	[redacted]	[redacted]	£17,379	0.68	[redacted]	[redacted]	£50,447
ERG changes (1-7) +8: HRQoL and cost assumption for long-term survivors in PFS (time threshold from 2 years to 3 years)	7.1.2.3	[redacted]	[redacted]	£17,658	0.68	[redacted]	[redacted]	£51,698

Preferred assumption	Section in ERG report	Pola + BR		BR		Inc. Costs (£)	Inc. QALYs	Cumulative ICER (£/QALY)
		Total Costs (£)	Total QALYs	Total Costs (£)	Total QALYs			
ERG changes (1-8) +9: Available vial size (only 140 mg)	7.1.2.3	[redacted]	[redacted]	£17,658	0.68	[redacted]	[redacted]	£64,549
ERG changes (1-9) +10: Treatments can be administered longer than 6 cycles, in line with the observed TTOT curves	7.1.2.3	[redacted]	[redacted]	£17,794	0.68	[redacted]	[redacted]	£67,478
ERG changes (1-10) +11: Applying one-off SCT costs to the patients who received SCT or CAR-T treatments after progression from the first line	7.1.2.3	[redacted]	[redacted]	£19,511	0.68	[redacted]	[redacted]	£67,438
ERG changes (1-11) +12: Applying the updated AE incidences	7.1.2.3	[redacted]	[redacted]	£19,904	0.68	[redacted]	[redacted]	£67,499

Abbreviations: AE = adverse event; BR = bendamustine + rituximab; ERG = Evidence Review Group; HRQoL= health related quality of life; ICER = incremental cost effectiveness ratio; Inc. = incremental; IRC = independent research committee; OS = overall survival; PFS = progression free survival; pola = polatuzumab; QALY = quality adjusted life year; SCT = stem cell transplant; TTOT= time on treatment;

7.4 Conclusions of the cost effectiveness section

To assess the cost-effectiveness of polatuzumab vedotin (Pola), in combination with bendamustine and rituximab (BR), compared to BR alone, the company developed a three state partitioned survival model that includes the following health states: progression-free, progressed disease and death. Transitions between health states were informed by extrapolated survival curves for PFS and OS from the GO29365 trial. Patients started in the progression-free state, where they remained until progression or death. Upon progression, patients either remained in the progressed disease state, or they died. After 2 years in the progression-free state, patients were considered to have characteristics similar to those of the general population. Therefore, age/sex adjusted general population utility values and zero healthcare resource use cost values were assigned to those patients who did not progress in their first two years. Cost and health outcomes were discounted at 3.5%.

In the progression-free state, patients received treatment according to TTOT data from GO29365. However, also a maximum number of six treatment cycles of three weeks was applied for Pola+BR, as well as for BR. An additional scenario was performed to assess cost-effectiveness against a different comparator: a combination of rituximab, gemcitabine, and oxaliplatin (R-GemOx). For R-GemOx, effectiveness was assumed to be equivalent to BR, and a maximum number of three treatment cycles of three weeks was assumed. It is unclear to what extent these assumptions, particularly that of equivalent effectiveness, reflect the actual comparative effectiveness in clinical practice. Therefore, the ERG are cautious about the use of the R-GemOx comparator in this model.

The company base-case assumed cure mixture models for both OS and PFS extrapolation. Instead of using standard cure mixture modelling codes available in statistical programs, the company developed its own code, which was not transparent and clear enough for the ERG to assess the correctness of the implementation of the methods in the provided code. The "cure" assumption of the company was based on: literature from the natural history of newly diagnosed DLBCL patients, which suggested no significant difference between the mortality of those patients event free at 2 years and the age- and sex-matched general population; clinical expert opinion; the company's observation of low risk of relapse or death in the KM plots for Pola+BR towards the end of follow-up and the precedent for cure mixture modelling accepted in previous NICE appraisals in R/R DLBCL patients.[3-5] However, the ERG felt that there was a lack of robust long-term evidence to be confident in a cure assumption, especially given the small number of patients remaining alive and event free at the end of a relatively short follow-up period. The ERG also note that the previous technology appraisals were for CAR-T therapies which represent a distinct form of therapy and alternative literature suggests that excess mortality in DLBCL remains for at least five years. [6] Additionally, the company's base-case assumptions of cure-mixture models led to OS and PFS hazard ratios, which were not in line with the empirical hazard plots for OS and PFS from the GO29365 trial and which conferred an overly optimistic treatment benefit, even decades after the treatment is received. Therefore, the ERG explored alternative independent standard parametric survival extrapolation models in their base-case and scenario analyses, and also a logical constraint is enforced, which ensures that the OS extrapolation from the trial provides a lower survival estimate from the age/sex adjusted general population at any given point time.

The ERG considered the company's assumption of no excess mortality in DLBCL long-term survivors compared to the general population to be overly optimistic. This assumption was based on a US study by Maurer et al (2014) which found no statistically significant difference between the mortality of newly diagnosed DLBCL who survived event free to two years and the age- and gender-matched general population.[4] However a more recent study based on a substantially larger sample of DLBCL patients suggests that excess mortality remains up to five years and that overall, DLBCL survivors are at excess

risk of mortality due to non-cancer causes as well as the risk of late relapse. [6] Therefore this excess mortality due to non-cancer causes was incorporated into the ERG base-case.

Another important issue was the way the non-cancer background mortality was included in the model. In contrast to the cohort-based approach followed for modelling the cancer-related progression and death events, the company followed an individual patient-level approach while modelling the non-cancer, background mortality risks. The economic model calculates the weighted mortality risk from the individual age- and sex-matched specific mortality risks from a cohort of 160 patients (50%-50% male-female, characterizing the age distribution of the GO29365 trial). This created an inconsistency, as the relatively younger patients' lifetable based survival estimates are taken into the weighted average, hence leading to instances where a significant proportion is still alive after 40 or 50 years, which is not realistic from a cohort modelling perspective, as the average age of the cohort was 69. Therefore, the ERG switched to cohort based modelling for non-cancer background mortality risks, as well.

Additional important sources of uncertainty in the model are the assumptions made regarding the HRQoL and costs of long-term survivors. In the company submission, the argument of a lack of statistically significant excess mortality at two years, was extended to argue that the HRQoL of DLBCL patients would be equivalent to that of the age- and sex-matched general population after two years in the PFS state. When the ERG requested evidence specific to HRQoL, the company provided two literature reviews which provided some support for equivalence in HRQoL in long term survivors.[7] However, one of these explicitly specified that HRQoL between these two groups was more comparable after three years. [8] Given the parallel uncertainty regarding the assumption of equivalent healthcare costs after two years, which have been previously noted in TA559, in the ERG base-case the assumption of two years was extended to three years for both HRQoL and costs to provide a more conservative estimate.

AEs were incorporated for Pola+BR and BR based on incidences from GO29365, and for R-GemOx based on findings from the study by Mournier et al., 2013. [9] The ERG identified several inconsistencies between the AE incidences used in the model and the incidences presented in clinical effectiveness section of this ERG report for the GO29365 trial, in terms of the number of serious AEs reported in each treatment arm. Therefore the ERG updated the model incidences to reflect the incidences for the most frequently reported Grade 3-5 adverse events (>5%).

In response to a lack of HRQoL data collection in the GO29365 trial, the company conducted a thorough literature search for relevant health state utility values. The base-case utility values, estimated from the safety management population of the ZUMA-1 trial using the EQ-5D-5L were based on a small sample (34 patients provided 87 observations) of mixed histology lymphoma patients. The progressed disease value in particular was based on a very small sample as it was estimated from only five observations. The patient characteristics of the members of the ZUMA-1 trial who provided HRQoL data were not available and therefore it is unclear how similar this group were to the GO29365 population or the R/R DLBCL patients who would be expected to receive polatuzumab in clinical practice. However, despite these limitations the ERG agree that none of the alternative utility sources identified provided a better alternative when considering the alignment with the NICE reference case and therefore this source of utility values were retained in the ERG base-case. Disutilities for those AEs included in the model were appropriately sourced from previous appraisals in R/R DLBCL.

The economic analysis was performed from the NHS and PSS perspective and included state-specific costs for drug acquisition and administration, treatment-related AEs, routine supportive care (professional and social services, health care professionals and hospital resource use, treatment follow-up; for a maximum of two years), and subsequent treatment costs. Healthcare unit costs were obtained

from the National Audit Office 2008[10], Personal Social Services Research Unit (PSSRU) 2018[11], and NHS reference costs.[12] The frequencies of healthcare resource use were primarily sourced from TA306.[13] Drug costs were taken from the British National Formulary (BNF) and electronic Market Information Tool (eMIT) databases. The dose information was derived from the GO29365 trial, whereas for the R-GemOx, it was obtained from Mounier et al.[9] Administration and adverse event costs were mostly obtained from NHS reference costs and percentage of the treatments used in the subsequent treatments were from the GO29365 trial and clinical expert opinion.

The ERG was also concerned with several assumptions made in the company base-case regarding costs and resource use. Polatuzumab is currently only available in 140 mg vials. However, in the company base-case the company also included 30 mg vials, stating that they plan to provide these from [redacted]. However, given that this statement is subject to uncertainty and no formal agreement is in place, the ERG feel that the base-case should conservatively assume that the current situation will remain. The ERG also felt that the costing of a maximum of six cycles of Pola+BR and BR, contrary to the included TTOT data from the trial was incorrect. Since the treatment effectiveness from the trial is based on the application of the treatment longer than six cycles, not including the costs of these treatments beyond cycle six would create a bias. In the ERG base-case these treatments were costed according to the TTOT data provided. The company also excluded the costs of SCT and CAR-T, despite these having been received by trial participants. The ERG feels that this was inappropriate and therefore attempted to include these costs in the ERG base-case. CAR-Ts are currently available of the NHS only under confidential PAS and therefore the cost of SCT was utilised for both treatments.

Alongside their clarification response the company submitted an updated model using data from the latest data cut-off point of the clinical trial, corrected utility values for the proximity to death scenario, corrected administration costs for R-GemOx and corrected AE incidences for R-GemOx. This resulted in an updated company base-case ICER of £25,307.

Following this, the ERG fixed several errors identified in the models PSA and corrected the calculation of general population mortality to follow the standard cohort approach. The ERG also replaced the mixture-cure model survival curves with appropriate parametric distributions, updated the estimate of excess mortality from an SMR of 1 to 1.41 to reflect the increased risk of death from non-cancer causes in DLBCL survivors, updated the time point at which the costs and HRQoL of long term survivors were assumed to be equivalent to the general population from two to three years, allowed only 140 mg vials and utilised the provided TTOT data in the calculation of treatment costs for polatuzumab and included the costs of subsequent SCT and CAR-T therapies (both costed using the price of SCT). This resulted in an ERG base-case of £67,499, approximately 2.5 times the size of the company base-case ICER. The ERG PSA results provided an ICER of £68,619, with the vast majority of simulations falling in the north-east quadrant of the CE plane. The CEAC showed that the probability that polatuzumab is cost effective at WTP thresholds of £20,000 and £30,000 is 0%.

The ERG scenario analyses which had the biggest impact on the ICER were those assumptions surrounding survival extrapolation, treatment effect duration, vial sharing and available vial sizes. The remaining scenarios did not have a substantial impact on the ICER.

8. END OF LIFE

Table 37 of the CS indicated that the company wished end of life criteria to be taken into account in this appraisal. According to the NICE criteria for End of Life, the following should be satisfied:

- The treatment is indicated for patients with a short life expectancy, normally less than 24 months and;
- There is sufficient evidence to indicate that the treatment offers an extension to life, normally of at least an additional 3 months, compared to current NHS treatment.

In regard to life expectancy, the company provided evidence from the research literature of the poor survival outcomes in relapsed and refractory DLBCL. They also stated that '*The median OS for the comparator arm (BR) in the GO29365 study was* [redacted]. *The average survival estimated in the economic analysis was 12.2 months.*'[14]

In regard to an extension of life with pola +BR, the company stated that '*The estimated mean OS gain of Pola+BR over BR in the model was 4.1 years.*' [14]

ERG comment: The ERG believes that end of life criteria are met. The prognosis of untreated patients is poor as witnessed by the median survival time in the control group of GO29365. In a study by Crump and colleagues, patients with refractory DLBCL had a median overall survival of 6.3 months: only 20% of patients were alive at two years.[17] The extension to life identified in the GO29365 was a difference in medians of about [redacted]. The model predicted a much larger gain due to the cure-mixed approach taken but this should be interpreted with some caution. Nevertheless, the ERG base-case showed a total 2.08 life years gain between two interventions.

9. REFERENCES

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Appendix 1: Eligibility criteria for the systematic review

Inclusion Criteria		Exclusion Criteria
Population	Adult patients (≥18years) with R/R DLBCL who are receiving second or third-line (or beyond) therapy Subgroups of interest include: • SCT ineligible • Failed transplant patients • Duration of response to prior therapy: ≤12 months vs. >12 months • Disease burden: high vs. low • Age (≤60 vs. >60) • Stage of Disease (I–II vs. III–IV) • Prior systemic therapy • Refractory vs. relapse • Extranodal-site involvement (0–1 vs. 2–4) • Eastern Cooperative Oncology Group (ECOG) Score	Animal/in vitro studies
Interventions	Polatuzumab vedotin in combination with bendamustine plus rituximab	
Comparators	Licensed or investigational pharmaceutical treatment available for R/R DLBCL patients: Bendamustine+/–rituximab Brentuximab vedotin CEPP (Cyclophosphamide, Etoposide, Procarbazine) +/– rituximab CEOP (Cyclophosphamide, Etoposide, Vincristine) +/– rituximab DA-EPOCH (Cyclophosphamide, Doxorubicin, Etoposide, Vincristine) +/– rituximab GDP (Cisplatin, Dexamethasone, Gemcitabine) +/–rituximab Carboplatin, Dexamethasone, Gemcitabine +/– rituximab Gemox (Gemcitabine, Oxaliplatin) +/– rituximab Gemcitabine + vinorelbine +/– rituximab Lenalidomide +/– rituximab Rituximab Ibrutinib Pixantrone CAR-T (Axicabtagene ciloleucel or Tisagenlecleucel) MOR208 Venetoclax Apatinib DHAP (dexamethasone, cytarabine, cisplatin) +/– rituximab ICE (ifosfamide, etoposide, carboplatin) +/– rituximab MINE (mesna, ifosfamide, mitoxantrone, etoposide) +/– rituximab ESHAP (etoposide, methylprednisolone, cytarabine, cisplatin) +/– rituximab IME (ifosfamide, mitoxantrone, etoposide) +/– rituximab IVE (ifosfamide, epirubicin and etoposide) +/– rituximab CEPP R+/–PECC (Rituximab-Prednisone, Etoposide, Chlorambucil, Lomustine) BSC/placebo .	First-line treatments Non-pharmacological therapies

Inclusion Criteria		Exclusion Criteria
Outcomes	Efficacy: • OS • PFS • TTP • EFS • Duration of response • Response rates (CR, PR, SD) • Any response rates reported as PET-CR (i.e. metabolic CR) or using older criteria (e.g. CRu), or a mixture of various different criteria (Lugano, modified Lugano) • ORR • DCR • Duration of treatment and duration of treatment beyond progression Safety • All-grade treatment related AE • Treatment related Grade 3 or 4 AEs • Treatment related SAEs • Tolerability: dose reductions and interruptions, discontinuation (any reason), discontinuation (due to AEs) • HRQoL and PRO measures (e.g. EORTC QLQ-C30)	Outcome(s) not listed
Study design / setting	RCTs, any duration (irrespective of blinding) Prospective single arm studies Comparative observation studies	Reviews/editorials, case reports/case series Retrospective single arm studies
Language of publication	English language publications	Non-English language publications without an English abstract.
Date of publication	No restriction	
Countries	No restriction	

Source: Appendix D of the CS[14]

AE = adverse event; BSC = best supportive care; CR = complete response; DCR = disease control rate; ECOG = Eastern Cooperative Oncology Group; EFS = event free survival; EORTC QLQ-C30 = The European Organization for Research and Treatment of Cancer quality of life questionnaire; HRQoL = Health-related quality of life; ORR = objective response rate; OS = overall survival; PFS = progression free survival; PR = partial response; RCT = randomised controlled trial; R/R DLBCL = relapse/refractory diffuse large B-cell lymphoma; SAE = serious adverse events; SCT = stem cell transplantation; SD = stable disease; SLR = systematic literature review; TTP, time to progression

Appendix 2: Supplementary Information - Searching

Table A2.1: Data sources for the clinical effectiveness systematic review

Search strategy element	Resource	Host/source	Reported date range	Date searched
Electronic databases	Medline	OVID	1946-June 07 2019	6 September 2018 Update searches on 10 June 2019
	Medline Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Medline Daily			
	Embase		1974- 2018 Week 36 1980-2019 Week 23	
	Cochrane CENTRAL	EBM Reviews via OVID	October 2017 No date in update	
	CDSR		2005 – 29 November 2016 No date in update	
	DARE		Up to 1st Quarter 2016	
	NHS EED		Up to 1st Quarter 2016	
Conference Proceedings	EHA	Not reported	2015-2018	4-5 October 2018
	ICML			
	ASH			
	ASCO			
	ESMO			
	ISPOR			
	HTAi			
HTA Agencies	NICE	Not reported		4-5 October 2018
	SMC			
	AWMSG			
	INESSS			
	PBAC			
	HAS			
	CADTH (including pCODR)			
Trials Registries	WHO ICTRP	Not Reported		7 November 2018

Search strategy element	Resource	Host/source	Reported date range	Date searched
	Clinicaltrials.gov			
Other Resources	Latin American and Caribbean Health Sciences Literature	Not Reported		4-5 October 2018
Reference lists of included publications were and relevant SLRs were screened.				
CDSR = Cochrane Database Systematic Reviews; DARE = Database of Abstracts of Reviews of Effects; NHS EED = NHS Economic Evaluation Database; EHA = European Hematology Association; ICML = International Conference on Malignany Lymphoma; ASH = American Society of Hematology; ASCO = American Society of Clinical Oncology; ESMO = European Society for Medical Oncology; ISPOR= International Society for Pharmacoeconomics and Outcomes Research; HTAi = Health Technology Assessment International; NICE = National Institute for Health and Care Excellence; SMC = Scottish Medicine Consortium; AWMSG = All Wales Medicines Strategy Group; INESSS = Institut National D'excellence en Services Sociaux; PBAC = Pharmaceutical Benefits Advisory Committee; HAS = Haute Autorite de Sante; CADTH = Canadian Agency for Drugs and Technologies in Health				

Table A2.2: Data sources for the cost-effectiveness and HRQoL systematic reviews

Search strategy element	Resource	Host/source	Date range	Date searched
Electronic databases	Medline	OVID	1946-Present	4 Sept 2018
	Medline Epub Ahead of Print, In-Process & Other Non-Indexed Citations		Not provided	
	Medline Daily			
	Embase		1974- Present	4 Sept 2018
	HTA Database	OVID	Not provided	4 Sept 2018
	NHS EED		Not provided	
	Econlit	OVID	1961-present	4 Sept 2018
Conference proceedings	EHA	Not reported	2015-2018	8/9 October 2018
	ICML			
	ASH			
	ASCO			
	ESMO			
	ISPOR			
	HTAi			
	SMDM			
HTA Agencies	NICE, SMC, AWMSG, PBAC, CADTH, INESSS, HAS	Not reported	2015-2018	8/9 October 2018 Updated search conducted list sent with clarification response

Additional resources	CEA Registry, RePEc, INAHTA, NIHR HTA database, CRD databases, ScHARRHUD, Latin American and Caribbean Health Sciences Literature	Websites links provided		8/9 October 2018
Bibliographies of all included studies and relevant SLRs were manually searched to identify additional primary studies.				
HTA Database = Health Technology Assessment Database; NHS EED = NHS Economic Evaluation Database; EHA = European Hematology Association; ICML = International Conference on Malignancy Lymphoma; ASH = American Society of Hematology; ASCO = American Society of Clinical Oncology; ESMO = European Society for Medical Oncology; ISPOR= International Society for Pharmacoeconomics and Outcomes Research; HTAi = Health Technology Assessment International; SMDM = Society for Medical Decision Making; NICE = National Institute for Health and Care Excellence; SMC = Scottish Medicine Consortium; PBAC = Pharmaceutical Benefits Advisory Committee; CADTH = Canadian Agency for Drugs and Technologies in Health; INESSS = Institut National D'excellence en services sociaux; HAS = Haute Autorite de Sante; RePEc = Research Papers in Economics; INAHTA = International Network of Agencies for Health Technology Assessment;				

Table A2.3: Data sources for the cost and healthcare resource identification, measurement and valuation

Search strategy element	Resource	Host/source	Date range	Date searched
Electronic databases	Medline	OVID	1946-Nov 16 2018	19 November 2018
	Medline Epub Ahead of Print, In-Process & Other Non-Indexed Citations		Up to Nov 16 2018	
	Medline Daily			
	Embase		1974- 16 Nov 2018	19 November 2018
	HTA Database	OVID	CRD York	19 November 2018
	NHS EED		CRD York	
	Econlit	EBSCO	1866-Nov 2018	19 November 2018
Conference proceedings	ESMO	Website links provided	2016-2018	Searched between 21 Nov/4 Dec 2018
	ASCO			
	EHA			
	ASH			
	ICML			
	ISPOR			
	HTAi			

Search strategy element	Resource	Host/source	Date range	Date searched
	SMDM			
HTA Agencies	NICE	NICE website	No date provided	29 Nov 2018
Bibliographies of all included studies and relevant SLRs were manually searched to identify additional primary studies.				
HTA Database = Health Technology Assessment Database; NHS EED = NHS Economic Evaluation Database; ESMO = European Society for Medical Oncology; ASCO = American Society of Clinical Oncology; EHA = European Hematology Association; ASH = American Society of Hematology; ICML = International Conference on Malignancy Lymphoma; ISPOR= International Society for Pharmacoeconomics and Outcomes Research; HTAi = Health Technology Assessment International; SMDM = Society for Medical Decision Making; NICE = National Institute for Health and Care Excellence				

Appendix 3: Summary of GO29365 study methodology

Study	GO29365 (NCT02257567)
Trial design	Phase Ib/II, multicentre, open-label study of Pola+BR in patients with R/R DLBCL. Six patients enrolled to receive Pola+BR in Phase I safety run, 80 patients randomised 1:1 to Pola+BR vs BR in Phase II randomisation.
Eligibility criteria	**Inclusion criteria** Age ≥18 years' old ECOG PS 0–2 Histologically confirmed DLBCL Must have received at least one prior therapy for DLBCL. Patients must have either relapsed or have become refractory to a prior regimen, defined as: Patients who were ineligible for second-line stem cell transplant, with progressive disease or no response (stable disease) <6 months from start of initial therapy (2L refractory) Patients who were ineligible for second-line stem cell transplant, with disease relapse after initial response ≥6 months from start of initial therapy (2L relapsed) Patients who were ineligible for third-line (or beyond) stem cell transplant, with progressive disease or no response (stable disease) <6 months from start of prior therapy (3L+ refractory) Patients who were ineligible for third-line (or beyond) stem cell transplant, with disease relapse after initial response ≥6 months from start of prior therapy (3L+ relapsed) Response duration on prior bendamustine must have been >1 year (for patients who had relapse disease after a prior regimen) At least one bi-dimensionally measurable lesion on imaging scan defined as >1.5cm in its longest duration Life expectancy of at least 24 weeks Adequate haematologic function unless inadequate function is due to underlying disease e.g. extensive bone marrow involvement. Adequate haematologic function defined as: ANC ≥1.5 $\times 10^9$/L Platelet count ≥75 $\times 10^9$/L Haemoglobin ≥9.0 g/dL For women who were not post-menopausal or surgically sterile, agreement to remain abstinent or to use single highly effective or combined contraceptive methods that result in a failure rate of <1% per year during the treatment period and for ≥12 months after the last dose of rituximab For men, agreement to remain abstinent or to use a combination of contraceptive methods that together result in a failure rate of <1% per year during the treatment period and for at least 6 months after the last dose of study drug Able and willing to provide written informed consent and to comply with the study protocol **Key exclusion criteria (please refer to CSR for further detail)** [65] History of severe allergic or anaphylactic reactions to humanised or murine monoclonal antibodies (or recombinant antibody-related fusion proteins)

Study	GO29365 (NCT02257567)
	Contraindication to bendamustine or rituximab Prior use of any monoclonal antibody, radioimmunoconjugate, or ADC within five half-lives or four weeks, whichever was longer, before Cycle 1 Day 1 Ongoing corticosteroid use >30mg/day prednisone or equivalent, for purposes other than lymphoma symptom control Completion of autologous stem cell transplant within 100 days prior to Cycle 1 Day 1 Prior allogenic stem cell transplant Eligibility for autologous stem cell transplant History of transformation of indolent disease to DLBCL Primary or secondary central nervous system lymphoma Current grade >1 peripheral neuropathy History of other malignancy that could affect compliance with the protocol or interpretation of results Evidence of significant, uncontrolled concomitant diseases that could affect compliance with the protocol or interpretation of results, including significant cardiovascular disease (such as New York Heart Association Class III or IV cardiac disease, myocardial infarction within the last 6 months, unstable arrhythmias, or unstable angina) or significant pulmonary disease (including obstructive pulmonary disease and history of bronchospasm) Known active bacterial, viral, fungal, mycobacterial, parasitic, or other infection (excluding fungal infections of nail beds) at study enrolment or any major episode of infection requiring treatment with intravenous antibiotics or hospitalisation (relating to the completion of the course of antibiotics) within 4 weeks prior to Cycle 1 Day 1 Positive test results for chronic hepatitis B virus or hepatitis C virus Known history of human immunodeficiency virus Any of the following abnormal laboratory values, unless abnormal laboratory values were due to underlying lymphoma per the investigator: Creatinine >1.5 X ULN or a measured creatinine clearance < 40 mL/min AST or ALT >2.5 X ULN Total bilirubin ≥1.5 X ULN INR or prothrombin time >1.5 X ULN in the absence of therapeutic anticoagulation PTT or aPTT >1.5 X ULN in the absence of a lupus anticoagulant
Trial drugs and concomitant medications	**Trial drugs** **Polatuzumab vedotin:** IV, 1.8 mg/kg on Day 2 of Cycle 1 and then Day 1 of subsequent Cycles 2-6**;** **Bendamustine:** IV, 90 mg/m^2 q3w on two consecutive days, Days 2 and 3 of Cycle 1, then Days 1 and 2 of subsequent Cycles 2–6; **Rituximab:** IV, 375 mg/m^2, on Day 1 of Cycles 1–6 **Dose modifications** Permanent dose reduction of **pola** (from 1.8 mg/kg to 1.4 mg/kg) was mandated for Grade 2 or 3 PN (including its signs and symptoms) which had recovered following dose delay to Grade ≤1 within ≤14 days of the

Study	GO29365 (NCT02257567)
	scheduled date of the next cycle. Dose reductions below 1.8 mg/kg of pola for neutropenia or thrombocytopenia were not allowed No dose modifications (reductions) of **rituximab** were allowed The **bendamustine** dose (90 mg/m^2) could be reduced to 70 mg/m^2 in the event of Grade 3 or 4 neutropenia or thrombocytopenia (first episode or recurrent), if ANC recovered to >1 X 10^9/L (for neutropenia) or platelet count recovered to >75 X 10^9/L (for thrombocytopenia) on or after Day 8 of the scheduled date for the next cycle. If prior bendamustine dose reduction had occurred, bendamustine dose could be further reduced to 50 mg/m^2 for recurrent Grade 3 or 4 neutropenia or thrombocytopenia. No more than two dose reductions of bendamustine were allowed. **Pre-medications** All rituximab infusions were to be preceded by premedication with oral acetaminophen/paracetamol and an antihistamine 30–60 minutes before the start of each infusion (unless contraindicated) to minimise the risk of IRRs. **Concomitant medications** **Permitted concomitant medications included:** Continued use of oral contraceptives, hormone-replacement therapy, or other maintenance therapies Use of G-CSF for the treatment of neutropenia Mandatory premedication with acetaminophen/paracetamol and antihistamine prior to administration of each rituximab infusion Mandatory premedication with oral allopurinol or a suitable alternative treatment (with adequate hydration) prior to Cycle 1, Day 1 and subsequent cycles of treatment if deemed appropriate by the investigator for all patients with high tumour burden and considered to be at high risk for TLS Anti-infective prophylaxis for viral, fungal, bacterial, or *Pneumocystis* infections Necessary supportive measures for optimal medical care throughout study according to institutional standards, including growth factors (e.g., erythropoietin) and anti-emetic therapy, if clinically indicated **Prohibited concomitant medications:** Cytotoxic chemotherapy, other than bendamustine and intrathecal chemotherapy for CNS prophylaxis Immunotherapy or immunosuppressive therapy, other than study treatments Radioimmunotherapy or radiotherapy Hormone therapy, other than contraceptives, stable hormone-replacement therapy, or megestrol acetate Biologic agents other than haematopoietic growth factors, which are allowed if clinically indicated and used in accordance with instructions provided in the package inserts Any therapy (other than intrathecal CNS prophylaxis) intended for the treatment of lymphoma
Primary outcome	**Primary endpoint:**

Study	GO29365 (NCT02257567)
	PET-defined CR rate at the time of primary response assessment (6–8 weeks after Cycle 6 Day 1 or last dose of study medication) as defined by the IRC
Other outcomes used in the economic model/specified in the scope	**Secondary endpoints:** CR at the time of primary response assessment based on PET-CT, as determined by investigator OR (CR or PR) at the time of primary response assessment, based on PET-CT, as determined by investigator and IRC CR at the time of primary response assessment based on CT only, as determined by investigator and IRC OR at the time of primary response assessment based on CT only, as determined by investigator and IRC BOR (CR or PR) while on study either by PET-CT or CT only, as determined by investigator and IRC DOR, based on PET-CT or CT, as determined by IRC PFS, based on PET-CT or CT, as determined by IRC **Exploratory objectives:** DOR based on PET-CT or CT only as determined by the investigator PFS based on PET-CT or CT only as determined by the investigator EFS based on PET-CT or CT only as determined by the investigator OS **Safety endpoints:** Safety and tolerability of Pola+BR Immunogenicity of Pola+BR, as measured by the formation of ADAs **Patient-reported outcomes:** Peripheral neuropathy symptom severity and interference on daily functioning and to better understand treatment impact, tolerability, and reversibility, as measured by the Therapy-Induced Neuropathy Assessment Scale (TINAS) v1.0
Pre-planned subgroups	OS and PFS efficacy of Pola+BR in pre-specified demographic and baseline characteristics

Source: CS, pages 27-31
ADA = anti-drug antibodies; ALT = alanine aminotransferase; ANC = absolute neutrophil count; AST = aspartate aminotransferase; BOR = best overall response; BR = bendamustine + rituximab; CNS = central nervous system; CR = complete response; DLBCL = diffuse large B-cell lymphoma; DOR = duration of response; ECOG PS = Eastern Cooperative Oncology Group performance status; EFS = event-free survival; G-CSF = granulocyte-colony stimulating factor; IRC = Independent Review Committee; IRR = infusion-related reaction; OR = overall response; OS = overall survival; PET-CT = positron emission tomography-computed tomography; PFS = progression-free survival; PN = peripheral neuropathy; Pola = polatuzumab vedotin; PR = partial response; (a)PTT = (activated) partial thromboplastin time; R/R = relapsed/refractory; TINAS = Therapy-Induced Neuropathy Assessment Scale; TLS = tumour lysis syndrome; ULN = upper limit of normal

Appendix 4: Goodness of fit assessment of parametric survival models received with the response to the clarification letter ([redacted])

This appendix presents a summary of the goodness of fit assessment based on AIC/BIC values and visual fit of the parametric curves vs. KM data as presented in the electronic model after clarification ([redacted]).

