

# NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

## Appraisal consultation document

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

The Department of Health and Social Care has asked the National Institute for Health and Care Excellence (NICE) to produce guidance on using polatuzumab vedotin with rituximab and bendamustine in the NHS in England. The appraisal committee has considered the evidence submitted by the company and the views of non-company consultees and commentators, clinical experts and patient experts.

**This document has been prepared for consultation with the consultees.**

It summarises the evidence and views that have been considered and sets out the recommendations made by the committee. NICE invites comments from the consultees and commentators for this appraisal and the public. This document should be read along with the evidence (see the [committee papers](#)).

The appraisal committee is interested in receiving comments on the following:

- Has all of the relevant evidence been taken into account?
- Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?
- Are the recommendations sound and a suitable basis for guidance to the NHS?
- Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?

**Note that this document is not NICE's final guidance on this technology. The recommendations in section 1 may change after consultation.**

After consultation:

- The appraisal committee will meet again to consider the evidence, this appraisal consultation document and comments from the consultees.
- At that meeting, the committee will also consider comments made by people who are not consultees.
- After considering these comments, the committee will prepare the final appraisal document.

Subject to any appeal by consultees, the final appraisal document may be used as the basis for NICE's guidance on using polatuzumab vedotin with rituximab and bendamustine in the NHS in England.

For further details, see [NICE's guide to the processes of technology appraisal](#).

**The key dates for this appraisal are:**

Closing date for comments: 18 March 2020

Second appraisal committee meeting: TBC

Details of membership of the appraisal committee are given in section 5.

# 1 Recommendations

- 1.1 Polatuzumab vedotin with rituximab and bendamustine is not 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.
- 1.2 This recommendation is not intended to affect treatment with polatuzumab vedotin with rituximab and bendamustine that was started in the NHS before this guidance was published. People having treatment outside this recommendation may continue without change to the funding arrangements in place for them before this guidance was published, until they and their NHS clinician consider it appropriate to stop.

## 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. The evidence also suggests that they live longer, but it is not known by how much because the final data from the trial are not available yet.

The cost-effectiveness estimates for polatuzumab vedotin with rituximab and bendamustine are very uncertain because of limitations in the data and methods. It is considered a life-extending treatment at the end of life, but the cost-effectiveness estimates are too uncertain. Therefore, it cannot be recommended for routine use in the NHS or for use in the Cancer Drugs Fund.

## 2 Information about polatuzumab vedotin

### *Marketing authorisation indication*

- 2.1 Polatuzumab vedotin (Polivy, Roche) in combination with bendamustine and rituximab has a conditional marketing authorisation 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 recommended dose of polatuzumab vedotin is 1.8 mg per kg, given as intravenous infusion every 21 days in combination with bendamustine and rituximab for 6 cycles. When administered with polatuzumab vedotin, the recommended dose of bendamustine is 90 mg per m<sup>2</sup> per day on day 1 and day 2 of each cycle and the recommended dose of rituximab is 375 mg per m<sup>2</sup> on day 1 of each cycle. It is recommended that polatuzumab vedotin does not exceed the dose of 240 mg per cycle.

### *Price*

- 2.3 The cost per item from the company’s submission is £11,060 per 140-mg vial (excluding VAT). The company estimates that the average cost of a course of treatment is £50,416.
- 2.4 The company has a commercial arrangement, which would have applied if the technology had been recommended.

## 3 Committee discussion

The appraisal committee (section 5) considered evidence submitted by Roche, a review of this submission by the evidence review group (ERG), and the technical report developed through engagement with stakeholders. 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:

- 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 adults with relapsed or refractory diffuse large B-cell lymphoma 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 the GO29365 trial. 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 the clinical trial was broadly 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 the polatuzumab vedotin arm. 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 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, but further follow up would establish the amount of long-term benefit. The clinical experts 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 also 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. The committee 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 results of 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 generalised gamma 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 a standardised mortality ratio-adjusted general population mortality risk from the start of the trial. They were assumed to use no healthcare resources after 2 years and were assigned general population utilities adjusted for age and gender. 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 ciloleucel](#) and [tisagenlecleucel](#). 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 and that it was difficult to infer the plausibility of long-term remission from the progression-free survival data. The committee considered that sensitivity analyses in which the assumed cure rate was varied would be informative. The committee was concerned about the reliability of the model outputs because of the large unexplained difference between the company’s deterministic and probabilistic results. The committee also noted that the company’s probabilistic analysis estimated the number of life years for the comparator arm to be more than 2 years, which seemed unrealistic and inconsistent with clinical opinion, and would cast doubt on whether polatuzumab vedotin meets the end-of-life criteria. The committee was also aware that instead of using a standard cure-mixture modelling software package the company had developed its own code, which was not transparent, and that the ERG had been unable to assess the implementation of the methods. The committee would have preferred the company to have used a standard software package or to have made its own code sufficiently transparent that it could be easily and completely verified by the ERG. The committee concluded that the results of the company’s cure-mixture model were highly uncertain because the assumed cure rate was not sufficiently justified or investigated in sensitivity analyses, it was uncertain whether the model had been

correctly implemented, and the probabilistic model results lacked face validity.

