

## 5.08 POLATUZUMAB VEDOTIN, Powder for I.V. infusion 30 mg, Powder for I.V. infusion 140 mg, Polivy<sup>®</sup>, Roche Products Pty Ltd.

### 1 Purpose of submission

- 1.1 The Category 2 submission requested Section 100 Efficient Funding of Chemotherapy, Authority Required (Streamlined) listing for polatuzumab vedotin in combination with rituximab plus cyclophosphamide, doxorubicin and prednisone (Pola+R-CHP) for the treatment of diffuse large B cell lymphoma (DLBCL) in previously untreated patients with an international prognostic index (IPI) score of 3-5. The PBAC had not previously considered polatuzumab vedotin for this indication.
- 1.2 Listing was requested on the basis of a cost-effectiveness analysis versus rituximab in combination with cyclophosphamide, doxorubicin, vincristine, and prednisolone (R-CHOP), administered over a 21-day cycle for 6 cycles, as the main comparator.

**Table 1: Key components of the clinical issue addressed by the submission**

| Component      | Description  |
|----------------|--|
| Population     | Patients with previously untreated DLBCL and an IPI score of 3–5   |
| Intervention   | 6 cycles of Pola+R-CHP plus 2 cycles of rituximab monotherapy (21 day cycles)  |
| Comparator     | 6 cycles of R-CHOP plus 2 cycles of rituximab monotherapy (21 day cycles)  |
| Outcomes       | Primary endpoint: PFS<br>Secondary/exploratory endpoints: EFSeff, CR, OS, AEs  |
| Clinical claim | Pola+R-CHP in patients with previously untreated DLBCL and an IPI score of 3–5 is associated with superior comparative efficacy and non-inferior comparative safety to R-CHOP. |

Source: Table 1.1, p 3 of the submission

AEs = adverse events; DLBCL = diffuse large B-cell lymphoma; CR = complete response; EFSeff = event-free survival-efficacy; IPI = international prognostic Index score; OS = overall survival; PFS = progression-free survival; Pola+R-CHP=polatuzumab vedotin plus rituximab, cyclophosphamide, doxorubicin and prednisone; R-CHOP=Rituximab plus cyclophosphamide, doxorubicin, vincristine and prednisone

### 2 Background

#### **Registration status**

- 2.1 The submission was made under the TGA/PBAC Parallel Process. The TGA Delegate’s Overview was made available on 1 November 2022. The requested indication was for: “Polatuzumab vedotin (Polivy) in combination with rituximab, cyclophosphamide, doxorubicin, and prednisone (R-CHP) is indicated for the treatment of adult patients with previously untreated diffuse large B-cell lymphoma (DLBCL).”

The Delegate was not persuaded that Pola+R-CHP was a superior regimen to R-CHOP and sought the advice of the ACM to assist with the considerations as to whether the

evidence is sufficient to accept Pola+R-CHP as an alternative to R-CHOP in first line DLBCL. The ACM had not considered Pola+R-CHP at the time of PBAC consideration<sup>1</sup>.

- 2.2 Polatuzumab vedotin is currently TGA approved (since October 2019) for use in combination with bendamustine and rituximab in previously treated adult patients with DLBCL who were not candidates for haematopoietic stem cell transplant.

***Previous PBAC consideration***

- 2.3 The PBAC had previously considered listing polatuzumab vedotin in combination with bendamustine and rituximab for the treatment of relapsed and/or refractory DLBCL in November 2019. The committee did not recommend polatuzumab vedotin for that indication because the validity of the clinical effectiveness data presented was ‘very uncertain’ and likely favoured polatuzumab vedotin. The committee also did not accept the submission’s nominated comparator, bendamustine in combination with rituximab, as bendamustine was not TGA-registered or PBS-listed for relapsed and/or refractory DLBCL (paragraphs 7.1 and 7.4, Polatuzumab vedotin Public Summary Document (PSD), November 2019 PBAC meeting).

*For more detail on PBAC’s view, see section 7 PBAC outcome.*

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<sup>1</sup> Note: The indication has subsequently been approved and is now registered on the ARTG.

### 3 Requested listing

| MEDICINAL PRODUCT form   | Dispensed price for maximum amount  | Maximum amount | No. of Rpts |
|--|---|----------------|-------------|
| Polatuzumab vedotin Powder for injection   | <p><u>Published</u><br/>Public: \$18,588.55<br/>Private: \$18,888.61</p> <p><u>Effective</u><br/>Public: \$<br/>Private: \$</p> | 200 mg         | 5           |
| Polivy<br>Polatuzumab vedotin 140 mg powder for injection, vial<br>Polatuzumab vedotin 30 mg powder for injection, vial  |   |                |             |
| <b>Category / Program:</b> Section 100 – Efficient Funding of Chemotherapy   |   |                |             |
| <b>Prescriber type:</b> <input type="checkbox"/> Dental <input checked="" type="checkbox"/> Medical Practitioners <input type="checkbox"/> Nurse practitioners <input type="checkbox"/> Optometrists <input type="checkbox"/>  |   |                |             |
| <b>Restriction type:</b> <input checked="" type="checkbox"/> Authority Required (STREAMLINED)  |   |                |             |
| <b>Condition:</b> Diffuse Large B-Cell Lymphoma  |   |                |             |
| <b>Indication:</b> Previously untreated Diffuse Large B-Cell Lymphoma  |   |                |             |
| <b>Treatment Phase:</b> Initial and continuing treatment   |   |                |             |
| <b>Clinical criteria:</b><br>The patient must have an IPI score of 3–5; AND<br>The condition must have been previously untreated; AND<br>The treatment must be in combination with rituximab, cyclophosphamide, doxorubicin and prednisone; AND<br>Patient must not receive more than 6 cycles of treatment under this restriction |   |                |             |
| <b>Prescribing Instructions:</b> Treatment must be discontinued in patients who experience disease progression while on treatment  |   |                |             |
| <b>Administrative Advice:</b><br>Patients may qualify for PBS-subsidised treatment under this restriction once only.<br>No increase in the maximum number of repeats may be authorised.<br>Special pricing arrangements apply.   |   |                |             |

Source: Table 1.7 to 1.9, p 14-16 of the submission

- 3.1 The submission requested a Section 100 Efficient Funding of Chemotherapy listing for polatuzumab vedotin 140 mg vial and 30 mg vial, with a maximum amount of 200 mg and 5 repeats. The requested maximum amount and number of repeats provide for a complete course of treatment for patients weighing up to 110 kg (i.e. 6 cycles at 1.8 mg/kg/cycle). A higher maximum amount (e.g. 210 mg) may be reasonable to provide for the small proportion of patients weighing more than 110 kg.
- 3.2 The submission proposed an Authority Required - Streamlined restriction to align with the current listings of R-CHOP (rituximab has an Authority Required - Streamlined restriction and the other concomitant chemotherapies have unrestricted listings). The evaluation considered an Authority Required – Written restriction may be more appropriate given the considerable potential for leakage outside of the proposed PBS population.
- 3.3 The submission proposed a Special Pricing Arrangement (SPA). For the 140 mg vial, the submission proposed a published ex-manufacturer price of \$12,951.59 and an effective ex-manufacturer price of \$  
|. For the 30 mg vial, the submission proposed a published ex-manufacturer price of \$2,775.34 and an effective ex-manufacturer price

of \$**1**. The corresponding public and private maximum dispensed prices presented in the table above reflect dispensing fees and mark-ups at June 2022. The pre-PBAC response proposed a **1**% reduction in the effective ex-manufacturer prices of polatuzumab vedotin (140 mg = \$**1**; 30 mg = \$**1**).

- 3.4 The requested restriction criteria would limit use of polatuzumab vedotin on the PBS (in combination with chemotherapy as part of Pola+R-CHP) to patients with previously untreated DLBCL and an IPI score of 3-5. The proposed PBS restriction is narrower than the proposed TGA indication (silent in terms of patient risk factors such as IPI) as well as the key clinical evidence presented in the submission (the POLARIX trial included patients with an IPI score of 2-5). The submission stated that excluding patients with an IPI 2 would 'ensure use is restricted to patients who are most likely to benefit from Pola+R-CHP', however, it was noted during the evaluation the proposed population (IPI score 3-5) was based on results of an exploratory post-hoc subgroup analysis in the POLARIX trial.
- 3.5 The ESC considered that there was limited evidence and rationale for restricting access to polatuzumab vedotin to patients with an IPI score of 3-5 and advised that it would be more reasonable to consider PBS listing for the broader intention to treat (ITT) population (IPI 2-5) of the POLARIX trial. The pre-PBAC response disagreed with the ESC highlighting that subgroup analyses from the POLARIX trial demonstrated that DLBCL patients with an IPI score of 3-5 had a clinically meaningful improvement in PFS (HR = 0.65; 95% CI: 0.47, 0.88), whereas those with an IPI score of 2 did not (HR = 0.99; 95% CI: 0.63, 1.56). In addition, the pre-PBAC response stated that clinician feedback indicated that patients with an IPI score of 2 were less likely to be treated with Pola+R-CHP due to a range of clinical factors such as lower clinical need, age and toxicity.
- 3.6 Aside from the IPI score, the requested restriction criteria were relatively broad. For example, the restriction criteria did not limit use to CD79b positive DLBCL (polatuzumab vedotin's mechanism of action is facilitated by binding to the CD79b surface marker on B-cells) and would allow use in patients excluded from the key trial (e.g. Eastern Cooperative Oncology Group (ECOG) score > 2, patients with central nervous system involvement).
- 3.7 The submission requested a grandfathering restriction with identical criteria for (approximately 59) patients enrolled in a planned patient access program.

*For more detail on PBAC's view, see section 7 PBAC outcome.*

## **4 Population and disease**

- 4.1 DLBCL is an aggressive type of non-Hodgkin lymphoma (NHL) that develops from the B-cells in the lymphatic system and has heterogeneous clinicopathology. Morphologically, the disease is characterised by complete or partial effacement of the nodal architecture by sheets of large atypical lymphoid cells. Immunophenotypically, the disease is characterised by the expression of pan B-cell antigens (CD19, CD20, CD22, CD79a, and CD79b) and surface and/or cytoplasmic immunoglobulin

expression. Distinct genetic features have further sub-classified DLBCL to reveal complex molecular patterns and distinct signalling mechanisms. The most frequently dysregulated genes include BCL6, BCL2 and MYC. Double-hit lymphoma (DHL, dual translocations in BCL2 or BCL6 and MYC) and double expressing lymphoma (DEL, overexpression of BCL2 and MYC) are two DLBCL subgroups with particularly poor outcomes with standard-of-care therapies. Gene expression profiling has also revealed more than two distinct molecular subsets of patients with DLBCL that further subtype the disease into germinal centre B-cell-like (GCB), activated B-cell-like (ABC) and unclassifiable subgroups.

- 4.2 There are several prognostic indices commonly used for non-Hodgkin lymphoma based on clinical characteristics prior to treatment, where higher scores are associated with greater risk of relapse and worse survival. The original IPI and the age-adjusted IPI (aa-IPI) date back prior to the development of rituximab, whereas the revised-IPI and the NCCN-IPI were created in the post-rituximab era. The IPI, aa-IPI and revised-IPI are all based on similar risk factors (e.g. age, LDH above normal, ECOG, extranodal disease), whereas the NCCN-IPI incorporates additional risk factors such as evidence of tumour spread to specific extranodal sites like the bone marrow. The Australasian guidelines considered the NCCN-IPI score provided the best discrimination between the prognostic groups, but also noted other important risk factors independent of the IPI including tumour bulk (>7.5 cm in maximal diameter) and pathobiological factors (such as cell-of-origin, protein expression and chromosomal translocation subtypes). The Pre-Sub-Committee Response (PSCR) noted that although Australasian guidelines considered the NCCN-IPI score provided the best discrimination between the prognostic groups, a recent study (Chorão 2022) found that ‘outside of a clinical trial, differences between the NCCN-IPI and the IPI may not be sufficient to result in better treatment decisions’.
- 4.3 DLBCL is curable with relatively high response rates following first-line treatment with a rituximab-based regimen, commonly 6 cycles of R-CHOP administered over a 21-day cycle (i.e. R-CHOP-21). However, approximately 10% of patients are refractory to first-line treatment and approximately 30% of patients will relapse (the majority of relapses occurring within the first 24 months). Despite effective treatments for relapsed and/or refractory DLBCL including stem cell transplant (SCT) and chimeric antigen receptor T cells (CAR-T), avoiding disease relapse or progression following first-line treatment has the greatest impact on overall survival (OS) and health-related quality of life.
- 4.4 Based on the clinical algorithm presented in the submission, patients under 60 years and ‘fit’ patients over 60 years with an IPI score of 3-5 (intermediate-high or high risk) currently receive either first-line treatment with R-CHOP-21 or another rituximab-based regimen (including the dose reduced regimen R-mini-CHOP for patients over 60 years). Under the requested PBS restriction for polatuzumab vedotin, the Pola+R-CHP regimen would become an alternative first-line treatment option for those patients. That is, polatuzumab vedotin in the Pola+R-CHP regimen would replace vincristine in the R-CHOP-21 regimen (both polatuzumab vedotin and vincristine are microtubule

inhibitors with similar toxicities). The treatment algorithm presented in the submission and the focus on IPI in determining treatment choice appeared to align more closely with the European Society for Medical Oncology (ESMO) clinical practice guidelines<sup>2</sup> than other guidelines, but there was a preference for 6 cycles of R-CHOP-21 in most patients across all guidelines including the Australasian guidelines. It was also unclear whether Pola+R-CHP would replace R-mini-CHOP given such patients require a reduced-dose regimen.

- 4.5 Polatuzumab vedotin is a CD79b-targeted antibody-drug conjugate that preferentially delivers a potent anti-mitotic agent (monomethyl auristatin E, MMAE) to B-cells, which results in the killing of malignant B cells. For previously untreated patients, the recommended dose in the draft product information (PI) is polatuzumab vedotin 1.8 mg/kg given as an intravenous infusion (IV) every 21 days for 6 cycles in combination with rituximab, cyclophosphamide, doxorubicin and prednisone (i.e. the Pola+R-CHP regimen), followed by 2 cycles of rituximab as monotherapy.

*For more detail on PBAC's view, see section 7 PBAC outcome.*

## 5 Comparator

- 5.1 The ESC noted that the submission appropriately nominated R-CHOP-21 (hereafter referred to as R-CHOP) as the main comparator. Data in the Australian Lymphoma and Related Diseases Registry found 66.8% (N = 273/410) of newly diagnosed patients with DLBCL received R-CHOP as first-line treatment in 2019, which was consistent with a clinician survey (N=30) finding that 97% of patients with newly diagnosed DLBCL in Australia received active treatment and R-CHOP was the most common (65%) first-line treatment. The submission also stated that R-CHOP would be a reasonable clinical proxy for other first-line treatments given none of the other rituximab-based regimens had demonstrated a meaningful benefit over R-CHOP.
- 5.2 Patients enrolled in the key clinical trial in the submission were randomised to either 6 cycles of Pola+R-CHP followed by 2 cycles of rituximab monotherapy or 6 cycles of R-CHOP followed by 2 cycles of rituximab monotherapy. Based on the current Australasian guidelines, it was unclear whether patients in Australia would receive 2 cycles of rituximab monotherapy post 6 cycles of R-CHOP. The 8 cycles of rituximab (in the key clinical trial) appeared to be based on the ESMO clinical practice guidelines (2015) and would be permitted on PBS, but more recent evidence from PETAL<sup>3</sup> suggest no benefit in survival outcomes in CD20 positive lymphoma patients who achieved a negative interim PET scan (by cycle 2).

*For more detail on PBAC's view, see section 7 PBAC outcome.*

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<sup>2</sup>Tilly, H., et al. "Diffuse large B-cell lymphoma (DLBCL): ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up." *Annals of oncology* 26 (2015): v116-v125.

