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16th September 2022

Dr Mark Chakravarty

Lead Non-Executive Director for Appeals

National Institute for Health and Care Excellence

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2 Redman Place

London, E20 1JQ

Dear Dr Chakravarty,

**APPEAL AGAINST THE FINAL APPRAISAL DOCUMENT FOR TAFASITAMAB WITH LENALIDOMIDE FOR TREATING RELAPSED OR REFRACTORY DIFFUSE LARGE B-CELL LYMPHOMA [ID3795].**

# Executive Summary

Incyte Biosciences UK Ltd (“Incyte”), wish to appeal the above Final Appraisal Document (“FAD”) and the Committee’s conclusion that tafasitamab should not be recommended for routine funding.

Incyte’s appeal is based on the following grounds:

**Ground 1a**

1a.1 The Committee has not taken loss of lenalidomide exclusivity and the associated impact on lenalidomide costs into account in the context of this appraisal

1a.2 The Committee’s conclusions regarding the cost-effectiveness of tafasitamab and lenalidomide lack transparency and are therefore unfair

1a.3 The Committee’s decision that tafasitamab and lenalidomide should not be recommended for use through the Cancer Drugs Fund in view of the lack of comparative evidence is procedurally unfair

**Ground 2**

2.1 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

2.2 The Committee’s conclusion that the company’s base case ICERs were not plausible because the model survival outputs were not consistent with TA 649 disregards the evidence generated since that appraisal

2.3 The Committee’s conclusion that the evidence presented did not demonstrate that tafasitamab is innovative is inconsistent with the Promising Innovative Medicine (PIM) designation by MHRA and the Committee’s own conclusions elsewhere in the FAD

# Introduction

We provide below background information in relation to diffuse B-cell lymphoma (DLBCL) and tafasitamab in order to assist the Appeal Panel. This information does not however replace the more detailed information supplied to NICE in the original submission from Incyte, to which we refer for the purposes of this appeal.

## Diffuse large B-cell lymphoma (DLBCL)

Diffuse large B-cell lymphoma (DLBCL) is a rare form of lymphoma affecting just under 5,000 individuals in the UK, and therefore meeting orphan disease criteria. DLBCL is a high-grade, aggressive subtype of B-cell non-Hodgkin’s lymphoma (NHL) and comprises large neoplastic B lymphoid cells that express pan B-cell antigens, including CD19 and CD20. The disease and its treatment produces material detrimental effects on the quality of life of affected patients and substantially impacts the lives of patients, their families and caregivers

## DLBCL treatment pathway

First-line (1L) treatment for DLBCL is chemoimmunotherapy with rituximab, cyclophosphamide, doxorubicin hydrochloride (hydroxydaunorubicin), vincristine sulphate and prednisone (R-CHOP). While 1L treatment initially results in good outcomes, 10-20% of patients are refractory to 1L R-CHOP and an additional ~40% of patients relapse following an initial complete response (CR) to R-CHOP. For patients with relapsed or refractory (R/R) DLBCL, prognosis is poor, with median overall survival (OS) estimates ranging from 5.0 to 22.2 months across 11 of 20 studies identified in a systematic literature review (SLR; June 2019; Thuresson P-O *et al.* *Adv Ther.* 2020;37(12):4877-4893).

Potentially curative options for R/R DLBCL include high-dose chemotherapy (HDCT) followed by autologous stem cell transplant (ASCT), and chimeric antigen receptor T-cell therapy (CAR-T; currently available only through the Cancer Drugs Fund (“CDF”) as third line treatment). However, these treatment options are intensive, and about 50% of patients are not eligible for ASCT at relapse due to older age or comorbidities. A further proportion of patients do not respond to HDCT or relapse after ASCT (or CAR-T); therefore, most patients with R/R DLBCL may ultimately become ineligible for ASCT

For patients with R/R DLBCL who are ineligible for ASCT, there are limited treatment options. Following NICE TA649, in September 2020 standard of care (SoC) with polatuzumab vedotin with bendamustine and rituximab (POLA+BR) has been established.(1) However, for a substantial proportion of patients, there remains a considerable unmet need for effective and well tolerated therapies to manage this aggressive and difficult-to-treat disease.

