NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Appraisal consultation document

Polatuzumab vedotin in combination for untreated diffuse large B-cell lymphoma [ID3901]

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 in combination 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, sex, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?

Issue date: September 2022

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 in combination 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: 19 October 2022

Second appraisal committee meeting: 1 November 2022

Details of membership of the appraisal committee are given in section 4.

1 Recommendations

1.1 Polatuzumab vedotin with rituximab, cyclophosphamide, doxorubicin and prednisolone (R-CHP) is not recommended, within its marketing authorisation, for untreated diffuse large B-cell lymphoma (DLBCL) in adults.

1.2 This recommendation is not intended to affect treatment with polatuzumab vedotin 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

Standard treatment for untreated DLBCL is rituximab, cyclophosphamide, doxorubicin, vincristine and prednisolone (R-CHOP).

Clinical evidence suggests that people having polatuzumab vedotin with R-CHP have more time before their cancer gets worse than people having R-CHOP alone. But there is not enough evidence to know if polatuzumab vedotin with R-CHP increases how long people live because the clinical trials would need to be done for much longer to find this out.

The cost-effectiveness estimates for polatuzumab vedotin with R-CHP are uncertain because there is not enough clinical evidence. They are also higher than what NICE usually considers an acceptable use of NHS resources. So, it is not recommended for routine use. Collecting more data would not resolve the uncertainties, so it is not recommended for use in the Cancer Drugs Fund.

2 Information about polatuzumab vedotin

Marketing authorisation indication

2.1 Polatuzumab vedotin (Polivy, Roche) in combination with rituximab, cyclophosphamide, doxorubicin and prednisolone is indicated for 'the treatment of adult patients with previously untreated diffuse large B-cell lymphoma (DLBCL)'.

Dosage in the marketing authorisation

2.2 The dosage schedule is available in the summary of product characteristics for polatuzumab vedotin.

Price

2.3 Polatuzumab vedotin costs £2,370 per 30 mg vial or £11,060 per 140 mg vial (excluding VAT, BNF online accessed September 2022).

The company has a commercial arrangement. This makes polatuzumab vedotin available to the NHS with a discount and it would have also applied to this indication if the technology had been recommended. 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 considered evidence submitted by Roche, a review of this submission by the evidence review group (ERG), and responses from stakeholders. See the committee papers for full details of the evidence.

Clinical need and treatment pathway

There is a high unmet need for a first-line treatment that stops diffuse large B-cell lymphoma progressing

3.1 Diffuse large B-cell lymphoma (DLBCL) 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 people. The clinical experts explained that current treatment for untreated DLBCL is rituximab, cyclophosphamide, doxorubicin, vincristine and prednisolone. They noted that first-line treatment has the best chance of cure. They explained there is an unmet need to stop the disease from progressing. This is because treatment options for relapsed or refractory disease are associated with significant burden and toxicity. The clinical experts explained that relapsed or refractory disease has poor survival rates. A patient expert submission to NICE explained that DLBCL is difficult to live with because of the symptoms of both the disease and treatment. Common symptoms include painless swellings at single or multiple sites (lymph node and non-lymph node), excessive night sweating, unexplained fever and weight loss. The patient expert submission also highlighted the psychological effects of relapsed or refractory disease for both patients and carers. People may have insomnia, anxiety and a constant fear of relapse and death. The committee agreed that DLBCL is an aggressive form of lymphoma that needs intensive treatment. It concluded that there is an unmet need for first-line treatments that prevent disease progression.

It is appropriate to only consider DLBCL with an IPI score of 2 to 5

3.2 The International Prognostic Index (IPI) risk group is usually used to predict DLBCL prognosis. IPI risk group is categorised based on independent predictors for outcomes like overall survival and progression-free survival. IPI risk group is determined by the number of predictors met: 0 or 1 is low risk, 2 is low-intermediate risk, 3 is high-intermediate risk, and 4 or 5 is high risk. The company positioned polatuzumab vedotin with

rituximab, cyclophosphamide, doxorubicin and prednisolone (R-CHP) for DLBCL with an IPI score of 2 to 5. This is because the clinical trial excluded those with an IPI score of 0 to 1. However, the committee recalled that the marketing authorisation is 'adult patients with previously untreated DLBCL' and does not restrict by IPI risk group. The clinical experts explained that the outcomes for IPI 0 to 1 were usually very good and only a small proportion of people with DLBCL have an IPI score of 0 to 1. They noted that it was appropriate to exclude DLBCL with an IPI score of 0 to 1. The committee concluded that it was appropriate to exclude DLBCL with an IPI score of 0 to 1 for this appraisal.

