NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Appraisal consultation document

Tafasitamab with lenalidomide 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 tafasitamab with lenalidomide 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: June 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 tafasitamab with lenalidomide 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: 14 July 2022

Second appraisal committee meeting: 02 August 2022

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

1 Recommendations

1.1 Tafasitamab with lenalidomide is not recommended, within its marketing authorisation, for treating relapsed or refractory diffuse large B-cell lymphoma in adults who cannot have an autologous stem cell transplant.

1.2 This recommendation is not intended to affect treatment with tafasitamab with lenalidomide 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

People with relapsed or refractory diffuse large B-cell lymphoma who cannot have an autologous stem cell transplant usually have polatuzumab vedotin with rituximab and bendamustine.

The clinical evidence is from a small study that did not directly compare tafasitamab plus lenalidomide with anything else. The committee considered that the study results were promising because they show that some people's disease responds to tafasitamab plus lenalidomide. Indirect evidence suggests people who have tafasitamab plus lenalidomide have more time before their disease gets worse than people who have polatuzumab vedotin plus rituximab and bendamustine. It also suggests that they live longer. But there is uncertainty about these results because the survival times for people who have polatuzumab vedotin plus rituximab and bendamustine used in the modelling does not reflect the estimated survival in NICE's guidance on polatuzumab vedotin plus rituximab and bendamustine. The methods used for the indirect comparisons are also not clear.

People on standard treatment for relapsed or refractory diffuse large B-cell lymphoma are likely to live for longer than 2 years so do not meet one of NICE's criteria for end of life.

All the cost-effectiveness estimates for tafasitamab plus lenalidomide are above the range normally considered by NICE to be a cost-effective use of NHS resources. Therefore, it cannot be recommended for routine use in the NHS.

Because the cost-effectiveness estimates are very high and uncertain, and further evidence is unlikely to resolve this uncertainty, it also cannot be recommended for use in the Cancer Drugs Fund.

2 Information about tafasitamab with lenalidomide

Marketing authorisation indication

2.1 Tafasitamab (Minjuvi, Incyte) is indicated, in combination with lenalidomide followed by tafasitamab monotherapy, for 'the treatment of adult patients with relapsed or refractory diffuse large B-cell lymphoma who are not eligible for autologous stem cell transplant'.

Dosage in the marketing authorisation

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

Price

2.3 Tafasitamab costs £705 per 200-mg powder for concentrate for solution for infusion (excluding VAT; company submission). Tafasitamab costs £120,639 for 12 months of treatment in year 1 and £95,049 for year 2 onwards. The list price of lenalidomide per 21-capsule pack varies according to capsule size: £3,426.00 (2.5 mg), £3,570.00 (5 mg), £3,675.00 (7.5 mg), £3,780.00 (10 mg), £3,969.00 (15 mg), £4,168.50 (20 mg) and £4,368.00 (25 mg; all prices excluding VAT; BNF online accessed May 2022).

2.4 The company has a commercial arrangement, which would have applied if the technology had been recommended.

3 Committee discussion

The appraisal committee considered evidence submitted by Incyte, 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

People with diffuse large B-cell lymphoma would welcome a new treatment option that is more tolerable and improves outcomes

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 10% to 15% of people have primary refractory disease and a further 20% to 30% relapse. Submissions from the patient expert explained that the prognosis for people with relapsed or refractory disease is extremely poor. Treatments are very intensive, needing long stays in hospital and potentially incurring serious side effects even after treatment has ended. Any treatment delivered in an outpatient setting would have a significant, positive effect on the quality of life of people and their families. The psychological, social and economic impact of the disease for both the person and their carers is considerable. The clinical experts explained that relapsed or refractory disease is treated using salvage chemotherapy followed by an autologous stem cell transplant if the person can have intensive therapy. Clinical experts explained that approximately 10% to 20% of people with relapsed or refractory disease who can have intensive therapy are cured of the disease after an autologous stem cell transplant. People who cannot have a transplant, or whose disease relapses after a transplant, are usually offered polatuzumab vedotin with bendamustine and rituximab or other rituximab-based chemotherapy regimens. The committee concluded that relapsed or refractory diffuse large B-cell lymphoma is a devastating condition with a poor prognosis and that people with the condition have a high unmet need for effective treatments with manageable side effects.