As discussed previously, the ERG considered that the cure mixture models do not provide realistic long-term extrapolations and the evidence substantiating the need for cure mixture models is lacking. Furthermore, the ERG considers the visual fit of independent models to be better in comparison to the dependent models. On the other hand, the ERG is unsure about the level of credibility for the visual fits, as some errors are suspected in the Kaplan Meier curves, as explained in the clinical effectiveness part of this report.

From the goodness of fit results presented below, independently fitted generalised gamma and lognormal provided the lowest AIC/BIC values for pola+BR and BR arms for PFS and lognormal and log-logistic distribution provided the lowest AIC/BIC values for the OS.

Based on the visual fit, the ERG considered independently fitted lognormal to be more plausible for PFS, as the independently fitted generalised gamma extrapolation has a quite heavy tail for pola+BR For the OS, the ERG considered generalised gamma extrapolation to be more plausible, considering the visual fit of the distribution in comparison to others. The model outcomes and the corresponding KM curves for OS and PFS are provided in Figure A4.9 and Figure A4.10 below.

Table A4.1. Ranking of PFS distributions for Pola+BR and BR based on AIC and BIC

Parametric distribution		Pola+BR AIC (rank)	Pola+BR BIC (rank)	BR AIC (rank)	BR BIC (rank)
Standard (dependent fit)[a]	Exponential	408.9 (6)	413.6 (6)	NA	NA
	Weibull	404.4 (5)	411.5 (5)	NA	NA
	Gompertz	396.2 (4)	403.3 (4)	NA	NA
	Log-Normal	391.5 (2)	398.6 (1)	NA	NA
	Generalised Gamma	391.0 (1)	400.5 (3)	NA	NA
	Log-Logistic	393.3 (3)	400.4 (2)	NA	NA
Standard (independent fit)	Exponential	225.8 (5)	227.5 (5)	183.1 (6)	184.8 (6)
	Weibull	225.9 (6)	229.2 (6)	180.4 (5)	183.8 (5)
	Gompertz	221.8 (4)	225.2 (4)	175.0 (3)	178.4 (3)
	Log-Normal	219.7 (2)	223.0 (2)	173.8 (1)	177.1 (1)
	Generalised Gamma	216.9 (1)	222.0 (1)	175.4 (4)	180.5 (4)
	Log-Logistic	221.3 (3)	224.6 (3)	173.8 (2)	177.2 (2)
Cure-mixture	Exponential	49.3 (3)	131.2 (1)	86.2 (5)	168.1 (1)
	Weibull	51.9 (6)	154.8 (5)	87.4 (6)	190.3 (5)
	Gompertz	49.4 (4)	152.3 (4)	84.9 (4)	187.8 (4)

	Log-Normal	47.8 (2)	150.7 (3)	81.7 (1)	184.7 (2)
	Generalised Gamma	49.8 (5)	168.5 (6)	83.7 (3)	202.5 (6)
	Log-Logistic	47.6 (1)	150.5 (2)	82.3 (2)	185.2 (3)

[a]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; BR, bendamustine + rituximab; KM, Kaplan-Meier; NA, not available; Pola+BR, polatuzumab + bendamustine + rituximab

Table A4.2. Ranking of OS models for Pola+BR and BR based on AIC and BIC

Model		Pola+BR AIC (rank)	Pola+BR BIC (rank)	BR AIC (rank)	BR BIC (rank)
Standard (dependently fit)[a]	Exponential	403.5 (5)	408.3 (5)	NA	NA
	Weibull	404.6 (6)	411.8 (6)	NA	NA
	Gompertz	400.7 (4)	409.7 (4)	NA[c]	NA[c]
	Log-Normal	396.3 (1)	403.4 (1)	NA	NA
	Generalised gamma	397.9 (3)	407.4 (3)	NA	NA
	Log-logistic	397.0 (2)	404.1 (2)	NA	NA
Standard (independently fit)	Exponential	210.8 (4)	212.5 (2)	192.7 (5)	194.4 (4)
	Weibull	212.8 (6)	216.2 (6)	193.5 (6)	196.9 (6)
	Gompertz	211.5 (5)	214.9 (4)	190.9 (3)	194.3 (3)
	Log-Normal	209.0 (1)	212.4 (1)	189.3 (2)	192.6 (2)
	Generalised gamma	210.3 (3)	215.3 (5)	191.2 (4)	196.3 (5)
	Log-logistic	210.0 (2)	213.3 (3)	189.0 (1)	192.4 (1)
Cure-mixture (dependent, not informed by PFS)[b]	Exponential	131.9 (3)	188.5 (1)	NA	NA
	Weibull	133.6 (5)	236.5 (5)	NA	NA
	Gompertz	133.5 (4)	236.4 (4)	NA	NA
	Log-Normal	130.9 (2)	233.8 (3)	NA	NA
	Generalised Gamma	138.6 (6)	257.3 (6)	NA	NA
	Log-Logistic	130.5 (1)	233.4 (2)	NA	NA
Cure-mixture (independent, OS informed by PFS)	Exponential	88.0 (5)	169.8 (1)	86.7 (2)	168.5 (1)
	Weibull	87.3 (3)	190.2 (4)	88.1 (5)	191.0 (4)
	Gompertz	88.8 (6)	191.7 (5)	89.5 (6)	192.4 (5)
	Log-Normal	86.6 (2)	189.5 (3)	87.1 (3)	190.0 (3)

	Generalised Gamma	87.5 (4)	206.3 (6)	87.8 (4)	206.5 (6)
	Log-Logistic	85.6 (1)	188.5 (2)	85.8 (1)	188.7 (2)

[a]The presented statistics represent the overall fit of the dependent model to both arms of the trial. AIC/BIC statistics are therefore not presented.

AIC, Akaike Information Criterion; BIC, Bayesian Information Criterion; BR, bendamustine + rituximab; KM, Kaplan-Meier; NA, not available; Pola+BR, polatuzumab + bendamustine + rituximab

Figure A4.1: OS standard extrapolation functions (dependent fit, GO29365, [redacted])

Obtained from economic model after clarification. The Gompertz extrapolation was not considered for either arm for OS due failure of parameterisation for this function for OS; this extrapolation is therefore not presented.
BR, bendamustine + rituximab; KM, Kaplan-Meier; Pola+BR, polatuzumab + bendamustine + rituximab

Figure A4.2: OS standard extrapolation functions (independent fit GO29365, [redacted])

Obtained from economic model after clarification. The Gompertz extrapolation was not considered due failure of parameterisation for this function for OS; BR, bendamustine + rituximab; KM, Kaplan-Meier; Pola+BR, polatuzumab + bendamustine + rituximab

Figure A4.3: OS cure mixture model extrapolation functions (OS informed by PFS, from GO29365, [redacted])

Obtained from economic model after clarification. The Gompertz extrapolation was not considered due failure of parameterisation for this function for OS; BR, bendamustine + rituximab; KM, Kaplan-Meier; Pola+BR, polatuzumab + bendamustine + rituximab

Figure A4.4: OS cure mixture model extrapolation functions (OS not informed by PFS, same OS for not-long-term survivors, data from GO29365, [redacted])

Obtained from economic model after clarification. The Gompertz extrapolation was not considered due failure of parameterisation for this function for OS; BR, bendamustine + rituximab; KM, Kaplan-Meier; Pola+BR, polatuzumab + bendamustine + rituximab

Figure A4.5: PFS standard extrapolation functions (dependent fit, GO29365, [redacted])

Obtained from economic model after clarification. BR, bendamustine + rituximab; IRC, independent review committee; KM, Kaplan-Meier; PFS, progression-free survival; OS, overall survival; Pola+BR, polatuzumab + bendamustine + rituximab

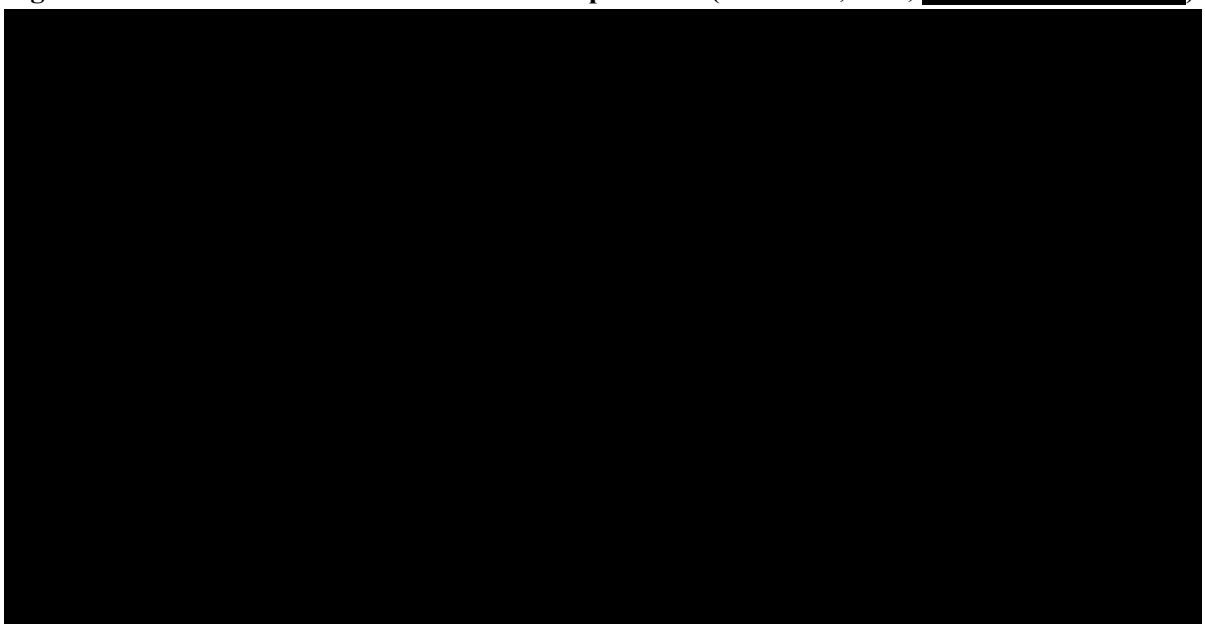
Figure A4.6: PFS standard extrapolation functions (independent fit, GO29365, [redacted])

Obtained from economic model after clarification. BR, bendamustine + rituximab; IRC, independent review committee; KM, Kaplan-Meier; PFS, progression-free survival; OS, overall survival; Pola+BR, polatuzumab + bendamustine + rituximab

Figure A4.7: PFS cure-mixture modelling based extrapolation functions (independent fit, GO29365, [redacted])

Obtained from economic model after clarification. BR, bendamustine + rituximab; IRC, independent review committee; KM, Kaplan-Meier; PFS, progression-free survival; OS, overall survival; Pola+BR, polatuzumab + bendamustine + rituximab

Figure A4.8: ERG base case PFS and OS extrapolations (GO29365, IRC, [redacted])



Obtained from economic model after clarification. BR, bendamustine + rituximab; IRC, independent review committee; KM, Kaplan-Meier; PFS, progression-free survival; OS, overall survival; Pola+BR, polatuzumab + bendamustine + rituximab

Figure A4.9: ERG base case PFS model outcomes

Obtained from economic model after clarification. BR, bendamustine + rituximab; IRC, independent review committee; KM, Kaplan-Meier; PFS, progression-free survival; OS, overall survival; Pola+BR, polatuzumab + bendamustine + rituximab

Figure A4.10: ERG base case OS model outcomes

Obtained from economic model after clarification. BR, bendamustine + rituximab; IRC, independent review committee; KM, Kaplan-Meier; PFS, progression-free survival; OS, overall survival; Pola+BR, polatuzumab + bendamustine + rituximab

National Institute for Health and Care Excellence

Centre for Health Technology Evaluation

ERG report – factual accuracy check

Polatuzumab vedotin with rituximab and bendamustine for treating relapsed or refractory diffuse large B-cell lymphoma [ID1576]

You are asked to check the ERG report to ensure there are no factual inaccuracies contained within it.

If you do identify any factual inaccuracies, you must inform NICE by **5pm on Friday 11 October 2019** using the below comments table. All factual inaccuracies will be highlighted in a report and presented to the Appraisal Committee and will subsequently be published on the NICE website with the committee papers.

The factual accuracy check form should act as a method of detailing any inaccuracies found and how and why they should be corrected.

Issue 1 Wording in pathway

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
p. 15, p.52 “ASCT (and become ineligible because of that)”	Please consider wording: “ASCT (and relapse but become transplant ineligible due to not being able to receive a repeat ASCT)”	Clearer description on the reason for ineligibility to further transplants.	Not a factual inaccuracy.

Issue 2 Wording in pathway

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
p. 21 “are refractory at the first-line therapy stage”	Please consider wording: “are refractory to first-line therapy”	Aligned with wording used in the literature	Not a factual inaccuracy.

Issue 3 Wording

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
p. 32 “16 of 80 patients who had received an ASCT.”	Please consider wording: “16 of 80 patients who had received a prior ASCT.”	Increased clarity on ASCT in the pathway.	Not a factual inaccuracy.

Issue 4 Wording in pathway

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
p. 22 “Tolerance of the treatment is used to determine if ASCT is suitable”	Please consider adding: “Tolerance and response….”	Response to salvage treatment is also required before attempting to transplant.	Amended accordingly.

Issue 5 Wording in pathway

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
p. 22 “Pixantrone monotherapy is recommended by NICE as a third- or fourth-line option for adults with DLBCL but the company state that it…”	Please consider re-wording to “Pixantrone monotherapy is recommended by NICE as a third- or fourth-line option for adults with R/R/DLBCL but based on clinical opinion…”	Pixantrone is only approved for relapsed or refectory DLBCL patents. We based our statement on use in UK practice clinical opinion (also expressed in previous CAR-T TAs) as stated in the submission. The current wording suggests this would only be Roche’s opinion.	Amended accordingly.

Issue 6 Wording on statistical methods

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
p. 39: "…given the small sample size of this phase II study, were likely to be underpowered"	Please consider removing this statement.	Statistical power is determined by the event rate (i.e., difference in OS events, for example) and not by the actual number of patients. The ERG does not comment on the event rates in this study in relation to its statistical power.	Not a factual inaccuracy.

Issue 7 Reporting of updated trial results

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
p.40 "After 24 months the number of patients with a PFS event (PD or death) was higher in the BR arm (80% [32/40 patients]) compared to the Pola+BR arm (72.5% [29/40 patients]) (see Table 4.5). The risk of PD or death was reduced compared to BR (stratified HR=0.38; 95% CI: 0.23, 0.65)" p.52 "After 24 months…"	Please correct: "After 30 months medium follow up of patients with a PFS event (PD or death) was higher in the BR arm [redacted] compared to the Pola+BR arm [redacted] (see Table 4.5). The risk of PD or death was reduced compared to BR (stratified [redacted] "After 30 months median follow up…"	The data reported refers to the 30 months median follow up (medians and HR are reported on 30 months median follow up). The data from the latest data cut is also needs to be marked as AIC.	Amended accordingly and marked as AIC.

Issue 8 Description of approach to background mortality modelling

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
p. 15, 84, 133 "the company followed an individual patient-level approach while modelling the non-cancer, background mortality risks"	Please consider re-wording to "the company followed an approach where the age distribution of the cohort was used while modelling the non-cancer, background mortality risks"	Our approach taken to model mortality is still a cohort approach. The difference between our approach and the ERGs approach is simply the age distribution used: we used an age distribution of the cohort based on the GO29365 data to derive background mortality whereas the ERG used a 'delta distribution' where all patients are exactly 69 years old at the start of treatment. Our approach is in line with using the weight distribution to calculate dosing in the cohort as opposed to average weight only.	Not a factual inaccuracy. We thank the company for the additional clarification. However, we disagree with the company's view that their approach was "in line with using the weight distribution to calculate dosing in the cohort as opposed to average weight only". First of all, unlike the patient weight, the baseline age has a direct influence on the non-cancer related death and therefore the long-term prognosis. Also, in their model, the company created 160 patients (1:1 female/male with age distribution mimicking the GO29365 trial). From each individual patient, non-cancer death extrapolation was conducted from the UK lifetable and

			individual patient's characteristics. Afterwards the average of these 160 extrapolations were taken and used in the model. This is an example of individual-based modelling. The company's approach could have been considered as a "cohort approach" if the company had sampled the baseline age from a distribution, and extrapolated the non-cancer deaths from that sampled baseline age, accordingly. (Note that this approach would not be ideal, since heterogeneity would be incorporated as parametric uncertainty in the analyses.)

Issue 9 Clarity on the data cuts

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
p.68 paragraph " In the original CS, data from the October 2018 data cut point…" p.76 paragraph "For the	Please consider adding: "In response to clarification questions the company provided an updated model and analyses for PFS, OS and AEs based on a later data	To clarify to the reader that analyses based on the latest available data cut was provided. In the current report this data is	Not a factual inaccuracy. The current report is structured as the summary and critique of the original

extrapolation of OS in the model, the company used OS data from the October 2018 data cut-off from the GO29365 trial"	cut from March 2019"	referred to later and the reader may not realize this.	submission and the additional data/ analyses in response to the clarification letter are explained in the corresponding section of the ERG report.

Issue 10 Clarity on the assumptions for people in long-term remission

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
p. 89 "The assumption of a two-year cure point is based on evidence from the findings of a single study …"	Please consider re-wording; "UK clinical opinion on outcomes for people with R/R DLBCL achieving 2 years remission and evidence from the findings of a single study…"	Our primary justification for long-term remission and survival was based on clinical opinion. Literature sources from the font-line setting were used as additional evidence.	Text changed to: "The assumption of a two-year cure point is based on clinical expert opinion and evidence from the findings of a single study of no statistically significant excess mortality between newly diagnosed DLBCL patients who survive to two years and the general population [4]. However, the details of the clinical expert meeting(s) were not provided and a more recent and larger study suggests that excess mortality remains up to five years."

Issue 11 Clarity on HRQoL discussion

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
p. 89 “Furthermore, the company extend the identified evidence of no excess mortality beyond two years, to argue that it is therefore likely that the HRQoL of the two groups would …. ”	Please consider spelling out which two groups are referred to in this statement (two arms in the study?)	Unclear which two groups are referred to.	Inserted: “(patients who are progression free longer than 2 years and non-cancer patients)” …before: “…would be equivalent from two years.

Issue 12 Wording on treatment effect and cure point assumptions

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
p. 120 paragraph 7.3.3.3: “The company and ERG base-cases assume that the treatment effect for PFS and OS is maintained over the patient’s remaining life.”	Please consider re-wording: “The company and ERG base-cases assume that the future treatment effect could be extrapolated by independently fitted parametric models over the patient’s remaining life.”	The ERGs preferred assumption and our original base-case are based on independent fits to the treatment arms and therefore do not make explicit assumptions on treatment effect, as opposed to proportional hazard models where there is an explicit assumption of constant treatment effect over time.	Text changed to: “The company and ERG base-cases assume that the future treatment effect could be extrapolated by independently fitted parametric models over the patient’s remaining life. This extrapolation led to an increasing treatment effect in the long-term, as can be seen in Figure 5.14 in this report.”

Issue 13 Reporting of context

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
p. 83 “Also, the empirical hazard rate plots for the OS data from the GO29365 trial presented as below (Figure 5.12) do not seem to approach zero in either of the plots.”	Consider adding: “However, smoothed hazard plots should be interpreted with caution at the end of the follow up period. A decline in hazard at the end of the follow up period was observed in cumulative”.	We stated in our response to clarification questions that hazard plots from individual patient level data are highly uncertain at the end of the follow up period due to the low number of events. In addition, the smoothing algorithm is likely to introduce artefacts. The pots therefore need to be interpreted with caution and this should be highlighted o the reader.	Not a factual inaccuracy. Not all the points from the clarification letter response could be included in the ERG report. Furthermore, the company’s judgements on the reliability of the smoothed hazard plots should be supported with evidence / statistical details

Issue 14 Minor wording & typos

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
-p. 14 “relapsed or refractory DLCBL” p. 22: “, including R-GDP, R-, with R-Gem-Ox” -p. maximum number of three treatment cycles - p.42 “data from Pola+BR and	- Please change to “relapsed or refractory DLBCL” - Should be read: “R-GDP, R-DHAP, R-ICE and R-ESHAP with…” -Should read “data from Pola+BR and Pola+BG “ -Should read “as shown in Table 4.6”	- spelling - missing chemo regimens? - There was no TTOT data for R-GemOx available. Hence, the model was set up to include the costs of 3 treatment cycles (average number equal to maximal number) to achieve the	• “DLCBL” changed to “DLBCL” in eight locations. • p.22 amended accordingly. • Statement regarding number of treatment cycles is not a factual

Pola+BR “ -p. 43 “as shown in Table 4.9”		average of 3 cycles used in the TA source. -Typo -Incorrect table reference.	inaccuracy. • p.42 amended. • p.43 amended.

(please cut and paste further tables as necessary)

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Draft technical report

Polatuzumab vedotin with rituximab and bendamustine for treating relapsed or refractory diffuse large B-cell lymphoma

This document is the draft technical report for this appraisal. It has been prepared by the technical team with input from the lead team and chair of the appraisal committee.

The technical report and stakeholder's responses to it are used by the appraisal committee to help it make decisions at the appraisal committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the appraisal committee meeting.

The technical report includes:

- topic background based on the company's submission
- a commentary on the evidence received and written statements
- technical judgements on the evidence by the technical team
- reflections on NICE's structured decision-making framework.

This report is based on:

- the evidence and views submitted by the company, consultees and their nominated clinical experts and patient experts and
- the evidence review group (ERG) report.

The technical report should be read with the full supporting documents for this appraisal.

1. Topic background

1.1 Disease background: Non-Hodgkin lymphoma (NHL)

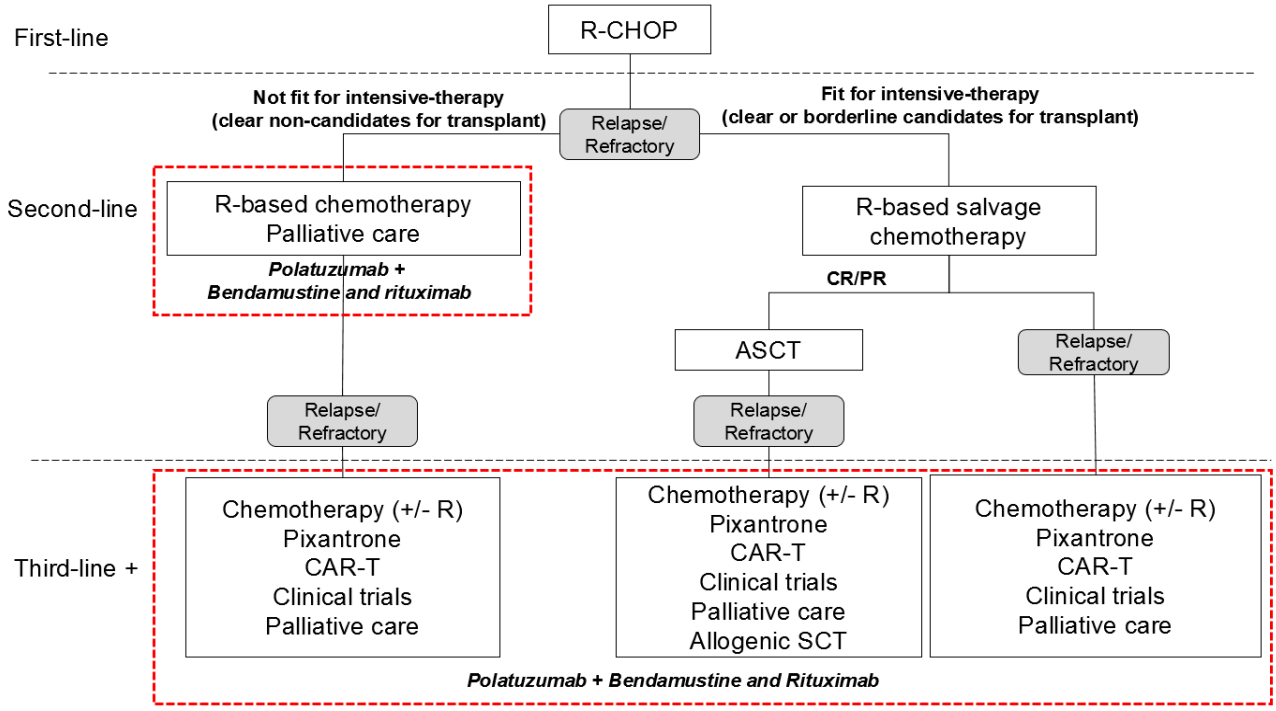
- NHL is a heterogeneous group of lymphoproliferative malignancies, with 80–95% of cases arising from B-cells and the remaining from T-cells. Diffuse large B-cell lymphoma (DLBCL), a high-grade B-cell NHL, represents approximately 40% of all lymphoma cases globally.
- The Haematological Malignancy Research Network (HMRN) estimates that there are 5,510 new cases of DLBCL each year in the UK, which accounts for approximately 40% of all UK NHL cases.
- Approximately 600 patients per year are treated for relapsed or refractory (R/R) DLBCL not suitable for hematopoietic stem cell transplant.
- The prognosis is poor for patients with R/R DLBCL, with a median survival of 10 months. Fewer than half of relapsed patients (41%) survive for 12 months. Age is an important prognostic indicator in DLBCL patients who relapse; patients aged ≥65 years have a poorer prognosis compared to those aged <65 years
- Outcomes are worse for patients who are refractory to first-line therapy. The SCHOLAR-1 study, the largest pooled retrospective analysis of patients with refractory DLBCL, showed that median overall survival was 6.3 months for these patients, with 22% of patients alive at 2 years.

