NICE National Institute for Health and Care Excellence

# Single Technology Appraisal

# Polatuzumab vedotin in combination for untreated diffuse large B-cell lymphoma [ID3901]

# Committee Papers

**NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE**

**SINGLE TECHNOLOGY APPRAISAL**

# Polatuzumab vedotin in combination for untreated diffuse large B-cell lymphoma [ID3901]

**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**

3. **Patient group, professional group and NHS organisation submission** from:
   a. Lymphoma Action

4. **Evidence Review Group report** prepared by Southampton Health Technology Assessments Centre (SHTAC)

5. **Technical engagement response** from Roche

6. **Technical engagement responses & expert statements from experts:**
   a. Chris Fox, clinical expert – nominated by NCRI-ACP-RCP-RCR
   b. Wendy Osborne, clinical expert – nominated by Roche

7. **Evidence Review Group critique of company response to technical engagement** prepared by Southampton Health Technology Assessments Centre (SHTAC)

*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

# Polatuzumab vedotin in combination with R-CHP for untreated diffuse large B-cell lymphoma [ID3901]

## Document B

## Company evidence submission

## March 2022

| File name | Version | Contains confidential information | Date |
|---|---|---|---|
| ID3901_Pola_DLBCL_DocB_[Redacted]_v3.0 | 3.0 | Yes | 25 March 2022 |



# Contents





# Tables and figures





# Abbreviations

| | |
|---|---|
| ABC | activated B-cell |
| ADC | antibody-drug conjugate |
| AE | adverse event |
| AEPI | adverse events of particular interest |
| AIC | Akaike Information Criterion |
| AUC | area under the curve |
| BIC | Bayesian Information Criterion |
| BICR | blinded independent central review |
| BNF | British National Formulary |
| BOR | best overall response |
| BSA | body surface area |
| BSH | British Society of Haematology |
| CCOD | clinical cut-off date |
| CHMP | Committee for Medicinal Products for Human Use |
| CI | confidence interval |
| CLL | chronic lymphocytic leukaemia |
| CMH | Cochran Mantel-Haenszel |
| CMM | cure-mixture model |
| COO | cell of origin |
| COVID | coronavirus |
| CSR | clinical study report |
| CTCAE | Common Terminology Criteria for Adverse Events |
| DFS | disease-free survival |
| DHL | double-hit lymphoma |
| DLBCL | diffuse large B-cell lymphoma |
| DOR | duration of response |
| DSA | deterministic sensitivity analysis |
| DSU | Decision Support Unit |
| EBV | Epstein-Barr virus |
| ECG | electrocardiogram |
| ECOG | Eastern Cooperative Oncology Group |

| | |
|---|---|
| EFS | event-free survival |
| EORTC | European Organisation for Research and Treatment of Cancer |
| EOT | end of treatment |
| EPAR | European Public Assessment Report |
| ERG | Evidence Review Group |
| ESMO | European Society for Medical Oncology |
| FACT/GOG-NTX | Functional Assessment of Cancer Therapy/Gynecologic Oncology Group – Neurotoxicity |
| FDG-PET | fluorodeoxyglucose-positron emission tomography |
| GCB | germinal centre B-cell |
| GCP | Good Clinical Practice |
| G-CSF | granulocyte colony-stimulating factor |
| HGBL | high-grade B-cell lymphoma |
| HRG | Healthcare Resource Group |
| ICER | incremental cost-effectiveness ratio |
| ICH | International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use |
| IHC | immunohistochemistry |
| INV | investigator |
| IPI | International Prognostic Index |
| IRC | Independent Review Committee |
| ISRT | involved site radiation treatment |
| ITT | intention-to-treat |
| KSHV | Kaposi's sarcoma-associated herpesvirus |
| LDH | lactate dehydrogenase |
| LYG | life-years gained |
| LYSA | Lymphoma Study Association |
| MDD | minimal detectable difference |
| MHRA | Medicines and Healthcare Products Regulatory Agency |
| MMAE | monomethyl auristatin E |
| MRI | magnetic resonance imaging |
| MUGA | multiple-gated acquisition scan |

| | |
|---|---|
| NALT | new anti-lymphoma treatment |
| NCI | National Cancer Institute |
| NHL | Non-Hodgkin lymphoma |
| NHS | National Health Service |
| NICE | National Institute for Health and Care Excellence |
| NOS | not otherwise specified |
| ODD | Orphan Drug Designation |
| OS | overall survival |
| PAS | Patient Access Scheme |
| PD | progressive disease |
| PET-CT | positron emission tomography- computed topography |
| PFS | progression-free survival |
| POLA | polatuzumab vedotin |
| PRO | patient-reported outcomes |
| PSA | probabilistic sensitivity analysis |
| PSM | partitioned survival model |
| PSS | Personal Social Services |
| PSSRU | Personal Social Services Research Unit |
| QALY | quality-adjusted life year |
| R/R | relapsed/refractory |
| R-CHOP | rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisolone |
| R-CHP | rituximab, cyclophosphamide, doxorubicin, and prednisolone |
| SAE | serious adverse event |
| SCT | stem cell transplant |
| SD | standard deviation |
| SLL | small lymphocytic lymphoma |
| SLR | systematic literature review |
| SOC | standard of care |
| THL | triple-hit lymphoma |
| TTOT | time-to-off-treatment |
| ULN | upper limit of normal |
| WHO | World Health Organization |

# 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 untreated diffuse large B-cell lymphoma | As per final scope issued by NICE | N/A |
| **Intervention** | Polatuzumab vedotin with R-CHP (rituximab, cyclophosphamide, doxorubicin, and prednisolone) | Prednisone as well as prednisolone | Prednisolone is used in UK clinical practice. It is referred as prednisone in the context of the POLARIX study as per clinical trial protocol. The two terms are used interchangeably throughout the submission. |
| **Comparator(s)** | Chemoimmunotherapy (including R-CHOP) | As per final scope issued by NICE | N/A |
| **Outcomes** | The outcome measures to be considered include:<br>• Overall survival<br>• Progression-free survival<br>• Response rate<br>• Adverse effects of treatment<br>• Health-related quality of life | The outcome measures to be considered include:<br>• Progression-free survival (primary endpoint)<br>• Overall survival (secondary endpoint)<br>• Response rate (secondary endpoint)<br>• Adverse effects of treatment<br>• Health-related quality of life | The listed outcome measures are as per final scope issued by NICE. |
| **Subgroups to be considered** | If the evidence allows, the following subgroups will be considered. These include:<br>• Germinal centre DLBCL, and<br>• Post-germinal centre DLBCL | No subgroup analysis to be considered. | The POLARIX subgroup analyses were exploratory/signal seeking and not confirmatory. |

## *B.1.2 Description of the technology being appraised*

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

**Table 2: Technology being appraised**

| | |
|---|---|
| **UK approved name and brand name** | Polatuzumab vedotin (Polivy®) |
| **Mechanism of action** | Polatuzumab vedotin (pola) is an antibody-drug conjugate (ADC) that contains a humanized IgG1 anti-human CD79b monoclonal antibody (MCDS4409A) and a potent anti-mitotic agent, mono-methyl auristatin E (MMAE), linked through a protease-cleavable linker, maleimidocaproyl-valine-citrulline-p-aminobenzyloxycarbonyl (mc-vc-PAB).<br><br>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 (NHLs) (1, 2). Relating specifically to diffuse large B-cell lymphoma (DLBCL), CD79b is expressed in essentially all tumour cells (3, 4), enabling its use in all subtypes of DLBCL independent of dominant signalling pathways.<br><br>Binding of pola to CD79b triggers internalisation of the pola molecule (Figure 8). The stable valine-citrulline (VC) linker within pola is cleaved by lysosomal proteases, releasing MMAE (5).<br><br>MMAE has a mode of action that is similar to that of all vinca-alkaloids, including vincristine. MMAE binds to microtubules and exerts cytotoxicity by inhibiting polymerisation, disrupting cell division, and triggering apoptosis (6, 7). |
| **Marketing authorisation/CE mark status** | An application of a Type II variation for pola to add to its current indication, as well as an Orphan Drug Designation (ODD) application, were submitted to the MHRA on 28 Jan 2022. 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:<br><br>• Polivy in combination with rituximab, cyclophosphamide, doxorubicin, and prednisolone, is indicated for the treatment of adult patients with previously untreated diffuse large B-cell lymphoma (DLBCL). |
| **Method of administration and dosage** | Polatuzumab vedotin in combination with rituximab, cyclophosphamide, doxorubicin, and prednisolone every 21 days for 6 cycles:<br><br>**Polatuzumab vedotin**<br>• 1.8 mg/kg intravenous (IV) infusion on Day 1<br><br>**Rituximab**<br>• 375 mg/m$^2$ IV infusion on Day 1<br>• 375 mg/m$^2$ IV infusion as monotherapy in Cycles 7 and 8<br><br>**Cyclophosphamide**<br>• 750 mg/m$^2$ IV infusion on Day 1<br><br>**Doxorubicin**<br>• 50 mg/m$^2$ IV infusion on Day 1<br><br>**Prednisolone**<br>• 100 mg/day orally (PO) given on Days 1-5 of every 21-day cycle for 6 cycles |
| **Additional tests or investigations** | No additional test or investigations are required. |
| **List price and average cost of a course of treatment** | **Polatuzumab vedotin**<br>• £2,370 per 30mg vial<br>• £11,060 per 140mg vial (no discount)<br><br>Average course of treatment:<br>• [redacted] (with discount)<br>• £71,718 (no discount) |
| **Patient access scheme (if applicable)** | Existing PAS [redacted] |

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

### B.1.3.1 Disease overview

#### *Incidence, prevalence and mortality*

Non-Hodgkin lymphoma (NHL) is a heterogeneous group of disorders characterised by malignant proliferation of lymphoid cells, originating from B- and T-lymphocytes. In 2020, 544,352 new NHL cases were estimated worldwide (8). In the UK, 14,200 new NHL cases are diagnosed every year, accounting for 4% of all new cancer cases (9).

NHL is divided between high and low grade NHL subtypes (8). Diffuse large B-cell lymphoma (DLBCL) is a high grade B-cell NHL with an aggressive clinical course. DLBCL is the most common type of NHL and accounts for up to 40% of all newly diagnosed NHL cases (10). In the UK, around 4,820 people are diagnosed with DLBCL each year (11). The 10-year prevalence is estimated at 27,790 cases (11). As with other types of NHL, the incidence of DLBCL increases with age and most patients are diagnosed between ages 65–74. If left untreated, patients with DLBCL have a median survival of less than a year (12).

#### *Histophysiology and genomics*

DLBCL has distinct morphologic, immunophenotypic, and genetic features. Morphologically, DLBCL is characterised by complete or partial effacement of the nodal architecture by sheets of large atypical lymphoid cells. Immunophenotypically, the disease is characterised by the expression of pan B-cell antigens (CD19, CD20, CD22, CD79a, and CD79b), as well as surface and/or cytoplasmic immunoglobulin expression (IgA and IgM) (2, 13).

A significant proportion of DLBCL remains biologically heterogeneous and is defined as DLBCL, not otherwise specified (DLBCL, NOS). Most cases of DLBCL, NOS are CD20 positive (CD20+). Distinct genetic features have further sub-classified DLBCL by revealing complex molecular patterns and distinct signalling mechanisms. Although there is no single somatic genetic change that defines the disease, the majority of cases have step-wise alterations in the immunoglobulin-heavy gene (14). The most frequently dysregulated

genes include *BCL6* (rearrangement in 35–40%; mutation in 5′ noncoding region in 70%), *BCL2* (translocation 15%, amplification 24%), and *cMYC* (5–15%) (15). Gene expression profiling has identified gene expression patterns that further subtype the disease into germinal centre B-cell (GCB) and activated B-cell (ABC) subgroups that have different oncogenic pathways (16).

***Classification and staging***

In the 2016 World Health Organization (WHO) classification of tumours of haematopoietic and lymphoid tissues, DLBCL is classified as a mature B-cell neoplasm. DLBCL has been further classified in the 2016 WHO update with multiple classification systems including cell of origin, MYC protein expression and rearrangement, and distinct somatic mutations (e.g., CREBBP/EP300, TP53, EZH2, and MYD88) (17).

The revised staging system for the classification of primary nodal lymphomas is used routinely to classify the extent of disease on the basis of the distribution and number of involved sites, as well as the presence or absence of extranodal involvement and constitutional symptoms (18).

**Table 3: Ann Arbor Staging System for lymphoma**

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

Extent of disease is determined by positron emission tomography/computed tomography (PET-CT) for avid lymphomas and CT for nonavid histologies. Tonsils, Waldeyer's ring, and spleen are considered nodal tissues.

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

***Diagnosis and causes***

DLBCL is diagnosed from an excisional tissue biopsy, usually of an involved lymph node or from an extranodal site. While an excisional lymph node biopsy is the preferred diagnostic test for most patients, some patients may not present with easily accessible lymphadenopathy or require the pathologic evaluation of another tissue e.g. pleural fluid, spleen, for diagnosis. Histological evaluation is performed in accordance with the WHO Classification for Lymphoid Malignancies, which categorises lymphomas based on cytology, immunophenotype, and genetic and clinical features (17). Approximately 45–60% of patients present with advanced-stage disease (Ann Arbor Stage III or IV, see Table 3) at diagnosis.

Most cases of DLBCL, NOS arise *de novo*; however, this diagnosis also includes progression or transformation of low-grade B-cell malignancy, such as follicular lymphoma (FL), chronic lymphocytic leukaemia (CLL) and small lymphocytic lymphoma (SLL) (19). Other DLBCL subtypes are associated with the Epstein-Barr virus (EBV) (20, 21) and the Kaposi's sarcoma-associated herpesvirus (KSHV) (22).

The causes of DLBCL are not well understood for the vast majority of patients. Several risk factors have been identified for development of the disease, including hereditary and acquired immune deficiencies, occupational exposures, and pharmacological immunosuppression in the setting of transplantation or treatment of autoimmune diseases.

***Prognosis***

Prognosis of patients with aggressive NHL is most commonly predicted using the International Prognostic Index (IPI). IPI is based on five risk factors obtained at diagnosis that are independent predictors for outcomes such as overall survival (OS) and progression-free survival (PFS):

- Age (≤60 vs. >60 years)
- Serum lactate dehydrogenase (LDH; normal vs. elevated) level
- Eastern Cooperative Oncology Group (ECOG) performance status (PS) (0/1 vs. 2–4)
- Ann Arbor Stage (I or II vs. III or IV)
- Number of extranodal sites (0 or 1 vs. 2–4)

Patients with higher IPI scores, combined with biologically defined higher-risk patients (including the ABC subtype, double-hit lymphoma [DHL], and double-expressor lymphoma [DEL] DLBCL), represent the subset of patients with the poorest outcomes with current therapies. On the basis of the number of negative prognostic features present at the time of diagnosis (age >60 years, Stage III/IV disease, elevated serum LDH, ECOG PS ≥2, >1 extranodal site of disease), four discrete outcome groups have been identified, with 5-year OS ranging from 26–73% (Table 4) (23).

In 2007, Sehn *et al*. confirmed the validity of the IPI in the rituximab era in a cohort of 365 patients treated with rituximab in combination with the CHOP regimen (cyclophosphamide, doxorubicin, vincristine, and prednisolone) (24). However, the IPI was able to distinguish only three rather than the four risk groups in the original IPI. The authors proposed a revised IPI (R-IPI) by redistributing the IPI factors into three prognostic groups: 'very good' (0 risk factors), 'good' (1–2 factors), and 'poor' (3–5 factors). The 4-year OS was 94%, 79%, and 55% in the three groups, respectively. Although the original IPI remains valid in the rituximab + cyclophosphamide, doxorubicin, vincristine, and prednisolone (R-CHOP) era, it now has more limited ability to predict patients who will suffer a particularly aggressive course, since even the 'high-risk' group has a greater than 50% 4-year OS (25).

**Table 4: Treatment outcomes in DLBCL**

| **International Prognostic Index (IPI)** | | | |
|---|---|---|---|
| **Number of risk factors** | **Risk group** | **5-year OS, % (without rituximab)** | **3-year OS, % (with rituximab)** |
| 0 or 1 | Low risk | 73 | 91 |
| 2 | Low-intermediate risk | 51 | 81 |
| 3 | High-intermediate risk | 43 | 65 |
| 4 or 5 | High risk | 26 | 59 |
| **Revised IPI (R-IPI)** | | | |
| **Number of risk factors** | **Risk group** | **-** | **4-year OS, % (with rituximab)** |
| 0 | Very good | - | 94 |
| 1 or 2 | Good | - | 79 |
| 3, 4, or 5 | Poor | - | 55 |

Key: DLBCL, diffuse large B-cell lymphoma; OS, overall survival.
Source: (23) 5-year OS, (25) for 3-year OS, (24) for 4-year OS.

Bulky disease has been defined as an adverse prognostic factor (18) and the ABC subtype has been shown to be associated with a more aggressive clinical course than the GCB subtype (18, 19). Finally, several individual biomarkers assessed by immunohistochemistry or gene expression profiling have been identified as having prognostic significance in DLBCL, such as TP53 mutations (26), MYC rearrangement and BCL2 expression (27), although the introduction of rituximab to standard chemotherapy seems to ameliorate the negative prognostic impact of BCL2 expression (28). 'Double-hit' lymphomas with dual translocations involving both MYC and BCL2, or BCL6, have a particularly aggressive clinical course and poor response to standard chemotherapy (25). These biomarkers are not routinely used in clinical practice due to cost, technical complexity, and tissue requirements and they do not currently influence treatment choices.

***Quality of life***

DLBCL is an aggressive, high-grade lymphoma that is fatal without treatment. Untreated DLBCL patients have an estimated life expectancy of less than one year (4). Symptom presentation in DLBCL is variable and dependent on the site of disease involvement. Patients with DLBCL typically present with a rapidly enlarging symptomatic mass, most commonly nodal enlargement in the neck or abdomen, or, in the case of primary mediastinal large B-cell lymphoma, the mediastinum, but may also present as a mass lesion anywhere in the body. The most common extranodal sites are the gastrointestinal tract, head and neck, and skin and soft tissue. Bone marrow is involved in 10–15% of cases (29). Systemic B symptoms, such as fever, unintentional weight loss, and recurrent night sweats, are observed in approximately 30% of patients, and the serum lactate dehydrogenase (LDH) is elevated in over 50% of patients.

There are limited data on the impact of first-line (1L) DLBCL on patients' quality of life (QoL). However, studies have shown that the QoL burden was higher and more impaired in patients who did not respond well to 1L treatments, patients with an aggressive form of NHL, and in younger DLBCL patients:

- In a systematic review by Chadda *et al.*, DLBCL patients who achieved complete response after 1L treatment had significantly greater improvements on QoL compared to non-complete responders (30).

- A study by Alawi *et al.* compared QoL in patients with indolent and aggressive lymphoma. It was found that patients with the aggressive form of NHL demonstrated a somewhat lower QoL, including physical, social/family, emotional, and functional well-being, as well as higher anxiety and lower positive affect than patients with indolent NHL (31).

- A study by van der Poel *et al.* found that younger DLBCL survivors (aged 18–59 years) showed worse scores on dyspnoea, cognitive and social functioning, as well as financial problems compared to their age- and sex- matched normative population (32). This suggests that DLBCL has a greater impact on younger than older survivors.

It is evident that disease-related symptoms are frequent in most DLBCL patients. Most importantly, current treatment options are not effective in all patients (see section B.1.3.2), and subsequent therapy only offer a curative option in a minority group of patients. Patients who are refractory to or relapse following 1L treatment experience even greater anxiety due to the poorer prognosis of their condition and the need for further, often more intensive treatment. The cumulative burden of toxicity on patients' physical and psychological health further impact their QoL negatively. This is partly related to uncertainties towards the prognosis of their disease, side effects of treatment and fear of relapse (33), especially given the disappointing efficacy of standard salvage regimens prior to transplant (34). Additionally, this will also increase the demand on hospital services and the use of skilled nursing facilities and hospice services (35).

Compared to 1L patients, advanced DLBCL patients have a higher burden of illness, including increases in admissions, emergency room visits, use of skilled nursing facilities, home health agencies, and hospice services (36). In other words, targeted 1L DLBCL treatments have the potential to reduce disease progression and significantly improve patients' QoL, allowing for a more cost-effective, budgeted treatment paradigm in the overall management of DLBCL.

### B.1.3.2 Current clinical practice in the UK

According to the British Society of Haematology (BSH) (37) and the Pan-London Haemato-Oncology Clinical Guidelines (38), the current 1L therapy in previously untreated DLBCL is rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisolone (R-CHOP). Depending on staging, patients are treated with 3–6 cycles of R-CHOP, sometimes followed by involved site radiation treatment (ISRT). However, standard R-CHOP regimen is only effective in 50–70% of patients (39). Among patients for whom R-CHOP therapy fails, 10–15% suffer from primary refractory disease (disease does not enter complete remission and/or progresses during or soon after treatment), whereas 20–30% relapse after achieving complete remission (37). The chance for long-term cure in DLBCL diminishes with each subsequent line of therapy; therefore, obtaining the best possible outcome for previously untreated patients is of critical importance.

In the setting of 1L DLBCL, the majority of disease relapse occurs within the first 24 months after starting treatment. Recent analyses have demonstrated that patients with DLBCL who have remained in remission after this period have survival equivalent to that of age-, sex-, and country-matched general population (40). However, approximately half of the patients will not respond to subsequent therapy because of refractory disease (34). Thus, optimising the initial treatment options in settings with curative intent would have a substantial impact on the overall outcome for DLBCL.

Since the introduction of R-CHOP, there has been no advancement in treatment options for previously untreated DLBCL patients for over 20 years. While R-CHOP may cure approximately 60% of patients with previously untreated DLBCL (41), the majority of randomised studies and alternative strategies have so far been unable to demonstrate meaningful benefit over R-CHOP. These include:

- Increased dose density with R-CHOP given at 14-day intervals (42, 43);
- Dose intensification with dose-adjusted etoposide plus prednisolone, vincristine, cyclophosphamide, doxorubicin and rituximab (DA-EPOCH-R) (44);
- Substitution strategies, such as the anti-CD20 monoclonal antibody obinutuzumab (45);

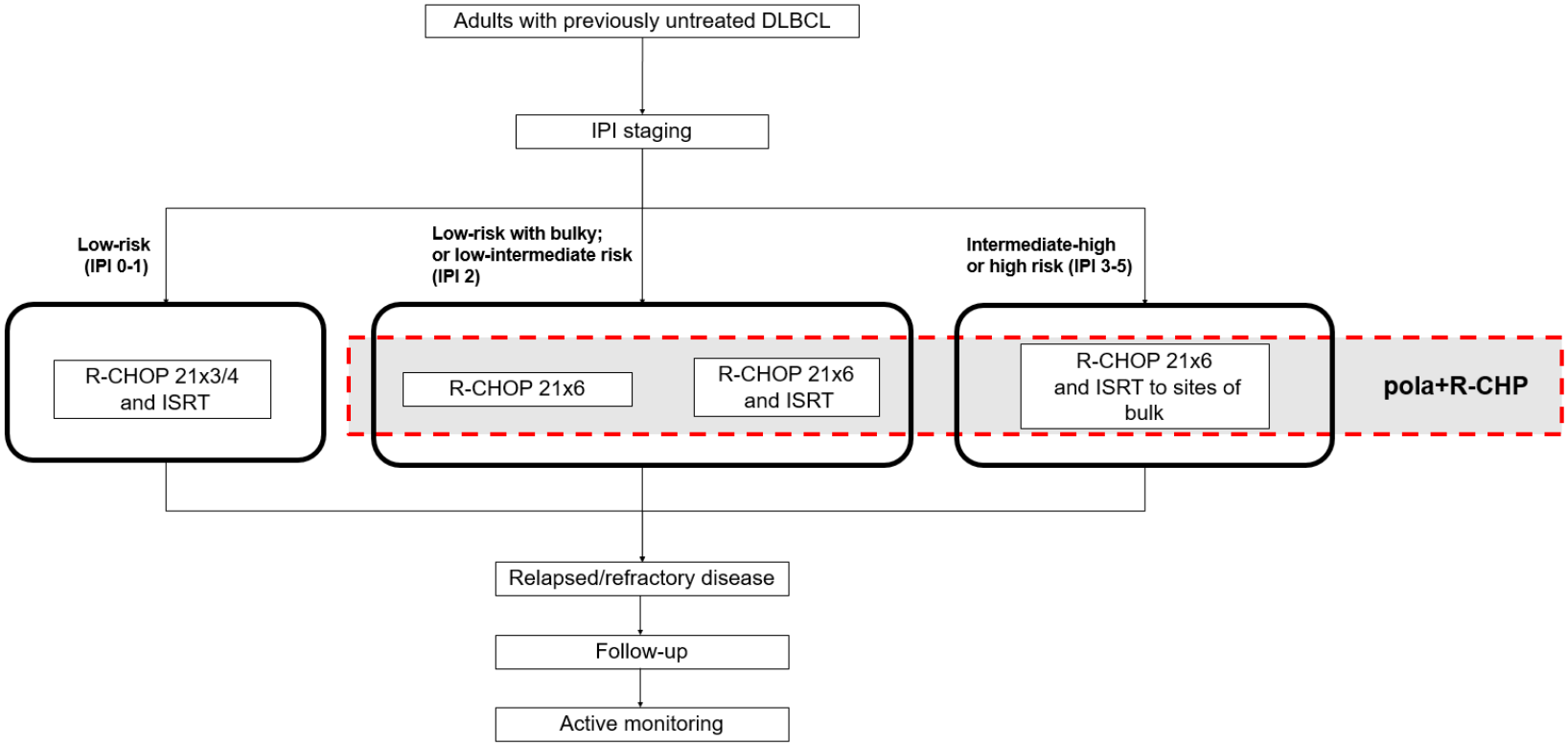
- Additive agents to R-CHOP, such as bevacizumab (46), bortezomib (47), ibrutinib (48), and lenalidomide (49); and
- Maintenance strategies after R-CHOP with lenalidomide (50), everolimus (51), and enzastaurin (52).

In some of these cases, new treatment regimens may have been quite promising in the early phase studies of DLBCL; however, the feasibility of adding therapies to R-CHOP or increasing dose density resulted in higher rates of adverse events and complications or limited tolerability of the treatment. Therefore, there is a significant unmet medical need in the 1L DLBCL setting and a strong rationale for introducing novel therapeutic agents that can build upon R-CHOP and improve outcomes in patients with previously untreated DLBCL by preventing or delaying relapse.

### B.1.3.3 Disease management pathway

The proposed treatment pathway and position of polatuzumab vedotin is summarised in Figure 1. The information presented below is based on NICE, BSH, and National Health Service (NHS) guidelines for the diagnosis and management of DLBCL (37, 38).

**Figure 1: Current treatment pathway for adult patients (aged 18-80) with previously untreated DLBCL (including Pola+R-CHP positioning)**




The grey box indicates the proposed positioning of Pola+R-CHP for patients with an IPI of 2–5.
Key: IPI, International Prognostic Index; ISRT, involved site radiotherapy.

### *B.1.4 Equality considerations*

The technology is not likely to raise any equality issues.

## 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 5: Clinical effectiveness evidence**

| | | | | | |
|---|---|---|---|---|---|
| **Study** | POLARIX (study GO39942) | | | | |
| **Study design** | Phase III, global, multicentre, randomised, double-blind, placebo-controlled study | | | | |
| **Population** | Adult patients with previously untreated diffuse large B-cell lymphoma | | | | |
| **Intervention(s)** | Polatuzumab vedotin plus rituximab, cyclophosphamide, doxorubicin and prednisolone (Pola+R-CHP) | | | | |
| **Comparator(s)** | Rituximab, cyclophosphamide, doxorubicin, vincristine and prednisolone (R-CHOP) | | | | |
| **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** | POLARIX is a Phase III trial providing efficacy and safety evidence for the combination of Pola+R-CHP in patients with DLBCL. Data from POLARIX were used to inform the efficacy and safety of Pola+R-CHP in the economic model. Data for PFS and OS from the most recent data cut (28 June 2021) was used to inform the economic model. | | | | |
| **Reported outcomes specified in the decision problem** | • Progression-free survival (primary endpoint)<br>• Overall survival (secondary endpoint)<br>• Response rate (secondary endpoint)<br>• Adverse effects of treatment<br>• Health-related quality of life | | | | |
| **All other reported outcomes** | • Duration of response<br>• Event-free survival | | | | |

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

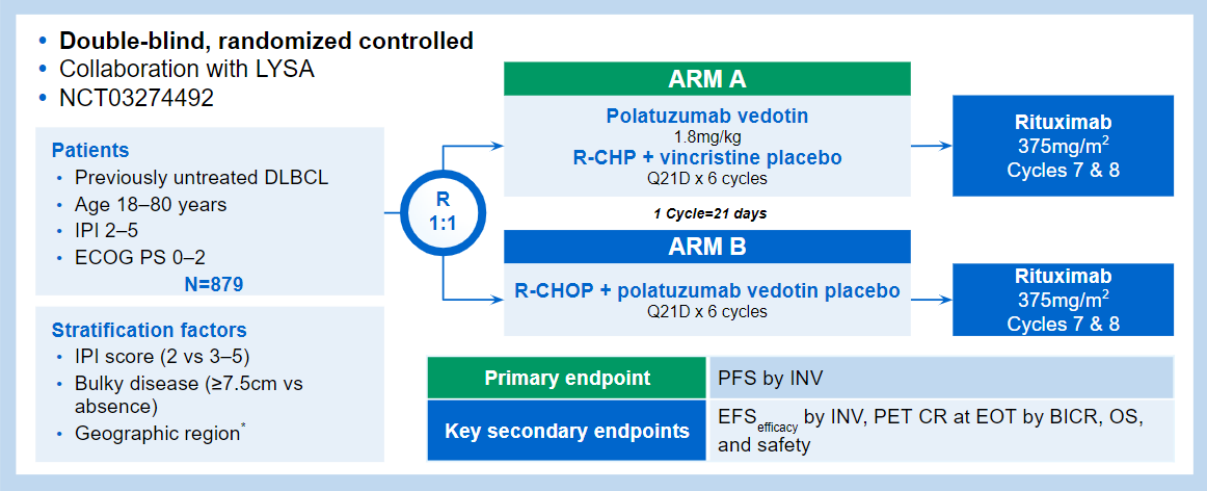
Unless otherwise stated, B.2.3–B.2.6 is based on the POLARIX (study GO39942) clinical study report (CSR) (data on file).

### B.2.3.1 Study methodology

#### *Study design*

POLARIX (study GO39942) is a Phase III, multicentre, randomised, double-blind, placebo-controlled trial comparing the efficacy and safety of polatuzumab vedotin in combination with rituximab and CHP (R-CHP) versus rituximab and CHOP (R-CHOP) in previously untreated patients with diffuse large B-cell lymphoma. The study schema is shown in Figure 2.

**Figure 2: Overview of the design of POLARIX (study GO39942) (53)**




*Western Europe, United States, Canada and Australia vs Asia vs Rest of World.

Key: BICR, blinded independent central review; CR, complete response; ECOG PS, Eastern Cooperative Oncology Group performance status; $EFS_{efficacy}$, event-free survival for efficacy causes (time from randomization to the earliest occurrence of disease progression/relapse, death due to any cause, initiation of any non-protocol specified anti-lymphoma treatment, or biopsy-confirmed residual disease after treatment completion); EOT, end of treatment; INV, investigator; IPI, International Prognostic Index; LYSA, Lymphoma Study Association; PET, positron emission tomography; Q21D, every 21 days; R, randomization; R-CHP, rituximab plus cyclophosphamide, doxorubicin, prednisolone; R-CHOP, rituximab plus cyclophosphamide, doxorubicin, vincristine, prednisolone.

#### *Inclusion/exclusion criteria*

Patients with previously untreated CD20-positive DLBCL were enrolled in POLARIX. See Appendix E for a full list of inclusion/exclusion criteria.

***Randomisation and cycles of treatment***

A total of 879 patients were randomised in a 1:1 ratio to either Arm A or Arm B as defined below. Both patients and the investigator were blinded to the assigned active microtubule inhibitor (i.e., polatuzumab vedotin or vincristine) and placebo control. Patients received six cycles of either Pola+R-CHP or R-CHOP chemotherapy at 21-day intervals. Both arms then received two additional cycles of single agent rituximab.

- **Arm A, Pola+R-CHP (investigational arm):** polatuzumab vedotin 1.8 mg/kg IV, placebo for vincristine IV, rituximab 375 mg/m$^2$ IV, cyclophosphamide 750 mg/m$^2$ IV, and doxorubicin 50 mg/m$^2$ IV each given on Day 1 and prednisolone 100 mg/day orally (PO) given on Days 1–5 of every 21-day cycle for 6 cycles. Rituximab 375 mg/m$^2$ IV was given as monotherapy in Cycles 7 and 8.

- **Arm B, R-CHOP (control arm)**: placebo for polatuzumab vedotin, rituximab 375 mg/m$^2$ IV, cyclophosphamide 750 mg/m$^2$ IV, doxorubicin 50 mg/m$^2$ IV, and vincristine 1.4 mg/m$^2$ IV (maximum 2 mg/dose) each given on Day 1 and prednisolone 100 mg/day PO given on Days 1–5 of every 21-day cycle for 6 cycles. Rituximab 375 mg/m$^2$ IV was given as monotherapy in Cycles 7 and 8.

POLARIX was stratified to ensure there was an equal spread of patients. Patients were randomised using the following stratification factors:

- International Prognostic Index IPI score (IPI 2 versus IPI 3–5)
- Bulky disease, defined as one lesion ≥ 7.5 cm (present versus absent)
- Geographical region (Western Europe, United States, Canada, and Australia versus Asia versus Rest of World [remaining countries])

No crossover to the investigational arm was allowed. Patients were assessed for disease response by the investigator using regular clinical and laboratory examinations, dedicated computed tomography (CT) or magnetic resonance imaging (MRI) scans, and fluorodeoxyglucose positron emission tomography (FDG-PET; hereafter referred to as PET-CT) according to the Lugano Response Criteria for Malignant Lymphoma.

***Assessment***

Response was evaluated at the end of study treatment, or sooner in the event that a patient discontinued early. After completion of therapy, all patients were followed-up at clinic visits conducted every 3 months for 24 months, and then every 6 months until Month 60. After 5 years, patients were followed only for survival and initiation of a new anti-lymphoma therapy

(NALT) approximately every 6 months until study termination, patient withdrawal of consent or death.

Safety was evaluated by monitoring all adverse events (AEs), serious adverse events (SAEs), and abnormalities identified through physical examinations, vital signs, and laboratory assessments. Such events were graded using the National Cancer Institute Common Terminology Criteria for Adverse Events, Version 4.0 (NCI CTCAE v4.0). Laboratory safety assessments included routine monitoring of haematology and blood chemistry, and tests of immunologic parameters.

### B.2.3.2 Endpoints and assessments

POLARIX evaluated the efficacy, safety, pharmacokinetics, and PROs of pola plus chemoimmunotherapy (Pola+R-CHP) compared with SoC chemoimmunotherapy (R-CHOP) in previously untreated patients with CD20-positive DLBCL.

***Primary efficacy endpoint***

The primary study endpoint was PFS as assessed by the investigator. PFS was defined as the time from randomisation to the first occurrence of disease progression or relapse as assessed by the investigator, using the Lugano Response Criteria for Malignant Lymphoma, or death from any cause, whichever occurs earlier.

***Secondary efficacy endpoints***

Key secondary endpoints included in the hierarchical testing procedure:

- Event-free survival ($EFS_{eff}$) as determined by the investigator
- Complete response (CR) rate at end of treatment by FDG-PET as determined by blinded independent central review (BICR)
- Overall survival (OS)

Additional secondary endpoints that were not adjusted for testing multiplicity:

- Disease-free survival (DFS)
- Best overall response (BOR) rate as determined by investigator
- Duration of response (DOR)

***Exploratory endpoints***

- Subgroup analysis
- Patient-reported outcomes (PROs) endpoints

- All scales of the EORTC QLQ-C30, the FACT-Lym LymS, and FACT/GOG-NTX peripheral neuropathy

### B.2.3.3 Patient demographics and baseline characteristics

Key demographic and baseline disease characteristics from the primary analysis (CCOD 28 June 2021) are provided in Table 6.

The stratification was not designed to show statistical significance between the different factors. The proportions of patients in each category by IPI score, bulky disease, and geographical region were similar in the two treatment arms and there were no imbalances in stratification factors between the two arms. Treatment arms were balanced with respect to baseline biomarker assessments performed centrally.

**Table 6: Summary of key demographic data and disease characteristics at baseline**

| Baseline characteristics | Pola+R-CHP (n=440) | R-CHOP (n=439) |
|---|---|---|
| **Age (years)** | | |
| ≥60 | 231 (52.5%) | 236 (53.8%) |
| Median (Min–Max) | 65.0 (19–80) | 66.0 (19–80) |
| **Sex** | | |
| Male | 239 (54.3%) | 234 (53.3%) |
| [redacted] | | |
| [redacted] | [redacted] | [redacted] |
| [redacted] | [redacted] | [redacted] |
| [redacted] | [redacted] | [redacted] |
| [redacted] | [redacted] | [redacted] |
| [redacted] | [redacted] | [redacted] |
| [redacted] | | |
| [redacted] | [redacted] | [redacted] |
| [redacted] | [redacted] | [redacted] |
| **ECOG PS** | | |
| 0–1 | 374 (85.0%) | 363 (82.7%) |
| 2 | 66 (15.0%) | 75 (17.1%) |
| **Geographic region (IxRS)** | | |
| Asia | 81 (18.4%) | 79 (18.0%) |
| Rest of World | 57 (13.0%) | 59 (13.4%) |
| Western Europe/United States/Canada/Australia | 302 (68.6%) | 301 (68.6%) |
| **IPI at screening (IxRS)** | | |
| 2 | 167 (38.0%) | 167 (38.0%) |
| 3–5 | 273 (62.0%) | 272 (62.0%) |
| **Bulky disease (IxRS)** | | |
| Absent | 247 (56.1%) | 247 (56.3%) |

| Baseline characteristics | Pola+R-CHP (n=440) | R-CHOP (n=439) |
|---|---|---|
| Present | 193 (43.9%) | 192 (43.7%) |
| **Baseline LDH** | | |
| ≤1 x ULN | 146 (33.2%) | 154 (35.1%) |
| >1 x ULN | 291 (66.1%) | 284 (64.7%) |
| **Bone marrow involvement at diagnosis** | | |
| Indeterminate | 11 (2.5%) | 11 (2.5%) |
| Negative | 342 (77.7%) | 349 (79.5%) |
| Positive | 76 (17.3%) | 72 (16.4%) |
| **Ann Arbor Stage** | | |
| I or II | 47 (10.7%) | 52 (11.8%) |
| III or IV | 393 (89.3%) | 387 (88.2%) |
| **No. of extranodal sites** | | |
| 0–1 | 227 (51.6%) | 226 (51.5%) |
| ≥2 | 213 (48.4%) | 213 (48.5%) |
| **IPI at screening (per eCRF)** | | |
| 1 | 1 [a] (0.2%) | 0 |
| 2 | 164 (37.3%) | 165 (37.6%) |
| 3 | 174 (39.5%) | 156 (35.5%) |
| 4 | 76 (17.3%) | 96 (21.9%) |
| 5 | 25 (5.7%) | 22 (5.0%) |
| **NHL histologic diagnosis (eCRF [b])** | | |
| DLBCL NOS, ABC, GCB | 373 (84.8%) | 367 (83.6%) |
| HGBL, NOS, DHL/THL | 43 (9.8%) | 50 (11.4%) |
| Other large B-cell [c] | 24 (5.5%) | 22 (5.0%) |
| **COO [d]** | | |
| ABC | 102 (30.9%) | 119 (35.2%) |
| GCB | 184 (55.8%) | 168 (49.7%) |
| Unclassified | 44 (13.3%) | 51 (15.1%) |
| Unknown | 110 | 101 |
| **Double-expressor lymphoma [d]** | | |
| DEL | 139 (38.4%) | 151 (41.3%) |
| non-DEL | 223 (61.6%) | 215 (58.7%) |
| Unknown | 78 | 73 |
| **Double/triple-hit lymphoma [d]** | | |
| DH/TH+ | 26 (7.9%) | 19 (5.7%) |
| DH/TH- | 305 (92.1%) | 315 (94.3%) |
| Unknown | 109 | 105 |

a This patient with IPI "1" per eCRF is a data entry error, and was randomised as IPI "2".
b Based on local diagnosis.
c Epstein Barr virus-positive (EBV+) DLBCL and T-cell/histiocyte rich large B-cell lymphoma (LBCL).
d Based on central review, and percentages are based on biomarker evaluable population (i.e., by excluding patients with unknown status).

Key: ECOG PS, Eastern Cooperative Oncology Group Performance Status; eCRF, electronic case report form; IPI, International Prognostic Index; LDH, lactate dehydrogenase; COO, cell of origin; DLBCL, diffuse large B-cell lymphoma; NOS, not otherwise specified; HGBL, high-grade B-cell lymphoma; ABC, activated B-cell; GCB, germinal centre B-cell; DHL/THL, double hit lymphoma/triple-hit lymphoma.

Patient disposition is summarised in Table 7. At the CCOD for the primary analysis (28 June 2021), patients had median duration of survival follow-up of 28.1 months in the Pola+R-CHP arm and 28.2 months in the R-CHOP arm.

**Table 7: Patient disposition – intention-to-treat (ITT) population**

| | Pola+R-CHP (n=440) | R-CHOP (n=439) |
|---|---|---|
| **End of treatment status** | | |
| Completed treatment | 387 (88.0%) | 377 (85.9%) |
| Discontinued treatment | 49 (11.1%) | 60 (13.7%) |
| **End of study status** | | |
| Ongoing on study | 374 (85.0%) | 363 (82.7%) |
| Discontinued study | 66 (15.0%) | 76 (17.3%) |

Key: R-CHOP, rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisolone; R-CHP, rituximab plus cyclophosphamide, doxorubicin, and prednisolone.

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

See Appendix D.2 for details of the number of eligible participants and patient disposition for the POLARIX trial.

### *Determination of sample size*

In total, enrolment of 875 patients was planned and expected to complete in approximately 23 months, leading to an average monthly recruitment of 38 patients per month.

The sample size considerations were based on the following assumptions:

- 1:1 randomisation ratio in Pola+R-CHP versus R-CHOP
- A one-sided log-rank test
- 80% power at the 2.5% significance level
- A 31% reduction in the risk of disease progression, relapse, or death (i.e. PFS hazard ratio of 0.69).
- PFS in the control arm was assumed to follow a piece-wise exponential distribution, and the hazard rate over time h(t) is estimated using the historical data obtained from the GOYA study among patients with IPI 2–5 who received R-CHOP (data on file).

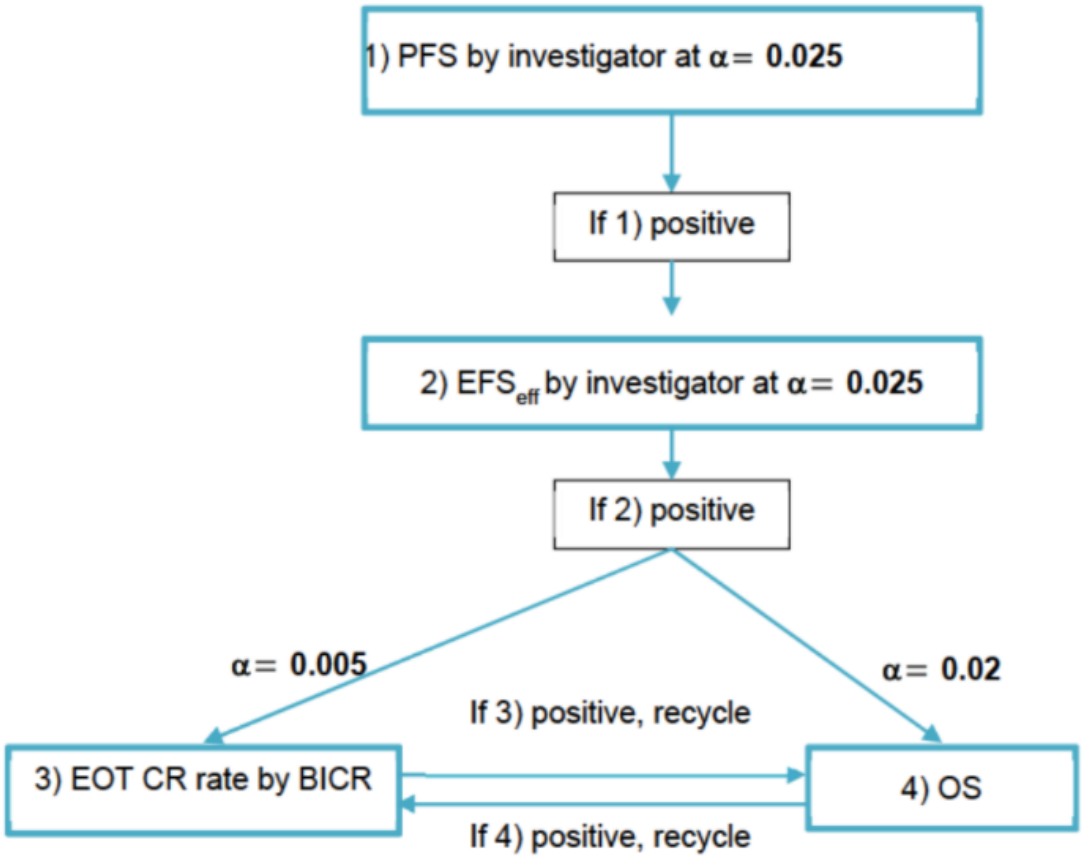
Based on these assumptions, approximately 228 investigator-assessed PFS events were needed to detect a hazard ratio of 0.69 in PFS (3-year PFS rates of 62–72%), with 80% power for the primary analysis of PFS. The minimal detectable difference (MDD) for PFS hazard ratio at the final PFS analysis was 0.771 (i.e. 22.9% reduction in the risk of disease progression, relapse, or death). 3-year PFS was expected to improve from 62–70% under the MDD.

***Efficacy analyses***

The analysis population for the primary and secondary efficacy analyses consisted of all randomised patients, with patients grouped according to their assigned treatment.

To control the overall type I error rate at a one-sided 0.025 level of significance, a hierarchical testing procedure, including possible $\alpha$ recycling (54), was used to adjust for multiple statistical testing of the primary and key secondary efficacy endpoints. The POLARIX statistical analysis plan is summarised below (Figure 3).

**Figure 3: POLARIX statistical analysis plan**



1. First, the primary efficacy endpoint, PFS by investigator in the ITT population, was tested at $\alpha$=0.025.

2. If the primary PFS endpoint was statistically positive, a formal statistical test of $EFS_{eff}$ by investigator in the ITT population between the two arms was performed at a one-sided $\alpha$=0.025 using a stratified log-rank test.

3. If the secondary $EFS_{eff}$ endpoint was statistically positive, the EOT CR rate by IRC in the ITT population was tested using a stratified Cochran-Mantel-Haenszel (CMH) test at a one-sided $\alpha$=0.005.

4. If the EOT CR rate by BICR in was statistically significant, the final OS analysis was tested at a one-sided $\alpha$=0.025; otherwise, the final OS was tested at a one-sided $\alpha$=0.02.

### *B.2.5 Quality assessment of the relevant clinical effectiveness evidence*

The quality assessment of the POLARIX trial is shown below (**Table *8***). See Appendix D.3 for the complete quality assessment of other relevant trials.

**Table 8: Risk of bias assessment for POLARIX**

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

## *B.2.6 Clinical effectiveness results of the relevant trials*

The key efficacy findings from the POLARIX trial are summarised below, which provides an overview of the efficacy in patients with previously untreated DLBCL.

### B.2.6.1 Primary efficacy endpoint: progression-free survival (PFS)

A statistically significant and clinically meaningful improvement in the primary endpoint of Investigator-assessed PFS was demonstrated following treatment with Pola+R-CHP compared to R-CHOP, in patients with previously untreated DLBCL (Table 9).

**Table 9: Summary of investigator-assessed PFS (ITT population)**

| | **Pola+R-CHP (n=440)** | **R-CHOP (n=439)** |
|---|---|---|
| **No. of events, n (%)** | 107 (24.3) | 134 (30.5) |
| Earliest contributing event, n | | |
| Death | 19 | 20 |
| Disease progression or relapse | 88 | 114 |
| **Stratified analysis*** | | |
| p-value (Log-rank) | 0.02 | |
| Hazard ratio (95% CI) | 0.73 (0.57–0.95) | |
| **12-Month PFS rate† (95% CI)** | 83.9 (80.4–87.4) | 79.8 (75.9–83.6) |
| **24-Month PFS rate† (95% CI)** | 76.7 (72.7–80.8) | 70.2 (65.8–74.6) |

*Stratified for IPI score (IPI 2 vs IPI 3–5), bulky disease (present vs absent), and geographical region (Western Europe, United States, Canada and Australia versus Asia versus Rest of World [remaining countries]).

†Kaplan–Meier estimate.

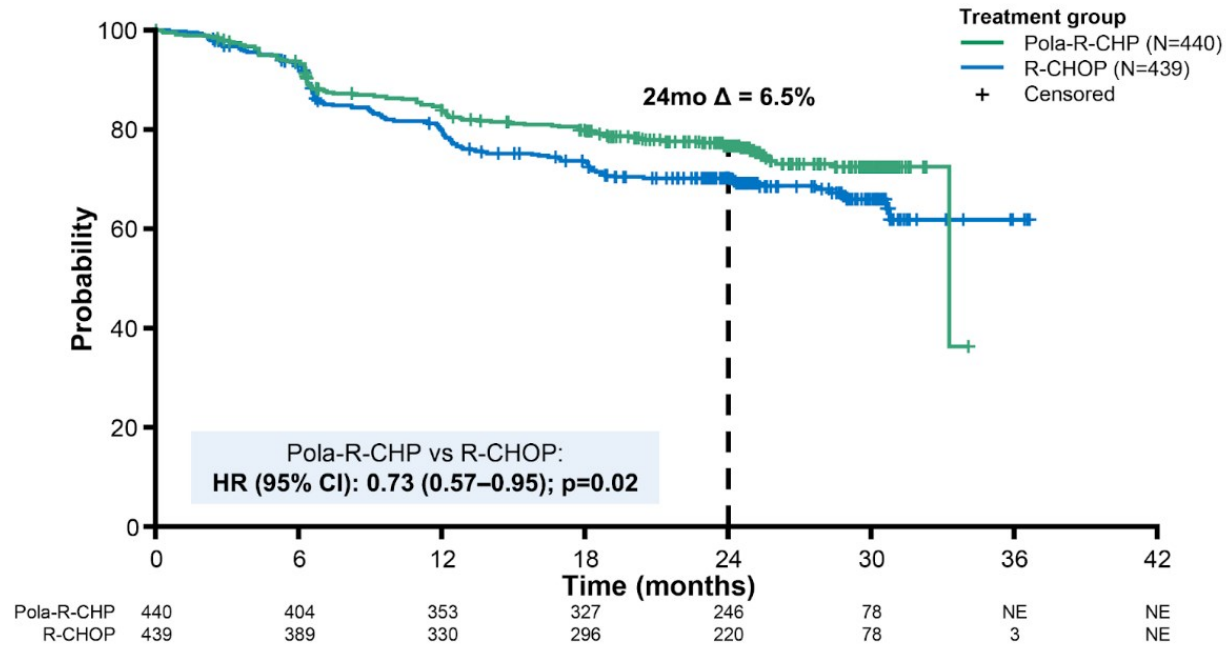
Key: CI, confidence interval.

Fewer patients in the Pola+R-CHP arm had progressed or died compared to the R-CHOP arm (107 [24.3%] vs.134 [30.5%]). Treatment of patients with previously untreated DLBCL with the Pola+R-CHP regimen resulted in a statistically significant and clinically meaningful reduction in the risk of progression, relapse or death by 27% compared with patients treated with the R-CHOP regimen (stratified HR: 0.73 [95% CI: 0.57–0.95]; p=0.0177). Results of the unstratified analysis were consistent with the results of the stratified analysis (HR: 0.76 [95% CI: 0.59–0.98]; p=0.0326).

The separation in the KM curves at approximately 6 months of observation coincides with treatment completion assessments (Figure 4). The majority of PFS events occurred within 24 months of randomisation in both arms, with a higher proportion of patients remaining alive and progression-free in the Pola+R-CHP arm compared to the R-CHOP arm at 12-Month (83.9% [95% CI: 80.43–87.39] vs 79.8% [95% CI: 75.92–83.61]), and 24-Month (76.7% [95% CI:72.65–80.76] vs 70.2% [95% CI: 65.80–74.61]). The observed treatment difference

in PFS event-free rate increased from the 12-Month milestone (4.14 [95% CI: -1.05–9.32]) to the 24-Month milestone (6.5 [95% CI: 0.52–12.49]).

**Figure 4: Kaplan-Meier plot of time to investigator-assessed PFS (ITT population) (53)**




## B.2.6.2 Secondary efficacy endpoints

Key secondary endpoints included in the hierarchical testing procedure are as follows:

- $EFS_{eff}$ as determined by the investigator
- CR rate at end of treatment by FDG-PET as determined by BICR
- OS

Key findings from the secondary endpoints are summarised below in Table 10.

**Table 10: Key secondary efficacy endpoint results for pola (ITT population)**

| | Pola+R-CHP (n=440) | R-CHOP (n=439) |
|---|---|---|
| **INV-assessed $EFS_{eff}$** [1] | | |
| Patients with event (%) | 112 (25.5%) | 138 (31.4%) |
| Median time to $EFS_{eff}$ – Months (95% CI) | 33.3 (33.3–NE) | NE (NE) |
| Stratified HR (95% CI) | 0.75 (0.58–0.96) | |
| p-value (log-rank) | 0.0244 | |
| 12-Month $EFS_{eff}$ rate (95% CI) | 82.5 (78.9–86.1) | 78.7 (74.8–82.6) |
| 24-Month $EFS_{eff}$ rate (95% CI) | 75.6 (71.5–79.7) | 69.4 (65.0–73.8) |

| | Pola+R-CHP (n=440) | R-CHOP (n=439) |
|---|---|---|
| **BICR-assessed CR rate at end of treatment (by PET-CT) [2]** | | |
| Complete Responders (%) (95% CI) | 78.0% (73.8–81.7) | 74.0% (69.7–78.1) |
| Difference in response rate (95% CI) | 3.9 (-1.9–9.7) | |
| Stratified p-value (CMH) | 0.1557 | |
| **Overall Survival [3]** | | |
| Patients with event (%) | 53 (12.0%) | 57 (13.0%) |
| Median time to OS - months (95% CI) | NE | NE |
| Stratified HR (95% CI) | 0.94 (0.65–1.37) | |
| p-value (log-rank) | 0.7524 | |
| Unstratified HR (95% CI) | 0.92 (0.63–1.34) | |
| 12-Month OS rate (95% CI) | 92.2 (89.6–94.7) | 94.6 (92.5–96.8) |
| 24-Month OS rate (95% CI) | 88.7 (85.7–91.7) | 88.6 (85.6–91.6) |

1 Summaries of $EFS_{eff}$ by Investigator (median, percentiles) are Kaplan-Meier estimates. 95% CI for median was computed using the method of Brookmeyer and Crowley. Hazard ratios were estimated by Cox regression.

2 95% CI for rate were constructed using the Clopper-Pearson method. 95% CI for difference in response rates were constructed using Wilson method.

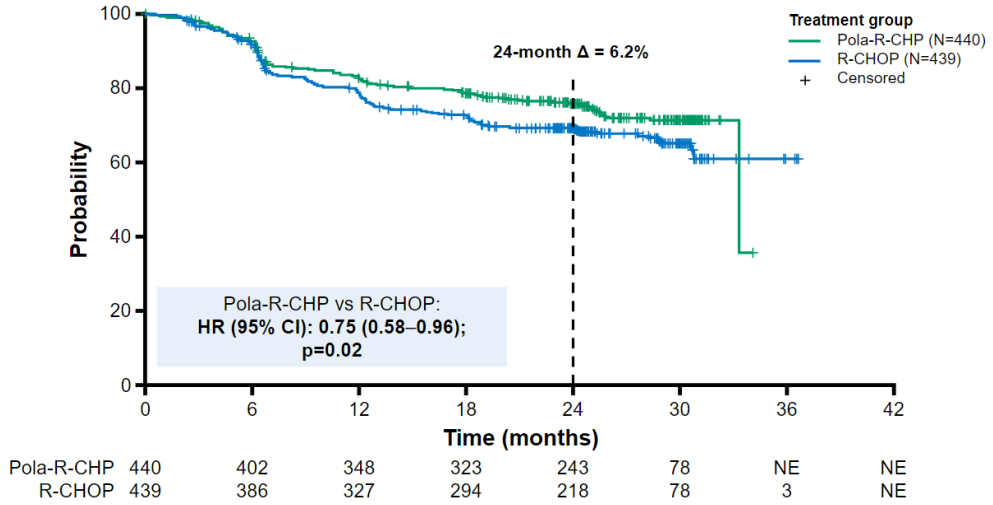
3 Summaries of OS (median, percentiles) are Kaplan-Meier estimates. 95% CI for median was computed using the method of Brookmeyer and Crowley. Hazard ratios were estimated by Cox regression.

Key: CR, complete response; BICR, blinded independent central review; CMH, Cochran-Mantel-Haensze; $EFS_{eff}$, event-free survival for efficacy reasons; HR, hazard ratio; INV, investigator; pola, polatuzumab vedotin; ITT, intent-to-treat; PET-CT, positron emission tomography-computed tomography; R-CHOP, rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisolone; R-CHP, rituximabplus cyclophosphamide, doxorubicin, and prednisolone.

### *Investigator-assessed event-free survival ($EFS_{eff}$)*

At the time of the CCOD, 112 patients (25.5%) in the Pola+R-CHP arm, and 138 patients (31.4%) in the R-CHOP arm had an EFS event. Results of the secondary endpoint $EFS_{eff}$ were statistically significant, highly consistent with results of the primary endpoint of investigator-assessed PFS, and supportive of the clinical benefit for Pola+R-CHP compared with R-CHOP. A statistically significant reduction by 25% in the risk of an $EFS_{eff}$ event was observed in the Pola+R-CHP arm compared with the R-CHOP arm (stratified HR: 0.75 [95% CI: 0.58–0.96], p=0.0244). The KM curves for $EFS_{eff}$ began to separate at approximately 6 months after randomisation in favour of Pola+R-CHP and the separation was maintained for the duration of follow-up (Figure 5).

**Figure 5: Kaplan-Meier plot of investigator-assessed $EFS_{eff}$ (ITT population) (53)**




Subsequent lymphoma therapy was collected as new anti-lymphoma therapy (NALT). Amongst the patients who received NALT, the majority received it after a PFS event. Therefore, $EFS_{eff}$ includes an additional definition of an event as NALT due to efficacy or biopsy-positive lymphoma after study treatment in the absence of a PFS event, which accounts for important clinical considerations in DLBCL where biopsy documented residual disease or additional planned therapies represent undesired efficacy outcomes from treatment.

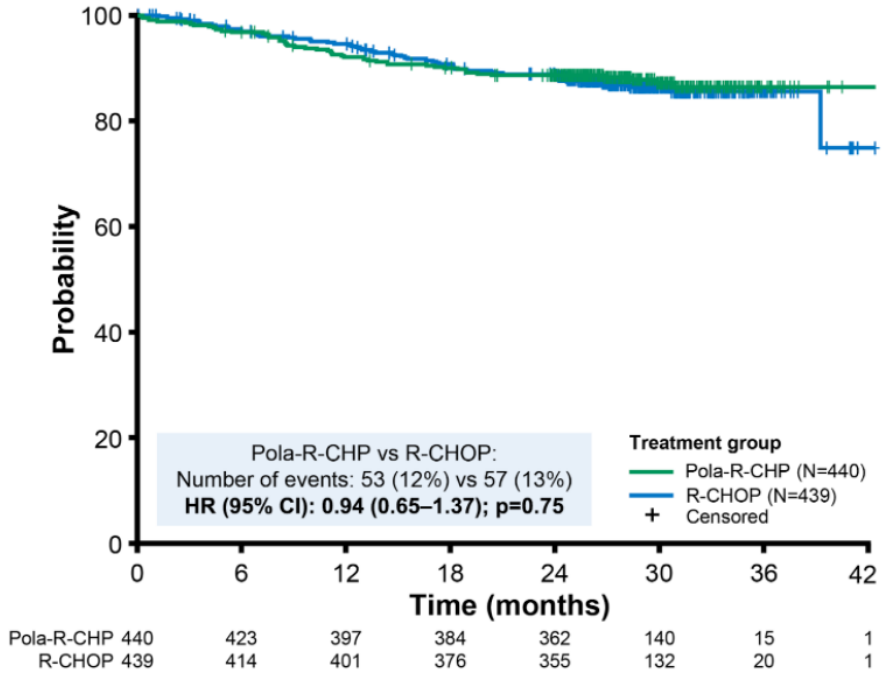
***BICR-assessed complete response rate at end of treatment (by PET-CT)***

At the end of the treatment, BICR-assessed CR rate was high in both arms. A numerically higher proportion of patients treated with Pola+R-CHP had complete response at the end of treatment compared to patients treated with R-CHOP (78.0% [95% CI: 73.79–81.74] vs. 74.0% [95% CI: 69.66–78.07]). The treatment difference was 3.9% (95% CI: -1.9–9.7) and was not statistically significant (p=0.1557).

***Overall survival (OS)***

The frequency of OS events (deaths) were low in both arms. A total of 53 deaths (12.0% patients) were reported in the Pola+R-CHP arm, and 57 deaths (13.0% patients) were reported in the R-CHOP arm. With very few events in both arms, OS results were still immature at the time of the interim analysis of OS and did not meet the pre-specified threshold for statistical significance (stratified HR: 0.94 [95% CI: 0.65–1.37]; p=0.7524). The unstratified analysis of OS showed results similar to the stratified analysis. A KM curve is shown below in Figure 6. Milestone OS results for the Pola+R-CHP arm and the R-CHOP arm were 92.2% and 94.6% at 12-Month, and 88.7% and 88.6% at 24-Month, respectively.