## Tafasitamab in combination with lenalidomide

Tafasitamab with lenalidomide followed by tafasitamab monotherapy (tafasitamab and lenalidomide) is a novel immunological, chemotherapy-free combination indicated for patients with R/R DLBCL who are not eligible for ASCT. The pivotal study supporting the submission for tafasitamab and lenalidomide in R/R DLBCL is L-MIND, a phase II, single-arm open-label international clinical trial which enrolled 81 patients with R/R DLBCL who were ineligible for ASCT.

Based on the promising results of L-MIND, tafasitamab was granted a Promising

Innovative Medicines (PIM) designation by the Medicines and Healthcare products Regulatory Agency (MHRA) in the UK (January 2020 – PIM 2019/0012) and accelerated approval from the US Food and Drug Administration (FDA; 1 July 2020).

A conditional marketing authorisation was granted for tafasitamab by the European Commission in August 2021 and by the MHRA in October 2021; conditional marketing authorisations are granted where comprehensive clinical data are not yet complete but the benefit of immediate availability of the medicine outweighs the risk inherent in the fact that additional data are still required. Orphan designation for tafasitamab was maintained/granted in 2021 after the EMA and MHRA concluded that duration of response could be clinically relevant and supportive of a significant benefit over POLA+BR (based on matching adjusted indirect comparison [MAIC] analysis).

## Comparative effectiveness assessment

Comparators for the submission were rituximab-based chemoimmunotherapies. The Committee agreed that the key comparator was POLA+BR; bendamustine with rituximab (BR) and rituximab with gemcitabine and oxaliplatin (R-GemOx) were also considered relevant comparators: BR was the comparator for POLA+BR in NICE TA649; while R-GemOx is a chemoimmunotherapy commonly used as a comparator in clinical trials and in UK clinical practice prior to introduction of POLA+BR.

As the submission was based on the single-arm L-MIND study, comparative efficacy was assessed via indirect treatment comparisons: a MAIC of published evidence for TAFA+LEN versus comparators,(2) and the RE-MIND2 study, which used 1:1 matching of patients in L-MIND to patients in a retrospective cohort receiving NCCN guideline-recommended treatments.

# Procedural history of the appraisal

|  |  |
| --- | --- |
| **Date**  | **Event**  |
| 05 January 2021  | Referral to NICE  |
| 21 September 2021  | Final scope for appraisal  |
| 23 November 2021  | Incyte submission to NICE  |
| December 2021 – January 2022  | Clarifications  |
| 10 March – May 2022  | Technical engagement  |
| 01 June 2022  | Committee meeting 1  |
| 23 June 2022  | Appraisal Consultation Document issued: “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.”  |
| 14 July 2022  | Incyte submits response to consultation on ACD  |
| 02 August 2022  | Committee meeting 2  |
| 02 September 2022  | Final appraisal document issued: proposed recommendations unchanged from ACD  |

# Grounds of appeal

**1. Ground 1: In making the assessment that preceded the recommendation, NICE has a) failed to act fairly or b) exceeded its powers**

# 1.1. The Committee has not taken loss of lenalidomide exclusivity and the associated impact on lenalidomide costs into account in the context of this appraisal

The assessment of cost effectiveness of tafasitamab and lenalidomide uses drug costs as set out at paragraphs 2.3 and 2.4 of the FAD. For lenalidomide, paragraph 2.3 refers to costs taken from the BNF online, accessed in August 2022, with prices for a 21 capsule pack of branded Revlimid varying between £3,426.00 and £4,168.50 depending on capsule size.

