SMC2524

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

Roche Products Ltd

09 June 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 reassessment under the end of life and orphan equivalent medicine process

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

Indication Under Review: in combination with bendamustine and rituximab for the treatment of adult patients with relapsed or refractory diffuse large B-cell lymphoma (DLBCL) who are not candidates for haematopoietic stem cell transplant (HSCT).

In a phase Ib/II study, polatuzumab vedotin in combination with bendamustine and rituximab resulted in an increase in complete response rate compared with bendamustine and rituximab alone.

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.

SMC previously accepted polatutuzumab for use in this indication on an interim basis (SMC2282). This supersedes that advice.

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.[1-3] It is licensed in combination with bendamustine and rituximab for the treatment of adult patients with relapsed or refractory diffuse large B-cell lymphoma (DLBCL) who are not candidates for haematopoietic stem cell transplant (HSCT).[2, 3] Polatuzumab was accepted for use on an interim basis by SMC for this indication under review in September 2020 (SMC2282). Interim acceptance eligibility was based on an EMA conditional marketing authorisation at the time, whose conditions have since been met resulting in a full MHRA marketing authorisation in July 2022 for this indication.
For relapsed and refractory DLBCL, the recommended dose of polatuzumab is 1.8 mg/kg given as an intravenous (IV) infusion every 21 days in combination with bendamustine and rituximab for six cycles. Please see the summary of product characteristics for further information.[2, 3]

1.2. Disease background

DLBCL is the most common non-Hodgkin lymphoma, accounting for approximately 25% of all newly diagnosed cases. The incidence of this aggressive disease increases with age and varies considerably across Europe. Treatment should be stratified according to age, International Prognostic Index (IPI) and feasibility of dose-intensified approaches. Primary refractory disease occurs in 10% to 15% of DLBCL patients and a further 20% to 30% relapse. The prognosis is poor for patients who are ineligible for autologous HSCT or have refractory disease after any line of treatment with a median overall survival of 6 to 11 months and 6.1 to 7.1 months respectively.[1, 4-6]

1.3. Treatment pathway and relevant comparators

For patients who relapse following first line therapy, guidelines recommend salvage chemotherapy followed, in responsive patients, by high dose chemotherapy and autologous HSCT. However, many refractory or relapsed patients are ineligible for autologous HSCT due to age, co-morbidities or chemotherapy insensitive disease. The aim of treatment for those unsuitable for autologous HSCT is to induce disease control and remission for as long as possible to prolong survival. Clinical experts consulted by SMC suggested that there is no defined standard salvage chemotherapy and a variety of different regimens may be used including off-label platinum and/or gemcitabine-based regimens; entry into clinical studies or palliative care are other alternative options.[1, 5] The chimeric antigen receptor (CAR) T-cell therapies, axicabtagene ciloleucel (SMC2189) and tisagenlecleucel (SMC2200) are also licensed and accepted by SMC for relapsed or refractory DLBCL, after two or more prior lines of systemic therapy. However, their use is limited by the complex and timely manufacturing process, patient tolerability of the condition regimen and risk of adverse events.[1]

1.4. Category for decision-making process

Eligibility for a PACE meeting
Polatuzumab meets SMC end of life and orphan criteria for this indication.

2. Summary of Clinical Evidence

2.1. Evidence for the licensed indication under review

Evidence to support polatuzumab comes from GO29365. Details are summarised in Table 2.1.

Table 2.1. Overview of relevant study

Criteria	GO29365 study[4, 7, 8]
Study Design	Phase Ib/II, multicentre, randomised, open-label study. Please note that this submission only focuses on the DLBCL components of the study (arms C, D, G, and H) and not the components involving obinutuzumab. Phase I of the study consisted of a safety run in and phase II consisted of a randomised phase (arms C and D); this was followed by an extended phase where a cohort received the now commercialised lyophilised formulation of polatuzumab (arms G and H).

