

**NATIONAL INSTITUTE FOR HEALTH AND CARE
EXCELLENCE**

Final appraisal document

**Polatuzumab vedotin with rituximab and
bendamustine for treating relapsed or
refractory diffuse large B-cell lymphoma**

1 Recommendations

- 1.1 Polatuzumab vedotin with rituximab and bendamustine is recommended, within its marketing authorisation, as an option for treating relapsed or refractory diffuse large B-cell lymphoma in adults who cannot have a haematopoietic stem cell transplant. It is recommended only if the company provides polatuzumab vedotin according to the commercial arrangement (see section 2).

Why the committee made these recommendations

There is no standard treatment for relapsed or refractory diffuse large B-cell lymphoma in people who cannot have a haematopoietic stem cell transplant. They could be offered rituximab with bendamustine, although this is not standard care in the NHS. Clinical evidence shows that people having polatuzumab vedotin plus rituximab and bendamustine have more time before their disease gets worse than people having rituximab and bendamustine alone. It also suggests that they live longer.

Polatuzumab vedotin plus rituximab and bendamustine is considered to be a life-extending treatment at the end of life. The cost-effectiveness estimates are within the range that NICE considers an acceptable use of NHS resources. Therefore, polatuzumab vedotin plus rituximab and bendamustine is recommended.

2 Information about polatuzumab vedotin

Marketing authorisation indication

- 2.1 Polatuzumab vedotin (Polivy, Roche) in combination with bendamustine and rituximab is indicated 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’.

Dosage in the marketing authorisation

- 2.2 The dosage schedule is available in the [summary of product characteristics](#).

Price

- 2.3 The cost per item from the company’s submission is £11,060 per 140-mg vial (excluding VAT; British national formulary online accessed July 2020). The company estimates that the average cost of a course of treatment is £50,416.
- 2.4 The company has a commercial arrangement (simple discount patient access scheme). This makes polatuzumab vedotin available to the NHS with a discount. The size of the discount is commercial in confidence. It is the company’s responsibility to let relevant NHS organisations know details of the discount.

3 Committee discussion

The appraisal committee (section 6) considered evidence submitted by Roche, a review of this submission by the evidence review group (ERG), the technical report developed through engagement with stakeholders, the responses to the appraisal consultation document and the ERG’s review of the company’s consultation response. See the [committee papers](#) for full details of the evidence.

The appraisal committee was aware that several issues were resolved during the technical engagement stage, and agreed that:

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- There are no known safety or efficacy issues with using the lyophilised formulation of polatuzumab vedotin instead of the liquid formulation. The committee noted that the company is to supply polatuzumab vedotin in its lyophilised formulation whereas data from the clinical trial were generated with a liquid formulation. The committee considers that this is a regulatory issue.
- Polatuzumab vedotin meets the criteria to be considered a life-extending treatment at the end of life because the prognosis of untreated patients is poor (median 10 months estimated by the company) and extension of life is greater than 3 months.

It recognised that there were remaining areas of uncertainty associated with the analyses presented and took these into account in its decision making. It discussed the following issues, which were outstanding after the technical engagement stage.

Clinical need and treatment pathway

There is a high unmet need for effective treatments

- 3.1 Diffuse large B-cell lymphoma is an aggressive disease. Symptoms usually develop rapidly and progress quickly. The disease is treated with the aim of cure, but it is refractory to treatment or relapses after initial treatment in up to 50% of patients. The patient expert explained that the prognosis for patients with relapsed or refractory disease is extremely poor with median survival of less than 1 year. Patients can be extremely unwell for many months and often spend many weeks in hospital. The clinical and patient experts explained that relapsed or refractory disease is treated using salvage chemotherapy followed by a haematopoietic stem cell transplant if the person is fit enough for intensive therapy. People who are not fit enough to have a transplant, or whose disease relapses after a transplant, are offered low-intensity chemotherapy regimens. The clinical and patient experts explained that there is a high unmet clinical need in this group of patients for an alternative to palliative care, or regimens with poor outcomes or unacceptable toxicities. The patient expert also

highlighted the psychological effects of relapsed or refractory disease for both the patient and their carers, with patients experiencing insomnia, anxiety and a constant fear of relapse and death. The committee concluded that relapsed or refractory diffuse large B-cell lymphoma is a devastating condition with a poor prognosis and that patients have a high unmet need for effective treatments with manageable side effects.