1.2 Treatment pathway

- No consensus on best treatment for R/R DLBCL.
- Standard chemotherapy for the first-line treatment of DLBCL is rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisolone (R-CHOP).

- After first-line treatment with R-CHOP, a reported 20% of patients experience primary refractory disease, while 30% of patients relapse after complete remission.
- The next step is to determine if the patient is fit for salvage therapy and whether autologous stem cell transplant (ASCT) is suitable for them.
- Salvage therapy in the UK typically consists of platinum-based treatment regimens including R-GDP (rituximab with gemcitabine, dexamethasone and cisplatin) or R-GemOx (rituximab plus gemcitabine plus oxaplatin) for older patients.
- For patients who are ineligible for ASCT after intensive therapy, palliative care is the typical approach and there appear to be no universally established therapies.

Treatment pathway and proposed positioning of polatuzumab vedotin in combination with bendamustine and rituximab (polatuzumab vedotin + BR)



Source: company submission, section B.1.3.3, figure 2

- The company states that the following patients will be considered eligible for polatuzumab vedotin with bendamustine and rituximab (polatuzumab vedotin+BR):
  - people with R/R disease who are clear non-candidates for transplant (unfit for intensive therapy based on physician assessment), either as second-line treatment or as a third-line treatment and beyond for patients who have relapsed following or are refractory to their last-line of therapy.
  - people with R/R disease which does not respond to salvage therapy (and are therefore cannot have ASCT)
  - people with R/R disease who received salvage therapy and ASCT but subsequently relapsed.

1.3 Polatuzumab vedotin with bendamustine and rituximab

Anticipated marketing authorisation	Polatuzumab vedotin in combination with bendamustine and rituximab is indicated for the treatment of adult patients with relapsed/refractory diffuse large B-cell lymphoma (DLBCL) who are not candidates for haematopoietic stem cell transplant.
Method of administration and dosage	Polatuzumab vedotin in combination with bendamustine and rituximab every 3 weeks for 6 cycles: ***Polatuzumab vedotin*** • 1.8 mg/kg intravenous infusion (IV) on day 1 • The initial dose should be administered as a 90-minute infusion • If well tolerated, subsequent doses may be administered as a 30-minute infusion ***Bendamustine*** • 90 mg/m^2 IV on days 1 and 2 ***Rituximab*** 375 mg/m^2 IV on day 1
Additional tests or investigations	No additional test or investigations are required.
List price and average cost of a course of treatment	[redacted] per 140mg vial. [redacted] average treatment costs
Patient access scheme (if applicable)	A patient access scheme is not in place.

Source: company submission, section B.1.2. **Error! Reference source not found.**. Appendix C details the draft summary of product characteristics (SmPC) and European Public Assessment Report (EPAR).

1.4 Decision problem

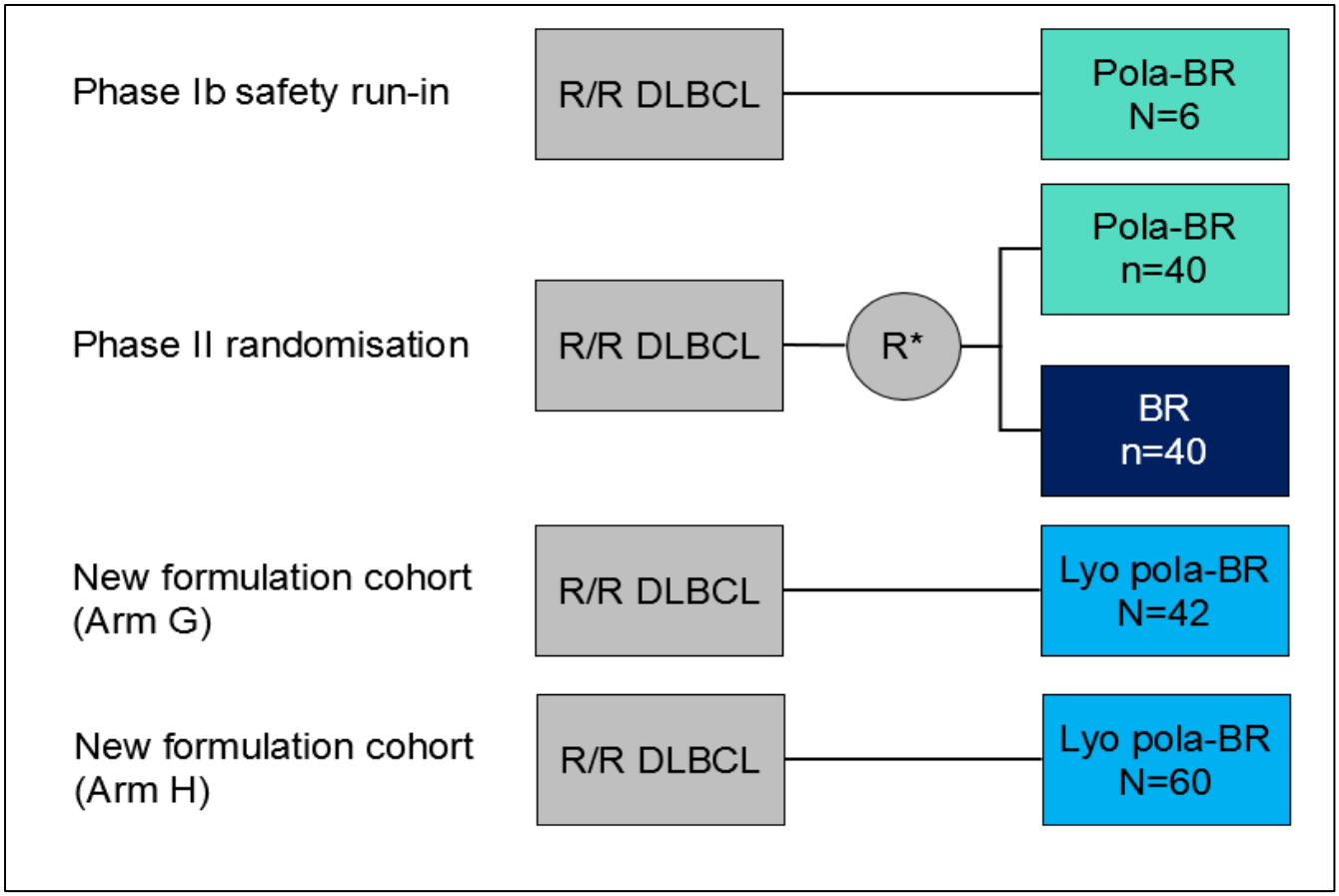
	NICE scope	Company's decision problem	Rationale if different
Population	Adults with relapsed or refractory diffuse large B-cell lymphoma for whom hematopoietic stem cell transplant is not suitable.	As per scope	N/A
Intervention	Polatuzumab vedotin (with rituximab and bendamustine)	As per scope	N/A
Comparators	Rituximab with one or more chemotherapy agents such as: - R-GemOx (rituximab, gemcitabine, oxaliplatin) - R-Gem (rituximab gemcitabine) - R-P-MitCEBO (rituximab, prednisolone, mitoxantrone, cyclophosphamide, etoposide bleomycin, vincristine) - (R-)DECC (rituximab, dexamethasone, etoposide, chlorambucil, lomustine) - BR (bendamustine, rituximab)	- BR - R-GemOx	- No standard of care - Comparator in trial: BR - Not feasible to conduct robust indirect comparison with other comparators - Clinical opinion and the limited data suggest no significant difference in outcomes between the comparators - R-GemOx assumed to have equal efficacy as BR in scenario analysis
Outcomes	Overall survival Progression-free survival Response rates Adverse effects of treatment Health-related quality of life	As per scope	N/A

Source: adapted from company submission, section B.1.1. Table 1

1.5 Clinical evidence

- One relevant trial of polatuzumab vedotin+BR was identified: GO29365 is a multicentre, open-label study in patients with R/R DLBCL.
- GO29365 also investigated polatuzumab vedotin with bendamustine and obinutuzumab in patients with R/R follicular lymphoma but this is not relevant to the current appraisal and is not discussed further.
- R/R DLBCL component of the study consisted of a safety run-in stage and randomised and expansion stage.

GO29365 study design schema (R/R DLBCL pola+BR)



Source: company submission, section B.2.3.1 Figure 3

GO29365 study details

Study design	Phase Ib/II, multicentre, open-label study
PopulationPopulation	Patients with R/R DLBCL • Age ≥18 years • ECOG PS 0–2 • At least 1 bi-dimensionally measurable lesion ≥1.5 cm in its longest dimension • Adequate haematologic function • If received prior bendamustine, response duration must have been >1 year
Intervention(s)	Polatuzumab vedotin plus bendamustine and rituximab (polatuzumab vedotin+BR)
Comparator(s)	Bendamustine and rituximab (BR)

Outcomes	• Complete response (CR) – primary outcome • Overall survival • Progression-free survival • Event-free survival • Duration of response • Adverse effects of treatment • Health-related quality of life Data for PFS and OS shown in this report are from [redacted] data cut (submitted at clarification stage and used in the model). For other endpoints an earlier data cut (30th Apr 2018) is reported.

Source: CS, Table 6, page 24. DLBCL, diffuse large B cell lymphoma; ECOG PS, Eastern Cooperative Oncology Group performance status; and rituximab; R/R, relapsed/refractory.

1.6 Key trial results

Complete response rate with PET-CT at primary response assessment (IRC-assessed)

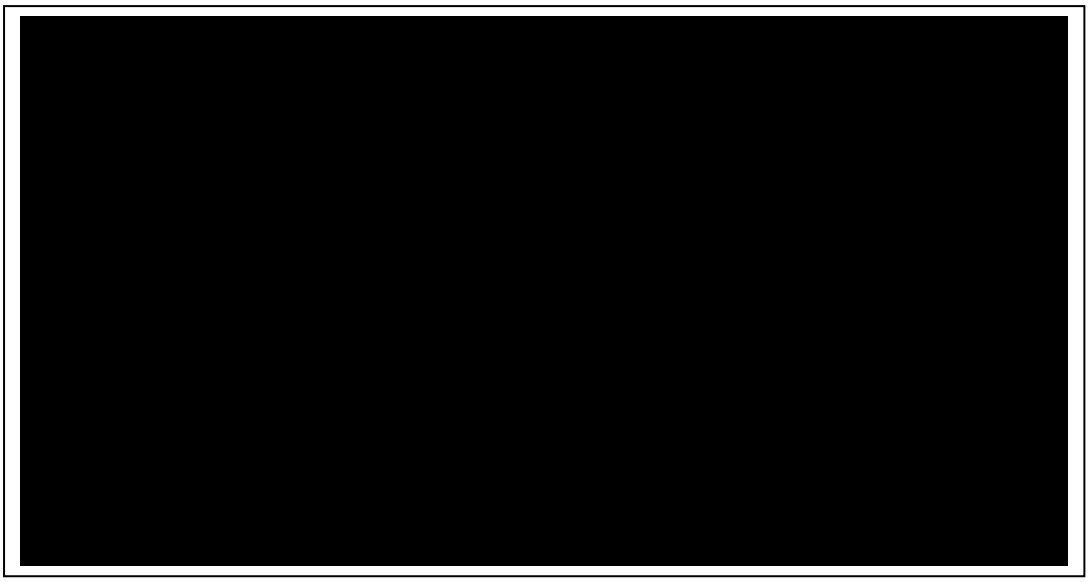
Outcome	**Polatuzumab vedotin+BR n=40**	**BR n=40**
Complete response, n (%) 95% CI	16 (40.0) (24.86, 56.67)	7 (17.5) (7.34, 32.78)
Difference in response rates, n (%) (95% CI) p value	22.5 (2.62, 40.22) p=0.0261	
Source: CS, Table 11, page 3		

Progression-free survival (IRC-assessed*)

Outcome	**Polatuzumab vedotin+BR n=40**	**BR n=40**
Patients with event, n (%)	[redacted]	[redacted]
Earliest contributing event, n Disease progression Death	[redacted]	[redacted]
Median time to event, months 95% CI	[redacted]	[redacted]

Stratified HR % (95% CI) p value (log-rank)	[redacted]
Source: Response to clarification, Table 15, page 26 [redacted] HR, hazard ratio *Company also presented results for investigator assessed PFS. However, the ERG considers the Independent review committee (IRC) results to be more reliable	

Kaplan-Meier Curve for PFS by IRC cut-off date [redacted]

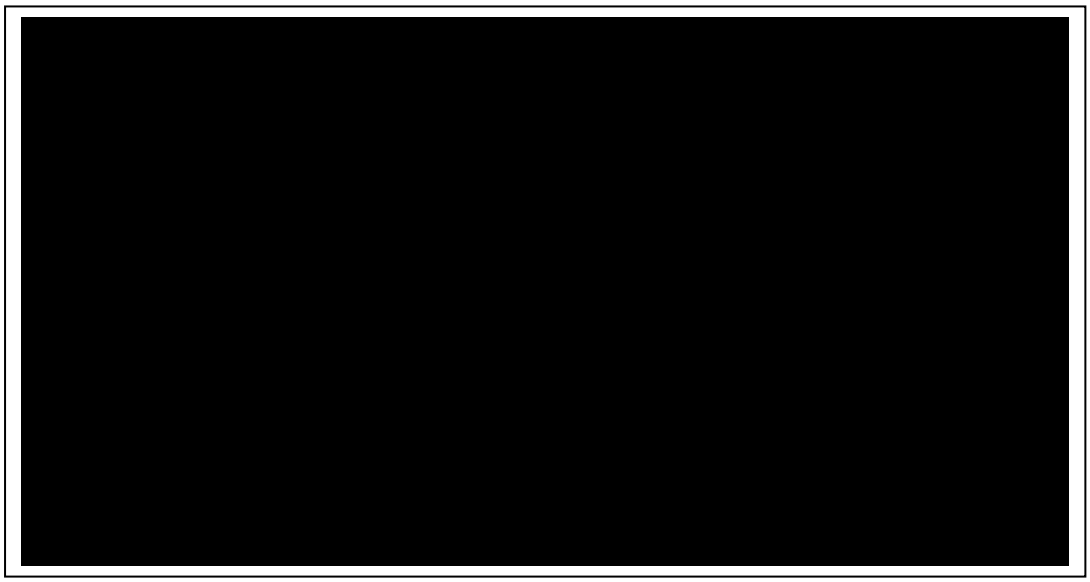


Source: Response to clarification, Figure 3, page 27 of company submission

Overall survival

Outcome	Polatuzumab vedotin+BR n=40	BR n=40
Patients with event, n (%)	[redacted]	[redacted]
Median time to event, months 95% CI	[redacted]	[redacted]
Stratified HR % (95% CI) p value (log-rank)	[redacted]	
Source: Response to clarification, Table 17, page 28. Clinical cut-off date: [redacted] HR = hazard ratio; NE = not estimated		

Kaplan-Meier Curve for OS cut-off date [redacted]



Source:

Response to clarification, Figure 5, page 29 from the company submission.

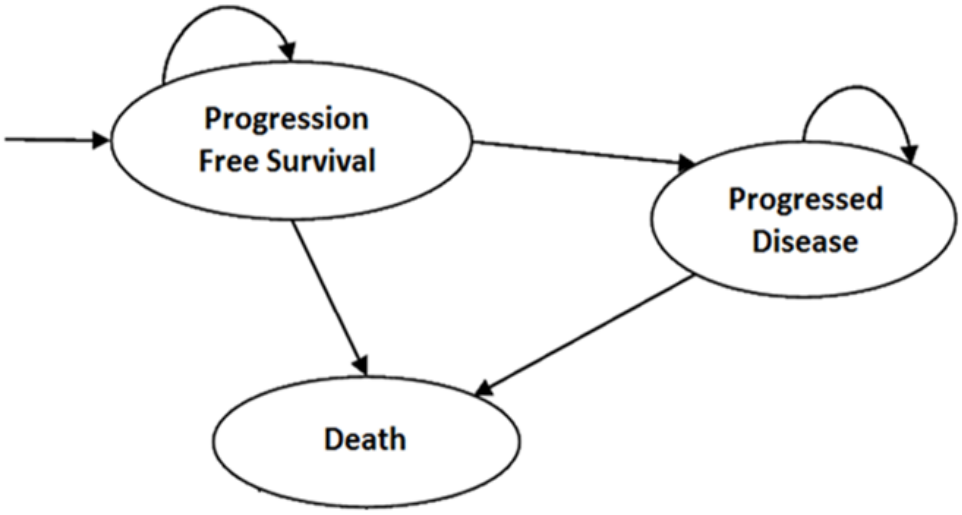
- The ERG asked the company at the clarification stage to conduct an analysis excluding the 16 patients (10 in polatuzumab vedotin+BR arm; 6 in BR arm) who had received an ASCT. The results were very similar and were slightly improved in the polatuzumab vedotin+BR arm.

1.7 Model structure

- A partitioned survival model was built with three mutually exclusive health states: progression-free state (PFS), progressed disease (PD) and death. The proportion of alive patients falling into PFS or PD was defined by extrapolated PFS and OS survival curves from GO29365.
- Patients who enter the progressed disease state, remain there until their death. Transitions between health states are determined by PFS and OS survival curves calculated from the GO29365 trial data, with the proportion of patients in the PD health state calculated as the difference between OS and PFS at any given time point. The proportion of the patients on treatment is informed by the time to off treatment (TTOT) curves.

- The company employed a cure mixture modelling approach, where it is implicitly assumed that a proportion of patients entered long-term remission (PFS) and are therefore likely to experience long-term survival similar to the general population. In line with this assumption, for the patients who are still in the PFS state after 2 years, it is assumed that there is no healthcare resource utilisation and age/gender adjusted general population utilities are assigned to them.

Company model structure



Source: company submission, section B.3.2.2, Figure 9

1.8 Key model assumptions

Intervention	Polatuzumab vedotin+BR given every 3 weeks for a max 6 cycles, modelled in line with dosing schedule in GO29365 and anticipated marketing authorisation
Population characteristics	Patients with R/R DLBCL ineligible for SCT, starting age 69 years, 50% male, mean weight 74.86 kg, mean body surface area, m^2 1.84. Most characteristics from G029365 trial (not % males which was 66% in trial)
Comparator	Base case comparator is BR. In a scenario analysis R-GemOx was included as a comparator assuming equal efficacy with BR.
Natural history	Transitions between states based on G029365 trial. After 2 years in PFS patients are assumed cured and general population mortality, utility and cost values apply
Treatment effectiveness	OS and PFS of polatuzumab vedotin+BR and BR are based on extrapolation curves fitted to the Kaplan-Meier data from G029365 (cure-mixture modelling using generalised gamma distribution for PFS and OS). For extrapolation of PFS, the company used investigator-assessed data.
Adverse events	Grade 3-5 AEs from G029365 for polatuzumab vedotin+BR and BR: one-off cost and utility decrement applied based on trial data, previous appraisals & other literature
HRQL	Base case utilities taken from TA559 using data from ZUMA-1 trial of axicabtagene in patients with mixed hystology lymphoma incl DLBCL
Time horizon	45 years
Perspective	NHS and Personal Social Sevices
Discount rates	3.5% for costs and outcomes
Costs	Drug acquisition, administration, supportive care & subsequent treatment costs. Sourced from NHS reference costs, PSSRU, BNF and eMIT. Base case acquisition costs for p+BR based on 140 mg and 30 mg vials, the latter of which is not yet available
Clinical Study (GO29365)	Clinical data based on the 80 patients in GO29365 which company considers is generalisable to the UK.

2. Summary of the draft technical report

2.1 In summary, the technical team considered the following:

Issue 1 **Formulation of polatuzumab vedotin:** The company is to supply polatuzumab vedotin in its lyophilised formulation and not the liquid formulation assessed in the clinical trial. The technical team is not aware of any reason for the two formulations to have different efficacy and safety and believes that this is a regulatory issue.

Issue 2 **Relevant comparators:** The company has compared polatuzumab vedotin in combination with bendamustine and rituximab (polatuzumab vedotin+BR) with BR alone as there is direct evidence from the clinical trial. A network could not be constructed to inform an indirect comparison between polatuzumab vedotin +BR and other comparators in the scope (for the other comparators, see section 1.4). The company also presented a scenario analysis in which rituximab, gemcitabine and oxaliplatin (R-GemOx) was included as a comparator, under the assumption of equivalent efficacy to BR. Clinical advice is sought on whether this assumption is appropriate and whether BR and R-GemOx are a reasonable reflection of the treatments used in clinical practice to treat people who would be eligible for polatuzumab vedotin+BR. .

Issue 3 **Generalisability of the clinical trial population to UK clinical practice:** Clinical evidence comes from the multicentre trial GO29365 of polatuzumab vedotin +BR in patients with R/R DLBCL. This was an open label trial that included 40 patients in each arm, 3 from the UK. More than two thirds were white, and most had an ECOG performance status of 0 or 1. There were some baseline imbalances between treatment groups including more patients in the polatuzumab vedotin +BR having a lower International Prognostic Index score and more patients in the BR group having bulky disease. Clinical opinion would be valued on the generalisability of the trial to UK clinical practice.

Issue 4 **Is polatuzumab vedotin a curative treatment, and if so at what stage can cure be assumed? :** The way in which the company and ERG model progression-free survival and overall survival has the largest impact on the cost effectiveness results, changing the ICER by £14,664. The company used a cure-mixture model but the ERG considers that there is a lack of robust long-term evidence to be confident in a cure assumption. The ERG's base case therefore uses independent standard parametric survival extrapolation. Clinical opinion is sought on whether a cure assumption is appropriate, and if so, at what stage a cure can be assumed.

Issue 5 **Cost assumptions**: Polatuzumab vedotin will initially be available only in a 140 mg-vial size which would create waste due to a lack of flexibility in vial sizes to tailor the dose to patients' individual weights. The company plans to make polatuzumab vedotin available in additional 30 mg vials and therefore it calculated the treatment costs according to both vial sizes. In the absence of a formal agreement on the availability of the 30 mg vial, the ERG and the NICE technical team believe that the base case analysis should assume acquisition costs of polatuzumab vedotin based on the 140 mg vial only, and no vial sharing, which increases the ICER by over £12,000. Expert advice is sought on whether this is the most plausible approach, and on whether patients would be likely to have polatuzumab vedotin treatment beyond 6 cycles in clinical practice.

Issue 6 **Modelling of non-cancer background mortality:** The company followed an individual patient-level approach for modelling non-cancer background mortality risks whereas the ERG adopted a cohort-based modelling approach to be consistent with the methods used for modelling progression-free survival and overall survival. The ERG believes that having different methods for the survival extrapolation (cohort-based) and the background mortality modelling (individual patient-level based) causes inconsistency and leads to instances where a significant proportion of patients is still alive after 40 or 50 years. The ERG's approach increases

the ICER by £10,480. Expert advice is sought on whether an individual patient-level approach or a cohort-based approach is appropriate.

Issue 7 Health-related quality of life (HRQL): was not directly measured in trial GO29365. The company's base-case utility values were estimated from the ZUMA-1 trial based on a small sample of patients with mixed histology lymphoma, using the EQ-5D-5L. The ERG identified some alternative utility sources but did not consider these to be any better than those used by the company. Clinical advice is sought on whether the utility values used in the model reflect the HRQL of people with R/R DLBCL.

Issue 8 Model time horizon: The company's base case model has a time horizon of 45 years, and the average patient age is 69 years. The cost effectiveness results are sensitive to changes to the time horizon. Expert advice is sought on whether a time horizon of 45 years is appropriate.

Issue 9 **End of life criteria**: The ERG and the company believe that the end of life criteria are met based on; the prognosis of untreated patients is poor (median 10 months estimated by the company) and extension of life is greater than 3 months as demonstrated by their respective base-case models. The technical team agrees that the end of life criteria are met.

2.2 The technical team recognised that the following uncertainties would remain in the analyses and could not be resolved:

- The randomised clinical trial evidence is based on small patient numbers (n=80).
- Clinical trial arms with the lyophilised formulation of polatuzumab vedotin are still on-going in the GO29365 trial.
- HRQL was not measured in GO29365.
- Transplant-eligible patients were not within the NICE scope or the decision problem but 16 patients in the trial had received an ASCT and were included in the economic analysis.

2.3 Taking these aspects into account, the technical team believes the incremental cost-effectiveness ratio (ICER) could be as high as £67,499 per QALY gained.

2.4 The intervention meets the end-of-life criteria.

2.5 The company considers that polatuzumab vedotin belongs to an innovative class of anticancer treatments (antibody-drug conjugates [ADCs]) and is the only ADC targeting CD79b. However, the technical team is not aware of any relevant benefits associated with the drug that are not captured in the model.

2.6 Equity considerations were not reported by the company in its submission.

3. Key issues for consideration

Issue 1 – Formulation

Questions for engagement	1. Is it reasonable to assume that the liquid and lyophilised formulations have similar effectiveness?
Background/description of issue	Data from the Phase Ib and the randomised Phase II portion of GO29365 was generated with a liquid formulation of polatuzumab; however the company is to supply polatuzumab vedotin in its lyophilised formulation. **Company**: Results reported in its submission are from patients treated with the liquid formulation of polatuzumab vedotin; however, this is not anticipated to be different from that seen with the lyophilised formulation, as reflected by preliminary safety and PK data that has been submitted to EMA. Furthermore, the FDA and EMA have allowed the company to file for marketing authorisation based on results from the liquid formulation. In late 2017, the trial protocol was amended to add a new formulation (NF) cohort (Arm G [N=42]), which was designed primarily to assess pharmacokinetic and safety of the lyophilised formulation of polatuzumab in combination with BR in R/R DLBCL. Efficacy was evaluated as a secondary objective; [redacted]. In October 2018, another arm was added to the NF cohort (Arm H) recruiting an additional 60 R/R DLBCL patients using the lyophilised formulation of polatuzumab in combination with BR. [redacted]. **ERG**: In the absence of full evidence, the committee will need to decide if it is satisfied that the lyophilised formulation of polatuzumab will have similar efficacy and safety to the liquid formulation.
Why this issue is important	The ERG highlighted that the formulation of polatuzumab used in the trial (liquid) is not the formulation intended for commercial use (lyophilised), and that it is uncertain whether the two formulations will have the same efficacy and safety in clinical practice.
Technical team	The technical team is unaware of any reason for the two formulations to have different safety and efficacy and believes that this is a regulatory issue that does not require discussion by the appraisal committee.

preliminary judgement and rationale	

Issue 2 – Comparators

Questions for engagement	1. Are bendamustine + rituximab (BR) and rituximab, gemcitabine and oxaliplatin (R-GemOx) a reasonable reflection of the comparators currently used in clinical practice to treat people who would be eligible for polatuzumab vedotin + BR? 2. Is it reasonable to base a decision on a comparison with BR? 3. Are there any other relevant comparators? if so, how would the efficacy and safety of these comparators be expected to differ from BR in clinical practice? 4. In the absence of direct evidence, is it reasonable to assume that R-GemOx has equivalent effectiveness and safety as BR (as per the company's assumption in the model)? 5. Does the assumption that a maximum number of 3 treatment cycles of 3 weeks of R-GemOx reflect treatment in clinical practice?
Background/description of issue	**Company**: There is no universally accepted standard of care regimen for treating patients with R/R DLBCL who are not candidates for ASCT. The main comparison for polatuzumab vedotin +BR is against BR using direct evidence from the GO29365 clinical trial. The feasibility of an indirect treatment comparison of polatuzumab vedotin +BR with comparators other than BR identified in the NICE scope was investigated based on the results of a systematic literature review. In the NICE final scope a number of potential regimens used in NHS clinical practice were identified (R-GemOx, R-Gem, R-P-MitCEBO and R-DECC), in addition to BR. The systematic review identified 19 studies: 6 RCTs and 13 single-arm studies. However, the feasibility assessment showed that a connected network of evidence could not be constructed based on evidence identified. The company concluded that a robust indirect comparison was not feasible because of the limited evidence. The studies identified were only relevant to one other comparator listed in the NICE scope (R-GemOx, 3 single arm studies identified). Only one of these studies included a group of patients that

	had received rituximab in a prior treatment line (rituximab pre-treated patients). However, the study did not report KM data for rituximab pre-treated and naïve patients separately and it was therefore not feasible to conduct a robust match-adjusted treatment comparison with R-GemOx. The company did however present a scenario analysis in which R-GemOx was included as a comparator, under the assumption of equivalent efficacy to BR. The company reported that the assumption of equivalent efficacy with BR is supported by recent real-world evidence demonstrating no overall survival (OS) difference between people with R/R DLBCL treated with BR and R-GemOx. In addition to this recent real-world data, reported outcomes in prospective studies fall into a similar range. **ERG**: examined the RCTs identified and agreed that a network could not be constructed to inform an indirect comparison between polatuzumab vedotin +BR and other comparators in the NICE scope. Equally, in examination of the observational studies a match-adjusted indirect comparison did not appear to be appropriate given the differences identified by the company in populations and line of treatment across the studies. Therefore, the only study presented in relation to clinical effectiveness was the Phase Ib/II, multicentre, open-label trial (GO29365) of polatuzumab vedotin in combination with BR in patients with R/R DLBCL. Whilst the comparator in the main GO29365 trial is consistent with the scope, it seems likely that it is not the only suitable one. For example, there is some evidence that R-GemOx is used increasingly in clinical practice. There are no comparative data of R-GemOX and BR. However, studies of R-GemOx report higher OS than for BR in the GO29365 trial. In the absence of direct evidence, it is not clear if R-GemOx can be assumed to have equal efficacy and safety outcomes to BR. In a scenario analysis the company assumed that the effectiveness of R-GemOx was equivalent to BR, and a maximum number of 3 treatment cycles of 3 weeks was assumed. It is unclear to what extent these assumptions, particularly that of equivalent effectiveness, reflect the actual comparative effectiveness in clinical practice. Therefore, the ERG is cautious about the use of the R-GemOx comparator in this model.
Why this issue is important	The robustness of modelling relies on a comparison of the intervention against the most relevant comparators to demonstrate whether the intervention is cost-effective compared with currently used treatments in the NHS.