Eligible Patients	• Adults (≥18 years) with histologically confirmed relapsed or refractory DLBCL with ≥ one prior line of therapy.
	• ECOG PS score of 0, 1 or 2.
	• If the patient had received prior bendamustine, response duration must have been at least one year (for patients who have relapsed disease after a prior regimen).
	• Patients who are ineligible for second-line autologous HSCT:
	  ○ with progressive disease or no response <6 months from start of initial therapy (second-line refractory).
	  ○ with disease relapse after initial response ≥6 months from start of initial therapy (second-line relapsed).
	• Patients who are ineligible for third-line (or beyond) autologous HSCT:
	  ○ with progressive disease or no response <6 months from start of prior therapy (third-line refractory).
	  ○ with disease relapse after initial response ≥6 months from start of prior therapy (third-line relapsed).

Treatments	In the phase II part of the study patients received: IV polatuzumab (liquid formulation) plus IV bendamustine and IV rituximab (n=40; arm C) or IV bendamustine and IV rituximab (n=40; arm D). Arms G (n=42) and H (n=64) received the now commercialised lyophilised formulation of IV polatuzumab plus IV bendamustine and IV rituximab. Bendamustine 90mg/m^2 was administered on Days 2 and 3 of Cycle 1, then Days 1 and 2 of subsequent Cycles 2 to 6. Rituximab 375mg/m^2 was administered on Day 1 of Cycles 1 to 6. Polatuzumab 1.8mg/kg was administered on Day 2 of Cycle 1, and then on Day 1 of subsequent cycles. The use of G-CSF was permitted for the treatment of neutropenia.
Randomisation	Patients in the phase II part of the study were randomised equally to receive bendamustine and rituximab alone or in combination with polatuzumab; though the extended phase allocation (arms G and H) was not randomised. Randomisation was stratified according to duration of response to prior therapy (≤12 months versus >12 months).
Primary outcome	IRC-assessed CR rate as measured at the primary response assessment at the end of treatment (6 to 8 weeks after Day 1 of cycle 6 or the last dose of study medication) by PET-CT scan.
Secondary outcomes	IRC-assessed ORR; IRC-assessed PFS; IRC-assessed DOR. Overall survival was an exploratory outcome.
Statistical analysis	There was no pre-specified statistical hypothesis in this Phase Ib/II clinical trial; no formal statistical testing was planned or carried out, and all analyses were exploratory only.

Abbreviations: BR = bendamustine and rituximab; CR = complete response; DLBCL = diffuse large B-cell lymphoma; DOR = duration of response; ECOG PS = Eastern Cooperative Oncology Group performance status; G-CSF = granulocyte colony stimulating factor; HSCT = haematopoietic stem cell transplant; IRC = independent review committee; IV = intravenous; ORR = objective response rate; PET-CT = positive emission tomography-computed tomography; PFS = progression-free survival.

At the primary analysis (data cut-off 30 April 2018), the independent review committee (IRC)-assessed complete response (CR) rate at the end of treatment was higher in the polatuzumab plus bendamustine plus rituximab group compared to the bendamustine plus rituximab group; the investigator-assessed CR rate followed a similar trend to the IRC assessment. IRC-assessed progression-free survival (PFS) and overall survival were secondary and exploratory outcomes respectively; these produced median absolute improvements of 5.8 months and 7.7 months respectively, which were considered clinically meaningful by a regulatory authority.[4, 8]

Since SMC acceptance on an interim basis in September 2020, results from an updated analysis (data cut-off 07 July 2020)[7] and the final analysis (data cut-off 21 October 2021)[9-11] have become available; these were similar to the findings from the primary analysis (data cut-off 30 April 2018). Additionally, the required data from the lyophilised polatuzumab plus bendamustine plus rituximab extension cohort (hereafter referred to as the extension cohort), as per the conditional marketing authorisation, showed similar results to the polatuzumab plus bendamustine plus rituximab group. However, compared with the median IRC-assessed PFS of 9.5 months for the polatuzumab plus bendamustine plus rituximab group (data cut-off 30 April 2018), there were slight reductions in median IRC-assessed PFS for the polatuzumab plus bendamustine plus rituximab group (9.2 months) and the extension cohort (7.0 months) at the later 21 October 2021 cut-off. See table 2.2 for detailed results.

