

## **Single Technology Appraisal**

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

## **Committee Papers**

**NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE**

**SINGLE TECHNOLOGY APPRAISAL**

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

**Contents:**

The following documents are made available to consultees and commentators:

- 1. Response to consultee, commentator and public comments on the Appraisal Consultation Document (ACD)**
- 2. Comments on the Appraisal Consultation Document from Roche**
- 3. Evidence Review Group critique of company comments on the ACD**

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

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

**Single Technology Appraisal**

**Response to consultee, commentator and public comments on the Appraisal Consultation Document (ACD)**

**Type of stakeholder:**

**Consultees** – Organisations that accept an invitation to participate in the appraisal including the companies, national professional organisations, national patient organisations, the Department of Health and Social Care and the Welsh Government and relevant NHS organisations in England. Consultees can make a submission and participate in the consultation on the appraisal consultation document (ACD; if produced). All non-company consultees can nominate clinical experts and/or patient experts to verbally present their personal views to the Appraisal Committee. Company consultees can also nominate clinical experts. Representatives from NHS England and clinical commissioning groups invited to participate in the appraisal may also attend the Appraisal Committee as NHS commissioning experts. All consultees have the opportunity to consider an appeal against the final recommendations, or report any factual errors, within the final appraisal document (FAD).

**Clinical and patient experts and NHS commissioning experts** – The Chair of the Appraisal Committee and the NICE project team select clinical experts and patient experts from nominations by consultees and commentators. They attend the Appraisal Committee meeting as individuals to answer questions to help clarify issues about the submitted evidence and to provide their views and experiences of the technology and/or condition. Before they attend the meeting, all experts must either submit a written statement (using a template) or indicate they agree with the submission made by their nominating organisation..

**Commentators** – Commentators can participate in the consultation on the ACD (if produced), but NICE does not ask them to make any submission for the appraisal. Non-company commentator organisations can nominate clinical experts and patient experts to verbally present their personal views to the Appraisal Committee. Commentator organisations representing relevant comparator technology companies can also nominate clinical experts. These organisations receive the FAD and have opportunity to report any factual errors. These organisations include comparator technology companies, Healthcare Improvement Scotland any relevant National Collaborating Centre (a group commissioned by NICE to develop clinical guidelines), other related research groups where appropriate (for example, the Medical Research Council and National Cancer Research Institute); other groups such as the NHS Confederation, the NHS Commercial Medicines Unit, the Scottish Medicines Consortium, the Medicines and Healthcare Products Regulatory Agency, the Department of Health and Social Care, Social Services and Public Safety for Northern Ireland).

**Public** – Members of the public have the opportunity to comment on the ACD when it is posted on the Institute's web site 5 days after it is sent to consultees and commentators. These comments are usually presented to the appraisal committee in full, but NICE reserves the right to summarise and edit comments received during consultations, or not to publish them at all, where in the reasonable opinion of NICE, the comments are voluminous, publication would be unlawful or publication would be otherwise inappropriate.

**Please note:** Comments received in the course of consultations carried out by NICE are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the submissions that NICE has received, and are not endorsed by NICE, its officers or advisory committees.

| Comment number | Type of stakeholder | Organisation name | Stakeholder comment  | NICE Response   |
|----------------|---------------------|-------------------|--|---|
| 1              | Company             | Roche Products    | <p><b><u>Introduction</u></b></p> <p>Roche appreciates the opportunity to comment on the NICE Appraisal Consultation Document (ACD) for Polatuzumab vedotin in combination for untreated diffuse large B-cell lymphoma [ID3901].</p> <p>Roche is dedicated to finding solutions in collaboration with NICE for the concerns raised within the ACD such that Polatuzumab vedotin may be considered for a positive recommendation for use within the NHS. There is a high unmet need for patients with DLBCL. After 20 years, POLARIX is the first robust randomised controlled Phase III trial to successfully demonstrate a clinically and statistically significant PFS improvement over R-CHOP for previously untreated DLBCL patients with an IPI 2–5.</p> <p>Rationale is provided in the comments below for instances where Roche would like to encourage the Committee to reconsider its conclusions. Roche has also resubmitted an amended model to reflect the changes suggested in the ACD.</p> <p>This response covers the following key points, addressing the concerns raised in the ACD:</p> <ul style="list-style-type: none"> <li>- Correction of the curves in the model</li> <li>- Weight distribution of the POLARIX patients</li> <li>- PD supportive care costs</li> <li>- End-of-life costs</li> <li>- Scenario: Inclusion of CAR-Ts</li> <li>- Scenario: Cost-effectiveness results in the IPI 3–5 population</li> </ul> | <p>Thank you for your comment.</p> <p>The committee acknowledged the high unmet need for first-line treatment of diffuse large B-cell lymphoma (DLBCL); see section 3.1 of the Final Appraisal Document [FAD]) and the innovative nature of polatuzumab vedotin (see section 3.17 of the FAD). Innovation was taken into account when considering the acceptable incremental cost effectiveness range that should be considered for this appraisal (see section 3.18).</p> <p>The committee</p> |

| Comment number | Type of stakeholder | Organisation name | Stakeholder comment  | NICE Response   |
|----------------|---------------------|-------------------|--|---|
|                |                     |                   | <p>The revisions outlined below change the incremental cost-effectiveness ratio (ICER) to £26,097 for the IPI 2–5 population.</p> <p>As noted above, Roche feels strongly that Polatuzumab vedotin can address a significant unmet need for an effective treatment for DLBCL patients in the UK, and wishes to note that the ICER presented herein - following the revisions requested by the committee - is cost-effective. Roche is committed to enabling people with DLBCL to gain access to Polatuzumab vedotin and is open and willing to continue collaboration as needed with NICE and NHS England to make this happen.</p>   | <p>concluded that the cost-effectiveness estimates for polatuzumab vedotin with R-CHP were higher than the acceptable incremental cost effectiveness range and therefore did not recommend its use in the NHS.</p> <p>The other points raised in this comment have been addressed in the responses to the comments below.</p> |
| 2              | Company             | Roche Products    | <p><b><u>Correction of the curves in the model</u></b></p> <p>The company would like to re-clarify to the committee and the ERG that a curve correction is required in the model to ensure technical accuracy. The OS and PFS curves cross in the model. Put simply, this indicates that some patients within the model remain in progression-free survival, despite dying. Clearly, this is an error, and a technical impossibility, therefore a curve correction is required to amend it.</p> <p>This has been previously highlighted in our technical engagement response, however, was incorrectly implemented in the model.</p> <p>As such, alongside this response, Roche has provided an adjusted model with curve corrections. In this model, at the point the PFS extrapolation estimates meet and exceed the OS extrapolation estimates, they are capped in line with the OS extrapolation. The adjustments can be found in Column U and Column R in “Pola+R-CHP” tab and “R-CHOP”</p> | <p>Thank you for your comment. The committee acknowledged the error in the model and the company’s correction of this error (see section 3.8 of the FAD). However, based on the information provided in this comment and verbally during the second appraisal committee, the committee concluded</p>                          |

| Comment number | Type of stakeholder | Organisation name | Stakeholder comment   | NICE Response  |
|----------------|---------------------|-------------------|---|--|
|                |                     |                   | tab, respectively.  | that it did not have enough information to understand the nature of the error and what had been done to correct it. It concluded that it was unclear if the company's correction was appropriate. It also noted that when the committee's preferred assumptions were applied to the model, the inclusion or removal of the company's correction did not have an impact on decision making (see section 3.19 of the FAD). |
| 3              | Company             | Roche Products    | <p><b><u>Weight distribution in the POLARIX trial (Scenario 1, Table 3)</u></b></p> <p>The company would like to note that in the POLARIX trial the mean weight for the total patient population was 75.9 kg; the mean weight for females is 69.5 kg and the mean weight for males is 81.6 kg. The mean weight in the UK population as reported by the Health Survey for England in 2019 is 72.1 kg for females and 85.4 kg for males.</p> <p>The company would also like to note that whilst there is a small difference between the mean weight of the UK patient population and the POLARIX patient population, most DLBCL patients are expected to lose weight in the year prior to diagnosis, with a mean weight loss of around 5% (O'Brian K et al 2017). This means that the average UK female DLBCL patient weight is estimated to be 68.5 kg and the average UK male DLBCL weight is</p> | Thank you for your comment. The committee acknowledged the evidence presented in O'Brian et al. (see section 3.10 of the FAD). However, the committee concluded that this study was not generalisable to the population with DLBCL currently in the NHS. It also   |