Clinical management

Polatuzumab vedotin with bendamustine and rituximab is standard care for people who cannot have an autologous stem cell transplant

3.2 Tafasitamab has a marketing authorisation in combination with lenalidomide for treating relapsed or refractory diffuse large B-cell lymphoma in adults who cannot have an autologous stem cell transplant. The comparators in the NICE scope were:

- chemotherapy with or without rituximab
- pixantrone
- polatuzumab vedotin with bendamustine and rituximab
- best supportive care.

The company submission only included:

- rituximab with gemcitabine and oxaliplatin
- polatuzumab vedotin with bendamustine and rituximab
- bendamustine with rituximab as comparator treatments.

The reduced number of comparators was based on clinical expert interviews done by the company that suggested that these 3 regimens were the main treatments used in the NHS. The company also justified the choice of comparators by saying that there was limited data for the other comparators. And it pointed out that bendamustine with rituximab was considered a reasonable proxy for standard care in NICE's technology appraisal guidance on polatuzumab vedotin with bendamustine and rituximab for treating relapsed or refractory diffuse large B-cell lymphoma. The committee heard from clinical experts at the committee meeting that some of the low-intensity chemotherapy regimens (with or without rituximab) are rarely used. Polatuzumab vedotin with bendamustine and rituximab has largely replaced other options and is now standard care for people with relapsed or refractory disease who cannot have an autologous stem cell transplant. The committee

concluded that the company's choice of comparators was appropriate, and that polatuzumab vedotin with bendamustine and rituximab was the main comparator.

Clinical evidence

The lack of a direct comparison with any treatment makes the clinical data difficult to interpret

3.3 The clinical evidence for tafasitamab with lenalidomide came from the phase 2 L-MIND study. This is an ongoing multicentre, single-arm, open-label study of tafasitamab with lenalidomide in people with relapsed or refractory diffuse large B-cell lymphoma who could not have an autologous stem cell transplant. Because the study is open label, people and their healthcare professionals are aware of treatment allocation. The committee highlighted that the study was small, with 81 people recruited, 5 of whom were from the UK. At the October 2020 data cut, median duration of exposure to tafasitamab with lenalidomide was 9.2 months. The primary end point of objective response rate (partial and complete response) was 58%. Median overall survival was 33.5 months and median progression-free survival was 11.6 months. The ERG highlighted several important differences in the baseline characteristics of people in L-MIND compared with Northend et al., a retrospective analysis of real-world data from the UK. For example, the proportion of men in Northend et al. was 69% compared with 54% in L-MIND. Differences were also identified for the presence of bulky disease, International Prognostic Index scores, number of lines of prior therapy, and refractoriness to prior treatment. The committee considered that the study results were promising. However, it concluded that the lack of a direct comparison with any treatment makes the data difficult to interpret.

The results of the indirect treatment comparisons are very uncertain

3.4 Because L-MIND is a single-arm study, indirect treatment comparisons were needed to establish the relative efficacy of tafasitamab plus