<sup>3</sup>Duhrsen, U., S. Muller, B. Hertenstein, et al. 2018. "Positron Emission Tomography-Guided Therapy of Aggressive Non-Hodgkin Lymphomas (PETAL): A Multicenter, Randomized Phase III Trial." *J Clin Oncol* 36(20):2024-2034.

## 6 Consideration of the evidence

### **Sponsor hearing**

6.1 The sponsor requested a hearing for this item. The clinician described the unmet need for new treatments in patients DLBCL. The clinician also described the IPI score and stated that it was the most reliable method to identify patients with high-risk disease (i.e. an IPI score of 3-5) who would most likely benefit from treatment with Pola+R-CHP. The clinician also addressed other matters in response to the Committee’s questions relating to the POLARIX trial. The PBAC considered that the hearing was informative as it provided a clinical perspective on treating this disease.

### **Consumer comments**

6.2 The PBAC noted and welcomed the input from organisations (3) via the Consumer Comments facility on the PBS website. The PBAC noted the advice received from Lymphoma Australia, the Leukaemia Foundation and Rare Cancers Australia. The organisations described the high clinical need for new and effective therapies for the treatment of DLBCL to allow clinician and patient choice. The PBAC noted that the advice was supportive of the evidence provided in the submission.

### **Clinical trials**

6.3 The submission was based on one head-to-head trial, POLARIX, comparing Pola+R-CHP versus R-CHOP in previously untreated patients with an IPI score of 2-5. To align with the proposed PBS population, the submission presented clinical evidence for the subgroup of patients with IPI 3-5 as well as the ITT population.

6.4 Details of the POLARIX trial presented in the submission are provided in Table 2.

**Table 2: Trials and associated reports presented in the submission**

| Trial ID                            | Protocol title/ Publication title   | Publication citation  |
|-------------------------------------|---|---|
| GO39942<br>(POLARIX)<br>NCT03274492 | Study GO39942 (POLARIX) –A Phase III, Multicenter, Randomized, Double-Blind, Placebo-Controlled Trial Comparing the Efficacy and Safety of Polatuzumab Vedotin in Combination with Rituximab and CHP (R-CHP) versus Rituximab and CHOP (R-CHOP) in Previously Untreated Patients with Diffuse Large B-Cell Lymphoma. Data-cut off 28 June 2021<br><br>Tilly, Morschhauser, Sehn <i>et al.</i> Polatuzumab vedotin in previously untreated diffuse large B-cell lymphoma | CSR October 2021<br><br>New England Journal of Medicine 2022, 386(4):351-363. |

Source: Table 2.4, p 27 of the submission

6.5 The key features of the POLARIX are summarised in Table 3. Patients were randomised 1:1 to Pola+R-CHP (6 cycles followed by 2 cycles of rituximab monotherapy) or R-CHOP (6 cycles followed by 2 cycles of rituximab monotherapy). To balance potential prognostic factors, patients were stratified during randomisation by IPI score (IPI 2 versus IPI 3-5), bulky disease (present versus absent) and geographical region (Western Europe, United States, Canada & Australia versus Asia versus other countries).

Table 3: Key features of POLARIX

| Population                   | N   | Design/<br>duration  | Risk of<br>bias | Patient population                                       | Outcomes             | Use in modelled<br>evaluation |
|------------------------------|-----|----------------------|-----------------|--|----------------------|-------------------------------|
| <b>Pola+R-CHP vs. R-CHOP</b> |     |                      |                 |  |                      |                               |
| ITT                          | 875 | R, DB<br>28.0 months | Low             | Previously untreated DLBCL,<br>IPI of 2-5 and ECOG PS ≤2 | PFS, OS,<br>EFS, AEs | Not used                      |
| <b>Subgroup analysis</b>     |     |                      |                 |  |                      |                               |
| IPI 3-5 (Subgroup)           | 545 | R, DB<br>28.0 months | High            | Previously untreated DLBCL,<br>IPI of 3-5 and ECOG PS ≤2 | PFS, OS,<br>EFS, AEs | Used                          |
| IPI = 2 (Complement)         | 330 | R, DB<br>28.0 months | High            | Previously untreated DLBCL,<br>IPI of 2 and ECOG PS ≤2   | PFS                  | Not used                      |

Source: Constructed during the evaluation

AE = adverse event; DB = double blind; MC = multi-centre; DLBCL=diffuse large B-cell lymphoma; ECOG PS Eastern Cooperative Oncology Group Performance Score; EFS = event free survival; IPI = International Prognostic Index; OS = overall survival; PFS = progression-free survival; R = randomised., Pola = polatuzumab vedotin; R-CHP = rituximab, cyclophosphamide, hydroxydaunorubicin hydrochloride (doxorubicin hydrochloride), and prednisone; R-CHOP = rituximab, cyclophosphamide, hydroxydaunorubicin hydrochloride (doxorubicin hydrochloride), vincristine (Oncovin) and prednisone

- 6.6 Overall, the risk of bias for the ITT analysis was generally low but the risk of bias was high for the subgroup analyses. Though IPI was a stratification factor (IPI 2 vs IPI 3-5), the trial was not designed or powered to show statistically significant differences between subgroups, the subgroups were not part of the testing hierarchy and there were no methods of statistical adjustment to account for multiple subgroup analyses.
- 6.7 Randomisation appeared successful, but there were small numerical differences across some prognostic factors. Specifically, a slightly smaller proportion of patients in the Pola+R-CHP arm had the higher IPI scores; ABC cell-of-origin; high-grade B-cell lymphoma; and DEL. Given these factors are each associated with worse prognosis following standard-of-care treatment<sup>4,5</sup>, patients randomised to the Pola+R-CHP may have potentially been more likely to respond to treatment compared to patients randomised to R-CHOP. Whether these small differences actually affected the trial results was unknown.
- 6.8 The primary outcome in POLARIX was PFS and key secondary endpoints included in the hierarchical testing procedure were investigator-assessed event free survival, complete response at the end of treatment and OS. Other secondary endpoints were objective response at the end of treatment, best overall response, disease free survival, duration of response and PFS at 24 months.
- 6.9 The submission stated that PFS is the preferred outcome in lymphoma because it is interpretable earlier than OS and not confounded by the administration of subsequent therapy. Prolonging the period without disease progression and poorly tolerated chemotherapy represents a clinical benefit for patients with an aggressive disease. The submission also stated that PFS at 24 months is both a clinically meaningful and an established surrogate endpoint for OS in DLBCL because the majority of relapse

<sup>4</sup> Rosenwald, Wright, et al. (2002). "The Use of Molecular Profiling to Predict Survival after Chemotherapy for Diffuse Large-B-Cell Lymphoma." *N Engl J Med* 346(25): 1937-1947.

<sup>5</sup> Rutherford and Leonard (2018). "Dlbcl Cell of Origin: What Role Should It Play in Care Today?" *Oncology* 32(9): 445-449

occurs within the first two years. The surrogate relationship is important because the modelled economic evaluation presented in the submission assumed that patients without disease progression at approximately 2 years were 'cured' (see Economic analysis).

- 6.10 Though PFS at 24 months is a widely used surrogate endpoint in this setting<sup>6</sup>, data from Maurer et al 2014<sup>7</sup>, Maurer et al 2018<sup>8</sup>, and other similar studies<sup>9</sup> generally do not support a perfect relationship between PFS at 24 months and 'cure'. Across the literature, the five-year relapse rates given PFS at 24 months ranged from 5% to 13% (i.e. not 0%) and the estimated standardised mortality rates (SMR) given PFS at 24 months were higher than populations norms. The PSCR cited the ESMO guidelines which state 'Patients with DLBCL who are event free at 2-years have an identical OS to that of the general population, emphasising the need to only specifically monitor for the disease in this early period (Tilly, 2015)', and stated that therefore, the use of PFS at 24 months is appropriate and a reliable estimate to inform the mixture-cure model. The ESC considered that the use of PFS at 24 months is generally accepted in DLBCL as an indication of a likely cure.

### **Comparative effectiveness**

- 6.11 Table 4 and Figure 1 presents PFS and OS in POLARIX at the June 2021 data cut (median follow-up was 28.2 months). The submission did not present the results for the complement IPI 2 subgroup (only limited results were available for PFS).
- 6.12 The ESC noted that the sponsor also provided results of the final OS analysis at the June 2022 data cut (median follow-up was 39.7 months), but the findings were essentially unchanged from the interim OS analysis. An additional 21 events were observed in the approximately 12-month period after the interim analysis (11 in the

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<sup>6</sup> Assouline, Wiesinger, *et al.* (2022). "Validity of Event-Free Survival as a Surrogate Endpoint in Haematological Malignancy: Review of the Literature and Health Technology Assessments." *Critical Reviews in Oncology/Hematology*: 103711.

Maurer, Ghesquières, *et al.* (2014). "Event-Free Survival at 24 Months Is a Robust End Point for Disease-Related Outcome in Diffuse Large B-Cell Lymphoma Treated with Immunochemotherapy." *Journal of Clinical Oncology* **32**(10): 1066.

Witzig, LaPlant, *et al.* (2017). "High Rate of Event-Free Survival at 24 Months with Everolimus/Rchop for Untreated Diffuse Large B-Cell Lymphoma: Updated Results from Ncctg N1085 (Alliance)." *Blood cancer journal* **7**(6): e576-e576.

<sup>7</sup> Maurer, Ghesquieres, *et al.* (2014). "Event-Free Survival at 24 Months Is a Robust End Point for Disease-Related Outcome in Diffuse Large B-Cell Lymphoma Treated with Immunochemotherapy." *J Clin Oncol* **32**(10): 1066-1073.

<sup>8</sup> Maurer, Habermann, *et al.* (2018). "Progression-Free Survival at 24 Months (Pfs24) and Subsequent Outcome for Patients with Diffuse Large B-Cell Lymphoma (DLbcl) Enrolled on Randomized Clinical Trials." *Ann Oncol* **29**(8): 1822-1827.

<sup>9</sup> Srour, Zheng, *et al.* (2016). Efs24 as a Predictor of Outcome in a Population-Based Cohort of Patients with DLbcl in British Columbia (Bc), American Society of Clinical Oncology.

Jakobsen, Bøgsted, *et al.* (2017). "Minimal Loss of Lifetime for Patients with Diffuse Large B-Cell Lymphoma in Remission and Event Free 24 Months after Treatment: A Danish Population-Based Study." *J Clin Oncol* **35**(7): 778-784.

Abu Sabaa, Mörth, *et al.* (2021). "Age Is the Most Important Predictor of Survival in Diffuse Large B-Cell Lymphoma Patients Achieving Event-Free Survival at 24 Months: A Swedish Population-Based Study." *British Journal of Haematology* **193**(5): 906-914.

Pola+R-CHP arm, 10 in the R-CHOP arm) and results continued to show no difference in OS between the treatment arms (HR = 0.94; 95% CI: 0.67, 1.33).

**Table 4: PFS (INV assessed) and OS in POLARIX (June 2021 data cut)**

| Outcome                                | ITT Population             |                | Subgroup: IPI 3-5        |               | Compliment: IPI 2              |        |
|--|----------------------------|----------------|--------------------------|---------------|--------------------------------|--------|
|  | Pola+R-CHP                 | R-CHOP         | Pola+R-CHP               | R-CHOP        | Pola+R-CHP                     | R-CHOP |
| <b>Progression-free survival (PFS)</b> |                            |                |                          |               |                                |        |
| Events, n/N (%)                        | 107/440 (24.3)             | 134/439 (30.5) | 70/273 (25.6)            | 97/272 (35.7) | NR                             | NR     |
| Median TTE, months (95% CI)            | 33 (33.3, NE) <sup>a</sup> | NE             | NR                       | NR            | NR                             | NR     |
| HR (95%)                               | <b>0.73 (0.57, 0.95)</b>   |                | <b>0.65 (0.47, 0.88)</b> |               | 0.99 (0.63, 1.56) <sup>b</sup> |        |
| <b>Overall survival (OS)</b>           |                            |                |                          |               |                                |        |
| Events, n/N (%)                        | 53/440 (12.1)              | 57/439 (13.0)  | 40/273 (14.7)            | 43/272 (15.8) | NR                             | NR     |
| Median TTE, months (95% CI)            | NE                         | NE             | NE                       | NE            | NR                             | NR     |
| HR (95%)                               | 0.94 (0.65, 1.37)          |                | 0.93 (0.60, 1.43)        |               | NR                             |        |

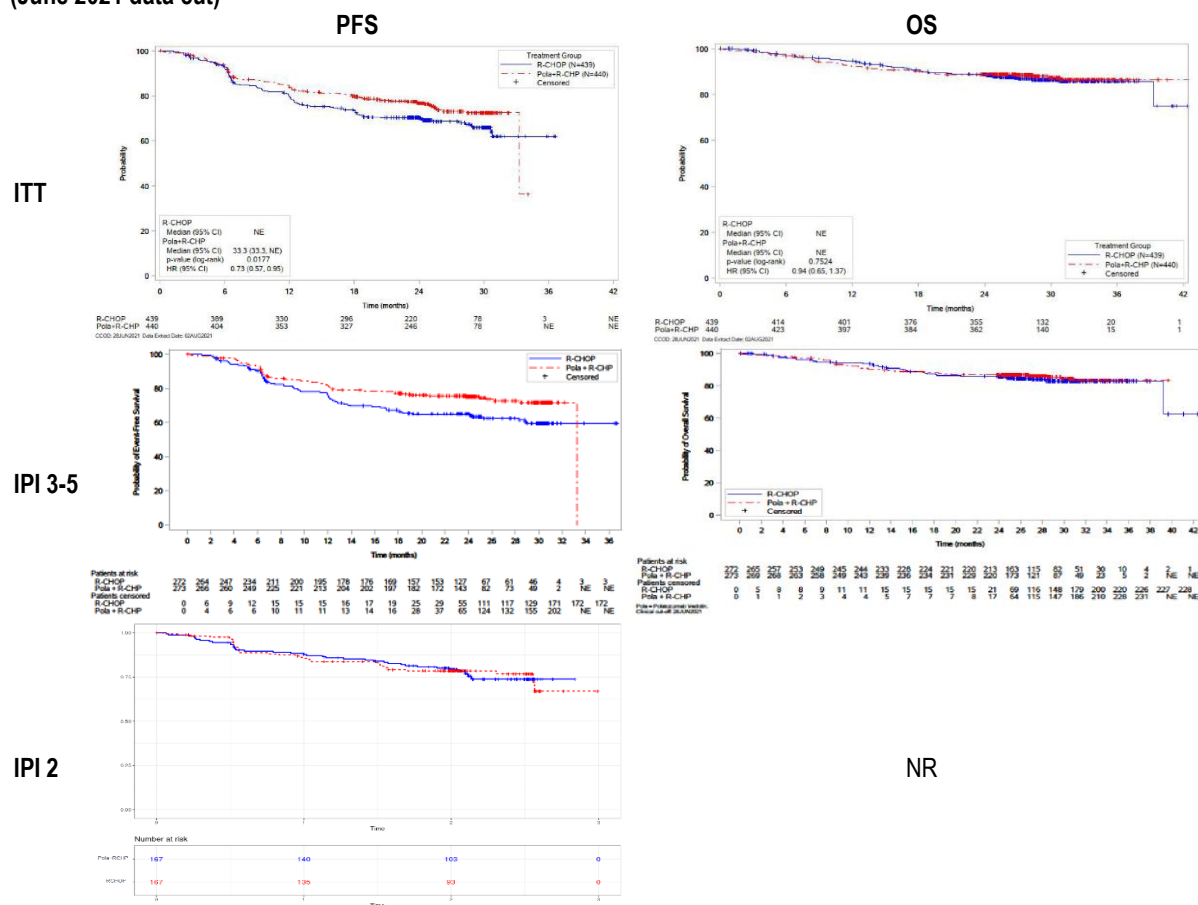
Source: Table 2.14, p 41, Table 2.26, p 59 and Figure 2.8, p 56 of the submission; Table 2.27, p 61 of the submission

CI = confidence interval; INV = investigator; ITT = intention-to-treat; PFS = progression-free survival; Pola = polatuzumab vedotin; R-CHOP = rituximab plus cyclophosphamide, doxorubicin, vincristine and prednisone; R-CHP = rituximab plus cyclophosphamide, doxorubicin and prednisone; TTE = time to event; **Bold** = statistically significant

<sup>a</sup> The ESC noted that the median PFS for Pola was not reliable as it was estimated due to an artefact of the censoring where the PFS curve is vertical at the end and crosses the 50% probability threshold at that point.