| Comment number | Type of stakeholder | Organisation name | Stakeholder comment   | NICE Response   |
|----------------|---------------------|-------------------|---|---|
|                |                     |                   | <p>estimated to be 81.1 kg instead of the average weights 72.1 kg and 85.4 kg. Given the similarity in these figures, we believe that the mean weight in the POLARIX trial is representative of the UK patient population as the Health Survey for England in 2019 mean population weight includes all patients whether they suffer from DLBCL or not.</p> <p>In addition, in response to the ACD, we have consulted with a number of UK clinicians who have confirmed that the POLARIX weight distribution is representative of the UK DLBCL patient population.</p> <p>However, as requested by the committee, the company has provided a scenario analysis that shows the impact on the ICER if we are to utilise the weight distribution of the POLARIX Western patient population (Table 3). The company used the POLARIX Western patient population instead of the POLARIX UK patient population as only 12 UK patients' weights were recorded in the trial. Due to these small numbers, it is not possible for the company to use the UK patient population as the base case or as a scenario. Using the Western patient population accounts for 598 of the 879 patients recruited to the trial including the UK population.</p> <p>The company's scenario analysis includes the height and weight of the Western patient population in the POLARIX trial (Europe, Australia, US and Canada). The mean weight for the Western population in the POLARIX trial was 80.1 kg, 72.9 kg for females and 85.9 kg for males. Table 3 shows the ICER results when the POLARIX Western patient population is applied as opposed to the total POLARIX patient population. This change results in a 10.5% increase in the ICER compared to the base case.</p> <p>The company would like to note that the base case does not include any vial sharing and thus assumes the most conservative approach to calculating the drug acquisition cost for Polatuzumab vedotin. In the UK clinical setting, however, the availability of 30mg and 140mg Polatuzumab vedotin vials alongside NHSE dose banding, allows for minimal wastage for patients treated with Polatuzumab vedotin.</p> | <p>considered the subgroup analysis of the Western patient population from POLARIX and concluded that this was more generalisable to people who are treated for DLBCL in the NHS than the full POLARIX population. Therefore, it agreed that it was appropriate to use the weight distribution of the Western subgroup in the model.</p> <p>The committee was aware that no vial sharing was assumed in the model and that this may be a conservative approach (see section 3.10 of the FAD).</p> |
| 4              | Company             | Roche Products    | <p><b><u>PD supportive care costs (Scenario 2, Table 4 to – Table 6)</u></b></p>  | <p>Thank you for your comment. The</p>  |



| Comment number         | Type of stakeholder   | Organisation name                          | Stakeholder comment  | NICE Response |   |  |                        |   |   |   |
|------------------------|---|--|--|---------------|---|--|------------------------|---|---|---|
|                        |   |  | <p>The company acknowledges the comments made by NICE and the ERG that some of the resource frequency use in the PD state is overestimated and does not reflect what is seen in UK clinical practice.</p> <p>As a result, the company conducted a PD resource use questionnaire with 3 clinicians from different trusts to understand the resource frequency use in progressed DLBCL patients who receive 2L treatment (<b>Table 1</b>). The company would like to note that these estimates only account for second-line treatment resources for progressed patients and on average patients in the POLARIX trial received more than one subsequent treatment.</p> <p>In addition, the company wants to note that all the clinicians we discussed resource use with agreed that the resource use suggested by the ERG is too low as it is based on a previous assessment being done in Follicular Lymphoma (TA243), which is not an aggressive, high-grade (fast-growing) NHL type as DLBCL.</p> <p>The company has combined the questionnaires of the clinicians, who individually reported similar resource use units, and calculated the average resource use for both one-off costs and follow-up costs (please see below). Please note that clinicians have added additional resources such as day case, PET-CT, Transfusion, Dietician, MDT review and Psychology review which was previously not accounted for by the company.</p> <p>The procedures were added to the model alongside their respective costs, which were sourced from NHS reference costs 2019/20.</p> <p><b>Table 1: ERG and company PD frequency use</b></p> <table border="1" data-bbox="618 1137 1720 1398"> <thead> <tr> <th data-bbox="618 1137 987 1337">Procedure</th> <th data-bbox="994 1137 1352 1337">Revised company base case: Frequency use (based on clinical expert opinion) per patient</th> <th data-bbox="1359 1137 1720 1337">ERG base case (based on TA243) per patient</th> </tr> </thead> <tbody> <tr> <td data-bbox="618 1342 987 1398">Residential care (day)</td> <td data-bbox="994 1342 1352 1398">0</td> <td data-bbox="1359 1342 1720 1398">0</td> </tr> </tbody> </table> | Procedure     | Revised company base case: Frequency use (based on clinical expert opinion) per patient | ERG base case (based on TA243) per patient | Residential care (day) | 0 | 0 | <p>committee acknowledged the company's updated progressed disease supportive care costs, including the method used to calculate these costs (see section 3.11 of the FAD). Based on information provided by the company during the second appraisal committee meeting, the committee discussed that the survey the company conducted may have produced biased results. It concluded that the progressed disease supportive care costs were likely to be lower than the costs estimated by the company and that if lower costs were included in the model it would increase the ICER (see section 3.19 of the FAD).</p> |
| Procedure              | Revised company base case: Frequency use (based on clinical expert opinion) per patient | ERG base case (based on TA243) per patient |  |               |   |  |                        |   |   |   |
| Residential care (day) | 0   | 0  |  |               |   |  |                        |   |   |   |

| Comment number | Type of stakeholder | Organisation name | Stakeholder comment      |      |     | NICE Response |
|----------------|---------------------|-------------------|--------------------------|------|-----|---------------|
|                |                     |                   | Day care (day)           | 0    | 0   |               |
|                |                     |                   | Home care (day)          | 0    | 0   |               |
|                |                     |                   | Hospice (day)            | 0    | 0   |               |
|                |                     |                   | Oncologist (visit)       | 3.3  | 13  |               |
|                |                     |                   | Haematologist (visit)    | 9.8  | 0   |               |
|                |                     |                   | Radiologist (visit)      | 1.1  | 0   |               |
|                |                     |                   | Nurse (visit)            | 0    | 0   |               |
|                |                     |                   | Specialist nurse (visit) | 11.7 | 0   |               |
|                |                     |                   | GP (visit)               | 1.8  | 0   |               |
|                |                     |                   | District nurse (visit)   | 3.4  | 0   |               |
|                |                     |                   | CT scan                  | 1.5  | 3   |               |
|                |                     |                   | Inpatient day (day)      | 11.1 | 0   |               |
|                |                     |                   | Day case (day)           | 10.2 | n/a |               |
|                |                     |                   | Palliative care team     | 0    | 0   |               |
|                |                     |                   | Full blood counts        | 19.1 | 13  |               |
|                |                     |                   | LDH                      | 3.3  | 13  |               |
|                |                     |                   | Liver function           | 17.9 | 13  |               |
|                |                     |                   | Renal function           | 17.9 | 13  |               |
|                |                     |                   | Immunoglobulin           | 1.5  | 6.5 |               |

| Comment number    | Type of stakeholder | Organisation name | Stakeholder comment   | NICE Response  |     |     |        |     |     |             |     |     |           |     |     |            |     |     |                   |     |     |  |
|-------------------|---------------------|-------------------|---|--|-----|-----|--------|-----|-----|-------------|-----|-----|-----------|-----|-----|------------|-----|-----|-------------------|-----|-----|--|
|                   |                     |                   | <table border="1" data-bbox="620 217 1720 595"> <tr> <td>Calcium phosphate</td> <td>5.8</td> <td>6.5</td> </tr> <tr> <td>PET-CT</td> <td>2.2</td> <td>n/a</td> </tr> <tr> <td>Transfusion</td> <td>2.1</td> <td>n/a</td> </tr> <tr> <td>Dietician</td> <td>4.2</td> <td>n/a</td> </tr> <tr> <td>MDT review</td> <td>1.4</td> <td>n/a</td> </tr> <tr> <td>Psychology review</td> <td>0.6</td> <td>n/a</td> </tr> </table> <p data-bbox="620 635 1767 703">Table 2 shows the ICER with the new estimated frequency use by clinicians and the new company base case.</p> <p data-bbox="620 751 1800 900">The company has also included a scenario analysis in Table 4 to – Table 6 to showcase what happens to the ICER if the PD costs were varied by 10%. For Scenario 2, Table 4 shows the scenarios for the PD costs and – Table 6 shows what happens to the ICER if the PD costs were to increase or decrease by 10%.</p> | Calcium phosphate  | 5.8 | 6.5 | PET-CT | 2.2 | n/a | Transfusion | 2.1 | n/a | Dietician | 4.2 | n/a | MDT review | 1.4 | n/a | Psychology review | 0.6 | n/a |  |
| Calcium phosphate | 5.8                 | 6.5               |   |  |     |     |        |     |     |             |     |     |           |     |     |            |     |     |                   |     |     |  |
| PET-CT            | 2.2                 | n/a               |   |  |     |     |        |     |     |             |     |     |           |     |     |            |     |     |                   |     |     |  |
| Transfusion       | 2.1                 | n/a               |   |  |     |     |        |     |     |             |     |     |           |     |     |            |     |     |                   |     |     |  |
| Dietician         | 4.2                 | n/a               |   |  |     |     |        |     |     |             |     |     |           |     |     |            |     |     |                   |     |     |  |
| MDT review        | 1.4                 | n/a               |   |  |     |     |        |     |     |             |     |     |           |     |     |            |     |     |                   |     |     |  |
| Psychology review | 0.6                 | n/a               |   |  |     |     |        |     |     |             |     |     |           |     |     |            |     |     |                   |     |     |  |
| 5                 | Company             | Roche Products    | <p data-bbox="620 951 869 978"><b><u>End-of-life costs</u></b></p> <p data-bbox="620 1031 1809 1214">In response to the ACD, the company has consulted with a number of clinical experts to confirm the resource use of DLBCL patients that have progressed. One of the clinical experts noted that certain costs, such as consulting with palliative care prior to needing end-of-life treatment, are common. Therefore, these costs would be accrued by patients whilst their disease is progressing as well as at end-of-life.</p> <p data-bbox="620 1262 1809 1331">However, the company has agreed to remove the requested resources as stated by NICE and the ERG to be more conservative. The following costs have been removed and set to 0:</p> <ul data-bbox="665 1370 860 1398" style="list-style-type: none"> <li>- Residential</li> </ul>  | <p data-bbox="1845 951 2123 1350">Thank you for your comment. The committee acknowledged that the company removed the costs associated with end of life from the progressed disease supportive care costs (see section 3.11 of the FAD).</p> |     |     |        |     |     |             |     |     |           |     |     |            |     |     |                   |     |     |  |

