NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Tafasitamab with lenalidomide for treating relapsed or refractory diffuse large B-cell lymphoma [ID3795]

Committee Papers

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SINGLE TECHNOLOGY APPRAISAL

Tafasitamab with lenalidomide for treating relapsed or refractory diffuse large B-cell lymphoma [ID3795]

Contents:

The following documents are made available to consultees and commentators:

1. **Final appraisal document (issued August 2022)**

2. **Appeal panel decision**

Any information supplied to NICE which has been marked as confidential, has been redacted. All personal information has also been redacted.

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Final appraisal document

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

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 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

Issue date: August 2022

the survival times for people having polatuzumab vedotin plus rituximab and bendamustine used in the modelling do not reflect the 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.

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

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. 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 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 August 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. 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 would have a significant, positive effect on the quality of life of patients 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 bendamustine and rituximab 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., 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: 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 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. 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 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; 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 bendamustine and rituximab. The committee concluded 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 the polatuzumab vedotin with bendamustine and rituximab guidance.

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

Tafasitamab with lenalidomide does not meet the end of life criteria

3.8 The committee considered the criteria regarding 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. 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 section 6.2.10 in 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. 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 is a single arm phase 2 study of 80 patients (L-MIND). The relatively small size of this study, short median follow up (13.2 months) and lack of data comparing 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 those estimates in NICE's technology appraisal guidance on polatuzumab vedotin. The recent Northend et al. 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. (median survival 12.4 months) than the estimates from the polatuzumab vedotin guidance (X). 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 subsequently had chimeric antigen receptor T-cell therapy. The ERG acknowledged this aspect of the study but explained that it does not expect the impact on results to be large due to the low number of patients affected.

- **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. (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 patients 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 overall survival with tafasitamab from the company's base case and ERG's base case models (X and Y respectively).

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

- End of life criterion 2 was met. Despite uncertainty in the indirect comparisons and modelling, the estimated increases in mean survival with tafasitamab with lenalidomide are unlikely to be such overestimates that it is reasonable to conclude that it 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 at the considerable divergence between the estimates of survival from the literature and those from the guidance on polatuzumab vedotin. It was aware that measuring survival using means and medians often give different values, but the appeal panel in the avelumab appraisal 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 these would be such overestimates as to conclude that people who have polatuzumab vedotin in the NHS would have a life expectancy of less than 24 months.

The committee therefore 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) 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 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. 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 between the company's and ERG's base-case estimates, noting 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

The criteria are not 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. 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.

Additional benefits of tafasitamab with lenalidomide may not be captured in the QALYs, but were not estimated by the company

3.11 In response to the appraisal consultation document, the company highlighted that in submissions to NICE, clinical experts considered that tafasitamab with lenalidomide may result in health-related benefits not captured in the QALY calculation. The company explained that this could be because tafasitamab has a different mechanism of action to other treatments, representing a shift in the treatment paradigm for this condition, with the potential for longer treatment durations due to possibly more acceptable toxicity. The committee also heard from clinical experts that tafasitamab with lenalidomide is considered to be innovative, but not necessarily a step change. The company noted that uncaptured benefits of tafasitamab with lenalidomide may include reducing the impact of the condition on patient anxiety and carer time and wellbeing, as well the advantage of being administered in the outpatient setting. The committee noted the methods guide states 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 tafasitimab.

Other factors

3.12 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

3.13 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 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.

Stephen O'Brien
Chair, appraisal committee
August 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.

Owen Swales
Technical lead

Charlie Hewitt and Louise Crathorne
Technical advisers

Louise Jafferally
Project manager

ISBN: [to be added at publication]

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

APPEAL HEARING

Advice on Tafasitamab with lenalidomide for treating relapsed or refractory diffuse large B-cell lymphoma [ID3795]

Decision of the panel

Introduction

1. An appeal panel was convened on 14 November 2022 to consider an appeal against the final appraisal document (FAD), to the NHS, on tafasitamab with lenalidomide for treating relapsed or refractory diffuse large B-cell lymphoma [ID3795].

2. The appeal panel consisted of:

• Peter Groves	Chair
• Justin Whatling	Non-executive director of NICE
• Chris Rao	Health Service representative
• Kawitha Helme	Industry representative
• Catherine White	Lay representative

3. None of the members of the appeal panel had any competing interest to declare.

4. The panel considered appeals submitted by Incyte Corporation (Incyte), Lymphoma Action (LA), and a joint appeal from the National Cancer Research Institute, Association of Cancer Physicians and Royal College of Physicians of London (NCRI-ACP-RCP)

5. Incyte were represented by:

• Shevani Naidoo	Director Market Access UK, Incyte

	Corporation
• Patrick De Barr	Medical Director UK, Incyte Corporation
• Peter Williams	General Manager UK, Incyte Corporation
• Adela Williams	Legal Representative, Arnold Porter

6. LA were represented by:

• Tara Steeds	Policy and Public Affairs Advisor, Lymphoma Action
• Dallas Pounds	Director of Services, Lymphoma Action
• Zack Pemberton-Whiteley	CEO, Leukaemia Care
• Corrin Hoyes	Patient representative, Lymphoma Action

7. NCRI-ACP-RCP were represented by:

• Kate Cwynarski	Consultant Haematologist and Clinical Lead Lymphoma UCLH
• Andrew Davies	Director Southampton CRUK/NCRI Experimental Cancer Medicines Centre

8. In addition, the following individuals involved in the appraisal were present and available to answer questions from the appeal panel:

• Stephen O'Brien	Chair, Technology Appraisal Committee C, NICE
• Ross Dent	Associate director, NICE
• Natalie Hallas	Committee member, Technology Appraisal Committee C, NICE
• Owen Swales	Technical analyst, NICE

9. The panel's legal adviser Alistair Robertson, of DAC Beachcroft LLP, was also present.

10. Under NICE's appeal procedures, members of the public are admitted to observe appeal hearings and several members of the public and NICE staff observed the proceedings which were held via Zoom.

11. There are two grounds under which an appeal can be lodged:

Ground One: In making the assessment that preceded the recommendation, NICE has:

(a) Failed to act fairly; and/or

(b) Exceeded its powers.

Ground Two: The recommendation is unreasonable in light of the evidence submitted to NICE.

12. Mark Chakravarty, NICE Lead Non-executive Director for Appeals, in preliminary correspondence had confirmed that Incyte had valid grounds for appeal under Ground 1(a). He also confirmed that Incyte, LA and NCRI-ACP-RCP had submitted valid appeal points under Ground 2.

13. The appraisal that is the subject of this appeal provided advice to the NHS on the use of tafasitamab with lenalidomide for treating relapsed or refractory diffuse large B-cell lymphoma.

14. Diffuse large B-cell lymphoma (DLBCL) is a rapidly progressive disease. After initial treatment, 10-15% of people have refractory disease and 20-30% relapse after initial treatment. Relapsed or refractory DLBCL is treated using salvage chemotherapy followed by autologous stem cell transplantation if the person is fit enough for intensive therapy. The standard care for people who are not fit enough for transplant (50%), or whose disease relapses after a transplant (10-

20%), is polatuzumab vedotin with bendamustine and rituximab. Tafasitamab is a cytolytic CD19 antibody. It has a marketing authorisation in combination with lenalidomide for treating relapsed or refractory DLBCL and people who cannot have autologous stem cell transplantation.

15. The numbering of appeal points in this decision letter reflects those that were used during the hearing. Reference is also made to their corresponding number in the original appeal letters. The text of this letter does not represent a verbatim account of the proceedings nor a documentation of the order of events that took place but rather, provides a summary that has been agreed by the appeal panel of the appellant and committee submissions for the points that were discussed.

