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

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

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. **Response to consultee, commentator and public comments on the Appraisal Consultation Document (ACD)**

2. **Comments on the Appraisal Consultation Document from Incyte**

3. **Consultee and commentator comments on the Appraisal Consultation Document** from:
   a. National Cancer Research Institute-Association of Cancer Physicians-Royal College of Physicians-Royal College of Radiologists

4. **Comments on the Appraisal Consultation Document received through the NICE website**

5. **Evidence Review Group critique of company comments on the ACD**

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

Appraisal title

Single Technology Appraisal

Response to consultee, commentator and public comments on the Appraisal Consultation Document (ACD)

Type of stakeholder:

Consultees – Organisations that accept an invitation to participate in the appraisal including the companies, national professional organisations, national patient organisations, the Department of Health and Social Care and the Welsh Government and relevant NHS organisations in England. Consultees can make a submission and participate in the consultation on the appraisal consultation document (ACD; if produced). All non-company consultees can nominate clinical experts and/or patient experts to verbally present their personal views to the Appraisal Committee. Company consultees can also nominate clinical experts. Representatives from NHS England and clinical commissioning groups invited to participate in the appraisal may also attend the Appraisal Committee as NHS commissioning experts. All consultees have the opportunity to consider an appeal against the final recommendations, or report any factual errors, within the final appraisal document (FAD).

Clinical and patient experts and NHS commissioning experts – The Chair of the Appraisal Committee and the NICE project team select clinical experts and patient experts from nominations by consultees and commentators. They attend the Appraisal Committee meeting as individuals to answer questions to help clarify issues about the submitted evidence and to provide their views and experiences of the technology and/or condition. Before they attend the meeting, all experts must either submit a written statement (using a template) or indicate they agree with the submission made by their nominating organisation..

Commentators – Commentators can participate in the consultation on the ACD (if produced), but NICE does not ask them to make any submission for the appraisal. Non-company commentator organisations can nominate clinical experts and patient experts to verbally present their personal views to the Appraisal Committee. Commentator organisations representing relevant comparator technology companies can also nominate clinical experts. These organisations receive the FAD and have opportunity to report any factual errors. These organisations include comparator technology companies, Healthcare Improvement Scotland any relevant National Collaborating Centre (a group commissioned by NICE to develop clinical guidelines), other related research groups where appropriate (for example, the Medical Research Council and National Cancer Research Institute); other groups such as the NHS Confederation, the NHS Commercial Medicines Unit, the Scottish Medicines Consortium, the Medicines and Healthcare Products Regulatory Agency, the Department of Health and Social Care, Social Services and Public Safety for Northern Ireland).

Public – Members of the public have the opportunity to comment on the ACD when it is posted on the Institute's web site 5 days after it is sent to consultees and commentators. These comments are usually presented to the appraisal committee in full, but NICE reserves the right to summarise and edit comments received during consultations, or not to publish them at all, where in the reasonable opinion of NICE, the comments are voluminous, publication would be unlawful or publication would be otherwise inappropriate.

Please note: Comments received in the course of consultations carried out by NICE are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the submissions that NICE has received, and are not endorsed by NICE, its officers or advisory committees.

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
1		NCRI-ACP-RCP-RCR	We are not convinced that the summaries of clinical and cost effectiveness are reasonable interpretations of the evidence. Thus, the summaries of clinical and cost effectiveness are not reasonable interpretations of the evidence. Patients who are not eligible for haematopoietic stem cell transplant for relapsed or refractory diffuse large B-cell lymphoma are not likely to live for longer than 2 years. This is usually less than 12-18 months if they receive the present standard of care treatment with Rituximab with Bendamustine and Polatuzumab (RB-Pola). Median survival in 152 patients with R/R DLBCL treated with RB-Pola was just 12.4 months (95% CI: 9.0-32.0) when reported with a median of 48 months follow-up. The 24 months overall survival probability was only 38% (95% CIL 22.5-53.9)(Sehn Blood Advances 2022) The survival times for people who have polatuzumab vedotin plus rituximab and bendamustine used in the modelling does not reflect the estimated survival in NICE's guidance on polatuzumab vedotin plus rituximab and bendamustine. Without such consistency it is both confusing and potentially flawed and undermines any further interpretation. As noted in the report '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.' As outlined in the document 'it would have preferred to see different modelling approaches used that both fitted the underlying hazards of the data and produced outcomes aligned with the polatuzumab vedotin with bendamustine and rituximab guidance.'	Thank you for your comment. The committee has discussed survival estimates for polatuzumab vedotin plus rituximab and bendamustine and accepted that the ERG base case likely overestimates survival for polatuzumab vedotin plus rituximab and bendamustine when considering this comment and other comments provided. However, the committee noted considerable uncertainty in survival extrapolations, specifically how the absolute and relative benefit of polatuzumab vedotin plus rituximab and bendamustine over rituximab and bendamustine alone is not reflected. The committee did request additional modelling approaches to be presented by the company in response to the appraisal consultation document to address these uncertainties but unfortunately this was not provided (see FAD – section 3.6). The committee also concluded that even if the survival outcomes estimated in NICE's technology appraisal guidance on polatuzumab vedotin were overestimated, they were unlikely to be overestimated to an extent that would mean concluding that tafasitamab with lenalidomide does meet the end of life criteria if corrected (see FAD – section 3.8).
2		Incyte Biosciences UK Ltd	**Introduction** We have carefully considered the Committee's assessment of the evidence submitted for the single technology appraisal for tafasitamab with lenalidomide for treating patients with relapsed or refractory diffuse B-cell lymphoma (DLBCL) who are not eligible for autologous stem cell transplant. We are disappointed by the conclusions reached by the Committee and the resulting preliminary guidance not to recommend tafasitamab. We appreciate the opportunity to provide a response to the Appraisal Consultation Document	Thank you for your comment. As this comment is a summary of other comments, please see NICE responses to comments 3, 4, 5, 6, 7 and 8.

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			(ACD). Considering the Committee's feedback and the points noted below, we present a revised case and PAS [redacted] with additional scenarios are presented in a separate appendix. The base case and cost-effectiveness of TAFA+LEN are discussed in Comment 4 and Comment 5. *Tafasitamab with lenalidomide meets end of life criteria* DLBCL is an aggressive form of lymphoma, with poor outcomes once relapsed or refractory disease occurs following first-line treatment.[1,2] We do not believe that all the relevant evidence and clinical experience has been taken into account by the committee in its decision making. • Feedback from clinical experts during the committee meeting, as well as additional expert feedback collected following publication of the ACD, highlights that: normal survival expectations are below 24 months with POLA+BR based on their experience since POLA+BR became available in the UK; and that the average 4-year survival cited in the ACD is a substantial overestimate of expected survival for patients with R/R DLBCL not eligible for transplant. • The reason for the committee's view appears to be a concern regarding an apparent inconsistency with the modelled extension to life accepted by the Committee who appraised polatuzumab vedotin (TA649). However additional evidence has become available since publication of TA649 in September 2020 • Life expectancy predictions in TA649 were based on data in 40 patients receiving polatuzumab vedotin with bendamustine and rituximab (POLA+BR) in the GO29365 study. Since TA649 publication, additional evidence that has become available includes further follow-up of the GO29365 randomised cohort, and a GO29365 extension cohort (N=106).[3] Additionally, UK real-world data collected since publication of TA649 (N=133, including 78 patients receiving standalone POLA+BR therapy) have shown that life expectancy following treatment with polatuzumab vedotin is lower than observed in the GO29365 trial (median 10.2 months in the standalone treatment cohort vs. 12.5 months).[3,4] • The totality of the evidence, including new published evidence since TA649 release, and clinical expert opinion now that POLA+BR is established in routine clinical practice, demonstrate that patients with R/R DLBCL, particularly those who are not eligible for stem cell transplant, survive less than 24 months, and therefore tafasitamab satisfies criterion 1 of the end-of-life criteria. *Robust methodology was used for indirect treatment comparisons* Due to the unmet clinical need of patients with R/R DLBCL and the associated accelerated approval for tafasitamab, randomised controlled trial data are not available and indirect treatment comparisons are required to inform assessment of tafasitamab clinical effectiveness. The indirect comparisons for this submission rigorously followed	

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			NICE DSU 17 and 18 guidance. In section 2 we provide further explanation and clarification of the methodology used. *Clinical experts believe that survival extrapolations used by the company are more plausible than higher survival predictions* We do not believe all the evidence has been considered when assessing plausibility of the overall survival extrapolations, including published real-world evidence and experience in routine clinical practice. In addition, some patients in the GO29365 trial received subsequent treatment with chimeric antigen receptor-T-cell therapy (CAR-T), which may contribute to the potential plateau observed in the overall survival curve. This aspect should be carefully considered as CAR-T costs were excluded in economic analyses for this submission due to current inclusion in the Cancer Drugs Fund.[5] We discuss these points further in Comment 5. *Tafasitamab with lenalidomide provides benefit not fully captured in the quality-adjusted life year (QALY) calculation* Tafasitamab with lenalidomide is an innovative, chemotherapy-free immunotherapy for relapsed or refractory DLBCL in patients not eligible for stem cell transplant. Tafasitamab has received both a Promising Innovative Medicines (PIM) designation from the MHRA and Orphan designation from the EMA. It has received accelerated approval from both the EMA and MHRA due to the high unmet need and "potential significant benefit" of tafasitamab as shown in the pivotal L-MIND clinical trial, and matched adjusted indirect treatment comparison (MAIC) analysis of duration of response for tafasitamab with lenalidomide vs. polatuzumab with bendamustine and rituximab.[5] The submissions received by NICE, both in writing and orally, from patients and healthcare providers, have highlighted the substantial burden and poor prognosis for patients with R/R DLBCL, particularly for those who are not eligible for transplant, and have confirmed that tafasitamab in combination with lenalidomide provides important benefit to patients that are not reflected in the QALY assessment. We discuss this point further in Comment 6. We hope that this response has addressed the concerns expressed by the Committee in the ACD and will be sufficient to provide a positive recommendation for tafasitamab with lenalidomide for patients with R/R DLBCL who are not eligible for stem cell transplant.	
3		Incyte Biosciences UK Ltd	**Issues raised in the ACD: End of life Criterion 1 not met** We are pleased that the Committee has confirmed that end-of-life criterion 2 has been met, with TAFA+LEN providing more than 3 months additional survival compared with POLA+BR as recently established standard of care. However, we do not agree with the committee's view that end of life criterion 1 is not met and do not believe that all relevant evidence has been taken into account in the committee's decision making. NICE guidelines on criterion 1 state that *"the treatment is indicated for patients with a short life expectancy, normally less than 24 months".* In this response, we would like to highlight the following key points:	Thank you for your comment. During discussions the committee was mindful of the need to consider the "totality of the data and analysis" regarding the short life expectancy criterion and the interpretation of the word normally. However, the committee was also mindful of being satisfied that assumptions used in the reference case economic modelling are plausible, objective and robust. The committee did not feel satisfied that this was the case for the

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			• Additional evidence has become available since publication of TA649 for polatuzumab vedotin in September 2020, which was based on data in 40 patients receiving POLA+BR in the GO29365 study (compared with 40 patients receiving BR alone).[6,7] The assessment of end-of-life criterion 1 should take into account all available evidence, including mean and median data from clinical trials and real world evidence, as well as clinical expert opinion. • The evidence provided to the committee from scientific literature, experience in clinical practice and clinical expert opinion is consistent in indicating that life expectancy for patients with relapsed or refractory DLBCL who are not eligible for stem cell transplant is normally below 24 months, including with POLA+BR treatment. • The inclusion of the word 'normally' to define end of life criterion 1 can be interpreted in different ways. For example, to reflect survival expectations for the majority of the patient population, or that there is flexibility in the 24-month threshold. The wording does not refer to a specific measure that should be applied to assess expected or "normal" survival. *All available evidence should be considered, including recent UK real-world evidence* The NICE committee have appeared to rely mostly on analyses performed as part of NICE TA649 for determining whether TAFA+LEN meets end of life criteria. We strongly believe that this view should be reconsidered in light of more recent published evidence becoming available and clinical experience following implementation of the TA649 guidance. Additional evidence published since September 2020 when TA649 was released includes data from longer follow-up of the randomised cohort (n=40) and the extension cohort (n=106) of the GO29365 study, and real-world evidence from UK clinical practice (N=133, including 78 patients receiving standalone POLA+BR therapy).[3,4] These studies were presented to NICE during technical engagement, along with a recent SLR by Thuresson et al;[1] all studies indicate that survival in the real-world setting is below that seen in the GO29365 study for most patients. • In the GO29365 trial (Sehn 2022), median survival was 12.4 months and 12.5 months for POLA+BR in the randomised arm and extension cohorts, respectively; both of which are substantially below 24 months.[3] • In the randomised arm of the GO29365 study, at 24 months, overall survival probability was 38% with POLA+BR in the randomised cohort, slightly below the 39.9% estimate in the company's base case.[3] • Overall survival estimates from UK real-world evidence (Northend et al. 2022) suggest that expected survival with POLA+BR in UK clinical practice may be lower than shown in the GO29365 trial, with median OS of 10.2 months and 8.2 months for the standalone treatment and overall cohorts, respectively (24-month survival estimates are not yet available for this study).[4]	different survival estimations presented (see FAD – section 3.8). The committee discussed survival estimates for polatuzumab vedotin plus rituximab and bendamustine and accepted that the ERG base case likely overestimates survival for polatuzumab vedotin plus rituximab and bendamustine when considering the responses to the appraisal consultation document from clinical experts. However, the committee noted considerable uncertainty in survival extrapolations, specifically how the absolute and relative benefit of polatuzumab vedotin plus rituximab and bendamustine over rituximab and bendamustine alone is not reflected. The committee did request additional modelling approaches to be presented by the company in response to the appraisal consultation document to address these uncertainties but unfortunately this was not provided (see FAD – section 3.6). The committee also concluded that even if the survival outcomes estimated in NICE's technology appraisal guidance on polatuzumab vedotin were overestimated, they were unlikely to be overestimated to an extent that would mean concluding that tafasitamab with lenalidomide does meet the end of life criteria if corrected (see FAD – section 3.8).