There is no standard of care for treating the disease in people who cannot have a haematopoietic stem cell transplant

3.2 Polatuzumab vedotin has a conditional marketing authorisation in combination with bendamustine and rituximab for treating relapsed or refractory diffuse large B-cell lymphoma in adults who cannot have a haematopoietic stem cell transplant. The clinical experts explained that this encompasses 3 main groups of people who:

- are older and/or have co-morbidities and would not be fit enough to have a stem cell transplant
- have had a stem cell transplant but whose disease then relapsed again
- are fit enough for a stem cell transplant but their disease is not sufficiently in remission to proceed with this.

The clinical experts explained that there is no standard of care for patients with relapsed or refractory disease who are not able to have a transplant. A number of low-intensity chemotherapy regimens (with or without rituximab, depending on the amount the patient has already had) are currently used, but there is no evidence to show that one regimen is better than another. The committee concluded that there is no standard of care for relapsed or refractory disease in people who cannot have a haematopoietic stem cell transplant.

Rituximab with bendamustine is a reasonable proxy for standard of care

3.3 The comparators for polatuzumab vedotin in the NICE scope were rituximab with 1 or more chemotherapy agents, including rituximab with bendamustine (the comparator in the clinical trial). Direct evidence for

polatuzumab vedotin compared with the other rituximab and chemotherapy combinations listed in the scope is not available, and the company and the ERG agreed that a network could not be constructed to inform an indirect comparison. The committee therefore considered whether rituximab with bendamustine could be considered a reasonable proxy for standard of care in the NHS. The clinical experts explained that rituximab with bendamustine is not commonly used to treat diffuse large B-cell lymphoma in the UK, and it is not routinely funded. However, it is standard of care in other indications such as chronic lymphocytic leukaemia. The clinical experts explained that there is a lack of information on the relative effectiveness of different treatments used in relapsed or refractory diffuse large B-cell lymphoma. However, rituximab with bendamustine would not be expected to have inferior efficacy or tolerability to other treatments and therefore it would be reasonable to use it as a proxy for standard care. The committee concluded that rituximab with bendamustine is a reasonable proxy for standard of care in the NHS in relapsed or refractory diffuse large B-cell lymphoma when a haematopoietic stem cell transplant is not an option.

Clinical evidence

The GO29365 trial is generalisable to UK clinical practice

3.4 The clinical evidence came from trial GO29365. This was a multicentre, randomised, open-label trial of polatuzumab vedotin with rituximab and bendamustine, compared with rituximab with bendamustine alone, in patients with relapsed or refractory disease. Because the trial was open label, patients and their healthcare professionals were aware of treatment allocation. The trial was small (40 patients were randomised to each arm) and 3 patients were from the UK. The clinical experts explained that the trial population was broadly reflective of the population seen in UK clinical practice in terms of age and previous treatments including haematopoietic stem cell transplants. The committee noted the ERG's comment that non-white people were underrepresented in the trial. However, the clinical

experts explained that ethnicity is not a factor when considering efficacy or toxicity. The committee also noted the ERG's comment that most patients had an Eastern Cooperative Oncology Group (ECOG) status of 0 or 1. The clinical experts explained that 14 of the 80 people in the trial had an ECOG status of 2, which is consistent with how polatuzumab vedotin would be used in clinical practice. The committee concluded that trial GO29365 is generalisable to the UK.

The company's adjustments for imbalances between the treatment arms are appropriate

3.5 The ERG highlighted that there were imbalances between treatment arms in some prognostic factors such as bulky disease and International Prognostic Index (IPI) score. More people had bulky disease in the comparator arm than in the polatuzumab vedotin arm (37.5% compared with 25%), which could favour polatuzumab vedotin. Conversely, more people in the polatuzumab arm had a lower (more favourable) IPI score (22.5% compared with 7.5% had a score of 0 to 1), which could also favour polatuzumab vedotin. The committee heard from the clinical experts that it was difficult to determine the importance of these imbalances given the small patient numbers involved. The company acknowledged the imbalance of these prognostic factors in its response to technical engagement and conducted multivariable regression and propensity score weighted regression models to adjust the progression-free survival and overall survival for the imbalances. The ERG considered that the company's methods of adjustment were appropriate, with a range of methods tested in sensitivity analyses. The committee concluded that the company's adjustments for the imbalances between the treatment arms were appropriate.