16. Before the appeal panel inquired into the detailed appeal points the following made preliminary statements: Shevani Naidoo on behalf of Incyte, Tara Steeds and Corrin Hoyes on behalf of LA, Andrew Davies on behalf of NCRI-ACP-RCP, and Stephen O'Brien on behalf of NICE.

17. The panel noted the personal and moving statement by Corrin Hoyes about her experience both as a person with relapsed DLBCL, and her experience supporting other people with refractory and relapsed DLBCL. The panel noted the significant implications for survival of refractory and relapsed DLBCL and the substantially reduced quality of life of people with refractory and relapsed DLBCL, their family and carers.

18. The appeal panel chair proposed in written correspondence prior to the appeal hearing that, given the similarity of the appeal points raised by each of the three appellants under ground 2, the appeal points under ground 2 would be heard together. No objections were raised by any participant.

Appeal Ground 1(a): In making the assessment that preceded the recommendation, NICE has failed to act fairly.

Incyte Appeal point 1(a)1: The recommendation was unfair because "the Committee has not taken loss of lenalidomide exclusivity and the associated impact on lenalidomide costs into account in the context of this appraisal".

19. Adela Williams, for Incyte, stated that NICE used the NHS list price for lenalidomide as the basis for its recommendations. She stated that the committee was aware from the outset that lenalidomide price exclusivity was ending and that the results of a national tendering process for generic lenalidomide could have been made available to the committee on request. She stated that as generically priced lenalidomide is now nationally available, the appraisal committee's conclusions are outdated even before guidance was issued. Adela Williams stated that it was procedurally flawed to rely on outdated pricing information.

20. Adela Williams stated that in the case of Ixazomib with lenalidomide and dexamethasone for treating relapsed or refractory multiple myeloma [ID1635], the appraisal committee had paused the appraisal process on 17 June 2022 until NHS England confirmed the new pricing policy for lenalidomide. She argued that this would have been a more appropriate way to evaluate the cost-effectiveness of tafasitamab with lenalidomide in the present appraisal.

21. Ross Dent, for NICE, in response to direct questioning about the approach and process that NICE use to ensure that the costs considered in cost-effectiveness analyses are truly reflective of NHS practice, stated that, given net price confidentiality, it is difficult to be transparent about exactly which costs are used. He noted that paragraph 3.9 of the Final Appraisal Document (FAD) says that all confidential discounts were considered. Ross Dent drew the appeal panel's attention to the slides from the confidential part of the second appraisal committee meeting which show that the committee had

considered the interim tender price for lenalidomide. He stated that the committee had considered the tender price for lenalidomide in all of the analysis on which it had based its decision making, although it could not report what that price was since it is highly confidential.

22. Asked to explain the steps taken to arrive at a price, Ross Dent explained that NICE had requested information from the NHS Commercial Medicines Unit (CMU) about the likely tender price for lenalidomide and were provided with indicative figures prior to the committee meeting in June 2022, including lowest and highest likely tender prices, on the understanding that NICE did not disclose these to the public or stakeholders. He stated that he was not aware if the indicative figures from the tender process supplied by the CMU were congruent with the final price. He said, however, that the committee had considered a scenario in which there was no charge for lenalidomide and that, even in this circumstance, tafasitamab with lenalidomide was not cost-effective.

23. Adela Williams stated that the evidence submitted by Ross Dent is not reflected in the FAD. She said that the FAD stated that the price used was the list price. She stated that there was no indication in the FAD that loss of exclusivity had been taken into account and that it was not clear that the committee had based its decisions on the indicative tender prices for lenalidomide. She stated that this is unsatisfactory and reflects a lack of transparency.

24. Ross Dent accepted that the FAD could be amended to make clearer that confidential prices including the indicative tender prices for lenalidomide had been considered by the committee.

25. Adela Williams, in response, submitted that stakeholders cannot evaluate on what basis tafasitamab is not cost-effective using the available information in the FAD. For example, she remained unclear how the indicative tender prices had been taken into account and

expressed the view that it is unclear whether application of End of Life (EOL) criteria would mean that the intervention would be considered cost-effective.

26. Owen Swales, for NICE, explained that paragraph 2.3 of the FAD does not say that the committee used the list price, it just states the list price. He stated that paragraph 3.9 of the FAD makes clear that confidential prices were used. He also said that para 3.9 of the FAD does mention that the company's and ERG's base case probabilistic Incremental Cost-Effectiveness Ratios (ICERs) (including all the confidential discounts) were higher than the range normally considered a cost-effective use of NHS resources, even for end-of-life treatments.

27. Adela Williams submitted that paragraph 2.3 of the FAD describes the costs for tafasitamab and list price for lenalidomide. She stated that whilst paragraph 2.4 of the FAD refers to the company commercial arrangement, no reference is made to anything other than the list price ever being considered for lenalidomide by the committee. She expressed the view that this did not meet the high standards for decision-making advocated by NICE.

28. Adela Williams stated that her understanding was that there were cost-effective scenarios when EOL criteria and a discounted price for lenalidomide were applied. She stated that from a company perspective the NICE decision-making process seems like a 'black box.'

29. Following questioning by the appeal panel, Ross Dent shared his reflections on communication, openness, and transparency in relation to the current FAD. He stated that the information in section 2 of the FAD is factual information about the price of the drugs to the NHS. At the time that the FAD was issued, the NHS tender process was not complete so the appraisal committee could not comment about this, and it could not be included in section 2.3 of the FAD. He stated that

the committee did consider scenarios with indicative tender prices and that could have been made clearer. He also explained that all of the ICERs, taking into account all of the discounts of various treatments in the modelling, were over the £50,000/QALY EOL threshold.

30. Ross Dent reiterated that paragraph 3.9 of the FAD is based on the interim tender price for lenalidomide that the committee were given.

31. Stephen O'Brien, for NICE, stated that given the constraints and confidences the appraisal committee have to observe, the second section of paragraph 3.9 of the FAD is the most informative it could be without revealing confidential information.

32. Owen Swales indicated that the drug prices had been checked the day before the appraisal committee meeting and the appropriate prices were used in the meeting. He stated that Peter Clark from the cancer drugs fund (CDF) also attended the meeting and provided live updates during the meeting.

33. Shevani Naidoo, for Incyte, submitted that the national tender would have been awarded by 1 September 2022, and so the tendered price would have been available at the time of publication of the FAD on 2 September. Ross Dent confirmed that the FAD was published on 2 September 2022, but also explained that it was circulated a week earlier to the company and other stakeholders.

34. Ross Dent explained that if the committee becomes aware that a change in the price of a drug under appraisal is imminent, it has the option to pause the appraisal process to take account of the new price. He observed, however, that drug prices change frequently so NICE need to be careful and selective about invoking a pause in appraisals on this basis. He clarified that on this occasion this was not relevant as the tender price was available for consideration.

35. Adela Williams expressed the view that it was very interesting that NICE had taken the loss of price exclusivity into account during this appraisal, but stated that this was not explained anywhere in the FAD. She stated that it was a defect in the transparency of that document. She stated that at the time that the FAD was published the NHS tendering process had not been completed.[1] She stated that in the case of Ixazomib with lenalidomide and dexamethasone for treating relapsed or refractory multiple myeloma [ID1635], NICE decided to pause the appraisal until after 30 September 2022 when the generic price for lenalidomide would be available. She stated that it cannot be right to pause one but not another appraisal under similar circumstances. She considered that the appraisal process had been opaque, with no transparency about the approach NICE had taken. She suggested that the principal reason for pausing would be so that actual data can be used, and stakeholders can be given transparent information. She said NICE does have the option of publishing ICER ranges which was not done in this case. She stated that this could have been done and would have prevented the current situation where there is no way for stakeholders to form a view on the committee's conclusions about cost-effectiveness.