Clinical evidence

Progression-free survival estimates for the IPI 2 subgroup are uncertain

3.3 The main clinical evidence was from the POLARIX trial. POLARIX was the pivotal trial for polatuzumab vedotin in untreated DLBCL. It was a multicentre phase 3, double-blind, placebo-controlled study in adults with previously untreated DLBCL with a IPI score of 2 to 5. POLARIX compared polatuzumab vedotin plus R-CHP with R-CHOP. The primary end point was progression-free survival. People who had polatuzumab vedotin with R-CHP had a 24-month progression-free survival rate of 76.7 (95% confidence interval [CI] 72.7 to 80.8) compared with 70.2 (95% CI 65.8 to 74.6) for people who had R-CHOP. The hazard ratio for disease progression or death was 0.73 (95% CI 0.57 to 0.95, p=0.02). The company did exploratory subgroup analyses, dividing by IPI risk group, among other things. For the IPI 3 to 5 subgroup it was 0.7 (95% CI 0.5 to 0.9). The committee noted that some subgroups, such as IPI 2, age above 60, presence of bulky disease, and women, showed a small or no effect size. It noted that in the IPI 2 subgroup, which was 38% of the trial population, the hazard ratio for disease progression or death was 1.0 and 95% CIs ranged from 0.6 to 1.6, suggesting a lack of progression-free survival benefit in this group. The company explained that the subgroup analyses in the trial were exploratory and not confirmatory, so they should

not be used in decision making. It also explained that because IPI 2 disease is lower risk and progression or death occurs less often in this population the effect may not be picked up in the trial. The ERG explained that noise in the data could be a reason there is no effect in some of the subgroups. The clinical experts agreed with the company that IPI 2 disease is a lower risk group and that it is difficult to draw conclusions from the subgroup analysis when it is exploratory. The committee concluded that polatuzumab vedotin with R-CHP improves progression-free survival in the IPI 2 to 5 group, and that the exploratory subgroup analyses suggested that more benefit was derived in the higher-risk groups. It further concluded that the IPI 2 to 5 group should be included in the cost-effectiveness analysis.

The overall survival benefit for polatuzumab vedotin with R-CHP is uncertain

3.4 People who had polatuzumab vedotin with R-CHP had a 24-month overall survival rate of 88.7 (95% CI 85.7 to 91.7) compared with 88.6 (95% CI 85.6 to 91.6) for R-CHOP. The hazard ratio for death was 0.94 (95% CI 0.65 to 1.37). The company explained that the overall survival results are immature and follow up is not long enough to capture the effect of polatuzumab vedotin with R-CHP on survival. The ERG explained that the POLARIX overall survival analysis did not show a statistically significant difference between polatuzumab vedotin with R-CHP and R-CHOP because the confidence interval crossed 1. The committee concluded that it was uncertain if there was an overall survival benefit of polatuzumab vedotin with R-CHP compared with R-CHOP.

Survival modelling

A mixture-cure model was used to extrapolate progression-free and overall survival

3.5 The company and ERG both used a mixture-cure model to extrapolate progression-free survival and overall survival. The mixture-cure model

assumed the population consisted of 2 groups: a 'cured' population and a population whose disease would progress. The 'cured' population is assumed to have the same risk of death as the age- and sex-matched general population after 2 years. The committee concluded that a mixture-cure model was a reasonable approach.