### **The ERG's standard parametric survival modelling is uncertain**

3.9 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 noted that the ERG's analyses did not capture the potential cure aspect of the disease and therefore it may be conservative in its interpretation of the evidence. The committee considered that the ERG's analyses were a more standard approach. 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. The committee concluded that the mismatch between the predictions for progression-free survival and overall survival creates uncertainty about the robustness of the extrapolations.

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

3.10 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, 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 trial GO29365, 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 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 not appropriate**

3.11 The company 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, which was consistent with the methods used for modelling progression-free survival and overall survival. The ERG considered that using different methods to model disease progression and mortality (cohort-based) and background mortality (individual patient-level based) is inconsistent and created instances in which about 4% of patients were still alive at age 105 years. In the ERG's cohort-based modelling approach no patients were alive at the end of the 45-year time horizon. The committee agreed with the ERG that the company's model produced implausible results. It also considered that using cohort and individual-level modelling within the same model was inappropriate. The committee therefore concluded that the ERG's approach to modelling background mortality was appropriate.

### ***Health-related quality of life***

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

3.12 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 the GO29365 trial, and it did not endorse the approach of basing utility values for this condition on the ZUMA-1 trial.

### ***Cost-effectiveness estimate***

#### **Polatuzumab vedotin with rituximab and bendamustine has not been shown to be cost effective compared with rituximab and bendamustine alone**

3.13 The committee considered that the most plausible ICER was highly uncertain. It noted that the ICERs presented by the company using its cure-mixture model were within the range normally considered a cost-effective use of NHS resources for life-extending treatments at the end of life. However, the committee had concerns about the methods and assumptions used in the model, and it was not confident that the results were robust (see section 3.8). The committee also had concerns about the outputs of the ERG's base case (see section 3.9) and it noted that the probabilistic ICER was above the level usually considered cost effective for life-extending treatments at the end of life. The committee recognised the need for effective treatments in relapsed or refractory diffuse large B-cell lymphoma. However, it was not convinced that polatuzumab vedotin had been shown to be a cost-effective use of NHS resources.

Therefore, it concluded that polatuzumab vedotin could not be recommended for routine use in the NHS.

## ***Cancer Drugs Fund***

### **The criteria have not been met for inclusion in the Cancer Drugs Fund**

3.14 Having concluded that polatuzumab vedotin with rituximab and bendamustine could not be recommended for routine use, the committee considered whether it could be recommended for use within the Cancer Drugs Fund. It discussed the arrangements for the Cancer Drugs Fund agreed by NICE and NHS England in 2016, noting NICE's [Cancer Drugs Fund methods guide \(addendum\)](#). The committee recognised that people with diffuse large B-cell lymphoma have a high unmet clinical need, and that the availability of new treatments is very important. It heard from the company that further data cuts for the clinical trial are planned for 2020, which will provide further evidence on overall survival. However, the committee was concerned about the robustness of the model results (see section 3.13) and it was not persuaded that they demonstrated a plausible potential for cost effectiveness. Therefore, it concluded that polatuzumab vedotin did not meet the criteria for inclusion in the Cancer Drugs Fund.

## ***Conclusion***

### **Polatuzumab vedotin with rituximab and bendamustine is not 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. However, there is substantial uncertainty in the modelling and the committee was not persuaded that polatuzumab vedotin has been shown to be cost effective. Therefore, polatuzumab vedotin with rituximab and bendamustine is not recommended for

relapsed or refractory diffuse large B-cell lymphoma in adults who cannot have a haematopoietic stem cell transplant.

## 4 Proposed date for review of guidance

4.1 NICE proposes that the guidance on this technology is considered for review by the guidance executive 3 years after publication of the guidance. NICE welcomes comment on this proposed date. 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

February 2020

## 5 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

**Zoe Charles**

Technical adviser

**Thomas Feist**

Project manager

ISBN: [to be added at publication]