36. Owen Swales stated that whilst he had not been involved in the Ixazomib appraisal, he suspected that the committee had paused the appraisal because the change in lenalidomide price could have moved Ixazomib (with lenalidomide and dexamethasone) into a cost-effective ICER range. He stated that in this appraisal, the committee covered this eventuality by considering the modelled cost-effectiveness of tafasitamab with no cost for lenalidomide.

[1] While Adela Williams stated this, in fact the new tender price became available on 1 September 2022, and the FAD was published on 2 September 2022

37. Owen Swales stated that from the beginning of the appraisal, NICE was aware of the imminent arrival of the new tendered lenalidomide price. At each stage of the appraisal process, the price was checked, and the most up-to-date price was used. He explained that the FAD stated that confidential price reductions were included in the analysis and that was all that could be stated. He submitted that, in this regard, the hands of the appraisal committee were tied, but NICE had made it clear throughout that confidential prices were included in its analysis.

38. In response to questioning by the appeal panel about what information was shared with stakeholders about the tendering process, Owen Swales stated that whilst he could remember discussion of the tendering process in the second (confidential) part of the second committee meeting he could not remember if it had been mentioned in the first part.

39. The appeal panel concluded as follows:

40. The appeal panel reminded itself that the appeal point was that the recommendation was unfair because “the committee has not taken loss of lenalidomide exclusivity and the associated impact on lenalidomide costs into account in the context of this appraisal.”

41. The appeal panel were satisfied that, based on the oral evidence presented, the committee had taken appropriate steps to ensure that the appraisal was informed by the most relevant and current estimates of the cost of lenalidomide to the NHS and had therefore appropriately taken loss of lenalidomide exclusivity and the associated impact on lenalidomide cost into account.

42. The panel accepted that it is clear, from the oral evidence presented in the appeal hearing and the confidential slides presented in the second part of the appraisal committee meetings, that the cost-effectiveness analysis had considered both the tendered cost of generic lenalidomide

and a scenario analysis in which lenalidomide was used at no cost at all.

43. The appeal panel were satisfied, based on the oral evidence presented in the appeal hearing and the confidential slides from the second part of the appraisal committee meetings, that tafasitamab with lenalidomide for treating relapsed or refractory DLBC was not cost-effective in any scenario, even when lenalidomide was considered at no cost at all and when EOL criteria (a cost-effectiveness threshold of £50,000/QALY) were applied.

44. The appeal panel concluded, therefore, that there was no evidence of procedural unfairness on this issue and dismissed the appeal point.

45. While the panel acknowledged that the FAD must not disclose confidential pricing information, the appeal panel recommended that NICE consider amending the wording of section 2 and section 3.9 of the FAD to better reflect the efforts that had been made to acquire the most relevant estimates of medication costs to the NHS and the extensive sensitivity analyses undertaken on behalf of the appraisal committee.

Incyte Appeal point 1(a)2: The recommendation was unfair because "the Committee's conclusions regarding the cost-effectiveness of tafasitamab and lenalidomide lack transparency"

46. Adela Williams, for Incyte, stated that the requirement for transparency is trite law i.e. self-evident and widely accepted. She explained that transparency has previously been considered by the courts, including with reference to NICE. Adela Williams argued that transparency is important because firstly, it is a marker of rigorous decision making and secondly, because it allows stakeholders to understand why they have been unsuccessful in their application. She acknowledged that transparency is more challenging when confidential information is involved, however, in those circumstances, NICE procedures allow for the publication of ICER ranges.

47. Adela Williams submitted that in the case of this appraisal, the FAD states that the ICER is higher than the range normally considered cost effective. She argued that whilst it may not be possible to report exact ICER results because of confidential discounts, no explanation was given for the failure to disclose ICER ranges. She stated that Incyte were informed by NICE that there was no requirement to report ICER ranges because all were higher than the cost-effectiveness threshold. Adela Williams argued that this was not consistent and that it is impossible to understand the decision or make any progress to achieve a positive outcome.

48. Ross Dent, for NICE, explained that maintaining both transparency and confidentiality is a very difficult line to tread. He stated that NICE try to ensure that all of the scenarios the committee consider are reported transparently in the slides for the public section of the committee meetings, even if the detailed results of those scenarios cannot be specified.

49. Ross Dent stated that paragraph 3.9 of the FAD confirms the company and ERG base case ICERs were above the cost-effectiveness threshold. This meant that the company were aware of the lower estimate of the most plausible ICER range (i.e., the company's base case ICER) but that this ICER could not be reported in the FAD because the company retains confidentiality on this issue.

50. Ross Dent explained that NICE have had discussions with the Association of the British Pharmaceutical Industry (ABPI) about whether tighter ICER ranges, for example ranges to the nearest £10,000/QALY, could be presented in guidance when confidentiality is an issue. He stated that unfortunately no agreement has been reached on this, and that whilst the company under appraisal may want tighter ICER ranges quoted, this represents an increased risk of breaching a confidential pricing discount for the companies that produce comparator drugs.

51. Ross Dent suggested that there is a trade-off and a need for NICE to balance transparency with the benefit to the NHS of companies being willing to offer confidential pricing discounts in order to enable patient access to therapies.

52. The appeal panel sought clarification from NICE about how it addresses the balance between transparency and confidentiality in regard to the publication of ICER ranges in the FAD bearing in mind that section 3.1.22 of the NICE Guide to the processes of technology appraisal, states that: “Although the results of these analyses are classed as commercial in confidence, NICE will have to publish an ICER range that informs the recommendation(s), after taking into account the exact level of the discount provided in the commercial arrangement for the comparator”.

53. Ross Dent stated that the agreement NICE currently has with the ABPI is that ICERs derived from confidential pricing agreements can only be reported with reference to the accepted cost-effectiveness thresholds (less than £20,000/QALY, £30,000/QALY, or £50,000/QALY).

54. Adela Williams expressed the view that this approach significantly compromises transparency. She submitted that when there are multiple confidential discounts, such as in this appraisal, it makes it easier for NICE to provide more helpful and clearer information about ICERs than is provided in the current FAD without giving away any particular discount. She argued that this opportunity had not been taken in this FAD.

55. In response, Ross Dent explained that while it may be possible to do this when there are multiple discounts, NICE make the health economic model available to other stakeholders (which makes it easier to look at multiple variables) and there is therefore still a risk of compromising confidential information in doing so, particularly if the model is linear. He stated that it is therefore difficult to be confident that NICE can

provide a tighter range without jeopardising any confidential pricing discount.

56. Following questioning from the appeal panel, Ross Dent stated that it should be clear to the company what the lowest value of the upper ICER range was since they have access to their own discounts and know that the ICERs will increase if discounts are applied to comparators as well.

57. Owen Swales, for NICE, added that paragraph 3.9 of the FAD describes how uncertainty also prevented NICE from specifying a numerical range and moved NICE away from specifying numbers.

58. Adela Williams explained that knowledge of the upper boundary of the ICER range is important to the company and that the Courts have indicated that NICE has a particular requirement to do everything it can within its powers to make information available about its decision-making. She argued that this includes responding to requests for disclosure of information. She concluded that the FAD in this appraisal did not disclose sufficient information to understand the committee's conclusions.

59. Ross Dent stated that Incyte were asked to agree to the disclosure of information that would allow more detail to be given about ICER estimates in the FAD, but had declined to do so.