Polatuzumab vedotin is a promising new treatment

3.6 The primary outcome of trial G029365 was complete disease response as judged on PET-CT. Polatuzumab vedotin with bendamustine and rituximab led to a statistically significant 22.5 percentage point greater

complete response rate than rituximab and bendamustine alone (95% confidence interval 2.62 to 40.22, $p=0.0261$). There were also statistically significant benefits in the secondary outcomes of progression-free survival and overall survival. When the company adjusted the results for imbalances in prognostic factors between the 2 arms (see section 3.5) the progression-free survival and overall-survival benefits remained but were less than in the trial. The committee noted that these adjusted estimates were used in the company's updated model that was submitted in response to technical engagement. The committee noted that the progression-free survival data from trial G029365 are mature but heard from the company that further overall-survival data are expected within the next 2 years. The committee concluded that polatuzumab vedotin is a promising new treatment and that the evidence from the trial to date suggests that it extends both progression-free survival and overall survival.

There is a lack of robust long-term evidence on remission and cure

3.7 The company assumed that a proportion of patients having polatuzumab vedotin who are progression free at 2 years are 'cured' from the disease, because it considered that a high complete response rate is associated with improved outcomes in diffuse large B-cell lymphoma. The committee considered whether this assumption is clinically plausible. It noted the company's comments that at 30-month follow up, 23% of patients in the polatuzumab vedotin arm were in disease remission (8 complete, 1 partial) compared with 5% in the rituximab with bendamustine arm. The committee heard from the clinical experts that it is too early to say whether polatuzumab vedotin will be a curative treatment. However, at least for the first-line treatment of diffuse large B-cell lymphoma, long-term survival may be improved when there has been an ongoing complete response lasting more than 24 months, and this is independent of the treatment used. The clinical experts explained that the evidence so far is suggestive of improved long-term survival in a small cohort of patients with relapsed or refractory disease. They also explained that patients who have had

several lines of therapy might have improved long-term survival or be 'cured' but would be unlikely to have exactly the same risk of mortality as the general population. This is because some patients would relapse and the treatments themselves can affect long-term survival. The clinical experts estimated that 2-year survival with existing treatments such as rituximab and bendamustine would be around 5 to 10%, although there is no robust data to inform this estimate. In response to the appraisal consultation document the company provided data from a later data cut on progression-free survival and overall survival, which included 1 further event in the polatuzumab vedotin arm. The committee agreed that further follow up would establish the amount of long-term benefit of both treatments. It concluded that there is a lack of robust evidence on long-term remission and cure with polatuzumab vedotin in patients with relapsed or refractory disease. However, the data from the trial so far suggest that a small proportion of people may have a durable response that could indicate cure.

The company's economic model

The assumptions about cure in the company's cure-mixture model are highly uncertain

3.8 The company presented a 3-state partitioned survival model to estimate the cost effectiveness of polatuzumab vedotin plus rituximab and bendamustine compared with rituximab and bendamustine alone. The company and the ERG used different methods to extrapolate progression-free survival and overall survival and this was the key driver of the cost-effectiveness results. The company used a cure-mixture model, which assumed that the population consisted of 2 groups: a 'cured' population and a population whose disease would progress. About two-thirds of those who were progression-free at 2 years were considered 'cured'. These 'cured' patients had an increased relative risk of mortality (standardised mortality ratio of 1.41) compared to the general population from the start of the model. They were assumed to use no healthcare

resources after 3 years and were assigned general population utilities adjusted for age and gender. The company's initial base case used a generalised gamma cure-mixture model. In response to the appraisal consultation document, the company updated its base case model to a log-normal cure-mixture model. The committee considered whether the company's approach in using a cure-mixture model was appropriate. It noted that the ERG had several concerns about the approach, including the lack of a plateau in the Kaplan–Meier curve for progression-free survival. A plateau would be expected for a treatment that is curative. The ERG also considered that smoothed hazard plots for overall survival and progression-free survival do not suggest a 'cure', and that the company's model overestimates progression-free survival in the intervention arm and underestimates it in the comparator arm towards the end of follow up. The ERG also highlighted NICE's appraisals of [axicabtagene ciloleuce](#) and [tisagenlecleuce](#). These used cure-mixture models, in which the Kaplan–Meier curves for progression-free survival and overall survival plateaued towards the end of follow up. The committee agreed with the ERG's concerns about the company's modelling approach. It considered that the cure rate assumed by the company was not sufficiently justified because it was based on 2-year progression-free survival in a small trial that only had 40 people in each arm. Also, progression-free survival may not be appropriate for estimating long-term remission. In response to the appraisal consultation document the company presented sensitivity analyses with varied cure rates. The committee considered that it was unclear which of the assumed cure rates was most plausible or how these rates were derived. The clinical experts explained that the assumed rates for the polatuzumab vedotin arm were at the top end of the range of estimates of long-term survival. The committee concluded that there was insufficient evidence to justify assuming a cured proportion from the outset of the model and that the estimate of a cure rate was highly uncertain.

