NICE National Institute for Health and Care Excellence

NICE guidance

Tafasitamab with lenalidomide for treating relapsed or refractory diffuse large B-cell lymphoma

Technology appraisal guidance
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Your responsibility

The recommendations in this guidance represent the view of NICE, arrived at after careful consideration of the evidence available. When exercising their judgement, health professionals are expected to take this guidance fully into account, alongside the individual needs, preferences and values of their patients. The application of the recommendations in this guidance is at the discretion of health professionals and their individual patients and do not override the responsibility of healthcare professionals to make decisions appropriate to the circumstances of the individual patient, in consultation with the patient and/or their carer or guardian.

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Commissioners and/or providers have a responsibility to provide the funding required to enable the guidance to be applied when individual health professionals and their patients wish to use it, in accordance with the NHS Constitution. They should do so in light of their duties to have due regard to the need to eliminate unlawful discrimination, to advance equality of opportunity and to reduce health inequalities.

Commissioners and providers have a responsibility to promote an environmentally sustainable health and care system and should assess and reduce the environmental impact of implementing NICE recommendations wherever possible.

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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 plus rituximab and bendamustine.

The clinical evidence is from a small study that did not directly compare tafasitamab plus lenalidomide with any other treatment. 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 that 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 having polatuzumab vedotin plus rituximab and bendamustine used in the modelling do not reflect the real-world survival times of the treatment in clinical practice, compared with bendamustine and rituximab alone. The methods used for the indirect comparisons are also not clear.

Tafasitamab plus lenalidomide meets NICE's criteria to be considered a life-extending treatment at the end of life. This is because people on standard treatment (polatuzumab vedotin plus rituximab and bendamustine) for relapsed or refractory diffuse large B-cell lymphoma are likely to live on average less than 2 years. But all the cost-effectiveness estimates for tafasitamab plus lenalidomide are above the range that NICE normally considers to be an acceptable use of NHS resources for end of life treatments. Therefore,

it cannot be recommended for routine use in the NHS.

Because the cost-effectiveness estimates are 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 vial of 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 February 2023).

2.4 The company has a commercial arrangement for tafasitamab, which would have applied if the technology had been recommended. There is a nationally available discount for lenalidomide with the Commercial Medicines Unit. The prices agreed through the framework are commercial in confidence.

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. A submission from a 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 involving serious side effects even after treatment has ended. Any treatment delivered in an outpatient setting (that is, that did not require a stay in hospital) would have a significant, positive effect on the quality of life of people with the condition 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 about 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 the following as comparator treatments:

- rituximab with gemcitabine and oxaliplatin
- polatuzumab vedotin with bendamustine and rituximab
- bendamustine with rituximab.

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. In addition, 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 rituximab and bendamustine for treating relapsed or refractory diffuse large B-cell lymphoma. The clinical experts said 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 in the trial and their healthcare professionals are aware of treatment allocation. The committee highlighted that the study is small, with 81 people recruited, 5 of whom are from the UK. At the October 2020 data cut, median duration of exposure to tafasitamab with lenalidomide was 9.2 months. The primary endpoint 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. (2022), 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 previous therapy, and refractoriness to previous 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: propensity score matching against RE-MIND2 and matching-adjusted indirect comparisons against published studies. 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 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 done in the matching-adjusted indirect comparisons. Adjusting the L-MIND population differently for each comparator treatment population may have led 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 used 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 overall and progression-free survival extrapolations for polatuzumab vedotin with bendamustine and rituximab are highly uncertain

3.6 The ERG questioned the validity of the company's 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 the proportional hazards test failed. However, the ERG was concerned that the resulting overall survival extrapolation underestimated survival for polatuzumab vedotin with bendamustine and rituximab compared with NICE's technology appraisal guidance on polatuzumab vedotin with rituximab and bendamustine. The previous NICE appraisal estimated around 3.1 mean life years and 2.1 quality-adjusted life years (QALYs). In contrast, the company's extrapolation estimated 2.2 mean life years and 1.5 QALYs. 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 QALYs 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 that 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 handle the time-varying nature of the observed hazard ratio. The committee agreed that the company should have looked at more ways to include the data from Sehn et al. (2022) in the indirect comparisons. 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; this would have created a partially anchored indirect comparison. The committee was disappointed that the company did not provide such additional analyses in response to the appraisal consultation document. 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 fully 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. However, the committee also took into account feedback from clinical experts on outcomes observed in clinical practice submitted in response to the appraisal consultation document.