<sup>b</sup> Constructed during evaluation

Figure 1: Kaplan-Meier curves for PFS (INV- assessed) and OS in POLARIX (red = Pola+R-CHP; blue = R-CHOP) (June 2021 data cut)



Source: Figure 2.4, p 42 and Figure 2.9, p 59 of the submission; Figure 2.6 p 45 and Figure 2.12, p 62 of the submission  
 IPI = International Prognostic Indicator; ITT = intention-to-treat; INV = investigator; NE = not evaluable; Pola = polatuzumab vedotin; R-CHOP = rituximab plus cyclophosphamide, doxorubicin, vincristine and prednisone; R-CHP = rituximab plus cyclophosphamide, doxorubicin and prednisone

Note: The results presented in Figure 1 are derived from analyses conducted by the applicant specifically for the purposes of informing the PBAC consideration. Interpretation of the results and their application should therefore be limited to seeking to understand the basis for the PBAC outcome and should not be used for any other purpose.

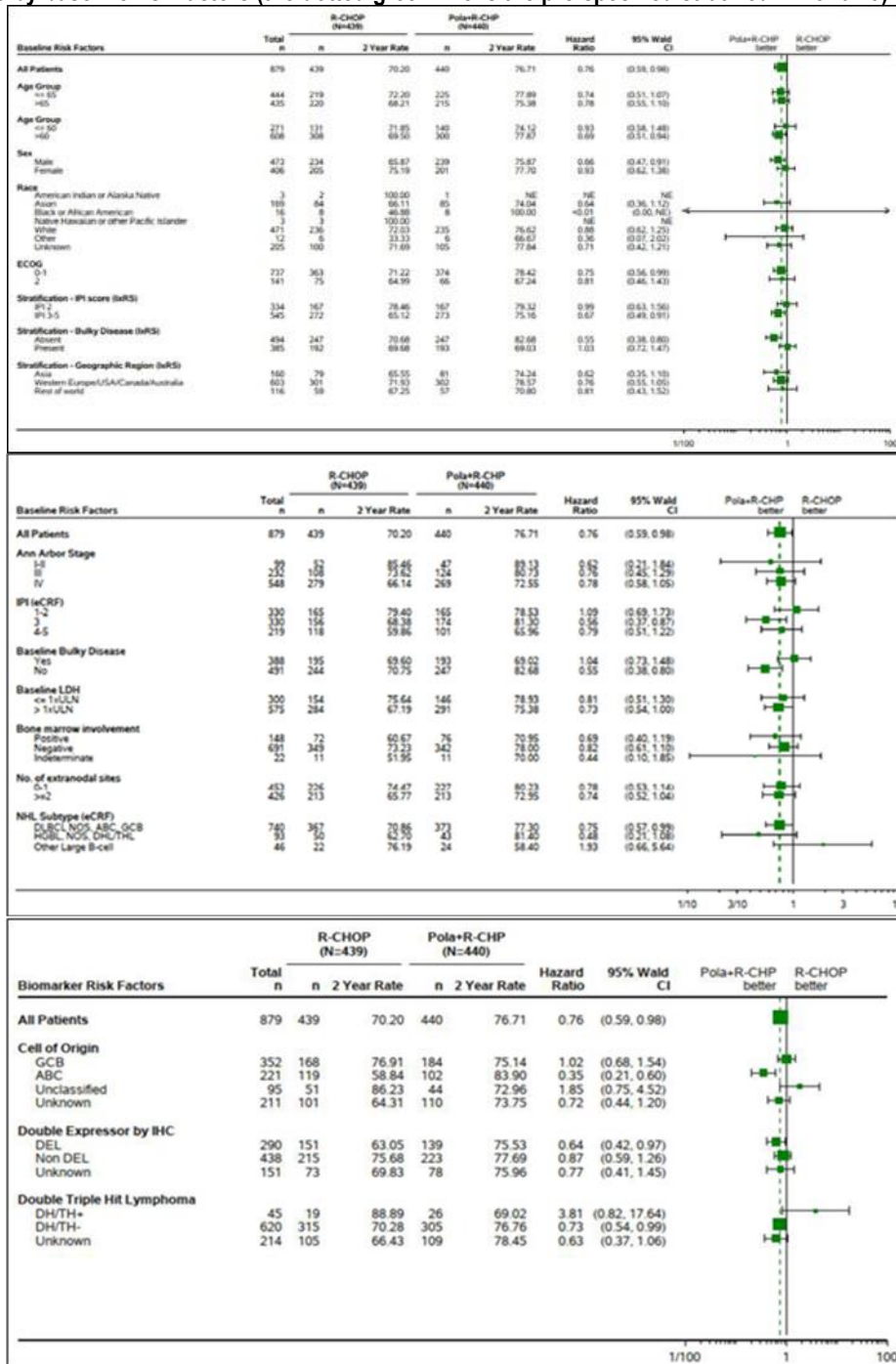
6.13 In the ITT population, the results showed that PFS was significantly longer for patients randomised to Pola+R-CHP compared to R-CHOP with a statistically significant reduction in the risk of progression (HR = 0.73; 95% CI: 0.57, 0.95), but there was no statistically significant difference in OS (HR = 0.94; 95% CI: 0.65, 1.37). The ESC considered that the improvement in PFS of Pola+R-CHP over R-CHOP was modest.

6.14 Based on the results of the exploratory subgroup analysis, the submission stated that the treatment effect for PFS in the ITT population was driven by results in the IPI 3-5 subgroup (HR = 0.65; 95% CI: 0.47, 0.88). The submission did not present any evidence that the treatment effect for PFS statistically differed across the IPI subgroups. The POLARIX trial was not designed nor powered to show statistically significant differences between the subgroups and the trial report cautioned that the 'results

should not be over-interpreted and there is no statistical evidence for heterogeneity of treatment effect in any of the subgroups’.

- 6.15 Figure 2 presents PFS results for the unstratified exploratory subgroup analysis in POLARIX (without adjusting for multiplicity). The forest plot illustrates that there was a relatively consistent treatment effect across the numerous subgroups and nearly all of the 95% CIs included the estimated HR in the ITT population. The subgroup analysis by IPI on the electronic case report form (rather than by randomisation strata) found a statistically significant reduction in the risk of progression with Pola+R-CHP for patients with IPI 3 but no significant difference for patients with IPI 4-5. Overall, the ESC considered that PFS results varied depending on demographic and disease characteristics.

Figure 2: PFS by baseline risk factors (the dotted green line is the pre-specified stratified HR of 0.73).



Source: Figure 5, p 90 of the CSR, Figure 5, p 91 of the CSR, Figure 11, p 121 of the CSR  
 ABC = activated B-cell type; DHL = Double-hit lymphoma; CI = confidence interval; ECOG = Eastern Cooperative Oncology Group; eCRF = electronic case report form; GCB = germinal center B-cell type; IHC = immunohistochemistry; IPI = International Prognostic Index; ITT = intention to treat; IxRS = interactive voice or Web-based response system; HGBl = High-grade B-cell lymphoma; NOS = not otherwise specified; Pola = polatuzumab vedotin; R-CHOP = rituximab plus cyclophosphamide, doxorubicin, vincristine and prednisone; R-CHP = rituximab plus cyclophosphamide, doxorubicin and prednisone; SD = standard deviation; ULN = upper limit of normal; THL = Triple-hit lymphoma

- 6.16 Results across other secondary endpoints showed a statistically significant improvement in event-free survival, duration of response and disease-free survival for patients randomised to Pola+R-CHP compared to R-CHOP, but no difference in the proportion of patients with a complete and/or partial response at the end of treatment or best overall response. The results in the IPI 3-5 subgroup were consistent with the ITT populations. Overall, the results suggest that response was more durable for patients randomised to Pola+R-CHP. At 24 months, fewer patients randomised to Pola+R-CHP had experienced a progression event (absolute difference = 6.50%; 95% CI: 0.52, 12.49 in the ITT population, 10.05%; 95% CI: 2.20, 17.89 in the IPI 3-5 subgroup).

### ***Comparative harms***

- 6.17 Table 5 summarises the adverse events (AEs) in POLARIX for the safety population, including AEs of special interest for polatuzumab vedotin.

Table 5: Adverse events reported in POLARIX (safety population)

|   | Pola+R-CHP, N = 435 | R-CHOP, N = 438 | RR (95% CI)              |
|---|---------------------|-----------------|--------------------------|
| <b>Summary outcomes</b>                   |                     |                 |                          |
| Any AE                                    | 426 (97.9)          | 431 (98.4)      | 1.00 (0.98, 1.01)        |
| Any Grade 3-5 AE                          | 264 (60.7)          | 262 (59.8)      | 1.01 (0.91, 1.13)        |
| Any Grade 5 AE                            | 13 (3.0)            | 10 (2.3)        | 1.31 (0.58, 2.95)        |
| Any SAE                                   | 148 (34.0)          | 134 (30.6)      | 1.11 (0.92, 1.35)        |
| Any AE resulting in death                 | 13 (3.0)            | 11 (2.5)        | 1.19 (0.54, 2.63)        |
| AE leading to trial discontinuation       | 27 (6.2)            | 29 (6.6)        | 0.94 (0.56, 1.56)        |
| AE leading to dose interruption           |                     |                 |                          |
| Any drug                                  | 103 (23.7)          | 111 (25.3)      | 0.93 (0.74, 1.18)        |
| Polatuzumab vedotin/vincristine           | 61 (14.0)           | 62 (14.2)       | 0.99 (0.71, 1.37)        |
| AE leading to dose reduction              |                     |                 |                          |
| Any drug                                  | 40 (9.2)            | 57 (13.0)       | 0.71 (0.48, 1.04)        |
| Polatuzumab vedotin/vincristine           | 24 (5.5)            | 45 (10.3)       | <b>0.54 (0.33, 0.87)</b> |
| <b>Adverse events of special interest</b> |                     |                 |                          |
| Peripheral neuropathy event               | 230 (52.9)          | 236 (53.9)      | 0.98 (0.87, 1.11)        |
| Neuropathy peripheral                     | 105 (24.1)          | 99 (22.6)       | 1.07 (0.84, 1.36)        |
| Peripheral sensory neuropathy             | 85 (19.5)           | 94 (21.5)       | 0.91 (0.70, 1.18)        |
| Paraesthesia                              | 29 (6.7)            | 20 (4.6)        | 1.46 (0.84, 2.54)        |
| Neutropenia event                         | 200 (46.0)          | 187 (42.7)      | 1.08 (0.93, 1.25)        |
| Neutropenia                               | 134 (30.8)          | 143 (32.6)      | 0.84 (0.78, 1.15)        |
| Febrile neutropenia                       | 62 (14.3)           | 35 (8.0)        | <b>1.78 (1.20, 2.64)</b> |
| Neutrophil count decreased                | 36 (8.3)            | 33 (7.5)        | 1.10 (0.70, 1.73)        |
| Anaemia                                   | 125 (28.7)          | 118 (26.9)      | 1.06 (0.86, 1.31)        |
| Thrombocytopenia                          | 58 (13.3)           | 58 (13.2)       | 1.01 (0.72, 1.41)        |
| Infections                                | 216 (49.7)          | 187 (42.7)      | <b>1.16 (1.01, 1.34)</b> |
| Upper respiratory tract                   | 31 (7.1)            | 39 (8.9)        | 0.80 (0.51, 1.26)        |
| Pneumonia                                 | 32 (7.4)            | 28 (6.4)        | 1.15 (0.71, 1.88)        |
| Urinary tract infection                   | 35 (8.0)            | 24 (5.5)        | 1.47 (0.89, 2.43)        |
| Hepatic toxicity events                   | 46 (10.6)           | 32 (7.3)        | 1.45 (0.94, 2.23)        |
| Carcinogenicity                           | 4 (0.9)             | 5 (1.1)         | 0.88 (0.22, 2.98)        |
| Pulmonary toxicity                        | 7 (1.6)             | 7 (1.6)         | 1.01 (0.36, 2.85)        |
| Infusion-related reactions                | 58 (13.3)           | 70 (16.0)       | 0.83 (0.60, 1.15)        |
| Tumour Lysis Syndrome                     | 2 (0.5)             | 4 (0.9)         | 0.50 (0.09, 2.73)        |
| Cardiac arrhythmia                        | 13 (3.0)            | 20 (3.7)        | 0.65 (0.33, 1.30)        |
| Hyperglycaemia                            | 26 (6.0)            | 27 (6.2)        | 0.97 (0.58, 1.63)        |

Source: Table 2.22, p49 and Table 2.28, p64 of the submission

AE = adverse events, CI = confidence interval; ITT = intention-to-treat; IPI = international prognostic index; NR = not reported; Pola = polatuzumab vedotin; R-CHOP = rituximab plus cyclophosphamide, doxorubicin, vincristine and prednisone; R-CHP = rituximab plus cyclophosphamide, doxorubicin and prednisone; SAE = serious adverse events; RR = relative risk; bold = statistically significant at p < 0.05.

6.18 The safety profile of Pola+R-CHP was comparable to R-CHOP, with a similar incidence of any AEs, Grade 3-5 AEs, serious AEs, AEs leading to discontinuation and AEs leading to any study dose interruption. The submission stated that the higher incidence of serious neutropenia events (i.e. febrile neutropenia) likely explained the higher rates of infections observed in the Pola+R-CHP arm. Overall, the safety outcomes reported in POLARIX were consistent with the known safety profiles of individual agents for Pola+R-CHP and R-CHOP.

## Benefits/harms

6.19 A summary of the comparative benefits and harms for Pola+R-CHP versus R-CHOP in the ITT population (IPI 2-5) is presented in Table 6.