Table 2.2. Outcome results for GO29365.

Data cut-off	**30 April 2018[4, 8]**		**21 October 2021[9-11]**		
	Phase II randomised cohorts		**Phase II randomised cohorts**		**Phase II extension cohort**
	Pola + BR (n=40)	**BR (n=40)**	**Pola + BR (n=40)**	**BR (n=40)**	**Lyophilised pola + BR (n=106)**
Primary outcome: IRC-assessed CR rate					
IRC-assessed CR rate, % (n)	40% (16)	18% (7)	43% (17)	18% (7)	40% (42)
Difference (95% CI)	22% (2.6% to 40%)		25% (4.9% to 43%)		-
Secondary outcome: IRC-assessed ORR					
ORR (CR/PR), % (n)	45% (18)	18% (7)	43% (17)	18% (7)	43% (46)
PR, % (n)	5% (2)	0	0	0	3.8% (4)
Secondary outcome: IRC-assessed PFS					
Median PFS follow-up (months)	NR	NR	NR	NR	NR
PFS events, n	25	32	31	32	81
Median PFS (months)	9.5	3.7	9.2	3.7	7.0
HR (95% CI)	0.36 (0.21 to 0.63)		0.39 (0.23 to 0.66)		-
KM estimated PFS at 24 months	NR	NR	28%	9.1%	22%

Secondary outcome: IRC-assessed DOR					
Median DOR (months)	NE	7.7	10.9	10.6	13.4
Exploratory outcome: overall survival					
Median overall survival follow-up (months)	22.3	22.3	59.9	59.4	29.2
Deaths, n	23	28	26	30	65
Median overall survival (months)	12.4	4.7	12.4	4.5	12.3
HR (95% CI)	0.42 (0.24 to 0.75)		0.41 (0.24 to 0.70)		-
KM estimated overall survival at 24 months	NR	NR	38%	16%	38%

BR = bendamustine plus rituximab; CI = confidence interval; CR = complete response; DOR = duration of response; NE = not estimable; HR = hazard ratio; IRC = independent review committee; KM = Kaplan-Meier; NR = not reported; ORR = objective response rate; PET-CT = positive emission tomography-computed tomography; PFS = progression-free survival; Pola = polatuzumab; PFS = progression-free survival; PR= partial response.

There was an imbalance in baseline prognostic factors including IPI 4-5, refractoriness to last prior therapy, ECOG performance status, and bulky disease that favoured the polatuzumab plus bendamustine plus rituximab group. To address this imbalance, three types of analyses were explored for the initial EMA marketing authorisation application via multivariate regression, backward selection and propensity score weighted regression models. Five key outcomes were assessed: IRC-assessed CR at end of treatment, IRC-assessed best objective response, IRC-assessed PFS, investigator-assessed PFS, and overall survival. The results confirmed the favourable trend in PFS and overall survival for the polatuzumab plus BR group.[8]

2.2. Health-related quality of life outcomes

Patient-reported outcomes for peripheral neuropathy symptom severity, and its interference on daily functioning, were evaluated using Therapy-Induced Neuropathy Assessment Scale (TINAS) v1.0 questionnaires. This instrument asks patients to rate the severity of their neuropathy-related symptoms in the previous 24 hours; 11 items are scored on a scale of 0 (symptom is absent) to 10 (the symptom is as severe as you can imagine). The proportion of patients completing at least one item of the TINAS at each weekly assessment was typically not greater than 50%. No significant change from baseline was identified from pooled polatuzumab plus bendamustine plus rituximab or polatuzumab plus obinutuzumab data from the phase Ib and II groups.[8]