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			• In the SLR by Thuresson et al. (2019) overall survival time ranging between 5.0 and 22.0 months across 6 randomised controlled trials and 13 prospective, observational, single-arm trials.[1] These estimates for median survival time for the overall population with R/R DLBCL not eligible for transplant indicate that survival is usually below 24 months. *Experience in routine clinical practice suggests normal life expectancy is substantially below 24 months* There is some clinical uncertainty about the prognosis of R/R DLBCL for transplant-ineligible patients due to recent emergence of POLA+BR as standard of care in the UK. However, clinical expert opinion for the overall population with R/R DLBCL not eligible for transplant indicates that survival is usually below 24 months, consistent with the published evidence. Clinical experts consulted by NICE during technical engagement and the committee meeting stated that based on their experience life expectancy is less than 24 months (pages 667, 688 and 727 of the Committee papers). Indeed the ACD notes that *"clinical experts shared results from published literature in their submission. These showed median overall survival for people with the condition having polatuzumab vedotin with bendamustine and rituximab ranging from 8.2 to 12.5 months. The clinical experts also said their expectation of survival was less than 24 months".* We have also received feedback from 7 UK clinicians during the appraisal consultation process, which highlighted the following considerations. • All clinicians advised that, based on their experience treating patients with POLA+BR, their expectations for survival are below 24 months. One clinician noted that 24 months is reasonable as a best-case scenario [for survival] for a subset of patients, but that many will fare worse; it was noted that "long-term survivors are a minority" Others commented that conversations about survival with patients are in "months not years" or that their expectations for survival in this population are below 12 months. • Planning for palliative and end of life care. often occurs at relapse for patients who are ineligible for transplant. One clinician noted that they invite their palliative nurse to join the consultation for transplant ineligible [DLBCL] patients. *Interpretation of the word "normally" from a patient and clinician perspective.* Assessment should take into account both mean and median survival data, consider interpretation of the word "normally" from a patient and clinician perspective. • Clinicians commented that if clinical trial evidence is discussed with their patients, they state the median values and give life expectancies in months. The mean value was not considered appropriate for communicating average survival; one clinician advised that *"using mean survival as the outliers will substantially extend the timelines and this is not reflective of practice in "the real*	

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			world"" • In the ACD, the committee comments that, with POLA+BR considered standard of care *"more than 1 in 3 people were alive at 24 months in the company's and the ERG's base case models, which was also consistent with data from Sehn et al."* This equates to 39.9% and 44.9% survival at 24 months in the company and ERG base cases respectively. This suggests at least 55.1–60.1% of patients still do not survive 24 months after diagnosis with R/R DLBCL in patients not eligible for stem cell transplant. These estimates are slightly higher than the actual 2-year survival estimate of 38% observed in the GO29365 study randomised cohort,[3] which suggest that both the company and ERG modelled estimates at 2 years may be overly optimistic predictions of POLA+BR survival, with up to 65% of patients surviving less than 24 months based on the observed data. o With more than half of patients – the majority – not surviving 24 months, we suggest that most people would conclude survival for this population is "normally" less than 24 months. This interpretation is supported by the appeal decision for NICE TA788 (September 2021; avelumab in metastatic bladder cancer).[8] *The evidence supporting survival for patients with relapsed or refractory DLBCL are robust.* The ACD notes a comment from the ERG "on pg. 170 of the ERG report, there is outstanding uncertainty about the robustness of the evidence related to the end-of-life criteria: 'The above issues taken together leave the ERG uncertain about the strength and relevance of evidence selected to underpin the company's claim in relation to meeting the NICE end-of-life criteria…The ERG has highlighted this as a key issue.'" The data presented to the committee during technical engagement included data from Sehn et al. 2022 (GO29365 additional follow-up [n=40] and extension cohort (n=106),[3] the Northend 2022 UK retrospective cohort study (n=133, including 78 patients receiving standalone POLA+BR therapy).[4] and a systematic literature review in R/R DLBCL by Thuresson et al. (2019)[1] showing overall survival time ranging between 5.0 and 22.0 months across 6 randomised controlled trials and 13 prospective, observational, single-arm trials; we consider these sources to be robust.	
4		Incyte Biosciences UK Ltd	**Issues raised in the ACD: Indirect comparisons** We have reviewed the discussion by the committee of the indirect treatment comparisons in this submission, which raise concerns particularly around the comparison of TAFA+LEN versus POLA+BR driven by the fact that the source of evidence for TAFA+LEN is a single-arm study. We acknowledge that randomised treatment comparisons are preferable. However, as indicated above, Incyte's reliance on the single-arm L-MIND study for the purposes of this appraisal followed accelerated approval by regulatory authorities to make TAFA+LEN available to patients as quickly as possible, based on the promising results observed in L-MIND.	Thank you for your comment. The committee discussed the indirect treatment comparisons and was disappointed that the company did not provide the additional analyses requested in response to the appraisal consultation document. The information raised in this comment was discussed by committee previously. As no new evidence has been submitted, the committee's conclusions remain as seen in FAD – section 3.4 and 3.6.

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			The indirect treatment comparisons for this submission rigorously followed NICE TSD 17 and 18 guidelines for generating relative efficacy estimates leveraging non-randomised evidence.[9,10] Despite some limitations in the analyses, which are clearly acknowledged, all relative efficacy estimates derived using indirect evidence (through either MAIC, nearest neighbour matching, inverse probability of treatment weighting, overlap weighting and regression adjustment) provided consistent results showing improved efficacy for TAFA+ LEN over POLA+BR, albeit in some instances only a numerical advantage (i.e. without statistical significance). Moreover, it is worth noting that the EMA and MHRA accepted the MAIC results (for duration of response) to maintain the orphan drug designation for TAFA+LEN at the time of authorisation. *Proportional Hazards Assumption* We are pleased that the ERG and committee agreed that the proportional hazard assumption does not hold in the comparison of TAFA+LEN vs. POLA+BR. The committee suggested that, because of the likely violation of the proportional hazard assumption, more complex approaches beyond the company proposed piecewise constant hazard ratios (HRs) with splitting at 4 months might be needed. Although the use of fractional polynomials was considered (i.e. as an alternative approach for estimating time-varying HRs), this approach was discounted for 2 reasons. • Firstly, clinical and statistical evidence pointed to the choice of a splitting point at 4 months: changes in the pattern of the hazards were observed around 4 months in the log-cumulative hazard plots, clinically 4 months corresponds to a landmark point in the POLA + BR therapy, as it can only be given for 6 cycles (approximately 4 months). • Secondly, the comparison was supported by a small effective sample size (ESS) (ESS of 29 patients for the weighted TAFA+LEN sample and 40 POLA+BR patients). Particularly, towards later timepoints in the study, the number of patients at risk was very low (16 in the TAFA + LEN arm and 19 in the POLA + BR arm at 12 months; 13 in the TAFA + LEN arm and 11 in the POLA + BR arm at 24 months). Estimating time-varying HRs based on such a small sample size could lead not only to high uncertainty but also introduce potential bias in the long-term extrapolations, which can have a considerable impact on the economic evaluation. For these reasons, we believe that the use of piecewise constant HRs is more appropriate. *Alignment with TA649* On page 10 of the ACD, the ERG and Committee agree that a constant hazard ratio is not appropriate due to violation of the proportional hazards assumption but prefer use of a constant hazard ratio to align with results in TA649. While TA649 was based on the best evidence available at the time, the randomised controlled trial GO29365,[6] further evidence following implementation of TA649, including real world studies (Northend 2022)[4] together with clinical opinion, indicate that the benefit of POLA + BR therapy in	

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			R/R DLBCL might be lower than observed in GO29365. As quoted in the ACD, the clinical expert panel present during the committee meeting highlighted that the estimates from the company preferred base case extrapolation of survival were aligned with their expectation of survival for patients treated with POLA+BR and closer to their expectations than those proposed by the ERG. *Population matching in RE-MIND2* The L-MIND trial did not include a comparator arm because it was not designed as a registrational trial. RE-MIND (observational trial with matched lenalidomide-only comparator cohort) and RE-MIND2 (retrospective, observational cohort study) were undertaken to assess the contribution of tafasitamab to the combination and characterise the effectiveness of tafasitamab and lenalidomide relative to commonly administered systemic therapies for ASCT ineligible patients with R/R DLBCL. On page 8 of the ACD the committee notes: *"The ERG highlighted that RE-MIND2 consists of pooled individual participant data and is preferred in principle to the intervention population adjustment undertaken in the matching-adjusted indirect comparisons. Adjusting the L-MIND population differently for each comparator treatment population can lead to bias. However, there was uncertainty about the methods used for RE-MIND2 because the baseline characteristics of the tafasitamab with lenalidomide cohort varied depending on the comparator."* We would like to take the opportunity to restate the clarification on the methods used for RE-MIND2 1:1 matching provided in the technical engagement. Specifically: • Logistic regression models were fitted to derive the propensity score used in the nearest neighbour 1:1 matching without replacement of the L-MIND patient population vs each comparator population (a separate regression model for each comparator). • Main results of the RE-MIND2 study were obtained through the use of logistic regression models that included the same list of covariates for all comparators: age, Ann-Arbor staging, refractoriness to last therapy line, number of prior lines of therapy, history of primary refractoriness, prior treatment with ASCT, neutropenia at baseline, anaemia at baseline, elevated lactate dehydrogenase (LDH) at baseline. Of note, in the comparison of TAFA+LEN v. POLA+BR multiple imputation was used. • The 1:1 matching of RE-MIND-2 patients vs each comparator population was achieved as follows: o Estimated propensity score (ePS), reflecting the probability of being treated with TAFA + LEN conditional on the patients' characteristics o For each L-MIND patient, a patient from the comparator population with the closest ePS was selected as their 1:1 match o One might expect that this process should provide the same number of L-MIND-matched patients vs each comparator. However, it is possible that	

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			a different sample size of L-MIND patients may be obtained vs each comparator population when some patients of the comparator population cannot be matched with L-MIND patients (e.g. if distance in the ePS differs more than the pre-specified calliper). It is worth noting however that most of the patients enrolled in the efficacy population of the L-MIND study were retained in the matched comparison versus BR and R-GemOx (75 and 74 patients out of 80, respectively). However, only 36 patients enrolled in RE-MIND2 and treated with POLA+BR had complete data for all covariates required for propensity score estimation. This is likely because POLA+BR was still a relatively novel treatment when the RE-MIND2 study was conducted. Hence, not all TAFA+LEN treated patients in L-MIND could be given a POLA+BR-treated match, despite the use of multiple imputation on the ePS to increase the size of the POLA+BR cohort available for matching as acknowledged in the original submission and the TE. • The same regression method was used to estimate relative efficacy vs each comparator. i.e. Cox proportional hazards (PH) regression (a separate regression model for each comparator) We hope that this further explanation addresses the ERG's point and confirms to the Committee that the same modelling approach was used for all comparators (i.e. the same regression method to derive the ePS, the same list of covariates, the same procedures to derive the callipers, and the same regression method for estimating relative efficacy).	
5		Incyte Biosciences UK Ltd	**Issues raised in the ACD: Overall Survival and progression-free survival (PFS) extrapolations for POLA+BR** In section 3.6, page 11 of the ACD, it is noted that "the committee concluded that the company's parametric extrapolations for polatuzumab vedotin with bendamustine and rituximab were implausible. It found that estimates from the ERG's base case were more plausible because the outcomes were more aligned with NICE's technology appraisal guidance on polatuzumab vedotin with bendamustine and rituximab. However, it would have preferred to see different modelling approaches used that both fitted the underlying hazards of the data and produced outcomes aligned with the polatuzumab vedotin with bendamustine and rituximab guidance." During the appraisal committee meeting, both clinical experts indicated that the POLA+BR OS extrapolations from the time-varying piecewise hazard ratios were more plausible than the constant HR extrapolations, based on the available published evidence and their experience in clinical practice. In addition, as noted above in relation to end of life criteria, additional clinical evidence and experience with POLA+BR has been gained since TA649 and primary completion of the GO29365 trial. While we understand that the NICE committee has tried to be consistent between technology appraisals, and that decisions in NICE TA649 were made with the best available evidence at the time, newer published data for POLA+BR have since become available and there is more experience with POLA+BR in UK clinical practice, which is reflected in recent clinical expert testimony. • The GO29365 trial, which informed TA649, provides direct evidence of the	Thank you for your comment. The committee discussed survival estimates for polatuzumab vedotin plus rituximab and bendamustine and accepted that the ERG base case likely overestimates survival for polatuzumab vedotin plus rituximab and bendamustine when considering the responses to the appraisal consultation document from clinical experts. However, the committee noted considerable uncertainty in survival extrapolations, specifically how the absolute and relative benefit of polatuzumab vedotin plus rituximab and bendamustine over rituximab and bendamustine alone is not reflected. The committee did request additional modelling approaches to be presented by the company in response to the appraisal consultation document to address these uncertainties but unfortunately this was not provided (see FAD – section 3.6). The committee also concluded that even if the survival outcomes estimated in NICE's technology appraisal guidance on polatuzumab vedotin were overestimated, they were unlikely to be significantly overestimated. The

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			efficacy of POLA+BR vs BR, but included a relatively small sample of patients on POLA+BR (n=40).[3,6] UK-specific real-world evidence from Northend 2022 on POLA+BR survival has since been published (N=133; n=78 in standalone POLA+BR cohort), which suggests that POLA+BR survival in practice may be lower than observed in the GO23965 trial, as described above in comment 1.[3,4] • As mentioned above, clinical experts interviewed following publication of the ACD also provided further indication that the ERG preferred extrapolations overestimated OS for POLA+BR. o One clinical expert interviewed noted that "for these patients, I will invite my palliative nurse to join the consultation. I would not do this if the life expectancy was 4 years" o Another clinical expert commented that the mean survival of 4-years generated by the ERG model was "grossly excessive", and that much more was now known about POLA+BR from various published data (including Northend 2022 and GO29365 follow-up data, as well as Greek and German data), which should be considered over this extrapolated estimate. • Furthermore, while a potential plateau was observed in the tail of the OS curves from the GO39265 trial (Sehn 2022), some patients received subsequent treatment with CAR-T which may introduce bias into the OS data from the GO29365 trial when applied without consideration of CAR-T costs in the cost-effectiveness analyses. o The following text is stated in the Sehn 2022 publication on the GO23965 trial, at the end of the results section (pages 537 and 538): *"Of all patients treated with pola + BR in the study (including the extension cohort), 4 patients proceeded to receive consolidative stem cell transplant (autologous [n = 1] or allogeneic [n = 3]). Nine patients received CAR T-cell therapy after pola + BR, including 1 patient who discontinued pola + BR after 3 cycles to bridge to CAR T-cell therapy. For patients treated with CAR T-cell therapy after pola + BR, OS after treatment with pola + BR ranged from 11.5 to 28.0 months; 4 patients are alive and remain in follow-up."* While it is not entirely clear how many of these patients receiving subsequent were in the randomised cohort, this implies that CAR-T therapy may have contributed to longer survival among some patients in the POLA+BR cohort, with the survival estimates of 11.5 to 28.0 months representing survival after POLA+BR treatment, without including the additional OS contribution from POLA+BR treatment itself prior to treatment with CAR-T. o NICE's position statement on the consideration of products recommended for use in the Cancer Drugs Fund as comparators, or in a treatment sequence, in the appraisal of a new cancer product states that: *"products recommended for use in the Cancer Drugs Fund after 1 April 2016 should*	committee heard from the ERG that the inclusion of patients treated with polatuzumab vedotin with bendamustine who also received chimeric antigen receptor cell therapy may bias the results, but the effect is not expected to be large (see FAD – section 3.8).