**Table 6: Summary of comparative benefits and harms for Pola + R-CHP and R-CHOP – ITT/safety population**

| Event  | Pola + R-CHP         | R-CHOP               | Absolute Difference       | HR (95% CI)              |        |                     |
|--|----------------------|----------------------|---------------------------|--------------------------|--------|---------------------|
| <b>Benefits</b>  |                      |                      |                           |                          |        |                     |
| <b>Progression free survival (median duration of follow up 28.2 months months)</b> |                      |                      |                           |                          |        |                     |
| Progressed, n/N (%)  | 107/440 (24.3)       | 134/439 (30.5)       |                           | <b>0.73 (0.57,0.95)</b>  |        |                     |
| Median PFS, months (95% CI)  | 33 (33.3, NE)        | NE                   | NE                        |                          |        |                     |
| PFS at 24 months, % (95% CI)   | 76.71% (72.65,80.76) | 70.20% (65.80,74.61) | <b>6.50% (0.52,12.49)</b> |                          |        |                     |
| <b>Harms</b>   |                      |                      |                           |                          |        |                     |
|  | Pola+R-CHP           | R-CHOP               | RR (95% CI)               | Event rate/100 patients* |        | RD (95% CI)         |
|  |                      |                      |                           | Pola+R-CHP               | R-CHOP |                     |
| AE leading to dose reduction (polatuzumab/vincristine), n/N (%)                    | 24 (5.5)             | 45 (10.3)            | <b>0.54 (0.33,0.87)</b>   | 5.5                      | 10.3   | <b>-5% (-8, -1)</b> |
| Infections, n/N (%)  | 216 (49.7)           | 187 (42.7)           | <b>1.16 (1.01,1.34)</b>   | 49.7                     | 42.7   | <b>7% (0, 14)</b>   |
| Febrile neutropenia, n/N (%)   | 62/435 (14.3)        | 35/438 (8.0)         | <b>1.78 (1.20,2.64)</b>   | 14.3                     | 8.0    | <b>6% (2, 10)</b>   |

Source: Table 2.14-2.16, pp 41-43, Table 2.22, p49, Table 2.26-2.27, pp 58-61 of the submission

CI = confidence interval; IPI = International Prognostic Indicator; ITT = intention-to-treat; HR =hazard ratio; PFS = progression-free survival; Pola = polatuzumab vedotin; R-CHOP = rituximab plus cyclophosphamide, doxorubicin, vincristine and prednisone; R-CHP = rituximab plus cyclophosphamide, doxorubicin and prednisone; RD = risk difference; RR = risk ratio; **Bold** = statistically significant

6.20 On the basis of direct evidence presented by the submission, for every 100 patients (IPI 2-5) treated with Pola+R-CHP in comparison to R-CHOP:

- Approximately 7 additional patients will remain progression free at 24-months follow-up;
- Approximately 7 additional patients will experience infection;
- Approximately 6 additional patients will experience febrile neutropenia.

## Clinical claim

6.21 The submission described Pola+R-CHP as superior in terms of effectiveness and non-inferior in terms of safety compared to R-CHOP in previously untreated DLBCL patients with an IPI score of 3-5.

6.22 The clinical evidence presented in the submission potentially supported the claim of superior effectiveness for patients with an IPI 2-5, but the claim was no more certain in the subgroup of patients with an IPI score of 3-5. As discussed above, the POLARIX trial met its primary endpoint demonstrating a statistically significant improvement in PFS with Pola+R-CHP compared to R-CHOP in the ITT population (IPI 2-5). There was no statistical evidence for heterogeneity of treatment effect in any of the exploratory subgroups including IPI and any numerical differences between the estimated treatment effects for patients with an IPI 3-5 compared to an IPI 2 should not be over interpreted given the known limitations of exploratory subgroup analyses. Overall, the

- ESC considered that the improvement in PFS of Pola+R-CHP over R-CHOP was modest in all patients (i.e. the ITT population of the POLARIX trial with an IPI score of 2-5). The ESC noted that Pola+R-CHP did not demonstrate an advantage over R-CHOP in terms of OS or the proportion of patients experiencing a complete or partial response.
- 6.23 The PBAC considered that the claim of superior comparative effectiveness in patients with an IPI score of 3-5 was potentially reasonable in terms of PFS only. The PBAC considered that Pola+R-CHP did not provide a benefit compared to R-CHOP in terms of OS.
- 6.24 The ESC considered that the clinical evidence presented generally supported the claim of non-inferior safety given a similar incidence of AEs, including serious and grade 3-5 AEs. However, the ESC considered it likely that the modest improvements in PFS may be offset by a slightly higher incidence of infections and febrile neutropenia observed with Pola+R-CHP compared to R-CHOP. Overall, the ESC considered the relatively high proportion of patients completing all cycles of treatment and low number of AEs leading to dose interruptions/reductions suggested that AEs were manageable.
- 6.25 Overall, the PBAC considered that the claim that Pola+R-CHP was non-inferior compared to R-CHOP in terms of safety may not be reasonable given the increased incidence of febrile neutropenia with Pola+R-CHP, although noted that the AEs appeared manageable in the context of a clinical trial.

### **Economic analysis**

- 6.26 The submission presented a cost-utility analysis comparing Pola+R-CHP versus R-CHOP in patients with previously untreated DLBCL, based on extrapolated data from POLARIX. The submission specified the base case for the subgroup of patients with an IPI 3-5, but also provided results for the ITT population (IPI 2-5). Results of the economic evaluation for both the ITT and IPI 3-5 subgroup are presented below.

**Table 7: Key components of the economic evaluation**

| Component                        | ITT model   | IPI 3-5 subgroup      | Justification/comments   |
|----------------------------------|---|-----------------------|--|
| Population                       | Patients with IPI 2-5   | Patients with IPI 3-5 | The submission presented the IPI 3-5 subgroup model as the main analysis. IPI 3-5 was a subgroup of the trial, chosen as patients appeared to show greater response to polatuzumab vedotin. As such, both the ITT and IPI 3-5 subgroup model methods and results are presented throughout.   |
| Type of analysis                 | Cost-utility  |                       | Appropriate.   |
| Outcomes                         | Life years gained (LYG), quality-adjusted life years (QALYs)  |                       | Appropriate.   |
| Time horizon                     | 25 years in the model base case vs. 28.2 months in POLARIX.   |                       | A 25-year time horizon may be reasonable for patients who achieve 'cured' status, but it was extrapolated from short-term trial data. The time horizon was reduced to 20 years in the revised base case presented in the pre-PBAC response (p2).   |
| Methods used to generate results | Mixture-cure model. The submission stated that patients assumed cured if progression free at 2 years. This statement appeared to be a justification for the general approach rather than an |                       | Uncertain. Although the estimated models cure fractions were uncertain due to limited evidence of cure (i.e. there was no plateau of survival curves) used to fit the models, the ESC considered that it was reasonable, from a clinical perspective, to define a patient as cured if they remained progression free after 2 years. However, the mixture-cure model does not |

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| Component                | ITT model  | IPI 3-5 subgroup  | Justification/comments   |
|--------------------------|--|---|--|
|                          | assumption of the mixture-cure model itself.   |   | adjust mortality for benefits of potentially curative subsequent treatments such as stem cell transplant and CAR-T in 'uncured' patients, despite attributing costs for these treatments.  |
| Health states            | PFS, Progressed Disease (PD), Dead   |   | Reasonable.  |
| Cycle length             | 1 week, with half cycle correction.  |   | The short cycle length may be too granular compared to the uncertain future events which were modelled on long range extrapolations. The half cycle correction also likely contributed to underestimating the mean number of treatment cycles (1% patients were not costed for any treatment and 50% patients were not costed for a 6 <sup>th</sup> cycle of polatuzumab vedotin compared to 15% without the half cycle correction). The PSCR provided a revised base case in which the half cycle correction for first-line drug costs only were removed. A further revision is presented in Table 11 in which the half cycle correction for all costs and benefits is removed.   |
| Transition probabilities | <p>Based on the submitted Excel model:<br/>PFS and OS ITT KM data from POLARIX to 28.2 months followed by <u>independent gamma</u> extrapolations averaged for cured and non-cured patients.</p> <p>PFS mortality (i.e. in cured patients only from 28.2 months) each cycle had to be at least equal to OS mortality (i.e. combination of cured and uncured patients) each cycle. OS was restricted to not exceed general population survival.</p> <p>Time on treatment modelled separately with KM data from POLARIX.</p> | <p>PFS and OS <b>IPI 3-5 subgroup</b> KM data from POLARIX to 28.2 months followed by <u>independent log-normal</u> extrapolations averaged for cured and non-cured patients.</p> <p>PFS mortality each cycle had to be at least equal to OS mortality each cycle. OS was restricted to not exceed general population survival.</p> <p>Time on treatment modelled separately with KM data from POLARIX.</p> | <p>No difference in OS was observed in POLARIX. In the models, differences in OS were driven by the proportions assumed 'cured' (cure fraction) in each arm. Cure fractions were estimated from POLARIX, but results varied widely depending on the parametric distribution used (72-77% Pola+R-CHP, 55-63% R-CHOP for IPI 3-5 subgroup extrapolations, excluding Gompertz which estimated 0% cure fraction). Also, the Weibull, Gamma and log-logistic distributions could not be fitted to the mixture-cure model (i.e., did not converge in at least one arm according to the submitted R code), which the submission did not explain. Furthermore, only aggregate OS curves for each treatment arm rather than separate cured and non-cured OS curves were presented.</p> <p>Due to the models' construction, extrapolations for the mixture-cure model were not able to be reproduced or explored during the evaluation (including altering either cure time point or setting a fixed cure fraction).</p> <p>Patients deemed 'cured' were assumed to follow general population mortality based on the Human Mortality Database adjusted for patients' geographic location in POLARIX.</p> <p>From 28.2 months, PFS should be equivalent to OS for 'cured' patients (i.e general population mortality) according to the mixture-cure approach, however the model restricted PFS to be equivalent to overall OS (which was an average of 'cured' and 'non-cured' patients in the model). This defeated the purpose of adopting the mixture cure approach. The PSCR presented a revised base case which adjusted the PFS extrapolation so that PFS was only equal to OS in the event that the PFS extrapolation estimate was higher than the OS extrapolation estimate.</p> <p>Transition probabilities also did not include the possibility of future curative therapies for patients who progress, therefore did not accurately reflect the therapeutic options available.</p> |

| Component        | ITT model  | IPI 3-5 subgroup | Justification/comments  |
|------------------|--|------------------|---|
| Utilities        | PFS 0-2 years 0.795 (POLARIX ITT data)<br>PFS >2 years: age dependent population utility, 0.80 (age 75-90) to 0.85 (age 55).<br>PD 0.749 (POLARIX ITT data)  |                  | PFS 0-2 years and PD utilities were based on ITT data for both models. Patients with IPI 3-5 may have worse utility than those with IPI 2 as IPI score increases with worse health/prognosis factors.<br>The submission did not justify the PFS >2 years utilities. Lin 2018 <sup>a</sup> systematic review suggested a return to general population utility was seen after a minimum of 3 years. The models also did not include a disutility for AEs.   |
| Costs            | The models included costs for Pola+R-CHP, R-CHOP, management of AEs (one-off costs for anaemia, neutropenia, diarrhoea, and febrile neutropenia), medical service use (specialists, blood tests, imaging), subsequent treatment post progression (one-off cost applied at progression based on proportion of RT, R-GemOX, SCT, CAR-T in each treatment arm of POLARIX) and end of life costs. The models assumed that the likelihood of each subsequent treatment was dependent upon the initial treatment received. |                  | The included costs were generally reasonable, except: <ul style="list-style-type: none"> <li>• The number of cycles of treatment appeared to be underestimated compared to the mean values in POLARIX (e.g. 5.3 cycles of polatuzumab vedotin vs 5.8), resulting in lower incremental costs. As noted above, the PSCR provided a revised base case which removed the half cycle correction which underestimated the cost of first line treatment.</li> <li>• The proportional use of subsequent treatment post progression in the model was based on treatments received during the (relatively short) POLARIX follow-up period. It was unclear whether the trial data would capture all subsequent therapies post progression or whether the trial data would reflect current use of treatments in Australia. In addition, the submission's approach implied that patients with disease progression in the Pola+R-CHP arm of the model were less likely to use SCT (15% vs 19%) or CAR-T (8% vs 10%) compared to the R-CHOP arm, which may not be reasonable. The pre-PBAC response (p2) presented a revised base case in which the same proportions of subsequent therapies were applied across both treatment arms.</li> <li>• Cost of CAR-T did not have a verifiable source (Lymphoma website gave an estimate of &gt;\$500,000 but no calculation for this value).</li> <li>• Subsequent therapy costs were also applied in the cycle that the patients progressed, meaning the cost of these therapies was not subject to discounting over time. Also, while costs of subsequent therapies were included, benefits were not. The clinical evidence suggests a proportion of patients receiving 2+ lines of treatment can also achieve 'cure' status. The economic evaluation however effectively assumed all patients with disease progression following first-line treatment would remain 'uncured'.</li> </ul> |
| Software package | R, Excel 2016  |                  | Appropriate, however R analyses used to estimate mixture-cure model could not be reproduced as IPD data was required (which were not provided by the sponsor).  |

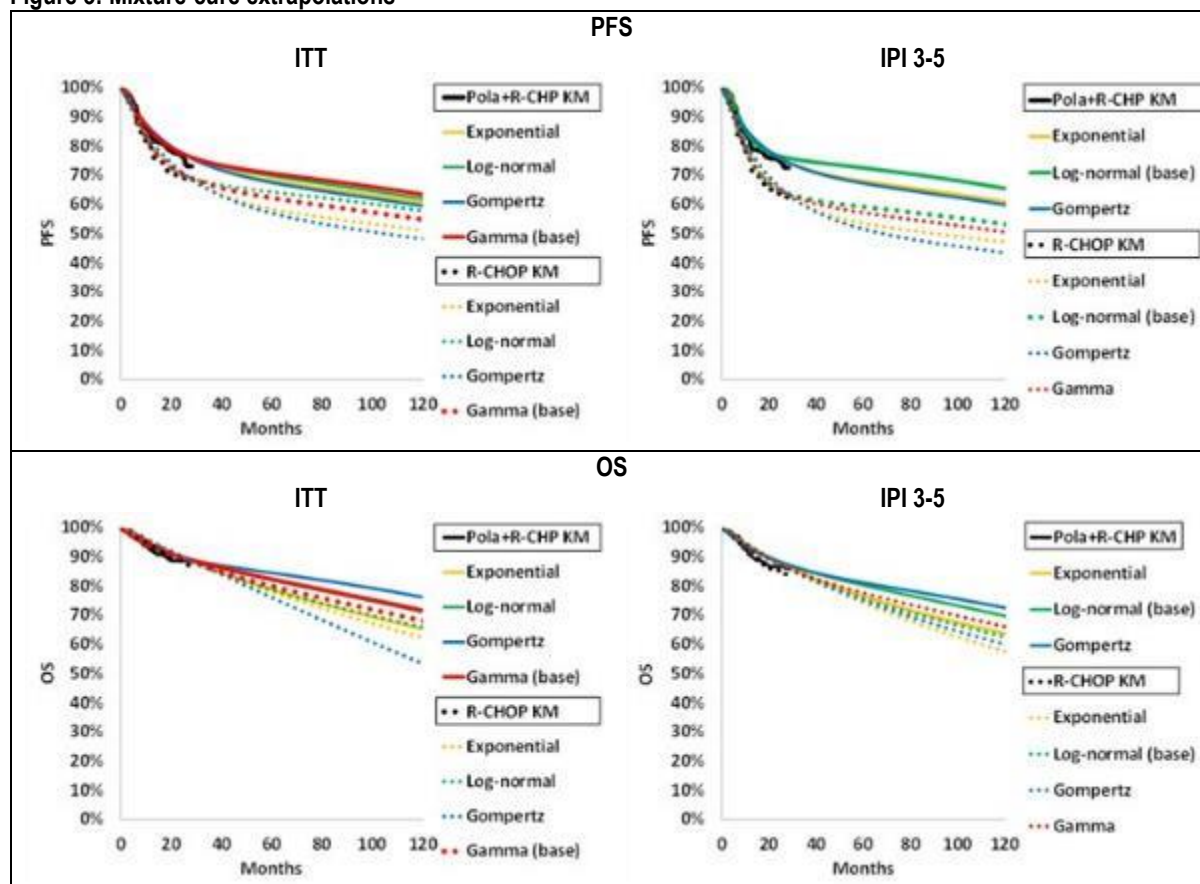
Source: compiled during the evaluation

AE = adverse event, CAR-T = chimeric antigen receptor T cell therapy, IPI = international prognostic index, IPD = individual patient data, ITT = intention to treat, KM = Kaplan-Meier, OS = overall survival, PD = progressed disease, PFS = progression free survival, Pola+R-CHP = polatuzumab vedotin in combination with cyclophosphamide, doxorubicin and prednisone, R-CHOP = rituximab in combination with cyclophosphamide, doxorubicin, vincristine and prednisone, R-GemOX = rituximab in combination with gemcitabine and oxaliplatin, RT = radiotherapy, SCT = stem cell therapy

<sup>a</sup> Lin V, Blaylock B, Epstein J, Purdum A (2018) Systematic literature review of health-related quality of life among aggressive non-Hodgkin lymphoma survivors, Current Medical Research and Opinion, 34:8, 1529-1535, DOI: 10.1080/03007995.2018.1474091

- 6.27 The submission presented a partition survival model with three health states: PFS, progressed disease (PD) and death. Patients entered the model in the PFS health state and could remain in PFS or transition to PD or dead each cycle; patients in PD either remained in PD or transition to dead each cycle. Allocation to the health states was based on 28.2 months of POLARIX PFS and OS Kaplan Meier (KM) data, then extrapolated survival functions to 25 years. To extrapolate PFS and OS beyond 28.2 months, the submission estimated a mixture-cure model for the base case analysis. Mixture-cure models assume that the trial KM data reflects the weighted average for two sub-populations: i) cured patients with the same risk of mortality as the matched general public (age, gender, country); and ii) uncured patients with higher risk of mortality due to DLBCL. The cure fraction (% cured) can either be pre-specified or estimated jointly with parameters of the chosen parametric function that best explains the observed time to event data. For the POLARIX data, the submission estimated the cure fraction from the PFS trial data based on the assumption that PFS in the cured population would reflect the OS of the matched general population because long-term survivors would not experience disease progression. The submission then specified the estimated cure fraction to extrapolate the OS trial data; hence, the estimated improvement in the cure fraction, based on differences in PFS, resulted in long-term survival gains.
- 6.28 Figure 3 and Table 8 present the estimated mixture-cure model extrapolations and corresponding cure fractions, respectively. For the base case analysis, the submission chose independent gamma functions to extrapolate PFS and OS in the ITT model and independent log-normal functions to extrapolate PFS and OS in the IPI 3-5 model.