Technical team preliminary judgement and rationale	The comparison with BR is the most robust because there is direct evidence, but it is unclear whether BR is a good proxy for the range of regimens used in the NHS.

Issue 3 – Generalisability of the clinical trial to UK population

Questions for engagement	1. Is the GO29365 trial generalisable to the UK population considering the ERG's comments that 3 patients were from the UK, non-white participants were underrepresented, and most patients had an Eastern Cooperative Oncology Group (ECOG status) of 0 or 1? 2. Are there any other factors that limit the generalisability of the trial to UK clinical practice? 3. More patients in the polatuzumab vedotin +BR arm had a lower International Prognostic Index (IPI) score and more patients in the BR group had bulky disease. The company did not make an adjustment to PFS for the differences between the treatment groups in bulky disease. To what extent would these factors be expected to bias the results?
Background/description of issue	The clinical trial GO29365 is a phase Ib/II, multi-centre open-label trial providing efficacy and safety evidence for the combination of polatuzumab vedotin+BR in patients with R/R DLBCL, compared with BR. Data from GO29365 were used to inform the efficacy and safety of polatuzumab vedotin+BR in the economic model. The median age of patients in the trial was 66.5 in the polatuzumab vedotin+BR group and 71.0 in the BR group. Most patients were white (67.4%) and had an ECOG status of 0 or 1 (84.7%). The median number of prior treatment lines was 2 and approximately 30% had received one prior treatment. **Company**: Any differences in incidence of demographic characteristics by category observed between BR and polatuzumab vedotin+BR treatment arms in the randomised Phase II were less than 10% (accounted for by 4 patients or fewer). **ERG**: Although the trial was multinational, it was relatively small (40 patients were randomised to each arm) so the evidence on which results are based is limited. Three patients included in GO29365 were from the UK. The company was asked to justify the applicability of the trial to UK clinical practice. They stated that the baseline characteristics of the population of GO29365 were similar to a UK study of pixantrone in R/R DLCBL patients. The company also obtained advice from clinical experts who '*confirmed that*

	the baseline characteristics of patients enrolled in GO29365 are reflective of the population seen in UK clinical practice and corroborates the comparison to the retrospective analysis'. The ERG considered this reasonable but noted that non-white participants were underrepresented in the trial and that most patients had an ECOG status of 0 or 1. The ERG also noted that there were some baseline imbalances between the treatment groups including more patients in the Polatuzumab vedotin+BR having a low IPI score (e.g. 22.5% compared with 7.5% had a score of 0-1) and more patients in the BR group having bulky disease (25.0% compared with 37.5%). Adjustment to overall survival (OS) was performed for both of these factors, but not to progression-free survival (PFS) for bulky disease, which could favour Polatuzumab vedotin+BR.
Why this issue is important	The outcomes of the clinical trial data used in the economic model should be generalisable to the UK population as the economic evaluation is intended to inform the NHS decision makers.
Technical team preliminary judgement and rationale	The population of the GO29365 clinical trial broadly reflects the population who would be eligible for treatment with polatuzumab vedotin+BR in the NHS.

Issue 4 – Is polatuzumab vedotin a curative treatment, and if so at what stage can cure be assumed?

Questions for engagement	1. Is it reasonable to assume from the evidence that a proportion of patients treated for R/R DLBCL enter long-term remission after being progression-free for 2 years and have the same risk of mortality as the general population? 2. Is the cure assumption clinically plausible? Is the model prediction that 21.2% of patients on polatuzumab vedotin+BR have long-term remission and 20.6% are long term survivors (compared with 0% for BR) clinically plausible and an accurate reflection of the clinical trial? 3. Which progression-free survival data are most robust for use in the model, investigator-assessed or independent review committee (IRC)? 4. Can rates of long-term remission from studies of newly diagnosed DLBCL be generalised to the R/R setting? 5. Can the long-term survival associated with CAR-T cell therapy be compared to polatuzumab vedotin+BR?

	6. What is the company's justification for using its own code instead of standard cure-mixture modelling codes available in statistical programmes? Please can the company provide more information to enable the ERG to assess the methods used.
Background/description of issue	The **company** used a cure-mixture model, where it implicitly assumed that a proportion of patients entered long-term remission and are therefore likely to experience long-term survival compared to the general population. In line with this assumption, for the patients who are still in the PFS state after 2 years, it is assumed that there is no healthcare resource utilisation and also age/gender adjusted general population utilities are assigned to them. Given the uncertainty surrounding the cure assumption, discussed in section 5.2.6 of the ERG report, the **ERG** preferred to use independent parametric distributions to model progression-free survival and overall survival rather than a cure-mixture model. **Company**: cure-mixture models represent an approach to modelling cancer therapies for which there is evidence to support that a proportion of treated patients enter long-term remission, and subsequently experience mortality aligned with that of the general population. Cure-mixture models assume the patient population comprises two subpopulations; the first subpopulation is considered to be at the same risk of mortality as the age- and sex-matched general population, whilst the mortality rate of the second subpopulation is defined by a selected standard parametric survival curve. The proportion of patients falling into the first population (known as the 'cure fraction') is estimated through logistic regression of trial data. The extrapolations for each subpopulation are then combined via the cure fraction to obtain extrapolations for the population as a whole. In the company's base case cure mixture generalised gamma model, 21.2% of patients in the polatuzumab vedotin+BR arm and 0.0% in the BR arm were predicted to be in long term remission, while 20.6% and 0% were predicted to be long term survivors. PFS and OS data from the GO29365 study demonstrate that compared to current standard of care, polatuzumab vedotin+BR is likely to offer patients an improved probability of achieving long-term remission (and therefore long-term survival), as evidenced by the statistically significantly improved rate of PFS vs BR. The company believes that a very low risk of relapse or death can be observed in the KM plots for PFS and OS for polatuzumab vedotin+BR towards the end of follow-up, indicative of a very low risk of relapse or death for patients who were still alive towards the end of follow-up. The company also commented that the precedent of cure-mixture modelling in NICE appraisals for

	R/R DLBCL was established in TA567 and TA559 (NICE appraisals of Chimeric antigen receptor-T cell (CAR-T) therapies), where the respective Committees accepted that patients who are able to demonstrate sustained remission are likely to benefit from long-term survival. The company modelled PFS using investigator-assessed data rather than IRC data. The company's rationale for this is that treatment decisions for patients included in the trial, for example, to move a patient to the next line of treatment, were based on progression as measured by the investigator and therefore these data are more consistent with the treatment pathway experienced by patients in the trial. The ERG considered that PFS extrapolation using IRC data was more reliable and used these in its modelling – see below. **ERG**: Instead of using standard cure-mixture modelling codes available in statistical programmes, the company developed its own code, which was not transparent and clear enough for the ERG to assess the correctness of the implementation of the methods in the provided code. The company's "cure" assumption was based on literature on the natural history of newly diagnosed DLBCL patients treated with immunochemotherapy that showed that patients who did not experience a progression or death event after 2 years went on to experience subsequent survival equivalent to that of the age- and sex-matched general population. An equivalent study has not been performed in the R/R DLBCL setting. However, the company's clinical experts believed that patients who achieve 2 years in PFS are at very low risk of subsequent progression, and their risk of death can be assumed to have returned to a level close to that of the matched general population. The company also observed the low risk of relapse or death in the Kaplan–Meier (KM) plots for polatuzumab vedotin+BR towards the end of follow-up and the precedent for cure-mixture modelling accepted in previous NICE appraisals in R/R DLBCL patients. However, the ERG felt that there was a lack of robust long-term evidence to be confident in a cure assumption, especially given the small number of patients remaining alive and event free at the end of a relatively short follow-up period. The ERG disagrees with the company in its interpretation of the KM plots, as at least 2 events could be observed after 24 months in the polatuzumab vedotin+BR

	arm from the PFS KM curve (shown in Figure 4.2 of the ERG report). Death events could also be observed towards the end of follow up time in the OS KM curve (Figure 5.12 of the ERG report). The ERG also highlighted that the study cited by the company to support its modelling approach was in people with newly diagnosed DLBCL and is doubtful if the results would hold for the indicated population for polatuzumab vedotin+BR i.e. R/R DLBCL. The ERG also notes that the previous technology appraisals cited by the company as evidence of the precedent of cure-mixture modelling in NICE appraisals for R/R DLBCL were for CAR-T therapies which represent a distinct form of therapy compared with the current intervention being appraised. The ERG also highlighted that a more recent study with a larger sample of DLBCL patients found that excess mortality remained up until 5 years and overall patients experienced excess mortality from non-cancer causes of 1.41. Additionally, the company's base-case assumptions of cure-mixture models led to OS and PFS hazard ratios, which were not in line with the empirical hazard plots for OS and PFS from the GO29365 trial and which conferred an overly optimistic treatment benefit, even decades after the treatment is received. Therefore, the ERG explored alternative independent standard parametric survival extrapolation models in their base-case and scenario analyses, and also a logical constraint was enforced, which ensured that the OS extrapolation from the trial provided a lower survival estimate from the age/sex adjusted general population at any given point time. ERG assumed: • OS from the general population with excess mortality must always be higher than or equal to the OS extrapolations from the GO29365 survival data. • PFS extrapolation using IRC data was selected from a standard lognormal distribution independently fitted to both arms. OS extrapolation was selected from a standard generalised gamma distribution independently fitted to both arms.
Why this issue is important	The assumption with the largest impact on the ICER was changing the way that progression-free survival and overall survival are modelled (from cure-mixture models to standard independently fitted parametric models). Using the ERG's approach increases the ICER by £14,664 per QALY gained.
Technical team preliminary judgement and rationale	There is a lack of robust long-term evidence to support the company's assumptions about long-term remission and cure. Therefore, the ERG's approach to extrapolation appears to provide a more

	plausible estimate of cost effectiveness. The technical team also considers that modelling PFS using IRC data is more reliable than using investigator-assessed data given the open label nature of the study.

Issue 5 – Cost assumptions

Questions for engagement	1. The ERG base-case models the 140mg vial only and assumes no vial sharing, is this the most plausible approach? 2. Is it likely that patients would have polatuzumab vedotin treatment beyond 6 cycles in clinical practice? 3. The marketing authorisation may specify 6 cycles of treatment, whereas 5% of people in the polatuzumab vedotin+BR arm of the trial had treatment for longer than 6 months. How would a 6-cycle treatment cap affect the generalisability of the trial results?
Background/description of issue	Polatuzumab vedotin will initially be available only in a 140 mg vial size at a list price of [redacted] per vial. The 30 mg vial is in development and is planned to be available at an equivalent per mg price ([redacted] per 30 mg vial) in [redacted]. The use of the 140 mg vial alone prior to the availability of the 30 mg vial could initially create waste for individual NHS Trusts due to a lack of flexibility in vial sizes to tailor the dose to patients' individual weights. Given an average dose of 143.9 mg based on the GO29365 study, nearly half is wasted when only 140 mg vials are available, and no vial sharing is assumed. **Company**: Because of the plans to make polatuzumab vedotin available in 140 mg and 30 mg vials (lyophilised product prepared for reconstitution prior to infusion), the company calculated the treatment costs according to both vial sizes with no vial sharing. In consultation with NHS compounding service providers, the company is planning to put arrangements in place so hospitals can obtain bags ready for infusion with the correct patient-specific dosing from these service providers without incurring any wastage costs. Trusts would therefore only be charged on a per mg basis for the drug acquisition costs, resulting in a 'no waste' or 'full vial sharing' scenario. The use of compounders is already common practice for other

	chemotherapies in an increasing number of NHS Trusts. Upon availability of the 30-mg vial, it is envisaged that NHS Trusts will be able to prepare doses in-house, incurring minimal wastage. Time-to-off-treatment (TTOT) data from the GO29365 study were mature, as the polatuzumab vedotin+BR and BR arm comprised of treatment for up to 6 cycles only. TTOT KM estimates were therefore used directly in the model base case, using separate curves for each medicine in the respective regimens. **ERG**: Given that the availability of a 30 mg vial size is uncertain and no formal agreement is in place, the ERG feel that the base-case should conservatively assume that the current situation will remain, and that it is more appropriate to explore the impact of the future availability of different vial sizes in scenario analyses. Therefore, in its base case analysis the ERG assumes acquisition costs of polatuzumab vedotin based on the 140 mg vial only, with no vial sharing. The ERG applied treatment costs for the polatuzumab vedotin+BR and BR regimens for as long as patients in the trial received treatment (i.e. based on TTOT data) instead of up to a maximum of 6 treatment cycles assumed in the company's base case. The ERG considered that the costing of a maximum of 6 cycles of polatuzumab vedotin+BR and BR, contrary to the included TTOT data from the trial, was incorrect. Since the treatment effectiveness from the trial is based on the application of the treatment longer than 6 cycles, not including the costs of these treatments beyond cycle 6 would create a bias. In the ERG base-case these treatments were costed according to the TTOT data provided. The ERG confirmed that in the pivotal clinical trial around 5% of the patients received more than 6 cycles (7 or more) of the treatments in the polatuzumab vedotin+BR arm. Around 2% of the patients received more than 6 cycles (7 or more) of the treatments in the BR arm.
Why this issue is important	Assumptions around vial sizes have a large impact on the ICER. Calculating polatuzumab vedotin treatment costs based on the currently available vial size (140 mg) increases the ICER by £12,851, meaning there is a high degree of uncertainty in the cost of treatment and associated waste. In addition, the ERG's changes to the assumption about length of treatment increase the ICER by around £3000.
Technical team preliminary judgement and rationale	In the absence of a formal agreement on the availability of the 30 mg vial, the base case analysis should assume acquisition costs of polatuzumab vedotin based on the 140 mg vial only. For consistency with the proposed marketing authorisation treatment should be given for a maximum of 6 cycles.

Issue 6 – Modelling of non-cancer background mortality

Questions for engagement	1. Which method is the most appropriate for modelling non-cancer background mortality: individual patient-level approach or the cohort-based modelling?
Background/description of issue	Another important issue was the way non-cancer background mortality was included in the model. The company used a cure mixture model to extrapolate PFS and OS, which assumed that a proportion of patients were long term survivors (see Issue 4). This followed a cohort-based approach. The long-term survivor patients were subject to non-cancer related mortality in the model. In addition, patients who did not die among the non-long-term survivors were subject to non-cancer related mortality in the model. Despite the cohort-based approach in the OS/PFS survival modelling, the **ERG** considers that the company followed an individual based approach for modelling the non-cancer background mortality risks i.e. background mortality was based on the age and sex of each patient included in the trial. The model calculates the weighted mortality risk from the individual age- and sex-matched specific mortality risks from a cohort of 160 patients (50%-50% male-female, characterizing the age distribution of the GO29365 trial). The **ERG** used a cohort-based modelling approach for non-cancer background mortality risks for consistency with the PFS and OS modelling. The ERG believes that the company's method created an inconsistency, as the relatively younger patients' lifetable based survival estimates are taken into the weighted average, hence leading to instances where a significant proportion is still alive after 40 or 50 years, which is not realistic from a cohort modelling perspective, as the average age of the cohort was 69. The ERG assumed general population mortality based on "average patient" (i.e. cohort approach instead of individual patient level approach). The **company** believes that its approach to modelling is still a cohort approach and that the difference between the two approaches is simply the age distribution used: the company used an age distribution of the cohort based on the GO29365 data to derive background mortality whereas the ERG used a 'delta distribution' where all patients are exactly 69 years old at the start of treatment. The company believes its approach is in line with using the weight distribution to calculate dosing in the cohort as opposed to average weight only. However, the **ERG** disagrees with this. Firstly, unlike the patient weight, the baseline age has a direct influence on the non-cancer related death and therefore the long-term prognosis. Secondly, in their model, the company created

	160 patients (1:1 female/male with age distribution mimicking the GO29365 trial). From each individual patient, non-cancer death extrapolation was conducted from the UK lifetable and individual patient's characteristics. Afterwards the average of these 160 extrapolations was taken and used in the model. The ERG considers that this is an example of individual-based modelling. The company's approach could have been considered as a "cohort approach" if the company had sampled the baseline age from a distribution, and extrapolated the non-cancer deaths from that sampled baseline age, accordingly (please note that this approach would not be ideal, since heterogeneity would be incorporated as parametric uncertainty in the analyses).
Why this issue is important	The ERG preferred a cohort approach to modelling background mortality, instead of a patient-level approach, which increased the ICER by £10,480.
Technical team preliminary judgement and rationale	Having different methods for the survival extrapolation (cohort-based) and the background mortality modelling (individual patient-level based) causes inconsistency and leads to instances where a significant proportion of patients is still alive after 40 or 50 years. The technical team agrees with the ERG that this is not realistic given that the average in the model is 69 years, and therefore supports the ERG's approach for a cohort-based approach for the background mortality in line with the approach used for the PFS/OS extrapolation.

Issue 7 – Health-related quality of life

Questions for engagement	1. Do the utility values used in the model reflect the health-related quality of life of people with R/R DLBCL? 2. Are more robust estimates from larger/more relevant samples available?
Background/description of issue	Health-related quality of life was not directly measured in trial GO29365. The **company's** base-case utility values were estimated from the ZUMA-1 trial based on a small sample (34 patients provided 87 observations) of mixed histology lymphoma patients, using the EQ-5D-5L (as in TA 559). The progressed disease value was based on a very small sample of 5 observations. The company justified using HRQL data collected in the ZUMA-1 trial on the basis that they were used in a previous NICE technology appraisal (TA559). The utility values used in the base case were 0.72 for the progression-free health state and 0.65 for progressed disease (PD).

	Eight sources of utility were identified by the company in total. data Three of these were used in previous NICE appraisals; • TA306 - pixantrone monotherapy for treating multiply relapsed or refractory aggressive non-Hodgkin's B-cell lymphoma • TA567 - tisagenlecleucel for treating relapsed or refractory diffuse large B-cell lymphoma after 2 or more systemic therapies • TA559) - axicabtagene ciloleucel for treating diffuse large B-cell lymphoma and primary mediastinal large B-cell lymphoma after 2 or more systemic therapies These three studies each provided utility values for the required PFS and PD health states. Of the remaining five sources of utility values, three utilised published sources of utility values, one used a non-published source of utility data and one based its utility values on real world data. None of these five potential sources of values provided relevant utility values for both model health states. Additionally, studies based on existing published sources of utility data tended to be based on older data, with the most recent source being from 2006 and the oldest from 1999. Values were also often not specific to DLBCL patients. The **ERG** identified alternative utility sources but did not consider these to be any better that the estimates presented by the company. The ERG tested the impact of using different health state utility values identified by the company in a series of scenario analysis (table 7.13 of ERG report). The utility values from TA306 provided the highest ICER at £67,596, while the utilities from TA567 provided the lowest ICER of £63,353. However, the small variation in ICERs shows that the utility values themselves are not big drivers of model results. The patient characteristics of the members of the ZUMA-1 trial who provided HRQL data were not available and therefore it is unclear how similar this group is to the GO29365 population or the R/R DLBCL patients who would be expected to receive polatuzumab in clinical practice. However, despite these limitations, the ERG agrees that none of the alternative utility sources identified provide a better estimate of HRQL when considering the alignment with the NICE reference case, and therefore this source of utility values was retained in the ERG base-case. Disutilities for those adverse events (AEs) included in the model were appropriately sourced from previous appraisals in R/R DLBCL.

Why this issue is important	The data informing the utility estimates in the model are from a small sample that is not specific to DLBCL. Health-related quality of life data from a larger and more relevant sample may have more of an impact in the model.
Technical team preliminary judgement and rationale	The company has used the best available data, but this is based on a small sample that is not specific to R/R DLBCL and may not be reliable.

Issue 8 – Model time horizon

Questions for engagement	1. Is a model time horizon of 45 years appropriate for R/R DLBCL, or should it be shorter given that the patient age in the model was 69 years?
Background/description of issue	The company's base case model has a time horizon of 45 years, and the average patient age was 69 years. The ERG described the 45-year time horizon as "appropriate" but the technical team is concerned that this may be too long given that the average patient age of 69 years and given that the results were sensitive to large changes to the time horizon. The company's scenario analyses show that a shorter time horizon increases the ICER (see table 6.6 in ERG report). Assuming a time-horizon of 10 years increased the ICER by £15,800. Increasing the time-horizon to 20 and 30 years decreased the ICER by £3,306 and £752 respectively.
Why this issue is important	The cost effectiveness results were sensitive to changes to the time horizon.
Technical team preliminary judgement and rationale	The 45 year time horizon assumed in the model seems long given that the average age of patients is 69, and is longer than the 30-40 years that is typically used.

Issue 9 – End of life criteria

Questions for engagement	3. Does polatuzumab vedotin + BR fulfil the criteria to be considered a "life-extending treatment at the end of life"?
Background/description of issue	**Company**: presented evidence to suggest that polatuzumab vedotin+BR meet the NICE criteria for End of Life: • For life expectancy, the company provided evidence from the research literature of the poor survival outcomes in relapsed and refractory DLBCL. They also stated that '*The median OS for the comparator arm (BR) in the GO29365 study was* [redacted]. *The average survival estimated in the economic analysis was 12.2 months.* • In regard to an extension of life with polatuzumab vedotin +BR, the company stated that '*The estimated mean OS gain of Polatuzumab vedotin+BR over BR in the model was 4.1 years.*' **ERG**: believes that end of life criteria are met. The prognosis of untreated patients is poor as shown by the median survival time in the control group of GO29365. In a study by Crump and colleagues, patients with refractory DLBCL had a median overall survival of 6.3 months: only 20% of patients were alive at two years.17 The extension to life identified in the GO29365 was a difference in medians of about 7.7 months. The model predicted a much larger gain due to the cure-mixed approach taken but this should be interpreted with some caution. Nevertheless, the ERG base-case showed a total 2.08 life years gain between two interventions.
Why this issue is important	According to the Guide to the methods of technology appraisal, if a technology fulfils the criteria to be considered a "life-extending treatment at the end of life" the committee will consider the impact of giving a greater weight to QALYs achieved in the later stages of terminal disease, with a maximum weight of 1.7. This increases the upper end of the range normally accepted as cost-effective use of NHS resources to £50,000 per QALY gained.
Technical team preliminary judgement and rationale	The NICE technical team is satisfied that the end of life criteria are met.

4. Issues for information

Tables 1 to 3 are provided to stakeholders for information only and not included in the technical report comments table provided.

Table 1: ERG's preferred assumptions and impact on the cost-effectiveness estimate

Preferred assumption	Section in ERG report	Polatuzumab vedotin + BR		BR		Inc. Costs (£)	Inc. QALYs	Cumulative ICER (£/QALY)	Change from base-case
		Total Costs (£)	Total QALYs	Total Costs (£)	Total QALYs				
Company base-case	6.1	[redacted]	[redacted]	£18,019	0.68	[redacted]	[redacted]	**£26,877**	£0
Company updated base-case (after clarification)	7.1.1	[redacted]	[redacted]	£17,440	0.67	[redacted]	[redacted]	£25,307	£1,570
ERG changes (1 –3): Fixing the errors	7.1.2.1	[redacted]	[redacted]	£17,440	0.67	[redacted]	[redacted]	£25,307	£1,570
ERG changes (1-3)+4: Following a cohort approach in background mortality	7.1.2.2	[redacted]	[redacted]	£17,249	0.64	[redacted]	[redacted]	£35,787	+£8,910
ERG changes (1-4)+5: Logical constraint on OS (OS from the extrapolation can be at maximum equal to the OS estimated from the age/sex adjusted general population with excess mortality)	7.1.2.2	[redacted]	[redacted]	£17,249	0.64	[redacted]	[redacted]	£35,787	+£8,910

Preferred assumption	Section in ERG report	Polatuzumab vedotin + BR		BR		Inc. Costs (£)	Inc. QALYs	Cumulative ICER (£/QALY)	Change from base-case
		Total Costs (£)	Total QALYs	Total Costs (£)	Total QALYs				
ERG changes (1-5) +6: Changing the OS and PFS extrapolation from cure-mixture models to standard independently fitted parametric models (using IRC PFS data)	7.1.2.3	[redacted]	[redacted]	£17,386	0.68	[redacted]	[redacted]	£50,451	+£23,574
ERG changes (1-6) +7: Changing the excess mortality for non-cancer related deaths from 1.0 to the literature-based value of 1.41	7.1.2.3	[redacted]	[redacted]	£17,379	0.68	[redacted]	[redacted]	£50,447	+£23,570
ERG changes (1-7) +8: HRQoL and cost assumption for long-term survivors in PFS (time threshold from 2 years to 3 years)	7.1.2.3	[redacted]	[redacted]	£17,658	0.68	[redacted]	[redacted]	£51,698	+£24,821
ERG changes (1-8) +9: Available vial size (only 140 mg)	7.1.2.3	[redacted]	[redacted]	£17,658	0.68	[redacted]	[redacted]	£64,549	+£37,672
ERG changes (1-9) +10: Treatments can be administered longer than 6 cycles, in line with the observed TTOT curves	7.1.2.3	[redacted]	[redacted]	£17,794	0.68	[redacted]	[redacted]	£67,478	+£40,601

Preferred assumption	Section in ERG report	Polatuzumab vedotin + BR		BR		Inc. Costs (£)	Inc. QALYs	Cumulative ICER (£/QALY)	Change from base-case
		Total Costs (£)	Total QALYs	Total Costs (£)	Total QALYs				
ERG changes (1-10) +11: Applying one-off SCT costs to the patients who received SCT or CAR-T treatments after progression from the first line	7.1.2.3	[redacted]	[redacted]	£19,511	0.68	[redacted]	[redacted]	£67,438	+£40,561
ERG changes (1-11) +12: Applying the updated AE incidences	7.1.2.3	[redacted]	[redacted]	£19,904	0.68	[redacted]	[redacted]	£67,499	+£40,622
Abbreviations: AE = adverse event; BR = bendamustine + rituximab; ERG = Evidence Review Group; HRQoL= health related quality of life; ICER = incremental cost effectiveness ratio; Inc. = incremental; IRC = independent research committee; OS = overall survival; PFS = progression free survival; QALY = quality adjusted life year; SCT = stem cell transplant; TTOT= time on treatment;									

Table 2: Outstanding uncertainties in the evidence base

Area of uncertainty	Why this issue is important	Likely impact on the cost-effectiveness
Small patient numbers in the pivotal study GO29365	Patient numbers in the GO29365 trial were too small to provide meaningful subgroup results by type of patient or line of therapy. The small patient numbers issue also add uncertainty to the overall trial results.	Unknown cost effectiveness in subgroups.
Lyophilised formulation of polatuzumab vedotin being studied in on-going clinical trial.	Data from the Phase Ib and the randomised Phase II portion of GO29365 were generated with a liquid formulation of polatuzumab vedotin; however, clinical trial arms with the lyophilised formulation suitable for commercialisation are still ongoing. In late 2017, the protocol was amended to add a new formulation (NF) cohort (Arm G [N=42]), which was designed primarily to assess pharmacokinetic and safety of the lyophilised formulation. Efficacy was evaluated as a secondary objective; [redacted].	Unknown impact on clinical and cost effectiveness.
Transplant-eligible patients were not within the NICE scope and the decision problem	The company confirmed that transplant-eligible patients were not within the NICE scope and the decision problem. The company provided results of the GO29365 trial excluding the 16 patients who had received an ASCT but the economic analysis was not updated to exclude these patients.	The clinical effectiveness results for polatuzumab vedotin+BR were slightly favourable when the 16 patients were excluded from the analysis. Impact on cost-effectiveness is unknown.