These suggested that the estimates from the ERG's base case may be overestimated, despite alignment with NICE's technology appraisal guidance on polatuzumab vedotin with rituximab and bendamustine. The committee concluded that it would have preferred to see different modelling approaches that both fitted the underlying hazards of the data and produced outcomes more closely reflecting the absolute and relative benefits of polatuzumab vedotin with bendamustine and rituximab compared with bendamustine and rituximab alone, as seen in NICE's guidance on polatuzumab vedotin with rituximab and bendamustine.

Overall and progression-free survival parametric extrapolations for tafasitamab with lenalidomide are appropriate, despite the uncertainty

3.7 The company and ERG agreed that the log-normal parametric extrapolation of L-MIND overall survival data for tafasitamab with lenalidomide was the most appropriate approach. Initially, the company chose 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 log-normal distribution. However, the ERG noted the resulting hazard profile was inconsistent with the predictions of the clinical experts consulted by the company and overestimated progression-free survival in the long term. The committee noted that there was uncertainty in the modelled progression-free survival extrapolations for tafasitamab with lenalidomide because of heavy patient censoring towards the end of the L-MIND Kaplan–Meier curve. However, it agreed it was appropriate to consider the log-normal distribution chosen by the ERG. In response to the appraisal consultation document, the company updated its base-case model using the committee's preferred assumption of the log-normal parametric extrapolation of L-MIND progression-free survival data for tafasitamab with lenalidomide. The committee concluded that the company's approach to modelling tafasitamab with lenalidomide survival was appropriate in its updated base case, while noting the inherent uncertainty.

End of life (before the appeal)

Tafasitamab with lenalidomide does not meet the end of life criteria

3.8 The committee considered the criteria for life-extending treatments for people with a short life expectancy in section 6.2.10 of NICE's guide to the methods of technology appraisal 2013. These are:

- the treatment is indicated for people with a short life expectancy, normally less than 24 months and
- there is sufficient evidence to indicate that the treatment has the prospect of offering an extension to life, normally of a mean value of at least an additional 3 months, compared with current NHS treatment.

In considering these criteria the committee was also aware, from the methods guide, that it should be satisfied that 'the assumptions used in the reference case economic modelling are plausible, objective and robust'.

The committee was also aware of the appeal panel conclusions about the short life expectancy criteria as part of NICE's technology appraisal guidance on avelumab for maintenance treatment of locally advanced or metastatic urothelial cancer after platinum-based chemotherapy, particularly section 87 of the appeal decision (see the final appraisal determination 2 committee papers). This states, based on the evidence in that particular appraisal: 'The appeal panel felt that the key stakeholders of NICE would consider it unreasonable to state that life expectancy was not "normally less than 24 months", even if the mean life expectancy was greater than 24 months, if 65% of patients, the significant majority, in the modelled cohort had died prior to 24 months.'

The committee carefully reviewed these points and considered the following:

- **There is limited clinical trial data for tafasitamab with lenalidomide.** The only source of trial evidence for this appraisal was a single-arm phase 2 study of 80 people (L-MIND). The relatively small size of this study, short median follow up (13.2 months) and lack of data comparing it with usual NHS treatments makes it difficult to assess the comparative clinical effectiveness of

tafasitamab with lenalidomide. This introduces considerable uncertainty in the modelling.

- **The real-world experience in the NHS with polatuzumab vedotin with bendamustine and rituximab.** In response to the appraisal consultation document, the clinical experts explained that less favourable survival outcomes have been seen in clinical practice than the estimates in NICE's technology appraisal guidance on polatuzumab vedotin with rituximab and bendamustine. The recent Northend et al. (2022) study reported on real-world data from the UK including 133 people (78 having standalone treatment rather than bridging to chimeric antigen receptor T-cell therapy). Clinical experts explained that their experience was more consistent with the estimates from Northend et al. (median survival 10.2 months) and Sehn et al. (2022; median survival 12.4 months) than the estimates from NICE's guidance on polatuzumab vedotin (mean undiscounted survival of over 48 months). Based in part on this evidence, the company and clinical experts considered that end of life criterion 1 was met. The company also suggested that the Sehn et al. survival estimates may be biased by including people who had polatuzumab vedotin with bendamustine and rituximab and then also had chimeric antigen receptor T-cell therapy. The ERG acknowledged this but explained that it did not expect it to have a big impact on the results because it only affected a few people in the study.

- **There are different survival estimates for polatuzumab vedotin with bendamustine and rituximab.** The committee considered survival estimates for polatuzumab vedotin with bendamustine and rituximab from the original Sehn et al. (2019) study and the Sehn et al. (2022) follow-up study. The ERG highlighted that the results of the follow-up study analyses 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). The committee noted that this figure was also more consistent with the mean undiscounted life years estimates from both the company's (29 months) and the ERG's (48 months) modelling for this appraisal (both estimates longer than 24 months).

