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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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The authors declare none.

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**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]

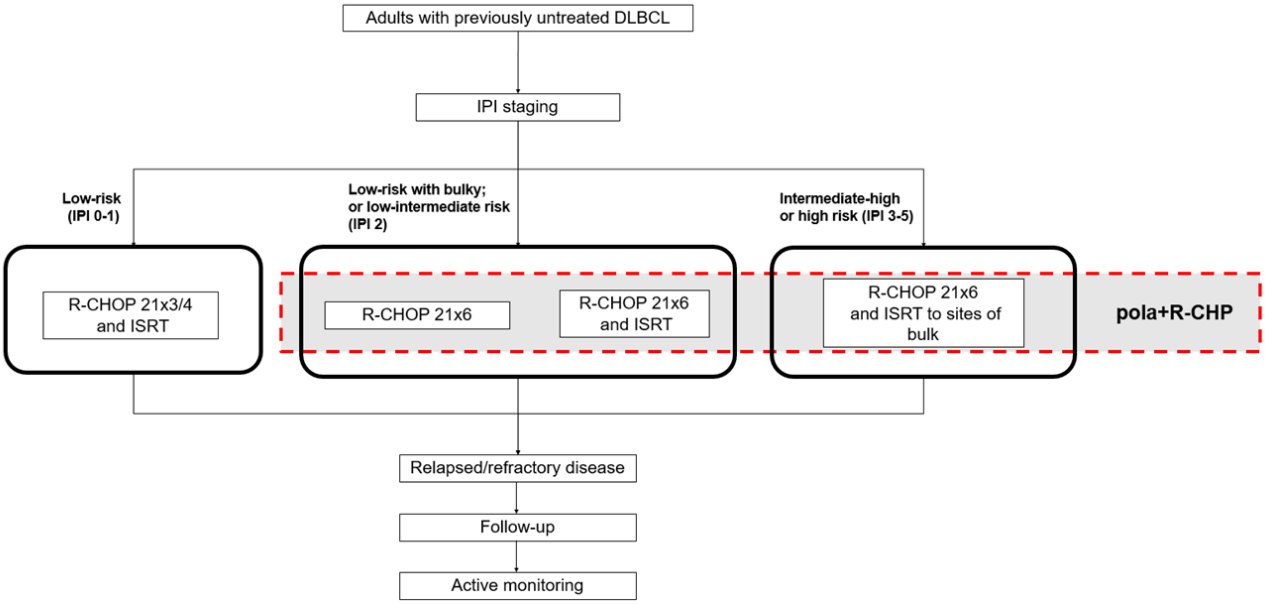
The CS states an application of a Type II variation for polatuzumab to its current indication, as well as an Orphan Drug Designation application, were submitted to the MHRA on 28th January 2022, with an approval expected in [redacted]. The anticipated indication is polatuzumab in combination with rituximab, 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.

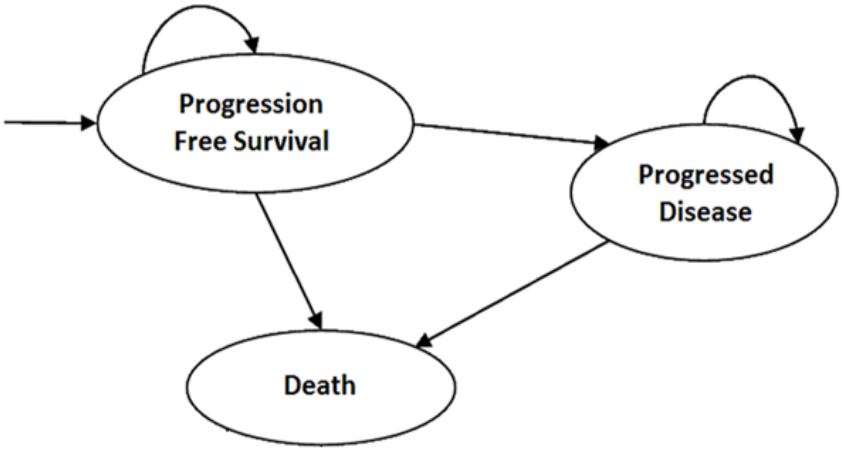



**Figure 2 Structure of economic model**

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