

## Technology Guidance

# Polatuzumab vedotin for previously untreated diffuse large B-cell lymphoma

Technology Guidance from the MOH Drug Advisory Committee

### Guidance Recommendations

The Ministry of Health's Drug Advisory Committee has recommended:

- ✓ Polatuzumab vedotin 30 mg and 140 mg powder for concentrate for solution for infusion, in combination with rituximab biosimilar (subsidised brand), cyclophosphamide, doxorubicin and prednisone, for previously untreated diffuse large B-cell lymphoma (DLBCL) with an international prognostic index (IPI) score of 3 to 5.

### Funding status

Polatuzumab vedotin 30 mg and 140 mg powder for concentrate for solution for infusion are recommended for inclusion on the Medication Assistance Fund (MAF), for the abovementioned indication from 1 March 2024.

MAF assistance **does not** apply to previously untreated diffuse large B-cell lymphoma in patients with an IPI score below 3.

***Clinical indications, subsidy class and MediShield Life claim limits for polatuzumab vedotin are provided in the Annex.***

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## Factors considered to inform the recommendations for funding

### Company-led submission

- 1.1. At the March 2023 meeting, the MOH Drug Advisory Committee (“the Committee”) considered the evidence submitted by the company and a review of the submission by one of ACE’s evidence review centres for the technology evaluation of polatuzumab vedotin (“polatuzumab”), in combination with rituximab, cyclophosphamide, doxorubicin and prednisone (Pola+R-CHP), for previously untreated diffuse large B-cell lymphoma (DLBCL) in patients with an international prognostic index (IPI) score of 3 to 5.
- 1.2. Expert opinion was obtained from the MOH Cancer Drug Subcommittee and patient experts from local patient and voluntary organisations, who assisted ACE to ascertain the clinical value of polatuzumab.
- 1.3. The evidence was used to inform the Committee’s deliberations around four core decision-making criteria:
  - Clinical need of patients and nature of the condition;
  - Clinical effectiveness and safety of the technology;
  - Cost-effectiveness (value for money) – the incremental benefit and cost of the technology compared to existing alternatives; and
  - Estimated annual technology cost and the number of patients likely to benefit from the technology.
- 1.4. Additional factors, including social and value judgments, may also inform the Committee’s funding considerations.
- 1.5. Following a negative recommendation during the March 2023 meeting, based on unfavourable cost-effectiveness, the company submitted a revised proposal, which the Committee considered at the June 2023 DAC meeting.

### Clinical need

- 2.1. The Committee noted that DLBCL is an aggressive disease with a median survival of less than one year in untreated patients. Approximately 300 patients are diagnosed with DLBCL each year in Singapore. While the majority of previously untreated patients respond to the current standard of care (rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone [R-CHOP]), approximately 30-40% experience relapse or are refractory to initial treatment.
- 2.2. The prognosis of patients with DLBCL is usually predicted using the IPI. Approximately 35% of patients with DLBCL in Singapore have an IPI score of 3 to 5. These patients are considered to have higher risk and exhibit poorer health outcomes

than those with lower IPI scores (0 to 2). The company's requested listing for polatuzumab was specific to patients with an IPI score of 3 to 5, although the approved HSA indication does not restrict use according to IPI risk group. The Committee accepted that the highest clinical need was in patients with an IPI score of 3 to 5.

- 2.3. The Committee considered testimonials from local patient experts about living with lymphoma and their experience with different treatments. They heard that lymphoma had a significant, negative impact on patients' lives, as symptoms limited their daily activities, and impacted their sleep, diet, exercise and social activities. They noted that patients also reported anxiety, self-pity and depression, with financial worries and fears of dying and disease recurrence being their greatest concerns. The Committee acknowledged that patients who received chemoimmunotherapy, such as R-CHOP, felt that their treatment worked well to control the cancer. However, patients were also concerned it was expensive, inconvenient and had several side effects including body weakness, weight loss and fatigue. Patients considered that any new treatments for lymphoma should be able to extend survival and prevent recurrence, be more affordable, be orally administered, and have fewer side effects.