However, Revlimid has now lost data exclusivity with the result that a number of generic versions of lenalidomide have been launched on the UK market during the course of 2022 (six generic products are currently listed in the BNF, as well as Revlimid). In these circumstances, the price charged to the NHS for lenalidomide will inevitably have fallen dramatically, consistent with the effect of generic product entering the market across Europe [publically available information confirms generic prices for lenalidomide in Italy and Germany have now dropped by 96 to 98% of Revlimid list price; similar price erosion has also been reported in other EU countries]. The costs for lenalidomide stated in paragraphs 2.3 and 2.4 of the FAD (the Revlimid list price) bear no relationship to actual costs incurred by the NHS, the cost-effectiveness calculations are incorrect and the proposed guidance for tafasitamab and lenalidomide is outdated even before it has been published.

* This situation was notified to NICE by Incyte in its original dossier submitted on 23 November 2021 at Section B.3.5.1:

“In the base case, price discounts were only considered for lenalidomide. As generic lenalidomide options are expected to soon be available on the UK market, it was anticipated that the price of lenalidomide would experience a considerable reduction. Comparisons of branded lenalidomide prices prior to genetic entry against generic lenalidomide prices in Canada indicates generic lenalidomide to have a ~75% discount relative the price of branded lenalidomide. As price discounts for generics are expected to be more substantial in the UK market and price erosion faster, a discount of 90% was assumed in the base case analysis”.

* The issue was also drawn to the attention of NICE by Incyte in its response to the ACD dated 14 July 2022

“Incyte are aware that generic lenalidomide is now being used across several NHS trusts in England, with the tender process expected to be completed soon, and as such believe that it is appropriate to consider the impact of discounts for lenalidomide relative to the current list price”.

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NICE’s Guide to the Methods of Technology Appraisal, as applicable to this appraisal, states at section 5.5.2:

“When there are nationally available price reductions, for example for medicines procured for use in secondary care through contracts negotiated by the NHS Commercial Medicines Unit, then the reduced price should be used in the reference-case analysis to best reflect the price relevant to the NHS”.

The NICE Commercial Liaison Team is able to liaise between the CMU and the Appraisal Committee in order to obtain these prices for the purposes of NICE appraisals.

Reflecting this situation, in its response to the ACD, Incyte submitted pricing scenario analyses for tafasitamab and lenalidomide incorporating an updated PAS discount for tafasitamab and exploring variations in the price of lenalidomide, which could reflect pricing of generics. (Incyte has no visibility of lenalidomide pricing and was therefore unable to include actual prices charged by generics companies nationally to the NHS in its modelling.)

In the above circumstances, the failure by the Committee to take account of loss of exclusivity for lenalidomide with the resulting impact on costs is both unfair and inconsistent with NICE’s own published procedures.

 **1.2. The Committee’s conclusions regarding the cost-**

# effectiveness of tafasitamab and lenalidomide lack transparency and are therefore unfair

The Committee’s conclusions regarding the cost effectiveness of tafasitamab and lenalidomide are set out at paragraph 3.9 of the FAD. The Committee states:

“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 to be cost-effective”.

The Committee’s conclusions regarding the most plausible ICER are therefore unclear and it is uncertain whether the Committee’s most plausible ICER is close to the company’s estimate or the ERG’s and if so where it lies. Incyte recognises that some of the net prices for medicinal products in this appraisal are confidential and that actual ICER values may not therefore be disclosed. However for this appraisal to be comprehensible and the recommendations of the Committee understood, it is essential that ICER ranges, providing an indication of the Committee’s conclusions are disclosed.

Transparency is required in order to demonstrate rigorous decision making and also as a central component of procedural fairness. Its particular importance in the context of NICE’s appraisals is recognised in NICE’s procedures, including at paragraphs 6.1.9 and 6.1.10 of NICE’s Guide to the Methods of Technology Appraisal 2013. Paragraph 6.1.9 provides:

“The credibility of the guidance produced by the Institute is dependent on the transparency of the Appraisal Committee's decision-making process. It is crucial that the Appraisal Committee's decisions are explained clearly with reference to all the available evidence, and that the contributions of clinical specialists, commissioning experts, patient experts and the views of people who responded to consultation during the appraisal are considered. The reasoning for the Committee's decision will be explained, with reference to the factors that have been taken into account, in the 'Considerations' section of the guidance”.