**Figure 6: Kaplan-Meier plot of time to overall survival (ITT population) (53)**




The final OS analysis will be performed (two-sided alpha boundary = 0.04) in the 2nd half of 2022.

***New anti-lymphoma treatment (NALT)***

NALT could be administered after the patient had completed study treatment, and included both radiotherapy or systemically administered therapies. NALT was allowed to be administered with or without a disease progression documented in the patient.

The total number of patients with at least one NALT was higher in the R-CHOP arm (30.3%) compared to the Pola+R-CHP arm (22.5%), consistent with the higher number of patients who had a PFS event (Table 11). Similarly, the total number of NALT treatments administered was higher in the R-CHOP arm (290) compared to the Pola+R-CHP arm (179). The number of patients each receiving radiotherapy, systemic therapy, stem cell transplants and chimeric antigen receptors cell therapy (CAR-T) were also higher in the R-CHOP arm compared to the Pola+R-CHP arm (see Table 11).

The percentage of patients receiving radiotherapy (pre-planned or unplanned) was lower in the Pola+R-CHP group than in the R-CHOP group (9.3% vs. 13.0%), as was the percentage of patients receiving systemic therapy (17.0% vs. 23.5%), including stem-cell transplantation

(3.9% vs. 7.1%) and chimeric antigen receptor (CAR) T-cell therapy (2.0% vs. 3.6%). After disease progression, unblinding was permitted for individual patients, and 8 patients (all in the R-CHOP group) received pola as part of a subsequent therapy.

**Table 11: Follow-up anti-lymphoma treatments (ITT population)**

| | Pola+R-CHP (n=440) | R-CHOP (n=439) |
|---|---|---|
| Total number of patients with at least one subsequent anti-lymphoma treatment, n (%)* | 99 (22.5) | 133 (30.3) |
| Total number of subsequent anti-lymphoma treatments (radiotherapy and systemic), n* | 179 | 290 |
| Total number of radiotherapy treatments, n | 42 | 73 |
| Patients with at least one radiotherapy treatment, n (%) | 41 (9.3) | 57 (13.0) |
| Total number of systemic therapy regimens, n (%)† | 137 | 217 |
| Patients who received at least one systemic therapy | 75 (17.0) | 103 (23.5) |
| Patients who received stem cell transplant | 17 (3.9) | 31 (7.1) |
| Patients who received CAR T-cell therapy | 9 (2.0) | 16 (3.6) |

*Subsequent anti-lymphoma treatment is defined as non-protocol anti-lymphoma therapy (NALT), and does not include intrathecal central nervous system disease prophylaxis as part of treatment; pre-planned radiotherapy is included within radiotherapy here, though is not included as an event in EFS analyses;

†Includes any monotherapy, multi-drug, or cell-based regimen.

Key: CAR, chimeric antigen receptor; EFS, event-free survival; ITT, intention-to-treat.

### *Additional secondary efficacy endpoints (not formally tested)*

The results of additional (non $\alpha$-controlled) secondary endpoints further support pola's positive treatment effect observed on investigator-assessed PFS (Table 12).

**Table 12: Other selected secondary endpoints (not formally tested)**

| | Pola+R-CHP (n=440) | R-CHOP (n=439) |
|---|---|---|
| **Investigator-assessed DOR [1]** | [redacted] | [redacted] |
| Patients with event, n (%) | [redacted] | [redacted] |
| Median DOR - Months (95% CI) | [redacted] | [redacted] |
| Stratified HR (95% CI) | [redacted] | |
| 12-Month DOR rate (95% CI) | [redacted] | [redacted] |
| 24-Month DOR rate (95% CI) | [redacted] | [redacted] |
| **Investigator-assessed BOR [2]** | [redacted] | [redacted] |
| Responders, n (%) [95% CI] | [redacted] | [redacted] |
| CR, n (%) [95% CI] | [redacted] | [redacted] |
| **Investigator-assessed DFS [1]** | n=381 | n=363 |
| Patients with event, n (%) | 62 (16.3%) | 79 (21.8%) |
| Median DFS - Months (95% CI) | 30.5 (30.5–NE) | NE (NE) |
| Stratified HR (95% CI) | 0.70 (0.50–0.98) | |
| 12-Month DFS rate (95% CI) | 90.08 (87.04–93.11) | 83.36 (79.45–87.27) |
| 24-Month DFS rate (95% CI) | 81.79 (77.43–86.15) | 77.35 (72.73–81.96) |

[1] Summaries of $EFS_{all}$/DFS/DOR by investigator (median, percentiles) were Kaplan-Meier estimates. 95% CI for median was computed using the method of Brookmeyer and Crowley. Hazard ratios were estimated by Cox regression.

[2] 95% CI for rate were constructed using the Clopper-Pearson method. 95% CI for difference in response rates were constructed using Wilson method.

Key: BOR, best overall response; DFS, disease-free survival; DOR, duration of response.

***Investigator-assessed duration of response (DOR) and best overall response (BOR)***

In patients who achieve partial or complete response (PR or CR), DOR favoured Pola+R-CHP compared to R-CHOP (stratified HR 0.74 [95% CI: 0.56–0.98]). Treatment with Pola+R-CHP reduced the risk of progression or death in patients with a CR or PR by 26% compared to patients with a CR or PR who received treatment with R-CHOP. BOR showed high response rates (i.e. best response of CR or PR while on study) in both the Pola+R-CHP arm [redacted] and the R-CHOP arm [redacted]. Treatment difference was [redacted] in favour of Pola+R-CHP.

***Investigator-assessed disease-free survival (DFS)***

In patients who achieve CR, the favourability of the Pola+R-CHP arm compared to the R-CHOP arm in DFS suggests that even though CR was high in both treatment arms, remission status was more durable in the Pola+R-CHP arm; treatment with Pola+R-CHP reduced the risk of progression or death by 30% compared to treatment with R-CHOP (stratified HR 0.70 [95% CI: 0.50–0.98]).

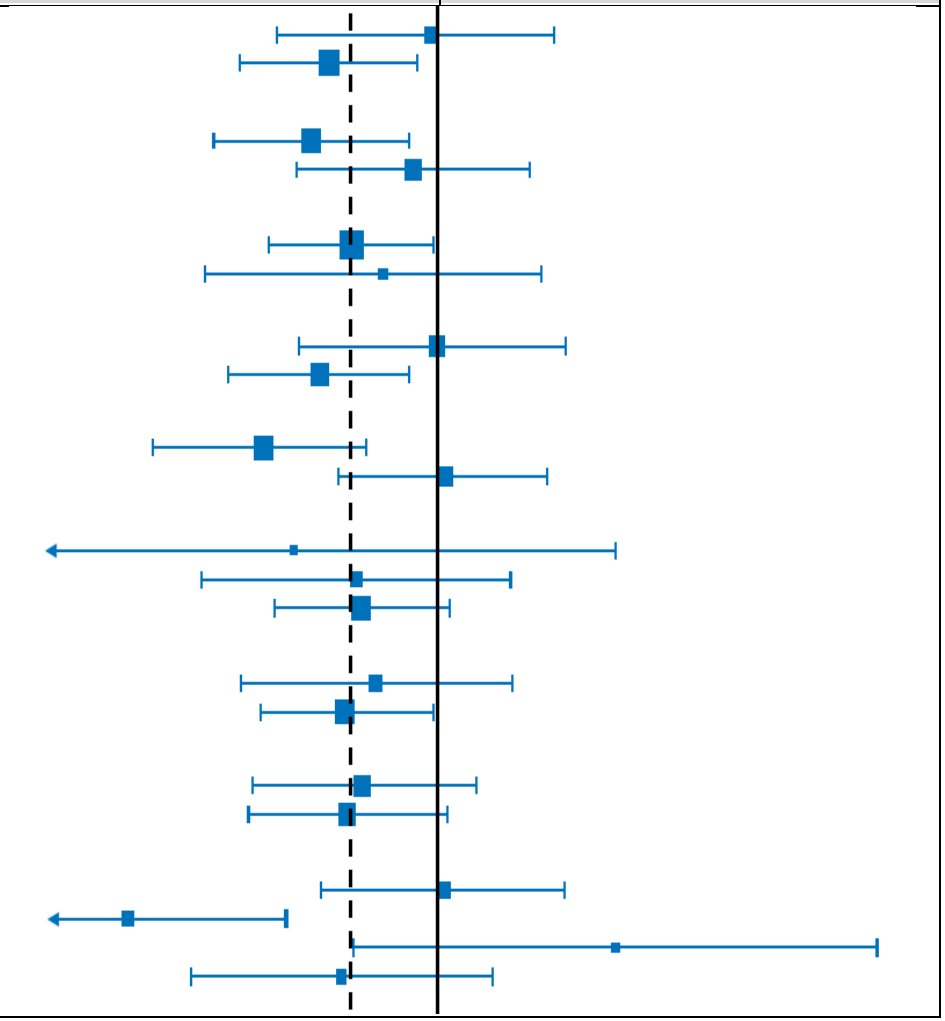
## *B.2.7 Subgroup analysis*

POLARIX was not designed or powered to compare patient subgroups. The univariate INV-PFS subgroup analyses were exploratory, unstratified, pre-planned, and signal seeking. There was a directionally consistent treatment effect supporting the PFS benefit of Pola+R-CHP in the majority of subgroups (HR<1), including patient demographic and patient characteristics, local histopathologic diagnosis, and centrally tested biologic subgroups (Table 13). Additionally, all subgroups included a confidence interval that favoured Pola+R-CHP. However, event numbers and sample size were limited, and the balance of patient baseline characteristics in the study arms might not be retained in the subgroups.

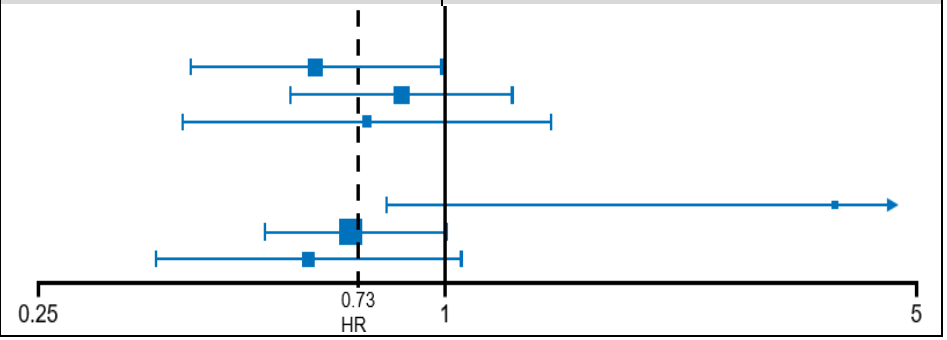
Given the known limitations of the exploratory subgroup analyses, results should not be over-interpreted and there was no statistical evidence for heterogeneity of treatment effect in any of the subgroups. Further biomarker analyses are ongoing to better understand the observed differences in the study population.

**Table 13: Investigator-assessed PFS by subgroup (unstratified)**

| Baseline risk factors | N | Pola+R-CHP (n=440) | | R-CHOP (n=439) | | Hazard ratio | 95% Wald CI |
|---|---|---|---|---|---|---|---|
| | | n | 2-year rate | n | 2-year rate | | |
| **Age group** | | | | | | | |
| ≤60 | 271 | 140 | 74.1 | 131 | 71.9 | 0.9 | 0.6–1.5 |
| >60 | 608 | 300 | 77.9 | 308 | 69.5 | 0.7 | 0.5–0.9 |
| **Sex** | | | | | | | |
| Male | 473 | 239 | 75.9 | 234 | 65.9 | 0.7 | 0.5–0.9 |
| Female | 406 | 201 | 77.7 | 205 | 75.2 | 0.9 | 0.6–1.4 |
| **ECOG PS** | | | | | | | |
| 0–1 | 737 | 374 | 78.4 | 363 | 71.2 | 0.8 | 0.6–1.0 |
| 2 | 141 | 66 | 67.2 | 75 | 65.0 | 0.8 | 0.5–1.4 |
| **IPI score** | | | | | | | |
| IPI 2 | 334 | 167 | 79.3 | 167 | 78.5 | 1.0 | 0.6–1.6 |
| IPI 3–5 | 545 | 273 | 75.2 | 272 | 65.1 | 0.7 | 0.5–0.9 |
| **Bulky disease** | | | | | | | |
| Absent | 494 | 247 | 82.7 | 247 | 70.7 | 0.6 | 0.4–0.8 |
| Present | 385 | 193 | 69.0 | 192 | 69.7 | 1.0 | 0.7–1.5 |
| **Ann Arbor stage** | | | | | | | |
| I–II | 99 | 47 | 89.1 | 52 | 85.5 | 0.6 | 0.2–1.8 |
| III | 232 | 124 | 80.7 | 108 | 73.6 | 0.8 | 0.5–1.3 |
| IV | 548 | 269 | 72.6 | 279 | 66.1 | 0.8 | 0.6–1.1 |
| **Baseline LDH** | | | | | | | |
| ≤ULN | 300 | 146 | 78.9 | 154 | 75.6 | 0.8 | 0.5–1.3 |
| >ULN | 575 | 291 | 75.4 | 284 | 67.2 | 0.7 | 0.5–1.0 |
| **No. of extranodal sites** | | | | | | | |
| 0–1 | 453 | 227 | 80.2 | 226 | 74.5 | 0.8 | 0.5–1.1 |
| ≥2 | 426 | 213 | 73.0 | 213 | 65.8 | 0.7 | 0.5–1.0 |
| **Cell-of-origin** | | | | | | | |
| GCB | 352 | 184 | 75.1 | 168 | 76.9 | 1.0 | 0.7–1.5 |
| ABC | 221 | 102 | 83.9 | 119 | 58.8 | 0.4 | 0.2–0.6 |
| Unclassified | 95 | 44 | 73.0 | 51 | 86.2 | 1.9 | 0.8–4.5 |
| Unknown | 211 | 110 | 73.8 | 101 | 64.3 | 0.7 | 0.4–1.2 |



| Baseline risk factors | N | Pola+R-CHP (n=440) | | R-CHOP (n=439) | | Hazard ratio | 95% Wald CI | Pola+R-CHP better | R-CHOP better |
|---|---|---|---|---|---|---|---|---|---|
| | | n | 2-year rate | n | 2-year rate | | | | |
| **Double expressor by IHC** | | | | | | | | | |
| DEL | 290 | 139 | 75.5 | 151 | 63.1 | 0.6 | 0.4–1.0 | | |
| Non DEL | 438 | 223 | 77.7 | 215 | 75.7 | 0.9 | 0.6–1.3 | | |
| Unknown | 151 | 78 | 76.0 | 73 | 69.8 | 0.8 | 0.4–1.5 | | |
| **Double- or triple-hit lymphoma** | | | | | | | | | |
| Yes | 45 | 26 | 69.0 | 19 | 88.9 | 3.8 | 0.8–17.6 | | |
| No | 620 | 305 | 76.8 | 315 | 70.3 | 0.7 | 0.5–1.0 | | |
| Unknown | 214 | 109 | 78.5 | 105 | 66.4 | 0.6 | 0.4–1.1 | | |




Key: ECOG PS, Eastern Cooperative Oncology Group - Scale of Performance Status; IHC, immunohistochemistry; IPI, International Prognostic Index; LDH, lactate dehydrogenase.

## *B.2.8 Meta-analysis*

No meta-analysis was conducted for this submission.

## *B.2.9 Indirect and mixed treatment comparisons*

No indirect and mixed treatment comparisons were conducted for this submission.

## *B.2.10 Adverse reactions*

### B.2.10.1 Overview of safety

Out of the 879 patients randomised in the study, 873 received treatment (435 in the Pola+R-CHP arm; 438 in the R-CHOP arm) and were included in the safety-evaluable population.

Pola in combination with R-CHP in patients with previously untreated DLBCL was generally well tolerated and toxicities were manageable. The safety profile of the Pola+R-CHP regimen was comparable to R-CHOP and in line with the known safety profiles of each individual component and the underlying disease. A comparable incidence of AEs leading to any treatment discontinuations between the treatment arms was noted and a lower incidence of AEs leading to any dose reductions in the Pola+R-CHP arm driven by fewer dose reductions due to peripheral neuropathy (PN) was noted, demonstrating that tolerability of Pola+R-CHP was comparable and descriptively better than that of R-CHOP. No new safety signals were identified.

Overall safety findings are summarised below and a summary of key AE-related safety is presented in Table 14:

- The incidence of AEs of any grade in patients in the Pola+R-CHP arm (97.9%) was comparable with the R-CHOP arm (98.4%).
- The most common AEs (AEs affecting over 50% of patients) by System Organ Class (SOC) in either treatment arm (with percentages expressed as Pola+R-CHP vs. R-CHOP) were: [redacted].
- The most common AEs by Preferred Term (PT) (reported by at least 20% of patients in either arm, with percentages expressed as Pola+R-CHP vs. R-CHOP) were: nausea (41.6% vs 36.8%), neutropenia (30.8% vs 32.6%), constipation (28.7% vs

29.0%), anaemia (28.7% vs 26.0%), fatigue (25.7% vs 26.5%), diarrhoea (30.8% vs 20.1%), alopecia (24.4% vs 24.0%), PN (24.1% vs 22.6%), and peripheral sensory neuropathy (19.5% vs 21.5%).

- [redacted].
- The incidence of Grade 5 AEs was comparable between Pola+R-CHP (3.0%) and R-CHOP (2.3%). Most of the Grade 5 AEs in both arms were due to infections or complications of infection.
- The incidence of SAEs was comparable between Pola+R-CHP (34.0%) and R-CHOP (30.6%). The most common SAE in the Pola+R-CHP and R-CHOP arms (≥5% of patients in either arm) was [redacted].
- The proportion of patients who experienced AEs leading to discontinuation of any study treatment in the Pola+R-CHP arm (6.2%) was comparable to the R-CHOP arm (6.6%).
- The proportion of patients who experienced AEs leading to discontinuation of pola study treatment in the Pola+R-CHP arm (4.4%) was comparable to the proportion of patients who experienced AEs leading to discontinuation of vincristine study treatment in the R-CHOP arm (5.0%).
  [redacted] This difference was primarily driven by a higher incidence of AEs related to PN in the R-CHOP arm.
- The proportion of patients who experienced AEs leading to any study treatment dose reduction was lower in the Pola+R-CHP arm (9.2%) compared to the R-CHOP arm (13.0%).
  [redacted]

**Table 14: POLARIX safety profile (safety-evaluable population)**

| AE, n (%) | Pola+R-CHP (n=435) | R-CHOP (n=438) |
|---|---|---|
| Any-grade AEs | 426 (97.9) | 431 (98.4) |
| Grade 3–4 AEs | [redacted] | [redacted] |
| SAEs | 148 (34.0) | 134 (30.6) |
| Grade 5 AEs | 13 (3.0) | 10 (2.3) |
| AEs leading to treatment discontinuation | | |
| Any treatment | 27 (6.2) | 29 (6.6) |
| Polatuzumab vedotin/vincristine | 19 (4.4) | 22 (5.0) |
| AEs leading to dose reduction (any treatment) | 40 (9.2) | 57 (13.0) |

Key: AE, adverse event; SAE, serious adverse event.

***Exposure to study treatment***

Overall, the majority of patients treated with Pola+R-CHP and R-CHOP received their planned doses of chemotherapy.

[redacted]

For the investigational agents that were administered in a blinded fashion, a higher number of patients received all six planned doses of pola in the Pola+R-CHP arm (91.7% [435 patients]) compared to the number of patients who received all six planned doses of vincristine in the R-CHOP arm (88.5% [436 patients]).

Patients in the Pola+R-CHP arm received a median of 6 cycles of pola (range 1-6), corresponding to a median treatment duration of [redacted]. A total of 91.7% (399 patients) received 6 cycles of pola treatment.

[redacted]

Patients in the R-CHOP arm received a median of 6 cycles of vincristine (range 1–6), corresponding to a median treatment duration of [redacted]. A total of 88.5% (386 patients) received 6 cycles of vincristine treatment.

[redacted]

### B.2.10.2 Adverse events (AEs)

The proportion of patients with at least one AE in the pola+R-CHP arm (97.9% [426 patients]) was comparable to the R-CHOP arm (98.4% [431 patients]).

The most common AEs (≥ 50% of patients in either arm) by SOC were (Pola+R-CHP arm and R-CHOP arm, respectively):

The most commonages (≥10% of patients in either arm) by PT are shown in Table 15.

AEs by PT with a difference (≥5%) in incidence between the Pola+R-CHP and R-CHOP arms were diarrhea (30.8% vs. 20.1%) and febrile neutropenia (14.3% vs. 8.0%). All other AEs occurred with a less than 5% difference in incidence between treatment arms.

**Table 15: Summary of AEs with an incidence rate of at least 10% by preferred term (safety-evaluable population)**

| MedDRA preferred terms | Pola+R-CHP (n=435) | R-CHOP (n=438) |
|---|---|---|
| Nausea | 181 (41.6%) | 161 (36.8%) |
| Neutropenia | 134 (30.8%) | 143 (32.6%) |
| Constipation | 125 (28.7%) | 127 (29.0%) |
| Anaemia | 125 (28.7%) | 114 (26.0%) |
| Fatigue | 112 (25.7%) | 116 (26.5%) |
| Diarrhoea | 134 (30.8%) | 88 (20.1%) |
| Alopecia | 106 (24.4%) | 105 (24.0%) |
| [redacted] | [redacted] | [redacted] |
| [redacted] | [redacted] | [redacted] |
| Decreased appetite | 71 (16.3%) | 62 (14.2%) |
| Vomiting | 65 (14.9%) | 63 (14.4%) |
| Pyrexia | 68 (15.6%) | 55 (12.6%) |
| Headache | 56 (12.9%) | 57 (13.0%) |
| Cough | 56 (12.9%) | 53 (12.1%) |

| | | |
|---|---|---|
| Weight decreased | 55 (12.6%) | 52 (11.9%) |
| Asthenia | 53 (12.2%) | 53 (12.1%) |
| Dysgeusia | 49 (11.3%) | 57 (13.0%) |
| Febrile neutropenia | 62 (14.3%) | 35 (8.0%) |
| [redacted] | [redacted] | [redacted] |
| [redacted] | [redacted] | [redacted] |

Percentages are based on 'n' in the column headings. For frequency counts by preferred term, multiple occurrences of the same AE in an individual are counted only once. Includes treatment-emergent AEs during AE reporting period only, which is defined as new or worsening AE from the first dose of any study drug through 90 days after the last dose of any study drug or prior to NALT, whichever is earlier.

***Serious adverse events (SAEs)***

The proportion of patients with at least one SAE in the Pola+R-CHP arm (34.0% [148 patients]) was comparable with the R-CHOP arm (30.6% [134 patients]).

SAEs were most commonly reported (≥5% of patients in either arm) in the following SOCs (Pola+R-CHP arm and R-CHOP arm, respectively):

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

A summary of the most common SAEs (≥1% of patients in either arm) by PT is shown in Table 16. The most common PTs are contained within the most commonly reported SOCs.

The only SAEs by PT with differences (≥1% between the arms) were (Pola+R-CHP arm and R-CHOP arm, respectively):

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

No patients in either treatment arm discontinued study treatment due to the SAEs of febrile neutropenia, diarrhea or urinary tract infection.

**Table 16: Summary of SAEs with an incidence rate of at least 1% (safety-evaluable population)**

| MedDRA Preferred Term | Pola+R-CHP (n=435) | R-CHOP (n=438) |
|---|---|---|
| [redacted] | [redacted] | [redacted] |
| [redacted] | [redacted] | [redacted] |
| [redacted] | [redacted] | [redacted] |
| [redacted] | [redacted] | [redacted] |
| [redacted] | [redacted] | [redacted] |
| [redacted] | [redacted] | [redacted] |
| [redacted] | [redacted] | [redacted] |
| [redacted] | [redacted] | [redacted] |
| [redacted] | [redacted] | [redacted] |
| [redacted] | [redacted] | [redacted] |

Percentages are based on n in the column headings. For frequency counts by preferred term, multiple occurrences of the same AE in an individual are counted only once. Includes treatment-emergent AEs during AE reporting period only, which is defined as new or worsening AE from the first dose of any study drug through 90 days after the last dose of any study drug or prior to NALT, whichever is earlier.

***Adverse events of particular interest (AEPIs)***

AEPIs are identified or potential risks of pola for which additional analyses are presented to support the benefit-risk assessment. AEPIs were generally comparable between the Pola+R-CHP and R-CHOP arms, with some numerical differences in certain AEPI categories but the overall safety profile was consistent with the known safety profile of each drug as well as the underlying disease.

**<u>Neutropenia, including febrile neutropenia</u>**

[redacted]

[redacted] No Grade 5 neutropenia events were reported.

[redacted]

Neutropenia is an identified risk and an adverse drug reaction of pola, which partially explains the higher incidence of febrile neutropenia in the Pola+R-CHP arm. The relatively lower incidence of prophylactic granulocyte colony-stimulating factor (G-CSF) use in the Pola+R-CHP (90.1%) arm compared to the R-CHOP (93.2%) arm may partially contribute to the higher incidence of febrile neutropenia in Pola+R-CHP arm. The higher incidence of

febrile neutropenia in the Pola+R-CHP arm did not lead to an increase in study treatment discontinuations, dose reductions or study treatment interruptions compared with the R-CHOP arm.

[redacted]

**Peripheral neuropathy (PN)**

The overall incidence of PN was comparable between the Pola+R-CHP and R-CHOP arms (52.9% vs 53.9%).

[redacted]

A later time to onset of PN events in the Pola+R-CHP arm compared with the R-CHOP arm, in combination with a similar median time to PN resolution between the treatment arms, likely contributed to more patients with unresolved PN events in the Pola+R-CHP arm at the time of CCOD. This is consistent with the observations from the PRO data on PN, which descriptively suggest later time to onset and lower severity of PN events in the Pola+R-CHP arm compared with the R-CHOP arm.

**Anaemia**

The incidence, seriousness and reversibility of anaemia events were comparable between the Pola+R-CHP and R-CHOP arms. The majority of anaemia events were Grade 1 or 2. A slightly higher incidence of Grade 3–4 anaemia was observed in the Pola+R-CHP arm compared to R-CHOP arm (12.0% vs 8.4%), however this did not lead to an increase in study treatment discontinuation, dose reduction or treatment interruptions compared with the R-CHOP arm. The majority of the anaemia events were reported as resolved as of the clinical cut-off date.

***Deaths***

At the time of CCOD on 28 June 2021,

[redacted]

[redacted]

[redacted]

[redacted]

- [redacted]

- [redacted]

***Safety conclusion***

Overall, the Pola+R-CHP regimen in patients with previously untreated DLBCL achieved a safety profile consistent with the known risks of each individual component and the underlying disease, and no new safety signals were identified. The safety profile of the Pola+R-CHP combination was comparable to that of R-CHOP. Numerically fewer patients experienced dose reductions due to AEs in the Pola+R-CHP arm compared to the R-CHOP arm and were driven by fewer dose reductions due to PN. The data in this double-blinded study suggests that the safety and tolerability of Pola+R-CHP was comparable to that of R-CHOP, a regimen that is generally well-tolerated and typically administered in the outpatient setting.

## B.2.11 Ongoing studies

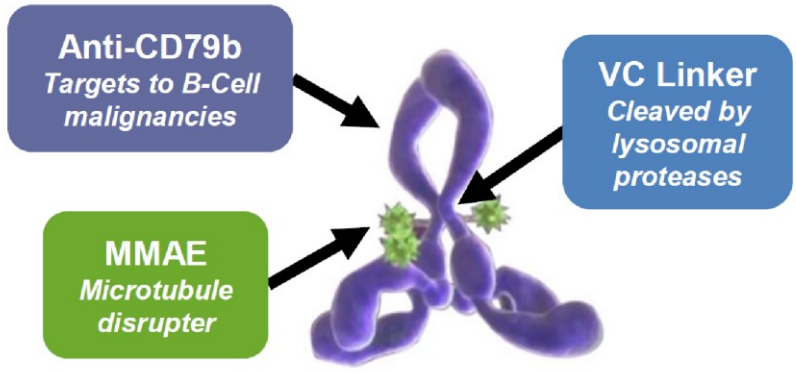
The POLARIX study design stipulated that all patients be followed for at least 24 months after treatment initiation, which covers the period when most of the disease relapses occurred, thus ensuring that the observed treatment benefits of pola were reliable, particularly with respect to the primary endpoint of PFS. After completion of therapy, all patients were followed at clinic visits conducted every 3 months for 24 months, and then every 6 months until Month 60. Final analyses are planned for PFS in the ITT population and OS (which were immature at the time of the interim analysis).

## B.2.12 Innovation

### *Mode of action*

Polatuzumab vedotin (pola) is an anti-CD79b antibody-drug conjugate (ADC). 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 (55). 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 (56). 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 (57).

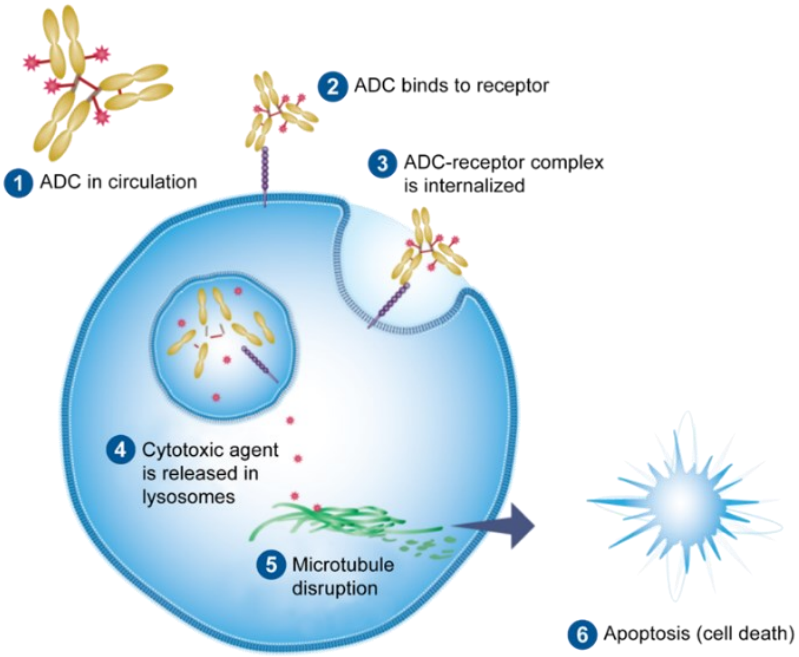
**Figure 7: Polatuzumab vedotin molecule**




The pola molecule consists of a potent anti-mitotic agent (monomethyl auristatin E [MMAE]) covalently attached to a CD79b directed humanised IgG1 monoclonal antibody through a protease cleavable linker, maleimidocaproyl valine citrulline p aminobenzyloxycarbonyl (7) (Figure 7). 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. Pola is the only ADC targeting CD79b, which allows it to preferentially deliver MMAE to B cells, resulting in anti-cancer activity against B cell malignancies. 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 (Figure 8). 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 (2, 6). 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**




***Unmet need***

Since the introduction of R-CHOP, there has been no advancement in treatment options for previously untreated DLBCL patients for over 20 years. 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 (58) (see Section B.1.3.2). Patients who achieved a complete response (CR) after 1L treatment have demonstrated significant improvements in QoL compared to non-complete responders (30). However, approximately half of the patients will not respond to subsequent therapy because of refractory disease (34), and a significant number are ineligible for this intensive therapy because of age, comorbidities or chemotherapy-insensitive disease (34, 59).

Following 1L treatment failure, patients experience even greater anxiety due to the poorer prognosis of their condition and the need for further, often more intensive treatment as they enter the refractory/relapse space. Patients with high grade NHL demonstrated 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 (31). This is partly related to uncertainties towards the prognosis of their disease, side effects of treatment and fear of relapse (33), especially given the disappointing efficacy of standard salvage regimens prior to transplant (34). This will also increase the demand on hospital services and the use of skilled nursing facilities and hospice services (35).

Additionally, the use of rituximab-containing 1L therapy may be making it more difficult to salvage patients who have entered the relapse/refractory space. The CORAL study demonstrated that among patients who had failed initial induction, those who had been exposed to rituximab were 28% less likely to proceed to second randomisation (60). The 3-year EFS was merely 21% in patients who were refractory or had experienced relapse <1 year after R-CHOP. The ORCHARRD study attempted to explore the potential of ofatumumab, an anti-CD20 monoclonal mAb that targets a different epitope to rituximab, though no difference in efficacy was found between ofatumumab and rituximab as salvage treatment for relapsed/refractory DLBCL (61). The chance for long-term cure in DLBCL diminishes with each subsequent line of therapy; therefore, obtaining the best possible outcome for previously untreated patients is of critical importance.

POLARIX is the first trial in over 20 years to show a meaningful improvement in the benefit-risk profile over R-CHOP in an international Phase III double-blind, randomised controlled trial. In the randomised phase of the study, Pola+R-CHP clearly demonstrated a statistically significant and clinically meaningful INV-PFS improvement over R-CHOP in the ITT population, inclusive of high-risk subpopulations with poor prognostic factors. The observed HR of 0.73 represents a 27% decrease in relative risk of disease progression, relapse, or death; or, in other words, Pola+R-CHP spares approximately 1 out of 4 patients who would otherwise have a PFS event with R-CHOP from having that event. The avoidance of PFS events represents curative outcomes for previously untreated patients with DLBCL: patients avoid experiencing all of disease relapse, disease progression, and death from any cause.

At the 24-Month mark, treatment with Pola+R-CHP resulted in a higher proportion of patients alive and progression-free compared to R-CHOP (76.7% vs 70.2%, respectively). The PFS results from the POLARIX study are considered sufficiently mature and are not likely to change appreciably with longer follow-up based on the magnitude of treatment effect observed with Pola+R-CHP over R-CHOP, and the stability of HR estimates.

[redacted]

### *B.2.13 Interpretation of clinical effectiveness and safety evidence*

The POLARIX study was a robust Phase III study that included a large global patient population with well-balanced baselines characteristics between treatment arms, standardised chemotherapy regimen, and standardised endpoints powered to show differences between treatment arms. The trial was conducted in accordance with the Good Clinical Practice (GCP) guidelines of the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) and the principles of the Declaration of Helsinki (DoH). Safety data was reviewed regularly by an independent Data and Safety Monitoring Committee during the conduct of the trial.

POLARIX met its primary endpoint, demonstrating a statistically significant and clinically meaningful improvement in investigator-assessed PFS following treatment with Pola+R-CHP, compared to R-CHOP, in patients with previously untreated DLBCL. Treatment with Pola+R-CHP resulted in a 27% reduction in the risk of progression/relapse, or death, compared with treatment with R-CHOP (stratified HR: 0.73 [95% CI: 0.57–0.95]; two-sided log-rank p-value=0.0177, two-sided $\alpha$=0.05). A clear separation of the Kaplan-Meier curves after 6 months favouring Pola+R-CHP over R-CHOP treatment was observed. The separation was maintained and continued to widen during follow-up. On the basis of Kaplan-Meier estimates, treatment with Pola+R-CHP resulted in a higher proportion of patients alive and progression-free compared to R-CHOP at 12-Month (83.9% vs 79.8%). The estimated 24-Month INV-assessed PFS was 76.7% in patients treated with Pola+R-CHP compared to 70.2% in patients treated with R-CHOP (absolute difference of 6.5% [95% CI: 0.52–12.5]).

Results of the secondary endpoint $EFS_{eff}$, were statistically significant and highly consistent with the primary endpoint of INV-assessed PFS results and supportive of clinical benefit for Pola+R-CHP compared with R-CHOP. BICR-assessed CR rates at end of treatment (by PET-CT), although not statistically significant, numerically favour Pola+R-CHP compared to R-CHOP. While there was numeric improvement in the CR-rate by BICR favouring the Pola+R-CHP arm, the durability of responses for patients who achieve a CR, and patients who achieve CR or partial response (PR) favoured the Pola+R-CHP arm compared to R-CHOP in terms of disease-free survival (DFS) and duration of response (DOR) analyses.

The median follow-up in the POLARIX study was 28.2 months, which was not long enough to observe any effect of the PFS benefit on OS. However, other studies have indicated that PFS and 24-Month EFS are often surrogates for OS in patients with DLBCL (63, 64). OS results were immature at this interim analysis and will require longer-term follow-up and patients will be monitored as survival data matures.

The safety profile of Pola+R-CHP in patients with previously untreated DLBCL was generally well-tolerated with manageable toxicities. It was comparable to R-CHOP and in line with the known safety profiles of each individual component and the underlying disease. No new safety signals were identified. The incidence of adverse events of any grade in patients in the Pola+R-CHP arm (97.9%) was comparable with the R-CHOP arm (98.4%). Incidences of any grade AEs, Grade 3–4 AEs, Grade 5 AEs and SAEs were comparable between the treatment arms. Most of the fatal AEs in both arms were due to infections or complications of infection. The incidence of Grade 5 AEs observed in POLARIX was similar to that observed in other randomised Phase III studies involving R-CHOP in 1L DLBCL (e.g. GOYA, PHOENIX and ROBUST ((45), (65), and (66), respectively).

In this double-blind study, drug delivery was not impeded by the replacement of vincristine with polatuzumab vedotin. The delivery of rituximab, doxorubicin, and cyclophosphamide was maintained, with median relative dose intensities of greater than 99% in both treatment groups. Moreover, the percentage of patients who received all the planned doses of polatuzumab vedotin was slightly higher than the percentage who received all the planned doses of vincristine (91.7% in the Pola+R-CHP group and 88.5% in the R-CHOP group), and fewer patients in the Pola+R-CHP group than in the R-CHOP group had adverse events that led to dose reductions.

Regarding the AEPIs discussed in B.2.10.2, the majority of cases of peripheral neuropathy were Grade 1 with similar incidence and severity in the two treatment groups. The occurrence of peripheral neuropathy is expected in patients treated with antibody-drug conjugates containing MMAE and has been described in a study of single-agent polatuzumab vedotin (1) and in studies of polatuzumab vedotin in combination with other agents (67-69).

Although the incidence of febrile neutropenia was higher among patients who received Pola+R-CHP than among those who received R-CHOP in the POLARIX trial (14.3% vs. 8.0%), this finding did not translate into a higher overall incidence of infection, treatment discontinuation, or dose reductions and was similar to the percentages reported in recent R-CHOP trials (9.0–15.2%) (45, 65, 66).

## B.3 Cost effectiveness

**Summary of cost-effectiveness analysis for Pola+R-CHP vs R-CHOP**

- No published economic analyses were identified for polatuzumab vedotin or the comparators in the NICE final scope in DLBCL; therefore, a *de novo* cost-effectiveness model was developed.
- A cure mixture model was built to evaluate the cost-effectiveness of Pola+R-CHP vs. R-CHOP.
- The model possesses a cycle length of 1 week, a lifetime (60 year) time horizon and costs and benefits discounted at 3.5% as per the NICE reference case (70).
- In the base case, R-CHOP was selected as the comparator to Pola+R-CHP, as it was deemed representative of current standard of care for DLBCL patients in the UK, and a robust comparison to Pola+R-CHP using data from the randomised POLARIX trial was possible.
- Survival analysis was performed to identify appropriate parametric survival functions to extrapolate PFS and OS. A cure mixture model was 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 POLARIX KM data and plausibility of the long-term extrapolations, the generalised gamma distribution was selected for the base case for PFS and OS. The OS extrapolation was informed by the 'cure fraction' for PFS.
- Base case utilities were modelled by health state and used from the GOYA trial (weighted). AE disutilities were applied based on CTCAE Grade $\geqslant$3 AEs from POLARIX and were sourced from recent NICE appraisals. Patients who remained in PFS for >2 years reverted to age- and sex-matched general population utilities.
- Categories of costs included in the model were acquisition, administration, supportive care and subsequent treatment costs. Costs were sourced from NHS Reference Costs 2019-2020, PSSRU 2019, and the BNF and eMIT (both accessed December 2021). Patients who remained in PFS for >2 years no longer accrued supportive care costs. Alternative scenarios were explored in the scenario analysis.
- The base case acquisition costs for polatuzumab vedotin were based on the availability of both 140 mg and 30 mg vials.
- The base case results of the analysis Pola+R-CHP vs R-CHOP produced an ICER of £34,398 per QALY. This was driven by the greater QALY gain vs R-CHOP and

the reduction in supportive care costs and subsequent treatment costs accrued by R-CHOP patients.

- The DSA and scenario analyses demonstrated the robustness of the base case results. The DSA did not identify any parameters that resulted in a significant change in the ICER range relative to 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. Alternative survival modelling extrapolations statistically, visually and clinically underestimated the long-term survival benefit of Pola+R-CHP and R-CHOP.

- 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+R-CHP is a cost-effective treatment option vs R-CHOP, which may be considered representative of standard of care for 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 H.

## *B.3.2 Economic analysis*

No published cost-effectiveness analyses were available for the technology or comparator regimens identified in the scope, therefore, a de novo economic model was developed using an area under der curve model (AUC) approach to inform decision-making.

### B.3.2.1 Patient population

The patient population included in the economic evaluation includes adults with untreated DLBCL. This is in line with the proposed marketing authorisation and the decision problem addressed in this submission. The main body of clinical evidence for Pola+R-CHP compared to R-CHOP is derived from the POLARIX trial (71).

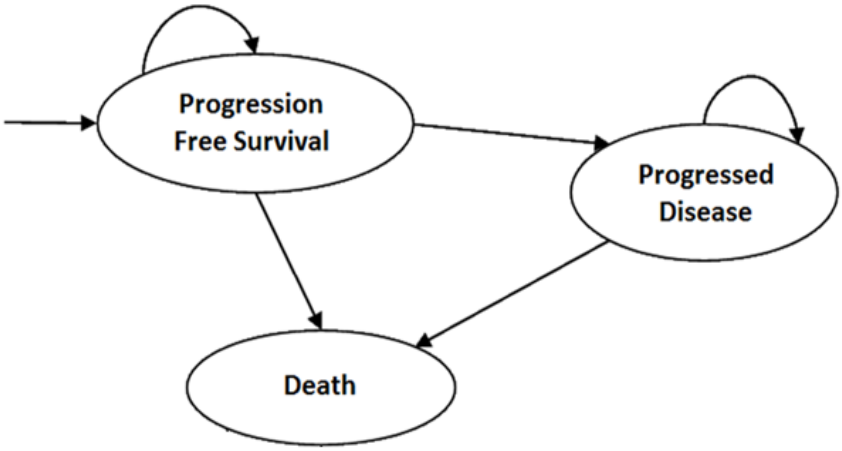
### B.3.2.2 Model structure

An AUC or partitioned survival model (PSM) was developed in Microsoft Excel. The AUC model structure is in line with NICE Decision Support Unit (DSU) guidance and is consistent with previous appraisals conducted in the relapse refractory (RR) disease setting. 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 survival profile of patients treated with Pola+R-CHP.

The model includes three mutually exclusive health states: “progression-free (PF)”, “progressed disease (PD)” and “death” as shown in Figure 9.

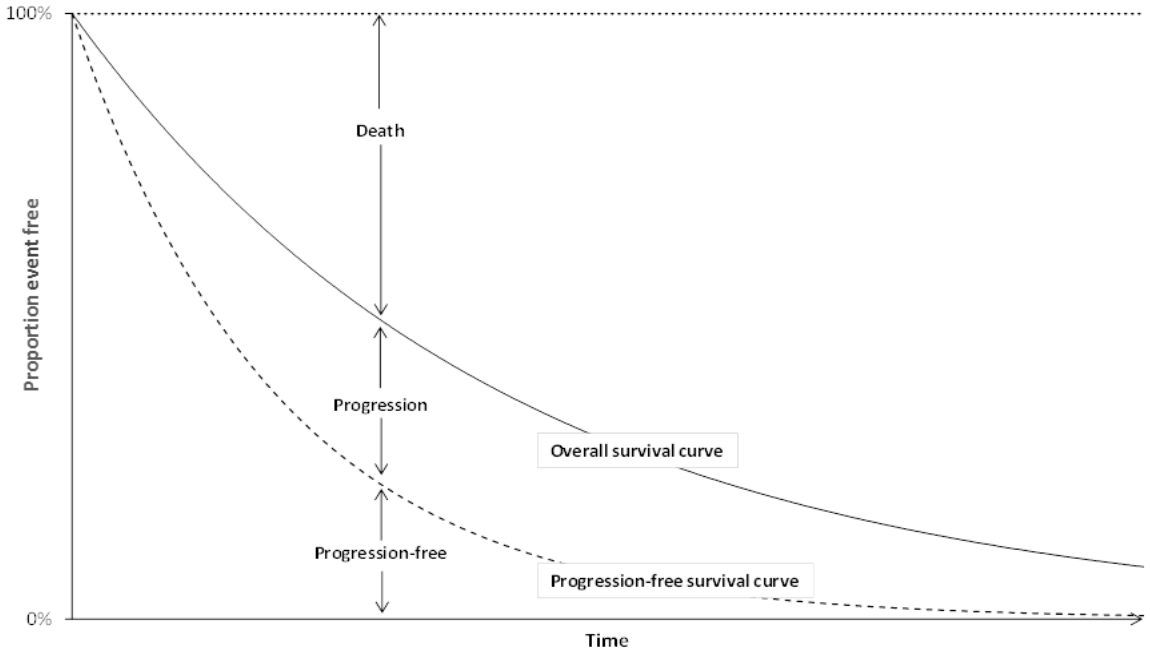
**Figure 9: Economic model structure**




All patients enter the model in the PF 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 PF), 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 into “PF” and “PD” at discrete time points, based on the PFS and OS curves from POLARIX. The proportion of patients falling into the PF health state is represented by those patients in PFS. 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.3.4.

**Figure 10: Example of a partitioned survival model**




Key: PSM, Partitioned survival model.

### Features of the *de novo* analysis

For each health state, a specific cost (Section B.3.5) and utility (Section B.3.4.5) is assigned for each time period (represented by a model cycle). Treatment costs are modelled by time-to-off treatment (TTOT) (71). Costs and utilities are multiplied by state occupancy to calculate the weighted costs and quality-adjusted life years (QALYs) per cycle. These can be added across all cycles in the model time horizon to find the total costs and QALYs. These in turn can be used to calculate the model results of the incremental cost per life years gained (LYG) and the incremental cost per QALY gained.

A model cycle length of one week was considered appropriate to reflect the patterns of treatment administration and the transitions to disease progression. Transition between health states can occur at any time within the cycle. In line with previous submissions, a half-cycle correction was applied to mitigate bias. This is also consistent with previous NICE STAs in this disease area.

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 (70). The model inputs for the Pola+R-CHP versus R-CHOP comparison (efficacy, safety and tolerability) are based on the results of the randomised phase III study POLARIX (see Section B.2).

The economic model uses a time horizon of 60 years, which takes into account the age distribution (19–80 years) in the POLARIX trial. Based on the economic model, less than approximately 1% of patients are still alive at 60 years for Pola+R-CHP. Therefore 60 years was deemed appropriate to reflect important differences in costs and outcomes between the technologies being compared. This takes into consideration:

1. Prognosis of patients treated in this setting
2. Expected survival times following present NHS treatment in this setting
3. The maximum plausible impact of improved outcomes following treatment with Pola+R-CHP.

The time horizon is consistent with previous economic models developed for recent NICE submissions in R/R DLBCL as seen in Table 17. Scenario analyses are provided that consider shorter and longer time horizons.

In addition to the time horizon, as DLBCL is a heterogeneous disease that can occur in younger and older patients, the risk of death is modelled using an age distribution cohort approach. Since the POLARIX trial included a broad range of ages (19–80 years), see Figure 11, the age distribution approach was considered more appropriate to reflect the natural disease progression of untreated DLBCL patients. Figure 12 displays the difference between comparing a cohort of only 63-year olds compared with the full age distribution as observed in POLARIX.

**Figure 11: Age distribution in the POLARIX trial**

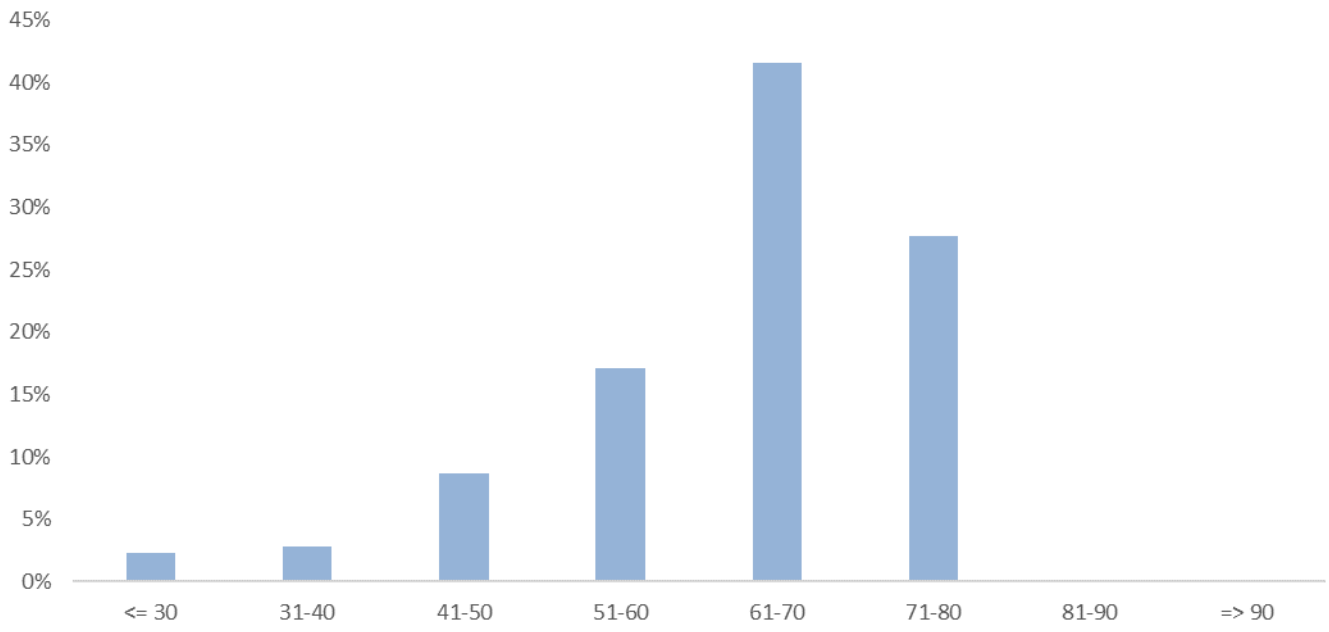
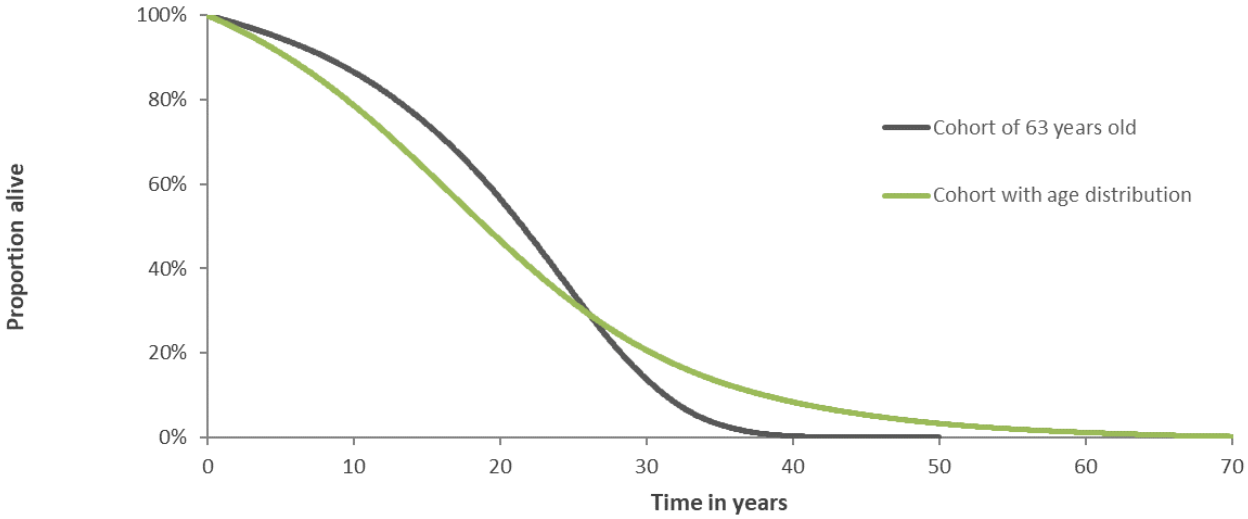


**Figure 12: Comparison of the general survival of cohort of 63 years only versus a cohort having the same age distribution as in POLARIX**




Model results are reported in terms of costs per QALY gained, reflecting the decision problem. Table 17 highlights the main features of this economic analysis compared with previous NICE appraisals in R/R DLBCL.

**Table 17: Features of the economic analysis**

| Factor | Previous appraisals | | | Current appraisal | | |
|---|---|---|---|---|---|---|
| | TA306 (72) | TA567 (73) | TA559 (74) | TA649 (75) | Chosen values | Justification |
| Time horizon | Lifetime (23 years) | Lifetime (46 years) | Lifetime (44 years) | Lifetime (45 years) | Lifetime (60 years) | To capture costs and benefits over a lifetime horizon, as per the NICE reference case (70). |
| 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) | 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) | Values based on GOYA trial (PFS: 0.816; PD: 0.734) | Utilities were validated by clinicians and GOYA trial utilities were considered more reflective of UK clinical practice and 1L DLBCL patients than POLARIX trial utilities. 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 reference costs and PSSRU. | Type and frequency of resource based on clinical trial and NICE guideline (NG52) (76). Intervention incurred additional service costs. Unit costs from eMIT, BNF, NHS reference costs and PSSRU. | Type and frequency of resource based on TA306 for SOC (72). Intervention incurred additional service costs. Unit costs from eMIT, NHS reference costs and PSSRU. | Based on TA306 for SOC and intervention (72). Unit costs from NHS reference costs, PSSRU and BNF. | Based on TA306 for SOC and intervention (72). Unit costs from NHS reference costs, PSSRU and BNF. | Resource use based on accepted values from previous NICE appraisal. NHS Reference Costs and PSSRU are standard sources of UK-relevant costs. See Section B.3.5 for full justification. |

Key: PD, progressed disease; PFS progression free survival; BNF, British National Formulary, DLBCL, diffuse large B cell; SOC, standard of care; OS, overall survival, PSSRU, Personal Social Services Research Unit; eMIT, electronic market information tool.

### B.3.2.3 Intervention technology and comparators

The final scope intervention is Pola+R-CHP, as described in Section B.1.2. For the purposes of this economic evaluation, the primary comparator is R-CHOP.

**Intervention: Pola+R-CHP**

Pola+R-CHP was included in the model as per the proposed licensed dosing regimen. Pola+R-CHP was modelled to follow the dosing schedule implemented in POLARIX, see Section 3.5, and in accordance with the anticipated marketing authorisation.

**Comparator: R-CHOP**

In line with the comparator assessed in POLARIX and the current standard of care in the UK, the comparator included in the economic evaluation is R-CHOP. R-CHOP was modelled to follow the dosing schedule implemented in POLARIX, see Section 3.5, and in accordance with the anticipated marketing authorisation.

## *B.3.3 Clinical parameters and variables*

The primary source of clinical data in the economic model for the intervention and comparator is the POLARIX study; a Phase III, randomized controlled trial comparing Pola+R-CHP to R-CHOP. Data from the latest available data cut (June 2021) have been used to inform the clinical parameters for PFS and OS (results data for which are reported in Section B.2.6.3). This study is also the data source for adverse events and treatment for Pola+R-CHP and R-CHOP. All patients had completed treatment with Pola+R-CHP and R-CHOP by June 2021.

### B.3.3.1 Survival inputs and assumptions

PFS and OS results from POLARIX were extrapolated to the time-horizon of the model as lifetime results are not available for subjects in the POLARIX study. The minimum PFS follow-up was 24 month and maximum was 37 months. Median OS follow-up was 28 months and maximum was 43 months (28 June 2021 data cut).

Guidance from the NICE DSU was followed to identify base case parametric survival models for OS and PFS (70). Specifically, the following points were performed:

- Visual inspection of the OS and PFS log-cumulative hazard plots, based on patient level data for the two arms of POLARIX, 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 POLARIX

- 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, Gamma and log-logistic) were 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 assumes the patient population comprises two subpopulations. The first subpopulation is considered to be cured and at the same risk of mortality as the age- and sex-matched general population (sourced from the Office for National Statistics for this model (77), 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 alongside other survival estimates when using a parametric model. The extrapolations for each subpopulation are then combined via the cure fraction to obtain extrapolations for the population as a whole. The cure mixture model adjusts for age, sex and country of the individual patient trial data in order to estimate the hazards linked to background mortality.

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 progress or die after two years went on to experience subsequent survival equivalent to that of the age- and sex-matched general population (63). 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 (78). Hence, the cure mixture model is an appropriate method to capture the long-term remission of 1L DLBCL patients who receive R-CHOP or Pola+R-CHP as a treatment. PFS and OS data from the POLARIX study demonstrate that compared to current standard of care, Pola+R-CHP is likely to offer patients an improved probability of achieving long-term remission,

which is evidenced by the hazard ratio (HR) of 0.73 (p=0.02) and a clinically meaningful improvement of 6.5% in the number of patients avoiding relapse with Pola+R-CHP vs R-CHOP (71). In addition to clinical expert validation, a cumulative incidence plot is presented in Figure 13, which further confirms the suitability of using the cure mixture model. Finally, precedent of cure mixture modelling in NICE appraisals for R/R DLBCL was established in TA567 (73), TA649 (75) and TA559 (74), where the respective committees accepted that patients who are able to demonstrate sustained remission are likely to benefit from long-term survival.

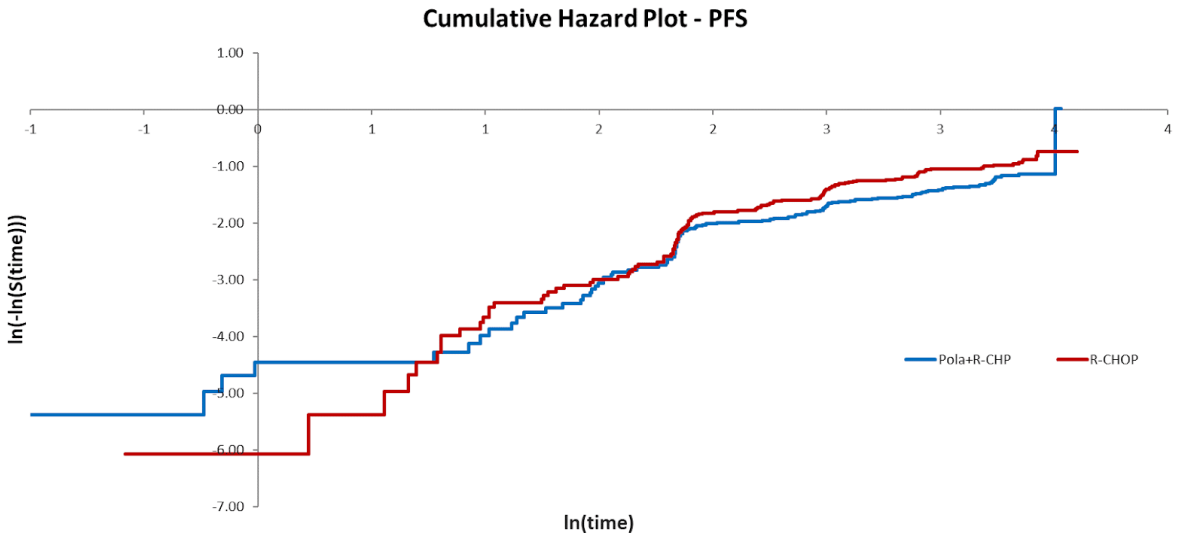
## Cure mixture model

### B.3.3.2 Extrapolation of PFS

#### Proportional hazards assessment: PFS

The validity of the PH assumption between treatments was assessed. This was tested via the visual inspection of the log-cumulative hazard plots. The log-cumulative hazard plot for PFS is presented in Figure 13. It is evident by the non-parallel lines observed for Pola+R-CHP and R-CHOP that the ratio of hazard rates between the arms does not remain constant over the follow-up period. Based on this graphical assessment, it can be concluded that the PH assumption does not hold. Therefore, independent parametric models for each treatment arm were fitted for PFS.