| Comment number | Type of stakeholder | Organisation name | Stakeholder comment  | NICE Response   |
|----------------|---------------------|-------------------|--|---|
|                |                     |                   | <ul style="list-style-type: none"> <li>- Home care</li> <li>- Palliative</li> <li>- Day care</li> </ul> <p>Nevertheless, the company would like to reiterate that we feel this is a conservative approach.</p>   |   |
| 6              | Company             | Roche Products    | <p><b><u>Revised base case and conclusions:</u></b></p> <p>There is a high unmet need for DLBCL patients, and despite recent advances, prognosis for relapsed/refractory DLBCL patients remains poor with patients going on to receive 2L treatment and beyond or best supportive care. These treatments are associated with high costs, physical and psychological impact for the patient as well as increased use of NHS services.</p> <p>The best chance for getting a DLBCL patient into durable remission is in the first line setting, where R-CHOP as the current standard of care cures about 60% of patients (Sarkozy et al 2018). Polatuzumab vedotin in combination with R-CHP has demonstrated an absolute risk reduction in PFS at 24 months of 6.5% compared to R-CHOP equating to a 27% relative reduction of progression for patients, which is practice changing according to the UK clinical community.</p> <p>Roche is committed to achieving reimbursement for Polatuzumab vedotin for all eligible patients, and therefore alongside this response includes an offer to increase the PAS discount to [REDACTED] contingent on a positive recommendation in the ITT population (IPI 2–5). Roche updated base case, which can be found in Table 2.</p> <p>Nevertheless, given the unmet need, we are strongly opposed to any further delay in reimbursement. Therefore, we have also included a scenario analysis for the IPI 3–5 population at the [REDACTED] as seen in Scenario 4, Table 9.</p> <p>As acknowledged previously, current cost-effectiveness results do not truly reflect the</p> | <p>Thank you for your comment. The committee considered the cost-effectiveness estimates including the relevant PAS discounts as described in this comment.</p> <p>The committee did not consider cost-effectiveness estimates including the inclusion of CAR-T therapies as subsequent treatments. This is in line with NICE’s position statement on comparator and subsequent treatments in the Cancer Drugs Fund, which states that while comparator or subsequent treatments are recommended within</p> |

| Comment number | Type of stakeholder | Organisation name | Stakeholder comment  | NICE Response  |                 |            |              |                |          |            |              |               |            |            |            |            |            |            |            |        |        |  |
|----------------|---------------------|-------------------|--|----------------|-----------------|------------|--------------|----------------|----------|------------|--------------|---------------|------------|------------|------------|------------|------------|------------|------------|--------|--------|--|
|                |                     |                   | <p>DLBCL treatment pathway in place in the UK where CAR-T treatments have been established in the 3L+ setting. Whilst we understand NICE's positioning on the inclusion of CAR-Ts in the base case ICERs, Roche feel it is still important to highlight the potential impact on the ICER if CAR-Ts were to be included - in line with standard practice in the UK. Therefore, scenario analyses have been provided below. As seen in Tables 5 and 6, including CAR-Ts as a subsequent treatment for patients results in a decrease of 81% and 31% in the ICER compared to the company base case, the former assuming list price and the latter assuming a 50% discount for CAR-Ts.</p> <p>In conclusion, based on the revisions made by the company Polatuzumab vedotin is cost-effective, which can also be seen in the different scenario analyses presented in the tables below. The company is proposing a new discount of [REDACTED] with the revised base case in Table 2 for the ITT population (IPI 2–5). However, to prevent further delays to access if reimbursement for the full population is not possible, the company have also presented cost-effectiveness results for the subgroup of IPI 3-5 with [REDACTED]</p> <p>Table 2 highlights the revised company base case with a new proposed discount [REDACTED] for reimbursement in the ITT population (IPI 2–5).</p> <p><b>Table 2: Company revised base case at the proposed discount for the ITT population</b></p> <table border="1" data-bbox="616 1045 1816 1398"> <thead> <tr> <th data-bbox="622 1050 772 1241">Technologies</th> <th data-bbox="779 1050 902 1241">Total costs (£)</th> <th data-bbox="909 1050 1032 1241">Total LYG</th> <th data-bbox="1039 1050 1162 1241">Total QALYs</th> <th data-bbox="1169 1050 1292 1241">Inc. costs (£)</th> <th data-bbox="1299 1050 1422 1241">Inc. LYG</th> <th data-bbox="1429 1050 1552 1241">Inc. QALYs</th> <th data-bbox="1559 1050 1682 1241">ICER (£/LYG)</th> <th data-bbox="1688 1050 1816 1241">ICER (£/QALY)</th> </tr> </thead> <tbody> <tr> <td data-bbox="622 1246 772 1393">Pola+R-CHP</td> <td data-bbox="779 1246 902 1393">[REDACTED]</td> <td data-bbox="909 1246 1032 1393">[REDACTED]</td> <td data-bbox="1039 1246 1162 1393">[REDACTED]</td> <td data-bbox="1169 1246 1292 1393">[REDACTED]</td> <td data-bbox="1299 1246 1422 1393">[REDACTED]</td> <td data-bbox="1429 1246 1552 1393">[REDACTED]</td> <td data-bbox="1559 1246 1682 1393">22,334</td> <td data-bbox="1688 1246 1816 1393">26,097</td> </tr> </tbody> </table> | Technologies   | Total costs (£) | Total LYG  | Total QALYs  | Inc. costs (£) | Inc. LYG | Inc. QALYs | ICER (£/LYG) | ICER (£/QALY) | Pola+R-CHP | [REDACTED] | [REDACTED] | [REDACTED] | [REDACTED] | [REDACTED] | [REDACTED] | 22,334 | 26,097 | <p>the Cancer Drugs Fund, they should not be considered routine practice and they should not be included within the economic model used for a technology appraisal.</p> <p>When taking into account its preferred assumptions, the committee concluded that the cost-effectiveness estimates for polatuzumab vedotin with R-CHP were higher than the acceptable incremental cost effectiveness range and therefore did not recommend its use in the NHS.</p> |
| Technologies   | Total costs (£)     | Total LYG         | Total QALYs  | Inc. costs (£) | Inc. LYG        | Inc. QALYs | ICER (£/LYG) | ICER (£/QALY)  |          |            |              |               |            |            |            |            |            |            |            |        |        |  |
| Pola+R-CHP     | [REDACTED]          | [REDACTED]        | [REDACTED]   | [REDACTED]     | [REDACTED]      | [REDACTED] | 22,334       | 26,097         |          |            |              |               |            |            |            |            |            |            |            |        |        |  |