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			not be considered as comparators, or appropriately included in a treatment sequence, in subsequent relevant appraisals. Companies of new cancer products under appraisal should therefore not include treatments recommended for use in the Cancer Drugs Fund as comparators, or treatment sequence products in their economic modelling."[11] o As the ERG preferred to exclude the cost of CAR-T therapy in line with the NICE position statement, aligning the OS extrapolations to those from updated GO29365 trial results[3] may bias the results in favour of POLA+BR by including potential health benefits of CAR-T, without including the associated costs. In terms of PFS, similar to OS, both clinical experts during the committee meeting indicated that the POLA+BR PFS from the time-varying (piecewise constant) HRs were more plausible than the constant HR extrapolations, based on the available published evidence and their experience in clinical practice. As shown on slide 27 of the NICE committee slides, the PFS extrapolation for POLA+BR when using the time-varying hazard ratios produced a survival curve closer to the observed PFS for the randomised cohort in the Sehn 2022 publication. Median PFS was 9.2 months and 1-year PFS was ~42%.[3] Given the clinical expert feedback provided during the committee meeting and the better alignment with the updated PFS data from Sehn 2022, we strongly believe that the time-varying HR extrapolations for POLA+BR PFS have both better clinical and external validity than the constant HR-based PFS extrapolation preferred by the ERG.	
6		Incyte Biosciences UK Ltd	**Issues raised in the ACD: PFS extrapolations for TAFA+LEN** Incyte accepts the committee's comments preferring the lognormal model for extrapolating TAFA+LEN progression-free survival. Revised company base case results using the lognormal model for TAFA+LEN PFS are provided in the Appendix, along with additional pricing scenarios. In Section 3.7 of the ACD, it is stated that *"The ERG accepted that the lognormal distribution overestimates progression-free survival for the first 20 months but pointed out that it provides the smallest overestimation in the long term."* However, the lognormal model underestimates longer-term PFS after 20 months relative to the TAFA+LEN KM curve. As such, we suggest that the statement could be amended as follows: "The ERG accepted that the lognormal distribution overestimates progression-free survival for the first 20 months but pointed out that it provides a smaller underestimation of the observed KM curve in the long term compared to the log-logistic, Weibull and exponential models."	Thank you for your comment. The updated company base case has been reflected in the FAD – see section 3.7. The suggested amendment is no longer applicable as the sentence has been removed based on the updated company base case.
7		Incyte Biosciences UK Ltd	**Issues raised in the ACD: TAFA+LEN is not cost-effective** In Section 3.9 of the ACD, the following statements are included: • "The committee considered that the most plausible incremental cost-effectiveness ratio (ICER) was highly uncertainty, because of issues with the indirect comparisons and modelling (see sections 3.4, 3.6 and 3.7). It noted that the base case ICERs presented by the company for tafasitamab with lenalidomide compared with polatuzumab vedotin with bendamustine and	Thank you for your comment and revised base case analyses, scenario analyses and appendix. It is not appropriate to present ICERs to committee that include a company's assumed discount for comparators. Therefore, the company's base case ICERs were adjusted to remove assumed discounts as the company base case was not updated even

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			rituximab were higher than the range normally considered a cost-effective use of NHS resources, even for end-of-life treatments." • "However, tafasitamab with lenalidomide had not been shown to be a cost-effective use of NHS resources in any analyses presented to the committee." In Section 3.13 of the ACD, the following is stated: • "However, there is substantial uncertainty in the modelling and the committee was not presented with any analysis showing tafasitamab with lenalidomide was cost effective." We wish to clarify that the company did submit a cost-effective ICER versus POLA+BR during technical engagement. The company base case included an estimated price discount for lenalidomide to reflect imminent generic entry onto the market and produced an ICER for TAFA+LEN versus POLA+BR of [redacted] which is cost-effective when considering a willingness to pay threshold normally applied for end-of-life treatments. [redacted] The majority of discussion about the cost-effectiveness of TAFA+LEN was completed in part 2 of the committee meeting, and therefore the company has limited information to fully understand the position taken by the NICE committee. Incyte is aware that a PAS for polatuzumab is in place, and it was at the Committee meeting that that pola+BR was confirmed as the suitable comparator for this appraisal. [redacted]. Revised base case analyses, as well as additional scenarios, are provided in the Appendix.	when this issue was raised by the NICE technical team and the ERG. This did result in ICERs that were not cost-effective being submitted. Assumed discounts are not appropriate because decision-making ICERs are based on prices for all treatments that are most relevant to the NHS.
8		Incyte Biosciences UK Ltd	Issues raised in the ACD: Additional benefit not captured in the QALYs On page 15 of the ACD, the committee note that they were not presented with evidence of additional benefit that had not been captured in the quality-adjusted life year (QALY) calculation. However, clinicians consulted by NICE during the submission believed that tafasitamab would result in health-related benefits, including some that may not be captured in the QALY calculation (pages 661 and 680 of the Committee papers). • As noted in the company submission (e.g., in the innovation section of Document B) the value of tafasitamab is reflected in the PIM designation from the MHRA (January 2020 – PIM 2019/0012) additionally tafasitamab maintained orphan designation in R/R DLBCL after EMA and MHRA assessed that DoR could be clinically relevant and supportive of a significant benefit over Pola+BR (based on MAIC analysis).[5] • Tafasitamab is a chemotherapy-free treatment option that does not target CD20, the target of rituximab, representing a shift in the treatment paradigm for R/R DLBCL not eligible for transplant o Many patients undergo CD20-negative transformation following rituximab treatment, a key component of chemoimmunotherapy regimens for DLBCL	Thank you for your comment. The committee discussed the possibility of uncaptured benefits but the committee concluded that without an estimate of the uncaptured benefit, the impact on the cost-effectiveness results cannot be assessed. The comment and the committee conclusion have been included in the FAD – see section 3.11.

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			and first and subsequent lines of therapy.[12-18] In L-MIND, 34/81 (42%) of patients were rituximab-refractory at baseline.[19] o The tolerability profile of tafasitamab also means that, following TAFA+LEN treatment, tafasitamab monotherapy can be continued until disease progression for most patients, while current chemotherapy-based regimens are given for a fixed treatment duration. In L-MIND, 10/81 (12%) of patients discontinued treatment with TAFA+LEN due to adverse events, and there was only 1 treatment discontinuation during the extended tafasitamab monotherapy phase, in a patient with recurrence of previously-diagnosed marginal zone lymphoma that had been documented as an adverse event.[19,20] • The main goal of treatment is to prolong remission. The submission from Lymphoma Action highlighted that patients and their families experience substantial anxiety due to fear of relapse; treatments with greater chances of long remissions such as tafasitamab with lenalidomide could help alleviate some of that anxiety. • Lymphoma Action also noted the challenges of caring for someone with DLBCL, which is time-consuming and emotionally challenging. In addition, tafasitamab can be administered in an outpatient setting with minimal training required for its introduction to the treatment pathway, as other monoclonal antibodies are administered in routine clinical practice. Incyte has requested that clinical and patient experts attend the second appraisal committee meeting to address the clinical uncertainties and give a voice to patients respectively.	
9	Web comment	Public 1	• Has all of the relevant evidence been taken into account? Overall I think it has. As ever NICE has been thorough in its approach which is to be congratulated. However I would say that the original BR+pola randomised trial was clearly in a select patient group as we have sadly not been able to replicate the excellent outcomes seen in this paper in the real world. Whilst Pola+BR is a useful regimen and an appropriate comparator, the Northend et al data is the more appropriate data to use. • Are the summaries of clinical and and cost effectiveness reasonable interpretations of the evidence? I do not feel it's appropriate to use the Sehn et al pola+BR clinical trial as comparator data as this does not represent the patients we treat in the real world with pola+BR. 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'. I therefore WOULD regard that the end of life criteria are met by the tafa+len submission. In my practise (which covers an extended MDT population of 2.2 million people), life expectancy when using pola+BR is < 2 years (no-where near 4 years sadly). I would be using tafa+len for a similar indication and	Thank you for your comment. The committee discussed survival estimates for polatuzumab vedotin plus rituximab and bendamustine and accepted that the ERG base case likely overestimates survival for polatuzumab vedotin plus rituximab and bendamustine when considering the responses to the appraisal consultation document from clinical experts. However, the committee noted considerable uncertainty in survival extrapolations, specifically how the absolute and relative benefit of polatuzumab vedotin plus rituximab and bendamustine over rituximab and bendamustine alone is not reflected. The committee also discussed Northend et al. and heard from experts that the real world study included patients with different histology to the clinical trials and that mixing real world and clinical trial data can add uncertainty. Regarding the end of life criteria, the committee concluded that even if the survival

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			therefore life expectancy would be similar without it. Due to the phase 2 efficacy data I would expect prolongation of survival by more than 3 months in this setting. • Are the recommendations a sound and suitable basis for guidance to the NHS? Currently I do not think this is suitable guidance for the needs of NHS patients. I agree there is considerable uncertainty. However my view is this should be funded within the CDF and during this time longer follow up from the phase 2 will emerge. More importantly though, data can be collected on patients treated in England (which can be lead by PHE or by an engaged clinician) and presented. This will provide more reliable data on which to re-appraise tafa+len for suitability for routine commissioning. This has been done for other drugs and indications (the brentuximab vedotin in patients with Hodgkin who failed 2 lines of treatment and were ineligible for stem cell transplantation comes to mind). I would also add that tafa+len adds a very useful treatment option for patients who have less marrow reserve as Pola+BR is very myelosuppressive with high risk of febrile neutropenia. • Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, sex, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity? Not that I'm aware of.	outcomes estimated in NICE's technology appraisal guidance on polatuzumab vedotin were overestimated, they were unlikely to be overestimated to an extent that would mean concluding that tafasitamab with lenalidomide does meet the end of life criteria if corrected (see FAD – section 3.8). The committee also discussed CDF access and determined that the inclusion criteria were not met due to the low possibility of being cost-effective and the absence of ongoing Phase 3 data being collected. See FAD – section 3.10.
10	Web comment	Public 2	• Has all of the relevant evidence been taken into account? Yes. • Are the summaries of clinical and and cost effectiveness reasonable interpretations of the evidence? No. Undue weight seems to have been given to the Pola BR efficacy assumptions made at the NICE TA. Average OS of >24 months is not something we see in clinical practice with Pola BR in R/R DLBCL setting. Published data doesnt support this assumption either. In an extended cohort analysis of the Pola BR study which reported on 106 patients, median OS and PFS were around 12 and 6 months respectively (Sehn LH, et L. Blood Adv (2022) 6 (2): 533–543). Meidan OS and PFS were only 8.2 and 4.8 months in a UK RWE analysis reporting on 131 patients. These figures are more in keeping with our clinical experience in the UK (Northend M, et L. Blood Adv 2022). In fact even with R-Gem Ox regimen, median OS was just over 12 months and PFS around 6 months in a phase 2 Lysa Study (Mounier N, et al. Haematologica 2012). Therefore the current available evidence and clinical experience doesnt allow us to conclude that Pola BR has transformed outcomes of R/R DLBCL in transplant ineligible patients. At best it represents	Thank you for your comment. The committee discussed survival estimates for polatuzumab vedotin plus rituximab and bendamustine and accepted that the ERG base case likely overestimates survival for polatuzumab vedotin plus rituximab and bendamustine when considering the responses to the appraisal consultation document from clinical experts. However, the committee noted considerable uncertainty in survival extrapolations, specifically how the absolute and relative benefit of polatuzumab vedotin plus rituximab and bendamustine over rituximab and bendamustine alone is not reflected. The committee also discussed Northend et al. and heard from experts that the real world study included patients with different histology to the clinical trials and that mixing real world and clinical trial data can add uncertainty. Regarding the end of life criteria, the committee concluded that even if the survival outcomes estimated in NICE's technology appraisal

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			an additional treatment option for these patients but their expected median survival is still way short of 24 months. With all the short comings listed, the L-MIND data on Tafa/Len compares quite favourably against this backdrop. Median OS and PFS of 33.5 months and 11.6 months respectively for the 80 patients treated in this trial (Duell J, et al. Oral presentation at Virtual ICML 2021; Abstract 28) does represent a significant step forward. • Are the recommendations a sound and suitable basis for guidance to the NHS? No. The committee seems to have given undue weightage to survival assumptions made at a previous NICE TA for Pola BR regimen. The phase 2 randomised Pola BR study was a very small study with only 40 patients in each arm. The control arm in the study was BR which is not standard in the UK. Neither the trial data nor subsequent data from extended cohort analysis or UK RWE would suggest average OS of 24 months with this regimen. The committee view that Pola BR should be considered standard of care in management of R/R DLBCL in transplant inelgible patients is not supported by available evidence or clinical experience. To deny patients access to other effective treatments (such as Tafa/Len) would be doing injustice and would stifle access to novel therapies for the UK patients. • Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, sex, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity? No.	guidance on polatuzumab vedotin were overestimated, they were unlikely to be overestimated to an extent that would mean concluding that tafasitamab with lenalidomide does meet the end of life criteria if corrected (see FAD – section 3.8).
11	Web comment	Public 3	• Has all of the relevant evidence been taken into account? My comments are in relation to the end of life criteria as the evidence for auto ineligible patients (Norton et al/ Sehn et al ritux,pola, benda) DECC (Maddox , Osborne) is a survival of months, maybe up to a year with a survival of 2 years unlikely. • Are the summaries of clinical and and cost effectiveness reasonable interpretations of the evidence? Clinical survival data for RR DLBCL auto ineligible is not as I have interpreted the evidence, as discussed above. • Are the recommendations a sound and suitable basis for guidance to the NHS? In view of the unmet need for pts with RR DLBCL and the tolerability of tafa len I would support approval.	Thank you for your comment. The committee discussed survival estimates for polatuzumab vedotin plus rituximab and bendamustine and accepted that the ERG base case likely overestimates survival for polatuzumab vedotin plus rituximab and bendamustine when considering the responses to the appraisal consultation document from clinical experts. However, the committee noted considerable uncertainty in survival extrapolations, specifically how the absolute and relative benefit of polatuzumab vedotin plus rituximab and bendamustine over rituximab and bendamustine alone is not reflected. The committee also discussed Northend et al. and heard from experts that the real world study included patients with different histology to the clinical trials and that mixing real world and clinical trial data can add uncertainty. Regarding the end of life criteria, the

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			• Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, sex, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity? No. • Recommendations – section 1 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. I am therefore not clear where the data for this end of life criteria are from. Even patients who are started on rbendapola have a survival of less than a year in trial and this was reduced further in the UK real world data.	committee concluded that even if the survival outcomes estimated in NICE's technology appraisal guidance on polatuzumab vedotin were overestimated, they were unlikely to be overestimated to an extent that would mean concluding that tafasitamab with lenalidomide does meet the end of life criteria if corrected (see FAD – section 3.8).

NICE National Institute for Health and Care Excellence

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

	Please read the checklist for submitting comments at the end of this form. We cannot accept forms that are not filled in correctly. The Appraisal Committee is interested in receiving comments on the following: • has all of the relevant evidence been taken into account? • are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence? • are the provisional recommendations sound and a suitable basis for guidance to the NHS? NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that the preliminary recommendations may need changing in order to meet these aims. In particular, please tell us if the preliminary recommendations: • could have a different impact on people protected by the equality legislation than on the wider population, for example by making it more difficult in practice for a specific group to access the technology; • could have any adverse impact on people with a particular disability or disabilities. Please provide any relevant information or data you have regarding such impacts and how they could be avoided or reduced**.**
Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	Incyte Biosciences UK Ltd
Disclosure **Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.**	None

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NICE National Institute for Health and Care Excellence

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

Name of commentator person completing form:	[redacted]
Comment number	**Comments** Insert each comment in a new row. Do not paste other tables into this table, because your comments could get lost – type directly into this table.
	Introduction We have carefully considered the Committee's assessment of the evidence submitted for the single technology appraisal for tafasitamab with lenalidomide for treating patients with relapsed or refractory diffuse B-cell lymphoma (DLBCL) who are not eligible for autologous stem cell transplant. We are disappointed by the conclusions reached by the Committee and the resulting preliminary guidance not to recommend tafasitamab. We appreciate the opportunity to provide a response to the Appraisal Consultation Document (ACD). Considering the Committee's feedback and the points noted below, we present a revised base case and PAS [redacted] with additional scenarios are presented in a separate appendix. The base case and cost-effectiveness of TAFA+LEN are discussed in Comment 4 and Comment 5. *Tafasitamab with lenalidomide meets end of life criteria* DLBCL is an aggressive form of lymphoma, with poor outcomes once relapsed or refractory disease occurs following first-line treatment.[1,2] We do not believe that all the relevant evidence and clinical experience has been taken into account by the committee in its decision making. • Feedback from clinical experts during the committee meeting, as well as additional expert feedback collected following publication of the ACD, highlights that: normal survival expectations are below 24 months with POLA+BR based on their experience since POLA+BR became available in the UK; and that the average 4-year survival cited in the ACD is a substantial overestimate of expected survival for patients with R/R DLBCL not eligible for transplant. • The reason for the committee's view appears to be a concern regarding an apparent inconsistency with the modelled extension to life accepted by the Committee who appraised polatuzumab vedotin (TA649). However additional evidence has become available since publication of TA649 in September 2020 • Life expectancy predictions in TA649 were based on data in 40 patients receiving polatuzumab vedotin with bendamustine and rituximab (POLA+BR) in the GO29365 study. Since TA649 publication, additional evidence that has become available includes further follow-up of the GO29365 randomised cohort, and a GO29365 extension cohort (N=106).[3] Additionally, UK real-world data collected

since publication of TA649 (N=133, including 78 patients receiving standalone POLA+BR therapy) have shown that life expectancy following treatment with polatuzumab vedotin is lower than observed in the GO29365 trial (median 10.2 months in the standalone treatment cohort vs. 12.5 months).[3,4]

- The totality of the evidence, including new published evidence since TA649 release, and clinical expert opinion now that POLA+BR is established in routine clinical practice, demonstrate that patients with R/R DLBCL, particularly those who are not eligible for stem cell transplant, survive less than 24 months, and therefore tafasitamab satisfies criterion 1 of the end-of-life criteria.

