

5.09 POLATUZUMAB VEDOTIN, Powder for injection, 140 mg vial, Polivy[®], Roche Products Pty Limited.

1 Purpose of Application

- 1.1 The submission requested a Section 100, Efficient Funding of Chemotherapy listing for polatuzumab vedotin in combination with bendamustine and rituximab (Pola+BR) for treatment of relapsed or refractory diffuse large B-cell lymphoma (R/R DLBCL) that are ineligible for stem cell transplantation (SCT). Polatuzumab vedotin has not previously been considered by the PBAC in this or any other indication.
- 1.2 The requested listing was based on a cost-effectiveness analysis of Pola+BR compared with bendamustine in combination with rituximab (BR) in patients with R/R DLBCL who are ineligible for SCT. The key components of the clinical issue addressed by the submission are summarised below.

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

| Component | Description |
|----------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Population | Patients with R/R DLBCL who are ineligible for SCT. |
| Intervention | Pola+BR for up to 6 cycles. |
| Comparator | Bendamustine in combination with rituximab (BR) as proxy for standard practice. |
| Outcomes | <p>Primary endpoint: Complete Response</p> <p>Secondary/exploratory endpoints:</p> <ul style="list-style-type: none"> • Progression-free survival • Best overall response • Adverse Events • Overall survival • Duration of response |
| Clinical claim | Pola+BR is associated with superior comparative efficacy and inferior, but acceptable, comparative safety to standard practice in patients with R/R DLBCL who are ineligible for SCT. |

R/R = relapsed or refractory; DLBCL = diffuse large B-cell lymphoma; SCT = stem cell transplant. Pola+BR = polatuzumab vedotin in combination with bendamustine and rituximab.

Source: Table 1.1, p12 of the submission.

2 Requested listing

- 2.1 The submission requested the listing provided below and a Grandfathering restriction. Suggestions and additions proposed by the Secretariat are added in italics and suggested deletions are crossed out with strikethrough. As per the suggestions and additions proposed by the Secretariat the Grandfathering restriction has been incorporated in the requested listing provided below and hence is not presented separately.

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| Name, Restriction, Manner of administration and form | Max. Amount | No. of Rpts | Dispensed Price for Max. Qty | Proprietary Manufacturer | Name and |
|------------------------------------------------------------|-----------------------------|-------------|-------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------|--------------------------------------|
| POLATUZUMAB VEDOTIN Powder for injection, 140mg vial | 200 mg 210 mg | 5 | Published price: \$ [redacted] (public) \$ [redacted] (revised) \$ [redacted] (private) \$ [redacted] (revised) | Polivy | Roche Product s Pty Limited |
| | | | Effective price ([redacted] % rebate): \$ [redacted] (public) \$ [redacted] (revised) \$ [redacted] (private) \$ [redacted] (revised) | | |

| | |
|------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Category / Program: | Section 100 – Efficient Funding of Chemotherapy |
| Prescriber type: | <input type="checkbox"/> Dental <input checked="" type="checkbox"/> Medical Practitioners <input type="checkbox"/> Nurse practitioners <input type="checkbox"/> Optometrists <input type="checkbox"/> Midwives |
| Severity: | Relapsed or refractory |
| Condition: | D diffuse L large B- C cell L ymphoma |
| PBS Indication: | Relapsed or refractory diffuse large B-cell lymphoma [new concept] |
| Treatment phase: | Initial and continuing treatment |
| Restriction Level / Method: | <input type="checkbox"/> Restricted benefit <input type="checkbox"/> Authority Required – In Writing <input type="checkbox"/> Authority Required – Telephone/Electronic/Emergency <input checked="" type="checkbox"/> Streamlined |

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| | |
|---------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Clinical criteria: | <p>The condition must have relapsed or be refractory to at least one prior therapy [17702]</p> <p>AND</p> <p>The treatment must be in combination with bendamustine [18817]</p> <p>AND</p> <p>The treatment must be in combination with rituximab [17325]</p> <p>AND</p> <p>Patient must not have received an allogeneic haematopoietic stem cell transplant [new concept]</p> <p>AND</p> <p>Patient must not be eligible for stem cell transplantation [17329]</p> <p>AND</p> <p>Patient must have had a World Health Organisation (WHO) Eastern Cooperative Oncology Group (ECOG) performance status score of 2 or less prior to initiating treatment with this drug for this condition. [22209]</p> <p>AND</p> <p>The condition must not be central nervous system lymphoma, transformed follicular lymphoma or grade 3b follicular lymphoma [new concept]</p> <p>AND</p> <p>Patient must not receive more than 6 cycles of treatment under this restriction [18819]</p> <p>Patient must not receive more than 6 doses in a lifetime for this condition[21587]</p> <p>AND</p> <p>The treatment must be discontinued in patients who experience disease progression whilst on treatment [17714]</p> |
| Prescriber Instructions: | <p>Treatment must be discontinued in patients who experience disease progression while on treatment</p> <p>A patient may qualify for PBS-subsidised treatment under this restriction once only [12980]</p> <p>Grandfathered patient who has previously received non-PBS subsidised treatment with this drug for this condition prior to <LISTING DATE> must have met all the initial restriction criteria prior to initiating non-PBS subsidised treatment. A Grandfathered patient may qualify for PBS-subsidised treatment under this restriction once only. A Grandfathered patient must not receive more than 6 doses of combined PBS-subsidised and non-PBS-subsidised therapy for this condition.</p> |
| Administrative Advice: | <p>Patient may qualify for PBS-subsidised treatment under this restriction once only</p> <p>No increase in the maximum number of repeats may be authorised [7607]</p> <p>Special Pricing Arrangements apply [7608]</p> |

- 2.2 The submission proposed a Special Pricing Arrangement (SPA) with the effective polatuzumab vedotin ex-manufacturer price incorporating a ■% rebate on the proposed ex-manufacturer price.
- 2.3 Only one size vial (140mg) of polatuzumab vedotin is currently available. At a dose of 1.8mg/kg, as proposed by the submission and used in the key trial (GO29365), patients who weigh ≥80kg will likely require 2 vials of polatuzumab vedotin per dose, which will result in substantial wastage. Market research data presented in the submission

indicated that, in Australia, █% of R/R DLBCL patients ineligible for SCT weighed ≥ 81 kg. The submission stated a 30mg formulation of polatuzumab vedotin is intended for submission to the TGA in Q2, 2020.

- 2.4 The submission proposed an Authority Required (STREAMLINED) listing. However, the PBAC considered that an Authority Required (Written) listing would be more appropriate for polatuzumab vedotin to ensure that patients are either ineligible for autologous transplant, or have already failed an autologous transplant.
- 2.5 The submission noted that bendamustine is not currently PBS listed in the R/R DLBCL setting and therefore a separate listing for bendamustine would be required for use in combination with polatuzumab vedotin and rituximab. Bendamustine is also not currently TGA registered for use in the proposed population and is not currently owned by the sponsor. The Pre-Sub-Committee Response (PSCR) acknowledged that BR is not TGA registered. However, the PSCR argued that the TGA Clinical Evaluation Report (CER) for Pola+BR concluded that the proposed indication (see paragraph 3.2) is acceptable and recommended that the application be approved. Hence, the PSCR argued that upon TGA registration of Pola+BR, by association bendamustine would be indicated for use in R/R DLBCL on the condition it is prescribed in combination with polatuzumab vedotin and rituximab.
- 2.6 Rituximab is currently PBS listed for use in relapsed and refractory CD20 positive lymphoid cancer. Therefore, any DLBCL patients who do not express CD20 will not be eligible for rituximab and consequently not eligible for Pola+BR.
- 2.7 The requested listing did not specify that eligible patients should have CD79b surface marker expression on B-cells. The draft product information stated that CD79b is expressed in over 95% of DLBCLs. Polatuzumab vedotin is a CD79b-targeted antibody drug conjugate that preferentially delivers the potent anti-mitotic vedotin molecule (monomethyl auristatin E, or MMAE) to B-cells, which results in the killing of malignant B-cells. The treatment mechanism of polatuzumab vedotin relies upon the rapid uptake of the highly toxic vedotin molecule into the target B-cells; this uptake is facilitated by CD79b. Vedotin is 200 times more potent than vinblastineⁱ, and cannot be used as a drug itself due to its toxicity. The pharmacokinetic and pharmacodynamic profile of polatuzumab vedotin in CD79b-negative patients was not provided. Compared to CD79b-positive patients, CD79b-negative patients could suffer a significantly higher plasma level of conjugated and unconjugated vedotin for a longer duration, given the absence of the mechanism of rapid sequestration into target B-cells. This could lead to significant off-target toxicity in CD79b-negative patients. In addition, these patients would receive unknown treatment benefit from polatuzumab vedotin. The PSCR stated that CD79b is ubiquitously expressed on DLBCL cells, including R/R and previously untreated DLBCL and argued that there is no biological

ⁱ Dosio F, Brusa P, Cattell L. Immunotoxins and anticancer drug conjugate assemblies: the role of the linkage between components. *Toxins (Basel)*. 2011;3(7):848–883.

rationale as to why the rates of CD79b would differ amongst Australian DLBCL patients. In addition, the PSCR noted that eligibility to enrol in GO29365 did not require CD79b receptor expression. Nonetheless, CD79b expression was 96.4%. The Economics Sub-Committee (ESC) noted that no concerns regarding off-target toxicity in CD79b-negative patients were raised in the TGA CER for polatuzumab vedotin.

2.8 The population eligible for the proposed listing may be broader than the population in the key trial.

- The clinical criteria in the proposed listing specified that “the condition must have relapsed or be refractory to at least one prior therapy”, while the key trial (GO29365) enrolled patients who were relapsed or refractory to at least one prior chemotherapy regimen. Given the range of therapies used in patients with DLBCL (including radiotherapy, novel therapies/trials and comfort measures), a diverse population may be eligible for treatment under the proposed listing. The PBAC considered the clinical criteria should specify that “the condition must have relapsed or be refractory to at least one prior immunochemotherapy”.
- The key trial excluded patients who had a history of prior allogeneic SCT and who had a history of transformation of indolent disease to DLBCL. These eligibility criteria were not reflected in the proposed listing. The PBAC agreed with the ESC that the subgroup of patients with a history of prior allogeneic SCT in this context would be small and considered that they should not be excluded from the listing. In addition, the PBAC considered the clinical need to be high for patients with central nervous system lymphoma, transformed follicular lymphoma or grade 3b follicular lymphoma and advised that they should not be excluded from the listing.
- No restriction in terms of Eastern Cooperative Oncology Group (ECOG) performance status was specified in the proposed listing. The key trial enrolled patients with an ECOG Performance Status of 0-2. Market research data presented in the submission reported that up to █% of the R/R transplant ineligible DLBCL patients in Australia have an ECOG of 3+. The ESC noted the proportion of R/R DLBCL patients in Australia with an ECOG of 3+ and considered the restriction should allow clinician judgement regarding the appropriateness of treatment based on ECOG status.

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

3 Background

Registration status

3.1 The submission was made under TGA/PBAC Parallel Process. At the time of evaluation for PBAC consideration, no TGA evaluation report was available. The submission noted

that TGA approval would be expected in Q3, 2019. The first round TGA CER was received on the 24th September 2019 with the Delegates Overview received on the 30th September 2019. Polatuzumab vedotin was TGA registered for R/R DLBCL on 21 October 2019.

- 3.2 The TGA indication is: polatuzumab vedotin in combination with bendamustine and rituximab for the treatment of previously treated adult patients with diffuse large B-cell lymphoma who are not candidates for hematopoietic stem cell transplant.
- 3.3 The PBAC noted that Delegates Overview stated that ‘the Delegate considers the uncertainty in the scale of additional effectiveness offered by Pola+BR compared to BR alone to be significant because the Pola+BR combination imposes an additional burden of toxicity on patients compared to BR alone. If the true additional efficacy benefit were to be at the ‘low’ end this may alter than risk-benefit assessment of therapy with Pola+BR. Toxicity also has the potential to influence compliance with therapy and overall survival results in the long term.’