Table 3: Other issues for information

To note the issues highlighted below had a small impact on the ICER and are not therefore included as key issues.

Issue	Comments
Adverse Events incidences	The **company** includes "serious" grade 3 and above adverse events (AEs) in the GO29365 trial. The justification was that the "serious" AEs are the ones which would lead to costs to the NHS. The **ERG** identified several inconsistencies between the AE incidences used in the model and the incidences presented in clinical effectiveness section of this ERG report for the GO29365 trial, in terms of the number of serious AEs reported in each treatment arm. Therefore, the ERG updated the model incidences to reflect the incidences for the most frequently reported Grade 3-5 AEs (>5%). The impact on the ICER was negligible.
Excess mortality for long term survivors	The **company** assumed of no excess mortality in DLBCL long-term survivors compared to the general population, which the **ERG** believed to be overly optimistic. Assumption was based on a US study by Maurer et al (2014) which found no statistically significant difference between the mortality of newly diagnosed DLBCL who survived event free to 2 years and the age- and gender-matched general population. However, a more recent study based on a substantially larger sample of DLBCL patients suggests that excess mortality remains up to 5 years and that overall, DLBCL survivors are at excess risk of mortality due to non-cancer causes as well as the risk of late relapse. Therefore, excess mortality (SMR = 1.41) due to non-cancer causes was incorporated into the ERG base-case. Negligible impact on ICER.
HRQoL and costs of long-term survivors	The **company** base case assumed that the HRQoL of patients in PFS after 2 years is equivalent to the age-and sex-matched general population, based on evidence from literature suggesting no statistically significant difference in mortality for those DLBCL patients' event free at 2 years and limited evidence of no difference in HRQoL between long-term survivors and general population. The ERG extended this to 3 years to provide a more conservative estimate. The ERG preferred assumption increased the ICER by £1,251.
Costs for SCT and CAR-T	The **company** excluded the costs of stem-cell transplant (SCT) and CAR-T treatment, despite these having been received by trial participants. The company considered that these are not standard therapies that are used post-progression. The **ERG** feels that this was inappropriate and therefore attempted to include these costs in the ERG base-case. CAR-Ts are currently available of the NHS only under confidential PAS and therefore the cost of SCT was utilised for both treatments. Since the effectiveness data are based on those patients who received SCT and CAR-T therapies after progression, ignoring these would cause an inconsistency. The ERG's change had a negligible impact on the ICER.

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Technical engagement response form

Polatuzumab vedotin with rituximab and bendamustine for treating relapsed or refractory diffuse large B-cell lymphoma (ID1576)

As a stakeholder you have been invited to comment on the technical report for this appraisal. The technical report and stakeholders' responses are used by the appraisal committee to help it make decisions at the appraisal committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

We need your comments and feedback on the questions below. You do not have to answer every question. The text boxes will expand as you type. Please read the notes about completing this form. We cannot accept forms that are not filled in correctly. Your comments will be summarised and used by the technical team to amend or update the scientific judgement and rationale in the technical report.

Deadline for comments by 5pm **Friday 13 December 2019.**

Thank you for your time.

Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Notes on completing this form

- Please see the technical report which summarises the background and submitted evidence. This will provide context and describe the questions below in greater detail.
- Please do not embed documents (such as PDFs or tables) because this may lead to the information being mislaid or make the response unreadable. Please type information directly into the form.
- Do not include medical information about yourself or another person that could identify you or the other person.
- Do not use abbreviations.
- Do not include attachments such as journal articles, letters or leaflets. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.
- If you provide journal articles to support your comments, you must have copyright clearance for these articles.
- Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.

- Please underline all confidential information, and separately highlight information that is submitted under [redacted], all information submitted under [redacted], and all information submitted under [redacted] in pink. If confidential information is submitted, please also send a second version of your comments with that information replaced with the following text: 'academic/commercial in confidence information removed'. See the Guide to the processes of technology appraisal (sections 3.1.23 to 3.1.29) for more information.

We reserve the right to summarise and edit comments received during engagement, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received during engagement are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

About you

Your name	[redacted]
Organisation name – stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank)	**Roche Products Ltd**
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	**None**

Questions for engagement

Issue 1: Formulation	
Is it reasonable to assume that the liquid and lyophilised formulations have similar effectiveness?	The company agrees with the NICE Technical Team that this is a regulatory issue and there is no reason for there to be any difference in the safety and efficacy profiles of the liquid and lyophilised formulations of polatuzumab vedotin.
Issue 2: Comparators	
Are bendamustine + rituximab (BR) and rituximab, gemcitabine and oxaliplatin (R-GemOx) a reasonable reflection of the comparators currently used in clinical practice to treat people who would be eligible for polatuzumab vedotin + BR?	There are no universally established therapies for patients with R/R DLBCL who are ineligible for transplant or who relapse after transplant, resulting in a considerable amount of variability on the selected regimen for these patients in clinical practice. BR has been shown to be active in transplant-ineligible patients with R/R DLBCL with a manageable haematological toxicity profile (1-4). During the Technical Engagement teleconference, clinical experts corroborated advice that the Company had received during the appraisal process by confirming that BR is among the possible regimens for this patient population but there is no evidence to demonstrate superiority of one regimen over another.
Is it reasonable to base a decision on a comparison with BR?	As no prior randomised trials have established the superiority of one regimen over another for this population, the Company believes that BR is a suitable comparator for this appraisal. This was corroborated by clinical expert opinion during the Technical Engagement teleconference.
Are there any other relevant comparators? If so, how would the efficacy and safety of these comparators be expected to differ from BR in clinical practice?	As stated above and by the clinical experts during the Technical Engagement teleconference, there are other possible comparators for patients with transplant-ineligible R/R DLBCL; however,

	in the absence of randomised trials demonstrating superiority of one regimen over another for this population, there is no evidence to suggest that BR is inferior to any of these. The clinical experts also mentioned during the teleconference that there is considerable overlap in the toxicity between different regimens and overall the safety profile of BR is not expected to be any worse than other treatment options for this population. Furthermore, the experience of clinicians using BR for patients with follicular lymphoma in clinical practice is that this is a well-tolerated regimen.
In the absence of direct evidence, is it reasonable to assume that R-GemOx has equivalent effectiveness and safety as BR (as per the company's assumption in the model)?	As above, there is no clinical evidence to demonstrate superiority of R-Gem-Ox over BR therefore it is reasonable to assume equivalent effectiveness and safety between the two regimens.
Does the assumption that a maximum number of 3 treatment cycles of 3 weeks of R-GemOx reflect treatment in clinical practice?	During the teleconference call, the clinical experts stated that some patients may receive up to 8 cycles of R-GemOx but very few patients would be fit enough to receive this many cycles; the median number of cycles in clinical practice used is 3–4. The model scenario comparing polatuzumab vedotin + BR with R-GemOx was based on an average of 3 cycles (as time on treatment data was not available from the literature, the maximum as set equal to the average). This was deemed a reasonable approach based on the opinion from experts above and the average number of BR cycles based on GO29365 time on treatment data being 3.2.
Issue 3: Generalisability of the clinical trial to UK population	
Is the GO29365 trial generalisable to the UK population considering the ERG's comments that 3 patients were from the UK, non-white participants were underrepresented, and most patients had an Eastern Cooperative Oncology Group (ECOG status) of 0 or 1?	The study population from GO29365 is largely reflective of the R/R DLBCL population in the UK. The baseline patient characteristics of R/R DLBCL patients enrolled in GO29365 is very similar to the population enrolled in a retrospective study evaluating the efficacy of pixantrone in R/R DLBCL patients (median age 66.5 vs 65.9, respectively, proportion refractory to last prior anti-lymphoma therapy 76% vs 85%) (5). Furthermore, advice obtained from clinical experts confirmed that the baseline characteristics of patients enrolled in GO29365 are reflective of the population seen in UK clinical practice and corroborates the comparison to the retrospective analysis; clinical experts reported that most patients in their clinic have stage 3–4 disease and 75–80% are refractory to

	last prior therapy) (6). Moreover, the range of lines of prior therapy ranged from 1 to 7 in the pola+BR arm, reflecting the broad population in the transplant-ineligible setting that is seen in current clinical practice. During the Technical Engagement teleconference, the clinical experts stated that there are a proportion of patients with ECOG PS 2 are seen in clinical practice and would be deemed eligible for Pola+BR. They added that there is no evidence to suggest pola or BR would behave differently in patients of different ethnicities (this is not a factor considered during multi-disciplinary team meetings), therefore the low proportion of non-white participants in GO29365 does not influence the generalisability of the study population to UK clinical practice.
Are there any other factors that limit the generalisability of the trial to UK clinical practice?	The company is unaware of any other factors that limit the generalisability of the trial to UK clinical practice. No issues were highlighted when obtaining clinical expert advice during the appraisal process regarding the generalisability of GO29365, and the clinical experts did not highlight any additional factors during the Technical Engagement teleconference.
More patients in the polatuzumab vedotin +BR arm had a lower International Prognostic Index (IPI) score and more patients in the BR group had bulky disease. The company did not make an adjustment to PFS for the differences between the treatment groups in bulky disease. To what extent would these factors be expected to bias the results?	During the Technical Engagement teleconference, the clinical experts noted that bulky disease is one of many relevant factors in DLBCL, and while there is a small difference in the proportion of patients with bulky disease between treatment arms, it is difficult to determine the level of significance of this given the small patient numbers. The company acknowledges the imbalance of prognostic factors (including IPI 4–5, refractory to last prior therapy, bulky disease, etc.) that numerically favour the pola+BR arm, which consequently may impact the magnitude of the observed treatment benefit from the addition of pola to BR. To address such concerns, two types of analyses were conducted: multivariable regression models and propensity score weighted regression models (see Appendix). After adjusting for imbalances of baseline prognostic covariates, the propensity score weighted model demonstrated consistent treatment benefit for pola+BR across different endpoints including PFS and OS, with narrower 95% CI indicating more precise estimates of treatment effect than multivariate models. Comparable results were obtained from all other models. Therefore, the

	Company concludes that the observed imbalance on some baseline prognostic factors did not affect the treatment benefit of pola+BR. When accounting for the influence of baseline covariates the OS HR was adjusted to [redacted] (7). This was based on the multivariable regression model with backwards selection, resulting in the most conservative estimate for the adjusted OS HR (see Appendix). In our revised economic analysis, the BR arm was adjusted using the backward selection method for revised PFS and OS extrapolations. As described in the Appendix and Issue 4 below, this resulted in higher long-term survival estimates in the base case in the BR arm, overlapping more with values cited by clinical experts for the current standard of care.
Issue 4: Is polatuzumab vedotin a curative treatment, and if so at what stage can cure be assumed?	
Is it reasonable to assume from the evidence that a proportion of patients treated for R/R DLBCL enter long-term remission after being progression-free for 2 years and have the same risk of mortality as the general population?	At the time of the most recent data analysis (15 March 2019) after a median of 30 months follow-up, 9/40 (23%) of patients in the pola+BR arm had an ongoing response (8 complete response, 1 partial response). 2/40 (5%) in the BR arm had an ongoing response (8). Of the nine patients in the pola+BR arm, eight had a duration of response ranging from 22+ months to 34+ months; one patient was consolidated with allogenic stem cell transplant. A high CR rate has been associated with improved outcomes in DLBCL. During the Technical Engagement teleconference, the clinical experts stated that a proportion of DLBCL patients who remain in remission 2 year after a line of therapy (regardless of treatment class) “may be considered cured” although it would be difficult to assume that these patients have the same risk of mortality as the general population as some patients will still relapse. Clinical experts also confirmed that the assumption of long-term remission and survival is independent of technology used, in particular the assumptions made in the recent technology appraisals of CAR-Ts would therefore hold: in TA567 it was concluded that surviving patients would have background population mortality after between 2 and 5 years (9). In TA559 the

	background mortality in the conservative ERGs scenario was assumed from the point of the PFS and OS curved crossing in their model (at 52 months) (10). As such, our base case model is consistent with these judgements as patients that are in PFS for 2 years are still at increased risk of progression and death at 2 years in the pola+BR and BR arms (only a proportion is considered at background risk). At around 5 years, PFS and OS curves get close (see Appendix), with mortality being closer to the background mortality. The company has also adjusted the background mortality with the standardised mortality ratio (SMR) of 1.41 as preferred by the ERG. This is more conservative than assumptions made for CAR-Ts (SMR= 1.0 and 1.09), in particular as the adjustment is made over the entire model horizon (see Appendix). However, even at 5 years our model approach assumes a mortality above the adjusted background mortality and presents therefore a more conservative approach to PFS and OS extrapolation in comparison to those deemed plausible in the CAR-T appraisals.
Is the cure assumption clinically plausible? Is the model prediction that 21.2% of patients on polatuzumab vedotin+BR have long-term remission and 20.6% are long term survivors (compared with 0% for BR) clinically plausible and an accurate reflection of the clinical trial? Which progression-free survival data are most robust for use in the model, investigator-assessed or independent review committee (IRC)?	The actual observed Kaplan Meier 2-year PFS rate (IRC) for Pola+BR in GO29365 is [redacted]%. This estimate is robust and unlikely to change due the maturity of the data with 30 months median follow up. Therefore, the estimate that approximately two-thirds of the patients in PFS at 2 years are in long-term remission is plausible. In the BR arm, the long-term remission rates in the adjusted analysis now fall in the range of [redacted]% to [redacted]% (depending on the parametric model), this is overlapping with the range that is expected in current clinical practice by experts (5% to 10%). In the Appendix the estimated 5-years PFS rates were also compared to predictions from standard parametric models, with the exception of the Generalized Gamma function, these models underestimate 2-year PFS and predict that the majority of patients in PFS at 2 years would progress or die by 5 years, contrary to the potential for long-term remission discussed above. We consider investigator-assessed (INV) PFS more relevant for the model. The treating clinician's assessment would be more holistic and drive treatment decisions similar to actual clinical practice rather than an independent review of patient data alone. For example, one of the late PFS events was only the patient's death in the IRC assessment whereas the investigator had detected progression earlier. However, the INV and IRC data are in general consistent and we have provided our revised base case on the IRC assessment as preferred by the ERG.

Can rates of long-term remission from studies of newly diagnosed DLBCL be generalised to the R/R setting?	There are no assumptions made in our model approach on rates of long-term remission derived from the font line setting. Long-term remission rates were derived by fitting cure-mixture models to GO29369 data as described in our submission. However, the curative nature of front line treatment with R-chemo is supportive of a potential to reach long-term survival in the relapsed or refractory setting for some patients as discussed above. In addition, data on non-disease related mortality for long-term survivors from the front-line setting (11) could be used as proxy for the relapsed or refractory setting as preferred by the ERG.
Can the long-term survival associated with CAR-T cell therapy be compared to polatuzumab vedotin+BR?	During the Technical Engagement call, the clinical experts stated that there is no reason to believe that the long-term survival associated with CAR-T cell therapy would not also apply to pola+BR. There is no evidence to suggest the potential for long-term survival is associated with a specific treatment class rather than the natural history of the disease and the proportion of patients achieving a durable remission for more than two years.
What is the company's justification for using its own code instead of standard cure-mixture modelling codes available in statistical programmes? Please can the company provide more information to enable the ERG to assess the methods used.	The company had developed in-house code prior to the fexsurv R package being made available. We continued with using our in-house code for the following key reasons: first, we can be certain it closely replicates the original cure-mixture approach described in the literature by Lambert et al. (see or response to clarification questions) as there is limited documentation on the implementation in the flexsurvcure package. Secondly, we could include covariate dependent background mortality hazard for the cured potion as described in the literature, whereas we could not accomplish this in the same way with the flexsurvcure package. Finally, it was possible to implement more complex models – such as dependent models and models restricting OS cure-rates by PFS as discussed in our submission, in a straightforward way. Further details are in the Appendix.
Issue 5: Cost assumptions	
The ERG base-case models the 140mg vial only and assumes no vial sharing, is this the most plausible approach?	The company has submitted a patient access scheme (PAS) with a simple discount applicable when the 30mg vial is available and a higher discount while only the 140mg vial is available to compensate for higher waste in this scenario (see Appendix). This equalises the net drug acquisition costs for both scenarios, i.e., with and without availability of a 30mg vial. In the model,

	both scenarios assume no vial sharing. In the revised base case and scenarios, ICERs and costs are therefore the same for both scenarios of vial sizes.
Is it likely that patients would have polatuzumab vedotin treatment beyond 6 cycles in clinical practice?	We do not expect additional cycles being given in clinical practice as this is not within the SmPC and not in the GO29365 protocol (7, 12).
The marketing authorisation may specify 6 cycles of treatment, whereas 5% of people in the polatuzumab vedotin+BR arm of the trial had treatment for longer than 6 months. How would a 6-cycle treatment cap affect the generalisability of the trial results?	The KM time-to-off-treatment (TTOT) curve is not zero after 6 times 21 days cycles (18 weeks) because of delayed cycles given to some patients (26 patients in the pola+BR arm; Interim CSR p. 235). No patients received more than 6 cycles in the study. The actual timing of infusions is captured in the TTOT as the time between the first and last cycle given. However, the cohort model in the economic analysis does not allow for such delays and applies the per cycle drug costs exactly every 21 days to the entire proportion on treatment (as determined by KM TTOT). Delayed doses are therefore counted at the time point when they should have occurred. As such, delayed doses are included in the calculation and the maximum number of cycles needs to be limited to 6 cycles in the model to avoid double counting delayed doses. The average time on treatment (mean calculated from KM TTOT) is 12.5 weeks equating to an average of 4.2 21-day cycles. Our base case with a maximum of 6 cycles results in an average of 4.4 cycles being applied in the model and is therefore correctly estimating drug acquisition costs.
Issue 6: Modelling of non-cancer background mortality	
Which method is the most appropriate for modelling non-cancer background mortality: individual patient-level approach or the cohort-based modelling?	The company approach is a more accurate approach to modelling the background mortality risk. The approach acknowledges that there is an age distribution in the trial cohort of R/R DLBCL patients, as in clinical practice. While the average patient age is 69 there were patients treated in the trial that are younger or older than the average. To compare the overall survival outcomes in the trial cohort accurately with the survival of a general population control cohort or to adjust model results, the actual age distribution needs to be taken into account. Therefore accounting for the fact, that the patients younger than the average will have a lower mortality risk and the patients older than the average a higher mortality risk than the average 69 year old. Our approach

	to derive background mortality models the overall survival of a cohort matched in age distribution to a general population cohort of the same age distribution, rather than assuming a single age (see Appendix).
Issue 7: Health-related quality of life	
Do the utility values used in the model reflect the health-related quality of life of people with R/R DLBCL?	The company is not aware of more suitable estimates of utility values. The values selected in our base case were deemed the most appropriate and also result in the most conservative ICER estimates for the sets identified.
Are more robust estimates from larger/more relevant samples available?	See response above.
Issue 8: Model time horizon	
Is a model time horizon of 45 years appropriate for R/R DLBCL, or should it be shorter given that the patient age in the model was 69 years?	The model time horizon was selected to capture all costs and health effects according to the life-tie horizon for the cohort of patients with R/R DLBCL. This time horizon is up to 45 years due to two reasons: firstly, there is a potential for long-term remission and survival for a proportion of patients in the Pola+B and BR arms. Secondly, not all patients in our cohort are 69 years old. As explained above, our model considers an age distribution that includes younger patients (and older patients) with R/R DLBCL that, if they achieve long-term remission, could be expected to survive longer than the average 69 year old.
Issue 9: End of life criteria	
Does polatuzumab vedotin + BR fulfil the criteria to be considered a “life-extending treatment at the end of life”?	The Company acknowledges the NICE Technical Team is satisfied that the end of life criteria are met.

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

ID1576: Polatuzumab vedotin with rituximab and bendamustine for treating relapsed or refractory diffuse large B-cell lymphoma

Appendix to Technical Engagement Response

File name	Version	Contains confidential information	Date
ID1576_Polatuzumab vedotin RR DLBCL_Appendix TE ACIC 131219	FINAL	Yes [redacted] + [redacted]	13th December 2019

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Introduction: Revised company base case and model

Based on the report by the Evidence Review Group (ERG) and the technical draft report and technical engagement questions from NICE for this appraisal, a revised base case for the economic analysis has been proposed, as outlined in Table 1.

Table 1. Revised company base case

Input	Assumption	Justification
Data set	Inclusion of covariate-adjusted PFS and OS data from the GO29365 March 2019 data cut, based on further analyses conducted as part of the marketing authorisation application to the EMA (further details on these analyses are provided in the 'Sensitivity analyses based on imbalances in prognostic factors in GO29365' section).	This assumption is conservative as it accounts for the baseline characteristic imbalances between treatment arms in GO29365 that may favour pola+BR over BR.
PFS and OS extrapolation models	PFS is extrapolated using cure-mixture modelling (Generalized Gamma), and OS is extrapolated using cure-mixture modelling informed by PFS (Generalized Gamma). PFS-IRC was the selected outcome.	As per original company base case. Based on external validity of long-term remission and survival for people achieving 24-month remission. PFS-IRC was the method preferred by the ERG.
Background mortality distribution	A cohort-based approach was used to model background mortality based on the age distribution in the GO29365 trial.	As per original company base case. This approach was deemed more realistic compared to the ERG's preferred approach, which modelled background mortality based on a single age cohort.
Background mortality adjustment	An increased relative risk of mortality of 1.41 for long-term survivors applied to model excess mortality compared to the general population.	A conservative assumption by the ERG reflecting an increased risk of mortality for long-term survivors.
Survival limited by background mortality	Survival limited by general population mortality for all scenarios.	ERG amendment to the model.
Time point for assuming background cost and QALYs for long-term remission	HRQoL and costs of patients in PFS health state equivalent to age- and sex-matched general population after 3 years.	The ERG's preferred assumption given the uncertainty surrounding the costs and HRQoL of long-term survivors.
Vial size scenarios	Calculated treatment costs according to vial sizes of 140 mg with no vial sharing.	Based on the proposed PAS, vial sizes of 30 mg and 140 mg will have the same acquisition costs and ICERs.

PAS for polatuzumab vedotin	PAS prices	As above
Number of maximum cycles for Pola+BR or BR	Assumed a maximum of 6 cycles of Pola+BR and BR were received in the model.	This was considered a realistic estimate of the average number of cycles based on TTOT data in the model. This was also considered to be in line with the licence.
AE incidence	All AEs reported as Grade 3 and above in the company submission, wherever possible.	A conservative assumption and the ERG's preferred approach.
Subsequent treatment cost	The costs for post-progression SCT were included in the model	ERG preferred assumption.

AE, adverse event; BR, bendamustine with rituximab; Pola+BR, polatuzumab vedotin with bendamustine and rituximab; EMA, European Medicines Agency; ERG, Evidence Review Group; HRQoL, health-related quality of life, ICER, incremental cost-effectiveness ratio; IRC, independent review committee; NA, not applicable; PAS, patient access scheme; PFS progression free survival; OS overall survival; SCT, stem cell transplant; TTOT, time-to-off-treatment; QALY, Quality Adjusted Life Years

PFS and OS extrapolation with covariate adjusted data

PFS and OS were adjusted with the backwards selection model submitted to the EMA as described in the 'Sensitivity analyses based on imbalances in prognostic factors in GO29365' section below. Of the models used to explore imbalances in prognostic factors in GO29365, this model resulted in the most conservative estimate for the OS HR for Pola+BR versus BR ([redacted]) and is cited in the draft SmPC for polatuzumab vedotin (1). To incorporate the adjustment for prognostic factors into the economic model, the backward selection algorithm was applied to the BR arm to generate adjusted Kaplan-Meier (KM) curves and extrapolation functions for PFS and OS. Compared to the unadjusted ITT population, this increased estimates for PFS and OS in the BR arm, bringing them closer to clinical expectations for standard of care in R/R DLBCL, in particular for the proportion of long-term survivors derived from cure-mixture models (described below). Incorporating the adjusted analysis into the base case therefore resulted in a conservative estimate compared to the unadjusted ITT analysis, and reduced uncertainty created by a potential imbalances between the treatment arms in the randomised phase of the GO29365 study.

When updating the model with the adjusted PFS and OS analysis, the following extrapolations were adjusted to cover all relevant scenarios:

1. Independent cure-mixture models for PFS (IRC and INV)
2. Cure-mixture models for OS informed by PFS
3. Standard independent parametric models for PFS and OS.

Figure 1 shows the adjusted GO29365 KM data and cure-mixture models for PFS-IRC in the adjusted analysis.

Figure 1. PFS cure-mixture extrapolation functions (adjusted analysis, COO March 2019)

BR, bendamustine + rituximab; Pola+BR, polatuzumab + bendamustine + rituximab

Table 2 presents the cure fractions (i.e. the proportion of patients achieving long-term remission) predicted by each of the cure-mixture extrapolations for each arm in the adjusted analysis. The proportion of patients achieving long-term remission falls into a range of [redacted] (PFS IRC) in the Pola+BR arm, and [redacted] in the BR arm. Due to the adjustment, estimated long-term remission and survival rates for BR now overlap with the 5–10% range cited by clinical experts for the current standard of care, as discussed in the company submission.