2.3. Supportive studies

The POLARIX (GO39942) study is an international, multicentre, randomised, double-blind, phase III study that recruited adult patients with previously untreated DLBCL. Polatuzumab, in combination with R-CHP (rituximab, cyclophosphamide, doxorubicin, prednisone), resulted in a statistically significant improvement in investigator-assessed PFS compared with rituximab, cyclophosphamide, vincristine, doxorubicin and prednisone (R-CHOP).[1, 12] A regulatory authority determined that the efficacy and safety data provided from this study (with untreated patients) could be considered as confirmatory safety and efficacy data for treatment of patients with relapsed/refractory DLCBL.[1]

3. Summary of Safety Evidence

In 2019, the regulatory authority concluded that the safety profile of polatuzumab is not negligible but is still manageable in the context of a severe condition like relapsed or refractory DLBCL in those not eligible for HSCT.[8] Additionally, the safety data provided from the POLARIX study (with untreated patients) could be considered as confirmatory safety data for the treatment of patients with relapsed or refractory DLBCL.[1]

In the GO29365 study at the final analysis (data cut-off 21 October 2021), the median duration of treatment in the polatuzumab plus bendamustine plus rituximab group was 5 cycles; was 3 cycles in the bendamustine plus rituximab group; and was 5 cycles in the extension cohort. The safety evaluable population consisted of all patients who were administered at least one dose of study drug. Any treatment-emergent adverse event (AE) was reported by 100% (39/39) of patients in the polatuzumab plus bendamustine plus rituximab group; 97% (38/39) in the bendamustine plus rituximab group; and 99% (105/106) of patients in the extension cohort.[11]

In the polatuzumab plus bendamustine plus rituximab group, the bendamustine plus rituximab group, and the extension cohort respectively: patients reporting a grade 3 or 4 AE were 87%, 72%, and 78%; patients with a reported serious AE were 69%, 62%, and 54%; the proportion of AEs that led to dose interruptions were 54%, 36%, and 50%; and patients discontinuing therapy due to an AE was 33%, 13%, and 15%.[11]

At the final analysis (data cut-off 21 October 2021), in the polatuzumab plus bendamustine plus rituximab group, the bendamustine plus rituximab groups, and the extended cohort respectively; higher proportions of patients in the polatuzumab plus bendamustine plus rituximab group experienced: any grade of neutropenia (64%, 54%, and 54%), and grade 3 to 4 neutropenia (59%, 46%, and 46%); there were similar rates of febrile neutropenia (10%, 13%, and 9.4%) though one patient in the extended cohort had a fatal neutropenic AE due to neutropenic sepsis. The proportion of patients who received at least one G-CSF treatment were 64%, 62%, and 99%, respectively; it should be noted that G-CSF use was mandatory for the extended cohort.[11]

At the final analysis (data cut-off 21 October 2021), in the polatuzumab plus bendamustine plus rituximab group, the bendamustine plus rituximab groups, and the extended cohort respectively; higher proportions of patients in the polatuzumab plus bendamustine plus rituximab group experienced grade 3-4: infections (26%, 21%, and 21%); thrombocytopenia (41%, 26%, and 21%); and anaemia (54%, 28%, and 7.5%).[11]

In studies GO39442 (POLARIX) and GO29365, 1.4% (6/427) and 5.2% (12/233) of patients tested positive for antibodies against polatuzumab, respectively, of which none were positive for neutralising antibodies. The SPC has been updated accordingly; please see this for further information.[1]

4. Summary of Clinical Effectiveness Considerations

4.1. EMA conditional marketing authorisation specific obligations and previous interim acceptance criteria

At the time of interim acceptance by SMC (September 2020) polatuzumab had an EMA conditional marketing authorisation with the following obligations[8]; these have since all been fulfilled according to the regulatory authority[1]:

