SMC2525

polatuzumab vedotin powder for concentrate for solution with infusion (Polivy®)

Roche Products Ltd

05 May 2023

The Scottish Medicines Consortium (SMC) has completed its assessment of the above product and advises NHS Boards and Area Drug and Therapeutic Committees (ADTCs) on its use in NHSScotland. The advice is summarised as follows:

ADVICE: following a full submission assessed under the orphan medicine process

polatuzumab vedotin (Polivy®) is accepted for restricted use within NHSScotland.

Indication Under Review: in combination with rituximab, cyclophosphamide, doxorubicin, and prednisone (R-CHP) for the treatment of adult patients with previously untreated diffuse large B-cell lymphoma (DLBCL).

SMC restriction: patients with an International Prognostic Index (IPI) score of 2 to 5

Polatuzumab vedotin, in combination with R-CHP, resulted in a statistically significant improvement in investigator-assessed progression-free survival compared with rituximab, cyclophosphamide, vincristine, doxorubicin and prednisone (R-CHOP).

This advice applies only in the context of an approved NHSScotland Patient Access Scheme (PAS) arrangement delivering the cost-effectiveness results upon which the decision was based, or a PAS/ list price that is equivalent or lower.

This advice takes account of the views from a Patient and Clinician Engagement (PACE) meeting.

Chair
Scottish Medicines Consortium

1. Clinical Context

1.1. Medicine background

Polatuzumab vedotin (hereafter referred to as polatuzumab) is a CD79b targeted antibody-drug conjugate that preferentially delivers a potent anti-mitotic agent (monomethyl auristatin E) which results in the killing of malignant B-cells.[1, 2] The licence has been extended to first-line use in adult patients with DLBCL, in combination with rituximab, cyclophosphamide, doxorubicin, and prednisone (R-CHP). SMC has issued separate advice for use of polatuzumab in relapsed or refractory DLBCL (SMC2524).

For previously untreated DLBCL, the recommended dose of polatuzumab is 1.8mg/kg (given as an intravenous [IV] infusion) every 21 days in combination with rituximab, cyclophosphamide, doxorubicin, and prednisone (R-CHP) for 6 cycles. Prednisone is administered on Days 1 to 5 of each cycle. Cycles 7 and 8 consist of rituximab as monotherapy.[1]

1.2. Disease background

DLBCL is the most common subtype of non-Hodgkin's lymphoma (NHL), accounting for approximately 25% to 40% of newly diagnosed NHL cases worldwide.[2, 3] According to published data from the South East Scotland Cancer Network (SCAN) and the West of Scotland Cancer Network (WoSCAN), there were 112 and 230 newly reported cases respectively of DLBCL in 2018-2019.[4, 5] The incidence of this aggressive condition increases with age and if left untreated, patients with DLBCL have a median survival of less than one year.[2, 3, 6] The international prognostic index (IPI) for aggressive NHL identifies five patient factors obtained at diagnosis used to stratify prognosis and overall survival. The IPI factors reflect clinical features, each representing one point, and are a combination of patient characteristics (age >60 years, Eastern Cooperative Oncology Group Performance Status >2) and disease-related findings (Ann Arbor Stage III or IV, elevated Lactate Dehydrogenase, and extranodal involvement in more than one site).[2]

1.3. Company proposed position

The submitting company has requested that polatuzumab is restricted for use in patients with an International Prognostic Index (IPI) score of 2 to 5, as per the POLARIX study population.

1.4. Treatment pathway and relevant comparators

The standard of care for previously untreated patients with DLBCL is combined chemotherapy and immunotherapy, mainly as rituximab, cyclophosphamide, vincristine, doxorubicin and prednisone (R-CHOP), which may be curative for approximately 60% of patients. To date, other regimens have been unable to demonstrate any meaningful benefit over R-CHOP.[7, 8] Clinical experts consulted by SMC confirmed that current first-line therapy for previously untreated DLBCL predominantly consists of R-CHOP.

1.5. Category for decision-making process

Eligibility for a PACE meeting
Polatuzumab meets SMC orphan criteria.

2. Summary of Clinical Evidence

2.1. Evidence for the licensed indication under review

Evidence to support the efficacy and safety of polatuzumab comes from the POLARIX study, which assesses the effects of replacing vincristine in R-CHOP with polatuzumab. Details are summarised in Table 2.1.