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

4 Population and disease

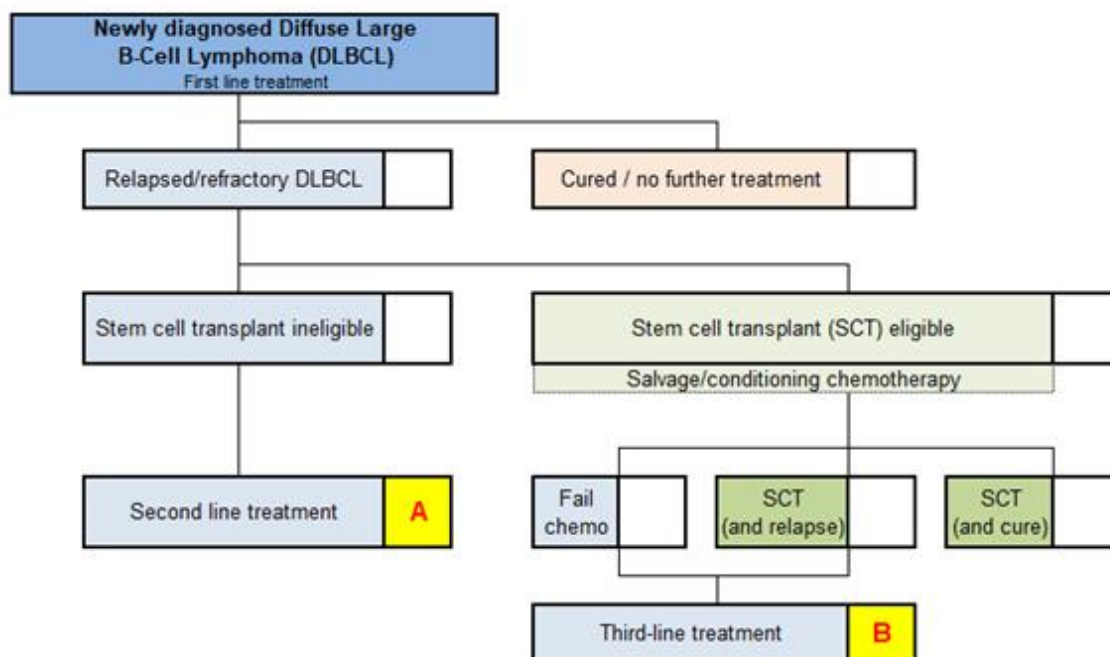
- 4.1 Diffuse Large B-cell lymphoma is an aggressive non-Hodgkin lymphoma, characterised by tumour cells with prominent nucleoli and basophilic cytoplasm, a diffuse growth pattern and a high proliferation fraction.ⁱⁱ After failure of first-line therapy, the main consideration for determining the treatment approach is whether the patient is a SCT candidate.^{iii iv}
- 4.2 For patients initially considered transplant eligible, salvage (conditioning) chemotherapy followed by SCT may offer a second chance of cure. Of these patients, some will subsequently be considered SCT ineligible following salvage (conditioning) chemotherapy (i.e. do not proceed to SCT), and the remainder who do undergo a SCT will be cured or again relapse.
- 4.3 The target population is patients with R/R DLBCL who have failed prior therapies, and are either ineligible for SCT (due to comorbidities, age or a failed salvage regime), or who have had disease relapse following SCT.
- 4.4 The submission proposed the following clinical management algorithm:

ⁱⁱ Freedman A, Aster J. Epidemiology, clinical manifestations, pathologic features, and diagnosis of diffuse large B cell lymphoma. 2018.

ⁱⁱⁱ NCCN. National Comprehensive Cancer Network. Diffuse Large B-Cell Lymphoma. Version 2.2019. 2019.

^{iv} Tilly H, Gomes da Silva M, Vitolo U, Jack A, Meignan M, Lopez-Guillermo A, et al. Diffuse large B-cell lymphoma (DLBCL): ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up†. *Annals of Oncology*. 2015;26(suppl_5):v116-v25.

Figure 1: Proposed clinical management algorithm



It is proposed that patients in second- and third-line treatment settings (highlighted as groups 'A' and 'B') should be eligible to receive polatuzumab vedotin + BR as therapy of choice.

Source: Figure 1.3, p. 18 of the Submission.

- 4.5 The ESC considered that management practices for R/R DLBCL are rapidly changing with the emergence of novel therapeutic options (e.g. Chimeric Antigen Receptor T-Cell (CAR-T) therapy). The ESC considered that this may impact on the clinical need for Pola+BR. The pre-PBAC response argued that polatuzumab vedotin is an immediately accessible, well tolerated treatment option of fixed duration which is less costly and resource intensive for healthcare systems than other treatments.

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

5 Comparator

- 5.1 The submission nominated BR as the main comparator, assuming BR is a proxy for standard management of R/R DLBCL.
- 5.2 BR may not be an appropriate proxy for current treatment of R/R DLBCL. Bendamustine is not currently PBS-listed for use in R/R DLBCL patients, whereas RGemOx (rituximab plus gemcitabine and oxaliplatin) is PBS-listed for this indication. The ESC noted that bendamustine is more expensive than gemcitabine and oxaliplatin.
- 5.3 RGemOx is more commonly used for the proposed population in Australian clinical practice than BR, and therefore, may be a more appropriate comparator than BR. In the financial estimates, the submission acknowledged that RGemOx is considered the

treatment regimen most likely to be used in the proposed patient population in Australian clinical practice.

- 5.4 The PSCR stated that treatment guidelines outline an assortment of potential therapies as best supportive care, as no one therapy has been shown to be effective in this population. The PSCR argued that what constitutes best supportive care, however, is not well defined as there is a paucity of evidence regarding the superiority of one regimen over another in randomised studies. The ESC agreed with the PSCR that there are no clear guidelines for R/R DLBCL patients who are ineligible for SCT or who have had disease relapse following SCT. However, the ESC considered that the use of BR as a proxy for standard management does not reflect current clinical practice in Australia as bendamustine is not TGA registered or PBS-listed for this indication. The ESC considered that treatment protocols such as R-GemOx, R-GemVin (rituximab plus gemcitabine and vincristine) or R-ICE (rituximab, ifosfamide, carboplatin, etoposide) would be more appropriate as a proxy for standard management of R/R DLBCL. The pre-PBAC response stated that clinicians consider current standard management therapies equivalent and argued that this has been reaffirmed by Ittu (2018) showing no difference observed between the survival outcomes for patients treated with BR or R-GemOx.

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

6 Consideration of the evidence

Sponsor hearing

- 6.1 There was no hearing for this item.

Consumer comments

- 6.2 The PBAC noted and welcomed the input from individuals (2), health care professionals (2) and organisations (3) via the Consumer Comments facility on the PBS website. The comments described a range of benefits of treatment with polatuzumab vedotin including improvements in PFS. The comments also highlighted the need for new treatment options for patients with R/R DLBCL that are ineligible for SCT.

Clinical trials

- 6.3 The submission was based on a comparison between the relevant randomised treatment arms in SCT ineligible, R/R DLBCL patients (Arm C (Pola+BR; N=40) vs. Arm D (BR; N=40)) from an open-label, head-to-head, multi-cohort Phase Ib/II clinical trial (GO29365).
- 6.4 A liquid formulation of polatuzumab vedotin was used in Arm C of the trial. Arms C and D were the relevant treatment arms from the randomisation phase of GO29365 and provided both efficacy and safety data in R/R DLBCL patients.

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- 6.5 An additional single arm G, to which patients were not randomised, was included in the study design (single arm new formulation cohort phase) to assess the pharmacokinetics and safety of the lyophilised formulation of polatuzumab vedotin. This is the formulation of polatuzumab vedotin that the sponsor intends to register in Australia. The submission noted that the lyophilised formulation enables the use of intravenous (IV) bags with IV giving sets for simpler administration compared to the intravenous infusion pumps required for the liquid formulation. The safety results of Arm G were presented in the submission alongside the safety results observed in Arms C and D. There were no efficacy data from Arm G of GO29365.
- 6.6 Details of the trial presented in the submission are provided in the table below. One publication^v in Table 2.3 p28 of the submission could not be verified from an independent search and was therefore excluded from Table 2.

Table 2: Trials and associated reports presented in the submission

| Trial ID | Protocol title/ Publication title | Publication citation |
|----------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------|
| GO29365 | Clinical Study Report. A Phase Ib/II study evaluating the safety, tolerability, and anti-tumor activity of polatuzumab vedotin (DCDS4501A) in combination with rituximab (R) or obinutuzumab (G) plus bendamustine (B) in relapsed or refractory follicular or diffuse large B-cell lymphoma. Data cutoff 30 April 2018. Supplemental results report for study GO29365 - Arm G. Data cutoff 29 May 2018. (Pharmacokinetics and safety). Updated Efficacy Analysis for Arms C and D of the GO29365 trial. Data cutoff 11 October 2018. | November 2018 |
| | Sehn, L et al. Polatuzumab vedotin (POLA) plus bendamustine (B) with rituximab (R) or obinutuzumab (G) in relapsed/refractory (R/R) diffuse large B-cell lymphoma (DLBCL): Updated results of a phase (PH) IB/II study." Data cutoff 30 April 2018. | <i>Blood</i> 2018; (132):1683 |
| | Sehn, L et al. Addition of polatuzumab vedotin to bendamustine and rituximab (BR) improves outcomes in transplant-ineligible patients with relapsed/refractory (r/r) diffuse large b-cell lymphoma (DLBCL) versus BR alone: Results from a randomized phase 2 study." Data cutoff 3 May 2017. | <i>Blood</i> 2017; (130):2821 |
| | Sehn, L et al. Adding polatuzumab vedotin (POLA) to bendamustine and rituximab (BR) treatment improves survival in patients with relapsed/refractory dlbc: Results of a phase 2 clinical trial. Data cutoff 24 Oct 2017. | <i>HemaSphere</i> 2018; 2: 348-349. |

Source: Table 2.3 on p 28 of the submission.

- 6.7 The key features of the direct randomised trial are summarised in the table below.

^v As presented in the submission: Sarkozy C et al. Randomized phase 2 trial of polatuzumab vedotin (pola) with bendamustine and rituximab (BR) in relapsed/refractory (r/r) FL and DLBCL. Data cutoff 24 Oct 2017. *Journal of Clinical Oncology* 2018; 36(15)

Table 3: Key features of the included evidence

| Trial | N | Design/ duration | Risk of bias | Patient population | Outcome(s) | Use in modelled evaluation |
|-----------------------|-----|--------------------|--------------|---------------------------------|------------------|----------------------------|
| Pola+BR vs. BR | | | | | | |
| GO29365 | 80* | R, OL 26.5 mths | High | R/R DLBCL ineligible for SCT | CR**, PFS, OS | Used |

R=randomised; OL=open label; R/R = relapsed or refractory; DLBCL = diffused large B-cell lymphoma; CR = complete response; OS=overall survival; PFS=progression-free survival;

*the number of patients in Arms C and D that provided comparative efficacy outcomes of Pola+BR versus BR in the target population.

**Primary outcome

Source: Sections 2.3-2.4 of the submission.

6.8 There were substantial differences in the distribution of important baseline prognostic characteristics between the Pola+BR and the BR treatment arms:

- A higher proportion of patients in the Pola+BR treatment arm had a better prognostic profile than the BR treatment arm, based on the International Prognostic Index (IPI), where a higher number indicates worse prognosis. The proportion of patients with an IPI of 0-1 at baseline in the Pola+BR treatment arm was approximately 3-fold that in the BR alone treatment arm. Correspondingly, the proportion of patients in the BR alone treatment arm, with an IPI score of 4-5, was approximately twice that in the Pola+BR treatment arm. The IPI score has been shown to be a major prognostic factor for overall survival in R/R DLBCL.^{vi vii viii ix x}
- The proportion of patients with bulky disease ≥ 7.5 cm at baseline (a factor associated with poor outcomes in DLBCL patients)^{xi} was higher in the BR alone treatment arm compared to that in the Pola+BR treatment arm (37.5% vs. 25%).
- Patients were older in the BR alone vs Pola+BR treatment arms (median 71 years vs. 67 years). There was also a higher proportion of patients in the BR alone arm who were ≥ 65 years of age (65%) than in the Pola+BR arm (57.5%). In addition,

^{vi} Crump M, Neelapu SS, Farooq U, Van Den Neste E, Kuruvilla J, Westin J, et al. Outcomes in refractory diffuse large B-cell lymphoma: results from the international SCHOLAR-1 study. *Blood*. 2017 Oct 19;130(16):1800-8.