**Figure 13: Visual check of PH assumption - log-cumulative hazard for INV-PFS IPI 2–5**

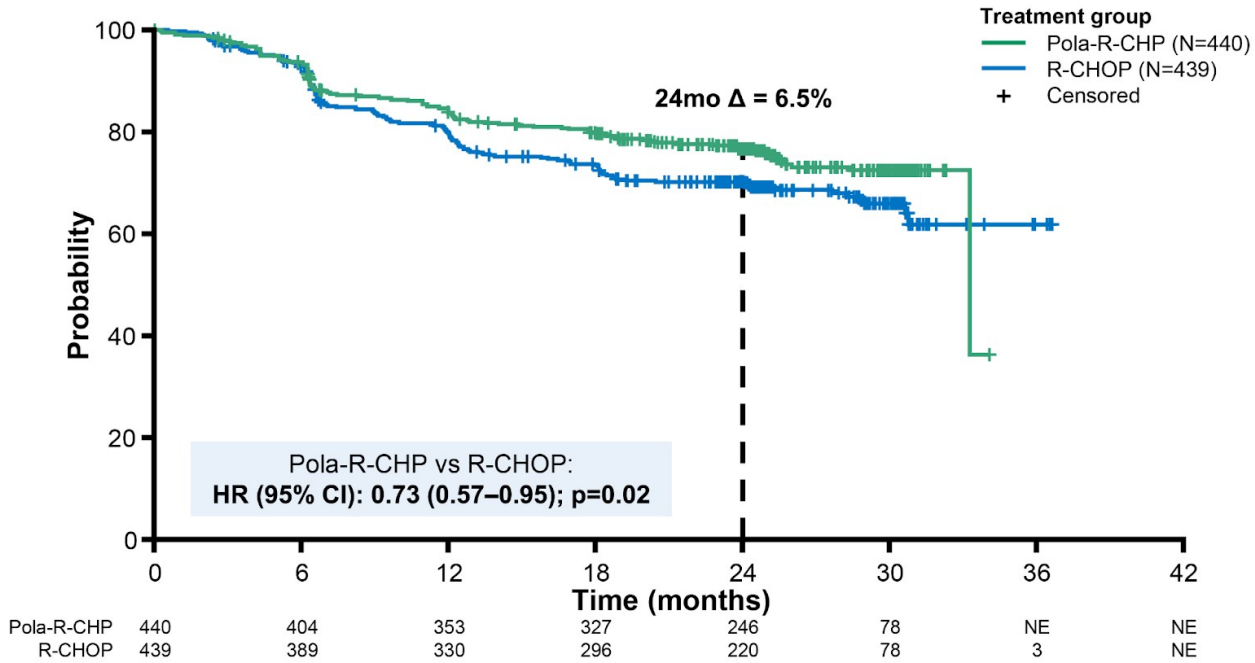



Key: PFS, progression-free survival.

**Assessment for cure mixture modelling**

The suitability of the POLARIX PFS data to the application of cure mixture modelling was assessed. To support the use of cure mixture modelling, the trial data must indicate that a proportion of patients enter long-term remission. Evidence from the literature and clinical opinion suggest that patients with 1L DLBCL remaining progression-free for two years are expected to demonstrate survival aligned with that of the general population. The INV-PFS KM data from the POLARIX trial presented in Figure 14 demonstrates a very low rate of progression for Pola+R-CHP and R-CHOP by the 24-month time point, suggesting a fraction of patients may achieve long-term survival. The assumption will be supported by the upcoming final data cut (June 2022).

**Figure 14: KM plot for INV-PFS (POLARIX; data cut: June 2021)**




**Statistical fit of models to the observed data**

The AIC and BIC goodness of fit results for the functions used to model PFS for Pola+R-CHP and R-CHOP in POLARIX, as well as a qualitative impression of visual fit to the observed KM curve are provided below in Table 18.

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 PFS for both arms, parameterisation for the Weibull and Log-logistic model did not converge. As such, AIC/BIC values are therefore not

presented for these models. Accordingly, the Weibull and Log-logistic extrapolation would ultimately not be selected for OS or as a base case for this economic evaluation.

For the cure mixture models, minimal variation was observed among the statistics. In the Pola+R-CHP arm, functions typically either overestimated PFS 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, Gamma and log-normal provided the most reasonable fit in the Pola+R-CHP arm. In the R-CHOP arm, the Generalised Gamma, log-logistic and log-normal appeared to fit the observed data reasonably well. The cure mixture model appropriately captures the survival benefit of Pola+R-CHP and R-CHOP beyond the 24-Month time point as seen in Figure 15 and Figure 16, which is consistent with clinical expert opinion and external sources (79). Table 18 presents the cure fractions (i.e. the proportion of patients achieving long-term remission) predicted by each of the cure mixture extrapolations for both arms. With exception of Gompertz distribution, the proportion of patients achieving long-term remission falls into a narrow range from 71–76% in the Pola+R-CHP arm, and 60–70% in the R-CHOP arm. A narrow range of values demonstrates consistency in the cure fraction estimation across parametric models, further supporting the suitability of this modelling approach.

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 exponential extrapolations were explored in scenarios. The final base case extrapolations are shown alongside the selected OS extrapolation in Figure 24 in Section B.3.3.4, where the long-term plausibility of the selected extrapolations for both outcomes is also discussed.

**Table 18: Ranking of PFS distribution for Pola+R-CHP and R-CHOP based on AIC, BIC, long-term survival estimate and assessment of their visual fit.**

| | Parametric distribution | Pola+R-CHP (AIC) | Pola+R-CHP (BIC) | Pola+R-CHP Long-term survival estimate | Visual fit | R-CHOP (AIC) | R-CHOP (BIC) | R-CHOP Long-term survival estimate | Visual fit |
|---|---|---|---|---|---|---|---|---|---|
| **Cure-mixture** | Exponential | 510.68 (4) | 518.66 (1) | 71% | ~ | 621.55 (4) | 629.49 (4) | 60% | ~ |
| | Weibull | NA | NA | NA | NA | NA | NA | NA | NA |
| | Log-logistic | NA | NA | NA | NA | NA | NA | NA | NA |
| | Log-normal | 507.46 (1) | 519.43 (2) | 73% | ✓ | 598.43 (1) | 610.35 (1) | 68% | ✓ |
| | Generalised Gamma | 508.92 (3) | 524.88 (5) | 75% | ✓ | 599.47 (2) | 615.35 (3) | 64% | ✓ |
| | Gompertz | 512.84 (5) | 524.81 (4) | 0% | ~ | 624.21 (5) | 636.12 (5) | 0% | ~ |
| | Gamma | 507.81 (2) | 519.79 (3) | 76% | ✓ | 602.54 (3) | 614.46 (2) | 70% | ✓ |

Key: AIC, Akaike Information Criterion; BIC, Bayesian Information Criterion; ✓ 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.

**Figure 15: PFS cure mixture extrapolation functions - Pola+R-CHP**

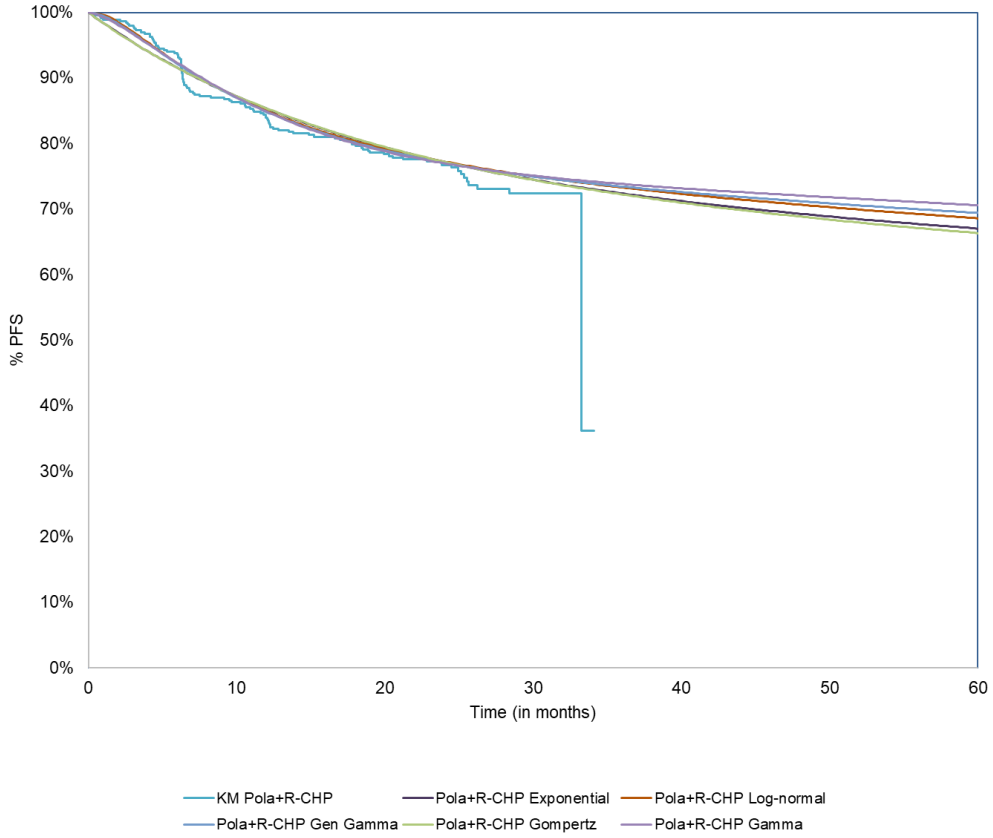



**Figure 16: PFS cure mixture extrapolation functions - R-CHOP**

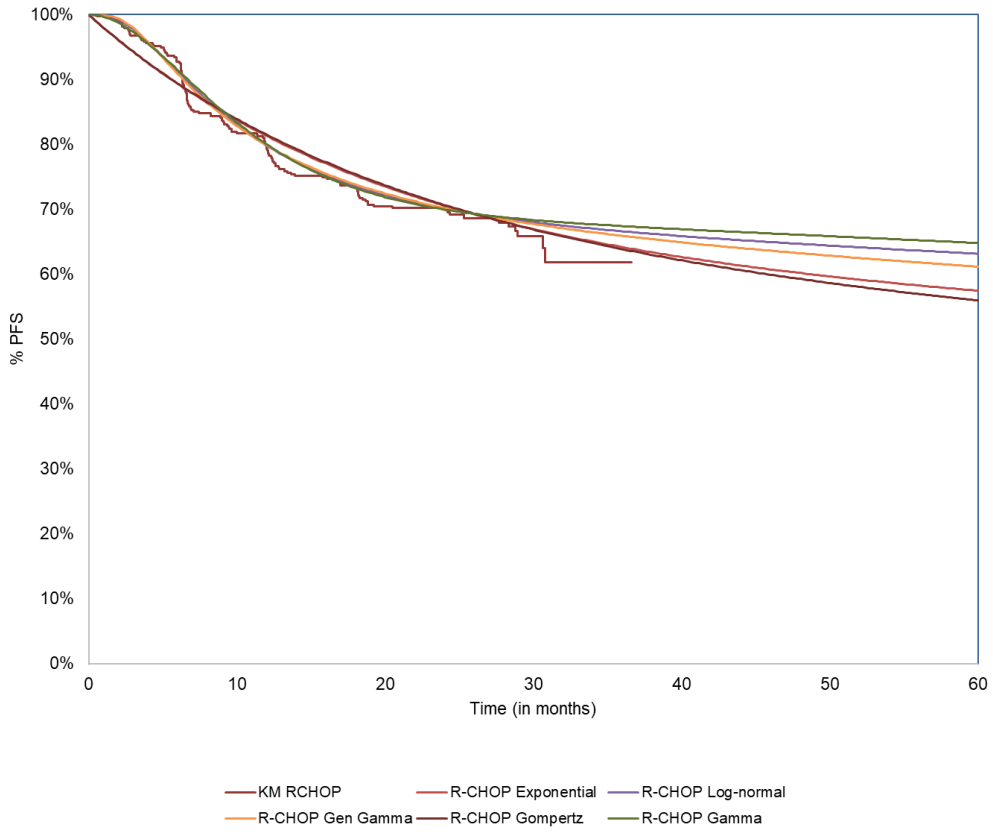
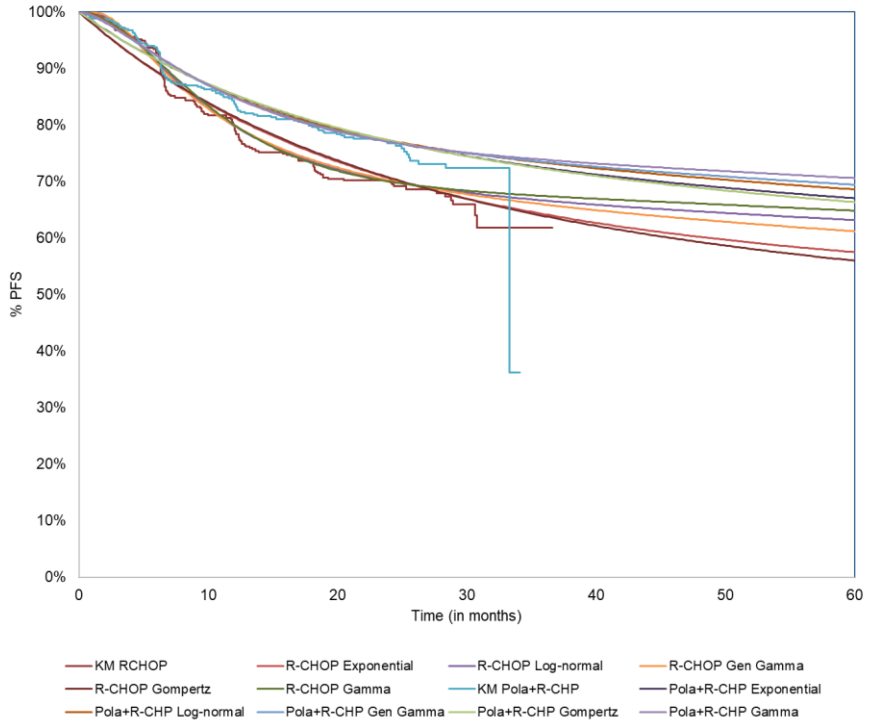


**Figure 17: PFS mixture-cure extrapolation functions – +Pola+R-CHP and R-CHOP**

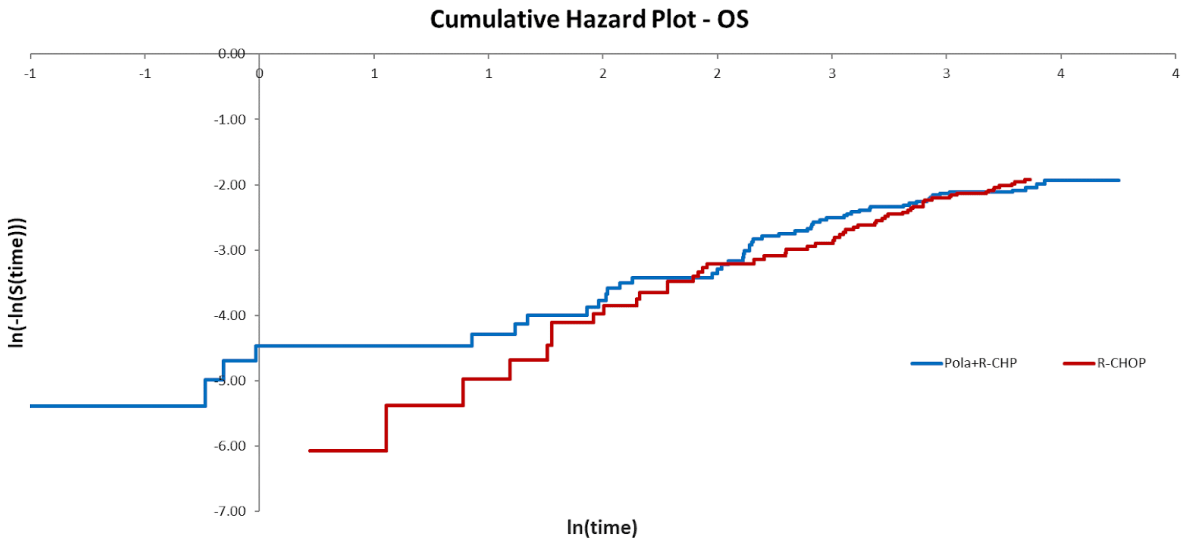



## B.3.3.3. Extrapolation of OS

### Proportional hazards assessment: OS

In line with PFS, the proportional hazards assumption does not hold for OS. This is evident by the diverging lines between Pola+R-CHP and R-CHOP that can be observed in Figure 18, indicating that the ratio of hazard rates between arms does not remain constant over the follow-up period. Therefore, independent parametric models for each treatment arm were fitted for OS.

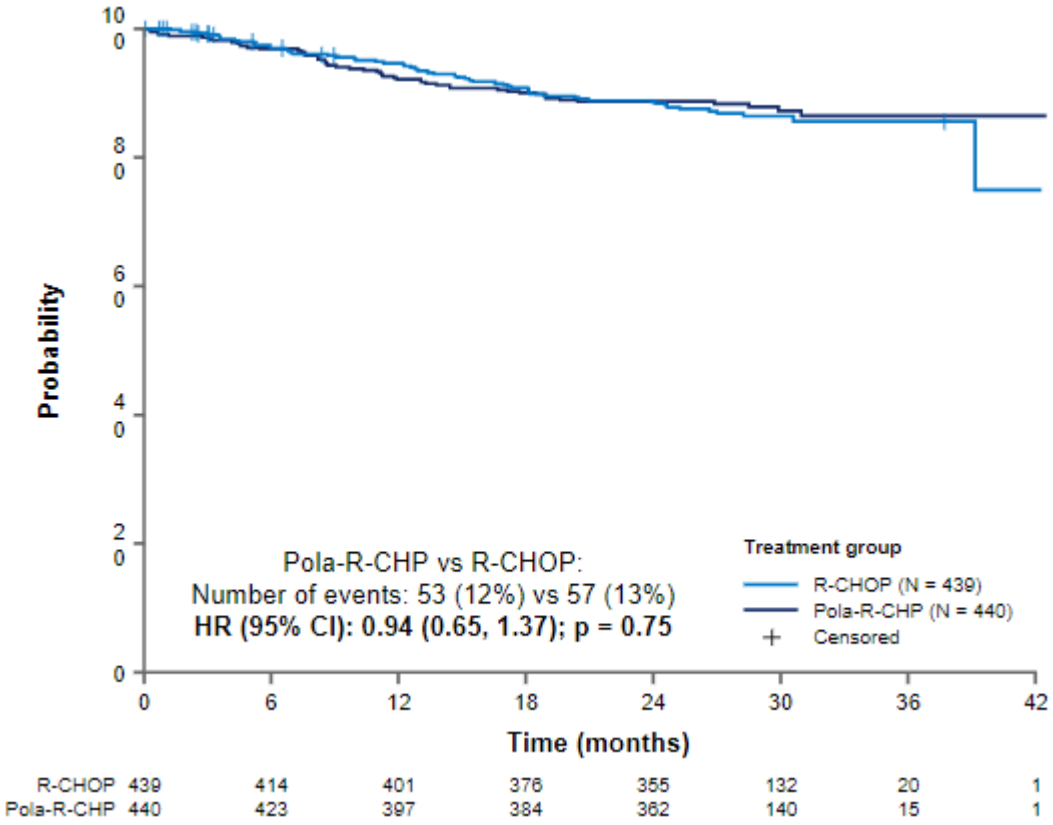
**Figure 18: Visual check of PH assumption - KM OS**



**OS extrapolation**

Due to the immaturity of the OS data and limited OS events, it was not possible to directly estimate the proportion of patients who would experience long-term survival. As a result, with guidance provided by clinical experts and assuming that patients who have not yet progressed can be considered to be long-term survivors, OS was informed by the long-term remission fraction (i.e. the OS cure fraction was informed by the PFS cure fraction).

**Figure 19: KM plot for INV OS (POLARIX; data cut: June 2021)**




The Generalised Gamma, exponential, log-normal,Gompertz and Gamma distributions were fitted to both arms as seen in Table 19. Since the log-logistic and Weibull distributions did not converge for the PFS extrapolations, they were not presented in the OS extrapolation.

As was the case for PFS when applying a cure mixture model, AIC and BIC values indicated a similar statistical fit to the KM and IPD data for both arms. Based on the AIC and BIC values and the visual fit for Pola+R-CHP, the best fitting parametric model for OS is the log-normal, Generalised Gamma and Gompertz curve. Based on the AIC and BIC values and visual fit for R-CHOP, the best fitting parametric model for OS is the Generalised Gamma curve.

All parametric models were also assessed for visual fit to the Kaplan-Meier data as seen in Figure 20 and Figure 21. Most of the parametric distributions underestimate the long-term benefit of Pola+R-CHP and R-CHOP. However, in Figure 20 we can observe that the Gompertz, Generalised Gamma and Log-normal provide the best visual fit since a plateau can be observed towards the end of the curve, which is expected to be seen with Pola+R-CHP and R-CHOP. Figure 22 shows the combined OS extrapolations for Pola+R-CHP and R-CHOP.

**Table 19: Ranking of OS distribution for Pola+R-CHP and R-CHOP based on AIC, BIC, long-term survival estimate and assessment of their visual fit**

| | Parametric distribution | Pola+R-CHP (AIC) | Pola+R-CHP (BIC) | Pola+R-CHP Long-term survival estimate | Visual Fit | R-CHOP (AIC) | R-CHOP (BIC) | R-CHOP Long-term survival estimate | Visual Fit |
|---|---|---|---|---|---|---|---|---|---|
| **Cure-mixture** | Exponential | 330.17 (5) | 333.32 (5) | 71% | × | 358.99 (5) | 362.15 (5) | 60% | ~ |
| | Weibull | NA | NA | NA | NA | NA | NA | NA | NA |
| | Log-logistic | NA | NA | NA | NA | NA | NA | NA | NA |
| | Log-normal | 326.51 (3) | 329.67 (3) | 73% | ✓ | 355.5 (2) | 358.65 (2) | 68% | ~ |
| | Generalised Gamma | 326.44 (2) | 329.6 (2) | 75% | ✓ | 355.07 (1) | 358.22 (1) | 64% | ✓ |
| | Gompertz | 324.86 (1) | 328.01 (1) | 0% | ✓ | 358.84 (4) | 361.99 (4) | 0% | × |
| | Gamma | 328.26 (4) | 331.41 (4) | 76% | ~ | 357.11 (3) | 360.27 (3) | 70% | ~ |

Key: AIC, Akaike Information Criterion; BIC, Bayesian Information Criterion. ✓ 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.

**Figure 20: Visual fit of OS distributions to POLARIX data - Pola+R-CHP (informed by PFS)**

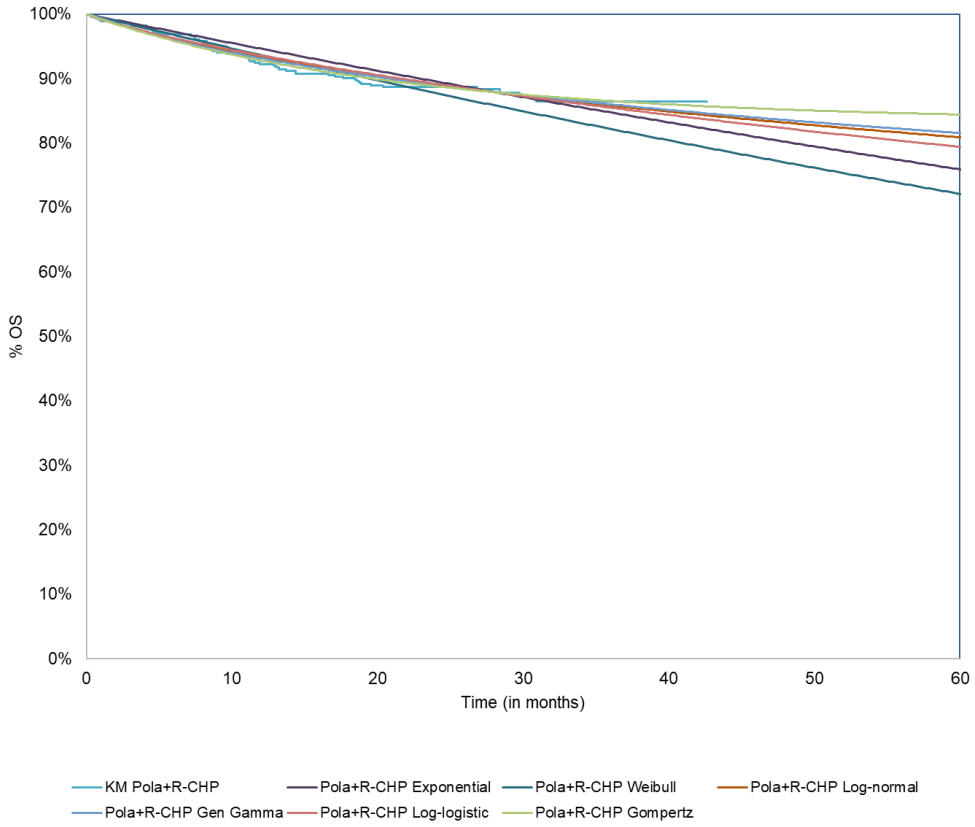



**Figure 21: Visual fit of OS distributions to POLARIX data - R-CHOP (informed by PFS)**

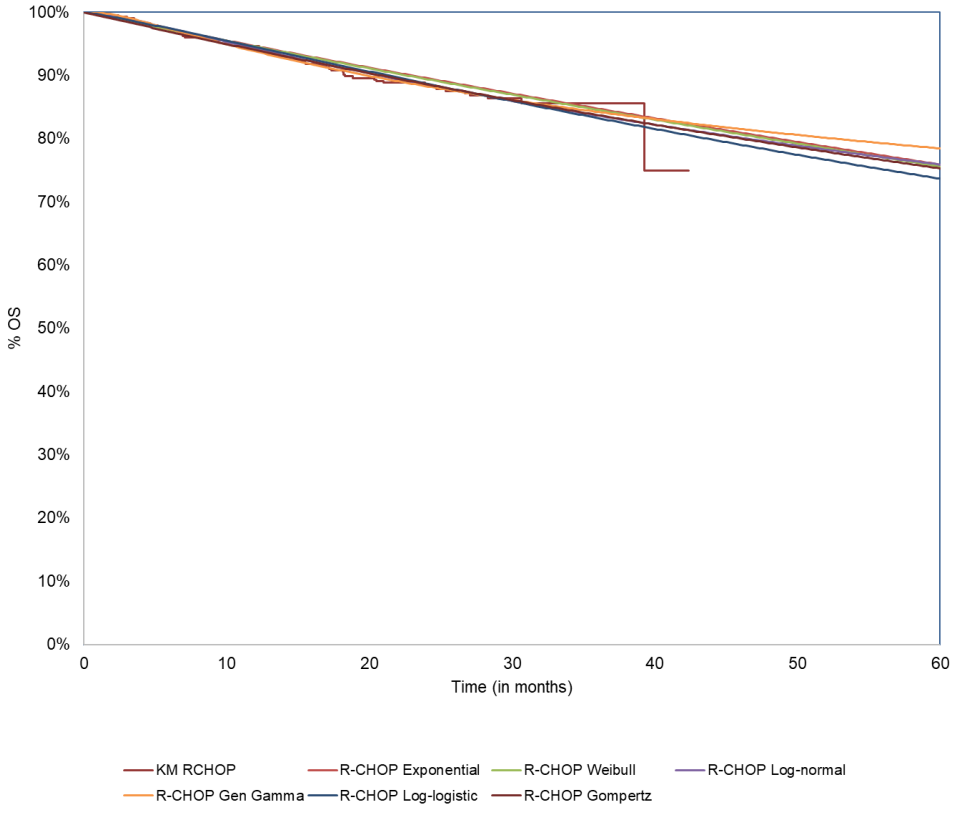
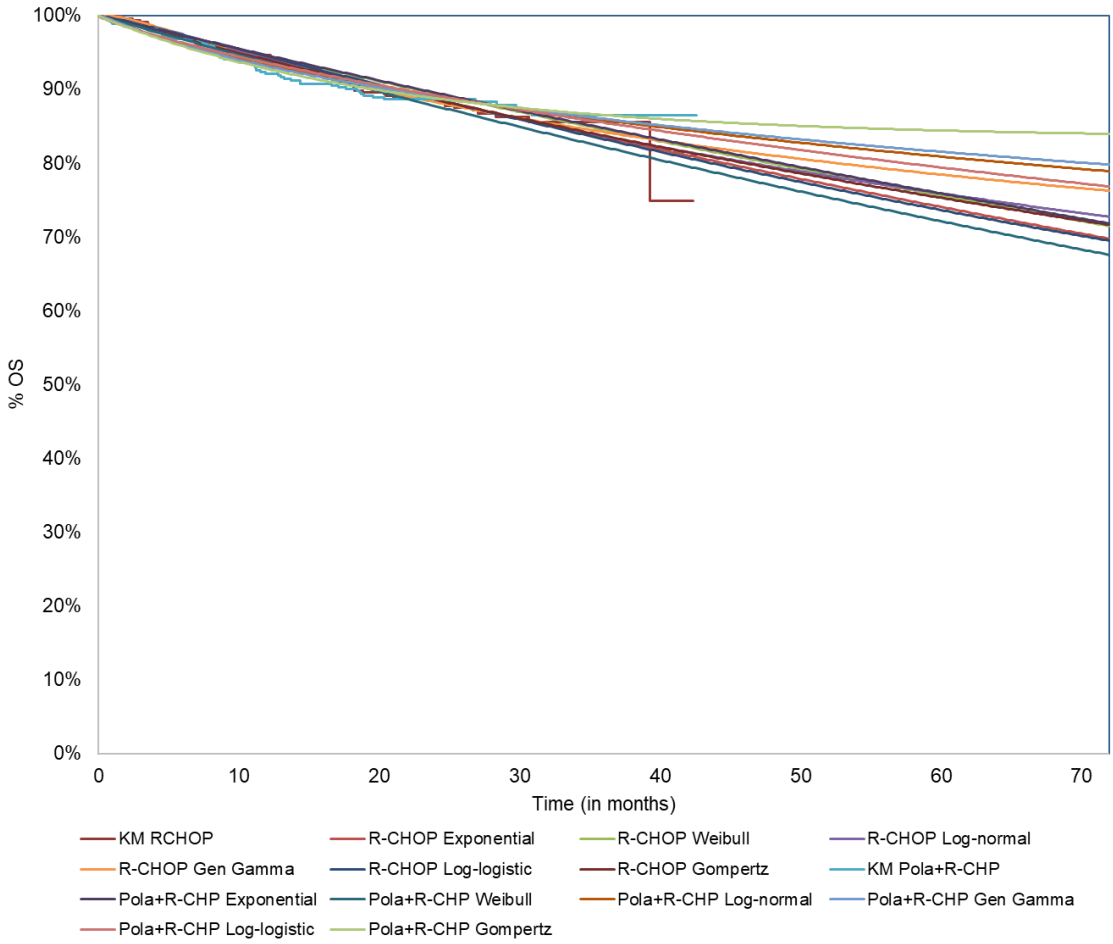


**Figure 22: OS standard extrapolation functions – Pola+R-CHP and R-CHOP (informed by PFS)**




Based on the fit to the observed data of all extrapolations in both the Pola+R-CHP and R-CHOP arms, the Generalised Gamma offered the best fit based on statistical ranking (AIC/BIC) and visual fit, reaffirming Generalised Gamma as the most appropriate extrapolation for the base case. The log-normal and exponential distributions were investigated as scenario analyses. Once AIC and BIC was evaluated and the visual fit for the Pola+R-CHP and R-CHOP curves were assessed, the cure rate for each extrapolation was evaluated. The cure rates predicted by each model are presented in Table 19. As previously described, it was assumed that patients who have not progressed with or died from DLBCL can be considered long-term survivors and can be expected to follow the age and gender matched survival in general population. The PFS data produced an estimated proportion of patients with long-term remission ranging from 0% to 76% and 0% to 70% in the Pola+R-CHP arm and the R-CHOP arm, respectively and these estimates were used to inform the long term survival when fitting the mixture cure rate model for OS. The OS improvement in the Pola+R-CHP arm can be attributed to the increase in patients who are considered in remission after 2 years and are in long-term remission, as validated by clinicians and

external data sources such as the GOYA trial (80). As a result, based on the cure mixture model using the Generalised Gamma distribution, we can estimate that 75% of patients who receive Pola+R-CHP will experience long-term survival compared to 64% who receive R+CHOP as shown in Table 19.

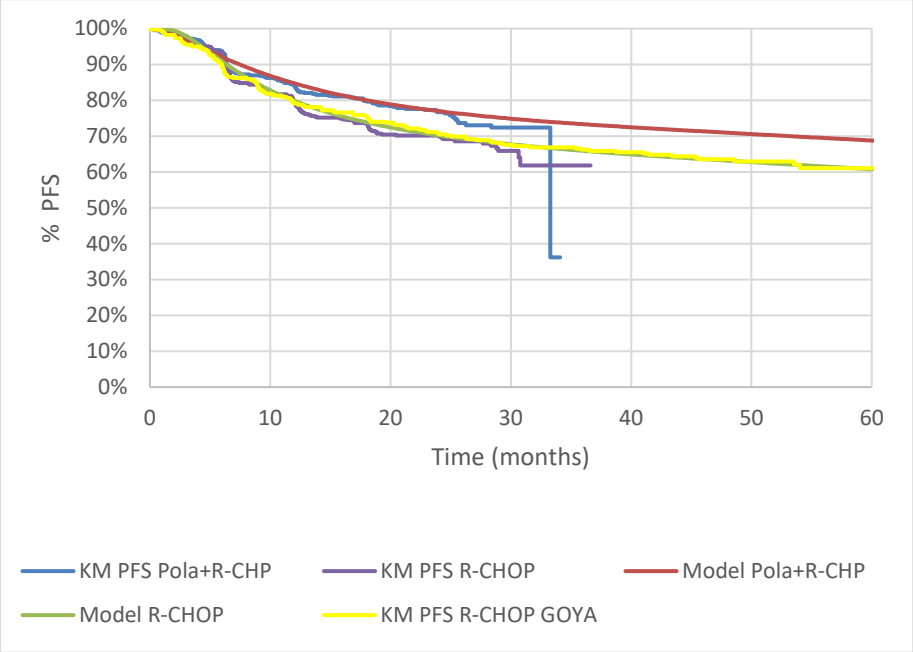
**External validation with the GOYA trial data (adjusted)**

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 long-term outcomes expected in clinical practice.

As mentioned in Section 3.3.2, the GOYA trial (80), which was adjusted for imbalances in patient characteristics and imbalances, was used to assess the clinical validity of the selected extrapolations for PFS and OS.

A 5-Year R-CHOP PFS rate is available from the GOYA clinical trial final data cut. As seen in Figure 23, the Generalised Gamma long-term survival estimate for adults with untreated DLBCL in the POLARIX R-CHOP arm is aligned with the long-term survival estimate (KM data) from the GOYA R-CHOP arm (adjusted) (64% vs 64%). Therefore, the Generalised Gamma distribution can be considered the most appropriate distribution for both treatment arms to model PFS and OS in the POLARIX trial. As the R-CHOP PFS rate in POLARIX and GOYA align, we can deduce that the estimate of 75% patients who receive Pola+R-CHP will experience long-term remission is accurately estimated. Figure 23 shows the visual fit of the GOYA R-CHOP KM curve, POLARIX R-CHOP extrapolation (Generalised Gamma) and POLARIX Pola+R-CHP extrapolation (Generalised Gamma).

**Figure 23: PFS extrapolation with the cure mixture model (Generalised Gamma distribution)**

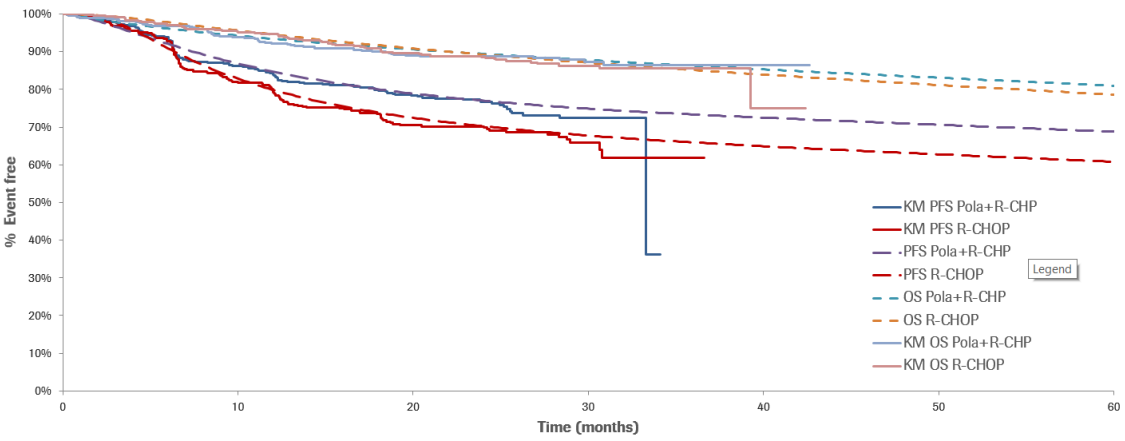



### B.3.3.4. Base case extrapolations of PFS and OS

Following NICE advice (81), it was deemed most appropriate to select the same distribution to model PFS and OS in both treatment arms. Based on all aspects of the curve selection mentioned above, the Generalised Gamma curves were selected as the most clinically plausible curves to represent both Pola+R-CHP and R-CHOP for PFS and OS and were therefore used in the economic model base case. Alternative curve choices were investigated in scenario analyses.

Figure 24 demonstrates the base case for PFS and OS for the POLARIX ITT population using the cure mixture model.

**Figure 24: Base case for PFS and OS for the ITT population (cure mixture model)**




Key: PFS, progression-free survival, OS, overall survival. Gen gam, Generalised Gamma, ITT, Intention to treat.

### B.3.3.5 Treatment duration in the economic model

All patients in the POLARIX study completed their planned treatment by the time of data cut off (June 2021). The rate of treatment discontinuation was low in both treatment arms as seen in Figure 25 and Figure 26. The most common reason for treatment discontinuation in the R-CHOP arm was due to adverse events n=17 (3.9%) and the progression of disease n=17 (3.9%). In the Pola+R-CHP arm, the corresponding numbers were n=9 (2.0%) and n=12 (2.7%). Dose reduction was more common in the R-CHOP arm n=51 (11.6%) vs n=30 (6.9%) in the Pola+R-CHP arm. Any uncertainty around the treatment duration was captured in the probabilistic sensitivity analysis (PSA) using the Greenwood formula.

**Figure 25: Kaplan-Meier curves showing time-to-off treatment (TTOT) for Pola+R-CHP**

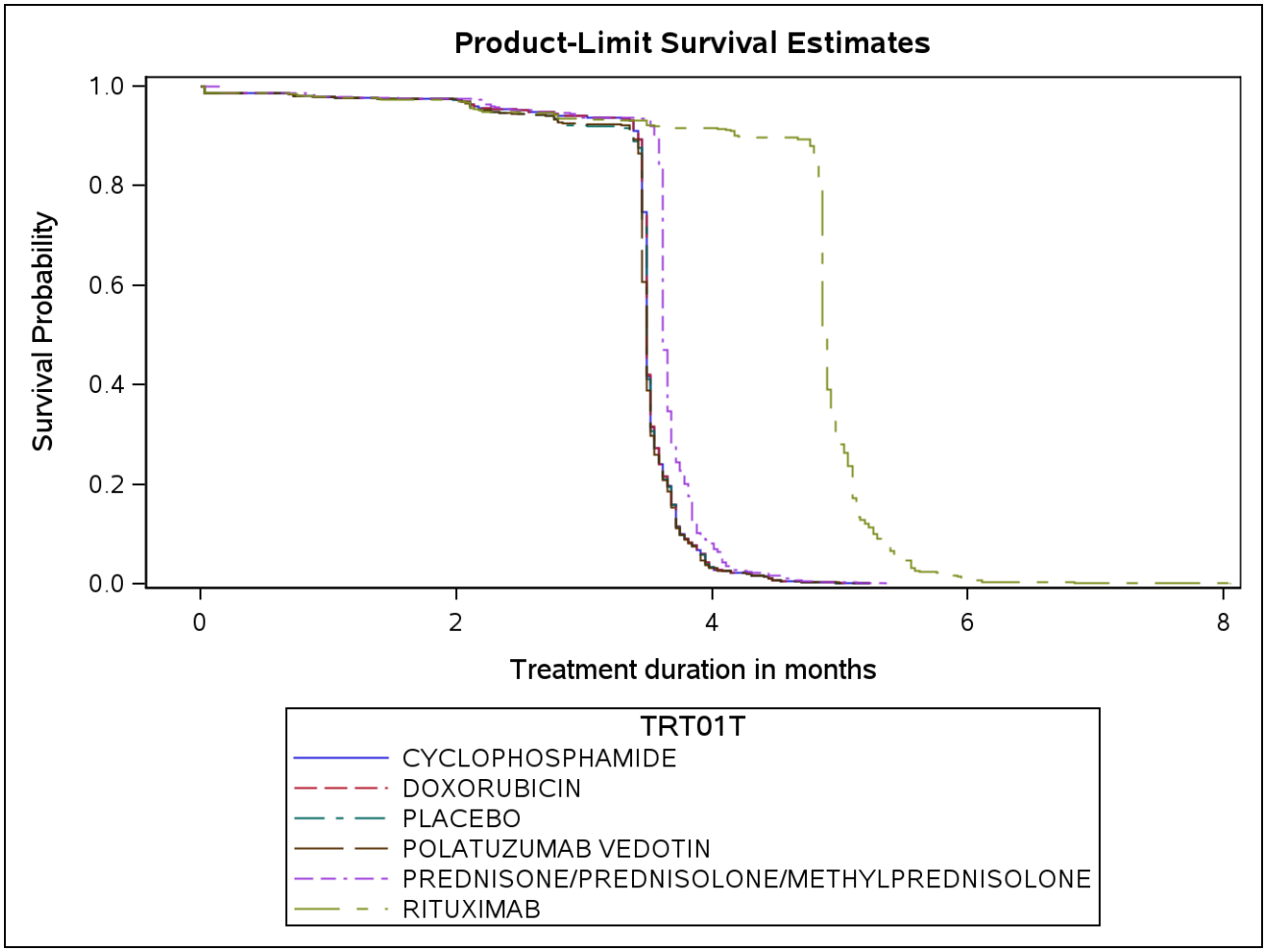


**Figure 26: Kaplan-Meier curves showing TTOT for R-CHOP**

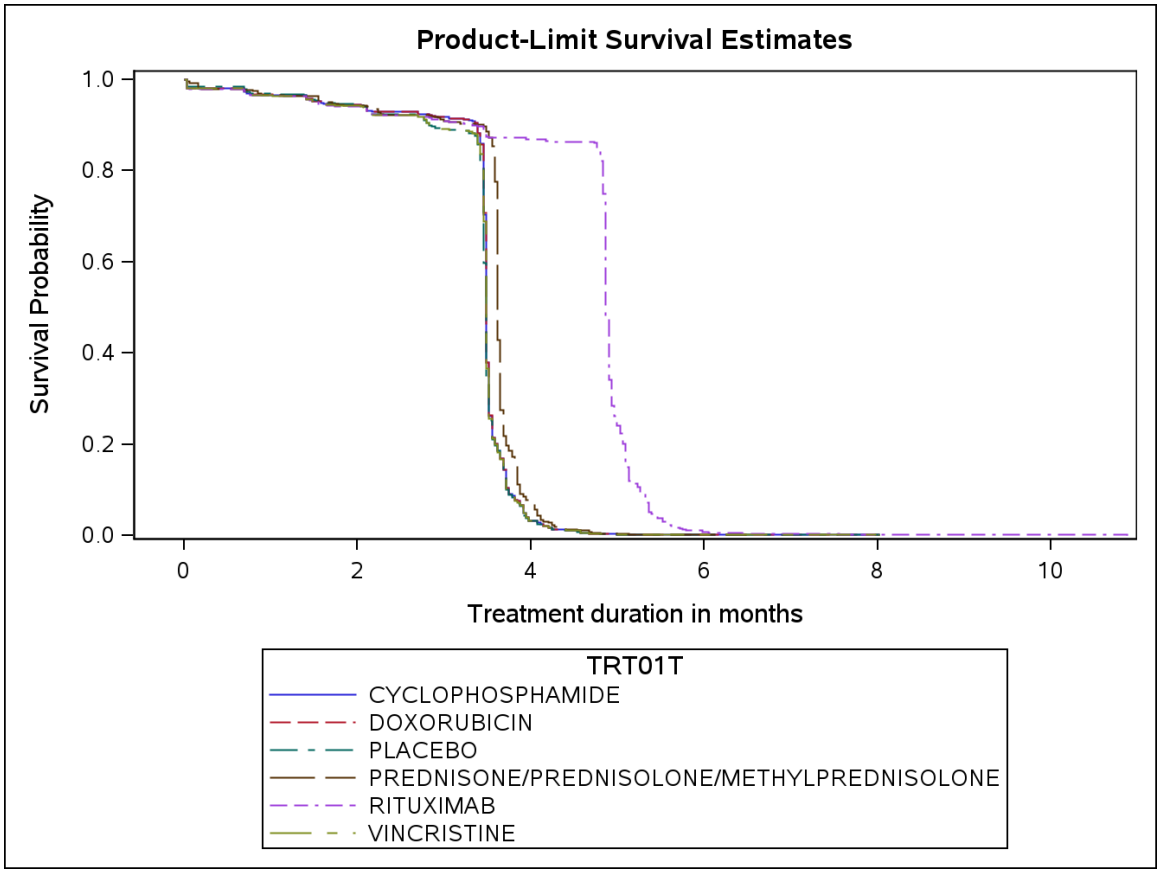



Table 20 and Table 21 show the time-to-off treatment duration and average treatment cycle for patients in the POLARIX trial.

**Table 20: Time-to-off treatment in months for Pola+R-CHP and R-CHOP (POLARIX)**

| | Pola+R-CHP (n=440) | R-CHOP (n=439) |
|---|---|---|
| **Polatuzumab** | | |
| Median | 3.7 | - |
| Mean | 3.6 | - |
| **Rituximab** | | |
| Median | 5.1 | 5.1 |
| Mean | 4.9 | 4.7 |
| **Cyclophosphamide** | | |
| Median | 3.7 | 3.7 |
| Mean | 3.6 | 3.5 |
| **Doxorubicin** | | |
| Median | 3.7 | 3.7 |
| Mean | 3.6 | 3.5 |
| **Prednisolone** | | |
| Median | 3.7 | 3.7 |
| Mean | 3.7 | 3.6 |
| **Vincristine** | | |
| Median | - | 3.7 |
| Mean | - | 3.5 |

**Table 21: Average treatment cycles for Pola+R-CHP and R-CHOP (POLARIX)**

| | Pola+R-CHP (n=440) | R-CHOP (n=439) |
|---|---|---|
| Polatuzumab | 5.2 | - |
| Rituximab | 7.1 | 6.9 |
| Cyclophosphamide | 5.2 | 5.1 |
| Doxorubicin | 5.2 | 5.1 |
| Prednisolone | 5.3 | 5.2 |
| Vincristine | - | 5.1 |

### B.3.3.6 Adverse events

All Grade ≥3 adverse events for Pola+R-CHP and R-CHOP, with an incidence of ≥2% in at least one treatment arm were sourced from the POLARIX clinical study (data cut-off, June 2021). Duration of AE data were sourced from TA306. Disutilities and costs were applied for each AE in the relevant arm (see Sections B.3.4.4 and B.3.5.3., respectively) (72). Adverse events included in the model are outlined below in Table 22.

**Table 22: POLARIX adverse events included in the economic model (events occurring at Grade 3–5, affecting 2% or more of patients)**

| AEs | Grade | Duration (days) | Reference | % AE | |
|---|---|---|---|---|---|
| | | | | Pola+R-CHP | R-CHOP |
| Anaemia | 3 | 16 | MS TA306 | [redacted] | [redacted] |
| Diarrhoea | 3 | 2 | Assumption | [redacted] | [redacted] |
| Febrile neutropenia | 3 | 6 | MS TA306 | [redacted] | [redacted] |
| | 4 | 6 | MS TA306 | [redacted] | [redacted] |
| Neutropenia | 3 | 15 | MS TA306 | [redacted] | [redacted] |
| | 4 | 15 | MS TA306 | [redacted] | [redacted] |
| Neutrophil count decreased | 3 | 15 | Assume same as neutropenia | [redacted] | [redacted] |
| | 4 | 15 | Assume same as neutropenia | [redacted] | [redacted] |
| Pneumonia | 3 | 14 | MS TA306 | [redacted] | [redacted] |

## *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 sourced from the GOYA trial (see Section B.3.4.5) (80).

### B.3.4.1 Health-related quality-of-life data from clinical trials

HRQoL data were collected in the POLARIX study directly from first line DLBCL patients via the EQ-5D-5L questionnaire. EQ-5D-5L results were mapped to EQ-5D-3L, using the van Hout algorithm (82). The base case model uses the weighted GOYA trial utilities as referenced in Section 3.4.5.

### B.3.4.2 Mapping

The POLARIX phase III randomised controlled trial collected EQ-5D-5L, which were mapped to EQ-5D-3L, using the van Hout algorithm.

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

A SLR was conducted to identify HRQoL evidence in the treatment of patients with 1L DLBCL.

### B.3.4.4 Adverse reactions

All grade ≥3 adverse events for Pola+R-CHP and R-CHOP, with an incidence of ≥2% in at least one treatment arm were sourced from the POLARIX study.

There are two approaches that could be taken regarding the inclusion of adverse event impacts on HRQoL:

1. The assumption that any disutility has already been incorporated into the base case health state utilities through trial derived EQ-5D utilities, and incorporating an additional disutility could be considered double counting.

2. The assumption that averaged trial-derived utilities underestimate disutilities associated with adverse events, and therefore an additional disutility must be applied.

Despite the POLARIX trial collecting adverse events, the base case analysis takes the latter assumption since the GOYA trial utility values were used in the base case.

Disutilities were sourced from published literature and the NICE appraisal TA306 (72). 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 by multiplying the disutility with the duration of AEs. This approach aligns with the rationale that AEs are treatment related and occur soon after treatment initiation. A summary of the adverse events and QALY losses included in the economic model is provided in Table 23.

**Table 23: Summary of adverse events and disutilities included in the economic model (events occurring at Grade 3–5, affecting 2% or more of patients)**

| AEs | Disutility | SE | Reference | Pola+R-CHP | R-CHOP | AE duration (days) | Reference |
|---|---|---|---|---|---|---|---|
| Anaemia | 0.25 | 0.05 | TA306 | 11.49% | 6.62% | 16 | MS TA306 |
| Diarrhoea | 0.103 | 0.0103 | Lloyd 2006 | 3.91% | 0.91% | 2 | Assumption |
| Febrile neutropenia (Grade 3) | 0.15 | 0.015 | Lloyd 2006 | 14.02% | 5.48% | 6 | MS TA306 |
| Febrile neutropenia (Grade 4) | 0.15 | 0.015 | Lloyd 2006 | 3.91% | 2.51% | 6 | MS TA306 |
| Neutropenia (Grade 3) | 0.09 | 0.009 | Nafees 2008 | 10.11% | 13.01% | 15 | MS TA306 |
| Neutropenia (Grade 4) | 0.09 | 0.009 | Nafees 2008 | 23.68% | 26.94% | 15 | MS TA306 |
| Neutrophil count decreased (Grade 3) | 0.09 | 0.009 | Assume same as Neutropenia | 2.53% | 1.83% | 15 | Assume same as Neutropenia |
| Neutrophil count decreased (Grade 4) | 0.09 | 0.009 | Assume same as Neutropenia | 8.05% | 5.71% | 15 | Assume same as Neutropenia |
| Pneumonia | 0.2 | 0.02 | Beusterein 2010 | 2.99% | 3.65% | 14 | MS TA306 |

Key: AE, adverse evets; SE, standard error.

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

As mentioned in Section B 3.4.1, HRQoL data were collected in the POLARIX study via the EQ-5D-5L questionnaire and mapped to the EQ-5D-3L using the van Hout algorithm (82). Once the POLARIX utility values were mapped, the POLARIX and the weighted GOYA trial utility values were validated with clinicians. The weighted GOYA trial utility values were considered more appropriate than the mapped POLARIX utility values for two reasons: longer follow-up data was available for the GOYA trial and the GOYA trial utility values where more reflective of the quality of life observed in 1L DLBCL patients.

As a result, the GOYA trial utility values were deemed a reliable and appropriate source for informing this cost-effectiveness analysis. The mapped POLARIX utility values are explored as a scenario analysis.

In agreement with the assumptions adopted in TA559 (74), TA649 (75) and TA567 (73), in the base case, patients who remain in the PFS state for two years revert to age- and sex-matched general population utilities for the UK, which are based on Ara and Brazier 2010 (83). This is further evident in Launonen A et al 2021 (84), who demonstrated that after 1L DLBCL patients reach PFS24, their quality of life returns to the same level as the general population, adjusted for country and age. This assumption aligns with clinical expert feedback on the natural history of DLBCL and evidence from Jakobsen LH et al. 2017 (63), who suggested that patients who achieve sustained remission for up to two years are considered to experience mortality rates and quality of life aligned to that of the general population. It is therefore assumed that a similar utility to the general population is accrued in these patients. A scenario analysis has been conducted returning the quality of life to the same as the general population after 3 years.

A summary of utility values used in the economic model is provided in Table 24. Table 25 shows the utility values that will be applied in scenario analyses to test the robustness of this economic evaluation.

**Table 24: Summary of utility values for cost-effectiveness analysis**

| State | Utility value: mean (standard error) | Reference in submission (section and page number) | Justification |
|---|---|---|---|
| Health state utility values | | | |
| PF | 0.816 (0.01) | GOYA trial | Values validated by clinicians. GOYA and POLARIX have the same PFS definition and GOYA IPD was available and used to effectively rebalance the patient characteristics to match POLARIX patient population. |
| PD | 0.734 (0.01) | GOYA trial | |

| | | | |
|---|---|---|---|
| PFS: long-term follow up | Age- and sex-matched general population utility values from Ara and Brazier 2010 (112) | N/A | 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 (83). In addition, Launonen A et al 2021 (84) demonstrated that after patients reach PFS24, their QoL returns to the same level as the general population, adjusted for country and age. This assumption aligns with clinical expert feedback on the natural history of DLBCL and evidence from Jakobsen LH et al. 2017 (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. |
| Treatment disutilities | Disutility values sourced from relevant NICE appraisal TA306 and the literature. | | |

Key: PD, progressed disease; PF, progression-free.

**Table 25: Summary of utility values for cost-effectiveness analysis (scenario analyses)**

| Scenario | PFS utility value (standard error) | PD utility value (standard error) | Source |
|---|---|---|---|
| POLARIX (cross walk to 3L) IPI 2–5 | 0.843 | 0.800 | POLARIX trial |
| Utility values general population | After three years, the utility values of 1L DLBCL patients reverts back to the same quality of life as the general population. | | |

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

An SLR was conducted to identify studies presenting novel cost and resource use data associated with 1L DLBCL, relevant to the economic model presented herein. Detailed descriptions of the search strategy, search terms and extraction methods, as well as details of the included studies, are provided in Appendix J. In total, 18 publications met the SLR inclusion criteria.

Parameter input costs for the model were derived from NHS reference costs (85), electronic Marketing Information Tool (eMIT) (86) and the British National Formulary (BNF) (87).

### B.3.5.1 Intervention and comparators' costs and resource use

The economic analysis was conducted from the NHS and PSS perspective, with appropriate unit cost sources, such as NHS reference costs (2019–20) (85), eMIT (86), and BNF online (87) used to inform model cost inputs.

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), 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 previous NICE submissions TA306 (72), TA649 (75) and TA559 (74). Based on the ESMO guidelines recommending routine follow-up of up to 24 months (79), it is assumed that patients remaining PFS for two years are discharged and therefore do not incur further supportive costs associated with DLBCL. Clinicians validated the assumption that patients are considered to be in remission after 2 years in the PFS state. Additional scenario analyses varying the time point at which patients are discharged have been included in Section 3.8.3.

#### B.3.5.1.1 Drug acquisition costs

Drug acquisition costs for the treatments included in the economic model are summarised in Table 26. For medicines available to the NHS as generic medicines, prices are taken from eMIT, which reports the average price paid by the NHS for a generic medicine for the last period (85). For medicines only available to the NHS as proprietary medicines, prices are taken at the list price stated in the BNF (87). For pola, a patient access scheme (PAS) is currently available which offers a simple discount of [redacted]

**Pola+R-CHP drug acquisition costs and dose calculations**

Drug acquisition costs and the cost per cycle for Pola+R-CHP are presented in Table 26. For the Pola+R-CHP regimen, patients are assumed to receive up to six cycles (21 days per cycle) of Pola+R-CHP, administered at mean doses of 1.8 mg/kg on Day 1 of each cycle for polatuzumab vedotin, 375 mg/m2 on Day 1 of each cycle for rituximab (both on Day 1 of each cycle), 750 mg/$m^2$ on Day 1 of each cycle for cyclophosphamide,50 mg/$m^2$ on Day 1 of each cycle for doxorubicin, 100 mg/day PO for prednisolone (on Days 1-5 of every 21-day) and 2 cycles of rituximab monotherapy, 375 mg/$m^2$ for rituximab (both on Day 1 of each cycle). The mean treatment doses were derived from the weight (75.92kg) and body surface area (BSA) (1.86 $m^2$) distribution of patients enrolled in the POLARIX study.

Costs per cycle in the model base case are calculated based on the availability of 140 mg and 30 mg vials under the conservative assumption of 'no vial sharing'. Based on the weight distribution of patients enrolled in the POLARIX study, a dose of 1.8 mg/kg resulted in a mean per cycle cost of £11,604.89 per cycle at list price and [redacted] with a PAS of [redacted]

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 (Rixathon®/Truxima®, BNF 2021) (88). In the 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). The rituximab dose is calculated based on the BSA distribution of the POLARIX patient cohort. Patients were assumed to receive a dose of 375 mg/m2 of rituximab administered on Day 1 of each cycle. Assuming no vial sharing, the average cost per cycle for rituximab was calculated to be £582.09.

Cyclophosphamide is now available as a generic formulation of 500 mg and 2000 mg at a cost of £8.21 and £28.22 per vial, respectively (BNF) (89). Patients were assumed to receive 750 mg/$m^2$ for cyclophosphamide (on Day 1 of each cycle) based on the BSA distribution of the POLARIX cohort. Assuming no vial sharing, the cost per cycle for cyclophosphamide was calculated to be £28.26.

Doxorubicin is now available as a generic formulation of 10 mg and 200 mg at a cost of £2.83 and £20.02 per vial, respectively (86). Patients were assumed to receive 50 mg/$m^2$ on Day 1 of each cycle based on the BSA distribution of the POLARIX cohort. Assuming no vial sharing, the cost per cycle for doxorubicin was calculated to be £20.02.

Prednisolone is now available as a generic formulation of 5 mg and 25 mg at a cost of £0.41 per dose and £17.72, respectively (86). Patients were assumed to receive 100 mg/day PO

for prednisolone (on Days 1-5 of every 21-dayThe cost per cycle for prednisone/prednisolone was calculated to be £1.64.

**Comparator drug acquisition costs and dose calculations**

Drug acquisition costs for R-CHOP are presented in Table 26, with calculations for the per cycle cost of cyclophosphamide, doxorubicin, and prednisolone remaining the same as those specified for Pola+R-CHP.

Vincristine is now available as a generic formulation of 1 mg at a cost of £3.43 and 2 mg at a cost of £6.48 per dose, respectively (86). Patients were assumed to receive 1.4 mg/m$^2$ IV on Day 1 of each cycle. Assuming no vial sharing, the cost per cycle for vincristine was calculated to be £10.18.

**Table 26: Treatment acquisition costs (with PAS)**

| Drug | Vial/total pack size (mg) | Vial/pack price | Dosing | Cycle length (days) | Cost per cycle |
|---|---|---|---|---|---|
| Polatuzumab vedotin | 30 | £2,370.00 | 1.8 mg/kg on Day 1 of each cycle | 21 | [redacted] (no vial sharing) |
| | 140 | £11,060.00 | | | |
| Rituximab | 100 | £78.59 | 375 mg/m$^2$ on Day 1 of each cycle | 21 | £582.09 (no vial sharing) |
| | 500 | £392.92 | | | |
| Cyclophosphamide | 500 | £8.21 | 750 mg/m$^2$ on day 1 of each cycle | 21 | £28.26 (no vial sharing) |
| | 2000 | £28.22 | | | |
| Doxorubicin | 10 | £2.83 | 50 mg/m$^2$ on Day 1 of each cycle | 21 | £20.02 (no vial sharing) |
| | 200 | £20.02 | | | |
| Prednisolone | 5 | £0.41 | 100 mg/day PO given on Days 1-5 of every 21-day | 21 | £1.64 |
| | 25 | £17.72 | | | |
| Vincristine | 1 | 3.43 | 1.4 mg/m$^2$ IV on Day 1 of each cycle | 21 | £10.18 (no vial sharing) |
| | 2 | £6.48 | | | |

Key: BNF, British National Formulary; eMIT, electronic market information tool.

**B.3.5.1.2 Drug administration costs**

Administration costs for chemotherapy included in the model are presented in Table 27, with the unit cost per resource as reported in the NHS reference cost schedule 2019–20 (85).

Pharmacy costs for the preparation of IV infusions were not considered separately in previous TAs in R/R DLBCL (72, 73, 75), 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 the preparation of each cycle of a regimen containing polatuzumab vedotin 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 (90), resulting in a per cycle cost of £31.20. This is consistent with the approach taken in TA649 (75).

**Table 27: NHS reference costs 2019–20 for chemotherapy administration**

| HRG tariff | Description | Unit cost |
|---|---|---|
| SB13Z | Deliver more complex parenteral chemotherapy at first attendance | £331.15 |
| SB14Z | Deliver complex chemotherapy, including prolonged infusional treatment, at first attendance | £431.72 |
| SB15Z | Deliver subsequent elements of a chemotherapy cycle | £365.91 |

Key: HRG, Health Resource Group.

The total per cycle drug administration costs for the Pola+R-CHP and R-CHOP treatment regimens are summarised in Table 28. For Pola+R-CHP and R-CHOP, the administration costs are separated into administration costs for the first administration (first cycle) and subsequent administrations (subsequent cycles). Expected costs per treatment cycle were calculated using weekly average treatment costs and TTOT KM data (Section B.3.3.3).