Robust methodology was used for indirect treatment comparisons

Due to the unmet clinical need of patients with R/R DLBCL and the associated accelerated approval for tafasitamab, randomised controlled trial data are not available and indirect treatment comparisons are required to inform assessment of tafasitamab clinical effectiveness. The indirect comparisons for this submission rigorously followed NICE DSU 17 and 18 guidance. In section 2 we provide further explanation and clarification of the methodology used.

Clinical experts believe that survival extrapolations used by the company are more plausible than higher survival predictions

We do not believe all the evidence has been considered when assessing plausibility of the overall survival extrapolations, including published real-world evidence and experience in routine clinical practice. In addition, some patients in the GO29365 trial received subsequent treatment with chimeric antigen receptor-T-cell therapy (CAR-T), which may contribute to the potential plateau observed in the overall survival curve. This aspect should be carefully considered as CAR-T costs were excluded in economic analyses for this submission due to current inclusion in the Cancer Drugs Fund.[5] We discuss these points further in Comment 5.

Tafasitamab with lenalidomide provides benefit not fully captured in the quality-adjusted life year (QALY) calculation

Tafasitamab with lenalidomide is an innovative, chemotherapy-free immunotherapy for relapsed or refractory DLBCL in patients not eligible for stem cell transplant. Tafasitamab has received both a Promising Innovative Medicines (PIM) designation from the MHRA and Orphan designation from the EMA. It has received accelerated approval from both the EMA and MHRA due to the high unmet need and “potential significant benefit” of tafasitamab as shown in the pivotal L-MIND clinical trial, and matched adjusted indirect treatment comparison (MAIC) analysis of duration of response for tafasitamab with lenalidomide vs. polatuzumab with bendamustine and rituximab.[5]

The submissions received by NICE, both in writing and orally, from patients and healthcare providers, have highlighted the substantial burden and poor prognosis for patients with R/R DLBCL, particularly for those who are not eligible for transplant, and have confirmed that tafasitamab in combination with lenalidomide provides important benefit to patients that are not reflected in the QALY assessment. We discuss this point further in Comment 6.

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

	We hope that this response has addressed the concerns expressed by the Committee in the ACD and will be sufficient to provide a positive recommendation for tafasitamab with lenalidomide for patients with R/R DLBCL who are not eligible for stem cell transplant.
1	**Issues raised in the ACD: End of life Criterion 1 not met** We are pleased that the Committee has confirmed that end-of-life criterion 2 has been met, with TAFA+LEN providing more than 3 months additional survival compared with POLA+BR as recently established standard of care. However, we do not agree with the committee's view that end of life criterion 1 is not met and do not believe that all relevant evidence has been taken into account in the committee's decision making. NICE guidelines on criterion 1 state that *"the treatment is indicated for patients with a short life expectancy, normally less than 24 months".* In this response, we would like to highlight the following key points: • Additional evidence has become available since publication of TA649 for polatuzumab vedotin in September 2020, which was based on data in 40 patients receiving POLA+BR in the GO29365 study (compared with 40 patients receiving BR alone).[6,7] The assessment of end-of-life criterion 1 should take into account all available evidence, including mean and median data from clinical trials and real world evidence, as well as clinical expert opinion. • The evidence provided to the committee from scientific literature, experience in clinical practice and clinical expert opinion is consistent in indicating that life expectancy for patients with relapsed or refractory DLBCL who are not eligible for stem cell transplant is normally below 24 months, including with POLA+BR treatment. • The inclusion of the word 'normally' to define end of life criterion 1 can be interpreted in different ways. For example, to reflect survival expectations for the majority of the patient population, or that there is flexibility in the 24-month threshold. The wording does not refer to a specific measure that should be applied to assess expected or "normal" survival. *All available evidence should be considered, including recent UK real-world evidence* The NICE committee have appeared to rely mostly on analyses performed as part of NICE TA649 for determining whether TAFA+LEN meets end of life criteria. We strongly believe that this view should be reconsidered in light of more recent published evidence becoming available and clinical experience following implementation of the TA649 guidance. Additional evidence published since September 2020 when TA649 was released includes data from longer follow-up of the randomised cohort (n=40) and the extension cohort (n=106) of the GO29365 study, and real-world evidence from UK clinical practice (N=133, including 78 patients receiving standalone POLA+BR therapy).[3,4] These studies were presented to NICE during technical engagement, along with a recent SLR by Thuresson et al;[1] all studies indicate that survival in the real-world setting is below that seen in the GO29365 study for most patients.

- In the GO29365 trial (Sehn 2022), median survival was 12.4 months and 12.5 months for POLA+BR in the randomised arm and extension cohorts, respectively; both of which are substantially below 24 months.[3]
- In the randomised arm of the GO29365 study, at 24 months, overall survival probability was 38% with POLA+BR in the randomised cohort, slightly below the 39.9% estimate in the company's base case.[3]
- Overall survival estimates from UK real-world evidence (Northend et al. 2022) suggest that expected survival with POLA+BR in UK clinical practice may be lower than shown in the GO29365 trial, with median OS of 10.2 months and 8.2 months for the standalone treatment and overall cohorts, respectively (24-month survival estimates are not yet available for this study).[4]
- In the SLR by Thuresson et al. (2019) overall survival time ranging between 5.0 and 22.0 months across 6 randomised controlled trials and 13 prospective, observational, single-arm trials.[1]

These estimates for median survival time for the overall population with R/R DLBCL not eligible for transplant indicate that survival is usually below 24 months.

Experience in routine clinical practice suggests normal life expectancy is substantially below 24 months

There is some clinical uncertainty about the prognosis of R/R DLBCL for transplant-ineligible patients due to recent emergence of POLA+BR as standard of care in the UK. However, clinical expert opinion for the overall population with R/R DLBCL not eligible for transplant indicates that survival is usually below 24 months, consistent with the published evidence.

Clinical experts consulted by NICE during technical engagement and the committee meeting stated that based on their experience life expectancy is less than 24 months (pages 667, 688 and 727 of the Committee papers). Indeed the ACD notes that *"clinical experts shared results from published literature in their submission. These showed median overall survival for people with the condition having polatuzumab vedotin with bendamustine and rituximab ranging from 8.2 to 12.5 months. The clinical experts also said their expectation of survival was less than 24 months".*

We have also received feedback from 7 UK clinicians during the appraisal consultation process, which highlighted the following considerations.

- All clinicians advised that, based on their experience treating patients with POLA+BR, their expectations for survival are below 24 months. One clinician noted that 24 months is reasonable as a best-case scenario [for survival] for a subset of patients, but that many will fare worse; it was noted that "long-term survivors are a minority" Others commented that conversations about survival with patients are in "months not years" or that their expectations for survival in this population are below 12 months.
- Planning for palliative and end of life care. often occurs at relapse for patients who are ineligible for transplant. One clinician noted that they invite their palliative nurse to join the consultation for transplant ineligible [DLBCL] patients.

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	Interpretation of the word "normally" from a patient and clinician perspective. Assessment should take into account both mean and median survival data, consider interpretation of the word "normally" from a patient and clinician perspective. • Clinicians commented that if clinical trial evidence is discussed with their patients, they state the median values and give life expectancies in months. The mean value was not considered appropriate for communicating average survival; one clinician advised that *"using mean survival as the outliers will substantially extend the timelines and this is not reflective of practice in "the real world""* • In the ACD, the committee comments that, with POLA+BR considered standard of care *"more than 1 in 3 people were alive at 24 months in the company's and the ERG's base case models, which was also consistent with data from Sehn et al."* This equates to 39.9% and 44.9% survival at 24 months in the company and ERG base cases respectively. This suggests at least 55.1–60.1% of patients still do not survive 24 months after diagnosis with R/R DLBCL in patients not eligible for stem cell transplant. These estimates are slightly higher than the actual 2-year survival estimate of 38% observed in the GO29365 study randomised cohort,[3] which suggest that both the company and ERG modelled estimates at 2 years may be overly optimistic predictions of POLA+BR survival, with up to 65% of patients surviving less than 24 months based on the observed data. o With more than half of patients – the majority – not surviving 24 months, we suggest that most people would conclude survival for this population is "normally" less than 24 months. This interpretation is supported by the appeal decision for NICE TA788 (September 2021; avelumab in metastatic bladder cancer).[8] *The evidence supporting survival for patients with relapsed or refractory DLBCL are robust.* The ACD notes a comment from the ERG "on pg. 170 of the ERG report, there is outstanding uncertainty about the robustness of the evidence related to the end-of-life criteria: 'The above issues taken together leave the ERG uncertain about the strength and relevance of evidence selected to underpin the company's claim in relation to meeting the NICE end-of-life criteria…The ERG has highlighted this as a key issue.'" • The data presented to the committee during technical engagement included data from Sehn et al. 2022 (GO29365 additional follow-up [n=40] and extension cohort (n=106),[3] the Northend 2022 UK retrospective cohort study (n=133, including 78 patients receiving standalone POLA+BR therapy).[4] and a systematic literature review in R/R DLBCL by Thuresson et al. (2019)[1] showing overall survival time ranging between 5.0 and 22.0 months across 6 randomised controlled trials and 13 prospective, observational, single-arm trials; we consider these sources to be robust.
2	**Issues raised in the ACD: Indirect comparisons** We have reviewed the discussion by the committee of the indirect treatment comparisons in this submission, which raise concerns particularly around the comparison of TAFA+LEN versus POLA+BR driven by the fact that the source of evidence for TAFA+LEN is a single-arm study.

We acknowledge that randomised treatment comparisons are preferable. However, as indicated above, Incyte's reliance on the single-arm L-MIND study for the purposes of this appraisal followed accelerated approval by regulatory authorities to make TAFA+LEN available to patients as quickly as possible, based on the promising results observed in L-MIND.

The indirect treatment comparisons for this submission rigorously followed NICE TSD 17 and 18 guidelines for generating relative efficacy estimates leveraging non-randomised evidence.[9,10] Despite some limitations in the analyses, which are clearly acknowledged, all relative efficacy estimates derived using indirect evidence (through either MAIC, nearest neighbour matching, inverse probability of treatment weighting, overlap weighting and regression adjustment) provided consistent results showing improved efficacy for TAFA+ LEN over POLA+BR, albeit in some instances only a numerical advantage (i.e. without statistical significance). Moreover, it is worth noting that the EMA and MHRA accepted the MAIC results (for duration of response) to maintain the orphan drug designation for TAFA+LEN at the time of authorisation.

Proportional Hazards Assumption

We are pleased that the ERG and committee agreed that the proportional hazard assumption does not hold in the comparison of TAFA+LEN vs. POLA+BR. The committee suggested that, because of the likely violation of the proportional hazard assumption, more complex approaches beyond the company proposed piecewise constant hazard ratios (HRs) with splitting at 4 months might be needed. Although the use of fractional polynomials was considered (i.e. as an alternative approach for estimating time-varying HRs), this approach was discounted for 2 reasons.

- Firstly, clinical and statistical evidence pointed to the choice of a splitting point at 4 months: changes in the pattern of the hazards were observed around 4 months in the log-cumulative hazard plots, clinically 4 months corresponds to a landmark point in the POLA + BR therapy, as it can only be given for 6 cycles (approximately 4 months).
- Secondly, the comparison was supported by a small effective sample size (ESS) (ESS of 29 patients for the weighted TAFA+LEN sample and 40 POLA+BR patients). Particularly, towards later timepoints in the study, the number of patients at risk was very low (16 in the TAFA + LEN arm and 19 in the POLA + BR arm at 12 months; 13 in the TAFA + LEN arm and 11 in the POLA + BR arm at 24 months). Estimating time-varying HRs based on such a small sample size could lead not only to high uncertainty but also introduce potential bias in the long-term extrapolations, which can have a considerable impact on the economic evaluation. For these reasons, we believe that the use of piecewise constant HRs is more appropriate.

Alignment with TA649

On page 10 of the ACD, the ERG and Committee agree that a constant hazard ratio is not appropriate due to violation of the proportional hazards assumption but prefer use of a constant hazard ratio to align with results in TA649. While TA649 was based on the best evidence available at the time, the randomised controlled trial GO29365,[6] further evidence following implementation of TA649, including real world studies (Northend 2022)[4] together with clinical opinion, indicate that the benefit of POLA + BR therapy in R/R DLBCL might be lower than observed in GO29365. As quoted in the ACD, the clinical

expert panel present during the committee meeting highlighted that the estimates from the company preferred base case extrapolation of survival were aligned with their expectation of survival for patients treated with POLA+BR and closer to their expectations than those proposed by the ERG.

Population matching in RE-MIND2

The L-MIND trial did not include a comparator arm because it was not designed as a registrational trial. RE-MIND (observational trial with matched lenalidomide-only comparator cohort) and RE-MIND2 (retrospective, observational cohort study) were undertaken to assess the contribution of tafasitamab to the combination and characterise the effectiveness of tafasitamab and lenalidomide relative to commonly administered systemic therapies for ASCT ineligible patients with R/R DLBCL.