- To further confirm the safety and efficacy profiles, the primary CSR for study GO29365 including the primary analysis of Arm H (n=64) as well as a pooled analysis of Arm G (n=42) and Arm H (n=64) was provided. This provided evidence of the size and duration of effect in a larger population (approximately 100 further patients) and using the lyophilised formulation. As mentioned, the safety and efficacy from this pooled extension cohort was consistent with that of the polatuzumab plus bendamustine plus rituximab group (arm C).
- To further confirm the safety and efficacy of polatuzumab in DLBCL, results from the GO39942 (POLARIX) study were provided; this is a randomised, double-blind, placebo-controlled trial that evaluated polatuzumab in combination with R-CHP versus R-CHOP in patients with previously untreated DLBCL.
- Distinct histology subtypes were analysed within Arm H of the GO29365 study, as well as the GO39942 (POLARIX) study.

4.2. Key strengths

- Since SMC acceptance on an interim basis in September 2020 following the original submission (SMC2282), results from the final analysis (data cut-off 21 October 2021)[9-11] of the key study, GO29365, have become available.
- At the originally assessed data cut-off (30 April 2018), the study reported an improvement of 22% for IRC-assessed CR rate in favour of the polatuzumab group. This favourable trend in response rate is supported by the secondary outcomes of investigator-assessed CR rate and objective response, and are reflected in PFS and overall survival outcomes. The regulatory authority deemed the absolute improvements in IRC-assessed PFS and overall survival to be clinically meaningful.[4, 8]
- The final analysis (data cut-off 21 October 2021) has shown slight improvement in some of the above outcomes, which provides reassurance that the original results are robust. However, there was a slight reduction in median PFS for the polatuzumab plus bendamustine plus rituximab group.[9-11]
- As per one of the requirements of the EMA conditional marketing authorisation, the final analysis (data cut-off 21 October 2021) includes data from an extension cohort of patients (n=106) who received the commercially available lyophilised version of polatuzumab. In general, this cohort has shown similar rates of efficacy and safety outcomes to those in the polatuzumab plus bendamustine plus rituximab group, who received the liquid formulation of polatuzumab. However, there was a slight reduction in median PFS for the extension cohort when compared to the polatuzumab plus bendamustine plus rituximab group at the original data cut off (30 April 2018).[9-11]

4.3. Key uncertainties

- GO29365 was an open-label, exploratory phase Ib/II trial in a heterogeneous population in terms of prognosis; the DLBCL component was nested in an umbrella trial where the activity of polatuzumab in both DLBCL and follicular lymphoma (FL) was studied.[8] Additional data have been provided from an extension cohort as previously specified, but allocation was not randomised in this cohort, and was also open-label.
- As the study was exploratory, the regulatory authority noted that there was no overarching type-1 error control (controlling for the risk of falsely inferring the existence of a difference between the two groups that does not exist; a false positive).[8]
- Baseline characteristics were imbalanced suggesting patients in the polatuzumab plus bendamustine plus rituximab group may have had a less severe condition.[8]
- All-grade and grade ≥3 neutropenia, infections, thrombocytopenia, and anaemia were more frequently reported in the polatuzumab plus bendamustine plus rituximab group compared with the bendamustine plus rituximab group.[9-11]
- There is a lack clinical evidence against relevant comparators. The submitting company considered bendamustine plus rituximab, and R-GemOx (rituximab, gemcitabine, oxaliplatin) to be relevant comparators. However, guidelines and clinical experts consulted by SMC suggested there is no defined standard of care for this patient population and no experts regarded bendamustine plus rituximab to be a widely used regimen in Scottish clinical practice. Some experts did mention R-GemOx as a potential option for this indication.
- Due to programming issues and low patient completion rates, patient-reported outcome data are limited and there are no data to assess the impact on quality of life.[8]

4.4. Clinical expert input

Clinical experts contacted by SMC considered polatuzumab to be a therapeutic advancement, as there is a lack randomised controlled trials in this patient population and no defined standard of care. It was noted that since interim acceptance, polatuzumab has been used for this patient group.

4.5. Service implications

Clinical experts contacted by SMC considered that the introduction of polatuzumab has had a limited impact on the patient and/or service delivery.