The overall survival extrapolations are highly uncertain

3.6 The company explained that it was not possible to estimate long term survival from the overall survival data in POLARIX because the overall survival data was immature (see section 3.43.4). Because of this, the overall survival mixture-cure model was informed by the progression-free survival cure fraction. The ERG explained that the approach seemed logical given the immaturity of the overall survival data in POLARIX. The committee noted that if the overall survival data was mature, it would be unlikely to estimate the same levels of survival as the company's model because of the uncertainty in the model methodology. It was uncertain if the extrapolations would accurately represent overall survival for polatuzumab vedotin in combination with R-CHP and R-CHOP. The committee concluded that the overall survival extrapolations are highly uncertain.

It is not appropriate to include treatment effect waning

3.7 POLARIX showed no statistically significant survival benefit for polatuzumab vedotin with R-CHP compared with R-CHOP (hazard ratio 0.94; 95% CI 0.65 to 1.37). However, the company's extrapolation (based on the mixture-cure model, see section 3.5) assumed a continued survival benefit for polatuzumab vedotin with R-CHP over R-CHOP. The company explained that because DLBCL is curable in first line a waning effect should not be applied. The company considered that because overall survival estimated in the model is informed by progression-free survival from POLARIX, it is likely to underestimate the long-term efficacy of polatuzumab vedotin with R-CHP. The ERG explained that there is uncertainty in the overall survival benefit from POLARIX and other

subsequent treatments would affect long-term survival. So it applied a waning effect to overall survival to try to account for some of the uncertainty. The company also presented evidence from first-line and relapsed and refractory DLBCL trials to support a continued survival benefit. The ERG noted that the additional trial evidence provided by the company supported a continued overall survival benefit in DLBCL. But it explained that these trials had different treatment regimens, different patient characteristics and study lengths, which limited how applicable this evidence was to polatuzumab vedotin with R-CHP. The ERG highlighted that the waning effect is in the context of a mixture-cure model. This means waning is applied to the whole population, even those whose disease is cured, which is a more conservative approach than the company's. The clinical experts explained that most death and relapse would occur within 2 years and that subsequent treatments are associated with significant toxicity. The committee noted that applying treatment waning to the whole population in the context of the mixture-cure model, meant that there is a 'cured' population initially, whose disease is then considered 'uncured' later. It noted that the company's approach was favourable to polatuzumab vedotin with R-CHP and associated with uncertainty but considered it to be a more clinically plausible scenario than the ERG's. Because of this, the committee concluded that treatment effect waning should not be included.

Economic modelling

The company's model structure is suitable for decision making

3.8 The company used a 3-state partitioned survival model to estimate the cost effectiveness of polatuzumab vedotin with R-CHP compared with R-CHOP. It had 3 health states: progression-free, progressed disease and death. The committee considered that the partitioned survival model is a standard approach to estimating the cost effectiveness of cancer drugs and concluded that it was appropriate in this instance.

Patient weight used in the model may not be generalisable to NHS clinical practice

3.9 The model used patient weight distributions from the POLARIX trial. The committee noted that the mean patient weight from POLARIX was 75.92 kg, which is lower than calculated in the 2019 NHS Health Survey for England on overweight and obesity in adults and children. So the committee questioned if the weight distribution used in the model represented NHS clinical practice. It noted that this could affect the number of vials needed for each person, which would in turn influence costs. The committee concluded that it would like to see patient weight distributions from the UK sites of the POLARIX trial and the impact of this on weight-based dosing and wastage.

Neither the company nor ERG base case progressed disease supportive care costs reflect NHS clinical practice

3.10 Supportive care costs are applied every weekly cycle in the model for the duration of the time they are in the health state. For progressed disease, this is every year until the disease is cured or death occurs. The company used resource use data for progressed disease based on NICE's technology appraisal guidance on polatuzumab vedotin (TA649) which used progressed disease resource data from NICE's technology appraisal guidance on pixantrone monotherapy (TA306). Both these appraisals are in relapsed or refractory DLBCL. The company explained that these costs were most appropriate because there are no NICE appraisals in untreated DLBCL. It highlighted that in POLARIX people had approximately 2 more treatments after first-line treatment but that its base case did not account for any resource costs beyond second-line treatment. So the company explained the approach was conservative. The ERG considered that resource use and therefore the costs of progressed disease to be overestimated. This was because people having third- and fourth-line treatments (as considered in TA649) would be in poorer health and need more resources than people having second-line treatment. It also