On page 8 of the ACD the committee notes: *"The ERG highlighted that RE-MIND2 consists of pooled individual participant data and is preferred in principle to the intervention population adjustment undertaken in the matching-adjusted indirect comparisons. Adjusting the L-MIND population differently for each comparator treatment population can lead to bias. However, there was uncertainty about the methods used for RE-MIND2 because the baseline characteristics of the tafasitamab with lenalidomide cohort varied depending on the comparator."*

We would like to take the opportunity to restate the clarification on the methods used for RE-MIND2 1:1 matching provided in the technical engagement. Specifically:

- Logistic regression models were fitted to derive the propensity score used in the nearest neighbour 1:1 matching without replacement of the L-MIND patient population vs each comparator population (a separate regression model for each comparator).
- Main results of the RE-MIND2 study were obtained through the use of logistic regression models that included the same list of covariates for all comparators: age, Ann-Arbor staging, refractoriness to last therapy line, number of prior lines of therapy, history of primary refractoriness, prior treatment with ASCT, neutropenia at baseline, anaemia at baseline, elevated lactate dehydrogenase (LDH) at baseline. Of note, in the comparison of TAFA+LEN v. POLA+BR multiple imputation was used.
- The 1:1 matching of RE-MIND-2 patients vs each comparator population was achieved as follows:
    - Estimated propensity score (ePS), reflecting the probability of being treated with TAFA + LEN conditional on the patients' characteristics
    - For each L-MIND patient, a patient from the comparator population with the closest ePS was selected as their 1:1 match
    - One might expect that this process should provide the same number of L-MIND-matched patients vs each comparator. However, it is possible that a different sample size of L-MIND patients may be obtained vs each comparator population when some patients of the comparator population cannot be matched with L-MIND patients (e.g. if distance in the ePS differs more than the pre-specified calliper). It is worth noting however that most of the patients enrolled in the efficacy population of the L-MIND study were

	retained in the matched comparison versus BR and R-GemOx (75 and 74 patients out of 80, respectively). However, only 36 patients enrolled in RE-MIND2 and treated with POLA+BR had complete data for all covariates required for propensity score estimation. This is likely because POLA+BR was still a relatively novel treatment when the RE-MIND2 study was conducted. Hence, not all TAFA+LEN treated patients in L-MIND could be given a POLA+BR-treated match, despite the use of multiple imputation on the ePS to increase the size of the POLA+BR cohort available for matching as acknowledged in the original submission and the TE. • The same regression method was used to estimate relative efficacy vs each comparator. i.e. Cox proportional hazards (PH) regression (a separate regression model for each comparator) We hope that this further explanation addresses the ERG's point and confirms to the Committee that the same modelling approach was used for all comparators (i.e. the same regression method to derive the ePS, the same list of covariates, the same procedures to derive the callipers, and the same regression method for estimating relative efficacy).
3	**Issues raised in the ACD: Overall Survival and progression-free survival (PFS) extrapolations for POLA+BR** In section 3.6, page 11 of the ACD, it is noted that "the committee concluded that the company's parametric extrapolations for polatuzumab vedotin with bendamustine and rituximab were implausible. It found that estimates from the ERG's base case were more plausible because the outcomes were more aligned with NICE's technology appraisal guidance on polatuzumab vedotin with bendamustine and rituximab. However, it would have preferred to see different modelling approaches used that both fitted the underlying hazards of the data and produced outcomes aligned with the polatuzumab vedotin with bendamustine and rituximab guidance." During the appraisal committee meeting, both clinical experts indicated that the POLA+BR OS extrapolations from the time-varying piecewise hazard ratios were more plausible than the constant HR extrapolations, based on the available published evidence and their experience in clinical practice. In addition, as noted above in relation to end of life criteria, additional clinical evidence and experience with POLA+BR has been gained since TA649 and primary completion of the GO29365 trial. While we understand that the NICE committee has tried to be consistent between technology appraisals, and that decisions in NICE TA649 were made with the best available evidence at the time, newer published data for POLA+BR have since become available and there is more experience with POLA+BR in UK clinical practice, which is reflected in recent clinical expert testimony. • The GO29365 trial, which informed TA649, provides direct evidence of the efficacy of POLA+BR vs BR, but included a relatively small sample of patients on POLA+BR (n=40).[3,6] UK-specific real-world evidence from Northend 2022 on POLA+BR survival has since been published (N=133; n=78 in standalone POLA+BR cohort), which suggests that POLA+BR survival in practice may be lower than observed in the GO23965 trial, as described above in comment 1.[3,4]

	• As mentioned above, clinical experts interviewed following publication of the ACD also provided further indication that the ERG preferred extrapolations overestimated OS for POLA+BR. o One clinical expert interviewed noted that "for these patients, I will invite my palliative nurse to join the consultation. I would not do this if the life expectancy was 4 years" o Another clinical expert commented that the mean survival of 4-years generated by the ERG model was "grossly excessive", and that much more was now known about POLA+BR from various published data (including Northend 2022 and GO29365 follow-up data, as well as Greek and German data), which should be considered over this extrapolated estimate. • Furthermore, while a potential plateau was observed in the tail of the OS curves from the GO39265 trial (Sehn 2022), some patients received subsequent treatment with CAR-T which may introduce bias into the OS data from the GO29365 trial when applied without consideration of CAR-T costs in the cost-effectiveness analyses. o The following text is stated in the Sehn 2022 publication on the GO23965 trial, at the end of the results section (pages 537 and 538): *"Of all patients treated with pola + BR in the study (including the extension cohort), 4 patients proceeded to receive consolidative stem cell transplant (autologous [n = 1] or allogeneic [n = 3]). Nine patients received CAR T-cell therapy after pola + BR, including 1 patient who discontinued pola + BR after 3 cycles to bridge to CAR T-cell therapy. For patients treated with CAR T-cell therapy after pola + BR, OS after treatment with pola + BR ranged from 11.5 to 28.0 months; 4 patients are alive and remain in follow-up."* While it is not entirely clear how many of these patients receiving subsequent were in the randomised cohort, this implies that CAR-T therapy may have contributed to longer survival among some patients in the POLA+BR cohort, with the survival estimates of 11.5 to 28.0 months representing survival after POLA+BR treatment, without including the additional OS contribution from POLA+BR treatment itself prior to treatment with CAR-T. o NICE's position statement on the consideration of products recommended for use in the Cancer Drugs Fund as comparators, or in a treatment sequence, in the appraisal of a new cancer product states that: *"products recommended for use in the Cancer Drugs Fund after 1 April 2016 should not be considered as comparators, or appropriately included in a treatment sequence, in subsequent relevant appraisals. Companies of new cancer products under appraisal should therefore not include treatments recommended for use in the Cancer Drugs Fund as comparators, or treatment sequence products in their economic modelling."*[11] o As the ERG preferred to exclude the cost of CAR-T therapy in line with the NICE position statement, aligning the OS extrapolations to those from updated GO29365 trial results[3] may bias the results in favour of POLA+BR by including potential health benefits of CAR-T, without including the associated costs.

	In terms of PFS, similar to OS, both clinical experts during the committee meeting indicated that the POLA+BR PFS from the time-varying (piecewise constant) HRs were more plausible than the constant HR extrapolations, based on the available published evidence and their experience in clinical practice. As shown on slide 27 of the NICE committee slides, the PFS extrapolation for POLA+BR when using the time-varying hazard ratios produced a survival curve closer to the observed PFS for the randomised cohort in the Sehn 2022 publication. Median PFS was 9.2 months and 1-year PFS was ~42%.[3] Given the clinical expert feedback provided during the committee meeting and the better alignment with the updated PFS data from Sehn 2022, we strongly believe that the time-varying HR extrapolations for POLA+BR PFS have both better clinical and external validity than the constant HR-based PFS extrapolation preferred by the ERG.
4	**Issues raised in the ACD: PFS extrapolations for TAFA+LEN** Incyte accepts the committee's comments preferring the lognormal model for extrapolating TAFA+LEN progression-free survival. Revised company base case results using the lognormal model for TAFA+LEN PFS are provided in the Appendix, along with additional pricing scenarios. In Section 3.7 of the ACD, it is stated that *"The ERG accepted that the lognormal distribution overestimates progression-free survival for the first 20 months but pointed out that it provides the smallest overestimation in the long term."* However, the lognormal model underestimates longer-term PFS after 20 months relative to the TAFA+LEN KM curve. As such, we suggest that the statement could be amended as follows: "The ERG accepted that the lognormal distribution overestimates progression-free survival for the first 20 months but pointed out that it provides a smaller **underestimation** of the observed KM curve in the long term compared to the log-logistic, Weibull and exponential models."
5	**Issues raised in the ACD: TAFA+LEN is not cost-effective** In Section 3.9 of the ACD, the following statements are included: • "The committee considered that the most plausible incremental cost-effectiveness ratio (ICER) was highly uncertainty, because of issues with the indirect comparisons and modelling (see sections 3.4, 3.6 and 3.7). It noted that the base case ICERs presented by the company for tafasitamab with lenalidomide compared with polatuzumab vedotin with bendamustine and rituximab were higher than the range normally considered a cost-effective use of NHS resources, even for end-of-life treatments." • "However, tafasitamab with lenalidomide had not been shown to be a cost-effective use of NHS resources in any analyses presented to the committee." In Section 3.13 of the ACD, the following is stated:

	• "However, there is substantial uncertainty in the modelling and the committee was not presented with any analysis showing tafasitamab with lenalidomide was cost effective." We wish to clarify that the company did submit a cost-effective ICER versus POLA+BR during technical engagement. The company base case included an estimated price discount for lenalidomide to reflect imminent generic entry onto the market and produced an ICER for TAFA+LEN versus POLA+BR of [redacted] which is cost-effective when considering a willingness to pay threshold normally applied for end-of-life treatments. [redacted]. The majority of discussion about the cost-effectiveness of TAFA+LEN was completed in part 2 of the committee meeting, and therefore the company has limited information to fully understand the position taken by the NICE committee. Incyte is aware that a PAS for polatuzumab is in place, and it was at the Committee meeting that that pola+BR was confirmed as the suitable comparator for this appraisal. [redacted]. Revised base case analyses, as well as additional scenarios have been provided in the Appendix.
6	Issues raised in the ACD: Additional benefit not captured in the QALYs On page 15 of the ACD, the committee note that they were not presented with evidence of additional benefit that had not been captured in the quality-adjusted life year (QALY) calculation. However, clinicians consulted by NICE during the submission believed that tafasitamab would result in health-related benefits, including some that may not be captured in the QALY calculation (pages 661 and 680 of the Committee papers). • As noted in the company submission (e.g., in the innovation section of Document B) the value of tafasitamab is reflected in the PIM designation from the MHRA (January 2020 – PIM 2019/0012) additionally tafasitamab maintained orphan designation in R/R DLBCL after EMA and MHRA assessed that DoR could be clinically relevant and supportive of a significant benefit over Pola+BR (based on MAIC analysis).[5] • Tafasitamab is a chemotherapy-free treatment option that does not target CD20, the target of rituximab, representing a shift in the treatment paradigm for R/R DLBCL not eligible for transplant o Many patients undergo CD20-negative transformation following rituximab treatment, a key component of chemoimmunotherapy regimens for DLBCL and first and subsequent lines of therapy.[12-18] In L-MIND, 34/81 (42%) of patients were rituximab-refractory at baseline.[19] o The tolerability profile of tafasitamab also means that, following TAFA+LEN treatment, tafasitamab monotherapy can be continued until disease progression for most patients, while current chemotherapy-based regimens

	are given for a fixed treatment duration. In L-MIND, 10/81 (12%) of patients discontinued treatment with TAFA+LEN due to adverse events, and there was only 1 treatment discontinuation during the extended tafasitamab monotherapy phase, in a patient with recurrence of previously-diagnosed marginal zone lymphoma that had been documented as an adverse event.[19,20] • The main goal of treatment is to prolong remission. The submission from Lymphoma Action highlighted that patients and their families experience substantial anxiety due to fear of relapse; treatments with greater chances of long remissions such as tafasitamab with lenalidomide could help alleviate some of that anxiety. • Lymphoma Action also noted the challenges of caring for someone with DLBCL, which is time-consuming and emotionally challenging. In addition, tafasitamab can be administered in an outpatient setting with minimal training required for its introduction to the treatment pathway, as other monoclonal antibodies are administered in routine clinical practice. Incyte has requested that clinical and patient experts attend the second appraisal committee meeting to address the clinical uncertainties and give a voice to patients respectively.

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NICE National Institute for Health and Care Excellence

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

Appendix: Changes to the company base case analysis

Following publication of the ACD, Incyte has made the following changes to the company base case analysis:

- Use of lognormal model for TAFA+LEN PFS instead of generalised gamma, in line with the ERG preferred base case
- Update to the PAS price discount for tafasitamab from [redacted] to [redacted]
- Updating the price discount applied for lenalidomide from [redacted] to [redacted]
- Inclusion of a price discount for polatuzumab of [redacted]

The following changes to the scenario analyses were also included:

- Scenario analysis for generalised gamma PFS curve for TAFA+LEN (given use of lognormal as the base case)
- Exploration of a 5-year cure point instead of cure at the point of OS and PFS curves crossing (due to the previous scenarios no longer impacting the ICERs following use of the lognormal model for TAFA+LEN PFS)

In addition, the following pricing scenarios have also been explored:

- Variations of the lenalidomide price discount between [redacted] and [redacted]
- Excluding the polatuzumab price discount, and variations of the price discount between [redacted] and [redacted]

Base case deterministic results:

The base-case cost-effectiveness results for TAFA+LEN and each model comparator (POLA+BR, BR and R-GemOx) are presented in Table 1. While TAFA+LEN generated increased total costs against each model comparator, it also produced

substantial increases in total life years (2.88-3.49) and QALYs ([redacted]). Undiscounted life year gains for TAFA+LEN were 3.97, 4.66 and 4.41 vs POLA+BR, BR and R-GemOx, respectively.

The ICERs for TAFA+LEN against POLA+BR, BR and R-GemOx were [redacted], [redacted] and [redacted] per QALY, respectively.

Table 1. Base-case results

Intervention	Total costs (£)	Total LYG	Total QALYs	TAFA+LEN vs comparator			
				Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)
TAFA+LEN	[redacted]	5.08	[redacted]	-	-	-	-
POLA+BR	[redacted]	2.20	1.42	[redacted]	2.88	[redacted]	[redacted]
BR	[redacted]	1.60	1.02	[redacted]	3.49	[redacted]	[redacted]
R-GemOx	[redacted]	1.82	1.16	[redacted]	3.26	[redacted]	[redacted]

Abbreviations: BR = bendamustine and rituximab; ICER = incremental cost-effectiveness ratio; LYG = life year gained; POLA+BR = polatuzumab vedotin with bendamustine and rituximab; R-GemOx = rituximab in combination with gemcitabine and oxaplatin; QALY = quality-adjusted life year; TAFA+LEN = tafasitamab + lenalidomide

Incremental analysis results are shown below in Table 2. [redacted].

Table 2: Base case results – full incremental analysis

Intervention	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY) vs previous non-dominated alternative
R-GemOx	[redacted]	1.16	-	-	-
BR	[redacted]	1.02	[redacted]	[redacted]	[redacted]
POLA+BR	[redacted]	1.42	[redacted]	[redacted]	[redacted]
TAFA+LEN	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: Tafa+Len, tafasitamab + lenalidomide; POLA+BR, polatuzumab + bendamustine + rituximab; BR, bendamustine + rituximab; R-GemOx, rituximab + gemcitabine + oxaplatin; QALYs, quality-adjusted life-years; ICER, incremental cost-effectiveness ratio

Probabilistic sensitivity analysis results:

Mean probabilistic results are presented in Table 3 alongside the deterministic base-case results. Mean PSA total costs for TAFA+LEN and R-GemOx were fairly similar to the deterministic results from the base-case analysis, with values within 1.0% of the base-case estimates, while mean PSA costs were higher for POLA+BR and BR by 7.1% and 13.1%, respectively. Similarly, mean PSA total QALYs were fairly close to the base case analysis for TAFA+LEN and R-GemOx (within 1.0% of the base case values), while mean PSA total QALYs were also higher for POLA+BR and BR than the deterministic base-case results (11.6% and 15.0%, respectively).

Table 3. Mean PSA results

Intervention	Deterministic results		Mean PSA results	
	Total costs	**Total QALYs**	**Total costs (95% CI)**	**Total QALYs (95% CI)**
TAFA+LEN	[redacted]	[redacted]	[redacted]	[redacted]
POLA+BR	[redacted]	1.42	[redacted]	1.59 (0.65 to 3.29)
BR	[redacted]	1.02	[redacted]	1.18 (0.36 to 2.72)
R-GemOx	[redacted]	1.16	[redacted]	1.18 (0.87 to 1.56)

Abbreviations: BR = bendamustine and rituximab; CI = confidence interval; ICER = incremental cost-effectiveness ratio; LYG = life year gained; POLA+BR = polatuzumab vedotin with bendamustine and rituximab; R-GemOx = rituximab in combination with gemcitabine and oxaplatin; QALY = quality-adjusted life year; TAFA+LEN = tafasitamab + lenalidomide

The distribution of incremental costs and QALYs for TAFA+LEN vs. POLA+BR, BR and R-GemOx is shown in Figure 1,

Figure 2, Figure 3, respectively.