5. Patient and clinician engagement (PACE)

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 **end of life and orphan equivalent** 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. The symptom burden associated with DLBCL and first-line chemotherapy is high, and can profoundly affect the

physical, emotional, and psychological wellbeing of patients. Although the aim of first-line treatment is cure, up to 50% of patients will relapse or are refractory to first-line treatment, and many of these patients are unlikely to be eligible for a haematopoietic stem cell transplant (HSCT). Prognosis in these patients is very poor.

- There is a significant unmet need for patients with relapsed or refractory DLBCL who are ineligible for HSCT. Alternative treatments (prior to the availability of polatuzumab) have limited efficacy and are often associated with significant toxicity, which affects tolerability.

- There are likely to be significant health-related benefits for patients who respond to treatment with polatuzumab in combination with bendamustine and rituximab. Longer progression-free survival and overall survival is expected to improve quality of life and allow patients to spend more time with friends and family while they are well. PACE participants highlighted that since interim acceptance by SMC, polatuzumab is being used in this patient setting and they described the positive impact the medicine has already had on the physical and mental wellbeing of patients.

- PACE participants noted that in practice polatuzumab appears to be well tolerated, with an acceptable safety profile. Patients who respond have a longer time period off treatment and potentially a reduced risk of toxicity. This would also reduce the burden of care for families and carers.

- Polatuzumab plus bendamustine and rituximab is administered in a day unit setting. The frequency of hospital visits is likely to be acceptable to patients and their carers given the potential benefits. This treatment is currently used within NHSScotland following previous SMC interim acceptance and therefore services are already in place and no significant service implications are expected.

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 submitted 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 (defined as 45 years based on a starting age of 69 years) with a one-week cycle length.
Population	The population in the analysis reflected the full licensed population: of adult patients with R/R DLBCL who are not candidates for HSCT.
Comparators	Pola+BR is compared with (i) bendamustine and rituximab (BR) and (ii) rituximab in combination with gemcitabine and oxaliplatin (R-GemOx). The company states that there is no universally accepted standard of care regimen R/R DLBCL patients ineligible for HSCT, with patients typically prescribed one regimen from a range of available gemcitabine and/or platinum-based therapies, or BR. According to clinical experts the company has consulted, none of the regimens used has superior efficacy to any other regimen and outcomes for BR can be considered representative of other treatment options.
Model description	A standard three-state partitioned survival model with 3 main health states: progression-free (subdivided by whether patients were on or off treatment), progressed disease and death.
Clinical data	The primary source of clinical data used in the economic evaluation is the GO29365 trial (October 2021 data-cut).[4, 7, 8] This was used to inform PFS, OS, time-to-off-treatment (TTOT), and treatment-related adverse events (TRAEs) for Pola+BR, and BR. R-GemOx was assumed to have equivalent efficacy (PFS and OS) to BR, while TTOT for this comparator was based on assumptions used in SMC2200 and TRAE on data from a Phase 2 study for GemOx in a population of R/R DLBCL patients.
Extrapolation	A cure-mixture approach with a lognormal distribution to extrapolate PFS and OS was used. This estimated a higher cure-fraction for Pola+BR than for BR/R-GemOx with statistical cure patients assumed to have excess mortality rate of 1.41.
Quality of life	EQ-5D-5L data collected in the ZUMA-1 study of axicabtagene ciloleucel in patients with refractory DLBCL who are ineligible for SCT, 'cross-walked' to EQ-5D-3L utility values based on a valuation set for the general population in England.[13] It was assumed that patients in remission after 2 years, experience health-related quality-of-life equal to the general population for their age and sex. Disutilities associated with TRAE were sourced from previous NICE TAs in R/R DLBCL and R/R systemic anaplastic large cell lymphoma.
Costs and resource use	Medicine related costs included acquisition and administration costs for the intervention, comparators, and post-progression treatments. Other healthcare resource use accounted for included that incurred within primary care (general practitioner appointments and visits from a district nurse), secondary care (outpatient appointments with consultant physicians, inpatient care and medical scans/tests), and personal/social services (residential care, home care and hospice care).
PAS	A 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

Base case results at list price for all medicines are presented in Table 6.2. SMC would wish to present the with-PAS cost-effectiveness estimates that informed the SMC decision. However, owing to the commercial in confidence concerns regarding the PAS, SMC is unable to publish these results. As such, only the list price results can be presented.