lenalidomide compared with other treatments. The company used 2 indirect treatment comparison approaches: RE-MIND2 and matching-adjusted indirect comparisons. RE-MIND2 was an observational, retrospective cohort study of 3,454 adults with relapsed or refractory diffuse large B-cell lymphoma, including 115 people from the UK. The company used nearest neighbour propensity score matching to balance the cohorts for comparator treatments with L-MIND based on 9 baseline covariates. In the matching-adjusted indirect comparisons the company adjusted the L-MIND population using propensity score weighting to be comparable to the populations in 4 published trials of comparator treatments, which were selected using a systematic literature review and expert input. The company used RE-MIND2 for rituximab with gemcitabine and oxaliplatin and the matching-adjusted indirect comparisons for polatuzumab vedotin with bendamustine and rituximab as well as bendamustine and rituximab. The company chose indirect evidence sources based on alignment to published outcomes. This resulted in RE-MIND2 not being selected for polatuzumab vedotin with bendamustine and rituximab. All of the indirect comparisons suggested that tafasitamab with lenalidomide improved progression-free and overall survival compared with the comparators, but this was not always statistically significant. The ERG highlighted that RE-MIND2 consists of pooled individual participant data and is preferred in principle to the intervention population adjustment undertaken in the matching-adjusted indirect comparisons. Adjusting the L-MIND population differently for each comparator treatment population can lead to bias. However, there was uncertainty about the methods used for RE-MIND2 because the baseline characteristics of the tafasitamab with lenalidomide cohort varied depending on the comparator. The ERG suggested that it was unclear what type of treatment effect is estimated in RE-MIND2. The committee concluded that, because of the complexity in the methods adopted for the indirect treatment comparisons, and the potential biases, the results of the indirect comparisons were very uncertain.

The company's economic model

The company's economic model structure is appropriate for decision-making

3.5 The company presented a 3-state partitioned survival model to estimate the cost effectiveness of tafasitamab plus lenalidomide compared with rituximab plus gemcitabine and oxaliplatin, polatuzumab vedotin plus bendamustine and rituximab, and bendamustine plus rituximab. The committee agreed that the company's model structure was appropriate for decision making.

The ERG's overall and progression-free survival extrapolations for polatuzumab vedotin with bendamustine and rituximab are more plausible than the company's

3.6 The ERG questioned the validity of the overall and progression-free survival parametric extrapolations for polatuzumab vedotin with bendamustine and rituximab. The company calculated separate hazard ratios for up to month 4 and after month 4 for both survival outcomes from the matching-adjusted indirect treatment comparison. It applied these hazard ratios to the survival distributions for tafasitamab with lenalidomide to calculate the survival distributions for polatuzumab vedotin with bendamustine and rituximab. The company justified this piecewise approach to estimating hazard ratios by saying that the alternative, a constant hazard ratio, was not possible because its proportional hazards test failed. However, the ERG was concerned that the resulting overall survival extrapolation underestimated survival compared with NICE's technology appraisal guidance on polatuzumab vedotin. The previous NICE appraisal estimated around 3.1 mean life years and 2.1 quality-adjusted life years for polatuzumab vedotin with bendamustine and rituximab. In contrast, the company's extrapolation estimated 2.2 mean life years and 1.5 quality-adjusted life years. On this basis, the ERG preferred to apply a constant hazard ratio from the matching-adjusted

indirect comparison, leading to 3.4 mean life years and 2.2 quality-adjusted life years for polatuzumab vedotin with bendamustine and rituximab. The clinical experts considered that the company's estimates were reasonable because they were closer to the published literature estimates of median overall survival for polatuzumab vedotin with bendamustine and rituximab (between 8.2 and 12.5 months) than the ERG's. The company justified its methodology by saying it was verified by clinical experts, produced the results most aligned with real-world evidence, and avoided unnecessary complexity. However, the committee noted that tests for proportional hazards did not support a constant hazard. So, it considered that it was not appropriate to apply constant hazard ratios to the L-MIND data, even using the piecewise approach. It also identified that better approaches were needed to handling the time-varying nature of the observed hazard ratio. The committee agreed that the company should have included the data from Sehn et al. in the indirect comparisons in more ways. For example, the polatuzumab vedotin with bendamustine and rituximab hazard ratio from Sehn et al. could be applied to the survival outcomes for the propensity score matched bendamustine and rituximab population. Or, independent survival models could be fitted to the Sehn et al. Kaplan–Meier curves, adding a third arm for tafasitamab with lenalidomide against bendamustine and rituximab from the matching-adjusted indirect comparison. It determined that a crucial factor was that the estimated outcomes of the company base case did not align with evidence seen in NICE's technology appraisal guidance on polatuzumab vedotin. In addition to the ERG's arguments about the company's modelling not reflecting the absolute benefits of polatuzumab vedotin with bendamustine and rituximab, the committee considered that the modelling poorly reflected the relative benefit compared with bendamustine and rituximab alone. For example, Sehn et al. reported a hazard ratio for overall survival of 0.42 for polatuzumab vedotin plus bendamustine and rituximab compared with bendamustine and rituximab alone. The clinical experts also confirmed that polatuzumab vedotin plus