Figure 1. PSA cost-effectiveness plane for TAFA+LEN vs. POLA+BR

Abbreviations: ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life year

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

Figure 2. PSA cost-effectiveness plane for TAFA+LEN vs. BR

Abbreviations: ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life year

Figure 3. PSA cost-effectiveness plane for TAFA+LEN vs. R-GemOx

Abbreviations: ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life year

The cost-effectiveness acceptability curve (CEAC) for TAFA+LEN vs. POLA+BR, BR and R-GemOx is shown in **Figure 4** for willingness to pay (WTP) thresholds between £0 and £200,000 per QALY, in increments of £4,000 per QALY. The CEAC indicates that .

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Figure 4. CEAC

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Deterministic sensitivity analysis results:

Tornado diagrams illustrating the key drivers of ICER values in the comparison are shown in

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Figure **5**, Figure 6 and

Figure 7. [redacted]

[redacted].

Figure 5. Tornado diagram of ICER results for TAFA+LEN vs. POLA+BR

Abbreviations: 2L+ = second line and later; HR = hazard ratio; OS = overall survival; PFS = progression-free survival; Tx Disc = treatment discontinuation

Figure 6. Tornado diagram of ICER results for TAFA+LEN vs. BR

Abbreviations: 2L+ = second line and later; HR = hazard ratio; OS = overall survival; PFS = progression-free survival; Tx Disc = treatment discontinuation

Figure 7. Tornado diagram of ICER results for TAFA+LEN vs. R-GemOx

Abbreviations: 2L+ = second line and later; OS = overall survival; PFS = progression-free survival; Tx Disc = treatment discontinuation

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Scenario analysis results:

Scenarios exploring alternative long-term extrapolations and data sources for survival parameters, cure assumptions, utilities and vial sharing, along with shorter model time horizons and lower discount rates, are summarised in Table 4. As use of the lognormal PFS model for TAFA+LEN resulted in none of the OS and PFS curves crossing across comparators within the time horizon of the model, a 5-year cure assumption was explored instead, also assuming 100% cured at 5 years.

Scenarios with the largest increases in the ICER were shorter time horizons ([redacted] and [redacted] for BR, [redacted] and [redacted] for R-GemOx for five and 10-year time horizons, respectively), use of the Weibull model for TAFA+LEN OS ([redacted] to [redacted] across comparators), use of MAIC constant HRs for POLA+BR ([redacted] increase in ICER vs. POLA+BR) and applying MAIC HRs and median TTD data for R-GemOx ([redacted] increase in ICER vs. R-GemOx).

Scenarios generating the largest decreases in the ICER were the cure assumption scenarios, with scenarios 16 and 17 generating the largest ICER decreases of between [redacted] to [redacted] across comparators followed by scenarios 20 and 21 ([redacted] to [redacted] across comparators), use of the generalised model for TAFA+LEN PFS ([redacted] to [redacted]), as well as use of RE-MIND2 data for POLA+BR ([redacted]), health state utilities from NICE TA567 ([redacted] to [redacted]) and assuming vial-sharing for all IV therapies ([redacted] to [redacted]). Shorter time horizons of 5 and 10 years decreased the ICER for TAFA+LEN compared to POLA+BR by [redacted] and [redacted], respectively.

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Table 4. Scenario analysis results

Scenario #	Scenario	ICER vs. POLA+BR (£/QALY)	ICER vs. BR (£/QALY)	ICER vs. R-GemOx (£/QALY)
-	**Base-Case**	[redacted]	[redacted]	[redacted]
1	5-year time horizon	[redacted]	[redacted]	[redacted]
2	10-year time horizon	[redacted]	[redacted]	[redacted]
3	1.5% discount rate for costs and outcomes	[redacted]	[redacted]	[redacted]
4	TAFA+LEN OS parametric model: generalised gamma	[redacted]	[redacted]	[redacted]
5	TAFA+LEN OS parametric model: Weibull	[redacted]	[redacted]	[redacted]
6	TAFA+LEN PFS parametric model: generalised gamma	[redacted]	[redacted]	[redacted]
7	POLA+BR: apply MAIC HRs with 11-month split for OS and PFS	[redacted]	[redacted]	[redacted]
8	POLA+BR: apply constant MAIC HRs for OS and PFS	[redacted]	[redacted]	[redacted]
9	POLA+BR: apply RE-MIND2 survival data (generalised gamma for OS, exponential for PFS, TTD KM data)	[redacted]	[redacted]	[redacted]
10	BR: apply RE-MIND2 survival data (lognormal for OS and PFS, TTD KM data)	[redacted]	[redacted]	[redacted]
11	R-GemOx OS parametric model: Gompertz	[redacted]	[redacted]	[redacted]

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Scenario #	Scenario	ICER vs. POLA+BR (£/QALY)	ICER vs. BR (£/QALY)	ICER vs. R-GemOx (£/QALY)
12	R-GemOx PFS parametric model: generalised gamma	[redacted]	[redacted]	[redacted]
13	Applying MAIC HR estimates for OS/PFS and median TTD duration for R-GemOx	[redacted]	[redacted]	[redacted]
14	Fixed 2-year cure point with 78.6% of PFS patients at 2 year achieving cure: general population mortality only	[redacted]	[redacted]	[redacted]
15	Scenario 14 + apply general population utility to cured patients	[redacted]	[redacted]	[redacted]
16	Scenario 15 + assume patients discontinue treatment at the cure point	[redacted]	[redacted]	[redacted]
17	Scenario 16 + apply prolonged PFS monitoring and disease management costs for cured patients	[redacted]	[redacted]	[redacted]
18	Cure point at crossing of OS and PFS curves: general population mortality only	[redacted]	[redacted]	[redacted]
19	Scenario 18 + apply general population utility to cured patients	[redacted]	[redacted]	[redacted]
20	Scenario 19 + assume patients discontinue treatment at the cure point	[redacted]	[redacted]	[redacted]

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Scenario #	Scenario	ICER vs. POLA+BR (£/QALY)	ICER vs. BR (£/QALY)	ICER vs. R-GemOx (£/QALY)
21	Scenario 20 + apply prolonged PFS monitoring and disease management costs for cured patients	[redacted]	[redacted]	[redacted]
22	Utility of 0.83 for PFS and 0.71 for PD based on NICE TA567	[redacted]	[redacted]	[redacted]
23	Vial sharing for all IV administered treatments	[redacted]	[redacted]	[redacted]

Abbreviations: BR = bendamustine and rituximab; ICER = incremental cost-effectiveness ratio; IV = intravenous; KM = Kaplan-Meier; MAIC = matching-adjusted indirect comparison; NICE = National Institute for Health and Care Excellence; OS = overall survival; PD = progressive disease; PFS = progression-free survival; POLA+BR = polatuzumab vedotin with bendamustine and rituximab; QALY = quality-adjusted life year; R=GemOx = rituximab in combination with gemcitabine, oxaliplatin; TAFA+LEN = Tafasitamab + lenalidomide; TTD = time to treatment discontinuation

Pricing scenario results

Pricing scenario analyses for TAFA+LEN compared to POLA+BR are shown below in **Table 5** using the updated PAS price discount for tafasitamab of [redacted], exploring variations in the lenalidomide price discount of [redacted] and the polatuzumab price discount of [redacted]. Base case results are highlighted in bold.

Table 5. Pricing scenario results

Scenario #	Lenalidomide price discount	Polatuzumab price discount	ICER vs. POLA+BR (£/QALY)
1	[redacted]	[redacted]	[redacted]

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Scenario #	Lenalidomide price discount	Polatuzumab price discount	ICER vs. POLA+BR (£/QALY)
2		[redacted]	[redacted]
3		[redacted]	[redacted]
4		[redacted]	[redacted]
5		[redacted]	[redacted]
6		[redacted]	[redacted]
7		[redacted]	[redacted]
8	[redacted]	[redacted]	[redacted]
9		[redacted]	[redacted]
10		[redacted]	[redacted]
11		[redacted]	[redacted]
12		[redacted]	[redacted]
13		[redacted]	[redacted]
14		[redacted]	[redacted]
15	[redacted]	[redacted]	[redacted]
16		[redacted]	[redacted]
17		[redacted]	[redacted]
18		[redacted]	[redacted]
19		[redacted]	[redacted]

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Scenario #	Lenalidomide price discount	Polatuzumab price discount	ICER vs. POLA+BR (£/QALY)
20		[redacted]	[redacted]
21		[redacted]	[redacted]

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Consultation on the appraisal consultation document – deadline for comments 5pm on Thursday 14 July 2022. Please submit via NICE Docs.

	Please read the checklist for submitting comments at the end of this form. We cannot accept forms that are not filled in correctly. The Appraisal Committee is interested in receiving comments on the following: • has all of the relevant evidence been taken into account? • are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence? • are the provisional recommendations sound and a suitable basis for guidance to the NHS? NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that the preliminary recommendations may need changing in order to meet these aims. In particular, please tell us if the preliminary recommendations: • could have a different impact on people protected by the equality legislation than on the wider population, for example by making it more difficult in practice for a specific group to access the technology; • could have any adverse impact on people with a particular disability or disabilities. Please provide any relevant information or data you have regarding such impacts and how they could be avoided or reduced**.**
Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	NCRI-ACP-RCP-RCR
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	None
Name of commentator person completing form:	[redacted]

Comment number	Comments

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Consultation on the appraisal consultation document – deadline for comments 5pm on Thursday 14 July 2022. Please submit via NICE Docs.

	Insert each comment in a new row. Do not paste other tables into this table, because your comments could get lost – type directly into this table.
	The NCRI-ACP-RCP-RCR is grateful for the opportunity to respond to the above consultation. We have liaised with our experts and would like to comment as follows.
1	We are not convinced that the summaries of clinical and cost effectiveness are reasonable interpretations of the evidence. Thus, the summaries of clinical and cost effectiveness are not reasonable interpretations of the evidence. Patients who are not eligible for haematopoietic stem cell transplant for relapsed or refractory diffuse large B-cell lymphoma are not likely to live for longer than 2 years. This is usually less than 12-18 months if they receive the present standard of care treatment with Rituximab with Bendamustine and Polatuzumab (RB-Pola). Median survival in 152 patients with R/R DLBCL treated with RB-Pola was just 12.4 months (95% CI: 9.0-32.0) when reported with a median of 48 months follow-up. The 24 months overall survival probability was only 38% (95% CIL 22.5-53.9)(Sehn Blood Advances 2022) The survival times for people who have polatuzumab vedotin plus rituximab and bendamustine used in the modelling does not reflect the estimated survival in NICE's guidance on polatuzumab vedotin plus rituximab and bendamustine. Without such consistency it is both confusing and potentially flawed and undermines any further interpretation. As noted in the report '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.' As outlined in the document 'it would have preferred to see different modelling approaches used that both fitted the underlying hazards of the data and produced outcomes aligned with the polatuzumab vedotin with bendamustine and rituximab guidance.'

Insert extra rows as needed

Checklist for submitting comments

- Use this comment form and submit it as a Word document (not a PDF).
- Complete the disclosure about links with, or funding from, the tobacco industry.
- Combine all comments from your organisation into 1 response. We cannot accept more than 1 set of comments from each organisation.
- Do not paste other tables into this table – type directly into the table.
- Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise and all information submitted under 'academic in confidence' in yellow. If confidential information is submitted, please also send a 2nd version of your comment with that information replaced with the following text: 'academic / commercial in confidence information removed'. See the Guide to the processes of technology appraisal (section 3.1.23 to 3.1.29) for more information.
- Do not include medical information about yourself or another person from which you or the person could be identified.

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Consultation on the appraisal consultation document – deadline for comments 5pm on Thursday 14 July 2022. Please submit via NICE Docs.

- Do not use abbreviations
- Do not include attachments such as research articles, letters or leaflets. For copyright reasons, we will have to return comments forms that have attachments without reading them. You can resubmit your comments form without attachments, it must send it by the deadline.
- If you have received agreement from NICE to submit additional evidence with your comments on the appraisal consultation document, please submit these separately.

Note: We reserve the right to summarise and edit comments received during consultations, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received during our consultations are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

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Comments on the ACD received from the public through the NICE Website

Name	[redacted]
Role	Not specified
Other role	Not specified
Organisation	Not specified
Location	Not specified
Conflict	No
Notes	

Comments on the ACD:

- Has all of the relevant evidence been taken into account?

Overall I think it has. As ever NICE has been thorough in its approach which is to be congratulated. However I would say that the original BR+pola randomised trial was clearly in a select patient group as we have sadly not been able to replicate the excellent outcomes seen in this paper in the real world. Whilst Pola+BR is a useful regimen and an appropriate comparator, the Northend et al data is the more appropriate data to use.

- Are the summaries of clinical and and cost effectiveness reasonable interpretations of the evidence?

I do not feel it's appropriate to use the Sehn et al pola+BR clinical trial as comparator data as this does not represent the patients we treat in the real world with pola+BR. 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'. I therefore WOULD regard that the end of life criteria are met by the tafa+len submission. In my practise (which covers an extended MDT population of 2.2 million people), life expectancy when using pola+BR is < 2 years (no-where near 4 years sadly). I would be using tafa+len for a similar indication and therefore life expectancy would be similar without it. Due to the phase 2 efficacy data I would expect prolongation of survival by more than 3 months in this setting.

- Are the recommendations a sound and suitable basis for guidance to the NHS?

Currently I do not think this is suitable guidance for the needs of NHS patients. I agree there is considerable uncertainty. However my view is this should be funded within the CDF and during this time longer follow up from the phase 2 will emerge. More importantly though, data can be collected on patients treated in England (which can be lead by PHE or by an engaged clinician) and presented. This will provide more reliable data on which to re-appraise tafa+len for suitability for routine commissioning. This has been done for other drugs and indications (the brentuximab vedotin in patients with Hodgkin who failed 2 lines of treatment and were ineligible for stem cell transplantation comes to mind). I would also add that tafa+len adds a very useful treatment option for patients who have less marrow reserve as Pola+BR is very myelosuppressive with high risk of febrile neutropenia.

- Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, sex, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?

Not that I'm aware of.

Name	[redacted]
Role	Not specified
Other role	Not specified
Organisation	Not specified
Location	Not specified
Conflict	No
Notes	

Comments on the ACD:

- Has all of the relevant evidence been taken into account?

Yes.

- Are the summaries of clinical and and cost effectiveness reasonable interpretations of the evidence?

No. Undue weight seems to have been given to the Pola BR efficacy assumptions made at the NICE TA. Average OS of >24 months is not something we see in clinical practice with Pola BR in R/R DLBCL setting. Published data doesnt support this assumption either. In an extended cohort analysis of the Pola BR study which reported on 106 patients, median OS and PFS were around 12 and 6 months respectively (Sehn LH, et L. Blood Adv (2022) 6 (2): 533–543). Meidan OS and PFS were only 8.2 and 4.8 months in a UK RWE analysis reporting on 131 patients. These figures are more in keeping with our clinical experience in the UK (Northend M, et L. Blood Adv 2022). In fact even with R-Gem Ox regimen, median OS was just over 12 months and PFS around 6 months in a phase 2 Lysa Study (Mounier N, et al. Haematologica 2012). Therefore the current available evidence and clinical experience doesnt allow us to conclude that Pola BR has transformed outcomes of R/R DLBCL in transplant ineligible patients. At best it represents an additional treatment option for these patients but their expected median survival is still way short of 24 months. With all the short comings listed, the L-MIND data on Tafa/Len compares quite favourably against this backdrop. Median OS and PFS of 33.5 months and 11.6 months respectively for the 80 patients treated in this trial (Duell J, et al. Oral presentation at Virtual ICML 2021; Abstract 28) does represent a significant step forward.