The probabilistic results from the company's cure-mixture model are implausible and the model is not suitable for decision making

3.9 The probabilistic analysis for the company's cure-mixture model estimated that the number of life years gained in the comparator arm with bendamustine and rituximab is more than 2 years. The committee noted that the model included discount rates and, therefore, the true value would be higher. The committee agreed that this seemed unrealistic and inconsistent with clinical opinion and would cast doubt on whether polatuzumab vedotin meets the end of life criteria. The committee agreed that the company's probabilistic analysis for its cure-mixture model lacked face validity. Because of this and the uncertainty around the cure rates (see section 3.8), the committee concluded that the company's cure-mixture model was not suitable for decision making.

Standard parametric survival modelling is preferred

3.10 Because of concerns about the lack of robust long-term evidence to support the cure assumption, the ERG used standard independent parametric survival modelling to extrapolate progression-free survival and overall survival. The committee considered that the ERG's analyses were a more standard approach, noting that they also captured long-term survival. However, it was concerned that the proportion of people predicted to be alive at 5 or 10 years was substantially higher than the proportion predicted to be progression free at the same time points, indicating that some patients had long-term survival with progressed disease. The committee considered that this was not consistent with the comments from clinical experts that survival is associated with an ongoing complete response. In response to the appraisal consultation document, the company presented a scenario analysis using a standard independent parametric survival model with a generalised gamma distribution. The ERG also presented 2 additional scenario analyses that assumed a generalised gamma distribution for progression-free survival and either a log-logistic or log-normal distribution for overall survival. The ERG explained that the difference between the analyses was the method of

extrapolating overall survival and that all other parameters were the same. The committee appreciated that the new analyses resulted in a smaller difference in the number of people predicted to be alive at 5 or 10 years and progression-free at the same time points, compared with the ERG's base case. It concluded that the revised standard parametric modelling was appropriate.

The company's assumption of a maximum of 6 cycles of treatment is appropriate

3.11 The company's model assumes a maximum of 6 cycles of treatment in line with the licence for polatuzumab vedotin and the protocol for trial GO29365. The committee heard from the clinical experts that a maximum of 6 cycles of treatment would be given in clinical practice. However, the ERG had concerns about whether this was appropriate because 5% of patients appeared to have more than 6 cycles in trial GO29365, based on the company's Kaplan–Meier curve for time to off-treatment. The company explained that no patients had more than 6 cycles in the trial, but the time to off-treatment curve is not zero after 4.15 months (the time point corresponding to 6 cycles) because some patients had delayed doses of treatment. The ERG considered that it was not clear how the time to off-treatment curve was constructed and how the delayed doses were included in the company's calculations. Therefore, the ERG's revised base case included drug costs for patients who had delayed doses of polatuzumab vedotin. The committee noted that this change had a small effect on the cost-effectiveness results, increasing the incremental cost-effectiveness ratio (ICER) by less than £2,000 per quality-adjusted life year (QALY) gained. The committee concluded that this was not a key driver of the results and that the company's approach was appropriate because it reflected clinical practice and the marketing authorisation for polatuzumab vedotin.

The company's modelling of background mortality is appropriate

3.12 The company initially used an individual patient-level approach based on the age distribution in the trial for modelling background mortality. However, the ERG used a single age cohort-based modelling approach in its revised base case. This was consistent with the methods used for modelling progression-free survival and overall survival, which the committee agreed were appropriate. In response to the appraisal consultation document, the company updated its base-case model using the committee's preferred assumption of a single-age cohort of 69 years. The committee concluded that the company's single-age cohort approach was appropriate for modelling background mortality in its updated base case.

Health-related quality of life

The utility values are uncertain, but not a driver of the model results

3.13 Health-related quality of life was not directly measured in trial GO29365. The company's base-case utility values were estimated from the ZUMA-1 trial based on a small sample of patients with mixed histology lymphoma, using the EQ-5D-5L. The ERG identified some alternative utility sources but did not consider these to be any better than those used by the company. In response to technical engagement the company highlighted that the values chosen for their base case produced the most conservative ICER estimates. The ERG considered that the small variation in the ICERs shows that the utility values are not major drivers of the model results. The committee concluded that even though the company had used the best available data there was considerable uncertainty about the utility values, but these are not a key driver of the cost-effectiveness results for this appraisal. However it was disappointed that no health-related quality of life data were available from trial GO29365, and it did not endorse the approach of basing utility values for large B-cell lymphoma on data from the ZUMA-1 trial.