| Comment number | Type of stakeholder | Organisation name | Stakeholder comment  |                |          |            |              |               |   |   | NICE Response |                 |           |             |                |          |            |              |               |            |   |   |   |   |   |   |        |        |        |   |        |       |   |   |   |   |   |   |
|----------------|---------------------|-------------------|--|----------------|----------|------------|--------------|---------------|---|---|---------------|-----------------|-----------|-------------|----------------|----------|------------|--------------|---------------|------------|---|---|---|---|---|---|--------|--------|--------|---|--------|-------|---|---|---|---|---|---|
|                |                     |                   | R-CHOP   | █              | 11.728   | 8.829      | -            | -             | - | - | -             |                 |           |             |                |          |            |              |               |            |   |   |   |   |   |   |        |        |        |   |        |       |   |   |   |   |   |   |
| 7              | Company             | Roche Products    | <p><b>Key scenario analyses:</b></p> <ul style="list-style-type: none"> <li>Scenario 1: POLARIX Western patient population (Table 3)</li> <li>Scenario 2: Amended PD costs (Table 4 to – Table 6)</li> <li>Scenario 3: Inclusion of CAR-Ts as a subsequent therapy (Table 7 and Table 8)</li> <li>Scenario 4: IPI 3–5 population (█discount) (Table 9)</li> </ul> <p><b>Scenario 1 – Table 3: POLARIX Western patient population weight distribution</b></p> <table border="1"> <thead> <tr> <th>Technologies</th> <th>Total costs (£)</th> <th>Total LYG</th> <th>Total QALYs</th> <th>Inc. costs (£)</th> <th>Inc. LYG</th> <th>Inc. QALYs</th> <th>ICER (£/LYG)</th> <th>ICER (£/QALY)</th> </tr> </thead> <tbody> <tr> <td>Pola+R-CHP</td> <td>█</td> <td>█</td> <td>█</td> <td>█</td> <td>█</td> <td>█</td> <td>24,669</td> <td>28,826</td> </tr> <tr> <td>R-CHOP</td> <td>█</td> <td>11.728</td> <td>8.829</td> <td>-</td> <td>-</td> <td>-</td> <td>-</td> <td>-</td> </tr> </tbody> </table> <p>For Scenario 2, <b>Table 4</b> shows the scenarios for the PD costs and – <b>Table 6</b> shows what happens to the ICER if the PD costs were to increase or decrease by 10%.</p> |                |          |            |              |               |   |   | Technologies  | Total costs (£) | Total LYG | Total QALYs | Inc. costs (£) | Inc. LYG | Inc. QALYs | ICER (£/LYG) | ICER (£/QALY) | Pola+R-CHP | █ | █ | █ | █ | █ | █ | 24,669 | 28,826 | R-CHOP | █ | 11.728 | 8.829 | - | - | - | - | - | <p>Thank you for your comment. The committee considered the relevant scenario analyses presented, including the confidential discounts available for cyclophosphamide, doxorubicin, prednisolone and rituximab. It also considered the progressed disease costs presented, in the context of how these costs had been derived (see comment above).</p> <p>The committee concluded that the inclusion of CAR-T therapies as subsequent treatment and the IPI 3 to 5 population were not relevant scenarios. This was based on its decisions that CAR-T</p> |
| Technologies   | Total costs (£)     | Total LYG         | Total QALYs  | Inc. costs (£) | Inc. LYG | Inc. QALYs | ICER (£/LYG) | ICER (£/QALY) |   |   |               |                 |           |             |                |          |            |              |               |            |   |   |   |   |   |   |        |        |        |   |        |       |   |   |   |   |   |   |
| Pola+R-CHP     | █                   | █                 | █  | █              | █        | █          | 24,669       | 28,826        |   |   |               |                 |           |             |                |          |            |              |               |            |   |   |   |   |   |   |        |        |        |   |        |       |   |   |   |   |   |   |
| R-CHOP         | █                   | 11.728            | 8.829  | -              | -        | -          | -            | -             |   |   |               |                 |           |             |                |          |            |              |               |            |   |   |   |   |   |   |        |        |        |   |        |       |   |   |   |   |   |   |

| Comment number | Type of stakeholder | Organisation name | Stakeholder comment   |                              |                              |                      |                                      | NICE Response   |                   |               |
|----------------|---------------------|-------------------|---|------------------------------|------------------------------|----------------------|--------------------------------------|---|-------------------|---------------|
|                |                     |                   | <b>Scenario 2 – Table 4: PD costs base cases and PD costs scenario analyses range</b> |                              |                              |                      |                                      | <p>therapies should not be included as subsequent treatments because they are not routinely commissioned (see section 3.14 of the FAD) and that the IPI 2 to 5 subgroup was the appropriate population for decision making (see section 3.3 of the FAD).</p> <p>When taking into account its preferred assumptions and all the relevant confidential discounts, the committee concluded that the cost-effectiveness estimates for polatuzumab vedotin with R-CHP were higher than the acceptable incremental cost effectiveness range and therefore did not recommend its use in the NHS.</p> |                   |               |
|                |                     |                   | <b>ERG base case (£)</b>  |                              | <b>Company base case (£)</b> |                      | <b>Company revised base case (£)</b> |   |                   |               |
|                |                     |                   | <b>Cost</b>   | <b>Pola+R-CHP</b>            | <b>R-CHOP</b>                | <b>Pola+R-CHP</b>    | <b>R-CHOP</b>                        |   | <b>Pola+R-CHP</b> | <b>R-CHOP</b> |
|                |                     |                   | <b>One-off cost</b>   | 202.11                       | 281.27                       | 202.11               | 281.27                               |   | 2,227.99          | 2,227.99      |
|                |                     |                   | <b>Cost per cycle</b>   | 61.40                        | 61.40                        | 253.64               | 253.64                               |   | 341.40            | 341.40        |
|                |                     |                   | <b>Scenario 2 – Table 5: PD costs scenario analyses range</b>                         |                              |                              |                      |                                      |   |                   |               |
|                |                     |                   | <b>No.</b>  | <b>Parameter</b>             | <b>Base Case</b>             | <b>Scenario</b>      |                                      |   |                   |               |
|                |                     |                   | 1   | PD one-off costs             | 2,227.99                     | 2,005.19             |                                      |   |                   |               |
|                |                     |                   |   |                              |                              | 2,450.79             |                                      |   |                   |               |
|                |                     |                   | 2   | PD follow-up costs           | 341.40                       | 307.26               |                                      |   |                   |               |
|                |                     |                   |   |                              |                              | 375.54               |                                      |   |                   |               |
|                |                     |                   | <b>Scenario 2 – Table 6: PD cost scenario analysis results</b>                        |                              |                              |                      |                                      |   |                   |               |
|                |                     |                   | <b>Parameter modified</b>   | <b>Incremental costs (£)</b> | <b>Incremental QALYs</b>     | <b>ICER (£/QALY)</b> | <b>% change from base case ICER</b>  |   |                   |               |

| Comment number | Type of stakeholder | Organisation name | Stakeholder comment   |                        |                  |                    |                       | NICE Response   |                   |                     |                      |
|----------------|---------------------|-------------------|---|------------------------|------------------|--------------------|-----------------------|-----------------|-------------------|---------------------|----------------------|
|                |                     |                   | <b>Base case</b>  |                        | 26,097           |                    |                       |                 |                   |                     |                      |
|                |                     |                   | <b>PD costs</b>   |                        |                  |                    |                       |                 |                   |                     |                      |
|                |                     |                   | PD one-off costs, -10%  | ■                      | ■                | 26,143             | 0.18%                 |                 |                   |                     |                      |
|                |                     |                   | PD one-off costs, +10%  | ■                      | ■                | 26,052             | -0.17%                |                 |                   |                     |                      |
|                |                     |                   | PD follow-up costs, -10%  | ■                      | ■                | 29,122             | 11.59%                |                 |                   |                     |                      |
|                |                     |                   | PD follow-up costs, +10%  | ■                      | ■                | 23,073             | -11.59%               |                 |                   |                     |                      |
|                |                     |                   | <b>Scenario 3 – Table 7: Inclusion of CAR-Ts (list price) as a subsequent treatment</b>   |                        |                  |                    |                       |                 |                   |                     |                      |
|                |                     |                   | <b>Technologies</b>   | <b>Total costs (£)</b> | <b>Total LYG</b> | <b>Total QALYs</b> | <b>Inc. costs (£)</b> | <b>Inc. LYG</b> | <b>Inc. QALYs</b> | <b>ICER (£/LYG)</b> | <b>ICER (£/QALY)</b> |
|                |                     |                   | Pola+R-CHP  | ■                      | ■                | ■                  | ■                     | ■               | ■                 | 4,247               | 4,962                |
|                |                     |                   | R-CHOP  | ■                      | 11.728           | 8.829              | -                     | -               | -                 | -                   | -                    |
|                |                     |                   | For Scenario 3, as seen in <b>Table 8</b> , including CAR-Ts as a subsequent treatment for patients results in a decrease of 31% in the ICER compared to the base case (assuming a 50% discount). |                        |                  |                    |                       |                 |                   |                     |                      |