60. Shevani Naidoo, for Incyte, stated that transparency about the price of tafasitamab was not material to the decision-making of the company, but, rather, the company were trying to understand what the price discounts were for lenalidomide and polatuzumab vedotin.

61. Adela Williams asked if any effort was made to understand whether disclosure of narrower ICER ranges would have been acceptable to other companies involved.

62. Ross Dent explained that NICE did not and do not routinely approach other stakeholders about these issues. Furthermore, he stated that Shevani Naidoo had said that the company wanted more information to enable them to calculate the discount for lenalidomide and polatuzumab vedotin, but that this is highly confidential information, and it is exactly for this reason that more information on the ICER ranges could not be disclosed.

63. Stephen O'Brien, for NICE, explained that in principle, NICE would like to make more information available and that similar discussions take place regularly in technology appraisal committee meetings since there is a recurring tension between, on the one hand, getting value-for-money by acquiring price discounts, and on the other, the need for transparency.

64. Stephen O'Brien stated that consistency with other appraisals is also an important consideration for the committee and that NICE often state in FADs that the most plausible ICER is considerably above the usual threshold.

65. The appeal panel concluded as follows:

66. The appeal panel acknowledged that specific ICER estimates represent commercially confidential and potentially valuable information, allowing stakeholders with appropriate expertise and knowledge of model structures the opportunity to back-calculate the cost of undisclosed model parameters such as the discounted cost of comparator therapies manufactured by competitors.

67. The appeal panel were satisfied that disclosure of the numerical upper and lower limits of the most plausible ICER range could have resulted in the inadvertent disclosure of confidential information about the pricing discounts of lenalidomide and polatuzumab vedotin in this appraisal.

68. The panel noted the reluctance of Incyte to allow public disclosure by NICE of the lower boundary of the plausible ICER range and considered that this illustrated the commercially sensitive nature of this information.

69. The appeal panel considered carefully the responsibilities of NICE in balancing transparency with confidentiality in their approach to publishing specific ICER ranges in FADs. It recognised the responsibility of NICE committees to take all reasonable steps to publish relevant information in the FAD to explain their decision-making around cost effectiveness, without compromising commercial confidentiality.

70. From the evidence presented in this hearing, the panel were satisfied that the committee had given sufficient information to comply with the NICE process guide with regard to the need for the publication of ICER ranges and that they had provided as much information as they could in the FAD by referring to the (non-numeric) most plausible ICER range without compromising commercially sensitive information.

71. The appeal panel concluded, therefore, that there was no evidence of procedural unfairness on this issue and dismissed the appeal point.

Appeal Ground 1(b): In making the assessment that preceded the recommendation, NICE has exceeded its powers.

72. There was no appeal under this ground.

Appeal Ground 2: The recommendation is unreasonable in the light of the evidence submitted to NICE.

Incyte Appeal point 2.1: The recommendation is unreasonable because "the Committee's conclusion that patients eligible for treatment with tafasitamab and lenalidomide do not meet the end-of-life criteria does not reflect the balance of the available evidence"

LA Appeal point 2.1: The recommendation is unreasonable because "the Committee's conclusion that patients eligible for treatment with

tafasitamab and lenalidomide do not meet the end-of-life criteria does not reflect the balance of the available evidence"

NCRI-ACP-RCP Appeal point 2.1: The recommendation is unreasonable because "it is unreasonable to conclude that the short life expectancy criterion of the end-of-life policy is not met"

73. Patrick De Barr, for Incyte, explained that the key data used by the committee to estimate the life expectancy of people with relapsed or refractory DLBCL treated with conventional therapy was from TA 649 (Polatuzumab vedotin with rituximab and bendamustine for treating relapsed or refractory diffuse large B-cell lymphoma). He stated that this review had been undertaken in 2019-2020 and was based on a very small study. Patrick De Barr stated that the trial was underpowered but represented the best available evidence at the time.

74. Patrick De Barr described that since 2020, several new studies have reported survival data, and these were presented to the committee. Furthermore, he submitted that experts using polatuzumab in clinical practice consider that estimates of survival used in TA649 were optimistic. He stated that median survival in the relevant population is 8-12 months in contrast to the four years mean survival reported in TA649. Furthermore, he explained that in the appeal panel hearing on avelumab (TA788 - avelumab for maintenance treatment of locally advanced or metastatic urothelial cancer after platinum-based chemotherapy) the panel concluded that all relevant data, including mean, median and clinical judgement were relevant in considering life expectancy to inform decisions about the applicability of EOL criteria. He stated that in the view of Incyte, it would not be possible to explain to patients why they were considered to have a life expectancy of greater than two years.

75. Zack Pemberton Whitely, for LA, stated that the appraisal committee chose to use estimates of mean rather than median survival. He expressed the view, however, that the median was the most appropriate because the interpretation of the word "normally" in the

NICE EOL criteria should be what is considered reasonable according to the interpretation of stakeholders, and what would be explained to patients. He stated that it would be hard to argue that patients or clinicians would consider that the appraisal committee's interpretation of the word "normally" was reasonable.

76. Zack Pemberton Whitely submitted that the median survival for patients with relapsed or refractory DLBCL treated with conventional therapy in all the models was significantly less than 24 months so that the majority of patients were not alive at 24 months. He pointed out that all experts consulted had reported that they would not explain to patients in this situation they would be likely to be alive after 24 months. He submitted that the evidence presented to the committee showed that polatuzumab vedotin median survival is 10.2 or 12.4 months and lower than that assumed in TA649, and that normal survival is therefore far below 24 months.

77. Zack Pemberton Whitely concluded that it was not possible or reasonable for the appraisal committee to conclude that someone with relapsed DLBCL would normally be alive 24 months later. He expressed the view that the committee had erred by choosing mean survival over median survival in considering the applicability of EOL criteria and that the decision was therefore unreasonable.

78. Kate Cwynarski, for NCRI-ACP-RCP, stated that clinicians think of survival in terms of months rather than years for this cohort of patients since a very small number of patients are expected to live beyond two years. Polatuzumab vedotin offers palliation. She estimated that a median survival of 10.2 months accurately reflects her own clinical practice experience.

79. Kate Cwynarski informed the hearing that she had been involved with the TA649 appraisal as a clinical expert. She stated that she had tried to review all of the data, but, as a clinician, had found it challenging to

be able to judge whether the models that were presented were reasonable. She recalled that the ERG in that appraisal had produced very optimistic survival curves that were difficult to refute with such scant data but nonetheless, from her own practice, would expect patients to survive less than 24 months when treated in this situation with polatuzumab vedotin.

80. Stephen O'Brien, for NICE, referred the appeal panel to the slides presented at the second appraisal committee meeting during which EOL criteria were discussed. He clarified that for this appeal, the EOL criterion that survival should normally be less than 24 months was the one under consideration since there was agreement that the treatment offers an extension of life of at least 3 months. He explained that if both criteria were met, it changed the willingness-to-pay threshold from £20-30,000/QALY to £50,000/QALY

81. Stephen O'Brien explained that five factors were considered by the committee in regard to expected survival, the first of which was median survival. He stated that while many stakeholders consider that median survival is most clinically relevant and forms the basis of discussions between clinicians and patients, the NICE methods guide does not mandate that median survival should be used to inform decisions about the applicability of EOL criteria. Nonetheless, he acknowledged that all estimates of median survival considered by the committee were less than 24 months.

82. Stephen O'Brien explained that the second metric that was considered by the committee was mean survival. He explained that the mean survival is preferred in health economic analysis since some patients live a long time and accrue considerable additional costs. He noted that all estimates of mean survival considered by the committee were more than 24 months.