Cost-effectiveness estimate

Polatuzumab vedotin with rituximab and bendamustine is cost effective compared with rituximab and bendamustine alone

3.14 Following consultation, the company submitted cost-effectiveness analyses incorporating an updated commercial arrangement. The committee considered that the most plausible ICER would be derived from a standard parametric survival model (see section 3.10). It noted that the probabilistic and deterministic ICERs from the company's standard parametric model and the ERG's standard parametric analyses (£35,663 to £48,839 per QALY gained) were within the range normally considered a cost-effective use of NHS resources for life-extending treatments at the end of life. Therefore, the committee concluded that polatuzumab vedotin could be recommended for routine use in the NHS.

Conclusion

Polatuzumab vedotin with rituximab and bendamustine is recommended for relapsed or refractory diffuse large B-cell lymphoma

3.15 There is a high unmet need for effective treatments in relapsed and refractory diffuse large B-cell lymphoma. Clinical trial evidence shows that polatuzumab vedotin with rituximab and bendamustine increases progression-free survival and overall survival compared with rituximab and bendamustine alone. The committee agreed that all plausible cost-effectiveness estimates were within the range considered to be cost-effective for life-extending treatments at the end of life. Therefore, polatuzumab vedotin with rituximab and bendamustine is recommended for relapsed or refractory diffuse large B-cell lymphoma in adults who cannot have a haematopoietic stem cell transplant.

4 Implementation

4.1 [Section 7\(6\) of the National Institute for Health and Care Excellence \(Constitution and Functions\) and the Health and Social Care Information](#)

[Centre \(Functions\) Regulations 2013](#) requires clinical commissioning groups, NHS England and, with respect to their public health functions, local authorities to comply with the recommendations in this appraisal within 3 months of its date of publication.

- 4.2 [Chapter 2 of Appraisal and funding of cancer drugs from July 2016 \(including the new Cancer Drugs Fund\) – A new deal for patients, taxpayers and industry](#) states that for those drugs with a draft recommendation for routine commissioning, interim funding will be available (from the overall Cancer Drugs Fund budget) from the point of marketing authorisation, or from release of positive draft guidance, whichever is later. Interim funding will end 90 days after positive final guidance is published (or 30 days in the case of drugs with an Early Access to Medicines Scheme designation or fast track appraisal), at which point funding will switch to routine commissioning budgets. The [NHS England and NHS Improvement Cancer Drugs Fund list](#) provides up-to-date information on all cancer treatments recommended by NICE since 2016. This includes whether they have received a marketing authorisation and been launched in the UK.
- 4.3 The Welsh ministers have issued directions to the NHS in Wales on implementing NICE technology appraisal guidance. When a NICE technology appraisal recommends the use of a drug or treatment, or other technology, the NHS in Wales must usually provide funding and resources for it within 2 months of the first publication of the final appraisal document.
- 4.4 When NICE recommends a treatment ‘as an option’, the NHS must make sure it is available within the period set out in the paragraphs above. This means that, if a patient has relapsed or refractory diffuse large B-cell lymphoma and cannot have a haematopoietic stem cell transplant and the doctor responsible for their care thinks that polatuzumab vedotin with

rituximab and bendamustine is the right treatment, it should be available for use, in line with NICE's recommendations.

5 Review of guidance

- 5.1 The guidance on this technology will be considered for review by the guidance executive 3 years after publication. The guidance executive will decide whether the technology should be reviewed based on information gathered by NICE, and in consultation with consultees and commentators.

Jane Adam

Chair, appraisal committee

August 2020

6 Appraisal committee members and NICE project team

Appraisal committee members

The 4 technology appraisal committees are standing advisory committees of NICE. This topic was considered by [committee A](#).

Committee members are asked to declare any interests in the technology to be appraised. If it is considered there is a conflict of interest, the member is excluded from participating further in that appraisal.

The [minutes of each appraisal committee meeting](#), which include the names of the members who attended and their declarations of interests, are posted on the NICE website.

NICE project team

Each technology appraisal is assigned to a team consisting of 1 or more health technology analysts (who act as technical leads for the appraisal), a technical adviser and a project manager.

Roshni Maisuria

Technical lead

Albany Meikle

Technical lead

Zoe Charles

Technical adviser

Thomas Feist

Project manager

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