| Comment number | Type of stakeholder | Organisation name | Stakeholder comment  |                |          |            |              |               | NICE Response |                 |           |             |                |          |            |              |               |            |   |   |   |   |   |   |        |        |        |   |        |       |   |   |   |   |   |              |                 |           |             |                |          |            |              |               |            |   |   |   |   |   |   |        |        |        |   |        |       |   |   |   |   |   |  |
|----------------|---------------------|-------------------|--|----------------|----------|------------|--------------|---------------|---------------|-----------------|-----------|-------------|----------------|----------|------------|--------------|---------------|------------|---|---|---|---|---|---|--------|--------|--------|---|--------|-------|---|---|---|---|---|--------------|-----------------|-----------|-------------|----------------|----------|------------|--------------|---------------|------------|---|---|---|---|---|---|--------|--------|--------|---|--------|-------|---|---|---|---|---|--|
|                |                     |                   | <p><b>Scenario 3 – Table 8: Inclusion of CAR-Ts (assuming a 50% discount) as a subsequent treatment</b></p> <table border="1"> <thead> <tr> <th>Technologies</th> <th>Total costs (£)</th> <th>Total LYG</th> <th>Total QALYs</th> <th>Inc. costs (£)</th> <th>Inc. LYG</th> <th>Inc. QALYs</th> <th>ICER (£/LYG)</th> <th>ICER (£/QALY)</th> </tr> </thead> <tbody> <tr> <td>Pola+R-CHP</td> <td>█</td> <td>█</td> <td>█</td> <td>█</td> <td>█</td> <td>█</td> <td>15,494</td> <td>18,105</td> </tr> <tr> <td>R-CHOP</td> <td>█</td> <td>11.728</td> <td>8.829</td> <td>-</td> <td>-</td> <td>-</td> <td>-</td> <td>-</td> </tr> </tbody> </table> <p><b>Scenario 4 – Table 9: IPI 3-5 patient population results with a current discount █</b></p> <table border="1"> <thead> <tr> <th>Technologies</th> <th>Total costs (£)</th> <th>Total LYG</th> <th>Total QALYs</th> <th>Inc. costs (£)</th> <th>Inc. LYG</th> <th>Inc. QALYs</th> <th>ICER (£/LYG)</th> <th>ICER (£/QALY)</th> </tr> </thead> <tbody> <tr> <td>Pola+R-CHP</td> <td>█</td> <td>█</td> <td>█</td> <td>█</td> <td>█</td> <td>█</td> <td>13,790</td> <td>16,830</td> </tr> <tr> <td>R-CHOP</td> <td>█</td> <td>10.889</td> <td>8.230</td> <td>-</td> <td>-</td> <td>-</td> <td>-</td> <td>-</td> </tr> </tbody> </table> |                |          |            |              |               | Technologies  | Total costs (£) | Total LYG | Total QALYs | Inc. costs (£) | Inc. LYG | Inc. QALYs | ICER (£/LYG) | ICER (£/QALY) | Pola+R-CHP | █ | █ | █ | █ | █ | █ | 15,494 | 18,105 | R-CHOP | █ | 11.728 | 8.829 | - | - | - | - | - | Technologies | Total costs (£) | Total LYG | Total QALYs | Inc. costs (£) | Inc. LYG | Inc. QALYs | ICER (£/LYG) | ICER (£/QALY) | Pola+R-CHP | █ | █ | █ | █ | █ | █ | 13,790 | 16,830 | R-CHOP | █ | 10.889 | 8.230 | - | - | - | - | - |  |
| Technologies   | Total costs (£)     | Total LYG         | Total QALYs  | Inc. costs (£) | Inc. LYG | Inc. QALYs | ICER (£/LYG) | ICER (£/QALY) |               |                 |           |             |                |          |            |              |               |            |   |   |   |   |   |   |        |        |        |   |        |       |   |   |   |   |   |              |                 |           |             |                |          |            |              |               |            |   |   |   |   |   |   |        |        |        |   |        |       |   |   |   |   |   |  |
| Pola+R-CHP     | █                   | █                 | █  | █              | █        | █          | 15,494       | 18,105        |               |                 |           |             |                |          |            |              |               |            |   |   |   |   |   |   |        |        |        |   |        |       |   |   |   |   |   |              |                 |           |             |                |          |            |              |               |            |   |   |   |   |   |   |        |        |        |   |        |       |   |   |   |   |   |  |
| R-CHOP         | █                   | 11.728            | 8.829  | -              | -        | -          | -            | -             |               |                 |           |             |                |          |            |              |               |            |   |   |   |   |   |   |        |        |        |   |        |       |   |   |   |   |   |              |                 |           |             |                |          |            |              |               |            |   |   |   |   |   |   |        |        |        |   |        |       |   |   |   |   |   |  |
| Technologies   | Total costs (£)     | Total LYG         | Total QALYs  | Inc. costs (£) | Inc. LYG | Inc. QALYs | ICER (£/LYG) | ICER (£/QALY) |               |                 |           |             |                |          |            |              |               |            |   |   |   |   |   |   |        |        |        |   |        |       |   |   |   |   |   |              |                 |           |             |                |          |            |              |               |            |   |   |   |   |   |   |        |        |        |   |        |       |   |   |   |   |   |  |
| Pola+R-CHP     | █                   | █                 | █  | █              | █        | █          | 13,790       | 16,830        |               |                 |           |             |                |          |            |              |               |            |   |   |   |   |   |   |        |        |        |   |        |       |   |   |   |   |   |              |                 |           |             |                |          |            |              |               |            |   |   |   |   |   |   |        |        |        |   |        |       |   |   |   |   |   |  |
| R-CHOP         | █                   | 10.889            | 8.230  | -              | -        | -          | -            | -             |               |                 |           |             |                |          |            |              |               |            |   |   |   |   |   |   |        |        |        |   |        |       |   |   |   |   |   |              |                 |           |             |                |          |            |              |               |            |   |   |   |   |   |   |        |        |        |   |        |       |   |   |   |   |   |  |



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

**Consultation on the appraisal consultation document – deadline for comments 5pm on 19 October 2022. Please submit via NICE Docs.**

|   |   |
|---|---|
| <b>Organisation name – Stakeholder or respondent</b><br>(if you are responding as an individual rather than a registered stakeholder please leave blank): | <b>Roche Products Ltd.</b>  |
| <b>Disclosure</b><br>Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.                             | n/a   |
| <b>Name of commentator person completing form:</b>  | Katharina Wodenitscharow (Health Economist, Health Economics, Reimbursement and Outcomes) |

| <b>Comment number</b> | <b>Comments</b>   |
|-----------------------|---|
| <b>1</b>              | <p><b><u>Introduction</u></b></p> <p>Roche appreciates the opportunity to comment on the NICE Appraisal Consultation Document (ACD) for Polatuzumab vedotin in combination for untreated diffuse large B-cell lymphoma [ID3901].</p> <p>Roche is dedicated to finding solutions in collaboration with NICE for the concerns raised within the ACD such that Polatuzumab vedotin may be considered for a positive recommendation for use within the NHS. There is a high unmet need for patients with DLBCL. [REDACTED]</p> <p>Rationale is provided in the comments below for instances where Roche would like to encourage the Committee to reconsider its conclusions. Roche has also resubmitted an amended model to reflect the changes suggested in the ACD.</p> <p>This response covers the following key points, addressing the concerns raised in the ACD:</p> <ul style="list-style-type: none"> <li>- Correction of the curves in the model</li> <li>- Weight distribution of the POLARIX patients</li> <li>- PD supportive care costs</li> <li>- End-of-life costs</li> <li>- Scenario: Inclusion of CAR-Ts</li> <li>- Scenario: Cost-effectiveness results in the IPI 3–5 population</li> </ul> <p>The revisions outlined below change the incremental cost-effectiveness ratio (ICER) to £26,097 for the IPI 2–5 population.</p> |

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|                 |  |
|-----------------|--|
|                 | <p>As noted above, Roche feels strongly that Polatuzumab vedotin can address a significant unmet need for an effective treatment for DLBCL patients in the UK, and wishes to note that the ICER presented herein - following the revisions requested by the committee - is cost-effective. Roche is committed to enabling people with DLBCL to gain access to Polatuzumab vedotin and is open and willing to continue collaboration as needed with NICE and NHS England to make this happen.</p>   |
| <p><b>2</b></p> | <p><b><u>Correction of the curves in the model</u></b></p> <p>The company would like to re-clarify to the committee and the ERG that a curve correction is required in the model to ensure technical accuracy. The OS and PFS curves cross in the model. Put simply, this indicates that some patients within the model remain in progression-free survival, despite dying. Clearly, this is an error, and a technical impossibility, therefore a curve correction is required to amend it.</p> <p>This has been previously highlighted in our technical engagement response, however, was incorrectly implemented in the model.</p> <p>As such, alongside this response, Roche has provided an adjusted model with curve corrections. In this model, at the point the PFS extrapolation estimates meet and exceed the OS extrapolation estimates, they are capped in line with the OS extrapolation. The adjustments can be found in Column U and Column R in “Pola+R-CHP” tab and “R-CHOP” tab, respectively.</p>  |
| <p><b>3</b></p> | <p><b><u>Weight distribution in the POLARIX trial (Scenario 1, Table 3)</u></b></p> <p>The company would like to note that in the POLARIX trial the mean weight for the total patient population was 75.9 kg; the mean weight for females is 69.5 kg and the mean weight for males is 81.6 kg. The mean weight in the UK population as reported by the Health Survey for England in 2019 is 72.1 kg for females and 85.4 kg for males.</p> <p>The company would also like to note that whilst there is a small difference between the mean weight of the UK patient population and the POLARIX patient population, [REDACTED]</p> <p>[REDACTED]</p> <p>[REDACTED] This means that the average UK female DLBCL patient weight is estimated to be 68.5 kg and the average UK male DLBCL weight is estimated to be 81.1 kg instead of the average weights 72.1 kg and 85.4 kg. Given the similarity in these figures, [REDACTED]</p> <p>[REDACTED]</p> <p>[REDACTED]</p> <p>[REDACTED]</p> <p>In addition, in response to the ACD, we have consulted with a number of UK clinicians who have confirmed that the POLARIX weight distribution is representative of the UK DLBCL patient population.</p> |