highlighted that the company base case included 2 end of life costs, 1 as part of the resource use for progressed disease and 1 applied to those who died in the model. The ERG also noted that the costs estimated by the company were higher than a UK real world evidence study on treatment cost and life expectancy of DLBCL and NICE's technology appraisal guidance on obinutuzumab. The ERG preferred to estimate resource use based on NICE's technology appraisal guidance on rituximab (TA243). It explained that resource use from TA243 would more closely represent the resource use in second-line treatment of DLBCL. The clinical experts considered the ERG estimates of supportive care resources to be too low. They explained that they see people with relapsed or refractory DLBCL twice a week on average and that they need resources such as positron emission tomography (PET) scans, which have a high cost. They highlighted that DLBCL is one of the most resource-intensive lymphomas and supportive care would likely cost several thousand pounds per year rather than several hundred pounds. However, they also noted that some of the company resource estimates, such as number of district nurse visits, are likely to be overestimated. Overall, the clinical experts explained that the company base case was more plausible than the ERG base case but that it did not accurately reflect resource use for DLBCL. The committee concluded that neither the company nor ERG base case represented supportive care resource use for DLBCL in the NHS. It further concluded that end of life costs should be removed from progressed disease resource use.

Utility for progressed disease may not have been fully accounted for

3.11 The company used utility values from the GOYA trial because it had a longer follow up than POLARIX. GOYA was a phase 3, open-label study of obinutuzumab plus CHOP compared with R-CHOP in adults with previously untreated CD20-positive DLBCL with an IPI score of 2 to 5. The company explained that 11 clinicians had confirmed that the GOYA utility values were more representative of DLBCL than the POLARIX utility values. The company presented several reasons why the POLARIX

utilities were not representative of people with relapsed or refractory DLBCL seen in the NHS. Some people whose disease progressed did not report health-related quality of life (the exact number is considered confidential by the company and cannot be reported here) and those who did report had better health outcomes than those who did not. The company also explained that the timing of collection of the health-related quality of life data affected its applicability. The company considered the timing to be confidential so it cannot be reported here. The ERG noted that the GOYA utility values were similar to those used in NICE's technology appraisal guidance on polatuzumab vedotin (TA649) so agreed to use the GOYA utility values in the base case. The ERG also age adjusted the progressed disease utility values using Ara and Brazier UK general population utility values. The committee queried the timing of the health-related quality of life data collection in the GOYA trial, which the company explained was before second-line treatment. The committee questioned whether the valuation of health-related quality of life data was overestimated because the GOYA data was collected before later-line treatments were started. Clinical experts explained that the toxicity of later line treatments is significant and that they would expect this to contribute to quality of life. The committee noted it would have preferred to have seen GOYA utilities after second-line treatment was started. However, it concluded that the company's approach was acceptable for decision making but uncertain.

CAR-T therapies should not be included as subsequent treatments

3.12 In its initial submission, the company included 2 chimeric antigen receptor (CAR) T-cell therapies as subsequent treatments in the model. These CAR-T therapies are currently in the CDF; see NICE's technology appraisal guidance on axicabtagene ciloleucel (TA559) and NICE's technology appraisal guidance on tisagenlecleucel (TA567). NICE's position statement is that technologies with CDF recommendations should not be considered as comparators. The committee acknowledged the relevance of TA559 to this appraisal, and noted that it is currently being

reviewed with guidance due in January 2023. At technical engagement, the company explained that CAR-T therapies have high costs, which may make polatuzumab vedotin with R-CHP more cost effective in the long term. But it agreed to remove CAR-T therapies as subsequent treatments from the model. At the first committee meeting, the committee concluded that CAR-T therapies should not be included as subsequent treatments because they are not routinely commissioned.