- Are the recommendations a sound and suitable basis for guidance to the NHS?

No. The committee seems to have given undue weightage to survival assumptions made at a previous NICE TA for Pola BR regimen. The phase 2 randomised Pola BR study was a very small study with only 40 patients in each arm. The control arm in the study was BR which is not standard in the UK. Neither the trial data nor subsequent data from extended cohort analysysis or UK RWE would suggest average OS of 24 months with this regimen. The committee view that Pola BR should be considered standard of care in management of R/R DLBCL in transplant inelgible patients is not supported by available evidence or clinical experience. To

deny patients access to other effective treatments (such as Tafa/Len) would be doing injustice and would stifle access to novel therapies for the UK patients.

- Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, sex, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?

No.

Name	[redacted]
Role	Not specified
Other role	Not specified
Organisation	Not specified
Location	Not specified
Conflict	No
Notes	

Comments on the ACD:

- Has all of the relevant evidence been taken into account?

My comments are in relation to the end of life criteria as the evidence for auto ineligible patients (Norton et al/ Sehn et al ritux,pola, benda) DECC (Maddox , Osborne) is a survival of months, maybe up to a year with a survival of 2 years unlikely.

- Are the summaries of clinical and and cost effectiveness reasonable interpretations of the evidence?

Clinical survival data for RR DLBCL auto ineligible is not as I have interpreted the evidence, as discussed above.

- Are the recommendations a sound and suitable basis for guidance to the NHS?

In view of the unmet need for pts with RR DLBCL and the tolerability of tafa len I would support approval.

- Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, sex, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?

No.

- Recommendations – section 1

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. I am therefore not clear where the data for this end of life criteria are from. Even patients who are started on rbendapola have a survival of less than a year in trial and this was reduced further in the UK real world data.

in collaboration with:

Erasmus School of Health Policy & Management

Maastricht University

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

Addendum – ERG critique of the Company's ACD Response

Produced by Kleijnen Systematic Reviews (KSR) Ltd, in collaboration with Erasmus University Rotterdam (EUR) and Maastricht University

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Date completed 22/07/2022

Table of Contents

1. INTRODUCTION

This addendum contains the ERGs critique of the company's updated analyses and base-case assumptions, provided in the company's response to the Appraisal Consultation Document (ACD).

The ERG's critique to the new evidence submitted by the company is provided in Section 2. The company's updated cost effectiveness results are presented in Section 3, followed by the ERG's updated cost effectiveness results in Section 4.

2. ADDITIONAL EVIDENCE AND CLARIFICATION PROVIDED BY THE COMPANY IN RESPONSE TO THE ACD

2.1 End-of-life criteria

In issue 1 of the response to the ACD, the company *"do not agree with the committee's view that end of life criterion 1 is not met and do not believe that all relevant evidence has been taken into account in the committee's decision making"*.[1] The response highlighted three key issues, namely additional evidence, evidence provided to the committee, and the interpreation of the term "normally".

The ERG notes that the additional evidence has been presented as part of the technical engagement thus the ERG commented on this previously, concluding that "*depending on the comparator being considered, TAFA+LEN may not meet criterion 1 of the NICE EOL criteria"*.

The other points, i.e. the interpretation of evidence and the term "normally" by the committee, are outside the remit of the ERG.

2.2 Indirect treatment comparisons

The company state that the indirect treatment comparisons *"… rigorously followed NICE TSD 17 and 18 guidelines for generating relative efficacy estimates leveraging non-randomised evidence. Despite some limitations in the analyses, which are clearly acknowledged, all relative efficacy estimates derived using indirect evidence (through either MAIC, nearest neighbour matching, inverse probability of treatment weighting, overlap weighting and regression adjustment) provided consistent results showing improved efficacy for TAFA+ LEN over POLA+BR, albeit in some instances only a numerical advantage (i.e. without statistical significance)".*

The ERG stated in the ERG report that it was unclear precisely how some of the ITCs were conducted for POLA+BR, which appeared not to have been clarified at technical engagement, the ERG stating in their critique of the company response: *"In contrast to the figures for BR and RGemOx, the figure for Pola-BR suggests that it was not the ATT that was estimated because "less comparator patients were recruited compared to treated patients" and that instead what was estimated was the "average treatment effect on the treated patients for whom a comparator patients could be found". Notwithstanding the grammatical error, this appears to be consistent with the speculation expressed in the ERG report that the "average treatment effect on those treated with the comparator" was estimated.*" The ERG did conclude that, in addition to a MAIC, the following analyses using IPD from REMIND 2 were conducted for the comparison with POLA+BR:

- Matching of 6 or 9 covariates
- IPTW to estimate the ATT
- Regression adjustment
- Overlap weights to estimate the ATE for OS only

2.3 Survival curves extrapolations for pola-BR

In section 3.6, page 11 of the ACD, "*the committee concluded that the company's parametric extrapolations for polatuzumab vedotin with bendamustine and rituximab were implausible. It found that estimates from the ERG's base case were more plausible because the outcomes were more aligned with NICE's technology appraisal guidance on polatuzumab vedotin with bendamustine and rituximab. However, it would have preferred to see different modelling approaches used that both fitted the underlying hazards of the data and produced outcomes aligned with the polatuzumab vedotin with bendamustine and rituximab guidance*".[1]

The company disagrees with the abovementioned statement for the reasons summarised below:

- During the appraisal committee meeting, clinical experts indicated that the company's pola-BR OS extrapolations (time-varying piecewise hazard ratios) were more plausible than the ERG's OS extrapolations (constant HR). This was based on the more recent published evidence and their experience in clinical practice.
- The GO29365 trial, used to inform TA649,[2] provided direct evidence of the efficacy of pola-BR vs. BR, but included a relatively small sample of patients on pola-BR (n=40).[3, 4] More recently, the study by Northend et al. 2022, which included UK-specific real-world evidence on pola-BR survival has been published, and it was based on a larger sample (N=133; n=78 in standalone pola-BR cohort). According to the company, this study suggests that pola-BR survival in practice may be lower than observed in the GO23965 trial.[4, 5]
- The company also indicated that, while a potential plateau was observed in the tail of the OS curves from the GO39265 trial (Sehn et al. 2022),[4] some patients received subsequent treatment with CAR-T, which may have introduced bias into the OS data from the GO29365 trial when applied without consideration of CAR-T costs in the cost effectiveness analyses.
    - Sehn et al. 2022 (pages 537 and 538) mentions the following: *"Of all patients treated with pola-BR in the study (including the extension cohort), 4 patients proceeded to receive consolidative stem cell transplant (autologous [n = 1] or allogeneic [n = 3]). Nine patients received CAR T-cell therapy after pola-BR, including 1 patient who discontinued pola-BR after 3 cycles to bridge to CAR T-cell therapy. For patients treated with CAR T-cell therapy after pola-BR, OS after treatment with pola-BR ranged from 11.5 to 28.0 months; 4 patients are alive and remain in follow-up".*[4] While it is not entirely clear how many of these patients receiving subsequent CAR-T therapy were in the randomised cohort, CAR-T therapy may have contributed to longer survival among some patients in the pola-BR cohort.
    - The company also mentioned that NICE's position statement on products recommended for use in the Cancer Drugs Fund as comparators, or in a treatment sequence, in the appraisal of a new cancer product states that: *"products recommended for use in the Cancer Drugs Fund after 1 April 2016 should not be considered as comparators, or appropriately included in a treatment sequence, in subsequent relevant appraisals. Companies of new cancer products under appraisal should therefore not include treatments recommended for use in the Cancer Drugs Fund as comparators, or treatment sequence products in their economic modelling".* [6]
    - The company concluded that, since the ERG preferred to exclude the cost of CAR-T therapy in line with the NICE position statement, aligning the OS extrapolations to those from updated GO29365 trial results may bias the results in favour of pola-BR by including potential health benefits of CAR-T,[4] without including the associated costs.
- In terms of PFS, clinical experts also indicated that the company's pola-BR PFS extrapolations were more plausible than the ERG's PFS extrapolations.
- The company referred to slide 27 of the NICE committee slides,[7] to explain that the PFS extrapolation for pola-BR using time-varying hazard ratios resulted in a survival curve which is closer to the observed PFS for the randomised cohort in the Sehn et al. 2022, where the median PFS was 9.2 months and the 1-year PFS was approximately 42%.[4]
- Regarding PFS, the company concluded that the time-varying HR extrapolations for pola-BR PFS have both better clinical and external validity than the constant HR-based PFS extrapolation preferred by the ERG.

ERG comment: The ERG would like to emphasise the following:

- As discussed in the ERG report and during the committee meeting,[8] the ERG's rationale for selecting OS extrapolations for pola-BR based on constant HR's was to align the results with those in TA649. The ERG acknowledged though that assuming constant HRs was methodologically incorrect and would most likely overestimate pola-BR benefits. This approach was still preferred because it can be considered as conservative.
- Whereas it is true that clinical experts indicated that the company's pola-BR OS extrapolations (time-varying piecewise hazard ratios) were more plausible than the ERG's OS extrapolations, the ERG considers that the following issue is still unresolved in the company's approach. A time-varying HR was assumed for pola-BR and a PH model (constant HR compared to TAFA+LEN) for BR. This choice implies a treatment waning for pola-BR compared to BR, since the OS curves get closer over time, while the TAFA+LEN compared to pola-BR seems to increase and the effect compared to BR stays constant. There is no clear rationale for this assumption, which seems to lead to an underestimation of the effect of pola-BR compared to BR, and possibly compared to TAFA+LEN too (see Table 4.18 in ERG report).[8]
- The ERG agrees with the company that the benefits of CAR-T may have biased the OS results in favour of pola-BR. However, the number of patients receiving CAR-T in Sehn et al. 2022 is low and while the effect is unknown, it is not expected to be large.[4]
- Similar comments apply to PFS.

The ERG would like to conclude that since the survival estimates in TA649 for pola-BR seem to be invalid, it is unclear what the long-term benefit of pola-BR compared to BR alone (or to R-Gem-ox) is. Therefore, with the available evidence, the ERG considers that it is highly uncertain to properly estimate the cost effectiveness of TAFA+LEN compared to pola-BR, BR and R-GemOx. Including more recent available studies (e.g. Northend 2022 and Sehn 2022) in a MAIC and in the cost effectiveness model,[4, 5] could help reducing this uncertainty.

2.4 Progression-free survival extrapolations for TAFA+LEN

The company has accepted the committee's comments preferring the lognormal model for extrapolating TAFA+LEN progression-free survival and this change is included in the revised company's base-case as shown in Section 3.

2.5 Cost effectiveness of TAFA+LEN

The company referred to the following statements included in Section 3.9 of the ACD:

- "*The committee considered that the most plausible incremental cost-effectiveness ratio (ICER) was highly uncertainty, because of issues with the indirect comparisons and modelling (see sections 3.4, 3.6 and 3.7). It noted that the base case ICERs presented by the company for tafasitamab with lenalidomide compared with polatuzumab vedotin with bendamustine and rituximab were higher than the range normally considered a cost-effective use of NHS resources, even for end-of-life treatments*".[1]
- "*However, tafasitamab with lenalidomide had not been shown to be a cost-effective use of NHS resources in any analyses presented to the committee*".[1]

The company also referred to the following statement included in Section 3.13 of the ACD:

- "*However, there is substantial uncertainty in the modelling and the committee was not presented with any analysis showing tafasitamab with lenalidomide was cost effective*".[1]

The company considered that a cost effective ICER vs. pola-BR was provided during technical engagement. The company's base-case, which included an estimated price discount for lenalidomide to reflect imminent generic entry onto the market, produced an ICER of [redacted], which can be considered cost effective under the willingness to pay threshold normally applied for end-of-life treatments. [redacted].

The company is also aware that a PAS for polatuzumab is in place, and it was at the Committee meeting that pola-BR was confirmed as the most relevant comparator for this appraisal. [redacted].

ERG comment: The ERG would like to emphasise that generic or PAS prices should be included for all treatments included in the model, and not only for lenalidomide or polatuzumab. Also, these prices should not be based on the company's expectations but on real prices. A confidential addendum has also been prepared by the ERG and provides the results of the cost effectiveness analyses based on the lowest nationally available prices of the drugs against which tafasitamab is compared, co-medications and subsequent treatments included in the economic model. These prices were provided by the Commercial Medicines Unit and the prices of generic drugs in equivalent formulations were derived from the electronic market information tool.

The ICER vs. pola-BR presented by the company in response to the ACD, produced an ICER of [redacted], which according to the company can be considered cost effective under the willingness to pay threshold normally applied for end-of-life treatments. Despite this base-case including an estimated price discount for lenalidomide and polatuzumab, which according to the ERG is incorrect, it is important to mention that, in the context of multiple comparators, focusing on only one comparator could be misleading, even if it is believed that it is the most relevant one. For example, the PSA results presented by the company in response to the ACD indicated that at the of £50,000 per QALY gained, the estimated probability that TAFA+LEN is a cost effective alternative to the other comparators was approximately [redacted]. As shown in Section 3.1 and 3.2 below, when list prices for lenalidomide and polatuzumab are assumed, the ICER vs. pola-BR increased to [redacted], and the estimated probability that TAFA+LEN is a cost effective alternative to the other comparators was [redacted].

2.6 TAFA+LEN additional benefit not captured in the QALYs

The company referred to page 15 of the ACD, where the committee noted that they were not presented with evidence of additional benefit that had not been captured in the QALY calculation.[1] However, clinical experts consulted by NICE during the submission considered that tafasitamab may result in health-related benefits, including some that may not be captured in the QALY calculation (pages 661 and 680 of the Committee papers).[9] Regarding this issue, the company indicated the following:

- The value of tafasitamab is reflected in the PIM designation from the MHRA (January 2020 – PIM 2019/0012). Additionally, tafasitamab maintained orphan designation in R/R DLBCL

after EMA and MHRA assessed that DoR could be clinically relevant and supportive of a significant benefit over Pola+BR (based on the MAIC analysis).[10]

- Tafasitamab is a chemotherapy-free treatment that does not target CD20, the target of rituximab, representing a shift in the treatment paradigm for R/R DLBCL not eligible for transplant:
    - Many patients undergo CD20-negative transformation following rituximab treatment, a key component of chemoimmunotherapy regimens for DLBCL and first and subsequent lines of therapy.[11-17] In the L-MIND trial, 34/81 (42%) of patients were rituximab-refractory at baseline.[18]
    - Following TAFA+LEN, tafasitamab monotherapy can be continued until disease progression for most patients, while current chemotherapy-based regimens are given for a fixed treatment duration. In the L-MIND trial, 10/81 (12%) of patients discontinued treatment with TAFA+LEN due to adverse events. There was one treatment discontinuation during the extended tafasitamab monotherapy phase, in a patient with recurrence of previously-diagnosed marginal zone lymphoma that had been documented as an adverse event.[18, 19]
- The main goal of TAFA+LEN treatment is to extend remission. The submission from Lymphoma Action highlighted that patients and their families experience substantial anxiety due to fear of relapse. Therefore, treatments with expected longer remission could help alleviate some of that anxiety.
- Lymphoma Action also noted the challenges of caring for someone with DLBCL, which is time-consuming and emotionally challenging.
- Finally, the company emphasised that tafasitamab can be administered in an outpatient setting with minimal training required for its introduction to the treatment pathway, as other monoclonal antibodies are administered in routine clinical practice. The company has requested that clinical and patient experts attend the second appraisal committee meeting to address the clinical uncertainties and give a voice to patients, respectively.

ERG comment: While it is possible that TAFA+LEN treatment is associated with additional benefit for patients, without a proper estimate of this assumed benefit, the ERG cannot assess its impact on the cost effectiveness results.