^{vii} El Gnaoui T, Dupuis J, Belhadj K, Jais J-P, Rahmouni A, Copie-Bergman C, et al. Rituximab, gemcitabine and oxaliplatin: an effective salvage regimen for patients with relapsed or refractory B-cell lymphoma not candidates for high-dose therapy. *Annals of Oncology*. 2007;18(8):1363-8.

^{viii} Gisselbrecht C, Van Den Neste E. How I manage patients with relapsed/refractory diffuse large B cell lymphoma. *Br J Haematol*. 2018;182(5):633-43.

^{ix} Mounier N, El Gnaoui T, Tilly H, Canioni D, Sebban C, Casasnovas R-O, et al. Rituximab plus gemcitabine and oxaliplatin in patients with refractory/relapsed diffuse large B-cell lymphoma who are not candidates for high-dose therapy. A phase II Lymphoma Study Association trial. *Haematologica*. 2013;98(11):1726-31.

^x Ziepert M, Hasenclever D, Kuhnt E, Glass B, Schmitz N, Pfreundschuh M, et al. Standard International prognostic index remains a valid predictor of outcome for patients with aggressive CD20+ B-cell lymphoma in the rituximab era. *Journal of clinical oncology*. 2010;28(14):2373-80.

^{xi} Song M-K, Chung J-S, Sung-Yong O, Lee G-W, Kim S-G, Seol Y-M, et al. Clinical impact of bulky mass in the patient with primary extranodal diffuse large B cell lymphoma treated with R-CHOP therapy. *Annals of hematology*. 2010;89(10):985-91.

the proportion of patients who were ineligible for SCT, due to age, comorbidity and performance status, was higher in the BR alone vs the Pola+BR treatment arm (55% vs. 35.5%). These differences may have favoured Pola+BR over BR alone, in terms of health outcomes.

- 6.9 Overall, the GO29365 results were unreliable given the small number of patients and the dissimilarities in prognostic factors between treatment arms. This makes it difficult to isolate the prognostic effect from the true treatment effect associated with Pola+BR and thus the results should be interpreted with a high level of caution.
- 6.10 The PSCR argued that R/R DLBCL is a rare disease and it is therefore difficult to perform large phase III studies in this group. In addition, the PSCR argued that the GO29365 trial was a well-controlled Phase II study where the design and execution of the trial was acceptable and complied with European Medicines Agency (EMA) anti-cancer agent guidelines. The ESC noted that DLBCL is the most common subtype of non-Hodgkin's lymphoma with around 35% of patients progressing to R/R DLBCL after first-line treatment. The ESC noted the small sample size for the GO29365 trial and that only 11 patients received Pola+BR as second-line therapy as allowed in the proposed restriction. In addition, the ESC agreed with the evaluation that the risk of bias for the GO29365 trial was high as, although the randomisation process was standard, imbalances between treatment arms for baseline data indicated randomisation was not successful. The ESC considered that the high risk of bias identified favoured Pola+BR. The pre-PBAC response argued that randomisation was successful as the differences between baseline prognostic factors, in particular IPI scores and bulky disease, were not statistically significantly different. The PBAC noted the differences at baseline in IPI scores across the Pola+BR and BR alone arms (IPI score 0-1: Pola+BR 22.5%, BR 7.5%; IPI score 2: 22.5%, 20.0%, IPI score 3: 32.5%, 30.0% IPI score 4-5: 22.5%, 42.5%).
- 6.11 Arm G of GO29365 (N=25: Lyophilised formulation of polatuzumab vedotin (+BR)): The key outcomes in Arm G were pharmacokinetic and safety outcomes. Evaluation of the comparative efficacy and safety of the lyophilised formulation of polatuzumab vedotin (proposed for registration in Australia), was hampered by the i) lack of randomisation to improve comparability with Arms C and D, ii) limited data on patient baseline characteristics for this treatment arm, and iii) small number of patients and the lack of clinically relevant efficacy data such as progression-free survival (PFS)/overall survival (OS). A TGA evaluation report was not available during the evaluation. The TGA CER was provided post the evaluation with the PSCR stating that as the TGA clinical evaluator has recommended the application be approved, it is anticipated that the lyophilised formulation administered in Arm G (proposed for registration) will be considered bioequivalent to the liquid formulation (administered in Arm C of GO29365). The PBAC noted that the product submitted and subsequently recommended for approval in the TGA CER was the lyophilised formulation of polatuzumab vedotin.

Comparative effectiveness

6.12 Median durations of follow-up for the GO29365 trial, by data cutoff, are summarised below. The ESC considered the duration of follow-up to be appropriate as R/R DLBCL is a rapidly progressive disease.

Table 4: Durations of follow-up by data cutoff in GO29365.

| GO29365 trial | Cut off | Median duration of follow up |
|---------------|-----------------|------------------------------|
| Arms C and D | 30 April 2018 | 22.3 months |
| Arms C and D | 11 October 2018 | 26.5 months |

ARM C=Pola+BR (liquid form of polatuzumab vedotin); ARM D=BR (bendamustine + rituximab);

Source: Table 2.7, p36 of the submission

6.13 Results for the primary outcome of complete response (CR) are summarised below. The CR rate, as determined by the independent review committee (IRC), was statistically significantly higher in the Pola+BR vs. the BR alone treatment arm (40% vs 17.5%; Difference 22.5%; p=0.0261). Results were similar for CR as assessed by trial investigator.

Table 5: Primary outcome of complete response (GO29365) – Data cut off 18 April 2018

| Endpoint | Pola+BR N=40 | BR N=40 | Relative risk (95% CI) | p- value | Risk difference ^a (95% CI) | p- value |
|-----------------------------------------------|--------------------------|--------------------------|---------------------------|-------------|---------------------------------------------|-------------|
| Complete Response (IRC assessed), n (%), [CI] | 16 (40%) [24.9, 56.7] | 7 (17.5%) [7.3, 32.8] | 2.29 (1.06, 4.95) | 0.04 | 22.5% (2.6, 40.2) | 0.0261 |
| Complete Response (INV assessed), n (%), [CI] | 17 (42.5%) [27.0, 59.1] | 6 (15%) [5.7, 29.8] | 2.83 (1.25, 6.44) | 0.01 | 27.5% (7.7, 44.7) | 0.0061 |

^aCochran-Mantel-Haenszel χ^2 test adjusted for randomisation stratification factors: Duration of response to prior therapy (≤ 12 months vs > 12 months)

CI = confidence interval; CR = complete response; n = number of participants with event; N = total participants in group; IRC=Independent Review Committee; INV = investigator.

Source: Table 2.14, p45 of the submission.

6.14 Results for secondary outcomes of PFS and OS are summarised below.

Table 6: Progression-free survival and overall survival results in GO29365 - (Arm C vs Arm D)

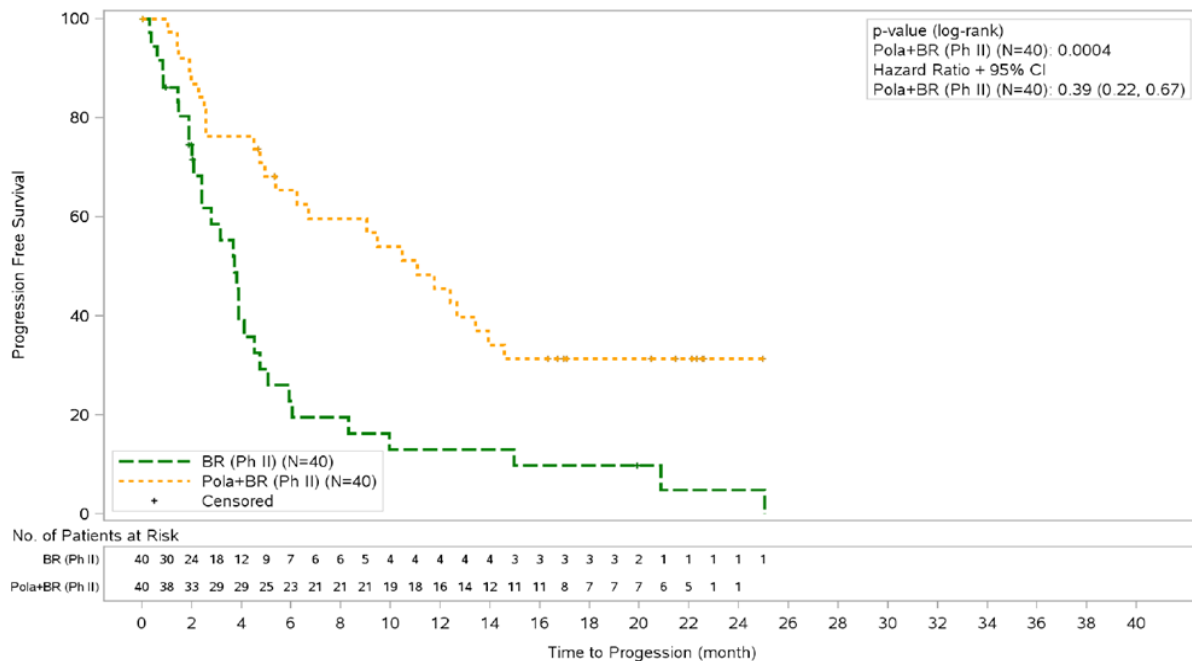
| Outcome | Pola+BR | | BR | | Stratified P value (log rank test) | Hazard ratio (95% CI) (stratified) |
|-------------------------------------------------------------------------------------------------------|---------------------------------|----------------------------------------|---------------------------------|----------------------------------------|------------------------------------|------------------------------------|
| | n/N with event ^a (%) | Median time, months, to event (95% CI) | n/N with event ^a (%) | Median time, months, to event (95% CI) | | |
| Data cutoff 30 April 2018 – median duration of follow-up 22.3 months | | | | | | |
| PFS (IRC assessed) | 25/40 (62.5%) | 11.1 (6.2, 13.9) | 31/40 (77.5%) | 3.7 (2.4, 4.5) | 0.0002 | 0.36 (0.21, 0.63) |
| PFS (INV assessed) | 27/40 (67.5%) | 7.6 (6.0, 17.0) | 35/40 (87.5%) | 2.0 (1.5, 3.7) | <0.0001 | 0.34 (0.20, 0.57) |
| OS | 23/40 (57.5%) | 12.4 (9.0, NE) | 28/40 (70.0%) | 4.7 (3.7, 8.3) | 0.0023 | 0.42 (0.24, 0.75) |
| Data cutoff 11 October 2018 (IRC data not provided) – median duration of follow up 26.5 months | | | | | | |
| PFS (INV assessed) | 29/40 (72.5%) | 7.5 (4.9, 17.0) | 35/40 (87.5%) | 2.0 (1.5, 3.7) | <0.0001 | 0.33 (0.20, 0.56) |
| OS | 24/40 (60.0%) | 12.4 (9.0, 28.0) | 28/40 (70.0%) | 4.7 (3.7, 8.3) | 0.0010 | 0.40 (0.23, 0.70) |

^aEvent for PFS are progression or death and for OS death.

CI=confidence interval; INV=investigator, IRC=independent review committee, PFS=progression free survival; OS = overall survival; NE=not estimable.