Figure 3: Mixture-cure extrapolations



Source: compiled during the evaluation from Excel files 'Economic Evaluation\_ITT.xlsx' and 'Economic Evaluation\_IPI 3-5.xlsx'  
 ITT = intention to treat; IPI = International Prognostic Index, KM = Kaplan-Meier, OS = overall survival, PFS = progression free survival; Pola+R-CHP = polatuzumab vedotin in combination with rituximab, cyclophosphamide, doxorubicin and prednisone; R-CHOP = rituximab in combination with cyclophosphamide, doxorubicin, vincristine and prednisone

Table 8: Estimated cure fractions

|                                   | Pola+R-CHP                 |                           | R-CHOP                     |                            |
|-----------------------------------|----------------------------|---------------------------|----------------------------|----------------------------|
|                                   | ITT                        | IPI 3-5                   | ITT                        | IPI 3-5                    |
| PFS 24 months surrogate (POLARIX) | 76.71% (72.65, 80.76)      | 75.16% (69.91, 80.42)     | 70.20% (65.80, 74.61)      | 65.12% (59.29, 70.94)      |
| Exponential                       | 71.4% (61.4, 81.4%)        | 71.7% (61.7, 81.8%)       | 60.1% (47.2, 72.9%)        | 55.3% (41.1, 69.6%)        |
| Gamma                             | <b>74.7% (65.4, 84.0%)</b> | *                         | <b>63.6% (44.8, 82.3%)</b> | 59.0% (39.5, 78.5%)        |
| Gompertz                          | 0.0% (-640.4, 640.1%)      | 0.0% (-472.0, 472.0%)     | 0.0% (-539.4, 539.4%)      | 0.0% (-867.8, 867.8%)      |
| Log-logistic                      | *                          | *                         | *                          | *                          |
| Log-normal                        | 72.6% (59.7, 85.6%)        | <b>77.1% (70.5-83.7%)</b> | 68.1% (61.3, 74.9%)        | <b>62.7% (54.4, 70.9%)</b> |
| Weibull                           | *                          | *                         | *                          | *                          |

Source: compiled during the evaluation from 'POLARIX statistical outputs\_ITT.xlsx' and 'POLARIX statistical outputs\_IPI 3-5.xls'  
 ITT = intention to treat, IPI = International Prognostic Index, PFS = progression free survival, Pola+R-CHP = polatuzumab vedotin in combination with cyclophosphamide, doxorubicin and prednisone, R-CHOP = rituximab in combination with cyclophosphamide, doxorubicin, vincristine and prednisone

**Bold** indicates the chosen base case extrapolation, \* indicates extrapolations that failed to converge.

6.29 Visually, the mixture-cure extrapolations tended to overestimate the KM data, particularly the chosen base case extrapolations, and especially towards the end of the KM data for the Pola+R-CHP arms. There was also high uncertainty in the cure fraction estimates, which were not explored in the submission and could not be

explored during the evaluation, as the cure fractions were simultaneously estimated with the extrapolations. Furthermore, the mean cure fraction seen in POLARIX for R-CHOP (based on PFS at 24 months proxy) was consistently underestimated by the mixture-cure extrapolations.

- 6.30 The submission also independently fit standard parametric survival functions to the PFS and OS KM data from POLARIX for each treatment arm. Overall, the standard parametric extrapolations visually fit the KM data better than the mixture-cure approach, particularly for OS, but had much more variable extrapolations, demonstrating the high level of uncertainty associated with predicting 25 years of extrapolations from 28.2 months of data. The extrapolations were difficult to interpret and several appeared to underestimate expected survival for DLBCL patients. While it may be clinically plausible for PFS and OS to have long tails (patients can achieve long remission/cured status, there are downstream curative treatments available), it may be best to take a more conservative approach in the absence of long-term data in both models.
- 6.31 The submission claimed the standard parametric extrapolations for PFS were not clinically plausible and the preferred gamma functions underestimated PFS compared to propensity score matched data from the GOYA trial, illustrated in Figure below. GOYA was a multicentre phase 3 trial in untreated DLBCL comparing obinutuzumab-CHOP and R-CHOP, with longer follow-up (up to 78.2 months with a median observation time of 47.4 months) available compared to the POLARIX trial. The figure includes the 'corrected' extrapolations estimated during the evaluation that do not impose an assumption that PFS mortality rate cannot be less than the OS mortality rate. The PSCR stated that the propensity score weighting method was used to minimise any bias or confounding due to differences in the distributions of clinical baseline characteristics or geographical regions between GOYA and POLARIX. The ESC considered that there were some concerns with the validation, including that i) GOYA presented data to 5 years only, ii) the model overestimated PFS compared to GOYA at 5 years, and iii) there was no validation of the OS estimates.

Figure 4: Comparison of POLARIX PFS extrapolations to GOYA trial data



Source: adapted from Figures 3.9 and 3.10 in the submission.

KM = Kaplan-Meier, IPI = International Prognostic Index, ITT = intention to treat, Pola+R-CHP = polatuzumab vedotin in combination with cyclophosphamide, doxorubicin and prednisone, R-CHOP = rituximab in combination with cyclophosphamide, doxorubicin, vincristine and prednisone

6.32 Despite some concerns about whether the POLARIX and GOYA populations were adequately matched, the external validation of the PFS curves for R-CHOP at 5 years does not validate the key assumptions of the submission's mixed cure model or the implications these assumptions have for deriving the predicted survival benefit with Pola+R-CHP. Though it is reasonable to account for cured patients when modelling the costs and consequences of treatments for DLBCL, the submission's implementation of a mixture-cure model was not reasonable for the following reasons:

- The assumptions of the mixture-cure model presented in the submission imply that patients who develop progressing disease following first-line treatment (informed by the PFS trial data) would not be cured following second- or third-line treatments. In practice, patients can receive further therapies with curative intent, including stem cell transplant and CAR-T. Consequently, the model predicts a sharp divergence in OS between the treatment arms beyond 28.2 months, which may not be realistic (the trial evidence showed no difference in OS up to 28.2 months). This also means that while the model included costs from subsequent treatments, the benefits of these treatments were not included. The PSCR stated that the use of the cure fraction did not mean that patients who progress following first-line treatment will not benefit from subsequent treatment, as this benefit was inherently captured in the OS trial data from POLARIX and is maintained with extrapolation of OS over the time horizon in the model. The ESC noted that although the OS trial data does capture the benefits of some subsequent treatments, the model estimated a much higher excess rate of mortality for patients in the R-CHOP arm despite no significant difference in OS in the trial. This was because the estimated cure fraction following first-line treatment was lower (i.e. the treatment effect observed for PFS (first-line treatment) was used as a surrogate to manufacture a difference in the OS extrapolations). The ESC considered that the model ignored the potential benefits of subsequent treatments on OS and implied that patients who progress following first-line treatment will die

from DLBCL, resulting in the sharp divergence in OS between the Pola+R-CHP and R-CHOP arms beyond the trial period (28 months).

- The KM data in the POLARIX trial at the presented data-cut (June 2021) appeared too immature to estimate a reliable mixture-cure model, particularly a model that jointly estimates the cure fractions and survival functions. The estimated functions do not appear to have a good visual fit of the KM data (overestimates PFS for Pola+R-CHP and OS in both arms) and there was considerable variation around the cure fractions and differences in the cure fractions. As noted in Grant 2020, cure fractions should only be statistically calculated from mature KM data that is plateauing, but the POLARIX data does not meet these criteria (median PFS, OS not achieved, limited evidence of plateauing PFS). The ESC agreed with the evaluation that it is difficult to detect a plateau in PFS at 24 months from the evidence provided. However, the ESC considered that the assumption to define a patient as cured if they remained progression free at 2 years was reasonable from a clinical perspective for this condition. However, ESC considered the modelled cure rates (74.7% vs 63.6% for the ITT population and 77.1% vs 62.7% for the IPI3-5 subgroup) were poorly supported and the incremental difference was optimistic.
- Based on the submission's preferred log-normal function (used in the base case analysis for the PBS subgroup), the estimated cure fraction for Pola+R-CHP (77.1%) was higher than PFS at 24 months in the trial (75.16%) whereas the estimated cure fraction for R-CHOP (62.7%) was lower than the PFS at 24 months in the trial (65.12%). The corresponding cure points were also relatively early in the model where the vast majority of 'uncured' patients had disease progression by 2 years, compared to the literature that suggested a further 5% to 13% develop progressing disease between 2 years to 5 years. The PSCR stated that the cure fraction was estimated using background mortality and the hazard of event as a function of time in all the observed data. The PSCR further stated that as this fraction is estimated jointly with parameters of the chosen standard parametric survival function using the maximum likelihood method, the cure fraction also takes into consideration the late events that are expected to occur after trial follow-up. The ESC considered that although the cure fraction was not measured at a specific time point, it should represent the total proportion of patients cured after first-line treatment by the end of follow-up, and therefore, should not exceed the proportion who were considered cured at an earlier time point in the trial (e.g. 2 years).
- In the extrapolated portion of the base case (28.2 months to 25 years), mortality for patients in PFS each cycle had to be less than or equal to mortality for all patients. This restriction meant that patients in PFS and PD had the same mortality rate for most of the time horizon, which is inconsistent with the assumption of the mixture-cure model that uncured patients have worse survival than cured patients. However, if extrapolations were run from time 0, PFS was not adjusted for OS at all and PFS could exceed OS. Indeed, under the base case choice of extrapolations (log-

normal for PFS and OS) in the IPI 3-5 model, PFS exceeded OS from Week 2 to Week 14, resulting in negative numbers of patients in PD during this time.

- Even when the mixture-cure extrapolations were implemented as expected (i.e. followed the estimated PFS and OS curves, without an additional restriction on the mortality rate), survival remained high for uncured patients. In the IPI 3-5 model >20% of uncured patients alive at 28.2 months remained alive at 20 years in the Pola+R-CHP arm (versus ~14% in the R-CHOP arm). In the ITT model, survival for uncured patients was better in both arms, with 31-33% of the patients alive and in progressed disease at 28.2 months still alive at 20 years. The IPI 3-5 model therefore predicted both a larger proportion of cured patients on Pola+R-CHP versus R-CHOP and better survival for uncured patients who received Pola+R-CHP versus those who received R-CHOP. This additional benefit favoured the Pola+R-CHP arm in the IPI 3-5 model, and was not justified by the submission.

6.33 The model estimated treatment costs for Pola+R-CHP and R-CHOP based on time to treatment discontinuation (TTD) data from POLARIX, independent of PFS. The model applied a half cycle correction to estimate the proportion of patients on each treatment each 21 day cycle, and then restricted time on treatment to not exceed 6 (polatuzumab vedotin and CHP) or 8 cycles (rituximab). The treatment costs per cycle were based on the approved AEMP (mark up and fees at June 2022), recommended doses, and average weight or body surface area of patients enrolled in POLARIX ITT. The submission's approach considerably underestimated the mean number of treatment cycles compared to those reported in POLARIX (see Table 9). If cost of treatment was based on the mean number of cycles in POLARIX, the ITT model incremental cost effectiveness ratio (ICER) increased from \$115,000 to < \$135,000 in the base case to \$115,000 to < \$135,000 per quality adjusted life year (QALY) gained. Mean number of cycles were not reported for the IPI 3-5 subgroup, but are likely similar to the ITT based on the TTD KM data and therefore the ICER would increase from \$55,000 to < \$75,000 per QALY gained in the base case to \$55,000 to < \$75,000 per QALY gained. The submission also overestimated the cost of vincristine, but this error had minimal impact on the ICER because the cost of vincristine is comparatively small. The PSCR provided a revised model which removed the half cycle correction for first line drug costs and corrected the vincristine cost.

**Table 9: Number of cycles of first line treatment included in the economic evaluation**

| Resource item       | Unit cost / treatment cycle | Mean cycles in model |        |            |        | Mean cycles in POLARIX |        |
|---------------------|-----------------------------|----------------------|--------|------------|--------|------------------------|--------|
|                     |                             | ITT                  |        | IPI 3-5    |        | ITT                    |        |
|                     |                             | Pola+R-CHP           | R-CHOP | Pola+R-CHP | R-CHOP | Pola+R-CHP             | R-CHOP |
| Polatuzumab vedotin | \$█ / treatment cycle       | 5.35                 | -      | 5.32       | -      | 5.8                    | N/A    |
| Rituximab           | \$591.89 / treatment cycle  | 7.20                 | 6.99   | 7.16       | 6.82   | 7.6                    | 7.4    |
| Cyclophosphamide    | \$151.86 / treatment cycle  | 5.38                 | 5.28   | 5.35       | 5.18   | 5.8                    | 5.7    |
| Doxorubicin         | \$146.40 / treatment cycle  | 5.38                 | 5.28   | 5.35       | 5.18   | 5.8                    | 5.7    |
| Vincristine         | \$202.00 / treatment cycle  | -                    | 5.24   | -          | 5.15   | N/A                    | 5.7    |
| Prednisone          | \$2.69 / treatment cycle    | 5.47                 | 5.33   | 5.45       | 5.23   | 5.8                    | 5.7    |

Source: compiled during the evaluation from Sheets 'Pola+R-CHP' and 'R-CHOP' of Excel files 'Economic Evaluation\_ITT.xlsx' and 'Economic Evaluation\_IPI 3-5.xlsx'

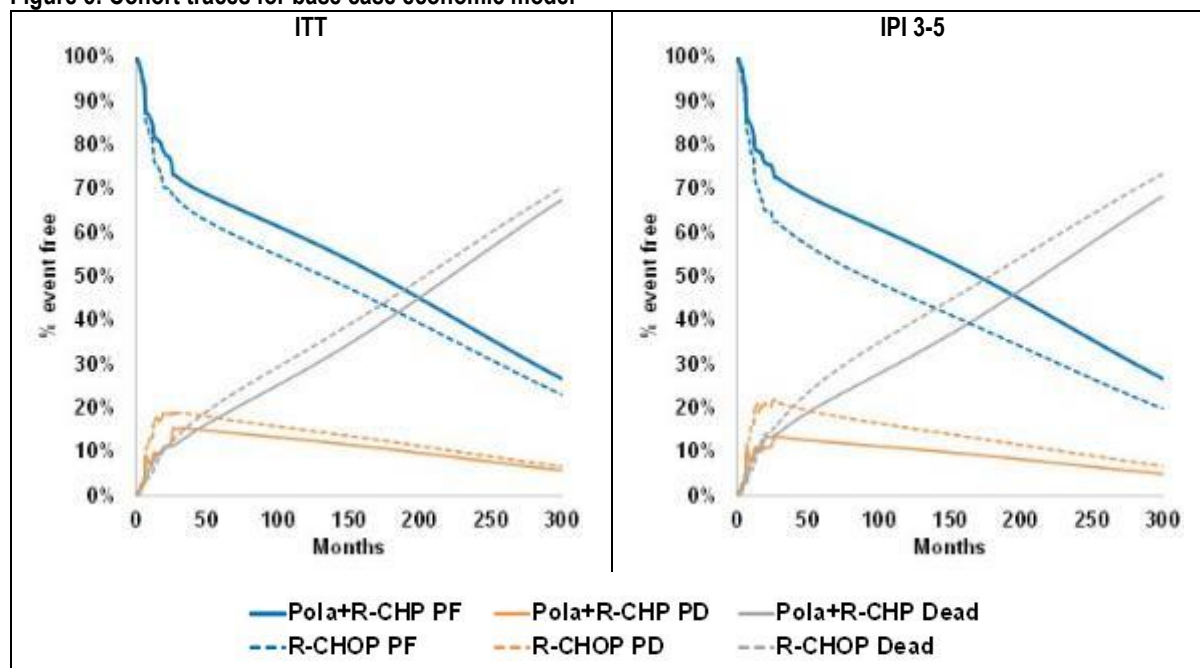
IPI = International Prognostic Index, ITT = intention to treat, PD = progressed disease, PF = progression free, Pola+R-CHP = polatuzumab vedotin in combination with cyclophosphamide, doxorubicin and prednisone, R-CHOP = rituximab in combination with cyclophosphamide, doxorubicin, vincristine and prednisone

<sup>a</sup> cycles calculated during time on treatment. MRU costs continued for patients who were off treatment and progression free.