## Clinical effectiveness and safety

- 3.1. The Committee reviewed the clinical evidence, presented in the company's submission, from an ongoing phase III randomised controlled trial (POLARIX), which compared Pola+R-CHP with R-CHOP in patients with previously untreated DLBCL with an IPI score of 2 to 5. The Committee noted that the submission relied on results of subgroup analyses (IPI 3 to 5) to inform the clinical claim. However, the Committee agreed it would be more appropriate to use results from the intention-to-treat (ITT) population to represent the target population, as the subgroup analyses were not powered for statistical significance or adjusted for multiplicity, and a test for interaction between the IPI score 3 to 5 subgroup and its complement (IPI score 2) did not demonstrate treatment effect modification.
- 3.2. The Committee noted that the POLARIX trial included an additional two cycles of rituximab monotherapy administered following six cycles of R-CHOP, which was not reflective of local clinical practice. However, the Committee considered it unlikely to result in an overestimation of efficacy in the R-CHOP arm.
- 3.3. At a median follow-up of 28.2 months (June 2021 data cut-off), results of the ITT population in POLARIX showed that compared with R-CHOP, Pola+R-CHP led to statistically significant improvements in progression-free survival (PFS) by investigator assessment, as well as event-free survival due to efficacy reasons (EFS<sub>eff</sub>). However, overall survival (OS) data was immature, with no statistically significant difference between the two treatment groups. Given evidence from a long-term study of patients with DLBCL showed the median OS for R-CHOP was not reached until approximately 8 years, the Committee noted that OS data was unlikely

to be mature at the final data cut-off of POLARIX (June 2022). There was also no statistically significant difference in the positron emission tomography complete response at end of treatment (PET-CR at EOT) by blinded independent central review (BICR) between the treatment arms.

**Table 1: Results for PFS, EFS<sub>eff</sub>, OS and CR at EOT in POLARIX trial**

June 2021 data cut-off	Pola+R-CHP (N=440)	R-CHOP (N=439)
<b>PFS by investigator assessment (primary endpoint)</b>		
Patients with event, n (%)	107 (24.3)	134 (30.5)
Median PFS, months (95% CI)	33.3 (33.3 to NE)	NE
Stratified HR (95% CI)	<b>0.73 (0.57 to 0.95), p=0.0177</b>	
<b>EFS<sub>eff</sub> by investigator assessment</b>		
Patients with event, n (%)	112 (25.5)	138 (31.4)
Median EFS, months (95% CI)	33.3 (33.3 to NE)	NE
Stratified HR (95% CI)	<b>0.75 (0.58 to 0.96), p=0.0244</b>	
<b>OS</b>		
Patients with event, n (%)	53 (12.0)	57 (13.0)
Median OS, months (95% CI)	NE	NE
Stratified HR (95% CI)	0.94 (0.65 to 1.37), p=0.7524	
<b>CR at EOT by BICR assessment</b>		
Complete responders, n (%) [95% CI]	343 (78.0) [73.8 to 81.7]	325 (74.0) [69.7 to 78.1]
Difference in response rate, % (95% CI)	3.92 (-1.89 to 9.70), p=0.1557	

Abbreviations: BICR, blinded independent central review; CR at EOT, complete response at end of treatment; CI, confidence interval; EFS<sub>eff</sub>, event-free survival due to efficacy reasons; HR, hazard ratio; NE, not evaluable; OS, overall survival; PFS, progression-free survival; Pola, polatuzumab vedotin; R-CHOP, rituximab plus cyclophosphamide, doxorubicin, vincristine and prednisone; R-CHP, rituximab plus cyclophosphamide, doxorubicin and prednisone.