83. Stephen O'Brien explained that the third factor that was considered by the committee was the percentage of patients alive at two years. He stated that the appraisal committee considered this very carefully and noted that in paragraph 87 of the avelumab appeal judgement, the appeal panel considered that it was reasonable to conclude that life expectancy was 'normally less than 24 months' since 65% of patients had died at 24 months. He stated that the appeal panel had been presented with figures of 34% to 44% of patients alive after 24 months (i.e., between 66% and 56% of patients had died at 24 months).

84. Stephen O'Brien, for NICE, explained that the fourth and fifth considerations of survival that were considered by the committee were the opinions of experts and the published 'real-world' data.

85. Stephen O'Brien acknowledged that the appraisal committee had accepted that TA649 may have overestimated survival in this patient population, but after very careful consideration of all of the evidence, the appraisal committee concluded that EOL criteria had not been met. He stated that, while the health economists preferred the use of mean survival, this was not the only consideration. He further acknowledged that the use of median survival carries more weight in clinical discussions with patients, and that while 'real world' data and expert opinion were considered relevant by the committee, they were given less weight in the decision-making than the consideration of 'hard data.'

86. Following questioning by the appeal panel, Stephen O'Brien stated that 'real world' data were derived from single arm phase 2 trials with inherent limitations and potential sources of bias and confounding factors that fall short of comparative randomised controlled evidence. Nonetheless, he explained that in the absence of comparative studies, the 'real world' data was considered and certainly not dismissed by the committee. Stephen O'Brien was later asked by the appeal panel if the appraisal committee were concerned about any particular weaknesses

in the single-arm studies considered but he was unable to recall any specific bias or confounding factors.

87. Andrew Davies, for NCRI-ACP-RCP, stated that the Northend et al 2022 study collected data from 28 sites and that 78 patients met the inclusion criteria. He explained that this study represents a good selection of 'real-world' clinical data derived from UK institutions that deliver care that is representative of NHS practice. He stated that the NHS adviser involved in the appraisal initially considered it unrepresentative of the relevant population for this review, but he forwarded a contrary opinion himself.

88. Andrew Davies explained that the mean survival will always be affected by 'super-responders' that do not behave as the rest of the patient population would be expected to. He stated that for this reason, it is much more helpful to consider median survival in clinical practice.

89. Patrick De Barr submitted that the conclusions about expected survival with conventional treatment that were presented in TA649 were based on a very small phase 2 study with no control arm and could therefore not reasonably be considered 'hard data'. He stated that the only 'hard' evidence available was the objective response rates contained in the evidence that led to marketing authorisation. He expressed the view that less weight in determining survival should be given to TA649 and more weight should be given to 'real world' data.

90. Patrick De Barr explained that Sehn et al 2022 reported outcomes from a cohort in which a number of patients went on to receive Chimeric antigen receptor T-cell (CAR-T) therapy and that in the tail of the study, only 9 or 10 patients were still alive by the end. He suggested that some of these may have been 'super responders' or had received CAR-T therapy, so more weight should be placed on 'real world' evidence.

91. Zack Pemberton-Whiteley submitted that the explanation for why the committee's approach to considering 'normally' expected survival in this appraisal differed from previous NICE appraisals had not been clearly explained in the FAD. He stated that the critical issue, as explained in the avelumab appeal judgement, is the question about what would be considered as a survival of 'normally' less than 24 months by patients and clinicians and he made the point that it would be difficult to communicate to patients and clinicians what clinically expected survival is if this was not clearly explained in the FAD.

92. Ross Dent, for NICE, suggested that the appraisal committee's conclusions in the EOL paragraph of the Appraisal Consultation Document (ACD) were very clear and he explained that NICE had received comments on that paragraph from the company and other stakeholders which were considered in the second committee meeting.

93. Owen Swales, for NICE, stated that the ERG acknowledged that the effect of CAR-T therapy may have disproportionately prolonged survival in a small number of patients leading to an overestimation of overall survival in the whole cohort, although this effect was not expected to be large.

94. Stephen O'Brien accepted that the conclusions about survival in TA649 were based on a small single arm phase 2 study but he explained that the present appraisal was undertaken by a different committee who were not obliged to follow the same thinking. He further stated that the appraisal committee acknowledged that modelled survival with polatuzumab vedotin in this clinical situation in TA649 was optimistic.

95. Ross Dent stated that TA649 was completed relatively recently and was not regarded as historic. He pointed out that it had been undertaken according to NICE process and methods and was based on the best evidence available at the time. He submitted that the committee made it clear in the FAD that it was likely to have presented

an optimistic estimate of survival, so it was correct to reduce these. He added that even if a pessimistic estimate of survival was concluded from the company model, a mean survival of 29 months was still longer than the EOL threshold.

96. Adela Williams, for Incyte, stated that paragraph 3.9 of the FAD gives reasons for the rejection of the company's ICERs, but the only reason given is that the committee considered the company base case was not plausible because modelled outputs were not consistent with TA649. She submitted that the reliance of the committee on the conclusions of TA649 had been extensive and important despite what was now being described to the appeal hearing.

97. Andrew Davies stated that he could see no indication that new published evidence since TA649 had been taken into account during this appraisal.

98. Stephen O'Brien responded that the appraisal committee had looked at updated data from Sehn et al 2022, which had focused on estimates of median survival.

99. Natalie Hallas, for NICE, stated that the committee were presented with an evidence package in regard to estimated survival and had considered the totality of that evidence. She stated that the committee were aware of the additional published evidence that was submitted to them but had concluded that not all of that was relevant to the population under consideration. She explained that "normally" in this context would be taken to be the mean survival derived from a valid cost-effectiveness model. She stated that the committee had indeed considered 'real-world' data, published data, patient, and expert opinions, and also the percentage of patients alive at 2 years. She stated that both the ERG base case and Company base case had reported modelled means over 24 months, so these data were also available for considerations. She concluded that she did not think that

the appraisal committee had placed undue weight on TA649 in coming to its decisions about 'normally' expected survival and that whilst the committee knew that it was an optimistic estimate of survival, they thought it was unlikely that true survival would be as little as half of the survival modelled in TA649.

100. Following questioning from the panel, Natalie Hallas explained that the committee were mindful of previous NICE appraisal decisions but needed to evaluate the evidence presented to them in this appraisal and make their own decisions. She explained that NICE typically use mean survival in this situation and that while she appreciated that the median survival is easier to understand and is used in trials, the mean survival is more meaningful in capturing all of the costs and benefits rather than just a single point in time.

101. Shevani Naidoo, for Incyte, stated that the company model and evidence submission was made towards the end of 2020 and that this was the best available evidence at that time. She explained that Sehn et al 2022 included longer follow-up and survival rates, but the company was not able to include these in their original submission.

102. Patrick De Barr stated that the fact that 62% of patients were no longer alive at 2 years was very similar to the 65% cited in the avelumab appeal. He stated, however, that there is significantly more uncertainty in this appraisal about survival rates since the avelumab analysis was based on evidence that included 700 patients, while in this appraisal the numbers were much smaller. He also stated that since some patients had received CAR-T therapy, of which the ERG concluded the impact was small, it is difficult to know how many patients were alive at 2 years. For these reasons, he submitted that more weight should be placed on other evidence sources.

103. Stephen O'Brien expressed the view that the "35% alive after 2 years" was a useful threshold that the appraisal committee had used on

several occasions since the avelumab appeal. He stated that the outcome of that appeal had been very clear and carried significant weight in the minds of the committee in their decision-making. In regard to estimates of survival, he cited 3 sources of data for the percentage of patients alive at 2 years: Sehn et al 2022 reported 38%; the company model (which did not include updated Sehn data) reported 34%; and the ERG model reported 44%. He submitted that the threshold of normally expected 2-year survival in regard to the consideration of EOL criteria in the avelumab appeal decision was 35%. He concluded that 2 data sources considered by the committee were above 35% and one very slightly below. For this reason, and also taking into account rates of means and median survival presented, the appraisal committee had concluded that the EOL criterion had not been met.