Table 2.1. Overview of relevant study

<table>
<tr><th>Criteria</th><th>POLARIX study[2, 9]</th></tr>
<tr><td>Study Design</td><td>An international, multicentre, randomised, double-blind, phase III study.</td></tr>
<tr><td>Eligible Patients</td><td>• Patients aged 18 to 80 years of age with an ECOG PS of 0 to 2.
• Baseline IPI score of 2 to 5.
• Previously untreated CD20-positive DLBCL.
• Life expectancy of ≥12 months.
• No known CNS lymphoma or history of follicular lymphoma grade 3B.</td></tr>
<tr><td>Treatments</td><td>Six cycles of one of the following two treatment regimens at 21-day intervals:
<table>
<tr><th>Pola-R-CHP</th><th>R-CHOP</th></tr>
<tr><td>• IV polatuzumab 1.8mg/kg
• IV placebo (in place of vincristine)
• IV rituximab 375mg/m^2
• IV cyclophosphamide 750mg/m^2
• IV doxorubicin 50mg/m^2
• Oral prednisolone or prednisone 100mg (Days 1 to 5)</td><td>• IV placebo (in place of polatuzumab)
• IV vincristine 1.4mg/m^2
• IV rituximab 375mg/m^2
• IV cyclophosphamide 750mg/m^2
• IV doxorubicin 50mg/m^2
• Oral prednisolone or prednisone 100mg (Days 1 to 5)</td></tr>
</table>
All of these treatments were given on day 1 of each 21-day cycle, except prednisolone or prednisone. IV rituximab 375mg/m^2 monotherapy was also administered on day 1 in cycles 7 and 8 in both treatment groups. G-CSF was mandatory during the first six cycles as primary prophylaxis against neutropenia.</td></tr>
<tr><td>Randomisation</td><td>Patients were randomised equally to receive either pola-R-CHP or R-CHOP. Randomisation was stratified according to IPI score (2 versus 3 to 5), status with respect to bulky disease (present [≥1 lesions ≥7.5cm in greatest dimension] versus absent), and geographic region.</td></tr>
<tr><td>Primary outcome</td><td>Investigator-assessed PFS, calculated in a time-to-event analysis, in which investigator-assessed disease progression and relapse or death from any cause were counted as events.</td></tr>
<tr><td>Key Secondary outcomes</td><td>• Investigator-assessed EFS (efficacy) – as assessed in a time-to-event analysis, in which an event was defined as investigator-assessed disease progression or relapse, death from any cause, initiation of any subsequent anti-lymphoma treatment that was not specified in the protocol, or biopsy-confirmed residual disease after treatment completion.
• BICR-assessed CR rate at the EOT (by PET-CT) - defined as the percentage of patients with CR at the end of treatment by PET-CT.
• Overall survival.</td></tr>
<tr><td>Statistical analysis</td><td>A hierarchical statistical testing strategy was applied in the study with no formal testing of outcomes after the first non-significant outcome in the hierarchy. Therefore the results reported for these outcomes are descriptive only and not inferential (no p-values reported). The order of the hierarchical statistical testing analysis was investigator-assessed PFS, then the key secondary outcomes as outlined above.</td></tr>
</table>

BICR = blinded independent central review; CNS = central nervous system; CR = complete response; DLBCL = diffuse large B-cell lymphoma; ECOG PS = Eastern Cooperative Oncology Group Performance Status; EFS (efficacy) = event free survival for efficacy causes; EOT = end of treatment; G-CSF = granulocyte colony-stimulating factor; IPI = international Prognostic Index; IV = intravenous; PET-CT = positron-emission tomography and computed tomography; PFS = progression-free survival.

At the primary analysis (data cut-offs of 28 June 2021), there was a statistically significant improvement in investigator-assessed progression-free survival (PFS) in the pola-R-CHP group compared with the R-CHOP group. Results for the key secondary outcomes of EFS (efficacy) also significantly favoured the pola-R-CHP group. The complete response rate assessed independently at the end of treatment (BICR-assessed CR rate at the EOT) was higher in the pola-R-CHP group but the difference was not significant. Interim analysis of overall survival was also assessed at the time. Results are presented in Table 2.2.