**Table 28: Drug administration costs per cycle**

| Administration cycle | Tariff cost (HRG code applicable) | Pharmacy cost | Cost per cycle |
|---|---|---|---|
| Pola+R-CHP first cycle | £431.72 (SB14Z) | £62.40 | £494.12 |
| Pola+R-CHP subsequent cycles | £365.91 (SB15Z) | £62.40 | £428.31 |
| R-CHOP first cycle | £431.72 (SB14Z) | £31.20 | £462.92 |
| R-CHOP subsequent cycles | £365.91 (SB15Z) | £31.20 | £397.11 |

### B.3.5.2 Health-state unit costs and resource use

#### Supportive care costs

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 (72), 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. The resources listed consist of three separate categories (professional and social services, healthcare professionals and hospital resource use, and treatment follow-up). Table 29 presents the cost per unit for each type of resource included in the model, whilst Table 30 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:

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

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

**Table 29: Supportive care resource use unit costs included in the model**

| Procedure | Cost per unit | Source |
|---|---|---|
| **Professional and social services** | | |
| Residential care (day) | £121.66 | Crude average of Local authority & private; Curtis, L. & Burns, A. (2018) Unit Costs of Health and Social Care 2018, Personal Social Services Research Unit = £114.5; Inflation factor from 2017/18 to 2019/20 = 1.06; Inflated per diem cost of home care = £121.66,University of Kent, Canterbury. https://doi.org/10.22024/UniKent/01.02.70995? |
| Day care (day) | £61.63 | Curtis, L. & Burns, A. (2018) Unit Costs of Health and Social Care 2018, Personal Social Services Research Unit = £58; Inflation factor from 2017/18 to 2019/20 = 1.06; Inflated per diem cost of home care = £61.63, University of Kent, Canterbury. https://doi.org/10.22024/UniKent/01.02.70995? |
| Home care (day) | £35.51 | National Audit Office 2008<br>Per diem cost of community care = £28 (assumed by the National Audit Office to be the same as the cost of home care);<br>Inflation factor from 2007/08 to 2019/20 = 1.27<br>Inflated per diem cost of home care = £35.51 |
| Hospice (day) | £167.40 | National Audit Office 2008; Per diem cost of hospice care = £132; Inflation factor from 2007/08 to 2019/20 = 1.27; Inflated per diem cost of home care = £167.40 |

| | | |
|---|---|---|
| **Health care professionals and hospital resource use** | | |
| Oncologist (visit) | £200.20 | NHSSRC 2019/20; WF01A, Service code 370, Medical oncology, face-to-face, non-admitted |
| Haematologist (visit) | £171.18 | NHSSRC 2019/20; WF01A, Service code 303, clinical haematology, face-to-face, non-admitted |
| Radiologist (visit) | £151.30 | NHSSRC 2019/20; WF01A, Service code 800, Clinic oncology(Radiotherapy), face-to-face, non-admitted |
| Nurse (visit) | £43.46 | NHSSRC 2019/20; N02AF; District Nurse, Adult, Face to face |
| Specialist nurse (visit) | £43.46 | NHSSRC 2019/20; N02AF; District Nurse, Adult, Face to face |
| GP (visit) | £39.74 | Curtis, L. & Burns, A. (2018) Unit Costs of Health and Social Care 2018, Personal Social Services Research Unit = £37.4; Inflation factor from 2017/18 to 2019/20 = 1.06; Inflated per diem cost of home care = £39.74, University of Kent, Canterbury. https://doi.org/10.22024/UniKent/01.02.70995? |
| District nurse (visit) | £43.46 | NHSSRC 2019/20; N02AF; District Nurse, Adult, Face to face |
| CT scan | £145.61 | NHSSRC 2019/20; RD26Z; Complex CT |
| Inpatient day | £407.44 | NHSSRC 2017/18; SA17G; Non-elective excess bed day; Inflation factor from 2017/18 to 2019/20 = 1.06 |
| Palliative care team | £150.00 | NHSSRC 2019/20; SD03A; Palliative care team inpatient |
| **Treatment follow-up** | | |
| Full blood counts | £2.51 | RD28Z; Complex CTa |
| LDH | £2.51 | DAPS05; Haematology |
| Liver function | £2.51 | DAPS05; Haematology |
| Renal function | £2.51 | DAPS05; Haematology |
| Immunoglobulin | £2.51 | DAPS05; Haematology |
| Calcium phosphate | £2.51 | DAPS05; Haematology |
| **One-off costs, PD** | | |
| Oral palliative chemo (2 cycles DECC) | £717.38 | Cost of DECC (please refer to the table in the mode for the calculation) |
| Allogenic stem cell transplant | £ 89,076.80 | Yescarta submission |
| Radiotherapy | £1,361.00 | NHSSRC 2019/20; SC42Z |
| ECG | £87.00 | NHSSRC 2019/20; RD51A, Diagnostic Imaging |
| MUGA | £250.66 | NHSSRC 2019/20; RN22Z, Diagnostic Imaging |
| PET-CT | £958.49 | NHSSRC 2019/20; RN01A, Diagnostic Imaging |

| | | |
|---|---|---|
| Bone marrow biopsy | £593.97 | NHSSRC 2019/20; SA33Z, Day case |
| MRI | £173.38 | NHSSRC 2019/20; DIM004, Outpatient procedures |

Key: PF, progression-free; 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, PD, progressed disease.

Resource use was assumed to be the same for both arms, in accordance with clinical expert opinion (78). For the PFS health state, resource use was specified for patients whilst they were on- or off-treatment. 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 (79). A scenario analysis was conducted that included additional supportive care costs beyond the 2-year time point.

Based on the unit costs and the annual frequencies presented above, the average per cycle supportive care costs for each health state were calculated as shown in Table 31.

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

**Table 30: Annual frequency of resource use in PFS (on and off treatment) and PD**

| Procedure | PFS on treatment (%) | PFS off-treatment (up to 2 years) (%) | PD (%) | Source (72) |
|---|---|---|---|---|
| **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 37a |
| 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 | 2.1 | 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 | 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 | 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] |

| One-off costs, PD | | | | |
|---|---|---|---|---|
| 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] |
| 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] |
| MRI | 4.0 | 4.0 | 4.0 | TA306, ERG report Table 41[a] |

[a] TA306 (72). [b] One-off costs weighted by the proportion of patients requiring the respective resource.

Key: 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; PD, progressed disease.

**Table 31: 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) | PFS One-off cost Pola+R-CHP | PFS One-off cost R-CHOP | PD | PD One-off cost Pola+R-CHP | PD One-off cost R-CHOP |
|---|---|---|---|---|---|---|---|
| £480.29 | £167.21 | £0 | £77.33 | £83.71 | £398.47 | £385.10 | £452.50 |

### B.3.5.3 Adverse reaction unit costs and resource use

All Grade ≥3 treatment-related adverse events with an incidence of ≥2% in either the Pola+R-CHP or R-CHOP arms of the POLARIX study are included in the base case analysis.

The costs of treating adverse events are accounted for per episode. Where possible, the NHS Reference Costs (2019/2020) were applied to adverse events.

The cost of adverse events for each treatment arm is calculated by multiplying total frequency of adverse events by the unit cost. Adverse event costs are applied as a one-off cost in the first cycle of treatment only, hence it is assumed that the adverse event occurs at treatment initiation, only once across the time horizon of the model.

The frequency and unit costs associated with the management of the identified AEs are presented in Table 32.

**Table 32: Resources associated with adverse events**

| Event (grade) | Unit cost | Source |
|---|---|---|
| Anaemia | £351 | Weighted average of SA01G-K, SA03G-H, SA04G-L, SA05G-J; DC |
| Diarrhoea | £1,021 | "Weighted average of FD10J, FD10K, FD10L, FD10M; Day Case" |
| Febrile neutropenia (Grade 3) | £1,848 | TA306 (£1,627) ; inflated to 2019/2020 |
| Febrile neutropenia (Grade 4) | £1,848 | TA306 (£1,627) ; inflated to 2019/2020 |
| Neutropenia (Grade 3) | £503 | Weighted average of SA35A-E; DC |
| Neutropenia (Grade 4) | £503 | Weighted average of SA35A-E; DC |
| Neutrophil count decreased (Grade 3) | £120 | Weighted average of WF01A and WF01C |
| Neutrophil count decreased (Grade 4) | £120 | Weighted average of WF01A and WF01C |
| Pneumonia | £2,487 | Weighted average of DZ11K-V; NES |

Key: NHS, National Health Service.

### B.3.5.4 Subsequent treatment costs

Data on the type and duration of subsequent treatment was available in POLARIX. Time to new anti-lymphoma (NALT) therapy was used to estimate the patients who would undergo subsequent lines of therapy after first-line treatment with Pola+R-CHP and R-CHOP. The model only considered subsequent treatments that could be classified into the following categories, which reflect what is currently used in UK clinical practice.

- Chemotherapy
- Chemotherapy + R
- ASCT
- Salvage Therapy (intention to proceed with transplant)
- Salvage Therapy + R (intention to proceed with transplant)
- Rituximab monotherapy
- Pola+R-CHP
- Bridging treatment + CAR-T
- Allogeneic hematopoietic cell transplant

The costs of subsequent lines of therapy are included in the progressed disease health state of the model. Although data on the treatment and duration of subsequent therapy were collected in POLARIX, these were not considered fully representative of UK clinical practice. As a result, clinical input was collected to determine a more representative breakdown of subsequent treatments. Values obtained from clinicians are used in the base case, and values from the POLARIX trial are explored in a scenario analysis.

The proportion of each subsequent systemic treatment received are represented in Table 33. The average number of systemic treatments received after 1L are represented in Table 34.

**Table 33: Subsequent systemic treatment (UK clinical input)**

| Subsequent treatment | Pola+R-CHP | R-CHOP |
|---|---|---|
| Autologous stem cell transplant | [redacted] | [redacted] |
| Salvage Therapy + R (intention to proceed with transplant) | [redacted] | [redacted] |
| Chemo + R | [redacted] | [redacted] |
| DECC | [redacted] | [redacted] |
| Pola+R-CHP | [redacted] | [redacted] |
| Bridging treatment + CAR-T | [redacted] | [redacted] |
| Pixantrone | [redacted] | [redacted] |

**Table 34: Number of subsequent systemic treatments after 1L**

| | Pola+R-CHP | R-CHOP |
|---|---|---|
| Average number of systemic treatments after 1L | [redacted] | [redacted] |

The cost of autologous and allogeneic SCT included two components: stem cell harvesting and the SCT procedure. The cost of stem cell harvesting and the cost of the procedure were based on NHS reference costs as seen in Table 35 (85). The cost of stem cell harvesting was estimated based on the weighted average of elective SA18Z Bone Marrow Harvest and SA34Z Peripheral Blood Stem Cell Harvest.

**Table 35: SCT cost inputs**

| HRG tariff | Description | Unit cost |
|---|---|---|
| SB26A | Peripheral Blood Stem Cell Transplant, Autologous, 19 years and over | £15,065.25 |
| SA18Z | Bone Marrow Harvest (elective) | £3,459.55 |

| | | |
|---|---|---|
| SA34Z | Peripheral Blood Stem Cell Harvest (elective) | £5,237.61 |
| SA40Z | Peripheral Blood Stem Cell Transplant, Allogeneic (Donor Type Not Specified) | £43,377.00 |
| - | Long-term follow-up cost ASCT | £7,781.73 |
| - | Long-term follow-up cost AlloSCT (73) | £41,325.56 |

Key: HRG, Health Resource Group. ASCT, autologous stem cell transplant, AlloSCT, allogeneic stem cell transplant.

The subsequent treatment administration cost per cycle are summarised in Table 36.

**Table 36: Subsequent treatment administration costs**

| Cycle | Treatment | Cost estimate | Source |
|---|---|---|---|
| First administration | Subsequent treatment | £329.75 | Tariff SB13Z Daycase |
| Subsequent administration | Subsequent treatment | £363.37 | Tariff SB15Z, Daycase |

**Total cost of subsequent treatments**

The total cost of subsequent treatments was applied as a one-off cost at the time point of progression in the model. Table 37 shows the pooled cost for each treatment arm based on the POLARIX trial.

**Table 37: Subsequent treatment costs based on POLARIX data**

| | Subsequent treatment costs |
|---|---|
| Pola+R-CHP | £22,456 |
| R-CHOP | £39,752 |

### B.3.5.5 Miscellaneous unit costs and resource use

A separate cost of death was not applied in 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

A table summarising the full list of variables applied in the economic model is presented in Table 38.

**Table 38: 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 | 60 years | B.3.2 |
| **Patient characteristics** | | |
| Average age, years | 63 | B.3.2 |
| Male, % | 53.81 | B.3.2 |
| Mean weight, kg | 75.92 | B.3.5.2 |
| Mean BSA, m2 | 1.86 | B.3.5.2 |
| **Clinical inputs** | | |
| PFS (Pola+R-CHP and R-CHOP) | Generalised Gamma cure mixture distribution | B.3.2 |
| OS (Pola+R-CHP and R-CHOP) | Generalised Gamma cure mixture distribution informed by PFS | B.3.3 |
| TTOT (Pola+R-CHP and R-CHOP) | TTOT KM data from POLARIX | B.3.3.4 |
| AE frequency | Various | B.3.5 |
| AE duration | Various | B.3.5 |
| **Utilities** | | |
| PFS | 0.816 | B.3.4.5 |
| PFS (>2 years) | Age- and sex-matched general population mortality | B.3.4.5 |
| PD | 0.734 | 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) | £582.09 | B.3.5.2 |
| Cyclophosphamide, acquisition cost per cycle (no vial sharing) | £28.26 | B.3.5.2 |
| Doxorubicin, acquisition cost per cycle (no vial sharing) | £20.02 | B.3.5.2 |
| Prednisolone, acquisition cost per cycle | £1.64 | B.3.5.2 |
| Vincristine, acquisition cost per cycle (no vial sharing) | £10.18 | B.3.5.2 |
| Pola+R-CHP, administration cost per cycle (first cycle) | £494.12 | B.3.5.3 |

| | | |
|---|---|---|
| Pola+R-CHP, administration cost per cycle (subsequent cycles) | £428.31 | B.3.5.3 |
| R-CHOP, administration cost per cycle (first cycle) | £462.92 | B.3.5.3 |
| R-CHOP, administration cost per cycle (subsequent cycles cycle) | £397.11 | B.3.5.3 |
| Subsequent therapy, first cycle | £362.35 | B.3.5.3 |
| Subsequent therapy, subsequent treatment cycles | £397.11 | B.3.5.3 |
| PFS on-treatment supportive care, cost per cycle | £480.29 | B.3.5.4 |
| PFS off-treatment (up to 2 years) supportive care, cost per cycle | £167.21 | B.3.5.4 |
| PD supportive care, cost per cycle | £398.47 | B.3.5.4 |
| Subsequent treatment costs, Pola+R-CHP | £22,456 | B.3.5.4 |
| Subsequent treatment costs, R-CHOP | £39,752 | B.3.5.4 |
| Adverse event management costs | Various | B.3.6.5 |

Key: AE, adverse event; BSA, body surface area; CI, confidence internal; KM, Kaplan Meier; OS, overall survival; PD, progressed disease; PFS, progression-free survival.

### B.3.6.2 Assumptions

A table summarising the key assumptions in the economic model is presented in Table 39.

**Table 39: Key assumptions used in the economic model**

| Assumption | Justification | Addressed in scenario analysis |
|---|---|---|
| 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. The cumulative incidence of progression plot from POLARIX and GOYA for PFS demonstrate a decline in the rate of progression and death, respectively, towards the end of follow-up, which indicates a slowdown in progression and death for 1L DLBCL patients. In addition, this assumption has been validated by clinicians and the literature that patients enter remission after 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.<br><br>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 independently were explored in scenario analyses for both PFS and OS. 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 obtained from the GOYA trial and differences in the AE profile were captured through modelling AEs disutilities for ≥Grade 3 treatment-related AEs deemed to be serious. | Because weighted GOYA trial utilities were used in the base case, no differences in health state utility values were assumed. This assumption was consistent with the approach taken in TA649 (75). | Alternative health state utility values sourced from POLARIX 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). | In agreement with the assumptions adopted in TA559, TA649 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 (83). In addition, Launonen A et al 2021 (84) demonstrated that after patients reach PFS24, their QoL returns to the same level as the general population, adjusted for country and age. This assumption aligns with clinical expert feedback on the natural history of DLBCL and evidence from Jakobsen LH et al. 2017 (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. | A scenario in which the time point at which patients switch to general population utility is extended to two years. |
| 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. This approach is consistent with TA649 (75). | 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 polatuzumab vedotin, rituximab, cyclophosphamide, doxorubicin, and vincristine. | 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 (78) and is consistent with the approach taken in TA649 (75). | This assumption was deemed to be associated with a minimal impact on cost-effectiveness, and was therefore not tested in a scenario. |

Key: AE, adverse events; BS, biosimilar 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; OS, overall survival; PFS, progression-free survival; RCT, randomised controlled trial, TA, technology appraisal; UK, United Kingdom, AIC, Akaike information criterion; BIC, Bayesian information criterion; EQ-5D, EuroQol- 5 Dimension; HRQoL, health-related quality of life, TTOT, time-to-off treatment .

## *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+R-CHP vs R-CHOP are presented in Table 40. The clinical outcomes and disaggregated base case cost-effectiveness results are presented in Appendix K.

The base case cost-effectiveness results demonstrate that Pola+R-CHP is cost-effective vs R-CHOP, at an incremental cost-effectiveness ratio (ICER) of £34,398 per QALY with a PAS of [redacted] Pola+R-CHP accrued a greater health benefit compared to R-CHOP, as demonstrated by a QALY gain of [redacted]

**Table 40: Base case results (with PAS for POLIVY)**

| Technologies | Total costs (£) | Total LYG | Total QALYs | Inc. costs (£) | Inc. LYG | Inc. QALYs | ICER (£/ LYG) | ICER (£/ QALY) |
|---|---|---|---|---|---|---|---|---|
| Pola+R-CHP | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | 27,104 | 34,398 |
| R-CHOP | [redacted] | 11.832 | 9.004 | - | - | - | - | - |

Key: ICER, incremental cost-effectiveness ratio; LYG, life years gained; PAS, patient access scheme; 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 41). 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:

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

**Table 41: PSA parameter inputs**

| Parameter | Distribution | Mean | | SE |
|---|---|---|---|---|
| **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 | Covariance matrix | 0.843 | 0.01 | (0.80, 0.83) |
| Utility in PD, both treatment arms | Covariance matrix | 0.800 | 0.02 | (0.69, 0.77) |
| **Disutility due to adverse events** | | | | |
| Anaemia | Normal | 0.250 | 0.050 | N/A<br>Parameter input variation (SE) equal to 10% of mean estimate |
| Diarrhoea | Normal | 0.103 | 0.010 | |
| Febrile neutropenia (grade 3) | Normal | 0.150 | 0.015 | |
| Febrile neutropenia (grade 4) | Normal | 0.150 | 0.015 | |
| Neutropenia (grade 3) | Normal | 0.090 | 0.009 | |
| Neutropenia (grade 4) | Normal | 0.090 | 0.009 | |
| Neutrophil count decreased (grade 3) | Normal | 0.090 | 0.009 | |
| Neutrophil count decreased (grade 4) | Normal | 0.090 | 0.009 | |
| Pneumonia | Normal | 0.200 | 0.020 | |
| **Administration costs, Pola+R-CHP (£)** | | | | |
| Administration cost, first treatment cycle | Log-normal | 461.26 | 0.1014 | N/A<br>Parameter input variation (SE) calculated from upper and lower estimates of base case value ±20% |
| Pharmacy cost, first treatment cycle | Log-normal | 58.25 | 0.1014 | |
| Administration cost, subsequent treatment cycles | Log-normal | 317.66 | 0.1014 | |
| Pharmacy cost, subsequent treatment cycles | Log-normal | 47.50 | 0.1014 | |
| Administration cost, subsequent therapy, first cycle | Log-normal | 360.96 | 0.1014 | |
| Pharmacy cost, subsequent therapy, first cycle | Log-normal | 32.17 | 0.1014 | |
| Administration cost, subsequent therapy, subsequent treatments | Log-normal | 300.54 | 0.1014 | |
| Pharmacy cost, subsequent therapy, subsequent treatments | Log-normal | 32.84 | 0.1014 | |
| **Administration costs, R-CHOP (£)** | | | | |

| | | | | |
|---|---|---|---|---|
| Administration cost, first treatment cycle | Log-normal | 439.71 | 0.1014 | N/A<br>Parameter input variation (SE) calculated from upper and lower estimates of base case value ±20% |
| Pharmacy cost, first treatment cycle | Log-normal | 34.48 | 0.1014 | |
| Administration cost, subsequent treatment cycles | Log-normal | 406.73 | 0.1014 | |
| Pharmacy cost, subsequent treatment cycles | Log-normal | 33.70 | 0.1014 | |
| Administration cost, subsequent therapy, first cycle | Log-normal | 360.96 | 0.1014 | |
| Pharmacy cost, subsequent therapy, first cycle | Log-normal | 32.17 | 0.1014 | |
| Administration cost, subsequent therapy, subsequent treatments | Log-normal | 300.54 | 0.1014 | |
| Pharmacy cost, subsequent therapy, subsequent treatments | Log-normal | 32.84 | 0.1014 | |
| **Supportive care costs (£)** | | | | |
| Residential care (day) | Log-normal | 121.66 | 0.1014 | N/A<br>Parameter input variation (SE) calculated from upper and lower estimates of base case value ±20% |
| Day care (day) | Log-normal | 61.63 | 0.1014 | |
| Home care (day) | Log-normal | 35.51 | 0.1014 | |
| Hospice (day) | Log-normal | 167.40 | 0.1014 | |
| Oncologist (visit) | Log-normal | 200.20 | 0.1014 | |
| Haematologist (visit) | Log-normal | 171.18 | 0.1014 | |
| Radiologist (visit) | Log-normal | 151.30 | 0.1014 | |
| Nurse (visit) | Log-normal | 43.46 | 0.1014 | |
| Specialist Nurse (visit) | Log-normal | 43.46 | 0.1014 | |
| GP (visit) | Log-normal | 39.74 | 0.1014 | |
| District Nurse (visit) | Log-normal | 43.46 | 0.1014 | |
| Inpatient day | Log-normal | 407.44 | 0.1014 | |
| CT Scan | Log-normal | 145.61 | 0.1014 | |
| Full blood counts | Log-normal | 2.53 | 0.1014 | |
| LDH | Log-normal | 2.53 | 0.1014 | |
| Liver function | Log-normal | 2.53 | 0.1014 | |
| Renal function | Log-normal | 2.53 | 0.1014 | |
| Immunoglobulin | Log-normal | 2.53 | 0.1014 | |
| Calcium phosphate | Log-normal | 2.53 | 0.1014 | |
| Palliative care team | Log-normal | 150.00 | 0.1014 | |
| Oral palliative chemo (2 cycles DECC) | Log-normal | 717.38 | 0.1014 | |
| Autologous stem cell transplant | Log-normal | 34783.96 | 0.1014 | |
| Radiotherapy | Log-normal | 1361.00 | 0.1014 | |
| EGC | Log-normal | 87.00 | 0.1014 | |

| | | | | |
|---|---|---|---|---|
| MUGA | Log-normal | 250.66 | 0.1014 | |
| PET-CT | Log-normal | 958.49 | 0.1014 | |
| Bone marrow biopsy | Log-normal | 593.97 | 0.1014 | |
| MRI | Log-normal | 173.38 | 0.1014 | |
| **Subsequent treatment, one-off cost** | | | | |
| Pola+R-CHP | Log-normal | 142,356.05 | 0.1014 | N/A<br>Parameter input variation (SE) calculated from upper and lower estimates of base case value ±20% |
| R-CHOP | Log-normal | 148,127.99 | 0.1014 | |
| **Adverse event management costs (£)** | | | | |
| Anaemia | Log-normal | 351.10 | 0.101 | N/A<br>Parameter input variation (SE) calculated from upper and lower estimates of base case value ±20% |
| Diarrhoea | Log-normal | 1,020.81 | 0.101 | |
| Febrile neutropenia (grade 3) | Log-normal | 1,848.13 | 0.101 | |
| Febrile neutropenia (grade 4) | Log-normal | 1,848.13 | 0.101 | |
| Neutropenia (grade 3) | Log-normal | 502.94 | 0.101 | |
| Neutropenia (grade 4) | Log-normal | 502.94 | 0.101 | |
| Neutrophil count decreased (grade 3) | Log-normal | 120.41 | 0.101 | |
| Neutrophil count decreased (grade 4) | Log-normal | 120.41 | 0.101 | |
| Pneumonia | Log-normal | 2,487.45 | 0.101 | |

Key: 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; PSA, probabilistic sensitivity analysis; SE, standard error.

The results of the PSA are presented in Table 42. The mean incremental costs and QALYs from the PSA were [redacted] and [redacted] respectively, resulting in a mean ICER value of £33,727 per QALY.

**Table 42: Mean probabilistic results (with PAS)**

| Intervention | Total costs (£) | Total LYG | Total QALYs | Incremental costs (£) | Incremental LYG | Incremental QALYs | ICER (£/ LYG) | ICER (£/QALY) |
|---|---|---|---|---|---|---|---|---|
| Pola+R-CHP | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | 26,323 | 33,727 |
| R-CHOP | [redacted] | 11.680 | 8.873 | - | - | - | | - |

Key: LYG, life years gained; QALY, quality of life; ICER incremental cost-effectiveness ratio.

The cost-effectiveness plane is presented in Figure 27. The cost-effectiveness acceptability curve (CEAC) for Pola+R-CHP versus R-CHOP is presented in Figure 28. From the CEAC,

at a willingness to pay (WTP) threshold of £50,000, the probability of Pola+R-CHP being cost-effective relative to R-CHOP was [redacted]

**Figure 27: Cost-effectiveness plane for Pola+R-CHP vs. R-CHOP**

**Figure 28: Cost-effectiveness acceptability curve for Pola+R-CHP vs R-CHOP**

### B.3.8.2 Deterministic sensitivity analysis

A deterministic sensitivity analysis (DSA) was performed to investigate key drivers of the base case results. Each input parameter was set to its respective upper or lower bound and the deterministic results for the model recorded. Generally, the base case parameter values were varied across their 95% CI. The parameter values used in the DSA are displayed in Table 43.

**Table 43: Parameter values used for DSA (with PAS for POLIVY)**

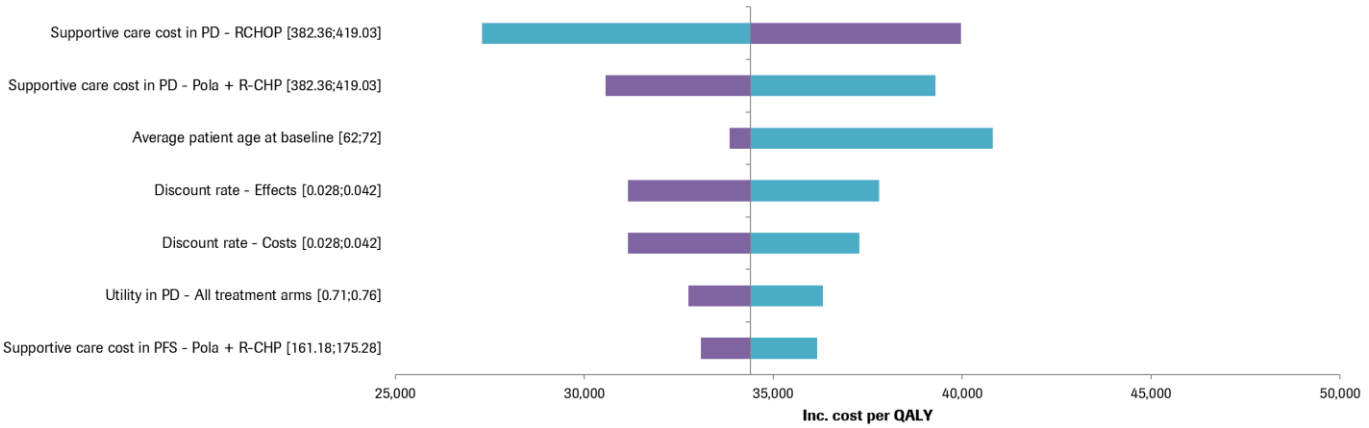
| Parameter | Base case value | Upper value | Lower value | Upper value ICER(£/QALY) | Lower value ICER(£/QALY) | Range (£/QALY) |
|---|---|---|---|---|---|---|
| **Base case** | | | | 34,398 | | |
| **Discount rates** | | | | | | |
| Discount rate, costs | 3.5% | 4% | 3% | 37,275 | 31,147 | 6,128.49 |
| Discount rate, effects | 3.5% | 4% | 3% | 37,806 | 31,160 | 6,646.10 |
| **Patient Characteristics** | | | | | | |
| Average patient age at baseline (+/- 5 years) | 63 | 72 | 62 | 40,808 | 33,842 | 6,966.41 |
| **Utilities** | | | | | | |
| Utility in PFS, all treatment arms | 0.816 | 0.83 | 0.81 | 34,397 | 34,397 | 0.00 |
| Utility in PD, all treatment arms | 0.734 | 0.76 | 0.71 | 36,313 | 32,750 | 3,562.94 |
| AE disutility, Pola+R-CHP | Various | 0.004 | 0.003 | 34,435 | 34,072 | 362.70 |
| AE disutility, R-CHOP | | 0.003 | 0.003 | 34,394 | 34,670 | -276.48 |
| **Adverse event costs** | | | | | | |
| AE management cost per patient, Pola+R-CHP | 668.67 | 716.09 | 631.90 | 34,523 | 34,295 | 228.75 |
| AE management cost per patient, R-CHOP | 481.13 | 514.03 | 456.68 | 34,314 | 34,468 | -153.36 |
| **Administration costs** | | | | | | |
| Administration cost (first cycle) Pola+R-CHP | 494.12 | 522.98 | 441.12 | 35,068 | 34,052 | 1,016.69 |
| Administration cost (subsequent cycle) Pola+R-CHP | 428.31 | 478.70 | 384.09 | 34,559 | 34,314 | 244.89 |
| Administration cost (first cycle) R-CHOP | 462.92 | 522.98 | 409.46 | 34,314 | 34,542 | -227.37 |
| Administration cost (subsequent cycle) R-CHOP | 397.11 | 447.84 | 354.39 | 34,077 | 34,934 | -857.37 |
| **Supportive care costs** | | | | | | |

| | | | | | | |
|---|---|---|---|---|---|---|
| Supportive care cost in PFS, Pola+R-CHP | 167.21 | 175.28 | 161.18 | 36,163 | 33,079 | 3,083.68 |
| Supportive care cost in PFS, Pola+R-CHP on treatment | 480.29 | 505.06 | 460.85 | 35,823 | 33,282 | 2,541.02 |
| Supportive care cost in PFS, R-CHOP | 167.21 | 175.28 | 161.18 | 32,731 | 35,642 | -2,910.88 |
| Supportive care cost in PFS, R-CHOP on treatment | 480.29 | 505.06 | 460.85 | 33,011 | 35,483 | -2,472.23 |
| Supportive care cost in PD, Pola+R-CHP | 398.47 | 419.03 | 382.36 | 39,289 | 30,565 | 8,724.42 |
| Supportive care cost in PD, R-CHOP | 398.47 | 419.03 | 382.36 | 27,294 | 39,962 | -12,667.89 |
| One-off costs, PD, Pola+R-CHP | 385.10 | 334.75 | 273.89 | 34,451 | 34,343 | 107.90 |
| One-off costs, PD, R-CHOP | 452.50 | 408.89 | 334.55 | 34,314 | 34,481 | -166.58 |

Key: DSA, deterministic sensitivity analysis; ICER, incremental cost-effectiveness ratio; PAS, patient access scheme; PD, progressed disease; PFS, progression free survival; AE, adverse events.

A tornado diagram demonstrating the key drivers of the ICER are presented in Figure 29. As shown below, the three parameters most influential on the model ICER value were supportive care costs in PD for R-CHOP, supportive care costs in PD for Pola+R-CHP and the average patient age at baseline.

**Figure 29: Tornado diagram, Pola+R-CHP vs R-CHOP**



### B.3.8.3 Scenario analysis

Scenario analyses were conducted to assess uncertainty around the assumptions in the model. The list of scenarios explored in the model are listed in Table 44. Results including the Polivy PAS are presented in Table 45.

Deterministic ICER values from the scenario analyses listed ranged by -31.09% to 75.54%. The three most influential (groups of) scenarios were the application of standard parametric survival modelling, the application of the log-normal distribution to the cure mixture model and the application of the POLARIX IPI 2–5 utilities, which resulted in approximate increases to the ICER of 75.54%, 33.83% and 14.56% relative to the base case. These scenarios are discussed below. No other scenario exceeded a change in the ICER of over 75.54%.

**Table 44: Parameters varied in the scenario analysis**

| No. | Parameter | Base case | Scenario |
|---|---|---|---|
| 1 | Time horizon | 60-years | 35-years |
| 2 | | | 40-years |
| 3 | | | 45-years |
| 4 | Average patient weight | 75.92 | 71 |
| | | | 81 |
| 5 | Average patient BSA | 1.86 | 67.02 |
| | | | 84.82 |
| 6 | OS curve selection for Pola+R-CHP and R-CHOP | Generalised Gamma | log-normal |
| 7 | | | exponential |
| 8 | PFS curve selection for Pola+R-CHP and R-CHOP | Generalised Gamma | log-normal |
| | | | exponential |
| 10 | Model Structure | Cure mixture model | Standard parametric model |
| 11 | Excess mortality | 1 | 1.1 |
| 12 | Supportive care costs | 2 years | 3 years |
| 13 | Utility values | GOYA trial (weighted) | POLARIX (cross walk to 3L) IPI 2–5 |
| 14 | Utility values general population | 2 years | 3 years |

Key: OS, overall survival; PD, progressed disease; PF, progression-free; PFS, progression-free survival.

**Table 45: Parameters varied in the scenario analysis**

| Parameter modified | Incremental costs (£) | Incremental QALYs | ICER (£/QALY) | % change from base case ICER |
|---|---|---|---|---|
| **Base case** | 34,398 | | | |
| **Model time horizon** | | | | |
| Time horizon, 35 years | [redacted] | [redacted] | 36,608 | 6.42 |
| Time horizon, 40 years | [redacted] | [redacted] | 35,521 | 3.26 |
| Time horizon, 45 years | [redacted] | [redacted] | 34,944 | 1.58 |
| **Patient baseline characteristics** | | | | |

| | | | | |
|---|---|---|---|---|
| Average patient weight (-5 kg) | [redacted] | [redacted] | 28,056 | -18.43 |
| Average patient weight (+5 kg) | [redacted] | [redacted] | 34,398 | 0.0 |
| Average patient BSA ($m^2$) (-5%; average body weight set to 66.35 kg) | [redacted] | [redacted] | 23,702 | -31.09 |
| Average patient BSA ($m^2$) (+5%; average body weight set to 83.96 kg) | [redacted] | [redacted] | 33,872 | -1.52 |
| **Survival modelling** | | | | |
| Cure mixture model (OS, PFS), log-normal | [redacted] | [redacted] | 46,038 | 33.83 |
| Cure mixture model (OS, PFS), exponential | [redacted] | [redacted] | 9,439 | -72.56 |
| Standard parametric model, Generalised Gamma | [redacted] | [redacted] | 60,385 | 75.54 |
| Excess mortality for long-term survivors (>2 years; excess hazard = 1.1) | [redacted] | [redacted] | 37,443 | 8.85 |
| **Supportive care costs** | | | | |
| Supportive care costs, 3 years | [redacted] | [redacted] | 35,332 | 2.71 |
| **Utility values** | | | | |
| POLARIX (Cross Walk to 3L) IPI 2–5 | [redacted] | [redacted] | 39,408 | 14.56 |
| Utility values general population | [redacted] | [redacted] | 34,334 | -0.18 |
| **Subsequent treatment** | | | | |
| POLARIX subsequent treatment | [redacted] | [redacted] | 32,195.23 | -4.31 |

Key: OS, overall survival; PD, progressed disease; PF, progression-free; PFS, progression-free survival, BSA, Body Surface Areal.

### Standard parametric model

The application of standard parametric models for PFS and OS extrapolation produced a change in ICER value of 75.54%. It should be noted, however, that the standard parametric extrapolations are less clinically plausible with regards to long-term patient survival in DLBCL. As seen in Figure 23, the long-term survival estimated by the cure mixture model aligned with the long-term survival KM data observed in clinical practice. In addition, the standard parametric survival models do not directly capture patients who go on to achieve sustained remission and subsequent long-term survival following treatment. Therefore, relative to the base case, application of the standard parametric extrapolations is likely to underestimate the survival benefit and thus the cost effectiveness of Pola+R-CHP vs R-CHOP.

**Excess mortality**

An increase in the excess mortality value of long-term remission DLBCL patients from 1 to 1.1 would be expected to result in a difference in ICER value of 8.85% relative to the base case. This is on the basis that long-term remission DLBCL patients after 2 years will not have the same mortality rate as the general population, following treatment with Pola+R-CHP (as discussed previously). Increasing the excess mortality from long-term remission DLBCL patients from 1 to 1.1 is not reflective of what is seen in the literature, therefore, achieving the same mortality rates as the general population after two years is used as the base case.

**Time horizon**

A reduction in time horizon would be expected to result in a 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+R-CHP. A short time horizon would therefore not capture the full benefits derived from treatment with Pola+R-CHP; therefore, a lifetime horizon of 60 years was used as the base case.

**Supportive care costs**

An increase in the incurred supportive care costs from 2 years to 3 years would be expected to result in a difference in ICER value of 2.71% relative to the base case. This is on the basis that a proportion of patients will incur supportive care costs for longer after achieving sustained remission and long-term survival following treatment with Pola+R-CHP. Increasing the supportive care costs from 2 years to 3 years is not reflective of UK clinical practice, so the base case applies the two-year time point.

**Subsequent treatment**

The application of the POLARIX subsequent treatment breakdown produced a change in ICER value of -4.31%, which resulted in a minimal change relative to the base case. However, implementing UK clinical input subsequent treatment breakdown is more reflective of UK clinical practice and was therefore used in the base case.

### B.3.8.4 Summary of sensitivity analyses results

From the PSA, at a willingness to pay (WTP) threshold of £50,000, the probability of Pola+R-CHP being cost-effective relative to R-CHOP was [redacted] 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 the supportive care costs in the PD health state for Pola+R-CHP and R-CHOP as well as the average patient age at baseline had the greatest impact on the ICER, none was found to result in a range of ICER values greater than a total of £8724.42.

The scenarios considered in Section B.3.8.3 resulted in ICER values that ranged £9,439 to £60,385. 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. The application of the standard parametric survival modelling, the log-normal distribution to the cure mixture model and the use of the POLARIX IPI 2–5 utility values were found to have had the largest effect on ICER values.

In conclusion, the DSA, PSA 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 (81), clinical expert validation and precedent of Committee acceptance in recent appraisals for interventions in R/R. The model was built to align with the NICE reference case (70), 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, in line with NICE's position statement (91).

Clinical expert opinion was sourced during model development to validate the assumptions in the model, to ensure they were clinically valid and/or aligned with UK clinical practice for DLBCL patients. Specifically, an advisory board of nine UK clinicians was held in October 2021 and an advisory board of 6 clinicians was held in February 2022 to discuss the natural history of DLBCL and standard clinical practice in the UK in order to inform the model (78). The plausibility of long-term extrapolations for PFS was validated through comparison to long-term data for polatuzumab vedotin regimens in DLBCL (see Section B.3.3.3).

### *B.3.11 Interpretation and conclusions of economic evidence*

A *de novo* economic analysis was conducted to evaluate the cost-effectiveness of Pola+R-CHP vs R-CHOP in the treatment of untreated DLBCL patients in the UK. The patient population included in the analysis reflects the POLARIX trial and is aligned with the population specified in the NICE final scope (92).

The economic analysis can be considered generalisable to the UK; the patient population in POLARIX is aligned with the population to be treated in UK clinical practice. The analysis was conducted from an NHS and PSS perspective, with health state resource utilisation based on a survey of UK physicians (72). Finally, key clinical assumptions in the model were validated in a recent advisory board of clinicians treating DLBCL patients in the UK (78).

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 POLARIX 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 that DLBCL patients who achieve two years' PFS are likely to subsequently experience long-term remission and survival aligned to the general population (78). The long-term plausibility of the cure-mixture models selected for the base case was validated against long-term survival data currently available for the GOYA trial.

An inherent limitation in the field of DLBCL is the lack of robust and comparable studies assessing therapies for DLBCL patients, thus limiting the number of interventions from the NICE scope that could be included in the model. However, robust comparative evidence between Pola+R-CHP and R-CHOP available from the randomised POLARIX study enabled R-CHOP to be selected as the key comparator to Pola+R-CHP in the model base case.

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. 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+R-CHP offers a new treatment option for untreated DLBCL patients who have a high unmet medical need, who may be rapidly progressing and need urgent disease control. Cost-effectiveness of Pola+R-CHP is driven by the substantially reduced progression in PFS as well as the reduction in supportive care and subsequent treatments patients receive when R-CHOP is administered. To summarise, Pola+R-CHP has the potential to prevent a significant number of DLBCL patients relapsing and becoming refractory to the disease. In addition, it has the potential to be cost-saving for the NHS in the long-term by reducing the supportive care and subsequent treatments costs.

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# NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

## Single technology appraisal

# Polatuzumab vedotin in combination for untreated diffuse large B-cell lymphoma [ID3901]

## Clarification responses

**March 2022**

| File name | Version | Contains confidential information | Date |
|---|---|---|---|
| ID3901_Pola_DLBCL_Clarification Responses_[redacted]_v1.0 | 1.0 | Yes | 01 June 2022 |



 

# Contents





 

 

 

 

# Tables and figures





 

# Section A: Clarification on effectiveness data

## *Decision problem*

**A1. Priority question. In company submission (CS) Table 1, the population in the column headed "Final scope issued by NICE" is stated as *"Adults with untreated diffuse large B-cell lymphoma*" and the population in the column headed "Decision problem addressed in the company submission" is stated as "*As per final scope issued by NICE*". The draft SPC also gives the population as**

[redacted] **However, the proposed treatment pathway and position of polatuzumab vedotin in CS Figure 1 shows that polatuzumab vedotin is for patients with an International Prognostic Index (IPI) score ranging from 2 to 5. Furthermore, CS Appendix E.1 states that one of the inclusion criteria of the POLARIX study was an IPI score of 2 to 5. Could the company please clarify whether or not the intended population for polatuzumab vedotin is restricted to adult patients with previously untreated diffuse large B-cell lymphoma (DLBCL) with an IPI score of 2 to 5?**

We can confirm that the intended patient population for polatuzumab vedotin in combination with rituximab, cyclophosphamide, doxorubicin, and prednisolone (R-CHP) is specific to adult patients with previously untreated diffuse large B-cell lymphoma (DLBCL) with an IPI score of 2 to 5 as per the POLARIX study population.

**A2. In CS Table 1, the comparator in the column headed "Final scope issued by NICE" is "Chemoimmunotherapy (including R-CHOP)", and the comparator in the column headed "Decision problem addressed in the company submission" is stated as "As per final scope issued by NICE". However, the CS only considers R-CHOP as a comparator. Can the company please clarify**



 

**whether any alternative comparator treatments were considered for inclusion in their submission?**

The only direct comparator used in the submission for Pola+R-CHP for 1L DLBCL is R-CHOP as per the POLARIX study. R-CHOP is the current UK standard of care for previously untreated DLBCL according to the British Society of Haematology (BSH) (1) and the Pan-London Haemato-Oncology Clinical Guidelines (2).

## *POLARIX trial*

**A3. CS section B.2.3.1 states *"Response was evaluated at the end of study treatment, or sooner in the event that a patient discontinued early. After completion of therapy, all patients were followed-up at clinic visits conducted every 3 months for 24 months, and then every 6 months until Month 60. After 5 years, patients were followed only for survival and initiation of a new anti-lymphoma therapy (NALT) approximately every 6 months until study termination, patient withdrawal of consent or death*." We note that the POLARIX Clinical Study Report (page 1) describes the study as ongoing. Can the company therefore please clarify:**

a) **Is the study currently ongoing?**

The POLARIX study is ongoing. This was the primary PFS analysis and occurred when both of the following conditions were met:

- Occurrence of approximately 228 INV-assessed PFS events
- At least 24 months after enrolment of the last patient

At the clinical cut off date (CCOD) of 28 June 2021, 879 patients were enrolled and 241 PFS events were observed. The median follow-up period was 28.2 months.



 

**b) Which data cuts are used in the CS clinical effectiveness sections and do these include all participants?**

The CCOD used for the clinical effectiveness section was the 28th June 2021 and includes all participants.

**c) Which data cuts are used in the health economics sections and do these include all participants?**

The CCOD used for the health economics section was the 28th June 2021 and includes all participants.

## *Systematic literature review*

**A4. CS B.2.1 states *"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."* CS Appendix D.1.1 states *"As part of the evidence generation strategy for polatuzumab vedotin in the 1L setting, a series of health technology assessment (HTA)-compliant systematic literature reviews (SLRs) were conducted to identify published studies (primary focus RCTs) for regimens in patients with previously untreated DLBCL*." CS Appendix D Table 9 states that interventions for the SLR were "*any pharmacological intervention used as first-line treatment*" and comparisons were "*No restrictions*". CS Appendix D Figure 1 (PRISMA flow diagram (original and update SLR)) shows that 69 primary publications were included in the review. However, CS B.2.2 only lists one study, the POLARIX study, as relevant clinical effectiveness evidence. Could the company please clarify how the systematic review described in CS Appendix D relates to the one study presented as relevant clinical effectiveness evidence in CS B.2.2.**

The objective of the SLR described in Appendix D was to identify published studies for any regimens used in the treatment of first-line DLBCL. Within the 69 unique trials identified, the POLARIX study was the only study identified that was deemed relevant to the decision problem of the current appraisal by providing evidence of the clinical effectiveness of Pola+R-CHP for the



 

treatment of 1L DLBCL. As the remaining studies identified were not included in the Section B.2.2 since they do not provide evidence of the clinical effectiveness of polatuzumab.

**A5. Please could the company provide details of how many reviewers were involved in the following processes. If more than one reviewer was involved, could the company clarify whether they worked independently of one another or not.**

**a) Screening of titles and abstracts**

All titles and abstracts identified through the literature searches were independently reviewed by two investigators to assess eligibility according to the population, interventions, and study designs of the Population, Intervention, Comparison, Outcomes and Study (PICOS) selection criteria corresponding with the research question. No articles were excluded at this stage for lack of reporting on an outcome of interest. Once title and abstract screening was completed, the investigators reconciled any discrepancies between studies selected as eligible as well as reasons for exclusion. If a consensus was not reached, a third investigator provided arbitration.

**b) Screening of full papers**

The same two investigators independently screened full texts of all articles deemed eligible for inclusion at the title and abstract screening phase. Once full-text screening was complete, the investigators reconciled any discrepancies between included studies as well as reasons for exclusion. If a consensus was not reached, a third investigator provided arbitration. This resulted in the final list of included studies that proceeded to the data extraction phase.

**c) Quality assessment**

In the first instance, studies were assessed using a validated tool by an investigator. A second independent investigator checked the assessments against the source publication. Once this second check was completed, the investigators



 

reconciled any discrepancies and if a consensus was not reached, a third investigator provided arbitration.

**d) Data extraction**

In the first instance, relevant data were extracted into pre-approved summary tables by an investigator. A second independent investigator checked the extractions against the source publication and checked whether there were any additional relevant data for extraction. Once data extraction was completed, the investigators reconciled any discrepancies and if a consensus was not reached, a third investigator provided arbitration.

**A6. CS Appendix D Figure 1 (PRISMA flow diagram (original and update SLR)) shows that 208 full text articles were excluded from the systematic review. CS Appendix D Figure 2 (PRISMA flow diagram (original SLR May 2016)) shows 208 full text articles were excluded, and CS Appendix D figure 3 (PRISMA flow diagram (update SLR January 2022)) shows that 103 full text articles were excluded. Could the company therefore clarify whether the number of full text articles in figure 1 is correct?**

Figure 1 in Appendix D provides details of the original SLR with the identified studies from the updated search (n=53) added at the bottom to provide the updated total of publications across both reviews. As such, the number of excluded full text articles indicated in Figure 1 (n=208) relates to the original SLR only and is not a combination of the two individual literature searches.

**A7. CS Appendix D.1.7 states "A list of studies excluded on the basis of full publication review is provided in Table 11, along with the rationale for exclusion". CS Appendix D Table 11 however only shows studies excluded at full publication review from the SLR update (N=103). Could the company clarify why they only list studies excluded at full publication for the SLR update?**

The original SLR and SLR update were conducted by two separate vendors. The new vendor received the original 2016 SLR to update the searches, but the report



 

did not contain the list of studies excluded at full publication. Please refer to Appendix D Table 11 for the SLR update in line with NICE's current guidelines for SLR searches.

**A8. CS B.2.5 states "*The quality assessment of the POLARIX trial is shown below (Table 8). See Appendix D.3 for the complete quality assessment of other relevant trials*." Appendix D.3 states "*Quality (risk of bias) assessment of RCTs reported as full publications was conducted using the seven-criteria checklist provided in Section 2.5 of the NICE single technology appraisal user guide. This approach is based on guidance provided by the Centre for Reviews and Dissemination (CRD) for assessing the quality of studies included in SLRs and assesses the likelihood of selection, performance, attrition and detection bias. Details of the assessment are included in Table 13*." However, CS Appendix D Table 13 appears to show an appraisal of health economic evaluation studies. Our assumption is that this is an error - the table should show QA of RCTs but instead shows a QA of economic evaluations. Could the company please clarify if this is correct, and supply the missing table of the QA of RCTs.**

Indeed, thank you for spotting this error. Please see Table 1 below for the correct list of QA of RCTs.

Please note, of the 69 publications identified, only 63 underwent quality assessment. The six publications listed below were not assessed as these were identified as conference abstracts and no full text manuscripts were available for these studies.

The excluded abstracts were:

- Bologna 2021
- Feng 2018
- Philips 2020
- Shi 2019
- Shi 2021
- Zhang 2021



 

**Table 1: Quality assessment results for parallel-group RCTs**

| Source | Trial | Random sequence generation (selection bias) | Allocation concealment (selection bias) | Blinding of participants and personnel (performance bias) | Blinding of outcome assessment (detection bias) | Incomplete outcome data (attrition bias) | Selective reporting (reporting bias) | Other bias |
|---|---|---|---|---|---|---|---|---|
| original SLR | ANZINTER3 (Merli, 2012) | Unclear risk | Unclear risk | Low risk | Low risk | Low risk | Low risk | Low risk |
| original SLR | ECOG4494/ CALGB97933 (Habermann, 2006) | Low risk | Low risk | Low risk | Low risk | Low risk | Low risk | Low risk |
| original SLR | Elly 2016 | Low risk | Low risk | Low risk | Low risk | Low risk | Low risk | Low risk |
| original SLR | Ferreri 2016 | Low risk | Low risk | Low risk | Low risk | Low risk | Low risk | Low risk |
| original SLR | Fridrik 2016 | Low risk | Low risk | Low risk | Low risk | Low risk | Low risk | Low risk |
| original SLR | Gobbi 2006 | Low risk | Low risk | Low risk | Low risk | Low risk | Low risk | Low risk |
| original SLR | Gonzalez-Barca 2015 | Low risk | Low risk | Low risk | Low risk | Low risk | Low risk | Low risk |
| original SLR | Goto 2014 | Low risk | Low risk | Low risk | Low risk | Low risk | Low risk | Low risk |
| original SLR | Herbrecht 2013 | Low risk | Low risk | Low risk | Low risk | Low risk | Low risk | Low risk |
| original SLR | Hoffmann-La Roche Ltd 2016 | Low risk | Low risk | Low risk | Low risk | Low risk | Low risk | Low risk |
| original SLR | Leonard 2015 | Low risk | Low risk | Low risk | Low risk | Low risk | Low risk | Low risk |
| original SLR | Lin 2015 | Low risk | Low risk | Low risk | Low risk | Low risk | Low risk | Low risk |
| original SLR | MAIN (Seymour, 2014) | Low risk | Low risk | Low risk | Low risk | Low risk | Low risk | Low risk |
| original SLR | Merli 2007 | Low risk | Low risk | Low risk | Low risk | Low risk | Low risk | Low risk |



 

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|---|---|---|---|---|---|---|---|---|
| original SLR | Molina 2014 | Low risk | Low risk | Low risk | Low risk | Low risk | Low risk | Low risk |
| original SLR | Morel 2010 | Low risk | Low risk | Low risk | Low risk | Low risk | Low risk | Low risk |
| original SLR | Mounier 2003 | Low risk | Low risk | Low risk | Low risk | Low risk | Low risk | Low risk |
| original SLR | Offner 2015 | Low risk | Low risk | Low risk | Low risk | Low risk | Low risk | Low risk |
| original SLR | Oki 2013 | Low risk | Low risk | Low risk | Low risk | Low risk | Low risk | Low risk |
| original SLR | Pfreundschuh 2006 | Low risk | Low risk | Low risk | Low risk | Low risk | Low risk | Low risk |
| original SLR | Rigacci 2013 | Low risk | Low risk | Low risk | Low risk | Low risk | Low risk | Low risk |
| original SLR | Rossille 2014 | Low risk | Low risk | Low risk | Low risk | Low risk | Low risk | Low risk |
| original SLR | Salah-Eldin 2014 | Low risk | Low risk | Low risk | Low risk | Low risk | Low risk | Low risk |
| original SLR | Sparano 2010 | Low risk | Low risk | Low risk | Low risk | Low risk | Low risk | Low risk |
| original SLR | UK NCRI (Cunningham, 2013) | Low risk | Low risk | Low risk | Low risk | Low risk | Low risk | Low risk |
| original SLR | Xia 2009 | Low risk | Low risk | Low risk | Low risk | Low risk | Low risk | Low risk |
| original SLR | Zhang 2009 | Low risk | Low risk | Low risk | Low risk | Low risk | Low risk | Low risk |
| SLR update | Advani 2018 HERILY | Low risk | Low risk | Low risk | Low risk | Low risk | Low risk | Low risk |
| SLR update | Alliance/CALGB 50303 (Bartlett, 2019) | Low risk | Low risk | Low risk | Low risk | Low risk | Low risk | Low risk |
| SLR update | Bagova 2021 | Low risk | Low risk | Low risk | Low risk | Low risk | Low risk | Low risk |
| SLR update | Candelaria 2019 | Low risk | Low risk | Low risk | Low risk | Low risk | Low risk | Low risk |
| SLR update | DLCL04 (Chiappella, 2017) | Low risk | Low risk | Low risk | Low risk | Low risk | Low risk | Low risk |



 

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|---|---|---|---|---|---|---|---|---|
| SLR update | FLYER (Poeschel, 2019) | Low risk | Low risk | Low risk | Low risk | Low risk | Low risk | Low risk |
| SLR update | Frontzek 2021 | Low risk | Low risk | Low risk | Low risk | Low risk | Low risk | Low risk |
| SLR update | GOYA (Vitolo, 2017) | Low risk | Low risk | Low risk | Low risk | Low risk | Low risk | Low risk |
| SLR update | Hara 2018 | Low risk | Low risk | Low risk | Low risk | Low risk | Low risk | Low risk |
| SLR update | Hegazy 2021 | Low risk | Low risk | Low risk | Low risk | Low risk | Low risk | Low risk |
| SLR update | Hu 2017 | Low risk | Low risk | Low risk | Low risk | Low risk | Low risk | Low risk |
| SLR update | Ji 2016 | Low risk | Low risk | Low risk | Low risk | Low risk | Low risk | Low risk |
| SLR update | Le Gouill 2021 GAINED | Low risk | Low risk | Low risk | Low risk | Low risk | Low risk | Low risk |
| SLR update | Leonard 2017 | Low risk | Low risk | Low risk | Low risk | Low risk | Low risk | Low risk |
| SLR update | Lugtenberg 2020 HOVON-84 | Low risk | Low risk | Low risk | Low risk | Low risk | Low risk | Low risk |
| SLR update | LYSA/GOELAMS (Lamy, 2018) | Unclear risk | Low risk | Low risk | Low risk | Low risk | Low risk | Low risk |
| SLR update | MabEase (Lugtenburg, 2017) | Low risk | Low risk | Low risk | Low risk | Low risk | Low risk | Low risk |
| SLR update | NCT00355199 (Cortelazzo, 2016) | Low risk | Low risk | Low risk | Low risk | Low risk | Low risk | Low risk |
| SLR update | NCT01793844 (Li, 2019) | Low risk | Low risk | Low risk | Low risk | Low risk | Low risk | Low risk |
| SLR update | NHL-001 (Xu, 2019) | Low risk | Low risk | Low risk | Low risk | Low risk | Low risk | Low risk |



 

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|---|---|---|---|---|---|---|---|---|
| SLR update | Nowakowsi 2021 ROBUST | Low risk | Low risk | Low risk | Low risk | Low risk | Low risk | Low risk |
| SLR update | Nowakowski 2021b ECOG-ACRIN trial E1412 | Low risk | Low risk | Low risk | Low risk | Low risk | Low risk | Low risk |
| SLR update | Nowakowski 2022 | Low risk | Low risk | Low risk | Low risk | Low risk | Low risk | Low risk |
| SLR update | Oberic 2021 SENIOR | Low risk | Low risk | Low risk | Low risk | Low risk | Low risk | Low risk |
| SLR update | Ohmachi 2021 JCOG0601 | Low risk | Low risk | Low risk | Low risk | Low risk | Low risk | Low risk |
| SLR update | PETAL (Dührsen, 2018) | Low risk | Low risk | Low risk | Low risk | Low risk | Low risk | Low risk |
| SLR update | PHOENIX (Younes, 2019) | Low risk | Low risk | Low risk | Low risk | Low risk | Low risk | Low risk |
| SLR update | PILLAR-2 (Witzig, 2018) | Low risk | Low risk | Low risk | Low risk | Low risk | Low risk | Low risk |
| SLR update | REMARC (Thieblemont , 2017) | Unclear risk | Unclear risk | Low risk | Low risk | Low risk | Low risk | Low risk |
| SLR update | REMoDL-B (Davies, 2019) | Low risk | Low risk | Low risk | Low risk | Low risk | Low risk | Low risk |
| SLR update | Rummel 2017<br><br>PrefMab | Low risk | Low risk | Low risk | Low risk | Low risk | Low risk | Low risk |



 

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|---|---|---|---|---|---|---|---|---|
| SLR update | Sancho 2021 | Low risk | Low risk | Low risk | Low risk | Low risk | Low risk | Low risk |
| SLR update | Shi 2020 | Low risk | Low risk | Low risk | Low risk | Low risk | Low risk | Low risk |
| SLR update | Song 2021 | Low risk | Low risk | Low risk | Low risk | Low risk | Low risk | Low risk |
| SLR update | Tilly 2022<br><br>POLARIX | Low risk | Low risk | Low risk | Low risk | Low risk | Low risk | Low risk |
| SLR update | Viswabandya 2019 | Low risk | Low risk | Low risk | Low risk | Low risk | Low risk | Low risk |



# Section B: Clarification on cost-effectiveness data

**B1. Priority question. Unless already submitted, please provide mean (plus standard deviation) EQ-5D-5L index values for both arms of the GOYA and POLARIX trials at baseline and all assessment time points, and any statistical analysis comparing these.**

We would like to inform you before providing mean (plus SE) EQ-5D-5L index values for both arms of POLARIX, an error was made when the POLARIX IPI 2-5 utility values (Cross Walk to 3L) were calculated. The reason for the miscalculation was POLARIX IPI 2-5 utility values (Cross Walk to 3L) estimated the mapped 3L values at the 5L baseline level, which is incorrect.

Therefore, instead of using the utility values below (Table 2) as submitted in the model on the 10th March:

**Table 2: Incorrect POLARIX IPI 2-5 utility values (Cross Walk to 3L)**

| Health state | Mean | SE | Lower CI | Upper CI |
|---|---|---|---|---|
| Progression-free survival | 0.843 | 0.01788 | 0.7644 | 0.8346 |
| Progressive disease | 0.800 | 0.008998 | 0.8174 | 0.8527 |

Legend: SE, standard error; CI, confidence intervals.

Please refer to the values below (Table 3):

**Table 3: Correct POLARIX IPI 2-5 utility values (Cross Walk to 3L)**

| Health state | Mean | SE | Lower CI | Upper CI |
|---|---|---|---|---|
| Progression-free survival | 0.812 | 0.01319 | 0.84 | 0.79 |
| Progressive disease | 0.769 | 0.01779 | 0.80 | 0.73 |

Legend: SE, standard error; CI, confidence intervals.

The utility values, SE and lower as well as upper CI were updated in the “utility values raw” tab in the model and the model will be resubmitted with the new utility values. The utility values in Table 3 result in a new scenario analysis. When using



POLARIX IPI 2-5 utility values (Cross Walk to 3L) as a scenario instead of the GOYA utility values (base case) the ICER changes to £36,722.

Table 4 shows the mean (plus standard error) EQ-5D-5L index values for both arms of the POLARIX trial at baseline and all assessment time points.



**Table 4: POLARIX study – mean (plus standard error) EQ-5D-5L index values for both arms at baseline and all assessment time points (3)**

| Treatment Group | Pola+R-CHP | | | | R-CHOP | | | |
|---|---|---|---|---|---|---|---|---|
| Visit** | Mean* | SE | 95% Lower CI | 95% Upper CI | Mean* | SE | 95% Lower CI | 95% Upper CI |
| Baseline | 0.8121 | 0.009393 | 0.7937 | 0.8306 | 0.811 | 0.009364 | 0.7926 | 0.8294 |
| Cycle 2 Day 1 | 0.8422 | 0.00867 | 0.8252 | 0.8592 | 0.8467 | 0.00866 | 0.8297 | 0.8637 |
| Cycle 3 Day 1 | 0.8532 | 0.008691 | 0.8361 | 0.8702 | 0.8422 | 0.008733 | 0.8251 | 0.8594 |
| Cycle 5 Day 1 | 0.8511 | 0.008733 | 0.834 | 0.8683 | 0.8365 | 0.008737 | 0.8193 | 0.8536 |
| Treatment comp or early discontinuation | 0.8432 | 0.008345 | 0.8269 | 0.8596 | 0.8453 | 0.008228 | 0.8292 | 0.8615 |
| Follow-up Month 3 | 0.8541 | 0.01456 | 0.8256 | 0.8827 | 0.8683 | 0.01429 | 0.8403 | 0.8963 |
| Follow-up Month 6 | 0.8516 | 0.009097 | 0.8337 | 0.8694 | 0.8669 | 0.009006 | 0.8493 | 0.8846 |
| Follow-up Month 9 | 0.8645 | 0.03706 | 0.7919 | 0.9372 | 0.8506 | 0.03704 | 0.778 | 0.9232 |
| Follow-up Month 12 | 0.8573 | 0.009146 | 0.8394 | 0.8753 | 0.8626 | 0.009365 | 0.8442 | 0.881 |
| Follow-up Month 15 | - | - | - | - | 0.8797 | 0.1025 | 0.6788 | 1.0805 |
| Follow-up Month 18 | 0.8594 | 0.009297 | 0.8411 | 0.8776 | 0.8658 | 0.00942 | 0.8473 | 0.8843 |
| Follow-up Month 24 | 0.87 | 0.01225 | 0.846 | 0.894 | 0.8565 | 0.01276 | 0.8314 | 0.8815 |

Legend: SE, standard error; CI, confidence intervals.