bendamustine and rituximab improves survival compared with bendamustine and rituximab alone. However, this is not reflected in the company's modelling, with only a small difference in survival estimated. The committee concluded that the company's parametric extrapolations for polatuzumab vedotin with bendamustine and rituximab were implausible. It found that estimates from the ERG's base case were more plausible because the outcomes were more aligned with NICE's technology appraisal guidance on polatuzumab vedotin with bendamustine and rituximab. However, it would have preferred to see different modelling approaches used that both fitted the underlying hazards of the data and produced outcomes aligned with the polatuzumab vedotin with bendamustine and rituximab guidance.

Progression-free survival parametric extrapolations for tafasitamab with lenalidomide are uncertain

3.7 The company and ERG both agreed that the lognormal parametric extrapolation of L-MIND overall survival data for tafasitamab with lenalidomide was the most appropriate approach. However, the company selected a generalised gamma distribution fitted to the data from L-MIND to model progression-free survival for tafasitamab with lenalidomide, and the ERG preferred a lognormal distribution. The company justified the generalised gamma approach based on statistical and visual fit to the observed data from L-MIND. The ERG recognised the uncertainty caused by the wide-ranging survival curves estimated for different parametric functions. But it suggested that the generalised gamma model overpredicts long-term progression-free survival, and the resulting hazard profile is inconsistent with the predictions of the clinical experts consulted by the company. The ERG accepted that the lognormal distribution overestimates progression-free survival for the first 20 months but pointed out that it provides the smallest overestimation in the long term. Clinical experts expressed great uncertainty about whether the company's or ERG's modelled curves would best reflect long-term outcomes with tafasitamab plus lenalidomide. But they did note that some people can

have a complete response with this treatment, adding some support to the company's approach. The committee concluded that there was considerable uncertainty in the modelled progression-free survival extrapolations for tafasitamab with lenalidomide. It noted that heavy patient censoring towards the end of the L-MIND Kaplan–Meier curve adds to the uncertainty. It therefore agreed it was appropriate to consider the lognormal distribution chosen by the ERG.

End of life

Tafasitamab with lenalidomide does not meet the end of life criteria

3.8 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 heard that the company, ERG, and clinical experts agreed that criterion 2 was met because tafasitamab with lenalidomide is expected to extend life by at least 3 months compared with current NHS treatment. The company and clinical experts explained to the committee that they believed that criterion 1 was met also, because people with relapsed or refractory diffuse large B-cell lymphoma face a short life expectancy of less than 24 months. Clinical experts shared results from published literature in their submission. These showed median overall survival for people with the condition having polatuzumab vedotin with bendamustine and rituximab ranging from 8.2 to 12.5 months. The clinical experts also said their expectation of survival was less than 24 months. The committee heard from the ERG that some references shared in support of poor life expectancy were of limited relevance, poor quality, or both. The ERG also highlighted that these results differed substantially from those accepted by the committee for NICE's technology appraisal guidance on polatuzumab vedotin. That appraisal estimated survival with polatuzumab vedotin with bendamustine and rituximab of over 4 years (undiscounted). This figure was also more consistent with the mean estimates from both the company's and the ERG's modelling for this appraisal of tafasitamab with lenalidomide. These estimated