Paragraph 5.4.2 of NICE’s Health Technology Evaluations: the Manual states:

“NICE aims to publish an ICER range within the draft or final draft guidance document that informs the recommendations, after taking into account the exact level of the discount provided in the commercial arrangements”.

In this case however, Incyte has been provided with no information about the Committee’s preferred ICER and no range of values has been disclosed. We have been informed verbally that the ICER range exceeds the threshold of cost effectiveness that NICE would typically view as a cost effective use of NICE resources and therefore there is no requirement to provide the details. We disagree. Based on the current information, it is impossible for Incyte to understand whether the Committee’s conclusions in relation to the most plausible ICER are soundly based or whether they are unreasonable and should be the subject of appeal. Further, Incyte cannot know what (in the Committee’s view) it needs to do in order to achieve a positive recommendation in this appraisal. This situation is a clear breach of fundamental standards of procedural fairness and NICE’s own procedures. It is particularly unacceptable, given the innovative nature of the product and the Committee’s recognition of the clinical need of patients eligible for treatment.

# 1.3. The Committee’s decision that tafasitamab and lenalidomide should not be recommended for use through the Cancer Drugs Fund in view of the lack of comparative evidence is procedurally unfair

The Committee’s decision regarding use of tafasitamab and lenalidomide through the CDF is set out at paragraph 3.10 of the FAD. While the Committee recognised the high unmet clinical need of patients with R/R DLBCL, the Committee declined to recommend CDF usage on the basis (a) that no additional comparative evidence would be produced and (b) because the Committee stated that it had been presented with no analysis showing that tafasitamab and lenalidomide at the potential to be cost-effective at the proposed price. Reason (b) is addressed through other points of Incyte’s appeal and here we explain why reason (a) is unfair.

Throughout this appraisal, the Committee has criticised tafasitamab and lenalidomide on the basis that the clinical data comprise the single arm L-MIND study, rather than a randomised controlled trial, involving a direct comparison with an alternative treatment (see for example paragraph 3.3 of the FAD). However L-MIND was not originally intended to be the basis for registration of tafasitamab and only became so as a result of the positive outcome of the study and the resulting decision by the European Medicines Agency (EMA) and the MHRA to recommend grant of marketing authorisations on the basis of that study on the basis that the benefit of immediate availability of the medicine outweighed the risk inherent in the fact that additional clinical data were still required. Based on the results from L-MIND and the decisions of the Licensing Authorities in EU and UK there was no basis for the conduct of randomised controlled trials of tafasitamab and lenalidomide with other licensed treatments in the population of patients under consideration in this appraisal. In these circumstances and in view of the high unmet clinical need it is unfair to reject usage through the CDF on the basis of lack of a direct treatment comparison, particularly given the fact that a CDF recommendation would allow particular uncertainties identified by the Committee (specifically in relation to overall and progression free survival (paragraph 3.7 of the FAD) and the additional benefits of tafasitamab and lenalidomide not currently captured by the QALY calculation (paragraph 3.11) to be addressed.

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

# 2.1. 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

At paragraph 3.8 of the FAD, the Committee considered the application of the end of life criteria and concluded that, while the second criterion (extension to life of at least 3 months) was met, the first criterion (short life expectancy, normally less than 24 months) was not. The reasons for the Committee’s conclusions in relation to the first criterion were as follows:

“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.”

Incyte firmly believes that the Committee’s conclusions do not reflect the balance of the evidence for the life expectancy of patients eligible for treatment with tafasitamab and lenalidomide and are therefore unreasonable. Such evidence is summarised in Table 1 below.