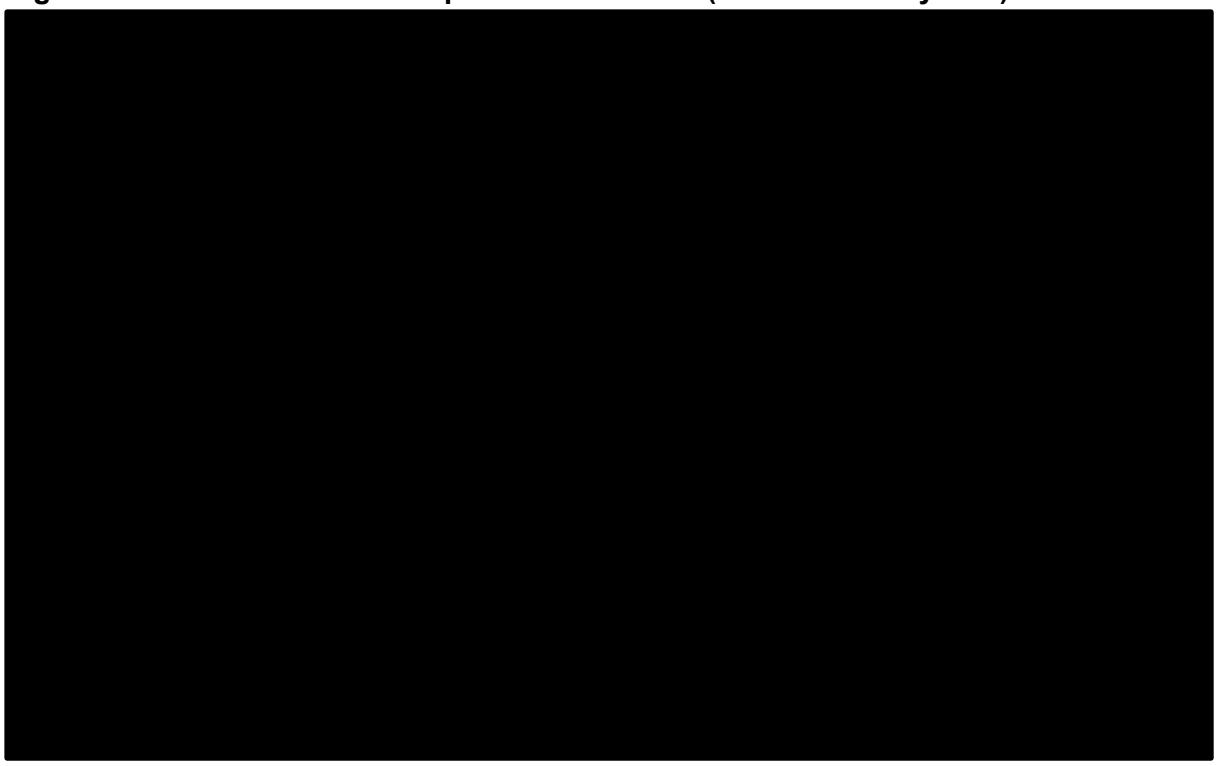
Table 2. Predicted long-term remission (cure fraction) from PFS cure-mixture model extrapolations (adjusted analysis, COO March 2019)

Parametric distribution	Cure fraction Pola+BR	Cure fraction BR
Exponential	[redacted]	[redacted]
Weibull	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]
Generalised gamma	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]

BR, bendamustine + rituximab; Pola+BR, polatuzumab + bendamustine + rituximab

The cure-mixture models for OS informed by PFS in the adjusted analysis are presented in Figure 2, and the respective cure fractions are presented in Table 3.

Figure 2. OS cure-mixture extrapolation functions (OS informed by PFS)



BR, bendamustine + rituximab; OS, overall survival; PFS, progression-free survival; Pola+BR, polatuzumab + bendamustine + rituximab

Table 3. Predicted long-term survival (cure fractions) from OS informed by PFS-IRC cure-mixture model extrapolations (adjusted analysis, COO March 2019)

Parametric distribution	Cure fraction Pola+BR	Cure fraction BR
Exponential	[redacted]	[redacted]
Weibull	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]
Generalised gamma	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]

BR, bendamustine + rituximab; NA: not available; Pola+BR, polatuzumab + bendamustine + rituximab

Comparison of company's in-house cure-mixture code to the R flexsurvcure package

In-house code to fit cure-mixture models had been developed prior to the flexsurvcure R package becoming available. We have continued to use our in-house code in the base case model for the following key reasons:

1. Firstly, the company's in-house code was developed to closely replicate the original cure-mixture approach described in the literature by Lambert et al. (2). However, there is limited documentation on the implementation on the flexsurvcure package, and it is therefore unclear whether the package aligns with the Lambert et al. approach. For example, it was not possible to run flexsurvcure models using a baseline characteristic-dependent background mortality hazard for the cure fraction. In the company's model, background hazard for the cure fraction was set by age, gender, country, and year of trial (note that the mortality of the cured fraction is required for an accurate classification of cured patients in the model fitting).

2. Secondly, implementation of more complex models such as dependent models and models restricting OS cure-rates by PFS, as discussed in the company submission, was facilitated by using our in-house code.

Nevertheless, to further explore potential differences between the in-house code and the flexsurvcure package, independent cure-mixture models were run using both codes on PFS-IRC data from the pola+BR arm. Note that in this analysis, it was assumed that cured patients were immortal (parameter for background mortality hazard=0), i.e. we did not use background mortality for reasons mentioned above. The main consequence of this is that less patients would be classified as cured, resulting in a reduction in cure-rate estimates. As shown in Table 4 below, both sets of code resulted in similar cure fraction estimates. However, the Generalized Gamma model did not converge to plausible cure-rate estimates in the in-house code. This may be due to differences in the parameterisation of the functions between the in-house code and the flexsurvecurve code, and the fact that the standard Generalized Gamma model has a long survival tail (leading to low long-term hazards for the entire cohort). This could render the classification of cured proportions, especially under the scenario with a background mortality hazard of 0, more difficult.

Table 4. Comparison of cure fraction estimates for cure-mixture models for PFS-IRC pola+BR between the company's in-house code and Flexsurvcure code (no background hazard for cure proportion)

Parametric distribution	In-house code	Flexsurvcure
Exponential	[redacted]	[redacted]
Weibull	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]
Generalized Gamma	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]

NA: not available

External validity of cure-mixture models

Based on clinical expert opinion and observations from studies with long-term follow-up, a proportion of patients that achieve 2-year remission (i.e. patients in PFS) are expected to remain in long-term remission, and are considered to be long-term survivors (3). For example, PFS and OS KM data from a study by Mounier et al. indicates that the majority of patients in PFS at 24 months remain in PFS at 5 years (3).

To determine the clinical validity of different model extrapolations, PFS values at 2 and 5 years are presented in Table 5. The 2-year PFS rates can also be compared with the actual observed KM PFS-IRC rate for Pola-BR of [redacted]%. This estimate is robust and unlikely to change due the maturity of the data (median follow-up of 30 months).

As shown in Table 5, cure-mixture models reproduce the 2-year PFS rate well and predict a proportion of these patients to remain in long-term remission, as indicated by the 5-year PFS rates and the estimated proportions (cure-fractions) in Table 2. It should be noted that these models still predict that a proportion of patients in PFS at 2 years will regress or die. However, approximately 2/3 of those reaching 2 years PFS can be considered in long-term remission. On the other hand, standard models tend to under-estimate the observed 2-year PFS rate and predict that the majority of patients in PFS at 2 years will progress or die by 5 years (with the exception of the Generalized Gamma model). Standard models therefore do not represent a clinically plausible long-term extrapolation.

Table 5. Model predictions for PFS-IRC Pola+BR (COO March 2019)

Parametric distribution	Cure fraction model 24-month PFS	Standard independent model 24-month PFS	Cure fraction model 60-month PFS	Standard independent model 60-month PFS
Exponential	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]	[redacted]	[redacted]
Generalised gamma	[redacted]	[redacted]	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]

The standard Gompertz extrapolation did not converge. PFS values for this extrapolation are therefore not presented. PFS, progression-free survival

It should be noted that previous NICE appraisals of CAR-T therapies in DLBCL also made such an assumption regarding long-term survival, and clinical experts confirmed that the potential for long-term survival in DLBCL is expected to be independent of the technology. In

TA567, the Committee concluded that surviving patients would have background population mortality after between 2 and 5 years. In TA559, the Committee concluded that the ERG's base case was conservative, as it assumed background mortality only from the point of the PFS and OS curves crossing (at 52 months).

This is consistent with our base case where patients are still at increased risk of progression and death at 2 years in the pola+BR arm as only a proportion of patients in PFS at 2-years are considered in long-term remission. At approximately the 5-year timepoint, the PFS and OS curves start to become aligned [Figure 5]), with mortality tending towards general population mortality (Figure 3). However, even at 5 years, our model approach assumes a higher mortality rate compared to adjusted background mortality, as indicated by the ratio of hazards of PFS or OS in relation to background hazard (Figure 3). Therefore, the company's base case presents a conservative approach to long-term PFS and OS extrapolation in comparison to those deemed plausible in the CAR-T appraisals.

Figure 3: Ratio of modelled hazards (PFS or OS) Pola+BR versus background morality

BR, bendamustine + rituximab; PFS, progression free survival; Pola+BR, polatuzumab + bendamustine + rituximab OS, overall survival

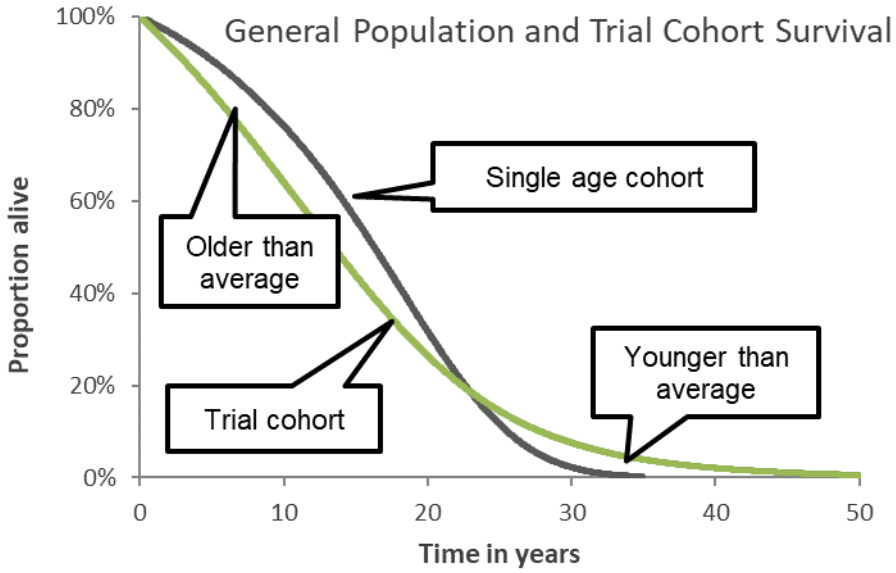
Background mortality

The limit to overall survival by background mortality for all scenarios introduced by the ERG was used in the revised base case.

Based on clinical expert opinion, there may be an increased risk of non-cancer related mortality for long-term survivors. Therefore, a standardised mortality ratio (SMR) of 1.41 preferred by the ERG was used in the revised base case as a conservative assumption. This assumption was considered conservative as it has been applied over the entire model time horizon of 45 years, whereas mortality was not elevated for survivors of more than 5 years from treatment initiation (SMR= 0.99) (4). In the recent appraisals of CAR-Ts, only scenarios with a SMR of 1.09 were investigated.

In the revised base case, background mortality was based on the age distribution in the trial (as per the original company base case) rather than assuming a single-age cohort as preferred by the ERG. This approach is a more realistic way of modelling non-disease related background mortality by averaging mortality over the age distribution, rather than assuming all patients have the same background mortality. This approach is also more reflective of clinical practice where a distribution of ages similar to the trial is expected. The consequence of our approach is that short-term background survival is lower than in a single age cohort (due to people in the trial cohort being older than the average in the single cohort age), whereas long-term survival is higher in the trial cohort due to people being younger than the average of the single cohort, as illustrated in Figure 4.

Figure 4. Non-disease related mortality model



Revised cost assumptions

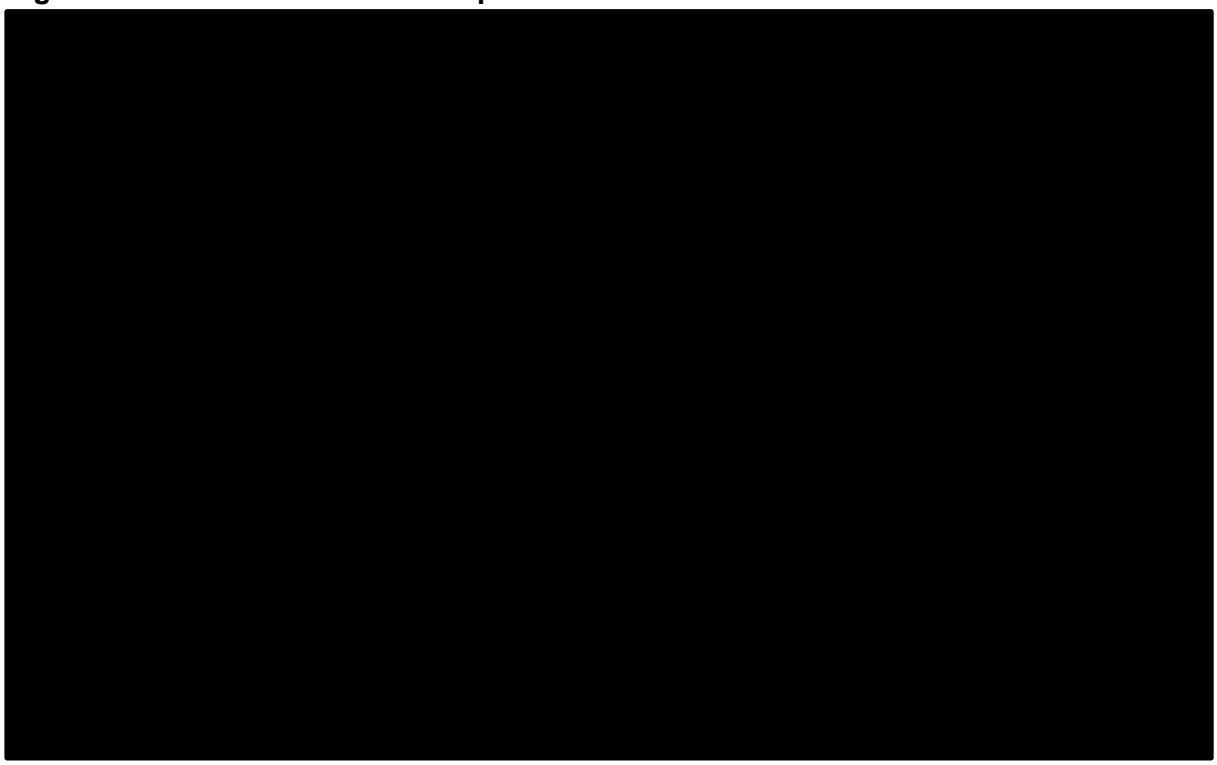
Roche has submitted a PAS with a simple discount of [redacted]%, applicable when the 30 mg vial becomes available ([redacted]) resulting in a net price of £[redacted] for the 30 mg vial and £[redacted] for the 140 mg vial, respectively. While the 30 mg vial is in development, the 140 mg vial net price is £[redacted] ([redacted]% discount) to compensate for higher waste and equalise the net drug acquisition costs for both scenarios (i.e. with and without the availability of a 30 mg vial). In the model, both scenarios assume no vial sharing. In the revised base case and scenarios, ICERs and costs are therefore the same for both vials.

The maximum number of treatment cycles remains limited to 6 cycles as per the protocol and the SmPC. The KM TTOT curve may not be zero after 6 21-day cycles (18 weeks) due to delayed cycles given to some patients (TTOT is the time between the first and last cycle given; 26 patients had delayed cycles in the Pola+BR arm, interim CSR p. 235). However, the cohort model does not allow for such delays and applies the per cycle drug costs to the proportion on treatment every 21 days (as determined by KM TTOT). The average time-on treatment (mean calculated from KM TTOT) is 12.5 weeks equating to an average of 4.2 21-day cycles. The revised base case, with a maximum of 6 cycles, resulted in an average of 4.4 cycles. This is higher than the number of cycles based on the TTOT mean because everyone in the model cohort that is deemed on treatment is assumed to receive the cycle without delay. Allowing for more than 6 cycles in the model, as in the ERGs scenario, results in an average of 4.7 cycles being applied in the model. This overestimates the drug acquisition cost because it does not factor in the possibility of cycles being delayed, resulting in longer treatment duration without increasing the maximum number of cycles given. In the model, the ERG's adjustment in effect leads to double counting of delayed doses.

Base case results

The base case extrapolations for PFS and OS in the adjusted analysis are presented in Figure 5 below.

Figure 5. Revised base case extrapolations for PFS and OS



BR, bendamustine + rituximab; OS, overall survival; PFS, progression-free survival; Pola+BR, polatuzumab + bendamustine + rituximab

Base case incremental cost-effectiveness analysis results

The base case pairwise comparison results for Pola+BR vs. BR are presented in Table 6. The base case cost-effectiveness results demonstrate that Pola+BR is cost-effective vs. BR, at an incremental cost-effectiveness ratio (ICER) of £30,793 per QALY. Pola+BR accrued a greater health benefit compared to BR, as demonstrated by an incremental QALY value of [redacted].

Table 6. Revised base case deterministic results (with PAS)

Intervention	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)
Pola+BR	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	30,793
BR	21,061	[redacted]	[redacted]	-	-	-	-

BR, bendamustine + rituximab; ICER, incremental cost-effectiveness ratio; LYG, life years gained; Pola+BR, polatuzumab + bendamustine + rituximab; QALYs, quality-adjusted life years

Sensitivity analyses

Probabilistic sensitivity analysis

The uncertainty arising from the imprecision associated with model input parameter estimates was investigated via probabilistic sensitivity analysis (PSA). A Monte-Carlo simulation was conducted using 1,000 iterations based upon model inputs randomly drawn from distributions around the mean (summarised in Table 7). Variation in the parameterisation of the PFS and OS extrapolations was based on normal distributions and where appropriate, covariance matrices.

Where available, the standard error (SE) calculated from the same data used to derive the mean value estimate was used to inform the distribution of the input parameter. Alternatively, the SE was calculated for AE disutility inputs as 10% of the mean estimate, or for cost inputs via the following equation:

$$SE = (LN(mean + 20\%) - LN(mean - 20\%))/4$$

Table 7. PSA parameter inputs

Parameter	Distribution	Mean	SE	Alpha	Beta
Survival modelling					
Parametric estimates for OS and PFS	Normal distribution around parameter estimates, informed where appropriate, by covariance matrices				
Utilities					
Utility in PFS, both treatment arms	Beta	0.72	0.03	62.44	160.56
Utility in PD, both treatment arms	Beta	0.65	0.06	21.76	40.42
Disutility due to adverse events					
Acute kidney injury	Normal	0.27	0.027	N/A Parameter input variation (SE) equal to 10% of mean estimate	
Atrial fibrillation	Normal	0.37	0.037		
Atrial flutter	Normal	0.37	0.037		
Anaemia	Normal	0.25	0.025		
Cytomegalovirus infection	Normal	0.15	0.015		
Decreased appetite	Normal	0.37	0.037		
Diarrhoea	Normal	0.10	0.010		
Febrile neutropenia	Normal	0.15	0.015		
Herpes virus infection	Normal	0.15	0.015		
Leukoencephalopathy	Normal	0.37	0.037		
Leukopenia	Normal	0.09	0.009		
Lower respiratory tract infection	Normal	0.20	0.020		
Meningoencephalitis herpetic	Normal	0.15	0.015		
Myelodysplastic syndrome	Normal	0.37	0.037		
Neutropenia	Normal	0.09	0.009		
Neutropenic sepsis	Normal	0.15	0.015		
Oedema peripheral	Normal	0.37	0.037		
Pneumonia	Normal	0.20	0.020		
Pulmonary oedema	Normal	0.37	0.037		
Pyrexia	Normal	0.11	0.011		
Septic shock	Normal	0.37	0.037		
Supraventricular tachycardia	Normal	0.37	0.037		
Thrombocytopenia	Normal	0.11	0.011		
Vomiting	Normal	0.05	0.005		
Administration costs, Pola+BR (£)					
Administration cost, first treatment cycle	Log-normal	686.86	0.1014		

Pharmacy cost, first treatment cycle	Log-normal	62.40	0.1014	N/A Parameter input variation (SE) calculated from upper and lower estimates of base case value ±20%
Administration cost, subsequent treatment cycles	Log-normal	686.86	0.1014	
Pharmacy cost, subsequent treatment cycles	Log-normal	62.40	0.1014	
Administration costs, BR (£)				
Administration cost, first treatment cycle	Log-normal	686.86	0.1014	N/A Parameter input variation (SE) calculated from upper and lower estimates of base case value ±20%
Pharmacy cost, first treatment cycle	Log-normal	31.20	0.1014	
Administration cost, subsequent treatment cycles	Log-normal	686.86	0.1014	
Pharmacy cost, subsequent treatment cycles	Log-normal	31.20	0.1014	
Supportive care costs (£)				
Residential care (day)	Log-normal	114.50	0.1014	N/A Parameter input variation (SE) calculated from upper and lower estimates of base case value ±20%
Day care (day)	Log-normal	58.00	0.1014	
Home care (day)	Log-normal	33.32	0.1014	
Hospice (day)	Log-normal	157.08	0.1014	
Oncologist (visit)	Log-normal	165.85	0.1014	
Haematologist (visit)	Log-normal	164.80	0.1014	
Radiologist (visit)	Log-normal	187.30	0.1014	
Nurse (visit)	Log-normal	38.45	0.1014	
Specialist nurse (visit)	Log-normal	38.45	0.1014	
GP (visit)	Log-normal	37.40	0.1014	
District nurse (visit)	Log-normal	38.45	0.1014	
CT scan	Log-normal	163.66	0.1014	
Full blood counts	Log-normal	2.51	0.1014	
LDH	Log-normal	2.51	0.1014	
Liver function	Log-normal	2.51	0.1014	
Renal function	Log-normal	2.51	0.1014	
Immunoglobulin	Log-normal	2.51	0.1014	
Calcium phosphate	Log-normal	2.51	0.1014	
Inpatient day	Log-normal	383.47	0.1014	
Palliative care team	Log-normal	117.84	0.1014	
Subsequent care costs, PD				
Chemotherapy	Log-normal	1,312.30	0.1014	N/A Parameter input variation (SE) calculated
R + chemotherapy	Log-normal	3,056.88	0.1014	

Rituximab	Log-normal	2,961.73	0.1014	from upper and lower estimates of base case value ±20%
Radiotherapy	Log-normal	162.88	0.1014	
ECG	Log-normal	107.84	0.1014	
MUGA	Log-normal	285.04	0.1014	
MRI	Log-normal	140.60	0.1014	
PET-CT	Log-normal	470.71	0.1014	
Bone marrow biopsy	Log-normal	519.82	0.1014	
Adverse event management costs (£)				
Acute kidney injury	Log-normal	332.50	0.101	N/A Parameter input variation (SE) calculated from upper and lower estimates of base case value ±20%
Atrial fibrillation	Log-normal	670.13	0.101	
Atrial flutter	Log-normal	670.13	0.101	
Anaemia	Log-normal	309.09	0.101	
Diarrhoea	Log-normal	392.26	0.101	
Febrile neutropenia	Log-normal	1,847.50	0.101	
Leukopenia	Log-normal	291.00	0.101	
Neutropenia	Log-normal	291.00	0.101	
Pneumonia	Log-normal	495.81	0.101	
Lower respiratory tract infection	Log-normal	377.90	0.101	
Pyrexia	Log-normal	309.56	0.101	
Septic shock	Log-normal	1,037.71	0.101	
Thrombocytopenia	Log-normal	281.96	0.101	
Vomiting	Log-normal	382.30	0.101	
Cytomegalovirus infection	Log-normal	393.65	0.101	
Decreased appetite	Log-normal	382.30	0.101	
Supraventricular tachycardia	Log-normal	670.13	0.101	
Herpes virus infection	Log-normal	377.90	0.101	
Meningoencephalitis herpetic	Log-normal	3,652.18	0.101	
Myelodysplastic syndrome	Log-normal	556.99	0.101	
Neutropenic sepsis	Log-normal	1,847.50	0.101	
Oedema peripheral	Log-normal	343.16	0.101	
Leukoencephalopathy	Log-normal	3,609.61	0.101	
Pulmonary oedema	Log-normal	2,189.85	0.101	

BR, bendamustine + rituximab; CT, computed tomography; ECG, electrocardiogram; GP, General Practitioner; LDH, lactate dehydrogenase test; MRI, magnetic resonance imaging; MUGA, multiple gated acquisition scan; N/A, not applicable; OS, overall survival; PD, progressed disease; PET-CT, positron emission tomography-computed tomography; PFS, progression-free survival; Pola+BR, polatuzumab + bendamustine + rituximab; R, rituximab; PSA, probabilistic sensitivity analysis; SE, standard error

The results of the PSA are presented in Table 8. The mean incremental costs and QALYs from the PSA were £[redacted] and [redacted] respectively, resulting in a mean ICER value of £41,246 per QALY.

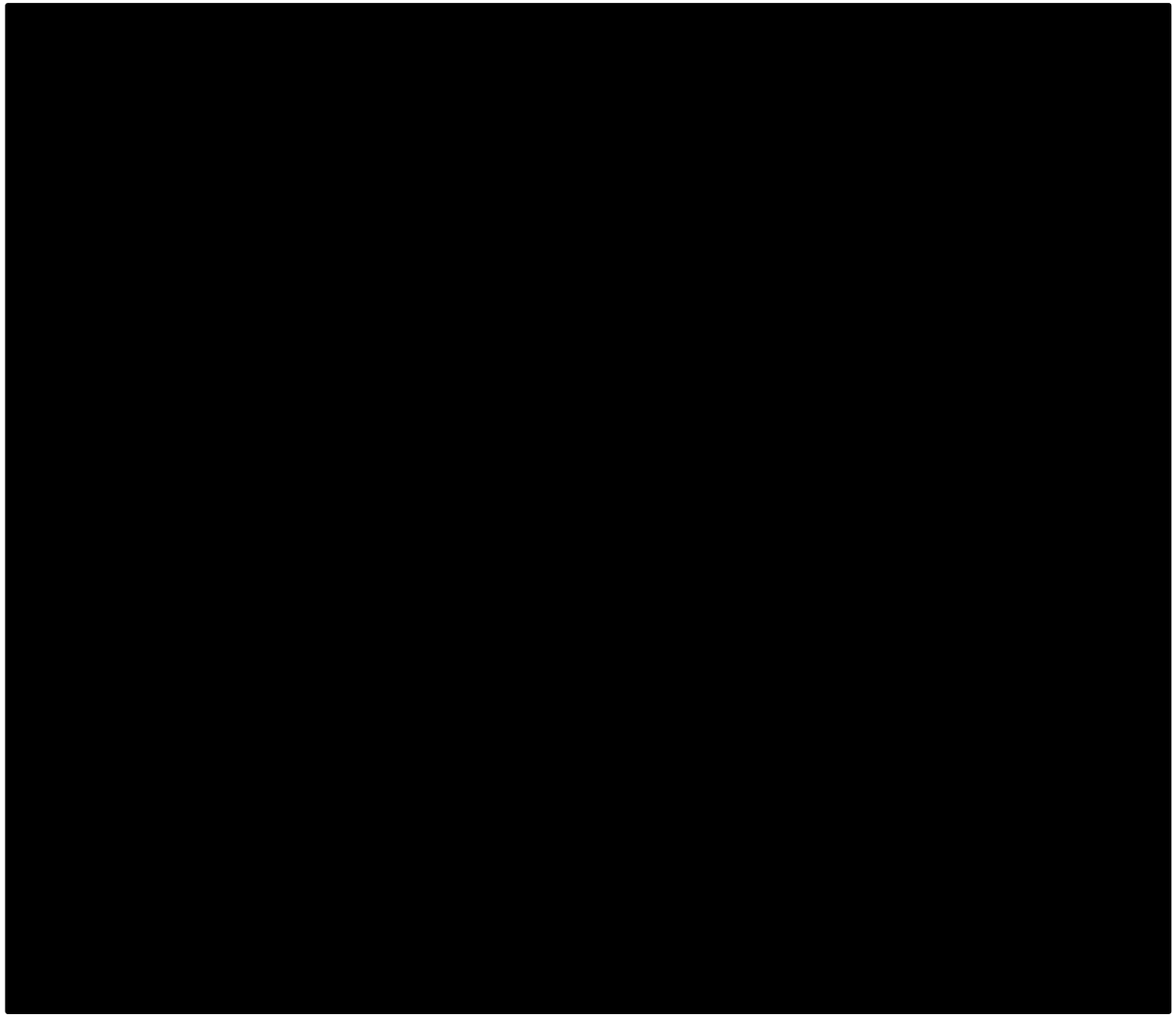
Table 8. Mean probabilistic results (with PAS)

Intervention	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)
Pola+BR	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	41,246
BR	38,301	[redacted]	[redacted]	-	-	-	-

Costs and QALYs are discounted at 3.5%. BR, bendamustine + rituximab; ICER, incremental cost-effectiveness ratio; LYG, life years gained; Pola+BR, polatuzumab + bendamustine + rituximab; QALYs, quality-adjusted life years

The cost-effectiveness plane is presented in Figure 6, including the percentile ranges (2.5% and 97.5%) for both incremental costs and QALYs and the 95% credibility ellipse. The cost-effectiveness acceptability curve (CEAC) for Pola+BR versus BR is presented in Figure 7. From the CEAC, at a willingness to pay (WTP) threshold of £50,000, the probability of Pola+BR being cost-effective relative to BR was [redacted].