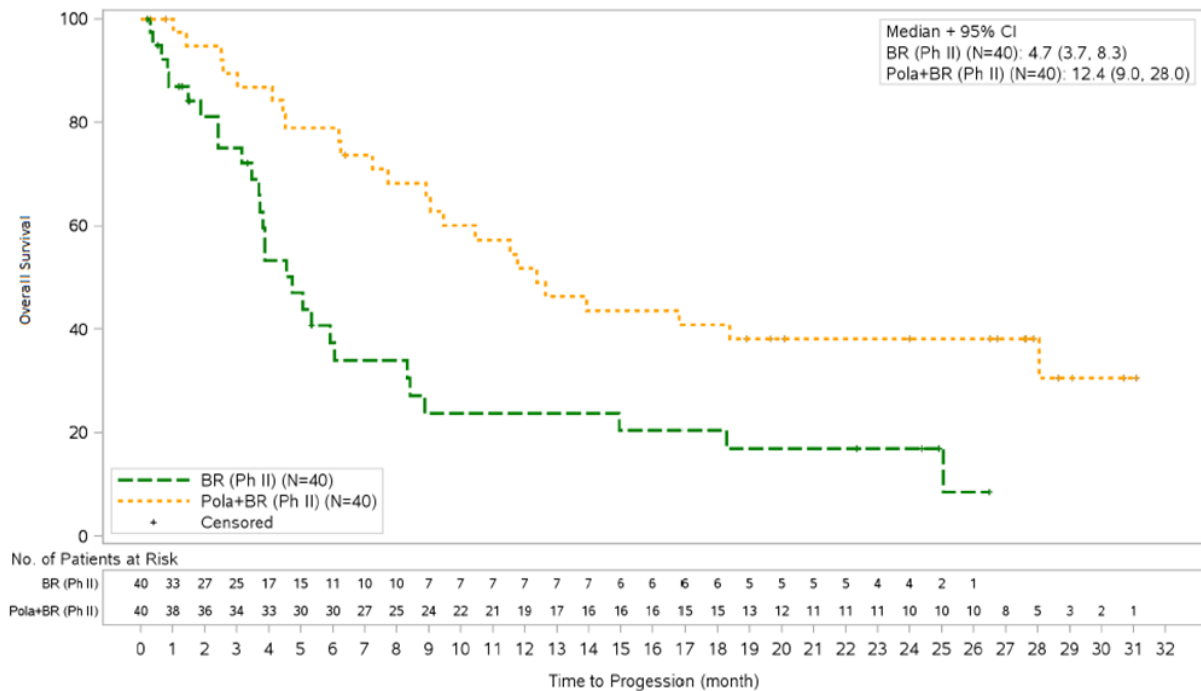
Source: Table 2.16, and Table 2.18, p47 and p50 of the submission

Figure 2: Kaplan-Meier plot of progression-free survival (IRC-assessed): Pola+BR versus BR (Data cutoff April 2018) – GO29365



Source: Figure 2.3, p47 of the submission.

Figure 3: Kaplan-Meier plot of updated overall survival: Pola+BR versus BR (data cutoff Oct 2018) – GO29365



Source: Figure 2.4, p48 of the submission.

- 6.15 PFS data, as determined by independent review committee (IRC) (data cutoff April 2018) indicated median PFS durations of 11.1 months and 3.7 months in the Pola+BR and BR alone treatment arms, respectively (difference of 7.4 months), favouring the Pola+BR treatment arm. This corresponded to a statistically significant 64% reduction in the hazard of progression or death in Pola+BR treated patients, compared to those treated with BR alone (HR 0.36; 95% CI: 0.21, 0.63).
- 6.16 Investigator assessed PFS showed improvement of 5.5 months PFS favouring Pola+BR over BR alone (7.5 months vs. 2.0 months) which corresponded to a 67% reduction in the hazard of progression or death (October 2018 cutoff: HR 0.33; 95% CI: 0.20, 0.56). Results for investigator assessed PFS were similar between the April and October 2018 data cutoffs.
- 6.17 Results for OS were similar between the April and October 2018 data cutoffs. Updated OS data (data cutoff October 2018) indicated median OS durations of 12.4 months and 4.7 months in the Pola+BR and BR alone treatment arms, respectively (difference of 7.7 months), favouring the Pola+BR treatment arm. This corresponded to a statistically significant reduction of 60% in the hazard of death in Pola+BR treated patients, compared to those treated with BR alone (HR 0.40; 95% CI: 0.23, 0.70).
- 6.18 Overall, baseline data from GO29365 indicated patients in the BR alone treatment arm were likely to be sicker or have a poorer prognosis compared to patients in the Pola+BR treatment arm. Hence there was high risk of confounding of efficacy which may have favoured the Pola+BR treatment arm. As such, it is difficult to segregate,

and thus quantify, the prognostic effect from the true treatment effect associated with the addition of polatuzumab vedotin to BR.

- 6.19 The PSCR stated that multiple Cox-regression analyses were conducted for PFS and OS controlling for Ann Arbor Stage, baseline ECOG performance status, bulky disease and IPI score. After adjusting for the potential prognostic factors and baseline characteristics, the PSCR argued that the treatment effect of Pola+BR vs BR remained robust. The ESC noted that baseline IPI in the GO29365 trial was divided into four categories, with the largest imbalances evident where IPI scores were 0-1 or 4-5 (see paragraph 6.6). The ESC noted the multiple Cox-regression analyses for IPI score reported on in the PSCR divided the score into two subgroups (IPI ≥ 3 and IPI < 3) which the Committee considered did not accurately represent the greatest imbalances (in the 0-1 and 4-5 groups). The ESC agreed with the evaluation that the validity of the clinical effectiveness data presented was uncertain as the results were likely confounded in favour of Pola+BR.

Comparative harms

- 6.20 Results for safety are summarised below. Statistical analyses of the safety data were unreliable due to the small sample size.

Table 7: Overview of adverse events and deaths GO29365 (safety population)

| | Arm G (lyophilised) Pola+BR (N=25) | Arm C (liquid) Pola+BR (N=39) | Arm D BR (N=39) | Arm C vs Arm D Relative Risk (95% CI) | Arm C vs Arm D Risk Difference (95% CI) |
|---------------------------------------------|---------------------------------------------|----------------------------------------|-----------------------|---------------------------------------------|-----------------------------------------------|
| Patients with at least one of: | | | | | |
| Any AE | 24 (96%) | 39 (100%) | 38 (97%) | 1.03 (0.98, 1.08) | 3% (-2%, 8%) |
| Any Grade 3-4 AE | 18 (72%) | 33 (85%) | 28 (72%) | 1.18 (0.93, 1.50) | 13% (-5%, 31%) |
| Any SAE | 10 (40%) | 25 (64%) | 24 (62%) | 1.04 (0.74, 1.47) | 3% (-19%, 24%) |
| AE leading to discontinuation of: | | | | | |
| polatuzumab vedotin | 2 (8%) | 12 (31%) | - | - | - |
| Any study drug | 3 (12%) | 13 (33%) | 6 (15%) | 2.17 (0.92, 5.12) | 18% (-1%, 37%) |
| AE leading to modification/interruption of: | | | | | |
| polatuzumab vedotin | 6 (24%) | 22 (56%) | - | - | - |
| Any study drug | 6 (24%) | 28 (72%) | 19 (49%) | 1.47 (1.01, 2.15) | 23% (2%, 44%) |
| Total number of deaths | 3 (12%) | 23 (59%) | 28 (72%) | 0.82 (0.59, 1.14) | -13% (-34%, 8%) |
| Deaths due to PD | NR | 14 (36%) | 17 (44%) | 0.82 (0.47, 1.43) | -8% (-29%, 14%) |
| AEs to monitor | | | | | |
| Grade ≥ 2 Periph. neuropathy | 0 | 6 (15%) | 2 (5%) | 3.00 (0.64, 13.96) | 10% (-3%, 24%) |
| Grade ≥ 3 Neutropenia | 10 (40%) | 23 (59%) | 18 (46%) | 1.28 (0.83, 1.96) | 13% (-9%, 35%) |
| Grade ≥ 3 Hepatotoxicity | 2 (8%) | 2 (5%) | 1 (3%) | 2.00 (0.19, 21.16) | 3% (-6%, 11%) |
| Grade ≥ 3 Infections and infestations | 4 (16%) | 13 (33%) | 12 (31%) | 1.08 (0.57, 2.07) | 3% (-18%, 23%) |

AEs by category with $\geq 10\%$ difference between Arm C (Pola+BR) and Arm D (BR) are shown in bold

AE=adverse event, SAE=serious adverse event; CI=confidence interval, PD=progressive disease.

Source: Table 2.19, p55 of the submission and supplementary results for Arm G provided in the clinical attachment accompanying the submission.

Table 8: Selected adverse events/adverse events of special interest GO29365 (safety population)

| Adverse event | Arm C Pola+BR N=39, n (%) | Arm D BR N=39, n (%) | Arm C vs Arm D Risk Difference % (95% CI) ^a |
|-----------------------------|---------------------------------|----------------------------|--------------------------------------------------------------|
| Peripheral Neuropathy | | | |
| • All grades | 17 (43.6%) | 3 (7.7%) | 35.9% (18.2%, 53.6%) |
| • Grades ≥2 | 6 (15.4%) | 2 (5.1%) | 10.3% (-3.0%, 23.5%) |
| Neutropaenia Grade 3-4 | 23 (59%) | 18 (46%) | 12.8% (-9.2%, 34.8%) |
| Anaemia Grade 3-4 | 11 (28.2%) | 7 (17.9%) | 10.2% (-8.3%, 28.8%) |
| Thrombocytopenia all grades | 20 (51.3%) | 13 (33.3%) | 17.9% (-3.6%, 39.5%) |
| Diarrhoea all grades | 15 (38.5%) | 11 (28.2%) | 10.3% (-10.5%, 31.1%) |

^aStatistical analyses performed during the evaluation.

Statistically significant results are bolded. These analyses remain exploratory.

SAE=Serious adverse event; CI=confidence interval.

Source: GO29365 CSR (Appendix 1 to the CSR/pp330, 2671 and 2776)

- 6.21 There was a higher rate of adverse events in the Pola+BR treatment arm (Arm C) vs. the BR alone treatment arm ($\geq 10\%$ difference) in terms of Grade 3-4 AEs, AEs leading to discontinuation of any study drug (approximately twice as many patients in the Pola+BR treatment arm), Grade ≥ 3 neutropenia, and peripheral neuropathy (PN). The difference in the rate of PN was statistically significant (risk difference: 35.9%; 95% CI: 18.2%, 53.6%).
- 6.22 The rates of AEs were lower in Arm G compared to Arm C. However, a comparison of the rate of AEs between Arm G and Arm C within the GO29365 trial should consider that Arms G and C were not randomised and that Arm G (patients still in the treatment phase; median number of cycles = 3) provided less mature data than Arm C (patients in follow-up; median number of cycles = 5).

Benefits/harms

- 6.23 A summary of the comparative benefits and harms for Pola+BR versus BR, based on the results from GO29365, is presented in the table below.

Table 9: Summary of comparative benefits and harms for Pola+BR versus BR

| Benefits | | | | | |
|-----------------------------------------------------------------------------|-------------------------|------------------------|-----------------------------------|------|-----------------------------|
| Progression free survival (median duration of follow up 26.5 months) | | | | | |
| Event | Pola+BR | BR | Absolute Difference (Pola+BR –BR) | | HR (95% CI) |
| Progressed, n (%) | 29/40 (72.5%) | 35/40 (87.5%) | | | 0.3 (0.20, 0.6) P<0.0001 |
| Median PFS (months) | 7.5 | 2.0 | 5.5 | | |
| % not progressed at 24 months (95% CI) | 28.3% (13.8%, 42.8%) | 5.6% (0.00, 17.3%) | 22.8% | | |
| Overall survival (median duration of follow up 26.5 months) | | | | | |
| Deaths, n/N (%) | 24/40 (60.0%) | 28/40 (70.0%) | | | 0.4 (0.2, 0.7) P=0.0010 |
| Median OS (months) | 12.4 | 4.7 | 7.7 | | |
| % Alive at 24 months (95% CI) | 38.2% (22.5%, 53.9%) | 17.0% (3.6%, 30.4%) | 21.2% | | |
| Harms (median duration of follow-up 22.3 months). | | | | | |
| Adverse event | Pola+BR n/N | BR n/N | Event rate/100 patients | | RD % (95% CI) ^a |
| | | | Pola+BR | BR | |
| Any grade peripheral neuropathy | 17/39 | 3/39 | 43.6 | 7.7 | 35.9% (18.2%, 53.6%) |
| Grade 3-4 AE | 33/39 | 28/39 | 85.0 | 72.0 | 13.0% (-5%, 31%) |

^aStatistical analyses performed during the evaluation.