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**Table 1**. **Life expectancy in patients with R/R DLBCL eligible for tafasitamab with lenalidomide.**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Source**  | **Population**  | **Life Expectancy (months)**  | **OS at 12 months**  | **OS at 24 months**  | **Notes**  |
| MAIC - time-varying HR (Company base-case)  | Patients with R/R DLBCL not eligible for stem-cell transplant receiving POLA+BR  | Median = 14.8 Modelled mean (undiscounted) = 29  | 58%  | 34%  |   |
| MAIC - constant HR (ERG base-case)  | Patients with R/R DLBCL not eligible for stem-cell transplant receiving POLA+BR  | Median = 18.7 Modelled mean (undiscounted) = 48  | 61%  | 44%  |   |
| NICE Appraisal of polatuzumab vedotin [TA649]  | Patients with R/R DLBCL not eligible for stem-cell transplant treated with polatuzumab vedotin with rituximab and bendamustine  | Median = 12.4 Modelled mean (discounted) = 37 months  | NA  | NA  |   |
| **Published literature in patients with R/R DLBCL not eligible for transplant receiving POLA+BR**  |  |

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Source**  | **Population**  | **Life Expectancy (months)**  | **OS at 12 months**  | **OS at 24 months**  | **Notes**  |
| **Study**  | **No. of patients**  | **Prior tx lines,** median (range) | **OS, median (95% CI),** months | **OS at 12 months**  | **OS at 24 months**  | **Notes**  |
| **Studies referenced by Incyte in its written submissions**  |
| Sehn 2022 (GO29365 trial)(3)  | 40  | 2 (1-7)  | Median (95% CI) = 12.4 (9.0-32.0)  | ~54%  | 38%  |   |
| Sehn 2022 (GO29365 trial) – extension cohort(3)  | 106  | 2 (1-7)  | Median (95% CI) = 12.5 (8.2-23.1)  | 50%  | ~35%  |   |
| Northend 2022 – standalone treatment patients(4)  | 78  | 1 (1-6)  | Median (95% CI) = 10.2 (5.2-14.3)  | NA  | NA  |   |
| Northend 2022 - all patients(4)  | 133  | 2 (1-6)  | Median (95% CI) = 8.2 (5.9-14.3)  | ~43%  | NA  |   |
| Terui 2022(5)  | 35  | 2 (1-7)  | Median (95% CI) = NR (8.4-NE)  | ~59%  | NA  |   |
| Liebers 2021 (salvage cohort) (6)  | 54  | 3 (2-8)  | 5.4  | 28%  | NA  | 22/54 patients received other POLA combination regimens  |
| Liebers 2021 (bridging cohort) (6)  | 51  | 3 (2-6)  | 8.1  | 59%  | NA  |   |
| Dujmovic 2020(7) | 23  | 3 (1-5)  | Median = 9.0  | ~41%  | NA  |   |
| **Additional studies referenced by Clinical Experts in their written submissions**  |

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Source**  | **Population**  | **Life Expectancy (months)**  | **OS at 12 months**  | **OS at 24 months**  | **Notes**  |
| Dimou 2022(8)  | 49  | 2 (1-9)  | Median (95% CI) = 8.5 (3.1-13.8)  | 45%  | NA  |   |
| Wang 2022(9) | 40  | 4 (2-11)  | 8.5 (range: 0.3-30.2)  | 36%  | ~26%  | 19/40 patients received POLA monotherapy or other POLA combination regimens  |
| **RE-MIND2 study - systemic therapies pooled cohort (patients receiving NCCN guideline-recommended treatments)**  |
| RE-MIND2 - Systemic pooled therapies cohort matched to LMIND (MAS) (10)  | 76  | 1 (1-3)  | Median (95% CI) = 11.6 (8.8-16.1)  | 48%  | 36%  | 3/76 patients received POLA+BR and 1/76 patient received POLA+R  |
| **Additional studies in patients receiving POLA+BR**  |
| Avivi 2022(11) | 41  | Mean ± SD: 3.2 (± 1.2)  | 10.8 (2.2-19.4)  | ~50%  | ~32%  | 10/41 patients were treated with POLA+R rather than POLA+BR  |
| Dal 2022(12)  | 71  | 3 (2-5)  | Median = 5.0  | NA  | NA  |   |
| Vodicka 2022(13)  | 21  | 3 (2-7)  | Median (range) = 8.7 (0.7-9.5)  | NA  | NA  |   |
| Smith 2021(14)  | 69  | 3 (1-9)  | 5.3  | NA  | NA  |   |
| Segman 2021 (overall cohort) (15)  | 47  | 3 (2-4)  | 8.3 (IQR: 5.03-14.80)  | ~47%  | NA  | 15/47 patients received POLA+R  |
| **Source**  | **Population**  |  | **Life Expectancy (months)**  | **OS at 12 months**  | **OS at 24 months**  | **Notes**  |
| Tsai 2020(16)  | 32  | 4 (2-11)  | 8.9 (6.2-NE)  | NA  | NA  | 12/32 patients received other POLA combination regimens  |