**Bold** indicates statistically significant result.

3.4. While the submission had proposed that PFS at 24 months (difference in event-free rate: 6.50%, 95% CI: 0.52 to 12.49) was a suitable surrogate endpoint for OS, the Committee considered the PFS-OS surrogacy relationship in POLARIX to be uncertain, due to a number of reasons. These included no significant difference in CR at EOT (an independent predictor of PFS and OS for patients with untreated DLBCL) between treatment arms<sup>a</sup>, along with a high degree of censoring in POLARIX, which reduced the confidence in a sustained treatment effect of Pola+R-CHP over R-CHOP beyond the trial period. It was also noted that the upper confidence boundary of PFS in POLARIX exceeded a trial-level PFS-OS correlation surrogate threshold effect<sup>b</sup>, and the PFS via investigator assessment might have introduced subjective bias that overestimated the results.

<sup>a</sup> Broglio K, Kostakoglu L, Ward C, et al. PET-CR as a potential surrogate endpoint in untreated DLBCL: meta-analysis and implications for clinical trial design. *Leukemia & Lymphoma*. 2022; 63(12):2816-2831.

<sup>b</sup> Shi (2018) reported a surrogate threshold effect (STE, i.e. minimum treatment effect on the surrogate necessary to confidently predict a significant treatment effect on OS) HR of  $\leq 0.89$  for PFS which indicated that an observed HR  $\leq 0.89$  would predict a significant treatment effect on OS. Although the point estimate for PFS in POLARIX (HR 0.73, 95% CI: 0.57 to 0.95) would meet the STE to predict a significant treatment effect OS, its upper confidence boundary exceeded the STE, thus raising uncertainty regarding the magnitude of OS benefit associated with Pola+R-CHP.

- 3.5. In terms of safety, the Committee noted that the incidence of grade  $\geq 3$  adverse events and serious adverse events were similar across arms. Although a higher proportion of patients in the Pola+R-CHP arm experienced grade 3 to 4 (13.8% vs 8.0%) and serious (9.9% vs 6.4%) febrile neutropenia compared to the R-CHOP group, the Committee considered these differences to be small.
- 3.6. The submission described Pola+R-CHP as superior in terms of effectiveness and similar in terms of safety compared with R-CHOP for patients with previously untreated DLBCL with an IPI score of 3 to 5. Based on the available evidence, the Committee concluded that Pola+R-CHP did not provide a benefit compared with R-CHOP in terms of OS. While Pola+R-CHP was considered to be superior to R-CHOP in terms of PFS and EFS<sub>eff</sub>, the magnitude and sustainability of treatment effect was uncertain. In terms of safety, the Committee considered the claim of non-inferior safety for Pola+R-CHP compared with R-CHOP to be reasonable.

## Cost effectiveness

- 4.1. In March 2023, the Committee considered the results of the cost-utility analysis that compared Pola+R-CHP with R-CHOP for previously untreated DLBCL in patients with an IPI score of 3 to 5, based on POLARIX trial. Key components of the economic evaluation provided in the submission are summarised in Table 2.

**Table 2: Key components of the company-submitted economic evaluation**

Component	Description
Type of analysis	Cost-utility analysis
Population	Previously untreated DLBCL in patients with IPI score 3 to 5
Outcomes	Total and incremental direct medical costs; total and incremental LY gained; total and incremental QALYs; ICER
Perspective	Singapore healthcare system
Type of model	Partitioned survival model
Time horizon	20 years in the model base case, based on a median follow up of 28.2 months in the POLARIX trial
Health states	Progression-free; post-progression; death
Cycle length	1 week
Extrapolation methods used to generate results	<p>Transitions were informed by PFS and OS curves of Pola+R-CHP and R-CHOP in the IPI score 3 to 5 subgroup from POLARIX and extrapolated using standard parametric distributions in the base case:</p> <ul style="list-style-type: none"> <li>• PFS for both treatment arms = generalised gamma distribution</li> <li>• OS for both treatment arms = log-normal distribution</li> </ul> <p>No treatment waning was applied in the base case.</p> <p>In the Pola+R-CHP arm approximately 80% of total LYs and QALYs gained and 40% of total costs occurred in the extrapolated period. In</p>