Figure 6. Cost-effectiveness plane for Pola+BR versus BR



BR, bendamustine + rituximab; Pola+BR, polatuzumab + bendamustine + rituximab; QALY, quality-adjusted life year

Figure 7. Cost-effectiveness acceptability curve for Pola+BR versus BR

BR, bendamustine + rituximab; Pola+BR, polatuzumab + bendamustine + rituximab; WTP, willingness to pay

Deterministic sensitivity analysis

Deterministic sensitivity analysis (DSA) was conducted by varying all parameters for which there were single input values. Each input parameter was set to its respective upper or lower bound and the deterministic results for the model recorded. For simplicity, the totals for each cost category were varied for the DSA whilst the impact of AE disutilities was investigated using the average disutility of all AEs, weighted by frequency and duration. The upper and lower bounds around the mean value for each input parameter were based upon the 10% and 90% percentile values obtained from the PSA input distribution. Where percentile estimates were not available, the input parameter was varied by ±20% (alternatively ±5 kg for mean weight, ±5% for mean BSA).

The DSA inputs and corresponding ICER values are summarised in Table 9.

Table 9. DSA results

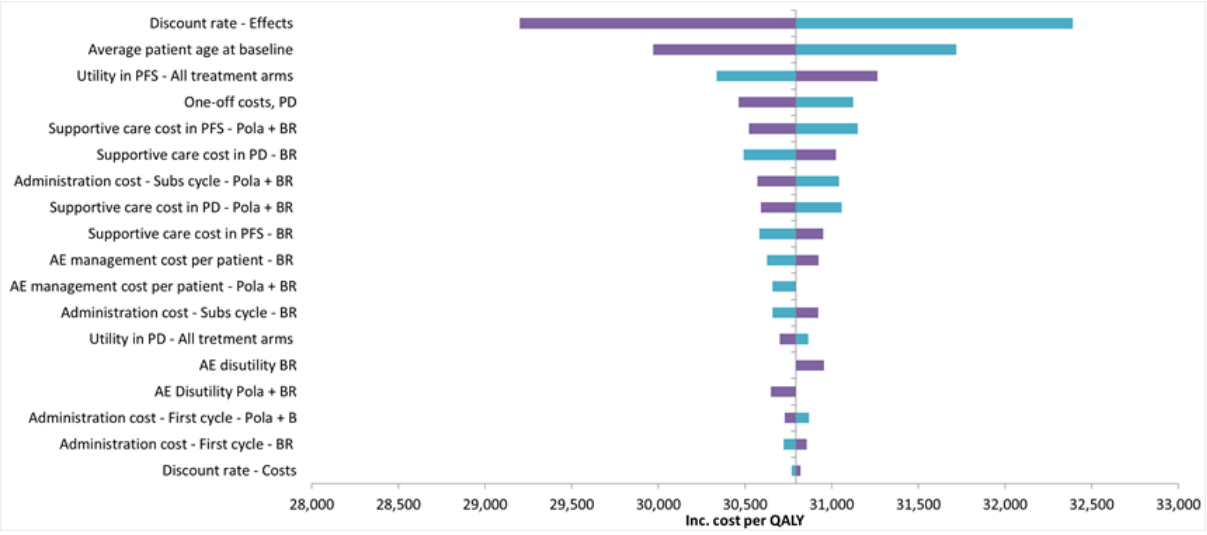
Parameter modified	Base value	Upper value	Lower value	Upper value ICER (£/QALY)	Lower value ICER (£/QALY)	Range (£/QALY)	% of base case
Base case				30,793		-	
Model settings							
Discount rate, costs	3.5%	4.2%	2.8%	30,770	30,820	50	0.16%
Discount rate, effects	3.5%	4.2%	2.8%	32,392	29,199	3,193	10.37%
Patient baseline characteristics							
Average patient age at baseline (+/- 5 years)	69.0	74.0	64.06	31,720	29,969	1,751	5.69%
Utilities							
Utility in PFS, all treatment arms	0.72	0.76	0.68	30,336	31,265	929	3.02%
Utility in PD, all treatment arms	0.65	0.71	0.57	30,864	30,700	164	0.53%
AE disutility, Pola+BR[b]	0.012	0.025	0.006	30,793	30,648	145	0.47%
AE disutility, BR[b]	0.014	0.027	0.007	30,793	30,955	162	0.53%
AE management costs							
AE management cost per patient, Pola+BR	855.02	1,064.48	675.87	30,657	30,657	0	0.00%
AE management cost per patient, BR	718.05	936.63	546.21	30,627	30,924	297	0.96%
Administration costs, Pola+BR							
Administration cost (first cycle)	749.26	847.66	666.00	30,868	30,730	138	0.45%
Administration cost (subsequent cycle)	749.26	844.68	664.09	31,043	30,571	472	1.53%
Administration costs, BR							

Administration cost (first cycle)	718.06	812.38	634.81	30,722	30,857	135	0.44%
Administration cost (subsequent cycle)	652.76	732.14	577.12	30,658	30,922	264	0.86%
Supportive care costs							
Supportive care cost in PFS - Pola+BR	160.21	167.70	154.57	31,151	30,524	627	2.04%
Supportive care cost in PFS - Pola+BR on treatment	460.22	484.05	442.23	30,793	30,793	0	0.00%
Supportive care cost in PFS - BR	160.21	167.70	154.57	30,583	30,952	369	1.20%
Supportive care cost in PFS - BR on treatment	460.22	484.05	442.23	30,793	30,793	0	0.00%
Supportive care cost in PD, Pola+BR	363.64	382.31	349.40	31,058	30,592	466	1.51%
Supportive care cost in PD, BR	363.64	382.31	349.40	30,492	31,023	531	1.72%
One-off costs, PD	2,374.08	2,848.90	1,899.26	31,124	30,463	661	2.14%

[a]Input parameter varied ±20% for the DSA; [b]Average of all AEs weighted by frequency and duration. AE, adverse event; BR, bendamustine + rituximab; BSA, body surface area; DSA, deterministic sensitivity analysis; ICER, incremental cost-effectiveness ratio; OS, overall survival; PD, progressed disease; PFS, progression-free survival; Pola+BR, polatuzumab + bendamustine + rituximab; QALY, quality-adjusted life year

A tornado diagram demonstrating the key drivers of ICER value in the comparison between Pola+BR and BR are presented in Figure 8.

Figure 8. Deterministic sensitivity analysis – tornado diagram of influential parameters for Pola+BR versus BR



BR, bendamustine + rituximab; PD, progressed disease; PFS, progression-free survival; Pola+BR, polatuzumab + bendamustine + rituximab; QALY, quality-adjusted life year

Scenario analysis

Scenarios using alternative assumptions were explored based on the feedback received from the ERG. All scenarios are presented using the adjusted ITT and unadjusted ITT data (original ITT). Both sets of analyses used the March 2019 data cut.

The model base case settings are presented in Table 10.

Table 10. Model base case settings

Variable	Cells/Base case setting (Model Inputs Sheet)
Population	I24=ITT-CHMP
Background mortality	I42=Age distribution as in trial I86=1.41
Treatment duration	I121=6
PFS extrapolation	I165=cure-mixture I168=generalised gamma I169=generalised gamma
OS extrapolation	I206=cure-mixture I209= generalised gamma I210= generalised gamma

Six key scenarios were explored in this cost-effectiveness appendix, as described below:

1. **Use of ERG-preferred extrapolation methods for PFS and OS (standard, independent parametric functions: log-normal for PFS-IRC and generalised gamma for OS)**

The rationale for inclusion of this scenario was to explore the impact of the ERG's preferred extrapolation assumptions on the base cost-effectiveness results. The adjustments made to the current model to produce this scenario are as follows:

Cells: Base case values (Table 10), plus

I165=Not proportional

I168=Log-normal

I169=Log-normal

I206=Not proportional

2. **Use of ERG-preferred assumptions on extrapolation for PFS and OS (as per scenario 1), excess mortality and maximum number of treatment cycles for Pola+BR and BR**

The rationale for the inclusion of this scenario was to explore the impact of the ERG's preferred assumptions for PFS and OS extrapolation, excess mortality for long-term survivors and maximum number of treatment cycles for Pola+BR and BR on the base cost-effectiveness results. The adjustments made to the current model to produce this scenario are as follows:

Cells: as per Scenario 1, plus

I42=Single Age Cohort

I131=>6

3. **Use of the company base case extrapolation assumptions for PFS and OS, with the ERG's preferred assumptions for excess mortality and maximum number of Pola+BR and BR treatment cycles**

The rationale for the inclusion of this scenario was to explore the impact of the ERG's preferred assumptions for excess mortality for long-term survivors and maximum number of treatment cycles for Pola+BR and BR on the base cost-effectiveness results. The adjustments made to the current model to produce this scenario are as follows:

Cells: Base case values (Table 10), plus

I42=Single Age Cohort

I131=>6

4. **Use of alternative cure-mixture models (exponential functions) for PFS and OS**

The rationale for the inclusion of this scenario was to explore the impact of using exponential cure-mixture extrapolations for PFS and OS on the base case cost-effectiveness results. Use of the exponential function models a greater proportion of long-term survivors and results in a shorter time for the cohort mortality to reach background mortality compared to the base case. The adjustments made to the current model to produce this scenario are as follows:

Cells: Base case values (Table 10), plus

I168=Exponential

I169= Exponential

I209= Exponential

I210= Exponential

5. **Use of the company base case settings with background mortality close to the general population**

The rationale for the inclusion of this scenario was to explore an alternative assumption for excess mortality for long-term survivors, in which it more closely aligned with that of the general population. The adjustments made to the current model to produce this scenario are as follows:

Cells: Base case values (Table 10), plus

I86=1.0

6. **Use of standard independent generalised gamma models for PFS and OS**

The rationale for the inclusion of this scenario was to explore the impact of a more conservative assumption for the extrapolation of PFS and OS: use of standard, independent, generalised gamma models for both outcomes, as opposed to cure-mixture models. The adjustments made to the current model to produce this scenario are as follows:

Cells: Base case values (Table 10), plus

I165=Not proportional (cure-mixture)

I206=Not proportional (cure-mixture)

The results of the six scenario analyses for the original ITT and CHMP ITT population are presented in Table 11.

Table 11: Scenario analysis results

Parameter modified	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)	% change from base case ICER
Base case	[redacted]	[redacted]	30,793	0
Scenario 1 – ERG preferred standard parametric extrapolations (OS and PFS)				
Unadjusted ITT population	[redacted]	[redacted]	[redacted]	[redacted]
Adjusted ITT population	[redacted]	[redacted]	46,035	49%
Scenario 2 – ERG preferred assumptions for extrapolations, background mortality and number of Pola+BR treatment cycles				
Unadjusted ITT population	[redacted]	[redacted]	[redacted]	[redacted]
Adjusted ITT population	[redacted]	[redacted]	49,590	61%
Scenario 3 – Company base case with ERG preferred assumptions for background mortality and number of Pola+BR treatment cycles				
Unadjusted ITT population	[redacted]	[redacted]	[redacted]	[redacted]
Adjusted ITT population	[redacted]	[redacted]	33,677	9%
Scenario 4 – Company base case with exponential cure-mixture models for PFS and OS				
Unadjusted ITT population	[redacted]	[redacted]	[redacted]	[redacted]
Adjusted ITT population	[redacted]	[redacted]	32,485	5%
Scenario 5 – Company base case with general population background mortality				
Unadjusted ITT population	[redacted]	[redacted]	[redacted]	[redacted]
Adjusted ITT population	[redacted]	[redacted]	26,752	-13%
Scenario 6 – Company base case with standard independent generalised gamma models for PFS and OS				
Unadjusted ITT population	[redacted]	[redacted]	[redacted]	[redacted]
Adjusted ITT population	[redacted]	[redacted]	30,820	0.09%

CHMP, Committee for Medicinal Products for Human Use; ERG, Evidence Review Group; ICER, incremental cost-effectiveness ratio; ITT, intent-to-treat; Pola+BR, polatuzumab + bendamustine + rituximab; PFS, progression-free survival; OS, overall survival; QALY, quality-adjusted life year

Sensitivity analyses based on imbalances in prognostic factors in GO29365

The company acknowledges the imbalance of prognostic factors in GO29365 noted by the ERG, including IPI 4–5, refractoriness to last prior therapy and bulky disease, that numerically favour the Pola+BR arm, and may consequently impact the magnitude of the observed treatment benefit from the addition of pola to BR. Although the randomised DLBCL cohorts implemented 1:1 stratified permuted block randomisation (block size = 4; stratification factor: duration of response (DOR) to prior therapy: ⩽12 months vs. >12 months), due to the limited sample size in each arm (n=40 each arm), imbalances between arms could still occur by random chance in some baseline characteristics.

Demographics and baseline characteristics, including these prognostic factors, were previously supplied in the original company submission (see Document B, Section B.2.3.3, Table 7, page 32). The following is a list of prognostic factors favouring the Pola+BR arm (with 10% or higher difference between arms):

- No bulky disease (75.0% for Pola+BR vs. 62.5% for BR)
- IPI 0–3 (77.5% vs. 57.5%)
- Non-refractory to last prior anti-lymphoma therapy (25.0% vs. 15.0%)
- Primary non-refractory (47.5% vs. 32.5%)
- No prior bone marrow transplant (75.0% vs. 85.0%)

To address these concerns, three types of analyses were explored for the EMA marketing authorisation application, multivariable regression models, backward selection model and propensity score weighted regression models, for the following four key efficacy endpoints:

- IRC-assessed complete response (CR) at the end of treatment (EoT)
- IRC-assessed best overall response (BOR)
- IRC-assessed progression-free survival (PFS)
- Overall survival (OS)

The analysis population used in the modelling was as follows:

- Randomised cohorts Pola+BR (n=40) vs. BR (n=40)

Results were obtained from the snapshot of clinical data with a cut-off date of 15th March 2019.

A comprehensive list of 12 baseline covariates that could potentially affect prognosis were included in both the multivariable regression model, backward regression model and propensity score model, as follows:

- Sex (M vs. F)
- Age (<65 vs. ⩾65 years)
- Baseline Eastern Cooperative Oncology Group (ECOG) performance status (0/1 vs. 2)
- DOR to prior therapy (≤12 vs. >12 months)
- IPI (0–3 vs. 4–5)
- Extranodal involvement at study entry (Y vs. N)
- Bulky disease (Y vs. N)
- Ann Arbor stage (I/II vs. III/IV)
- Prior lines of lymphoma therapy (1 vs. 2+)
- Refractory to last prior anti-lymphoma therapy (Y vs. N)
- Primary refractory status (Y vs. N)
- Primary bone marrow transplant (Y vs. N)

Race was not included in the modelling because the majority of patients enrolled were white.

The multivariate model suffered from limited degrees of freedom in the parameter estimates when adjusting a large number of covariates simultaneously with relatively small treatment arm sizes. Propensity score modelling is superior to multivariate models since it preserves the power of detecting treatment effect whilst still balancing the baseline characteristics. In summary, the following sets of analyses were performed:

- Full multivariate model with all 12 baseline covariates adjusted simultaneously
- Backward selection models based on a p-value threshold of 0.1 from the full multivariate model
- Propensity score models by inverse probability of treatment weighting approach, with propensity score by a logistic regression of treatment assignment on the 12 baseline covariates simultaneously

For CR/BOR, the odds ratios of Pola+BR versus BR were estimated from logistic models, and the HR of PFS/OS was estimated from Cox regression models.

Multivariable model, backward selection model, and propensity score weighted model

The results produced by the three models for the four efficacy endpoints are shown in Table 12. P-values shown in the analyses are nominal without adjusting for multiplicity. Due to the

exploratory nature of the multivariable regression analyses when adjusting for prognostic factors, including IPI score, the model is not fully powered to detect the treatment effect at a 5% alpha level. Therefore, the observation of “no statistical significance” does not rule out an association between treatment and response. However, the backward variable selection method was performed with a p-value threshold of 0.1 or less to select variables in the model, and most of the imbalanced prognostic covariates were kept in the final model.

The full multivariate model and backward selection model show similar point estimates of odds ratios and HRs for the four outcomes, and a meaningful treatment effect was observed across endpoints. Nevertheless, wide confidence intervals around the odds ratios for CR and BOR indicated that the estimates produced by the full multivariate model or the backward selection model were associated with low accuracy, due to the small sample size of the treatment arms. The inaccuracy of these models was illustrated in particular for the BOR outcome, with odds ratio estimates of 4.17, [redacted] and [redacted] produced in the unadjusted logistic model, full multivariate model and backward selection model, respectively, which was contradictory to the assumption that the imbalance of baseline prognostic factors favoured the Pola+BR arm.

As described above, to minimise the power loss when adjusting for a large number of covariates for the limited sample size in the randomised cohorts, the propensity score models by inverse probability of treatment weighting were performed (5, 6). The propensity score for each patient being randomised to Pola+BR vs. BR was calculated by performing a logistic regression of treatment assignment on the 12 baseline covariates simultaneously. Then the inverse of the propensity score was incorporated into the weighted regression model in order to balance the baseline covariates between arms.

Although a marginal decrease in treatment effect was consistently observed across endpoints in the propensity score weighted models, a meaningful treatment benefit from the addition of polatuzumab vedotin to BR was nonetheless demonstrated consistently across all four endpoints. The propensity score weighted model thereby also supports the conjecture that the imbalance of baseline prognostic covariates favours the Pola+BR arm. Furthermore, narrower 95% CIs of estimates observed in propensity score models indicate its improved accuracy over the multivariable model and backward selection model.

Table 12: Full multivariate model, backward selection model and propensity score weighted model results in randomised Pola+BR (n=39) vs. BR (n=39)*

	Unadjusted model	Full multivariable model	Backward selection model	Propensity score weighted model
Odds ratio for CR at EoT 95% CI p-value	[redacted]	[redacted]	[redacted]	[redacted]
Odds ratio for BOR 95% CI p-value	[redacted]	[redacted]	[redacted]	[redacted]
PFS HR 95% CI p-value	[redacted]	[redacted]	[redacted]	[redacted]
OS HR 95% CI p-value	[redacted]	[redacted]	[redacted]	[redacted]

*Two patients (one from each arm) without ECOG at baseline were excluded from the analysis population; both of them are non-responders

Conclusions

After adjusting for imbalances of baseline prognostic covariates, the propensity score weighted model demonstrated a consistent treatment benefit from the addition of pola to BR, which is meaningful across all four endpoints. Comparable results were obtained from all other models. Importantly, the propensity score weighted model produced narrower 95% CIs around the outcome point estimates, indicating more precise estimates of treatment effect compared to the full multivariate model or backward selection model. Therefore, the company concludes that the observed imbalance on some baseline prognostic factors did not affect the treatment benefit of Pola+BR.

The backwards selection model presents the most conservative adjustment in terms of the OS benefit, with the adjusted HR of [redacted] being cited in the draft SmPC. This scenario was selected to adjust the observed GO29365 KM data and the extrapolations for PFS and OS by adjusting the BR arm to the Pola+BR patient characteristics in the revised economic analysis.

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Technical engagement response form

Polatuzumab vedotin with rituximab and bendamustine for treating relapsed or refractory diffuse large B-cell lymphoma (ID1576)

As a stakeholder you have been invited to comment on the technical report for this appraisal. The technical report and stakeholders' responses are used by the appraisal committee to help it make decisions at the appraisal committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

We need your comments and feedback on the questions below. You do not have to answer every question. The text boxes will expand as you type. Please read the notes about completing this form. We cannot accept forms that are not filled in correctly. Your comments will be summarised and used by the technical team to amend or update the scientific judgement and rationale in the technical report.

Deadline for comments by 5pm **Friday 13 December 2019.**

Thank you for your time.

Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Notes on completing this form

- Please see the technical report which summarises the background and submitted evidence. This will provide context and describe the questions below in greater detail.
- Please do not embed documents (such as PDFs or tables) because this may lead to the information being mislaid or make the response unreadable. Please type information directly into the form.
- Do not include medical information about yourself or another person that could identify you or the other person.
- Do not use abbreviations.
- Do not include attachments such as journal articles, letters or leaflets. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.
- If you provide journal articles to support your comments, you must have copyright clearance for these articles.
- Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.

- Please underline all confidential information, and separately highlight information that is submitted under [redacted], all information submitted under '[redacted], and all information submitted under '[redacted] in pink. If confidential information is submitted, please also send a second version of your comments with that information replaced with the following text: 'academic/commercial in confidence information removed'. See the Guide to the processes of technology appraisal (sections 3.1.23 to 3.1.29) for more information.

We reserve the right to summarise and edit comments received during engagement, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received during engagement are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

About you

Your name	[redacted]
Organisation name – stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank)	**Roche Products Ltd**
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	**None**

Questions for engagement

		ERG response
Issue 1: Formulation		
Is it reasonable to assume that the liquid and lyophilised formulations have similar effectiveness?	The company agrees with the NICE Technical Team that this is a regulatory issue and there is no reason for there to be any difference in the safety and efficacy profiles of the liquid and lyophilised formulations of polatuzumab vedotin.	Given the lack of submission of new evidence, the ERG have nothing further to add.
Issue 2: Comparators		
Are bendamustine + rituximab (BR) and rituximab, gemcitabine and oxaliplatin (R-GemOx) a reasonable reflection of the comparators currently used in clinical practice to treat people who would be eligible for polatuzumab vedotin + BR?	There are no universally established therapies for patients with R/R DLBCL who are ineligible for transplant or who relapse after transplant, resulting in a considerable amount of variability on the selected regimen for these patients in clinical practice. BR has been shown to be active in transplant-ineligible patients with R/R DLBCL with a manageable haematological toxicity profile (1-4). During the Technical Engagement teleconference, clinical experts corroborated advice that the Company had received during the appraisal process by confirming that BR is among the possible regimens for this patient population but there is no	Given the lack of submission of new evidence, the ERG have nothing further to add.

	evidence to demonstrate superiority of one regimen over another.	
Is it reasonable to base a decision on a comparison with BR?	As no prior randomised trials have established the superiority of one regimen over another for this population, the Company believes that BR is a suitable comparator for this appraisal. This was corroborated by clinical expert opinion during the Technical Engagement teleconference.	Given the lack of submission of new evidence, the ERG have nothing further to add.
Are there any other relevant comparators? If so, how would the efficacy and safety of these comparators be expected to differ from BR in clinical practice?	As stated above and by the clinical experts during the Technical Engagement teleconference, there are other possible comparators for patients with transplant-ineligible R/R DLBCL; however, in the absence of randomised trials demonstrating superiority of one regimen over another for this population, there is no evidence to suggest that BR is inferior to any of these. The clinical experts also mentioned during the teleconference that there is considerable overlap in the toxicity between different regimens and overall the safety profile of BR is not expected to be any worse than other treatment options for this population. Furthermore, the experience of clinicians using BR for patients with follicular lymphoma in clinical practice is that this is a well-tolerated regimen.	Given the lack of submission of new evidence, the ERG have nothing further to add.
In the absence of direct evidence, is it reasonable to assume that R-GemOx has equivalent effectiveness and safety	As above, there is no clinical evidence to demonstrate superiority of R-Gem-Ox over BR	Given the lack of submission of new evidence, the ERG have nothing further to add.

as BR (as per the company's assumption in the model)?	therefore it is reasonable to assume equivalent effectiveness and safety between the two regimens.	
Does the assumption that a maximum number of 3 treatment cycles of 3 weeks of R-GemOx reflect treatment in clinical practice?	During the teleconference call, the clinical experts stated that some patients may receive up to 8 cycles of R-GemOx but very few patients would be fit enough to receive this many cycles; the median number of cycles in clinical practice used is 3–4. The model scenario comparing polatuzumab vedotin + BR with R-GemOx was based on an average of 3 cycles (as time on treatment data was not available from the literature, the maximum as set equal to the average). This was deemed a reasonable approach based on the opinion from experts above and the average number of BR cycles based on GO29365 time on treatment data being 3.2.	Given the lack of submission of new evidence, the ERG have nothing further to add.
Issue 3: Generalisability of the clinical trial to UK population		
Is the GO29365 trial generalisable to the UK population considering the ERG's comments that 3 patients were from the UK, non-white participants were underrepresented, and most patients had an Eastern Cooperative Oncology Group (ECOG status) of 0 or 1?	The study population from GO29365 is largely reflective of the R/R DLBCL population in the UK. The baseline patient characteristics of R/R DLBCL patients enrolled in GO29365 is very similar to the population enrolled in a retrospective study evaluating the efficacy of pixantrone in R/R DLBCL patients (median age 66.5 vs 65.9, respectively, proportion refractory to last prior anti-lymphoma therapy 76% vs 85%) (5). Furthermore, advice obtained from clinical experts confirmed that the baseline characteristics of patients enrolled in GO29365 are reflective of the population seen in UK	The ERG would also identify that there is a greater discrepancy between GO29365 and this retrospective study in ECOG PS 0-1 (84.7% vs 46%); IPI score 3-5 (52.2% vs 73%) (5). The ERG can confirm the finding regarding the clinical experts, as reported in the advisory board meeting.

	clinical practice and corroborates the comparison to the retrospective analysis; clinical experts reported that most patients in their clinic have stage 3–4 disease and 75–80% are refractory to last prior therapy) (6). Moreover, the range of lines of prior therapy ranged from 1 to 7 in the pola+BR arm, reflecting the broad population in the transplant-ineligible setting that is seen in current clinical practice. During the Technical Engagement teleconference, the clinical experts stated that there are a proportion of patients with ECOG PS 2 are seen in clinical practice and would be deemed eligible for Pola+BR. They added that there is no evidence to suggest pola or BR would behave differently in patients of different ethnicities (this is not a factor considered during multi-disciplinary team meetings), therefore the low proportion of non-white participants in GO29365 does not influence the generalisability of the study population to UK clinical practice.	
Are there any other factors that limit the generalisability of the trial to UK clinical practice?	The company is unaware of any other factors that limit the generalisability of the trial to UK clinical practice. No issues were highlighted when obtaining clinical expert advice during the appraisal process regarding the generalisability of GO29365, and the clinical experts did not highlight any additional factors during the Technical Engagement teleconference.	Given the lack of submission of new evidence, the ERG have nothing further to add.