6.34 Costs for subsequent therapies (e.g. radiotherapy, rituximab plus gemcitabine and oxaliplatin (R-GemOx), SCT, CAR-T, etc) were based on the occurrence of subsequent treatment in POLARIX ITT. Costs of subsequent therapies were based on published literature, PBS items and AR-DRG codes. Cost of CAR-T was assumed as \$500,000 per patient. As median PFS was not yet reached, it was possible that subsequent treatment patterns could look very different with longer-term data and that not all subsequent treatments were yet captured. It was also not clear why proportions of treatments were not averaged across treatment arms, as the benefits of the treatments were unlikely to be captured by the data and the submission's approach implied that patients who relapsed after Pola+R-CHP would be less likely to receive stem cell transplants (15% vs 19%) or CAR-T (8% vs 10%) than patients who received R-CHOP. The ESC considered that this was unreasonable, noting that there was no clinical reason why the proportional split of subsequent therapies would differ between the treatment arms. As subsequent therapy costs were the largest cost offset in the model, the ICER was moderately sensitive to the cost of subsequent therapies. The pre-PBAC response presented a revised base case in which the same proportions of subsequent therapies were applied across both treatment arms.

6.35 Cohort traces are presented for model validation in Figure 5. Long-term survival and PFS for the Pola+R-CHP arm were similar across the ITT and IPI 3-5 models, but PFS (and to some extent OS) was worse for the IPI 3-5 model for R-CHOP arm. For the majority of the time horizon patients were either in PFS or dead state, with a low percentage of patients entering the PD health state, which was consistent with the assumptions of the mixture-cure model, estimated cure fractions and the additional restriction on the assumed mortality rates. At the end of the 25-year time horizon, 20-30% patients remained alive and progression free, and around 10% patients remained alive and in progressed disease.

Figure 5: Cohort traces for base case economic model



Source: compiled during the evaluation from Excel files 'Economic Evaluation\_ITT.xlsx' and 'Economic Evaluation\_IPI 3-5.xlsx'. IPI = International Prognostic Index, ITT = intention to treat, PD = progressed disease, PF = progression free, Pola+R-CHP = polatuzumab vedotin in combination with cyclophosphamide, doxorubicin and prednisone, R-CHOP = rituximab in combination with cyclophosphamide, doxorubicin, vincristine and prednisone

6.36 The modelled PFS rates for R-CHOP generally aligned with the estimated rates in the matched GOYA analysis (see Figure 4) and the broader literature at 2 years, but may overestimate PFS beyond this point. Similarly, the model estimates of survival seem broadly in line with published estimates, if towards the high end, for the first 5 years, but there is high uncertainty beyond this point and may be overestimated, particularly for an Australian population where mean age of diagnosis with NHL is over 70 years (based on AIHW numbers from 2020<sup>10</sup>).

6.37 The key drivers of the model are reported in Table 10.

<sup>10</sup> Australian Institute of Health and Welfare (AIHW) 2022 Cancer Data in Australia; Canberra: AIHW. <<https://www.aihw.gov.au/reports/cancer/cancer-data-in-australia/>>.

Table 10: Key drivers of the model

| Description                  | Method/Value  | Impact<br>Base case: \$■ <sup>1</sup> /QALY gained   |
|------------------------------|---|--|
| Patient population           | The subgroup of patients with IPI score 3-5 was chosen as the base case, but this was not a well-justified subgroup of the ITT population of POLARIX (who had scores IPI 2-5).  | High, favoured Pola+R-CHP. When modelling the ITT population, the ICER increased to \$■ <sup>2</sup> /QALY.  |
| Time horizon                 | The time horizon was 25 years extrapolated from median follow-up in POLARIX (28.2 months). The majority of the benefit for Pola+R-CHP vs R-CHOP was gained during the extrapolated period.  | High, favoured Pola+R-CHP. ICER increased to \$■ <sup>3</sup> /QALY when time horizon was reduced to 15 years.   |
| Extrapolation approach       | Treatment effect continued beyond 28.2 month trial period for up to 25 years using the mixture-cure assumptions. The implementation of the mixture-cure approach was likely inappropriate given the data had not yet plateaued and as such the mixture-cure extrapolations poorly fitted the data and led to an increase in OS for Pola+R-CHP which was not observed in the data. | High, favoured Pola+R-CHP. If PFS extrapolations were based on best fitting standard parametric survival functions the ICER increased to \$■ <sup>3</sup> /QALY. If no OS benefit was assumed after KM the ICER increased to \$■ <sup>4</sup> /QALY. |
| Time on first line treatment | Time on treatment was based on TTD KM data from POLARIX capped at 6 cycles (for Pola and CHP) or 8 cycles (for rituximab) with half cycle correction applied. This resulted in fewer cycles of treatment (mean 5.3) than reported in POLARIX (mean 5.8).  | Moderate, favoured Pola+R-CHP. When mean cycles were taken from POLARIX, the ICER increased to \$■ <sup>1</sup> /QALY.   |
| Subsequent therapies         | Subsequent therapies were the largest cost-offset in the model and calculated as one-off costs based on distribution of subsequent therapies in POLARIX, by treatment arm. POLARIX likely does not capture all future subsequent therapies and the submission did not justify why introduction of polatuzumab vedotin would alter the likelihood of some subsequent therapies.    | Moderate, favoured Pola+R-CHP. If proportions of subsequent therapies were equal across arms the ICER increased to \$■ <sup>1</sup> /QALY. If cost of CAR-T was reduced to \$300,000 the ICER increased to \$■ <sup>1</sup> /QALY.                   |

Source: compiled during the evaluation from Excel files 'Economic Evaluation\_ITT.xlsx' and 'Economic Evaluation\_IPI 3-5.xlsx'

The redacted values correspond to the following ranges:

<sup>1</sup> \$55,000 to < \$75,000

<sup>2</sup> \$115,000 to < \$135,000

<sup>3</sup> \$75,000 to < \$95,000

<sup>4</sup> \$155,000 to < \$255,000

6.38 Base case results for both ITT and IPI 3-5 models are presented in Table 11. The majority of the incremental costs were accrued in the first 28.2 months of the model, and the majority of benefits were accrued in the extrapolated time horizon. The base case ICER for the ITT population was \$115,000 to < \$135,000 per QALY gained versus \$55,000 to < \$75,000 for the IPI 3-5 model. Incremental costs were similar across the models, with larger incremental life year and QALY gains in the IPI 3-5 model.

6.39 The PSCR presented a revised model which corrected for 3 errors (half cycle correction was removed from the first-line drug costs, the price of vincristine was corrected and the PFS extrapolation was adjusted so the PFS was only equal to OS in the event that the PFS extrapolation was higher than the OS extrapolation estimate). This resulted in a base case ICER of \$55,000 to < \$75,000 per QALY gained for the IPI 3-5 model. A further analysis, which removed the half cycle correction from all costs and benefits, resulted in an ICER of \$55,000 to < \$75,000 per QALY gained for the IPI 3-5 model and \$115,000 to < \$135,000 per QALY gained for the ITT population.

Table 11: Results of the stepped economic evaluation (base case)

| Step and component  | ITT        |          |                        | IPI 3-5    |          |                        |
|---|------------|----------|------------------------|------------|----------|------------------------|
|   | Pola+R-CHP | R-CHOP   | Increment              | Pola+R-CHP | R-CHOP   | Increment              |
| <b>Step 1: Time horizon, trial based: 28.2 months, treatment costs only</b>                               |            |          |                        |            |          |                        |
| Costs   | \$█        | \$7,692  | \$█                    | \$█        | \$7,542  | \$█                    |
| LYs   | 2.11       | 2.12     | -0.01                  | 2.08       | 2.08     | 0.00                   |
| QALYs   | 1.67       | 1.68     | -0.00                  | 1.65       | 1.64     | 0.01                   |
| <b>Incremental cost/extra QALY gained</b>   |            |          | <b>Dominated</b>       |            |          | <b>█<sup>3</sup></b>   |
| <b>Step 2: Time horizon 25 years, treatment costs only</b>  |            |          |                        |            |          |                        |
| Costs   | \$█        | \$7,692  | \$█                    | \$█        | \$7,542  | \$█                    |
| LYs   | 10.43      | 9.98     | 0.45                   | 10.14      | 9.33     | 0.81                   |
| QALYs   | 8.33       | 7.95     | 0.39                   | 8.11       | 7.41     | 0.70                   |
| <b>Incremental cost/extra QALY gained</b>   |            |          | <b>\$█<sup>1</sup></b> |            |          | <b>\$█<sup>4</sup></b> |
| <b>Step 3: Time horizon 25 years, treatment and MRU costs</b>   |            |          |                        |            |          |                        |
| Costs   | \$█        | \$10,362 | \$█                    | \$█        | \$10,118 | \$█                    |
| LYs   | 10.43      | 9.98     | 0.45                   | 10.14      | 9.33     | 0.81                   |
| QALYs   | 8.33       | 7.95     | 0.39                   | 8.11       | 7.41     | 0.70                   |
| <b>Incremental cost/extra QALY gained</b>   |            |          | <b>\$█<sup>1</sup></b> |            |          | <b>\$█<sup>4</sup></b> |
| <b>Step 4: Time horizon 25 years, treatment, MRU, AE costs</b>  |            |          |                        |            |          |                        |
| Costs   | \$█        | \$12,415 | \$█                    | \$█        | \$12,170 | \$█                    |
| LYs   | 10.43      | 9.98     | 0.45                   | 10.14      | 9.33     | 0.81                   |
| QALYs   | 8.33       | 7.95     | 0.39                   | 8.11       | 7.41     | 0.70                   |
| <b>Incremental cost/extra QALY gained</b>   |            |          | <b>\$█<sup>1</sup></b> |            |          | <b>\$█<sup>4</sup></b> |
| <b>Step 5: Time horizon 25 years, treatment, MRU, AE, subsequent therapy costs</b>                        |            |          |                        |            |          |                        |
| Costs   | \$█        | \$43,930 | \$█                    | \$█        | \$47,115 | \$█                    |
| LYs   | 10.43      | 9.98     | 0.45                   | 10.14      | 9.33     | 0.81                   |
| QALYs   | 8.33       | 7.95     | 0.39                   | 8.11       | 7.41     | 0.70                   |
| <b>Incremental cost/extra QALY gained</b>   |            |          | <b>\$█<sup>2</sup></b> |            |          | <b>\$█<sup>5</sup></b> |
| <b>Step 6: Time horizon 25 years, all costs</b>   |            |          |                        |            |          |                        |
| Costs   | \$█        | \$44,884 | \$█                    | \$█        | \$48,156 | \$█                    |
| LYs   | 10.43      | 9.98     | 0.45                   | 10.14      | 9.33     | 0.81                   |
| QALYs   | 8.33       | 7.95     | 0.39                   | 8.11       | 7.41     | 0.70                   |
| <b>Incremental cost/extra QALY gained</b>   |            |          | <b>\$█<sup>2</sup></b> |            |          | <b>\$█<sup>5</sup></b> |
| <b>Revised base case presented in PSCR</b>  |            |          |                        |            |          |                        |
| Costs   | NR         | NR       | NR                     | \$█        | \$48,155 | \$█                    |
| LYs   | NR         | NR       | NR                     | 10.14      | 9.33     | 0.81                   |
| QALYs   | NR         | NR       | NR                     | 8.14       | 7.45     | 0.69                   |
| <b>Incremental cost/extra QALY gained</b>   |            |          | <b>NR</b>              |            |          | <b>\$█<sup>5</sup></b> |
| <b>Revised base case presented in PSCR with half cycle correction removed from all costs and benefits</b> |            |          |                        |            |          |                        |
| Costs   | \$█        | \$46,151 | \$█                    | \$█        | \$50,126 | \$█                    |
| LYs   | 10.43      | 9.99     | 0.45                   | 10.14      | 9.33     | 0.81                   |
| QALYs   | 8.35       | 7.96     | 0.39                   | 8.14       | 7.45     | 0.69                   |
| <b>Incremental cost/extra QALY gained</b>   |            |          | <b>\$█<sup>2</sup></b> |            |          | <b>\$█<sup>5</sup></b> |

Source: Tables 3.20-3.26 pp107-110 of the submission, the PSCR and compiled during the evaluation from Sheet 'Results' Excel files 'Economic Evaluation\_ITT.xlsx' and 'Economic Evaluation\_IPI 3-5.xlsx'

AE= adverse event, IPI = International Prognostic Index, ITT = intention to treat, LY = life year, MRU = medical resource use, Pola+R-CHP = polatuzumab vedotin in combination with cyclophosphamide, doxorubicin and prednisone, QALY = quality adjusted life year R-CHOP = rituximab in combination with cyclophosphamide, doxorubicin, vincristine and prednisone

Costs for Pola+R-CHP arm in Step 1 and 2 were misreported as \$█ in the submission. The LYs, QALYs and ICER in Step 1 of the submission were based on rounding the time horizon down to the nearest week for the benefits (Steps 2-6 rounded up) and therefore differed slightly: \$█

The redacted values correspond to the following ranges:

<sup>1</sup> \$135,000 to < \$155,000

<sup>2</sup> \$115,000 to < \$135,000

<sup>3</sup> > \$1,055,000

<sup>4</sup> \$75,000 to < \$95,000

<sup>5</sup> \$55,000 to < \$75,000

- 6.40 The cost of polatuzumab vedotin was the largest contributor to incremental cost (133.2% and 142.1% of total incremental cost in ITT and IPI 3-5 models respectively), and cost of subsequent therapy the largest cost offset (-32.0% and -41.1% in ITT and IPI 3-5 models respectively). Total costs were similar but higher in the IPI 3-5 model compared to the ITT model, driven largely by the higher cost of subsequent therapy for both polatuzumab vedotin and R-CHOP arms.
- 6.41 Most life years and QALYs were accrued in the PFS health state for both treatment arms, and was the largest contributor to the incremental QALYs with Pola+R-CHP (160.3% and 164.8% in the ITT and IPI 3-5 model respectively). The R-CHOP arm accrued more QALYs in the progressed disease health state than the Pola+R-CHP arm. Incremental life years were similar to the incremental QALYs within each model, suggesting the incremental life years drove the benefit gain seen in the models. As noted previously, this life year gain was driven entirely by the assumptions of mixture-cure modelling that improved PFS following first-line treatment will lead to sustained survival benefit over the lifetime of the patient.
- 6.42 Table 12 presents key sensitivity analyses in the ITT and PBS models. The ICERs were most sensitive to the method of extrapolation, time horizon and time on treatment.