	the R-CHOP arm approximately 78% of total LYs and QALYs gained and 47% of total costs occurred in the extrapolated period.
Health-related quality of life	<p>The health state utility values were informed by EQ-5D-5L (cross walked to 3L) data from the IPI score 3 to 5 subgroup in POLARIX:</p> <ul style="list-style-type: none"> <li>• Progression-free = 0.79</li> <li>• Post-progression = 0.75</li> </ul> <p>Disutility values due to AEs were not applied in the base case.</p>
Types of healthcare resources included	<ul style="list-style-type: none"> <li>• Drug and drug administration</li> <li>• Disease management cost</li> <li>• Healthcare resource use</li> <li>• Subsequent treatment costs</li> <li>• AE management costs</li> </ul>

Abbreviations: AEs, adverse events; DLBCL, diffuse large B-cell lymphoma; ICER, incremental cost-effectiveness ratio; IPI, international prognostic index; LY, life years; QALY, quality-adjusted life-years; OS, overall survival; PFS, progression-free survival.

4.2. The base case incremental cost-effectiveness ratio (ICER) at the proposed price was between SG\$15,000 and SG\$45,000 per quality-adjusted life year (QALY) gained. However, the Committee considered the ICER to be highly uncertain and likely underestimated, in view of the following:

- The submission used data from the IPI 3 to 5 subgroup of the POLARIX trial to inform comparative efficacy of the treatments in the economic model. The PFS hazard ratio (HR) reported for the IPI score 3 to 5 subgroup (HR 0.65, 95% CI 0.47 to 0.88) demonstrated a larger treatment effect than the ITT population (HR 0.73, 95% CI 0.57 to 0.95), which biased the incremental costs and outcomes in favour of Pola+R-CHP. The Committee considered that it was more appropriate and robust to inform efficacy in the economic model using results of the ITT population.
- The submission assumed that the treatment effect of Pola+R-CHP compared with R-CHOP would be maintained over the entire time horizon; patients who were progression-free at 2.5 years did not incur further ongoing disease management costs and progression-free utilities reflected the age- and sex-matched general population utilities beyond that timepoint. Although there was a separation in PFS favouring Pola+R-CHP over R-CHOP within the trial period, the Committee considered that it was optimistic to assume that this treatment effect would be maintained indefinitely, and a continued separation of OS curves may be implausible given the immature OS data and uncertain PFS-OS surrogacy relationship.
- The model was highly sensitive to the extrapolation of PFS in both treatment arms. Given that the disease management costs in the progression-free and post-progression health states contributed to a large proportion of total costs, the time spent in these health states (as a result of the PFS extrapolations) was a key driver of the model. Consequently, any inputs or assumptions that influenced the

transition between states (e.g. selection of extrapolation function, cure assumption or efficacy input) or impacted the disease management costs in these health states had a notable impact on the ICER.

- Healthcare resource use in the submitted model was based on the NICE (UK) evaluation of polatuzumab in relapsed/refractory DLBCL. The Committee heard that local clinical experts considered the healthcare resource use in the previously untreated DLBCL setting to be substantially lower than that used in the submitted model. Hence, the Committee considered this an overestimation of healthcare resource utilisation and cost which favoured the Pola+R-CHP arm.
- 4.3. The Committee considered the revised base case, which accounted for the uncertainties in the company's model. Key changes included the use of efficacy results from the ITT population, incorporation of treatment waning, and applying healthcare resource use parameters that reflected local practice. These changes substantially increased the ICER to between SG\$105,000 and SG\$135,000 per QALY gained.
  - 4.4. The Committee noted that based on one-way sensitivity analysis of the revised economic evaluation, the key model drivers were the cost of polatuzumab and disease management costs in the post-progression health state. The Committee also noted that the use of a different population, cure assumptions, and survival extrapolation in the scenario analyses resulted in a wide range of ICERs.
  - 4.5. In June 2023, following a revised proposal, the Committee considered polatuzumab to be an acceptable use of healthcare resources.