Table 2.2 Primary and selected secondary outcomes from the POLARIX study (data cut-off 28 June 2021).[2, 9]

	Pola-R-CHP (n=440)	**R-CHOP (n=439)**
Median follow-up	28.2 months	
Primary outcome: investigator-assessed PFS		
Events, n	107	134
HR (95% CI), p-value	0.73 (0.57 to 0.95), p=0.02	
Median PFS (months)	NE	NE
KM estimated PFS at 24 months	77%	70%
Secondary outcome: investigator-assessed EFS (efficacy)		
Events, n	112	138
HR (95% CI), p-value	0.75 (0.58 to 0.96), p=0.02	
Median EFS (efficacy)	NE	NE
KM estimated EFS (efficacy) rate at 24 months	76%	69%
Secondary outcome: BICR-assessed CR rate at the EOT (by PET-CT)		
Complete responders, n (%)	343 (78%)	325 (74%)
Difference in response rate (95% CI)	3.92 (-1.89 to 9.70)[a]	
Secondary outcome: overall survival		
Deaths, n	53	57
HR (95% CI)	0.94 (0.65 to 1.37)[a]	
Median overall survival	NE	NE
KM estimated overall survival rate at 24 months	89%	89%

BICR = blinded independent central review; CI = confidence interval; CR = complete response; EFS (efficacy) = event free survival for efficacy causes; EOT = end of treatment; HR = hazard ratio; KM = Kaplan-Meier; NA = not assessed; NE = not estimable; PET-CT = positron-emission tomography and computed tomography; PFS = progression-free survival

[a]this result was not statistically significant.

The submitting company also provided preliminary results from a pre-specified final analysis of overall survival (median follow-up of 39.7 months), as well as an updated analysis of investigator-assessed PFS and other secondary outcomes (data cut-off 15 June 2022). The final overall survival analysis (data cut-off 15 June 2022) reported an HR of 0.94 (95% CI: 0.67 to 1.33).[10, 11]

2.2. Health-related quality of life outcomes

Health-Related Quality of Life was assessed using the FACTLym LymS and EORTC QLQ-C30 questionnaires (to evaluate important disease and treatment-related symptoms), as well as the FACT/GOG-NTX questionnaire (to evaluate peripheral neuropathy). There were similar improvements in patient-reported physical functioning, fatigue, and lymphoma symptoms for both treatment groups. There were no improvements in treatment-related symptoms and peripheral neuropathy observed between both treatment groups.[2]

*Other data were also assessed but remain commercially confidential.**

3. Summary of Safety Evidence

Safety analyses were performed in all patients who had received at least one dose of study medicine (n=873).[2] In the POLARIX study at data cut-off 28 June 2021, the median exposure to treatment was 6 cycles in both treatment groups.[2, 9]

Any treatment-emergent adverse event (AE) was reported by 98% (426/435) of patients in both groups. In the pola-R-CHP and R-CHOP groups respectively, patients reporting a grade 3 or higher AE were 61% versus 60%, patients with a reported serious AE were 34% versus 31%, patients with a dose reduction due to treatment-emergent AEs were 9.2% versus 13%, the proportion of AEs that led to dose interruptions were 24% versus 25% and patients discontinuing at least one study treatment due to an AE was 6.2% versus 6.6%.[2, 9]

The most frequently reported treatment-emergent AEs of any grade with an incidence >20% in the pola-R-CHP group versus the R-CHOP group were: nausea (42% versus 37%), neutropenia (31% versus 33%), constipation (29% in both treatment groups), anaemia (29% versus 26%), fatigue (26% in both treatment groups), grade 2 diarrhoea (31% versus 20%), alopecia (24% in both treatment groups), peripheral neuropathy (24% versus 23%), and peripheral sensory neuropathy (20% versus 21%).[2, 9]

In the pola-R-CHP and R-CHOP groups respectively, higher proportions of patients in the pola-R-CHP group experienced: any grade of infection (50% versus 43%); serious infections (14% versus 10%); and grade 3 to 4 infections (14% versus 11%). The rates of grade 5 infections were similar between the two treatment groups (1.1% versus 1.4%) as was the proportions of infection AEs leading to study drug discontinuation, reduction or interruption (8.0% versus 8.2%).[2]

Adverse events that resulted in death were reported in 13 patients in the pola-R-CHP group and in 10 patients in the R-CHOP group; these events were primarily related to infections including pneumonia (4 patients) and sepsis (4 patients).[2, 9]