Note: “~” indicates digitised estimates from available Kaplan-Meier survival plots rather than reported figures.

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| --- |
| **Clinical experts and patient group feedback and estimates**  |
| **Respondent**  | **Source**  | **Comments on life expectancy**  |
| Patient organisation submission from Lymphoma Action  | Patient and caregiver survey data  | *“The prognosis for patients with relapsed or refractory* *DLBCL is poor, with median survival of around a year.”*  |
| Clinical Expert response to technical engagement (Committee Papers for ACM1)  | Clinical expert opinion and interpretation of the literature  | *“The efficacy of therapies for people with relapsed or refractory DLBCL are disappointing, even for those treated with intensive therapies and with curative intent.”…* *“Longer follow-up of the POLA+BR data would indicate that the Company [model] estimates are more appropriate [i.e. mean 2.20 LYG in the company base case vs. mean 3.36 LYG in the ERG base case].”…* *“Yes, they [the end-of-life criteria] are met as the standard of care is palliative. This therapy is for transplant ineligible patients and that situation will not change.”*  |
| Clinician estimates from ACM1 (ACM1 minutes)  | Clinical expert opinion  | Clinician 1 stated that expectations for survival among non-transplant eligible R/R DLBCL patients is less than 24 months, which is supported by the available literature. While a stepwise improvement for POLA+BR was shown over previous treatments, survival is still expected to be less than 24 months.  Clinician 2 agreed with clinician 1 and noted that while they would like to be more optimistic, the expectation is that survival would be less than 24 months.  |
| Clinical Expert response to ACD (Committee papers for ACM2)  | Clinical expert opinion and interpretation of the literature  | “*Average OS of >24 months is not something we see in clinical practice with Pola BR in R/R DLBCL setting.”* *“Neither the trial data nor subsequent data from extended cohort analysis or UK RWE would suggest average OS of 24 months with this regimen.”* *“When I speak with patients about Pola+BR I would typically say: 'this regimen is not curative and at best may give you 6 months remission. When the lymphoma comes back your life expectancy is measured in months not years'.”* *“In my clinical practice I would discuss with patients who have RR DLBCL (and not eligible for auto) that unfortunately their survival is most likely months and unlikely to be more than a year.”*  |

At the time of the second Appraisal Committee meeting, the Committee had been provided with data obtained from 7 published scientific papers reporting on actual outcomes in a total of 450 patients receiving polatuzumab (listed in Table 1), indicating that median survival in patients with R/R DLBCL not eligible for stem cell transplant who receive treatment with polatuzumab vedotin with rituximab and bendamustine is between 5.3 and 12.5 months. Mean data on overall survival are not reported. One year after commencement of treatment with polatuzumab vedotin with rituximab and bendamustine approximately 41 - 72% of patients had died and after two years, approximately 62 - 74% of patients had died. These data are consistent with the views of the clinical experts referenced in Table 1 (and also multiple responses to consultation on the ACD received through the website) and with those of Lymphoma Action consulted during this appraisal.

For completeness, the Appeal Panel should be aware that, in addition to the published scientific papers considered by the Committee, a further 6 published studies are available (also listed in Table 1). Taken together with the studies considered by the Committee this provides data on outcomes in a total of 737 patients receiving polatuzumab. The survival estimates including these data are consistent with those reported in the published scientific literature referenced in the previous paragraph.