*Due to missing data very likely not filling the assumption of missing completely at random, the reported Means and corresponding SE's are based on Least Square Mean values (LSmeans). These estimates are derived using an mixed model for repeated measurements approach, where baseline, age, gender, visit, health state, randomized treatment, treatment visit interaction where fitted as fixed effects. To account for repeated measurements Combound Symmetry structure was fitted for the covariance variance matrix (The model was not converging with Unstructured covariance variance matrix). Kennward Rogers approximation was used for the degrees of freedom. The LSmeans are estimated at mean baseline utility value of 0.81 and mean age of 63. The analysis were done using SAS System 9.4 PROC MIXED-procedure.

**EQ5D data was primarily collected during study visits when patients were still in progression free health state, EQ-5D-5L would be captured in progressed health state when disease progression was detected at the study visit with a pre scheduled tumour assessment following a pre-scheduled EQ5D-5L data collection. Of the 5155 post baseline Utility index values only 140 (2.7%) were derived at EQ-5D-5L values reported in Progressed Health state.



Table 5 shows that there is no statistically significant difference between the two treatment arms when the EQ-5D-5L utility index values were collected (p=0.0016).

**Table 5: Type 3 tests of fixed effects (3)**

| Effect | Num DF | Den DF | F Value | Pr > F |
|---|---|---|---|---|
| Baseline | 1 | 811 | 312.82 | <.0001 |
| Randomised treatment group | 1 | 1627 | 0 | 0.9569 |
| Health state PFS vs PD | 1 | 4548 | 9.19 | 0.0024 |
| Study visit | 10 | 4184 | 2.83 | 0.0016 |
| Treatment by visit | 9 | 4180 | 1.41 | 0.1789 |
| Age at baseline | 1 | 771 | 8.96 | 0.0028 |
| Gender | 1 | 775 | 16.77 | <.0001 |

Legend: Num DF, numerator degrees of freedom; Den DF, denominator degrees of freedom.

.

The company was not able to provide the mean (plus standard deviation) EQ-5D-5L index values for both arms of the GOYA trial at baseline and all assessment time points because the GOYA utility values were measured with the EQ-5D-3L index.

**B2. Priority question. Please compare the long-term overall survival for R-CHOP in the economic model with the long-term data from the GOYA study and comment on which distribution provides the best long-term fit.**

As mentioned in Document B of ID1309, the GOYA trial, which was adjusted for imbalances in patient characteristics, was used to assess the clinical validity of the selected extrapolations for PFS in the POLARIX trial.

The adjusted PFS curve from the GOYA trial demonstrated a good alignment with the PFS curve from the POLARIX trial (hazard ratio 0.96, 95% CI 0.74–1.25). Therefore, the adjusted PFS curve from the GOYA trial can be used to validate the extrapolations of the cure-mixture model as seen in Figure 1 and

Figure 2. However, the same alignment cannot be observed in the GOYA and POLARIX OS curves (hazard ratio 0.673, 95% CI 0.459–0.989 after the GOYA R-CHOP arm was weighted to match the POLARIX R-CHOP-arm prognostic factors) as seen in Figure 3. This OS difference can partially be attributed to the change of



available standard of care in R/R DLBCL patients from the inception of GOYA to now. Therefore, it was not possible to compare long-term OS for R-CHOP in the POLARIX trial to the long-term data from the GOYA study.

**Figure 1: PFS curves from POLARIX and GOYA adjusted trial – R-CHOP**

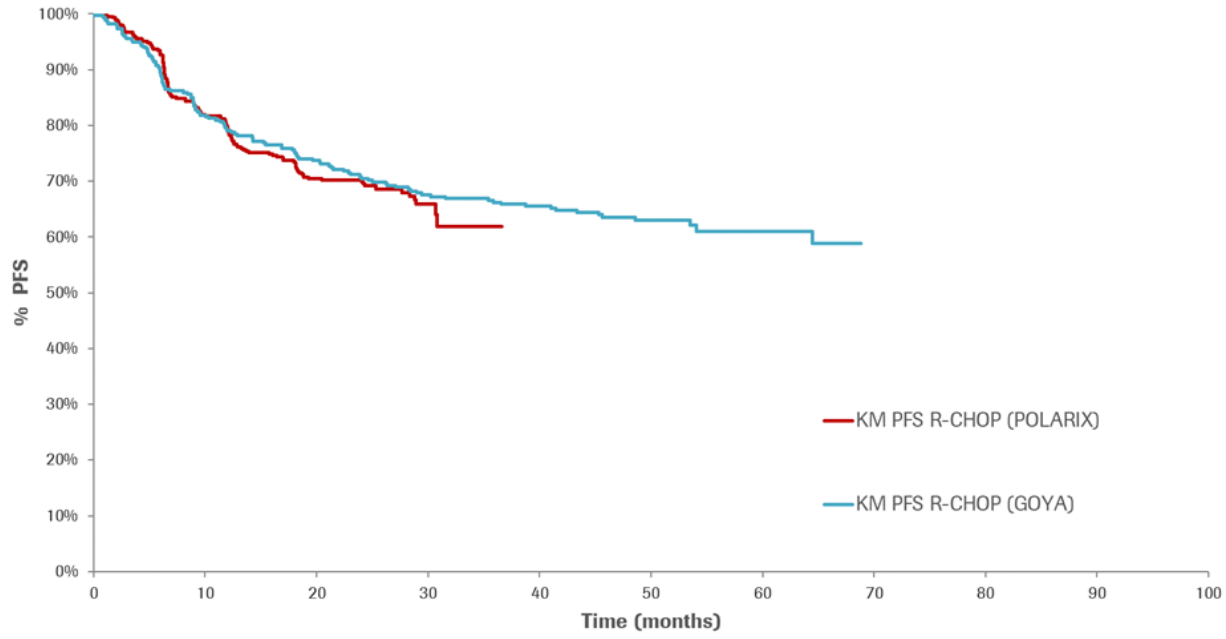



**Figure 2: External validation of mixture-cure model – R-CHOP**

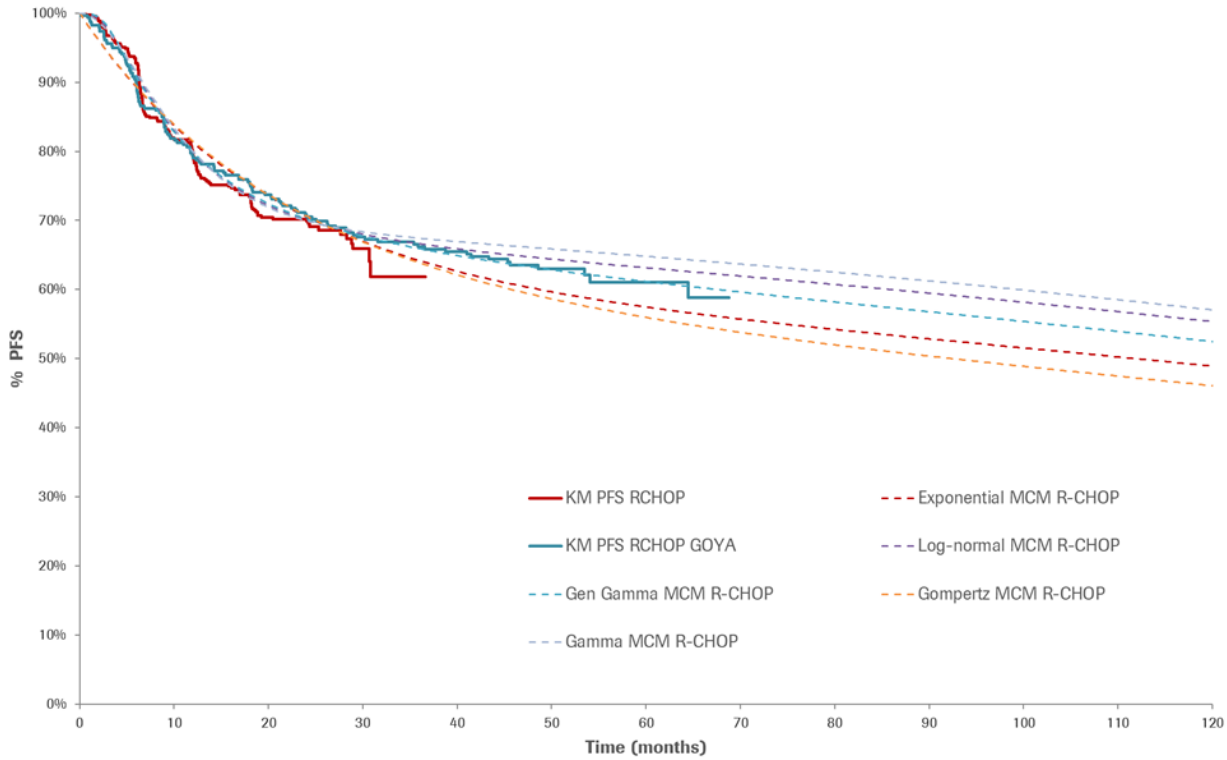
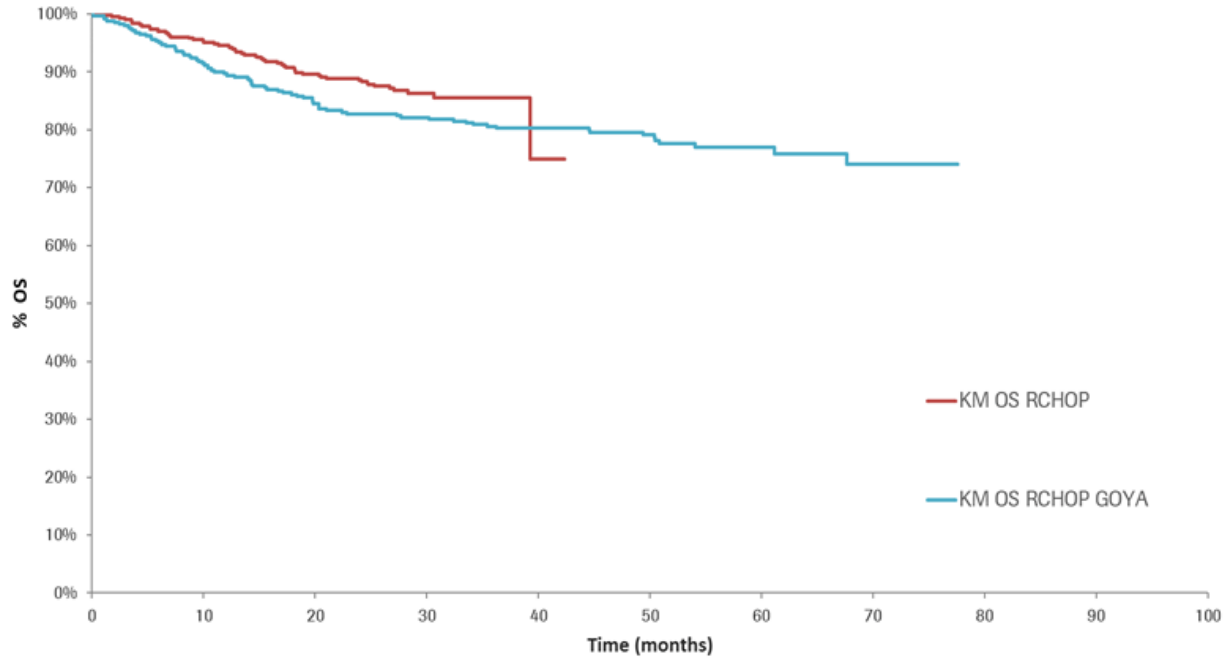




**Figure 3: OS curves from POLARIX and GOYA adjusted trial – R-CHOP**




**B3. Priority question. Please provide more details on how the cure fraction has been calculated. Also, please explain why it is not possible to fit a cure mixture model using the Weibull and log-logistic distributions.**

The cure-mixture model was developed using R software with a methodology that is based on Felizzi et al 2021 (4). Cure-mixture models assume that the patient population comprises of two subpopulations; the first subpopulation is considered "statically cured" and to be at the same risk of mortality as the age- and sex-matched general population (long-term remission or cured patients), whilst the second population has a reduced life expectancy. This disease related excess mortality in the second population functions (non long-term remission or non cured patients) is modelled using standard parametric survival. As the cure rate or long-term remission rate was estimated using PFS instead of OS, the long-term remission patients are not expected to experience progression or death from DLBCL during their life time. Therefore, PFS for long-term remission patients can be modelled based on the overall survival of the general population.



Non long-term remission patients are expected to experience progression and death from DLBCL, therefore, their PFS can be modelled based on time to progression and death from DLBCL.

The Progression free survival function $S_o$ (t+a) **(1)** in the overall patient population with mean age a at time t since randomization (measured in years) is a weighted average of the PFS in the cured and non-cured population.

The expected overall Survival $S_b$ (t+a) of the matched general population is weighted by the cure fraction π to account for the survival in the cured patients.

The function $S_u(t)$ describes the time to progression or death due to DLBCL among the patients with no long-term remission. This is modeled using standard parametric survival functions, weighted by the non-cure fraction rate (1-π) and multiplied by the survival probabilities of the matched general population $S_b$ (t+a) to account for the background mortality.

**(1)**

$$S_o(t+a) = S_b(t+a) \times \left(\pi + (1-\pi)S_u(t)\right)$$

The overall hazard function $h_o(a+t)$ **(2)** can be obtained as a negative derivative of the log $S_0(t + \alpha)$ and is a sum of the two hazard components.

The average background mortality hazard rate for the whole patient population is $h_b(a+t)$**.** The excess hazard of progression or death due to DLBCL in the non-cured fraction can be expressed as a function of $f_u(t)$, the density function of $F_u(t)=1- S_u(t)$ $S_u(t)$ and the cure fraction rate -π:



**(2)**

$$h_o(t) = h_b(t+a) + \frac{(1-\pi) \times f_u(t)}{\pi + (1-\pi) \times S_u(t)}$$

The $h_o(a+t)$ and $S_b(t+a)$ are considered known and are averages of the background hazard rate and survival probabilities derived for each patient based on age, gender, calendar year, and geographic region matched external life tables from mortality.org.

The cure fraction is estimated jointly with parameters of the chosen standard parametric survival function using the maximum likelihood method. The log likelihood function logL **(3)** is maximised to find the unknown cure fraction rate and survival function parameters that best explain the observed censored time to event data for N patients:

**(3)**

$$\log L = \sum_{i=1}^{N} d_i \times \log h_o(t_i) + \sum_{i=1}^{N} \log S_o(t_i)$$

Where,

$d_i$=1 if the i patient died and 0 if the patient i was censored.

$t_i$ is the time of death or censoring for patient i.



$h_o(t_i)$ is the hazard of PFS events for the patient i at time $t_i$ and can be obtained from the function above **(2)** by replacing the average background mortality hazard term $h_b(a+t)$ with patient specific age, gender, geographical region and calendar time matched background hazard $hb_i(t_i)$.

$So(t_i)$ is patient i's probability of surviving (progression free) until $t_i$ and can be obtained from function **(1)** for each patient by replacing the average general population survival $S_b(t+a)$ with the patient specific age, gender, geographical region and calendar time matched background survival probability from randomisation until $t_i$.

For those patients in long-term remission, no excess mortality was considered since the results from the recent HMRN analysis showed that the mortality of the patients with long term remission is identical to that of the general population (Figure 5).

A limited-memory BFGS optimization algorithm was utilised to find the maximum likelihood estimates. FlexSurv package was used to generate the standard functions (weibull, exp, gengamma etc). The R functions for estimating the hazard, survival and likelihood functions can be found in the github linked to Felizzi et al 2021 https://github.com/felizzi/Cure_models.

For all survival functions explored for PFS for both arms, parameterization for Weibull and log-logistic did not converge, therefore it was not possible to fit a mixture-cure model. We also explored these two distributions using the R-CHOP arm from the adjusted GOYA trial (longer follow-up), and the Weibull and log-logistic did not converge. We can therefore conclude that this lack of convergence was not due to the follow-up of the POLARIX trial.



**Figure 4: HMRN Cumulative incidence of death in IPI 2-5 1L DLBCL patients treated with R-CHOP who were progression free at 24 months vs matched general population.**

**B4. In CS B, Tables 44 and 45, scenario analysis, there are two scenarios for which the ERG is not able to reproduce the reported results:**

- **Average patient BSA ($m^2$) (-5%; average body weight set to 66.35 kg)**
- **Average patient BSA ($m^2$) (+5%; average body weight set to 83.96 kg)**

**Please provide information on how to reproduce these scenarios. The ERG also notes that the average body weight for these scenarios in Table 44 differs from those in Table 45. Please explain this discrepancy.**

We would like to thank you for noticing the difference in average body weight in Table 44 and Table 45. The correct values are in Table 44.We are submitting a revised model replacing the formulas in these cells with the correct values as shown in Table 6 below.



**Table 6: Scenario analysis**

| Scenario analysis | Value | How it was calculated | Cell (name) |
|---|---|---|---|
| BSA minimum | 67.3 | Variation of -5% of the average body weight (75.92) | E37 |
| BSA maximum | 85.2 | Variation of +5% of the average body weight (75.92) | F37 |
| Average patient weight minimum | 70.9 | Average patient weight (75.92) - 5 kg | E38 |
| Average patient weight maximum | 80.9 | Average patient weight (75.92) + 5 kg | F38 |

## *Subsequent treatment*

**B5. Priority question. Please provide more details on the costs and dosages of the subsequent drug regimens described in CS Table 33. Please also comment on whether these treatments are recommended by NICE.**

Table 7 and Table 8 provide detailed information about the costs and dosages of the subsequent treatments included in the model. All the treatments included were recommended by NICE to treat DLBCL patients and clinical experts validated their use in the UK.



**Table 7: Summary of subsequent treatment cost included in the model**

| Regimen | Drug | Composition (mg) | List price (£) | Discount | Net price (£) | Composition (mg) | List price (£) | Discount | Net price (£) | Source |
|---|---|---|---|---|---|---|---|---|---|---|
| R-GemOx | Gemcitabine | 200 | 2.56 | 0% | 2.56 | 1000 | 7.89 | 0% | 7.89 | eMIT 2021 (7) |
| R-GemOx | Oxaliplatin | 50 | 4.91 | 0% | 4.91 | 200 | 22.90 | 0% | 22.90 | eMIT 2021 (7) |
| R-GemOx | Rituximab | 100 | 157.17 | 50% | 78.585 | 500 | 785.84 | 50% | 392.92 | BNF 2021 (8) |
| Pola + BR | Polatuzumab | 30 | 2370 | [redacted] | [redacted] | 140 | 11060 | [redacted] | [redacted] | BNF 2021 (8) |
| Pola + BR | Bendamustine | 25 | 27.55 | 0% | 27.55 | 100 | 65.56 | 0% | 65.56 | eMIT 2021 (7) |
| Pola + BR | Rituximab | 100 | 157.17 | 50% | 78.585 | 500 | 785.84 | 50% | 392.92 | BNF 2021 (8) |
| R-GDP | Gemcitabine | 200 | 2.56 | 0% | 2.56 | 1000 | 7.89 | 0% | 7.89 | eMIT 2021 (7) |
| R-GDP | Dexamethasone | 2 | 4.93 | 0% | 4.93 | 4 | 83.35 | 0% | 83.35 | eMIT 2021 (7) |
| R-GDP | Cisplatin | 50 | 6.03 | 0% | 6.03 | 100 | 8.97 | 0% | 8.97 | eMIT 2021 (7) |
| R-GDP | Rituximab | 100 | 157.17 | 50% | 78.585 | 500 | 785.84 | 50% | 392.92 | BNF 2021 (8) |
| Yescarta | Axicabtagene ciloleucel | 1 | 282000 | 0% | 282000 | 1 | 282000 | 0% | 282000 | AMP (9) |
| Yescarta | Fludarabine | 50 | 20.28 | 0% | 20.28 | 50 | 20.28 | 0% | 20.28 | eMIT 2021 (7) |
| Yescarta | Cyclophosphamide | 500 | 8.21 | 0% | 8.21 | 1000 | 28.22 | 0% | 28.22 | BNF 2021 (8), eMIT 2021 (7) |
| Rituximab | Rituximab | 100 | 157.17 | 50% | 78.585 | 500 | 785.84 | 50% | 392.92 | BNF 2021 (8) |
| DECC | Dexamethasone | 8 | 2.40 | 0% | 2.4002 | 8 | 2.40 | 0% | 2.40 | Assumption |
| DECC | Chlorambucil | 2 | 0.45 | 0% | 0.45 | 2 | 0.45 | 0% | 0.45 | BNF 2021 (8) |
| DECC | Etoposide | 100 | 3.84 | 0% | 3.84 | 500 | 9.94 | 0% | 9.94 | eMIT 2021 (7) |
| DECC | Lomustine | 40 | 39.04 | 0% | 39.04 | 40 | 39.04 | 0% | 39.04 | BNF 2021 (8) |
| Pixantrone | Pixantrone | 29 | 553.50 | 0% | 553.50 | 29 | 553.50 | 0% | 553.50 | BNF 2021 (8) |

Key: AMP, Actual Medicinal Product; BNF, British National Formulary; eMIT, electronic market information tool.

**Table 8: Treatment cycles of the subsequent line of treatments**

| Regimen | Drug | Dosing | Dose per cycle (mg) | Cycle length (days) | Cycles | Reference |
|---|---|---|---|---|---|---|
| R-GemOx | Gemcitabine | mg/m$^2$ | 1000 | 14 | 6 | https://nssg-test.oxford-haematology.org.uk/documents/243/L-100-r-gem-ox.pdf (10) |
| R-GemOx | Oxaliplatin | mg/m$^2$ | 100 | 14 | 6 | https://nssg-test.oxford-haematology.org.uk/documents/243/L-100-r-gem-ox.pdf (10) |
| R-GemOx | Rituximab | mg/m$^2$ | 375 | 14 | 6 | https://nssg-test.oxford-haematology.org.uk/documents/243/L-100-r-gem-ox.pdf (10) |
| Pola + BR | Polatuzumab | mg/kg | 2 | 21 | 4.4 | Time-to-off-treatment data GO29365 |
| Pola + BR | Bendamustine | mg/m$^2$ | 180 | 21 | 4.2 | Time-to-off-treatment data GO29365 |
| Pola + BR | Rituximab | mg/m$^2$ | 375 | 21 | 4.3 | Time-to-off-treatment data GO29365 |
| R±GDP | Gemcitabine | mg/m$^2$ | 2000 | 21 | 3 | Crump et al. 2014 (11) |
| R±GDP | Dexamethasone | mg | 160 | 21 | 3 | Crump et al. 2014 (11) |
| R±GDP | Cisplatin | mg/m$^2$ | 75 | 21 | 3 | Crump et al. 2014 (11) |
| R+GDP | Rituximab | mg/m$^2$ | 375 | 21 | 3 | Crump et al. 2014 (11) |
| Yescarta | Axicabtagene ciloleucel | fixed | 1 | 1 | 1 | FDA 2017b (12) |
| Yescarta | Fludarabine | mg/m$^2$ | 90 | 1 | 1 | FDA 2017b (12) |
| Yescarta | Cyclophosphamide | mg/m$^2$ | 1500 | 1 | 1 | FDA 2017b (12) |
| DECC | Dexamethasone | mg/m$^2$ | 30 | 28 | 2 | Northern Cancer Alliance 2016 (3) |
| DECC | Chlorambucil | mg/m$^2$ | 60 | 28 | 2 | Northern Cancer Alliance 2016 (3) |
| DECC | Etoposide | mg/m$^2$ | 450 | 28 | 2 | Northern Cancer Alliance 2016 (3) |
| DECC | Lomustine | mg/m$^2$ | 80 | 28 | 2 | Northern Cancer Alliance 2016 (3) |
| Pixantrone | Pixantrone | mg/m$^2$ | 150 | 28 | 2 | Eyre et al. 2016 (13) |
| Rituximab | Rituximab | mg/m$^2$ | 375 | 7 | 8 | Tobinai et al. 2004 (14) |



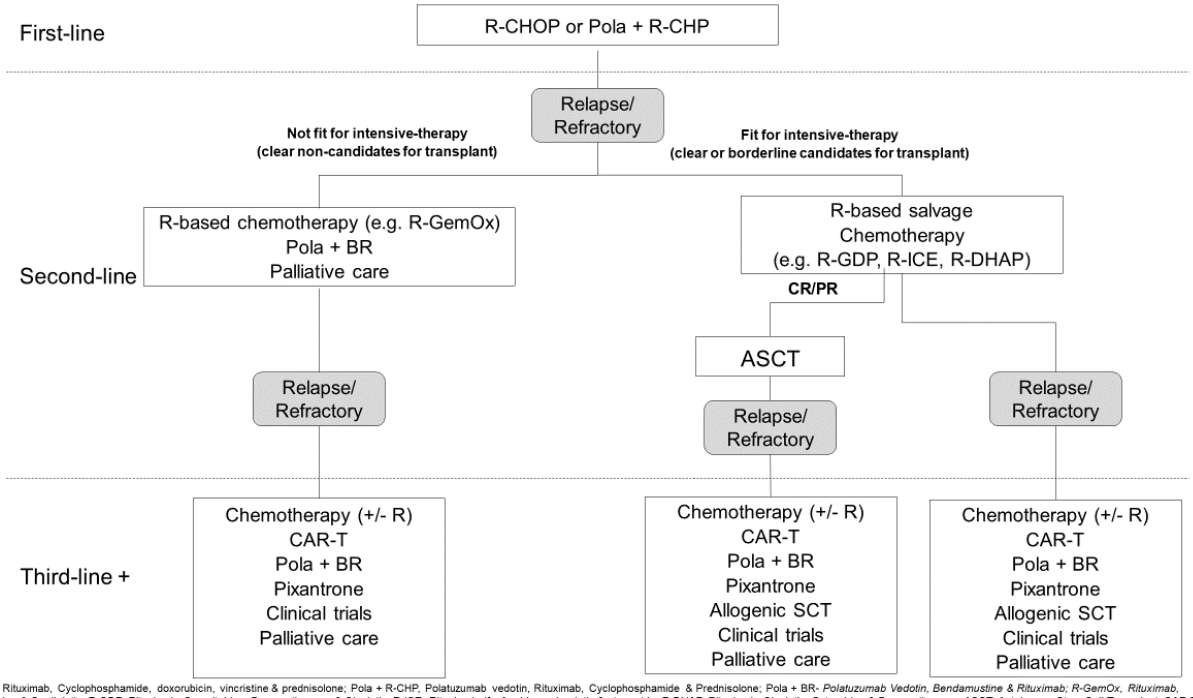
 

**B6. Please explain why the subsequent treatments used in the economic model for patients with progressed disease differ from those in the NICE scope for TA649 (Polatuzumab vedotin with rituximab and bendamustine for treating relapsed or refractory diffuse large B-cell lymphoma).**

The NICE scope for TA649 (Polatuzumab vedotin with rituximab and bendamustine for treating relapse or refractory diffuse large B-cell lymphoma [R/R DLBCL]) (15) only focused on a specific subpopulation of adult R/R DLBCL patients, specifically those for whom a haematopoietic stem cell transplant (SCT) is not suitable, therefore narrowing the subsequent treatment options that could be used in the TA649 economic model.

For this submission (ID1309) all potential treatment options depicted in Figure 6 come into scope for patients who are treated with either Pola+R-CHP or R-CHOP treatment in the first line DLBCL setting and then go on to develop R/R DLBCL . This pathway has been validated by clinical experts and is adapted from NICE and BSH guidelines.

**Figure 5: Subsequent treatment options available for patients with R/R DLBCL following R-CHOP or Pola+R-CHP treatment**




R-CHOP, Rituximab, Cyclophosphamide, doxorubicin, vincristine & prednisolone; Pola + R-CHP, Polatuzumab vedotin, Rituximab, Cyclophosphamide & Prednisolone; Pola + BR- *Polatuzumab Vedotin, Bendamustine & Rituximab; R-GemOx, Rituximab, Gemcitabine & Oxaliplatin; R-GDP, Rituximab, Gemcitabine, Dexamethasone & Cisplatin; R-ICE, Rituximab, ifosfamide, carboplatin & etoposide; R-DHAP, Rituximab, Cisplatin, Cytarabine & Dexamethasone; ASCT, Autologous Stem Cell Transplant; CAR-T, Chimeric Antigen Receptor T-Cell*



Adapted from NICE guidelines (16), BSH guidelines (1), and in collaboration with clinical experts (17).

**B7. Please provide the confidence intervals for the number of subsequent systemic treatments after first line (CS Table 34).**

Below are the confidence interval for the number of subsequent treatments for the average patient in the ITT population as seen in Table 9. We have also provided the CI's for the total number of subsequent treatments. Please note that this is based on limited data follow-up (June 2021 data cut) and is due to change when we receive the June 2022 data cut.



**Table 9: Confidence intervals subsequent treatments POLARIX**

| Treatment | ITT (n) | Patients with any subsequent treatment (n) | Subsequent treatments (n) | Average number of subsequent treatments among patients with any subsequent lines after 1L treatment | Average number of subsequent lines per patient in ITT | 95% confidence interval for the average number of treatment lines in ITT* | | 95% confidence interval for subsequent treatment lines** | |
|---|---|---|---|---|---|---|---|---|---|
| Pola+R-CHP | 440 | 69 | 123 | 1.78 | 0.28 | 0.23 | 0.33 | 101.26 | 144.74 |
| R-CHOP | 439 | 100 | 197 | 1.97 | 0.45 | 0.39 | 0.51 | 169.49 | 224.51 |

*CI based on normal approximation, assuming number of treatment lines following a Poisson distribution.

** CI derived from the CI for average number of treatment lines per patient in ITT

## *Adverse events*

**B8. In the CS section B.3.5.3 it states that the cost of treating adverse events were taken from NHS reference costs (2019/20), whereas in the economic model it states that 2017/2018 reference costs were used (sheet AE costs). Please clarify which source was used. In addition, for each adverse event, please state whether the costs were taken from the total HRG costs or from a different category.**

Apologies, the reference in the model was incorrect. All adverse event costs were taken from the 2019/2020 NHS reference costs. Please find the updated adverse events in Table 10.

**Table 10: Adverse events unit costs**

| Event | Unit cost | Source (All HRGs from the 2019-20 NHS reference costs) |
|---|---|---|
| Anaemia | £351 | Average unit cost of SA01G-K, SA03G-H, SA04G-L, SA05G-J; **Day Case** |
| Diarrhoea | £1,021 | Average unit cost of FD10J, FD10K, FD10L, FD10M; **Day Case** |
| Febrile neutropenia (Grade 3) | £1,848 | TA306 (£1,627); Inflated to 2019-20 using the UK GDP implicit price deflators from 2017-18 to 2019-20 = 1.06, as recommended by Turner H et al 2019 (18) |
| Febrile neutropenia (Grade 4) | £1,848 | TA306 (£1,627); Inflated to 2019-20 using the UK GDP implicit price deflators from 2017-18 to 2019-20 = 1.06, as recommended by Turner H et al 2019 (18) |
| Neutropenia (Grade 3) | £503 | Average unit cost of SA35A-E; **Day Case** |
| Neutropenia (Grade 4) | £503 | Average unit cost of SA35A-E; **Day Case** |
| Neutrophil count decreased (Grade 3) | £120 | Average of WF01A and WF01C; **NCL**; Medical Oncology |
| Neutrophil count decreased (Grade 4) | £120 | Average of WF01A and WF01C; **NCL**; Medical Oncology |
| Pneumonia | £2,487 | Average unit cost of DZ11K-V; **NES** |



**B9. Please explain why the frequency of serious adverse events reported in CS Table 16 differs from that reported in CS Table 23. Please refer to the tables in the CSR where these data in CS Table 23 are reported.**

CS Table 23 only includes treatment-related adverse events with toxicity grade 3 or higher, which were either serious AEs or required care (requiring additional treatment, surgical procedure, or study discontinuation). Any grade 3 or higher AEs that did not generate ~~any~~ costs were excluded; hence, there is discrepancy between CS Table 16 and CS Table 23.

## *Supportive care costs*

**B10. CS B, Table 29 reports the supportive care resource use unit costs included in the model. We were unable to match the following costs to the sources ((Curtis and Burns, 2018) and those in TA306, ERG report Table 37). Please provide further information on how these costs have been calculated and explain why the following costs do not match the sources.**

- **Residential care (day)**

The residential care (day) cost was extracted from Curtis and Burns 2018 (19), which reported an establishment cost of £158 per permanent resident day (local authority) and £101 for establishment cost plus personal living expenses and external services per permanent resident day (private sector). The model assumed the average estimate of 129.5 =((158+101)/2). This value was then inflated with a correction of 1.06, resulting in 137.27 = (129.5* 1.06).

- **Day care (day)**

The day care (day) cost was extracted from ~~the~~ Curtis and Burns, 2018 (£58 per client attendance - Local authority own-provision day care for older people (age 65+). This value was inflated with a correction of 1.06, resulting in 61.48= (58* 1.06).

**B11. CS B Table 30 reports one-off costs for the progressed disease state. We were unable to match the following costs to the source (TA306, ERG report**



**Table 41). Please provide further information on how these costs have been calculated and explain why the following costs do not match the economic model and the source. The parameters are Radiotherapy, ECG, MUGA, PET-CT, Bone marrow transplant, and MRI.**

Table 30 provides the proportion of patients who used the parameters mentioned in one-off cost for progressed disease state. The right title for this table is “One-off costs, PD (Proportion of patients requiring resource)” as seen in Table 11. The proportion of patients using radiotherapy came from the POLARIX trial. For the ECG, MUGA, PET-CT, bone marrow and MRI the proportion of patients was estimated following the TA306 submission. They were calculated using the proportion of their use from TA306 (ERG report Table 41) and they were applied to the proportion of patients who had a subsequent treatment in the model.

**Table 11: One-off costs, PD (proportion of patients requiring resource)**

| Treatment | Pola+R-CHP | R-CHOP | Source |
|---|---|---|---|
| Radiotherapy | 18.2% | 27.2% | POLARIX NALT data, pooled |
| ECG | (69/440)*67%= 10.5% | (100/439)*67%=15.3% | TA306 (20), ERG report Table 41[a b] |
| MUGA | (69/440)*33%= 5.2% | (100/439)*33%=7.5% | TA306 (20), ERG report Table 41[a b] |
| MRI | (69/440)*7%= 1.1% | (100/439)*7%=1.6% | TA306 (20), ERG report Table 41[a b] |
| PET-CT | (69/440)*57%= 8.9% | (100/439)*57%=13.0% | TA306 (20), ERG report Table 41[a b] |
| Bone marrow biopsy | (69/440)*70%= 11.0% | (100/439)*70%=15.9% | TA306 (20), ERG report Table 41[a b] |

[a] TA306. [b] One-off costs weighted by the proportion of patients requiring the respective resource.

Key: CT, computed tomography; ECG, electrocardiogram; MRI, magnetic resonance imaging; MUGA, multiple-gated acquisition scan; PD, progressed disease; PET-CT, positron emission tomography–computed tomography; PFS, progression-free survival; PD, progressed disease.



**B12. CS B, Table 30 reports the annual frequency of resource use in PFS and PD. We were unable to match the following resources to the sources. Please provide further information on how these costs have been calculated and explain why these resources' values do not match with the source**

- **Home care (day) (source TA306, ERG report, Table 37)**
- **Radiologist (visit) (source TA306, ERG report, Table 38)**
- **Nurse (visit) (source TA306, ERG report, Table 38)**
- **CT scan (source TA306, ERG report, Table 38)**

These costs were calculated based on TA306 (20). Table 37 and Table 38 from TA306 (ERG report) provide the frequency in 28 days. In the model, these frequencies were converged to annual frequency as shown below. After checking the source we noticed that four (highlighted in pink) annual frequencies did not match the source. Thank you for spotting this error, we are sending the corrected model and the updated Table 12 below.

**Table 12: Annual frequency of resource use in PFS and PD**

| | PFS | PFS on treatment | PD | Source |
|---|---|---|---|---|
| Home care (day) | **1.17*52.2/4 = 15.3** | 4.67*52.2/4 = 60.9 | 9.33*52.2/4 = 121.7 | TA306 (20), ERG report Table 37 |
| Radiologist (visit) | 0.33*52.2/4 = 4.3 | **1.33*52.2/4 = 17.3** | 0.00*52.2/4 = 0.0 | TA306 (20), ERG report Table 38 |
| Nurse (visit) | 1.00*52.2/4 = 13.0 | 4.00*52.2/4 = 52.2 | **= 2.00** | TA306 (20), ERG report Table 38 and Table 40 |
| CT scan | 0.31*52.2/4 (PFS) = 4.0 | 0.31* 52.2/4 (PFS on treatment) = 4.0 | **0.03*52.2/4 = 0.4** | TA306 (20), ERG report Table 38 |

# Section C: Textual clarification and additional points

Based on the errors identified and mentioned above, the updated base case is the following as seen in Table 13.



**Table 13: Base case results (with PAS for Polivy)**

| Technologies | Total costs (£) | Total LYG | Total QALYs | Inc. costs (£) | Inc. LYG | Inc. QALYs | ICER (£/ LYG) | ICER (£/ QALY) |
|---|---|---|---|---|---|---|---|---|
| **Pola+R-CHP** | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | 26,899 | 34,138 |
| **R-CHOP** | [redacted] | 11.832 | 9.001 | - | - | - | - | - |

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NICE National Institute for Health and Care Excellence

# Patient organisation submission

## Polatuzumab vedotin in combination for untreated diffuse large B-cell lymphoma [ID3901]

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on conditions and their treatment that is not typically available from other sources.

To help you give your views, please use this questionnaire with our guide for patient submissions.

You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type. [Please note that declarations of interests relevant to this topic are compulsory].

**Information on completing this submission**

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 10 pages.

| **About you** | |
|---|---|
| 1.Your name | [redacted] |

| | |
|---|---|
| 2. Name of organisation | Lymphoma Action |
| 3. Job title or position | [redacted] |
| 4a. Brief description of the organisation (including who funds it). How many members does it have? | Lymphoma Action is a national charity, established in 1986, registered in England and Wales and in Scotland. We provide high quality information, advice and support to people affected by lymphoma – the 5th most common cancer in the UK. We also provide education, training and support to healthcare practitioners caring for lymphoma patients. In addition, we engage in policy and lobbying work at government level and within the National Health Service with the aim of improving the patient journey and experience of people affected by lymphoma. We are the only charity in the UK dedicated to lymphoma. Our mission is to make sure no one faces lymphoma alone.<br><br>Our work is made possible by the generosity, commitment, passion and enthusiasm of all those who support us. 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. Has the organisation received any funding from the manufacturer(s) of the technology and/or comparator products in the last 12 months? [Relevant | Roche - £22,000 for Digital Patient Services, Lymphoma Management, Nurses Training |

| | |
|---|---|
| manufacturers are listed in the appraisal stakeholder list.]<br><br>If so, please state the name of manufacturer, amount, and purpose of funding. | |
| 4c. Do you have any direct or indirect links with, or funding from, the tobacco industry? | None |
| 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 six 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 | DLBCL is an aggressive lymphoma. Patients have said it is *"difficult"* to live with DLBCL. 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. DLBCL in the stomach or bowel can cause abdominal discomfort or pain, diarrhoea or bleeding and DLBCL in the chest can cause a cough or breathlessness. Around 1 in 3 people with DLBCL experience fevers, night sweats and |

| | |
|---|---|
| experience when caring for someone with the condition? | unexplained weight loss. Fatigue, loss of appetite and severe itching are also common. Symptoms of DLBCL usually develop rapidly and progress quickly.<br><br>DLBCL is treated with the aim of cure. During treatment, patients often spend many weeks in hospital, isolated from family and friends. One patient commented, *"Life was completely on hold".*<br><br>Side effects of intensive chemotherapy, such as sickness, diarrhoea, hair loss and neutropenia can be extremely debilitating, affecting many aspects of life. 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. Financially, it can be hard to cope: "*Not earning has inevitably raised some questions regarding future financial stability*." Another patient said that they and their wife had struggled with the initial diagnosis, but that *"the relatively good percentage overall survival, even 'cure' in my type helped. We are both mainly retired so our finances were not greatly affected, and apart from domestic concerns for our grown up kids we live fairly normal lives."*<br><br>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. Others have told us of repeated infections requiring hospital admission. Late effects of treatment are also a psychological and physical challenge. One patient described the side effects from their treatment: *"Fatigue, constipation, hair loss, lack of appetite, change of taste, sore mouth, sore gums, lack of sleep, muscle pain, weakness and low mood."*<br><br>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 their family. One patient said their quality of life was impacted and day to day living was difficult. Even after successful treatment, the relief of getting back into some kind of normal life is marred by the anxiety of relapse: *"For about a year I lived in fear of recurrence".*<br><br>People with DLBCL can be very ill and require a huge amount of support: *"I had little quality of life during treatment as it dominated my life and that of my husband who had to take on the role of carer despite my being his registered carer. We both suffered considerable stress and anxiety".* It can be very difficult for carers to understand what their loved one is experiencing: *"They see the problems you are experiencing,* |

| | |
|---|---|
| | *but feel helpless. During treatment they can see the visible effects in your health and appearance which can be very difficult for them to grasp".*<br>DLBCL has a significant emotional and psychological impact on any dependants: *"My wife was my carer… emotionally she found it very difficult. Even to this day she worries about me and my health and I was diagnosed 17 years ago. If I have the slightest ache or pain she tends to think the worst."* |
| **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. 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: *"Long term side effects such as feet that are constantly frozen isn't nice".*<br>Treatment has a long-lasting impact on physical and mental wellbeing. Most patients felt it took many years to recover from their treatment but were grateful to have received it: *"I feel so grateful for the treatment/s I had. I received an extension to my life and were it not for the prompt treatment I received… I would not be here now".* Some found that aftercare was limited. |
| 8. Is there an unmet need for patients with this condition? | Patients felt there is an unmet need for an effective, less demanding treatment with fewer side effects: *"It is good when new drugs are introduced to reduce side effects."* |
| **Advantages of the technology** | |
| 9. What do patients or carers think are the advantages of the technology? | One patient summarised the advantages as: *"Speedier treatment, more targeted. Less side effects."*<br>Some patients had attributed some of their side effects from R-CHOP to Vincristine, so were encouraged by its absence in this new treatment: *"It appears Vincristine is not included in this treatment which if so, is a bonus. Living with feet that are permanently cold is not all that pleasant. I understand Vincristine to be* |

| | |
|---|---|
| | *the cause of this."* Another patient said: *"It is very similar to R-CHOP. As it does not contain vincristine I would consider that an advantage."* |
| **Disadvantages of the technology** | |
| 10. What do patients or carers think are the disadvantages of the technology? | Patients who had had received R-CHOP felt that "*the benefit side of Vincristine would need to be addressed in Polatuzumab". Another patient said: "From the outside its overall profile of side effects is not greatly different to R-CHOP. It's important to remember that R-CHP still has several very toxic elements."* |
| **Patient population** | |
| 11. Are there any groups of patients who might benefit more or less from the technology than others? If so, please describe them and explain why. | One patient wrote: *"From preliminary data I have seen it seems to prolong progression free survival compared to R-CHOP and some sub-groups such as older people or less fit people may do better."* |

| | |
|---|---|
| **Equality** | |
| 12. Are there any potential equality issues that should be taken into account when considering this condition and the technology? | No equality considerations. |
| **Other issues** | |
| 13. Are there any other issues that you would like the committee to consider? | None. |
| **Key messages** | |
| 14. In up to 5 bullet points, please summarise the key messages of your submission:<br><br>• Any new treatment offers a potential lifeline.<br>• Current treatments are very intensive, requiring long stays in hospital away from the support of family and friends and incurring serious side effects and late effects.<br>• People with 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. | |

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## Evidence Review Group Report commissioned by the NIHR Evidence Synthesis Programme on behalf of NICE

## Polatuzumab vedotin in combination for untreated diffuse large B-cell lymphoma

| | |
|---|---|
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**Declared competing interests of the authors and advisors**

The authors declare none.

Dr David Wrench is a voluntary member of the Healthcare Professional Advisory Panel for the charity Blood Cancer UK.



**Rider on responsibility for report**

The view expressed in this report are those of the authors and not necessarily those of the NIHR Pro Evidence Synthesis Programme. Any errors are the responsibility of the authors.

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**Contributions of authors**

Emma Maund critically appraised the clinical effectiveness systematic review, and drafted the report; Keith Cooper critically appraised the health economic systematic review, critically appraised the economic evaluation, and drafted the report; Marcia Tomie Takahashi critically appraised the health economic systematic review, critically appraised the economic evaluation, and drafted the report; Jonathan Shepherd critically appraised the clinical effectiveness systematic review, drafted the report and is the project co-ordinator and guarantor.

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# LIST OF ABBREVIATIONS

| | |
|---|---|
| ABC | Activated B-cell |
| AE | Adverse event |
| AIC | Akaike Information Criterion |
| BIC | Bayesian Information Criterion |
| BICR | Blinded independent central review |
| BNF | British National Formulary |
| BOR | Best overall response |
| BSA | Body surface area |
| CAR-T | Chimeric antigen receptors cell therapy |
| CI | Confidence interval |
| CIC | Commercial in confidence |
| CMM | Cure mixture model |
| CR | Complete response |
| CRD | Centre for Reviews and Dissemination |
| CS | Company submission |
| CSR | Clinical study report |
| CTCAE | Common Terminology Criteria for Adverse Events |
| DFS | Disease free survival |
| DOR | Duration of response |
| DSU | Decision Support Unit |
| DLBCL | diffuse large B-cell lymphoma |
| ECOG | Eastern Cooperative Oncology Group |
| EFSeff | Event-free survival - efficacy |
| EMA | European Medicines Agency |
| EMC | Electronic Medicines Compendium |
| EORTC | European Organization for Research and Treatment of Cancer; |
| EPAR | European Public Assessment Report |
| EQ-5D-3L | European Quality of Life Working Group Health Status Measure 3 Dimensions, 3 Levels |
| EQ-5D-5L | European Quality of Life Working Group Health Status Measure 5 Dimensions, 5 Levels |
| ERG | Evidence Review Group |
| FACT/GOG-NTX | Functional Assessment of Cancer Treatment/Gynecologic Oncology Group-Neurotoxicity |

| | |
|---|---|
| FACT-Lym LymS | Functional Assessment of Cancer Therapy - Lymphoma Lymphoma Subscale |
| FDG-PET | Fluorodeoxyglucose positron emission tomography |
| GCB | Germinal centre B cells |
| HRG | Healthcare Resource Group |
| HRQoL | Health-related quality of life |
| HTA | Health technology assessment |
| ICER | Incremental cost-effectiveness ratio |
| IPD | Individual patient level data |
| IPI | International Prognostic Index |
| ISRT | Involved site radiation treatment |
| ITT | Intent to treat |
| KM | Kaplan Meier |
| LDH | lactate dehydrogenase |
| mITT | Modified intent to treat |
| NALT | New anti-lymphoma treatment |
| NHL | Non-Hodgkin lymphoma |
| NHS | National Health Service |
| NICE | National Institute for Health and Care Excellence |
| NR | Not reported |
| PET | Positron emission tomography |
| PET-CT | Positron emission tomography-computerised tomography |
| PFS | Progression Free Survival |
| PH | Proportional hazard |
| Pola | Polatuzumab vedotin |
| Pola+R-CHP | Polatuzumab vedotin plus rituximab, cyclophosphamide, doxorubicin, and prednisolone |
| PRO | Patient reported outcome |
| PSA | Probabilistic sensitivity analysis |
| PSS | Personal Social Services |
| QALY | Quality-adjusted life year |
| QoL | Quality of life |
| PH | Proportional hazards |
| RCT | Randomised controlled trial |
| RR | Relative risk/risk ratio |

| | |
|---|---|
| R-CHOP | Rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisolone |
| R-CHP | Rituximab, cyclophosphamide, doxorubicin, and prednisolone |
| SAE | Serious adverse event |
| SD | Standard deviation |
| SE | Standard error |
| SmPC | Summary of product characteristics |
| TA | Technology appraisal |
| TEAE | Treatment-emergent adverse event |
| TSD | Technical Support Document |
| TTOT | time-to-off-treatment |
| UK | United Kingdom |
| US | United States |

# 1 EXECUTIVE SUMMARY

This summary provides a brief overview of the key issues identified by the evidence review group (ERG) as being potentially important for decision making. It also includes the ERG's preferred assumptions and the resulting incremental cost-effectiveness ratios (ICERs).

Section 1.1 provides an overview of the key issues. Section 1.2 provides an overview of key model outcomes and the modelling assumptions that have the greatest effect on the ICER. Sections 1.3 to 1.6 explain the key issues in more detail. Background information on the condition, health technology, evidence and information on the issues are in the main ERG report.

All issues identified represent the ERG's view, not the opinion of the National Institute for Health and Care Excellence (NICE).

## 1.1 Overview of the ERG's key issues

**Table 1 Summary of key issues**

| Issue number | Headline description | ERG report sections |
|---|---|---|
| 1 | Uncertainty about the potential use of Pola+R-CHP in low risk untreated DLBCL | 2.3 |
| 2 | The survival benefit for Pola+R-CHP vs R-CHOP is very uncertain | 4.2.6.2 |
| 3 | The health care resources have been overestimated | 4.2.8.3 |
| 4 | Exclusion of chimeric antigen receptors cell therapy (CAR-T) as possible subsequent-line treatments | 4.2.8.3 |

## 1.2 Overview of key model outcomes

NICE technology appraisals compare how much a new technology improves length (overall survival) and quality of life in a quality-adjusted life year (QALY). An incremental cost effectiveness ratio (ICER) is the ratio of the extra cost for every QALY gained.

The company submitted revised base case results as part of their response to the clarification questions. The revised base case results included minor corrections to some of the resources and costs included in the model. The revised base case results are shown below in Table 2 (clarification response document Table 13). The results show that Pola+R-

CHP is associated with an increase of [redacted] QALYs at an additional cost of [redacted]. The ICER of Pola+R-CHP vs R-CHOP is £34,138 per QALY.

**Table 2 Base case results (with PAS price discount for polatuzumab)**

| Technologies | Total costs (£) | Total LYG | Total QALYs | Inc. costs (£) | Inc. QALYs | ICER (£/ QALY) |
|---|---|---|---|---|---|---|
| Pola+R-CHP | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | £34,138 |
| R-CHOP | [redacted] | 11.832 | 9.001 | - | - | - |

PAS Patient access scheme; Pola+R-CHP Polatuzumab vedotin plus rituximab, cyclophosphamide, doxorubicin, and prednisolone; R-CHOP; Rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisolone

### 1.3 The decision problem: summary of the ERG's key issues

**Issue 1 Uncertainty about the potential use of Pola+R-CHP in low risk DLBCL**

| **Report section** | 2.3 Critique of the company's definition of the decision problem |
|---|---|
| **Description of issue and why the ERG has identified it as important** | The company submission estimates clinical effectiveness and cost effectiveness of Pola+R-CHP in adult patients with previously untreated DLBCL, restricted to patients with an International Prognostic Index (IPI) score of 2 to 5 (low-intermediate risk to high-risk disease). Evidence for patients with an IPI score of 0-1 (low risk disease) is not presented, however the anticipated marketing authorisation (and the NICE scope) includes all untreated DLBCL patients irrespective of risk classification. Expert clinical advice to the ERG suggests that IPI 0-1 patients comprise 10-15% of the untreated DLBCL patient population and they would currently receive standard care as per IPI 2 to 5 patients, albeit a less intensive regimen. |
| **What alternative approach has the ERG suggested?** | The ERG assumes that, in clinical practice, IPI 0-1 patients would be potential candidates for Pola+R-CHP if available. However, it is not fully clear on what criteria clinicians would use to select patients to try Pola+R-CHP and whether any IPI 0-1 patients selected would require a less intense regimen as is currently the case for standard care. |
| **What is the expected effect on the cost-effectiveness estimates?** | Exploratory subgroup analysis of the pivotal phase III trial suggests the relative progression free survival benefit Pola+R-CHP is greater in patients with higher prognostic risk (IPI 3-5). There appears to be no difference in PFS between Pola+R-CHP and standard care for the IPI 2 patient group. It could be assumed that in the IPI 0-1 group any relative PFS benefit would be of a smaller magnitude. Overall, the ICER for Pola+R-CHP versus standard care could potentially increase if IPI 0-1 patients were included. |
| **What additional evidence or analyses might help to resolve this key issue?** | Further expert clinical opinion on what treatment regimens IPI 0-1 patients currently receive, and whether they would potentially be eligible for Pola+R-CHP if it was available.<br>Any available clinical effectiveness evidence of Pola+R-CHP in the treatment of IPI 0-1 could inform cost effectiveness modelling. |

### 1.4 The clinical effectiveness evidence: summary of the ERG's key issues

The ERG has not identified any key issues with the clinical effectiveness evidence.

### 1.5 The cost-effectiveness evidence: summary of the ERG's key issues

**Issue 2 The survival benefit for Pola+R-CHP vs R-CHOP is very uncertain**

| **Report section** | ERG report section 4.2.6.2 (Treatment effectiveness and extrapolation: Overall survival) |
|---|---|
| **Description of issue and why the ERG has identified it as important** | There is no statistically significant difference in overall survival between Pola+R-CHP and R-CHOP (HR 0.94 CI 0.65 to 1.37) based on current (immature) trial data. However, the company's extrapolation assumes a continued survival benefit for Pola+R-CHP over R-CHOP. |
| **What alternative approach has the ERG suggested?** | The ERG suggests that the overall survival benefit of Pola+R-CHP would not last indefinitely. We assume that the treatment benefit is unlikely to last for more than five years, and after this point the probability of death is the same in both arms. We assume that the treatment effect wanes from 30 months. |
| **What is the expected effect on the cost-effectiveness estimates?** | Limiting the treatment effect for OS to five years increases the ICER for Pola+R-CHP vs R-CHOP from £34,306 to £75,241 per QALY. |
| **What additional evidence or analyses might help to resolve this key issue?** | Longer trial follow-up data should provide more certainty on the magnitude and duration of the relative OS benefit for Pola+R-CHP versus R-CHOP. |

**Issue 3 The health care resources have been overestimated**

| **Report section** | ERG report section 4.2.8.3 (Health state costs) |
|---|---|
| **Description of issue and why the ERG has identified it as important** | The health care resources for this appraisal are based upon those previously estimated for third and fourth-line treatment of DLBCL (NICE TA306, pixantrone for treating multiply relapsed or refractory aggressive non-Hodgkin's B-cell lymphoma). Such patients may be in poorer health, and require greater health care resources than previously untreated patients. It can be assumed, therefore, that the resources and costs applied to untreated DLBCL have been overestimated. |
| **What alternative approach has the ERG suggested?** | The ERG prefers to use a one-off cost for those patients who die (end of life cost) as previously used in other oncology appraisals, and based on advice from our clinical experts. |
| **What is the expected effect on the cost-effectiveness estimates?** | Using the ERG's health care resource estimates increases the ICER for Pola+R-CHP vs R-CHOP from £34,306 to £68,417 per QALY. |
| **What additional evidence or analyses might help to resolve this key issue?** | Further expert clinical opinion on appropriate health care resources for DLBCL patients receiving first-line treatment. |

**Issue 4 Inclusion of chimeric antigen receptors cell therapy (CAR-T) as a subsequent anti-lymphoma treatment**

| **Report section** | ERG report section 4.2.8.3 (Health state costs) |
|---|---|
| **Description of issue and why the ERG has identified it as important** | CAR-T treatments axicabtagene ciloleucel and tisagenlecleucel are currently included in the economic model as subsequent-line treatments for patients whose disease progresses after first-line treatment. |
| **What alternative approach has the ERG suggested?** | CAR-T treatments should be excluded from the economic model as they are currently recommended by NICE for use within the Cancer Drugs Fund, rather than being available on the NHS through routine commissioning. |
| **What is the expected effect on the cost-effectiveness estimates?** | Excluding CAR-T from subsequent anti-lymphoma treatment increases the ICER for Pola+R-CHP vs R-CHOP from £34,306 to £64,664 per QALY. |
| **What additional evidence or analyses might help to resolve this key issue?** | NICE appraisals of axicabtagene ciloleucel (TA559) and tisagenlecleucel (TA567) will be updated in 2022-2023 following further data collection required as a condition of inclusion in the Cancer Drugs Fund. If recommended by NICE for use in the NHS these treatments can be included in health economic modelling. |

The following issues identified by the ERG in the cost effectiveness evidence are not considered as key issues as they only have a small impact on the model results:

- **Extrapolation of OS**: the ERG notes the uncertainty in estimating OS and therefore prefers using the KM data from the clinical trial with an extrapolated tail.
- **Health state utility values**: we prefer to use the values estimated from the POLARIX trial.
- **End of life costs**: We use an end-of-life cost of £6,950.29.
- **Rituximab list price:** We exclude the company's estimated rituximab price discount.

### 1.6 Summary of ERG's preferred assumptions and resulting ICERs

Based on the ERG critique of the company's model (discussed in section 5.3.5), we have identified seven key aspects of the company base case with which we disagree. Our preferred model assumptions are the following:

1. **Extrapolation of OS:** we use the KM data with a generalised gamma extrapolated tail. The tail begins at 30 months.
2. **Treatment waning:** We apply a linear decrease of the treatment benefit for OS to the Pola+R-CHP arm between 30 and 60 months waned to the R-CHOP survival curve.
3. **Resource use:** We use an end-of-life cost of £6,950.29.

4. **Health state utilities:** We use HRQoL values from the pivotal phase III POLARIX trial, rather than from an external source (the GOYA trial).
5. **Supportive care costs:** we estimated supportive care resources, based on advice from our clinical experts
6. **Treatment costs:** We exclude the rituximab price discount.
7. **Subsequent therapies:** We exclude CAR-T therapy from the subsequent treatments.

The ICER obtained using the ERG's preferred assumptions (Table 3) increases from £34,306 to £255,923 per QALY.

**Table 3 Cumulative cost-effectiveness results for ERG's preferred model assumptions (discounted, PAS price for polatuzumab)**

| Scenario | Incremental cost | Incremental QALYs | ICER (£/QALY) |
|---|---|---|---|
| Company's updated base case | [redacted] | [redacted] | £34,306 |
| + OS with KM + generalised gamma with an extrapolated tail at 30 months (25% of patients at risk) | [redacted] | [redacted] | £44,627 |
| + Treatment waning assumption for OS; between 30 months and 60 months | [redacted] | [redacted] | £93,705 |
| + End of life costs per patient of £6950.29 | [redacted] | [redacted] | £93,438 |
| + Utility values from the POLARIX trial, rather than from the GOYA trial | [redacted] | [redacted] | £107,071 |
| + Supportive care costs | [redacted] | [redacted] | £178,525 |
| + Rituximab list price | [redacted] | [redacted] | £176,824 |
| + No CAR-T in subsequent treatment | [redacted] | [redacted] | £255,923 |
| ERG's preferred base case | [redacted] | [redacted] | £255,923 |

Modelling errors identified and corrected by the ERG are described in section 5.3.4. For further details of the exploratory and sensitivity analyses done by the ERG, see section 6.2.

# 2 INTRODUCTION AND BACKGROUND

## 2.1 Introduction

This report is a critique of the company's submission (CS) to NICE from Roche on the clinical effectiveness and cost effectiveness of polatuzumab [POLIVY®] for treating adult patients with previously untreated diffuse large B-cell lymphoma (DLBCL). It identifies the strengths and weaknesses of the CS. Clinical experts were consulted to advise the evidence review group (ERG) and to help inform this report.

Clarification on some aspects of the CS was requested from the company by the ERG via NICE on 4th April 2022. A response from the company via NICE was received by the ERG on 25th April 2022 and this can be seen in the NICE committee papers for this appraisal.

## 2.2 Background

### 2.2.1 Background information on previously untreated diffuse large B-cell lymphoma (DLBCL)

The CS (section B1.3.1) provides a clear and accurate overview of diffuse large B-cell lymphoma (DLBCL), including its definition, cause, prevalence, diagnosis, prognosis, mortality and effect on health-related quality of life (HRQoL). We summarise the key facts of relevance from the CS together with supplemental information, where appropriate, below.

Non-Hodgkin lymphoma (NHL) is a diverse group of blood cancers that affect lymphocytes (white blood cells that help fight infections). In the UK approximately 14,200 new cases of NHL are diagnosed each year.[1] The majority of NHL cases arise from B-cells, with the remainder arising from T-cells and natural killer cells. NHL can be classified as low grade (indolent, slow growing) or high grade (aggressive, fast growing). DLBCL is a high grade lymphoma, with a median survival of one year in untreated patients,[2] and is the most common NHL, with approximately 5,500 new cases diagnosed in the UK each year.[3]

There are various subtypes of DLBCL (e.g. T-cell/histiocyte-rich large B-cell lymphoma, Epstein-Barr virus positive DLBCL) however approximately 90% of cases are classified as DLBCL not otherwise specified (DLBCL NOS).[3 4] One of our clinical experts commented that there is no significant difference in prognosis between DLBCL NOS and other subtypes, while a second believed prognosis is heterogenous (i.e. it can differ by subtype). Both experts, however, were in agreement that standard care is the same for DLBCL regardless of subtype.