RD=risk difference; CI=confidence interval; Tables 1 and 2, p2 and p4 of the Updated Efficacy analyses CSR accompanying the submission and original CSR for safety (Data Cutoff Date 30 April 2018)

6.24 On the basis of direct evidence presented by the submission, for every 100 patients treated with Pola+BR in comparison to BR

- Over a median duration of follow-up 26.5 months, approximately 21 additional patients would remain alive at 24 months;
- Over a median duration of follow-up 22.3 months, approximately 36 and 13 additional patients will have peripheral neuropathy or a Grade 3-4 AE, respectively.

6.25 The ESC agreed with the evaluation that the comparative benefit/harm should be interpreted with caution, in the context of small number of patients in the trial and potential important differences in baseline prognostic factors between the two treatment arms that may have biased the results in favour of Pola+BR.

Clinical claim

6.26 The clinical claim made by the submission was that Pola+BR is superior in terms of effectiveness compared with BR and inferior (“but acceptable”) in terms of safety compared to BR. This claim was not adequately supported by the key evidence presented.

- 6.27 The impact of confounding factors on the clinical benefit observed in the GO29365 trial, as a result of imbalances in key prognostic factors between the Pola+BR and BR alone treatment arms, is highly uncertain. In addition, the data were unreliable due to small patient numbers. The PSCR argued that R/R DLBCL is a rare disease and it is therefore difficult to perform large phase III studies in this group. In addition, the PSCR argued that multiple Cox-regression analyses conducted adjusting for potential prognostic factors and baseline characteristics indicated the treatment effect of Pola+BR remained robust. The ESC noted that DLBCL is the most common subtype of non-Hodgkin's lymphoma with around 35% of patients progressing to R/R DLBCL after first-line treatment. The ESC considered that the multiple Cox-regression analysis for IPI score provided in the PSCR did not accurately represent the greatest imbalances evident between Pola+BR and BR treatment arms. The ESC advised that the validity of the clinical effectiveness data presented was uncertain as the results were likely confounded in favour of Pola+BR. The ESC considered that, as randomisation in the GO29365 trial did not appear successful, more mature data are unlikely to eliminate uncertainty. The pre-PBAC response argued that randomisation was successful as the differences between baseline prognostic factors, in particular IPI scores and bulky disease, were not statistically significantly different.
- 6.28 The mean age of the study population in the Pola+BR arm was 64.7 years and only 2.5% were SCT ineligible due to comorbidities. IPSOS data provided with the submission suggest that the Australian R/R DLBCL population is older (mean age [redacted])^{xii} and likely to constitute a higher proportion of patients with co-morbidities^{xii,xiii}. This raises concern that the observed efficacy of Pola+BR from GO29365 may be an overestimate of what would be expected in clinical practice, and likewise, the risk of harm may be higher in clinical practice.
- 6.29 The approach taken in the submission was to assume that BR was a valid proxy for standard of care in Australia which includes RGemOx. This assumption was based on the observation that BR and RGemOx had similar OS benefit (11 months and 13 months, respectively) in a small sponsor-funded study by Ittu (2018)^{xiv}.
- 6.30 The comparative effectiveness, safety, and cost-effectiveness of BR relative to RGemOx would require a formal assessment by the PBAC. Furthermore, the Ittu (2018) and GO29365 trial populations differed substantially in terms of disease stage and lines of therapy. The efficacy of BR in Ittu (2018) was not applicable to the BR treatment arm in GO29365 (BR median OS durations in the GO29365 and Ittu studies were 4.7 months vs. 11.0 months, respectively).

^{xii} IPSOS Global Oncology Monitor – NHL Treatment Landscape. Q4, 2018.

^{xiii} Roche Lymphoma Advisory Board: Executive Summary, p. 3, May 2019.

^{xiv} Ittu RI, Shang A, Velde NV. Comparable Overall Survival with Rituximab-Bendamustine (R-Benda) and Rituximab-Gemcitabine-Oxaliplatin (R-GemOx) When Used As Second-Line (2L) Treatment for Diffuse Large B-Cell Lymphoma (DLBCL): A Real-World Study Using US Veterans Health Administration Data. *Blood*. 2018;132(Suppl 1).

- 6.31 The PBAC considered that the claim of superior comparative effectiveness was not adequately supported by the data.
- 6.32 The PBAC considered that the claim of inferior comparative safety was adequately supported by the data.

Economic analysis

- 6.33 The submission presented a trial-based economic evaluation based on the direct randomised trial GO29365, and then used a stepped approach to implement a modelled evaluation. The type of economic evaluation presented was a cost-utility analysis. The model structure and rationale are summarised below.

Table 10: Summary of model structure and rationale

| Component | Summary |
|----------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Time horizon | 15 years in the model base case versus a median follow-up of 26.5 months in trial |
| Outcomes | LYG and QALYs |
| Methods used to generate results | Partitioned survival (area under the curve) analysis |
| Health states | Progression-free on treatment, Progression-free off treatment, Progressive disease, and Dead. |
| Cycle length | 1 week |
| Transition probabilities | Health state allocation over time was determined by PFS and OS Kaplan-Meier curves directly from GO29365 to average follow-up (10.3 months). Beyond 10.3 months these curves were extrapolated to the modelled time horizon. The (ITT) proportion of patients from the trial who received each cycle of treatment was used to inform the proportion of patients remaining on treatment. |

LYG = life-years gained; QALY = quality-adjusted life-year; PFS = progression-free survival; OS = overall survival; ITT = intention to treat. Source: Table 3.2, p76 of the submission.

- 6.34 The key drivers of the model are summarised below.

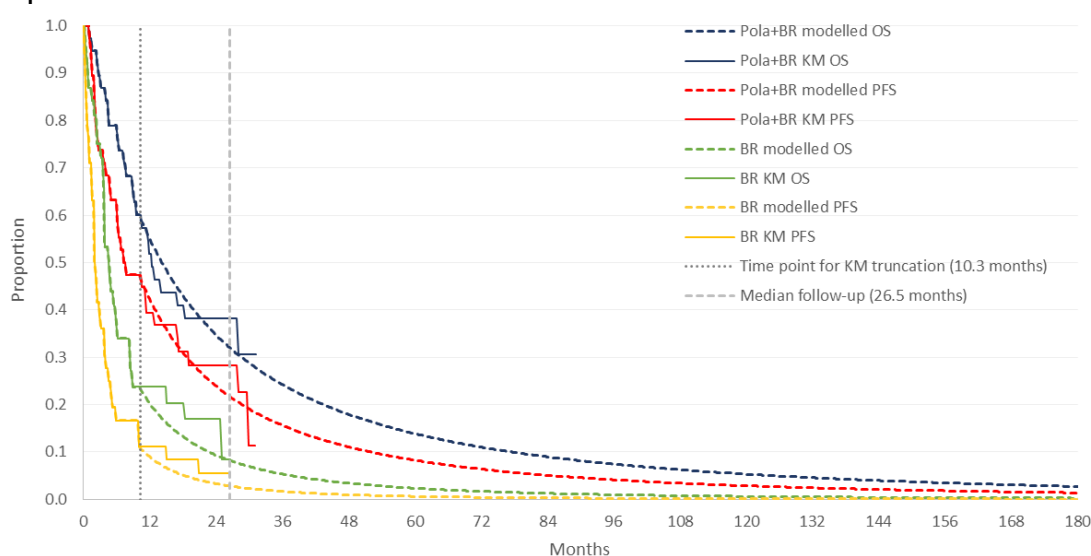
Table 11: Key drivers of the model

| Description | Method/Value | Impact |
|----------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------|
| Extrapolation | Treatment effect continued throughout the modelled time horizon, the PFS and OS curves of the two treatment arms did not converge; and Time point of Kaplan-Meier truncation for OS | High, favours Pola+BR |
| Time horizon | 15 years | High, favours Pola+BR |
| Utilities | High values for model health states taken from literature and no additional disutility for higher rate of adverse events for Pola+BR arm | Moderate, favours Pola+BR |
| No. of polatuzumab vedotin vials | The number of vials applied in the base case does not account for the proportion of patients in the trial and in practice who weigh more than 80 kg and who receive two 140 mg vials. The ICER is sensitive to this change as it is associated with substantial wastage. However the sponsor intends to register a 30 mg preparation in early-to-mid 2020 which results in an ICER similar to the base case estimate. | High (only 140 mg preparation available) to low (30 mg preparation also available), favours Pola+BR |

PFS = progression-free survival; OS = overall survival; Pola+BR = polatuzumab vedotin in combination with bendamustine and rituximab. Source: Compiled during evaluation.

- 6.35 The submission extrapolated the PFS and OS results using parametric functions from the (truncated) mean duration of follow-up in the trial (10.3 months). At the model time horizon, 2.7% of patients treated with Pola+BR were still alive (1.4% progression-free), compared to 0.3% with BR treatment (0% progression-free). The submission has not justified the plausibility of the long-term survival estimates with Pola+BR. The ESC noted a systematic review of survival outcomes post-relapse in DLBCL reported that median survival in those who initiated a subsequent line of therapy was 13 months.^{xv}
- 6.36 During the extrapolation period, the benefit of Pola+BR relative to BR was maintained in terms of PFS and OS and the PFS and OS curves between the two treatment arms did not converge throughout the modelled time horizon in the base case of the model. In addition, the ESC considered that the key trial (GO29365) did not provide a reliable basis for estimating the treatment effect of Pola+BR (given the small number of patients and imbalance in prognostic factors between arms). The Kaplan-Meier and modelled PFS and OS curves are presented below.

Figure 4: Kaplan-Meier and modelled curves for PFS and OS



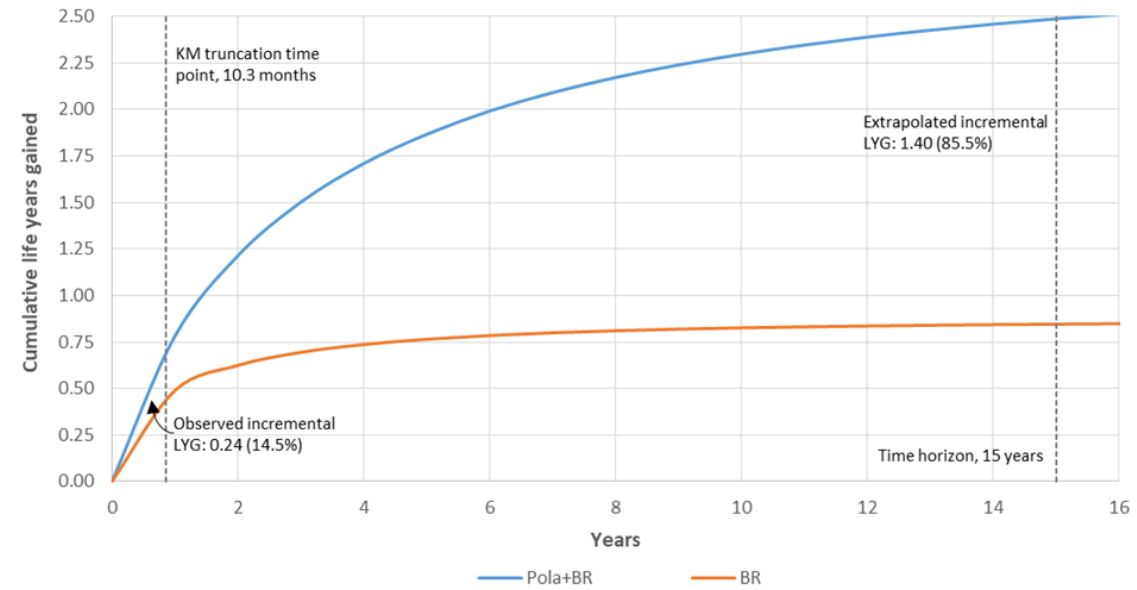
BR = rituximab used in combination with bendamustine; KM = Kaplan-Meier; OS = overall survival; PFS = progression-free survival; Pola+BR = polatuzumab vedotin in combination with bendamustine and rituximab.