More patients in the polatuzumab vedotin +BR arm had a lower International Prognostic Index (IPI) score and more patients in the BR group had bulky disease. The company did not make an adjustment to PFS for the differences between the treatment groups in bulky disease. To what extent would these factors be expected to bias the results?	During the Technical Engagement teleconference, the clinical experts noted that bulky disease is one of many relevant factors in DLBCL, and while there is a small difference in the proportion of patients with bulky disease between treatment arms, it is difficult to determine the level of significance of this given the small patient numbers. The company acknowledges the imbalance of prognostic factors (including IPI 4–5, refractory to last prior therapy, bulky disease, etc.) that numerically favour the pola+BR arm, which consequently may impact the magnitude of the observed treatment benefit from the addition of pola to BR. To address such concerns, two types of analyses were conducted: multivariable regression models and propensity score weighted regression models (see Appendix). After adjusting for imbalances of baseline prognostic covariates, the propensity score weighted model demonstrated consistent treatment benefit for pola+BR across different endpoints including PFS and OS, with narrower 95% CI indicating more precise estimates of treatment effect than multivariate models. Comparable results were obtained from all other models. Therefore, the Company concludes that the observed imbalance on some baseline prognostic factors did not affect the treatment benefit of pola+BR.	The methods employed by the company to adjust for baseline imbalances appeared to be appropriate and a range of methods was tested in sensitivity analyses. Importantly, both IPI score and presence or not of bulky disease were both included in all analyses, although it is unclear whether the final model produced by backward selection retained these variables. As expected from the observed imbalance, adjustment for PFS and OS resulted in a reduced HR, i.e. reduced benefit for pola+BR. Nevertheless, there continued to be benefit and where the 95% confidence interval did not overlap the point of no difference except for two of the three models for OS. The company stated that the backward selection model was used for both PFS and OS in the revised economic analysis because for OS it produced the least benefit for pola+BR. It is unclear why the propensity score weighted model was not used for PFS given it produced the least benefit in terms of PFS. This model also produced the most precise estimates with no overlap of the point of no difference for the 95% confidence interval. Besides the sensitivity analyses on the treatment effect, the ERG has concerns on how these covariate adjustments were included in the model. In the Appendix, it

	When accounting for the influence of baseline covariates the OS HR was adjusted to 0.59 (7). This was based on the multivariable regression model with backwards selection, resulting in the most conservative estimate for the adjusted OS HR (see Appendix). In our revised economic analysis, the BR arm was adjusted using the backward selection method for revised PFS and OS extrapolations. As described in the Appendix and Issue 4 below, this resulted in higher long-term survival estimates in the base case in the BR arm, overlapping more with values cited by clinical experts for the current standard of care.	was mentioned that: (p29) *''The backwards selection model presents the most conservative adjustment in terms of the OS benefit, with the adjusted HR of 0.59 being cited in the draft SmPC. This scenario was selected to adjust the observed GO29365 KM data and the extrapolations for PFS and OS by adjusting the BR arm to the Pola+BR patient characteristics in the revised economic analysis."* Firstly, it was not clear why the PFS and OS extrapolations for the BR arm were revised to reflect the Pola+BR patient characteristics and not the other way around. Secondly, contrary to the company's statement, in the economic model, for the cure mixture models, the PFS and OS extrapolations were updated for both BR and Pola+BR arms.
Issue 4: Is polatuzumab vedotin a curative treatment, and if so at what stage can cure be assumed?		
Is it reasonable to assume from the evidence that a proportion of patients treated for R/R DLBCL enter long-term remission after being progression-free for 2 years and have the same risk of mortality as the general population?	At the time of the most recent data analysis (15 March 2019) after a median of 30 months follow-up, 9/40 (23%) of patients in the pola+BR arm had an ongoing response (8 complete response, 1 partial	We would like to emphasize that the time point of 2 years (or 3 years as in the ERG base case) was not used in the survival modelling. These were used in determining the healthcare resource use and utility inputs.

	response). 2/40 (5%) in the BR arm had an ongoing response (8). Of the nine patients in the pola+BR arm, eight had a duration of response ranging from 22+ months to 34+ months; one patient was consolidated with allogenic stem cell transplant. A high CR rate has been associated with improved outcomes in DLBCL. During the Technical Engagement teleconference, the clinical experts stated that a proportion of DLBCL patients who remain in remission 2 year after a line of therapy (regardless of treatment class) "may be considered cured" although it would be difficult to assume that these patients have the same risk of mortality as the general population as some patients will still relapse. Clinical experts also confirmed that the assumption of long-term remission and survival is independent of technology used, in particular the assumptions made in the recent technology appraisals of CAR-Ts would therefore hold: in TA567 it was concluded that surviving patients would have background population mortality after between 2 and 5 years (9). In TA559 the background mortality in the conservative ERGs scenario was assumed from the point of the PFS and OS curved crossing in their model (at 52 months) (10). As such, our base case model is consistent with these judgements as patients that are in PFS for 2	In the economic model, the company did not consider a response-based landmark model (e.g. considering that the patients who were responders at year 2 would not have cancer related mortality afterwards but would have a SMR-adjusted general population mortality risk) On the contrary, in the economic model, the company chose cure-mixture modelling and therefore, a part of the patient population was assumed to be "cured" and therefore these cured patients were only at risk of SMR-adjusted general population mortality risk from the beginning of the trial. It should be noted that in the ERG's preferred choice (independent generalised gamma for OS extrapolation), we can see that the hazard rate for OS gradually decreases in time and the SMR-adjusted general population mortality risks were used towards the end of the time horizon. Therefore, it is not that the ERG does not believe, like the company does, that some of the cohort might have long term survival that is better than that implied solely by the trial data. However, the ERG does not believe that the survival of a proportion of the cohort is most plausibly estimated by assuming "cure" from the outset.

	years are still at increased risk of progression and death at 2 years in the pola+BR and BR arms (only a proportion is considered at background risk). At around 5 years, PFS and OS curves get close (see Appendix), with mortality being closer to the background mortality. The company has also adjusted the background mortality with the standardised mortality ratio (SMR) of 1.41 as preferred by the ERG. This is more conservative than assumptions made for CAR-Ts (SMR= 1.0 and 1.09), in particular as the adjustment is made over the entire model horizon (see Appendix). However, even at 5 years our model approach assumes a mortality above the adjusted background mortality and presents therefore a more conservative approach to PFS and OS extrapolation in comparison to those deemed plausible in the CAR-T appraisals.	For the other comments related to long-term remission/ survival and "cure mixture modelling", please refer to our response to the next question.
Is the cure assumption clinically plausible? Is the model prediction that 21.2% of patients on polatuzumab vedotin+BR have long-term remission and 20.6% are long term survivors (compared with 0% for BR) clinically plausible and an accurate reflection of the clinical trial? Which progression-free survival data are most robust for use in the model,	The actual observed Kaplan Meier 2-year PFS rate (IRC) for Pola+BR in GO29365 is [redacted]%. This estimate is robust and unlikely to change due the maturity of the data with 30 months median follow up. Therefore, the estimate that approximately two-thirds of the patients in PFS at 2 years are in long-term remission is plausible. In the BR arm, the long-term remission rates in the adjusted analysis now fall in the range of [redacted]% to [redacted]% (depending on the parametric model), this is overlapping with the range that is expected in current clinical practice by experts (5% to 10%). In the Appendix the estimated 5-years PFS rates were	The ERG agrees that estimates from the GO29365 trial are unlikely to change given the maturity of the data. However, it is difficult to see how one can infer the plausibility of long-term remission from a figure of [redacted]% PFS at year two and [redacted] PFS at month 34. The main concerns of the ERG on the plausibility of the cure assumption were: 1- the lack of a plateau shape in the KM

investigator-assessed or independent review committee (IRC)?	also compared to predictions from standard parametric models, with the exception of the Generalized Gamma function, these models underestimate 2-year PFS and predict that the majority of patients in PFS at 2 years would progress or die by 5 years, contrary to the potential for long-term remission discussed above. We consider investigator-assessed (INV) PFS more relevant for the model. The treating clinician's assessment would be more holistic and drive treatment decisions similar to actual clinical practice rather than an independent review of patient data alone. For example, one of the late PFS events was only the patient's death in the IRC assessment whereas the investigator had detected progression earlier. However, the INV and IRC data are in general consistent and we have provided our revised base case on the IRC assessment as preferred by the ERG.	curve. Between month 24 and month 32, the PFS% has dropped from [redacted] to [redacted]. 2- Smoothed hazard plots for OS and PFS from the GO29365 trials did not seem to suggest a "cure' behaviour and the details of how the smoothed hazards and how the OS/PFS extrapolations fitted to the empirical hazards were not presented. 3-Cure-mixture PFS extrapolation with generalised gamma distribution seems to overestimate the Pola+BR and underestimate the BR arm's KM curves towards the end of the follow-up. In TA559 and TA567 appraisals, where the cure mixture models were accepted, plateau structures were observed towards the end of the PFS and OS KM curves. Given no new evidence, the ERG continue to consider the independent assessment from the IRC to be more robust. Based on the discussion above, the ERG considers that the extrapolation choices in the ERG report (i.e independent generalised gamma for OS and independent lognormal for PFS) are more plausible.

Can rates of long-term remission from studies of newly diagnosed DLBCL be generalised to the R/R setting?	There are no assumptions made in our model approach on rates of long-term remission derived from the font line setting. Long-term remission rates were derived by fitting cure-mixture models to GO29369 data as described in our submission. However, the curative nature of front line treatment with R-chemo is supportive of a potential to reach long-term survival in the relapsed or refractory setting for some patients as discussed above. In addition, data on non-disease related mortality for long-term survivors from the front-line setting (11) could be used as proxy for the relapsed or refractory setting as preferred by the ERG.	The ERG does not understand the reference to what the company states is "…preferred by the ERG."
Can the long-term survival associated with CAR-T cell therapy be compared to polatuzumab vedotin+BR?	During the Technical Engagement call, the clinical experts stated that there is no reason to believe that the long-term survival associated with CAR-T cell therapy would not also apply to pola+BR. There is no evidence to suggest the potential for long-term survival is associated with a specific treatment class rather than the natural history of the disease and the proportion of patients achieving a durable remission for more than two years.	Given the lack of submission of new evidence, the ERG have nothing further to add.
What is the company's justification for using its own code instead of standard cure-mixture modelling codes available in statistical programmes? Please can the company provide more information to	The company had developed in-house code prior to the fexsurv R package being made available. We continued with using our in-house code for the following key reasons: first, we can be certain it closely replicates the original cure-mixture approach described in the literature by Lambert et al. (see or response to clarification questions) as there is limited	The company's justification for using the in-house code was not deemed to be persuasive by the ERG. The covariate dependent background mortality hazards could be integrated to

enable the ERG to assess the methods used.	documentation on the implementation in the flexsurvcure package. Secondly, we could include covariate dependent background mortality hazard for the cured potion as described in the literature, whereas we could not accomplish this in the same way with the flexsurvcure package. Finally, it was possible to implement more complex models – such as dependent models and models restricting OS cure-rates by PFS as discussed in our submission, in a straightforward way. Further details are in the Appendix.	the cure mixture models obtained by the flexsurvcure package as explained in Ouwens et al. 2019[1]. Also via the flexsurvcure package, it is possible to implement non-mixture cure models, as well. In the Appendix document submitted after Technical Engagement, (based on Table 4), the company claimed that their in-house code and the flexsurvcure package are comparable because both generated similar cure fractions. However, besides the cure fractions, the other survival regression parameters were not compared. Therefore, it was not clear to the ERG if the company's in-house code results were indeed similar to the results from the flexsurvcure package. Another reason why the ERG would have preferred to use the flexsurvcure package results was because of the fact that the goodness of fit statistics (AIC/BIC) of the mixture cure models from the flexsurvcure package are comparable to those from the standard parametric models. Hence the ERG could have chosen the distribution with the best statistical fit among all independently fitted models (mixture as well as standard models).In

[1] Ouwens, M. J., Mukhopadhyay, P., Zhang, Y., Huang, M., Latimer, N., & Briggs, A. (2019). Estimating Lifetime Benefits Associated with Immuno-Oncology Therapies: Challenges and Approaches for Overall Survival Extrapolations. *PharmacoEconomics*, 1-10.

		contrast, if the company's in-house code is used, there is a substantial discrepancy between the AIC/BIC results from mixture cure models and those from the standard parametric models. Therefore, they could not be compared with each other.
Issue 5: Cost assumptions		
The ERG base-case models the 140mg vial only and assumes no vial sharing, is this the most plausible approach?	The company has submitted a patient access scheme (PAS) with a simple discount applicable when the 30mg vial is available and a higher discount while only the 140mg vial is available to compensate for higher waste in this scenario (see Appendix). This equalises the net drug acquisition costs for both scenarios, i.e., with and without availability of a 30mg vial. In the model, both scenarios assume no vial sharing. In the revised base case and scenarios, ICERs and costs are therefore the same for both scenarios of vial sizes.	The ERG has checked the implementation of the PAS discounts and can confirm that they were correctly implemented in the economic model. The higher discount while only 140 mg vial is available would yield the same drug acquisition costs when the lower discount is applied when both 30 mg and 140 mg vials are available.
Is it likely that patients would have polatuzumab vedotin treatment beyond 6 cycles in clinical practice?	We do not expect additional cycles being given in clinical practice as this is not within the SmPC and not in the GO29365 protocol (7, 12).	Given the lack of submission of new evidence, the ERG have nothing further to add.
The marketing authorisation may specify 6 cycles of treatment, whereas 5% of people in the polatuzumab vedotin+BR arm of the trial had treatment for longer than 6 months. How would a 6-cycle	The KM time-to-off-treatment (TTOT) curve is not zero after 6 times 21 days cycles (18 weeks) because of delayed cycles given to some patients (26 patients in the pola+BR arm; Interim CSR p. 235). No patients received more than 6 cycles in the study. The actual timing of infusions is captured in	It was not clear to the ERG how the delayed doses were already included in the company's calculations. The details of the TToT KM curves were not explained. However, it looks like what the company did would be conservative in that they

treatment cap affect the generalisability of the trial results?	the TTOT as the time between the first and last cycle given. However, the cohort model in the economic analysis does not allow for such delays and applies the per cycle drug costs exactly every 21 days to the entire proportion on treatment (as determined by KM TTOT). Delayed doses are therefore counted at the time point when they should have occurred. As such, delayed doses are included in the calculation and the maximum number of cycles needs to be limited to 6 cycles in the model to avoid double counting delayed doses. The average time on treatment (mean calculated from KM TTOT) is 12.5 weeks equating to an average of 4.2 21-day cycles. Our base case with a maximum of 6 cycles results in an average of 4.4 cycles being applied in the model and is therefore correctly estimating drug acquisition costs.	seem to count the total cost of 6 cycles when they 'should have occurred' i.e. with no delay and instead of as they actually occurred in the trial i.e. with a delay in some cases. Nevertheless, the new ERG base case (see Addendum 1) adjusts TTOT to account for the delay.
Issue 6: Modelling of non-cancer background mortality		
Which method is the most appropriate for modelling non-cancer background mortality: individual patient-level approach or the cohort-based modelling?	The company approach is a more accurate approach to modelling the background mortality risk. The approach acknowledges that there is an age distribution in the trial cohort of R/R DLBCL patients, as in clinical practice. While the average patient age is 69 there were patients treated in the trial that are younger or older than the average. To compare the overall survival outcomes in the trial cohort accurately with the survival of a general population control cohort or to adjust model results, the actual age distribution needs to be taken into account.	The ERG considers that using an individual patient level approach for modelling non-cancer mortality (which was applied as a cap towards the end of the time horizon) is inconsistent with the cohort level approach used for modelling cancer mortality. This inconsistency due to using an individual patient-level approach is also illustrated by the implausible overall survival results towards the tail, e.g.

	Therefore accounting for the fact, that the patients younger than the average will have a lower mortality risk and the patients older than the average a higher mortality risk than the average 69 year old. Our approach to derive background mortality models the overall survival of a cohort matched in age distribution to a general population cohort of the same age distribution, rather than assuming a single age (see Appendix).	around 4% of the patients were still alive at age 105. As demonstrated in Figure 4 of the Appendix document submitted after Technical Engagement, using a cohort level approach for cancer related mortality (applied in the earlier years) and using a patient level approach for non-cancer mortality (applied in the later years) would overestimate the actual mean overall survival. Based on the discussion above, the ERG considers that using cohort level approach for non-cancer related mortality to be more plausible, since the cancer related mortality was also modelled using a cohort-level approach.
Issue 7: Health-related quality of life		
Do the utility values used in the model reflect the health-related quality of life of people with R/R DLBCL?	The company is not aware of more suitable estimates of utility values. The values selected in our base case were deemed the most appropriate and also result in the most conservative ICER estimates for the sets identified.	As stated in the ERG report, the small variation in ICERs shows that the utility values themselves are not big drivers of model results.
Are more robust estimates from larger/more relevant samples available?	See response above.	Given the lack of submission of new evidence, the ERG have nothing further to add.

Issue 8: Model time horizon		
Is a model time horizon of 45 years appropriate for R/R DLBCL, or should it be shorter given that the patient age in the model was 69 years?	The model time horizon was selected to capture all costs and health effects according to the life-tie horizon for the cohort of patients with R/R DLBCL. This time horizon is up to 45 years due to two reasons: firstly, there is a potential for long-term remission and survival for a proportion of patients in the Pola+B and BR arms. Secondly, not all patients in our cohort are 69 years old. As explained above, our model considers an age distribution that includes younger patients (and older patients) with R/R DLBCL that, if they achieve long-term remission, could be expected to survive longer than the average 69 year old.	The model time horizon of 45 years would correspond to a life time horizon under the ERG preferred settings, if the background non-cancer mortality is also modelled using a cohort approach.
Issue 9: End of life criteria		
Does polatuzumab vedotin + BR fulfil the criteria to be considered a “life-extending treatment at the end of life”?	The Company acknowledges the NICE Technical Team is satisfied that the end of life criteria are met.	Given the lack of submission of new evidence, the ERG have nothing further to add.

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in collaboration with:

ERASMUS UNIVERSITEIT ROTTERDAM
INSTITUTE OF HEALTH POLICY & MANAGEMENT

Maastricht University

ID1576: Polatuzumab vedotin with rituximab and bendamustine for treating relapsed or refractory diffuse large B-cell lymphoma

Addendum 1

Produced by

Kleijnen Systematic Reviews Ltd. in collaboration with Erasmus University Rotterdam (EUR) and Maastricht University

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The purpose of this addendum is to update the ERG base case and exploratory analyses. However, the ERG would also like to draw attention to the difference between the mean PSA and the deterministic base case ICER results. It should be noted that, [redacted] The ERG also considered the shape of the polatuzumab scatter plots on the cost-effectiveness plane (not an elliptic shape) and the pattern on the CEAC (not monotonically increasing or decreasing with WTP) rather peculiar, but the root cause of these could not be found.

1.1 Revised ERG base-case

The ERG implemented the following changes on the revised company base case. Furthermore, the ERG corrected an error in the revised model (i.e. in the company model, excess mortality was not applied on top of the general population mortality when it was modelled using a cohort approach).

- The OS and PFS extrapolations as in the ERG report (independent generalised gamma for OS and independent lognormal for PFS)
- Cohort modelling approach instead of individual modelling approach for background non-cancer mortality
- Including the delayed polatuzumab doses given beyond sixth cycle

The revised ERG preferred base case is given in Table 1.

Table 1. Revised base case deterministic results (with PAS)

Intervention	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)
Pola+BR	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	49,540
BR	25,162	[redacted]	[redacted]	-	-	-	-

Source: revised electronic model by ERG

BR, bendamustine + rituximab; ICER, incremental cost-effectiveness ratio; LYG, life years gained; Pola+BR, polatuzumab + bendamustine + rituximab; QALYs, quality-adjusted life years

The mean PSA results are given in Table 6, together with the CE plane and CEAC curves in Figure 1 and Figure 2, respectively.

Table 2. Mean probabilistic results (with PAS)

Intervention	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)
Pola+BR	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	54,027
BR	28,964	[redacted]	[redacted]	-	-	-	-

Source: revised electronic model by ERG

BR, bendamustine + rituximab; ICER, incremental cost-effectiveness ratio; LYG, life years gained; Pola+BR, polatuzumab + bendamustine + rituximab; QALYs, quality-adjusted life years

1.2 Exploratory scenario analyses

The ERG conducted a series of additional scenario analyses in order to explore important areas of uncertainty in the model. Some of these scenarios (sets 1 to 3) were constructed in the same way as in

the original ERG report. One additional scenario (set 4) was added to encompass the uncertainty regarding number of treatment cycles.

Scenario set 1: changing PFS parametric distributions

Alternative scenarios surrounding the extrapolation of PFS were explored by the ERG, with results displayed in Table 3.

Table 3: ERG PFS scenario analyses

PFS distribution	Pola+BR		BR		Incr. Costs (£)	Incr. QALYs	ICER (£)
	Costs (£)	QALYs	Costs (£)	QALYs			
Cure-mixture generalised gamma (CS)	[redacted]	[redacted]	21,261	[redacted]	[redacted]	[redacted]	37,626
Independent log-logistic model	[redacted]	[redacted]	24,800	[redacted]	[redacted]	[redacted]	47,365
Independent generalised gamma model	[redacted]	[redacted]	22,713	[redacted]	[redacted]	[redacted]	35,180
Independent log-normal model (ERG)	[redacted]	[redacted]	25,162	[redacted]	[redacted]	[redacted]	49,540

Source: revised electronic model by ERG

BR = bendamustine + rituximab; CS = company submission; ERG = Evidence Review Group; ICER = incremental cost-effectiveness ratio; Incr. = incremental; PFS = progression free survival; pola = polatuzumab; QALY = quality-adjusted life year

Scenario set 2: Changing OS parametric distributions

Alternative scenarios surrounding the extrapolation of OS were explored by the ERG, with results displayed in Table 4.

Table 4: ERG OS scenario analyses

OS scenario	Pola+BR		BR		Incr. Costs (£)	Incr. QALYs	ICER (£)
	Costs (£)	QALYs	Costs (£)	QALYs			
Cure-mixture generalised gamma (CS)	[redacted]	[redacted]	25,343	[redacted]	[redacted]	[redacted]	48,716
Independent log-normal model	[redacted]	[redacted]	22,623	[redacted]	[redacted]	[redacted]	58,280

OS scenario	Pola+BR		BR		Incr. Costs (£)	Incr. QALYs	ICER (£)
	Costs (£)	QALYs	Costs (£)	QALYs			
Independent log-logistic model	[redacted]	[redacted]	22,538	[redacted]	[redacted]	[redacted]	57,038
Independent generalised gamma model (ERG)	[redacted]	[redacted]	25,162	[redacted]	[redacted]	[redacted]	49,540

Source: revised electronic model by ERG
BR = bendamustine + rituximab; CS = company submission; ERG = Evidence Review Group; ICER = incremental cost-effectiveness ratio; Incr. = incremental; OS = overall survival; pola = polatuzumab; QALY = quality-adjusted life year

Scenario set 3: Alternative approach to modelling long-term mortality (explicit vs. no explicit cure point)

Given the ERGs uncertainty surrounding the maintenance of the long-term treatment effect, assumed in both the company and ERG base-cases, scenarios were tested, examining the impact of steadily declining treatments effects from 30 months to zero at 120 months for OS, PFS and both curves together. The results are presented in Table 5.

Table 5: ERG treatment effect scenario analyses

Treatment effect	Pola+BR		BR		Incr. Costs (£)	Incr. QALYs	ICER (£)
	Costs (£)	QALYs	Costs (£)	QALYs			
Treatment effect maintained (CS and ERG BC)	[redacted]	[redacted]	25,162	[redacted]	[redacted]	[redacted]	49,540
Declining OS treatment effect duration	[redacted]	[redacted]	25,162	[redacted]	[redacted]	[redacted]	54,850
Declining PFS treatment effect duration	[redacted]	[redacted]	25,162	[redacted]	[redacted]	[redacted]	51,713
Declining OS and PFS treatment effect duration	[redacted]	[redacted]	25,162	[redacted]	[redacted]	[redacted]	57,632

Source: revised electronic model by ERG
BC = base case; BR = bendamustine + rituximab; CS = company submission; ERG = Evidence Review Group; ICER = incremental cost effectiveness ratio; Incr. = incremental; OS = overall survival; PFS = progression free survival; pola = polatuzumab; QALY = quality-adjusted life year

Scenario set 4: different treatment duration assumptions for polatuzumab

Given the ERGs uncertainty surrounding the treatment duration, scenarios were tested, examining the impact of different time on treatment duration assumption (1-ERG base case: using TTOT curve, including delayed doses given after sixth cycle, 2-company base case: using TTOT curve, excluding the delayed doses given after sixth cycle, 3-additional scenario: polatuzumab is given to all patients who did not progress within the first six months). The results are presented in Table 6.

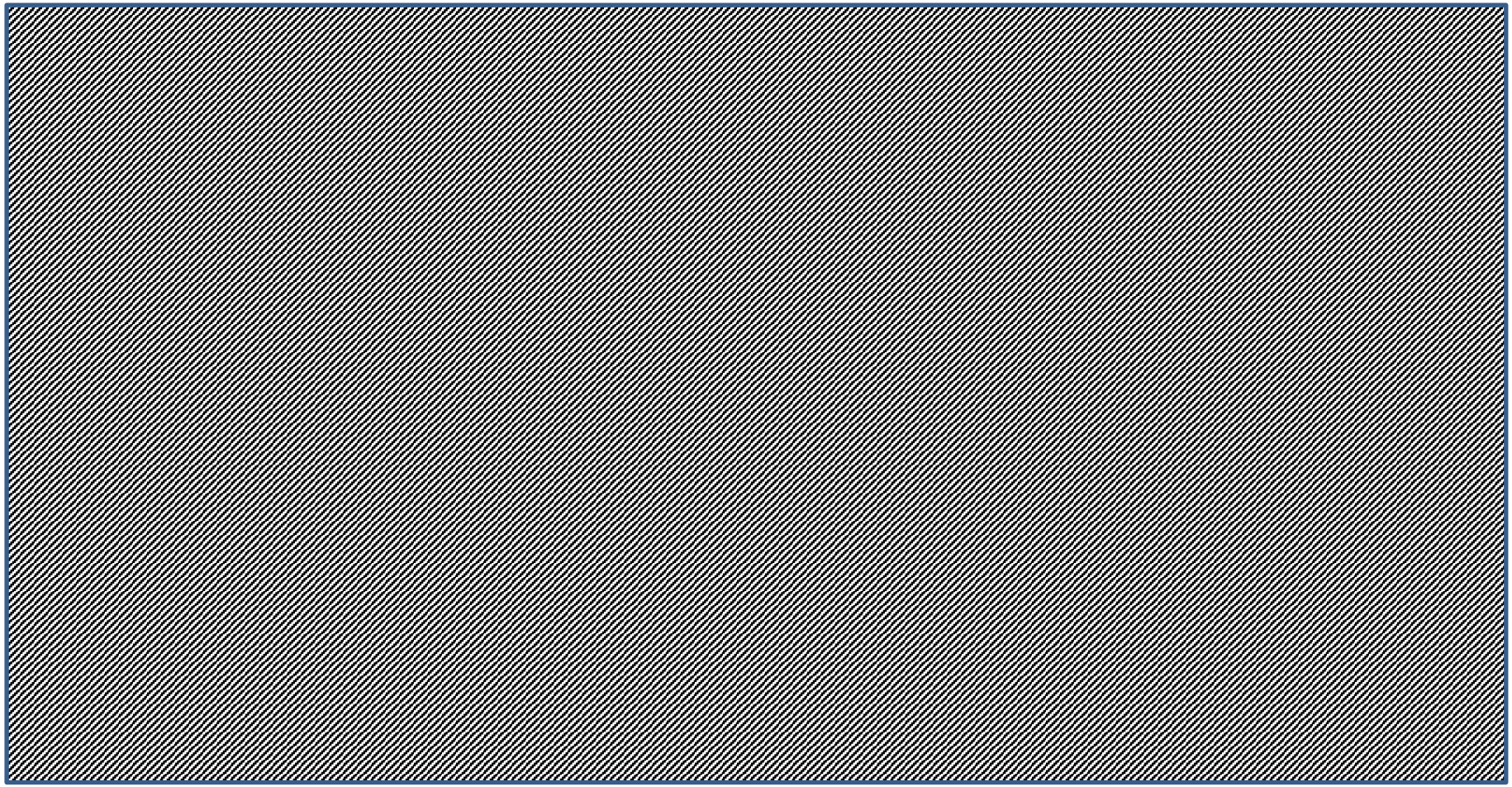
Table 6: ERG polatuzumab treatment duration scenario analyses

Treatment effect	Pola+BR		BR		Incr. Costs (£)	Incr. QALYs	ICER (£)
	Costs (£)	QALYs	Costs (£)	QALYs			
TTOT curve, including delayed doses given after sixth cycle (ERG BC)	[redacted]	[redacted]	25,162	[redacted]	[redacted]	[redacted]	49,540
TTOT curve, excluding delayed doses given after sixth cycle (company BC)	[redacted]	[redacted]	25,026	[redacted]	[redacted]	[redacted]	47,545
During PFS in the first six months	[redacted]	[redacted]	25,026	[redacted]	[redacted]	[redacted]	52,529

Source: revised electronic model by ERG

BC = base case; BR = bendamustine + rituximab; CS = company submission; ERG = Evidence Review Group; ICER = incremental cost effectiveness ratio; Incr. = incremental; TTOT = time on treatment; PFS = progression free survival; pola = polatuzumab; QALY = quality-adjusted life year

Figure 1. Cost-effectiveness plane for Pola+BR versus BR [Redacted]



BR, bendamustine + rituximab; Pola+BR, polatuzumab + bendamustine + rituximab; QALY, quality-adjusted life year

Figure 7. Cost-effectiveness acceptability curve for Pola+BR versus BR [Redacted]

`BR, bendamustine + rituximab; Pola+BR, polatuzumab + bendamustine + rituximab; WTP, willingness to pay