4. Summary of Clinical Effectiveness Considerations

4.1. Key strengths

- In the POLARIX study, pola-R-CHP treatment resulted in a statistically significant improvement in investigator-assessed PFS compared with current standard of care (R-CHOP) after a median follow-up of 28 months (estimated improvement in PFS rate at 24 months of approximately 6%).[2, 9]
- Improvement in PFS is supported by the secondary outcomes EFS (efficacy) where a statistically significant reduction in the risk of occurrence of disease was observed in patients treated with pola-R-CHP compared to R-CHOP.[2, 9]

4.2. Key uncertainties

- The statistical significance for EFS (efficacy) was only achieved following a protocol amendment which resulted in BICR-assessed CR rate at EOT (by PET-CT) being moved to a lower position in the statistical testing hierarchy.[2]
- The available data do not show a benefit in overall survival for pola-R-CHP over R-CHOP. At the pre-specified final analysis of overall survival (data cut-off 15 June 2022) and with a median follow-up of 39.7 months, overall survival results were still immature and did not meet the pre-specified threshold for statistical significance;[10, 11] this is perhaps unsurprising since the study lacks power for overall survival, even for the final analysis.[2] Given that the expected cure rate for the R-CHOP arm is approximately 60%, it will take a significant length of follow-up to demonstrate any differences in overall survival, if any, between the two treatment groups.[2]
- Subsequent treatments may confound overall survival results, and the submitting company suggest that the advances in the relapsed/refractory DLBCL setting could explain the low number of overall survival events. As of the 28 June 2021 data cut-off, 22% (99/440) of patients in the pola-R-CHP group and 30% (133/439) of patients in the R-CHOP group had received at least one subsequent course of therapy for lymphoma that was not specified in the protocol. In the pola-R-CHP and R-CHOP groups respectively, higher proportions of patients in the R-CHOP group received: pre-planned or unplanned radiotherapy (9.3% versus 13.0%); systemic therapy (17% versus 24%); stem-cell transplantation (3.9% versus 7.1%); and chimeric antigen receptor (CAR) T-cell therapy (2.0% versus 3.6%).[2, 9] However, the impact of initiation of subsequent anti-lymphoma treatment prior to or in the absence of subsequent death or disease progression was assessed by performing sensitivity analyses by discount method, and by censoring PFS at the last adequate tumour assessment before the initiation of the subsequent treatment. Results from these analyses were consistent with the result of analysis of the primary endpoint indicating that there was minimal impact of subsequent anti-lymphoma treatment prior to progressive disease on the PFS results.[2]
- In the POLARIX study, G-CSF was mandated during cycles 1 to 6 of treatment for primary prophylaxis against neutropenia. The submitting company considered that the slightly lower incidence of prophylactic G-CSF use in the pola-R-CHP (90%) group compared to the R-CHOP (93%) group may have partially contributed to the higher incidence of febrile neutropenia in pola-R-CHP group.[2] However, clinical experts contacted by SMC suggest that the high usage of

G-CSF in the study would be more than would be used in clinical practice; this could possibly result in higher rates of neutropenia in clinical practice than what was seen in both groups in the POLARIX study.

- There are some generalisability issues. Firstly, 11% (99/879) of patients in the POLARIX study were Ann Arbor stages I or II (essentially early stage disease). In NHS Scotland, patients with early stage lymphoma would potentially only receive three cycles of R-CHOP followed by involved site radiotherapy (IRST). Secondly, the POLARIX study used six cycles of R-CHOP or pola-R-CHP followed by two cycles of rituximab monotherapy; clinical experts contacted by SMC suggest that this may not reflect standard practice in Scotland.
- Subgroup analysis suggested a lack of PFS benefit in patients with an IPI score of 2 (38% of patients in the POLARIX study). However, subgroup analyses were exploratory and the POLARIX study was not powered to compare subgroups.[2, 9]

*Other data were also assessed but remain commercially confidential.**

4.3. Clinical expert input

Clinical experts consulted by SMC considered that polatuzumab is a therapeutic advancement due to its statistically significant improvement in investigator-assessed PFS over R-CHOP. They considered that the place in therapy of polatuzumab would be in place of R-CHOP for patients with an IPI score of 2 to 5 who were fit enough for chemotherapy.

4.4. Service implications

Clinical experts consulted by SMC suggested that the introduction of the polatuzumab regimen will increase time required for treatment administration and post-infusion observations.[12] Additionally, some experts contacted by SMC suggest that replacing pola-R-CHP with R-CHOP could mean arranging an additional two doses of rituximab monotherapy (this is not current practice for R-CHOP), which could affect day-unit capacity.