Source: Figure constructed during the evaluation from the 'Economic Evaluation.xlsx' workbook included in the submission.

- 6.37 Given the highly uncertain extrapolation that assumed a continued treatment effect of Pola+BR versus BR, the result of the economic model was sensitive to the time horizon. The modelled OS in the extrapolated portion of the curves accounts for the majority (86%) of the total OS benefit (in terms of life-years gained) in the model (see Figure 5 below). Furthermore, 61% of the life years gained were obtained beyond the median duration of trial follow-up.

^{xv} McMillan A, Martín A, Haioun C, Chiappella A, Di Rocco A, Rueda A, et al. Post Relapse Survival Rates in Diffuse Large B-Cell Lymphoma. *Blood*. 2016;22(128):4204.

Figure 5: Cumulative life years gained over the time horizon of the model (undiscounted)

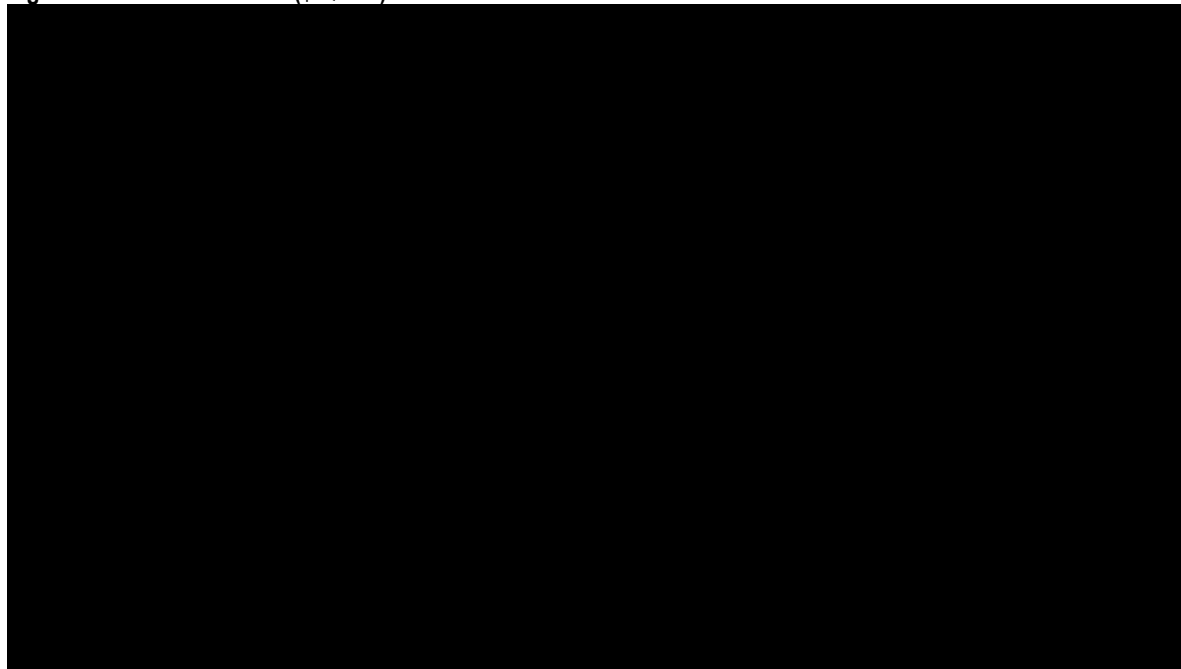


BR = rituximab used in combination with bendamustine; KM = Kaplan-Meier; LYG = life year gained; Pola+BR = polatuzumab vedotin in combination with bendamustine and rituximab.

Source: Figure constructed during the evaluation based on 'Results Table' worksheet in the 'Economic Evaluation.xlsx' workbook included in the submission.

6.38 The change of ICER with the time horizon is presented below in Figure 6.

Figure 6: Trace of the ICER (\$/QALY) over the time horizon of the model



ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life years.

Source: Figure constructed during the evaluation based on 'Results Table' worksheet in the 'Economic Evaluation.xlsx' workbook included in the submission.

- 6.39 The ESC considered that 15 years may not be an appropriate time horizon in this clinical setting as studies have shown that the proportion of patients alive at 5 years post second line treatment initiation was on average 30%,^{xv} or 22% in patients aged ≥65 years, who may represent a large proportion of the PBS population. The ESC considered that the extrapolation of unreliable trial data from G029365 (with a mean duration of follow-up of 10.3 month) to 15 years further increased the uncertainty in the cost-effectiveness estimates.
- 6.40 Trial G029365 did not measure patient-reported outcomes that could be used to derive utility weights, so estimates of utility values for each health state were derived from the published literature. The utility weight for progression-free off treatment (0.83) and progressive disease (0.71) for both treatment arms were as modelled in the NICE Technology Appraisal of tisagenlecleucel in patients with R/R DLBCL who had received ≥2 systemic therapies and were ineligible or failed autologous SCT.^{xvi} The ESC noted that these utilities were the highest of those identified. Since the incremental life-years and quality-adjusted life-years (QALYs) were gained in every health state and the vast majority were accumulated in the progression-free off treatment health state, the ESC noted that any application of alternative lower utility values, particularly in the progression-free off treatment health state, leads to increases in the incremental cost-effectiveness ratio (ICER). The ESC considered that due to the limitations in the clinical data presented, the use of more conservative utility values from the NICE TA559 study^{xvii} would be more appropriate.
- 6.41 The submission applied the same disutility associated with both Pola+BR and BR treatments in the progression free on treatment health state, which was inappropriate and biased the results in favour of Pola+BR, given that a higher rate of AEs was observed in the Pola+BR arm relative to the BR arm in G029365. The submission included the cost of managing the additional AEs in the Pola+BR arm but did not apply a utility decrement.
- 6.42 As noted above, bendamustine is not PBS listed for the proposed indication and the cost-effectiveness of bendamustine at the price used in the model for R/R DLBCL has not been established. Given that RGenOx is more commonly used in Australian clinical practice, and is cheaper than BR, the evaluation considered that it may be more appropriate to apply the cost of RGenOx in the model, and assume that there is no difference in treatment effect between BR and RGenOx. However, the ESC considered that the impact on the incremental treatment effect of Pola+BR (versus using RGenOx rather than BR) was not adequately addressed in the submission.
- 6.43 The results of the economic evaluation are presented below.

^{xvi} NICE. National Institute for Health and Care Excellence. Tisagenlecleucel-T for treating relapsed or refractory diffuse large B-cell lymphoma [ID1166]. 2018.

^{xvii} NICE. National Institute for Health and Care Excellence. Axicabtagene ciloleucel for treating diffuse large B-cell lymphoma and primary mediastinal B-cell lymphoma after 2 or more systemic therapies [ID1115]. 2018

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Table 12: Results of the stepped economic evaluation

| Step and component | Pola+BR | BR | Increment |
|-----------------------------------------------------------------------------------------------------------------------------------|---------------|---------------|---------------|
| Step 1: Trial-based costs and outcomes (based on approximately 26 months of data) | | | |
| Costs | \$ [REDACTED] | \$ [REDACTED] | \$ [REDACTED] |
| LY gained | 1.2239 | 0.6944 | 0.5295 |
| QALY gained | [REDACTED] | [REDACTED] | [REDACTED] |
| Incremental cost/extra LY gained | | | \$ [REDACTED] |
| Incremental cost/extra QALY gained | | | \$ [REDACTED] |
| Step 2: Extension of time horizon to 15 years by extrapolation of PFS and OS from the mean trial follow-up of 10.31 months | | | |
| Costs | \$ [REDACTED] | \$ [REDACTED] | \$ [REDACTED] |
| LY gained | 2.1833 | 0.7973 | 1.3860 |
| QALY gained | [REDACTED] | [REDACTED] | [REDACTED] |
| Incremental cost/extra LY gained | | | \$ [REDACTED] |
| Incremental cost/extra QALY gained | | | \$ [REDACTED] |
| Step 3: Inclusion of medical resource use costs | | | |
| Costs | \$ [REDACTED] | \$ [REDACTED] | \$ [REDACTED] |
| LY gained | 2.1833 | 0.7973 | 1.3860 |
| QALY gained | [REDACTED] | [REDACTED] | [REDACTED] |
| Incremental cost/extra LY gained | | | \$ [REDACTED] |
| Incremental cost/extra QALY gained | | | \$ [REDACTED] |
| Step 4: Inclusion of adverse event related costs | | | |
| Costs | \$ [REDACTED] | \$ [REDACTED] | \$ [REDACTED] |
| LY gained | 2.1833 | 0.7973 | 1.3860 |
| QALY gained | [REDACTED] | [REDACTED] | [REDACTED] |
| Incremental cost/extra LY gained | | | \$ [REDACTED] |
| Incremental cost/extra QALY gained | | | \$ [REDACTED] |
| Step 5: Inclusion of end of life costs | | | |
| Costs | \$ [REDACTED] | \$ [REDACTED] | \$ [REDACTED] |
| LY gained | 2.1833 | 0.7973 | 1.3860 |
| QALY gained | [REDACTED] | [REDACTED] | [REDACTED] |
| Incremental cost/extra LY gained | | | \$ [REDACTED] |
| Incremental cost/extra QALY gained (base case) | | | \$ [REDACTED] |

Note: Estimates in italics were revised during the evaluation to 1) apply the effective price through all steps in the analysis (not just in step 7, as was presented in the submission); 2) correct for minor errors identified relating to the quality-of-life adjustment in the progression-free off treatment health state up to cycle 18 and the cost per 100 mg vial of rituximab used; and 3) to use the current fees (as of July 1, 2019) for the efficient funding of chemotherapy drugs and MBS items 105, 13915 and 13918.

BR = rituximab used in combination with bendamustine; LY = life years; Pola+BR = polatuzumab vedotin in combination with bendamustine and rituximab; QALY = quality-adjusted life years.

Source: Compiled during the evaluation based on 'Results Table' worksheet in the 'Economic Evaluation.xlsx' workbook included in the submission.

6.44 The ESC considered that the results of the model were not reliable and the key issue was the uncertainty of the clinical data from Trial GO29365 (given the small number of patients and confounding due to the imbalance in prognostic factors between arms).