undiscounted life years, equivalent to 29 and 48 months respectively, were longer than 24 months. The committee considered whether these estimates could have been skewed by a small proportion of people surviving for a very long time. However, it noted that more than 1 in 3 people were alive at 24 months in the company's and the ERG's base case models, which was also consistent with data from Sehn et al. The committee was concerned about the substantial discrepancy between the estimate of survival from NICE's guidance on polatuzumab vedotin with bendamustine and rituximab and other estimates from the literature. The committee noted that it had heard from the clinical experts that polatuzumab vedotin with bendamustine and rituximab is an effective treatment and that there was no reason to doubt the conclusions of NICE's guidance on it. The committee was aware that NICE's guide to the methods of technology appraisal states that "as far as possible, the committee will want to ensure that their judgements regarding the cost-effective use of NHS resources are consistently applied between appraisals". The committee considered that people with this condition having polatuzumab vedotin with bendamustine and rituximab, which is now standard treatment, cannot be expected to usually have a life expectancy less than 24 months when the best estimate from NICE's guidance on polatuzumab vedotin with bendamustine and rituximab is around 4 years. The committee concluded that tafasitamab with lenalidomide does not meet the end of life criteria.

Cost-effectiveness estimates

Tafasitamab with lenalidomide is not cost effective

3.9 The committee considered that the most plausible incremental cost-effectiveness ratio (ICER) was highly uncertain, because of issues with the indirect comparisons and modelling (see sections 3.4, 3.6 and 3.7). It noted that the base case ICERs presented by the company for tafasitamab with lenalidomide compared with polatuzumab vedotin with bendamustine and rituximab were higher than the range normally

considered a cost-effective use of NHS resources, even for end of life treatments. The exact results cannot be reported here because they include confidential discounts for other treatments. However, the committee concluded that the company's base case ICERs were not plausible, because the model outputs were not consistent with NICE's technology appraisal guidance on polatuzumab vedotin. It considered that the ERG's base case was more closely aligned with these outputs, despite some concerns (see section 3.6). The committee noted that the ERG's base case ICER was considerably higher than the company's and considerably higher than the level usually considered cost effective. The committee recognised the need for effective treatments in relapsed or refractory diffuse large B-cell lymphoma. However, tafasitamab with lenalidomide had not been shown to be a cost-effective use of NHS resources in any analyses presented to the committee. Therefore, it concluded that tafasitamab with lenalidomide 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

3.10 Having concluded that tafasitamab with lenalidomide 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 relapsed or refractory 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 L-MIND clinical study are planned for 2022, which will provide further evidence on survival and response outcomes. However, the committee was concerned that the single-arm phase 2 study will not provide additional comparative evidence. The model would still rely on indirect evidence for comparator

treatments so this would not resolve a key uncertainty. In addition, the committee was not presented with any analysis demonstrating that tafasitamab with lenalidomide has the plausible potential to be cost effective at the proposed price. Therefore, it concluded that tafasitamab with lenalidomide did not meet the criteria for inclusion in the Cancer Drugs Fund.

Other factors

3.11 No equality or social value judgement issues were identified.

3.12 The committee heard from clinical experts that tafasitamab with lenalidomide is considered to be innovative, though not necessarily a step change. The committee was not presented with any evidence of additional benefits that had not been captured in the quality-adjusted life years (QALYs).

Conclusion

Tafasitamab with lenalidomide is not recommended for relapsed or refractory diffuse large B-cell lymphoma

3.13 There is a high unmet need for effective treatments in relapsed and refractory diffuse large B-cell lymphoma. Indirect evidence suggests that tafasitamab with lenalidomide may increase progression-free survival and overall survival compared with polatuzumab vedotin with rituximab and bendamustine. However, there is substantial uncertainty in the modelling and the committee was not presented with any analysis showing tafasitamab with lenalidomide was cost effective. Therefore, tafasitamab with lenalidomide is not recommended for relapsed or refractory diffuse large B-cell lymphoma in adults who cannot have an autologous stem cell transplant.

4 Proposed date for review of guidance

4.1 NICE proposes that the guidance on this technology is considered for review 3 years after publication of the guidance. NICE welcomes comment on this proposed date. NICE will decide whether the technology should be reviewed based on information gathered by NICE, and in consultation with consultees and commentators.

Stephen O'Brien
Chair, appraisal committee
June 2022

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 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.

Owen Swales
Technical lead

Charlie Hewitt and Louise Crathorne

Technical advisers

Louise Jafferally

Project manager

ISBN: [to be added at publication]