Table 12: Results of model sensitivity analyses

| Analyses  | ITT model   |      |                  | IPI 3-5 model |      |                   |
|---|-------------|------|------------------|---------------|------|-------------------|
|   | Incremental |      | ICER             | Incremental   |      | ICER              |
|   | Cost        | QALY |                  | Cost          | QALY |                   |
| <b>Base case</b>  | \$█         | 0.39 | \$█ <sup>1</sup> | \$█           | 0.70 | \$█ <sup>2</sup>  |
| Discounting (base 5% costs and benefits)  |             |      |                  |               |      |                   |
| 0%  | \$█         | 0.70 | \$█ <sup>2</sup> | \$█           | 1.26 | \$█ <sup>9</sup>  |
| 1.5%  | \$█         | 0.58 | \$█ <sup>3</sup> | \$█           | 1.04 | \$█ <sup>10</sup> |
| 3.5%  | \$█         | 0.46 | \$█ <sup>4</sup> | \$█           | 0.82 | \$█ <sup>11</sup> |
| Time horizon (base 25 years)  |             |      |                  |               |      |                   |
| 10 years  | \$█         | 0.17 | \$█ <sup>5</sup> | \$█           | 0.30 | \$█ <sup>7</sup>  |
| 15 years  | \$█         | 0.27 | \$█ <sup>6</sup> | \$█           | 0.49 | \$█ <sup>3</sup>  |
| 20 years  | \$█         | 0.34 | \$█ <sup>7</sup> | \$█           | 0.62 | \$█ <sup>2</sup>  |
| No half cycle correction  | \$█         | 0.39 | \$█ <sup>1</sup> | \$█           | 0.70 | \$█ <sup>2</sup>  |
| Extrapolations (base mixture-cure model, ITT model PFS and OS gamma, IPI 3-5 model PFS and OS log-normal) |             |      |                  |               |      |                   |
| Standard parametric survival (same functions as base case)  | \$█         | 0.34 | \$█ <sup>1</sup> | \$█           | 0.75 | \$█ <sup>11</sup> |
| Standard parametric survival (OS same functions as base case, PFS Pola+R-CHP log-normal, R-CHOP gamma)    | \$█         | 0.32 | \$█ <sup>6</sup> | \$█           | 0.66 | \$█ <sup>3</sup>  |
| OS curves equal after KM<br>Pola+R-CHP match R-CHOP   | \$█         | 0.13 | \$█ <sup>5</sup> | \$█           | 0.21 | \$█ <sup>6</sup>  |
| Utilities (base from POLARIX)   |             |      |                  |               |      |                   |
| Tran 2017   | \$█         | 0.38 | \$█ <sup>1</sup> | \$█           | 0.70 | \$█ <sup>2</sup>  |
| Wang 2018   | \$█         | 0.36 | \$█ <sup>1</sup> | \$█           | 0.66 | \$█ <sup>2</sup>  |
| GOYA  | \$█         | 0.40 | \$█ <sup>4</sup> | \$█           | 0.72 | \$█ <sup>2</sup>  |
| Mean number of cycles directly from POLARIX (base case TTD KM, with cap and half cycle correction)        | \$█         | 0.39 | \$█ <sup>1</sup> | \$█           | 0.70 | \$█ <sup>2</sup>  |
| Proportion subsequent therapies (base options differ by treatment arm)                                    |             |      |                  |               |      |                   |
| Equal options across treatment arms   | \$█         | 0.39 | \$█ <sup>1</sup> | \$█           | 0.70 | \$█ <sup>2</sup>  |
| Cost of CAR-T (base \$500,000)  |             |      |                  |               |      |                   |
| \$300,000   | \$█         | 0.39 | \$█ <sup>1</sup> | \$█           | 0.70 | \$█ <sup>2</sup>  |
| \$700,000   | \$█         | 0.39 | \$█ <sup>1</sup> | \$█           | 0.70 | \$█ <sup>11</sup> |
| <b>Multivariate sensitivity analysis</b>  |             |      |                  |               |      |                   |
| PSCR model + 15 year TH, OS equal in both arms and subsequent therapies equal in both arms                | \$█         | 0.11 | \$█ <sup>8</sup> | -             | -    | -                 |

Source: Table 3.28, p112 of the submission and compiled during the evaluation from Excel files 'Economic Evaluation\_ITT.xlsx' and 'Economic Evaluation\_IPI 3-5.xlsx'

ICER = incremental cost effectiveness ratio, IPI = International Prognostic Index, ITT = intention to treat, OS= overall survival, PFS = progression free survival, Pola+R-CHP = polatuzumab vedotin in combination with cyclophosphamide, doxorubicin and prednisone, QALY = quality adjusted life year R-CHOP = rituximab in combination with cyclophosphamide, doxorubicin, vincristine and prednisone, TH = time horizon

The redacted values correspond to the following ranges:

<sup>1</sup> \$115,000 to < \$135,000

<sup>2</sup> \$55,000 to < \$75,000

<sup>3</sup> \$75,000 to < \$95,000

<sup>4</sup> \$95,000 to < \$115,000

<sup>5</sup> \$255,000 to < \$355,000

<sup>6</sup> \$155,000 to < \$255,000

<sup>7</sup> \$135,000 to < \$155,000

<sup>8</sup> \$455,000 to < \$555,000

<sup>9</sup> \$25,000 to < \$35,000

<sup>10</sup> \$35,000 to < \$45,000

<sup>11</sup> \$45,000 to < \$55,000

- 6.43 Overall, the ESC considered that the economic analyses presented in the submission and the PSCR were optimistic. The ESC considered that the model should reflect the modest benefit in PFS. In addition, the ESC considered that it was uncertain whether the improvement in PFS would lead to an improvement in OS, and if so, considered that only a small magnitude of effect would be clinically plausible, as no difference in OS or complete response was observed in the POLARIX trial. The ESC also considered that any future model should reduce the time horizon, and apply the same proportions of subsequent therapies across both treatment arms.
- 6.44 The pre-PBAC response presented a revised model building on the changes presented in the PSCR (see paragraph 6.39) which removed the half cycle correction from all costs and benefits, applied the same proportions of subsequent therapies across both treatment arms, reduced the time from 25 to 20 years and reduced the effective ex-manufacturer price of polatuzumab vedotin by |%, resulting in an ICER of \$35,000 to < \$45,000 per QALY gained for the IPI 3-5 model and \$75,000 to < \$95,000 per QALY gained for the ITT population.

***Pola+R-CHP cost/patient/course (base ITT: \$█, IPI 3-5: \$█ based on submission price)***

- 6.45 When the cost of vincristine was corrected to \$44.61 for 5 x 1 mg vials (rather than \$44.61 for 1 x 1 mg vial in the submission), based on the price for polatuzumab vedotin proposed in the submission the modelled cost per cycle for Pola+R-CHP was \$| for cycles 1-6, and \$| for cycles 7-8, resulting a total cost of \$| per patient in the ITT model and \$| per patient in the IPI 3-5 model. In comparison the modelled cost per cycle for R-CHOP was \$1,022.85 for cycles 1-6, and \$591.89 for cycles 7-8, resulting a total cost of \$6,406 per patient in the ITT model and \$6,264 per patient in the IPI 3-5 model. As noted in Table 9, the model underestimated the mean number of cycles compared to the trial data.
- 6.46 The financial estimates assumed equal costs of rituximab, cyclophosphamide and prednisone across treatment arms, and therefore only costed for polatuzumab vedotin and vincristine. Based on the polatuzumab vedotin price proposed in the submission, this resulted in an incremental cost/patient/course of \$| (total net cost PBS/RPBS) and \$| (total net cost to PBS/RPBS and MBS) compared to \$| and \$| in the ITT and IPI 3-5 models respectively.
- 6.47 The pre-PBAC response proposed a █% reduction in the effective ex-manufacturer prices of polatuzumab vedotin (140 mg = \$|; 30 mg = \$|).

***Estimated PBS usage & financial implications***

- 6.48 This submission was not considered by DUSC.
- 6.49 The submission estimated the financial implications of the proposed listing using an epidemiological approach, including only incident patients given the aggressive nature of DLBCL (i.e., relatively short duration from diagnosis to first-line treatment). The

submission did not separately estimate the number of grandfathered patients because the proposed epidemiological approach would capture these patients.

**Table 13: Data sources and parameter values applied in the utilisation and financial estimates**

| Data  | Value  | Source   | Comment   |
|---|--|--|---|
| <b>Eligible population</b>  |  |  |   |
| Number of NHL patients  | Yr 1: 6,839<br>Yr 2: 7,079<br>Yr 3: 7,306<br>Yr 4: 7,552<br>Yr 5: 7,805<br>Yr 6: 8,067 | Australian Cancer Incidence and Mortality (ACIM) book for NHL (2021). For the years 2018 to 2028, the submission extrapolated incidence rates using the average annual growth over the last 10 years (2008-2017). Annual growth appeared to be 3.36% for Yr 1 to Yr 6. | The submission did not provide sufficient detail to verify these estimates. During the evaluation, attempts were made to estimate the number of NHL patients by using linear extrapolation and by assuming an average annual growth of 3.41%. These methods resulted in lower patient numbers (by 6-7%) than the submission's estimate. The PSCR confirmed that the annual growth rate applied in the submission was 3.36%.   |
| % of NHL patients with DLBCL  | 36%.<br>Reduced to 35% in PSCR.  | METIS Healthcare Research (2021). Sponsor-commissioned market research, which interviewed 30 clinicians about the characteristics and treatment of previously untreated DLBCL patients   | Likely an overestimate. Other studies/data in Australia (Van Leeuwen et al 2014 <sup>a</sup> ), Canada (Ye et al 2017 <sup>b</sup> ) and the US (The Surveillance, Epidemiology and End Results (SEER) fact sheets <sup>c</sup> ) estimate that a lower proportion of NHL patients have DLBCL, approximately 18%-29%. Further, DUSC previously 'considered that a more accurate proportion of NHL comprised of DLBCL may be between 25% - 35%' (p4 of 5.09 DUSC advice for polatuzumab vedotin). The PSCR reduced the proportion to 35% but stated that the application of 36% was appropriate as it was from the most recent Australian specific data and within the range reported by the Leukaemia Foundation of 30-40%. |
| % of DLBCL patients who fit enough for treatment                        | 88%.<br>Reduced to 82% in the PSCR.  | Based on METIS Healthcare Research (2021), which estimated that 72% of patients are treated with R-CHOP and 16% with R-mini-CHOP.  | Likely an overestimate, as R-mini-CHOP patients, who are able unable to manage the toxicities of R-CHOP are unlikely to be fit enough for treatment with Pola+R-CHP. The PSCR reduced the proportion to 82% in the PSCR, but stated that exclusion of patients receiving R-mini-CHOP was inappropriate unless other intensified regimens were also considered (i.e. patients treated with DA-EPOCH-R or R-CHEOP-14).  |
| % of DLBCL patients with IPI 3-5  | 30%.<br>Increased to 50.9% in the PSCR.  | METIS Healthcare Research (2021).  | Likely an underestimate. Recent Australian data (2019) from the Lymphoma and Related Diseases Register provided in the submission found 49.3% of newly diagnosed patients have a revised-IPI score 3-5, while an older population-based study by Sehn et al 2007 <sup>d</sup> found 46% of patients treated with R-CHOP in Canada had an IPI 3-5. The PSCR agreed with the evaluation, citing an updated estimate from the LaRDR 2022 report, which stated that 50.9% of Australian DLBCL patients have an IPI score of 3 to 5.   |
| Grandfathered patients  | 0  | The estimated 59 patients currently accessing treatment are assumed to be included by using the above methods  | -   |
| Prevalent patients  | 0  | Submission does not anticipate a prevalent pool of previously untreated DLBCL patients   | -   |
| <b>Treatment utilisation</b>  |  |  |   |
| Uptake rate   | Yr 1: █ %<br>Yr 2: █ %<br>Yr 3: █ %<br>Yrs 4-6: █ %                                    | Assumption.  | Potential underestimate, given the claim of superior efficacy and non-inferior safety compared to R-CHOP.   |
| Mean scripts of polatuzumab vedotin per patient treated with Pola+R-CHP | 5.8 scripts (140 mg per script)  | Based on the recommended dose in the draft PI, and the average weight/ cycles administered in POLARIX  | Generally reasonable, although it may be more appropriate to cost the scripts based on the number/type of vials required using the distribution of patient weight (i.e. 4x30 mg vials for   |

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| Data  | Value  | Source   | Comment  |
|---|--|--|--|
|   |  |  | 51-67 kg; 1x140 mg vial for 68-78 kg; 5x30 mg vials for 79-83 kg; etc.).   |
| Mean scripts of vincristine per patient treated with R-CHOP | 5.7 scripts (2 mg per script)                                      | Based on the recommended dose in the PI, and the body surface area / cycles administered in POLARIX.                                     | -  |
| <b>Costs</b>  |  |  |  |
| Polatuzumab vedotin   | Weighted dispense price per 140 mg dose: \$ [REDACTED] (effective) | Based on the proposed effective AEMP, proportional use in private and public hospitals and the EFC mark ups in June 2022.                | Consistent with the proposed effective AEMP.   |
| Vincristine   | Weighted dispense price per 2 mg dose: \$202.00                    | Based on the published AEMP for vincristine, assumed proportional use in private and public hospitals and the EFC mark ups in June 2022. | The submission incorrectly assumed the AEMP for vincristine corresponded to 1x1 mg vials rather than 5x1 mg vials. Based on the correct AEMP per vial (i.e. \$44.61 / 5 = approx. \$8.92), the weighted dispense price for 2 mg vincristine equals \$130.00. Overall, this error had minimal impacts on the net financial estimates and results were subsequently not updated during the evaluation. |
| Reduction in patients requiring an ASCT due to Pola + R-CHP | 4%   | Assumption.  | Uncertain. In the ITT population of POLARIX, 3.2% fewer patients in the Pola+R-CHP arm had received a stem cell transplant compared to R-CHOP at the end of the trial follow-up. It was unknown whether the trial follow-up period would capture all subsequent therapy or whether the use of treatments in the global trial would reflect use of treatments in Australia.                           |
| MBS costs for ASCT  | \$910.25   | MBS items: 71146 and 13760.  | -  |
| MBS benefit   | 80%  | Assumption   | -  |

Source: Tables 4.2, p120 of the submission and the financial model

ASCT = autologous stem cell transplant; BSA = body surface area; CART = Chimeric antigen receptor T cells; DA-EPCOH-R = dose-adjusted rituximab, etoposide, prednisolone, vincristine, cyclophosphamide and doxorubicin; DLBC = Diffuse large B cell lymphoma; IPI = international prognostic indicator; LaRDR = Lymphoma and related diseases registry; NHL = non-Hodgkin's lymphoma; R-CHEOP-14 = biweekly rituximab, cyclophosphamide, hydroxydaunorubicin hydrochloride (doxorubicin hydrochloride), etoposide, vincristine (Oncovin) and prednisone; R-CHOP = rituximab, cyclophosphamide, hydroxydaunorubicin hydrochloride (doxorubicin hydrochloride), vincristine (Oncovin) and prednisone; WAC = weighted average cost

<sup>a</sup> Van Leeuwen, et al. (2014). Lymphoid Neoplasm Incidence by Who Subtype in Australia 1982–2006. *International journal of cancer* 135(9): 2146-2156

<sup>b</sup> Ye et al. (2017). Long-Term Time Trends in Incidence, Survival and Mortality of Lymphomas by Subtype among Adults in Manitoba, Canada: A Population-Based Study Using Cancer Registry Data. *BMJ Open* 7(7)

<sup>c</sup> SEER. (2022). Cancer Stat Facts from <https://seer.cancer.gov> (incidence: NHL = 19.0 per 100,000, DLBCL = 5.6 per 100,000).