6.45 The results of the key sensitivity analyses are summarised below.

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Table 13: Results of key sensitivity analyses

| Analyses | Incremental cost | Incremental QALY | ICER | % change |
|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------|--------------------------------------------------------------------|-----------------------------------------------------------------------------------|------------------------------------------------------------------------------|
| Base case | \$ [REDACTED] | [REDACTED] | \$ [REDACTED] | |
| No. of polatuzumab vedotin vials (base case: 1 140 mg vial) 1.35 140 mg vials (average estimated from GO29365)* 0.58 140 mg vials and 2.13 30 mg vials (average from GO29365, allowing for the availability of the 30 mg preparation)* | \$ [REDACTED] \$ [REDACTED] | [REDACTED] [REDACTED] | \$ [REDACTED] \$ [REDACTED] | [REDACTED] % [REDACTED] % |
| Comparator costs RGenOx (base case: BR) (#6) * ^a | \$ [REDACTED] | [REDACTED] | \$ [REDACTED] | [REDACTED] % |
| Time horizon (base case: 15 years) 2.2 years (trial time horizon)* 7.5 years (#4)* 10 years | \$ [REDACTED] \$ [REDACTED] \$ [REDACTED] \$ [REDACTED] | [REDACTED] [REDACTED] [REDACTED] [REDACTED] | \$ [REDACTED] \$ [REDACTED] \$ [REDACTED] \$ [REDACTED] | [REDACTED] % [REDACTED] % [REDACTED] % [REDACTED] % |
| Extrapolation of PFS (base case: log-normal) Exponential extrapolation (#2)* Weibull extrapolation | \$ [REDACTED] \$ [REDACTED] \$ [REDACTED] | [REDACTED] [REDACTED] [REDACTED] | \$ [REDACTED] \$ [REDACTED] \$ [REDACTED] | [REDACTED] % [REDACTED] % [REDACTED] % |
| Extrapolation of OS (base case: log-normal) Exponential extrapolation (#3) Weibull extrapolation* Gompertz extrapolation* | \$ [REDACTED] \$ [REDACTED] \$ [REDACTED] \$ [REDACTED] | [REDACTED] [REDACTED] [REDACTED] [REDACTED] | \$ [REDACTED] \$ [REDACTED] \$ [REDACTED] \$ [REDACTED] | [REDACTED] % [REDACTED] % [REDACTED] % [REDACTED] % |
| OS and PFS KM truncation time point (base case: 10.3 months) Median OS and PFS (#1)* | \$ [REDACTED] | [REDACTED] | \$ [REDACTED] | [REDACTED] % |
| Source of utility weights (base case: NICE 2018b) Utility weights from Roth (2018) ^b Utility weights from Wang (2018) ^c EQ-5D-5L Utility weights from Wang (2018) ^c EQ-5D-3L Utility weights from NICE for TA559 (2018a) | \$ [REDACTED] \$ [REDACTED] \$ [REDACTED] \$ [REDACTED] \$ [REDACTED] | [REDACTED] [REDACTED] [REDACTED] [REDACTED] [REDACTED] | \$ [REDACTED] \$ [REDACTED] \$ [REDACTED] \$ [REDACTED] \$ [REDACTED] | [REDACTED] % [REDACTED] % [REDACTED] % [REDACTED] % [REDACTED] % |
| Applying treatment-related AE disutilities (base case: not included) (#5) * ^d | \$ [REDACTED] | [REDACTED] | \$ [REDACTED] | [REDACTED] % |
| Multivariate analyses | | | | |
| #1, #2 AND #3 (i.e. extrapolation and KM truncation time point)* | \$ [REDACTED] | [REDACTED] | \$ [REDACTED] | [REDACTED] % |
| #1, #2, #3 AND #4 (as above + time horizon)* | \$ [REDACTED] | [REDACTED] | \$ [REDACTED] | [REDACTED] % |
| #1, #2, #3, #4 AND #5 (as above + AE disutility)* | \$ [REDACTED] | [REDACTED] | \$ [REDACTED] | [REDACTED] % |
| #1, #2, #3, #4, #5 AND #6 (as above + RGenOx costs)* | \$ [REDACTED] | [REDACTED] | \$ [REDACTED] | [REDACTED] % |

* Denotes analyses conducted during the evaluation. All results were conducted around base case estimates which had been revised during the evaluation to correct for minor errors identified relating to the quality-of-life adjustment in the progression-free off treatment health state up to cycle 18 and the cost per 100 mg vial of rituximab used; and to use the current fees (as of July 1, 2019) for the efficient funding of chemotherapy drugs and MBS items 105, 13915 and 13918.

^a The cost of RGenOx was based on [REDACTED] mg of rituximab (weighted average cost per treatment cycle of \$ [REDACTED]), [REDACTED] mg gemcitabine (weighted average cost of \$ [REDACTED]) and [REDACTED] mg oxaliplatin (weighted average cost of \$ [REDACTED]). This totalled \$ [REDACTED] per treatment cycle. Cycles were administered every two weeks over one day, assuming an average of [REDACTED] cycles per patient (based on the proportion on patients in the progression-free on treatment health state in cycles 0, 2, 4, 6, 8, 10, 12 and 14). Cost per treatment cycle of medical resource use (i.e. specialists attendances and blood tests), and the cost of treating AE, were as for BR.

^b Roth JA, Sullivan SD, Lin VW, Bansal A, Purdum AG, Navale L, et al. Cost-effectiveness of axicabtagene ciloleucel for adult patients with relapsed or refractory large B-cell lymphoma in the United States. Journal of medical economics. 2018 Dec;21(12):1238-45.

^c Wang H, Manca A, Crouch S, Bagguley T, Yu G, Aas E, et al. Health-state utility values in diffuse large B-cell lymphoma. Value in Health. [Conference Abstract]. 2018;21:S74.

^d Estimation of differential disutility was based on the rates of treatment-related AEs from GO29365, with application of AE disutilities identified in the NICE Technology Appraisal of Axicabtagene ciloleucel (NICE TA559).

AE = adverse event; BR = rituximab used in combination with bendamustine; ICER = incremental cost-effectiveness ratio; KM = Kaplan-Meier; OS = overall survival; PFS = progression-free survival; Pola+BR = polatuzumab vedotin in combination with bendamustine and rituximab; QALY = quality-adjusted life year; RGenOx = rituximab in combination with gemcitabine and oxaliplatin.

Source: Compiled during the evaluation based on Section 3.9 and the 'Results Table' worksheet in the 'Economic Evaluation.xlsx' workbook included in the submission.

- 6.46 The PBAC noted that the number of polatuzumab vedotin vials applied was a key driver of the model with the ICER increasing to \$45,000/QALY - \$75,000/QALY when the number of 140 mg vials increased from 1 to 1.35. The PBAC considered that, as █% of R/R DLBCL patients ineligible for SCT would require 2 vials (see paragraph 2.3), listing without availability of the 30 mg vial would result in significant wastage and increase the level of uncertainty about the cost-effectiveness of polatuzumab vedotin.
- 6.47 As noted above, the submission assumed a continued treatment effect throughout the modelled time horizon, which was not justified. Among all the parametric functions presented in the submission, only the Weibull, Gompertz and exponential distributions showed convergence of OS curves for the two treatment arms within the model time horizon and of these, the exponential model fitted to the trial data best. The ICER increased to \$45,000/QALY - \$75,000/QALY when using the exponential function to extrapolate OS. However, the exponential function still assumed a prolonged treatment effect of Pola+BR versus BR and the modelled OS curves for the two treatment arms did not converge until approximately 12 years. Therefore, extrapolation using the exponential function may still overestimate the benefit of Pola+BR.
- 6.48 The chosen parametric functions for PFS extrapolation had a smaller impact on the result of the economic model, although all of these parametric functions assumed continued PFS benefit of Pola+BR.
- 6.49 The submission did not present multivariate analyses. These were conducted in a step-wise manner during the evaluation in Table 13. While the results of the multivariate analysis address a number of the uncertainties present in the submission's model, this does not account for the underlying uncertainty associated with the prognostic imbalances between the trial arms in GO29365, or the assumption of a prolonged treatment effect of Pola+BR relative to BR alone.

Drug cost/patient/course

- 6.50 Patients can receive up to six cycles of Pola+BR or BR treatment. In Trial GO29365, patients randomised to Pola+BR received, on average, █ cycles of Pola+BR. At an average cost per treatment cycle of polatuzumab vedotin of \$█, the average cost per treatment course of polatuzumab vedotin is estimated to be \$█. The average costs per treatment course of bendamustine and rituximab when used in combination with polatuzumab vedotin are \$█ and \$█ (revised: \$█), respectively. The total average treatment course cost of Pola+BR is estimated to be \$█ (revised: \$█). In the financial analysis, patients were assumed to receive 5 cycles of Pola+BR, which was based on the median number of cycles received in GO29365. The cost per treatment course costed was therefore \$█ (revised:

\$ [REDACTED]). In this case, it may not be reasonable to have assumed different costs in the economic and financial analyses.

- 6.51 In Trial GO29365, patients randomised to BR received, on average, [REDACTED] cycles of treatment. The average costs per treatment course of bendamustine and rituximab are estimated to be \$ [REDACTED] and \$ [REDACTED] (revised: \$ [REDACTED]). The total average treatment course cost of BR is estimated to be \$ [REDACTED] (revised: \$ [REDACTED]).
- 6.52 In the financial analysis, the submission assumed that in the absence of Pola+BR, patients would receive [REDACTED] cycles (i.e. a full treatment course) of RGeMox treatment. This is not reasonable given that patients on the comparator treatment in GO29365 received approximately half of the planned number of treatment cycles (primarily due to disease progression). The cost per treatment course of RGeMox was estimated to be \$ [REDACTED] (revised: \$ [REDACTED]).
- 6.53 A comparison of the costs applied in the model relative to those estimated in the financial analysis is presented in Table 14.

Table 14: Drug cost per patient for proposed and comparator drugs

| | Pola+BR Trial dose and duration | Pola+BR Model | Pola+BR Financial estimates | BR Trial dose and duration | BR Model | RGeMox Financial estimates |
|--------------------------|-------------------------------------------------------------------------------------|------------------|-------------------------------------------------------------------------------------|--------------------------------------------------------------|-------------|-------------------------------------------------------------------------------------|
| Mean dose | Pola: [REDACTED] mg B: [REDACTED] mg R: [REDACTED] mg | | Pola: [REDACTED] mg B: [REDACTED] mg R: [REDACTED] mg | B: [REDACTED] mg R: [REDACTED] mg | | R: [REDACTED] mg Gem: [REDACTED] mg Ox: [REDACTED] mg |
| Mean duration | [REDACTED] cycles (GO29365 mean) | | 5 cycles (GO29365 median) | [REDACTED] cycles (GO29365 mean) | | [REDACTED] cycles (assumption) |
| Cost/patient/ /course | Pola: \$ [REDACTED] B: \$ [REDACTED] R: \$ [REDACTED] Total: \$ [REDACTED] | | Pola: \$ [REDACTED] B: \$ [REDACTED] R: \$ [REDACTED] Total: \$ [REDACTED] | B: \$ [REDACTED] R: \$ [REDACTED] Total: \$ [REDACTED] | | R: \$ [REDACTED] Gem: \$ [REDACTED] Ox: \$ [REDACTED] Total: \$ [REDACTED] |
| Revised* | Pola: \$ [REDACTED] B: \$ [REDACTED] R: \$ [REDACTED] Total: \$ [REDACTED] | | Pola: \$ [REDACTED] B: \$ [REDACTED] R: \$ [REDACTED] Total: \$ [REDACTED] | B: \$ [REDACTED] R: \$ [REDACTED] Total: \$ [REDACTED] | | R: \$ [REDACTED] Gem: \$ [REDACTED] Ox: \$ [REDACTED] Total: \$ [REDACTED] |

*Denotes estimates revised during the evaluation to correct for minor errors identified relating to the cost per 100 mg vial of rituximab used and to use the current fees (as of July 1, 2019) for the efficient funding of chemotherapy drugs.

BR = rituximab used in combination with bendamustine; Pola+BR = polatuzumab vedotin in combination with bendamustine and rituximab; RGeMox = rituximab in combination with gemcitabine and oxaliplatin.

Source: Compiled during the evaluation based on the 'Economic Evaluation.xlsx' and the 'Section 4 Workbook.xlsx' workbooks included in the submission.

Estimated PBS usage & financial implications

- 6.54 This submission was considered by DUSC. The submission used an epidemiological approach to estimate the financial impact of Pola+BR.
- 6.55 The estimated use and financial implications of listing Pola+BR (as estimated in the submission) are summarised below. At year 6, the estimated number of treated

patients was less than 10,000 and the net cost to the PBS/RPBS would be \$20 - \$30 million.