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|                 |   |
|-----------------|---|
|                 | <p>However, as requested by the committee, the company has provided a scenario analysis that shows the impact on the ICER if we are to utilise the weight distribution of the POLARIX Western patient population (Table 3). The company used the POLARIX Western patient population instead of the POLARIX UK patient population as only 12 UK patients' weights were recorded in the trial. Due to these small numbers, it is not possible for the company to use the UK patient population as the base case or as a scenario. Using the Western patient population accounts for 598 of the 879 patients recruited to the trial including the UK population.</p> <p>The company's scenario analysis includes the height and weight of the Western patient population in the POLARIX trial (Europe, Australia, US and Canada). The mean weight for the Western population in the POLARIX trial was 80.1 kg, 72.9 kg for females and 85.9 kg for males. Table 3 shows the ICER results when the POLARIX Western patient population is applied as opposed to the total POLARIX patient population. This change results in a 10.5% increase in the ICER compared to the base case.</p> <p>The company would like to note that the base case does not include any vial sharing and thus assumes the most conservative approach to calculating the drug acquisition cost for Polatuzumab vedotin. In the UK clinical setting, however, the availability of 30mg and 140mg Polatuzumab vedotin vials alongside NHSE dose banding, allows for minimal wastage for patients treated with Polatuzumab vedotin.</p> |
| <p><b>4</b></p> | <p><b><u>PD supportive care costs (Scenario 2, Table 4 to – Table 6)</u></b></p> <p>The company acknowledges the comments made by NICE and the ERG that some of the resource frequency use in the PD state is overestimated and does not reflect what is seen in UK clinical practice.</p> <p>As a result, the company conducted a PD resource use questionnaire with 3 clinicians from different trusts to understand the resource frequency use in progressed DLBCL patients who receive 2L treatment (<b>Table 1</b>). The company would like to note that these estimates only account for second-line treatment resources for progressed patients and on average patients in the POLARIX trial received more than one subsequent treatment.</p> <p>In addition, the company wants to note that all the clinicians we discussed resource use with agreed that the resource use suggested by the ERG is too low as it is based on a previous assessment being done in Follicular Lymphoma (TA243), which is not an aggressive, high-grade (fast-growing) NHL type as DLBCL.</p> <p>The company has combined the questionnaires of the clinicians, who individually reported similar resource use units, and calculated the average resource use for both one-off costs and follow-up costs (please see below). Please note that clinicians have added additional resources such as day case, PET-CT, Transfusion, Dietician, MDT review and Psychology review which was previously not accounted for by the company.</p>   |

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The procedures were added to the model alongside their respective costs, which were sourced from NHS reference costs 2019/20.

**Table 1: ERG and company PD frequency use**

| <b>Procedure</b>         | <b>Revised company base case: Frequency use (based on clinical expert opinion) per patient</b> | <b>ERG base case (based on TA243) per patient</b> |
|--------------------------|--|---|
| Residential care (day)   | 0  | 0   |
| Day care (day)           | 0  | 0   |
| Home care (day)          | 0  | 0   |
| Hospice (day)            | 0  | 0   |
| Oncologist (visit)       | 3.3  | 13  |
| Haematologist (visit)    | 9.8  | 0   |
| Radiologist (visit)      | 1.1  | 0   |
| Nurse (visit)            | 0  | 0   |
| Specialist nurse (visit) | 11.7   | 0   |
| GP (visit)               | 1.8  | 0   |
| District nurse (visit)   | 3.4  | 0   |
| CT scan                  | 1.5  | 3   |
| Inpatient day (day)      | 11.1   | 0   |
| Day case (day)           | 10.2   | n/a   |
| Palliative care team     | 0  | 0   |
| Full blood counts        | 19.1   | 13  |
| LDH                      | 3.3  | 13  |
| Liver function           | 17.9   | 13  |
| Renal function           | 17.9   | 13  |
| Immunoglobulin           | 1.5  | 6.5   |
| Calcium phosphate        | 5.8  | 6.5   |

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|                   |  |        |     |     |             |     |     |           |     |     |            |     |     |                   |     |     |  |  |  |
|-------------------|--|--------|-----|-----|-------------|-----|-----|-----------|-----|-----|------------|-----|-----|-------------------|-----|-----|--|--|--|
|                   | <table border="1"> <tr> <td>PET-CT</td> <td>2.2</td> <td>n/a</td> </tr> <tr> <td>Transfusion</td> <td>2.1</td> <td>n/a</td> </tr> <tr> <td>Dietician</td> <td>4.2</td> <td>n/a</td> </tr> <tr> <td>MDT review</td> <td>1.4</td> <td>n/a</td> </tr> <tr> <td>Psychology review</td> <td>0.6</td> <td>n/a</td> </tr> </table>  | PET-CT | 2.2 | n/a | Transfusion | 2.1 | n/a | Dietician | 4.2 | n/a | MDT review | 1.4 | n/a | Psychology review | 0.6 | n/a |  |  | <p>Table 2 shows the ICER with the new estimated frequency use by clinicians and the new company base case.</p> <p>The company has also included a scenario analysis in Table 4 to – Table 6 to showcase what happens to the ICER if the PD costs were varied by 10%. For Scenario 2, Table 4 shows the scenarios for the PD costs and – Table 6 shows what happens to the ICER if the PD costs were to increase or decrease by 10%.</p> |
| PET-CT            | 2.2  | n/a    |     |     |             |     |     |           |     |     |            |     |     |                   |     |     |  |  |  |
| Transfusion       | 2.1  | n/a    |     |     |             |     |     |           |     |     |            |     |     |                   |     |     |  |  |  |
| Dietician         | 4.2  | n/a    |     |     |             |     |     |           |     |     |            |     |     |                   |     |     |  |  |  |
| MDT review        | 1.4  | n/a    |     |     |             |     |     |           |     |     |            |     |     |                   |     |     |  |  |  |
| Psychology review | 0.6  | n/a    |     |     |             |     |     |           |     |     |            |     |     |                   |     |     |  |  |  |
| <p><b>5</b></p>   | <p><b><u>End-of-life costs</u></b></p> <p>In response to the ACD, the company has consulted with a number of clinical experts to confirm the resource use of DLBCL patients that have progressed. One of the clinical experts noted that certain costs, such as consulting with palliative care prior to needing end-of-life treatment, are common. Therefore, these costs would be accrued by patients whilst their disease is progressing as well as at end-of-life.</p> <p>However, the company has agreed to remove the requested resources as stated by NICE and the ERG to be more conservative. The following costs have been removed and set to 0:</p> <ul style="list-style-type: none"> <li>- Residential</li> <li>- Home care</li> <li>- Palliative</li> <li>- Day care</li> </ul> <p>Nevertheless, the company would like to reiterate that we feel this is a conservative approach.</p> |        |     |     |             |     |     |           |     |     |            |     |     |                   |     |     |  |  |  |
| <p><b>6</b></p>   | <p><b><u>Revised base case and conclusions:</u></b></p> <p>There is a high unmet need for DLBCL patients, and [REDACTED]<br/> [REDACTED]<br/> [REDACTED] physical and psychological impact for the patient as well as increased use of NHS services.</p> <p>[REDACTED]<br/> [REDACTED]</p>   |        |     |     |             |     |     |           |     |     |            |     |     |                   |     |     |  |  |  |

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

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[REDACTED]

Roche is committed to achieving reimbursement for Polatuzumab vedotin for all eligible patients, and therefore alongside this response includes an offer to increase the PAS discount to [REDACTED], contingent on a positive recommendation in the ITT population (IPI 2–5). Roche updated base case, which can be found in Table 2.

Nevertheless, given the unmet need, we are strongly opposed to any further delay in reimbursement. Therefore, we have also included a scenario analysis for the IPI 3–5 population at the [REDACTED] [REDACTED] [REDACTED] Table 9.

As acknowledged previously, current cost-effectiveness results do not truly reflect the DLBCL treatment pathway in place in the UK where CAR-T treatments have been established in the 3L+ setting. Whilst we understand NICE’s positioning on the inclusion of CAR-Ts in the base case ICERs, Roche feel it is still important to highlight the potential impact on the ICER if CAR-Ts were to be included - in line with standard practice in the UK. Therefore, scenario analyses have been provided below. As seen in Tables 5 and 6, including CAR-Ts as a subsequent treatment for patients results in a decrease of 81% and 31% in the ICER compared to the company base case, the former assuming list price and the latter assuming a 50% discount for CAR-Ts.