## Estimated annual technology cost

- 5.1. Using an epidemiological approach, the submission estimated that the annual cost impact to the public healthcare system would be between SG\$3 million and SG\$5 million over the first five years of listing Pola+R-CHP on the MOH List of Subsidised Drugs for previously untreated DLBCL in patients with an IPI score of 3 to 5.
- 5.2. In March 2023, the Committee considered that the submission estimates and price-volume agreement (PVA) caps were high due to an overestimation of eligible DLBCL patients, treatment cost and duration, and an optimistic uptake rate for Pola+R-CHP. Based on the revised budget impact model, the annual cost impact to the public healthcare system was estimated to be less than SG\$3 million.
- 5.3. In June 2023, the Committee considered the revised PVA adequate to manage the uncertainty of the overall budget impact.

## Recommendations

- 6.1. In June 2023, the Committee recommended polatuzumab vedotin 30 mg and 140 mg powder for concentrate for solution for infusion, in combination with rituximab biosimilar (subsidised brand), cyclophosphamide, doxorubicin and prednisone, to be listed on MAF for patients with previously untreated DLBCL with an IPI score of 3 to 5, in view of the clinical need and acceptable clinical- and cost-effectiveness compared with current treatment options.



## ANNEX

### Recommendations by the MOH Drug Advisory Committee

Drug preparation	Clinical indication	Subsidy class (implementation date)	MediShield Life claim limit per month (implementation date)
Polatuzumab vedotin 30 mg and 140 mg powder for concentrate for solution for infusion plus rituximab biosimilar concentrate for infusion (100 mg/10 mL, 500 mg/50 mL)	Polatuzumab in combination with rituximab biosimilar (subsidised brand), cyclophosphamide, doxorubicin, and prednisone for previously untreated diffuse large B-cell lymphoma (DLBCL) in patients with an international prognostic index (IPI) score of 3 to 5.	MAF (1 Mar 2024)	\$3400 (1 Mar 2024)
Polatuzumab vedotin 30 mg and 140 mg powder for concentrate for solution for infusion plus rituximab concentrate for infusion (100 mg/10 mL, 500 mg/50 mL)	Polatuzumab in combination with rituximab (non-subsidised brand), cyclophosphamide, doxorubicin, and prednisone for previously untreated diffuse large B-cell lymphoma (DLBCL) in patients with an international prognostic index (IPI) score of 3 to 5.	Not recommended for subsidy	\$3000 (1 Mar 2024)
	Polatuzumab in combination with rituximab, cyclophosphamide, doxorubicin, and prednisone for previously untreated diffuse large B-cell lymphoma (DLBCL).	Not recommended for subsidy	\$3000 (1 Mar 2024)

Abbreviation: MAF, Medication Assistance Fund.

 Agency for Care Effectiveness - ACE  Agency for Care Effectiveness (ACE)

### About the Agency

The Agency for Care Effectiveness (ACE) was established by the Ministry of Health (Singapore) to drive better decision-making in healthcare through health technology assessment (HTA), clinical guidance, and education.

As the national HTA agency, ACE conducts evaluations to inform government funding decisions for treatments, diagnostic tests and vaccines, and produces guidance for public hospitals and institutions in Singapore.

This guidance is based on the evidence available to the MOH Drug Advisory Committee as at 7 March 2023 and 13 June 2023. It is not, and should not be regarded as, a substitute for professional or medical advice. Please seek the advice of a qualified healthcare professional about any medical condition. The responsibility for making decisions appropriate to the circumstances of the individual patient remains with the healthcare professional.

*Find out more about ACE at [www.ace-hta.gov.sg/about](http://www.ace-hta.gov.sg/about)*

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