Redistributing CAR-T therapy use to other subsequent treatments is acceptable

3.13 After technical engagement, in the model the company redistributed people having CAR-T therapies to have other subsequent treatments. The ERG explained this meant the total use of subsequent treatments was more than 100%, which is implausible. Instead, the ERG did not adjust the proportion of people having each subsequent treatment when CAR-T therapies were removed at technical engagement. This made total subsequent treatment use 97%. The committee noted that use of subsequent treatments in the model was more than 100% before the redistribution of CAR-T therapies. The company explained that this was because chemotherapy and stem cell transplants were considered separately in the model (that is, if someone had chemotherapy and a stem cell transplant, this would be counted as 2 subsequent treatments, meaning the percentage would be higher than 100%). The committee concluded that people would have other treatments if CAR-T therapy was not available, so it agreed with the company's redistribution of CAR-T therapies to other subsequent treatments.

End of life

End of life criteria are not met for polatuzumab vedotin with R-CHP

3.14 The committee considered the advice about life-extending treatments for people with a short life expectancy in NICE's guide to the methods of technology appraisal. The committee was aware that the mean life

expectancy for people with untreated DLBCL who had R-CHOP was more than 24 months. So, it concluded that polatuzumab vedotin with R-CHP did not meet the end of life criteria.

Innovation

Polatuzumab vedotin with R-CHP is innovative

3.15 Clinical experts explained that POLARIX is the first international double blind randomised controlled trial in over 20 years to show meaningful improvement in the benefit-risk profile of another treatment over R-CHOP. The committee concluded that polatuzumab vedotin with R-CHP is innovative.

Cost-effectiveness estimates

An acceptable ICER is between £20,000 and £30,000 per QALY gained

3.16 NICE's guide to the methods of technology appraisal notes that above a most plausible incremental cost-effectiveness ratio (ICER) of £20,000 per quality-adjusted life year (QALY) gained, judgements about the acceptability of a technology as an effective use of NHS resources will take into account the degree of certainty around the ICER. The committee will be more cautious about recommending a technology if it is less certain about the ICERs presented. The committee considered polatuzumab vedotin with R-CHP innovative but noted that the clinical evidence was uncertain. So, it agreed that an acceptable ICER would be between £20,000 and £30,000 per QALY gained.

The most plausible cost-effectiveness estimates are above £30,000 per QALY gained

3.17 Because of confidential commercial arrangements for cyclophosphamide, doxorubicin, prednisolone and rituximab, the exact ICERs are confidential and cannot be reported here. The committee noted that the company's

base case had an ICER in the region of £30,000 per QALY gained and included the committee's preferences of:

- no treatment waning effect (see section 3.7)
- exclusion of CAR-T therapies (see section 3.12)
- redistribution of CAR-T therapy use to other subsequent treatments (see section 3.13).

However, the committee noted that the company base case supportive care resource use for progressed disease is likely to be an overestimate. It also noted using the committee preferences with the ERG progressed disease costs resulted in an ICER that was significantly higher than £30,000 per QALY gained. There was also significant uncertainty about the overall survival benefit, and utility values. Because of this, the committee considered that it did not have an ICER that reflected all its preferred assumptions. The committee would like to see:

- weight distributions in the model that reflect NHS practice (see section 3.9)
- updated supportive care resource use for progressed disease that better reflects clinical practice (see section 3.10).

Taking into account all confidential discounts the most plausible ICER was above £30,000 per QALY gained. The committee concluded that the cost-effectiveness estimates for polatuzumab vedotin with R-CHP were higher than what NICE considers a cost-effective use of NHS resources. So the committee did not recommend polatuzumab vedotin with R-CHP for use in the NHS.

Cancer Drugs Fund

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

3.18 Having concluded that polatuzumab vedotin with R-CHP 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 company explained that there was a further data cut in August 2022 and that there would be no further data cuts after this date. Based on the company's and ERG's extrapolations, it is unlikely that the survival data will be sufficiently mature within a reasonable timeframe to reduce the uncertainty around a survival benefit. The committee noted that most uncertainties in the appraisal were related to the modelling approach, which could not be resolved in the Cancer Drugs Fund. So it concluded that polatuzumab vedotin did not meet the criteria for inclusion in the Cancer Drugs Fund.

Stephen O'Brien
Chair, appraisal committee
September 2022

4 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 C.

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.

Sarah Wilkes
Technical lead

Fatima Chunara
Technical adviser

Kate Moore
Project manager

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