In conclusion, based on the revisions made by the company Polatuzumab vedotin is cost-effective, which can also be seen in the different scenario analyses presented in the tables below. The company is proposing a new discount of [REDACTED] with the revised base case in Table 2 for the ITT population (IPI 2–5). However, to prevent further delays to access if reimbursement for the full population is not possible, the company have also presented cost-effectiveness results for the subgroup of IPI 3-5 with [REDACTED]

Table 2 highlights the revised company base case with a new proposed discount [REDACTED] for reimbursement in the ITT population (IPI 2–5).

**Table 2: Company revised base case at the proposed discount for the ITT population**

| Technologies | Total costs (£) | Total LYG | Total QALYs | Inc. costs (£) | Inc. LYG | Inc. QALYs | ICER (£/LYG) | ICER (£/QALY) |
|--------------|-----------------|-----------|-------------|----------------|----------|------------|--------------|---------------|
|              |                 |           |             |                |          |            |              |               |



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|  |                   |        |        |        |        |        |        |        |        |
|--|-------------------|--------|--------|--------|--------|--------|--------|--------|--------|
|  | <b>Pola+R-CHP</b> | ██████ | ██████ | ██████ | ██████ | ██████ | ██████ | 22,334 | 26,097 |
|  | <b>R-CHOP</b>     | ██████ | 11.728 | 8.829  | -      | -      | -      | -      | -      |

**7** **Key scenario analyses:**

- Scenario 1: POLARIX Western patient population (Table 3)
- Scenario 2: Amended PD costs (Table 4 to – Table 6)
- Scenario 3: Inclusion of CAR-Ts as a subsequent therapy (Table 7 and Table 8)
- Scenario 4: IPI 3–5 population (██████ discount) (Table 9)

**Scenario 1 – Table 3: POLARIX Western patient population weight distribution**

| Technologies | Total costs (£) | Total LYG | Total QALYs | Inc. costs (£) | Inc. LYG | Inc. QALYs | ICER (£/LYG) | ICER (£/QALY) |
|--------------|-----------------|-----------|-------------|----------------|----------|------------|--------------|---------------|
| Pola+R-CHP   | ██████          | ██████    | ██████      | ██████         | ██████   | ██████     | 24,669       | 28,826        |
| R-CHOP       | ██████          | 11.728    | 8.829       | -              | -        | -          | -            | -             |

For Scenario 2, **Table 4** shows the scenarios for the PD costs and – **Table 6** shows what happens to the ICER if the PD costs were to increase or decrease by 10%.

**Scenario 2 – Table 4: PD costs base cases and PD costs scenario analyses range**

| Cost                  | ERG base case (£) |        | Company base case (£) |        | Company revised base case (£) |          |
|-----------------------|-------------------|--------|-----------------------|--------|-------------------------------|----------|
|                       | Pola+R-CHP        | R-CHOP | Pola+R-CHP            | R-CHOP | Pola+R-CHP                    | R-CHOP   |
| <b>One-off cost</b>   | 202.11            | 281.27 | 202.11                | 281.27 | 2,227.99                      | 2,227.99 |
| <b>Cost per cycle</b> | 61.40             | 61.40  | 253.64                | 253.64 | 341.40                        | 341.40   |

**Scenario 2 – Table 5: PD costs scenario analyses range**

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| No. | Parameter          | Base Case | Scenario |
|-----|--------------------|-----------|----------|
| 1   | PD one-off costs   | 2,227.99  | 2,005.19 |
|     |                    |           | 2,450.79 |
| 2   | PD follow-up costs | 341.40    | 307.26   |
|     |                    |           | 375.54   |

**Scenario 2 – Table 6: PD cost scenario analysis results**

| Parameter modified       | Incremental costs (£) | Incremental QALYs | ICER (£/QALY) | % change from base case ICER |
|--------------------------|-----------------------|-------------------|---------------|------------------------------|
| <b>Base case</b>         | 26,097                |                   |               |                              |
| <b>PD costs</b>          |                       |                   |               |                              |
| PD one-off costs, -10%   | ██████                | ██████            | 26,143        | 0.18%                        |
| PD one-off costs, +10%   | ██████                | ██████            | 26,052        | -0.17%                       |
| PD follow-up costs, -10% | ██████                | ██████            | 29,122        | 11.59%                       |
| PD follow-up costs, +10% | ██████                | ██████            | 23,073        | -11.59%                      |

**Scenario 3 – Table 7: Inclusion of CAR-Ts (list price) as a subsequent treatment**

| Technologies | Total costs (£) | Total LYG | Total QALYs | Inc. costs (£) | Inc. LYG | Inc. QALYs | ICER (£/LYG) | ICER (£/QALY) |
|--------------|-----------------|-----------|-------------|----------------|----------|------------|--------------|---------------|
| Pola+R-CHP   | ██████          | ██████    | ██████      | ██████         | ██████   | ██████     | 4,247        | 4,962         |
| R-CHOP       | ██████          | 11.728    | 8.829       | -              | -        | -          | -            | -             |

For Scenario 3, as seen in **Table 8**, including CAR-Ts as a subsequent treatment for patients results in a decrease of 31% in the ICER compared to the base case (assuming a 50%

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discount).

**Scenario 3 – Table 8: Inclusion of CAR-Ts (assuming a 50% discount) as a subsequent treatment**

| Technologies | Total costs (£) | Total LYG | Total QALYs | Inc. costs (£) | Inc. LYG | Inc. QALYs | ICER (£/LYG) | ICER (£/QALY) |
|--------------|-----------------|-----------|-------------|----------------|----------|------------|--------------|---------------|
| Pola+R-CHP   | ██████          | ██████    | ██████      | ██████         | ██████   | ██████     | 15,494       | 18,105        |
| R-CHOP       | ██████          | 11.728    | 8.829       | -              | -        | -          | -            | -             |

**Scenario 4 – Table 9: IPI 3-5 patient population results with a current discount**

██████

| Technologies | Total costs (£) | Total LYG | Total QALYs | Inc. costs (£) | Inc. LYG | Inc. QALYs | ICER (£/LYG) | ICER (£/QALY) |
|--------------|-----------------|-----------|-------------|----------------|----------|------------|--------------|---------------|
| Pola+R-CHP   | ██████          | ██████    | ██████      | ██████         | ██████   | ██████     | 13,790       | 16,830        |
| R-CHOP       | ██████          | 10.889    | 8.230       | -              | -        | -          | -            | -             |

**References:**

O’Brian, Katuscia, et al. “Short- and Long-Term Weight Changes among United States Veterans with Diffuse Large B-Cell Lymphoma Treated with Chop Chemotherapy.” *Leukemia & Lymphoma*, vol. 57, no. 2, 2015, pp. 313–319., <https://doi.org/10.3109/10428194.2015.1056183>.

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

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

Evidence Review Group's summary and critique of the company's  
response to the appraisal consultation document

|                          |   |
|--------------------------|---|
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### 1. Introduction

This document is the Evidence Review Group’s (ERG) summary and critique of the response by the company, Roche, to the issues raised by the company in response to the appraisal consultation document. The ERG received the company’s response on 20/10/22.

The company’s ACM response form contains the following information:

- A written response to each of the four issues.
- A set of revised cost-effectiveness results, incorporating:
  - An updated confidential Patient Access Scheme (PAS) price discount for polatuzumab

- Additional evidence and/or analyses provided by the company in response to the ACD.
- An updated version of the company's economic model accompanies the response form.

In this report we present the following:

- Our critique of the company's response to each of the four issues raised by the company (Section 2)
- A validation of the results of the company's updated cost-effectiveness analysis, and the results of ERG scenario analyses (Section 3)

## **2. Critique of the company's response to key issues for ACD**

### **2.1 Issue 1 – Correction of the curves in the model**

The company stated that a curve correction was required to ensure technical accuracy. They state that the OS and PFS curves cross in the model and this indicates that some patients within the model remain in the PFS despite dying.

The ERG has investigated the correction. We note that the error referred to is that the probability of death is higher than the probability of progression, rather than the OS and PFS curves crossing. However, we consider that the correction produces counter-intuitive results when changes are made to overall survival. For example, we decreased overall survival and this produced an increase in PFS which is counter-intuitive. For this reason, we prefer to not use this correction.

### **2.2 Issue 2 – Weight distribution in the POLARIX trial**

The ACD queried whether the use of patient body weight distributions from the POLARIX trial were generalisable to NHS clinical practice, given that mean patient weight in the POLARIX trial was lower than that based on figures from the 2019 NHS Health Survey for England overweight and obesity in adults and children report. The ACD therefore wanted to see patient weight distributions from the UK sites of the POLARIX trial, as this could influence the number of vials used and therefore cost.

In response to this query, the company provided a scenario analysis based on the POLARIX Western population (Europe, Australia, USA, Canada,; n=598 patients), which the ERG

considers appropriate given the company reported only 12 UK patients in the POLARIX trial had data recorded for weight.