<sup>d</sup> Sehn et al (2007). The revised International Prognostic Index (R-IPI) is a better predictor of outcome than the standard IPI for patients with diffuse large B-cell lymphoma treated with R-CHOP. *Blood*. 107:5.

6.50 Table 14 summarises the estimated net financial implications to the PBS/RPBS and the MBS for the proposed listing of polatuzumab vedotin over the first six years (assumed as 2023 to 2028). Updated utilisation and financial impact estimates from the PSCR are included, as are financial impact estimates incorporating the 4% price reduction proposed in the pre-PBAC response.

Table 14: Estimated use and financial implications

|   | Year 1 | Year 2 | Year 3 | Year 4 | Year 5 | Year 6 |
|---|--------|--------|--------|--------|--------|--------|
| <b>Estimated extent of use</b>  |        |        |        |        |        |        |
| Number of patients treated  | 1      | 1      | 1      | 1      | 1      | 1      |
| Number of scripts dispensed <sup>a</sup>  | 1      | 1      | 1      | 1      | 1      | 1      |
| <b>Estimated financial implications of polatuzumab vedotin</b>  |        |        |        |        |        |        |
| Cost to PBS/RPBS less copayments <sup>b</sup>   | \$2    | \$2    | \$4    | \$4    | \$4    | \$4    |
| <b>Estimated financial implications for vincristine</b>   |        |        |        |        |        |        |
| Cost to PBS/RPBS less copayments <sup>c</sup>   | 3      | 3      | 3      | 3      | 3      | 3      |
| <b>Net financial implications to the PBS/RPBS and MBS for the proposed listing of polatuzumab vedotin</b> |        |        |        |        |        |        |
| Net cost to PBS/RPBS <sup>b,c</sup>   | \$2    | \$2    | \$4    | \$4    | \$4    | \$4    |
| Net cost to MBS   | 3      | 3      | 3      | 3      | 3      | 3      |
| Net cost to PBS/RPBS and MBS  | \$2    | \$2    | \$4    | \$4    | \$4    | \$4    |
| <b>Revised estimates provided in the PSCR</b>   |        |        |        |        |        |        |
| <b>Estimated extent of use</b>  |        |        |        |        |        |        |
| Number of patients treated  | 1      | 1      | 1      | 1      | 1      | 1      |
| Number of scripts dispensed <sup>a</sup>  | 1      | 1      | 1      | 1      | 1      | 7      |
| <b>Net financial implications to the PBS/RPBS and MBS for the proposed listing of polatuzumab vedotin</b> |        |        |        |        |        |        |
| Net cost to PBS/RPBS <sup>b,c</sup>   | \$4    | \$5    | \$5    | \$1    | \$1    | \$6    |
| Net cost to MBS   | 3      | 3      | 3      | 3      | 3      | 3      |
| Net cost to PBS/RPBS and MBS  | \$4    | \$5    | \$5    | \$6    | \$6    | \$6    |
| <b>Revised estimates provided in the pre-PBAC response</b>  |        |        |        |        |        |        |
| <b>Net financial implications to the PBS/RPBS and MBS for the proposed listing of polatuzumab vedotin</b> |        |        |        |        |        |        |
| Net cost to PBS/RPBS <sup>b,c</sup>   | \$2    | \$2    | \$2    | \$4    | \$4    | \$4    |
| Net cost to MBS   | 3      | 3      | 3      | 3      | 3      | 3      |
| Net cost to PBS/RPBS and MBS  | \$2    | \$2    | \$2    | \$4    | \$4    | \$4    |

Source: Tables 4.3 to 4.21, pp121-132 of the submission, the financial model, the POLIVY\_DLBCL\_Section 4 Workbook\_PSCR.xlsx and Table 1, p2 of the pre-PBAC response,

DLBC = Diffuse large B cell lymphoma and Table 1, p2 of the pre-PBAC response

<sup>a</sup> Assuming 5.8 per year as estimated by the submission.

<sup>b</sup> The submission only applied the patient co-payment (\$20.92) once per patient for polatuzumab vedotin. Overall, this error had minimal impact on the net financial estimates and results were subsequently not updated during the evaluation

<sup>c</sup> The submission incorrectly assumed the AEMP for vincristine corresponded to 1x1mg vials rather than 5x1mg vials. Based on the correct AEMP per vial (i.e. \$44.61 / 5 = approx. \$8.92), the weighted dispense price for 2mg vincristine equals \$130.00. Overall, this error had minimal impacts impact on the net financial estimates and the results were subsequently not updated during the evaluation

The redacted values correspond to the following ranges:

<sup>1</sup> 500 <5,000

<sup>2</sup> \$20 million to <\$30 million

<sup>3</sup> net cost saving

<sup>4</sup> \$30 million to <\$40 million

<sup>5</sup> \$40 million to <\$50 million

<sup>6</sup> \$50 million to <\$60 million

<sup>7</sup> 5,000 to < 10,000

6.51 The submission estimated a total cost to the PBS/RPBS of \$30 million to < \$40 million in Year 6 and \$100 million to < \$200 million over the first six years of listing. The PSCR updated the total cost to the PBS/RPBS to \$50 million to < \$60 million in Year 6 and \$200 million to < \$300 million over the first 6 years of listing. The ESC considered that the financial implications of listing polatuzumab vedotin were high, particularly as the proposed estimates were for the IPI 3-5 subgroup only and noted that there was a considerable financial risk to the government should polatuzumab vedotin be used in the broader DLBCL population with lower IPI scores. In addition, the ESC considered

the updated estimates would also have implications for the thresholds of the proposed Risk Sharing Arrangement (RSA). The financial impact was reduced in the pre-PBAC response to \$30 million to < \$40 million in Year 6 and \$100 million to < \$200 million over the first 6 years.

### Financial Management – Risk Sharing Arrangements

6.52 The Sponsor proposed a RSA to mitigate the financial risks to government should doctors prescribe polatuzumab vedotin to patients that do not meet the proposed IPI 3-5 criteria. The submission stated that the proposed effective ex-manufacturer price would be ‘implemented as a  $\frac{1}{2}$ % rebate’ on the proposed published ex-manufacturer price. The submission then proposed to increase this rebate from  $\frac{1}{2}$ % to  $\frac{1}{3}$ % between threshold 1 (IPI 3-5 base case estimate) and threshold 2 (IPI 2-5 sensitivity analysis), and to  $\frac{1}{3}$ % above threshold 2. The submission stated that a  $\frac{1}{3}$ % discount is required to achieve the same cost-effectiveness in the ITT population (IPI 2-5) as the PBS subgroup (IPI 3-5). Both thresholds assume the same proposed effective price incorporating the proposed  $\frac{1}{2}$ % rebate (i.e. \$ $\frac{1}{2}$  weighted average dispense price per script) but threshold 2 assumes  $\frac{1}{3}$ % (absolute) lower uptake rate each year than threshold 1.

Table 15: Risk Share agreement thresholds (Cost to PBS/RPBS)

|  | 2023 \$ | 2024 \$ | 2025 \$ | 2026 \$ | 2027 \$ | 2028 \$ |
|--|---------|---------|---------|---------|---------|---------|
| Threshold 1 (IPI 3-5 base case)                |         |         |         |         |         |         |
| Threshold 2 (IPI 2-5 sensitivity) <sup>a</sup> |         |         |         |         |         |         |
| Pre-PBAC response                              |         |         |         |         |         |         |

Source: Table 4.24, p135 of the submission and Table 2, p2 of the pre-PBAC response

RSA = Risk Share Agreement

<sup>a</sup> The submission assumed 67% of patients meet the IPI 2-5 criteria (from 30% in the base case) and uptake in patients with IPI 2-5 would be  $\frac{1}{3}$ % (from  $\frac{1}{2}$ % in the base case)

6.53 Irrespective of the actual thresholds and corresponding assumptions, the ESC considered that the rationale for the proposed rebate between threshold 1 and 2 was flawed. As the use of polatuzumab vedotin below threshold 1 captures patients with an IPI of 3-5 and use between threshold 1 and 2 captures patients with an IPI of 2, then the proposed rebate between threshold 1 and 2 should be based on the cost-effectiveness of treatment in the IPI 2 subgroup rather than the ITT population (IPI 2-5). A rebate of  $\frac{1}{3}$ % above threshold 2 was appropriate, given there is no evidence for use in previously untreated patients with an IPI of 0-1 and potential leakage into the relapsed and/or refractory setting.

6.54 The pre-PBAC response proposed a single expenditure threshold based on the net cost of polatuzumab vedotin to the PBS/RPBS (less copayment) proposed in the pre-PBAC response, beyond which a  $\frac{1}{2}$ % rebate would apply.

*For more detail on PBAC’s view, see section 7 PBAC outcome.*

## 7 PBAC Outcome

- 7.1 The PBAC did not recommend the listing of polatuzumab vedotin in combination with rituximab plus cyclophosphamide, doxorubicin and prednisone (Pola+R-CHP) for the treatment of diffuse large B cell lymphoma (DLBCL) in previously untreated patients with an international prognostic index (IPI) score of 3-5. The PBAC considered that Pola+R-CHP did not provide a benefit compared to the comparator, rituximab plus cyclophosphamide, doxorubicin, vincristine and prednisone (R-CHOP), in terms of overall survival (OS). In addition, the PBAC considered that the estimated incremental cost effectiveness ratio (ICER) was optimistic and the financial impact of listing polatuzumab vedotin was high.
- 7.2 The PBAC noted the input from the organisations which highlighted the need for new treatment options for patients with DLBCL. The PBAC accepted that the highest clinical need was in patients with an IPI score of 3-5.
- 7.3 The PBAC considered that R-CHOP was the appropriate comparator.
- 7.4 The PBAC noted the results from the randomised controlled trial, POLARIX, which compared Pola+R-CHP with R-CHOP at a median follow up of 28.2 months. The PBAC noted that in terms of progression free survival (PFS), Pola+R-CHP demonstrated a modest improvement in PFS, as measured in the trial, in the intention to treat (ITT) population (HR = 0.73; 95% CI: 0.57, 0.95) and the subgroup of patients with an IPI score of 3-5 (HR = 0.65; 95% CI: 0.47, 0.88), but not in patients with an IPI score of 2 (HR = 0.99; 95% CI: 0.63, 1.56). The PBAC noted that POLARIX did not demonstrate a clinically significant benefit in terms of OS in either the ITT population (HR = 0.94; 95% CI: 0.65, 1.37) or the IPI 3-5 subgroup (HR = 0.93; 95% CI: 0.60, 1.43). The PBAC noted that Pola+R-CHP did not result in a statistically significant benefit compared to R-CHOP in terms of the proportion of patients who achieved a complete and/or partial response or best overall response. The PBAC also noted updated OS data provided to the TGA which, at a median follow up of 39.7 months, did not demonstrate a statistically significant difference (HR = 0.94; 95% CI: 0.67, 1.33).
- 7.5 Overall, the PBAC considered that POLA+R-CHP resulted in no more than a modest benefit compared to R-CHOP in patients with an IPI score of 3-5 in terms of PFS and considered the claim of superior comparative effectiveness for these patients was potentially reasonable for this outcome only. The PBAC considered that although Pola+R-CHP increased the duration of response, based on the evidence provided in POLARIX, Pola+R-CHP resulted in no benefit in terms of OS or the proportion of patients who achieved a complete and/or partial response.
- 7.6 The PBAC noted that Pola+R-CHP was associated with a similar incidence of any adverse events (AEs), Grade 3-5 AEs, serious AEs, AEs leading to treatment discontinuation and AEs leading to dose interruption compared to R-CHOP. The PBAC noted that Pola+R-CHP was associated with a higher rate of febrile neutropenia compared to R-CHOP.

- 7.7 Overall, the PBAC considered that the claim that Pola+R-CHP was non-inferior compared to R-CHOP in terms of safety may not be reasonable given the increased incidence of febrile neutropenia with Pola+R-CHP, although noted that the AEs appeared manageable in the context of a clinical trial.
- 7.8 In terms of the economic evaluation, the PBAC noted that the submission presented a cost utility analysis based on a partition survival model. Kaplan-Meier data were used up to 28.2 months, after which extrapolation was based on a mixture-cure model. The PBAC noted that the model assumed patients were cured if they remained progression free at two years. The PBAC considered that this was generally accepted in clinical practice, although noted that relapses can occur in patients who have remained progression free for two years.
- 7.9 The PBAC noted that despite there being no difference in OS during the POLARIX trial period (39.7 months), the mixture-cure model predicted a large survival benefit for Pola+R-CHP patients beyond the trial period. The PBAC noted that the differences in OS were driven by the proportions assumed cured in each arm which were determined using data from the PFS Kaplan Meier curves at two years. The PBAC considered that the model was optimistic as (i) the extrapolated functions did not fit the trial data, with the estimated cure fraction for the Pola+R-CHP arm overestimated (77.1% in the model compared to 75.2% of patients remaining progression free in the POLARIX trial) and underestimated for the R-CHOP arm (62.7% in the model compared to 65.1% in the POLARIX trial), and (ii) the model did not adjust for patients who would be cured from subsequent therapies
- 7.10 The PBAC noted that the base case ICER in the submission for patients with an IPI score of 3-5 was \$55,000 to < \$75,000 per quality adjusted life year (QALY) gained. The PBAC noted that the pre-PBAC response presented a revised base case which corrected for the errors identified during evaluation (see paragraph 6.39), reduced the time horizon, applied the same proportion of subsequent therapies across both treatment arms and included a price reduction for polatuzumab vedotin. These changes resulted in an ICER of \$35,000 to < \$45,000 per QALY for patients with an IPI score of 3-5. However, the PBAC considered that the revised base case ICER remained optimistic as it was uncertain whether the modest benefit in PFS would lead to the modelled improvement in OS, which was not observed in the POLARIX trial.
- 7.11 The PBAC considered that the estimated financial impact of listing polatuzumab vedotin was high (approximately \$100 million to < \$200 million over the first six years when using the estimates provided in the pre-PBAC response), particularly when considered in the context of the modest PFS benefit and lack of benefit in terms of OS. The PBAC noted the uncertainty with respect to the uptake rate and some of the parameters for defining the patient population as outlined in Table 13. The PBAC also considered that there was a considerable financial risk should polatuzumab vedotin be used in the broader DLBCL population with lower IPI scores.

7.12 The resubmission may be lodged at any future standard due date for PBAC submissions using the standard re-entry pathway.

7.13 The PBAC noted that this submission is eligible for an Independent Review.

**Outcome:**

Not recommended

## **8 Context for Decision**

The PBAC helps decide whether and, if so, how medicines should be subsidised through the Pharmaceutical Benefits Scheme (PBS) in Australia. It considers applications regarding the listing of medicines on the PBS and provides advice about other matters relating to the operation of the PBS in this context. A PBAC decision in relation to PBS listings does not necessarily represent a final PBAC view about the merits of the medicine or the circumstances in which it should be made available through the PBS. The PBAC welcomes applications containing new information at any time.

## **9 Sponsor's Comment**

The sponsor had no comment.