The incidence of DLBCL increases with age, with a median age at diagnosis in the UK of approximately 70 years, and is slightly more common in males than females.[4 5]

DLBCL can occur in patients without a history of lymphoma or can progress from low grade lymphomas e.g. follicular lymphoma. Risk factors include family history of any type of blood cancer, B-cell activating autoimmune disorders (e.g. Sjögren's syndrome), solid organ transplantation, immunodeficiency (e.g. HIV), obesity as a young adult, viral exposure (e.g Epstein Barr virus, hepatitis B or C) and occupational or environmental exposure (e.g. ionising radiation, pesticides).[6 7]

The most common symptom of DLBCL is one or more painless swellings at single or multiple nodal (lymph node) or extranodal (non-lymph node) sites. Other common symptoms include excessive sweating at night, unexplained fever and weight loss.[3]

#### 2.2.1.1 Diagnosis and disease staging

Diagnosis is made by surgical or core biopsy and positron emission tomography-computerised tomography (PET-CT) scanning, along with haematological, biochemical, virological and histopathological testing.[8 9] The **Lugano staging classification**, based on the Ann Arbor staging classification, is used to classify how many areas of the body are affected by cancer and where they are located. The Lugano classification consists of four stages, which can be further subdivided based on the presence of certain disease characteristics e.g. the presence of bulky disease (i.e. tumour diameter >7.5-10cm). Stages I and II define limited/early stage disease, stage II bulky can be treated as limited or advanced disease depending on histology and prognostic factors, and stage III and IV advanced disease. [9 10] The Lugano staging classification can inform treatment decisions, while the **Lugano Response Criteria for Malignant Lymphoma** can be used to assess response to treatment.[7-9]

Currently, DLBCL prognosis is predicted using the **International Prognostic Index (IPI).** The IPI consists of five risk factors:

- Age at diagnosis (>60 years)
- Serum lactate dehydrogenase level (> upper limit of normal)
- Eastern Cooperative Oncology Group (ECOG) performance status (≥2)
- Ann Arbor Stage (stage III or IV)
- Number of extranodal sites (>1 site).

Based on the number of risk factors present, patients are assigned to one of four risk groups: low (0 or 1 factors), low-intermediate (2 factors), high-intermediate (3 factors), high (4 or 5 factors). [8 Trust, 2020 #38 11] Estimated five year overall survival after treatment with standard care ranges from 88% in the low risk group to 54% in the high risk group.[12] Revised versions of the IPI exist, e.g. the National Comprehensive Cancer Network IPI (NCCN-IPI).[13] One of our clinical experts commented that original version is used in the NHS to estimate survival and inform treatment decisions, while a second commented that both original and revised versions are used, with the NCCN-IPI having better discriminatory power between high and low risk groups.

#### 2.2.1.2 Prognosis

Bulky disease, defined as a tumour with a diameter >7.5-10cm, is associated with a worse prognosis, and its presence informs treatment decisions.[8 10]

Other prognostic factors, which are currently not used to determine treatment, include:

- **Cell of origin (COO)**:
    - germinal centre B cells (GCB)
    - activated B cells (ABC)
    - unclassified.

  DLBCL originating from non-GCB (i.e. ABC or unclassified) has a worse prognosis than GBC cell of origin.[7 14]
- **MYC, BCL2 and/or BCL 6 gene and protein expression** - *MYC*, *BCL2* and *BCL6* are three genes with important roles in cell regulation. DLBCL with rearrangement in *MYC* and *BCL2* or *BCL6* genes are known as “double hit lymphomas”, and those with rearrangements in all three genes are known as” triple hit lymphomas.” Both double and triple hit lymphoma are associated with a poorer prognosis. DLBCL that do not have gene rearrangement but over-express MYC and BCL2 proteins are known as “double expressor lymphomas”. Double expressor lymphoma is associated with a worse prognosis.[7-9 15]

#### 2.2.1.3 Clinical management of DLBCL

The CS (section B.1.3.2 and Figure 1 – reproduced as Figure 1 below) provides a limited overview of how untreated DLBCL is managed in UK clinical practice according to the British Society of Haematology and the Pan-London Haemato-Oncology Clinical Guidelines.[8 9] Our clinical experts were in agreement with the company that:

- Current first-line therapy for untreated DLBCL is rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisolone (**R-CHOP**). (NB. In the 'R-CHOP' acronym doxorubicin is represented by the 'H' for doxorubicin hydrochloride and vincristine is represented by the 'O' for its brand name Oncovin). Depending on staging, patients are treated with three to six 21-day cycles of R-CHOP sometimes followed by involved site radiation treatment (ISRT).
- However, in contrast to the CS and clinical guidelines, one of our experts commented that in clinical practice patients with an IPI of 0 receive four 21-day cycles of R-CHOP plus two doses of rituximab and no radiotherapy,[16] with R-CHOP only (six 21-days cycles) or R-CHOP (three or four 21-day cycles) and ISRT as alternative treatment regimens. Our expert confirmed this practice is based on the results of the FLYER study,[16] which showed that in patients with an IPI of 0, four 21-day cycles of R-CHOP plus two doses of rituximab and no radiotherapy was non-inferior to six 21-day cycles of R-CHOP only.

The ERG however, notes:

- In CS figure 1 the company have stratified standard care first-line treatment regimens according to "IPI staging" (IPI score) while the clinical guidelines use the Lugano classification staging (see Table 4 below).[8 9] One of our experts stated that CS figure 1 is fair summary of treatment, with a second confirming they use the IPI (original or revised versions) to determine standard care first-line treatment regimens. However, our third expert uses both IPI score and Lugano classification stage to inform treatment decisions with Lugano the stronger determinant. This clinical expert highlighted that a patient could have advanced disease (i.e. Lugano classification stage III or IV) but have an IPI of 1, with a second expert commenting that IPI score cannot be extrapolated from Lugano classification stage and vice versa.

The ERG notes the following aspects of care are not mentioned in the CS:

- **R-CHOP variations.** Variations to the number of R-CHOP cycles and use/non-use of ISRT, as mentioned in the clinical guidelines and used by our clinical experts (see Table 4).[8 9]
- **R-CHOP ineligibility**. Approximately 20 to 25% of patients are not candidates for treatment with R-CHOP because of poor fitness related to age, comorbidities or organ impairment (e.g. cardiac dysfunction).[7] In agreement with the clinical guidelines,[8 9] our experts advised that these patients receive pre-treatment steroids and/or modified R-CHOP regimens (e.g. patients with cardiac dysfunction cannot receive doxorubicin and so etoposide or gemcitabine is used instead).

**Table 4 First-line treatment regimens for untreated DLBCL according to the different staging criteria used in the CS and in British clinical guidelines**

| Treatment regimen | IPI staging in CS Figure 1 | Lugano classification staging in British clinical guidelines[8 9] |
|---|---|---|
| R-CHOP (**three to four** 21-day cycles) and ISRT | **IPI 0-1** (low risk) | **Stage IA** non-bulky (tumour <7.5cm)<br><br>Alternative regimen: If ISRT is inappropriate due to site of disease use **six** 21-day cycles of R-CHOP only<br><br>(ERG clinical expert opinion: For IPI 0 standard care is **four** 21-day cycles of R-CHOP plus two doses of rituximab only) |
| R-CHOP (**six** 21-day cycles) | **IPI 2** (low risk with bulky; or low-intermediate risk) | **Stage IIA** non-bulky (tumour <7.5cm)<br><br>Alternative regimen: if the disease is amenable for radiotherapy use R-CHOP (three or four 21-day cycles) and ISRT |
| R-CHOP (**six** 21-day cycles) and ISRT | | **Bulky stage IA/IIA** (tumour ≥7.5cm) |
| R-CHOP (**six** 21-day cycles) and ISRT to sites of bulk | **IPI 3-5** (intermediate - high or high risk) | **Stage III and IV** |

Source: partly reproduced from CS Figure 1

IPI: International Prognostic Index; ISRT: involved site radiation treatment; R-CHOP: rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisolone

- **Alternative treatments.** The CS does not mention **R-ACVBP** (rituximab, doxorubicin, vincristine, cyclophosphamide, bleomycin and prednisolone), which the NICE scope states can be used instead of R-CHOP. Two of our clinical experts, however, commented that R-ACVBP is not used in clinical practice.
- **Central nervous system (CNS)-directed prophylaxis**. A proportion of patients (10-20%) are at increased risk of secondary CNS lymphoma, which has a poor prognosis.[17] Risk factors (anatomical, clinical and biological) vary somewhat between guidelines.[9 17-19] Prophylactic treatments include intrathecal chemotherapy or high dose intravenous methotrexate (HD-MTX). The British Society for Haematology recently found no strong evidence to support the effectiveness of intrathecal chemotherapy in reducing CNS relapse and a lack of consensus regarding delivery (timing, dose and number of cycles) of HD-MTX.[17] Two of our experts were of differing opinions on the use of intrathecal chemotherapy and on the timing of delivery of HD-MTX (early in treatment versus post treatment with R-CHOP).

Approximately 50-60% of patients treated with R-CHOP are considered cured,[20] with patients who are progression free at 24 months from the onset of initial therapy having survival clinically indistinguishable from the age-, sex-, and country-matched background population.[21] However, treatment with R-CHOP fails in approximately 40-50% of patients.[20] with 15% to 25% having primary refractory disease (i.e. incomplete response or relapse soon after treatment), and an additional 20% to 30%, who relapse after achieving complete remission. Prognosis for these patients, particularly those with refractory disease, is poor and worsens with each line of therapy thereafter.[8 22]

The CS accurately describes that modifying R-CHOP regimens (e.g. by reducing the number of days between cycles or adding additional drugs) has shown no benefit over R-CHOP as first-line treatment for DLBCL.[7]

### 2.2.2 Background information on polatuzumab vedotin

The company provides details of the health technology under appraisal, polatuzumab vedotin (Pola), in CS sections B1.2 and B2.12.

As the CS describes, polatuzumab is an antibody-drug conjugate. It consists of an anti-human-CD79b monoclonal antibody combined with a substance called mono-methyl auristatin E (MMAE). The monoclonal antibody attaches to CD79b, a protein found on the surface of normal and malignant B cells, which causes MMAE to be released inside the B cell. MMAE acts by stopping the B cell dividing and growing and causes cell death.

Polatuzumab, in combination with bendamustine and rituximab, is already licensed for use in the UK and was recommended by NICE in September 2020 for the treatment of adult patients with relapsed/refractory DLBCL who cannot have a haematopoietic stem cell transplant (NICE TA649).[23]

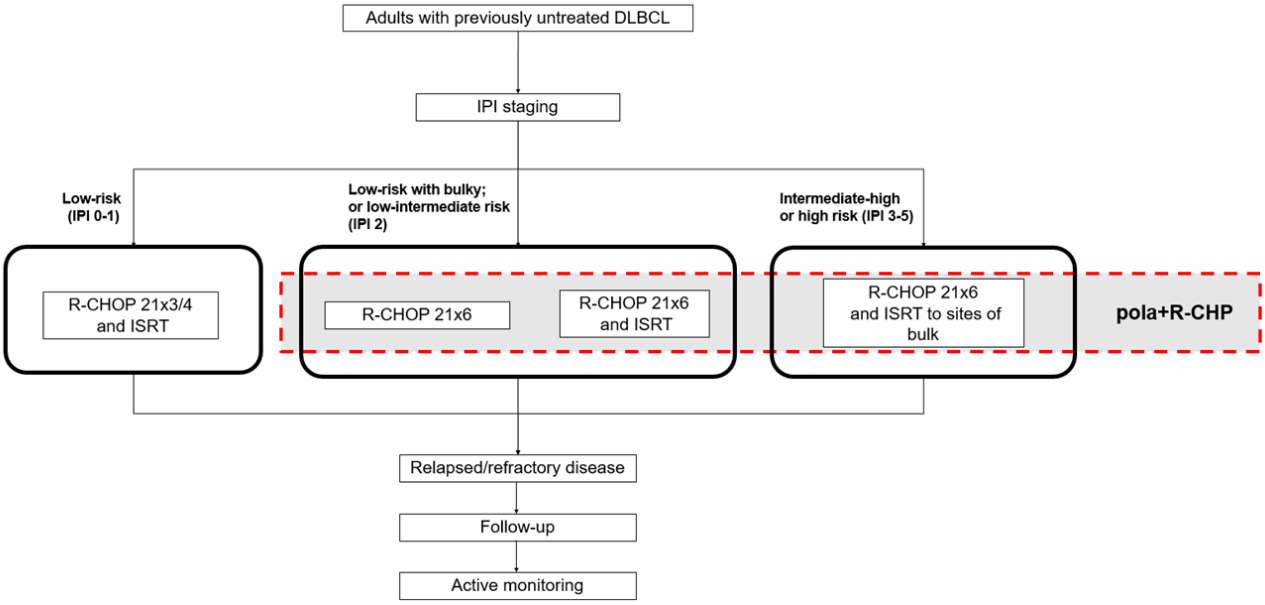
The CS states an application of a Type II variation for polatuzumab to its current indication, as well as an Orphan Drug Designation application, were submitted to the MHRA on 28th January 2022, with an approval expected in [redacted]. The anticipated indication is polatuzumab in combination with rituximab, cyclophosphamide, doxorubicin, and prednisolone, for the treatment of adult patients with previously untreated diffuse large B-cell lymphoma (DLBCL).

In line with the draft SmPC, the company states that polatuzumab 1.8 mg/kg, should be given as intravenous infusion in combination with rituximab, cyclophosphamide, doxorubicin and prednisolone (R-CHP) every 21 days for six cycles followed by two monotherapy cycles of rituximab (cycles seven and eight). Two of our clinical experts commented that in the NHS, only six doses of rituximab are received for R-CHOP, rather than the eight proposed for R-CHP in the draft SmPC. One of our experts anticipated that if polatuzumab was licensed on the basis of six cycles of R-CHP plus two monotherapy cycles of rituximab, clinicians would probably administer eight cycles of rituximab for the first year and then revert to six cycles of rituximab (i.e. six cycles of R-CHP only) thereafter.

All three of our clinical experts were familiar with polatuzumab through its current use as a treatment for adult patients with relapsed/refractory DLBCL who cannot have a haematopoietic stem cell transplant. One expert stated that they anticipate no issue with substituting vincristine with polatuzumab except for a longer infusion time. Two experts were of the opinion that polatuzumab is well tolerated and similar to R-CHOP in safety.

### 2.2.3 The position of polatuzumab vedotin in the treatment pathway

CS Figure 1, reproduced in Figure 1 below, shows the company's proposed position of Pola+R-CHP in the disease management pathway. The company proposes Pola+R-CHP as a first-line treatment for adults aged 18-80 with previously untreated DLBCL and an IPI score of 2 to 5. The ERG notes that the anticipated licence indication includes all untreated DLBCL patients irrespective of IPI score, and therefore the company intends Pola+R-CHP to be used in a narrower patient population. We discuss the implications of this below in section 2.3.




Source: CS Figure 1

The grey box indicates the proposed positioning of Pola+R-CHP for patients with an IPI of 2–5.

Key: IPI, International Prognostic Index; ISRT, involved site radiotherapy.

**Figure 1 Current treatment pathway for adult patients (aged 18-80) with previously untreated DLBCL (including Pola+R-CHP positioning)**

CS section B.2.12 outlines the current unmet need for untreated DLBCL. In summary, approximately 30–50% of patients with untreated DLBCL are not cured by standard care treatment with R-CHOP. These patients experience reduced quality of life and their chance of being cured reduces with each successive line of therapy.

Two of our clinical experts stated that most/all clinicians would be keen to use Pola+R-CHP as a first-line treatment if it were available. Our third clinical expert stated that clinicians would want to use Pola-RCHP as a first-line therapy, but IPI score, MYC rearrangement and double expressor lymphoma status would be important factors to consider when prescribing given results of subgroup analyses in the pivotal phase III trial of polatuzumab (POLARIX) in the CS (described in section 3.2.5.4 of this report). Furthermore, given the exclusion criteria of the POLARIX study in relation to ECOG performance status (ECOG-PS) score >2 (see section 3.2.1.2 of this report), our expert believed it was important for clinicians to consider whether patients with ECOG-PS score >2 due to DLBCL, rather than comorbidities, could also benefit from treatment.

### 2.3 Critique of the company's definition of the decision problem

Table 5 compares the company's decision problem to the final scope for this appraisal issued by NICE. The ERG considers that the decision problem adheres to the NICE scope but with the following caveats.

#### 2.3.1 Population

The population specified in the NICE scope and the draft SmPC indication is adult patients with previously untreated DLBCL (CS Figure 2). CS Table 1 states that the relevant patient population is "as per the final scope issued by NICE". However, in response to an ERG clarification question (A1) the company report that the intended patient population is adult patients with previously untreated DLBCL with an IPI score of 2 to 5 (low-intermediate risk to high risk) as per the population of the pivotal study (the POLARIX study). The decision problem as stated in the CS (CS Table 1) is, therefore, incorrect. In actuality it excludes patients with an IPI score of 0-1 (low risk) even though the anticipated marketing authorisation (and the NICE scope) includes all untreated DLBCL patients irrespective of risk classification. Expert clinical advice to the ERG is that IPI 0-1 patients represent around 10 to 15% of the untreated DLBCL population. These patients would receive fewer cycles of R-CHOP (e.g. three or four) plus either ISRT or two cycles of single agent rituximab (see section 2.2.1.3). It is unclear whether, in clinical practice, IPI 0-1 patients would be candidates for Pola+R-CHP if available.

#### 2.3.2 Comparator

The comparator specified in the NICE scope is "chemoimmunotherapy (including R-CHOP)". The CS includes R-CHOP as a comparator but does not include any other comparators. The ERG asked the company to clarify if any alternative comparator treatments had been considered for inclusion (clarification question A2). In response the company stated that R-CHOP is the current UK standard of care for previously untreated DLBCL according to the British Society of Haematology (BSH) and the Pan-London Haemato-Oncology Clinical Guidelines. This assertion was corroborated by two of the ERG's clinical experts. Thus, it does not appear that any commonly used first-line chemoimmunotherapies have been unnecessarily excluded from the decision problem.

#### 2.3.3 Outcomes

The decision problem adheres to the NICE scope in terms of relevant outcome measures to be included, namely:

- Overall survival

- Progression-free survival
- Response rate
- Adverse effects of treatment
- Health-related quality of life (HRQoL)

### 2.3.4 Subgroups to be considered

The NICE scope specifies that if the evidence allows, cell of origin subgroups (germinal centre (GCB) DLBCL, and Post-germinal centre DLBCL) should be considered. The company states in CS Table 1 that no subgroup analysis is considered and that [redacted]

CS Table 13 presents investigator-assessed progression-free survival for a set of pre-planned exploratory patient subgroups from the phase III POLARIX trial. Cell of origin is one of these subgroups. Although subgroup data are available from the trial the company's economic model does not assess cost-effectiveness according to subgroups. The ERG does not necessarily disagree with this decision, as trial subgroup analyses may be subject to bias and error, though this does not preclude subgroups being included in exploratory economic scenario analyses if considered informative.

**Table 5 Summary of the decision problem**

| | Final scope issued by NICE | Company's decision problem (CS Table 1) | Differences between scope and Decision problem |
|---|---|---|---|
| Population | Adults with untreated diffuse large B-cell lymphoma | As per final scope issued by NICE | Company clarification A1 states that the intended patient population *"is specific to adult patients with previously untreated diffuse large B-cell lymphoma (DLBCL) with an IPI score of 2 to 5 as per the POLARIX study population".*<br><br>The ERG note additional key inclusion criteria of the POLARIX study (CS Figure 2) were CD20-positive DLBCL, age 18 to 80 years with an ECOG performance status of 0, 1, or 2. |
| Intervention | Polatuzumab vedotin with R-CHP (rituximab, cyclophosphamide, doxorubicin, and prednisolone) | Prednisone as well as prednisolone | None - Decision problem matches scope |
| Comparators | Chemoimmunotherapy (including R-CHOP) | As per final scope issued by NICE | Company clarification A2 cites clinical guidelines stating that R-CHOP is the current UK standard of care for previously untreated DLBCL. The ERG clinical advisors agree. |
| Outcomes | The outcome measures to be considered include:<br>● Overall survival<br>● Progression-free survival<br>● Response rate<br>● Adverse effects of treatment<br>● Health-related quality of life | The outcome measures to be considered include:<br>● Progression-free survival (primary endpoint)<br>● Overall survival (secondary endpoint)<br>● Response rate (secondary endpoint)<br>● Adverse effects of treatment<br>● Health-related quality of life | The CS reports results for all outcomes but does not provide results for all measures of health-related quality of life.<br><br>. |

| | | | |
|---|---|---|---|
| Subgroups | If the evidence allows, the following subgroups will be considered. These include:<br>● Germinal centre DLBCL,<br>● Post-germinal centre DLBCL | No subgroup analysis to be considered. | The company's economic model does not assess cost-effectiveness according to these subgroups |
| Source: partly reproduced from CS Table 1 | | | |

# 3 CLINICAL EFFECTIVENESS

## 3.1 Critique of the methods of review(s)

Table 6 provides a summary of the ERG's critical appraisal of the company's systematic review of clinical effectiveness. The ERG considers the systematic review conforms to accepted methodological standards in evidence synthesis and is at low risk of bias.

## 3.2 Critique of studies of the technology of interest, the company's analysis and interpretation (and any standard meta-analyses of these)

### 3.2.1 Included studies

The company's systematic review of clinical effectiveness included a total of 69 clinical trials, reported in a total of 86 publications (CS Appendix D.1.5). The 69 trials evaluated a range of treatments for people with untreated DLBCL, published over a period spanning 2003 to 2022. Many of the trials assessed R-CHOP or R-CHOP-based treatment regimens. However, only one of the 69 trials evaluated the intervention of relevance to the decision problem, Pola+R-CHP. This is the aforementioned **POLARIX** trial and is the focus of the company's systematic review of clinical effectiveness.

#### 3.2.1.1 Study characteristics

The POLARIX study (study GO39942**;** ClinicalTrials.gov number NCT03274492) is an ongoing phase III, multicentre, randomised, double-blind, placebo-controlled trial comparing the efficacy and safety of Pola+R-CHP versus R-CHOP in previously untreated patients with DLBCL. Patients were enrolled from 22 countries world-wide, including the UK. The trial results support the company's regulatory application for marketing authorisation and it also informs assessments of cost-effectiveness in the company's economic model (see sections 4, 5 and 6 of this report).

Participants with previously untreated CD20-positive DLBCL (n=879) were randomised to receive:

- **Pola+R-CHP.** Polatuzumab vedotin plus rituximab, cyclophosphamide, doxorubicin and prednisolone + *vincristine placebo* (investigational arm, n=440), or
- **R-CHOP.** Rituximab, cyclophosphamide, doxorubicin, vincristine and prednisolone + *Polatuzumab vedotin placebo* (control arm, n=439)

**Table 6 ERG appraisal of the company's systematic review of clinical effectiveness methods**

| Systematic review components and processes | ERG response | ERG comments |
|---|---|---|
| Was the review question clearly defined using the PICOD framework or an alternative? | Yes | |
| Were appropriate sources of literature searched? | Yes | There was good coverage of appropriate sources of evidence |
| What time period did the searches span and was this appropriate? | See 'ERG comments' | Clinical effectiveness search: 1998 to 25th January 2022.<br>The clinical effectiveness searches are sufficiently up to date with respect to randomised trials, but only up to May 2016 for observational studies. Given the availability of relevant randomised trial evidence (i.e. the phase III RCT POLARIX trial) the ERG does not consider this a limitation.<br>Other searches:<br>● Cost effectiveness: 2016 to 25th August 2021<br>● HRQoL: 2019 to 25th August 2021<br>● Cost and resource use: 25th August 2021 |
| Were appropriate search terms used and combined correctly? | Yes | Search terms cover the PICOD elements of the decision problem. Appropriately, a combination of subject headings and free text terms were used. |
| Were inclusion and exclusion criteria specified?<br>If so, were these criteria appropriate and relevant to the decision problem? | Yes<br><br>Yes | <br><br>Inclusion criteria were broader than the decision problem, stated as "any pharmacological intervention used as first-line treatment" (CS Appendix D Table 9). Since this could include Pola+R-CHP as an intervention there is no risk of bias with regard to the decision problem. |
| Were study selection criteria applied by two or more reviewers independently? | Yes | Assessed from the company's response to ERG clarification question A5 |
| Was data extraction performed by two or more reviewers independently? | No | Assessed from the company's response to ERG clarification question A5. Data extracted by the first reviewer were checked against source publication by a second reviewer and any discrepancies were resolved between them. The ERG considers this acceptable. |
| Was a risk of bias assessment or a quality assessment of the included | Yes | Results of risk of bias assessment presented in CS Table 8 for the POLARIX trial. The company used the seven-criteria checklist recommended by NICE, based on guidance provided by the Centre for Reviews and Dissemination (CRD). [24] |

| | | |
|---|---|---|
| studies undertaken? If so, which tool was used? | | |
| Was risk of bias assessment (or other study quality assessment) conducted by two or more reviewers independently? | No | Assessed from the company's response to ERG clarification question A5. Risk of bias assessments made by the first reviewer were checked against source publication by a second reviewer and any discrepancies were resolved between them. The ERG considers this acceptable. |
| Is sufficient detail on the individual studies presented? | Yes | CS sections B.2.3 to B.2.7; CS appendices D to G. However, limited detail was provided in the CS on the POLARIX trial's statistical procedures, but these were available in the trial CSR. |
| If statistical evidence synthesis (e.g. pairwise meta-analysis, ITC, NMA) was undertaken, were appropriate methods used? | N/A | The CS states that no meta-analysis, indirect and mixed treatment comparisons were conducted for this submission, but does not elaborate further. The ERG notes that the POLARIX trial provides a direct comparison of Pola+R-CHP versus the current standard of care, R-CHOP and thus an indirect treatment comparison is not required. |

N/A Not applicable

Patients received six cycles of either Pola+R-CHP or R-CHOP chemotherapy at 21-day intervals. Both arms then received two additional cycles of single agent rituximab.

Randomisation was stratified to ensure an equal distribution of patients with particular characteristics across the trial arms. These were:

- International Prognostic Index IPI score (IPI 2 versus IPI 3–5).
- Bulky disease, defined as one lesion ≥ 7.5 cm (present versus absent).
- Geographical region (Western Europe, United States, Canada, and Australia versus Asia versus Rest of World [remaining countries])

No crossover from the control arm to the investigational arm was allowed. Patients could receive new anti-lymphoma treatments after completion of study treatment, including both radiotherapy or systemic therapies. New anti-lymphoma treatments were permitted with or without documented disease progression.

Safety and efficacy response was assessed at the end of study treatment, or sooner if a patient discontinued early. After completion of therapy, all patients were assessed at follow-up visits every three months for 24 months, and then every six months until Month 60. After five years, patients were followed only for survival and initiation of a new anti-lymphoma therapy approximately every six months until study termination, patient withdrawal of consent or death.

The first patient was randomised on 15 November 2017, and the last on 27 June 2019. The CS reports interim trial results from a data cut 28th June 2021. This data cut includes the primary analysis of the primary outcome (investigator-assessed PFS) and interim results of secondary efficacy outcomes (including OS) and safety. Results from the June 2021 data cut are reported in a journal article published online in January 2022.[25] A final data cut is planned for June 2022 and will include updated PFS results and final OS analyses.

#### 3.2.1.2 Patients' characteristics

Key inclusion criteria of the POLARIX study (CS Figure 2) included presence of CD20-positive DLBCL, age 18 to 80 years and an Eastern Cooperative Oncology Group Performance Status (ECOG PS) of 0, 1, or 2. As mentioned earlier, the trial restricted inclusion to patients with an IPI score of 2-5, thus excluding the estimated 10-15% of DLBCL patients with low risk disease (IPI score 0–1).

Expert clinicians advising the ERG were of the opinion that the trial population is reasonably representative of patients typically seen in practice, though such patients tend to be older and less fit, with a higher average ECOG performance status than the trial participants. Our clinical experts also confirmed that almost all DLCBL is CD20-positive, thus the company's eligibility criteria, which only permits inclusion of CD20 patients, is appropriate.

Our experts advised that in clinical practice patients aged over 80 or with an ECOG PS >2 usually receive a reduced or modified chemotherapy regimen compared to standard care. Two of our experts therefore expressed a wish to give a modified dose of Pola+R-CHP to patients with an ECOG PS > 2, if ECOG PS was due to DLBCL rather than co-morbidities. However, one of our experts stated they would not treat a patient with Pola-RCHP if they were aged ≥70 years of age with an ECOG 3 or 4.

**ERG comment on included studies**

The POLARIX trial is generally representative of patients with DLBCL, though the trial patient population is younger and fitter than would be seen in practice. Furthermore, the trial restricted inclusion to patients with IPI score of 2-5 (low-intermediate risk to high risk).

### 3.2.2 Risk of bias assessment

The company's methodological quality assessment (also referred to as risk of bias assessment) of the POLARIX trial is presented in CS Table 8. The ERG independently critically appraised the trial using the same criteria, and an overview of our judgements alongside those of the company is presented in Table 7 below. The company did not provide a justification for their judgements; we have given our justification in Appendix 1.

**Table 7 Overview of company and ERG risk of bias judgements**

| Criterion | Company judgement | ERG judgement |
|---|---|---|
| Was randomisation carried out appropriately? | Yes | Yes |
| Was the concealment of treatment allocation adequate? | Yes | Yes |

| | | |
|---|---|---|
| Were the groups similar at the outset of the study in terms of prognostic factors? | Yes | Yes |
| Were the care providers, participants, and outcome assessors blind to treatment allocation? | Yes | Yes |
| Were there any unexpected imbalances in drop-outs between groups? If so, were they explained or adjusted for? | No | No |
| Is there any evidence to suggest that the authors measured more outcomes than they reported? | No | No for efficacy and safety outcomes; **yes for specific HRQoL outcomes** |
| 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 | Yes for primary efficacy analysis and safety; **unclear for analyses relating to certain secondary efficacy outcomes and to HRQoL outcomes.** |
| Source: Partly reproduced from CS Table 8.<br>Note. Bold text shows where the ERG's judgement differed to the company's.<br>HRQoL: Health-Related Quality of Life | | |

In general, the ERG agrees with the company's critical appraisal judgements However, although the CSR (page 234) states [redacted] the ERG are unclear about the risk of attrition bias in the company's analysis of some secondary efficacy outcomes (complete response (CR) rate, best overall response (BOR) rate, disease free survival (DFS) and duration of response (DOR)) and HRQoL outcomes due to lack of reporting on the quantity of missing data or the handling of missing data. Furthermore, the ERG considers there is a high risk of selective reporting bias in relation to HRQoL outcomes, specifically EORTC QLQ C-30. This outcome is listed in Appendix 1 of the study protocol however, results were neither reported in the CS nor the CSR.

In summary, the POLARIX trial was generally well-conducted, but the ERG are unclear about the risk of attrition bias relating to certain secondary efficacy outcomes and to HRQoL outcomes. This introduces some uncertainty (of unknown magnitude and direction) to

estimates reported in the CS and CSR relating to these outcomes. Furthermore, specific HRQoL outcomes are at high risk of selective reporting bias.

### 3.2.3 Outcomes assessment

All outcomes included in the NICE scope (OS, PFS, response rate, adverse effects and HRQoL) were measured in the POLARIX trial. The CS reports results for all outcomes specified in the scope and decision problem, except for HRQoL. The CSR and study protocol provide further details of the primary, secondary, exploratory and HRQoL outcomes, including results for a subset of the HRQoL outcomes assessed (see Table 8 below).

**Table 8 List of NICE scope and decision problem related outcomes reported in the POLARIX trial**

| Endpoint | Outcome | Definition |
|---|---|---|
| Primary | Progression free survival (PFS) as assessed by the investigator | Time from randomisation to the first occurrence of disease progression or relapse as assessed by the investigator, using the Lugano Response Criteria for Malignant Lymphoma, or death from any cause, whichever occurs earlier. (CS section B.2.3.2) |
| Key secondary endpoints[a] | Event-free survival - efficacy (EFSeff) as determined by the investigator | Time from the date of randomization to the earliest occurrence of disease progression/relapse, death, biopsy that is positive for residual disease after treatment completion, or start of a new anti-lymphoma treatment (NALT) due to efficacy reasons (CSR section 5.1.3.1) |
| | Complete response (CR) rate at end of treatment by fluorodeoxyglucose positron emission tomography (FDG-PET) as determined by blinded independent central review (BICR) | At treatment completion as assessed using the Lugano Response Criteria for Malignant Lymphoma (Trial protocol, section 4.5.5) |
| | Overall survival (OS) | Period from the date of randomization until the date of death from any cause (Trial protocol, section 6.4.2) |
| | Safety | All adverse events (AEs), serious adverse events (SAEs), and abnormalities identified through physical examinations, vital signs, and laboratory assessments (CS section B.2.3.1) |

| | | |
|---|---|---|
| Additional secondary endpoints[b] | Disease-free survival (DFS) | Time from the date of the first occurrence of a documented CR to the date of relapse or death from any cause for the subgroup of patients with a BOR of CR, all assessed by the investigator. (CSR section 5.1.3.9) |
| | Best overall response (BOR) rate as determined by investigator | Best response of CR or partial response (PR) while on study (CSR section 5.1.3.7) |
| | Duration of response (DOR) | Time from the date of the first occurrence of a documented clinical response (CR or PR) to the date of progression, relapse, or death from any cause for the subgroup of patients with a BOR of CR or PR, all assessed by the investigator. (CSR section 5.1.3.8) |
| Exploratory endpoints[b] | Patient-reported outcomes (PROs) endpoints: All scales of the EORTC QLQ-C30, the FACT-Lym LymS, and FACT/GOG-NTX peripheral neuropathy[c],[d] | Not applicable |
| Other[b,c,e] | EQ-5D-5L | Not applicable |

Source: partly reproduced from CS section B.2.3.2

[a] Defined as key secondary endpoints in CS figure 2, efficacy endpoints included in the hierarchical testing procedure
[b] Endpoints that were not adjusted for testing multiplicity
[c] Health-Related Quality of life outcomes
[d] Results omitted from CS. CSR Table 1 states "[redacted]" however, CSR sections 5.1.3.12 and 5.1.4.1, pages 477-513 report results for responder analysis, time to deterioration analysis, summary of mixed-effect model repeated measures and changes from baseline by visit for EORTC QLQ-C30 Physical Functioning and Fatigue Scales, FACT-Lym LymS and FACT/GOG-NTX.
[e] Relevant HRQoL outcome omitted from CS. The CSR reports that EQ-5D-5L was assessed but does not report any results.

BICR: Blinded independent central review; BOR: Best overall response; CR: Complete response; DFS: Disease free survival; DOR: Duration of response; EFSeff: Event-free survival; EORTC: European Organization for Research and Treatment of Cancer Quality of Life-Core 30 questionnaire; EQ-5D-5L: European Quality of Life Working Group Health Status Measure 5 Dimensions, 5 Levels; FDG-PET:Fluorodeoxyglucose positron emission tomography; FACT/GOG-NTX: Functional Assessment of Cancer Treatment/Gynecologic Oncology Group-Neurotoxicity; FACT-Lym LymS: Functional Assessment of Cancer Therapy - Lymphoma Subscale; NALT: New anti-lymphoma treatment.

The company confirmed that the clinical data cut-off date for all outcomes presented in the clinical effectiveness and the health economics sections was 28th June 2021 (median follow-

up period of 28.2 months), and includes all POLARIX trial participants (clarification question A3).

Outcomes informing the economic model were:

- Investigator-assessed PFS
- OS
- Adverse events
- HRQoL via the EQ-5D-5L (mapped to the EQ-5D-3L) (CS section B.3.4.5)

Trial protocol Appendix 1 (schedule of activities) shows the methods, frequency and timing of all outcome assessments was identical between trial arms, reducing the risk of evaluation time bias.

#### 3.2.3.1 Efficacy outcome(s)

Outcomes directly relating to disease (lymphoma) response include: PFS, event-free survival - efficacy (EFSeff), complete response (CR) rate, disease-free survival (DFS), best overall response (BOR), and duration of response (DOR).

CS section B.2.3.1 reports that "Patients were assessed for disease response by the investigator using regular clinical and laboratory examinations, dedicated computed tomography (CT) or magnetic resonance imaging (MRI) scans, and fluorodeoxyglucose positron emission tomography (FDG-PET; hereafter referred to as PET-CT) according to the Lugano Response Criteria for Malignant Lymphoma." Lugano Response Criteria for Malignant Lymphoma provides detailed definitions of complete response and partial response,[10] with one of our clinical experts advising it is the current international standard for assessing disease response to treatment. The analyses of the primary and key secondary endpoints, with the exception of CR rate at the end of treatment by PET-CT, were based on the investigator's assessment of disease response. In the POLARIX trial, both patients and investigators were blind to treatment assignment. As we report later (section 3.2.3.3) the adverse event profile for Pola+R-CHP is comparable to R-CHOP, therefore reducing the likelihood of pharmacological adverse events compromising investigator blinding and leading to evaluation bias.

At the time of the analysis presented in the CS, PFS data were mature while OS data were immature (median survival not yet reached). The ERG notes that patients with DLBCL who are progression free at 24 months from the onset of initial therapy have survival clinically

indistinguishable from the age-, sex-, and country-matched background population.[21] Two of our clinical experts agreed that PFS at 24 months is a key clinical outcome, with one of the aforementioned clinical experts stating that patients who are progression free at 24 months are considered to be in long term remission (effectively considered cured) and are discharged from their care.

CS section B.2.6.1 refers to a "clinically meaningful improvement in the primary endpoint of Investigator-assessed PFS", however the ERG could find no definition of this is the CS, the CS appendices, or the POLARIX protocol and CSR. Consequently, the ERG sought advice from our three clinical experts on what would constitute a minimum clinically important difference in PFS between treatments. All three of the aforementioned experts believed results of the POLARIX study showed a clinically significant difference, as will be presented in more detail in section 3.2.5.1 of this report. One of the aforementioned experts also commented that a 1% improvement with no additional adverse events or cost would also be seen as important

#### 3.2.3.2 HRQoL outcomes

HRQol was assessed using patient (self) reported, reliable and validated instruments.[26-28] These included:

- One generic instrument (the EQ-5D-5L) evaluating the day the questionnaire was self-administered. The company used EQ-5D data from a trial of a different investigational agent for untreated DLBCL (the GOYA trial[29]) in their base case (see section 4.2.7) and EQ-5D-5L data from the POLARIX study, mapped to the EQ-5D-3L, were used to inform a health economic model scenario analysis (CS section B.3.4.5). EQ-5D-5L utility data at baseline and end of trial for each arm of the trial are not presented in the CS, its appendices or in the CSR, however, these data were provided in response to an ERG clarification question (B1).
- Three disease-specific instruments measured HRQoL:
    - **EORTC QLQ-C30.** European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 items.
    - **FACT-Lym LymS**. The Functional Assessment of Cancer Therapy—Lymphoma subscale,
    - **FACT/GOG-NTX**. Functional Assessment of Cancer Treatment/Gynecologic Oncology Group-Neurotoxicity subscale.

  Data for these instruments are not presented in the CS or its appendices. However, the CSR (sections 5.1.3.12 and 5.1.4.1 and pages 477-513) report results for

responder analysis, time to deterioration analysis, summary of mixed-effect model repeated measures and changes from baseline by visit for EORTC QLQ-C30 Physical Functioning and Fatigue Scales, FACT-Lym LymS and FACT/GOG-NTX.

#### 3.2.3.3 Safety outcomes

Safety was evaluated by monitoring all adverse events, serious adverse events, and abnormalities identified through physical examinations, vital signs, and laboratory assessments. All verbatim adverse event terms occurring on or after first study treatment were mapped to the Medical Dictionary for Regulatory Activities (MedDRA). Severity of adverse events were graded with the commonly used National Cancer Institute Common Terminology Criteria for Adverse Events, Version 4.0 (NCI CTCAE v4.0). (CSR 6.4)

Adverse events of special interest, which had to be immediately reported to the sponsor, included: cases of potential drug-induced liver injury; suspected transmission of an infectious agent by the study drug, grade 2 or higher peripheral neuropathy (sensory and/or motor), grade 3 or higher infections (Trial protocol, section 5.2.3)

**ERG comment on outcomes assessment**

Overall, we consider the efficacy, HRQoL and safety outcomes to be appropriate to the decision problem and scope. Data on OS are currently immature. Results for HRQoL are not reported in the CS. The CSR reports a subset of results for disease-specific HRQoL outcome measures and a company clarification question response provided EQ-5D-5L data.

### 3.2.4 Statistical methods of the included studies

A summary and ERG critique of the statistical methods used in the POLARIX trial are presented in Table 9, below.

**Table 9 Summary and ERG critique of the statistical methods used in the POLARIX trial**

| **Sample size and power calculation** | |
|---|---|
| PFS (primary outcome)<br>228 investigator-assessed PFS events provided 80% power to detect a 31% reduction in the risk of disease progression, relapse, or death (HR=0.69) for Pola+R-CHP over R-CHOP based on a on a logrank test with α =0.025 (one-sided). Approximately 875 patients needed. (Trial protocol, section 6.1.1) | |
| ERG comment | Target sample size was reached, therefore the trial can be considered sufficiently powered for the primary outcome. |

| | |
|---|---|
| **Analysis populations** | |
| ITT population, defined as all randomized patients, with patients grouped according to their assigned treatment (Trial protocol, section 6.4) (POLARIX n=879)<br>Safety population, defined as all randomized patients who received at least one dose of study treatment with patients grouped according to the treatment regimen actually received. (Trial protocol, section 6.5) (POLARIX n=873) | |
| ERG comment | Definition of ITT population accords with "true" ITT definition. Safety population as a proportion of the total number randomised was 99.3%, thus minimal attrition bias. |
| **Methods to account for multiplicity** | |
| A hierarchical testing procedure, including possible α recycling, was used to adjust for multiple statistical testing of the primary and key secondary efficacy endpoints (CS section B.2.4).<br><br>Outcomes included in the hierarchical testing procedure, and therefore subject to formal statistical testing, were: PFS as assessed by the investigator, EFSeff as assessed by the investigator, BICR-assessed CR rate at end of treatment, and OS. | |
| ERG comment | Appropriate procedures were followed in the trial to prevent statistically significant effects being detected by chance to be appropriate. |
| **Methods of analysis** | |
| Primary analysis of PFS was performed on the ITT population, incorporating the randomisation stratification factors ((IPI 2 vs. IPI 3-5), bulky disease (present versus absent) and geographical region (Western Europe, United States, Canada, and Australia versus Asia versus Rest of World [remaining countries])). The Kaplan-Meier (KM) method was used to summarise time-to-event outcomes. The Cox proportional-hazards model was used to estimate hazard ratios (with 95% CI). The same methods were used for EFSeff, and OS.<br><br>BICR-assessed CR rate at end of treatment was compared using the Cochran-Mantel-Haenszel test by randomization stratification factors.<br><br>For safety outcomes only descriptive statistics (e.g., frequency, counts) were used. | |
| ERG comment | Appropriate analytical methods were used for primary and key secondary outcomes |
| **Disease progression assessments** | |
| The censoring rules for the primary analysis of investigator-assessed PFS were not presented in the CS or its appendices but reported in the CSR (CSR Table 15). Patients who did not experience a PFS event were censored at the date of last disease assessment before data cutoff. Any patients who commenced new anticancer therapy, and did not experience a PFS event, were censored at the date of last disease assessment before data cutoff.<br><br>The CS does not discuss missing data. Censoring rules for the primary analysis in the CSR (Table 15) specified date of progression or censoring relating to missing assessments in the primary analysis:<br>● No adequate post-baseline assessment and no deaths were censored at baseline;<br>● Time of death or disease progression following one or more consecutive missed assessments was the date of earliest disease progression or death, before data cutoff; | |

| | |
|---|---|
| One or more missed assessments followed by no adequate assessments or death was censored at date of last adequate assessment before data cutoff. | |
| ERG comment | The ERG considers the censoring criteria and approaches to handling missing PFS data appropriate |
| **Sensitivity analysis** | |
| Details of sensitivity analysis of investigator-assessed PFS were not reported in the CS or its appendices, but briefly reported in the CSR (Table 15). A variety of censoring scenarios were included. In general the proportion of patients censored across the scenarios was low and comparable between trial arms. Sensitivity analysis tested the consistency of PFS estimates according to different censoring rules including missing scheduled tumour assessments and commencement of new-anti cancer treatment (see section 3.2.5.1 of this report for a summary of the results). | |
| ERG comment | The use of sensitivity analyses to test the consistency of PFS estimates across censoring criteria appear to be appropriate and comprehensive. However, the CSR does not appear to give results for all scenarios tested. |
| **Subgroup analyses** | |
| A preplanned, unstratified, exploratory subgroup analysis of investigator-assessed PFS was performed. Subgroups included patient demographics, IPI risk factors, cell of origin, double expressor status and double/triple hit lymphoma status. | |
| ERG comment | These chosen subgroups are appropriate to this disease. Interpretation of the results should be made with caution given their exploratory nature. |
| BICR: Blinded independent central review CR: Complete response; DFS: Disease-free survival; DOR: Duration of response; EFS: Event free survival efficacy; IPI: International Prognostic Index; ITT: Intention to treat; NALT: New anti-lymphoma treatment (NALT); OS: Overall survival; PFS: Progression free survival | |

**ERG comment on study statistical methods**

The CS provided limited details of the statistical methods used in POLARIX trials in the CS, with additional detail to be found in the study protocol and CSR. The ERG are satisfied that the company's approach to statistics is generally appropriate: the study was adequately powered and suitable methods were used for the analysis of the primary efficacy outcome.

### 3.2.5 Efficacy results of the intervention studies

Below we summarise available results from the POLARIX trial for the outcome measures which directly inform estimates of cost effectiveness in the company's economic evaluation, namely PFS, OS, HRQoL (EQ-5D-5L) and adverse effects. Results for other outcomes (e.g. tumour response) are available in the CS and/or the trial CSR.

#### 3.2.5.1 Progression free survival (PFS)

Table 10 summarises the primary analysis of the primary outcome of PFS in the ITT population. At the 28th June 2021 data cut a total of 241 PFS events had been recorded,

slightly exceeding the 228 PFS events required for the primary analysis. The median duration of PFS follow-up was 24.7 months in the Pola+R-CHP arm (range: 0-34 months) and 24.7 months in the R-CHOP arm (range: 0-37 months), exceeding the milestone of 24 months after enrolment of the last patient required for the primary analysis.

**Table 10 Primary analysis of PFS (primary outcome) in the POLARIX trial**

| | **Pola+R-CHP (n=440)** | **R-CHOP (n=439)** |
|---|---|---|
| **No. of events, n (%)** | 107 (24.3) | 134 (30.5) |
| Earliest contributing event, n | | |
| Death | 19 | 20 |
| Disease progression or relapse | 88 | 114 |
| **Stratified analysis** | | |
| p-value (Log-rank) | 0.02 | |
| Hazard ratio (95% CI) | 0.73 (0.57–0.95) | |
| **12-Month PFS rate (95% CI)** | 83.9 (80.4–87.4) | 79.8 (75.9–83.6) |
| **24-Month PFS rate (95% CI)** | 76.7 (72.7–80.8) | 70.2 (65.8–74.6) |
| Source: CS Table 9 | | |

Fewer patients in the Pola+R-CHP arm progressed or died compared to the R-CHOP arm (n=107 [24.3%] vs.134 [30.5%], a difference of **6.2%**). The stratified HR was 0.73 (0.57–0.95) signifying a 27% reduction in the risk of disease progression or death in patients receiving Pola+R-CHP. Results of the unstratified analysis were consistent (HR: 0.76 [95% CI: 0.59, 0.98]; two-sided p-value=0.0326).

The Kaplan-Meier plot of time to investigator-assessed PFS (CS Figure 4, not reproduced here) shows a separation of the survival curves after six months, progressively widening over the first 24 months follow-up, during which the majority of PFS events occurred. A consistently higher proportion of patients remained alive and progression-free in the Pola+R-CHP arm compared to the R-CHOP arm at the 12 and 24-month assessments.

Sensitivity analyses to evaluate the impact of missing assessments and receipt of new anti-lymphoma treatment are not reported in the CS,

[redacted]

[redacted] We summarise the results of preplanned subgroup analyses of investigator-assessed PFS below in section 3.2.5.4.

The CS describes the PFS results as clinically meaningful though does not elaborate further on how this is defined. The ERG's clinical experts agree with the company's assertion that the delay in disease progression achieved with Pola+R-CHP is clinically significant. One expert observed that the increase in PFS seen in POLARIX has not been achieved by any previous alternatives to R-CHOP.

The final data cut (June 2022) will show the proportion of patients remaining alive and progression-free in the trial arms over the full study period. The CS states that PFS results from the POLARIX study are considered sufficiently mature and unlikely to change appreciably with longer follow-up, due to the magnitude of treatment effect observed with Pola+R-CHP over R-CHOP. The company anticipates that a proportion of patients will remain progression free after two years, and this will support the assumption that survival rates in progression free patients at this time will be similar to that of the general population. This is a key assumption in the company's 'cure mixture' economic model, which we discuss in section 4.2.6 of this report.

#### 3.2.5.2 Overall survival (OS)

Table 11 gives a summary of secondary outcome OS at the 28th June 2021 interim data cut. At this time only a small proportion of deaths had occurred (13%) and median OS had not been reached. The results are therefore immature and caution is advised in their interpretation. The proportion of deaths was similar between the trial arms. The stratified HR was 0.94 (95% CI 0.65–1.37) (p=0.7524), indicating a non-statistically significant reduction in the risk of death. The unstratified HR was similar to the stratified analysis. Final analysis of OS will be performed at the final data cut in June 2022.

**Table 11 Interim analysis of OS (secondary outcome) in the POLARIX trial**

| | Pola+R-CHP (n=440) | R-CHOP (n=439) |
|---|---|---|
| **Overall Survival** | | |
| Patients with event (%) | 53 (12.0%) | 57 (13.0%) |
| Median time to OS - months (95% CI) | NE | NE |
| Stratified HR (95% CI) | 0.94 (0.65–1.37) | |

| | | |
|---|---|---|
| p-value (log-rank) | 0.7524 | |
| Unstratified HR (95% CI) | 0.92 (0.63–1.34) | |
| 12-Month OS rate (95% CI) | 92.2 (89.6–94.7) | 94.6 (92.5–96.8) |
| 24-Month OS rate (95% CI) | 88.7 (85.7–91.7) | 88.6 (85.6–91.6) |
| Source: CS Table 10 | | |

In section 4.2.6 we describe how OS and PFS estimates from POLARIX inform estimates of cost-effectiveness in the company's economic model.

#### 3.2.5.3 HRQoL outcomes

The CS does not report data from administration of the EQ-5D-5L questionnaire in the POLARIX trial, however, these were supplied following a request by the ERG (clarification question B1). A table is given showing Least Square Mean EQ-5D-5L index values (with accompanying standard errors and 95% CIs) for the respective trial arms at baseline and at each study visit, starting with treatment cycles 2, 3, 5, treatment completion (or early discontinuation), and 3-monthly follow-up visits up to 24 months.

No commentary or interpretation of the results is provided. The number of patients analysed is not reported and there are no explicit details of missing data (the only statement given is that missing data "is very likely not to be missing completely at random", hence the use of Least Square Means).

In summary:

- At baseline mean EQ-5D-5L index values were similar between the trial arms: 0.8121 (95% CI 0.7937 to 0.8306) and 0.811 (95% CI 0.7926 to 0.8294) in the Pola+R-CHP and R-CHOP arms, respectively.
- Following commencement of treatment mean index values increased slightly in both arms (data not shown here).
- At completion of treatment or early discontinuation, mean index values were 0.8432 (95% CI 0.8269 to 0.8596) and 0.8453 (95% CI 0.8292 to 0.8615) in the Pola+R-CHP and R-CHOP arms, respectively.
- Between completion of treatment and the end of 24-Month follow-up the mean index values fluctuated slightly in both trial arms between 0.85 – 0.88.
- At the final follow-up visit at 24-Months the mean index values were 0.87 (95% CI 0.846 to 0.894) in the Pola+R-CHP arm and 0.8565 (95% CI 0.8314 to 0.8815) in the

R-CHOP arm. This represented an increase from baseline of 0.0579 and 0.0455 in the Pola+R-CHP and R-CHOP arms, respectively.

Statistical significance values for the differences between trial arms at the respective study visits were not reported. However, the company reports "There is no statistically significant difference between the two treatment arms when the EQ-5D-5L utility index values were collected". This is based on the results of 'Type 3 tests of fixed effects' though there is no description of the purpose or application of this test. The ERG are unclear on the interpretation of the results of the test and the meaning of the company's statement.

The ERG's overall interpretation of the findings is that HRQoL, as measured by EQ-5D-5L, modestly improved during the course treatment in both trial arms, with improvements generally maintained over the 24-month follow-up period. There is no discernible difference between the treatments in the extent to which HRQoL improved. Caution is advised in the interpretation of the findings as key details such as the number of patients analysed and the volume of missing data is unclear.

#### 3.2.5.4 Subgroup analyses

CS Table 13 reports a forest plot of pre-planned exploratory subgroup analyses for the primary outcome of investigator-assessed PFS at the June 28th 2021 data cut (primary analysis for PFS). Sub-groups included baseline patient demographic characteristics (age, sex) and measures of baseline disease status (e.g. IPI score, Ann Arbor stage, presence or absence of bulky disease).

The company describes the results as showing a "directionally consistent treatment effect supporting the PFS benefit of Pola+R-CHP in the majority of subgroups (HR<1)…all subgroups included a confidence interval that favoured Pola+R-CHP" (CS page 39). The ERG concurs that the direction of effects generally favours Pola+R-CHP, but we disagree with the company's assertion that all subgroups included confidence intervals favouring Pola+R-CHP. For example, for Ann Arbour subgroups stages I-II, III and IV the upper bounds of the 95% Wald CIs were 1.8, 1.3 and 1.1 respectively, thus not ruling out a possible PFS benefit favouring the comparator treatment, R-CHOP. The ERG notes that the POLARIX journal publication [25] provides a descriptive summary of the subgroup results which is consistent with the forest plot in CS Table 13. The publication cites subgroups that did not show a clear benefit with Pola-R-CHP, including patients aged 60 years of age or younger, and patients who had bulky disease.

Also of note:

**Cell of origin** (i.e. GCB, ABC, unclassified), the subgroup of relevance to the NICE scope.

- For the GCB subgroup (who generally have a more favourable survival prognosis) there was no difference between Pola+R-CHP and R-CHOP in investigator-assessed PFS, with an HR of 1.0 (95% CI 0.7–1.5).
- In contrast, in the ABC subgroup (who have a less favourable survival prognosis) there was a marked PFS benefit favouring Pola+R-CHP, with a HR of 0.4 (95% CI 0.2–0.6).

**IPI risk score**

- For the IPI 2 subgroup (low-intermediate risk) there was no difference between Pola+R-CHP and R-CHOP in investigator-assessed PFS, with an HR of 1.0 (95%CI 0.6–1.6).
- In contrast, for IPI 3-5 (high-intermediate to high risk) the HR was 0.7 (95%CI 0.5–0.9), which is more in line with the HR for the ITT population (0.73).
- These results cautiously suggest that, in delaying disease progression, Pola+R-CHP is more clinically effective in patients with greater risk. The lack of difference between treatments in the IPI 2 subgroup is of note given that the company's intention is for Pola+R-CHP to be a treatment option for DLBCL patients with an IPI risk classification between 2-5.

Caution, however, is required in the interpretation of these subgroup results given that the trial was not powered to demonstrate statistically significant treatment differences according to subgroups. The random allocation of participants to trial arms in this trial will not necessarily reduce the risk of selection bias affecting the subgroups (although IPI and bulky disease were random stratification factors and hence, should be evenly distributed). Furthermore, current results (from the June 28th 2021 data cut) may be regarded as interim as regards the subgroups (they can only be considered primary for the ITT population). It is unlikely that the results of the final data cut (June 2022) will differ substantially, but confidence intervals may narrow as further events are recorded.

The CS does not report whether subgroup analyses were done for any other outcome measures from POLARIX. As noted earlier in this report, cost-effectiveness estimates in the CS are presented for the whole patient population only, with no subgroup analyses performed.

### 3.2.5.5 Safety outcomes

As mentioned earlier (section 3.2.4) the POLARIX safety-evaluable population (all randomized patients who received at least one dose of study treatment) included a total of 873 of 879 randomised patients. Table 12 gives a summary of the key safety results at the 28th June 2021 data cut.

**Table 12 Summary of POLARIX adverse event profile (safety evaluable population)**

| Adverse event (AE), n (%) | Pola+R-CHP (n=435) | R-CHOP (n=438) |
|---|---|---|
| Any-grade AEs | 426 (97.9) | 431 (98.4) |
| Grade 3–4 AEs | [redacted] | [redacted] |
| SAEs | 148 (34.0) | 134 (30.6) |
| Grade 5 AEs | 13 (3.0) | 10 (2.3) |
| AEs leading to treatment discontinuation | | |
| Any treatment | 27 (6.2) | 29 (6.6) |
| Polatuzumab vedotin/vincristine | 19 (4.4) | 22 (5.0) |
| AEs leading to dose reduction (any treatment) | 40 (9.2) | 57 (13.0) |

Source: CS Table 14
AE Adverse events, SAEs Serious Adverse Events

The CS reports that the safety profile of Pola+R-CHP regimen was comparable to R-CHOP and in line with the known safety profiles of each individual component and the underlying disease. As seen in Table 14 the incidence of different classes of adverse events were similar between the trial arms: [redacted], Grade 5 AEs, SAEs, adverse events leading to any treatment discontinuation. Adverse events leading to dose reduction were lower in the Pola+R-CHP arm.

[redacted]

The most commonly reported adverse events (≥ 50% of patients in either arm) included

[redacted]

[redacted]

Of the 10 serious adverse events with an incidence rate of at least 1% (CS Table 16) there were three with ≥1% difference in incidence between the arms (Pola+R-CHP arm and R-CHOP arm, respectively):

[redacted]

### 3.2.6 Pairwise meta-analysis of intervention studies

The CS states that no meta-analysis was conducted for this submission, but does not elaborate further. The ERG notes that, other than the POLARIX trial, there are no other apparent RCTs of Pola available. Hence, it is not possible to conduct a meta-analysis of Pola until the results of at least one other trial are available.

## 3.3 Critique of studies included in the indirect comparison and/or multiple treatment comparison

The company did not include an indirect comparison in their submission to NICE. The ERG notes that a direct comparison of Pola+R-CHP versus R-CHOP is available from the POLARIX trial. Hence, an indirect comparison is not required to inform this technology appraisal.

## 3.4 Critique of the indirect comparison and/or multiple treatment comparison

Please see section 3.3. above.

## 3.5 Results from the indirect comparison

Please see section 3.3. above.

## 3.6 Additional work on clinical effectiveness undertaken by the ERG

None.

# 4 COST EFFECTIVENESS

## 4.1 ERG comment on company's review of cost-effectiveness evidence

The company conducted a systematic review to identify all relevant health economic evaluation studies for patients with previously untreated DLBCL (CS Appendix H). The company performed their searches in relevant electronic databases, conference websites and Health Technology Assessment (HTA) databases (CS Appendix H.2). Databases were searched in August 2021. The eligibility criteria are shown in CS Appendix H Table 23.

There were 13 studies that met the inclusion criteria, after full text screening. However, none of the studies included Pola+R-CHP. Only one study was conducted in the UK (Wang et al).[30] Most treatment comparisons were between R-CHOP and CHOP (n=7). More details of the included studies are reported in CS Appendix H.5. The studies date in year of publication from 2005-2021. The ERG conducted additional searches and did not identify any other relevant studies.

The ERG considers the study by Wang et al[30] to be most relevant as this study is conducted in the UK. Wang et al. was a 'real world' evidence modelling study that followed newly diagnosed patients with DLBCL in the UK's population-based Haematological Malignancy Research Network (www.hmrm.org) from 2007 to 2013. to obtain cost information and treatment pathways. A patient-level simulation was developed with a lifetime horizon.

**ERG conclusion**

The ERG considers the company's review of economic evaluation evidence comprehensive and appropriate. The included economic evaluations predominantly assess R-CHOP versus CHOP, and no studies of Pola+R-CHP were identified.

## 4.2 Summary and critique of the company's submitted economic evaluation by the ERG

The CS reports the company's de novo economic evaluation to assess the incremental cost effectiveness of Pola+R-CHP vs R-CHOP in the treatment of untreated DLBCL patients in the UK. In the following subsections we review and critique the methods used to construct a partitioned survival model economic model to estimate cost-effectiveness.

### 4.2.1 NICE reference case checklist

Table 13 shows the ERG's assessment of the concordance of the company's model to the NICE reference case. We consider that the company's model is consistent with the refence case.

**Table 13 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 | Yes |
| Perspective on costs | NHS and PSS | Yes |
| Type of economic evaluation | Cost–utility analysis with fully incremental analysis | Yes |
| Time horizon | Long enough to reflect all important differences in costs or outcomes between the technologies being compared | Yes |
| Synthesis of evidence on health effects | Based on systematic review | Yes. Evidence from the POLARIX trial |
| 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. | Yes |
| Source of data for measurement of health-related quality of life | Reported directly by patients and/or carers | Yes |
| Source of preference data for valuation of changes in health-related quality of life | Representative sample of the UK population | Yes |
| Equity considerations | An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit | Yes |
| 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 | Yes |
| Discounting | The same annual rate for both costs and health effects (currently 3.5%) | Yes |

### 4.2.2 Model structure

#### 4.2.2.1 Overview of the model structure

The company developed a partitioned survival model in Microsoft Excel. The CS states that this approach is consistent with NICE DSU guidance and previous NICE appraisals of DLBCL conducted in the relapsed refractory disease setting. The model structure is described in CS B.3.2.2 and illustrated in CS Figure 9, reproduced in Figure 2 below. The

model contains three mutually exclusive health states: progression free (PF); progressed disease (PD) and death. Patients start in the PF state, following initiation of one of the included first-line treatments. At disease progression, patients transition to the PD state, which is irreversible, so patients cannot return from PD to PF. Patients in the PF and PD states may die from cancer or other causes.