5. Summary of Patient and Carer Involvement

A patient and clinician engagement (PACE) meeting with patient group representatives and clinical specialists was held to consider the added value of polatuzumab (Polivy®), as an orphan medicine, in the context of treatments currently available in NHSScotland.

The key points expressed by the group were:

- Diffuse large B-cell lymphoma (DLBCL) is a rare and aggressive disease associated with significant symptoms and rapid progression. The aim of first-line treatment is cure however up to 50% of patients will be refractory to treatment or relapse. The chemotherapy regimens used for relapse and refractory disease are generally more intensive and potentially followed by haematopoietic stem cell transplant (HSCT). Many of these patients are not eligible for HSCT and have very limited second-line treatment options. These patients have a particularly poor prognosis. This causes significant emotional and psychological stress for patients and their families.

- There is significant unmet need in this patient group. R-CHOP is the main first-line chemotherapy regimen for treatment of DLBCL and prior to polatuzumab there have been no recent developments of other efficacious treatments. Patients who relapse or are refractory to first-line treatment have limited further treatment options often associated with high toxicity and low efficacy. PACE participants noted that delaying time to progression is therefore extremely beneficial in this patient group.
- Polatuzumab in combination with R-CHP has been shown to delay disease progression, compared to R-CHOP. This means that, in patients who respond, there is a delay in the requirement of often toxic and sometimes ineffective second-line chemotherapy treatments and patients remain well for longer. This has significant positive physical and psychological implications for patients and their families, allowing them to participate in usual daily activities and have improved quality of life.
- The safety profiles of polatuzumab plus R-CHP and R-CHOP appear to be comparable overall, and it therefore seems unlikely that the addition of polatuzumab would negatively impact a patient's quality of life.
- PACE participants highlighted that staff already have experience of polatuzumab treatment in the second-line DLBCL setting, and that the required infrastructure (e.g. day-unit set-up) is already in place to deliver this treatment. Administration times would be slightly longer, particularly during the first cycle however PACE participants did not expect this to have significant implications for the service or patients. Delaying progression may translate into future service benefits since there would be a reduction in hospital admissions to administer second-line treatments (including HSCT) or manage second-line treatment-related side effects.

Additional Patient and Carer Involvement

We received a patient group submission from Lymphoma Action, which is a registered charity. Lymphoma Action has received 6.7% pharmaceutical company funding in the past two years, including from the submitting company. A representative from Lymphoma Action participated in the PACE meeting. The key points of their submission have been included in the full PACE statement considered by SMC.

6. Summary of Comparative Health Economic Evidence

6.1. Economic case

The submitting company provided an economic case as described in Table 6.1.

Table 6.1 Description of economic analysis

Criteria	Overview
Analysis type	Cost-utility analysis
Time horizon	Lifetime (60 years)
Population	The company requested the SMC considered polatuzumab in combination with rituximab, cyclophosphamide, doxorubicin, and prednisone (pola-R-CHP) in previously untreated patients with diffuse large B-cell lymphoma (DLBCL), who have an International Prognostic Index (IPI) score of 2 to 5.

Comparators	Rituximab, cyclophosphamide, vincristine, doxorubicin, and prednisone (R-CHOP)
Model description	Partitioned survival model with three health states; progression-free, progressed and dead.
Clinical data	Investigator-assessed progression-free survival (PFS), overall survival (OS), safety data, and baseline patient characteristics were obtained from the POLARIX study.
Extrapolation	Long-term PFS was extrapolated using the generalized gamma mixture cure model in both arms. The predicted cure fraction was 64% for R-CHOP and 75% for pola-R-CHP. The 30-month OS K-M data from POLARIX were used, followed by the generalized gamma model, aligning with the PFS model. The cured cohort is assumed to revert to age and sex-adjusted general population all-cause mortality, following the age distribution of the POLARIX study.
Quality of life	Health state-specific utility weights from the GOYA trial were used with treatment-specific utility decrements associated with adverse events applied in the first cycle of the model. These were 0.816 for the progression-free state and 0.734 for the progressed state. The progression-free cohort assumes the general population age-adjusted utility weight after 2 years.
Costs and resource use	Apart from medicine acquisition and administration costs, other cost included in the analysis were health-state specific supportive care (social care, health care professionals and hospital resource use), treatment of adverse events, subsequent treatments and end of life care. The progression-free cohort assumes no costs after 2 years.
PAS	A revised PAS was submitted by the company and assessed by the Patient Access Scheme Assessment Group (PASAG) as acceptable for implementation in NHSScotland. Under the PAS, a discount was offered on the list price.