- **The summary of modelled and literature-based survival outcomes.** The committee considered the following survival outcomes:

  - Median overall survival estimates from Northend et al. (2022; 10.2 months)

and Sehn et al. (2022; 12.4 months).

- Mean overall survival estimates from the company's base-case model for polatuzumab vedotin (29 months undiscounted), the ERG's base case model (48 months undiscounted) and NICE's technology appraisal guidance on polatuzumab vedotin (over 48 months undiscounted).
- Estimates of the percentage of people alive at 24 months from the company's base-case model (34%), the ERG's base-case model (44%) and Sehn et al. (2022; 38%).
- The increase in mean undiscounted overall survival with tafasitamab from the company's base-case and ERG's base-case models (29 and 48 months respectively, difference of 19 months).

The committee carefully considered the totality of the data and analysis and concluded the following:

- End of life criterion 2 was met. The indirect comparisons and modelling were uncertain. But it was reasonable to conclude that tafasitamab with lenalidomide is expected to extend life by at least 3 months compared with current NHS treatment.
- End of life criterion 1 was not met. The committee was concerned by how different the survival estimates for polatuzumab vedotin with rituximab and bendamustine were from the literature and from NICE's technology appraisal guidance on polatuzumab vedotin with rituximab and bendamustine. It was aware that survival estimates measured using means and medians often give different values. But the appeal panel for NICE's guidance on avelumab agreed that all the evidence should be considered in making the decision. The committee acknowledged that the estimates from the guidance on polatuzumab vedotin may be too optimistic. But it did not consider that they were so overestimated that it was likely that people who have polatuzumab vedotin with rituximab and bendamustine in the NHS have a life expectancy of less than 24 months.

  The committee therefore concluded that tafasitamab with lenalidomide did not meet the end of life criteria.

Cost-effectiveness estimates (before the appeal)

Tafasitamab with lenalidomide is not cost effective

3.9 The committee considered that the most plausible incremental cost-effectiveness ratio (ICER) in the updated company base case 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 company's and ERG's base-case probabilistic ICERs (including all the confidential discounts) for tafasitamab plus lenalidomide compared with polatuzumab vedotin plus 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. The committee considered that the company's base-case ICERs were not plausible, because the model survival outputs were not consistent with NICE's technology appraisal guidance on polatuzumab vedotin. It acknowledged that, although the ERG's base case was more closely aligned with these survival outputs, they may overestimate survival for polatuzumab vedotin with bendamustine and rituximab (see section 3.6). The committee concluded that the most plausible ICER was likely to be between the company's and ERG's base-case estimates. It 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. So it concluded that tafasitamab with lenalidomide could not be recommended for routine use in the NHS.

Cancer Drugs Fund (before the appeal)

The Cancer Drugs Fund inclusion criteria are not met

3.10 Having concluded that tafasitamab with lenalidomide could not be recommended for routine use, the committee considered if 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. The company said 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 because 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 showing 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.

After the appeal

Appeals against the first final appraisal document were submitted and considered by an independent appeal panel. The panel convened for an oral hearing in November 2022 and upheld 1 appeal point, referring the appraisal back to committee for further consideration.

The committee has considered the appeal point upheld by the appeal panel and the company's revised patient access scheme

3.11 At the third appraisal committee meeting, the committee considered the appeal panel's decision to uphold 1 appeal point. The upheld appeal point asked the committee to:

- appraise the technology on the basis that the NICE end of life criteria apply
- consider the extent, if any, to which this influences the eligibility of tafasitamab for use in the Cancer Drugs Fund.

The committee considered this point, including a revised patient access scheme, and the latest confidential discounts for comparator and subsequent treatments.

Tafasitamab with lenalidomide meets the end of life criteria

3.12 The committee reconsidered its decision that tafasitamab with lenalidomide does not meet the short life expectancy criterion (see section 3.8). It noted that the appeal panel had a different interpretation of section 6.2.10 of NICE's guide to the methods of technology appraisal 2013. The panel considered that the interpretation of the word 'normally' should be what NICE's stakeholders would reasonably expect the word 'normally' to mean. The appeal panel agreed with the appeal panel for NICE's technology appraisal guidance on avelumab that stakeholders would consider it unreasonable to find that life expectancy was not 'normally less than 24 months' if most people in a trial had died before 24 months, even if mean survival was greater than 24 months. The panel concluded that the dominant evidence used to determine this end of life criterion should reflect survival metrics that are the most meaningful to stakeholders. It also concluded that the 'less than 35% alive after 2 years' cited by the appeal panel for NICE's guidance on avelumab was not setting a precedent for a threshold for applying end of life criteria. The committee accepted the appeal panel's conclusion that the short life expectancy criterion was met. The committee therefore concluded that tafasitamab with lenalidomide meets the criteria to be considered a life-extending treatment at the end of life.