The base case incremental cost-effectiveness ratio (ICER) at list prices for all medicines is £45,308 per QALY versus BR, and £47,653 per QALY versus R-GemOx. These results represent a reduction in the cost-effectiveness of Pola+BR relative to its initial submission during 2020. The increase in the ICER versus each of these comparators is driven by a reduction in the estimated cure-fraction for Pola+BR, leading to an increase in the proportion of patients experiencing disease progression and incurring the cost of post-progression treatment options. This increase in incremental costs associated with Pola+BR is only partially offset by an increase in estimated life expectancy for non-cure patients.

Table 6.2: Base case economic results at list prices

Treatment	Total Cost (£)	Incremental Cost vs comparators (£)	ICER (£/QALY)
Pola+BR	107,507	-	-
BR	32,050	75,457	45,308
R-GemOx	28,241	79,266	47,653

Abbreviations: Pola+BR = polatuzumab + bendamustine + rituximab; BR = bendamustine + rituximab; R-GemOx = rituximab + gemcitabine + oxaliplatin; NA = not applicable

6.3. Sensitivity analyses

A number of sensitivity analyses were provided and the key scenarios summarised in Table 6.3. These suggest that economic results versus BR and R-GemOx are relatively stable, with only a reduction in time horizon having a significant upwards impact; however, these scenarios do not adequately test the cure-mixture modelling approach utilised by the company. Further scenario analyses designed to investigate the impact of alterations in the cure fraction have been requested but are still to be received.

Table 6.3: Key scenario analyses (list prices)

		ICER vs BR (£/QALY)	ICER vs R-GemOx (£/QALY)
Base case (reference)		45,308	47,653
Time horizon			
1	Time horizon 10	57,427	59,248
2	Time horizon 20	47,248	49,549
3	Time horizon 30	45,625	48,019
Health related quality of life			
4	Utilities from TA 567	43,099	45,322
5	Utilities from TA 306	44,006	46,280

6	Long-term survivor utility aligned to general population after 5 years	45,606	47,967
Alternative curve choices for the mixture-cure model			
7	Cure-mixture model (OS, PFS), Generalised gamma	45,749	48,872
Alternative modelling methodology (using a standard parametric extrapolation)			
8	Independent parametric distribution function (OS, PFS), log-normal	49,275	57,359
Alternate OS assumption			
9	OS informed by PFS (cure-mixture extrapolation), generalised gamma (PFS and OS)	47,010	44,614
Comparator choices			
10	Versus CAR-T axicabtagene ciloleucel	Less costly and less effective	Less costly and less effective
11	Versus CAR-T tisagenlecleucel	Dominant	Dominant
Alternative cure fraction rates			
12	Cure fraction of 7.5% for all treatments	49,569	44,676
13	Cure fraction of 10% for Pola+BR, 7.5% for comparators	48,534	43,543

Abbreviations: BR = bendamustine + rituximab; BSA = body surface area; ICER = incremental cost-effectiveness ratio; OS = overall survival; PD = progressed disease; PFS = progression-free survival; Pola+BR = polatuzumab + bendamustine + rituximab; QALY = quality-adjusted life year; R-GemOx = gemcitabine + oxaliplatin + rituximab; NR = not reported

6.4. Key strengths

- Direct comparative data from a Phase Ib/II, multicentre, open-label study that compared Pola+BR with BR in adult patients with relapsed or refractory DLBCL that can be used to inform the relative effectiveness and safety of Pola+BR versus at least one potential comparator.
- The systematic literature review of health-related quality-of-life (HRQoL) data conducted by the company facilitates a comparison of their selected health state utility values versus other values that have been estimated in the literature.
- A wide range of disutility (or decrements to health state utilities) were identified and included by the company in their analysis.