6.2. Results

The company-provided base case results showed that polatuzumab was the dominant treatment i.e. cheaper and more effective than R-CHOP. The results include the PAS for polatuzumab in first-line and second-line (in the comparator arm only). The QALY gain is primarily driven by the modelled improvement in PFS and cure rates and the associated assumed improvement in OS and quality of life. The cost differences are driven by higher medicine acquisition costs in first line treatment in the pola-R-CHP arm, which are offset by higher cost of subsequent treatments and other healthcare resource use associated with progression.

6.3. Sensitivity analyses

A number of sensitivity analyses were provided by the company with the main scenarios additionally requested by SMC. Key scenarios are summarised in Table 6.2. This illustrates that the result can change to one of dominance to an ICER of £26k-£35k when alternative assumptions are made.

Table 6.2: Selected scenario analyses (with PAS)

	Scenario	Base case	ICER
0	Base case	-	Dominant
1	Time horizon 30 years	Time horizon: 60 years	Dominant
2	Mixture cure model: log-normal (PFS and OS); Polatuzumab+R-CHP: 73%; R-CHOP: 68%; Best statistical fit	Mixture cure model: generalized gamma (PFS and OS); Polatuzumab+R-CHP: 75%; R-CHOP: 64%;	£25,983

3	Utility weights based on EQ-5D-5L mapped to 3L from POLARIX, no AEs for adverse events	Utility weights from GOYA + Utility decrements for AEs	Dominant
4	Average weight from POLARIX: upper end of SD 95.27 kg	Average weight from POLARIX: 75.92 kg	Dominant
5	Combined: all scenarios above	-	£35,000
Abbreviations: R-CHP, rituximab, cyclophosphamide, doxorubicin, and prednisone; R-CHOP, Rituximab, cyclophosphamide, vincristine, doxorubicin, and prednisone; ICER, incremental cost-effectiveness ratio;PFS, progression-free survival; OS, overall survival;			

6.4. Key strengths

Key strengths of the analysis include the use of an appropriate model structure, appropriate comparator, availability and use of a phase III RCT clinical efficacy and safety data.

6.5. Key uncertainties

The analysis is associated with the following uncertainties:

- Modelling of improvement in cure rates and survival for pola-R-CHP based on the improvement in PFS, observed in POLARIX. No difference in survival was shown in the main clinical study, although data are immature. There are uncertainties that improvement in PFS would translate into improvement in cure rates, and thus overall survival and health-related quality of life. In addition, the improvement in PFS is also uncertain as described in the clinical section of this DAD. Using the log-normal cure mixture model, which has the best statistical fit and estimates a much smaller difference in cure rates, has a substantial upward effect on the ICER (Table 6.2, scenario 2) and demonstrates the sensitivity of the results to less optimistic modelling assumptions on cure and survival rates.
- The assumption that patients who have not progressed in the first 24 months, experience general population mortality is associated with uncertainty. The company presented a Danish study, which compared the survival of patients in long-term remission (progression-free 24 or 48 months after the end of treatment) with the general population mortality in support of their assumption. However, the study reports excess mortality for this patient population, especially for patients >50 years of age.[13]
- Polatuzumab is currently used in second line, following first-line treatment with R-CHOP and this has been reflected in the comparator arm in the economic model. It is likely that the potential benefit of polatuzumab in second line in comparison with the standard of care has not been fully captured and thus the long-term comparator efficacy may have been underestimated. Cure rates for subsequent treatments have not been incorporated.
- The use of alternative utility weights from POLARIX does not have major impact on the ICER (scenario 3). However, it should be noted that the effect of adverse events on quality of life may not be fully captured in the analysis. Pola-R-CHP seems to be more toxic than R-CHOP in terms of grade 3 and 4 febrile neutropenia. There is no evidence in support of the company's assumption that patients in long-term remission revert to general population quality of life.