The Appraisal Committee expressed concern that the data from the published literature was different to the estimates relied upon for the purposes of NICE’s guidance for polatuzumab vedotin with rituximab and bendamustine [TA 649]. The recommendations in TA649 were based on GO29365, a single open label trial, in which 40 patients received polatuzumab vedotin with rituximab and bendamustine resulting in a median overall survival of 12.4 months (Sehn 2020). Overall survival data were immature (and were viewed as confidential) and the Committee’s recommendations were therefore based on estimates calculated using standard independent parametric survival modelling (also confidential). This was the only way to proceed at the time of the appraisal of polatuzumab vedotin with rituximab and bendamustine in 2020. However since that time substantial additional experience of polatuzumab vedotin with rituximab and bendamustine has been obtained and it is unreasonable to rely on the modelled estimates from TA 649, over real-world outcomes from clinical experience in the NHS. It is relevant in this context that the ERG who considered this appraisal stated that “the survival estimates in TA649 for pola-BR seem to be invalid” (Addendum – ERG critique of the Company’s ACD Response : sections 2.3, 3.4 and 4.5).

 The Committee stated that while the estimates from the appraisal of polatuzumab vedotin with rituximab and bendamustine might be too optimistic, it did not believe they 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. No reasons for the Committee’s view is provided, despite the strength of the opposing view from the published scientific literature since the date of that appraisal and the view of the ERG that the survival estimates from TA649 are “invalid”.

The application of the end of life criteria and specifically the interpretation of the short life expectancy criterion was considered carefully by the Appeal Panel who heard the appeal against the FAD for avelumab for maintenance treatment of locally advanced or metastatic urothelial cancer after platinum-based chemotherapy. They made the following points:

* In interpreting the short life expectancy criterion “the paramount consideration should be what the key stakeholders of NICE: the general public, patients, clinicians, policy makers and industry would consider a reasonable interpretation of the word “normally”.
* They stated that “the end of life criteria are a standalone test that have to be considered on their own terms” and did not agree that “the mean survival of 24 months must be used as the threshold for application of end of life criteria to maintain consistency with the methodology used to calculate the incremental cost-effectiveness ratio”.
* “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 Panel did not suggest “there is a general rule that median is preferable to mean or vice versa”, but said that “the question is it reasonable to conclude that life expectancy is below 24 months” and all the data, including the mean, median and clinical opinion, are relevant to that judgment.

 Applying the conclusions of the Appeal Panel that heard the avelumab appeal to the current appraisal of tafasitamab and lenalidomide, the position is very similar. In particular:

1. All of the median overall survival estimates for patients eligible to be treated with tafasitamab and lenalidomide are well below 24 months.
2. The data suggest that around 65% of patients treated with polatuzumab vedotin with rituximab and bendamustine have died by 24 months. (There are two outlier figures included in Table 1, one of which (the ERG’s modelled estimate) suggests that 56% have died and one of which (Wang (2022) suggests that 74% have died by that time.)
3. If all of the data are taken into consideration, the balance of the evidence is overwhelmingly in favour of a life expectancy of normally less than 24 months for patients eligible for treatment with tafasitamab and lenalidomide.

In summary, the balance of the available evidence confirms that the “normal” life expectancy for patients eligible for treatment with tafasitamab and lenalidomide is less than 24 months. Given this material, consistent with the view of the Appeal Panel that heard the appeal against the FAD for avelumab, Incyte considers that it would not be possible to explain to patients or clinicians why the Committee concluded that these patients would have a life expectancy in excess of 24 months.

For these reasons, the conclusions of the Committee were unreasonable.

**2.2.**   **The Committee’s conclusion that the company’s base case ICERs were not plausible because the model survival outputs were not consistent with TA 649 disregards the evidence generated since that appraisal**

At paragraph 3.9 of the FAD, the Committee provides its reasons for rejecting the ICERs submitted by Incyte:

 “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”.