104. Stephen O'Brien expressed the view that the word 'normally' in the EOL criterion is open to interpretation. He explained that the committee had thought very carefully about the conclusions of the appeal panel in the avelumab appeal, including the very specific number of 65% of people who had not survived to 2 years being considered to be a sufficient "majority" to lead to a conclusion that patients would not normally be alive at 2 years. He explained that the committee had concluded that it did not feel able to come to a new definition of 'majority' in the face of the avelumab appeal decision, but (as above) he accepted that the use of the term 'normally' is open to interpretation.

105. Following questioning by the appeal panel, Stephen O'Brien stated that the committee had considered the opinions of clinical experts who had expressed disagreement with the expectation that people treated with polatuzumab vedotin in this clinical situation are likely to live more than 2 years. He stated that the appraisal committee had considered these opinions carefully but had concluded that they should come to their

decision about survival on the basis of the best available evidence in a manner that was objective and as robust as possible.

106. Kate Cwynarski stated it was very helpful to hear and consider patient experiences in undertaking such appraisals. She explained that she has concluded from the published evidence that overall survival in this cohort of patients at 2 years is 25-35% and that this informs her discussions with individual patients. She would not be unduly influenced by the results of an optimistic economic model undertaken by the ERG. She concluded that while she does not have any robust evidence on which to base a conversation with a patient about their expected survival, she would think of it in terms of months.

107. Andrew Davies stated that accepting the committee's interpretation of two-year survival rates for this cohort of patients would completely change the framework of conversations he has with patients and would raise patient expectations unrealistically. He stated that if this appeal point is not accepted, the reasons would need to be very carefully explained to patients and relatives since a conclusion of expected survival normally beyond 24 months flies in the face of everything he currently tells patients.

108. Dallas Pounds, for LA, stated that it is not their experience that people survive beyond 2 years with relapsed or refractory DLBCL. She explained that LA support people from the time of their diagnosis to the end of their lives. She suggested that in the absence of reliable 'hard data' maybe the best approach should be to listen to stakeholders who 'walk alongside' these people.

109. Stephen O'Brien concluded that he finds it hard to disagree with clinical colleagues about the clinical utility of median survival rates. He also explained that he talks to patients about trial data in his day-to-day role as a clinician and often uses those data points. He stated, however, that the committee is charged with looking at cost-effectiveness as well

as clinical effectiveness, and that mean data is very important in informing decisions about cost-effectiveness. He explained that the drugs under consideration in this appraisal are very expensive and that if the committee were to only consider median survival rates, they would not be doing their job properly.

110. Zack Pemberton-Whiteley expressed the view that the appraisal committee had interpreted the appeal panel judgement for avelumab incorrectly and too rigidly. Citing paragraph 87 of the previous appeal panel judgement, he submitted that the appraisal committee were incorrectly interpreting the 65% figure of 2 year mortality in the avelumab appeal judgement as a threshold of reasonableness rather a figure that happened to be true in the case of the avelumab appraisal appeal and which was being used to illustrate the unreasonableness of the original appraisal committee decision.

111. Shevani Naidoo submitted that the ERG model predicted 44% 2-year survival rate was driven by a desire for consistency with TA649 in decision-making between appraisals.

112. Patrick De Barr expressed the view that the totality of the evidence needs to be considered. He concluded that there was a large gap between median and mean 2-year survival rates and noted that the ERG themselves had stated that results of TA649 appear to be invalid. He concluded that the survival figure in TA649 is an outlier, and he drew the appeal panel's attention to the table of all the evidence that Incyte had submitted during the appeal process and suggested that it showed remarkable consistency with median 2-year survival rates. He also concluded that it was unreasonable to rely, in decision-making, on an ERG model which they themselves had concluded was invalid.

113. Owen Swales explained that the ERG had not used conclusions from TA649 as the starting point in estimating 2-year survival but had used them to validate their own estimates.

114. Stephen O'Brien added that the committee had agreed that the ERG overall survival mean was not reasonable and that they "didn't hang our hat completely" on that modelling. He stated that the company's own model showed a mean survival of 29 months. He acknowledged the company's position that if they had had the most recent Sehn et al 2022 data, their modelled mean might have been different, but the committee had to consider the data that was presented to them. He further stated that even if the ERG modelled mean data were dispensed with altogether, the 2-year survival rates of 34% and 38% are close and the committee agonised about the appropriate percentage to settle on. He said the committee acknowledges that the figure of "35% alive after 2 years" considered in the avelumab appeal is somewhat arbitrary, but reiterated it is useful to have as a figure. He concluded from this discussion that "it's almost dancing on the head of a pin, but 38% is higher than 35%" and that it is difficult to resolve, given uncertainties about 2-year survival rates.

115. Following questioning from the appeal panel regarding whether, having noted the relevance of the mean for health economics, the committee applies the EOL criterion "independent of the health economics", Stephen O'Brien stated that the committee put a lot of weight on means, partly because this is important in health economics, but it also listens to clinicians and tries very hard to weigh everything up.

116. Following questioning from the appeal panel as to exactly how the committee interpret the EOL criterion ("The treatment is indicated for patients with a short life expectancy, normally less than 24 months"), and in particular whether the committee assesses against 24 months or "short life expectancy", Stephen O'Brien stated that 24 months is used fairly rigidly by the committee as the criterion to be met in its decision-making, although a more flexible approach is taken to considering whether data provided to the committee meets that criterion.

117. Ross Dent added that there have been occasions in previous appraisals when the committee have agreed that the long-term survival of relatively few patients is contributing to a mean survival over 24 months, and on that basis have decided the EOL criterion is met.

118. Patrick De Barr expressed the view that this is exactly the case in this appraisal in which a small number of 'super responders', including those who may have had CAR-T, are influencing the mean survival.

119. Kate Cwynarski made the point that patients encountered in 'real world' clinical practice tend to be different to those included in clinical trial cohorts. 'Real world' data tends to report outcomes that are a bit worse than those seen in the trials.

120. Adela Williams stated that she has been listening to NICE appeals for 20 years and reported that many submissions have been made on the basis of the results of RCTs which are over optimistic because they do not reflect 'real world' practice. She submitted that the avelumab appeal decision stated that there was not a requirement to use the same methodology that is used for analysing cost-effectiveness when assessing EOL criteria. Instead, she submitted that decisions on EOL should reflect the 'real world' since EOL reflects the experiences of clinicians and patients.

121. Stephen O'Brien stated that the 'real-world' data from Northend et al 2022 showed a median survival of 10.2 months but the paper did not report a mean survival or a proportion of patients who were alive at 2 years, so the committee certainly considered that evidence but came to its conclusion based on the entirety of the wider evidence.

122. The appeal panel concluded as follows:

123. The panel reminded itself that the EOL criteria in paragraph 6.2.10 of the NICE's methods guide 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.

124. As to the latter criterion, the appeal panel noted that there was a consensus between the appellants and the appraisal committee that an improvement in survival of in excess of three months resulted from treatment with tafasitamab with lenalidomide in refractory or relapsed DLBCL. There was therefore agreement that this EOL criterion had been met in this appraisal.