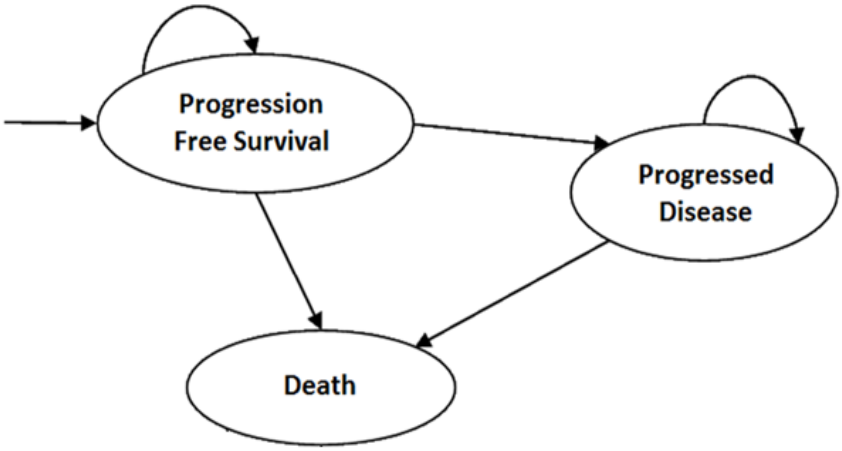



**Figure 2 Structure of economic model**

Reproduced from CS B.3.2.2 Figure 9

At the end of each model cycle, patients in the PF state may remain in this state or transition into a different state (PD or death). Patients in the PD state stay in that state until death. The proportion of patients in each health state at different time points is based on the PFS and OS curves from the POLARIX trial. Logically, the proportion of patients alive at any time is greater than those with PFS. The proportion of patients progressing to the PD health state is the difference between OS and PFS (see CS Figure 10).

**ERG comment on model structure**

The three-state partitioned survival model used in the company's economic evaluation is a standard modelling approach and has been applied in previous NICE appraisals for DLBCL and is commonly used in models for oncology. We consider that the model structure and partitioned survival approach is appropriate.

### 4.2.3 Population

The modelled population is adults with untreated DLBCL. Baseline characteristics of the modelled cohort are based on those in the POLARIX trial, with a mean age of [redacted] years and [redacted] male. The CS states that the population is in line with the proposed marketing authorisation and the decision problem for this appraisal (CS Table 1). As noted earlier, the

POLARIX trial only included patients with IPI scores between 2 and 5 and excluded IPI 0-1 patients. Thus, the company's decision problem is narrower than the marketing authorisation. Clinical experts advising the ERG commented that patients with IPI scores 0-1 may receive less intensive standard care regimens (see section 2.2.1.3 for more details of clinical management for patients with DLBCL). However, it is not fully clear on what criteria clinicians would use to select patients to try Pola+R-CHP and whether any IPI 0-1 patients selected would require a less intense regimen as is currently the case for standard care. With the exception of IPI scores mentioned above, the ERG agrees that the modelled population matches the NICE scope for this appraisal.

As mentioned earlier in section 2.3.4, the company has not assessed cost effectiveness according to patient subgroups as they consider the POLARIX subgroup analyses (which is reported only for the outcome of investigator-assessed PFS) to be [redacted]

### 4.2.4 Interventions and comparators

As already noted, the economic model compares the incremental cost-effectiveness of Pola+R-CHP compared to the current standard of care R-CHOP. Pola+R-CHP and R-CHOP are given for up to six cycles each lasting 21 days. Details on the dosing of these therapies are given in Table 19.

The ERG notes that the NICE scope for this appraisal states 'chemoimmuntherapy (including R-CHOP)' as the relevant comparator, which implies that R-CHOP is not exclusive as a comparator. However, based on expert clinical advice there does not appear to be any other alternatives commonly used in practice.

**ERG comment on intervention and comparators**

The intervention and comparators in the economic model are consistent with the NICE scope.

### 4.2.5 Perspective, time horizon and discounting

The perspective of the analysis is the NHS and Personal Social Services (PSS). Costs and QALYs are discounted at 3.5% in the base case, as per the NICE reference case.[31] In the base case, the model has a lifetime horizon of 60 years. The CS states that this time horizon was chosen as at 60 years less than 1% of patients are still alive. This time horizon is consistent with previous NICE appraisals for DLBCL (TA306,[32] TA567,[33] TA559,[34] TA649)[23]

The ERG notes that using a time horizon of 60 years results in a patient age of 123 years at the end of the simulation. Generally, it is more standard for the lifetime horizon to end at age 100 years, however as the model results are similar with a time horizon of 40 years or 60 years (CS table 45) we have kept the same time horizon as the company.

**ERG conclusion**

The company adopted the recommended perspective and discounting rates and an appropriate time horizon, which are all in line with NICE guidelines[31] and previous NICE appraisals for DLCBL.

### 4.2.6 Treatment effectiveness and extrapolation

PFS and OS KM data from the POLARIX trial were extrapolated over the 60-year time horizon using parametric survival models, as recommended in NICE DSU TSD 14.[35] For internal validation the company compared the goodness-of-fit of parametric survival models using the Akaike Information Criterion (AIC) / Bayesian Information Criterion (BIC) and visual inspection of the of the extrapolated PFS and OS curves alongside the KM data. The long-term extrapolations were compared to the external sources recommended by the company's clinical experts.

The CS states that **cure mixture** models may be appropriate in cases where there is evidence to support the assumption that a proportion of patients enter long-term remission and have long-term prognosis similar to the general population. Cure mixture models assume that there are two distinct subpopulations: the cured population, which is considered to have the same risk of mortality as the age and sex matched general population; and the subpopulation that remains affected by the disease in question. For the non-cured population, the mortality rate is defined by a selected standard parametric survival curve. The proportion of people in the cured population is known as the 'cure fraction' and is estimated alongside other survival estimates when using a parametric model. The extrapolations for each subpopulation are then combined using the cure fraction to obtain the extrapolations for the whole population. The ERG requested further information from the company on how the cure fraction was calculated (clarification question B3). The company provided further information on the methodology used. This was based upon the tutorial article by Felizzi et al.[36]

The CS states that cure mixture modelling is appropriate in this instance, with reference to supporting evidence:

- A study by Jakobsen et al[37] demonstrated that patients who remained in remission after 24 months had similar lifetime survival (albeit slightly lower) than matched age and sex individuals in the general population.
- The CS notes that cure mixture modelling has previously been used in NICE appraisals for relapsed and refractory DLBCL (TA567,[33] TA649[23] and TA559[34]).
- The CS also notes that the POLARIX PFS KM data supports the use of cure mixture modelling as there was a very low rate of progression for Pola-R-CHOP and R-CHOP after 24 months.

In principle, the ERG agrees with the company's rationale for using cure mixture modelling in this appraisal.

#### 4.2.6.1 Progression-free survival

The company checked whether the proportional hazards (PH) assumption is supported by visual inspection of the log-cumulative hazard plots (CS Figure 13). They concluded that the PH assumption does not hold as the lines in the figure are non-parallel and therefore the ratio of the hazard rates between arms does not remain constant over the follow-up period. As the PH assumption does not hold, independent parametric models were fitted for each treatment arm for PFS.

The fitted parametric distributions compared to the observed data are shown in CS Figures 15-17. The best fitting models for PFS for the POLARIX trial were the generalised gamma and the log-normal (CS Table 18) (although the CS observed that there were minimal variation between the AIC and BIC statistics for the different distributions). The Weibull and log-logistic distributions did not converge and so were not suitable. The generalised gamma distribution was chosen for the base case for PFS in both treatment arms as it provided a good fit to the observed data from the POLARIX trial and aligns with the OS distribution (see below). The exponential and lognormal extrapolations were explored in scenario analyses. The cure fraction for the generalised gamma was 75% for Pola+R-CHP and 64% for R-CHOP.

The long-term predictions of PFS were compared with long-term follow-up data (5 years) for the R-CHOP arm of the GOYA trial. The GOYA trial was a phase III study comparing obinutuzumab or rituximab plus CHOP in patients with previously untreated DLBCL.[29] The company concluded that the generalised gamma parametric survival distribution in the

POLARIX R-CHOP arm adjusted to match the patient characteristics from the GOYA trial provided a good fit to the long-term GOYA R-CHOP arm (64% vs 64%).

The ERG agrees with the company's assessment of the PH assumption. Furthermore, the ERG considers that the generalised gamma is a suitable distribution for PFS based on the fit to the observed PFS data from POLARIX and its alignment with the long-term data from the GOYA trial. The modelled PFS is compared to the trial data from the POLARIX and GOYA trials in Table 14.

**Table 14 PFS predictions for the generalised gamma distribution vs the KM data from the POLARIX and GOYA trials**

| | Pola+R-CHP arm | | R-CHOP arm | | |
|---|---|---|---|---|---|
| **Year** | Generalised gamma | POLARIX trial | Generalised gamma | POLARIX trial | GOYA trial |
| **1** | 84.8% | 84.9% | 79.9% | 81.2% | [redacted] |
| **2** | 77.0% | 77.3% | 70.2% | 70.2% | [redacted] |
| **5** | 68.8% | - | 60.8% | - | [redacted] |
| **10** | 58.3% | - | 50.5% | - | - |
| Source: Company model | | | | | |

#### 4.2.6.2 Overall survival

The company considered whether the PH assumption held for OS. Similar to PFS, they concluded that the PH assumption did not hold because the log-cumulative hazard plots (CS Figure 18) showed diverging lines between Pola+R-CHP and R-CHOP. This indicates that the ratio of the hazard rates between arms does not remain constant over the follow-up period. As the PH assumption does not hold, independent parametric models were fitted for each treatment arm for OS.

The CS notes that the OS KM data is immature as there were few deaths at the interim data cut. Pola+R-CHP did not show a statistically significant benefit in OS over R-CHOP in the POLARIX trial with a hazard ratio of 0.94 (95% CI 0.65 to 1.37). For this reason, the OS cure fraction was informed by the PFS cure fraction. The fitted parametric distributions compared to the observed data are shown in CS Figures 20-22. The best fitting survival distributions for OS in the POLARIX trial were the generalised gamma and log-normal (CS Table 19). The Weibull and log-logistic distributions did not converge and so were not suitable. The CS comments that the Gompertz, generalised gamma and log-normal are more plausible distributions as a plateau can be observed towards the end of the curve, which is expected

these treatments. The generalised gamma distribution was chosen for the base case for OS in both treatment arms as it provided a good fit to the observed data from the POLARIX trial. The exponential and lognormal extrapolations were explored in scenario analyses. The cure fraction for the generalised gamma was 75% for Pola+R-CHP and 64% for R-CHOP (as for PFS). The CS comments that the OS improvement in the Pola+R-CHP arm can be attributed to the increase in patients who are considered in remission after 2 years and are in long-term remission.

The ERG asked the company to compare the long-term OS for R-CHOP from the economic model to that of the GOYA trial[29] (Clarification question B2). In reply, the company stated that there was no alignment between the POLARIX and GOYA OS curves (survival better for the POLARIX trial). They suggested the OS difference can partially be attributed to the change in the available standard of care in relapsed and refractory DLBCL patients from when the GOYA trial was conducted. Clarification response document Figure 4 shows the OS curves from the POLARIX and GOYA trials.

The ERG agrees with the company's judgement that the PH assumption is not supported. We note that there is little difference in OS between the Pola+R-CHP and R-CHOP arms based on interim data. However, it is appropriate to model the life expectancy and QALYs, through the use of the survival curves in the trial, rather than assuming the survival in both arms should be taken as equal.

Patients in the R-CHOP arm of POLARIX have a slightly higher probability of survival until around month 24 onwards when Pola+R-CHP has a slightly higher survival probability (i.e. the KM survival curves cross over) (CS Figure 6). Given the small differences in survival between the arms, we consider a better approach is to use the KM data for the trial period with an extrapolated tail. Further, the ERG considers that the generalised gamma is a suitable distribution top extrapolate OS based on the fit to the observed OS data from POLARIX. Given that there is no statistically significant benefit for Pola+R-CHP vs R-CHOP for OS, we consider that the long-term difference between arms is uncertain and it is overly optimistic to assume that the treatment effect will be maintained indefinitely. We have therefore assumed that the duration of the treatment effect is limited to five years, after which the probability of mortality will be the same for both treatment arms and will begin to wane linearly after 30 months. We consider that by five years other factors will have a large influence on OS, such as the use of subsequent anti-lymphoma treatments. Treatment effect waning was estimated to start soon after the median follow-up of the trial (28.2 months). We test alternative assumptions in scenario analyses. The extrapolated tail is assumed to start

when 25% of patients are still at risk (30 months). The effect on incremental life years for Pola+R-CHP vs R-CHOP using a treatment effect maintained over time (company assumption) and limited to five years (ERG assumption) are shown in Table 15.

**Table 15 The effect on incremental life years for Pola+R-CHP vs R-CHOP using different assumptions for the duration of the treatment effect for OS**

| | **Effect is maintained over time** | | **Effect limited to 5 years (effect wanes from 2.5 years)** | |
|---|---|---|---|---|
| | Generalised gamma | Exponential | Generalised gamma | Exponential |
| Additional life years for Pola+R-CHP vs R-CHOP | [redacted] | [redacted] | [redacted] | [redacted] |

**Table 16 OS predictions for the generalised gamma vs the KM data from the POLARIX and GOYA trials**

| | **Pola+R-CHP arm** | | | **R-CHOP arm** | | | |
|---|---|---|---|---|---|---|---|
| **Yr** | Generalised gamma | KM + Generalised gamma[a] | POLARIX trial | Generalised gamma | KM + Generalised gamma[a] | POLARIX trial | GOYA trial |
| **1** | 93.4% | 92.2% | 92.2% | 94.6% | 94.6% | 94.6% | [redacted] |
| **2** | 89.4% | 88.7% | 88.7% | 89.3% | 88.6% | 88.6% | [redacted] |
| **5** | 81.0% | 79.6% | - | 78.7% | 78.0% | - | [redacted] |
| **10** | 68.7% | 66.0% | - | 65.2% | 64.6% | - | - |

Source: Company model;[a] treatment effect wanes between 2.5 and 5 years and extrapolated tail begins at 30 months

Figure 3 shows the company and ERG base case extrapolations for OS.

**Figure 3 Company and ERG base extrapolations of OS for Pola-R-CHP and R-CHOP**

#### 4.2.6.3 Treatment duration in the economic model

Patients in the POLARIX trial received up to six cycles of Pola+R-CHP or R-CHOP, plus two cycles of rituximab alone. The CS states that treatment discontinuation was low in both arms

and was most commonly due to adverse events and progression of disease. Dose reduction occurred in 6.9% of patients in the Pola+R-CHP arm and 11.6% of patients in the R-CHOP arm. The treatment duration for Pola+R-CHP and R-CHOP are shown in CS Figure 25 and Figure 26 respectively. CS Table 20 and CS Table 21 show the time to off treatment duration and the average treatment cycle for patients in the POLARIX trial.

#### 4.2.6.4 Adverse events

Adverse events with grade ≥ 3 were included in the economic model for both arms of the POLARIX trial, if they had an incidence of ≥2%. The frequency of serious adverse events is reported in CS Table 22 and included events such as anaemia, diarrhoea and febrile neutropenia. Disutilities and costs were applied for each adverse event. The duration of the adverse event were based on those used in NICE TA306. The ERG notes that the frequency of serious adverse events differs in different tables of the CS (CS Tables 15,16, and 23). We queried these differences in clarification question B9. The company replied that CS Table 23 only includes treatment-related adverse events with toxicity grade 3 or higher, which were either serious adverse events or those that required care (additional treatment, surgical procedure, or study discontinuation). Any grade 3 or higher adverse events that did not incur treatment costs were excluded; hence, the discrepancy between CS Table 16 and CS Table 23.

**ERG comment on treatment effectiveness and extrapolation**

The benefits for OS from Pola+R-CHP compared to R-CHOP are uncertain at present due to immature POLARIX trial data. Based on interim data analysis there was no statistically significant difference in OS between trial arms (HR 0.94; 95% CI 0.65 to 1.37). However, it is appropriate to estimate life expectancy and QALYs based on the trial's survival curves, rather than assuming that OS in both arms would be equivalent. The company's approach to modelling assumes that the OS benefit for Pola+R-CHP compared to R-CHOP persists indefinitely. We consider this assumption unlikely, and therefore in the ERG base case we have limited the duration of treatment effect to five years. In addition, we consider that a better modelling approach for OS is to use the trial KM data with an extrapolated tail, starting at 30 months.

### 4.2.7 Health related quality of life

#### 4.2.7.1 Systematic literature review of HRQoL utility

The company conducted a systematic review to identify HRQoL utility data for patients with DLBCL treated in the first-line setting (CS Appendix I). The searches were performed in August 2021 and the eligibility criteria are shown in CS Appendix Table 31.

Four studies were identified, and these are summarised in CS Appendix Table 32. Three studies were available as conference abstracts and one study was published in full. Two studies were conducted in the UK. The methods used to derive utilities in the four studies were EQ-5D-3L and EQ-5D-5L.

#### 4.2.7.2 Study-based health related quality of life

HRQoL data were collected from patients in the POLARIX study using the EQ-5D-5L questionnaire. The mean index values for the trial arms at each study assessment were supplied by the company to the ERG on request (clarification question B1), and a summary of these is presented earlier in this report (section 3.2.5.3). EQ-5D-5L utility values were mapped to the EQ-5D-3L using the van Hout crosswalk.[38] In response to clarification question B1 the company provided corrected utility values following discovery of an error in their original analysis. The corrected utility values from the POLARIX trial are shown in Table 17 for the PFS and PD health states (Clarification response document Table 3). There were no statistically significant differences between the two treatment arms (Clarification response document Table 5).

**Table 17 Summary of corrected utility values from the POLARIX trial**

| | PFS utility value | PD utility value |
|---|---|---|
| POLARIX trial EQ-5D-5L (crosswalk to EQ-5D-3L), IPI 2–5 | 0.812 | 0.769 |

#### 4.2.7.3 Health state utility values used in the economic model

Health state utility values used in the economic model were taken from the aforementioned GOYA trial.[29] The CS states that clinical experts to the company considered that the utility values from the GOYA trial were more representative of UK patients than those from the POLARIX trial. Additionally, longer follow-up data are available for the GOYA trial. The utility values from the POLARIX trial were used in a scenario analysis.

The CS states that the utility values from the GOYA trial were adjusted so that the patient characteristics match the POLARIX trial patient population. However, limited information was supplied by the company about the collection and analysis of HRQoL data in the GOYA trial.

For patients who remain in the PFS health state for more than two years, their utility is considered to be similar to those in the general population, based on clinical advice and studies by Launonen et al[39] and Jakobsen et al 2017.[37] Launonen et al[39] investigated HRQoL in patients receiving first-line treatment for DLBCL in the GOYA trial, and demonstrated that those patients with PFS after 24 months had similar HRQoL as the general population. General population utilities are taken from Ara and Brazier.[40] In the model, the PFS utility values are adjusted after two years according to the general population utility values.[40]

Disutilities were applied for patients experiencing adverse events of CTCAE grade 3 or above. Disutility values were taken from the literature and are shown in CS Table 23. Disutilities are applied by multiplying the disutility by the duration of the adverse event. The utility values used in the economic model are shown in Table 18 for the PFS and the PD health states (CS Table 25).

**Table 18 Summary of utility values for cost-effectiveness analysis**

| State | Utility value: mean (standard error) | Source | Company justification |
|---|---|---|---|
| Health state utility values | | | |
| PFS | 0.816 (0.01) | GOYA trial | Values validated by clinicians. Longer patient follow-up in GOYA trial. |
| PD | 0.734 (0.01) | GOYA trial | |
| PFS: long-term follow up | Age- and sex-matched general population utility values. | From Ara and Brazier 2010 (112) | 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 [40]. |
| Treatment disutilities | Disutility values sourced from NICE TA306 and the literature. | | |

The ERG notes that the utility values for the PFS state from the POLARIX and GOYA trials are similar to the age- and sex-matched general population utility values. We also note that for patients who remain in PFS, their utility value in the economic model will become lower than that of patients with PD after age 80 years. This seems implausible and therefore the

ERG suggests that the utility values for the PD health state are also adjusted using the general population utility values from Ara and Brazier et al.[40]

The ERG prefers to use the utility values from the POLARIX trial, for consistency with the trial's survival data.

**ERG conclusion on HRQoL**

The company's approach to estimating utility values is generally reasonable and consistent with the NICE reference case. However, the use of values from the POLARIX trial is preferable to other sources used by the company. We note that age-adjusted utility has been included for the PFS health state but not for the PD health state, which results in implausible values for PD. We suggest that the utility values for PD should also be age-adjusted to maintain consistency with those for PFS.

### 4.2.8 Resources and costs

The costs included in the economic model consist of drug acquisition and administration costs for first and subsequent treatments, supportive care costs, and costs for managing adverse events.

The company conducted a literature search in August 2021 to identify costs and resources used in the first-line treatment and management of DLBCL. Details of the search strategy and eligibility criteria are shown in CS Appendix J. A total of 18 studies met the systematic review inclusion criteria, but none of these were conducted in the UK. The studies are shown in CS Appendix J Table 41. The ERG considers that the company's literature review is likely to reflect the available evidence. The costs and resources used in the CS are based on NICE TA306 for pixantrone monotherapy for treating multiply relapsed or refractory aggressive non-Hodgkin's B-cell lymphoma.

#### 4.2.8.1 Drug acquisition

Polatuzumab vedotin is administered every 21 days for up to six cycles as an IV infusion on day one of each cycle. The mean dose is 1.8 mg/kg and polatuzumab vedotin is available in 30mg and 140mg vials with list prices of £2,370 and £11,060 respectively. Polatuzumab vedotin is available with a patient access scheme (PAS) price discount of [redacted].

R-CHOP (rituximab, cyclophosphamide, doxorubicin, prednisolone and vincristine) is administered as IV infusions on day 1 of each 21-day cycle, except prednisolone which is

taken orally on days 1-5 of each 21 day cycle. The dosages and vial sizes are shown in Table 19 (CS Table 26). No vial sharing was assumed for all treatments. Costs of the treatments are taken from the British National Formulary (BNF) for rituximab and cyclophosphamide and from the electronic market information tool (eMIT) for the other treatments. Rituximab is also available with a confidential PAS discount. The ERG has replicated the company's analyses using all applicable PAS prices in a separate confidential appendix to this report.

The ERG notes that there is a minor discrepancy in the price of cyclophosphamide. This is corrected in the model, see section 5.3.4. In the company's base case a discount of 50% off the price for rituximab is assumed. On advice from NICE, we have instead used the list price for rituximab in the ERG base case (section 6.1), i.e. no discount.

#### 4.2.8.2 Drug administration

The same administration costs are used for Pola+R-CHP and R-CHOP and are taken from NHS Reference costs 2019-20.[41] The administration cost of the first cycle is £431.72 and subsequent cycles is £365.91 (CS Table 28). Pharmacy costs are assumed for the preparation of IV infusions. The pharmacy cost per cycle was £62.40 for Pola+R-CHP and £31.20 for R-CHOP. The CS states that this is consistent with the approach taken in TA649.[23]

**Table 19 Treatment acquisition costs (with PAS)**

| Drug | Vial/total pack size (mg) | Vial/pack price | Dosing | Cycle length (days) | Cost per cycle |
|---|---|---|---|---|---|
| Polatuzumab vedotin | 30 | £2,370.00 | 1.8 mg/kg on Day 1 of each cycle | 21 | [redacted] (no vial sharing) |
| | 140 | £11,060.00 | | | |
| Rituximab | 100 | £78.59 | 375 mg/m$^2$ on Day 1 of each cycle | 21 | £582.09 (no vial sharing) |
| | 500 | £392.92 | | | |
| Cyclophosphamide | 500 | £8.21 | 750 mg/m$^2$ on day 1 of each cycle | 21 | £28.26 (no vial sharing) |
| | 2000 | £28.22 | | | |
| Doxorubicin | 10 | £2.83 | 50 mg/m$^2$ on Day 1 of each cycle | 21 | £20.02 (no vial sharing) |
| | 200 | £20.02 | | | |

| | | | | | |
|---|---|---|---|---|---|
| Prednisolone | 5 | £0.41 | 100 mg/day PO given on Days 1-5 of every 21-day | 21 | £1.64 |
| | 25 | £17.72 | | | |
| Vincristine | 1 | 3.43 | 1.4 mg/m$^2$ IV on Day 1 of each cycle | 21 | £10.18 (no vial sharing) |
| | 2 | £6.48 | | | |

Key: BNF, British National Formulary; eMIT, electronic market information tool.

Source: CS Table 26

#### 4.2.8.3 Health state costs

Health state costs are categorised as professional and social services, health care professionals and hospital resource use and treatment follow-up. The frequency of resource use is shown in CS Table 30. These are taken from a survey of clinicians reported in the manufacturer's submission for NICE TA306 (Pixantrone monotherapy for treating multiply relapsed or refractory aggressive non-Hodgkin's B-cell lymphoma). The resource use unit costs are shown in CS Table 29. The costs are taken from NHS Reference costs 2019/20[41] and Unit Costs of Health and Social Care.[42]

Resource use was assumed to be the same for both treatment arms for the PFS and PD health states. For the PFS health state, patients incurred a lower cost whilst they were no longer on treatment. Patients remaining in PFS for more than two years were assumed to have no additional health care costs. There were also one-off costs incurred when patients start treatment and when their disease progresses, which were slightly different between the Pola+R-CHP and R-CHOP treatment arms. The health state costs used in the model are shown in Table 20 (CS Table 31).

**Table 20 Per cycle supportive care costs for PFS and PD health states**

| | **Health state cost** | | | **One-off cost** | | | |
|---|---|---|---|---|---|---|---|
| | PFS on-treatment | PFS off-treatment (up to 2 years) | PD | PFS Pola+R-CHP | PFS R-CHOP | PD Pola+R-CHP | PD R-CHOP |
| **Company original submission** | £480.29 | £167.21 | £398.47 | £77.33 | £83.71 | £385.10 | £452.50 |
| **Revised values** | £479.06 | £165.42 | £399.43 | £77.33 | £83.71 | £422.35 | £624.14 |

In response to clarification question B11, the company provided further detail on the calculation of the one-off costs for PD. They changed some of the proportions of patients receiving these treatments in their updated model. The updated proportions of patients receiving these resources are shown in clarification response document Table 11.

In response to clarification question B12, the company provided further detail on the calculation of the resources for PFS and PD. They discovered several errors and updated the model with the corrected values (see clarification response document Table 12). The corrected health state costs following clarification response are shown in Table 20.

The ERG notes that in contrast to the current appraisal's focus on first-line treatment, NICE TA306 comprises patients receiving their third- or fourth-line DLBCL treatment. Furthermore, patients are assumed to incur health care costs for PD indefinitely, whilst it is likely that many patients would respond to subsequent treatments and no longer incur these costs, as assumed in NICE TA649 (Polatuzumab vedotin with rituximab and bendamustine for treating relapsed or refractory diffuse large B-cell lymphoma). We therefore consider that the health care costs have been overestimated. Further, we propose a better approach is to include residential care and hospice care as an end-of-life cost. Using an end-of-life cost is commonly used in oncology technology appraisals, for example for breast cancer (NICE TA458),[43] prostate cancer (NICE TA740)[44] and renal cell carcinoma (NICE TA785).[45]

We estimate the cost of terminal care to be £6,950.29 based upon a King's Fund Report on the costs of community and acute care for patients with cancer in the last eight weeks of their life.[46] The reported costs have been inflated to 2020/21 levels with inflation indices from the Unit Costs of Health and Social Care.[42]

We based the health care resources on those reported in NICE TA243 (Rituximab for the first-line treatment of stage III-IV follicular lymphoma) and advice from our clinical experts. For PFS on treatment, it was assumed that patients had outpatient consultations and blood tests every three weeks. Costs of radiotherapy visits were based on 17 radiotherapy daily treatments with only 10% of patients receiving radiotherapy over the initial 18-week period.

For PFS off treatment, it was assumed that patients had outpatient consultations and blood tests every three months. The resources for the PD health state are assumed to be 25% less than the PFS on treatment costs, to allow for the proportion of patients who have a complete response to second line treatment. The ERG's preferred estimates of the health resources are

shown in Table 21. The weekly cost of health resources is [redacted] for PFS on treatment and [redacted] for PFS off treatment and [redacted] for PD.

**Table 21 Annual frequency of resource use in PFS (on and off treatment) and PD**

| Procedure | PFS on treatment (%) | PFS off-treatment (up to 2 years) (%) | PD (%) | Source |
|---|---|---|---|---|
| Oncologist / haematologist (visit) | 17.3 | 4 | 13 | ERG assumption, based on NICE TA243 and clinical advice |
| CT scan | 4 | 1 | 3 | |
| Full blood counts | 17.3 | 4 | 13 | |
| LDH | 17.3 | 4 | 13 | |
| Liver function | 17.3 | 4 | 13 | |
| Renal function | 17.3 | 4 | 13 | |
| Immunoglobulin | 8.7 | 2 | 6.5 | |
| Calcium phosphate | 8.7 | 2 | 6.5 | |
| Radiotherapy visits | 5 | 0 | 2 | Based on clinical advice |
| LDH, lactate dehydrogenase test; PFS, progression-free survival; PD, progressed disease. | | | | |

#### 4.2.8.4 Subsequent anti-lymphoma treatment costs

Patients who discontinue first-line treatment can commence a new anti-lymphoma treatment. The proportion of patients receiving each subsequent treatment was based on clinical advice. The POLARIX trial collected data on the type and duration of subsequent treatments, but this was not considered to be fully representative of UK practice. Estimates of subsequent treatment from the POLARIX trial were therefore explored in a scenario analysis. The proportion of each subsequent treatment received are shown in Table 22 (CS Table 33).

**Table 22 Subsequent systemic treatments (UK clinical input)**

| Subsequent treatment | Pola+R-CHP | R-CHOP |
|---|---|---|
| Autologous stem cell transplant | [redacted] | [redacted] |
| Salvage Therapy + R (intention to proceed with transplant) | [redacted] | [redacted] |
| Chemo + R | [redacted] | [redacted] |
| DECC | [redacted] | [redacted] |
| Pola+R-CHP | [redacted] | [redacted] |
| Bridging treatment + CAR-T | [redacted] | [redacted] |
| Pixantrone | [redacted] | [redacted] |
| Source: CS Table 33 | | |

The company assumed that the average number of systemic treatments after first-line in the Pola+R-CHP arm was 1.78 and for R-CHOP was 1.97. The company did not report full details of the costs of the subsequent treatments, but supplied further details on request from the ERG (Clarification response document Table 7 and 8). All treatments included were recommended by NICE for the treatment of DLBCL. In response to clarification question B6, the company provided a pathway of treatment options available to patients with relapsed or refractory DLBCL following R-CHOP or Pola+R-CHP treatment (Clarification response document Figure 6).

The ERG notes that there are some minor discrepancies in the prices of subsequent treatments: ifosfamide, mesna, axicabtagene ciloleugel and tisagenlecleucel. These are corrected in the model, see section 5.3.4.

NICE advised the ERG that the CAR-T treatments axicabtagene ciloleucel and tisagenlecleucel are currently recommended by NICE for a finite period via the Cancer Drugs Fund. NICE appraisals of these treatments will be updated in 2022-2023 with new data to determine whether they meet cost effectiveness criteria to be recommended for routine NHS use. At the present time, however, they should not be included as comparators or subsequent treatments in NICE appraisals because they are not routinely available treatments. We have, therefore, removed these subsequent treatments from the ERG base case analysis in section 6.1.

#### 4.2.8.5 Adverse event costs

The resources used for the management of adverse events were mainly derived from NICE TA306.[32] Unit costs were taken from the latest NHS reference costs 2019/20.[41] Adverse event costs are calculated by multiplying the total frequency of the adverse events by the unit cost. The costs are applied as a one-off in the first cycle of treatment only. The unit costs of the management of adverse events are shown in CS Table 32.

**ERG conclusions on resources and costs**

The company's approach to estimating resources and costs in the economic model is consistent with the NICE reference case and previous technology appraisals for DLBCL. The approach taken is largely reasonable, with the exception of i) overestimation of health care costs use based on third and fourth line treatments and ii) some discrepancies between the sources and the values used for some of the

costs. The ERG proposes alternative health care costs, based on advice from our clinical experts and we correct the discrepancies in costs. Some subsequent treatments included are not currently available routinely in the NHS and their inclusion is not appropriate.

# 5 COST EFFECTIVENESS RESULTS

## 5.1 Company's cost effectiveness results

CS Section B.3.7.1 reports the base case results for Pola+R-CHP vs R-CHOP. Disaggregated results by health state are shown in CS Appendix K, Tables 43, 44, and 45. The results show that Pola+R-CHP has an incremental cost of [redacted] and an incremental QALY gain of [redacted] compared with R-CHOP, resulting in an ICER of £34,398 per QALY (Table 23). The cost-effectiveness results presented include a confidential PAS discount price for polatuzumab and the company's assumed 50% discount for rituximab. However, they do not include existing discounts for the other anti-lymphoma therapies in the model (these will be included in a separate confidential addendum to this report). Therefore, the ICERs do not reflect the actual prices that would be paid by the NHS.

**Table 23 Company's base case results (with PAS price for polatuzumab, 50% discount for rituximab, and list prices for all other treatments)**

| Technologies | Total costs (£) | Total LYG | Total QALYs | Inc. costs (£) | Inc. QALYs | ICER (£/ QALY) |
|---|---|---|---|---|---|---|
| Pola+R-CHP | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | £34,398 |
| R-CHOP | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | - |

Source: CS Table 40
Key: ICER, incremental cost-effectiveness ratio; LYG, life years gained; PAS, patient access scheme; QALYs, quality-adjusted life years.

## 5.2 Company's sensitivity analyses

### 5.2.1 Deterministic sensitivity analyses

CS section B.3.8.2 reports the deterministic sensitivity analysis results for Pola + R-CHP versus R-CHOP. CS Table 43 presents a list of the parameters included alongside their base case values and the ranges used in the deterministic sensitivity analyses. The upper and lower bounds of the parameters were varied according to the 95% CI, which the ERG considers is reasonable and standard practice for testing the sensitivity of individual parameters.

Most of the relevant input parameters appear to be included in the deterministic sensitivity analysis:

- Discount rate – costs and effects
- Average patient age at baseline
- Utility values – PFS and PD for both arms
- Adverse event disutilities
- Adverse event management costs per patient for both arms
- Supportive care costs (all combinations)
- Administration costs (various)
- One-off costs, PD (both arms)

The ERG notes that the survival curves and the model structure were tested in the probabilistic sensitivity analysis and the scenario analysis, and the patients' characteristics were tested in the scenario analysis.

### 5.2.2 Scenario analysis

The company explored a range of scenarios to test structural and methodological uncertainty (CS Table 44). Generally, the company tested scenarios using data that were not used in the base case. We consider the following parameters explored by the company to be reasonable.

- Time horizon (35, 40, and 45 years)
- Patient baseline characteristics (average patient weight and average patient BSA)
- Survival modelling – cure mixture model (OS, PFS) log-normal and exponential
- Survival modelling – standard parametric model, generalised gamma
- Survival modelling - excess mortality for long-term survivors
- Supportive care costs (3 years)
- Utility values – POLARIX (cross-walk to 3L) for patients with IPI of 2-5
- Utility values - general population
- Subsequent treatment – based on the POLARIX trial instead of the GOYA trial

We extend the range of scenario analyses in the ERG additional analyses (see section 6).

### 5.2.3 Probabilistic sensitivity analysis

The company's probabilistic sensitivity analysis results were estimated for 2000 simulations, and are summarised in scatterplots, cost effectiveness acceptability curves (CEACs) (CS Figures 27 and 28) and in tables with the mean probabilistic base case results (CS Table

42). The probabilistic results are stable and consistent with the deterministic results. The results show that Pola+R-CHP is a cost-effective treatment option at a willingness to pay threshold over [redacted].

All the variables that were included in this analysis are summarised in CS Table 41 along with the following distributions:

- Covariance matrix: utilities in PFS and PD, both treatment arms.
- Normal distribution: disutility due to adverse events (anaemia, diarrhoea, febrile neutropenia (grades 3 and 4), neutropenia (grades 3 and 4), pneumonia). Parameter estimates for PFS and OS.
- Lognormal distribution: administration costs (both arms), supportive care costs, subsequent treatment, one-off costs (both arms), and adverse event management costs. This is an acceptable distribution to vary cost parameters.

**ERG conclusions**

We consider the distributions assigned by the company to the parameter values to be adequate. All relevant input parameters are included in the probabilistic sensitivity analyses, with the exception of drug costs.

## 5.3 Model validation and face validity check

### 5.3.1 Company's model validation

The company briefly describes their approach to model validation in CS section B.3.10. Clinical experts from the UK validated some of the company's key assumptions, including the natural history of DLBCL and standard clinical practice in the UK.

The company has not provided any other details about the external validation of the model parameters; therefore, we conducted some additional comparisons as part of the ERG's model validation (see section 5.3.2). There is no mention of whether the company conducted a cost-effectiveness model review for quality assurance.

**ERG conclusions**

The company conducted a basic face validity check. We believe that the company could have provided more detailed internal and external validity checks. Moreover, the company did not report any comparison of the model results against results from models included in previous NICE technology appraisals of DLBCL (TA306, TA649 and TA559).

### 5.3.2 ERG model validation

The ERG checked the economic model for transparency and validity. We conducted a range of tests to verify model inputs, calculations and outputs:

- Cross-checking all parameter inputs against values reported in the CS and cited sources;
- Checking all model outputs against results cited in the CS, including the base case, deterministic sensitivity analyses, scenario analyses and probabilistic sensitivity analyses;
- Checking the individual equations within the model;
- Manually running scenarios and checking model outputs against results reported in the CS for the deterministic sensitivity analyses and scenario analyses;
- Applying a range of extreme value and logic tests to check the plausibility of changes in results when parameters are changed ('black box' checks);

The model is generally well-implemented, although, we also spotted minor discrepancies in the following parameter values and the values in the referenced sources:

- Treatment costs for drugs (cyclophosphamide, ifosfamide, mesna, axicabtagene ciloleugel, tisagenlecleucel)
- Supportive care costs

In addition, we consider that age-adjusted quality of life should be included for PD as explained above in section 4.2.7.3.

The company provided updated data tables and an updated model with their clarification question response, correcting any errors identified.

#### 5.3.2.1 Internal validity checks

The ERG compared the company's modelled estimates of the PFS and OS with the patient data observed in the POLARIX and GOYA trials. The comparison is presented in section 4.2.6. Table 14 compares the observed KM data and the parametric curves for the PFS curve and Table 16 compares the observed KM data and the parametric curves for the OS curve.

For PFS, the generalised gamma curve (company's and ERG's base case, Table 14) shows comparable survival estimates to both the POLARIX trial up to 2 years, and the GOYA trial with the long-term data up to 5 years. For more information, see section 4.2.6.1

For OS, the generalised gamma curve (company's base case), Gompertz and the exponential curve extrapolates survival comparable to the POLARIX trial estimates at one and two years, and the GOYA trial at five years. The generalised gamma was chosen as it provided a good fit (see Table 16), and Gompertz and exponential curves are explored in scenario analysis. The ERG considers a better approach for the OS curve would be to use the KM data for the POLARIX trial period with an extrapolated tail (generalised gamma curve). For more information, see section 4.2.6.2.

#### 5.3.2.2 External validity checks

We assessed the external validity of the model by comparing the mean discounted life years for patients treated with R-CHOP from the aforementioned 'real world' evidence modelling study of newly diagnosed patients with DLBCL by Wang 2017[30] (see section 4.1), and the results are shown in Table 24. Wang et al. included UK DLBCL patients and adopted an NHS and social services perspective. We note that the company's estimates of life years in the current appraisal are higher than those for the estimates in Wang et al (see Table 24). In addition, the total costs in the model are considerably higher than those from Wang et al. The total cost difference is related to the supportive care costs; in the company's total cost, the supportive care cost represents 60% of the total cost. In the ERG's view, the supportive costs used by the company are overestimated.

**Table 24 Comparison of company submission vs Wang 2017**

| | R-CHOP | Wang 2017 |
|---|---|---|
| Life years | [redacted] | 10.047 |
| Total cost | [redacted] | £22,122 |
| Source: Wang et al. 2017[30], CS Table 40 | | |

#### 5.3.3 Company corrections to the model (clarification response)

In their response to ERG clarification questions the company amended some parameter values listed below:

- Corrected POLARIX IPI 2-5 utility values for PFS and PD (CS section 3.4.5. Table 25; clarification response B1, Table 3)
- The adverse event costs to the 2019/2020 NHS reference costs (CS section B.3.5.3; clarification response B8, Table 10)
- Residential care costs and day care costs referent to the supportive care costs (CS Table 29, clarification response B10)
- The proportion of patients who use the resources mentioned at one-off costs in progressive disease state (CS Table 30, clarification response B11)

- Annual frequency of resource use in PFS and PD states (CS Table 30, clarification response B12)

The updated results led to a marginal decrease in the ICER from £34,398 to £34,138 per QALY gained for Pola+R-CHP versus R-CHOP. Although the total QALYs were marginally affected, the incremental QALYs remained the same.

**Table 25 Company's corrected base case results (with PAS for polatuzumab)**

| Technologies | Total costs (£) | Total LYG | Total QALYs | Inc. costs (£) | Inc. QALYs | ICER (£/ QALY) |
|---|---|---|---|---|---|---|
| Pola+R-CHP | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | £34,138 |
| R-CHOP | [redacted] | [redacted] | [redacted] | - | - | - |

The company assumed a 50% discount on the biosimilar rituximab list price (see section 4.2.8.1). As requested by NICE, we have run an analysis without the discount for rituximab and the results are shown in Table 26.

**Table 26 Corrected company base case results with list price for rituximab (discounted)**

| Assumption | Treatments | Total costs | Total QALYs | Incremental costs | ICER (£/QALY) |
|---|---|---|---|---|---|
| Company base-case | Pola+R-CHP | [redacted] | [redacted] | [redacted] | £34,138 |
| | R-CHOP | [redacted] | [redacted] | - | |
| Company base-case with list price for rituximab | Pola+R-CHP | [redacted] | [redacted] | [redacted] | £33,656 |
| | R-CHOP | [redacted] | [redacted] | - | |

### 5.3.4 ERG corrections to the company model

The company's original model had some inconsistencies, identified by the ERG (see section 5.3.2). These were amended by the company as part of the clarification responses (see section 5.3.3) and the company's updated model. The ERG amended some costs (Table 27) and the PD utility values (section 4.2.7.3) and re-ran the analysis.

**Table 27 Drug and subsequent treatment costs corrected**

| | Dose | Drug costs | Corrected costs |
|---|---|---|---|
| *First-line treatment cost* | | | |
| Cyclophoshamide | 2000mg | £28.22 | £27.50 |
| Cyclophoshamide | 500mg | £8.21 | £8.23 |

| *Subsequent anti-lymphoma treatment costs* | | | |
|---|---|---|---|
| Ifosfamide | 1000mg | £119.27 | £120.69 |
| Ifosfamide | 2000mg | £234.94 | £234.84 |
| Mesna | 1000mg | £441.15 | £425.31 |
| Mesna | 400mg | £201.15 | £211.71 |
| Axicabtagene ciloleugel | | £282,000 | £280,451 |
| Tisagenlecleucel | | £285,000 | £282,000 |
| Source: CS B section 3.5.1.1, Clarification response Table 7 | | | |

The overall effect of this change is marginal, i.e., a change in the ICER from £34,138 to £34,306 for Pola+R-CHP vs R-CHOP (Table 28).

**Table 28 Cost effectiveness results from the ERG correction of administration costs (discounted)**

| Assumption | Treatments | Total costs | Total QALYs | Incremental costs | ICER (£/QALY) |
|---|---|---|---|---|---|
| Company base-case | Pola+R-CHP | [redacted] | [redacted] | [redacted] | £34,138 |
| | R-CHOP | [redacted] | [redacted] | - | |
| ERG correction to the administration cost | Pola+R-CHP | [redacted] | [redacted] | [redacted] | £34,306 |
| | R-CHOP | [redacted] | [redacted] | | |

### 5.3.5 ERG summary of key issues and additional analyses

A full summary of ERG observations on key aspects of the company's economic model is presented in Table 29.

**Table 29 ERG observations of the key aspects of the company's economic model**

| Parameter | Company base case | ERG comment | ERG base case |
|---|---|---|---|
| Progression free survival (PFS) | Cure mixture model with generalised gamma parametric curve | We agree | No change |
| Overall survival (OS) | Cure mixture model with generalised gamma parametric curve | As there is little difference between OS for the treatment arms, we prefer to use the observed data with an extrapolated data. | Cure mixture model with KM + generalised gamma extrapolated tail. Tail begins at 30 months. |
| Treatment duration | Shown in CS Figure 25 and 26 and CS Table 20 and 21. | We agree | No change |
| Treatment effect waning | Not included in the base case | We consider it is plausible to assume that treatment effects do not continue | Treatment effect waning between 30 and 60 months |

| | | | |
|---|---|---|---|
| | | indefinitely for OS, as there are no statistical differences between treatment arms. | |
| **Utilities** | | | |
| Health state utilities | Estimates from GOYA trial (CS Table 24) | For consistency, HRQoL values should be from POLARIX trial | HRQoL values from POLARIX |
| AE disutility | Table CS Table 23 | We agree. | No change |
| Age-related disutility | Only included for PFS after 2 years | As has not been included for PD, after 20 years PD has better QoL than PFS. | Included after 2 years for PFS and PD. |
| Subsequent therapy utilities | Not included in the base case | We agree | No change |
| **Resource use and costs** | | | |
| Administration costs | CS Table 28 | We agree | No change |
| Subsequent therapy | Subsequent treatment costs | We consider that CAR-T treatments should not be included in the modelling as they are currently only recommended for use in the Cancer Drugs Fund | Exclude CAR-T costs from subsequent therapy costs |
| | Distribution of subsequent therapies informed by company's clinical experts (Table 33) | We agree | No change |
| AE costs | CS Table 32 | We agree | No change |
| Resource use | Resource use shown in CS Table 30 | We consider the resources used to be overestimated. We prefer to use an end of life cost. | End of life cost of £6,950.29. ERG estimate of resource use shown in Table 21. |
| Treatment costs | CS section 5.3.1.1 and Table 26 | We consider the company's estimated rituximab price discount should not be used in the base case analysis. | Exclude the rituximab price discount |

# 6 ERG'S ADDITIONAL ANALYSES

## 6.1 ERG's preferred assumptions

Based on the ERG critique of the company's model discussed in Table 29, we have identified seven key aspects of the company base case with which we disagree. Our preferred model assumptions are the following:

- **Extrapolation of OS:** We use the KM data with an extrapolated tail with the generalised gamma parametric distribution starting at 30 months (25% of patients remaining at risk).
- **Treatment effect waning:** We apply a linear decrease of the treatment benefit for OS to the Pola+ R-CHP arm between 30 and 60 months,
- **Resource use:** We use end of life costs per patient of £6950.29,
- **Utility values:** from the POLARIX trial, rather than from the GOYA trial,
- **Supportive care costs:** We estimated supportive care resources, based on advice from our clinical experts (see Table 21),
- **Treatment costs:** we exclude the company's assumed rituximab price discount,
- **Subsequent therapies**: We exclude CAR-T therapy from the subsequent anti-lymphoma treatments.

### 6.1.1 Results from the ERG's preferred model assumptions

Table 30 shows the cumulative cost-effectiveness results of applying the ERG preferred model assumptions to the corrected company's base case. Incorporating the ERG assumptions leads to an increase in the ICER from £34,306 to £255,923 per QALY.

The changes that have the most significant impact on the cost-effectiveness results are:
- The treatment effect waning assumption for OS (between 30 months and 60 months),
- Alternative supportive care costs
- Exclusion of CAR-T subsequent treatments.

The changes that have a small impact on the ICER:
- Estimation of OS using the POLARIX trial KM data with an extrapolated tail with the generalised gamma distribution from 30 months,
- Using the utility values from the POLARIX trial, instead of the GOYA trial,

**Table 30 Cumulative change from the ERG corrected company base case with the ERG preferred model assumptions**

| Assumption | Treatments | Total costs | Total QALYs | Incremental costs | ICER (£/QALY) |
|---|---|---|---|---|---|
| ERG corrected company base-case | Pola+R-CHP | [redacted] | [redacted] | [redacted] | £34,306 |
| | R-CHOP | [redacted] | [redacted] | [redacted] | |
| OS with KM + generalised gamma with an extrapolated tail at 30 months (25% of patients at risk) | Pola+R-CHP | [redacted] | [redacted] | [redacted] | £44,627 |
| | R-CHOP | [redacted] | [redacted] | [redacted] | |

| | | | | | |
|---|---|---|---|---|---|
| Treatment effect waning assumption for OS; between 30 months and 60 months | Pola+R-CHP | [redacted] | [redacted] | [redacted] | £93,705 |
| | R-CHOP | [redacted] | [redacted] | | |
| End of life costs per patient of £6950.29 | Pola+R-CHP | [redacted] | [redacted] | [redacted] | £93,438 |
| | R-CHOP | [redacted] | [redacted] | | |
| Utility values from the POLARIX trial, rather than from the GOYA trial | Pola+R-CHP | [redacted] | [redacted] | [redacted] | £107,071 |
| | R-CHOP | [redacted] | [redacted] | | |
| Supportive care costs | Pola+R-CHP | [redacted] | [redacted] | [redacted] | £178,525 |
| | R-CHOP | [redacted] | [redacted] | | |
| Rituximab list price | Pola+R-CHP | [redacted] | [redacted] | [redacted] | £176,824 |
| | R-CHOP | [redacted] | [redacted] | | |
| No CAR-T in subsequent treatment | Pola+R-CHP | [redacted] | [redacted] | [redacted] | £255,923 |
| | R-CHOP | [redacted] | [redacted] | | |
| ERG base case | Pola+R-CHP | [redacted] | [redacted] | [redacted] | £255,923 |
| | R-CHOP | [redacted] | [redacted] | | |
| ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life years; OS, overall survival; KM: Kaplan-Meier curve | | | | | |

### 6.2 Scenario analyses conducted on the ERG's preferred assumptions

We performed a range of scenario analyses with the ERG base case to analyse the impact of changing some model assumptions on the final cost-effectiveness results. We replicated the company's scenario analyses, as previously described in section 5.2.2. Table 31 below summarises the results of the company's scenario analyses on the ERG base case. The scenarios that have the most significant effect on the cost-effectiveness are:

- OS and PFS curves selection for Pola+R-CHP and R-CHOP is exponential (an increase of £159,802 per QALY), and OS and PFS curves selection for Pola+R-CHP and R-CHOP is lognormal (a decrease of £43,721 per QALY)
- Model structure, using a standard parametric model (a decrease of £42,986 per QALY)
- Average patient BSA: -5% BSA (decrease of £27,490 per QALY), and +5% BSA (increase of £29,160 per QALY)
- Average patient weight: -5kg weight (decrease of £16,329 per QALY) and a +5 kg weight (an increase of £15,760 per QALY).

The ICERs varied less than 3% per QALY in the other scenarios.

The remaining scenarios in Table 31 were conducted to assess the model assumptions which had the most impact on the ERG base case in section 6.1.1

- Applying treatment effect waning has the most impact in the ERG base case. The scenario with a treatment effect maintained over time (the company's assumption) decreases the ICER by £155,474 per QALY. Varying the treatment waning interval

also has an impact on the ICER. The ERG base case assumed an interval for treatment waning from 30 to 60 months. Reducing the treatment effect interval by one year (30 to 48 months) increases the ICER by £58,576 per QALY. Assuming a wider interval decreases the ICER by £34,259 per QALY (30 to 72 months) and £56,658 per QALY (30 to 84 months).

- Assuming the OS curve with a generalised gamma distribution (company's assumption) increases the ICER by £47,095 per QALY. Considering the OS with KM+ generalised gamma with an extrapolated tail at 24 months instead of 30 months increases the ICER by £74,313 per QALY.
- Including CAR-T in subsequent treatment costs decreases the ICER by £79,099 per QALY.

**Table 31 Scenarios with the ERG preferred base case**

| Assumption | ERG Base case | ICER (£/QALY) |
|---|---|---|
| ERG preferred base case | | £255,923 |
| Time horizon: 35 years | 60 years | £260,013 |
| Time horizon: 40 years | | £257,991 |
| Time horizon: 45 years | | £256,922 |
| Average patient weight: 70.92 kg | 75.92 kg | £239,594 |
| Average patient weight: 80.92 kg | | £271,683 |
| Average patient BSA: 1.76 (67.3 kg) | BSA of 1.86 | £228,433 |
| Average patient BSA: 1.95 (85.2 kg) | | £285,083 |
| OS and PFS curves selection for Pola+R-CHP and R-CHOP – lognormal | Generalised gamma | £212,202 |
| OS and PFS curves selection for Pola+R-CHP and R-CHOP – exponential | | £415,725 |
| Model structure – standard parametric model | Cure mixture model | £212,937 |
| Excess mortality: 1 year | 1 year | £263,743 |
| Supportive care costs: 3 years | 2 years | £256,150 |
| Utility values general population: 3 years | 2 years | £255,256 |
| **ERG additional scenarios** | | |
| Treatment waning assumption for OS; between 30 months and 48 months | Treatment waning assumption for OS; between 30 months and 60 months | £314,499 |
| Treatment waning assumption for OS; between 30 months and 72 months | | £221,664 |
| Treatment waning assumption for OS; between 30 months and 84 months | | £199,265 |
| Treatment effect maintained over time | | £100,449 |
| OS with KM + generalised gamma with an extrapolated tail at 24 months | OS with KM + generalised gamma with an extrapolated tail | £330,236 |

| Assumption | ERG Base case | ICER (£/QALY) |
|---|---|---|
| | at 30 months (25% of patients at risk) | |
| OS with a generalised gamma distribution | OS with KM + generalised gamma with an extrapolated tail at 30 months (25% of patients at risk) | £303,018 |
| Include CAR-T in subsequent treatment costs | No CAR-T in subsequent treatment costs | £176,824 |
| ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life years; | | |

### 6.3 Conclusions on the cost effectiveness evidence

The company's de novo partitioned cure mixture survival model generated a (corrected) base case ICER of £34,138 per QALY for Pola-R-CHP vs R-CHOP.

The ERG identified a set of alternative clinical assumptions and input parameter values to those of the company and we have incorporated these into the ERG base case. Overall, the ERG's preferred assumptions have a large impact on the model results: an increase in the ICER to £255,923 per QALY for Pola+R-CHP vs R-CHOP. These estimates are most sensitive to changes in the assumptions related to treatment effect waning for OS, supportive care costs and the exclusion of CAR-T therapy.

# 7 END OF LIFE

The CS does not discuss whether the NICE end of life considerations are applicable. The ERG is of the opinion that Pola+R-CHP does not meet the first end of life criterion as the life expectancy of patients with previously untreated DLBCL treated with R-CHOP would normally be greater than 24 months. The company base case estimates the life expectancy for patients treated with R-CHOP to be 11.8 years (CS Table 40).

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# 9 Appendices

### Appendix 1 Company and ERG risk of bias assessments for the POLARIX trial

| Criterion | Company judgement | ERG judgement |
|---|---|---|
| Was randomisation carried out appropriately? | Yes | Yes (=low risk of selection bias) |
| Rationale | Not reported | Use of Interactive voice or Web-based response system for treatment assignment (Protocol section 4.2) |
| Was the concealment of treatment allocation adequate? | Yes | Yes (=low risk of selection bias) |
| Rationale | Not reported | Use of Interactive voice or Web-based response system for treatment assignment (Protocol section 4.2) |
| Were the groups similar at the outset of the study in terms of prognostic factors? | Yes | Yes (=low risk of selection bias) |
| Rationale | Not reported | Baseline characteristics were similar in the two treatment groups (CSR Table 6) |
| Were the care providers, participants, and outcome assessors blind to treatment allocation? | Yes | Yes (=low risk of performance and detection biases) |
| Rationale | Not reported | Patients, study personnel (with appropriate exceptions) and investigators were blind to treatment assignment, (Protocol section 4.2)<br><br>Adverse events were comparable between arms (CS B.2.10.1) reducing likelihood of investigator blind being broken.<br><br>Accidental unblinding of staff (0.3%) or patients (0.8%) was low and similar between the two treatment groups (CSR Table 4) |
| Were there any unexpected imbalances in drop-outs between groups? If so, were they explained or adjusted for? | No | No (=low risk of attrition bias in relation to this aspect of imbalances in missing data) |
| Rationale | Not reported | Drop outs were similar between arms - 17% in R-CHOP arm versus 15% in Pola+R-CHP arm. The main reason was due to death - 13% in R-CHOP arm and |

| | | |
|---|---|---|
| | | 11.6% Pola+R-CHP arm (CSR Figure 3 and CSR page 245) |
| Is there any evidence to suggest that the authors measured more outcomes than they reported? | No | No for efficacy and safety outcomes; **Yes for HRQoL outcomes** (=low risk of reporting bias for efficacy and safety outcomes; **high risk of bias for HRQoL outcomes**) |
| Rationale | | Efficacy and safety outcomes in protocol match those reported in CSR.<br><br>For HRQoL outcomes, the protocol (Appendix 1) reports EORTC QLQ C-30 and EQ-5D-5L as outcomes to be assessed. The CSR (pages 465-467) report compliance up to 24 months for completion of EORTC QLQ-C30 but only reports outcomes for EORTC QLQ-C30 Physical Functioning Scale and Fatigue Scale (CSR pages 477, 478, 480 to 483, 502). CSR Table 1 also states [redacted] Results for EQ-5D-5L are also not reported in CSR. CSR Table 1 states [redacted] Results for EQ-5D-5L were however presented in company clarification B1. |
| 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 | Yes for primary outcome (PFS), some secondary outcomes (EFS and OS) and safety**;** (=low risk of attrition bias in relation to this aspect of imbalances in missing data for PFS, EFS, OS and safety outcomes; **Unclear risk for remaining secondary efficacy outcomes and HRQoL outcomes)** |
| Rationale | Not reported | ALL EFFICACY OUTCOMES: [redacted] (Protocol section 6.4) [redacted] (CSR page 234)<br><br>PRIMARY EFFICACY ENDPOINT: [redacted] |

| | | |
|---|---|---|
| | | [redacted] (CSR section 5.1.2.1)<br>[redacted] (CSR section 5.1.2.2.1)<br><br>KEY SECONDARY ENDPOINTS INCLUDED IN THE HIERARCHICAL TESTING PROCEDURE:<br>Missing data was low (<5%) and comparable between arms for EFS (4.1% (R-CHOP) vs. 3.0% (Pola+R-CHP), CSR page 462) and OS (0.2% (R-CHOP) vs. 0.5% (Pola+R-CHP), CSR page 463)<br>Missing data was higher (>5%) but comparable between arms for CR rate (7.5% (R-CHOP) vs. 6.8% (Pola+R-CHP), CSR page 443)<br><br>ADDITIONAL SECONDARY ENDPOINTS THAT WERE NOT ADJUSTED FOR TESTING MULTIPLICITY:<br>No information on missing data reported in the CS or CSR for DFS, BOR rate and DOR<br><br>HRQOL OUTCOMES (REPORTED IN THE CSR ONLY):<br>Missing data was high at timepoints after baseline<br>[redacted] (CSR section 5.1.3.12.1)<br>No information on handling of missing data reported.<br><br>ADVERSE EVENTS:<br>[redacted] (Protocol section 6.5) 99% of the randomised population formed the safety analysis population (CSR Table 5) |

Source: partly reproduced from CS Table 8
Note. Bold text shows where the ERG's judgement differed to the company's.