6.5. Key uncertainties

- While clinical evidence consists of a comparative study of Pola+BR versus BR, there is limited clinical evidence comparing Pola+BR to the range of other comparators in this population. The submitting company has therefore relied on the opinion of clinical experts they have consulted who state that none of the regimens used have superior efficacy to any other regimen, therefore outcomes for BR can be considered representative of other options. If BR is not representative of these comparators, this could lead to a decrease or increase in the cost-effectiveness of Pola+BR.

- The small sample size (n=80) of the GO29365 study confers uncertainty in PFS and OS data observed that is used in the economic evaluation. In addition, as the number of patients at risk of disease progression or death over-time is relatively small, this also increases uncertainty associated with the GO29365 study.
- Length of follow-up (max: 64 months) is significantly shorter than time period over which the economic evaluation is conducted (45 years). PFS and OS data therefore require extrapolation far beyond the follow-up period used in the trial. The extent of extrapolation required, due to the magnitude of difference in these time periods, introduces significant uncertainty in PFS and OS extrapolations used in the economic evaluation. Sensitivity analysis provided by the company using alternative modelling approaches (scenarios 7-9) and also reducing the time horizon (scenarios 1-3) provided reassurance that the approach used to extrapolate the data was reasonable.
- The company's clinical experts estimated that 5% to 10% of patients who are progression- free at 2-years post treatment will remain in remission and experience life expectancy akin to the general population, which was used to validate their selected PFS and OS extrapolations. However, the log-normal function used by the company for their base case analysis underestimated the cure fraction for BR. To address this issue, additional sensitivity analysis was provided which showed the results remained robust to alternative cure fractions (scenarios 12 and 13).
- No HRQoL data suitable for informing health state utility values was collected during the GO29365 trial. Health state utility values for the PFS and PD health states were therefore sourced from the ZUMA-1 trial in patients with refractory DLBCL who are ineligible for SCT transplant, although this appears to be a slightly different patient population to the licensed indication under review for Pola+BR. Alternative utility values were tested in sensitivity analysis and produced similar results to the base case analysis.

7. Conclusion

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

After considering all the available evidence and the output from the PACE process, and after application of the appropriate SMC modifiers, 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; therefore no specific recommendations were made for this medicine. The guidance makes recommendations in relapsed / refractory disease, only in patients who are eligible for transplant.[5]

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. In patients unsuitable for transplant who have experienced a first relapse or progression platinum- and / or gemcitabine-based regimens or enrolment in clinical trials with novel drugs should be considered. In patients who have experienced two or more relapses, the guideline recommends enrolment in clinical trials with novel drugs, allogeneic transplant or palliative care.[6]

The National Comprehensive Cancer Network (NCCN) published clinical practice guidelines in oncology: B-cell lymphomas in July 2020. The NCCN guidance recommends a number of second 11 line treatments for patients with DLBCL who are not suitable for HSCT including; gemcitabine-based regimens with rituximab or polatuzumab vedotin with/without bendamustine and with/without rituximab (after ≥2 prior therapies). The guidance also recommends axicabtagene ciloleucel and tisagenlecleucel as treatments for patients with in refractory or relapsed DLBCL who have received two or more prior lines of systemic therapy.[14]

9. Additional Information

9.1. Product availability date

16 January 2020

9.2. Summary of product characteristics

See the SPCs for further information including dosing and safety. Available from: polatuzumab vedotin 140mg powder for concentrate for solution for infusion (Polivy®) and polatuzumab vedotin 30mg 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 (if <78kg)**

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

The submitting company estimated the population eligible for treatment to be 28 patients eligible for treatment with polatuzumab in year 1 rising to 29 patients from year 3 onwards, to which confidential uptake rates were applied.

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.