125. The appeal panel then considered the arguments regarding the meaning and application of the former criterion ("the treatment is indicated for people with a short life expectancy, normally less than 24 months") in detail. The appeal panel noted that there was agreement between the appellants and the appraisal committee that the evidence considered in this appraisal showed a median survival for people with refractory or relapsed DLBCL of significantly less than 24 months but that the modelled mean survival was greater than 24 months.

126. The appeal panel noted that the NICE Methods guide and the NICE Decision Support Unit (which provides NICE with technical support on the implementation of methods and reporting standards, and advice on methods development) do not specify how the word "normally" should be interpreted. Furthermore, the appeal panel noted that in previous NICE appraisals both the mean and median survival have been considered.

127. The appeal panel were aware that the NICE EOL criteria were founded on the principles in NICE's "guide to the use of Social Value Judgements". Consequently, the panel concluded that when interpreting and applying the EOL criterion, the paramount

consideration should be what the key stakeholders of NICE (i.e., the public, patients, relatives of patients, clinicians, policy makers and industry) would reasonably expect the word “normally” to mean. In this regard, the appeal panel agreed with the conclusion of the previous avelumab appeal panel that where a significant majority of patients had died prior to 24 months, NICE stakeholders would consider it unreasonable to find that life-expectancy was not “normally less than 24 months”, even if the mean life expectancy was greater than 24 months.

128. In the case of patients with refractory or relapsed DLBCL for whom treatment with tafasitamab and lenalidomide is indicated, the appeal panel noted that recently published ‘real-world’ data suggests that the significant majority of patients will have died within 10-13 months if they received conventional comparator treatment.

129. Appeal panels are not bound by the decisions of previous appeals, but the appeal panel acknowledged the value of a consistent approach and of identifying rational reasons for a change in approach. The appeal panel considered that the figure no more than “35% alive after 2 years” cited by the appeal panel in the avelumab appeal was intended by that panel to illustrate the panel’s view that it was unreasonable of the NICE recommendations on avelumab to conclude that life expectancy was in excess of 24 months when a significant majority of patients had died at 24 months. The panel agreed that the intention of the appeal panel in avelumab had not been to set a precedent or define a new numerical threshold that should be used in future NICE technology appraisals applying the EOL criteria. Therefore, they considered the relevant test remained that set out in NICE’s Methods guide, i.e., “the treatment is indicated for patients with a short life expectancy, normally less than 24 months.” As described above, the appeal panel considered that this test should be applied in line with the reasonable expectations of NICE’s stakeholders, who would likely consider that where a significant

majority of patients had died prior to 24 months, life-expectancy is "normally less than 24 months".

130. In applying the evidence against this test, the panel understood the rationale for the preference of the committee, in this appraisal, to use the mean survival as the dominant consideration to inform the decision that the EOL criteria were not met, in view of the health economic implications of doing so. It concluded, however, that since the evidence showed that the median survival for patients with refractory or relapsed DLBCL is consistently less than 2 years and the significant majority of patients with this condition have died before 2 years, the committee's conclusion that the treatment does not meet the EOL requirement because it is not "indicated for patients with a short life expectancy, normally less than 24 months." does not adequately reflect how NICE's stakeholders would reasonably interpret and apply this criterion, as set out above .

131. The appeal panel considered that NICE's stakeholders would reasonably expect that the dominant evidence in determining qualification for the EOL criterion should reflect metrics of survival that are the most meaningful to patients, relatives, carers, clinicians, and the general public. In this regard, it noted the consistent evidence in the appraisal and hearing submitted by clinical and patient experts who referred to survival in the 'real world' that is considerably less than the modelled mean survival and more in keeping with the median survival reported in the literature.

132. The appeal panel, concluded therefore, that the committee decision that the first EOL criterion was not met in this appraisal was unreasonable in light of the evidence submitted to NICE and upheld the appeals on this point.

Incyte Appeal point 2.4: The recommendation is unreasonable "for NICE not to recommend tafasitamab and lenalidomide for use through the Cancer Drugs Fund (CDF) on the basis of the Committee's conclusion

that any further evidence gathered would not address evidential uncertainties identified in the appraisal."

133. Shevani Naidoo, for Incyte, stated that throughout the appraisal, the committee had criticised the single-armed L-MIND study but she explained that this study had not originally been intended to be the basis of registration. She explained that L-MIND became the basis for registration following positive trial outcomes, which had subsequently led to the Medicines and Healthcare products Regulatory Agency (MHRA) and the European Medicines Agency (EMA) granting immediate registration for tafasitamab. She stated that this was driven by the patient benefits that would follow from immediate access and argued that there was no basis for mandating the undertaking of a randomised controlled trial. Consequently, she submitted that it was unreasonable to deny access to the CDF simply because this would not allow the generation of comparative clinical efficacy data. She expressed the view that entry into the CDF would allow other uncertainties to be addressed.

134. Stephen O'Brien, for NICE, stated that there was uncertainty in the minds of the committee members about the clinical effectiveness of tafasitamab with lenalidomide compared to alternative interventions for the treatment of refractory or relapsed DLBCL. Furthermore, he explained that the appraisal committee had concluded that further information from L-MIND, or indeed from the collection of NHS data on tafasitamab use in the Systemic-Anti-Cancer Therapy (SACT) database, would not help to resolve the uncertainties. He stated that Peter Clark, from the CDF, had advised the committee during its discussions of these issues.

135. Following questioning from the appeal panel, Stephen O'Brien stated that the committee's decision relating to the CDF was significantly informed by the fact that they had not been presented with plausibly cost effective ICERs from the health economic analysis. Furthermore,

the committee had concluded that further clinical follow-up data would be unlikely to resolve uncertainties about comparative clinical and cost effectiveness.

136. Ross Dent, for NICE, emphasised the importance of plausible cost effectiveness in informing decisions about the suitability of new treatments for use through the CDF. He further explained that it was important that an intervention had the potential to be cost-effective in certain scenarios since all drugs included in the CDF are subjected to re-appraisal and if there are no scenarios under which they prove to be cost-effective, approval for long-term use will not be granted, even if the clinical evidence is robust.

137. Stephen O'Brien stated that in an ideal world the committee would have liked to see the company continuing the recruitment of patients to the L-MIND study or to embark on a phase III study. He expressed the view that there will always be limitations about collecting evidence through SACT and explained that in this case, the appraisal committee would have liked to have been presented with more trial data that included larger numbers of patients, followed up for a longer period of time. He stated that the committee thought carefully about whether further follow-up and data collection, albeit from a single arm, would be helpful. He explained, however, that because the source of the committee's concern was the lack of comparative cost-effectiveness data, similar data would need to be collected for comparator treatments, and the committee concluded that this was unlikely to happen bearing in mind the company's CDF proposals.

138. Shevani Naidoo re-stated that L-MIND had not been intended to be a registrational study, but that when positive early outcomes were evident, the company sought scientific advice from the regulators, who suggested that the company pursue licensing on the basis of L-MIND results, since only a few treatment options are available in this patient population. She explained that as part of the conditional marketing

authorisation, there is an expectation that the company would re-run L-MIND and drew the appeal panel's attention to references to this in the company's data submission. She acknowledged, however, that this would not resolve the uncertainty about comparative efficacy. She stated that the company had presented, in the evidence dossier submitted to NICE, a commitment to undertake the RE-MIND 2 study, which is a proposed matched cohort study that includes competitor treatments such as polatuzumab vedotin. She clarified, however, that no comparative clinical trial was planned for patients with refractory or relapsed DLBCL.

139. Andrew Davies, for NCRI-ACP-RCP, stated that in the spirit of confirmatory evidence, members of the lymphoma community have undertaken to collect evidence, so new evidence will be available.