BOR: Best overall response; CR: Complete response; DFS: Disease-free survival; DOR: Duration of response; EFS: Event free survival EORTC QLQ C-30: European Organization for Research and Treatment of Cancer Quality of Life-Core 30 questionnaire; EQ-5D-5L: European Quality of Life Working Group Health Status Measure 5 Dimensions, 5 Levels HRQoL: Health-Related Quality of Life OS: Overall survival; PFS: Progression free survival

# NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

# Polatuzumab vedotin in combination with R-CHP for untreated diffuse large B-cell lymphoma [ID3901]

## Technical Engagement Response

**July 2022**

**Table 1: About you**

| | |
|---|---|
| **Your name** | [redacted] |
| **Organisation name: stakeholder or respondent**<br>**(if you are responding as an individual rather than a registered stakeholder, please leave blank)** | Roche Products Ltd |
| **Disclosure**<br>**Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.** | |

**Table 2: Key issues and responses**

| Key issues | Does this response contain new evidence, data or analyses? | Response |
|---|---|---|
| Issue 1. Uncertainty about the potential use of Pola+R-CHP in low risk untreated DLBCL | No | The company would like to note for this submission the intended patient population for Pola+R-CHP is specific to adult patients with previously untreated diffuse large B-cell lymphoma (DLBCL), with an IPI score of 2–5 as per the POLARIX study population.<br><br>There is no data available for the use of Pola+R-CHP in low-risk (IPI 0–1) previously untreated DLBCL, therefore, we are not planning to include this patient population. |
| Issue 2. The survival benefit for Pola+R-CHP vs R-CHOP is very uncertain | No | DLBCL is a high-grade lymphoma, which is a curable disease in the first line (1L) setting. The aim of 1L treatment is to kill the malignant clone so that there are no residual clones, meaning that the effect of treatment is maintained and does not wane after a period of time. Most relapses occur within the first 2 years of treatment. Patients who do not relapse after their 1L treatment have been shown to have similar mortality to the general population. |

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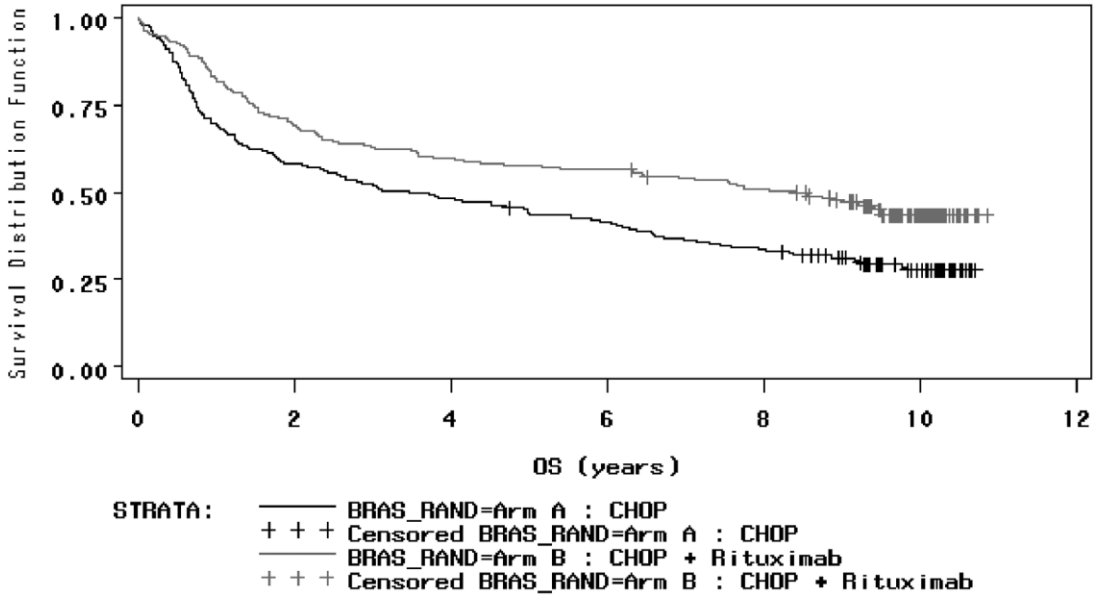
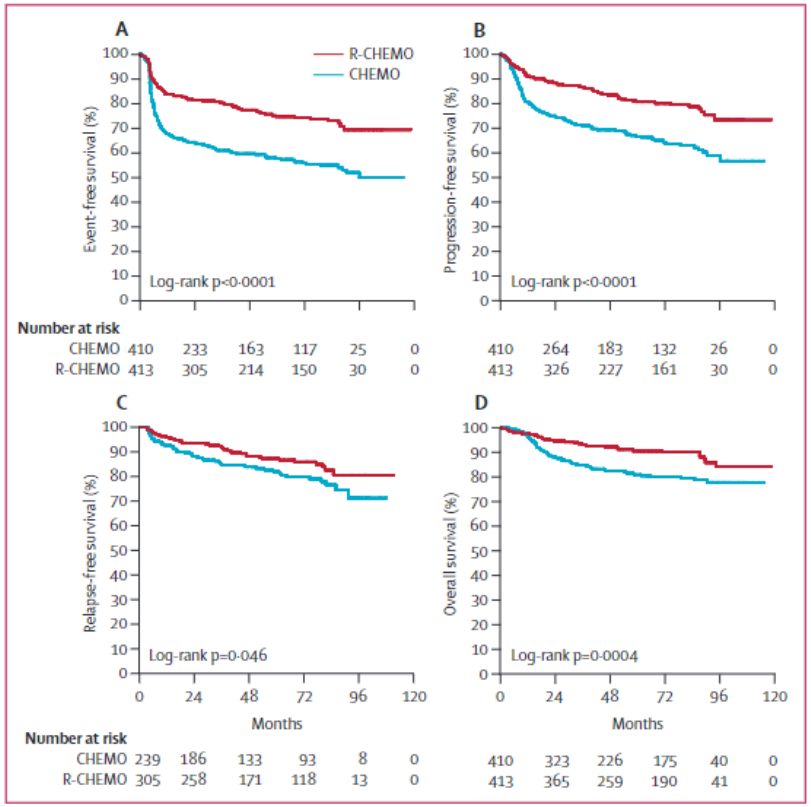
| | | The following evidence, both from the 1L as well as the relapsed/refractory (R/R) DLBCL setting, supports the assertion that the effect of Pola+R-CHP will be maintained over time:<br><br>In the LNH-98.5 trial, the first randomised study comparing R-CHOP to CHOP in 1L DLBCL patients, the benefits of the addition of rituximab (R) to CHOP persisted over a 10-year follow-up period (<br>Figure ***1***) (1).<br><br>**Figure 1: Overall survival in 399 patients treated with CHOP and R-CHOP**<br><br>Median overall survival (OS) was 3.5 years (95% CI: 2.2-5.5) in the CHOP arm and 8.4 years (95% CI: 5.4-not reached) in the R-CHOP arm (P=0.0001) (1)<br><br>  <br> |

The MInT study compared CHOP-like chemotherapy with/without rituximab in young patients in 1L DLBCL. Reported benefits of the addition of rituximab were maintained after 6 years (Figure 2). It showed improvements in event-free, progression-free, and overall survival without increased toxicity (2).

**Figure 2: Event-free (A), progression-free (B), relapse-free (C), and overall survival (D) of 823 patients assigned to six cycles of CHOP-like chemotherapy (CHEMO) or the same chemotherapy plus six applications of rituximab (R-CHEMO)** (2)



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| | | A randomised phase II trial that compared Pola+BR with BR in R/R DLBCL (GO29365), demonstrated improved PFS and OS in the Pola+BR arm compared to BR with a median follow up of 48.9 months and 48.3 months, respectively (3). Although it is in R/R DLBCL, Figure 3 and<br>Figure **4** demonstrate that the treatment effect of Pola+BR persists over time and there is no evidence of decline in effect compared to BR.<br><br>If the treatment effect persists in the non-curative R/R setting, there is no reason to assume the Pola+R-CHP treatment effect in the 1L DLBCL curative setting would decline.<br><br>**Figure 3: Kaplan-Meier Curves of overall survival (OS) for Pola+BR [blue curve] versus BR [red curve] randomised arms (New unpublished data cut [October 2021])**<br><br>  |

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| | | **Figure 4: Cumulative hazard plot – overall survival**<br>  <br>The evidence discussed above supports the assumption that the treatment effect of Pola+R-CHP for 1L DLBCL will be maintained with patients remaining progression free. This assumption was also further supported by therapy area experts in an advisory board, who agreed that in this curative setting, based on their experience, they would not expect waning of the treatment effect. A recently published ASCO abstract (independent from Roche) looking at the cost-effectiveness of Pola+R-CHP in 1L DLBCL also presented similar estimates in line with the base-case utilised in this submission [5 year OS for Pola+R-CHP and R-CHOP: 81.8% versus 77.7% (4); compared to our base case: 80.5% versus 78.0%].<br><br>The ERG considers that by five years, other factors, such as the use of subsequent anti-lymphoma treatments will influence OS. For this reason, the ERG suggests a scenario where treatment effect starts to wane after the median follow-up of the trial (28.2 months) until there is no treatment effect on OS at 5 years. Therapy area experts attending an advisory board in February 2022 agreed that they expect the increased cure rate to translate into a long-term benefit, supporting the company's submission. |

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| | | Pola+R-CHP increases the proportion of patients in long-term remission by 11% versus R-CHOP (75% versus 64%) (5). As shown in Figure 5, patients with long-term remission have similar mortality compared to the general population. In the below risk model with relapse as a competing event, the life expectancy of 1L DLBCL patients (6) in long-term remission after reaching PFS24 is similar to the general population ([redacted]). These same findings were supported by a Danish population based study (7). The survival of these patients is also modelled in the cure mixture model.<br><br>**Figure 5: Life expectancy differences between cases and control in cases who are progression-free at 24 months**<br><br>  <br><br>As a reminder, the 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. |

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| | | This is reflected in the parameterisation of cure mixture models, which assumes the patient population comprises of two subpopulations. The first subpopulation is considered to be cured and at the same risk of mortality as the age- and sex-matched general population (sourced from the Office for National Statistics for this model (8), whilst the mortality rate of the second subpopulation is defined by a selected standard parametric survival curve.<br>In other words, this means that the long-term remission fraction, 75% for Pola+R-CHP and 64% for R-CHOP, is already accounting for the non-long-term remission patients since it was jointly estimated based on the two subgroups characterised by a cure mixture model. Please note the R-CHOP long-term remission was clinically validated with the GOYA trial after adjusting with propensity score weighting.<br><br>Furthermore, in our model, the OS is informed by PFS, which means that the OS curves are likely underestimating the efficacy of Pola+R-CHP long-term. Applying a treatment waning effect would not only underestimate the OS benefit of Pola+R-CHP but it would also disrupt the cure mixture model as the cure fraction of patients is not estimated based on a specific time point but on the extrapolated PFS curves in both treatment arms.<br><br>In conclusion, based on the available trial and economic modelling evidence included above, the company believes that the treatment effect of Pola+R-CHP in the 1L DLBCL setting will be maintained and not wane after 30 months. |

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| Issue 3. The health care resources have been overestimated | No | The company would like to note that there is currently no 1L DLBCL submission available to reference in the submission. As a result, the company took the same approach as the Pola+BR submission (TA649)(9) in DLBCL 2L+, Kymriah (TA567)(10) and Yescarta (TA559)(11) for DLBCL 3L+, which used the TA306 health care resource costs to account for resources use and costs for patients receiving subsequent treatments. TA306 is a submission in relapsed or refractory aggressive non-Hodgkin's B-cell lymphoma (12).<br><br>Therefore, we believe that as a company, we have been consistent with the approach taken by previous appraisals in 2L+ and 3L+ DLBCL and our costs are reflective of what is observed in the UK clinical setting.<br><br>We recognise that based on the above submissions, we could potentially be overestimating some of the PFS costs and resource use. Therefore, the company agrees to amend the resource use for patients in the PFS health state with the values suggested by the ERG.<br><br>However, the company believes that we are taking a conservative approach to the resource and supportive care costs in the PD state, which are perhaps underestimated. In POLARIX, on average, patients received [redacted] and [redacted] lines of subsequent treatments. In other words, patients got two more additional treatments after 1L on average. The company's base-case does not account for any additional resource costs beyond the second line, i.e. when patients moved from second line to third line or from third line to fourth line. |

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| Issue 4. Exclusion of chimeric antigen receptors T-cell therapy (CAR-T) as possible subsequent-line treatments | No | As mentioned during the technical engagement call, there are a number of reasons why the company believed that it is appropriate to include CAR-Ts in ID3901.<br><br>Polivy has the potential to be a cost-saving treatment long-term; therefore, the company considers it appropriate to include CAR-Ts in their submission as this is a highly expensive treatment increasingly used for progressed (relapsed or refractory) DLBCL patients.<br><br>A UK RWE study by Kuhnl et al (2022) shows that 300 patients were infused with CAR-Ts between December 2018–Nov 2020 (13). With a constantly increasing number of CAR-T centres across the UK, the percentage of R/R DLBCL patients treated in the UK by now is estimated to be closer to [redacted] (UK clinical input estimate). CAR-Ts are also included in regional UK guidelines such as the Pan-London Haemato-Oncology and the Thames Valley Strategic Clinical Network guidelines where they are recommended as a subsequent treatment option for progressed DLBCL patients.<br><br>Lastly, CAR-Ts were included as a subsequent treatment in the POLARIX trial; therefore, the company believes that it is important to include the CAR-T costs in the submission since the benefit is already accounted for.<br><br>Despite all of the above reasons, the company has agreed to remove CAR-Ts from their base case and evenly redistributed the CAR-Ts, which are a third line DLBCL treatment, to other third line DLBCL treatments. As confirmed by UK clinical experts, currently around [redacted] of patients receive CAR-T treatment in the 3L+ R/R DLBCL setting and reallocated these treatments to Chemo+R and Pola+BR (in the R-CHOP arm).<br><br>The company would like to note that the first CAR-T is currently being reappraised by NICE, with an expected publication in January 2023 (Axicabtagene ciloleucel for treating diffuse large B-cell lymphoma and primary mediastinal large B-cell lymphoma after 2 or more systemic therapies (CDF review of TA559) [ID3980])(11) and may be reimbursed in base-line funding very soon. If the company were to include CAR-Ts in their revised base-case, the company would be cost-effective with the current discount (£27,122 ICER). |

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| Additional ERG issue: Extrapolation of OS | No | The company has reviewed the approach the ERG has suggested and accepts the suggested change by the ERG. |
| Additional ERG issue: Health state utility values | No | As previously mentioned by the company, 11 clinicians have confirmed during two separate advisory boards that the GOYA utility values are more reflective of current UK clinical practice. Clinicians specifically commented that the PD values from the POLARIX trial are too high and not reflective of what is observed in UK clinical practice.<br><br>There are several reasons why we believe the POLARIX utility values are currently not the best utility values to use for this submission:<br><br>1. Firstly, of the [redacted] patients who progressed, only [redacted] reported any EQ-5D-5L outcomes. The values were reported at a median of [redacted] from the day of when progression was recorded. This means that [redacted] of PD state utility values are "missing" from the progressed patients. Of the [redacted] of patients who didn't record their utility values after progression, it was observed that patients with no reported EQ-5D data in the PD state had a worst prognosis in post progression survival, after adjusting for age, gender, baseline utility-value, and time from randomisation to disease progression (all significant at nominal 5% level), and their risk of death was more than [redacted] compared to the patients who reported their PD state utility [redacted]. This observation indicates that the current PD values in the POLARIX trial are underestimating the true utility of patients who progress in 1L with DLBCL.<br><br>2. Secondly, the EQ-5D-5L data collected in the PD state was collected [redacted] from the progression assessment, more specifically [redacted] There were only [redacted] patients who reported their PD state EQ-5D-5L after starting a 2L therapy, which further indicates that the PD state utility are not reflective of what is observed in UK clinical practice. |

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| | | 3. Lastly, although the POLARIX study did not collect data on patients who respond to later line therapies, we can estimate based on the POLARIX New Antilymphoma therapy data that the patient's disease was deteriorating rapidly: The median time from 2L to 3L therapy or death was [redacted], the median time from 3L treatment to 4L or death was [redacted], the data is still immature to have robust estimates on the 4L+ setting. This further indicates that current PD state utilities are overestimating patients' utility due to the rapid progression of patients in later lines of treatment.<br><br>In summary, it would be too optimistic to assume that the health state utility values in the progressed health state would remain stable at level of [redacted], as currently estimated from the POLARIX trial. Therefore, we believe that the GOYA utility values are more reflective of the real world progressive health state and therefore at this moment in time more appropriate to be used instead of the POLARIX utility values.<br><br>The company would also like to note separately that we have applied the PD age adjusted correction to the half cycle corrected and discounted QALYs, something which was not applied by the ERG. This change is reflected in the model and in the ICER. |
| Additional ERG issue:<br>End of life costs | No | Although 1L DLBCL patients who do not relapse after 24 months are considered to enter into long-term remission, we recognise that an end of life cost is routinely used in NICE oncology submission.<br><br>Therefore, the company has reviewed the approach the ERG has suggested and accepts the suggested change by the ERG. |

# Additional issues

**Table 3: Additional issues from the ERG report**

| Issue from the ERG report | Relevant section(s) and/or page(s) | Does this response contain new evidence, data or analyses? | Response |
|---|---|---|---|
| Additional issue 1: Rituximab list price | p.15 | No | The company has no response to this issue and accepts this change as per the ERG report. |

# Summary of changes to the company's cost-effectiveness estimate(s)

**Table 4: Changes to the company's cost-effectiveness estimate**

| Key issue(s) in the ERG report that the change relates to | Company's base case before technical engagement | Change(s) made in response to technical engagement | Impact on the company's base-case incremental cost-effectiveness ratio (ICER) |
|---|---|---|---|
| Issue 6 and 7 | In the original submission, the company has not included an end of life cost and has not used KM and an extrapolated tail to model OS. | In the revised base case, the company will apply an end of life cost and use KM and an extrapolated tail to model OS. | £ 254,677 |

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| Issue 2. | In the original submission, the company has not included a treatment waning effect. | In the revised base case, based on the response above, the company will not apply a treatment waning effect. In addition, the company has adjusted the ERG's OS treatment waning formula to prevent the intersection of the PFS curve with the OS curve. | £ 98,257 |
| Issue 3. | In the original submission, the company has included resource use from TA306. | In the revised base case, based on the response above, the company has decided to keep the same resource use referenced from TA306 for PD; however, the company has changed the PFS resource use and costs. | £ 61,656 |
| Issue 4 | In the original submission, the company has included CAR-Ts as a subsequent treatment. | In the revised base case, the company has removed CAR-Ts as a subsequent treatment but has redistributed CAR-Ts to other 3L+ treatments. | £ 53,635 |

| | | | |
|---|---|---|---|
| Issue 5 | In the original submission, the company used the GOYA IPI 2-5 utilities. | In the revised base case the company has kept the GOYA IPI 2-5 utility values and applied the age-adjusted PD utilities to the half-cycle corrected and discounted ICER. | £45,644 |

**Table 5: Revised base-case by the company at the current discount of [redacted]**

| Technologies | Total costs (£) | Total LYG | Total QALYs | Inc. costs (£) | Inc. LYG | Inc. QALYs | ICER (£/ LYG) | ICER (£/ QALY) |
|---|---|---|---|---|---|---|---|---|
| Pola+R-CHP | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | 39,399 | 45,644 |
| R-CHOP | [redacted] | 11.728 | 8.829 | - | - | - | - | - |

Please note, since the time of submission in March 2022, a higher discount of [redacted] for Pola has been approved. The below results include the updated discount.

**Table 6: Revised base case by the company at the proposed new discount [redacted]**

| Technologies | Total costs (£) | Total LYG | Total QALYs | Inc. costs (£) | Inc. LYG | Inc. QALYs | ICER (£/ LYG) | ICER (£/ QALY) |
|---|---|---|---|---|---|---|---|---|
| Pola+R-CHP | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | 23,420 | 27,132 |
| R-CHOP | [redacted] | 11.728 | 8.829 | - | - | - | - | - |

## Sensitivity analysis around revised base case

**Table 7: Revised base case by the company including CAR-Ts at the new discount** [redacted]

| Technologies | Total costs (£) | Total LYG | Total QALYs | Inc. costs (£) | Inc. LYG | Inc. QALYs | ICER (£/ LYG) | ICER (£/ QALY) |
|---|---|---|---|---|---|---|---|---|
| Pola+R-CHP | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | 6,344 | 7,350 |
| R-CHOP | [redacted] | 11.728 | 8.829 | - | - | - | - | - |

Please note, if the company were to include CAR-Ts in their revised base case, they would be cost-effective with the original [redacted] discount (£27,122 ICER).

**Table 8: Revised company base case with CAR-Ts**

| Treatment | Pola+R-CHP | R-CHOP |
|---|---|---|
| Autologous stem cell transplant | [redacted] | [redacted] |
| Salvage therapy + R (intention to proceed with transplant) | [redacted] | [redacted] |
| Salvage therapy (intention to proceed with transplant) | [redacted] | [redacted] |
| Chemotherapy | [redacted] | [redacted] |
| Chemo+R | [redacted] | [redacted] |
| Pola+BR | [redacted] | [redacted] |
| DECC | [redacted] | [redacted] |
| Bridging treatment + CAR-T | [redacted] | [redacted] |
| Pixantrone | [redacted] | [redacted] |

# References


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NICE National Institute for Health and Care Excellence

# Clinical expert statement and technical engagement response form

## Polatuzumab vedotin in combination for untreated diffuse large B-cell lymphoma [ID3901]

Thank you for agreeing to comment on the evidence review group (ERG) report for this appraisal, and for providing your views on this technology and its possible use in the NHS.

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature. The ERG report and stakeholder 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.

## Information on completing this form

In part 1 we are asking for your views on this technology. The text boxes will expand as you type.

In part 2 we are asking for your views on key issues in the ERG report that are likely to be discussed by the committee. The key issues in the ERG report reflect the areas where there is uncertainty in the evidence, and because of this the cost effectiveness of the treatment is also uncertain. The key issues are summarised in the executive summary at the beginning of the ERG report (section 1). You are not expected to comment on every key issue but instead comment on the issues that are in your area of expertise.

A clinical perspective could help either:

- resolve any uncertainty that has been identified OR
- provide missing or additional information that could help committee reach a collaborative decision in the face of uncertainty that cannot be resolved.

In part 3 we are asking you to provide 5 summary sentences on the main points contained in this document.

Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable. Please type information directly into the form.

Do not include medical information about yourself or another person that could identify you or the other person.

We are committed to meeting the requirements of copyright legislation. If you want to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.

Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.

Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise, all information submitted under 'academic in confidence' in yellow, and all information submitted under 'depersonalised data' in pink. If confidential information is submitted, please also send a second version of your comments with that information 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.

**Please note, part 1** can be completed at any time. We advise that **part 2** is completed after the expert engagement teleconference (if you are attending or have attended). At this teleconference we will discuss some of the key issues, answer any specific questions you may have about the form, and explain the type of information the committee would find useful.

Deadline for comments by **5pm** on **13 July 2022.** Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Thank you for your time.

Clinical expert statement

**We reserve the right to summarise and edit comments received during engagement, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.**

**Comments received during engagement are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.**

NICE National Institute for Health and Care Excellence

# Part 1: Treating untreated diffuse large B-cell lymphoma and current treatment options

**Table 1 About you, aim of treatment, place and use of technology, sources of evidence and equality**

| | |
|---|---|
| **1. Your name** | Professor Christopher Fox |
| **2. Name of organisation** | Nottingham University Hospitals NHS Trust (RCP/NCRI nominating body) |
| **3. Job title or position** | Professor of Haematology and Consultant Haematologist |
| **4. Are you (please tick all that apply)** | ☒ An employee or representative of a healthcare professional organisation that represents clinicians?<br>☒ A specialist in the treatment of people with untreated diffuse large B-cell lymphoma?<br>☒ A specialist in the clinical evidence base for untreated diffuse large B-cell lymphoma or technology?<br>☐ Other (please specify): |
| **5. Do you wish to agree with your nominating organisation's submission?**<br>(We would encourage you to complete this form even if you agree with your nominating organisation's submission) | ☒ Yes, I agree with it<br>☐ No, I disagree with it<br>☐ I agree with some of it, but disagree with some of it<br>☐ Other (they did not submit one, I do not know if they submitted one etc.) |
| **6. If you wrote the organisation submission and/or do not have anything to add, tick here.**<br>(If you tick this box, the rest of this form will be deleted after submission) | ☒ Yes |
| **7. Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.** | Nil |

| | |
|---|---|
| **8. What is the main aim of treatment for untreated diffuse large B-cell lymphoma?**<br>(For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability) | To offer the best chance of long-term remission or cure with first-line therapy |
| **9. What do you consider a clinically significant treatment response?**<br>(For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount) | Key outcomes are PFS and OS<br>Reducing the risk of relapse is clinically very significant |
| **10. In your view, is there an unmet need for patients and healthcare professionals in untreated diffuse large B-cell lymphoma?** | Yes as 30-40% of such patients will experience relapsed or refractory DLBCL.<br><br>Although some effective therapies are available as 2nd and subsequent therapy lines, the treatment burden/toxicity for patients is substantial and the healthcare resource costs are significant |
| **11. How is untreated diffuse large B-cell lymphoma currently treated in the NHS?**<br>• Are any clinical guidelines used in the treatment of the condition, and if so, which?<br>• 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.)<br>• What impact would the technology have on the current pathway of care? | RCHOP is the widely accepted standard of care and has been so for nearly 2 decades.<br>National (BSH and NICE) and international guidelines are clear on this. NHS pathway well defined.<br><br>A number of large global phase 3 trials aiming to improve upon RCHOP have been conducted over 2 decades but all to-date have failed (no PFS difference) – RCHOP has therefore remained the standard<br><br>This technology would not substantially change the pathway – could readily be incorporated into current treatment pathways without difficulty |
| **12. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?** | This technology would not substantially change the pathway – could readily be incorporated into current treatment pathways without difficulty |

| | |
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| • How does healthcare resource use differ between the technology and current care?<br>• In what clinical setting should the technology be used? (for example, primary or secondary care, specialist clinic)<br>• What investment is needed to introduce the technology? (for example, for facilities, equipment, or training) | I don't expect significant differences in healthcare resource utilisation<br><br>Will be used in the same setting as current – secondary care: district general hospitals and university hospitals who currently use RCHOP<br><br>Nil |
| **13. Do you expect the technology to provide clinically meaningful benefits compared with current care?**<br>• Do you expect the technology to increase length of life more than current care?<br>• Do you expect the technology to increase health-related quality of life more than current care? | Yes the PFS difference is statistically and clinically significant since it reduces the risk of early relapse for a proportion of patients. Relapsed DLBCL is a devastating event associated with poorer QoL, a significant further treatment burden (for patient and healthcare system) and higher risk of death |
| **14. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?** | As per trial eligibility criteria= IPI 2-5 newly diagnosed DLBCL |
| **15. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use?**<br>(For example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed) | No significant differences |

| | |
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| **16. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?** | As per standard pathway – no additional testing |
| **17. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation?**<br>• Do the instruments that measure quality of life fully capture all the benefits of the technology or have some been missed? For example, the treatment regimen may be more easily administered (such as an oral tablet or home treatment) than current standard of care | No I don't think so |
| **18. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met?**<br>• Is the technology a 'step-change' in the management of the condition?<br>• Does the use of the technology address any particular unmet need of the patient population? | Yes - innovative.<br><br>I consider this a clinically significant improvement – incremental rather than paradigm-shifting - but nevertheless the first improvement in first-line DLBCL treatment we have seen in 20 years. The reduction in relapse risk for patients is significant (see previous comments) -given downstream implications of relapse |
| **19. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?** | No substantial differences in toxicities between current care and proposed therapy – as per POLARIX trial data |
| **20. Do the clinical trials on the technology reflect current UK clinical practice?**<br>• If not, how could the results be extrapolated to the UK setting? | Yes – reflect UK practice |

| | |
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| • What, in your view, are the most important outcomes, and were they measured in the trials?<br>• If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?<br>• Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently? | PFS and OS *and* burden of subsequent treatments for those who relapse<br><br>The vast majority of events (progression and death) occur within 2 years following diagnosis of DLBCL. Later events are very uncommon.<br><br>Not that I am aware of |
| **21. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?** | No |
| **22. How do data on real-world experience compare with the trial data?** | Not aware of real-world datasets yet as not licensed to-date |
| **23. NICE considers whether there are any equalities issues at each stage of an appraisal. Are there any potential equality issues that should be taken into account when considering this condition and this treatment? Please explain if you think any groups of people with this condition are particularly disadvantaged.**<br><br>Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics.<br>Please state if you think this appraisal could<br>• exclude any people for which this treatment is or will be licensed but who are protected by the equality legislation | No |

| | |
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| • lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population<br>• lead to recommendations that have an adverse impact on disabled people.<br>Please consider whether these issues are different from issues with current care and why.<br>More information on how NICE deals with equalities issues can be found in the NICE equality scheme.<br>Find more general information about the Equality Act and equalities issues here. | |

# Part 2: Technical engagement questions for clinical experts

We welcome your comments on the key issues below, but you may want to concentrate on issues that are in your field of expertise. If you think an issue that is important to clinicians or patients has been missed in the ERG report, please also advise on this in the space provided at the end of this section.

The text boxes will expand as you type. Your responses to the following issues will be considered by the committee and may be summarised and presented in slides at the appraisal committee meeting.

For information: the professional organisation that nominated you has also been sent a technical engagement response form (a separate document) which asks for comments on each of the key issues that have been raised in the ERG report. These will also be considered by the committee.

**Table 2 Issues arising from technical engagement**

| | |
|---|---|
| **Issue 1. Uncertainty about the potential use of Pola+R-CHP in low risk untreated DLBCL**<br>**Questions:** what treatment regimens do people with International Prognostic Index (IPI) 0-1 untreated diffuse large B-cell lymphoma (DLBCL) currently have? Would they potentially be eligible for Pola+R-CHP if it was available?<br><br>Pola+R-CHP: polatuzumab vedotin in combination with | DLBCL patients with IPI 0-1 typically receive *abbreviated* chemotherapy with 3-4 cycles of RCHOP with/without radiotherapy. It was appropriate to exclude this population – who represent a minority of all DLBCL patients - from the POLARIX trial. Thus, they wouldn't be eligible for Pola-R-CHP if it was available. |

| | |
|---|---|
| rituximab, cyclophosphamide, doxorubicin, and prednisone) | |
| **Issue 2. The survival benefit for Pola+R-CHP vs R-CHOP is very uncertain**<br>**Question:** How long would you expect to see an overall survival treatment benefit from Pola+R-CHP for?<br><br>R-CHOP: rituximab, cyclophosphamide, hydroxydaunorubicin hydrochloride (doxorubicin hydrochloride), vincristine (Oncovin) and prednisone | I don't fully understand this question since there was no significant OS seen in the POLARIX trial.<br><br>The PFS curves separate ~6 months and remain parallel beyond this. This is consistent with the behaviour of DLBCL – the vast majority of relapse and death events occur within 2 years of diagnosis. I would therefore expect any PFS difference to be stable longer-term |
| **Issue 3. The health care resources have been overestimated**<br>**Questions:** What health care resources are used for first line untreated DLBCL? Would you expect untreated DLBCL to require fewer resources than relapsed or refractory DLBCL? How does resource use vary for people with untreated DLBCL who: | Happy to discuss in committee. I agree with the ERG that using healthcare resources from the relapsed/refractory setting are not entirely appropriate for the first-line setting.<br><br>Progression-free and off treatment – similar healthcare utilisation to the normal population |

| | |
|---|---|
| 1. are progression free and on treatment, 2. are progression free and off treatment (up to 2 years), 3. have progressed? | |
| **Issue 4. Exclusion of chimeric antigen receptors cell therapy (CAR-T) as possible subsequent-line treatments** | I understand why CAR-T has been excluded since it is CDF-funded and not NICE-approved for routine commissioning.<br><br>However, CAR T therapy is fundamentally important to consider for this appraisal given it is currently used (3rd line) for r/r DLBCL and will soon be appraised for 2nd line. It would be astonishing if CAR-T was not available going forward. CAR-T has been a paradigm shift for r/r DLBCL yet comes with significant treatment burden, toxicity and substantial drug and healthcare resource costs. It therefore needs to be carefully considered as a major factor when interpreting the health economics. |
| **Additional ERG issue: Extrapolation of OS**<br>**Questions:** What proportion of people with untreated DLBCL would be expected to be alive at year 1, 2, 5 and 10 when treated with R-CHOP? What proportion of people with untreated DLBCL would be expected to be alive at year 1, 2, 5 and 10 when treated with pola+R-CHP? | Need to understand whether the question means OS or PFS (alive without progression) and whether this refers to patients treated in the real world setting rather than on this clinical trial |
| **Additional ERG issue: Health state utility values** | No specific comments |

| | |
|---|---|
| **Additional ERG issue: End of life costs** | No specific comments |
| **Are there any important issues that have been missed in ERG report?** | No |

## Part 3: Key messages

In up to 5 sentences, please summarise the key messages of your statement:

- This is the first RCT in 2 decades to demonstrate a PFS improvement over standard RCHOP
- PFS is very important to patients and to the NHS given the treatment burden/toxicity/cost of relapsed disease
- This technology confers a significant improvement against standard of care, without significant increased toxicity and would be straightforward to implement in the pathway
- CAR-T therapy needs to be considered in the overall evaluation given its current and future place in therapy for relapsed DLBCL

Click or tap here to enter text.

Thank you for your time.

## Your privacy

The information that you provide on this form will be used to contact you about the topic above.

☐ **Please tick this box** if you would like to receive information about other NICE topics.

For more information about how we process your personal data please see our privacy notice.

NICE National Institute for Health and Care Excellence

# Clinical expert statement and technical engagement response form

## Polatuzumab vedotin in combination for untreated diffuse large B-cell lymphoma [ID3901]

Thank you for agreeing to comment on the evidence review group (ERG) report for this appraisal, and for providing your views on this technology and its possible use in the NHS.

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A clinical perspective could help either:

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Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.

Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise, all information submitted under 'academic in confidence' in yellow, and all information submitted under 'depersonalised data' in pink. If confidential information is submitted, please also send a second version of your comments with that information 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.

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Deadline for comments by **5pm** on **13 July 2022.** Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Thank you for your time.

Clinical expert statement

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NICE National Institute for Health and Care Excellence

# Part 1: Treating untreated diffuse large B-cell lymphoma and current treatment options

**Table 1 About you, aim of treatment, place and use of technology, sources of evidence and equality**

| | |
|---|---|
| **1. Your name** | Dr Wendy Osborne |
| **2. Name of organisation** | Newcastle upon Tyne Hospitals NHS Foundation Trust |
| **3. Job title or position** | Consultant Haematologist |
| **4. Are you (please tick all that apply)** | ☒ An employee or representative of a healthcare professional organisation that represents clinicians?<br>☒ A specialist in the treatment of people with untreated diffuse large B-cell lymphoma?<br>☒ A specialist in the clinical evidence base for untreated diffuse large B-cell lymphoma or technology?<br>☐ Other (please specify): |
| **5. Do you wish to agree with your nominating organisation's submission?**<br>(We would encourage you to complete this form even if you agree with your nominating organisation's submission) | ☒ Yes, I agree with it<br>☐ No, I disagree with it<br>☐ I agree with some of it, but disagree with some of it<br>☐ Other (they did not submit one, I do not know if they submitted one etc.) |
| **6. If you wrote the organisation submission and/or do not have anything to add, tick here.**<br>(If you tick this box, the rest of this form will be deleted after submission) | ☒ Yes |
| **7. Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.** | Nil |

| | |
|---|---|
| **8. What is the main aim of treatment for untreated diffuse large B-cell lymphoma?**<br>(For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability) | Aim to achieve long term cure |
| **9. What do you consider a clinically significant treatment response?**<br>(For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount) | Obtaining a CR<br>Progression free survival |
| **10. In your view, is there an unmet need for patients and healthcare professionals in untreated diffuse large B-cell lymphoma?** | Yes, about 35 % of pts relapse and at that point need high dose chemo and an autologous stem cell transplant which is associated with significant morbidity. This high dose therapy is only effective in about 20 % of pts and then they need CAR T therapy 3rd line which is effective in about 40 % of pts but at high cost to the NHS and toxicity / psychological toxicity to the pt. |
| **11. How is untreated diffuse large B-cell lymphoma currently treated in the NHS?**<br>• Are any clinical guidelines used in the treatment of the condition, and if so, which?<br>• 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.)<br>• What impact would the technology have on the current pathway of care? | RCHOP X 6<br><br>BSH and NICE<br><br>Yes, international standard of care<br><br>If approved would not change the current pathway, would be 6XpolaRCHP delivered in same hospitals as before |
| **12. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?**<br>• How does healthcare resource use differ between the technology and current care? | No significant change, treatment time may increase slightly per pt but will be delivered in same hospital outpatient setting |

| | |
|---|---|
| • In what clinical setting should the technology be used? (for example, primary or secondary care, specialist clinic)<br>• What investment is needed to introduce the technology? (for example, for facilities, equipment, or training) | Given in same setting as RCHOP, DGH as well as specialist cancer centres<br><br>None, already have experience in using polatuzumab as on CDF for 2nd line and beyond as well as CAR T bridging |
| **13. Do you expect the technology to provide clinically meaningful benefits compared with current care?**<br>• Do you expect the technology to increase length of life more than current care?<br>• Do you expect the technology to increase health-related quality of life more than current care? | The POLARIX data show an improvement in PFS and fewer relapse events. A relapse event in high grade lymphoma is devastating for the patient and requires 3 months of high dose chemo and then a month in hospital for an autologous stem cell transplant which is associated with significant toxicity. |
| **14. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?** | Trial included pts IPI 2-5 and therefore I would not use in pts with IPI1 or limited stage disease |
| **15. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use?**<br>(For example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed) | The same |

| | |
|---|---|
| **16. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?** | As per current standard which is continuing chemo if good response on mid-point CT |
| **17. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation?**<br>• Do the instruments that measure quality of life fully capture all the benefits of the technology or have some been missed? For example, the treatment regimen may be more easily administered (such as an oral tablet or home treatment) than current standard of care | I think that the benefits should be captured if the toxicity of 2nd line chemo and auto and 3rd line treatments are considered. |
| **18. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met?**<br>• Is the technology a 'step-change' in the management of the condition?<br>• Does the use of the technology address any particular unmet need of the patient population? | Using antibody drug conjugates is innovative in DLBCL<br><br>The PFS is of clinical benefit and it is impt to try and prevent a relapse event. No OS benefit was seen, this maybe because we have many other lines of therapy for pts but these come at high cost to pt and NHS |
| **19. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?** | Toxicity profile similar to RCHOP in study |
| **20. Do the clinical trials on the technology reflect current UK clinical practice?**<br>• If not, how could the results be extrapolated to the UK setting? | Yes |

| | |
|---|---|
| • What, in your view, are the most important outcomes, and were they measured in the trials?<br>• If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?<br>• Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently? | PFS and OS which were measured<br><br>If pts remain progression free at 2 years then they are unlikely to relapse afterwards and we would discharge from clinic at 2 yrs<br><br>No |
| **21. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?** | No |
| **22. How do data on real-world experience compare with the trial data?** | There is currently no access to polatuzumab first line and so there are not any real world data. |
| **23. NICE considers whether there are any equalities issues at each stage of an appraisal. Are there any potential equality issues that should be taken into account when considering this condition and this treatment? Please explain if you think any groups of people with this condition are particularly disadvantaged.**<br><br>Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics.<br>Please state if you think this appraisal could<br>• exclude any people for which this treatment is or will be licensed but who are protected by the equality legislation | No |

| | |
|---|---|
| • lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population<br>• lead to recommendations that have an adverse impact on disabled people.<br>Please consider whether these issues are different from issues with current care and why.<br>More information on how NICE deals with equalities issues can be found in the NICE equality scheme.<br>Find more general information about the Equality Act and equalities issues here. | |

# Part 2: Technical engagement questions for clinical experts

We welcome your comments on the key issues below, but you may want to concentrate on issues that are in your field of expertise. If you think an issue that is important to clinicians or patients has been missed in the ERG report, please also advise on this in the space provided at the end of this section.

The text boxes will expand as you type. Your responses to the following issues will be considered by the committee and may be summarised and presented in slides at the appraisal committee meeting.

For information: the professional organisation that nominated you has also been sent a technical engagement response form (a separate document) which asks for comments on each of the key issues that have been raised in the ERG report. These will also be considered by the committee.

**Table 2 Issues arising from technical engagement**

| | |
|---|---|
| **Issue 1. Uncertainty about the potential use of Pola+R-CHP in low risk untreated DLBCL**<br>**Questions:** what treatment regimens do people with International Prognostic Index (IPI) 0-1 untreated diffuse large B-cell lymphoma (DLBCL) currently have? Would they potentially be eligible for Pola+R-CHP if it was available?<br><br>Pola+R-CHP: polatuzumab vedotin in combination with | Patients with IPI of 1 usually have early stage disease which is often treated with 3-4 cyles of RCHOP and sometimes radiotherapy or 6 cycles of RCHOP depending on site of disease. These pts were excluded from the trial and I think they should be ineligible for PolaRCHP. The outcomes for these pts is usually very good |

| | |
|---|---|
| rituximab, cyclophosphamide, doxorubicin, and prednisone) | |
| **Issue 2. The survival benefit for Pola+R-CHP vs R-CHOP is very uncertain**<br>**Question:** How long would you expect to see an overall survival treatment benefit from Pola+R-CHP for?<br><br>R-CHOP: rituximab, cyclophosphamide, hydroxydaunorubicin hydrochloride (doxorubicin hydrochloride), vincristine (Oncovin) and prednisone | In the initial data an OS benefit was not seen which may have been due to subsequent treatments available. The extrapolation does show survival benefit, but I agree that this is uncertain although there will be significant toxicity form subsequent high dose treatments and may account for longer term survival in extrapolation. |
| **Issue 3. The health care resources have been overestimated**<br>**Questions:** What health care resources are used for first line untreated DLBCL? Would you expect untreated DLBCL to require fewer resources than relapsed or refractory DLBCL? How does resource use vary for people with untreated DLBCL who: | First line DLBCL treatment will require fewer resources than in a RR setting. At fist line most pts just attend for a few hours every 3 weeks. For pts have 2nd line high dose therapy they need review twice each week, chemo weekly for 2 out of 3 weeks, stem cell harvest and then 3-4 week inpt stay for autologous stem cell transplant. |

| | |
|---|---|
| 1. are progression free and on treatment, 2. are progression free and off treatment (up to 2 years), 3. have progressed? | If pts are progression free then they would not be on treatment and would have 2 OP clinic rv (often remote) a year for 2 years. If they have progressed they will need intensive treatment as written above. |
| **Issue 4. Exclusion of chimeric antigen receptors cell therapy (CAR-T) as possible subsequent-line treatments** | This is currently the 3rd line used although not NICE approved. Only 20 % of pts have long term response to high dose and auto, for older pts not fit for auto who have Rgemox 2nd line then only 10 % will respond. Currently majority of pts will proceed to CAR T due to the poor efficacy of 2nd line treatment.<br>CAR T is standard of care now 3rd line and beyond across USA and Europe and has just received FDA approval 2nd line for pts who relapse within 12 months |
| **Additional ERG issue: Extrapolation of OS**<br>**Questions:** What proportion of people with untreated DLBCL would be expected to be alive at year 1, 2, 5 and 10 when treated with R-CHOP? What proportion of people with untreated DLBCL would be expected to be alive at year 1, 2, 5 and 10 when treated with pola+R-CHP? | This is difficult as the POLARIX data does not show survival improvement.<br>For RCHOP pts :<br>At 1 year 75%, 2 year 65% , 5 yrs 63% 10 yrs 60% the extrapolation may show improvements in this for polaRCHP as discussed above in view of impact late effects of relapse therapy |
| **Additional ERG issue: Health state utility values** | |
| **Additional ERG issue: End of life costs** | |

| | |
|---|---|
| **Are there any important issues that have been missed in ERG report?** | No |

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## Part 3: Key messages

In up to 5 sentences, please summarise the key messages of your statement:

PFS benefit over RCHOP

Relapse with high grade lymphoma requires intensive chemo and auto

2nd line treatments have 20% less success rate requiring high-cost 3rd line treatments

No increase toxicity and easy to deliver polaRCHP

Well designed RCT

Thank you for your time.

## Your privacy

The information that you provide on this form will be used to contact you about the topic above.

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**Evidence Review Group Report commissioned by the**
**NIHR Evidence Synthesis Programme on behalf of NICE**

# Polatuzumab vedotin in combination for untreated diffuse large B-cell lymphoma

**Evidence Review Group's summary and critique of the company's response to technical engagement**

| | |
|---|---|
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| **Date completed** | 3rd August 2022 |

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## 1. Introduction

This document is the Evidence Review Group's (ERG) summary and critique of the response by the company, Roche, to the key issues for technical engagement (TE) proposed in the ERG report for this appraisal (submitted to NICE on 23/05/2022). The ERG received the company's response on 14/07/22.

The company's TE response form contains the following information:

- A written response to each of the four key issues and a response to three additional (non-key) issues raised in the ERG report, none of which include new evidence and/or analyses (see Table 1).
- A set of updated cost-effectiveness results, incorporating:
    - An updated confidential Patient Access Scheme (PAS) price discount for polatuzumab
    - Additional evidence and/or analyses provided by the company in response to some of the key issues for TE.
- An updated version of the company's economic model accompanies the response form.

In this report we present the following:

- Our critique of the company's response to each of the four issues for technical engagement and the three additional non-key issues (Section 2)
- A validation of the results of the company's updated cost-effectiveness analysis, and the results of an updated ERG base case and scenario analyses (Section 3)

**Table 1 Summary of key issues for technical engagement**

| Issue number | Summary of issue | Does this response contain new evidence, data or analyses? |
|---|---|---|
| 1 | Uncertainty about the potential use of Pola+R-CHP in low risk DLBCL | No |
| 2 | The survival benefit for Pola+R-CHP vs R-CHOP is very uncertain | No |
| 3 | The health care resources have been overestimated | No |
| 4 | Inclusion of chimeric antigen receptors cell therapy (CAR-T) as a subsequent anti-lymphoma treatment | No |
| Additional issue 1 | Uncertainty in the extrapolation of OS | No |
| Additional issue 2 | Source of the health state utility values | No |
| Additional issue 3 | End of life costs | No |

## 2. Critique of the company's response to key issues for technical engagement

### 2.1 Issue 1 – Uncertainty about potential use of Pola+R-CHP in low risk DLBCL

**Summary of the issue**

The company submission estimates clinical effectiveness and cost effectiveness of Pola+R-CHP in adult patients with previously untreated DLBCL, restricted to patients with an International Prognostic Index (IPI) score of 2 to 5 (low-intermediate risk to high-risk disease). This aligns with the eligibility criteria of the POLARIX trial but is a narrower population than the that covered by the marketing authorisation. The exclusion of IPI 0-1 patients, and the clinical rationale for this, was not explicitly stated in the company submission. The ERG notes that low risk patients are currently treated with a shortened regimen of R-CHOP. We suggested seeking further expert clinical opinion on potential use of Pola+R-CHP in low-risk patients.

**Critique of the company's response**

The company reiterate that the intended patient population for Pola+R-CHP is adult DLBCL patients with an IPI score of 2–5. As no data is available for the use of Pola+R-CHP in low-risk (IPI 0–1) patients they do not plan to include this population. Again, they do not give a clinical rationale for this. However, two clinical experts consulted by NICE during technical engagement were both of the opinion that it was appropriate to exclude IPI 0-1 patients from the POLARIX trial, noting that they are a minority of DLBCL patients and their outcomes are usually very good. These comments accord with those of the ERG clinical experts, thus we consider this key issue now resolved.

### 2.2 Issue 2 – Survival benefit for POLA-R-CHP

**Summary of the issue**

There is uncertainty in the overall survival (OS) estimate for POLA-R-CHP vs RCHOP. In the POLARIX trial there was a very small difference in OS favouring Pola+R-CHP with a wide confidence interval indicating no statistically significant difference (HR 0.94 CI 0.65 to 1.37). This is based immature data from an interim data-cut. However, the company's OS extrapolation assumes a continued survival benefit for Pola+R-CHP compared to R-CHOP. Given the current uncertainty we assume the survival benefit is unlikely to last for more than five years, and after this point the probability of death is the same in both trial arms. We also assume.

**Critique of the company's response**

The company consider that the survival benefit of Pola+R-CHP in first-line DLBCL will be maintained, with no waning. They cite a selection of studies which, in their view, supports this assertion:

- The treatment effect persisted in first line DLBCL over a 10-year follow-up in the LNH-98.5 trial[1] the first randomised trial of R-CHOP vs CHOP.
- Benefits were maintained after 6 years follow-up in the MinT study comparing CHOP-like chemotherapy with/without rituximab in young patients[2];
- Long-term follow up of the RCT G029365 comparing Pola+BR (bendamustine and rituximab) versus BR in relapsed / refractory DLBCL demonstrated improved PFS and OS favouring Pola+BR, over a median follow-up of around 48 months.[3] If the treatment effect persists in the (non-curative) relapsed / refractory setting, the company suggest there is no reason to assume that the Pola+R-CHP treatment effect in the first line DLBCL curative setting would decline.
- Clinical expert advice to the company agreed that in the curative setting they would not expect treatment effect waning.

- OS is informed by PFS, which means that the OS curves are likely underestimating the efficacy of Pola+R-CHP long-term.

The ERG acknowledges the above evidence, though differences in treatment regimens, patient characteristics and study time periods limits their applicability to the current appraisal. While this evidence suggests that survival benefit can be maintained, in the absence of more mature survival data the ERG takes a conservative approach and assumes the Pola+R-CHP treatment effect will be limited to five years, with waning of the effect from 30 months onwards. The company does not follow the ERG's approach in their revised base case. The OS curves for the scenarios including and not including treatment effect waning are shown in Figure 1.

**Figure 1 Overall survival for Pola+R-CHP vs R-CHOP including and not including treatment effect waning**

### 2.3 Issue 3 – Health care resources have been overestimated

**Summary of the issue**

The ERG considered that the health care resources included in the economic evaluation are overestimated as they were based upon on resources associated with later treatment lines (third and fourth-line treatment of DLBCL) for which patients tend to be in poorer health and require greater health care resources than previously untreated patients in the current appraisal.

**Critique of the company's response**

The company notes the absence of any existing NICE appraisal of a first-line DLBCL treatment on which they could base their approach to costing and resource estimation. Their approach is consistent with that taken in previous NICE appraisals of second and third line DLBCL treatments. However, the company acknowledges potential overestimation of some

PFS costs and resource use, and agree to amend the resource use estimates for patients in the PFS health states using the values suggested by the ERG. With regard to the resources and supportive care costs for the progressed disease (PD) health state, the company consider their approach to be conservative. As patients received two more additional treatments, on average, after first-line treatment, the company argues that their base case does not account for any additional resource costs beyond the second-line. For this reason no adjustments are made to these costs and resource use estimates

The ERG, however, maintains that health state costs for PD have been overestimated. As stated in the ERG report section 4.2.8.3, health care costs are taken from NICE TA306[4] (Pixantrone monotherapy for treating multiply relapsed or refractory aggressive non-Hodgkin's B-cell lymphoma) which comprises patients receiving third- or fourth-line DLBCL treatment, i.e. patients with more severe disease.

Patients are assumed to incur health care costs for PD indefinitely, whilst it is likely that many patients would respond to subsequent treatments and no longer incur these costs, as assumed in NICE TA649[5] (Polatuzumab vedotin with rituximab and bendamustine for treating relapsed or refractory diffuse large B-cell lymphoma). Costs for residential, day care, home care and hospice care, are also included in the end-of-life costs (see Additional issue 3) so in the company estimate for PD health costs, these costs have been double counted. The total costs remain considerably higher than reported in Wang et al,[6] who conducted real world cost modelling of newly diagnosed patients with DLBCL in the UK, and the PD costs are considerably higher than in other similar NICE cancer drugs appraisals, such as TA513 (Obinutuzumab for untreated advanced follicular lymphoma).[7]

### 2.4 Issue 4 – Exclusion of CAR-T subsequent treatments

**Summary of the issue**

Chimeric antigen receptors cell therapy (CAR-T) treatments axicabtagene ciloleucel and tisagenlecleucel were included in the economic model as subsequent-line treatments for patients whose disease progresses after first-line treatment. CAR-T treatments should be excluded from the economic model as they are currently recommended by NICE for use within the Cancer Drugs Fund, rather being available on the NHS through routine commissioning.

**Critique of the company's response**

The company agreed to remove CAR-T treatments from their base case and adjusted the usage of the other subsequent treatments accordingly. The company noted that CAR-T treatments are increasingly used in the UK, and regional UK guidelines recommend them as a subsequent treatment option for progressed DLBCL patients. Further, they note that the first CAR-T to be appraised by NICE, axicabtagene cilolucel, will soon exit the Cancer Drugs Fund and be reappraised by NICE (guidance is expected in January 2023). A positive NICE recommendation would allow CAR-T treatment to be available routinely in the NHS which, in turn, would make it appropriate for inclusion as a subsequent treatment in economic modelling of first line DLBCL treatment.

The ERG agrees with excluding CAR-T from the analysis at the current time. The total usage of subsequent treatments is greater than 100% in the company base case so the ERG consider that it is more appropriate to remove the CAR-T treatments without adjusting the other treatments (total usage 97%).

### 2.5 Additional issue – Extrapolation of OS

The ERG suggested that, given the small differences in OS between the treatment arms in POLARIX, a better approach is to use the Kaplan-Meier data for the trial period with an extrapolated tail. The company reviewed the approach the ERG suggested and agreed with this change.

### 2.6 Additional issue – Health related quality of life

The ERG preferred to use the utility values from the POLARIX trial, for consistency with the clinical effectiveness data from that trial. The company's base case included utility values from the GOYA trial, an evaluation of a different investigational agent for untreated DLBCL. The company provided limited data in their submission and response to clarification questions about the collection and analysis of the HRQoL data in the GOYA trial, which limited a full ERG critique of their approach.

In response to technical engagement the company argues that the progressed disease utility values from the POLARIX trial may not be representative of this population for several reasons:

- The EQ-5D 5L values were collected in the PD state within a few days of progression and most patients had yet to start second-line treatment;

- There were a large number of missing values from progressed patients and these patients had a worse prognosis in post progression survival compared to the patients who reported their PD state utility.
- Patients' quality of life is likely to deteriorate quickly due to the rapid progression of patients in later lines of treatment.

Therefore, the company maintained that the GOYA trial data is a more appropriate source of utility values than the POLARIX trial data.

We note that the utility values from the GOYA trial for PD are similar to those reported in second line treatment for DLBCL from the ZUMA-1 study in NICE TA649.[5] (Polatuzumab vedotin with rituximab and bendamustine for treating relapsed or refractory diffuse large B-cell lymphoma). On this basis, we agree to use the GOYA trial utility values in our base case.

### 2.7 Additional issue – End of life costs

The ERG suggested the use of a one-off cost for patients who die (end of life cost), as previously used in other cancer drugs appraisals. The company reviewed the ERG's approach agreed with this change.

### 2.8 Company modelling adjustments

The following modelling adjustments were made by the company:

- Adjustment of the ERG's OS treatment waning formula to prevent the intersection of the PFS curve with the OS curve. However, the ERG notes this adjustment appears to be incorrect and allows the curves to intersect, which leads to some implausible values for PD. We therefore did not include the company's adjustment in our analysis.
- Application of the PD age-adjusted correction to the calculation of discounted QALYs, as it had only been applied to the undiscounted QALYs. The ERG agrees with this correction.
- An adjustment to the end of life cost calculation, applicable only to patients whose cause of death was cancer. The ERG consider that end of life costs may also apply to patients who die from other conditions, although some may die of natural causes. As the company's adjustment makes only a small change to the ICER the ERG have accepted this change and we apply end of life costs to all patients in a sensitivity analysis.

## 3. Updated cost-effectiveness results - ERG summary and critique

### 3.1 Company's revised base case cost-effectiveness results

The results of the company's revisions to their original base case, including a new PAS discount price, are shown in Table 2 (see the company response document Table 4). The revised base case results in a reduction in the base case ICER from £34,306 to £27,132.

**Table 2 Company's changes to their original base case**

| Scenario | Treatment | Total costs | Total QALYs | Increm. costs | Increm. QALYs | ICER (£/QALY) |
|---|---|---|---|---|---|---|
| Company original base case | Pola+R-CHP | [redacted] | [redacted] | [redacted] | [redacted] | £34,306 |
| | R-CHOP | [redacted] | [redacted] | | | |
| Rituximab list price | Pola+R-CHP | [redacted] | [redacted] | [redacted] | [redacted] | £33,656 |
| | R-CHOP | [redacted] | [redacted] | | | |
| OS with KM + generalised gamma with an extrapolated tail at 30 months (25% of patients at risk) | Pola+R-CHP | [redacted] | [redacted] | [redacted] | [redacted] | £44,032 |
| | RCHOP | [redacted] | [redacted] | | | |
| End of life costs included, only in patients who died from the disease | Pola+R-CHP | [redacted] | [redacted] | [redacted] | [redacted] | £43,283 |
| | R-CHOP | [redacted] | [redacted] | | | |
| Adjust the ERG's OS treatment waning formula | Pola+R-CHP | [redacted] | [redacted] | [redacted] | [redacted] | £31,323 |
| | R-CHOP | [redacted] | [redacted] | | | |
| Resource use from TA306 for PD' modified resource use and costs for PFS | Pola+R-CHP | [redacted] | [redacted] | [redacted] | [redacted] | £29,599 |
| | R-CHOP | [redacted] | [redacted] | | | |
| Exclude CAR-T as a subsequent treatment | Pola+R-CHP | [redacted] | [redacted] | [redacted] | [redacted] | £49,914 |
| | R-CHOP | [redacted] | [redacted] | | | |
| Apply age-adjusted PD utilities correction | Pola+R-CHP | [redacted] | [redacted] | [redacted] | [redacted] | £45,526 |
| | R-CHOP | [redacted] | [redacted] | | | |
| New PAS discount for Pola+R-CHP of [redacted] | Pola+R-CHP | [redacted] | [redacted] | [redacted] | [redacted] | £27,132 |
| | RCHOP | [redacted] | [redacted] | | | |
| Company revised base case | Pola+R-CHP | [redacted] | [redacted] | [redacted] | [redacted] | £27,132 |
| | R-CHOP | [redacted] | [redacted] | | | |

ICER, incremental cost-effectiveness ratio; KM, Kaplan-Meier, QALYs, quality-adjusted life years

The ERG ran the probabilistic sensitivity analysis (PSA) with the company's revised base case and the results are shown in Table 3. The ICERs are similar.

**Table 3 Company's revised PSA results**

| Scenario | Incremental costs | Incremental QALYs | ICER (£/QALY) |
|---|---|---|---|
| Company revised base case | [redacted] | [redacted] | £27,132 |
| Company PSA results | [redacted] | [redacted] | £29,849 |

ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life years

### 3.2 ERG's revised preferred assumptions

Following the company's response to technical engagement, there remain some differences between the company and ERG base case.

### 3.3 Cost-effectiveness results based on ERG preferred model assumptions

The ERG's revised base case assumptions and resulting ICERs are shown in Table 4. The ERG's base case ICER of £142,647 is considerably higher than the company's revised base case ICER £27,132.

**Table 4 Cumulative results for the ERG's preferred model assumptions**

| Scenario | Treatment | Total costs | Total QALYs | Increm. costs | Increm. QALYs | ICER (£/QALY) |
|---|---|---|---|---|---|---|
| Company revised base case | Pola+R-CHP | [redacted] | [redacted] | [redacted] | [redacted] | £27,132 |
| | R-CHOP | [redacted] | [redacted] | | | |
| Remove company PFS adjustment. Treatment effect waning assumption for OS between 30 months and 60 months | Pola+R-CHP | [redacted] | [redacted] | [redacted] | [redacted] | £75,271 |
| | R-CHOP | [redacted] | [redacted] | | | |
| ERG supportive care cost | Pola+R-CHP | [redacted] | [redacted] | [redacted] | [redacted] | £129,630 |
| | RCHOP | [redacted] | [redacted] | | | |
| Subsequent therapies without CAR-T | Pola+R-CHP | [redacted] | [redacted] | [redacted] | [redacted] | £142,647 |
| | R-CHOP | [redacted] | [redacted] | | | |
| ERG's preferred assumptions | Pola+R-CHP | [redacted] | [redacted] | [redacted] | [redacted] | £142,647 |
| | R-CHOP | [redacted] | [redacted] | | | |

ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life years

The ERG ran the PSA with the ERG's revised base and the results are shown in Table 5.

**Table 5 ERG revised PSA results**

| Scenario | Incremental costs | Incremental QALYs | ICER (£/QALY) |
|---|---|---|---|
| ERG revised base case | [redacted] | [redacted] | £142,647 |
| ERG PSA results | [redacted] | [redacted] | £145,089 |

ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life years

### 3.4 Scenario analyses conducted on the ERG's revised preferred assumptions

We conducted scenario analyses for parameters where there remains uncertainty (Table 6). The scenario with the lowest ICER, £68,535 per QALY, assumed the survival benefit of Pola+R-CHP is maintained over time. Inclusion of CAR-T as a subsequent treatment cost also lowered the ICER, to £84,800 per QALY. Of the combined scenarios tested, the lowest ICER (£45,421 per QALY) was based on the company's assumption that the survival benefit of Pola+R-CHP is maintained over time (i.e. no waning) and the company's assumed PD resource use from NICE TA306.

**Table 6 Scenario analysis results for the ERG's preferred model assumptions**

| Scenario | Treatment | Total costs | Total QALYs | Increm. costs | Increm. QALYs | ICER (£/QALY) |
|---|---|---|---|---|---|---|
| ERG's preferred assumptions | Pola+R-CHP | [redacted] | [redacted] | [redacted] | [redacted] | £142,647 |
| | R-CHOP | [redacted] | [redacted] | | | |
| Treatment effect maintained over time | Pola+R-CHP | [redacted] | [redacted] | [redacted] | [redacted] | £68,535 |
| | R-CHOP | [redacted] | [redacted] | | | |
| Include CAR-T in subsequent treatment costs | Pola+R-CHP | [redacted] | [redacted] | [redacted] | [redacted] | £84,800 |
| | R-CHOP | [redacted] | [redacted] | | | |
| Utility values from the POLARIX trial, rather than from the GOYA trial | Pola+R-CHP | [redacted] | [redacted] | [redacted] | [redacted] | £161,565 |
| | R-CHOP | [redacted] | [redacted] | | | |
| Exclude CAR-T but redistribute treatment proportion to other 3rd line treatments (Company assumption) | Pola+R-CHP | [redacted] | [redacted] | [redacted] | [redacted] | £129,630 |
| | R-CHOP | [redacted] | [redacted] | | | |
| End of life costs applied to all patients | Pola+R-CHP | [redacted] | [redacted] | [redacted] | [redacted] | £144,066 |
| | R-CHOP | [redacted] | [redacted] | | | |
| Resource use from TA306 for PD + modified resource use and costs for PFS | Pola+R-CHP | [redacted] | [redacted] | [redacted] | [redacted] | £88,288 |
| | R-CHOP | [redacted] | [redacted] | | | |
| Treatment effect mantained over time + resource use from TA306 for PD + modified resource use and costs for PFS | Pola+R-CHP | [redacted] | [redacted] | [redacted] | [redacted] | £45,421 |
| | R-CHOP | [redacted] | [redacted] | | | |
| Treatment effect maintained over time + exclude CAR-T but redistribute treatment proportion to other 3rd line treatments | Pola+R-CHP | [redacted] | [redacted] | [redacted] | [redacted] | £62,389 |
| | R-CHOP | [redacted] | [redacted] | | | |

ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life years

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