The company also note in their response that the difference in mean patient body weight in the POLARIX trial versus that based on data from the 2019 NHS Health Survey for England report, could be explained by expected weight loss in patients with DLBCL in the year prior to diagnosis and cite a study by Brian et al., 2017. In this cohort study of predominately male (97%) US veterans, there was a mean weight loss of approximately 5% in the year prior to a diagnosis of DLBCL. The ERG agree that weight loss can be a symptom of DLBCL (e.g. Cancer Research UK states that losing a lot of weight (more than 10% of total body weight) is a general symptom of DLBCL).

The company also report mean body weight values from the 2019 Health Survey for England 2019 adjusted for a 5% weight loss i.e. to represent the average UK DLBCL patient weight (see Table 1). The ERG note that the body weights of the Western population of the POLARIX trial are similar to those of the 2019 NHS Health Survey for England, while 2019 NHS Health Survey for England figures, adjusted for an approximate 5% weight loss are similar to those of the whole POLARIX trial (see Table 1)

**Table 1 Mean body weight in kg by sex**

| <b>Source</b>  | <b>Female mean body weight (kg)</b> | <b>Male mean body weight (kg)</b> |
|--|-------------------------------------|-----------------------------------|
| POLARIX trial  | 69.5                                | 81.6                              |
| POLARIX trial (Western population only)                            | 72.9                                | 85.9                              |
| NHS Health Survey for England 2019                                 | 72.1                                | 85.4                              |
| NHS Health Survey for England 2019 - adjusted for ≈ 5% weight loss | 68.5                                | 81.1                              |

### **2.3 Issue 3 – PD supportive care costs**

In order to estimate PD supportive care costs, the company conducted a PD response use questionnaire with three clinicians. The combined resource use is shown in

Table 2 of the company response to ACD document. The follow-up costs are 15% lower than their original estimates. The one-off costs are much higher than in the original estimates due to higher proportions of patients receiving investigations such as PET-CT scans. The



company use these PD supportive care costs in their revised base case and scenario varying the resource costs by +/-10%.

**Table 2 Company revised costs for PD resource use**

| Parameter   | Original estimates | Revised estimate |
|---|--------------------|------------------|
| PD One-off costs  | £385.10*           | £2,227.99        |
| Follow-up costs   | £398.47            | £341.40          |
| *Estimate for Pola+RCHP; estimate for RCHOP is £452.50. |                    |                  |

The ERG welcomes the company's survey of resources used in progressed disease. We raise the following concerns:

- 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<sup>1</sup> (Polatuzumab vedotin with rituximab and bendamustine for treating relapsed or refractory diffuse large B-cell lymphoma). Other patients may have exhausted their treatment options and may receive palliative care only.
- The mean time spent in the PD state is higher for patients in the RCHOP arm than for those in Pola+R-CHP arm, so these patients have higher PD costs. In practice the length of time patients receive intensive treatment in both arms may be similar.
- The total costs remain considerably higher than reported in Wang et al,<sup>2</sup> who conducted real world cost modelling of newly diagnosed patients with DLBCL in the UK.

We attempt to estimate the duration that patients would receive treatment in the progressed disease health state. We note that the median time to progression for patients with relapsed / refractory DLBCL disease was 6.7 months with treatment with bendamustine plus rituximab (ie. mean time to progression of 9.7 months). {Ohmachi, 2013 #128} Assuming the same time to progression for second and third line treatments, ■ subsequent treatments for Pola+R-CHP and ■ subsequent treatments for RCHOP gives total subsequent treatment duration of ■ months and ■ months respectively. Time for the PD health state in the model is 3.2 years for Pola+R-CHP and 4 years for R-CHOP. We estimate that patients would be on subsequent treatment for ■ of the time they are in the PD state for Pola-RCHP and ■ for R-CHOP. We, therefore, estimate that the PD costs should be 50% of the company's estimate for both treatment arms (£171.70). We conduct scenarios assuming that PD costs are reduced by either 25% or 50% (Section 3.1).

## 2.4 Issue 4 – End of life costs

In response to the ACD, the company has removed the resource use associated with end-of-life care (residential, home care, palliative and day care). The company noted there may still be some additional resource use such as consulting with palliative care prior to needing end-of-life treatment.

The ERG welcomes the change in resource use costs to avoid double counting for end-of-life resource use. The ERG raised this issue in their technical engagement response.

## 2.5 Company revised base case and conclusions

The company has made the following changes to their base case in light of the comments in the ACD:

- Increase in the PAS discount from [REDACTED] to [REDACTED].
- Remove health resource costs associated with end-of-life.
- Correction of the PFS curves.

The revised company base case is shown in Table 2 of the company ACD response and show a revised ICER of £26,097 per QALY.

## 2.6 Company scenario analyses

The company provides four scenarios as follows:

- Scenario 1: POLARIX Western patient population (Company response **Error! Reference source not found.**)
- Scenario 2: Amended PD costs (Company response **Error! Reference source not found.** to **Error! Reference source not found.**)
- Scenario 3: Inclusion of CAR-Ts as a subsequent therapy (Company response **Error! Reference source not found.** and **Error! Reference source not found.**)
- Scenario 4: IPI 3–5 population ([REDACTED] discount) (Company response **Error! Reference source not found.**)

The results of the scenarios are summarised in Table 3 below.

**Table 3 Company scenarios using revised company base case**

| <b>Scenario</b>  | <b>ICER (£/QALY)</b> |
|--|----------------------|
| 1. POLARIX Western patient population weight distribution                  | £28,826              |
| 2. PD follow-up costs, -10%  | £29,122              |
| 3. Inclusion of CAR-Ts (assuming a 50% discount) as a subsequent treatment | £18,105              |
| 4. IPI 3-5 patient population results with a current discount (██████)     | £16,830              |

The ERG has checked the company analyses and scenario analyses. We have not been able to replicate the IPI 3-5 patient population scenario. The company has not provided guidance on how to run this scenario.

## **2.8 Other issues raised by the ERG – extrapolation of OS**

The ERG would also like to raise concerns with the company's approach to extrapolation of OS. The company's approach is to assume that treatment benefits for OS continue indefinitely. However, in the POLARIX trial there was a very small difference in OS favouring Pola+R-CHP with a wide confidence interval indicating no statistically significant difference (HR 0.94 CI 0.65 to 1.37). We note:

- OS is a big driver of the cost-effectiveness, with most of the QALY gains related to OS (>75%).
- There is no evidence of a difference in treatment effect for OS as the results are not statistically significantly different.
- The ERG prefers to take a conservative approach and not assume long term treatment benefit for OS for Pola + RCHP in the absence of evidence.
- OS beyond the end of the trial will also be influenced by subsequent treatments and these are likely to be favourable to the R-CHOP treatment arm.

We conduct scenarios on the extrapolation of OS in section 3.1 with different assumptions.

## **3. Updated cost-effectiveness results - ERG summary and critique**

### **3.1 ERG's cost-effectiveness scenarios**

We provide further scenarios using the company's revised base case with changes to the assumptions for PD resource costs and OS extrapolation. As discussed above we do not consider the company's model correction appropriate so this has been removed. The results are shown in Table 4. The ERG's preferred assumptions are a reduction of 50% in PD costs and for no further OS benefit after 60 months. The ERG base case ICER is £73,512 per QALY.

**Table 4 ERG scenarios using the company's revised base case model**

|  | Technologies | Total costs (£) | Total QALYs | ICER (£/ QALY) |
|--|--------------|-----------------|-------------|----------------|
| Company revised base case without model correction   | Pola+R-CHP   | ████            | ████        | 34,339         |
|  | R-CHOP       | ████            | 8.779       | -              |
| Scenario PD: Assume reduction of 25% of PD costs   | Pola+R-CHP   | ████            | ████        | 40,313         |
|  | R-CHOP       | ████            | 8.779       | -              |
| Scenario PD: Assume reduction of 50% of PD costs   | Pola+R-CHP   | ████            | ████        | 46,288         |
|  | R-CHOP       | ████            | 8.779       |                |
| Scenario OS: Assume no difference in OS between arms   | Pola+R-CHP   | ████            | ████        | 93,627         |
|  | R-CHOP       | ████            | 8.871       |                |
| Scenario OS: Assume no difference in OS between arms after 60 months   | Pola+R-CHP   | ████            | ████        | 52,722         |
|  | R-CHOP       | ████            | 8.779       | -              |
| ERG base case: Assume reduction of 50% of PD costs + Assume no difference in OS between arms after 60 months | Pola+R-CHP   | ████            | ████        | 73,512         |
|  | R-CHOP       | ████            | 8.779       | -              |

## References

1. National Institute for Health and Care Excellence (NICE). Polatuzumab vedotin with rituximab and bendamustine for treating relapsed or refractory diffuse large B-cell lymphoma - Technology appraisal guidance [TA649]. 2020
2. Wang HI, Smith A, Aas E, et al. Treatment cost and life expectancy of diffuse large B-cell lymphoma (DLBCL): a discrete event simulation model on a UK population-based observational cohort. *Eur J Health Econ* 2017;18(2):255-67. doi: 10.1007/s10198-016-0775-4 [published Online First: 2016/03/13]