140. Shevani Naidoo stated that it is difficult to untangle all of the appeal points being considered in this hearing, as one of the criteria for entry into the CDF is that the medication under consideration should be plausibly cost-effective. She continued that whilst Stephen O'Brien had said that tafasitamab was not plausibly cost-effective, if EOL criteria were applied this may change. Similarly, the publicly available price of lenalidomide would impact on the cost-effectiveness of tafasitamab. In response to this, the appeal panel chair emphasised that each appeal point needed to be considered individually in their own right. This appeal point is about the reasonableness of the decision not to recommend for use through the CDF specifically on the basis of the committee's conclusion that any further evidence gathered would not address evidential uncertainties identified in the appraisal.

141. Adela Williams, for Incyte, submitted that whilst phase III trials are the traditional 'gold standard,' regulators are increasingly using adaptive registration pathways, when the undertaking of large phase III trials are either not practical or even ethical. She expressed the view that it

would be worrying if NICE were not to apply a correspondingly flexible approach to evidence appraisal.

142. Stephen O'Brien accepted that the landscape is changing and that more phase II single arm trials are being considered during appraisals of new treatments. However, he also said that there is a debate to be had about how such evidence is handled. He illustrated this by pointing to a recent study from Kings College that he said suggested that 50% of cancer drugs authorised by the EMA were in fact not effective.

143. Ross Dent stated that in the past, treatments have been recommended for use in the CDF when uncertainties about effectiveness could be resolved by single-arm studies. He explained that in previous appraisals, it has been considered that uncertainties (for example about the legitimacy of projected long-term survival) could be resolved by the gathering of longer-term data. He stated that in this case, however, the main uncertainty was around the effectiveness of tafasitamab compared with polatuzumab vedotin and the committee had concluded that further data collection in the manner proposed would not help to resolve that uncertainty.

144. Owen Swales, for NICE, added that section 3.4 of the FAD explains the considerable uncertainty about the comparative effectiveness of tafasitamab.

145. Shevani Naidoo stated the company's submission should be considered on its own merits and expressed the view that Incyte had provided rigorous and robust information about treatment comparisons, but these data were dismissed by the committee because the results were not aligned to the previous polatuzumab vedotin appraisal.

146. Shevani Naidoo stated that Incyte had provided two strategies to resolve uncertainties about comparative efficacy, and drew the appeal panel's attention to the documentary evidence of this. She explained that the company's preferred strategy had been to use comparative

data from RE-MIND 2, but following concerns raised by the ERG an alternative strategy using matched comparison data from L-MIND and published data on polatuzumab vedotin was proposed.

147. Following questioning from the appeal panel, Shevani Naidoo explained that if tafasitamab was accepted into the CDF for the treatment of people with refractory or relapsed DLBCL, further assessment of comparative efficacy could be explored using the REMIND-2, cohort matching study, and data from L-MIND and other studies. She conceded that the cohort may not be large enough to provide robust evidence but explained that there are options now with the availability of the Northend et al 2022 study to collect more robust comparative data about the relative efficacy of tafasitamab and polatuzumab vedotin in this cohort of patients.

148. Natalie Hallas, for NICE, stated that the company had submitted a variety of scenarios but explained that following requests by the committee for further analyses, none were forthcoming for consideration at the second committee meeting.

149. Shevani Naidoo stated that the company had considered NICE's proposals to further explore effectiveness but had concluded that they could not reduce uncertainty. She expressed the view that the committee's proposed approach would introduce additional uncertainty and also explained that the company's conclusion was that there was not enough time to incorporate the proposed changes.

150. Ross Dent stated that while possible options for future data collection had been described during the course of this appeal hearing by the company, the committee had not been fully informed about these during the course of the appraisal. He expressed the view that the company had not submitted proposals about data collection through use in the CDF that would reduce uncertainties about comparative effectiveness.

151. The appeal panel concluded as follows:

152. The appeal panel were satisfied that during this appraisal, the committee had considered all of the evidence presented to it in order to determine the relative effectiveness of tafasitamab with lenalidomide compared to polatuzumab vedotin for the treatment of refractory or relapsed DLBCL. Furthermore, it accepted that the committee had concluded that, in the absence of comparative studies, there was uncertainty about relative clinical efficacy which influenced the assessment of cost effectiveness. The appeal panel considered that it was not unreasonable for the appraisal committee, having considered all of the evidence presented to it, to have reached the conclusion that the greatest uncertainty about cost-effectiveness related to this uncertainty about comparative clinical effectiveness.

153. The appeal panel concluded that it was not unreasonable that the appraisal committee determined that the company's proposal for data collection within the CDF would not significantly resolve the uncertainty associated with the comparative effectiveness of tafasitamab compared to polatuzumab vedotin.

154. The appeal panel were satisfied that in this appraisal the committee had considered the extent to which any proposals that were submitted by Incyte for additional data collection through use in the CDF might resolve the uncertainties about the comparative clinical and cost effectiveness of tafasitamab. They noted that the committee had determined that Incyte had not advanced a robust plan for how these uncertainties would be resolved by tafasitamab being made available through the CDF. The appeal panel were satisfied that, in determining that Incyte had not advanced a robust plan, the committee had considered all of the evidence presented to it and had reached a reasonable conclusion having done so.

155. The appeal panel were persuaded that the committee had considered, in light of the evidence available, whether the use of tafasitamab with lenalidomide in this clinical context could be plausibly cost-effective, a criterion for entry into the CDF. It was satisfied that the committee had not acted unreasonably in reaching the conclusion that there was insufficient plausibility of cost effectiveness for the recommendation for use through the CDF. The panel acknowledged that the committee had reached this conclusion without the application of EOL criteria, although it noted the evidence submitted during the appeal hearing by NICE that even if EOL criteria had been applied, ICERs submitted to the committee did not meet the accepted threshold for cost effectiveness.

156. The appeal panel concluded, therefore, that there was no evidence of unreasonableness and dismissed the appeal point.

157. The appeal panel concluded, however, that following this appeal decision, as it has been determined by the panel that EOL criteria were indeed met, then this provides an opportunity for the committee to reconsider the issue of plausible cost-effectiveness and whether this treatment should or should not be recommended for use through the CDF.

Conclusion and effect of the appeal panel decision

158. The appeal panel upheld the appeal by Incyte Corporation on point 2.1, Lymphoma Action on point 2.1, and the joint appeal from the National Cancer Research Institute, Association of Cancer Physicians and Royal College of Physicians of London on point 2.1.

159. The appeal panel dismissed all other appeal points but would draw the attention of NICE to section 45 of this appeal decision that suggests further clarification in the FAD following the panel's consideration of appeal point 1(a).1 submitted by Incyte.

160. The appraisal of this technology is remitted to the appraisal committee who must now take all reasonable steps to address the following issues before publishing final guidance:

    a. The appraisal committee must appraise the technology on the basis that the NICE EOL criteria apply (Incyte Corporation point 2.1, Lymphoma Action point 2.1, and the joint appeal from the National Cancer Research Institute, Association of Cancer Physicians and Royal College of Physicians of London point 2.1). The committee should then consider the extent, if any, to which this influences the eligibility of tafasitamab for use through the CDF.

    b. The appeal panel suggest that the committee consider rewording the FAD to more clearly explain the efforts that were made to acquire the most relevant estimates of the cost of lenalidomide to the NHS at the time of publication of the FAD, as well as the sensitivity analyses that were undertaken around these costs, which were presented to the committee for their consideration.

161. There is no possibility of further appeal against this decision of the appeal panel. However, this decision and NICE's decision to issue the final guidance may be challenged by applying to the High Court for permission to apply for a judicial review. Any such application must be made within three months of NICE publishing the final guidance.