As explained in Incyte’s appeal at point 2.1 above, NICE’s guidance on polatuzumab vedotin relied on estimates produced through modelling of data from a single clinical trial, in which 40 patients received treatment with polatuzumab vedotin. That was all the data available to the Committee which considered that appraisal at that time. Since then however, substantial further experience with polatuzumab vedotin has been obtained (see Table 1 above) from over 700 patients (data from over 500 patients were available to the Committee at the second Committee meeting), which indicates consistently that the estimates from TA649 were optimistic. Incyte’s model survival outputs reflect those data, taken from published literature.

While NICE may wish to maintain consistency between conclusions reached in different appraisals, it is unreasonable to insist on consistency in circumstances where additional data have become available which suggest that the modelled estimates relied upon in TA649 were more favourable than indicated by subsequent data. In particular, it is not reasonable to base decisions on modelled estimates from 40 patients rather than actual outcomes from over 400 patients, without a sound justification for such an approach.

# 2.3. The Committee’s conclusion that the evidence presented did not demonstrate that tafasitamab is innovative is inconsistent with the Promising Innovative Medicine (PIM) designation by MHRA and the Committee’s own conclusions elsewhere in the FAD

At paragraph 3.11 of the FAD, the Committee states that the evidence submitted for tafasitamab did not demonstrate that the product added ““demonstrable and distinctive benefits of a substantial nature which may not have been adequately captured in the reference case QALY measure”.

This conclusion is however inconsistent with the conclusions of the MHRA, who granted the treatment “Promising Innovative Medicine” designation and the US Food and Drug Administration, who awarded it “Breakthrough Therapy” designation and there is no indication that the Committee considered the conclusions of these other bodies in reaching its own decision that the evidence presented did not demonstrate that tafasitamab is innovative.

In addition, at paragraph 3.1 of the FAD, the Committee itself recognised the enormous psychosocial, social and economic impact of R/R DLBL on patients and their carers and observed “any treatment delivered in an outpatient setting would have a significant, positive effect on the quality of life of patients and their families”, before concluding that “people with the condition have a high unmet need for effective treatments with manageable side effects”. At paragraph 3.11 the Committee notes the company’s submissions that uncaptured benefits include the advantage of administration in an outpatient setting and more acceptable toxicity, but despite the data supporting both of these elements concluded that tafasitamab did not qualify as innovative.

Overall therefore, the Committee’s conclusions regarding the innovative nature of tafasitamab are inconsistent with the determinations of both the MHRA and FDA, even though the Committee has failed to recognise these determinations and no reasons have been given for diverging from the assessments of those bodies. Furthermore the Committee’s own recognition of the importance of outpatient treatment and improved toxicity profile at paragraph 3.1 is inconsistent with its unexplained conclusion at paragraph 3.11 that, despite the benefits of tafasitamab on those parameters, it is nevertheless not innovative.

## **Requested outcome following appeal**

The Appeal Panel is respectfully requested to return this appraisal for further consideration by the Appraisal Committee with the following directions:

* Tafasitamab and lenalidomide satisfies the requirements for the end of life criteria;
* The impact of loss of Revlimid data exclusivity, with resulting generic entry, on the cost of lenalidomide to the NHS should be taken into account when considering the cost-effectiveness of tafasitamab and lenalidomide in this appraisal;
* That caution should be exercised when considering the conclusions reached in TA649 in view of the substantial weight of conflicting evidence generated since that appraisal;
* The Committee should provide greater transparency in relation to its assessment of cost-effectiveness; and
* The Committee should reconsider the innovative nature of tafasitamab and lenalidomide in the context of the conclusions of MHRA and FDA and its benefits in terms of outpatient treatment and reduced toxicity relative to other treatments.

## **Conclusion**

Incyte Biosciences UK requests that this appeal should be determined at an oral hearing.

We thank you in advance for considering the company’s submissions in this appeal. We are available to answer any questions you may have or provide further clarifications.

Yours sincerely,

Incyte Biosciences UK Ltd

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