Tafasitamab with lenalidomide is not a cost-effective use of NHS resources

3.13 The committee considered that the most plausible ICER in the updated company base case was highly uncertain, because of issues with the indirect comparisons and modelling (see sections 3.4, 3.6 and 3.7). In considering the decision-making ICERs, the committee accounted for all the confidential discounts for comparator and subsequent treatments. This included the impact of the loss of price exclusivity on the price for lenalidomide. During the second committee meeting, it considered the live interim tender price for lenalidomide as provided by the Cancer Drugs Fund lead. It also considered pricing scenarios including the estimated price discount for generic lenalidomide up to and including a 100% discount (that is, no cost for lenalidomide). During the third committee meeting, the committee considered the nationally available

tender price for generic lenalidomide as confirmed by the Commercial Medicines Unit. The prices agreed through the framework are commercial in confidence. The committee noted that the company's and the ERG's base-case probabilistic ICERs (accounting for all the confidential discounts including lenalidomide) for tafasitamab with lenalidomide compared with polatuzumab vedotin plus bendamustine and rituximab were higher than the range normally considered a cost-effective use of NHS resources for treatments given at the end of life. The exact results cannot be reported here because they include confidential discounts for other treatments. The committee further considered that accepting the appeal panel's conclusion that the short life expectancy criterion is met created an inconsistency. The modelled survival with polatuzumab vedotin plus bendamustine and rituximab was inconsistent between:

- the company's and ERG's base cases (mean undiscounted survival of 29 and 48 months respectively) and
- the 10 to 13 months' real-world survival accepted by the appeal panel as reflecting expected survival.

The committee was not presented with ICERs based on a model with survival in the comparator arm closer to real-world expectations. The committee considered that such a change would have an impact on incremental costs and benefits. Survival for the polatuzumab arm is estimated by applying a hazard ratio to survival for tafasitamab (see section 3.6). Based on this relationship between tafasitamab and polatuzumab survival in the model, the committee concluded that ICERs reflecting real-world survival for polatuzumab were not likely to be lower than those in the company's base case. It was possible that these could increase markedly. So the committee concluded that the most plausible ICER was likely to be closer to the ERG's base-case estimates. It 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 for end of life treatments. The committee recognised the need for effective treatments in relapsed or refractory diffuse large B-cell lymphoma. But tafasitamab with lenalidomide had not been shown to be a cost-effective use of NHS resources in any analyses presented. So it concluded that tafasitamab with lenalidomide could not be recommended for routine use in the NHS.

The Cancer Drugs Fund inclusion criteria are not met

3.14 Having concluded that tafasitamab with lenalidomide could not be recommended for routine use, the committee reconsidered whether it could be recommended for use in the Cancer Drugs Fund. The committee still had the same concerns and conclusion as in section 3.10. It recalled that further evidence collection will not generate additional comparative evidence. The model would still rely on indirect evidence for comparator treatments, so this would not resolve a key uncertainty. Also, the committee was not presented with any analysis showing that tafasitamab with lenalidomide has the plausible potential to be cost effective. This was even taking into account the updated patient access scheme for tafasitamab and the decision that end of life criteria were met. So it concluded that tafasitamab with lenalidomide did not meet the criteria for inclusion in the Cancer Drugs Fund.

Tafasitamab is not innovative, based on the evidence presented

3.15 In response to the appraisal consultation document, the company highlighted that clinical experts had said in their submissions that they thought that tafasitamab with lenalidomide may have health-related benefits not captured in the QALY calculation. It explained that this could be because tafasitamab has a different mechanism of action to other treatments. It thought this could be a shift in the treatment paradigm for this condition, with the potential for longer treatment durations because of possibly more acceptable toxicity. The committee heard from clinical experts that tafasitamab with lenalidomide was considered to be innovative, but not necessarily a step change. The company said that tafasitamab with lenalidomide could have uncaptured benefits from less patient anxiety and improvements in carers' free time and wellbeing. It said that it also had the advantage of people being able to take it without needing an overnight hospital stay. The committee noted that section 6.3.3 of NICE's guide to the methods of technology appraisal 2013 says that to be considered innovative the technology should add 'demonstrable and distinctive benefits of a substantial nature which may not have been adequately captured in the reference case QALY measure'.

It concluded that, based on the evidence presented, this was not the case for tafasitamab.

Other factors

3.16 No equality or social value judgement issues were identified.

Conclusion

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

3.17 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 that tafasitamab with lenalidomide is 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 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

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