3. COMPANY'S UPDATED COST EFFECTIVENESS RESULTS

3.1 Company's updated deterministic results

The company made the following changes in their base-case assumptions:

- Use of lognormal model for TAFA+LEN PFS instead of generalised gamma, in line with the ERG preferred base-case.
- Update to the PAS price discount for tafasitamab from [redacted]% to [redacted]%.
- Updating the price discount applied for lenalidomide from [redacted]% to [redacted]%.
- Inclusion of a price discount for polatuzumab of [redacted]%.

NICE requested the ERG to present the company's results excluding the price discount assumed for lenalidomide and polatuzumab. Therefore, the results presented in the remaining of Section 3 and in Section 4 are based on lenalidomide and polatuzumab list prices. The results including lenalidomide and polatuzumab assumed discounts can be found in the company's response to the ACD.[1] Table 3.1 shows the deterministic CE results of the updated company's base-case analysis (with lenalidomide and polatuzumab list prices). All results are discounted and reported in a full incremental way. Pairwise ICERs of TAFA+LEN vs. each of the comparators are also reported for completeness. Results indicated that

[redacted]

Table 3.1: Company base-case deterministic cost effectiveness results (tafasitamab PAS price, lenalidomide and polatuzumab list price)

Technologies	Total costs (£)	Total LYG	Total QALYs	Inc. costs (£)	Inc. LYG	Inc. QALYs	ICER (£/QALY)	Pairwise ICER* (£/QALY)
BR	[redacted]	1.60	1.02	[redacted]				[redacted]
R-GemOx	[redacted]	1.82	1.16					[redacted]
Pola-BR	[redacted]	2.20	1.42	[redacted]				[redacted]
TAFA+LEN	[redacted]	5.08	[redacted]	[redacted]	3.26	[redacted]	[redacted]	

Based on the updated model provided alongside the response to ACD,[1] and including the new PAS discount for tafasitamab.

* All pairwise ICERs are calculated vs. TAFA+LEN

BR = bendamustine + rituximab; ICER = incremental cost effectiveness ratio; Inc. = incremental; LEN = lenalidomide; LYG = life years gained; Pola-BR = polatuzumab vedotin with bendamustine and rituximab; QALY = quality-adjusted life year; R-GemOx = rituximab in combination with gemcitabine and oxaliplatin; TAFA = tafasitamab

ERG comment: In TA649 pola-BR was deemed as a cost effective alternative compared to BR.[2] With the results obtained by the company in Table 3.1, the ICER for the comparison pola-BR vs. BR was [redacted].

3.2 Probabilistic sensitivity analysis

The average PSA results are summarised in Table 3.2. These are in line with the deterministic ones and also in the PSA [redacted]

Table 3.2: Company base-case probabilistic cost effectiveness results (tafasitamab PAS price, lenalidomide and polatuzumab list price)

Technologies	Total costs (£)	Total LYG	Total QALYs	Inc. costs (£)	Inc. LYG	Inc. QALYs	ICER (£/QALY)	Pairwise ICER* (£/QALY)
BR	[redacted]	1.85	1.166	[redacted]				[redacted]
R-GemOx	[redacted]	1.84	1.174					[redacted]
Pola-BR	[redacted]	2.39	1.53	[redacted]				[redacted]
TAFA+LEN	[redacted]	5.07	[redacted]	[redacted]	3.23	[redacted]	[redacted]	

Based on the updated model provided alongside the response to ACD,[1] and including the new PAS discount for tafasitamab.

* All pairwise ICERs are calculated vs. TAFA+LEN

BR = bendamustine and rituximab; ICER = incremental cost effectiveness ratio; Inc. = incremental; LEN = lenalidomide; LYG = life years gained; NR = not reported; Pola-BR = polatuzumab vedotin with bendamustine and rituximab; QALY = quality-adjusted life year; R-GemOx = rituximab + gemcitabine + oxaliplatin; TAFA = tafasitamab

The company also plotted the PSA outcomes on a CE-plane, which can be seen in Figure 3.1. This figure shows that [redacted]. From the PSA results, a cost effectiveness acceptability curve (CEAC) was also calculated and plot in Figure 3.2. The CEAC plot indicates that [redacted]. At the common thresholds of £20,000, £30,000 and £50,000 per QALY gained, the estimated probability that TAFA+LEN is a cost effective alternative to the other comparators was [redacted].

Figure 3.1: Probabilistic sensitivity analysis cost effectiveness plane (tafasitamab PAS price, lenalidomide and polatuzumab list price)

Based on the updated model provided alongside the response to ACD,[1] and including the new PAS discount for tafasitamab.
ICER = incremental cost effectiveness ratio; PAS = patient access scheme; QALY = quality-adjusted life year

Figure 3.2: Probabilistic sensitivity analysis cost effectiveness acceptability curve (tafasitamab PAS price, lenalidomide and polatuzumab list price)

Based on the updated model provided alongside the response to ACD,[1] and including the new PAS discount for tafasitamab.
PAS = patient access scheme.

3.3 Deterministic sensitivity and scenario analyses

As mentioned above, NICE requested the ERG to present the company's results excluding the price discount assumed for lenalidomide and polatuzumab. However, due to time constraints, the base-case and the PSA analyses were prioritised over the deterministic sensitivity and scenario analyses. Thus, the results of the deterministic sensitivity and scenario analyses assuming list prices for lenalidomide and polatuzumab are not presented in this section. The results including lenalidomide and polatuzumab assumed discounts can be found in the company's response to the ACD.[1]

3.4 Model validation and face validity check

The main concerns of the ERG regarding validation were extensively discussed in the ERG report and during the committee meeting. These concerns were mainly related to the validity of the OS/PFS extrapolations for the pola-BR arm, which in turn resulted in CE results very different to those obtained in TA649.[2] The ERG heard from the clinical experts in the committee meeting that, in their opinion, results for pola-BR, as presented in TA649, do not match with their experience in clinical practice. Experts indicated that patients treated with pola-BR have a substantially lower life expectancy than that

estimated in TA649, which could be even below two years. Thus, assuming that the survival estimates in TA649 for pola-BR are invalid, it is unclear what the long-term benefit of pola-BR compared to BR alone (or to R-Gem-ox) is. Therefore, with the available evidence, the ERG considers that it is highly uncertain to properly estimate the cost effectiveness of TAFA+LEN compared to pola-BR, BR and R-GemOx. Including more recent available studies (e.g. Northend 2022 and Sehn 2022) in the MAIC and in the cost effectiveness model,[4, 5] could help reducing this uncertainty.

4. EXPLORATORY AND SCENARIO ANALYSES UNDERTAKEN BY THE ERG

4.1 ERG revised base-case

The ERG's preferences regarding alternative assumptions led to the following changes to the company base-case analysis:

- OS pola-BR: assuming MAIC based on constant HR (the company chose a MAIC with a time-varying HR).
- PFS pola-BR: assuming MAIC based on constant HR (the company chose a MAIC with a time varying HR).

4.2 Impact on the ICER of additional clinical and economic analyses undertaken by the ERG

4.3.1 Results of the ERG preferred base-case scenario

Table 4.1 shows the deterministic CE results of the ERG preferred base-case analysis. All results are discounted. Results indicated that [redacted]

Table 4.1: ERG preferred base-case deterministic cost effectiveness results

Technologies	Total costs (£)	Total LYG	Total QALYs	Inc. costs (£)	Inc. LYG	Inc. QALYs	ICER (£/QALY)	Pairwise ICER* (£/QALY)
BR	[redacted]	1.60	1.02	[redacted]				[redacted]
R-GemOx	[redacted]	1.82	1.16					[redacted]
Pola-BR	[redacted]	3.36	2.20	[redacted]				[redacted]
TAFA+LEN	[redacted]	5.08	[redacted]	[redacted]	3.26	[redacted]	[redacted]	

Based on the ERG preferred base-case model and including the PAS discount for tafasitamab.
* All pairwise ICERs are calculated vs. TAFA+LEN
BR = bendamustine + rituximab; ICER = incremental cost effectiveness ratio; Inc. = incremental; LEN = lenalidomide; LYG = life years gained; Pola-BR = polatuzumab vedotin with bendamustine and rituximab; QALY = quality-adjusted life year; R-GemOx = rituximab in combination with gemcitabine and oxaliplatin; TAFA = tafasitamab

4.3.2 ERG preferred probabilistic base-case cost effectiveness results

The average PSA results of the ERG preferred base-case are summarised in Table 4.2. These are broadly in line with the deterministic ones; [redacted]

Table 4.2: ERG preferred base-case probabilistic cost effectiveness results

Technologies	Total costs (£)	Total LYG	Total QALYs	Inc. costs (£)	Inc. LYG	Inc. QALYs	ICER (£/QALY)	Pairwise ICER* (£/QALY)
BR	[redacted]	1.84	1.16	[redacted]				[redacted]
R-GemOx	[redacted]	1.83	1.18					[redacted]
Pola-BR	[redacted]	3.55	2.29	[redacted]				[redacted]
TAFA+LEN	[redacted]	5.11	[redacted]	[redacted]	3.26	[redacted]	[redacted]	

Based on the ERG preferred base-case model and including the PAS discount for tafasitamab.
* All pairwise ICERs are calculated vs. TAFA+LEN
BR = bendamustine and rituximab; ICER = incremental cost effectiveness ratio; Inc. = incremental; LEN = lenalidomide; LYG = life years gained; NR = not reported; Pola-BR = polatuzumab vedotin with bendamustine and rituximab; QALY = quality-adjusted life year; R-GemOx = rituximab + gemcitabine + oxaliplatin; TAFA = tafasitamab

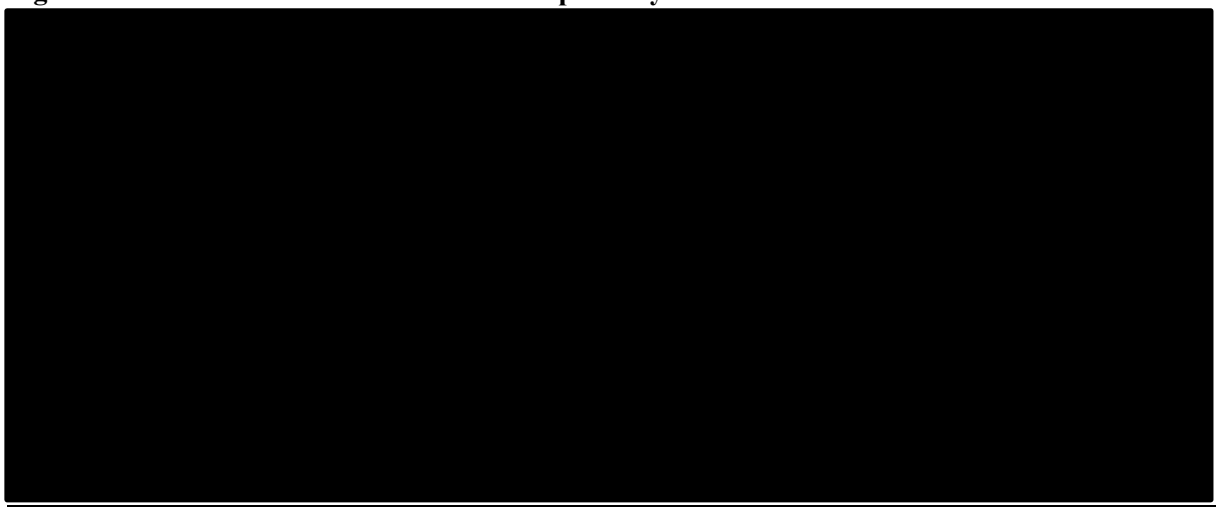
The plot of the PSA outcomes on the CE-plane can be seen in Figure 4.1. This figure shows that [redacted].
From the PSA results, a CEAC was also calculated and plot in Figure 4.2. The CEAC plot indicates that [redacted]. At the common thresholds of £20,000, £30,000 and £50,000 per QALY gained, the estimated probability that TAFA+LEN is a cost effective alternative to the other comparators was [redacted].

Figure 4.1: ERG PSA cost effectiveness plane

[redacted]

Based on the updated model provided alongside the response to ACD,[1] and including the new PAS discount for tafasitamab.
ERG = Evidence Review Group; ICER = incremental cost effectiveness ratio; LEN = lenalidomide; PAS = patient access scheme; Pola-BR = polatuzumab vedotin with bendamustine and rituximab; PSA = probabilistic sensitivity analysis; QALY = quality-adjusted life year; TAFA = tafasitamab

Figure 4.2: ERG PSA cost effectiveness acceptability curve



Based on the updated model provided alongside the response to ACD,[1] and including the new PAS discount for tafasitamab.
ERG = Evidence Review Group; PAS = patient access scheme; PSA = probabilistic sensitivity analysis

4.3.3 Results of the ERG additional exploratory scenario analyses

No additional scenario analyses were conducted by the ERG.

4.4 ERG preferred assumptions

Table 4.3 shows the changes made by the ERG to the company base-case and the one-by-one impact of each change on the results.

Table 4.3: Incremental impact of ERG preferred assumptions (one-by-one)

Preferred assumption	ICER vs. Pola-BR (£/QALY)	ICER vs. BR (£/QALY)	ICER vs. R-GemOx (£/QALY)
1. Post-ACD company BC + PAS discount for TAFA	[redacted]	[redacted]	[redacted]
2. 1 + OS for pola-BR based on MAIC with constant HR	[redacted]	[redacted]	[redacted]
3. 1 + PFS for Pola-BR based on MAIC with constant HR	[redacted]	[redacted]	[redacted]
4. Post-ACD ERG BC (1 + 2 + 3)	[redacted]	[redacted]	[redacted]

ACD = appraisal committee document; BC = base-case; BR = bendamustine and rituximab; ERG = evidence review group; HR = hazard ratio; ICER = incremental cost effectiveness ratio; MAIC = matching-adjusted indirect comparison; OS = overall survival; PFS = progression-free survival; Pola-BR = polatuzumab vedotin with bendamustine and rituximab; QALY = quality-adjusted life year; R-GemOx = rituximab + gemcitabine + oxaliplatin; TAFA = tafasitamab

4.5 Conclusions of the cost effectiveness section

Results of the company's base-case analysis (including the new PAS discount for tafasitamab, and list prices for lenalidomide and polatuzumab) indicated that

[redacted] The average PSA results were in line with the deterministic ones, but at the common thresholds of £20,000, £30,000 and £50,000 per QALY gained, the estimated probability that TAFA+LEN is a cost effective alternative to the other comparators was [redacted].

The ERG still selected for their preferred base-case OS and PFS models based on MAIC constant HR's for pola-BR to be in line with TA649, even though it was heard from the clinical experts at the committee meeting that this is likely to overestimate the benefits of pola-BR as observed in clinical practice. Consequently, these results should be interpreted with caution. The results of the ERG's base-case analysis indicated that [redacted] The average PSA results of the ERG preferred base-case were also in line with the deterministic ones, but at the common thresholds of £20,000, £30,000 and £50,000 per QALY gained, the estimated probability that TAFA+LEN is a cost effective alternative to the other comparators was [redacted].

The ERG considers that, given that the survival estimates in TA649 for pola-BR seem to be invalid, it is uncertain what the long-term benefit of pola-BR compared to BR alone (or to R-Gem-ox) is. Therefore, with the available evidence, it is highly uncertain to properly estimate the cost effectiveness of TAFA+LEN compared to pola-BR, BR and R-GemOx. Including more recent available studies (e.g., Northend 2022 and Sehn 2022) in the MAIC and in the cost effectiveness model,[4, 5] could help reducing this uncertainty.

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