Table 15: Estimated use and financial implications (as estimated in submission)

| | Year 1 | Year 2 | Year 3 | Year 4 | Year 5 | Year 6 |
|------------------------------------------------------------------------------|--------|--------|--------|--------|--------|--------|
| Estimated extent of use | | | | | | |
| Number of patients treated | | | | | | |
| Number of scripts dispensed ^a | | | | | | |
| polatuzumab vedotin | | | | | | |
| bendamustine | | | | | | |
| rituximab | | | | | | |
| Total administrations | | | | | | |
| Estimated financial implications of Pola+BR | | | | | | |
| Cost to PBS/RPBS Revised* | | | | | | |
| Copayments | | | | | | |
| Cost to PBS/RPBS less copayments Revised* | | | | | | |
| Estimated cost offsets due to reduction in use of RGenOx ^b | | | | | | |
| Cost offsets to PBS/RPBS Revised* | | | | | | |
| Copayments | | | | | | |
| Cost offsets to PBS/RPBS less copayments Revised* | | | | | | |
| Net financial implications | | | | | | |
| Net cost to PBS/RPBS Revised* | | | | | | |
| Net cost to MBS Revised* | | | | | | |
| Net cost to Government Revised* | | | | | | |

*Denotes estimates revised during the evaluation to use the updated fees and mark-ups, effective July 1st, 2019. In addition, the price per 100 mg rituximab vial was based on the ex-manufacturer price per vial of two 100 mg vials. The current price per 100 mg vial from the applicable chemotherapy PBS items (4614W and 7257Y: \$308.90) has been used in the revised estimates. As the submission did not include the \$20.00 additional compound fee paid directly to TGA-licensed compounders, this has not been included in the revised estimates.

^a Assuming median 5 scripts per patient for polatuzumab vedotin and rituximab, and 10 scripts for bendamustine as estimated by the submission.

^b The submission assumed [redacted] cycles of RGenOx would be offset per patient.

Source: Table 4.12, 4.13, 4.14, pp 119-120, Tables 4.17, 4.21, pp 123 and p127, Table 4.25, p 130 of the submission.

6.56 The submission estimated the incidence of NHL using a linear regression model, extrapolating NHL incidence in Australia from 1996 to 2015 reported in the Australian Cancer Incidence and Mortality (ACIM) book for NHL. The commentary noted that the submission’s estimates were lower than those estimated by the AIHW ^{xviii}.

6.57 The submission estimated that DLBCL would comprise 30% to 40% of all NHL in Australia, based on a combination of Australian and global data. It used the data for a

^{xviii} Australian Institute of Health and Welfare. Cancer data in Australia. Canberra: AIHW; 2019; Available from: <https://www.aihw.gov.au/reports/cancer/cancer-data-in-australia/contents/summary>

single year collected in QLD in 2009 to arrive at a DLBCL proportion of 36% of NHL. Review articles and population statistics taken from Australia (DLBCL proportion of 20%)^{xix}, Canada (23%)^{xx} and the US (28.6%)^{xxi xxii} suggest the submission likely overestimated the incidence of DLBCL as a proportion of NHL.

- 6.58 The submission assumed that, in the absence of Pola+BR, all patients would have received a PBS-subsidised therapy, nominated to be RGemOx (noting that this differed from the comparator presented in the clinical evidence and modelled economic evaluation).
- 6.59 Furthermore the commentary considered that, in some patients, RGemOx use may be displaced to a later line of therapy rather than replaced. It is noted that ■% of patients in the Pola+BR arm of key trial GO29365 received subsequent anti-lymphoma treatment. Thus the cost offsets presented in the submission may be further overestimated.
- 6.60 In calculating the cost-offset from RGemOx, the submission assumed that patients would be receiving ■ cycles of RGemOx in current clinical practice. The commentary considered that it may not have been reasonable to assume that patients will be able to receive a full treatment course of RGemOx, particularly when the median treatment duration in the BR comparator arm in GO29365 was 50% of a full course, with only 23.1% completing the full course.
- 6.61 In summary, the submission overestimated the cost-offset from the substitution for RGemOx should Pola+BR be listed on the PBS.
- 6.62 DUSC considered that the estimates presented in the submission were underestimated. The main issues were:
- The proportion of patients with DLBCL may be overestimated. However, DUSC considered that overall the submission's forecast of the treated population was underestimated as most other assumptions informing the estimates were underestimated.
 - There was no consideration of a prevalent population who would become refractory or relapsing over time.
 - Growth in the elderly population was not accounted for.
 - The eligible population was underestimated, as the failure rate of stem cell transplantation (SCT) was likely to be higher than estimated.

^{xix} van Leeuwen MT, Turner JJ, Joske DJ, Falster MO, Srasuebku P, Meagher NS, et al. Lymphoid neoplasm incidence by WHO subtype in Australia 1982-2006. *Int J Cancer*. 2014 Nov 1;135(9):2146-56.

^{xx} Ye X, Mahmud S, Skrabek P, Lix L, Johnston JB. 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*. 2017 Jul 17;7(7):e015106.

^{xxi} SEER. Cancer Stat Facts: NHL - Diffuse Large B-Cell Lymphoma (DLBCL). 2019.

^{xxii} SEER. Cancer Stat Facts: Non-Hodgkin Lymphoma. 2019; Available from: <https://seer.cancer.gov/statfacts/html/nhl.html>.

- The uptake rate will likely be higher than the submission's assumption of ■%, particularly in the later years, as polatuzumab vedotin in combination with bendamustine and rituximab (Pola+BR) may become the standard practice in the target population and as clinicians become familiar with the management of its adverse effects.
 - Cost-offsets from the substitution for RGemOx (rituximab plus gemcitabine and oxaliplatin) were overestimated.
 - The higher rate of Grade 3-4 adverse events observed in the Pola+BR arm were not costed.
 - There is potential for wastage due to the availability of only one vial size (140 mg).
- 6.63 In response to the issues raised by DUSC, the pre-PBAC response argued that given the aggressive nature of R/R DLBCL there is not expected to be a prevalent pool of patients who would risk further progression of their disease and awaiting PBS listing of Pola+BR. The sponsor also accepted the use of AIHW estimates (see paragraph 6.56), which the sponsor considered would allow for growth in the entire population (inclusive of the elderly population) and that the use of ■ cycles of RGemOx instead of a full ■ cycles would be appropriate. In addition, the pre-PBAC response reiterated the intent of the sponsor to submit a 30 mg polatuzumab vedotin vial size to minimise wastage.

Financial Management – Risk Sharing Arrangements

- 6.64 The submission did not propose any risk sharing arrangements.

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 bendamustine and rituximab (Pola+BR) for the treatment of patients with relapsed or refractory diffuse large B-cell lymphoma (R/R DLBCL) who are ineligible for stem cell transplantation (SCT). The PBAC considered that the validity of the clinical effectiveness data presented was very uncertain as the results were likely confounded in favour of Pola+BR. Given the limitations with the clinical data, the PBAC considered the estimated incremental cost-effectiveness ratio (ICER) was very uncertain.
- 7.2 The PBAC welcomed the input from individuals, health care professionals and organisations which highlighted the need for new treatment options for patients with R/R DLBCL that were ineligible for SCT.
- 7.3 The PBAC accepted the proposed clinical place for Pola+BR which was for use in patients with R/R DLBCL who have failed prior therapies, and are either ineligible for SCT, or who have had disease relapse following SCT.
- 7.4 The PBAC did not accept bendamustine in combination with rituximab (BR), the

nominated comparator, as an appropriate proxy for standard of care in R/R DLBCL. The PBAC agreed with the ESC that BR does not reflect current clinical practice in Australia as bendamustine is not TGA registered or PBS-listed for this indication. As such the PBAC considered the cost-effectiveness of BR for R/R DLBCL in Australia is unknown. The PBAC agreed with the submission that RGeMox (rituximab plus gemcitabine and oxaliplatin) is the treatment regimen most likely to be used in the proposed population in Australian clinical practice. The PBAC noted the similar overall survival (OS) benefit reported for BR and RGeMox in the Ittu (2018) study but did not agree with the submission that based on these results the regimens are equivalent. Instead, the PBAC considered that the Ittu (2018) and key trial (GO29365) populations differed substantially in terms of disease stage and lines of therapy and hence the efficacy of BR reported in Ittu (2018) was not applicable to the BR treatment arm in GO29365.

- 7.5 The PBAC considered the results from the randomised phase of the GO29365 trial, which compared Pola+BR with BR, to be unreliable given the small numbers of patients and the dissimilarities in baseline prognostic factors between treatment arms. The PBAC agreed with the ESC that the imbalances evident were not adequately addressed by the multiple Cox-regression analyses for IPI score as the greatest imbalances between Pola+BR and BR treatment arms were not accurately represented. The PBAC also noted the pre-PBAC response's argument that the differences between baseline prognostic factors, in particular International Prognostic Index (IPI) scores and bulky disease, were not statistically significantly different. The PBAC considered that small patient numbers likely contributed to the lack of statistically significant difference between treatment arms. In addition, the PBAC considered the nearly 2-fold higher proportion of patients with IPI score of 4-5 in the BR arm would likely affect treatment outcomes despite the lack of an observed statistically significant difference. The PBAC concluded that randomisation in the GO29365 trial did not appear successful with the differences in baseline prognostic factors biased in favour of Pola+BR as patients in the BR arm were likely to be sicker or have a poorer prognosis.
- 7.6 The PBAC noted that the GO29365 trial reported treatment benefits for Pola+BR over BR alone for complete response (CR), progression-free survival (PFS) and OS. However, the PBAC considered that the imbalance in prognostic factors makes it difficult to determine whether the observed treatment effect is attributable to Pola+BR. The PBAC concluded that the validity of the clinical effectiveness data presented was uncertain as the results were likely confounded in favour of Pola+BR.
- 7.7 Due to concerns regarding the appropriateness of BR as the nominated comparator, the likely impact of confounding factors on the clinical benefit observed in the GO29365 trial and small patient numbers in the trial, the PBAC considered that the clinical claim was not adequately supported by the evidence presented in the submission.

- 7.8 The PBAC noted the higher rate of Grade 3-4 adverse events (AEs), AEs leading to discontinuation of any study drug, Grade ≥ 3 neutropenia and peripheral neuropathy in the randomised Pola+BR arm of the GO29365 trial compared to the BR arm. However, the PBAC considered that the relative safety may differ in clinical practice as the imbalance in baseline prognostic factors outlined in paragraph 7.5 raises concerns regarding the true incidence of AE reported for Pola+BR.
- 7.9 In addition, the PBAC was concerned regarding the applicability of the GO29365 trial to the proposed Australian PBS population. The PBAC noted the latter is likely to be older and have more comorbidities than participants in the GO29365 trial, potentially leading to an overestimation of the efficacy and an underestimation of the AEs that would be observed in clinical practice with Pola+BR.
- 7.10 The PBAC considered that the economic model was unreliable due to the uncertainties in the underpinning clinical data from the GO29365 trial and the use of BR as the nominated comparator. In addition, the PBAC considered that the extrapolation of unreliable trial data from GO29365 (with a mean duration of follow-up of 10.3 month) to 15 years further increased the uncertainty in the cost-effectiveness estimates. The PBAC considered that the model's assumption of a continued treatment effect of Pola+BR versus BR throughout the modelled time horizon was not adequately supported by the available data. The PBAC considered the 15 year time horizon and the extrapolated PFS and OS benefits reported over this period to be inconsistent with the prognosis for R/R DLBCL. The PBAC noted the time horizon to be a key driver of the model and advised that a 15 year time horizon did not seem clinically plausible based on the evidence available.
- 7.11 Further, the PBAC noted that the literature-based utility values used to inform the economic model were the highest of the published values identified. The PBAC considered that, due to the limitations in the clinical data presented, more conservative utility values should be used with additional disutility incorporated in the model for the higher rate of AEs associated Pola+BR. The PBAC considered the resulting ICER very uncertain due to the aforementioned reasons.
- 7.12 The PBAC considered the financial estimates to be moderately uncertain and likely underestimated. The PBAC agreed with DUSC that consideration of a prevalent population who would become refractory or relapsing over time was required and that, in the absence of a 30 mg vial, there would be significant wastage of polatuzumab vedotin that would need to be accounted for in financial arrangements.
- 7.13 The PBAC proposed that any future submission should be a major submission. However, the PBAC considered that as randomisation in the GO29365 trial did not appear successful, more mature data are unlikely to eliminate uncertainty. The PBAC considered that further assessment of BR compared to standard of care R/R DLBCL regimens such as RGenOx may be required, for example an indirect comparison. However, the PBAC considered this would still not overcome the limitations of the GO29365 study. The PBAC noted that treatment costs will need to reflect the likely

high degree of uncertainty in any future clinical and economic evaluations.

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

Outcome:

Rejected

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.