- The use of standard NHS Reference Cost sources for treatment administration may not fully reflect the impact on the service in practice from additional staff time that will be required to administer polatuzumab instead of vincristine. Additionally, the cost of treatment of febrile neutropenia seems to be too low to capture the associated high hospitalization rates, but additional sensitivity analysis provided by the company showed that using alternative costs did not have a significant impact on the cost-effectiveness estimates.
- Health-related resource use in the economic model (supportive care) was based on a clinical expert opinion survey, conducted by the company, for patients with advanced/metastatic non-Hodgkin's lymphoma. This is a more severe disease, which is likely to be associated with more resource use, than that in the current indication. This approach is likely to create a bias in favour of pola-R-CHP due to the higher cure fraction assumed in the model. Again, the company provided some additional sensitivity analysis using alternative costs to show that this aspect did not exert a significant impact on the results.

*Other data were also assessed but remain confidential.**

7. Conclusion

The Committee considered the benefits of polatuzumab in the context of the SMC decision modifiers that can be applied when encountering economic uncertainty and agreed that as polatuzumab is an orphan equivalent medicine, SMC can accept greater uncertainty in the economic case.

After considering all the available evidence and the output from the PACE process, the Committee accepted polatuzumab for use in NHSScotland.

8. Guidelines and Protocols

The British Committee for Standards in Haematology published Guidelines for the management of DLBCL in 2016. Note this guidance predates the availability of polatuzumab;[14] therefore no specific recommendations were made for this medicine.

The European Society for Medical Oncology (ESMO) published DLBCL: ESMO clinical practice guidelines for diagnosis, treatment and follow-up in 2002. This guidance was subsequently updated in 2012 and again in 2015. This guideline predates the availability of polatuzumab; therefore no specific recommendations were made for this medicine.[15]

9. Additional Information

9.1. Product availability date

18 July 2022.

9.2. Summary of product characteristics

See the SPC for further information including dosing and safety. Available from: polatuzumab vedotin powder for concentrate for solution for infusion (Polivy®).

Table 9.1 List price of medicine under review

Medicine	Dose regimen	Cost per course (£)
Polatuzumab vedotin	**1.8mg/kg given as an intravenous (IV) infusion every 21 days for six cycles**	**66,360**

Costs from BNF online on 03 February 2023. Costs calculated based on adult weighing 70kg and using the full cost of vials assuming wastage. Costs do not take any patient access schemes into consideration.

10. Company Estimate of Eligible Population and Estimated Budget Impact

SMC is unable to publish the with PAS budget impact due to commercial in confidence issues. A budget impact template is provided in confidence to NHS health boards to enable them to estimate the predicted budget with the PAS.

*Other data were also assessed but remain confidential.**

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This assessment is based on data submitted by the applicant company up to and including 17 March 2023.

*Agreement between the Association of the British Pharmaceutical Industry (ABPI) and the SMC on guidelines for the release of company data into the public domain during a health technology appraisal:*https://www.scottishmedicines.org.uk/about-us/policies-publications/

Medicine prices are those available at the time the papers were issued to SMC for consideration. SMC is aware that for some hospital-only products national or local contracts may be in place for comparator products that can significantly reduce the acquisition cost to Health Boards. These contract prices are commercial in confidence and cannot be put in the public domain, including via the SMC Detailed Advice Document. Area Drug and Therapeutics Committees and NHS Boards are therefore asked to consider contract pricing when reviewing advice on medicines accepted by SMC.

Patient access schemes: A patient access scheme is a scheme proposed by a pharmaceutical company in order to improve the cost-effectiveness of a medicine and enable patients to receive access to cost-effective innovative medicines. A Patient Access Scheme Assessment Group (PASAG), established under the auspices of NHS National Services Scotland reviews and advises NHSScotland on the feasibility of proposed schemes for implementation. The PASAG operates separately from SMC in order to maintain the integrity and independence of the assessment process of the SMC. When SMC accepts a medicine for use in NHSScotland on the basis of a patient access scheme that has been considered feasible by PASAG, a set of guidance notes on the operation of the scheme will be circulated to Area Drug and Therapeutics Committees and NHS Boards prior to publication of SMC advice.

Advice context:

No part of this advice may be used without the whole of the advice being quoted in full.

This advice represents the view of the Scottish Medicines Consortium and was arrived at after careful consideration and evaluation of the available evidence. It is provided to inform the considerations of Area Drug & Therapeutics Committees and NHS Boards in Scotland in determining medicines for local use or local formulary inclusion. This advice does not override the individual responsibility of health professionals to make decisions in the exercise of their clinical judgement in the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.